A) NITROTHIOACETAMIDES: SYNTHESIS AND CHEMICAL TRANSFORMATIONS;

B) STUDY OF SOME WEAK INTERACTIONS OF THE THIOCARBONYL GROUP.

A Thesis
submitted to the

UNIVERSITY OF POONA

For the Degree of

DOCTOR OF PHILOSOPHY

(In Chemistry)

BY

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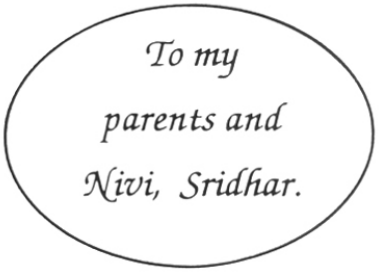
APRIL, 1992.


To my
parents and
Nivi, Sridhar.

Contents...

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I take this opportunity to express my deep sense of gratitude to Dr.S. Rajappa, FNA, for his valuable guidance and keen interest throughout the course of this investigation.

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K V Reddy

(K.Venodhar Reddy)

National Chemical Laboratory,

PUNE.

April, 1992.

CERTIFICATE

*Certified that the work incorporated in the thesis entitled "**A) Nitrothioacetamides: Synthesis and Chemical Transformations; B) Study Of Some Weak Interactions Of The Thiocarbonyl Group**", by K. Venodhar Reddy was carried out by the candidate under my supervision. Such material as had been obtained from other sources has been duly acknowledged in the thesis.*

(Dr.S. Rajappa)

April, 1992.

Research Guide

General Remarks

1. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range 60-80°c.

2. All the temperatures are in °c. All the melting points and boiling points are in °c and are uncorrected.

3. Infrared spectra were recorded as either liquid film or nujol mull in, on Perkin-Elmer "Infracord - 137B", and/or 683 model spectrometer using NaCl optics. The following abbreviations are used: s = strong, w = weak, m = medium.

4. ^{1}H NMR spectra were recorded on Bruker WH-90, WH-300 FT and Bruker -200Mz spectrometers and chemical shifts were measured in δ units, TMS was used as internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet and m = multiplet.

5. Mass spectra were recorded on CEC-21-110B spectrometer.

6. The numbers assigned to the structures given in each chapter refer to that particular chapter.

7. References pertaining to each chapter are given at the end of that particular chapter.

8. All optical rotations were measured using sodium D lines on JASCO-181-digital polarimeter at ambient temperatures. The reported $[\alpha]_D$ values are at concentration range 1-2.

Abbreviations

Ar	Aryl
Bz	Benzyl
DBU	1,8-Diazobicyclo [5,4,0] Undec-7-ene
Et	Ethyl
eq.	Equivalents
g	Gram/s
h	Hour/s
IR	Infrared
M^+	Molecular ion
Me	Methyl
m.p.	Melting point
MS	Mass Spectrum
nm	Nanometer
NMR	Nuclear Magnetic Resonance
PTC	Phase Transfer Catalyst
Ph	Phenyl
TEA	Triethylamine

ABSTRACT

CHAPTER I: Synthesis of Nitrothioacetamides

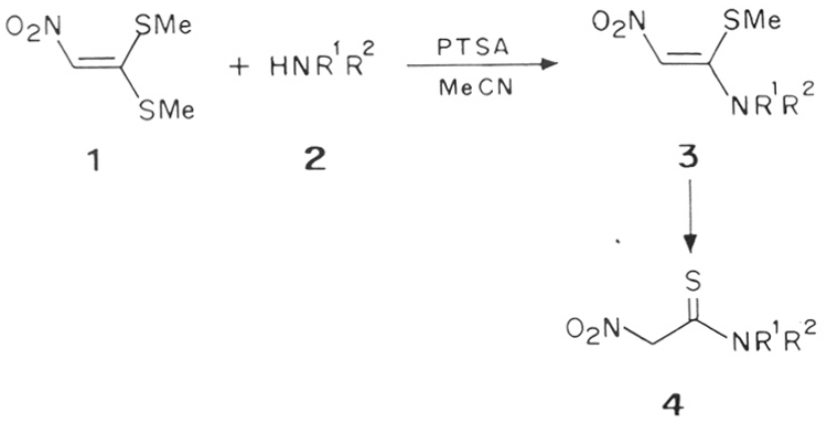
The nitroacetyl group has found application as a novel peptide synthon - especially for the synthesis of peptides incorporating unnatural aminoacids. As an extension of this, it was felt that nitrothioacetyl derivatives of aminoacids might prove very useful in synthesis. Such nitrothioacetyl derivatives of aminoacids or peptides may be potential precursors of thiopeptides, in which the thiocarbonyl group occupies a predetermined location, thus leading to regiospecific synthesis of thiopeptides.

There is no report in the literature on the use of nitrothioacetamides either in the synthesis of amino acids or peptides. Prior to our work, there were only two reports known in the literature on the synthesis of nitrothioacetamides. Both these methods involve the same strategy of trapping nitrothioketene with amines. This approach is neither simple nor practical under laboratory conditions and yields are not high. Interestingly, the attempt by J.A. Joule et al to convert nitroacetamides into the nitrothioacetamides with conventional thionating agents like P_4S_{10} and Lawesson reagent resulted in failure.

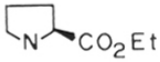
Two routes for the synthesis of nitrothioacetamides were envisaged starting from a common precursor, 1-methylthio-1-substituted amino-2-nitroethene. One is the cleavage of the thioether bond with Lewis acids, leading to the retention of the S atom of the starting material in the resulting nitrothioacetamides; the other route is replacement of the $-SCH_3$ by SH *via* an addition - elimination mechanism, by means of a suitable sulfur nucleophile.

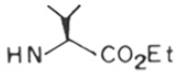
In our method 1,1-bismethylthio-2-nitrothene (**1**) was allowed to react with different amines (**2**) in acetonirile to afford the respective intermediates, 1-methylthio-1-amino-2-nitroethenes (**3a-f**). These on reaction with Na_2S in EtOH/AcOH gave the required nitrothioacetamides (**4a-f**) in good yields (**Scheme** 1). Various reagents that have been tried in this conversion and the importance of sequence of reagent addition are discussed in this chapter.

SCHEME-1



$-NR^1R^2$

a) 
b) 
c) $PhCH_2NH-$
d) 

e) 
f) 

N-Nitrothioacetyl derivative of ethyl/benzyl prolinate (**4d/e**) and ethyl N-nitrothioacetyl valinate (**4f**) have been synthesized by this method. ^1H NMR spectrum of ethyl/benzyl N-nitrothioacetylproline showed cis/trans rotamers in solution. Apart from the spectral evidence, chemical evidence is also discussed for nitrothioacetamide formation. The nitrothioacetamides were transformed into the corresponding nitroacetamides with $DMSO/H_2SO_4$.

CHAPTER 2 : Reactions of Nitrothioacetamides.

Nitrothioacetamides are very reactive molecules. In this chapter alkylation, allylation, reduction reactions and the reaction of phenacyl bromide, bromoacetone and p-nitro phenacyl bromide with nitrothioacetamides are discussed.

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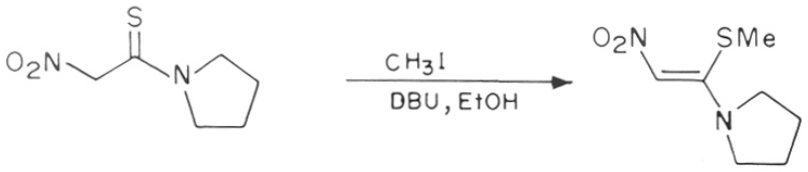
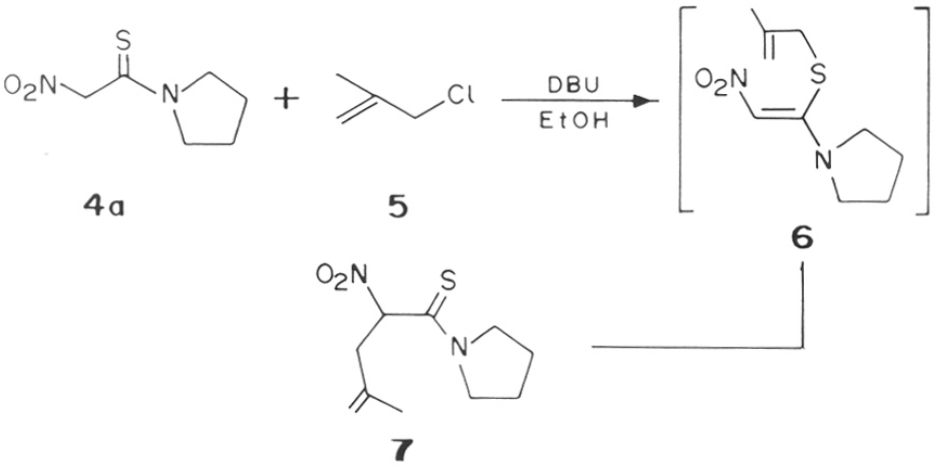


4a 3a

SCHEME-3



4a 5 6

7

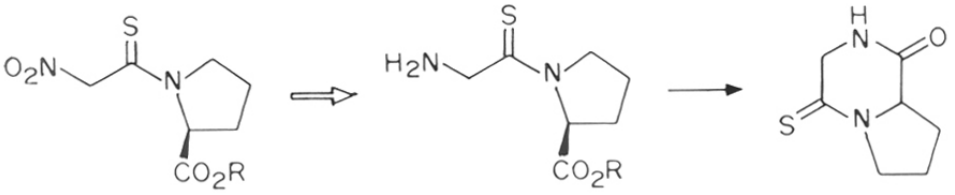
Alkylation of N-nitrothioacetylpyrrolidine (**4a**) with CH_3I in presence of DBU yielded S-methylated compound, 1-methylthio-1-pyrrolidino-2-nitroethene (**3a**) in quantitative yield. This shows that the site of attack is the S atom (**Scheme 2**). Allylation reaction was carried out on N-nitrothioacetylpyrrolidine with crotyl bromide to afford α-substituted N-nitrothioacetylpyrrolidine. In the reaction with methallyl chloride,

N-nitrothiacetylpyrrolidine gave α-methallyl N-nitrothioacetylpyrrolidine (**7**). In this reaction we could get the ^{1}H NMR spectrum of the intermediate S-allylated product (**6**) (**Scheme 3**) which provides strong evidence for the thio-Claisen rearrangement.

Nitrothioacetamides were allowed to react with α-bromo-carbonyl compounds like phenacyl bromide, bromoacetone and p-nitrophenacyl bromide in presence of a base to afford 2-N-pyrrolidino-3-nitro-4-alkyl/aryl thiophene derivatives in good yields.

Though the reduction of nitro group to amino group is a well known reaction, reducing nitro group in presence of a labile thioamide functional group is a challenging problem. Various methods tried for the reduction of nitro group of nitrothioacetamides keeping C=S intact, are discussed in this chapter. If at all this reduction is achieved, this could be a better route for the regioselective synthesis of thiopeptides (**Scheme 4**).

SCHEME-4



4 d/e **8** d/e **9** d/e

Unfortunately we could neither achieve the reduction of nitro group nor characterize the products formed in this reaction.

CHAPTER 3: Diastereoselectivity in thio-Claisen rearrangement

There has been a renaissance of interest in the aliphatic Claisen rearrangement as a technique for organic synthesis. Much has been studied about transition state structure and substituent effects on the rates of the reaction. It is somewhat surprising that there

has been no systematic study of these aspects in the thio-Claisen rearrangement. The biggest hurdle could be the labile nature of thiocarbonyl compounds compared to the corresponding carbonyl compounds.

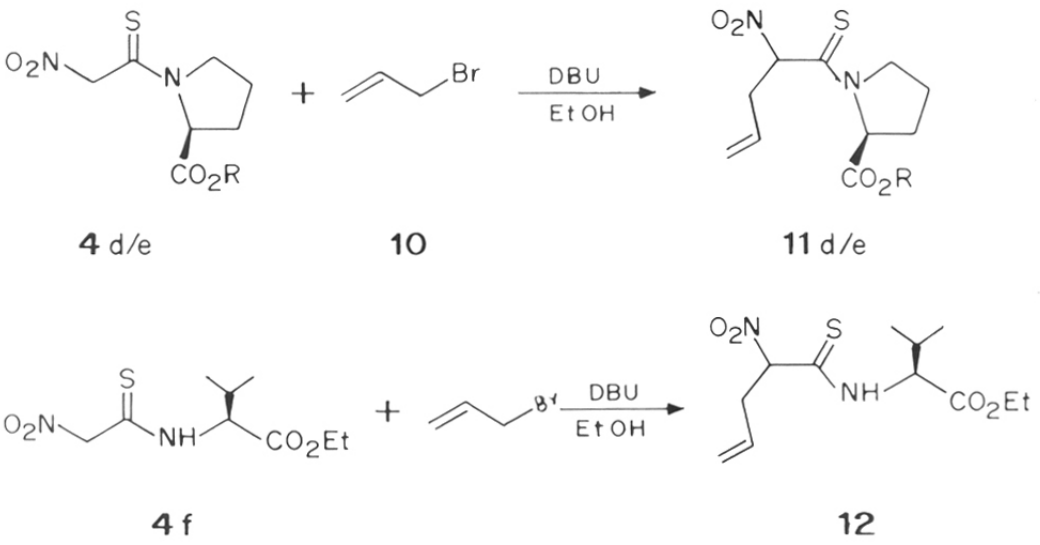
There have been several reports on chiral induction in [3,3] sigmatropic rearrangements. However, though such chiral induction in the Claisen rearrangement has been studied a similar study on thio-Claisen rearrangement has not been reported. Interestingly the only asymmetric effects discussed thus far have been related strictly to C_4 carbon, *an integral part of the Claisen rearrangement framework.*

It was planned to study chiral induction by the asymmetric center which is not an integral part of the [3,3] sigmatropic rearrangement framework. For the first time we studied the chiral induction in thio-Claisen rearrangement. Ethyl/Benzyl N-nitrothioacetylprolinate was allylated with allyl bromide in EtOH to get α-allyl N-nitrothioacetylproline ethyl/benzyl ester (**11d/e**) in good yields. From ^{1}H and ^{13}C NMR spectra the ***de*** was estimated to be 66%. Similar results were obtained with ethyl N-nitrothioacetylvalinate except that ***de*** in this case was lower (33%) (**Scheme 5**).

Various chemical and spectral attempts to assign the absolute configuration at the newly formed chiral center of the diastereomers (**11**) are discussed in this chapter. The absolute configuration was assigned by comparing the ^{13}C NMR spectra of α-allyl N-nitrothioacetylproline ethyl ester and α-allyl N-nitroacetylproline ethyl ester and by the ^{1}H NMR studies using chiral shift reagents. The absolute configuration of the major diastereomer was assigned as **RS** and the minor diastereomer as **SS** configuration.

The rearrangement proceeds under very mild reaction conditions. Hence, the substituent effects *i.e.* the effect of push-pull system) on the rate of thio-Claisen rearrangement is discussed in this chapter.

SCHEME-5

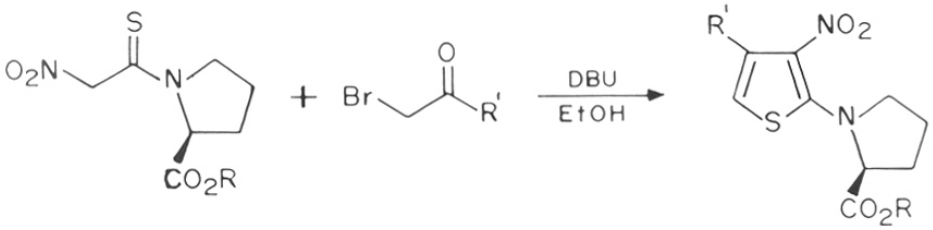


CHAPTER 4: Designing Organic Molecules For Non Linear Optics.

Organic molecules, capable of frequency conversion of laser are currently under intensive investigation. The high nonlinear efficiencies of these organic molecules results from a double optimisation, which involves two steps. The first step is, the design of an active molecule having high hyperpolarizability in relation to its transparency range. The second step is obtaining a crystal of such a compound having a non-centrosymmetric space group. Keeping these aspects in mind we synthesized thiophene derivatives (**14**) with a chiral center from N-nitrothioacetamides (**Scheme 6**).

In principle compound **14** is double optimized and we expected it to show the second order hyperpolarizability. However, experimental results show that these molecules are inactive. Donor-acceptor charge transfer contribution to the second order

SCHEME-6



4 d/e

14

R' : a) Me , b) Ph , c) $C_6H_4NO_2$

hyperpolarizability is well established. The possible reasons for the molecule to be inactive despite having donor-acceptor charge transfer interactions and non-centrosymmetric space group are discussed in this chapter.

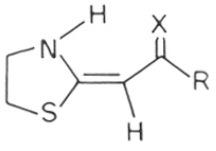
The rotation around C_2-N bond in these molecules is restricted and only one conformer is observed in $CDCl_3$ solution. This observation forced us to think of possible non-bonded attractive interaction between S atom and O atom of ester carbonyl group as being responsible for this preference. After pursuing this problem carefully we found that the restricted rotation is not because of non-bonding interactions but because of steric hindrance caused by the nitro group at the adjacent carbon on the thiophene ring.

CHAPTER 5: Non-bonded Attractive Interactions Involving S and O Atoms

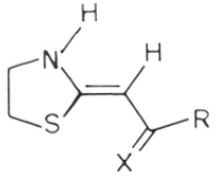
Non-bonding interactions assume importance because of their potential role in biomolecular conformations. In this chapter we discuss the non covalent interactions between the ring sulfur and the oxygen of carbonyl group, as well as that between the ring

sulfur and the sulfur of the thiocarbonyl group of the thiazolidine derivatives (**15**) (**Scheme 7**).

SCHEME-7



15 E



15 Z

a) R = Me , X = O
b) R = Me ; X = S

c) R = Ph ; X = O
d) R = Ph ; X = S

It is interesting to see that E,Z isomer population of compound **15** is solvent dependent. In nonpolar solvent ($CDCl_3$), E-isomer is preferred because of NH..O/NH..S hydrogen bonding, once the intramolecular hydrogen bonds are broken in polar solvents (DMSO-d_6), the population of Z-isomer increases, indicative of an attractive S..O or S..S interaction. The strength of S..O interaction is of the order of a typical NH..O hydrogen bond and S..S interaction is much weaker than S..O interaction.

CHAPTER 1

Synthesis of Nitrothioacetamides

1.1. Introduction

Background

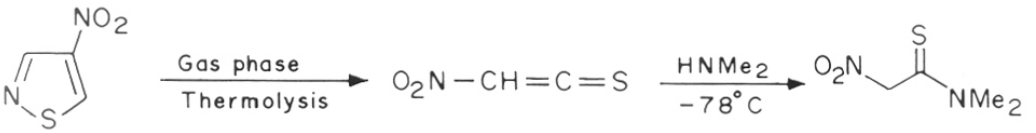
The nitroacetyl group has found application as a novel peptide synthon - especially for the synthesis of peptides incorporating unnatural amino acids. As an extension of this, it was felt that nitrothioacetyl derivatives of aminoacid derivatives might prove very useful in synthesis. There are several reasons for this. Thioacetamides in general exhibit a greater diversity of reactions than acetamides, especially those reactions that are a consequence of the enhanced nucleophilicity of sulfur compared to oxygen. Furthermore, such nitrothioacetyl derivatives of aminoacids or peptides may be potential precursors of thiopeptides, in which the thiocarbonyl group occupies a predetermined location, thus leading to regiospecific synthesis of thiopeptides. The *soft* nature of S (compared to O in nitroacetamides) in nitrothioacetamides can be exploited in designing the synthesis of materials that could have useful applications. There is no report in the literature on the use of nitrothioacetamides either in the synthesis of aminoacids or peptides. Prior to our work, there were only two reports known in the literature on the synthesis of nitrothioacetamides.

Synthesis of nitrothioacetamides; Literature survey

From Substituted Isothiazoles (**Scheme 1**)

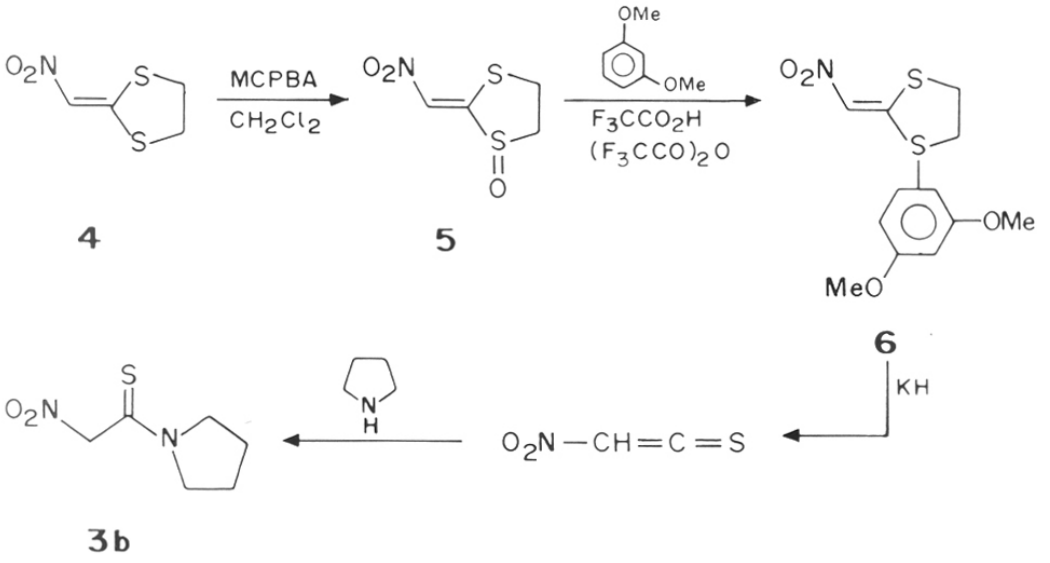
The first report on nitrothioacetamides came in 1978, by H.E.Bertorello[1]. In this paper a new synthesis of thioketenes (**2**) by the gas phase thermolysis of 4 or 5-substituted isothiazoles (**1**) has been carried out; the product has been trapped by reaction with N,N-dimethylamine at -78°C which afforded nitrothioacetamide (**3a**). No spectral or physical data have been provided.

SCHEME-1



1 2 3a

SCHEME-2



4 5 6 3b

From 2-alkylidene-1,3-dithiolanes (**Scheme 2**)

The only other report on the synthesis of nitrothioacetamides has come from E.Schaumann[2]. Oxidation of 2-alkylidene-1,3-dithiolanes(**4**) with one equivalent of m-chloroperbenzoic acid gave S-monoxides(**5**). S-Arylation of these by reaction with m-dimethoxybenzene under acidic conditions provided sulfonium salts (**6**) as a mixture presumably of the 2- and 4-aryl derivatives. The crude salts were transformed into S-ylides. Using potassium hydride, cycloreversion was carried out to get thioketenes(**2**). Trapping of these thioketenes with the amine afforded nitrothioacetamides (**3**) in 53% yield.

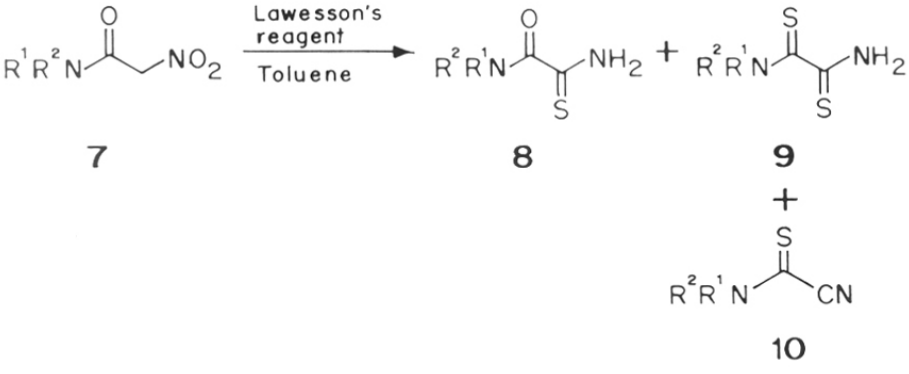
The above two methods involve the same strategy of trapping nitrothioketene(**2**) with amines. This approach is neither simple nor practical under laboratory conditions and yields are not high.

From Nitroacetamides (7)

A large number of publications have appeared on the thionation of amides to the corresponding thioamides. Elemental sulfur in HMPA[3], O,O-dialkyl-dithiophosphoric acids[4], tetramethylthiophosphoric diamide[5] , $SOCl_2$[6], potassium xanthate[7], sodium hydrogen sulfide[8], thioacetic acid[6], P_4S_{10}[9], bis (tricyclohexyl tin)-sulfide and BCl_3[10] and Lawesson's reagent(LR)[11] are a few thionating agents which have been employed. It is also reported that nitro groups survive Lawesson's thionation conditions. J.A. Joule[12] et al have attempted in vain to convert nitroacetamides(**7**) into the thioamide analogues with conventional thionating agents like P_4S_{10} and Lawesson reagent. No trace of the required nitrothioacetamide could be detected in the product mixture, which consisted of compounds arising from fragmentation, and redox reactions, in addition to thionation. (**Scheme 3**).

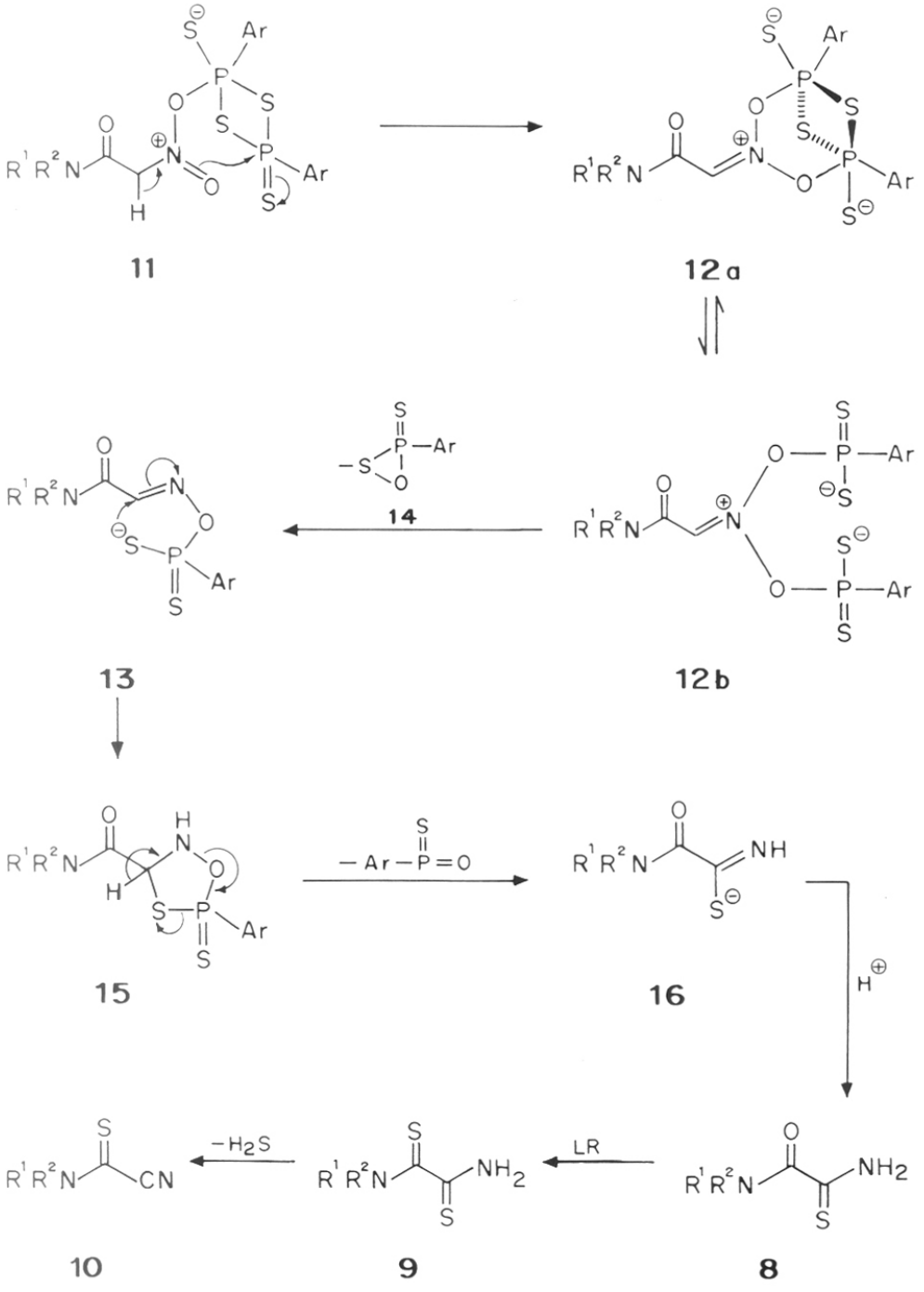
The reaction of Lawesson's reagent with nitroacetamides might involve the attack on the phosphorous of Lawesson's reagent by the nucleophilic oxygen of the nitro group via intramolecular delivery (**Scheme 4**).

SCHEME-3



a) $R^1 = H$, $R^2 = Me$ b) $R^1 = H$, $R^2 = H$ c) $R^1 = R^2 = Me$

SCHEME-4



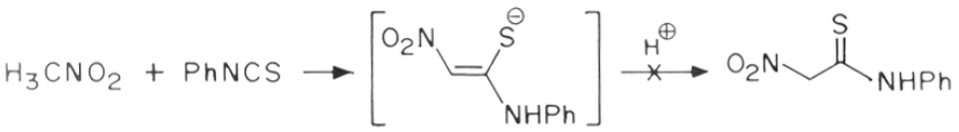
The initial adduct **11**, by proton loss and interaction of the second oxygen of the nitro group with phosphorous would produce **12**a/b. Reduction at nitrogen to **13** and **14**, with subsequent loss of sulfur from complete redox cycle. Amidethioamide formation would proceed from **13** via intramolecular delivery of sulfur, then fragmentation and protonation.

Similar results were obtained with P_4S_{10}. To sum up, nitrothioacetamides cannot be synthesized from the corresponding nitroacetamides.

From the salts of Nitrothioacetamides

Nitromethane can be reacted with phenyl isocyanate in presence of NaH in DMF to form the salt (**16**)[13,14]. This salt has been used for the synthesis of nitroketeneaminals. But there is no report on the protonation of this salt to get nitrothioacetamides; infact it leads to resin formation (**Scheme 5**).

SCHEME-5



So we felt the need for an elegant and practical methodology for the synthesis of nitrothioacetamides.

1.2. Results and Discussion

1.2.1 Synthesis of Nitrothioacetamides of simple amines

Two synthetic routes for the synthesis of nitrothioacetamides were envisaged starting from a common precursor, 1-methylthio-1-substituted amino-2- nitroethene(**18**). One is the cleavage of the thioether bond with Lewis acids, leading to the retention of the S atom of the starting material in the resulting nitrothioacetamides[15]; the other route is replacement of the -SCH_3 by SH, *via* an addition - elimination mechanism, by means of a suitable sulfur nucleophile.

1.2.2 Attempted Cleavage With Lewis Acids

Thioethers are in general less reactive towards protonic and Lewis acids than the corresponding ethers. The reason may be that the sulfur atom is too large to allow effective orbital overlap with a proton or with electron deficient atom of a Lewis acid. Therefore formation of the intermediate sulfonium compound is difficult.

Keeping the size of electron deficient atom of Lewis acids in mind, we have opted for trimethylsilyl iodide which is known to cleave ether linkages[16].

Trimethylsilyl iodide was generated in situ by adding trimethylsilyl chloride (5mmol) to a solution of NaI (15mmol) in acetonitrile (15ml); 1-methylthio -1-pyrrolidino-2-nitroethene(**16**) in acetonitrile (10ml) was added to the above solution and stirred for 2h. under nitrogen atmosphere.

The required nitrothioacetamide could not be isolated from the product mixture; nor could any other pure product be isolated and identified. Later we came to know that Olah[17] et al have deoxygenated sulfoxides to get thioethers by trimethylsilyl iodide. The use of other Lewis acids such as boron compounds was not attempted, since it was felt that these reagents might react with the nitro group.

1.2.3 Replacement of -SCH_3 by -SH

A variety of nucleophilic reagents like NaSH, H_2S, Na_2S/dil HCl, Na_2S/ethanolic HCl and Na_2S/AcOH have been tried to displace the thiomethyl group of 1-methylthio-

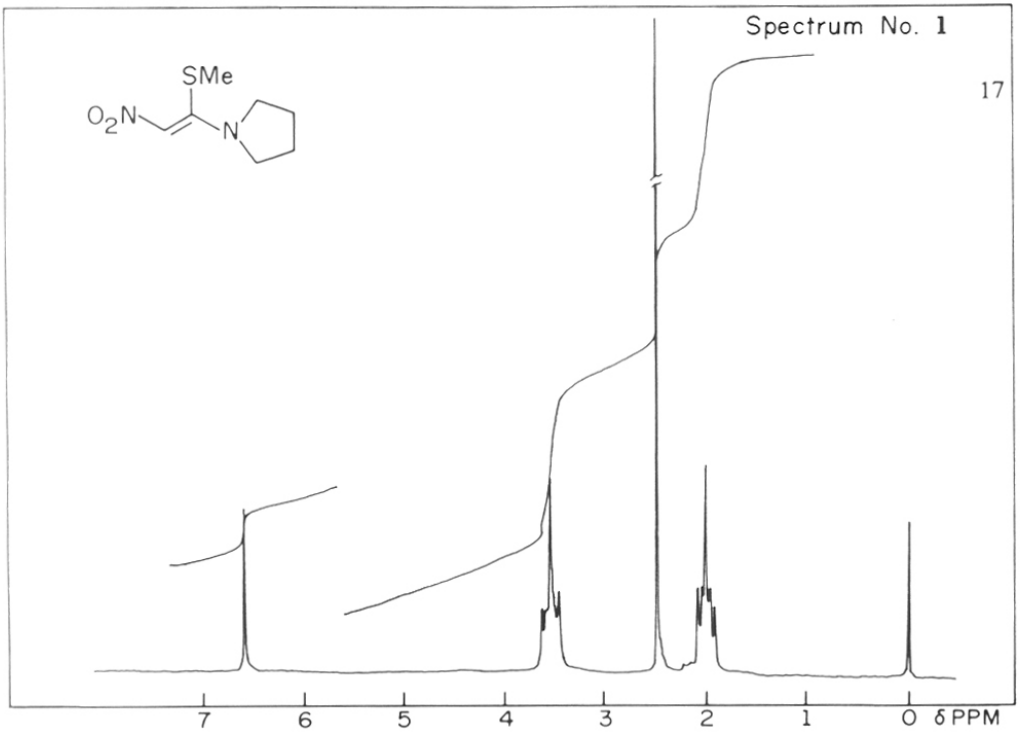
1-pyrrolidino-2-nitroethene (**18b**). Na_2S (6mmol) was added in portions to a solution of (**18b**) (5 mmol) in EtOH, stirred at rt. till the starting material disappeared. It was expected that under these conditions, the salt (**19**) would be formed; the mixture was therefore worked up by acidification with dil HCl or ethanolic HCl or acetic acid. However, in every case only intractable tars resulted.

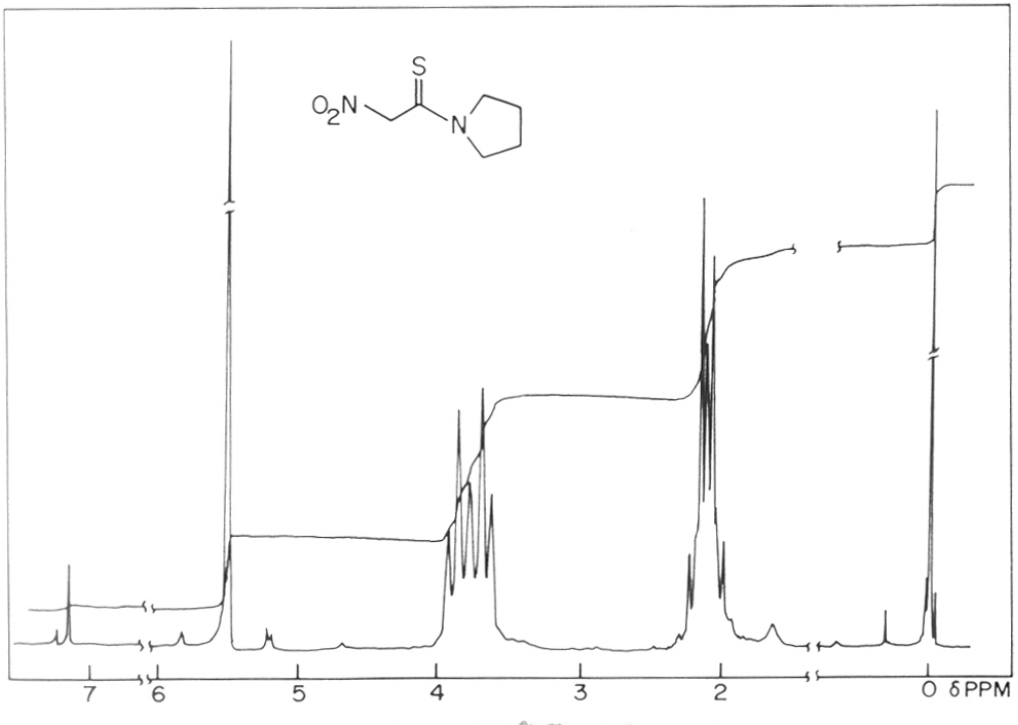
This is in agreement with the earlier observations made by R.Gompper et al[13,14].

Later it was found that the sequence of reagent addition had a crucial role in this reaction. Success was ultimately achieved when acetic acid (2eq.) was added first to the solution of 1-methylthio-1-pyrrolidino-2-nitroethene (**18b**) in dry EtOH followed by Na_2S (1.5eq.) in small portions. The solvent was removed and the contents taken into benzene. Inorganic salts were removed and the filtrate was concentrated to get a thick gum which was chromatographed on a silica column (benzene as eluent) to get the pure N-nitrothioacetyl pyrrolidine (**3b**) (**Scheme 6**)

(**Spectra 1 and 2**)

TH-649





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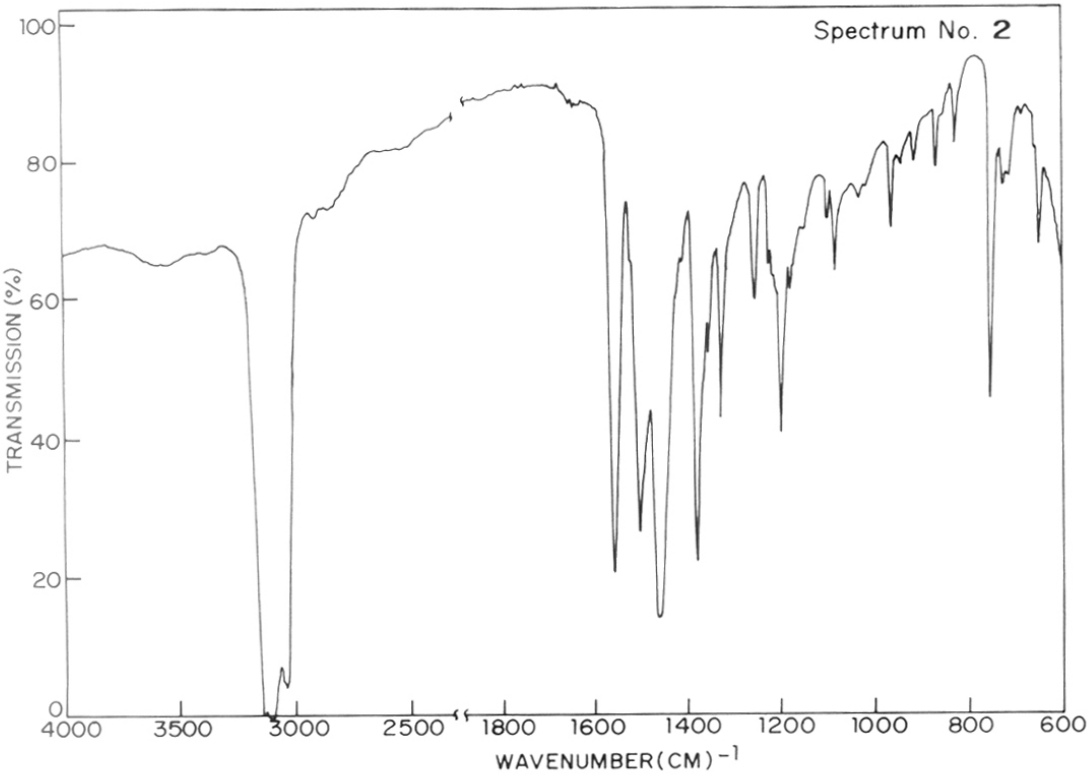
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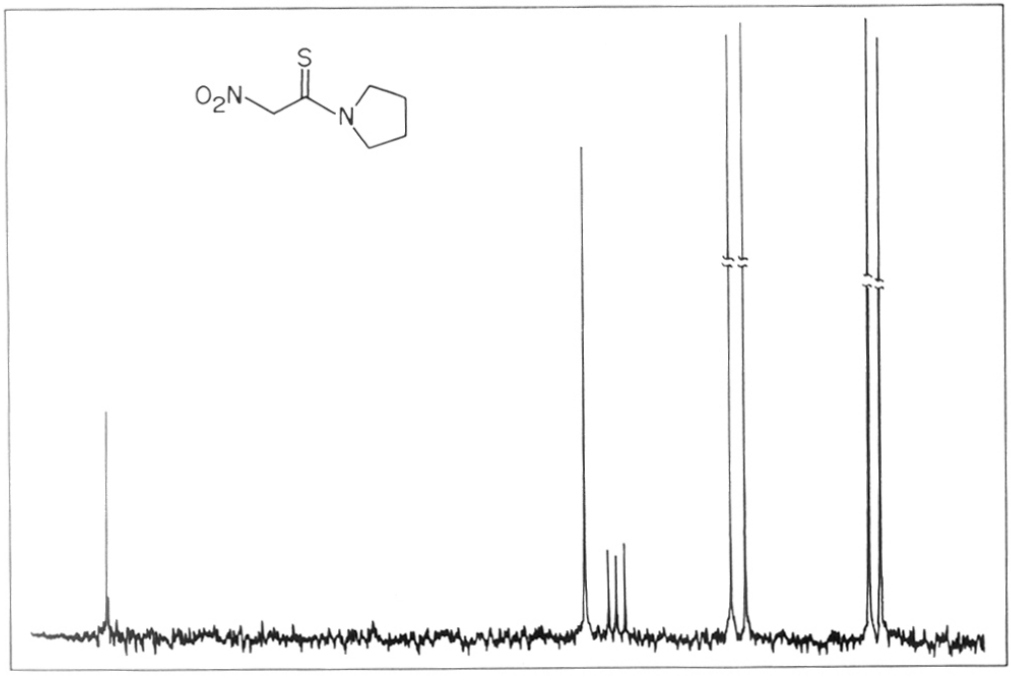
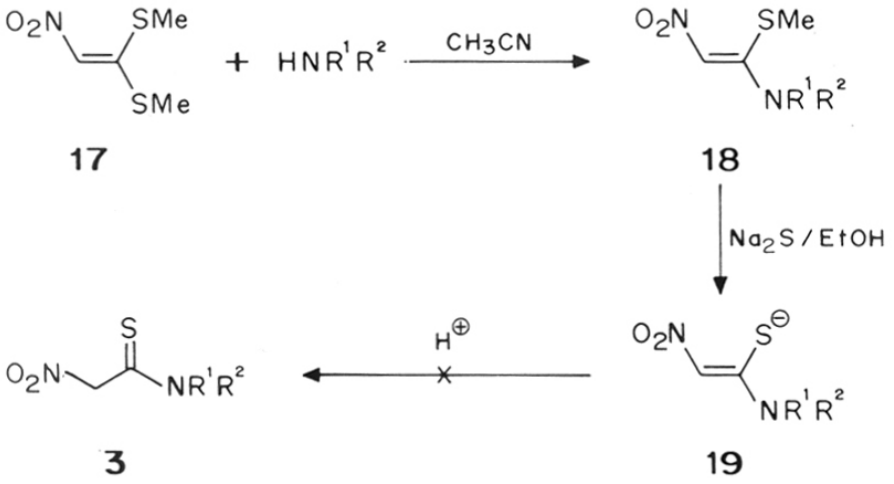
800
600
WAVENUMBER(CM)$^{-1}$


S
O_2N
N



$-NRR^1$

a) NMe_2

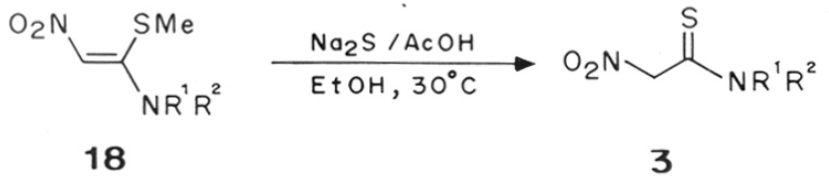
b) 

c) 

d) $PhCH_2-NH_2$

SCHEME-6

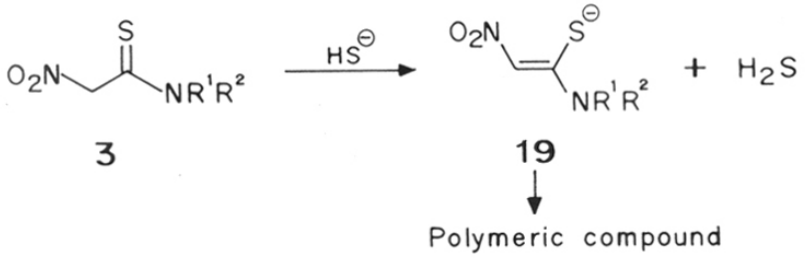
SCHEME-7



18 **3**

in 68% yield; m.p.78°c (lit.81°c); **IR**(nujol): 2700, 1560,1500,1460,1260;^{1}**H NMR** ($CDCl_3$): 2.08 (m,4H), 3.75 (m,4H), 5.48 (s,2H);

SCHEME-8



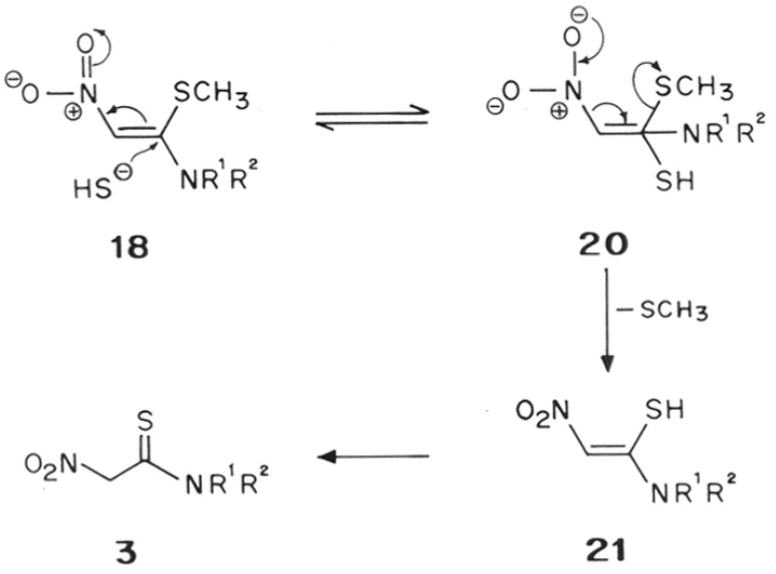
The signal at 5.48 is assigned to O_2N-CH_2 protons, the one at 3.75 for NCH_2 protons and 2.08 is for other two methylene group protons of pyrrolidine moiety. A down field shift for all the protons of N-nitrothioacetyl pyrrolidine(**3b**) has been observed compared to the protons of N-nitroacetyl pyrrolidine[19]. Particularly the methylene protons adjacent to the nitro group display a large down field shift because of the stronger anisotropic effect of thiocarbonyl compared to the carbonyl group[18]. The structure of the product was confirmed by the observation of molecular ion peak in the mass spectrum. **MS**(m/e): 174(M^+), 144(M^+-NO), 128(M^+-NO_2).

1.3. Possible Mechanism

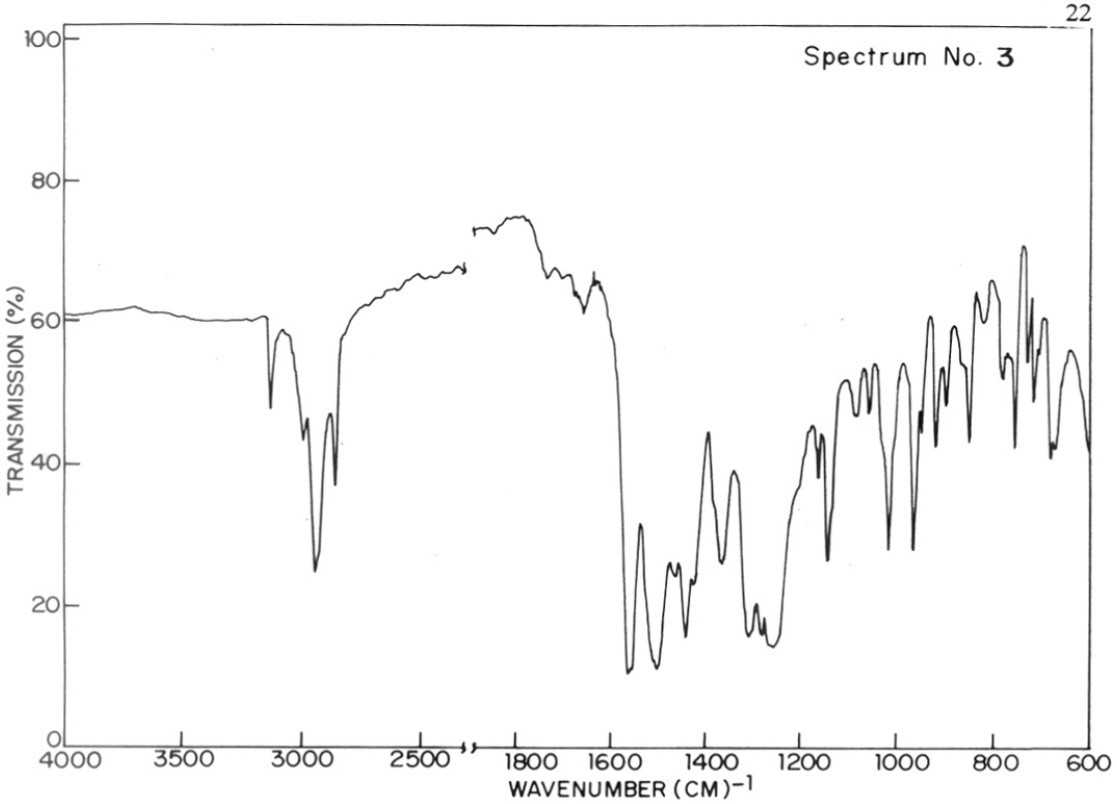
In this reaction the nucleophile could be either HS^- or H_2S, generated *in situ*. The lack of success when NaHS was used as the reagent cannot be regarded as evidence against HS^- being the active species in this reaction, since in the former case, excess HS^- could have deprotonated the highly acidic nitrothioacetamide, leading to polymerization. At acidic pH, as in the present successful experiment, such deprotonation would not occur. Once the medium is acidic and the nucleophile is available, the reaction can proceed by addition - elimination, as in **Scheme 9**.

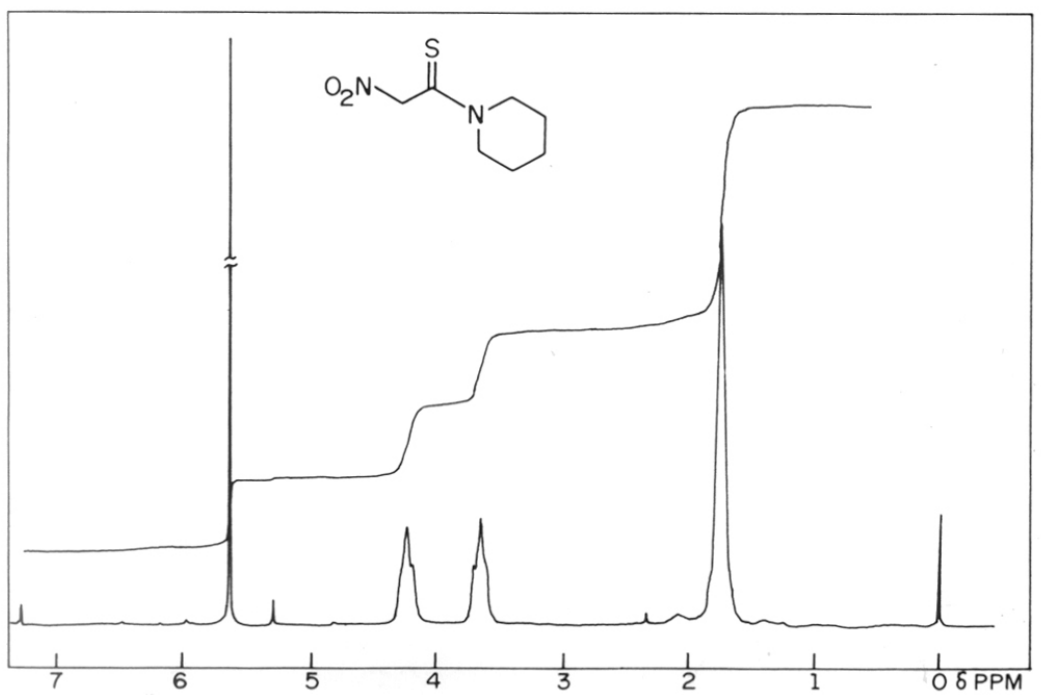
Moreover the very low yields (5%) of the product obtained with H_2S as the reagent compared to the yields in the above reaction with *in situ* generated nucleophile (68%), allow us to say that HS^- is the attacking nucleophile.

SCHEME-9

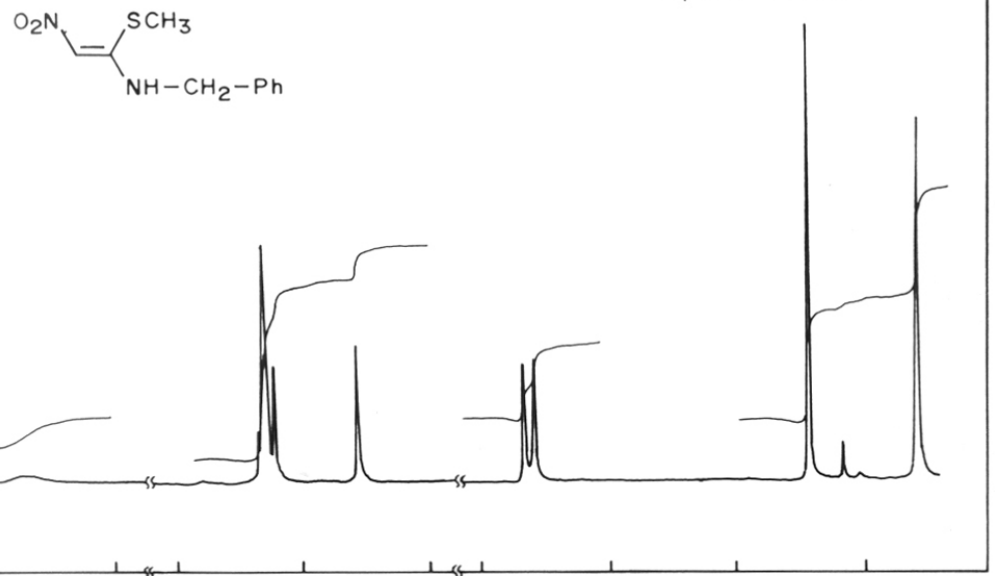


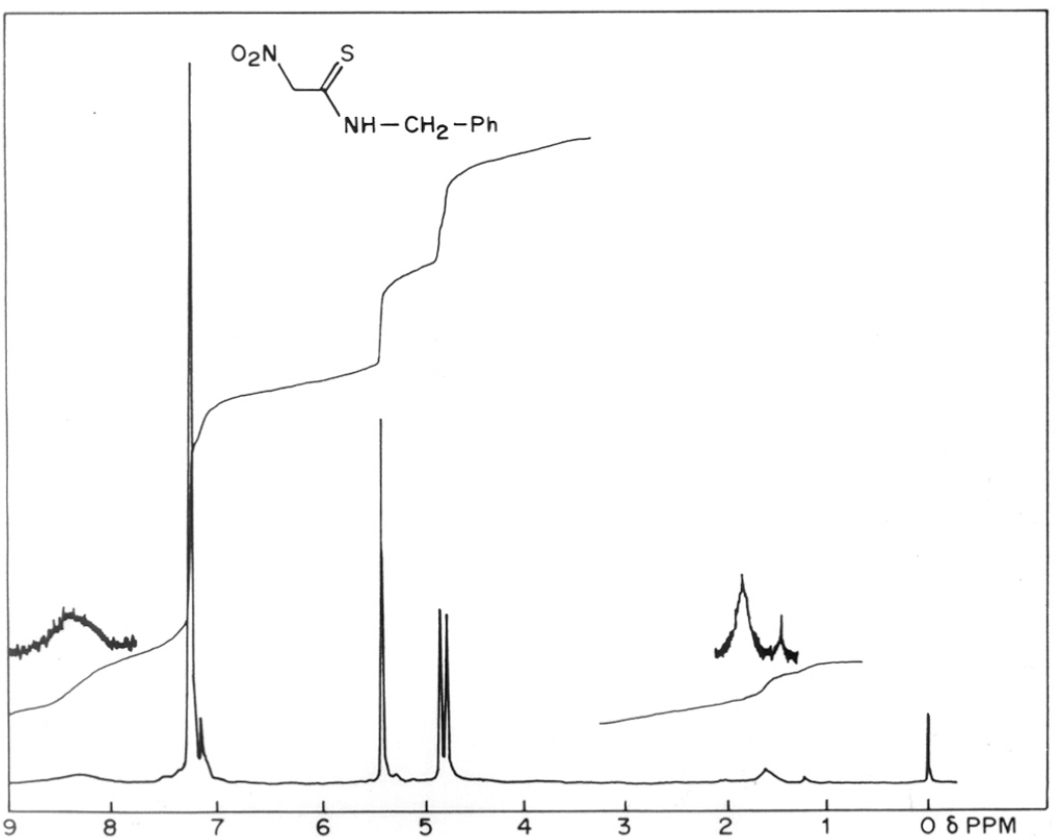
Using this methodology, the nitrothioacetyl derivatives of different amines (**scheme 7**) were synthesized (**Spectra 3 and 4**)
by the same procedure. Various attempts to purify nitrothioacetamides of phenethylamine, N,N-dimethylamine and morpholine were unsuccessful. But in all these cases we have observed the formation of the required nitrothioacetamides from the **^{1}H NMR** spectrum of the crude reaction product. Interestingly none of the nitrothioacetamides exists in the ene-thiol form in the solvents studied.


Spectrum No. 3
TRANSMISSION (%)
100
80
60
40
20
0
4000
3500
3000
2500
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM)$^{-1}$


S
O_2N
N
7
6
5
4
3
2
1
0 δ PPM

Spectrum No. 4

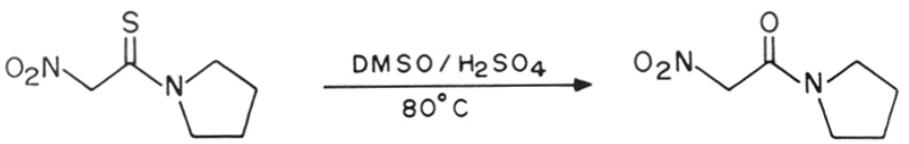




1.4. Structure Proof

Despite the spectral evidence we had in support of nitrothioacetamide formation, the lack of correct microanalysis value for some of the nitrothioacetamides and the labile nature of these compounds forced us to look for further evidence for their structure. The spectral data for nitroacetamides[19] is available in literature. We have transformed[20] the nitrothioacetamides to nitroacetamides and compared the data with the reported ones and found that they are identical. This gives concrete evidence for the formation of nitrothioamides(**Scheme 10**) in our new reaction.

SCHEME-10



3b **7**

The N-nitrothioacetylpyrrolidine was allowed to react with excess DMSO in presence of a catalytic amount of H_2SO_4 for 12h. at 80°c under nitrogen atmosphere. The reaction was monitored by tlc. The contents were poured into water and the compound was extracted with benzene. The organic layer was washed thrice with water and dried over Na_2SO_4, the solvent was evaporated to get the solid in 75% yield. The compound was further purified by passing through a short silica gel column (benzene as eluent); m.p. 105 - 106°c; **IR**(nujol): 2700, 1650, 1570, 1460 and 1380cm^{-1}; ^{1}H NMR($CDCl_3$): 1.87(m,4H), 3.42(m,4H), 5.125(s,2H). The spectral data exactly matches with that of N-nitroacetylpyrrolidine.

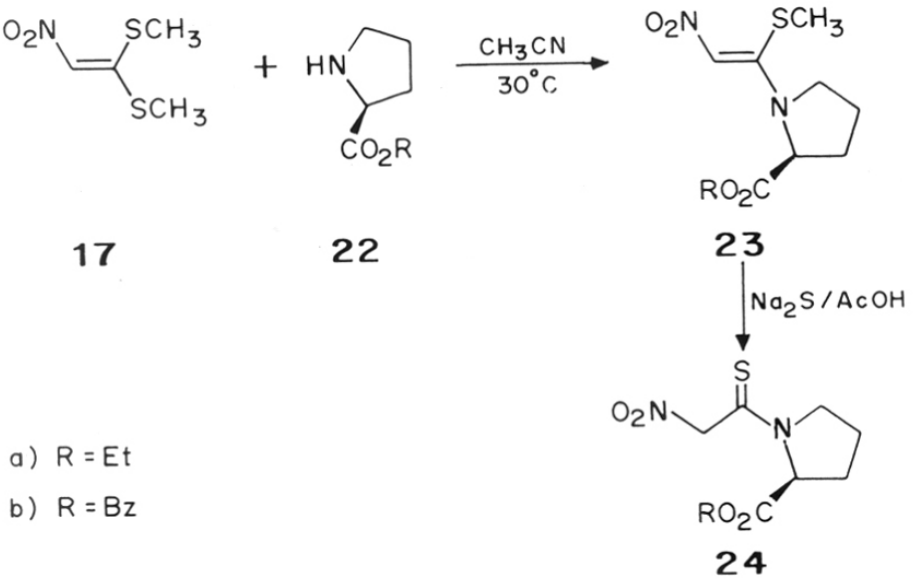
1.5. N-Nitrothioacetylproline ethyl ester(24a)

1.5.1 Synthesis

The above method described for the synthesis of nitrothioacetamides has been conveniently used in the synthesis of N-nitrothioacetylproline ethyl ester (**24a**) (**Scheme 11**).

Thus the reaction of ethyl L-prolinate (**22a**) with 1,1-bis- methylthio- 2-nitroethene (**17**) at 30°c in CH_3CN for 24h. gave the intermediate ethyl N-(1-methylthio-2-nitroethenyl) prolinate(**23a**) in 70% yield. Singlets at 6.65 and 2.4δ in 1:3 ratio, assigned to =CH and SCH_3, confirmed the structure. Preserving this intermediate for long periods is not advisable as it will undergo hydrolysis to afford N-nitroacetylproline ethyl ester. Ethyl N-(1-methylthio-2- nitroethenyl) prolinate (**23a**) was allowed to react with Na_2S under specified reaction conditions to afford N-nitrothioacetylproline ethyl ester(**24a**) in 75% yield; $[\alpha]^{EtOH}$ = -120.2°; **IR**(neat): 1740,1570, 1480, 1370cm^{-1}. The **^{1}H** and **^{13}C NMR** spectra of this product are discussed separately.

SCHEME-11

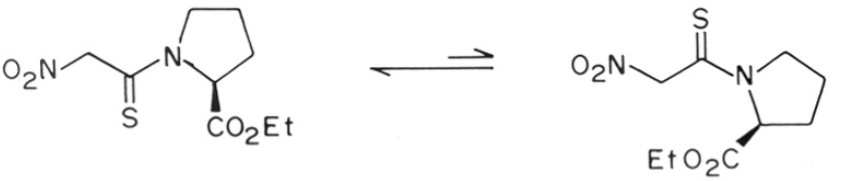


17 22 23 24

a) R = Et

b) R = Bz

SCHEME-12



Trans 24a Cis 24b

1.5.2 Discussion on ^{1}H and ^{13}C NMR spectra

Because of the restricted rotation around the amide bond we have observed peak doubling in both ^{1}H NMR and ^{13}C NMR due to the existence of *cis* and *trans* conformers in nitroacetamides[19] and nitrothioacetamides. The barrier to rotation around C(S)-N bond is greater in thioamides than that of CO-N in amides[21]. Many criteria have been used for NMR signal assignment of *cis/trans* conformers like **a**) inequality in *cis/trans* coupling constants, **b**) differential solvent shifts, **c**) NOE effects.

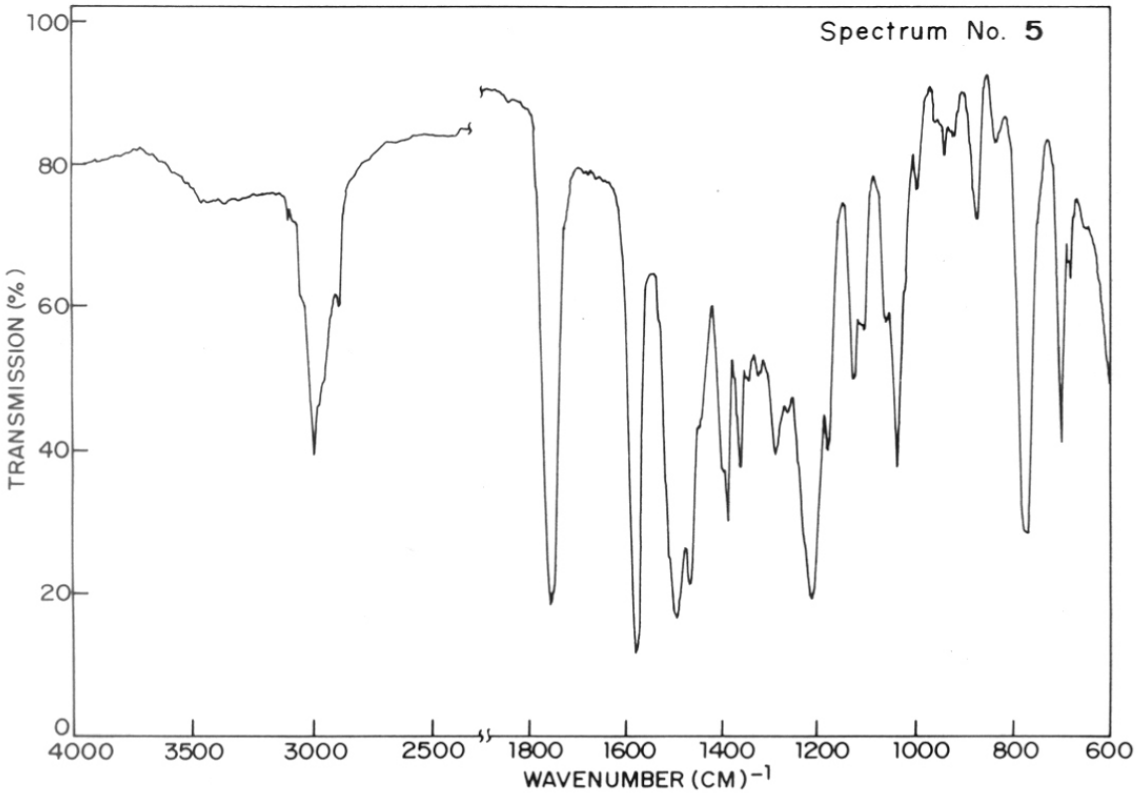
It has been proved that *trans* conformer is the major one in many amides and thioamides[22]. Based on these observations we assume that *trans* conformer is major contributor in nitrothioacetamides also, which was confirmed by the energy calculations.

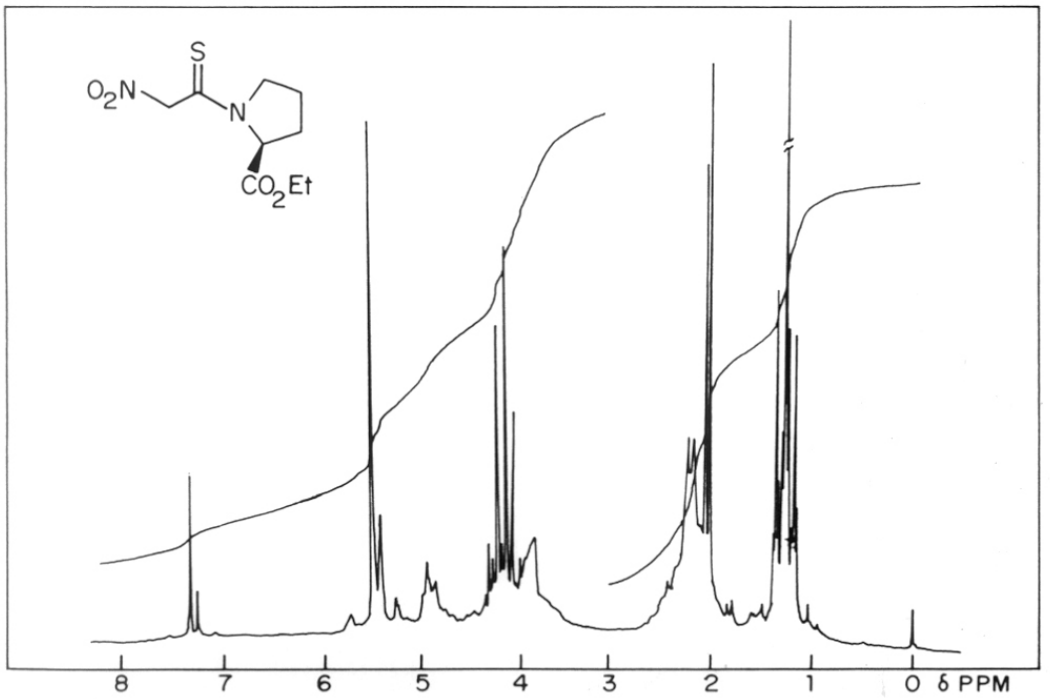
Because of the presence of a chiral center in N-nitrothioacetylproline ethyl ester (**24a**), the methylene protons of the molecule are diastereotopic. Hence in **^{1}H NMR** they resonate at different frequencies (**Spectrum No. 5**).

Thus O_2N-CH_2 methylene protons gave an AB quartet at 5.53δ and a complex pattern was observed for NCH_2 and other methylene protons of the proline moiety. Two sets of signals were observed for the protons of OCH_2, CH_3 and O_2N-CH_2 groups corresponding to *cis* and *trans* conformers. Likewise, in the **^{13}C NMR** spectrum (**Spectrum No. 6**) also, two sets of peaks are observed corresponding to the two conformers in solution.

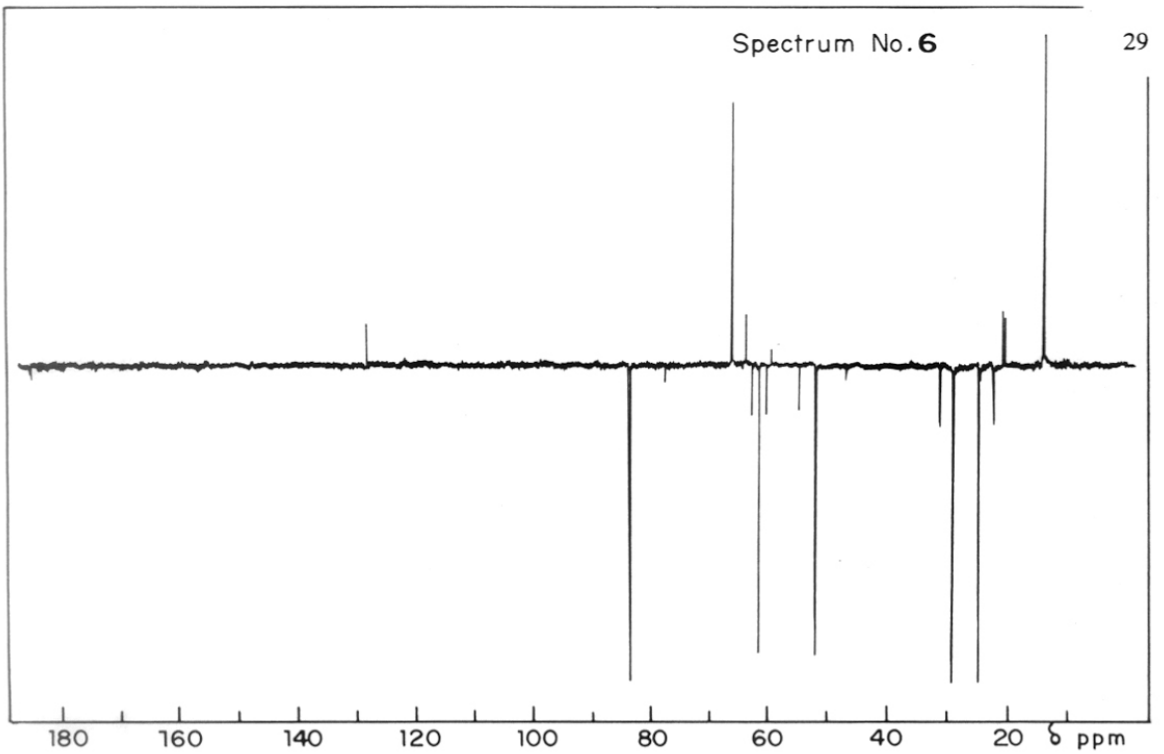
It is the general experience that carbon atoms which are *syn* to the carbonyl oxygen of amides are shielded relative to those which are *anti*[23]. Extending the same logic to the nitrothioacetamides, one would expect the α-carbon of the *trans* conformer to be more shielded relative to that of *cis* conformer (**Scheme 12**).

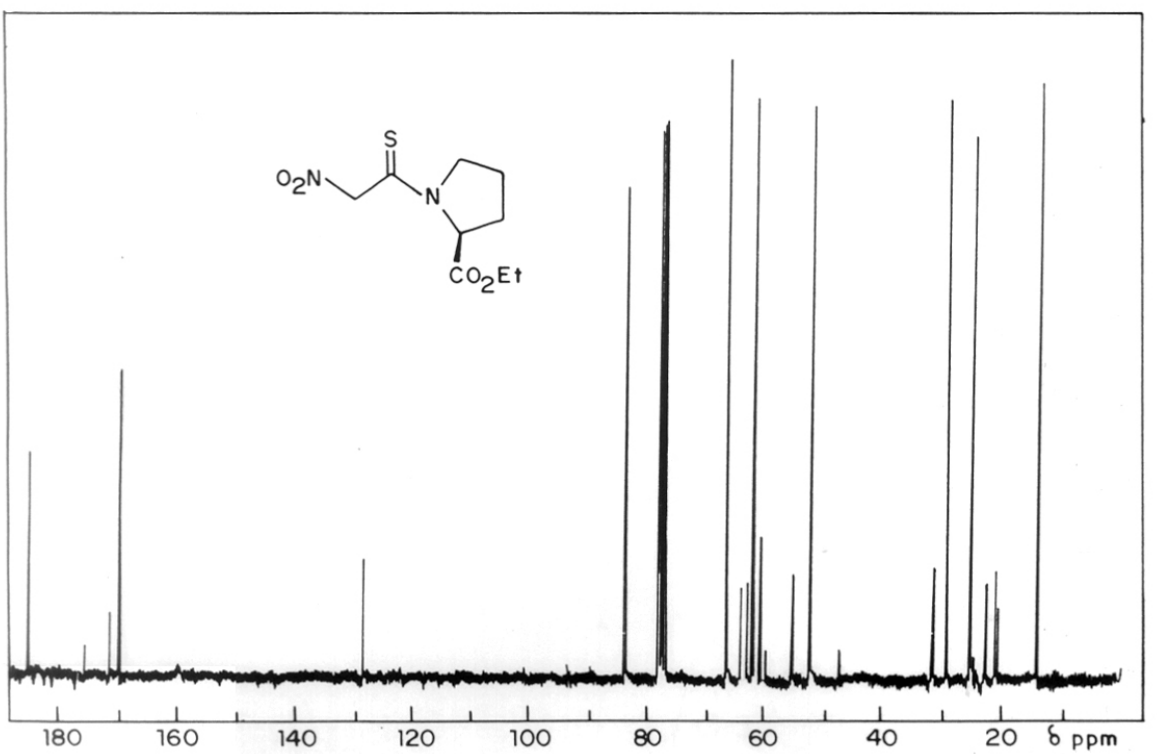
Thus we assigned the peak at 61.19 for the α-carbon of the *trans* conformer and 62.31 for the *cis* conformer. A similar anisotropic effect was observed on the beta carbon, hence the signal at 28.92 was assigned for β-carbon of the *trans* conformer and the one at 30.92 for β-carbon of the *cis* conformer.


Spectrum No. 5
TRANSMISSION (%)
100
80
60
40
20
0
4000
3500
3000
2500
1800
1600
1400
1200
1000
800
600
WAVENUMBER (CM)$^{-1}$


S
O_2N
N
CO_2Et
8
7
6
5
4
3
2
1
0 δ PPM

Spectrum No. **6**





However the γ-carbon was more shielded in the *cis* conformer. The signal at 22.14 was assigned for the γ-carbon of the *cis* conformer and the signal at 24.64 for the gamma carbon of the *trans* conformer. Similarly the signals at 51.57 and 54.45 were assigned to δ-carbon of *trans* and *cis* conformers respectively.

From the above ^{13}**C** and ^{1}**H NMR** studies the *trans/cis* ratio was found to be 7:1 which is the same as that observed in nitroacetamides.

1.6. N-Nitrothioacetylproline benzyl ester (24b)

1.6.1 Synthesis

This compound was easily prepared by the general method explained above, in 65.7% yield after column chromatographic purification (scheme). $[\alpha]^{EtOH}$= -77.2°; m.p.:63°C; **IR**(nujol):1740, 1560, 1470, 1450, 1380cm^{-1}.

1.6.2 Discussion of ^{1}H NMR spectrum

N-Nitrothioacetylproline benzyl ester (**24b**) like N-nitrothioacetylproline ethyl ester showed two sets of signals corresponding to the *cis/trans* conformers as well as magnetic nonequivalence for the geminal protons of the prochiral methylene groups. NCH_2 protons gave two multiplets at 3.75 and 3.85δ and β methylene protons showed another two multiplets at 2.15 and 2.45δ and a complex pattern is observed for γ methylene protons. Apart from this, peak doubling is observed for O_2N-CH_2 protons [*trans* conformer: 5.55δ; *cis* conformer: 5.4δ], benzylic methylene protons [*trans* conformer: 5.2δ; *cis* conformer: 5.25δ] and α-methine proton [*trans* conformer: 5.05δ; *cis* conformer: 4.85δ]

From the ^{1}**H NMR** spectrum the *trans* to *cis* ratio was found to be 7.5:1

1.7. N-Nitrothioacetylvaline ethyl ester(27a)

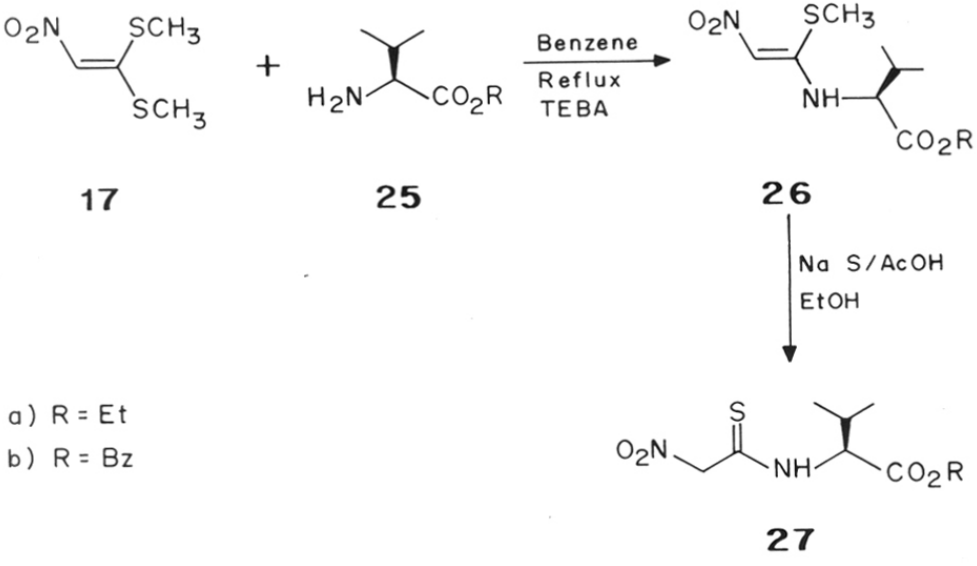
1.7.1 Synthesis

The reaction of ethyl L-valinate (**25a**) with 1,1-bismethylthio -2-nitro- ethene (**17**) at 30°C in benezne gave the intermediate ethyl N-(1-methyl-thio-2-nitroethenyl) valinate (**26a**) in 55%yield; $[\alpha]^{EtOH}$ = +120.2°; **IR**(neat): 3500, 1750, 1570 and 1350 cm^{-1}; In ^{1}**H**

NMR spectrum the signal at 2.42 and 6.56 δ in 3:1 ratio for SCH_3 and =CH shows the formation of the required compound and is further confirmed by the presence of M^+ peak at 262 in the mass spectrum.

The above ethyl N-(1-methylthio-2-nitroethenyl) valinate (**26a**) was allowed to react with Na_2S in acetic acid to get N-nitrothioacetylvaline ethyl ester (**27a**) (**Scheme 13**)

SCHEME-13



in 75% yield after purification, $[\alpha]_{\varphi}^{EtOH}$= -19.06°; In the infrared spectrum, the compound showed peaks at 3300, 1740, 1570, 1380 cm^{-1}; the ^{1}**H NMR** spectrum is discussed separately, and the structure is further confirmed by the presence of molecular ion peak at 248.

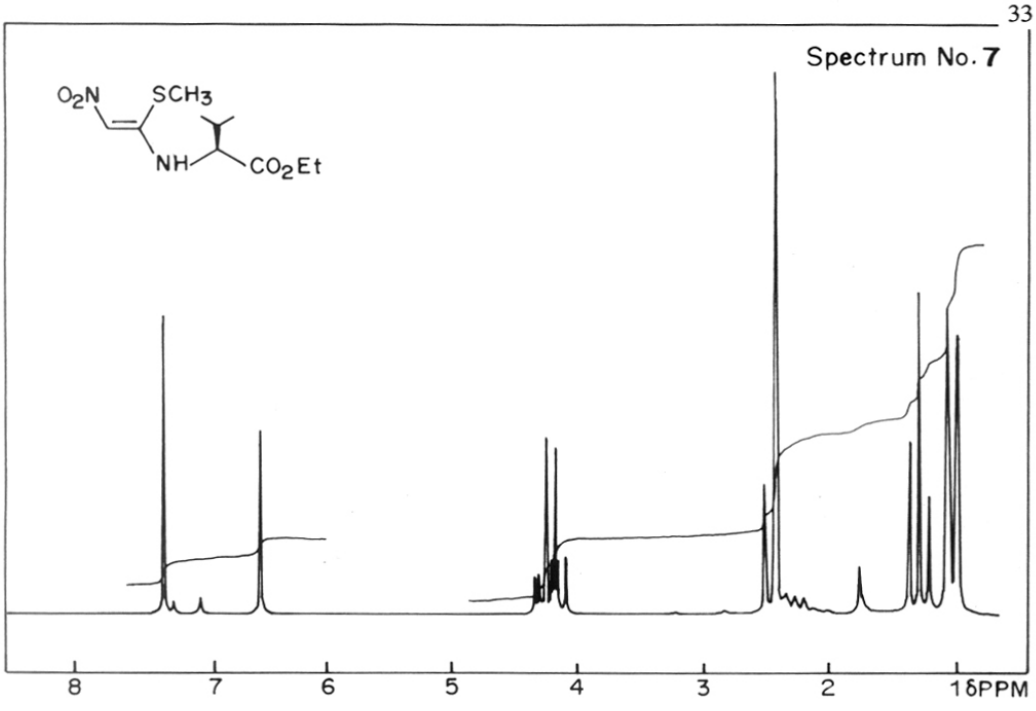
1.7.2 Discussion of ^{1}H NMR

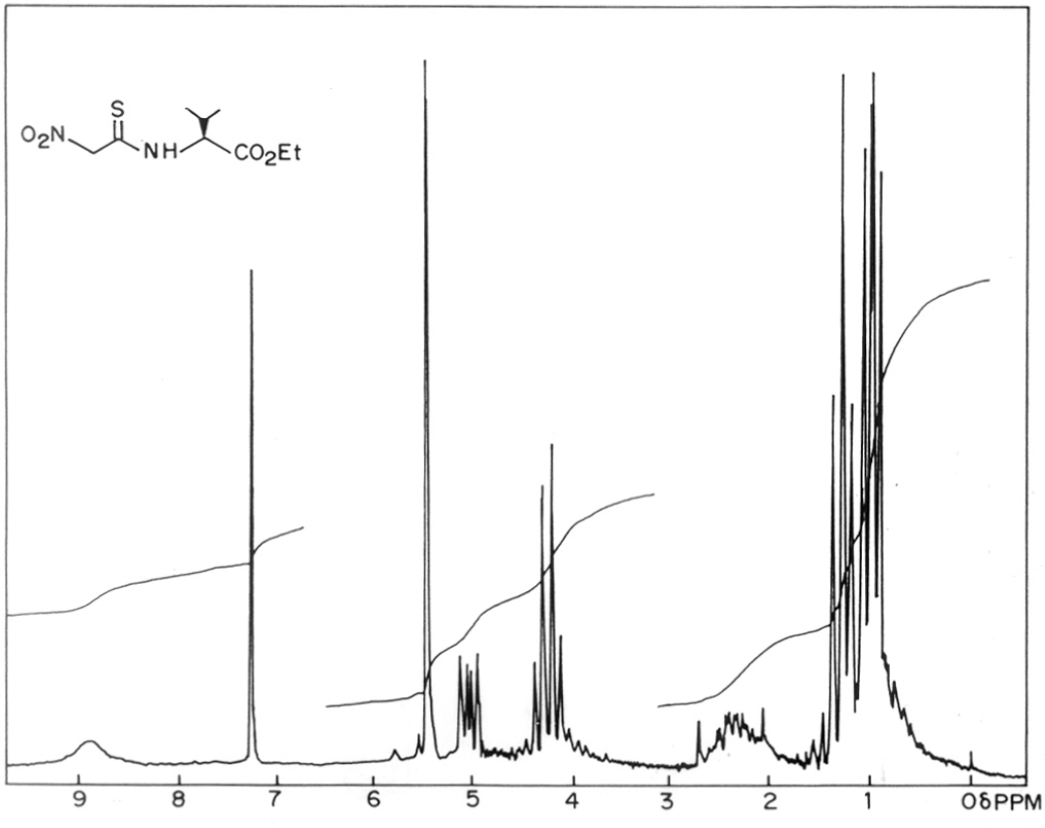
Unlike in the case of N-nitrothioacetylproline esters (**24**), cis/trans isomerism around the thioamide bond was not seen in N-nitrothioacetylvaline ethyl ester(**27**). The reasons could be, fast rotation around the C-N bond, so that only the average signals for cis/trans isomers are observed; another possible reason is that the existance of only one isomer, probably the trans is present because of possible H-bonding between the nitro group and NH.

Since a chiral center is present in N-nitrothioacetylvaline ethyl ester(**27a**), all *diastereotopic* groups showed magnetic nonequivalence (**Spectrum No. 7**).

Two doublets were observed for the two methyls of valine moiety at 1.07 and 0.98δ, a complex triplet and quartet pattern was observed at 1.32 and 4.21δ for the protons of the ethyl group, a complex multiplet at 2.36δ was assigned for Me_2CH and a *dd* at 5.04δ for N-CH which coalesce to a doublet after D_2O exchange. Signals at 5.47 and 8.91δ were assigned to O_2N-CH_2 and NHprotons. Efforts to synthesize N-nitrothioacetylvaline benzyl ester and N-nitrothioacetylphenethylamine were not fruitful.

Spectrum No. 7





1.8. Experimental Section

Synthesis Of Ethyl L-Prolinate/ L-Valinate (22a/25a)

Thionyl chloride (9ml,120 mmol) was slowly added to a suspension of L-proline/ L-valine (40 mmol) in dry ethanol (75 ml) at 0°c. A clear solution was obtained and the solution was stirred at 30°c for 1h. and 60°c for 10h. The solvent ethanol was removed under vacuum to get a gum. The gum was taken in CH_2Cl_2 (30ml) and the solution was made basic by the addition of triethylamine(TEA) in methylene chloride at 0°c. The white solid was filtered off and the filtrate was concentrated to get a light yellow liquid which was used as such for further reaction.

Ethyl L-Prolinate: Yield: 80%; **IR**(neat): 3350, 1740, 1450, 1200, 1120cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.2δ (t, 3H, -**CH_3**), 1.5-2.0δ (m, 4H, 2**CH_2**), 2.1δ (s, 1H, **NH**), 2.7-3.1δ (m, 2H, N**CH_2**), 3.4-3.7δ (t, 1H, N**CH**), 3.9-4.3δ (q, 2H, O**CH_2**)

Synthesis of Benzyl L-Prolinate/ L-Valinate (22b/25b)

Thionyl chloride was added to the benzyl alcohol, solution was cooled to 0^0c, then L-proline/ L-Valine was added in portions. A clear solution was obtained which was stirred at 60^0c for 24h. HCl was removed under vaccume, and the solution was poured in to solvent ether (200ml) to get a solid, which was taken into methylene chloride and made basic with TEA in CH_2Cl_2, stirred for 1h. white sold was filtered off and CH_2Cl_2 was removed to get benzyl ester of L-proline/ L-valine, which was used as such for further reaction.

Synthesis of 1-methylthio-1-substitutedamino-2-nitroethene (18)

General Procedure: A solution of amine(10mmol) in CH_3CN(15ml) was added slowly to a suspension of 1,1-bismethylthio-2-nitroethene(**17**)(10mmol) and catalytic amount of PTSA in acetonitrile at rt. A clear solution was obtained and the evolution of methanethiol was observed by it's characteristic odor. The reaction mixture was stirred at ambient temperature for 3-24h. Solvent was removed under vacuum to get a gum. The unreacted

starting material(**17**) was precipitated by treating the gum with ice cold EtOH, and filtered off, the filtrate was concentrated to get a gum. This was washed twice with hexane or pet.ether to remove dimethyl disulfide. Final purification was done by column chromatography to get the product(**18**).

1-Methylthio-1-pyrrolidino-2-nitroethene (18b)

Light yellow solid, yield: 80%; m.p.: 70-71°C; **IR**(nujol): 3100, 1520, 1450, 1380cm^{-1}; **^{1}H NMR**($CDCl_3$): 2.0δ (m, 4H, 2C**H**$_2$), 2.6δ (s, 3H, -SC**H**$_3$), 3.5δ (m, 4H, 2NC**H**$_2$),6.6δ (s, 1H, =C**H**); **MS**(m/e): 188(M^+,17%), 173(M_+-CH_3), 158(M^+-NO), 147(M^+-SCH_3), 142(M^+-NO_2); **Found**, C,45.4, H,6.9, N,14.2%, **calculated** for $C_7H_{12}N_2O_2S$, C,44.7, H,6.4, N,14.8%.

1-Methylthio-1-piperidino-2-nitroethene (18c)

Light yellow solid, yield: 75%; m.p.: 66^{0C}; **IR**(neat): 3150, 1550, 1450, 1400, 1320cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.62δ (m, 6H, 3C**H**$_2$), 2.4δ (s, 3H, SC**H**$_3$), 3.5δ (m, 4H, 2NC**H**$_2$), 6.12δ (s, 1H, =C**H**); **MS**(m/e): 202(M^+,10%), 185(M^+-NO), 168(M^+-NO_2), 84(100%); **Found,** C,47.9, H,7.1, N,13.5%, **calculated** for $C_8H_{14}N_2O_2S$, C,47.5, H,6.9, N,13.9%.

1-Methylthio-1-benzylamino-2nitroethene (18d)

Light yellow solid, m.p.:112^{0}C; yield: 70%; **IR**(nujol): 3120, 1560, 1460, 1380, 1350, 1210cm^{-1}; **^{1}H NMR** ($CDCl_3$): 2.44δ (s, 3H, SC**H**$_3$), 4.62 δ (d, 2H, NC**H**$_2$), 6.58δ (s, 1H, =C**H**), 7.32δ (s, 5H, Ph), 10.69δ (b, 1H, N**H**); **MS**(m/e): 224(M^+), 190, 178, 130, 91; **Found,** C,54.1, H,5.9, N,12.2%, **calculated** for $C_{10}H_{12}N_2O_2S$, C,53.57, H,5.36, N,12.5%.

Ethyl N-(1-methyl thio-2-nitroethenyl) prolinate (23a)

Yellow gum, yield: 70%; $[\alpha]_D^{EtOH}$= -58.59°; **IR**(neat): 3110, 1740, 1680, 1565, 1520, 1450, 1380cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.25δ (t, 3H, C**H**$_3$), 1.8-2.3δ (m, 4H, 2C**H**$_2$), 2.4δ (s,

3H, SCH_3), 3.35-3.65δ (m, 2H, NCH_2), 4.2δ (q, 2H, OCH_2), 4.45-4.8δ (m, 1H, NCH), 6.65δ (s, 1H, =CH); **Found,** C,46.8, H,6.4, N,10.3%, **calculated** for $C_{10}H_{16}N_2O_4S$, C,46.2, H,6.2, N,10.8%.

Benzyl N-(1-methylthio-2-nitroethenyl) prolinate (23b)

Light yellow gum, yield: 75%; $[\alpha]_D^{EtOH}$= -20.66°; **IR**(neat): 1760, 1580, 1530, 1470, 1340cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.89-2.22δ (m, 4H, $2CH_2$), 2.33δ (m, 3H, SCH_3), 3.36-3.73δ (m, 2H, NCH_2), 4.62-4.89δ (m, 1H, NCH), 5.16δ (s,2H,- OCH_2), 6.76δ (s, 1H, =CH), 7.44δ (s, 5H, Ph); **MS**(m/e): 322(M^+), 292(M^+-NO), 276(M^+-NO_2), 91(100%); **Found,** C,56.2, H,5.8, N,8.5%, **calculated** for $C_{15}H_{18}N_2O_4S$, C,55.9, H,5.6, N,8.7%.

Ethyl N-(1-methylthio-2-nitroethenyl) valinate (26a)

A solution of valine ethyl ester (10.1mmol) in benzene(20ml) was added in 3h. to the solution of 1,1-bismethylthio-2-nitroethene(**17**)(10mmol) and catalytic amount of PTSA in benzene (15ml) at 60°C. The contents were stirred overnight at the same temperature. Benzene was removed under vacuum to get gum. The unreacted starting material(**17**) was precipitated by treating the gum with ice cold EtOH, and was filtered off, the filtrate was concentrated to afford a gum which was washed few times with hexane to remove dimethyl disufide. It was further purified by the column chromatography, benzene was used as eluent.

Gum, yield: 55%; $[\alpha]_D^{EtOH}$= +102.2°; **IR**(neat): 3500, 1750, 1570, 1350, 1150cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.03δ (d, 6H, $2CH_3$), 1.29δ (t, 3H, CH_3), 2.13-2.53δ (m, 1H, Me_2CH), 2.42δ (s, 3H, SCH_3), 4.16-4.29δ (dd, 1H, NCH), 4.22δ (q, 2H, OCH_2), 6.56δ (s, 1H, =CH), 10.67δ (d, 1H, NH); **MS**(m/e): 262 (M^+,44%), 232 (M^+-NO), 215 (M^+-SCH_3), 189 (M^+-CO_2Et,100%); **Found,** C,46.1, H,7.2, N,10.2%, **calculated** for $C_8H_{18}N_2O_4S$, C,45.8, H,6.9, N,10.7%.

Benzyl N-(1-methylthio-2-nitroethenyl) valinate (26b)

Gum, yield: 52%; $[\alpha]_D^{EtOH}$= +31.98°; **IR**(neat): 3400, 1740, 1570, 1360cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.0δ (d, 6H, 2C**H**$_3$), 2.13-2.5δ (m, 1H, Me_2C**H**), 2.38δ (s, 3H, SC**H**$_3$), 4.24δ (dd, 1H, NC**H**), 6.51δ (s, 1H, =C**H**), 7.3δ (s, 5H, Ph), 10.62δ (d, 1H, N**H**); **MS**(m/e): 324(M^+), 294(M^+-NO), 278(M^+-NO_2), 277(M^+-SCH_3), 91(100%); **Found,** C,55.8, H,6.5, N,8.2%, **calculated** for $C_{15}H_{20}N_2O_4S$, C,55.6, H,6.2, N,8.6%.

Synthesis of Nitrothioacetamides

General Procedure

1-methylthio-1-substituted-2-nitroethene was dissolved in dry EtOH (deoxygenated by flushing with nitrogen gas) containing acetic acid (2eq.) and kept under N_2 atmosphere. Fused Na_2S(1.5eq.) was added in many portions through a solid addition funnel. This solid addition funnel is designed in such a way that a closed system will be maintained throughout the course of the reaction. The solvent was removed and contents were taken into benzene, undissolved salts were filtered off. The filtrate was concentrated to get thick gum which was column chromatographed to get pure Nitrothioacetamides.

N-Nitrothioacetylpyrrolidine (3b)

Light yellow solid, yield: 68%; m.p.: 78°C(lit.81°C); **IR**(nujol): 2700,1560, 1500, 1460, 1360, 1269cm^{-1}; **^{1}H NMR**($CDCl_3$): 2.08δ (m, 4H, 2C**H**$_2$), 3.75δ (m, 4H, 2NC**H**$_2$), 5.48δ (s, 2H, O_2NC**H**$_2$); **^{13}C NMR**($CDCl_3$): 23.68 and 25.9 ($2CH_2$), 51.13 and 54.1 ($2NCH_2$), 83.27 (CNO_2), 182.3 (CS); **MS**(m/e): 174 (M^+), 144(M^+-NO), 128(M^+-NO_2), 70(100%); **Found,** C,41.9, H,5.9, N,15.9, S,18.8%, **calculated** for $C_6H_{10}N_2O_2S$, C,41.4, H,5.8, N,16.1, S,18.4%.

N-Nitrothioacetylpiperidine (3c)

Gum, yield: 55%;**IR**(neat): 1560, 1500, 1440, 1370cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.75δ (m, 6H, 3C**H**$_2$), 3.67δ (m, 2H, NC**H**$_2$), 4.24δ (m, 2H, NC**H**$_2$), 5.64δ (s, 2H, O_2NC**H**$_2$); **MS**(m/e): 188 (M^+), 158 (M^+-NO), 155 (M^+-H_2S), 142 (M^+-NO_2), 43 (100%); **Found,** C,44.9, H,6.5, N,14.2%, **calculated** for $C_7H_{12}N_2O_2S$, C,44.7, H,6.4, N,14.9%.

N-Nitrothioacetylbenzyl amine (3d)

Gum,yield: 60%; **IR**(neat): 3200, 1560, 1460, 1350cm^{-1}; **^{1}H NMR**($CDCl_3$): 4.82δ (d, 2H, NCH_2), 5.43 (s, 2H, O_2N-CH_2), 7.37(s, 5H, Ph), 8.5(b, 1H, NH); **MS**(m/e): 210 (M^+), 180 (M^+-NO), 176 (M^+-H_2S), 146 (M^+-NO_2); **Found,** C,51.9, H,4.76, N,13.12%, **calculated** for $C_9H_{10}N_2O_2S$, C,51.43, H,4.76, N,13.33%.

N-Nitrothioacetylproline ethyl ester (24a)

Gum, yield: 65%; $[\alpha]_D^{EtOH}$= -120.2°; **IR**(neat): 1740, 1570, 1480, 1450, 1370cm^{-1}; **^{1}H NMR**($CDCl_3$,δ): ***Trans conformer***, 1.25(t, 3H, CH_3), 1.8-2.6 (m, 4H, $2CH_2$), 3.65-3.9(m, 2H, NCH_2), 4.18(q, 2H, OCH_2), 4.7-5.1(m, 1H, NCH), 5.53 (dd, 2H, O_2NCH_2), ***Cis conformer***, 1.29(t, 3H, CH_3), 1.8-2.6(m, 4H, $2CH_2$), 3.65-3.9(m, 2H, NCH_2), 4.21(q, 2H, OCH_2), 4.7-5.1(m, 1H, NCH), 5.38(dd, 2H, O_2NCH_2); **^{13}C NMR**($CDCl_3$): ***Trans conformer***, 13.67(CH_3), 24.64(γ-C), 28.92 (β-C), 51.57(δ-C),61.19(α-C), 65.78(O-C), 83.19(O_2N-C), 169.12(C=0), 184.64(C=S), ***Cis conformer***, 20.59(CH_3), 22.14(γ-C), 30.92(β-C), 54.45(δ-C), 62.31(α-C), 63.30(O-C), 83.19(O_2N-C),169.04(C=O), 184.85(C=S); **IR**(m/e): 246(M^+), 216(M^+-NO), 200(M^+-NO_2), 173(M^+-CO_2Et), 70(100%); **Found,** C,44.3, H,5.9, N,11.1, S,13.3%, **calculated** for $C_9H_{14}N_2O_4S$, C,43.9, H,5.7, N,11.4, S,13.01%.

N-Nitrothioacetylproline benzyl ester (24b)

Solid, yield: 65.7%; m.p.: 63°C; $[\alpha]_D^{EtOH}$= -77.2^0; **IR**(nujol): 1740,1560,1470,1450,1380cm^{-1}; **^{1}H NMR**($CDCl_3$,δ): ***Trans conformer***, 2.15-2.45 (m, 4H, $2CH_2$), 3.75-3.85(m, 2H, NCH_2), 5.05(dd, 1H, NCH), 5.2(d, 2H, OCH_2), 5.55(s, 2H, O_2NCH_2), 7.41(s, 5H, Ph), ***Cis conformer***, 2.15-2.45(m, 4H, $1CH_2$), 3.75-3.85(m, 2H, NCH_2), 4.85(dd, 1H, NCH), 5.4(dd, 2H, O_2NCH_2), 7.39(s, 5H, Ph); **MS**(m/e): 308(M^+), 278(M^+-NO,100%), 262(M^+-NO_2), 91($PhCH_2^+$); **Found,** C,54.9, H,5.4, N,8.7%, **calculated** for $C_{14}H_{16}N_2O_4S$, C,54.6, H,5.2, N,9.1%.

N-Nitrothioacetylvaline ethyl ester (27a)

Gum, yield: 70%; $[\alpha]_D^{EtOH}$= -19.06^0; **IR**(neat): 3300, 1740, 1570, 1380cm^{-1}; **^{1}H NMR**($CDCl_3$,δ): 0.9(d, 3H, CH_3), 1.07(d, 3H, CH_3), 1.32(t, 3H, CH_3), 2.09-2.64(m, 1H, Me_2CH), 4.21(q, 2H, OCH_2), 5.04(dd, 1H, NCH), 5.47(s, 2H, O_2NCH_2), 8.91(b, 1H, NH); **MS**(m/e): 248(M^+), 218(M^+-NO), 214(M^+-H_2S), 202(M^+-NO_2),159(100%); **Found**, C,44.1, H,6.6, N,11.2, **calculated** for $C_9H_{16}N_2O_4S$, C,43.6, H,6.5, N,11.3%.

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CHAPTER 2

Reactions of Nitrothioacetamides

2.1. Introduction

It will be interesting to study the reactivity of a new class of compounds *i.e.*, nitrothioacetamides for many reasons. The nitrothioacetamides have an active methylene group flanked by a nitro group and a thiocarbonyl group. Obviously the chemical transformations involving active methylene groups can be tried on nitrothioacetamides. The nitro group itself is a potential precursor for a few functional groups, hence several manipulations are possible. In addition to the typical features of carbonyl chemistry, the presence of the sulfur atom in thio carbonyl group leads to some reactions which are characteristic of such compounds. In sharp contrast to the carbonyl compounds, the nucleophilic attack may occur on the sulfur atom of C=S bond, but also the conventional primary attack on the carbon gives rise to some unusual reactions[1]. Electrophilic attack is regiospecific on the thiocarbonyl sulfur[2]. In general thiocarbonyl compounds are more reactive than their carbonyl congeners; this is well supported by MO calculations which indicate a higher HOMO and lower LUMO for the thiocarbonyl compounds than the corresponding carbonyl compounds[3].

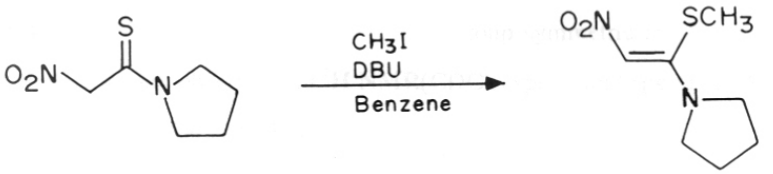
2.2. Alkylation Reactions

Alkylation reactions on thionamides are well documented in the literature; different alkylating agents have been used for the purpose, like alkyl halides[4], alkyl sulfates[4], diazomethane[5], aryldiazonium salts[6]. Irrespective of the reagents and conditions used, the alkylation occurs only on the *sulfur* atom of the thioamides. A number of examples of N-alkylation of primary and secondary thioamides are known but there is enough evidence that this proceeds via a kinetically controlled S-alkylation followed by rearrangement[7].

To find out whether the presence of the nitro group has any influence on the course of alkylation reactions, N-nitrothioacetylpyrrolidine (**1**) was alkylated with methyl iodide. N-Nitrothioacetylpyrrolidine was taken in benzene and 1.1eq. of CH_3I, 1.1eq. DBU were added to the solution, and stirred at 30°c for 1hr. After completion of the reaction the

solvent was evaporated to get a solid. The product formed was chromatographed using a silica gel column to get the pure product; m.p. 70-71°c. In the infrared spectrum, peaks at 3100, 1520, 1450 and 1380cm^{-1} were observed; the mass spectrum showed the molecular ion peak at 188. The **^{1}H NMR** spectrum of this product showed sharp singlets at 2.6δ and 6.6δ which correspond to SCH_3 group and olefinic proton respectively. The other signals were also matched exactly with proton signals of 1-methylthio-1-pyrrolidino-2-nitroethene (**2**). From other spectral data it was confirmed that the product formed was 1-methylthio-1-pyrrolidino-2-nitroethene (**Scheme 1**).

SCHEME-1



1 **2**

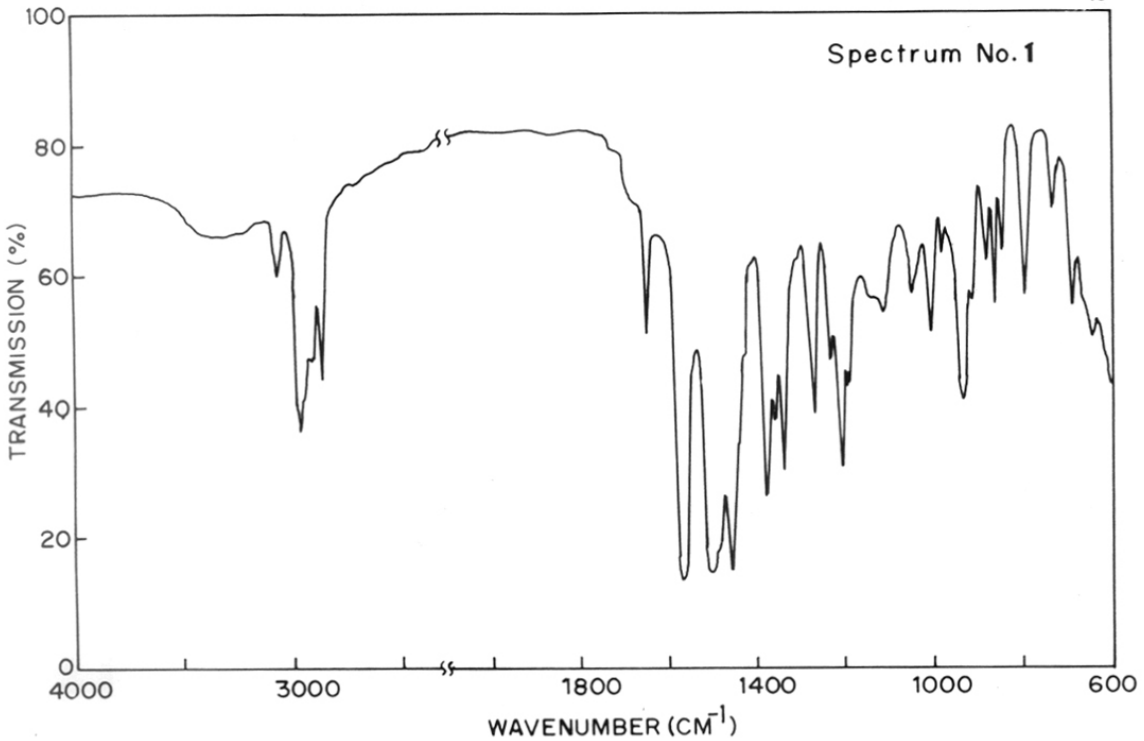
So it was proved that the site of attack by alkylating reagents will be the sulfur atom in nitrothioacetamides also and the nitro group did not affect the course of alkylation reaction of nitrothioacetamides. Hence, the '*soft*' character of sulfur is not affected by nitro group in nitrothioacetamides, which can be observed even in allylation reactions on nitrothioacetamides.

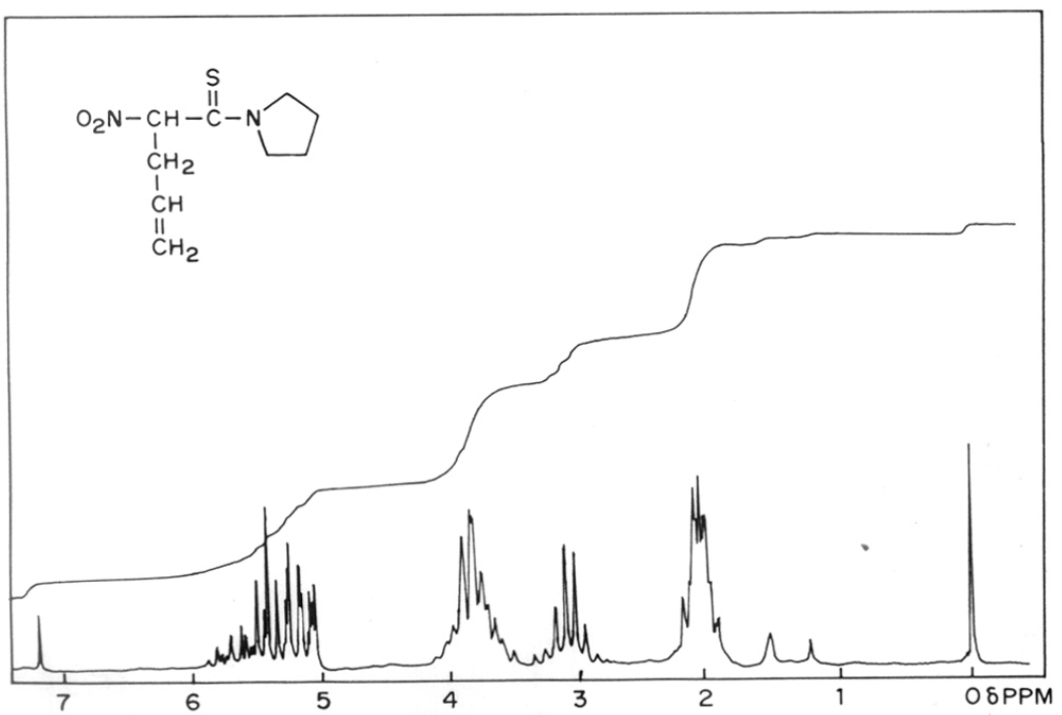
2.3. Allylation Reactions

Inspired by the allylation reactions on nitroacetamides, which were carried out by our group earlier, it was planned to study the mechanism of allylation reaction on nitro-thioacetamides. Such allylation reactions on simple thioamdes have been reported in the literature and C, N, S-allylated products have been obtained.

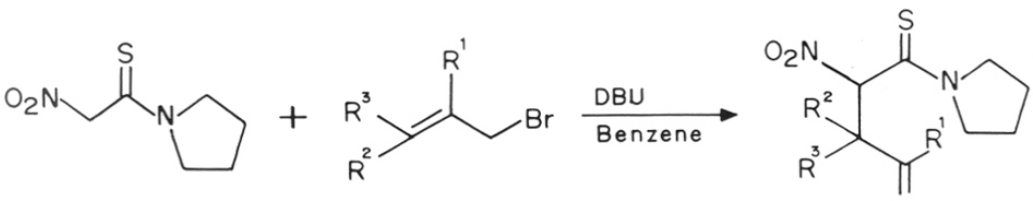
2.3.1 Reaction with allyl bromide

N-Nitrothioacetylpyrrolidine (174mg) was allowed to react with allyl bromide (134mg, 1.1eq.) in acetone (10ml) in presence of DBU (1.1eq.) at 56°c for 4hrs.; the solvent was evaporated to get a thick gum which was chromatographed on a silica gel column using benzene as an eluent to get the pure allylated N-nitrothioacetyl pyrrolidine (**3a**) in 55% yield; IR(neat): 2860-2960w,1650w corresponding to C=C stretching frequency, 1560 and 1370cm^{-1} corresponding to NO_2 group symmetric and asymmetric stretching frequencies were observed. In **^{1}H NMR**($CDCl_3$) spectrum (**Spectrum No. 1**), the multiplets at 2.06 and 3.8δ were assigned to pyrrolidine ring protons, multiplet at 3.07 to allylic methylene protons, triplet at 5.42δ to α-methine proton and multiplet at 5.44δ was assigned for three olefinic protons of the allyl moiety. The N-[2-nitro-2-(prop-2-en-1-yl)thioacetyl]-pyrrolidine (**3a**) formation was further confirmed by it's **^{13}C NMR** spectrum. The signals at 23.67, 25.89, 51.26 and 54.32 were assigned to the carbon nuclei of pyrrolidine ring, 37.01 to allylic carbon, 88.94 to α-methylene carbon, 119.8 and 130.48 to the olefinic carbons of allyl group and signal at 187.73 was assigned to the thiocarbonyl carbon. Mass spectrum showed molecular ion peak at 214 (1.3%), and other peaks at 184, 168; the compound **analysed** for $C_9H_{14}N_2O_2S$.


Spectrum No. 1
TRANSMISSION (%)
100
80
60
40
20
0
4000
3000
1800
1400
1000
600
WAVENUMBER (CM⁻¹)


O2N–CH–C–N
S
CH2
CH
CH2
7
6
5
4
3
2
1
0 δPPM

SCHEME-2



1 **3**

a) $R^1 = R^2 = R^3 = H$ d) $R^1 = R^2 = H$, $R^3 = Ph$

b) $R^1 = R^2 = H$, $R^3 = Me$ e) $R^1 = Me$, $R^2 = R^3 = H$

c) $R^1 = H$, $R^2 = R^3 = Me$

Though in this allylation reaction the C-allylated product was obtained, it leaves behind an interesting problem, whether the reaction was a direct C-allylation or initial S-allylation followed by a thioClaisen rearrangement. Hence allylation reactions were carried out with substituted allyl bromides to find out the actual reaction path.

2.3.2 Reaction with cinnamyl and prenyl bromides

It was anticipated that from the position of attachment of suitably substituted ally derivatives, such as α-prenyl or α-cinnamyl N-nitrothioacetylpyrrolidine (**3c**,**3d**), one could predict the mechanism of this allylation reaction on nitrothioacetamide. But, surprisingly neither C-allylated nor S-allylated products were obtained with cinnamyl bromide and prenyl bromide; instead, N-nitroacetylpyrrolidine and some intractable tars were obtained. This led us to the conclusion that the sulfur anion of N-nitrothioacetylpyrrolidine was allylated first and before the cinnamyl or prenyl group rearranges to the α-carbon of nitrothioacetamide, the S-allyl group was hydrolysed to afford nitroacetamide. As the

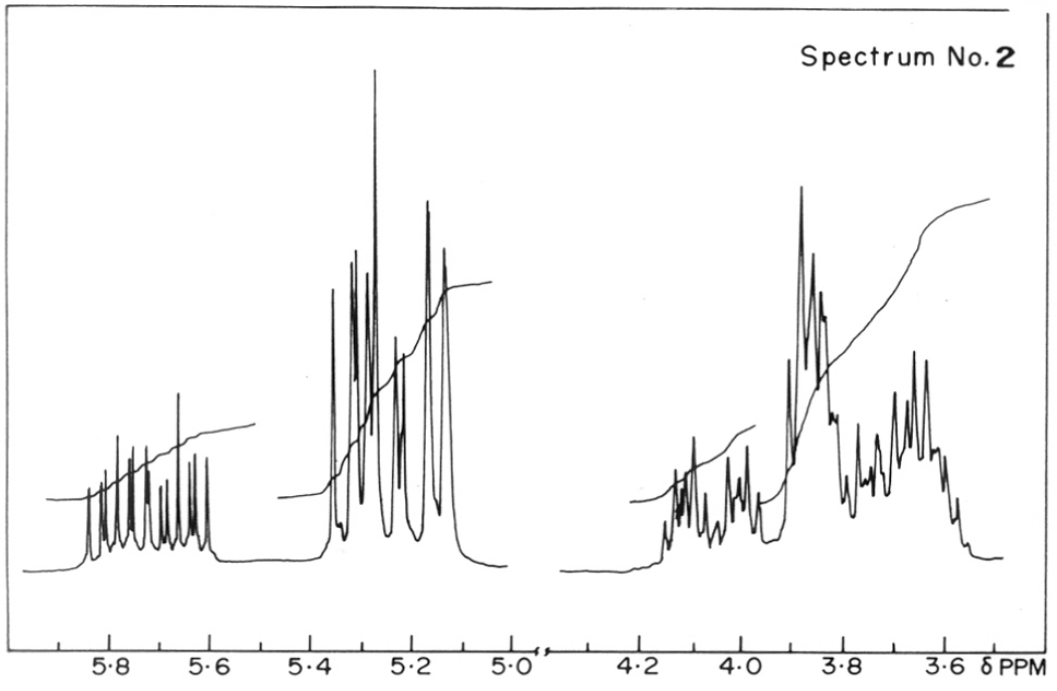
bulky phenyl group or two methyl groups were involved in this expected rearrangement, the steric crowding may be hindering the migration of cinnamyl or prenyl group to the α-carbon (**Scheme 2**).

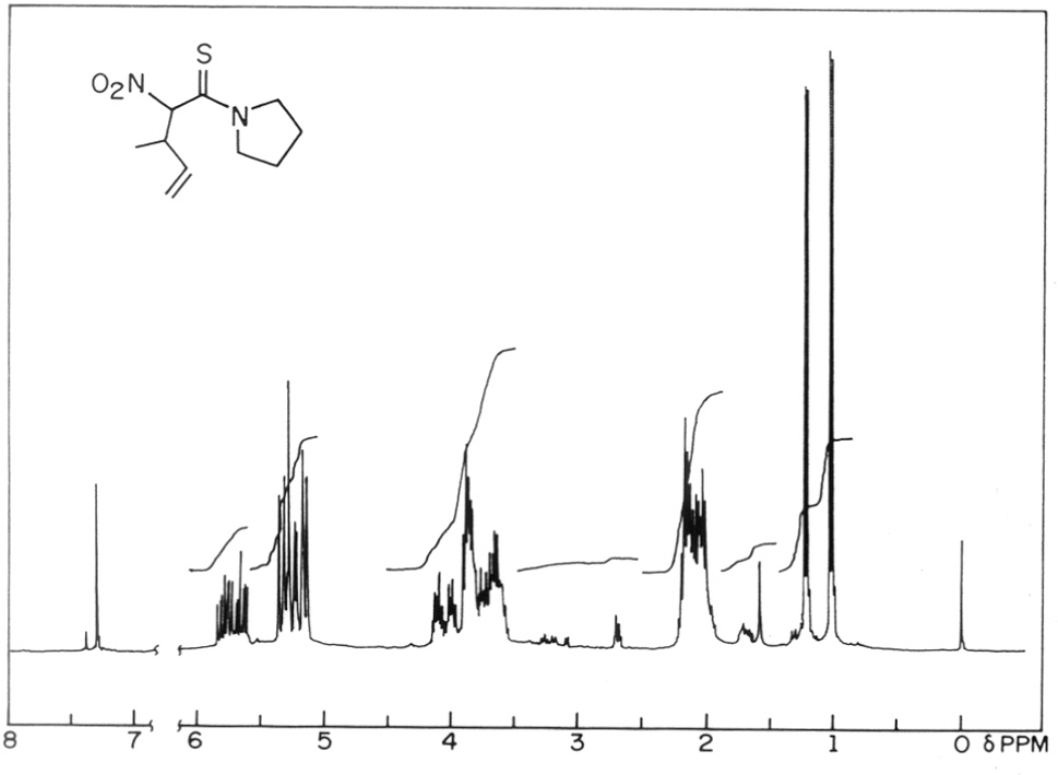
Though the reactions mentioned above suggest that the sulfur of nitrothioacetamide is attacked by 3-substituted allyl bromides, it does not constitute positive evidence for a thio-Claisen rearrangement. As the role of steric crowding was suspected in preventing this [3,3] sigmatropic rearrangement, an allyl bromide bearing only one substituentat the 3-position, a methyl group, *i.e.* crotyl bromide was tried in the reaction.

2.3.3 Reaction with crotyl bromide

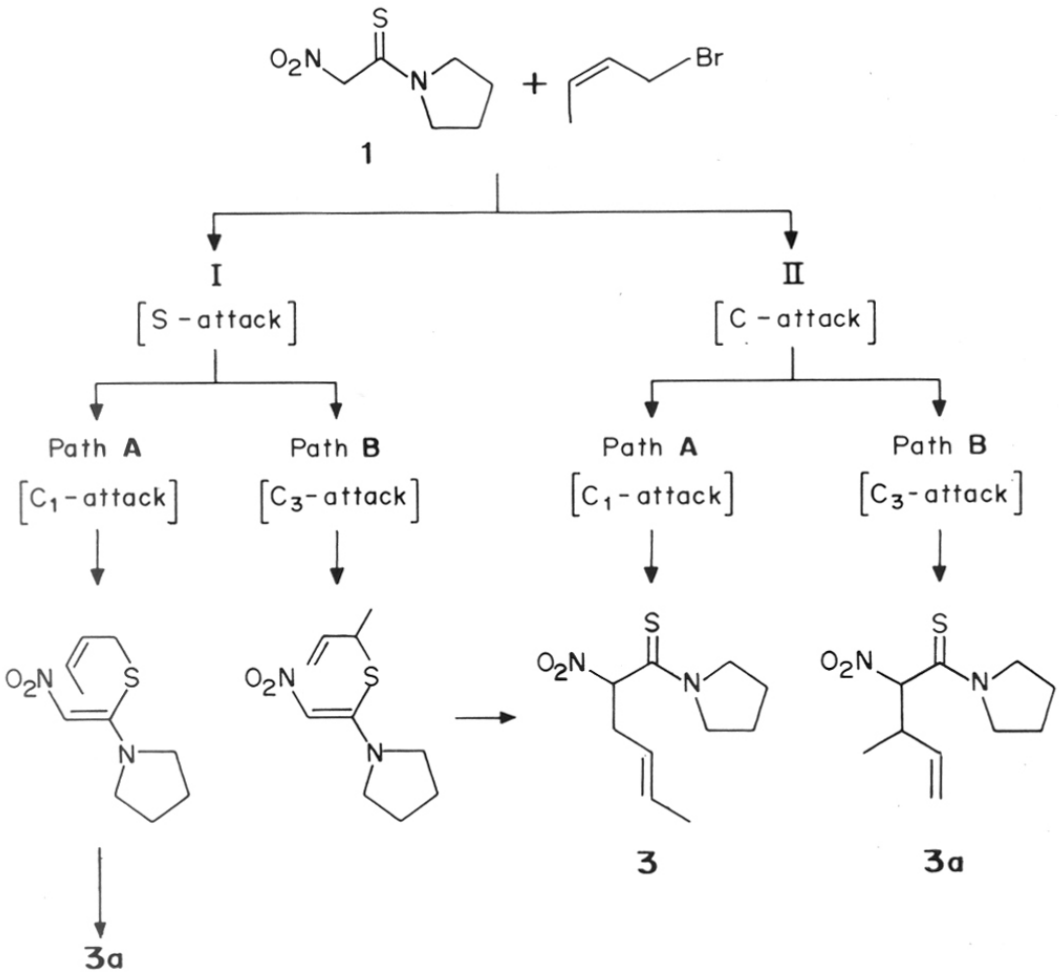
Crotyl bromide was allowed to react with N-nitrothioacetylpyrrolidine under the conditions described in the experimental section. After the preliminary workup and chromatographic purification on silica gel column (benzene), the pure N-[2-nitro-(1-methylprop-2-en-1-yl)] thioacetylpyrrolidine was obtained in 40% yield; gum; IR(neat): 2900-3000w, 1650w, 1570 and 1380cm^{-1}; In **^{1}H NMR** spectrum (**Spectrum No. 2**), two signals (doublets) for CH_3 group on allyl moiety were seen at 1.03 and 1.21δ. From the chemical shift values (1.03 and 1.21δ) of the methyl group it was clear that the methyl group was attached to an sp^3 carbon; moreover, the coupling constant (6.7Hz) was the same for both the doublets. Hence it was concluded that these doublets arose from the two diastereomers of the same structure. There are four possible products in this reaction, arising from attack at S or C, with or without allylic migration. The chemical shift of the methyl group helps in identifying the product as **3b**.

The multiplets at 2.1, 3.65 and 3.85δ were assigned to the protons of pyrrolidine moiety, 4.0δ for the β-methine proton, the corresponding signal of the diastereomer appeared at 4.1δ. The signal at 5.25 was assigned to the $CHNO_2$ proton and the $=CH_2$ protons of crotyl group. The multiplet at 5.7δ was assigned to the remaining olefinic proton of crotyl group. The isolation of **3b** strongly suggests that the reaction has taken place through an initial S-allylation followed by S → C migration. However, this would mean

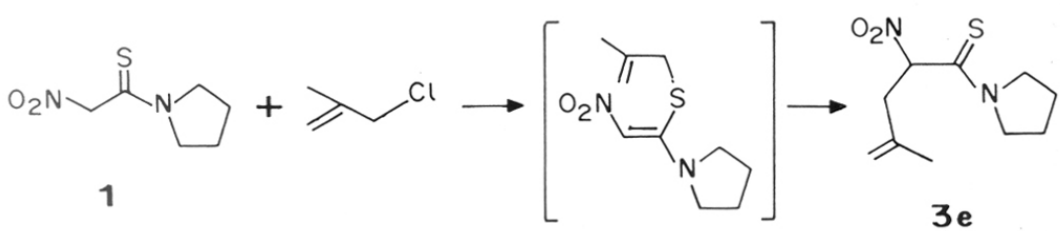

Spectrum No. 2
5·8
5·6
5·4
5·2
5·0
4·2
4·0
3·8
3·6
δ PPM


S
O2N
N
8
7
6
5
4
3
2
1
0
δ PPM

SCHEME-3a



SCHEME-3b

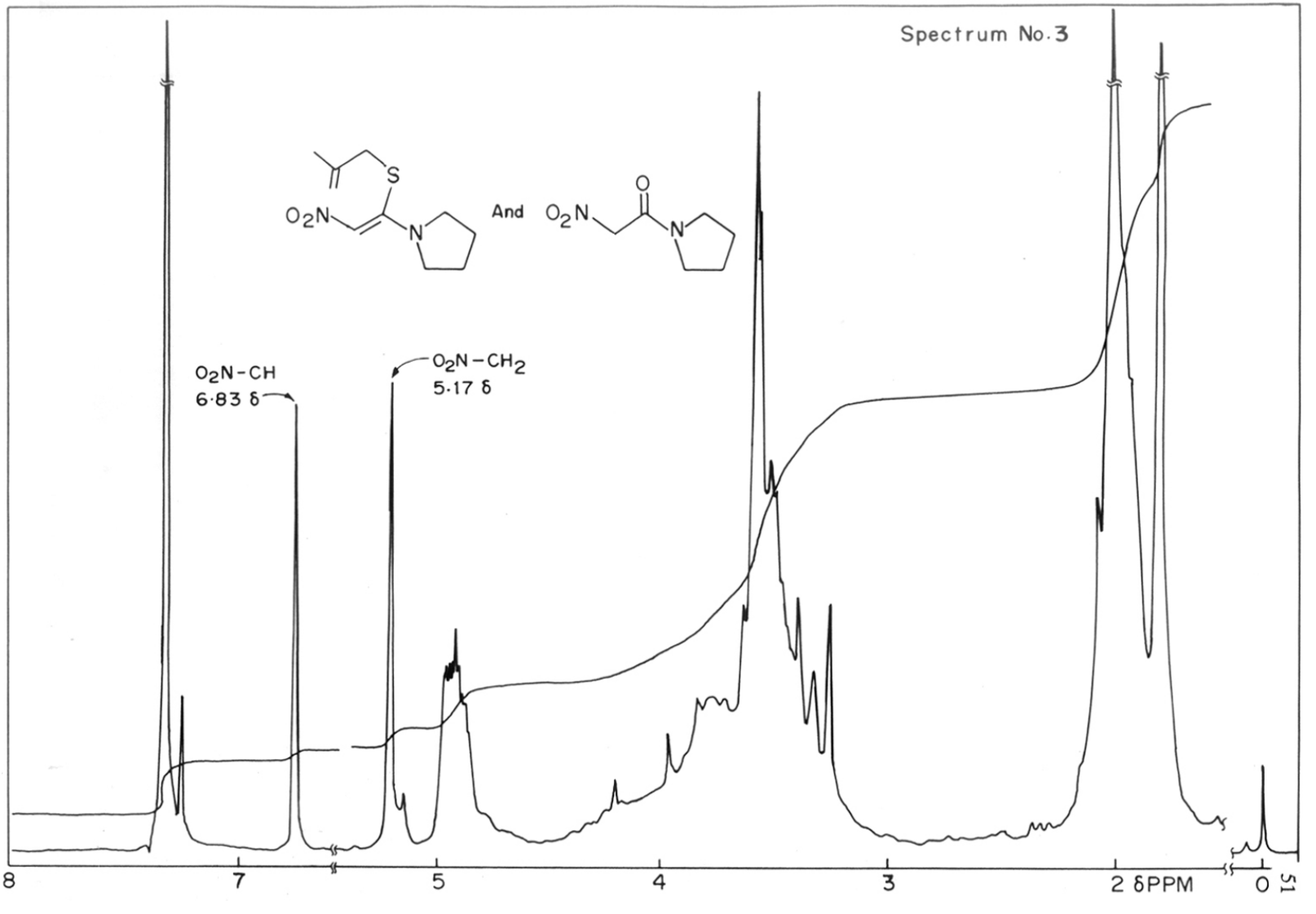


that the initial attack took place without allylic migration - contrary to the voluminous literature on the preference for C-1 attack on allyl bromides. This problem could be resolved only by isolation of the intermediate S-allylated product (**Scheme 3a**).

2.4. Isolation of the intermediate

Many attempts to isolate the intermediate formed in the reaction of allyl bromides with N-nitrothioacetylpyrrolidine reaction failed; but fortunately the ^{1}H NMR spectrum (**Spectrum No. 3**)

of one S-allylated intermediate from the reaction of methallyl chloride with N-nitrothioacetylpyrrolidine could be scanned after a quick preliminary workup. A singlet was observed at 1.85δ for methyl group protons and another singlet at 3.51δ for SCH_2 group protons, a multiplet at 5δ for the olefinic protons of methallyl moiety and a sharp singlet at 6.83δ for olefinic proton of nitroenamine group. This provides a concrete proof for the formation of an S-allyl intermediate (**Scheme 3b**). The multiplets at 2.03, 3.75δ were also observed for protons of pyrrolidine moiety. From this intermediate, on thermolysis (50°c), the rearranged product, N-[2-nitro-2- (2-methylprop-2 -en-1-yl)thioacetyl]-pyrrolidine (**3e**) was obtained in 51% yield; gum; IR(neat): 3100w, 1660w, 1570 and 1380cm^{-1}; **^{1}H NMR**($CDCl_3$): singlet at 1.89δ assigned to the methyl group protons, multiplets at 2.16 and 3.87δ for protons of pyrrolidine ring, a doublet of doublet of a doublet at 3.04δ to the allylic methylene protons, a doublet at 4.84 to the olefinic protons and a multiplet at 5.67δ was assigned to the α-methyne proton. The structure of the compound was further confirmed by it's **^{13}C NMR** spectrum and from the molecular ion peak at 228 (1.3%) in mass spectrum. This ruled out the reaction path IIB of **scheme 3a**, and unequivocally proved that C-allylation of nitrothioacetamides arises from a thio-Claisen rearrangement.

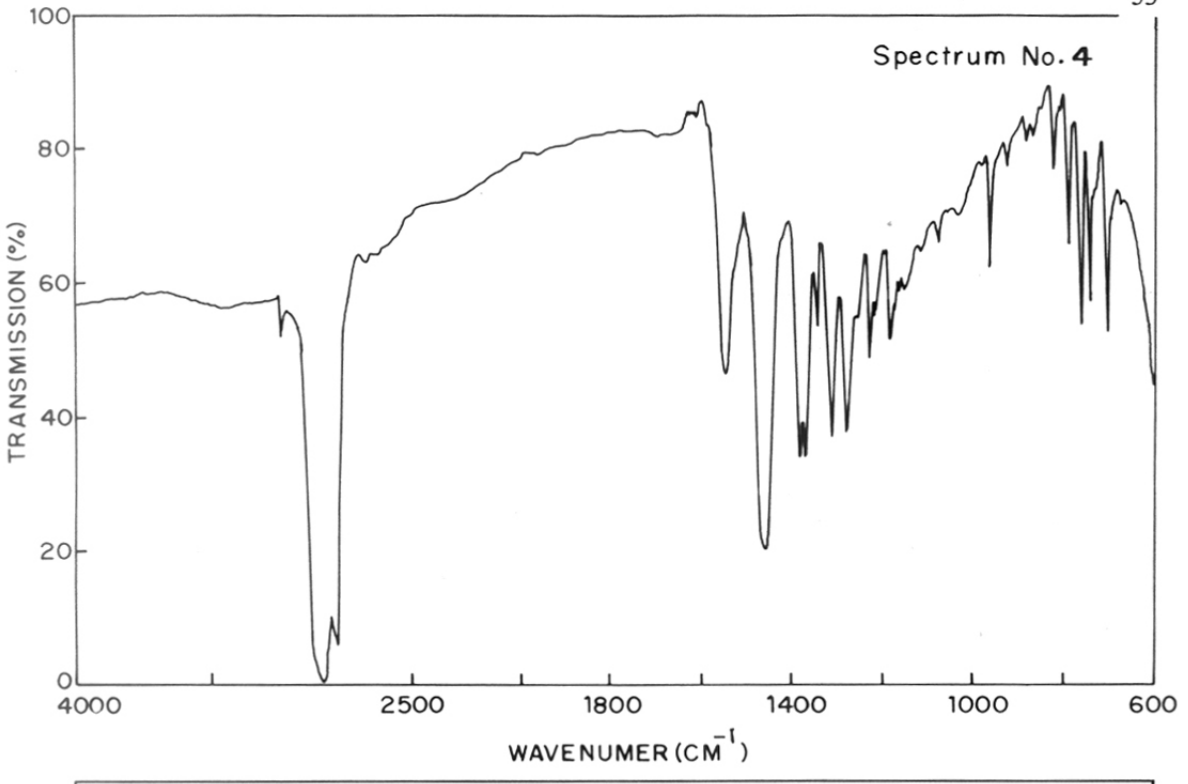

Spectrum No. 3
And
O_2N-CH
6·83 δ
O_2N-CH_2
5·17 δ
8
7
5
4
3
2 δPPM
0
51

2.5. Synthesis of thiophenes

Intra and inter molecular cyclisations are considered to be the most versatile and important reactions of thioamides. As a part of our study on the chemical reactions of nitrothioacetamides, the nitrothioacetamides were allowed to react with α-halocarbonyl compounds like phenacyl bromide, p-nitro phenacyl bromide and bromo acetone.

According to the literature reports H. Hartmann *etal.* have synthesized 2-amino-thiophenes from phenacyl bromides and tertiary thionamides[8]. The position of aryl group in the thiophene derivative will depend on the position where the initial alkylation takes place. If the sulfur atom of thioamide is the site of attack, then the aryl group will be at position 3 whereas it will be at position 4 if the initial site of attack is carbon (**Scheme 4**).

The mechanism of this reaction was confirmed by the characterization of the salt **7**, and from the similar results observed by Schafer[9] etal. Thinking on similar grounds it was proposed to synthesize thiophene derivatives incorporating a nitroenamine push - pull system. N-Nitrothioacetylpyrrolidine was allowed to react with phenacyl bromide in presence of a base, DBU (1.1eq), in benzene. This afforded a deep yellow coloured thiophene derivative, 2-N- pyrrolidinyl-3-nitro-4-phenylthiophene in quantitative yield, m.p. 114°c, which showed strong absorption at 1540 and 1360cm_{-1} in IR spectrum. In ^{1}**H NMR** spectrum (**Spectrum No. 4**),


Spectrum No. 4
TRANSMISSION (%)
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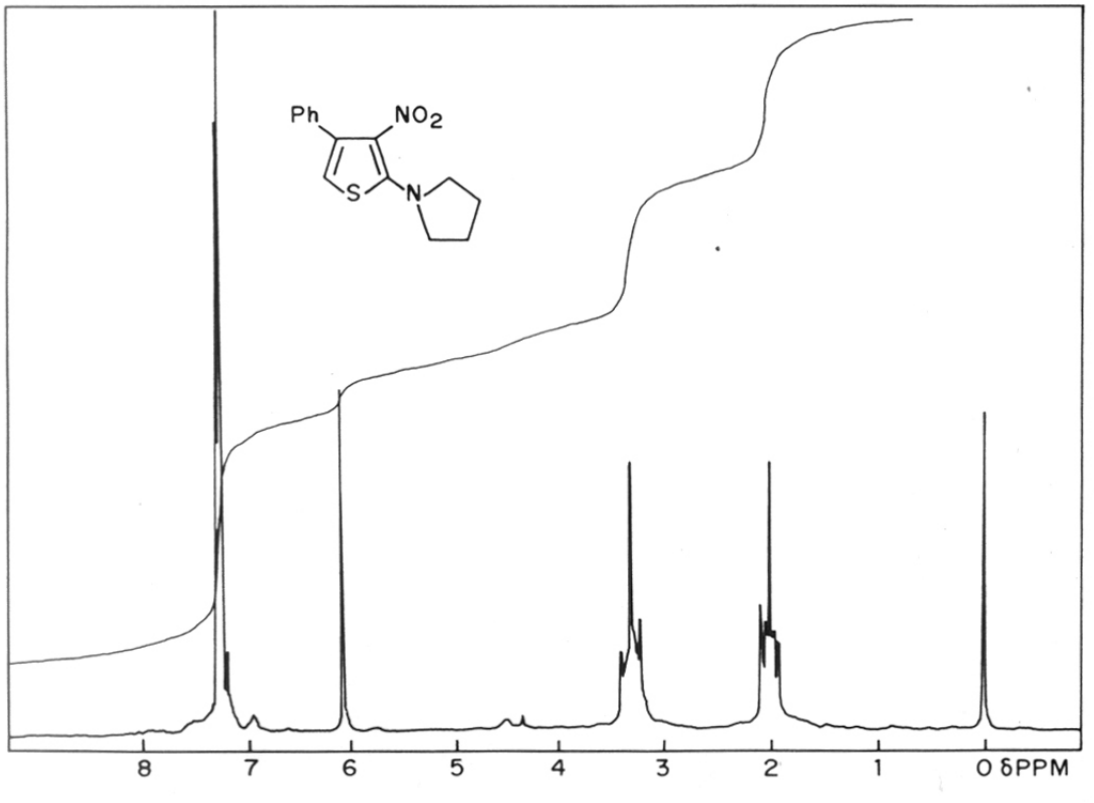
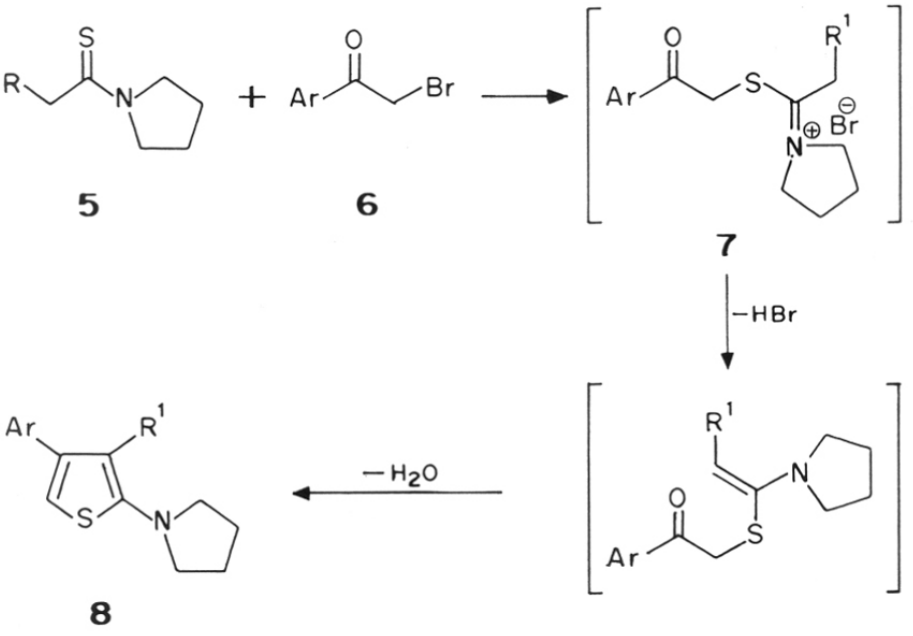
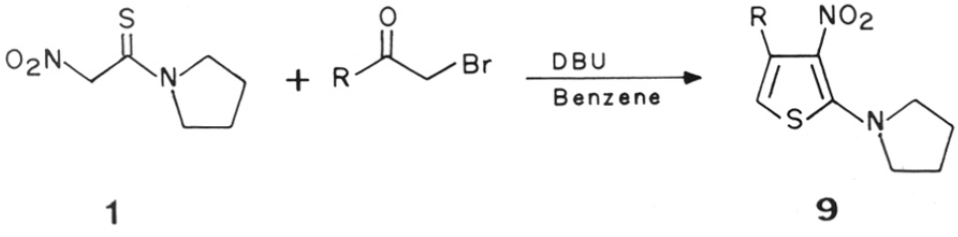
80
60
40
20
0
4000
2500
1800
1400
1000
600
WAVENUMER (CM⁻¹)


Ph
NO2
S
N
8
7
6
5
4
3
2
1
0 δPPM

SCHEME-4



SCHEME 5

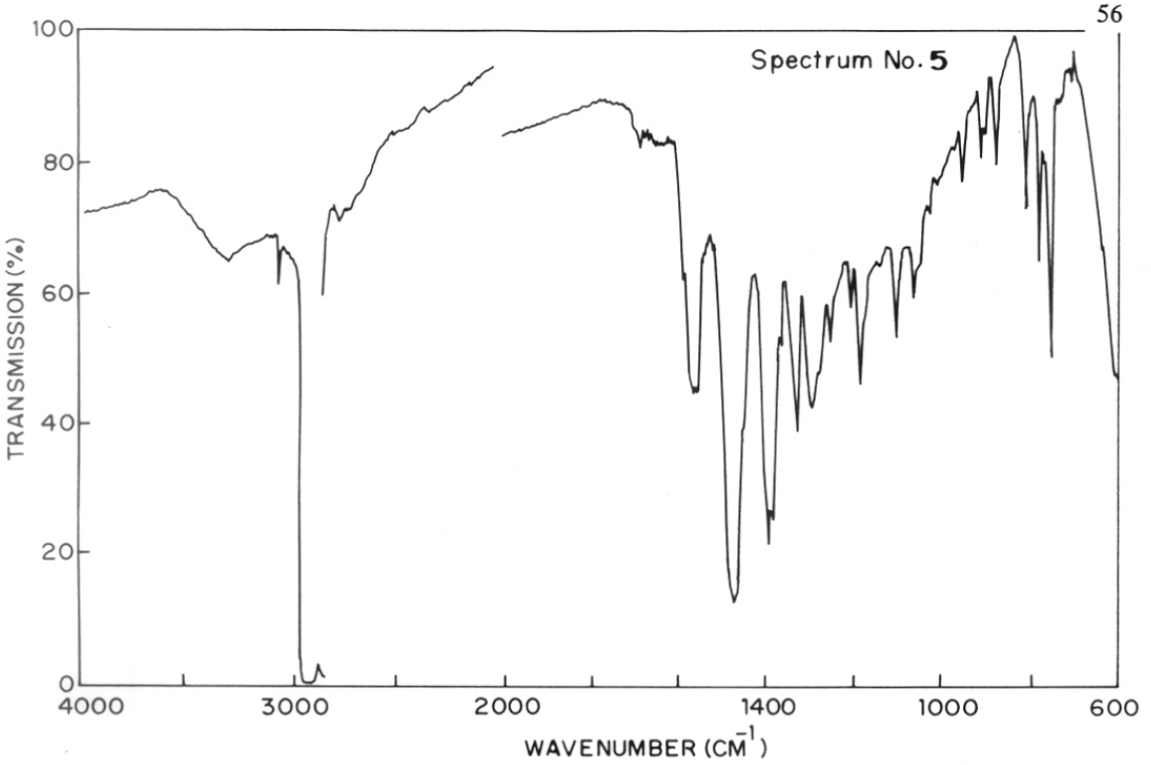


a) R = Ph b) R = C_6H_4–NO_2 c) R = Me

the multiplets at 2.05 and 3.35δ were assigned to the eight protons of the pyrrolidine moiety, a sharp singlet at 6.1δ for the olefinic proton of thiophene ring and singlet at 7.2δ corresponding to five protons was assigned to the protons of phenyl ring (**Scheme 5**).

In the ^{13}**C NMR** spectrum signals at 25.38 and 52.65 were assigned to the four carbon nuclei of the pyrrolidine moiety and signals at 105.10 for C(5), 127.09, 127.21, 127.46, 127.78 for 6 carbons of phenyl ring, 135.39 for C(2), 137.44 for C(4) and 156.19 for C(3). The structure of the product was further confirmed by observing molecular ion peak at 274 in the mass spectrum and the results of elemental analysis. The structure **9** in which carbon 2 of the thiophene is attached to a sulfur and a nitrogen atom, and C-3 carries the strongly electron-withdrawing nitro group, is an example of a push-pull system.

Similarly 2-N-pyrrolidinyl-3-nitro-4(4′-nitrophenyl) thiophene (**9b**) and 2-N-pyrrolidinyl-3-nitro-4-methyl thiophene (**9c**) were prepared from N-nitrothioacetylpyrrolidine and the corresponding α-bromo ketones *viz.* 4′-nitrophenacyl bromide and bromoacetone respectively. The spectral data (**Spectra No. 5 and 6**) of these compounds have been included in the experimental section of this chapter.


Spectrum No. 5
TRANSMISSION (%)
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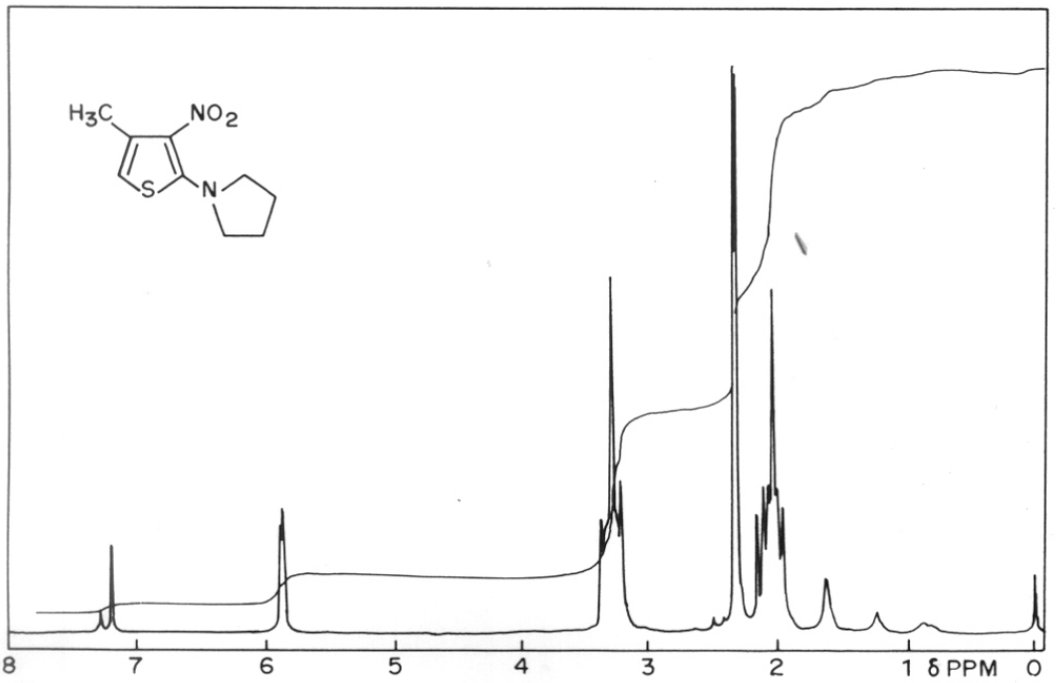
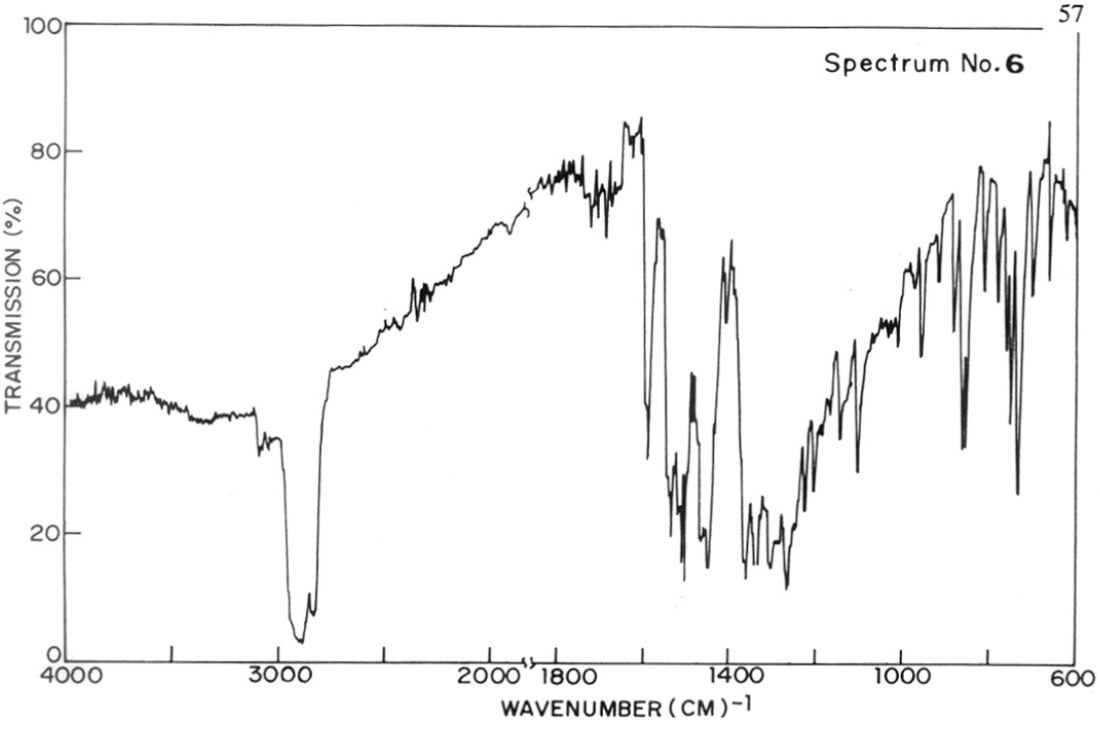
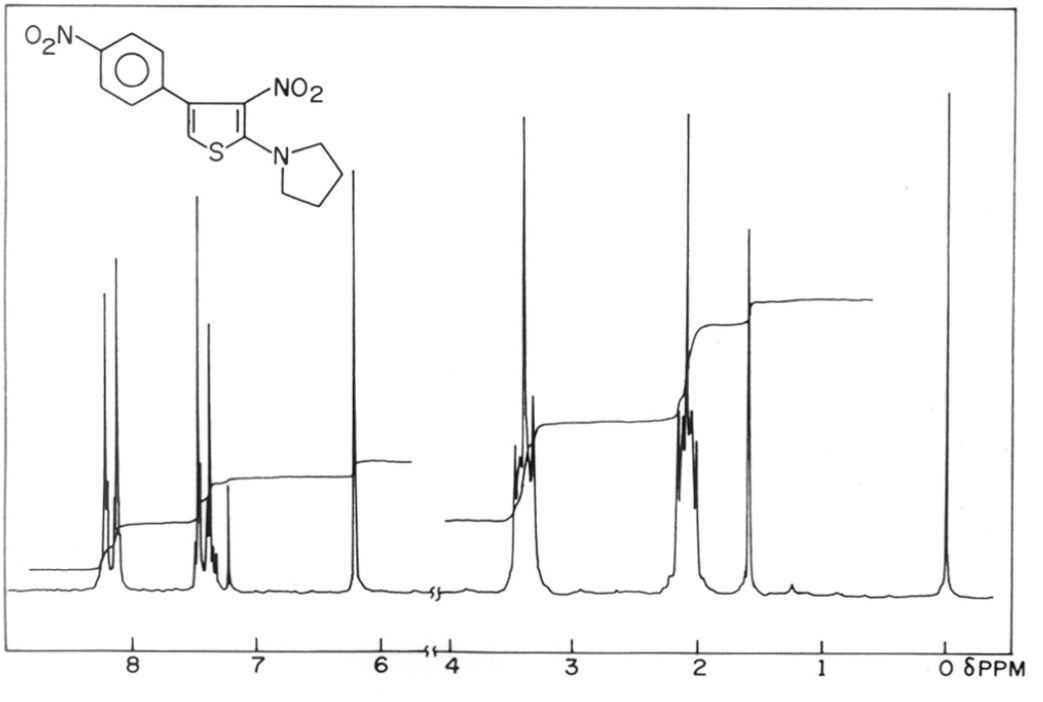
80
60
40
20
0
4000
3000
2000
1400
1000
600
WAVENUMBER (CM⁻¹)


H3C
NO2
S
N
8
7
6
5
4
3
2
1
δ PPM
0


Spectrum No. 6
TRANSMISSION (%)
100
80
60
40
20
0
4000
3000
2000
1800
1400
1000
600
WAVENUMBER (CM)$^{-1}$


O_2N
NO_2
S
N
8
7
6
4
3
2
1
0 δPPM

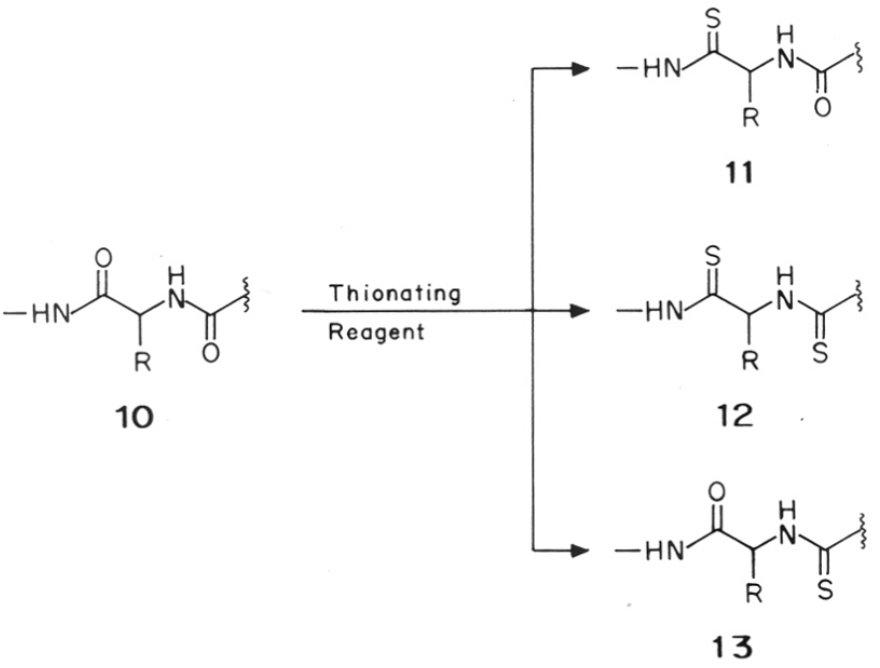
2.6. Reduction of nitro group of nitrothioacetamides

There is no good methodology available in the literature for the regioselective synthesis of thiopeptides. The methodology reported basically involves the thionation of preformed peptides. The biggest drawback in this methodology is lack of control over the regioselectivity (**Scheme 6**).

Our aim was to find out an alternative methodology with which one can synthesize the thiopeptides regioselectively. Our strategy is illustrated in scheme 7. However, reducing the nitro group in presence of a thioamide functional group is very difficult. Moreover the sulfur atom present in the molecule adds to the problem by poisoning the metal catalyst. Hence, the catalytic reduction was avoided. It became necessary to choose a reagent from the vast literature available.

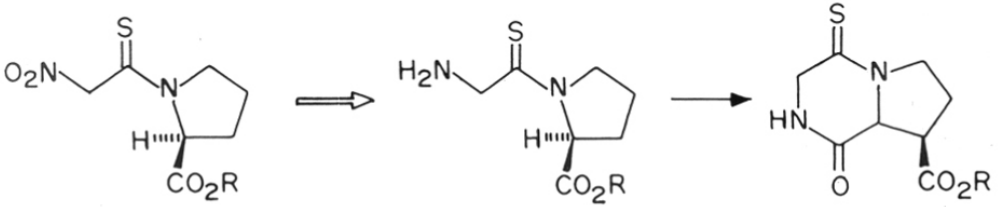
A few sulfides like Na_2S and $(NH_4)_2S$ are known to reduce the nitro group. Therefore, in presence of a phase-transfer catalyst (tetraethylammonium bromide) N-nitrothioacetyl pyrrolidine was allowed to react with Na_2S[10] in methanol. But a complex mixture of products was obtained in this reaction. Reduction with other reagents like a) ammonium formate, sodium phosphate mono basic in 1-methyl-2-pyrrolidinone[11], b) ethanolamine in pyridine[12], c) $Zn/CaCl_2$ in 78% ethanol[13], d) Zn/HCl and e) $Zn/AcOH/Ac_2O$ have been reported. However, in our hands, with our substrate, these reagents also gave only intractable products.

SCHEME-6



10 11 12 13

SCHEME-7



14 15 16

2.7. Experimental Section

Synthesis of α-allyl N-nitrothioacetamides

General procedure : N-nitrothioacetylpyrrolidine was taken in dry benzene and kept under nitrogen atmosphere, 1 equivalent of DBU was added to the solution, stirred at r.t. for 5 min., then allyl bromide (allyl, crotyl, methallyl, 1.1 equivalent) in benzene was added, and stirred at 40 - 55°c to get thick gum which on chromatographic purification on silica gel column yielded α-allyl N-nitrothioacetamides in good yields.

Allylation of N-nitrothioacetylpyrrolidine to N-[2-nitro-2-(prop-2-en-1-yl) thioacetyl] pyrrolidine (3a) : Gum, yield : 55%; **IR**(neat) : 2860 - 2960, 1650, 1560 and 1370cm^{-1}; **^{1}H NMR** ($CDCl_3$): 2.06 (m, 4H, 2N-C-CH_2), 3.07 (m, 2H, =C-CH_2), 3.8 (m, 4H,2NCH_2), 5.42 (t, 1H, O_2N-CH), 5.44 (m, 3H, H_2C=CH); **^{13}C NMR** ($CDCl_3$): 23.67, 25.89, 37.01, 51.26, 54.32, 88.94, 119.80, 130.48, 187.73; **MS(m/e)**: 214 (M^+ 1.3%), 184, 168(100%), 134, 70. **Found**, C,50.80, H,6.72; **calculated** for $C_9H_{14}N_2O_2S$, C,50.47, H,6.54%.

Crotylation of N-nitrothioacetylpyrrolidine to N-[2-nitro-(1-methylprop-2-en-1-yl)thioacetyl]-pyrrolidine (3b): Gum, yield: 40%; **IR**(neat) 2900-3000, 1650, 1570, 1500, 1460, 1380; **^{1}H NMR**($CDCl_3$): 1.03(d, 3H, Me)[1.21], 2.1(m, 4H, 2N-C-CH_2), 3.65 and 3.85(m, 4H, 2NCH_2), 4.0(m, 1H, O_2N-C-CH)[4.1], 5.25(m, 3H, =CH_2 and O_2NCH), 5.7(m, 1H, =CH); **MS**(m/e): 228(M^+), 198, 182(100%), 167, 148, 149, 134, 122, 114, 70. **Found**, C,52.94, H,7.41 **calculated** for $C_{10}H_{16}N_2O_2S$, C,52.63, H,7.02%.

Methallylation of N-nitrothioacetyl pyrrolidine to N-[2-nitro-2-(2-methylprop-2-en-1-yl)thioacetyl]-pyrrolidine (3e): Gum, yield: 51%; **IR**(neat): 2900-3000, 1660w, 1570 and 1380; **^{1}H NMR**($CDCl_3$): 1.89 (s, 3H, CH_3), 2.16(m, 4H, 2N-C-CH_2), 3.04(ddd, 2H, =C-CH_2), 3.87(m, 4H, 2NCH_2), 4.84(d, 2H, =CH_2), 5.67(m, 1H, O_2NCH); **^{13}C**

NMR($CDCl_3$): 22.72, 23.72, 26.00, 40.30, 51.17, 54.45, 88.42, 113.79, 138.73, 188.19; **MS**(m/e): 228(M^+), 198, 182(100%), 167, 149, 148, 134, 120, 114, 96, 77, 70. **Found**, C,52.81, H,7.31; **calculated** for $C_{10}H_{16}N_2O_2S$, C,52.63, H,7.02%.

Syntheses of 2-N-pyrrolidinyl-3-nitro-4-substituted thiophenes

General procedure: 1.1 equivalent of DBU was added to the solution of N-nitrothioacetyl pyrrolidine in dry benzene, followed by 1.1 equivalent of acyl bromide (phenacyl, 4′-nitro phenacyl, bromoacetone). The content were stirred at 60-80°c for 3-5 hrs. under nitrogen atmosphere. The reaction was followed by tlc. The intense yellow colour of the product could be seen on tlc plate even before the iodine absorption. The solvent was evaporated and the product was purified by the column chromatography (benzene as an eluent).

2-N-Pyrrolidinyl-3-nitro-4-phenylthiophene (9a): Solid, m.p.:114°c; yield: 100%; **IR**(nujol): 1540, 1460, 1380, 1360; **UV**(MeOH): λ_{max} 416nm 268 , 232 ; **^{1}H NMR**($CDCl_3$): 2.05 (m, 4H, $2CH_2$), 3.35 (m, $2NCH_2$), 6.1(s, 1H, =CH), 7.28 (s, 5H, Ph); **^{13}C NMR**($CDCl_3$): 25.38, 52.65, 105.10, 127.09, 127.21, 127.46, 127.78, 135.39, 137.44, 156.19; **MS**(m/e): 274 (M^+,100%), 257, 229, 158, 77, 71. **Found**, C,60.90, H,4.82; **calculated** for $C_{14}H_{14}N_2O_2S$, C,61.31, H,5.11%.

2-N-Pyrrolidinyl-3-nitro-4(4′-nitrophenyl) thiophene (9b): Light yellow solid; m.p. 171°c; yield: 76%; **IR**(nujol): 1590, 1540, 1450, 1360, 1300, 1260; **^{1}H NMR**($CDCl_3$): 2.09 (m, 4H, $2CH_2$), 3.4(m, 4H, NCH_2), 6.21 (s, 1H, =CH), 7.41 and 8.17 (m, 4H, $PhNO_2$); **MS**(m/e): 319 (M^+), 273, 258, 246, 234, 71(100%); **Found**, C,53.1, H,4.32; **calculated** for $C_{14}H_{13}N_3O_4S$, C,52.65, H,4.10%.

2-N-Pyrrolidinyl-3-nitro-4-methyl thiophene (9c) : Solid, m.p. 98-100°c, yield: 57%; **IR**(nujol): 1550, 1470, 1390, 1320, 1280; **UV**(MeOH): λ_{max} 420 , λ_{max} 258 , **^{1}H**

NMR ($CDCl_3$): 2.02 (m,4H, $2CH_2$), 2.31 (d, 3H, Me), 3.29 (m, 4H, $2NCH_2$), 5.89 (q, 1H, =CH); **MS**(m/e): 212 (M^+), 178, 166, 127, 124(100%), 71. **Found,** C,51.20, H,5.90; **calculated** for $C_9H_{12}N_2O_2S$, C,50.94, H,5.66%.

2.8 REFERENCES

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CHAPTER 3

Diastereroselectivity in thio Claisen rearrangement

3.1. Introduction

One of the most powerful methods developed during the past several decades for creating a new asymmetric center in a predictable configuration involves the use of sigmatropic rearrangements. It is because the most favorable transition state geometry can ordinarily be predicted from principles of conformational analysis and the stereochemical outcome is subject to prediction and control.

Since the first observation of chirality transfer in Claisen rearrangement made by Alexander[1] *et al.* in 1951, there have been several reports on chiral induction in [3,3] sigmatropic rearrangements. However, though such chiral induction in the Claisen rearrangement has been studied[2-5] a similar study on thio-Claisen rearrangement has not been reported. Interestingly, the only asymmetric effects discussed thus far have been related strictly to C_4 carbon, an ***integral part of the Claisen rearrangement framework***. In general, when the original center of asymmetry is located vicinal to the developing center of asymmetry, modest selectivity is observed[6-9] and when the original chiral center is farther removed from the reaction site, it's effect is diminished and selectivity drops[10,11]. But certainly it will be fascinating to study the effect of remote chirality, which is not in the Claisen rearrangement framework and its ability to induce diastereoselectivity in [3,3] sigmatropic rearrangements. The only report appeared in 1977, which describes the rearrangement of allyl vinyl ether (**1**), wherein the remote asymmetry at the quaternary center *i.e.* the chiral carbon located two carbons away from the C_6 carbon of the Claisen framework, renders the faces of the olefin diastereotopic. However, the reaction didnot give rise to any diastereoselection; both diastereomers (**2**) were produced in equal amounts[12] (**Scheme 1**)

Thio-Claisen rearrangement is less studied as compared to the Claisen rearrangement. Though the lone result on the effect of remote asymmetry in the Claisen rearrangement is not encouraging, it was planned to study chiral induction by the

SCHEME-1

1 2

asymmetric center which is ***not an integral part*** of the [3,3] sigmatropic rearrangement framework, *i.e.* a chiral carbon located two atoms away from the C_2 carbon of the thio-Claisen rearrangement framework.

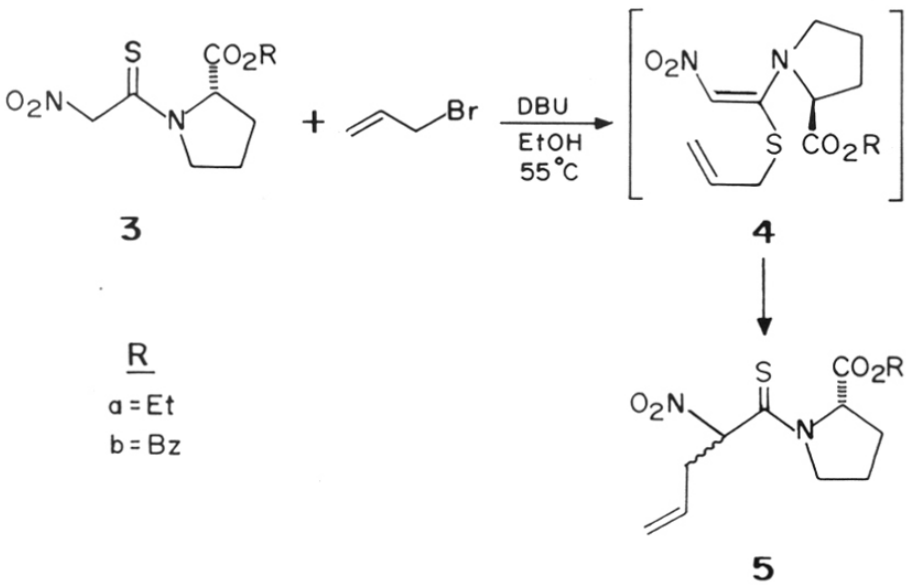
One has little control over the rates of pericyclic reactions, partly because they are insensitive to solvent effects[13]. It is somewhat surprising that there has been no systematic study of the substituent effects on the rates of sigmatropic rearrangements. In many cases the existing models by B.K. Carpenter and M.J.S. Dewar contradict each other in predicting the substituent effects. As there is no report so far on substituent effects on the rates of thio-Claisen rearrangement, the need for further understanding of substituent effects forced us to look into the effect of a ***push - pull*** system on the thio-Claisen rearrangements.

3.2. Results

Having proved that the thio-Claisen rearrangement is operative in the allylation reaction of N-nitrothioacetyl pyrrolidine [chapter 2]; the allylation reaction was carried out on N-nitrothioacetyl proline ethyl ester(**3**) (**Scheme 3**) to fulfil both the objectives, *i.e.*

to study chiral induction in thio-Claisen rearrangement and to determine the effect of the push-pull system on the rate of the reaction.

SCHEME-2



The experimental details of the allylation reaction are given in the experimental section, but a few details need to be mentioned here in this context. The thio-Claisen rearrangement was carried out at 55°c for 4hrs. and in order to minimize the epimerisation of the product formed, minimum amount of base (1.1eq. DBU) was used. Like their precursors, α-allyl N-nitrothioacetyl proline ethyl and benzyl esters are not stable compounds and extra care in purification is required. Generally dry cyclohexane as an eluent in column chromatography on activated silica gel column gave better results. α-Allyl N-nitrothioacetyl proline ethyl ester was obtained in 90% yield and it's **IR**(neat) spectrum showed a strong peak at 1750cm^{-1}, corresponding to ester carbonyl stretching frequency, a weak peak at 1650 for olefinic bond stretching frequency and strong peaks were seen at

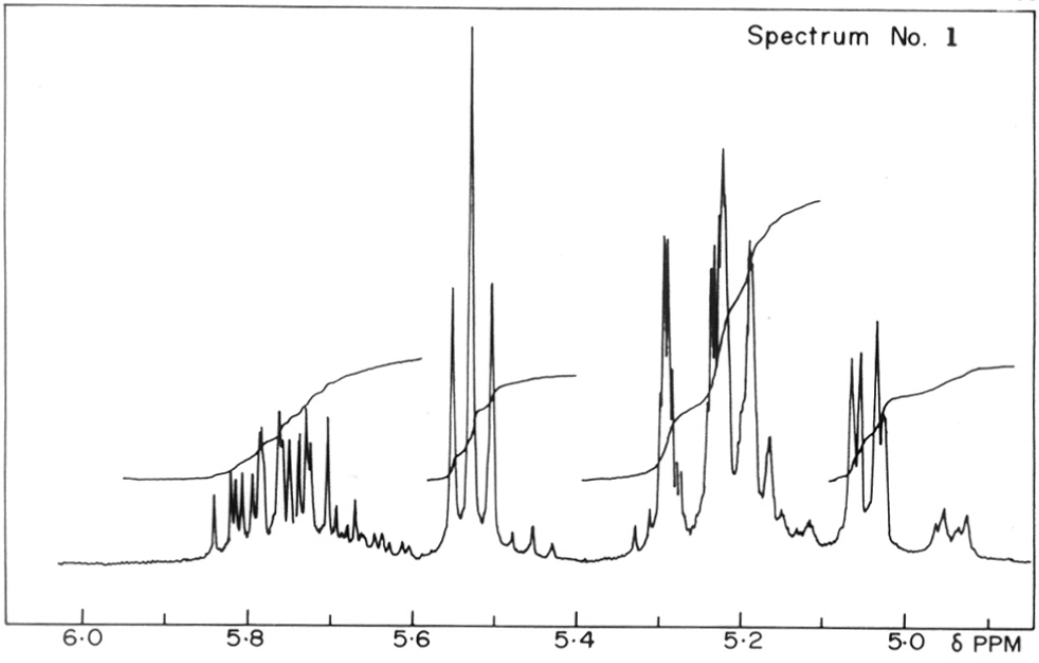
1570 and 1380 corresponding to NO_2 group stretching frequencies. The **^{1}H NMR** and **^{13}C NMR** spectra are discussed in detail separately. The structure is further confirmed by the observation of molecular ion peak in the mass spectrum.

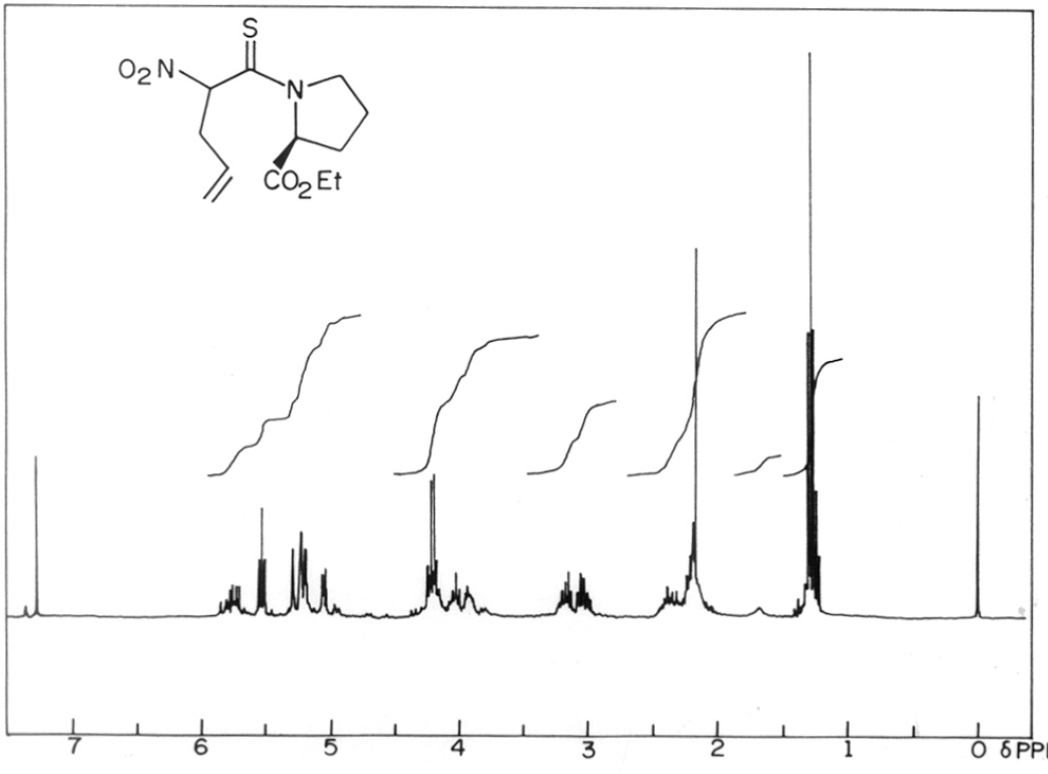
3.2.1 Estimation of Diastereoselectivity by ^{1}H and ^{13}C NMR spectra

The ^{1}H and ^{13}C spectra of α-allyl N-nitrothioacetyl proline ethyl ester are complex because of the presence of two diastereomers and *cis/trans* rotational isomers for each diastereomer. Thus four sets of peaks were seen in the spectra. Out of the four sets two had higher intensities and were from the trans rotamers of the two diastereomers. The diastereomeric excess (*de*) was estimated from the integration ratio of the corresponding proton signals and relative height of carbon signals of the two diastereomers. For practical purposes, the ratio of the signal intensity of the corresponding atoms in the ^{13}C spectrum of a diastereomeric mixture may be taken to indicate the ratio of diastereomers present in the solution[14].

The **^{1}H NMR** spectrum (**Spectrum No. 1**)

of α-allyl N-nitrothioacetyl proline ethyl ester showed four sets of triplets for the ester CH_3 protons at 1.24, 1.29, 1.31 and 1.32δ. Similarly four sets of quartets were seen for the OCH_2 protons in 4.19 to 4.25δ region. The multiplets around 2.1 - 2.4δ were assigned for $2CH_2$ protons of the proline ring and are too complex to analyze. The multiplet at 2.98 - 3.20δ is assigned for =C-CH_2 protons and other multiplets at 4.02 - 4.17δ were assigned for NCH_2 protons. The multiplets for NCH proton are clearly separated by about 0.1δ at 5.05 and 4.95δ and complex multiplets at 5.16 -5.29 and 5.7 - 5.81δ were assigned for olefinic protons of allyl moiety. The triplet at 5.52δ was assigned to O_2N-CH. The ***de*** was calculated from the ratio of the two triplets corresponding to the ester CH_3 group and another set of two multiplets corresponding to the NCH proton of the trans rotamers of the two diastereomers.

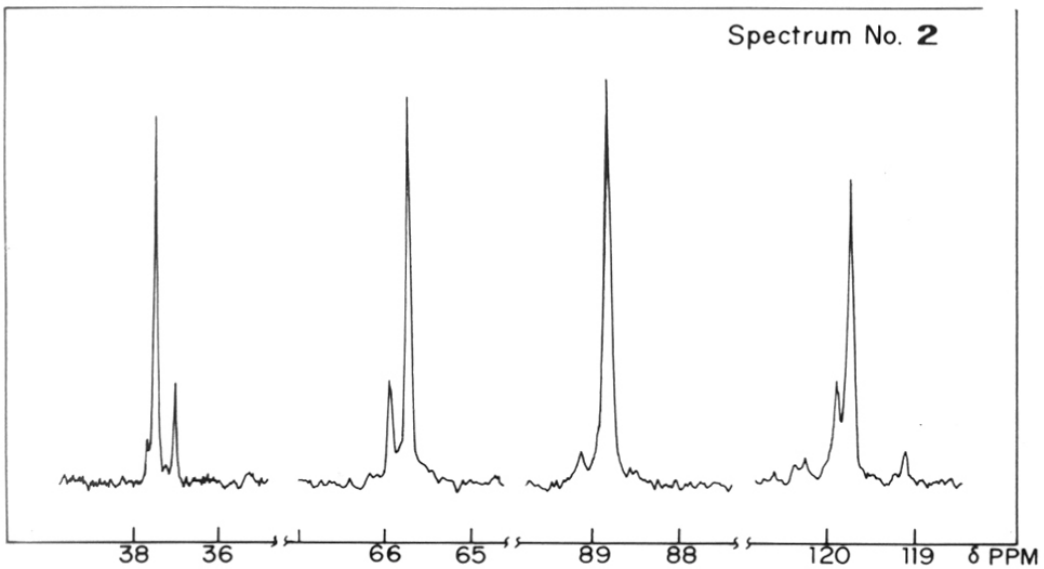

Spectrum No. 1
6·0
5·8
5·6
5·4
5·2
5·0
δ PPM

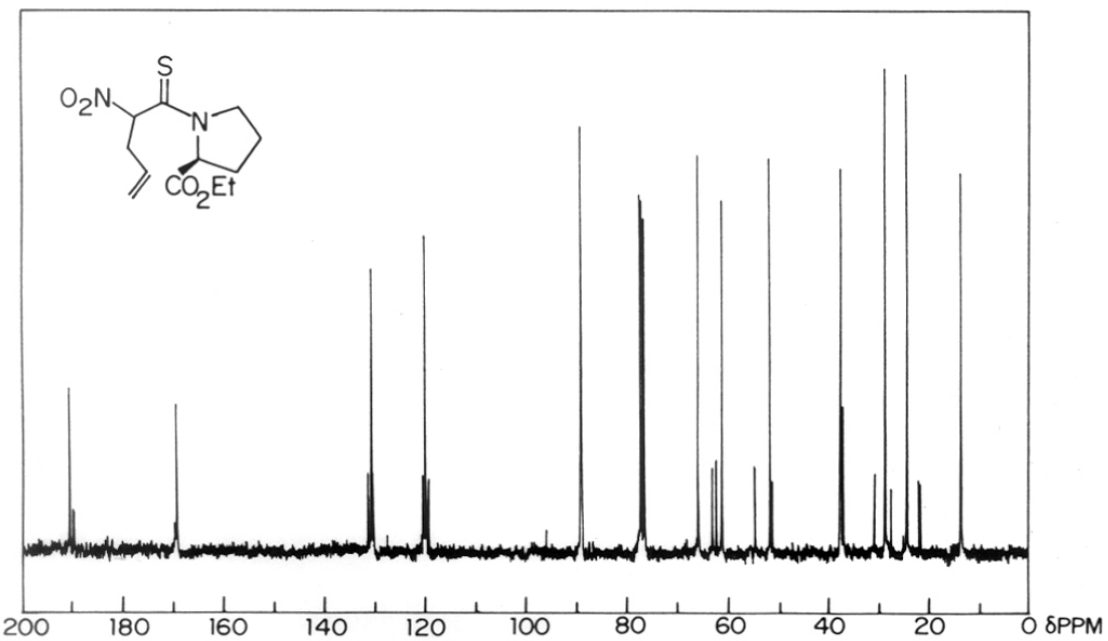

S
O2N
N
CO2Et
7
6
5
4
3
2
1
0
δPPM

The ^{13}C **NMR** spectrum (**Spectrum No. 2**)

of the compound displayed four sets of peaks, two sets of peaks having high intensity were from trans rotamers of two diastereomers. The chemical shift values for the trans rotamer of the major diastereomer are 13.76 (CH_3), 24.41 (Cγ), 28.65 (Cβ), 37.46 (=C-**C**), 51.62 (Cδ), 61.11 (Cα), 65.72 (O-C), 88.83 (O_2N-C), 119.73 (=CH_2), 130.37 (=CH), 169.06 (CO), 190.29 (CS), similarly chemical shift values for the trans isomer of minor diastereomer are 13.65 (CH_3), 22.09 (Cγ), 27.59 (Cβ), 37.00 (=C-**C**), 50.96(δ), 62.20 C(α), 65.95 (O-C), 89.13 (O_2N-C), 119.90 (=CH_2), 130.46 (=CH), 168.92 (CO), 189.46 (CS).

The ratio of the signal intensity of the carbon nuclei, C(α), C(δ), CNO_2 and of the proton nuclei, α CH and CH_3 were used for the calculation of ***de***. The ***de*** in allylation reaction (thio-Claisen rearrangement) of N-nitrothioacetyl proline ethyl ester was calculated to be 66% from ^{1}**H** and ^{13}**C NMR** spectra.

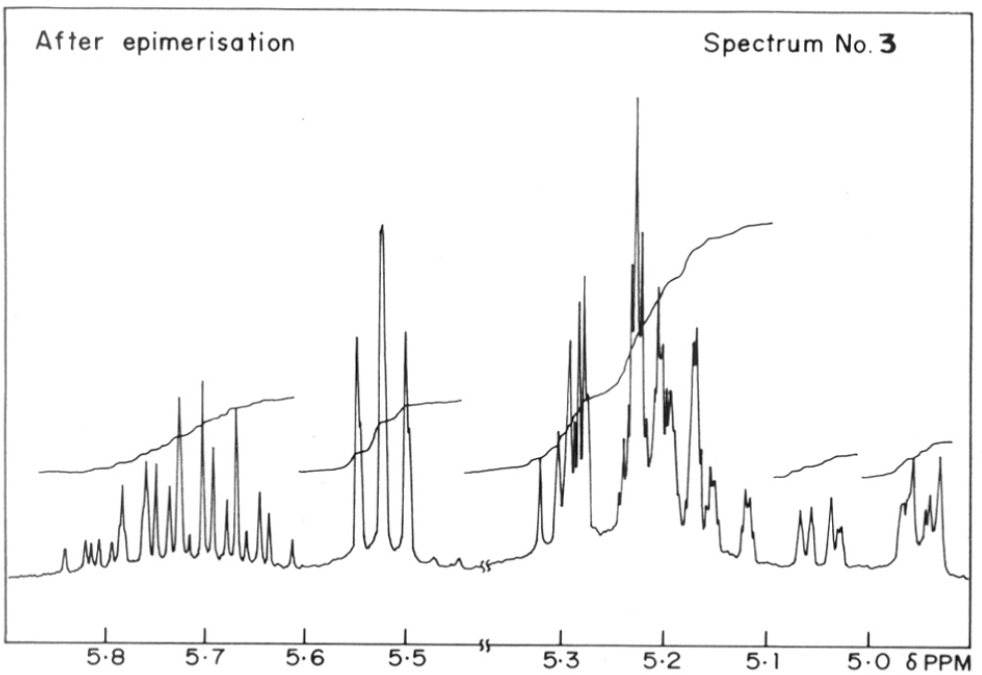

Spectrum No. 2
38
36
66
65
89
88
120
119
δ PPM

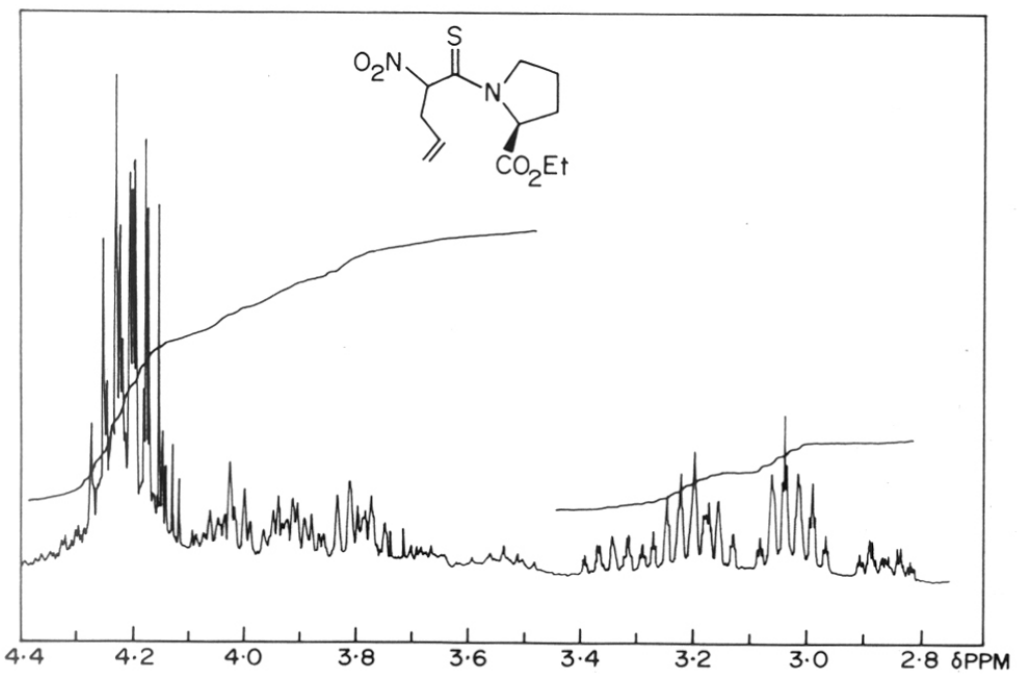

S
O2N
N
CO2Et
200
180
160
140
120
100
80
60
40
20
0 δPPM

3.2.2 Product of Kinetic control

In order to check whether the major diastereomer formed is kinetically controlled product or not, the diastereomeric mixture formed in the allylation reaction was treated with 1eq. of DBU in EtOH, stirred for 10min. then acidified with AcOH. The **^{1}H NMR** spectrum shows the intensity enhancement for the signal corresponding to the minor diastereomer (**Spectrum No. 3**).

Especially, the triplet at 1.23δ and the multiplet at 4.95δ (both correspond to the minor diastereomer) are quite distinguishable. This signal intensity enhancement clearly indicates that the major diastereomer formed is a kinetically controlled product.

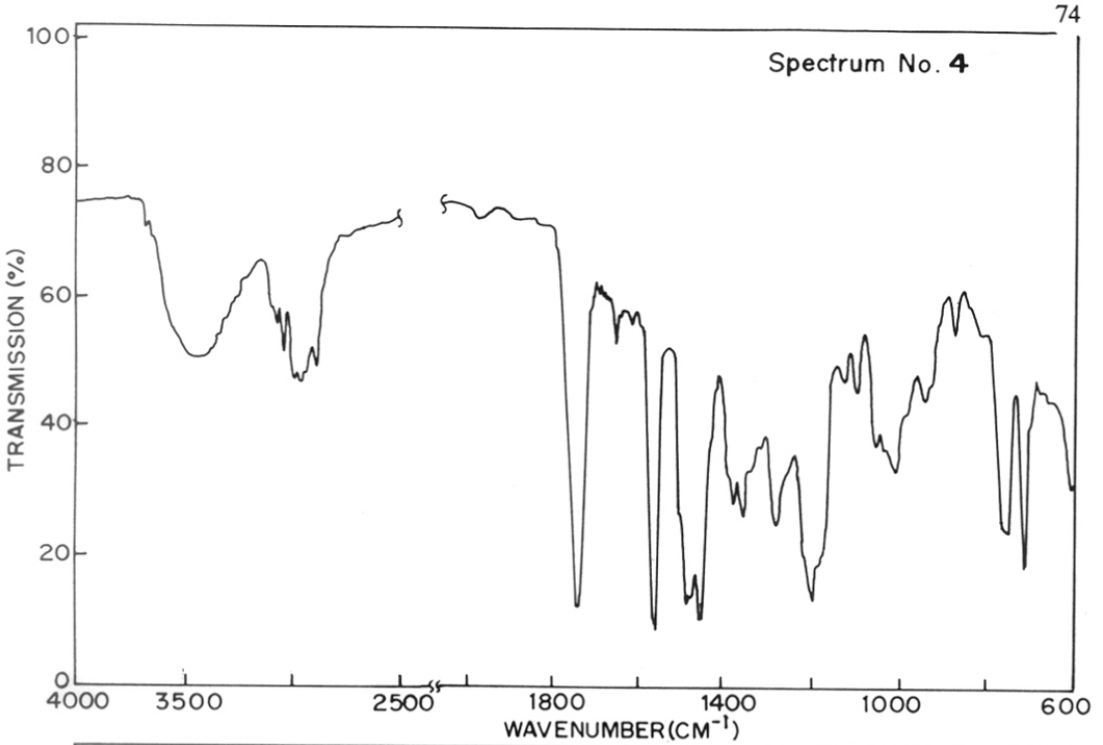

After epimerisation
Spectrum No. 3
5·8
5·7
5·6
5·5
5·3
5·2
5·1
5·0 δ PPM

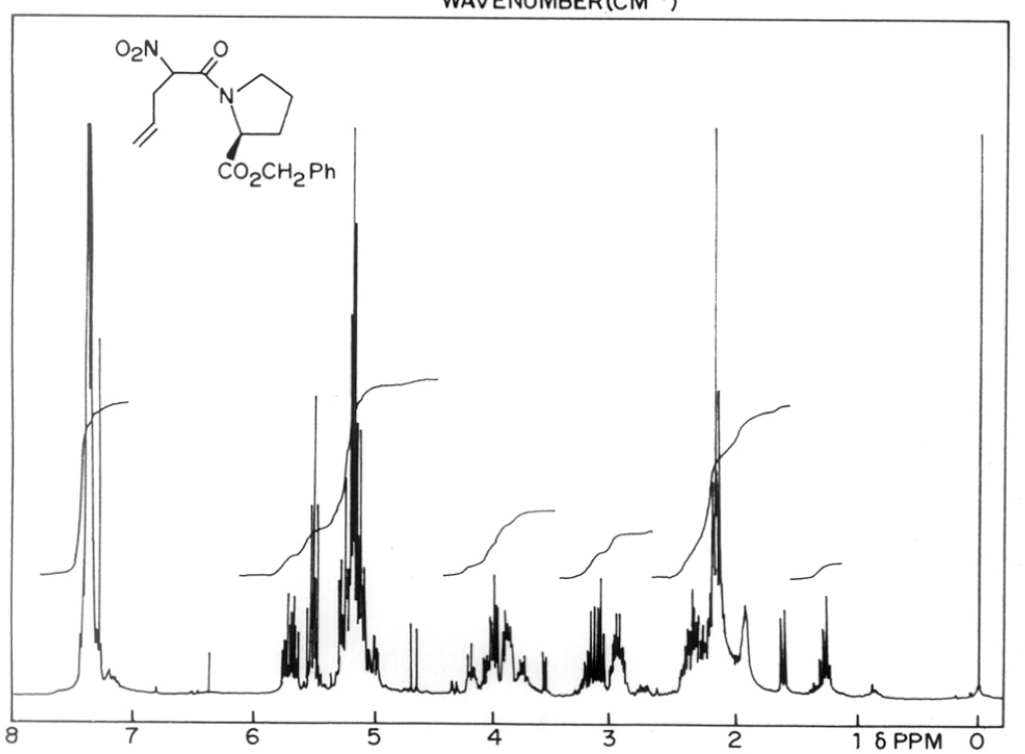

S
O2N
N
CO2Et
4·4
4·2
4·0
3·8
3·6
3·4
3·2
3·0
2·8 δPPM

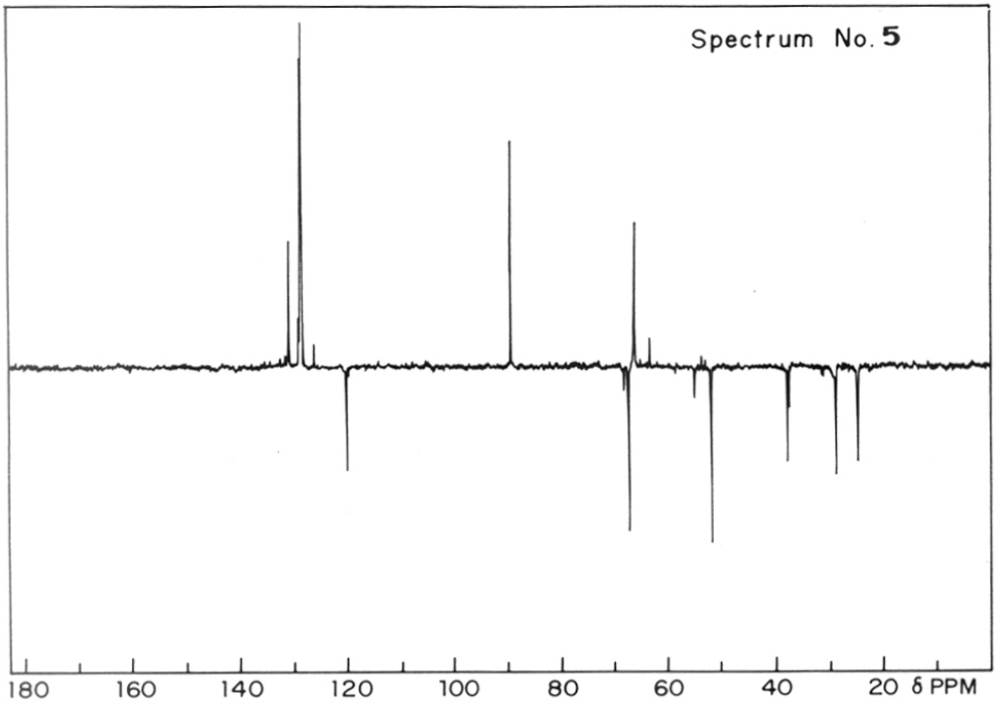
3.2.3 Effect of ester group on the diastereoselectivity

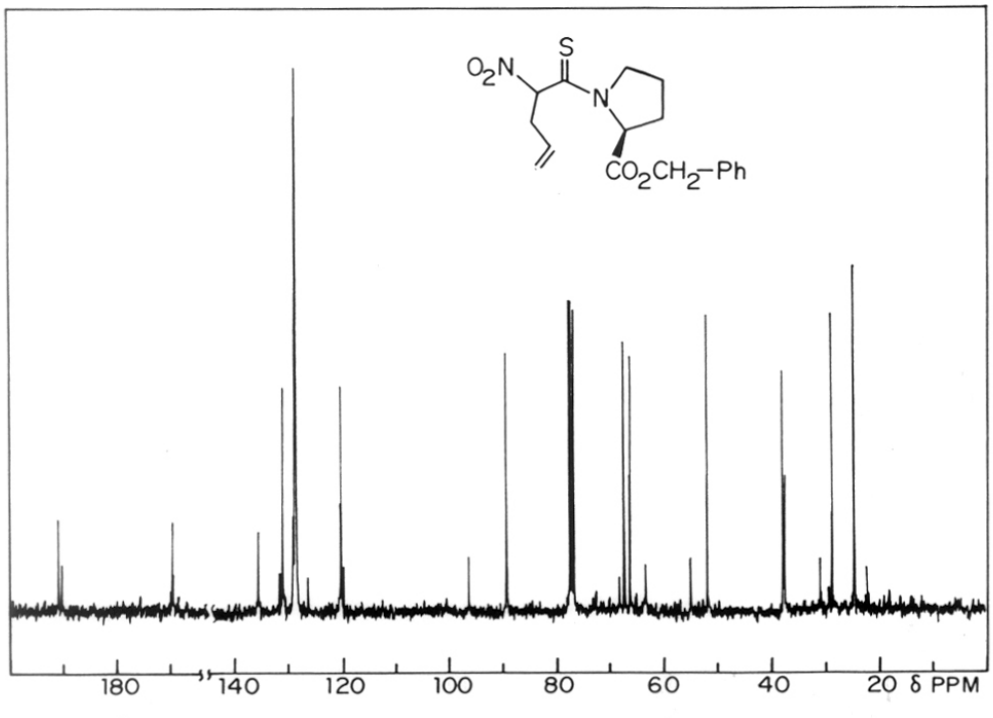
It will be interesting to know whether the steric bulk of the ester fragment has any role on diastereoselectivity. So, the N-nitrothioacetyl proline ***benzyl*** ester was allylated with allyl bromide under similar experimental conditions as earlier. The **^{1}H** and **^{13}C NMR** spectra of α-allyl N-nitrothioacetyl proline benzyl ester have four sets of peaks with two sets of signals having higher intensity (**Spectra No. 4 and 5**);

these were assigned to the trans rotamers of the two diastereomers. The ***de*** was calculated as in the case of α-allyl N-nitrothioacetyl proline ethyl ester. The ***de*** was found to be 66%, indicating that the steric bulk of the ester group has no effect on the diastereoselectivity.


Spectrum No. 4
100
80
60
40
20
0
TRANSMISSION (%)
4000
3500
2500
1800
1400
1000
600
WAVENUMBER(CM⁻¹)


O2N
O
N
CO2CH2Ph
8
7
6
5
4
3
2
1 δ PPM
0


Spectrum No. 5
180
160
140
120
100
80
60
40
20 δ PPM


S
O2N
N
CO2CH2–Ph
180
140
120
100
80
60
40
20 δ PPM

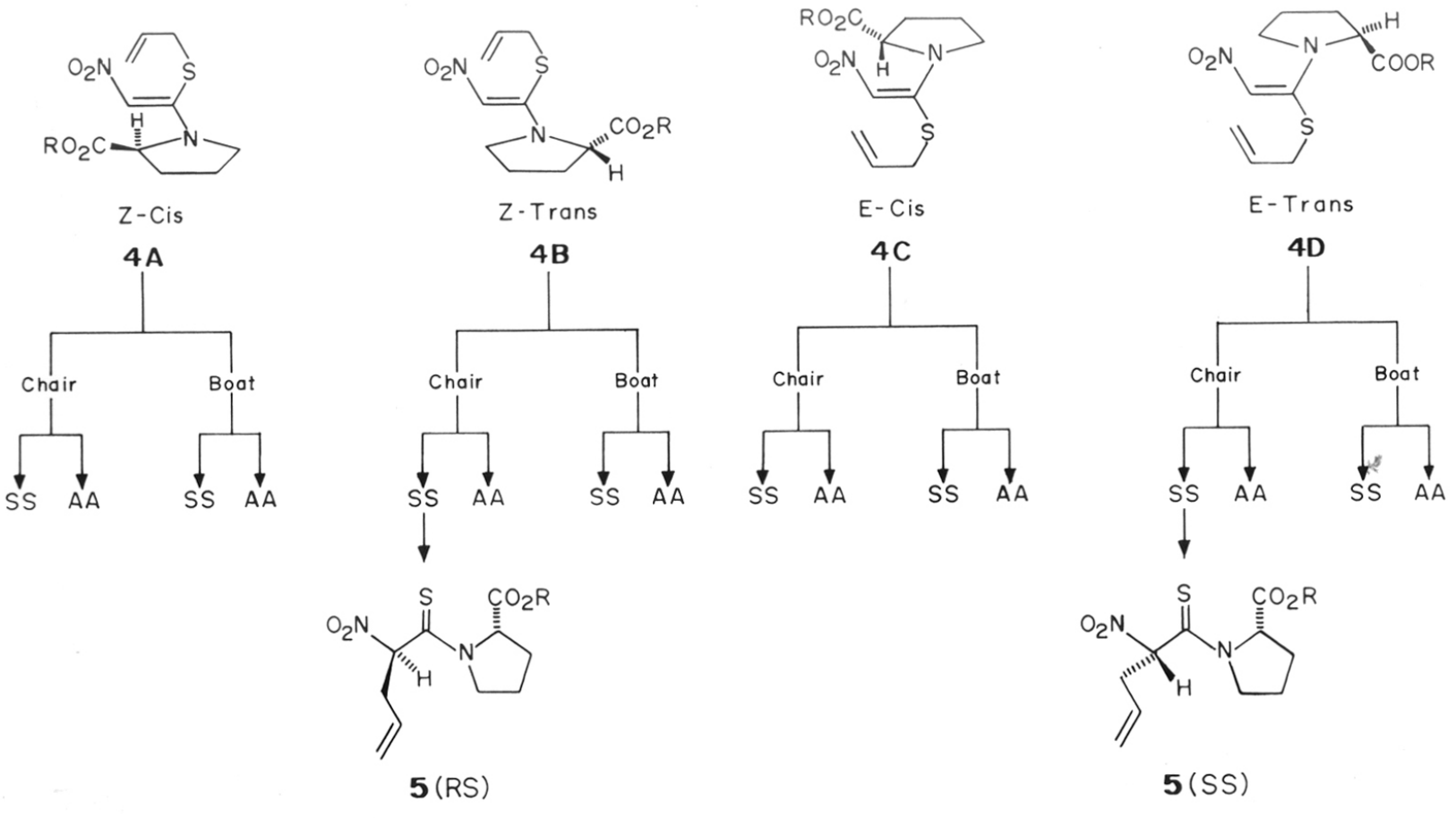
3.3. Discussion

The stereochemical outcome in this thio-Claisen rearrangement depends mainly on i) the geometry of vinyl double bond, ii) transition state structure and iii) mode of migration (supra-supra or antara-antara). All permutations of chair and boat conformations, cis/trans rotamers, E, Z configurations and supra supra and antara antara migrations lead to different isomers. The cis/trans rotamer ratio (around the thioamide bond) in ethyl or benzyl N-nitrothioacetylproline is found to be 1:7. Assuming similar rotamer population in the intermediate, the possible S-allylated intermediates (**4**), the *cis*-conformers **4A** and **4C** may be safely omitted from further consideration (**Scheme 3**). This leaves only **4B** and **4D** as likely candidates.

i) ***Vinyl double bond geometry*** **:** An important feature of the aliphatic Claisen rearrangement and all of it's variants is that the product stereochemistry is based on the olefin configuration.

In sharp contrast to the other carbonyl compounds[15,16], both the secondary and tertiary thioamides provide only one stereoisomer of enolate, irrespective of reaction conditions (kinetic or thermodynamic), different kinds of bases and different kinds of solvents[17]. The same should hold good for nitrothioacetamides also. Regarding the nitroenamines with no hydrogen atom on the nitrogen, *i.e.* those nitroenamines which do not derive any stabilization by H-bonding, consensus appears to be that they exist in the E configuration[18,19]. This preference for E configuration is believed to be a consequence of the tendency to minimize steric crowding. However, nitroenamines are typical push-pull ethylenes, hence E, Z isomerisation is generally characterised by low energy barriers. This E, Z ratio and the inter conversion energy barriers are strongly dependent on the solvent[20].

ii) Transition state geometry : For [3,3]-sigmatropic processes exemplified by the vast majority of Claisen, Cope and hetero Claisen rearrangements, two possible geometries have been considered for the cyclic transition state. Either a chairlike one or boat-like transition state. It is clear that for molecules which can readily adopt either arrangement,


Z-Cis
4A
Chair
Boat
SS
AA
SS
AA
Z-Trans
4B
Chair
Boat
SS
AA
SS
AA
5 (RS)
E-Cis
4C
Chair
Boat
SS
AA
SS
AA
E-Trans
4D
Chair
Boat
SS
AA
SS
AA
5 (SS)

SCHEME-3

the chairlike geometry is strongly favoured. Moreover, of the two alternative chairlike arrangements the one which minimizes 1,3-pseudo diaxial interaction is preferred. Structure **4B** can have two alternative chair like arrangements, *i.e.* Ch-1 and Ch-2 in equilibrium. But, the Ch-1 arrangement is not favoured for two reasons. First one is, both nitro and amino groups on vinylic double bond are in pseudo axial positions of a chair form, hence they are expected to exert 1,3 diaxial interactions. In Ch-2 arrangement both these groups are in pseudo equatorial positions. The second reason is, the original chiral center of the proline moiety will block the *Si* face of the vinylic double bond in both Ch-1 and Ch-2 arrangements. However in Ch-1 the allyl group has to migrate from the already crowded *Si* face whereas in Ch-2 arrangement, the migration takes place from the opposite face *i.e.* ***Re*** face, hence Ch-2 arrangement is more favoured than Ch-1 arrangement.

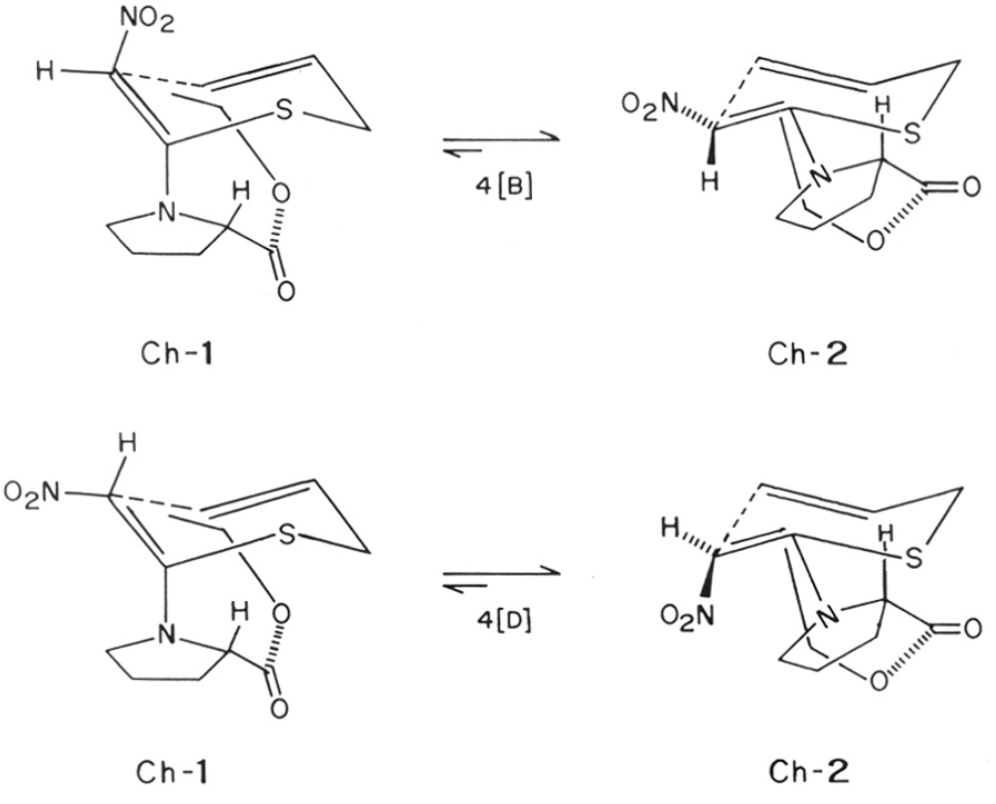
A similar argument holds good in favouring the Ch-2 arrangement of structure **4D**. Here also the ***Si*** face of vinylic double bond in both Ch-1 and Ch-2 arrangements is blocked by the original chiral center.

iii) ***The mode of migration*** **:** Normally antara interactions are not competitive with supra chairlike or boatlike interactions, since such twistlike process require high energy, which is not available in this thio-Claisen rearrangement reaction conditions. Hence, it is reasonable to rule out antara interactions.

Now it is apparent that the major diastereomer formed is from the supra chairlike interaction of **4B** and the minor diastereomer is from supra chairlike interaction of **4D** (**Scheme 4**).

By observing the stereochemical consequences of the transition state geometry and the configuration of the vinylic double bond, the configuration of newly generated chiral center is predicted to be **R** for the major diastereomer and **S** for the minor diastereomer of α-allyl N-nitrothioacetyl proline ethyl ester.

SCHEME-4



3.4. Determination of absolute configuration

The X-ray crystallographic technique is of no use in this case as the separation of the diastereomers is difficult to achieve. It is not clear whether the diastereomers are solids at all and the problem is much aggravated by the labile nature of α-allyl N-nitrothioacetylproline esters. Therefore, it was necessary to look for other alternative methods for determining the absolute configuration. Three methods were tried, a) converting α-allyl N-nitrothioacetylproline ethyl ester to α-allyl N-nitroacetylproline ethyl ester and comparing the product so obtained with two pure diastereomers reported earlier[21]

whose absolute configuration had been rigorously estabished by chemical correlation, b) comparison of ^{13}C NMR chemical shift values of the two diastereomers of α-allyl N-nitrothioacetyl proline ethyl ester with those of the oxo congener and c) using chiral shift reagents.

i) ***Transformation of α-allyl N-nitrothioacetyl proline ethyl ester to α-allyl N-nitroacetylproline ethyl ester*** :

The classical method of determining absolute configuration is to convert the compound with unknown configuration to a compound with known configuration without affecting the chiral centers. Hence it is necessary to protect the α-carbon asymmetry from epimerisation during the thiocarbonyl to carbonyl transformation. A number of reagents[22-31] are available for this conversion with varying degree of success. Based on the reaction mechanisms these reagents can be classified into three categories.

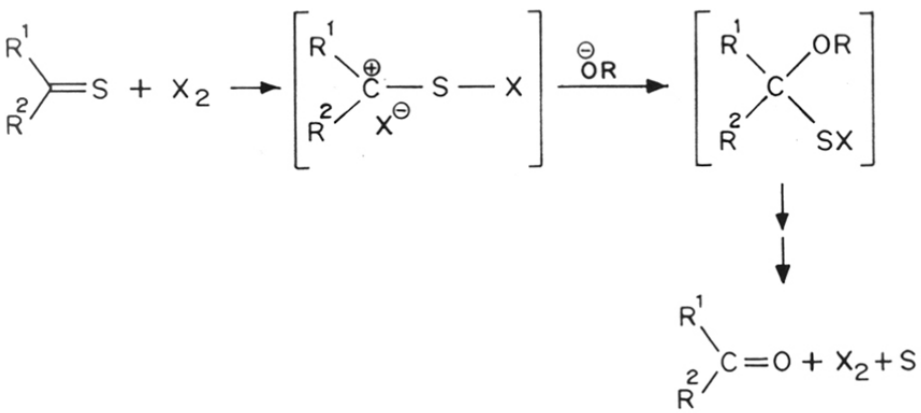
Category 1 : S-alkylation/halogenation and subsequent alkaline hydrolysis[26,28]: Thiocarbonyl compounds give S-alkylated or halogenated products with any alkyl halide or halogens, which on hydrolysis with a strong base like alkoxide or hydroxide affords carbonyl compounds in high yields.

But these reaction conditions are bound to epimerise the chiral center in α-allyl N-nitrothioacetylproline ethyl ester, hence reagents of this category were avoided.

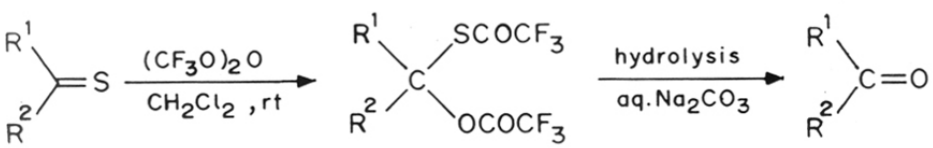
Category 2 : A few reagents like $(CF_3CO)_2O$ attack both C and S atoms of thiocarbonyl group to form an adduct which can be hydrolysed very rapidly under mild basic conditions[32].

Unfortunately $(CF_3CO)_2O$ failed to afford the required carbonyl compound from α-allyl N-nitrothioacetylproline ethyl ester, under similar experimental conditions and a complex mixture of products was obtained. Use of different solvents (benzene, ethanol) or lowering the temperature of reaction (-15°c) didnot provide any carbonyl compound.

SCHEME-5



SCHEME-6



Category 3 : Reagents like DMSO and DMSeO[25,31] react with C=S functional group to form a cyclic adduct which rearranges in such a way that the chiral centers on other atoms are unaffected (**Scheme 7**). Generally these reagents require either a strong acid or I_2 as a catalyst.

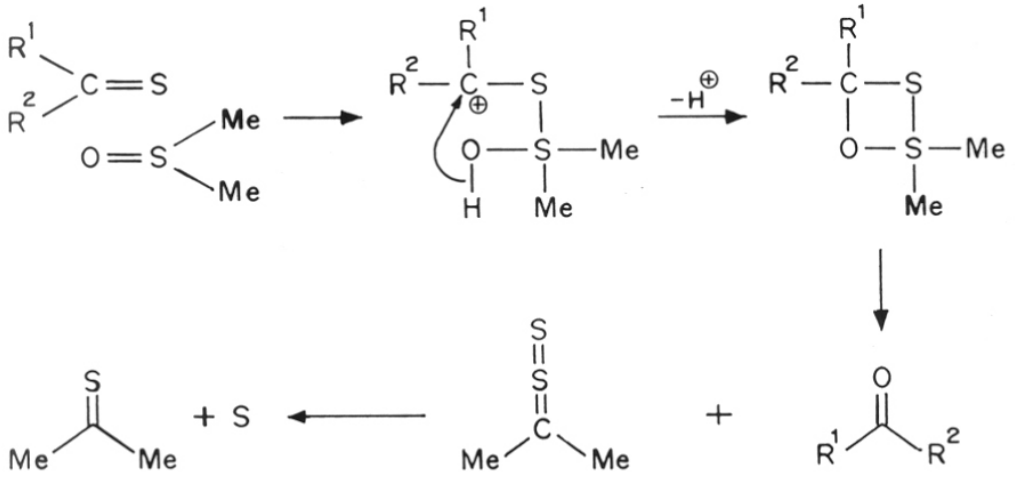
The pure major diastereomer [$[\alpha]_D^{EtOH}$ -88.2°] of α-allylnitrothioacetylproline ethyl ester was allowed to react with excess DMSO and 1 equivalent of H_2SO_4 and the reaction mixture was heated at 80°c under stirring for 12hrs. to afford 60% of corresponding carbonyl compound. The IR, MS and ^{1}H NMR spectra show the formation of carbonyl compound (**Scheme 8**).

But in the ^{1}H NMR spectrum, a second set of signals corresponding to the second diastereomer was observed, indicating that under these reaction conditions epimerisation is taking place. Since none of the reported methods was suitable for C=S to C=O conversion, it was decided to abandon the idea of thiocarbonyl to carbonyl conversion.

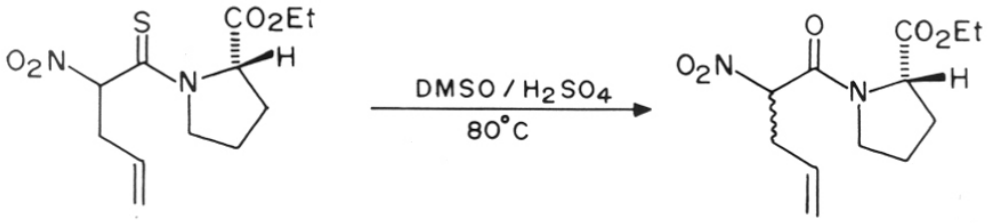
ii) *Comparison of* ^{13}C NMR *spectra* :

A comparison of the ^{13}C **NMR** spectra of α-allyl N-nitroacetyl and N-nitrothioacetylproline ethyl esters reveals some interesting features, which are helpful in assigning the absolute configuration. The carbon nuclei of asymmetric centers and carbons next to asymmetric centers were considered for the study. The peak positions of these nuclei (**C**β, =C-**C**, N**C**H, O_2N-**C**, **C**=O and **C**=S/**C**=O) of major and minor diastereomers are listed in the table **1**.

SCHEME-7



SCHEME-8



5a

PURE DIASTEREOMER

$[\alpha]_D^{EtOH} = -88{\cdot}20°$

Table 1. ^{13}C **NMR** spectral data :

	Oxo		Thio	
	Major	***Minor***	***Major***	***Minor***
Cβ	28.63	28.72	28.65	27.59
=C-C	33.91	33.91	37.46	37.00
NCH	59.40	59.20	61.11	62.20
O_2N-C	85.53	85.35	88.83	89.13
C=O	161.65	161.65	169.06	168.92
C=S/C=O	170.56	170.83	190.29	189.46

* Oxo = α-allyl N-nitroacetylproline ethyl ester

Thio= α-allyl N-nitrothioacetylproline ethyl ester

Cβ of the major diastereomer of α-allyl N-nitroacetylproline ethyl ester appears at 28.63 ppm and for minor diastereomer at 28.72 ppm *i.e.* the signal corresponding to the major diastereomer is seen up field compared to that of minor diastereomer, whereas for the same nucleus (Cβ) in α-allyl N-nitrothioacetyl proline ethyl ester the signal due to the minor diastereomer is seen upfield compared to the signal from the major diastereomer; this trend is exactly opposite to the earlier pattern. Similarly for other nuclei, the relative chemical shift values for the major and minor diastereomers observed for oxo compound is just the reverse of the thio compound (table **2**). The nuclei C=O and =C-C were over-looked as both minor and major diastereomers of oxo compound appears at the same position.

Table 2.

	Oxo		Thio	
	Major	***Minor***	***Major***	***Minor***
Cβ	Up field	Down field	Down field	Up field
NCH	Down	Up	Up	Down
O_2N-C	Down	Up	Up	Down
CS/CO	Up	Down	Down	Up

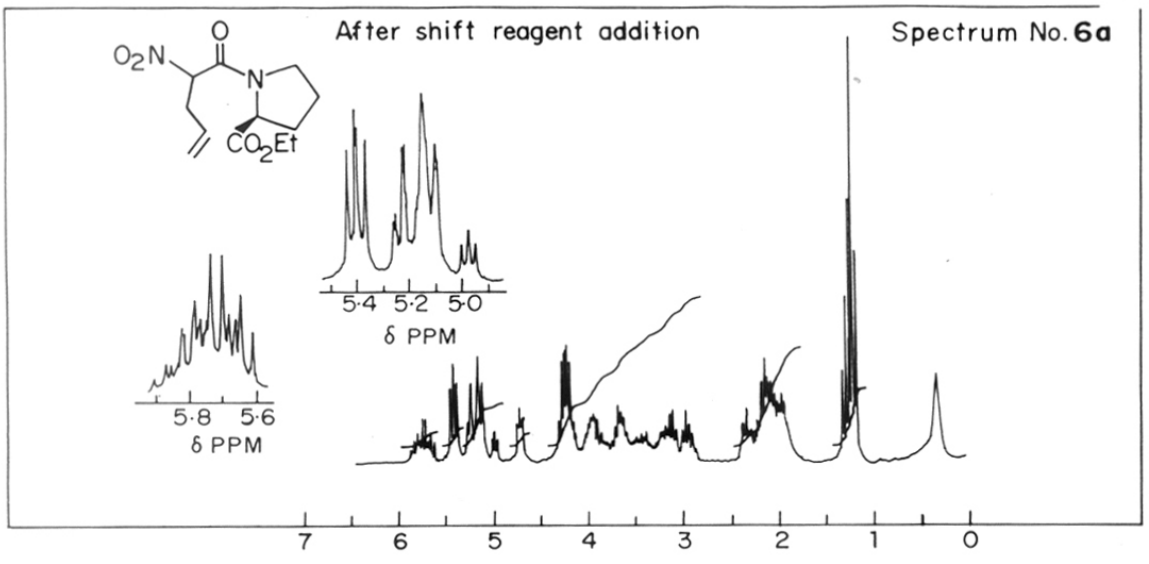
These observations clearly show that the absolute configuration of the major diastereomer of the oxo compound and the minor diastereomer of the thio compound (and vice versa) are identical. The absolute configuration of the major diastereomer of oxo compound[21] is **SS**, therefore it is most likely that the major diastereomer of the thio-Claisen rearrangement product has **RS** configuration and the minor diastereomer in this reaction, the **SS** configuration.

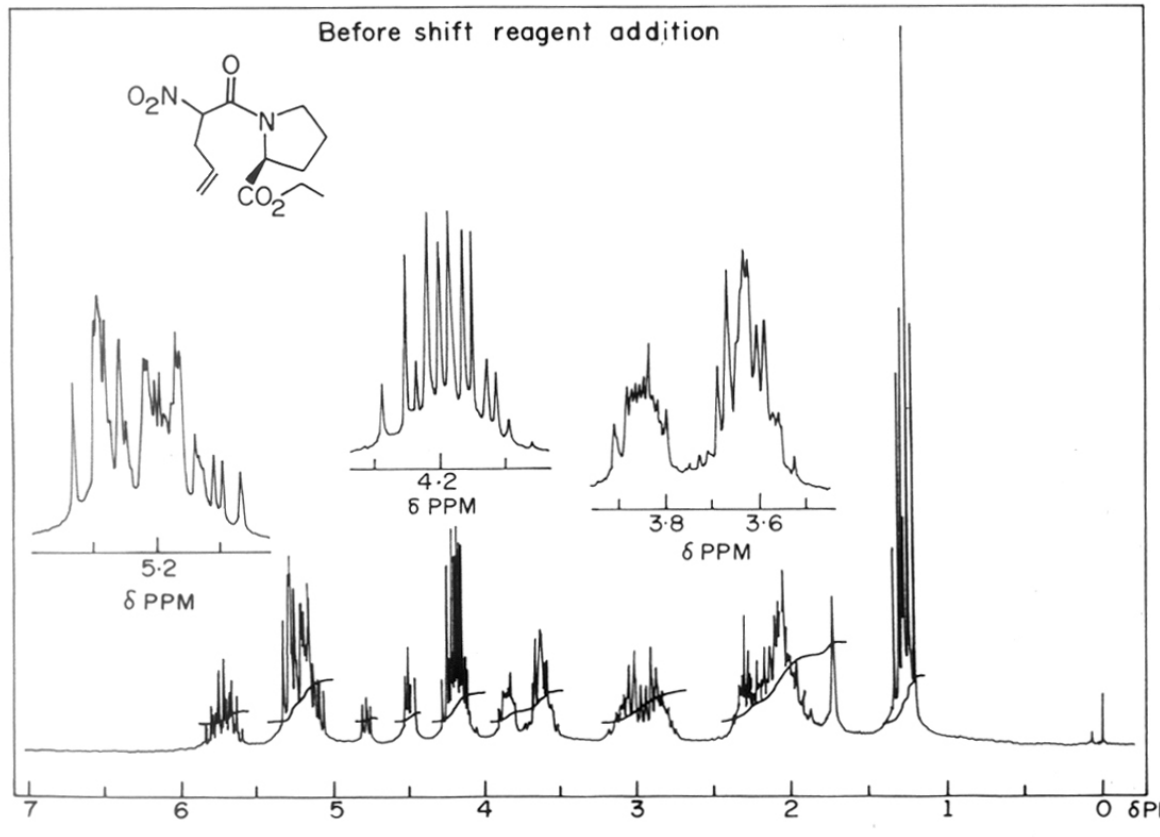
Similar analysis with **^{1}H NMR** spectra could not be carried out because of the complexity of the signals.

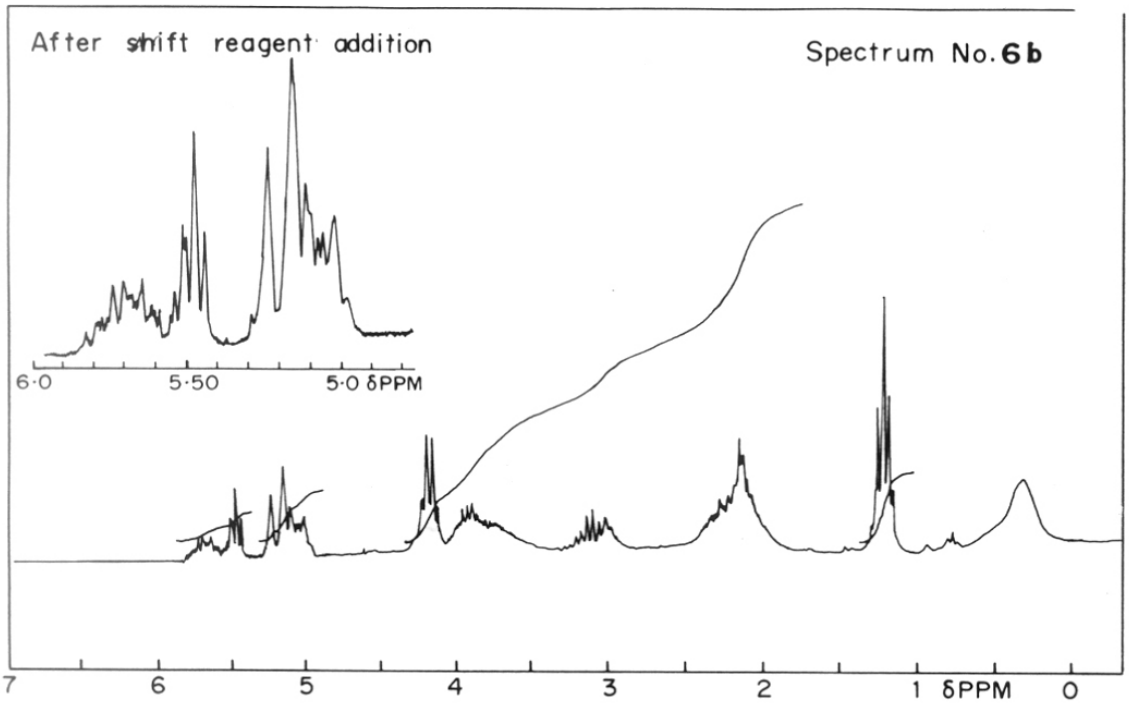
iii) ***Chiral Shift Reagents*** **:**

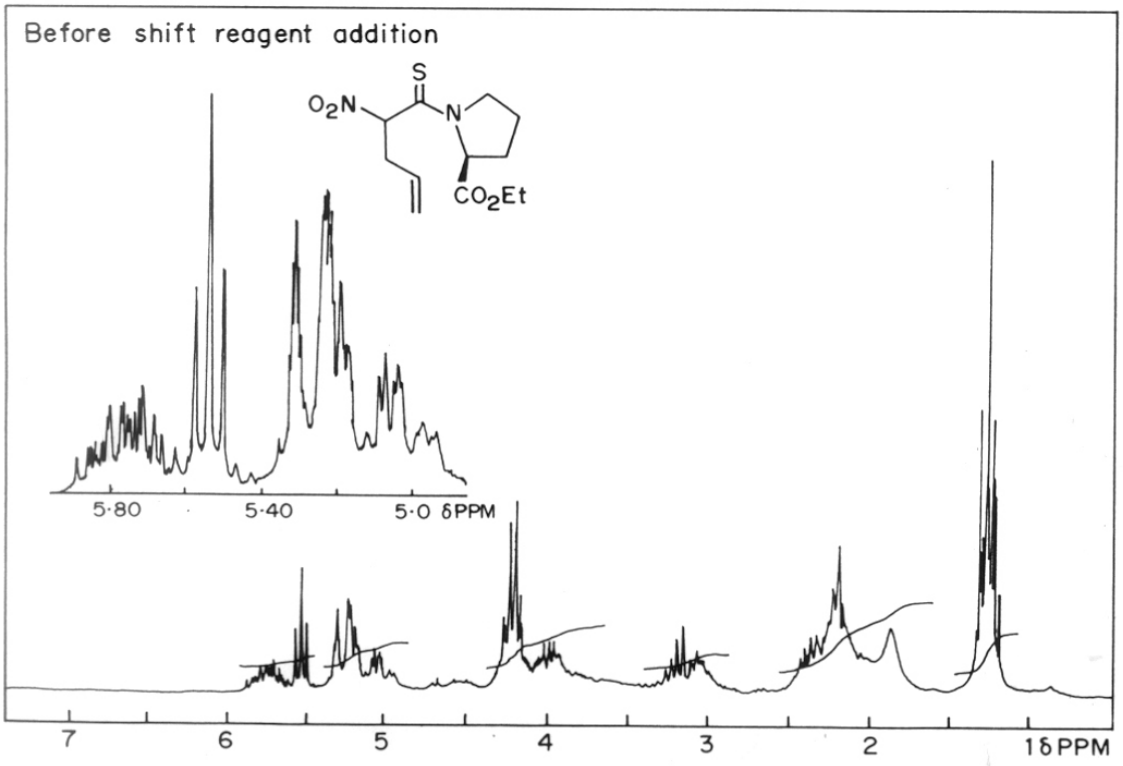
Two chiral shift reagents tris[3-(heptafluoropropyl hydroxy methylene)-(+)-camphorato] Eu(III) derivative and tris[3-(trifluoromethyl hydroxy methylene)-d-camphorato) Eu(III) derivative were tried and similar results were obtained with both these shift reagents. A 7 : 4 ratio of sample to shift reagent was found to be optimum for getting a good spectrum for both the shift reagents.

Under these conditions, in $CDCl_3$ solution, the following changes in the chemical shift of the protons in the oxo analogue were seen (**Spectrum No. 6a**).


After shift reagent addition
Spectrum No. 6a
O
O_2N
N
CO_2Et
5·4 5·2 5·0
δ PPM
5·8 5·6
δ PPM
7 6 5 4 3 2 1 0


Before shift reagent addition
O
O_2N
N
CO_2
5·2
δ PPM
4·2
δ PPM
3·8 3·6
δ PPM
7 6 5 4 3 2 1 0 δPPM


After shift reagent addition
Spectrum No. 6b
6·0
5·50
5·0 δPPM
7
6
5
4
3
2
1 δPPM
0


Before shift reagent addition
S
O2N
N
CO2Et
5·80
5·40
5·0 δPPM
7
6
5
4
3
2
1δPPM

These changes are recorded as $\Delta\delta$ values. An upfield shift of 0.2δ for the NCH_2 protons of the minor diastereomer was observed at 3.65δ. A down field shift of 0.2δ for the O_2NCH triplet of the major diastereomer was observed at 5.2δ.

Table 3. $\Delta\delta$ ***values for Oxo compound***

	NCH_2	O_2NCH
Major diastereomer	No change	Down field shift of 0.2
Minor diastereomer	Up field shift of 0.2	No change

Though slight changes were seen in the other signals of the spectrum, due to complexity of the signals, the exact change in the chemical shift values could not be determined.

In the case of α-allyl N-nitrothioacetylproline ethyl ester (the thio analog) (**Spectrum No. 6b**), the upfield shift of 0.6δ for O_2NCH triplet of the major diastereomer has been observed clearly.

Table 4. $\Delta\delta$ ***values for Thio compound***

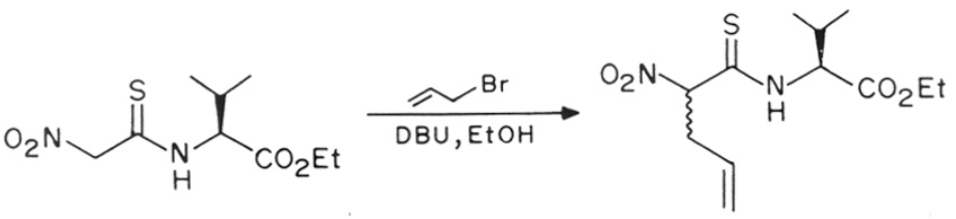
O_2NCH	*Major*	*Minor*
Thio	Upfield shift	No change
Oxo	Downfield shift	No change

The reversal of the $\Delta\delta$ values for the O_2N-C**H** proton of major diastereomers of oxo and thio congeners, gives an unambiguous evidence for the opposite absolute configurations for O_2N-C**H** chiral center of α-allyl N-nitroacetyl and thioacetylproline ethyl esters. The absolute configuration for O_2N-C**H** chiral center of both the diastereomers of α-allyl N-nitroacetylproline ethyl ester is well established; the major diastereomer has the **SS** configuration[23]. Hence the absolute configuration of the major diastereomer of α-allyl N-nitrothioacetylproline ethyl ester is assigned as **RS** the minor diastereomer consequently possesses the **SS** configuration. These assignments are in agreement with the earlier prediction of the stereochemistry based on the ^{13}**C NMR** chemical shift values alone.

3.5. Extension to Valine derivative

To confirm the role of remote asymmetric center, it was planned to carry out the allylation reactions on N-nitrothioacetylvaline ethyl ester(**5**), in which the asymmetric center has more freedom of rotation.

SCHEME-9



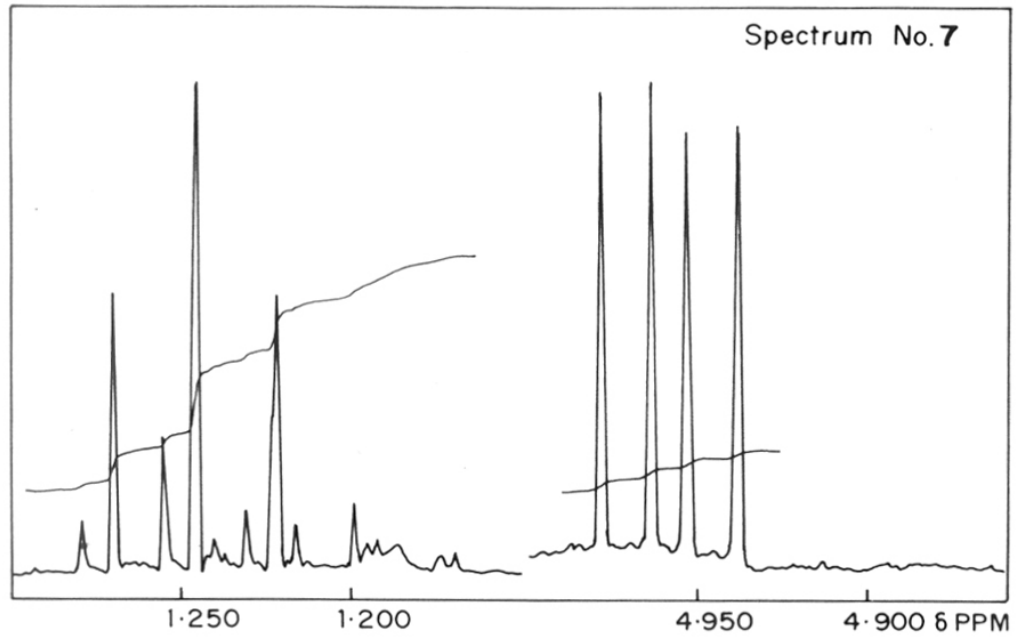
6 **7**

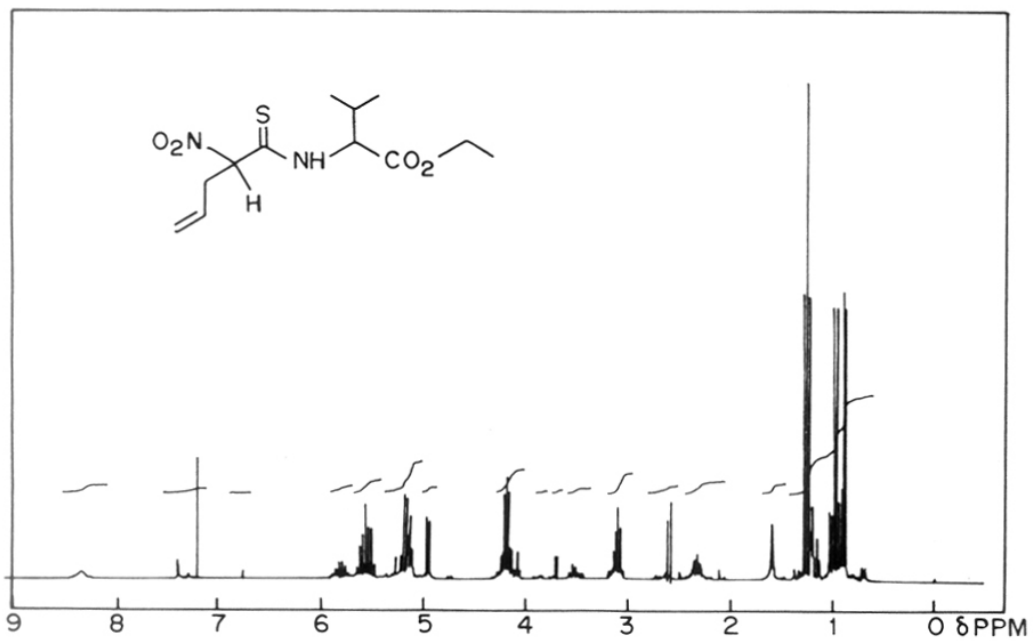
Some changes have been made to the experimental conditions of allylation. In order to make sure the presence of E configuration in the transition state, contents were cooled to -50°c before the allyl bromide addition. Then it was heated to 50°c to complete the thio-Claisen rearrangement. After the usual workup as described in the experimental section, α-allyl N-nitrothioacetyl valine ethyl ester(**6**) was obtained in 57% overall yield. **IR**(neat) spectrum showed a broad peak at 3310 cm^{-1} for NH group, 1740 cm^{-1} for ester carbonyl, a weak peak at 1650 cm^{-1} for C=C and strong peaks at 1570 and 1320cm^{-1} corresponding to nitro group. The major diastereomer showed 2 doublets in $_1$H NMR spectrum (**Spectrum No. 7**)

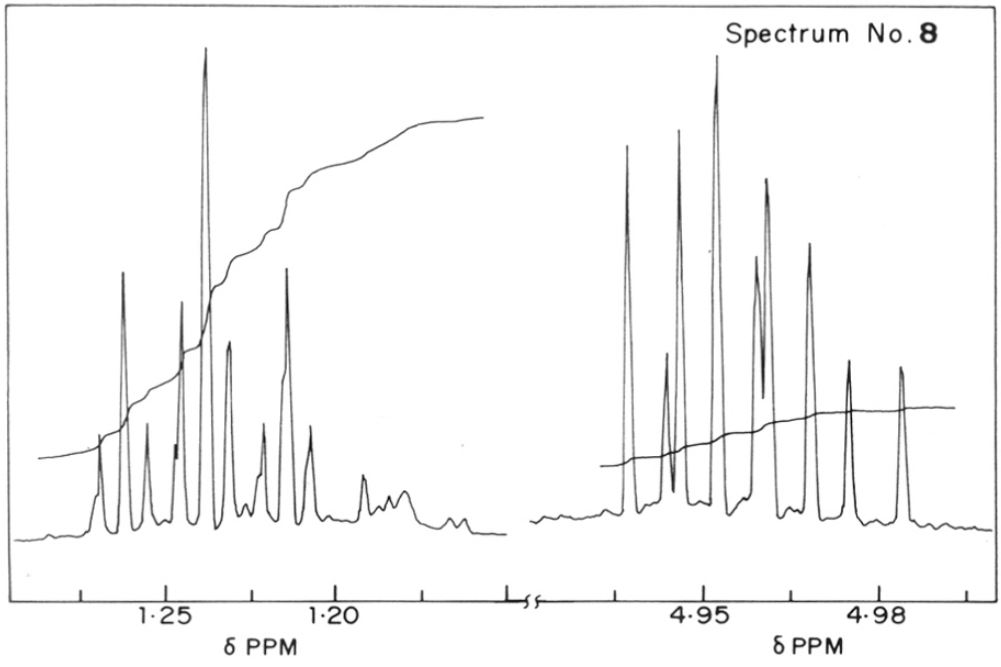
for 2 methyls of isopropyl group at 0.88 and 0.90δ a triplet at 1.25δ for Me of ester group, a multiplet at 2.32δ for $Me_2C\mathbf{H}$ and two multiplets at 3.1 and 4.1δ were assigned to =C-C**H** and O-C$\mathbf{H}_2$ protons, a doublet of doublet which becomes a doublet on D_2O exchange is assigned for N-C**H** proton and multiplets at 5.19δ is for =C**H** and O_2N-C**H**, and other multiplets at 5.5 and 5.8δ were assigned to =C$\mathbf{H}_2$ and a broad peak at 8.35δ for N**H** proton.

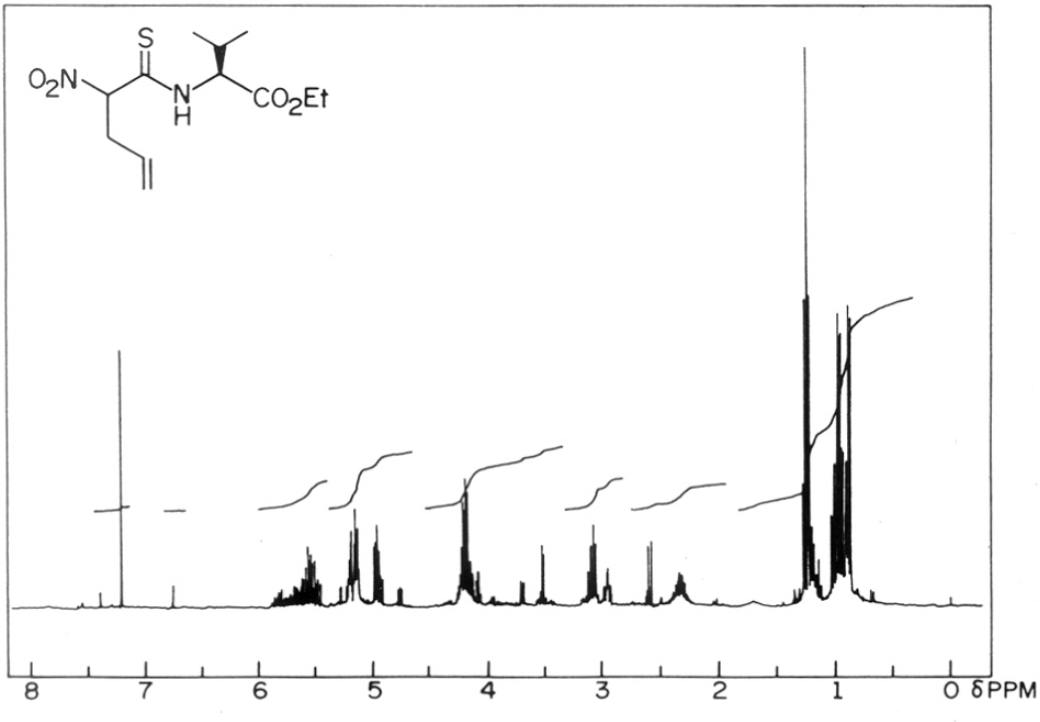
The signal assignment for minor diastereomer is as follows, 0.96, 0.99 (2d, 6H, 2Me), 1.26 (t, 3H, Me), 2.32 (m, 1H, Me2C**H**), 2.95 (m, 2H, =C-C$\mathbf{H}_2$), 4.2 (m, 2H, OC$\mathbf{H}_2$), 4.99 (dd, 1H, NC**H**), 5.19 (m, 2H, =C$\mathbf{H}_2$), 5.7 and 5.8 (m, 2H, =C**H** and O_2N-C**H**) and 8.75 (b, 1H, N**H**). **MS**(m/e): 288(M^+), 258, 242, 97(100%).

The signals for Me protons of ester group, $Me_2C\mathbf{H}$ protons and N**H** protons of both diastereomers were considered for the calculation of *de*, which was found to be 33% (**Spectrum No. 8**).


Spectrum No. 7
1·250
1·200
4·950
4·900 δ PPM

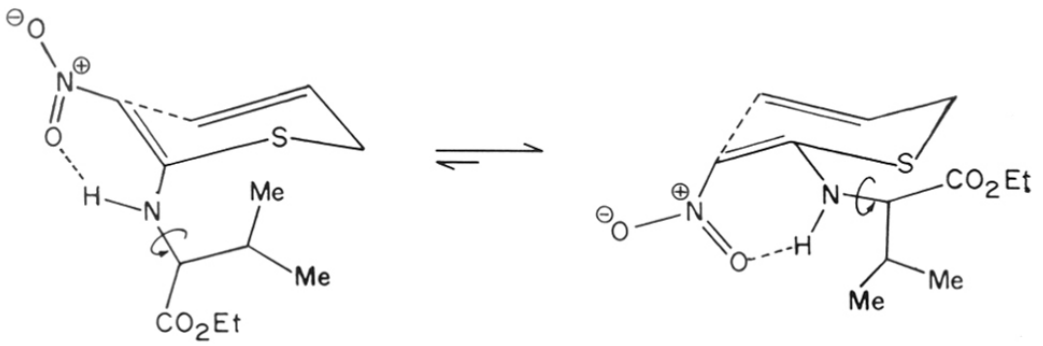

O2N
S
NH
CO2
H
9
8
7
6
5
4
3
2
1
0 δ PPM


Spectrum No. 8
1·25
1·20
δ PPM
4·95
4·98
δ PPM


S
O2N
N
H
CO2Et
8
7
6
5
4
3
2
1
0 δPPM

The considerable drop in *de* compared to proline derivative cannot be simply attributed to the geometry of vinylic double bond or transition state geometry. Nitrovinylamines possessing an NH, because of the stabilizing force (intra molecular H-bonding) the preferred configuration[33] is expected to be the one which involves H-bonded form, hence the transition state for the thio-Claisen rearrangement with the valine derivative is likely to have E-configuration for the vinylic double bond. The rearrangement can proceed from both chair arrangements in the transition state (**Scheme 10**).

SCHEME-10



Ch-1 Ch-2

Obviously Ch-2 is preferred over the Ch-1. However, unlike in proline moiety the original chiral center is free to rotate around N-C bond in the valine derivative. The original chiral center is supposed to block the ***Si*** face of the vinylic double bond of both the chair forms. But, because of freedom of rotation of the original chiral center, the ***Si*** facial migration of allyl group is less affected by the steric crowding. Hence, the drop in *de* was observed.

The efforts to perform thio-Claisen rearrangement on other esters of valine were not successful because of the highly labile nature of these nitrothioacetamides. The reaction with other allyl bromides like crotyl, prenyl bromides were also not successful, the products obtained were the corresponding carbonyl compounds of nitrothioacetamides obtained by hydrolysis. It is evident that with these allyl bromides S-allylation is occurring but may be because of steric crowding near C_1 carbon hindering the rearrangement.

3.6. Effect of push-pull system on thio Claisen rearrangement

A desired pericyclic transformation may require too high a temperature for the survival of sensitive functional groups. One approach to solving this problem would be to control the reaction rate by selection of substituents with appropriate electronic properties. The influence of certain types of substituents on the rates of pericyclic reactions have been elegantly demonstrated[35,36]. But so far it is not clear which electronic properties of the substituent at a given position accelerate (or decelerate) the pericyclic reaction. With the aim of contributing to the subject, the effect of the incorporation of donor - acceptor system on thio-Claisen rearrangement has been studied.

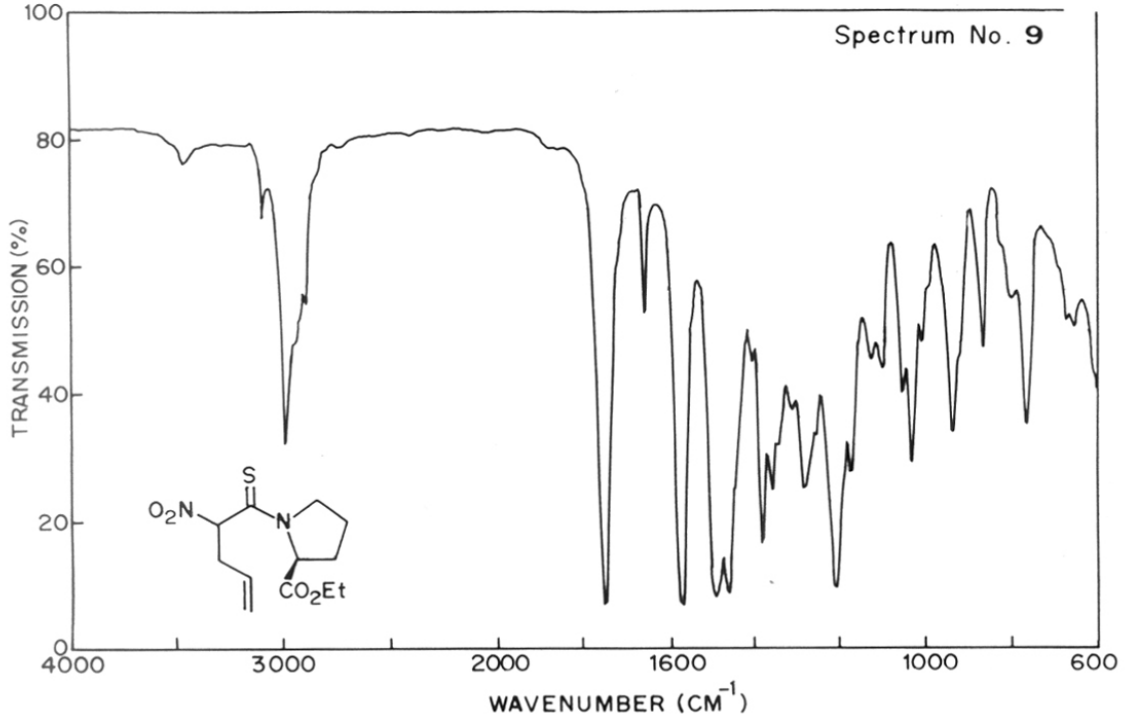
Uncatalysed thio-Claisen rearrangements generally proceed at very high temperatures ranging from 150-200°c. But the above described thio-Claisen rearrangements were carried out at 50-55°c. One would expect increased delocalisation in the transition state, since by definition, a pericyclic reaction proceeds through a transition state involving a cycle of completely conjugated orbitals. Hence the push - pull system, which is a part of the transition state, is expected to have it's own influence. Any simplistic picture is insufficient to explain the accelerating potential of any substituent. The model presented by B.K. Carpenter[36], is based on the assumption that the change in degree of delocalisation is the sole determinant of the substituent influence on the reaction rate. The theory predicts rate enhancement when the π electron donating substituent is positioned at C_2 carbon. In this thio-Claisen rearrangement the electron donor proline ester moiety is on C_2 carbon and according to Carpenter's model it should accelerate the rate of rearrangement. The

same model predicts a moderate rate deceleration by the electron withdrawing substituent at C_1 carbon. However, our results show an acceleration in the rate of rearrangement. This is probably because, the pull - push groups together have a different influence than the electron withdrawing group alone.

In a different model by Gajewski[37] for substituent effects on the rates of Claisen and Cope rearrangement, two extreme biradical structures were considered for 3,3-sigmatropic shift. Substituents might change the energy of transition state by selective stabilization of one of the biradical extremes. So, the effect of a group will be discussed in terms of its radical stabilizing properties rather than its acceptor or donor properties. According to this model the radical stabilizing substituent on C_1,C_4 and C_6 will stabilize the transition state to a greater extent[38].

Another theory, *i.e.* resonance theory[39] simply involves choosing the appropriate transition state valence model and counting the number of resonance structures. More the number of resonance structures, greater the stability of transition state. As the push and pull groups are in conjugation on C_2 and C_1 carbons of the transition state framework, they are expected to stabilize the transition state by resonance. Hence the push pull system facilitates the thio-Claisen rearrangement.

It is interesting to note that the only other reported thio-Claisen rearrangement proceeding with such ease also involves a push-pull system[40]. Ethyl 5-cyano-1,4-dihydro-2-methyl-4-phenyl-6-allylthio-3-pyridinecarboxylate, in ethanol undergoes thio Claisen rearrangement at 78°c to afford Ethyl-5-cyano-1,4,5,6-tetrahydro-2-methyl-4-phenyl-5-allyl-6-thioxo-3-pyridinecarboxylate. Perhaps the push - pull system of consisting amino and cyano groups facilite the rearrangement in this case too.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60
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20
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2000
1600
1000
600
WAVENUMBER (CM^{-1})
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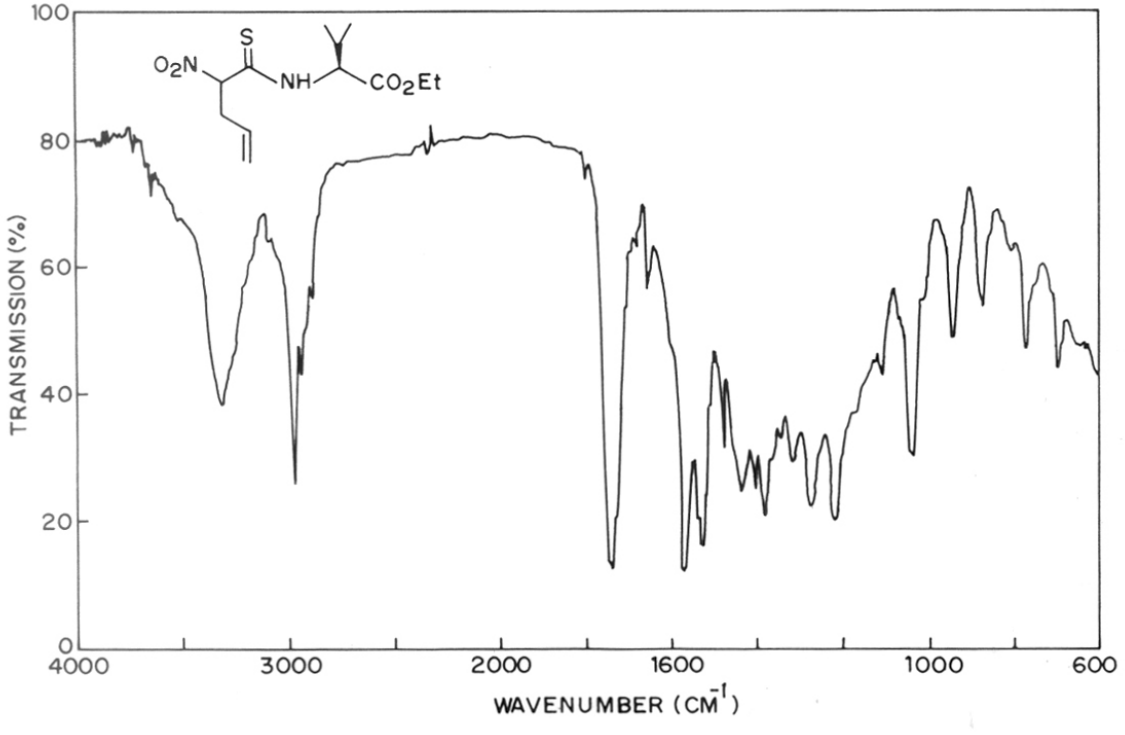
O_2N
N
CO_2Et


100
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40
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0
TRANSMISSION (%)
4000
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1600
1000
600
WAVENUMBER (CM^{-1})
S
O_2N
NH
CO_2Et

3.7. Experimental Section

Synthesis of α-allyl N-nitrothioacetylproline ethyl ester (5a): N-Nitrothioacetyl proline ethyl ester (350 mg) was taken into degassed dry EtOH (15 ml), DBU (1.1 eq.) in 5 ml was added and stirred at rt. for 0.5hrs. under nitrogen atmosphere. Allyl bromide (1.2 eq.) in EtOH (5ml) was added to it and stirred at 55°c for 4hrs. Solvent was evaporated and the product was purified by passing through short silica gel column (cyclo hexane as eluent) to get 90% of the pure product. Gum; **IR**(neat): 2880-3000, 1750, 1650, 1570, 1490, 1470, 1380, 1210cm^{-1}; **^{1}H NMR**($CDCl_3$): 1.28 (1.23) [t, 3H, Me], 2.1 - 2.4 [m, 4H, $2CH_2$], 2.98-3.2 [m, 2H, =C-CH_2], 4.02-4.17 [m, 2H, NCH_2], 4.19-4.25 [m, 2H, OCH_2], 5.0-5.1 (4.92-4.98) [m, 1H, NCH], 5.16-5.29 [m, 2H, $=CH_2$]; **^{13}C NMR**($CDCl_3$): 13.76 (13.65), 24.41 (22.09), 28.65 (27.59), 37.46 (37.00), 51.62 (50.96), 61.11 (62.20), 65.72 (65.95), 88.83 (89.13), 119.73 (119.90), 130.37 (130.46), 169.06 (168.92), 190.29 (189.46); **MS**(m/e): 286(M^+), 256, 240, 144, 142, 97, 70(100%); **Found**, C,50.72, H,6.54%, **calculated** for $C_{12}H_{18}N_2O_4S$, C,50.34, H,6.29%.

α-allyl N-nitrothioacetylproline benzyl ester (5b): This compound was synthesized by following the same procedure as described above, gum, yield: 58%, **IR**(neat): 1740, 1650, 1560, 1470, 1450, 1200; **^{1}H NMR** ($CDCl_3$): 2.00-2.41 (m, 4H, $2CH_2$), 2.90-3.33 (m, 2H, =C-CH_2), 3.81-4.09 (3.72-4.23) [m, 2H, NCH_2], 5.11 (4.97) [m, 1H, NCH], 5.14 - 5.31 [m, 4H, OCH_2, $=CH_2$], 5.49 (5.52) [t, 1H, O_2N-CH], 5.62-5.76 [m, 1H, =CH]; **^{13}C NMR**($CDCl_3$): 24.59 (24.59), 28.76 (28.76), 37.71 (37.25), 51.62 (51.62), 65.85 (66.08), 67.07 (67.07), 89.93 (88.03), 119.87 (120.12), 128.15, 128.33, 128.41, 128.66, 130.56, 135.08, 169.18 (168,90), 190.43 (190.01); **MS**(m/e): 348(M^+), 318, 302, 152, 123, 108, 91(100%); **Found**, C,58.95, H,5.83% , **calculated** for $C_{17}H_{20}N_2O_4S$, C,58.62, H,5.75%.

α-allyl N-nitrothioacetylvaline ethyl ester (7): N-ntrothioacetyl valine ethyl ester (262 mg) was taken into degassed dry EtOH (10 ml), DBU (1.1 eq.) was added to the solution and stirred at rt. for 15mts. Then cooled to -50°c and allyl bromide (152 mg) was added.

Slowly temperature was raised to 50°c and stirred for 3hrs. The reaction was monitored by tlc, solvent was evaporated and passed through short silica gel column (pet ether : ethyl acetate, 9.5:0.5), which yielded 57% of the product.

Gum, **IR**(neat): 3310, 1740, 1650, 1570, 1530, 1320; **^{1}H NMR** ($CDCl_3$): 0.90, 0.88 (0.99, 0.96) [2d, 6H, 2Me], 1.25 (1.26) [t, 3H, Me], 2.32 [m, 1H, Me_2CH], 3.1 (2.95) [m, 2H, =C-CH_2], 4.1 (4.2) [m, 2H, OCH_2], 4.95 (4.90) [dd, 1H, NCH], 5.19 [m, 2H, =CH_2], 5.50,5.80 (5.7O,5.80) [m, 2H, =CH and O_2N-CH], 8.75 (b, 1H, NH]; **MS**(m/e): 288, 258, 254, 242, 144, 114, 97(100%); **Found**, C,50.40, H,7.1, **calculated** for $C_{12}H_{20}N_2O_4S$, C,50.00, H,6.94%.

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CHAPTER 4

Designing Organinc Molecules for Non Linear Optics

4.1. Introduction

Nonlinear optical(NLO) properties arise as the result of the interactions of electromagnetic fields in various media. They produce new fields altered in phase, frequency, amplitude, or other propagation characteristics from the incident fields. Electromagentic radiation can be regarded as an oscillating electrical field. When a light beam (a form of electromagnetic radiation) is incident on, for example, an inorganic crystal, the ions in the crystal lattice are polarized and oscillate with the radiation. This polarization of ions in turn induces a small electrial field. This induced electrical field alters the direction of the electrical field of the incident light. In linear optics the polarization is proportional to the incident radiation and is responsible for phenomena such as refraction and reflection of the light. However, a laser beam may have a peak field strength of 10^7 v/m which is comparable to the forces binding the ions together in a crystal lattice. Thus polarization induced by laser can induce highly nonlinear oscillations. In other words the polarization is not proportional to the field strength of the incident radiation. This gives rise to the nonlinear phenomena such as optical mixing and harmonic generation.

The traditional linear optics are based on optical phenomena arising from the interaction between light and materials. The optical properties like refractive index, of these materials are independent of the intensity of incident light intensity. But in nonlinear optics the optical properties of the material are a function of the electric field strength of high intensity light (*i.e.* a laser) or an externally applied electric field. These materials are useful for applications in nonlinear optics such as second-harmonic generation (SHG, *i.e.* doubling the frequency of laser radiation) and electro optic phase modulation. The important second order nonlinear optical effects are the frequency doubling (or second harmonic generation, SHG), optical rectification and Pockels effect. SHG is the conversion

of coherent light of frequency ω into light of frequency 2ω. Optical rectification is the ability to induce a direct current(DC) voltage between electrodes placed on the surface of the crystal when an intense laser beam is directed into the crystal. Pockels effect (or linear electro optic effect) is manifested when a DC field is applied to a medium through which an optical wave propagates. All these effects arise through the hyperpolarisability, β of a crystal. The degree to which a material exhibits macroscopic second order nonlinear optical properties is dependent upon the microscopic nonlinear polarizabilities of the constituent molecules.

The origin of macroscopic NLO phenomena is given by the familiar equation 1. The bulk polarization[1] (P) of the material can be expressed as a power series of the applied electric field strength (E).

$$P = \chi^{1}_{IJ} E + \chi^{2}_{IJK} E^2 + \chi^{3}_{IJKL} E^3 + ... \qquad 1$$

The coefficients χ^{1}_{IJ}, χ^{2}_{IJK}, χ^{3}_{IJKL} in the above equation are the first-, second- and third-order susceptibilities. The IJKL.., refer to the coordinate system of the bulk material.

On a microscopic level, a similar expression can be written for the polarizability of a *molecule* in an applied electric field[2].

$$p_i = \alpha_{ij} E_j + \beta_{ijk} E_j E_k + \gamma_{ijkl} E_j E_k E_l + ... \qquad 2$$

The coefficients α_{ij}, β_{ijk}, γ_{ijkl} are the first-, second- and third-order polarizabilities and E_{ijk}... refer to the components of the applied field. Like macroscopic susceptibilities, the molecular hyperpolarizabilities are also tensorial quantities and they are determined by the geometry and electronic structures of the molecule.

The two state model expresses hyperpolarizability β interms of measurable spectroscopic and photophysical parameters. This model has been shown to give reasonable estimates of β for a number of organic molecules[3].

$$\beta = \frac{3\Delta\mu_1 m_1^2}{2h^2} \cdot \frac{\omega_1^2}{(\omega_1^2 - 4\omega^2)(\omega_1^2 - \omega^2)} .... \qquad 3$$

In this expression, ω_1 is the energy gap between the ground state and excited state. ω is the frequency of the incident (laser) light beam, $\Delta\mu_1$ is the dipole moment change between the ground state and excited state and m_1 is the transition moment for the optical transition between the two states. From the equation 3 it is evident that the hyperpolarizability (β) is a function of excited state properties of the molecule. In order to maximize β, it is necessary to maximize the absolute value of the induced dipole moment $\Delta\mu_1$.

Origin of opical nonlinearity in organic materials

Interst in organic materials has steadily grown since the 1980s. This is due to their potentially superior properties over inorganic compounds. In inorganic crystals the optical nonlinearity originates from oscillations of positive and negative ions. These ions have relatively large masses, hence the speed of oscillation and displacement are restricted. The origin of nonlinear optical phenomena in organic materials lies in their conjugated π-electrons. This phenomenon involves the complete transport of electrons. It is well known that the electron density of a π-bond is mobile. Hence the electron distribution can be perturbed very easily by the interaction with a radiation field produced by a laser. Therefore the NLO responses of organic molecules are both fast and large in magnitude compared to the inorganic solids. Virtually all organic NLO molecules contain π bonds such as the single short polar π-bond of the carbonyl as in urea or a more extended series of π-bonds as in benzene and substituted benzene.

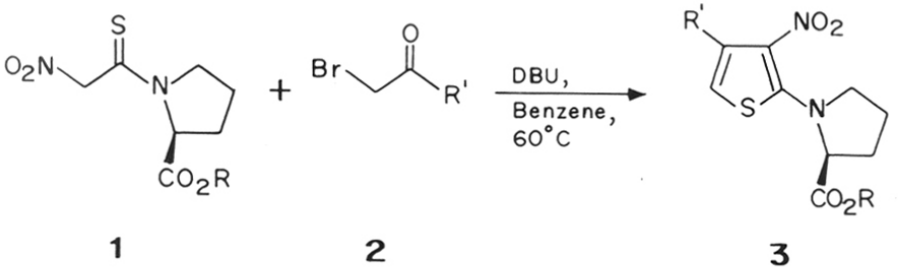
Molecular Engineering: Molecular engineering can be defined as the planned synthesis of materials providing the simulataneous optimization of molecular and crystal properties responsible for SHG. The first step involved is the design of an active molecule with high hyperpolarizability. The second step is to get an optimized crystal packing of the active molecule, *i.e.* the crystal should have a non cetrosymmetric structure.

4.2. Results

The synthesis of thiophene derivatives from N-nitrothioacetylpyrrolidine and phenacyl bromide or bromoacetone was discussed in the second chapter. Similar reaction

with N-nitrothioacetylproline ethyl ester and phenacyl bromide or bromoacetone afforded 2-(ethyl N-prolinyl)-3-nitro-4-alkyl/aryl thiophenes.

SCHEME-1



1 2 3

a) R = Et , R' = Ph c) R = Et , R' = Me

b) R = Bz , R' = Ph d) R = Et , R' = Ph $-NO_2$

i) 2-(Ethyl N-prolinyl)-3-nitro-4-phenylthiophene (**3a**): The experimental procedure for the synthesis of this compound is described in the experimental section (**Scheme 1**). It was obtained as a gum in 65% yield, $[\alpha]_D^{MeOH} = -250.93°$. In the infrared spectrum of this compound a peak at 1740cm^{-1} was observed for the ester carbonyl of proline moiety and a weak peak was seen at 1680^{-1} corresponding to olefinic CH stretching frequency. The peaks corresponding to nitro group stretching frequencies were seen at 1550 and 1380cm^{-1}. In the ultraviolet absorption spectrum, the compound showed an intense absorption band at λ_{max} 405nm,(ε: 1.94×10^5). This intense broad low energy transition of the donor-acceptor thiophene derivative was assigned to the intramolecular charge transfer (ICT) resulting from the donor (proline moiety nitrogen) to the acceptor (nitro) group. In addition to this broad ICT band, an intense transition at λ_{max} 234nm (ε: 1.56×10^6) was also observed and this was assigned to a π - π^* transition. The n - π^* transition band was not observed for

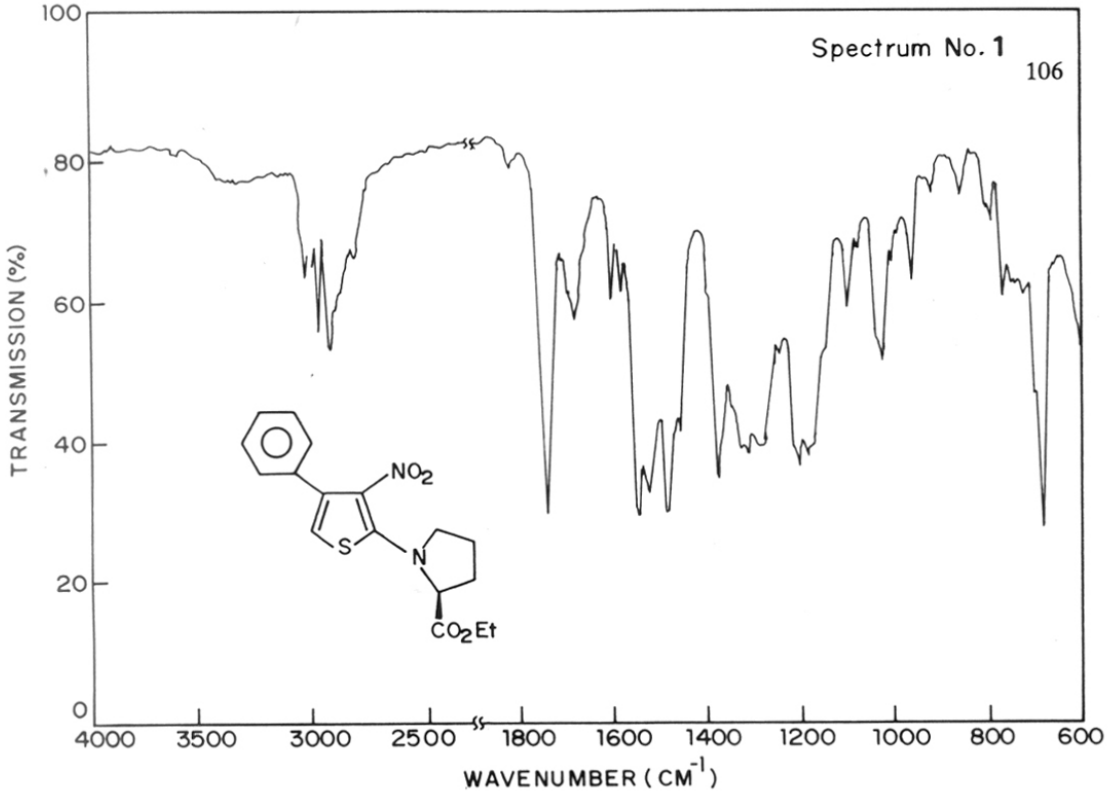
this compound. In the ^{1}H NMR spectrum (**Spectrum No. 1**),

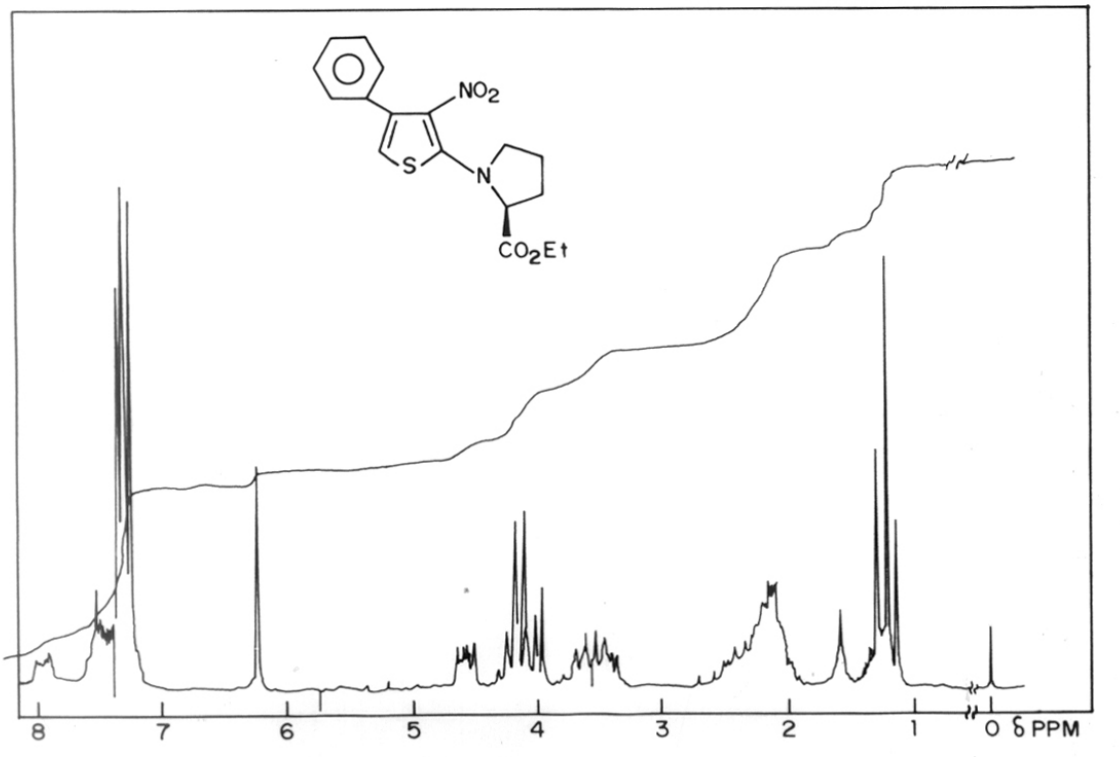
a triplet at 1.22δ was assigned for the protons of the methyl group, a multiplet at 2.13δ was assigned to the four protons on β and γ carbons of proline ring; the multiplet at 3.58δ was assigned to NCH_2 group protons and a quartet at 4.11δ to the OCH_2 group protons. The NCH proton showed up as a multiplet at 4.60δ. A sharp singlet was seen at 6.24δ for the lone proton of thiophene ring. The five protons of phenyl ring occured as a multiplet at 7.31δ. In the ^{13}**C NMR** spectrum in $CDCl_3$ (**Spectrum No. 2**), the signal assignment was made on the the basis of chemical shift values and the results of an INEPT experiment. The signal at 13.74ppm was assigned to the methyl group carbon, and the signals at 23.81 and 30.96 were assigned to the β and γ carbons of the proline moiety. The signals at 53.68 and 63.83 were assigned to the α and δ carbons. The signal at 61.19 was assigned to the OCH_2 group carbon and the signal at 106.61 for the C-5 carbon of the thiophene ring. The signals at 127.44, 127.82, 128.12, 128.45 were assigned to the phenyl ring carbons. The signals at 135.42, 137.64 and 154.62 were assigned to C-2, C-4 and C-3 carbons of the thiophene ring. The ester carbonyl was seen at 171.23ppm. The structure of the compound was further confirmed by its mass spectrum, in which the molecular ion peak was observed at 346(m/e); **MS**(m/e): 273, 212, 142, 141, 139 (100%). The compound analysed for $C_{17}H_{18}N_2O_4S$.

ii) ***2-(Benzyl N-prolinyl)-3-nitro-4-phenylthiophene*** (**3b**):

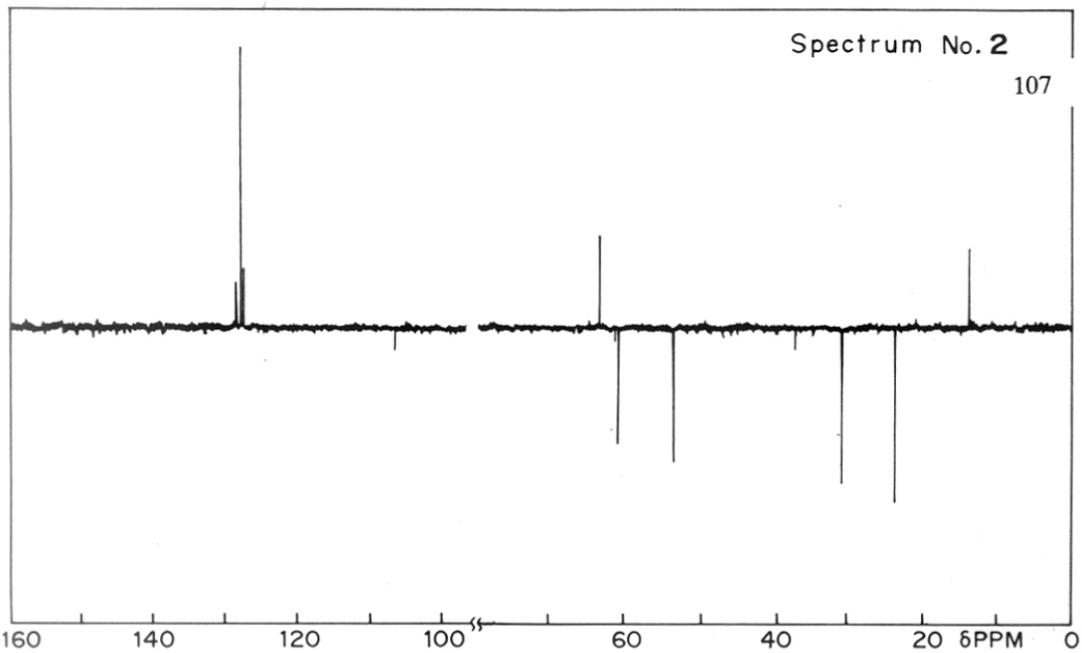
This compound was synthesized as described in the experimental section. The product was obtained as a thick gum in 60% yield; $[\alpha]_D^{MeOH}$ = -262.35°. In the infrared spectrum of this compound, a peak was seen at 1740cm^{-1} for the ester carbonyl group and the peaks at 1510 and 1370cm^{-1} corresponding to the nitro group stretching frequencies were observed. In the ^{1}**H NMR** spectrum (**Spectrum No. 3**),

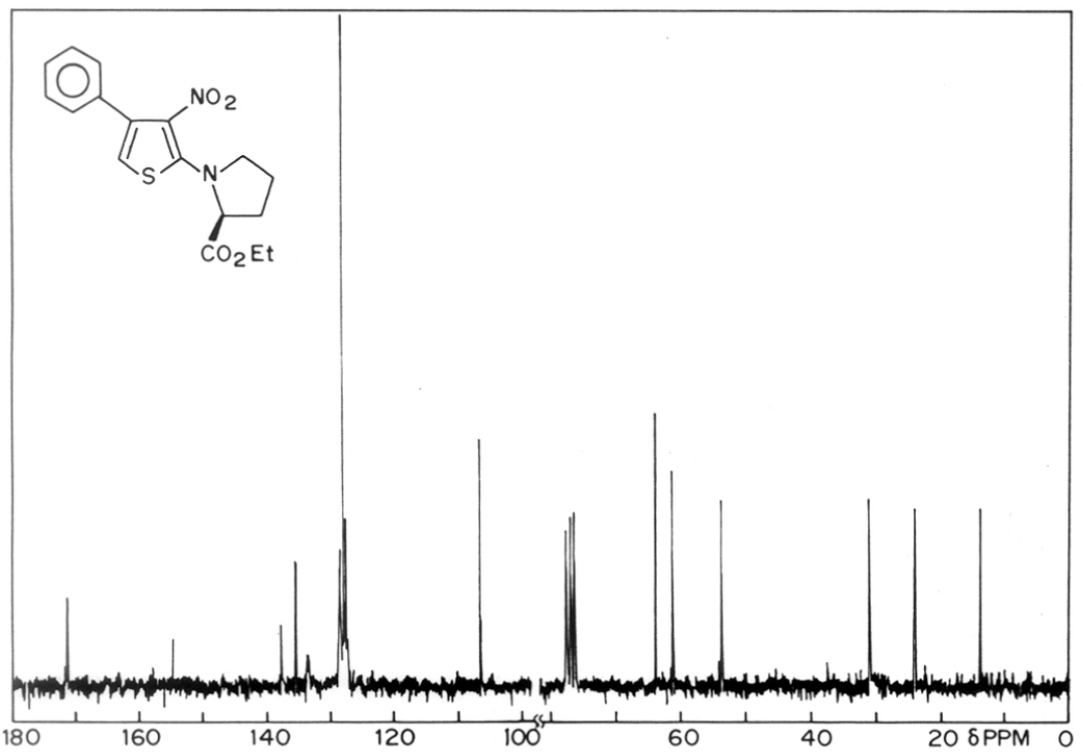
Spectrum No. 1

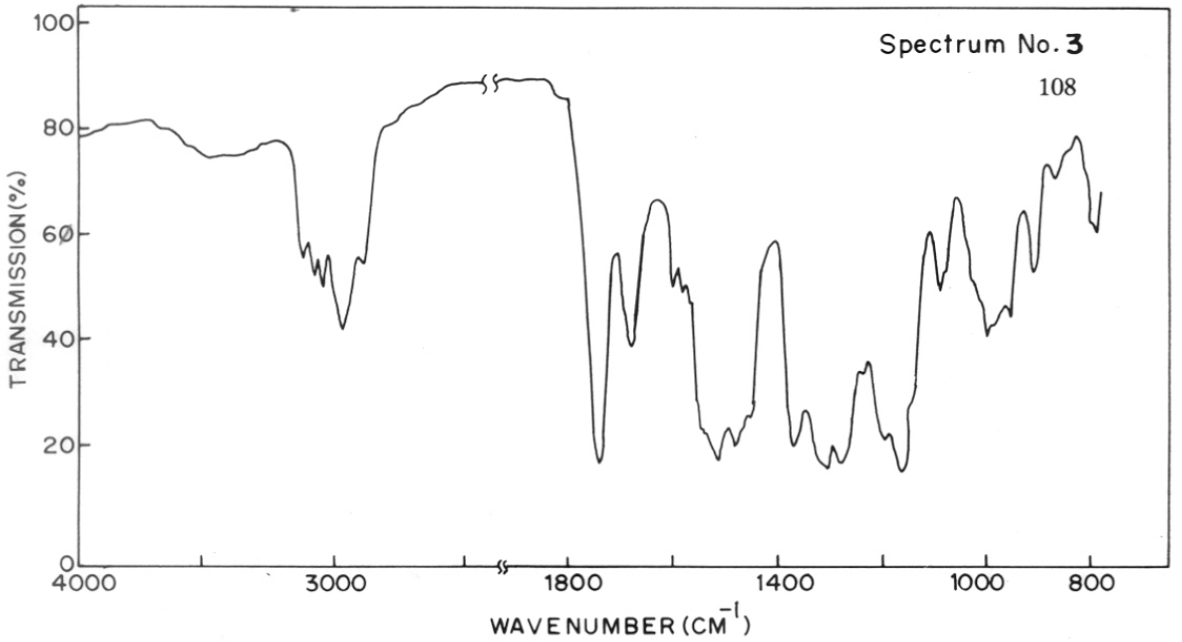




Spectrum No. 2






Spectrum No. 3
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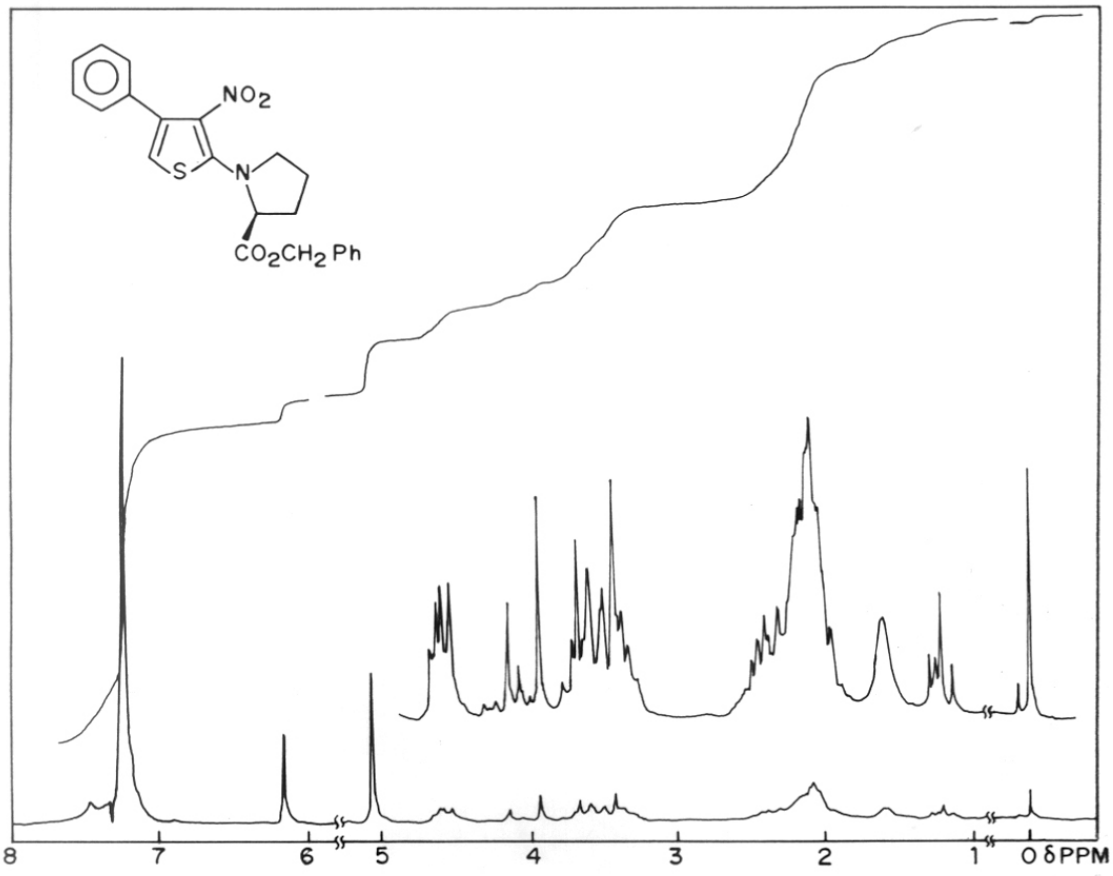
3000
1800
1400
1000
800
WAVENUMBER (CM⁻¹)


NO2
S
N
CO2CH2Ph
8
7
6
5
4
3
2
1
0 δPPM

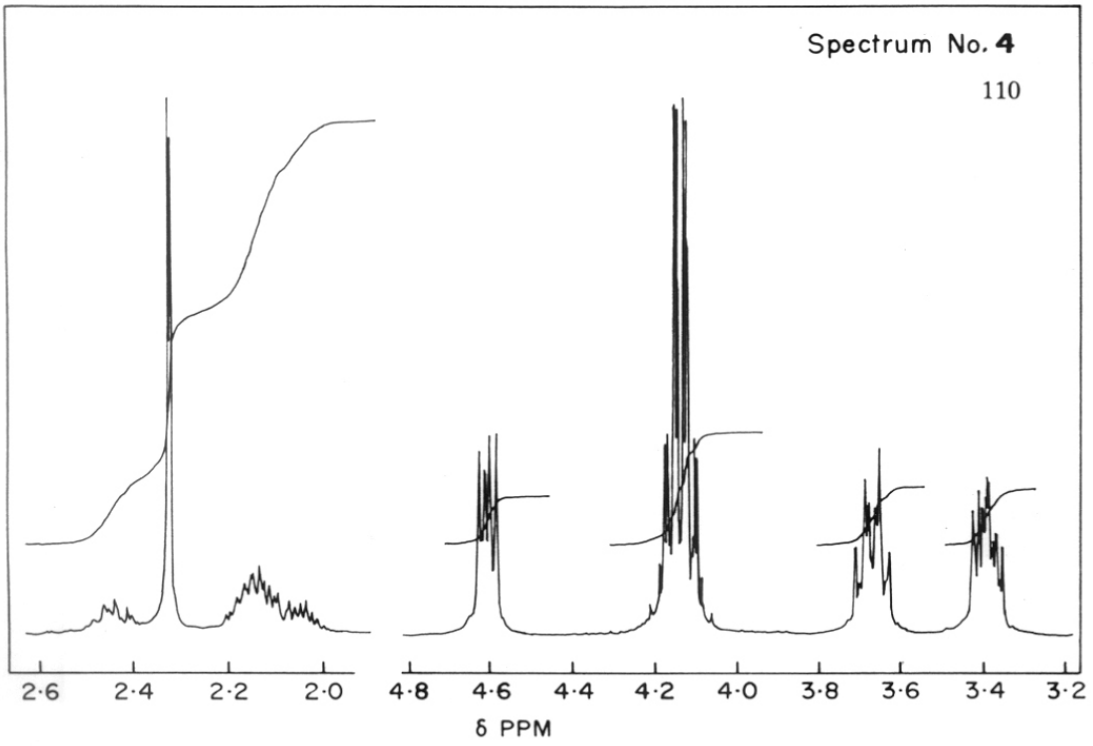
the multiplet at 2.07δ was assigned to the four protons on β and γ carbons on the proline ring. The multiplet at 3.53δ was assigned to the NCH_2 group protons, the multiplet at 5.07δ for the OCH_2 group protons and a sharp singlet at 6.16δ for the olefinic proton of the thiophene ring. The multiplet at 7.22δ was assigned for the protons of two phenyl rings; In the **^{13}C NMR** spectrum, the signals at 23.76, 30.03, 53.64 and 63.79 were assigned to the β, γ, α and α carbons of the proline moiety respectively and the signal at 66.93 was assigned to the benzylic carbon. The signal at 106.50 was assigned to the C-5 carbon of the thiophene ring. The signals at 127.40, 127.77, 127.84, 128.04, 128.25 and 128.39 were assigned to the carbons of phenyl rings. The signals at 135.07, 137.53and 135.26 were assigned to the C-2, C-3 and C-4 carbons of the thiophene ring. The signal at 171.06 was assigned to the carbon of the ester carbonyl group. The structure was further confirmed by the observation of molecular ion peak at 408 in the mass spectrum. **MS**(m/e): 346, 332, 273 (100%), 237, 135, 105, 91, 77. The compound analysed for $C_{22}H_{20}N_2O_4S$.

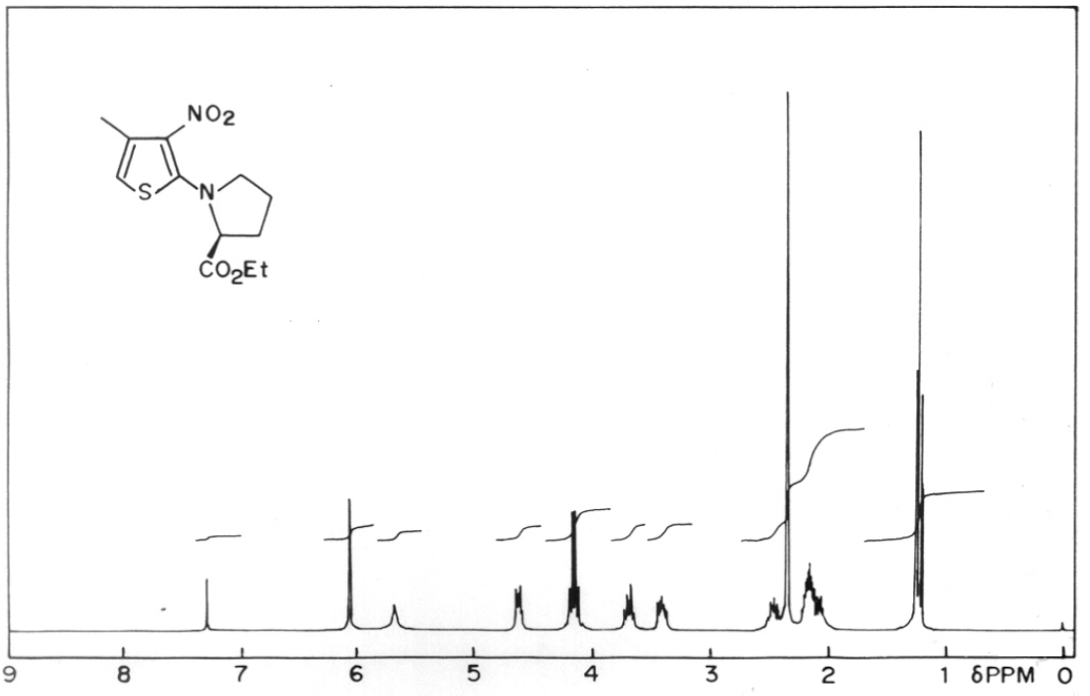
iii) ***2-(Ethyl N-prolinyl)-3-nitro-4-methylthiophene*** **(3c)**:

The synthesis of the compound is discussed in the experimental section. The compound was obtained as an orange coloured liquid in 70% yield; In the infrared spectrum, the peaks were seen at 2900-3000, 1750, 1560, 1530, 1380cm^{-1}; $[\alpha]^{MeOH}$ = -556.48°. In the ultraviolet absorption spectrum, the broad intense band at λ_{max} 416nm (ε 4.1×10^5) was assigned to the donor to acceptor intramolecular charge transfer transition and another band at 256nm (ε 0.97×10^6) was assigned to the $\pi - \pi^*$ transition. In the **^{1}H NMR** spectrum (**Spectrum No. 4**),

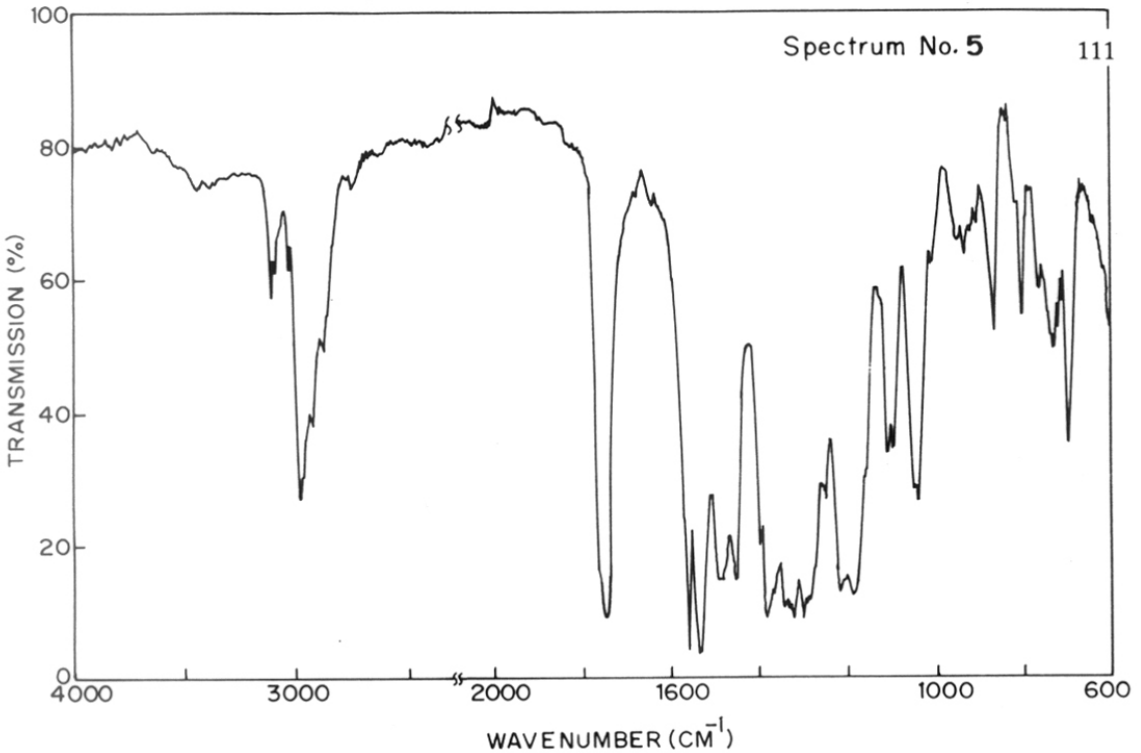
the triplet at 1.16δ was assigned to the methyl group protons. A set of multiplets at 2.108, 2.138 and 2.44δ were assigned to the four protons on the β and γ carbons of the proline moiety. A doublet at 2.35δ was assigned to =C-CH_3 protons, the coupling between these protons and the proton on C-5 carbon of thiophene ring was observed. The multiplets at 3.40 and 3.65δ were assigned to the two protons of NCH_2 group. The quartet at 4.09δ was assigned to the OCH_2 group protons. The multiplets at 4.65 and 6.04δ were assigned to

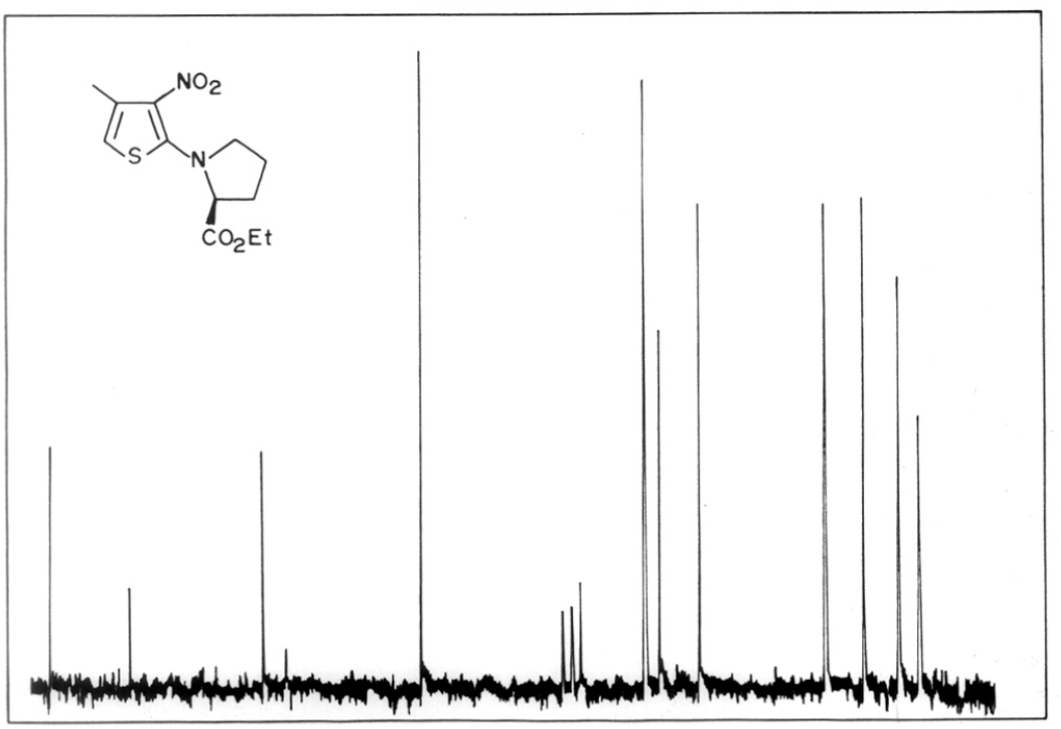
Spectrum No. **4**





Spectrum No. **5**





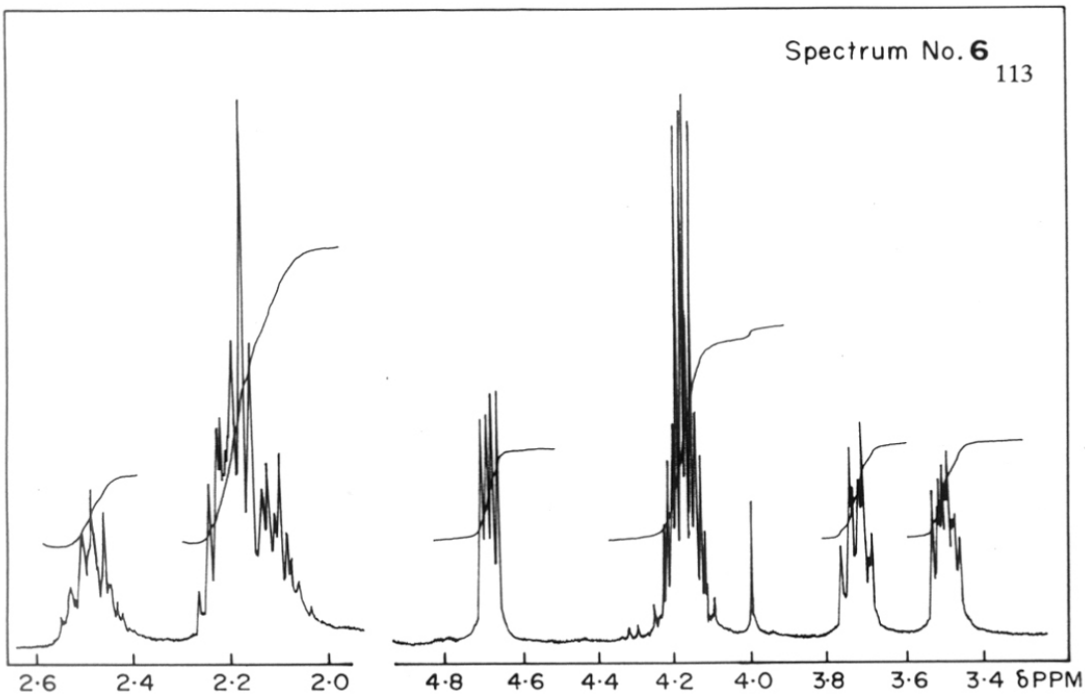
the protons of NCH and =CH groups respectively. In the ^{13}C **NMR** spectrum (**Spectrum No. 5**), the signals at 13.50 and 17.30 were assigned to the carbons of two methyl groups, the latter one being attached to the thiophene ring. The signals at 23.74, 30.39, 54.02 and 60.96 were assigned to the β, γ, α and δ carbons of the proline moiety. The signal at 63.64 was assigned to the carbon of OCH_2 group. The signals at 132.89, 156.58, 63.76 and 104.25 were assigned to the C-2, C-3, C-4, C-5 carbons of the thiophene moiety. The structure of the compound was confirmed by the observation of molecular ion peak at 284. **MS**(m/e) : 284(M^+), 211(100%), 193, 177, 165, 151, 139, 126 and 71. The compound analysed for $C_{12}H_{16}N_2O_4S$.

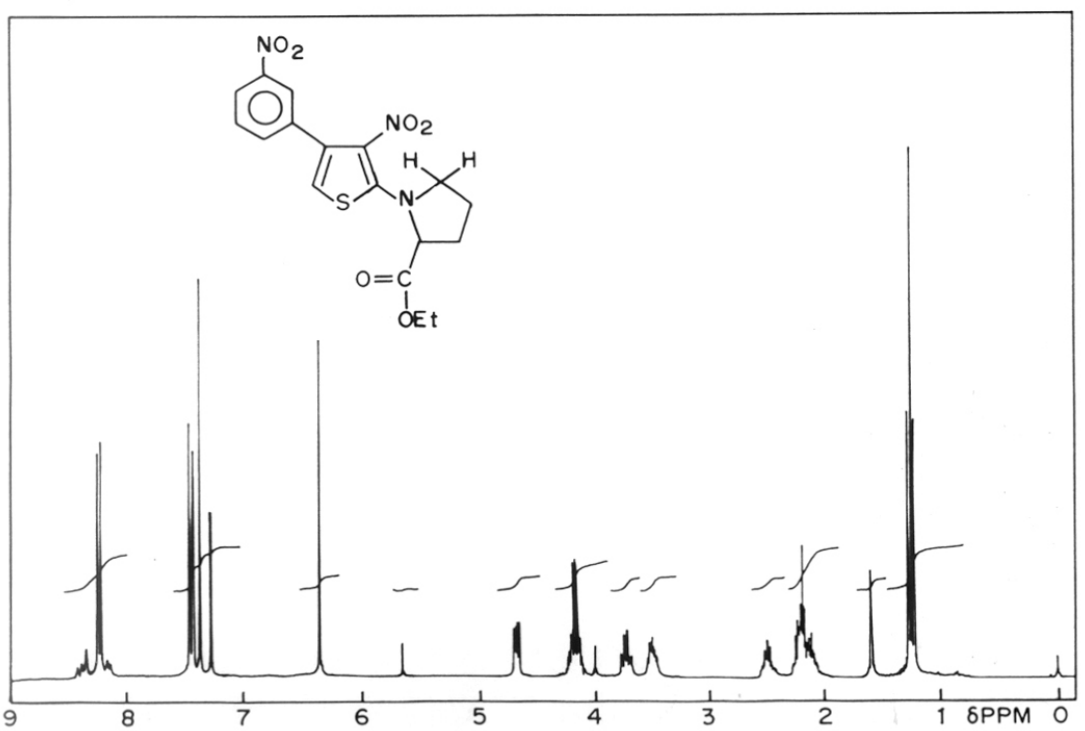
iv) ***2-(Ethyl N-prolinyl)-3-nitro-4-(4'-nitro phenyl)thiophene*** **(3d)**:

The compound was synthesized by following the procedure discussed in the experimental section. The compound was obtained in 81% yield, m.p. 132°c, $[\alpha]_D^{MeOH}$ = -320.83°. In the infrared spectrum, the peaks were seen at 1750, 1610, 1560, 1450, 1380cm^{-1}. In the ^{1}**H NMR** spectrum (**Spectrum No. 6**),

the triplet at 1.24δ was assigned to the methyl group protons. A set of multiplets at 2.09, 2.17 and 2.48δ were assigned to the four protons on the β and γ carbons of the proline ring and another set of multiplets at 3.48 and 3.71δ were assigned to the NCH_2 group protons. The quartet at 4.17δ was assigned to the OCH_2 group protons and a multiplet at 4.67δ was assigned to the NCH proton. The olefinic proton of the thiophene ring was seen as a sharp singlet at 6.35δ. A set of multiplets at 7.43 and 8.21δ was assigned to the protons of the phenyl ring. The structure of the compound was confirmed by observing the molecular ion peak at 391. The other fragment ion peaks were seen at 345, 142, 113. The compound analysed for $C_{17}H_{17}N_3O_6S$.

Spectrum No. **6**





4.3. Discussion

The reaction of ethyl N-nitrothioacetyl proline with phenacyl bromide resembles the classical Hantzsch synthesis of pyrrole. From our methodology it is possible to synthesize chiral thiophene derivatives. Apart from the chiral centre there is a strong push pull system in these thiophene derivatives.

The donor-acceptor charge transfer interactions are very strong in these compounds. This is evident from the significant spectral shifts as a result of low lying charge transfer interactions[4]. Hence it was anticipated that such donor-acceptor charge transfer interactions can lead to anomalously large nonlinear optical susceptibilities and thereby molecular hyper polarizabilities. Among these thiophene derivatives the compound **3d** was a solid. This compound also satisfied the necessary conditions for a molecule to be active in showing second order nonlinear optical properties; i) the crystal must be non-centrosymmetric: the chirality was used as an efficient strategy for achieving this condition. As the thiophene derivative is chiral the product has to crystallize in an acentric crystal structure. Because of push-pull interactions the C_2-N bond has the partial double bond charecter. Hence the rotation around C-N bond is restricted and is expected to contribute to make the crystal noncetrosymmetric. ii) The molecule has loosely bound electrons that can be displaced by the optical field. It is clear that the π-electrons of the push-pull ethylenes can be perturbed very easily. It is also proved that the magnitude of second order hyperpolarizability (β) increases with strong donor-acceptor combinations. The most dramatic effect is found when both a donor and an acceptor interact in mesomeric fashion[5]. Moreover for a fixed donor group, the nitro group is found to be the strongest acceptor group and for a fixed acceptor, the dialkyl amine group is found to be the strongest donor[6]. Since this thiophene derivative has the combination of strongest donor and strongest acceptor groups, it is anticipated to increase the hyperpolarizability. Moreover the other acceptor nitro group on phenyl ring and the donor sulfur atom of thiophene ring are in conjugation. This forms another push-pull system. The dipoles arising from these two

push-pull systems are parallel and pointing in the same direction. Hence it is likely to increase the ground state dipole moment of the molecule. It was of interest to us to see the impact of parallel dipoles on the magnitude of β.

But to our surprise, the molecule didnot show any second harmonic generation[7]. In spite of the compound's high dipole moment and crystallization in a noncetrosymmetric space group it shows no second order NLO property. There are two possible reasons this. It is clear that as the ground state molecular dipoles become larger, the electrostatic interaction between adjacent molecules will increase and the net molecular dipole alignment required to achieve the maximum crystal anisotropy becomes more energetically unfavorable. To avoid this the molecule adopts the quasi-antiparallel molecular packing in the unit cell[8]. As a result no second harmonic generation signals will be observed. The second reason is, the second harmonic efficiency depends on the change in dipole moment between an excited state and the ground state. It is likely that the difference in dipole moment of the excited and the ground state of this molecule is not significant.

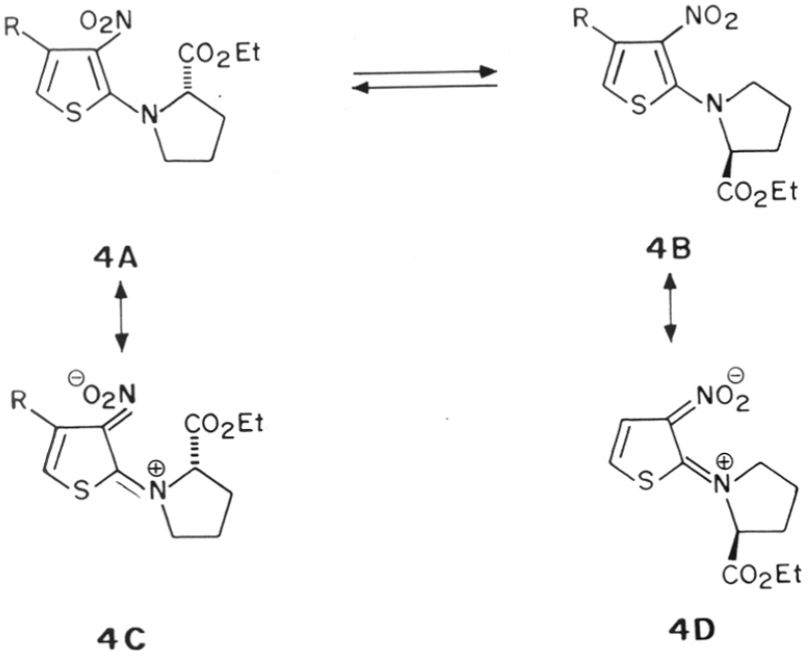
As a final comment on the molecular engineering, it is important to point out the value of an unprejudiced and objective approach. The molecule 4-nitrobenzonitrile breaks all the rules, and with a strict dogmatic approach one would reject the compound out of hand. But the molecular alignment is quite good and although electronically the molecule is not ideally substituted, *i.e.* two acceptor groups are disposed at para positions on the aromatic ring, it has a powder efficiency (2 × urea) which is larger than many other well intended and well engineered donor - acceptor molecules.

4.4. Conformational studies

The thiophene derivatives (**3a-d**) have a strong push-pull system in which the strong electron withdrawing nitro group is in conjugation with strong electron donating prolinyl group. This push-pull system is a part of an aromatic ring system. Because of the push-pull interaction between the nitro and prolinyl group the C_2-N bond will have a partial double

bond charecter as shown in structures **4C** and **4D** (**Scheme 2**). As a result these molecules (**3a-d**) can exist in two conformations.

SCHEME-2



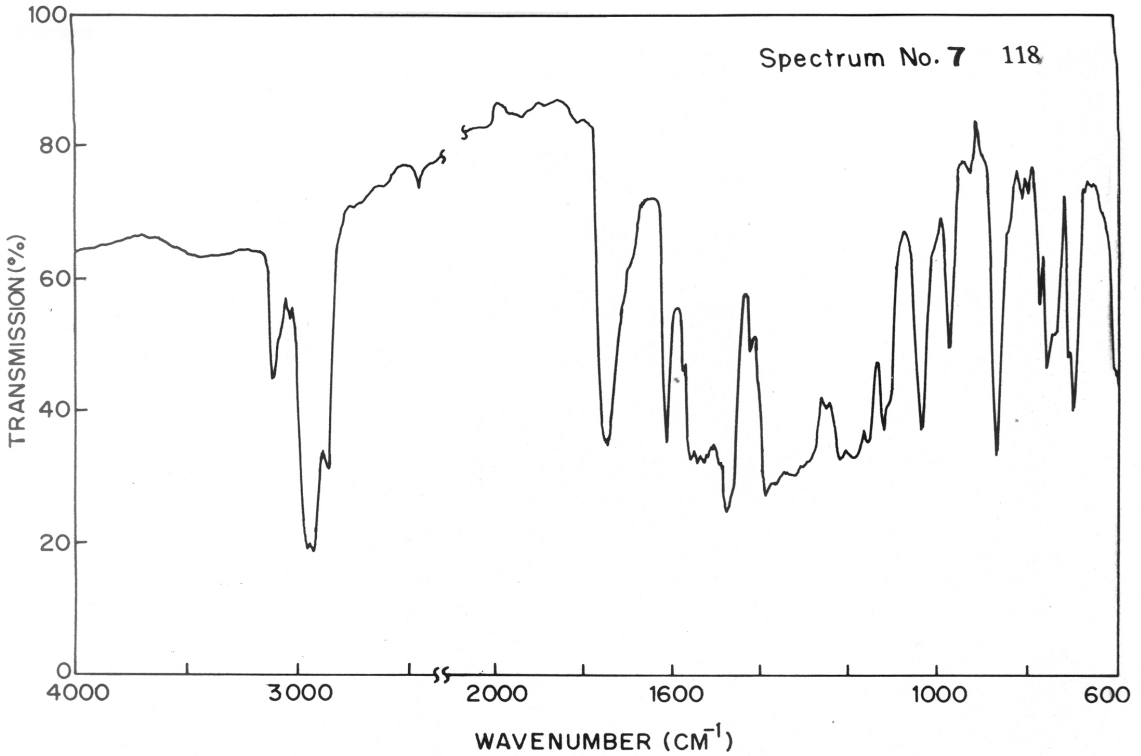
In one conformation the ester group on proline moiety is nearer to the nitro group on thiophene ring. In the second conformation the ester group is away from the nitro group.

Mannschreck observed that the two Me groups attached to the nitrogen in the nitro vinylamine, 1-dimethylamino-2-nitroethylene are nonequivalent[9]. This magnetic non-equivalence is ascribed to a barrier to free rotation around N-C_1 bond. The barrier to rotation around N-C bond in this compound is found to be 16.5kcals/mol. Similarly the

magnetic nonequivalence of two NCH_2 protons in 1-pyrrolidino-2-nitroethylene is ascribed to a barrier to free rotation around N-C_1 bond[10]. In general the barrier to rotation around C-N bond is more than 9kcals/mol.

In the ^{1}H NMR spectrum (**Spectrum No. 4**) of the compound **3c** only one set of signals is observed. Hence, of the two possible conformers(**4A** and **4B**) only one conformer is present. The two protons of the methylene group adjacent to the nitrogen atom of the proline unit in compound **3c** are differentiated in their chemical shift value. These protons show two multiplets at 3.4 and 3.65δ. The proton in the vicinity of the nitro group is deshielded and appears down field compared to the other proton. Similarly, the two protons on the γ carbon of the proline moiety are also magnetically nonequivalent. One which is nearer to the nitro group appeared down field (2.44δ) compared to the other proton (2.14δ). Hence the comformer present in $CDCl_3$ solution is **4B**. Similar observations were made in the ^{1}H NMR spectrum of compound **3d** (**Spectra No. 6 and 7**).

This preference for conformer **4B** of the two possible conformers indicates that this conformer might have lower energy than the other. There are two possible factors which could be responsible for this: i) Non-bonded attraction involving sulfur of thiophene ring and oxygen of ester group, ii) steric reasons.


Spectrum No. 7 118
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60
40
20
0
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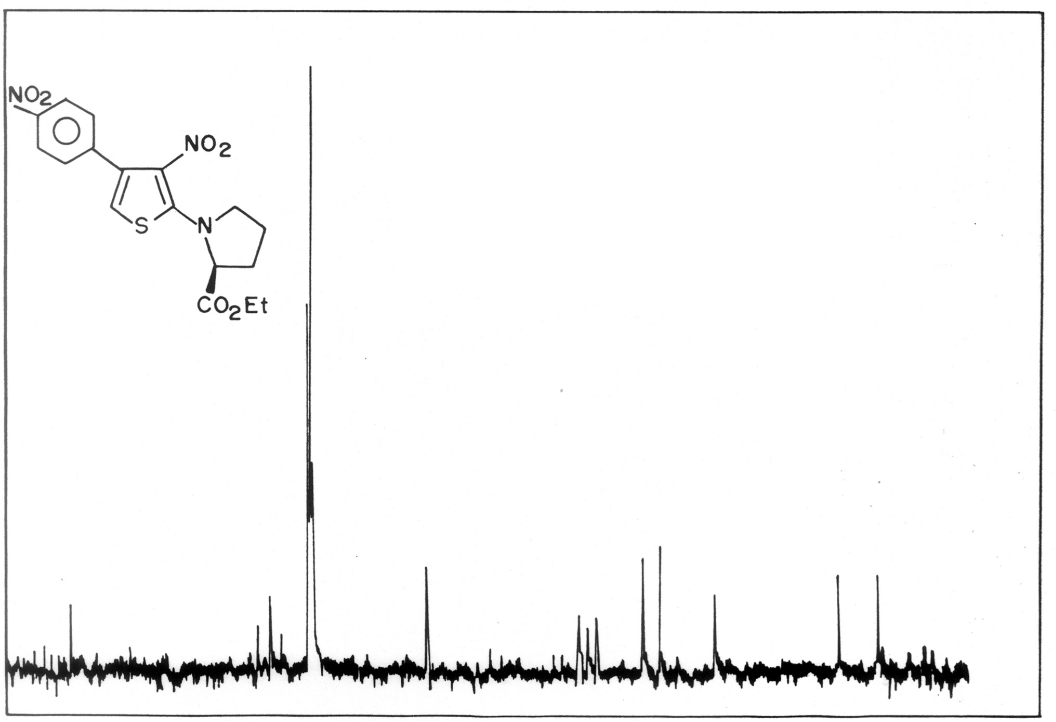
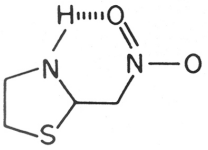
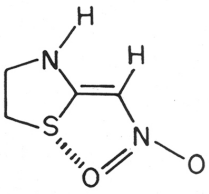
4000
3000
2000
1600
1000
600
WAVENUMBER (CM⁻¹)


NO2
NO2
S
N
CO2Et

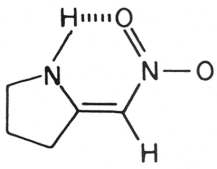
SCHEME-3



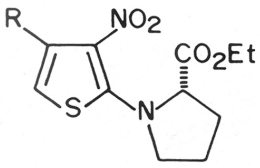
8E-isomer



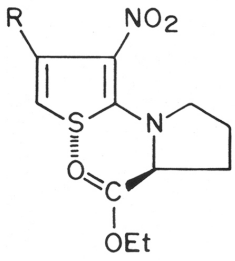
8 Z-isomer



9



4 B

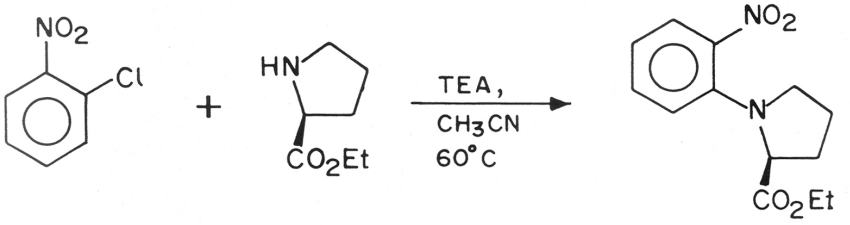


4C

i) ***Non-bonded attractive interaction*** : Previously, ^{1}H NMR studies on similar push-pull system (*i.e.* nitromethylene thiazolidine) had been carried out by our group[11]. Nitromethylene thiazolidine (**8**) exists in hydrogen bonded (E)-configuration in pure $CDCl_3$ (**Scheme 3**). Only one set of signals is seen corresponding to a single isomer. As DMSO-d_6 is added to the solution, the hydrogen bonds are broken and a second set of signals is observed. The second set of signals has been assigned to the Z-isomer. Other tautomeric forms are ruled out by its ^{15}N NMR spectrum. In pure DMSO-d_6 40% of the compound exists in Z-form. The preference for Z-configuration is due to the non-bonded attractive interaction between oxygen of the nitro group and sulfur atom of thiazolidine ring. The role of non-bonding attractive interaction was proved by carrying out similar ^{1}H NMR experiments on compound **9**. In this molecule the sulfur atom is replaced by a methylene

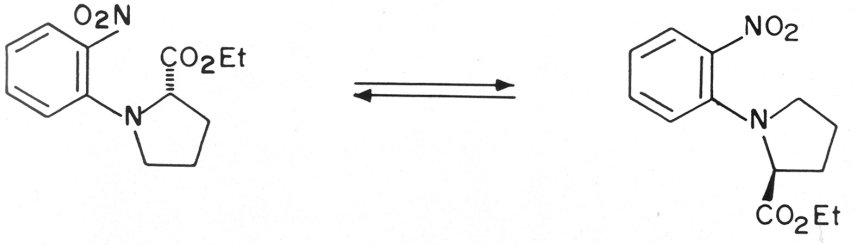
group, hence the possibility of S..O attractive interaction is ruled out. This compound exists only in hydrogen bonded form in both polar and nonpolar solvents. These observations support the argument that the non-bonded attractive interaction between sulfur of thiazolidine ring and the oxygen of nitro group is responsible for the presence of Z-isomer of compound **5**. These results prompted us to think of the role of similar attractive interactions for the relative preference for conformer **4B** (**Scheme 4**). In order to determine the possible role of non-bonded attractive interactions 2-(ethyl N-prolinyl) nitrobenzene (7) was synthesized and its conformation studied. In this molecule the sulfur atom is absent, hence there is no possibility for non-bonded interaction (**Scheme 5**). However, the environment (both electronic and steric) around nitro group and prolinyl group is the same as in the thiophene derivatives.

SCHEME-4



5 **6** **7**

SCHEME-5

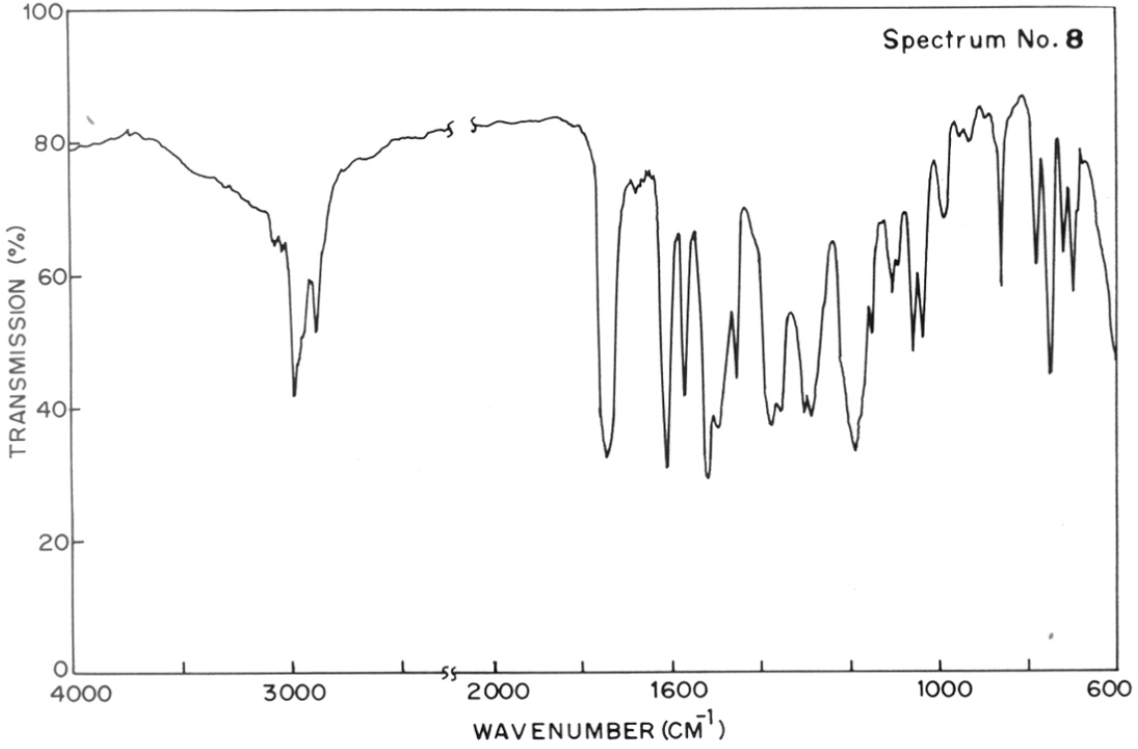


7a **7b**

2-Ethyl N-prolinyl nitrobenzene (7): The experimental procedure for the synthesis of this compound is discussed in the experimental section. It was obtained as a gum in 35% yield. In the infrared spectrum peaks at 1750, 1610, 1570, 1520 and 1380cm^{-1} are observed. In the ^{1}H NMR spectrum (**Spectrum No. 8**)

only one set of signals are seen corresponding to one conformer. The triplet at 1.19δ is assigned to the methyl group protons and a set of multiplets at 1.95, 2.17 and 2.43δ are assigned to four protons on β and γ carbons of proline ring. The two multiplets at 3.18 and 3.49δ are assigned to the two protons of the NCH_2 group. The proton nearer to the nitro group is observed down field compared to the other proton. Hence the conformation **9b** is present. A quartet at 4.13 is assigned to OCH_2 group protons. The multiplet at 4.40δ is assigned to the proton of the α-NCH group. A set of multiplets at 6.85, 7.40 and 7.69δ are assigned to the four protons on the aromatic ring. In the mass spectrum, the molecular ion peak is seen at 264 and other fragment ions are seen at 247, 191(100%), 91 and 77. The compound analysed for $C_{13}H_{16}N_2O_4$. Though there is no sulfur atom in the molecule, the CO_2Et group prefers to stay away from the nitro group. Obviously it is not because of non-bonded attractive interactions, but because of the steric interaction between the nitro group and CO_2Et group.

ii) ***Steric reasons*** : It is reasonable to extend the same logic to thiophene derivatives (3a-d). Hence it is concluded that the steric interaction between the nitro group and CO_2Et group is responsible for forcing the molecule **3c** to adopt the conformation **4B**.


Spectrum No. 8
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20
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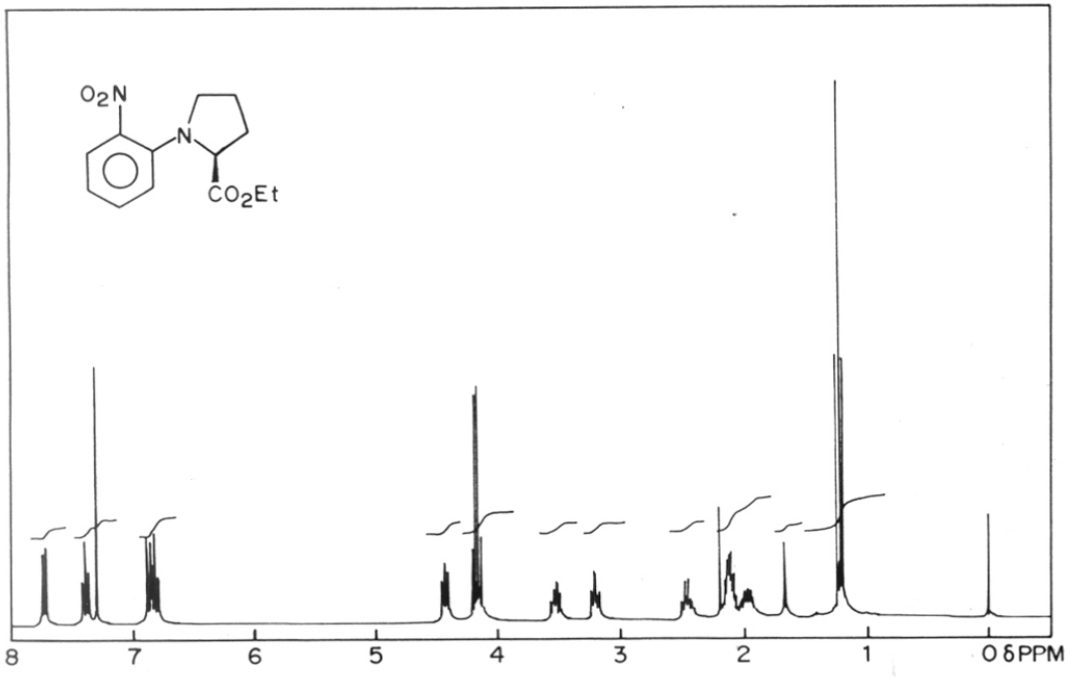
4000
3000
2000
1600
1000
600
WAVENUMBER (CM⁻¹)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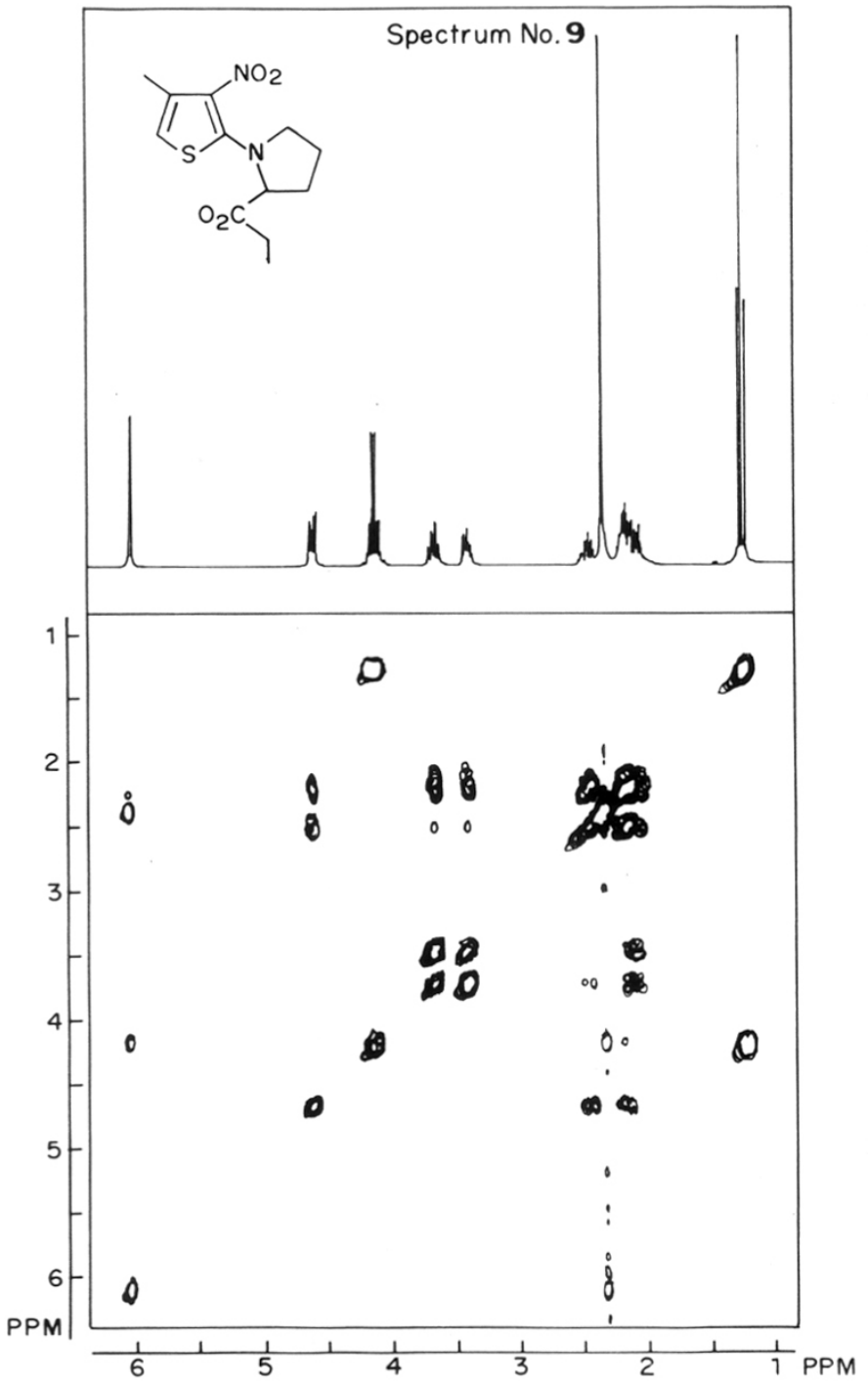
N
CO2Et
8
7
6
5
4
3
2
1
0 δPPM


Spectrum No. 9
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S
N
O2C
1
2
3
4
5
6
PPM
6
5
4
3
2
1
PPM

4.5. Experimental Section

Synthesis of 2-(ethyl N-prolinyl)-3-nitro-4-phenylthiophene (**3a**):

N-nitrothioacetylproline ethyl ester (492 mg) was taken in benzene (8 ml) and DBU (340 mg) was added to the solution. The contents were kept under nitrogen atomosphere and stirred for 10 minutes. Phenacyl bromide (438 mg) in benzene (7ml) was added to the flask. The reaction mixture was stirred at 60°c for 12h. The solvent was removed under reduced pressure. The mixture was chromatographed on a silica gel column (benzene: petroleum ether 3:1) to get 450mg of the pure product. Gum; yeild: 65%; $[\alpha]_D^{MeOH}$ = -250.93; **IR**(neat): 2900 - 3100, 1740, 1680(weak), 1550, 1480 and 1380; **^{1}H NMR**($CDCl_3$): 1.22(t, 3H, Me), 2.13(m, 4H, $2NCCH_2$), 3.58(m, 2H, NCH_2), 4.11(q, 2H, OCH_2), 4.60(m, 1H, NCH), 6.24(s, 1H, =CH), 7.31(m, 5H, Ph); **^{13}C NMR**($CDCl_3$): 13.74, 23.81, 30.96, 53.68, 61.19, 63.83, 106.61, 127.44, 127.82, 128.12, 128.45, 135.42, 137.64, 154.62, 171.23; **MS**(m/e): 346(M^+), 273, 212, 142, 141, 139(100%), 105, 85, 83, 77, 70; **UV**(MeOH): λ_{max} 405nm (ε 1.94 × 10^5), 234nm (ε 1.56 × 10^6). **Found**, C,59.03, H,5.32, S,9.27, N,8.12, **calculated** for $C_{17}H_{18}N_2O_4S$, C,58.96, H,5.20, S,9.25, N,8.09%.

Synthesis of 2-(benzyl N-prolinyl)-3-nitro-4-phenylthiophene (**3b**):

This compound was synthesized by following the same experimental procedure as described above. Thick gum, yield: 60%; $[\alpha]_D^{MeOH}$ = -262.35°c; **IR**(nujol): 2950-3100, 1740, 1510, 1370, 1300, 1160cm^{-1}; **^{1}H NMR**($CDCl_3$): 2.07(m, 4H, $2NCCH_2$), 3.53(m, 2H, NCH_2), 4.58(m, 1H, NCH), 5.07(s, 2H, OCH_2), 6.16(s, 1H, =CH), 7.22(s, 5H, Ph); **^{13}C NMR** ($CDCl_3$): 23.76, 30.03, 53.64, 63.79, 66.93, 106.58, 127.40, 127.77, 127.84, 128.04, 128.25, 128.39, 135.07, 135.26, 137.53, 171.06.; **MS**(m/e): 408(M^+), 346, 332, 273, 237, 221, 165, 135, 105, 91, 77. **Found**, C,64.95, H,4.97, S,7.92, N,6.95, **calculated** for $C_{22}H_{20}N_2O_4S$, C,64.71, H,4.90, S,7.84, N,6.86%.

Synthesis of 2-(ethyl N-prolinyl)-3-nitro-4-methylthiophene (**3c**)

N-nitrothioacetylproline ethyl ester (492 mg) was dissolved in benzene (dry, 10ml). Bromoacetone (275 mg) was added to the solution followed by K_2CO_3 and phase transfer catalyst (TEBA) was used in this reaction. The reaction mixture was stirred at 50°c for 3h. under nitrogen atmosphere. The solvent was removed under vacuum and the product was purified by the chromatography on the silica gel column (benzene : petroleum ether 3:1). Orange coloured liquid, yield: 70%; $[\alpha]_D^{MeOH}$ = -556.48°; **IR**(neat): 2900-3000, 1750, 1560, 1530 and 1380; ^{1}**H NMR**($CDCl_3$): 1.16(t, 3H, Me), 2.108, 2.138 and 2.44(m, 4H, $2NCCH_2$), 2.35(d, 3H, =C-Me), 3.40 and 3.65(m, 2H, NCH_2), 4.09(q, 2H, OCH_2), 4.65(m, 1H, NCH), 6.04(m, 1H, =CH); ^{13}**C NMR**($CDCl_3$): 13.58, 17.30, 23.74, 30.89, 54.02, 60.96, 63.64, 63.76, 104.25, 132.89, 156.58, 171.01; **MS**(m/e): 284(M^+), 211(100), 193, 177, 165, 151, 139, 126, 71, 66; **UV**(MeOH): λ_{max} 416nm, (ε 4.1 × 10^5), 256nm (ε 0.97 × 10^6). **Found**, C,50.92, H,5.85, S,11.51, N,9.95, **calculated** for $C_{12}H_{16}N_2O_4S$, C,50.79, H,5.63, S,11.27, N,9.86%.

Synthesis of 2-(ethyl N-prolinyl)-3-nitro-4-(4' nitro phenyl)thiophene (**3d**):

The N-nitrothioacetylproline ethyl ester (492 mg) was taken in dry benzene (15ml) and p-nitrophenacyl bromide (385 mg), K_2CO_3 (280 mg) and 25mg of phase transfer catalyst (TEBA) were added to the solution. The contents were stirred at 80°c for 4h. under nitrogen atmosphere. The product formation was not observed in the absence of phase transfer catalyst. The solvent was evaporated and the product was purified by the chromatographic separation using silica gel column. Yield: 81%, m.p.: 132°c, $[\alpha]_D^{EtOH}$ = -320.83°, **IR**(nujol): 1750, 1610, 1560, 1450, 1380cm^{-1}; ^{1}**H NMR**($CDCl_3$): 1.24(t, 3H, Me), 2.09, 2.17 and 2.48(m, 4H, $2NCCH_2$), 3.48 and 3.71(m, 2H, NCH_2), 4.17(q, 2H, OCH_2), 4.67(m, 1H, NCH), 6.37(s, 1H, =CH), 7.43 and 8.21(m, 4H, $C_6H_4NO_2$); **Found**, C,64.95, H,4.97, S,7.92, N,6.95%, **calculated** for $C_{22}H_{20}N_2O_4S$, C,64.71, H,4.90, S,7.84, N,6.86%.

Synthesis of 2-(ethyl N-prolinyl) nitrobenzene (7)

The proline ethyl ester (910mg) and ortho chloronitrobenzene (788mg) and excess triethylamine (4eq.) were taken in acetonitrile (20ml) and stirred at 60°c for 2 days. Even after 2 days the reaction was not complete. The solvent was evaporated and the product was purified by the chromatography on silica gel column (benzene as an eluent). The product was obtained in 35% yield (calculated from the amount of consumed starting material). Gum; **IR**(neat): 1750, 1610, 1570, 1520, 1380, 1360 and 1190. **^{1}H NMR**($CDCl_3$): 1.19(t, 3H, CH_3), 1.95, 2.17 and 2.43(m, 4H, $2NCCH_2$), 3.18 and 3.49(m, 2H, NCH_2), 4.13(q, 2H, OCH_2), 4.40(m, 1H, NCH), 6.85, 7.40 and 7.69(m, 4H, Ph); **MS**(m/e): 264(M^+), 247, 191(100%), 144, 131, 117, 104, 91 and 77. **Found**, C,59.21, H,6.25 and N,10.82%, **calculated** for $C_{13}H_{16}N_2O_4$, C,59.09, H,6.06, N,10.61%.

4.6. References

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CHAPTER 5

Non-bonded Attractive Interactions Involving S and O Atoms

5.1. Introduction

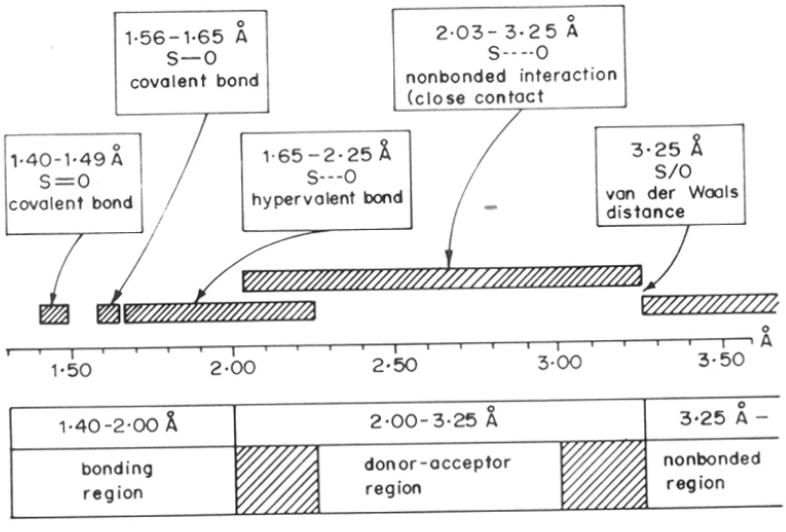
The nature and magnitude of non-covalent interactions involving sulfur have attracted considerable experimental and theoretical attention in recent years[1-12]. While the interaction is intrinsically interesting from the bonding point of view, additional significance is provided by its potential role in determining biomolecular conformations[5,13], and in enabling sulfide units to function as useful steering groups in crystal engineering applications[14].

Literature Survey : i) ***The S-O linkage*** : The S-O linkages can be classified into different regions depending on their bond lengths. The covalent S,O double bond is shortest of all S-O linkages, the bond length usually ranges from 1.40-1.49$\mathring{A}$. The next to follow is S-O covalent single bond (1.56-1.65$\mathring{A}$). Another type of S-O linkage is S-O hypervalent bond and it is markedly longer (1.65-2.25$\mathring{A}$) than the covalent S-O single bond. The region between 1.40-2.00$\mathring{A}$ is classified under bonding region. The bonding region is followed by the donor - acceptor region which spans from 2.00-3.25$\mathring{A}$. The non-bonding interactions come in this region (**Scheme 1**).

ii) ***Classification of close contacts***: In a general way, compounds exhibiting such non-bonded attraction can be represented as shown in scheme 2.

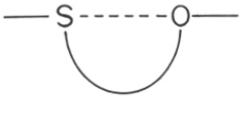
The S..O linkage thus completes a pseudo ring. Such compounds having non bonded sulfur and oxygen atom can be classified primarily by taking the size of the pseudo ring and sulfur valence state into consideration. (a) The size of the quasi ring including S..O moiety varies from 3 to 6, thus S,O contacts of 1,3, 1,4, 1,5 and 1,6 type are observed. (b) The valence state of the acceptor sulfur atom may be S^{II}, S^{IV} and S^{VI}. The most representative models of sulfur-oxygen close contact can be found among compounds having sulfur and oxygen atoms in 1,3 position followed by 1,5 position.

SCHEME-1



SULFUR-OXYGEN LINKAGE IN ORGANIC SULFUR COMPOUNDS.

SCHEME-2



Pseudo ring

iii) ***Examples of structures giving rise to short contact***: There are a number of compounds with non-bonded S..O distances of 2.00-3.00$\mathring{A}$ investigated by X-ray method. (The sum of corresponding van der Waals radii is 3.25$\mathring{A}$).

From the available data on nonbonding interactions, the following empirical rules have been formulated[3b].

i) S..O interaction seems to be controlled by the geometry of planar quasi rings including S..O moiety; hence 5 membered rings are more favourable for S..O interaction than rings of smaller size (**Scheme 3**).

ii) Highly effective S..O interaction requires conjugation of S-A=B-Y=O type (sulfur and oxygen atoms are in the 1,5 positions) with cis configuration around A=B, resulting in the formation of planar 5-membered ring with S..O close contact.

iii) In compounds with significant S,O interaction there is a nearly linear X-S..O sequence as shown in scheme 1.

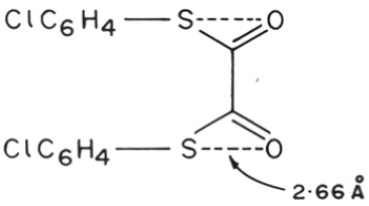
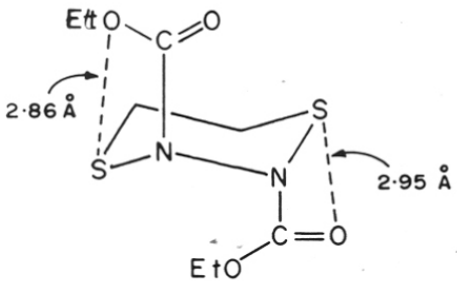
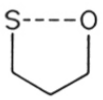
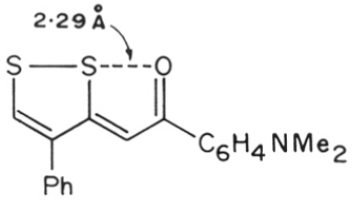
iv) Unusually short S..O distances often go with elongated X-S and O-Y bond lengths.

v) The bond lengths and the bond angles in quasi rings determined by the nature of the ring atoms A,B and Y, have a marked influence on S,O interaction.

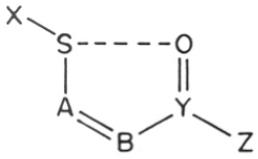
Theoretical aspects

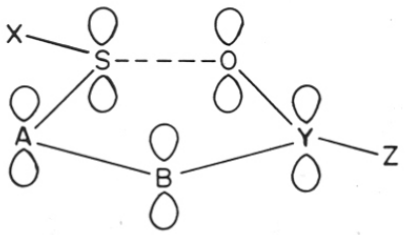
The delocalised π-system composed of the six electrons in p-orbitals perpendicular to the plane of the ring with S..O contact is expected to facilitate the nonbonding interactions (**Scheme 4**). The S..O interaction may also be explained qualitatively by the frontier orbital theory (**Scheme 5**). The close contact of sulfur and oxygen atoms in a linear X-S..O sequence gives rise to an oxygen - HOMO and Sulfur LUMO (X-S σ^*) overlap.

SCHEME-3

	TYPE	EXAMPLE
1,3		
1,4		
1,5		

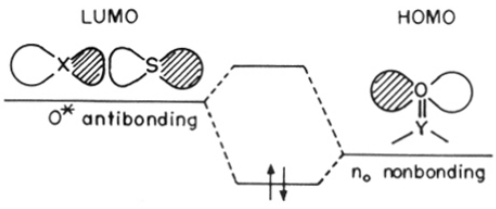
SCHEME-4





5 - membered ring
6 π - electrons

SCHEME-5



INTERPRETATION OF SULFUR-OXYGEN INTERACTION BASED ON FRONTIER ORBITAL THEORY

Evidence for such non-bonded interactions has so far been provided only by X-ray crystallographic data, supported by theoretical calculations, *i.e.*, these interactions were observed in the solid state only. Moreover, the effectiveness of S,O interaction was discussed in terms of the S,O distance, the X-S..O angle and the ring torsion angles. The S,O interaction will be particularly effective if the S,O distance is short, the X-S..O angle is near to 180° and the ring torsion angles are about 0°. It would be highly desirable to confirm experimentally whether the short contacts and directionality of interactions identified in the solid state are relevant in the solution phase. Further, the magnitude of S..X interactions needs to be quantified relative to other well understood attractive forces,

like the hydrogen bond. In this chapter, the S..O and S..S interactions observed in the solution phase have been discussed and these interactions have been qualitatively compared with the hydrogen bond strengths.

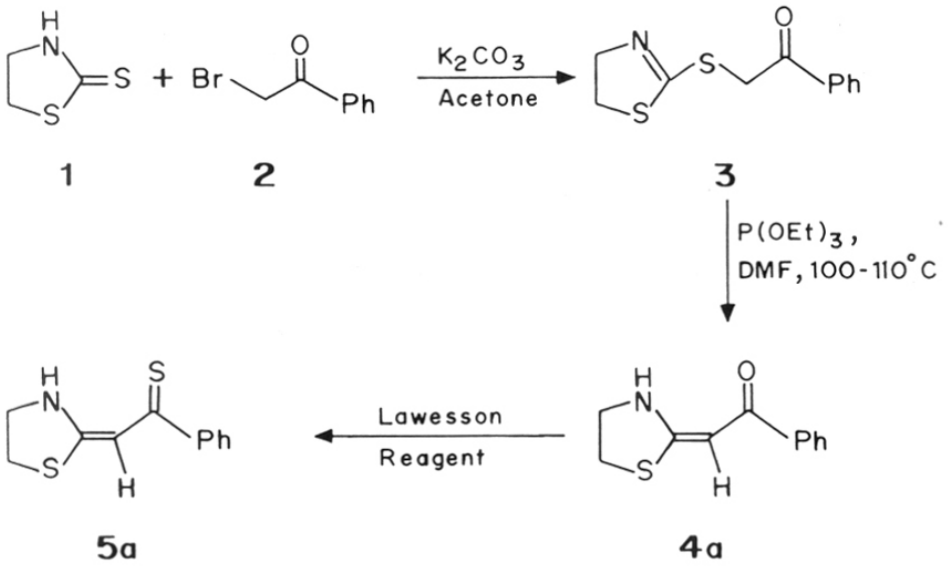
5.2. Results

i) ***Synthesis of 2-benzoyl methylenethiazolidine and 2-thiobenzoyl methylenethiazolidine*** **(4a & 5a)**: 2-benzoyl methylenethiazolidine(**4a**) was prepared by sulfide contraction method[15] (**Scheme 6**). A mixture of thiazolidine-2-thione, phenacyl bromide (1.2 eq.) and K_2CO_3 was stirred in acetone at 30°c for 2h. to get 2-phenacylthio thiazolidine in 80% yield. In the infrared spectrum, peaks at 1750 and 1590cm^{-1} were observed. In the ^{1}H NMR spectrum, the triplet at 3.38δ was assigned to SCH_2 protons of the ring and another triplet at 4.02δ was assigned to the NCH_2 group protons. A sharp singlet at 4.67δ was assigned to the SCH_2 protons and the multiplets at 7.45 and 7.93δ were assigned to phenyl ring protons. The Eschenmoser's sulfur extrusion reaction was carried out on 2-phenacyl thiothiazolidine with triethyl phosphite in DMF to get 2-benzoyl methylenethiazolidine (**4a**) in 69% yield. In the infrared spectrum, the compound showed a peak at 3200cm^{-1} corresponding to NH stretching frequency and other peaks at 1600 and 1580cm^{-1}. The structure of the compound was further confirmed by observing the molecular ion peak at 205 in the mass spectrum.

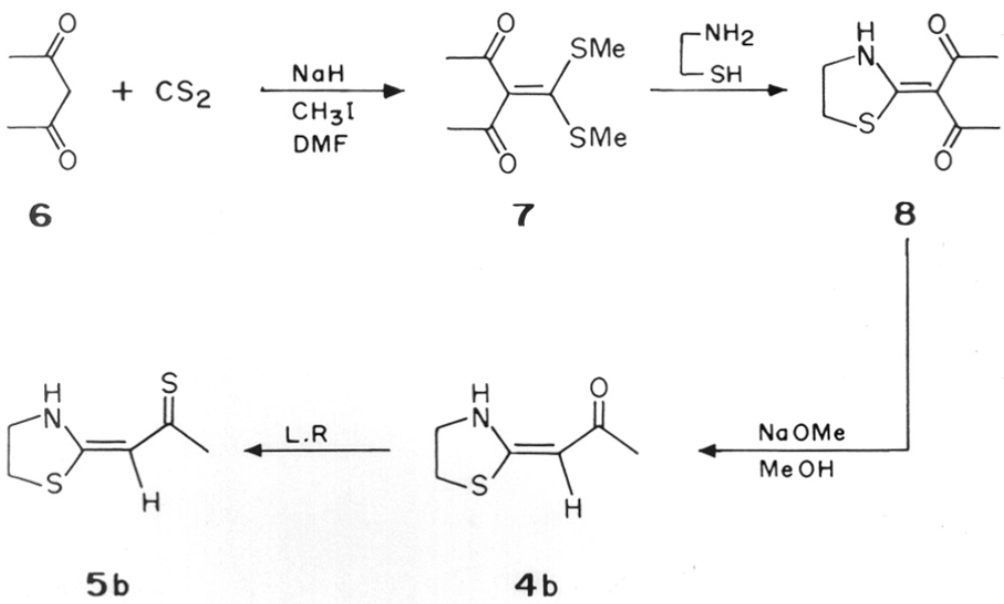
2-thiobenzoyl methylenethiazolidine (**5a**)was synthesized by thionating[16] the 2-benzoyl methylenethiazolidine with 0.6eq. of Lawessons's reagent (**Scheme 6**). The product was obtained in 75% yield. In the infrared spectrum, the peak at 1750cm^{-1} corresponding to the carbonyl stretching frequency of the starting material was disappeared. The compound showed peaks at 1570, 1550 and 1480cm^{-1}. In the mass spectrum, the molecular ion peak was observed at 221. The compound analyzed for $C_{11}H_{11}NS_2$.

ii) ***Synthesis of 2-acetyl methylenethiazolidine and 2-thioacetyl methylenethiazolidine*** **(4b & 5b)**: The attempts to synthesize these compounds by following the above procedure were not successful, hence they were synthesized by following a different route[15,17]

SCHEME-6



SCHEME-7

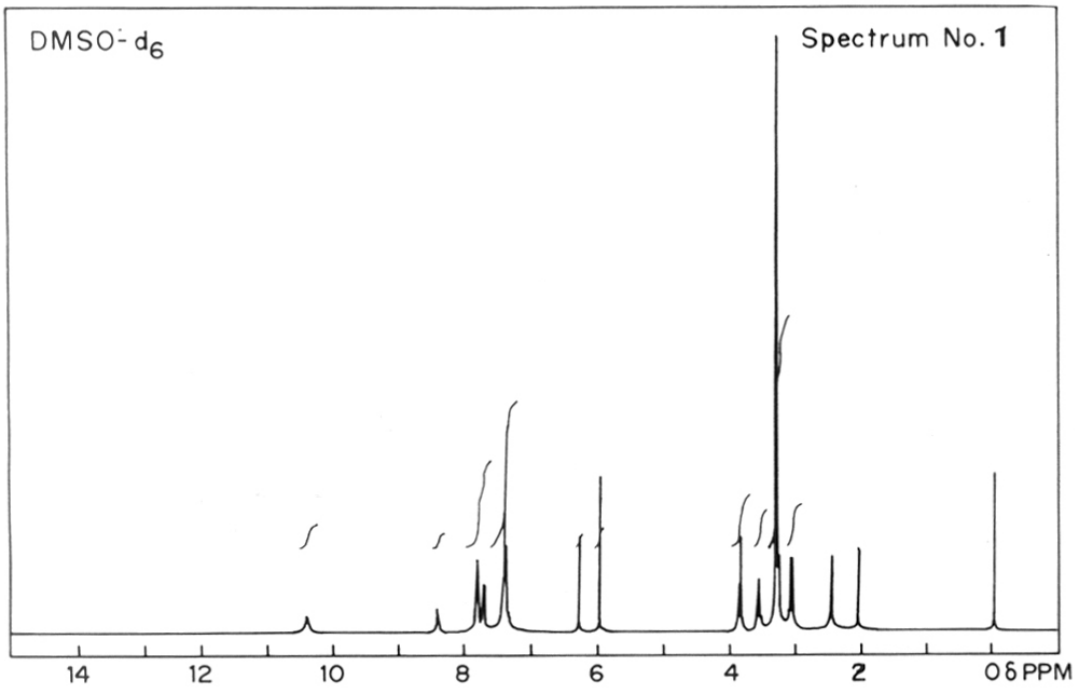


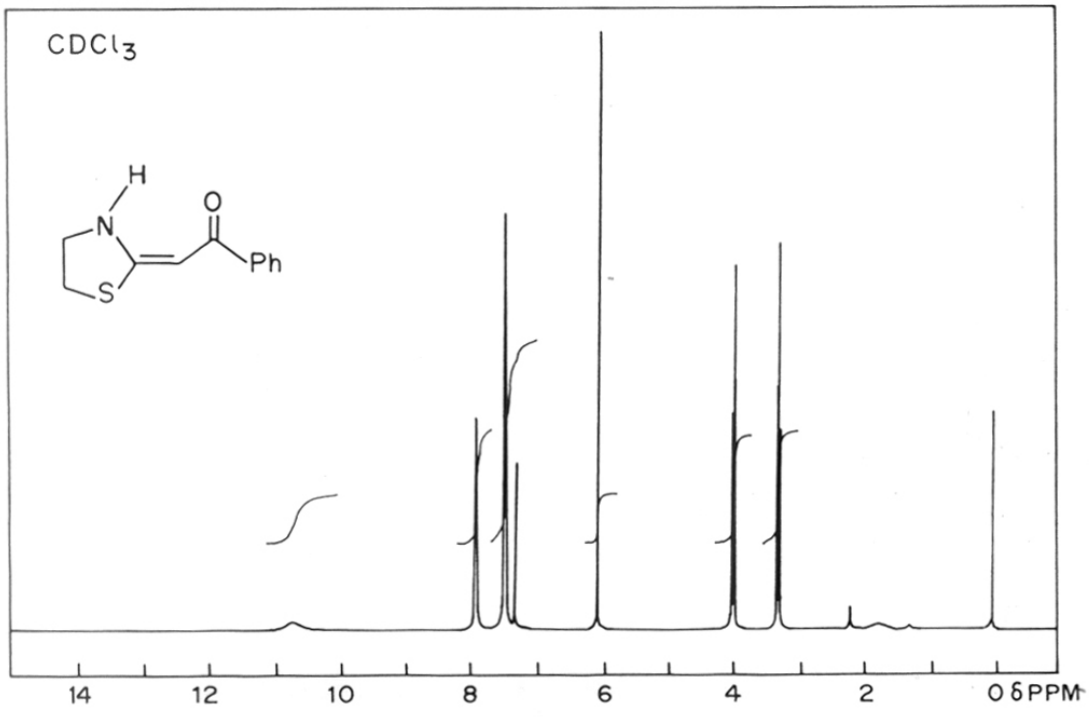
(**Scheme 7**). 2,4-Pentanedione was allowed to react with CS_2 in presence of NaH in a mixture of dry benzene and DMF. The contents were cooled to 10°c and CH_3I was added to get 1,1-bis methylthio-2,2-diacetyl ethylene in 50% yield. The S,S-ketene acetal was refluxed with amino ethanethiol in absolute ethanol to get 2,2-diacetyl methylene thiazolidine. One of the two acetyl groups was knocked off in the reaction with NaOMe in methanol. The required 2-acetyl methylenethiazolidine (**4b**) was obtained in 90% yield. In the infrared spectrum, the compound showed peaks at 3200 and 1610cm^{-1} corresponding to the NH and C=O stretching frequencies respectively. The structure was further confirmed by the observation of molecular ion peak at 143 in the mass spectrum.

2-Thioacetyl methylenethiazolidine (**5b**) was synthesized by the Lawesson's thionation of 2-acetyl methylenethiazolidine (**Scheme 7**). The product was obtained in 85% yield. In the infrared spectrum, the compound showed peaks at 3400, 1570 and 1470cm^{-1}. In the mass spectrum, the molecular ion peak was seen at 152, and other fragment ion peaks were seen at 131(100%), 126 and 112.

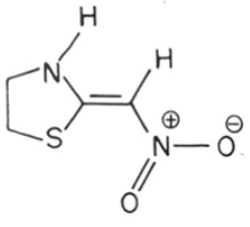
The thiazolidine derivatives (**4,5**) were chosen for the study of non-bonding interactions, since they fulfil the primary requirements for observing such interactions (**Scheme 8**). The physical data and the other spectral data like ir, mass spectra have been given in the experimental section.

NMR study: The conformational equilibria in two carbonyl compounds, 2-benzoyl methylenethiazolidine (**4a**) and 2-thioacetyl methylenethiazolidine (**4b**) were studied to probe attractive S..O interactions. The ^{1}H NMR spectra of both derivatives show a strong solvent dependence. In pure $CDCl_3$ at 20°c sharp signals characteristic of a single conformer were observed (**Spectrum No. 1**).

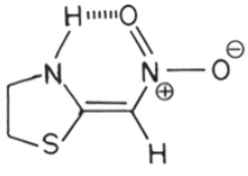

DMSO-d_6
Spectrum No. 1
14
12
10
8
6
4
2
0 δ PPM


$CDCl_3$
H
N
O
Ph
S
14
12
10
8
6
4
2
0 δ PPM

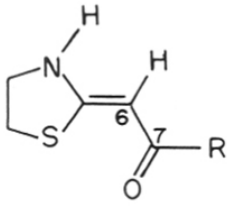
SCHEME-8



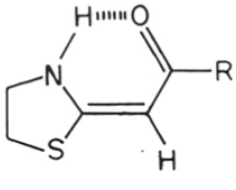
12(Z)



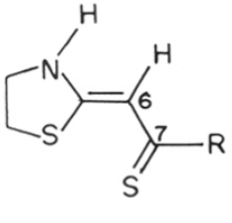
12(E)



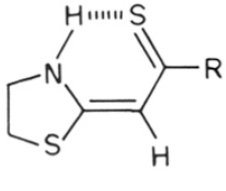
4(Z)



4(E)



5(Z)



5(E)

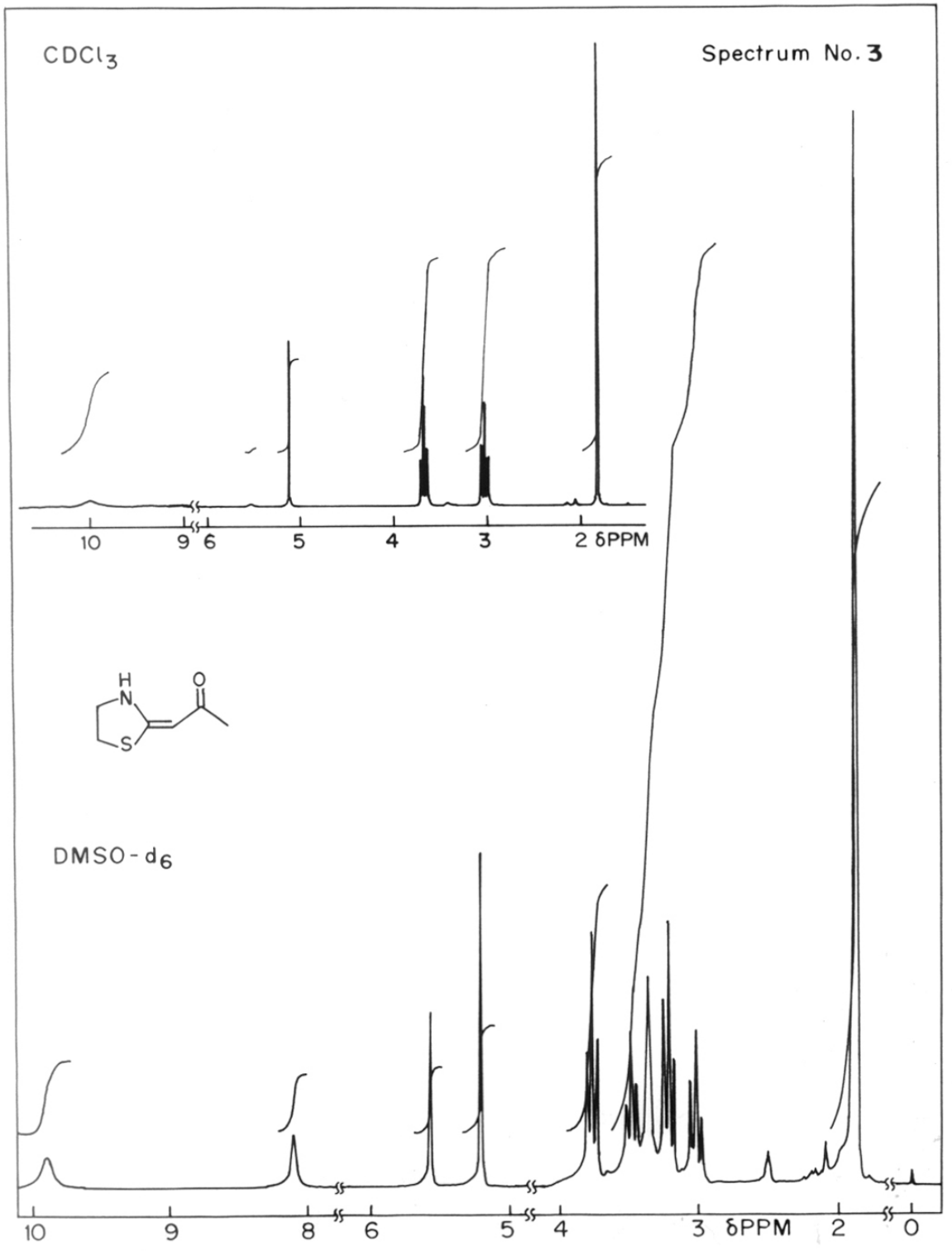
a) R = Ph ; b) R = CH_3

The compound **4a** showed a triplet at 3.22 corresponding to the SCH_2 protons. Another triplet at 3.88 was assigned for the NCH_2 protons and a sharp singlet at 5.91 for =CH proton, a broad signal at 10.58 for NH proton and a set of multiplets at 7.41 and 7.88 were assigned to the protons of phenyl ring. In this non-polar medium, the preferred geometry must correspond to the intramolecularly hydrogen bonded (E)-isomer. This was confirmed by the observed ir spectra of **4b**: the NH and C=O stretching frequencies appeared at 3210 and 1610cm^{-1} respectively. These frequencies remain unaffected by change in the sample concentration (1 - 5% solution), this confirms that the observed single conformer in the ^1H NMR spectrum will corresponds to the intramolecularly hydrogen bonded E-isomer. When DMSO-d_6 was added to the same solution of **4a** in $CDCl_3$ another set of signals corresponding to the second isomer appeared in the ^1H NMR spectrum (**Spectrum No. 1**). The new set of signals was assigned to the alternative (Z)-isomer. A triplet at 3.10 was assigned to the SCH_2 group protons, another triplet at 3.66 was assigned to the NCH_2 group protons. A sharp singlet at 6.40 was assigned to olefinic proton and a set of multiplets at 7.41 and 7.69 were assigned to the phenyl ring protons and a broad peak at 7.99 for NH proton. The considerable up field shift (by 2.60) observed in case of Z-isomer compared to the corresponding NH signal of (E)-isomer is indicative of a non hydrogen bonded NH proton.

The population of (Z)-isomer increased with increasing DMSO-d_6 content. The (E)/(Z) ratio in 4:1 $CDCl_3$:DMSO-d_6 solvent mixture was found to be 9:1. In pure DMSO-d_6 the ratio of (Z)-isomer reached to 38%. It is important to note that all the signals corresponding to both the isomers, E and Z were sharp.

Similar results were obtained for the acetyl derivative, **4b** also. The signals in ^1H NMR of **4b** in $CDCl_3$ (**Spectrum No. 3**)

were assigned as follows. A sharp singlet at 2.02 for Me group protons, two triplets at 3.19 and 3.85 for SCH_2 and NCH_2 group protons respectively and a sharp singlet at 5.28 for =CH proton and a broad signal at 10.09 was assigned for the NH proton. The peaks

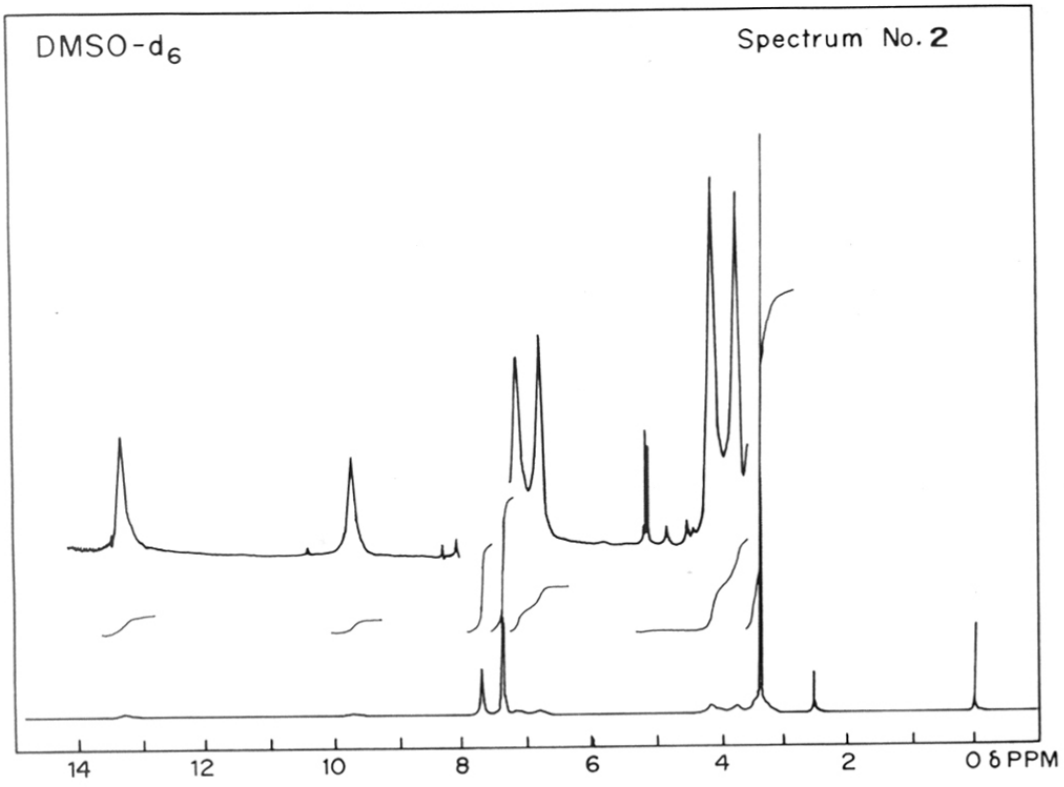

CDCl3
Spectrum No. 3
10
9
6
5
4
3
2 δPPM
H
N
O
S
DMSO-d6
10
9
8
6
5
4
3 δPPM
2
0

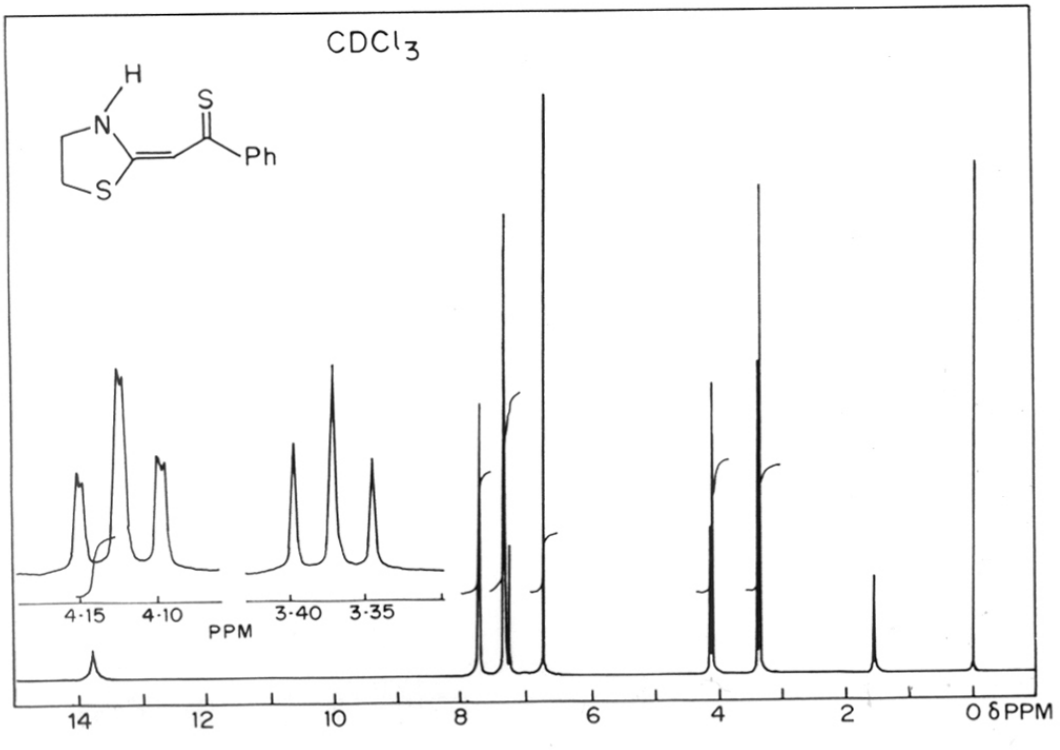
corresponding to (Z)-isomer were not seen in the mixture of solvents. Although the (Z)-isomer appeared only in pure DMSO-d_6, the (E)/(Z) ratio was nearly the same as that found for **4a**, *i.e.*, 37.5% (**Spectrum No. 3**). This could be because of stronger hydrogen bonding in **4b**. The (Z)-isomer of **4b** in DMSO-d_6 showed a singlet at 1.9 for the Me group protons; two triplets at 3.0 and 3.5 were assigned to SCH_2 and NCH_2 group protons respectively, a sharp singlet at 5.6 for =CH proton, and a broad peak at 8.10 was assigned to NH proton.

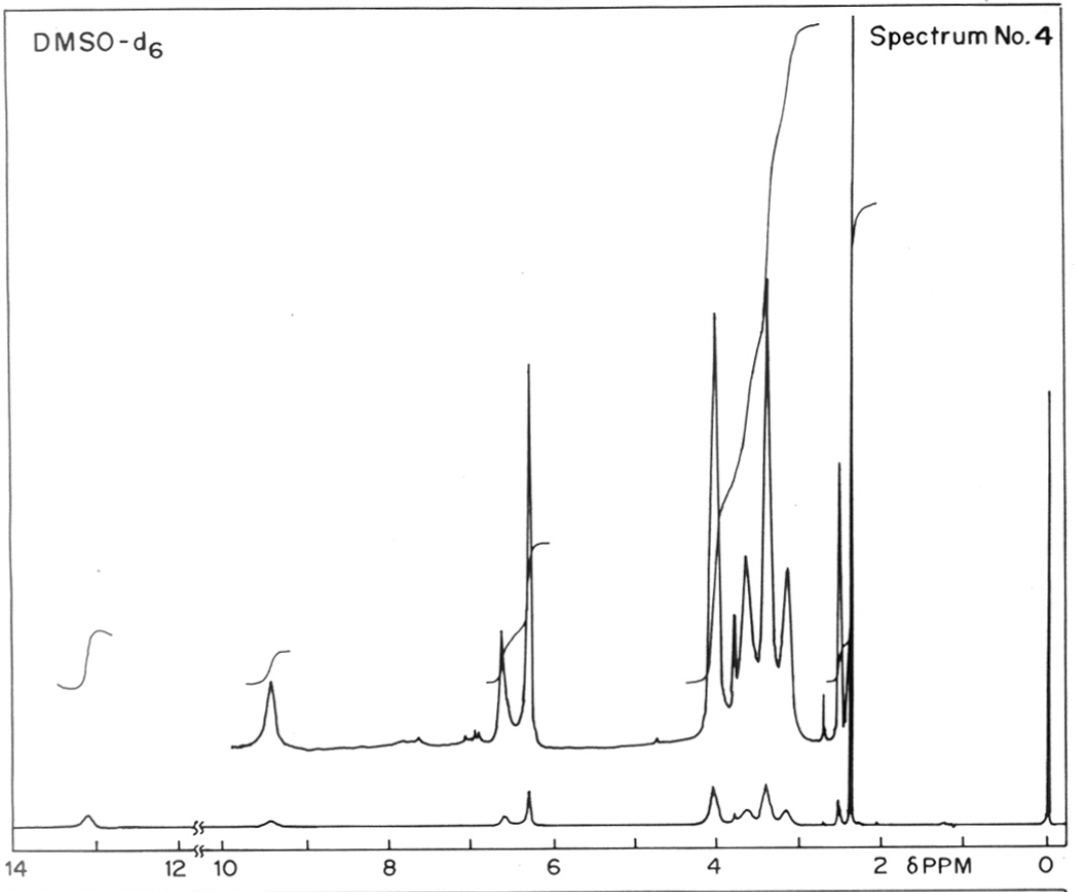
An analogous NMR spectral study was then carried out on the thiocarbonyl derivatives **5a** and **5b**. Again a single isomer, *viz.*, the (E)-isomer was observed in pure $CDCl_3$, while a mixture of (E) and (Z)-isomers were seen in DMSO-d_6.

In pure $CDCl_3$ compound **5a** (**Spectrum No. 2**),

corresponding to the E-isomer showed a triplet at 3.37 for SCH_2 group protons and another at 4.12 corresponding to NCH_2 group protons. A sharp singlet was observed for =CH proton at 6.73 and a set of multiplets at 7.33 and 7.73 for phenyl ring protons and a broad peak at 13.75 for NH proton. In the mixture of $CDCl_3$ and DMSO-d_6 (4:1) the E,Z ratio was found to be 9:1. The signals in the ^{1}H NMR spectrum for the (Z)-isomer were assigned as follows. The triplets at 3.25 and 3.80 were assigned to SCH_2 and NCH_2 group protons respectively. A sharp singlet at 7.18 was assigned to =CH proton, and a set of multiplets at 7.32 and 7.70 for phenyl ring protons and a broad peak at 9.34 was assigned to NH proton. In pure DMSO-d_6 the (E)/(Z) ratio was found to be 60:40 (**Spectrum No. 2**). In $CDCl_3$ all the signals of (E)-isomer were sharp. Whereas, in a mixture of $CDCl_3$ and DMSO-d_6 signals corresponding to the (E)-isomer were sharp, while signals for the (Z)-isomer were broad. In pure DMSO-d_6 signals corresponding to both (E) and (Z) isomers were broad. Very similar results were obtained with compound **5b** also. The ^{1}H NMR data have been included in ***table 1*** (**Spectrum No. 4**).


DMSO-d_6
Spectrum No. 2
14
12
10
8
6
4
2
0 δ PPM


CDCl3
H
N
S
S
Ph
4·15
4·10
3·40
3·35
PPM
14
12
10
8
6
4
2
0 δ PPM


DMSO-d6
Spectrum No. 4
14
12
10
8
6
4
2
δPPM
0

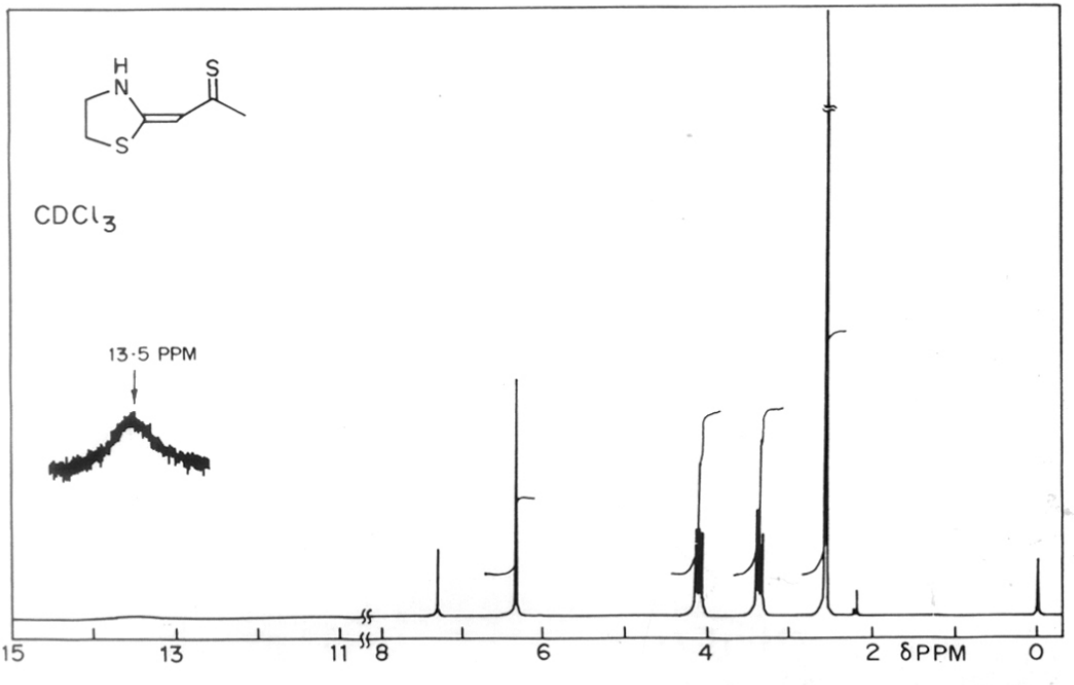

H
N
S
S
CDCl3
13·5 PPM
15
13
11
8
6
4
2
δPPM
0

Table 1. **^{1}H NMR Chemical shifts δ for 4a, 4b, 5a and 5b at 30°c.**

Solvent	NH		=CH		NCH_2		SCH_2	
	(E)	(Z)	(E)	(Z)	(E)	(Z)	(E)	(Z)
4a								
$CDCl_3$	10.58	-	5.91	-	3.88	-	3.22	-
DMSO-d_6	10.42	7.99	6.00	6.32	3.88	3.59	3.30	3.10
5a								
$CDCl_3$	13.77	-	6.73	-	4.12	-	3.37	-
DMSO-d_6	13.31	9.71	6.78	7.13	4.11	3.72	3.43	3.25
4b								
$CDCl_3$	10.09	-	5.28	-	3.85	-	3.19	-
DMSO-d_6	9.90	8.10	5.20	5.60	3.80	3.50	3.20	3.00
5b								
$CDCl_3$	13.50	-	6.31	-	4.08	-	3.34	-
DMSO-d_6	13.10	9.43	6.30	6.60	4.07	3.65	3.40	3.18

The relative amount of E and Z isomers of **4** and **5** are presented in ***table 2***.

Table 2. **E and Z ratio for compounds 4 and 5 at 20°c.**

		OXO (4)		THIO (5)	
R	Solvent	E%	Z%	E%	Z%
	$CDCl_3$	100	-	100	-
a	$CDCl_3$:DMSO-d_6 4:1	90	10	90	10
	DMSO-d_6	62	38	59	41
	$CDCl_3$	100	-	100	-
b	$CDCl_3$:DMSO-d_6 4:1	100	-	100	-
	DMSO-d_6	62.5	37.5	66.7	33.3

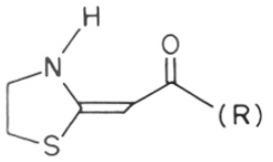
5.3. Discussion

In a non-polar medium like $CDCl_3$, the (E)-isomer is clearly preferred in view of the stabilizing NH..O (in **4**) or NH..S (in **5**) hydrogen bonding interaction. However, these substrates can exist in other tautomeric forms also (i - iii) (**Scheme 9**). But no signal was seen for CH_2 protons in the ^{1}H NMR spectra; hence it is reasonable to rule out the tautomer (ii). Earlier, in a similar study on the nitro compound **12**, the tautomer corresponding to (iii) had been eliminated also from ^{15}N NMR spectral studies[18].

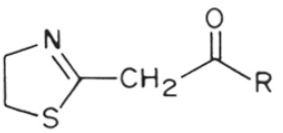
As DMSO-d_6 is added, the solvent is capable of functioning as a hydrogen bond acceptor. Although intramolecular hydrogen bonding remains highly favorable, carbonyl, thiocarbonyl and nitro groups in compounds **4,5** and **12** can reorient themselves, especially if alternative attractive interactions are possible. The (Z)-isomer provides the possibility of S..O interactions in **4** and **12**, S..S interactions in **5**.

Alternative explanations are conceivable for the observed conformational changes on changing the solvent. The population differences may be attributed to solvation of the

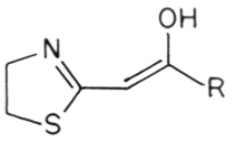
SCHEME-9



(i)

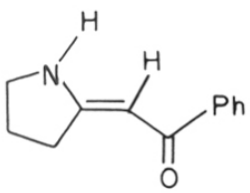


(ii)

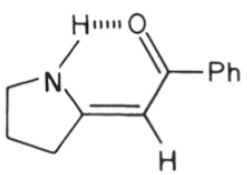


(iii)

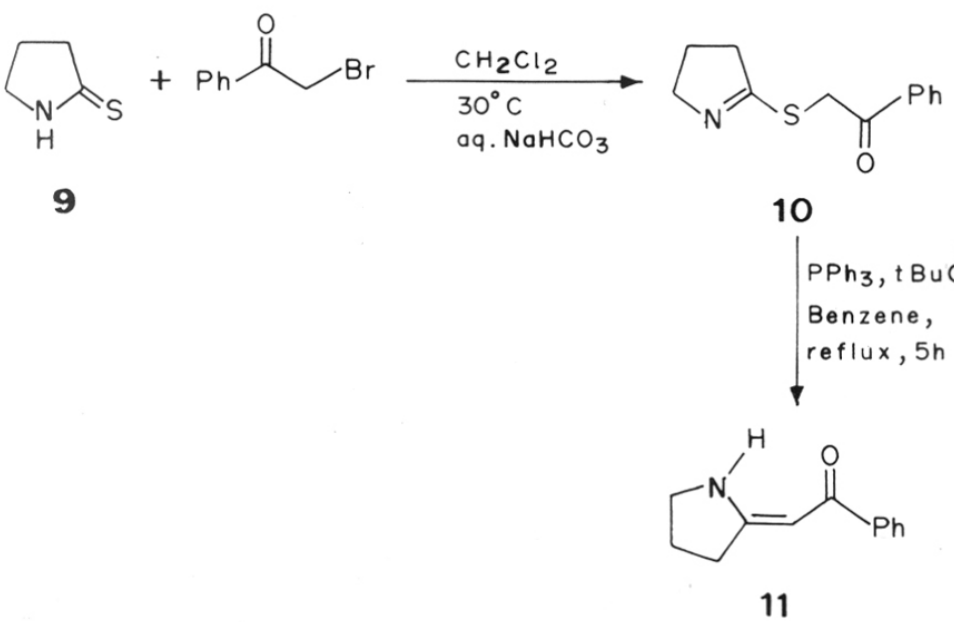
SCHEME-10



11 (E)



11 (Z)



9

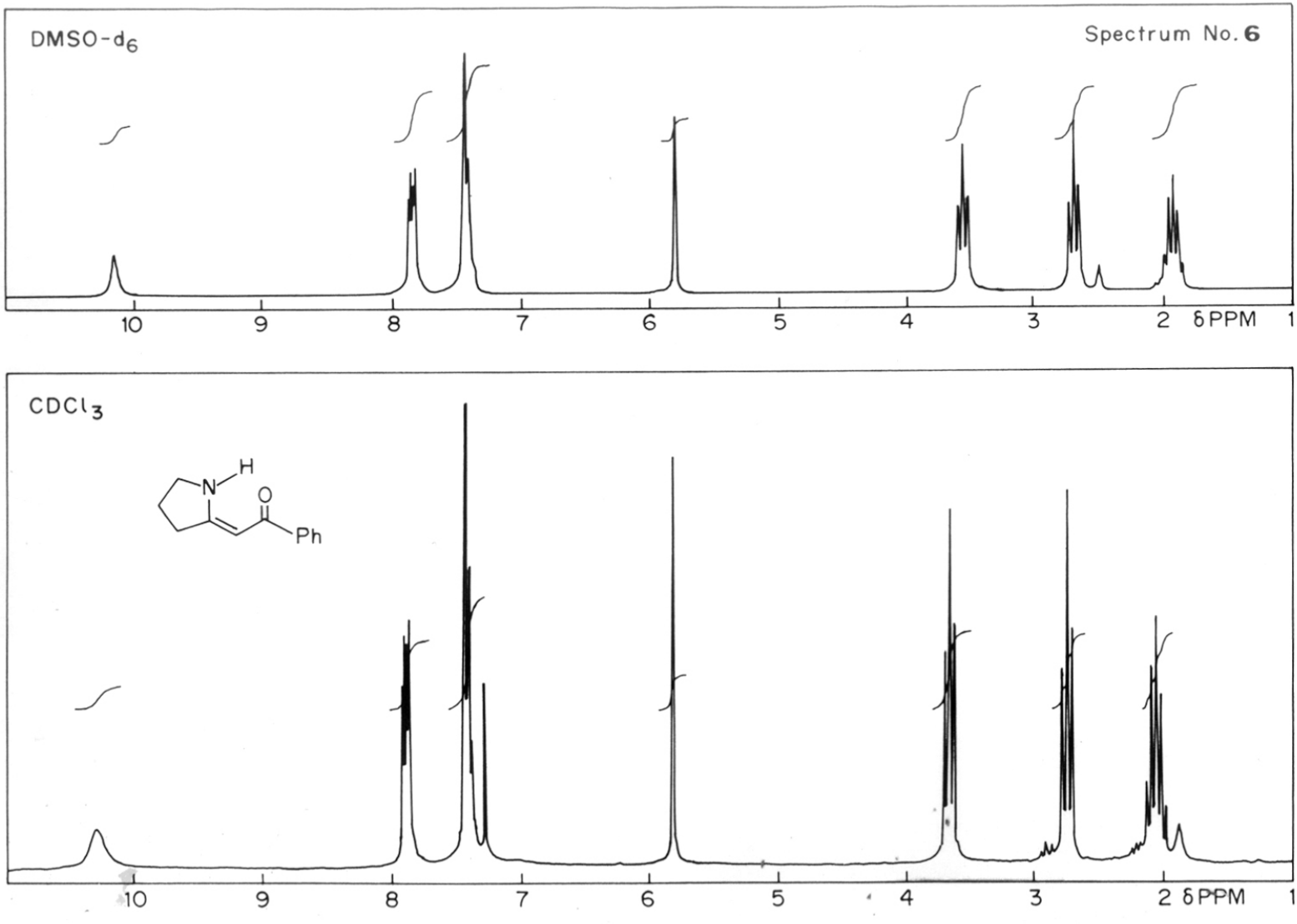
10

11

more polar conformer by DMSO. However, the (E)-isomers are expected to have a higher dipole moment in view of the relative parallel alignment of the bond dipoles. Hence the polarity effect can be discounted.

It is also possible that the steric effect of the bulky DMSO molecule has a role to play. The hydrogen bonding interaction between the N-H group and DMSO may be inhibited in the (E)-isomer. The crowding can be relieved by orienting the C-H bond, instead of the carbonyl unit, towards the N-H fragment, as in the (Z)-isomer. To rule out this plausible explanation and to establish the critical role of sulfur in producing the observed conformational changes, additional NMR studies were carried out on the pyrrolidinylidene derivative **11**.

2-Thiopyrrolidone was allowed to react with phenacyl bromide in presence of $NaHCO_3$ in methylene chloride to get the S-alkylated product. The sulfur extrusion reaction was carried out on this compound with PPh_3 in presence of catalytic amount of $tBuO^-K^+$ to get 1-phenyl-2-(2-pyrrolidinnylidine)-ethanone[19] in 96% yield (**Scheme 10**). In the infrared spectrum, the compound showed peaks at 1690, 1620, 1590 and 1540cm^{-1}. In the ^1H NMR spectrum, the multiplets at 2.10 and 2.75δ were assigned to the protons of the pyrrolinnylidine ring. A sharp singlet at 5.80δ was assigned to the C-6 carbon and the multiplets at 7.40 and 7.90δ were assigned to the protons on phenyl ring. A broad signal at 10.30δ was assigned to the NH proton. The structure of the compound was further confirmed by observing the molecular ion peak at 187 in the mass spectrum, the other fragment ion peaks were seen at 186, 110 and 77. In this model, the sulfur atom of **4a** is replaced by a methylene unit. While intramolecular NH..O hydrogen bonding is feasible, there is no possibility of non-bonded S..O interactions. Interestingly, the ^1H NMR spectra confirm that **11** exists exclusively in the (Z)-conformation, *i.e.*, hydrogen bonded form in both $CDCl_3$ and DMSO-d_6 solvents (**Spectrum No. 6**).


DMSO-d6
Spectrum No. 6
10
9
8
7
6
5
4
3
2
δPPM
1
CDCl3
H
N
O
Ph
10
9
8
7
6
5
4
3
2
δPPM
1

Therefore the role of steric effect on solvation by DMSO cannot be significant enough to cause (E) - (Z) conformational changes in these types of molecules. The only other plausible explanation for the observed conformer population differences, is based on S..O or S..S non-bonded interaction.

The relative magnitude of S..O and S..S interaction

The (E)/(Z) ratio of both the oxo and thio derivatives *i.e.*, compounds **4** and **5** in DMSO-d_6 is found to be 3:2. This constancy does not imply that S..O and S..S interactions are equally strong. The conformational equilibrium in **4** measures the strength of the S..O interaction relative to an intramolecular NH..O hydrogen bond. On the other hand, the corresponding processes in the thio derivatives, **5a** and **5b**, compare S..S interaction against the NH..S hydrogen bond. It is known that the NH..S hydrogen bond is weaker than the NH..O hydrogen bond[20]. The (E)/(Z) ratios of **4** and **5** in DMSO are similar despite the weak NH..S hydrogen bond; this indicates that the S..S interaction is weaker than the S..O attraction, each being slightly weaker than the corresponding (NH..S or NH..O) hydrogen bond strength.

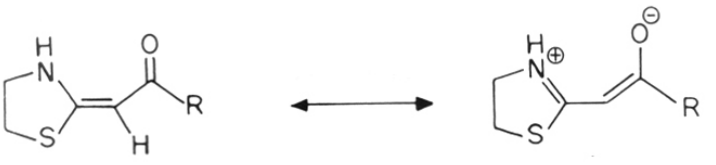
There is further spectral evidence for the relative weakness of the S..S interaction in **5**. The line widths of the peaks associated with the (E) and (Z) isomers of **4** and **5** show subtle differences. In $CDCl_3$, the signals are sharp in all the systems. However, in contrast to the spectra of **4**, the signals due to both the (E) and (Z)-isomers are broad for **5** in DMSO solvent. In a mixture of $CDCl_3$ and DMSO-d_6, the peaks assigned to the (E)-isomer of **5** are sharp, while line broadening was observed in all the signals due to the (Z)-isomer. These changes cannot be attributed to a hindered (E) - (Z) interconversion process, since the line widths of only the signals corresponding to the (Z)-isomer of thio compounds show temperature dependence in the mixed solvent system. Progressive lowering of the probe temperature from +20 to -35°c (solvent : 4:1 mixture of $CDCl_3$ and DMSO-d_6)

resulted in sharpening of the signals due to the (Z)-isomer of **5a**. At -35°c, all the lines are sharp. In contrast, the peaks due to the (E)-isomer are not broadened even at +20°c in the same solvent mixture.

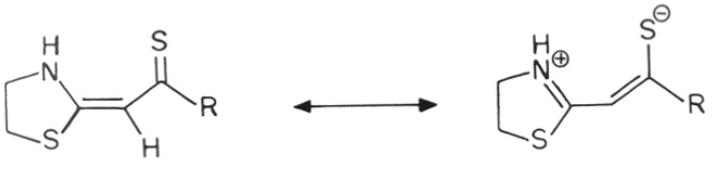
The above line broadening effects can be attributed to another conformational process, *viz.*, rotation about the C6-C7 bond (C=C-C=S torsion) in **5**. In the (E)-isomer, the intramolecular hydrogen bond would prevent such a rotation Since, 3a is exclusively in the (E) geometry in $CDCl_3$, all the signals are sharp, in the 4:1 solvent mixture of $CDCl_3$ and DMSO-d_6, the hydrogen bonds remain intact in the (E)-isomer, giving rise to sharp spectral lines. However, the (Z)-isomer, constituting *ca.* 10% of the total population undergoes restricted rotation about the C_6-C_7 bond leading to broadened lines. Clearly, the S..S attractive interaction in the (Z)-isomer is unable to prevent rotation about the C=C-C=S torsional angle. It may be concluded that the NH..S hydrogen bond is stronger than S..S interaction in **5**. Interestingly the intramolecular hydrogen bonds seem to be broken in the (E)-isomer in DMSO-d_6 medium. Since the solvent is capable of engaging the N-H unit in hydrogen bonding the rotation about the C_6-C_7 bond is enabled even in this isomer. Hence, line broadening is observed for all the signals, both (E), (Z) of **5a** in pure DMSO-d_6.

The corresponding line broadening effects were not seen in the oxo derivatives, **4**, in the same temperature range. This result can be interpreted in terms of a relatively strong S..O interaction. Such an attractive force in the (Z)-isomer is perhaps as effective as the NH..O hydrogen bond in the E-form in inhibiting rotation of the acetyl and the benzoyl groups, leading to sharp lines in the spectra of **4a** and **4b** in all the solvents examined. However, an additional factor may be responsible for the observed results. The push - pull interactions involving the carbonyl substituents are problably much more effective than in the corresponding thiocompounds The C_6-C_7 bond may have a larger bond order in the former, leading to a higher rotational barrier in **4** (see **Scheme 11**).

SCHEME-11



4



5

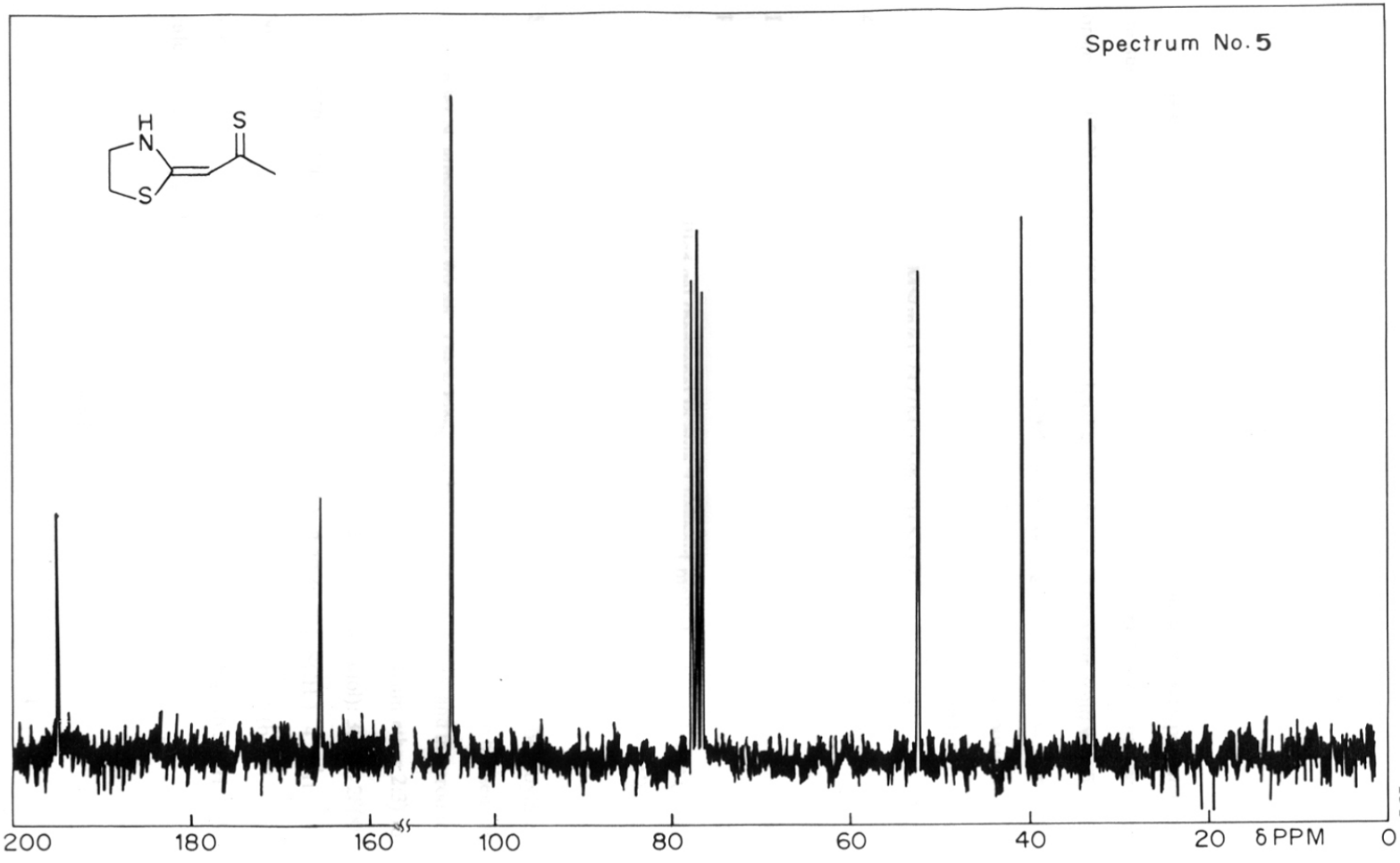
Hence the conformational constraints in the (Z)-isomer of **4a** and **4b** are perhaps a reflection of the π-delocalisation in these systems, rather than being just a measure of the strength of the S..O attractive interaction.

Based on the above experimental results, a relative order of magnitude among the four weak attractive forces S..O, S..S, NH..O and NH..S has been arrived at. The NH..O hydrogen bond is obviously the strongest among the four, followed by NH..S hydrogen bond. The magnitude of the S..O non-bonded interaction, according to the arguments made above, is larger than the S..S interaction. Hence, the order NH..O > NH..S > S..O > S..S is reasonable and logical.

5.4. Theoretical Results[21]

To provide support for the above spectral interpretations, a set of model systems related to the experimentally examined molecules were studied computationally by Prof. J. Chandrasekar at I.I.Sc., Bangalore. The semiempirical procedure[22], which lacks d orbitals was not used, since it is unable to reproduce the hypervalent nature of sulfur. Hence, by taking electronic effects into consideration, the *ab initio* methods (3-21G and 3-21G*) were used. The NH..O hydrogen bond strength in these systems was computed to be 6.5 kcals mol^{-1} and NH..S hydrogen bond 5.0 kcals mol^{-1}, S..O attractive interaction

3.1 kcals mol^{-1} and S..S interaction 1.1 kcals mol^{-1}. Thus, the magnitude of the interactions as computed is : NH..O > NH..S > S..O > S..S. This relative order is in agreement with that observed from the spectral study.


Spectrum No. 5
H
N
S
S
200
180
160
100
80
60
40
20
δ PPM
0

5.5. Experimental Section

Synthesis of 2-benzoyl methylenethaizolidine (4a): This compound was prepared by the sulfide contraction method[15]. A mixture of thiazolidine-2-thione (2.44g) and phenacyl bromide (4.0g)in acetone (35ml) was stirred at 30°c for 1h. The white solid was filtered and suspended in fresh acetone and stirred with K_2CO_3 (2.77g) for 1h. at 30°c. The solid was filtered off and the filtrate evaporated to leave a brown gum. This was purified on a silica column (benzene) to get 2-phenacylthio thiazolidine (3.8g) in 80% yield, m.p. 49°c; **IR**(nujol): 1750, 1590cm^{-1}; **MS**(m/e): 237 (M^+) (5%); ^{1}H NMR ($CDCl_3$): 3.38 (t, 2H, SCH_2), 4.02 (t, 2H, NCH_2), 4.67 (s, 2H, SCH_2), 7.33-7.56 (m, 3H, ArH), 7.87-8.0δ (d, 2H, ArH).

The above 2-phenacylthiothiazolidine (**3**) (2.38g) and triethylphosphite (1.66g) in DMF (35ml) was stirred under N_2 atmosphere at 100 - 110°c for 16h. The mixture was poured on ice-water (100ml) and the solid filtered. This was dried and purified by passage through a column of silica gel (benzene) to give 2-benzoyl methylenethiazolidine (1.4g) in 69% yield; m.p. 168°c; **IR** (nujol): 3200, 1600, 1580cm^{-1}; **MS**(m/e): 205 (M^+), 204 (100%).

Synthesis of 2-thiobenzoyl methylenethiazolidine (5a): A mixture of 2-benzoylmethylene thiazolidine (410mg) and Lawesson's reagent[16] (485mg) was stirred in benzene at 80°c under N_2 atmosphere for 4h. The solvent was then removed in *vacuo* and the product purified by chromatography on silica gel column (benzene and petroleum ether 2:3) to give 2-thiobenzoyl methylenethiazolidine, m.p.94°c; yield 75%; **IR**(nujol): 3000 - 2800, 1570, 1550, 1480, 1280, 1240cm^{-1}; ^{1}**H NMR** ($CDCl_3$): 3.37 (t, 2H, SCH_2), 4.12 (t, 2H, NCH_2), 6.73 (s, 1H, =CH), 7.33 (m, 3H, Ph), 7.73 (m, 2H, Ph) and 13.75δ (b, 1H, NH); **MS**(m/e): 221 (M^+, 83%), 220, 193, 128(100%), 121, 102, 77. **Found**, C,56.52, H,4.89, **calculated** for $C_{11}H_{11}NS_2$, C,56.17, H,4.68%.

Synthesis of 2-acetyl methylenethiazolidine[15,17] (4b)

i Synthesis of 1,1-Bis-methylthio-2,2-diacetyl ethylene (7): 2,4 pentanedione (10ml in dry benzene (150ml) was added to suspension of NaH (4.8g) in dry benzene (150ml). On addition of CS_2 (6ml) to the cooled mixture no reaction was evident, but on addition of DMF (150ml) the solution turned dark green and remaining NaH was consumed. The contents were cooled 10°c and CH_3I (12.5ml) was added. After 6h. stirring water(200ml) was added and the benzene layer was extracted with several portions of H_2O. Benzene was evaporated to get the S,S ketene acetal in 50% yield. The product was crystalized from MeOH, m.p. 59°c.

ii Synthesis of 2,2-diacetyl methylenethiazolidine (8): A mixture of 1,1-Bis-methylthio-2,2-diacetyl ethylene(4mmol) and 2-amino ethanethiol (4.1 mmol) is refluxed in absolute ethanol for 10h. On cooling the product crystalized out and is filtered and crystallized from absolute ethanol; **IR**(nujol): 3150, 1615, 1552, 1517cm^{-1}.

iii Synthesis of 2-acetyl methylenethiazolidine (4b): A mixture of 2,2-diacetyl methylenethiazolidine(1.85g) and NaOMe (1g Na in 30ml MeOH) is refluxed for 4h. Then 20ml of water was added extracted with $CHCl_3$ and solvent is evaporated to get the product in 90% yield; **IR**(neat): 3200, 1610, 1540, 1490, 1340cm^{-1}; ^{1}**H NMR**($CDCl_3$): 2.02 (s, 3H, CH_3), 3.19 (t, 2H, SCH_2), 3.85 (t, 2H, NCH_2), 5.28 (s, 1H, =CH), 10.09δ (b, 1H, NH); **MS**(m/e): 143 (M^+, 70%), 128 (100%), 101, 99, 97; ^{13}**C NMR**($CDCl_3$): 28.34 (CH_3), 28.88 (SCH_2), 49.47 (NCH_2), 89.99 (=CH), ^{13}**C NMR** (DMSO-d_6): 28.24, 28.53, NCH_2 peak is merged in DMSO-d_6 peaks, 89.33, 166.58, 190.42.

Synthesis of 2-thioacetyl methylenethiazolidine (5b): 2-Acetyl methylenethiazolidine (429mg) and Lawesson's reagent (0.6eq.) were stirred in dry benzene at 80°c for 12h. under nitrogen atmosphere. Solvent was evaporated and contents were taken into $CHCl_3$ and washed with water thrice, dried over Na_2SO_4. Solvent was removed to get relatively pure product in 85%; m.p. 100°c, **IR**(nujol): 3400, 1570, 1470, 1390, 1280cm^{-1}; ^{1}**H NMR**($CDCl_3$): 2.54 (s, 3H, Me), 3.34 (t, 2H, SCH_2), 4.08 (t, 2H, NCH_2), 6.31 (s, 1H, =CH),

13.50δ (b, 1H, NH); ^{13}C **NMR**($CDCl_3$): 33.12 (Me), 40.99 (SCH_2), 52.66 (NCH_2), 104.70 (=CH), 165.50 (N-C=), 194.81 (CS); ^{13}C **NMR**(DMSO-d_6): 29.16, 37.35, NCH_2 peak is merging in DMSO-d_6 peaks, 95.38 and S-C= and CS peaks are very weak; **MS**(m/e): 152 (M^+, 80%), 131 (100%), 126, 112, 99, 84, 66.

Synthesis of 1-phenyl-2-(2-pyrrolidinnylidene)-ethanone[15] (11): 2-Thiopyrrolidone (1.0g) and phenacyl bromide (2.2g, 1.1eq.) were stirred overnight at room temperature in methylene chloride. The solvent was removed and the contents were taken into benzene to get white solid which was washed with benzene. The solid was taken into methylene chloride and reacted with $NaHCO_3$ (1.0g) in water (15ml), stirred for 0.5h. at room temperature. The organic layer separated, washed with water and dried over Na_2SO_4. The solvent was evaporated to get the liquid; **IR**(neat): 1690, 1620, 1590, 1540cm^{-1}. The above liquid (1.09g) was taken into dry benzene (30ml) and PPh_3 (1.35g) and $tBuO^-K^+$ (20mg) were added to it and refluxed for 5h. Solvent was evaporated and the product was purified by column chromatography (benzene : ethyl acetate, 3:2), yield, 96%; m.p. 110 - 111°c, **IR**(nujol): 3300, 1625, 1610, 1590, 1540, 1470, 1390cm^{-1}; ^{1}**H NMR**($CDCl_3$): 2.10 (m, 2H, $NCCH_2$), 2.75 (t, 2H, =C-CH_2), 5.80 (s, 1H, =CH), 7.40 and 7.90 (m, 5H, Ph), 10.30δ (b, 1H, NH); ^{1}**H NMR**(DMSO-d_6): 1.90, 2.70, 3.60, 5.80, 7.40 and 7.85 and 10.20; **MS**(m/e): 187 (M^+, 70%), 186 (100%), 110, 105 and 77.

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