SYNTHESIS OF SUBSTITUTED TETRAHYDRO PYRIDO COUMARINS

BY

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CHAPTER ONE

SYNTHESIS OF SUBSTITUTED TETRAHYDRO PYRIDO COUMARINS

1. INTRODUCTION

The biological importance of coumapyran as an anticoagulant, aflatoxins as mycotoxins, and of coumestrol as an estrogen and a phytoalexin has led to a considerable amount of synthetic work in the field of coumarins with 3,4 - carbo-cyclic and 3,4 – heterocyclic fused ring systems. These systems sometimes serve as useful synthetic inter-mediates as, for example, in the synthesis of analogues of the naturally occurring citromycetin, tetrahydro-cannabinol, and 6-Ketorotenoids. Although much data are available on the synthetic and pharmacological properties of these systems, but it is impossible on our part to review it in this thesis. Our effort is to shed some light on this field of synthetic research. Literature available till the end of 1992 has been included in this modest review work.

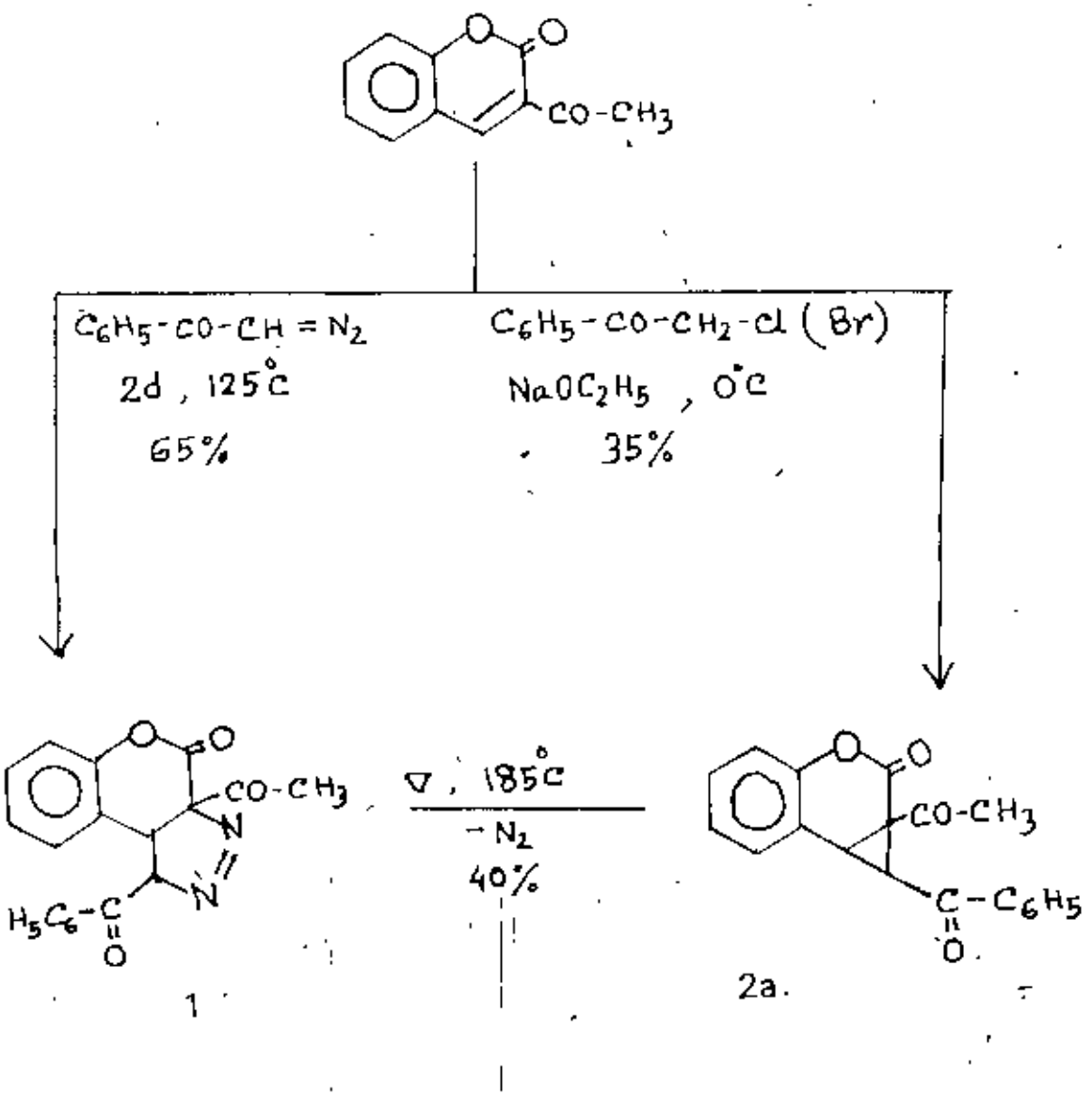
2. SYNTHETIC RING SYSTEMS

2.1. Carbocyclic Systems:

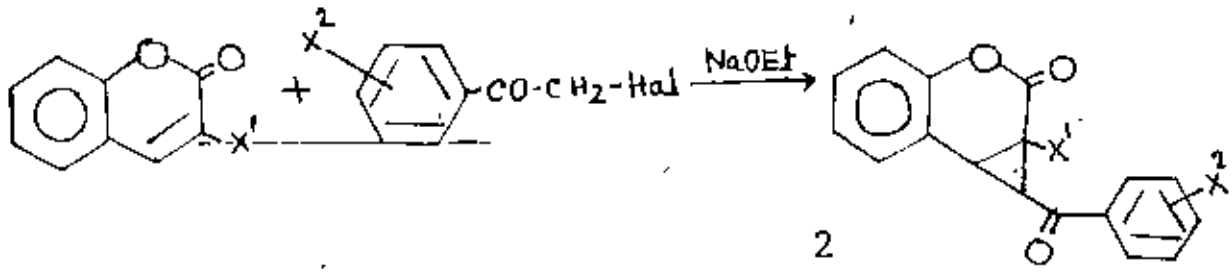
2.1.1. Three-Membered Ring

Widman prepared 3,4-phenacylidene-3-acetylcoumarin (2a; m.p. 184°C) by condensing 3-acetylcoumarin with phenacyl chlorides[1,2] in the presence of sodium ethoxide Later, compound 2a was prepared by heating the condensation product 1 of 3 - acetylcoumarin with diazoacetophenone[3] at 180°C. In both the

above procedures, a methylene insertion across the 3,4 - double bond of coumarin has taken place. However, the final product, formed in these cases, is a derivative of 3,4 - dihydro coumarin.



The phenacylidene-3-substituted coumarins **2** were prepared following the Widman procedure (Scheme-A).

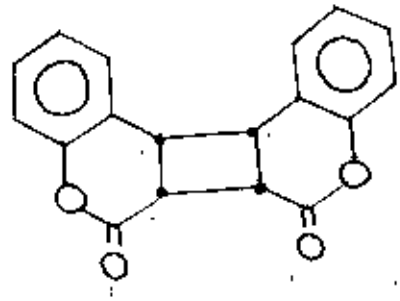


2

Scheme -A

2.1.2. Four - Membered Ring

Studies of photochemical reactions on the coumarin ring systems revealed that a dimerisation reaction was taking place, resulting in the formation of cyclobutane ring systems involving the 3,4-positions of coumarin. The photodimer 3 of coumarin was first prepared by irradiation of an ethanolic solution of coumarin with sunlight[4] and later in an aqueous suspension[6]. The photodimer from 3 - phenylcoumarin[5] was prepared in 90% yield by exposing a benzene solution to sunlight.



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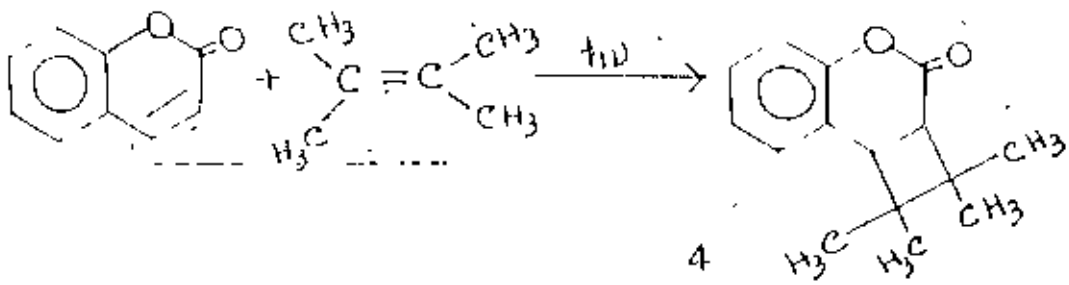
Coumarin-3,4 cyclobutane **4**[7] was prepared by irradiating a solution of coumarin and tetramethylethene in dioxane. The corresponding adducts with ketene diethylacetal (b.p 95-100°C/0.25 torr) or cyclopentene (50% yield m.p. 139°C have similarly been prepared.



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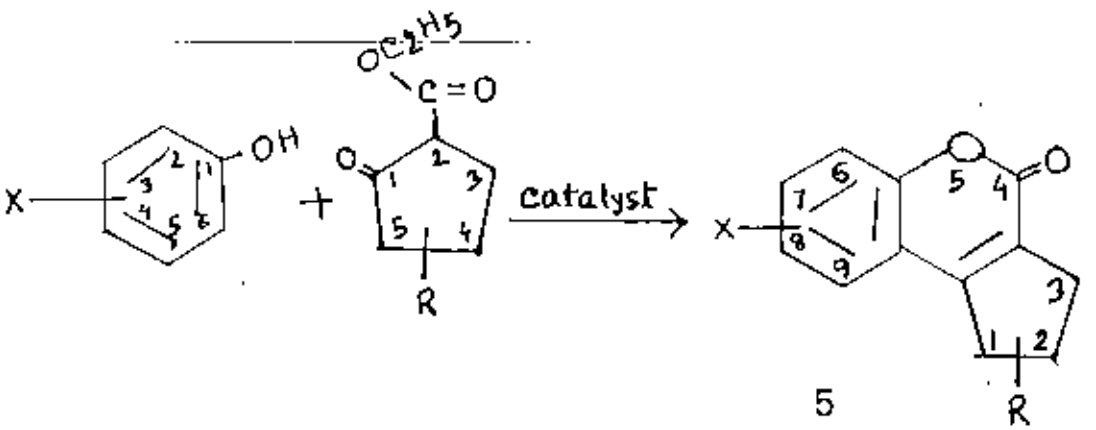
2.1.3. Five - Membered Ring

The synthesis of coumarins with a 3.4-fused 5-membered ring has been achieved following two different pathways. In the first, the appropriate phenol was condensed with cyclopentanone-2-carboxylate under Pechmann conditions resulting in the desired end product. In the second, a straight-chain β-ketoester was condensed with the appropriate phenol resulting in a coumarin with a propanoic acid residue in the 4-position. This was finally cyclised to result in a 5-membered ring.

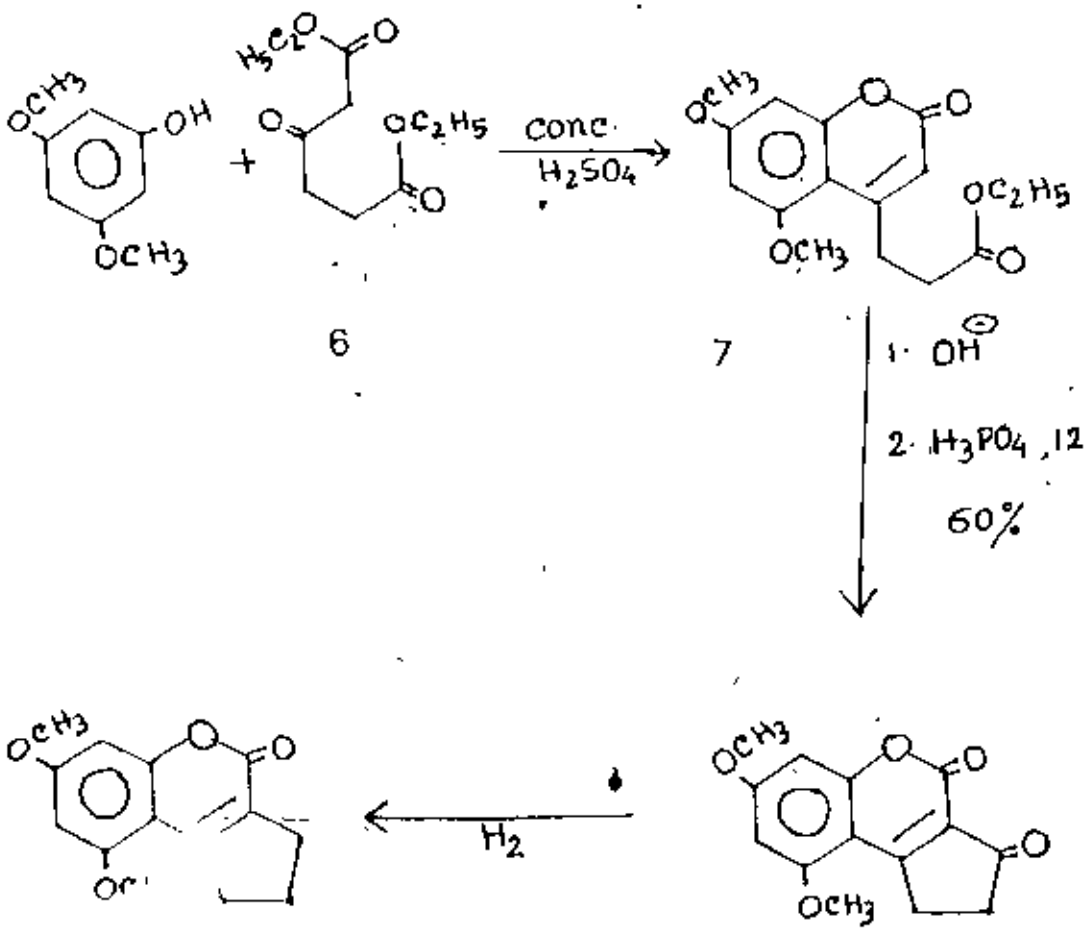
Pechmann condensation of cyclopentanone-2-carboxylate and 4 - methylcyclopentanone-2-carboxylate with phenols have been carried out successfully in the presence of concentrated sulphuric acid or phosphoryl chloride. Resorcinol[ii],4-ethyl-resorcinol[v], Orcinol[iii] and resacetophenone[v] gave good yields in the presence of concentrated sulphuric acid, phosphoryl

chloride, or aluminium chloride in nitrobenzene while phloroglucinol, 3,5 dihydroxytoluene, and 4,6-diethyl resorcinol condensed well in the presence of phosphoryl chloride. Resacetophenone condensed with ethylcyclopentanone 2-carboxylate in the presence of nitrobenzene and aluminium chloride to give 8-acetyl-9-hydroxy-1,2,3,4-tetrahydrocyclopenta [c][2] benzopyran **5**. However, resacetophenone condensed with ethyl-4-methylcyclopentanone -2- carboxylate in the presence of nitrobenzene and aluminium chloride giving 6-acetyl-9-hydroxy -4- methyl -1,2,3,4- tetrahydrocyclopenta [c][2] benzopyran. Ethyl-1,3-indandione-2- carboxylate[12] and 1-hydrindone-2-carboxylic acid[13] were also successfully condensed with resorcinol.



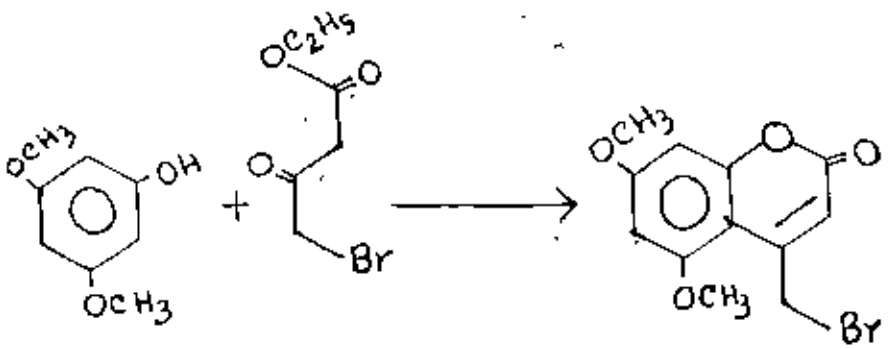
Scheme B

When the dimethyl ether of phloroglucinol was condensed with diethyl β-oxoadipate **6** in the presence of concentrated sulphuric acid, ethyl 3-(5,7-dimethoxycoumarin-4-yl)-propanoate **7** was obtained. Compound **7** was hydrolysed to the free acid by alcoholic sodium hydroxide and subsequently cyclised to **8** (m.p 232-233°C) using phosphoric acid. Catalytic hydrogenation of **8** yielded the product **9**[5,14] (m.p. 182-184°C).



6 7 8 9

4-Bromomethyl-5,7-dimethoxy coumarin **11**, obtained by Pechmann condensation of phloroglucinol dimethyl ether with bromoacetoacetic ester **10**, was condensed with malonic ester and the free acid **12** (m.p. 249°C), obtained by hydrolysis, was cyclised[15] to **8**.



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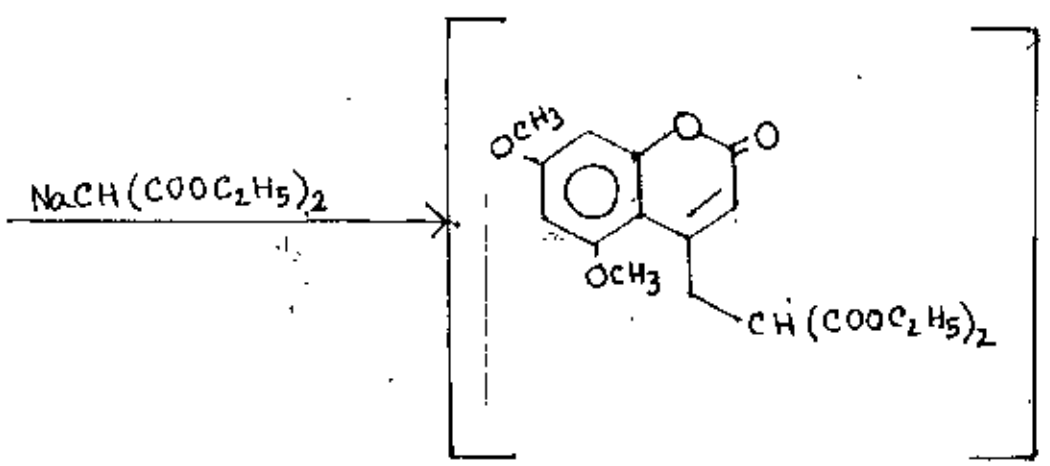
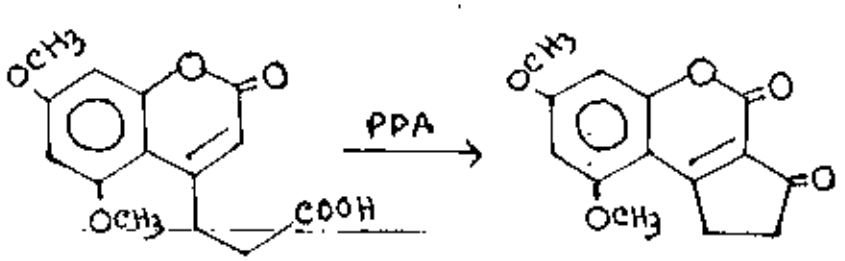
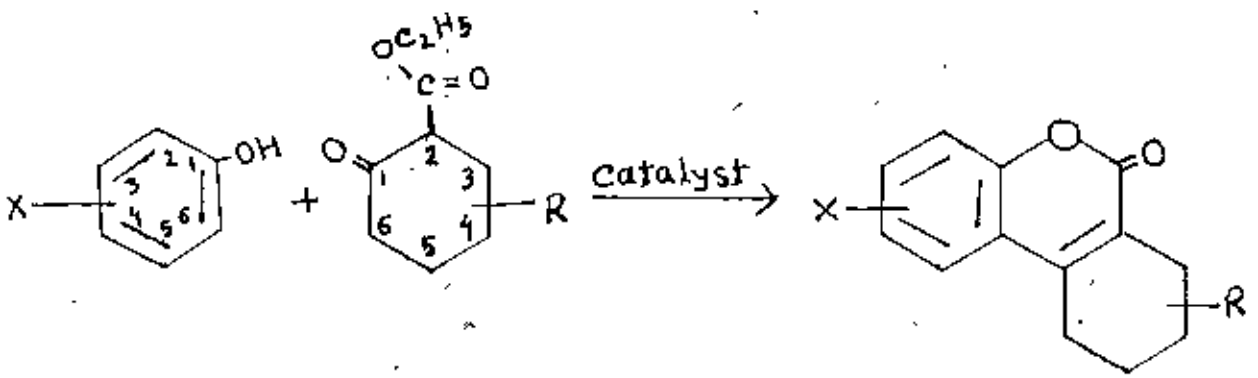




12 8

2.1.4. Six - Membered Ring

Pechmann condensation of 3-(n-pentyl)-phenol[16], m-cresol[17], resorcinol[8], phloroglucinol[19], orcinol[18,19], quinol[20], pyrogallol[21], and α - naphthol[18], while ethyl cyclohexanone -2-carboxylate using concentrated sulphuric acid[10,11,16-23], phosphoryl chloride[11,19,24-29], aluminium chloride/ nitrobenzene[11], zinc chloride/glacial acetic acid[17], or methanesulphonic acid[22] gave rise to the corresponding 7,8,9,10 - tetrahydrodibenzo - α - pyrones **13**.



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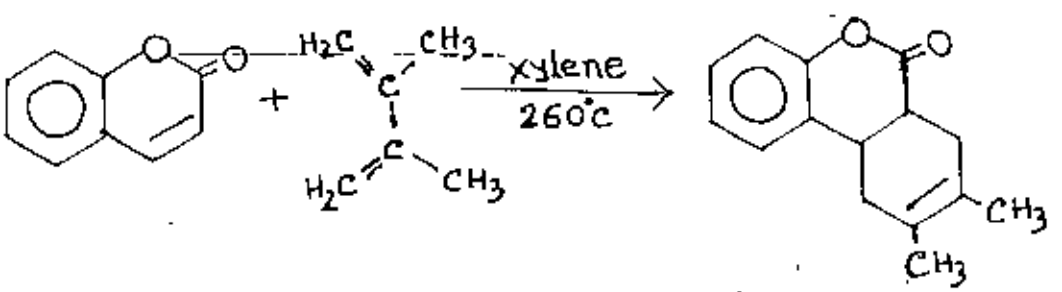
Scheme C

Coumarin functions as a dienophile in Deils-Alder reactions. It reacts with 2,3-dimethylbutadiene under forced conditions at 260°C to give poor yields of 8,9-dimethyl-6a,7,10,10a - tetrahydrodibenzo-α-pyrone **14**[30].



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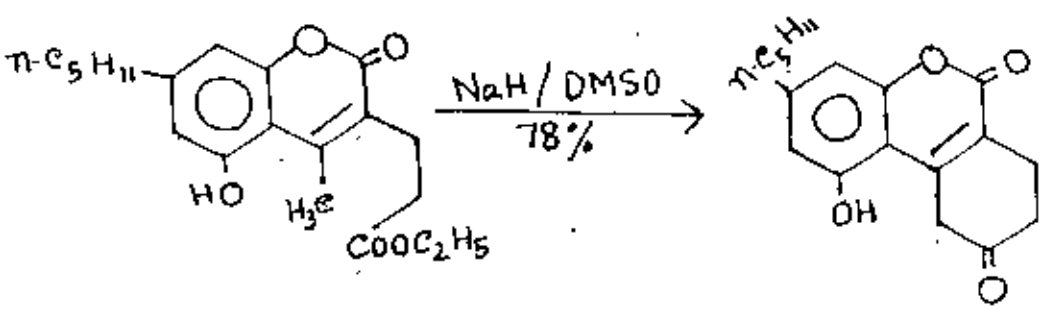
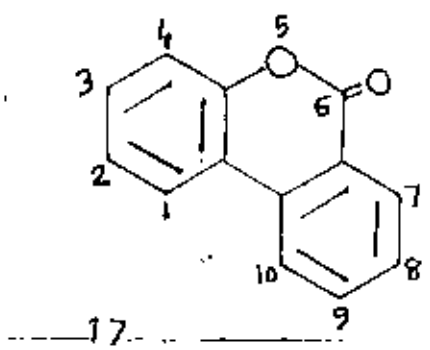
Cyclisation of coumarin **15** in the presence of sodium hydride in dimethyl sulphoxide solution resulted in the formation of **16**[31] (m.p. 203-206°C).



15 16

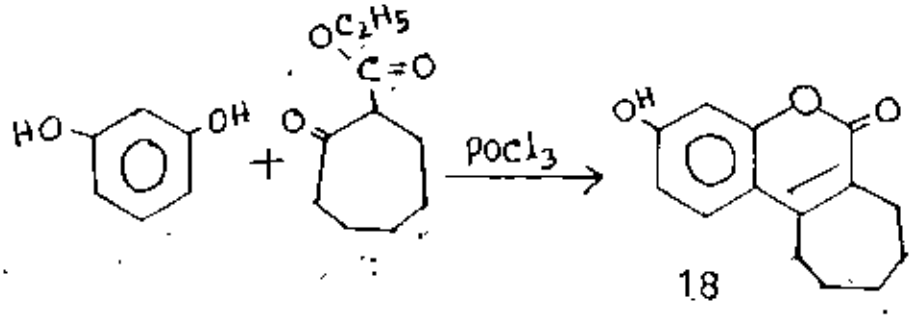
Dibenzo-α-pyrones (17,6-oxo-6H-dibenzo [b,d] pyrans) have been prepared through different routes. The condensations of phenols[32,33] with o-halobenzoic acids catalysed by copper ealts give fair yields of the dibenzo-α-pyrones[32]. Depending on the substitution pattern of the starting material and the reagent, the reaction is carried out in aqueous alkaline or neutral medium[34].

Dibenzo-α-pyrones have aleo been prepared by condensing phenols' with diazoanthranilic acids[35,36,37], by demethylative cyclisation of 2-methoxy-2'-carboxy diphenyls with hydrobromic acid[38,39], or oxidative cyclisation of 2' carboxy diphenyls[40].



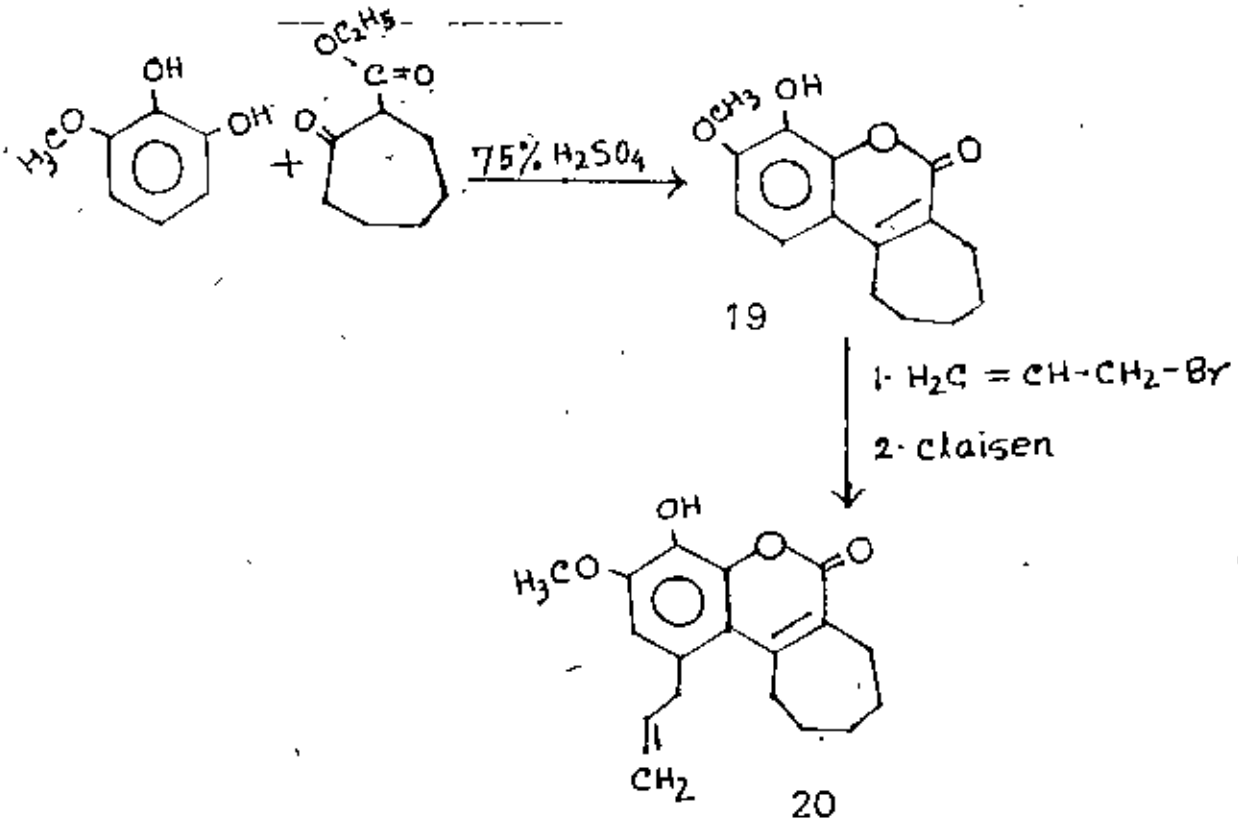
2.1.5. Seven - Membered Ring

Pechmann condensation of alkylphenols[29], resorcinol[29], Pyrogallol[22,42] and pyrogallol monomethyl ether[41,42], with ethyl cycloheptanone-2-carboxylate in the presence of phosphoryl chloride or concentrated sulphuric acid gave the corresponding benzocyclohepta-pyran-6-one; e.g., resorcinol afforded compound 18.

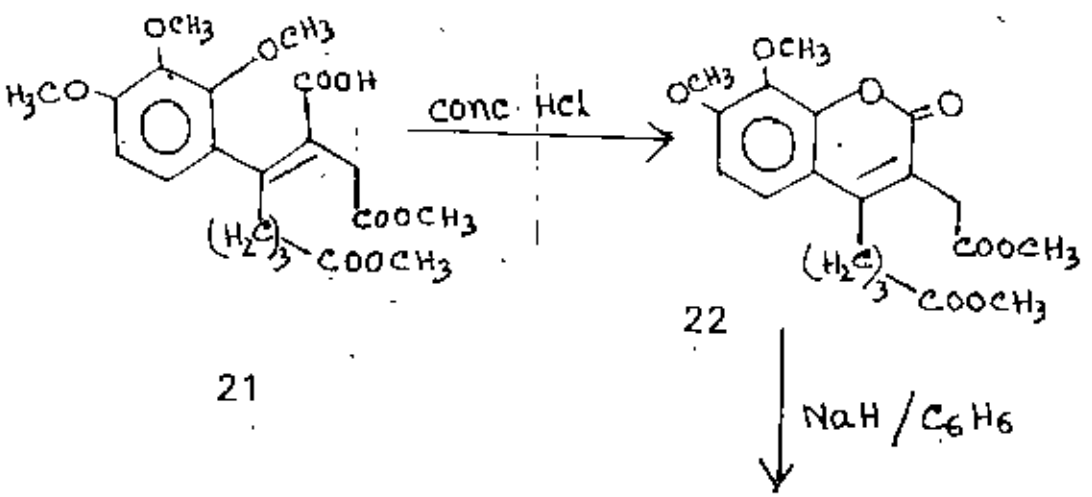


18

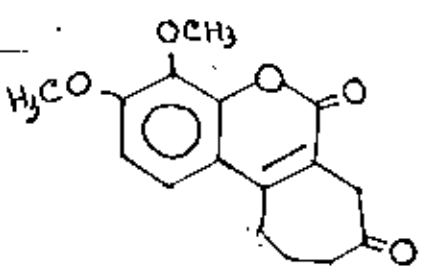
During the synthesis of colchicine, pyrogallol monomethyl ether has been condensed with ethyl 2-oxocycloheptane carboxylate using 75% sulphuric acid giving rise to 19[41]. The latter 15 (m.p. 176.5°C) was then allylated with allyl bromide and claisen migration afforded 16[43] (m.p. 166°C). The 1-formyl derivative[41] of 19 was prepared by potassium hydroxide-induced isomerisation of 20 to the 1-propenyl derivative (30% yield) and ozonolysis of the latter.



Stobbe condensation of methyl (2,3,4-trimethoxybenzoyl)-butanoate with dimethyl succinate in the presence of alkali t-butoxide in t-butanol gave only the half ester **21**, which cyclised on hydrolysis with mineral acid to a coumarin diacid analogue of **22**. Dieckmann cyclisation of the dimethyl ester **18** led to 6,8-dioxo-3,4-dimethoxybenz cycloheptapyran **23**[42].



21 22



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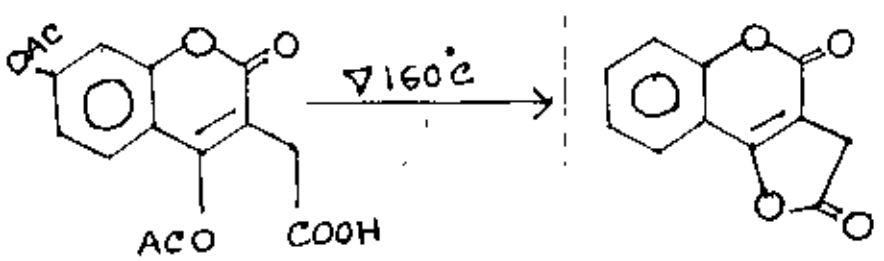
2.2. Heterocyclic Systems

Coumarins with 3,4-fused heterocyclic rings containing oxygen and nitrogen are described in this section.

2.2.1. Five - Membered Ring Containing one Oxygen

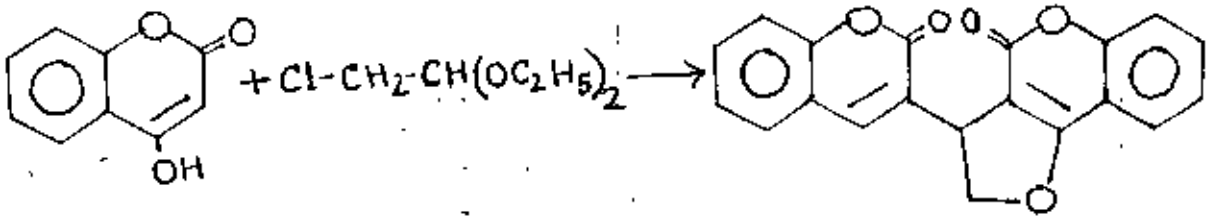
Furan can fuse in two possible ways to the 3,4 -positions of coumarins, depending on the position of oxygen in the ring systems. Both isomers can be prepared, starting from 3-or 4-hydroxy coumarins or indirectly, by the decarboxylation of carboxy derivatives obtained by the alkali cleavage of pyrano[c] benzpyrans.

4,7 - Diacetoxy coumarinyl -3-acetic acid **24**, when heated at 160°C, cyclises to 7-acetoxyfuro [3,2-c] [1] benzopyran-2,4 (4H) dione[45] (**25**; m.p. 208°C).



24 25

The condensation product of two mol 4-hydroxy coumarin with one mole α-chloroacetaldehyde diethyl acetal has been identified as 3-(hydroxy coumarin-3-yl)[3,2-b] dihydrofuranyl coumarin[46] (**26**; m.p. 256°C).



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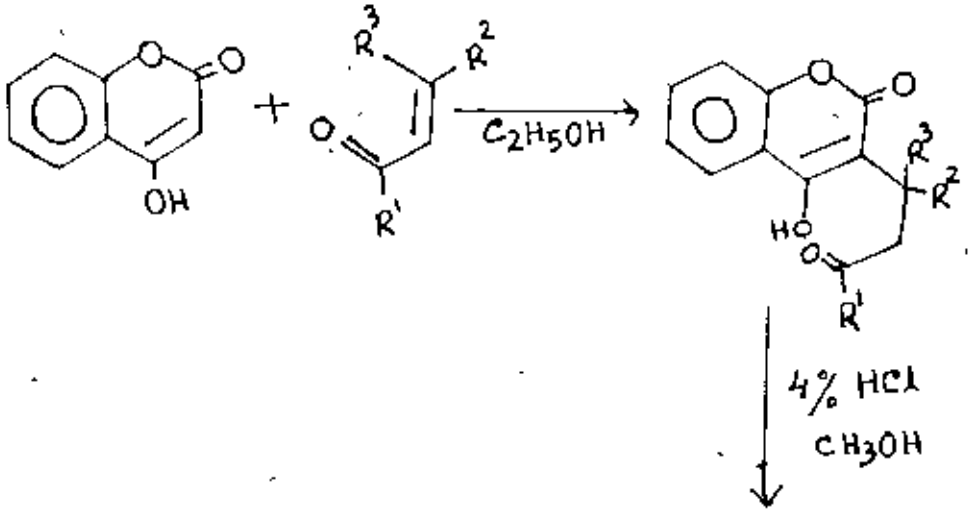
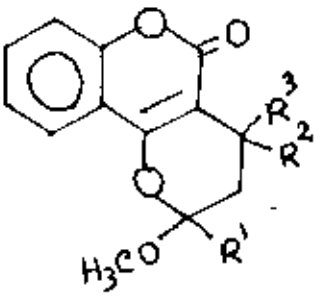
2.2.2. Six - Membered Ring Containing one Oxygen

Pyrans

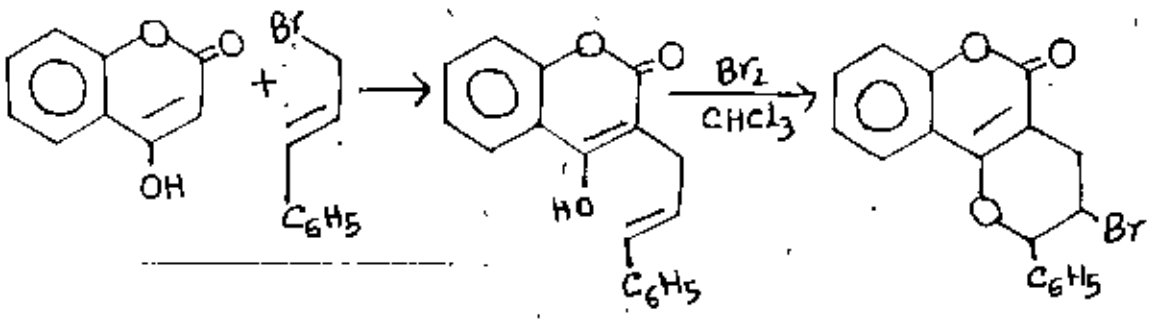
During the search for anti-coagulant compounds, various substituted hemiacetals have been prepared by Michael addition of 4-hydroxy coumarin with α,β-unsaturated ketones or α,β-unsaturated aldehydes and subsequent cyclisation of the Michael additior product under mild conditions. The hemiacetals of the type 27 have been prepared by condensation of α,β unsaturated ketones like ethylideneacetone, mesityl oxide benzalacetone, with 4-hydroxy coumarin in ethanol and then treated with 4% hydrochloric acid in absolute methanol to give the corresponding pyrano [3,2-c] [1] benzopyran-5 (2H) on **27**[47-52].





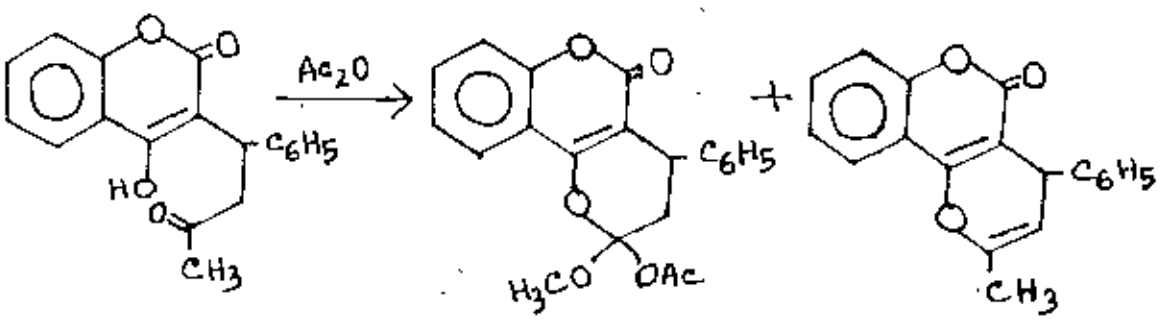
27

Condensations of 4-hydroxy coumarins have also been successful with unsaturated nitriles using pyridine and with acetylenes in acetic acid or sulphuric acid. 2-phenyl- 3-bromo pyranobenzopyran **28** m.p. 195-196°C was prepared by brominating 3-(3-phenyl - 2-propenyl) 4-hydroxy coumarin in chloroform[53].



28

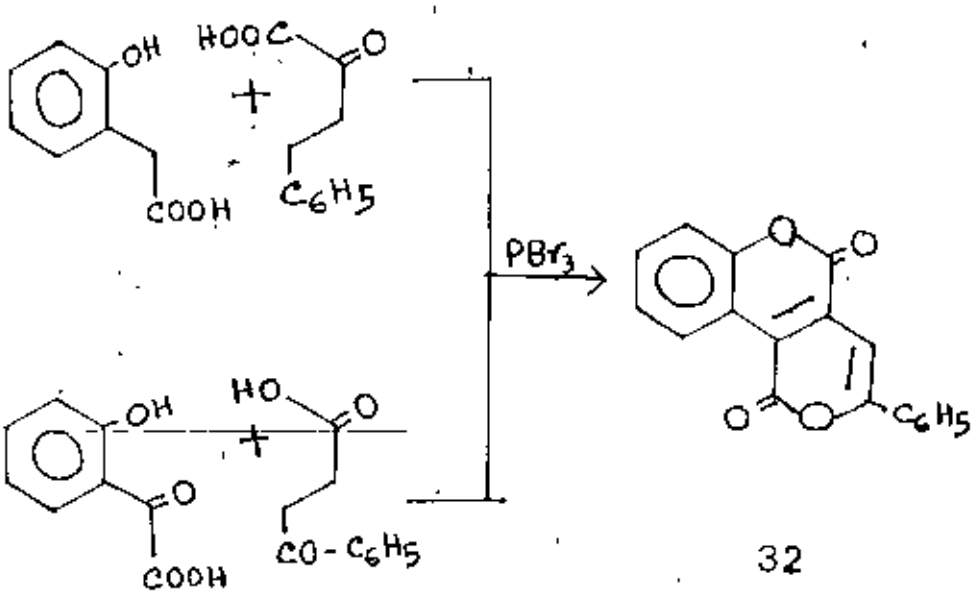
Warfarin or 3-(α-acetonylbenzyl)-4-hydroxy coumarin **29**, when refluxed with acetic anhydride in the presence of perchloric acid afforded **30** (m.p. 204-205°C) and **31**[54] (m.p. 145-146°C).



29 30 31

α - pyrones

Coumarino-α- pyrones have been synthesised by different methods include (a) condensation of o-hydroxy phenylacetic acid with benzylpyruvic acid, (b) 4-hydroxy-coumarin condensed with either benzylidene-malononitrile or with malonic acid or malic acid under Pechmann conditions, (c) cyclisation of 4-hydroxy coumarin-3-propanoic acid, (d) acylation of 3-acyl-4-hydroxy coumarin, 3-phenylpyrano [3,2-c] [1] benzopyran-1,5 dione (32; m.p.260°C)55, has been prepared by condensation of o-hydroxy phenylacetic acid and benzylpyruvic acid with phosphorus tribromide compound 32 has also been prepared by reacting o-hydroxy phenylpyruvic acid with 4-oxo-4-phenylbutanoic acid.



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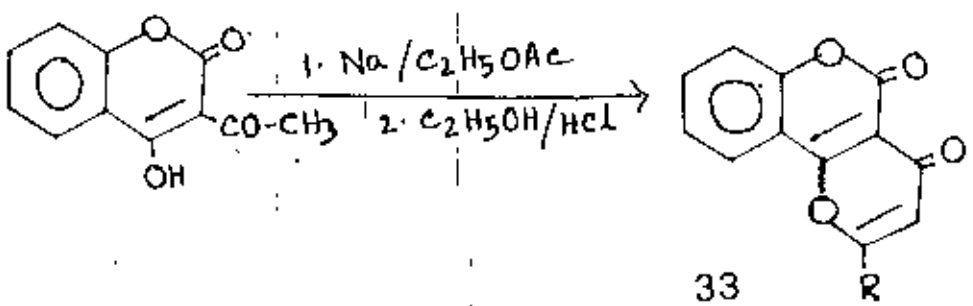
γ-pyrones

3-Acetyl-4-hydroxy coumarin on Kostanecki acylation or by Claisen condensation with ethyl acetate and subsequent cyclisation with ethanolic hydrochloric acid[56] formed 2-methyl-4,5-dioxo-pyrano [3,2-c][1] benzopyran (33, R=CH_3; m.p. 246°C)



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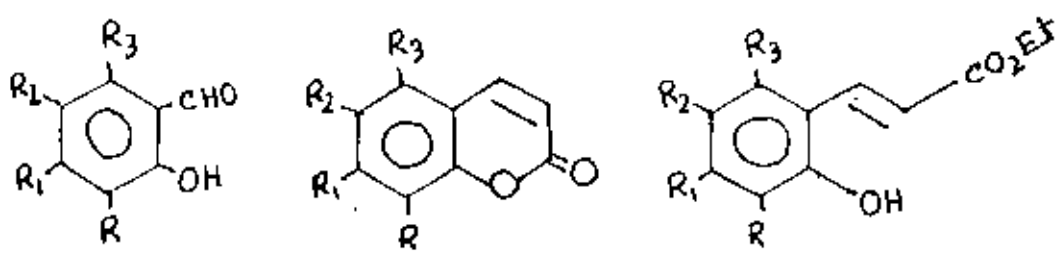
Coumarins

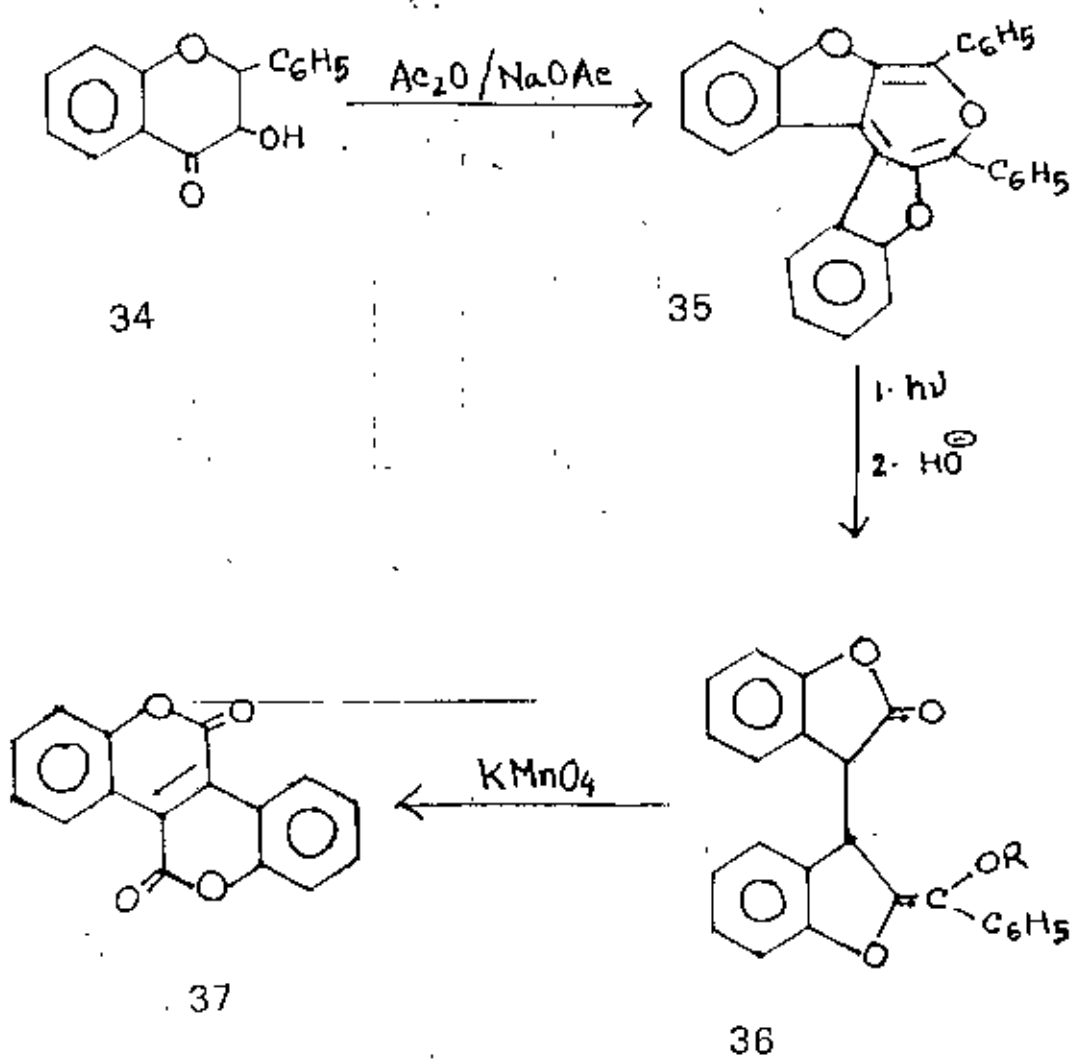
Reaction of salicylaldehydes I (R,R_1 = H, OMe; R_2, R_3, = H, Me,OMe,$OCHMe_2$) with carbethoxy methylene phosphorane in diethylaniline under reflux gave coumarins **II** in excellent yields[83].



I II III

Methoxy substituent at c_4 on **I** facilitated the formation of coumarins from trans-cinnamate **III**, which are first prepared by reaction of **I** with Witting reagent.

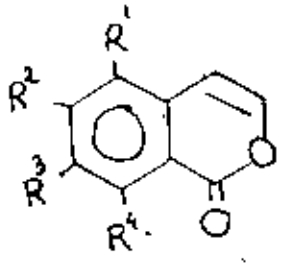
A synthesis of [1] benzopyrano [4,3-c][1] benzopyran-5,11-dione **37** involves treatment of 3-hydroxyflavanone **34**[57] with acetic anhydride and sodium acetate to give an intermediate **35** which, on irradiation in U.V. light and after alkaline hyrolysis, forms **36**. The latter is oxidised with potassium permanganate in acetone to yield the dilactone **37** m.p. 295-296°C.



34 35 36 37

Isocoumarins

Isocoumarins I (R^1-R^4 = H, F cl, C_{1-3} alkyl, C_{1-3} alkoxy, NO_2 etc.), which are useful as materials for isoquinolines and are widely used in perfumes, pharmaceuticals, agrochems, etc. are prepared by treatment of 2-methoxy carbonylstyrenes II (R = CH: CH_2, R^1 - R^4 = same as I) with 1,3 - propanediol or ethylene glycol in the presence of pd chloride and cucl under 0 and treatment of the resulting cyclic acetals II (R=Q; n = 2,3; R^1-R^4 = same as I) with acids. Treatment of 2-methoxy-caronylstyrene with 1,3 - propanediol, pd chloride and cucl in 1,2 -dimethoxy ethane under 0 at 50-60°C for 24-h gave 82% II (R=Q, n=3, R^1-R^4 = H), which was treated with 5% Hcl in EtoH for 2-h to afford 82% iso-coumarin[84].



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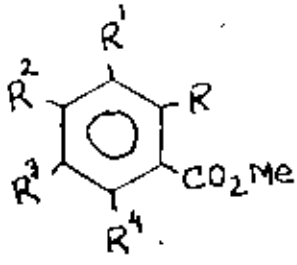
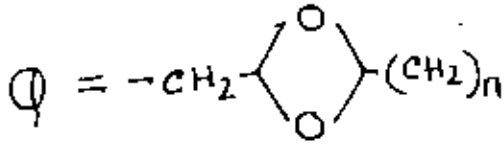
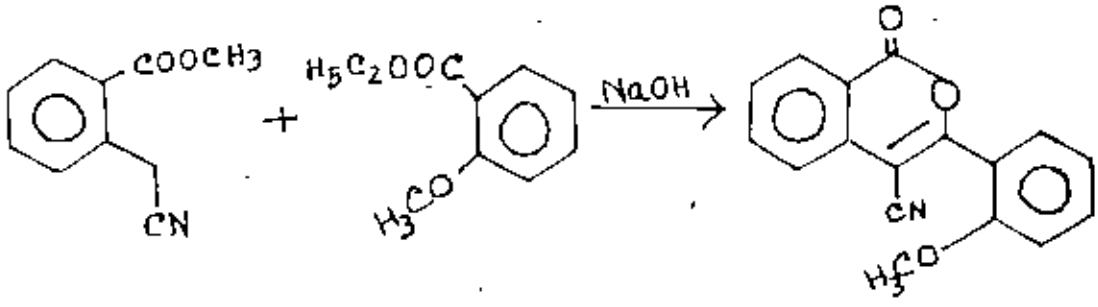


II



A coumarinoisocoumarin or [2] benzopyrano [4,3-c] [1] benzopyran - 6,11-dione (40; R=H)[58] has been prepared by dimethylative cyclisation of 3-(o-methoxy phenyl)-4- cyanoisocoumarin 39 using pyridine hydrochloride. The latter was obtained by condensing 2-methoxy carbonylbenzyl cyanide 38 and ethyl o-methoxybenzoate in the presence of sodium hydride.



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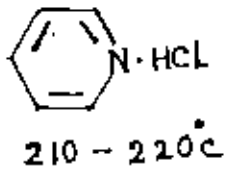
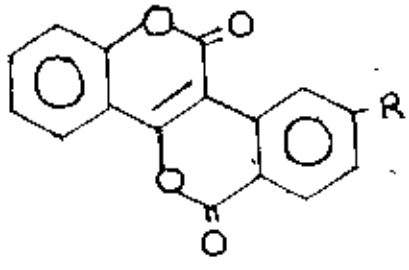
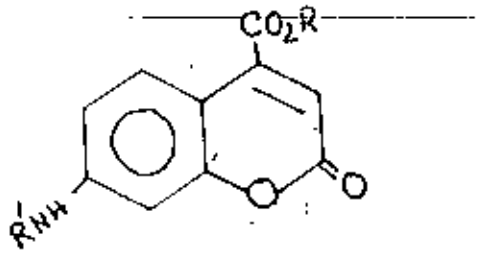




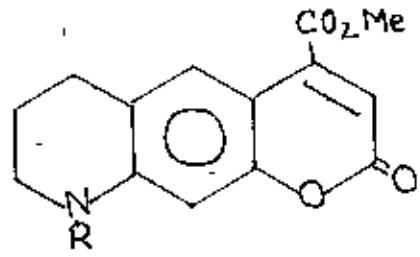
40

2.2.3. Six - Membered Ring Containing One Nitrogen

Heterobifunctional fluorescent reagents[85]; e.g. I (R=H,Me, CH_2 ph; R' = H,Ac) and II (R=H,Me, Ac) of coumarin type are synthesized.



I



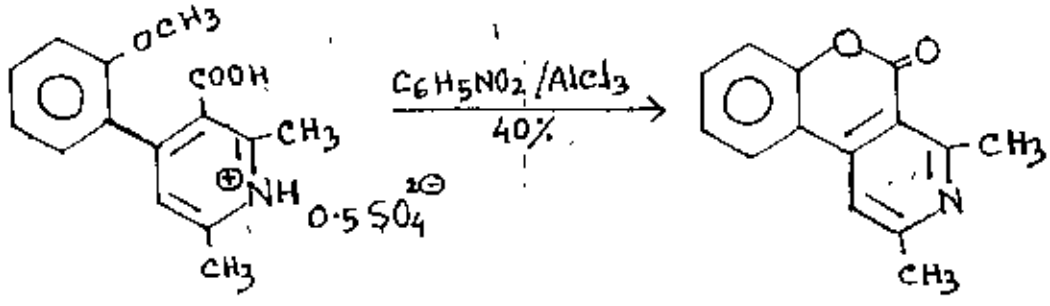
II

They posses, in position 7, an aminogroup and in position 3 or 4, a carboxylic function. The fluorescence characteristics of these compounds are described and compared with 7-amino-4-methyl-coumarin. The influence of the relative freedom of rotation of the amino group of the position of the acid function on the fluorescence properties are also studied.

Pyridines

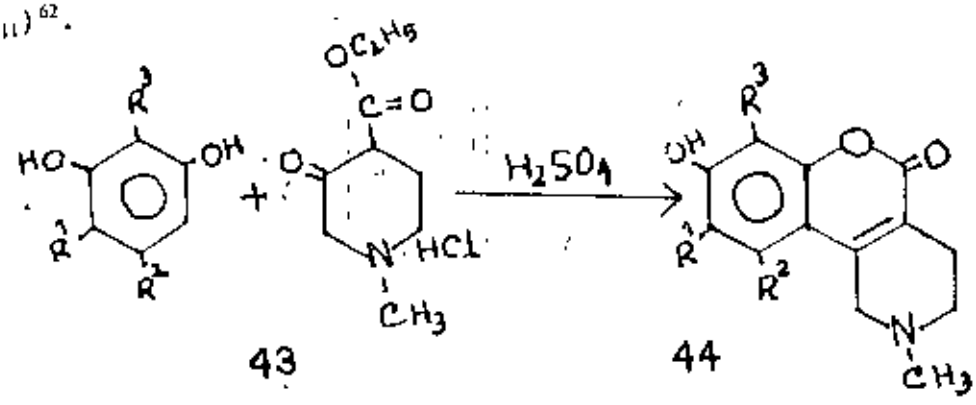
The insertion of nitrogen into the carbocyclic nucleus of tetrahydrocannabinol has long been of interest to chemists and pharmacologists because tetrahydrocannabinol has potent activity on the central nervous system. The ring systems

containing nitrogen in all 4 possible positions have been synthesised. Some of the methods available are ring closure of aryl-substituted pyridines, condensation of 3-acetyl coumarin with cyanoacetamide, reaction of flavones with malononitrile, reaction of substituted salicylaldehydes with malononitrile and acetophenones, Pechmann condensation of phenols with ethoxy carbonylpiperidones, and the Skraup synthesis starting from amino coumarin. Demethylative ring closure of the acid chloride of 4 (o-methoxyphenyl) - lutidine - 3- carboxylic acid sulphate **41** with aluminium chloride in nitrobenzene gave rise to 2,4 - dimethyl [1] benzopyrano [3,4-c] pyridine - 5(2H) - one (**42**, m.p. 257°C. dec)[59]. Similarly, the 1-cyano derivative of **42** was prepared by cyclising the intermediate using hydrobromic acid[60]. Fuming hydrochloric acid[61] was also used instead of aluminium chloride for cyclisation.

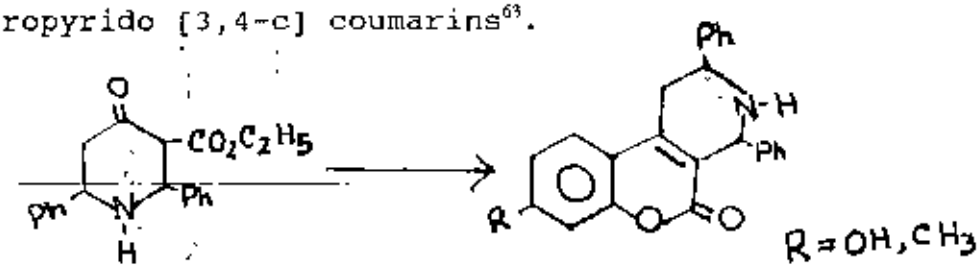


41 42

Pechmann condensation of olivetol with 4-ethoxy carbonyl 3-piperidone hydrochloride **43** in the presence of sulphuric acid and phosphoryl chloride gave 2-N-methyl-10-pentyl-8-hydroxy [1] benzopyrano [4,3-c] pyridine-5-one (**44**; $R^1=R^3$ = H, $R^2=C_5H_{11}$)[62].



Condensation of meta substituted phenol with 2,6-diphenyl-3 - carboethoxy-4-piperidone gave rise to a number of substituted tetrahydropyrido [3,4-c] coumarins[63].



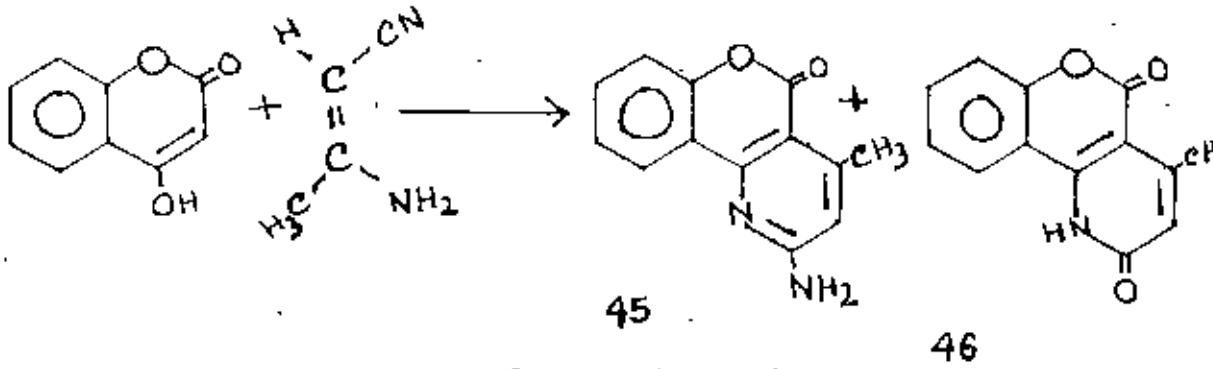
^{1}HNMR-spectral data of the synthesised compounds

	Chemical shift δ ppm				
R	H-1	H-2	H-4	CH_3 CH_2,OH	Aromatic protons
OH	2.90 & 3.40	4,34	5.30	-	7.25-7.90; 11H; 6,8 2H
CH_3	2.88 & 3.41	4.19	5.19	2.43	7.12-7.73; 13H.

Characteristics ions in mass spectra of the synthesised compounds

R	m/z										
	M^+	$(M-H)^+$	$(M-4H)^+$	$(M-R)^+$	$(M-Ph)^+$	Q_1	Q_2	Q_3	Q_4	Q_5	$C_6H_5^+$
OH	369	368	365	352	292	340	337	220	-	-	77
CH_3	367	366	363	352	290	338	335	218	-	-	77

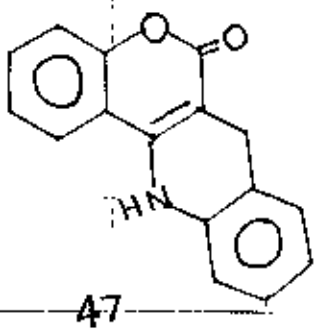
Benzopyranopyridines **45** and **46** have been prepared[64] in the following manner.



45 **46**

Quinolines

During the synthesis of nitrogen - containing heterocyclic lactones, a synthesis of 6-OxO [1] benzopyrano [4,3-b] quinoline **47**[65] was achieved in 40% yield by Ullmann-Fetvadjian-type condensation of 4-hydroxy-coumarin with aniline and paraformaldehyde.



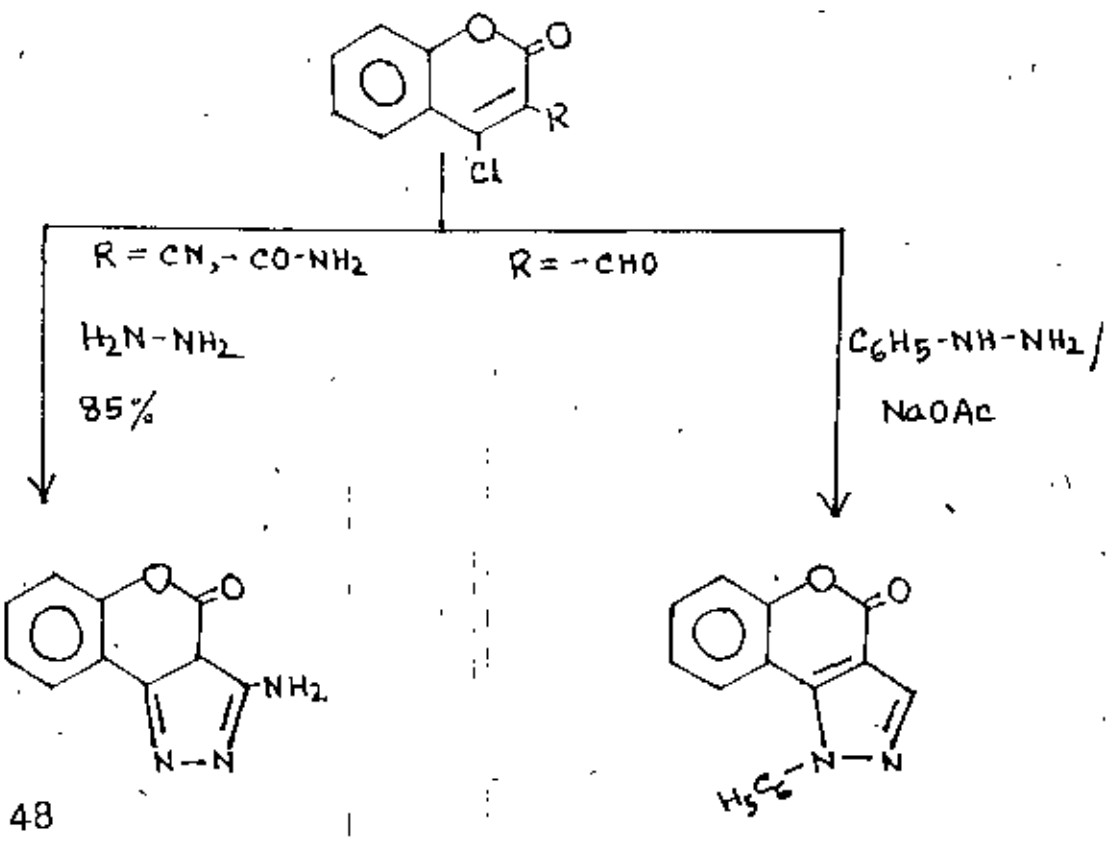
47

Another route to the synthesis of **47** involves condensation of 4-hydroxycoumarin with o-nitrobezaldehyde or dimethoxy - o-nitrobenzaldehyde in acetic acid/sodium acetate and subsequent reduction of the intermediate 3-(o-nitro-bezylidene)-chroman-2,4-dione with zinc dust[66].

2.2.4. Five - Membered Ring Containing two Nitrogens

Pyrazoles

3-Aminobenzopyrano [4,3-c] pyrazolin-4(2H)-one **48** was prepared by heating 4-chloro-3-cyano or 4-chloro3-aminocoumarin with hydrazine.

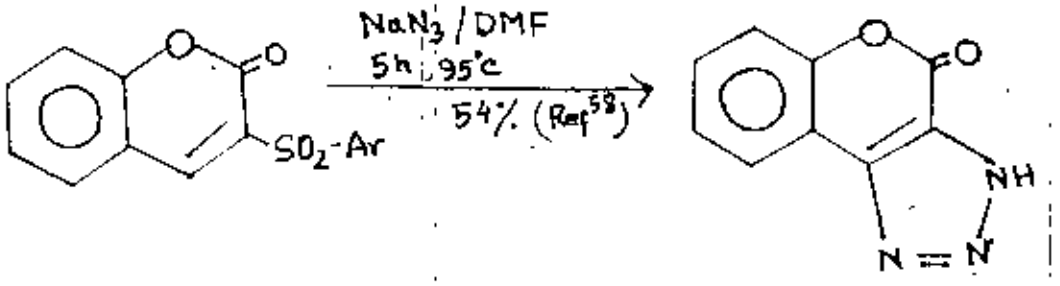


1-phenyl [1] benzopyrano [4,3-c] pyrazoline -4-one **49** was synthesised[67] from phenylhydrazones of 4-chloro-3-formylcoumarins.

2.2.5. Five-Membered Ring Containing Three Nitrogens

1,2,3-Triazoles: 1-Benzopyrano [3,4-d] [1,2,3] triazol 4(1H) - one 50[68] has been prepared in 45% yield by reacting sodium azide with 3-(4-methylphenylsulphonyl)-coumarin in dimethyl-formamide at 95°C. The same compouund was prepared in higher

yield from 3-(p-methoxy-nitrophenylsulphonyl)-coumarin[69] under similar conditions.



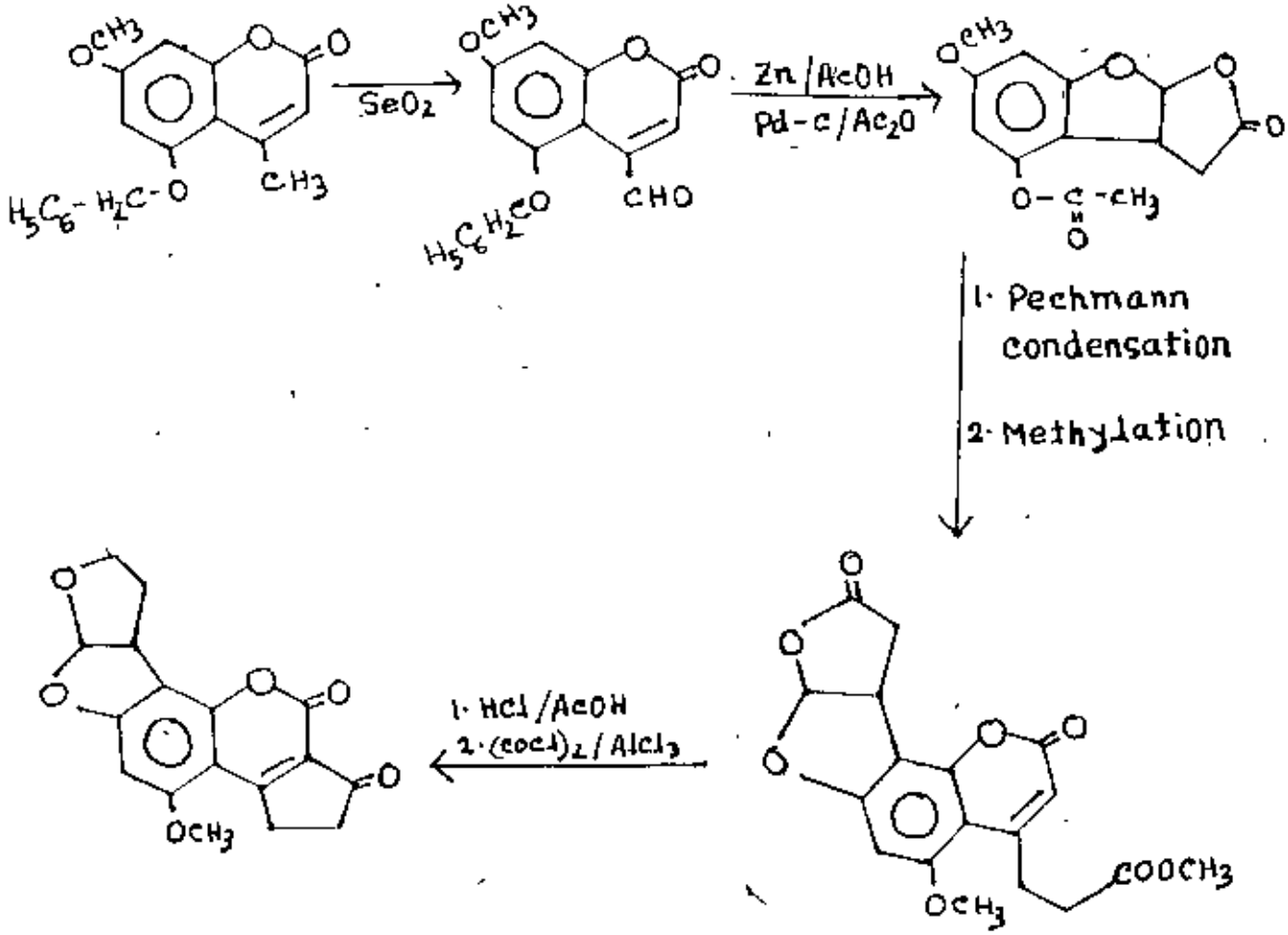
50

3. NATURALLY OCCURRING SYSTEMS

3.1. Aflatoxins

Aflatoxins form a group of acutely toxic and extremely carcinogenic, hepatotoxic metabolites produced by some strains of Aspergillus flavus which infest the feed ingredients during harvest or storage and cause toxicity in several domestic animals[70].

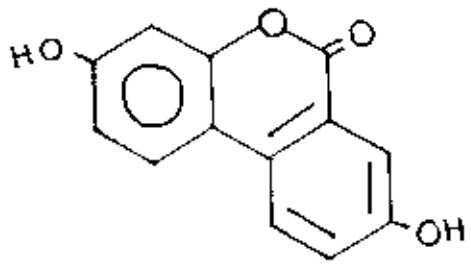
Possible biogenetic pathways to the synthesis of aflatoxins (B_1) were presented51[71].



51

3.2. Dibenzo-α-pyrones

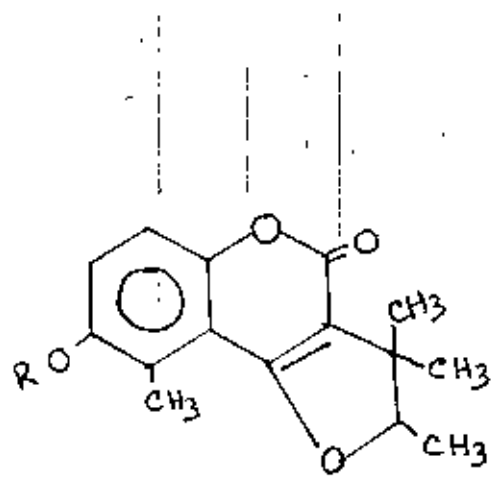
One of the two yellow pigments isolated from the scent glands of beaver (castor fibre) has been identified as 3,8 - dihydroxydibenzo-α-Pyrone 52[72]. The structure was finally confirmed by synthesis involving condensation of resorcinol with 2-bromo -5-hydroxybenzoic acid.



52

3.3. Furocoumarins

A furocoumarin glaupalol **53** was isolated from rhizomes of Glaucidium Palmatum (Ranunculaceae)[73,74]. It showed phenolic properties and was characterised as its monoacetate.



53

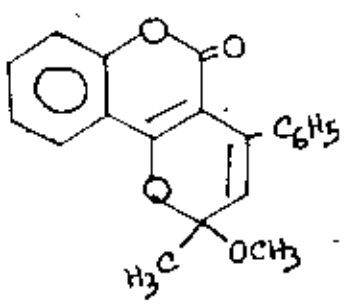
a R = H

b R = CH_3

4. BIOLOGICAL PROPERTIES

Natural and synthetic coumarins containing 3,4-ring systems are known to exhibit varied physiological properties[75,76].

Cyclocoumarol **54**[77] is one of the most active anticoagulants among the 106 synthetic compounds tested for their activity. Cyclocoumarol has 60% of the activity of dicoumarol **55**. In rabbits, dogs and healthy men, cyclocoumarol induced prolonged and intense hypoprothrombinemia in minimal doses. It was shown that 4-methyl-2,5-dioxo-3-phenyl-2H-5H-Pyrano [3,2-c] [1] bezopyran **56** exhibited consisderable anti-coagulant activity[78].



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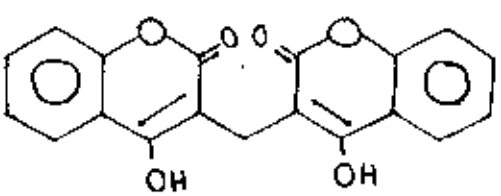

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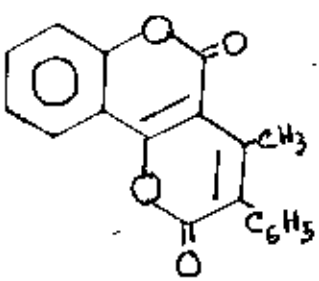


56

5. OBJECTIVE OF THE RESEARCH

Coumarin compounds are widely distributed in nature. Coumarin is a constitutent of many essential oils and extracts including lavender oil and vanilla. Coumarin is also the volatile component of clover blossoms that is responsible for

the characteristics odourof new-mown hay. Many 3-substituted derivatives of 4-hydroxy-coumarin are powerful blood anticoagulants and are used in drugs to control blood clotting and as rodenticides (warfarin), which cause death by hemorrhage. Besides, substituted coumarin derivatives have unique UV absorption and florescence properties. Pyrido-coumarins have recently drawn the attention of investigators for their possibility of being used as organic dyes in lasers. Moreover, they show a great deal of fungicidal activities.

The project is therefore, planned to synthesise some new substituted pyridocoumarins and find out their probable uses in different industries. It is also intended to make detailed structural studies of the compounds which are to be synthesised.

CHAPTER TWO

6. EXPERIMENTAL

6.1. General Techniques and Equipment

The general techniques and equipment that have been adopted and used during this research work are briefly described bellow:

6.2. Reagents and Solvents

All the reagents and solvents were used from the bottles except m-cresol and benzaldehyde. The reagents and solvents were of the analytical reagent grade bought either from BDH or E. Merck, or BCH or from Spectrochem.

Diethyl ether, Conc. HCl, ammonia, pet-ether (40-60^{0}C), ethyl acetate, chloroform, 3-methoxy phenol, acetone, Conc. H_2SO_4, ethyl acetoacetate, glacial acetic acid, 3-nitrobenzaldehyde, ammonium acetate, α-naphthol, 4-nitrobenzaldehyde, resorcinol, dry pyridine, alcohol(RS) and acetic anhydride were used from the respective bottles.

Purificaton of Benzaldehyde

Reagent grade benzaldehyde was purified by rotary vacuum evaporator under reduced pressure at 80^{0}C approximately.

Purification of m-cresol

Reagent grade m-cresol was distilled with a quick-fit simple distillation apparatus and the colourless fraction boiling between 202-204^{0}C was collected.

6.3. Separation of Reaction Mixtures

The reaction mixtures were separated by the following methods:

Solvent Extraction (Using Sparating Funnel)

Separation by extraction method involved the transfer of a substance from one material phase into a second phase. Solvent extraction method was employed, either for the isolation of dissolved substances from solutions, or from solid mixtures or for the removal of undesired soluble impurities from mixturee. Common extraction solvents were diethyl ether, benzene, chloroform and petroleum ether. The success of the separation was dependent upon the solubility of the substance to be extracted in that solvent and upon the case with which the solvent could be removed from the solute. Diethyl ether, owing to its powerful solvent proper-ties and its low boiling point (35°C), was the most used one during this work. Water, concentrated hydrochloric acid and ammonia were also used for this work.

Gravity Filtration (Using Fluted Filter Paper)

Gravity filtration was commonly used for the collection of a solid material that was insoluble in the liquid with which it was associated.

Suction Filtration (Using Buchner Funnel)

This method was employed for the collection of a solid that has crystallised from a solvent. Effective operation of the suction filtration technique depends on the extent of pressure reduction within the filter flask.

6.4. Drying of Products

The products were dried in oven and in air after separation and purification.

6.5. Determination of Melting Points

In general, a sharp melting point is one of the most characteristic properties of a pure organic compound. The melting points were determined by Gallencamp apparatuses.

6.6. Spectroscopic Analysis

Infra-Red (IR) Spectroscopy

The infra-red (IR) spectra were recorded as KBr on a IR-470, shimadzu, Japan spectrometer in the Department of Chemistry, Dhaka University, and with PERKIN-ELMER 983 spectophotometer at Moscow Institute of Reagents and Extra Pure Chemicals.

The absorption bands were expressed in cm^{-1}.

^{1}HNuclear Magnetic Resonance (^{1}HNMR) Spectroscopy

^{1}HNMR spectra were recorded on a JNM-PMX 60 NMR Spectrometer system in the Department of Chemistry, Dhaka University, Dhaka, Bangladesh and Xh-100-12 VARIAN Spectrometer of the Institute of Reagents and Extra Pure Chemicals Moscow, Russia. Deuterated acetone [$(CD_3)_2CO$], DMSO, deuterated chloroform ($CDCl_3$) were used as solvents whereas TMS (tetra methyl silane) was used as "internal standard".

Mass Spectroscopy

The mass spectra were recorded on a LKB 9000 spectrometer in Moscow, Russia.

6.7. Chromatographic Analysis

Thin Layer Chromatography

Thin layer chromatography (TLC) was applied as a method for the separation of reactants and products. The separation and identification of reaction mixture were carried out by tlc Anhydrous alumina chromatographic grade was used for making the static phase. A slurry was made with Alumina and water. The homogeneous slurry was made by well-shaking. Then a pair of cleared and dried slides (1" x 3") were dipped into the slurry and removed immediately. A uniform Alumina layer was formed on the plate. The plates were dried in the air for 24 hours. In the procedure employed for tlc a small amount of the sample to be analyzed was applied near one end of the adsorbent coated plate. The coated plate was then placed upright in a developing chamber that contained a shallow pool of the suitable solvent mixture as the mobile phase. The developing solvent rose along the coated surface of the plate by capillary action and carried the components of the sample with it. The components of a mixture move up the tlc plate at different rates, depending on the solubility of the component in the solvent and the degree to which the component was adsorbed by the stationary phase. The plates were removed when the solvent front had reached the top boundary of the plate, allowed to dry and then the chromatograms were developed in an iodine chamber. Finally, the R_f value of the seperated compounds were determined.

7. PREPARATION OF PIPERIDONE

7.1. 2,6-Diphenyl- 3-ethoxy Carbonyl-4-Piperidone

A mixture of ethylacetoacetate (12.38 gms, o.1 mole), benzaldehyde (19.46 gms, 0.2 mole) and ammonium acetate (7.7 gms, 0.1 mole) in glacial acetic acid (20 ml) was refluxed for about 30 minutes. The colour of reaction mixture changed from light yellow to light orange during refluxing. The unreacted benzaldehyde was removed under reduced pressure. When the viscous liquid was treated with a mixture of ether (200 ml), concentrated hydrochloric acid (20 ml) and water (20 ml), precipitate of 2,6 - diphenyl -3-ethoxy carbonyl -4-piperidone hydrochloride **I** was formed. The precipitate of compound **I** was separated by filtration and recrystallisation from alcohol (13.3 gms, 20.2%), yellow crystals of piperidone hydrochloride I, m.p (214-218^{0}C) was obtained. The piperidone hydrochloride I was treated with NH_3 (1:1) and the organic base was separated by etheral extraction. On removal of the solvent a reddish orange mass (13.9 gms) was obtained. Recrystallisation from alcohol gave yellowish orange crystals (12 gms, 20%) of 2,6 - diphenyl -3-ethoxy carbonyl -4-piperidone **II** melting at 212-214^{0}C. R_f 0.52 (Al_2O_3, pet. ether: ethyl acetate = 4:1).

7.2. 2,6-Di (3-nitrophenyl)-3 ethoxy carbonyl-4-Piperidone

A mixture of 3-nitrobenzaldehyde (60.4 gms, 0.4 mole), ethylacetoacetate (24.59 gms, 0.2 mole) and ammonium acetate (25.2 gms, 0.2 mole) was dissolved in glacial acetic acid (40 ml) and refluxed for 30 minutes. During the refluxing the colour changed from light yellow to reddish orange. When the viscous liquid was dissolved in ether (200 ml) and shaken with concentrated hydrochloric acid (40 ml) and water (40 ml),

precipitate of 2,6-di (3-nitro phenyl) -3-ethoxy carbonyl -4-piperidone hydrochloride III was formed. The precipitate of compound III was separated by filtration and washed with a mixture of glacial acetic acid and ether (1:1). On recrystallisation from alcohol yellow crystals (8.70 gms, 4.84%) of piperidone hydrochloride III, melting at (178-180^{0}C) was obtained.

Piperidone hydrochloride III was later treated with NH_3 (1:1) and the organic base was extracted with ether. The etheral solution was dried over anhydrous MgSO4. Removal of ether gave a reddish orange mass (9.2 gms). Recrystallisation from alcohol gave orange crystals (8 gms, 5%) of 2,6-di (3-nitrophenyl)-3-ethoxy carbonyl-4-Piperidone IV melting at (178-180^{0}C) R_f. 0.56 (Al_2O_3, Pet ether: ethyl acetate = 4:1).

IR spectrum of compound IV

The IR spectrum of the compound IV has the following important absorption bands: $\nu^{(cm-1)}$. 3484 (N-H vibration of piperidine ring), 1526 and 1350 (symmetric and asymmetric, -NO_2 group), 1640 ()CO group) and 1740 (-COOR group).

^{1}HNMR spectrum of compound IV

The ^{1}HNMR spectrum of this compound was taken in $CDCl_3$ with TMS as the internal standard. Signals of aromatic protons at δ=8.47 - 8.02 ppm and δ=7.92 -7.42 ppm. δ=4.10 ppm (methylenic protons), δ=1.20 ppm (methynic protons). δ= 1.78 ppm (N-H proton).

Mass Spectrum of compound IV

The mass spectrum of the compound **IV** has the following important peaks at m/z = 413 (5%, M)$^{+}$, 396(15%, M-OH)$^{+}$, 367(9%, M-NO_2)$^{+}$, 291(29%, M- $C_6H_4NO_2$)$^{+}$, 385 (100%, M-CO)$^{+}$, 340 (23%, M-$CO_2C_2H_5$)$^{+}$.

7.3. 2,6-Di (4-nitrophenyl)-3-ethoxycarbonyl-4-piperidone

To a mixture of 4-nitrobenzaldehyde (7.5 gms, 0.05 mole), ammonium acetate (1.9 gms, 0.025 mole) and ethylacetoacetate (3.09 gms, 0.025 mole), glacial acetic acid (20 ml) was added The mixture was refluxed for 30 minutes. When the viscous liguid was dissolved in ether (200 ml) and shaken with concentrated hydrochloric acid (20 ml) and water (20 ml), precipitate of 2,6-di (4-nitrophenyl)-3-ethoxy carbonyl-4-piperidone hydrochloride was formed. The precepitate was separated by filtration and washed with a mixture of glacial acetic acid and ether (1:1). On recrystallisation from alcohol. Piperidone hydrochloride was treated with NH_3 (1:1) and the base was extracted with ether. The etheral solution was dried over anhydrous $MgSO_4$. Removal of solvent gave a reddish orange mass (1.23 gms). Recrystallisation from alcohol gave orange crystals (1 gm, 5%) of 2,6--di (4-nitrophenyl)-3-ethoxy carbonyl-4-piperidone **V**, melting at (158-160°C) R_f 0.52 (Al_2O_3, pet ether: ethyl acetate =4:1).

8. PREPARATION OF COUMARIN

8.1. 8-Methoxy 2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin

To a mixture of 2,6-diphenyl-3-ethoxy carbonyl-4-piperidone II (5.75 gms, 17.6 mmol) and 3-methoxy phenol (2.82 gms, 17.6 mmol), concentrated H_2SO_4 (15 ml) was added. The mixture was thoroughly mixed and left for 48 hours and then poured into ice cold water. The precipitate obtained was separated by filtration and dried. The yield was 5 gms (73%) **VI** Recrystallisation from ethanol gave brownish crystals 8-methoxy 2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin, melting at (190-192°C). R_f 0.82 (Al_2O_3, pet ether: ethyl acetate = 4:1).

IR Spectrum of Compound VI

The IR spectrum of compound **VI** has the following absorption bands: $\nu^{(cm^{-1})}$: 3436 (N-H vibration), 1721 (lactonic C=O group) 1202 (C-O-Ar) and 754 (C-H, monosubstituted benzene ring).

^{1}HNMR spectrum of compound VI

The ^{1}HNMR spectrum of compound **VI** contains δ(ppm): 7.94-7.42 (11-H, aromatic protons), 1.0 (w,N-H), 3.80 (8-OCH_3 protons).

Mass Spectrum of Compound VI

The mass spectrum of the compound VI has the following peaks at m/z =383(10%,M)$^+$, 379(100%, M-4H)$^+$, 306 (7%, M-Ph)$^+$, 340(20%, M-CH_3CO)$^+$, 91(22%, C_7H_7)+, 77(35%, C_6H_5)$^+$.

8.2. 8-Methoxy 2,4-di (3-nitro Phenyl) 1,2,3,4-tétrahydropyrido [3,4-c] coumarin

Concentrated sulphuric acid (10 ml) was added to a mixture of 2,6-di (3-nitrophenyl)-3-ethoxy carbonyl -4-piperidone IV (0.48 gm, 1.5 mmol) and 3-methoxy phenol (1.31 gms, 1.5 mmol). The mixture was thoroughly mixed and left overnight. Next day, the product was poured into ice-cold water with stirring. Gel-type precipitate so formed was separated by filtration and washed with water. After drying in oven, 0.24 gm (43%) of 8-methoxy 2,4-di (3-nitro Phenyl) 1,2,3,4-tetrahydropyrido [3,4-c] coumarin VII was obtained, melting at (194-196^{0}C). R_f 0.78 (Al_2O_3, pet ether: ethylacetate = 4:1).

IR Spectrum of Compound VII

The IR spectrum of compound VII has the following important absorption bands: $\nu^{(cm^{-1})}$:
3415_b (N-H stretching), 1528, 1351$_s$ (-NO_2 symm and asymm), 1713_m (lactonic C=O); 1174 (Ar-O-C): 1611 (C=C, aromatic ring); 808 (Ar-H, bending).

^{1}HNMR Spectrum of compound VII

^{1}HNMR spectrum of compound **VII** has the following signals at δ(ppm): 8.64-8.27 (m.11-H), 1.1 (b.N-H); 3.79 (s, 3H, OCH_3).

Mass spectrum of the compound VII

The mass spectrum of the compound **VII** has the following important peaks at m/z = 473 (26%, M)$^+$, 469(47%, M-4H)$^+$, 323(23%, M-ArCH=N$^+$H$_2$)$^+$;351(8% M-$C_6H_4NO_2$)$^+$

8.3. 8-Methyl 2,4-di (3-nitrophenyl) 1,2,3,4-tetrahydropyrido [3,4-c) coumarin

A Mixture of 2,6-di (3-nitrophenyl)-3-ethoxy carbonyl-4-piperidone **IV** (2 gms,4.8 mmol) and m-cresol (2.06 gms,4.8 mmol was added to concentrated sulphuric acid (20 ml). The mixture was mixed thoroughly and kept overnight for complete reaction. Next day, the reaction mass was poured into ice-cold water with stirring and the solid obtained was filtered. After drying in oven, 1.34 gms (61%) of 8-methyl 2, 4-di-(3-nitrophenyl) 1,2,3,4-tetrahydropyrido [3,4-c) coumarin **VIII**, m.p. (160^{0}C-161^{0}C), R_f 0.80 (Al_2O_3, pet ether: ethyl acetate = 4:1).

IR spectrum of compound VIII

The IR spectrum of the compound has the following absorption bands, $\nu^{(cm-1)}$ 3430 (N-H stretching), 1520 and 1345 (-NO_2 symm and asymm), 1760 (lactonic C=0), 1160 (Ar-O-C), 1640 (C=C aromatic ring), 740 and 810 (Ar-H bending).

^{1}HNMR spectrum of compound VIII

The ^{1}HNMR spectrum has the following signals at δ(ppm): 8.57-8.24 (m.11-H); 1.2 (w.N-H), 2.49 (s, 3H, CH_3).

Mass Spectrum of Compound VIII

The mass spectrum of the compound **VIII** has the following important peaks at m/z=457 (3%,M)$^+$, 396(21%, M-CH_3-Ar)$^+$, 352 (5%, M-CH_3-Ar-CO_2)$^+$, 76(15%, C_6H_4)$^+$, 396 (20% M-CH_3NO_2)$^+$, 32tl(3%, $C_7H_7NO_2$)$^+$

8.4. 8-Hydroxy 2,4-di (3-nitrophenyl) 1,2,3,4-tetrahydropyrido [3,4-c) coumarin

Concentrated sulphuric acid (10 ml) was added to a mixture of 2,6-di (3-nitrophenyl)-3 ethoxy carbonyl-4-piperidone **IV** (1 gm, 2 mmol) and resorcinol (0.5 gm, 4.5 mmol). The reaction mixture was kept overnight for complete reaction and the product was poured into ice cold water. Gel-type precipitate so formed was collected by suction filtration. After drying in oven, the yield of product 8-hydroxy 2,4-di (3-nitrophenyl) 1,2,3,4-tetrahydropyrido [3,4-c) coumarin was 0.56 gm (51%) **IX**,. m.p. (170^{0}C-172^{0}C). R_f 0.77 (Al_2O_3, pet ether: ethyl acetate = 4:1).

IR spectrum of compound IX

The IR spectrum of the compound **IX** has the following absorption bands: $\nu^{(cm^{-1})}$max: 3550-3440 (b, N-H, O-H overlapped), 1536 and 1352 (-NO_2 symm and asymm), 1665 (C=O), 1162 (C-O-Ar), 736 and 815 (Ar-H bending).

^{1}HNMR spectrum of compound IX

The ^{1}HNMR spectrum of the compound **IX** contained the following signals at δ(ppm): 8.60-8.22 and 8.16-7.57 (m.11- H), 1.1 (w, N-H).

Mass spectrum of compound IX

The mass spectrum of the compound **IX** shows a molecular ion peak at m/z = 459 (M^+), 455 (12%, $M-4H)^+$, 396 (8%, $M-NO_2OH)^+$, 337 (2%, $M-C_6H_4NO_2)^+$.

8.5. 2,4-Di (3-nitrophenyl)-1,2,3,4-tetrahydrobenzo [h] pyrido [3,4-c] coumarin

To a mixture of 2,6-di (3-nitrophenyl)-3-ethoxy carbonyl-4-piperidone **IV** (1 gm, 2 mmol) and α- naphthol (0.9 gm, 6 mmol), concentrated sulphuric acid (10 ml) was added. The reaction mixture was allowed to stand overnight. Next day, it was poured into ice-cold water and the precepitate obtained was filtered and dried in oven. The yield was 1.1 gms (92%) of 2,4-di (3-nitrophenyl)-1,2,3,4-tetrahydrobenzo [h] pyrido [3,4-c] coumarin **X**, m.p. (170^{0}C-171^{0}C). R_f 0.8 (Al_2O_3, pet ether: ethyl acetate = 4:1).

IR spectrum of compound X

The IR spectrum of the compound **X** has the following absorption bands: $\nu^{(cm^{-1})}$: 3420 (s. N-H); 16[illegible] (C=O), 1520 and 1340 ($-NO_2$).

^{1}HNMR spectrum of compound X

The ^{1}HNMR spectr[illegible] of the compound X has the following signals at δ(ppm): 8.[illegible]4.27 and 8.12-7.47 (m, 8H $C_6H_4NO_2$), 8.75 (m,6H 1,2-[illegible]citu naphthaline); around 1.0 (w.N-H).

Mass spectrum of compound X

The mass spectrum of the compound **X** has the following peaks at m/z =489 (15% $M-4H)^+$, 367 (2%, $M-4H-C_6H_4NO_2)^+$, 249 (3%, $M-(C_6H_4NO_2)_2)^+$.

8.6. 8-Methoxy 2,4 di (4-nitro phenyl) 1,2,3,4 tetrahydropyrido [3,4-c) coumarin

To a mixture of 2,6-di (4-nitrophenyl)-3 ethoxy carbonyl-4-piperidone **V** (0.20 gm, 1.5 mmol) and 3-methoxy phenol (1.31 gms, 1.5 mmol), concentrated sulphuric acid (10 ml) was added. After allowing to stand for 72 hours, the reaction mixture was poured into ice-cold water and the gel-type precipitate obtained was filtered. After drying in air, the yield was 0.13 gm (57%) of 8-methoxy 2,4 di (4-nitro phenyl) 1,2,3,4 tetrahydropyrido [3,4-c) coumarin **XI**. Recrystallisation from ethanol gave brownish crystals melting at (165-169^{0}C). R_f 0.52 (Al_2O_3,pet ether:ethyl acetate = 4:1).

IR spectrum of compound XI

The IR spectrum of compound **XI** has the following absorption bands: $\nu^{(cm^{-1})}$ 3426 (b, N-H), 1713 (m. coumarin C=O), 1522 and 1347 (s, asymm and symm, NO_2), 1610 (C=C), 1200 (C-O).

Mass spectrum of compound XI

The mass spectrum of the compound **XI** has the following important peaks at m/z =473 (26%, $M)^+$, 469 (100%, $M-4H)^+$, 351 (50%, $M-C_6H_4NO_2)^+$, 323 (17%, $M-ArCH-NH_2)^+$

9. DERIVATIVE OF COUMARINS

9.1. 3-Acetyl-8-methoxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin

8-Methoxy 2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **VI** (0.5 gm,1.3 mmol) and acetic anhydride (4.5 gms, 40 mmol) was added in dry pyridine (4 ml). The mixture was left overnight. Next day, the product was poured into ice-cold water and the precipitate observed was collected and dried. The yield was 0.45 gm (90%) of 3-acetyl-8-methoxy-2,4-diphenyl-1,2,3,4-tetra-hydropyrido [3,4-c] coumarin **XII**, m.p. (198-200^{0}C). R_f 0.5 (Al_2O_3, pet. ether: ethyl acetate = 4:1).

IR Spectrum of Compound XII

The IR spectrum has the following important absorption bands, ν^{cm-1}: 2990 (A_r-H stretching), 1710 (lactonic C=0), 1632 (C=0), 1210 (C-0).

^{1}HNMR Spectrum of Compound XII

^{1}HNMR spectrum was taken in $CDCl_3$ with TMS as the internal standard. The NMR spectrum shows the presence of impurities. The ^{1}HNMR spectrum has the following signals at δ(ppm): 3.70 (3H, OCH_3), 2.3 (3H, $CO-CH_3$), 6.9 - 762 (13H, Aromatic).

Mass Spectrum of Compound XII

The mass spectrum of the compound **XII** has the following important peaks at m/z =425 (19% M)$^+$, 382(30%, M-CO-CH_3)$^+$, 384 (5% M-OCH_3)$^+$, 339 (M-CH_3-CO-NH_2)$^+$

9.2. 3-Acetyl -8-methyl-2,4 -di(3-nitrophenyl)-1,2,3,4-tetrahydro pyrido [3,4-c] coumarin

A solution of 8-methyl-2,4-di (3-nitrophenyl) 1,2,3,4,-tetrahydropyrido [3,4-c] coumarin **VIII** (1.32 gms, 2.8 mmol) and acetic anhydride (4.5 gms, 40 mmol) in dry pyridine (4 ml) was kept for a day. Later, the solution was poured into ice-cold water and the solid obtained was filtered off, washed and dried. The yield was 1.36 gms (95%) of 3-acetyl-8-methyl-2,4 -di(3-nitrophenyl)-1,2,3,4-tetrahydro pyrido [3,4-c] coumarin **XIII**, m.p. (194^0-196^0C) R_f 0.51 (Al_2O_3 pet ether: ethyl acetate = 4:1).

IR spectrum of compound XIII

IR ν^{cm-1} 1760 (lactonic C-O); 1520 and 1340 (NO_2 symm and asym), 1600 ($CO-CH_3$);

^{1}HNMR spectrum of Compound XIII

^{1}HNMR δ(ppm) (in $CDCl_3$): 7.45-8.4 (11-H); 2.45 ($8-CH_3$); 2.23 ($N-CO-CH_3$)

Mass spectrum of compound XIII

Important peaks at, m/z = 499(5%, M)$^+$, 498 (27%, M-H)$^+$, 456(100%, M-CO-CH_3)$^+$, 377 (20%, M-$C_6H_4NO_2$)$^+$.

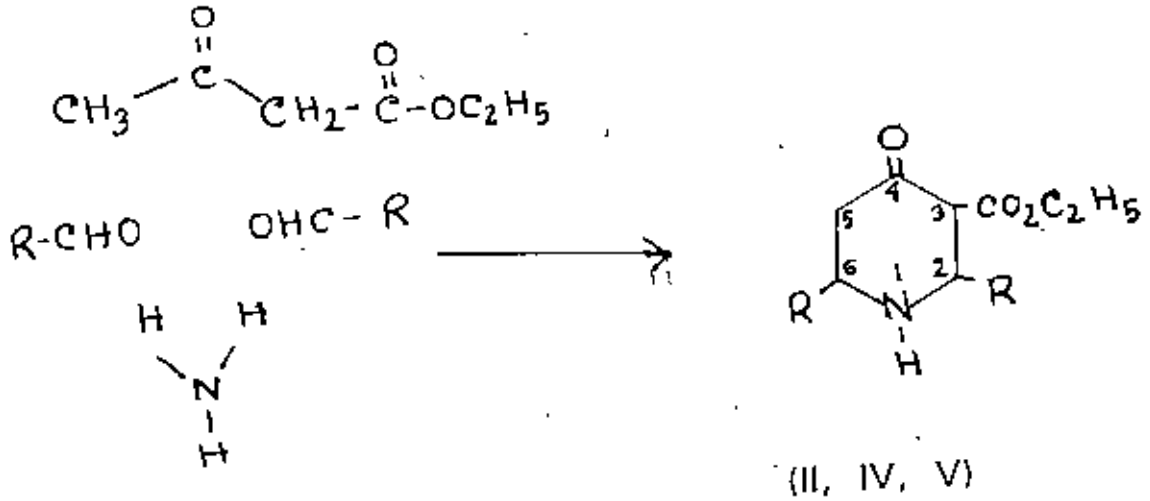
CHAPTER THREE

10. RESULTS AND DISCUSSION

10.1. RESULTS

Pyridocoumarins drew attention of researchers for the possibility of their use as organic dyes for lasers and as tracers in biological objects[79,80]. Keeping this objective in view some substituted 1,2,3,4 tetrahydropyrido [3,4-c] coumarins and 1,2,3,4-tetrahydrobenzo [h] pyrido coumarins were synthesised. Starting material for the end product were 2,6-diphenyl-3-ethoxy carbonyl piperidine-4-one **II** and 2,6-di(nitrophenyl)-3-ethoxy carbonyl piperidine-4-one (IV-V).

Substituted-piperidones-(II,IV,V) were prepared by condensing ethyl acetoacetate with aromatic aldehydes and ammonia in glacial acetic acid medium[80].



(II, IV, V)

$R = C_6H_5$ (II)

$R = 3\text{-}NO_2C_6H_4$ (IV)

$R = 4\text{-}NO_2C_6H_4$ (V)

Piperidone II was at first liberated as its hydrochloride I with a yield of about 20%. The melting point of piperidone-4 hydrochloride was found to match with the literature value[80].

The base 2,6 diaryl-3-ethoxy carbonyl-4-piperidone (II,IV,V) was liberated from an alcoholic solution of the hydrochlorides by adding excess of aqueous ammonia. Recrystallisation from alcohol gave crystals of 2,6-diphenyl-3-ethoxy carbonyl-4-piperidone (II, yield-20%) melting at 212-214^{0}C, 2,6-di(3-nitro phenyl)-3-ethoxy carbonyl-4-piperidone (IV, yield 5%) melting at 178-180^{0}C and 2,6-di (4-nitrophenyl)-3-ethoxy carbonyl-4-piperidone (V,yield-5%) melting at 158-160^{0}C[80].

The structure of compound IV was established from its spectroscopic data.

The IR spectrum [Fig. 1] of this compound contains absorption bands $\nu_{(cm^{-1})}$ at 3484 characteristic of N-H vibration of piperidine ring, two bands at 1526 and 1350 represents the symmetric and asymmetric vibrations of-NO_2 group. Absorption band at 1640 and 1740 characteristics the presence of carbonyl groups of the ring and that of ester group respectively.

The ^{1}HNMR spectrum [Fig. 2] of the compound IV contains two groups of signals of aromatic protons at δ=8.47-8.02 ppm and δ=7.92-7.42 ppm characteristic for meta nitrophenyl substituents, signals at δ=4.10 and 1.20 ppm represents the methylenic and methylic protons of carbethoxyl group. The broad single at 1.78 ppm characterises the signal of N-H proton of the piperidine ring. Expected signals of aliphatic protons of the piperidine ring at δ= 2-3 ppm. were not identified due to low concentration of the sample.

The structure of compound IV is further supported by its mass spectrum (**Fig. 3**). The fragmentation pattern is in agreement with the structure having m/z=413(5%,M)$^+$, 396(15%, M-OH)$^+$, 367(9% M-NO_2)$^+$, 291(29%, M-$C_6H_4NO_2$)$^+$, 385 (100%, M-CO)$^+$, 340(23%, M-$CO_2C_2H_5$)$^+$ (**Scheme - 1**).

Spectroscopic analysis of compounds II and V was not carried out. Their identities were established by their melting point determination only.

CHART NO. 861—7501

FIGURE 2 : HNMR SPECTRUM OF COMPOUND IV

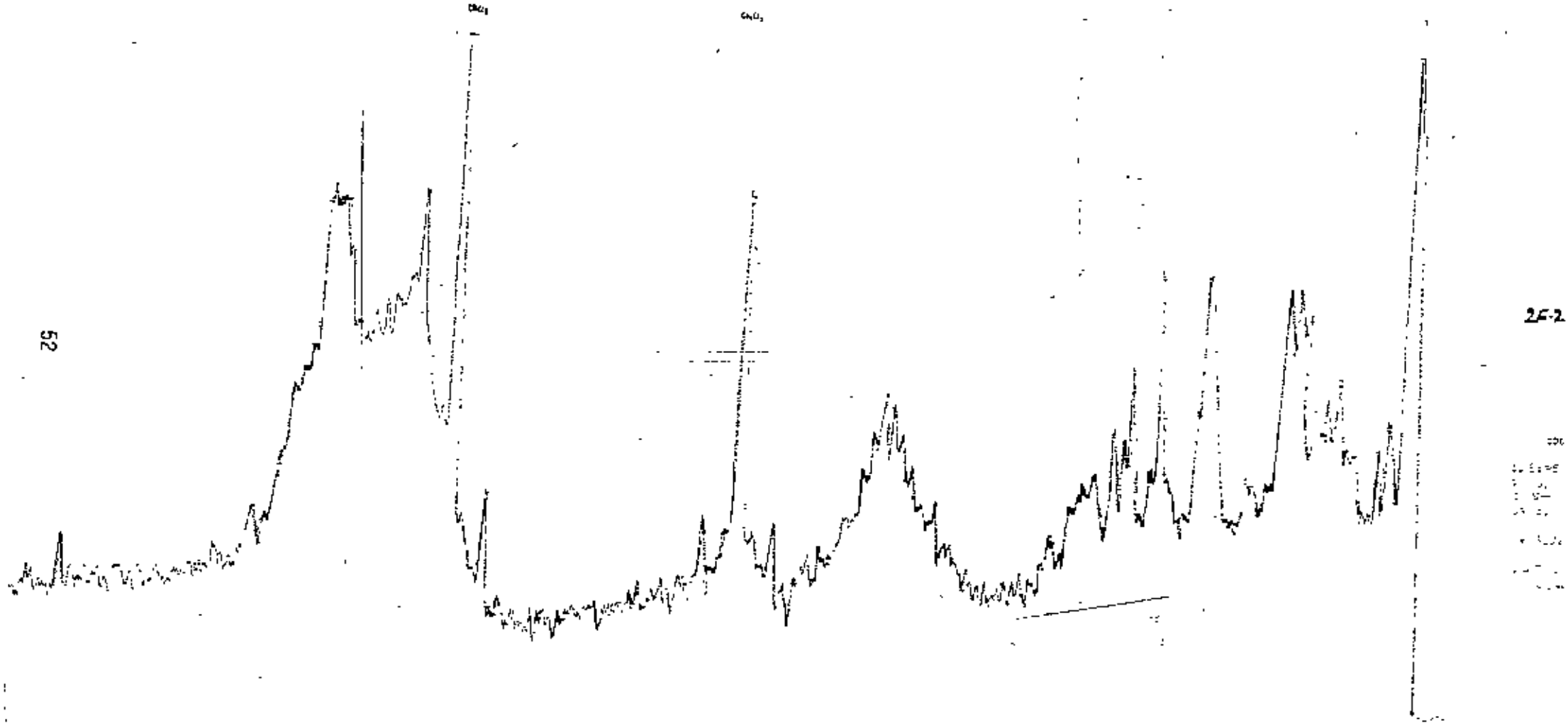
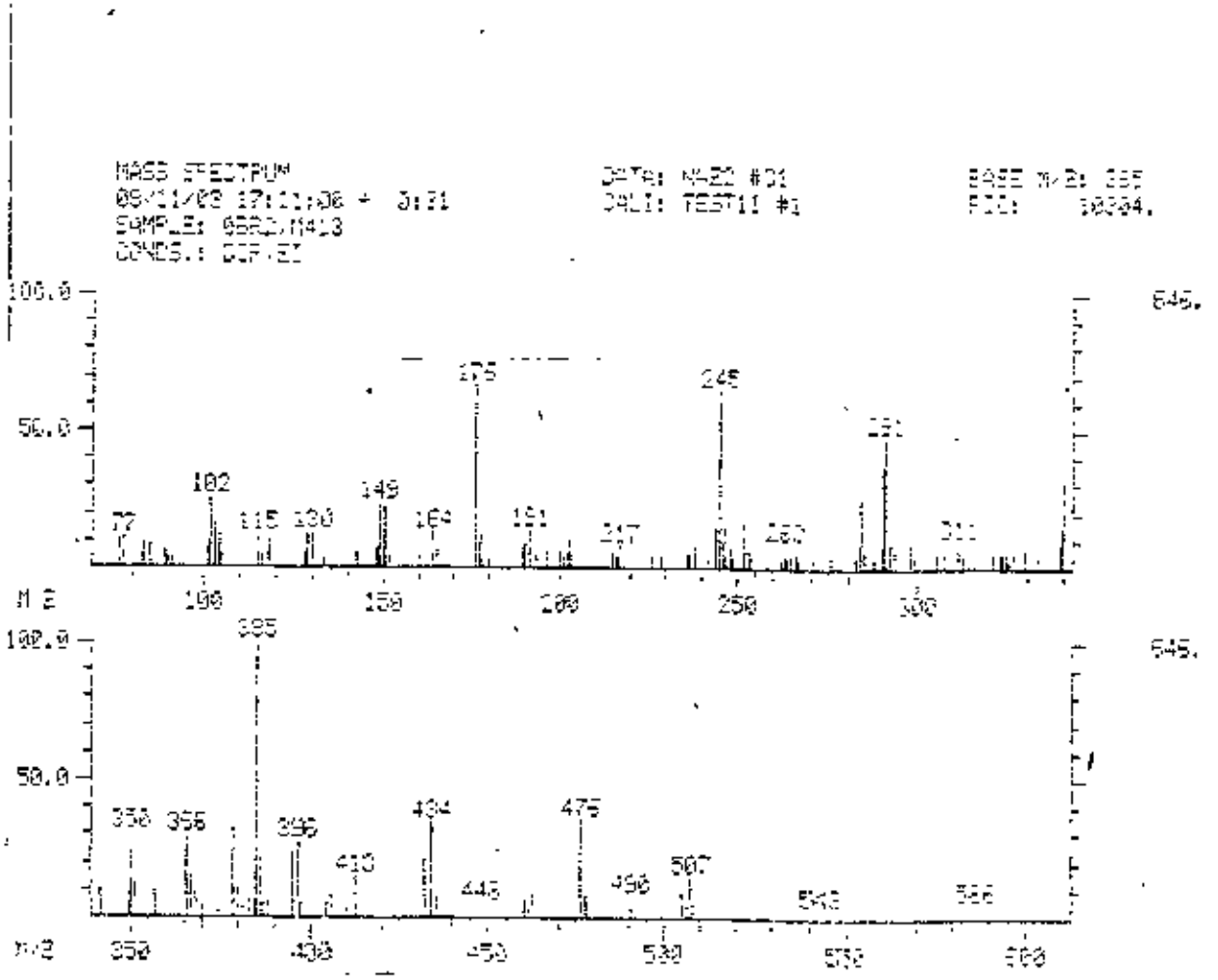
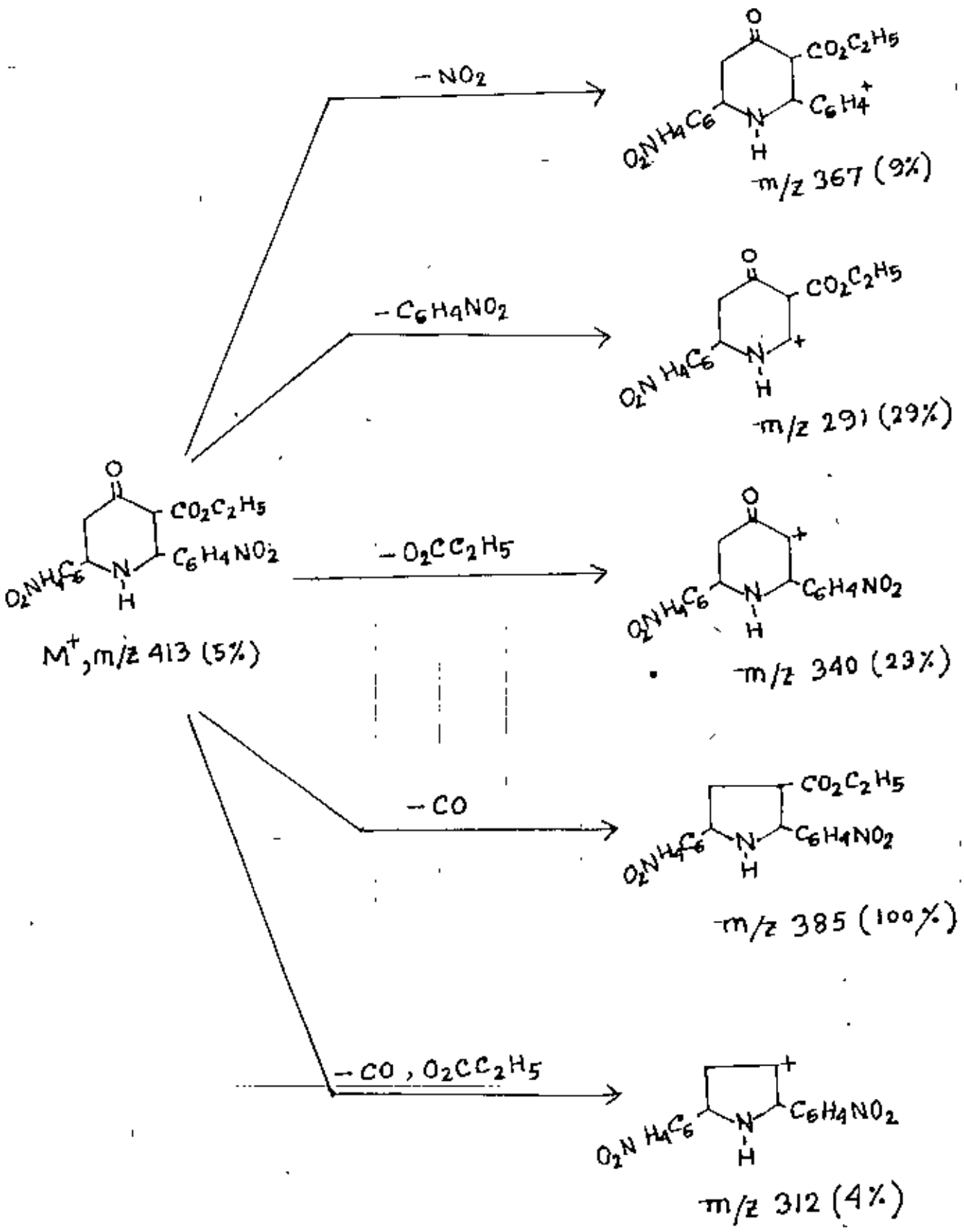


Figure – 3 : Mass spectrum of compound IV

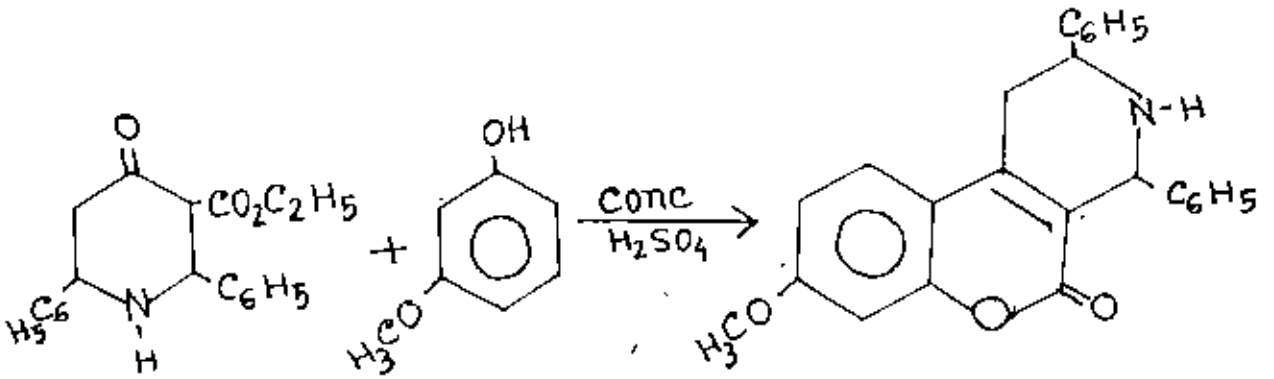


SCHEME 1 : FRAGMENTATION PATTERN OF COMPOUND IV



Reaction of 2,6-diaryl-3-ethoxy_carbonyl piperidine-4-one with 3-methoxyphenol

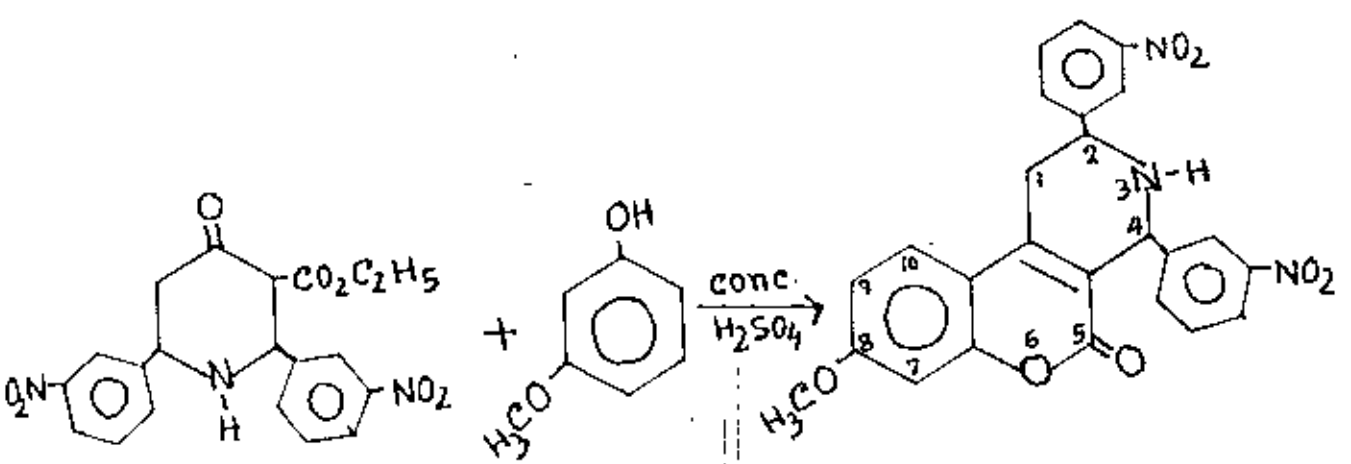
A.



II

VI

B.



IV

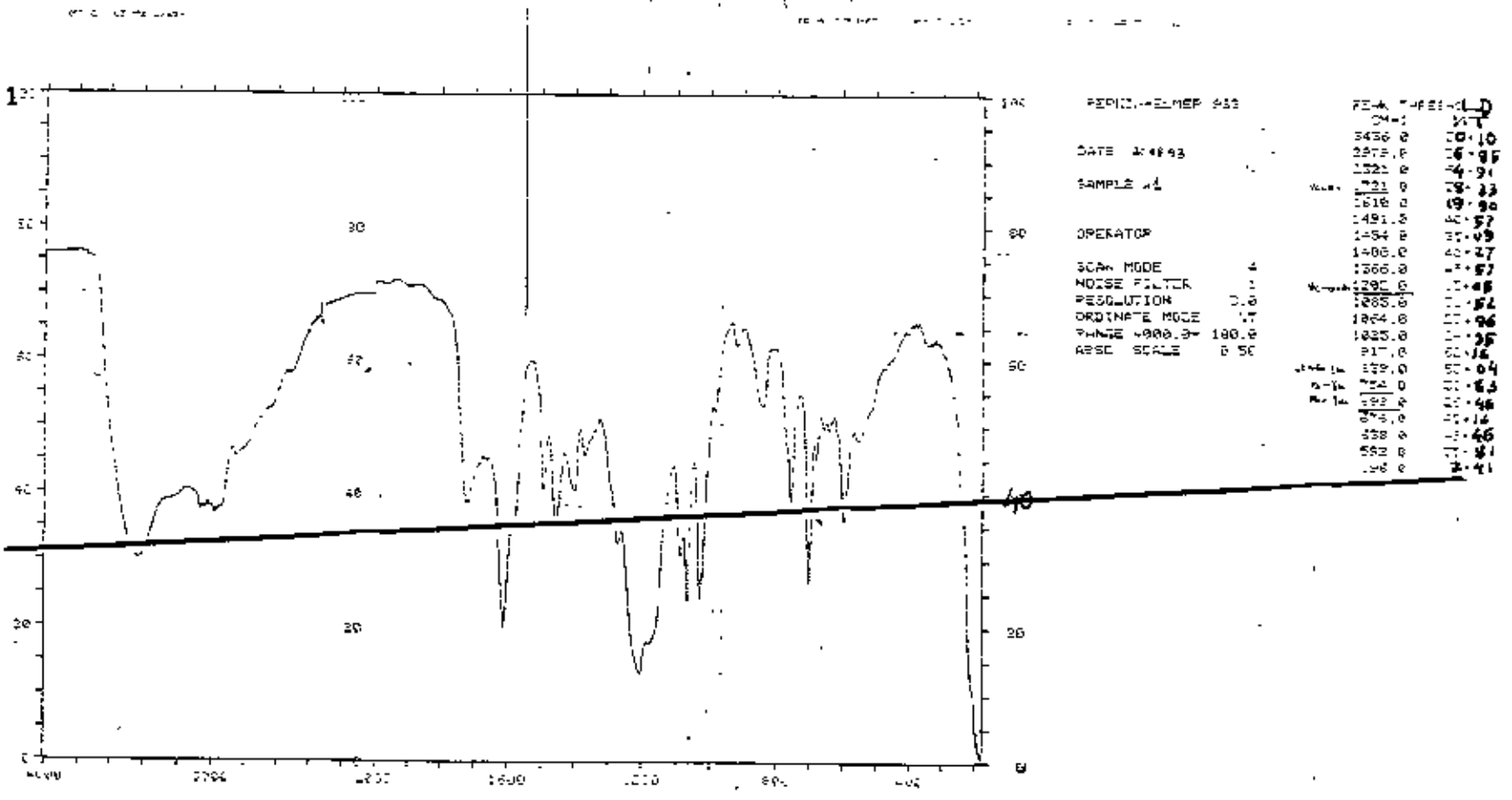
VII

The reaction of 2,6-dipheyl-3-ethoxy carbonyl piperidine-4-one **II** and 2,6-di(3-nitrophenyl)-3-ethoxy carbonyl piperidine-4-one [IV] with 3-methoxyphenol in presence of conc. H_2SO_4 at room temperature gave condensation products 8-methoxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-C] coumarin **VI** and 8-methoxy-2,4-di (3-nitrophenyl)-1,2,3,4 -tetrahydropyrido [3,4-c] coumarin **VII**.

(i) 8-methoxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **VI** was seperated as yellowish brown crystals, (5 gms 73%), melting at (190-192^{0}C, R_f0.82 (Al_2O_3, pet.ether: ethyl acetate=4:1). The structure of compound **VI** was established by spectroscopic data.

[The IR spectrum (**Fig. 4**) has the following absorption bands: ν^{cm-1}, the band at 3436 cm-1 is characteristic of N-H vibration of piperidine ring.

Figure – 4 : IR spectrum of compound VI



The band at 1721 corresponds to the absorption band of the lactonic carbonyl group and a band at 1202 cm^{-1} corresponds to the vibration frequency of C-O-Ar bond and at 754 cm^{-1} absorption band of monosubstituted benzene ring C-H vibration].

The ^{1}HNMR spectrum [Fig. 5] of the compound **VI** contains signals of aromatic protons in a small interval of δ=7.94-7.42 ppm, a weak broad signal of N-H proton at about δ=1.0 ppm. The signal at δ=3.80 ppm as a sharp singlet is attributed to 8-OCH_3 protons. The signals of protons at 1.2 and 4 were not visible due to the presence of impurities and solvents.

The mass spectrum [Fig. 6] of the compound further supports the structure. The fragmentation pattern is in agreement with the structure of coumarin derivatives having molecular ion peaks at m/z=383(10%,M)$^+$, 379(100% , M-4H)$^+$, 306(7%, M-Ph)$^+$, 340(20%, M-CH_3CO)+, 91(22%, C_7H_7)$^+$, 77(35%, C_6H_5)$^+$ **(Scheme - 2)**. Molecular ion peak $(M-4H)^+$ is due to the dehydrogenation of the piperidine ring. Presence of the fragment $(M-C_6H_5)^+$ is explained by the α position of the phenyl radical in the piperidine ring. This fragmentation pattern is similar to the one as cited in previous work[63].

FIGURE 5 : HNMR SPECTRUM OF COMPOUND VI

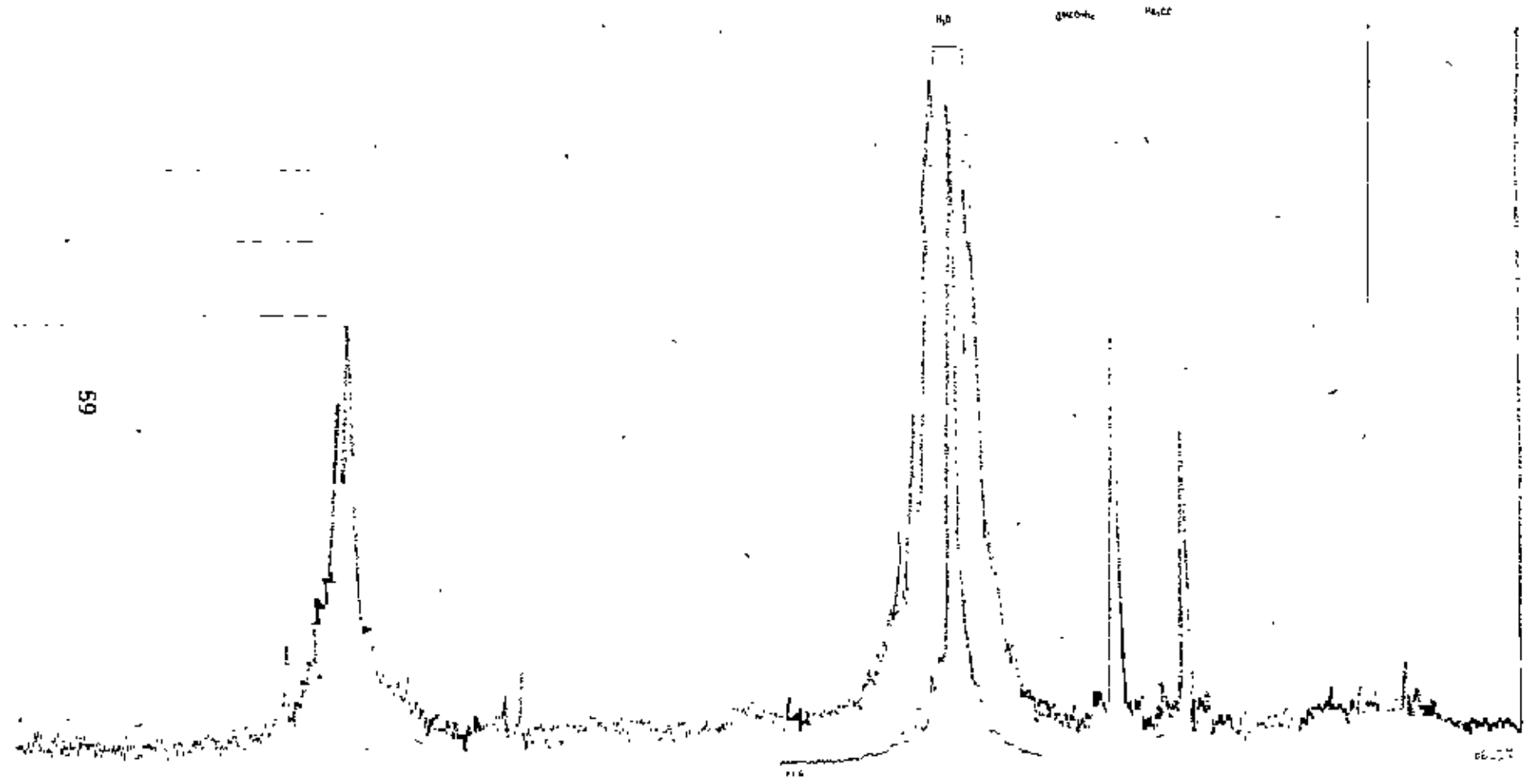
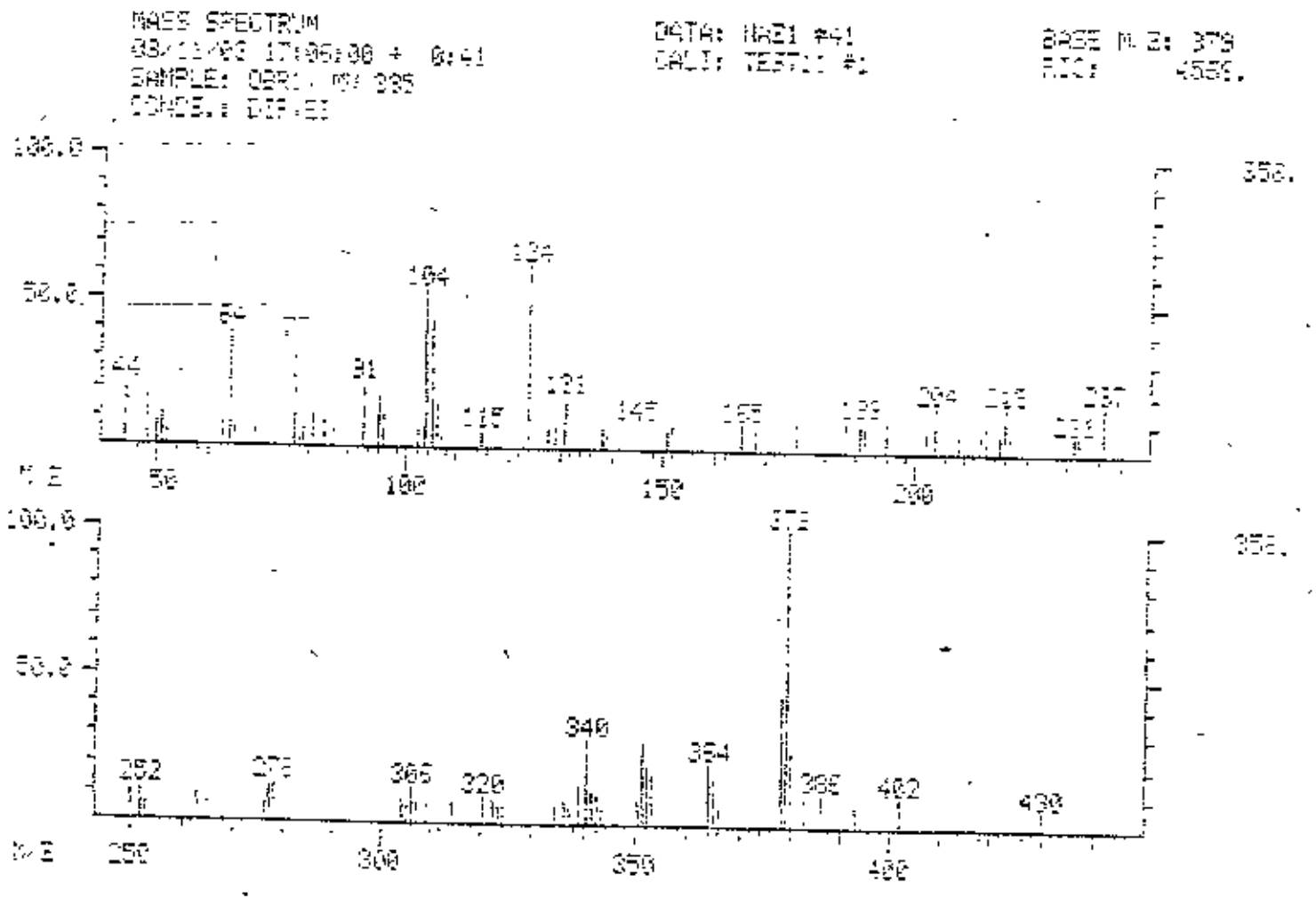
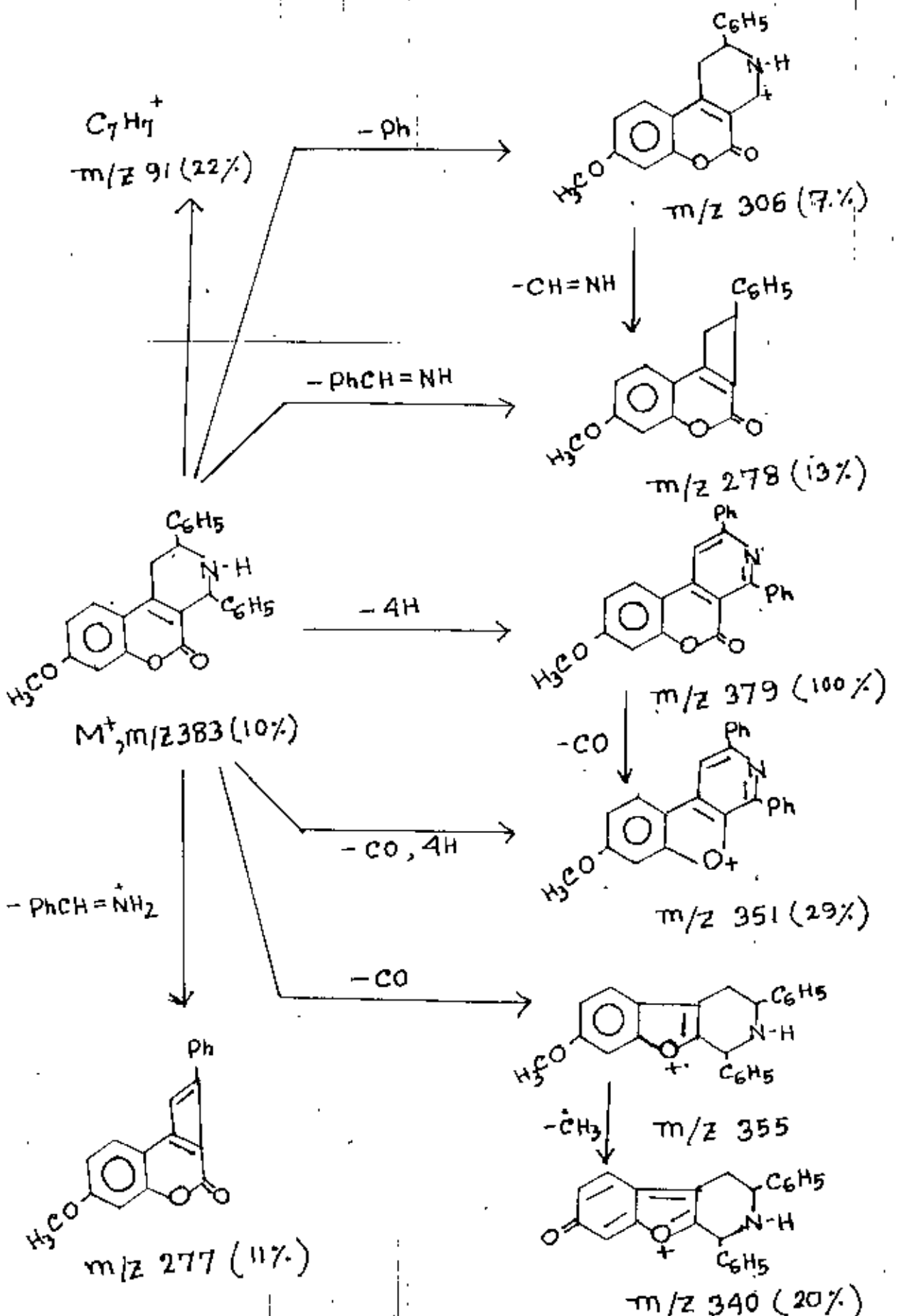


Figure - 6 : Mass spectrum of compound VI



SCHEME 2 : FRAGMENTATION PATTERN OF COMPOUND VI



(ii) 8-methoxy-2,4-di (3-nitrophenyl)-1,2,3,4-tetrahydropyrido - [3,4-C] coumarin **VII** was obtained as pale yellowish crystal, (0.24 gm, 43%), melting at 194-196^{0}C, R_f(0.78) (Al_2O_3, pet. ether: ethylacetate=4:1). The structure of compound **VII** was established by spectroscopic data.

[IR, **[Fig. 7]**, ν^{cm-1}] 3415 (N-H stretching), 1528, 1351$_s$ (-NO_2 **symm** and asymm); 1713$_m$ (lactonic C=O); 1174 (Ar-O-C); 1611 (C=C, aromatic ring); 808 (Ar-H, bending).

^{1}HNMR spectrum **[Fig. 8]** of compound **VII** has the following signals at δ(ppm): 8.64-8.27(m.11-H$_m$); 1.1 (b.N-H); 3.79 (s.3H, OCH_3).

The mass spectrum **[Fig. 9]** of the compound **VII** has the following important peaks at m/z = 473 (26%, M)$^+$; 469(47%, M-4H)$^+$; 323(23% M-ArCH=N$^+$H$_2$)$^+$; 351(8% M-$C_6H_4NO_2$)$^+$ **(Scheme-3)**.

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FIGURE - 7: IR SPECTRUM OF COMPOUND VII

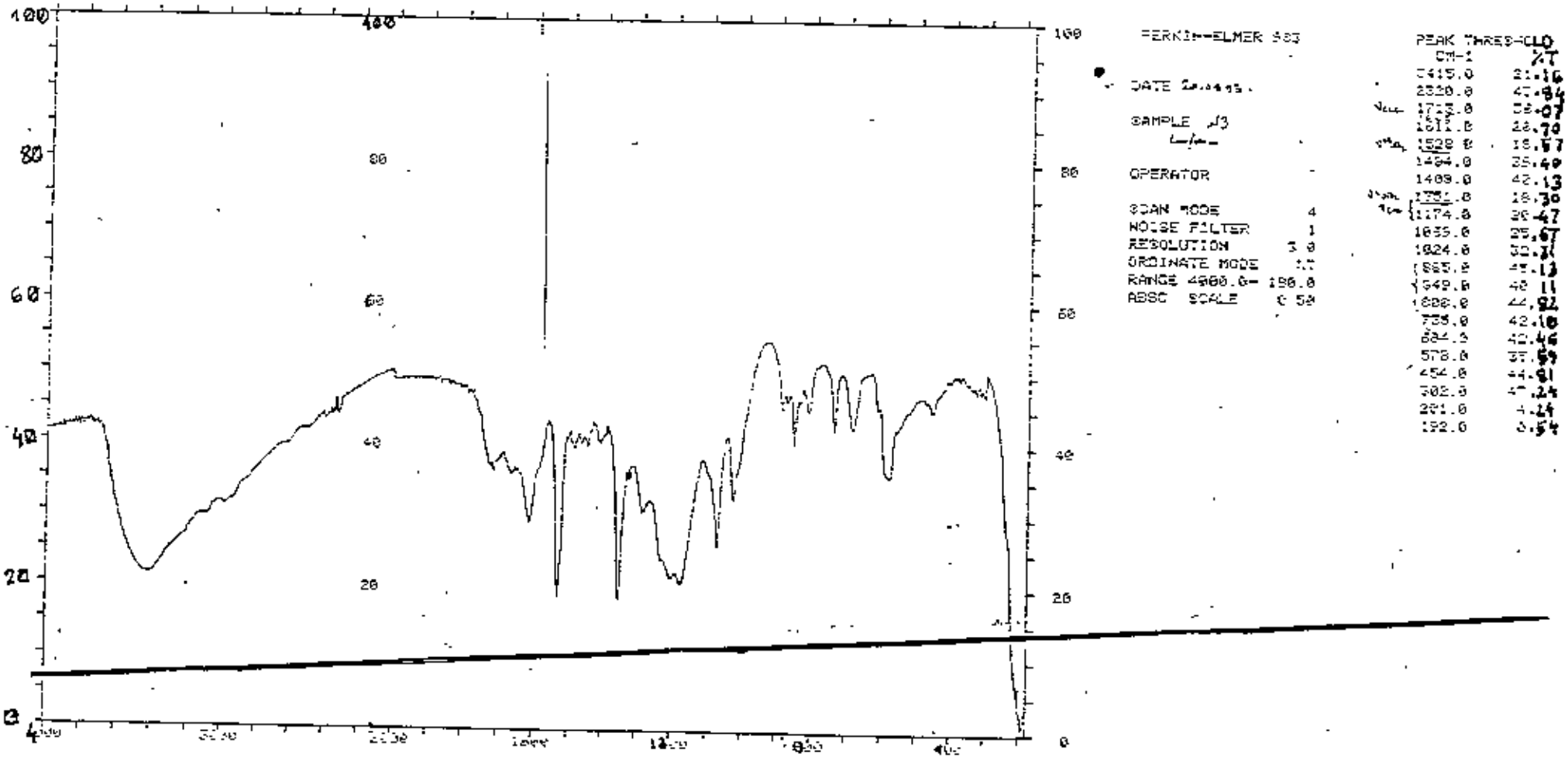


FIGURE 8 : HNMR SPECTRUM OF COMPOUND VII

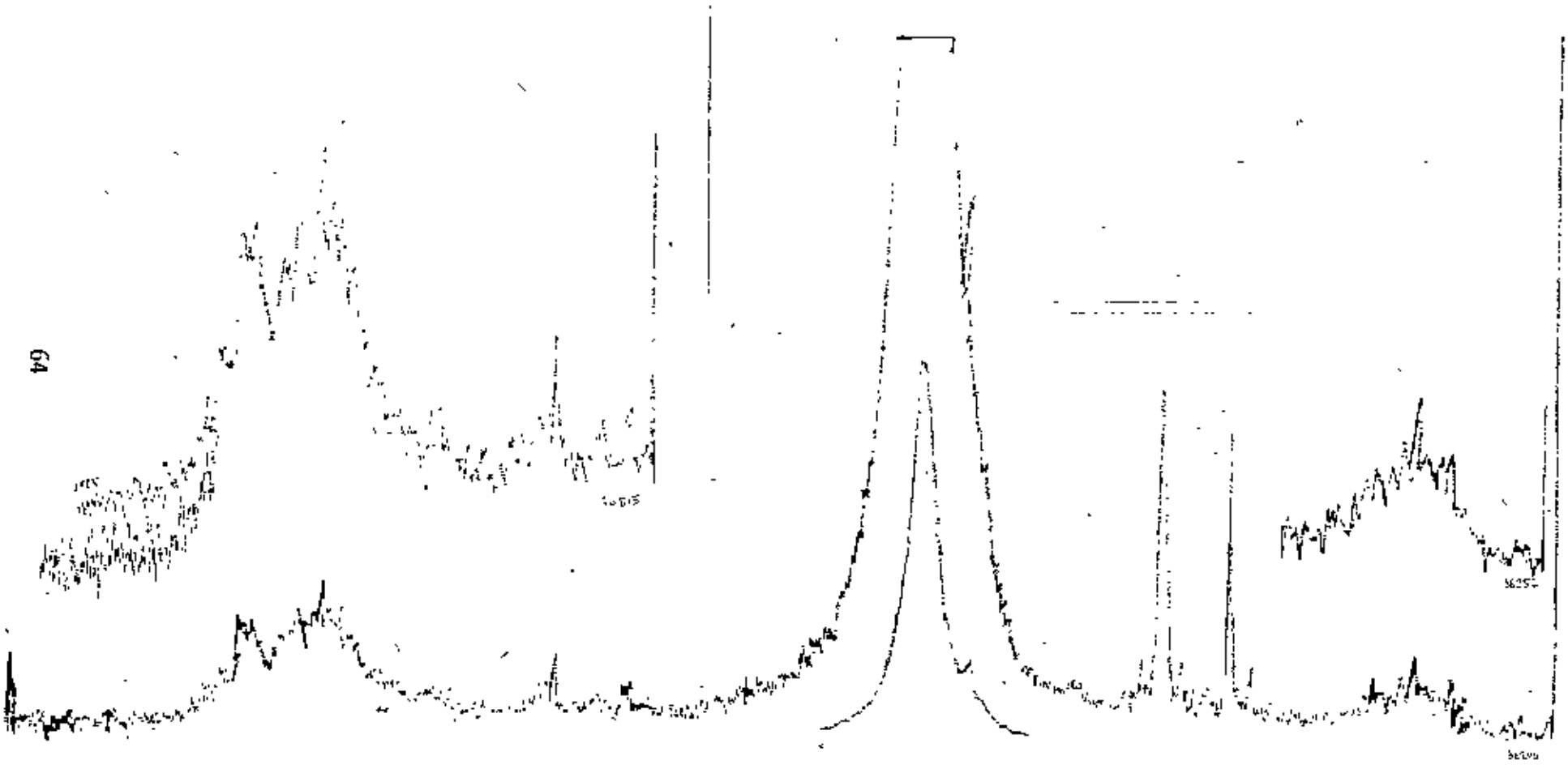
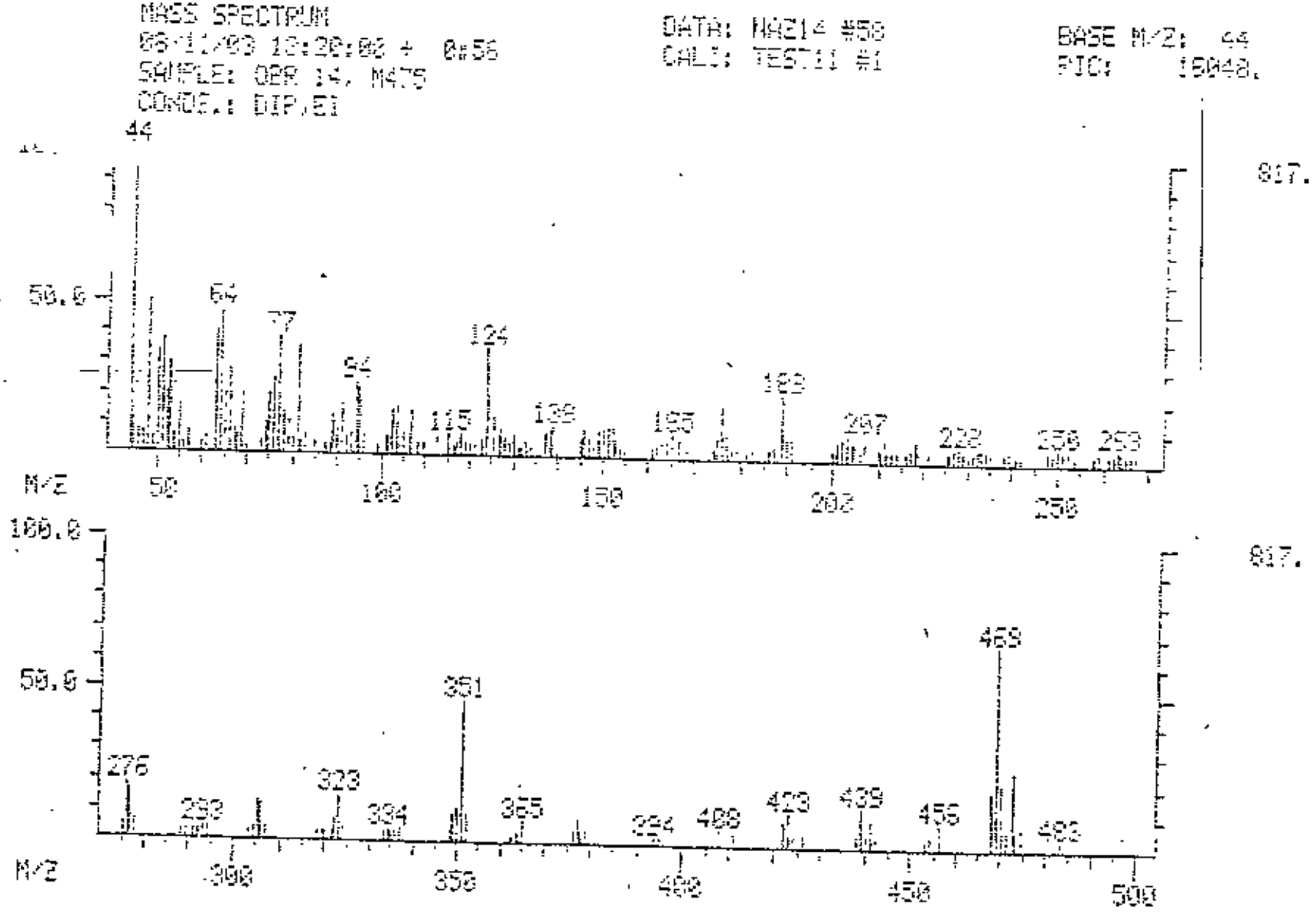
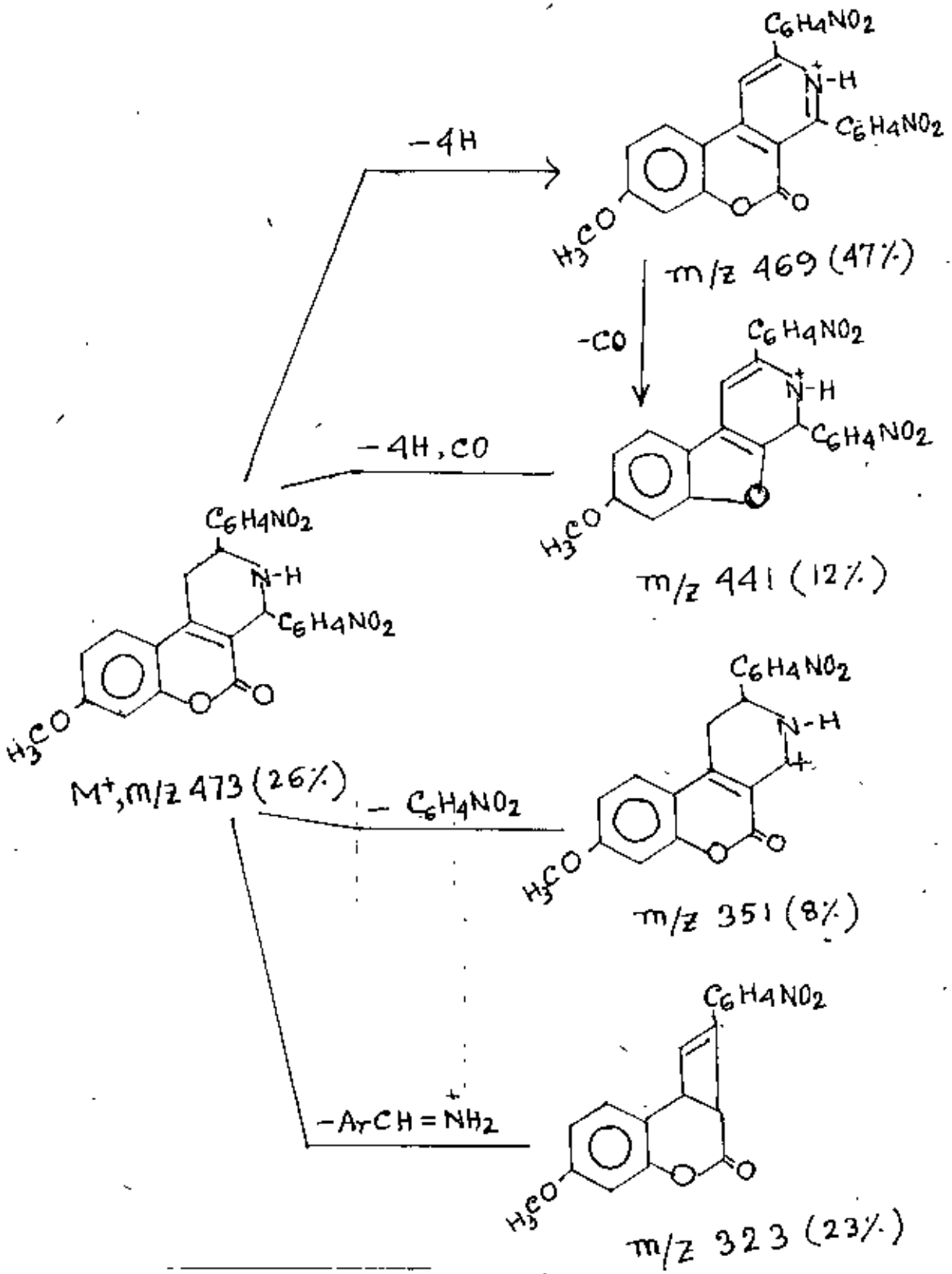


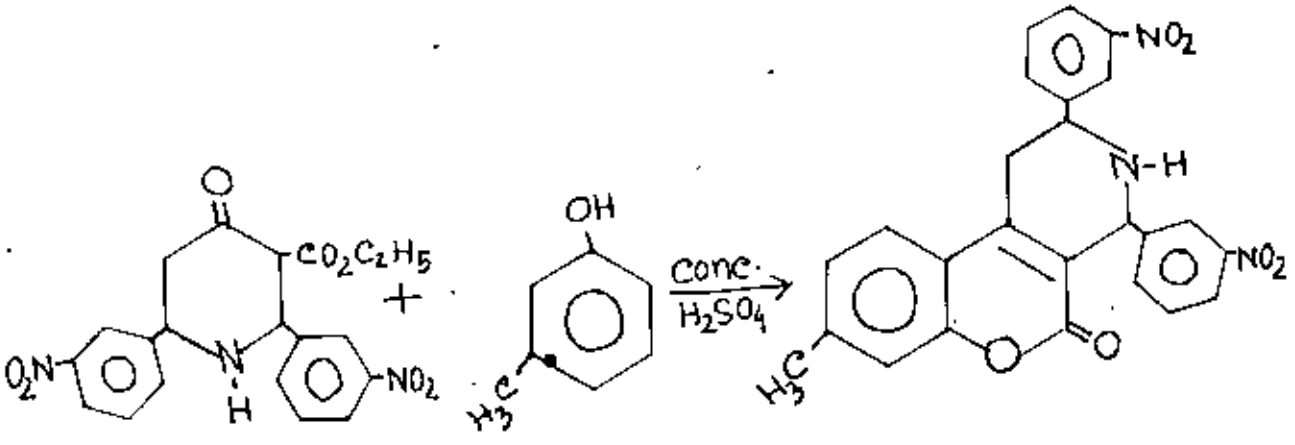
FIGURE – 9: MASS SPECTRUM OF COMPOUND VII



SCHEME 3 : FRAGMENTATION PATTERN OF COMPOUND VII



Reaction of 2,6-di (3-nitrophenyl)-3-ethoxy carbonyl Piperidine-4-one with m-Cresol



IV VIII

Piperidine-4-one **IV** and m-cresol were reacted in presence of conc.H_2SO_4 giving 8-methyl-2,4-di(3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-C] coumarin **VIII**, yield 1.34 gms (61%), melting at 160-162°C R_f-0.8 (Al_2O_3, pet. ether: ethyl acetate=4:1).

The structure of compound **VIII** was established by spectroscopic data.

[The IR spectrum **[Fig. 10]** of the compound has the following absorption bands; ν^{cm-1} 3430 (N-H stretching),1520 and 1345 ($-NO_2$ symm and asymm), 1760 (lactonic C=0), 1160 (Ar-O-C), 1640 (C=C aromatic ring), 740 and 810 (Ar-H-bending).

^{1}HNMR spectrum **[Fig. 11]** of compound **VIII** has the following signals at δ(ppm):8.57-8.24 (m.11 H); 1.2 (w.N-H),2.49 (s,3H,CH_3).

The mass spectrum **[Fig. 12]** of the compound **VIII** has the following important peaks at: m/z =457(3%, M)$^+$, 396(21%, M-CH_3-A_1)$^+$; 352 (5%, M-CH_3-A_1-CO_2)$^+$, 76(15% C_6H_4)$^+$; 396(20%, M-CH_3NO_2)$^+$, 321(3%; $C_7H_7NO_2$)$^+$.

FIGURE 10 : IR SPECTRUM OF COMPOUND VIII

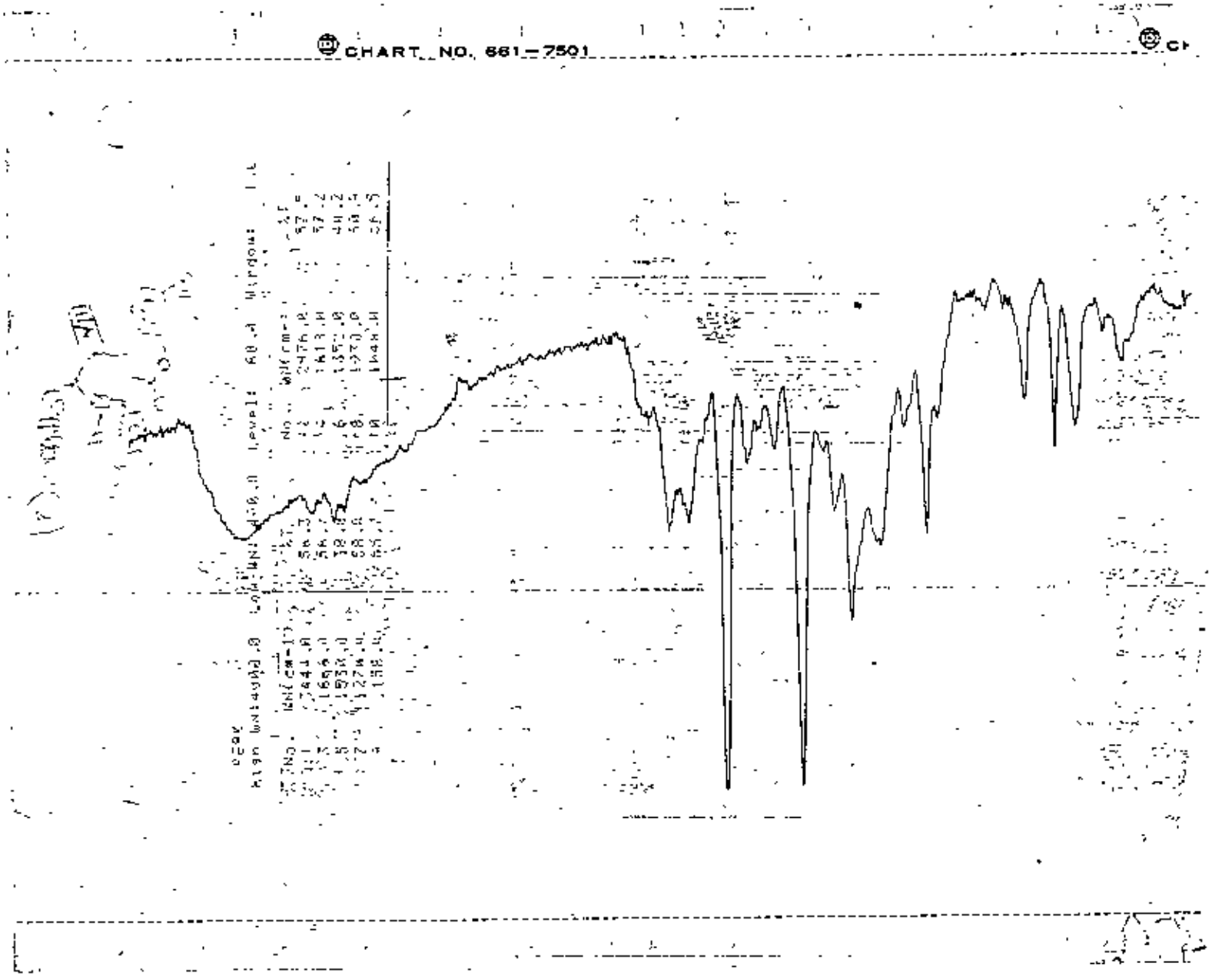


FIGURE 11 : HNMR SPECTRUM OF COMPOUND VIII

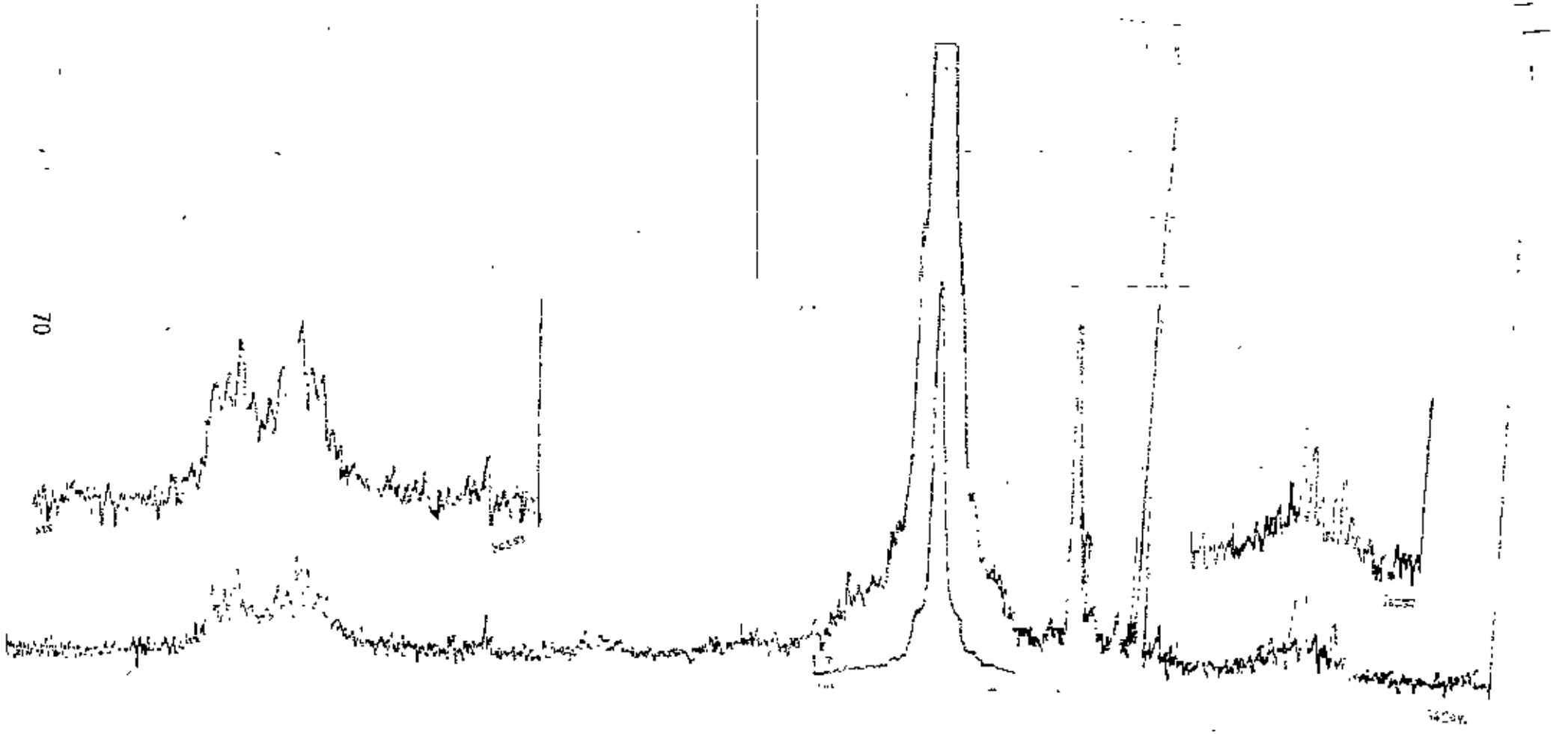
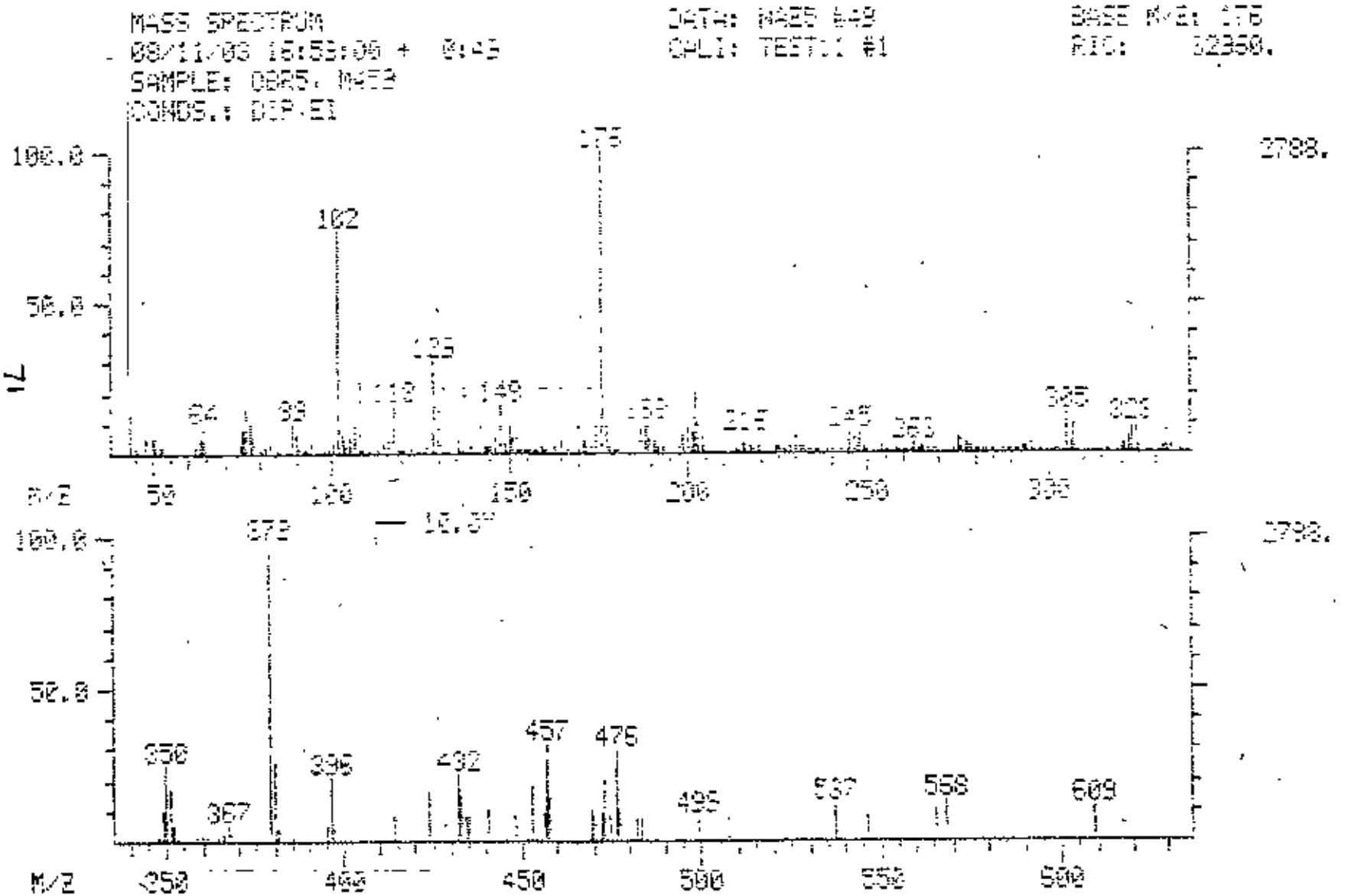
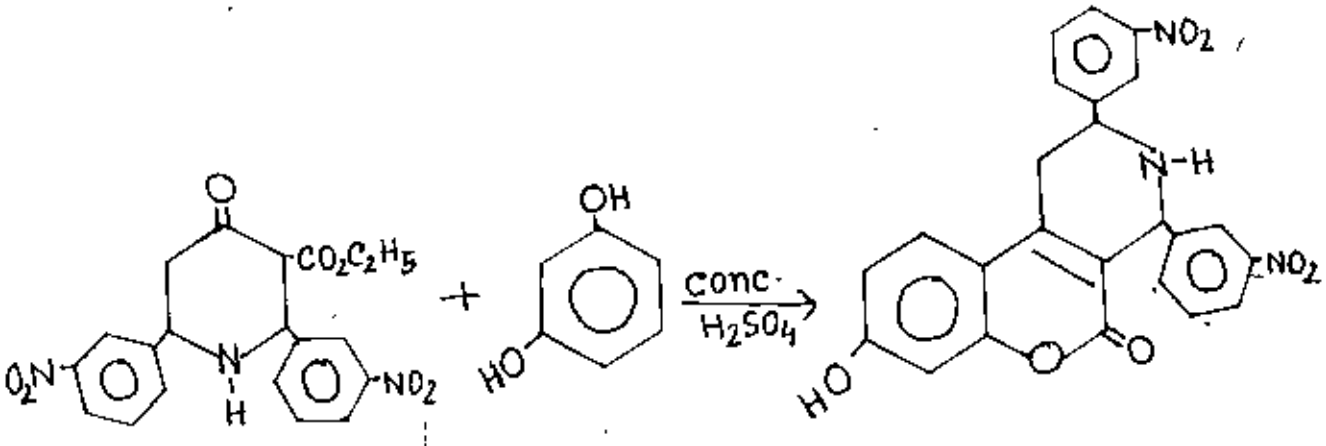


FIGURE 12 : MASS SPECTRUM OF COMPOUND VIII



Reaction of 2,6-di(3-nitrophenyl)-3-ethoxycarbonyl Piperidine-4-one with resorcinol



IV IX

Piperidine-4-one **IV** was reacted at room temperature with resorcinol in conc. H_2SO_4. The separated crystalline product 8-hydroxy-2,4-di(3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **IX** was 0.56 gm (51%), melting 170-172°C, R_f 0.77 (Al_2O_3, pet. ether: ethyl acetate = 4:1).

The structure of coumarin **IX** was also established by spectroscopic data.

The IR spectrum **[Fig. 13]** of the compound **IX** was in agreement with the structure of the compound. The IR spectrum of the compound has the following absorption bands: ν^{cm-1}: 3550-3440 (b,N-H,O-H overlapped), 1536 and 1352 ($-NO_2$ symm and asymm), 1665 (C=O), 1162 (C-O-A_r), 736 and 815 (A_r-H bending).

The ^{1}HNMR spectrum **[Fig. 14]** of the tetrahydro-pyridocoumarin **IX** was also in agreement with the structure. The spectrum con-tained the following signals of δ(ppm):0 8.60-8.22 and 8.16-7.57 (m 11 H), 1.1 (w, N-H). Signal of OH proton can not be identified due to the overlapping with the aromatic proton signals.

The mass spectrum **[Fig. 15]** of the tetrahydropyrido coumarin **IX** shows a weak molecular ion peak at m/z 459 (M^+). The rest of the spectrum has the following important peaks,at m/z = 455 (12%, M-4H)$^+$, 396(8%, M-NO_2OH)$^+$, 337 (2%, M-$C_6H_4NO_2$)$^+$.

FIGURE 13 : IR SPECTRUM OF COMPOUND IX

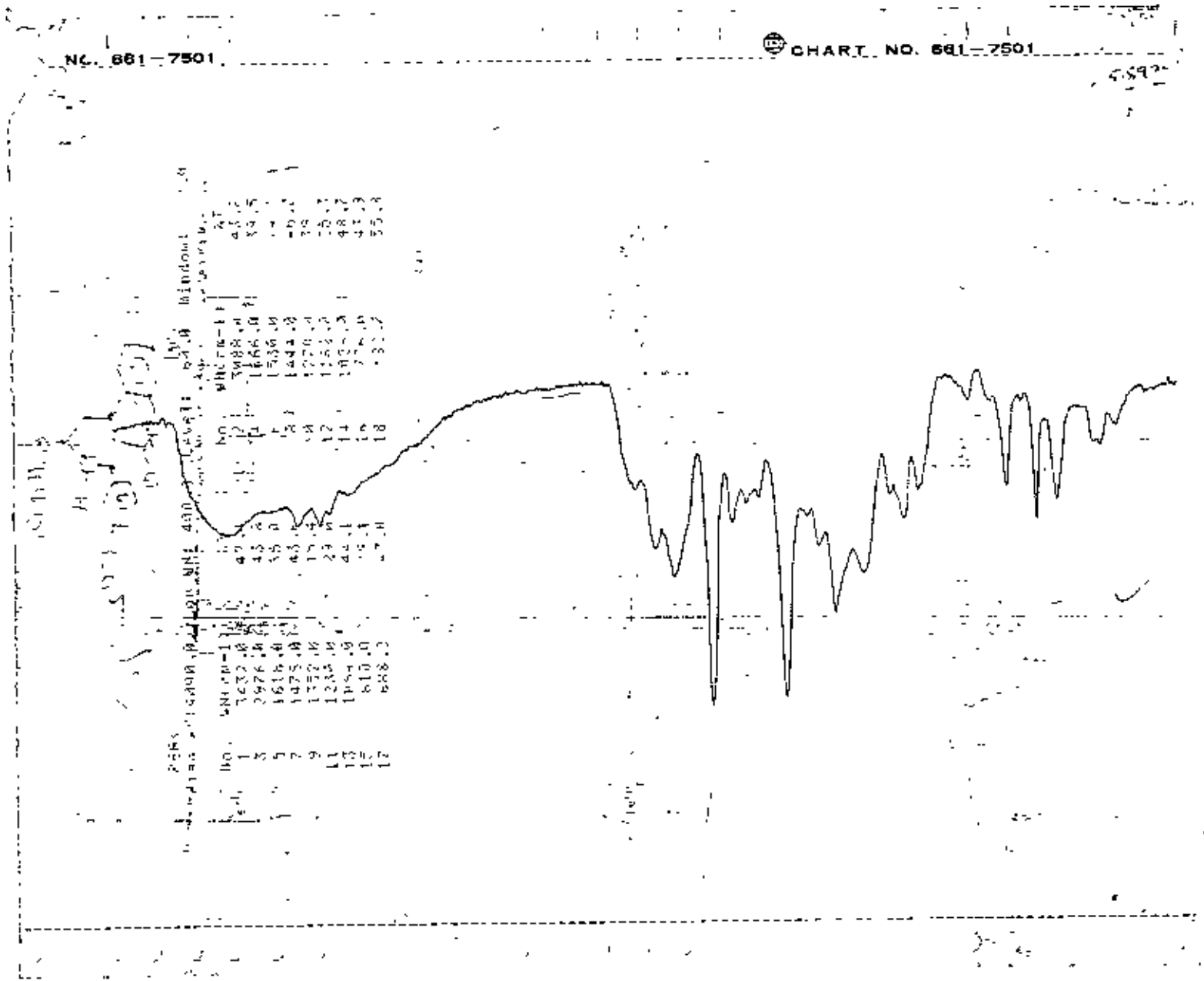


FIGURE 14 : HNMR SPECTRUM OF COMPOUND IX

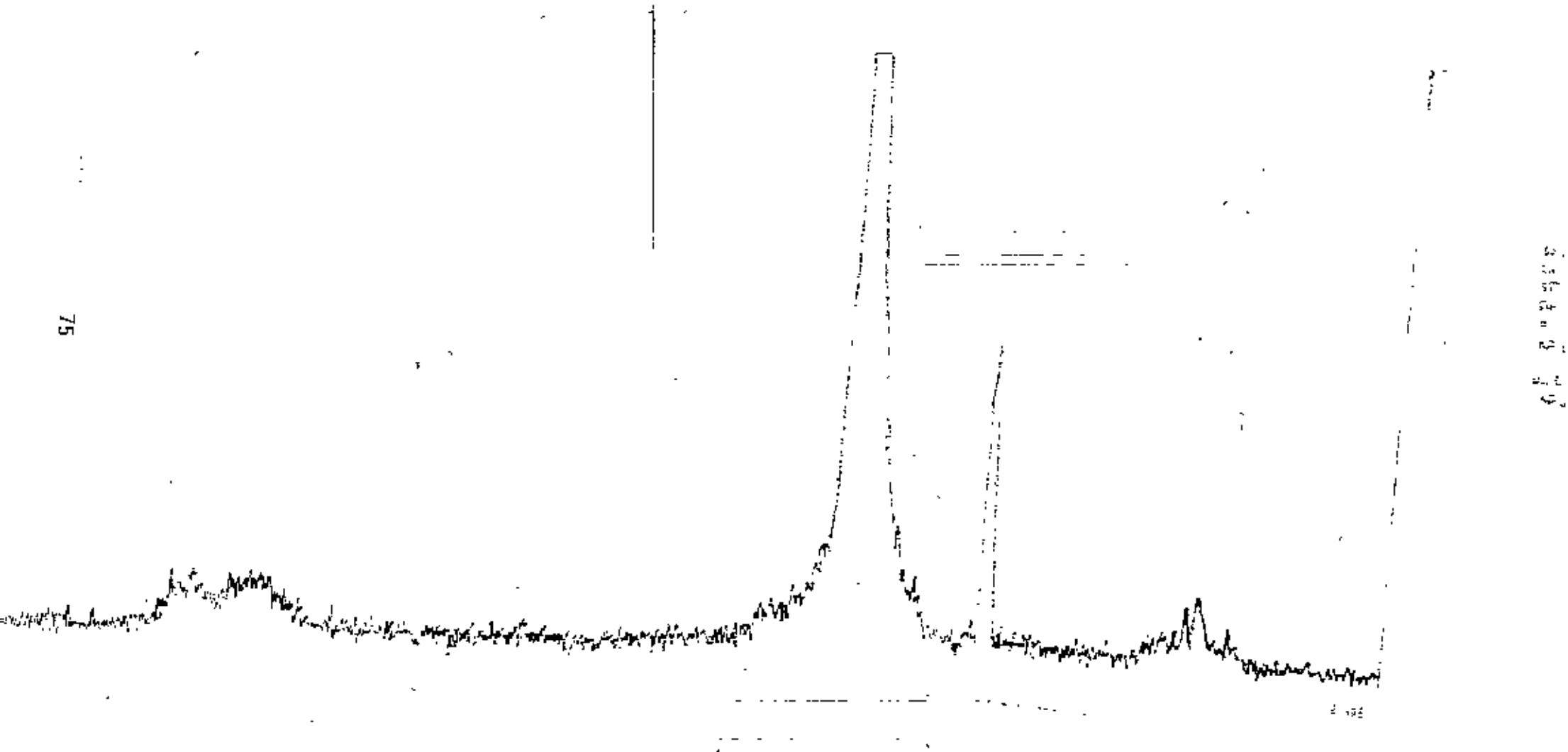
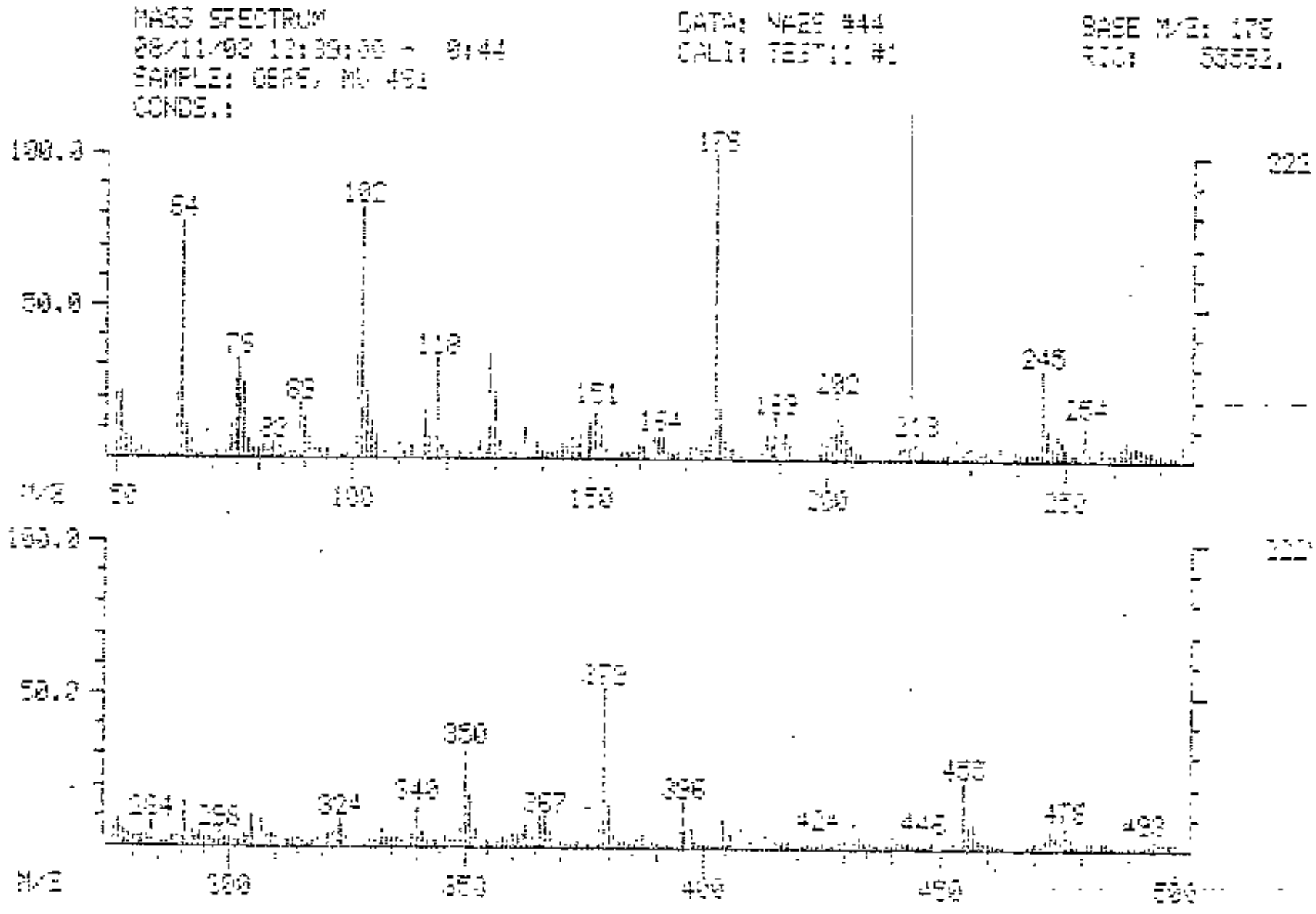
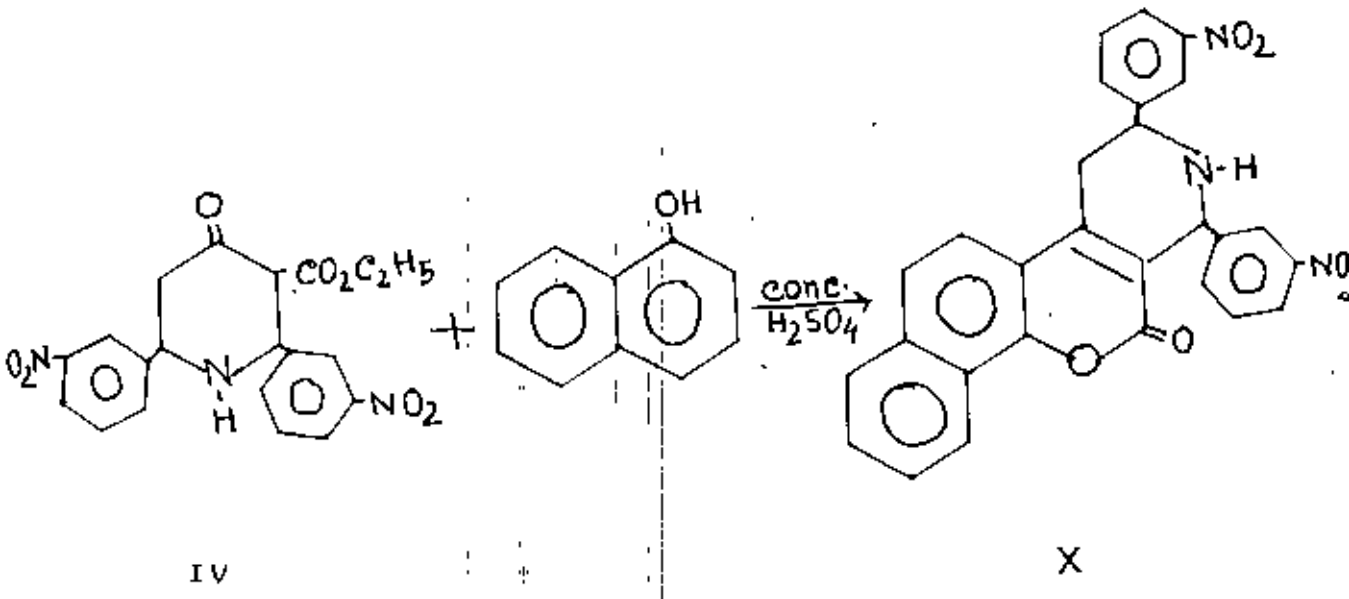


FIGURE 15 : MASS SPECTRUM OF COMPOUND IX



Reaction of 2,6-di(3-nitrophenyl)-3-ethoxy carbonyl piperidine-4-one with-α -naphthol



IV X

Piperidine-4-one-IV-and-α-naphthol were reacted in presence of conc. H_2SO_4 at room temperature to give 1.1 gm (92%) of yellowish crystalline compound 2,4-di(3-nitrophenyl)-1,2, 3,4-tetrahydrobenzo[h] pyrido [3,4-c] coumarin **X**, melting at 170-171°C, R_f 0.8 (Al_2O_3, pet. ether: ethyl acetate = 4:1).

The structure of the tetrahydrobenzopyrido-coumarin **X** was established by spectroscopic data.

The IR spectrum **[Fig. 16]** has the following absorption bands: $\nu^{cm^{-1}}$ 3420 (s.N-H); 1655 (C=O), 1520 and 1340 ($-NO_2$).

The ^{1}HNMR spectrum **[Fig. 17]** of the compound **X** has the following signals at δ(ppm): 8.54-8.27 and 8.12-7.47 (m. 8H $C_6H_4NO_2$), 8.75 (m,6H 1,2 substituted naphthalene); around 1.0 (w.N-H)

The mass spectrum **[Fig. 18]** of the compound **X** has the following important peaks at m/z = 489 (15%, $M-4H)^+$, 367 (2%, $M-4H-C_6H_4NO_2)^+$, 249(3%, $M-C_6H_4NO_2)_2)^+$

FIGURE 16 : IR SPECTRUM OF COMPOUND X

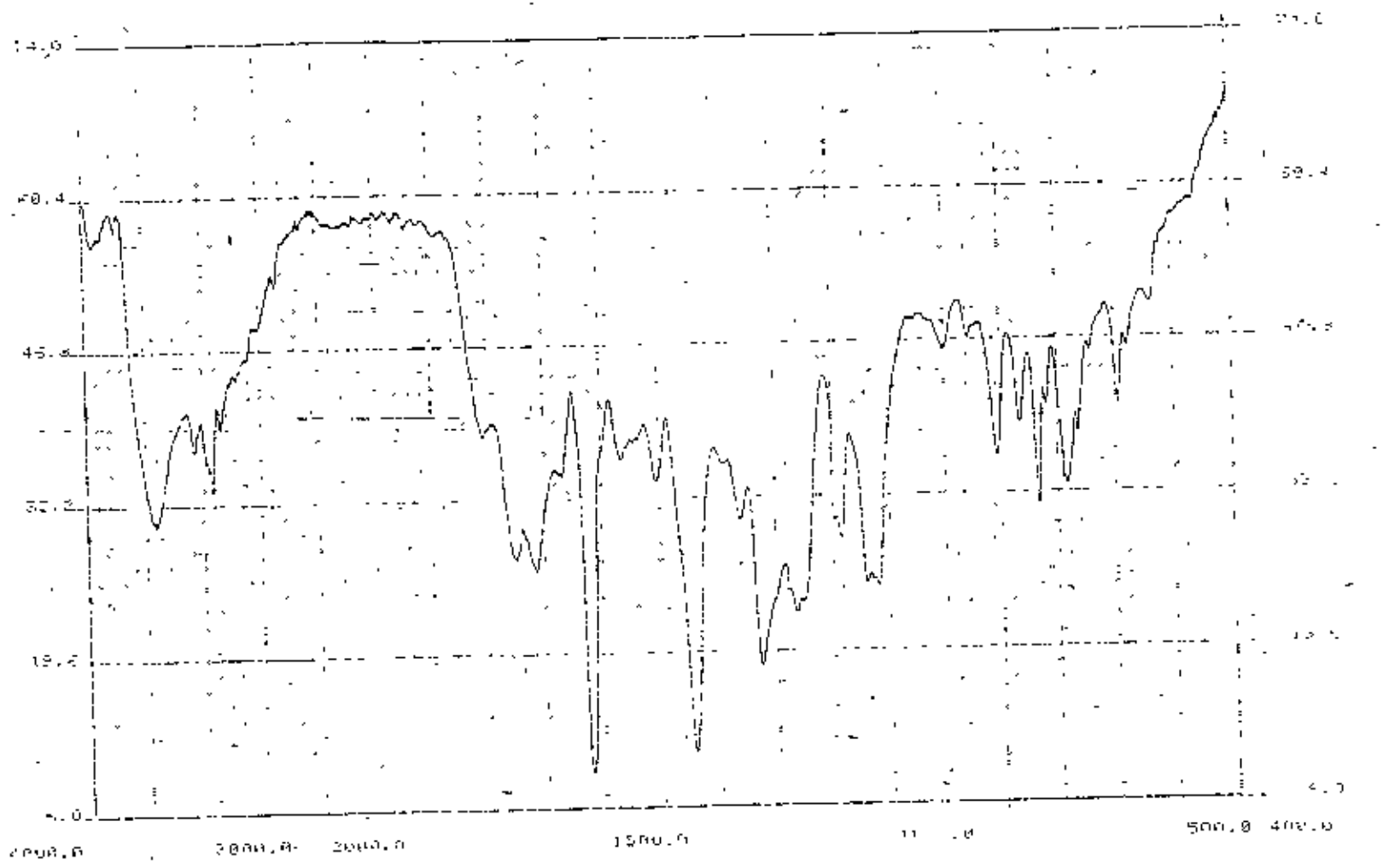


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FIGURE 17 : HNMR SPECTRUM OF COMPOUND X

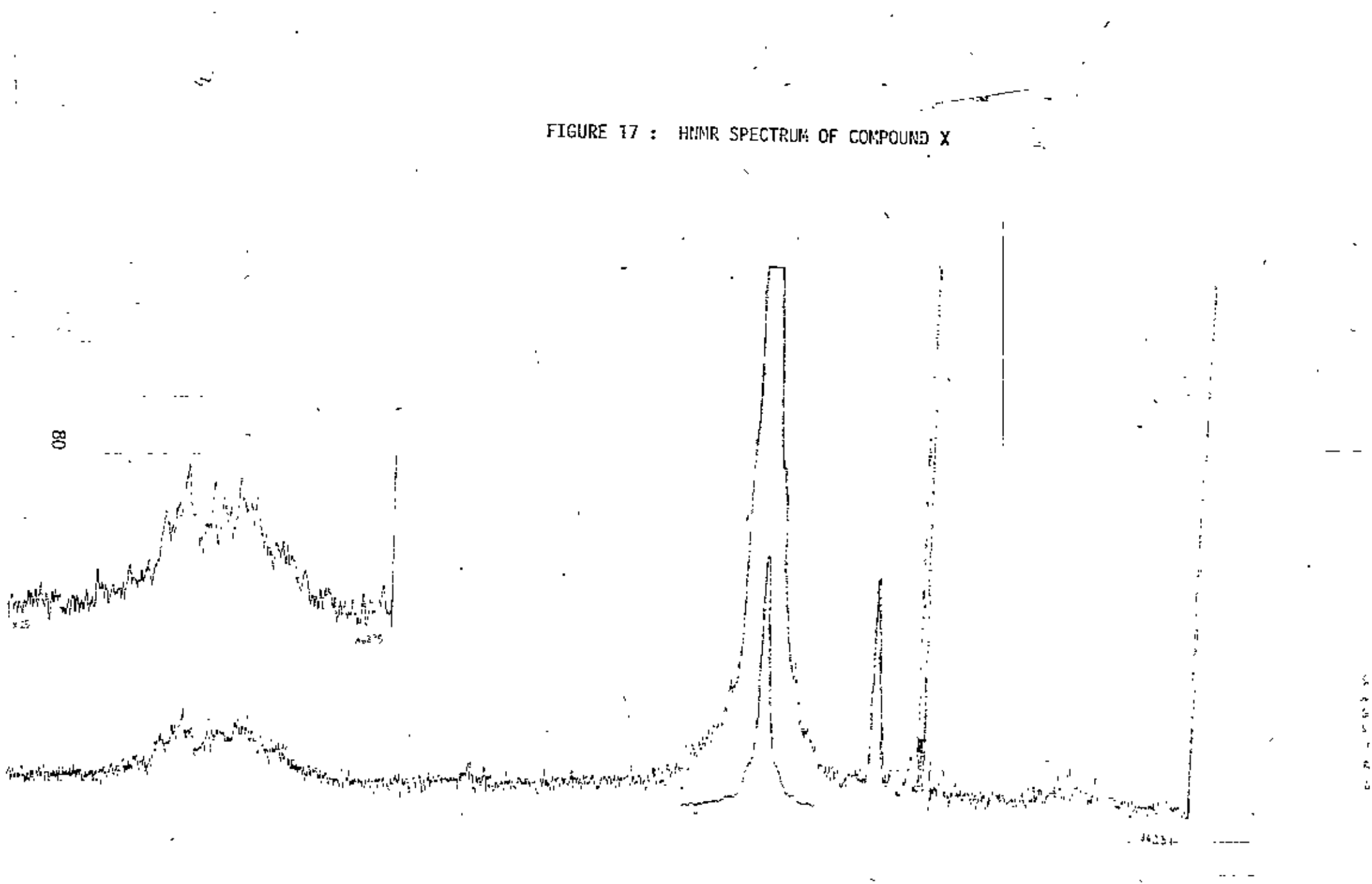
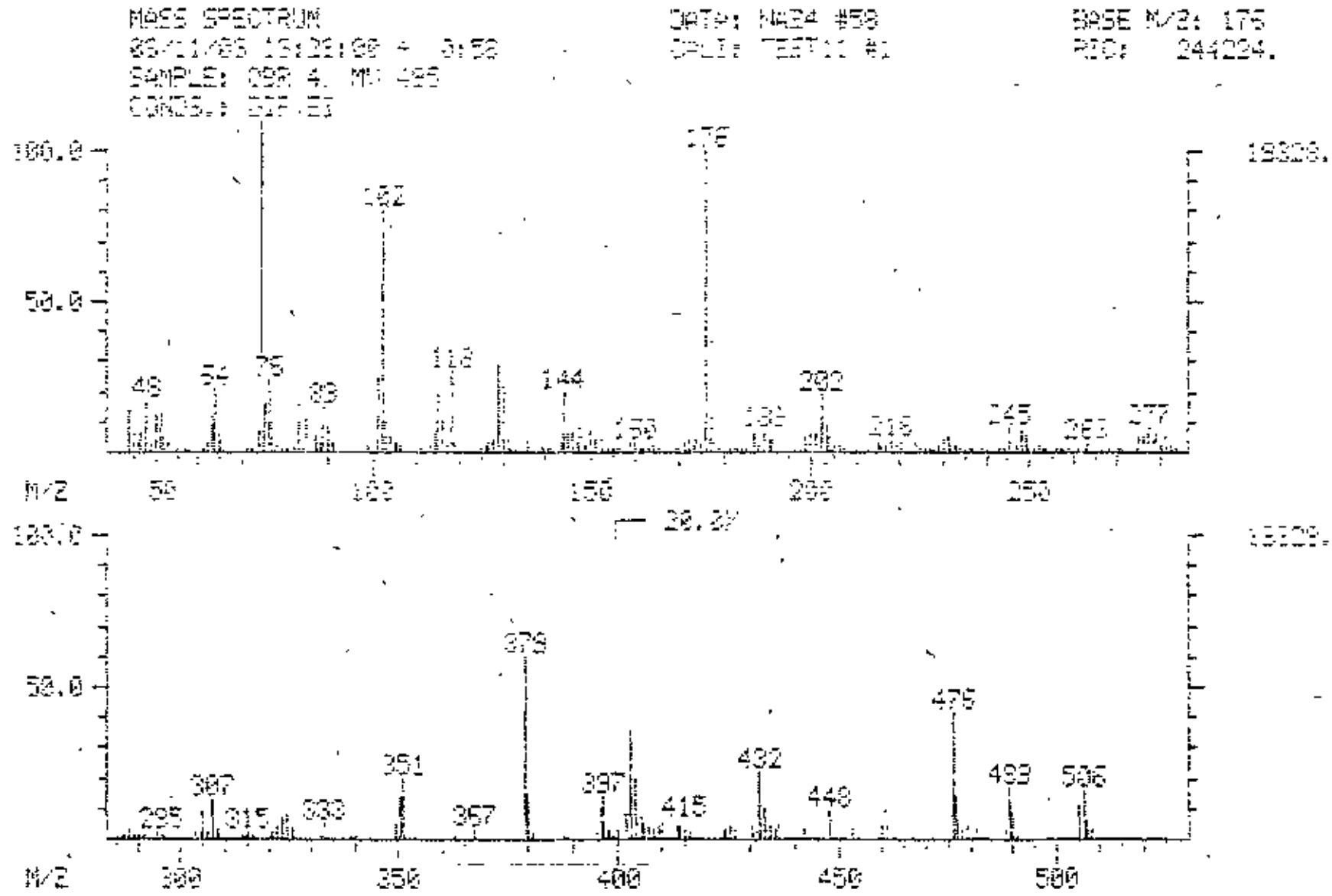
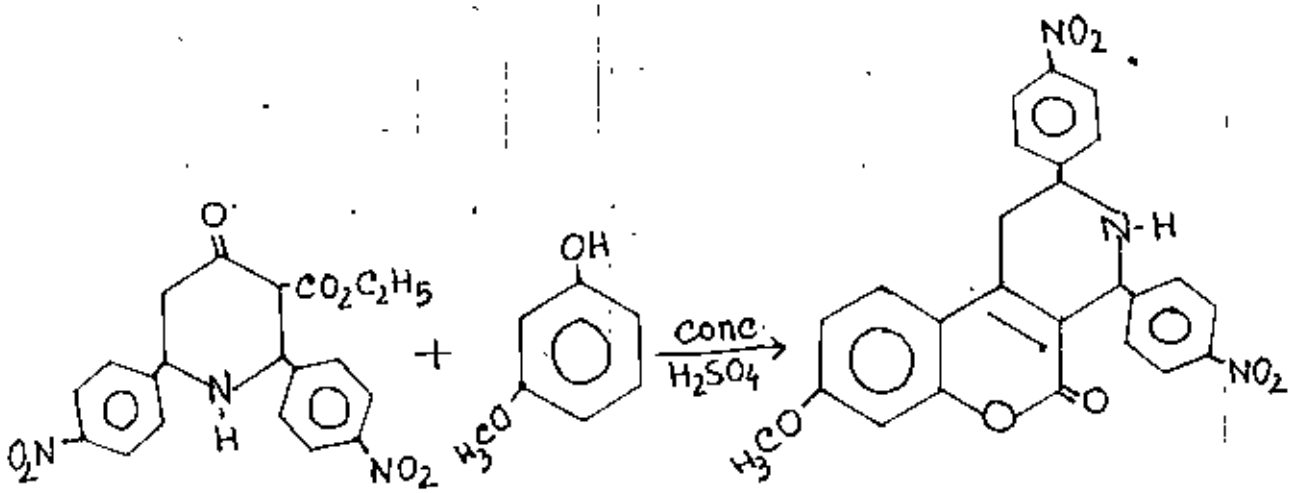


FIGURE 18 : MASS SPECTRUM OF COMPOUND X



Reaction of 2,6-di(4-nitrophenyl)-3-ethoxy carbonyl piperidine-4-one with 3-methoxy phenol



V XI

Piperidine-4-one V and 3-methoxy phenol were reacted in presence of conc. H_2SO_4 giving 0.13 gm (57%) of 8-methoxy - 2,4-di(4-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **X1**, melting at 165-169°C, R_f 0.52. (Al_2O_3, pet ether: ethyl acetate = 4:1).

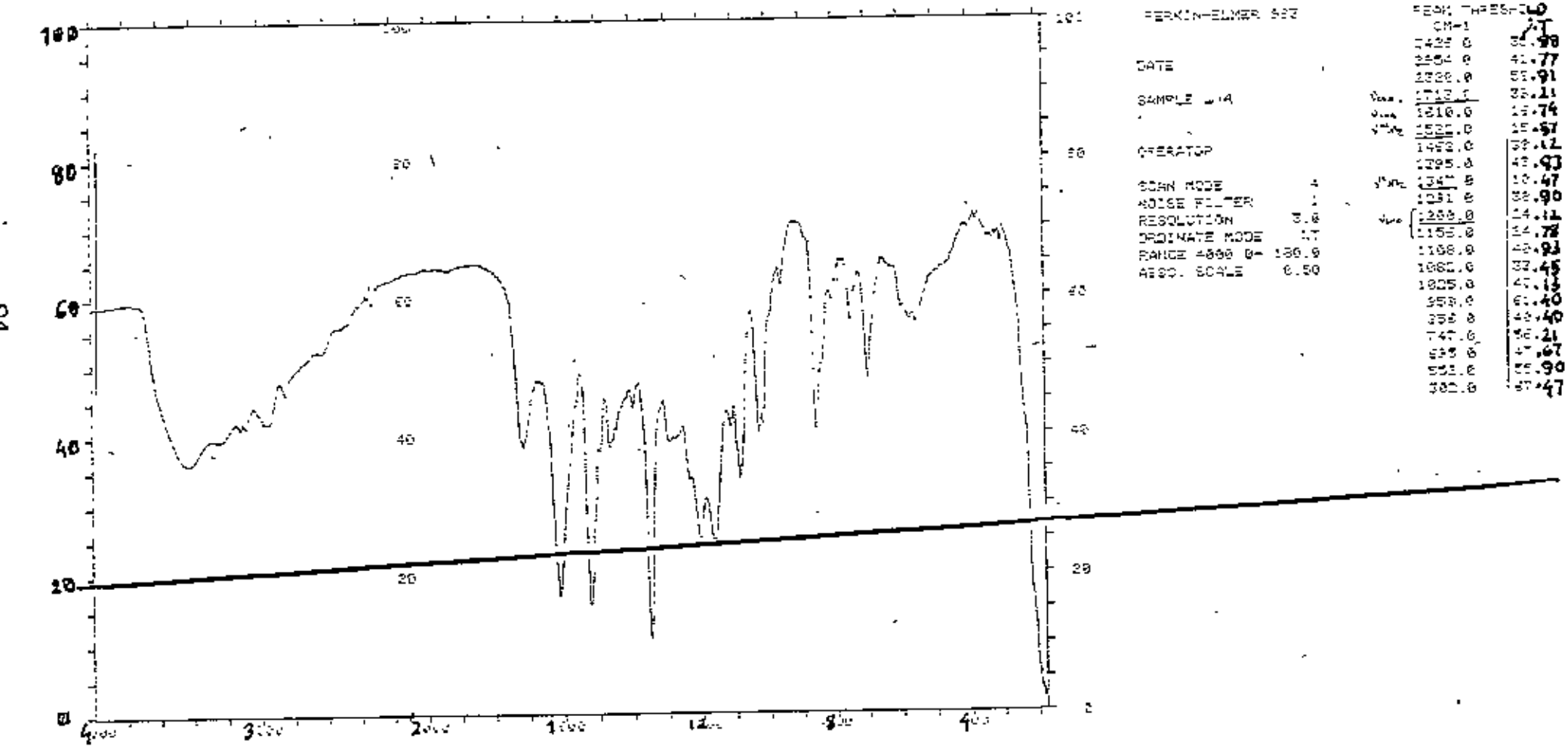
The structure of the tetrahydropyrido coumarin **XI** was established by spectroscopic data.

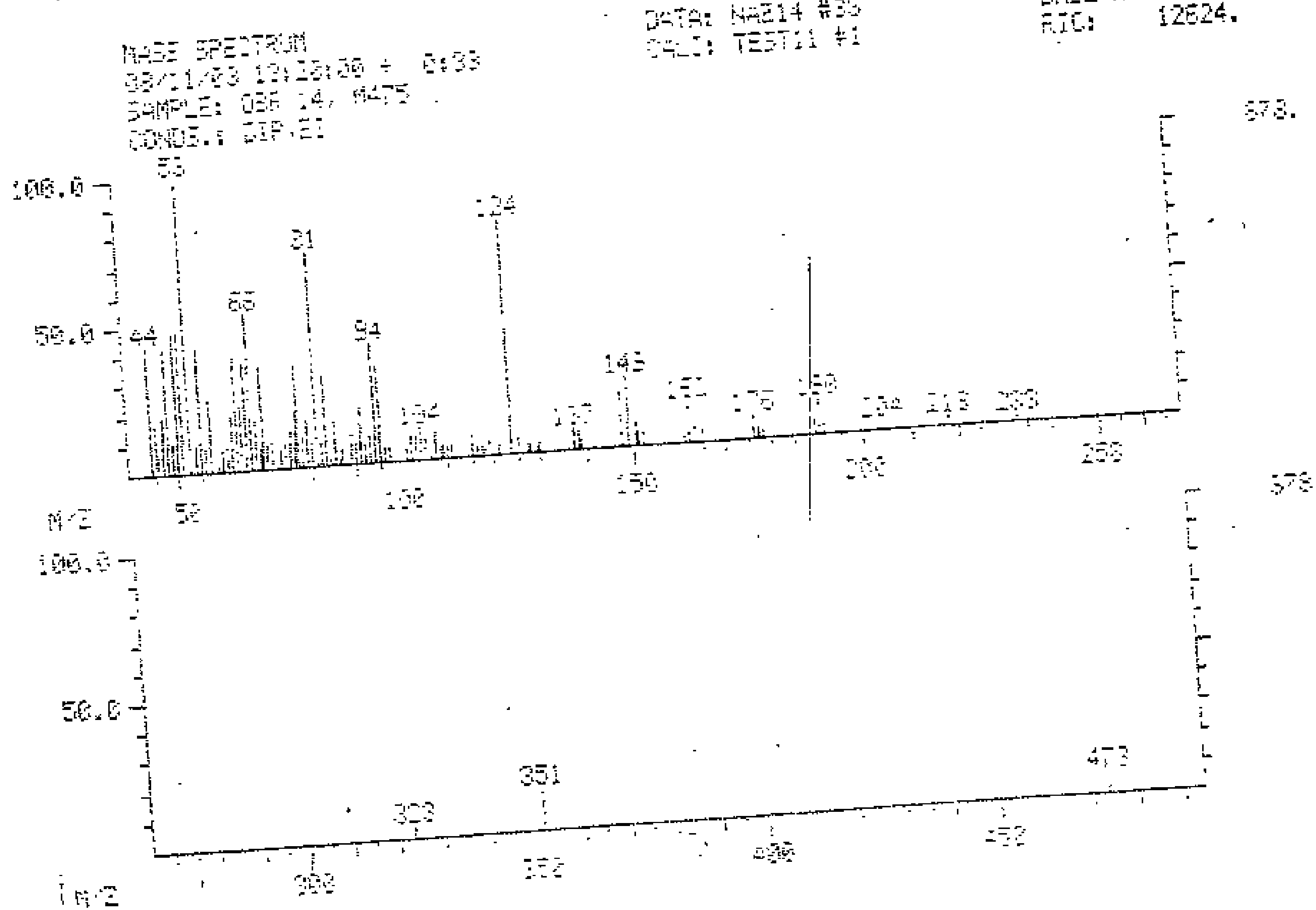
The IR **[Fig. 19]** spectrum has the following absorption bands: ν^{cm-1} 3426 (N-H), 1713 (coumarin C=O), 1522 and 1347 (asymm, and symm, NO_2), 1610 (C=C), 1200 (C-O).

The ^{1}HNMR spectrum **[Fig. 20]** of the compound **XI** was not taken due to insufficient quantity.

The mass spectrum **[Fig. 21]** of the compound **XI** has the following im-portant peaks at m/z = 473 (26%, $M)^+$, 469(100%, $M-4H)^+$, 351 (50%, $M-C_6H_4NO_2)^+$, 323 (17%, $M-ArCH=NH_2)^+$.

FIGURE 19 : IR SPECTRUM OF COMPOUND XI




MASS SPECTRUM
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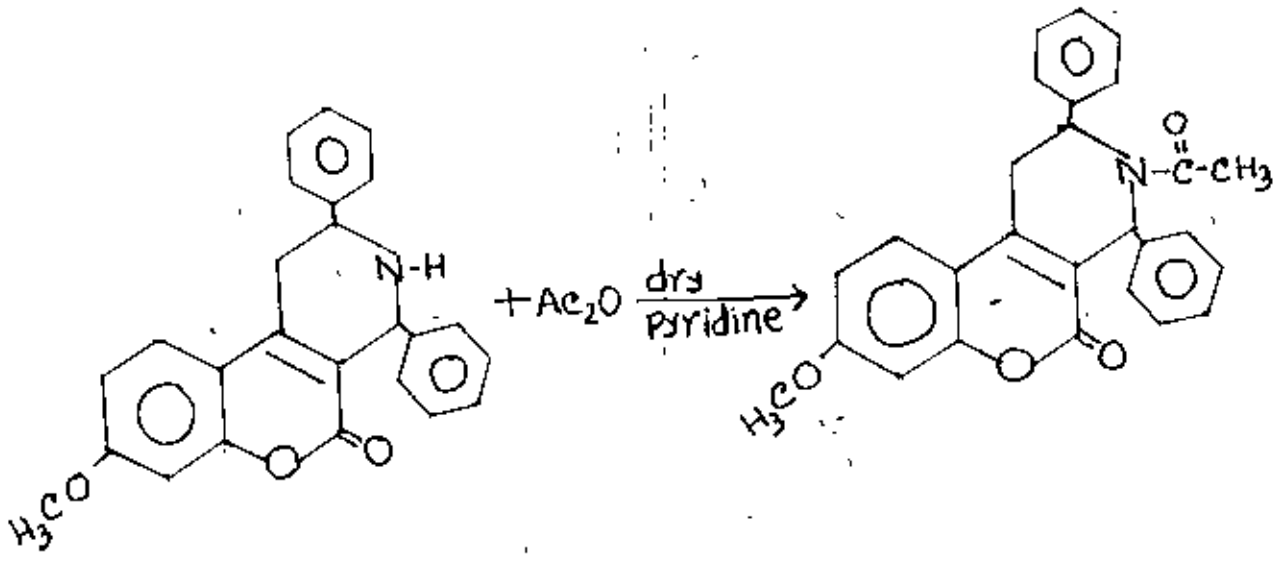
CALI: TEST11 #1
BASE M/Z
RIC: 12624.
SAMPLE: OSS 14, M475
CONDS.: DIP,EI
100.0
50.0
M/Z
53
81
124
66
94
44
145
50
100
150
200
250
578.
351
329
473
300
350
450

Reaction of 8-methoxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin with acetic anhydride.



VI XII

Diphenyl coumarin **VI** and acetic anhydride were reacted in dry pyridine giving 0.45 gm (90%) of 3-acetyl-8-methoxy- 2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **XII**, melting at 198-200°C. R_f 0.5 (Al_2O_3, pet. ether: ethyl acetate = 4:1).

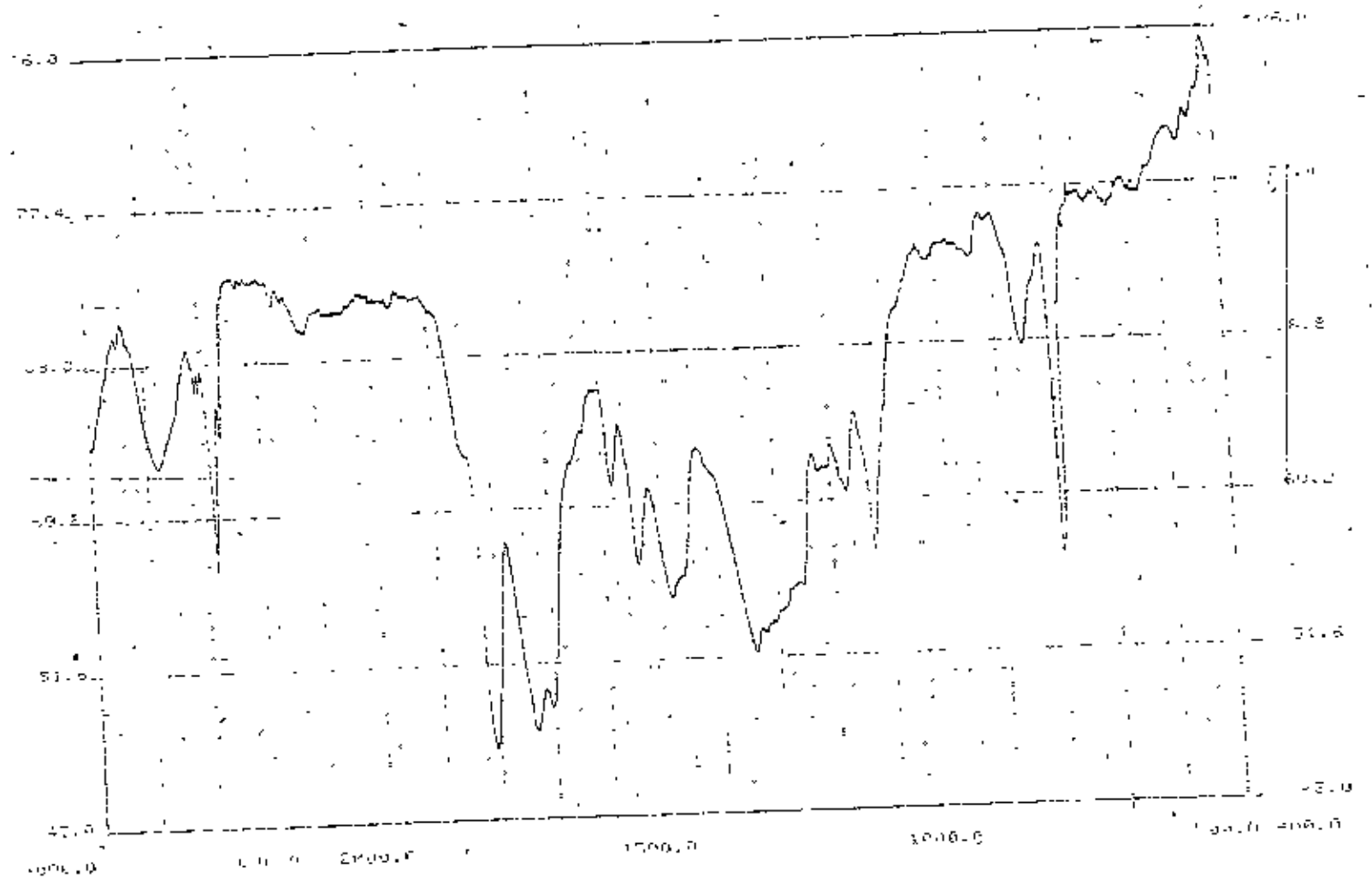
The structure of the compound **XII** was established by spectroscopic data.

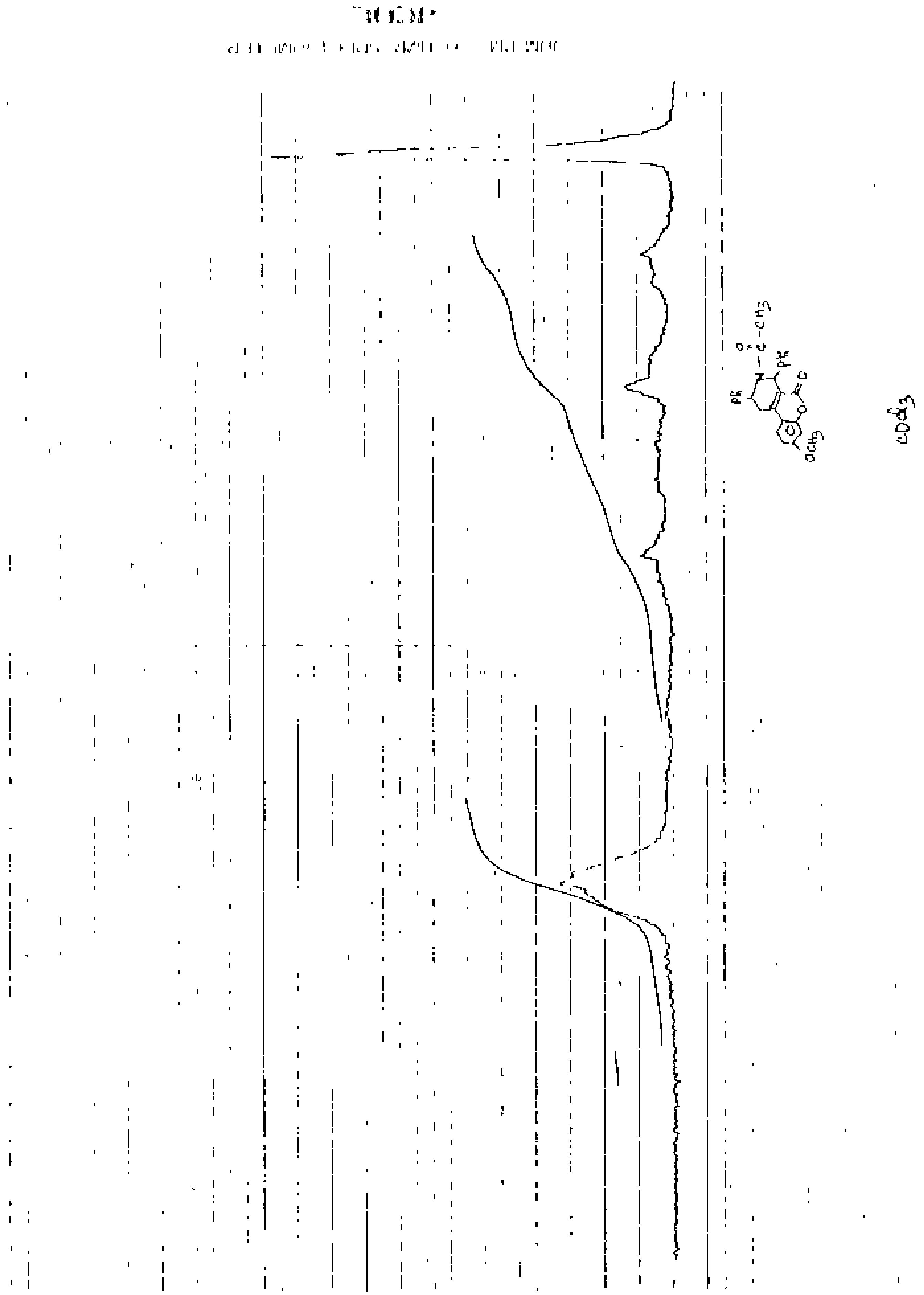
IR spectrum **[Fig. 22]** of compound **XII** has the following absorption bands: $\nu^{cm^{-1}}$ 2990 (Ar-H stretching), 1710 (lactonic C=O), 1632 (C=O), 1210 (C-O).

^{1}HNMR spectrum **[Fig. 23]** of compound **XII** has the following signals at δ(ppm): 3.70 (3H, OCH_3), 2.3 (3H, $CO-CH_3$), 6.9-7.62 (13H, aromatic).

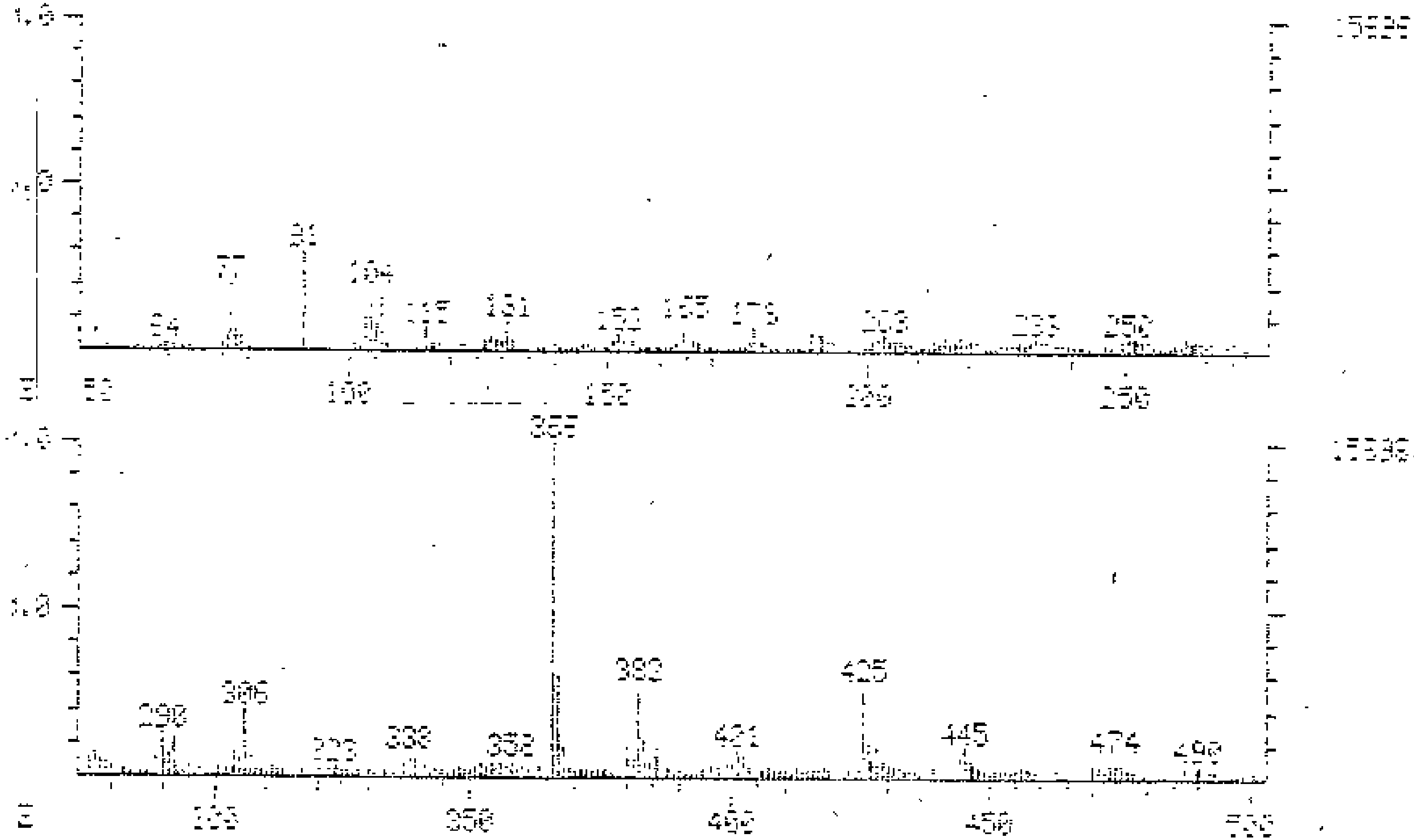
The mass spectrum **[Fig. 24]** of compound **XII** has the following peaks at m/z=425 (19% M)$^+$, 382 (30%, M-$CO-CH_3$)$^+$,384 (5% M-OCH_3)$^+$, 339 (M-CH_3-CO-NH_2)$^+$.

FIGURE 21 : IR SPECTRUM OF COMPOUND XII

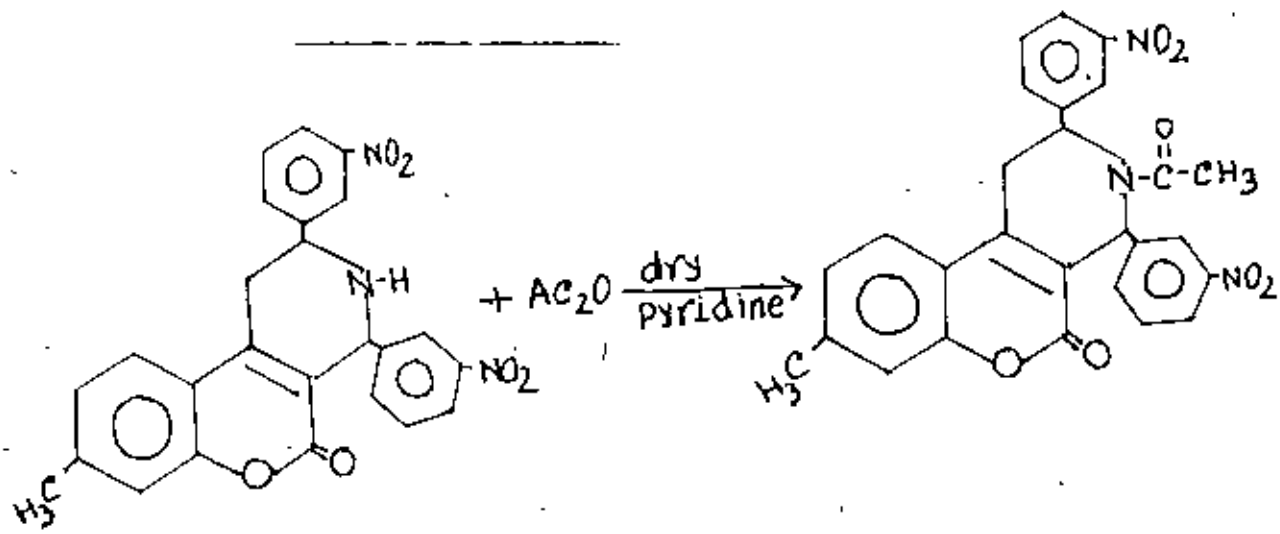




MASS SPECTRUM



Reaction of 8 - methyl -2,4-di (3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin with acetic anhydride



VIII XIII

Di(3-nitrophenyl) coumarin **VIII** and acetic anhydride were reacted in dry pyridine to give 3-acetyl 8-methyl-2,4-di-(3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **XIII**, melting at 194-196°C, R_f 0.51 (Al_2O_3, pet. ether: ethyl acetate = 4:1).

The structure of the compound **XIII** was established by spectroscopic data.

The IR spectrum **[Fig. 25]** of compound **XIII** has following absorption bands: ν^{cm-1} 1760 (lactonic C=O), 1520 and 1340 (NO_2 symm and asym), 1600 ($CO-CH_3$):

^{1}HNMR spectrum **[Fig. 26]** of compound **XIII** has the following signals δ(ppm): 7.45-8.4 (11 H), 2.45 (8-CH_3), 2.23 (N-CO-CH_3).

Mass spectrum **[Fig. 27]** of compound **XIII** has the following important peaks at m/z = 499 (5%, M)$^+$, 498(27%, M-H)$^+$, 456(100%, M-CO-CH_3)$^+$, 377(20%, M-$C_6H_4NO_2$)$^+$. **(Scheme - 4).**

Figure -24 : IR spectrum of compound XIII

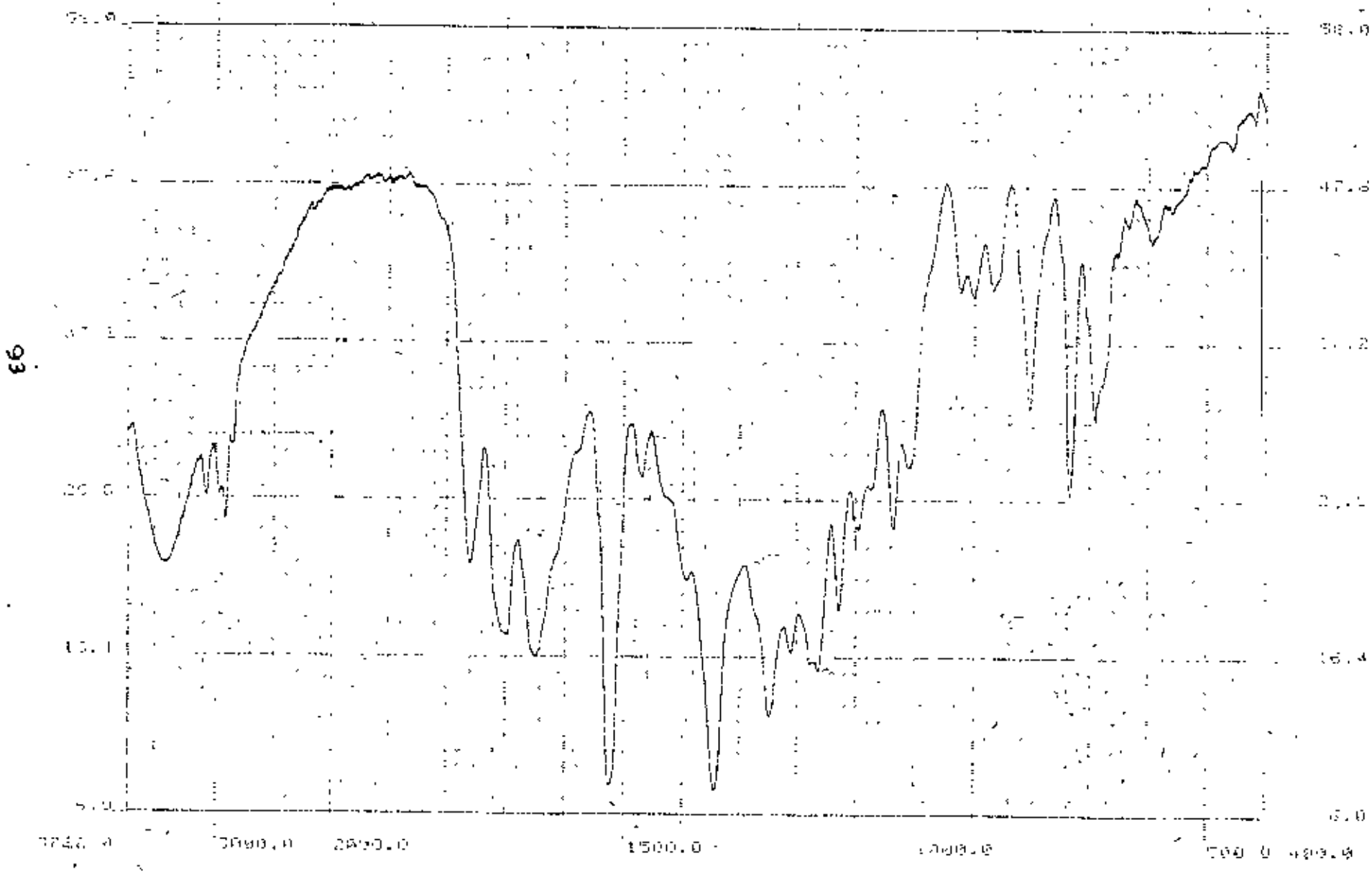
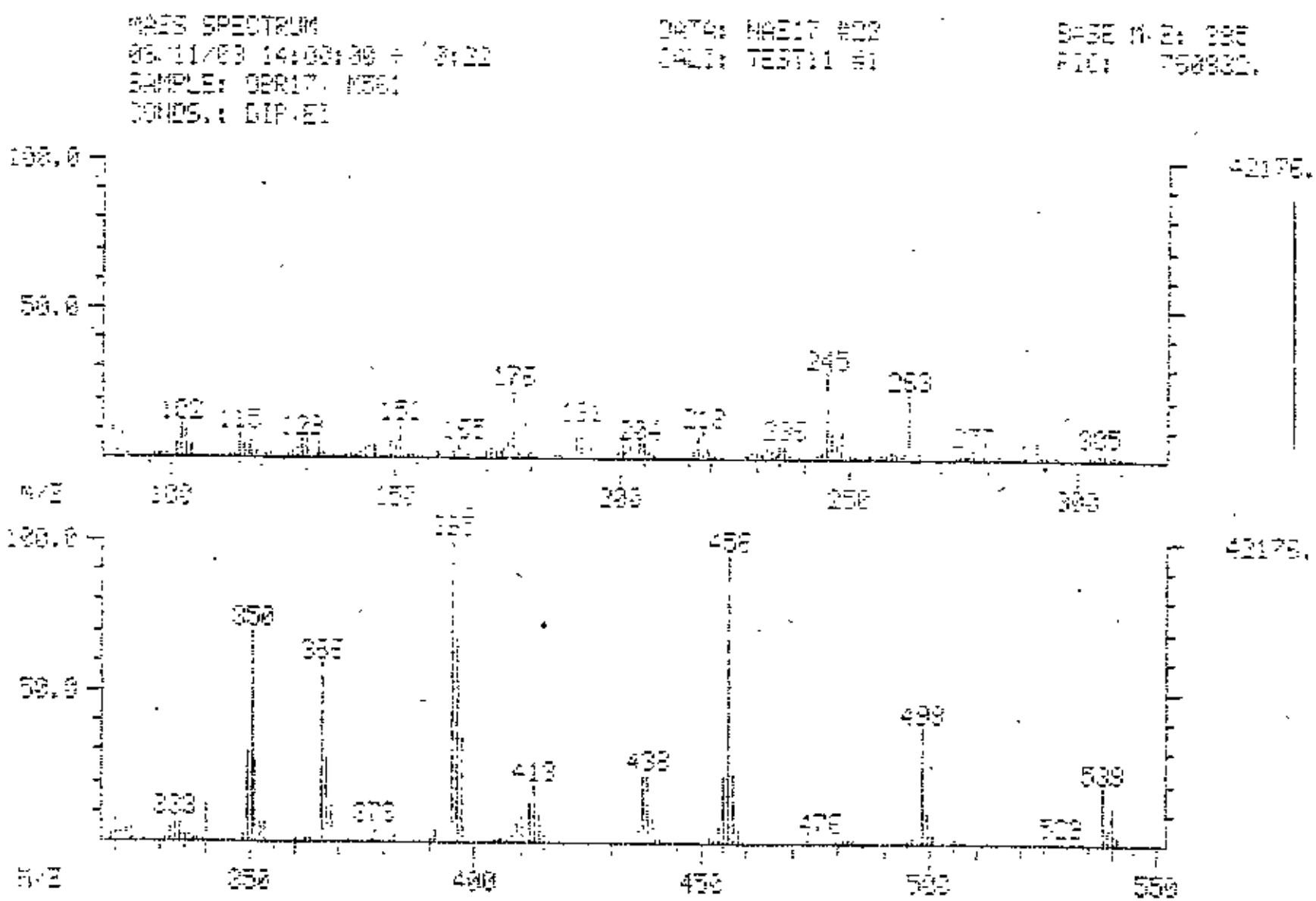
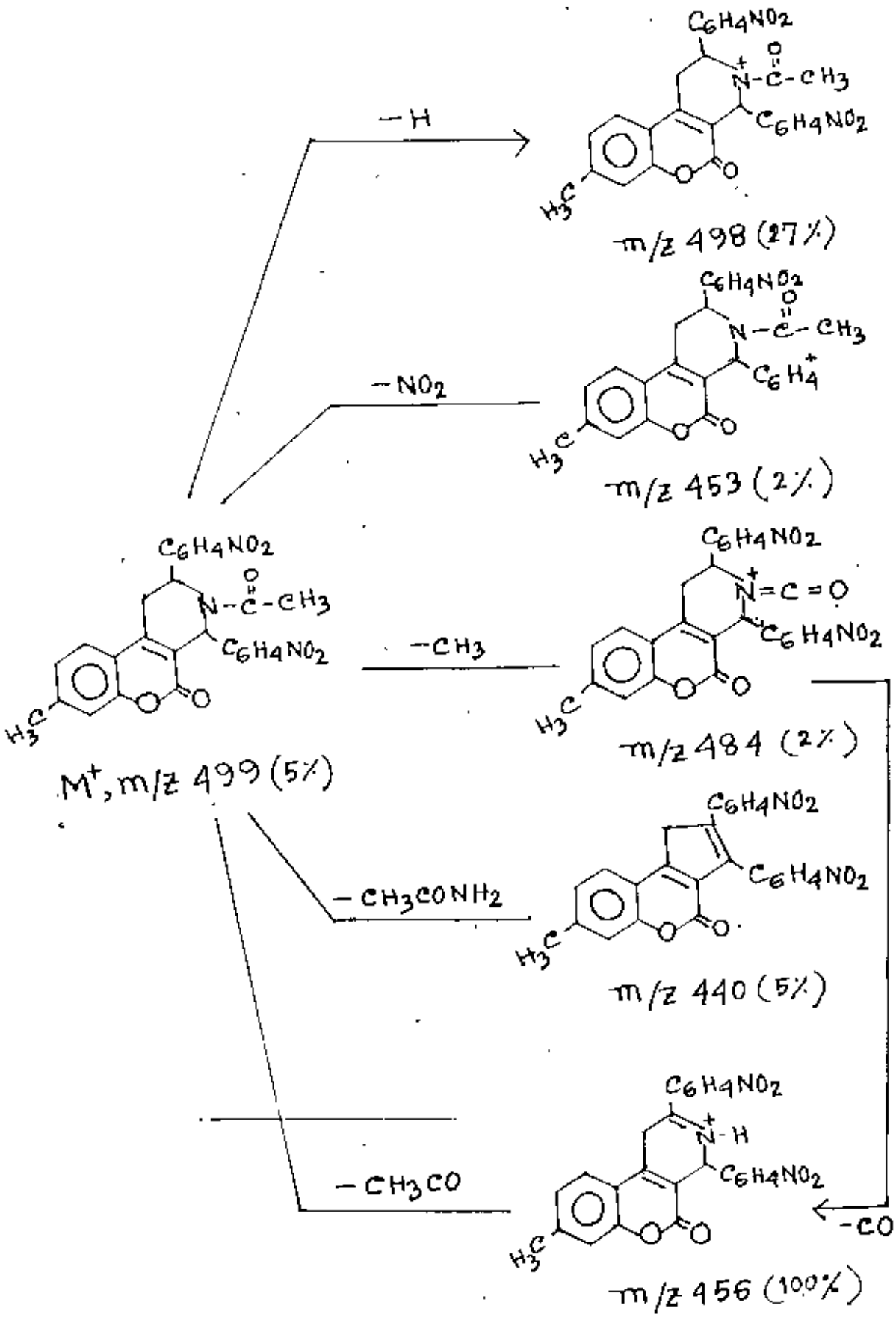


FIGURE 26 : MASS SPECTRUM OF COMPOUND XIII



SCHEME 4 : FRAGMENTATION PATTERN OF COMPOUND XIII



10.2. DISCUSSION

With an aim to study the fungicidal activity and use of coumarin compounds as tracers, some new substituted 1,2,3,4-tetrahydropyrido [3,4-c] coumarins and 1,2,3,4-tetrahydrobenzo [h] pyrido [3,4-c] coumarin (VI-XI) were synthesised by us. The starting material for our research work 2,6-diaryl-3-ethoxy carbonyl piperidine 4-one (II,IV,V) were also synthesised by us.

Pechmann condensation reaction of these β-ketoesters with 3-methoxy phenol, m-cresol, α-naphthol and resorcinol gave tetrahydro-pyridocoumarins (VI-IX,XI) and tetrahydrobenzopyridocoumarin **X** in good yield.

The structure of these tetrahydropyridocoumarins and tetrahydro-benzopyridocoumarins were established by comparing the spectroscopic data of the above compounds with almost similar coumarin derivatives.

The IR spectrum of the compounds show intensive absorption bands of lactonic carbonyl group, that of C=C and also absorption band of N-H of the piperidine fragment **(Table-1)**.

Table 1: Characteristics of Synthesised Compounds

Compound	Melting point	IR-Spectrum, $\nu^{cm^{-1}}max$	Brutto Formula	Mol Mass	Yield (%)
VI	190-192°C	3436cm^{-1}(-N-H), 1721 lactonic C-O), 1202 (C-O-Ar)	$C_{25}H_{21}O_3N$	383	73
VII	194-196°C	3415 (N-H),1528,1351 (NO_2), 1713 (lactonic C=O), 1611 (C=C) 1174 (C-O-Ar).	$C_{25}H_{19}O_7N_3$	473	43
VIII	160-162°C	3420(N-H),1520,1345/(-NO_2) 1760 (lactonic C=O), 1640 (C=C) 1160 (Ar-O-C), 740, 810 (Ar-H).	$C_{25}H_{19}O_6N_3$	457	61
IX	170-172°C	3550-3440 (N-H,O-H overlapped 1536,1352 (-NO_2), 1665 (C=O), 1162 (C-O-Ar)	$C_{24}H_{17}O_7N_3$	459	51
X	170-171°C	3420(N-H) 1655 (C=O) 1520, 1340 (-NO_2).	$C_{28}H_{19}O_6N_3$	493	92
XI	165-169°C	3426(N-H), 1713 (C=O), 1522, 1347 -NO_2), 1200 (C-O).	$C_{25}H_{19}O_7N_3$	473	57
XII	198-200°C	2990 (Ar-H) 1710 (lactonic C=O), 1632 (C=O), 1210(C-O).	$C_{27}H_{23}O_4N$	425	90
XIII	194-196°C	1760 (lactonic C=O), 1520, 1340 (-NO_2), 1600 (CO-CH_3).	$C_{27}H_{21}O_7N_3$	499	95

The ^{1}HNMR spectra of the synthesised compounds were carried out for the purpose of elementary identification of the compounds. Samples sent for NMR spectra seemed to contain traces of impurities and solvents. That is why in most cases the NMR spectral data were insufficient. The expected signals of H_1, H_2, and H_4 protons were expected to be seem in the range of δ 2.5-5. But unfortunately in the spectra of the synthesised compounds these signals could not be traced out. In our opinion this could be due to the presence of solvents and impurities and that was the reason why NMR data was not sufficient to establish the structure of the synthesised compounds. Detailed NMR analysis of the compounds are expected to be carried out in future. But as far as the present work is concerned ^{1}HNMR spectroscopic data are almost in agreement with the structure of the synthesised compounds **(Table-2)**.

Table 2: ^{1}HNMR Spectra Data of Synthesised Compounds

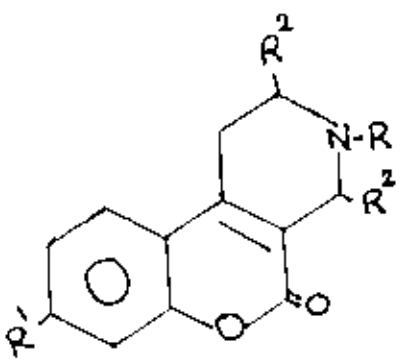
Compound	Chemical Shift, δ, PPM					
	H-1	H-2	H-4	CH_3, CH_2OCH_3	N-H	Aromatic Proton
VI				3.80	1.0	7.94-7.42; 11-H.
VII	-	-	-	3.79	1.1	8.64-8.27; 11-H.
VIII	-	-	-	2.49	1.2	8.57-8.24, 11-H.
IX	-	-	-	-	1.1	8.60-8.22, 11-H. 8.16-7.57
X	-	-	-	-	1.0	8.54-8.27, 8-H 8.12-7.47; 8.75 (m.6H-Naphthalene)
XI	-	-	-	-	-	- -
XII	-	-	-	3.70(OCH_3) 2.3(CH_3-CO)	-	6.9-7.62' 13-H
XIII	-	-	-	2.45(8-CH_3) 2.23(N-$COCH_3$)	-	7.45-8.4; 11-H.

Although data from ^{1}HNMR spectra were not enough to establish the structure of the synthesised compounds, but the mass spectra gave a lot of informations to do the same.

The mass spectrum of tetrahydropyrido coumarins (VI-IX,XI) and tetrahydro benzopyrido coumarin X were studied and compared with earlier works done in this field. The fragmentation patterns are almost similar. Basing on this comparison it was concluded that the spectral data are in agreement with the structures of the synthesised compounds. Molecular ion peaks were found to be intensive and absent as well. Their dissociative ionisation showed that the presence of peaks $(M-H)^+$, $(M-2H)^+$, $(M-4H)^+$ are due to dehydrogenation of piperidone ring[81,82]. During fragmentation of the studied compounds, the retrodienic cleavage and rearrangement phenomenon were observed. Appearance of the characteristic $(M-Ar)^+$ fragment

is due to the presence of aryl radical in alpha position to the piperidine ring. Formation of ions $(M-R)^+$ and $(M-R^1)^+$ are due to the presence of substituents linked with nitrogen atom and aryl rings. Loss of carbon monoxide in the fragmentation pattern of the synthesised compounds is an important process in such coumarin structures, but a further loss of carbon monoxide is unimportant. Instead a loss of methyl group as in compound **VI** and **VII, XI** is very much favoured, probably as a result of the relative stability of the conjugated quinonoid oxonium ion (scheme 3), loss of mythoxyl group from the parent ion $(M-OCH_3)$ is not of much importance. Increased substitution results in a considerably more complex fragmentation pattern.

It is interesting to observe that in the acyl derivatives of the synthesised coumarin compounds the loss of RNH_2 fragment from M^+ results into a rearranged fragment. Loss of CO and CO_2 from M^+ ion is also a characteristics phenomenon of acetyl derivatives of coumarin compounds.



$R^1 = CH_3O-$ (VI., VII, XI – XII), OH – (IX),
CH_3- (VIII, XIII)

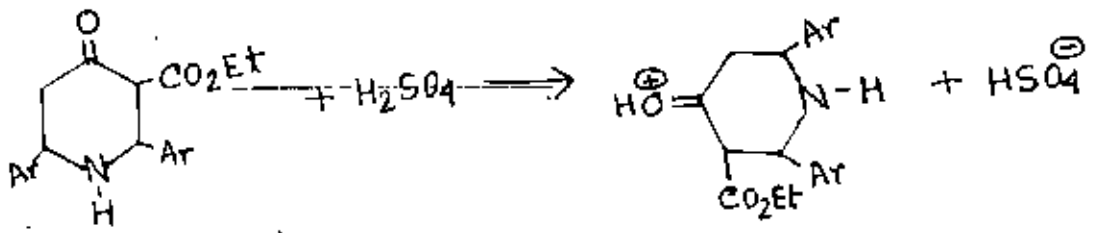
$R = H$ (VI – XI), AcO (XII – XIII)

$R^2 = C_6H_4NO_2$ (VII – XI, XIII)
C_6H_5 (VI, XII).

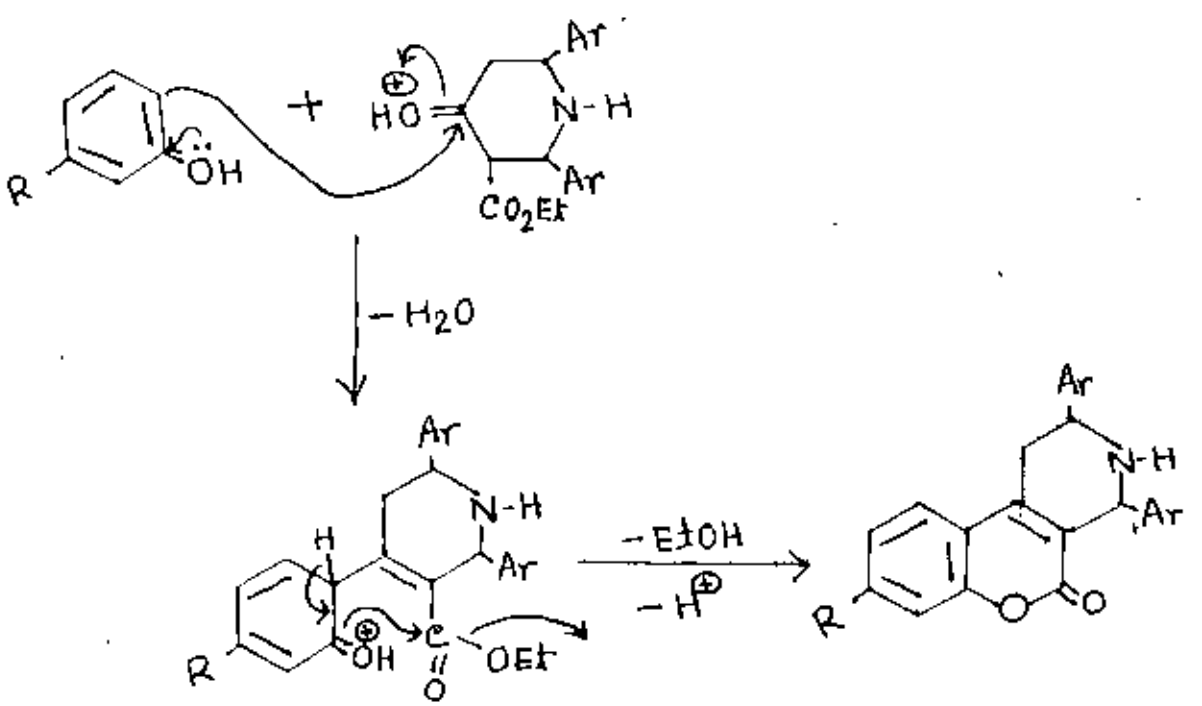
CHAPTER FOUR

The suggested mechanism of the condensation reaction of β - ketoester (piperidone **II**, **IV**, and **V** with m-methoxy phenol, m-cresol and others is as follows:

Step-1



Step-2



Hence R = OCH_3 , CH_3 , OH etc.

S U M M A R Y

During this research an up-to-date literature survey was carried out on coumarins and their derivatives.

In order to carry out the thesis work, three diaryl ethoxy carbonyl-4-piperidones (II,IV,V) were prepared by reacting ethyl acetoacetate with benzaldehyde and nitrobenzaldehyde and ammonia.
Later, Pechmann condensation reaction of the above mentioned piperidones (II,IV,V) were carried out with-3-methoxy phenol giving three new compounds 8-methoxy-2,4-diphenyl-1,2,3,4 - tetrahydropyrido [3,4-c] coumarin **VI**, 8-methoxy-2,4 - di (3-nitro phenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **VII** and 8-methoxy-2,4-di (4-nitrophenyl), 1,2,3,4-tetrahydropyrido coumarin **XI** in good yield.

Condensation of piperidone **IV** with m-cresol, α-naphthol and resorcinol gave in good quantity 8-methyl-2,4-di(3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **VIII**, 2,4-di (3-nitrophenyl)-1,2,3,4-tetrahydrobenzo [h] pyrido [3,4-c] coumarin **X** and 8-hydroxy-2,4-di (3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **IX**.

In the last part of the thesis work, acetylation of some of the pyridocoumarins was carried out.Reaction of tetrahydropyridocoumarins **VI** and **VIII** with acetic anhydride in pre-sence of dry pyridine gave 3-acetyl-8-methoxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **XII** and 3-acetyl-8-methyl 2,4-di (3-nitrophenyl)-1,2,3,4-tetrahydropyrido [3,4-c] coumarin **XIII** respectively in more than 90% yield.

Thus in this modest thesis work eight new compounds were synthesised by us, which we hope to send in future to study their biological and fungicidal activity.

R E F E R E N C E S

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