cyclopropyl group takes place most efficiently in the acyl cyclopropane oximes, less efficiently in the spiro series and least efficiently in the bicyclic series.

Aspects of the mechanism of the Beckmann rearrangement of the oximes are discussed, such as the effects of the various alkyl substituents, the unique case of the cyclopropyl ring opening with addition of HCl in the rearrangement of bicyclo [4.1.0] heptan-2-one oxime, as well as the Beckmann fragmentation reaction observed in a limited number of the oximes. It is suggested that the back lobe participation of the cyclopropyl σ-bond in the transition state is a significant factor only in the rearrangement of the acyl cyclopropane oximes.

The poor migratory aptitude of the cyclopropyl system in the bicyclic and spiro series has been explained as being due to the conformational restriction making the back lobe participation of the cyclopropyl σ-bond unattractive. It is concluded that in the absence of such conformational constraint the cyclopropyl carbon migrates as efficiently as a saturated or an unsaturated carbon.

TO THE PEOPLE OF MY COUNTRY

ACKNOWLEDGEMENTS

I should like to express my sincere gratitude to Dr. Z. Hamlet for suggesting this research project and for his guidance, encouragement and expert advice throughout the course of this investigation.

I wish to express my deepest respect to the souT of the late professor J. Lenoir who served on my research committee for three years.

I also wish to thank professors L. D. Colebrook and R. A. Westbury for serving on my research committee, as well as for their advice and support.

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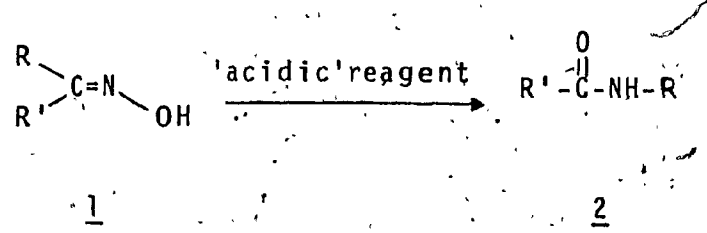
INTRODUCTION

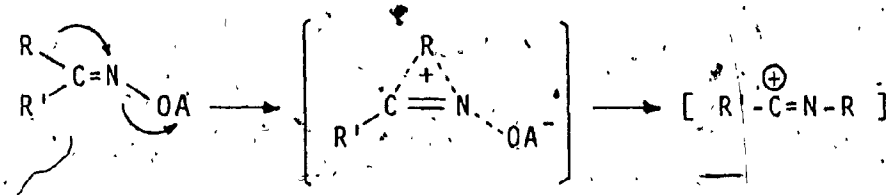
The conversion of a ketoxime 1 to a secondary amide 2 by an acidic reagent, a reaction first reported by Beckmann[1] in 1886, is known as the Beckmann rearrangement.



1 2

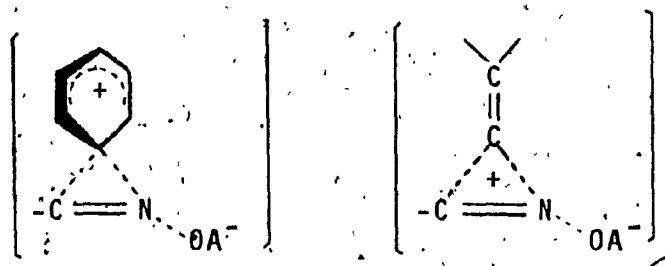
The reaction has since been extensively investigated and several reviews on the topic are available[2-8]. The usefulness of the reaction as a diagnostic tool for the configuration of the geometrically isomeric ketoximes lies in the fact that the group anti to the hydroxyl function (i.e. the group situated trans with respect to the OH group in 1) migrates preferentially[9].

The acidic reagent transforms the hydroxyl group of the oxime into a good leaving group. When an electron-deficient nitrogen is generated by departure of the leaving group (i.e. -OA in 3) the group trans to the leaving group (i.e. R = alkyl, aryl) migrates to the nitrogen with a pair of electrons to relieve



3 4 5

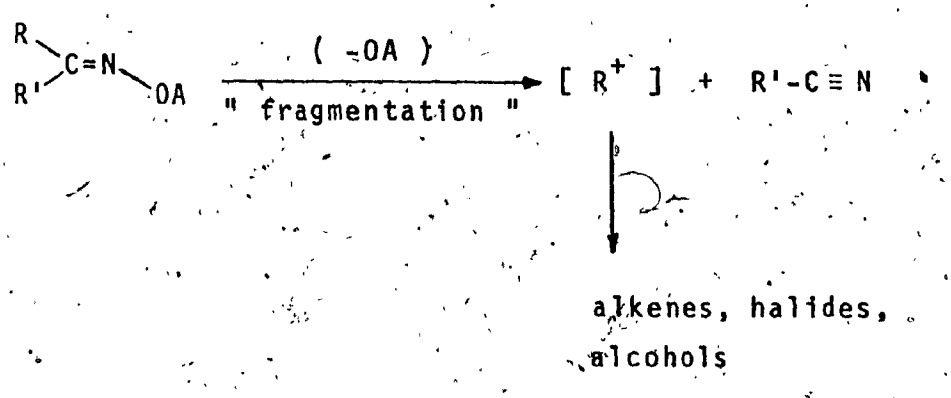
the electron-deficiency on this atom. The migration thus involves a 1,2-shift from carbon to nitrogen. The rearrangement is postulated to proceed intramolecularly in a concerted manner through a transition state 4 to give an intermediate 5 which subsequently produces the amide 2 upon hydrolysis. If the migrating group is a π-bonded system (i.e. R = Ph or a double bond) transition states of the type 6[10] and 7[11] can be envisaged.



6 Phenonium ion 7

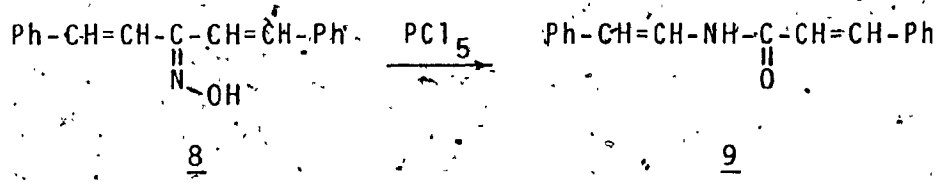
However, there are numerous instances in which oximes under the conditions used for the reaction (i.e. treatment with PCl_5) give products other than the expected secondary amide 2. The products in such cases are generally nitriles, olefins, alcohols and/or chlorides

which result from fragmentation of the oxime during the reaction. This sort of reaction has been variously refered to as " abnormal Beckmann rearrangement ", " second order Beckmann rearrangement " and " Beckmann fragmentation reaction "[8]. In this dissertation the terminology " Beckmann fragmentation reaction " will be used to refer to the reactions of the oximes resulting in products other than the expected amides or lactams.



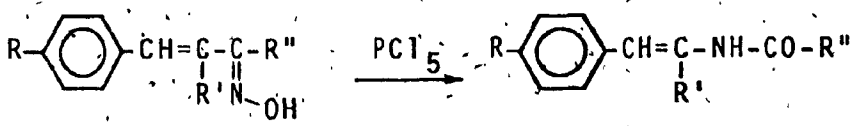
A number of studies of the Beckmann rearrangement of α,β-unsaturated oximes have been reported in the literature. The oximes studied include those in which the α,β-ethylenic bond was part of an acyclic system as well as those in which it was part of a cyclic system. In most cases it was observed that when the ethylenic group was situated <u>anti</u> to the oximino hydroxyl group, the double bond migrated to furnish the expected amides or lactams.

One of the earliest examples of an acyclic α,β-olefinic ketoxime subjected to the Beckmann rearrangement was the



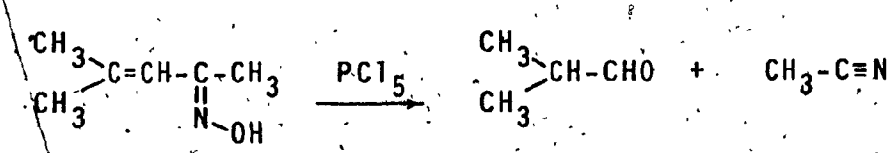
8 9

oxime of dibenzalacetone 8[12]. Unterhalt studied a number of α,β-unsaturated acyclic oximes 10 (where R, R', R" were a variety of different groups) and observed that the α-unsubstituted and α-phenyl oxime (10; R'= Ph) underwent the normal Beckmann rearrangement giving the expected amides 11, while oximes with α-alkyl substituents



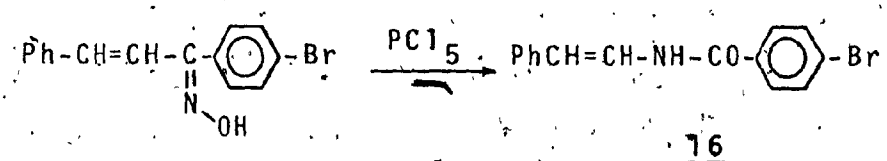
10 11

gave fragmentation products.[13] Fragmentation was observed as the exclusive result in the reaction of PCl_5 with the oxime of 4-methyl-3-penten-2-one (mesityl oxide), 12[14].



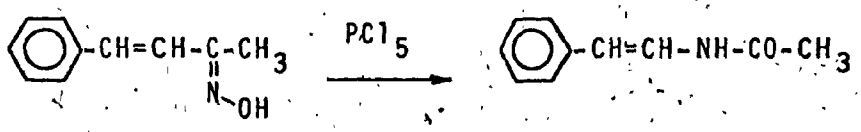
12 13 14

Blatt has observed that the anti oxime of benzal-p-bromoacetophenone 15 gave the amide 16, expected from the migration of the double bond in the PCl_5-induced Beckmann rearrangement[15]. Similar results were obtained



15 16

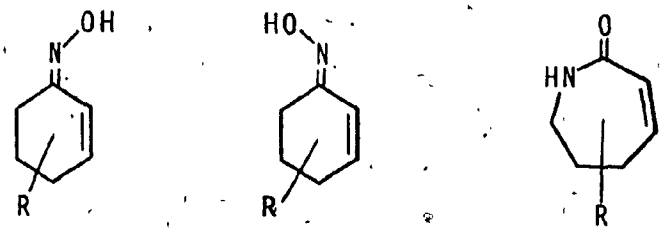
by Corbett and Davey[16] for the PCl_5-induced Beckmann rearrangement of several p-substituted benzylidene acetone oximes. More recent studies of the isomeric oximes (e.g. 17) of benzalacetone (benzylidene acetone) and several of its α- and β-substituted derivatives[17] have also demonstrated that in the PCl_5-induced Beckmann rearrangement of the double bond anti to the oximino hydroxyl migrates in accordance with expectation.



17 18 (refs. 11,17)

A number of studies pertaining to the Beckmann rearrangement in cyclic α,β-unsaturated ketoximes are reported in the literature. The conclusion arrived at

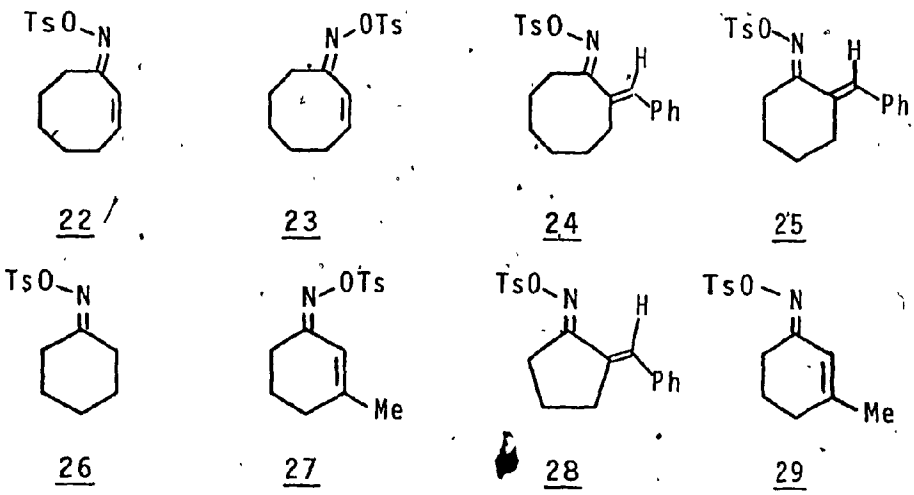
in one study was that, while syn oximes 19 undergo ready rearrangement to lactams of the type 21, the anti isomers 20, under similar conditions, resist the rearrangement[18]. It was concluded, therefore, that the olefinic carbon cannot migrate as effectively as the saturated carbon.



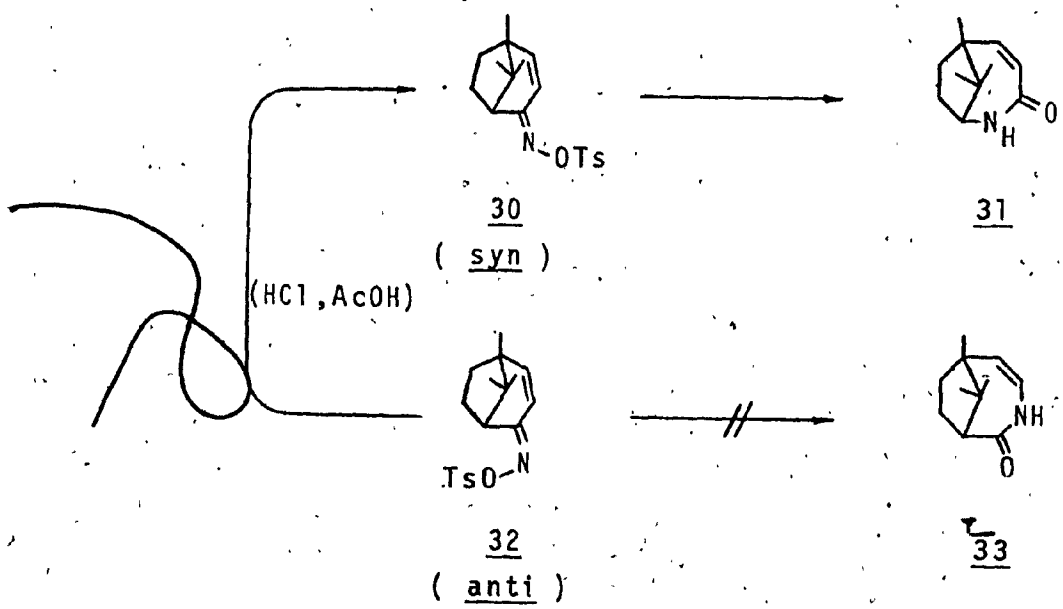
19 (syn) 20 (anti) 21

However, the conclusions reached in two other studies[19,20] have been that, in certain cyclic systems there was no preference for migration of a saturated carbon over an unsaturated carbon; groups located anti to the hydroxyl group migrated irrespective of whether they were " alkyl " or " olefinic ". Sato and co-workers[20] studied the solvolytic Beckmann rearrangement of several cyclic α,β-unsaturated ketoximes in order to obtain information on the migratory aptitude of the olefinic system. They have arranged the oxime tosylates 22 to 29 in descending order of their rates of solvolytic

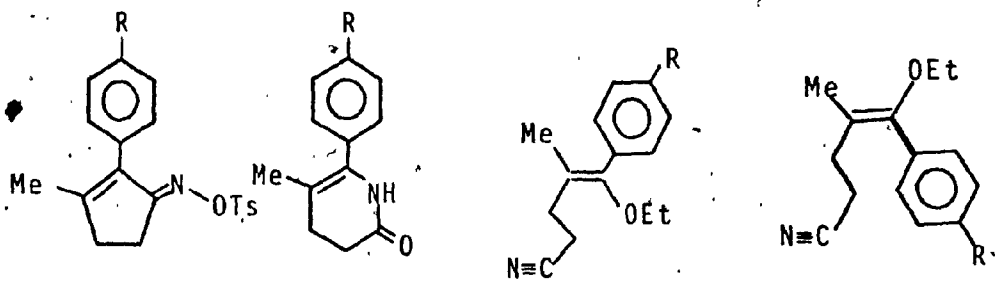
Beckmann rearrangement. The only tosylate in the series which failed to rearrange under various conditions was 29, and this result was interpreted in terms of a steric eff-



ect in the transition state for the rearrangement. A similar argument was advanced recently by Fleming and Woodward[21] for the failure of oxime tosylate 32 to rearrange to 33.



A series of such anti oxime tosylates in the 5-membered series 34 also failed to rearrange to the expected lactams 35, but gave products 36 and 37 resulting from the fragmentation, and/ or ketones from which the oximes are derived.[22]

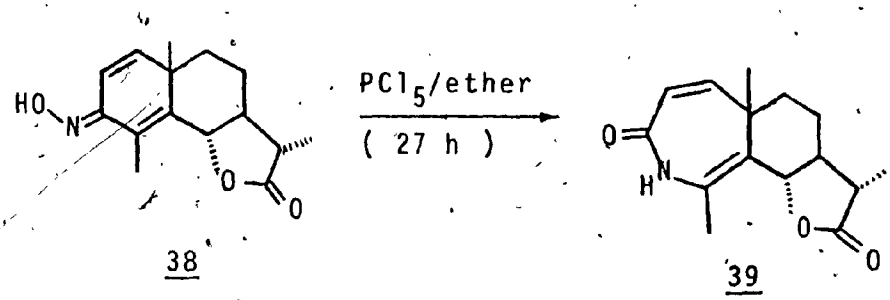


34 35 36 37

a: R = H
b: R = OMe
c: R = NMe_2

(ref. 22)

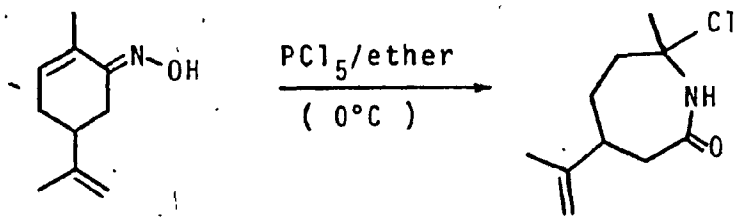
Other examples of cyclic anti oximes where the α,β-double bond is endocyclic which have been subjected to the PCl_5-induced Beckmann rearrangement include α-santonin oxime 38[23], and carvone oxime 40[11,19]. The santonin oxime 38 gave the expected lactam only on prolonged reaction and even then in poor yield. The carvone oxime 40 gave an extremely poor yield of a lactam which was identified as 41[11] where addition of elements of HCl had occurred across the conjugated double bond of the oxime during the



38 39

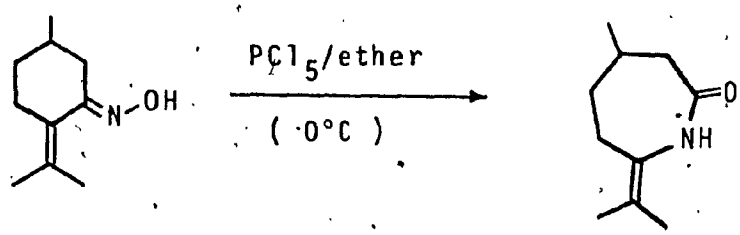
(26%)

(ref. 23)



40 41 (3%)

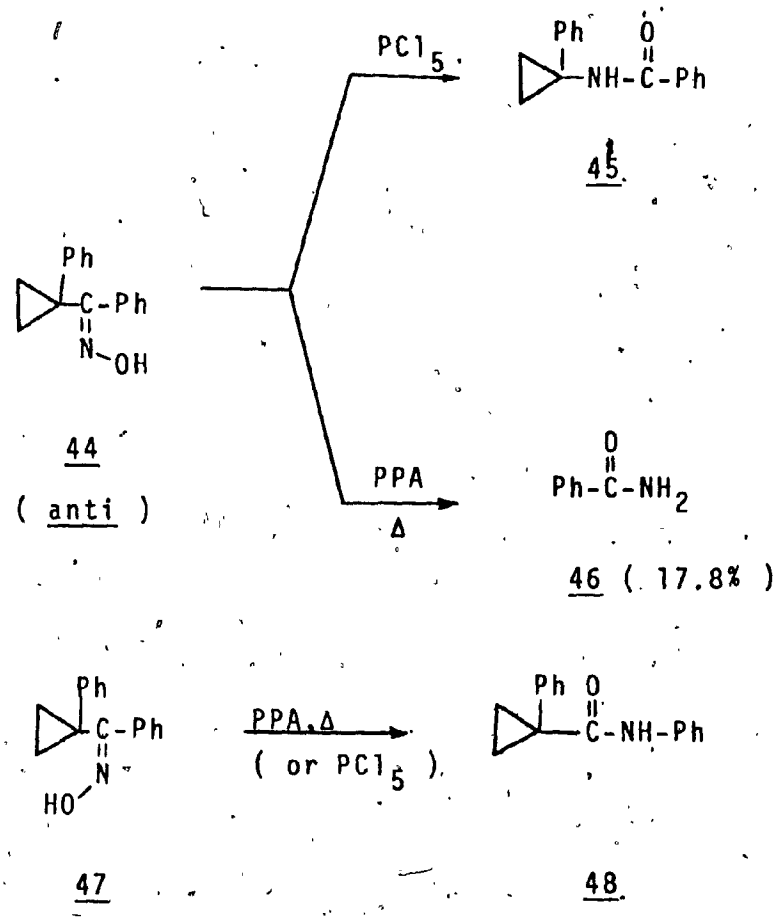
rearrangement. The anti oxime of pulegone 42 where the conjugated double bond is exocyclic rearranged to give the expected lactam 43 in good yield.[11]



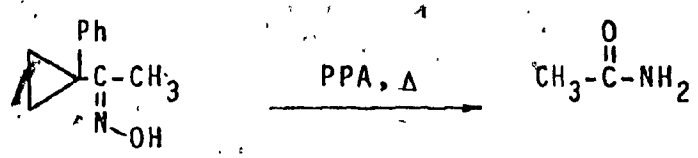
42 43 (71%)

No report of a systematic investigation aimed at studying the migratory aptitude of cyclopropyl ring system

in the Beckmann rearrangement of ketoximes seems to be available in the literature. However, some isolated reports are available which deal with the Beckmann rearrangement of oximes with a cyclopropyl ring alpha to the oximino function. Tencza[24] studied the rearrangement of both geometrical isomers of oximes of 1-benzoyl-1-phenylcyclopropane 44 and 47 using PCl_5 and polyphosphoric acid (PPA). The anti-isomer 44 underwent the

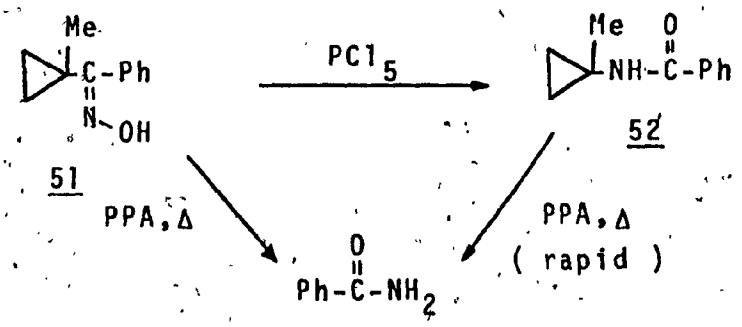


Beckmann fragmentation reaction with PPA to give benzamide 46 while with PCl_5 it gave the expected rearranged product 45. The syn-isomer 47 gave isomeric amide 48 in quantitative yield with either PCl_5 or PPA. It was also shown that anti-phenyl cyclopropyl methyl ketoxime 49 exhibited a behavior quite similar to anti-oxime 44 upon reaction with both PCl_5 and PPA to give acetamide 50 in 11.9% yield[24]. 1-Methyl cyclopropyl phenyl ket-

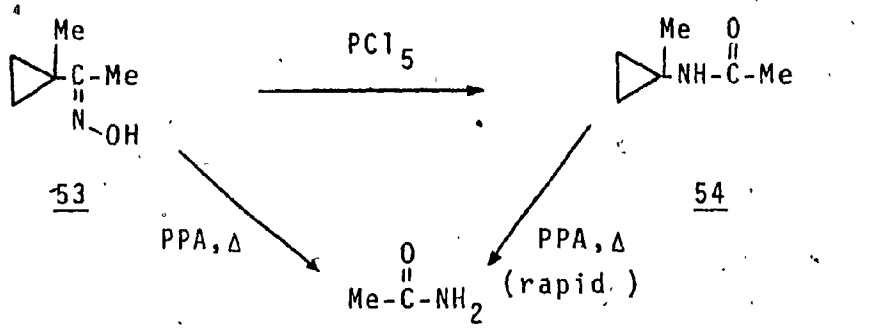


49 50 (11.9%)

oxime 51 and 1-methyl cyclopropyl methyl ketoxime 53 on treatment with PCl_5 gave expected amides 52 and 54 respectively. However, treatment of the oxime 51 and 53 with PPA resulted in complete fragmentation of both compounds.[24]

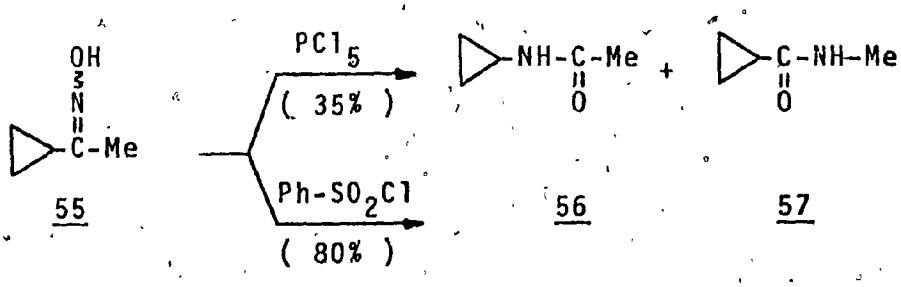


51 52 46

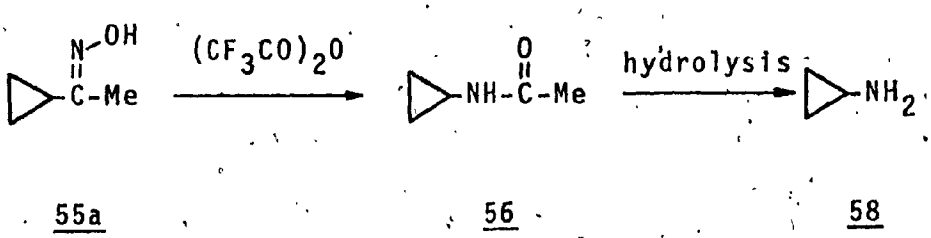


(ref. 24)

The Beckmann rearrangement of methyl cyclopropyl ketoxime 55 with PCl_5 was first reported by Roberts and Cambers[25]. A mixture of the geometrical isomers of 55 were found to give a mixture of isomeric amides 56 and 57 in total yield of 35%. Emmons[26] has carried out



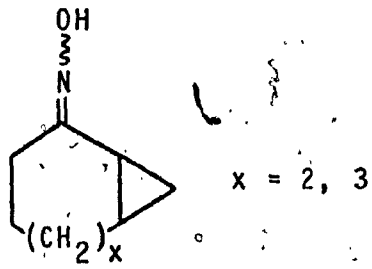
the Beckmann rearrangement of the oxime 55a using trifluoroacetic anhydride as the reagent in a preparation of cyclopropylamine 58. The Beckmann rearrangement of



dicyclopropyl ketoxime 59 to N-cyclopropyl cyclopropane carboxamide 60 was reported by Hart and Curtis[27] for the first time and later by Hirata.[28] Both of the reports have shown that the amide 60 is the only product of reaction of the oxime with PCl_5. These examples show that a cyclopropyl ring situated anti to the oximino hydroxyl migrates intact during the rearrangement.

59 60 (ref. 27)

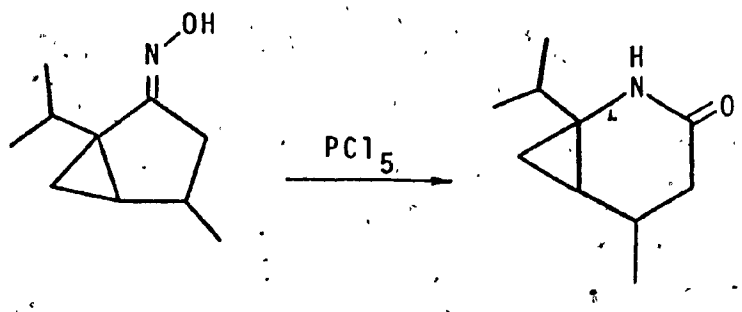
There are very few reports regarding the Beckmann rearrangement of bicyclo [n.1.0] alkan-2-one oximes 61.



61

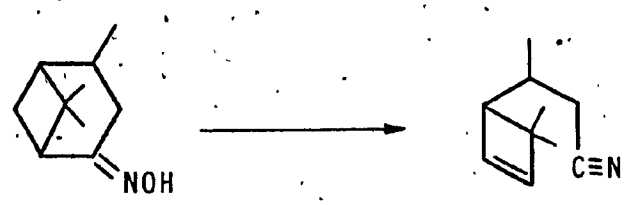
The oxime of β-dihydroumbellulone 62 seems to be the only case available in the literature where the migration of the cyclopropyl ring in a bicyclic system has been observed

under the Beckmann rearrangement conditions. It has been shown that the oxime gave the bicyclic lactam 63 in excellent yield under a variety of rearrangement conditions (p-Br-$C_6H_4SO_2Cl$, TsCl) without any evidence of fragmentation[29]. It is interesting to note that the bridged



62 63

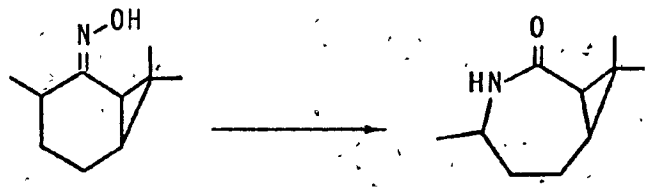
oxime 64 under similar reaction conditions gave only the nitrile 65 resulting from fragmentation.[29]



64 65

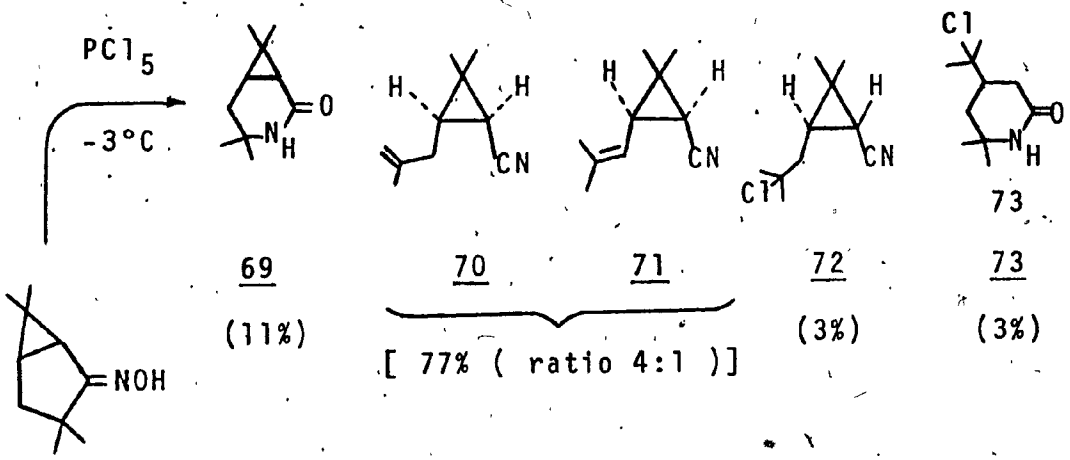
The Beckmann rearrangement of the optically active oxime of caran-2-one 66 in which the configuration of the

hydroxyl group is syn with respect to the cyclopropyl ring, has been investigated by Zabza and coworkers.[30] The oxime upon treatment with p-toluene sulfonyl chloride in aqueous acetone-NaOH yielded the corresponding lactam 67.



66 67

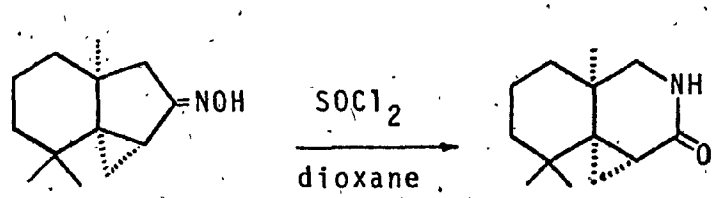
Julia and others[31] have studied the Beckmann rearrangement of the bicyclic ketoxime 68 in presence of PCl_5 and p-toluene sulfonyl chloride. They have shown that the bicyclic ketoxime 68 gives several fragmentation products 70, 71, 72 and 73 along with the rearranged product 69.



69 (11%) 70 71 [77% (ratio 4:1)] 72 (3%) 73 (3%)

68 TsCl 69 (50%) 70 71 (48%) (ref. 31)

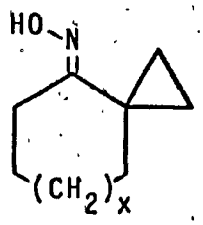
From the product 69 it would seem that in the oxime 68 the hydroxyl group is syn with respect to the cyclopropyl system, and therefore it is not involved in the migration. The tricyclic oxime 74[32] has been shown by Erdtman and Thoren[33] to undergo the Beckmann rearrangement in presence of thionyl chloride in dioxane to produce the tricyclic lactam 75. The authors have not stated the configuration



74 75

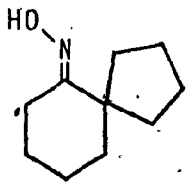
of the oximino group and also have not stated whether the rearrangement was accompanied by any fragmentation products. In this case also it is evident that the migrating group is not the cyclopropyl ring.

The Beckmann rearrangement of oximes where the alpha cyclopropyl ring system exists as a spiro structure (i.e. spiro [2.n] alkan-4-one oximes 76) seems not to have been studied. However, some larger spiro systems such as



76

77, 78, 79 and 80 have been investigated by Hill[34,35]. In presence of PCl_5, $SOCl_2$, p-CH_3-C_6H_4-SO_2Cl, PPA these oximes gave the lactams expected from the normal Beckmann rearrangement along with some fragmented products (nit-



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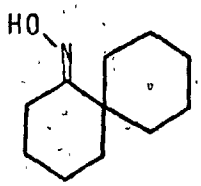
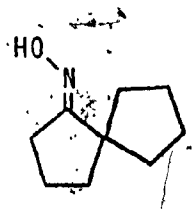


78



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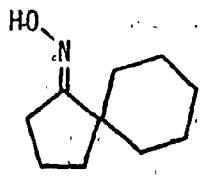
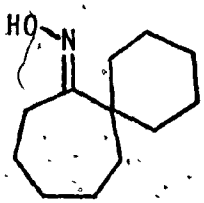


80

riles). Lukes and Hofman[36] have studied the Beckmann rearrangement of spiro [4.5] decan-6-one oxime 77, and spiro [5.6] dodecan-7-one oxime 81 using PCl_5 and P_2O_5. Both of the oximes underwent the fragmentation reaction to give the corresponding nitriles 82 and 82a respectively.



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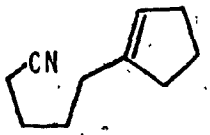

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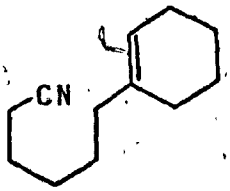


82a

From the examples cited above it is evident that a

systematic study of the migratory aptitude of the cyclopropyl ring system in the Beckmann rearrangement is not available in the literature. The somewhat limited data on the migratory aptitude of the ethylenic bond seem to suggest that, except where there are severe steric constraints in the transition state leading to the rearrangement, the alkenyl group (π-bonded carbon) migrates as efficiently as the alkyl group (sigma bonded carbon). The cyclopropyl ring system is well known to have some double bond-like character, and a cyclopropyl carbon can be considered as intermediate in character between a π-bonded (alkenyl) and a σ-bonded (alkyl) carbon[37,38]. Therefore, it was decided to undertake a study of the migratory aptitude of the cyclopropyl system in the PCl_5-induced Beckmann rearrangement and to see whether this system will migrate as readily as the 'alkyl' and 'alkenyl' group, or whether this system will undergo extensive fragmentation in view of the ring strain in the cyclopropyl ring.

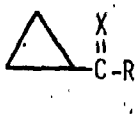
STATEMENT OF THE PROBLEM

The main objective of the present study was to investigate the migratory aptitude of the cyclopropyl ring in the PCl_5-induced Beckmann rearrangement of cyclopropyl-conjugated ketoximes.

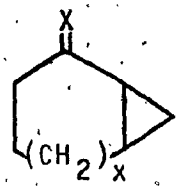
The decision to undertake the study was prompted by the fact that the cyclopropyl ring as a migrating group in the Beckmann rearrangement has received relatively less attention than saturated (alkyl) and unsaturated (aryl and alkenyl) groups, and the very limited amount of data available in the literature pertaining to the cyclopropyl group do not lead to definite conclusions regarding the migratory aptitude of this group.

In order to carry out a systematic study of the topic three categories of ketones 83a, 84a and 85a were sought as a first step with a view to converting them to the corresponding oximes 83b, 84b and 85b in which there exists a cyclopropyl ring in conjugation with (alpha to) the oximino function.

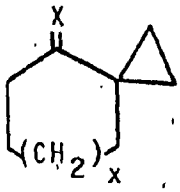
a: X = O
b: X = N~OH



83



84



85

The establishment of the stereochemistry of the oximes 83b, 84b and 85b, that is, whether the cyclopropyl ring and the hydroxyl group were in a syn (Z) or anti (E) relationship, was a crucial task, for the results of the reaction of the anti (E) isomer with PCl_5 were relevant to the main objective. The identification of the product(s) of the rearrangement reaction was therefore highly important.

Additional information sought for in the investigation was the effect of the ring size (i.e. the value of x) as well as the substituents upon the behavior of the cyclopropyl ring in bicyclo [n.1.0] alkan-2-one oximes (84b) and spiro [2.n] alkan-4-one oximes (85b) during the PCl_5-induced Beckmann rearrangement.

DISCUSSION

Cyclopropyl derivatives have been isolated from various natural sources and some of these have been shown to possess unusual biochemical[39] and biological[40] properties. Recently Soviet authors[41] have reported anti-convulsant and bacteriostatic activity for certain α-cyclopropyl ketoximes. Considerable attention has been focused in recent years on the conjugative properties of the cyclopropyl ring system.[38,42-46]

1. Bonding in the Cyclopropyl Ring

Theoretical and experimental studies have led to a description for the bonding in cyclopropane as pictured in Figure 1. The C-C bonds are best described as bent

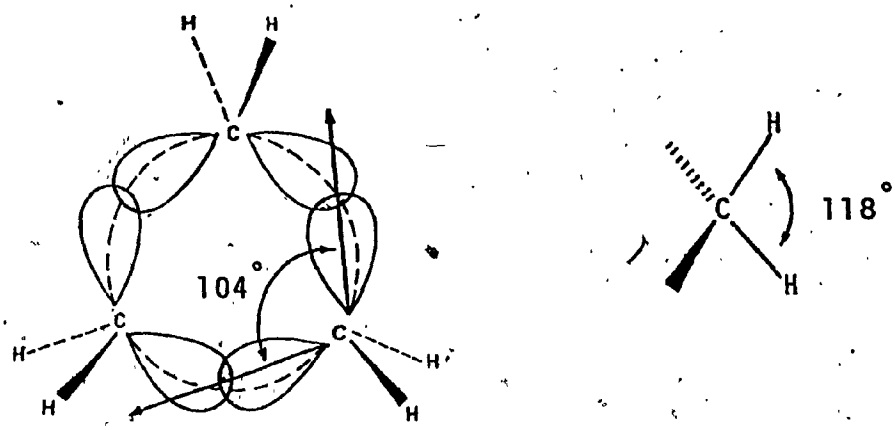
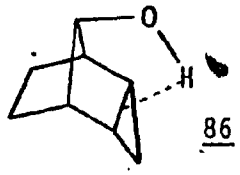
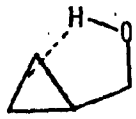


Figure 1. Orbital structure of cycloprpane ring showing bent-bond strain.

or " banana " bonds with an angle of 104° between the hybrid orbitals of the carbon which are used in σ-bond formation with the other two carbons[48]. Calculations[49] and NMR spectral data[50] indicate that the C-C bonding orbitals are sp^5-hybridized (more p character) and the C-H bonding orbitals are sp^2-hybridized (more s character) with the H-C-H bond angles of 118°. Regardless of the state of hybridization of the carbon, the overlapping atomic orbitals which form the C-C bonds in cyclopropane must lie outside the triangle formed by the three carbon atoms (Figure 1). This concentration of bonding electron density away from the internuclear axis provides a nucleophilic region which can be attacked by electrophilic reagents. The large " p-electron "-density in the plane of the cyclopropane ring produces a weak ring current as revealed by the substantial diamagnetic susceptibility[51] and the upfield proton chemical shifts (δ = 0.22) in the NMR spectrum. The p-character of the cyclopropane ring is also revealed in its proton-accepting role in forming hydrogen bonds[52]. For example, the compounds 86 and 87 exhibit intramolecular hydrogen bonding where the cyclopropyl system acts as the electron donor[53].

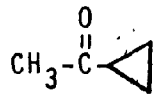


86

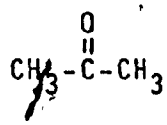


87

The three-membered ring in cyclopropyl ketones is known to possess a somewhat delocalized system of electrons. The delocalization has been attributed to the overlap of the bent bonding orbitals of the cyclopropyl C-C bonds and the π-system of the carbonyl group.[38,47] Evidence for such delocalization has been obtained from theoretical[54,55] and ultraviolet[56,57], infrared[56] and nuclear magnetic resonance studies.[58,59] Ultraviolet spectra[60,61] show that cyclopropyl conjugation shifts the absorption maxima of ketones by 8-30 nm. Infrared spec-



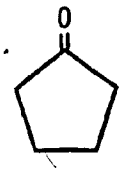
88



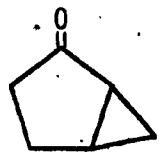
89

λ_{max} (208 nm) (193 nm)

tra[62,63] on the other hand reveal a lowering in the carbonyl stretching frequencies as illustrated in the examples 90-95. The same trend is observed in the



90



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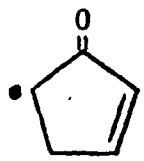
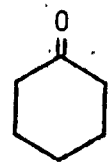
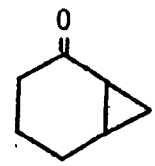
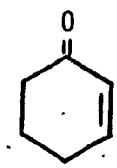


92

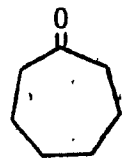
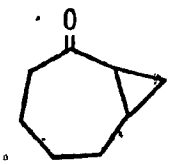
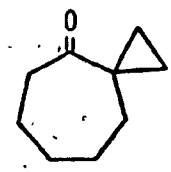
$\nu_{C=O}$ (1750 cm^{-1}) (1728 cm^{-1}) (1710 cm^{-1})

93 94 95

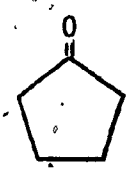
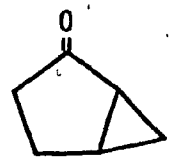
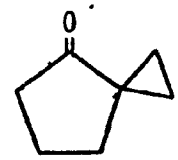
$\nu_{C=0}$ (1760 cm^{-1}) (1695 cm^{-1}) (1680 cm^{-1})

cyclopropyl conjugated cyclanones 97, 98 and 99 prepared in the present study. The bathochromic shift in the

96 97 98

$\nu_{C=0}$ (1703 cm^{-1}) (1695 cm^{-1}) (1690 cm^{-1})

90 91 99

$\nu_{C=0}$ (1750 cm^{-1}) (1728 cm^{-1}) (1732 cm^{-1})

cyclopentanone derivatives may be due, in part, to ring strain effects.[57,62-64]

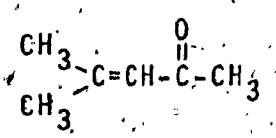
The delocalization effect of the cyclopropyl system existing in the α-cyclopropyl carbonyl compounds must also be present to approximately the same degree in the corresponding ketoximes because of the possibility of overlap of the π-orbitals of the C=N bond of the oximino function and the bent bonding orbitals of the three-membered ring.

2. Synthesis of α, β-Unsaturated Ketones

All the α, β-unsaturated ketones required for the present study were known compounds and many of these were purchased from commercial sources as indicated in the Experimental Section (page 110). Some of the ketones were synthesized using procedures described in the literature, and hence these procedures are not described in the experimental section of this thesis.

Mesityl oxide 100 was synthesized in 57 % yield starting from acetone as described by Conant et al.[65],

$$2\ CH_3\text{-}CO\text{-}CH_3 \xrightarrow{Ca(OH)_2} (CH_3)_2C(OH)\text{-}CH_2\text{-}CO\text{-}CH_3 \xrightarrow[(-H_2O)]{I_2}$$



(ref. 65)

100

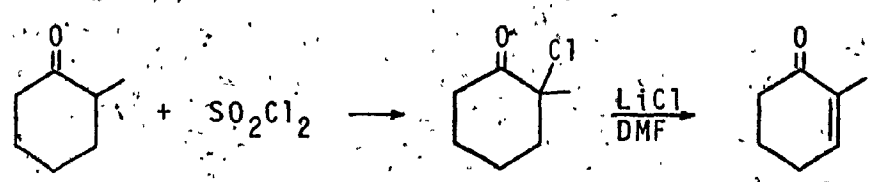
and benzalpinacolone 101 was obtained in 88 % yield

from pinacolone and benzaldehyde following the proce-

$$Me_3C\text{-}CO\text{-}CH_3 + Ph\text{-}CHO \xrightarrow{NaOH} Me_3C\text{-}CO\text{-}CH{=}CH\text{-}Ph$$

101

dure described by Hill *et al.*[66] 2-Methyl-2-cyclohexene-1-one (104) was prepared in 66% yield starting with 2-methylcyclohexanone 102 according to the procedure of

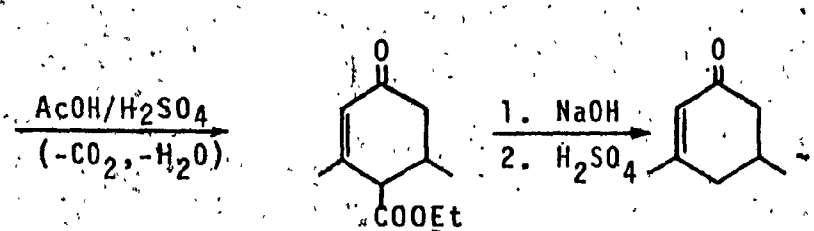


102 103 (82%) 104 (66%)

Warnhoff *et al.*[67] 3,5-Dimethyl-2-cyclohexen-1-one 107 was obtained by the procedure described by Horning.[68]

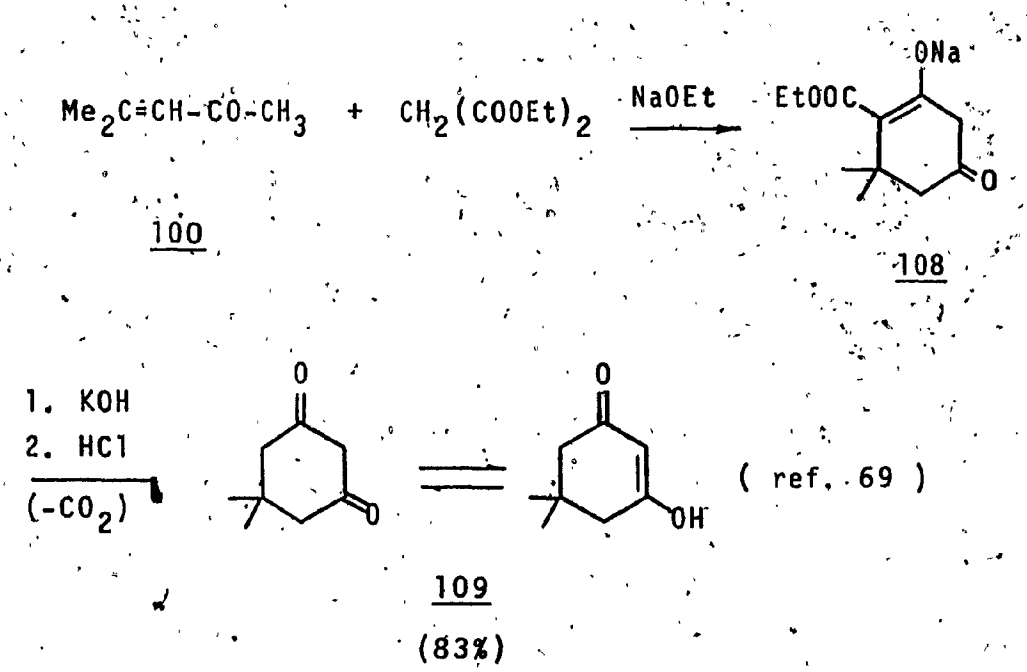
$$CH_3\text{-}CHO + 2Me\text{-}CO\text{-}CH_2\text{-}COOEt \xrightarrow{Piperidine} \begin{array}{c} Me\text{-}CO\text{-}CH\text{-}COOEt \\ | \\ CH_3\text{-}CH \\ | \\ Me\text{-}CO\text{-}CH\text{-}COOEt \end{array}$$

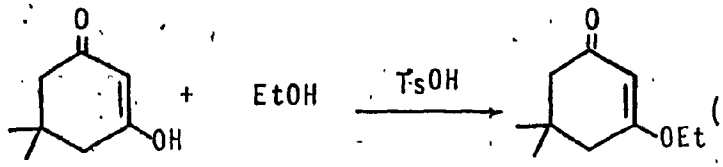
105



106 107 (53%)

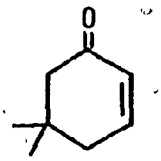
The synthesis of 5,5-dimethyl-2-cyclohexene-1-one (111) was carried out by two different methods reported in the literature, the starting material for both was methone (dimedone) 109, which was prepared following the method of Shriner and Todd[69]. The first method tried involved the conversion of methone 109 to 5,5-dimethyl-3-ethoxy-2-cyclohexene-1-one (110)[70] followed by reduction using lithium aluminum hydride[71]. In the reduction step the ketone 111 was obtained in only 18% yield. The low yield is attributed to the fact that the sample of lithium aluminum hydride used in the reaction was old. It was possible to obtain the same ketone in 66% yield from dimedone 109 by following the procedure described by Frank and Hall.[72]





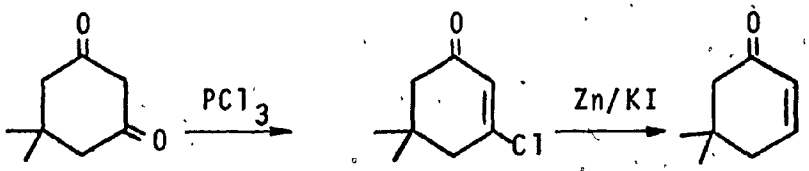
(ref. 70)

109 110 (91%)



110 1. $LiAlH_4$ 2. H_2SO_4 (ref. 70,71)

111 (18%)



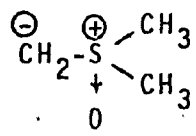
(ref. 72)

109 112 111 (66%)

3. Synthesis of α-Cyclopropyl Ketones.

One of the general methods of synthesis of cyclopropyl ketones has been the Simmons-Smith reaction[73] of α, β-ethylenic alcohols followed by the oxidation of the resulting cyclopropanated alcohols to the corresponding ketones[74,75]. The method used in the present study was the more recent general method reported by Corey and

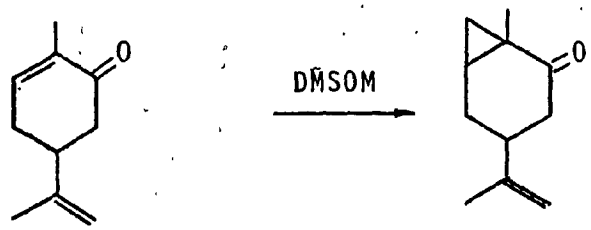
Chaykovsky[76]. The method involves the reaction of one equivalent of dimethyl sulfoxonium methylide[76-78] 113 (DMSOM) with α, β-olefinic ketones (Michael acceptors) which results in selective methylene transfer to the



(DMSOM)

113

α, β-double bond to produce α-cyclopropyl ketones as illustrated in the synthesis of the α-cyclopropanated ketones 115, 117, and 119[76] as well as 121[79].



(ref. 76)

114 115

(81.3%)

(ref. 76)

116 117

(53.6%)

(ref. 76)

118 119

(88.4%)

(ref. 79)

120 121

(80.2%)

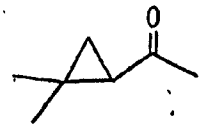
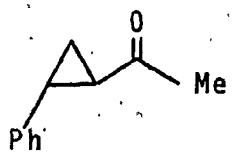
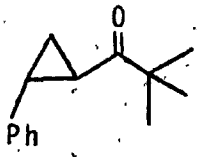
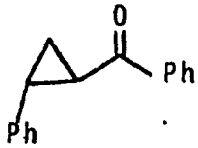
It is noteworthy that the methylene transfer is to the α,β-double bond rather than to the γ, δ-double bond in ketones 118 and 120. The synthetic utility of the ylid 113 is now well documented.[80,81]

3.1. Acyl Cyclopropanes.

The acyl cyclopropanes synthesized for the present study using the reaction of dimethyl sulfoxonium methylide (113)[76] on the corresponding α,β-unsaturated ketones are given in Table 1.

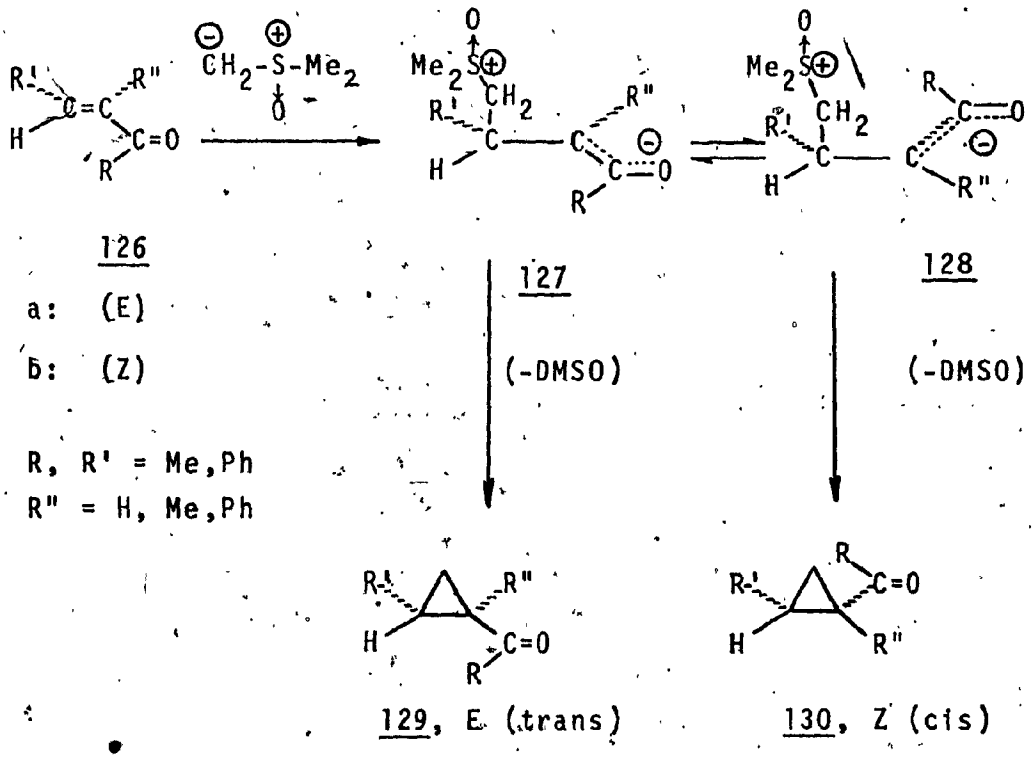
Table 1.

Acyl cyclopropanes

No.	Ketone	Bp°C/mp°C	% Yield	Reference
122		59-60(60 torr)	58.9	82-85
123		118 (2 torr)	85.4	86, 87
124		104-106(12torr)	87	———
125		41-44*	89.4	82, 88-90

(*)- Melting point

The stereochemistry of this cyclopropanation has recently been studied by Rocquet and Sevin[91]. They have observed that the reactivity of the ethylenic ketones 126 of trans (E) configuration is much greater than that of their cis (Z) isomers. The observed stereochemistry has been explained by these authors based on the conformational equilibrium as illustrated in Scheme 1. In the enolate intermediate 128 there is appreciable steric interaction between the groups R and R' which does not provide maximum overlap of the orbitals in the cyclization step leading to 130.



Scheme 1. Stereochemical formation of α-cyclopropyl ketones.

On the other hand 127 provides a more favorable geometry for the maximum delocalization of the charge during cyclization to give the cyclopropyl ketone 129. In conformity with these arguments the authors have observed only a single isomer of the cyclopropyl ketone in each case from a variety of E and Z isomers of the α,β-unsaturated ketones 126.[91] It is to be noted that if the group $COCH_3$ or COC_6H_5 is replaced by the less bulky group CN the reaction is less stereoselective leading to a mixture of cis and trans α-cyclopropyl nitriles.[82,92,93]

Agami[87] had earlier concluded that the cyclopropanation of benzalacetone (126; R = CH_3; R' = Ph; R'' = H) produces a mixture of cis and trans cyclopropyl ketones based on the NMR spectrum of the product of the reaction. This is in contradiction to the mechanistic conclusions of Rocquet and Sevin[91] described above. The conclusion arrived at in the present study is that only a single isomer of the cyclopropyl ketone 123 (trans) is produced which is in agreement with the proposal of Rocquet and Sevin[91]. The evidence obtained in the present study is indirect. The product 123 was homogeneous on TLC, and the NMR spectrum showed only a sharp singlet for the methyl group at δ 2.17. Moreover, the oximation of the ketone gave only two oximes which were identified as the syn-methyl and anti-methyl diastereomers of trans-1-phenyl-2-

acetyl cyclopropane 123. Evidence for this comes from the fact that each of the two oximes gave the expected amide upon Beckmann rearrangement using PCl_5. The amides were further identified by comparison with authentic samples prepared independently by an unambiguous route (*vide infra*).

3.2. Bicyclo [n.1.0] alkan-2-ones.

These ketones were synthesized by reacting dimethylsulfoxonium methylide 113 with the corresponding α,β -unsaturated cyclanones using the method of Corey and Chaykovsky[76], and are listed in Table 2. In the case of ketones 132 and 115 where diastereomerism is possible only one isomer was obtained in each case. The ketones 131 and 132 are not reported in the literature.

Table 2.

Bicyclo [n.1.0] alkan-2-ones

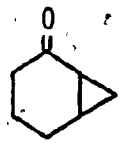
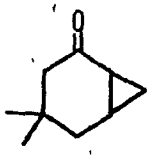
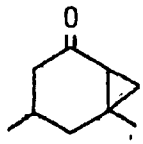
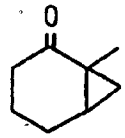
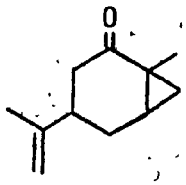
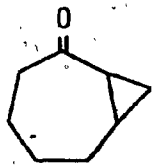
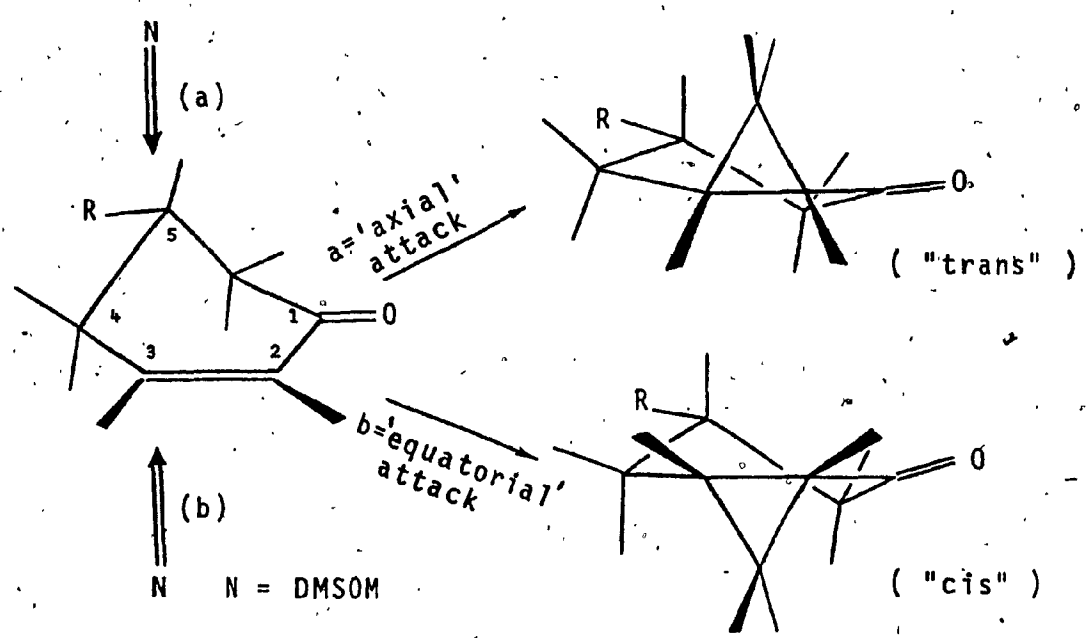
No.	Bicyclic ketone	Bp°C(torr)	% Yield	Reference
94		64-66(2)	52.3	82,94
131		84-85(2)	53.0	—

Table 2 (cont'd)

No.	Bicyclic ketone	Bp°C(torr)	%Yield	Reference
132		84-85(5)	80	———
133		57-58(4)	72.5	59,94,95
115		125 (15)	95.0	76,91,96
97		95-97(26)	62.0	44,97

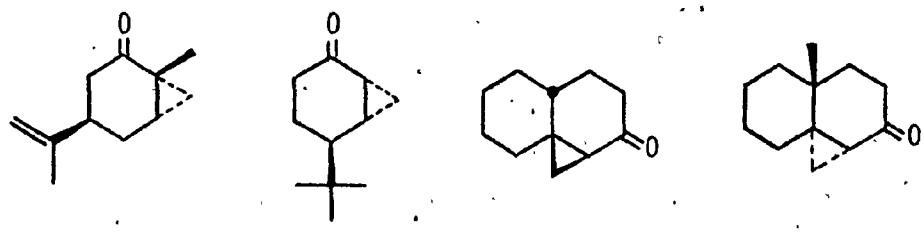
The stereochemical aspects of the reaction of dimethyl sulfoxonium methylide (DMSOM) with α, β-unsaturated cyclanones have been investigated[91]. In the formation of the bicyclo [n.1.0] alkan-2-ones the cyclopropyl system must of necessity be cis-locked with the other ring structure. Having made this assumption the authors have considered two directions of approach by the ylid 113 to the double bond of the α,β-unsaturated

cyclic ketone, as depicted in Scheme 2 for a simple cyclohexanone derivative. Unlike the case of the open chain α, β-unsaturated ketones considered earlier (page 32), the enolate intermediate formed after the attachment of the ylid at C-3 cannot undergo isomerization, and therefore leads to only one product of cyclization from this intermediate. The stereochemistry of the bicyclic [n.1.0] alkanone produced from the unsaturated ketone thus reflects the direction of addition of the ylid to the π-system existing between C-2 and C-3 in the starting ketone. The direction of attack (a) (cf. Scheme 2) is termed " axial attack " and the direction (b) is termed " equatorial attack " by the authors.



Scheme 2. Cyclopropanation of α,β-unsaturated cyclanones.

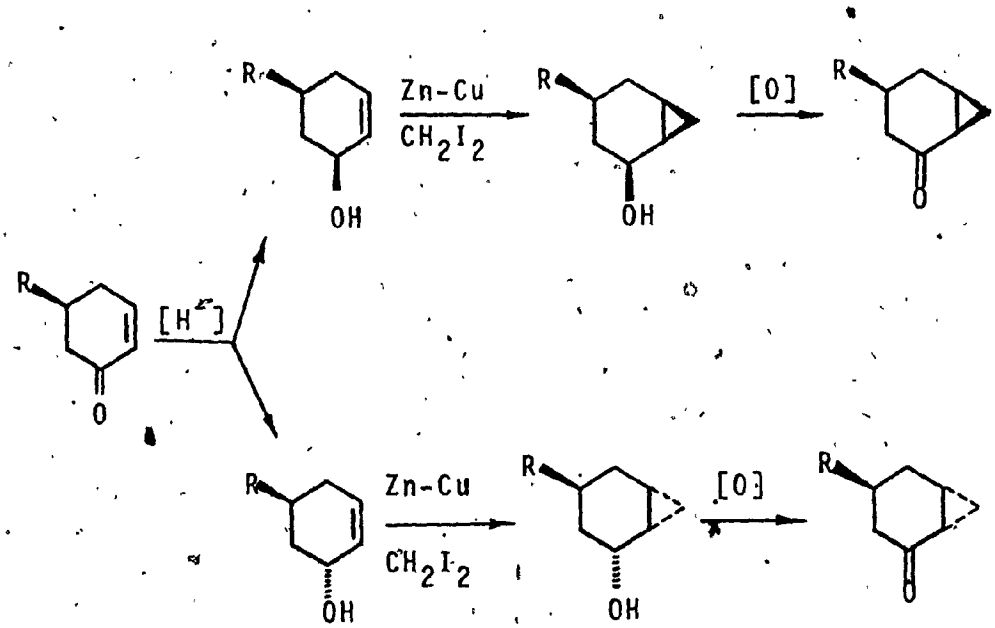
It was demonstrated by the authors[91] that the cyclopropyl ketones 115, 137, 138 and 139 were obtained as single isomers in the reaction of the ylid 113 with the corresponding α,β-unsaturated ketones:



115 137 138 139

Information regarding the orientation of the cyclopropane ring was obtained by comparison of the products with samples of known configuration synthesized independently by an unequivocal chemical route. Previous studies[74,75] have shown that the Simmons-Smith reaction on cyclohexenols leads to the methylenation (cyclopropanation) stereospecifically cis to the hydroxyl group. Thus knowing the configuration of the starting cycloalkenol will enable one to know the stereochemistry of the α-cyclopropyl alcohol and hence the stereochemistry of the cyclopropyl ketone obtained by the oxidation of the α-cyclopropyl alcohol. The sequence of reactions are indicated in Scheme 3. This procedure was followed

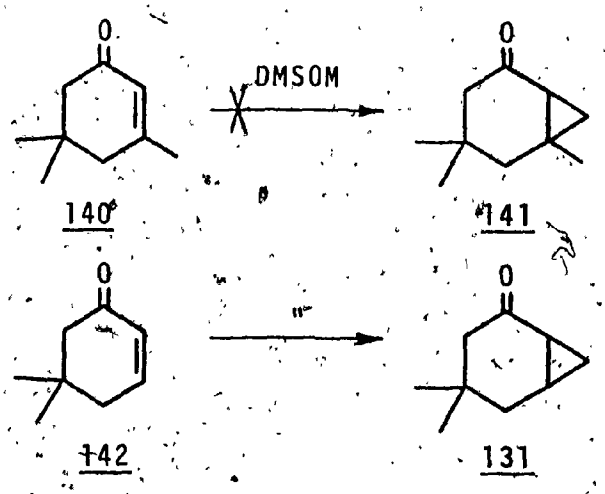
by the authors in assigning the stereochemistry of the α-cyclopropyl ketones obtained in the reaction of the ylid on the unsaturated ketones.



Scheme 3. Preparation of stereospecific α-cyclopropyl cyclohexanones.

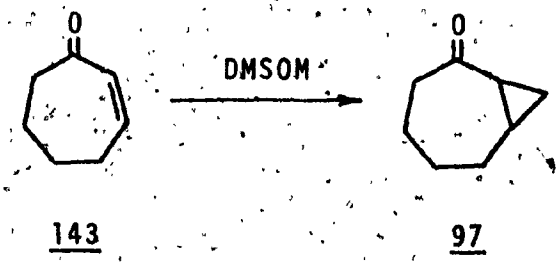
In the present study the cyclopropanation of isophorone (140) was attempted using dimethylsulfoxonium methylide, 113 (Corey reaction). Repeated attempts with freshly distilled isophorone resulted in the isolation of only unreacted starting ketone. No trace of any cyclopropyl derivative was detectable. However, Guillaud and co-workers[98] have recently claimed to have obtained a 50% yield of the cyclopropyl ketone 141 by using the Corey reaction on isophorone. No experiment-

al details of the synthesis were given by these authors in the paper,[98] but rather, only a reference to a thesis of one of the authors (J-L. Pierre, Thesis, Grenoble, 1966) was made. In the present study the analogous ketone, 5,5-dimethyl-2-cyclohexen-1-one (142) gave a 53% yield of the expected cyclopropyl ketone 131, in the

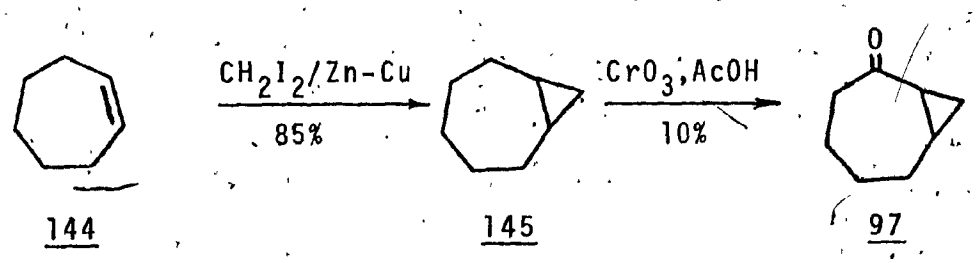


Corey reaction.

The cyclopropanation of cycloheptenone 143 using the Corey reaction proceeded smoothly to give a 76% yield of the expected cyclopropyl ketone 97. However, Guillaud et al.[98] have stated that, in their hands, the Corey reaction on cycloheptenone proved to be a total



failure in producing 97. They, therefore, resorted to a different route whereby cycloheptene 144 was converted to its cyclopropyl derivative 145 by the Simmons-Smith reaction followed by oxidation of 145 using CrO_3 to obtain a 10% yield of 97. The ketones 131 and 132, which



are hitherto unknown in the literature, were obtained by using the Corey reaction on the corresponding α,β-unsaturated ketones.

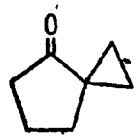
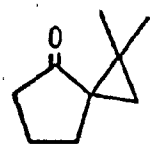
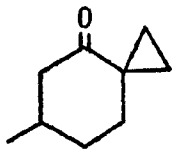
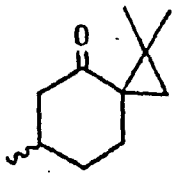
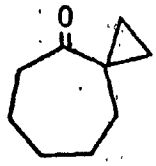
3.3. Spiro [2.n] alkan-4-ones.

Some of these spiroketones were synthesized by employing the Corey reaction on the appropriate α,β-unsaturated cyclanones, while some others, especially those having no substituents on the cyclopropyl ring, were synthesized by employing more lengthy routes. The spiroketones prepared in the present study are listed in Table 3.

The ketones 146 and 148 were prepared utilizing the Corey reaction on 2-(1-methylethylidene) cyclopentanone and pulegone respectively. In the case of the reaction of pulegone the cyclopropyl derivative 148 was isolated in

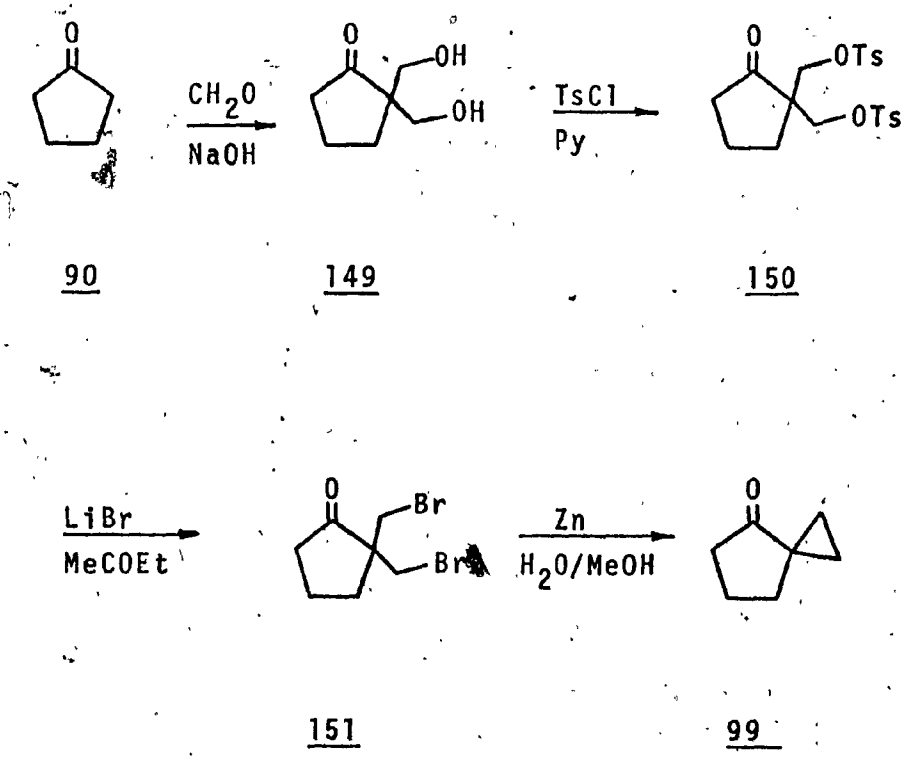
Table 3

Spiro [2.n] alkan-4-ones

Ketone	Bp°C(torr)	%Yield	Reference
 99	49(5)	59*	99,100
 146	67(8)	72.5	59
 147	80-82(12)	87*	99
 148	116-120(15)	92	82,91
 98	74-76(5)	90*	99

(*)- Yield of the final step of the Scheme 4.

92% yield, a significant improvement over 52% reported earlier.[91] The ketone 99 was prepared according to the procedure described by Leriverend and Conia[99], starting from cyclopentanone as indicated in Scheme 4. In this sequence the product of each step was isolated and purified before the subsequent step was attempted. The spiroketones 98 and 147 were also synthesized using the indicated sequence of reactions shown in Scheme 4, starting from cycloheptanone and 3-methyl cyclohexanone respectively.



Scheme 4. Synthesis of spiro [2.4] heptan-4-one

4. Synthesis of Oximes of Cyclopropyl Ketones.

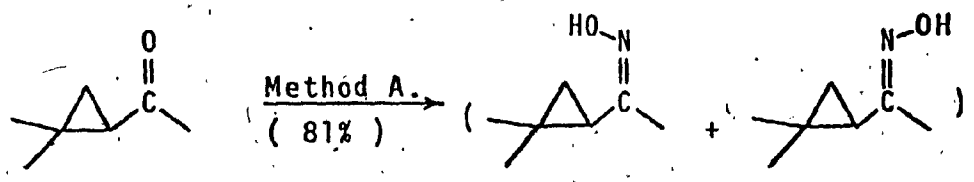
The oximation of the various cyclopropyl ketones was achieved by using hydroxylamine hydrochloride under different reaction conditions which were minor modifications of standard oximation procedures (cf. Experimental Section, page 116). The optimum reaction conditions were arrived at by attempting the oximation procedures under the varying conditions. The procedure of first choice was the standard one using hydroxylamine hydrochloride and sodium acetate in 95% ethanol as solvent (Method A).[101] The reaction mixture needed to be heated on a steam bath in most instances and the extent of oximation was monitored by thin layer chromatography. If prolonged heating still did not give good yields of the oxime, the reaction was reheated by replacing the sodium acetate with pyridine as the base (Method B).[102] In some cases even stronger base such as NaOH had to be used (Method C).[102] In general it was found that the more sterically hindered the carbonyl group was, the stronger the base that was needed and the longer the reaction time.

4.1. Oximes of Acyl Cyclopropanes.

The acyl cyclopropanes were converted to their oximes by a method described in the preceding section. A search of the literature indicated that the oximes of these cyclopropyl ketones have not been previously reported. There-

fore, the identification and determination of stereochemistry of these oximes were quite important. This task was achieved mainly by NMR spectroscopy as well as the Beckmann rearrangement of the oximes and comparing the products of rearrangement with authentic samples of the expected rearranged products.

The acyl cyclopropane derivative 122 was converted to the oxime by using Method A. The product was a liquid and it was found that it consisted of a mixture of the syn and anti isomers* in the indicated ratio proven by the NMR spectrum of the product of the Beckmann rearrangement of the mixture (vide infra). All attempts to separate the two isomers 152a and 152b by fractional distillation or chromatographic techniques were unsuccessful.

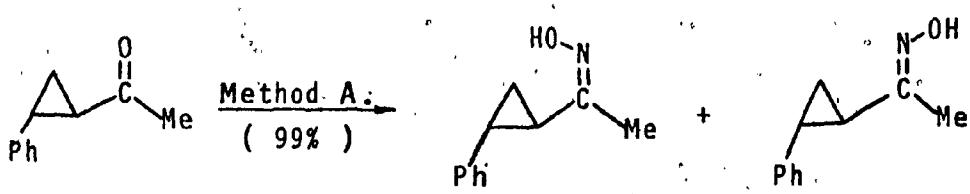


122 152a (33%) 152b (67%)

The oximation of the ketone 123 was also achieved by using Method A. The NMR spectrum of the crude reaction product indicated the two methyl signals at δ 1.73 (15%)

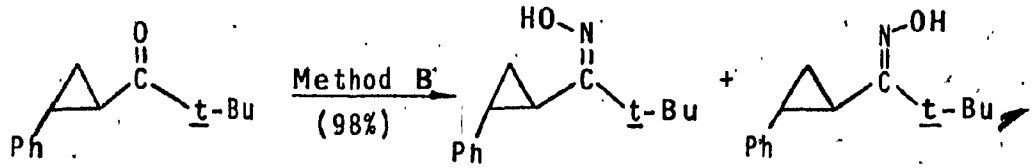
(*) Hereafter syn and anti refers to the disposition of the OH group with respect to the cyclopropyl system.

and 1.91(85%) and these were attributed to the isomers 153a and 153b respectively. In the anti isomer the OH group is closer to the CH_3 group and therefore is expected produce a deshielding effect on the CH_3 compared to the syn isomer. Assignments of configuration based on this deshielding effect due to the proximity of the oximino function have been used by other workers.[30,103-105] In this case the two isomers were separated by column chromatography using silica gel and a mixture of benzene-ether (1:1 (v/v)). It was observed that when a solution of the pure syn isomer 153a in $CDCl_3$ or CCl_4 was left at room temperature for prolonged periods isomerization of some of the syn isomer to the anti isomer took place as revealed by the NMR spectra of the solutions. For example, after two days at room temperature the syn and anti isomers were detected in solution in ca 1:1 ratio, whereas after 10 days the ratio was changed to 3:10. However, no such isomerization was observed for the pure anti isomer 153b in either $CDCl_3$ or CCl_4 solution at room temperature.



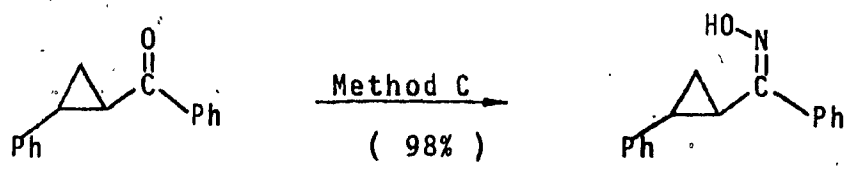
123 153a (15%) 153b (85%)

The tertiary butyl derivative 124 was oximated using Method B. The NMR spectrum of the reaction product exhibited two separate signals for the tert-butyl group at δ1.37 (15%) and 1.22 (85%) and these were assigned to the anti and syn isomers 154b and 154a respectively. In this case it was observed that the anti isomer 154b was unstable in $CDCl_3$, CCl_4 or ether solution at room temperature, yielding a mixture of the syn and anti isomers. In contrast, the syn isomer 154a was unchanged under similar conditions. The instability of the anti isomer 154b can be attributed to the severe steric interaction between the bulky tert-butyl group and the hydroxyl group. The syn and anti isomers were separated by repeated crystallization from aqueous methanol (cf. Experimental section). The syn isomer 154a melted at 129-30°C while the anti isomer 154b melted at 84-86°C. The configurations of the two oximes were further confirmed by the Beckmann rearrangement (vide infra).



124 154a (85%) 154b (15%)

For the oximation of the benzoyl cyclopropane derivative 125, Method C was employed. In this case only a single isomer of the oxime was isolated in 98% yield. The product was identified as the syn isomer 155 based on the position of the chemical shift of the hydroxyl resonance (δ 3.47) (cf. NMR spectrum No.1, p. 163), as well as from the product of the Beckmann rearrangement (vide infra). Of the four acyl cyclopropane oximated, 125 was the only one which produced a single isomer of the oxime. Interestingly, in the NMR spectrum of this product the OH resonance appeared at δ3.47 while the corresponding signals of all the other oximes of this class appeared between δ9.16 and 10.23.



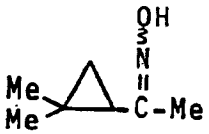
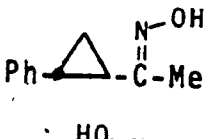
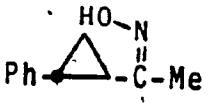
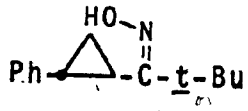
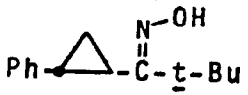
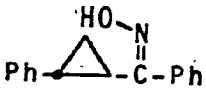
125 155

(98%)

The various oximes of the acyl cyclopropanes used for the Beckmann rearrangement are listed in Table 4.

Table 4.

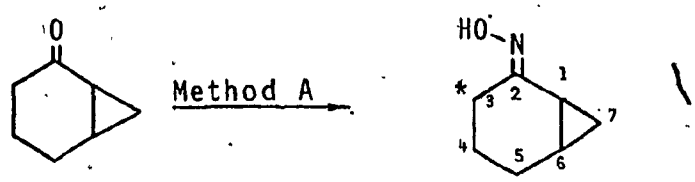
Oximes of acyl cyclopropanes

Ketoxime	Config.	%Yield	Mp°C	IR ($CHCl_3$) cm^{-1} νOH	νΔ*	νC=N	NMR (CCl_4) ppm δOH
	mixture	81	liq.[a]	3600,3250	3080,3060	1640	9.16
	anti	85	97-99	3580,3260	3080,3060	1645	10.00
	syn	15	80-82	3580,3260	3080,3060	1645	10.23
	syn	85	129-130	3580,3250	3080,3060	1655	9.16[b]
	anti	15	84-86	3580,3250	3080,3060	1655	9.41[b]
	syn	98	92-93.5	3580,3270	3080,3060	—	3.47

a. Bp 51-53°C (16 torr); b. Solvent $CDCl_3$; (*). Hereafter this symbol represents the C-H frequency of cyclopropyl ring.

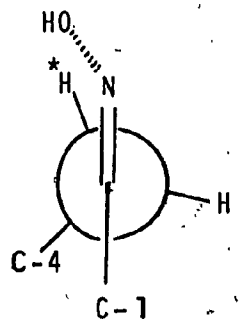
4.2. Oximes of Bicyclo [n.1.0] alkan-2-ones.

The oxime of bicyclo [4.1.0] heptan-2-one 156 has recently been reported in the literature.[41,106-108] In the present study the oxime 156 was obtained by the oximation of ketone 94 with hydroxylamine hydrochloride in the presence of sodium acetate (Method A). The product had a fairly sharp melting point (85-86°C), and exhibited only one spot on TLC using alumina or silica gel indicating that it

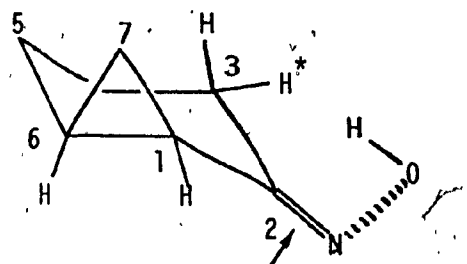


94 156

was isomerically pure. That the product has the anti configuration as depicted in structure 156 was concluded from its NMR spectrum which revealed a one-proton signal between δ2.42-2.88. This signal is ascribed to one of the α-hydrogens attached to the C-3 carbon (marked with an asterisk in 156). As shown in Figure 2, the protons on C-3 are in a syn relationship with respect to the hydroxyl group of the oximino function, and therefore should experience a deshielding effect, especially the quasi-equatorial proton (asterisk), as indicated in projection "A" in Figure 2. This deshielding effect of α-protons in cyclic



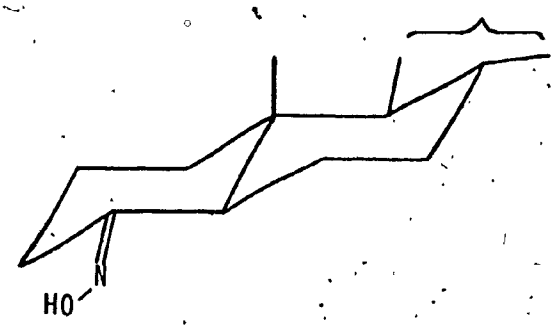
Projection "A"



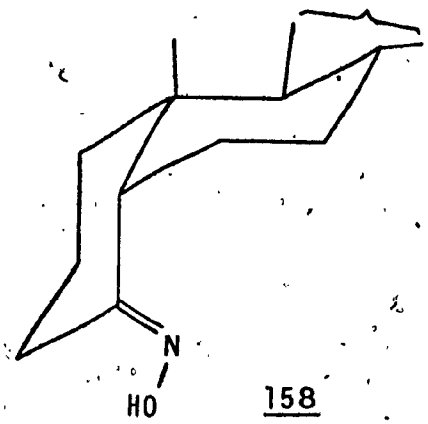
156 "A"

Figure 2. Conformation of bicyclo [4.1.0] heptan-2-one oxime.

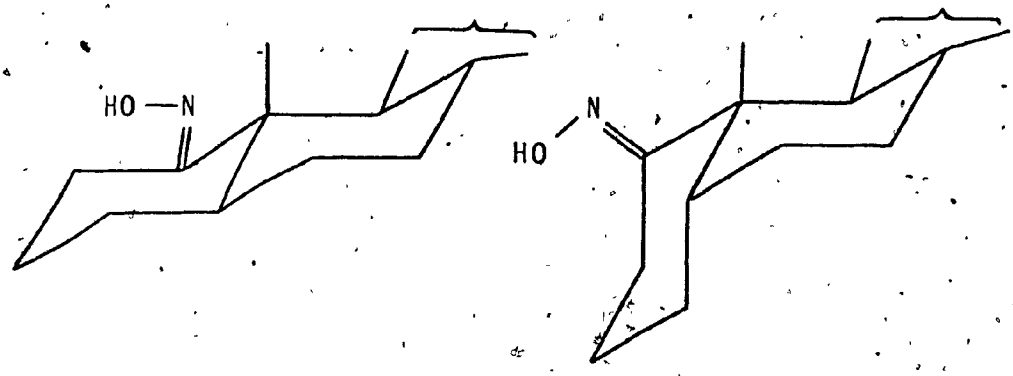
oximes have been well established.[30,103-105,109-110,112] Suginome and co-workers[103,105] have shown recently that the cholestanone oximes 157, 158, 159 and 160 exhibited a one-proton broad doublet at ca δ3.40 ascribable to the α-protons closer to the hydroxyl group. These authors have demonstrated that one of the α-methylene protons is nearly eclipsed by the C=N bond in these oximes.



157

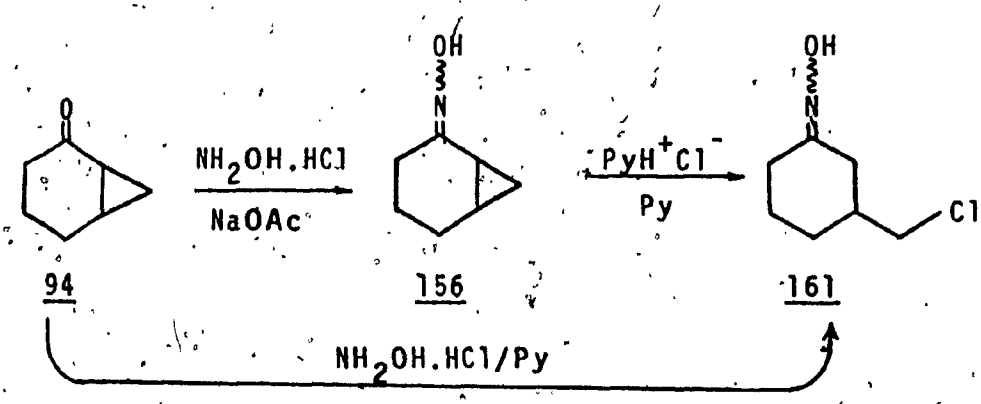


158



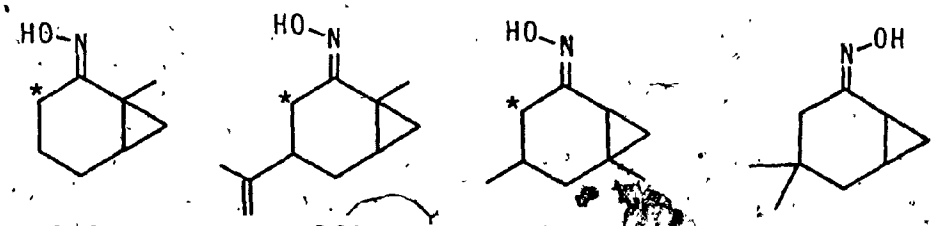
159 160

In conformity with the arguments described in the preceding paragraph the oxime of bicyclo [4.1.0] heptan-2-one prepared in the present study has been assigned as the anti configuration 156. Additional proof of this structure was gained from the NMR spectrum of the single product obtained in the PCl_5-induced Beckmann rearrangement of this oxime (vide infra). In the report by Tardella and co-workers[106] it was stated that the oxime 156 was obtained as a 1:1 mixture of syn and anti isomers when ketone 94 was oximated in presence of hydroxylamine hydrochloride and sodium acetate, conditions similar to those used in the present study for the oximation. Their conclu-



sion was based on the fact that the gas chromatographic analysis of the product showed two partially overlapped peaks of similar areas. However, their product melted within a very narrow range (83-86°C). It is possible that their product was also a single isomer (156), which at the elevated temperature employed for the gas chromatographic analysis underwent equilibration to the syn and anti isomers. No attempt at separating the individual isomers was reported by these authors.[106] The authors have made the interesting observation that pyridine hydrochloride brings about the cleavage of the cyclopropane ring of the oxime 156 to produce 3-chloromethylcyclohexanone oxime 161, also reported as a mixture of its syn and anti isomers. However, no attempt to separate isomers was made in this case as well. The starting ketone 94 also was reported to suffer the cleavage of the cyclopropyl ring in a similar fashion under the same conditions. Also, oximation of 94 using hydroxylamine hydrochloride and pyridine in ethanol solvent was shown to produce the oxime of 3-chloromethylcyclohexanone directly.[106] This type of cyclopropyl ring opening to a chloromethyl group has recently been observed as a general phenomenon in several α-cyclopropyl ketones when they are treated with pyridine hydrochloride in acetonitrile.[108]

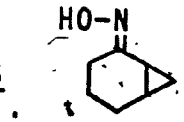
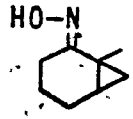
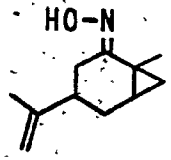
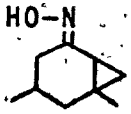
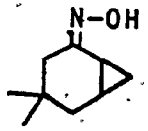
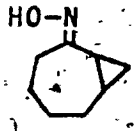
The oximes 162, 163, 164 and 165 were also synthesized in the present study by the oximation of the corresponding ketones using the hydroxylamine hydrochloride-sodium acetate



162 163 164 165

method. Only a single isomer was observed in each case. These oximes have not been previously reported in the literature. The oxime 164 was obtained as a viscous oil which was distilled in high vacuum (bp 124°C / 4 torr). Upon keeping in the refrigerator for approximately two months the distilled product solidified but melted over a wide range of temperature (42-52°C). The material produced only one spot on TLC using alumina or silica gel. The anti configuration was assigned to 162, 163, and 164 based on their NMR spectra (cf. NMR spectrum of 162, No. 2, p. 164) and the same arguments as were used for the assignment of configuration of the oxime 156. These oximes also exhibited the characteristic signals for the α-methylene protons (asterisk) between δ2.20-2.93 (cf. Table 5). Oxime 165 has been assigned the syn configuration based on its NMR spectrum which did not reveal the characteristic signal for C-3 α-methylene protons between δ2.0-3.0. Additional evidence for the assigned configurations of these oximes comes from the structure of the Beckmann rearrangement products of the oximes (vide infra). The pertinent experimental data about the oximes are given in Table 5.

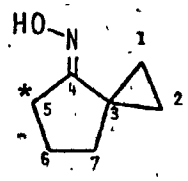
Table 5. Oximes of bicyclo [n.1.0] alkan-2-ones

No.	Oximes	%Yield	Mp°C	IR (CCl_4) cm^{-1} ν OH	νΔ	ν C=N	NMR (CCl_4) ppm δ OH	δ H (C-3)
156		95.8	85-86	3600,3250	3090	1645	10.33	2.42-2.88
162		87	51-52	3600,3250	3080	1645	10.20	2.20-2.75[a]
163		91.5	101-103	3600,3280	3080	1645	9.37[b]	2.53-2.91
164		70	42-52	3600,3250	3080	1650	9.73	2.42-2.93
165		74.5	139-140	3580,3250	3070[c]	1645	9.03	———
166		98	90-93[d]	3590,3250	3080	1645	9.78	———

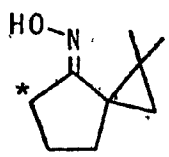
a. Two protons; b. Solvent $CDCl_3$; c. Solvent $CHCl_3$; d. Bp (0.4 torr);

4.3. Oximes of Spiro [2.n] alkan-4-ones.

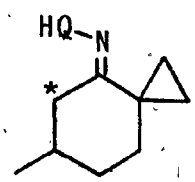
In the present study, the oximes of spiro [2.n]-alkan-4-ones (n = 4,5,6) were synthesized by reacting the corresponding ketones with hydroxylamine hydrochloride and sodium acetate. Such oximes have received little attention in the past, and only the oxime 167 has been reported in the literature.[111] The pertinent experimental data regarding these oximes are summarized in Table 6.



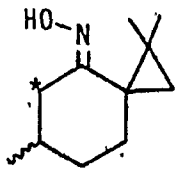
167



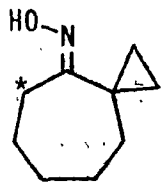
168



169



170

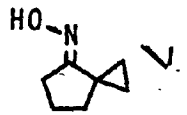
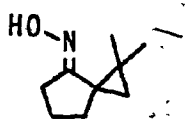
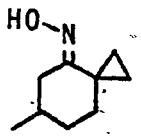
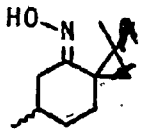
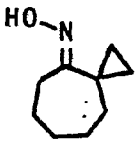


171

Under the conditions used for the oximation all the oximes 167-171 were obtained as single isomers having the hydroxyl groups of the oximino function in the anti relationship with respect to the cyclopropyl system. The conclusion regarding this configurational assignment was

Table 6.

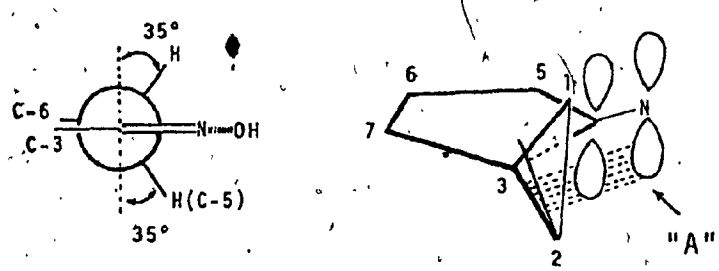
Oximes of spiro [2.n] alkan-4-ones

No.	Oxime	%Yield	Mp°C	IR (CCl_4) cm^{-1} νOH	νΔ	νC=N	NMR (CCl_4) ppm δOH	δH (C-5)	δCyclopropane
167		94	64-65	3600,3280	3080	1665	9.50	2.50-2.80	0.62-1.15
168		93	61-63	3600,3280	3060	1655	9.66	2.50-2.75	0.50-1.10
169		98	61-63	3600,3270	3080	1650	9.73	3.16-3.38*	0.41-0.58
170		92	82-84	3600,3280	3065	1660	9.80	2.75-3.55*	0.12-0.20
171		98	47-48	3600,3250	3075	1635	9.91	2.58-2.75	0.38-1.01

(*)- One proton.

based on the NMR spectra of the oximes as well as the structure of the Beckmann rearrangement products of the oximes (vide infra). The NMR spectra of all the oximes exhibited the characteristic, well separated signals for the α-methylene protons on C-5 in close proximity with the OH group (marked with (*) in 167-171).[30,103-105,109,110]

The NMR spectrum of 167 revealed the C-5 methylene signal as a multiplet between δ 2.50-2.80, and the spectrum of 168 revealed the corresponding signal between δ 2.50-2.80 (cf. NMR spectrum No. 3 , page 165 and NMR spectrum No. 4, page 166). Examination of the molecular models for these oximes indicated that the 5-membered ring is essentially perpendicular to the plane of the cyclopropane ring where the dihedral angle between the C-1 and C-3 bond and the p-orbital of the C=N bond is small. This is depicted in Figure 3. In this conformation both hydrogens on C-5 will be symmetrically placed on either side of the C=N bond (projection "A" in Figure 3), with a dihedral angle of ca 35° each. The symmetrical AA'BB' pattern for the signals

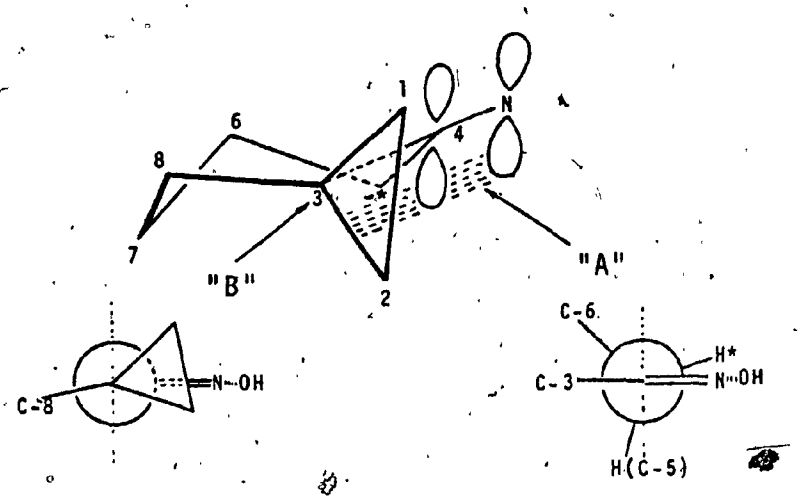


Projection "A"

Figure 3. Conformation of spiro [2.4] heptan-4-one oxime.

from the cyclopropyl hydrogens in the NMR spectra of these oximes are in agreement with this conformation.

In contrast to oximes 167 and 168, the NMR spectra of the oximes 169 and 170 exhibited unsymmetrical signals for the cyclopropyl hydrogens (e.g. NMR spectrum No 5 , page 167). In addition, the NMR spectrum of 169 revealed a broad one-proton signal between δ 3.16-3.38. In the case of 170 this one-proton signal appeared between δ 2.75-3.55. These signals are assigned to the quasi-equatorial hydrogen (asterisk) on C-5 in these oximes (see projection "A" in Figure 4). The NMR spectrum of 171 exhibited a symmetrical pair of multiplets for the cyclopropyl hydrogens centered around δ 0.50 and 0.9 and a broad multiplet centered around δ 2.66 for the α-methylene hydrogens.



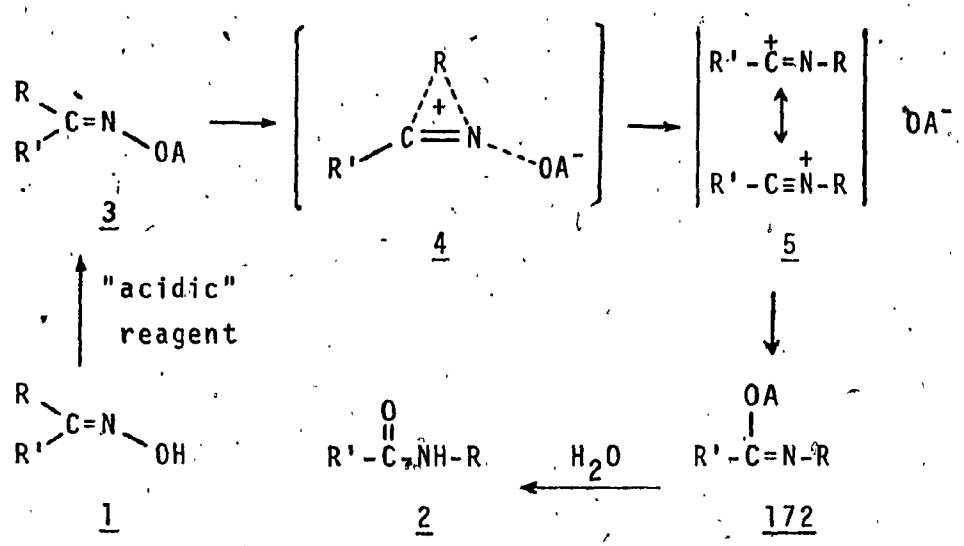
Projection "B" Projection "A"

Figure 4. Conformation of spiro [2.5] octan-4-one oximes.

5. Mechanistic Aspects of the Beckmann Rearrangement.

Before venturing into the discussion of the results of the present study of the Beckmann rearrangement of the α-cyclopropyl ketoximes, it is appropriate to outline briefly the salient features of the current state of our knowledge about the mechanism of the normal Beckmann rearrangement.

The most widely accepted mechanism of the Beckmann rearrangement of ketoximes, in very general terms, as mentioned in the Introduction (cf. pages 1-3), is outlined in Scheme 5. The heterolytic fission of the N-OA bond in 3 with concerted delocalization of the electrons of the R group situated anti to the OA function leads to the

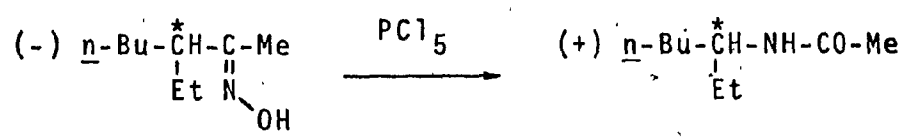


Scheme 5. Mechanism of the Beckmann rearrangement.

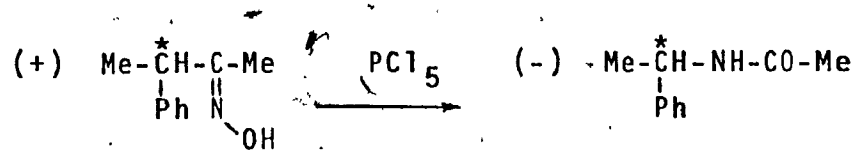
migration of the R group to the electron-deficient nitrogen *via* a transition state such as 4 to produce the imidoyl derivative 172, which upon subsequent hydrolysis yields the amide 2.

The choice of the "acidic" reagent is critical and depends not only on the structure of the oxime but also on the nature of the reaction medium[8]. Strong protic acids such as H_2SO_4 or HCl are capable of isomerizing the oxime prior to rearrangement, thereby producing amides not derived directly from the starting stereoisomer of the oxime. Phosphorus pentachloride has been recognized as the reagent least prone to catalyze prior isomerization of the oximes[4].

The postulated concerted mechanism requires that the stereospecific migration of the group situated *anti* to the leaving group be *intra*molecular, and therefore, should exhibit migration of the α-carbon with stereochemical integrity. This has been verified by Kenyon and co-workers.[113,114] Optically active oximes 173 and 174, upon rearrangement gave the optically active amides 175



173 175



174 176

and 176 respectively with retention of configuration of the migrating groups.

Recent Beckmann rearrangement studies of ketoximes with π-bonded systems situated alpha and anti to the oximino function have shown that, in general, such unsaturated systems migrated as effectively as alkyl groups.[11,19,20] In addition, it has also been established that in ketoximes with endocyclic α-double bonds the normal rearrangement takes place only where the planes of the C=C and C=N π-systems are approximately at right angles to each other: In oximes or their derivatives where such an arrangement is sterically unattractive the normal Beckmann rearrangement has either been totally suppressed,[11,20,21] or the products have been those resulting from a fragmentation pathway.[115]

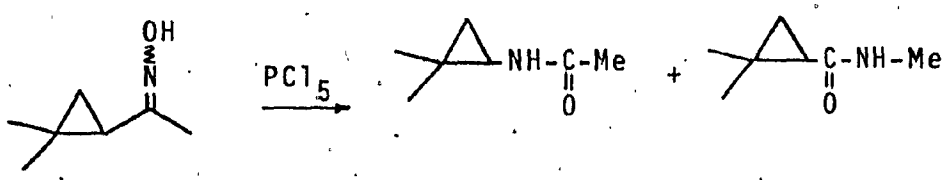
In contrast to the studies of the migratory aptitude of the olefinic group, there seems to have been no studies undertaken specifically to examine the migratory aptitude of a cyclopropyl group in the Beckmann rearrangement. Because of this, and because of the almost-double-bond-like character frequently observed for the cyclopropyl

system, the present study was undertaken with a view to investigating the behavior of the cyclopropyl system in the Beckmann rearrangement of ketoximes having such a system α to the oximino function. The α-cyclopropyl ketoximes employed in the present study include oximes of acyl cyclopropanes, of bicyclo [n.1.0] alkan-2-ones, and of spiro [2.n] alkan-4-ones, where the cyclopropyl system presents a variety of substitution patterns.

5.1. Beckmann Rearrangement of Oximes of Acyl cyclopropanes.

The oximes of the acyl cyclopropanes (cf. Section 4.1., page 43) were subjected to the Beckmann rearrangement using PCl_5 following the general procedure (cf. Experimental Section; page 129).

The oxime of 1-acetyl-2,2-dimethylcyclopropane (152) consisted of a mixture of the syn and anti isomers which could not be separated. Therefore, the rearrangement was carried out on the mixture. A mixture of the two secondary amides 177 and 178 was obtained in 92% yield. The NMR spectrum of the crude product indicated that the amides

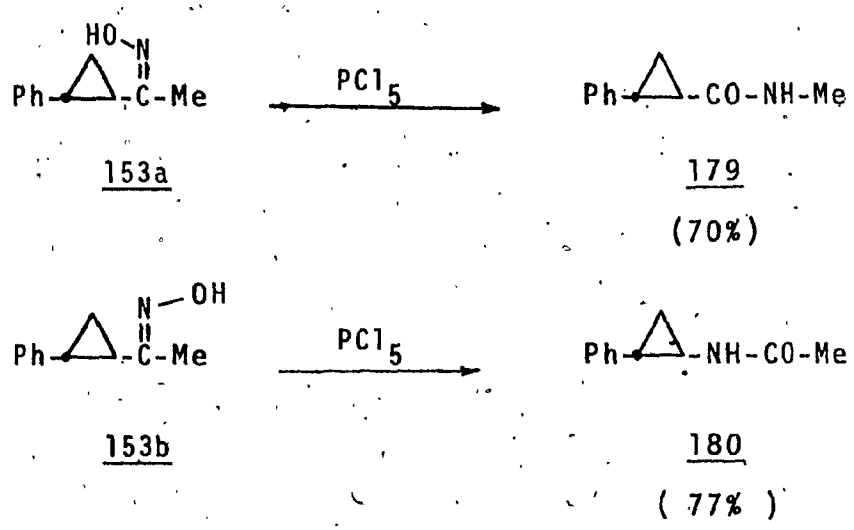


152 177 178

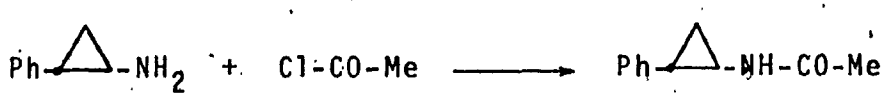
(67%) (33%)

177 and 178 were present in a 67:33 ratio. The methyl resonance of 177 appeared as a singlet at δ 2.00, while that of 178 appeared as a doublet at δ 2.83 which collapsed to a singlet upon addition of D_2O and a trace of triethylamine. By chromatography on alumina it was possible to obtain a pure sample of 177 (mp 54-56°C). However, it was not possible to obtain 178 in a pure form, it being not able to remove 177 completely from it. Assuming that no prior isomerization of the isomers in 152 took place, it can be assumed that 152 originally consisted of the syn (152a) and anti (152b) isomers in the ratio 33:67.

Treatment of the stereoisomeric oximes 153a and 153b separately with PCl_5 resulted in the expected secondary amides 179 and 180 respectively in good yields. The amide 180 is the result of the migration of the cyclopropyl system in 153b during the Beckmann rearrangement. The NMR

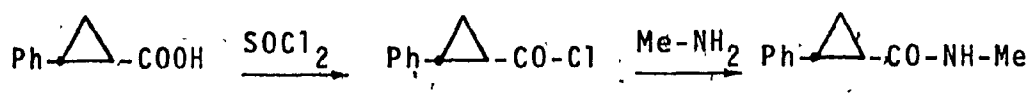


spectrum of this product exhibited a singlet for the methyl resonance at δ2.00 and a broad singlet at δ6.81 for the NH proton resonance. In the case of 179 the methyl resonance appeared as a doublet at δ2.85 (J = 5 Hz), and the NH proton resonance as a broad peak at δ6.68 (cf. NMR spectrum No. 6, page 168). That the doublet at δ2.85 is due to the coupling of the methyl protons and the NH proton in 179 was demonstrated by the fact that the methyl doublet collapsed to a singlet upon the addition of D_2O and a trace of triethylamine (cf. NMR spectrum No. 7, page 169). An authentic sample of 180 was synthesized by reacting trans-2-phenylcyclopropylamine (181) with acetyl chloride.



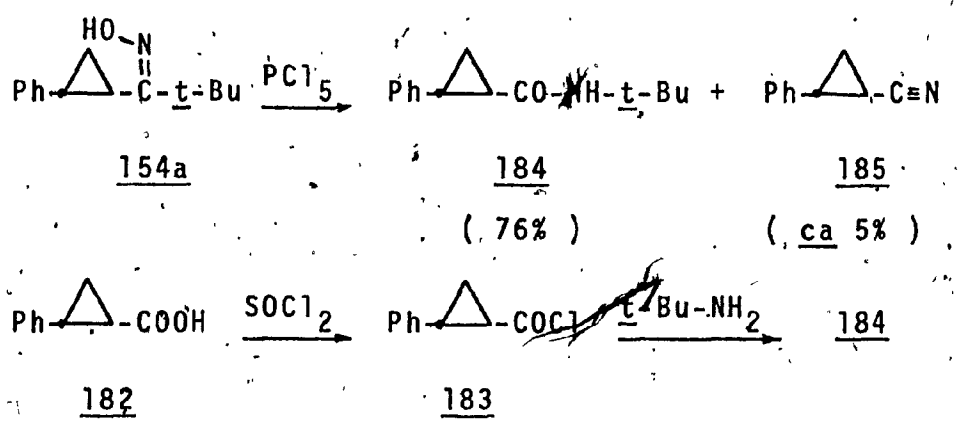
181 180

The authentic sample of the amide 179 was prepared by converting trans-2-phenyl cyclopropane carboxylic acid (182) to the corresponding acid chloride 183, followed by treatment of this acid chloride with methylamine.

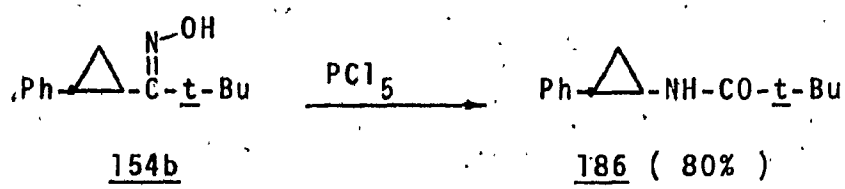


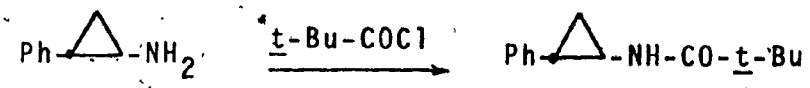
182 183 179

The Beckmann rearrangement of the syn oxime 154a gave the expected amide 184 in good yield, along with ca 5% yield of trans-1-cyano-2-phenyl cyclopropane 185, which evidently resulted from the Beckmann fragmentation of the oxime 154a during the reaction. The product 185 was identified by its IR and NMR spectra. The authentic sample of the amide 184 was prepared as illustrated starting from the acid 182. The anti oxime 154b gave, upon treat-



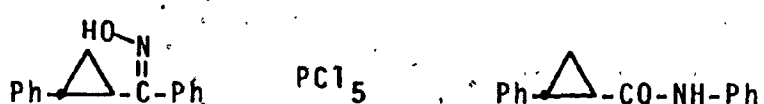
ment with PCl_5, exclusively the expected secondary amide 185 in 80% yield. The authentic sample of 186 was obtained by treatment of trans-2-phenylcyclopropylamine 181 with pivaloyl chloride.





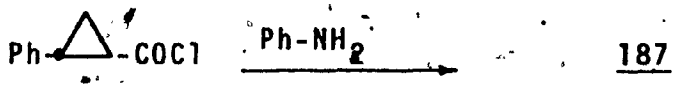
181 186

The Beckmann rearrangement of the oxime 155 gave a fair yield of the expected secondary amide 187. The authentic sample of 187 was obtained by treating the acid chloride 183 with aniline. The structure of the rearranged product 187 thus provided additional evidence for the syn configuration of the oxime 155.



155 187

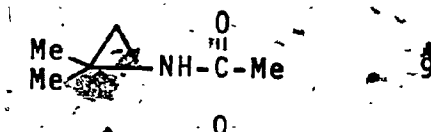
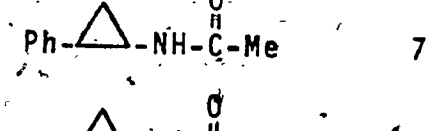
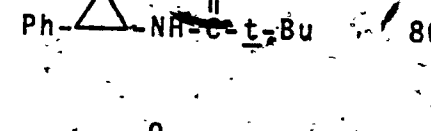
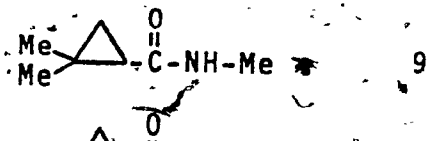
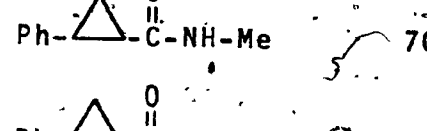
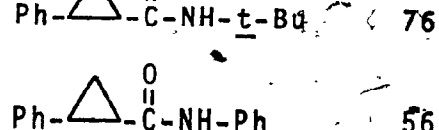
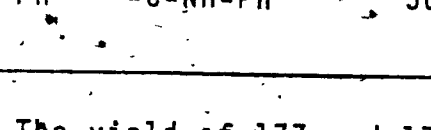
(56%)



183 187

The pertinent data concerning the amides isolated in the Beckmann rearrangement of the oximes of the acyl cyclopropanes are summarized in Table 7. Even though the number of examples available here are limited, it seems that the cyclopropyl ring migrates more efficiently than alkyl or phenyl groups as evidenced by the greater yields

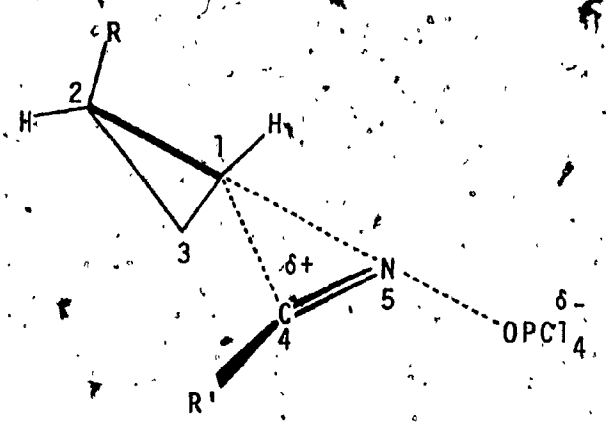
Table 7. Amides from the PCl_5-induced Beckmann rearrangement of oximes of acyl-cyclopropanes.

No.	Cyclopropyl amide	%Yield	Mp°C	IR ($CHCl_3$) cm^{-1} νNH	νΔ	νCO	NMR ($CDCl_3$) δNH(ppm)
177		92*	54-56	3445,3300	3080,3060	1650	8.25
180		77	94-96	3460,3340	3080,3060	1670	6.81
186		80	107-109	3460,3360	3080,3060	1655	6.27
178		92*		3445,3300	3080,3060	1650	7.42
179		70	93.5-95	3460,3325	3080,3060	1650	6.68
184		76	134-135	3440,3335	3080,3060	1655	5.66
187		56	143-144	3430,3320	3080,3060	1680	7.92

(*)- The yield of 177 and 178 together before separation.

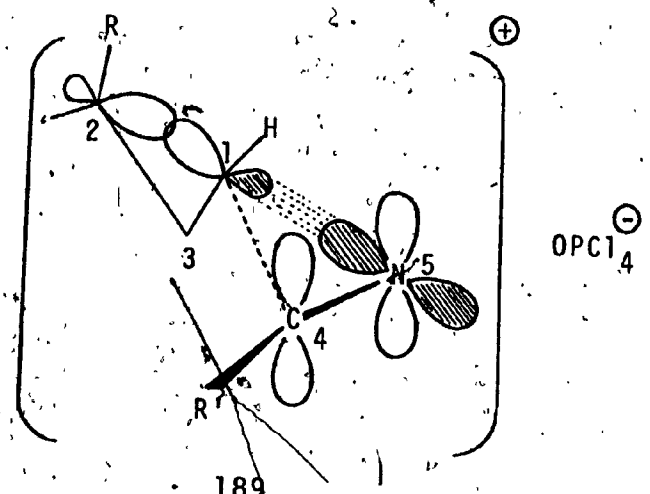
of the amides resulting from the anti oximes (cf. 153b and 154b vs. 153a, 154a, and 155).

In considering the mechanism of migration of the cyclopropyl system in the anti oximes during the Beckmann rearrangement, one can postulate, in analogy with the currently widely accepted mechanism[4,8], a transition state of the type 188. Concomitant with the partial bond formation between C-1 and the nitrogen, the bond between C-1 and C-4 is partially cleaved. It is interesting to consider the type of orbital interaction between the cyclopropyl system and the nitrogen atom in 188. Taking note of the fact that, in the rearrangement the cyclopropyl ring migrated efficiently without ring opened or ring enlarged products, it is conceivable that the transition state 188 is stabilized not by ring-edge participation (such as is thought to exist in ground state

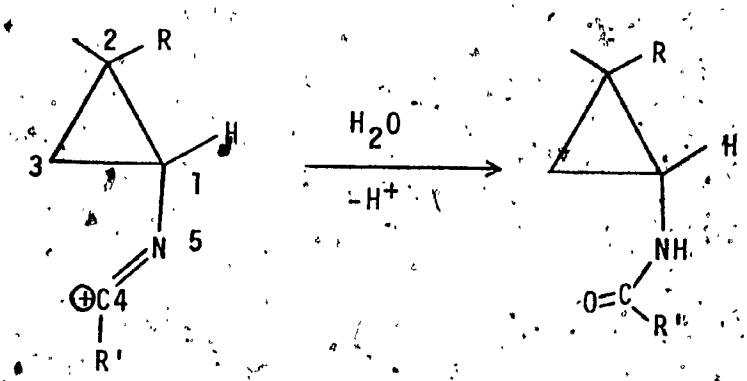


188

systems where the cyclopropyl rings exist in conjugation with unsaturated functions, e.g. C=N), but by ~~overlap~~ of the back lobe of the C-1,2 (or C-1,3) σ-bond orbital with the developing orbital on the nitrogen (shaded orbital) as depicted in 189.



189



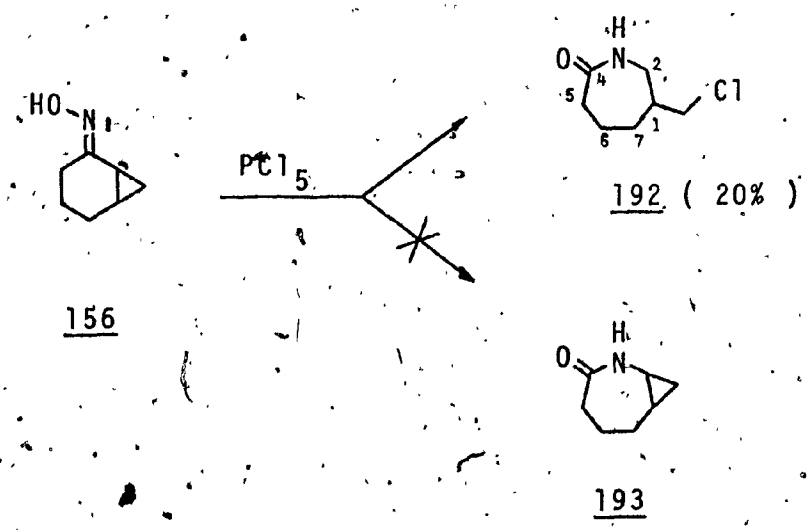
190 191

The possibility for such participation has been considered recently for the 1,2 cyclopropyl migration from carbon to nitrogen in the Schmidt reaction,[116] and for a 1,2 carbon to carbon migration in the solvolysis of 2-cyclopropyl-2-methylpropyl brosylate.[117] Bearing in mind that the C-C bonding orbitals are almost sp^5 hybridized, it is not unreasonable to assume that the back lobes of the cyclopropyl carbons extend sufficiently out of the ring for interaction with the developing nitrogen orbital as pictured in 189. It can be seen that the 1,2 migration of the cyclopropyl system by this mechanism from carbon to nitrogen to produce the intermediate 190 will proceed without ring opening or ring expansion and with stereochemical integrity at the migrating carbon, C-1.

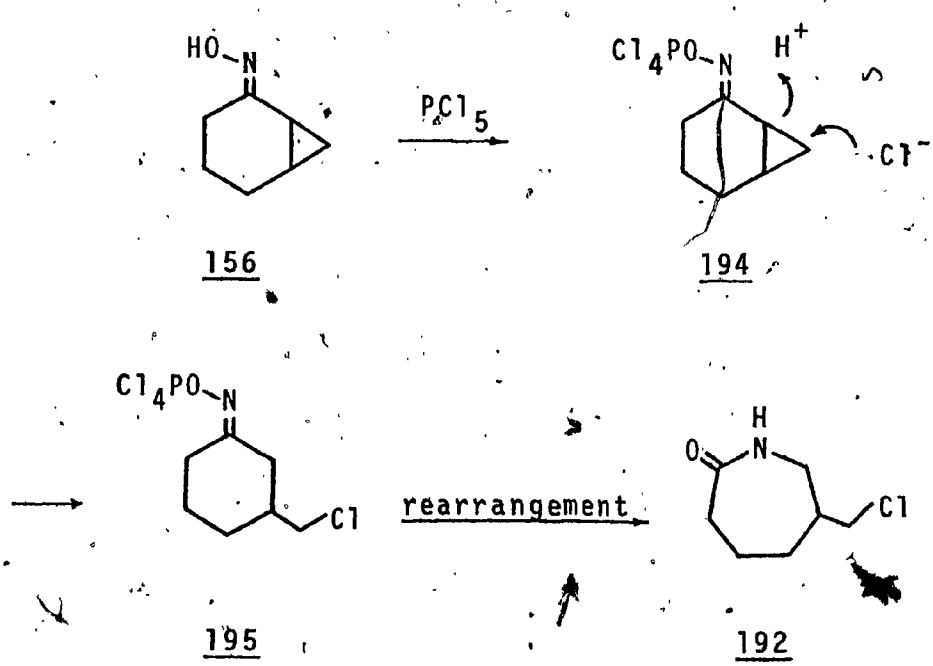
5. 2. Beckmann Rearrangement of Oximes of Bicyclo[n.1.0]-alkan-2-ones.

The anti oxime of bicyclo [4.1.0] heptan-2-one (156) was subjected to the Beckmann rearrangement using PCl_5 in the usual manner. The IR and NMR spectra as well as the TLC of the crude product indicated the presence of much unreacted oxime along with a lactam in which the cyclopropyl system seemed to be absent. Using column chromatography on silica gel the unreacted oxime 156 (20%) and the lactam 192 (20%) were separated. The NMR spectrum of the lactam 192 (cf. NMR spectrum No. 8, page 170)

showed the complete absence of the characteristic high-field signals for the cyclopropyl protons, but exhibited a two-proton doublet at δ 3.62 (J = 4.5 Hz), and a complex multiplet centered around δ 3.34 (2H) which collapsed to a broad peak with loss of fine structure upon treatment of the sample with D_2O and a trace of triethylamine. The lactam gave a positive Beilstein test for chlorine, and its elemental analysis corresponded to a molecular formula $C_7H_{12}ClNO$. Based on these facts, and keeping in mind the recent report of the conversion of the oxime 156 to anti-3-chloromethylcyclohexanone oxime 161 (page 51) in presence of pyridine hydrochloride[106], the lactam isolated was assigned the structure 192. The two-proton multiplet at δ 3.34 in its NMR spectrum is attributed to the C-2 methylene group situated between the NH and the chloromethyl group, and the two-proton doublet at δ3.62 is assigned to the chloromethyl group.

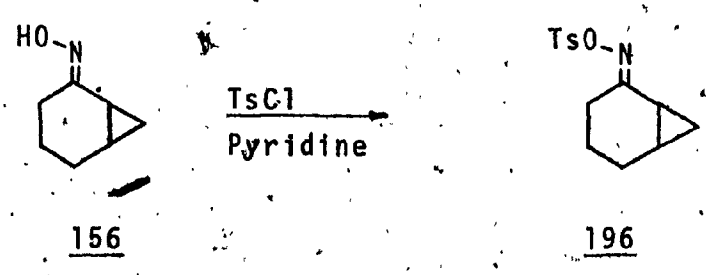


The results described above show that the expected lactam 193 resulting from the intact migration of the cyclopropyl ring was not produced in the Beckmann rearrangement of 156 using PCl_5. It is to be noted that the conversion to the rearranged product was not very efficient, as evidenced by the poor yield of the lactam and the recovery of considerable amount of starting material. Also noteworthy is the fact that no Beckmann fragmentation product (i.e. product resulting from the cleavage of the 6-membered ring) was observed among the reaction products. The lactam 192 is the result of cleavage of the cyclopropyl ring with concomitant addition of elements of HCl during the Beckmann rearrangement with PCl_5. It is the C-1,7 bond of the cyclopropyl system which is cleaved selectively. This is in accordance with a recent suggestion that this is the weakest bond because of its large orbital overlap with the adjacent system.[118] A plausible mechanism which will account for the formation of 192 is presented in Scheme 6. However, with the data available at present it is not possible to state with certainty, the sequence and manner in which addition of HCl and opening of the cyclopropyl ring takes place, or whether the ring opening precedes the rearrangement.

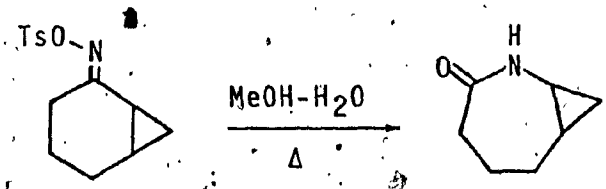


Scheme 6. Mechanism of nucleophilic ring opening of cyclopropyl system in the Beckmann rearrangement.

The oxime itself is unaffected by HCl as demonstrated by the fact that, after storing a solution of it in ether which has been saturated with HCl gas for 18 hours, 156 was recovered quantitatively after neutralization and workup. Interestingly, it was possible to prepare the tosylate 196 of the oxime in excellent yield by reacting

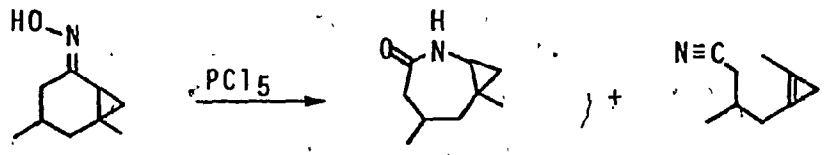


it with tosyl chloride in pyridine for 3 hours at ice-bath temperature. In view of the findings by Tardella and co-workers[106] that pyridine hydrochloride in pyridine causes the cyclopropyl ring in 156 to open with addition of HCl to produce the oxime 161, it was at first suspected that the tosylate produced might be that of the ring-opened oxime 161. However, the NMR (cf. NMR spectrum No. 12, page 174) and IR spectra of the product indicated the cyclopropyl ring has been preserved in the tosylate. The low reaction temperature, the shorter time, and the low concentration of pyridine hydrochloride are probably responsible for this result in the present study. The tosylate was rather unstable above room temperature, and therefore was difficult to recrystallize, being partially converted to the lactam. Upon heating a solution of the tosylate in methanol-water briefly over a steam bath the tosylate was converted to the lactam 193, in which the cyclopropyl ring was preserved. That the lactam has the structure indicated is evidenced by its NMR (cf. NMR spectrum No. 13, page 175), and IR (cf. IR spectrum No. 5, page 181) spectra as well as elemental analysis.



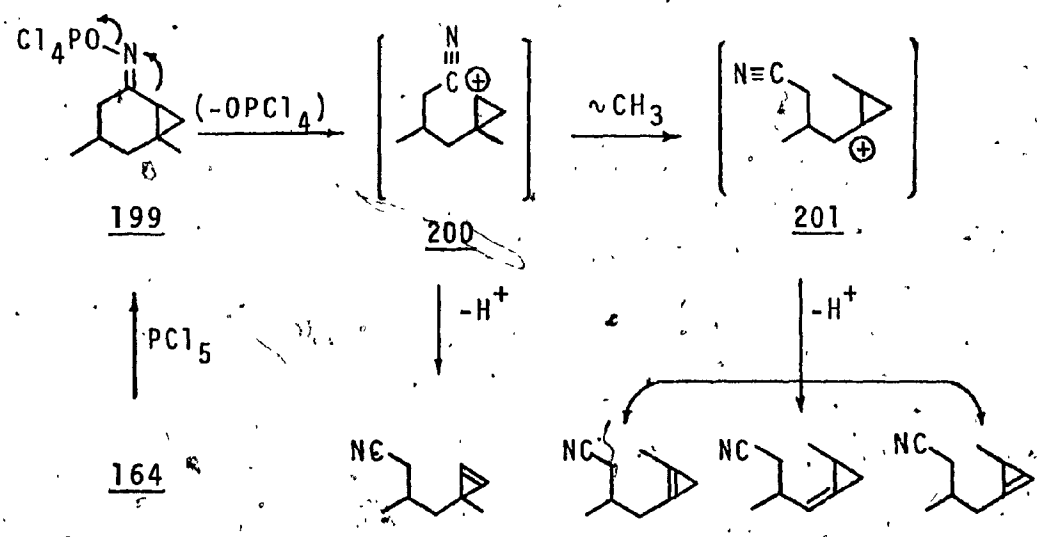
196 193

In the case of the oxime 164, however, the reaction with PCl_5 gave the expected lactam 197, although in poor yield (20%), along with much unchanged oxime (26%) and a trace amount of a nitrile. The IR spectrum of the



164 197 (20%) 198

crude product exhibited the characteristic bands for the C≡N and C=C functions at 2250 and 1725 cm^{-1} respectively. The nitrile arises from the Beckmann fragmentation during the reaction. The NMR spectrum of the crude product



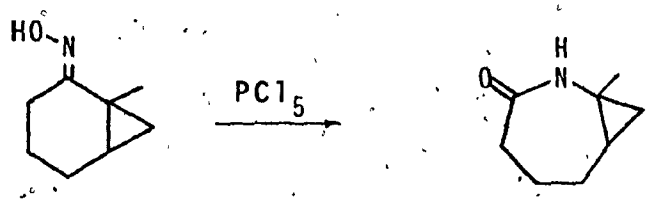
199 200 201

164 202 198 203 204

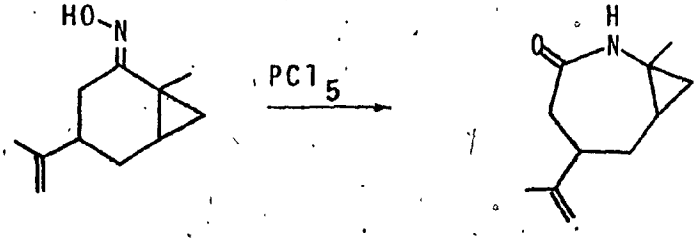
Scheme 7. Beckmann fragmentation of oxime 164.

exhibited signals between δ0.23-0.65 (2H) characteristic of cyclopropyl protons, but did not show any signals above δ2.35 indicating the absence of any vinylic hydrogens in the product. Of the several possible candidates for the nitrile product arising from the Beckmann fragmentation reaction of oxime 164 (shown in Scheme 7) only 198 has no vinylic hydrogen. Therefore, the nitrile observed is suspected to have the structure 198.

The oximes 162 and 163 gave higher yields of the expected lactams 205 and 206 respectively in the Beckmann rearrangement. In the case of 163 about 11% of the starting material remained unreacted. The NMR spectra of both



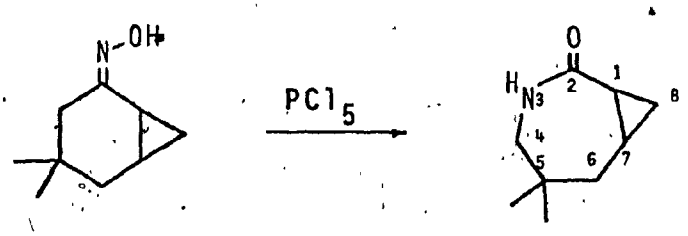
162 205 (56%)



163 206 (63%)

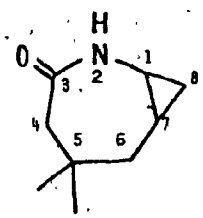
205 and 206 revealed the characteristic signals from the three cyclopropyl protons between δ0.50 and δ0.97 (cf. NMR spectrum No. 9 of 206, page 171). The higher yields of the normal rearrangement products in these two cases, as compared with oximes 156 and 164, indicate that when a methyl group is present at C-1 (the migrating carbon) the migration of the cyclopropyl ring is more efficient. The electron-releasing inductive effect of the methyl group increases the electron density at the migrating carbon, thereby enhancing the migratory aptitude of this carbon to the electron-deficient nitrogen during the reaction. It is also noteworthy here that, in spite of the fully substituted nature of the migrating carbon, no Beckmann fragmentation products were observed in the reactions of 162 and 163.

The syn oxime 165 gave a relatively high yield of the expected lactam 207 upon Beckmann rearrangement. The NMR spectrum of the lactam (cf. NMR spectrum No. 14, page 176) exhibited two sets of quartets centered around δ2.68 and δ3.58 (J = 7 Hz) which are attributable to the two



165 207 (52%)

hydrogens on C-4 with conformationally different environments in 207, and coupled to the NH proton. This was confirmed by the observation that the quartets collapsed to a pair of doublets upon the addition of D_2O and a trace of triethylamine to the sample. If the lactam had the structure 208, this particular observation would not have

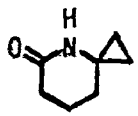
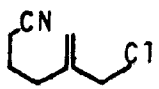
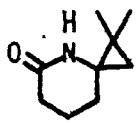
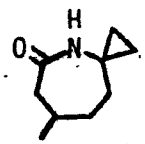
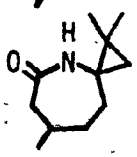
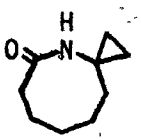


208

been possible. The observed results also provide additional evidence that the hydroxyl group of the oximino function is oriented in a syn relationship with respect to the cyclopropyl system in 165. The migrating group in oxime 165 is not the cyclopropyl group, and as such the result is not immediately relevant to the objective of the present study.

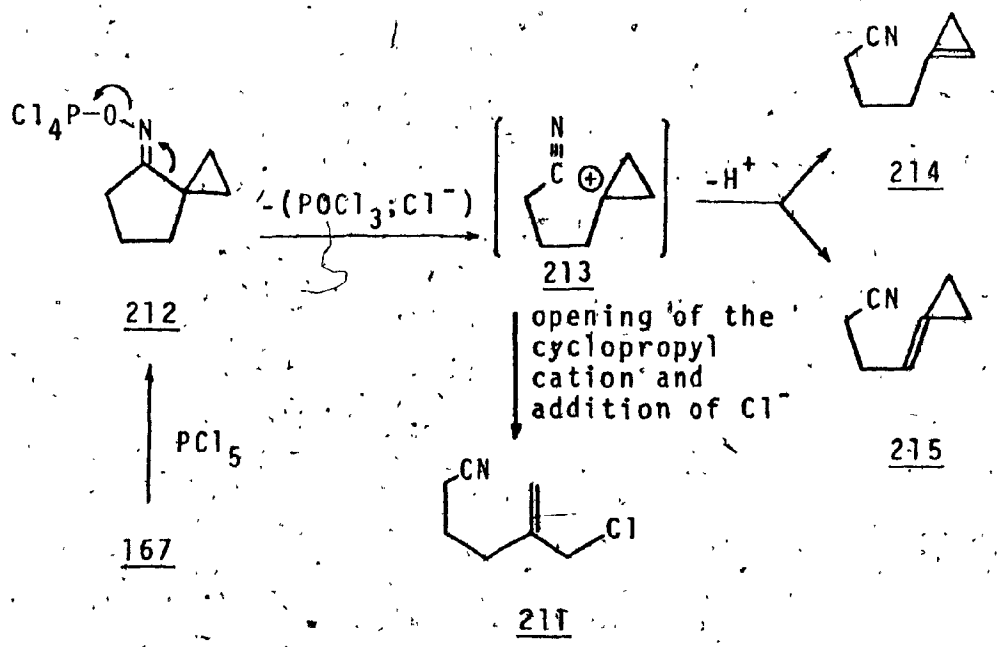
In the oxime 166 one has an example of an anti-α-cyclopropyl oxime where the oximino function is in a seven-membered ring system, unlike the oxime 156 where it is in a six-membered system. As in the case of the oxime 156, the oxime 166 also gave a poor yield of the lactam

Table 9. Lactams from the PCl_5-induced Beckmann rearrangement of oximes of spiro[2.n]-alkan-4-ones.

No.	Lactam	Fragmentation product(s)	%Yield*	Mp°C	IR (CCl_4) cm^{-1} νNH	νΔ	νC=O	NMR (CCl_4) ppm δNH	δCyclopropane
210			18	129-131	3400,3200	3080	1660	8.93	0.53-0.85
216		mixture of nitriles	76	112-114	3420,3200	3060	1655	8.91	0.33-0.81
226		none	64	100-101	3400,3200	3080	1655	8.60	0.63-0.83
227		none	66	126-127	3390-3200	3095	1650	8.55	0.35-0.91
228		none	44	97-99	3400,3200	3080	1665	8.53	0.72-0.86

(*)- Yield of rearranged product.

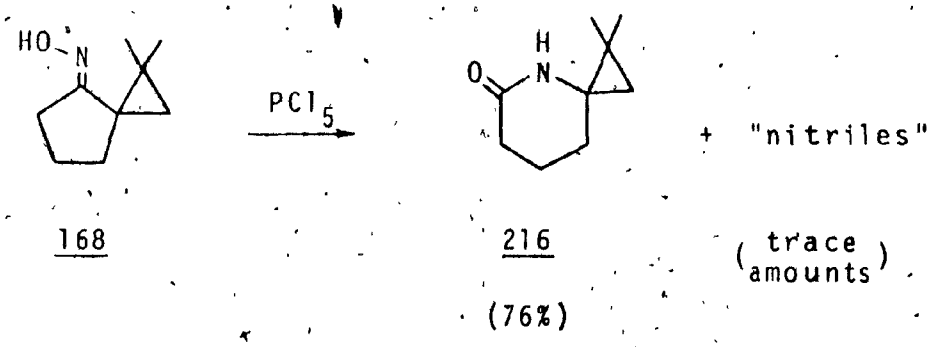
is unreliable. The nitrile must arise from the Beckmann fragmentation of the oxime, and some of the plausible modes of fragmentation are shown in Scheme 8. The nitriles 214



Scheme 8. Plausible modes of fragmentation of oxime of spiro [2.4] heptan-4-one (167).

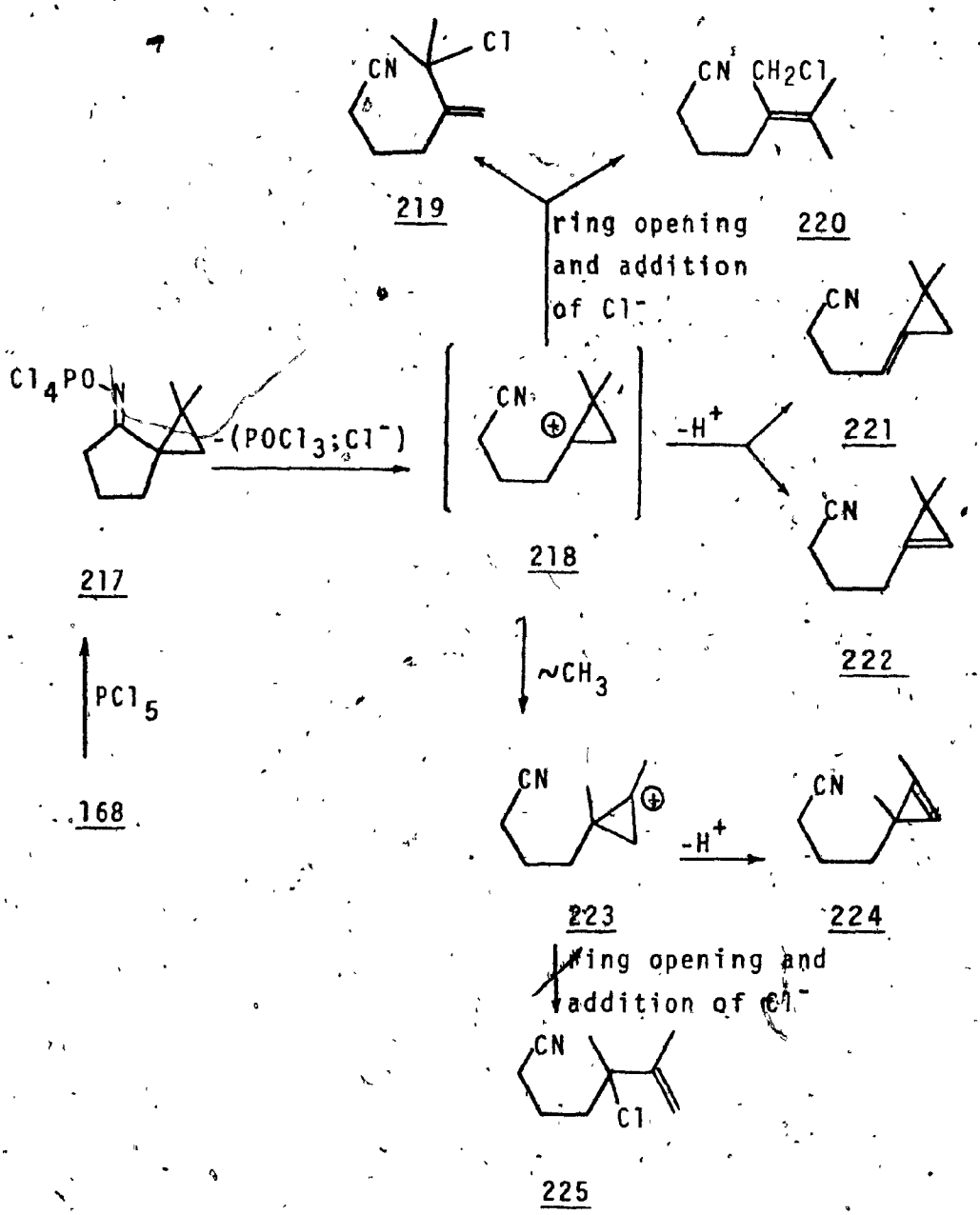
and 215 are not compatible with the observed NMR spectrum. The nitrile 211, which is assumed to be produced by the opening of the cyclopropyl cation 213 to the corresponding allyl cation followed by the addition of chloride ion, seems to accommodate both the IR and NMR spectral data. This assignment of structure is tentative and further work is necessary to establish the structure unequivocally.

With oxime 168 having gem dimethyl substitution at



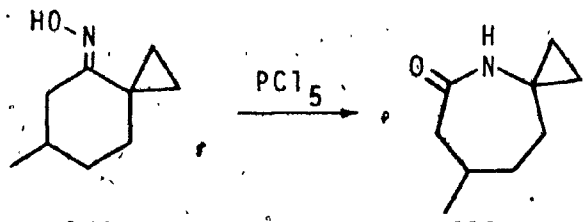
C-1 the yield of the lactam 216 rose to 76%. Here also a small fraction of the reaction took the Beckmann fragmentation pathway. Chromatography of the crude reaction product yielded trace amounts of a colorless liquid which showed only one spot on TLC. However, the IR and NMR spectra of this crude product seem to indicate that it is a mixture of open chain unsaturated nitriles. The IR spectrum showed characteristic bands for $=CH_2$ (3090 cm^{-1} with a shoulder at 3060 cm^{-1}), C≡N (2240 cm^{-1} with shoulder at 2220 cm^{-1}), and C=C (1660 cm^{-1}). The NMR spectrum showed complete absence of resonances in the rigion δ0.00- δ1.10 indicating the absence of cyclopropyl hydrogens in the material. There was an unresolved multiplet at δ5.33 (1H) and two overlapping unresolved multiplets at δ5.21 and δ5.17 (2H). The complex pattern of peaks between δ1.10 and δ2.70 integrated approximately for 11 hydrogens. At this juncture one can only speculate on the possible structures for the nitrile products from the Beckmann fragmentation reaction. Scheme 9 depicts some likely routes by which various nitriles can be produced. With the data available it is not

possible to state which two nitriles are obtained from the reaction.



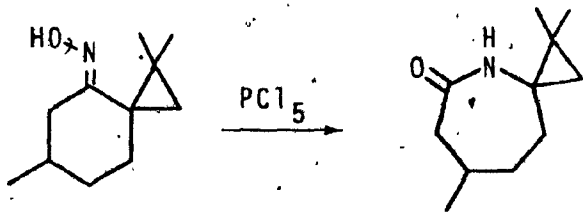
Scheme 9. Beckmann fragmentation of 1,1-dimethyl spiro-[2.4] heptan-4-one oxime (168)

All the other spiro oximes 169 and 170 in which the 4-oximino function is situated in 6-membered ring system and 171 in which it is in a 7-membered ring system, gave, upon reaction with PCl_5, fair yields of the expected spiro-lactams. In each case a trace amount of the starting oxime was also identified; however, no Beckmann fragmentation



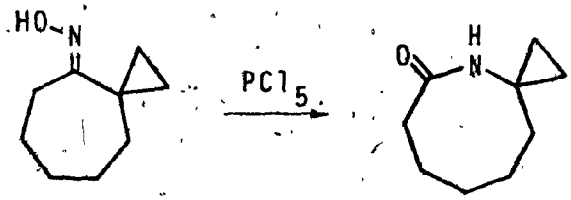
(64%)

169 226



(66%)

170 227

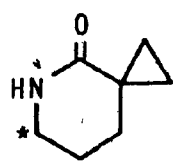


(44%)

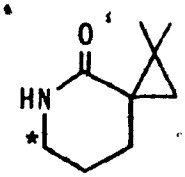
171 228

products were detectable. That the NH group in each of the lactams is situated between the carbonyl and cyclo-propyl system, was verified by the observation that, upon

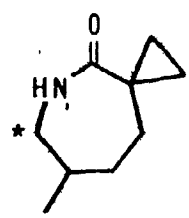
exchange of the N<u>H</u> proton with deuterium (D_2O-triethylamine), there was no change in the appearance of any of the other signals in the NMR spectrum. If, on the other hand, the lactams had the isomeric structures <u>229</u> – <u>233</u>, the signals from the two hydrogens of the methylene group α to the NH (marked with an asterisk), would show marked changes upon exchange of the N<u>H</u> protons with deuterium.



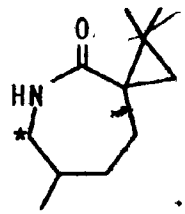
<u>229</u>



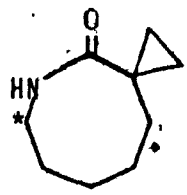
<u>230</u>



<u>231</u>



<u>232</u>



<u>233</u>

The fact that no such changes were observed in the NMR spectrum upon deuterium exchange, and the fact that each of the spiro oximes gave only a single lactam upon the Beckmann rearrangement, with the N<u>H</u> group adjacent to the cyclopropyl system, provide additional evidence that in the spiro oximes the hydroxyl group and the cyclopropyl

system are situated in an anti relationship to each other.

In the Beckmann rearrangement of each of the five spiro oximes studied, the migrating group was the carbon atom C-3 of the cyclopropyl ring. In all cases the cyclopropyl system migrated intact (cf. Table 9, page 86). In the case of the oxime 167 and 168 where the α-oximino function is in the 5-membered ring some fragmentation to nitriles is observed. The fragmentation in these two cases may partly be attributable to the ring strain. The oxime 167 gave a rather poor yield of the lactam 210 while 168 gave very good yield of the corresponding lactam 216. In the latter oxime the gem dimethyl substitution undoubtedly increases the electron density in the cyclopropyl ring and thus makes migrating carbon (C-3) electron-rich (compared to C-3 in 167), thereby increasing the migratory aptitude of the cyclopropane in 168.

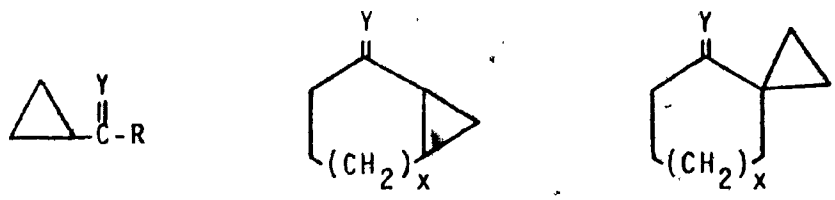
As the size of the ring carrying the oximino function increased to 6 atoms in oximes 169 and 170, and to 7 atoms in 171, the Beckmann fragmentation pathway was completely suppressed, and the sole product of rearrangement was the lactam in each case where the cyclopropyl ring system remained intact. The yields of the lactams from 169 and 170 are comparable demonstrating that the gem dimethyl substitution at C-1 in 170 has no special effect on the yields of lactams in the rearrangement. This fact is contrary to the observed results from oxime 167 and 168.

The reasons for this anomaly are not clear. Another point to be noted is the fact that with the 7-membered ring oxime 171 the yield of the lactam drops to 44%.

The data in Table 9 (page 86) seem to indicate that the yields of the lactam from the spiro oximes are dependent on several factors such as the size of the ring in which the oximino function is situated, ring strain and the presence of electron-releasing methyl substituents in the cyclopropyl system. Molecular models indicate that, as with the bicyclic oximes, back lobe participation of one of the σ bonds of the cyclopropyl ring is not going to be effective in the transition state for the rearrangement of the spiro oximes. This probably is one of the reasons that the yields of lactams are generally lower than those from the oximes of the acyl cyclopropanes (cf. Table 8, page 80). On the other hand, the yields of lactams from the spiro oximes are higher than those from the bicyclic oximes (cf. Table 9, page 86), and this would suggest that the migratory aptitude of the cyclopropyl ring is greater in the spiro systems.

SUMMARY AND CONCLUSIONS

In order to achieve the stated objectives of the present study three categories of α-cyclopropyl ketoximes 83b, 84b and 85b were synthesized by oximating the corresponding ketones 83a, 84a and 85a, most of which in turn were synthesized by the Corey method of cyclopropanation[76] of the corresponding α,β-unsaturated ketones.



83 84 85

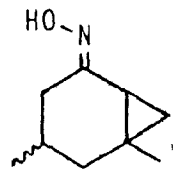
a: (Y = O) b: (Y = N⌇OH)

Some of the spiro ketones (85a) were prepared by adapting methods previously reported in the literature. Many of the cyclopropyl ketones and most of the oximes have not previously been reported.

All of the acyl cyclopropanes yielded both possible isomers (syn and anti) of the oxime, except trans-2-phenyl-1-benzoyl cyclopropane, which gave only the oxime in which the hydroxyl group was syn with respect to the cyclopropyl system. The syn and anti isomers of the oximes were separated in all cases, except that of the

oximes of 1-acetyl-2,2-dimethylcyclopropane. The syn isomer of trans-1-acetyl-2-phenyl cyclopropane oxime and the anti isomer of trans-1-pivaloyl-2-phenyl cyclopropane oxime were observed to undergo slow equilibrations to the syn-anti mixtures at ambient temperatures in chloroform or carbon tetrachloride. All the oximes of the acyl cyclopropanes yielded the expected amides upon treatment with PCl_5. The structures of the amides were established by comparison with authentic samples synthesized independently. Only in the case of the syn-isomer of trans-1-pivaloyl-2-phenyl cyclopropane oxime was there evidence for the Beckmann fragmentation during the reaction with PCl_5.

All the bicyclo [n.1.0] alkan-2-ones used in the present study gave only a single isomer of the oxime in each case (cf. Table 5, p. 54). The hydroxyl group of the oximino function and the cyclopropyl system were disposed in an anti relationship, except in the case of the oxime of 4,4-dimethyl bicyclo [4.1.0] heptan-2-one 165, where the hydroxyl function was syn with respect to the cyclopropyl group. The configurations of the oximes were established from their NMR spectra as well as from the structure of their Beckmann rearrangement products. The anti oxime 164 was the only oxime in the bicyclic series which was obtained as a liquid, but it solidified on prolonged storage in the refrigerator. The material melted over a wide range of temperature, but showed only a single



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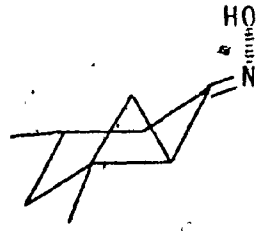
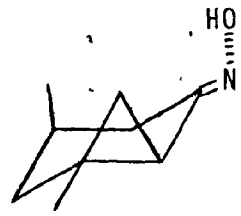


164a

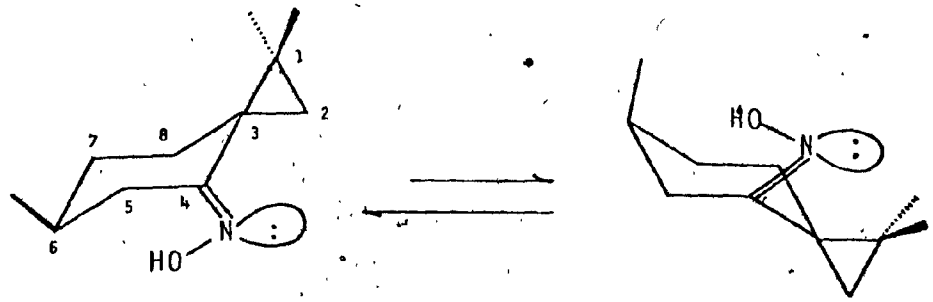


164b

spot on TLC. In view of the fact that it gave only a single lactam, albeit in poor yield, it seems reasonable to assume that the oxime is a single isomer with the two methyl groups cis to each other as in the conformation 164a. The isomer with the two methyls trans to each other as in conformation 164b will be thermodynamically less stable.

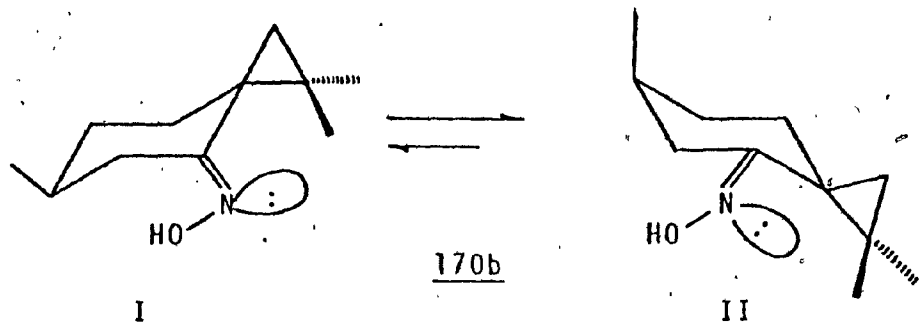
Oximation of spiro [2.n] alkan-4-ones also yielded only a single isomer of the oxime in each case and it was established by NMR spectroscopy that the hydroxyl group of the oximino function was oriented anti with respect to the cyclopropyl system. This was further confirmed by the elucidation of the structure of the single lactam obtained in the Beckmann rearrangement of each oxime. All oximes in the spiro series used in the present study, except the oxime 167 of spiro [2.4] heptan-4-one, were previously unknown in the literature. The structure of the oxime 170 merits some further speculation. The parent ketone 148 was obtained in excellent yield from (+)-pulegone by the

Corey cyclopropanation method.[76] Previous investigators have stated that the ketone thus obtained consisted of a 50:50 mixture of two possible diastereomers when the cyclopropanation was effected by using dimethylsulfoxonium methylide[91]; while a 60:40 mixture was obtained when the cyclopropanation was effected using (diethylamino)-methyloxosulfonium methylide[82]. However, the product obtained from (+)-pulegone in the present work gave only one spot on TLC, and gave an NMR spectrum consistent with a single isomer. It must also be pointed out that the oximation of this ketone gave a 92% yield of an oxime (170) which was also shown to be a single isomer. Furthermore, the Beckmann rearrangement of this oxime gave only one lactam in good yield as the sole product in the reaction. These results strongly suggest that the cyclopropyl ketone obtained from pulegone in the present study consisted of only one diastereomer. The oxime 170 was established to have the hydroxyl group and the cyclopropyl system anti to one another. However, with the data available at present it is not possible to conclude unequivocally whether it is the cis (170a) or trans (170b) diastereomer. Molecular models indicate that in the conformation 170a-I where the C-6 methyl is equatorial, the lone pair on the nitrogen atom is not hindered by one of the methyl groups on C-1 of the cyclopropyl ring, whereas, in 170a-II when the methyl group at C-6 is in



170a

I II



170b

I II

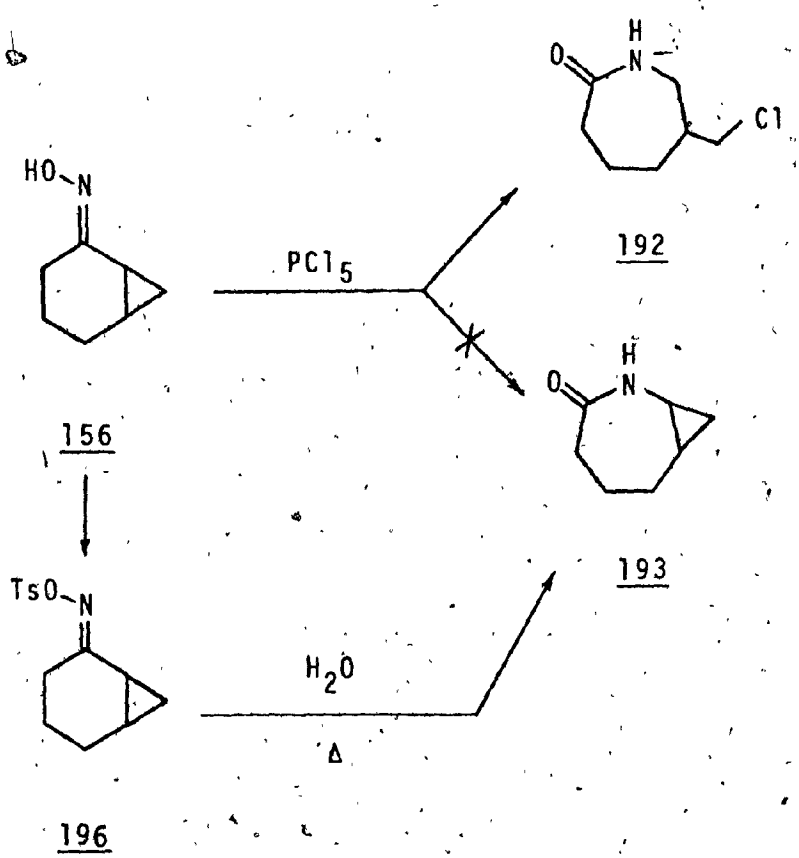
the less favorable axial position, a methyl group from the cyclopropyl system offers steric hindrance to the nitrogen lone pair. Therefore in the equilibrium of 170a conformer I will be favored. For the trans diastereomer (170b), in conformation I, although the C-6 methyl is equatorial, the nitrogen lone pair is in proximity with the methyl groups on the cyclopropyl ring. On the other hand, in conformation 170b-II, when the C-6 methyl group assumes the less attractive axial orientation the steric hinderance between the nitrogen lone pair and the methyl group from the cyclopropyl system

is removed. Therefore, it is not as easy to predict which conformer will predominate in the equilibrium. In the light of the foregoing discussion it seems reasonable to assume that the oxime 170 is the cis diastereomer existing in the more stable conformation 170a-I.

The oximes of acyl cyclopropanes gave good yields of the corresponding amides upon the Beckmann rearrangement in presence of PCl_5. The structures of the amides were confirmed by comparison with authentic samples prepared independently. Only in the case of the syn oxime (154a) of trans-1-pivaloyl-2-phenyl cyclopropane was there some evidence of the Beckmann fragmentation reaction, because in addition to a 76% yield of the expected amide 184, a small amount of trans-1-cyano-2-phenyl cyclopropane 185 was also isolated. The data from the rearrangement of the acyl cyclopropane oximes indicate that the cyclopropyl group migrates as efficiently as an alkyl group. In view of this facility for migration without ring cleavage during the process, a mechanism for the rearrangement is postulated whereby the transition state for the rearrangement is stabilized by the back lobe participation of the σ-bond orbital of the cyclopropyl system.

In contrast to the oximes of the acyl cyclopropanes, the anti oximes of bicyclo [n.1.0] alkan-2-ones gave only poor yields of the Beckmann rearrangement products. In the case of the anti oxime (156) of bicyclo [4.1.0]-

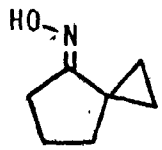
heptan-2-one some interesting results were obtained. Treatment of the oxime with PCl_5 did not yield the expected lactam, but instead, gave exclusively the lactam 192, albeit in poor yield. This lactam was shown to be the product of ring opening of the cyclopropane with addition of elements of HCl followed by the rearrangement. A mechanism to support this postulate has been advanced (cf. p. 73). Such cleavage of the cyclopropyl ring with addition of HCl during the Beckmann rearrangement using PCl_5 has not been observed previously. However, recently pyridine hydrochloride has been demonstrated to



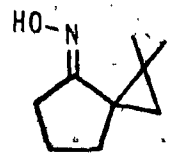
bring about the cleavage of the cyclopropyl system with addition of HCl in the same oxime.[106] The same reagent has also been found to react in the same manner with several α-cyclopropyl ketones producing γ-chloro (β-chloromethyl) ketones.[108] In the present study it was demonstrated that when the tosylate (196) of the oxime 156 was subjected to the solvolytic Beckmann rearrangement the lactam 193 was obtained in which the cyclopropyl system has been preserved. Interestingly, none of the other oximes in the bicyclic series did undergo such cyclopropyl ring opening with addition of HCl during the Beckmann rearrangement in presence of PCl_5. The oxime 164 gave, along with the lactam 197 resulting from the Beckmann rearrangement, trace amounts of a nitrile arising from the Beckmann fragmentation. A structure for this nitrile as well as a possible mechanism for its formation has been postulated (cf. p. 75). It was also noted that, in the anti oximes of the bicyclic series, the presence of an electron-releasing methyl substituent at C-1 increased the yields of lactams from such oximes. This has been rationalized as being due to the added electron density at this migrating carbon which enhances its migratory aptitude to the electron-deficient nitrogen during the rearrangement. The poor migratory aptitude of the cyclopropyl group in the bicyclic series (as evidenced by the poor yields of rearrangement products

when compared to the acyl cyclopropane oximes 7, has been explained as being due to conformational restrictions imposed by the bicyclic system in which the back lobe participation of the σ-bond of the cyclopropyl ring is ineffective, making the departure of the leaving group and the migration of the cyclopropyl system less of a concerted process in the rearrangement step.

All the oximes of spiro [2.n] alkan-4-ones studied in the present investigation had the hydroxyl group oriented anti to the cyclopropyl system. The configurational assignments have been made by NMR spectroscopy, and were further confirmed by the establishment of the structures of the lactams resulting from the Beckmann rearrangement. In the spiro series only oximes 167 and 168 gave, in addition to the corresponding lactams, trace amounts of nitriles resulting from the Beckmann fragmentation. The fragmentations observed have been attributed partly to the ring strain involved in these oximes where the oximino function is in a 5-membered ring. Possible



167



168

structures for the nitriles as well as the likely modes of their formation have been postulated (cf. p. 89). The results of the Beckmann rearrangement of the oximes of the spiro series indicate that the yields of lactams have been increased when electron-releasing methyl substituents were present at the C-1 carbon of the cyclopropyl ring. This can be rationalized as being due to the increased electron supply to the cyclopropyl system, thereby increasing the electron density of the migrating carbon and its migratory aptitude.

The general trend observed in the present study is that the migration of the cyclopropyl group during the Beckmann rearrangement takes place most effectively in acyl cyclopropane oximes, less effectively in the spiro series, and least effectively in the bicyclic series. It is suggested that in the rearrangement of the acyl cyclopropane oximes the back lobe participation of the cyclopropyl σ-bond is a dominant factor, whereas in the spiro and bicyclic series this phenomenon is nonexistant. One other noteworthyl fact is that, contrary to the general trend observed in the Beckmann rearrangements of α-trisubstituted ketoximes including α,α-disubstituted cycloalkanone oximes[8], many of the oximes of the bicyclic and spiro series studied here did not give rise to any Beckmann fragmentation products. It is also concluded from the data available from the present study

that, in the absence of special conformational restrictions, a cyclopropyl carbon migrates as effectively in the Beckmann rearrangement as a saturated or an unsaturated carbon.

SUGGESTIONS FOR FURTHER STUDY

In order to study the migratory aptitude of the cyclopropyl system under the usual Beckmann rearrangement conditions, three categories of oximes 83b, 84b, and 85b (cf. p. 94) having an α-cyclopropyl system were synthesized and subjected to the Beckmann rearrangement using PCl_5. Although an exhaustive list of variously substituted oximes was not used in each category, enough variety was available in each to achieve the stated objectives and to make valid conclusions regarding certain mechanistic aspects of the cyclopropyl migrations in the Beckmann rearrangement of such oximes.

An obvious extension of the present study would be to have more varied examples in each category with various patterns of substitution involving both electron-donating and electron-withdrawing groups. In the acyl cyclopropane oximes (83b) one could, for example, have aromatic systems having para substituents (both electron-withdrawing and electron-donating) at the β-carbon with respect to the oximino function, and study the effects of such substituents in the Beckmann rearrangement.

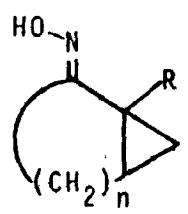
From the observed facility with which the cyclopropyl system migrated without ring cleavage in the acyl cyclopropane oximes, it was hypothesized that the transition

states for the rearrangement of these oximes were stabilized by considerable participation of the back lobes of the cyclopropyl σ-bond (cf. structure 189, p. 69). If such participation is significant, one would expect to observe variation in the rates of rearrangement with variation of the electron density in the cyclopropyl system. Therefore, it would be interesting to investigate the rates of solvolysis of a series of tosylates of the oximes in this series: For example, one should expect to see considerable differences in the rates of such tosylates with β-phenyl, β-para-nitrophenyl, and β-para-methoxyphenyl substituents. The para-methoxyphenyl substituents should exhibit anchimeric assistance in the solvolysis. It would also be interesting to compare the results of the solvolytic Beckmann rearrangement of the oxime tosylates with those of the PCl_5-induced rearrangement of the oximes themselves.

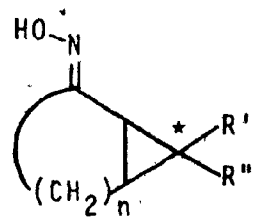
In the bicyclo (234) and spiro (236) series of oximes, if one were to vary systematically the size of the ring attached to the cyclopropyl system from 3 or 4 carbons (if possible) through 7 or 8 carbons, it would provide a more complete picture of the rearrangement processes, and put the conclusions on a firmer ground. In addition to varying the ring size one could also vary the types of substituents at the appropriate positions and study their effects in the rearrangement.

Here also it would be interesting to prepare the oxime tosylates and to compare the results of the solvolytic Beckmann rearrangement with those of the rearrangement induced by PCl_5.

The results of the Beckmann rearrangement of the bicyclic oximes (described in Section 5.2., p. 70) indicated that the presence of an electron-releasing methyl group on the migrating carbon (cf. oximes 162 and 163) enhanced the migratory aptitude of this carbon in the rearrangement. In this connection it would be interesting to study oximes (234) with a variety of substituents including electron-withdrawing ones which would be expected to decrease the migratory aptitude of cyclopropyl system. It would also be interesting to study



234

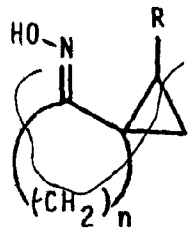


235

oximes having substituents R' and R" on the carbon marked with an asterisk as in 235. Here also electron-releasing substituents are expected to increase the migratory aptitude of the cyclopropyl system, while electron-withdrawing substituents are expected to show a

retardation effect.

In the spiro series of oximes also it would be interesting to study the effect on the rearrangement of both electron-releasing and electron-withdrawing substituents. For example, a series of oximes of the type 236 and their tosylates could be prepared and their Beckmann rearrangement could be investigated. An interesting aspect would be the study of the rates of solvolyses of



236

the tosylates as a function of the substituent R in 236. The syntheses of the ketones required for the various types of oximes suggested above should also provide interesting and challenging problems.

EXPERIMENTAL

Melting Points and Boiling Points: All melting and boiling points reported are uncorrected. Melting points were measured with a Gallenkamp MF-370 instrument.

Elemental Analyses: These were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Thin Layer Chromatography (TLC): Analytical TLC was accomplished on standard microscope slides coated in this laboratory with Baker Aluminum Oxide 9F(1-0541) or E. Merck Silica Gel GF-254. Components were detected by using a MINERALIGHT Model SL-2537 UV lamp with short wave filter, supplied by Ultra-Violet Products Inc., South Pasedana, California or MINERALIGHT UVS. II, supplied by Ultra-Violet Products Inc., San Gabriel, California, by use of iodine vapour or by use of conc. sulfuric acid spray followed by heating the slide on a hot plate.

Dry Column Chromatography: This was accomplished by the technique described by Loev and Goodman[119]. Fisher Alumina Acid, A-948 (80-200 Mesh, deactivated to Brockman Activity III) or Baker Silica Gel 3405 (60-200 Mesh) were generally used as the absorbents. A ratio of 1 gram of reaction mixture to 25-30 gram of

absorbent was usually used. Fractions of 10 mL were collected and monitored by TLC.

IR Spectra: These were routinely recorded with Perkin Elmer Model 457 and Perkin Elmer Model 599B Infrared Spectrophotometers, using chloroform or carbon tetrachloride as solvents. The intensities of the absorption bands are designated as strong (s), medium (m), or weak (w). Most spectra were recorded using a matched set of 0.1 mm NaCl cells. Wavelengths are accurate to $\pm$ 5 cm^{-1}

NMR Spectra: These were recorded with a Varian A-60A Spectrometer, or a Varian T-60 Spectrometer, on undegassed samples (as 5-10% solution in $CDCl_3$, CCl_4). All chemical shifts are expressed in ppm (δ) relative to TMS used as an internal standard. The peaks are designated as singlet (s), doublet (d), broad singlet (bs), multiplet (m), symmetrical multiplet (sym m), and quartet (q).

Reagents and Chemicals: Chemicals for the present study were obtained from various commercial sources as indicated below:

Aldrich Chemical Co. Inc.: (+)-Pulegone, Tech.; l-carvone, 98%; cyclopentanone; cyclohexanone; 2-cyclohexen-1-one; isophorone, 98%; 3-methyl cyclohexanone; 2-methyl-cyclohexanone; diethyl malonate; ethyl acetoacetate; trans-2-phenyl cyclopropane-1-carboxylic acid, 95%; trans-2-

phenyl cyclopropylamine hydrochloride, 97%.

J. T. Baker Chemical Co.: Silica Gel 5-3405 (60-200 Mesh).

Eastman Organic Chemicals: Benzalacetone (trans-4-phenyl-3-buten-2-one).

Fisher Scientific Company: Methyl iodide; dimethyl sulfoxide.

K & K Laboratories, Inc.: Pinacolone.

Mallinckrodt Chemical Works Hydroxylamine hydrochloride.

Matheson Coleman & Bell: Phosphorus pentachloride.

Sigma Chemical Co.: Alumina Acid, WA-1 (it was converted to activity III by addition of 6% distilled water).

General:

Detailed procedures are given only for reactions that gave identifiable products and for those reactions that gave known products by new routes. 'Petroleum ether' or ligroin refers to the fraction with boiling range 60-75°C unless stated otherwise. The terms "reduced pressure" and "high vacuum" refer respectively to the vacuum obtained with a water aspirator and an oil pump. Column chromatography implies the technique of dry column chro-

matography described previously. Solutions after extraction were washed with water and dried over anhydrous sodium sulfate unless indicated otherwise. Ethanol refers to 95% solution. All solvents for recrystallization, reaction and chromatography were dried and distilled before use.

General procedure of cyclopropanation of α,β-unsaturated olefinic ketones with dimethyl sulfoxonium methylide: The method described by Corey and Chaykovosky[76] and the procedure outlined by Fieser and Fieser[120] with minor modifications were followed. In a 500 mL three-necked flask equipped with a magnetic stirrer, pressure equalizing addition funnel, and reflux condenser was placed required amount of sodium hydride and 100-150 mL of dry DMSO, while the system was being flushed with dry nitrogen. The reaction vessel was cooled by a cold water bath (ca 5°C) and the required amount of trimethyl sulfoxonium iodide[76] was then added with stirring. Following the cessation of hydrogen gas evolution the mixture was stirred for an additional 15 min at room temperature. A solution of the required amount of the α,β-unsaturated ketone in 25-50 mL of dry DMSO was then added dropwise with stirring and cooling (ice-water bath). Following this the mixture was stirred for an additional 2 hours at room temperature and for 0.5 hour at 50°C. After cooling

to room temperature the reaction mixture was poured onto 100-200 g of crushed ice, stirred and extracted several times with ether. The ether extracts were combined and washed with water and brine and dried over anhydrous sodium sulfate. Ether was then evaporated to give the crude cyclopropyl ketone. After recording its IR and NMR spectra and the TLC characteristics the crude material was purified by distillation under reduced pressure or by column chromatography.

Trans-2-phenyl-1-pivaloyl cyclopropane (124):

The general procedure of cyclopropanation of α,β-unsaturated ketones was followed. The ylid was prepared from 1.51 g (0.063 mol) of NaH and 13.95 g (0.063 mol) of trimethyl sulfoxonium iodide in 30 mL of dry DMSO. To this solution a solution of 11.28 g (0.061 mol) of benzalpinacolone[66] in 20 mL of dry DMSO was added with cooling (ice bath), during 10 min. The mixture was stirred for 2 h at room temperature and 0.5 h at 50°C. The usual work-up gave 11.80 g of a yellowish oil which was distilled under reduced pressure to give 10.65 g (87%) of a colorless oil bp 104-106°C (at 12 torr). NMR (CCl_4) δ1.16 (9H, s, $3CH_3$), δ1.16-2.42 (4H, two sets of m, centered at δ1.50, 2.30, cyclopropane), δ7.13 (5H, m, Ph); IR (neat) 1690 (s, C=O), 1600, 1400, 700 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.03; H, 8.89.

Attempted reaction of dimethyl sulfoxonium methylide with isophorone: The general procedure of cyclopropanation of α,β-unsaturated ketones was followed. To a mixture of 0.5 g (0.022 mol) of NaH and 4.70 g (0.022 mol) of $(CH_3)_3SOI$ in 50 mL of dry DMSO was added a solution of 2.76 g (0.02 mol) of freshly distilled isophorone in 100 mL of dry DMSO. The solution was stirred for 2 h at room temperature and the resulting purple colored solution was heated for an additional 1 h at 50°C. The usual work-up gave 2.50 g of an oil. The IR and NMR spectra of this material indicated it to be the unchanged starting material. No change to the starting ketone was observed upon prolonging the time of the reaction, increasing the temperature or changing the solvent to dry THF.

4,6-Dimethyl bicyclo [4.1.0] heptan-2-one (132): To a mixture of 1.26 g (0.052 mol) of NaH and 11.55 g (0.052 mol) of $(CH_3)_3SOI$ in 40 mL of dry DMSO was added a solution of 6.20 g (0.05 mol) of 3,5-dimethyl-2-cyclohexen-1-one (107)[68] in 100 mL of dry DMSO. The dark purple reaction mixture was stirred 18 h at room temperature. The usual work-up gave 5.50 g (80%) of an oil bp 84°C (at 5 torr). NMR (CCl_4) δ 0.70-0.94 (3H, m, cyclopropane), δ 1.21 (3H, s, CH_3), δ 1.33 (3H, s, CH_3), δ 0.94-2.41 (5H, m); IR (neat) 3080,

1690 (s, C=O), 1450, 1375, 1290, 1270 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.27. Found: C, 78.16; H, 10.33.

4,4-Dimethyl bicyclo [4.1.0] heptan-2-one (131): Following the general procedure, from 6.20 g (0.05 mol) of 5,5-dimethyl-2-cyclohexen-1-one (111)[72] in 15 mL of dry DMSO and 1.26 g (0.051 mol) of NaH, 11.55 g (0.051 mol) of $(CH_3)_3SOI$ in 80 mL of dry DMSO after stirring for 2 h at room temperature and then 1 h at 50°C, followed by the usual work-up, was obtained 3.70 g (53%) of an oil bp 84-85°C (at 2 torr). NMR (CCl_4) δ 0.80-2.08 (8H, m), δ 0.96 (6H, s, $2CH_3$); IR (neat) 3070, 1675 (s, C=O), 1460, 1275 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found C, 78.29; H, 10.28.

1-Methyl bicyclo [4.1.0] heptan-2-one (known as 1-methyl-2-norcaranone[94]), (133): Following the general procedure, from 2.52 g (0.105 mol) of NaH, 23.1 g (0.105 mol) of $(CH_3)_3SOI$ in 50 mL of dry DMSO and 11 g (0.10 mol) of 2-methyl-2-cyclohexen-1-one[67] in 25 mL of dry DMSO after stirring for 2 h at room temperature and 0.5 h at 50°C, followed by the usual work-up, was obtained 10.24 g of a yellowish oil. Distillation of the crude oil gave an improved yield (9.0 g; 72.5% [lit.[95] 65%]) of a colorless material bp 57-58°C (at 4 torr), [lit.[94]

bp 88-90°C (at 19 torr)] and [lit.[59] bp 76-78°C (at 12 torr)]. NMR (CCl_4)* δ 0.70-2.50 (9H, m), δ 1.21 (3H, s, CH_3); IR (neat) 3080, 1670 (s, C=O), 1355 (s), 1125, 1100 (m) cm^{-1}.

1,1-Dimethyl spiro [2.4] heptan-4-one (146): Following the general procedure of cyclopropanation, 12.4 g (0.10 mol) of 2-(1-methyl ethylidene) cyclopentanone[59] in 25 mL of dry DMSO was added to the suspension of 2.64 g (0.11 mol) of NaH and 24.20 g (0.11 mol) of $(CH_3)_3SOI$ in 100 mL of dry DMSO at 7°C. After stirring for 15 h at room temperature, followed by the usual work-up was obtained 10.0 g (72%) of a colorless oil bp 67°C (at 10 torr), [lit.[59] bp 65-67°C (at 11 torr)]. NMR(CCl_4) δ 0.66 and δ 1.23* (centers of two d, 2H, cyclopropane, J = 4 Hz), δ 1.21 (6H, s, $2CH_3$), δ 1.83-2.40 (6H, m); IR (neat) 3040, 1710 (s, C=O), 1350, 1050, 820, 800 cm^{-1}.

General procedure of oximation of the ketones

A mixture of the required amount of the cyclopropyl ketone in 30-50 mL of 95% ethanol and a solution of the required amount (10-20% excess) of hydroxylamine hydrochloride ($NH_2OH.HCl$) and the required amount (10-20% excess) of sodium acetate in minimum amount

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(*)- Part of doublet at δ 1.23 was overlapped with the methyl resonance at δ 1.21.

of water (10-20 mL) was stirred at room temperature for 2-4 h. The reaction mixture was examined by TLC. If the unchanged ketone remained, it was refluxed over a steam bath for an additional 1-2 h. Cold water was then added, the solid material was filtered, washed and dried. In cases where the oxime oiled out, the crude oxime was extracted several times with diethyl ether. The ether extracts were combined, washed with water and $NaHCO_3$ solution followed by sodium chloride solution, and dried over anhydrous Na_2SO_4. The solvent was evaporated to leave an oil or solid material. IR, NMR spectra were routinely recorded and the product was examined by TLC. The crude oxime was purified by column chromatography, recrystallization or by distillation under high vacuum.

Oximes of 1-acetyl-2,2-dimethyl cyclopropane (152): The general procedure of oximation was followed. A mixture of a solution of 5.60 g (0.05 mol) of 1-acetyl-2,2-dimethyl cyclopropane (122)[82-85] in 50 mL of 95% ethanol and a solution of 4.92 g (0.06 mol) of NaOAc and 4.14 g (0.06 mol) of $NH_2OH.HCl$ in 15 mL of water was refluxed over a steam bath for 1 h. The reaction mixture was extracted with ether, washed and dried. Evaporation of the solvent gave an oil which was distilled under reduced pressure to give 5.15 g (81%) of a colorless material bp. 51-53°C (at 16 torr). This was assumed

to be a 2:1 mixture of the E- and Z-isomers of the oxime as estimated by the NMR study of the Beckmann rearrangement product of the material (see p 62 and p 63). NMR (CCl_4) δ0.35-0.92 (2H, m, cyclopropane), δ1.00 (3H, s, CH_3), δ1.16 (3H, s, CH_3), δ1.90 (3H, s, CH_3), δ9.16 (1H, s, OH); IR (CCl_4) 3600, 3250, 3080, 3060, 1640 (w, C=N), 1450, 1370, 1220, 970 cm^{-1}.

Oximes of trans-1-acetyl-2-phenyl cyclopropane (153): Following the general procedure of oximation, a mixture of 6.75 g (0.042 mol) of trans-1-acetyl-2-phenyl cyclopropane[86,87] in 50 mL of 95% ethanol and 6.91 g (0.084 mol) of NaOAc and 5.85 g (0.084 mol) of $NH_2OH.HCl$ in 20 mL of water was refluxed for 1 h over a steam bath. After ether extraction and work-up was obtained 7.30 g (98.9%) of an oil which solidified upon standing at room temperature, mp 72-84°C. Examination of the crude material by NMR indicated that it consisted of a mixture of the two isomers of the oxime in an approximate ratio of 6:1 (anti : syn). Recrystallization of the crude solid from petroleum ether (bp 65-110°C) gave 5.40 g (80%) of a white crystalline material which melted at 97-99°C. Based on the spectral and elemental analysis, the structure of this compound was assigned 153b (E-oxime). NMR (CCl_4) δ1.00-2.40 (4H, m, cyclopropane), δ1.91 (3H, s, CH_3), δ7.35 (5H, s, Ph), δ10.23 (1H, bs, OH); IR ($CHCl_3$) 3580, 3260, 3080, 3060, 1645

(w, C=N), 1600 (s), 1450, 950 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.22; H, 7.40; N, 7.92.

The syn-oxime (Z-isomer 153a) was obtained (0.9g; 15 %) as a solid upon chromatography of the mother liquor of recrystallization over 85 g of silica gel using a mixture of benzene-ether (1:1 (v/v)). It was recrystallized from petroleum ether, mp 80-82°C. NMR (CCl_4) δ 1.10-3.00 (4H, m, cyclopropane), δ 1.73 (3H, s, CH_3), δ 7.35 (5H, s, Ph), δ 10.0 (1H, bs, OH); IR ($CHCl_3$) 3580, 3260, 3080, 3060, 1645 (w, C=N), 1600, 928 cm^{-1}.

Oximes of trans-2-phenyl-1-pivaloyl cyclopropane (154): The general procedure of oximation did not result in any product. The procedure of Shriner[102] was then followed. To a solution of 8.0 g (0.04 mol) of 2-phenyl cyclopropane-1-t-butyl ketone (124) in 60 mL of abs. ethanol and 15 mL of pyridine, was added 5.50 g (0.08 mol) of $NH_2OH.HCl$. The mixture was refluxed for 15 h on a steam bath. The solvent was removed at reduced pressure followed by addition of 100 mL of water. The white solid which precipitated was suction filtered and washed with water until the complete removal of pyridine was achieved. Recrystallization from 250 mL of a mixture of methanol-water (4:1 (v/v)) gave 6.98 g (85%) of a white crystalline material, mp 129-130°C. This compound was assigned the structure 154a. NMR

($CDCl_3$) δ1.19-3.26 (4H, m, cyclopropane), δ1.22 (9H, s, $3CH_3$), δ7.10 (5H, m, Ph), δ9.16 (1H, bs, OH); IR ($CHCl_3$) 3580, 3250, 3080, 3060, 1655 (w, C=N), 1600, 1450, 950, 930, 700 (s) cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45. Found: C, 77.40; H, 8.93; N, 6.39.

The E-isomer (anti-oxime) 154b was obtained as a white solid 1.20 g (15%) mp 84-86°C upon evaporation of the mother liquor and recrystallization of the product from methanol-water. NMR ($CDCl_3$) δ1.63-2.72 (4H, m, cyclopropane), δ1.37 (9H, s, $3CH_3$), δ7.46 (5H, m, Ph), δ9.41 (1H, bs, OH); IR ($CHCl_3$) 3580, 3250, 3080, 3060, 2970, 1655 (w, C=N), 1600, 1450, 950, 930, 700 cm^{-1}.

Oxime of trans-1-benzoyl-2-phenyl cyclopropane (155): Following the general procedure of oximation, a mixture of 3.0 g (0.013 mol) of trans-2-phenyl-1-benzoyl cyclopropane 125 in 50 mL of ethanol and 1.47 g (0.018 mol) of NaOAc and 1.25 g (0.018 mol) of $NH_2OH.HCl$ in 10 mL of water was refluxed for 24 h over a steam bath. Examination of the mixture by TLC showed no oximation had taken place. To the same mixture an additional 2.0 g of $NH_2OH.HCl$ and 2.0 g of NaOH was added and the mixture was further refluxed over a steam bath for an additional 24 h. The TLC examination of the solution indicated the total consumption of the starting

ketone. Water was then added to the mixture and the white precipitate formed was extracted several times with chloroform. The combined extracts were washed with water, dried and evaporated to give 3.17 g (98%) of a solid material. This material was recrystallized from a mixture of methanol-water (20:1 (v/v)), mp 92-93.5°C. Only a single isomer was obtained whose structure was assigned 155 (Z-oxime). NMR ($CDCl_3$) δ 1.22-2.78 (4H, m, cyclopropane), δ 3.47 (1H, s, N-OH), δ 7.40-7.80 (10H, m, Ph), NMR spectrum (No. 1, p. 163); IR ($CHCl_3$) 3580, 3270, 3080, 3060, 3000, 1605, 1495, 695 (s) cm^{-1}.

Bicyclo [4.1.0] heptan-2-one oxime (known as 2-norcaranone oxime),[107] (156): The procedure described by Tardella and others[106] was followed with a minor modification. From 2.75 g (0.025 mol) of bicyclo[4.1.0]-heptan-2-one (94)[82,94] and a solution of 2.43 g (0.035 mol) of $NH_2OH.HCl$ and 2.98 g (0.035 mol) of NaOAc in 15 mL of water and 30 mL of ethanol, after refluxing for 1 h over a steam bath followed by ether extraction, was obtained 3.0 g (95.8%) of a white solid which was recrystallized from hexane, mp 85-86°C [lit.[106,107] mp 83-86°C (petroleum ether) and lit.[41] mp 87-88°C]. This oxime was assigned the structure (156), (E-configuration). NMR (CCl_4) δ 0.42-1.20 (2H, m, cyclopropane), δ 1.26-2.30 (7H, m), δ 2.42-2.88 (1H, m, on C-3), δ 10.33 (1H, bs,

=N-O<u>H</u>); IR (CCl_4) 3600, 3250, 3090, 1645 (w, C=N) cm^{-1}.

<u>(E)-1-methyl bicyclo [4.1.0] heptan-2-one oxime</u> (<u>162</u>): Following the general procedure of oximation, from 8.0 g (0.064 mol) of 1-methyl-2-norcaranone[59,94,95] in 150 mL of ethanol and a solution of 10.57 g (0.129 mol) of NaOAc and 14.0 g (0.129 mol) of $NH_2OH.HCl$ in 50 mL of water, after refluxing 2 h over a steam bath followed by ether extraction, was obtained 8.90 g of an oil. Distillation of the oil using a short column under vacuum gave 7.80 g (87%) of a colorless viscous oil bp 104-106°C (at 2 torr) which solidified upon standing. Recrystallization from petroleum ether (bp 30-60°C) gave cubic crystals mp 51-52°C. Based on spectral and elemental analysis this material was assigned the structure (<u>162</u>), in which the oxime hydroxyl group is <u>anti</u> to the C-1 methyl and cyclopropyl ring (E-configuration). NMR (CCl_4) δ0.50-1.18 (2H, m, cyclopropane), δ1.28 (3H, s, CH_3), δ1.43-2.03 (m), δ2.20-2.75 (2H, m, on C-3), δ10.20 (1H, bs, =N-O<u>H</u>), NMR spectrum (No. 2, p. 164). IR (CCl_4) 3600, 3250, 3080, 1645 (w, C=N), 1440, 950 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 68.98; H, 9.34; N, 10.01.

<u>(E)-4-isopropylidene-1-methyl bicyclo [4.1.0]-heptan-2-one oxime</u> (<u>163</u>): The general procedure of oximation was followed. A solution of 16.40 g (0.10

mol) of 1-methyl-4-isopropylidene bicyclo [4.1.0]-heptan-2-one[76,91,96] in 150 mL of ethanol was mixed with a solution of 12.30 g (0.15 mol) of NaOAc and 10.42 g (0.15 mol) of $NH_2OH.HCl$ in 80 mL of water and then the mixture was refluxed for 1 h over a steam bath. The solvent was removed under reduced pressure until the appearance of a white precipitate. Excess water was then added and the solid was suction filtered, washed with water and dried at room temperature to give 16.40 g (91.5%) of a white solid. Recrystallization from a mixture of water-methanol (1:1 (v/v)) gave 15 g of a crystalline material mp 102-103°C. This product was assigned the structure 163 in which the oxime hydroxyl group is anti to the C-1 methyl on the basis of its NMR spectrum. No other isomer could be obtained. NMR ($CDCl_3$) δ 0.55-1.08 (3H, m, cyclopropane), δ 1.30 (3H, s, CH_3), δ 1.73 (3H, s, CH_3), δ 1.91-2.23 (m), δ 2.53-2.91 (1H, m, on C-3), δ 4.76 (2H, unresolved s, $=CH_2$), δ 9.73 (1H, bs, OH); IR (CCl_4) 3600, 3280, 3080, 1645 (w, C=N), 900 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.79; H, 9.70; N, 7.70. Mass spectrum m/e 179 (M^+).

4,6-Dimethyl bicyclo [4.1.0] heptan-2-one oxime (164): The general procedure of oximation was followed. To 4.14 g (0.03 mol) of 4,6-dimethyl bicyclo [4.1.0]-

heptan-2-one (132) in 25 mL of ethanol, a solution of 4.92 g (0.06 mol) of NaOAc and 4.14 g (0.06 mol) of $NH_2OH.HCl$ in 15 mL of water was added and the mixture refluxed over a steam bath for 1 h. Ether extraction gave an oily material which was distilled using a short column to give 3.50 g (70%) of a colorless oil bp 124°C (at 4 torr). This oil solidified upon standing for ca 2 months in the refrigerator, mp 42-52°C. All attempts at recrystallization using different solvents failed. NMR (CCl_4) δ 0.48-0.82 (2H, m, cyclopropane), δ 0.96-1.03 (3H, d, CH_3, J = 4 Hz), δ 1.23 (3H, s, CH_3), δ 1.32-2.23 (m), δ 2.42-2.93 (1H, m, on C-3), δ 9.73 (1H, bs, OH); IR (CCl_4) 3600, 3250, 3080, 1650 (w, C=N).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.47; H, 9.77.

4,4-Dimethyl norcaranone oxime (4,4-dimethyl bicyclo-[4.1.0] heptan-2-one oxime) (165): The general procedure of oximation was followed. To a solution of 3.45 g (0.025 mol) of 4,4-dimethyl norcaranone (131) in 25 mL of ethanol was added a mixture of 3.45 g (0.05 mol) of $NH_2OH.HCl$ and 4.10 g (0.05 mol) of NaOAc in 15 mL of water. The mixture was refluxed over a steam bath for 3 h. Excess water was added to the reaction mixture and was placed in an ice bath for 1 h. The precipitated white solid was suction filtered, washed with water, dried

in the air and was recrystallized from methanol-water (1:1 (v/v)) to yield 2.85 g (74.5%) of white needle-shaped crystals mp 139-140°C. Based on the elemental analysis, NMR and IR spectra, this material was assigned the structure (165) in which the oxime hydroxyl group is syn to the cyclopropyl ring (Z-configuration). NMR ($CDCl_3$) δ 0.46-0.60 (1H, m, cyclopropane), δ 0.92 (6H, s, $2CH_3$), δ 1.16-2.61 (7H, m), δ 9.03 (1H, s, OH); IR ($CHCl_3$) 3580, 3250, 3070, 2940, 1645 (w, C=N), 1450 950 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87; N, 9.14. Found: C, 70.54; H, 9.98; N, 9.05.

Bicyclo [5.1.0] octan-2-one oxime (166): Following the general procedure of oximation, from 3.95 g (32 mmol) of bicyclo [5.1.0] octan-2-one[44,97*] in 30 mL of ethanol and a solution of 3.50 g (0.05 mol) of hydroxylamine hydrochloride and 4.25 g (0.05 mol) NaOAc in 15 mL of water, after refluxing 2 h over a steam bath and ether extraction, was obtained 4.39 g (98%) of a colorless oil. It was chromatographed over 100 g of silica gel using $CHCl_3$-acetone (4:1 (v/v)) and was then distilled under high vacuum to give 2.75 g of a viscous oil bp 90-

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(*)- Was prepared according to Padwa[97] with an improved yield of 62% (lit. yield 49%).

93°C (at 0.4 torr). NMR (CCl_4) δ 0.86-1.05 (2H, m, cyclopropane), δ 1.66 (m), δ 1.83-2.68 (m), δ 9.78 (1 H, bs, OH); IR (CCl_4) 3590, 3250, 3080, 1645 (C=N), 1440, 960 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 69.19; H, 9.54.

(E)-spiro [2.4] heptan-4-one oxime (167): The general procedure of oximation was followed. From 5.0 g (0.045 mol) of spiro [2.4] heptan-4-one (99)[99,100] in 40 mL of ethanol and a solution of 5.76 g (0.06 mol) of NaOAc and 4.72 g (0.06 mol) of $NH_2OH.HCl$ in 20 mL of water after stirring for 15 h at room temperature followed by ether extraction was obtained 5.30 g (94%) of a white solid which was recrystallized from hexane mp 64-65°C [lit.[111] mp 60-60.5°C]. NMR (CCl_4) δ 0.62-1.15 (4H, sym m, cyclopropane), δ 1.70-2.20 (4H, m), δ 2.50-2.80 (2H, m, on C-5), δ 9.50 (1H, s, OH), NMR spectrum (No.3 , p. 165); IR (CCl_4) 3600, 3280, 3080, 1665 (w, C=N), 1350, 950, 920 cm^{-1}.

(E)-1,1-dimethyl spiro [2.4] heptan-4-one oxime (168): The general procedure of oximation was followed. A solution of 8.25 g (0.06 mol) of 1,1-dimethyl spiro-[2.4] heptan-4-one (146)[59] in 60 mL of ethanol and a solution of 5.55 g (0.08 mol) of $NH_2OH.HCl$ and 5.10 g (0.08 mol) of NaOAc in 30 mL of water was refluxed over

a steam bath for 12 h. The ether extraction resulted in 8.60 g (93%) of an oil which solidified upon keeping at room temperature. It was recrystallized from 15 mL of hexane, mp 61-63°C (sublimed mp 62-64°C). Based on the spectral analysis, the structure 168 was assigned for this material in which hydroxyl group of the oximino function is anti to cyclopropane (E-configuration). NMR (CCl_4) δ 0.50-1.10 (2H, q, cyclopropane, J = 4.5 Hz), δ 1.18 (6H, s, $2CH_3$), δ 1.66-2.08 (4H, m), δ 2.50-2.75 (2H, m, on C-5), δ 9.66 (1H, bs, OH), NMR spectrum (No. 4, p. 166). IR (CCl_4) 3600, 3280, 3060, 1655 (w, C=N), 1450, 950, 920 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.35; H, 9.95.

(E)-6-methyl spiro [2.5] octan-4-one oxime (169): In accordance with the general procedure of oximation, a solution of 3.40 g (0.025 mol) of 6-methyl spiro [2.5]-octan-4-one (147)[99] in 20 mL of ethanol and a solution of 2.79 g (0.04 mol) of $NH_2OH.HCl$ and 3.40 g (0.04 mol) of NaOAc in 10 mL of water were mixed and stirred for 15 h at room temperature followed by refluxing over a steam bath for 0.5 h. Ether extraction of the reaction mixture gave 3.75 g (98%) of a viscous oil which solidified upon storage at room temperature. It was recrystallized from hexane, mp 59-61°C (sublimed mp 61-63°C). This material was assigned the structure 169 in which the OH function is

anti to the cyclopropane (E-configuration). NMR (CCl_4) δ0.41-0.58 (4H, m, cyclopropane), δ1.07 (3H, d, CH_3, J = 5 Hz), δ1.1-2.0 (6H, m), δ3.16-3.38 (1H, m, on C-5), δ9.73 (1H, bs, OH), NMR spectrum (No 5, p. 167); IR (CCl_4) 3600, 3270, 3080, 1650 (w, C=N), 1450, 1370, 1260. 1010, 940, 915 (s) cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.57; H, 9.72.

(E)-1,1,6-trimethyl spiro [2.5] octan-4-one oxime (170): Following the general procedure of oximation, a mixture of a solution of 4.75 g (28.5 mmol) of 1,1,6-trimethyl spiro [2.5] octan-4-one (148)[82,91] in 75 mL of ethanol and a solution of 4.0 g (58.0 mmol) of hydroxylamine hydrochloride and 4.67 g (58.0 mmol) of NaOAc in 20 mL of water was refluxed for 2 h over a steam bath. Extraction of the reaction mixture with ether gave 4.75 g (92%) of a solid material which was recrystallized from methanol-water (2:1 (v/v)), mp 82-84°C. The structure 170 was assigned for this material in which the OH group is in anti relationship with the cyclopropane ring (E-configuration). NMR (CCl_4) δ 0.12-0.2 (2H, m, cyclopropane), δ 1.02 (6H, s, $2CH_3$), δ 1.21 (3H, s, CH_3), δ 1.00-2.00 (5H, m), δ 2.78-3.55 (1H, m, on C-5), δ 9.80 (1H, bs, OH); IR (CCl_4) 3600, 3280, 3065, 1660 (w, C=N), 1450, 950, 930 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.90; H, 10.56; N,

7.73. Found: C, 72.86; H, 10.37; N, 7.66.

(E)-spiro [2.6] nonan-4-one oxime (171): The general procedure of oximation was followed. A mixture of a solution of 7.0 g (0.05 mol) of spiro [2.6] nonan-4-one (98)[99] in 40 mL of ethanol and a solution of 6.80 g (0.08 mol) of NaOAc and 5.55 g (0.08 mol) of $NH_2OH.HCl$ in 30 mL of water was stirred at room temperature for 18 h. Ether extraction of the reaction mixture gave 7.50 g (98%) of a white solid which was recrystallized from petroleum ether (bp 30-60°C), mp 47-48°C. NMR (CCl_4) δ 0.38-1.01 (4H, AA'BB' sym m, cyclopropane), δ 1.65 (8H, s), δ 2.58-2.75 (2H, m, on C-5), δ 9.91 (1H, bs, OH); IR (CCl_4) 3600, 3250, 3075, 1635 (w, C=N), 900, 700 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.53; H, 10.05.

General procedure of the Beckmann rearrangement of the cyclopropyl ketoximes with PCl_5:

In a 250 mL three-necked flask fitted with a mechanical stirrer, a pressure equalizing dropping funnel and a thermometer was placed the required amount of finely powdered PCl_5 in 50-100 mL of anhydrous diethyl ether and the reaction vessel was cooled to ice-bath temperature. To this solution the required amount of the oxime in 25-50 mL of anhydrous ether was then added dropwise over 5-10 min (<3°C). The mixture was kept stirred for 1 h

at room temperature. The reaction mixture was then poured onto 50-100 g of crushed ice with rapid stirring and was neutralized with 10% $NaHCO_3$ solution and saturated with NaCl and then was extracted with three 20-30 mL portions of ether. The combined ether solutions were washed with water, brine, dried over anhydrous sodium sulfate and evaporated by rotavapor to yield an oil or a solid material. IR spectrum of the crude material was routinely recorded. TLC on silica gel or alumina using appropriate solvents was employed to determine the number of products. The crude material was generally chromatographed over acid-washed alumina (activity III) or silica gel (Baker 5-3405). The solid products were recrystallized from appropriate solvents.

Beckmann rearrangement of oximes of 1-acetyl-2,2-dimethyl cyclopropane (152): The general procedure of the Beckmann rearrangement with PCl_5 was followed. From 0.7 g (5.5 mmol) of a mixture of syn, anti-oxime of 152 in 25 mL of anhydrous ether and 1.37 g (6.5 mmol) of PCl_5 in 50 mL of anhydrous ether, stirred for 1.5 h at ice-bath temperature, after the usual work-up was obtained 0.65 g (92%) of a brown oil. The NMR spectrum of this material indicated it to be a 1:2 mixture of 178 and 177. NMR (CCl_4) δ 0.25-0.68 (m, cyclopropane), δ 1.03, 1.07, 1.10, 1.13 (12H, all singlets $4CH_3$), δ 2.0

(s, CH_3), δ 2.83 (d, CH_3, J = 5 Hz), δ 4.8 (bs, N<u>H</u>), δ 7.42 (bs, N<u>H</u>). Chromatography of the crude material over alumina using ether-benzene (2:1 (v/v)) as eluent gave 0.22 g (34%) of a solid which was recrystallized from petroleum ether (bp 30-60°C), mp 52-55°C (sublimed mp 54-56°C). This compound was assigned 2,2-dimethyl-cyclopropane-1-acetamide structure <u>177</u> . NMR (CCl_4) δ 0.5 (2H, m, cyclopropane), δ 1.10 (3H, s, CH_3), δ 1.13 (3H, s, CH_3), δ 2.0 (3H, s, CH_3), δ 2.50 (2H, m, cyclopropane), δ 8.25 (1H, bs, N<u>H</u>); IR (CCl_4), 3445, 3280, 3080, 3060, 1650 (s, C=O), 1450, 1300 cm^{-1}.

Anal. Calcd for $C_7H_{13}NO$: C, 66.11; H, 10.30; N, 11.01. Found: C, 65.92; H, 10.53; N, 11.07.

<u>Beckmann rearrangement of (Z)-trans-1-acetyl-2-phenyl cyclopropane oxime</u> (<u>153a</u>): To a suspension of 0.80 g (3.80 mmol) of PCl_5 in 40 mL of anhydrous ether was added gradually 0.50 g (2.80 mmol) of well powdered (Z)-oxime* <u>153a</u>. After 1 h stirring at ice-bath temperature, the usual work-up gave 0.35 g (70%) of a white solid which was recrystallized from benzene-hexane (1:1 (v/v)), mp 93.5-95°C. This compound was assigned <u>trans</u>-2-phenyl-

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(*)- Solid oxime was directly added to PCl_5 suspension, due to the tendency of the oxime toward isomerization in ether solution.

cyclopropane-1-N-methyl carboxamide structure 179 . NMR ($CDCl_3$) δ 1.00-2.66 (4H, m, cyclopropane), δ 2.85 (3H, d*, CH_3, J = 5 Hz), δ 6.68 (1H, bs, NH), δ 7.40 (5H, m, Ph), NMR spectrum (No. 6, p. 168); IR ($CHCl_3$) 3460, 3325, 3080, 3060, 1650 (s, C=O), 700 cm^{-1}.

Beckmann rearrangement of (E)-trans-1-acetyl-2-phenyl cyclopropane oxime (153b): The general procedure of the Beckmann rearrangement was followed. To a suspension of 1.50 g (7.2 mmol) of PCl_5 in 100 mL of anhydrous ether was added a solution of 0.9 g (5.08 mmol) of the oxime 153b in 50 mL of anhydrous ether. The white suspension was stirred for 1 h at ice-bath temperature. The usual work-up gave 0.85 g of a dark brown oil which was chromatographed over 20 g of silica gel using ether-benzene (1:1 (v/v)) to give 0.70 g (77%) of a white solid material which was recrystallized from petroleum ether, mp 94-96°C. This compound was assigned trans-1-acetamido-2-phenyl cyclopropane structure 180 . NMR ($CDCl_3$) δ 1.05-1.30 (2H, m, cyclopropane), δ 2.0-2.26 (1H, m, cyclopropane), δ 2.8-3.15 (1H, m, cyclopropane), δ 2.0 (3H, s, CH_3), δ 6.81 (1H, bs, NH), δ 7.50 (5H, m, Ph); IR ($CHCl_3$) 3340, 3300, 3080, 3060, 3000, 1670 (s, C=O), 1600, 1450, 700 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99
Found: C, 75.44; H, 7.40; N, 7.94.

(*) The doublet collapsed to a singlet with D_2O and TEA. (cf. NMR spectrum No. 7, p. 169).

Beckmann rearrangement of (Z)-trans-2-phenyl-1-pivaloyl cyclopropane oxime (154a): Following the general procedure, to a suspension of 2.28 g (0.011 mol) PCl_5 in 50 mL of anhydrous ether was added a solution of 2.17 g (0.01 mol) of (Z)-oxime 154a in 70 mL of anhydrous ether. The mixture was stirred for 2 h at ice-bath temperature. The usual work-up gave 2.10 g of a white solid. Recrystallization of the crude material from a mixture of petroleum ether (bp 30-60°C) and benzene (1:1 (v/v)) gave 1.65 g (76%) of a crystalline material mp 134-135°C [lit.[40] mp 136-138°C; $(i\text{-}Pr)_2O$ solvent]. Based on spectral data and comparison with an authentic sample, this compound was identified as trans-2-phenyl cyclopropane-1-N-t-butyl carboxamide 184. NMR $CDCl_3$) δ 1.40 (9H, s, $3CH_3$), δ1.05-2.66 (4H, m, cyclopropane), δ5.66 (1H, bs, NH), δ7.42 (5H, m, Ph); IR ($CHCl_3$) 3440, 3335, 3080, 3060, 3000, 1655 (s, C=O), 1600, 1510 (s), 1450, 700 cm^{-1}.

The material from the mother liquor was chromatographed over 20 g alumina using petroleum ether (bp 30-60°C) and benzene (1:2 (v/v)) to give 0.10 g (5%) of a solid material mp 55°C (petroleum ether) [lit.[21] mp 53-56°C]. This compound was identified as the nitrile 185 . IR (CCl_4) 3090,3070, 3040, 2240 (s, C≡N), 1600, 700 (s) cm^{-1}.

Beckmann rearrangement of (E)-trans-2-phenyl-1-pivaloyl cyclopropane oxime (154b): To a suspension of 0.70 g (3.30 mmol) of PCl_5 in 20 mL of anhydrous ether was added 0.50 g (2.30 mmol) of the oxime 154b.* The mixture was stirred for 2 h at ice-bath temperature. The usual work-up gave 0.40 g (80%) of a yellowish solid which was recrystallized from a mixture of petroleum ether (bp 30-60°C) and benzene (3:1 (v/v)), mp 107-109°C. Based on the spectral data and comparison with an authentic sample, this compound was identified as the structure 186. NMR ($CDCl_3$) δ 1.03-1.30, 1.91-2.33, 2.98-3.15 (4H, three sets of m, cyclopropane), δ 1.22 (9H, s, $3CH_3$), δ 6.27 (1H, bs, NH), δ 7.45 (5H, s, Ph); IR ($CHCl_3$) 3460, 3360, 3080, 3060, 3000, 1655 (s, C=O), 1600, 1495 cm^{-1}.

Beckmann rearrangement of (Z)-trans-2-phenyl-1-benzoyl cyclopropane oxime (155): The general procedure of the Beckmann rearrangement was followed. A solution of 1.19 g (0.005 mol) of oxime 155 in 30 mL of anhydrous ether was added dropwise with stirring to a suspension of 1.56 g (0.0075 mol) of PCl_5 in 50 mL of anhydrous ether which was kept in an ice bath. The mixture was stirred for 1 h at ice-bath temperature followed by stirring for an additional 1 h at room temperature. The usual work-up gave 1.14 g of a yellowish solid, which was chromato-

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(*)- See footnote on p. 131.

graphed over a short column of alumina using chloroform as eluent. The crude material was recrystallized from benzene to give 0.70 g (58.8%) of a white solid, mp 143-144°C. Based on spectral data and comparison with an authentic sample this compound was identified as trans-2-phenyl cyclopropane-N-phenyl carboxamide (187). NMR ($CDCl_3$) δ1.15-1.88 (3H, m, cyclopropane), δ2.33-2.75 (1H, m, cyclopropane), δ7.0-7.67 (10H, m, 2Ph), δ7.92 (1H, bs, NH); IR ($CHCl_3$) 3430, 3320, 3080, 3060, 3000, 1680 (s, C=O), 1600, 1520, 1440, 690 cm^{-1}.

Authentic Samples:

Trans-2-phenyl cyclopropyl-1-acetamide (180): A solution of 3.56 (0.021 mol) of trans-2-phenyl-cyclopropylamine hydrochloride in 40 mL of water was neutralized by a dilute solution of 0.90 g (0.22 mol) of NaOH. The reaction mixture was extracted with two 30 mL portion of benzene and dried over anhydrous Na_2SO_4. This solution was added dropwise to a solution of 1.60 g (0.02 mol) of acetyl chloride in 25 mL of benzene in a flask which was kept in an ice-cold water bath and the mixture was stirred for an additional 15 min. It was poured onto 50 mL of ice-cold water and was neutralized by cautious addition of 10% NaOH solution. The benzene layer was separated, washed dried and evaporated to give 1.10 g (31%) of an oil which solidified upon standing at ambient

temperature. It was recrystallized from a mixture of hexane-benzene (1:2 (v/v)), mp 95-96°C. NMR ($CDCl_3$) δ 1.05-1.30, 2.0-2.26, 2.80-3.15 (4H, m, cyclopropane), δ2.0 (3H, s, CH_3), δ6.81 (1H, bs, N<u>H</u>), δ7.50 (5H, m, Ph); IR ($CHCl_3$) 3340, 3300, 3080, 3060, 3000, 1670 (s, C=O), 1600, 1450, 700 cm^{-1}. The admixture of this compound with the product obtained from the rearrangement of the oxime <u>153b</u> did not depress the melting point.

<u>Trans-2-phenyl cyclopropane-N-methyl carboxamide</u> (<u>179</u>) : A mixture of 8.10 g (0.05 mol) of <u>trans</u>-2-phenyl cyclopropane-1-carboxylic acid and 7.0 g (0.06 mol) of freshly distilled thionyl chloride in 60 mL of dry benzene was refluxed for 3 h. The solvent and excess of thionyl chloride were removed by distillation and 30 mL of fresh benzene was then added. The solution was cooled in an ice bath and excess methylamine (generated by gently heating a mixture of powdered methylamine hydrochloride and sodium hydroxide) was passed through it. The reaction mixture was then poured into ice-water, the organic layer was separated, washed and dried. The removal of the solvent yielded 8.0 g (92%) of a brown oil which solidified upon standing at room temperature. The material was recrystallized from a mixture of benzene-hexane (1:1 (v/v)) giving a white crystalline material mp 94-95°C [lit.[40] mp 98-99°C (ethyl acetate)].

NMR ($CDCl_3$) δ1.0-2.66 (4H, m, cyclopropane), δ2.85* (3H, d, CH_3, J = 5 Hz), δ6.68 (1H, bs, NH), δ7.40 (5H, m, Ph), NMR spectrum (No. 6, p. 168); IR ($CHCl_3$), 3460, 3325, 3080, 3060, 3000, 1650 (s, C=O), 700 cm^{-1}.

Trans-2-phenyl cyclopropane-N-t-butyl carboxamide (184): A mixture of 1.62 g (0.01 mol) of trans-2-phenyl cyclopropane-1-carboxylic acid and 4 mL of freshly distilled thionyl chloride in 20 mL of dry benzene was refluxed for 1 h. The solvent was removed and 5 mL of fresh benzene was then added. The solution was cooled in an ice bath and was added to a solution of 1.0 g (0.013 mol) of t-butylamine in 10 mL of benzene. The mixture was stirred and refluxed for an additional 10 min, cooled and was poured into 50 mL of ice-water, neutralized with $NaHCO_3$, and the solution was extracted with two 25 mL portions of benzene. The combined benzene layers were washed with water, and dried over Na_2SO_4. Evaporation of the solvent gave 2.0 g (92%) of a yellowish solid, which was recrystallized from a mixture of petroleum ether (bp 30-60°C) and benzene (1:1 (v/v)), mp 135-136°C [lit.[40] mp 136-138°C $(i\text{-}Pr)_2O$ solvent]. NMR ($CDCl_3$) δ1.05-2.68 (4H,

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(*)- This doublet collapsed to a singlet upon the addition of 2 drops of D_2O and one drop of triethyl amine to the solution. See NMR spectrum No. 6, and 7 on pages 168 and 169.

two sets of m, each centered at δ1.17 and δ2.50, cyclopropane), δ1.40 (9H, s, $3CH_3$), δ5.91 (1H, bs, NH), δ7.42 (5H, m, Ph); IR ($CHCl_3$) 3440, 3335, 3080, 3060, 3000, 1655 (s, C=O), 1600, 1450, 700 cm^{-1}. The admixture of this compound with the product from the rearrangement of the oxime 154a did not depress the melting point.

Trans-2-phenyl cyclopropyl-1-trimethyl acetamide (186): Solution A: A solution of 3.40 g (0.02 mol) of trans-2-phenyl cyclopropylamine hydrochloride in 25 mL of water was neutralized with 0.80 g (0.021 mol) of NaOH. The reaction mixture was extracted with 20 mL of benzene and dried over Na_2SO_4. Solution B: A solution of 2.0 g (0.02 mol) of trimethyl acetic acid (pivalic acid) in 100 mL dry benzene was refluxed with 4.80 g (0.04 mol) of freshly distilled thionyl chloride for 2 h. The solvent was distilled off and 10 mL of fresh benzene was then added and removed at reduced pressure (to eliminate the last traces of thionyl chloride). A further portion of 10 mL benzene was added and the solution was cooled to ice-bath temperature.

The solution A was added dropwise to the solution B in an ice bath. The mixture was stirred for an additional 10 min and was poured into 30 g of ice-water, and neutralized with 10% $NaHCO_3$ solution. The organic layer was separated and the solution was further extracted with benzene. The combined benzene layers were washed, dried and

evaporated to give 3.20 g (73%) of a yellowish solid. It was recrystallized from a mixture of petroleum ether (bp 30-60°C) and benzene (3:1 (v/v)), mp 106-108°C [lit.[40] mp 110-112°C; $(i\text{-}Pr)_2O$]. NMR ($CDCl_3$) δ1.03-1.30, 1.91-2.33, 2.98-3.15 (4H, all m, cyclopropane), δ1.22 (9H, s, $3CH_3$), δ6.27 (1H, bs, N<u>H</u>), δ7.45 (5H, s, Ph); IR ($CHCl_3$) 3460, 3360, 3060, 1655 (s, C=O), 1600, 1495, 700 cm^{-1}. The admixture melting point of this compound with the rearranged product of oxime <u>154b</u> remained unchanged.

<u>Trans-2-phenyl cyclopropane-N-phenyl carboxamide</u> (<u>187</u>): A mixture of 1.0 g (6.16 mmol) of <u>trans</u>-2-phenyl cyclopropane-1-carboxylic acid and 3 mL of freshly distilled thionyl chloride in 10 mL of dry benzene was refluxed for 2 h. The solvent and excess of thionyl chloride were removed by distillation. An additional 20 mL of benzene was then added and the solution was cooled in an ice bath. To this solution was added a solution of 0.80 g (6.40 mmol) of freshly distilled aniline in 10 mL of dry benzene. The mixture was stirred for 15 min at room temperature and then poured into 50 mL of ice-water. The benzene layer was separated and the aqueous layer was extracted with benzene. The combined extracts were washed, dried and evaporated to give 1.21 g (82.5%) of a solid material which was recrystallized from benzene, mp 143-144°C. Admixture of this material with the rearranged

product of oxime 155 did not depress the melting point. NMR ($CDCl_3$) δ 1.15-1.88 (3H, m, cyclopropane), δ 2.33-2.75 (1H, m cyclopropane), δ 7.0-7.67 (10H, m, 2Ph), δ 7.92 (1H, bs, NH); IR ($CHCl_3$) 3430, 3320, 3060, 3000, 1680 (s, C=O), 1600, 1520, 1440, 690 cm^{-1}.

Beckmann rearrangement of bicyclo [4.1.0] heptan-2-one oxime (156): The general procedure of the Beckmann rearrangement was followed. From 1.50 g (0.012 mol) of oxime 156 in 30 mL of anhydrous ether and 3.50 g (0.017 mol) of PCl_5 in 150 mL of anhydrous ether, after the usual work-up was isolated 0.75 g of a yellowish solid. The crude material was chromatographed over 18 g of silica gel (Baker) using a mixture of diethyl ether-hexane (3:1 (v/v)) to give 0.30 g of unchanged starting material (confirmed by ir spectrum and mp) as the first fraction. The second fraction (0.30 g ; 20%) was obtained as a white solid upon eluting the column with diethyl ether, and this material was recrystallized from a mixture of hexane-benzene (1:1 (v/v)), mp 122-123°C. This product was identified as 1-chloromethyl-3-azacycloheptan-4-one (192). NMR ($CDCl_3$) δ 1.50-2.16 (5H, m), δ 2.58-2.70 (2H, m), δ 3.22-3.46 (2H, m), δ 3.62 (2H, d, J = 4.5 Hz), δ 7.33 (1H, bs, NH), NMR spectrum (No. 8, p.170); IR ($CHCl_3$) 3420, 3300, 3230, 3070, 2940, 1658, 1440 cm^{-1}.

Anal. Calcd for $C_7H_{12}ClNO$: C, 52.01; H, 7.47. Found: C, 51.91; H, 7.60.

Attempted reaction of oxime of bicyclo [4.1.0] heptan-2-one (156) with HCl: Into a solution of 80 mg of the oxime (156) in 50 mL of anhydrous ether cooled by an ice bath, HCl gas was bubbled to the point of saturation. The resulting solution was stored, with stirring, at room temperature for 18 h. The reaction mixture was then poured into 25 g of crushed ice and was neutralized with a 10% solution of $NaHCO_3$. It was extracted with three 20 mL portions of ether, and the extracts were washed with water and dried over anhydrous sodium sulfate. Evaporation of the solvent gave 75 mg of a solid material which was identified as the starting oxime (156), (confirmed by NMR, IR, TLC and mp).

Solvolytic Beckmann rearrangement of the tosylate of bicyclo [4.1.0] heptan-2-one oxime (196): The oxime tosylate was prepared according to the procedure of Sato and coworkers.[20] To a solution of 300 mg of the oxime (156) in 10 mL of dry pyridine kept cold in an ice bath, was added a solution of purified p-toluene sulfonyl chloride in 10 mL of dry pyridine. The mixture was stirred at ice-bath temperature for 3 h and was then poured into 50 g of crushed ice containing 8 mL of conc. H_2SO_4. The solution was extracted with three 20 mL portions of chloroform. The combined extracts were washed with water, dried over anhydrous sodium sulfate, and evaporated to give 0.70 g (92%) of an oil which solidified upon stor-

age in the refrigerator. It was difficult to recrystallized this material from aprotic solvents. NMR (CCl_4) δ 0.33-0.98 (2H, m, cyclopropane), δ 1.70-2.33 (8H, m), δ 2.47 (3H, s, CH_3), δ 7.17-7.87 (4H, q, Ph, J = 8 Hz); NMR spectrum (No. 12, p. 174); IR ($CHCl_3$) 3015, 2940, 2865, 1655, 1600, 1370, 1190, 1180 ($-SO_2-$) cm^{-1}.

The solution of the crude oxime tosylate (196) in methanol was heated briefly (5 min) over a steam bath. To this solution 10 mL of water was then added and heated for an additional 5 min and the mixture was extracted several times with $CHCl_3$. The extracts were combined and washed with a solution of $NaHCO_3$, and dried over Na_2SO_4. Evaporation of the solvent gave 150 mg of a yellowish oil which was chromatographed over silica gel using hexane-ether (1:5 (v/v)) as the first eluent followed by ether, to give 70 mg (23%) of a colorless oil. The oily material solidified upon cooling and was recrystallized from hexane, mp 56-57°C. This compound was identified as 2-azabicyclo [5.1.0] octan-3-one (193). NMR (CCl_4) δ 0.34-0.84 (2H, q, cyclopropane, J = 4 Hz), δ 0.96-2.90 (8H, m), δ 7.40 (1H, bs, NH); NMR spectrum (No. 13, p. 175); IR ($CHCl_3$) 3400, 3240, 3080, 1663, 1450, 1350 cm^{-1}. IR spectrum (No. 5, p. 181).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 67.56; H, 9.12.

Beckmann rearrangement of (E)-1-methyl-2-norcaranone oxime (162): The general procedure of the Beckmann rearrangement was followed. To a suspension of 3.60 g (0.017 mol) of PCl_5 in 120 mL of anhydrous ether kept in an ice bath a solution of 1.60 g (0.016 mol) of oxime 162 in 50 mL of anhydrous ether was added dropwise over 15 min during which a white precipitate appeared. The reaction mixture was stirred 1 h at ice-bath temperature and 1 h at room temperature. The usual work-up gave 0.90 g (56%) of a pale yellow solid which was applied to a short column of silica gel and eluted with a mixture of ether-ligroin (1:1 (v/v)) to give a white solid which was recrystallized from petroleum ether, mp 111-112°C. Based on the elemental analysis and spectral data this material was identified as 1-methyl-2-azabicyclo [5.1.0] octan-3-one structure (205). NMR (CCl_4) δ0.50-0.91 (3H, m, cyclopropane), δ1.41 (3H, s, CH_3), δ1.60-2.90 (5H, m), δ7.83 (1H, bs, NH); IR (CCl_4) 3400, 3200, 3075, 1665 (s, C=O), 1450, 1260, 1170 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.13; H, 9.57; N, 10.15.

Beckmann rearrangement of (E)-1-methyl-4-isopropylidene bicyclo [4.1.0] heptan-2-one oxime (163): The general procedure for the Beckmann rearrangement was followed. To a suspension of 4.16 g (0.02 mol) of PCl_5 in 200 mL of

anhydrous ether was added a solution of 1.79 g (0.01 mol) of oxime 163 in 80 mL of dry ether. The mixture was stirred for 0.5 h at ice-bath temperature and for an additional 0.5 h at room temperature. The usual work-up gave 1.60 g of a brown oil which was chromatographed over silica gel using ether-benzene (1:1 (v/v)). As a first fraction 0.30 g of unchanged starting material was recovered. A second fraction was obtained (1.0 g; 62.5%) as a white solid, mp 72-73°C (ligroin). This compound was identified as 1-methyl-5-isopropylidene-2-azabicyclo [5.1.0] octan-3-one (206). NMR (CCl_4) δ0.50-0.91 (3H, m, cyclopropane), δ1.43 (3H, s, CH_3), δ1.91 (3H, s, CH_3), δ2.13-2.80 (5H, m), δ4.95 (2H, bs, $=CH_2$), δ8.33 (1H, bs, NH), NMR spectrum (No. 9, p. 171); IR (CCl_4) 3390, 3200, 3080, 1655 (s, C=O), 1440 cm^{-1}.

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.65; H, 9.58; N, 7.66.

Beckmann rearrangement of 4,6-dimethyl bicyclo [4.1.0]-heptan-2-one oxime (164): The general procedure of the Beckmann rearrangement was followed. From a solution of 1.50 g (0.10 mol) of oxime 164 in 20 mL of dry ether and a suspension of 2.50 g (0.112 mol) of PCl_5 in 100 mL of dry ether, after stirring for 1 h at ice-bath temperature and 1 h at ambient temperature, followed by the usual work-up was obtained 1.0 g of a brown oil. The crude oil

was chromatographed over 45 g of silica gel using chloroform as the first eluent followed by a mixture of hexane-ether (1:3 (v/v)). A liquid was obtained 0.06 g (4%) as the first fraction for which the structure 198 was assigned. IR (CCl_4) 3075, 2965, 2250 (C≡N), 1725, 1460, 1375 cm^{-1}. NMR (CCl_4) δ0.23-0.65 (2H, m, cyclopropane), δ1.00 (3H, s, CH_3), δ1.66 (3H, d, CH_3), J = 2 Hz), δ 1.55-2.66 (m). The second fraction 0.40 g (26%) was unchanged starting material. A third fraction was obtained (0.30 g; 20%) as a white solid, which was recrystallized from hexane, mp 113-114°C (sublimed mp 116-116.5°C). This product was identified as a lactam, and was assigned the structure 197 . NMR (CCl_4) δ0.40-0.78 (2H, m, cyclopropane), δ1.22-1.28 (6H, d, $2CH_3$, partially overlapped), δ1.58-2.62 (6H, m), δ8.08 (1H, bs, N<u>H</u>); IR (CCl_4) 3420, 3220, 3095, 2970, 1673 (s, C=O), 1450, 1385, 1288, 1210 cm^{-1}, IR spectrum (No. 3, p. 179).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.70; H, 9.93.

<u>Beckmann rearrangement of (Z)-4,4-dimethyl bicyclo-[4.1.0] heptan-2-one oxime</u> (165): Following the general procedure of the Beckmann rearrangement, from 0.67 g (4.37 mmol) of oxime 165 in 40 mL of anhydrous diethyl ether and 1.10 g (5.28 mmol) of PCl_5 in 60 mL of dry ether, after stirring for 1 h at ice-bath temperature and

1 h at room temperature followed by the usual work-up, was obtained 0.35 g (52%) of a pale yellowish solid. Recrystallization from hexane gave a white crystalline material mp 138-139°C. Based on the spectral and elemental analysis, this material was identified as 5,5-dimethyl-3-azabicyclo [5.1.0] octan-2-one (207). NMR (CCl_4) δ0.33-0.75 (2H, m, cyclopropane), δ0.93 (3H, s, CH_3), δ1.0 (3H, s, CH_3), δ1.32-2.03 (3H, m), δ2.50-2.86 (1H, q*, J = 7 Hz), δ3.42-3.75 (1H, q*, J = 7 Hz), δ 8.50 (1H, bs, NH); IR (CCl_4) 3425, 3210, 3070, 3000, 1662 (s, C=O), 1462 cm^{-1}. IR spectrum (No.1, p. 177).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.57; H, 9.93.

Beckmann rearrangement of (E)-bicyclo [5.1.0] octan-2-one oxime (166): Following the general procedure of the Beckmann rearrangement, from 1.0 g (7.18 mmol) of oxime 166 in 20 mL of anhydrous ether and 2.0 g (9.6 mmol) of PCl_5 in 80 mL of anhydrous ether, after stirring for 1 h at ice-bath temperature and 1 h at room temperature and the usual work-up, was obtained 0.53 g of an oil. Chromatography of the crude product over 15 g of silica gel using $CHCl_3$ as the eluent gave 0.04 g (4%) of the parent ketone (97) as the first fraction (confirmed by

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(*)- The quartet collapsed to a doublet upon addition of D_2O and a trace amount of triethylamine, (cf. NMR spectrum No. 14, p. 176).

IR spectrum). As a second fraction was obtained 0.25 g (25%) of a white solid, which was recrystallized from hexane, mp 89-90°C. This compound was identified as 2-azabicyclo [6.1.0] nonan-3-one (209). NMR (CCl_4) δ 0.33-0.40 (2H, d, cyclopropane, J = 4 Hz), δ 0.83-0.96 (2H, unresolved d), δ 1.10-2.25 (6H, m), δ 2.58-2.90 (2H, m), δ 8.12 (1H, bs, NH); IR (CCl_4) 3417, 3215, 3080, 3000, 2930, 1665 (s, C=O), 1440, 1360, 1350, 1180 cm^{-1}. IR spectrum (No. 2, p. 178).

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 69.26; H, 9.37.

Beckmann rearrangement of (E)-spiro [2.4] heptan-4-one oxime (167): To a suspension of 1.88 g (0.009 mol) of PCl_5 in 70 mL of anhydrous ether was added 1.0 g (0.008 mol) of oxime 167 in 20 mL of anhydrous ether. The reaction mixture was stirred 1 h at ice-bath temperature and 1 h at room temperature. The usual work-up gave 0.40 g of a brown oil which was chromatographed over silica gel. The column was eluted with 25 mL of $CHCl_3$ followed by 50 mL of a mixture of $CHCl_3$-acetone (4:1 (v/v)) and finally with acetone. The first fraction (20 mg; 2%) was identified tentatively as the nitrile 211 based on its spectra. NMR (CCl_4) δ 1.65-2.65 (m), δ 4.12 (2H, m), δ 5.17 (1H, m, vinylic proton), δ 5.36 (1H, m, vinylic proton); IR (CCl_4) 3080, 2945, 2240, 1643, 1435, 1252, 910 cm^{-1}.

As a second fraction was obtained 60 mg of unchanged starting oxime (confirmed by IR, mp). The third fraction (150 mg; 18%) was a white solid material which was recrystallized from a mixture of petroleum ether (bp 30-60°C) and benzene (9:1 (v/v)), mp 129-131°C. NMR (CCl_4) δ 0.53-0.85 (4H, q, cyclopropane, J = 4Hz), δ1.50-2.50 (6H, m), δ8.93 (1H, bs, NH); IR (CCl_4) 3400, 3200, 3080, 1660 (s, C=O), 1400, 1380 cm^{-1}. This compound was identified as 4-azaspiro [2.5] octan-5-one (210).

Anal. Calcd for $C_7H_{11}NO$: C, 67.17; H, 8.86. Found: C, 67.07; H, 9.04.

Beckmann rearrangement of (E)-1,1-dimethyl spiro [2.4]-heptan-4-one oxime (168): The general procedure of the Beckmann rearrangement was followed. From 1.24 g (8 mmol) of oxime 168 in 20 mL of dry ether and 1.88 g (9 mmol) of PCl_5 in 70 mL of dry ether after stirring for 1 h at ice-bath temperature and 1 h at room temperature was obtained 1.10 g of a yellowish amorphous solid material. This material was chromatographed over 40 g of silica gel using $CHCl_3$. As the first fraction an oil was obtained (0.05 g; 4%) which was identified as a mixture of nitriles (cf. p. 89). NMR (CCl_4) δ1.16-2.66 (m), δ1.96 (3H, s, CH_3), δ5.17-5.33 (m); IR (CCl_4) 3090, 3060, 2240,2220,(C≡N), 1660, 890 cm^{-1}. The second fraction was a solid (0.95 g; 76%) which was recrystallized from petroleum ether, mp 112-114°C.

This compound was identified as 1,1-dimethyl-4-azaspiro-[2.5] octan-5-one (216). NMR (CCl_4) δ0.33-0.81 (2H, q, AA'BB', cyclopropane, J = 5.5 Hz), δ1.15 (3H, s, CH_3), δ1.20 (3H, s, CH_3), δ1.66-2.50 (6H, m), δ8.91 (1H, bs, NH); IR (CCl_4) 3420, 3200, 3060, 2940, 1655 (s, C=O), 1460, 1400 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found: C, 70.72; H, 9.95.

Beckmann rearrangement of (E)-6-methyl spiro [2.5]-octan-4-one oxime (169): The general procedure of the Beckmann rearrangement was followed. From 1.0 g (6.5 mmol) of oxime 169 in 20 mL of anhydrous ether and 1.50 g (7.2 mmol) of PCl_5 after stirring for 1 h at ice-bath temperature and 2 h at room temperature followed by the usual work-up was obtained 0.78 g of a viscous oil. IR spectrum and TLC examination of the crude product indicated the presence of some unchanged starting oxime. The crude material was chromatographed on silica gel using a mixture of carbon tetrachloride-acetone (4:1 (v/v)) to obtain 0.13 g (13%) of the unchanged oxime as the first fraction, and 0.50 g (64%) of a white solid material as the second fraction. The solid was recrystallized from hexane, mp 99-101°C (sublimed mp 100-101°C). This compound was identified as 7-methyl-4-azaspiro [2.6] nonan-5-one (226). NMR (CCl_4) δ0.63-0.83 (4H, m, cyclopropane), δ1.07 (3H, d, CH_3, J = 5 Hz), δ1.25-2.16 (5H,

m), δ 2.38-2.53 (2H, d), δ 8.60 (1H, bs, NH); IR (CCl_4) 3400, 3200, 3080, 3000, 1655 (s, C=O), 1450, 1400 cm^{-1}, IR spectrum (No. 4, p. 180).

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.87. Found C, 70.50; H, 9.92.

Beckmann rearrangement of (E)-1,1,6-trimethyl spiro-[2.5] octan-4-one oxime (170): Following the general procedure of the Beckmann rearrangement, from the reaction of 0.90 g (5.0 mmol) of oxime 170 in 40 mL of dry ether and 1.70 g (6.0 mmol) of PCl_5 in 60 mL of dry ether, after stirring for 0.5 h at ice-bath temperature and for an additional 0.5 h at room temperature, was obtained 0.9 g of an oily material. Chromatography of the oil over 30 g of silica gel using ether-hexane (1:2 (v/v)) as eluent gave 0.12 g of unchanged starting oxime as the first fraction. The second fraction was 0.60 g (66%) of a white solid which was recrystallized from hexane, mp 126-127°C. This material was identified as 1,1,7-trimethyl-4-azaspiro-[2.6] nonan-5-one (227). NMR (CCl_4) δ 0.35-0.91 (2H, q, AA'BB' cyclopropane, J = 5.5 Hz), δ 1.04 (3H, d, CH_3, J = 5.5 Hz), δ 1.15 (3H, s, CH_3), δ 1.28 (3H, s, CH_3), δ 1.15-2.33 (7H, m), δ 8.55 (1H, bs, NH); NMR spectrum (No. 10, p. 172). IR (CCl_4) 3390, 3200, 3095, 2900, 1650 (s, C=O), 1420, 1400 cm^{-1}.

Anal. Calcd for $C_{11}H_{19}NO$: C, 72.90; H, 10.56; N, 7.73. Found: C, 72.99; H, 10.66; N, 7.70. Mass spect-

rum m/e 181 (M^+).

Beckmann rearrangement of (E)-spiro [2.6] nonan-4-one oxime (171): The general procedure of the Beckmann rearrangement was followed. To a suspension of 1.50 g (7.2 mmol) of PCl_5 in 50 mL of anhydrous ether was added a solution of 1.02 g (6.6 mmol) of oxime 171 in 20 mL of dry ether. The mixture was stirred for 1 h at ice-bath temperature and 0.5 h at room temperature. The usual work-up gave 0.70 g of a viscous oil. Examination of the crude product by TLC and IR spectroscopy indicated the presence of some unreacted oxime. This material was chromatographed over silica gel using $CHCl_3$-ether (4:1 (v/v)). The unreacted oxime was eluted as the first fraction (0.20 g) and a solid material (0.45 g; 44%) as the second fraction which was recrystallized from hexane, mp 97-99°C. This material was identified as 4-azaspiro [2.7] decan-5-one (228). NMR (CCl_4) δ 0.72-0.86 (4H, q, cyclopropane, J = 2Hz), δ 1.66 (10H, s, unresolved), δ 2.42-2.73 (2H, m), δ 8.53 (1H, bs, NH); NMR spectrum (No. 11, p. 173), IR (CCl_4) 3400, 3200, 3080, 1665 (s, C=O), 1450, 1400, 1020 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO$: C, 70.55; H, 9.97. Found: C, 70.68; H, 10.01.

BIBLIOGRAPHY

1. Beckmann, E., Chem. Ber., 19, 988 (1886).
2. Blatt, A. H., Chem. Rev., 12, 234 (1933).
3. Heldt, W. Z. and Donaruma, L. G., Organic Reactions, 11, 1 (1960).
4. Smith, P. A. S., in " Molecular Rearrangements ", de Mayo, P., Ed., Interscience Publishers, Inc., New York, 1963, Vol. 1, p. 483.
5. Uhlig, F. and Snyder, H. R., Advan. Org. Chem., 1, 35 (1960).
6. McCarthy, C. G., in." The Chemistry of the Carbon-Nitrogen Double Bond " Patai, S., Ed. Interscience Publishers, New York, 1970, Chapter 9.
7. Jones, B., Chem. Rev., 35, 335 (1944).
8. Conley, R. T. and Ghosh, S., in " Mechanisms of Molecular Migrations ", Vol. 4, Thyagarajan, B.S., Ed., Wiley-Interscience, New York, 1971, p. 197.
9. Meisenheimer, J., Chem. Ber., 54, 3206 (1921).
10. Huisgen, R., Witte, J. and Ugi, I., Chem. Ber., 90, 1844 (1966).
11. Rafizadeh, K., M.Sc. Thesis, Concordia University, 1977.
12. Auwers, K. v. and Brink, H., J. Prakt. Chem., 133, 154 (1932).
13. Unterhalt, B., Arch. Pharm. (Weinheim), 300 (9), 748 (1967).

14. Hiemann, J., Thoai, N. and Poksoon, H., Bull. Soc. Chim. Fr., 10, 3920 (1967).

15. Blatt, A. H. and Stone, J. F., J. Amer. Chem. Soc., 53, 4134 (1931).

16. Corbett, R. E. and Davey, C. L., J. Chem. Soc., 296 (1955).

17. Zielinski, W. and Goszeżynski, S., Roscz. Chem., 12, 2061 (1969); Chem. Abstr., 72, 100237n (1970).

18. Horning, E. C., Stromgerg, V. L. and Lloyd, H. A., J. Amer. Chem. Soc., 74, 5153 (1952).

19. Montgomery, R. S. and Dougherty, G., J. Org. Chem., 17, 832 (1952).

20. Sato, T., Wakatsuka, H. and Amano, K., Tetrahedron, 27, 5381 (1971).

21. Fleming, I. and Woodward, R. B., J. Chem. Soc., Perkin Trans, 1, 1653 (1973).

22. Grob, C. A. and Wenk, P., Tetrahedron Lett., 4195 (1976).

23. Alper, H. and Keung, E. C. H., J. Heterocyclic Chem., 10, 637 (1973).

24. Tencza, T. M., Ph.D. Dissertation, Seton Hall Univ., 1966; See ref. 8, p. 152.

25. Roberts, J. D. and Chambers, V. C., J. Amer. Chem. Soc., 73, 3176 (1951).

26. Emmons, W. D., J. Amer. Chem. Soc., 79, 6522 (1957).

27. Hart, H. and Curtis, O. E., J. Amer. Chem. Soc., 78, 112 (1956).

28. Hirata, Y., Nagoya Kogyo Daigaku Gakuho, 13, 60 (1961); Chem. Abstr., 62, 9025a.

29. Burrows, W. D. and Eastman, R. H., J. Amer. Chem. Soc., 79, 3756 (1957).

30. Zabza, A., Wawrzenczyk, C. and Kuczynski, H., Bull. Acad. Pol. Sci., Ser. Sci. Chim., 20 (6), 521 (1972); Lustig, E., J. Phys. Chem., 65, 491 (1961).

31. Julia, S., Julia, M. and Linstrumellé, G., Bull. Soc. Chim. Fr., 11, 3499 (1966); cf. Chem. Abstr., 66, 85867y.

32. Norin, T., Acta Chem. Scand., 15, 1676 (1961).

33. Erdtman, H. and Thoren, S., Acta Chem. Scand., 24, 87 (1970).

34. Hill, R. K. and Conley, R. T., Chem. & Ind (London), 1314 (1956).

35. Hill, R. K. and Conley, R. T., J. Amer. Chem. Soc., 82, 645 (1960).

36. Lukes, R. and Hofman, J., Collection Czechoslov. Chem. Communs., 26, 523 (1961); cf. Chem. Abstr., 55, 1536g.

37. Streitwieser, A. Jr., and Heathcock, C. H., " Organic Chemistry ", Macmillan Publishing Co., Inc., New York (1976), Chapter 23.

38. Padwa, A., Acc. Chem. Res., 4, 48 (1971).

39. Gensler, W. J., Floyd, M. B., Yanase, R. and Pober, K. W., J. Amer. Chem. Soc., 92, 2472 (1970).

40. Teotino, U. M., Della Bella, D., Gandini, A. and Benelli, G., J. Med. Chem., 10 (6), 1091 (1967).

41. Fridman, A. L., Zalesov, V. S., Dolbikin, K. V., Konshina, O. L. and Sivkova, M. P., Khim. Farm. Zh. (Pharm. Chem. J.) 12 (2), 88 (1978).

42. Cromwell, N. H. and Graff, M. A., J. Org. Chem., 17, 414 (1952).

43. Dauben, W. G., Shaffer, G. W. and Deviny, E. J., J. Amer. Chem. Soc., 92, 6273 (1970).

44. Dauben, W. G. and Berezin, G. H., J. Amer. Chem. Soc., 89, 3449 (1967).

45. Breslow, R., in " Molecular Rearrangements ", de Mayo, P., Ed., Interscience Publishers, Inc., New York, 1963, Vol. 1, Chapter 4.

46. Ferguson, L. N., " Highlights of Alicyclic Chemistry", Franklin Publishing Co. Inc., 1973, pt. 1, p. 210.

47. Parker, R, and Issacs, N., Chem. Rev., 59, 737(1959).

48. Goldish, E., J. Chem. Educ., 36, 408 (1959).

49. Berneff, W. A., J. Chem. Educ., 44, 17 (1967).

50. Weigert, F. J. and Roberts, J. D., J. Amer. Chem. Soc., 89, 5962 (1967).

51. Lacker, J. R., Pollock, J. W. and Park, J. D., J.

Chem. Phys., 20, 1047 (1952).

52. Joris, L., Schleyer, P. v. R. and Gleiter, R., J. Amer. Chem. Soc., 90, 327 (1968).

53. Strait, L. A., Ketchum, R., Jambotkar , D. and Shah, V. P., J. Amer. Chem. Soc., 86, 4682 (1964).

54. Walsh, A. D., Trans. Faraday Soc., 45, 179 (1949).

55. Coulson, C. A. and Moffitt, W., Phil. Mag., 40, 1 (1949).

56. Eastman, R. H., J. Amer. Chem. Soc., 76, 4115, 4118 (1954).

57. Kosower, E. M. and Ito, M., Proc. Chem. Soc., 25 (1962).

58. Shono, T., Morikawa, T., Oku, A. and Oda, R., Tetrahedron Lett. 791 (1964).

59. Marr, D. H. and Stothers, J. B., Can. J. Chem., 45, 225 (1967).

60. Heathcock, C. H. and Poulter, S. R., J. Amer. Chem. Soc., 90, 3766 (1968).

61. Jorgenson, M. J. and Leung, T., J. Amer. Chem. Soc., 90, 3769 (1968).

62. Deno, N. C. and Lincoln, D. N., J. Amer. Chem. Soc., 88, 5357 (1966); Gordon, A. J., J. Chem. Educ., 44, 461 (1967).

63. Eastman, R. H. and Freeman, S. K., J. Amer. Chem. Soc., 77, 6642 (1955).

64. Deno, N. C., Proger. Phys. Org. Chem., 2, 129(1964); Depuy, C. H. and Marshall, J. L., J. Org. Chem., 33, 3326 (1968).

65. Conant, J. B. and Tuttle, N., Org. Synth., Coll. Vol.1, John Wiley & Sons, Inc., New York,1941, pp.199,345.

66. Hill, G. A. and Bramann, G. M., Org. Synth., Coll. Vol. 1, John Wiley & Sons, Inc., New York, 1941, p. 81.

67. Warnhoff, E. W., Martin, D. G. and Johnson, W. S., Org. Synth., Coll. Vol. 4, John Wiley & Sons, Inc. New-York, 1963, p. 162.

68. Horning, E. C., Denekas, M. O. and Field, R. E., Org.-Synth., Coll. Vol. 3, John Wiley and Sons, Inc., New-York, 1955, p. 317.

69. Shriner, R. L. and Todd, H. R., Org. Synth., Coll.Vol. 2, John Wiley & Sons, Inc., New York, 1943, p. 200.

70. Gannon, W. F. and House, H. O., Org. Synth., Coll. Vol. 5, John Wiley & Sons, Inc., New York, 1973, pp.294,539.

71. Engelhart, J. E. and McDivitt, J. R., J. Org. Chem., 36(2), 367 (1971).

72. Frank, L. R. and Hall, H. K., Jr., J. Amer. Chem. Soc., 72, 1645 (1950).

73. Simmons, H. E., Cairns, T. L., Vladuchick, S. A. and Hoiness, C. M., Org. Reactions, 20, 1 (1973).

74. Dauben, W. G. and Berezin, G. H., J. Amer. Chem. Soc., 85, 468 (1963).

75. Chan, J. H. H. and Rickborn, B., J. Amer. Chem. Soc., 90, 6406 (1968).

76. Corey, E. J. and Chaykovsky, M., J. Amer. Chem. Soc., 87, 1353 (1965).

77. Mayer, R. T. and Hess, H. J., J. Org. Chem., 23, 1563 (1958).

78. Kuhn, R. and Trischmann, H., Ann., 611, 117 (1958).

79. Buchanan, G. L., Raphael, R. A. and Taylor, R., J. Chem. Soc. Perkin Trans.1, 373 (1973).

80. Trost, B. M. and Mervin, L. S., Jr., " Sulfur Ylides", Academic Press, New York, 1975.

81. Johnson, A. W., " Ylid Chemistry ", Academic Press, New York and London 1966, Chapter 9, p. 304.

82. Johnson, C. R. and Rogers, P. E., J. Org. Chem., 38, 1793 (1973).

83. Roberts R. M., Landolt, R. G., Greene, R. N. and Heyer, E. W., J. Amer. Chem. Soc., 89, 1404 (1967).

84. Corey, E. J. and Chaykovsky, M., J. Amer. Chem. Soc., 84, 867 (1962).

85. Dauben, W. G. and Wolf, R. E., J. Org. Chem. 35, 374 (1970).

86. Agami, C. and Aubouet, J., Bull. Soc. Chim. Fr (5), 1391 (1967).

87. Agami, C., C. R. Acad. Sci., Ser. C., 264, 1128 (1967).

88. Johnson, C. R. and Schroeck, C. W., J. Amer. Chem. Soc., 95, 7418 (1973).

89. Johnson, C. R., Haake, M. and Schroeck, C. W., J. Amer. Chem. Soc., 92, 6594 (1970).

90. Merz, A. and Markl, G. Angew Chem.,85, 867 (1973).

91. Rocquet, F. and Sevin, A., Bull. Soc. Chim. Fr., 888, 895 (1974).

92. Kaiser, C., Trost, B. M., Beeson, J. and Weinstock, J., J. Amer. Chem. Soc., 80, 3972 (1965); Hönig, H., Metzger, H. and Seelert, K., Chem. Ber., 98, 3712, 3724 (1966).

93. Agami, C., Bull. Soc. Chim., 7, 2299 (1967).

94. Gassman, P. G. and Atkins, T. J., J. Amer. Chem. Soc., 94, 7748 (1972).

95. Paquette, L. A., Wilson, S. E., Henzel, R. P. and Allen, G. R., Jr., J. Amer. Chem. Soc., 94, 7761 (1972).

96. Rocquet, F., Sevin, A. and Chodkiewicz, W., Tetrahedron Lett., 1049 (1971); Narayanaswamy, M., Sathe, V.-M. and Rao, A. S., Chem. and Ind., 921 (1969).

97. Padwa, A. and Battisti, A., J. Amer. Chem. Soc., 94, 521 (1972).

98. Guillaud, P., Pierre, J-L., and Arnaud, P., Ann. Chim., 6, 275 (1971).

99. Leriverend, P. and Conia, J. M., Bull. Soc. Chim. Fr., 116,121 (1966).

100. Crandal, J. K. and Seidewand, R. J., J. Org. Chem., 35, 697 (1970); J. Amer. Chem. Soc., 92, 4349 (1970).

101. Fieser, L. F., "Experiments in Organic Chemistry", 3rd. ed., D. C. Heath and Co., Boston, 1957, p 103.

102. Shriner, R. L., Fuson, R. C. and Curtin, D. Y., "The Systematic Identification of Organic Compounds", 4th E., John Wiley and Sons, Inc., New York, 1957, p. 254.

103. Suginome, H. and Yagihashi, F., J. Chem. Soc. Perkin I, 2488 (1977).

104. Suginome, H. and Takahashi, H., Tetrahedron Lett., 5119 (1970); Bull. Chem. Soc. Jpn., 48, 582 (1975).

105. Suginome, H. Takeda, H. and Masamune, T., Bull. Chem. Soc. Jpn., 52, 269 (1979).

106. Pellacani, L., Tardella, P. A. and Loreto, M. A., J. Org. Chem., 41, 1282 (1976).

107. Tardella, P. A., Pellacani, L. and Distazio, G., Gazz. Chim. Ital., 102, 822 (1976).

108. Bello, N. D., Pellacani, L., and Tardella, P. A., Synthesis, 227 (1978).

109. Karabatsos, G. J., Taller, R. A. and Vane, F. M., J. Amer. Chem. Soc., 58, 2326 (1963).

110. Grob, C. A., and Ide, J., Helv. Chim. Acta, 57, 2562 (1974).

111. Mayer, R. and Schubert, H. J., Chem. Ber., 91, 768 (1958).

112. Jackman, L. M. and Sternhell, S., "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd.ed., Pergamon Press, New York, N.-Y. 1969, p. 226.

113. Kenyon, J. and Young, D. P., J. Chem. Soc.,263(1941).

114. Campbell, A. and Kenyon, J., ibid, 25 (1946).

115. Grob, C. A. and Wenk, P., Tetrahedron Lett., 4191 (1976); Grob, C. A. and Wenk, P., ibid, 4195 (1976).

116. Fikes, L. E. and Shechter, H., J. Org. Chem., 44, 741 (1979).

117. Rhodes, Y. E. and Takno, T., J. Amer. Chem. Soc., 92, 5270 (1970).

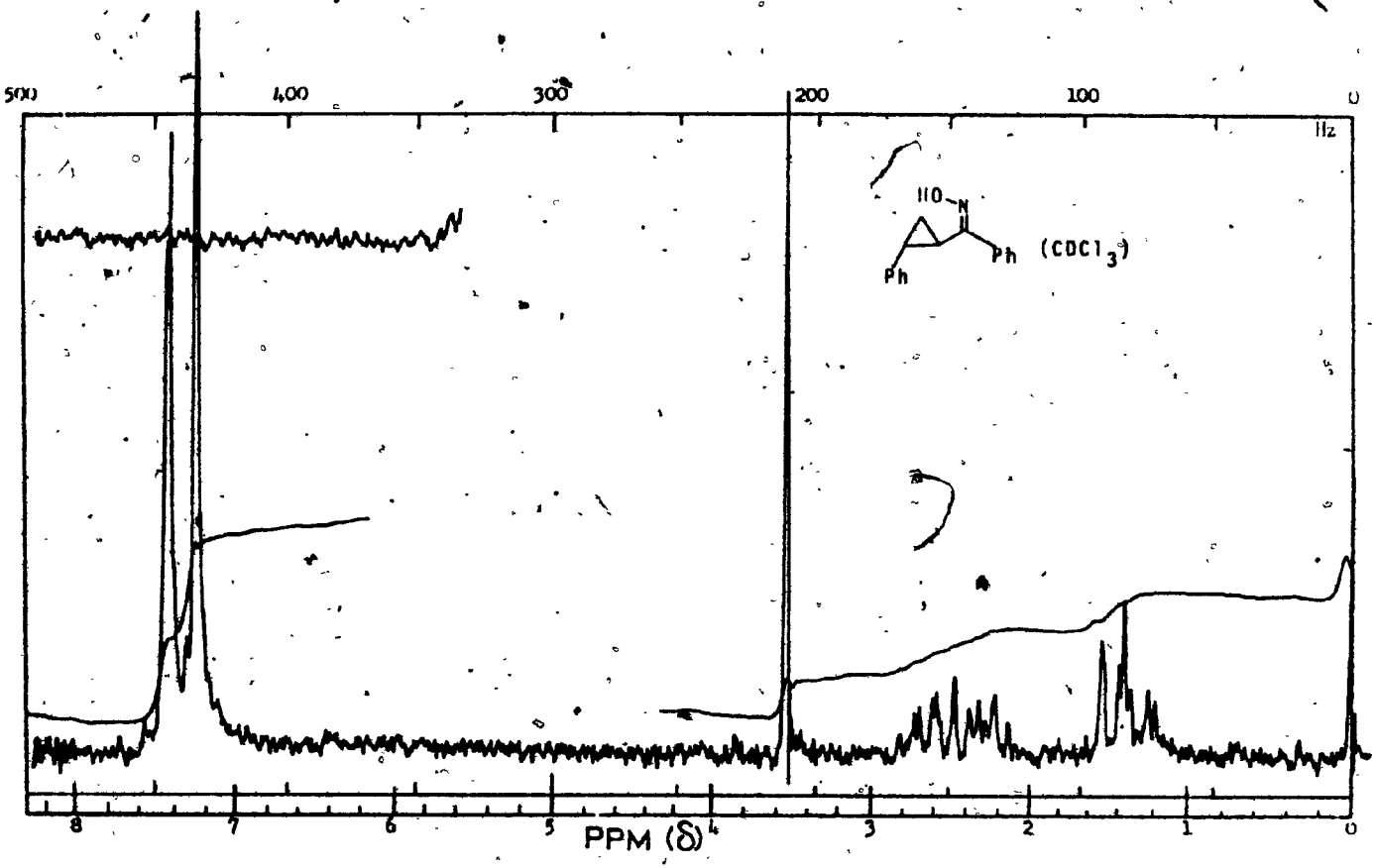
118. Dauben, W. G. and Wolf, R. E., J. Org. Chem., 35, 2361 (1970).

119. Loev, B., and Goodman, M. M., Intra-Science Chemistry Reports, 4, 283 (1970).

120. Fieser, L. F. and Fieser, M., "Reagents for Organic Synthesis", Vol. 1, John Wiley & Sons, Inc., New York, N. Y. 1967, p. 315.

121. Kaiser, C., Trost, B. M., Beeson, J. and Weinstock, J., J. Org. Chem., 30, 3972 (1965).

APPENDIX



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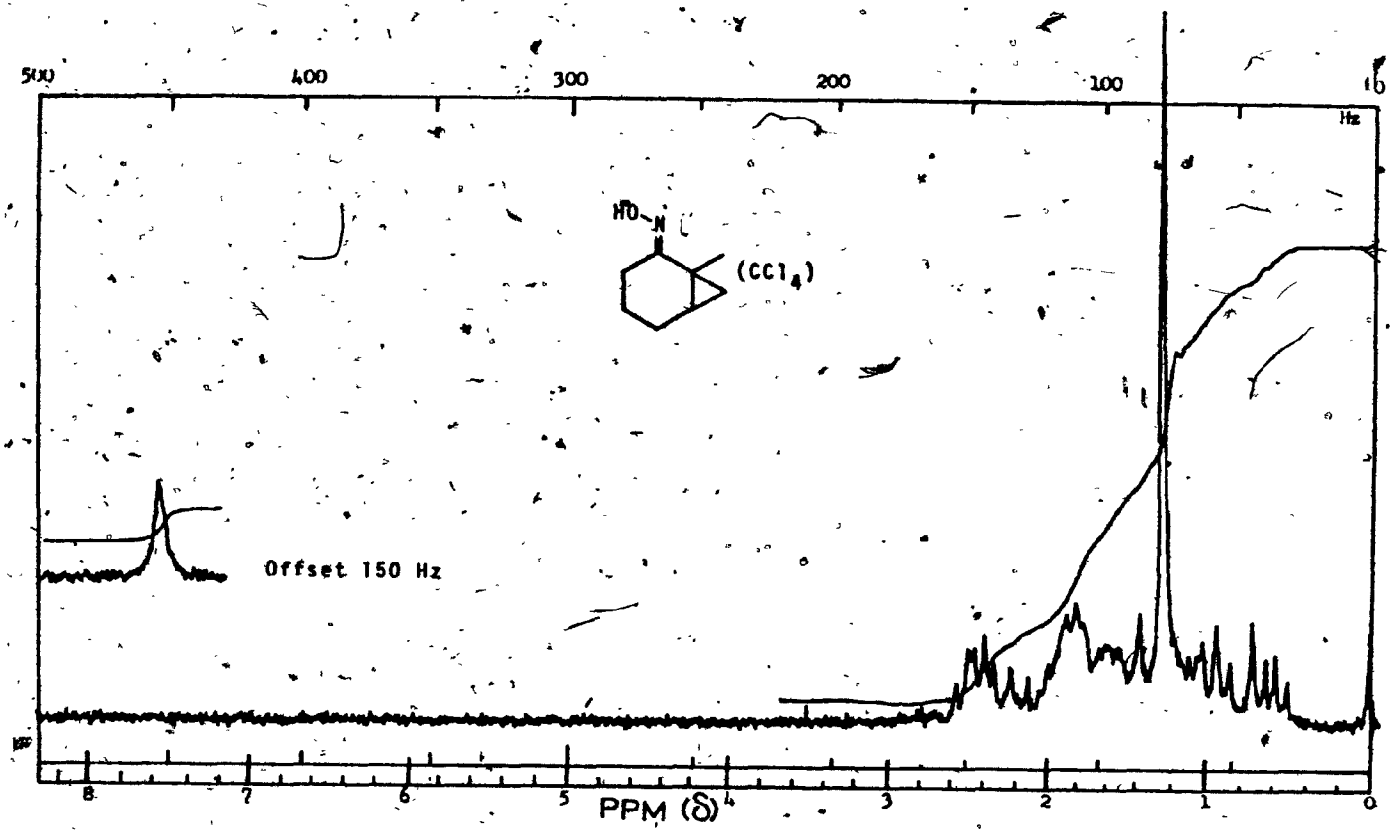

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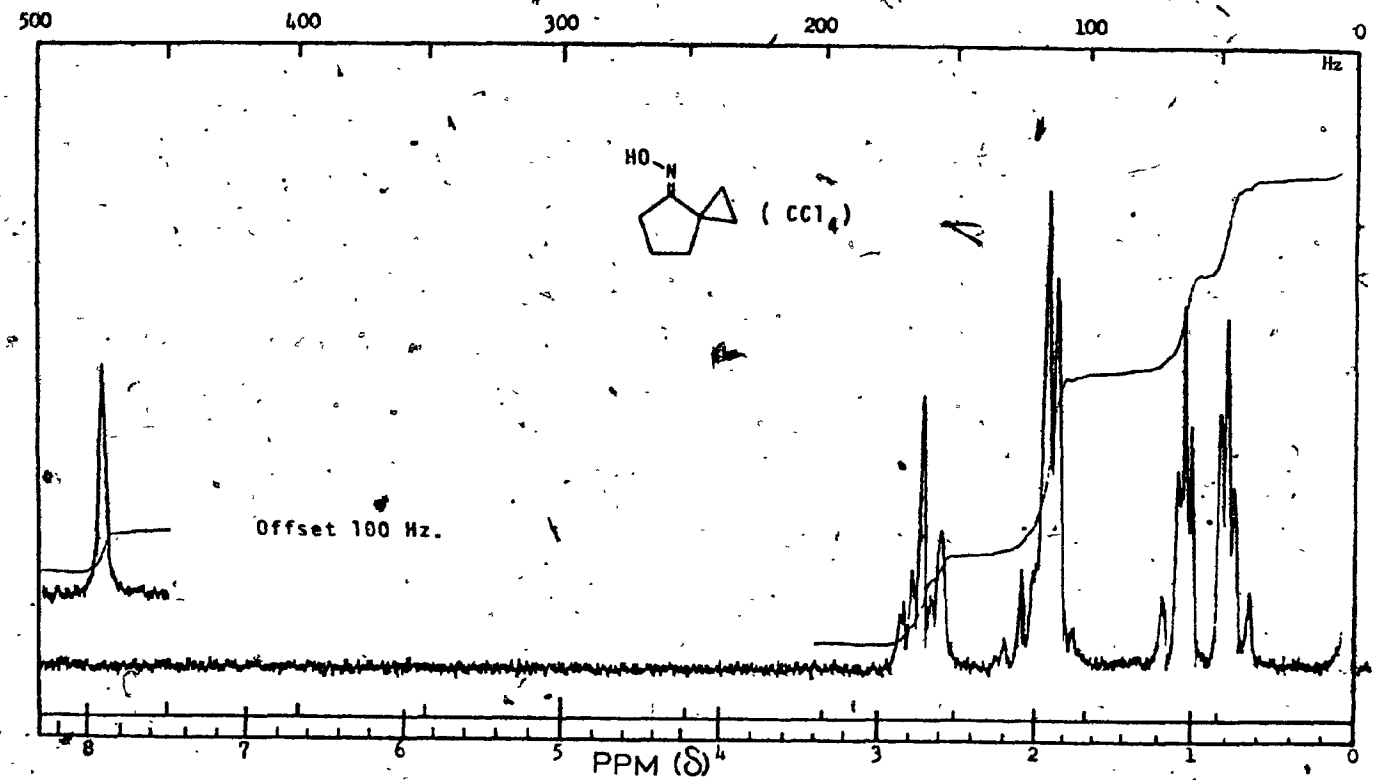

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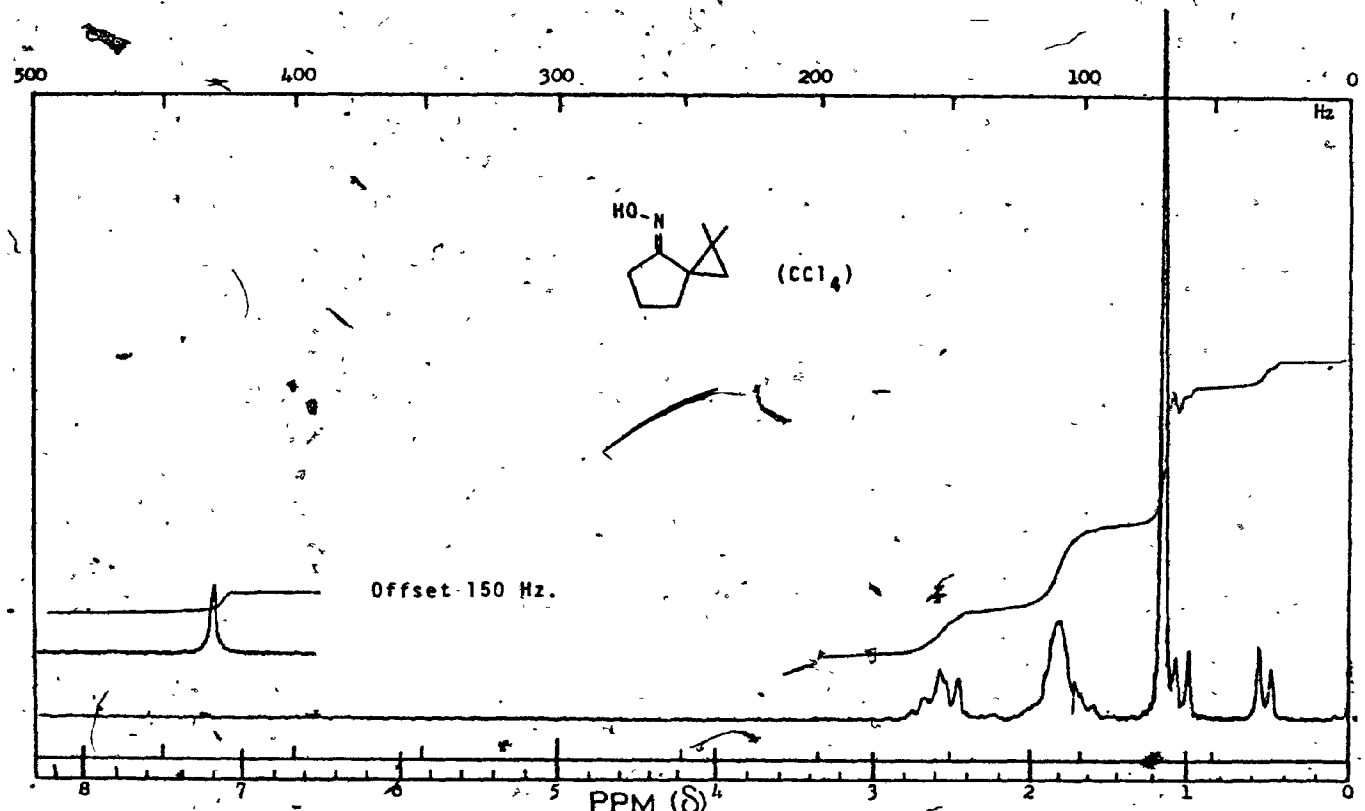

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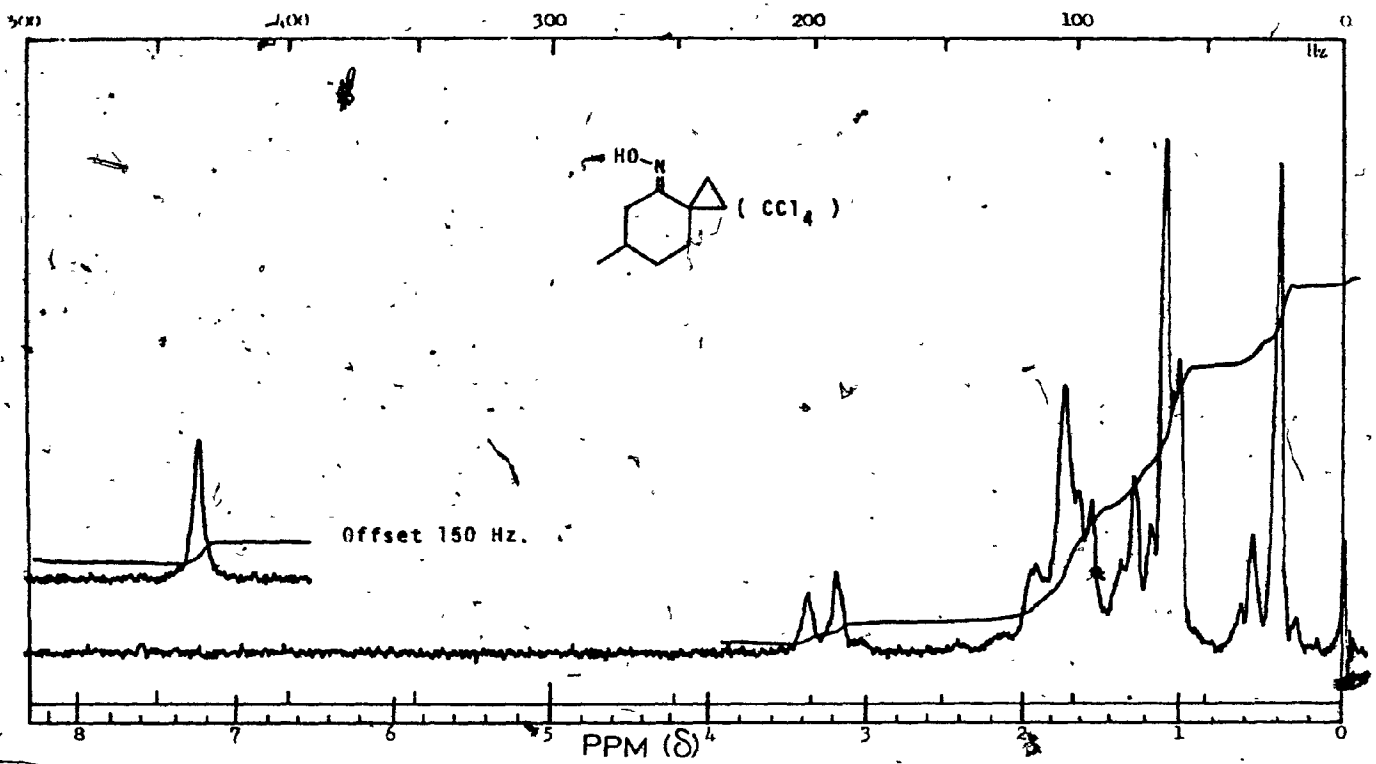

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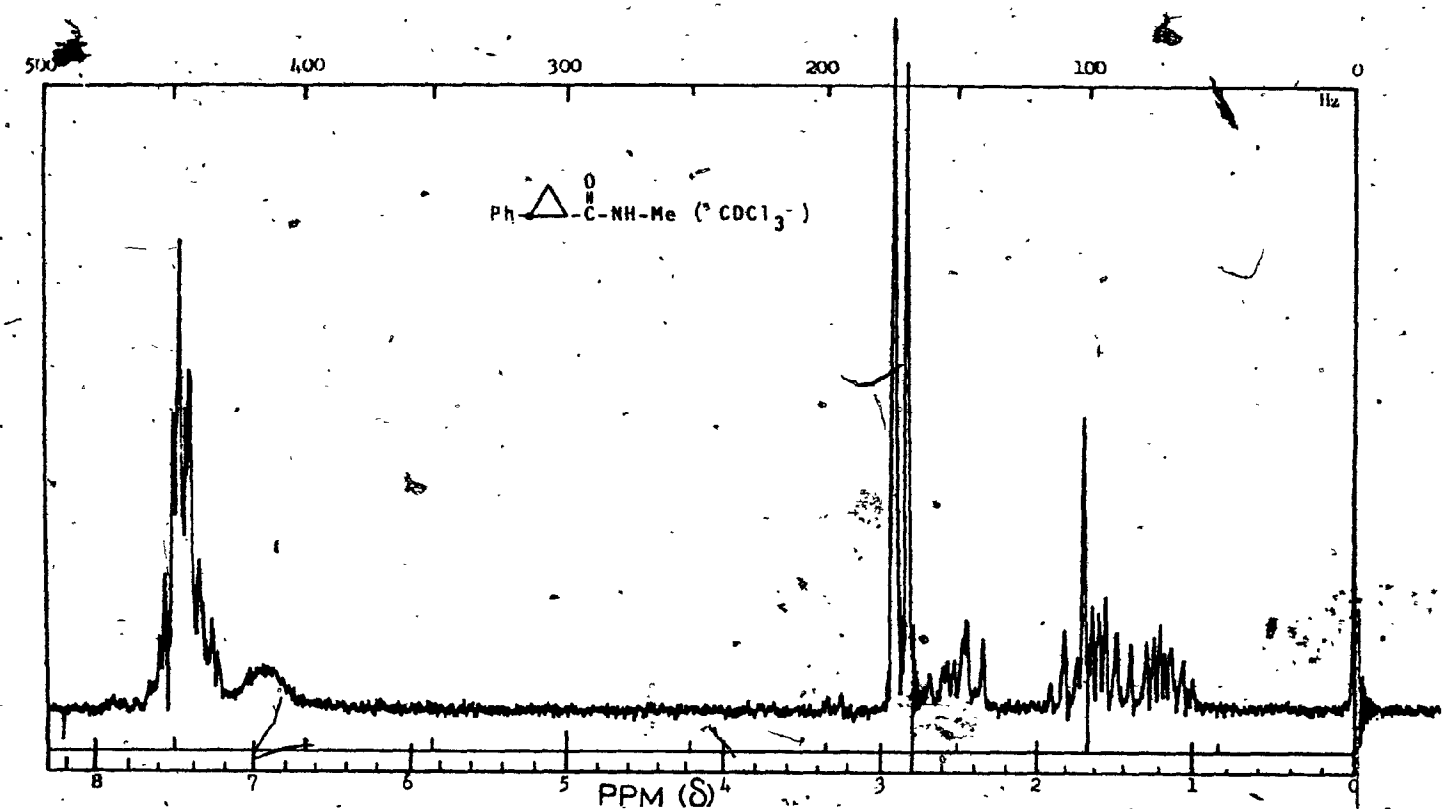

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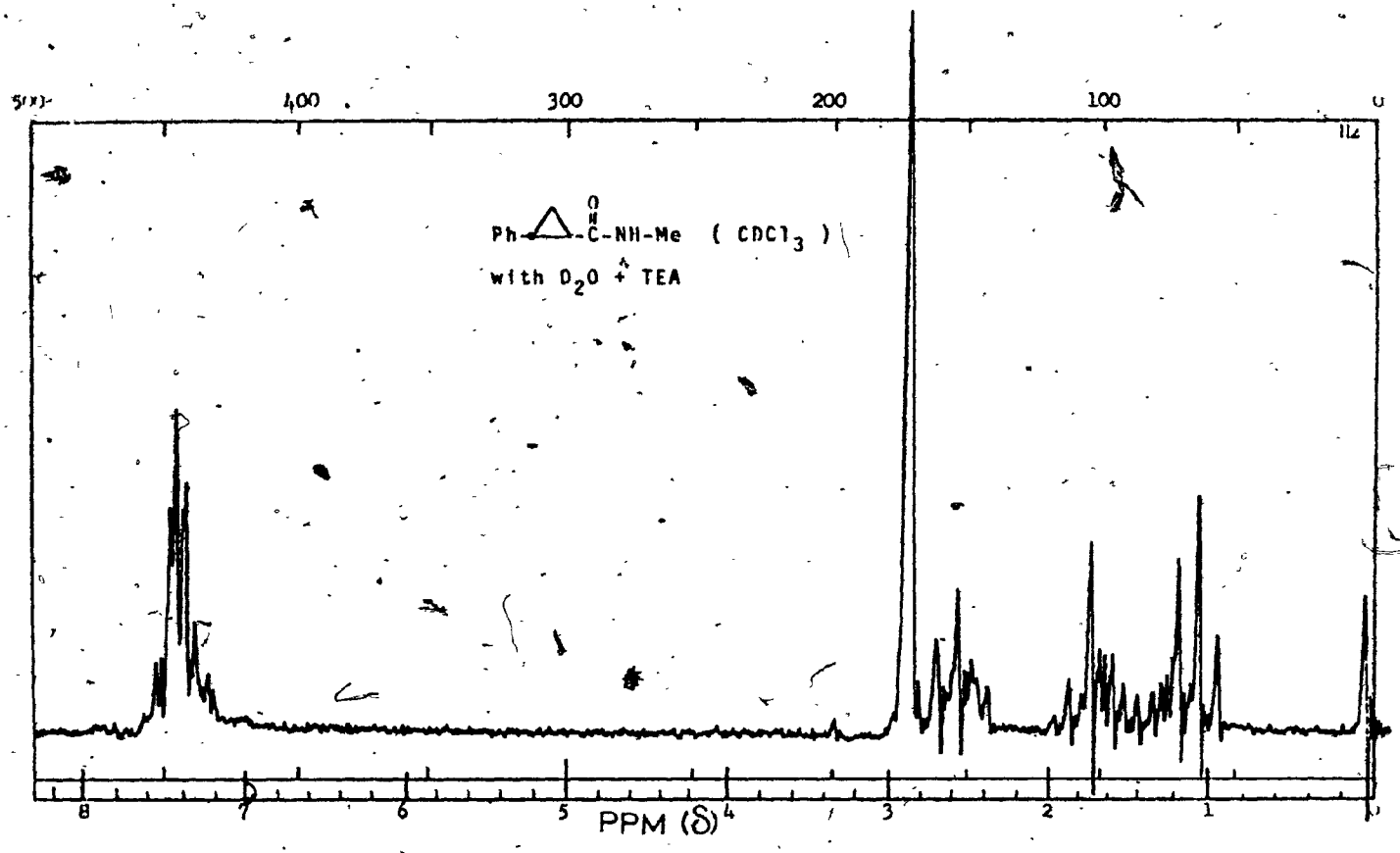

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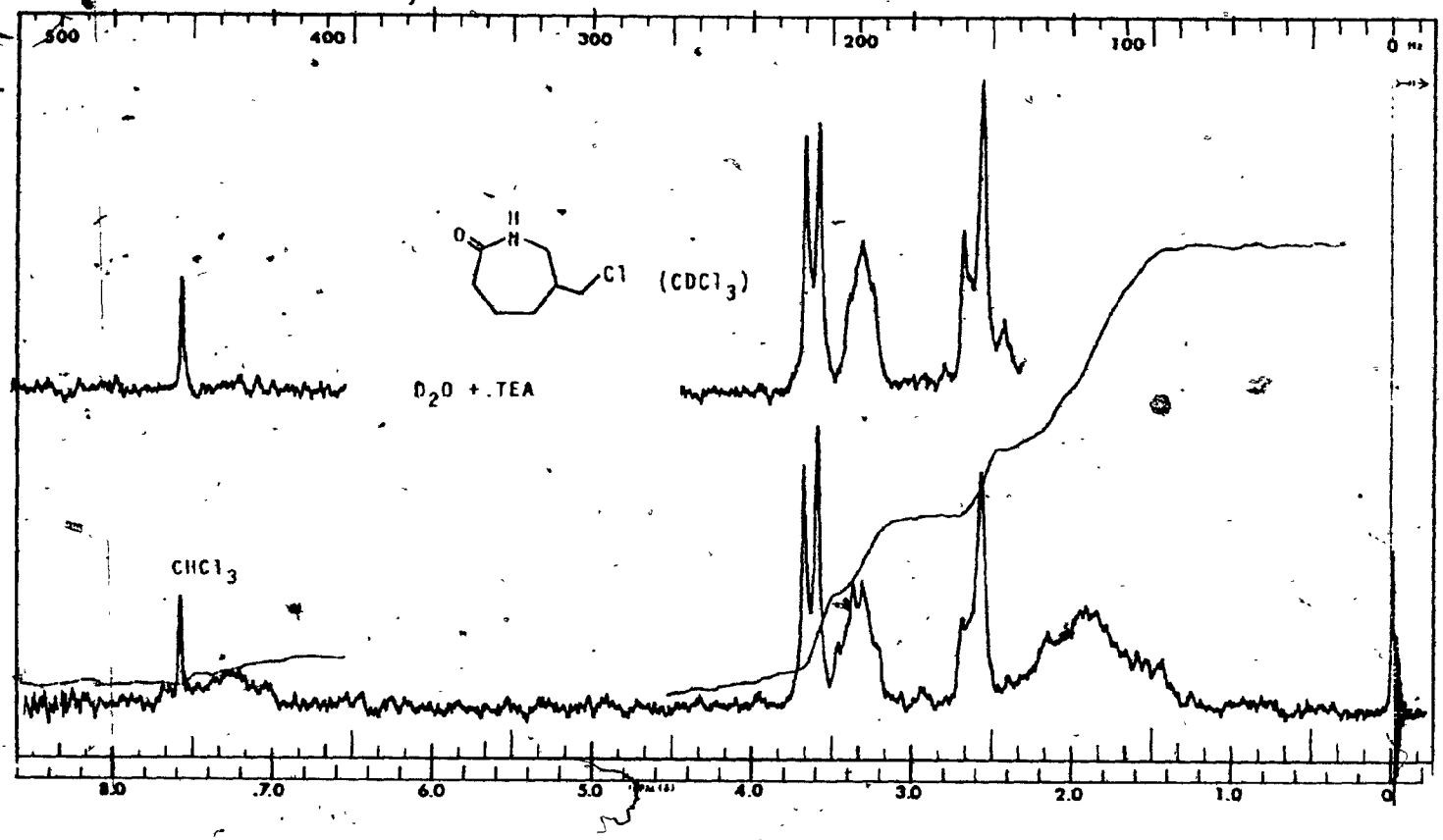

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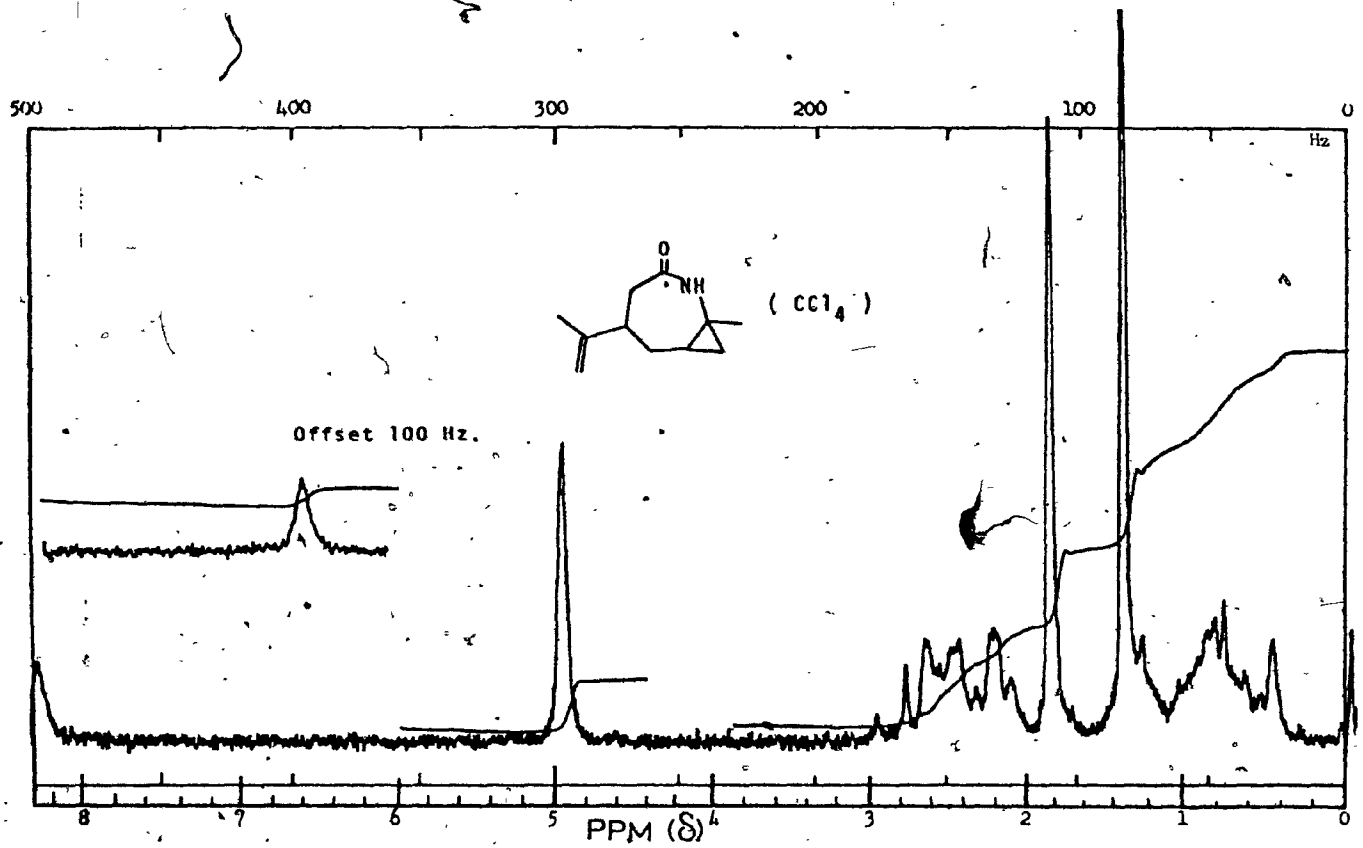

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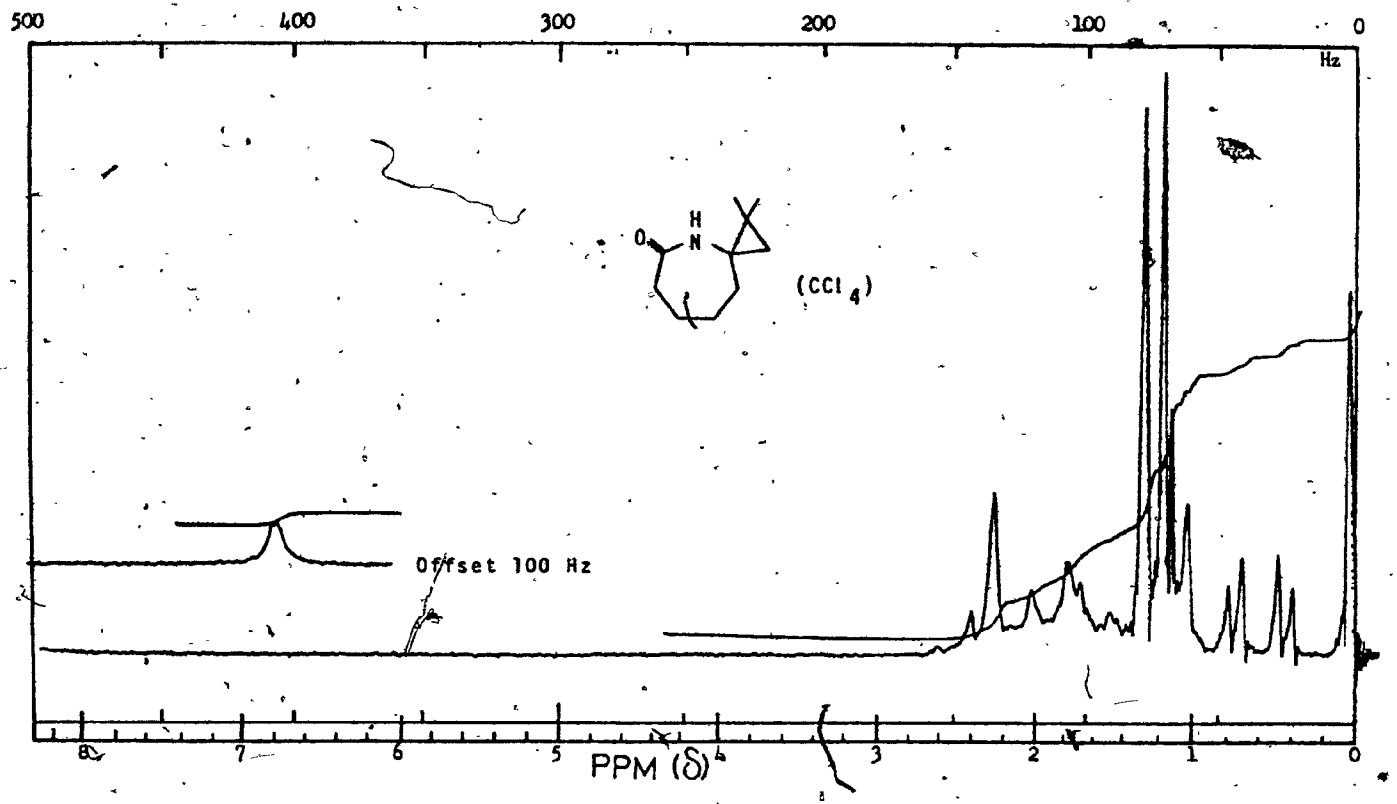

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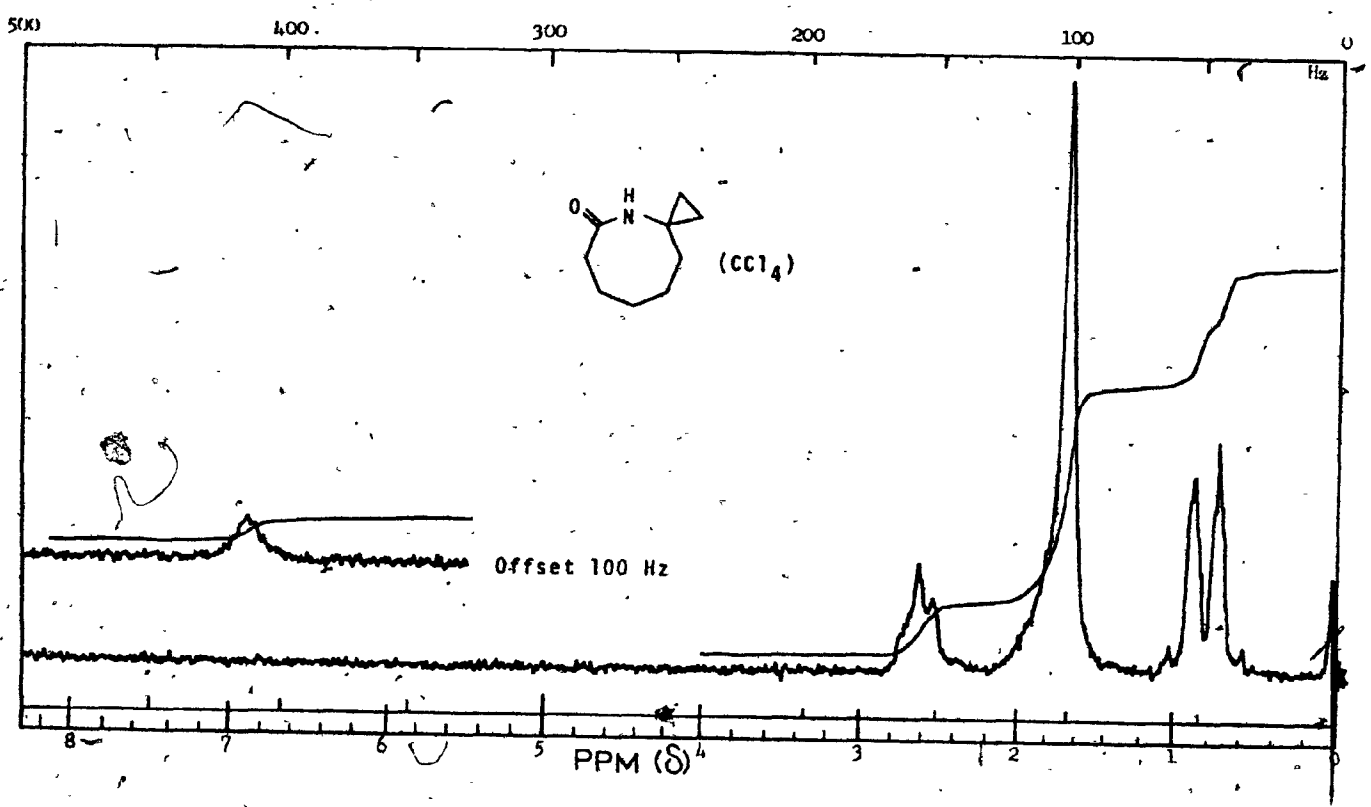

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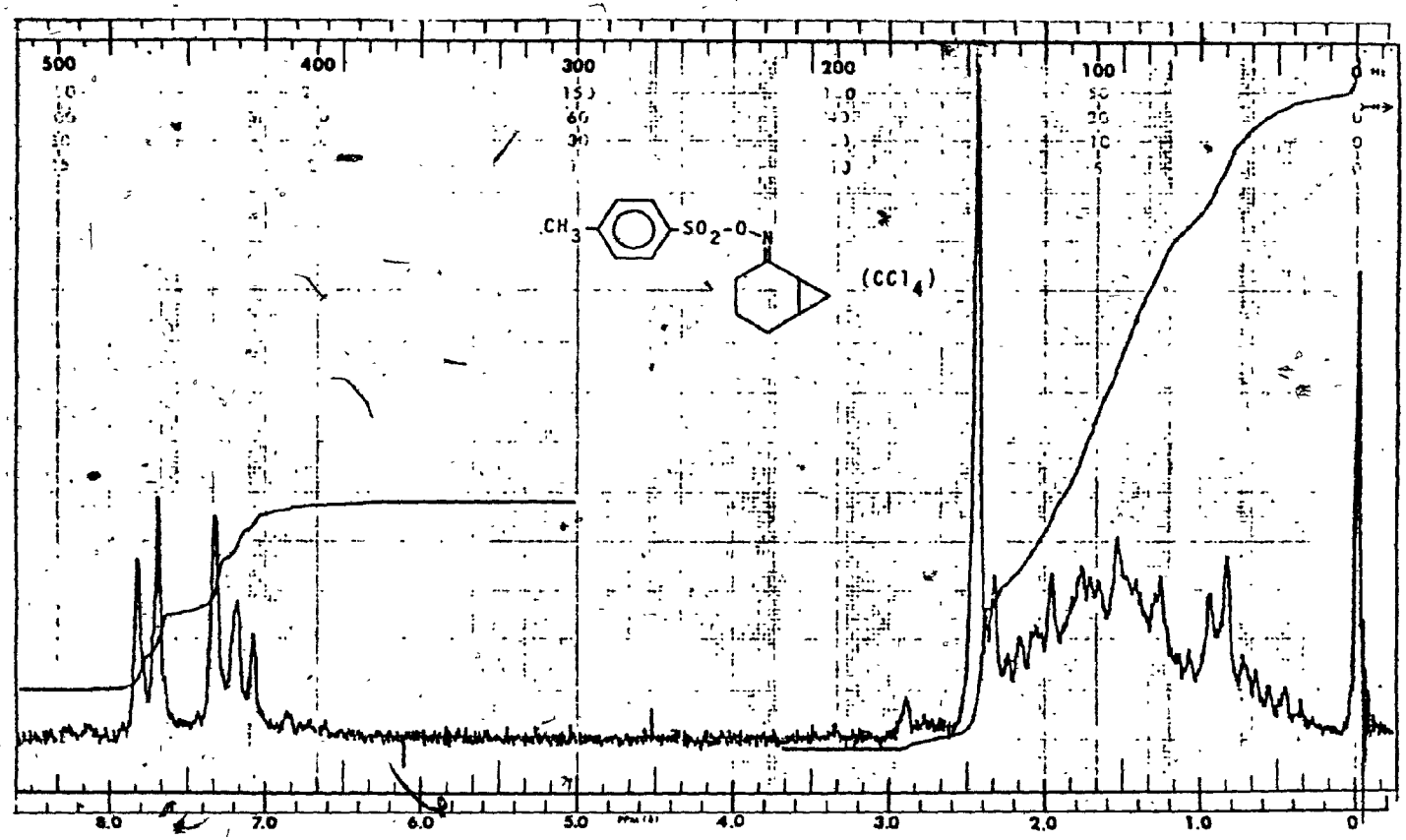

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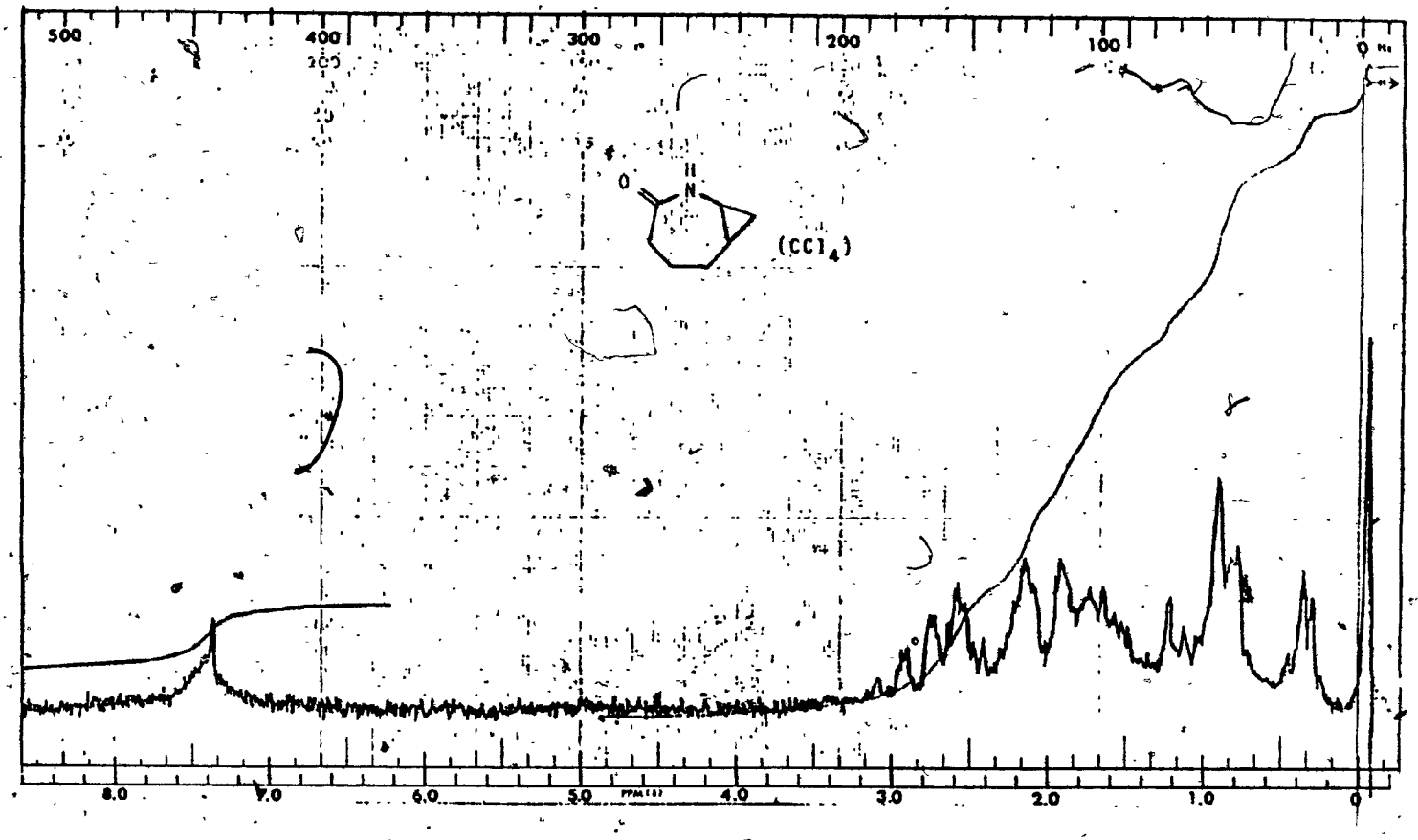

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