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CYCLOADDITIONS OF CYCLOPROPANES TO OLEFINS

by

SETH C. GRENETZ

A dissertation submitted to the Graduate
Faculty in Chemistry in partial fulfillment of the requirements for the degree
of Doctor of Philosophy, The City University of New York.

1972

Abstract

Cycloadditions of Cyclopropanes to Olefins

by

Seth C. Grenetz

Advisor: Dr. William F. Berkowitz

I. Discussion and Review of 1,3-Dipolar and Diradical Trimethylene Formation and Cycloadditions. Examples are given of previously proposed 1,3-dipolar and diradical species and evidence for their existence is discussed.

II. Cycloadditions of Cyclopropanes to Olefins. Two types of cycloadditions were attempted. One involved the thermal isomerization of appropriately substituted cyclopropanes whose ring openings would result in stabilized 1,3-dipolar zwitterions which could be trapped with olefins. Therefore, the attempted syntheses of 1,1-diethoxy-2,2-dicyanocyclopropane and 1-ethoxy-2,2-dicyanocyclopropane and the actual syntheses of ethyl 2-ethoxycyclopropane-1-carboxylate and 1,1-dimethyl-2,2-dicyanocyclopropane are described along with their attempted cycloadditions to various olefins.

The second type of cycloaddition involved the use of an olefin whose double bond provided a nucleophilic attack on a cyclopropane system, opening the ring and subsequently closing to a cyclopentane. The cycloaddition of N-pyrrolidinocyclohexene to 1,1-dimethyl-2,2-dicyanocyclopropane has provided such a system. This reaction, several degradation products and their structure proof are described.

This manuscript has been read and accepted for the Graduate Faculty in Chemistry in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

3/1/72
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I would like to thank Dr. Berkowitz for his patience and his teaching of competent research; Tony Ozorio and Mike Zudiker, my friends from Room 200C who helped to make the hours with my reactions more pleasurable; The National Institute of Health for fellowships during the summers of 1967, 1968 and 1969; The City University of New York for a fellowship in 1966-1967; and the Queens College Department of Chemistry for financial aid in the form of part-time lectureships.

A special thanks must go to my private secretary, my wife, Diane, who did all the typing and proofreading of this thesis. Her encouragement throughout my years of research has made this accomplishment seem all the more worthwhile.

Dedication

To Diane

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Part I. Discussion and Review of 1,3-Dipolar and Diradical Trimethylene Formation and Cycloadditions

Part II. Cycloadditions of Cyclopropanes to Olefins

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Part I

Discussion and Review of 1,3-Dipolar and Diradical Trimethylene Formation and Cycloadditions

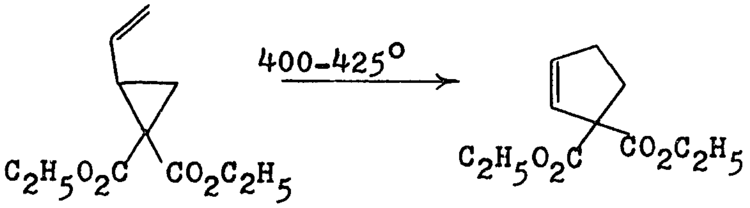
CYCLOADDITIONS OF CYCLOPROPANES TO OLEFINS

Part I

Introduction

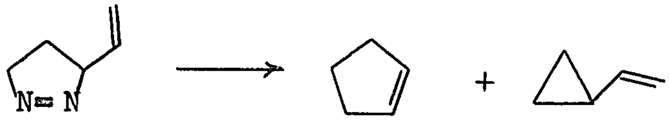
Thermal and photochemical cycloaddition reactions resulting in the formation of three-,[1,2,3] four-[4] and six-membered carbocyclic rings[5,6] have been well known for many years. However, a simple intermolecular cycloaddition, which could serve as a *general* route to a five-membered carbocyclic ring has not appeared in the literature.

Intramolecular cycloadditions of this type involving the thermal rearrangements of vinylcyclopropanes to cyclopentenes[7] have been known for some time (Eq. 1).



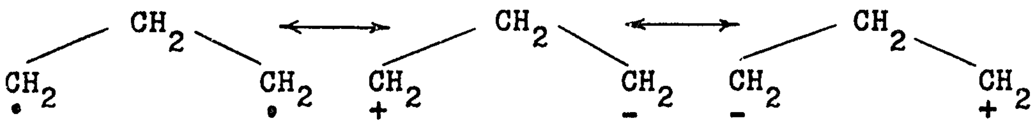
(1)

The decomposition of 3-vinyl-1-pyrazoline (**1**) has also been found to give cyclopentene and vinylcyclopropane.[8]



1

An *intermolecular* cycloaddition, on the other hand, would necessitate the addition to an alkene of a three-carbon fragment with reactive terminal carbon atoms, e.g., species such as **2A** or **2B**. The cycloaddition might occur in either a multistep or concerted manner. Structures **2A** and **2B** are resonance structures since the most stable trimethylene intermediate has been shown by Hoffmann to be a singlet.[28]

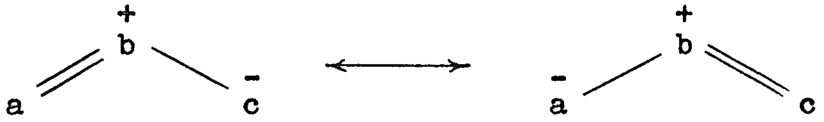


2A

2B

1,3-Dipolar Cycloadditions Involving Central Atoms With sp or sp^2 Hybridization

1,3-Dipolar cycloadditions involving dipoles with a central atom of sp^2 or sp hybridization (having the general structure 3) and carbon-carbon or heteroatomic double bonds have been studied quite extensively during the past decade by Huisgen[9-11] and other workers.[14-23b] These include species such as phenyldiazomethane or ozone, which already exist as three-membered chains, carbonyl ylids arising from ring openings as well as intermediates arising from cyclic structures, e.g., 4, from ring opening of an epoxide.



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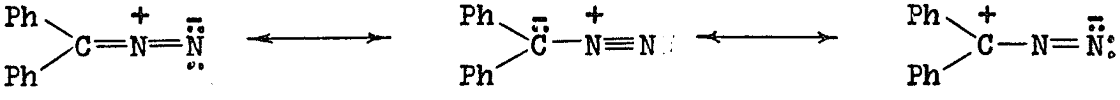

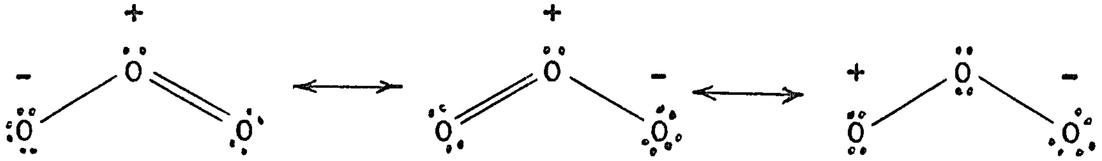

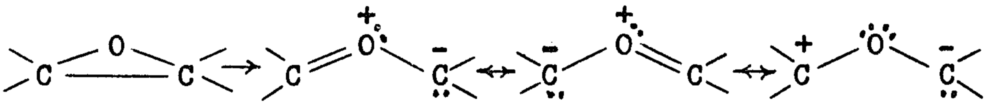

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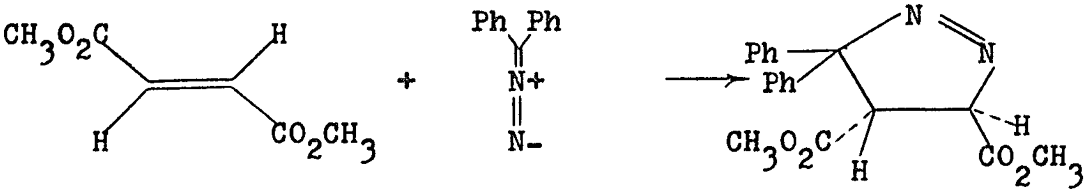
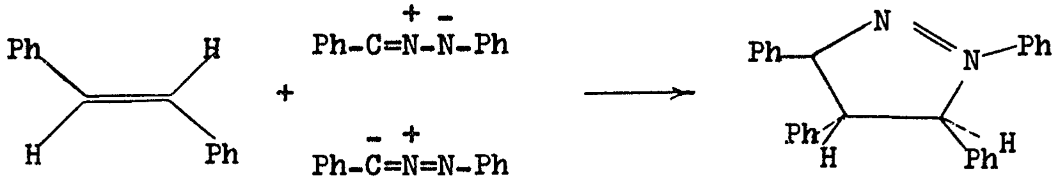
The following experimental evidence indicates that these cycloadditions generally occur in a concerted manner:[9,10]

A. The solvent effects observed during these reactions are quite small. When diphenyldiazomethane adds to dimethyl fumarate, for example, there is a rate factor of less than two when comparing reactions in dimethylformamide and benzene. It is well known that when dipolar transition states are formed from relatively nonpolar reactants, reactions proceed at a much faster rate in solvents of high dipole moment than low dipole moment.[11,12] The dipole moment of dimethylformamide is 3.82 D while that of benzene is zero.[142] Kosower has predicted that such a reaction should have a rate factor with these two solvents of about 10^4.[64a] This indicates a concerted reaction since a two-step reaction would require a fully charged transition state with resulting solvent effects.



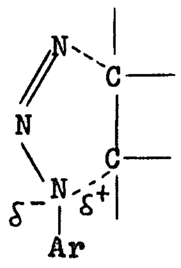
B. There is a high degree of stereoselectivity, which also indicates a concerted reaction, since a two-step mechanism would allow free rotation about the carbon-carbon single bond whether the intermediate was diradical or dipolar in nature (e.g., *trans*-stilbene (**5**) and diphenylnitrile imine (**6**) give the *cis*-adduct in 86% yield).



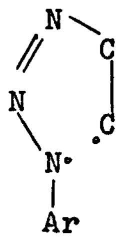
5 **6** **7**

C. The enthalpy of activation for many of the reactions was calculated to be approximately 15 kcal, while the entropy of activation gave a value of approximately -30 kcal/deg., clearly indicating a highly ordered transition state (i.e., most likely a concerted reaction).

On the other hand, electronic substituent effects seemed to indicate a transition state (**8A**) with partial positive and negative charge, caused by unequal rates of bond formation.



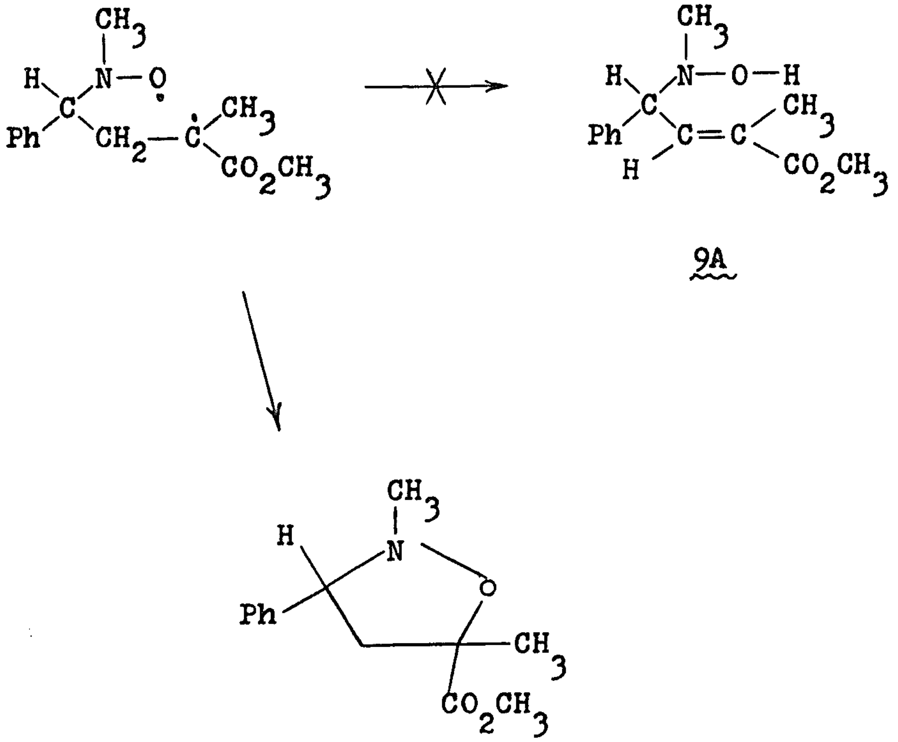
8A



8B

Contrary to a mechanism involving species 8A, Firestone[24a] has proposed a two-step mechanism for azide cycloadditions in which the first and rate-determining step is the formation of a spin-paired diradical. He has discounted the argument regarding stereospecificity (B, above) by suggesting that the activation energies for ring closure and reversion to the reactants are much smaller than that required for the bond rotation. Firestone also felt that 8B would be more consistent with the small solvent effects.

Huisgen defended his argument, however, on the basis of reactions such as the following, in which no disproportionation products were observed (e.g., 9A).

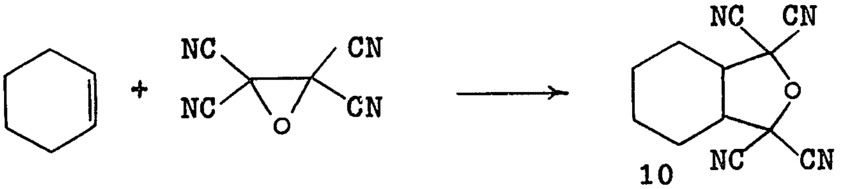


9A

9B

In addition, he calculated that the loss of π-delocalization in going from the original 1,3-dipolar species to the transition state would be less energetically favorable for a diradical intermediate than a dipolar species. With regard to solvent effects, Huisgen refuted Firestone's argument that a slight inverse solvent effect should occur if the transition state were polar because the cycloadducts often had higher dipole moments than the original 1,3-dipoles.[24b]

Tetracyanoethylene oxide is also known to add to olefins resulting in 2,2,5,5-tetracyanotetrahydrofuran ring systems (e.g., structure 10).[21-23b] Here, however, the nature of the reacting species is more questionable than in previous examples since the epoxide must first open. A "zwitterion-biradical hybrid" (11) has been proposed because neither pronounced solvent effects nor substituent effects were observed.



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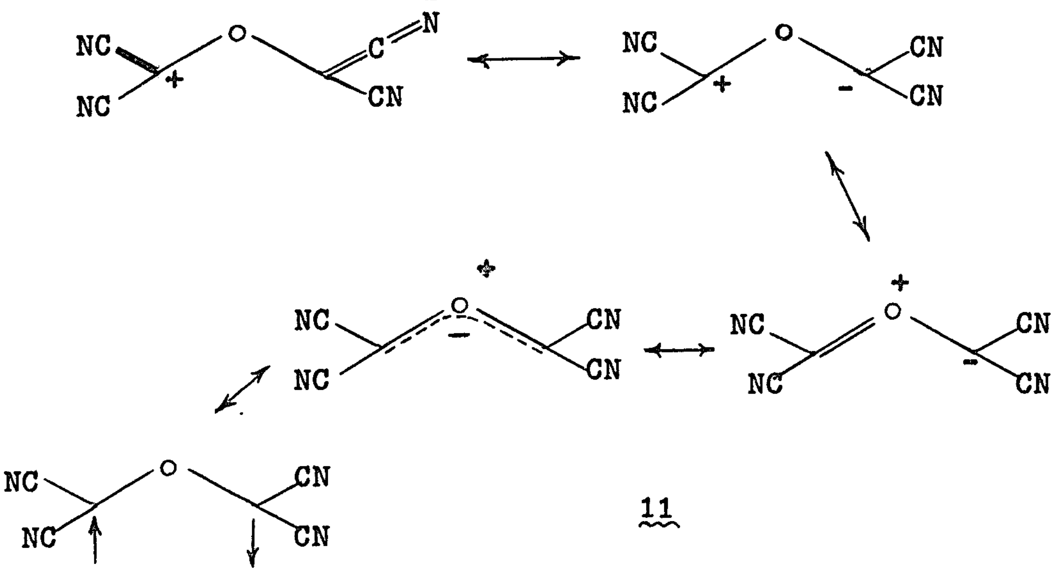
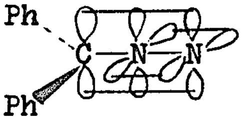


11

Analagous additions of aziridines to alkenes and alkynes are known.[25,26]

All of the species discussed so far have one common factor: they all contain a central atom, which is sp^2 or sp hybridized, or else at least one such resonance structure can be drawn. Thus they can provide an internal stabilization of the dipolar or diradical forms by virtue of the delocalization of charge over the three atoms (e.g., 12). However, the proof of existence of the three-carbon fragment 2 is almost non-existent. Without the necessary sp^2 or sp hybridization of the central atom, the trimethylene species 2 can only be expected to have a fleeting existence as an intermediate of a reaction (either as 2A, 2B or a combination of these). Varying the substituents on the atoms would be expected to control the amount of contribution of either 2A or 2B to the total structure of 2.



12

THE TRIMETHYLENE INTERMEDIATE

Recently, SCF-MO calculations have estimated the percent of diradical character present in the trimethylene intermediate resulting from a cyclopropane ring cleavage to be 80% (based on a calculated C-C-C bond angle of 120° in the trimethylene species.[27] These calculations have also been done for several species in which the central atom can aid in the delocalization of electrons (Table I). The calculations were based upon the electron density of each of the terminal orbitals. For 100% diradical character, the electron densities at the two terminal carbon atoms must be the same.

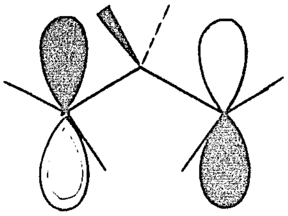
TABLE I

Molecule	Calculated Wt., %		% Diradical Character
	π_+^2	π_-^2	
Cyclopropane	40	60	80
Aziridine	15	85	30
Ethylene Oxide	19	81	38
Oxazirane	10	90	20
Ozone	15	85	30

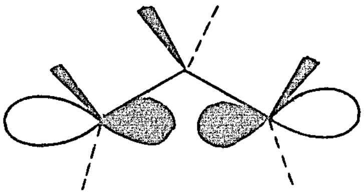
The calculations for Table I assume that the open intermediates are in the 0,0-form.[28,*] A positive correlation seems to exist between lack of stability of the

---

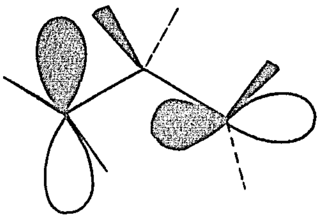
[*] The 0,0-form refers specifically to one of three extreme geometrical arrangements referred to by Hoffmann,[28] in which the hydrogen atoms on the terminal carbons lie within the plane of the species (i.e., at an angle of 0° with respect to the plane of the trimethylene intermediate, cf. **2A**, below). Two other possible extremes are the 90,90-form (i.e., one in which the bonds to the hydrogen atoms are perpendicular to the plane; cf. **2B**, below) and the 0,90-form (i.e. one in which the bonds to one pair of hydrogen atoms are in the plane of the species while the other terminal bonds are perpendicular to this plane; cf. **2C**).



2A



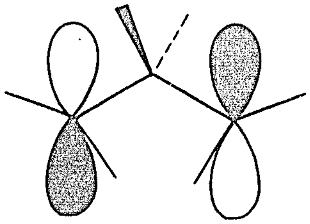
2B



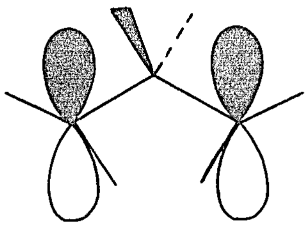
2C

intermediate and the percentage of diradical character. A greater amount of diradical character also indicates that a smaller fraction of the electronic wave function has a stereochemical preference. This has been exemplified by the pyrolysis of pyrazolines which proved to be only 30 to 40% stereoselective[29] (see pp. 9-11), while the addition of tetracyanoethylene oxide to olefins showed itself to be approximately 100% stereospecific.[21-23b]

Hoffmann has calculated the C-C-C bond angle at which the trimethylene intermediate is most stable to be approximately 125°,[28] with the terminal hydrogens in the plane of the species (0,0-form).[*] The interesting feature, however, is that at this angle, the energy of the antisymmetric terminal orbital arrangement 2A is 0.55 electron volts lower than that of the symmetric molecular orbital 2D. (The terms "antisymmetric" and "symmetric" are used with reference to the terminal p_z orbitals of the trimethylene species.) Thus, the ground state structure of the trimethylene intermediate is actually structure 2A and not the perhaps anticipated 2D.



2A



2D

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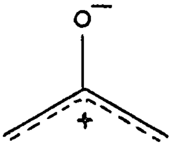
[*] See footnote, p. 8.

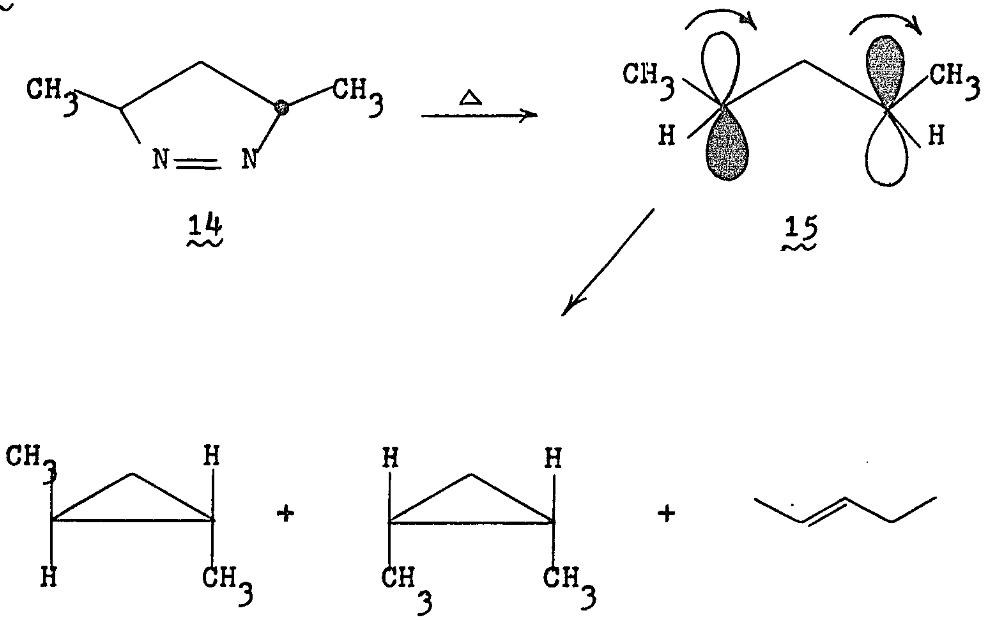
Woodward-Hoffmann rules predict that 2A will undergo a conrotatory ring closure.[30] We can see a definite <u>lack</u> of analogy here with the proposed Favorskii intermediate[50-55] 13 (mentioned later in this section) because this species is actually a 2π-system which is analogous to the allyl cation.[28,31] The rules would thus predict a disrotatory ring closure with Favorskii intermediates or cyclopropanone reactions.[59-62]



13

The cycloaddition of the trimethylene species 2C to the ethylene system involves a 2π + 2π situation. The thermal combination of two ethylene molecules in the ground state to form cyclobutane is <u>not</u> allowed. In order for this reaction to take place, photochemical excitation of the ethylene molecule to the first unoccupied orbital (which is antisymmetric) is required. However, since the orbitals in the trimethylene species are already antisymmetric in the ground state, analogous to the first excited state of ethylene, the trimethylene intermediate is expected to add stereospecifically, albeit antarafacially, to the olefins under thermal conditions.

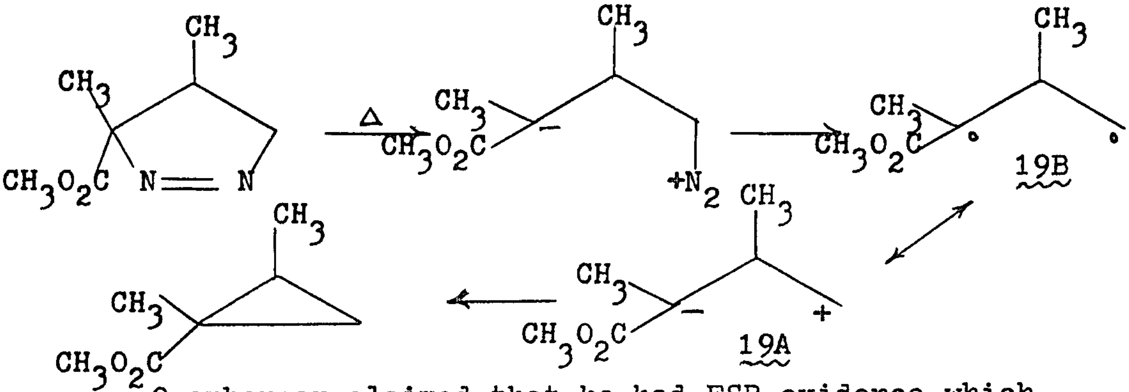
The predictions regarding ring closure of trimethylenes have, in fact, been experimentally verified. Crawford and his co-workers have decomposed various pyrazolines[29,32,33] and showed that the cyclopropanes formed are those predicted on the assumptions of a trimethylene species existing as a diradical[33] and undergoing a conrotatory ring closure. For example, *cis*-3,5-dimethyl-1-pyrazoline (14) decomposed upon heating to give predominantly *trans*-1,2-dimethylcyclopropane (16) which, as indicated below, is the expected product from the conrotatory ring closure of the trimethylene intermediate 15.



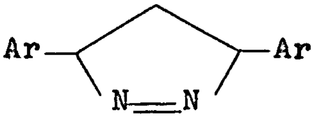
14 15 16 17 18

Although at first glance, the predominance of *trans* product 16 would be attributed to steric effects in the ring closure (smaller interaction of the methyl groups in the *trans* than the *cis* form) the analogous reaction with *trans*-3,5-dimethyl-1-pyrazoline yielded 75% of the *cis*-1,2-dimethylcyclopropane and 25% *trans*-1,2-dimethylcyclopropane. Thus the alignment of the orbitals and not the steric interactions seems to be the determining factor.

Other examples of cyclopropane formation from pyrazolines have been reported[34,35] indicating either zwitterionic (19A) or diradical (19B) structures as intermediates, sometimes occurring with stereospecificity and sometimes without. The temperature has also been shown to affect the degree of stereospecificity.[27]



Overberger claimed that he had ESR evidence which showed the existence of free radicals in the decomposition of 3,5-diaryl-1-pyrazolines (20).[35]



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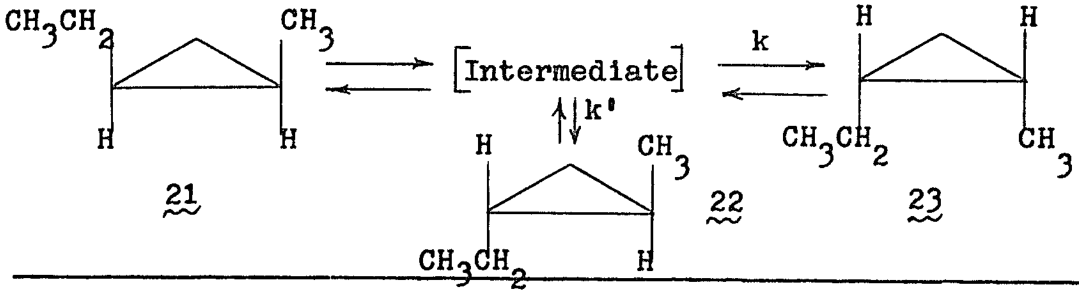
It seems apparent, if the various pyrazoline decompositions are examined, that a single general mechanism for thermal pyrazoline decompositions probably cannot be assigned. The decompositions were run in either benzene, xylene or neat. Although solvent studies might have elucidated the mechanism, at least with regard to the existence of a zwitterionic vs. a diradical intermediate, none have been reported to date. In addition, varying the substituents seems likely to cause a greater stabilization of zwitterionic structure **19A** at times, while in other cases aiding structure **19B**.**

Separate studies by Berson[36] and Bergmann[37,38] have indicated that the π_u-trimethylene intermediate **2A** obtained during the thermal decomposition of pyrazolines,[32,33,37] may not be the same intermediate obtained during the thermal cleavage of cyclopropanes.

For example, the rate of interconversion of L-cis-1-ethyl-2-methylcyclopropane (**21**) to racemic trans-1-ethyl-2-methylcyclopropane (**22**) at approximately 400° was compared to the rate of conversion of **21** to D-cis-1-ethyl-2-methylcyclopropane (**23**).



** There is precedence for this thought. Polar solvents, for example, are known to bolster the liklihood of polar mechanisms over radical mechanisms, see ref. 36. We have also seen that the trimethylene species has been shown to be predominantly diradical in character,[27,28] yet appropriate substituents have been able to help form a zwitterionic trimethylene intermediate.[78-81]

If the rate constant for the conversion of the L-*cis*-cyclopropane 21 to the D-compound, 23, k, is compared to the rate constant for the isomerization of 21 to the racemic *trans*-cyclopropane, 22, k', a ratio of the constants, k/k', should reveal the selectivity during pyrolysis of epimerization (21→23) *vs*. isomerization (21→22). For the cyclopropanes, k/k' is close to unity, thus showing little selectivity between the two reactions, while for pyrazolines the same factor was found to be approximately 3. Ignoring the factor of temperature differences for decomposition,‡ this would seem to indicate that the intermediate involved during the pyrazoline decomposition is not exactly the same as that for the cyclopropane ring opening.

Examples of Formation of Three Carbon Fragments

A. Thermal Isomerizations of Cyclopropanes

Thermal isomerizations of cyclopropanes to propenes have been documented since approximately the turn of the twentieth century.[40-50] On the basis of kinetic evidence, several authors have suggested the existence of a diradical species (e.g., 2A) as intermediate during the gas phase pyrolysis of cyclopropane at approximately 500°.[40,41]

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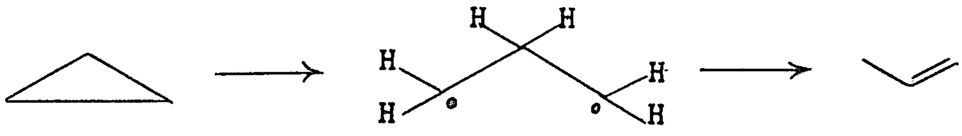
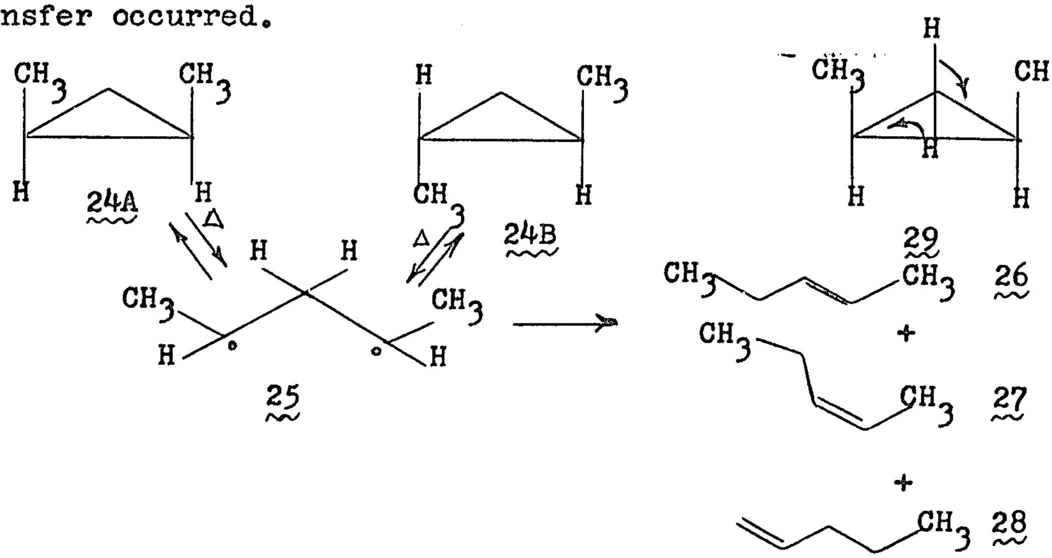
‡ There did not seem to be a large change in product ratios during the decomposition of 21 at different temperatures. Nevertheless, it could be a factor with which to contend. See footnote 24, reference 40.

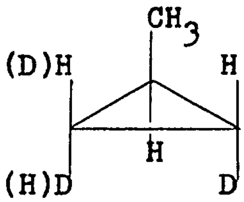


2A

Evidence has been accumulated, which is apparently consistent with a diradical intermediate, **25**, and a concerted hydrogen transfer type of mechanism as shown in **29**.[48,49] Pyrolysis of *cis*-1,2-dimethylcyclopropane (**24A**) and the corresponding *trans* compound, **24B**, at 400 to 450° gave the pentenes, **26**, **27** and **28**, as well as structural (*cis*→*trans* and *trans*→*cis*) isomerizations. Kinetic experiments indicated that the energy of activation of **24A** was about 2 kcal/mole lower than that of **24B**. This would tend to favor a mechanism involving a C-C bond extension, thus providing relief from the repulsion of the two methyl groups. In addition, the product ratio of *trans*-2-pentene (**26**) to *cis*-2-pentene (**27**) was the same, regardless of which isomer (**24A** or **24B**) was used. This appeared to indicate a C-CH_3 rotation *before* any hydrogen transfer occurred.



Contradictory evidence, however, was found by Sester and Rabinovitch in comparing the rates of pyrolysis of <u>cis</u> and <u>trans</u>-1,2-dideuterio-3-methylcyclopropane (30) with that of methylcyclopropane (31).[44]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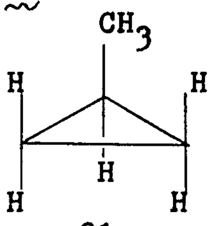
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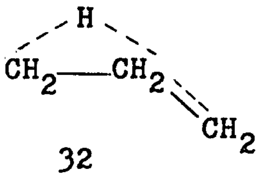
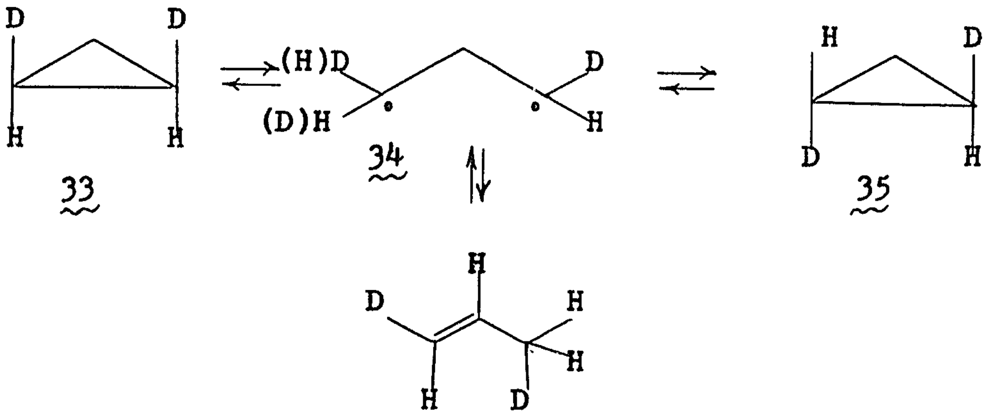

32

A primary isotope effect for structure 30 suggested that the C-H bond broke before or during the rate determining step. This would be inconsistent with diradical formation since the expected slow step of the reaction formation of the diradical, would be anticipated to occur before the hydrogen transfer. Although a secondary isotope effect was also considered, the magnitude of the k_H/k_D ratios led the authors to believe that the effect was mainly primary. Thus, a compromise transition state, 32, was proposed involving simultaneous C-C bond breakage and H-transfer.[‡]

Rabinovitch and co-workers[50] proposed a trimethylene diradical species 34 as a logical intermediate common to the simultaneous <u>cis-trans</u> isomerization of <u>cis</u>-1,2-dideuterio-cyclopropane (33) and the <u>trans</u> isomer and their isomerization to dideuteriopropene derivatives (e.g., 36).

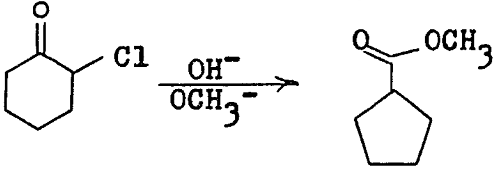
[‡] The possibility that a 2-step mechanism was occurring in which the bond-breaking step was faster than the subsequent hydrogen transfer, was not proposed.

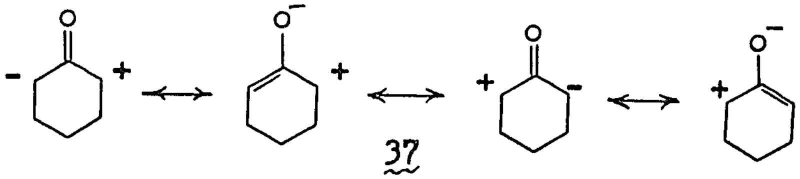


33 34 35 36

B. The Intermediate in the Favorskii and Related Rearrangements

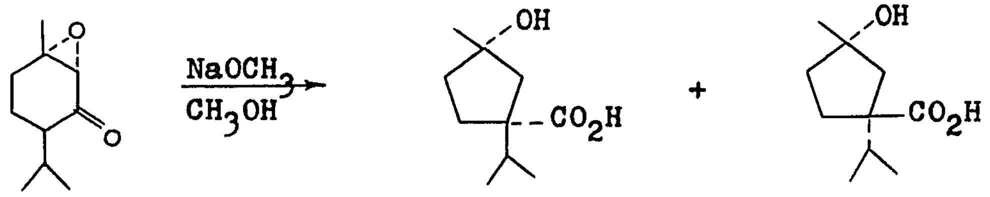
Much evidence, theoretical and experimental, has indicated that the intermediate in the Favorskii rearrangement most likely is a resonance stabilized 1,3-dipolar ion (e.g., 37).[51-56]



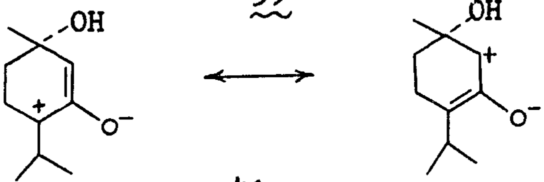


37

House has found that in reactions run with methanolic sodium methoxide the rearrangement products were stereospecific with respect to the starting materials.[52,53] When using this system, 1-isopropyl-3-methyl-cis-3-hydroxycyclopentanecarboxylic acid (39) and 1-isopropyl-3-methyl-trans-3-hydroxycyclopentanecarboxylic acid (40) were both rearrangement products of piperitone oxide (38). However, a relatively non-polar solvent and base, such as potassium tert-butoxide in 1,2-dimethoxyethane gave only the cis-isomer, 39. House thus envisioned a mechanism involving the intermediate 41 in the polar solvent, since a direct displacement reaction would be expected to yield products of a stereospecific nature (39 and 40).



38 39 40



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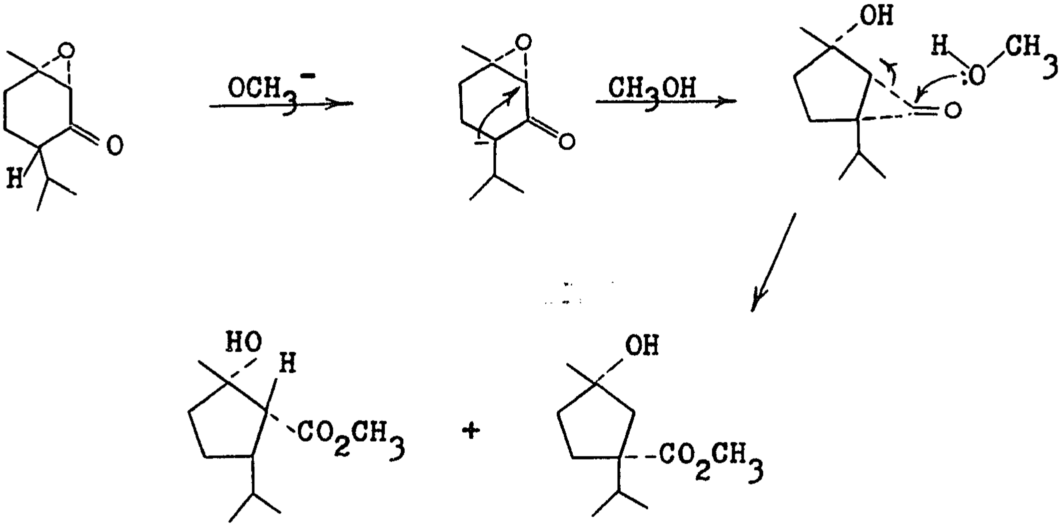
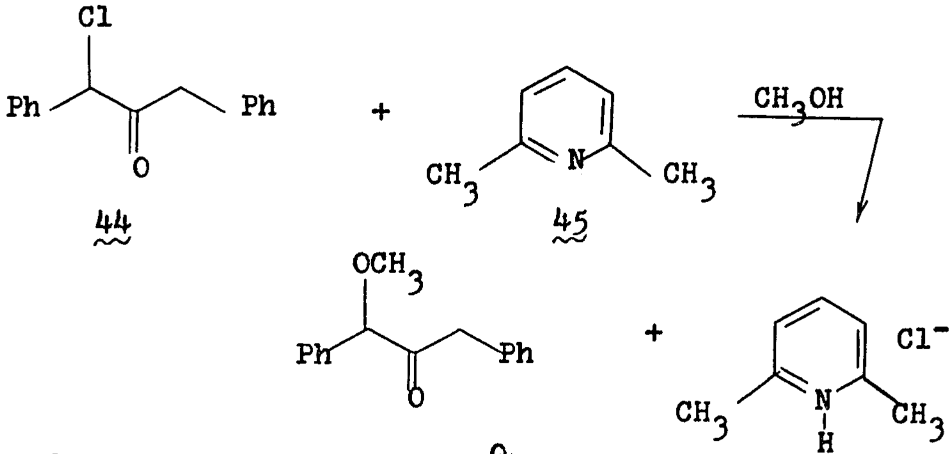
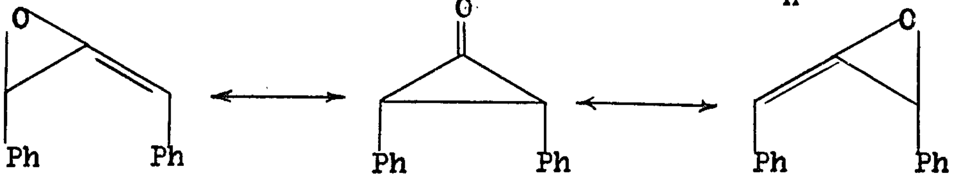


42 43

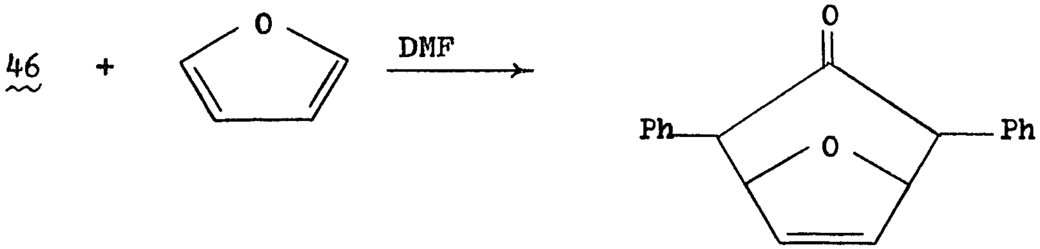
Further evidence for the existence of such a zwitterionic intermediate has been found by Fort.[54-56] He has shown that the methanolysis of α-chlorodibenzyl ketone (44), in the presence of 2,6-lutidine (45), proceeds readily, whereas chloracetone is unreactive. If the reaction involved merely the direct displacement of the chloride, chloroacetone should have given methoxyacetone, yet it was unreactive. Therefore, the proposal of intermediate **46**, involving resonance stabilization by the phenyl groups seemed reasonable.





46

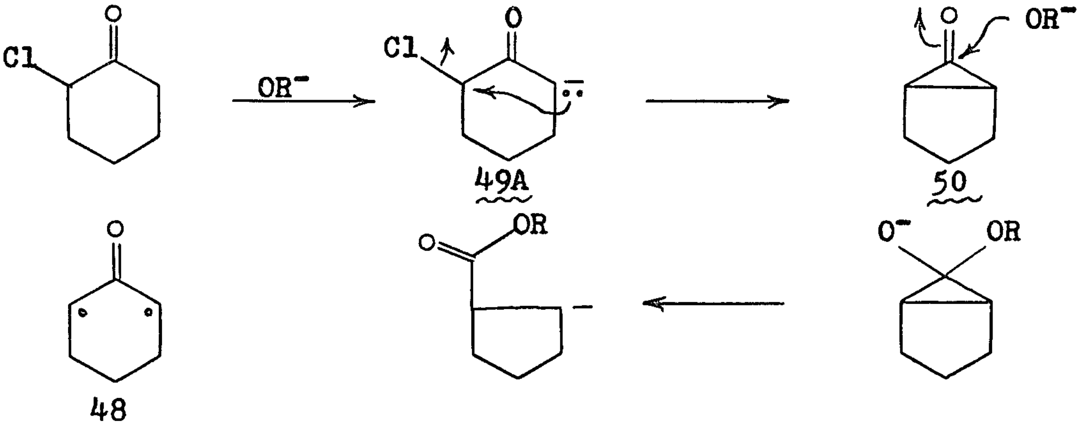
In addition, Fort has successfully trapped this intermediate **46** with furan using dimethylformamide as solvent to give **47**.[56] This reaction is predictable[31] as it is a thermally allowed (2π + 4π) electrocyclic process.



47

Burr and Dewar[57] suggested a 1,3-diradical intermediate

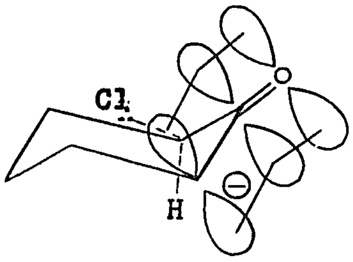
48 for the Favorskii rearrangement, rather than one involving a direct displacement 49A followed by 50. The direct displacement would be unlikely because the negatively charged sp^2 carbanion would have its p-orbital aligned perpendicular to the plane of the carbonyl group (see 49B). Hence it would be difficult to get any significant overlap for the S_N2 type of displacement, which would be necessary unless the orbitals were aligned as designated in structure 49C.



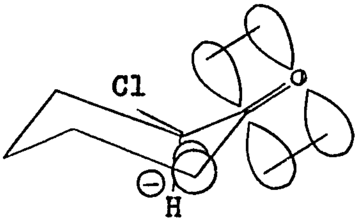
49A

50

48



49B

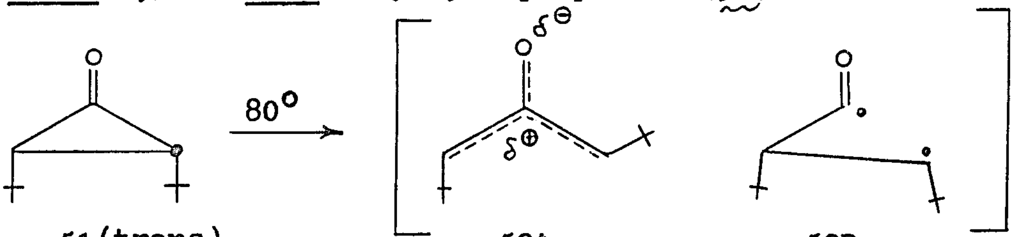


49C

We can question why species 48 would form at all. Burr and Dewar have calculated, using the LCAO-MO method, that an increase in conjugation energy of approximately 14 kcal is obtained in going from 50 to 48. In addition, electron density calculations have indicated significant contributions from dipolar resonance forms of **48**.

Although there is much evidence appearing to favor some sort of 1,3-dipolar or 1,3-diradical intermediate, it seems probable, depending on the nature of the reactants and the solvent, that *concerted* displacements are also possible.[61-63]

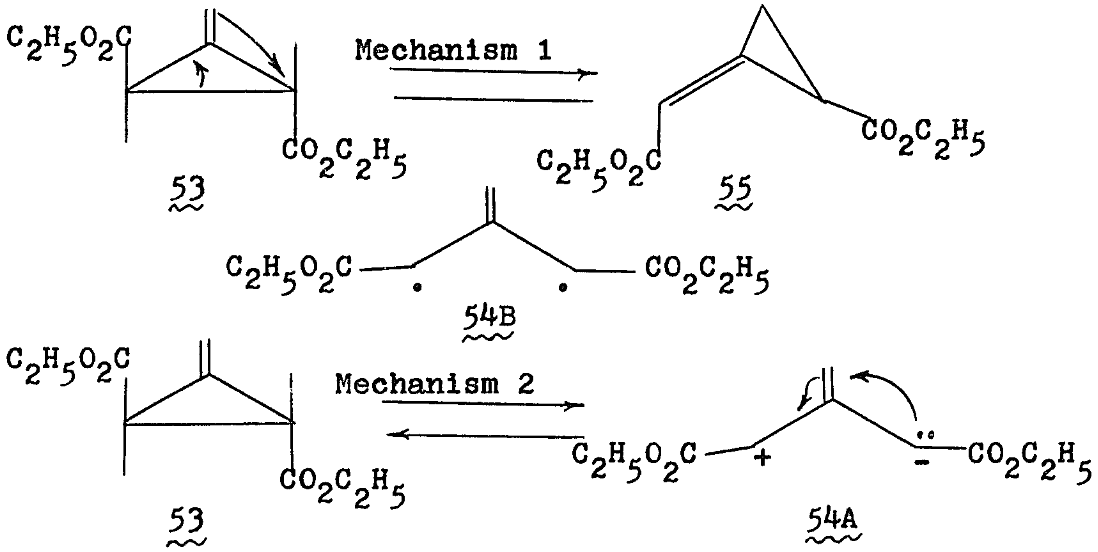
A 1,3-dipolar zwitterionic species similar to the Favorskii intermediate has been supported by Hammond and Turro[61-64] in additions of cyclopropanones to dienes (also predicted by Woodward-Hoffmann rules[31]) and has been thought of as an intermediate, **52A** or **52B** during the racemization of (+)-*trans*-2,3-di-*tert*-butylcyclopropanone (**51**).



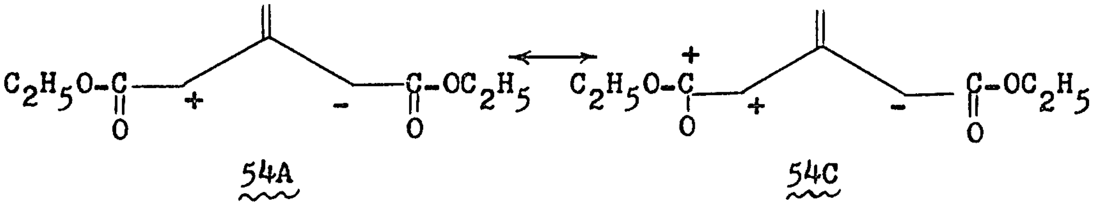
51 (trans) **52A** **52B**

C. Methylenecyclopropanes - Rearrangements and Cycloadditions

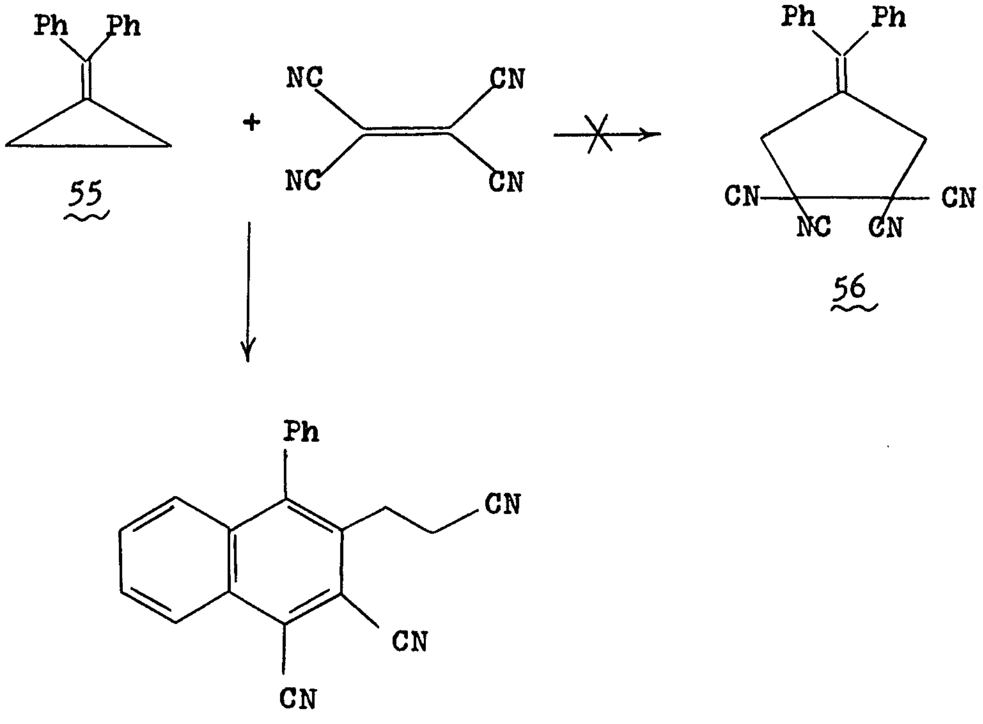
Zwitterions have also been proposed as intermediates in the isomerization of Feist's ester **53**,[65] which rearranges at 210° to the isomer **55**, a rather general reaction of methylenecyclopropanes.[66] Although a concerted mechanism could easily have been proposed (mechanism 1), mechanism 2, which involves a 1,3-dipolar intermediate, **54A**, quite similar to the proposed Favorskii intermediate **46B**, seemed preferable. This idea was based on the fact that when the reaction was stopped at 25% and 50% of completion, there was a loss in optical activity of the starting material, 53.[51-56]



The reason for eliminating 54B as a reasonable alternative to 54A was not discussed. In fact, this structure may be preferable to 54A since the resonance structure 54C is certainly a destabilizing one.



A recent reaction of a compound similar to Feist's ester (53), namely diphenylmethylenecyclopropane (55), with tetracyanoethylene, has led to the adduct 57, rather than the desired 56, most likely via a Diels-Alder step as part of the mechanism.[67] There has been no experimentation, as yet, to determine whether a (3+2) cycloaddition would occur if no phenyl or vinyl groups are attached to the cyclopropane methylene.



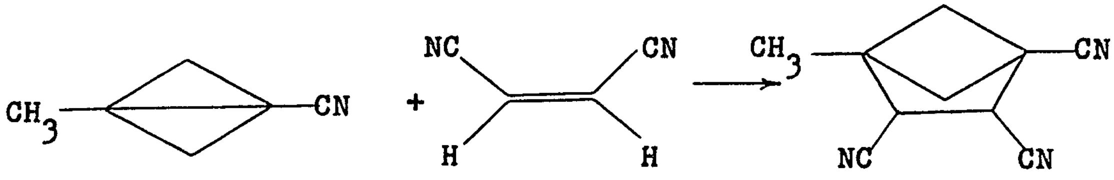
57

D. Decomposition of Highly Strained Cyclopropanes

Several three-carbon fragments have been readily trapped by virtue of the fact that they arose from a highly strained three-membered ring.

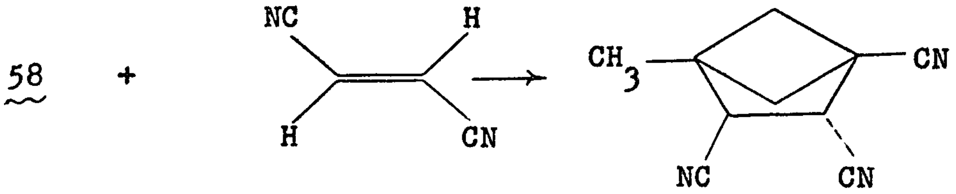
Electrophilic, nucleophilic[68] and radical[68] additions to [1.1.0] bicyclobutanes have previously been studied.

3-Methylbicyclo [1.1.0] butanecarbonitrile (58) has been shown by Cairncross and Blanchard to add maleonitrile, fumaronitrile, and other olefinic compounds, to form cycloaddition products such as 59 and 60.[68,70] They proposed the diradical intermediate 61,[59] because of the partial loss of stereochemistry observed during the reaction.



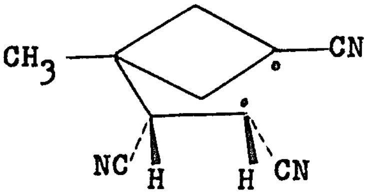
58

59



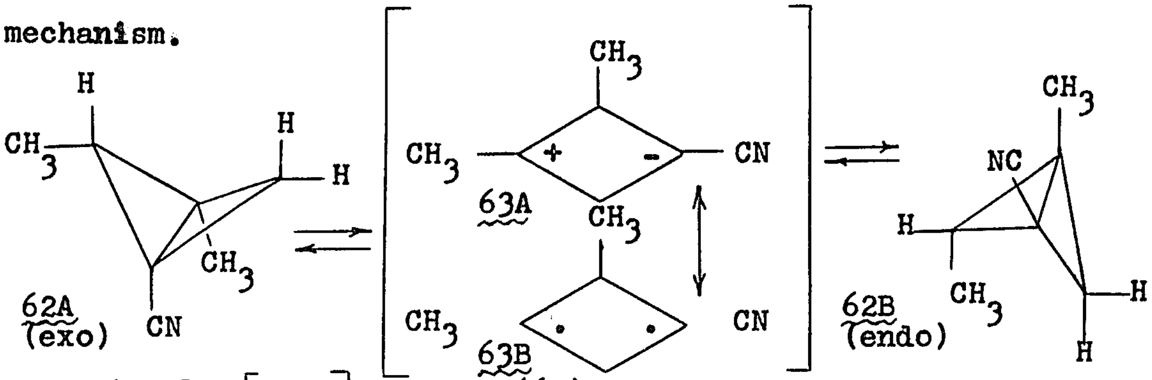
60

via:

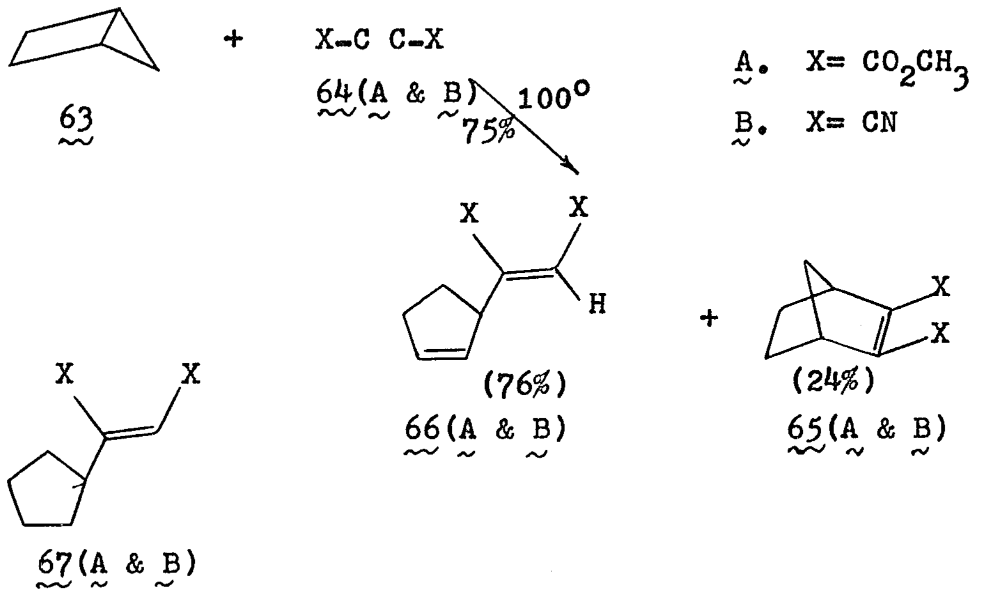


61

The possibility of a 1,3-dipolar intermediate (e.g., 63A) or a 1,3-diradical (e.g., 63B) was eliminated by heating the exo form, 62A, under the same conditions as the bicyclobutane 58, with no trapping agent present. If either 63A or 63B were indeed an intermediate, the *exo-endo* interconversion should have been observed. However, this was not the case. Thus a rate-determining bimolecular reaction was the preferred mechanism.



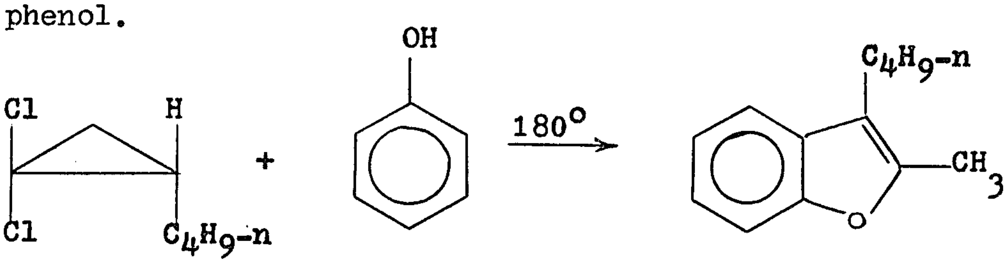
Bicyclo [2.1.0] pentane (63) reacted with dicarbomethoxyacetylene (64A) at 100° and dicyanoacetylene (64B) at room temperature to give the indicated adducts 65 and 66.[70-72]



The hypothesized common intermediate for this reaction was 67. A zwitterionic species was eliminated because there were no solvent effects (benzene, ethyl acetate and methanol were used). A concerted mechanism was ruled out because it would have necessitated two different transition states, one for formation of 65 and another for 66. In addition, the same ratio of 65:66 was obtained (24:76 for A and 58:11 for B) regardless of the solvent used. This would make a concerted mechanism unlikely since at least slightly different populations would be expected for the transition states leading to 65 and 66.

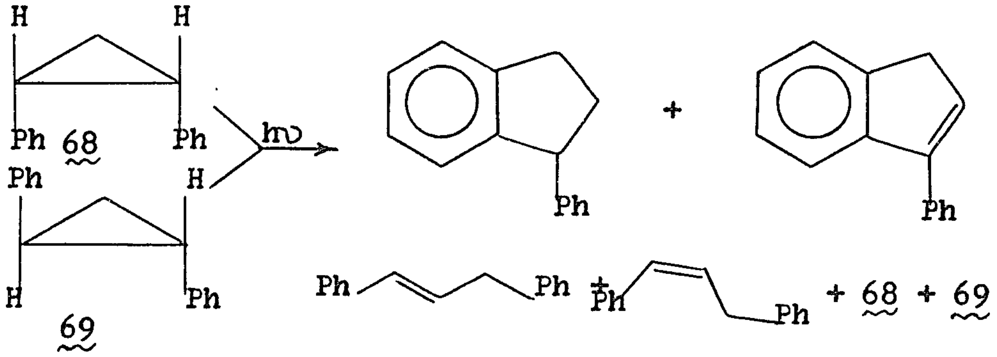
E. Trapped Trimethylenes

Several substituted cyclopropanes have also been trapped with phenol.[76]

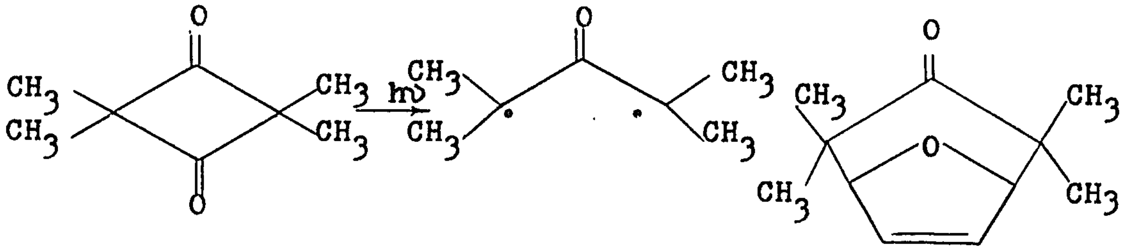


There have also been several examples of the photochemical production of three carbon diradicals.[74,76]

Cis-and trans-1,2-diphenylcyclopropane (68 and 69), for example, have been found to interconvert as well as to furnish various rearrangement products.[75,76] The reaction has been rationalized in terms of a 1,3-diradical intermediate.

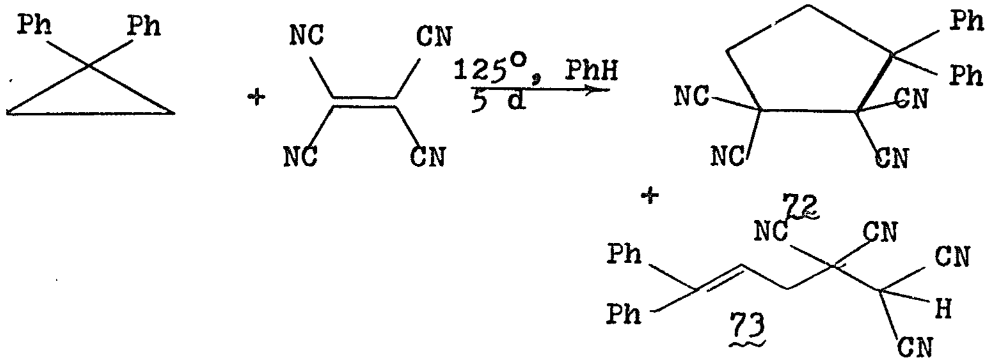


A trimethylene fragment from 2,2,4,4-tetramethyl-1,3-cyclobutadione (70) has been trapped with furan following photolysis.[74] A long-lived diradical 71 was proposed. This would appear to be in direct contradiction to the prediction that formation of the bicyclic product 47 and other cyclopropanone additions to dienes[56,61-64] would occur thermally.[31]



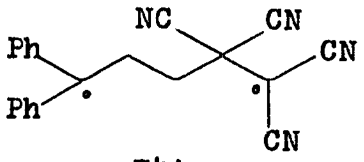
70 71

There has been one recent example of a trimethylene being trapped with an electrophilic olefin: 1,1-diphenylcyclopropane and tetracyanoethylene yielded both 1,1,2,2-tetracyano-4,4-diphenylcyclopentane (72) and 1,1-diphenyl-4,4,5,5-tetracyano-1-pentene (73) in total yield of 65%.[77] (The ratio of 72:73 was 1:1.3). 1,1-Diphenylcyclopropane was unreactive under comparable conditions, however, with maleic anhydride, fumaronitrile, and 1,1-dichloro-2,2-difluoroethylene. Although no evidence was presented, a common intermediate based on precedents[70-72] was suggested for formation of 72 and 73, namely 74A or 74B.

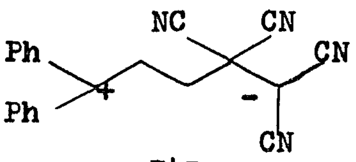


72

73



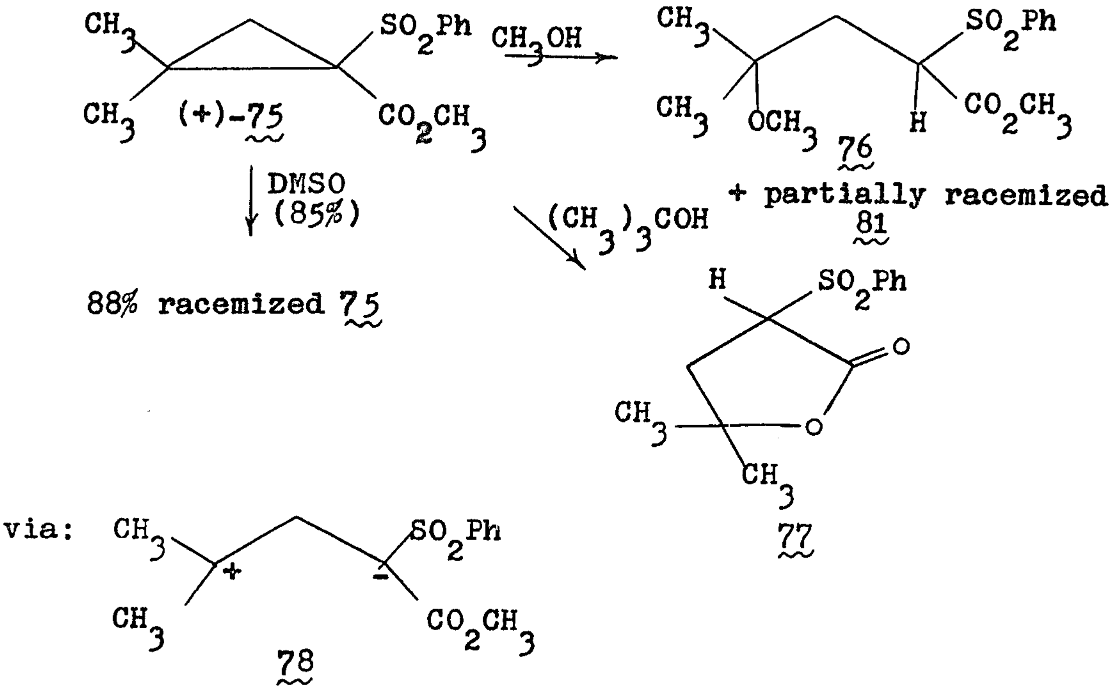
74A



74B

F. Evidence for the Existence of a 1,3-Dipolar Three-Carbon Fragment

The most conclusive evidence for the existence of a 1,3-dipolar three-carbon fragment has been shown by Cram and his co-workers.[78-81] (+)-2,2-Dimethyl-1-phenylsulfonyl-1-carbomethoxycyclopropane (75) was allowed to undergo the reactions shown below.



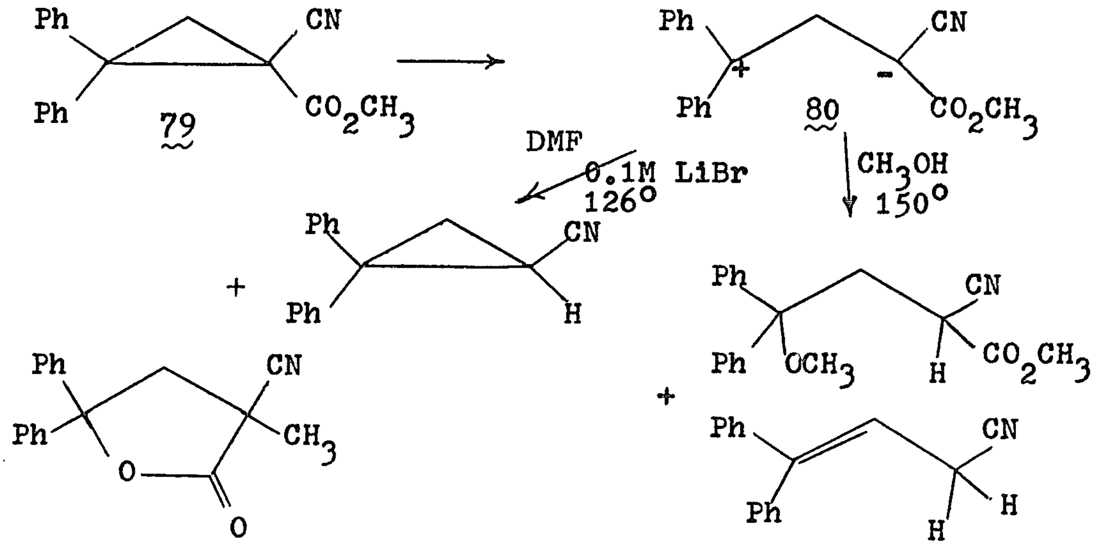
The resonance stabilized 1,3-dipolar intermediate 78 was suggested for these reactions on the basis of the following evidence.

A. Products 76 and 77 both would be expected from a zwitterion such as 78 rather than from a diradical.

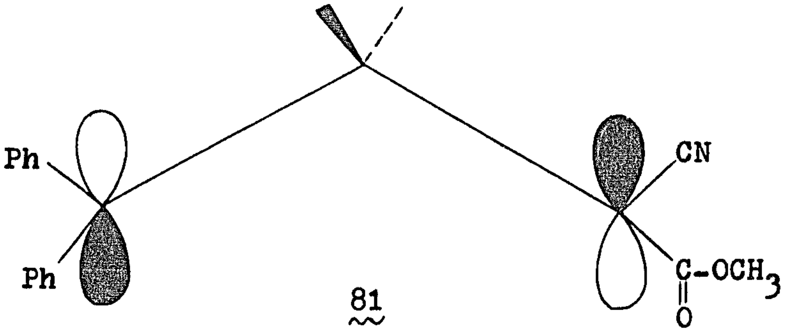
B. Both racemization and solvolysis products could be rationalized in terms of the same intermediate.

C. The ratio of the rate of solvolysis of 75 in methanol to that in *tert*-butyl alcohol is approximately 10. This is to be expected (since the methanol is more nucleophilic than the *tert*-butyl alcohol) provided there is a polar intermediate. In dimethyl sulfoxide, the rate is slightly higher than in methanol.

A similar intermediate, 80, has also been hypothesized for certain reactions of (+)-2,2-diphenyl-1-cyano-1-carbomethoxycyclopropane (79) on the basis of the product mixtures and the rate change with varying solvent.[79-81]



It was also concluded that Hoffmann's πυ-trimethylene (2A)[28] was unlikely in this situation in view of the resulting steric effects between the phenyl and carbomethoxy groups which would be present (see 81) and the solvent effects which appeared to favor a zwitterion over a diradical.



81

Conclusions From the Literature

In our studies to determine the feasibility of creating a 1,3-dipolar three-carbon fragment unaided by stabilization from the central carbon atom, several limitations were present which did not exist in most of the examples presented from the literature.

Central sp or sp^2 hybridized atoms, providing additional stabilization due to the delocalization of electrons, led to less synthetically desirable structures. These included Huisgen's 1,3-dipolar species,[9,10,13-23b] epoxide and aziridine ring openings,[19-23b,25,26] the Favorskii intermediate,[51-57] cyclopropanes,[61-64] and methylenecyclopropanes.[65-67]

The high temperatures needed to isomerize cyclopropanes[40-50] could not be used since most functional groups (including solvents and trapping agents) would be altered at such temperatures. Even strained cyclopropanes are often able to withstand moderate temperatures (100-200°) without decomposing (see next section of this thesis). Bicyclobutanes[68,70] and bicyclopentanes,[70-72] however, are so highly strained, that lower temperatures should effect ring openings. Pyrazolines,[8,29,32-35] in addition, have the advantage of being able to lose a molecule of nitrogen in the process of forming the trimethylene species, yet these species have not been trapped.

Some encouragement for the possibility of stabilization of trimethylene has been offered by the observation that 1,1-diphenylcyclopropane can be trapped by tetracyanoethylene[77] to give the appropriately substituted cyclopentane,[79] although the yield was only about 28%. In addition, Cram's work[78-81] has shown that suitable substituents appear to aid formation of a zwitterionic intermediate. However, no examples of an unaided 1,3-dipolar ion being trapped have been shown.

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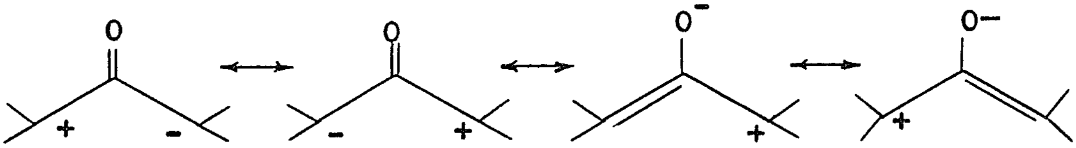
Part II

Cycloaddition of Cyclopropanes to Olefins

PART II

Statement of the Problem

Each example of five-membered carbocyclic ring syntheses in the discussion and review section of this thesis,[7,8,56,67-72,74,77] was quite specific. In two examples, highly strained ring systems were thermolyzed and trapped, namely the [1.1.0] bicyclobutane[68,69] and [2.1.0] bicyclopentane[69-72] systems. Trapping of the Favorskii intermediate,[51-57] cyclopropanones[61-64] and methylenecyclopropanes[67] were attributed to resonance stabilized intermediates such as 82.

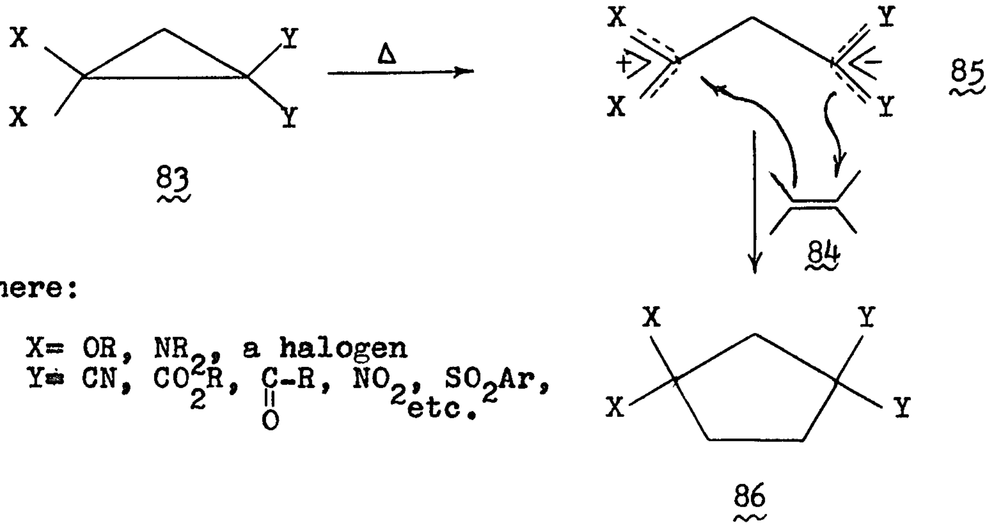


82

It was our intention to devise a system which would have general synthetic utility, without involving lengthy multistep syntheses.[82,85,151] We hoped to thermally isomerize appropriately substituted cyclopropanes whose ring opening would result in a stabilized 1,3-dipolar zwitterion which could be trapped with olefins (Mechanism 1). The specific substitution patterns used are discussed in the following pages.

A reasonable alternative to this approach would have been the use of an olefin whose double bond would provide a nucleophilic attack on a cyclopropane system, opening the ring and subsequently reclosing to a cyclopentane (Mechanism 2).

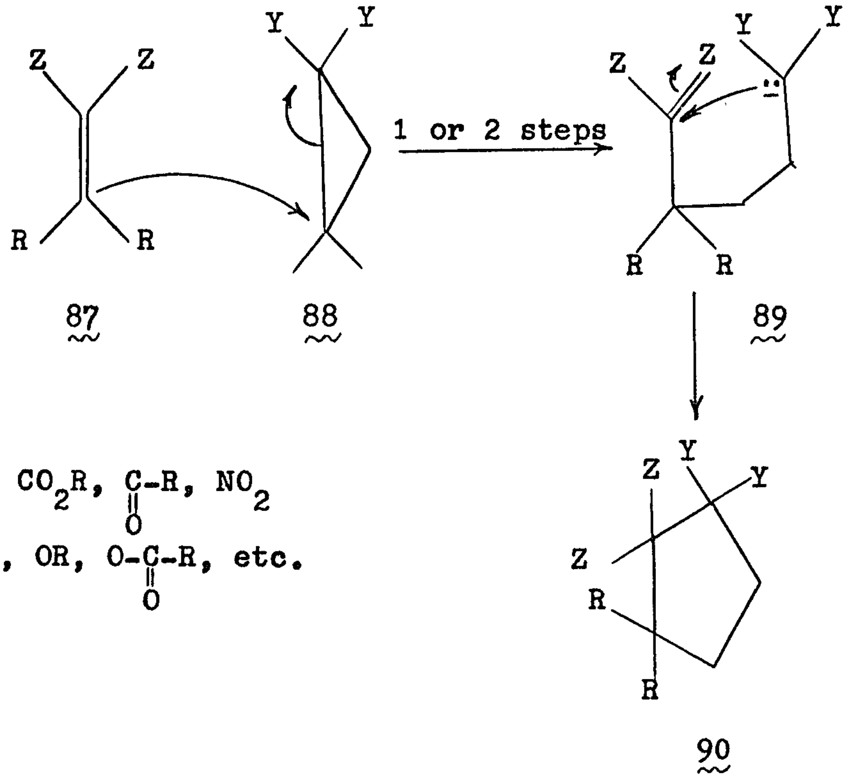
(Mechanism 1)



where:

X= OR, NR_2, a halogen
Y= CN, CO_2R, $\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\text{-R}$, NO_2, SO_2Ar, etc.

(Mechanism 2)



where:

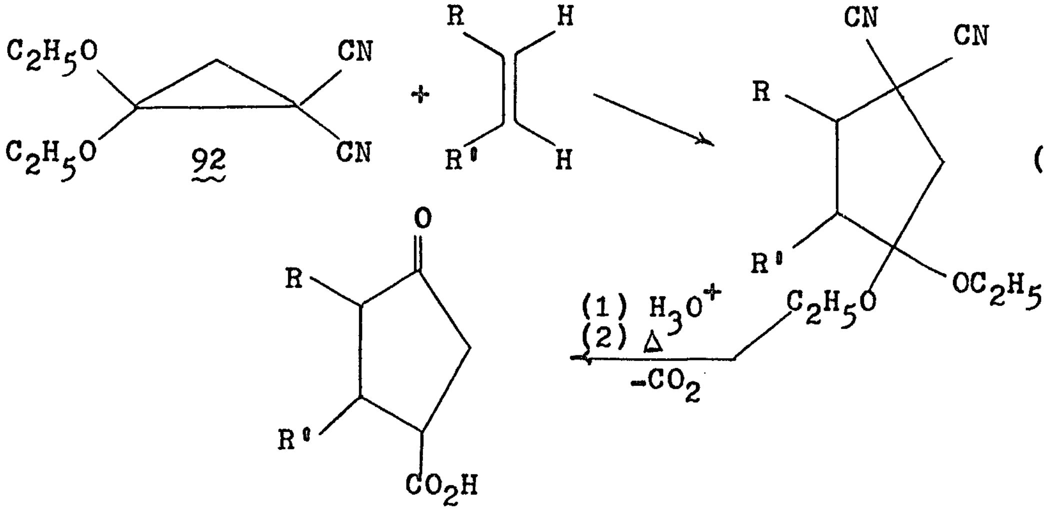
X= CN, CO_2R, $\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\text{-R}$, NO_2

Z= NR_2, OR, $\text{O-}\underset{\overset{\|}{\mathrm{O}}}{\mathrm{C}}\text{-R}$, etc.

Cyclopropane Syntheses

We attempted to synthesize two unknown cyclopropanes, 1,1-diethoxy-2,2-dicyanocyclopropane (92) and 1-ethoxy-2,2-dicyanocyclopropane (97), plus two previously synthesized cyclopropanes, ethyl *cis-* and *trans*-2-ethoxycyclopropanecarboxylate (95A and B)[110-112] and 1,1-dimethyl-2,2-dicyanocyclopropane (96).[113-115] The various attempted routes to these cyclopropanes, both the successful and the unsuccessful are shown in equations 1-7.

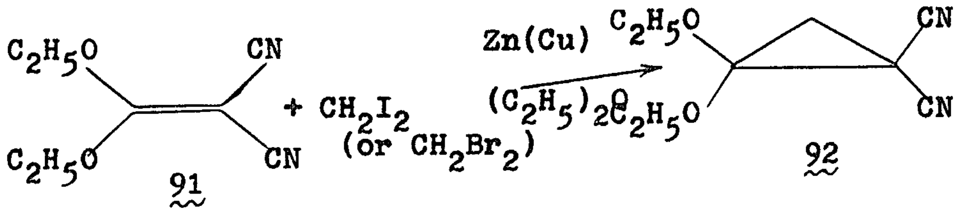
There were a number of advantages to the substitution pattern found in the cyclopropane: (A) Excellent charge stabilization would have been present in the zwitterionic intermediate 85; (B) Because of the tetrasubstitution, determining the stereochemistry (other than at the ring juncture) would not have presented a problem; (C) Upon trapping of the intermediate with an olefin, the resulting cyclopentane derivative would have had easily alterable substituents providing a means to unambiguous identification (e.g., see equation 1 below) and allow further synthetic elaboration.



(1)

Four different synthetic routes were used in our attempt to synthesize the cyclopropane 92.

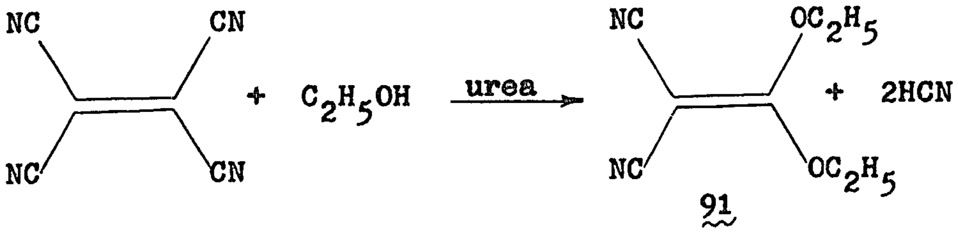
Attempted Preparation of 1,1-Diethoxy-2,2-dicyanocyclopropane (92) via the Simmons-Smith Reaction (Equation 2).



(2)

The Simmons-Smith reaction[1,2,83-89,92] offered several advantages, among them being discrimination toward double bonds, lack of rearrangements, and stereospecificity.

The dicyanoketene diethyl acetal (91) was synthesized by the method of Middleton and Engelhardt[90,91] from tetracyanoethylene and ethanol using urea as a catalyst (Equation 9).

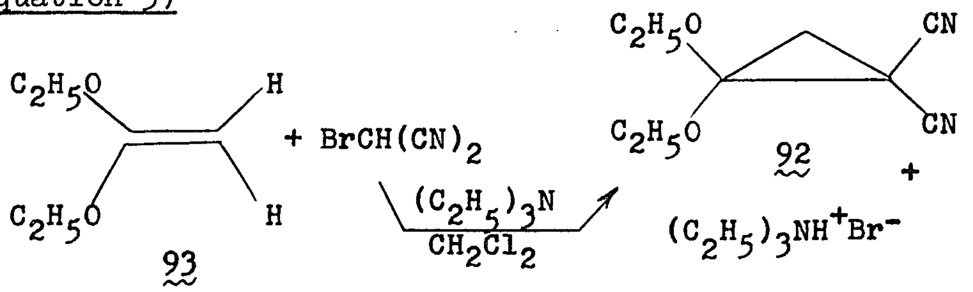


(9)

The zinc-copper couple was prepared by two different methods, that of Shank and Schechter[88] and that of LeGoff.[89,92] Both methylene iodide[84-87] and methylene bromide[89] were used as methylene transfer agents. Although diethyl ether was the[117] most common solvent used, 1,2-dimethoxyethane was also tried.

Reaction time was varied from one to three days; the reaction mixture was sometimes blanketed with nitrogen, but in all experiments only starting materials were recovered or polymerized products were obtained. Consequently this synthetic route was abandoned.

Attempted Preparation of 1,1-Diethoxy-2,2-dicyanocyclopropane (92) from Ketene Diethylacetal (93) and Bromomalononitrile (Equation 3)

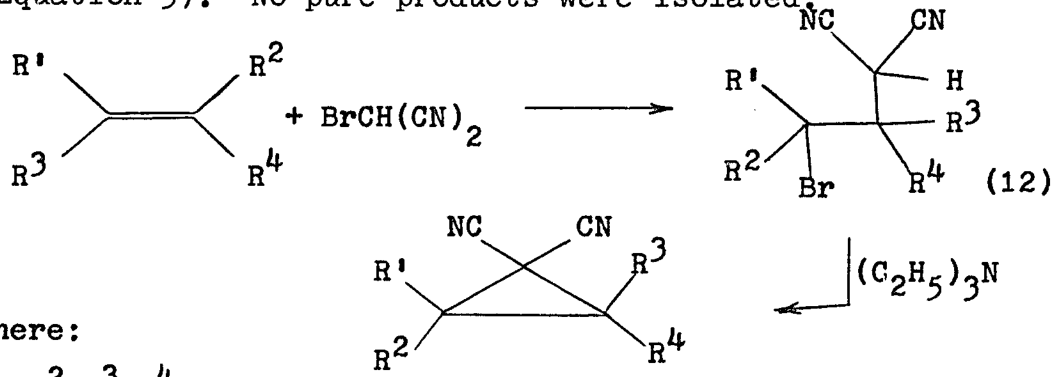


(3)

The ketene diethyl acetal (93) was prepared from bromoacetal and potassium t-butoxide (Equation 10).[94] Bromomalononitrile was prepared from malononitrile and bromine in water (Equation 11).

$$CH_2(CN)_2 + Br_2 \xrightarrow{H_2O} BrCH(CN)_2 \tag{11}$$

Boldt and Schulz had previously used this method to prepare dicyanocyclopropanes from alkenes and bromomalononitrile (Equation 12).[114,115] The analogous reaction using ketene diethyl acetal as the alkene was not successful (Equation 3). No pure products were isolated.

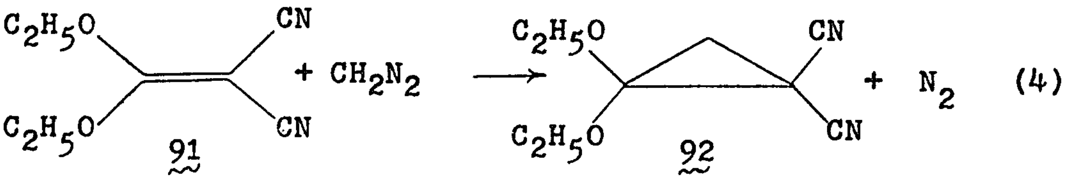


(12)

where:

R',R^2,R^3,R^4 = CH_3 or H

Attempted Preparation of 1,1-Diethoxy-2,2-dicyanocyclopropane (92) from Dicyanoketene Diethylacetal (91) and Diazomethane (Equation 4)



(4)

This method, which has precedent,*[1,2,83,95,96,98,100] was abandoned after two unsuccessful attempts, upon learning of the hazards of this system with diazomethane.**

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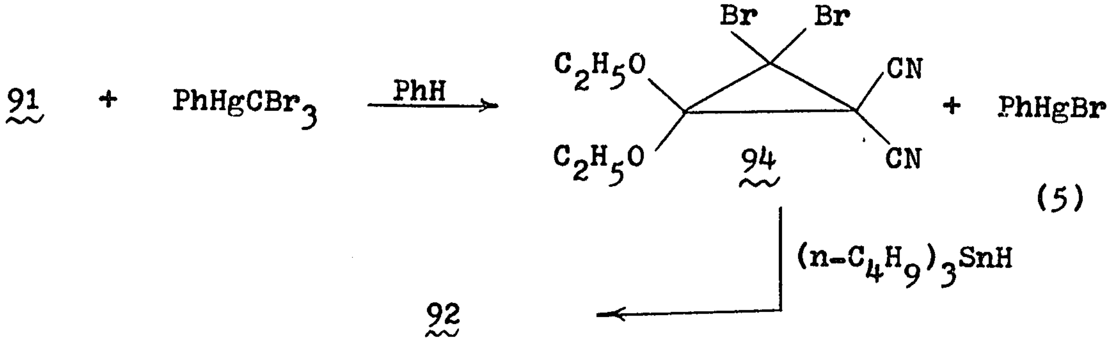
* The method used for the preparation of diazomethane was that described in "The Aldrich Company Catalog" (1967), p. 11, in which N-methyl-N-nitroso-p-toluenesulfonamide ("Diazald") was decomposed by potassium hydroxide in ethanol.

** We thank Dr. H.O. House for his advice concerning the hazards involved.

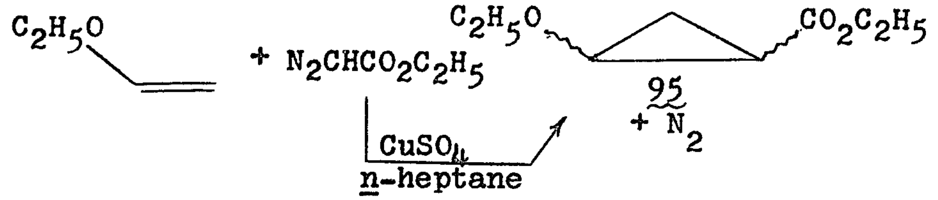
Attempted Preparation of 1,1-Dibromo-2,2-diethoxydicyanocyclopropane (94) from Phenyltribromomethylmercury Addition to Dicyanoketene Diethylacetal (91)[101-107] (Equation 5)



(5)

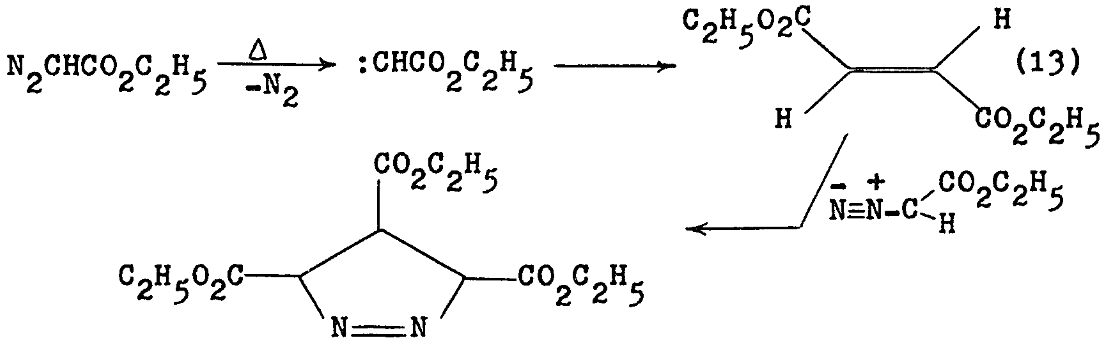
After synthesis of phenyltribromomomethylmercury via the method of Seyferth[106] from phenylmercuric bromide, bromoform and potassium *t*-butoxide,[108] its reaction with the dinitrile 91 gave only starting materials plus some polymeric residue. Since phenylmercuric bromide (a Lewis acid) is one of the expected products of the reaction (Equation 5), an acid catalyzed polymerization can occur here.[93]

Preparation of Ethyl 2-ethoxycyclopropanecarboxylate (95) (Equation 6)



(6)

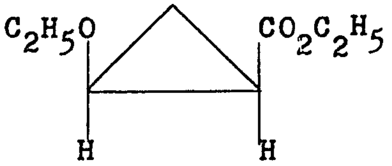
The attempt to prepare the ester 95 from ethyl vinyl ether and ethyl diazoacetate according to the literature method[110-112] in which ethyl vinyl ether is used as solvent, yielded only starting materials plus triethyl pyrazoline-3,4,5-tricarboxylate (98). This arose via the dimerization of carbethoxycarbene followed by a 1,3-dipolar cycloaddition[9,10] of ethyl diazoacetate (Equation 13).



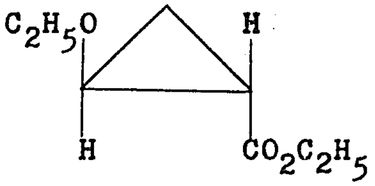
(13)

98

Addition of *n*-heptane, which increased the reaction temperature to 56° (an increase of 20° compared to ethyl vinyl ether as solvent) allowed the desired cycloaddition to occur giving a mixture of the *cis* and *trans* isomers (95A and 95B) respectively in 77% yield. The isomers were nearly completely separable on a spinning band column.

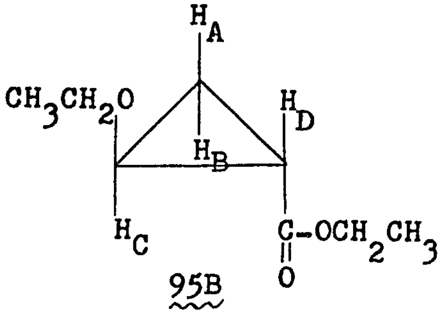


95A



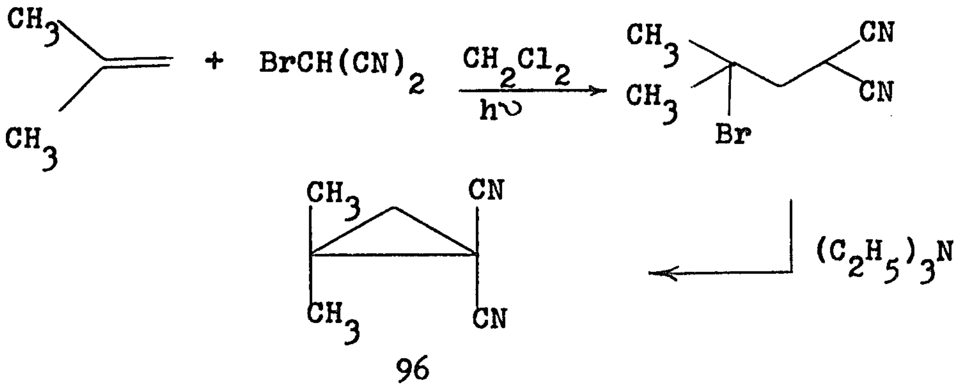
95B

The infrared spectrum was consistent with the structure of 95A showing an ester peak at 1724 cm^{-1} and several C-O stretching absorptions at 1160, 1115, 1096, 1070 and 1056 cm^{-1}. No double bond peaks were present. The nmr spectrum of the predominating isomer[‡] confirmed the structure of 95B as follows (see structure below). There were two 3H triplets, one at 8.84 and another at 8.77τ (J=7 Hz) indicative of the two methyl groups, a 2H multiplet in the region 8.67-9.02τ for H_A and H_B, another 1H multiplet between 8.15 and 8.50τ (H_C), a 1 H multiplet between 6.33 and 6.68τ for H_D, a 2H quartet centered at 6.50τ (J=7 Hz) indicating the ether methylene group and a 2H quartet centered at 5.98τ (J=7 Hz) for the ester methylene function.



95B

Preparation of 1,1-Dimethyl-2,2-dicyanocyclopropane (96) (Equation 7)



(7)

96

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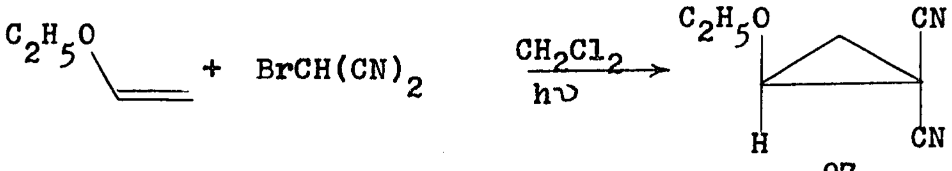
‡ Skell and Etter[110,111] claimed that when this reaction was run thermally (no heptane used) they obtained a 6:1 ratio of trans:cis isomer. Our ratio was 2.1:1.

This known cyclopropane was prepared in 84% yield from the photolytic reaction of isobutylene with bromomalononitrile followed by elimination of hydrogen bromide and ring closure with the use of triethylamine (see Equation 7).[115] The infrared and NMR spectra were consistent with the structure assigned and with the values given in the original description.[115]

Attempted Preparation of 1-Ethoxy-2,2-dicyanocyclopropane (97) (Equation 8)



97

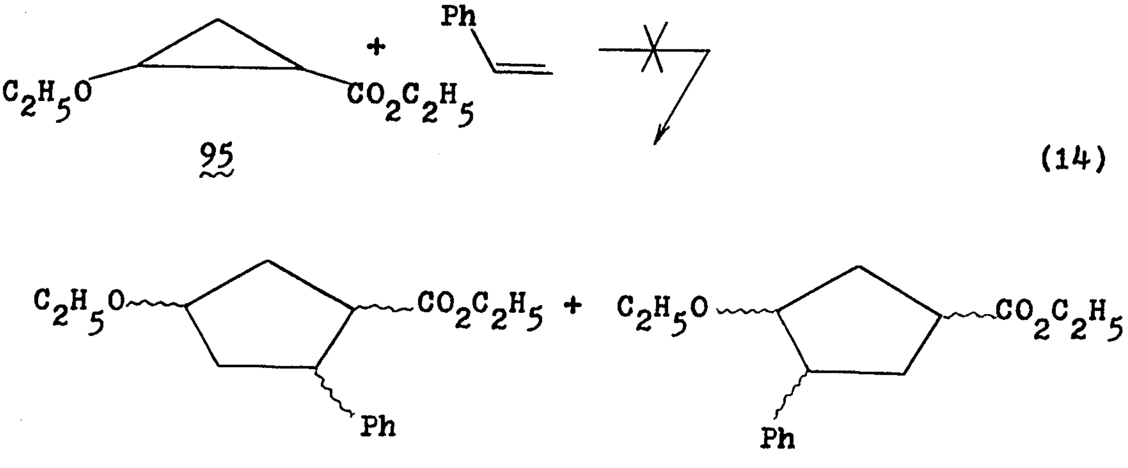
(8)

An attempt to prepare this cyclopropane via the method analogous to that used in the preparation of the dicyanocyclopropane 96 failed to produce any of the desired compound.

Attempted Additions of Cyclopropanes to Olefins

The two known cyclopropanes, ethyl 2- ethoxycyclopropane carboxylate (95) and 1,1-dimethyl-2,2-dicyanocyclopropane (96) were each treated with certain olefins under varied conditions (as shown in Equations 14-20).

CHART II

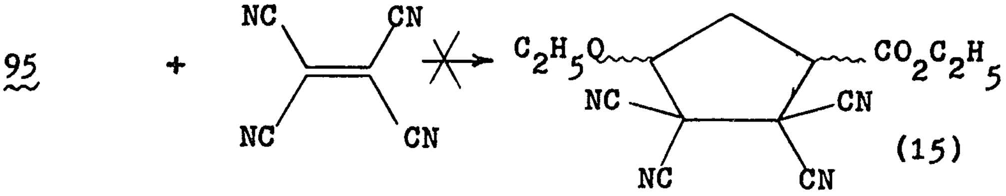


95

(14)

99A

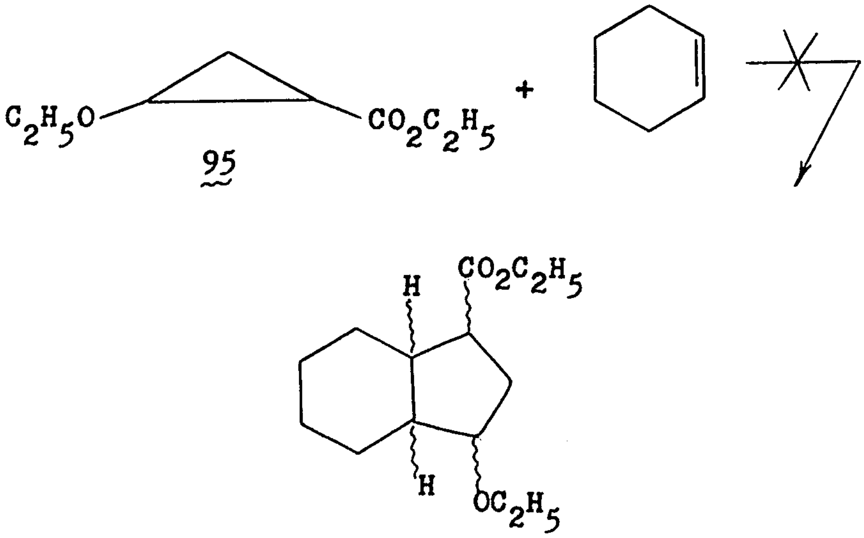
99B



95

100

(15)

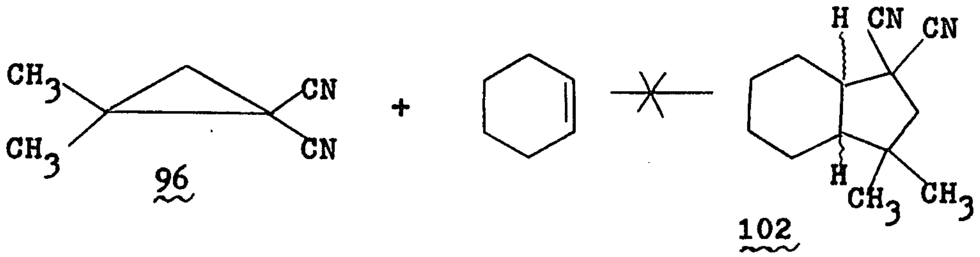


95

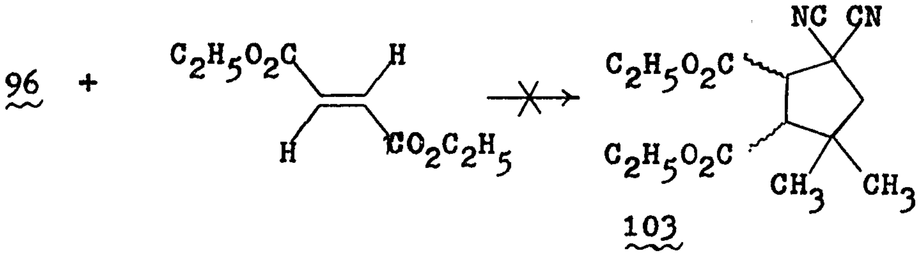
(16)

101

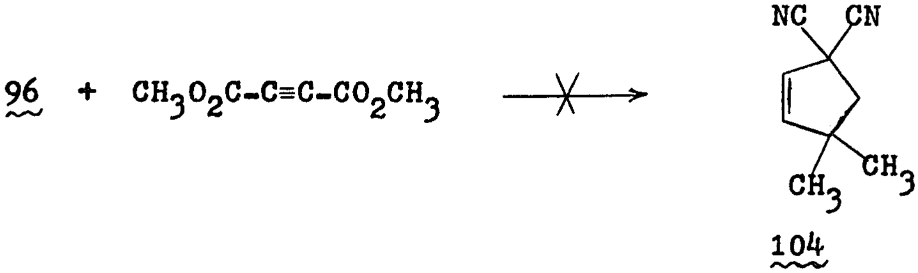
CHART II (CONTINUED)



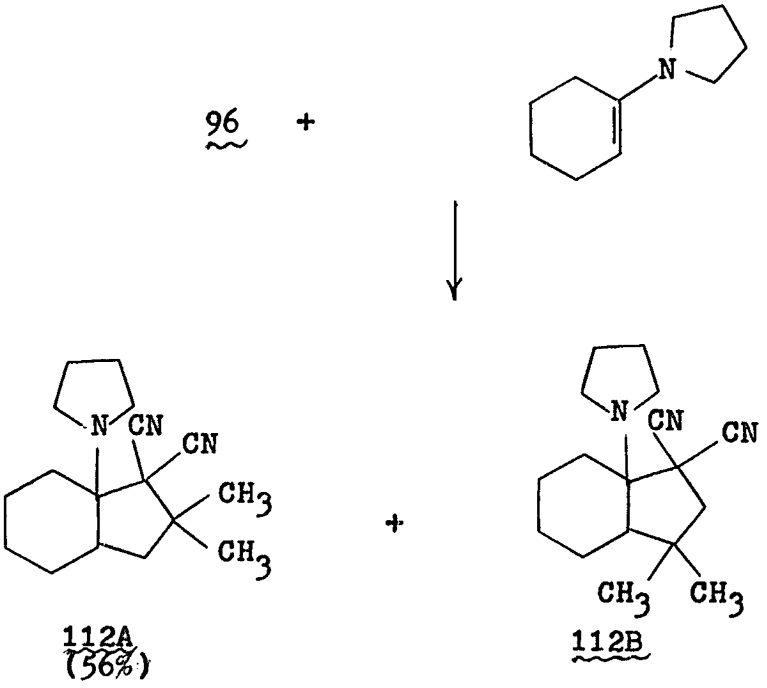
(17)



(18)



(19)



(20)

TABLE I *

Equation no.	Cyclo-propane	Alkene or Alkyne	Solvent System	Reaction Temp./Time	Result
14	**95**	Styrene	A	146°/30 min‡	Polymerization plus starting materials
14	**95**	Styrene	B	233°/26 hrs‡	Polymerization plus starting materials
14	**95**	Styrene	C	150°/79 hrs‡	Polymerization
15	**95**	Tetracyano-ethylene	C	140°/11 hrs	Polymerization plus undesired product
15	**95**	Tetracyano-ethylene	D	169°/7 hrs	Polymerization
16	**95**	Cyclohexene	C	137°/6days	Starting materials & undesired product
17	**96**	Cyclohexene	D	133°/6 days	No reaction
18	**96**	Diethyl fumarate (DEF)	A	218°/6 days	Undesired products
18	**96**	Diethyl fumarate (DEF)	C	145°/19 hrs	Polymerization

---

‡ A Varian 1200 chromatograph, fitted with a 5 ft x 1/8 in SE-30 on Chromosorb P column was used.

* See key to Table I, on page 15.

TABLE I (CONTINUED) *

Equation no.	Cyclopropane	Alkene or Alkyne	Solvent System	Reaction Temp./Time	Result
18	96	Diethyl fumarate (DEF)	E	428°/4 hrs	Charred
18	96	Diethyl fumarate (DEF)	E	330°/4 hrs	Polymerization
18	96	Diethyl fumarate (DEF)	E	280°/5 hrs	Charring plus undesired product
18	96	Diethyl fumarate (DEF)	E	255°/1¼ hrs	Same as 280°
18	96	Diethyl fumarate (DEF)	F	400°/25 sec	Starting material plus undesired product
19	96	Dimethyl acetylene dicarboxylate	A	100°/35 hrs	Undesired product
20	96	N-pyrrolidino-cyclohexene	G	148°/31 hrs	Obtained 112A (56%)
20	96	N-pyrrolidino-cyclohexene	C	141°/5 hrs	Obtained 116

* Key to TABLE I

A. No solvent (trapping agent acts as solvent)
B. Ph_2O
C. DMSO
D. DMF
E. gas phase pyrolysis - sealed tube
F. gas phase pyrolysis - flow tube
G. Xylene

When ethyl 2-ethoxycyclopropane-1-carboxylate (95) was heated with styrene, polymerization occurred whether solvent was used or not and whether or not hydroquinone was present. Most likely the styrene either copolymerized with the cyclopropane 95 or removed it from the system by trapping it within its own polymeric network, because gas chromatography showed that the starting material was not present at the end of each reaction.

Reaction of cyclopropane 95 with tetracyanoethylene also yielded polymeric residues, following workup. Even when some material was isolated, it melted above 400° and showed no cyano peaks in its infrared spectrum.

Cyclohexene proved useless as a trapping agent for cyclopropane 95 in dimethyl sulfoxide at 133°, except for the formation of a very small amount of white solid which contained no ester peaks in its infrared spectrum.

Cyclohexene also proved to be unreactive when used as a trapping agent for 1,1-dimethyl-2,2-dicyanocyclopropane (96) in dimethylformamide under similar conditions.

When cyclopropane 96 was dissolved in refluxing diethyl fumarate only dark brown oils, none of which contained any cyano functions (ir) were present. High-temperature sealed-tube reactions of cyclopropane 96 and diethyl fumarate provided charred material above 300°, and polymer plus some material containing no cyano groups at lower temperatures (see Table I and experimental section for details). Polymerization was also a problem when the cyclopropane 96 and diethyl fumarate were reacted in dimethyl sulfoxide.

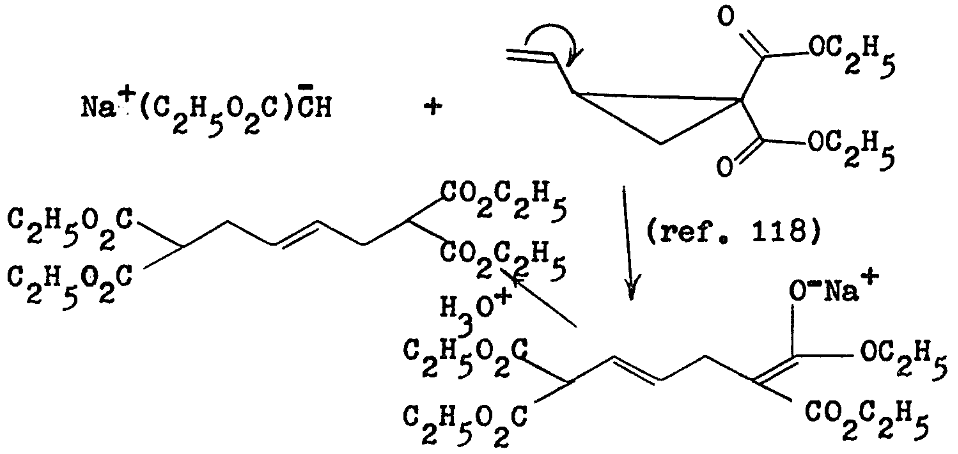
Dimethyl acetylenedicarboxylate had one advantage over all the other trapping agents used: only one cycloaddition product was possible, namely 104. However, after reaction under the indicated conditions, preparative thin layer chromatography yielded six materials, none containing cyano groups.

Neither of the cyclopropanes 95 or 96 was thus able to undergo cycloaddition prior to either polymerization of the trapping agent itself or the copolymerization of the cyclopropane with the olefin. Both cyclopropanes 95 and 96 were tested for polymerizability in dimethyl sulfoxide. Both were heated in dimethyl sulfoxide at 147° for five hours with no observable change. Although it was not investigated, a ring opening and closing certainly was a strong possibility in view of that proposed in Cram's work[78-81] (See Part I, also p. 28).

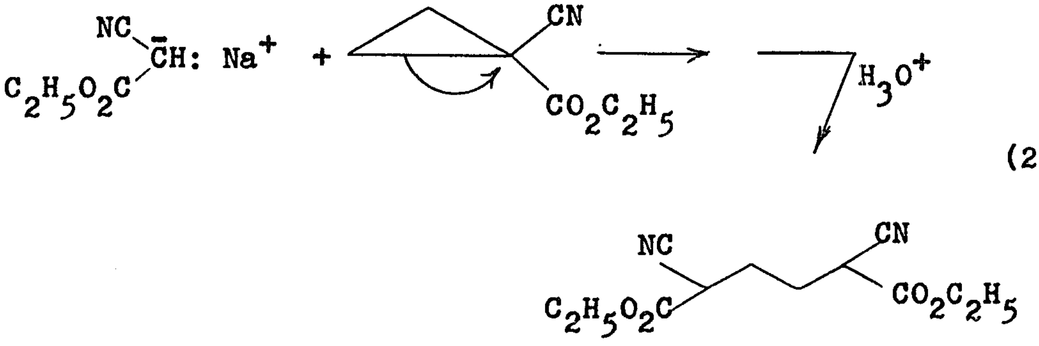
Michael Type of Cycloaddition of N-Pyrrolidinocyclohexene to 1,1-Dimethyl-2,2-Dicyanocyclopropane (96)

All of the previously mentioned trapping agents had one common property: they were all electrophilic or at least non-nucleophilic (cyclohexene).

Nucleophilic openings of cyclopropanes are well known[118-120] (Equations 21-23, for example).

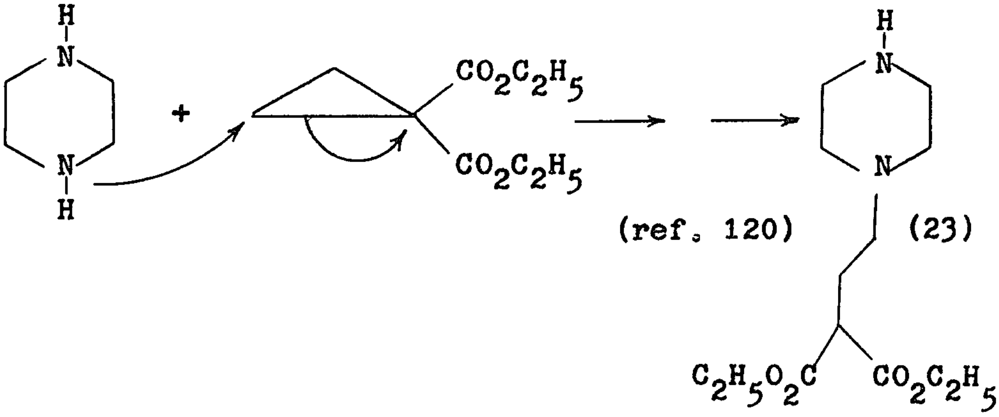


(21)



(22)

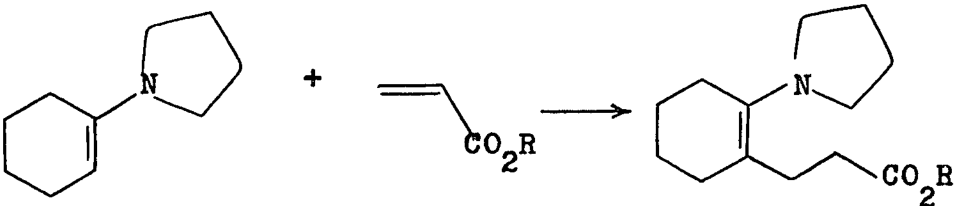
(ref. 119)



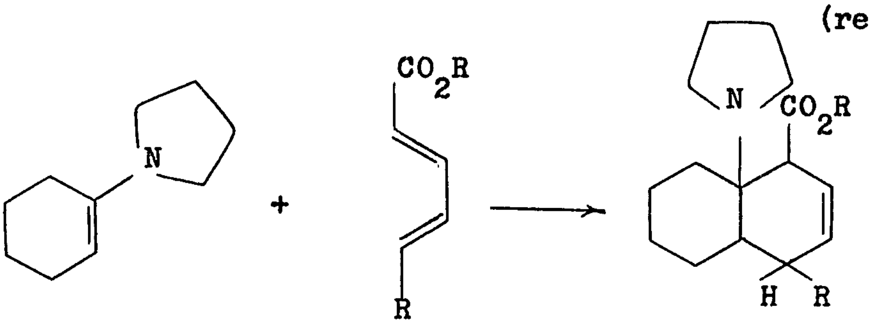
(ref. 120)

(23)

Nucleophilic additions and cycloadditions of enamines to various electrophiles are also well documented (Equations 24-27).[120-126]

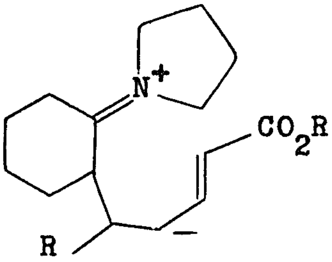

(24)

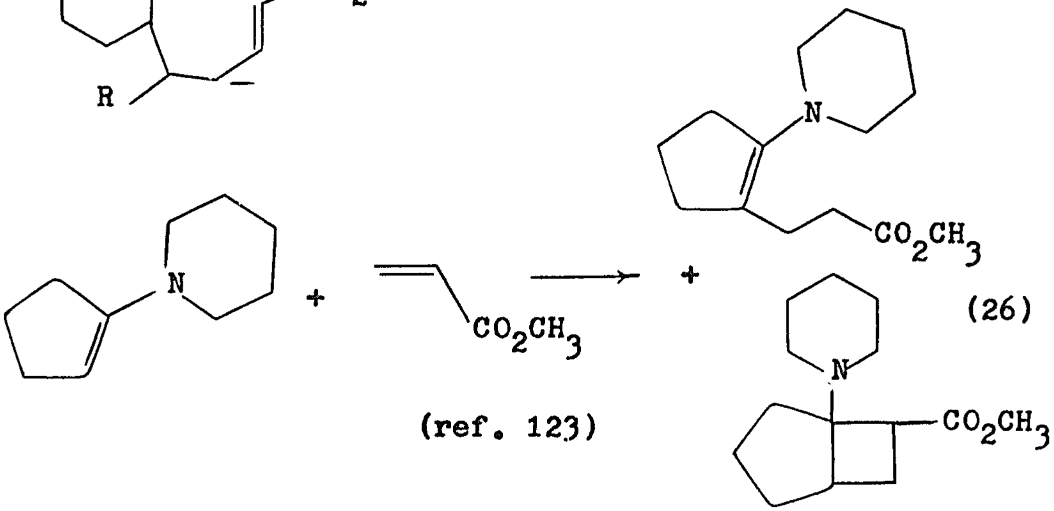
(ref. 114)


(25)

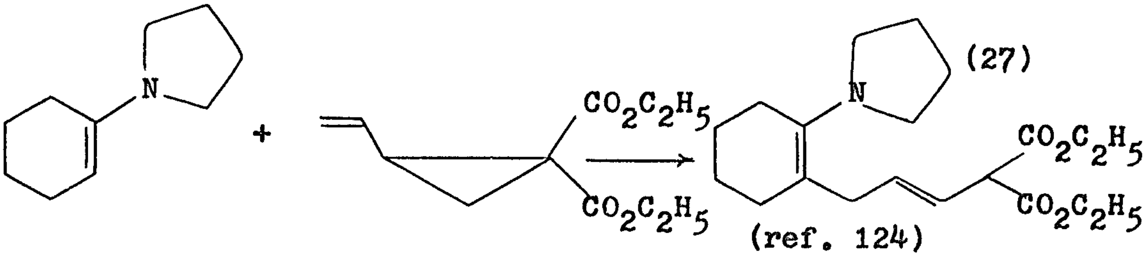
(ref. 115, 116)

via:



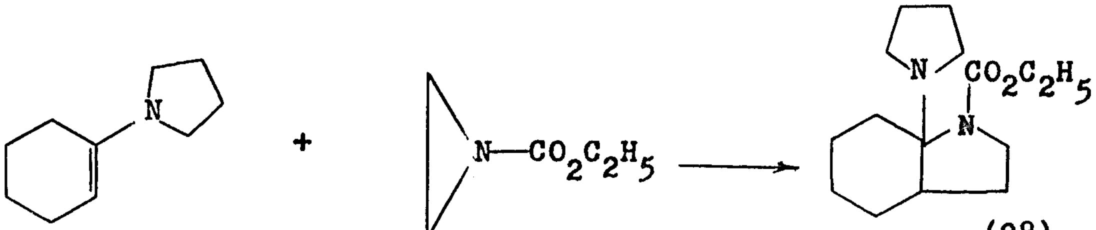

(26)

(ref. 123)


(27)

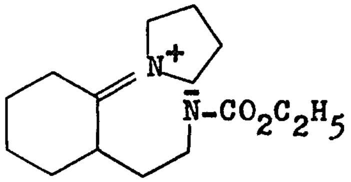
(ref. 124)

N-Pyrrolidinocyclohexene adds to N-carbethoxyaziridine[125] forming the cycloadduct 106.

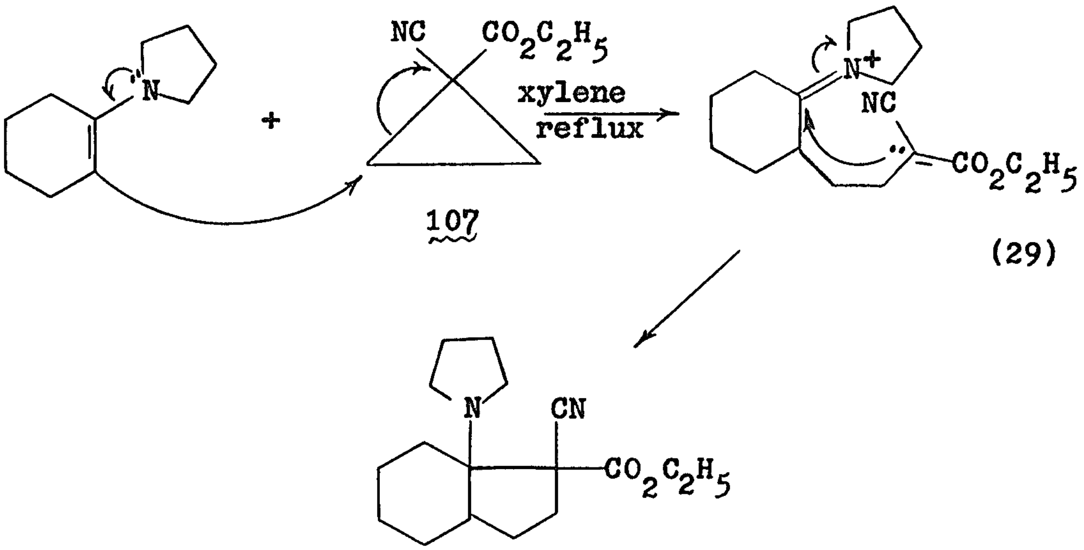


106 (28)

via:



There have only been two examples of nucleophilic attack on a cyclopropane by enamines.[127] N-Pyrrolidinocyclohexene reacted with ethyl 1-cyanocyclopropanecarboxylate (107) in refluxing xylene in a hypothesized Michael fashion to yield cycloadduct 108 in 41% yield (Equation 29).

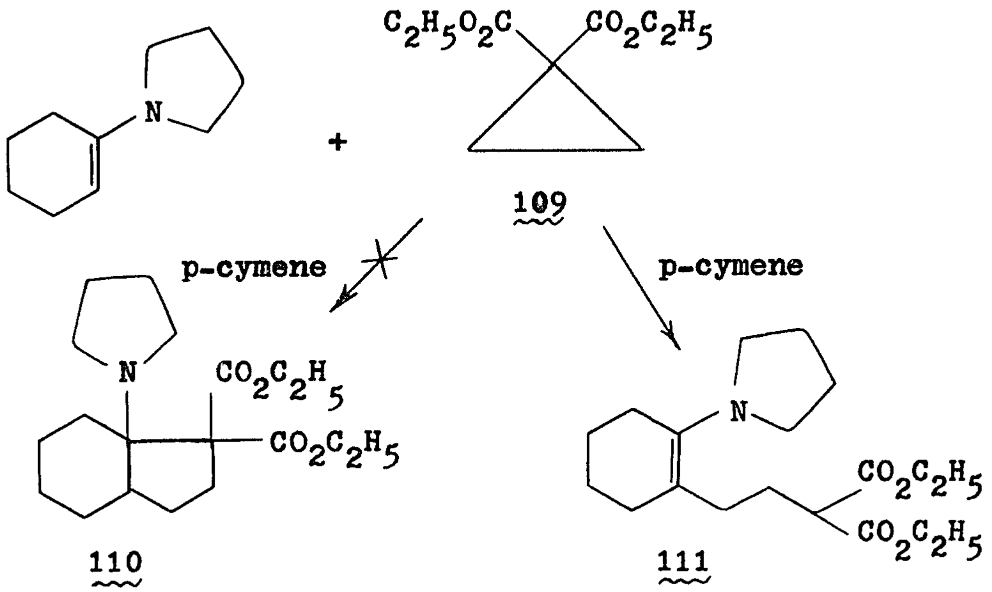


107

(29)

108

Yet the diester 109, in refluxing xylene or p-cymene, gave 111 rather than cycloadduct 110 (Equation 30). One possible explanation offered for the failure to undergo cycloaddition was the extra steric hindrance in the diester between the pyrrolidine ring and the ester group. This was not present in the cyano ester 108.

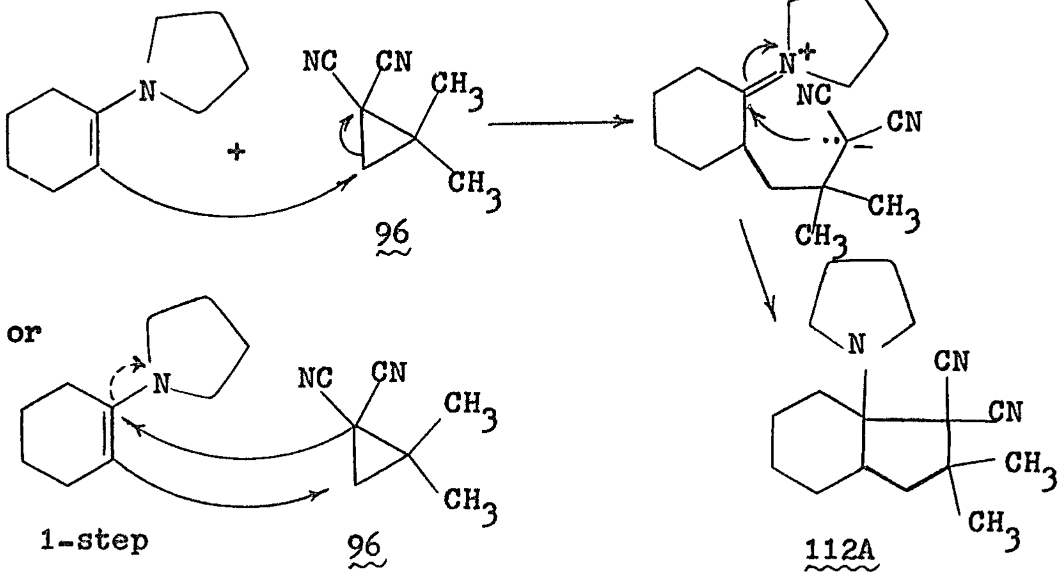


(30)

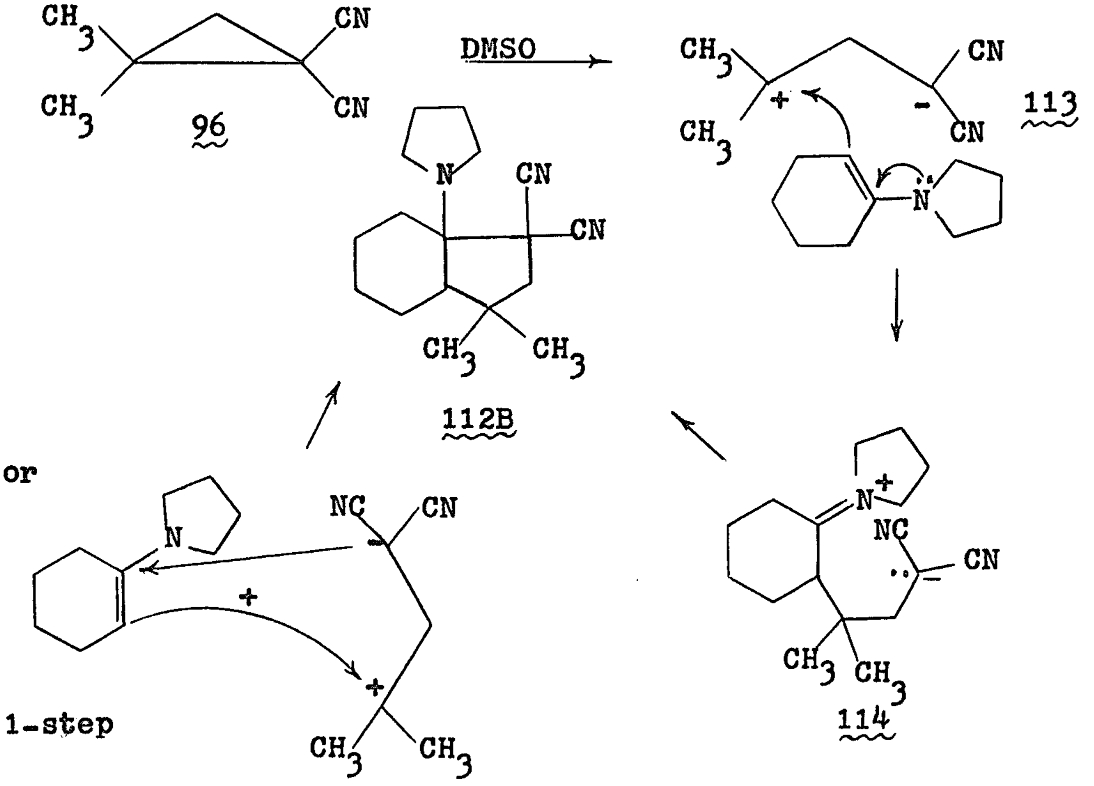
It was our intention to see if we could extend this reaction to cyclopropane 96. This system offered several advantages over that of the cyano ester 107. The presence of the dimethyl groups would force attack by the enamine on the unsubstituted carbon of cyclopropane 96 if attack did occur via the Michael addition route (Mechanism 1). If 112A was the cycloadduct, this would be evidence for a Michael reaction, although the question of whether the reaction took place in one or two steps would still be in doubt. If however, prior stabilization of the dipolar species 119 occurred, then adduct 112B should have been the major product (Mechanism 2).

We felt that it would also be of interest to compare the effect of dimethyl sulfoxide to that of xylene as solvent. Would the use of dimethyl sulfoxide aid stabilization of intermediate 113, leading to adduct 112B? Our past experience (see Part II, pp. 11-14), has shown us that such prior stabilization was unlikely.

(Mechanism 1)

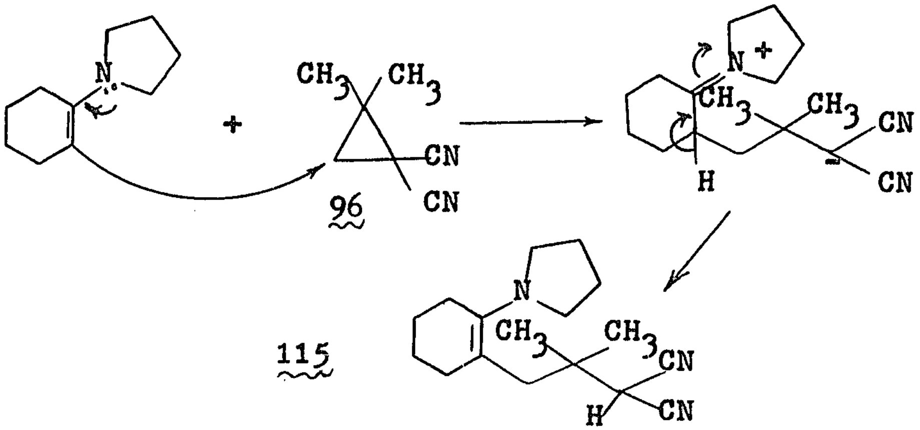


(Mechanism 2)

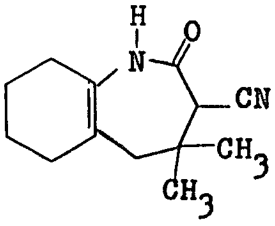


We therefore heated N-pyrrolidinocyclohexene and cyclopropane 96 in refluxing xylene for 31 hours and, after removing the solvent and excess enamine, obtained a yellow oily distillate which eventually crystallized yielding two white solids. The major product (most likely 112A was produced in 56% yield. It melted at 78-79° giving a proper analysis for an adduct with the formula $C_{17}H_{25}N_3$. The product was slightly alkaline (pH 8) and was quite soluble in 3N hydrochloric acid. The infrared spectrum ($CHCl_3$) showed peaks at 2934 and 2849 cm^{-1} (C-H) and a strong cyano peak at 2232 cm^{-1}. The NMR spectrum ($CDCl_3$) showed singlets due to the 2 methyl groups at 8.62 and 8.55τ, a complex multiplet between 6.40 and 8.50τ caused by the splittings of the ring methine and methylene hydrogens and an unresolved A_2B_2 multiplet at 6.90τ due to the hydrogens on the pyrrolidine ring. The actual integration was impossible to determine due to the overlap of the peaks. The mass spectrum indicated a parent peak corresponding to the adduct at m/e 271.

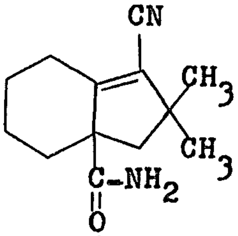
That the structure is indeed that of 112A or 112B and not 115 (arising from Mechanism 3, below), can be shown by the following evidence. Firstly, the adduct has no UV absorption above 210 mμ, whereas typical enamines absorb in the region 220 to 235 mμ (ϵ4 x 10^3 to 9 x 10^3).[128] Secondly, the adduct has no carbon-carbon double bond stretching peak in its infrared spectrum, whereas typical enamines absorb at approximately 1640 cm^{-1}.[129] The question of *cis* vs *trans* ring juncture still remains.



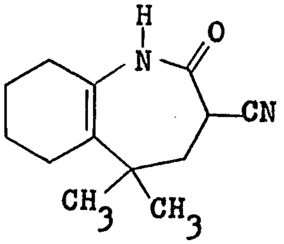
The other product, melting at 165-166°, did not arise solely from a simple cycloaddition, for its composition indicated the formula to be $C_{13}H_{18}N_2O$.



116A



116B

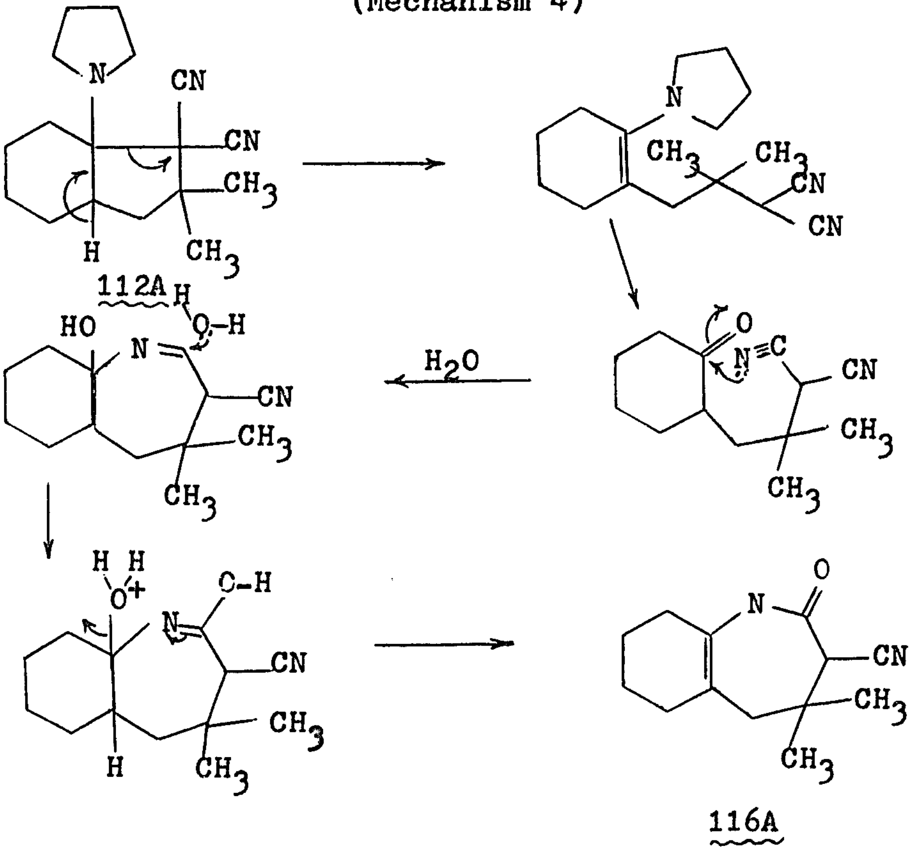


116C

The structure 116A or 116B is suggested, based on the following evidence. The UV spectrum showed a λmax at 264 mμ ($\epsilon 1.19 \times 10^4$), indicative of a conjugated system and could be consistent with either 116A or 116B. The infrared spectrum ($CHCl_3$) showed peaks at 3472 and 3367 ($-\underset{\overset{\|}{O}}{C}-NH_2$), 2188 (conjugated $-C{\equiv}N$), 1701 ($-\underset{\overset{\|}{O}}{C}-NH_2$), 1645, 1597 (N-H bending of $-\underset{\overset{\|}{O}}{C}-NH_2$) and 1376, 1364 (gem-dimethyl) cm^{-1}. The five indicated amide bands (i.e. 3472, 3367, 1701, 1645 and 1597 cm^{-1}) are classical for a primary amide.[129] This would appear to favor 116B. However, the NMR spectrum (acetone - d_6) appears to favor 116A, showing a singlet at 7.82τ (1H, $-\underset{\underset{H}{|}}{C}-CN$) and a broad singlet at 4.65τ (1H, $\overset{\overset{O}{\|}}{\wedge}NH-$) which washes out in D_2O. Other peaks in the spectrum were 2 singlets at 8.96 and 8.80τ (6H, $\begin{matrix}CH_3\\CH_3\end{matrix}\!>\!C\!<$), a singlet at 7.94τ (~2H, $\overset{\|}{\wedge}CH_2$), and a complex multiplet between 7.12 and 8.68τ (~8H, ring hydrogens). The possibility of 116C, although less likely, has not been eliminated by nmr. In addition, the adduct 112A, in refluxing 95% ethanol, gave 116 in quantitative yield. However, in refluxing absolute ethanol, no such conversion occurred.

We can hypothesize the formation of 116 (A or B) via Mechanism 4 or 5, respectively. There is precedent for formation of the lactam 116A.[153] Both the hydrolysis of the enamine (Mechanism 4) and the loss of the pyrrolidine ring (Mechanism 5) would be expected to occur only with the aid of acids. Conversion of nitriles to amides for that matter are usually done in refluxing acid (or occasionally basic hydrogen peroxide) although a few neutral catalytic conditions are known.[*][‡]

(Mechanism 4)



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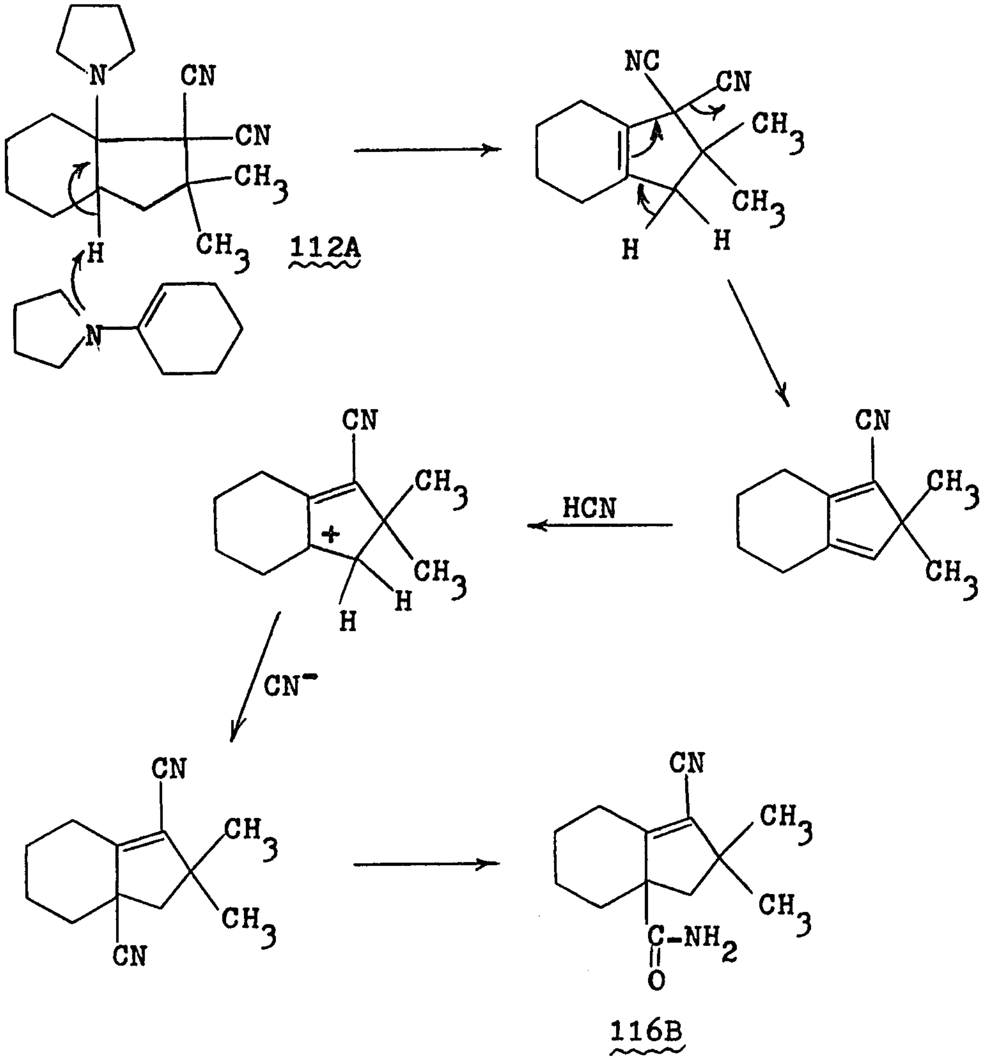
[*] Nitriles can be converted to amides with a zinc-nickel catalyst in boiling water or at room temperature in water with manganese dioxide as catalyst. See A.L.J. Beckwith in J. Zabicky, "The Chemistry of Amides," Interscience Publishers, N.Y. (1970), p. 124, ref. cit.

[‡] The unconjugated nitrile would appear to be more susceptible to hydrolysis, since that nitrile carbon is more electrophilic than the conjugated nitrile carbon, which can delocalize its partial positive charge into the double bond.

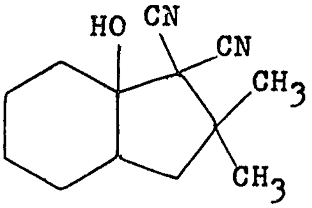
(Mechanism 5)



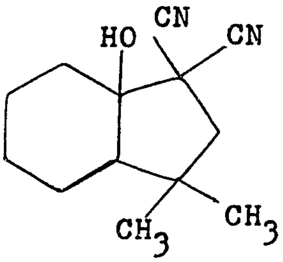
Although it seems easier to rationalize 116A as the correct structure, the occurrence of the infrared peak for a conjugated nitrile (2188 cm^{-1}) remains unexplained as do the peaks for the primary amide. Yet the NMR is inconsistent with 116B since the N-H singlet integrates for only one proton (consistent with 116A).

The existence of compound 116 also provides additional evidence for not considering the enamine structure for the adduct (i.e. 115) since the loss of a pyrrolidine ring, resulting in an amide, $C_{13}H_{18}N_2O$, would be impossible.

A second derivative of 112A was obtained by passing some of the original yellow oil, obtained upon fractionation of the reaction mixture through a chromatographic column (silica packed in n-hexane). Only two pure fractions were isolated; one was 116, the other, a compound which has tentatively been assigned the structure 117A (based on 112A) rather than 117B..



117A



117B

The cyano hydrindanol compound is isomeric with 116 and has the very interesting property of exhibiting three separate melting points, although analysis and spectra are identical in each case. Elution from the chromatography column yielded a compound melting at $108.0-108.8^\circ$. After recrystallization from boiling carbon tetrachloride, the melting point became $134.0-134.2^\circ$. A second identical recrystallization yielded the same substance melting at 95.0° C (sharp). It is not known if the three exhibiting melting points are due to different crystalline modifications.

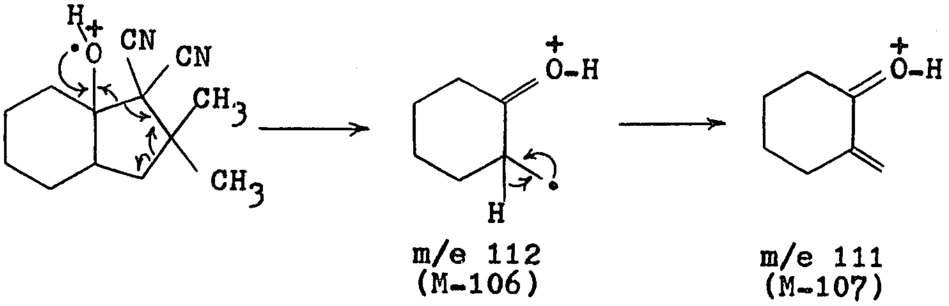
Spectral evidence for 117 included the fact that there was no UV absorption above 210 mμ . The infrared ($CHCl_3$) showed two bands at 3559 and 3333 cm^{-1} (O-H), a peak at 2247 (unconjugated CN), another peak at 1368 cm^{-1}, peaks at 1134 and 1109 cm^{-1} (tertiary OH).[129] The NMR ($CDCl_3$) indicated two singlets, one at 8.58τ and the other at 8.55τ (6H, $>C<^{CH_3}_{CH_3}$), a complex multiplet between 7.83 and 8.75τ (11H, ring hydrogens) and a singlet at 7.60τ (1H, washes out in D_2O, O-H). A parent peak in the mass spectrum at m/e 218 also lent support to the formula for 117.

The existence of a tertiary alcohol group was confirmed by a negative N-bromosuccinimide test.[130]

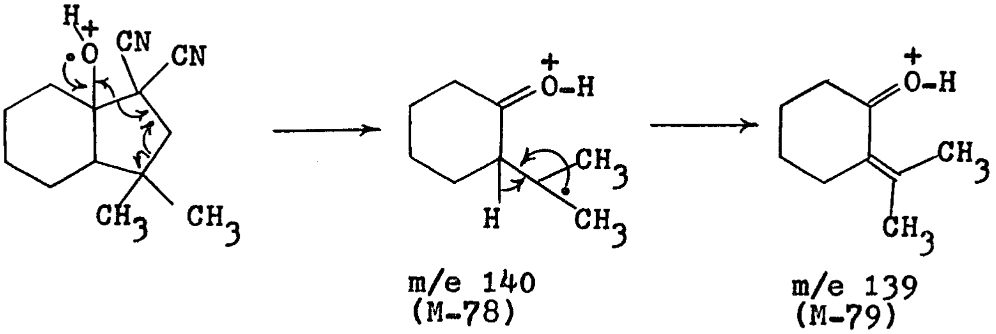
Although it seems fairly well established that cycloadduct 112 resulted from the cycloaddition of 1,1-dimethyl-2,2-dicyanocyclopropane (96) and N-pyrrolidinocyclohexene, the position of the methyl groups remains in question. As mentioned previously, the Michael type of cycloaddition shown on page 21 should lend support to cycloadduct 112A while a previously stabilized dipolar intermediate, 113, should lead to adduct 112B.

Two pieces of mass spectral evidence favor structure 112A rather than 112B. (See spectra on following pages). A mass spectrum of 117 shows the most abundant peak to be at m/e 111 and a peak at m/e 112, which is slightly more than half the height of the 111 peak. This can be rationalized via the decomposition shown in Mechanism 6 resulting from the hydrindanol 117A. The analogous decomposition for 117B (Mechanism 7) should result in peaks at m/e 139 and 140. However, neither peak is present.

(Mechanism 6)

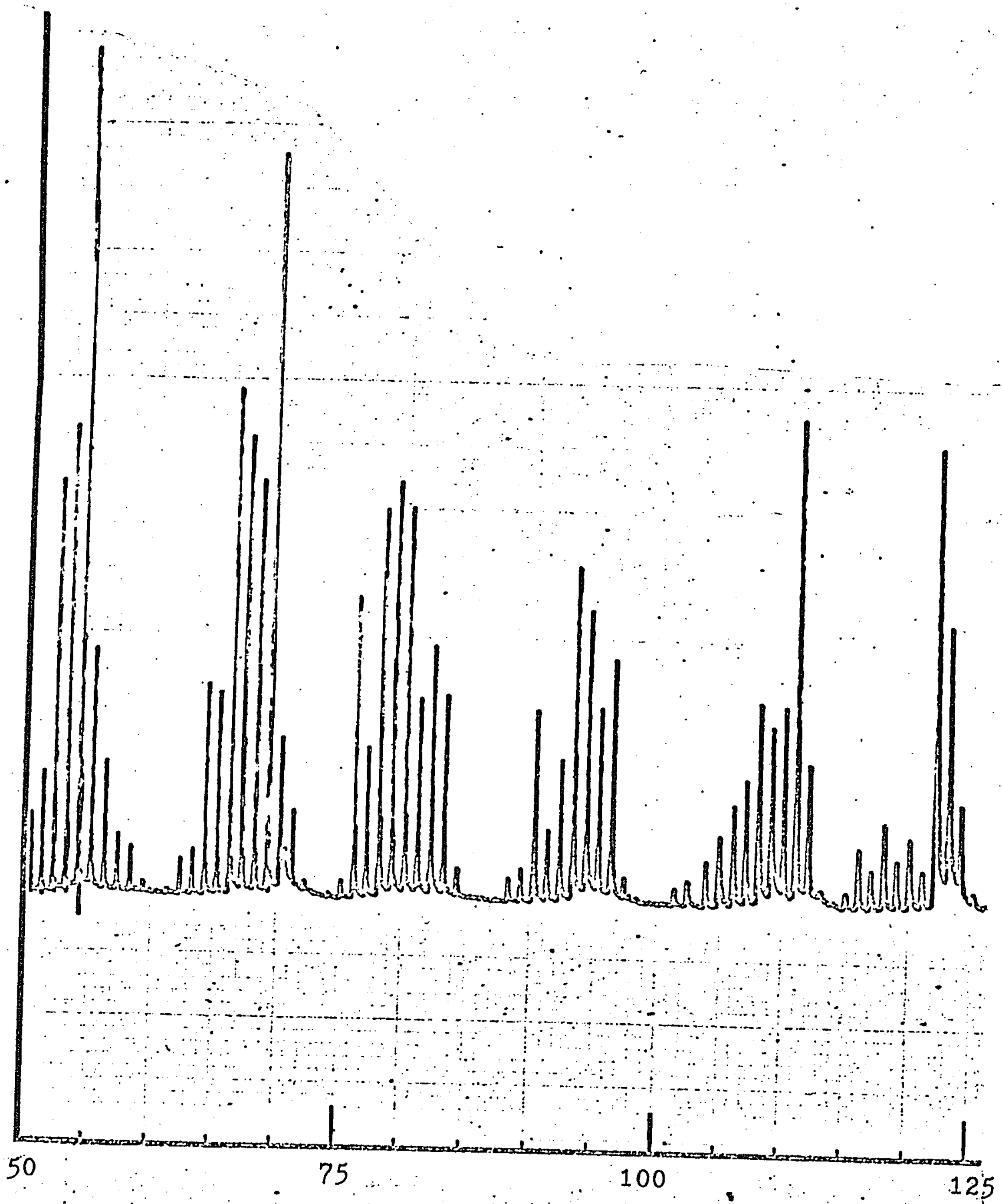


(Mechanism 7)

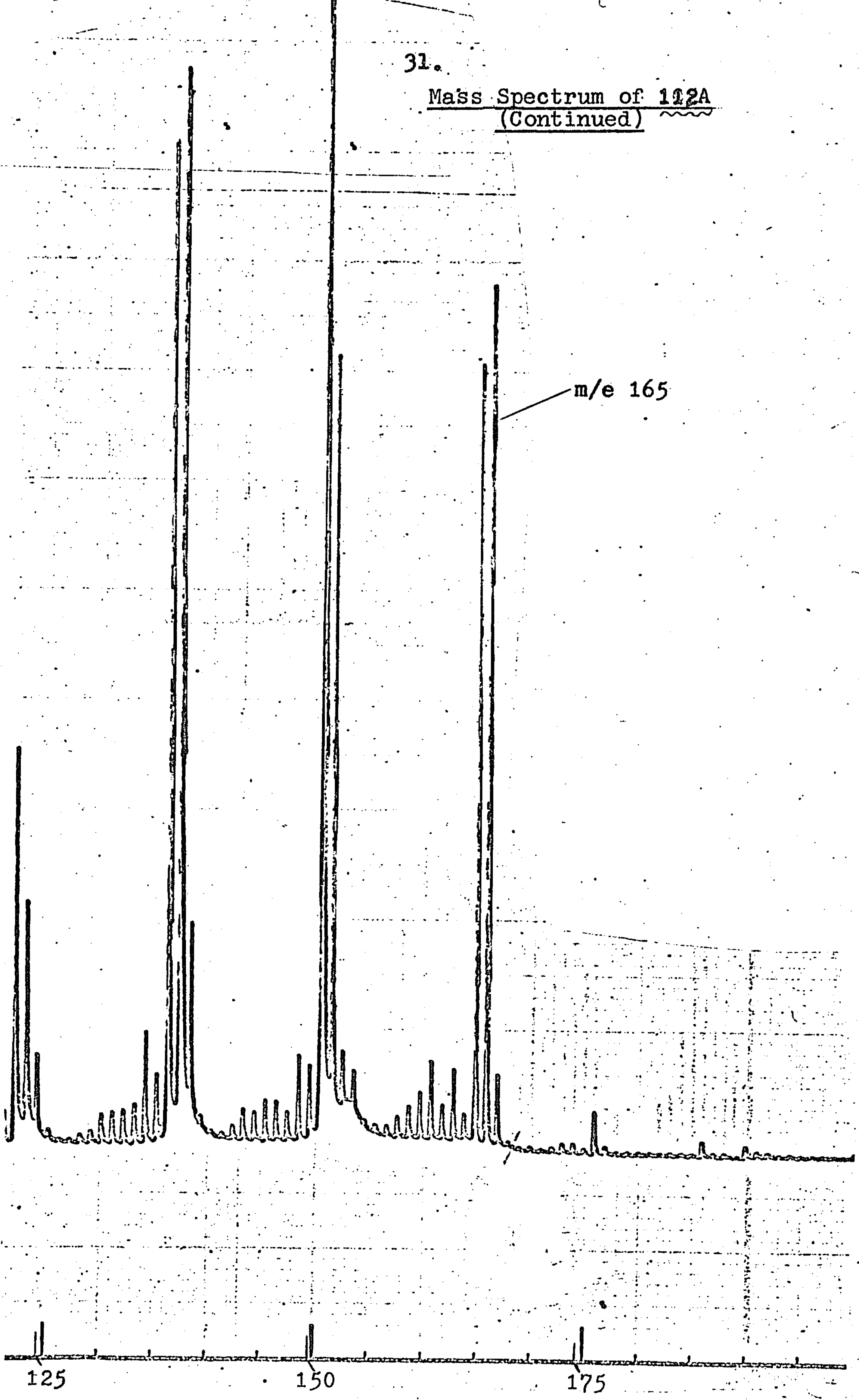


An analogous decomposition can be rationalized for the appearance of an abundant peak in the mass spectrum of 112A at m/e 164 and 165 (Mechanism 8). None, however, appears at m/e 192 or 193, which would correspond to the decomposition of 112B (Mechanism 9).

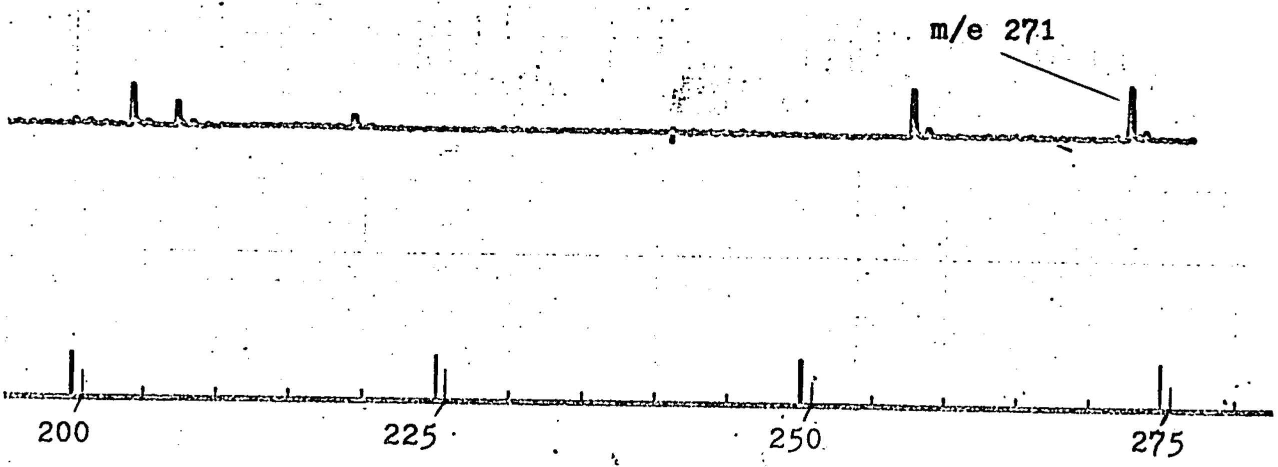
Mass Spectrum of 1,1-Dicyano-2,2-dimethyl-8-pyrrolidinohydrindane(**112A**)



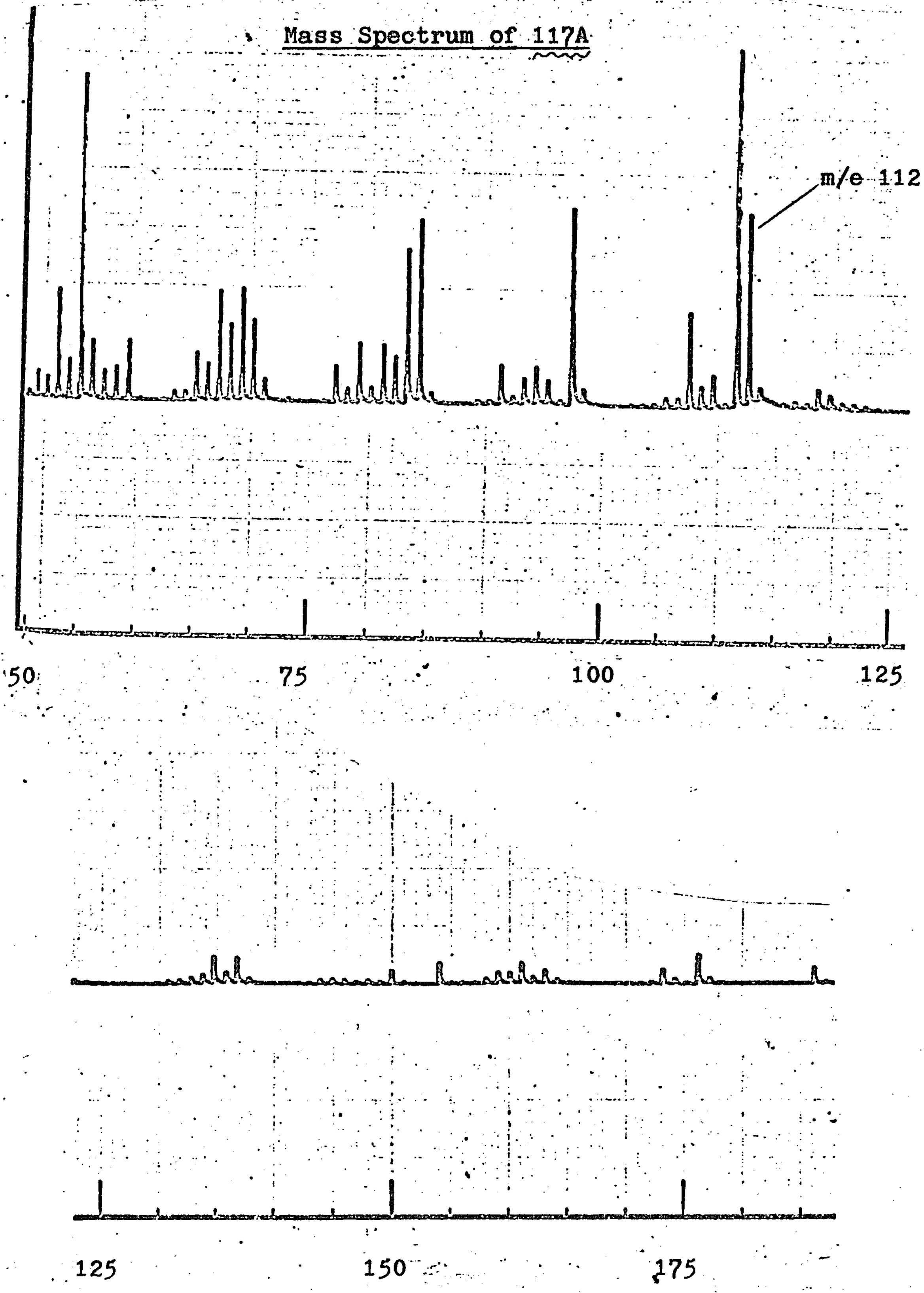
Mass Spectrum of 112A
(Continued)



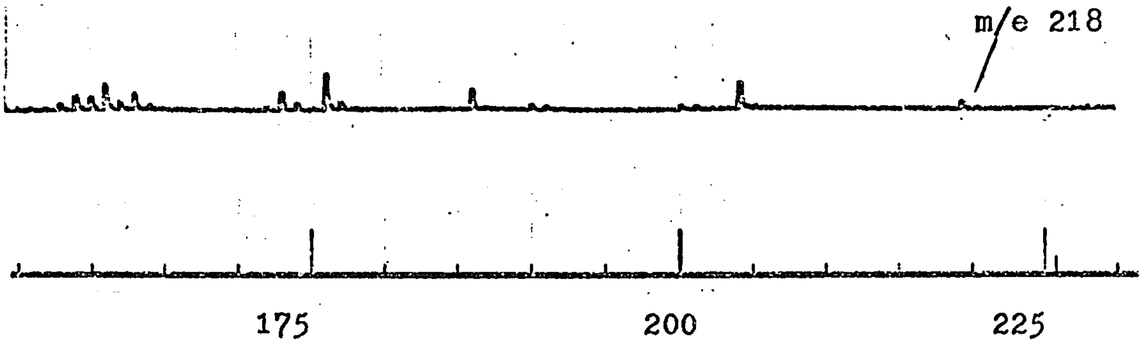
Mass Spectrum of 112A
(Continued)



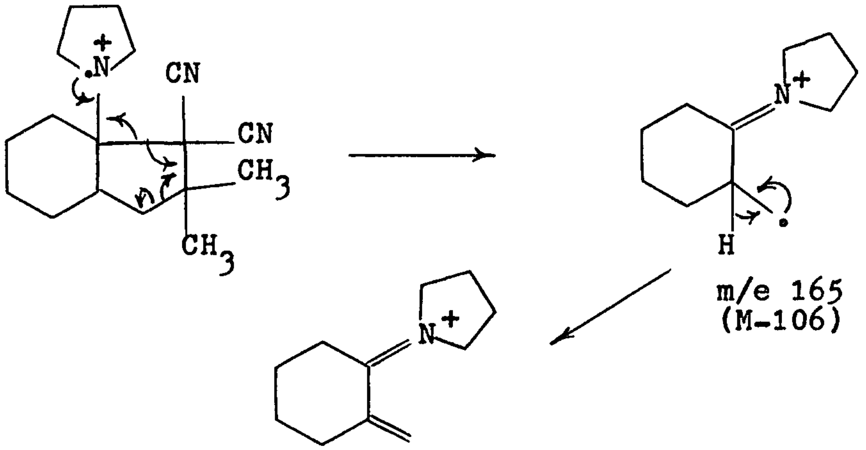
Mass Spectrum of 117A



Mass Spectrum of 117A (Continued)



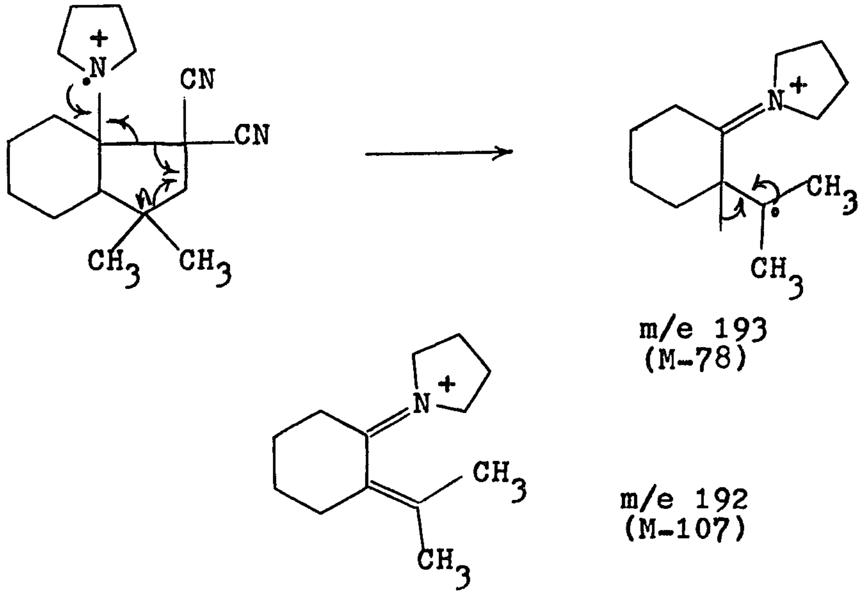
(Mechanism 8)



m/e 165
(M-106)

m/e 164
(M-107)

(Mechanism 9)



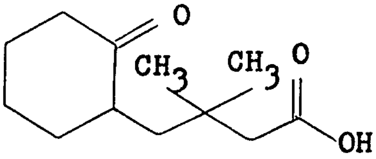
m/e 193
(M-78)

m/e 192
(M-107)

Since an unequivocal synthesis of cycloadduct 112A did not seem possible, the independent synthesis of a key derivative seemed reasonable as an alternative method of structure proof.

Attempted Structure Proof of Cycloadduct 112A

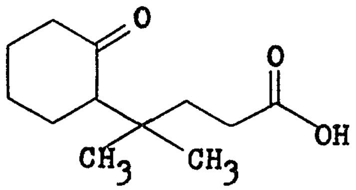
Thus, hydrolysis of cycloadduct 112A, using 70% sulfuric acid at 148° for 27 hours gave a small amount of keto acid (crude yield, 24%) which has been tentatively assigned the structure 118A on the basis of chemical and spectral evidence as well as precedent.[123,125]



118A

Evidence for the -COOH group included peaks in the infrared spectrum at 3472 cm^{-1} (COOH monomer) and a broad area between 2817 and 2513 cm^{-1} (COOH dimer). A peak at 1692 cm^{-1} was also present, probably due to both carbonyl peaks. The NMR spectrum (see Experimental, p. 68) clearly showed a one proton peak in the carboxylic acid region (-1.14τ), which was washed out with D_2O and the remainder of the spectrum was consistent with (although not confirmatory of) the structure. The analysis was also consistent with the formula for structure 118A.

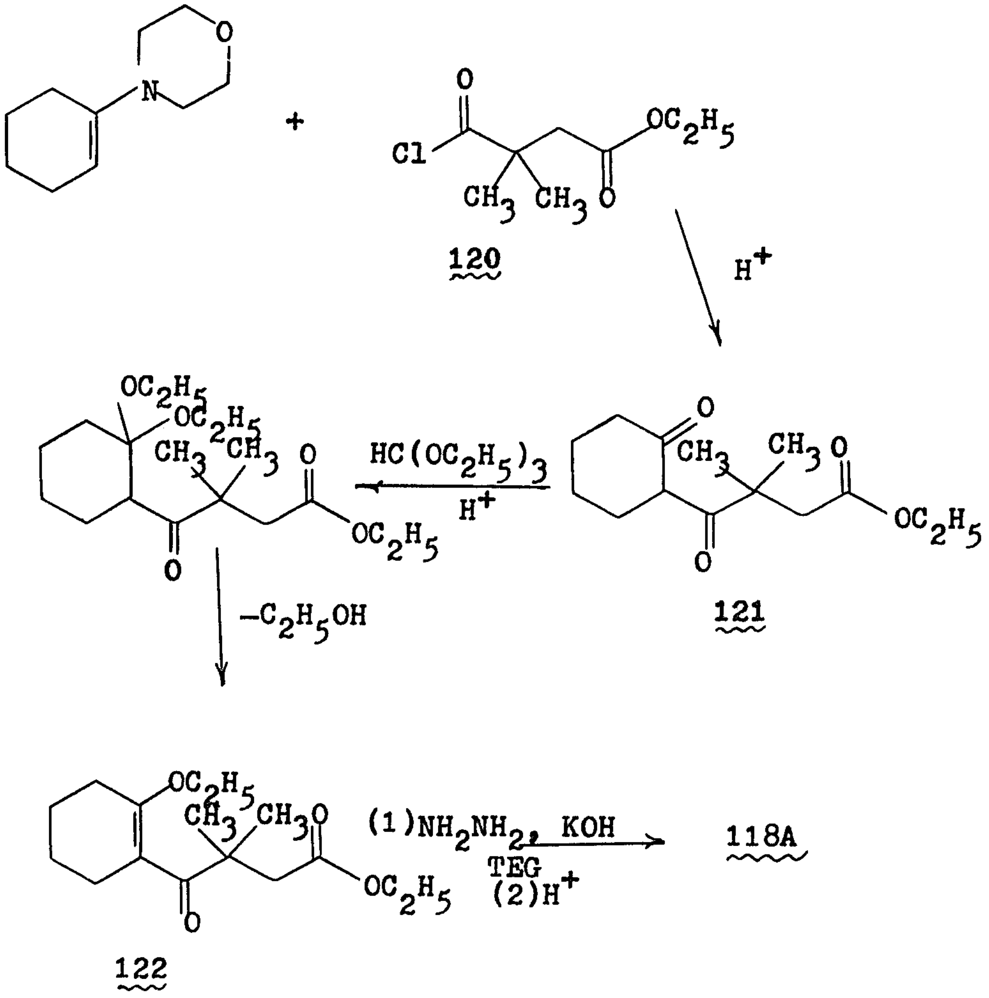
Thus, it remained for us to prove that the keto acid had structure 118A rather than structure 118B in order to confirm the structure proposed for 112A.



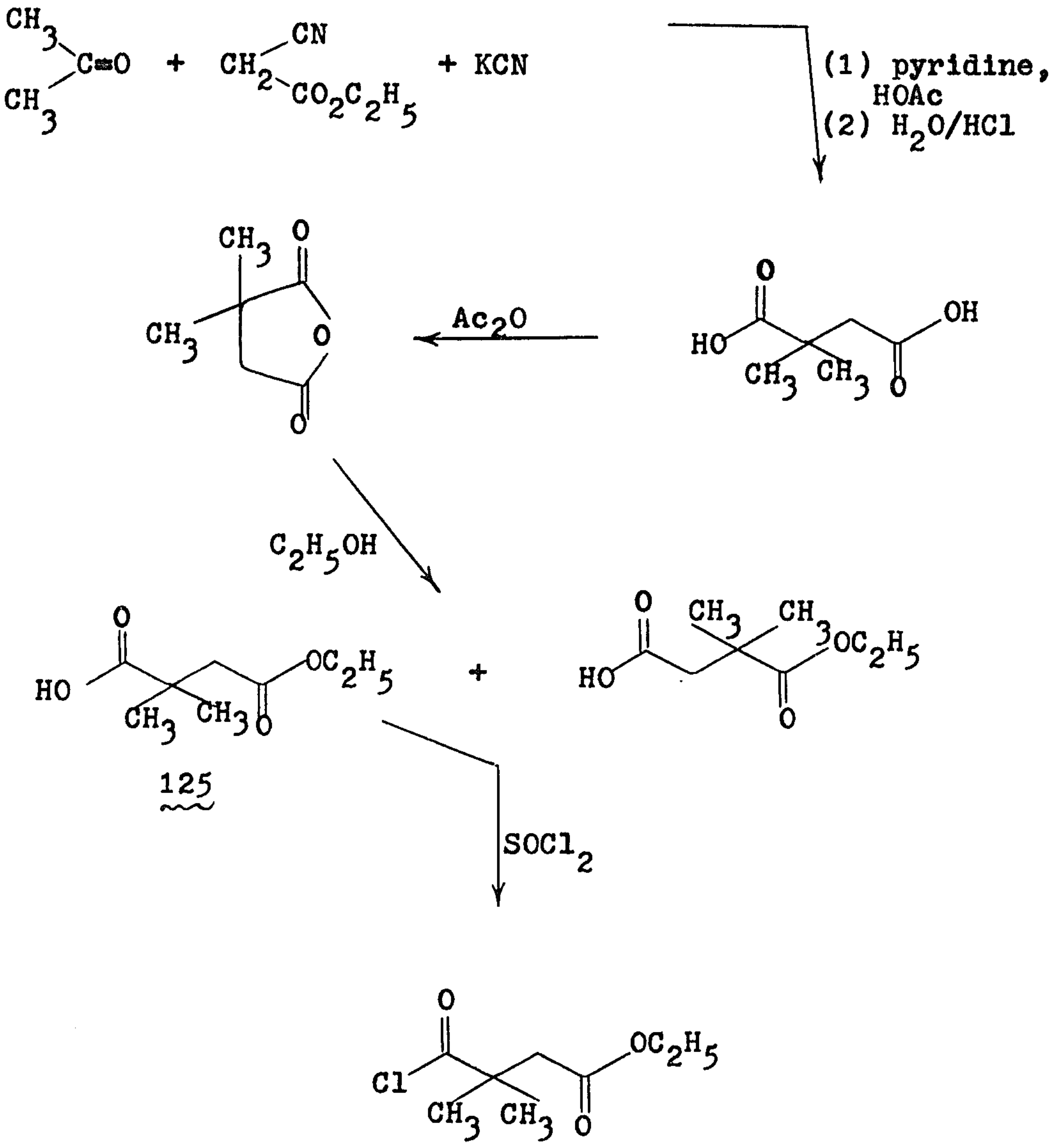
118B

We attempted to prove the structure of 118A by independent synthesis. Four different schemes were attempted as shown and described below (Schemes I-IV).

Scheme I



(32)

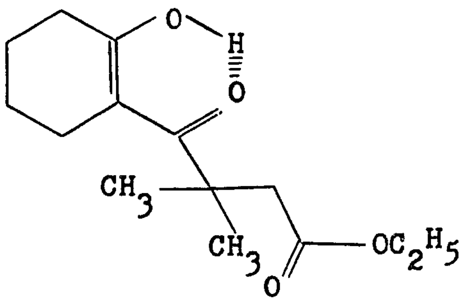


125

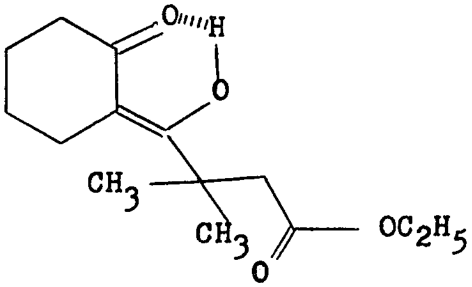
120 (84%)

Stork's enamine acylation[120,128] afforded the β-diketo ester **118**. It was expected that the carbonyl group on the ring of **118** was more sterically favored for ketalization (followed by formation of the enol ether **122**) than that on the side chain which is adjacent to the quarternery carbon and the ring. It was also expected, and proven by experience, that the reduction of 122 to 112A would be difficult.

The acylation step gave the β-diketone in 47% yield. Evidence for the existence of the enol form of the keto acid 118A included a positive ferric chloride test, indicative of either the stable enol structure 119A or 119B.



119A

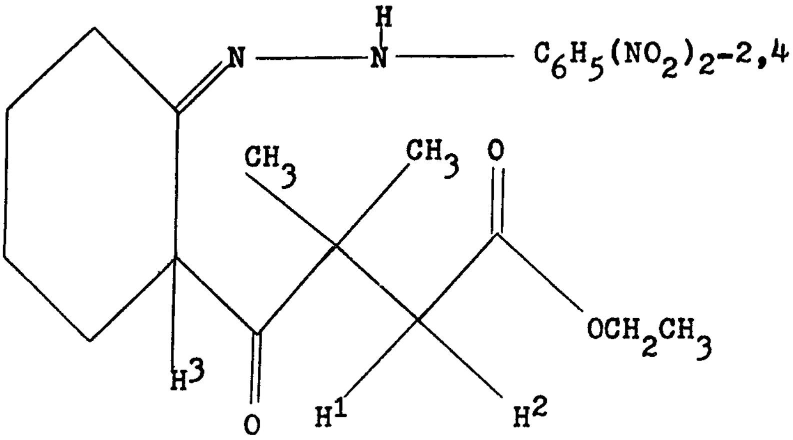


119B

The infrared spectrum was also consistent with this structure, showing peaks at 1730 ($-COOC_2H_5$), 1698 (C=O) and 1635 (C=C-OH) cm^{-1}. The NMR showed a peak at -6.0τ (integrating for a fraction of a proton) which was washed out with D_2O (C=C-OH), two major quartets centered at approximately 4.14τ (2H, 2 quartets, $CH_3CH_2\text{-}O\text{-}\underset{\underset{O}{\|}}{C}\text{-}$ for two different forms, keto and enol), a set of multiplets between 8.58 and 8.90τ (9H, two equally intense singlets, one triplet, $\mathrm{CH_3}\!>\!\mathrm{C}\!<\!\mathrm{CH_3}$ and $CH_3CH_2\text{-}O\text{-}\underset{\underset{O}{\|}}{C}\text{-}$) and extensive multiplets in the region 7.03 to 8.58τ.

Elucidation of the structure 121, however, was greatly aided by the NMR spectrum of the 2,4-dinitrophenylhydrazone of β-diketone 127, as shown on the following page.

Proposed Structure:



127A and B

NMR ($CDCl_3$):

τ	No. of Protons	Multiplicity (J cps)	Assignment
-1.10	1	Singlet	$>N-\underline{H}$
1.18 - 2.50	3	Multiplet	Aromatic H's
6.20	2	Quartet (7 cps)	$-\underset{\underset{O}{\|}}{C}-O-C\underline{H_2}CH_3$
Approx. 6.20	1	Multiplet	$-\underset{\underset{\underline{H}^3}{\mid}}{C}-\underset{\underset{O}{\|}}{C}-$
7.35-8.82	10	Broad mult.	Cyclohexane ring H's
7.64		Singlet	H^1 and H^2
7.75		Singlet	
8.96	3	Singlet	$C\underline{H_3}\!>\!C\!<\!C\underline{H_3}$
9.02	3	Singlet	
9.21	3	Triplet (7 cps)	$C\underline{H_3}CH_2-O-\underset{\underset{O}{\|}}{C}-$

The infrared spectrum ($CHCl_3$) was also consistent with the above structure, showing peaks at 3311 (N-H), 1724 ($-COOC_2H_5$ and C=O), 1618 (C=N), 1522 and 1350 (NO_2) cm^{-1}.

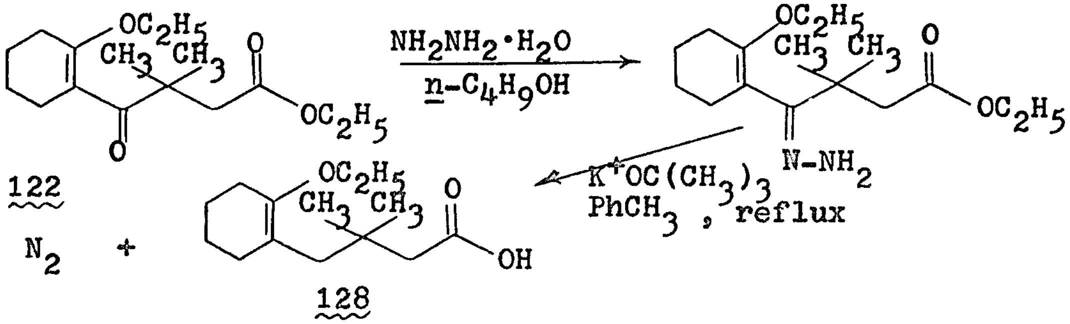
The next step involving synthesis of the diethyl ketal of the β-diketone, 121, was expected to directly furnish the enol ether, 122, due to the formation of an α,β-unsaturated ketone and this did, indeed, occur. Treatment of the β-diketone, 121, with a slight excess of triethyl orthoformate, using p-toluenesulfonic acid as a catalyst afforded the product we believe to be the enol ether 122 in 68% yield. Several pieces of evidence are in agreement with the structure 122. The ultraviolet spectrum shows two peaks: λ max 217 mμ (ε 1.69 x 10^3), 276 mμ (ε 1.09 x 10^3).[153] The infrared spectrum showed an absorption at 1735 ($COOC_2H_5$), 1711 (shoulder, C=O) 1638 (C=C), 1190, 1180, 1152, 1121 and 1034 ($C=C-OC_2H_5$) cm^{-1}.

A poorly resolved NMR (CCl_4), which was consistent with enol ether 122, showed two singlets and two triplets, 8.66 to 8.93τ (12H, four CH_3 groups), 5.91τ (singlet, $CH_3CH_2\text{-}O\text{-}\underset{\underset{O}{\|}}{C}\text{-}$), 6.40τ ($-CH_2C\text{-}O\text{-}C_2H_5$) and 5.90 to 8.50τ (extensive multiplets, ring H's). The ether methylene group was probably located amidst the other multiplets. The 2,4-DNP of the enol ether was identical to that obtained from its precursor β-diketone 121 as shown by its mixed melting point and infrared spectrum, thus providing good evidence for the structure of enol ether 122. Preparation of an analytical sample of the enol ether 122 using vapor phase chromatography under varying sets of conditions and several columns, in every case, showed decomposition of the enol ether.

We concluded that the structure of the enol ether was correct as indicated and decided to pursue the Wolff-Kishner reduction step.

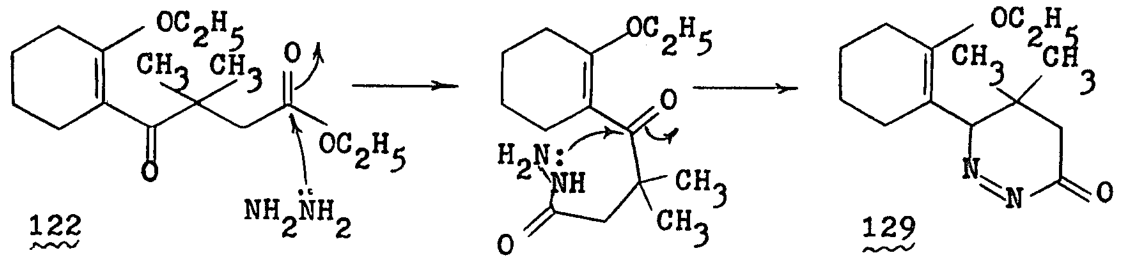
The reduction of the ketone was expected to be difficult because of the presence of the α,β-unsaturated carbonyl group and the steric hindrance in the carbonyl region.[132] From the numerous modifications of the Wolff-Kishner reduction, two were finally tried. One involved reducing α,β-unsaturated ketones (which had previously been known to give anomalous products) with potassium t-butoxide in toluene.[133] The second procedure was the Huang-Minlon modification, probably the most extensively used.[134]

Thus, the first method we used involved the reaction scheme shown below:

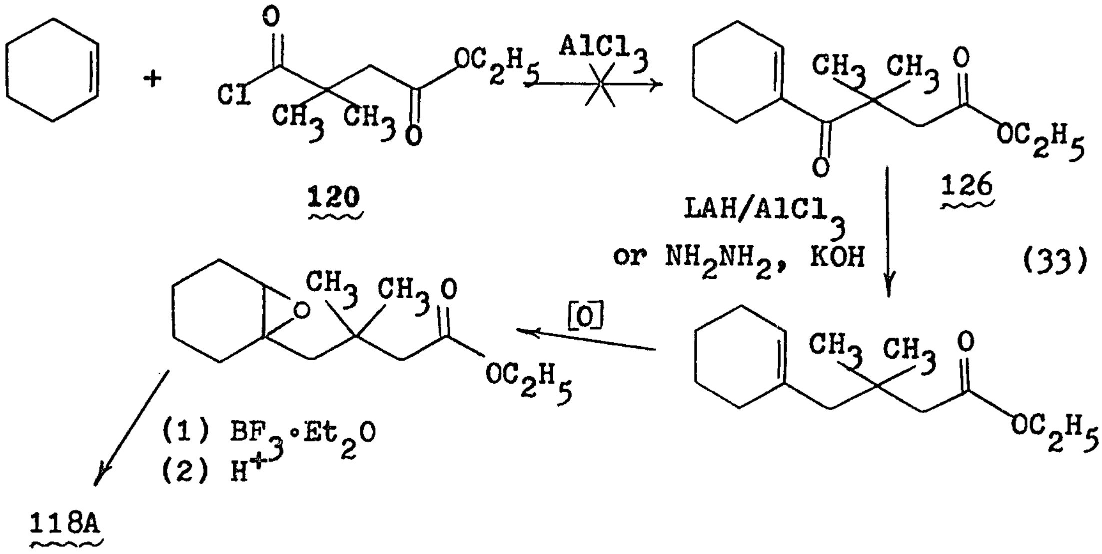


However, no nitrogen evolution was observed upon addition of the base and almost all of the starting materials were converted to a polymeric residue.

In the Huang-Minlon modification, analysis of the infrared spectrum of the reaction products indicated that no ester or acid group was present. Several key IR peaks, namely, 3333 (broad), 2924, 2865 and 1667 cm^{-1} indicated the possibility of a pyridazone derivative 129. Only one other product was isolated, namely a carboxylic acid, which was totally inconsistent with a Wolff-Kishner product. At this point, this method was abandoned.

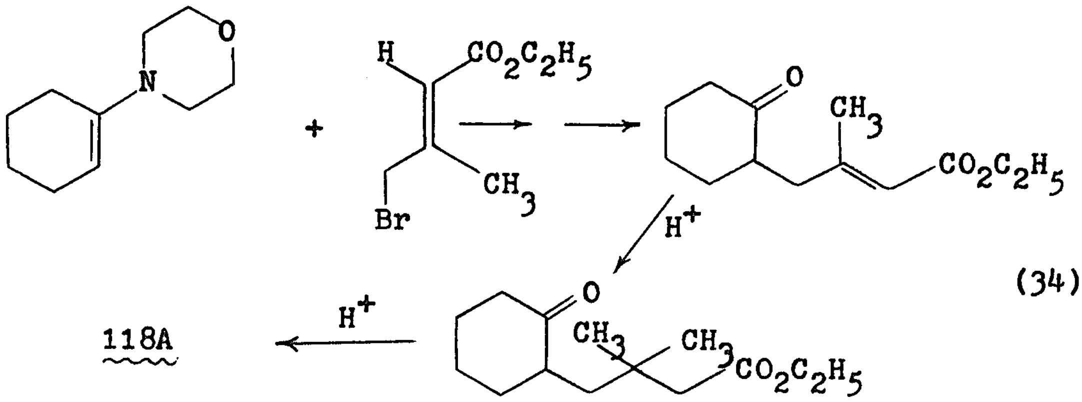


Scheme II



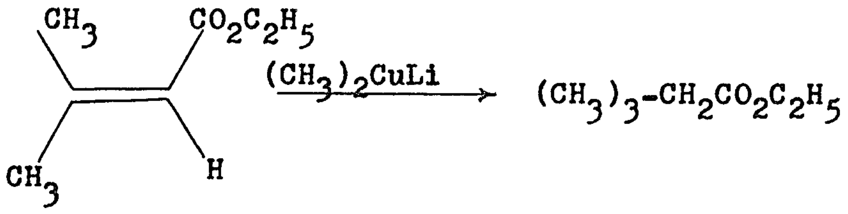
Two attempts to complete the Freidel-Crafts[136-139] step of this reaction failed. After maintaining cyclohexene, the acid chloride 120 and aluminum chloride for 30 minutes at -5 to -8°, workup yielded a product whose infrared spectrum had peaks at 1859 (weak), 1761 (medium), 1733 and 1715 (strong) and 1672 (weak) cm^{-1}, but no strong C=O peak indicative of an α,β-unsaturated ketone (expected at approximately 1675 cm^{-1}).[129] The method was not pursued.

Scheme III

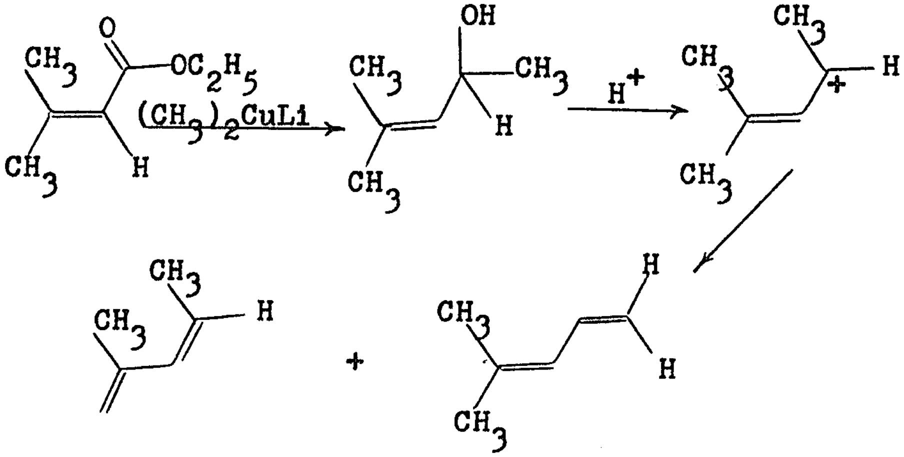


(34)

Conjugate additions of dimethyllithium cuprate to α,β-unsaturated esters were not known, but such additions to conjugated ketones were.[140,141] Therefore, it was best to attempt this type of addition first on the model compound, ethyl β,β-dimethylacrylate to obtain ethyl t-butylacetate.



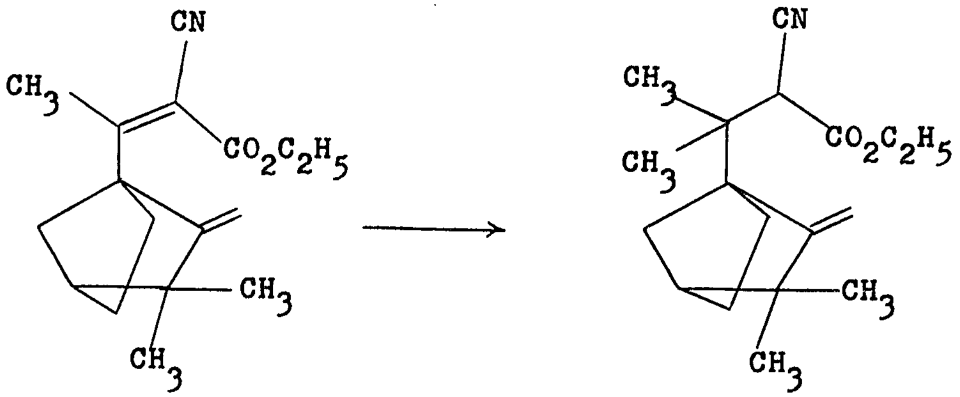
Reaction of dimethyllithium cuprate and ethyl β,β-dimethylacrylate following acidification, resulted in two liquid fractions: (A) bp 53-70°/760 mm, (B) bp 70-75°/760 mm. The literature value for the boiling point of ethyl t-butylacetate is 118.0-118.2°.[143] Thus it was quite obvious that we did not get a 1,4 addition. It is plausible that at least one of the products may have been either 4-methyl-1,3-pentadiene (bp 76.3°)[130] or 2-methyl-1,3-pentadiene (bp 76°)[130] arising as follows:



There is supporting evidence for this from the infrared spectrum with peaks at 3067 (C=C-H), 2950, 2907, 2849 (C-H), 1626 (C=C), and 890 ($C=CH_2$) cm^{-1}. The peak at 890 cm^{-1} seems to favor 4-methyl-1,3-pentadiene.[130]

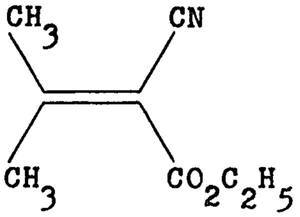
In the above reaction, 1.57 M methyllithium[143] in diethyl ether, (Ventron) was used to make the dimethyllithium cuprate. In another run, the methyllithium was freshly made from lithium metal and methyl iodide; it gave no reaction at all.

A possible alternative to the poor reactivity of ethyl β,β -dimethylacrylate was attempted upon discovery of the following reaction in the literature.[145]



The cyano group, together with the ester function should certainly increase the electrophilicity of the double bond and thus facilitate the 1,4 addition of the dimethyllithium cuprate.

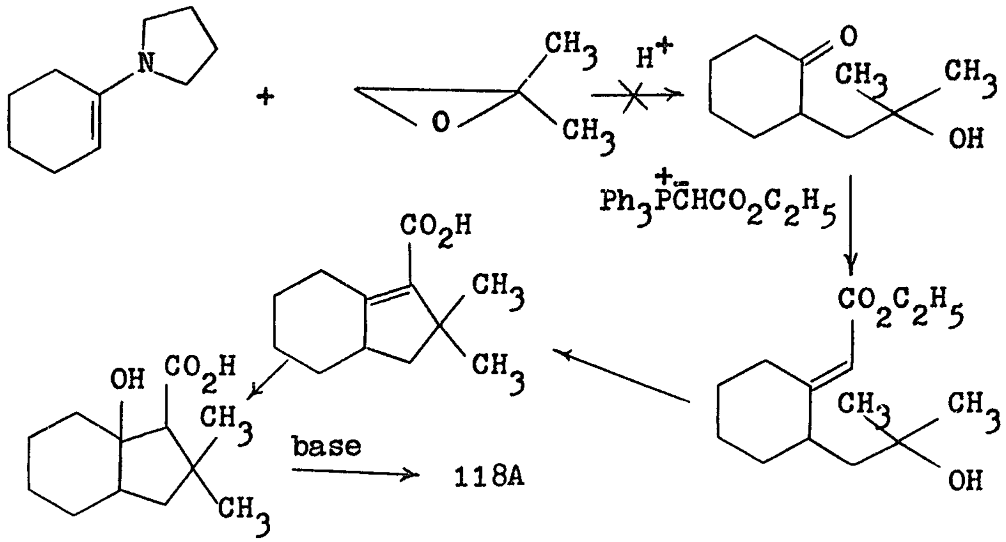
Therefore, ethyl isopropylidenecyanoacetate (130) was synthesized,[147] both as a model compound and for the eventual use as a starting material in the synthetic route analogous to the one previously described.



130

However, the cyano ester 130 and dimethyllithium cuprate yielded only a dark brown gummy residue which could not be distilled.

Scheme IV



In each of the several attempts to add N-pyrrolidinocyclohexene to the isobutylene oxide, only some polymeric non-distillable residue appeared. When p-toluenesulfonic acid was added as catalyst, no reaction occurred.

The most promising reaction sequence appears to be Scheme I. Further work remains to be done, however, in accomplishing the reduction step.

As mentioned earlier in this thesis (p. 21), it seems logical to see if an adduct different from 112A would be obtained (namely cycloadduct 112B) if the cycloaddition of 1,1-dimethyl-2,2-dicyanocyclopropane (96) to N-pyrrolidinocyclohexene were run using dimethyl sulfoxide instead of xylene as solvent.

We ran such an addition under conditions analogous to those used when xylene was solvent with the exception that a much shorter reaction time was required to consume all of the cyclopropane (as shown by VPC, only 5 hours were required using dimethyl sulfoxide instead of the 31 hours required with xylene). However, in addition to some polymeric residue, the only identifiable product was the cyano amide (or more likely, the enamide 116A) which we had previously obtained upon hydrolysis of cycloadduct 112A in refluxing 95% ethanol. The yield was 31%.

The rate enhancement in dimethyl sulfoxide might be evidence supporting a 2-step mechanism involving a transition state with charge separation for this reaction as shown in Mechanism 1 (p. 21). It was noted in Part I of this thesis that Huisgen[9] found a rate factor of less than 2, providing support for a concerted reaction sequence.

Thus, although both theoretical predictions based upon steric considerations and spectral evidence favor a Michael addition of N-pyrrolidinocyclohexene to 1,1-dimethyl-2,2-dicyanocyclopropane (96), an unequivocal synthesis of the keto-acid derivative still remains necessary for the absolute structure of the product 112A.

Experimental

All melting points and boiling points are uncorrected and were determined on a Meltemp melting point apparatus. Microanalyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were recorded on a Perkin-Elmer Model 237B spectrophotometer. Ultraviolet spectra were recorded in 95% ethanol solution on a Bausch and Lomb 505 spectrophotometer or a Cary 14 spectrophotometer. Nuclear magnetic resonance spectra were recorded at 60 Mc on a Varian A-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were determined on a modified Varian-Atlas model CH-7 mass spectrometer with perfluorokerosene as internal standard.

All gas Chromatography experiments were run on either a Varian Aerograph Autoprep (thermal ionization detector) or a Varian 1200 chromatograph (flame ionization detector). Unless otherwise stated, anhydrous magnesium sulfate was employed as a drying agent.

Cyclopropane Syntheses (cf. Chart I)

Attempted Preparation of 1,1-Diethoxy-2,2-dicyanocyclopropane (92) via Simmons-Smith Reaction

(A) Preparation of Dicyanoketene Diethyl Acetal (91)

The acetal 91 was prepared via the method of Middleton and Englehardt,[90] but the yields were consistently lower than the 72% yield claimed in the literature.[90] Our best yield was 47%; mp 59.0-60.0°, lit. 58-59°.[90]

(B) Preparation of the Zinc-Copper Couple

Three variations were used in making the couple; those of Shank and Schechter,[88] of LeGoff[89] and of LeGoff as modified by Christie and Holman.[92]

(C) Reaction of Zn (Cu) and Dicyanoketene Diethyl Acetal (91)

A typical run will be described here. Since there were so many variations used, they will be briefly mentioned immediately after this procedure.

Into a 50-ml round-bottomed flask equipped with a double-coil reflux condenser, a drying tube containing Drierite and a magnetic stirring bar, were placed 720 mg (11 mmol) of zinc-copper couple,[88] 6 ml absolute ether and two small crystals of iodine. The mixture was stirred for approximately 2 minutes, until the iodine color disappeared, after which 1.66 g (10 mmol) of dicyanoketene diethyl acetal (91) dissolved in 20 ml absolute ether and 2.43 g (11 mmol) of methylene iodide (distilled, bp 48-52°/0.25 mm and stored over copper wire) were added in one portion. The mixture was then refluxed for 3 hrs 45 min during which time its color changed from purple to yellow-brown and finely divided copper appeared. After the ether was decanted the residue was extracted with three 10-ml portions of ether followed by two 10-ml portions of water and then one 15-ml portion of ether. The combined ether layers were filtered and then extracted with three 10-ml portions of water. After the aqueous layer was extracted with 15 ml of ether, the organic layer was dried and the ether was removed under reduced pressure yielding 350 mg (21% recovery) of white crystals, mp 57.0-58.5°. The infrared spectrum and a thin layer chromatograph showed this to be starting material.

Workup of the aqueous layer yielded only a polymeric residue which could not be purified by any conventional means (acidification, followed by ether extraction, recrystallization or, column chromatography).

(D) In addition to varying the methods of preparation of the zinc-copper couple, methylene bromide was used in place of methylene iodide,[89] and ethylene glycol monomethyl ether was used in place of ether in the hope of precipitating the zinc iodide completely to prevent possible interaction with the ketene acetal 91.[116] Both solvents were used with methylene iodide and methylene bromide.

Preparation of Bromomalononitrile

Bromomalononitrile was prepared from malononitrile (freshly distilled, 66-69°/5 mm) and bromine in water by the method of Boldt, Schulz and Etzmuller in 65% yield; mp 64.5-66.0° (lit. 65-66°).[114]

Preparation of Ketene Diethyl Acetal (93)

Ketene diethyl acetal (93) was prepared from bromoacetal and potassium t-butoxide by the method of McElvain and Kundiger except that a 60-cm base-washed column containing glass helices was used. The acetal was obtained in 44% yield; bp 83-86°/

211 mm (lit. 83-86°/200 mm).[94]

Attempted Preparation of 1,1-Diethoxy-2,2-dicyanocyclopropane (92) via Addition of Ketene Diethyl Acetal (93) to Bromomalononitrile and Triethylamine

A mixture of 5.00 g (35 mmol) bromomalononitrile and 6.45 g (55 mmol) ketene diethyl acetal (93) was stirred under an atmosphere of prepurified nitrogen. Within one minute the color changed from yellow to orange to red to violet, while the temperature increased from 28 to 45°. After 2½ hr, a negative starch-iodide test indicated the lack of any further free bromine. At this point, 4.00 g (39 mmol) of freshly distilled triethylamine was added quickly while the mixture was kept in an ice-water bath. The temperature rose to 35° and then decreased. After stirring for 1 hr, the dark brown mixture was filtered and the filtrate was diluted with 50 ml of methylene chloride. The methylene chloride layer was then washed with three 50-ml portions of 3N hydrochloric acid, three 50-ml portions of 5% sodium bicarbonate and three 50-ml portions of water. Following extraction of the aqueous layer with 50 ml of chloroform, the combined organic layers were dried and the solvents were removed under reduced pressure. Only a gummy polymeric residue resulted (TLC, silica adsorbent, 2:1 petroleum ether: ethyl ether, showed 6 spots).

Attempted Preparation of 1,1-Diethoxy-2,2-Dicyanocyclopropane (92) from Dicyanoketene Diethyl Acetal (91) and Diazomethane

Diazomethane was prepared from N-methyl-N-nitroso-p-toluenesulfonamide ("Diazald"-Aldrich) decomposition[*] as follows.

In a 125-ml 3-necked Erlenmeyer flask (specially prepared, no ground glass joints) containing a magnetic stir bar and a nitrogen bubbler were placed 1.66 g (10 mmol) of dicyanoketene diethyl acetal (91) dissolved in 50 ml 95% ethanol. The reaction mixture was cooled to 0° with an ice/salt mixture. A mixture of 2.50 g (11 mmol) of "Diazald" and 150 mg cuprous bromide was added with stirring, after which 4 ml of a solution containing 7.5 g of potassium hydroxide in 100 ml 50% ethanol was added over a period of 35 min. The mixture was kept between 0 and 20° with the aid of an ice bath when necessary. After a total of 2 hr of stirring, the solution had changed color from a pale green to a cloudy deep green. Five ml of 20% acetic acid was added to react with excess diazomethane and potassium hydroxide followed by 30 ml of 5% aqueous sodium bicarbonate. Upon dilution with 250 ml of water, filtration, extraction with three 75-ml portions of ether and drying, the solvent was evaporated, under reduced pressure, yielding only starting material (shown by IR and mp).

This method was abandoned after discovering the hazards[**]

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[*] The method used for the preparation of diazomethane was that described in "The Aldrich Company Catalog" (1967), p. 11 in which N-methyl-N-nitroso-p-toluenesulfonamide ("Diazald") was decomposed by potassium hydroxide in ethanol.

[**] We thank Dr. H.O. House for his advice concerning the hazards involved.

involved.

Attempted Preparation of 1,1-Dibromo-2,2-diethoxydicyanocyclopropane (94) from Dicyanoketene Diethyl Acetal (91) and Phenyltribromomethylmercury[101-107]

Preparation of phenyl tribromomethylmercury was accomplished in 49% yield by the method of Seyferth[107] from phenylmercuric bromide (Woodridge Chemical Corp., purified via extraction with benzene for 12 hr in a Soxhlet extractor, mp 277-282°, bromoform (Aldrich), bp 65° (43 mm) and potassium *t*-butoxide[108] in benzene (distilled from calcium hydride).

A mixture of 3.45 g (6.6 mmol) of phenylmercuric bromide and 1.01 g (6.1 mmol) of dicyanoketene diethyl acetal (91) dissolved in 15 ml benzene was heated with stirring to 80° for 1 hr under a nitrogen atmosphere, during which time a white precipitate formed. After it had been cooled to room temperature, the mixture was filtered with suction leaving behind 1.65 g (70% yield) of phenylmercuric bromide. The filtrate was evaporated at 7 mm leaving 2.36 g of an oily dark brown residue. After removing the final traces of solvent in a vacuum desiccator with an oil pump, the brown oil was triturated with benzene and cyclohexane (equivolume mixture) yielding an additional 105 mg of phenylmercuric bromide. A column chromatograph (silica gel support) yielded only mixtures of dicyanoketene diethyl acetal (91) and polymer (TLC, silica adsorbent, benzene, 9:1 benzene: methanol and 4:1 cyclohexane: benzene.Each showed only phenyltribromomethylmercury plus a non-movable spot).

Preparation of Ethyl cis- and trans-2-ethoxycyclopropane-1-carboxylate (95A and 95B)

The cupric sulfate was dried before use for 3 hr at 155°. The ethyl vinyl ether (Aldrich) was distilled, 36-37°.

A mixture of 0.5 g anhydrous cupric sulfate, 50 ml ethyl vinyl ether and 80 ml n-heptane was heated to 50°, at which temperature 35.50 g (310 mmol) of ethyl diazoacetate, dissolved in an approximately equal volume of ethyl vinyl ether was added dropwise over a period of 1 hr. Nitrogen evolution began almost immediately and continued throughout the addition, during which time the reaction temperature remained between 54 and 64°. The gas evolution ceased about 2 min after the last drop of the diazo ester was added. After 15 min additional stirring, the mixture was cooled to room temperature. Excess ethyl vinyl ether and n-heptane were removed under reduced pressure. After filtration of the residue, distillation of the filtrate on a spinning band column (reflux ratio 50 to 1), yielded several fractions between 68 and 78°/10 mm consisting of different proportions of the cis and trans isomers (95A and 95B). Redistillation of the two main fractions on the spinning band column (reflux ratio 40 to 1) allowed nearly complete separation of the isomers (as indicated by gas chromatography on a 5 ft x ¼ in SE-30 on Chromosorb P column). The weight of the combined isomers was 30.05 g (77%), bp 1) 66-67°/10 mm, 2) 75-77°/10 mm. A "stringy" dark brown polymer remained behind. Infrared absorption of lower boiling isomer (CCl_4), 2976, 2933 (C-H), 1724 ($COOC_2H_5$), 1160, 1115, 1096, 1070, 1056 (C-O stretch) cm^{-1};

nmr ($CDCl_3$)τ 8.84 (triplet, 3H, J=7, $\underline{CH_3}CH_2O-$), 8.77 (triplet, 3H, J=7 Hz, $\underline{CH_3}CH_2O\underset{\underset{O}{\|}}{C}-$), 8.67-9.02 (mult, 2 H, H_A and H_B), 8.17-8.50 (mult., 1H, H_C), 6.33-6.68 (mult., 1H, H_D), 6.50 (quartet, 2H, J=7 Hz, $CH_3\underline{CH_2}O-$), 5.98 (quartet, 2H, J=7 Hz, $CH_3\underline{CH_2}O-\underset{\underset{O}{\|}}{C}-$).

Preparation of Triethyl Pyrazoline-3,4,5-tricarboxylate (98)

To a mixture of 0.13 g anhydrous cupric sulfate in 50 ml of boiling ethyl vinyl ether was added 6.76 g (59 mmol) of ethyl diazoacetate in 6 ml of ethyl vinyl ether over a period of 35 min. After 3 hr, the reaction mixture was cooled to room temperature and filtered. After removal of the excess reactants, nothing more distilled. The residual deep yellow oil crystallized in 30 days yielding 882 mg of white solid (21% yield of the pyrazoline ester 98); recrystallized twice from CCl_4, mp 96.2-96.7° (lit. 98-99°);[148,*] ir (KBr) 3289 (N-H), 1730 ($-COOC_2H_5$), 1691, 1686 ($-C{=}N$) cm^{-1}; nmr ($CDCl_3$)τ 8.53 to 8.84 (3 triplets, 9H, J=7 Hz, $\underline{CH_3}CH_2O-\underset{\underset{O}{\|}}{C}-$), 5.55 to 5.95 (3 quartets, 6H, J=7 Hz, $CH_3\underline{CH_2}O-\underset{\underset{O}{\|}}{C}-$) and (2H, multiplet, ring H's), 5.25 (doublet, 1H, J=6 Hz, N-H); Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.17; H, 6.31; N, 9.79; Found: C, 50.27; H, 6.19; N, 9.90.

Preparation of 1,1-Dimethyl-2,2-dicyanocyclopropane (96)

The literature method[114] was varied as indicated in the

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* See footnote, Part II, p. 9.

following procedure. Methylene chloride was purified by washing with concentrated sulfuric acid, followed by water, dried over anhydrous calcium chloride and distilled, bp 40-41°.[146] Triethylamine was dried over and distilled from calcium hydride, bp 88-89°.

In a 2-l. 3-necked round-bottom flask, equipped with a Dewar condenser containing dry ice, a thermometer and a gas inlet tube, were placed 125.0 g (867 mmol) of bromomalononitrile and 915 ml of dry methylene chloride. The solution was deaerated for 1 hr with prepurified nitrogen, after which 170 g (2.93 mols) of isobutylene was bubbled in while the reaction mixture was irradiated from a distance of approximately 30 cm with a 140 watt medium pressure mercury lamp for 8 hrs. After irradiation, 96.0 g (950 mmol) triethylamine, dissolved in 235 ml of dry methylene chloride was added during 15 min. The precipitate of triethylammonium bromide began to form when approximately half the triethylamine had been added.

After the addition, the mixture was stirred for 30 min at room temperature, filtered, and the filtrate was extracted with two 100-ml portions of water to dissolve any remaining triethylammonium bromide. After extracting the aqueous layer with two 50-ml portions of methylene chloride, the combined organic layers were dried and the solvent distilled at 38-42° after which the excess triethylamine was distilled under reduced pressure. The residue was then distilled twice through a 20-cm Vigreux column, 60°/1.5 mm, yielding 87.4 g of the cyclopropane **96**, a white solid, mp 37-8° (lit. 39.0-39.5°);[114]

ir and nmr consistent with data in the literature.[114]

Attempted Preparation of 1-Ethoxy-2,2-dicyanocyclopropane (97)

A solution containing 4.35 g (30 mmol) bromomalononitrile dissolved in 30 ml of dry methylene chloride with a trace of hydroquinone was deaerated with nitrogen. To this was added 2.15 g (31 mmol) of ethyl vinyl ether dissolved in 10 ml of methylene chloride during 1.5 hr while irradiating the solution with a 140 watt medium pressure mercury lamp at a distance of 45 cm. After irradiating for 8 hrs, 3.36 g (33 mmol) of triethylamine dissolved in 10 ml of methylene chloride was added over a period of 30 minutes, after which the mixture was washed with 100 ml water. The layers were separated, the organic layer was filtered and the filtrate eluted from a column of neutral alumina (Woelm) with methylene chloride. An infrared spectrum of each fraction revealed no cyano peaks.

Cycloadditions (cf. Chart II and Table I)

Attempted Cycloaddition of Ethyl 2-Ethoxycyclopropane-1-carboxylate (95) to Styrene (Equation 14)

Dimethyl sulfoxide was distilled from calcium hydride at 75-77°/12 mm and stored over Linde 4A molecular sieves. Styrene (Aldrich) was distilled at 42°/16 mm from a trace of hydroquinone and then stored over hydroquinone until used.

(A) In a 1-necked round-bottomed flask flushed with prepurified nitrogen were placed 1.58 g (10 mmol) of ethyl 2-ethoxycyclopropane-1-carboxylate (95) and a trace of hydroquinone. Then 14 ml of styrene was added and the mixture was heated at 146° (reflux) for 30 min, during which time polymerization occurred. Distillation yielded only small amounts of reactants, but mostly glassy polymeric material.

(B) A mixture of 1.020 g (6.45 mmol) of the cyclopropyl ester 95, 773 mg (7.43 mmol) styrene, 10.23 g of diphenyl ether and a trace of hydroquinone was stirred at 233-234° for 6 hrs under an atmosphere of prepurified nitrogen. Evaporation of the solvent yielded only reactants and polymer.

(C) A mixture of 1.011 g (6.39 mmol) of the cyclopropyl ester 95, 800 mg (7.68 mmol) styrene, 10 ml dimethyl sulfoxide and a trace of hydroquinone was stirred at 150° for 79 hrs under an atmosphere of prepurified nitrogen. Addition of 30 ml cold saturated sodium bicarbonate to the dark brown mixture was then followed by washing of the organic layer with three 25-ml portions of water and dried. Removal of excess solvent under reduced pressure yielded a polymeric residue.

Attempted Cycloaddition of Ethyl 2-ethoxycyclopropane-1-carboxylate (95) to Tetracyanoethylene (Equation 15)

Tetracyanoethylene was recrystallized from approximately 9 times its weight of chlorobenzene and then sublimed at 120° (1.2 mm). Dimethylformamide was distilled from barium oxide, 59.5-62°/30 mm and stored over Linde 4A molecular sieves.

(A) A mixture of 988 mg (6.2 mmol) of cyclopropyl ester 95 and 9.74 mg (7.6 mmol) tetracyanoethylene dissolved in 10 ml dimethyl sulfoxide was stirred at 140° for 11 hr under an atmosphere of prepurified nitrogen. The reaction mixture was cooled to room temperature and poured into an equal volume of ice-cold water, at which point a dark brown precipitate formed. The mixture was extracted with three 50-ml portions of ether, filtered and dried. Evaporation of the solvent, under reduced pressure, afforded a small amount of orange oil which could not be crystallized and showed no cyano peaks in its infrared spectrum. The bulk of the material recovered was polymer.

(B) A mixture of 1.010 g (6.4 mmol) of cyclopropyl ester 95 and 907 mg (7.1 mmol) tetracyanoethylene dissolved in 10 ml of dimethylformamide was stirred at 169° for 7 hr. After removing the solvent, under reduced pressure, a brown gummy residue remained behind which could not be crystallized (polymer). Column chromatography (silica gel, solvent) still yielded only gummy residue.

Attempted Cycloaddition of Ethyl 2-ethoxycyclopropane-1-carboxylate (95) to Cyclohexene (Equation 16)

A mixture of 294 mg (1.9 mmol) of cyclopropyl ester 95 and 1 ml cyclohexene (distilled before use, 83°) in 3 ml dimethyl sulfoxide was heated at 147° for 2 d. At this time, some white solid had deposited on the neck of the flask; mp (crude), 115-135° (with gas evolution). The infrared spectrum of the reaction mixture showed no ester peak and thus no further workup was attempted. Evaporation of the excess solvent and cyclohexene yielded only dark brown polymeric residue.

Attempted Cycloaddition of 1,1-Dimethyl-2,2-dicyanocyclopropane (96) to Cyclohexene (Equation 17)

To a solution of 1.38 g (16.8 mmol) of cyclohexene in 10 ml dimethylformamide at 133° was added a solution of 1.04 g (8.5 mmol) of 1,1-dimethyl-2,2-dicyanocyclopropane (96) in 7.5 ml dimethylformamide over a period of 2 hr. After 6 d, however, TLC showed that only reactants were present.

Attempted Cycloaddition of 1,1-Dimethyl-2,2-dicyanocycyloropane (96) to Diethyl Fumarate (Equation 18)

The diethyl fumarate was washed with 5% aqueous sodium carbonate followed by saturated aqueous calcium chloride, dried over anhydrous calcium chloride and distilled, 217-218°.[146]

(A) A mixture of 469 mg (3.8 mmol) of 1,1-dimethyl-2,2-dicyanocyclopropane (96) and 9.86 g (67 mmol) of diethyl fumarate was stirred at 218° (reflux) under an atmosphere of prepurified nitrogen for 6 d at which point gas chromatography* showed all

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* Collection of the product corresponding to a new peak was performed on a Varian Autoprep Gas Chromatograph fitted with a 10 ft x ¼ in SE-30 on Chromosorb P column.

of the cyclopropane **96** to have disappeared, plus a new compound to be present. An infrared spectrum of the collected fraction showed no cyano group to be present.** The spectrum was nearly identical to that of diethyl fumarate (probably dimethyl maleate).

(B) A mixture of 127 mg (1.1 mmol) of 1,1-dimethyl-2-2-dicyanocyclopropane (**96**) and 456 mg (3.1 mmol) of diethyl fumarate in 5 ml of dimethyl sulfoxide was stirred at 145° for 19 hr under an atmosphere of prepurified nitrogen. After removing excess solvent and excess ester under reduced pressure, 141 mg of a polymeric residue remained.

(C) Reactions were attempted in sealed tubes in an explosion-proof furnace at the indicated temperatures.

(1) A mixture of 386 mg (3.7 mmol) of cyclopropane **96** and 894 mg (5.2 mmol) of diethyl fumarate were heated at 428° for 4 hr resulting a total charring of the material; ir, no cyano peaks.

(2) A mixture of 372 mg (3.1 mmol) cyclopropane **96** and 864 mg (5.0 mmol) of diethyl fumarate was heated at 330° for 4 hr resulting in a dark brown gum which could not be crystallized (ir, no cyano peaks). TLC (silica adsorbent, eluent, 5:1 hexane: ethyl acetate) showed 4 spots.

** The products corresponding to the peaks were identified and collected on a Varian Autoprep Gas chromatograph fitted with a 20 ft x 3/8 in 28% Apiezon L on Chromosorb W column.

(3) A mixture of 357 mg (3.0 mmol) of cyclopropane **96** and 940 mg (5.5 mmol) of diethyl fumarate was heated at 280° for 5 hr resulting in some charred material plus liquid. Gas chromatography† showed no volatile material, however. Preparative thin layer chromatography (TLC) on silica plates, developed in ethyl acetate, yielded only a dark brown oil (ir, no cyano peaks).

(4) A mixture of 375 mg (3.1 mmol) of cyclopropane **96** and 1.031 g (6.0 mmol) of diethyl fumarate were heated at 255° for 75 min. Preparative TLC as in (3) yielded brown oils (ir, no cyano peaks).

(D) In a pyrolysis tube at 400°, packed with porcelain saddles and with a nitrogen flow rate of 100 cc/min, was dripped a mixture of 612 mg (5.1 mmol) of cyclopropane **96** and 1.48 g (8.6 mmol) of diethyl fumarate during a period of 30 min. The retention time in the tube was approximately 25 sec. The hot products were passed into a U tube cooled in liquid nitrogen. Gas chromatography of the pyrolysate showed peaks for starting material plus two new peaks. Both new fractions were collected* but neither appeared to be the desired cycloadduct **103**; ir of second peak (CCl_4) 2975, 2935, 2870 (C-H), 2230 (weak, CN), 1720 (weak-med, $COOC_2H_5$), 1603 (conjugated C=C) cm^{-1}; nmr

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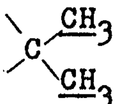
† Same as footnote, p. 61

* Same as footnote, p. 62

(microtube, CCl_4) τ 8.84, 8.72 (2 singlets,  $>C(CH_3)_2$), 6.93 (mult.), 2.78 (sing., vinyl H), 2.60 (sing, vinyl H). The integration and resolution were very poor (possible 3-methyl-1,1-dicyano-1-butene). However, this was obviously not the product. In addition, ir analysis of the other fraction indicated no cyano peak to be present.

Attempted Cycloadditions of 1,1-Dimethyl-2,2-dicyanocyclopropane (**96**) to Dimethyl Acetylenedicarboxylate (Equation 19)

A mixture of 503 mg (4.2 mmol) of cyclopropane **96**, 683 mg (4.8 mmol) dimethyl acetylenedicarboxylate and a trace of hydroquinone was heated at 100° under an atmosphere of prepurified nitrogen for 35 hr. Preparative TLC (Silica plates, 1:1 cyclohexane: ethyl acetate as eluent) yielded no new materials whose infrared spectrum contained cyano peaks.

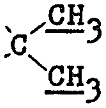
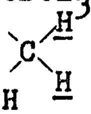
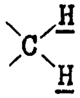
Heating of Ethyl 2-ethoxycyclopropane-1-carboxylate (**95**) in Dimethyl Sulfoxide (DMSO)

After cyclopropyl ester **95** had been heated in DMSO at 147° for 5 hr, gas chromatography showed no change. Evaporation of the solvent led to a complete recovery of the cyclopropyl ester **95** as indicated by its infrared spectrum.

Heating of 1,1-Dimethyl-2,2-dicyanocyclopropane (**96**) in Dimethyl Sulfoxide

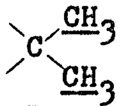
After cyclopropane **96** had been heated in DMSO at 147° for 5 hr, gas chromatography showed no change. The starting material was recovered upon evaporation of the solvent.

Preparation of 1,1-Dicyano-2,2-dimethyl-8-pyrrolidinohydrindane (**112A**)

Into a 1-l, 3-necked, round-bottomed flask, equipped with a reflux condenser, a magnetic stirring bar, and a thermometer were placed 67.0 g (445 mmol) of N-pyrrolidinocyclohexene (freshly distilled, bp 105-106°/10 mm), 35.0 g (292 mmol) of 1,1-dimethyl-2,2-dicyanocyclopropane (**96**) and 300 ml of xylene (isomeric mixture, distilled from calcium hydride, bp 136.5-138°/760 mm). The reaction mixture was refluxed for 31 hr under an atmosphere of prepurified nitrogen, cooled to room temperature, and then fractionated through a 20-cm Vigreux column. Three main fractions were collected: 1) 118-142°/0.05-0.07 mm, 2) 142-150°/0.08 mm and 3) 151-152°/0.08 mm, the total weight being 60.2 g. Each fraction was a viscous, yellow oil. Fractions 1 and 2 crystallized on standing at room temperature for about 48 hr. Fractions 1 and 2 were then combined and recrystallized from 95% ethanol (40-45°C). Crystallization was also accomplished with fraction 3 and the resulting white solids were combined furnishing a total of 28.5 g (56%) of cycloadduct **112A**; mp 78-79°; ir ($CHCl_3$) 2934, 2849 (C-H), 2232 (-C≡N) cm^{-1}; nmr ($CDCl_3$)τ 8.62, 8.55 (singlets,  $\gt C\begin{smallmatrix}\underline{CH}_3\\ \underline{CH}_3\end{smallmatrix}$), 6.4 to 8.5 (mult., C-$\underline{H}$ and  $\gt C\begin{smallmatrix}\underline{H}\\ \underline{H}\end{smallmatrix}$ on rings), 6.90 (mult., unresolved A_2B_2 pattern,  $\gt C\begin{smallmatrix}\underline{H}\\ \underline{H}\end{smallmatrix}$ from pyrrolidine ring).

The actual integration was impossible to determine because the peaks overlapped. Mass spectral analysis showed the parent ion at m/e 271.2; Anal. Calcd for $C_{17}H_{25}N_3$: C, 75.23; H, 9.28; N, 15.48; Found: C, 74.98; H, 9.42; N, 15.54.

Isolation of 1,1-Dicyano-2,2-dimethyl-8-hydroxyhydrindane (117A)

A portion (1.76 g of the impure fractions of the perhydrindane 112A) was dissolved in 5 ml of benzene and placed on a silica column packed in n-hexane. The column was eluted with 200-ml volumes of 1) n-hexane, 2) 19:1 n-hexane:benzene, 3) 4:1 n-hexane:benzene, 4) 1:1 n-hexane:benzene, 5), 6), 7) benzene, 8) 49:1 benzene: ether, 9) 19:1 benzene:ether 10)-17) 9:1 benzene: ether. Fractions 9) and 10) yielded a total of 606 mg of the hydroxyhydrinane 117A (a white solid), mp 108.0-108.8°. Recrystallization of the hydroxyhydrindane 117A from carbon tetrachloride changed the mp to 134.0-134.2°. A second recrystallization from carbon tetrachloride gave material with a new mp, 95.0°. The ir, nmr and analyses showed all three forms to be the same compound. The hydroxyhydrindane 117A gave a negative N-bromosuccinimide test;[130] ir ($CHCl_3$), 3559, 3333 (O-H), 2247 (unconjugated CN) cm^{-1}; nmr ($CDCl_3$)τ 8.58, 8.55 (both singlets, 3H, 3H  $>C\begin{smallmatrix}CH_3\\CH_3\end{smallmatrix}$), 7.83-8.75 (complex mult., 11H, ring H's), 7.60 (1H, singlet, washes out in D_2O, O-H); m/e 218, 112, 111; Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83; Found: C, 71.48; H, 8.29; N, 12.81.

Preparation of 4-Cyano-5,5-dimethyl-$\Delta^{1,7}$-2-azabicyclo[5.4.0]undecen-3-one (116A)

Fractions 13-17 above yielded 694 mg of white solid, mp 164-165° (95% ethanol); uv (95% C_2H_5OH), λ max, 264 mμ (ϵ1.19 x 10^4); ir ($CHCl_3$), 3472, 3367 ($-\underset{\underset{O}{\|}}{C}-N-H$), 2188 (conjugated CN), 1701 ($-\underset{\underset{O}{\|}}{C}-NH_2$), 1645, 1597 (-N-H) cm^{-1}; nmr (acetone - d_6), τ 8.96, 8.80 (6H, 2 singlets, $\rangle C\langle^{\underline{CH_3}}_{\underline{CH_3}}$), 7.94 (2H, singlet, $\diagdown \underline{CH_2}\overset{\|}{\diagup}\!\diagdown$), 7.82 (1H, $-\underset{\underset{H}{|}}{C}-CN$), 7.12-8.68 (8H, complex mult., ring H's), 4.65 (2H, broad singlet, washes out in D_2O, -C-NH-); Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83; Found: C, 71.52; H, 8.30; N, 12.84.

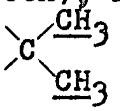
The amide 116 can also be prepared in quantitative yield by heating the perhydrindane 112A in boiling 95% ethanol for 5 min, evaporating the solvent and drying.

Preparation of 4-(2-Oxocyclohexyl)-3,3-dimethylbutyric Acid (118A)

Into a 100-ml round-bottomed flask equipped with a reflux condenser and a magnetic stirring bar were placed 3.07 g (11.3 mmol) of 1,1-dicyano-2,2-dimethyl-8-pyrrolidinohydrindane (112A) and 50 ml of 70% sulfuric acid. The reaction mixture was heated in an oil bath for 27 hr at 148°.

The mixture was than extracted with six 75-ml portions of ether which upon concentration gave 583 mg of a brown viscous oil from which no pure material was obtained upon sublimation or recrystallization.

The aqueous layer was then neutralized to pH 7 with 10%

aqueous sodium bicarbonate and then extracted with three 250-ml portions of ether in order to extract any non-acidic material. Concentration gave 120 mg of brown viscous oil. Reacidification of the aqueous layer with concentrated sulfuric acid and extraction with three 300-ml portions of ethyl acetate, followed by evaporation of the solvent, left 569 mg of yellow oil. The oil crystallized after about 12 hr. (Crude yield, based on the perhydrindane 112A is 24%). Recrystallization of the keto-acid 118A from hot n-hexane produced a white solid, mp 57°; ir ($CHCl_3$) 3472, 2857, 2817 to 2513 (-COOH), 1692 (COOH and C=O) cm^{-1}; nmr ($CDCl_3$)τ, 8.94 (sing.,  $>C(CH_3)_2$), 7.54 to 8.90, 7.70 (mult., ring and branch C-H), all peaks mentioned so far integrated for 19H, -1.14 (1H, sing., COOH, washed out in D_2O); m/e 271, 165, 164; Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.70; H, 9.50; Found: C, 67.89; H, 9.50.

4-[2'-(2",4"-dinitrophenylhydrazonocyclohexyl)] -3,3-dimethylbutyric acid was prepared in 61% yield, mp 126-130°.[150]

Preparation of α,α-Dimethyl-β-carboethoxypropionyl Chloride[131] (120)

Each of the starting materials was purified as follows.[146] Acetone was refluxed until it no longer decolorized $KMnO_4$, then dried over anhydrous calcium sulfate and distilled at 56°. Ethyl cyanoacetate was washed with two 75-ml portions of saturated aqueous sodium carbonate, followed by three 50-ml portions of water. It was then dried over sodium sulfate and fractionally distilled through a 20-cm Vigreux column, bp

100-103°/16 mm. Pyridine was refluxed over potassium hydroxide pellets and then distilled from the pellets through a 20-cm Vigreux column, bp 115-116°. Acetic anhydride was distilled from 1% of its weight of quinoline through a 32-cm Vigreux column, bp 72°/65 mm. Thionyl chloride was refluxed over sulfur for 30 min and then distilled through a 32-cm Vigreux column, bp 77-78°.

α,α-Dimethylsuccinic anhydride was prepared via the method of Baumgarten and Gleason[131] using 74.2 g (1.33 mols) of acetone, 150.7 g (1.33 mols) of ethyl cyanoacetate, 80.0 g (1.33 mols) of glacial acetic acid and 105.3 g (1.33 mols) of pyridine. The anhydride was distilled twice, once through a 20-cm Vigreux column and then redistilled through a spinning band column, 93.8 g (55%), bp 100-104°/15 mm.

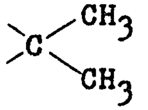
The acid ester 125 was prepared from the anhydride[131] giving a 77% yield; white crystals from hexane, mp 66.0-67.5°.

The acid chloride ester 120 was prepared from the acid ester as a yellow liquid, bp 58°/0.22 mm (84% yield).

Preparation of Ethyl 4-(2'-Oxocyclohexyl)-3,3-dimethyl-4-oxobutyrate (121)

Into a 1-l. 3-necked round-bottomed flask equipped with a reflux condenser, a magnetic stirring bar and flushed with prepurified nitrogen was placed 64.8 g (385 mmol) of N-morpholinocyclohexene (distilled, bp 116-119/10 mm) and 350 ml of dry benzene (distilled from calcium hydride). The solution was stirred vigorously while 36.8 g (175 mmol) of the acid chloride ester **120** was added in one portion. The mixture was then refluxed for 24 hr and cooled to room temperature.

The precipitate of N-morphilinocyclohexene hydrochloride (87% yield) was filtered with suction and washed with two 150-ml portions of ether. The filtrate and washings were diluted with 150 ml of 10% hydrochloric acid and the mixture was refluxed for 4.5 hr. After it had cooled to room temperature, the organic and aqueous layers were separated. The aqueous layer was washed with two 80-ml portions of benzene and the organic layers were combined, dried and concentrated under reduced pressure. The remaining yellow liquid, oxobutyrate **121** was fractionated through a spinning band column, bp 114-116°/0.43 mm, yielding 20.9 g (47%). The oxobutyrate **121** gave a positive $FeCl_3$ test; ir (CCl_4) 1730 (COOEt), 1698 (C=O), 1635 (C=C) cm^{-1}; nmr ($CDCl_3$)τ -6.0 (fraction of 1H, sing., washes out with D_2O, $C{=}C{-}O\underline{H}$), 4.14 (2H, 2 quartets, $CH_3\underline{CH_2}{-}O{-}\underset{\underset{O}{\|}}{C}{-}$, for both forms, keto and enol), 7.03 to 8.58 (remaining H's, extensive multiplets). Ethyl 4-[2'-(2",4"-dinitrophenylhydrazonocyclohexyl) -3,3-dimethyl-4-oxobutyrate (**127A**) was prepared in 25% yield,[150] mp 128.0-128.5°; ir ($CHCl_3$) 3311 (N-H), 1724 (COOEt,C=O probably hidden under this peak), 1618 (C=N), 1522, 1350 (NO_2) cm^{-1}; nmr ($CDCl_3$)τ -1.10 (1H, sing., $N{-}\underline{H}$), 1.18 to 2.50 (3H, mult., aromatic H), 6.20 (2H, quartet, $CH_3\underline{CH_2}{-}O{-}\underset{\underset{O}{\|}}{C}{-}$), approx. 6.20 (8H, mult., ring protons), 7.64, 7.75 (2H, 2 singlets, H^1 and H^2), 8.96, 9.02

(6H, 2 singlets,  $\rangle C \langle^{CH_3}_{CH_3}$), 9.21 (3H, triplet, $\underline{CH_3}CH_2\text{-}O\text{-}\underset{O}{C}\text{-}$); **Anal.** Calcd for $C_{20}H_{26}N_4O_7$: C, 55.29; H, 6.03; N, 12.90; Found: C, 54.92; H, 5.82; N, 12.78.

Preparation of Ethyl 4-(2'-Ethoxycyclohexenyl)-3,3-dimethyl-4-oxobutyrate (122)

A 50-ml portion of triethyl orthoformate was washed with two 15-ml portions of 5% aqueous sodium hydroxide, followed by drying over potassium hydroxide pellets and finally distilling immediately before using from calcium hydride, bp 140-143°.

In a 50-ml round-bottomed flask attached to a distillation apparatus with a 10-cm Vigreux column were placed 5.10 g (20 mmol) of ethyl 4-(2'-oxocyclohexyl)-3,3-dimethyl-4-oxobutyrate (121), 3.25 g triethyl orthoformate, 9 ml of absolute ethanol and 25 mg of p-toluenesulfonic acid monohydrate. The mixture was gradually heated until ethyl formate began to distill and the heating then continued until an infrared spectrum showed the absence of ethyl formate. This took approximately 4 hr at 78°C. The mixture was cooled to room temperature and washed with 5 ml of saturated aqueous sodium carbonate followed by 5 ml of water. The mixture was then diluted with ether to allow better separation of layers and less loss in drying. After washing with 5 ml of water and drying over potassium carbonate, the ether, ethanol and triethyl orthoformate were removed under reduced pressure. Distillation of the remaining liquid gave 3.75 g (68%) of a colorless liquid, bp 105-107.5°/0.03 mm; uv, λ_{max}^{EtOH} 217 mμ(ϵ1.60 x 10^3), 276 mμ(ϵ1.09 x 10^3); ir (CCl_4) 2970, 2925 (C-H), 1735 (COOEt), 1711 (C=O), 1638 (C=C), 1190, 1180, 1121, 1034 (C-O stretch) cm^{-1}; nmr (CCl_4)τ poorly resolved, 8.66 to 8.93 (12H, singlets and triplets, 4 methyl groups), 5.91 (2H, quartet, $CH_3\underline{CH_2}-O-\underset{\underset{O}{\|}}{C}-$),6.40 (2H, sing., $-\underline{CH_2}COOEt$), 5.90 to 8.50 (extensive multiplets).

Ethyl 4- 2'-(2",4"-dinitrophenylhydrazonocyclohexyl) - 3,3-dimethyl-4-oxobutyrate (**127B**) was prepared in 24% yield[151] from ethyl 4-(2'-ethoxycyclohexenyl)-3,3-dimethyl-4-oxobutyrate (**122**); mp 128.0-128.5°; ir ($CHCl_3$) is identical to that of **127A**; mixed mp with **127A**, 128.0-128.5°.

Attempted Reduction of Ethyl 4-(2'-ethoxycyclohexenyl)-3,3-dimethyl-4-oxobutyrate (122)

Potassium t-butoxide was prepared by the method of Speziale and Ratts[108] under an atmosphere of prepurified nitrogen using 700 mg (17.9 mmol) of potassium metal. Final traces of heptane were removed at 1 mm.

In a 100-ml round-bottomed flask were placed 2.5 g (8.85 mmol) of ethyl-4-(2'-ethoxycyclohexenyl)-3,3-dimethyl-4-oxobutyrate (**122**), 850 mg (17.0 mmol) of 99-100% hydrazine hydrate and 50 ml of dry n-butanol. After refluxing for 5 hr, the excess hydrazine was removed by distillation. Other excess materials were removed at 60°/50 mm, leaving 2.25 g of residue (86% theory, if hydrazone).

The residue was added through an addition funnel to the potassium *t*-butoxide (made as above) in 8 ml of dry refluxing toluene over a period of 10 min. After 28 hr, no nitrogen evolution had yet been observed with a nitrogen bubbler. The reaction mixture was cooled to room temperature and poured into 10 ml of 3N hydrochloric acid; the layers were then separated and the aqueous layer was extracted with three 10-ml portions of ether. After evaporating the dried organic solvents under reduced pressure, the residue was distilled through a 35-cm Vigreux column yielding 200 mg, 100-111°/0.07 mm. The residue could not be distilled even at a temperature of nearly 200°/0.03 mm.

Attempted Reduction of Ethyl 4-(2'-ethoxycyclohexenyl)-3,3-dimethyl-4-oxobutyrate (122) by the Huang-Minlon Method[134]

Triethylene glycol was dried over calcium chloride for 3 weeks (at least 1 week is recommended)[146] and then distilled through a spinning band column, bp 101°/0.28 mm, reflux ratio, 10:1.

A 100-ml round-bottomed flask with a magnetic stirring bar was connected to a 20-cm Vigreux column. In the flask were placed 40 ml of purified triethylene glycol and 4.50 g (80 mmol) of potassium hydroxide. The mixture was then heated to 90° and stirred until the potassium hydroxide dissolved. To the basic solution was then added 4.5 g (16 mmol) of the enol ether 122 and 4.0 g (8.0 mmol) of hydrazine hydrate (99%). The mixture was heated to 120° and stirred at this temperature for 1 hr. Hydrazine and water were then distilled until the temperature of the mixture reached 206°. (At this temperature, some gas evolution was observed with a nitrogen bubbler). After 5 hr at 206°, the reaction mixture was cooled to room temperature, an equal volume of water added, and the entire mixture was extracted with five 50-ml portions of ether. After drying and removing the ether, 1.26 g of a yellow liquid remained; ir (CCl_4) 3333 (broad, N-H), 2924, 2865 (C-H), 1667 cm^{-1}.

The remaining aqueous layer was acidified with 3N hydrochloric acid to pH 2, then extracted with seven 50-ml portions of ether and dried over magnesium sulfate. After evaporation of the ether under reduced pressure, there remained behind 1.43 g of a yellow partially solidified oil which, upon trituration with 1 ml of hot benzene, gave a white solid. Filtration of the solid, followed by washing with ice-cold petroleum ether, (bp 30-60°) and drying, yielded 228 mg of white solid which was purified by sublimation, approx. 100°/0.005 mm, mp 136.0-137.5°. The solid was soluble in aqueous sodium bicarbonate with evolution of gas. It also gave a negative ferric chloride test: ir (0.77% KBr) 2994, 2924, 2660 (broad), 1686 cm^{-1} (all of these peaks seemed to indicate a carboxylic acid); nmr ($CDCl_3$)τ 8.72 (6H, sing.), 7.38 (nearly 1H, sing.) 2.42 (2H, sing., washes out with D_2O) were the only peaks observed.

No indications that the desired product was formed were obtained.

Attempted Preparation of Ethyl 4-(1-cyclohexenyl)-3,3-dimethyl-4-oxobutyrate (126)

Cyclohexene was purified[146] by washing the aqueous sodium hydroxide, drying over anhydrous calcium chloride and distilling through a spinning band column over calcium hydride.

Methylene chloride was purified[146] by shaking with portions of concentrated sulfuric acid until the acid layer was colorless. The organic layer was then washed with water, 5% aqueous sodium carbonate, and water again. The material was dried over calcium chloride and then distilled through a 30-cm Vigreux column. The methylene chloride was stored over molecular sieves until ready for use.

In a 100-ml round-bottomed flask, with a reflux condenser and an addition funnel, was placed a suspension of 5.0 g (37.8 mmol) of aluminum chloride in 20 ml of dry methylene chloride, followed by addition of the acid chloride ester 120. After bubbling ceased, the reaction mixture was filtered through glass wool into a reaction flask at -5°, 2.05 g (25 mmol) of cyclohexene dissolved in 75 ml of methylene chloride was added dropwise, with stirring, at a rate such that the temperature was maintained at -5°. The mixture was stirred for an additional 30 min at -5° after the cyclohexene addition was complete, after which it was poured into 30 ml of 1.5N hydrochloric acid mixed with ice. The layers were separated and then the acid layer was extracted with two 15-ml portions of methylene chloride. The methylene chloride layer was then extracted with one 10-ml portion of water, two 15-ml portions of saturated sodium carbonate solution and two 15-ml portions of water again. After drying over anhydrous sodium sulfate, the mixture was distilled from anhydrous sodium carbonate, using a 10-cm Vigreux column, yielding two main fractions, 1) 1.006 g, bp 113-122°/0.43 mm, 2) 0.789 g, bp 122-128°/ 0.25 mm; ir of both fractions (CCl_4) 3021 (weak), 2959, 2933, 2857, 1859 (weak), 1761 (med.), 1733 (str.), 1715 (str.), 1672 (weak) cm^{-1}. If any substantial amount of α,β-unsaturated ketone were present, a strong peak at approximately 1675 cm^{-1} (C=O)[129] should have been present. The mixture was redistilled yielding 1.436 g liquid, bp 105-112°/0.05 mm with the same infrared peaks.

Reaction of Dimethyllithium Cuprate With Ethyl-α,α-Dimethylacrylate[140,141]

(A) A sample of 28.5 g (150 mmol) of cuprous iodide was dried at 130° for 5 hr after which it was cooled to room temperature in a desiccator containing calcium chloride.

A 1-l 3-necked round-bottomed flask equipped with a pressure-equalizing addition funnel, a mechanical stirrer and a double coil reflux condenser was flushed with prepurified nitrogen. The dried cuprous iodide together with 350 ml of anhydrous ether were placed in the flask and the mixture was cooled to -15° with an ice-salt mixture. Approximately 200 ml of methyllithium (1.57 M in ether,[143] Ventron, approximately 315 mmol) was forced into the addition funnel by a positive nitrogen pressure. The methyllithium solution was then added under nitrogen to the flask from the addition funnel over a period of 10 min. The mixture changed from an initial deep yellow (formation of methylcopper) to brown (formation of the dimethyllithium cuprate). The mixture was then stirred for an additional 15 min and 5.6 g (50 mmol) of ethyl α,α-dimethylacrylate dissolved in 100 ml of anhydrous ether was added during 20 min at a temperature of -10 to -15°. The mixture was stirred at this temperature for 3 hr, then left at room temperature for 1 d.

The mixture was poured slowly (much bubbling) into 300 ml of 15% aqueous ammonium chloride. When the bubbling stopped, the ether and aqueous layers were separated, and the aqueous layer was extracted with four 200-ml portions of ether. The combined ether layers were then washed successively with 150 ml of water, 150 ml of saturated aqueous sodium chloride, 150 ml of water and dried. The ether was removed at atmospheric pressure and the residue was distilled through a 20-cm Vigreux column, yielding two main fractions: 1) 1.05 g, bp 53-70°/760 mm, 2) 2.40 g, bp 70-75°/760 mm, plus two higher boiling fractions, total of 0.50 g, 70-85°/760 mm; ir of fractions 1) and 2) (CCl_4) 3067 (C=C-H), 2950, 2907, 2849 (C-H), 1626 (C=C), 890 ($C=CH_2$) cm^{-1}. No peaks at 1740 cm^{-1} indicative of the desired product ester were observed.

(B) The same reaction as in (A) above was attempted using freshly made methyllithium. In a round-bottomed flask equipped with an addition funnel, a double-coil reflux condenser, a mechanical stirrer, and glass tubing leading to a second reaction flask was placed 1.4 g (200 mmol) of lithium wire, cut into small pieces and 33 ml of anhydrous ether.

This flask was connected by means of the aforementioned tubing to another reaction flask which was equipped with a reflux condenser, a nitrogen bubbler, a mechanical stirrer and a sintered glass funnel placed on top of an addition funnel. The tubing from the first flask led into the sintered glass funnel by Tygon tubing. The entire system was flushed with prepurified nitrogen.

In the second flask was placed 7.60 g (40 mmol) of cuprous iodide (freshly dried in a drying pistol at 100° with phosphorous pentoxide for 6 hr) and 30 ml of anhydrous ether.

To the lithium wire was added 11.35 g (80 mmol) of methyl iodide (freshly distilled, bp 42°/760 mm and stored over copper wire) in 100 ml of anhydrous ether with stirring. Refluxing began immediately and was maintained during the addition of methyl iodide and then for additional hr. The methyllithium was then forced into the addition funnel of the second flask through the sintered glass funnel and was added to the cuprous iodide/ether slurry, which had been previously cooled to -5°.

The remainder of the workup was identical to that in part A. However, before distillation, infrared spectral analysis of the residue showed that almost all starting material was still present.

Reaction of Dimethyllithium Cuprate with Ethyl isopropylidenecyanoacetate (130)

Dimethyllithium cuprate was made as previously described from 5.31 g lithium wire in 30 ml of anhydrous ether and 42.6 g (300 mmol) of methyl iodide in 180 ml of anhydrous ether. This was mixed with 7.7 g (50 mmol) of the olefin and 2.4 g of a dark brown gummy residue was obtained upon workup. The residue could not be distilled even near 200°/0.04 mm.

Attempted Addition of N-Cyclohexenylpyrrolidine to Isobutylene Oxide

A typical attempt used 1.10 g (15 mmol) of isobutylene oxide and 5.55 g (30 mmol) of N-cyclohexenylpyrrolidine in 20 ml of dry benzene. The mixture was stirred from 2 to 9 d at 74-80° or 45-50°. Sometimes *p*-toluenesulfonic acid was used as a catalyst. All variants led only to enamine and a polymeric residue.

When dimethylformamide (previously distilled from barium oxide) was used as solvent, no reaction occurred.

Addition of N-Pyrrolidinocyclohexene to 1,1-Dimethyl-2,2-dicyanocyclopropane (96) in DMSO

In a 3-necked 250-ml round-bottomed flask, fitted with a reflux condenser previously flushed with prepurified nitrogen was placed 6.30 g (52.5 mmol) of 1,1-dimethyl-2,2-dicyanocyclopropane (96), 12.00 g (79.4 mmol) of N-pyrrolidinocyclohexene and 55 ml of dimethyl sulfoxide (distilled from calcium hydride, bp 77°/10 mm). The reaction mixture was stirred for 5 hr at 141-142° until VPC showed that none of the starting cyclopropane **96** remained. The DMSO was then distilled, bp 62°/5 mm, and the residue was fractionated through a 20-cm Vigreux column, bp 150-155°/0.08 mm (3.35 g). Charred material remained behind.

The ir of the distillate was identical to that of our previously discovered enamide (suggested structure **116A**). Recrystallization yielded white crystals melting at 164.5-166°, again identical to **116A**; mixed mp 164-166°.

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