OXADIAZOLINES AND AZOMETHINE IMINE YLIDS

SYNTHETIC AND MECHANISTIC STUDIES

RELATED TO

OXADIAZOLINES AND AZOMETHINE IMINE YLIDS

By

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ABSTRACT

Several new oxadiazolines have been synthesized by the cyclization of mixed carbohydrazones derived from aromatic aldehydes and aliphatic ketones. A mechanism for the cyclization is discussed on the basis of the regiospecificity observed in these reactions. Pyrolysis of these oxadiazolines led to the synthesis of a number of azomethine imine ylids, which could not be made by the only other existing route. The mechanism of this pyrolytic process was investigated by trapping experiments and spectroscopic methods and the intermediacy of an N-isocyanatoimine was established. Structures of the products formed by the trapping experiments were also determined.

ACKNOWLEDGEMENTS

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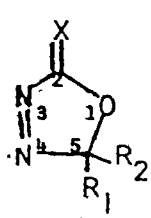
INTRODUCTION

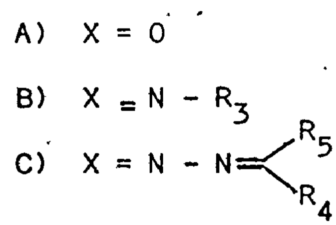
GENERAL

Synthesis and characterization of cyclic azo compounds constitutes an important part of heterocyclic chemistry. They are relatively unstable due to the cis-azo function, and can readily lose nitrogen by thermal or photochemical processes. This can lead to a variety of new products, depending on the structure of the starting azo compound. A large number of cyclic azo compounds is reported in the literature.[1] The azocarbonyl system is a recent addition to this family, but its chemistry has not been investigated in detail.

Oxidative cyclization of semicarbazones and carbohydrazones of ketones leads to the Δ^3 - 1,3,4, - oxadiazoline system (I) with a five membered ring skeleton and a cis-azo function. Apart from the azo group, there is an oxygen atom in the ring flanked by



(I)

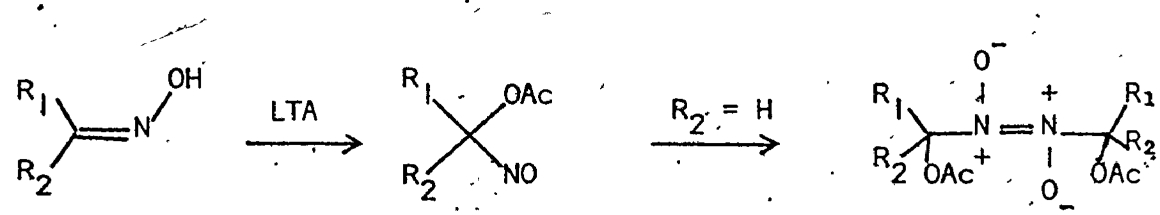


different substituents at the 2- and 5- positions. R_1 and R_2 are normally alkyl groups. But, if either of them is a hydrogen, the system is known to isomerize to the more stable oxadiazole. X can be varied in three different ways [I(a), I(b) and I(c)] as shown above. Oxidative cyclization of semicarbazones by lead tetraacetate yields I(b) which can be hydrolyzed to I(a). Carbohydrazones of carbonyl compounds can be cyclized to I(c) in a similar fashion.

OXIDATIVE CYCLIZATION

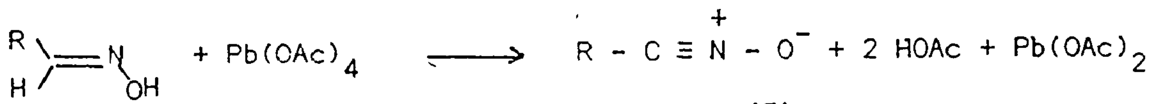
Although attempts have been made to use reagents like potassium permanganate[2] and manganese dioxide for the oxidative cyclization of organic substrates, lead tetraacetate is the most widely used reagent for this purpose. It is a very versatile reagent and its synthetic utility has been reviewed comprehensively[3,4]. Among the many nitrogenous organic compounds oxidized by LTA are included oximes, hydrazones and semicarbazones.

Oximes: The reaction of LTA with oximes generally leads to a range of products depending on the nature of the oxime, ratio of the reagent to the substrate, temperature and the medium. The reactions are characterized by the direct detection of the intermediates in many cases. The main products of oxidation of ketoximes (2) are the gem-nitrosoacetates (3) and the parent ketones[5]. Nitrosoacetate dimers (4) are obtained from aliphatic aldoximes. At



(2) (3) (4)

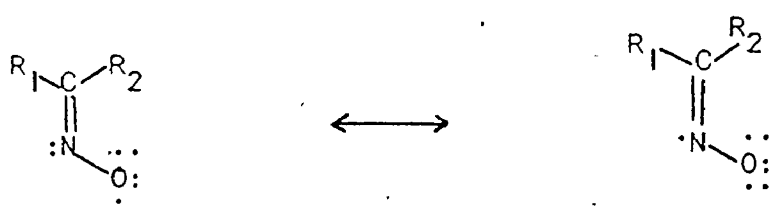
low temperatures, all syn- aldoximes yield nitrile oxides (5) under similar conditions[6].



syn

(5)

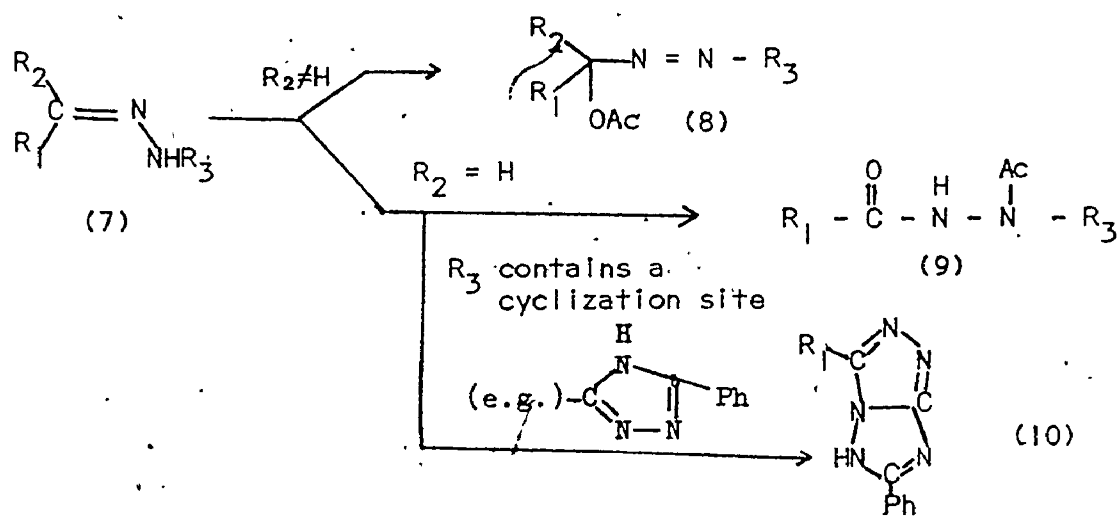
Various radical species have been identified by ESR spectroscopy as intermediates in the LTA- oxime system, the main one being the iminoxy radical (6)[4]. A free radical mechanism was proposed in order to account for these intermediates. This mechanism



(6)

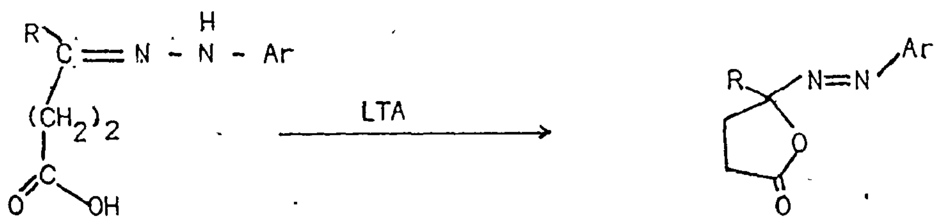
involves the abstraction of the OH hydrogen from the oxime by the acetoxy radical followed by further attack by a second acetoxy radical leading to a nitrosoacetate[7].

<u>Hydrazones</u>: In general, the oxidation of substituted hydrazones follows the scheme outlined below:

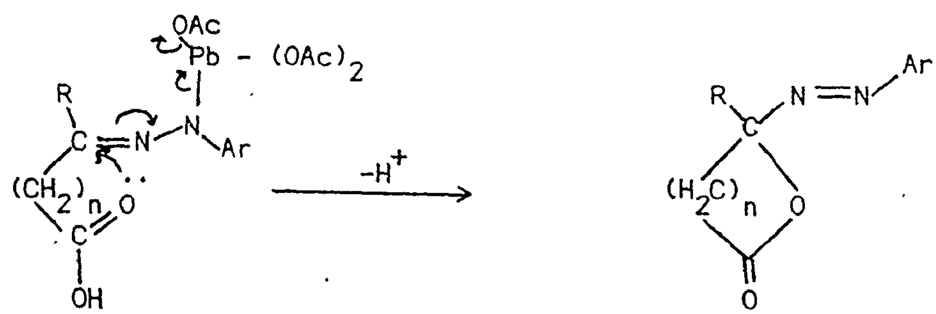


Ketohydrazones yield azoacetates (8) whereas, aldehyde hydrazones form acylhydrazines (9). Originally, a free radical mechanism was proposed [8, 9, 10] for the reaction of LTA with ketohydrazones. Although, ESR studies detected free radicals during the oxidation of oximes, there is no evidence for such intermediates in the oxidation of hydrazones[11]. The rates of these reactions were found to be more rapid in polar solvents suggesting a polar mechanism.

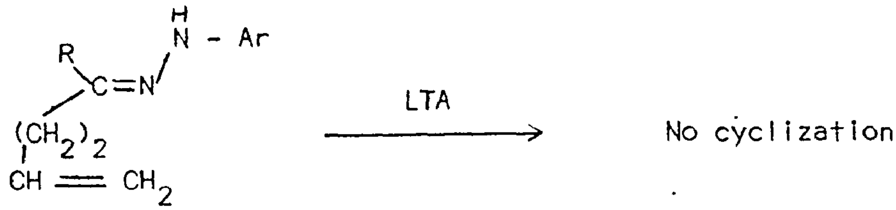
Oxidation of ketohydrazones having a suitable cyclization site in the ketone substituents at the fourth or fifth atom from the methine carbon leads to a cyclic product[12]. However, due to a competing reaction, small amounts of azoacetates are formed as byproducts. A probable mechanism for this cyclization is a nucleophilic



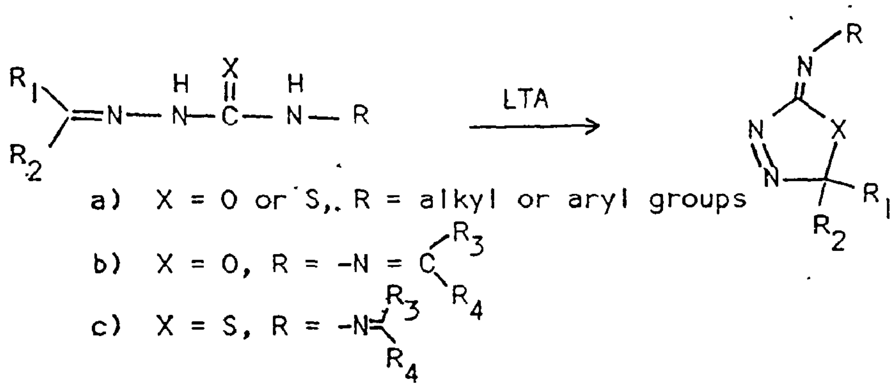
attack by the carbonyl oxygen on the sp^2 carbon. The fact that the cyclization does not occur when the carboxyl group is replaced by a



carbon-carbon double bond rules out the possibility of an electrophilic attack of a carbonium ion resulting from the loss of $Pb(O\bar{A}c)_3$ on the Π bond.

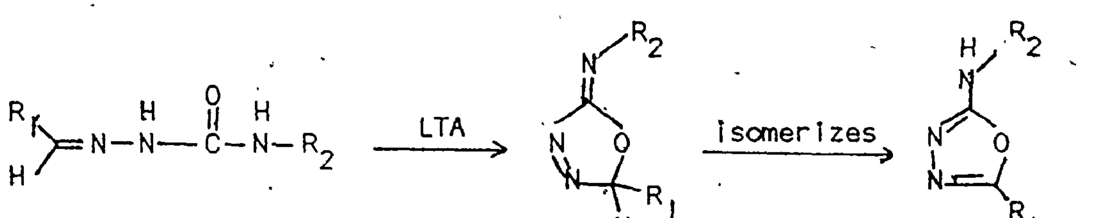


Semicarbazones: LTA oxidation of substituted ketone semicarbazones and thiosemicarbazones results in cyclization through oxygen or sulfur leading to the respective oxa- or thiadiazoline[13]. In the case of carbohydrazones [(b) and (c) below], the cyclization was



found to be highly regiospecific. In all the unsymmetrical carbohydrazones studied so far with alkyl groups at one end and aryl groups at the other end, cyclization occurred preferentially at the methine carbon bearing the aliphatic substituents.

Cyclization of aldehyde semicarbazones leads to the cyclic



(II)

azine (oxadiazole) system (II) due to the isomerization of the initial product.

SYNTHETIC USES OF OXIDATIVE CYCLIZATION

Oxidative cyclization by lead tetraacetate is a very general reaction with great synthetic potential. It is a convenient way of synthesizing several interesting heterocyclic ring systems from easily available starting materials. The following table will illustrate the generality of this synthetic procedure[4]. (Table I)

Substituted pyrazolines (12), on LTA oxidation, are converted to 3- acetoxy -2- pyrazolines (13) which are cyclic analogs of azoacetates[14]. Pyrolysis of (13) is an interesting synthesis of cyclopropyl acetates (14). If either R_2 or R_3 is a hydrogen, formation of pyrazole (15) by elimination of acetic acid and tautomerization is favoured (Page 8).

PYROLYSIS OF OXADIAZOLINES AND RELATED COMPOUNDS

Thermal and photochemical decomposition of open chain azo compounds is known to yield alkyl radicals and nitrogen[15]. The radicals formed can either combine immediately in the cage or

$$R - N = N - R_1 \longrightarrow R - \dot{N} = \dot{N}\ R_1 \longrightarrow \dot{R} + N_2 + {}^{\bullet}R_1$$

undergo typical abstraction and addition reactions.

Thermolysis of 1- pyrazolines, reported by Overberger and coworkers[16], is a typical example of the decomposition of a cyclic cis-azo compound at high temperature. This reaction is important from a synthetic point of view also because it is a new route to cyclopropanes. These studies indicated that 1- pyrazolines

Table 1

Products from Oxidative Cyclization with LTA

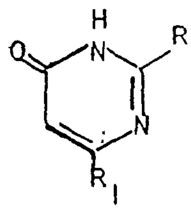
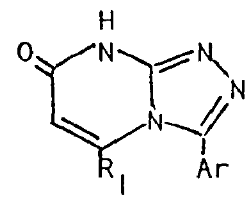
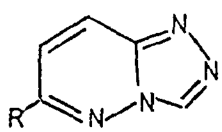
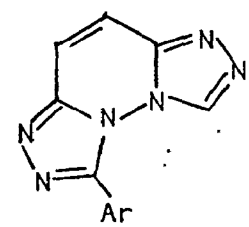
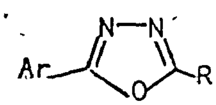
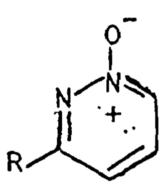
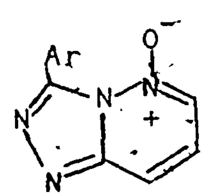
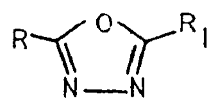
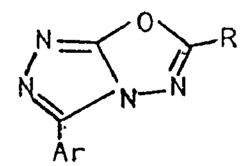
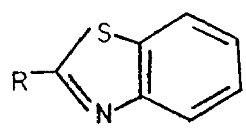
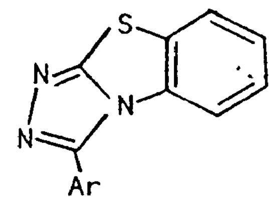
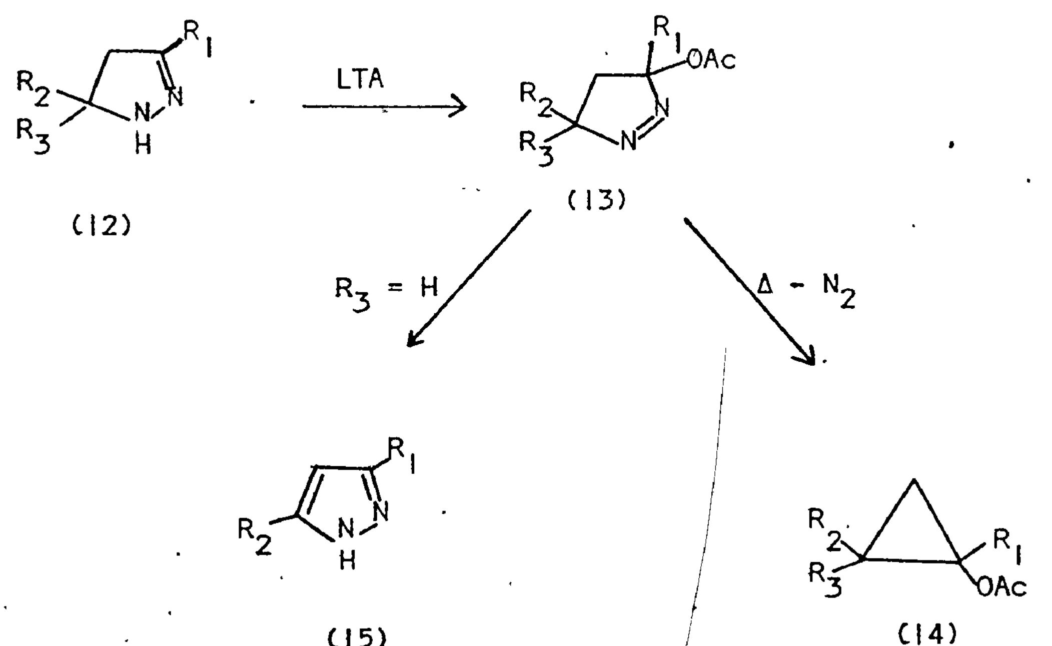
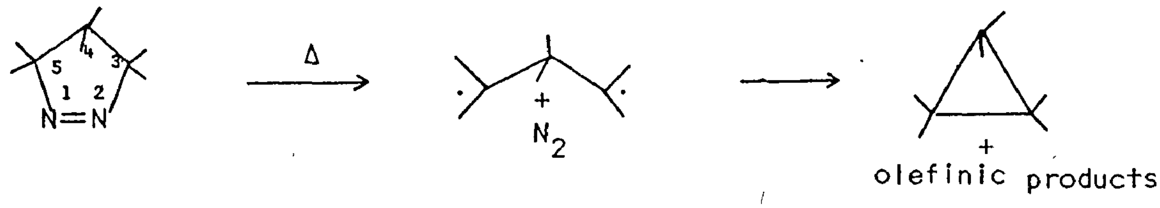
No.	Starting Material (R = $NH-N=C\langle^{H}_{Ar}$)	R_1	Product
1.		Me	
2.		--	
3.	$R-\overset{\underset{\|}{O}}{C}-R_1$	Ph, NPh_2	
4.		--	

Table I (contd.)

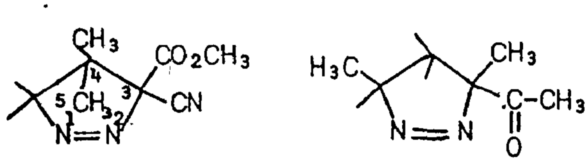
5.		Ph	
6.		--	





decompose much faster than the corresponding open chain compounds. The enhanced rate is attributed to the weakening of the C-N bonds resulting from the ring constraint. It is also observed that the cis-3,5, - disubstituted compounds decompose much more rapidly than the corresponding trans- isomers presumably due to the steric interactions in the ground state. The reaction is highly stereoselective and the resulting cyclopropanes always had the same geometry as the starting material in the case of 3, 5- trans- I - pyrazoline. Overberger postulated a concerted homolytic cleavage forming a biradical intermediate followed by rapid closure to the three membered ring.

McGreer and coworkers studied the pyrolysis of a series of I- pyrazolines with electron withdrawing substituents at the 3- position[17,18,19]. Pyrazoline (16) decomposes more rapidly in

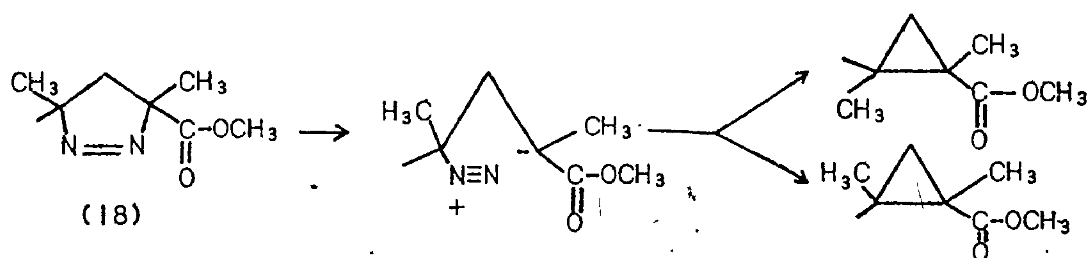


(16) (17) (18)

polar solvents than in non polar solvents yielding products arising from methyl migration from carbon 4 to carbon 5. McGreer postulated an ionic transition state in which methyl migration and nitrogen loss occur simultaneously.

The 3- acetylpyrazoline (17) gave dihydrofuran as one of the products of thermolysis as a result of closure to oxygen. The isomer in which the methyl groups are trans gave only very little ether product and hence it can be argued that the same zwitterionic intermediate is not formed in both the cases. The authors suggested a dipolar transition state in which the negative charge is delocalized over the carbonyl function, but partial bonding is retained between carbon 3 and nitrogen 2. Ring closure is either concerted with loss of nitrogen or occurs in a subsequent fast step.

The rates of decomposition of 3- carbomethoxy - 3,5 - dimethyl -1- pyrazoline (18) and its trans isomer are not enhanced by polar solvents. This suggests the absence of any ionic intermediate formed during the process. However, pyrazoline (18)

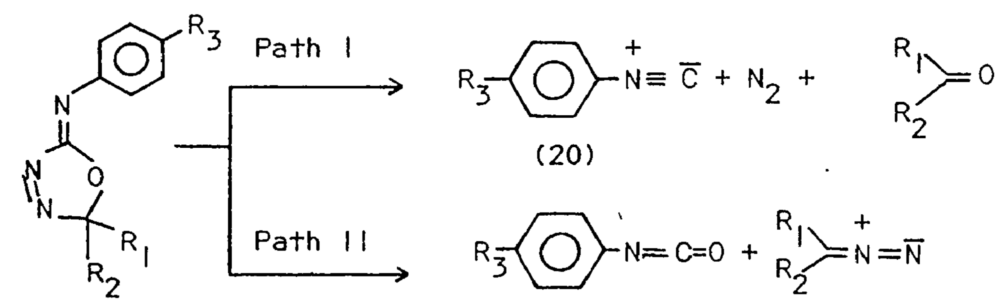


(18)

gives both of the cyclopropane isomers on decomposition which cannot be explained by a concerted loss of nitrogen. McGreer favoured a series of transition states similar to those proposed for open chain azo compounds. Depending on the ring substituents, the decomposition mechanism can vary from a fully concerted loss of nitrogen to a single heterolytic cleavage of the C-N bond. The cis and trans cyclopropanes can arise from geometrical distortion in the transition state, which favours inversion during ring closure.

The oxadiazoline ring system (1) is different in properties because one of the carbon atoms of the 1- pyrazolines is replaced by an oxygen atom. Therefore, the normal product of pyrolysis should be an iminooxirane analogous to the cyclopropane formed in the case of 1- pyrazolines. But, iminooxiranes are known to be extremely reactive and they are bound to undergo further reactions. It is also possible that the entire decomposition could occur through a different pathway in which the iminooxirane formation is avoided entirely.

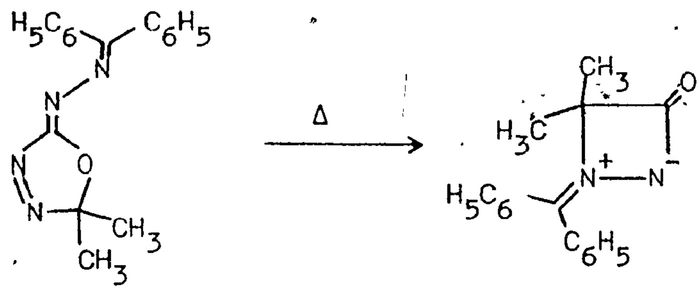
Pyrolysis of 2- arylimino -5,5- dialkyl - Δ^3 - 1,3,4- oxadiazolines (19)[20] was found to proceed through two different pathways. Infrared studies of the partially decomposed oxadiazoline



(19) (20) (21)

solutions indicated the presence of intermediates arising from these two pathways. Kinetic studies indicated that the isocyanate (21) concentration increased to a maximum of 23% and then decreased as the fragments tend to react together.

When another nitrogen was introduced in the side chain, the products of pyrolysis were found to be quite different[21]. For example, the pyrolysis of 2- diphenylmethylenehydrazono -5,5- dimethyl - Δ^3 - 1,3,4 - oxadiazoline (22) gave a crystalline solid in about 40% yield. The product was later characterized as 1- diphenylmethylene -4,4 - dimethyl - 3 - oxo - 1,2 - diazetidinium hydroxide, inner salt (23); a mesoionic structure. The minor products however, were not characterized. Although the existence



(22) (23)

of an iminooxirane intermediate was suggested, the actual mechanism of formation of (23) was not established.

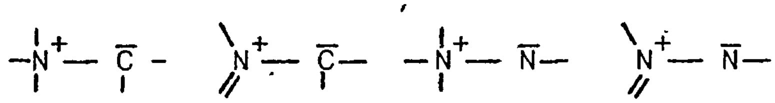
STRUCTURE AND STABILITY OF YLIDS

The first nitrogen ylid was isolated by Schlenk and Holtz[22] in 1916 when they attempted to prepare compounds with a pentavalent nitrogen. Further work to extend the scope of this

$$(Me)_4\,N^+Cl^- + Ph_3\bar{C}Na^+ \longrightarrow (Me)_4N^+\ \bar{C}Ph_3$$

reaction was not successful.

Several years later, different species of nitrogen ylids were prepared and characterized[23] and some of the interesting ones are listed below. The stability of these ylids is determined by the

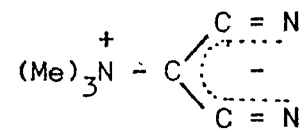


efficiency of the anion center adjacent to the quaternary nitrogen to stabilize the negative charge. Delocalization of charges by substituents attached to the cationic or anionic center is also important. As expected, the more electronegative the atom bearing the negative charge, the more stable is the ylid. For example, the following ylids are in the order of increasing stability from left to right, which is also the order of increasing electronegativity of the negatively charged atom. The stabilization of the anionic

$$(Me)_3\overset{+}{N}-\overline{C}H_2 \qquad (Me)_3\overset{+}{N}-\overline{N}H \qquad (Me)_3\overset{+}{N}-O^-$$

part by delocalization of the charge can be visualized by comparing the following compounds:

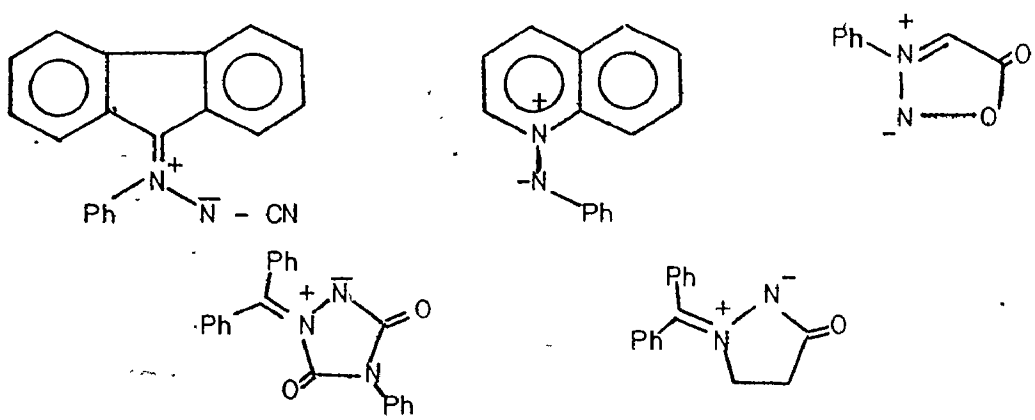
$$(Me)_3\overset{+}{N}-\overline{C}H_2 \qquad (Me)_3\overset{+}{N}-\overline{C}(CN)_2 \leftrightarrow$$



All the nitrogen ylids isolated so far have been those with substituents capable of stabilizing the negative charge through resonance. Several examples of nitrogen ylids, especially the

$$>\overset{+}{N}-\overline{X}-R \qquad X = CH \text{ or } N\ ; \quad R = Ar,\ CN \text{ etc.}$$

azomethine ylids are found in the literature[24]. A number of possible structures[25] for these ylids are shown below.



Ylids with four membered ring skeletons are found to be thermally stable and much less reactive towards 1,3- dipolarophiles than their five membered analogs[25], which is rather unexpected due to their more rigid geometry.

CRYSTAL STRUCTURE OF THE FOUR MEMBERED YLID

The crystal structure of 1- (p,p'- dichlorodiphenylmethylene) -4,4- dimethyl -3- oxo -1,2- diazetidinium hydroxide, inner salt (24)

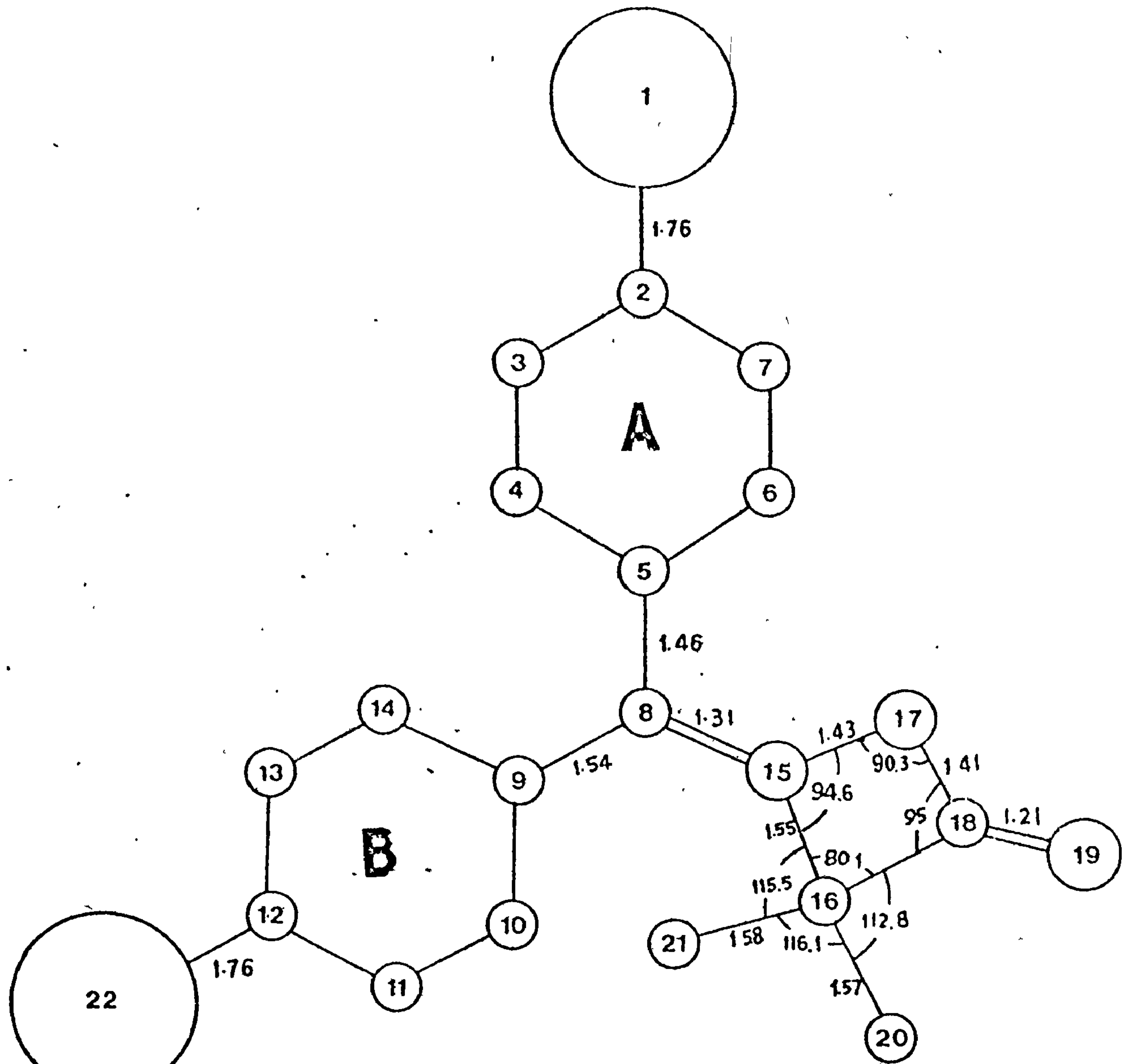
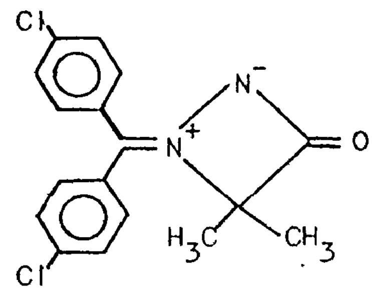


Fig. I. Structure of I- (di-p- chlorophenyl) methylene--4,4- dimethyl -3- oxo -1,2- diazetidinium hydroxide, inner salt (24).

was determined by single crystal X-ray diffraction using the heavy atom technique[26]. The mesoionic ring system showed certain interesting structural features. The bond distances and angles



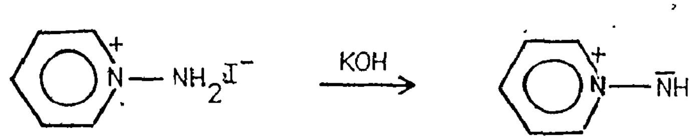
(24)

given in the figure indicate that the valence bond structure (24) is a fairly true representation of the molecule. The methylene oxo-azetidinium moiety is completely planar with C(8) - N(15) and C(18) - O(19) bond lengths of 1.31 Å and 1.21 Å, respectively. It was observed that within the crystal, the phenyl ring (A) is tilted from the plane of the four membered ring by an angle of 6°, whereas, the phenyl ring (B) is inclined about 90° to this plane. Another interesting feature is an intramolecular C-H-N hydrogen bonding between N(17) and the ortho hydrogen of ring (A) attached to C(6), which is a rather unusual phenomenon in organic molecules. The bond angle of 80.1° at C(16) is relatively small for a saturated carbon in a 4 membered ring. The bond angles at N(15) and C(18) are larger than this, yet too small for normal sp^2 configuration. Inspite of this geometrical constraint, the molecule is thermally stable and relatively unreactive towards 1,3- dipolarophiles like isocyanates and isothiocyanates. The mesoionic system exhibits some interesting spectral characteristics also which will be discussed elsewhere.

SOURCES OF AZOMETHINE IMINE YLIDS

The three basic approaches for the synthesis of azomethine imine ylids can be classified as: 1) Proton abstraction from suitably substituted N- amino compounds, 2) formation of the ylid by direct combination of organic compounds and 3) photochemical methods. It is an interesting fact that although these different approaches complement each other in generating a variety of ylids, it is almost impossible to synthesize the same ylid by more than one method. Therefore, the synthetic method should be carefully chosen depending on the structure of the product.

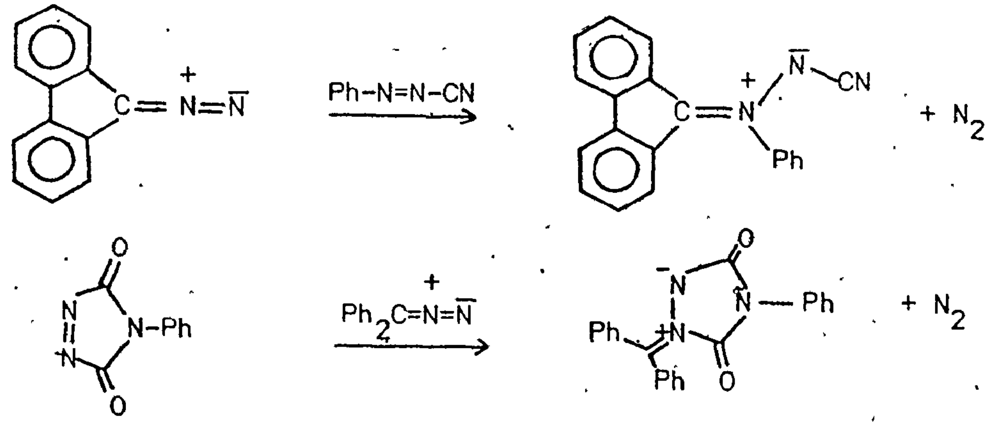
A simple example of the first method is the reaction of KOH with N- aminopyridinium iodide (25). Although, the pyridinium imine ylid (26) is stable only in solution, the corresponding



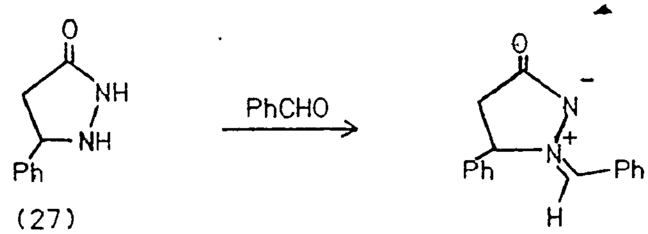
(25) (26)

N- aryl imines have been isolated[25].

The direct reaction of organic compounds to form ylid structures is employed in the following synthesis involving a substituted azo compound and a diazoalkane[27,24].

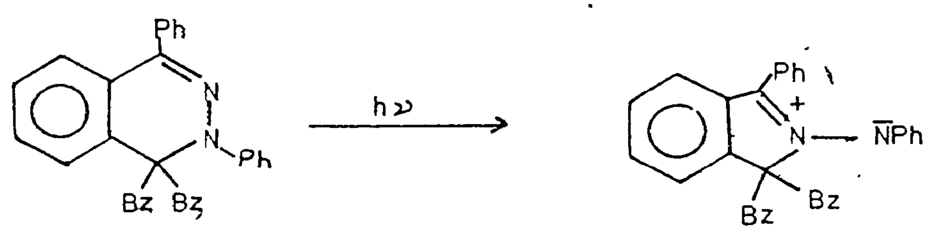


The reaction of a substituted hydrazine derivative (27) with a carbonyl compound to form an azomethine imine ylid (28) has also been reported[28].



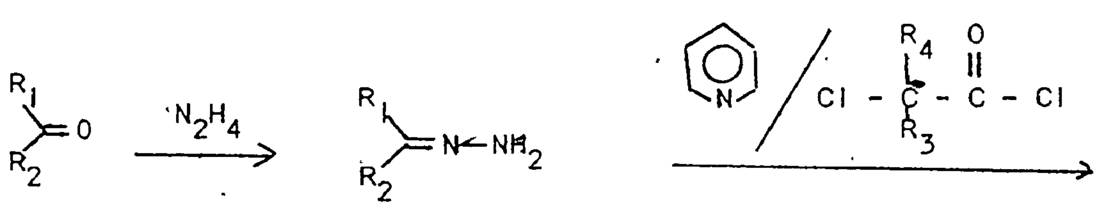
(27) (28)

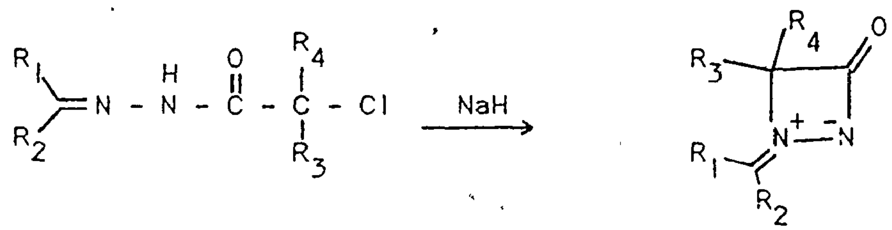
The only photochemical method for the generation of an azomethine imine ylid reported in the literature involves the ring contraction of a phthalazine (29) to an isoindole derivative (30)[29].



(29) (30)

All the methods described so far are limited to the synthesis of either five membered or acyclic ylids. Synthesis of a four membered ring azomethine imine ylid, where both the nitrogens are part of a rigid ring system, was first reported by Greenwald and Taylor[30]. Their method involved the synthesis of an α- chloroacetylhydrazone followed by treatment with base as shown in the following synthetic scheme.

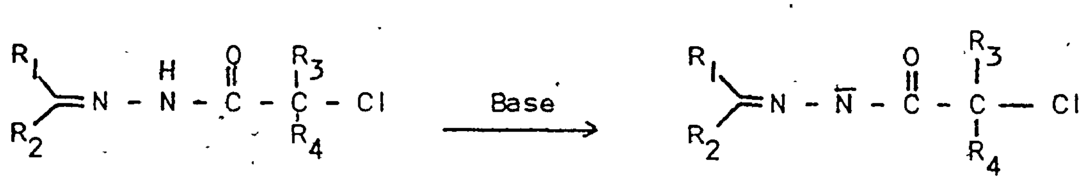




Taylor was successful in synthesizing a variety of azomethine imine ylids by this method and has also done some work on the chemistry of these compounds. But, this method is limited to α- chloroacylhydrazones of ketones only; ie. R_1 or R_2 cannot be a hydrogen. A further restriction is imposed by the steric factors associated with the structure of the hydra ne. Since the cyclization involves an internal nucleophilic displacement, one cannot afford to have bulky substituents adjacent to the leaving group (ie. R_3 and R_4). The reaction has been successful so far only with unsubstituted or monosubstituted systems and the yield was low in the latter case[25].

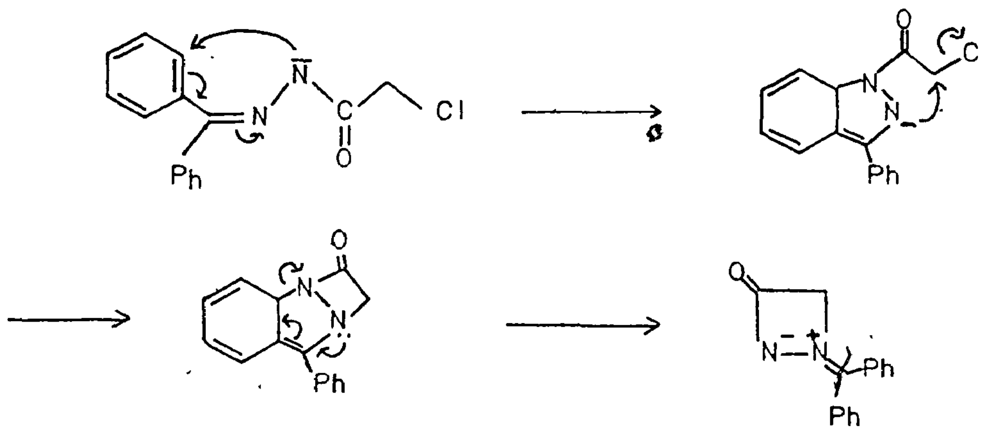
MECHANISTIC PROPOSALS

Several mechanistic pathways have been considered by Taylor and coworkers for this ring closure reaction[25]. The anion (32) derived from the α- chloroacylhydrazone (31) on treatment with base is a common intermediate in all the mechanisms considered.

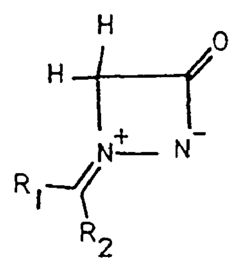


(31) (32)

The first mechanism proposed was limited to compounds where R_1 and R_2 are aryl groups, because it involves the participation of the aryl group. However, that mechanism cannot be correct in

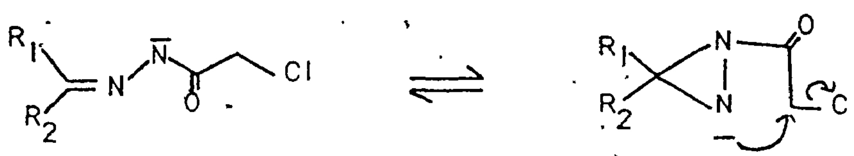


general because Taylor was able to isolate the ylid (33), where R_1 and R_2 are isopropyl groups in about 60% yield.



(33)

A second mechanism suggested by Greenwald and Taylor[30] postulates the attack of the anion at the SP^2 carbon of the hydrazone leading to a diaziridine anion intermediate (34). The validity of this mechanism, however, can also be questioned on the basis of a probable fragmentation of the intermediate diaziridine anion (35) into a diazo compound (36) and a ketene (37). The high



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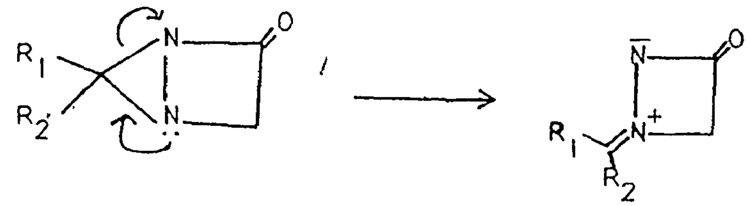
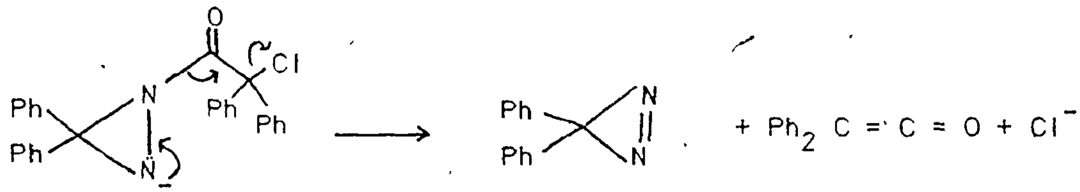
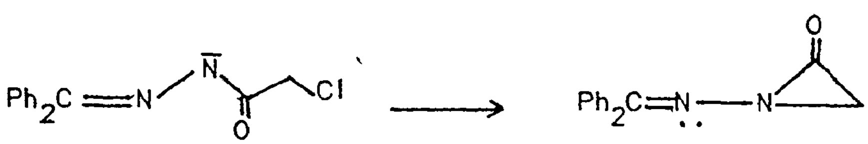




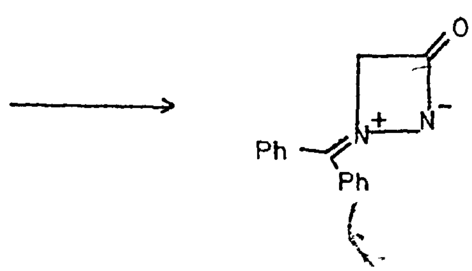
(35) (36) (37)

degree of stereospecificity observed in the ring closure also argues against this mechanism.

Two other pathways considered by the authors involve an α- lactam and an iminooxirane intermediate respectively. The intermediate anion formed on treatment with base can undergo an internal nucleophilic displacement, forming the N- imino α- lactam (38), followed by ring expansion to form the azomethine imine ylid. Although, this is conceivable, the cyclization of the

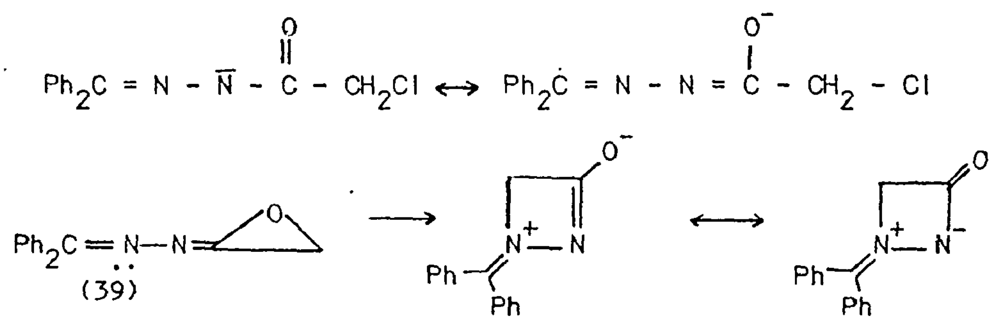


(38)

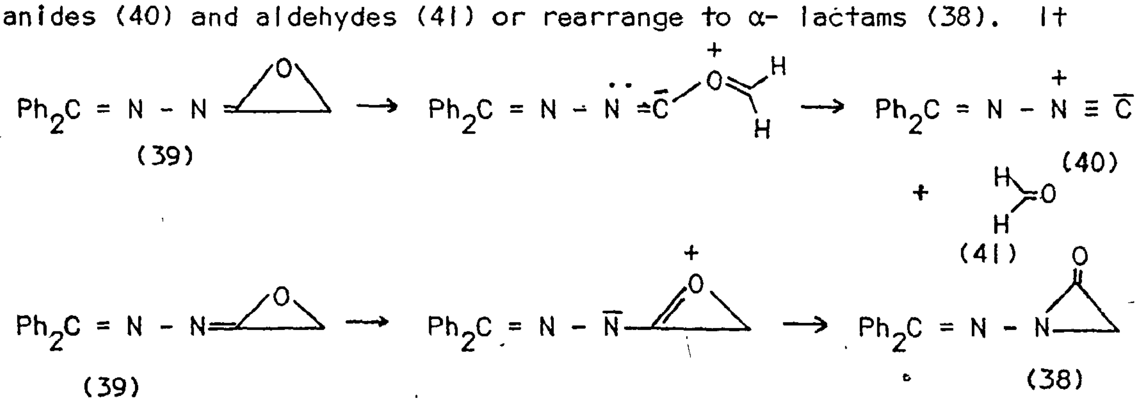


anion to the α- lactam seems to be quite unlikely because the anion is highly stabilized by delocalization of charge, whereas, the α- lactam is quite unstable. Furthermore, it is known that ring opening reactions of α- lactams occur via the cleavage of the acyl-nitrogen bond rather than the cleavage of the other carbon-nitrogen bond which is a requirement for the formation of the ylid.

Instead of nitrogen, if the oxygen functions as the nucleophile for the displacement of the chloride ion, an imino-oxirane (39) is formed rather than the α- lactam. This might not

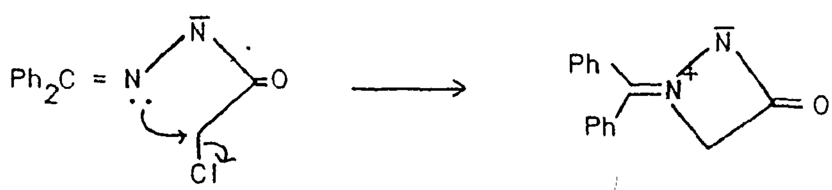


be unusual, because the nucleophilic reactions of amide oxygen is well precedented in the literature[31], although there is no precedence for the ring expansion. It is also probable that intermediates of this type either undergo fragmentation to isocyanides (40) and aldehydes (41) or rearrange to α- lactams (38). It

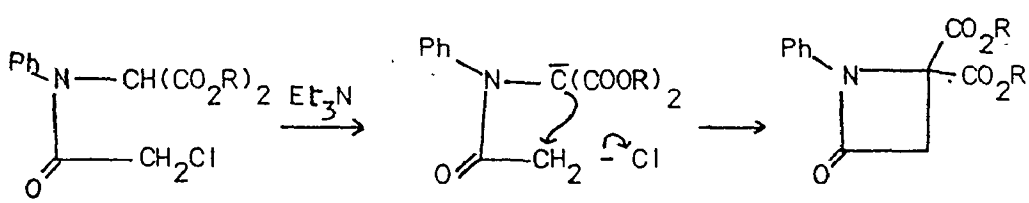


should also be noted that during the concerted ring expansion of the α- lactam or the iminooxirane, the system has to pass through a highly strained transition state which is energetically unfavourable. A stepwise process is also unlikely because it generates a primary cationic center.

After considering all these probabilities, the mechanism which Taylor and coworkers favoured is the one which involves a direct displacement of the chloride ion by the lone pair on the imine nitrogen. This was originally considered not feasible due



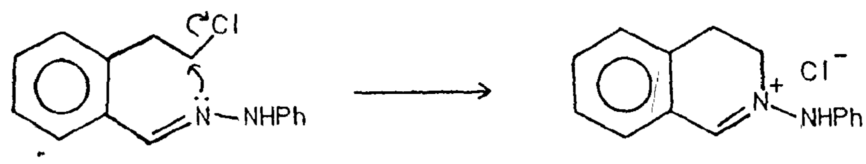
to stereochemical reasons. However, there are some notable exceptions to this argument in the literature. For example, α- haloacetamidomalonic ester (42) cyclizes to the four membered β- lactam (43) in high yield in the presence of triethylamine. Previous work



(42) (43)

reported by Huisgen[32] in 1960 also suggests that the intramolecular displacement of a halide by an SP^2 hybridized imine nitrogen lone pair is feasible. He found that simple heating of O- (2- chloroethyl)-benzaldehyde phenylhydrazone (44) gave N- phenylamino -3,4 -

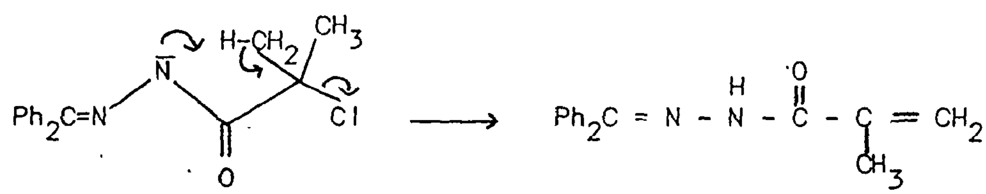
dihydroisoquinolinium chloride (45). The direct displacement



(44) (45)

mechanism explains all the experimental observations as well as the stereochemistry of the products.

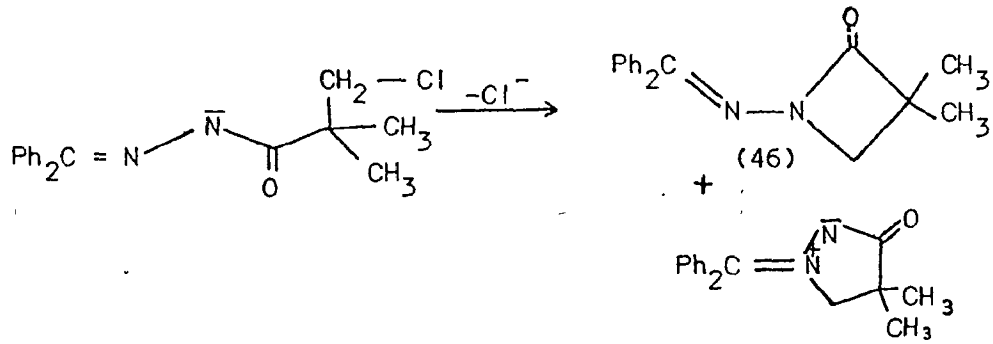
Taylor's group has some chemical evidence also to further support this mechanism as well as the stereoselective formation of the (E)- isomer. This was achieved by introducing two α- methyl groups in the starting chloroacetylhydrazone. The bulky methyl groups introduce severe steric hindrance and hence the (Z)- form is the preferred conformation which is not favourable for closure to the four membered ylid. Instead, this geometry is extremely favourable for the olefin formation and in fact, the olefin is



(Z) - amide anion

the only product isolated in this reaction.

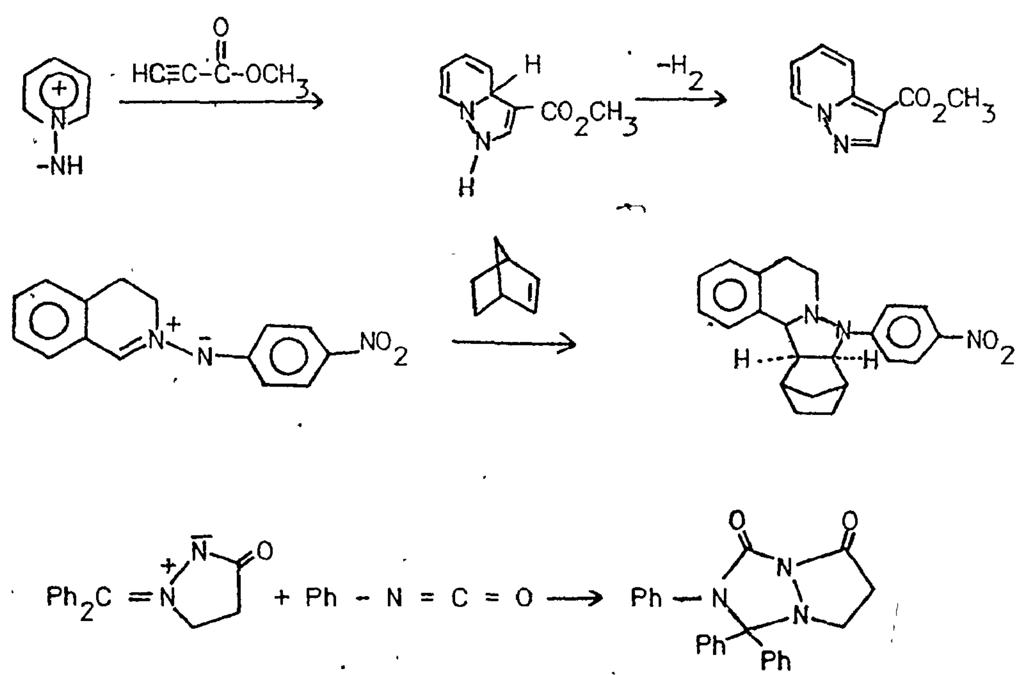
Treatment of 2,2- dimethyl -3- chloropropionyl benzophenonehydrazone with base provides additional evidence in support of the proposed cyclization mechanism. For the formation of the N- amino - β- lactam (46), the starting material should have the



(E)- conformation in which the amide anion can displace the chloride in an intramolecular SN_2 reaction.

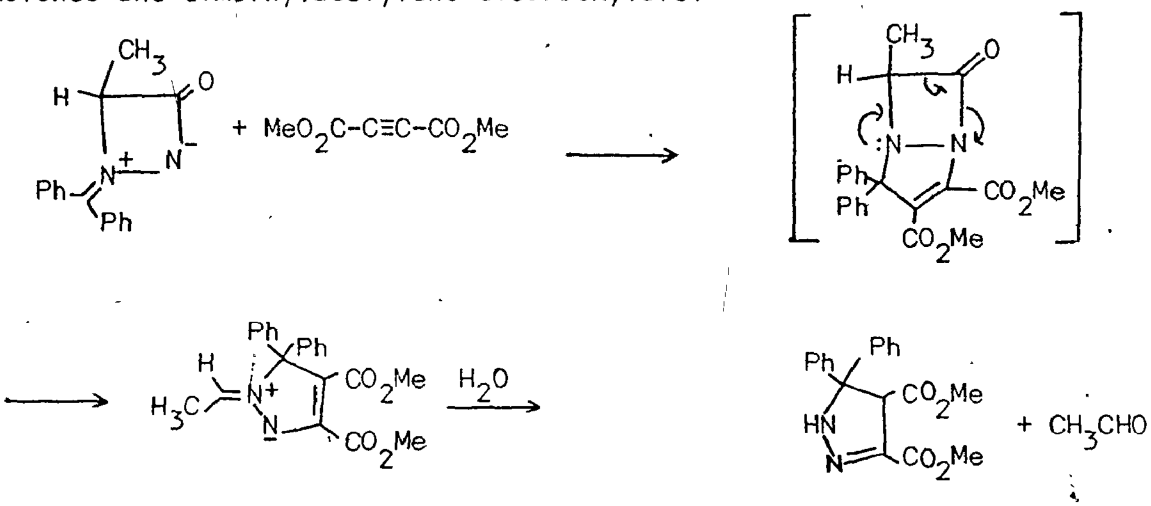
SYNTHETIC POTENTIAL OF AZOMETHINE IMINE YLIDS

The major interest in this area stems from the fact that the azomethine imine ylids can undergo 1,3- dipolar additions leading to new heterocyclic systems. The following examples will illustrate the synthetic potential of this class of compounds.



The four membered ring ylids are more sluggish in their reactions and therefore their synthetic applications are limited.

However they do react with more reactive 1,3- dipolarophiles like ketenes and dimethylacetylene dicarboxylate.



PRESENT WORK

The present work consists of synthetic and mechanistic investigations related to certain 2- hydrazono - Δ^3 - 1,3,4-oxadiazolines and the products of their pyrolysis. The work can be divided into the following four major parts.

1) Cyclization: Although, several carbohydrazones have been cyclized by lead tetraacetate in this laboratory by earlier workers, the work was limited to ketone carbohydrazones only. Our initial aim was to extend the scope of this reaction to carbohydrazones of cyclic ketones and to aldehyde carbohydrazones. The results indicated that the oxidative cyclization is a very general reaction. During the LTA oxidation of mixed carbohydrazones of alkyl and aryl carbonyl compounds, the cyclization occurred selectively at the methine carbon bearing aliphatic substituents. However, this preference can be reversed by introducing strongly electron donating p- substituents on the aryl part of the substrate.

During the cyclization of certain mixed carbohydrazones of aromatic aldehydes and acetone, it was found that the regiospecificity of the reaction is controlled by the nature of substituents on the benzene ring. This observation has led to the conclusion that electronic effects are more predominant than steric effect during the cyclization and on this basis we have postulated a mechanism for the oxidative cyclization.

2) Pyrolysis: The facile transformation of 2- hydrazono oxadiazolines to azomethine imine ylids under pyrolytic conditions prompted us to investigate this reaction in detail. This is a novel synthetic method and is fairly general for the preparation of these ylids. It was possible to synthesize a number of compounds whose syntheses is not feasible by previously known methods.

3) Mechanism of formation of cyclic ylids: Because of the unusual structural features of the four membered ylid system, we were interested in the mechanism of its formation from the oxadiazoline. A mechanism identical to one proposed by Taylor cannot operate in this case, because the substrates and reaction conditions are quite different. A number of speculations have been made before[21,33], but no attempts were made to determine the actual pathway. As it was not possible to isolate reactive intermediates, the approach was to trap them by using suitable reagents and to characterize the trapped products.

4) Synthesis based on trapping the intermediates: The trapping experiments have led to some interesting heterocyclic systems. Attempts have been made to establish the structure of the trapped

products and to rationalize their formation by mechanistic proposals. The spectral characteristics of all new compounds synthesized have been investigated in detail.

Various aspects of the work will be discussed in detail elsewhere in the thesis.

EXPERIMENTAL

SYNTHESIS OF 4-AMINOSEMICARBAZONES

1) Carbohydrazide: Diethyl carbonate (150 g, 1.271 mol) and 85% hydrazine hydrate (260 g, 4.420 mol) were heated on a steam bath under reflux. After 48 hr, 100 ml of ethanol was distilled out from the reaction mixture. The solution was allowed to cool to room temperature and the white solid which separated was collected and recrystallized from ethanol water mixture, in 88% yield; m.p. 155-156° (lit.[34] m.p. 154°).

2) Benzaldehyde -4- aminosemicarbazone: Carbohydrazide (5.0 g, 0.056 mol) and benzaldehyde (4.5 g, 0.042 mol) were heated under reflux in 50 ml of absolute alcohol for 1 hr. The initial heterogeneous mixture turned into a clear solution in 30 min. and the product precipitated out gradually. The solid was collected and washed with hot water to remove the unreacted carbohydrazide. Recrystallization from ethanol gave the product in 86% yield; m.p. 165° (lit.[35] m.p. 173°).

The following 4- aminosemicarbazones were prepared using procedure (2) above. As most of these compounds are sparingly soluble in common organic solvents, n.m.r. spectra were not obtained. All the compounds were characterized by their infrared spectra (KBr), (NH, 3350 and 3450 cm^{-1};CO, 1700 cm^{-1}) and molecular weight determination by low resolution mass spectrometry.

3) Acetophenone -4- aminosemicarbazone was prepared from acetophenone and carbohydrazide. The product was obtained in 60% yield on recrystallization from ethanol; m.p. 186°, mol. wt. calcd. for $C_9H_{12}N_4O$: 192. Found (m.s): 192.

4) p- Methoxybenzaldehyde -4- aminosemicarbazone was prepared in 75% yield from p- methoxybenzaldehyde and carbohydrazide; m.p. 175-177°, mol. wt. calcd. for $C_9H_{12}N_4O_2$: 208. Found (m.s): 208.

5) p- Tolualdehyde -4- aminosemicarbazone from p- tolualdehyde and carbohydrazide was obtained in 72% yield; m.p. 175-176°, mol. wt. calcd. for $C_9H_{12}N_4O$: 192. Found (m.s.): 192.

6) Furfural -4- aminosemicarbazone was obtained in 95% yield by reacting furfural with carbohydrazide; m.p. 167°, mol. wt. calcd. for $C_6H_8N_4O_2$: 168. Found (m.s): 168.

7) o- Chlorobenzaldehyde -4- aminosemicarbazone from o- chlorobenzaldehyde and carbohydrazide was formed in 88% yield; m.p. 208-209°, mol. wt. calcd. for $C_8H_9N_4OCl$: 212.5. Found (m.s.): 212 and 214.

8) Cyclopentanone -4- aminosemicarbazone was prepared in 60% yield from cyclopentanone and carbohydrazide; m.p. 203-204°, mol. wt. calcd. for $C_6H_{12}N_4O$: 156. Found (m.s.): 156.

9) p- Dimethylaminobenzaldehyde -4- aminosemicarbazone was made by reacting p- dimethylaminobenzaldehyde and carbohydrazide in 81% yield; m.p. 178°, mol. wt. calcd. for $C_{10}H_{15}N_5O$: 221. Found (m.s): 221.

10) <u>Benzophenone -4- aminosemicarbazone</u>: Benzophenone (41.0 g, 0.226 mol) and carbohydrazide (7.3 g, 0.081 mol) were refluxed in a mixture of 100 ml of ethanol and 50 ml of water for 6 hr. Benzophenone -4- aminosemicarbazone, which gradually deposited, was filtered, washed with hot water and recrystallized from absolute alcohol; 76% yield; m.p. 223-224° (lit.[34] m.p. 223-224°), mol. wt. calcd. for $C_{14}H_{14}N_4O$: 254. Found (m.s): 254.

11) <u>p,p'- Dichlorobenzophenone -4- aminosemicarbazone</u>: p,p'- Dichlorobenzophenone (11.3 g, 0.048 mol) and carbohydrazide (8.5 g, 0.106 mol) were refluxed for 40 hr. over a steam bath in a mixture of 250 ml of ethanol and 100 ml of water containing 2 ml of glacial acetic acid. The mixture was cooled and the white solid precipitated was filtered, washed and recrystallized from ethanol; 45% yield; m.p. 196-198° (lit.[21] m.p. 197-198°).

SYNTHESIS OF CARBOHYDRAZONES

Symmetrical carbohydrazones involving only one carbonyl compound were synthesized by heating excess of the carbonyl compound and carbohydrazide with or without a solvent. Crossed carbohydrazones were prepared by heating the 4- aminosemicarbazone with a carbonyl compound. Most of these compounds were characterized by molecular weight determination by low resolution mass spectrometry and characteristic infrared absorption (KBr), (CO, 1700 cm^{-1}; NH, 3300 cm^{-1}).

1) Acetone carbohydrazone: Carbohydrazide (5.0 g, 0.056 mol) was refluxed in 50 ml of acetone over a steam bath for 3 hrs. The reaction mixture, which was heterogenous in the beginning, became a clear solution after 2 hrs. The solution was cooled and the white crystals which separated were filtered and on recrystallization from methanol, the product was obtained in 85% yield; m.p. 160° (lit.[36] m.p. 160°).

2) Benzaldehyde carbohydrazone: Benzaldehyde (8.0 g, 0.075 mol) and carbohydrazide (3.6 g, 0.040 mol) were refluxed in 50 ml of ethanol for 4 hrs. The solution was cooled and the solid which separated was filtered and washed with hot water. This was recrystallized from ethanol and the pure material was obtained in 82% yield; m.p. 199° (lit.[37] m.p. 202°), mol. wt. calcd. for $C_{15}H_{14}N_4O$: 266. Found (m.s.): 266.

3) Acetophenone carbohydrazone was prepared by refluxing a solution of acetophenone and carbohydrazide in ethanol. The product was

recrystallized from ethanol; 60% yield; m.p. 236-239°, mol. wt. calcd. for $C_{17}H_{18}N_4O$: 294. Found (m.s): 294.

4) Benzaldehyde acetone carbohydrazone: A solution of benzaldehyde -4- aminosemicarbazone (20.0 g, 0.112 mol) in 80 ml of acetone was refluxed for 3 hr. The solution was concentrated to 20 ml and cooled. The crystals which separated (82% yield) were filtered and dried; m.p. 188-191°, mol. wt. calcd. for $C_{11}H_{14}N_4O$: 218. Found (m.s): 218.

A procedure similar to (4) above was employed for the preparation of the following crossed carbohydrazones, using 4- aminosemicarbazones as starting materials.

5) Benzaldehyde cyclopentanone carbohydrazone: This compound was prepared in 72% yield from cyclopentanone -4- aminosemicarbazone and benzaldehyde. The crude product was recrystallized from ethanol, m.p. 183-184°, mol. wt. calcd. for $C_{13}H_{16}N_4O$: 244. Found (m.s): 244.

6) Benzaldehyde cyclohexanone carbohydrazone was prepared in 68% yield from benzaldehyde -4- aminosemicarbazone and cyclohexanone. The recrystallized product had m.p. 159°; Mol. wt. calcd. for $C_{14}H_{18}N_4O$: 258. Found (m.s): 258.

7) p- Tolualdehyde acetone carbohydrazone: This compound prepared from p- tolualdehyde -4- aminosemicarbazone and acetone, in 71% yield, had m.p. 162-165°. Mol. wt. calcd. for $C_{12}H_{16}N_4O$: 232. Found (m.s): 232.

8) p- Methoxybenzaldehyde acetone carbohydrazone was obtained in 68% yield by reacting p- methoxybenzaldehyde -4- aminosemicarbazone with acetone, m.p. 149-151°, mol. wt. calcd. for $C_{12}H_{16}N_4O_2$: 248. Found (m.s): 248.

9) o- Chlorobenzaldehyde acetone carbohydrazone: This compound was made from o- chlorobenzaldehyde -4- aminosemicarbazone and acetone in 69% yield; m.p. 164-165°; mol. wt. calcd. for $C_{11}H_{13}N_4O\ Cl$: 252.5. Found (m.s): 252 and 254.

10) Acetophenone acetone carbohydrazone: This compound, prepared in 60% yield from acetophenone -4- aminosemicarbazone and acetone, had. m.p. 204-206°, mol. wt. calcd. for $C_{12}H_{16}N_4O$: 232. Found (m.s): 232.

11) p- Dimethylaminobenzaldehyde acetone carbohydrazone was obtained in 42% yield by reacting p- dimethylaminobenzaldehyde -4- aminosemicarbazone and acetone, m.p. 177-180°, mol. wt. calcd. for $C_{13}H_{19}N_5O$: 261. Found (m.s): 261.

12) Furfural acetone carbohydrazone: This compound, prepared from furfural -4- aminosemicarbazone and acetone, in 73% yield had m.p. 183°, mol. wt. calcd. for $C_9H_{12}N_4O_2$: 208. Found (m.s): 208.

13) Benzaldehyde methyl ethyl ketone carbohydrazone: Benzaldehyde -4- aminosemicarbazone (2.0 g, 0.023 mol) was refluxed in 10 ml of methyl ethyl ketone until the solution became clear (20-30 min). The solution was concentrated by distilling out 5 ml of the methyl ethyl ketone. The solid which separated on cooling was filtered and on recrystallization from ethanol, the product was obtained in 70% yield, m.p. 162°, mol. wt. calcd. for $C_{12}H_{16}N_4O$: 232. Found (m.s): 232.

14) Benzophenone acetone carbohydrazone: Benzophenone -4- aminosemicarbazone (6.0 g, 0.023 mol) was refluxed in 450 ml of acetone. The compound slowly dissolved after 2 hrs. The clear solution on cooling deposited white crystals of the carbohydrazone (62% yield) which were

filtered and dried, m.p. 203-204° (lit.[36] m.p. 200-202°).

15) p,p'- Dichlorobenzophenone acetone carbohydrazone: p,p' - Dichlorobenzophenone -4- aminosemicarbazone (5.0 g, 0.015 mol) was refluxed in 500 ml of acetone in the presence of 0.20 g of p- toluenesulphonic acid for 20 hr. The solid was allowed to settle before it was filtered to yield 90% of the product, m.p. 240° (lit.[21] m.p. 240°).

16) p,p'- Dimethylbenzophenone acetone carbohydrazone: p,p'- Dimethylbenzophenone (7.5 g, 0.027 mol) and carbohydrazide (2.5 g, 0.027 mol) were heated for 15 hr. at the reflux temperature in a mixture of 40 ml of ethanol and 20 ml of water containing 1 ml of glacial acetic acid. The solution was allowed to cool, the supernatant liquid was decanted, and 250 ml of acetone containing 1 ml of acetic acid was added to the solid. The resulting solution was refluxed for 12 hr. and cooled. The solid crystals deposited in 15% yield were filtered and dried, m.p. 225-227°, mol. wt. calcd. for $C_{19}H_{22}N_4O$: 322. Found (m.s): 322.

17) p- Bromobenzophenone acetone carbohydrazone: This compound was prepared in 20% yield by following a procedure similar to (16) above, using p- toluenesulphonic acid as catalyst instead of acetic acid. The product recrystallized from ethanol had m.p. 214-216°, mol. wt. calcd. for $C_{17}H_{17}N_4OBr$: 373. Found (m.s): 372 and 374.

CYCLIZATION OF CARBOHYDRAZONES

All the cyclization reactions were carried out by the oxidation of the carbohydrazones with lead tetraacetate at low temperature ($\sim 5^{o}C$). The infrared (Table 4) and p.m.r. (Table 8) spectra of all the oxadizaolines synthesized by this method are included in the section on results and discussion.

1) Lead tetraacetate [39]: A solution of 600 ml of glacial acetic acid and 400 ml of acetic anhydride was transferred to a three necked flask fitted with a mechanical stirrer. The flask was placed in an oil bath and the temperature was maintained at 55-80^{o}C. The mixture was continuously stirred, as red lead oxide (700 g, 1.030 mol) was added in 20 g lots. Fresh addition was made only after the orange color has disappeared. Upon completion ($\sim$ 12 hr), the brownish reaction mixture was cooled and the product filtered and washed with acetic acid. This was recrystallized from glacial acetic acid and the product obtained in 72% yield was stored in the refrigerator.

2) 5,5- Dimethyl -2- (benzylidenehydrazono) - Δ^{3} - 1,3,4- oxadiazoline: A pale yellow solution of lead tetraacetate (6.0 g, 0.0135 mol) in 25 ml of methylene chloride was cooled in an ice bath. The solution was stirred and dry nitrogen was bubbled through. Gradual addition of a solution of benzaldehyde acetone carbohydrazone (2.0 g, 0.0092 mol) in 10 ml of methylene chloride was completed in 10 min. Stirring was continued for another 15 min, the slurry was filtered through Celite and the filtrate was transferred to a separatory funnel. The organic

layer was washed with water (3×50 ml), with saturated sodium bicarbonate solution (50 ml), and again with water (3×50 ml) before it was dried over anhydrous magnesium sulfate. On filtration and evaporation of the solvent, a yellow solid was obtained (65% yield) which was recrystallized from petroleum ether, m.p. 95°. Anal. Calcd. for $C_{11}H_{12}N_4O$: C, 61.11 ; H, 5.56; N, 25.92. Found: C, 60.95; H, 5.78; N, 25.90.

A procedure similar to that described in (2) was followed for the preparation of the following 2- substituted oxadiazolines.

3) <u>5,5- Dimethyl -2- (α- methylbenzylidenehydrazono) - Δ^3- 1,3,4,- oxadiazoline</u> was prepared by the oxidation of acetophenone acetone carbohydrazone in 60% yield; m.p. 115-116°. Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.61; H, 6.09; N, 24.35. Found: C, 62.66; H, 6.50; N, 24.30.

4) <u>5- Methyl -5- ethyl -2- (benzylidenehydrazono) - Δ^3 - 1,3,4 - oxadiazoline</u> was made in 60% yield by the oxidation of benzaldehyde methyl ethyl ketone carbohydrazone, m.p. 44°, mol. wt. calcd. for $C_{12}H_{14}N_4O$: 230. Found (m.s): 230.

This material was not obtained in analytically pure form. Spectroscopic data [i.r, (Table 4) and p.m.r. (Table 8)] were consistent with the proposed structure.

5) <u>5,5- Dimethyl -2- (p- tolylmethylenehydrazono) -Δ^3- 1,3,4- oxadiazoline</u> was obtained in 62% yield by the oxidation of p- tolualdehyde acetone carbohydrazone, m.p. 108-110°. Anal. Calcd. for $C_{12}H_{14}N_4O$: C, 62.61; H, 6.09; N, 24.35. Found: C, 62.67; H, 6.23; N, 24.19.

6) <u>5,5- Dimethyl -2- (p- methoxybenzylidenehydrazono) - Δ^3- 1,3,4- oxadiazoline</u> was prepared in 45% yield by the oxidation of anisaldehyde acetone carbohydrazone, m.p. 142°. Anal. Calcd. for $C_{12}H_{14}N_4O_2$: C, 58.53; H, 5.69; N, 22.76. Found: C, 58.32; H, 6.00; N, 23.05.

7) <u>5,5- Pentamethylene -2- (benzylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline</u> was prepared by the oxidation of benzaldehyde cyclohexanone carbohydrazone. This compound was obtained in the form of an oil and was not analytically pure. However, the spectroscopic data [i.r (Table 4), p.m.r (Table 8)] were consistent with the proposed structure. Mol. wt. calcd. for $C_{14}H_{16}N_4O$: 256. Found (m.s): 256.

8) <u>5,5- Tetramethylene -2- (benzylidenehydrazono) -Δ^3- 1,3,4- oxadiazoline</u> was obtained in 45% yield by the oxidation of benzaldehyde cyclopentanone carbohydrazone, m.p. 104°. Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.46; H, 5.78; N, 23.11. Found: C, 64.25; H, 5.80; N, 23.35.

9) <u>5,5- Dimethyl -2- (o- chlorobenzylidenehydrazono) -Δ^3- 1,3,4- oxadiazoline</u> was obtained in 68% yield by the oxidation of o- chlorobenzaldehyde acetone carbohydrazone, m.p. 97°. Anal. Calcd. for $C_{11}H_{11}ClN_4O$: C, 52.69; H, 4.39; N, 22.34; Cl, 14.17. Found: C, 52.19; H, 4.51; N, 22.08; Cl, 14.47.

10) <u>5,5- Dimethyl -2- (furylmethylenehydrazono) - Δ^3 - 1,3,4- oxadiazoline</u> was prepared in 63% yield by the oxidation of furfural acetone carbohydrazone, m.p. 120-121°. Anal. Calcd. for $C_9H_{10}N_4O_2$: C, 52.42; H, 4.85; N, 27.18. Found: C, 52.40; H, 4.87; N, 26.89.

11) 5,5 - Dimethyl -2- (diphenylmethylenehydrazono) - Δ^3 - 1,3,4-oxadiazoline was obtained in 76% yield by the oxidation of benzophenone acetone carbohydrazone, m.p. 110-111° (lit.[21] m.p. 110-112).

12) 5,5- Dimethyl -2- (di- p- tolylmethylenehydrazono) - Δ^3 - 1,3,4-oxadiazoline was prepared in 60% yield by the oxidation of p,p'-dimethylbenzophenone acetone carbohydrazone, mp. 158-159°. Anal. Calcd. for $C_{19}H_{20}N_4O$: C, 71.25; H, 6.25; N, 17.50. Found: C, 71.40; H, 6.39; N, 17.75.

13) 5,5- Dimethyl -2- (isopropylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline was prepared in 72% yield by the oxidation of acetone carbohydrazone, b.p. 89-90° (5 mm) [lit.[36] b.p. 89-90° (5 mm)].

14) 5,5- Dimethyl -2- [α- (p- bromophenyl) benzylidenehydrazono] - Δ^3 - 1,3,4- oxadiazoline was prepared in 55% yield by the oxidation of p- bromobenzophenone acetone carbohydrazone, m.p. 92-94°. Anal. Calcd. for $C_{17}H_{15}N_4OBr$: C, 54.98; H, 4.04; N, 15.09. Found C, 55.09; H, 4.31; N, 14.80.

15) 5,5- Dimethyl -2- (di- p- chlorophenyl) methylenehydrazono - Δ^3 - 1,3,4- oxadiazoline: p,p'- Dichlorobenzophenone acetone carbohydrazone (4.5 g, 0.012 mol) was dissolved in 40 ml of glacial acetic acid and added at a slow rate (15 min) to a solution of lead tetraacetate (25.0 g, 0.0462 mol) in 70 ml of methylene chloride, cooled in an ice bath. The mixture was kept stirred under nitrogen atmosphere for 3 hr. The temperature was allowed to rise slowly and the mixture was allowed to stay at room temperature for another 12 hr. The unreacted lead tetraacetate was destroyed by adding 100 ml of cold water and stirring

for 15 min. The slurry was filtered over Celite and the organic layer was washed with water (3 x 50 ml) with saturated sodium bicarbonate solution (50 ml) and again with water (3 x 50 ml). Finally, it was dried over anhydrous magnesium sulfate, filtered and concentrated to one third of its initial volume. On addition of 30 ml of petroleum ether, a pale yellow solid separated, which was recrystallized from petroleum ether chloroform mixture to give the product in 58% yield, m.p. 144-145° (lit.[21] m.p. 143-145°).

16) Attempted Cyclization of Benzophenone -4- aminosemicarbazone: Benzophenone -4- aminosemicarbazone (2.0 g, 0.008 mol) was dissolved in 20 ml of methylene chloride and the solution was added by drops to a solution of lead tetraacetate (4.0 g, 0.009 mol) in 20 ml of methylene chloride. The reaction mixture was continuously stirred under nitrogen atmosphere and the temperature was maintained below 5°C. After the addition was completed, stirring was continued for another 10 min. and 50 ml of cold water was added. The slurry was filtered through Celite. The organic layer was washed with water (3 x 50 ml), with sodium bicarbonate solution (50 ml), and again with water (3 x 50 ml). After drying over anhydrous magnesium sulfate, the solvent was evaporated and the solid recrystallized from ethanol in 52% yield, m.p. 161-163° (lit.[38] m.p. 164°). The product was identified as benzophenone azine, instead of the expected oxadiazoline.

17) Cyclization of p- Dimethylaminobenzaldehyde Acetone Carbohydrazone: The cyclization of this material with lead tetraacetate was carried out using the same procedure followed in the case of other carbohydrazones. The yellow product isolated in 72% yield was identified as

the oxadiazole resulting from the cyclization at the aryl end and subsequent isomerization, m.p. 207-210°; p.m.r ($CDCl_3$) δ 1.80 (S, 3H), 2.05 (S, 3H), 3.00 (S, 6H), 7.00-8.00 (m, 4H); m.s. 259 (mol. ion). Anal. Calcd. for $C_{13}H_{17}N_5O$: C, 60.23; H, 6.56; N, 27.02. Found: C, 59.94; H, 6.47; N, 26.91.

PYROLYSIS OF OXADIAZOLINES

The following two procedures were followed for the pyrolysis of 2- substituted oxadiazolines to produce the azomethine imine ylids. Infrared stretching frequencies (Table 5) and p.m.r chemical shifts (Table 9) of the products are included in the section on results and discussion.

I) 1- (Z- Phenylmethylene) -4- dimethyl - 3 - oxo -1,2- diazetidinium Hydroxide, Inner Salt:

Method 1: 5,5- Dimethyl -2- (benzylidenehydrazono) - Δ^3 - 1,3,4-oxadiazoline (2.0 g, 0.009 mol), in a thick-walled, Pyrex glass tube with a long stem, was sealed under vacuum and kept in an oil bath maintained at 150°C for 24 hr. The tube was removed from the bath and allowed to cool down to the room temperature, before it was opened. The dark brown material was extracted with chloroform and the extract was concentrated after filtration. Addition of 30 ml of petroleum ether to the above solution precipitated a white solid, which was recrystallized from petroleum ether chloroform mixture to give the product in 21% yield; m.p. 191°, m.s. 188 (mol. ion).

Method 2: A solution of 5,5- dimethyl -2- (benzylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline (2.0 g, 0.009 mol) in 50 ml of dry chlorobenzene was refluxed for 20 hr. About 40 ml of the chlorobenzene was distilled out and the residual solution was allowed to cool. Addition of 30 ml of petroleum ether resulted in the precipitation of a white solid which was filtered and recrystallized from a mixture of petroleum ether and chloroform to give the ylid in 37% yield; m.p. 191°. Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.38; N, 14.89. Found: C, 69.76; H, 6.53; N, 14.76.

The compound displayed all the spectral characteristics of the product obtained from Method 1. Because of the higher yield and lack of formation of any tar, method 2 was followed for the pyrolysis of other oxadiazolines. The following azomethine imine ylids were synthesized by this method.

2) <u>1- (Diphenylmethylene) -4,4- dimethyl -3- oxo -1,2- diazetidinium Hydroxide, Inner Salt</u>: This compound was prepared in 34% yield by the pyrolysis of 5,5- dimethyl -2- (diphenylmethylenehydrazono) - Δ^3 - 1,3,4- oxadiazoline, m.p. 170-171° (lit.[21] m.p. 171-172.5°).

In this case, the filtrate which remained after isolation of the major product was concentrated on the rotary evaporator to remove the petroleum ether. Then, all the chlorobenzene was removed using a vacuum pump and the residual viscous oil was chromatographed over a column of silica gel. The fractions collected were not pure. Attempts to separate the mixture by high pressure liquid chromatography were also not successful and other methods of purification were not pursued.

3) <u>1- (Z- Phenylmethylene) -4- methyl -4- ethyl - 3- oxo - 1,2- diazetidinium Hydroxide, Inner Salt</u> was obtained in 35% yield by the pyrolysis of 5- methyl -5- ethyl -2- (benzylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline, m.p. 154°. Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: C, 71.33; H, 7.07; N, 13.80.

4) <u>1- (Z- p- Tolylmethylene) -4,4- dimethyl -3- oxo- 1,2- diazetidinium Hydroxide, Inner Salt</u> was prepared in 25% yield by the pyrolysis of 5,5- dimethyl -2- (p- tolylmethylenehydrazono) - Δ^3 - 1,3,4-oxadiazoline, m.p. 211°. Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.29; H, 6.93; N, 13.86. Found: C, 70.81; H, 7.20; N, 13.47.

5) <u>1- (di- p- Tolylmethylene) -4,4- dimethyl -3- oxo -1,2- diazetidinium Hydroxide, Inner Salt</u> was obtained in 26% yield by pyrolyzing 5,5- dimethyl -2- (di- p- tolylmethylenehydrazono) - Δ^3 - 1,3,4-oxadiazoline, m.p. 207-209°. Anal. Calcd. for $C_{19}H_{20}N_2O$: C, 78.08; H, 6,85; N, 9.58. Found: C, 77.90; H, 7.10; N, 9.47.

6) <u>1- (Z- Phenylmethylene) -4,4- tetramethylene -3- oxo -1,2- diazetidinium Hydroxide, Inner Salt</u> was obtained as an oily material by the pyrolysis of 5,5- tetramethylene -2- (benzylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline, mol. wt. calcd. for $C_{13}H_{14}N_2O$: 214. Found (m.s): 214.

As the compound was not obtained in pure form, an elemental analysis was not performed. However, its identity is based on p.m.r (Table 9) and mass spectromety.

7) <u>1- (Z- p- Chlorophenylmethylene) -4,4- dimethyl -3- oxo -1,2-diazetidinium Hydroxide, Inner Salt</u> was prepared in 36% yield by the pyrolysis of 5,5- dimethyl -2- (p- chlorobenzylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline, m.p. 237-238°. Anal. Calcd. for $C_{11}H_{11}N_2ClO$: C, 59.33; H, 4.94. Found: C, 59.07; H, 5.24.

8) <u>Attempted Pyrolysis of 5,5- Dimethyl -2- (α- methylbenzylidene-hydrazono) - Δ^3 - 1,3,4- Oxadiazoline</u>: A solution of the oxadiazoline (0.5 g, 0.022 mol) in 10 ml of dry chlorobenzene was heated at the reflux temperature. The solution turned black in 2 hr. and the product was a tar. The expected diazetidinium inner salt could not be extracted from this tar. The p.m.r. spectrum of the reaction mixture after 2 hr indicated several signals in the 1.5 - 2.5 δ region, which may be attributed to the possible products of isomerization during the pyrolysis and to the products of their decomposition.

9) <u>Attempted Pyrolysis of 5,5- Diphenyl -2- (diphenylmethylene-hydrazono) - Δ^3 - 1,3,4- Oxadiazoline</u>: A solution of the oxadiazoline (0.5 g, 0.0012 mol) in 10ml of dry chlorobenzene was refluxed for 20 hr. The solution turned pink in a few minutes and the color stayed throughout the reaction period. About 7 ml of the chlorobenzene was distilled out and the solution was allowed to cool. On addition of 20 ml of petroleum ether, a red solid precipitated, which was filtered and recrystallized from a mixture of chloroform and petroleum ether, yield 150 mg, m.p. 115-120°, m.s. 360 (highest peak), i.r. (KBr) 1750 and 1800 cm $^{-1}$. The structure of the product was not established, but the spectral data are not consistent with the expected mesoionic structure.

When the same reaction was carried out using benzene as the solvent, the product obtained was yellow and showed all the spectral properties of the pink product indicated above. Presumably, the pink color is due to some impurity.

TRAPPING EXPERIMENTS

Pyrolysis of 2- substituted oxadiazolines was carried out in the presence of phenyl isocyanate or phenyl isothiocyanate according to the procedure outlined below. Infrared spectra of these trapped products are included in Results and Discussion (Tables 6 and 7); p.m.r. spectra of some of the products are also shown (Table 10).

1) Reactions of 5,5- Dimethyl -2- (di- p- chlorophenyl) methylene-hydrazono - Δ^3 - 1,3,4- oxadiazoline.

a) With Phenyl isocyanate: 5,5- Dimethyl -2- (di- p- chlorophenyl) methylenehydrazono - Δ^3 - 1,3,4- oxadiazoline (0.5 g, 0.0014 mol) was added to a solution of phenyl isocyanate (0.6 g, 0.005 mol) in 10 ml of dry chlorobenzene. Nitrogen gas was bubbled through for 5 min and the solution was refluxed for 20 hr. The solution was concentrated, by distilling out 7 ml of chlorobenzene, and allowed to cool. The solid which precipitated on addition of 25 ml of petroleum ether was filtered and recrystallized from petroleum ether - chloroform to give the product in 77% yield, m.p. 249-250°. Anal. Calcd. for $C_{28}H_{18}N_4O_3Cl_2$: C, 63.52; H, 3.40; N, 10.58. Found: C, 63.40; H, 3.44; N, 10.03.

A byproduct isolated as an oil in this reaction was identified as an oxindole formed by the reaction of 1 mole of dimethyldiazomethane and 2 moles of phenyl isocyanate with the loss of 1 mole of N_2; i.r. ($CHCl_3$) 3320 cm^{-1} and 1737 cm^{-1}, p.m.r. ($CDCl_3$) 1.525 (s, 6H), 7.85 (m, 9H), m.s. 280 (mol. ion).

b) With Phenyl isothiocyanate: A procedure similar to the one described in (a) was followed using phenyl isothiocyanate as the trapping agent. The solid precipitate formed after the addition of petroleum ether was filtered and recrystallized from petroleum ether chloroform mixture to give the product in 34% yield, m.p. 202-203°, m.s. 467 (mol. ion). Anal. Calcd. for $C_{24}H_{19}OSCl_2$: C, 61.54; H, 4.06; N, 8.97; S, 6.84. Found C, 61.68; H, 4.04; N, 8.67; S, 6.90. The product was identified as 2- phenylimino -3- (di- p- chlorophenyl) methyleneimino -4- oxo -5- dimethyl -1,3- thiazolidine.

2) Reactions of 5,5- Dimethyl -2- (diphenylmethylenehydrazono) - Δ^3 - 1,3,4- oxadiazoline.

a) With Phenyl isocyanate: The same procedure as in 1(a) was followed and the product isolated in 71% yield was recrystallized from petroleum ether chloroform mixture, m.p. 222-223° (lit.[51] m.p. 218-219°).

b) With p- Bromophenyl isocyanate: The product of the trapping experiment isolated in 68% yield was recrystallized from a mixture of petroleum ether and chloroform, m.p. 244-246°. Elemental analysis was not performed as the structure of the compound was determined by single crystal X-ray diffraction.

c) With Phenyl isothiocyanate: The product was isolated in 10% yield, m.p. 158-160°, m.s. 399 (mol. ion). The material was not obtained in analytically pure form. Its i.r. (Table 7) and p.m.r. (Table 10) were consistent with the proposed structure of 2- phenylimino -3- diphenylmethyleneimino -4- oxo -5- dimethyl -1,3- thiazolidine.

d) With Methanol: The oxadiazoline (0.5 g, 0.0017 mol) was dissolved in a solution of 2 ml of methanol and 20 ml of chlorobenzene and refluxed for 20 hr before 18 ml of the solvent was distilled out. The concentrated solution was cooled and 30 ml of petroleum ether was added. The product which precipitated (26% yield) was recrystallized from ethanol, m.p. 122° (lit.[21] m.p. 119-120.5°). The product was identified as benzophenone methyl carbazate.

3) Reactions of 5,5- Diphenyl -2- (diphenylmethylenehydrazono) - Δ^3 - 1,3,4- oxadiazoline.

a) With Phenyl isocyanate: A white solid was isolated in 60% yield, m.p. 222-223°. This material was identified as the same one formed in 2(a).

b) With Phenyl isothiocyanate a dark tar was formed and no pure material could be isolated.

4) Reaction of 5,5- Dimethyl -2- (di- p- tolyl) methylenehydrazono - Δ^3 - 1,3,4- oxadiazoline: This compound when pyrolyzed in the presence of phenyl isocyanate gave a crystalline solid in 62% yield, m.p. 228-229°. Anal. Calcd. for $C_{30}H_{24}N_4O_3$; C, 73.77; H, 4.92; N, 11.47. Found: C, 73.30; H, 4.89; N, 11.49.

Pyrolysis of this compound in the presence of phenyl isothiocyanate was not carried out.

5) Reactions of 5,5- Dimethyl -2- (isopropylidenehydrazono) - Δ^3 - 1,3,4- oxadiazoline.

a) Pyrolysis of the above oxadiazoline in the presence of phenyl isocyanate produced only tar and no useful product was isolated.

b) A similar trapping experiment with phenyl isothiocyanate also gave a crude oil which could not be purified.

6) Reaction of 5,5- Dimethyl -2- α- (p- bromophenyl) benzylidene-hydrazono - Δ^3 - 1,3,4- oxadiazoline.

Pyrolysis of this oxadiazoline in the presence of phenyl isocyanate gave a white solid in 64% yield, m.p. 230-231°. Anal. Calcd. for $C_{28}H_{19}N_4O_3Br$: C, 62.34; H, 3.40; N, 10.58. Found: C, 62.12; H, 3.71; N, 10.28.

HYDROLYSIS OF TRAPPED PRODUCTS

1) Basic hydrolysis of the adduct formed during the pyrolysis of 5,5- dimethyl -2- (diphenylmethylenehydrazono) - Δ^3 - 1,3,4- oxadiazoline in the presence of phenyl isocyanate: The above adduct formed in the trapping experiment 2(a) (0.05 g, 0.00011 mol) was refluxed for 1.5 hr in a solution of 1 ml of water in 4 ml of ethanol containing 0.5 g of sodium hydroxide. The solution was cooled and acidified with 5% HCl. The white precipitate formed on acidification was extracted with ether and the extract was dried over anhydrous magnesium sulfate. On evaporation of the ether a white solid was isolated in 42% yield, m.p. 164° (lit.[40] 163°). This was identified as benzophenone -4- phenylsemicarbazone by a mixture melting point determination.

2) Basic hydrolysis of the adduct formed during the pyrolysis of 5,5- dimethyl -2- (di- p- chlorophenylmethylenehydrazono) - Δ^3 - 1,3,4- oxadiazoline in the presence of phenyl isothiocyanate: The adduct formed in the trapping experiment 1(b) (75 mg, 0.0016 mol) was refluxed for 3 hr with 500 mg of potassium hydroxide in a solution of 2 ml of water in 10 ml of ethanol. The solution was cooled and acidified with 5% HCl. The solid precipitated was extracted with ether and the ether solution was dried with anhydrous magnesium sulfate. On evaporation of the solvent, a pale yellow solid was isolated (41% yield), which was recrystallized from ethanol

m.p. 228–229° (lit.[36] m.p. 230–231°). A mixture m.p., as well as comparison of the i.r. spectrum with that of an authentic sample, confirmed that the product of hydrolysis is p,p'- dichlorobenzophenone -4- phenylsemicarbazone.

3) Acid hydrolysis of the adduct formed during the pyrolysis of 5,5- dimethyl -2- (di- p- chlorophenylmethylenehydrazono) - Δ^3 - oxadiazoline in the presence of phenyl isocyanate: The adduct (75 mg, 0.0016 mol) was dissolved in 5 ml of dry benzene containing 100 mg of p- toluene sulphonic acid monohydrate. The solution was refluxed for 4 hrs. It was then cooled and 20 ml of water was added and the organic layer was extracted with ether. On evaporation of the solvent, a white solid was obtained in 22% yield, m.p. 145° (lit.[34] m.p. 145°). The compound was identified as p,p'- dichlorobenzophenone.

INSTRUMENTS AND TECHNIQUES

Melting Points. All the melting points were determined by using a Thomas Hoover Capillary Melting Point apparatus. All the values reported are uncorrected.

Infrared Spectra. A Beckman IR-5 Infrared Spectrophotometer was used for this purpose. Spectra were recorded either from KBr pellets or from a solution of the material in chloroform.

NMR Spectra. Proton spectra were recorded on a Varian T-60 or Varian HA 100 instrument. ^{13}C spectra were taken on a Bruker 90 NMR Spectrometer.

Mass Spectra. A CEC Model 21-110 Mass Spectrometer was used for recording the low resolution spectra.

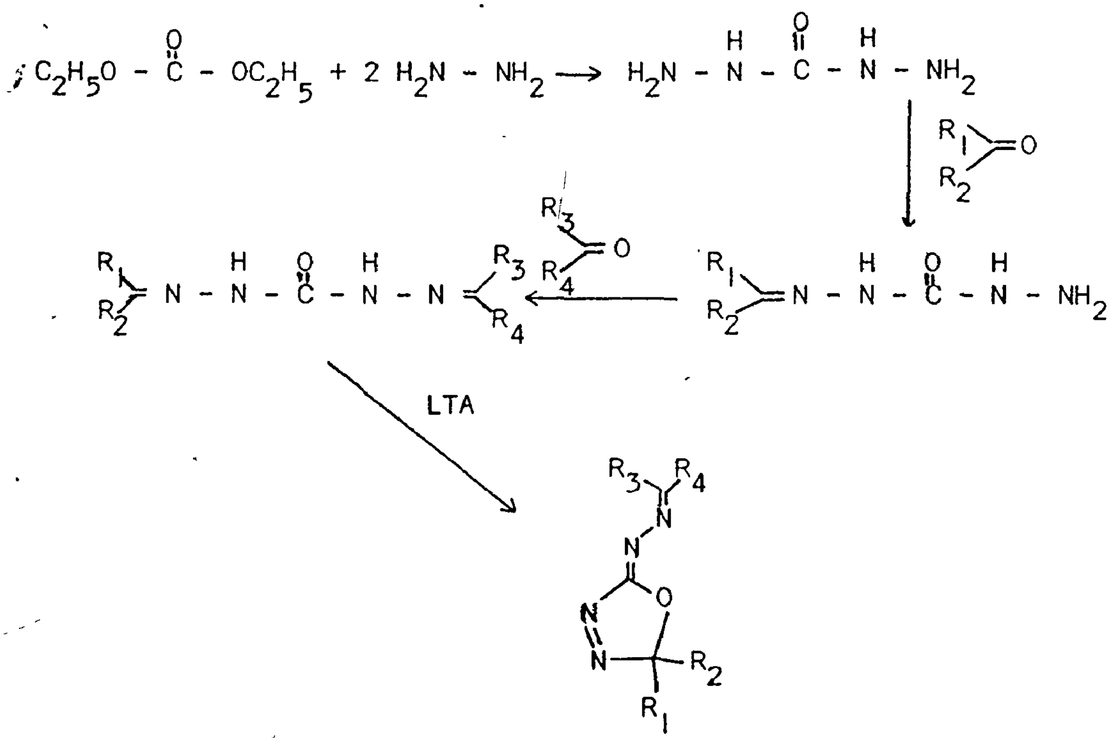
Chromatography. Plates for thin layer chromatography were prepared by using Baker Analyzed, Reagent Grade silica gel (60-200 mesh). The same material was used for column chromatography also. All the solvents used were of Analar grade.

Elemental Analysis. Microanalyses of all the new compounds synthesized were performed either by Schwarzkopf Microanalytical Laboratories, New York or Galbraith Laboratories, Inc., Knoxville, Tenn.

RESULTS AND DISCUSSION

SYNTHESIS OF 2- SUBSTITUTED OXADIAZOLINES

Oxidative cyclization of carbohydrazones is a convenient route for the synthesis of 2- hydrazono -Δ^3 - 1,3,4 - oxadiazolines. The general synthetic scheme is as outlined below[36].



(47)

Previous work had been concentrated mainly on the cyclization of ketone carbonhydrazones and the reaction was found to be fairly general. Extensive studies in this area[13,36] also indicated that the oxidation, with lead tetraacetate, of carbohydrazones with alkyl substituents at one end and aryl substituents at the other, resulted in selective cyclization at the methine carbon bearing the aliphatic substituents.

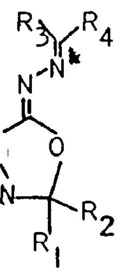
The present work extends the scope of this synthetic method to the cyclization of mixed carbohydrazones of aromatic aldehydes with aliphatic as well as cyclic ketones. The same selectivity of cyclization site is maintained unless the aryl ring is substituted with strongly electron donating groups. Table 2 lists a number of 2- hydrazono - Δ^3 - 1,3,4 - oxadiazolines (47) synthesized by this method.

Oxidative cyclization of carbohydrazones gave only one of the possible configurations at the exocyclic C = N bond as deduced from the sharp melting points of the products, from their p.m.r. spectra, and from thin layer chromatograms. By analogy, the Z- configuration can be assigned as the oxidation of 4- substituted semicarbazones of ketones always leads to the 2- imino -Δ^3 - 1,3,4-oxadiazolines with the Z- configuration[20]. From the steric point of view, it is also likely that the geometry at the carbon bearing the substituents R_3 and R_4 is the same as that of the starting carbohydrazone, with the N - N single bond anti to the larger substituent.

<u>Mechanism of Oxidative Cyclization</u>. A proposed mechanism for the cyclization of semicarbazones[20] by LTA involves the nucleophilic attack on lead by the amido nitrogen α- to the C = N bond. An analogous mechanism can be considered for the cyclization of the carbohydrazones as well.

Table 2

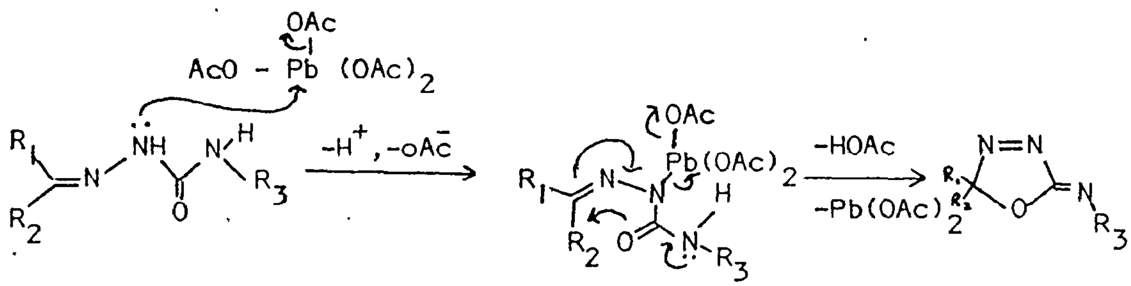
Oxadiazolines Synthesized by Cyclization with LTA

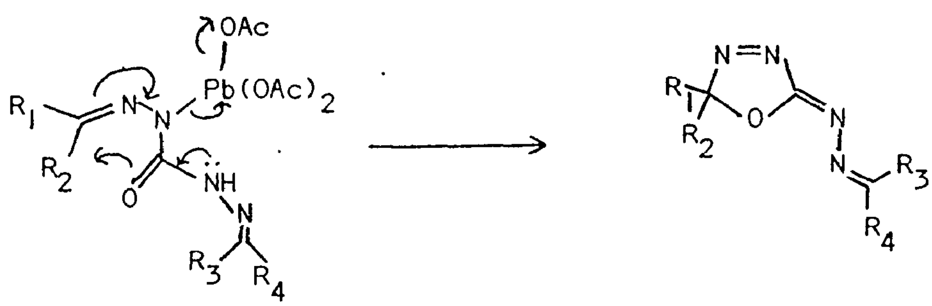


R_1	R_2	R_3	R_4
CH_3	CH_3	H	C_6H_5
CH_3	CH_3	H	p-$C_6H_4CH_3$
CH_3	CH_3	H	O-C_6H_4Cl
CH_3	CH_3	CH_3	C_6H_5
CH_3	CH_3	H	
CH_2CH_3	CH_3	H	C_6H_5
$(CH_2)_5$		H	C_6H_5
$(CH_2)_4$		H	C_6H_5
CH_3	CH_3	p-C_6H_4Cl	p-C_6H_4Cl

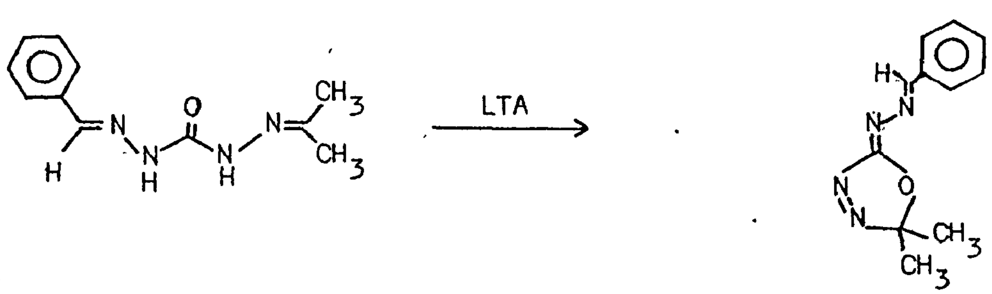
Table 2 (contd.)

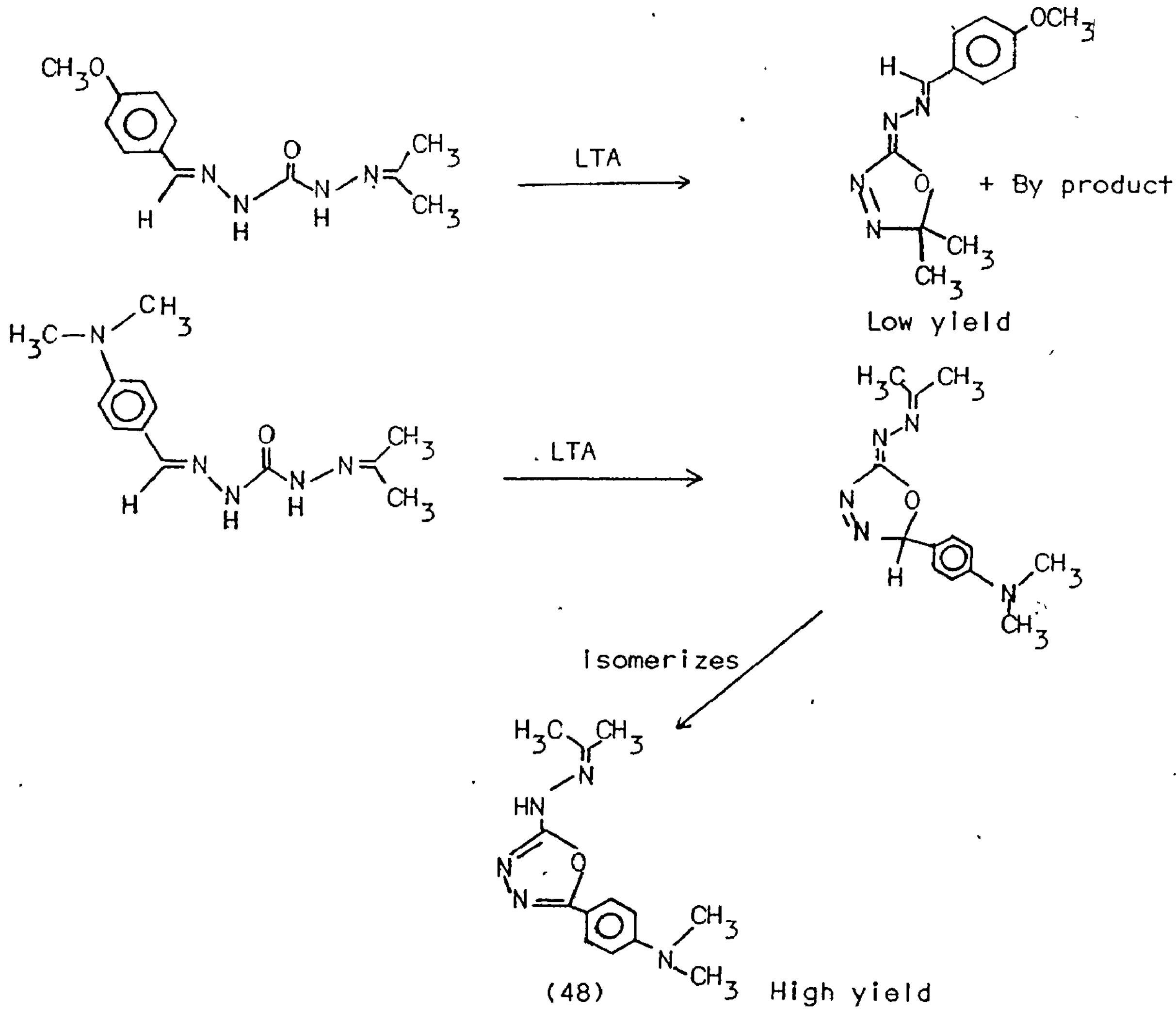
CH_3	CH_3	p-$C_6H_4CH_3$	p-$C_6H_4CH_3$
CH_3	CH_3	H	p-$C_6H_4OCH_3$
CH_3	CH_3	C_6H_5	p-C_6H_4Br





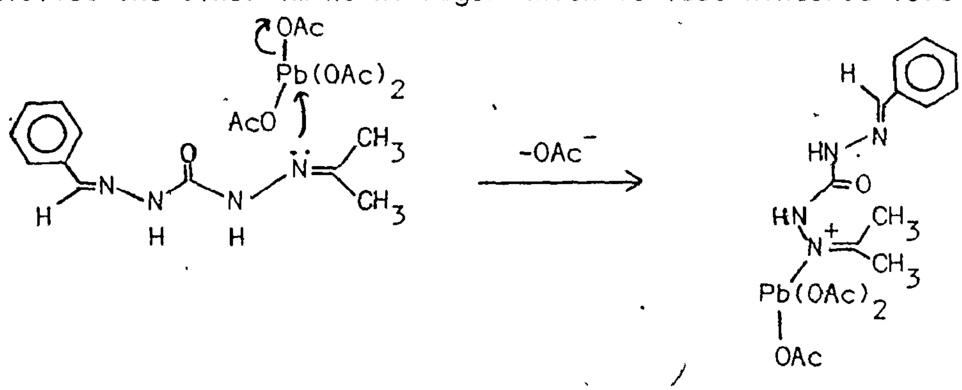
Our studies on the cyclization of certain carbohydrazones derived from aromatic aldehydes and acetone provided results which favour an alternative mechanism for this process. For example, when benzaldehyde acetone carbohydrazone was cyclized with lead tetra-acetate, the cyclization occurred almost exclusively at the alkyl end of the molecule.



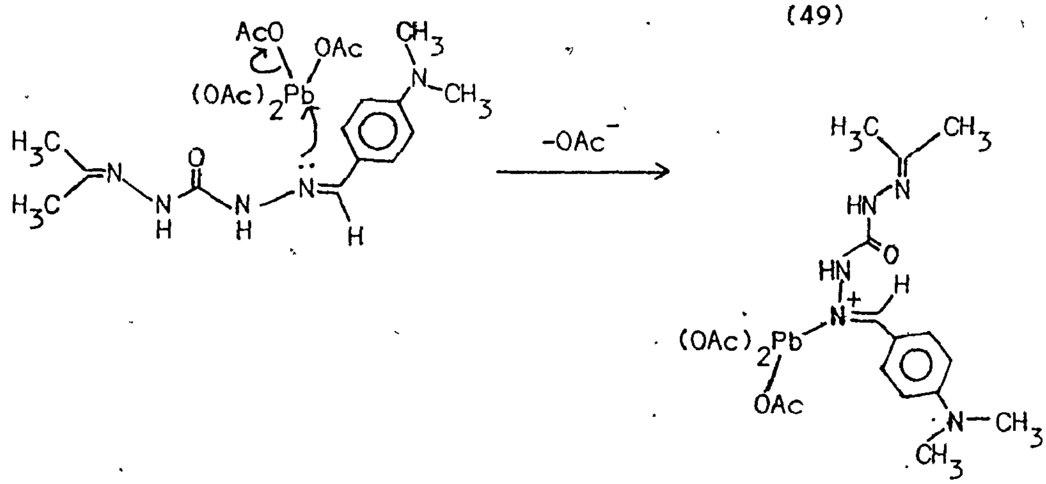


However, during the cyclization of p- methoxybenzaldehyde acetone carbohydrazone, a byproduct was isolated as a crude oil along with the expected oxadiazoline in lower yield. Although this byproduct was not obtained in pure form, its p.m.r spectrum indicated two methyl signals in 1:1 ratio. This, presumably, could be due to the isomer resulting from the cyclization at the aryl end, which leaves the sp^2 carbon bearing the methyl substituents intact. When the p-methoxyl group was replaced by a p- dimethylamino group, the only product isolated is the oxadiazole (48) which resulted from the cyclization at the aryl end followed by isomerization. The presence of an i.r absorption at 3187 cm^{-1} (NH) and the absence of the exocyclic C = N stretch as well as the presence of two methyl signals in the p.m.r spectrum are consistent with this structure.

In the above experiments, we have in fact, gradually increased the electron density in the conjugated Π system of the starting carbohydrazone, by introducing electron donating groups, keeping the steric factors nearly the same. The difference observed in the orientation of the cyclization, in the presence and absence of the strongly electron donating group, prompted us to propose a new mechanism for the cyclization. In the absence of any electron donating group, the steric effect is predominant which prevents the lone pair on the imino nitrogen adjacent to the benzene ring from attacking the lead. Therefore, the initial nucleophilic attack involves the other imino nitrogen which is less hindered leading to

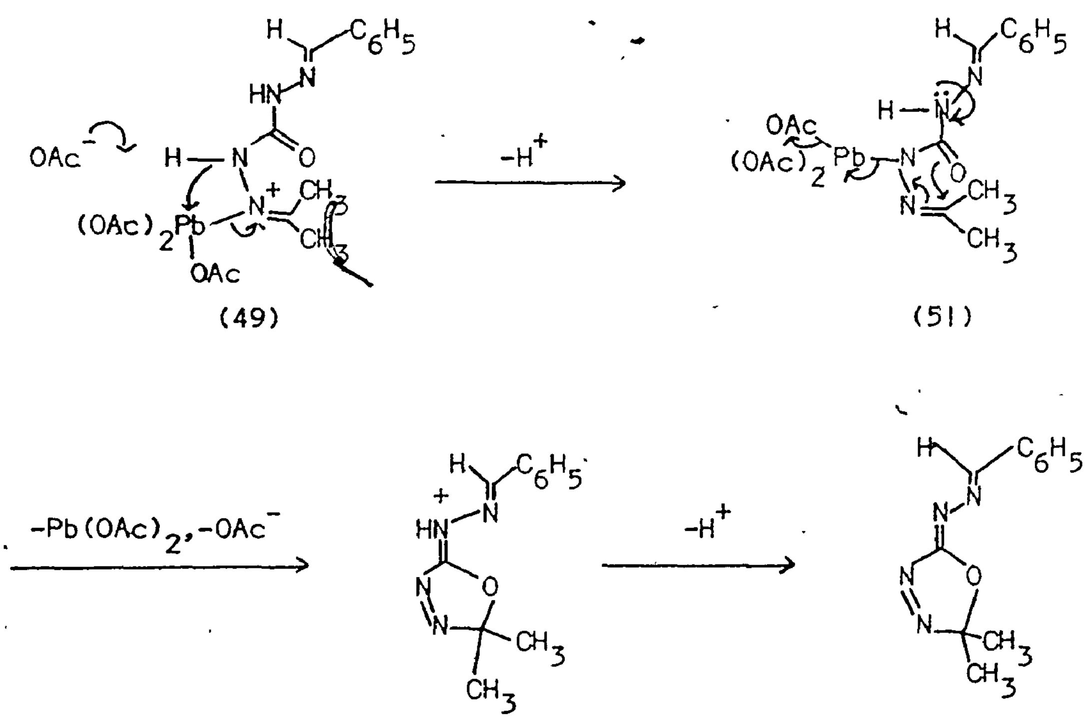


(49)



(50)

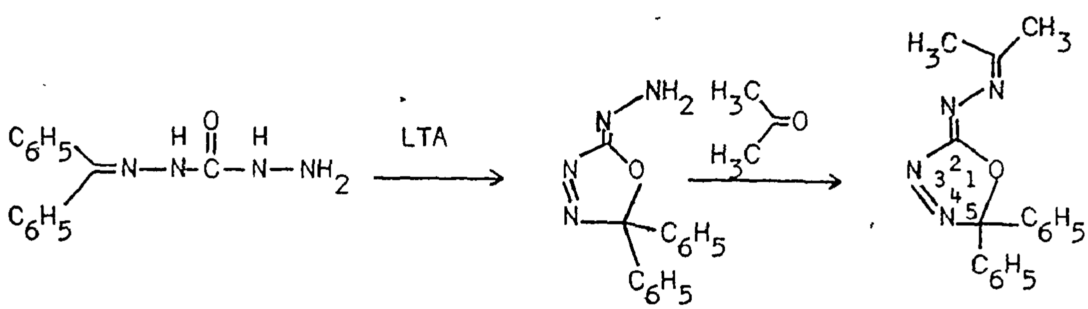
the intermediate (49). But, when the benzene ring is substituted by the p- dimethylamino group, the strong electronic effect offsets the steric effect and the intermediate (50) is formed, which is better stabilized by the electron donating group. However, neither of these intermediates can account for the stereochemistry at the exocyclic C=N bond in the product (N-N bond on the same side of the oxygen in the ring). Therefore, a 1,2 shift of lead, leading to the new intermediate (51) is postulated. The bulky Pb $(OAc)_3$



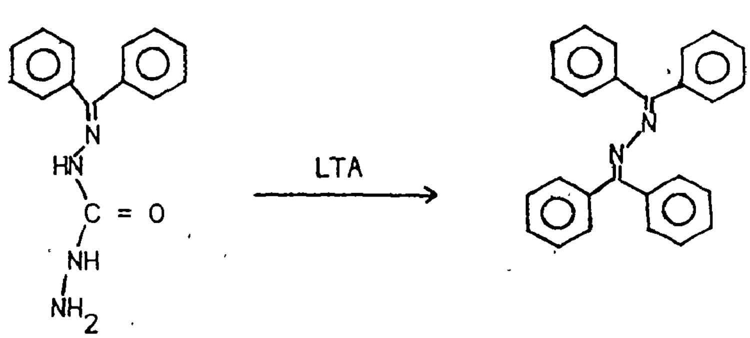
(49) (51)

group in (51) forces the side chain to eclipse the carbonyl oxygen and hence the stereochemistry of the product is determined. The preceding arguments account for the stereochemistry as well as the regiochemistry of the cyclization. This seems to be consistent, because, in the case of p- methoxy substituent, which is not as strongly electron donating as the p- dimethylamino group, the cyclization occurs at both the ends leading to two products. These observations also suggest that the regiospecificity of the cyclization is controlled by the nature of the substituent on the benzene ring.

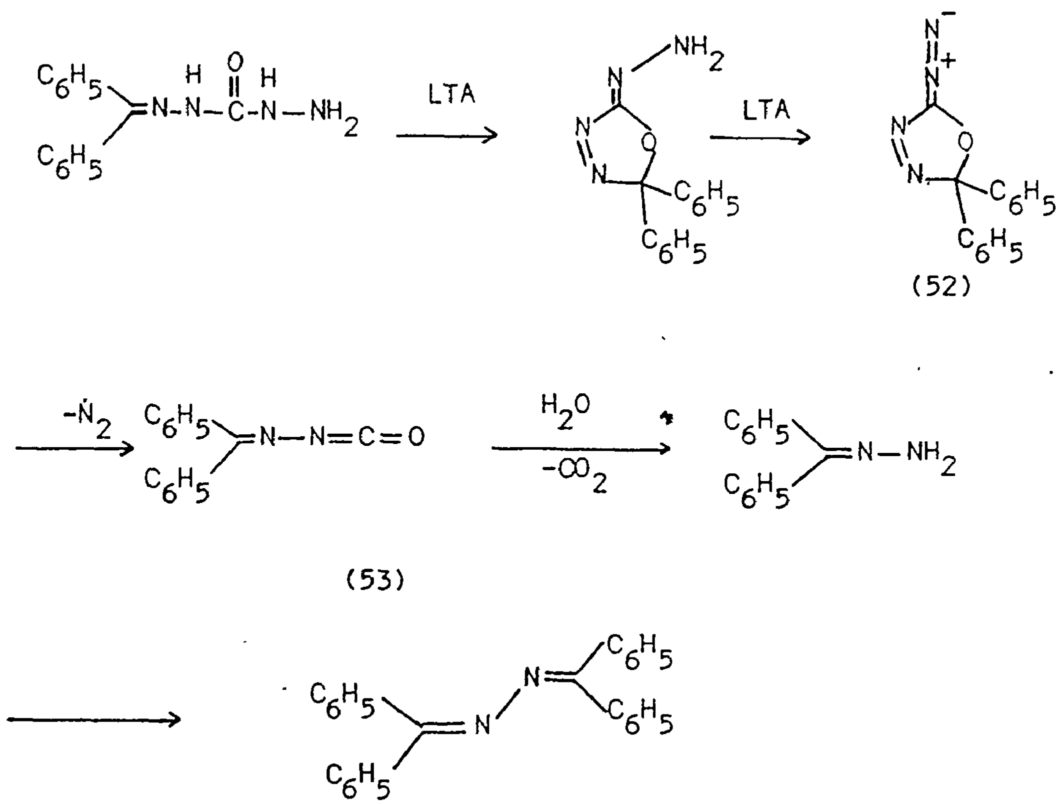
Due to this regioselectivity of the cyclization of carbohydrazones, it was not always possible to have aryl groups at the 5- position in the final oxadiazoline[13, 36]. As a possible alternative, the following cyclization of benzophenone -4- amino-semicarbazone was attempted, with a view to condensing the



with the aliphatic ketone in the final step. This method, however, was not successful because the oxidation resulted in the formation of the azine rather than the expected cyclized material. This was



rationalized on the basis of the possible oxidation of the cyclized product with LTA to the corresponding diazo compound (52) followed by the loss of nitrogen. The resulting conjugated isocyanatoimine



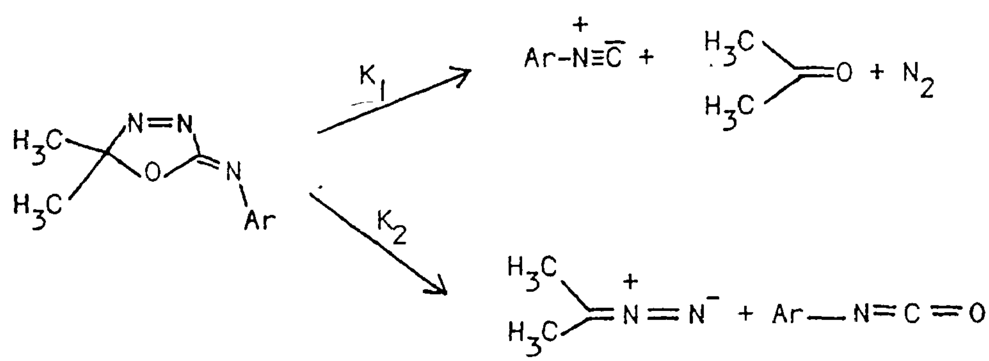
(52)

(53)

(53) is hydrolyzed to the unstable carbamic acid which is decarboxylated to the hydrazone. The isocyanatoimine is presumably stable under the reaction conditions ($\sim 5^{\circ}C$), although it is unstable at elevated temperatures. Formation of the azine by the disproportionation of the hydrazone is generally observed during the preparation of benzophenone hydrazone.

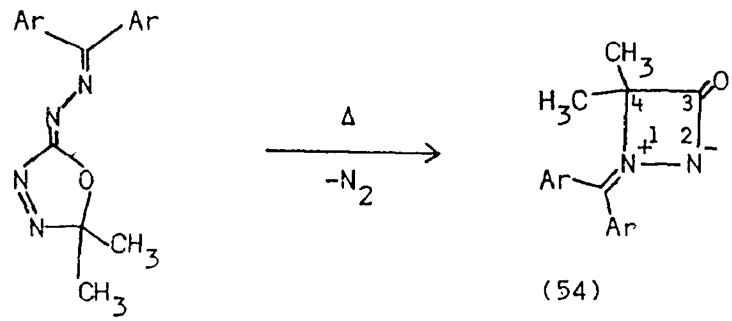
PYROLYSIS OF OXADIAZOLINES

Warkentin and coworkers have carried out studies on the pyrolysis of the Δ^3 - 1,3,4 - oxadiazoline system[20,21,36]. Thermal decomposition of 5,5- dimethyl -2- (arylimino) - Δ^3 - 1,3,4 - oxadiazolines in bromobenzene at 150° gave products arising from two modes of decomposition. However, only the aryl isocyanate and acetone could be identified from their characteristic infrared



absorptions. The diazomethane as well as the isonitrile were not stable enough to be detected in the infrared spectra, although the odour of the isonitrile was present in the solution. However, during the decomposition of the corresponding diphenyl compound, diphenyl-diazomethane could be detected by its characteristic infrared absorption at 2040 cm^{-1} [36].

Work on the decomposition of 5,5- dimethyl -2- (hydrazono) - Δ^3 - 1,3,4 - oxadiazolines led to some interesting results[21]. The



(54)

pyrolysis of this system produced a four membered azomethine imine ylid (54) in about 40% yield. This is a fairly general method for the preparation of four membered azomethine ylids. The other known synthetic route[25] to that mesoionic ring system has certain limitations and it was not possible to make compounds with two substituents at the 4- position or with a hydrogen in the place of an aryl group (see page 18).

Part of the present work deals with the investigation of this pyrolytic process in detail. It was possible to synthesize several compounds in the series which were not available by the alternate route. The following table of compounds added to the series indicates the scope of the present approach.

However, attempts to synthesize compounds where R_3 or R_4 is an alkyl group were not successful. A rationale for this

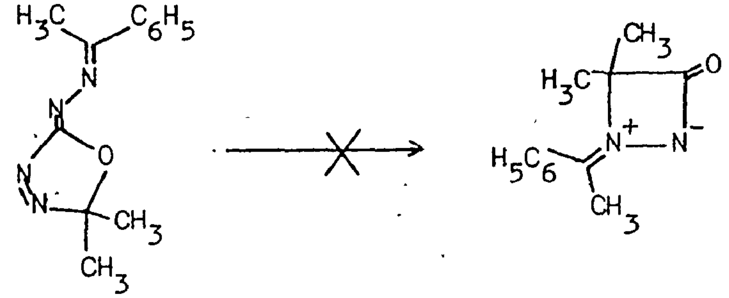
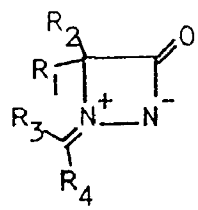


Table 3

Azomethine Ylids Prepared from Oxadiazolines



R_1	R_2	R_3	R_4
CH_3	CH_3	H	C_6H_5
CH_3	CH_3	H	p-$C_6H_4CH_3$
CH_3	CH_2CH_3	H	C_6H_5
CH_3	CH_3	H	p-C_6H_4Cl
CH_3	CH_3	p-$C_6H_4CH_3$	p-$C_6H_4CH_3$
CH_3	CH_3	p-C_6H_4Cl	p-C_6H_4Cl
$(CH_2)_4$*		H	C_6H_5

* The last compound in the table was not isolated in pure form. Its identity was based on p.m.r. and mass spectra.

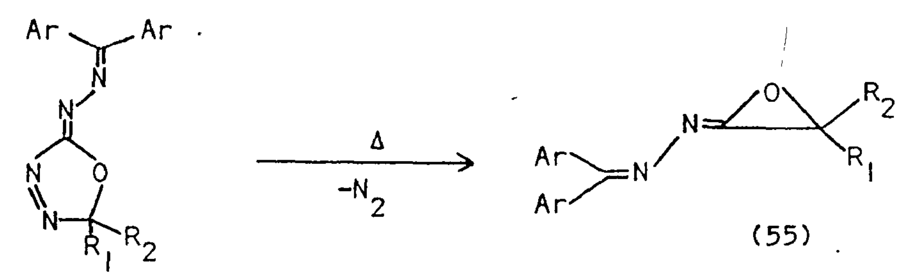
observation is given elsewhere in the thesis (page 73).

Pyrolysis of 5,5- diphenyl -2- (diphenylmethylene) hydrazono - Δ^3 - 1,3,4 - oxadiazoline also did not yield the expected mesoionic compound. Instead, a yellow solid whose structure is not known, was isolated in about 40% yield. This compound showed infrared absorption at 1750 cm^{-1} and 1800 cm^{-1} and its mass spectrum had the highest peak at 360, which incidentally corresponds to the molecular weight of benzophenone azine.

Spectral properties of the azomethine imine ylids and the mechanistic details of their formation will be discussed in subsequent parts of the thesis.

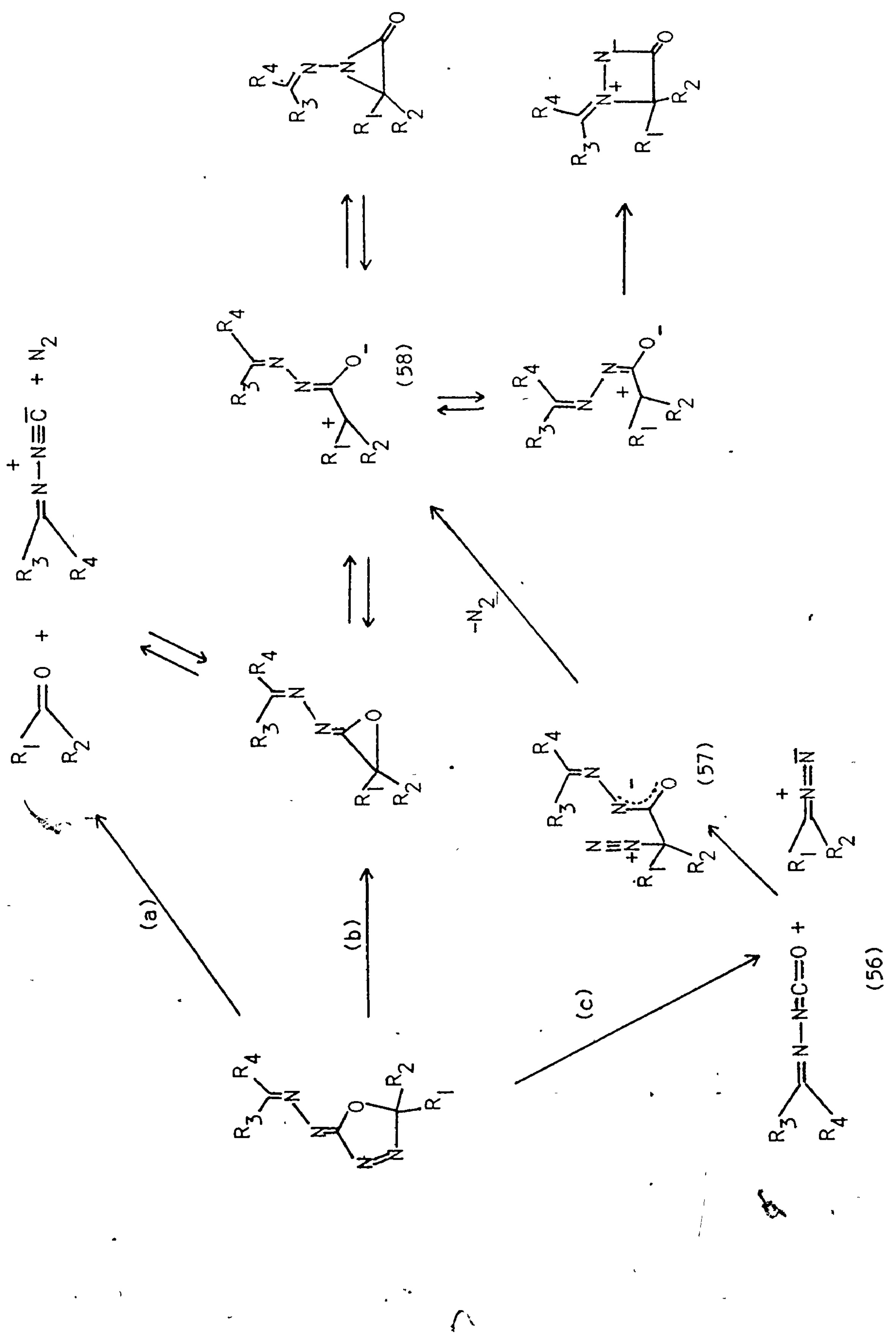
MECHANISM OF FORMATION OF AZOMETHINE IMINE YLIDS

The formation of the four membered mesoionic compound from the five membered oxadiazoline ring system is an interesting problem from a mechanistic point of view. By analogy to McGreer's work[17,18,19], quoted elsewhere in this thesis (page 9), on the pyrolysis of 1- pyrazolines to cyclopropanes, one could reasonably expect the formation of an iminooxirane (55) during the pyrolysis of a 5,5- dialkyl -2- (hydrazono) -Δ^3 - 1,3,4 - oxadiazoline. But,



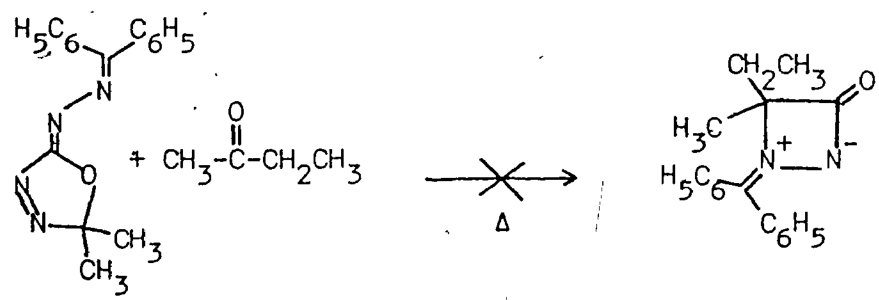
(55)

Iminooxiranes are known to be unstable[41,42] and they could either rearrange to the α- lactam or further fragment to isonitriles and carbonyl compounds. Therefore, it is conceivable that an iminooxirane intermediate is generated in the process, which subsequently rearranges to the azomethine imine ylid. Several mechanisms can be considered for this pyrolytic process and initially, we proposed the following three pathways, all of them involving the iminooxirane intermediate[33].


(a)
(b)
(c)
$-N_2$
(56)
(57)
(58)
$+ N_2$

Path (a) represents a three bond cleavage which fragments the oxadiazoline into a carbonyl compound, an isonitrile and molecular nitrogen. There is some precedence for this type of fragmentation as demonstrated by the pyrolysis of 2- arylimino - Δ^3 - 1,3,4 - oxadiazolines[20]. Reactions of isonitriles with ketones, leading to iminooxiranes have also been reported in the literature[43].

However, no ketone was detected during the pyrolysis either by infrared spectroscopy or by trapping with 2,4- dinitrophenylhydrazine. Another piece of evidence against path (a) was obtained when the oxadiazoline ($R_1 = R_2 = CH_3$, $R_3 = R_4 = C_6H_5$) was decomposed in the presence of 2- butanone without incorporating it into the product[21].



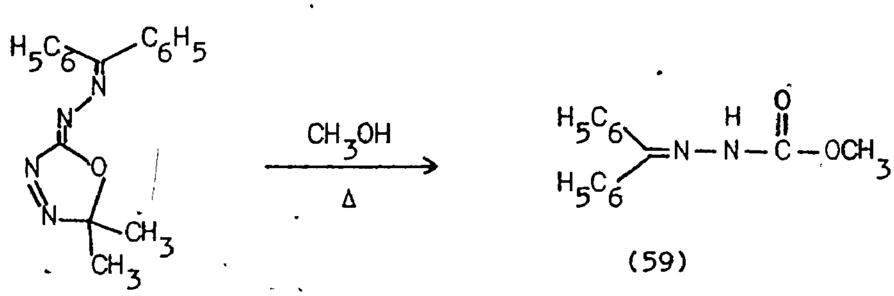
According to path (b), an iminooxirane is formed by the concerted loss of nitrogen. Although, this is mechanistically feasible, the strong evidence obtained in favour of path (c) makes it less likely.

Path (c) postulates the initial fragmentation of the oxadiazoline into a diazoalkane and a conjugated isocyanatoimine (56). These two fragments recombine to form the dipolar species (57), which is transformed by loss of nitrogen, into the dipolar form (58), which then rearranges to the azomethine imine ylid. As it was not possible to isolate and characterize the intermediates, experiments were carried out to trap them chemically. In order to achieve this, pyrolysis of the oxadiazolines was carried out in the presence of reagents like isocyanates and isothiocyanates.

For example, when the pyrolysis of 5,5- dimethyl -2- (diphenymethylene) hydrazono - Δ^3 - 1,3,4 - oxadiazoline was carried out in the presence of phenyl isocyanate in chlorobenzene solution under refluxing conditions ($\sim 130^{\circ}$), two products were isolated. Spectroscopic data indicated that these products are formed by the reaction of phenyl isocyanate separately with the two fragments formed according to path (c). Analysis of the p.m.r spectrum (Fig. 2) of the major compound isolated from the pyrolysis of 5,5- dimethyl -2- (di - p - tolyl) methylenehydrazono -Δ^3 - 1,3,4 - oxadiazoline in the presence of phenyl isocyanate indicated that it is a 1:2 adduct of the intermediate isocyanatoimine and phenyl isocyanate (aromatic to methyl proton ratio of 18:6). The highest peaks observed in the mass spectra of all the products from trapping experiments with isocyanates, including the one mentioned above, corresponded to that of a 1:1 adduct. However, an X-ray crystal structure confirmed that 1:2 adducts of isocyanatoimines and isocyanates are formed in the trapping experiments. The second product isolated as an oil in the trapping experiment was identified as an oxindole (67)* (page 80), which is a 1:2 adduct of the diazoalkane and the isocyanate less one mole of nitrogen. The structure of this product was confirmed by comparing its spectral properties with the authentic sample prepared by a different method[44].

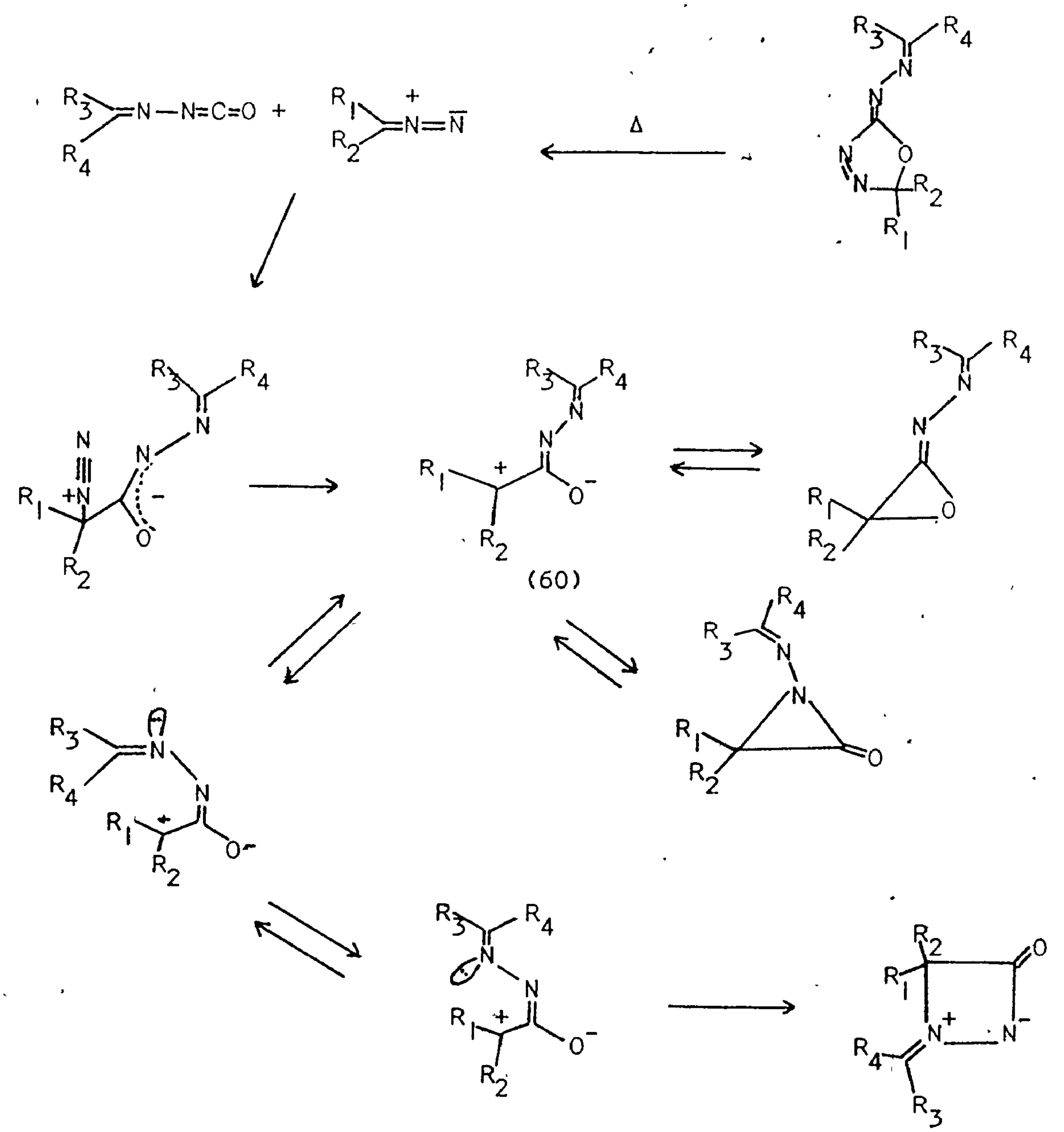
In addition to the above information, there was other spectroscopic evidence supporting the fragmentation represented by path (c). Mass spectra of all the oxadiazolines and the products formed in the trapping experiments with isocyanates displayed an intense peak corresponding to the respective isocyanatoimine. Electron impact processes are often complementary to the thermal fragmentation[63,64] and hence it is conceivable that similar intermediates are formed during the pyrolysis as well. A loss of 42 mass units (due to the loss of the -N = C = O moiety which is characteristic of all the isocyanates) from this peak was also characteristic of all these compounds. The infrared spectrum of the partially decomposed solution of 5,5 diphenyl -2- (diphenylmethylene) hydrazono -Δ^3 - 1,3,4 - oxadiazoline in chlorobenzene indicated a sharp peak at 2040 cm^{-1} suggesting the presence of diphenyldiazomethane which is also indicated by the pink color of the solution. The presence of diphenyldiazomethane implies the existence of the other fragment as well, which is the conjugated isocyanatoimine.

Further to this, when the pyrolysis of 5,5- dimethyl -2- (diphenylmethylene) hydrazono - Δ^3 - 1,3,4 - oxadiazoline was carried out in the presence of methanol, the product isolated was identified as benzophenone methyl carbazate (59), presumably formed as a result of the addition of methanol to the isocyanatoimine.

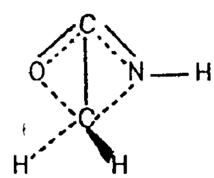


(59)

All the evidence obtained from these trapping experiments tends to suggest the formation of the conjugated isocyanatoimine (55) and the diazoalkane as the intermediates during the pyrolysis of the oxadiazoline. On the basis of this, path (a) and (b) which do not involve these intermediates can be ruled out and path (c) can be considered as the actual process. Consequently, the mechanism of this transformation can be represented as follows.



In a recent publication based on theoretical calculations[45], Talaty and Zandler suggest that the isomerization of an iminooxirane to the α- lactam does not have to go through the dipolar intermediate (60). They consider that an intermediate (61) involving an in plane bending of the carbonyl oxygen will have lower energy than the charge separated structure (60). However, the calculations are



(61)

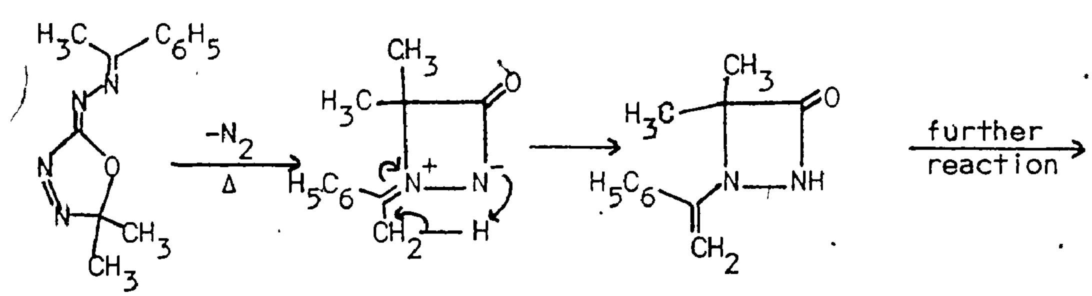
based on unsubstituted systems whereas, all the systems we have worked with involve a tertiary cationic centre and a resonance stabilized anionic part in the dipolar intermediate. Those features should favour the dipolar intermediate over a transition state similar to (61), with its severe angle strain.

So far, only the Z- isomer of the azomethine imine ylid has been isolated in the pyrolysis of 2- (hydrazono) - Δ^3 - 1,3,4 - oxadiazolines, where R_3 or R_4 is a hydrogen. As the geometry of the starting carbohydrazone is retained during the oxidative cyclization (E- configuration), in order to explain the Z- geometry of the ylid, we have to invoke the inversion of both the amido and imino nitrogens. The inversion of the amido nitrogen could occur in the zwitterion (60) which has a C-N bond order less than two due to the conjugation. The resulting configuration, however, is not geometrically suited for closure to the four membered ring.

Subsequent inversion of the imino nitrogen leads to the right geometry for closure to the Z- isomer. It is interesting to note that a rotation around the N - N bond instead of an inversion of the imino nitrogen would lead to the product with the E- configuration, which in fact has not been isolated.

The isocyanatoimine intermediate (56) postulated in the above mechanism has not been isolated so far, but recently similar conjugated isothiocyanatoimines have been detected by infrared spectroscopy[46]. They undergo rapid dimerization at room temperature and the dimers have been characterized by their molecular weight and spectroscopic properties. Certain unconjugated N- isothiocyanatoamines also have been reported in the literature[47,48,49].

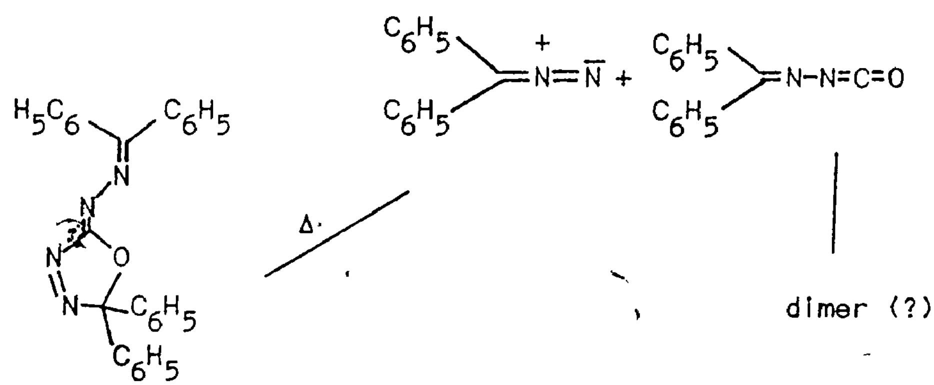
The reason for not obtaining the expected mesoionic compound during the pyrolysis of 5,5- dimethyl -2- (α- methylbenzylidene) hydrazono - Δ^3 - 1,3,4 - oxadiazoline (62) is not well understood. This could presumably be due to the isomerization of



(62) (63)

the initial product into an enamine (63) capable of undergoing further reactions[50].

A probable reason for the lack of formation of the expected mesoionic product from the pyrolysis of 5,5- diphenyl -2-(diphenylmethylene) hydrazono - Δ^3 - 1,3,4 - oxadiazoline could be the lower reactivity of diphenyldiazomethane, which is one of the products of the initial fragmentation. Under such circumstances, the most likely choice for the isocyanatoimine is to react with



itself forming a dimer or trimer. However the strucure of this product is not yet established.

Trapping experiments using phenyl isothiocyanate led to an interesting heterocyclic ring system whose formation also can be explained on the basis of the proposed mechanistic pathway (c). Structures of the products obtained from trapping experiments will be discussed in detail in the next section of the thesis.

STRUCTURE OF PRODUCTS FROM TRAPPING EXPERIMENTS

Although the spectral characteristics of the products from the trapping experiments and the observation of diphenyldiazomethane by infrared spectroscopy gave some idea about the thermal fragmentation of 2- (hydrazono) -Δ^3- 1,3,4- oxadiazolines, we were interested in the actual structure of these adducts.

Isocyanate Adducts: Phenyl isocyanate was found to be very effective in trapping the intermediates formed in the pyrolysis. The isolation of the major product was relatively easy and the yield was high (~ 80%). When the pyrolysis of 5,5- dimethyl -2- (di- p- tolyl) methylene hydrazono - Δ^3 - 1,3,4- oxadiazoline was carried out in the presence of phenyl isocyanate, the major product isolated appeared to be a 1:2 adduct of the intermediate isocyanatoimine and phenyl isocyanate as evidenced by the proton ratio in the p.m.r spectrum (Fig. 2). Spectroscopic or chemical methods were not of much use in conclusively establishing the structure of the adduct, although some information could be deduced from these data. Therefore, single crystal X-ray diffraction was used for the determination of the structure. For this purpose, 5,5- dimethyl -2- (diphenylmethylene) hydrazono - Δ^3 - 1,3,4- oxadiazoline was pyrolyzed in the presence of p- bromophenyl isocyanate. The crystallographic data confirmed the following structure (64) for the adduct.

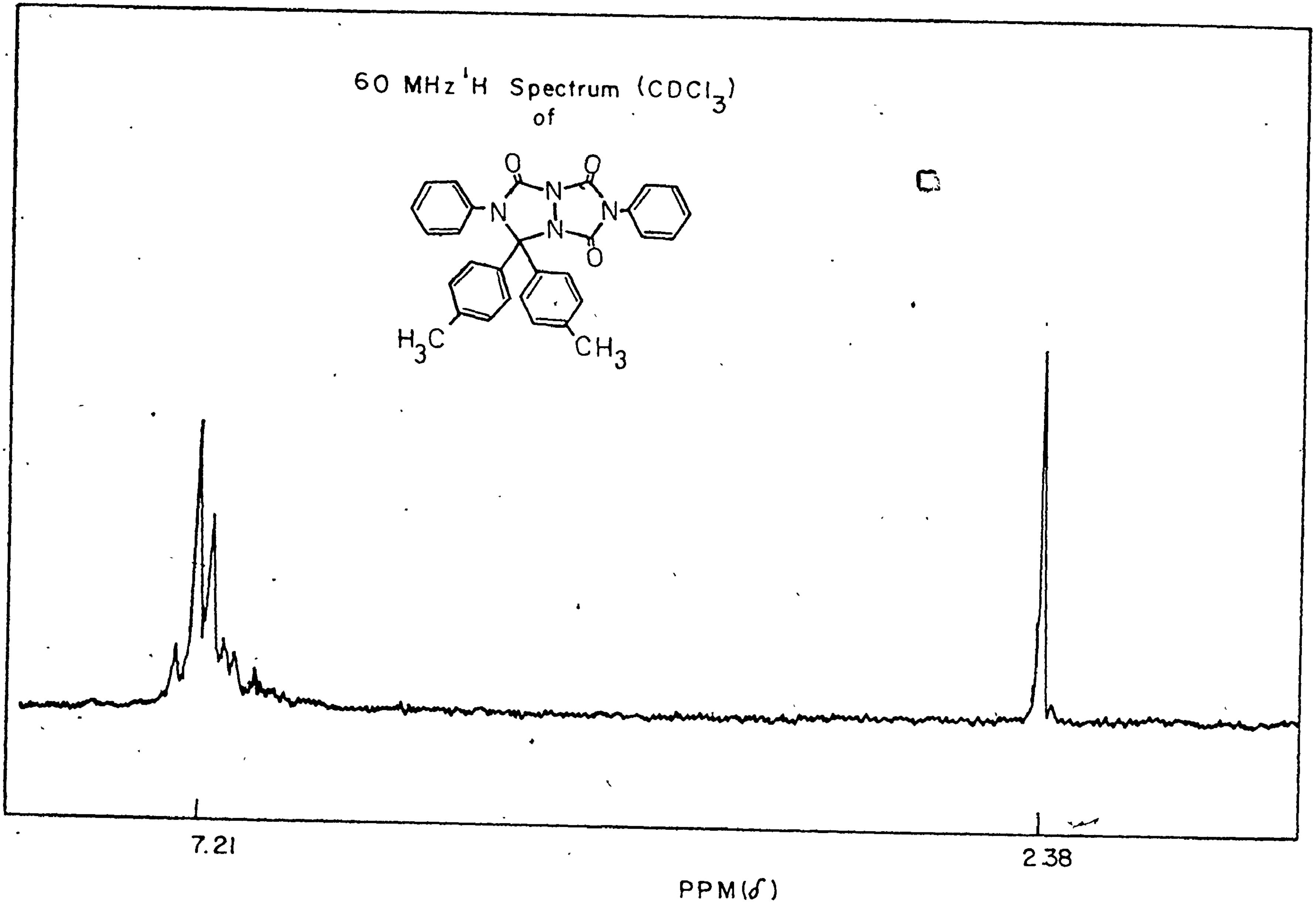
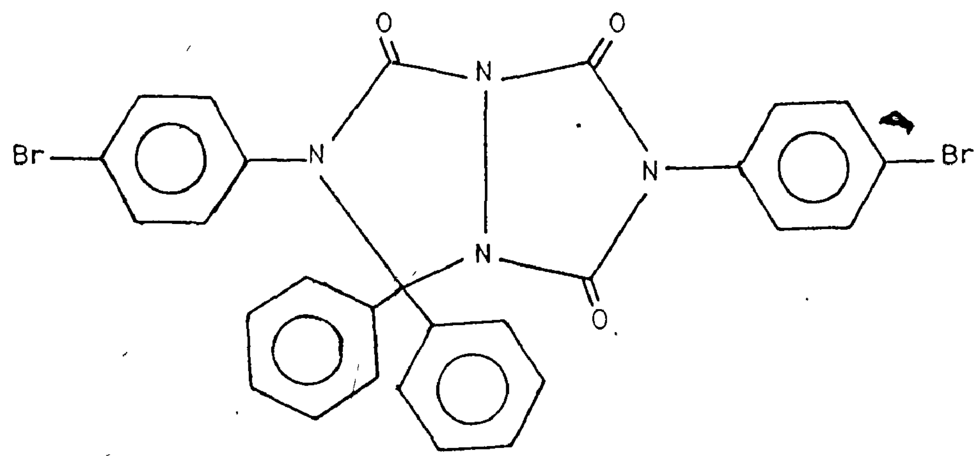
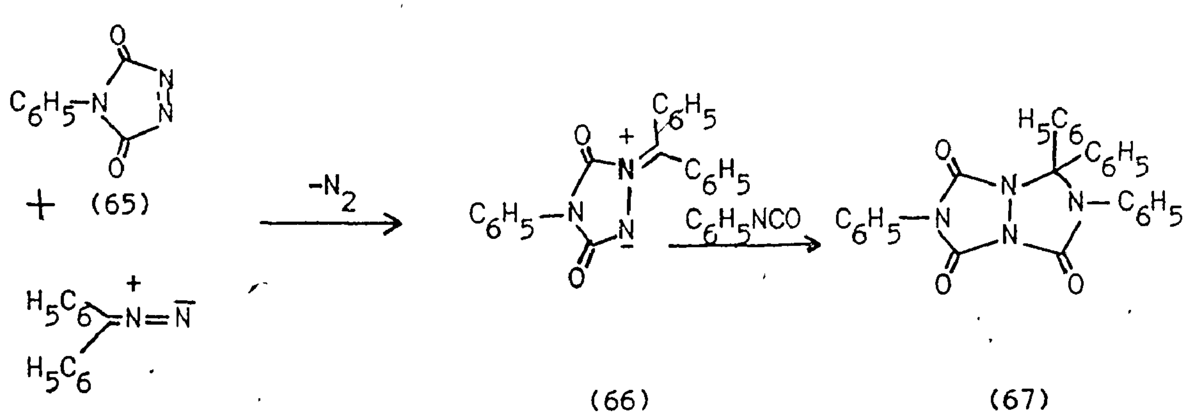


Fig. 2



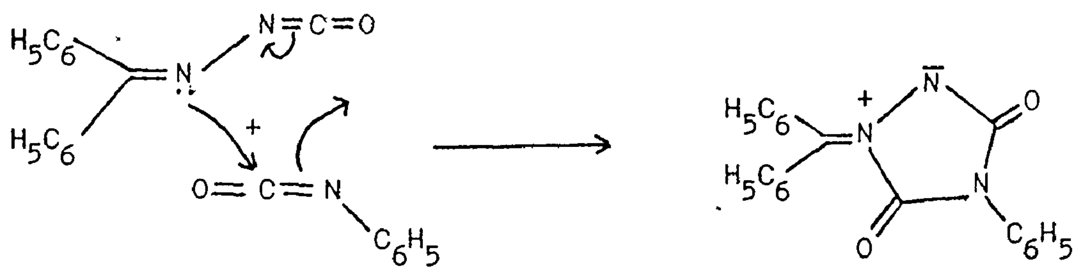
(64)

Once the structure of the product was known, it was of interest to find out the mechanism of its formation. Incidentally, a product similar to (64), with all the benzene rings unsubstituted, has been synthesized as illustrated in the following equations[51, 27].



(65) (66) (67)

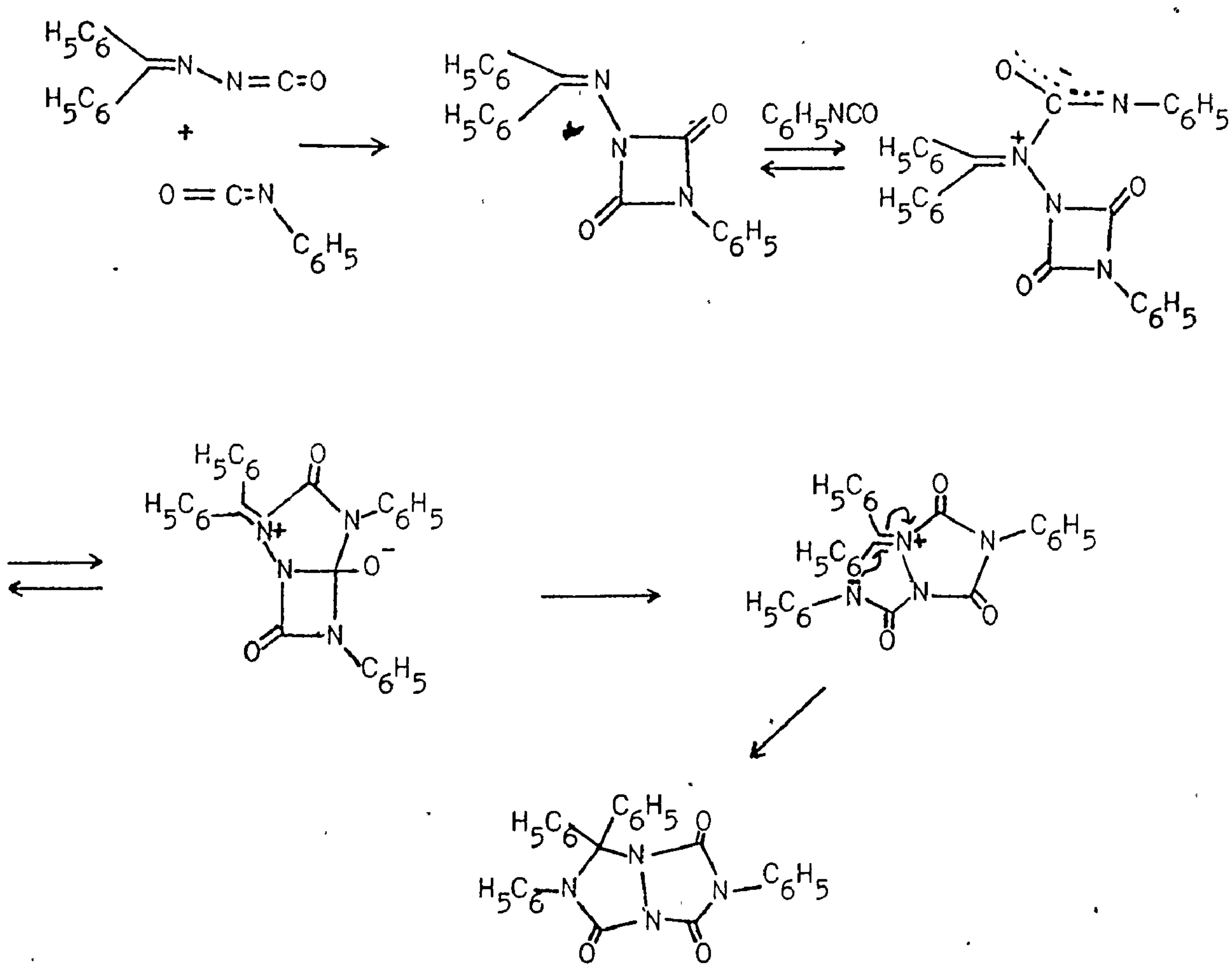
Although this is an interesting synthetic method with great potential, only compound (67) has been reported to date. That synthesis of (67) provided us with an analogy, for it is reasonable to presume that the dipolar species (66) is an intermediate in our trapping experiments as well. Therefore, the initial step in our reaction could be the combination of the isocyanatoimine and one mole of phenyl isocyanate to form (66). Although, this could be a symmetry-allowed, concerted 1,3- cycloaddition involving 6π electrons, it is interesting to note that all the 1,3- dipoles



(66)

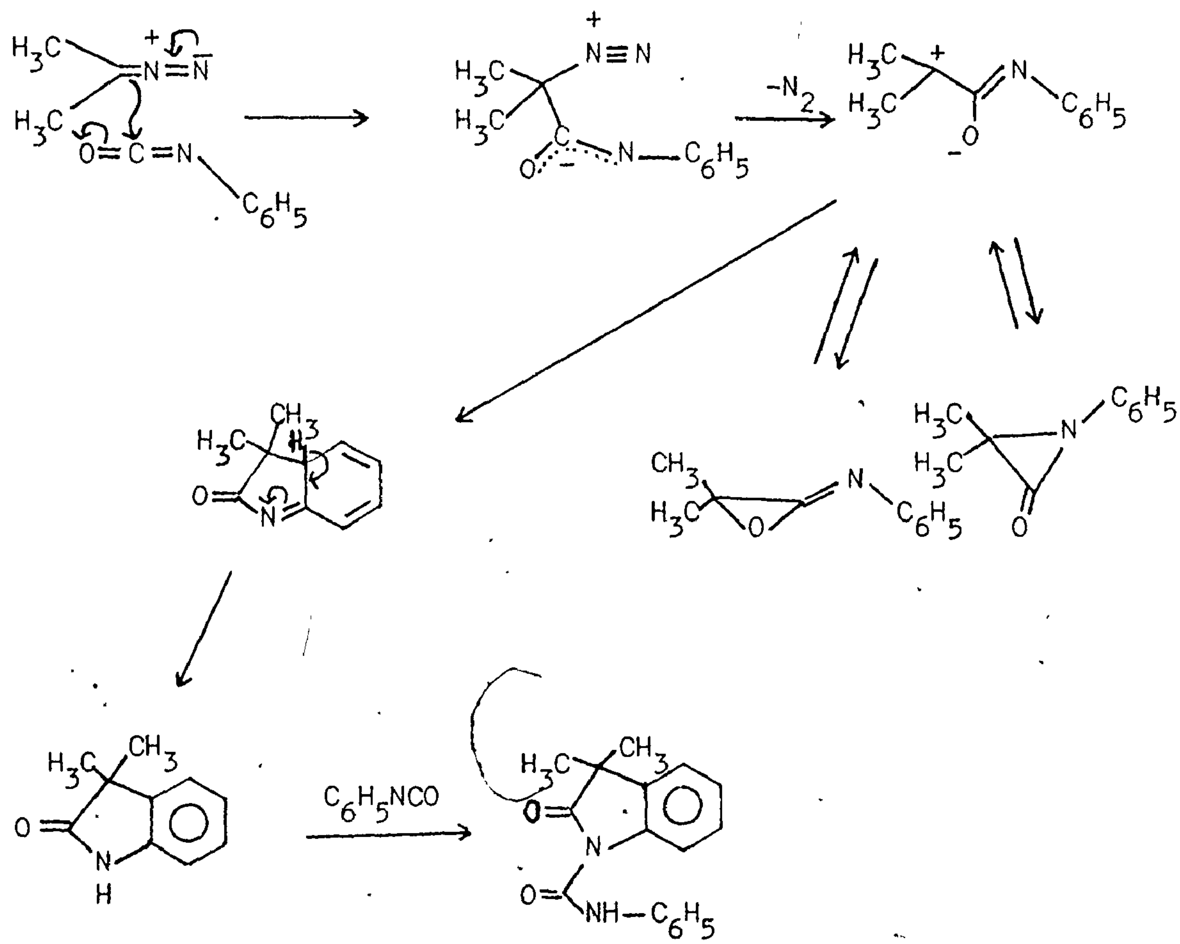
known to date have charge separated structures [52,53,54,55]. If this is the correct mechanism, it could be the first example in which a molecule without a formal dipole functions like a 1,3- dipole in reacting with a 1,3- dipolarophile to form a 1,3- dipolar structure. There are several examples in the literature[56,57,58] for the dimerization and trimerization of isocyanates, but nothing similar to the present case is known.

An alternative mechanism worth considering is the following which involves a 2 + 2 cycloaddition of the isocyanatoimine and phenyl isocyanate. The only argument against this pathway is the formation of a localized anion from a delocalized one in step 3 which is less likely.



(67)

A second product isolated as an oil in the trapping experiment with phenyl isocyanate, showed infrared, p.m.r., and mass spectra consistent with those of an oxindole (67)* synthesized through a different route[44]. The spectral properties suggested that it is a 1:2 adduct of the diazoalkane and phenyl isocyanate less one mole of nitrogen. There are several mechanistic possibilities leading to this product and the following is one among them.



(67)*

Isothiocyanate Adducts. The chemistry of the trapping experiments with the isothiocyanate was particularly interesting because it was quite different from that of the isocyanate. The pyrolysis of 5,5-dimethyl -2- (di- p- chlorophenyl) methylenehydrazono - Δ^3 - 1,3,4- oxadiazoline in the presence of phenyl isothiocyanate gave a solid product in about 40% yield. No minor product was isolated in this case. The parent peak at 467 in the mass spectrum and the ratio of the methyl to the aromatic protons (6:13) in the p.m.r. spectrum (Fig. 3) indicated that it is a 1:1 adduct of the starting oxadiazoline and phenyl isothiocyanate less one mole of nitrogen.

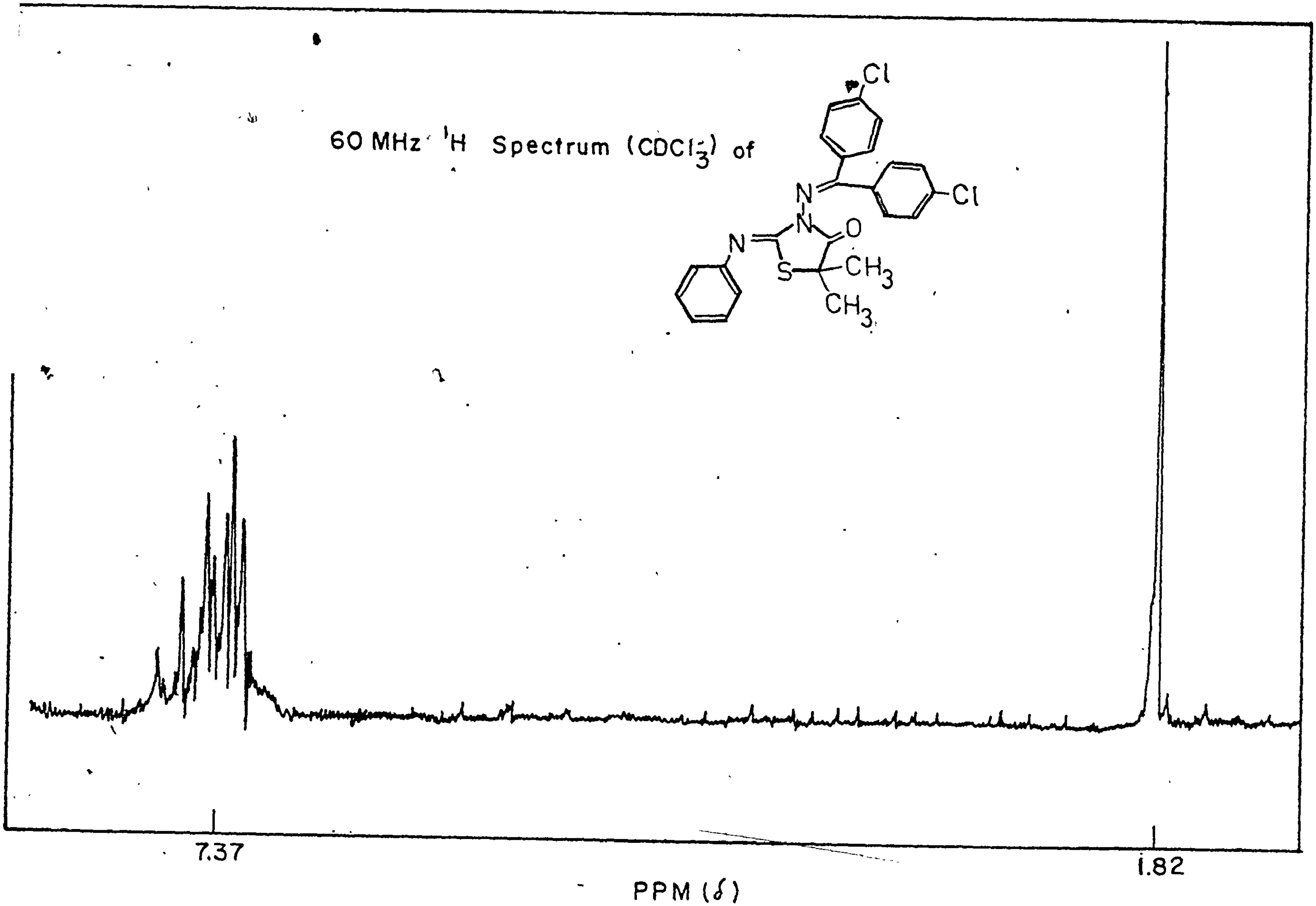
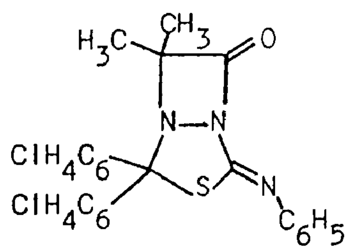

60 MHz ^1H Spectrum ($CDCl_3$) of
Cl
Cl
N
N
O
N
S
CH_3
CH_3
7.37
1.82
PPM (δ)

Fig. 3

The infrared absorption at 1650 cm^{-1} suggested the possible presence of an amide function[59] and there were no other higher frequency carbonyl absorptions. Taking these facts into consideration, the following four possible structures were considered for further investigation.



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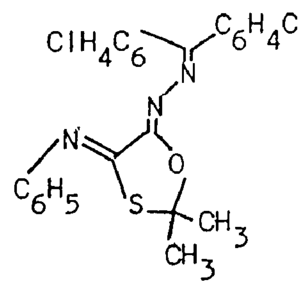

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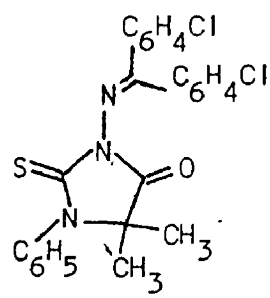
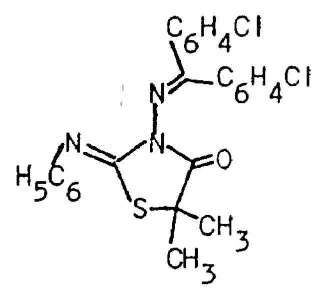
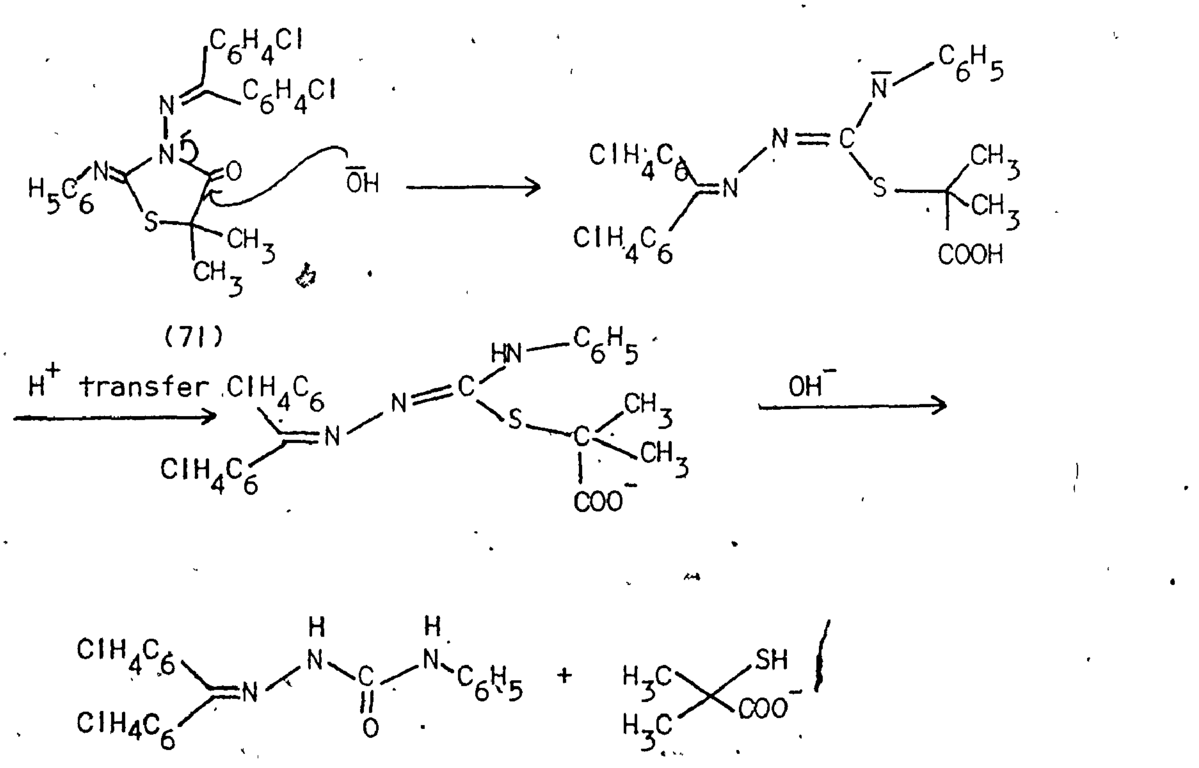


(70)



(71)

Structure (68) could result from the trapping of the azomethine imine, rather than another intermediate, by the isothiocyanate in a 1,3- dipolar cycloaddition. This possibility could be ruled out on the basis of the fact that similar four membered ring ylids are not reactive towards isocyanates or isothiocyanates[25]. Structure (69) was not favoured because of the absence of any amide function. If (69) were correct, the 1650 cm^{-1} absorption would have to be attributed to an exocyclic imine function. Although good models for (69) could not be found, an α- diimine should have a high frequency symmetric stretching vibration. Structures (70) and (71) were consistent with all the spectroscopic data for it was not possible to distinguish between them on the basis of the C = S stretch expected for (70) because of the other bands present in the region. To distinguish between these two structures, a basic hydrolysis in 75% ethanol was carried out. The formation of the N- phenylsemicarbazone of p,p'- dichloro-benzophenone (72) favours (71) as the most probable structure. The product of the hydrolysis under basic conditions can be explained as follows. The formation of (72) incidentally rules out structures

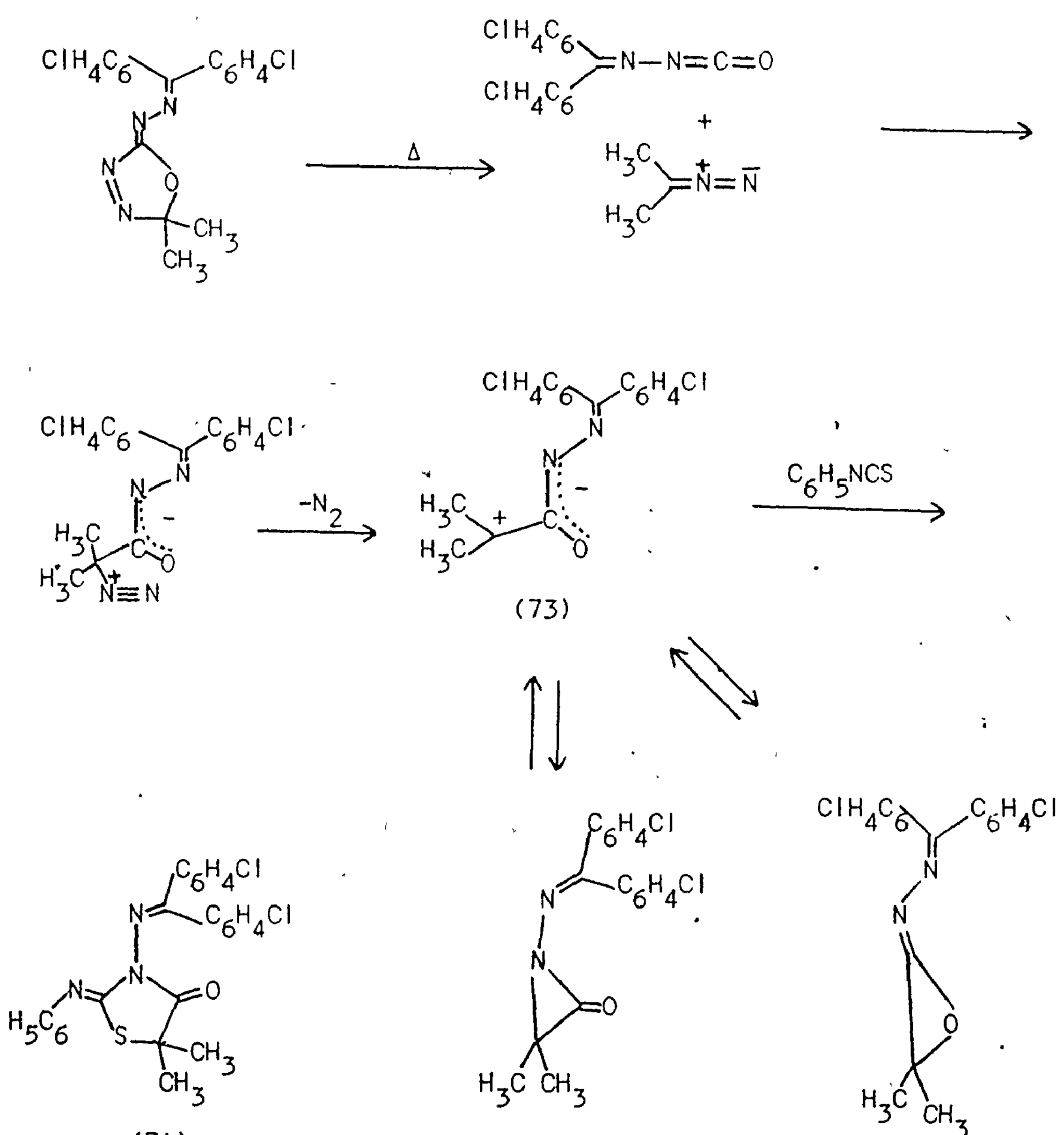


(71)

(72)

(68) and (69) as well.

Mechanistically, the formation of the isothiocyanate adduct (71) could involve the following sequence. This mechanistic

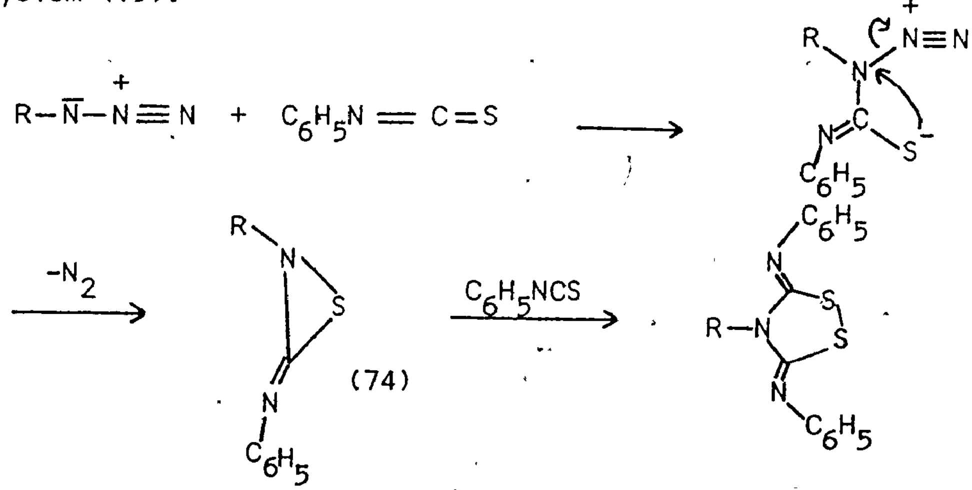


(73)

(71)

scheme is in complete agreement with the original mechanism proposed for the formation of the azomethine imine ylid (page 67), path (c). In the present case, however, the isocyanatoimine intermediate is not immediately captured by the trapping agent. This could be attributed to the lower reactivity of phenyl isothiocyanate towards diazopropane, which is consumed very fast by aryl isocyanates. As a consequence, the fragments from oxadiazoline decomposition react together to form the dipolar species (73), which, in fact is the second step in the formation of the azomethine imine ylid. It is interesting to note that by capturing this intermediate, an intramolecular process i.e. closure to the four membered ring is suppressed. This ring closure seems to be a slow process compared to many other intramolecular reactions, possibly because of the cisoid azine structure (page 71) that is necessary for closure.

A recent communication by Revitt[60] refers to an analogous case where a negatively charged nitrogen attacks the thiocarbonyl carbon of phenyl isothiocyanate leading to a heterocyclic system where sulfur is part of the ring system. The resulting unstable three membered ring (74) further reacts with another mole of phenyl isothiocyanate forming the stable five membered heterocyclic system (75).



(74)

(75)

SPECTRAL CHARACTERISTICS

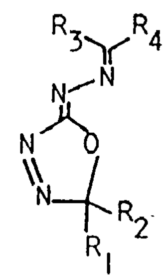
Spectroscopic methods have found extensive use in the characterization of the new compounds synthesized. Infrared, p.m.r. and mass spectra of all the oxadiazolines, azomethine imine ylids, and the products arising from trapping experiments have been recorded. Spectral characteristics of many of these compounds are interesting and a detailed discussion on this is presented below.

Infrared Spectra. Table 4 represents the infrared stretching frequencies of the oxadiazolines synthesized. The exocyclic C = N bond in 2- hydrazono - Δ^3 - 1,3,4- oxadiazolines gave rise to a fairly intense absorption around 1670 cm^{-1}. Although the normal C = N absorptions are weak, the intensity of the band is much enhanced if the bond is exocyclic[13]. A weak band between 1579 and 1612 cm^{-1}, present in the spectra of all the compounds in the series can be attributed to the other C = N bond present in the molecule. The absorption due to the cis - azo function presumably coincides with this band as evidenced by the observed N = N absorption of oxadiazolinones near 1575 cm^{-1}[61].

The azomethine imine ylids are expected to have two distinct absorptions in the infrared region due to the C = O and $\overset{+}{C} = N$ functions. Taylor and coworkers observed[25] that the carbonyl stretching frequency of the ylids resembles that of cyclobutanone (1775 cm^{-1}) rather than that of a β- lactam (1730 - 1760 cm^{-1}).

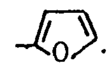
Table 4

Infrared Absorption Frequencies ($CHCl_3$) of 2- Hydrazono - Δ^3 - 1,3,4- Oxadiazolines

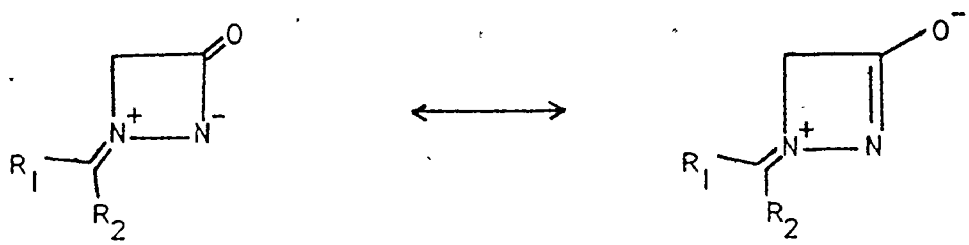


R_1	R_2	R_3	R_4	Exocyclic C=N stretch (cm^{-1})	Other Absorptions (cm^{-1})
CH_3	CH_3	H	C_6H_5	1672	1595, 1131, 856
CH_3	CH_3	H	p-$C_6H_4CH_3$	1670	1603, 1136, 865
CH_3	CH_3	H	p-$C_6H_4OCH_3$	1671	1610, 1132, 1035, 865
CH_3	CH_3	H	o-C_6H_4Cl	1669	1592, 1132, 857
CH_3	CH_3	p-$C_6H_4CH_3$	p-$C_6H_4CH_3$	1663	1612, 1132, 885
$(CH_2)_4$		H	C_6H_5	1669	1599, 1163, 962, 861

Table 4 (contd.)

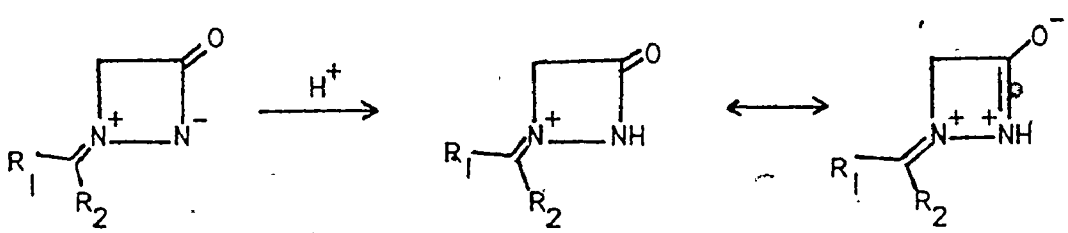
$(CH_2)_5$		H	C_6H_5	1683	1602, 875
CH_3	CH_2CH_3	H	C_6H_5	1671	1592, 1130, 860
CH_3	CH_3	H		1665	1603, 1128, 1015, 982, 880
CH_3	CH_3	p-C_6H_4Cl	p-C_6C_4Cl	1678	1597, 1088
CH_3	CH_3	C_6H_5	p-C_6H_4Br	1656	1579, 1125, 876
CH_3	CH_3	CH_3	C_6H_5	1668	1600, 1128, 1366, 1301, 955

This resemblance suggests that the resonance form (76) makes a larger contribution than the resonance form (77), although the



(76) (77)

crystal structure has shown that the N - C bond is shorter than the normal single bond indicating some amide resonance. Taylor found that upon protonation the carbonyl frequency increases to 1845 cm^{-1}, which clearly indicates that amide resonance is unimportant or absent in this case, probably because the presence of two adjacent positive charges makes the structure (78) energetically unfavourable. Therefore, the enhanced carbonyl stretching

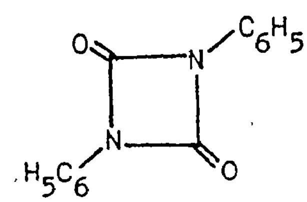


(78)

frequency in these ylids could be due to the partial inhibition of the amide resonance as well as the effect of a transannular quaternary nitrogen on the carbonyl group in a four membered ring.

Table 5 shows that the positions of the C = O and the C = $\overset{+}{N}$ bands in our compounds are in agreement with those reported by Taylor[25].

All the isocyanate adducts prepared showed two types of carbonyl bands (Table 6), a sharp absorption around 1820 cm^{-1} and a broad intense band between 1740 and 1761 cm^{-1}. These adducts have three different types of carbonyls [see structure (64)] and the broad band in the infrared spectrum is probably due to the asymmetric stretching of these carbonyl groups which is not well resolved. The sharp absorption near 1820 cm^{-1} can be attributed to the symmetric stretch. The symmetric stretch of the carbonyls in compound (79) was observed around 1930 cm^{-1} in the Raman spectrum[62]



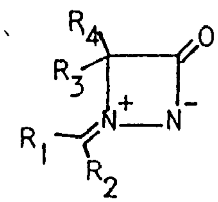
(79)

and it was not observed in the infrared. But, since the isocyanate adducts do not have a symmetric structure, it is possible to observe this in the infrared spectra and considering the ring size, the shift from 1930 cm^{-1} for (79) to 1820 cm^{-1} is in the right direction.

The absence of any high frequency absorption in the isothiocyanate adduct (Table 7) clearly indicates that a different type of product is formed in this trapping experiment. The stretching frequency observed at 1650 cm^{-1} is quite normal for an amide type of carbonyl function[58]. The exocyclic C = N stretch in (71) could not be distinguished, because it absorbs in the same

Table 5

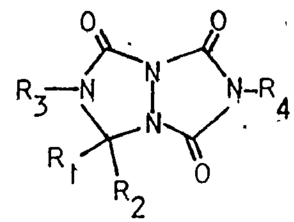
Infrared Absorption Frequencies ($CHCl_3$) of Azomethine Imine Ylids



R_1	R_2	R_3	R_4	$\overset{+}{C=N}$ stretch (cm^{-1})	C=O stretch (cm^{-1})
p-C_6H_4Cl	p-C_6H_4Cl	CH_3	CH_3	1587	1771
H	C_6H_5	CH_3	CH_3	1602	1776
H	C_6H_5	CH_3	CH_2CH_3	1605	1776
H	p-$C_6H_4CH_3$	CH_3	CH_3	1598	1774
H	p-C_6H_4Cl	CH_3	CH_3	1602	1782
p-$C_6H_4CH_3$	p-$C_6H_4CH_3$	CH_3	CH_3	1609	1756

Table 6

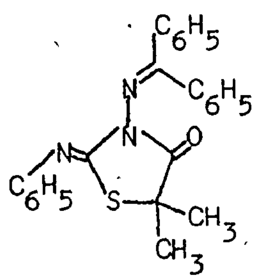
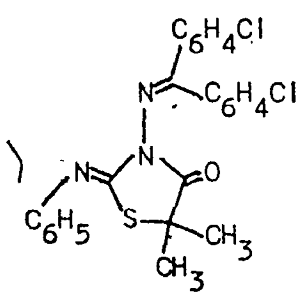
Infrared Absorption Frequencies (KBr) of Isocyanate Adducts



R_1	R_2	R_3	R_4	C = O stretch (cm^{-1})
C_6H_5	C_6H_5	C_6H_5	C_6H_5	1816, 1751
p-C_6H_4Cl	p-C_6H_4Cl	C_6H_5	C_6H_5	1818, 1760
C_6H_5	C_6H_4Br	C_6H_5	C_6H_5	1814, 1759
C_6H_5	C_6H_5	p-C_6H_4Br	p-C_6H_4Br	1822, 1761
p-$C_6H_4CH_3$	p-$C_6H_4CH_3$	C_6H_5	C_6H_5	1816, 1750

Table 7

Infrared Absorption Frequencies (KBr) of Isothiocyanate Adducts

Structure	C = O Stretch (cm^{-1})	C = N stretch (cm^{-1})
	1654	1597
	1650	1600

region as the amide band. The weak band near 1600 cm^{-1} can be assigned to the other C = N bond present in the molecule.

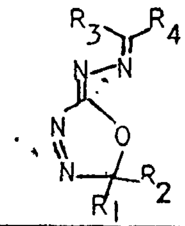
NMR Spectra. Chemical shifts of all the 5,5- disubstituted -2-(hydrazono) - Δ^3 - 1,3,4- oxadiazolines are listed in Table 8. Methyl substituents at the 5- position gave rise to a sharp singlet near 2.0 δ, whereas spiro systems with $(CH_2)_4$ or $(CH_2)_5$ at the 5-position displayed a broad multiplet near 1.8 δ which was not well resolved.

The low field region of the spectra had certain interesting features, especially in the case of compounds derived from the aldehyde carbohydrazones. The compounds prepared by the cyclization of mixed carbohydrazones of aromatic aldehydes and aliphatic ketones displayed a low field singlet (∿ 8.5 δ) in their p.m.r. spectra (Fig. 4), suggesting that only one of the possible isomers is formed. As the starting carbohydrazone is likely to have the E- configuration due to steric factors, it is quite probable that the same geometry is retained in the oxadiazoline, because the aryl end remains intact during the process of cyclization.

The p.m.r. spectra of the azomethine imine ylids derived from the above oxadiazolines also indicate that only the Z- isomer is isolated in the pyrolysis (Table 9), for they have only one sharp signal representing the hydrogen attached to the methine carbon. It is also interesting to note that the most significant change in the p.m.r. spectrum resulting from the transformation of the oxadiazoline to the azomethine imine ylid is the change of position of the p.m.r. signal from this particular hydrogen. That

Table 8

^{1}H Chemical Shifts ($CDCl_3$) of 2- Hydrazono - Δ^3 - 1,3,4 - Oxadiazolines



R_1	R_2	R_3	R_4	Chemical Shifts in ppm (δ)			
				H	CH_3	Aryl Protons	Other Protons
CH_3	CH_3	H	C_6H_5	8.58 (s,1H)	1.76 (s,6H)	7.40 (m,3H) 7.82(m,3H)	--
CH_3	CH_3	H	p-$C_6H_4CH_3$	8.60 (s,1H)	1.75(s,6H) 2.40(s,3H)	7.22(2H) 7.79(2H) abq	--
CH_3	CH_3	H	p-$C_6H_4OCH_3$	8.49 (s,1H)	1.74(s,6H) 3.84(s,3H)	6.91(2H) 7.78(2H) abq	--
CH_3	CH_3	H	C_6H_4Cl	8.85 (s,1H)	1.77 (s,6H)	7.44 (m,4H)	--
CH_3	CH_3	p-$C_6H_4CH_3$	p-$C_6H_4CH_3$	--	1.68(s,6H) 2.40(s,6H)	6.78 (m,8H)	--

Table 8 (contd.)

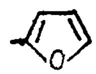
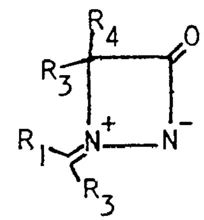
$(CH_2)_4$		H	C_6H_5	8.49 (s, 1H)	--	7.40(m,3H) 7.74(m,2H)	1.91(m,8H) $(CH_2)_4$
$(CH_2)_5$		H	C_6H_5	8.51 (s, 1H)	--	7.36(m,3H) 7.78(m,2H)	1.68(m,10H) $(CH_2)_5$
CH_3	CH_2CH_3	H	C_6H_5	8.62 (s, 1H)	1.71(s,3H)	7.42(m,3H) 7.82(m,2H)	0.88(t,3H),2.14 (q,2H) CH_2CH_3
CH_3	CH_3	H		8.40 (s, 1H)	1.71(s,6H)	--	6.52(q,1H) 6.90(d,1H), 7.56(d,1H)
CH_3	CH_3	p-C_6H_4Cl	p-C_6H_4Cl	--	1.67(s,6H)	7.41(m,8H)	--
CH_3	CH_3	C_6H_5	p-C_6H_4Br	--	1.64(s,6H)	7.50(m,9H)	--
CH_3	CH_3	CH_3	C_6H_5	--	1.65(s,6H) 2.45(s,3H)	7.42(m,3H) 7.84(m,2H)	--

Table 9

[1]H Chemical Shifts ($CDCl_3$) of Azomethine Imine Ylids

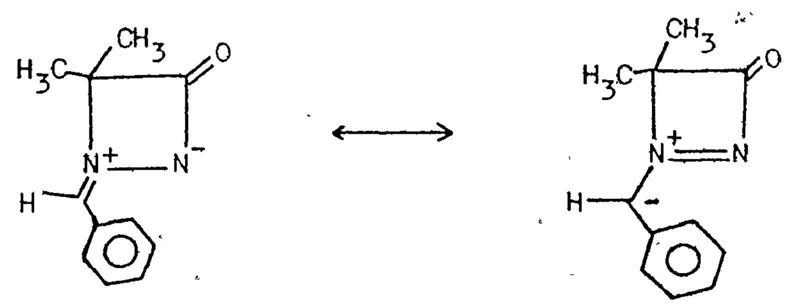


R_1	R_2	R_3	R_4	Chemical Shifts in ppm (δ)			
				H	CH_3	Aryl Protons	Other Protons
p-C_6H_4Cl	p-C_6H_4Cl	CH_3	CH_3	--	1.52(s,6H)	7.36(m,6H) 7.82(m,2H)	--
H	C_6H_5	CH_3	CH_2CH_3	7.16 (s,1H)	1.84(s,3H)	7.52(m,3H) 8.14(m,2H)	1.12(t,3H) 2.05(q,2H) CH_2CH_3
H	C_6H_5	CH_3	CH_3	7.10 (s,1H)	1.80(s,6H)	7.46(m,3H) 8.05(m,2H)	--
H	p-C_6H_4Cl	CH_3	CH_3	7.18 (s,1H)	1.79(s,6H)	7.48(2H) 8.02(2H) abq	--
H	p-$C_6H_4CH_3$	CH_3	CH_3	7.10 (s,1H)	1.78(s,6H) 2.41(s,3H)	7.37(2H) 8.01(2H) abq	--

Table 9 (contd.)

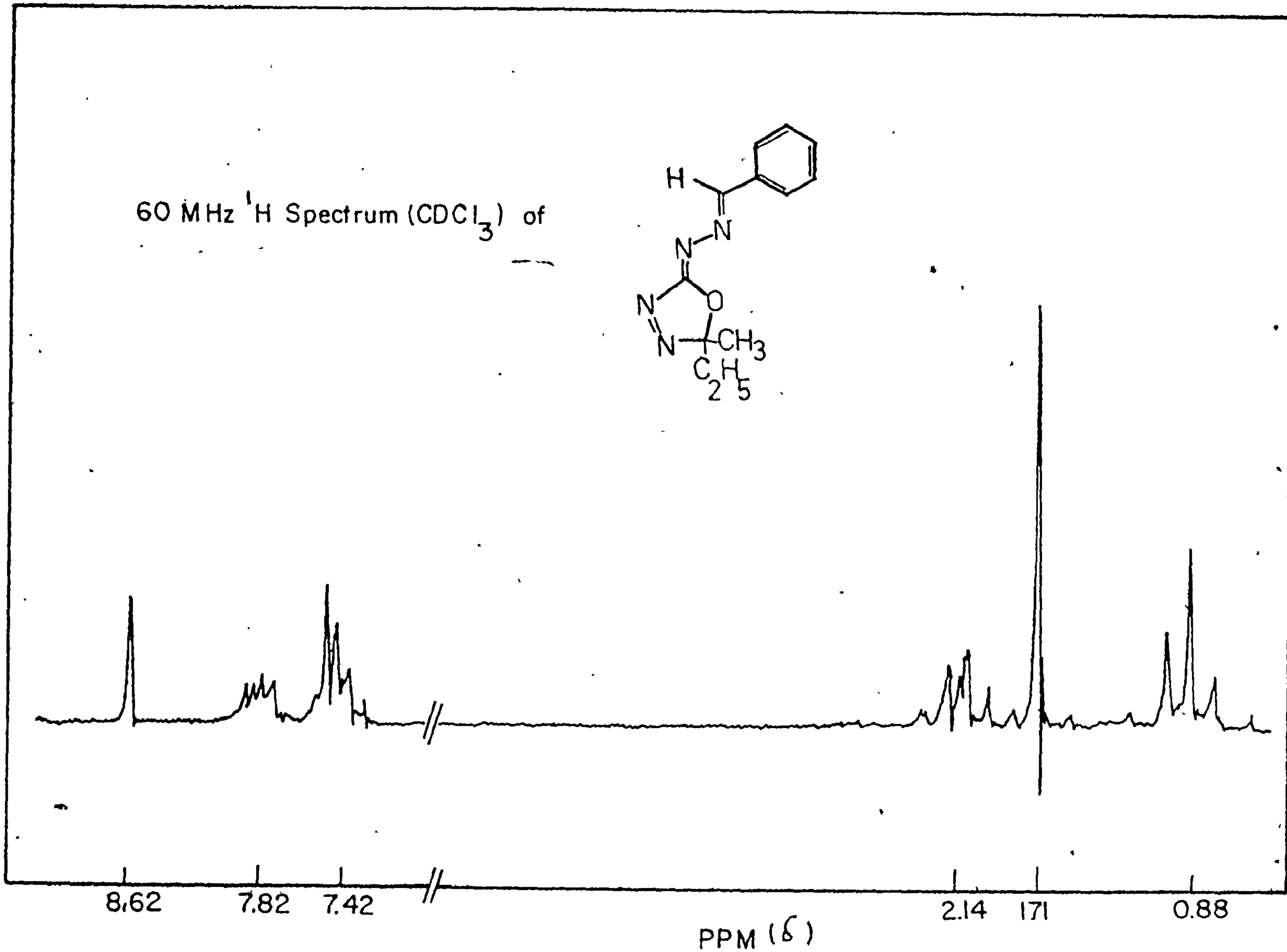
p-$C_6H_4CH_3$	p-$C_6H_4CH_3$	CH_3	CH_3	--	1.53(s,6H) 2.40(s,3H) 2.51(s,3H)	7.32(m,6H) 7.94(m,2H)	—
H	C_6H_5	$(CH_2)_4$		7.18 (s,1H)	--	7.40(m,3H) 8.11(m,2H)	1.98(m,4H) 2.42(m,4H) $(CH_2)_4$

signal is shifted to higher field (from 8.5 δ to 7.2 δ) whereas all the other signals remain nearly the same (Figs. 4 and 5). A probable rationale for this observation is that resonance form (80), which depicts the negative charge on the methine carbon makes



(80)

a substantial contribution. As a consequence, the signal of the hydrogen directly attached to this carbon shifts to a higher field compared to a hydrogen attached to a normal imine carbon or its protonated form. However, the bond lengths obtained from the crystal structure of one of the compounds in the series do not seem to support this sort of resonance. Also the presence of an $\overset{+}{N} = N$ bond brings additional constraint on an already rigid four membered ring. As there is no better explanation available, one has to presume that resonance is possible to some extent in solution making (80) a significant contributing structure. An alternative explanation would be that the absorption of this hydrogen occurs at unusually low field in the starting oxadiazoline, because of the presence of



60 MHz ^{1}H Spectrum ($CDCl_3$) of
H
N
N
N
N
O
CH_3
C_2H_5
8.62
7.82
7.42
2.14
1.71
0.88
PPM (δ)

Fig. 4

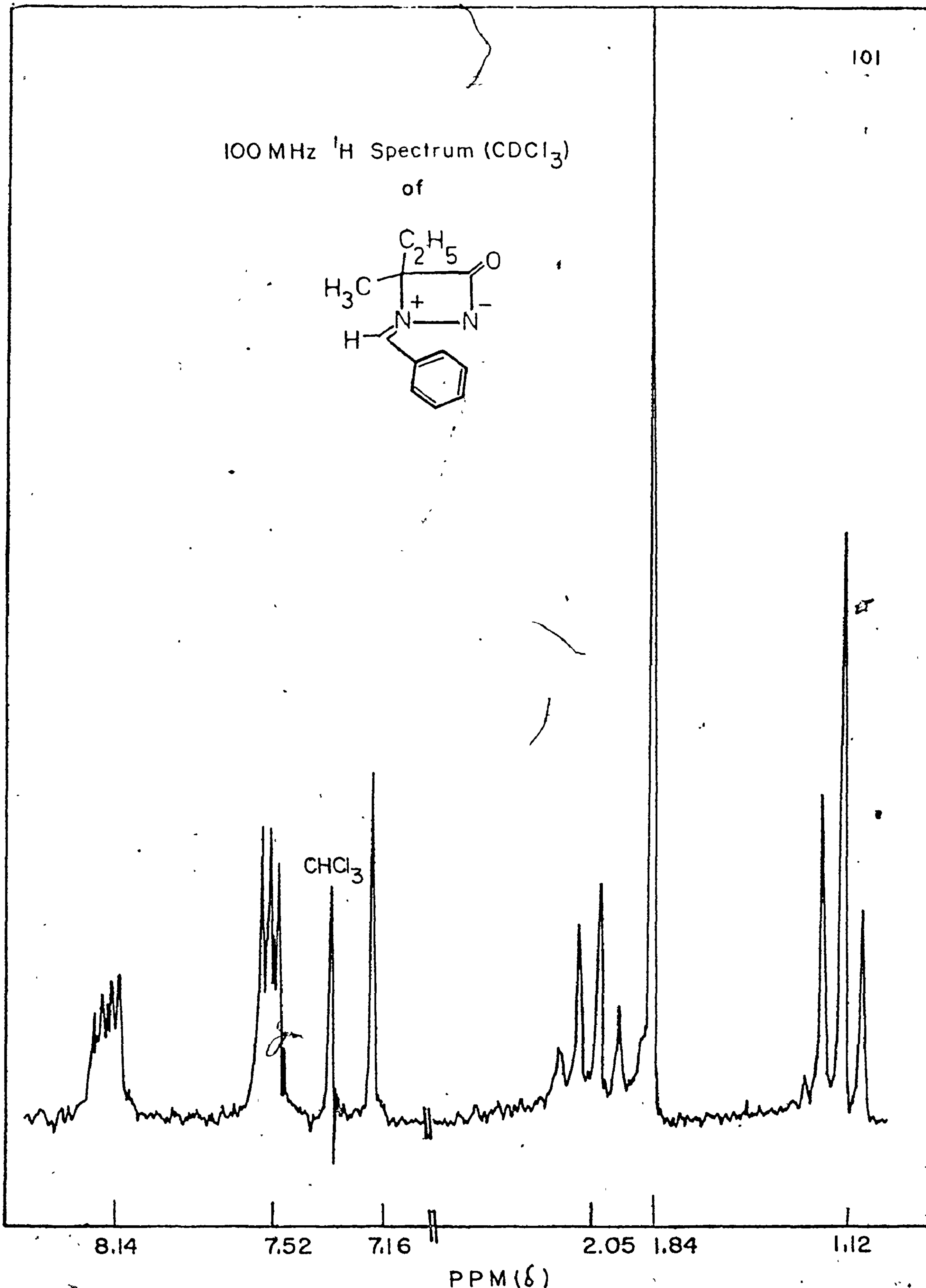
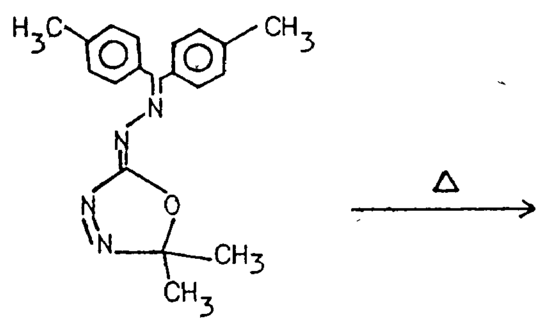

100 MHz ^{1}H Spectrum ($CDCl_3$)
of
C_2H_5
H_3C
O
N
N
H
$CHCl_3$
8.14
7.52
7.16
2.05
1.84
1.12
PPM (δ)

Fig. 5

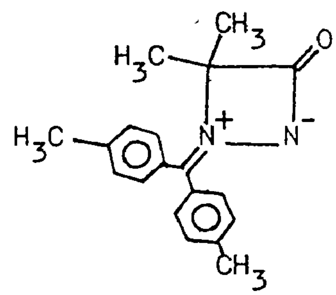
a conjugated system involving an electron withdrawing azo group. But this has been found to be incorrect because the chemical shift of a similar hydrogen (8.62) in benzaldehyde azine falls in the same range although it does not contain any azo group.

The aromatic protons of the azomethine imine ylids also exhibited some interesting characteristics. The ylids prepared from aromatic aldehyde carbohydrazones showed two well separated multiplets in a ratio of 2:3 in the aromatic region of the p.m.r. spectra and when the ring was p- substituted, an AB quartet was observed. The ylid derived from benzophenone acetone carbohydrazone, also indicated two distinct sets of aromatic protons in the ratio of 2:8. From this observation, one can infer that two aryl protons, irrespective of the carbohydrazone it is derived from. This phenomenon was observed also by Taylor's group[25] and they assigned these low field signals to the two ortho protons facing the negatively charged amide nitrogen in the four membered ring. Low temperature 100 MHz spectra recorded at -60^{o} and -90^{o}, of the ylid prepared from benzaldehyde acetone carbohydrazone, looked exactly the same as the one recorded at room temperature, indicating that the two ortho protons are magnetically equivalent either due to the rapid rotation of the phenyl ring or due to the accidental coincidence of the signals.

It is interesting to compare the p.m.r. spectrum of the oxadiazoline (81) with that of the azomethine imine ylid (82) derived from it (Figs. 6 and 7). The two p- methyl groups were only



(81)



(82)

partially resolved (1.5Hz) even in the 100 MHz spectrum of (81), whereas in (82) the two signals were clearly resolved (7Hz) in the 60 MHz spectrum. One possible explanation for this observation can be the presumably larger steric inhibition of resonance in (82) caused by the gem dimethyl group. The two low field signals in (82) can be attributed to the ortho protons of the tolyl ring facing the negatively charged nitrogen. The two meta protons in this ring as well as the four protons in the other tolyl ring form a multiplet which is not well resolved. The geometry of (82), as indicated by the crystal structure of one of its analogs, is such that the benzene ring away from the amide nitrogen is at an angle of 90° to the plane of the four membered ring. The same geometry is probably not retained in solution because there is not a large difference between the chemical shifts of the meta hydrogens of the two benzene rings or between the chemical shifts of the p- methyl substitutents. The small differences that are observed can readily be accounted for in terms of the slightly different conjugating ability of the two rings.

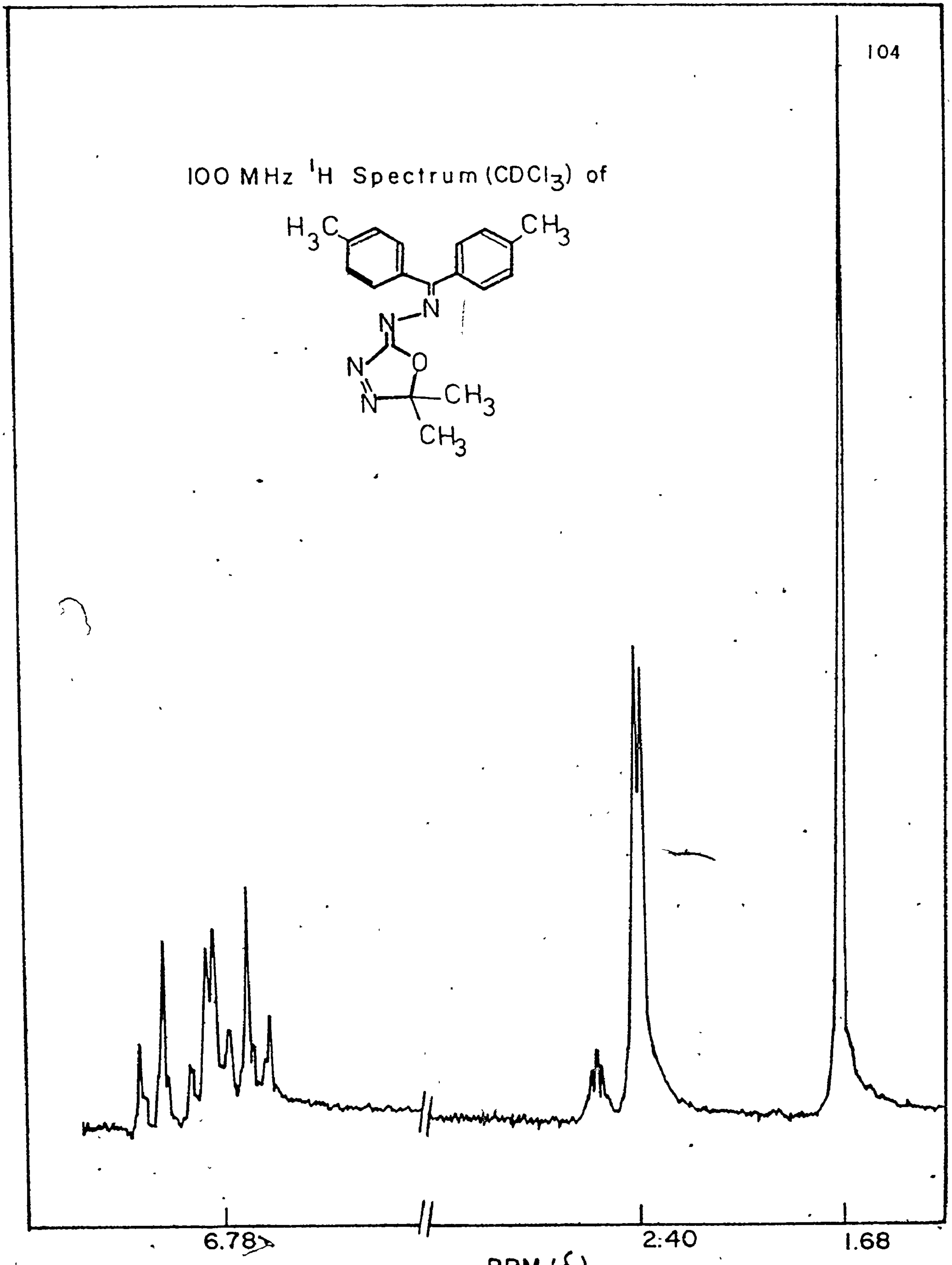
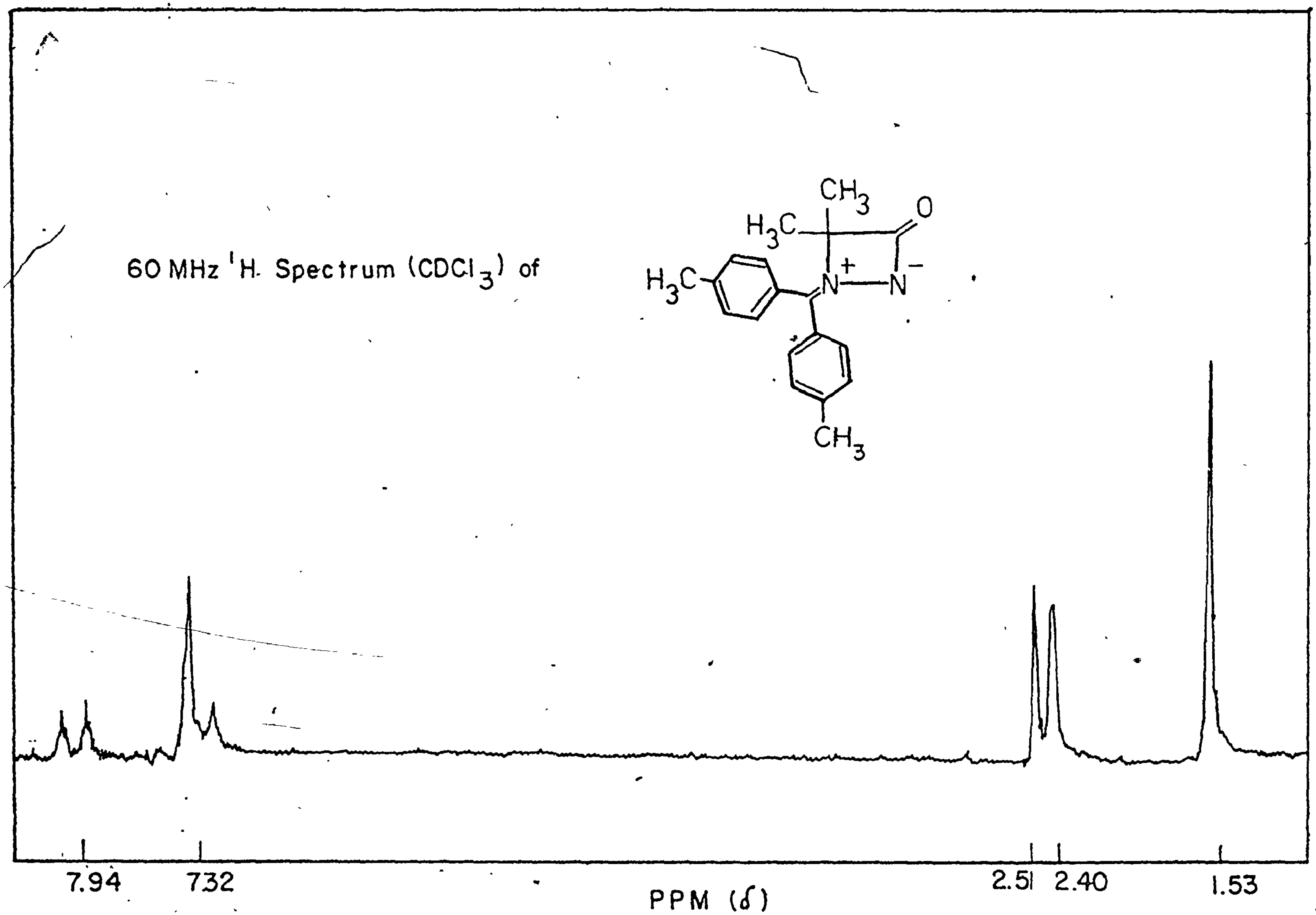

100 MHz 1H Spectrum (CDCl3) of
H3C
CH3
N
N
N
N
O
CH3
CH3
6.78
2.40
1.68
PPM (δ)

Fig. 6

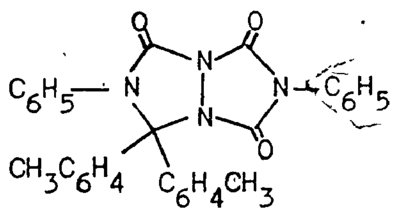
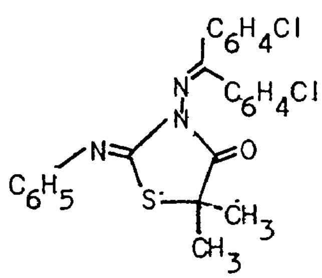
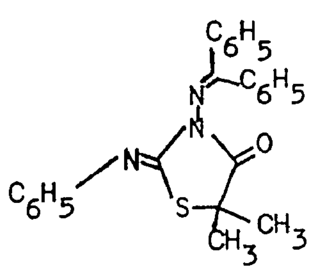


60 MHz ¹H. Spectrum (CDCl₃) of
CH3
H3C
O
H3C
N
N
CH3
7.94
7.32
2.51
2.40
1.53
PPM (δ)

Fig. 7

Table 10

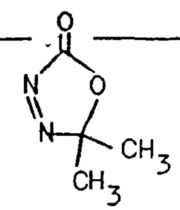
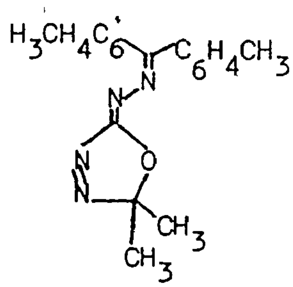
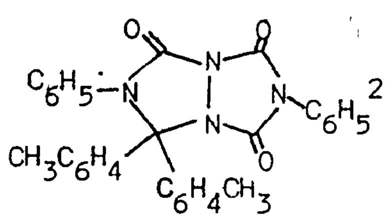
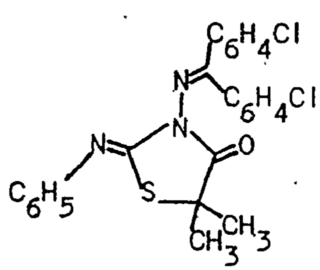
^{1}H Chemical Shifts ($CDCl_3$) of Products from Trapping Experiments *

Structure	Chemical Shifts in ppm (δ)	
	CH_3	Aryl Protons
	2.38 (s, 6H)	7.21 (m, 18 H)
	1.82 (s, 6H)	7.34 (m, 13 H)
	1.82 (s, 6H)	7.37 (m, 15 H)

* Chemical shifts of other products are not included as they contain only aromatic protons which appear as a multiplet around 7.20-7.60 ppm (δ)

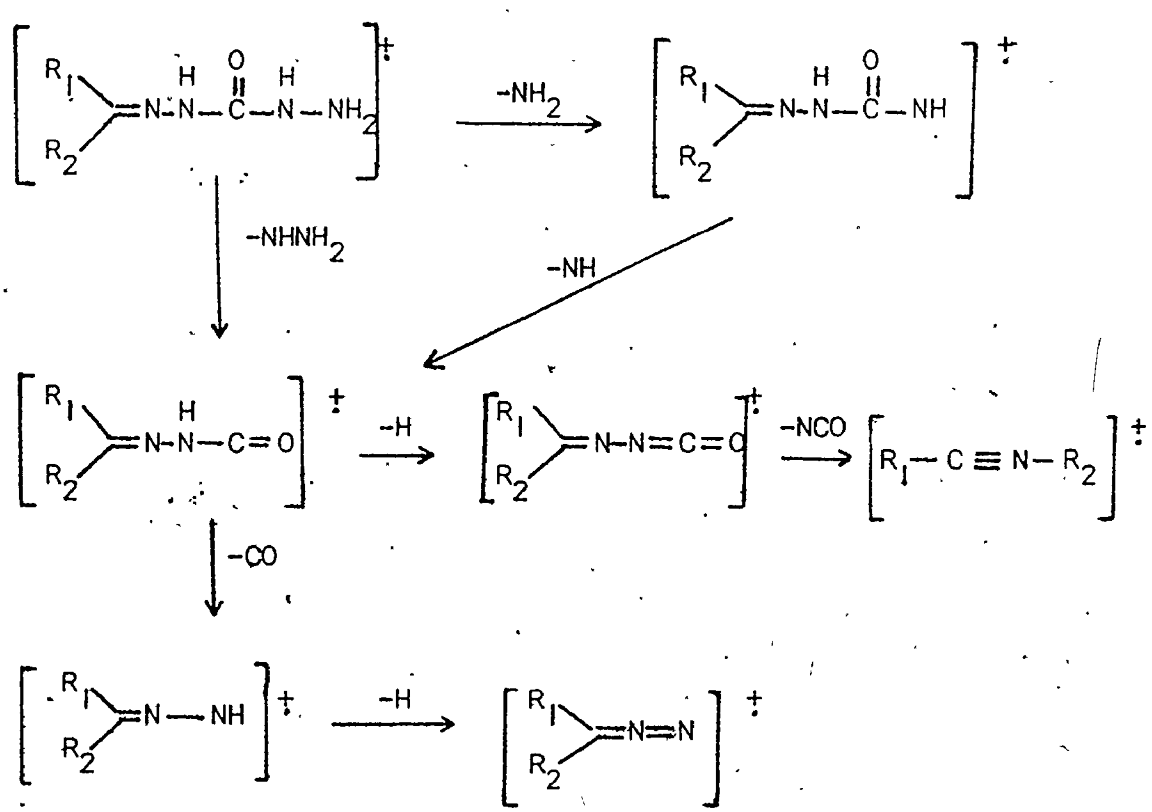
Table II

^{13}C Chemical Shifts ($CDCl_3$) of Selected Compounds

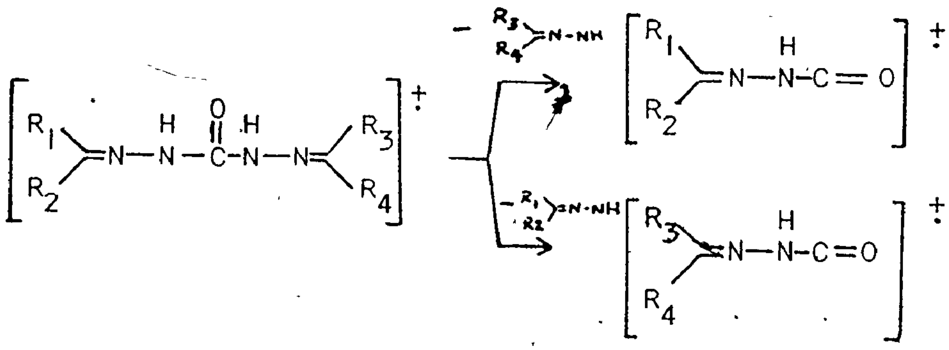
Structure	Chemical Shifts in ppm (δ)				
	CH_3	C	C = N	C = O	Aryl Carbons
	22.76	118.28	--	159.70	--
	21.46 23.76	123.15	139.43 140.80	--	128-132 (several lines)
	21.20	89.14	--	140.40 145.58 149.12	125-131 (several lines)
	27.65	96.23	129.58 130.46	135.80	127-133 (several lines)

^{13}C spectra were not recorded on a routine basis, because most of the structures could be identified by other means. However, it was interesting to compare the spectrum of oxadiazolinone with those of some of the products of trapping (Table II). For example, ^{13}C spectroscopy was quite helpful in establishing the presence of a quaternary carbon, as well as C = O and C = N functions in some of the products formed in trapping experiments by comparing their spectra with those of known compounds with such functionalities.

Mass Spectra. Mass spectroscopy has been one of the major tools for the identification of 4- aminosemicarbazones and carbohydrazones. All the 4- aminosemicarbazones indicated a strong peak due to the molecular ion and further fragmentation can be rationalized in the following way.

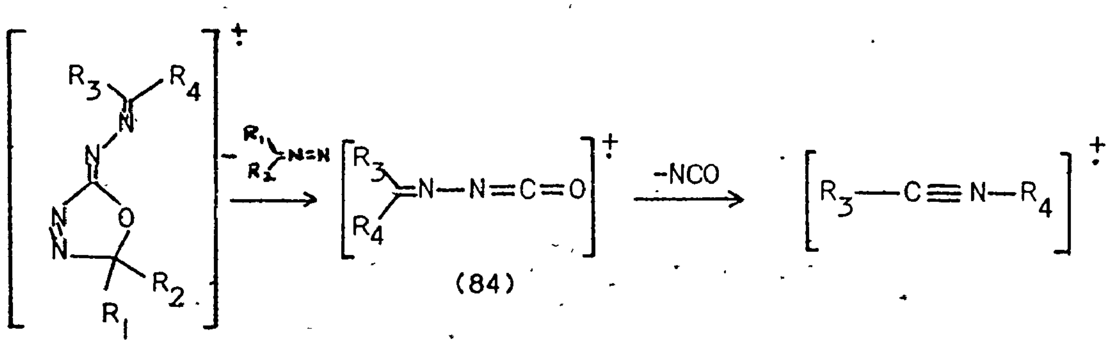


Carbohydrazones also indicated two major fragmentation patterns. All the compounds in this family indicated a strong parent peak and the fragmentation took place by the cleavage of either of the C - N bonds involving the carbonyl carbon. The nature of



further fragmentation was similar to that observed in 4- amino-semicarbazones.

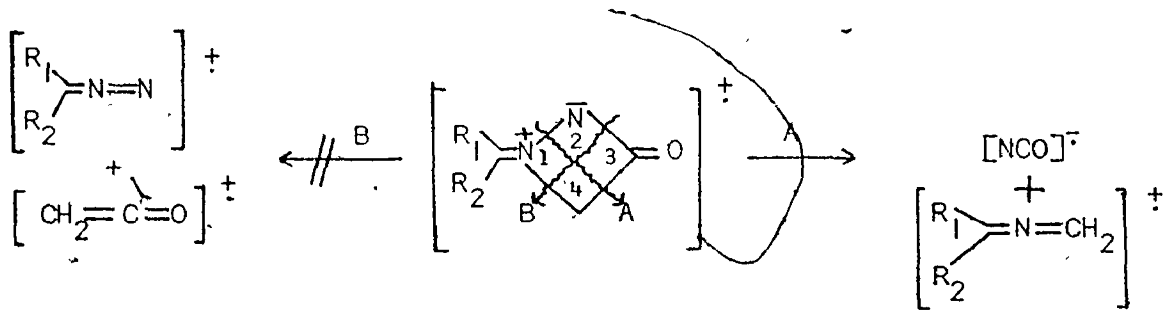
In the case of 2- arylimino - Δ^3 - 1,3,4- oxadiazolines, it was reported earlier that two modes of thermal fragmentation were possible[20]. But all the 2- hydrazono - Δ^3 - 1,3,4- oxadiazolines we have investigated, indicated that the following pathway is predominant in the mass spectral fragmentation, although these two systems have structural similarities. The loss of an -NCO



(84)

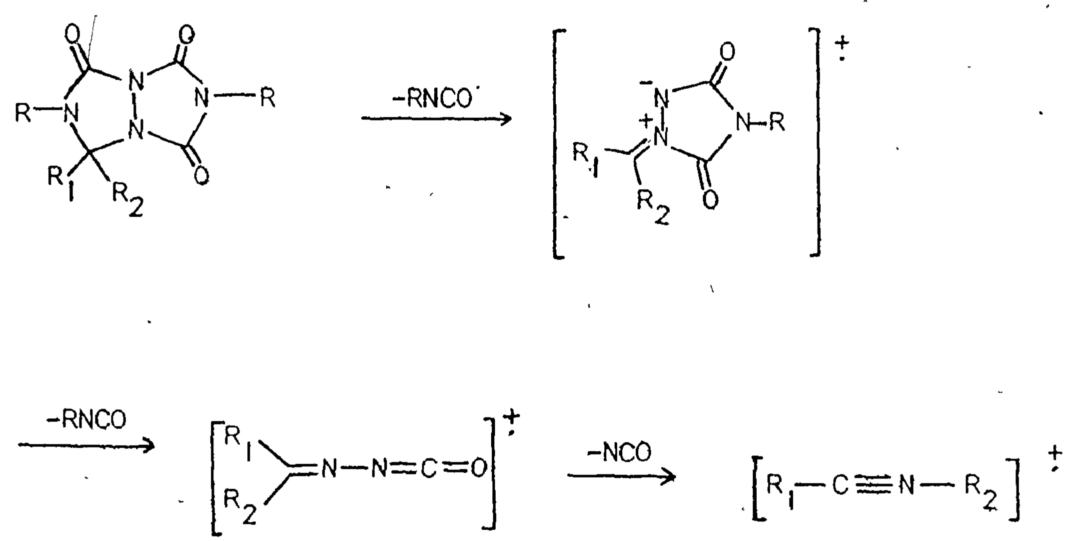
fragment from the isocyanate (84) is analogous to the loss of -NCS fragment from the isothiocyanatoimines[46]. Also, the presence of (84) is another supporting argument in favour of the mechanism proposed for the pyrolysis, as thermal processes are complementary to electron impact processes in many cases[63,64].

Taylor and coworkers investigated the mass spectral fragmentation of some of their azomethine imine ylids[25]. They found that, although two types of fragmentation patterns (A and B below)



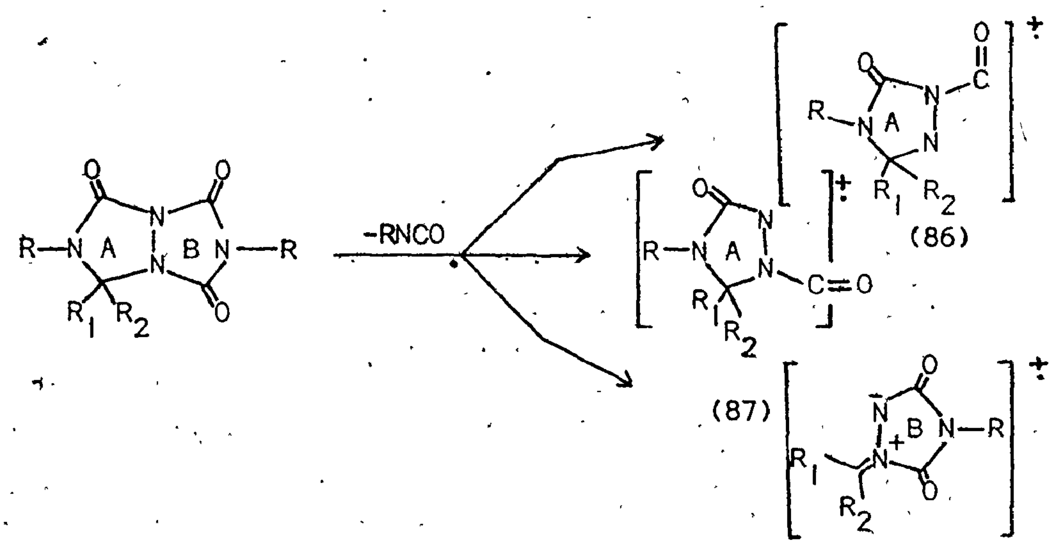
are conceivable, path A is always predominant. We have also observed the primary fragmentation step involving the ejection of the isocyanate anion radical, and path B was not observed. This is somewhat surprising because all the compounds we have studied had a quaternary carbon at the 4- position in the four membered ring which should make the fragmentation B much easier. The failure to observe path B cannot be accounted for in terms of a still better pathway; the loss of a substituent from C-4. Although loss of CH_3 fragments from 4,4- dimethyl systems was observed, it was a minor fragmentation process.

Investigation of the mass spectra of the isocyanate and isothiocyanate adducts was also interesting and informative. None of the isocyanate adducts showed the molecular ion. Presumably, one of the isocyanate units is lost readily from the adduct and the highest peak observed in the mass spectrum corresponds to the resulting 1:1 adduct of the isocyanate and the isocyanatoimine. This can lose



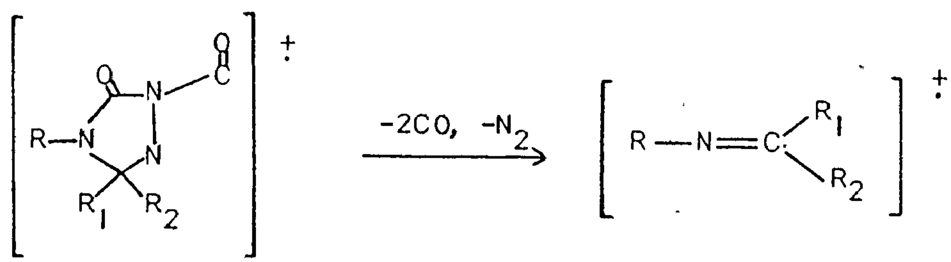
(85)

another RNCO fragment, leading to the isocyanatoimine fragment, followed by the loss of NCO. It is quite likely that the initial fragmentation leading to the loss of one isocyanate moiety could occur in three ways with the resultant formation of the ions (86), (87) or (88). Out of these, only structure (86) and (88)



(86) (87) (88)

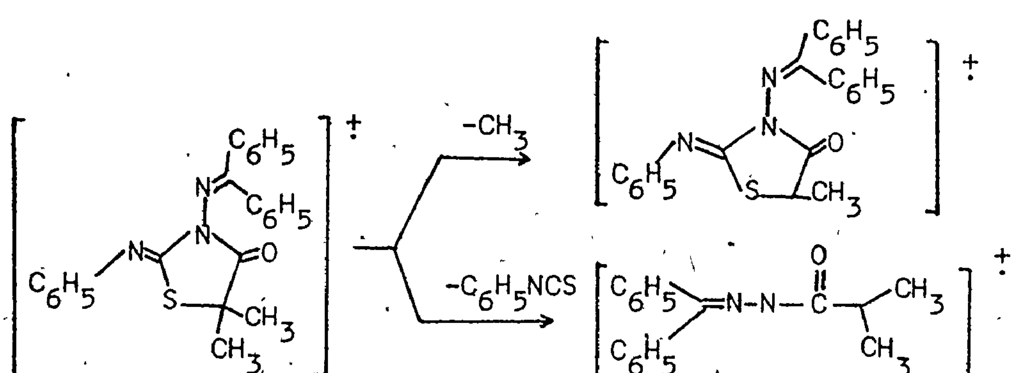
can readily lose another unit of RNCO leading to the isocyanato-imine. But, only structure (86) is likely to lose a mass unit of 84 (presumably N_2 and 2 CO) and an ion corresponding to this loss has been observed in the spectra of all the isocyanate adducts.



(89)

As evidenced by the lower abundance of (89) compared to (85), this is likely to be a minor process, although it strongly supports the argument that a mole of the isocyanate can be lost initally from either of the two rings.

Mass spectra of the isothiocyanate adducts were not as informative as those of the isocyanate adducts. However, they showed a strong parent peak as well as the loss of one unit of phenyl isothiocyanate from this, which indicates that phenyl isothiocyanate is incorporated in the molecule. A loss of



15 mass units from the molecular ion indicated the presence of methyl groups in the molecule. Peaks due to further fragmentation were not very informative as regards to the structure of the molecule.

In general, the mass spectra of the oxadiazolines and the isocyanate adducts indicate that they can be fragmented to the isocyanatoimines, which were postulated as intermediates in the formation of the azomethine imine-ylids. As it was not possible to isolate these intermediates, or observe them by other spectroscopic methods, mass spectroscopy is an effective method for demonstrating their existence.

SUMMARY

The oxidative cyclization of carbohydrazones and the pyrolysis of the resulting oxadiazolines have been investigated in detail. This has led to the synthesis of a series of 2-hydrazono - Δ^3 - 1,3,4- oxadiazolines and four membered ring azomethine imine ylids. Cyclization of certain mixed carbo-hydrazones of aromatic aldehydes and acetone by lead tetraacetate indicated that the regioselectivity of this reaction is controlled by the nature of substituents on the benzene ring. On the basis of these results, a new mechanism for the cyclization has been postulated.

Extensive studies have also been carried out in order to establish the mechanism of the pyrolytic process leading to the formation of the azomethine imine ylids. As it was not possible to isolate and characterize the intermediates involved in this process, experiments were carried out to trap them chemically. Trapping experiments with phenyl isocyanate and phenyl isothiocyanate established the presence of an N- isocyanatoimine intermediate during the pyrolysis.

The structure of the products formed as a result of trapping the isocyanatoimine intermediate by aryl isocyanates was solved by single crystal X-ray diffraction of one of the compounds in the series. The structure of the isothiocyanate adducts was established by spectroscopic and chemical means. In order to

explore the generality of these reactions, studies were carried out using different substrates and substituted isocyanates.

REFERENCES

1. R.E. Zangaro, Ph.D. Thesis, Polytech. Inst. of Brooklyn (1968).
2. J.K. Landquist, J. Chem. Soc. (C), 324 (1970).
3. J. Warkentin, Synthesis, 279 (1970).
4. R.N. Butler, F.L. Scott and T.A.F. O'Mahony, Chem. Rev., 73, 93 (1973).
5. D.C. Iffland and G.X. Criner, Chem. Ind. (London), 176 (1956).
6. G. Just and K. Dahl, Tetrahedron, 24, 5251 (1968).
7. H. Lemaire and A. Rassat, Tet. letters, 2245 (1964).
8. D.C. Iffland, L. Salisbury and W.R. Schafer, J. Am. Chem. Soc., 83, 747 (1961).
9. B.T. Gillis and M.P. LaMontagne, J. Org. Chem., 33, 762 (1968).
10. B.T. Gillis and M.P. LaMontagne, J. Org. Chem., 33, 1294 (1968).
11. M.J. Harrison, R.O.C. Norman and W.A.F. Gladstone, J. Chem. Soc., 735 (1967).
12. G.B. Gubelt and J. Warkentin, Can. J. Chem., 47, 3983 (1969).
13. A.M. Cameron, P.R. West and J. Warkentin, J. Org. Chem., 34, 3230 (1969).
14. J.P. Freeman, J. Org. Chem., 28, 885 (1963).

15. W.A.F. Gladstone and R.O.C. Norman, J. Chem. Soc. (A), 1527 (1966).

16. C.G. Overberger, N. Weinshenker and J.P. Anselme, J. Am. Chem. Soc., 87, 4119 (1965).

17. D.E. McGreer, R.S. McDaniel and M.G. Vinje, Can. J. Chem., 43, 1389 (1965).

18. D.E. McGreer, N.W.K. Chiu and M.G. Vinje, Can. J. Chem., 43, 1398 (1965).

19. D.E. McGreer, N.W.K. Chiu and M.G. Vinje, Can. J. Chem., 43, 1407 (1965).

20. A.M. Cameron, Ph.D. Thesis, McMaster University (1972).

21. P.C. Ip, M.Sc. Thesis, McMaster University (1973).

22. W. Schlenk and J. Holtz, Chem. Ber., 49, 603 (1916).

23. A.W. Johnson, "Ylid Chemistry", Academic Press, N.Y. (1966).

24. R. Huisgeh, Angew. Chem. Internat. Edit., 2, 565 (1963).

25. N.F. Haley, Ph.D. Thesis, Princeton University (1971).

26. C. Calvo, P.C. Ip, N. Krishnamachari and J. Warkentin, Can. J. Chem., 52, 2613 (1974).

27. G.F. Bettinetti and L. Capretti, Gazz. Chim. Ital., 95, 33 (1965).

28. W.O. Godtfredsen and S. Vangedal, Acta. Chem. Scand., 9, 1498, (1955).

29. B. Singh, J. Am. Chem. Soc., 91, 3670 (1969).

30. R. Greenwald and E.C. Taylor, J. Am. Chem. Soc., 90, 5272, (1968).

31. L.A. Cohen and B. Withop, "Molecular Rearrangements", Part II, Interscience, N.Y. (1964).

32. R. Huisgen, R. Grashey, P. Laur and H. Leiterman, Angew, Chem., 72, 416 (1960).

33. P.C. Ip, K. Ramakrishnan and J. Warkentin, Can. J. Chem., 52, 3671 (1974).

34. "Handbook of Chemistry and Physics", The Chem. Rubber Co., 52 Edit. (1971-72).

35. A.C. Brown, E.C. Pickering and F.J. Wilson, J. Chem. Soc., 107 (1927).

36. P.R. West, Ph.D. Thesis, McMaster University (1967).

37. O.Diels and H. Grube, Ber., 53 B, 854 (1920).

38. S.G. Cohen and C.H. Wang, J. Am. Chem. Soc., 77, 2457 (1955).

39. M. Fieser and L.F. Fieser, "Reagents for Organic Synthesis", Vol. I, Wiley - Inter Science (1969).

40. W. Borsche and C. Merkwitz, Ber., 37, 3177 (1904).

41. K. Bott, Tet. letters, 3323 (1968).

42. J.C. Sheehan and I. Lengyel, Angew, Chem. Internat. Edit., 7, 25 (1968).

43. T. Saegusa, N. Taka-ishi and H. Fujii, Tetrahedron, 24, 3795 (1968).

44. J.B. Fulton and J. Warkentin, Unpublished work (1974).

45. E.R. Talaty and M.E. Zandler, J. Heterocyclic Chem., 12, 151 (1975).

46. U. Anthoni and C. Berg, Acta Chem. Scand., 23, 3062 (1969).

47. U. Anthoni, Ch. Larson and P.H. Neilsen, Acta Chem. Scand., 20, 1714 (1966).

48. U. Anthoni, Ch. Larson and P.H. Neilsen, Acta Chem. Scand., 1439 (1969).

49. U. Anthoni, Ch. Larson and P.H. Neilsen, Acta Chem. Scand., 22, 309 (1968).

50. A.G. Cook, "Enamines: their Synthesis, Structure and Reactions", Marcel Dekker, N.Y. (1968).

51. G.F. Bettinetti, and P. Grünanger, Tet. letters, 30, 2553 (1965).

52. R. Huisgen, H. Stangle, H.J. Sturm and H. Wagenhofer, Angew. Chem., 73, 170 (1961).

53. R. Huisgen, Angew. Chem. Internat. Edit., 2, 565 (1963).

54. R. Huisgen, Angew. Chem. Internat. Edit., 2, 633 (1963).

55. R. Huisgen, J. Org. Chem., 33, 2291 (1968).

56. R.G. Arnold, J.A. Nelson and J.J. Verbanc, Chem. Rev., 57, 47 (1957).

57. V.V. Gizycki and G. Oertel, Angew. Chem. Internat. Edit., 1, 381 (1968).

58. W.J. Farrissey Jr., R.J. Ricciardi and A.A.R. Sayigh, J. Org. Chem., 33, 1913 (1968).

59. H.H. Willard, L.L. Merritt Jr., and J.A. Dean, "Instrumental Methods of Analysis", D. Van Nostrand Company Inc. (1965).

60. D.M. Revitt, J. Chem. Soc., Chem. Comm., 1, 24 (1975).

61. P. Knittel, S.L. Lee and J. Warkentin, Can. J. Chem., 50, 3248 (1972).

62. C. Fayat and A. Faucand, Bull. Soc. Chim. (Fr.), 12, 4491 (1970).

63. L. Freidman and D.F. Lindow, J. Am. Chem. Soc., 90, 2324 (1968).

64. J.D. Kelley and C.J. Wolf, J. Chromatogr. Sci., 8, 583 (1970).