PART - II

Reactions of diazomethane with cinnamic esters and other olefins.

CHAPTER - I

Section-A : A short review on the structure of diazomethane and 1,3 cyclo additions and various reactions of diazomethane with olefinic double bonds.

Diazomethane is an extremely useful reagent principally employed for the methylation of compounds containing active hydrogen. The reaction of diazomethane with aldehydes and ketones can be used as a method for chain or ring homologation for epoxidation. The homologation of carboxylic acids, the Arndt Eistert reaction, is a particularly valuable synthetic procedure.

Diazomethane has been found to add to certain types of unsaturated bonds to give pyrazoles and pyrazolines and some aromatic compounds give cyclopropane derivatives. The catalytic decomposition of diazomethane by cuprous salts or by irradiation in the presence of olefins or aromatic compounds gives cyclopropanes or cycloheptatriene derivatives. Various other insertion reactions have also been reported.

The structure of diazomethane may be expressed by the following mesomeric forms.

$$H_2\overset{+}{C}-N=\bar{N} \longleftrightarrow H_2C=\overset{+}{N}=\bar{N} \longleftrightarrow H_2\bar{C}-\overset{+}{N}=N \longleftrightarrow H_2\bar{C}-N=\overset{+}{N}$$

Ia Ib Ic Id

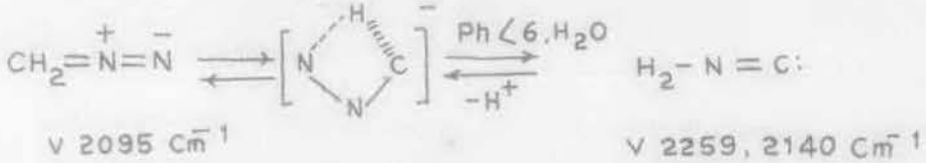
$$\longleftrightarrow H_2C=N\equiv N$$

Ie

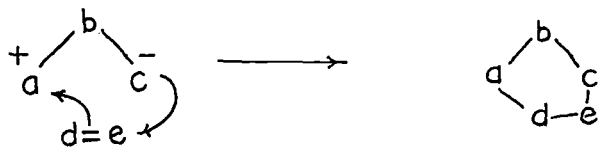
Undoubtedly, the ground state of the molecule is well represented by the two structures 1b and 1c, while 1a, 1d and 1e are less significant. However, it is just these higher energy (less contributing forms) which govern the electrophilic and neucleophilic character of these compounds.

Inspection of these 1a, 1d, 1e structures also disclose that the formal charges are inherent by interchargeable forms. Therefore it is in general, not meaningful to ascribe to certain centre electrophilic activity and to the second one nucleophilic activity.

The tautomerism of diazomethane has been discussed by Muller and Ludsteck



1,3-dipole may be defined as a system a-b-c, in which carries a formal positive charge (more or less vacant orbital) and (c) is an anionic centre having free electron pair. In the union of such a 1,3-dipole with a multiple bond system d = e, the so called dipolarophile, a cyclic shift of electrons accompanies and consummates closure of a five membered ring.

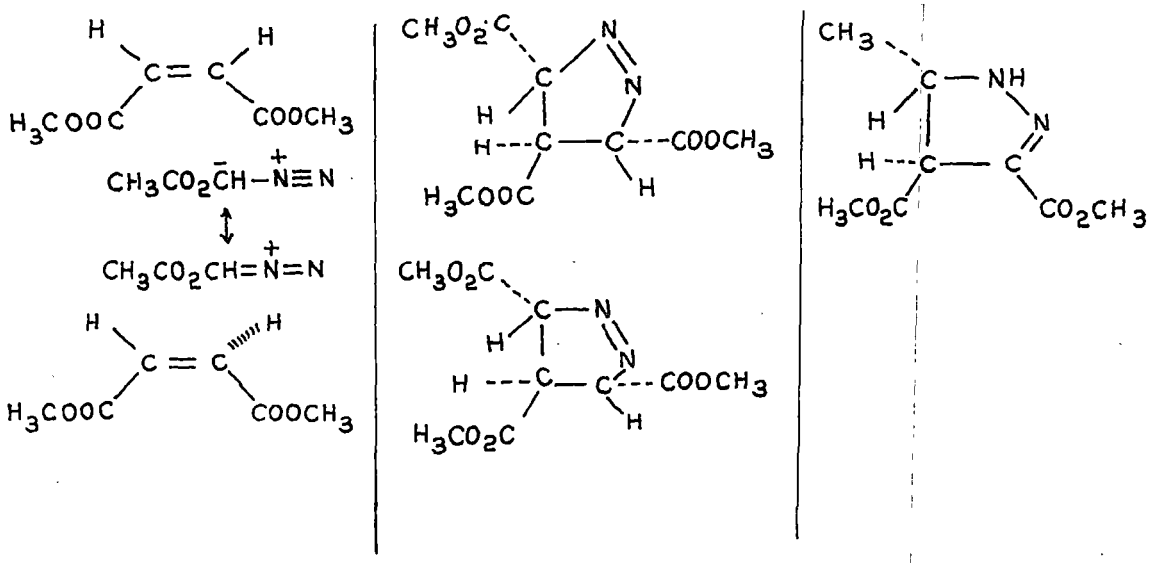


Compounds in which the positive centre a is an electron deficient carbon, nitrogen or oxygen atom are not capable of long lived existence. When the 1,3-dipole is an isolable substance, then the symbol employed above can only refer to a resonance structure of minor weight. Stabilisation of the reactive system is possible if a lone pair at fills the electron gap at a by forming an additional bond.

R.Carrie et al have shown that these reaction when carried out under no irradiation at low temperature proceed by way of the pyrazoline.

Formation of five membered rings through the addition of diazoalkanes toα β unsaturated esters was first observed in 1888 by Buchner (2).

The adduct from methyl diazoacetate and dimethyl fumarate is not the expected 1-pyrazoline, but instead the more stable 2-Pyrazoline-3,4-5bicarboxylate.



It is seen that both the esters give same product and this violation of cis addition is due to the tautomerisation of the initial 1-pyroazolines to 2-pyrozoline and thus loss of asymetric centre in question had occurred.

The addition of diazomethane to compounds containing carbon-carbon double bond has been found to give pyrazolines in high yield (3). In some cases unstable pyrazolines were formed which then decomposed to give either cyclopropane or C-methyl group. McGreer et al have suggested mechanism and conditions favouring cyclopropane or olefin formation.

The mechanism of the formation of pyrazolines has been the subject of much study and the original two stage process involving a diazonium betaine 4,5,6 (Fig. 54).

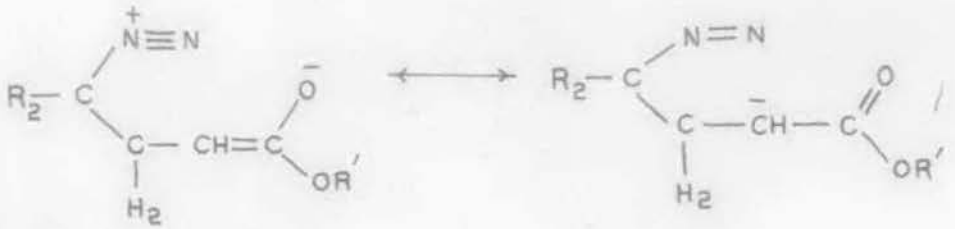


Fig – 54

This should readily lose nitrogen and should show rate enhancement with increasing solvent polarity. Many reactions, however, are known in which the pyrazoline are formed in excellent yield and for which there is no evidence of the production of cyclopropane intermediate. The addition of diphenyl diazomethane to

dimethyl fumerate using a number of solvents has been investigated and it was found that there is little difference in the rate factors (8). It was thus postulated by Huisgen (7) that the addition of diazoalkanes to carbon-carbon double bonds occurs by multicentre process (Fig. 55).

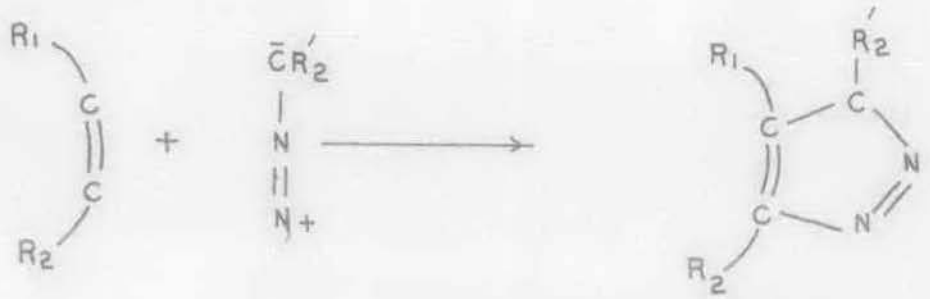
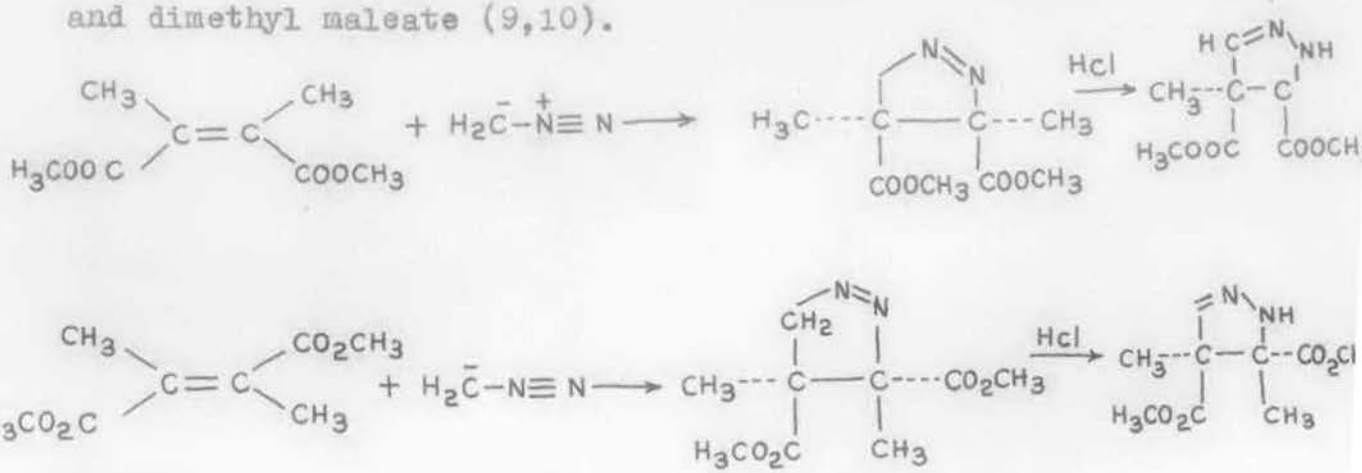


Fig - 55

This view point is supported by much evidence including the stereospecific addition of diazomethane to dimethyl fumerate and dimethyl maleate (9,10).

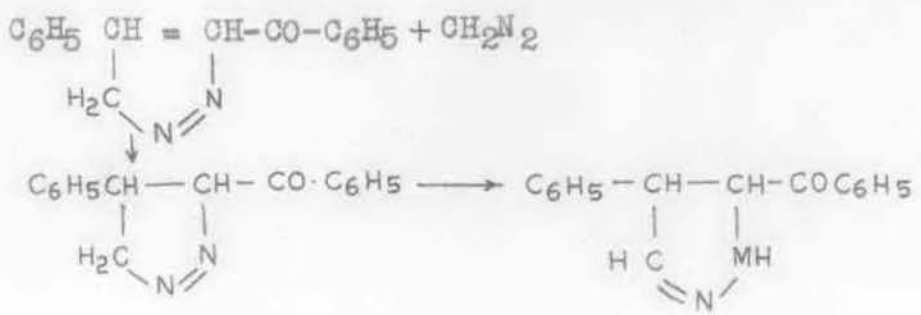


Rate studies indicate that they are electrophiles with low discriminatory ability among various alkenes. The carbene, catalyst, olefin are all involved in the transition step for addition.

Ledwith and Parry found that the reaction rates were independent of the polarity of the solvent and suggested a concerted 1,3 dipolar cyclo addition mechanism for the formation of pyrazolines from diazoalkanes and conjugated olefins.

It has also been found that both the rate of addition and the stability of pyrazoline is greatly affected by the structure of the alkane. Thus, conjugated carbonyl and nitrile groups increase both the rate of reaction and the stability of pyrazoline, and trans-alkenes are found to be more reactive than cis alkenes.

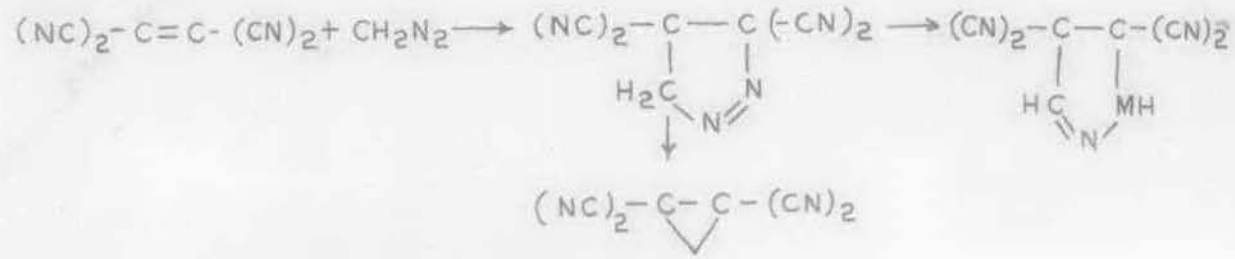
The pyrazolines formed have the structure expected from a consideration of electronic effects. The nucleophilic carbon of diazomethane becomes attached to the most electrophilic carbon of the double bond e.g. in the case of unsaturated esters and ketones, the β -carbon atom. These points are examplified by the addition of CH_2N_2 to benzal acetophenone (Fig. 56) to form 3-benzoyl-4-phenyl-1-pyrazoline which is readily transformed to the 2-pyrazoline (12 a,b).



(56)

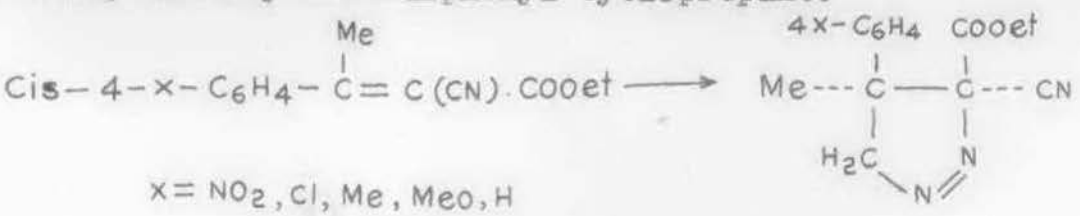
Electron releasing substituents have been found to decrease the rate of formation of the pyrazoline (13 a,b).

The addition of diazomethane to a variety of alkenes containing electron withdrawing substituents on the α-carbon atom has provided a convenient method for the formation of pyrazoline. Tetracyano ethylene in dry ether on treatment with CH_2N_2 in dry ether gave 3,3,4,4-tetra cyano-1-pyrazoline in 72% (14).



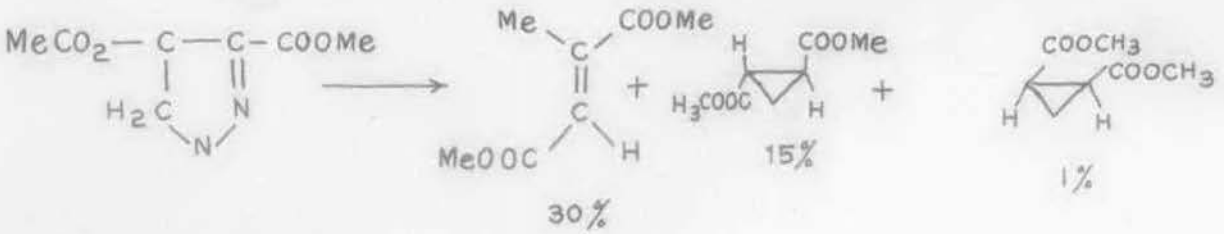
Certain $\alpha\beta$ unsaturated acids have been shown to give the methyl pyrazoline-3-carboxylates with diazomethane (15 a,b).

The addition of diazomethane in ether to ethyl α-cyano-β phenyl-4-substituted cinnamates at low temperatures proceeded in a stereo specific manner to give the corresponding cis or trans-1-pyrazolines (16). Ethyl α-cyano- β-phenyl-cinnamate gave an unstable pyrazoline which decomposes to 1-cyano-1-ethoxy carbonyl-2-2-diphenyl cyclopropane.



So from the above discussion it is seen that in certain cases, 1-pyrazoline, initially formed may then either lose nitrogen to give a cyclopropane or C-methyl derivatives or isomerise to a 2-pyrazoline. But these type of transformation from 1-pyrazoline involve an energy barrier.

Now formation of cyclopropanes by the action of diazomethane on an alkene may occur by several routes. In some cases an unstable pyrazoline is formed which may then lose nitrogen readily, or application of heat may be necessary to remove the nitrogen to form the cyclopropane or olefin. The direct formation of cyclopropanes has also been observed, generally by the photolytic decomposition of CH_2N_2 in the presence of some metal catalyst to give a methylene radical which then adds to alkene. Amongst the earliest worker's to record the formation of cyclopropanes from pyrazoline were Von Auwers and Koeng (10 a,b).

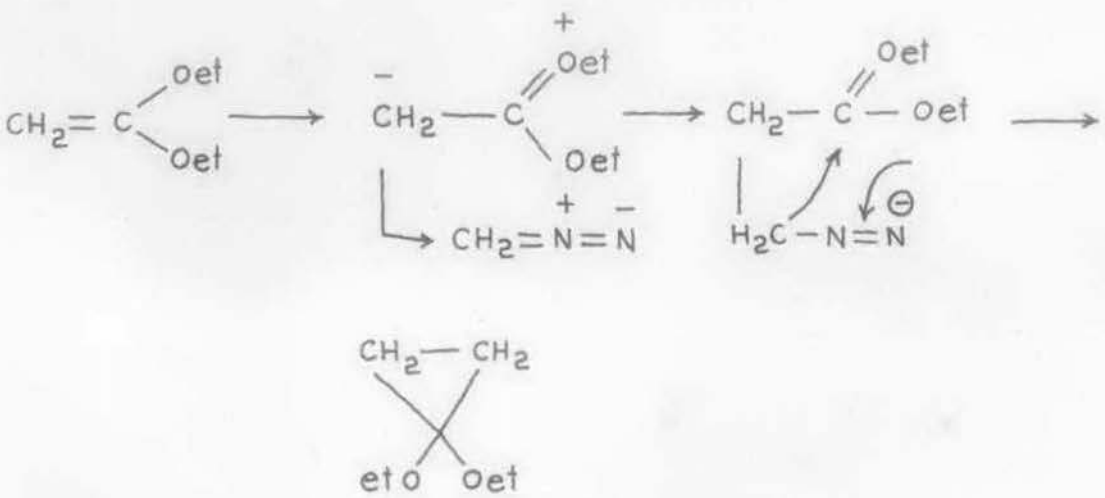


A paper by McGreer (17) confirmed the formation of both unsaturated esters and cyclopropanes and also gave evidence for the formation of both $\alpha\beta$ and $\beta\gamma$ unsaturated esters. The thermal

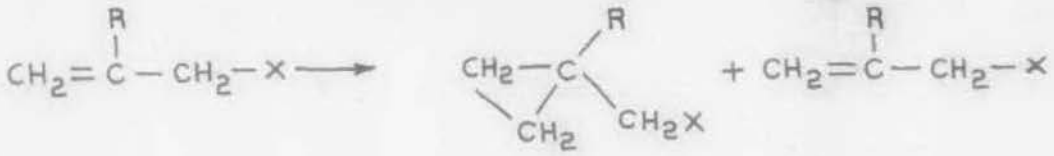
decomposition of pyrazolines to cyclopropanes has been found to occur in a nonstereospecific manner (18). Whereas photolytic decomposition of pyrazolines occurred in stereospecific manner.

The thermal break down of 2-pyrazolines has been investigated (20 a,b,c) and it was concluded that the products produced did not depend upon their relative thermolytic stabilities but were formed by decomposition of the tautomeric 1-pyrazolines and hence depended on the relative thermodynamic stabilities of the intermediate 1-pyrazolines.

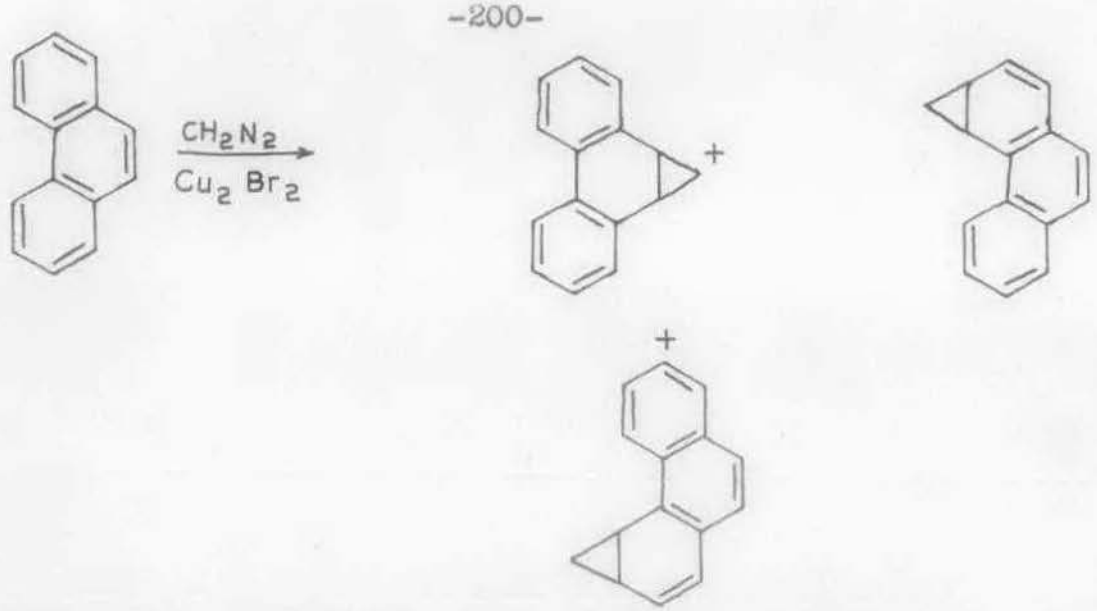
The direct addition of methylene to alkenes or aromatic compounds has been found to occur in the presence of cuprous salts as catalyst or using irradiation techniques. One of the first examples of the copper catalysed addition of diazomethane to alkenes was given by Dull and Abend (21) who found that ketone diethyl acetal and phenyl ketone diethyl acetal gave cyclopropanone diethyl acetal and phenyl cyclopropanone diethyl acetal respectively in presence of Cu_2Br_2 in 50% yield.



The formation of cyclopropanes by the addition CH_2N_2 to allyl halides has been investigated by Kirmse and his co-workers (22 a, b) and they found that two products were obtained. Cyclopropyl methyl halides and 4-halogenobutenes.



Certain heterocyclic aromatic compounds have been cyclo propanated with CH_2N_2 in the presence of Cu_2Br_2 (23). The formation of cyclopropane derivatives from certain polynuclear aromatic hydrocarbons, generally in the presence of a cuprous salt, has been investigated by numerous workers. The diazo-methane adds at both the most active sites and the most active double bonds in the molecule, and also sometimes gives insertion products. Phenanthrene, for example, gave a mixture of two cyclopropane derivatives in the ratio 3:1 respectively (24 a,b) and anthracene also gave a mixture of three homologues (25). Napthalene was found to react in an analogous manner to give both cyclopropane and tropilidene derivatives, the yield of cyclopropane increasing when the reaction was carried out at low temperature. Pyrene was also found to give a cyclopropane derivatives when treated with CH_2N_2 (26).



Section-B: Aims and Objects:

With a view to explore the case of c-alkylation some of different substituted ß-phenyl methyl acrylate i.e. cinnamic esters (trans), and compare yields, products formed and study reactivity of 1,3 dipolar cyclo addition of diazomethane to unsaturated esters. The substitution of the phenyl ring was varied viz. carbomethoxy and chloro (Fig. 57).

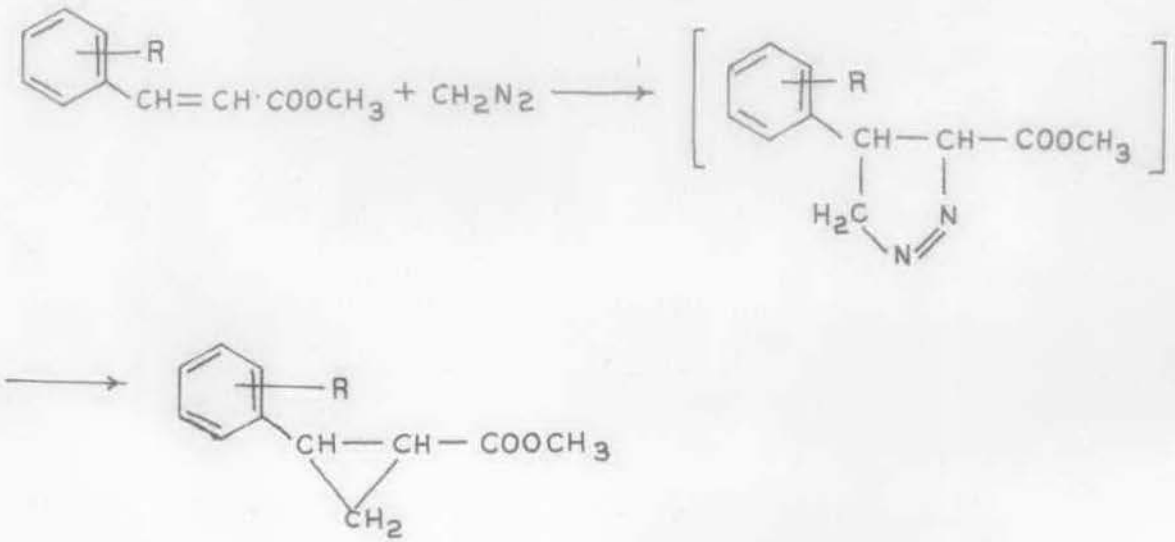


Fig- 57

Our observation in these reactions is that in all the cases 2-pyrazoline was isolated instead of 1-pyrazoline or C-methyl or cyclopropane derivatives. Probably intially formed 1-pyrazoline was easily isomerised to stable 2-pyrazoline (Fig. 58).

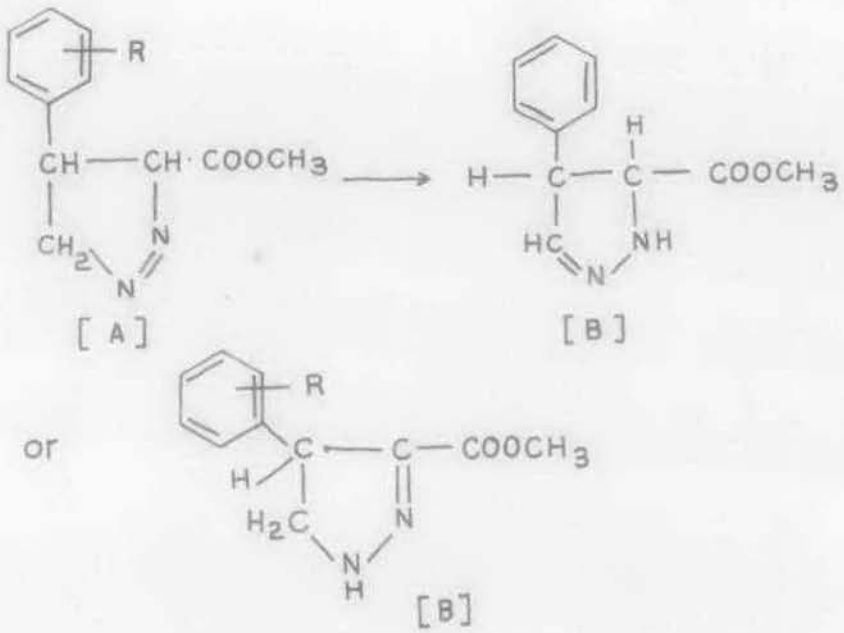


Fig- 58

These 2-pyrazoline were heated to reflux for a long time in xylene in order to eliminate nitrogen from the 2-pyrazoline and obtain cyclopropane derivatives. But in all cases 2-pyrazoline was recovered and so elimination of nitrogen was not facile. No trace of cyclopropane isolated in our subsequent work up. So the 2-pyrazolines prepared from trans o-substituted cinnamic ester (by electron with drawing groups) are highly stable at the boiling point of xylene and no tautomerism occurs at this temperature between A and B of the Fig. 58.

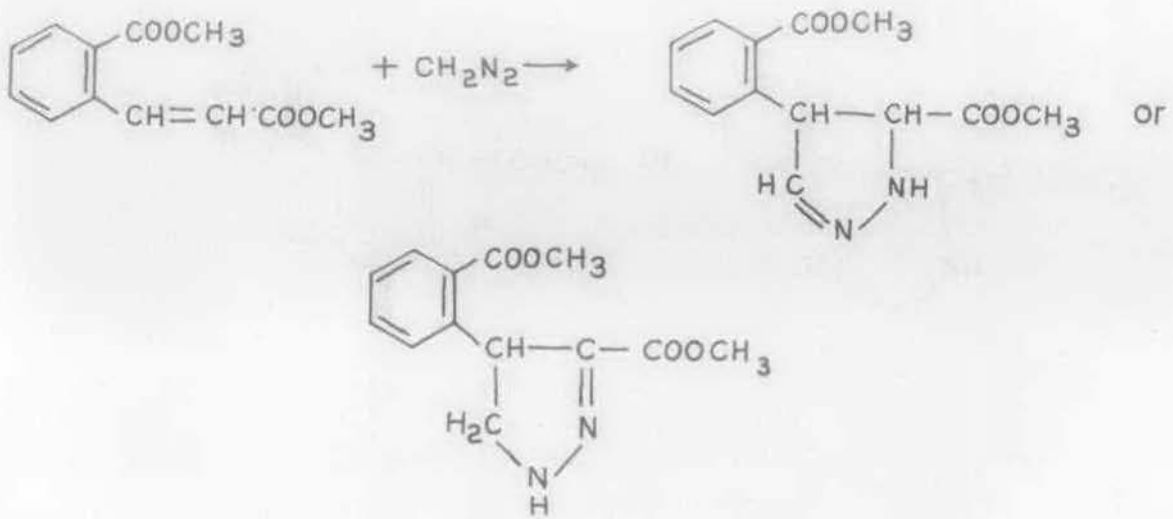
As 2-pyrazoline thus formed from the trans-substituted cinnamic esters (o or p-substitution by electron withdrawing group) is highly stable, so cyclopropane derivatives of these esters could not be synthesised with diazomethane without any catalyst.

Section-C: Results and Discussions

Reaction of diazomethane with dimethyl esters of o-carboxy cinnamic acid.

The reaction product of diazomethane and dimethyl ester of o-carboxy cinnamic acid was chromatographed and purified by repeated crystallisations. The structure of these product was confirmed to be 3-carbomethoxy-4-(o-carbomethoxy) phenyl-2-pyrazoline by elemental analysis, I.R., Mass and N.M.R.

I.R. band at 3400 cm^{-1} indicated for secondary NH group, M/e = 262.

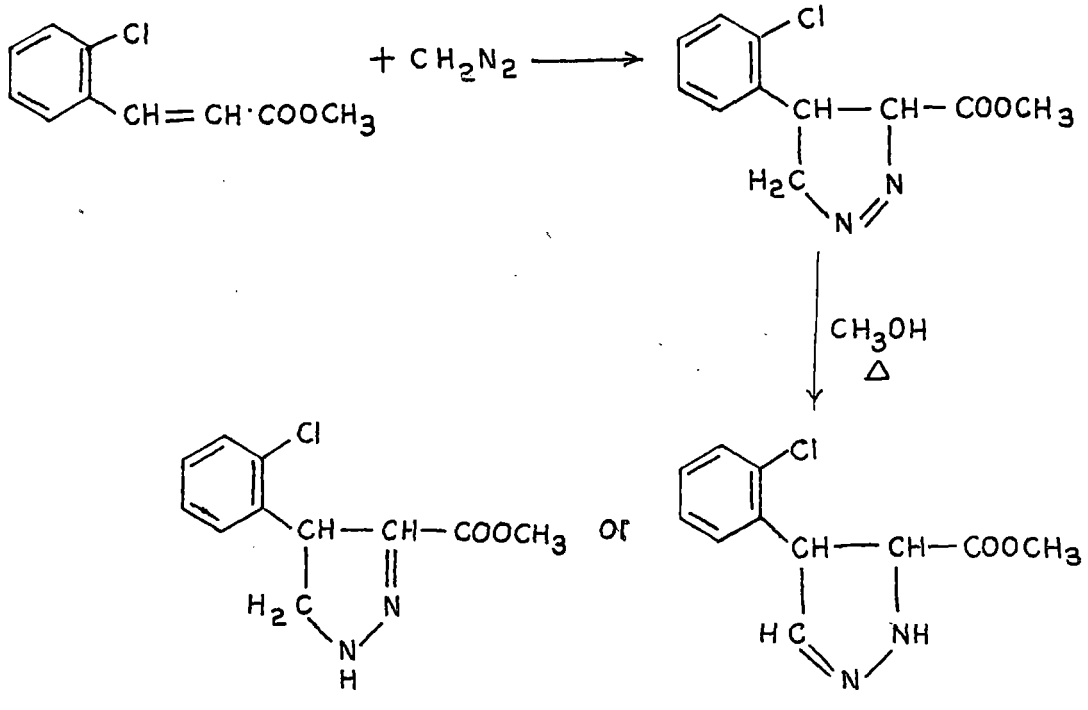


Reaction of diazomethane with o-chloro methyl cinnamate.

The crude reaction product of these two reactants was subjected to U.V, absorption and it was seen that it absorbed max 318 (Fig.). But as soon as it was crystallised from methanol, it UV max shifted to 280 nm. This indicated that there occurred a quick tautomerism in presence of methanol.

The structure of this product was confirmed to be 3-carbomethoxy-4-(o-chloro) phenyl-2-pyrazoline by means of elemental analysis, I.R. and mass spectta.

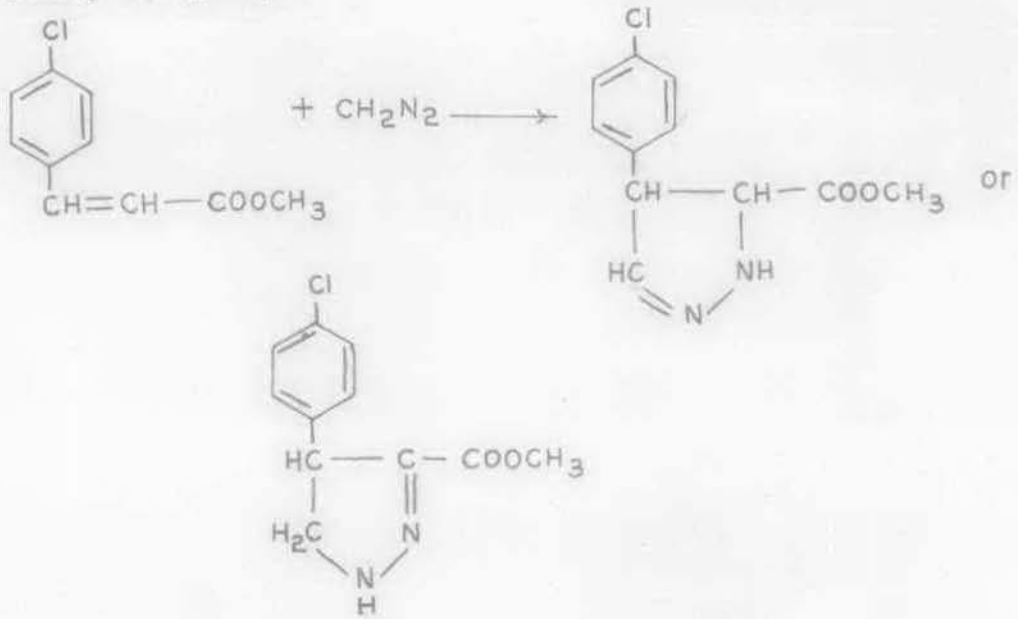
I.R. peak at 3400 cm^{-1} indicated for secondary NH group. M/e = 240.



Reaction of diazomethane with p-chloro methyl cinnamate.

The structure of the reaction product of these two substrates was also confirmed to be 3-carbomethoxy-4-(p-chloro) phenyl-2-pyrazoline by means of elemental analysis, I.R.

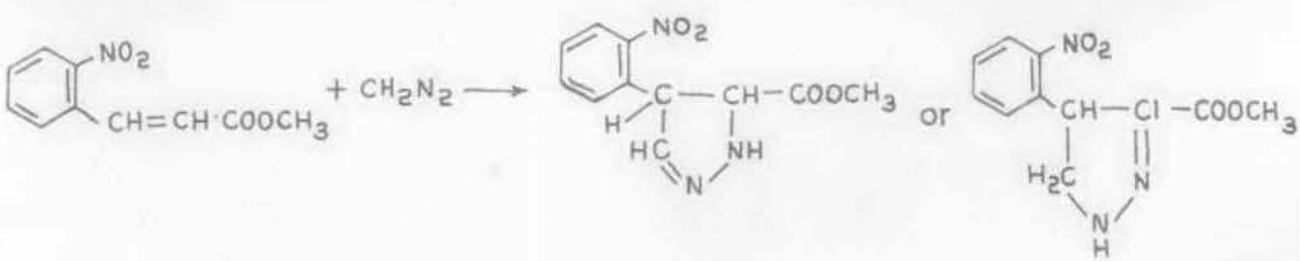
I.R. peak at 3400 cm^{-1} indicated the presence of secondary NH group.



Reaction of diazomethane with o-nitro methyl cinnamate.

The structure of the reaction product of these two substrates confirmed to be 3-carbomethoxy-4-(o-nitro) phenyl-2-pyrazoline by means of elemental analysis, I.R.

I.R. peak at 3400 cm^{-1} indicated the presence of NH group.



Reaction of diazomethane with mesityl oxide.

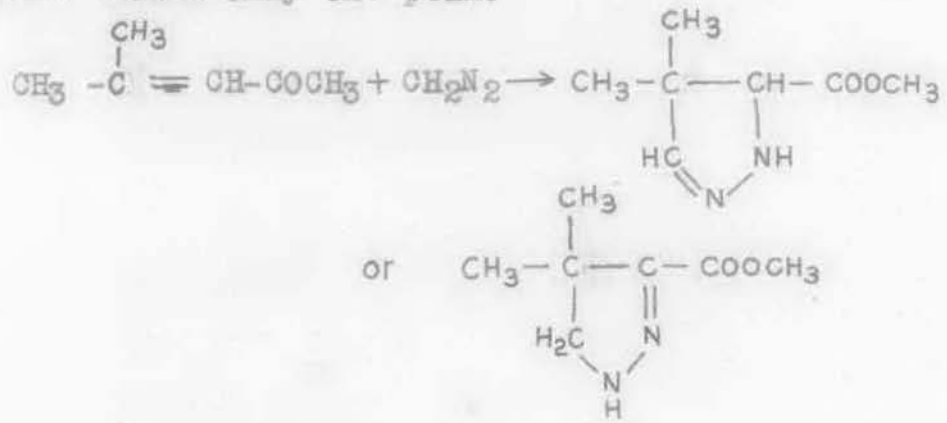
The crude reaction product of these two substrates showed U.V. max at 318 nm. But after purification by distillation, U.V. absorption max at 282 nm indicating the presence of $-N = C.COOCH_3$ group.

It's structure was confirmed to be 3-acetyl-4-methyl 2-pyrazoline by means of elemental analysis, I.R. G.L.C.

U.V. max at 282 nm.

I.R. peak at 3400 cm^{-1} (broad) indicated the presence of secondary NH group.

G.L.C showed only one peak.

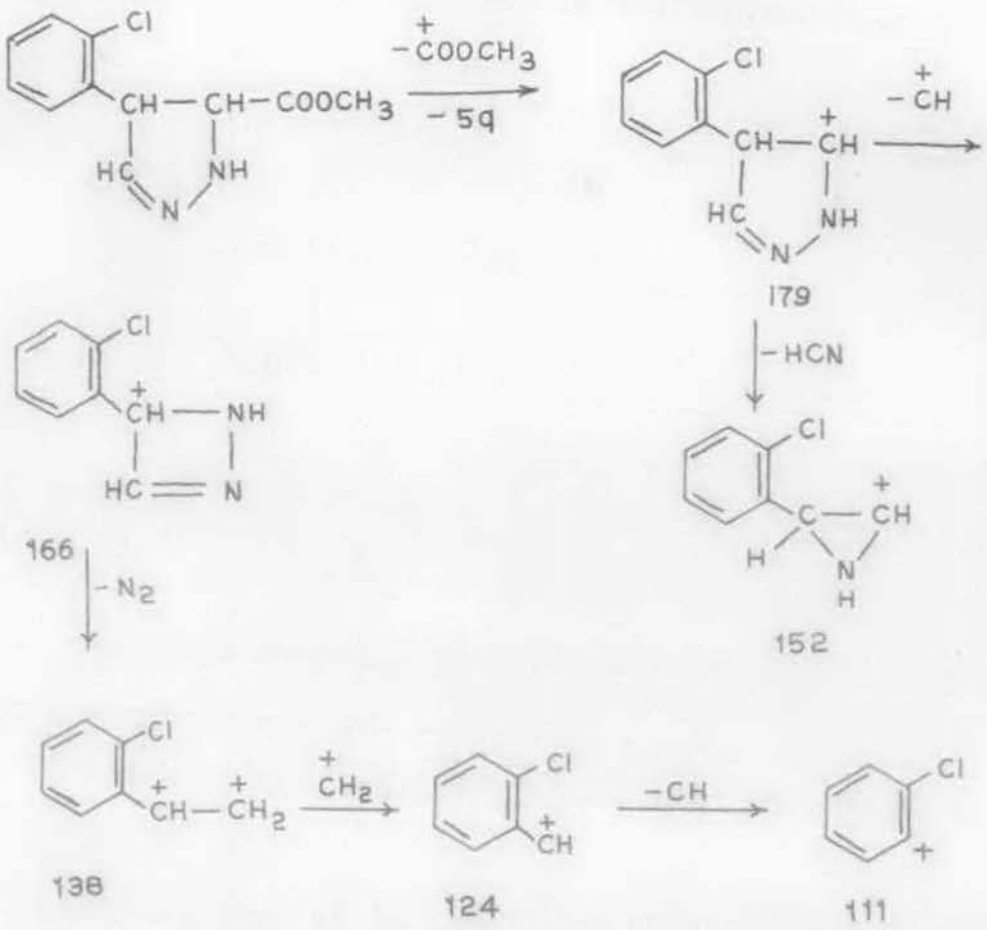


Mass spectrum of 2-pyrazoline.

Peaks of mass spectrum of 3-carbomethoxy-4-(o-chloro) phenyl-2-pyrazoline are as follow.

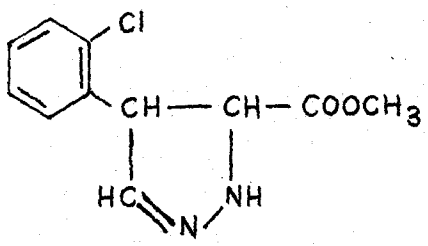
238, 179, 166, 152, 138, 124, 111, 72, 59, 44, 28.

So the decomposition had occurred in the following path.



Peaks at 44 indicating elimination of CO_2 from the compound and strong peak at 28 indicates that the compound contains two nitrogen atoms attached to each other.

These fragmentation patterns can well be explained if the structure of the compound is written as follow whose molecular wt. is found to be 238.



Mass spectrum peaks of 3-carbomethoxy-4-(o-carbomethoxy) phenyl 2-pyrazolene are as follow.

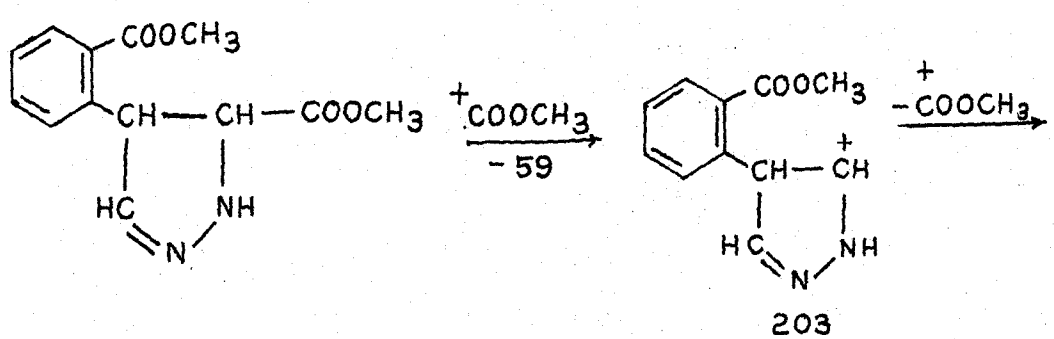
262(M^+), 203, 144, 131, 116, 103, 89, 76, 59,

44 and 28.

Strong peak at 28 indicated that the compound contains two nitrogen atoms attacked to each other.

Peak at 44 indicates the elimination of CO_2 from its ether function.

Other fragmentation of the product can be explained by the following way.



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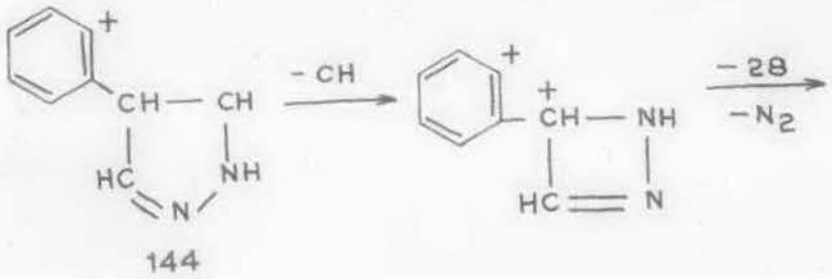

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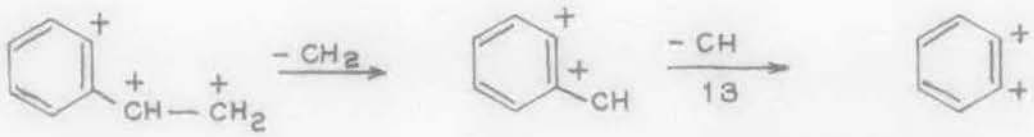
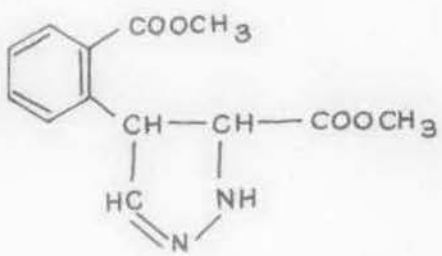


103 89 76

So on the basis of the mass fragmentations, the structure of this compound whose molecular wt. is 262 may be written as follows.



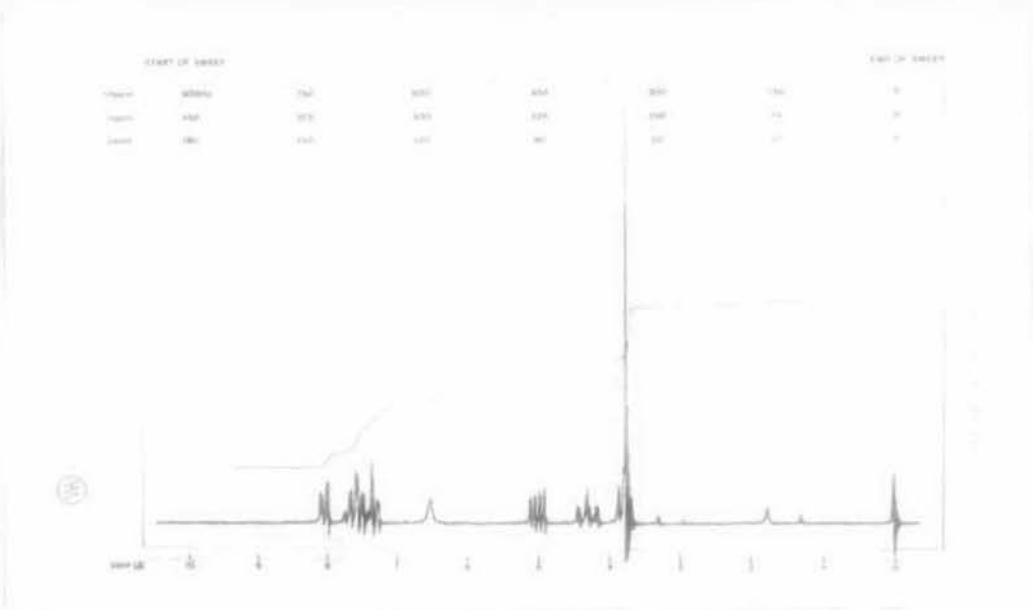


Fig. P.16 N.M.R. spectrum of 3-carbomethoxy-4-(o-nitro) phenyl-2-pyrazoline.

N.M.R. spectrum of 2-pyrazoline.

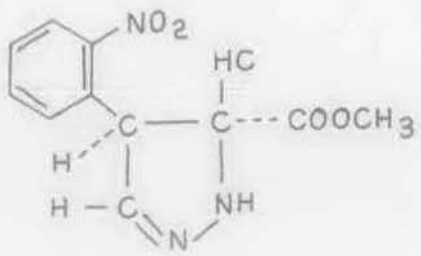
In the previous discussion about the structure of 2-pyrazoline, we had discussed I.R., U.V. and mass spectrum to explain the structure of 2-pyrazoline. Now with the help of N.M.R., we would like to confirm the structure of the reaction product of trans o-nitromethyl cinnamate and diazomethane.

It is reported (27) that proton signals for 4, 4.5, 5 tetramethyl-2-pyrazoline cis-3-carboxylate are as follows. δ 8.95 and 8.92 (12H), δ 6.78 (3H of carbomethoxy) and δ 4.2 broad (1H, NH). It is also reported in this paper also that all the 2-pyrazoline, there is a broad peak at δ 4.2 to δ 4.5. So it can be concluded that the characteristic peak of 2-pyrazoline is due to NH hydrogen.

N.M.R. signals of the reaction product of trans o-nitro methyl cinnamate and diazomethane in $CDCl_3$ are as follows. Fig. δ 7.3 to 8.1 (phenyl proton), δ 3.8 (CH_3 of carbomethoxy group), δ 5.2 broad (1H of NH), δ 6.5 (olefinic proton of CH = N)

and δ 4.15 to δ 4.45 quasi triplet (for H_a and H_b).

These results satisfy the structure given below for the reaction product.



Section-C: Experimental

Melting points and boiling points are uncorrected. Dry solvents were used where necessary. I.R. spectra were recorded in a Beckmann IR-20 Spectrophotometer. Mass spectrum were taken in a mass spectrophotometer in C.D.R.I., Lucknow. N.M.R. spectrum was determined on a VA-90 MHz N.M.R. Spectrophotometer using chloroform-d solution containing tetramethyl silane as internal reference.

1. Reaction of diazomethane with dimethyl ester of o-carboxy Cinnamic acid:

A mixture of 200 ml of ethereal solution of 1.47 gm of diazomethane (dried over potassium hydroxide pellets for 6 hrs.) and 50 ml ethereal solution of 2.2 gm of dimethyl ester of o-carboxy cinnamic acid was kept for 18 days in a dark and

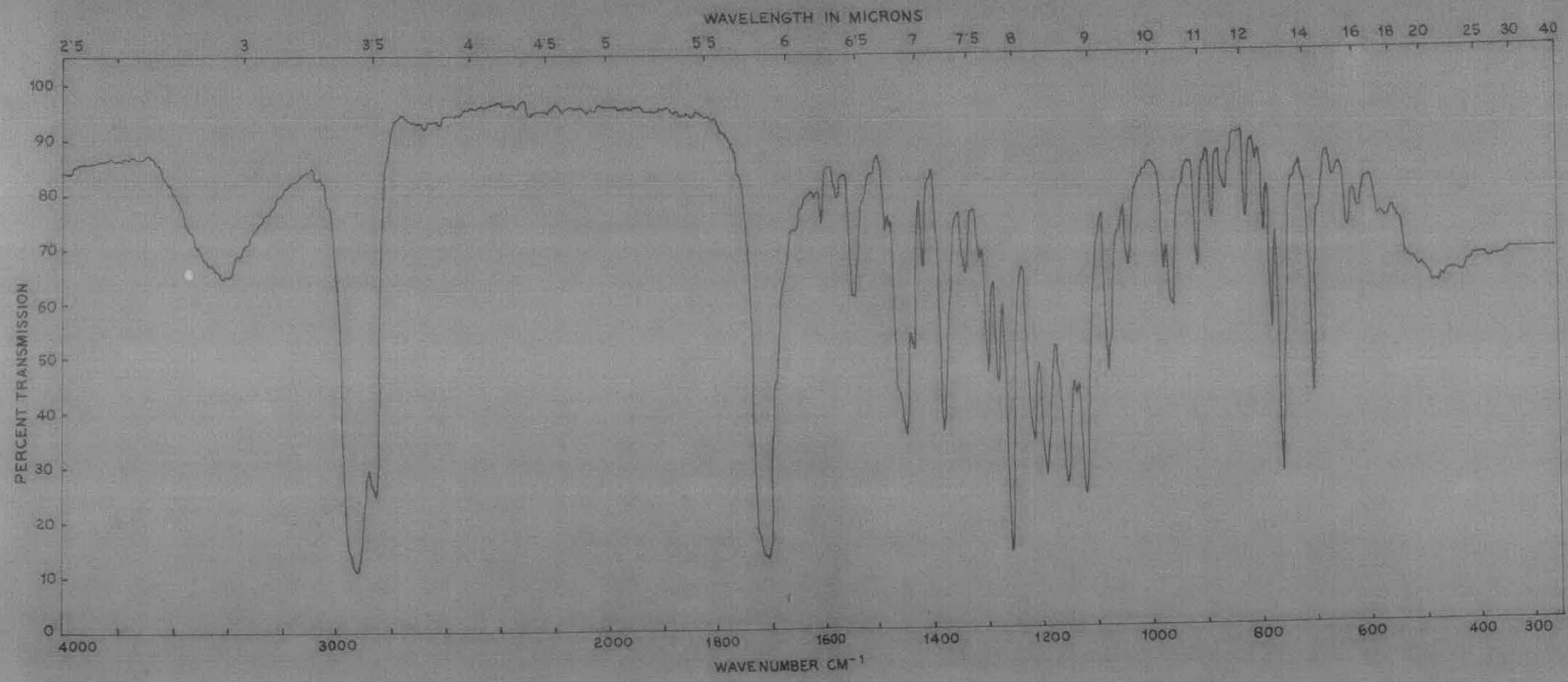


Fig- 48. 3- Carbomethoxy-4- (o- carbomethoxy) phenyl-2- pyrazoline.

cool place. When the colour of the diazomethane was no longer found to be present; ether was removed completely at reduce pressure. An oily liquid remained in the flask.

U.V. of this oily liquid showed peak at λ_{max} 314 nm and also positive test for nitrogen. Attempted crystallisation from dry methanol did not succeed.

It was then chromatographed over alumina and the fraction eluted with 60% benzene and 40% pet-ether solvent mixture crystallised from dry methanol. This, after several recrystallisation from dry methanol gave colourless crystals m.p. 191°. Yield-1.2 gm

I.R. shows peak at 3400 cm^{-1} for secondary NH grouping. Fig. 48.

Analysis found: C, 58.5%; H, 5.35%

Calculated for $C_{13}H_{14}O_2N_2$: C, 59.53%; H, 5.59%.

Mother liquor was further concentrated, but no crystals could be separated.

The alumina column was washed down with ether, which on evaporation did not afford any solid product. A semi solid product separated. which was identified as the ester starting material.

Mass spectrum Fig. P.19.

2. Reaction of diazomethane with methyl ester of o-chloro cinnamic acid.

A mixture of 200 ml of ethereal solution of diazomethane (1.2 gm) and 50 ml ethereal solution of 1.96 gm of the ester

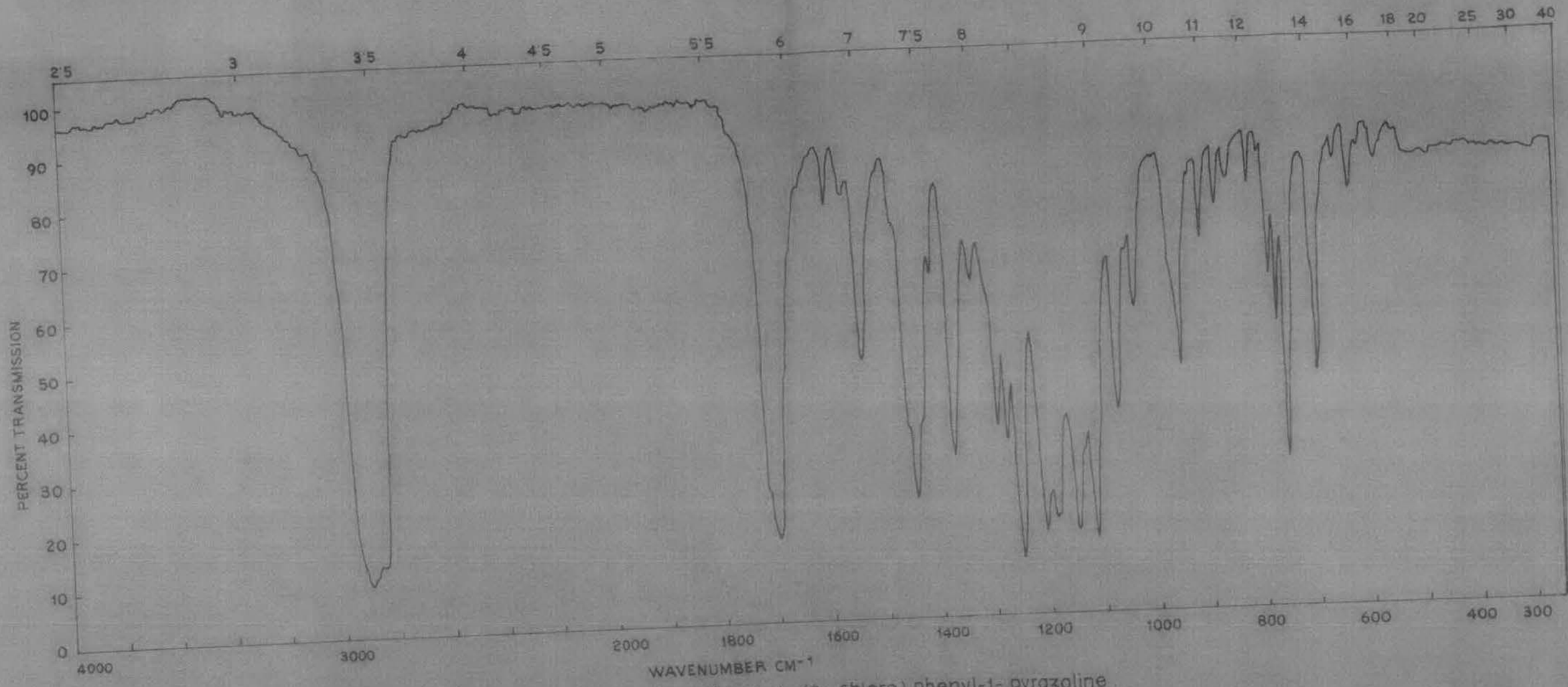


Fig- 49. 3- Carbomethoxy- 4- (o- chloro) phenyl-1- pyrazoline

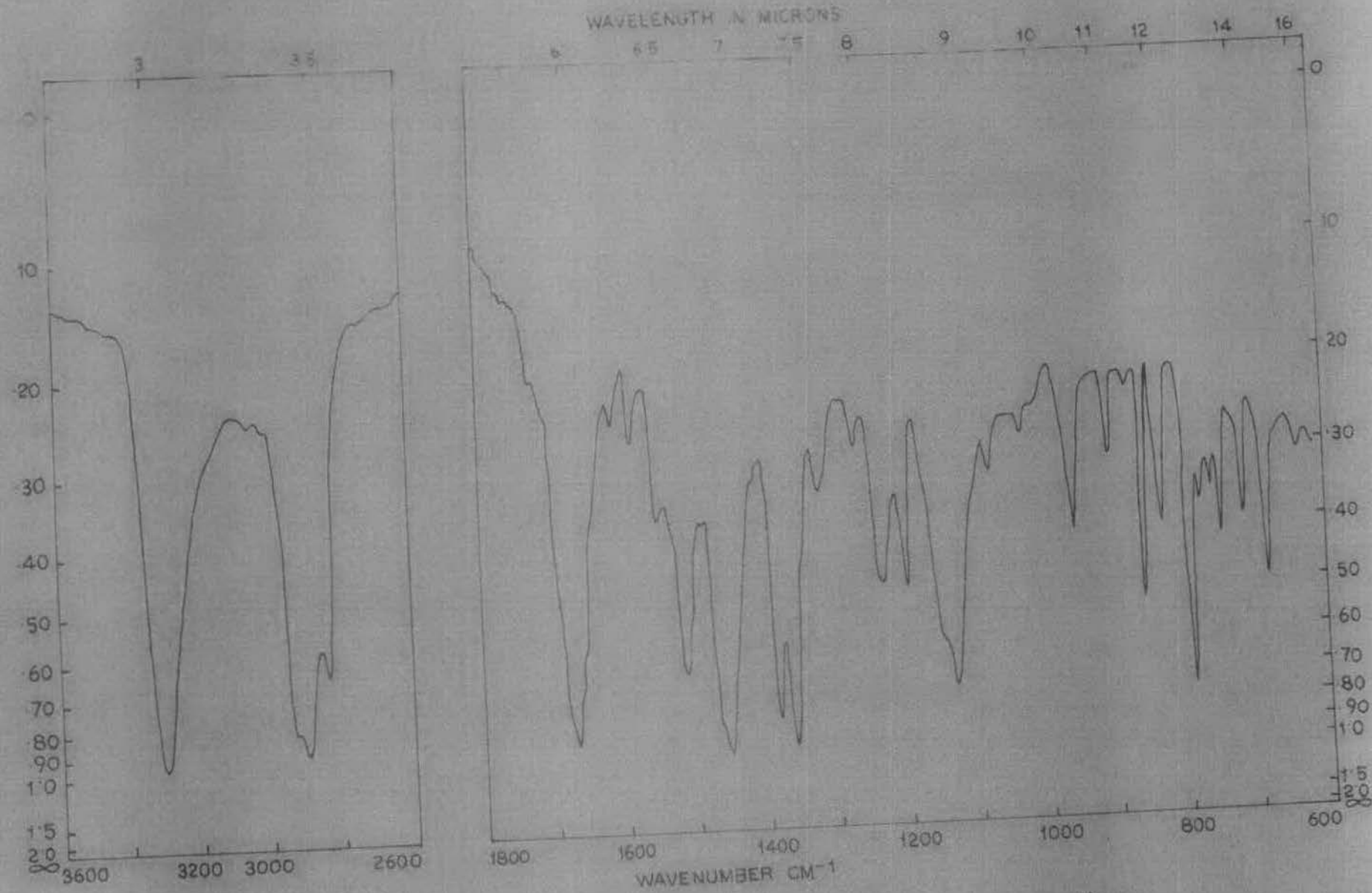


Fig- 50.

3- Carbomethoxy-4- (o- nitro) phenyl- 2- pyrazoline.

was kept at a dark and cool place for 18 days when no yellow colour of diazomethane was found to be present. Ether was removed at reduced pressure. The oily residue was crystallised from methanol when pale yellow coloured solid separated. This on recrystallisation from dry methanol gave colourless compound m.p. 165°C. Yield. 2 gm.

Analysis found: C, 55.21%; H, 4.63%

Calculated for $C_{11}H_{11}O_2N_2Cl$: C, 55.37%; H, 4.84%

I.R. (neat) - Fig. 49.

Mass spectrum Fig. P15

Mother liquor was further concentrated, but no solid product could be separated.

3. Reaction of diazomethane with o-nitro methyl cinnamate.

A mixture of 200 ml of ethereal solution of diazomethane (1.28 gm) and 50 ml of ether solution of 1.8 gms of o-nitro methyl cinnamate was kept in a dark and cool place for 20 days when the colour of the diazomethane was no longer present, ether was removed at room temperature under suction. The semi-solid product was crystallised from pet-ether and further recrystallisation afforded a solid product. m.p. 162°C. Yield 1.2 gm.

Analysis found:* C, 52.8%; H, 4.3%

Calculated for $C_{11}H_{11}O_4N_3$: C, 53.06%; H, 4.45%

C, 53·06 %; H, 4·45 %

I.R. (neat - Fig. 50

N.M.R. Fig. P16.

* Ref. No. CHY/SP/RSSC/2241 of 19.5.1979 by CDRS, Lucknow, India.

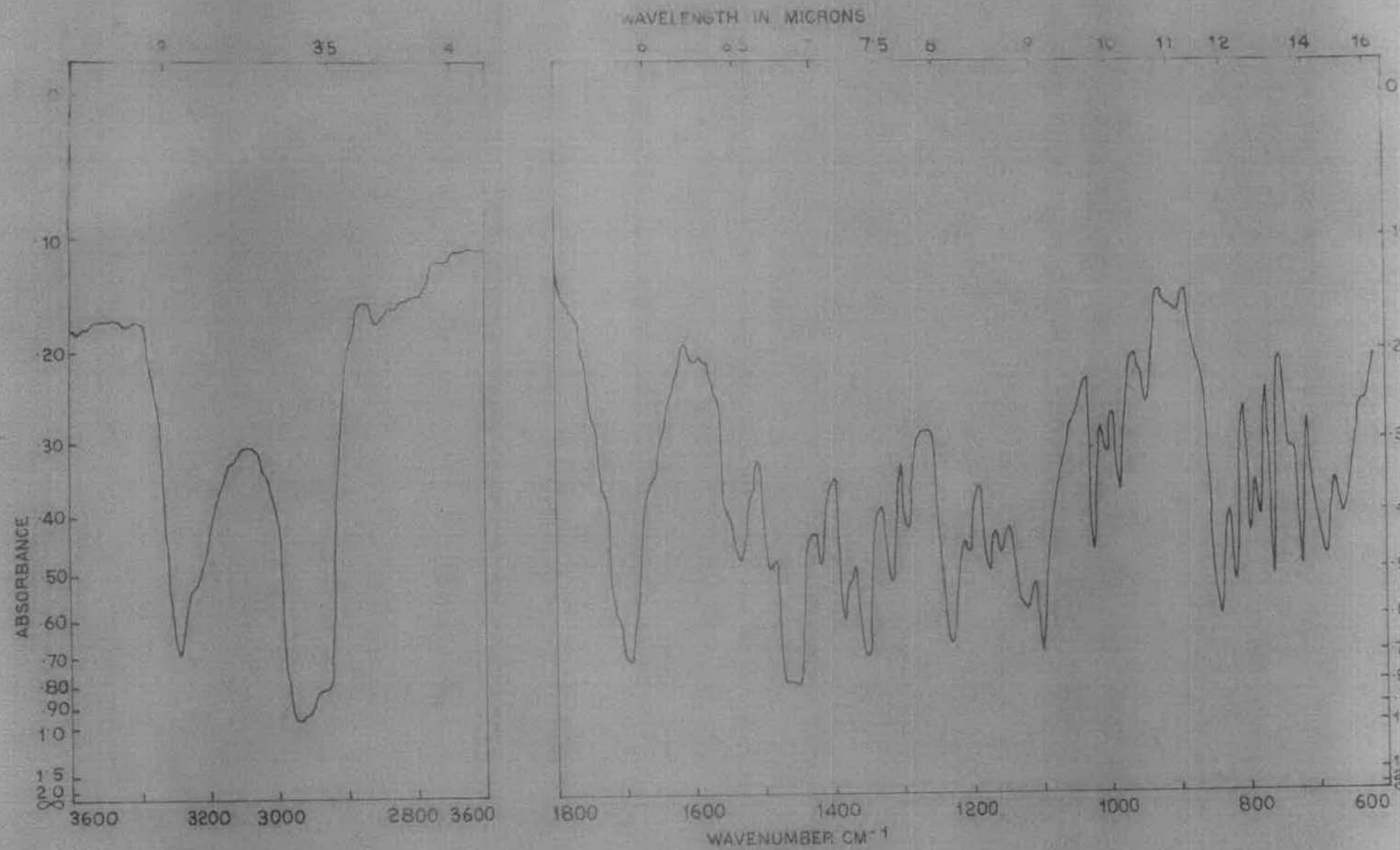


Fig- 51. 3- Carbomethoxy - 4- (P- chloro) phenyl- 2- pyrazoline.

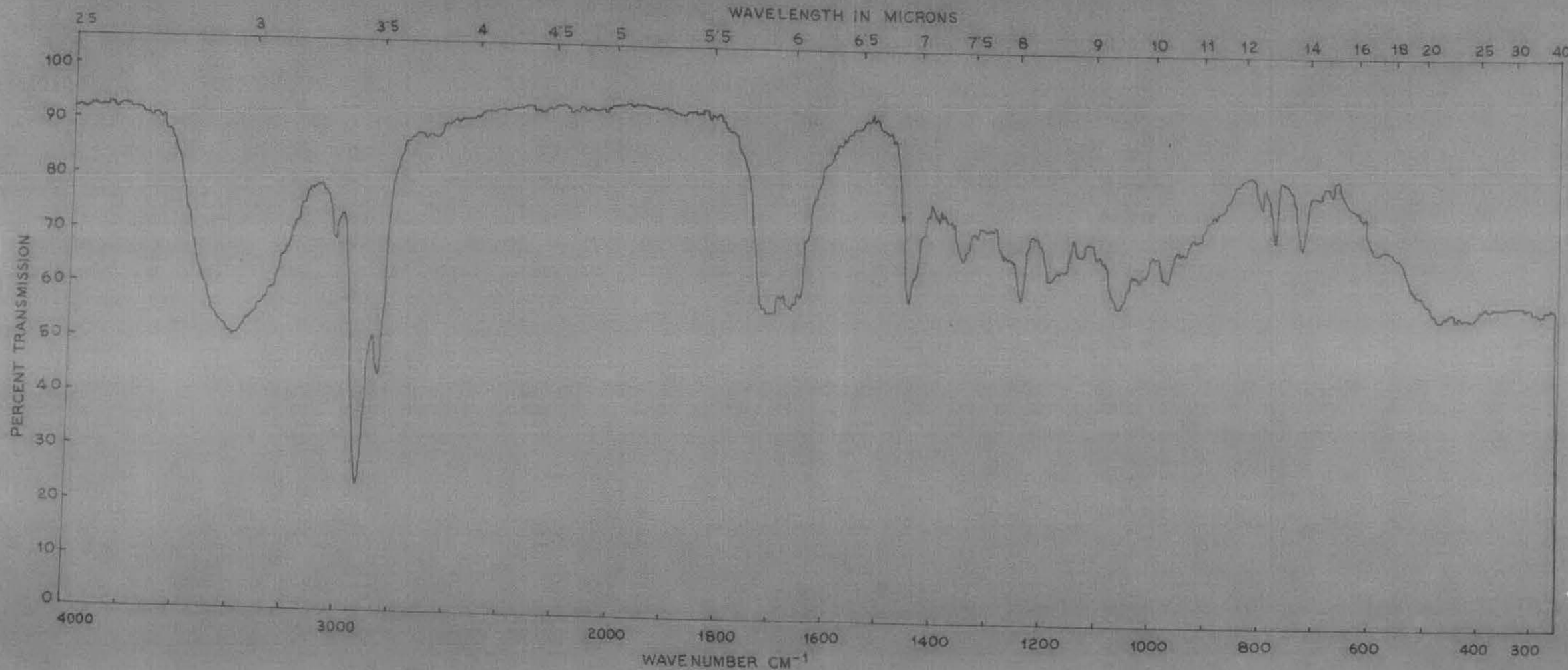


Fig- 52 3- acetyl- 4- methyl- 2- pyrazoline.

4. Reaction of diazomethane with trans-p-Chloro methyl cinnamate.

A mixture of 200 ml of ethereal solution of diazomethane (1.2 gm) and 50 ml ethereal solution of 1 gm ester was kept in a dry and cool place at room temperature for 18 days. When the colour of diazomethane was no longer present, ether was removed at room temperature under suction. A semi-solid residue remained was crystallised several times from pet-ether (60-80°) m.p. 110°C. Yield - 700 mg.

Analysis found: C, 55.1%; H, 4.57%

Calculated for $C_{11}H_{11}O_2N_2Cl$: C, 55.37%; H, 4.84%

I.R. Fig. 51

5. Reaction of diazomethane with mesityl oxide.

A mixture 200 ml of ethereal solution of diazomethane (5 gm) and 50 ml ether solution of 3 gm of mesityl oxide was kept in a dark and cool place for 15 days. When the colour of the diazomethane was no longer present, ether was removed at room temperature under suction. The liquid residue was distilled at 88°C/7 mm. Yield-1.3 gm. This compound was found to contain nitrogen.

Analysis found: C, 64.11%; H, 9.13%

Calculated for $C_6H_{10}ON_2$: C, 64.27%; H, 8.98%

I.R. (neat) Fig. 52