

C.1
MECHANISTIC STUDIES OF THE DECOMPOSITION
OF 1-PYRAZOLINES

by

SANDOR SZILAGYI

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Department of Chemistry

The University of British Columbia
Vancouver 8, Canada

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ABSTRACT

A series of pyrazolines having a carbomethoxy group on C-3 and a bridge (number of the carbon atoms = 3, 4, 5) connecting C-3 and C-4 was synthesized and studied. 1-Carbomethoxy-2,3-diazabicyclo (3.3.0)oct-2-ene-5d₁ was also prepared and the overall deuterium kinetic isotope effect determined. The calculations concerning the specific deuterium kinetic isotope effects for the different processes involved in the thermolysis led to values similar to those obtained from other experiments with the exception of that for cyclopropane formation which was found to have a "inverse" isotope effect

$$\left(\frac{k_H}{k_D} = 0.71 \right) .$$

3-tert-Butyl-3-carbomethoxy-1-pyrazoline was synthesized and its thermal and photo decomposition studied.

The effect of the size of the ester group on product distribution was also examined by undertaking a product study on 3-methyl-3-carbomethoxy-1-pyrazoline and 3-methyl-3-carbo-tert-butoxy-1-pyrazoline.

cis- and trans-3-Methyl-3-carbomethoxy-1-pyrazoline-4d₁ and trans-3-methyl-carbomethoxy-1-pyrazoline-4d₁ were prepared. Kinetic studies were done on the trans isomers and the specific deuterium kinetic isotope effects were calculated from the measured overall kinetic isotope effects. The n.m.r. studies of 1-methyl-1-carbomethoxycyclopropane-2d₁ obtained by both the thermal and sensitized photodecomposition of cis- and trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁ revealed that each of the samples isolated (collected from the gas chromatograph) from the four decomposition products contained equal amounts of cis- and trans-1-methyl-1-carbomethoxycyclopropane-2-d₁. Especially these results, but also the thermal and photodecomposition of cis- and trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazolines, suggested that the cyclopropane formation occurred via a diradical intermediate in which the free rotation about the carbon-carbon bond would be reduced or prevented by bulky substituents. The formation of deuterated β,γ-olefinic esters and ethyl and methyl angelate-4d₁ as well as ethyl and methyl tiglate-3d₁ from the trans-isomers corroborated McGreer's suggestion for stereospecific olefin formation.

Kinetic and product studies done on a series of cis- and trans-3-methyl-4-alkyl-3-carbomethoxy-1-pyrazolines (alkyl = isopropyl, isobutyl and tert-butyl) provided additional proof for stereospecific olefin formation and also substantiated the idea of restricted or

prevented rotation about the carbon-carbon bond in the 1,3-diradical intermediate.

Since both cis- and trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazolines gave only cyclopropane product upon thermolyses in contrast to most pyrazolines it became possible to undertake a direct measurement of the secondary β deuterium kinetic isotope effect for cyclopropane formation.

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INTRODUCTION

PREPARATION OF PYRAZOLINES

The addition of diazoalkanes to activated carbon-carbon double* bonds to give pyrazolines has been known for quite some time (1,2,3) but the mechanistic details of the reactions were revealed in 1958 by Huisgen and co-workers (4,5). They classified them as 1,3-cycloadditions, however, studies indicated that these reactions proceeded via isopolar transition states. The 1,3-dipolar formulation of this reaction is convenient for predicting results (6).

The fact that these reactions are one step multicenter and stereospecific, permits us to synthesize 1-pyrazolines of known stereochemistry. Usually the α -carbon of the diazoalkane binds to the carbon β to the activating group, although Parham and his co-workers (7) have found that certain nitroolefins reacted with diazoalkanes to give both ordinary and "reverse" addition products.

MECHANISM OF PYRAZOLINE DECOMPOSITION

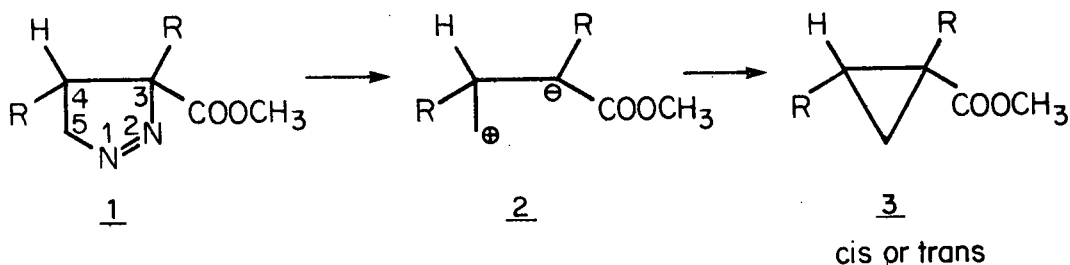
The pioneering work of von Auwers and Konig (3) on pyrazoline decomposition was focused exclusively on the isolation and identifi-

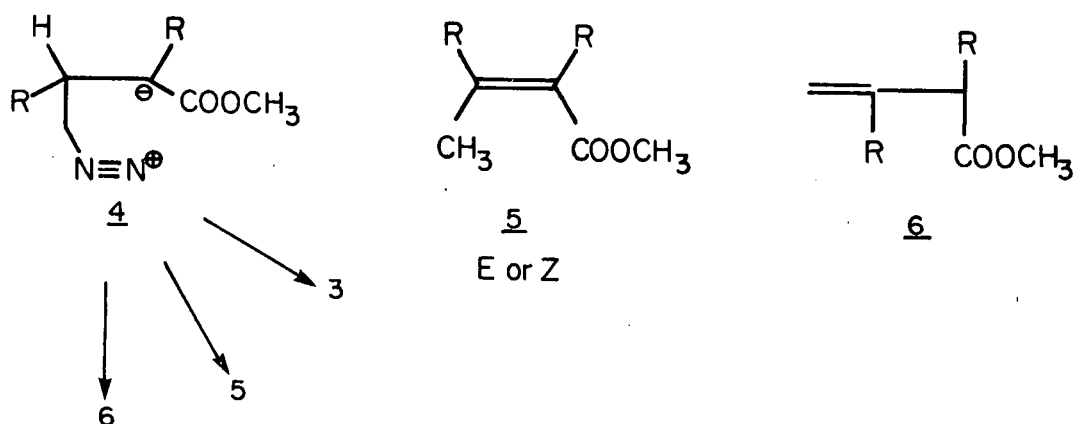
*NOTE: The addition of diazoalkanes to olefins containing no activating groups can be effected by the use of pressure (8,9,10,11).

cation of the components in the product mixtures. They concluded that the cyclopropane derivatives were formed with full retention of the stereochemistry of the parent pyrazolines, but no attempt was made to explain the results. The general stereospecificity was assumed to be valid for quite some time due to inadequate separation and analytical techniques. In 1962, Jones and Tai (12,13) found that it was not stereospecific, although some degree of stereoselectivity was shown. Their findings were substantiated by van Auken and Rinehart (14) and McGreer, *et al.* (15,16,17).

I. Ionic mechanism:

One of the first suggestions concerning the mechanism of 1-pyrazoline decomposition was an ionic pathway (14,18,19) in which the intermediate, depending upon the degree of bond breaking, could be either a nitrogen free zwitterion or a diazonium ion.

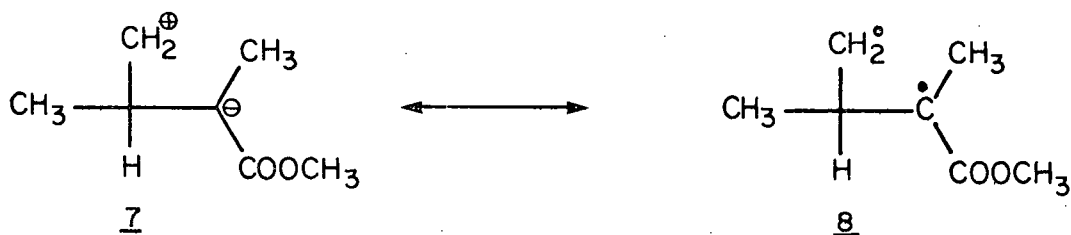




However, the following facts disfavor this mechanism:

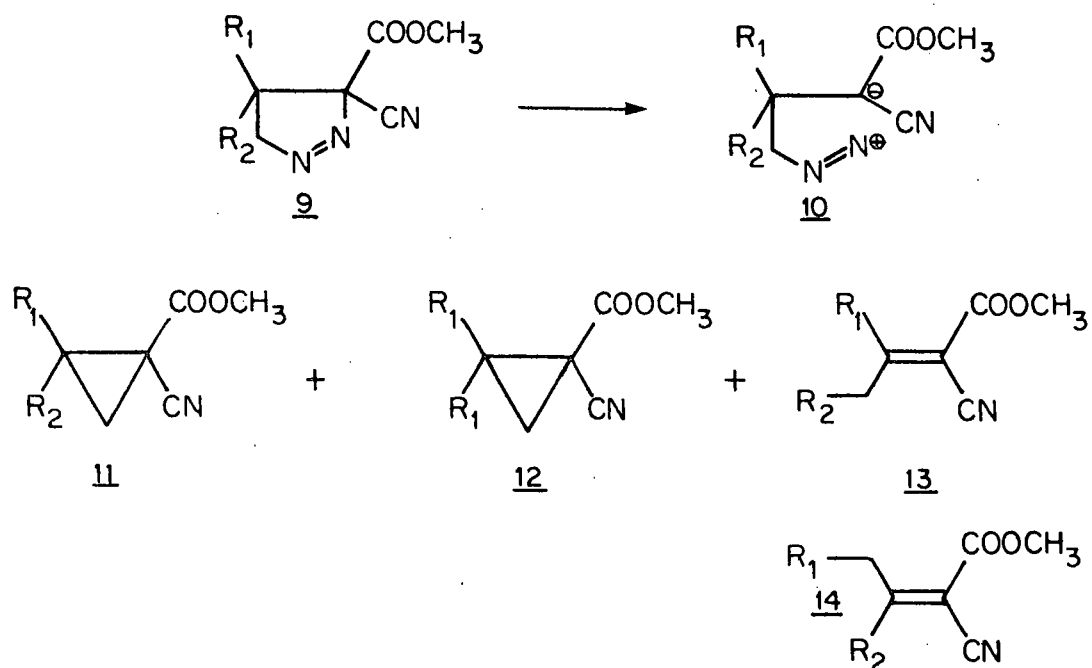
- a) the relative insensitivity of decomposition rates to solvent polarity.
- b) product distributions do not change significantly in going from apolar solvents to polar ones as one might expect on the grounds that polar solvents by stabilizing the zwitterions would allow greater equilibration of the ionic intermediate and would result in decreased stereoselectivity.
- c) lack of typical carbonium ion rearrangement products which readily occur in other systems having carbonium ion intermediates.
- d) H⁻ shifts are rare.

To counteract the deficiency of a clean-cut ionic mechanism, van Auken and Rinehart (14) suggested that the nitrogen free zwitterion was a resonance form of a singlet diradical, and could undergo cyclization.



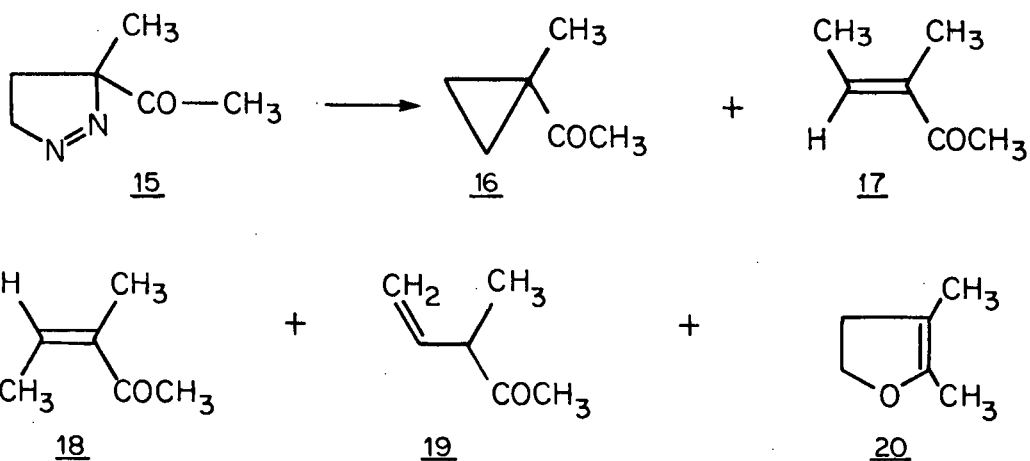
An ionic mechanism was proposed by McGreer et al. (20,21) for the thermal decomposition of 4,4'-dialkyl-3-cyano-3-carbo-methoxy-1-pyrazolines 9 as well as for the dihydrofuran formation observed in the decomposition of 3-methyl-3-acetyl-1-pyrazoline 15 and cis- and trans- 3,5-dimethyl-3-acetyl-1-pyrazolines. In the former system due to the two strongly electron withdrawing groups in C-3 one might expect that the bond breaking of C-3 to nitrogen is well advanced over the bond breaking of C-5 to nitrogen giving the intermediate a polar character.

The rate studies in solvents with different polarities principally support the idea of the ionic intermediate but the variation in the rate with the solvent polarity does not correlate with other polar reactions



in similar media. The formation of olefinic products can be explained by the concerted migration of the alkyl groups with nitrogen extrusion.

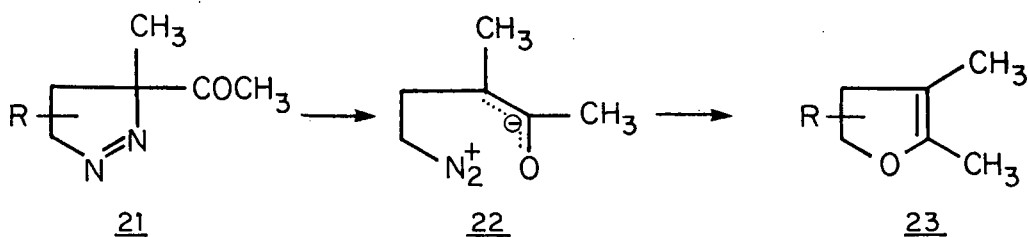
The thermal decomposition of 3-methyl-3-acetyl-1-pyrazoline (21) provided a rather complex product mixture:



The cis- and trans-3,5-dimethyl-3-acetyl-1-pyrazolines (21) gave similar products with the following two exceptions:

- 1) the cyclopropane product consists of a mixture of cis- and trans-1,2-dimethyl-1-acetyl-cyclopropanes.
- 2) the trans compound gave practically no dihydrofuran derivative.

According to McGreer et al., an ionic pathway could be responsible for the dihydrofuran formation in which the intermediate (22) has a negative charge delocalized into the carbonyl oxygen and if it is in a favorable position, it will be able to participate in the ring closure;



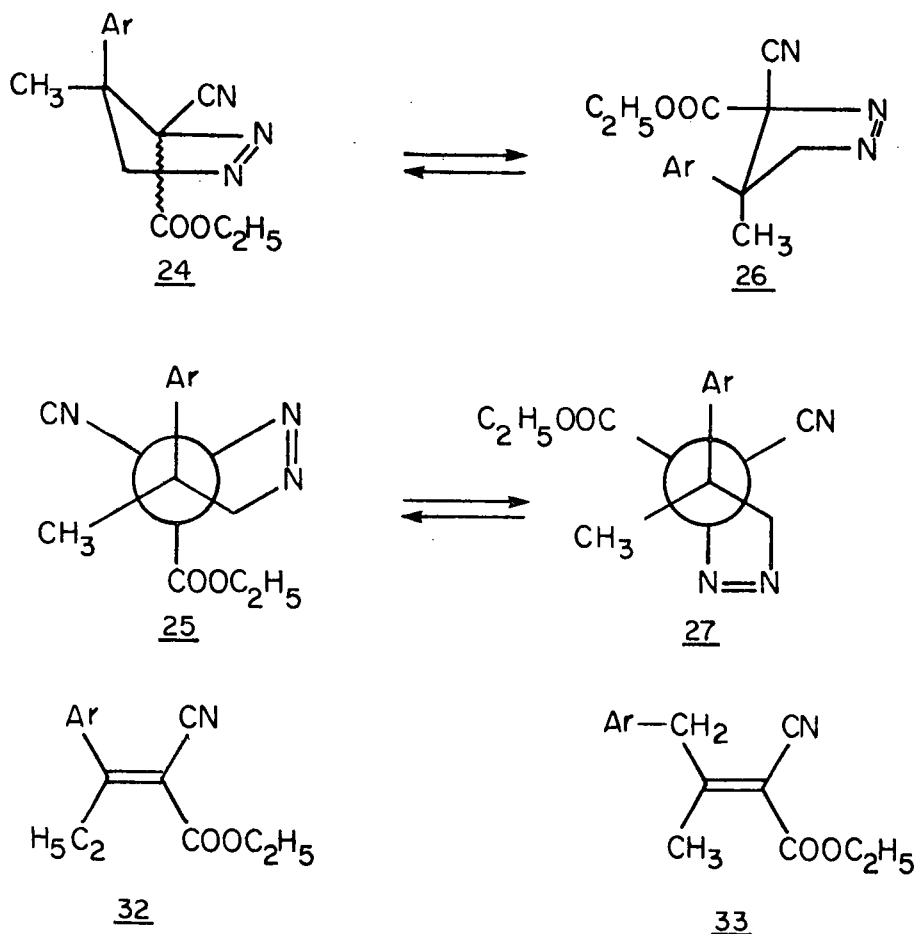
because the trans-3,5-dimethyl-3-acetyl-1-pyrazoline gave no dihydrofuran, the intermediate in that case could not undergo free rotation around the C-3 - C-4 bond to take up a favorable conformation for ring closure. McGreer et al. (21) assumed some bonding (either ionic or partially covalent) between C-3 and nitrogen. The intermediate (22) with rotation restricted around the C-3 - C-4 bond, was still influenced by steric factors present in the original pyrazoline and by solvent polarity as well.

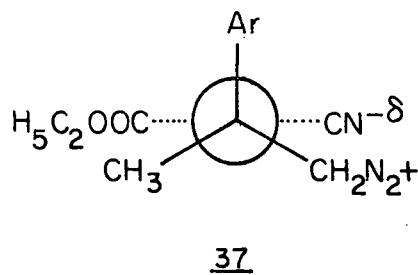
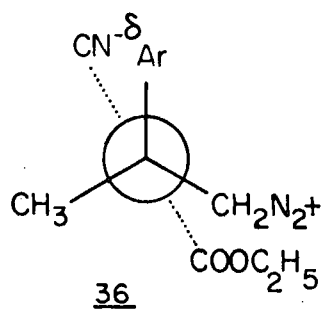
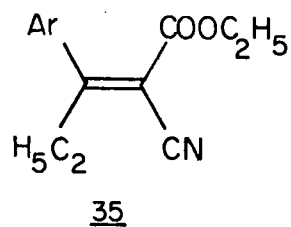
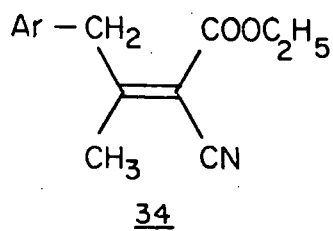
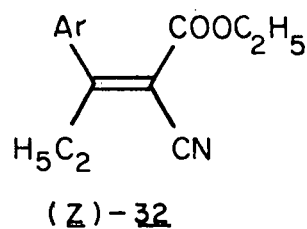
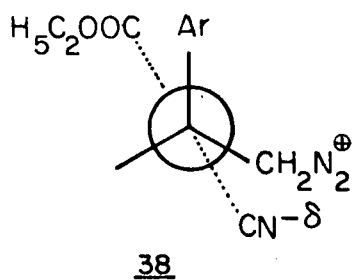
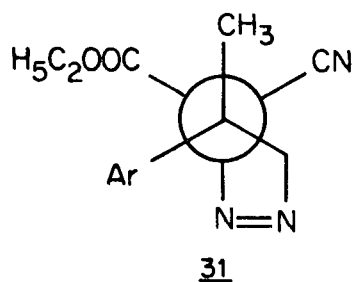
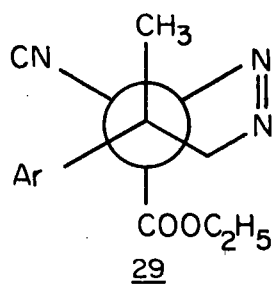
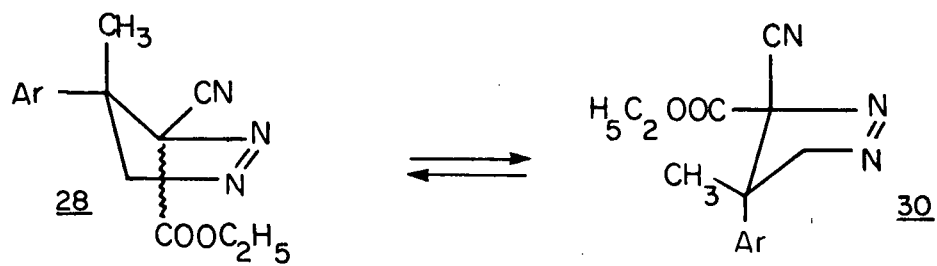
The studies of 3-cyano-3-carbethoxy-1-pyrazoline systems (22) showed that the formation of the olefinic products occurred via a stereoselective process. To explain this stereoselectivity Hamelin and Carrie assumed that there was a conformational equilibrium for each pyrazoline 24, 26 and 28, 30 or their Newman projections 25, 27 and 29, 31. Upon decomposition the first two conformers give rise to 32 and 33 while the two latter to 34 and 35 by methyl and aryl migration besides cyclopropane derivatives. They suggested two mechanistic pathways for the olefin formation, a concerted one in which migration and the nitrogen loss occur simultaneously and a stepwise path giving rise to an intermediate in which the rearrangement is faster than the rotation around the C-3 - C-4 bond. The intermediates for the latter pathway were suggested to be ionic species, 36 and 37 from conformers 28 and 30 respectively. The existence of an equilibrium between 36 and 37 was excluded on the

grounds that such an equilibrium would have allowed rotation around the C-3 - C-4 bond leading to the intermediate 38 which in turn would have given rise to (Z)-32. This compound was not found in the decomposition product mixture of 24 and 26.

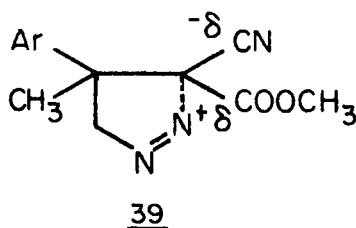
Since both the concerted and the ionic mechanisms could adequately explain the formation of olefinic product, the authors felt that kinetic studies would have to be done to see whether the bond breakage of C-3 and C-4 carbons to nitrogens take place successively or simultaneously.

The product studies also indicated that the aryl groups had a better migratory aptitude than the methyl.





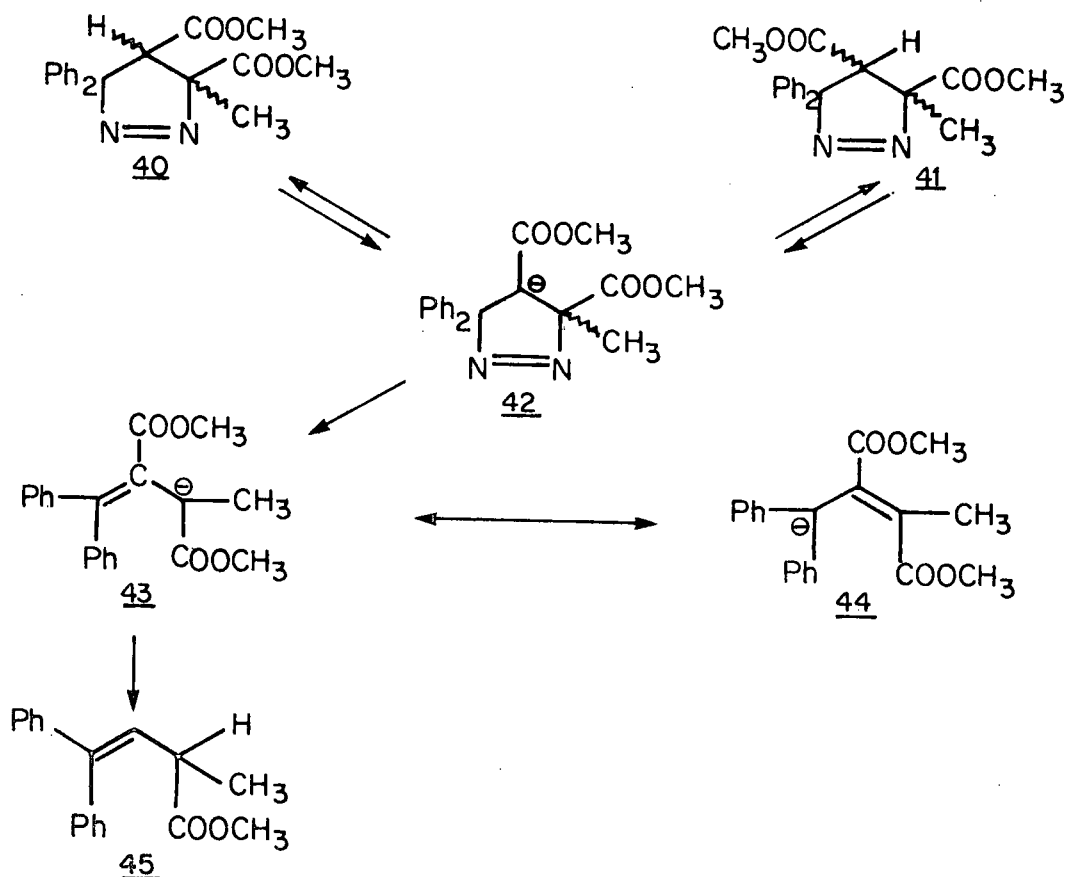
The kinetic studies done on a series of 3-cyano-3-carbomethoxy pyrazolines substituted at C-4 with a methyl and aryl groups (phenyl, p-methoxyphenyl or p-nitrophenyl) and on their analogues dideuterated at C-5 (22) provided the value of ^{the} secondary α -kinetic isotope effect; $\frac{k_H}{k_D} = 1.01 \pm 0.07$. This suggested that very little bond breaking of the C-5 to nitrogen occurred in the transition state. The proposed transition state 39 was polar with increased constraints in the degrees of freedom compared to the starting material. This was supported by the negative values of entropy of activation, -3.19, -5.65 and -9.58 e.u. for the different pyrazolines.



The product distribution indicated that the stereochemistry of the pyrazoline plays an important role in determining the stereochemistry of the products and there was no rotation taking place around the C-3 - C-4 bond in the transition state.

An interesting ionic pathway was proposed by Huisgen and Eberhard (24) for the decomposition of cis- and trans-3-methyl-5,5-diphenyl-1-pyrazoline-3,4-dicarboxylate 40, 41 in DMF or DMSO in the presence of a strong base (NaH in DMF and dimethylsodium in DMSO) at room temperature.

When the two pyrazolines were treated with the above mentioned bases in DMF or DMSO nitrogen elimination took place and the solution became red, lasting for days under proper care.



The existence of the 1-pyrazoline-4-yl anion 42 as an intermediate was proved by establishing a cis - trans equilibrium in NaOMe, MeOH solution without loss of N₂. By using deuterated solvents, the expected

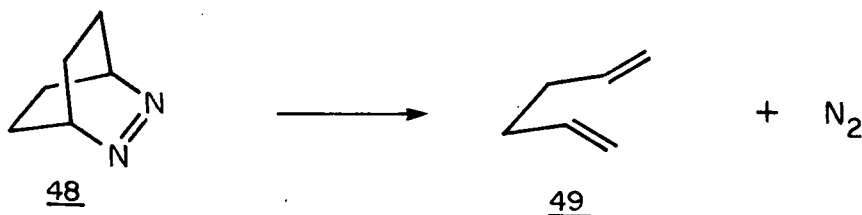
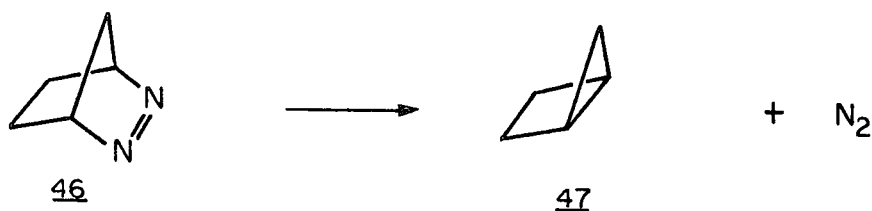
deuteration of the anion was found to be made faster than its cyclo-reversion.

The anion 42 eliminates nitrogen 10^{12} times faster than does the neutral pyrazoline, and the products are olefinic esters 45 in greater than 97% yield. The neutral pyrazolines gave mainly cyclopropanes of mixed stereochemistry.

Kinetic studies indicated that the 1,3-cycloreversion to allyl anion and N_2 has an activation energy more than 12 kcal mol^{-1} lower than that of the pyrazoline to cyclopropane process.

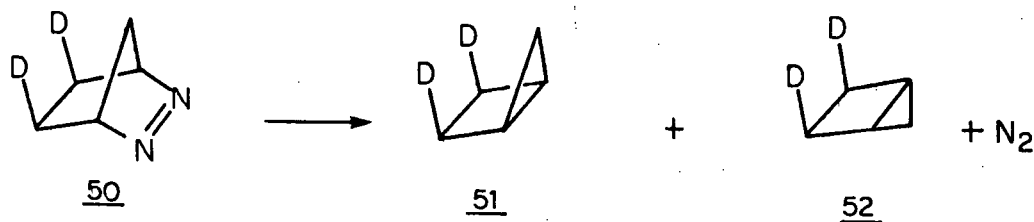
II. Diradical mechanism:

Since acyclic azo compounds decompose via free radical intermediates, it seemed reasonable to assume the same mechanism for cyclic azo compounds. Cohen and co-workers (25,26) were the first to investigate the kinetics of the decomposition of 2,3-diazabicyclo(2.2.1.)hept-2-ene 46 and 2,3-diazobicyclo(2.2.2.)oct-2-ene 48 in the gas phase and compare the obtained data with those of acyclic azo compounds.



They have suggested a diradical pathway with the simultaneous breakage of the two C-N bonds for the thermal decomposition of 46 and 48. 46 decomposed about 400 times faster than 48 and has lower activation energy and entropy of activation which was presumable due to the more highly strained structure of 46.

Roth and Martin (27) have used exo-5,6-dideutero-2,3-diazobicyclo(2,2.1)hept-2-ene 50 to study the stereochemistry of the decomposition.



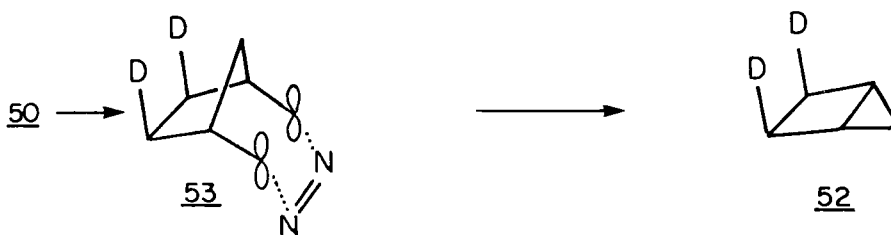
The ratio of the cis- and trans-2,3-dideuteriobicyclo(2.1.0)pentanes varied widely with the mode of decompositions and with the physical state of the sample.

TABLE I

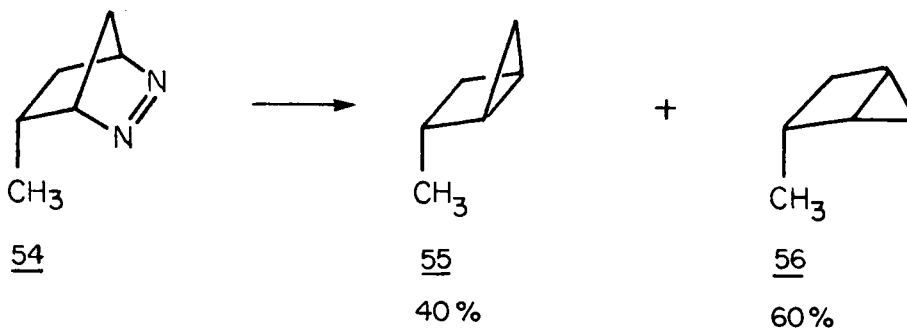
Decomp. prod. of exo-5,6-dideutero-2,3-diazabicyclo(2.2.1)hept-2-ene.

Mode of decomp.	physical state of the sample	Products	
		<u>51</u>	<u>52</u>
Δ	gas phase	25%	75%
hv	" " low pressure	50%	50%
"	" " high pressure	40%	60%
"	benzene	40%	60%
"	solid	66%	33%

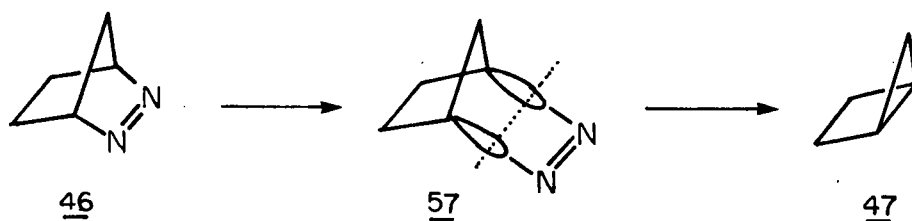
According to their explanation, the predominant inversion was due to the concerted elimination of nitrogen with accompanying back-side p-orbital overlap.



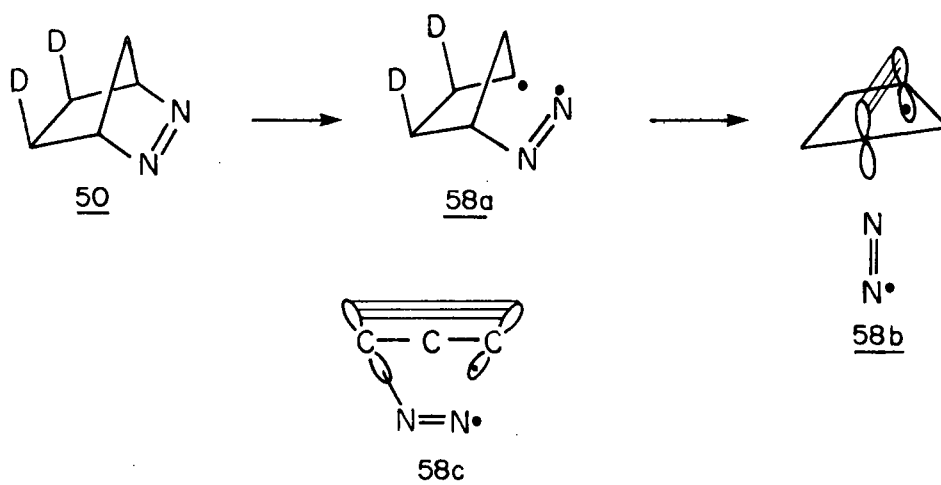
The low stereoselectivity (75%) indicates that the overlap in the transition state is incomplete. Their theory seemed to be supported by the product distribution in the gas phase pyrolysis of endo-5-methyl-2,3-diazabicyclo(2.2.1)hept-2-ene which showed somewhat lower stereoselectivity (60%) due to the steric hindrance by the methyl group in the transition state.



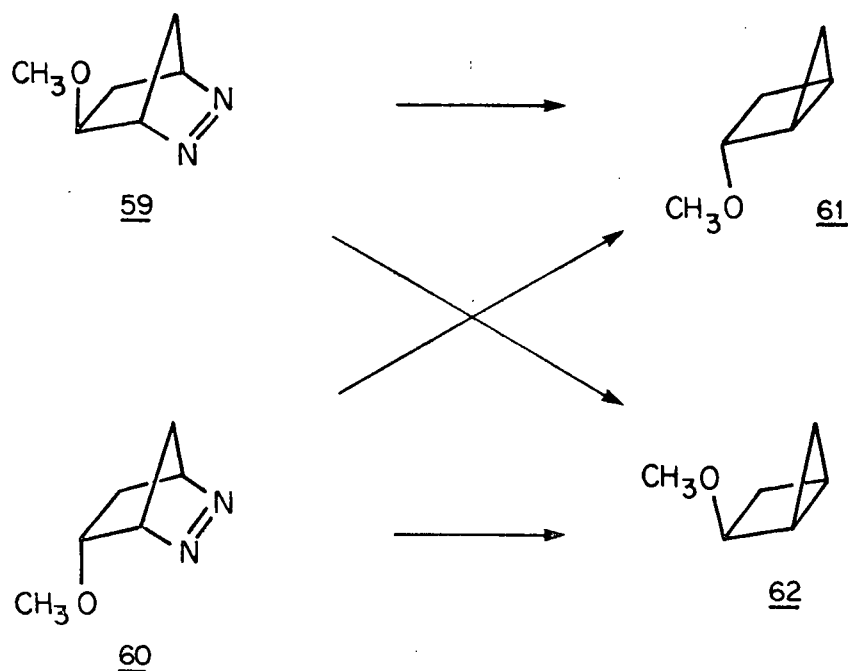
To explain the retention found in the decomposition products with respect to the parent azo compound, the following transition state can be envisaged (28).



Later Roth and Martin (29) proposed a two step mechanism for the decomposition of 50 involving a transitory nitrogen containing diradical. The inversion was attributed to the development of a back-side p-orbital overlap in the transition state leading to bicyclopentane and nitrogen. According to them, the energy requirement for inversion was supplied by the recoil energy released by the C-N bond breakage.



While maintaining the concept of a diradical pathway for the decomposition of bicyclopiazolines a different approach was used by Allred and Smith (28) to explain the stereochemical course of the reaction. They have studied the thermal and photodecomposition of the exo and endo epimers of 5-methoxy-2,3-diazabicyclo(2.2.1)hept-2-ene 59, 60. The different modes of decompositions have resulted in a widely differing ratio of 61 and 62 shown in Table II.



The thermal equilibration study showed that 62 is the more stable isomer.

TABLE II

Decomp. prod. of <u>exo</u> - and <u>endo</u> -5-methoxy- 2,3-diazabicyclo(2.2.1)hept-2-ene				
Comp.	Mode of decomp.	physical state of sample	Products	
			<u>62</u>	<u>61</u>
59 60	}	Δ sealed tube	63%	37%
			93.6%	6.4%
59 60	}	hv pentane solution piperylene added	42%	58%
			84%	16%
59 60	}	hv crystalline	97%	3%
			35%	65%
59 60	} benzophenone sensitized phot.	cyclohexane	78%	22%
			79%	21%

The results were rationalized in terms of an equilibrating, epimeric pair of pyramidal 1,3-diradicals. They have also proposed that the inversion is a consequence of recoil energy released by C-N bond breaking. *Note 1. The excess product of inverted structure indicates that ring closure occurs before the two epimeric diradicals can fully equilibrate. Benzophenone sensitized photolysis produced the same product mixture from both isomers. The most plausible explanation of these results is that the pyramidal diradical can interconvert at least several times before spin inversion occurs.

The first direct observation of free radical species by e.s.r. spectroscopy was achieved by Overberger et al. (31,32,33) in the photo-

Note #1. The recoil mechanism has been questioned on theoretical ground by Collins, George and Trindle (30).

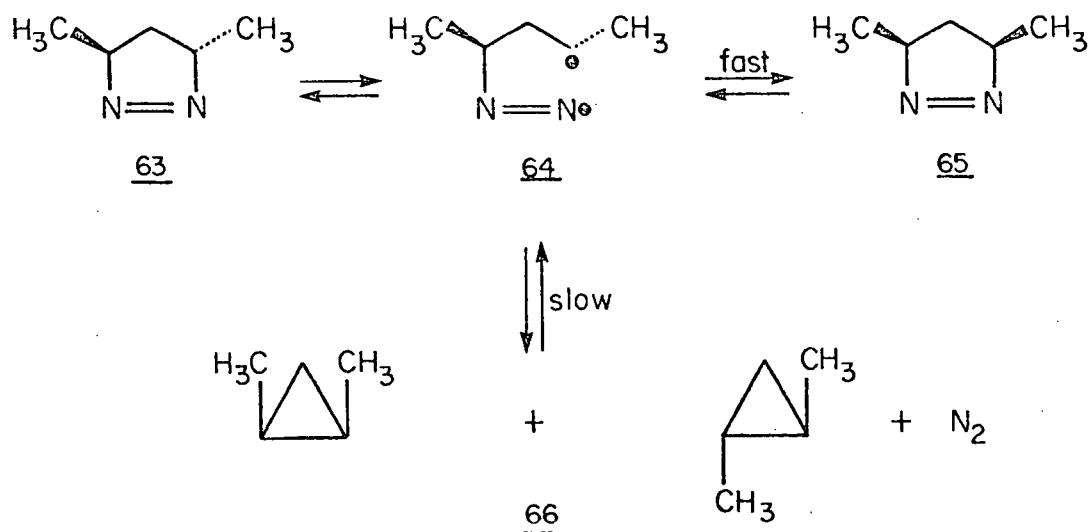
decomposition of 3,5-diaryl-1-pyrazolines (the thermal processes failed to show any sign of free radicals). Later reports on the detection of free radicals by e.s.r. will be discussed on pages 28 and 32.

Crawford and co-workers (34) have accumulated considerable evidence for a diradical pathway involving a 1,3-diradical or O,O-trimethylene like intermediate in the thermal decomposition of pyrazolines.

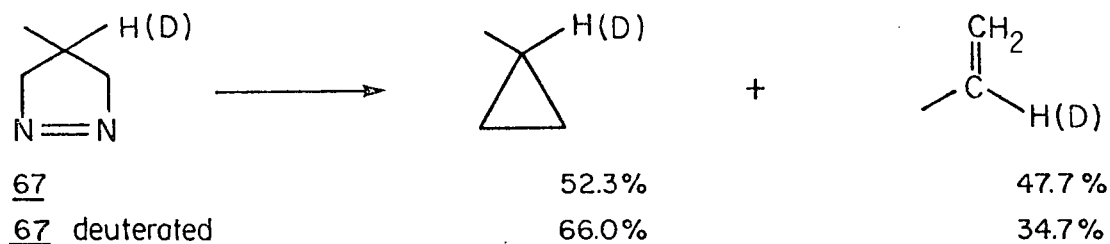
The kinetic studies on a series of methyl substituted pyrazolines showed a stepwise decrease in activation energies upon methyl substitution on the C-3 and C-5 positions. This general decrease was interpreted in the suggestion that both carbon nitrogen bonds are broken in the transition state. However, the obtained one kcal mol⁻¹ decrease for each methyl group is comparable to some conformational factors encountered in cyclic compounds, thus the increase in rate could arise from an increase in ground state energies. In order to remove any conformational complications, deuterated pyrazolines were used and the obtained results confirmed the previous assumption that both carbon-nitrogen bonds are breaking in the rate determining step (35). Kinetic studies done on 3-vinyl-1-pyrazoline and 3-vinyl-1-pyrazoline-5,5-d₂ also supported the idea of simultaneous breakage of both carbon-nitrogen bonds in the transition state (36).

The fact that cis- and trans- 3,5-dimethyl-1-pyrazolines 63 and 65 are not interconverted during their decomposition removes the possibility of an interconversion through a nitrogen containing intermediate 64 but it does not rule out the possible existence of an azo

diradical favored by several researchers (10,29,41).



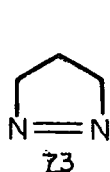
Kinetic and product studies done on 4-methyl-1-pyrazoline and its 4- d_1 isomer (**34**) led to the conclusion that the cyclopropanes came from a common nitrogen free intermediate since the product analysis showed a substantial decrease in olefin formation in going from the nondeuterated pyrazoline to the deuterated one while the overall kinetic isotope effect was found to be $\frac{k_H}{k_D} = 1.07$.



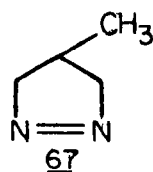
If we assume that $\frac{k_H}{k_D} = 1.0$ for cyclopropane formation, the olefin formation will have $\frac{k_H}{k_D} = 1.80$.

It can be seen from the overall kinetic isotope effect that in the rate determining step, a nitrogen free intermediate forms (nitrogen free because studies have been substantiating the simultaneous breakage of both C-N bonds) which undergoes a competitive ring closure and hydrogen shift exhibiting different kinetic isotope effects for each.

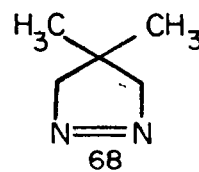
The geometry of the transition state was derived from kinetic studies done on methyl substituted pyrazolines. The introduction of one methyl group at C-4 has very little effect, whereas two methyl groups cause a great deal of decrease in the relative rate.



relative rate 1.0

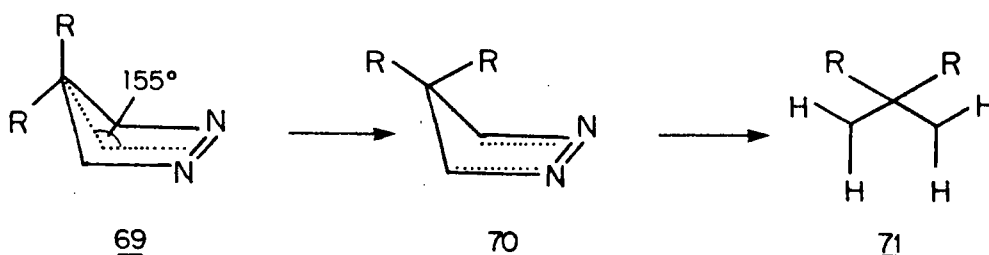


0.97



0.0079

Similarly to cyclopentane, the pyrazolines have an envelope like geometry with an angle about 155° between the two planes.

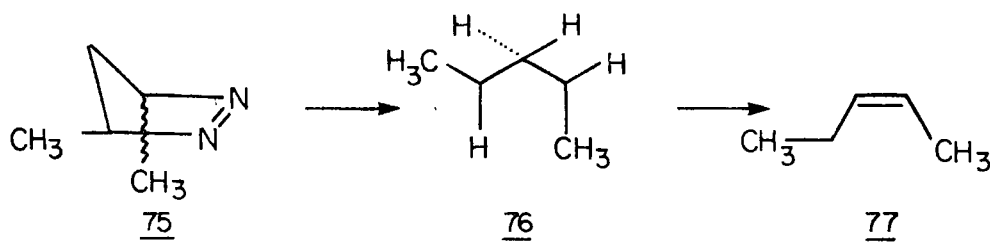
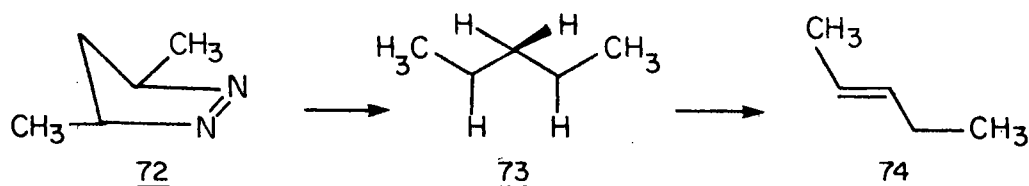


This angle presumably decreases as the carbon-nitrogen bonds lengthen. In the case of the monomethyl pyrazoline, the nitrogen departs trans to the methyl causing only very slight steric compression. But in the 4,4-dimethylpyrazoline one methyl is cis to the departing nitrogen and a large steric compression results in substantial rate decrease.

The geometry of 70 is a natural consequence of the azo link contraction from 1.25 \AA to 1.09 \AA as the formation of the π bond in nitrogen

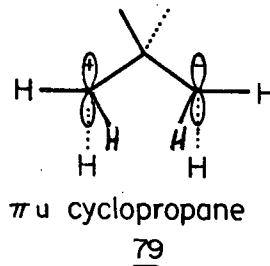
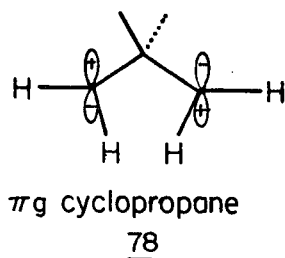
progresses. Alternatively, the slow rate would also be expected if an increase in C-3 - C-4 - C-5 bond angle were to occur, thus decreasing the $\text{CH}_3\text{-C-CH}_3$ angle and resulting in steric compression in the transition state.

The planar geometry for the terminal methylenes in the intermediate is supported by the olefinic products of cis- and trans-dimethyl-1-pyrazoline.

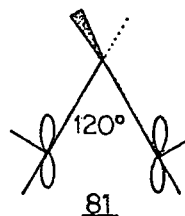
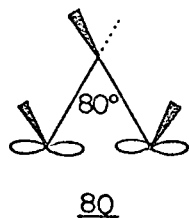


The migration of a hydrogen from C-4 in 73 to either C-3 or C-5 gives only trans-2-pentene 74 while the migration of a C-4 nitrogen in 76 results in trans-2-pentene 74 and cis-2-pentene 77 and 75 gave

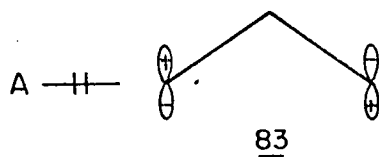
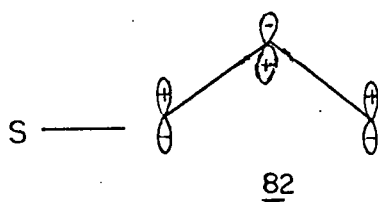
also cyclopropane products with predominant inversion of stereochemistry of the parent pyrazolines. The intermediate can be looked upon as a 1,3 diradical having $p\pi - p\pi$ bonding between the neighboring sp^2 carbons. According to spectroscopic notation, it would be a πg -cyclopropane. Calculations indicated that the interaction of the p-orbitals does not allow the "diradical" to behave as two independent radicals and also suggested 8-12 Kcal mol⁻¹ bonding energy.



Hoffmann (37,38) calculated the energy of trimethylene relative to cyclopropane as a function of the C-C-C angle and rotation of the terminal methylene groups. Two minima were observed on the ground state configuration potential surface corresponding to an opened cyclopropane 80 and to the trimethylene intermediate 81 where the terminal methylenes are coplanar with three carbons.



Hoffmann also found that the mixing of the orbitals of the central methylene group destabilizes the S level at large angles and stabilizes the A level at small angles.

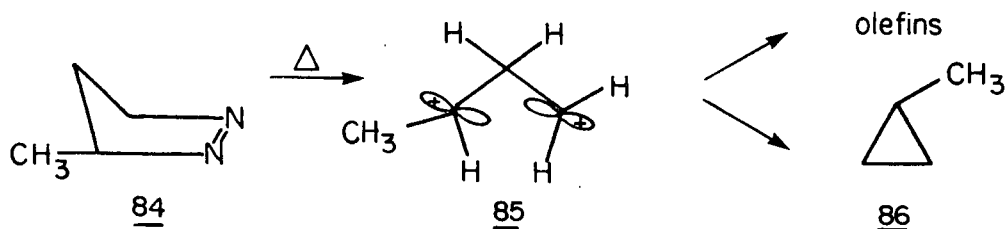


It is apparent that 83 should close to cyclopropane in a conrotatory manner resulting in inversion at one center compared to the original

pyrazoline if the trimethylene is properly substituted. 82 would close in a disrotatory manner leading to retention.

Calculations showed that species 82 and 83 are not greatly different in energy and there may be an equilibrium between them which could explain why the cyclopropane formation is stereoselective only.

Crawford and Erickson (39) have investigated whether the intermediate produced upon thermolysis of 85 has a plane of symmetry through the four carbons.

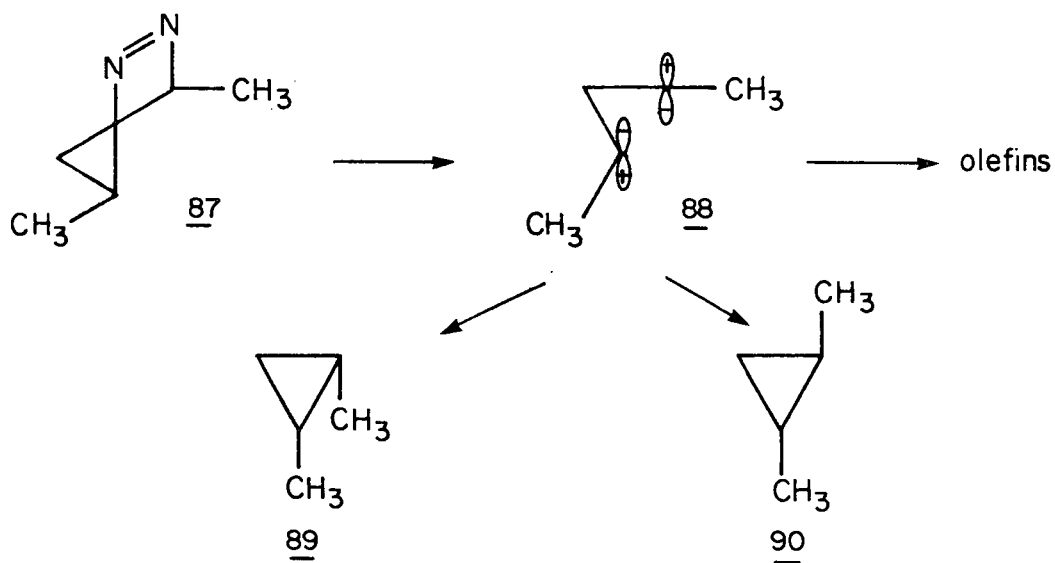


If this assumption is valid, the cis- and trans- 4-deutero-3-methyl-1-pyrazoline upon thermolysis should give the same intermediates and eventually the same product composition. The experimental results were in excellent agreement with the predictions.

The trimethylene intermediate suggested for pyrazoline thermolysis bears formal similarities to an adduct obtained by addition of a singlet methylene to an olefin. To see whether the trimethylene intermediate is involved in the singlet addition process, a study was undertaken by

Crawford and Ali (40). The compounds chosen were cis- and trans-3,4-dimethyl-1-pyrazoline and their C-5,5 -d₂ isomers which would provide upon thermolysis intermediates having the same spin state and stoichiometry as the adducts of singlet methylene to cis- and trans-butenes. The kinetic isotope effect indicated that the primary carbon to nitrogen bond was also breaking in the rate determining step. The product distribution led to the conclusion that the thermolysis is not stereospecific and the trimethylene intermediates are not on the reaction coordinate in the addition of a singlet methylene to cis- and trans-butene.

The thermolysis of (3R:5R)-(+)-trans-3,5-dimethyl pyrazoline 87 done by Crawford and Mishra (41) produced cis- and trans-dimethylcyclopropanes 89, 90 and some olefinic product.



Only 23% of the trans-cyclopropane 90 showed optical activity, S:S configuration indicating double inversion. If the intermediate 88 were a symmetrical species, as it had been suggested, it would give only a racemic mixture of trans-cyclopropane.

There are two alternative mechanisms which could account for the double inversion.

a) one which has been proposed by Roth and Martin (29) involving a nitrogen containing diradical intermediate.

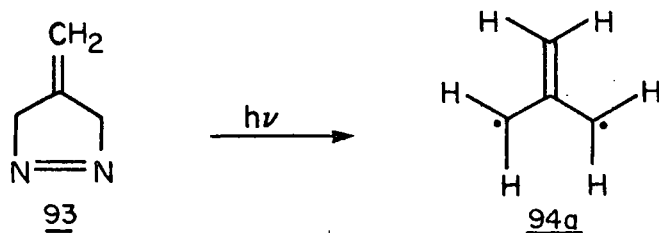


b) the other based on a pyramidal diradical intermediate idea put forward by Allred and Smith (28).



Quantum mechanical calculations predicted that the ground state of the trimethylenemethane should be a triplet diradical. By assuming that

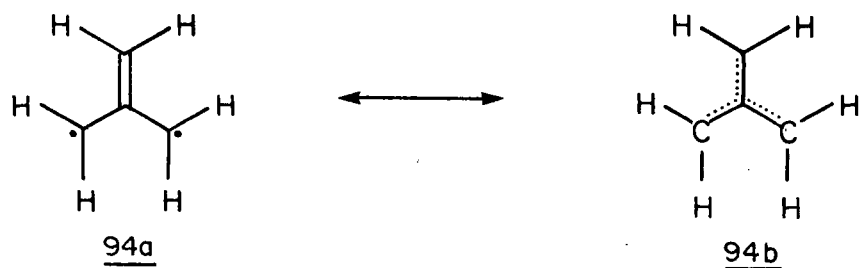
the 4-methylene-1-pyrazoline decomposes via a diradical pathway it seemed the most convenient source to generate this species. Indeed Dowd (42) showed by e.s.r. that 4-methylene-1-pyrazoline 93 upon photolysis at low temperature in hexafluorobenzene solution or in solid matrix, produced the desired triplet diradical 94 which had been predicted by theoretical calculation.



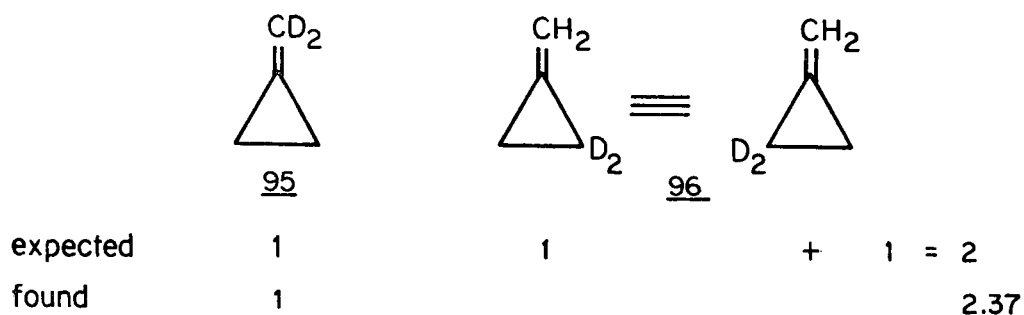
The e.s.r. spectrum also indicated that the diradical had a threefold (or higher) axis of symmetry.

Kinetic studies done by Crawford and Cameron (43) showed that both $E_a = 32.6 \text{ Kcal mol}^{-1}$ and $\Delta S^\ddagger = 1.1 \text{ e.u.}$ were lower for 93 than for 1-pyrazoline 73 ($E_a = 42.2 \text{ Kcal mol}^{-1}$, $\Delta S^\ddagger = 11.2 \text{ e.v.}$) These are consistent with the expectation that a triplet has a lower probability of formation.

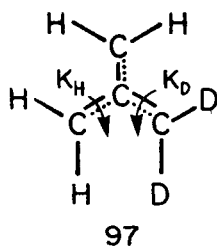
To check that a symmetrical intermediate 94b was indeed involved, 4-methylene-1-pyrazoline-3,3-d₂ had been prepared and decomposed.



Such a species would be expected to give methylene-cyclopropanes in the following ratio

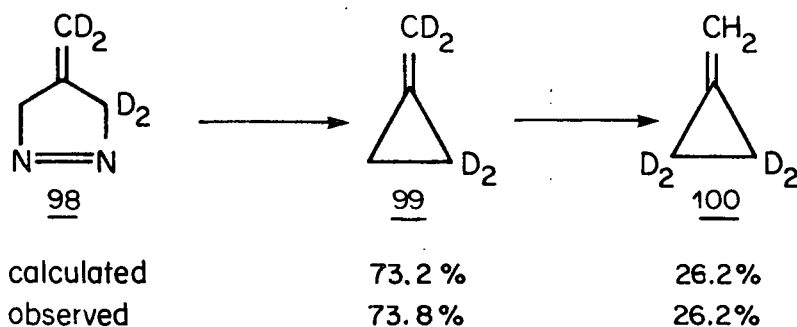


The explanation for this nonstatistical distribution is that by virtue of ^a/secondary isotope effect in the product determining step the dideutero methylenegroup is slower to rotate into the ring conformation than are the diprotiomethylene groups.



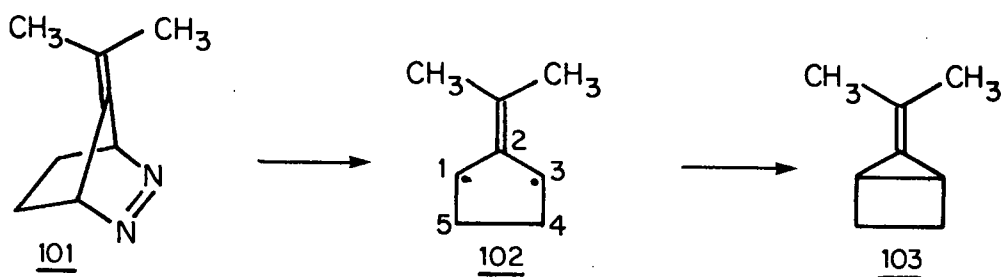
The isotope effect was found to be $\frac{k_H}{k_D} = 1.37$.

By preparing and pyrolysing the 4-methylene-1-pyrazoline-3,3,6,6-d₄ 98 and using the value of/isotope effect, they were able to predict the product ratios

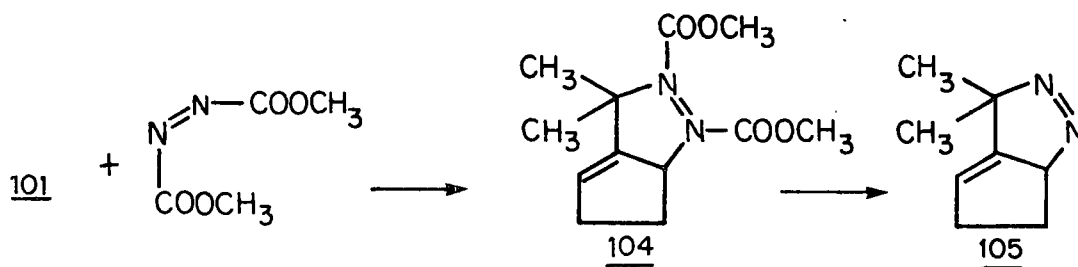


It is known that the simple trimethylene methane 94a undergoes a fast ring closure before it could add to olefinic acceptors. Berson et al.

(44,45,46) hoped to suppress the ring closure by incorporating the trimethylene methane into a ring system 101 which would give a highly strained hydrocarbon 103 on ring closure.

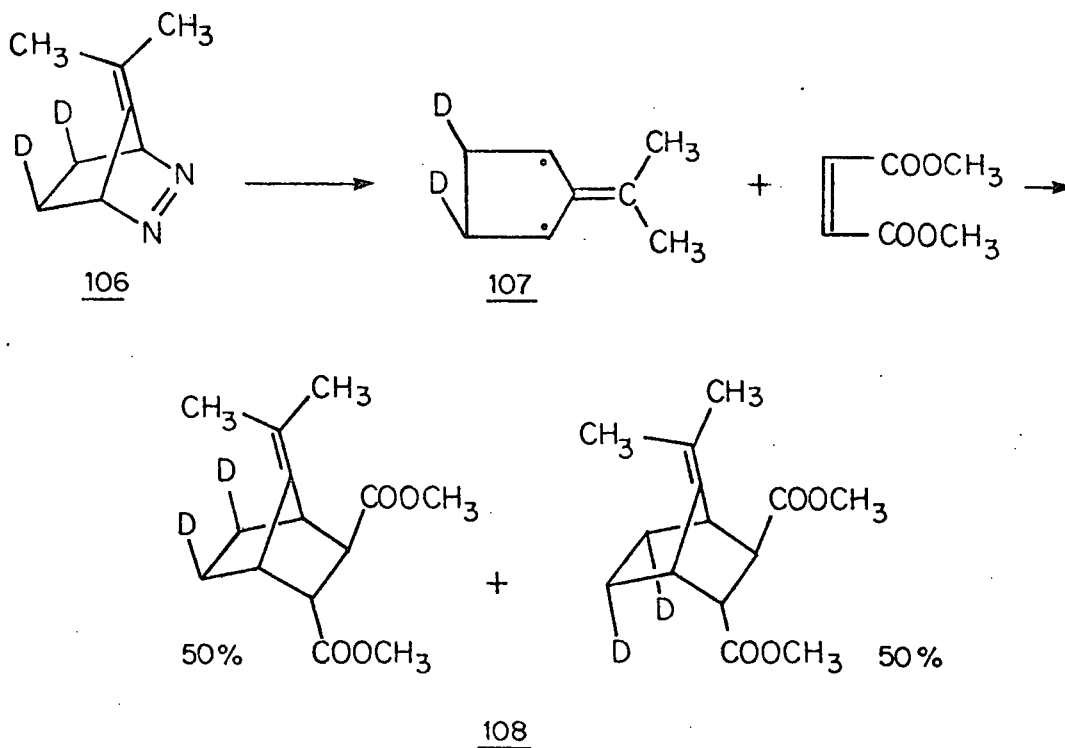


Indeed, the intermediate, 2-isopropylidenecyclopentane-1,3-diyli 102 underwent cycloaddition with olefins. One of the most interesting reactions of 101 is the "azo-transfer" reaction.



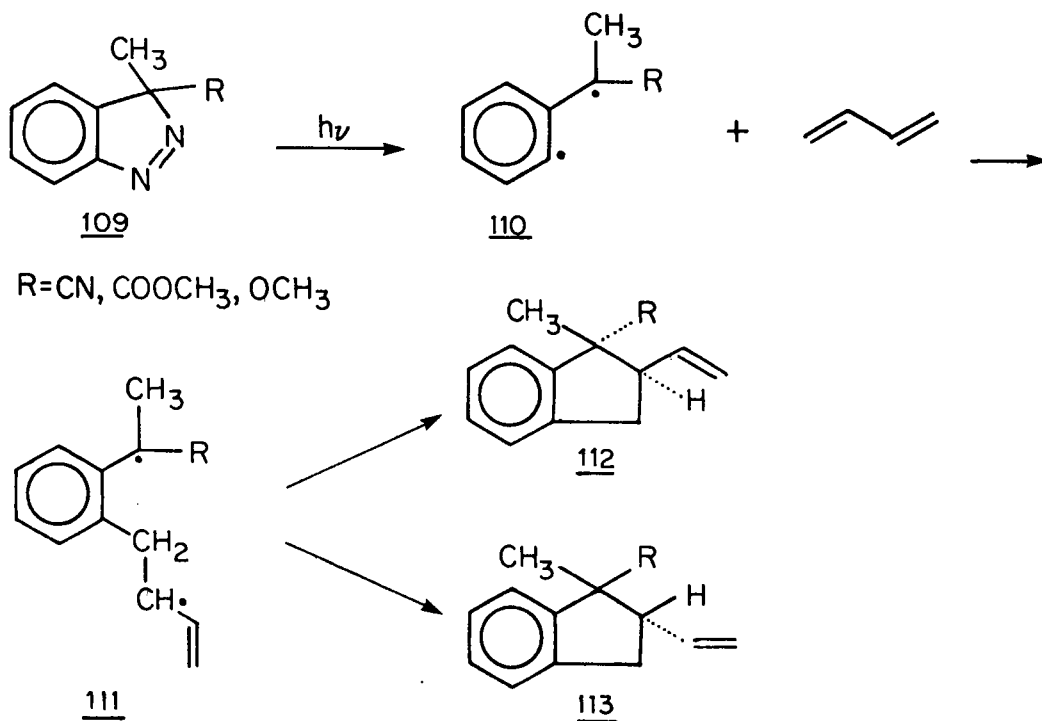
The resulting cycloadduct 104 can be converted by a hydrolysis-decarboxylation-oxidation sequence to a fused azo-compound 105 isomeric with 101.

The stereochemistry of the intermediate 102 was revealed when the dideuterated isomer of 101 was decomposed thermally in the presence of dimethyl maleate.



That shows that in the intermediate 107 the ring and proximal side-chain carbons are coplanar, or become coplanar before being trapped.

Perhaps one of the most impressive proofs for the intermediacy of 1,3-diradical species in the photodecomposition of pyrazolines was presented by Kaplan et al. (47,48). They not only identified the ground state triplet diradical obtained by the irradiation of 3H-indazol derivatives but could trap them with butadiene.



The assumption that the adduct formed via a two step addition maintaining the spin conservation was also substantiated by e.s.r. studies.

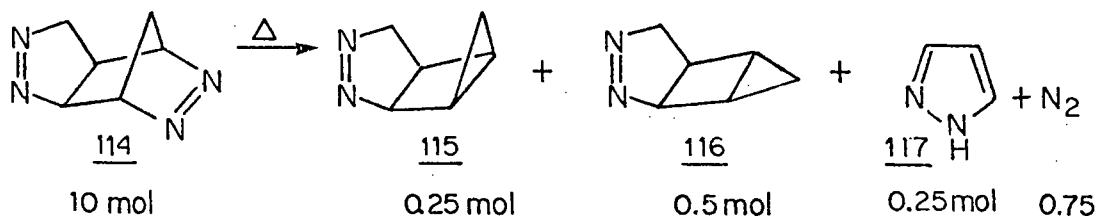
III. Concerted mechanism.

Up to date there have been only a few reports claiming concerted pathways for decomposition of cyclic azo compounds. Those which have been published can be classified into the following three groups:

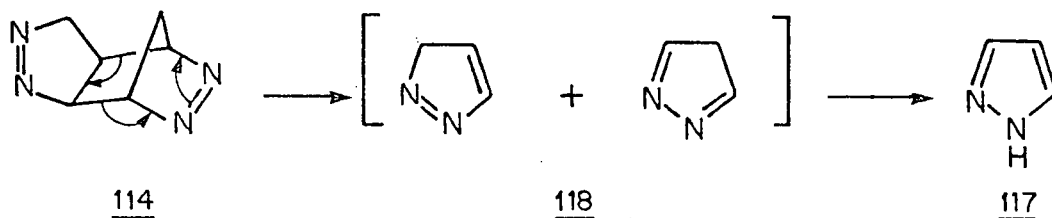
- retro Diels-Alder reactions.
- concerted olefin formation
- cyclopropane ring assisted decompositions.

(a) Retro Diels-Alder reactions.

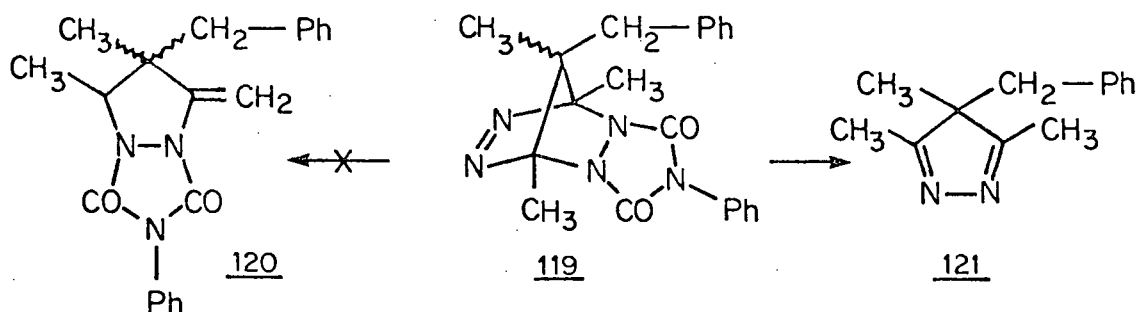
The unusual feature of this reaction is that no nitrogen extrusion takes place contrary to the majority of azo compound fragmentation. Hinshaw and Allred (49) have observed this kind of decomposition when they thermolyzed the rather complex tricyclic azo compound 114.



They suggested that 117 was formed by a retro Diels-Alder reaction.

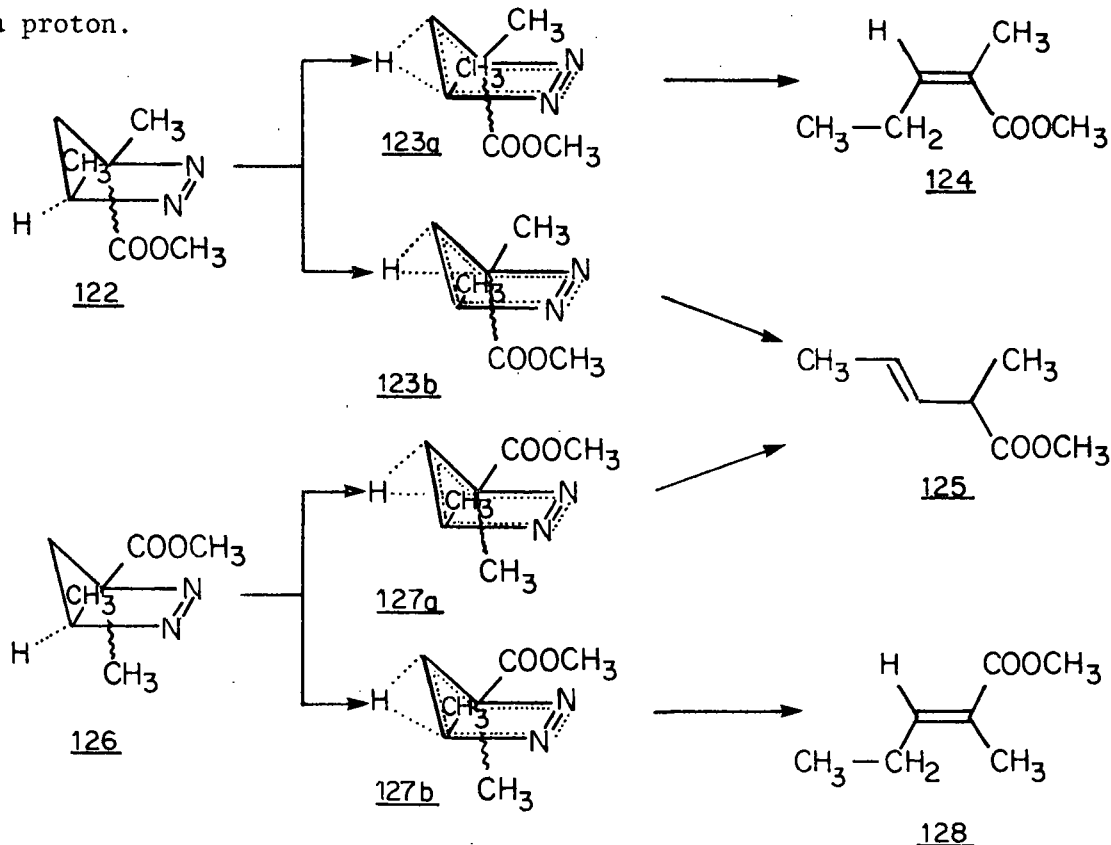


Retro Diels-Alder reaction was found to be (50) the only pathway for the thermal decomposition two geometrical isomeric azo system at the bridgehead 119.



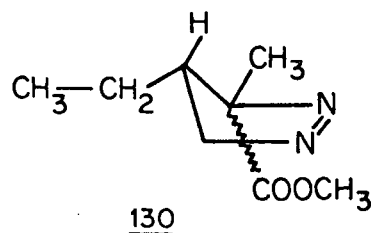
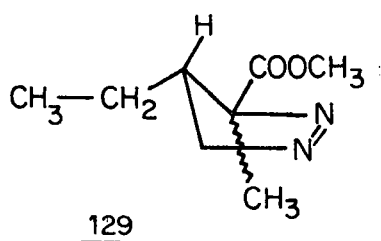
(b) Concerted olefin formation:

Using n.m.r. data McGreer et al. (51) determined the preferred conformations of cis- and trans-3,5-dimethyl-3-carbomethoxy-1-pyrazolines which upon thermolysis gave olefinic and cyclopropane products. The stereochemistry of the olefinic esters with respect to the preferred conformation of the parent pyrazolines showed that the olefinic products were formed in a stereospecific manner. They assumed that one of the C-4 hydrogens which was trans to the nitrogens would concertedly migrate in the transition state with the nitrogen extrusion to C-5 α,β -unsaturated ester and to C-3 to give β,γ -olefinic esters with trans geometry. They also suggested that the ratio of the α,β - and β,γ -esters would be the measure of the migrational aptitude of the hydrogen as a hydride or a proton.

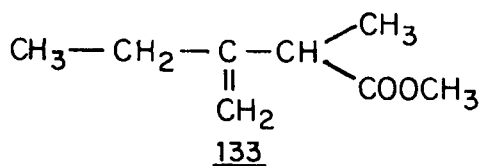
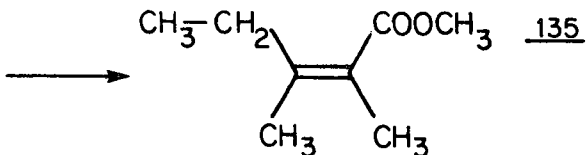
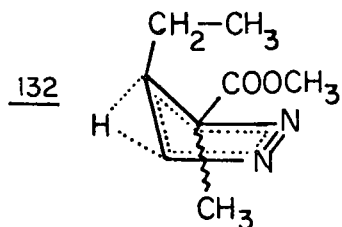
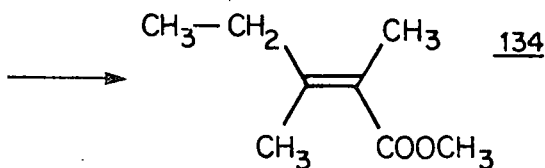
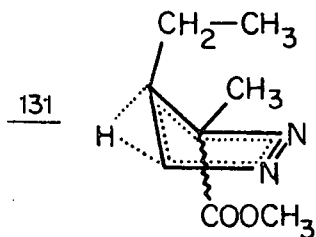


McGreer and Wu (52) have proposed a similar transition state for the stereospecific olefin formation in the thermal decompositions of the geometrically isomeric cis- and trans-3-methyl-4-ethyl-3-carbomethoxy-1-pyrazoline.

According to the preferred conformations, the C-4 hydrogen is in the pseudo axial and the C-4 ethyl group in the pseudo equatorial position.



But in the reaction, some conformational change will take place, 130 changes to 132 and 129 to 131.

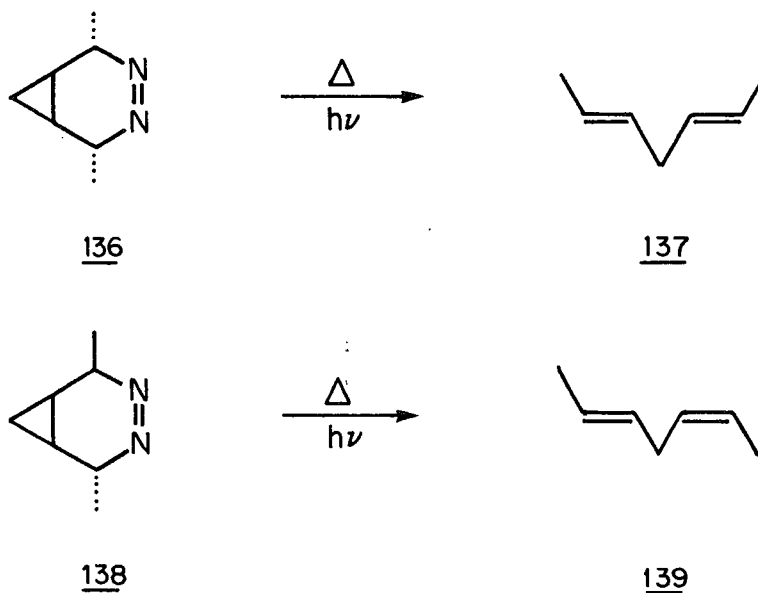


The advantage gained by the concerted migration of the hydrogen must be sufficient to overcome the steric compression in the transition state. The cyclopropanes were formed with predominant retention with respect to the parent pyrazoline.

(c) Cyclopropane ring assisted decompositions:

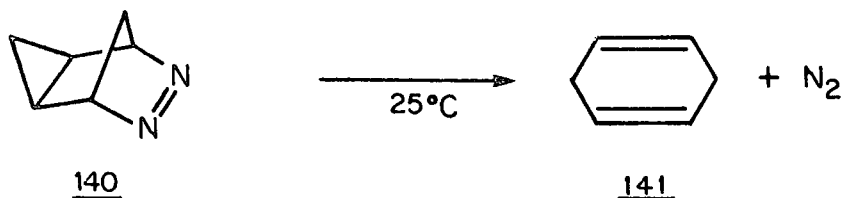
Exceptionally high rate and stereospecificity have been observed in the thermal decomposition of cyclic azo compounds having fused cyclopropane rings. The studies have also indicated that the orientation of the cyclopropane ring is critical in determining the reaction pathway.

Berson and Olin (53) have reported that the cyclopropane ring had a complete control over the stereochemical course of the decomposition of the following azo compounds;

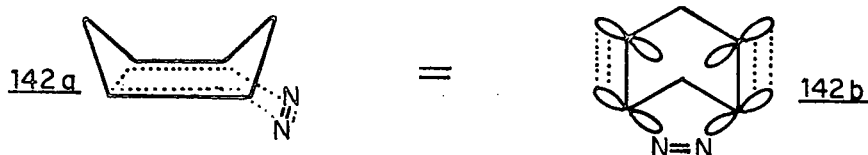


The high degree of stereospecificity and rate would suggest that the reaction should be a concerted orbital symmetry allowed retro Diels-Alder reaction if the photochemical decomposition did not give exactly the same products. The authors felt that in these cases factors other than orbital symmetry had complete control over the reaction. They introduced the concept of extrasymmetry factor as a general term for influences other than orbital symmetries which play a decisive role in determining the course of the reactions.

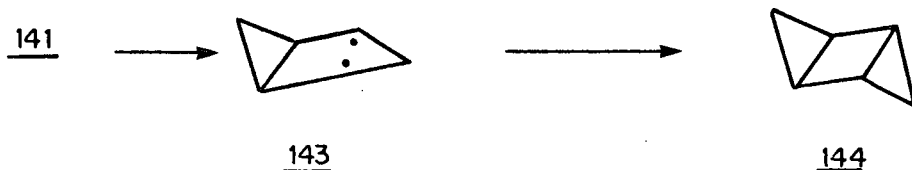
Allred et al. (54) have also found a 10^{11} times rate enhancement in the thermal decomposition of 140 in comparison to 2,3-diazanorbornene.



The authors attributed the rate enhancement to the intervention of an orbital-symmetry allowed process. The transition state is most likely the following:



They argue that if the reactions were diradical at least some trans-tricyclo (3.1.0.0.^{2,4}) hexane 144 would form which is stable under the reaction condition.

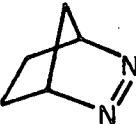

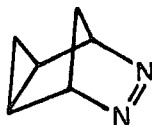

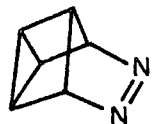

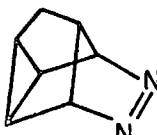

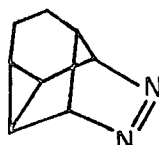

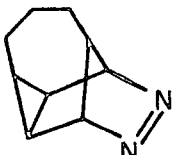



Tanida et al. (55) found later 144 in the photolytic product mixture of 140.

The works of Allred, Johnson (56) and Trost et al. (57,58) etc., provide evidence for the importance of the geometrical factors involved in the cyclopropyl participation. They have prepared a series of tricyclic compounds in which the bridgeheads and the cyclopropyl groups were connected with carbon bridges differing in lengths.

TABLE III

The activation parameters and relative rates of a series
of tricyclic azo compounds.

<u>COMPOUND</u>	<u>PRODUCT</u>	<u>E_a Kcal/mol</u>	<u>ΔS[‡] e.u.</u>	<u>rel.rate</u>
 <u>46</u>	 <u>47</u>	37.3	8.7	1 [62]
 <u>140</u>	 <u>141</u>	17.7	-13	2.2 x 10 ¹¹ [62]
 <u>145</u>	 <u>146</u>	—	—	—
 <u>147</u>	 <u>148</u>	36.5	8.3	9,2 [62]
 <u>149</u>	 <u>150</u>	23.3	-5	5.2 x 10 ¹¹ [62]
 <u>151</u>	 <u>152</u>	19.6	-6	1.9 x 10 ¹¹ [62]

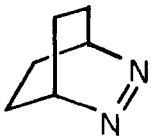
Data indicate that 147 decomposes to a diradical intermediate while 140, 145, 149, 151 follow a concerted, orbital symmetry allowed pathway.

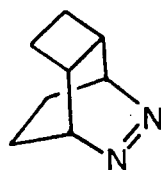
The considerable difference in reactivity among the compounds can be explained by the orientation of the cyclopropyl rings. In 140, 145, 149, 151 the cyclopropyl orbitals are more favorably oriented in the transition states for overlap as the C-N bonds break.

Allred and Voohees (59) have compared the influence of the cyclopropyl group being in exo- and endo- positions on the thermal reactivity of the azo compounds.

TABLE IV

The activation parameters and relative rates of a series of cyclic azo compounds having cyclopropyl groups exo and endo positions.

<u>COMPOUND</u>	<u>E_a Kcal/mol</u>	<u>ΔS[‡] e.u</u>	<u>rel. rate</u>
	44.6	10.5	1.0
<u>48</u>			

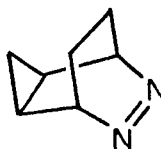


153

39.2

11.0

6.7×10^4

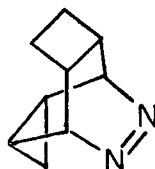


154

14.9

-21.0

1.1×10^{17}



155

41.4

10.3

8.8×10^2

All available criteria clearly indicate that 155 decomposes by a diradical pathway without participation of the cyclopropane ring.

OBJECTIVE OF PRESENT RESEARCH

The mechanistic details of thermo- and photodecompositions of cyclic azo compounds are still under intensive investigation. The survey of results and explanations indicates that the decomposition may involve single or multiple pathways depending upon the substituent pattern and the mode of decomposition.

A considerable amount of work has been done in these laboratories under the direction of Dr. D. E. McGreer on pyrazoline systems having an electron withdrawing group (acetyl, carbomethoxy, cyano) on C-3. As a continuation of the earlier research the studies were conducted mainly on 3-methyl-3-carbomethoxy-1-pyrazolines bearing different alkyl groups, deuterium or both on C-4.

Snyder's observation (60) that the replacement of the C-3 methyl group for an ethyl in the 3-methyl-3-carbomethoxy-1-pyrazoline decreased the rate of decomposition initiated the preparation and study of 3-tert-butyl-3-carbomethoxy-1-pyrazoline which showed exceptional thermal stability.

Crawford (9) and Bergman (10) reported that the incorporation of the pyrazoline ring in a bicyclic structure increased the amount

of olefinic products upon thermolysis relative to the simple system. In the hope that a similar system which in addition has a carbomethoxy group next to the N=N double bond would behave similarly 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene was prepared. Indeed the pyrolysis of this compound provided as much as 80% olefinic product. It also appeared worthwhile to synthesize 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene-5d₁ and the next two members of the series.

Since McGreer and Masters have undertaken a thorough study of 1-methyl-1-carbomethoxy-1-pyrazoline-4d₂, it seemed to be challenging to prepare stereospecifically monodeuterated pyrazolines to obtain the specific deuterium kinetic isotope effects for the different processes involved in pyrazoline decomposition.

Snyder (60) has also observed that the 3-methyl-3-carbobutoxy-1-pyrazoline exhibited a lower rate of decomposition than the corresponding methyl ester. Since he has not done any product study it seemed interesting to see the changes in product distribution too.

The studies of Van Auken et al. (14) on the decomposition of cis- and trans-3,4-dimethyl-3-carbomethoxy-1-pyrazolines and McGreer et al. (52) on cis- and trans-3-methyl-4-ethyl-3-carbomethoxy-1-pyrazolines have shown a certain pattern: stereospecific olefin formation and an increase in the amount of cyclopropane products with the increasing size of the C-4 alkyl substituents. In order to obtain some more information about the pattern the following alkyl substituents were placed in both cis and trans position at C-4: isopropyl, isobutyl and tert-butyl. It was also anticipated that one of these pyrazolines would give only cyclopropane product

which could lead to a clean-cut measurement of the deuterium kinetic isotope effect concerning the cyclopropane formation.

DISCUSSION

I. Some of the general features of thermal decomposition of 1-pyrazolines which served as a basis for research plans

Snyder's work (60) has shown that the rate of decomposition of 1-pyrazolines was increased by such substituents as carbomethoxy, acetyl, cyano and methyl groups at position 3 and 5, but the substitution of a methyl group at C-4 caused a rate decrease.

Similar but more detailed results are presented in Master's thesis (61). He made a comparison of relative rates of the substituted pyrazolines at 109.4°C in n-butyl phthalate solvent and found that the electron withdrawing ability of the substituents at C-3 had a large effect on the rate of pyrolysis. The rate increases in going from the 3-carbomethoxy to the 3-acetyl and to the 3-cyano pyrazolines roughly correlated with the increasing electron withdrawing power of the above mentioned groups.

In the case of the 3-acetyl and 3-cyano-1-pyrazolines, not only the rate of decomposition is changed but new products appear; dihydrofurans and HCN. The reexamination of the product studies done on 3-methyl-3-cyano-1-pyrazoline lead to slightly different results than

those obtained by I. Masters (61). The gas chromatographic analysis instead of six peaks gave only four. The first peak was most likely HCN (characteristic almond odor and positive benzidine blue test). The other three angelonitrile, 1-methyl-1-cyano-cyclopropane and tiglonitrile, identical to those found by I. Masters. The samples also contained a small amount of solid material. Up to date there has not been a thorough study concerning the mechanistic details of HCN formation.

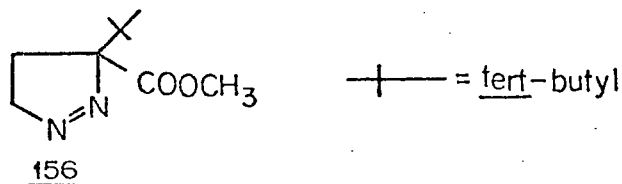
There is an eight to tenfold rate increase and a small ΔH decrease upon substitution of a methyl group at the five position, while the stereochemistry of the methyl group changes the rate of decomposition very little but alters the product distribution considerably. The substitution of a second methyl group at C-5 causes a decrease in the rate of fragmentation.

II. 3-Alkylpyrazolines

3-tert-Butyl-3-carbomethoxy-1-pyrazoline:

Snyder (60) found that the substitution of an ethyl group for the methyl at C-3 reduced the rate of nitrogen evolution. Although no explanation was given by the author, it was most likely due to the fact that the ethyl group is bulkier than the methyl. Unfortunately product studies have not been done to see the effect on the product distribution.

This compound had to be heated up to 160° to effect decomposition at a reasonable rate. This leads to the conclusion that 156 is one of the most stable pyrazolines having an alkyl and carbomethoxy groups at C-3.



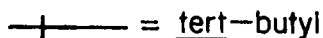
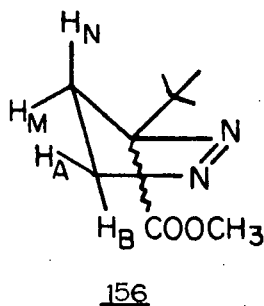
This compound turned out to be one of the most stable 1-pyrazolines to the present having a carbomethoxy and an alkyl substituent at C-3. To decompose it at a reasonable rate it should be heated up to 160°C.*

Its n.m.r. spectrum indicates that the hydrogen of the two methylenes exhibit an almost first order ABMN spin system. It was possible to calculate the best values for the six coupling constants and chemical shifts using a computer program.

$J_{AB} = -17.416 \text{ Hz}$	$H_A = 5.497 \tau$
$J_{AM} = 3.876 \text{ Hz}$	$H_B = 5.839 \tau$
$J_{AN} = 9.807 \text{ Hz}$	$H_M = 8.130 \tau$
$J_{BM} = 9.336 \text{ Hz}$	$H_N = 8.446 \tau$
$J_{BN} = 7.950 \text{ Hz}$	
$J_{MN} = -13.176 \text{ Hz}$	

* Kinetic studies could not be done on it using our apparatus because of the relatively high temperature to obtain a conveniently measurable rate.

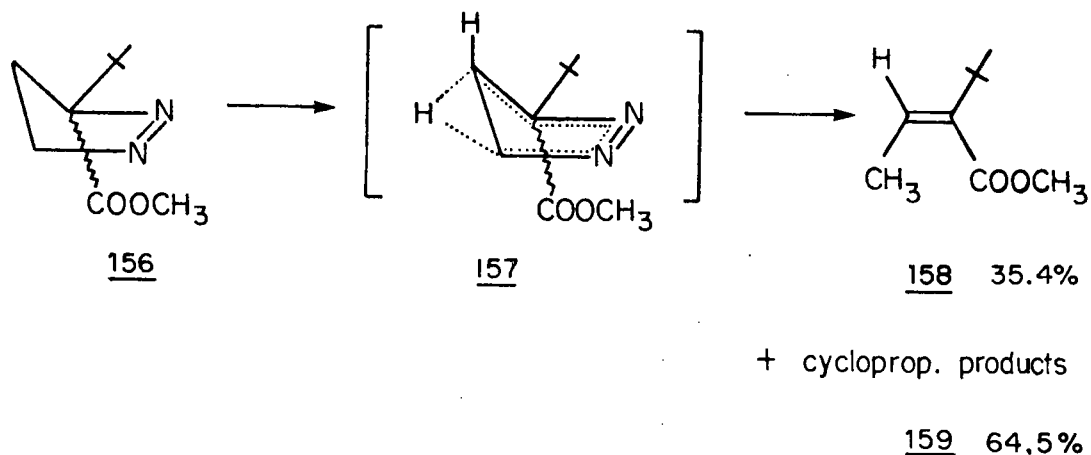
On the basis of the n.m.r. spectra of 3,3-dimethyl- and 3-methyl-3-carbomethoxy-1-pyrazolines, (51) in which the two C-4 and C-5 hydrogens form an ABX_2 spin system implicating the equivalence of the C-4 hydrogens which is the consequence of the fact that both conformations are equally populated at room temperature, one can conclude that the pyrazoline 156 is locked in one conformation by the large tert butyl group. To determine the preferred conformation of 156 one should most reasonably place the tert butyl group in the pseudo equatorial position (if the tert butyl group were pseudo axial the non-bonding interactions between the pseudo axial hydrogen in C-5 and the tert butyl group would be considerable).



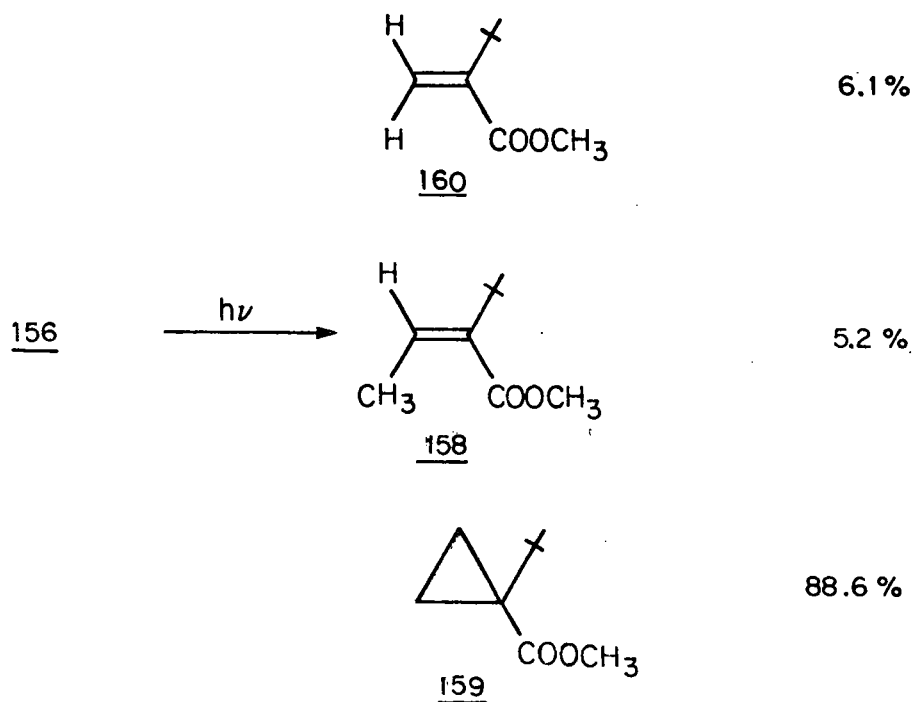
The inspection of n.m.r. spectra of other pyrazolines shows that the signal of the methyl in a pseudo axial carbomethoxy group appears around 6.38 τ and that in a pseudo equatorial around 6.15 τ due to the shielding and deshielding effect of the N=N double bond respectively.

The peak, due to the carbomethoxy group in the n.m.r. spectrum of 156, is at 6.35τ substantiating the former assumption. Perhaps it is worth while to mention that the carbomethoxy group of 164 cannot be in any other position but in pseudo axial and appears at 6.37τ close to the value of 156.

The stereochemistry of the olefinic product obtained from thermolysis also supports this assumption in accordance with McGreer's olefin formation scheme.

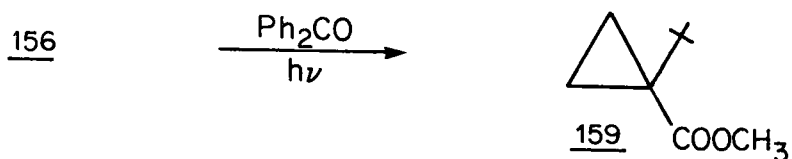


The direct photolysis in isopentane at 3100 \AA gave the following products:

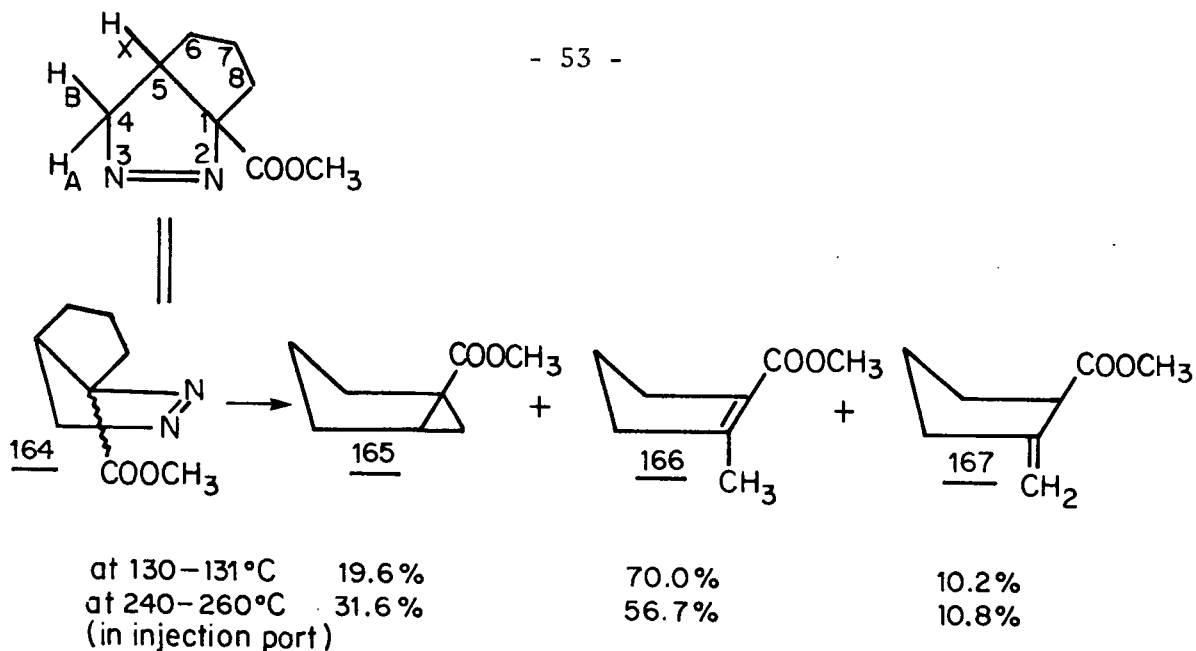


160 is most likely formed via a 1,2-diradical intermediate* and not by a reverse 1,3-cyclo addition. The mechanism of the formation of the 1,2-diradical and the other photoproducts 158, 159 is not clear yet.

The benzophenone sensitized photolysis at 3500 Å gave only cyclopropane product.

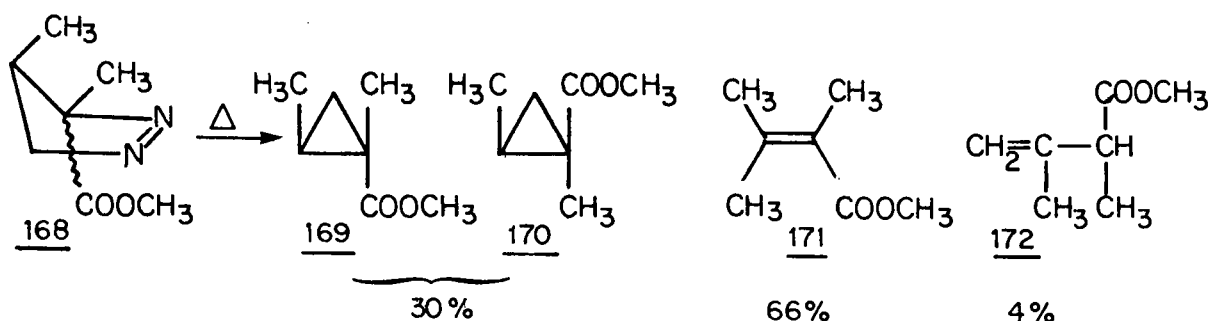


* A more detailed discussion will be given later.



$$\Delta S^\ddagger = -2.62 \text{ e.u.}$$

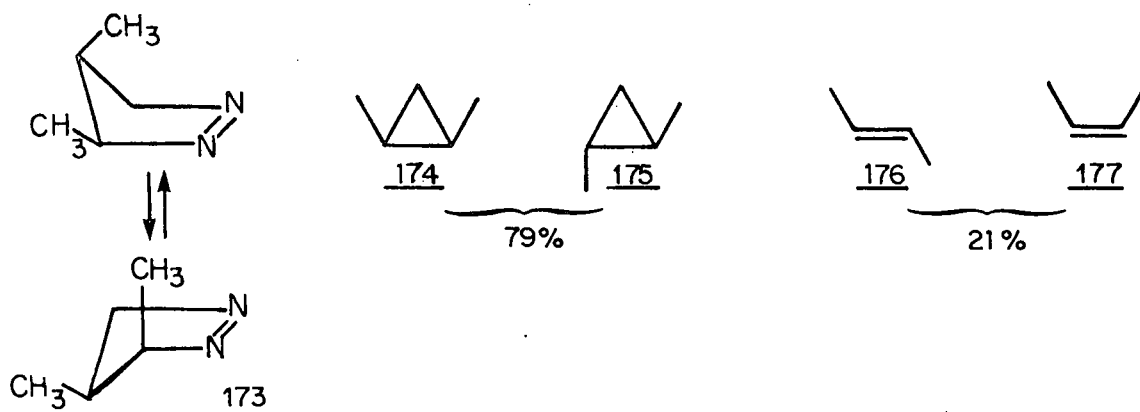
$$\Delta H = 28.3 \text{ Kcal.}$$



$$\Delta H^\ddagger = 33.8$$

$$\Delta S^\ddagger = 7.9$$

Van Auken *et al.* (14)

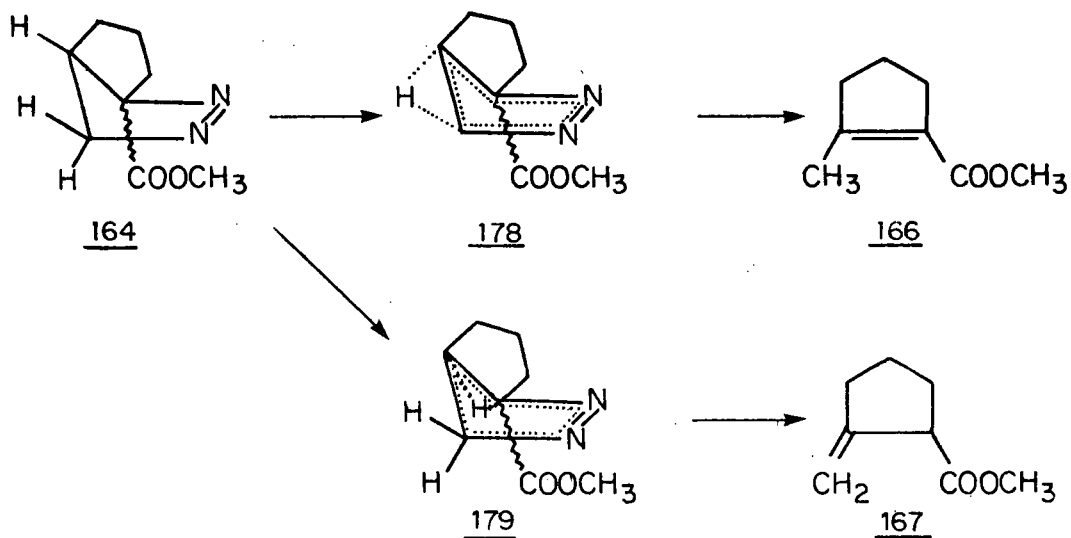


in gas phase

$$\Delta H^\ddagger = 39.0 \text{ Kcal}$$

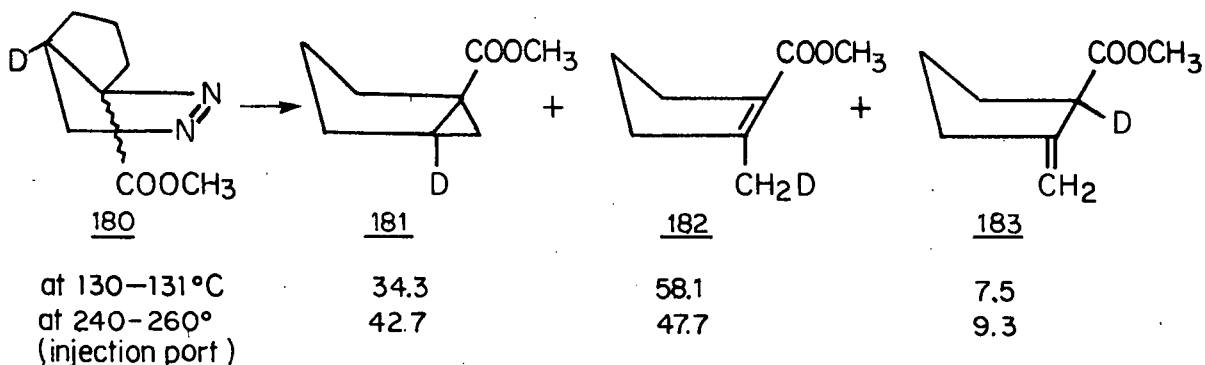
$$\Delta S^\ddagger = 6.3 \text{ e.u.}$$

Crawford *et al.* (40)



It is interesting to note that 168 gave less olefinic products than 164 in spite of the form and structural similarity (n.m.r. data, namely coupling constants do not conform). This difference can be best attributed to the difference in flexibility between the two pyrazolines.

The thermolysis of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)-oct-3-ene-5-d₁ gave rise to a product mixture shown below:



The comparison of product distributions of 160 and 164 shows that the electron withdrawing carbomethoxy group not only decreases the temperature required to bring about decomposition but also drastically alters the olefin cyclopropane ratio. Similar behavior can also be found among monocyclic pyrazolines, 84, 184 and 185.

The formation of olefinic products 166 and 167 most likely follows concerted pathways similar to those proposed by McGreer (51,52) via transition states 178 and 179 respectively. The large amount of olefinic compound in the product mixture seems to indicate that the C-5 hydrogen may be in a favorable position for migration.

Since Bergman et al. (10) have suggested a near planar pyrazoline ring structure for both exo- and endo-2-methyl-3,4-diazabicyclo[3.3.0]oct-3-enes on the basis of coupling constants ($J_{trans} = 3.0$ Hz for the exo and $J_{cis} = 7.0$ Hz for the endo compounds) it is worthwhile to compare the coupling constants of 164 ($J_{trans} = 8.5$ Hz and $J_{cis} = 3.3$ Hz) with those obtained by Bergman*. The coupling constants differ considerably unless we assume that the pseudoaxial hydrogen H_B (cis to H_x) appears at a lower field than the pseudoequatorial hydrogen, H_A because of the deshielding effect of the carbomethoxy group. However n.m.r. data of cis- and trans-3,5-dimethyl-3-carbomethoxy-1-pyrazolines (51) do not seem to substantiate this assumption since the chemical shift values of the pseudoaxial hydrogens were found to be almost identical in both isomers. Consequently Bergman's stereochemical argument is not applicable to 164.

* Unfortunately there are no data available on the chemical shift values of C-2 protons.

The relatively large $\frac{k_H}{k_D} = 1.24$ overall deuterium kinetic isotope effect for 18 and the change in product distribution corroborate McGreer's idea of concerted olefin formation. If the olefinic and cyclopropane products came from a common intermediate and no significant changes regarding the bonding situation of deuterium were taking place in the transition state of the rate determining step as in the case of 4-methyl-1-pyrazoline-4d₁ (34) the overall kinetic isotope effects would be quite small while changes in the product ratios would only be significant.

The kinetic isotope effect for the individual reaction which were obtained from the overall deuterium kinetic isotope effect and the product distributions are as follows.

$$\frac{k_H}{k_D} \text{ for } \beta, \gamma\text{-olefin formation} = 1.68$$

$$\frac{k_H}{k_D} \text{ for } \alpha, \beta\text{-olefin formation} = 1.49$$

$$\frac{k_H}{k_D} \text{ for cyclopropane formation} = 0.71$$

The "inverse" value for cyclopropane formation is contrary to other findings in the monocyclic pyrazolines but it cannot be attributed to experimental errors. The substitution of deuterium at C-5 caused a considerable increase in the activation parameters ($\Delta H^\ddagger = 32.4 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = 7.17 \text{ e.u.}$) relative to those ($\Delta H^\ddagger 28.3 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger -2.62 \text{ e.u.}$) for 164.

The change in product distribution upon the different mode of fragmentation (flask and injection port) may be attributed to the effect of phase changes. However, the low vapor pressure of the pyrazoline at the temperature of the injection port must also be considered.

The direct photolysis of 164 and 180 (3100 Å) gave only cyclopropane products in greater than 98% yield. Because of the easy access to starting materials and diazomethane and the high yield, it seems to be an ideal preparative route to bicyclo(3.1.0)hexane derivatives.

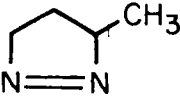
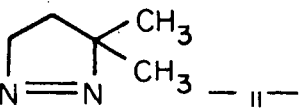
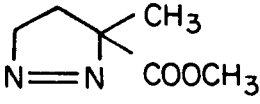
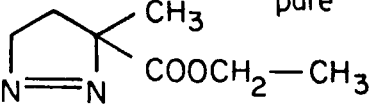
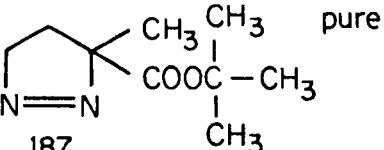
IV. Stereochemical factors affecting olefin formation

- (a) The effect of the size of the ester group on olefin formation, 3-methyl-3-carbalkoxy-1-pyrazolines.

Inspection of Table V shows that the introduction of a second methyl group at C-3 of 3-methyl-1-pyrazoline results in a slight increase in the yield of cyclopropane derivative upon thermolysis while the introduction of a carbomethoxy group brings about a substantial change in product distribution. The replacement of the methyl group of the carbomethoxy by ethyl and tert-butyl groups causes a small decrease in the yield of the olefinic products.

TABLE V

The yields of olefinic and cyclopropane products of a series of 3-methyl-3-carbalkoxy-1-pyrazolines upon thermolysis

<u>COMPOUND</u>	<u>OLEFINIC PROD.</u>	<u>CYCLOPROPANE PROD.</u>
 <u>84</u>	6.7% Crawford, Mishra (34)	93.3%
 <u>184</u>	3.3 % Crawford, Mishra (34)	96.7 %
 <u>185</u>	in gas phase 15 % pure 33.2 % (16) informamide 55.5 % McGreer, Masters (61)	85 % 66.8 % 44.5 %
 <u>186</u>	pure 29.6% in this work	70.4%
 <u>187</u>	pure 25.9% in this work	74.1%

The n.m.r. spectra of 184, 185 and 186 showed that the C-4 hydrogens are equivalent leading to the conclusion that both conformations are equally populated. This is not the case with 187 and probably the conformation in which the carboxy tert-butyl group is in the pseudo-equatorial position is slightly favored over the other.

A close inspection of Table V reveals that the substitution of a carbomethoxy for a methyl group brings about significant changes in product distribution. Simple stereochemical arguments cannot account for this change since the methyl group is not much larger in size than the carbomethoxy group. The assumption that the olefins are also formed via a 1,3-diradical intermediate similar to that proposed by Crawford (34) is untenable because it cannot explain the stereospecific olefin formation observed by McGreer et al (51,52), besides if we accept Ruchard's (64) claim that the methyl and the carbomethoxy groups have about the same stabilizing effects on simple radical centres (both decrease spin density) we should expect similar product distributions from both 184 and 185 which is not the case. A viable explanation which can account for the stereospecific olefin formation was put forward by McGreer et al. (51). They proposed a concerted path and pointed out the stereochemical requirements for olefin formation. Product studies done in solvents with differing polarity (61) showed that those which had higher polarity favored the olefin

formation. This is a clear indication that the transition state for olefin formation is more polar than that for cyclopropane formation.

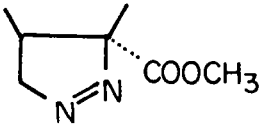
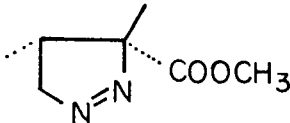
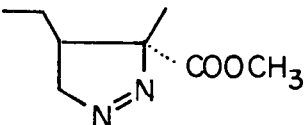
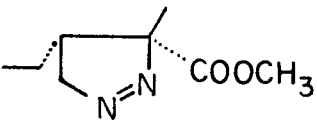
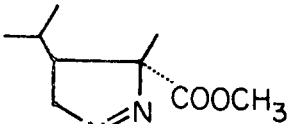
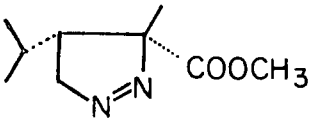
The other interesting feature of the thermal decomposition is the change in product distribution brought about by the size of the alkyl group in the ester part. It is difficult to give a clear explanation of it but it seems that it is due to stereochemical changes in the transition state.

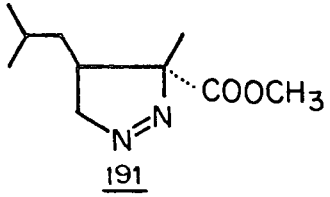
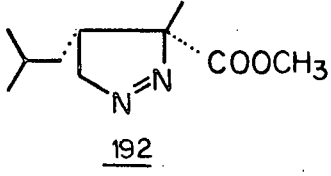
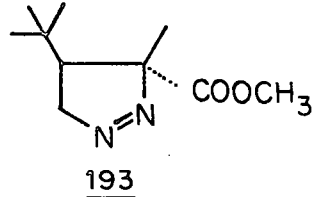
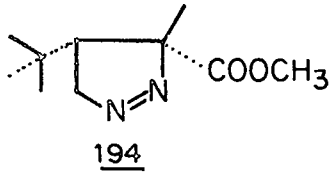
- (b) The effect of the size of the alkyl group in C-4 on olefin formation, *cis*- and *trans*-3-methyl-4-alkyl-3-carbomethoxy-1-pyrazolines.

The works of van Auken et al. (14) and McGreer et al. (52) indicated that the size and the position of the alkyl group in C-4 also affect the product distribution.

TABLE VI

The product distribution of *cis*- and *trans*-3-methyl-4-alkyl-3-carbomethoxy-1-pyrazolines upon thermolysis.

<u>COMPOUND</u>	<u>CYCLOPROPANES</u>		<u>OLEFIN α,β</u>		<u>OLEFIN β,γ</u>
	cis	trans	Z	E	
 <u>168</u>	17.6 %	12.32 %	65.75 %		4.0 %
			van Auken <u>et al.</u> 14		
 <u>188</u>	28.3 %	34.57 %	32.84 %		4.25 %
			van Auken <u>et al.</u> 14		
 <u>129</u>	31.0 %	9. %	0	56 %	4.0 %
			McGreer <u>et al.</u> 52		
 <u>130</u>	11.0 %	72 %	13 %	0	4.0 %
 <u>189</u>	43.0 %	3.6 %	0	48.9 %	4.2 %
			in this work		
 <u>190</u>	0	91.7 %	8.3 %	0	0
			in this work		

<u>COMPOUND</u>	<u>CYCLOPROPANES</u>		<u>OLEFIN. α,β</u>		<u>OLEFIN. β,γ</u>
	<u>cis</u>	<u>trans</u>	<u>Z</u>	<u>E</u>	
 <u>191</u>	42.7 %	0	0	44.0 %	13.0 % in this work
 <u>192</u>	100 %	79.1 %	100 %	0	0 in this work
 <u>193</u>	100 %	0	0	0	0 in this work
 <u>194</u>	0	100 %	0	0	0 in this work

* cis means that the alkyl and the methyl groups are cis to each other.

The following general remarks can be based on the results shown in Table IV:

- Trans- pyrazolines tend to give more cyclopropane products than the cis- ones.
- The bulkier the alkyl group at C-4, the more cyclopropane will form. The extreme case is the tert-butyl group when no olefin formation has been observed.

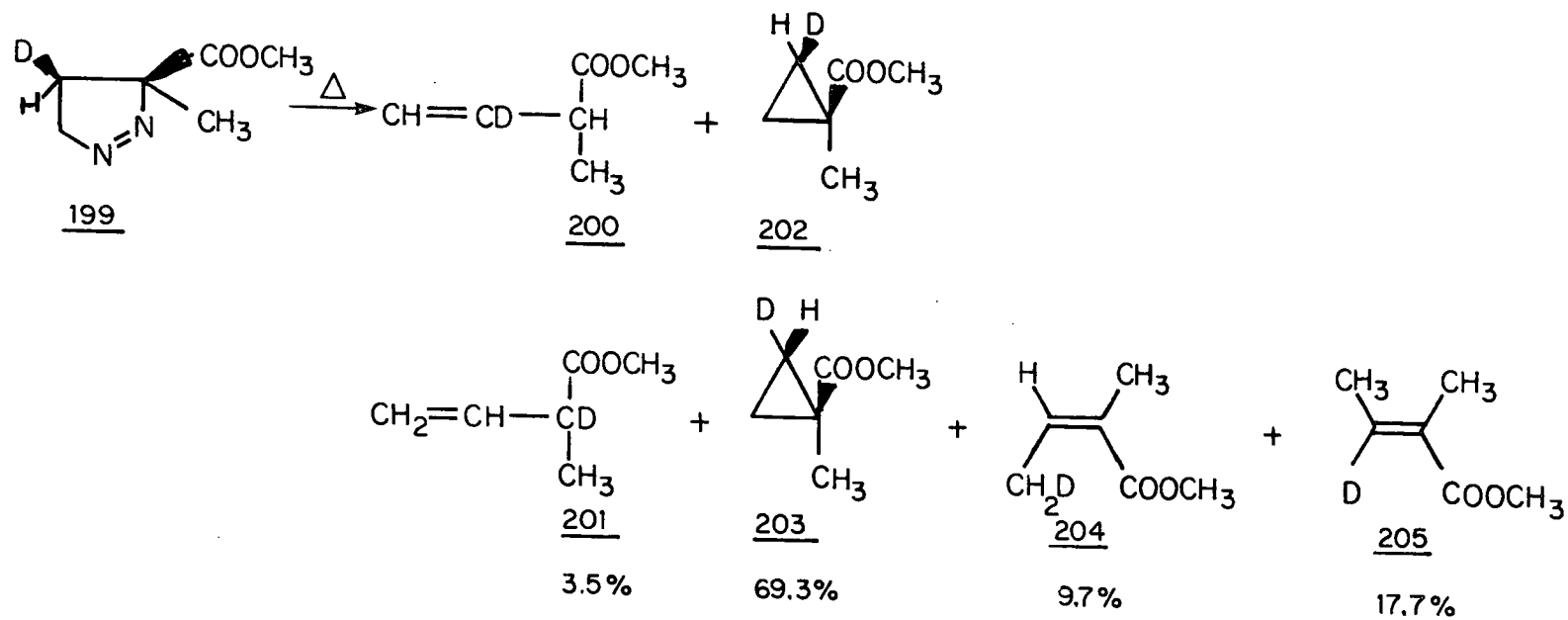
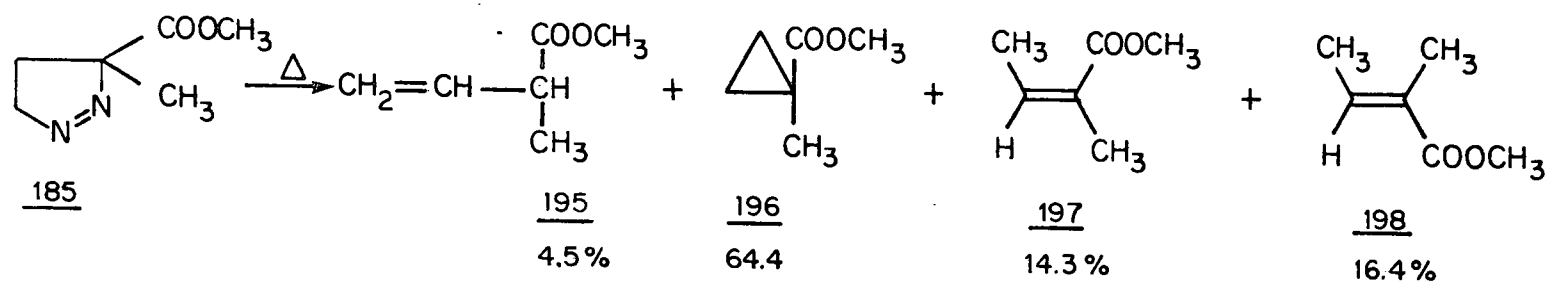
- The stereoselectivity of cyclopropane formation is higher in the case of trans-pyrazolines.
- The olefin formation is stereospecific, corroborating McGreer et al. findings.

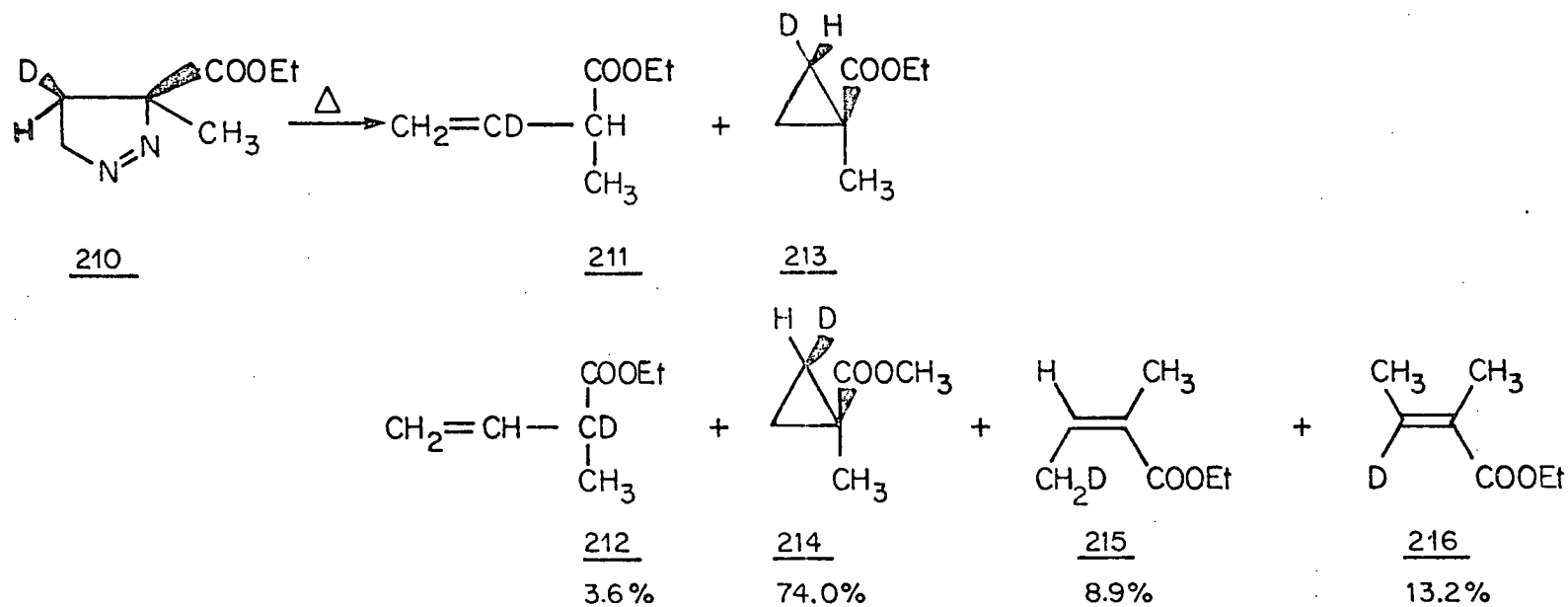
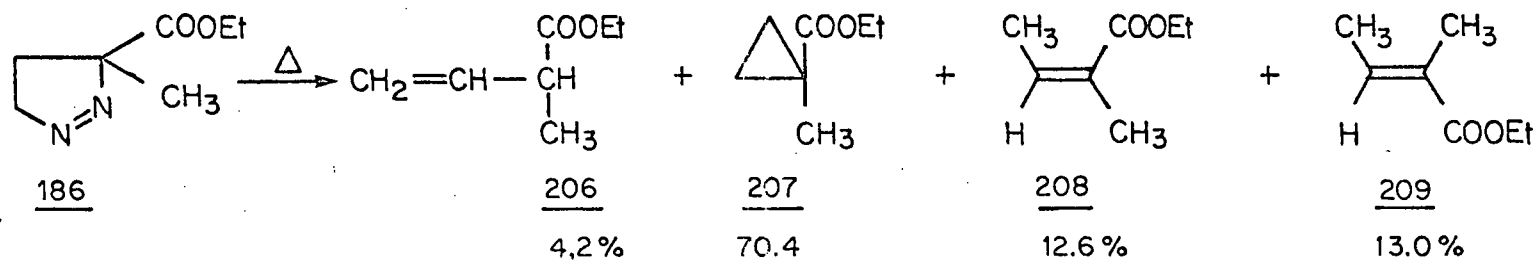
(c) Deuterium kinetic isotope effect of olefin formation, kinetic and product studies on 3-methyl-3-carbalkoxy-1-pyrazolines-4d₁.

The catalytic reduction of sodium (E)- β -bromomethacrylate with D₂ in D₂O and the subsequent work-up provided an acid mixture containing 89% (E)-, 9% (Z)-methacrylic acid-3d₁ and 2% methacrylic acid. This mixture was converted to the corresponding pyrazolines and used up for product studies. Further experiments indicated that it was possible to obtain (E)-methacrylic acid-3d₁ free of the (Z)-isomer by changing reaction conditions. Unfortunately the process became so slow and cumbersome that the available equipment seemed inadequate for preparation of the required 3-4g of pyrazoline for kinetic studies.

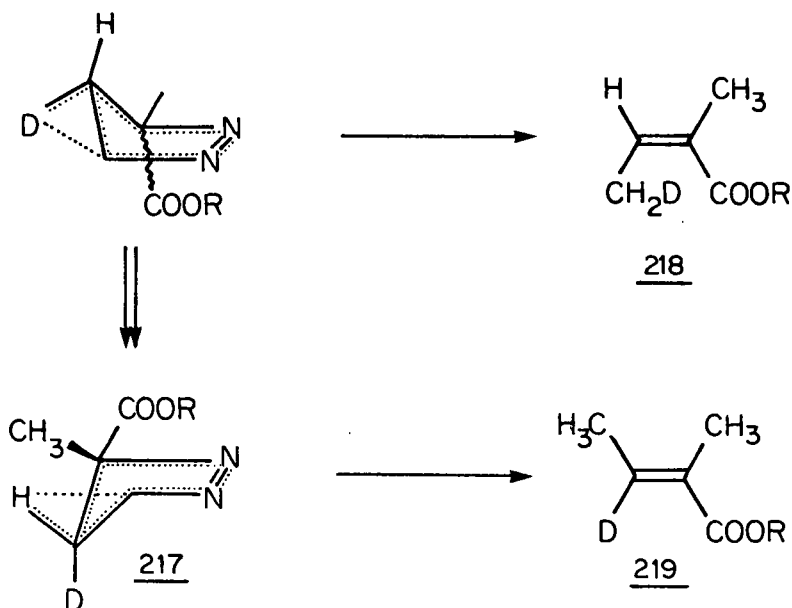
Most of the mono-deuterated methacrylic acid used in this study was the z-isomer and was made by the method of Towells (68). This isomer when reacted with diazomethane gives trans-3-methyl-3-carbalkoxy-1-pyrazolines-4d₁ (217).

Perhaps the best proof of the stereospecific olefin formation was obtained from the product distributions of trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁ 199 and trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁ 210.





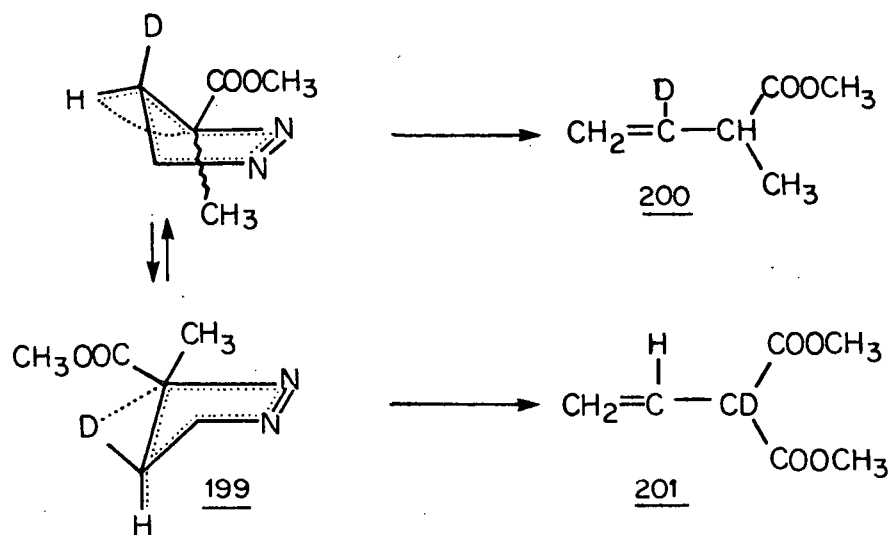
The substantial decrease in the amount of deuterated angelates can be best explained by the scheme of concerted olefin formation



The formation of angelates are retarded by the "relatively small" primary deuterium isotope effect $\frac{k_H}{k_D} = 1.74$ for the methyl ester and $\frac{k_H}{k_D} = 1.6$ for the ethyl ester, while the formation of tiglates is subjected to a secondary α -kinetic isotope effect, $\frac{k_H}{k_D} = 1.1$ for both esters.

(d) β,γ -olefin formation.

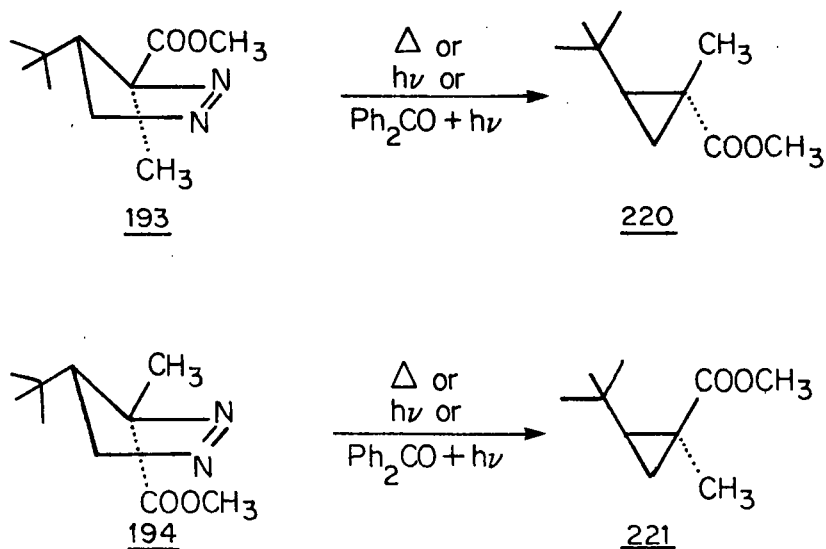
The thermolysis of trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁ provided β,γ -olefinic product in 3.5% yield. The integration of the n.m.r. spectrum of the isolated compound showed that it consisted of two components 200, 201. Their formation can be envisaged as follows:



The n.m.r. spectrum also indicated that 200 was present in larger amounts as anticipated if its formation was slowed by a secondary deuterium isotope effect (the n.m.r. spectrum was not good enough to measure the individual components quantitatively). The overall kinetic isotope effect for both was found to be $\frac{k_H}{k_D} = 1.4$. Similar results were obtained from the trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁; $\frac{k_H}{k_D} = 1.3$. The fact that β,γ -olefinic esters do not appear in the decomposition product mixtures of all pyrazolines, although their structure electronically is very similar, may indicate that the only governing factor in their formation is the stereochemistry, i.e., the geometrical position of the C-4 hydrogen in the transition state.

V. Mechanistic consideration of cyclopropane formation.

Product studies showed that 193 and 194 gave only cyclopropanes on thermolysis with full retention of the stereochemistry of the parent pyrazolines. The direct and sensitized photolyses of both pyrazolines gave rise to the same cyclopropane products as did the thermolyses.

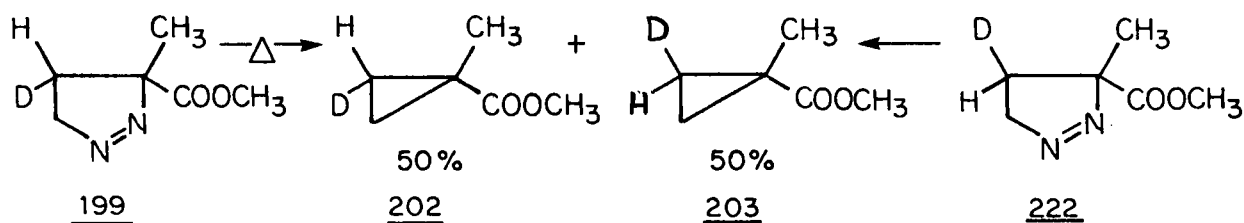


These results excluded the possibility of a symmetry controlled concerted reaction on the grounds that direct photolysis should have given products with opposite stereochemistry with respect to that obtained by thermolysis. Similar results have been reported by Berson and Olin

(53) and Schmit (65) although Inagaki and Fukui (66) could explain these findings by using the orbital interaction theory.

The two remaining mechanistic possibilities are the energetically concerted symmetry disallowed and diradical pathways.

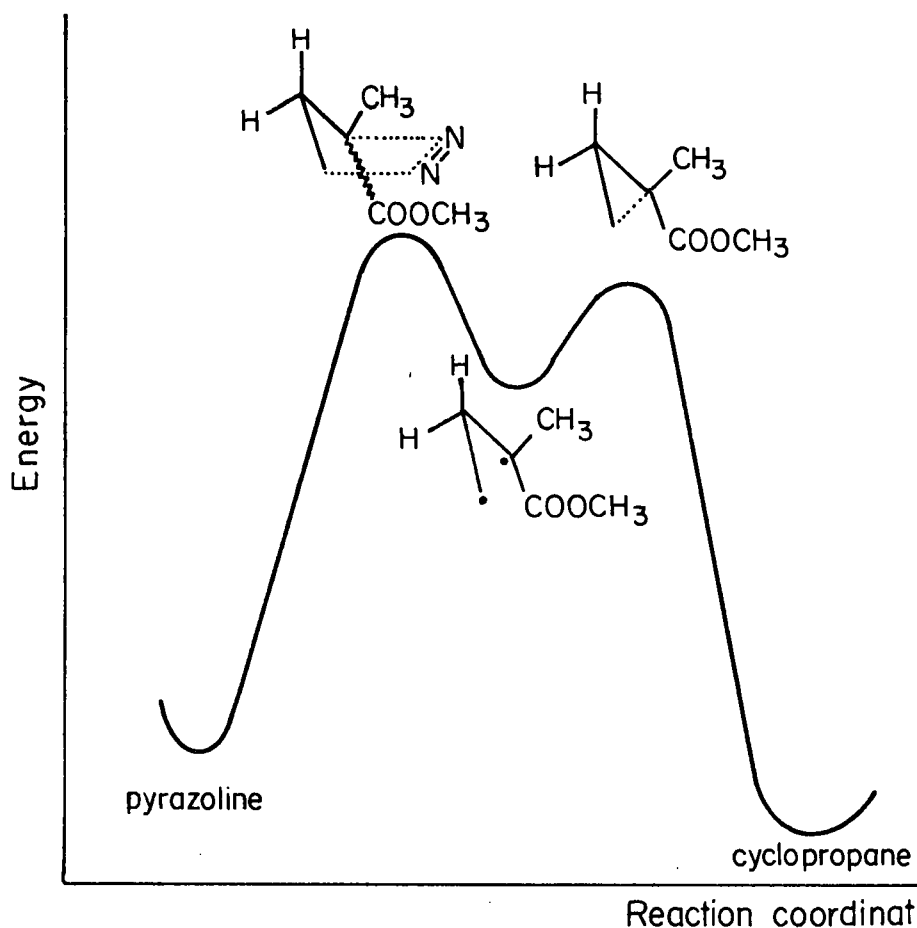
The thermal decomposition of cis- and trans-3-methyl-carbomethoxy-1-pyrazoline-d₁ provided the same mixture; 1:1 of cis- and trans-1-methyl-1-carbomethoxy-cyclopropane-2-d₁.



The benzophenone sensitized photolysis gave identical results with those of thermolysis concerning the ratio of the two isomers in the deuterio cyclopropane products, while the direct photolysis exhibited a slight ~5% retention. This means that the diradical in ground singlet state is not considerably different from the excited singlet state concerning the ring closure. In fact, there are two processes competing with each other, rotation and ring closure. It seems that the bond rotation is faster. In the case of sensitized photolysis the triplet diradical is produced. Its ring closure is

delayed by the relatively slow process of spin inversion.

The energy profile of the reaction is possibly the following:



The fact that the stereoselectivity of the cyclopropane formation increases with the bulkiness of the C-4 substituents, particularly in the case of trans- pyrazolines, is an indication that there is a competition between ring closure and rotation. The bulky substituents hinder or rule out rotation entirely even if the thermodynamically

less favorable cyclopropane isomer formation has to take place.

It is claimed by several authors (23,34,36) that simultaneous rupture of the two C-N bonds occurs during the decomposition of 1-pyrazolines. However, the inferences about the nature of the bond cleavage, whether it is concerted or stepwise (10.29), have been made from indirect evidence, mainly from deuterium kinetic isotope effects and product studies done mostly on more or less symmetrically substituted pyrazolines. Conceivably it is possible that altering the structure of the reactant such that the rupture of the C-N bonds are no longer equivalent in the transition state, i.e., one of the two C-N bonds is being broken to a larger degree than the other. Unfortunately, our results, which will be discussed, do not allow one to draw any definite conclusion about the bond breakage.

The fact that 193 and 194 gave only cyclopropanes upon decomposition made it possible to determine kinetic isotope effects for cyclopropane formation clearly. The rate measurements on cis-tert- and trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline-4-d₁ provided $\frac{k_H}{k_D} = 1.093 \pm 0.0078$ and $\frac{k_H}{k_D} = 1.069 \pm 0.024$ respectively. Similar results were obtained from the kinetic studies done on trans-3-methyl-3-carbomethoxy-1-pyrazoline-4-d₁, $\frac{k_H}{k_D} = 1.06$ and trans-3-methyl-3-carboethoxy-1-pyrazoline-4-d₁, $\frac{k_H}{k_D} = 1.06$ respectively. These results are in line with those obtained by McGreer and Masters $\frac{k_H}{k_D} = 1.20$ for two deuterions although a bit lower than Crawford's 13%.

The fluctuations in the values of $\frac{k_H}{k_D}$ for cyclopropane formation can be attributed to the error made in the kinetic measurements as well as in the gas chromatographic analysis of the individual components of the product mixture.

The reverse kinetic isotope effect calculated for cyclopropane formation ($\frac{k_H}{k_D} = 0.71$) in the thermal decomposition of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene and its analogous-5d₁ means that the reaction is not slowed down but accelerated by deuterium contrary to other results. An acceptable explanation of this irregularity is difficult to give at this time unless we assume that the formation of the bicyclo(3.1.0)hexane derivative 165 is favored on account of the smaller steric requirement for deuterium. (Since hydrogen and deuterium have very similar sizes, but the lower zero point energy of C-D implies a smaller amplitude for the vibration leading to a smaller steric requirement.) Although it is difficult to single out one of the several, rather controversial explanations concerning the origin of the secondary β -kinetic isotope effect and use it as a base to elucidate the measured effects, the most often encountered argument applies the concept of hyperconjugation. Hoffman (37,38) has shown that the hyperconjugation plays an important role in the stabilization of singlet trimethylene species. Because of hyperconjugation, the difference in vibrational energy between the C-H bond and the C-D bond in the transition state is less than it is in the ground state so the reaction is slowed by substitution of deuterium for hydrogen.

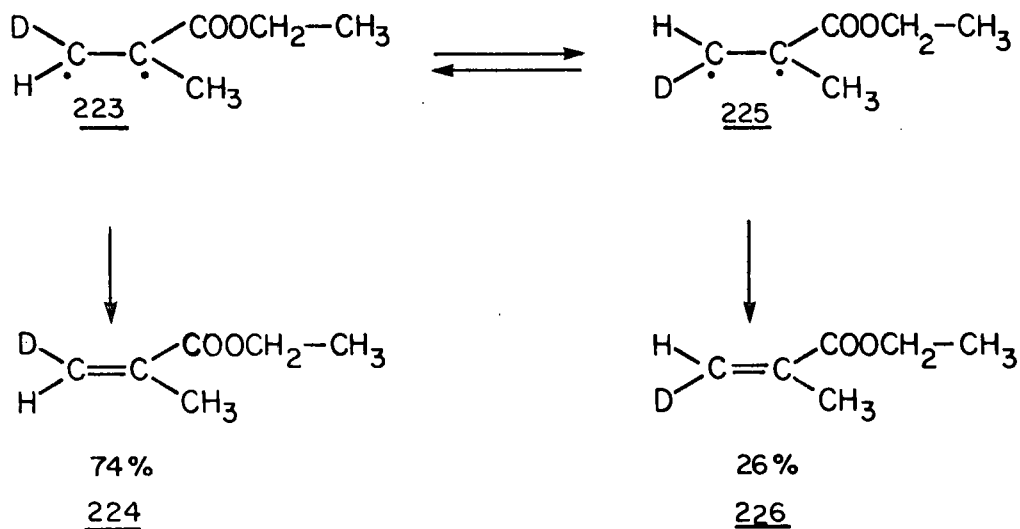
Similarly, Crawford and Mishra attributed the observed kinetic isotope effect to hyperconjugation. The slower rate of decomposition of 4-deuterated monocyclic pyrazolines is experimental fact - it does not matter for most purposes how this can be partitioned among the various possible causes (inductive, steric, hyperconjugative effects, bond strength changes with hybridization).

VI. Photolysis of pyrazolines.

The cycloaddition reaction involving thermal addition of diazomethane to a carbon-carbon double bond shows all the stereochemical properties of a concerted symmetry allowed process and theory supports this view. There are a few examples of thermally induced reversal or cycloreversion of this reaction. A much more frequent observation is a photochemical cycloreversion. Such a process would not be expected to be symmetry allowed, however all stereochemical information in the literature shows it to be stereospecific as expected for a concerted reaction. Such stereospecificity was not found in the photodecomposition of trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁.

The direct photolysis of trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁, 210 provided ethyl methacrylate-3d₁ in 14.2% yield. The n.m.r. spectrum of the isolated compound showed 75% retention with respect to the

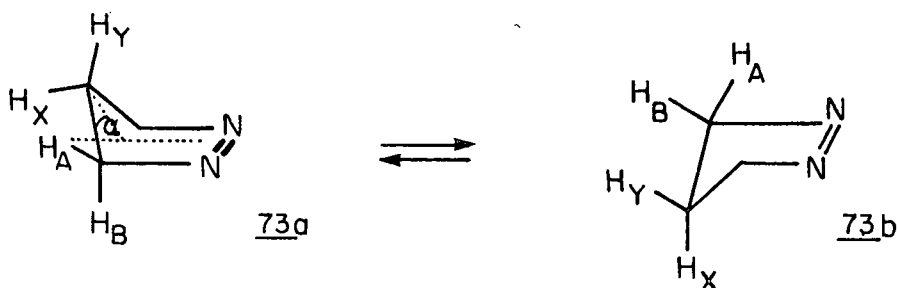
starting material. In order to see whether any cis-trans isomerization was taking place during irradiation a sample containing *methyl cis-methacrylate-3-d₁ was photolysed for 8 hours (same time as for the pyrazoline) and its n.m.r. spectrum recorded. Another sample containing deuterated methyl methacrylate and cis-3-methyl-4-tert-butyl-3-carbomethoxy pyrazoline was irradiated for 8 hours. The n.m.r. spectra of both compounds showed practically no changes. These experiments suggest that the carbon-carbon bond cleavage occurs by a mechanism other than 1,3-dipolar cycloreversion. Although there is no information available to date on the mechanistic details of carbon-carbon bond cleavage it most likely takes place by a non-concerted way. Results can be best explained by the intermediacy of a 1,2-diradical 223 which can undergo rotation and double bond formation.



* The ethyl ester was not available.

SUMMARY

Many authors have pointed out (21,22,23) that the stereochemical factors present in the pyrazoline play an important role in determining both the product distribution and product stereochemistry. In order to evaluate the stereochemical effects brought about by different substituents the pyrazoline ring itself should be scrutinized. It has been known for quite some time that the structure of the pyrazoline ring, like that of cyclopentene, resembles a folded envelope (52).



The n.m.r. studies indicated that the pyrazoline structure is quite mobile; it undergoes rapid conformational interconversion at room temperature. However, McGreer et al. (52) postulated that certain substituted pyrazolines may have a preference for one conformation. They have also calculated angle α 's for monocyclic pyrazolines using J_{cis} and J_{trans} coupling constants and the Karplus equation. On the

basis of these stereochemical facts about pyrazolines and the stereochemistry of olefinic products they put forward a suggestion concerning the mechanism of olefin formation. According to the mechanism proposed the olefin formation often takes place from the less stable conformation. Consequently it seemed evident that if conformational interconversion was a prerequisite for olefin formation the introduction of a suitably bulky substituent which could prevent that would rule out the olefin forming reaction. Inspection of Table VI reveals that the tert-butyl group placed on C-4 not only eliminated the olefin forming pathway but gave rise to only one cyclopropane product. On the other hand the incorporation of the pyrazoline ring in a bicyclic system led to 164, 227, 228 which produced large amounts of olefinic products upon thermolysis, Table VII. Considering these results one can come to the conclusion that in these bicyclic systems the atoms, especially the C-5 hydrogens, are held in such a geometrical arrangement which facilitates olefin formation.

The findings presented in Table V and Table VI in accord with the deuterium kinetic isotope effects for olefin formation corroborate McGreer's proposal that the olefin forming process involved in the thermal decomposition of 3-carbomethoxy-1-pyrazolines is a concerted reaction.

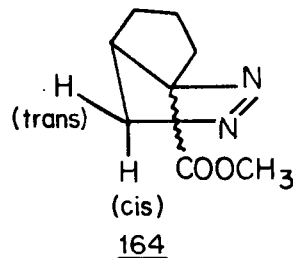
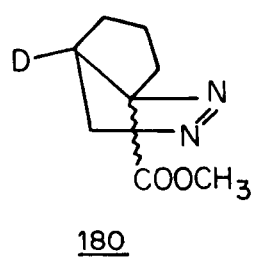
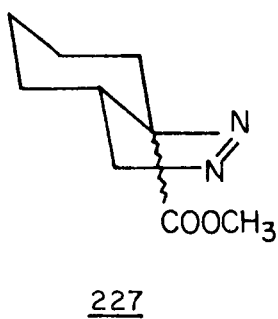
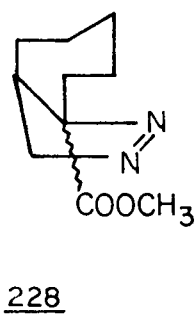
Another interesting feature of the olefin forming reaction is that the position of the carbomethoxy group may also affect the olefin-cyclopropane ratio. Table VI indicates that the cis-pyrazolines tend

to give a higher percentage of olefinic products than the corresponding trans ones. Considering the transition state for this step for cis-pyrazolines the carbomethoxy group is under the pyrazoline ring. It is conceivable that the ester group in this position might facilitate olefin formation more than in the equatorial position.

The product studies of cis- and trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazolines and cis- and trans-3-methyl-3-carbomethoxy-1-pyrazolines-4d₁ provided an unambiguous evidence for the intermediacy of a diradical in the cyclopropane forming reactions. The intermediate is assumed to be a 1,3-diradical which can undergo rotation around C-1 and C-2 bond before ring closure occurs in the absence of steric hindrance caused by substituents.

TABLE VII

The coupling constants and decomposition products
of a series of bicyclo pyrazolines

<u>COMPOUND</u>	<u>COUPLING CONSTANT</u>		<u>DECOMPOSITION PRODUCTS(at 131°)</u>		
	J(trans)	J(cis)	olefin β,γ	cycloprop.	olefin α,β
 <u>164</u>	8.5 Hz	3.3 Hz	10.2 %	19.6 %	70.0 %
 <u>180</u>	—	—	7.5 %	34.3 %	58.1 %
 <u>227</u>	6.3 Hz	7.5 Hz	4.5 %	15.3 %	80.2 %
 <u>228</u>	8.5 Hz	4.5 Hz	4.2 %	18.6 %	77.2 %

EXPERIMENTAL

I. General statements

Boiling points are uncorrected. They were determined by Mettler FPI melting and boiling point apparatus.

All infrared spectra were measured on liquid films between sodium chloride plates with a Perkin-Elmer Model 457 Grating Infrared Spectrophotometer.

All ultraviolet spectra were recorded on a Perkin-Elmer Model 202 Spectrophotometer.

60 MHz nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 Spectrometer by Miss P. Watson. 100 MHz nuclear magnetic resonance spectra were recorded on a Varian Associates Model XL-100 Spectrometer by Dr. E. Koster.

The analyses were done on an Aerograph Model A-90-P and an Aerograph Model A-90-P3.

The elemental microanalyses were performed by Mr. P. Borda of this Department.

II. Preparation of 3-methyl-3-cyano-1-pyrazoline

Methacrylonitrite and diazomethane in ether solution was allowed to stand in a cold room for several hours. After evaporating the ether, the pyrazoline was distilled in vacuum in a modified bulb-to-bulb distillation apparatus. Bath temp.: 50-55° (0.03 - 0.05 mm).

The product was a clear liquid and its spectral properties were identical to those reported by Masters [61].

Anal. Calcd. for $C_5H_7N_3$: C, 55.04; H, 6.42.

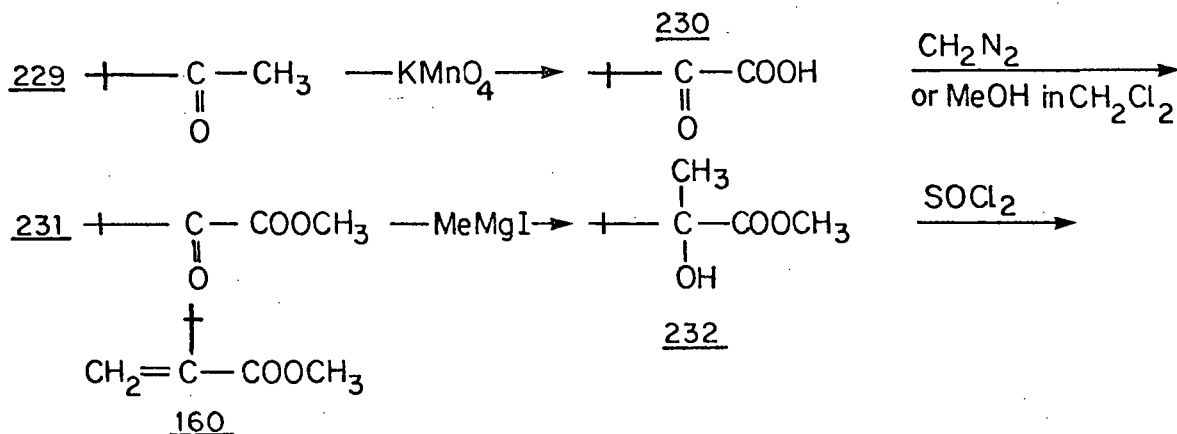
Found: C, 55.13; H, 6.57.

It was decomposed by heating at 120°C for three hours.

III. Preparation of 3-tert-butyl-3-carbomethoxy-1-pyrazoline

(a) Preparation of methyl 2-tert-butylpropen-2-oate.

The following equations illustrate the synthetic scheme;



1. 3,3-Dimethyl-2-oxobutanoic acid 230 (70).

A 120 g of KMnO_4 and 40 g of NaOH were dissolved in 3 litre of water and 40 g of pinacolone was added dropwise over a period of 2 hours. The oxidation was slightly exothermic and required some cooling. After 12 hours of stirring at room temperature, the precipitated MnO_2 was filtered off, the aqueous solution acidified with 260 ml cc HCl, and the acid extracted with three 200 ml portions of ether. The ethereal extract was dried (MgSO_4), concentrated giving 46 g (88.5%) which was used without further purification; n.m.r. (CCl_4) τ 1.63 (s, 1, COOH), τ 8.76 (s, 9, $(\text{CH}_3)_3\text{C}$).

2. Methyl 3,3-dimethyl-2-oxobutanoate 231

The esterification of the acid initially was accomplished with CH_2N_2 in ether solution. After drying over MgSO_4 , the ether was evaporated and the product distilled: b.p.: $83-85^\circ$ (52 mm), 160.1° (755 mm); n_D^{20} 1.4082; ir 1710 cm^{-1} (ester and ketone C=O); n.m.r. (CCl_4) τ 6.18 (s, 3, COOCH_3); 8.77 (s, 9, $(\text{CH}_3)_3\text{C}$).

Anal. Calcd. for $\text{C}_7\text{H}_{12}\text{O}_3$: C, 58.30; H, 8.33. Found: C, 58.38; H, 8.55.

3. Methyl 2,3,3-trimethyl-2-hydroxybutanoate 232

Methyl magnesium iodide made from 2.6 g of Mg turnings and 14.5 g of $\text{CH}_3\text{-I}$ in 80 ml of ether was added slowly to 14.4 g of 231 in 50 ml dry ether which was cooled in a dryice-acetone

ACETONE bath. The exothermic reaction yielded an orange slush which was added to 50 ml ice-cold 10% HCl. The organic phase was separated, washed with H₂O and 5% NaHCO₃, dried over MgSO₄, concentrated and distilled giving 12.5 g (80%) colourless liquid; b.p.: 75-77° (20 mm); n_D^{20} 1.4295; ir 3530 cm⁻¹ (OH), 1735 cm⁻¹ (CO ester); n.m.r. (CCl₄) τ 6.22 (s, 3, COOCH₃), 8.71 (s, 3, CH₃), 9.04 (s, 9, (CH₃)₃C); the presence of OH was verified by adding D₂O to the sample.

Anal. Calcd. for C₈H₁₆O₃: C, 59.95; H, 10.06. Found: C, 59.72; H, 10.26.

4. Methyl 2-tert-butylpropen-2-oate. 160

To a stirred solution of 11.6 g of 232, 12 g of pyridine and 30 ml of toluene, 10 g of thionyl chloride was added over a period of 1 hour. After the addition of thionyl chloride the mixture was refluxed and stirred for 5 hours. The heating was discontinued and when the temperature in the flask dropped to 50-52°, 100 ml of petroleum ether was added slowly. The dark mixture was allowed to cool to room temperature. The solidified byproduct was filtered off and washed with 50 ml of petroleum ether. The filtrate washed with 50 ml of water, 50 ml of 5% NaHCO₃ solution and 50 ml of water. After drying (MgSO₄) the petroleum ether was removed by flash evaporation and the remaining dark liquid was distilled through a 2 inch Vigreux column.

(During this distillation extremely bad smelling gases evolved.)

The fraction coming between 143-150° was collected and redistilled, giving 4.2 g (40.5 %) of 160 ; b.p.: 146.8°; n_D^{20} 1.4273; ir 1725 cm^{-1} (C=O ester), 1620 cm^{-1} (C=C); n.m.r. (CCl_4) τ 4.10 (s, 1, H cis to the ester group), 4.50 (s, 1, H), 6.30 (s, 3, COOCH_3), 8.82 (s, 9, $(\text{CH}_3)_3\text{C}$).

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.56; H, 9.93. Found: C, 67.66; H, 10.28.

(b) Preparation of 3-tert-butyl-3-carbomethoxy-1-pyrazoline.

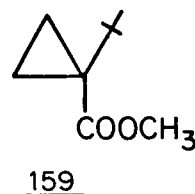
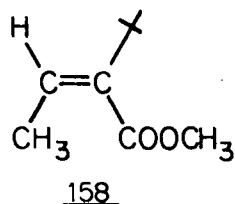
This pyrazoline was prepared by addition of diazomethane to methyl 3,3-dimethyl-2-methylene butanoate in ether solution. After 48 hours of standing at room temperature, the ether was flash evaporated and the crude pyrazoline purified by vacuum distillation using a modified bulb-to-bulb distillation apparatus: bath temp. 65-70°, 0.05 mm; n_D^{20} 1.4673; uv max (95% $\text{C}_2\text{H}_5\text{OH}$) 328 $\text{m}\mu$; ir 1730 cm^{-1} (ester C=O), 1560, 1568 cm^{-1} (N=N); n.m.r. (CCl_4) τ 5.00 - 6.00 (m, 2, C-5), 6.35 (s, 3, COOCH_3), 8.14 - 8.60 (m, 2, C-4), 9.96 (s, 9, $(\text{CH}_3)_3\text{C}$), (more information on n.m.r. spectrum of 156 can be found on page 48.

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_2$: C, 58.65; H, 8.76. Found: C, 58.50; H, 8.45.

IV. Product studies of 3-tert-butyl-3-carbomethoxy-1-pyrazoline
the synthesis of methyl (Z)-2-tert-butylbuten-2-oate.

(a) Thermal decomposition of 3-tert-butyl-3-carbomethoxy-1-
pyrazoline.

In a 5 ml round bottom flask equipped with a condenser, 1 g of pyrazoline was heated at 160° for 4 hours. The product, a yellowish liquid was analysed on a 6' by 1/4" diameter copper column packed with 20% Poly m-phenyl ether (5-ring) on chromosorb P; flowrate 80 ml He/min, column temp. 135°. Two components were separated and collected off the gas chromatograph. On the basis of their n.m.r. spectra the following structures were assigned to them.

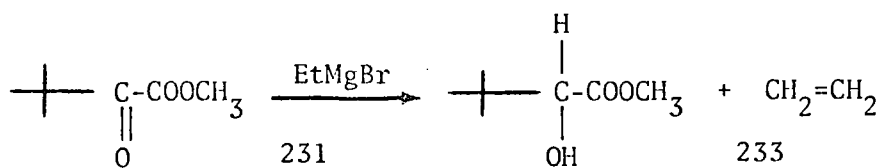


Methyl (Z)-2-tert-butylbuten-2-oate (158), b.p.: 164.7° (754 mm);
 n_D^{20} 1.4331; ir 1730 cm^{-1} (ester C=O), 1635 cm^{-1} (C=C); n.m.r. (CCl_4)
 τ 4.30 - 4.68 (q, 1, $J=6.4$ Hz, olefinic), 6.36 (s, 3, COOCH_3),
 8.41 (d, 3, $J=7.0$ Hz, CH_3), 8.93 (s, 9, $(\text{CH}_3)_3\text{C}$).

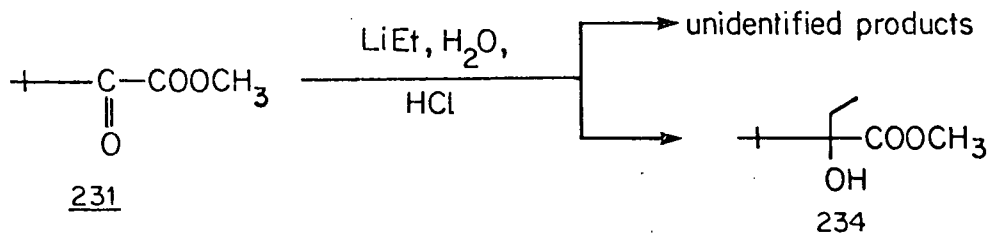
Anal. Calcd. for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.20; H, 10.22.

The geometric assignment was based on previous observation made by Fraser (71), McGreer (17,52), and in this work, that the olefinic proton signals of Z olefinic esters of general formula: $R_2-CH=CR_1COOCH_3$ appear between τ 3-4 which is somewhat lower than those of the E isomers at τ 4-5 due to the deshielding effect of the ester carbonyl. This is supported by the fact, as it was pointed out in the Discussion, that the bulky tert-butyl group does not allow conformational inter-conversion and the olefin is thus being formed stereospecifically so that only the Z isomer can form.

Several attempts were made to obtain 158 by a way other than from pyrazoline. It seemed reasonable to follow a synthetic sequence similar to the preparation of 160, but instead of addition, reduction took place when ethylmagnesium was bromide used.



It is known that alkyllithium compounds do not have the reductive properties of Grignard reagents but they add less selectively to differently substituted carbonyl groups.



Into a 250 ml three necked round bottom flask equipped with a mechanical stirrer, a rubber septum, a vent with a CaCl_2 drying tube and a gas inlet tube, 3.6 g of methyl 3,3-dimethyl-2-oxybutanoate and 40 ml of ether (distilled from CaH_2) were placed. The flask was cooled in a DRY ICE - propanol bath and purged with dry oxygen-free nitrogen for 10 minutes. To this solution 45 ml (about 10% excess) 22% of ethyl lithium solution was added by a syringe. The mixture was allowed to come to room temperature while the stirring was continued, and poured into 130 ml of ice-cold 10% HCl. The organic layer was separated, washed with 30 ml 5% NaHCO_3 solution and 50 ml water. After drying over MgSO_4 , the ether and benzene were removed by flash evaporation and the resulting yellowish liquid distilled in vacuum. The fraction coming over between 55-75°, 1.5 mm, was collected. It contained 234 with some other impurities, yield 18 g ~ 41%; n.m.r. (CCl_4) τ 6.14 (s, 3, COOCH_3), 6.90 (s, 1, OH), 8.0 - 8.5 (m, 2, $-\text{CH}_2$), 8.96 (s, 9 $(\text{CH}_3)_3\text{C}$). Unstable at room temperature.

The same dehydration procedure as was used to prepare 160, was used to obtain 158 in similar 40% yield. The n.m.r. spectrum was identical with those obtained from 156 upon thermolysis.

The gas chromatographic analysis of the crude product indicated the absence of the E isomer. Equilibrium of Z olefin also failed to produce the E isomer.

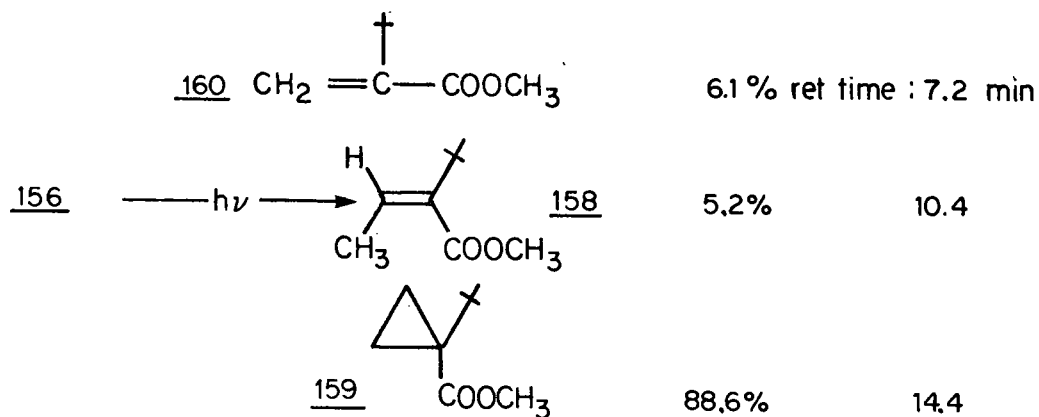
The other product 159 is 1-tert-butyl-1-carbomethoxy cyclopropane, b.p.: 154.6°; n_D^{20} 1.4379; ir 3100 and 3040 cm^{-1} (cyclopropane hydrogens),

1750 cm^{-1} (ester $\text{C}=\text{O}$); n.m.r. (CCl_4) τ 6.48 (s, 3, COOCH_3), 9.02 (s, 9+2, $(\text{CH}_3)_3\text{C} + \text{CH}-\text{CH}$ (cis to the carbomethoxy), 9.21 (m, 2, $\text{CH}-\text{CH}$ (trans)).

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}_2$: C, 69.19; H, 10.33. Found: C, 69.55; H, 10.49.

(b) Direct photolysis of 3-*tert*-butyl-3-carbomethoxy-1-pyrazoline.

A 0.5 g sample of pyrazoline was dissolved in 30 ml isopentane and photolysed in a Rayonet Photochemical Reactor using 3100 Å lamps until the sample showed no typical $\text{N}=\text{N}$ bond absorption in the uv. The solvent was evaporated and the product mixture was analyzed by gas chromatography. (The same column and conditions were used as for the analysis of thermal decomposition products.)



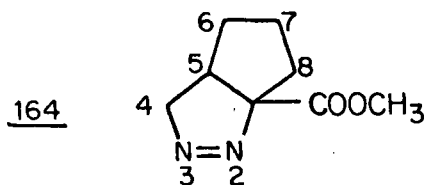
(c) Sensitized photolysis of 3-*tert*-butyl-3-carbomethoxy-1-pyrazoline.

Five grams of benzophenone and 0.5 g of pyrazoline were dissolved in 50 ml of isopentane (saturated solution of benzophenone). The

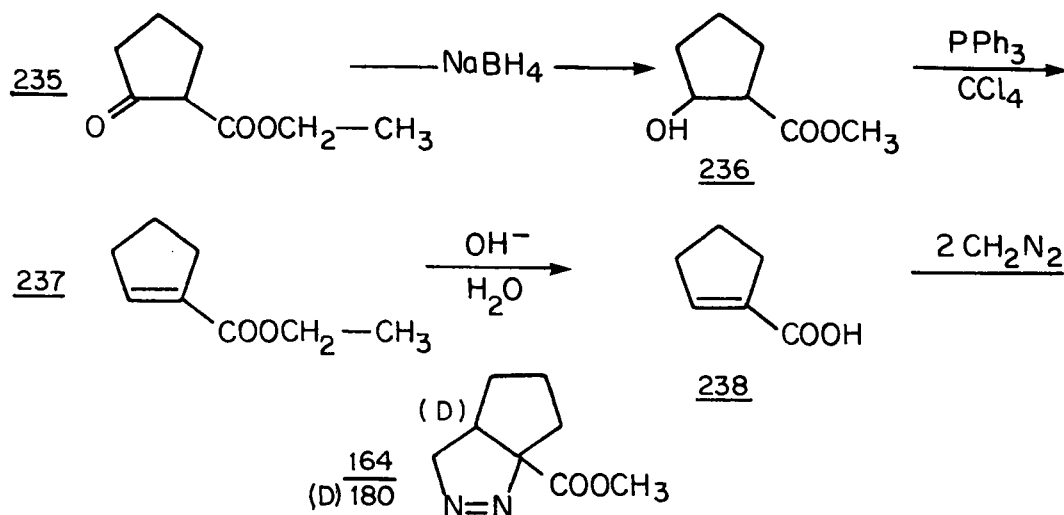
solution was irradiated in a Rayonet Photochemical Reactor for 24 hours using 3500 Å lamps. After several repetitions of the evaporation, cooling and filtration cycle a practically benzophenone free product had been obtained which was found to be only the cyclopropane product 159.

V. Preparation of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene and its analogue-5d₁.

(a) Preparation of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene.



The following synthetic sequence was chosen for the preparation of 238.



1. 1-Cyclopentenecarboxylic acid.

One gram of NaBH_4 was dissolved in 40 ml of methanol containing 1 ml of NaOH solution at -2°C . To this turbid solution 15.5 g of 2-carboethoxycyclopentanone was added while the temperature was kept at 0°C . The mixture was stirred overnight at room temperature and then 200 ml of water was added and the resulting solution was acidified with 10% HCl to pH \sim 3. The product was extracted with chloroform, washed with 10% Na_2CO_3 and water, and dried over MgSO_4 . Evaporation of chloroform yielded 16.0 g of crude product which was dehydrated with 30 g of triphenylphosphine in a solution of 150 ml dry CCl_4 . (See page 104.)

The crude product was purified by vacuum distillation. Yield was: 10.5 g (70.5%), b.p.: 92-93° (25 mm); ir 1715 cm^{-1} (ester C=O) 1622 cm^{-1} (C=C).

The ester was added to a solution containing 3.2g NaOH in 10 ml of H_2O and 20 ml of methanol and kept at 70°C for 24 hours. Then it was diluted with 100 ml of H_2O and acidified with 40 ml of 10% HCl. The free acid was extracted twice with 50 ml of ether. The ether extracts were combined and dried over MgSO_4 . After evaporation of the ether, the solid material was crystallized from hot petroleum ether (30-60°). Yield: 78%, 6.2 g of white crystals, m.p. 123°.

The acid was esterified with diazomethane after a portion had been taken for analytical purposes.

2. 1-Carbomethoxycyclopentene.

ir 1720 cm^{-1} (ester C=O), 1630 cm^{-1} (C=C); n.m.r. (CCl_4) τ 3.34 (s, 1, olefinic H), 6.34 (1, 3, COOCH_3), 7.48 (m, 4, C-3 and C-5 H's), 7.97 (m, 2, C-4 H's).

Anal. Calcd. for $\text{C}_7\text{H}_{10}\text{O}_2$: C, 66.64; H, 7.99. Found: C, 66.76; H, 8.06.

3. 1-Carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene.

Five grams of 1-carbomethoxy-cyclopentene was allowed to stand with an excess of diazomethane in ether solution at room temperature for a week. The ether was flash evaporated and the resulting compound was purified by vacuum distillation using a bulb-to-bulb distillation apparatus, bath temperature 50° (0.005 mm). Yield,

6.1 g (90%); ir 1732 cm^{-1} (ester C=O), 1552 cm^{-1} (N=N); n.m.r. (CCl_4) τ 5.47 (dd, 1, pseudoequatorial hydrogen on C-4, $J_{AB} = 18.7$, $J_{trans} = 8.3\text{ Hz}$), 5.61 (dd, 1, pseudoaxial hydrogen on C-4, $J_{AB} = 18.7\text{ Hz}$, $J_{cis} = 3.3\text{ Hz}$), 7.73 (dd, 1, C-5H, $J = 8.5\text{ Hz}$, 6.29 (s, 3, COOCH_3), 7.41 (m, 2, C-8 H's), 8.58 (m, 4, C-6 and C-7 H's).

Anal. Calcd. for $\text{C}_8\text{H}_{12}\text{O}_2\text{N}_2$: C, 57.12; H, 7.19. Found: C, 56.68; H, 7.10.

(b) Preparation of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)
2-ene-5d₁.

Basically the same synthetic sequence was followed as 164 but instead of NaBH_4 , NaBD_4 (98% isotopic purity) was used.

1. 1-Cyclopentenecarboxylic acid-2d₁.

White crystals from petroleum ether, m.p.: 119° ; n.m.r. (CDCl_3) τ 7.42 (m, 4 C-3 and C-5 H's), 8.00 (m, 2, C-4 H's), -1.89 (s, 1, COOH).

Anal. Calcd. for $\text{C}_6\text{H}_7\text{D}\text{O}_2$ C, 63.70; H, 7.24. Found: C, 63.79; H, 7.27

2. 1-Carbomethoxycyclopentene-2d₁.

The esterification of the deuterated acid with diazomethane gave a liquid ir 1720 cm^{-1} (ester C=O), 1630 cm^{-1} (C=C); n.m.r. (CCl_4) τ 6.32 (s, 3, COOCH_3), 7.50 (m, 4, C-3 and C-5 H's), 8.02 (m, 2, C-4 H's), peak at 2.97 due to the olefinic proton being absent.

3. 1-Carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene-5d₁.

The methyl ester was allowed to stand with an excess of diazomethane in ether solution for a week at room temperature. The work up was identical to that described earlier in the case of non deuterated compound.

ir 1732 cm⁻¹ (ester C=O), 1552 cm⁻¹ (N=N); n.m.r. (CCl₄) τ 5.0 (d, 1, pseudoequatorial hydrogen on C-4), 5.0 (d, 1, pseudoaxial hydrogen on C-4), 6.29 (s, 3, COOCH₃), 7.41 (m, 2, C-8 H's), 8.58 (m, 4, C-6 and C-7 H's).

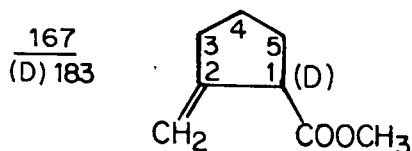
Anal. Calcd. for C₈H₁₁D₁₀N₂: C, 56.80; H, 7.25. Found: C, 56.36; H, 7.11.

VI. Product studies of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene and its analogue-5d₁.

(a) Thermal decomposition of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene and its analogue-5d₁.

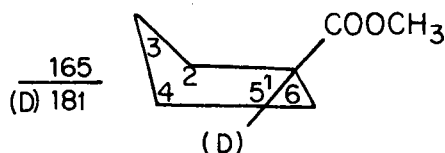
The thermal decomposition of the pyrazolines in a small round bottom flask equipped with a condenser at 131° provided a yellowish liquid consisting of three components. The products were separated by a 15' long ¼" diameter copper column packed with 20% Apiazon J on Chrom P, at 160-165°C, 100 ml He/min. The compounds were collected off the gas chromatograph and their ir and n.m.r. spectra were recorded.

The following structure was assigned to the compound having 7.1 min retention time.



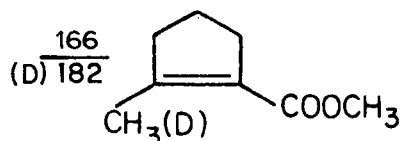
ir 3060 cm^{-1} ($=\text{CH}_2$), 1735 cm^{-1} (ester $\text{C}=\text{O}$), 1650 cm^{-1} ($\text{C}=\text{C}$); n.m.r. (CCl_4) τ 5.00 (m, 2, $=\text{CH}_2$), 6.33 (s, 3, COOCH_3), 6.80 (m, 1, C-1 H), 7.72 (m, 4, C-3 and C-5 H's), 8.10 (m, 2, C-4 H's). The n.m.r. spectrum of the deuterated compound lacked the signal at τ 6.80.

The next peak, ret. time 10 min was due to 1-carbomethoxy-bicyclo(3.1.0)hexane



ir 3010 cm^{-1} (cyclopropane H's), 1730 cm^{-1} (ester $\text{C}=\text{O}$); n.m.r. (CCl_4) τ 6.40 (s, 3, COOCH_3), 8.29 (m, 6, C-2, C-3 and C-4 H's), 8.71 and 9.29 (m, 3, cycloprop H's). The n.m.r. spectrum of the deuterated showed essentially identical spectrum with the exception of peaks appearing at τ 8.71 and 9.29 due to the presence of deuterium.

The last peak, ret. time 11.1 min was due to 2-methyl-1-carbomethoxy-cyclopent-1-ene.



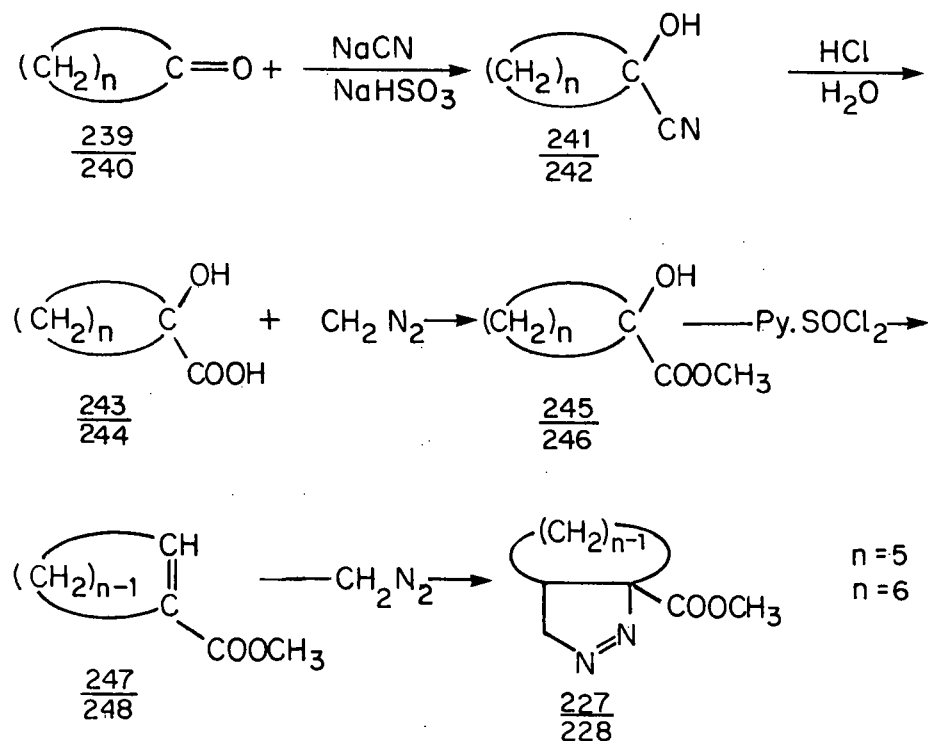
ir 1725 cm^{-1} (ester $\text{C}=\text{O}$), 1660 cm^{-1} ($\text{C}=\text{C}$); n.m.r. (CCl_4) τ 6.36 (s, 3, COOCH_3), 7.52 (m, 4, C-4 and C-5 H's), 7.94 (s, 3, CH_3), 8.20 (m, 2, C-3 H's). The n.m.r. spectrum of the 2-(methyl- d_1)-1-carbomethoxy cyclopent-1-ene showed an identical spectrum with the exception of the smaller, broader peak at τ 7.94 due to $-\text{CH}_2\text{D}$.

(b) Photolyses of 1-carbomethoxy-2,3-diazabicyclo(3.3.0)oct-2-ene and its analogue-5 d_1 .

In a Rayonet Photochemical reactor samples of 0.5 g pyrazolines in 30 ml of ether were irradiated for 12 hours using 3100 Å lamps. The ethereal solution was concentrated and analysed in the same manner described above. In both cases only cyclopropane products were isolated.

VII. Preparation of 1-carbomethoxy-2,3-diazabicyclo(4.3.0)non-2-ene
and 1-carbomethoxy-2,3-diazabicyclo(5.3.0)dec-2-ene.

The following synthetic sequence was used to prepare the two compounds (72):



In a three-necked round-bottom flask equipped with mechanical stirrer and a dropping funnel, 2.6 g NaCN was dissolved in 20 ml of water. After cooling the solution to -50° in a cooling bath, 5 g ketone (cyclohexanone, cycloheptanone freshly distilled) was added. To this

mixture a solution of 12 g NaHSO_3 dissolved in 25 ml of water was added slowly, then the reaction mixture was allowed to come to room temperature while the stirring was continued for 2 hours. The product was extracted with three 50 ml portions of ether, the ether flash evaporated and the residue refluxed with 30 ml of 36% HCl for 4 hours. The pinkish liquid was diluted with 100 ml of water and extracted with three 50 ml portions of ether. The organic phases were combined and dried (MgSO_4). The esterification with CH_2N_2 and the following flash evaporation of the ether provided a brownish liquid 5.3 g, which was used without purification.

Into a 100 ml three-necked round-bottom flask equipped with a mechanical stirrer, a condenser topped with a drying tube and a dropping funnel the crude ~ 5.3 g oxy-ester, 6.0 g pyridine and 40 ml of toluene were placed. To this mixture 6.0 g of SOCl_2 was added over a period of 2 hours and then the mixture was refluxed for 5 hours. The dark reaction mixture was cooled to room temperature which brought about some solidification in the mixture. Thirty milliliters of petroleum ether (30-60) was added and then the solid material was filtered off and washed with 30 ml of petroleum ether. The combined filtrates were washed with 50 ml of water, 50 ml of 5% HCl , 50 ml of water, 50 ml of 5% NaHCO_3 solution and 50 ml of water in this order. After drying (MgSO_4) the petroleum ether was flash evaporated. The remaining dark solution was fraction distilled. (During the distillation extremely bad smelling gases were formed.)

The fraction collected between 190-200° contained the 1-carbomethoxy-cyclohex-1-ene, which was purified by an additional distillation, 2.2 g (31%) b.p.: 194.1°; ir 1725 cm^{-1} (ester C=O), 1660 cm^{-1} (C=C); n.m.r. (CCl_4) τ 3.08 (m, 1, olefinic), 6.37 (s, 3, COOCH_3), 7.84 (m, 4, C-3 and C-6 H's), 8.41 (m, 4, C-4 and C-5 H's).

In the case of 1-carbomethoxy-cyclohept-1-ene the fraction which came over between 210-220 was redistilled to obtain the ester, 2.4 g (30%) b.p.: 216.7°; ir n.m.r. (CCl_4) τ 2.86 (tr. 1, olefinic), 6.37 (s, 3, COOCH_3), 7.64 (m, 4, C-3 and C-7 H's), 8.38 (m, 6, C-4, C-5 and C-6 H's).

The esters were allowed to stand with an excess of diazomethane in ether solution for a week. After the flash evaporation of ether the residues were distilled using a bulb-to-bulb distillation apparatus.

1-Carbomethoxy-2,3-diazabicyclo(4.3.0)non-2-ene; bath temp: 52° (0.002 mm); ir 1740 cm^{-1} (ester C=O), 1545 cm^{-1} (N=N); n.m.r. (CCl_4) τ 5.51 (dd, 1, pseudoaxial H on C-4, $J_{AX} = 7.5$ Hz, $J_{AB} = 16.5$ Hz), 5.84 (dd, 1, pseudoequatorial H on C-4, $J_{BX} = 6.4$ Hz), 6.27 (s, 3, COOCH_3), 7.65 (m, 1, C-5 H), 8.50 (m, 8, C-6, C-7, C-8 and C-9 H's).

Anal. Calcd. for $\text{C}_9\text{H}_{14}\text{N}_2\text{O}_2$: C, 59.34; H, 7.75 Found: C, 59.07; H, 7.86.

1-Carbomethoxy-2,3-diazabicyclo(5.3.0)dec-2-ene; bath temp: 57° (0.003 mm); ir 1740 cm^{-1} (ester C=O), 1545 cm^{-1} (N=N); n.m.r. (CCl_4) τ 5.53 (dd, 1, pseudoequatorial H on C-4 $J_{AX} = 8.5$ Hz, $J_{AB} = 18.0$ Hz),

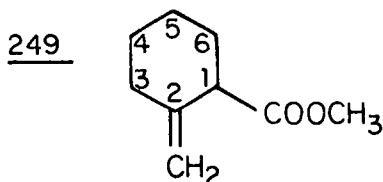
5.73 (dd, 1, pseudoaxial H on C-4, $J_{BX} = 4.5$ Hz, $J_{AB} = 18.0$ Hz), 6.28 (s 3, COOCH_3), 7.40 (m, 1, C-5 H), 8.52 (m 10, C-6, C-7, C-8, C-9 and C-10 H's).

Anal. Calcd. for $\text{C}_{10}\text{H}_{16}\text{N}_2\text{O}_2$: C, 61.19; H, 8.21. Found: C, 60.82; H, 8.32.

VIII. Product studies of 1-carbomethoxy-2,3-diazabicyclo(4.3.0)non-2-ene.

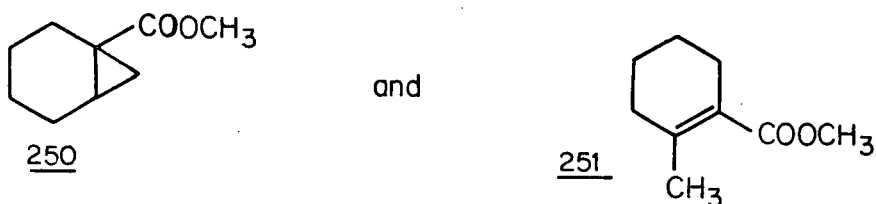
In a 5 ml round bottom flask equipped with a condenser 0.5 g pyrazoline was placed and heated at 131° for 6 hours. The preliminary test on a t.l.c. plate showed that the product mixture consisted of three components. The gas chromatographic analysis using a 15' long $\frac{1}{8}$ " diameter copper column packed with 20% Apiezon J on Chrom. P.; column temp. 180-185; flow rate 120 ml He/min showed only two peaks indicating that two of the components were not separated. Samples were collected off the gas chromatograph and their ir and n.m.r. spectra were recorded.

The first peak, ret. time 28 min was due to



ir 3100 cm^{-1} (exocyclic $=\text{CH}_2$), 1730 cm^{-1} (ester $\text{C}=\text{O}$), 1655 cm^{-1} ($\text{C}=\text{C}$);
n.m.r. (CCl_4) τ 5.39 (d, 2, $=\text{CH}_2$), 6.39 (s, 3, COOCH_3), 6.94 (m, 1, C-1 H), 8.01 (m, 4, C-3 and C-6 H's), 8.52 (m, 4, C-4 and C-5 H's).

The other peak, ret. time 41 min was due to the following two compounds:

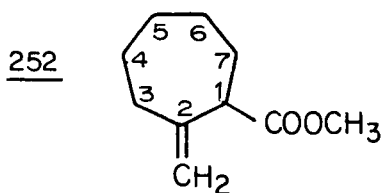


The ratio of the two were estimated from the integrations of the carbomethoxy peaks in the n.m.r. spectrum.

IX. Product studies of 1-carbomethoxy-2,3-diazabicyclo(5.3.0)dec-2-ene.

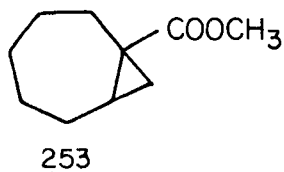
The pyrazoline was decomposed in a similar fashion to that of at 145° . The t.l.c. test indicated the presence of three components. The gas chromatographic analysis using 15' copper column packed with 20% Apiezon J on Chrom. P., column temp 190-195; flow rate 120 ml He/min, showed two peaks. Samples were collected off the gas chromatograph and their n.m.r. spectra recorded.

The first peak, ret. time 28 min, was due to the following olefin:

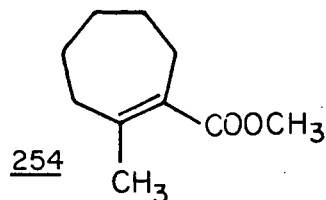


n.m.r. (CCl_4) τ 5.14 (s, 2, $=\text{CH}_2$), 6.37 (s, 3, COOCH_3), 6.94 (m, 1, C-1 H), 8.10 (m, 10, C-3, C-4, C-5, C-6, C-7 H's).

The other peak, ret. time 34 min, was due to the following two compounds:



and



The ratio of the two were estimated from the integration of the carbo-methoxy peaks in the n.m.r. spectrum.

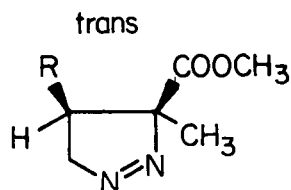
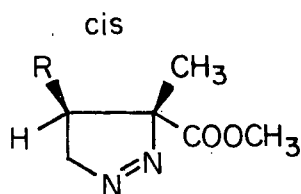
X. 3-Methyl-3-carbo-tert-butyl-1-pyrazoline.

The pyrazoline was made from commercial tert-butyl methacrylate and diazomethane. The crude product was purified by vacuum distillation using a bulb-to-bulb distillation apparatus; bath temp.: 65-70° (0.03 mm). Its properties were identical to those reported by Snyder (60). n.m.r. (CCl_4) τ 5.42 (m, 2, C-5 H's), 7.89 (m, 1, C-4 H), 8.56 (s, 12, $(\text{CH}_3)_3\text{C} + \text{CH}_3$ on C-3).

Two grams of sample were decomposed at 127° and the obtained product mixture was analysed on a 20' copper column packed with 20% di-iso-decylphthalate on Chrom W column temp.: 155°, flow rate 120 ml He/min. The average deviations were calculated from three gas chromatographic analyses of the same sample.

β,γ -olefin	=	$4.50 \pm 0.32\%$	ret. time	8.6 min
cyclopropane	=	$74.13 \pm 0.77\%$		10.5 "
angelate	=	$11.45 \pm 0.31\%$		12.0 "
tiglate	=	$9.94 \pm 0.22\%$		15.0 "

XI. Preparation of cis- and trans-3-methyl-4-alkyl-3-carbomethoxy
pyrazolines.



R =	<u>iso-propyl</u>	<u>189</u>	<u>190</u>
=	<u>iso-butyl</u>	<u>191</u>	<u>192</u>
=	<u>tert-butyl</u>	<u>193</u>	<u>194</u>

The preparation of pyrazolines followed the usual procedure in which the α,β -olefinic esters were treated with diazomethane in ether solution at room temperature. It is worth noting that the size of the alkyl group has a profound effect on the rate of cycloaddition. When R = iso-propyl, it requires 2 treatments in two weeks, when R = tert-butyl it takes 4-5 treatments in 5 months to achieve 85-90% conversion of the Z olefins. The E isomers are somewhat more reactive.

It was anticipated from the beginning that a few stereospecifically deuterated pyrazolines would also be required to study kinetic isotope effects. Consequently such synthetic sequences were chosen which could provide starting materials for both deuterated and undeuterated

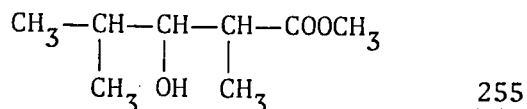
α,β -olefinic esters. The dehydration of β -hydroxy esters, which could be obtained in good yield by the Reformatsky reaction, were favored over other possibilities for the preparation of olefinic esters because their oxydation to β -keto esters and reduction with NaBD_4 followed by dehydration could give the required β -deutero olefinic esters.

(a) General procedure for the preparation of β -hydroxy esters.

Into a three necked flask equipped with a mechanical stirrer, reflux condenser topped with a CaCl_2 drying tube and a pressure equilibrating dropping funnel, 50 ml of dry ether, 22.5 g (0.3 m) Zn metal (Mesh 30) and a few crystals of iodine were placed. The mixture was refluxed and stirred for 30 min to activate the Zn. The heating was discontinued and a mixture of 0.3 m methyl α -bromopropionate and 0.32 m of aldehyde (both freshly distilled) was added dropwise. The colour change of the mixture indicated the start of the reaction. The rest of the mixture and 450 ml of dry ether were added to the reaction mixture over a period of 2 hours. After the addition the mixture was refluxed for 4 hours then cooled and 300 ml of water added to it. The voluminous white precipitate was dissolved by addition of the necessary amount of 20% H_2SO_4 . The organic phase was separated and the water phase was extracted with three 100 ml portions of ether. The combined ether solution was washed with 100 ml of 1% H_2SO_4 , 200 ml of water, 200 ml of 5% NaHCO_3 . After drying (MgSO_4), the ether was flash-

evaporated. The residue was distilled in vacuum. The fractions containing the β -hydroxy esters came over between 100-135° (25-30 mm).

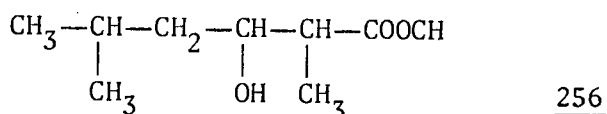
1. Methyl 2,4-dimethyl-3-hydroxypentanoate from isobutyraldehyde and methyl α -bromopropionate



Yield: 78.8%; n_D^{20} 1.4349; ir 3520 cm^{-1} (OH), 1735 cm^{-1} (ester C=O); n.m.r. (CCl_4) τ 6.36 (s, 3, COOCH_3), 6.18 (m, 1, C-3 H), 7.52 (m, 2, C-2 on d OH), 8.33 (m, 1, C-4 H), 9.01 (m, 9, CH_3 H's on C-2 and C-3, C-4 H's).

Anal. Calcd. for $\text{C}_8\text{H}_{16}\text{O}_3$: C, 59.97; H, 10.06. Found: C, 59.67; H, 10.31.

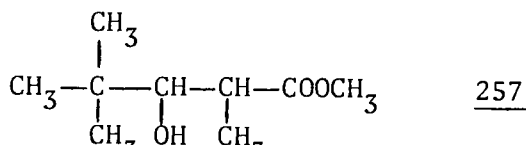
2. Methyl 2,5-dimethyl-3-hydroxyhexanoate from isovaleraldehyde and methyl α -bromopropionate



Yield: 67.1%; n_D^{20} 1.4351; ir 3500 cm^{-1} (OH), 1760 cm^{-1} (ester C=O); n.m.r. (CCl_4) τ 6.36 (s, 3, COOCH_3), 7.65 (m, 1, C-3 H), 8.70 (m, 2, C-2 H and OH), 8.90 (d, 3, CH_3 on C-2), 9.12 (dd, 6, CH_3 on C-5).

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{O}_3$: C, 62.04, H, 10.41. Found: C, 61.94; H, 10.46.

3. Methyl 2,4,4-trimethyl-3-hydroxypentanoate from pivaldehyde and methyl α -bromopropionate



Yield: 70.0%; n_D^{20} 1.4380; ir 355 cm^{-1} (OH), 1725 cm^{-1} (ester $\text{C}=\text{O}$); n.m.r. (CCl_4) τ 6.32 (s, 3, COOCH_3), 6.40 (m, 1, C-3 H), 7.40 (m, 2, C-2 H and OH), 8.73 (d, 3, CH_3 on C-2), 9.02 (s, 9, CH_3)₃C).

Anal. Calcd. for $\text{C}_9\text{H}_{18}\text{O}_3$: C, 62.04; H, 10.41. Found: C, 61.81; H, 10.45.

(b) General procedure for the preparation of olefinic esters.

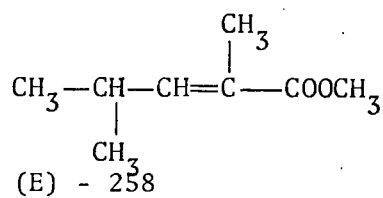
The dehydration of the β -hydroxy esters was effected by triphenylphosphine and carbon tetrachloride which served as reagent and solvent.

Into a 1 liter round bottom flask equipped with a condenser topped with a drying tube, 0.2 m of β -hydroxy ester, 0.22 m triphenyl phosphine and 400 ml of dry carbon tetrachloride were placed. The solution was refluxed for 24 hours. The excess CCl_4 and the formed CHCl_3 were evaporated on a rotary evaporator. The semi solid mass was worked up with 200 ml of petroleum ether (30-60). After keeping at 0° for a few hours, the solid material was filtered off and the cake washed with 50-70 ml of ice cold petroleum ether. The evaporation of petroleum ether provided a yellowish oil still containing some solid material. The purification of the crude olefins was achieved by vacuum distillation. The olefinic products came over between $80\text{-}120^\circ$ at 25-30 mm. The E and Z isomers as well as the β,γ -olefinic byproducts were separated and collected by gas chromatography using a 25' long 3/4" diameter copper column packed with 20% carbowax 4000 monostearate.

The individual olefins are as follows:

1. Methyl (E)- and (Z)-2,4-dimethylpenten-2-oate from 255.

Yield: 65.0%



(Z) - 259

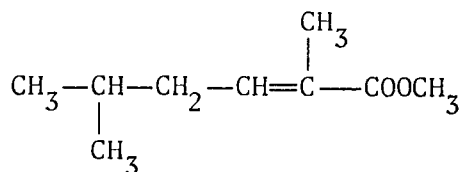
(E)-isomer; b.p.: 163.3°; n_D^{20} 1.4395; ir 1730 cm^{-1} (ester C=O), 1650 cm^{-1} (C=C); n.m.r. (CCl_4) τ 3.56 (d, 1, olefinic, J : 4.4 Hz), 6.34 (s, 3, COOCH_3), 7.50 (m, 1, C-4 H), 8.22 (d, 3, CH_3 on C-2), 8.98 (d, 6, $(\text{CH}_3)_2$).

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.60; H, 9.86. Found: C, 67.78; H, 9.69.

(Z)-isomer; b.p.: 150.1°, n_D^{20} 1.4345; ir 1740 cm^{-1} (ester C=O), 1650 cm^{-1} (C=C, very small); n.m.r. (CCl_4) τ 4.29 (d, 1, olefinic J = 3.8 Hz), 6.33 (s, 3, COOCH_3), 6.75 (m, 1, C-4 H), 8.17 (s, 3, CH_3 on C-2), 8.97 (d, 6, $(\text{CH}_3)_2$).

Anal. Calcd. for $\text{C}_8\text{H}_{14}\text{O}_2$: C, 67.60; H, 9.86. Found: C, 67.87; H, 9.89.

2. Methyl (E)- and (Z)-2,5-dimethylhexen-2-oate from 256.



(E) - 260

(Z) - 261

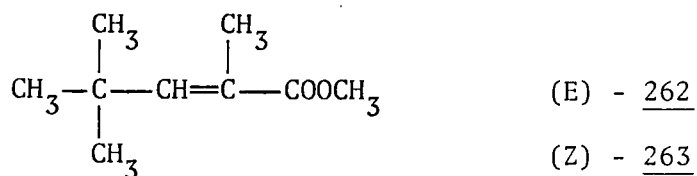
(E)-isomer; b.p.: 189.1°; ir 1725 cm⁻¹ (ester C=O), 1655 cm⁻¹ (C=C); n.m.r. (CCl₄) τ 3.36 (t, 1, olefinic), 6.33 (s, 3, COOCH₃), 8.00 (m, 2, C-4 H's), 8.13 (s, 3, CH₃ on C-2), 8.49 (m, 1, C-5 H), 9.05 (d, 6, (CH₃)₂).

Anal. Calcd. for C₉H₁₆O₂: C, 69.23; H, 10.25. Found: C, 68.96; H, 10.36.

(Z)-isomer; b.p.: 175.4°; ir 1725 cm⁻¹ (ester C=O), 1650 cm⁻¹ (C=C); n.m.r. (CCl₄) τ 4.11 (t, 1, olefinic), 6.31 (s, 3, COOCH₃), 6.76 (m, 2, C-4 H's), 8.15 (s, 3, CH₃ on C-2), 8.36 (m, 1, C-5 H), 9.10 (d, 6, (CH₃)₂).

Anal. Calcd. for C₉H₁₆O₂: C, 69.23; H, 10.25. Found: C, 69.01; H, 10.10.

3. Methyl (E)- and (Z)-2,4,4-trimethylpenten-2-oate from 257.



Yield: 80.0%

(E)-isomer; b.p.: 180.6°; n_D^{20} 1.4458; ir 1720 cm⁻¹ (ester C=O), 1645 cm⁻¹ (C=C); n.m.r. (CCl₄) τ 3.37 (m, 1, olefinic), 6.37 (s, 3, COOCH₃), 8.10 (s, 3, CH₃ on C-2), 8.80 (s, 9, (CH₃)₃C).

Anal. Calcd. for C₉H₁₆O₂: C, 69.23; H, 10.25. Found: C, 69.33; H, 10.06.

(Z)-isomer; b.p.: 162.3°; n_D^{20} 1.4322, ir 1740 cm^{-1} (ester C=O), 1660 cm^{-1} (C=C); n.m.r. (CCl_4) τ 4.60 (m, 1. olefinic), 6.33 (s, 3, COOCH_3), 8.19 (d, 3, CH_3 on C-2 $J = 1.6$ Hz), 8.91 (s, 9, $(\text{CH}_3)_3\text{C}$).

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{O}_2$: C, 69.23; H, 10.24. Found: C, 69.55; H, 9.98.

(c) Pyrazolines.

1. cis-3-Methyl-4-isopropyl-3-carbomethoxy-1-pyrazoline.

A liquid which solidifies on long standing at low temperature (-5°); ir 1762 cm^{-1} (ester C=O), 1550 cm^{-1} (N=N); n.m.r. (CCl_4) τ 5.23 (dd, 1, pseudoequatorial C-5 H, $J_{\text{trans}} = 8.4$ Hz, $J_{\text{gem}} = 17.0$ Hz, 6.20 (dd, 1, pseudoaxial C-5 H, $J_{\text{cis}} = 9.6$ Hz, $J_{\text{gem}} = 17.0$ Hz, 6.23 (s, 3, COOCH_3), 8.20 (m, 2, C-4 H and $\text{CH}-(\text{CH}_3)_2$), 8.81 (s, 3, CH_3 on C-3), 9.13 (d, 6, $(\text{CH}_3)_2\text{-CH}$).

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_2$: C, 58.67; H, 8.75. Found: C, 58.32; H, 8.60.

2. trans-3-Methyl-4-isopropyl-3-carbomethoxy-1-pyrazoline.

Liquid; ir 1740 cm^{-1} (ester C=O), 1557 cm^{-1} (N=N); n.m.r. (CCl_4) τ 5.70 (dd, 1, pseudoequatorial C-5 H, $J_{\text{trans}} = 8.2$ Hz, $J_{\text{gem}} = 17.2$ Hz, 6.01 (dd, 1, pseudoaxial C-5 H, $J_{\text{cis}} = 9.8$ Hz, $J_{\text{gem}} = 17.2$ Hz, 6.30 (s, 3, COOCH_3), 8.66 (m, 2, C-4 H and $\text{CH}-(\text{CH}_3)_2$), 9.05 (d, 6, $(\text{CH}_3)_2\text{-CH}$), 8.30 (s, 3, CH_3 on C-3).

Anal. Calcd. for $\text{C}_9\text{H}_{16}\text{N}_2\text{O}_2$: C, 58.67; H, 8.75. Found: C, 58.78; H, 8.90.

3. cis-3-Methyl-4-isobutyl-3-carbomethoxy-1-pyrazoline.

Liquid; ir 1760 cm^{-1} (ester C=O), 1550 cm^{-1} (N=N); n.m.r.

(CCl₄) τ 5.12 (dd, 1, pseudoequatorial C-5 H, $J_{\text{trans}} = 8.8\text{ Hz}$, $J_{\text{gem}} = 17.6\text{ Hz}$), 6.17 (dd, 1, pseudoaxial C-5 H, $J_{\text{cis}} = 9.8\text{ Hz}$, $J_{\text{gem}} = 17.6\text{ Hz}$), 6.21 (s, 3, COOCH₃), 7.72 (m, 1, C-4 H), 8.79 (s, 3, CH₃ on C-3), 9.14 (m, 9, (CH₃)₂-CH-CH₂-).

Anal. Calcd. for C₁₀H₁₈N₂O₂: C, 60.51; H, 9.14. Found: C, 60.60; H, 9.28.

4. trans-3-Methyl-4-isobutyl-3-carbomethoxy-1-pyrazoline.

Liquid; ir 1740 cm^{-1} (ester C=O), 1555 cm^{-1} (N=N); n.m.r.

(CCl₄) τ 5.19 (dd, 1, pseudoequatorial C-5 H, $J_{\text{trans}} = 8.4\text{ Hz}$, $J_{\text{gem}} = 16.4\text{ Hz}$), 6.10 (dd, 1, pseudoaxial C-5 H, $J_{\text{cis}} = 9.8\text{ Hz}$, $J_{\text{gem}} = 16.4\text{ Hz}$), 6.33 (s, 3, COOCH₃), 8.16 (m, 1, C-4 H), 8.40 (s, 3, CH₃ on C-3), 9.12 (m, 9, (CH₃)₂-CH-CH₂-).

Anal. Calcd. for C₁₀H₁₈N₂O₂: C, 60.51; H, 9.14. Found: C, 60.8; H, 9.20.

5. cis-3-Methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline.

Liquid; ir 1760 cm^{-1} (ester C=O), 1550 cm^{-1} (N=N),; n.m.r.

(CCl₄) τ 5.29 (dd, 1, pseudo equatorial C-5 H, $J_{\text{trans}} = 8.3\text{ Hz}$, $J_{\text{gem}} = 17.0\text{ Hz}$), 6.05 (dd, 1, pseudoaxial C-5 H, $J_{\text{cis}} = 11.6\text{ Hz}$, $J_{\text{gem}} = 17.0\text{ Hz}$), 6.22 (s, 3, COOCH₃), 8.76 (s, 3, CH₃), 9.12 (s, 9, (CH₃)₃C).

Anal. Calcd. for C₁₀H₁₈N₂O₂: C, 60.51; H, 9.14. Found: C, 60.52; H, 9.00.

6. trans-3-Methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline.

Liquid; ir 1740 cm^{-1} (ester C=O), 1550 cm^{-1} (N=N); n.m.r.

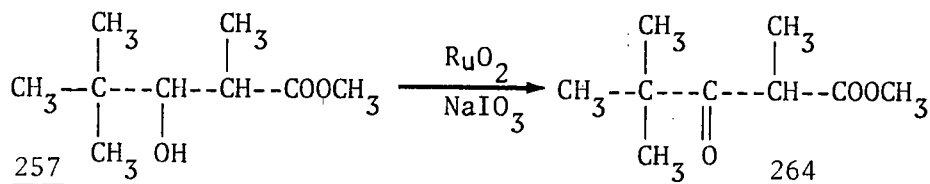
(CCl₄) 5.28 (dd, 1, pseudoequatorial C-5 H, $J_{\text{trans}} = 8.7\text{ Hz}$, $J_{\text{gem}} = 17.0\text{ Hz}$), 5.98 (dd, 1, pseudoaxial C-5 H, $J_{\text{cis}} = 11.8\text{ Hz}$, $J_{\text{gem}} = 17.0\text{ Hz}$), 6.40 (s, 3, COOCH₃), 8.29 (s, 3, CH₃ on C-3), 9.09 (s, 9, (CH₃)₃C).

Anal. Calcd. for C₁₀H₁₈N₂O₂: C, 60.51; H, 9.14. Found: C, 60.56; H, 9.06.

XII. Preparation of cis- and trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline-4d₁.

(a) Preparation of methyl 2,4,4-trimethyl-3-ketopentanoate.

The Reformatski reaction provided methyl 2,4,4-trimethyl-3-hydroxypentanoate which was oxidized to the corresponding β-keto ester by means of RuO₂/NaIO₃:



Into a 1 liter three-necked round-bottom flask equipped with a mechanical stirrer (preferably with a large stirring blade), a condenser and a dropping funnel, 100 ml of water, 17.4 g (0.1 m) β-hydroxy ester dissolved in 200 ml of carbon tetrachloride and 200 mg RuO₂ were placed. The solution of 27 g of sodium metaperiodate in 400 ml of water was added over a period of 4 hours to the stirred

reaction mixture. To control the pH of the mixture during the reaction 80 ml of 10% NaHCO_3 solution was also added in small portions. After the addition of sodium metaperiodate the mixture was stirred for 2 hours, 100 mg of RuO_2 was added and warmed to 70° for 2 hours. The organic phase showed a blackish-yellow colour indicating the presence of RuO_4 , the end of reaction. After cooling it to room temperature, the excess oxidizing agent was destroyed by addition of isopropanol. The separated organic phase was dried (MgSO_4) and distilled giving 12.8 g (82%) b.p.: $115-119^\circ$ (0.5 mm). The quality of the product was checked by gas chromatography using a 12' long stainless steel column packed with 20% Zonyl C-7 on Chrom. W; column temp 170° ; flow rate 60 ml He/min. The crude product contained 1-2% of starting material. After the vacuum distillation the gas chromatogram showed less than 0.5% starting material; n.m.r. (CCl_4) τ 6.17 (q, 1, C-2 H), 6.37 (s, 3, COOCH_3), 8.83 (s, 9, $(\text{CH}_3)_3\text{C}$), 8.93 (d, 3, CH_3 on C-2).

Anal. Calcd. for $\text{C}_9\text{H}_{15}\text{O}_3$: C, 62.71; H, 9.36. Found: C, 62.40; H, 9.33.

(b) Preparation of methyl 2,4,4-trimethyl-3-hydroxypentanoate-
3d₁.

In a 100 ml round bottom flask 30 ml of $\text{CH}_3\text{-OD}$ (98% isotopic purity), 0.1 ml of 30% NaOD in D_2O were placed. This mixture was cooled to -10° and 0.55 g of NaBD_4 (isotopic purity 98%). (The NaBD_4 was only partially dissolved.) To this mixture 8.3 g methyl 2,4,4-trimethyl-3-ketopentanoate was added slowly and stirred (magnetic)

overnight. The reaction product was taken up in 150 ml of water, the pH adjusted to ~ 3 with 10% HCl and extracted with three 50 ml portions of ether. The combined ethereal extract was washed with 20 ml of 5% NaHCO_3 solution, dried (MgSO_4) and concentrated. The vacuum distillation ($140\text{--}150^\circ$ at 10-15 mm) provided 7.2 g (85%) product; n.m.r. (CCl_4) τ 6.32 (s, 3, COOCH_3), 7.40 (m, 2, C-2 H and OH), 8.73 (d, 3, CH_3 on C-2), 9.02 (s, 9, $(\text{CH}_3)_3\text{C}$), peak at τ 6.40 was absent.

Anal. Calcd. for $\text{C}_9\text{H}_{17}\text{DO}_3$: C, 61.71; H, 10.40. Found: C, 61.82; H, 10.57.

(c) Preparation of methyl (E)- and (Z)-2,4,4-trimethylpenten-2-oate-3d₁.

The same procedure was used as for the non deuterated compounds. The olefinic mixture (5.0 g) contained 52% E and 47% Z isomers. Their separation was achieved by preparative gas chromatography, obtaining 1.8 g E and 1.4 g Z isomers.

1. (E)-isomer; ir 1720 cm^{-1} (ester C=O), 1645 cm^{-1} (C=C); n.m.r. (CCl_4) τ 6.37 (s, 3, COOCH_3), 8.10 (s, 3, CH_3 on C-2), 8.80 (s, 9, $(\text{CH}_3)_3\text{D}$), the peak at 3.37 due to the olefinic proton was absent.

Anal. Calcd. for $\text{C}_9\text{H}_{15}\text{DO}_2$: C, 68.79; H, 10.67. Found: C, 68.99; H, 10.15.

2. (Z)-isomer; it contained 1-2% (E)-isomer; ir 1740 cm^{-1} (ester (C=O)), 1660 cm^{-1} (C=C); n.m.r. (CCl_4) τ 6.33 (s, 3, COOCH_3), 8.19 (s, 3, CH_3 on C-2), 8.91 (s, 9, $(\text{CH}_3)_3\text{C}$), the peak at τ 4.60 due to the olefinic proton was absent.

Anal. Calcd. for $\text{C}_9\text{H}_{15}\text{DO}_2$: C, 68.79; H, 10.67. Found: C, 69.08; H, 10.84.

(d) Preparation of cis- and trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline-4d₁.

1. cis-3-Methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline-4d₁.

The treatment of 1.6 g (E)-olefin with diazomethane in ether provided 1.82 g crude pyrazoline which was purified by vacuum distillation (see the procedure for the undeuterated compound). n.m.r. (CCl_4) τ 5.28 (d, 1, pseudoequatorial C-5 H), 6.08 (d, 1, pseudoaxial C-5 H), 6.10 (s, 3, COOCH_3), 8.69 (s, 3, CH_3 on C-2), 9.00 (s, 9, $(\text{CH}_3)_3\text{C}$).

Anal. Calcd. for $\text{C}_{10}\text{H}_{17}\text{DN}_2\text{O}_2$: C, 60.26; H, 9.61. Found: C, 60.32; H, 9.63.

2. trans-3-Methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline-4d₁.

The treatment of 1.3 g olefin with diazomethane in ether solution gave 1.25 g crude product which was purified by the same way as the undeuterated: n.m.r. (CCl_4) τ 5.35 (d, 1, pseudoequatorial C-5 H), 6.01 (d, 1, pseudoaxial C-5 H), 6.40 (s, 3, COOCH_3),

8.29 (s, 3, $\underline{\text{CH}_3}$ on C-3), 9.09 (s, 9, $(\underline{\text{CH}_3})_3\text{C}$).

Anal. Calcd. for $\text{C}_{10}\text{H}_{17}\text{DN}_2\text{O}_2$: C, 60.26; H, 9.61. Found: C, 60.50; H, 9.44.

XIII. Preparation of trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁.

The precursor, ethyl (2)-methacrylate-3-d₁ was prepared by the method of Fowells et al. (68) using Merck Sharp et Dohm reagents (98% isotopic purity). Its n.m.r. spectrum was identical with those reported by Fowells et al., indicating the presence of 10% undeuterated compound. The crude ester was treated with diazomethane and purified by vacuum distillation using a bulb-to-bulb distillation apparatus. bath temp.: 55° (0.05 - 0.1 mm); n.m.r. (CCl_4) τ 5.48 (d, 2, C-5 H's), 5.82 (q, 2, ester $-\underline{\text{CH}_2}$), 8.08 (m, 1, C-4 H), 8.48 (s, 3, $\underline{\text{CH}_3}$ on C-2), 8.77 (t, 3, ester $\underline{\text{CH}_3}$).

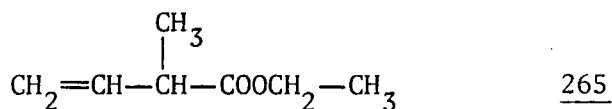
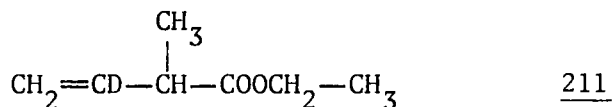
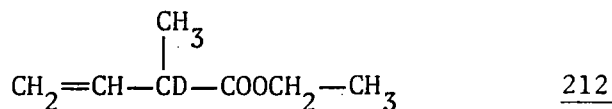
XIV. Product studies of trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁.

(a) Thermal decomposition of trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁.

The products of the thermolysis of trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁ at 127° were analysed on a 20' long, ¼" diameter copper column packed with 20% diisodecyl phthalate on Chrom. W., column temp 135°, flow rate 80 ml He/min. The structural assignments were based on the n.m.r. spectra.

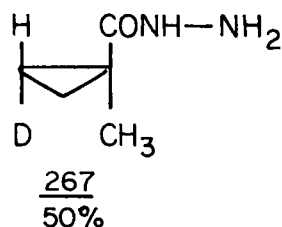
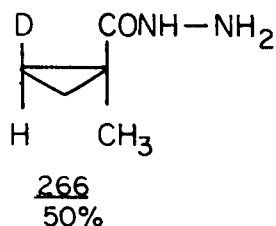
The following compounds were identified:

1. Ethyl 2-methylbuten-2-oate-d₁, β,γ-olefinic ester, ret. time: 12.4 min. The quite complex n.m.r. spectrum indicates the presence of the following three compounds:



n.m.r. (CCl₄) τ 4.96 (m, 2, CH₂=), 5.95 (q, 2 ester CH₂), 7.00 (m, C-3 H), 8.75 (m, ester CH₃, CH₃ on C₂ and C-2 H).

2. 1-Methyl-1-carbethoxycyclopropane-2d₁, ret. time: 16.6 min. n.m.r. (CCl₄) τ 6.03 (q, 2, ester CH₂), 8.80 (s, 3, CH₃), 8.81 (tr. ester CH₃ overlapping with the cyclopropane hydrogens), 9.48 (cyclopropane H). The ethyl ester was converted to hydrazide whose n.m.r. spectrum indicated the presence of the following two isomers:



3. Ethyl angelate-4d₁, ret. time: 18.6 min. n.m.r. (CCl₄)
 τ 4.00 (1, olefinic), 5.89 (q, 2, ester $\underline{\text{CH}_2}$), 8.19 (s, 1, $\underline{\text{CH}_3}$
 and $\underline{\text{CH}_2\text{D}}$), 8.77 (t, 3, ester $\underline{\text{CH}_3}$). (Due to separation difficulties
 only a small amount of compound could be collected, consequently
 the integration was hampered by a large noise to signal ratio.
 However, the shape and the integration of the methyl signals
 clearly showed that the deuterium was incorporated on the methyl
 group attached to the β -carbon.

4. Ethyl tiglate-3d₁, ret. time: 25.5 min, n.m.r. (CCl₄)
 τ 3.39 (broad, 0.10 - 0.2 due to the undeuterated ethyl tiglate,
 the integration was hampered by the large noise to signal ratio),
 5.85 (q, 2, ester $\underline{\text{CH}_2}$), 8.23 (s, 6, $\underline{\text{CH}_3}$'s), 8.73 (t, 3, ester
 $\underline{\text{CH}_3}$).

(b) Direct photolysis of *trans*-3-methyl-3-carbethoxy-1-pyrazoline-
4d₁.

Three grams of pyrazoline was dissolved in 50 ml of isopentane
 and irradiated for 15 hours in a Rayonet Photochemical reactor using
 3100 Å lamps. The careful evaporation of the isopentane yielded a
 product mixture containing the following components:

Ethyl methacrylate-3d ₁	14.2%	ret. time 10.5 min.
β, γ -olefin-d ₁	5.7%	12.4 min.
Cyclopropane prod-d ₁	71.0%	16.6 min.
Ethyl angelate-d ₁	4.4%	18.6 min.
Ethyl tiglate-d ₁	4.7%	25.2 min.

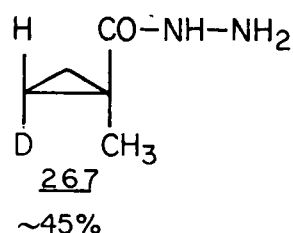
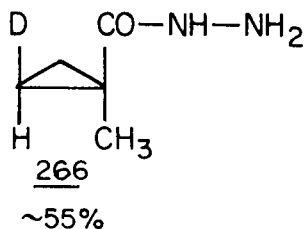
TABLE IX

Photoproducts of *trans*-3-methyl-3-carbethoxy-
 1-pyrazoline-4d₁

The analysis was performed under the same condition described earlier for the analysis of the product mixture obtained from thermolysis. Only the ethyl methacrylate-3d₁ and the 1-methyl-1-carbethoxycyclopropane-2d₁ were collected off the gas chromatograph, the latter was transformed into its hydrazid and the n.m.r. spectra of both were recorded.

The n.m.r. spectrum of the isolated ethyl methacrylate-3d₁ showed a considerable change 0.26; 0.74 in the relative areas of the two peaks at τ 3.96 and 4.54 with respect to the starting material in which the areas had been 0.1; 0.9. (A detailed description of the n.m.r. spectrum of the ethyl(Z-)methacrylate-3d₁ is given by Fowells *et al.* (68).

1-Methyl-1-hydrazidocyclopropane-2d₁ (CCl₄) τ 6.20 (broad, 3, NH-NH₂), 8.70 (s, 3, CH₃), 8.25 (m, 1.35 cycloprop), 9.43 (m, 1.65, cycloprop). The relative areas indicated that the following two isomers were present.



XV. Preparation of 3-methyl-3-carbethoxy-1-pyrazoline.

Commercial ethyl methacrylate was treated with diazomethane in ether. The workup was similar to other pyrazolines. n_D^{20} 1.4492; n.m.r. (CCl₄) τ 5.50 (t, 2, C-5 H's), 5.81 (q, 2, ester CH₂), 8.02 (m, 1, C-4 H), 8.50 (s, 3, CH₃ on C-3), 8.76 (t, 3, ester CH₃).

Anal. Calcd. for C₇H₁₂N₂O₂: C, 53.82; H, 7.68. Found: C, 53.64; H, 7.66.

The products of thermal decomposition were analysed on the same column, on the same day, under the same conditions as described earlier for its analogous-4d₁. The separated components with the exception of ethyl angelate also served as components for making up authentic mixtures.

XVI. Preparation of trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁.

The precursor methyl (Z)-methacrylate-3d₁ was prepared from the corresponding ethyl ester because of the low (5%) yield reported by Fowells et al. (68) by the direct preparation. Sixteen grams of crude ethyl ester was saponified with 100 ml of M sodium hydroxyde solution at room temperature. The solution was filtered and the filtrate extracted with 50 ml of ether to remove byproducts. The clear solution was cooled to -2° and acidified with 65 ml of 2 m HCl. The acid was extracted with three 50 ml portions of ether, dried (MgSO₄) and esterified with diazomethane. Its n.m.r. spectrum was identical with that reported by Fowells et al. (68). They claimed on the basis of the expanded peak at τ 3.96 with relative area 0.1 that it was due to the undeuterated isomer not to the (E)-isomer. In order to obtain more further proof on the presence of methyl methacrylate the methyl group was decoupled by irradiation which resulted in a coalesce of the six peaks (doublet of a quartet) into a doublet with $J_{H_1H_2} = 1.8$ Hz. Identical coupling constant was obtained from the experiment done with simple methyl methacrylate.

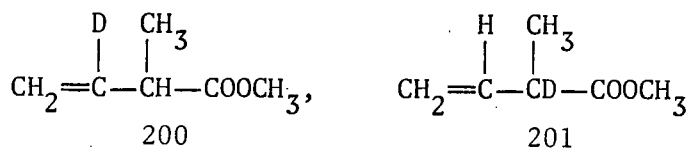
The crude ester was treated with diazomethane in ether and purified by vacuum distillation; n.m.r. (CCl_4) τ 5.43 (d, 1, C-5 H), 5.55 (d, 1, C-5), 6.32 (s, 3, COOCH_3), 8.55 (s, 3, CH_3), 8.61 (m, 1, C-4 H).

XVII. Product studies of trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁.

(a) Thermal decomposition.

Two grams of pyrazoline was decomposed thermally (at 127°) and the products were analysed on a 30' long $\frac{1}{4}$ " diameter copper column packed with 15% diisodecylphthalate on Chrom. W; column temp.: 110°; flowrate 80 ml He/min. The individual components were collected off the gas chromatograph and their n.m.r. spectra were recorded.

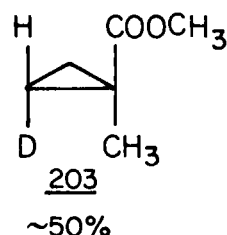
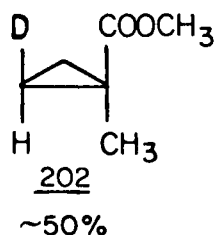
1. β,γ -Olefinic ester; ret. time: 8.2 min; n.m.r. (CCl_4) τ 4.88 (broad, 2, $=\text{CH}_2$), 5.06 (m \sim 0.2, $=\text{CH}$), 6.35 (s, 3, COOCH_3), 6.74 (m, \sim 0.7 - .8, C-2 H), 8.75 (s, 3, CH_3). The integration of the peaks indicated that the sample consisted of two compounds



major component. (The accuracy of the integration was reduced by the large signal to noise ratio.)

2. 1-Methyl-1-carbomethoxycyclopropane-2d₁; ret. time: 11.4 min; n.m.r. (CCl_4) τ 6.41 (s, 3, COOCH_3), 8.74 (s, 3, CH_3), 8.92 (s, 1.5, cyclopropane H's cis to carbomethoxy), 9.47 (s, 1.5, cyclopropane H's). The integration of the peaks at τ 8.92

and 9.47 indicated that the sample was a 1:1 mixture of the two isomers.



3. Methyl angelate-4d₁; ret. time: 12.5 min; n.m.r. (CCl₄)
 τ 4.00 (broad, 1, olefinic), 6.30 (s, 3, COOCH₃), 8.16 (s + shoulder, \sim 5, CH₃, CH₂D). The n.m.r. spectrum clearly indicated that the deuterium was on C-4 whose hydrogens appeared at somewhat lower fields due to the deshielding effect of the carbomethoxy group.

4. Methyl tiglate-3d₁; ret. time: 17.3 min; n.m.r. (CCl₄)
 τ 3.33 (broad, very small, due to the undeuterated isomer),
 6.31 (s, 3, COOCH₃), 8.20 (s, 6, the two CH₃).

(b) Direct photolysis of *trans*-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁.

The photolysis was carried out in a Rayonet Photochemical reactor in isopentane solution using 3100 Å lamps. The workup was similar to that described earlier for the ethyl ester. No quantitative analysis was done on the product mixture and only the cyclopropane product was

collected. The n.m.r. spectrum indicated a 45:55 mixture of 202 and 203.

(c) Sensitized photolysis of *trans*-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁.

Three grams of benzophenone and 0.3 g pyrazoline was dissolved in 30 ml isopentane and photolyzed using 3500 Å lamps. The workup followed a repetition of an evaporation-cooling-filtration cycle till about 0.5 - 0.6 ml yellowish liquid was obtained still containing some benzophenone. The decomposition products were distilled off the benzophenone in a bulb-to-bulb apparatus (bath temp.: 140-150°) and separated by gas chromatography. Only the cyclopropane derivative was collected and its n.m.r. spectrum recorded, showing that the sample consisted of 50:50 mixture of 202 and 203.

XVIII. Preparation of *cis*-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁.

The preliminary experiments showed that the bromine in β-bromo methacrylic acid could be replaced by hydrogen using copper-activated Zn-dust in refluxing methanol. The application of deuterated reagents gave a mixture containing 80 - 89% (E) and (Z)-methacrylic acid-3d₁.

Procedure: into a three-necked round bottom flask equipped with a mechanical stirrer and a condenser 10 g of dry sodium (Z)-β-bromomethacrylate, 30 ml of CH₃-OD, 4 ml of D₂O and 5 ml of 38% DCl in D₂O were added and stirred for 10 minutes. Ten grams of predried

Zn dust and 0.05 g Cu_2Cl_2 were added at once. The slurry was refluxed and stirred for 24 hours. The mixture was cooled to room temperature and 100 ml 10% HCl added to it. The freed acid was extracted with two 30 ml portions of ether, dried (MgSO_4) and esterified with diazomethane. Yield: 3.1 g (62%) estimated by gas chromatography.

Catalytic reduction of sodium (E)- β -bromomethacrylate in D_2O in the presence of equivalent amounts of NaOD or Et_3N also gave (E)- and (Z)-methacrylic acid - 3d_1 . The ratio of the E and Z isomers present in the product mixture was dependent on the activity and the amount of catalyst used. By applying only a small amount (0.5 - 1.0% of the sodium salt) of catalyst, 5% Pd or Pt on charcoal product mixtures were obtained containing 95 - 98% E isomer. The methods drawback is the relatively long reaction time of 2-3 days. During the reaction some polymerization has also taken place. The workup was similar to that described for the Zn reduction. Yields varied between 25 - 40%; n.m.r. (CCl_4) τ 3.98 (q, 1, olefinic H cis to the carbomethoxy), 4.54 (broad, small, olefinic H trans to the carbomethoxy), 6.32 (s, 3, COOCH_3), 8.12 (d, 3, CH_3). The origin of the small peak at τ 4.54 was attributed to the Z isomer on the basis of n.m.r. studies. The methyl group was decoupled by irradiation with the result that the six peaks (doublet of a quartet) at τ 4.54 collapsed into a singlet.

The ester was treated with diazomethane in ether. The evaporation of ether resulted in a yellowish liquid, the crude pyrazoline which was distilled in vacuum; n.m.r. (CCl_4) τ 5.30 (s, 1, C-5 H), 5.41 (s,

1, C-5 H), 6.19 (s, 3, COOCH₃), 7.49 (tt, 1, C-4 H), 8.41 (s, 3, CH₃).

XIX. Product studies of cis-3-methyl-3-carbomethoxy-1-pyrazoline.

(a) Thermal decomposition.

It was done in the same way described earlier for the trans-isomer. Quantitative product analysis has not been done and the cyclopropane product was collected only. Its n.m.r. spectrum indicated that the sample consisted of the two isomers

(b) Sensitized photolysis.

It was done in the same way as described for the trans-isomer. The results were also identical.

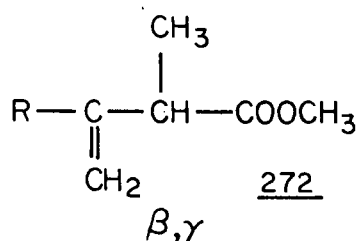
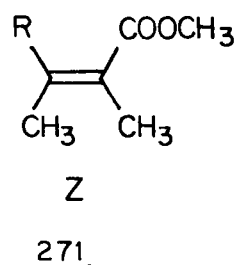
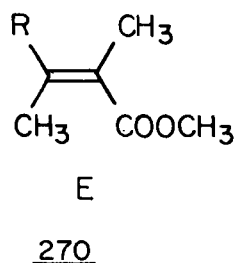
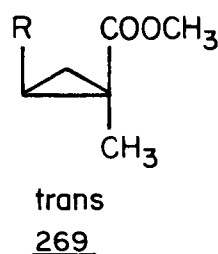
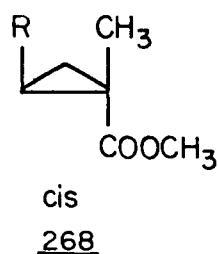
XX. Product studies of cis- and trans-3-methyl-4-alkyl-3-carbomethoxy-1-pyrazolines.

1. Thermal decomposition.

General procedure. In a 5 ml round bottom flask equipped with a condenser 1.0 - 1.5 g pyrazoline was placed and heated in an oil bath at an appropriate temperature for a period ten half life time. The resulting product mixture was analysed by gas chromatography. The structure assignment of the individual components were based on their n.m.r. and i.r. spectra. In some cases there was not enough sample available for isolation due to the low yields and retention

times were used for identification.

The thermal decomposition of cis- and trans-3-methyl-4-alkyl-3-carbomethoxy-1-pyrazolines produced a mixture consisting of cis- and trans-cyclopropane derivatives of (E) and (Z) olefinic esters (α,β) and β,γ -olefinic esters.



In order to determine the stereochemistry of the 1-methyl-2-alkyl-1-carbomethoxy cyclopropanes it was necessary to find out whether the two alkyl groups, i.e. R and methyl, were cis or trans to each other. The assignment was based on the comparison between the first

and the last member of a series and the assumption that if they showed similar patterns in n.m.r. spectroscopy, rate of saponification and gas chromatographic retention times they should have similar stereochemistry. The n.m.r. spectra of the cis isomers showed a proton signal around τ 9.6 due to the cyclopropane hydrogen while the trans isomer exhibits no signal in this region. The rate of saponification of the cis isomers are higher than for the trans ones due to stereochemical grounds (14). The trans isomers tend to have a shorter gas chromatographic retention time on most columns packed with polar or semipolar stationary phases on Chrom. P or W. Probably the best proof would be to synthesize the cyclopropane products by way of stereospecific methylene addition to the olefinic ester. One unsuccessful attempt has been made to add methyl generated by the method of Simons-Smith to both; methyl(E)- and (Z)-2,4,4-trimethylpentene-2-oate.

The amount of β,γ -olefinic esters in the product mixtures are quite small, in most cases n.m.r. spectroscopy was used to identify them.

The stereochemical assignment for the α,β -olefinic esters was based on n.m.r. spectroscopy and retention times. When the methyl group is cis to the carbomethoxy its signal tends to appear at lower field because of the deshielding effect of the carbomethoxy group. On most columns packed with polar or semipolar stationary phases the Z isomers have shorter retention times.

(a) cis-3-Methyl-4-isopropyl-3-carbomethoxy-1-pyrazoline.

The analysis was carried out on a 20' long copper column packed with 20% diisodeylphthalate on Chrom. P.; column temp.: 165°; flow-rate 120 ml He/min.

1. The first peak, ret. time: 8.1 min was due to methyl 2-methyl-3-isopropylbuten-3-oate; n.m.r. (CCl_4) τ 4.57 (broad, 2, $=\text{CH}_2$), 6.37 (s, 3, COOCH_3), 7.00 (q, 1, C-2 H), 8.64 (d, 3, CH_3 on C-2), 9.24 (m, 7, $\text{CH}(\text{CH}_3)_2$).

2. trans-1-Methyl-2-isopropyl-1-carbomethoxycyclopropane; ret. time: 1.2 min; n.m.r. (CCl_4) τ 6.39 (s, 3, COOCH_3), 8.74 (s, 3, CH_3 on cyc.), 8.97 (m, 10, $\text{CH}(\text{CH}_3)_2$ and cyclopropyl H's).

3. cis-1-Methyl-2-isopropyl-1-carbomethoxycyclopropane; ret. time: 15.0 min; n.m.r. (CCl_4) τ 6.40 (s, 3, COOCH_3), 8.73 (s, 3, CH_3 on cyclpr.), 9.00 (overlapping, 9, $\text{CH}(\text{CH}_3)_2$ and cyclopropyl H's), 9.66 (s, 1, cycloprop. H).

4. Methyl (E)-2,3,4-trimethylpenten-2-oate; ret. time: 19.4 min; n.m.r. (CCl_4) τ 6.40 (s, 3, COOCH_3), 9.19 (m, 1, C-4 H), 8.22 (s, 6, CH_3 's on C-2 and C-3), 9.09 (d, 6, CH_3)₂ C).

(b) trans-3-Methyl-4-isopropyl-3-carbomethoxy-1-pyrazoline.

It was decomposed at 150°. The resulting product mixture was analysed on the same column under the same conditions as that of cis-isomer.

1. trans-1-Methyl-2-isopropyl-1-carbomethoxycyclopropane; ret. time: 11.2 min; its n.m.r. spectrum was described earlier.
2. cis-1-Methyl-2-isopropyl-1-carbomethoxycyclopropane; ret. time: 15.0 min; its n.m.r. spectrum was described earlier.
3. Methyl (Z)-2,3,4-trimethylpenten-2-oate; ret. time: 16.5 min; n.m.r. (CCl₄) τ 6.32 (s, 3, COOCH₃), 6.70 (m, 1, C-4 H), 8.19 (s, 3, CH₃ on C-2), 8.37 (s, 3, CH₃ on C-3), 9.00 (d, 6, (CH₃)₂CH).

(c) cis-3-Methyl-4-isobutyl-3-carbomethoxy-1-pyrazoline.

It was decomposed at 150° and the analysis was carried out on a 20' long copper column packed with 20% diisodecylphthalate on Chrom. P; column temp.: 165°; flowrate 130 ml He/min. The following compounds were identified:

1. Methyl 2,5-dimethyl-3-methylenehexen-3-oate; ret. time: 13.8 min; n.m.r. (CCl₄) τ 5.15 (d, 2, CH₂=), 6.38 (s, 3, COOCH₃), 8.10 (m, 1, C-2 H), 8.78 (s, 3, CH₃ on C-2), 9.10 (m, 9, (CH₃)₂-CH-CH₂).

2. cis-1-Methyl-2-isobutyl-1-carbomethoxycyclopropane; ret. time: 18.6 min; n.m.r. (CCl_4) τ 6.39 (s, 3, COOCH_3), 8.73 (m, 2, $\text{CH}_2\text{-CH}$), 8.78 (s, 3, CH_3 on cycloprop.), 9.08 (d, 6, $(\text{CH}_3)_2\text{D}$, $\underline{J} = 6.0$ Hz), 9.68 (d (unresolved), 1, cyclopropane H).

3. Methyl E-2,3,5-trimethylhexen-3-oate; ret. time: 21.0 min; n.m.r. (CCl_4) τ 6.33 (s, 3, COOCH_3), 8.07 (m, 5, CH_3 on C-2 and C-4 H's), 8.17 (s, 3, CH_3 on C-3), 9.08 (d, 7, $(\text{CH}_3)_3\text{CH}$, $\underline{J} = 8.0$ Hz).

(d) trans-3-Methyl-4-isobutyl-3-carbomethoxy-1-pyrazoline.

It was decomposed and the resulting product mixture analysed in the same way as for the product mixture of the cis isomer.

1. The first peak, ret. time: 14.0 min, was due to trans-1-methyl-2-isobutyl-1-carbomethoxycyclopropane; n.m.r. (CCl_4) τ 6.21 (s, 3, COOCH_3), 8.60 (s, 3, CH_3 on cyclopr.), 9.00 (m, 12 $(\text{CH}_3)_2\text{CH-CH}_2\text{-}$ and cyclopropane H's).

2. Methyl (Z)-2,3,5-trimethylhexen-3-oate; ret. time: 17.8 min; n.m.r. (CCl_4), (due to poor separation the sample also contained cis-1-methyl-2-isobutyl-1-carbomethoxycyclopropane); τ 6.37 (s, 3, COOCH_3), 8.24 (complex, 6, CH_3 's on C-2 and C-3), 9.05 (complex, 9, $(\text{CH}_3)_2\text{-CH-CH}_2\text{-}$).

3. cis-1-Methyl-2-isobutyl-1-carbomethoxycyclopropane. It was described earlier.

(e) cis-3-Methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline.

It was decomposed at 155° giving only one product, 1-methyl-2-tert-butyl-1-carbomethoxycyclopropane; b.p. 190.3°; n.m.r. (CCl₄) τ 6.38 (s, 3, COOCH₃), 8.76 (s, 3, CH₃ on cyclopr.), 8.95 (s, 11, (CH₃)₃C and cycloprop. H's), 9.40 (d, 1, cyclopropyl H).

Anal. Calcd for C₁₀H₁₈O₂: C, 70.48; H, 10.65. Found: C, 70.77; H, 10.33.

(f) trans-3-Methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline.

It gave only cyclopropane product trans-1-methyl-2-tert-butyl-1-carbomethoxycyclopropane; b.p. 173.7°; n.m.r. (CCl₄) τ 6.40 (s, 3, COOCH₃), 8.75 (s, 3, CH₃ on cyclopr.), 9.08 (s, 11, (CH₃)₃C and cycloprop. H).

Anal. Calcd for C₁₀H₁₈O₂: C, 70.48; H, 10.65. Found: C, 70.22; H, 10.67.

2. Photodecompositions

The direct and benzophenone sensitized photolyses of cis- and trans-3-methyl-4-tert-butyl-1-carbomethoxy-1-pyrazolines gave only cis- and trans-1-methyl-2-tert-butyl-1-carbomethoxycyclopropanes respectively. The procedures for photolyses and work-up have been described earlier.

KINETIC MEASUREMENTS

The rates of decomposition of pyrazolines were determined by volumetric measurements of the evolved nitrogen using a slightly modified apparatus described by Peterson and coworkers (69). The reaction flask was immersed in a constant temperature bath made by the Haake Company. The thermostat could maintain the desired temperature within $\pm 0.02 - 0.05^{\circ}\text{C}$ under 135° as claimed by the manufacturer but above that the range became $\pm 0.1^{\circ}\text{C}$.

The solvent di-(n-butyl)-phthalate reagent grade was distilled twice at reduced pressure.

For kinetic runs standard solution of pyrazolines were prepared so that about 1 ml of pyrazoline solution would yield around 30 ml of nitrogen.

General Procedure for Kinetic Runs

Forty-nine ml of di-(n-butyl)-phthalate was preheated at the appropriate temperature, stirred and purged with nitrogen for 30 minutes, then when the nitrogen bubbling stopped it was stirred for an additional 30 minutes to allow equilibration. The solution of the pyrazoline was injected by a syringe through a rubber septum. All runs were followed

up to 80% completion and then kept for 10 half lives in the bath to obtain the final volume. The experimental and the calculated final volumes were within $\pm 2\%$. The barometric pressure changes were also monitored during the kinetic runs.

The kinetic runs with deuterated compounds were done immediately after the corresponding nondeuterated pyrazolines.

The rate constants were calculated on Hewett-Packard's desk calculator using the method of least squares.

Since the deuteration of the trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁ and the trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁ was only 90% correction had to be made in the rate of decomposition. The corrections were based on the assumption that the decompositions of the pyrazolines and their analogous -4d₁ are concurrent reactions, then the rate constants for the mixtures can be expressed as follows:

$$k_{D \text{ meas}} = 0.1 k_H + 0.9 k_D \quad (1)$$

The measured over-all deuterium kinetic isotope effect is given by eqn. (2).

$$\frac{k_H}{k_{D \text{ meas}}} = \frac{k_H}{0.1 k_H + 0.9 k_D} \quad (2)$$

If we assume that the individual processes involved in pyrazoline decompositions are parallel reactions we can calculate the specific deuterium kinetic isotope effects for each separate pathway from the over-all kinetic isotope effect and the product distributions.

The rate constant for the thermolysis of a pyrazoline can be expressed as follows:

$$k_H = k_{1H} + k_{2H} + \dots + k_{nH} \quad (3)$$

Similarly, the rate constant for the thermal decomposition of a deuterated pyrazoline can be given as

$$k_D = k_{1D} + k_{2D} + \dots + k_{nD} \quad (4)$$

where k_{1H} , k_{2H} , \dots , k_{nH} are the rate constants for the individual reactions involved in the decomposition of a pyrazoline and k_{1D} , k_{2D} , \dots , k_{nD} are the rate constants concerning the deuterated compound.

According to the rate law the formation of the individual reaction products can be expressed as

$$\frac{dC_{1H}}{dt} = k_{1H} C_H, \quad (5)$$

$$\frac{dC_{nH}}{dt} = k_{nH} C_H, \quad (6)$$

$$\frac{dC_{1D}}{dt} = k_{1D} C_D, \quad (7)$$

$$\frac{dC_{nD}}{dt} = k_{nD} C_D \quad (8)$$

where C_{1H} , C_{nH} are the concentration of products and C_{1D} , C_{nD} are the concentration of the deuterated products.

Dividing eqn. (5) by eqn. (6), and eqn. (7) by eqn. (8) we obtain,

$$\frac{dC_{1H}}{dC_{nH}} = \frac{k_{1H}}{k_{nH}}, \quad (9)$$

$$\frac{dC_{1D}}{dC_{nD}} = \frac{k_{1D}}{k_{nD}} \quad (10)$$

The integration of eqn. (9) and eqn. (10), assuming that C_{1H} , C_{2H} , ..., C_{nH} and C_{1D} , C_{2D} , ..., $C_{nD} = 0$ at $t = 0$, yields the results,

$$\frac{C_{1H}}{C_{nH}} = \frac{k_{1H}}{k_{nH}}, \quad (11)$$

$$\frac{C_{1D}}{C_{nD}} = \frac{k_{1D}}{k_{nD}} \quad (12)$$

It follows that,

$$C_{1H}:C_{2H}::\dots::C_{nH} = k_{1H}:k_{2H}::\dots::k_{nH} \quad (13)$$

$$C_{1D}:C_{2D}::\dots::C_{nD} = k_{1D}:k_{2D}::\dots::k_{nD} \quad (14)$$

The division of eqn. (3) by k_{1H} and eqn. (4) by k_{1D} yields,

$$\frac{k_H}{k_{1H}} = 1 + \frac{k_{2H}}{k_{1H}} + \dots + \frac{k_{nH}}{k_{1H}} = A \quad (15)$$

$$\frac{k_D}{k_{1D}} = 1 + \frac{k_{2D}}{k_{1D}} + \dots + \frac{k_{nD}}{k_{1D}} = B \quad (16)$$

Dividing eqn. (15) by eqn. (16) we get,

$$\frac{\frac{k_H}{k_{1H}}}{\frac{k_D}{k_{1D}}} = \frac{A}{B} \quad (17)$$

The rearrangement and substitution of D for $\frac{k_H}{k_D}$ give,

$$\frac{k_{1H}}{k_{1D}} = \frac{BD}{A} \quad (18)$$

The values of A and B are obtained from product studies and D from kinetic measurements.

I. Rate constants, activation parameters and overall deuterium kinetic isotope effect of 3-methyl-3-carbomethoxy-1-pyrazoline and trans-3-methyl-3-carbomethoxy-1-pyrazoline-4d₁.

(a) Rate constants.

Name of compound	t°	kx10 ⁻⁴	
3-methyl-3-carbomethoxy-1-pyrazoline	122.85	3.43	$\Delta H = 33.45 \text{ kcal}$
	122.85	3.25	
	124.85	4.31	$\Delta S = 9.52 \text{ e.u.}$
	124.85	4.54	
	127.27	5.37	
	127.26	5.36	
90% <u>trans</u> -3-methyl-3-carbomethoxy-1-pyrazoline-4d ₁ , + 10% undeuterated isomer	122.85	2.91	$\Delta H = 33.60 \text{ kcal}$
	124.85	3.87	
	127.32	4.65	$\Delta S = 9.61 \text{ e.u.}$

(b) Overall deuterium kinetic isotope effects.

$$1. \quad \frac{k_H}{k_D} = \frac{\frac{3.43 + 3.25}{2} \times 10^{-4}}{2.91 \times 10^{-4}} = 1.15$$

$$2. \quad \frac{k_H}{k_D} = \frac{\frac{4.31 + 4.54}{2} \times 10^{-4}}{3.87 \times 10^{-4}} = 1.14$$

$$3. \quad \frac{k_H}{k_H} = \frac{\frac{5.37 + 5.36}{2} \times 10^{-4}}{4.65 \times 10^{-4}} = 1.16$$

(c) Corrected overall deuterium kinetic isotope effects.

$$1. \quad \frac{k_H}{k_D} = 1.18$$

$$2. \quad \frac{k_H}{k_D} = 1.16 \quad \sim \quad \underline{\underline{1.17}}$$

$$3. \quad \frac{k_H}{k_D} = 1.18$$

(d) Specific deuterium kinetic isotope effects.

1. Deuterium kinetic isotope effect for β, γ -olefin formation:

$$\frac{k_H}{k_{\beta, \gamma H}} = 1 + \frac{64.4}{4.5} + \frac{14.3}{4.5} + \frac{16.45}{4.5} = 22.14$$

$$\frac{k_D}{k_{\beta, \gamma D}} = 1 + \frac{69.3}{3.5} + \frac{9.7}{3.5} + \frac{17.7}{3.5} = 27.62$$

$$\frac{\frac{k_H}{k_{\beta, \gamma H}}}{\frac{k_D}{k_{\beta, \gamma D}}} = \frac{22.14}{27.62} \quad \frac{k_H}{k_D} = \frac{1.17}{0.80} = 1.46$$

2. Deuterium kinetic isotope effect for cyclopropane formation:

$$\frac{k_H}{k_{cyc H}} = \frac{4.5}{64.4} + 1 + \frac{14.3}{64.4} + \frac{16.5}{64.4} = 1.55$$

$$\frac{k_D}{k_{cyc D}} = \frac{3.5}{69.3} + 1 + \frac{9.7}{69.3} + \frac{17.7}{69.3} = 1.46$$

$$\frac{\frac{k_H}{k_{cycH}}}{\frac{k_D}{k_{cycD}}} = \frac{1.55}{1.46} \quad \frac{k_H}{k_D} = \frac{1.17}{1.06} = \underline{\underline{1.10}}$$

3. Deuterium kinetic isotope effect for methyl angelate formation:

$$\frac{k_H}{k_{angH}} = \frac{4.5}{14.3} + \frac{64.4}{14.3} + 1 + \frac{16.5}{14.3} = 6.95$$

$$\frac{k_D}{k_{angD}} = \frac{3.5}{9.7} + \frac{69.3}{9.7} + 1 + \frac{17.7}{9.7} = 10.32$$

$$\frac{\frac{k_H}{k_{angH}}}{\frac{k_D}{k_{angD}}} = \frac{6.95}{10.32} \quad \frac{k_H}{k_D} = \frac{1.17}{0.673} = \underline{\underline{1.74}}$$

4. Deuterium kinetic isotope effect for methyl tiglate formation:

$$\frac{k_H}{k_{tigH}} = \frac{4.5}{16.5} + \frac{64.4}{16.5} + \frac{14.3}{16.5} + 1 = 6.04$$

$$\frac{k_D}{k_{tigD}} = \frac{3.5}{17.7} + \frac{69.3}{17.7} + \frac{9.7}{17.7} + 1 = 5.66$$

$$\frac{\frac{k_H}{ktig_H}}{\frac{k_D}{ktig_D}} = \frac{6.04}{5.66} \quad \frac{k_H}{k_D} = \frac{1.17}{1.07} = \underline{\underline{1.09}}$$

II. Rate constants, activation parameters and overall deuterium kinetic isotope effect of 3-methyl 3-carbethoxy-1-pyrazoline and trans-3-methyl-3-carbethoxy-1-pyrazoline-4d₁.

(a) Rate constants.

Name of compound	t°	kx10 ⁻⁴	
3-methyl-3- carbethoxy- 1-pyrazoline	117.89	1.74	ΔH = 33.20 kcal mol ⁻¹
	117.89	1.83	ΔS = 8.67 e.u.
	119.81	2.11	
	119.81	2.21	
	122.95	3.14	
	127.01	4.71	
	126.95	4.63	
<u>trans</u> -3-methyl-3- carbethoxy-1-pyrazoline- 4-d ₁	117.89	1.65	ΔH = 32.37 kcal mol ⁻¹
	117.89	1.67	ΔS = 6.14 e.u.
	119.81	1.98	
	122.95	2.82	
	126.95	4.18	
	127.01	4.30	

(b) Overall deuterium kinetic isotope effect.

$$1. \quad \frac{(1.74 + 1.83) \times 10^{-4}}{(1.65 + 1.67) \times 10^{-4}} = 1.07$$

$$2. \quad \frac{\frac{(2.11 + 2.21)}{2}}{1.98} = 1.09$$

$$3. \quad \frac{3.14 \times 10^{-4}}{2.82 \times 10^{-4}} = 1.11$$

$$4. \quad \frac{4.63 \times 10^{-4}}{4.18 \times 10^{-4}} = 1.11$$

$$5. \quad \frac{4.71 \times 10^{-4}}{4.30 \times 10^{-4}} = 1.09$$

(c) Corrected overall deuterium kinetic isotope effects.

$$1. \quad \frac{1.78}{0.178 + 0.9 K_D} = 1.070$$

$$\frac{k_H}{k_D} = 1.08$$

$$2. \quad \frac{k_H}{k_D} = 1.12$$

$$3. \quad \frac{k_H}{k_D} = 1.13$$

$$4. \quad \frac{k_H}{k_D} = 1.13 \quad \sim \quad \underline{\underline{1.12}}$$

$$5. \quad \frac{k_H}{k_D} = 1.10$$

(d) Specific deuterium kinetic isotope effects.

1. Deuterium kinetic isotope effect for β, γ -olefin formation:

$$\frac{k_H}{k_{\beta, \gamma H}} = 1 + \frac{70.4}{4.2} + \frac{12.6}{4.2} + \frac{13.0}{4.2} = 23.86$$

$$\frac{k_D}{k_{\beta, \gamma D}} = 1 + \frac{74.4}{3.6} + \frac{8.9}{3.6} + \frac{13.2}{3.6} = 27.81$$

$$\frac{\frac{k_H}{k_{\beta, \gamma H}}}{\frac{k_D}{k_{\beta, \gamma D}}} = \frac{23.86}{27.81} \quad \frac{k_H}{k_D} = \frac{1.12}{0.858} = \underline{\underline{1.30}}$$

2. Deuterium kinetic isotope effect for cyclopropane formation:

$$\frac{k_H}{k_{\text{cyc}_H}} = \frac{4.2}{70.4} + 1 + \frac{12.6}{70.4} + \frac{13.0}{70.4} = 1.424$$

$$\frac{k_D}{k_{\text{cyc}_D}} = \frac{3.6}{74.4} + 1 + \frac{8.9}{74.4} + \frac{13.2}{74.4} = 1.345$$

$$\frac{\frac{k_H}{k_{cyc_H}}}{\frac{k_D}{k_{cyc_D}}} = \frac{1.424}{1.345} \quad \frac{k_H}{k_D} = \frac{1.12}{1.058} = \underline{\underline{1.06}}$$

3. Deuterium kinetic isotope effect for ethyl angelate formation:

$$\frac{k_H}{k_{ang_H}} = \frac{4.2}{12.6} + \frac{70.4}{12.6} + 1 + \frac{13.0}{12.6} = 7.95$$

$$\frac{k_D}{k_{ang_D}} = \frac{3.6}{8.9} + \frac{74.4}{8.9} + 1 + \frac{13.2}{8.9} = 11.247$$

$$\frac{\frac{k_H}{k_{ang_H}}}{\frac{k_D}{k_{ang_D}}} = \frac{7.95}{11.247} = \frac{k_H}{k_D} = \frac{1.12}{0.707} = \underline{\underline{1.58}}$$

4. Deuterium kinetic isotope effect for ethyl tiglate formation:

$$\frac{k_H}{k_{tig_H}} = \frac{4.2}{13.0} + \frac{70.4}{13.0} + \frac{12.6}{13.0} + 1 = 7.704$$

$$\frac{k_H}{k_{tig_D}} = \frac{3.6}{13.2} + \frac{74.4}{13.2} + \frac{8.9}{13.2} + 1 = 7.583$$

$$\frac{\frac{k_H}{k_{tig_H}}}{\frac{k_D}{k_{tig_D}}} = \frac{7.704}{7.583} \quad \frac{k_H}{k_D} = \frac{1.12}{1.015} = \underline{\underline{1.10}}$$

III. Rate constants and activation parameters of *cis*- and *trans*-3-methyl-4-alkyl-3-carbomethoxy-1-pyrazolines.

Name of compound	t°	kx10 ⁻⁴ sec ⁻¹	
<u><i>cis</i>-3-methyl-4-iso-propyl-3-carbomethoxy-1-pyrazoline</u>	141.0	1.61	ΔH = 36.60 kcal mol ⁻¹
	147.0	2.74	ΔS = 11.75 e.u.
	151.0	4.40	
	151.3	4.79	
<u><i>trans</i>-3-methyl-4-iso-propyl-3-carbomethoxy-1-pyrazoline</u>	156.5	1.59	ΔH = 34.50 kcal mol ⁻¹
	160.5	2.71	ΔS = 3.91 e.u.
	164.5	4.41	
	169.6	5.77	
<u><i>cis</i>-3-methyl-4-iso-butyl-3-carbomethoxy-1-pyrazoline</u>	144.5	2.14	ΔH = 35.30 kcal mol ⁻¹
	147.0	2.80	ΔS = 8.55 e.u.
	154.5	5.85	
<u><i>trans</i>-3-methyl-4-iso-butyl-3-carbomethoxy-1-pyrazoline</u>	144.5	0.78	ΔH = 35.00 kcal mol ⁻¹
	147.1	0.94	ΔS = 5.76 e.u.
	150.0	1.36	
	152.5	1.68	

IV. Rate constants, activation parameters and deuterium kinetic isotope effect of *cis*-3-methyl-4-*tert*-butyl-3-carbomethoxy-1-pyrazoline and its analogue-4d₁.

Name of compound	t°	kx10 ⁻⁴ sec ⁻¹	ΔH = 35.67 kcal mol ⁻¹ ΔS = 9.90
<u><i>cis</i>-3-methyl-4-<i>tert</i>-butyl-3-carbomethoxy-1-pyrazoline</u>	141.00	2.02	
	147.00	3.73	
	151.00	5.17	
	151.39	5.39	
	151.49	5.51	
	154.20	6.97	
	154.50	7.57	

Name of compound	t°	kx10 ⁻⁴ sec ⁻¹	
<u>cis-3-methyl-4-tert-</u>	151.39	4.49	ΔH = 36.36 kcal mol ⁻¹
<u>butyl-3-carbomethoxy-</u>	151.49	5.01	ΔS = 11.32 e.u.
<u>1-pyrazoline-4-d₁</u>	154.20	6.44	
	154.50	6.89	

(a) Deuterium kinetic isotope effects.

$$\begin{aligned}
 1. \quad \frac{k_H}{k_D} &= \frac{5.39 \times 10^{-4}}{4.94 \times 10^{-4}} = 1.091 \\
 2. \quad \frac{k_H}{k_D} &= \frac{5.51 \times 10^{-4}}{5.01 \times 10^{-4}} = 1.099 \\
 &= \underline{\underline{1.093 \pm 0.008}} \\
 3. \quad \frac{k_H}{k_D} &= \frac{6.97 \times 10^{-4}}{6.44 \times 10^{-4}} = 1.082 \\
 4. \quad \frac{k_H}{k_D} &= \frac{7.57 \times 10^{-4}}{6.89 \times 10^{-4}} = 1.098
 \end{aligned}$$

V. Rate constants, activation parameters and deuterium kinetic isotope effect of trans-3-methyl-4-tert-butyl-3-carbomethoxy-1-pyrazoline and its analogue-4d₁.

Name of compound	t°	kx10 ⁻⁴ sec ⁻¹	
<u>trans-3-methyl-4-</u>	148.70	1.28	ΔH = 36.20 kcal mol ⁻¹
<u>tert-butyl-3-carbo-</u>	148.84	1.31	ΔS = 8.80 e.u.
<u>methoxy-1-pyrazoline</u>	150.96	1.59	
	153.30	1.97	
	154.00	2.30	

Name of compound	t°	kx10 ⁻⁴ sec ⁻¹	
<u>trans-3-methyl-4-</u>	148.84	1.20	ΔH = 36.67 kcal mol ⁻¹
<u>tert-butyl-3-carbo-</u>	150.96	1.48	ΔS = 9.74 e.u.
<u>methoxy-1-pyrazoline-</u>	153.30	1.89	
<u>4d₁.</u>			

(a) Deuterium kinetic isotope effects.

$$\begin{aligned}
 1. \quad \frac{k_H}{k_D} &= \frac{1.31 \times 10^{-4}}{1.20 \times 10^{-4}} = 1.091 \\
 2. \quad \frac{k_H}{k_D} &= \frac{1.59 \times 10^{-4}}{1.48 \times 10^{-4}} = 1.074 \quad \sim \underline{\underline{1.069 \pm 0.024}} \\
 3. \quad \frac{k_H}{k_D} &= \frac{1.97 \times 10^{-4}}{1.89 \times 10^{-4}} = 1.042
 \end{aligned}$$

VI. Rate constants, activation parameters and overall deuterium kinetic isotope effect of 1-carbomethoxy-2,3-diazabicyclo(3.3.0) oct-2-ene and its analogue-5d₁.

Name of compound	t°	kx10 ⁻⁴	
1-carbomethoxy-2,3-	127.75	7.82	ΔH = 28.30 kcal mol ⁻¹
diazabicyclo(3.3.0)	128.74	8.45	ΔS = -2.62 e.u.
oct-2-ene	129.74	9.40	
	131.74	11.22	
	132.74	12.01	
1-carbomethoxy-2,3-	127.75	6.20	ΔH = 32.40 kcal mol ⁻¹
diazabicyclo(3.3.0)-	128.74	6.64	ΔS = 7.17 e.u.
oct-2-ene-5d ₁	129.74	7.53	
	131.74	9.27	
	132.74	10.06	

(a) Overall deuterium kinetic isotope effect.

$$1. \quad \frac{k_H}{k_D} = \frac{7.82 \times 10^{-4}}{6.20 \times 10^{-4}} = 1.26$$

$$2. \quad \frac{k_H}{k_D} = \frac{8.45 \times 10^{-4}}{6.64 \times 10^{-4}} = 1.27$$

$$3. \quad \frac{k_H}{k_D} = \frac{9.40 \times 10^{-4}}{7.53 \times 10^{-4}} = 1.25 \quad \sim \underline{\underline{1.24}}$$

$$4. \quad \frac{k_H}{k_D} = \frac{1.122 \times 10^{-3}}{9.27 \times 10^{-4}} = 1.21$$

$$5. \quad \frac{k_H}{k_D} = \frac{1.201 \times 10^{-3}}{1.006 \times 10^{-3}} = 1.19$$

(b) Specific deuterium kinetic isotope effects.

1. Deuterium kinetic isotope effect for β, γ olefin formation:

$$\frac{k_H}{k_{\beta, \gamma H}} = 1 + \frac{19.6}{10.2} + \frac{70.0}{10.2} = 9.78$$

$$\frac{k_D}{k_{\beta, \gamma D}} = 1 + \frac{34.3}{7.5} + \frac{58.1}{7.5} = 13.323$$

$$\frac{\frac{k_H}{k_{\beta, \gamma H}}}{\frac{k_D}{k_{\beta, \gamma D}}} = \frac{9.78}{13.323} = 0.734 \quad \frac{k_H}{k_D} = \underline{\underline{1.68}}$$

2. Deuterium kinetic isotope effect for cyclopropane formation:

$$\frac{k_H}{k_{cyc_H}} = \frac{10.2}{19.6} + 1 + \frac{7.0}{19.6} = 5.09$$

$$\frac{k_D}{k_{cyc_D}} = \frac{7.5}{34.3} + 1 + \frac{58.1}{34.3} = 2.91$$

$$\frac{\frac{k_H}{k_{cyc_H}}}{\frac{k_D}{k_{cyc_D}}} = \frac{5.09}{2.91} = 1.745 \quad \frac{k_H}{k_D} = \underline{\underline{0.71}}$$

3. Deuterium kinetic isotope effect for α,β -olefin formation:

$$\frac{k_H}{k_{\alpha,\beta_H}} = \frac{10.2}{70} + \frac{19.6}{70} + 1 = 1.4257$$

$$\frac{k_D}{k_{\alpha,\beta_D}} = \frac{7.5}{58.1} + \frac{34.3}{58.1} + 1 = 1.72$$

$$\frac{\frac{k_H}{k_{\alpha,\beta_H}}}{\frac{k_D}{k_{\alpha,\beta_D}}} = \frac{1.4257}{1.72} = 0.83 \quad \frac{k_H}{k_D} = \underline{\underline{1.49}}$$

VII. Rate constants and activation parameters of 1-carbomethoxy-2,3-diazabicyclo(4.3.0)non-2-ene.

Name of compound	t°	$k \times 10^{-4}$	
1-carbomethoxy-2,3-diazabicyclo(3.3.0)-non-2-ene	128.74	8.21	$\Delta H = 29.5 \text{ kcal mol}^{-1}$
	131.74	10.81	$\Delta S = 0.13 \text{ e.u.}$
	132.74	11.81	

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APPENDIX

This appendix is aimed at correcting a deficiency in the thesis in the omission of error limits for much of the data.

Many studies have been reported in this thesis and that of Masters (61) on the rate of decomposition of 3-methyl-3-carbomethoxy-1-pyrazoline. The average error is as high as 5% but in spite of changing operators and equipment the values reported at 127° were the same within the error limits. It is felt that the major source of error is in our inability to reproduce and maintain the temperature at a given value. The variance in data can be reduced to 1% by doing a series of consecutive runs without altering the temperature controls on the constant temperature bath. For this reason runs for determining the kinetic isotope effect were done one after the other and alternating protio and deuterio samples.

A further source of errors comes from combining rate data and product composition data as was necessary to isolate the deuterium isotope effects for individual reactions. It should be noted that the isotope effect for cyclopropane formation from the 4-tert-butyl derivatives is not subject to these qualifications as in these cases the only product was a cyclopropane product.

To illustrate the effect of errors in the product mixture analysis on the derived isotope effects we will consider one set of data which

leads to the apparently anomalous inverse isotope effect for the cyclopropane formation from 1-carbomethoxy-2,3-diaza-bicyclo(3.3.0)oct-2-ene (164) (see p. 143). The data given on page 53 are derived from the following results of vapor chromatographic analyses at 160° (see p. 92).

Percent product distribution from pyrolysis
of 164 with average deviations

cyclopropane <u>165</u>	α,β -olefin <u>166</u>	β,γ -olefin <u>167</u>
21.0	68.0	10.7
20.5	69.0	10.7
20.5	69.0	10.3
19.0	70.2	10.6
19.2	70.8	10.0
18.7	73.0	8.3
18.6	70.5	11.0
19.6 \pm 0.9	70.1 \pm 1.5	10.2 \pm 0.9

Percent product distribution from pyrolysis

of 164-5d₁.

cyclopropane <u>181</u>	α,β -olefin <u>182</u>	β,γ -olefin <u>167</u>
34.7	58.0	7.2
34.7	57.5	7.7
33.8	59.2	7.0
34.6	58.4	7.0
34.2	57.3	8.4
34.2	57.3	8.4
34.4	59.6	7.1
34.4 \pm 0.3	58.2 \pm 0.7	7.5 \pm 0.5

Clearly the largest relative error is in the minor component. These data were used to calculate the deuterium isotope effect for the cyclopropane derivative on p. 143 and yielded a value for k_H/k_D of 0.71. If we make use of probable errors (0.845 x average deviation) carry the errors through the calculations ¹ the probable error in the specific deuterium isotope effect can be calculated.

$$\frac{k_H}{k_{cyc_H}} = \frac{10.2 \pm 0.8}{19.6 \pm 0.8} + 1 + \frac{70.1 \pm 1.3}{19.6 \pm 0.8}$$

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1. F. Daniels, Mathematical Preparation for Physical Chemistry, McGraw Hill, 1956, p. 224.

$$= .52 \pm 0.05 + 1 + 3.57 \pm 0.16 = 5.09 \pm 0.16$$

$$\frac{k_D}{k_{cyc_D}} = \frac{7.5 \pm 0.4}{34.4 \pm 0.3} + 1 + \frac{58.2 \pm 0.7}{34.4 \pm 0.3}$$

$$= 0.22 \pm 0.1 + 1 + 1.09 \pm 0.03 = 2.91 \pm 0.03$$

$$\frac{k_H}{k_D} \times \frac{k_{cyc_D}}{k_{cyc_H}} = \frac{5.09 \pm 0.16}{2.91 \pm 0.03} = 1.75 \pm 0.06$$

$$\frac{k_{cyc_H}}{k_{cyc_D}} = \frac{1.25 \pm 0.02}{1.75 \pm 0.06} = 0.71 \pm 0.03 \text{ or } \pm 4\%$$

A survey of the data suggest that in general the probable error is within 5% except in the cases of calculations on minor components. For example, the β,γ -olefin 167 gives a specific k_H/k_D of 1.68 ± 0.10 or 6%.

Finally the values of ΔH^\ddagger and ΔS^\ddagger which are derived from rate data at various temperatures will also show appreciable errors. If we assume 5% accuracy in the rate constants and a temperature interval of 10°C , the maximum error in ΔH^\ddagger can be estimated by the equation given by Wiberg²

$$\delta = 2R \cdot \frac{T'T'}{T'-T} \alpha$$

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2. K.B. Wiberg, "Physical Organic Chemistry", McGraw-Hill, 1940, p. 378.

α is the fractional error in the rate constant

δ is the maximum error in ΔH^\ddagger .

By using temperatures of 130 and 140°C we find

$$\delta = 3.3 \text{ kcal/mole or } \pm 10\%$$

For the maximum error in ΔS^\ddagger the following equation can be used

$$\delta = \delta \frac{1}{T} + \frac{T' - T}{2T'T}$$

$$\delta = 8.3 \text{ e.u.}$$

Clearly the values of ΔH^\ddagger and ΔS^\ddagger measured from a 10° interval have too large a probable error to be used in any definitive way.