CHAPTER—III

PART – I

SYNTHESIS OF SOME SCHIFF BASES OF COUMARIN DERIVATIVES

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INTRODUCTION

Imines, azomethines, anils or Schiff bases can be designated structurally as RR'C = NR". The nomenclature for compounds of this type is variable. When R is alkyl or aryl and R' is a H, the compound is referred to aldimines. When both R and R' are alkyl or aryl, the compound is referred as Ketimines. For convenience, it is felt that the term Schiff base should be limited to designating only those imines where R is an aryl group, R' is a H and R" either an alkyl or aryl groups. Anils should be limited to designating imines where R and R' are aliphatic, aromatic or H and R" is phenyl or a substituted phenyl group. In naming specific imines, the nomenclature following by Chemical Abstracts is used e.g.

$C_6H_5CH = NC_6H_5$ is named N-benzylideneaniline and

$CH_3CH_2CH(CH_3) - CH_2-C(CH_3) = NC_2H_5$ is named

N-2(4-methylheptylidene) ethylamine. In case R" is a H atom, the compound is given an imine name. e.g. $CH_3CH = NH$ is named ethylidenimine.

PHYSICAL PROPERTIES

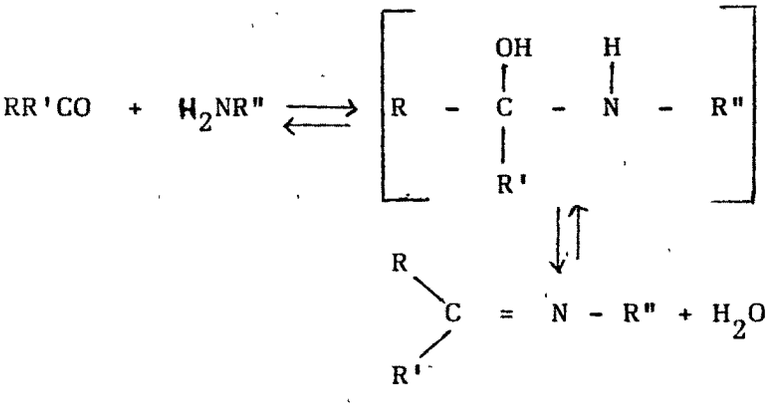
Certain imines are known to be liquid crystals.[1-2] Some imines have also been noted to exhibit phototropy and thermotropy.

UV and visible spectra of imines depend on substituents. In IR of imines (of the type $R_2C = NH$), all dialkyl ketimines absorbed in the region from 6.08 to 6.10 μ for C=N bond, while the more conjugated diaryl ketimines absorbed at higher wavelength about 6.29 μ . The deactivating groups such as halogen lower the wavelength of absorption. The NH bond absorbed in the region 3.09 to 3.12 μ . The C=N stretching frequency of various N-benzylidenaniline was absorbed at 1631 - 1613 cm^{-1}.

PREPARATION OF IMINES

(1) Reaction of aldehydes and ketones with amines

The most common method for preparing imines is the reaction of aldehydes and ketones with amines. This reaction was first discovered by Schiff[3] and imines are oftend referred to as Schiff bases.



The reaction is acid -catalysed and is generally carried out by refluxing the carbonyl compound and amine with an azeotroping agent if necessary and separating the water as formed.

Hammett[4] proposes that acids protonate the carbonyl group to give a carbonium ion which adds to the amine in a very fast reaction. The rate-determining step then is the deprotonation of this intermediate to give a carbinolamine (I), an unstable intermediate, which rapidly eliminates water to give the semicarbazone. Jencks[5] has cogently shown that the carbonyl and amine react rapidly to give the carbinolamine (I). This then is dehydrated to the semicarbazone in the rate determining step which is acid catalysed. Para substitution of the benzaldehyde with electron donating groups decreases the reaction rate, while the reverse is true for similarly para substituted aniline. The work agrees with both the Hammett and Jencks mechanism.

Primary aldehydes give polymeric materials with amines. Ammonia reacts uniquely with aldehydes and ketones, e.g. secondary aldehydes as isobutyraldehyde and ammonia give N,N'-diisobutylidene-1,1-isobutyldiamine.[6]

$$(CH_3)_2CHCHO + NH_3 \longrightarrow [(CH_3)_2CHCH = N]_2 \; CHCH(CH_3)_2$$

$$\downarrow$$

$$(CH_3)_2CHCH = N\,CH_2CH(CH_3)_2 + NH_3$$

Similarly, tertiary aldehyde as neopentaldehyde and ammonia gives N-neopentylidiene neopentylamine and t-butylcyanide.

$$(CH_3)_3\ C\ CHO + NH_3 \longrightarrow [(CH_3)_3\ C\ CH = N]_2\ CH\ C\ (CH_3)_2$$

$$\downarrow$$

$$(CH_3)_3\ C\ CH = N\ CH_2C\ (CH_3)_3 + (CH_3)_3\ C\ CN$$

(2) Reaction of Nitriles with Organometallic Compounds

Moureau and Mignonac[7] were the first to add an aryl or alkyl Grignard to an aryl cyanide to obtain after careful hydroysis at -15°C treatment with hydrochloric acid and finally with ammonia, the Ketimine.

$$PhCN + PhMgBr \longrightarrow Ph\ C\ (=NMgBr)\ Ph \xrightarrow[H^+]{H_2O}$$

$$Ph_2C = NH$$

(3) Reaction of Carbon – nitrogen double bond compounds with Organometallics

Busch[8,9] found that the chlorine atom in c-Chloro N-benzylideneanilines could be replaced by the alkyl or aryl groups to a Grignard reagent to give the corresponding imines.

$$Ph\ C(Cl) = N\ Ar + R\ Mg\ X \longrightarrow PhC\ (R) = N\ Ar$$

Montagne[10] later found that anilides which may be regarded as C-hydroxyimines, react with alkyl or aryl Grignards to give the corresponding imines.

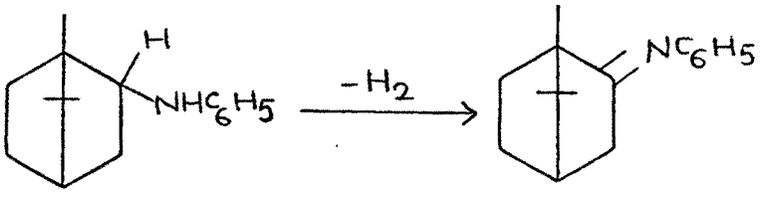
$$EtMgBr + PrCONHPh \longrightarrow Prc(Et) = N\,Ph$$

Grammatickis[11] has also found that oximes of aromatic aldehydes react with Grignard to give as the predominant product the benzylamine of the Grignard with the ketimine as the secondary product.

$$ArCH = NOH + RMgx \longrightarrow ArCHNHR + ArC(R) = NH$$

(4) Dehydrogenation of Amines

Ritter[12] was first to dehydrogenate amines to give imines. He found that isobornylaniline is readily dehydrogenated with sulfur at 220°C to give anil of Camphor (1).



(1)

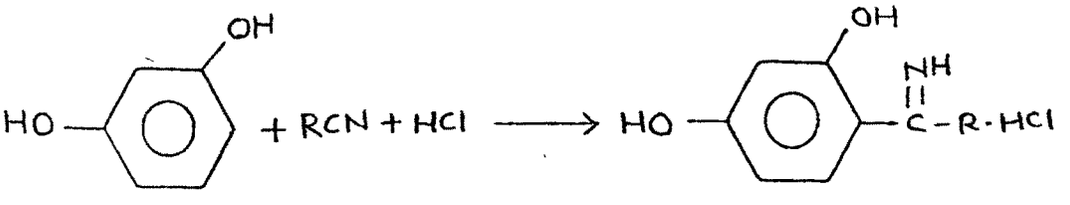
Secondary amines which are prepared from phenols, hexamethylenetetramine and 2-ethoxyethanol, are readily

dehydrogenated to the imine by heating hexamethylene-tetramine in acetic acid.[13]

$$(HOC_6H_4CH_2)_2NH \longrightarrow HOC_6H_4CH_2N = CHC_6H_4OH$$

(5) Reaction of Phenols and Phenol ethes with nitriles

Hoesch and Houben[14-16] found that phenols or their ethers react with alkyl or aryl cyanides in ether when catalysed by hydrochloric acid and or zinc chloride to give Ketimines (2). The reaction works readily for dihydroxy compounds or monoethers where the groups are meta to one another.



(2)

(6) Reduction of Carbon-Nitrogen Compounds

Oxime of aliphatic and aromatic ketones can be reduced with hydrogen and nickel under pressure to give Ketimines.[17]

$$R_2C = NOH + H_2 \longrightarrow R_2C = NH + H_2O$$

Nitriles when hydrogenated over nickel or platinum catalysts can give imines.[18]

$$RC \equiv N + H_2 \longrightarrow RCH = NH + H_2 \longrightarrow RCH_2NH_2$$

$$RCH = NH + R\,CH_2NH_2 \longrightarrow RCH_2NHCH_2R + NH_3$$

Lithium aluminium hydride in tetrahydrofuran has been found to reduce aromatic nitriles to give imine.

$$PhCN \xrightarrow{LiAlH_4} Ph\,CH_2NH_2 + Ph\,CH_2\,N = CHPh + NH_3$$

Nitriles also can be reduced to imines with stannous chloride in ethylacetate containing hydrochloric acid.[19]

α-Nitrostyrenes can be reduced with Lithium aluminium hydride to imine.[20]

$$PhCH = CHNO_2 \longrightarrow PhCH_2CH = NH$$

(7) Reaction of nitroso compounds with active hydrogen compouds

The reaction of active hydrogen compounds with nitroso compounds formed imines.

$$\text{>}CH_2 + RNO \longrightarrow CHN(OH)\,R \xrightarrow{-H_2O} \text{>}C = NR$$

$$CHN(OH)\,R \xrightarrow{-H_2} \text{>}C(=O) - NR$$

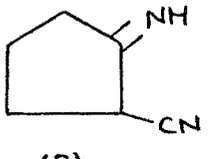
(8) Reaction of metal amides

An alkali metal or calcium salt of primary amines reacts with aromatic ketones to give imines.[21]

$$(C_6H_5)_2\ C = O \ + \ C_6H_5NHNa \ \longrightarrow \ (C_6H_5)_2\ C = NC_6H_5$$

The alkali, calcium, magnesium or aluminium metal amide of a secondary amine in ether reacts with dinitriles, as adiponitrile to give the cyclic α-cyanoimine (3).[22]

$$NC\ (CH_2)_4\ CN + NaNR_2 \longrightarrow$$



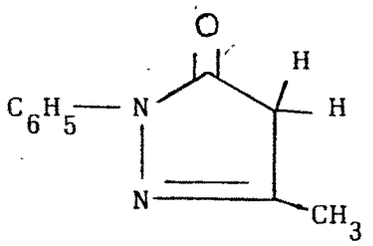
(3)

(9) Miscellaneous Methods

Imines react with other amines to give the exchange products.[23,24]

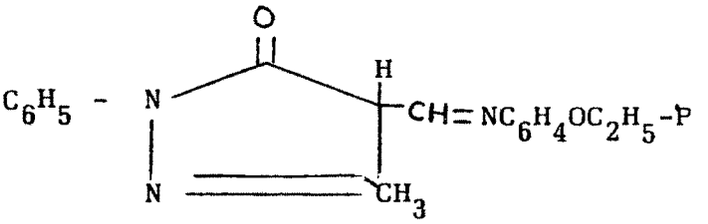
$$RNH_2 \ + \ R'N = C\Big\langle \rightleftharpoons \ R'\ NH_2 \ + \ RN = C\Big\langle$$

(4) reacts with diphenethyl formamidine in dioxane to give imine (4A).[25]



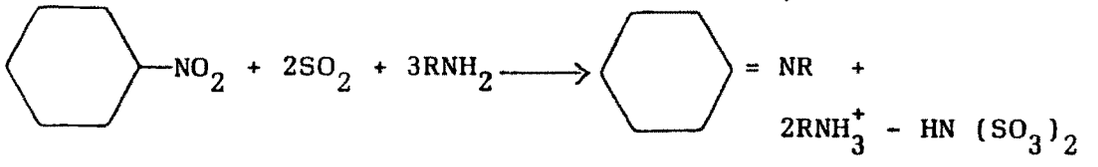
(4)

+ $(P - C_2H_5O\ C_6H_4NH)_2\ CO \longrightarrow$



(4a)

Secondary nitroalkanes react with primary amines to give imine (5).[26]



$$= NR + 2RNH_3^+ - HN\ (SO_3)_2$$

α -aminoacids react with sodium hypochlorite to give the chloramine intermediate which decomposes with the elimination of carbon dioxide and sodium chloride to give the imine.[27]

$$RR'\ (NHR")\ CO_2H + NaClO \dashrightarrow RR'\ C(NClR")\ CO_2\ Na$$

$$RR'C = NR" + CO_2 + NaCl$$

ADDITION REACTION OF IMINES

(1) Addition of Water

Reddelien and Danilof[28] have reported that anils are readily decomposed by aqueous mineral acids. Alumina and

thoria have been found to be effective catalyst for the hydrolysis of imines.[29]

Substituents on the benzylidene portion of N-benzylideneaniline have been found to facilitate hydrolysis when they are electron donating while electron withdrawing groups retard hydrolysis. The mechanism of the hydrolysis of imines have always been felt to proceed through the carbinol intermediate (I) with the acid catalysed dehydration of (I) being the rate-determining step in the reaction.

(2) Addition of hydrogen

Imines may be reduced either by a catalytic hydrogenation or by chemical reagents. Catalytic hydrogenations of imines are avoided when the corresponding amines are desired. Aliphatic aldimines give the secondary amines by a platinum catalytic reduction.[30] Aliphatic ketimines are also reduced to secondary amines by platinum catalysts.[31,32] Other catalysts such as nickel, copper chromite and 1000 psi of hydrogen also reduce imines.

Mailhe[33] reduced n-benzylideneaniline and N-isobutylideneaniline over nickel by vapour phase hydrogenations.

There are many chemical reagents which will reduce imines. Most of the reagents that are used to reduce ketones and aldehydes will reduce imines. e.g. sodium and refluxing alcohol [34,35] sodium amalgam, zinc and acetic acid,[36] magnesium in methanol,[37] lithium aluminium hydride[38-40] sodium aluminium hydride, sodium borohydride inmethanol.[41] Theimino group can be selectively reduced in the presence of other groups such as nitro, chloro, methoxy and hydroxyl with sodium borohydride.[42,43]

(3) Addition of Primary amines

The addition of primary and secondary amines take place just as water adds to imines. The intermediate 1,1-diaminoalkane (II) is not stable and in the case of secondary amines no reaction occurs because determination of the intermediate (II) can only give the starting materials.

$$\text{>C = NH} + \text{R'R" NR} \rightleftharpoons \text{>C (NR'R") N H R} \qquad \text{(II)}$$

The exchange reaction, in the case of primary amines, was first used by Reddelien[44] to obtain imines.

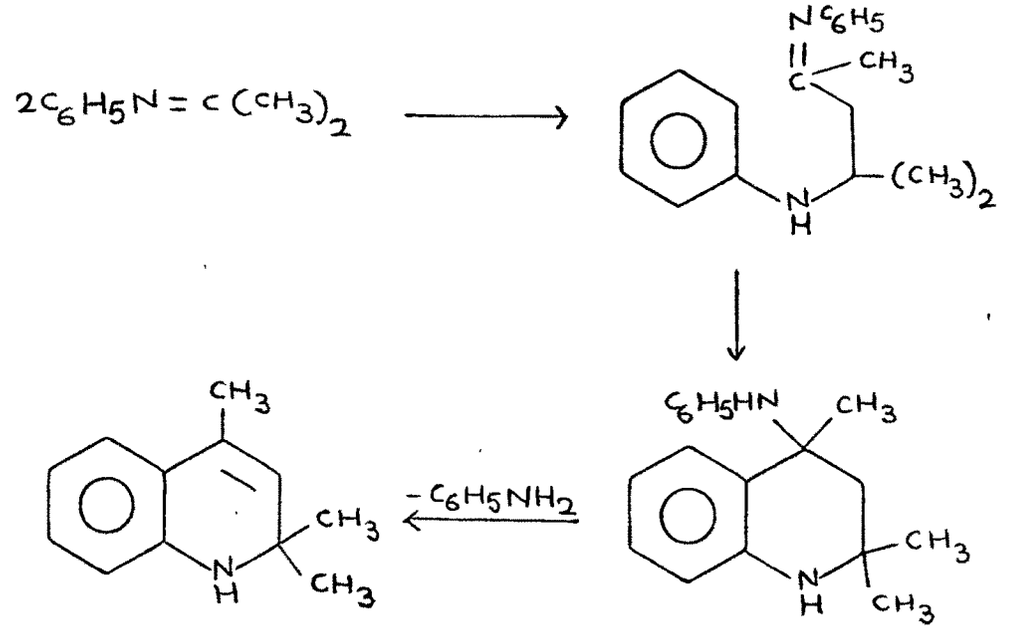
$$\text{>C = NR} + \text{H}_2\text{NR'} \rightleftharpoons \text{C(NHR') NHR} \rightleftharpoons \text{>C = NR'} + \text{H}_2\text{NR}$$

(4) Addition of active hydrogen compounds

Numerous compounds containing an active hydrogen add to the imines in the following manner.

$$RR'C = NR'' + R''' H \longrightarrow RR' R''' CNHR''$$

Imines derived from aliphatic aldehydes and ketones which contain an α-hydrogen undergo aldol condensation e.g. N-2-propylideneaniline reacts with itself in the presence of hydrogen chloride to give 2,2,4-trimethyl-hydroquinoline (6). This involves an aldol condensation, cyclisation and deamination.[45-47]



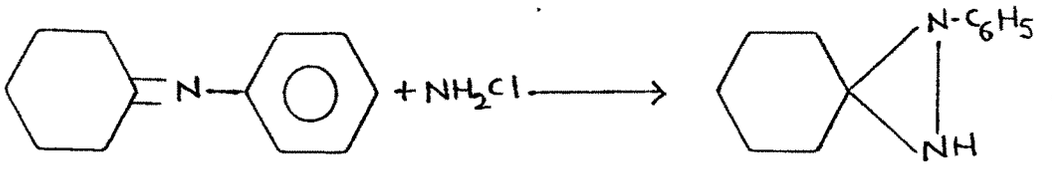
(6)

Most of the addition reactions of active hydrogen compounds with imines have been carried out with Schiff

bases. This imines have no α -hydrogens and cannot undergo self-aldol condensation.

(5) Addition of Miscellaneous Compounds

Chloramines add to imines to give diaziridines (7).[48]



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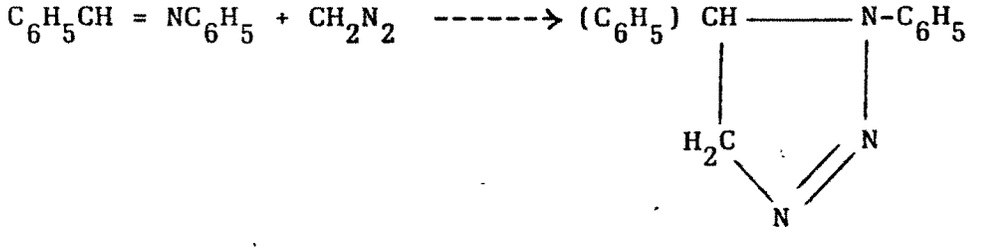
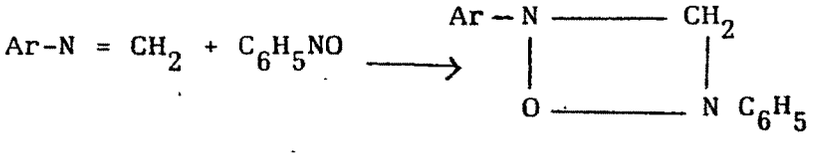
Mustata[49] was first to notice that diazomethane reacts with imines to give addition product, a 1,2,3-triazoline (8).



(8)

Ingold[50] has found that nitrosobenzene reacts with N-methylideneanilines to give the four-membered ring 1,2, 4-oxadiime (9).

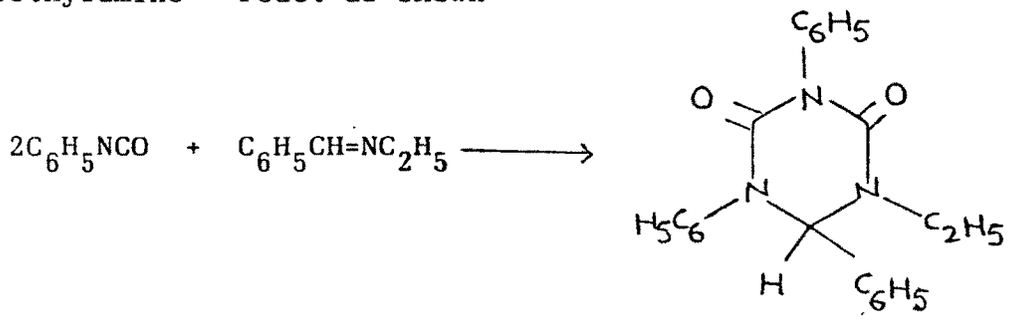


(9)

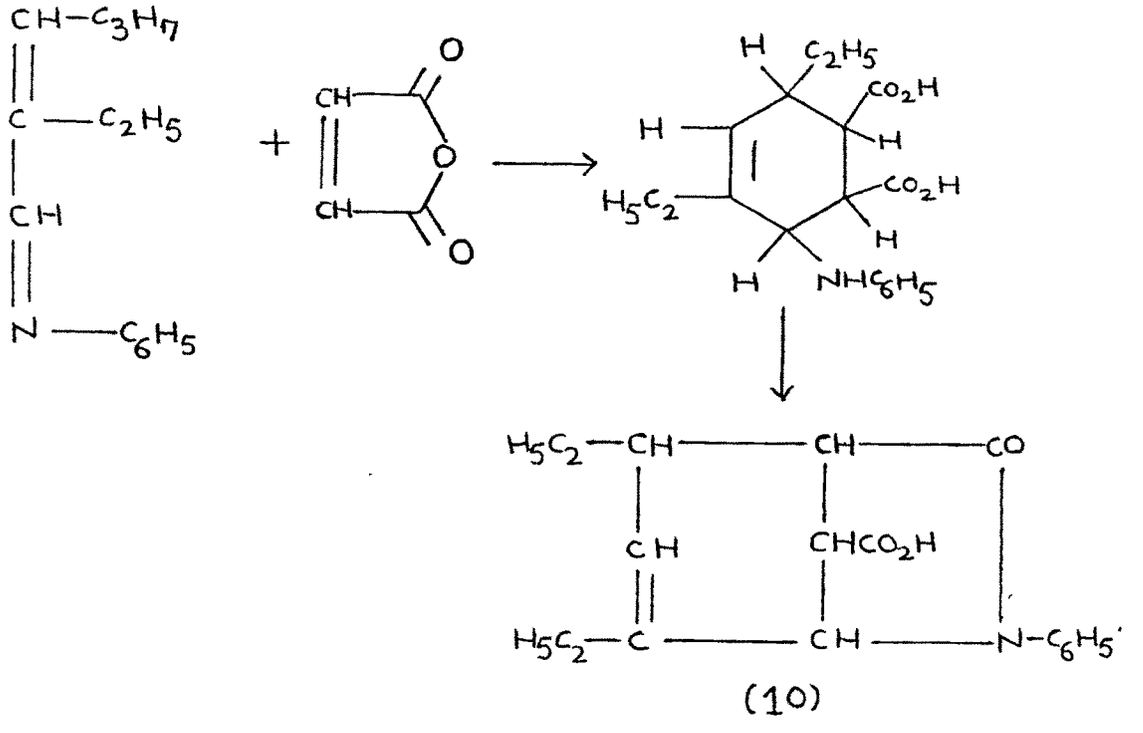
MISCELLANEOUS REACTIONS OF IMINES

(1) Reactions involving ring formation

When N-benzylidene propylamine is treated with hydrocyanic acid 1-propyl-6-phenyl-2,4-diketohexahydrocyanidene is obtained.[51] While phenyl isocyanate and N-benzylideneethylamine[52] react as shown

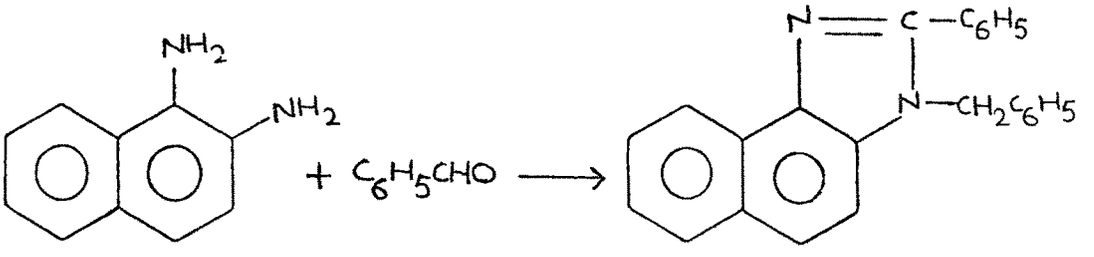


Snyder[53,54] has found that N-2-ethylhexen-2-ylidene-aniline and maleic anhydride gives a Diels - Alder type reaction which then cyclises to the amide, 5,7-diethyl-2-phenyl-2-azatricyclo-[2-3-1]-oct-6-ene-3-one carboxylic acid (10).



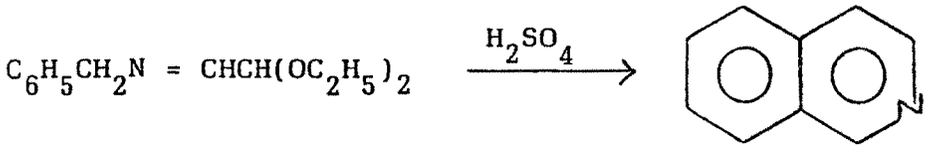
(10)

1,2-Diaminonaphthalene reacts with excess benzaldehyde to give the monoimine 2-N-benzylidene-1,2-diaminonaphthalene. In the presence of hydrochloric acid, N-benzyl-c-phenylnaphth [1,2] imidazole (11) is formed.[36]

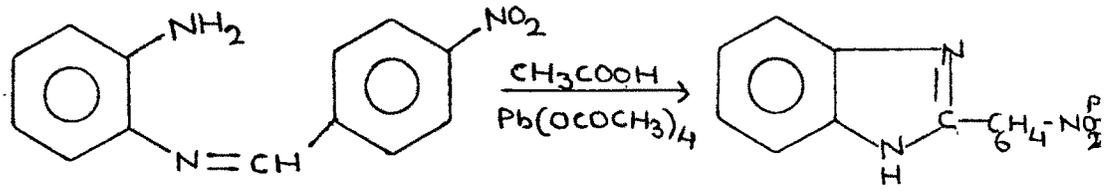


(11)

An improved Pomeranz - Fritsch isoquinoline synthesis utilizes N-2, 2'-ethoxy - ethylidenebenzylamine which is cyclised with sulfuric acid. Polyphosphoric acid and phosphoryl chloride are also effective catalysts and the thienylideneamine can also be cyclised.[55,56]

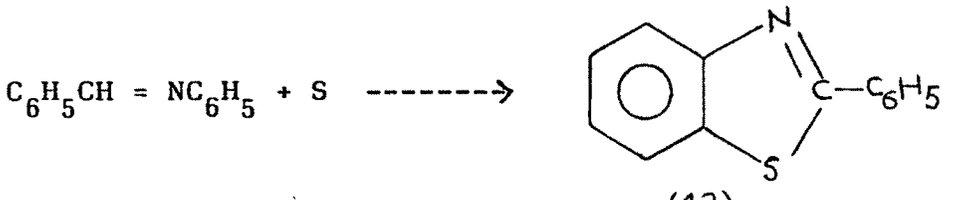


N-Nitrobenzylidene-o-phenylenediamines are oxidised with lead tetraacetate to give the nitro-substituted benzoxazoles (12).[57,58]



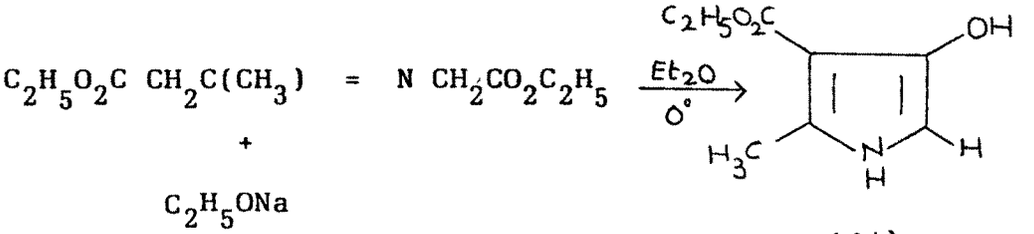
(12)

N-Benzylideneaniline and sulfur at 280°C gives 2-phenylbenzathiazole (13).[59]



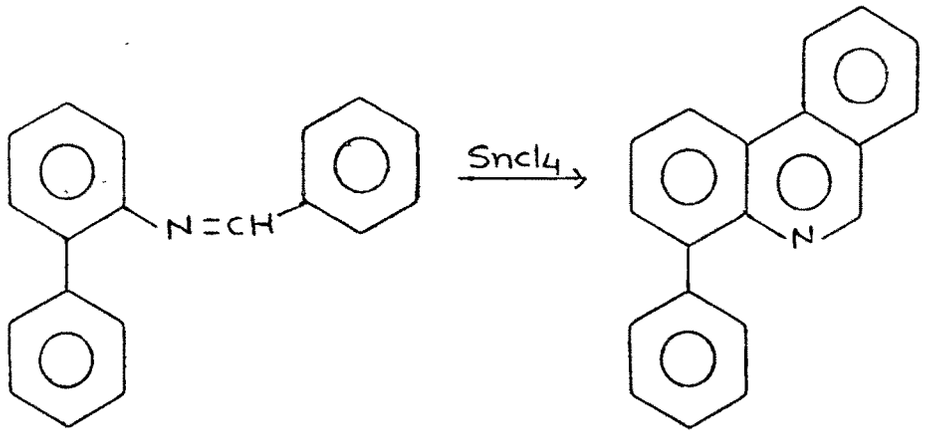
(13)

The imines of β-oxoacid ester, β-diketones and β-oxoaldehydes are cyclised to β-hydroxypyrroles (14).[60]



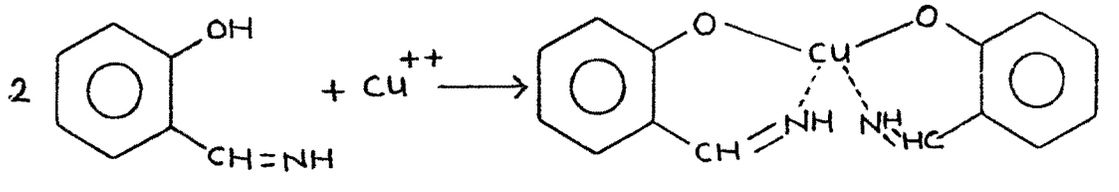
(14)

N-Benzylidene-2-phenylaniline is cyclised in stannic chloride in refluxing o-dichlorobenzene or with phosphorous pentachloride in trichlorobenzene.



(2) Reactions other than cyclisation

Certain imines can form complexes with metals. Imines which form such complexes are about the same as those carbonyl compounds which form similar complexes. They have the general characteristics of forming a five- or a six membered ring with the metal. The ring also contains one or two double bonds. e.g. imines of salicyl-aldehyde complex with metals (15).[61]



(15)

Syn-anti Isomerization of Imines

The fact that imines possess a double bond suggests that geometric isomers should be possible.

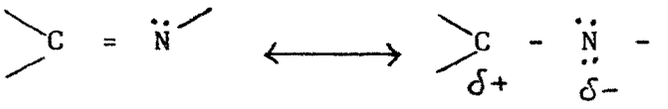
N-salicylidene-p-carbethoxy aniline was found to exist as yellow needles which melt at 145°. These needles when exposed to light are converted to orange-red needles which melt at 259°.[62] This was attributed to the isolation of the syn and anti isomers of this compound.

Aliphatic and aromatic imines, including N-salicylidene-p-carbethoxyaniline, were investigated in the ultraviolet and visible regions before and after illumination with ultraviolet light for 5 to 6 hrs. All of the imines investigated showed no difference in the absorption spectra. Consequently, no isomerisation was noted, and it was concluded that all the materials tested exist in the antiform.[63]

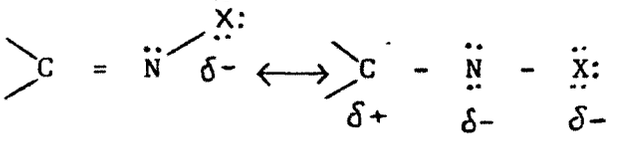
Taylor and Fletcher isolated two isomers on treating 2-nitrofluorenone with p-toluidine in the presence of an acid which have differences in both the ultraviolet and infrared spectra.

Curtin and Hausser[64] are the first workers to demonstrate that imines are capable of existence in syn and anti isomer forms. They have measured the rate of isomerisation of the imine obtained from p-nitro- or p-chlorobenzophenone dichloride and methylamine. Crystalline p-chlorobenzophenone methylimine exists as the syn isomer. The p-nitro compound exists as the anti isomer. In cyclohexane, at room temperature or above, these pure materials isomerise to an equilibrium mixture of the syn and anti isomers. The rate of isomerisation is very rapid but could be followed and determined by ultraviolet spectroscopy. The corresponding imines obtained from arylamines on crystallisation give only one isomer which isomerises too rapidly in solution to an equilibrium mixture to be followed instrumentally. The solution of these materials again shows an equilibrium of syn and anti isomers as determined by nuclear magnetic resonance spectroscopy. Mutarotations of substituted N-benzylidenebenzylamines in the pure state and in solution have been used to suggest syn-anti isomerisation.

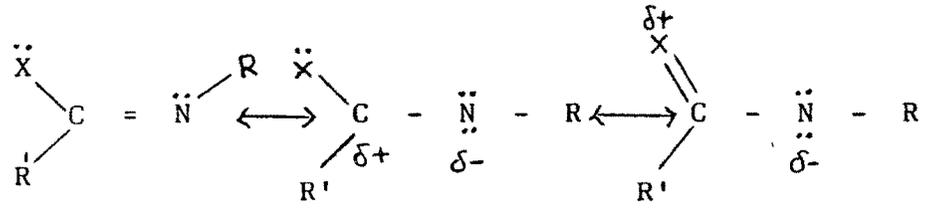
Imines cannot be isolated in both syn and antiforms due to the ease of free rotation about the carbon-nitrogen double bond. This probably arises from the fact that the electronegativity of the nitrogen compared to that of the carbon causes a lowering of the double bond character of the imino linkage by a polarisation.



No such polarisation forces are at work in the case of stilbene nor azobenzene where the geometric isomers have been isolated. Azoxybenzene also gives stable isomers. A number of materials which contains an imino group do have isolable syn and anti isomers. e.g. oximes, semicarbazones and N-chloro or bromoimines exist in two stable forms.[65] From this data it might be suggested that the presence of electronegative groups on the nitrogen of the imino group decrease the polarisation that normally occurs by an electrostatic repulsion due to adjacent negative changes in the following resonance structures.

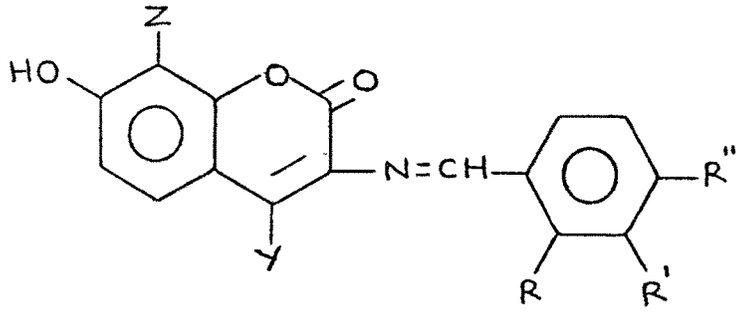


This would give the imino group more double bond character and would allow geometric isomers to be separable. In contrast to this, imide chlorides and imidates which have an electronegative group on the imino carbon exist only in the more stable anti configuration.[66,67] These groups could facilitate the polarisation of the imines group by their resonance contributions.

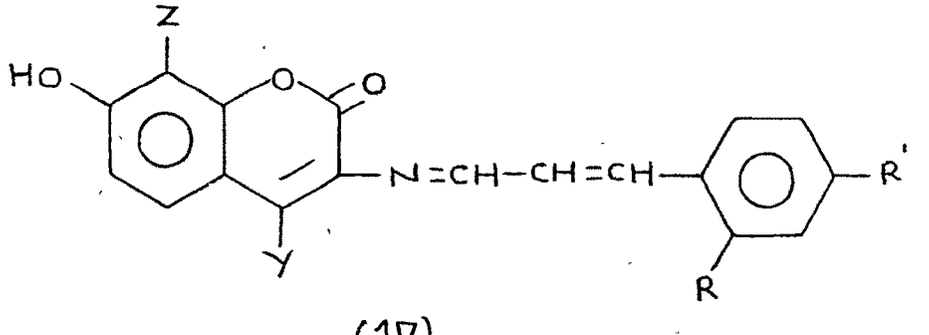


Some recent references of Schiff bases of coumarin derivatives are reviewed here briefly.

C. Antonello and G. Baretta[68] synthesised azomethines (16), (17) by treating 7, 8 (or -4)- dihydroxy-3-aminocoumarin with arene aldehydes. They reported that the compounds with the substituents Y and Z = H or OH and R, R', R" were H, Cl or NO_2, were found to be active against E. coli.



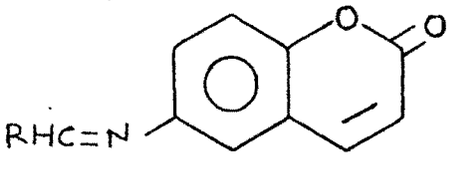
(16)



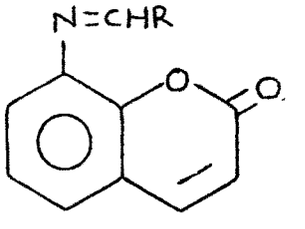
(17)

Datta and Daniels[69] prepared semicarbazones, p-nitrobenzoyl hydrazones and isonicotinoyl - hydrazones from unsubstituted and 3-substituted-4-phenyl-2-oxo-3-butenoic acid and 6-formyl-1,2-benzopyrone. They measured the toxicities and in vitro antitubercular activities. They found that three isonicotinoyl-hydrazones showed antitubercular activity.

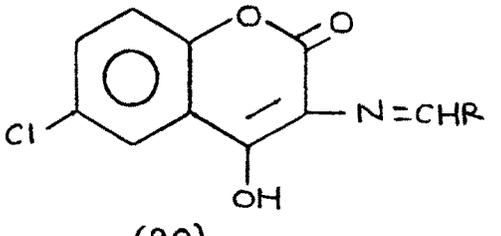
Trkovnik et al.[70,71] synthesised azomethines by condensing 6- and 8-aminocoumarin (18, 19) and 3-amino-4-hydroxy-6-chloro-coumarin (20), with various aldehydes.



(18)

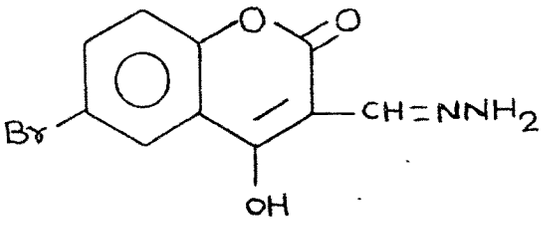


(19)

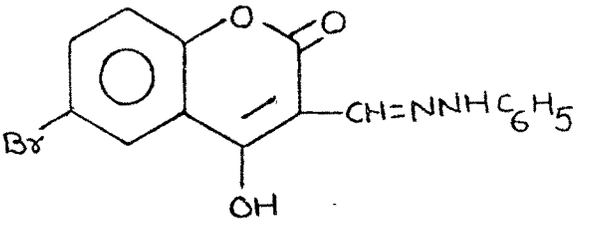


(20)

Bobarevic Blanka, Trkovnik Mladen and V. Knez[72] obtained hydrazones (21), (22) from 3-formyl-4-hydroxy-6-bromo coumarin and hydrazine hydrate and phenylhydrazine hydrate.

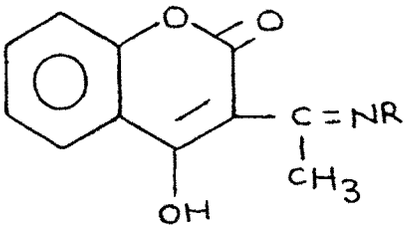


(21)



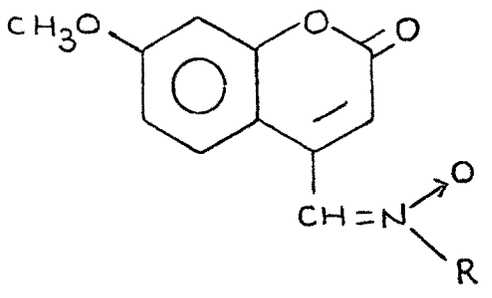
(22)

Strakov and co-workers[73] synthesised Schiff bases (23) from 3-acetyl-4-hydroxycoumarin and various primary amines.

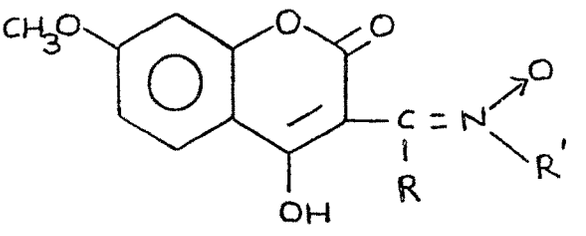


(23)

Shridhar et al.[74] prepared different nitrones (24), (25) by condensing 4-formyl-7-methoxy- and 3-formyl (or acetyl) 4-hydroxy-7-methoxycoumarin with HONHR or HONHR'. It was found that N-alkyl/aryl nitrones derived from somehetero-aromatic system were found as bactericides, fungicides and antiprotozoal agents.

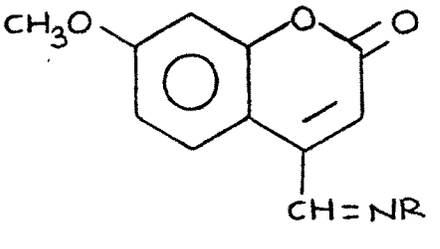


(24)



(25)

Shridhar, Vishwakarma and Bhujanga[75] synthesised Schiff bases (26) from 4-formyl-7-methoxycoumarin and appropriate amines. Schiff bases derived from 2,4-dichloroaniline, semicarbazide and N-amino-morpholine were found to possess antibacterial, antifungal, amebicidal and anthelmintic activities.



(26)

PRESENT WORK

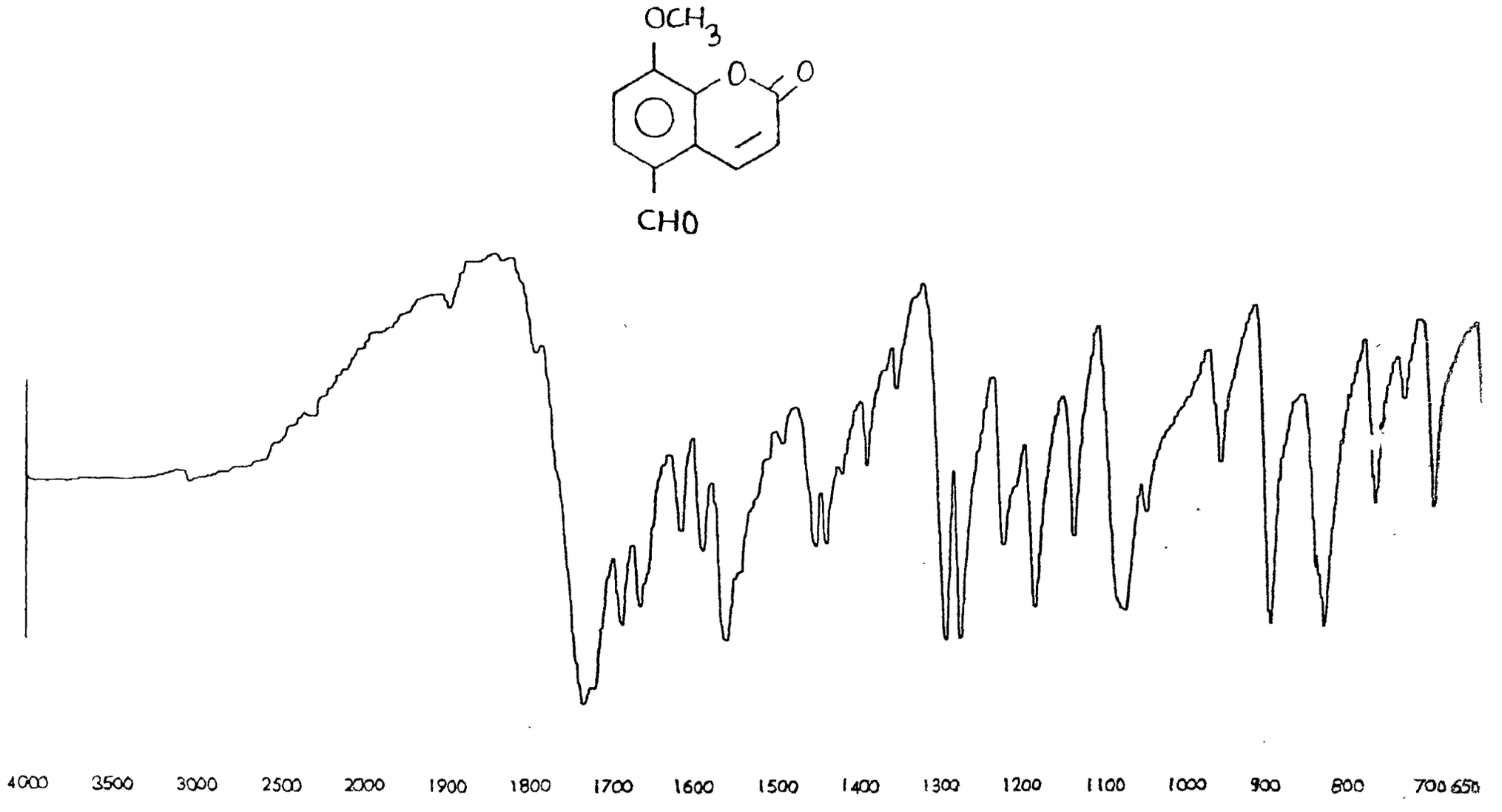
From the forgoing literature references, it has been observed that presence of azomethine linkage in the compound is found to exhibit or enhance antibacterial activity. Hence in order to have potent antibacterial agent, Schiff bases were derived from various 8-hydroxy-, 8-methoxy- and 7-hydroxy-coumarin derivatives and screened them for their antibacterial activity

8-Methoxy-5-formylcoumarin (28)

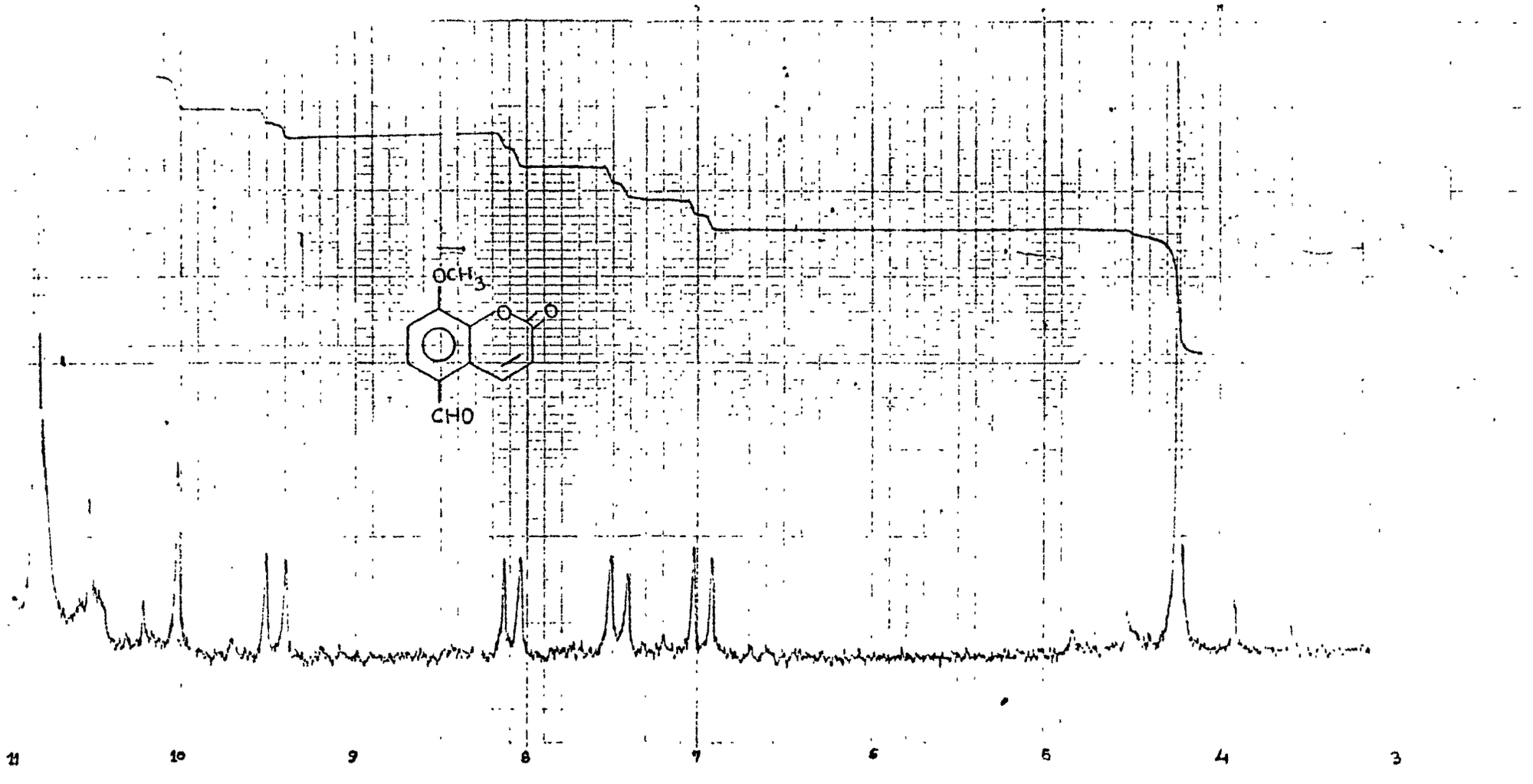
8-Methoxy-5-chloromethylcoumarin was treated with hexamethylenetetramine in chloroform solvent. The complex product which separated was decomposed with glacial acetic acid and 8-methoxy-5-formylcoumarin was obtained. The structure of the compound was established by following spectral analysis.

In IR (KBr) spectrum, the bands at 1740 - 1720 cm^{-1} of C=O (-CHO) group and C=O of lactone were appeared. It also exhibited bands at 1280 and 1080 cm^{-1} for C-O-C linkage (Fig. 1).

The NMR spectrum exhibited following signals :
(CF_3COOH) : A singlet at δ 3.8 for methoxy protons at C-8 position of coumarin ring ; a pair of doublets with J=9Hz at δ 6.5 and δ 9.06 for protons of C-3 and C-4 position respectively ; another pair of doublets with J-7Hz appeared at


OCH3
O
O
CHO
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
650

(Fig- 1) : 28



(Fig- 2) : 28

(0·4 ppm off set)

δ 7.1 and δ 7.7 for protons of C-7 and C-6 position respectively. One singlet appeared in the downfield at δ 9.6 due to formyl proton of HC =O group attached to position C-5 of coumarin ring (Fig. 2).

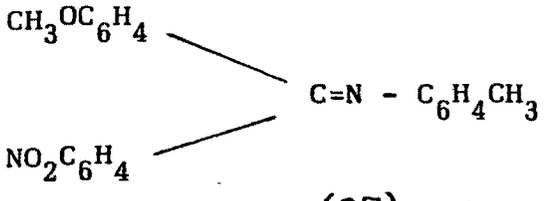
N-(8-methoxy-5-coumarilidine)-p'-methyl benzoic acid hydrazone (29, Table-I, 4)

A mixture of 8-methoxy-5-formylcoumarin and p-methyl benzoic acid hydrazide was refluxed in absolute alcohol with few drops of glacial acetic acid which furnished the product to which N-(8-methoxy-5-coumarilidine)-p'-methyl benzoic acid hydrazone structure was assigned. The structure was confirmed by following spectral data.

The IR spectrum exhibited characteistic absorption bands at 3300 (broad) cm^{-1} for NH stretching, 1710-1670 for lactonic carbonyl of coumarin ring system and NHCO-, 1580 for C=N stretching. (Fig. 3).

The NMR spectrum, taken in trifluoroacetic acid, exhibited singlet at δ 2.1, protons of methyl group attached to phenyl ring ; singlet at δ 3.75, methoxy protons linked to C-8 position of coumarin ring ; two doublets (J=9Hz) at δ 6.5 for C-3 proton and at δ 8.4 for C-4 proton. Aromatic protons and methyne proton appeared in the region δ 7.0-7.9.

The signal at δ 9.6 for a formyl proton was not observed which indicates the formation of azomethine linkage (Fig. 4). However, in the above NMR spectrum, it was observed that the signals of methoxy protons and methyl protons appeared as a partially resolved peaks having difference of 0.02 δ due to the isomerization in the solution form. David Curtin and Jack Hausser[65] also observed such type of partially resolved doublet in the case of p-methoxy-p'-nitro-benzophenone-p-tolylimine (27).



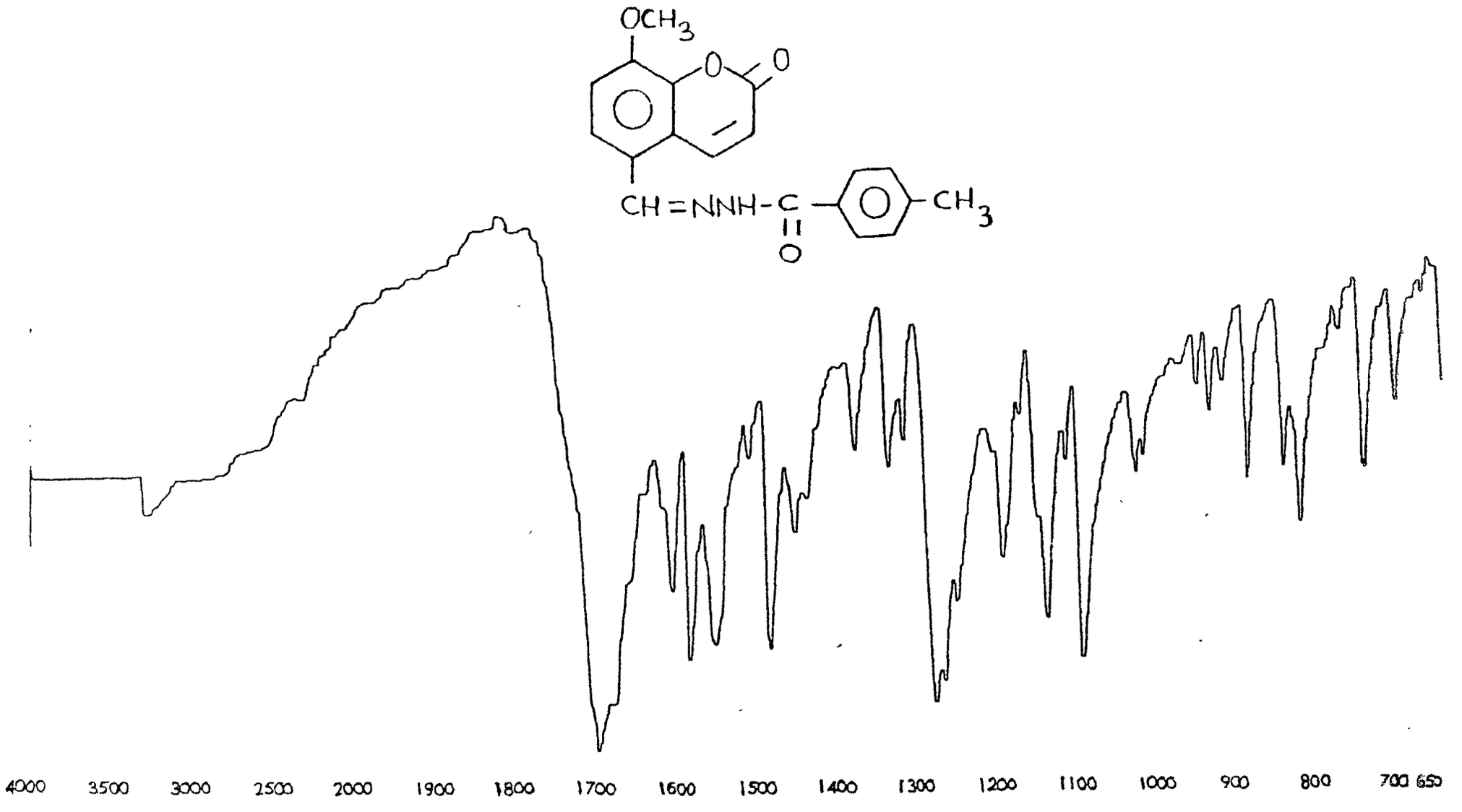
(27)

They reported that imines cannot be isolated in both syn and anti forms due to the ease of a free rotation about the carbon-nitrogen double bond.

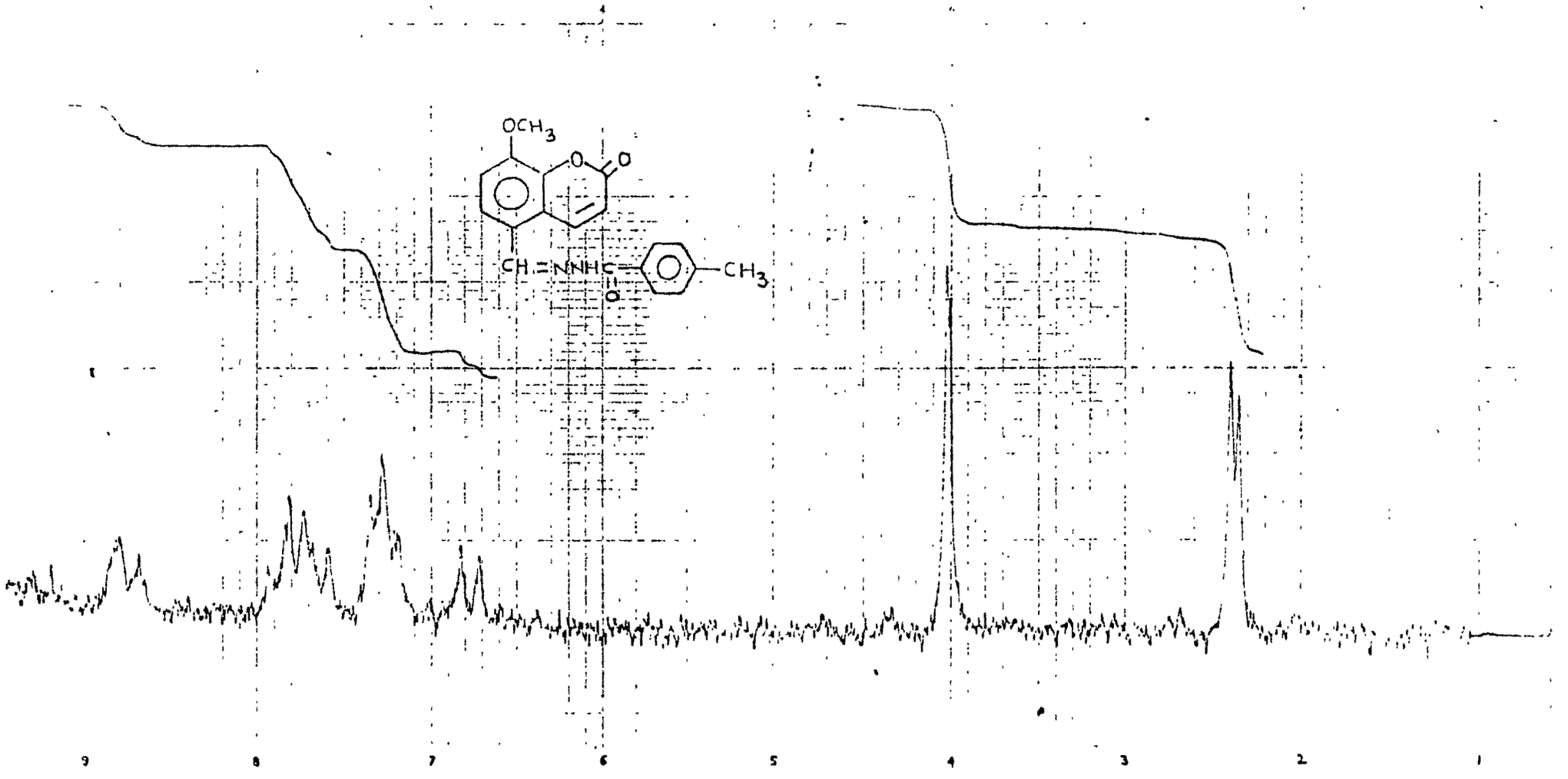
The melting point and the pattern of IR spectra remained the same even after repeated crystallisation of the Schiff base. This provide strong evidence that these compounds were obtained in a single stereoisomeric form but on solution, isomerisation occurs.

The mass spectrum showed following signals :

m/e : 336 (M^+ ion, 10%), 217 (8%), 119 (base peak, 100%),

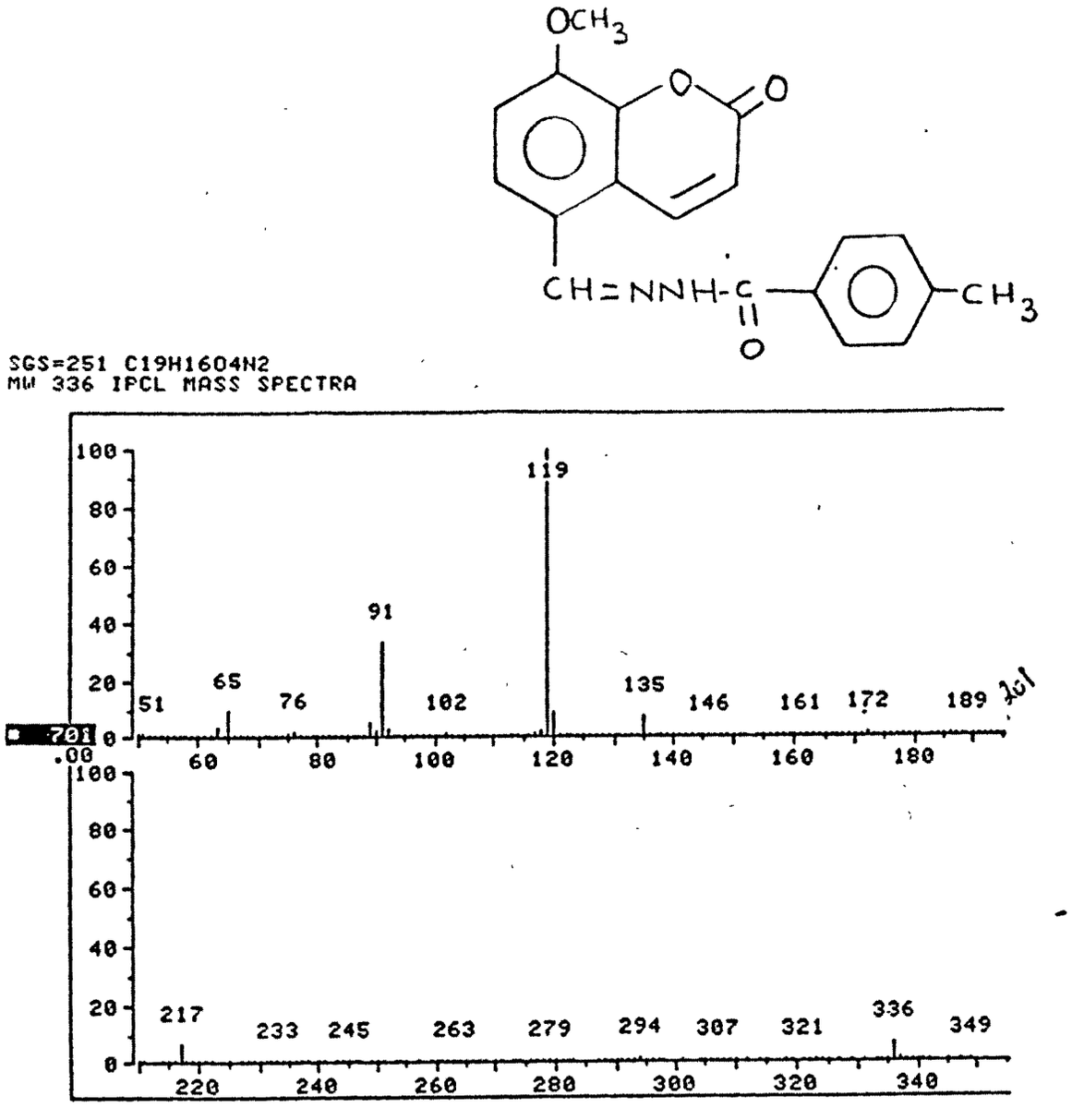


(Fig - 3) : 29, Table - I, 4



(Fig - 4) : 29, Table - I, 4

(0·3 ppm off set)



(Fig-5): 29, Table-I, 4

91 (35%), 65 (12%), (Fig. 5).

N-(8-methoxy-5-coumarilidine)-p'-nitro benzoic acid hydrazone (29, Table-I, 7)

8-Methoxy-5-formylcoumarin and p-nitrobenzoic acid hydrazide were condensed in absolute alcohol in presence of few drops of glacial acetic acid which gave a product to which n-(8-methoxy-5-coumarilidine)-p'-nitrobenzoic acid hydrazone structure was assigned.

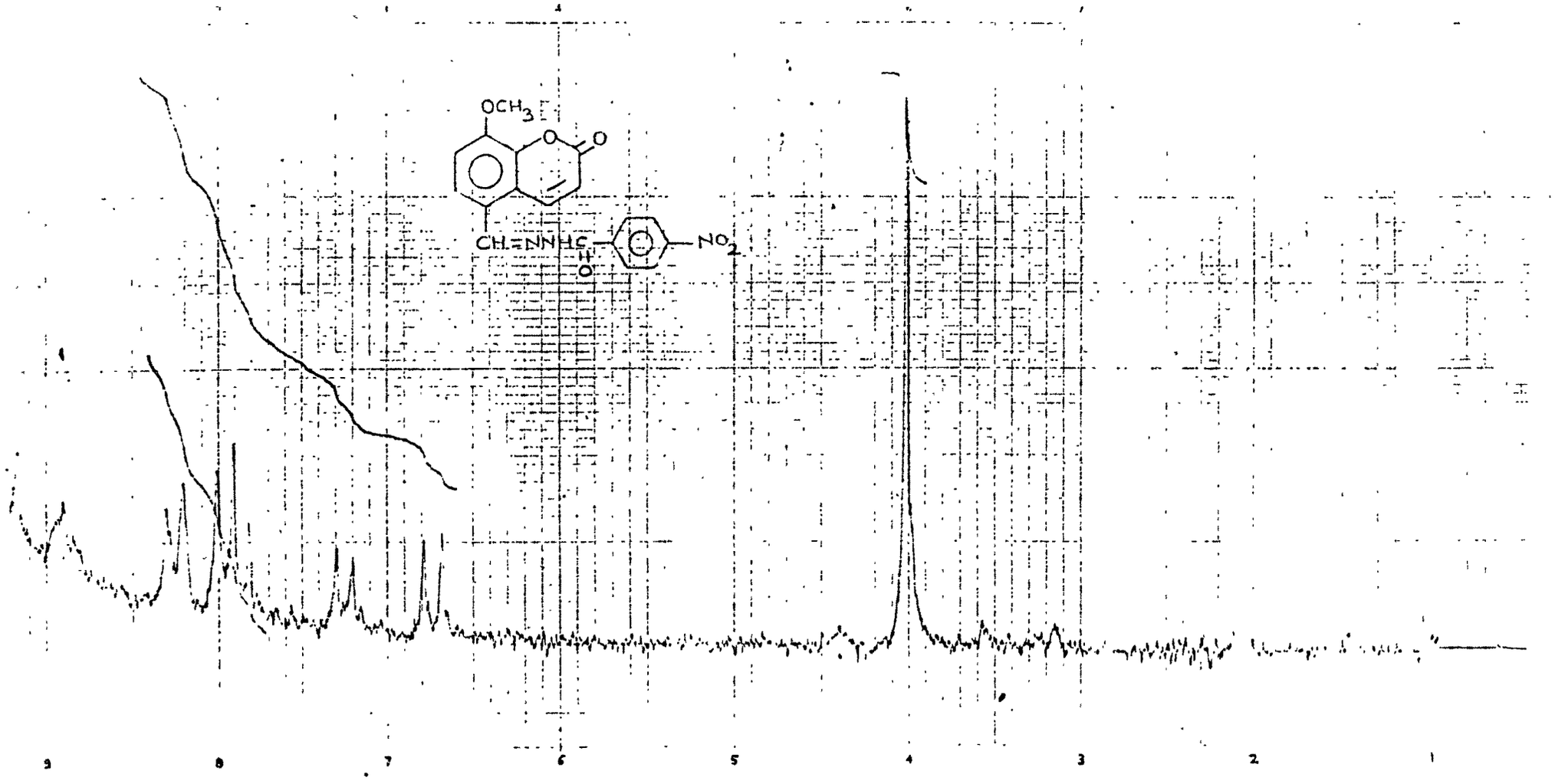
The IR (KBr) spectrum showed following bands, 3400(b), 1720 - 1690(b), 1580, 1280 cm^{-1}.

The structure of the compound was characterised on the basis of NMR (CF_3COOH) : δ 3.8, singlet, for three protons of methoxy group at C-8 position ; a proton at C-3 showed doublet with J=7Hz at δ 6.52 ; another doublet with J=7Hz appeared at δ 8.1 for a proton at C-4 position ; multiplet in the region δ 7-7.9 occured for methyne and aromatic protons (Fig. 6).

Other hydrazones were prepared in similar way (29, Table-I, 1-14).

8-Methoxy-5-[o-(N-5'-bromo-salicylidine)]anilinomethyl coumarin (30, Table-II, 10)

A mixture of 8-methoxy-5-(o-amino)-anilinomethyl coumarin



(0.2 ppm off set)

(Fig-6): 29, Table-I, 7

(2O, Chapter-II, Part II) and 5-bromo salicylaldehyde was refluxed in absolute alcohol when 8-methoxy-5-[o-(N-5'-bromo-salicylidine)]anilinomethyl coumarin was obtained.

The structure of the above compound was confirmed by the following NMR spectrum (CF_3COOH) : δ 3.5, singlet for methoxy group protons ; singlet at δ 4.45 for two protons of $C\underline{H}_2NH$ group ; δ 6.2, doublet (J=9Hz) for a C-3 proton, a doublet for a C-4 proton is found overlaping methyne proton and protons of aromatic nucleus appeared as multiplet in downfield region at δ 6.5-7.2 (Fig.7).

8-Methoxy-5-[o-(N-piperonalidine)]anilinomethyl coumarin (3O, Table-II, 12)

Above iminomethyl coumarin was obtained by condensing 8-methoxy-5-(o-amino)-anilinomethyl coumarin with piperonal. The product obtained was characterised by IR and NMR spectra.

In IR (KBr) spectrum, bands at 34OO (broad, NH stretching) 1735 (lactonic carbonyl of coumarin ring), 158O (C=N stretching) cm^{-1} were observed. (Fig. 8).

The NMR spectrum (CF_3COOH) exhibited signals at δ 3.65 ; singlet $OC\underline{H}_3$ protons at C-8 position of coumarin ring ; singlet for $C\underline{H}_2NH$ protons appeared at δ 5.65 slightly overlaping

Scheme:1

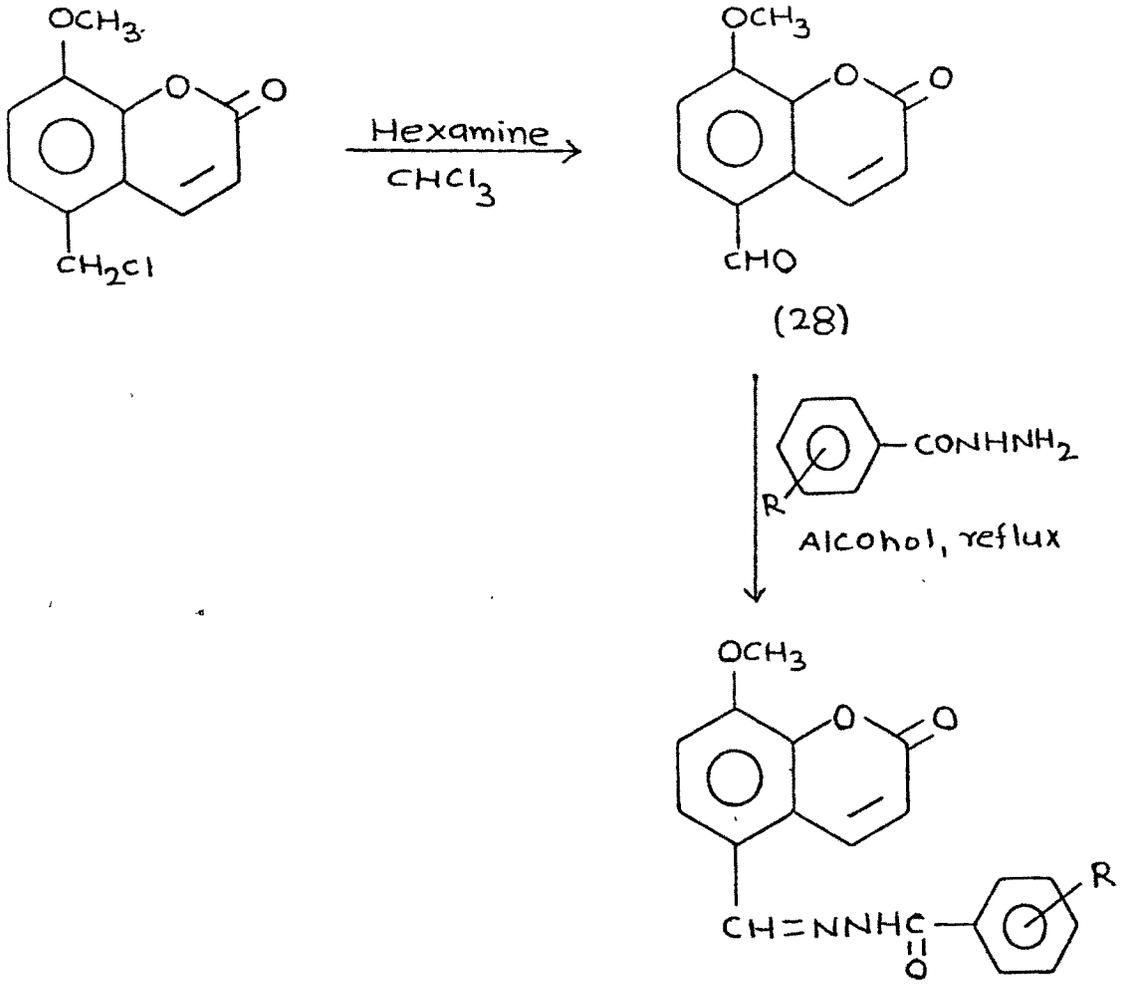


Table-I, 1-14

Scheme:2

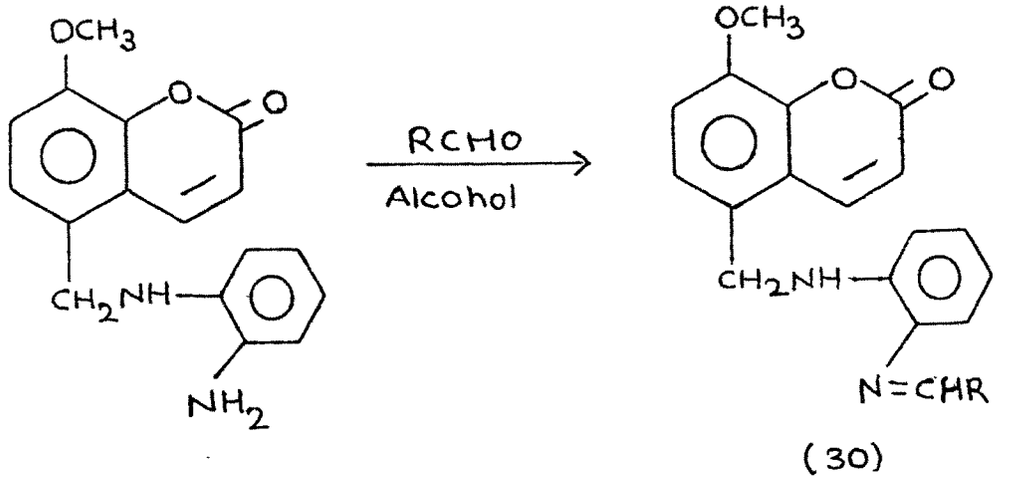
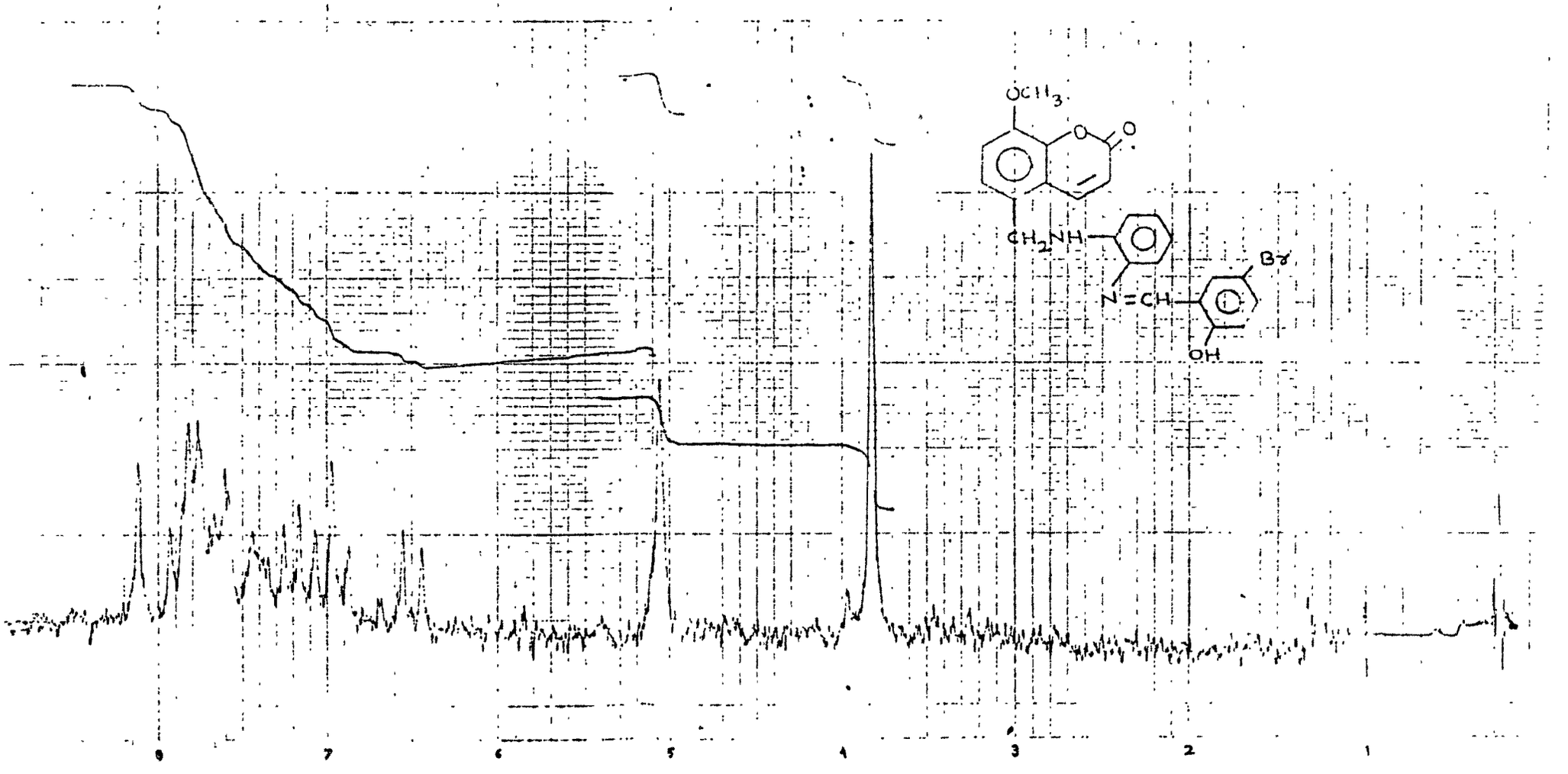
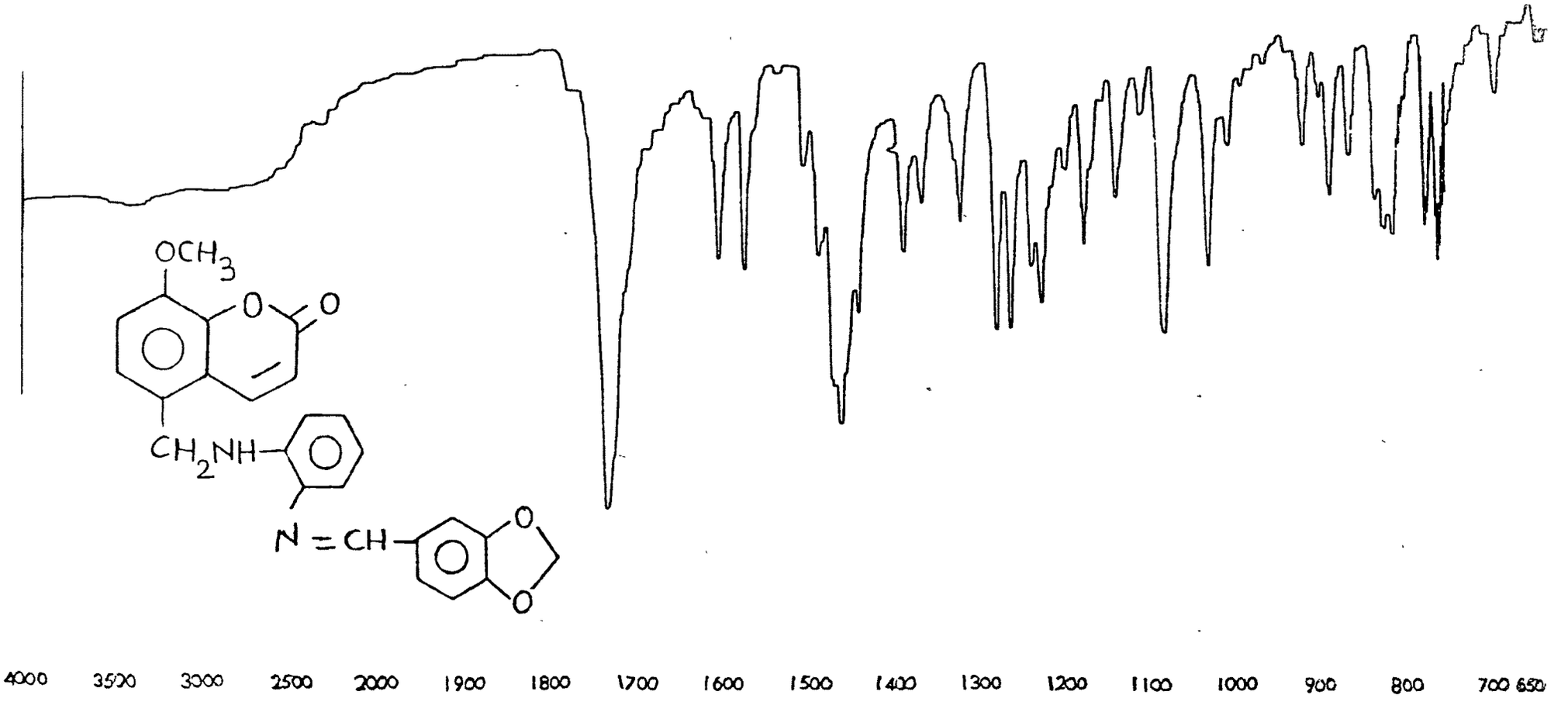


Table-II, 1-12

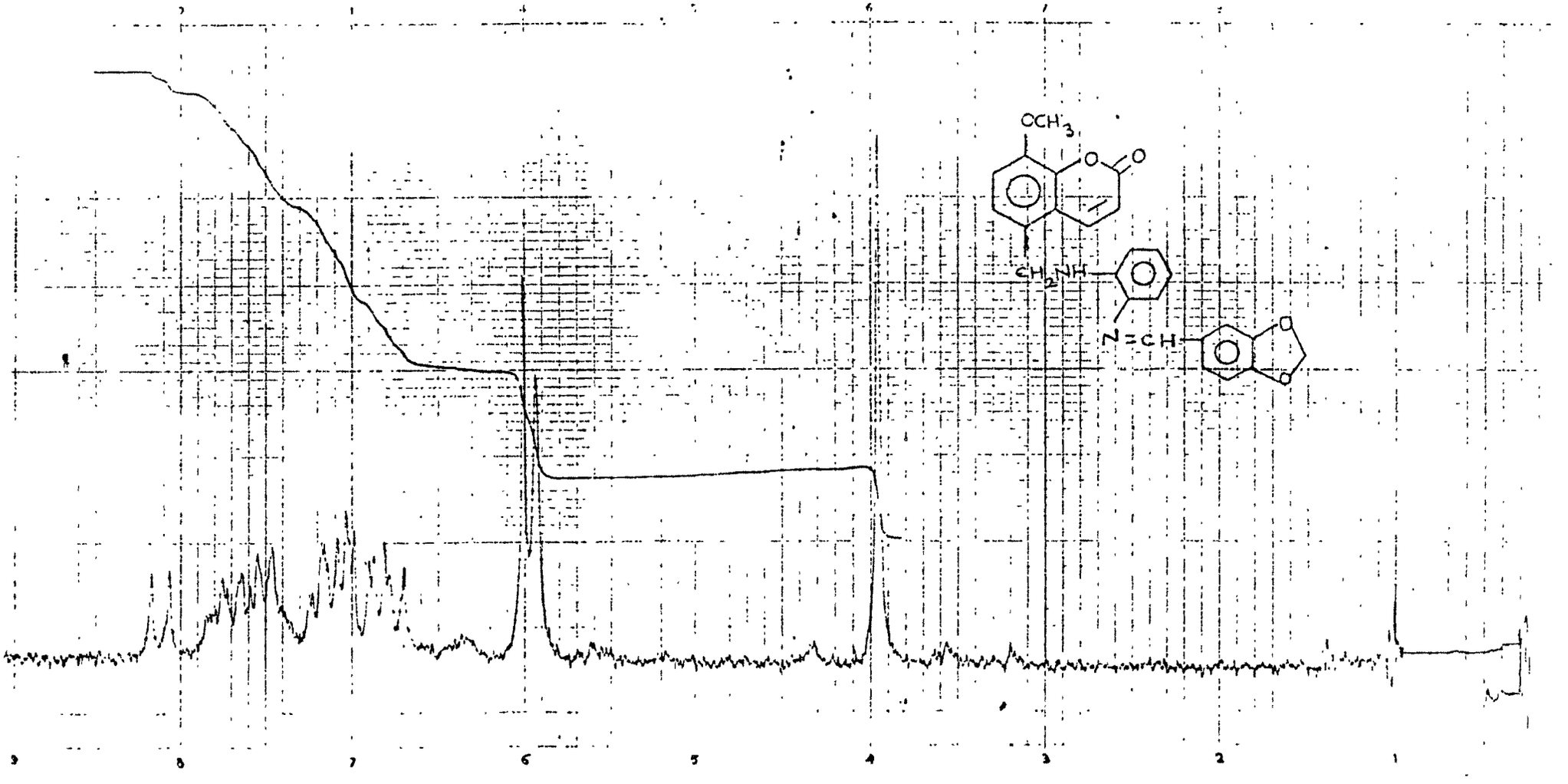


(Fig-7): 30, Table-II, 10

(0·3 ppm off set)



(Fig - 8) : 30, Table - II , 12



(Fig - 9) : 30, Table - II, 12

(0·3 ppm off set)

with another singlet at δ 5.8 appeared for O-CH_2-O protons. Methyne and aromatic protons were appeared as multiplet in the region δ 6.4-7.6 ; δ 6.4, doublet, a proton at C-3 position is found overlaping aomatic absorption while a proton at C-4 position appeared as doublet at δ 7.8 (Fig. 9).

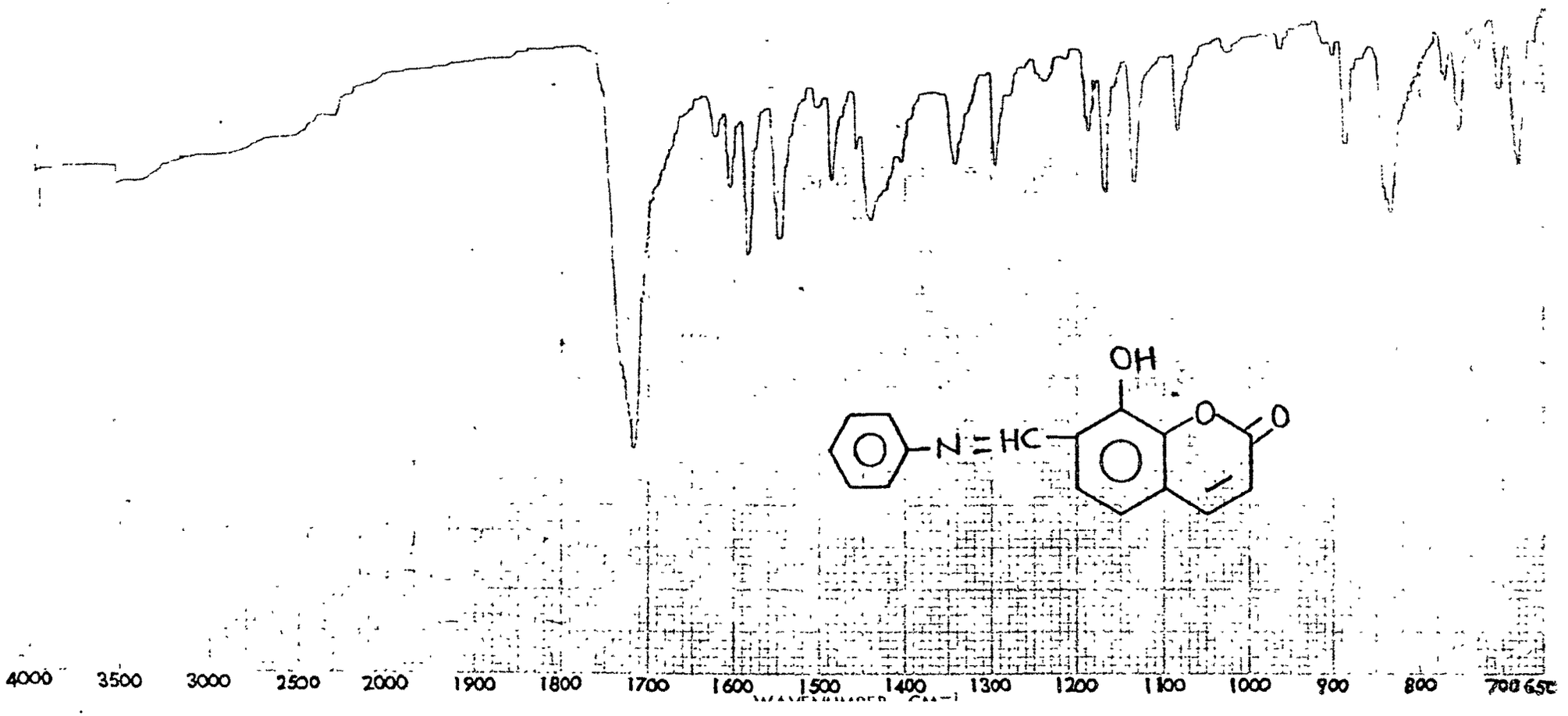
Similarly other Schiff bases were prepared from 8-methoxy-5-(o-amino)-anilinomethyl coumarin and various aldehydes (30, Table-II, 1-12).

7-(Phenyliminomethyl)-8-hydroxycoumarin (31, Table-III,1)

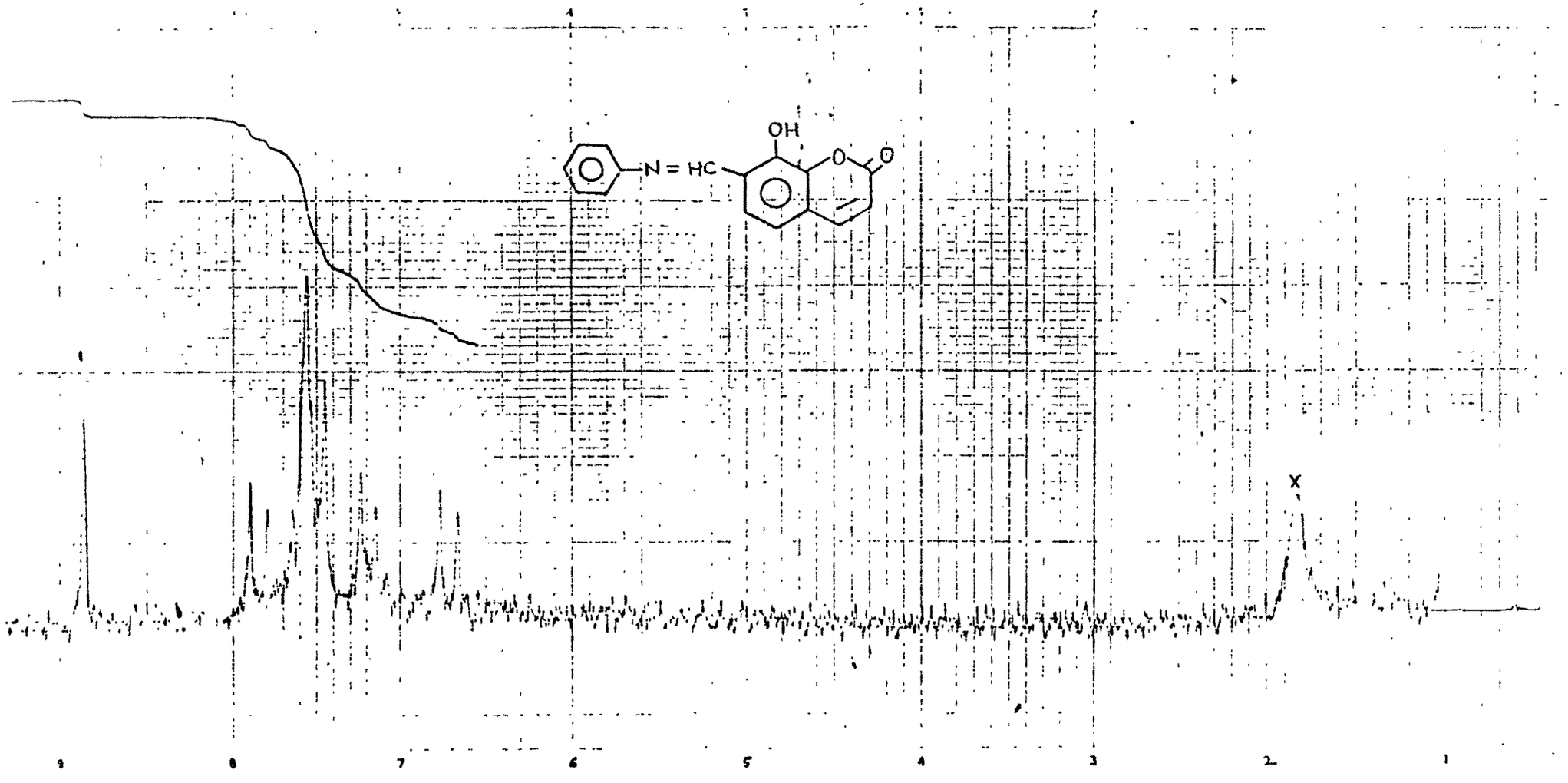
A mixture of 8-hydroxy-7-formylcoumarin[76] and aniline was refluxed in alcohol with few drops of glacial acetic acid. it gave a product whose structure was established on the basis of analytical data, IR, NMR and mass spectra.

IR spectrum (KBr) showed following bands :
3550 (broad, OH), 1720 (C=O of coumarin), 1550 (C=N), cm^{-1} (Fig. 10).

The NMR spectrum, taken in $CDCl_3$, exhibited following signals. The protons of C-3 and C-4 positions of coumarin ring appeared as two doublets, one at δ 6.4 and other at δ7.55 overlaping multiplet of aromatic protons in the region δ 6.9-7.55 ; singlet at δ 8.55 appeared for methyne proton (Fig. 11).

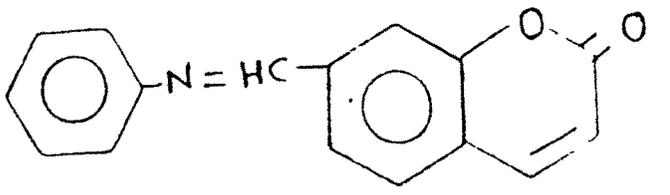


(Fig-10) : 31, Table-III, 1

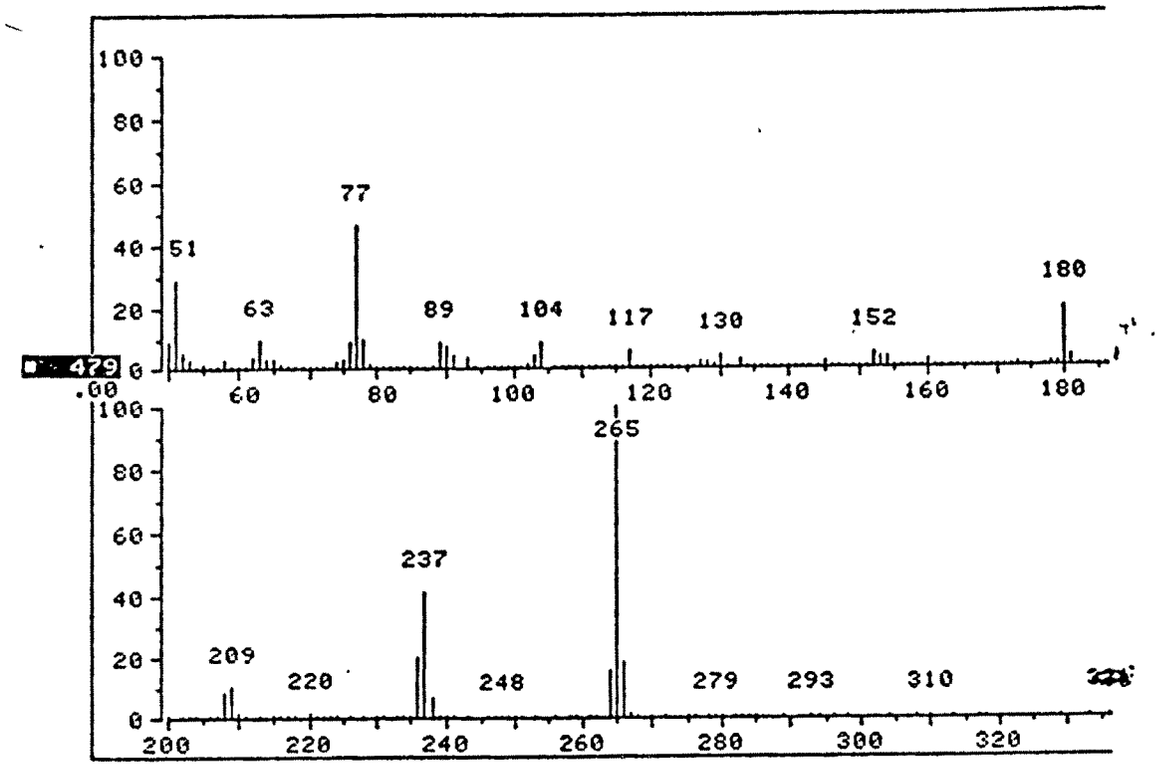


(Fig - 11) : 31, Table. III, 1

(0·3 ppm off set)



SGS-182
MASS SPECTRA-DR.BHATTACHARYA



(Fig - 12) : 31, Table - III , 1

Mass spectrum exhibited signals at m/e : 265 (M^+ ion, 100%), 237 (42%), 180 (20%), 77 (45%) (Fig.12).

Similarly other Schiff bases were prepared (31, Table-III, 1-4) by condensing 8-hydroxy-7-formylcoumarin and various substituted amines.

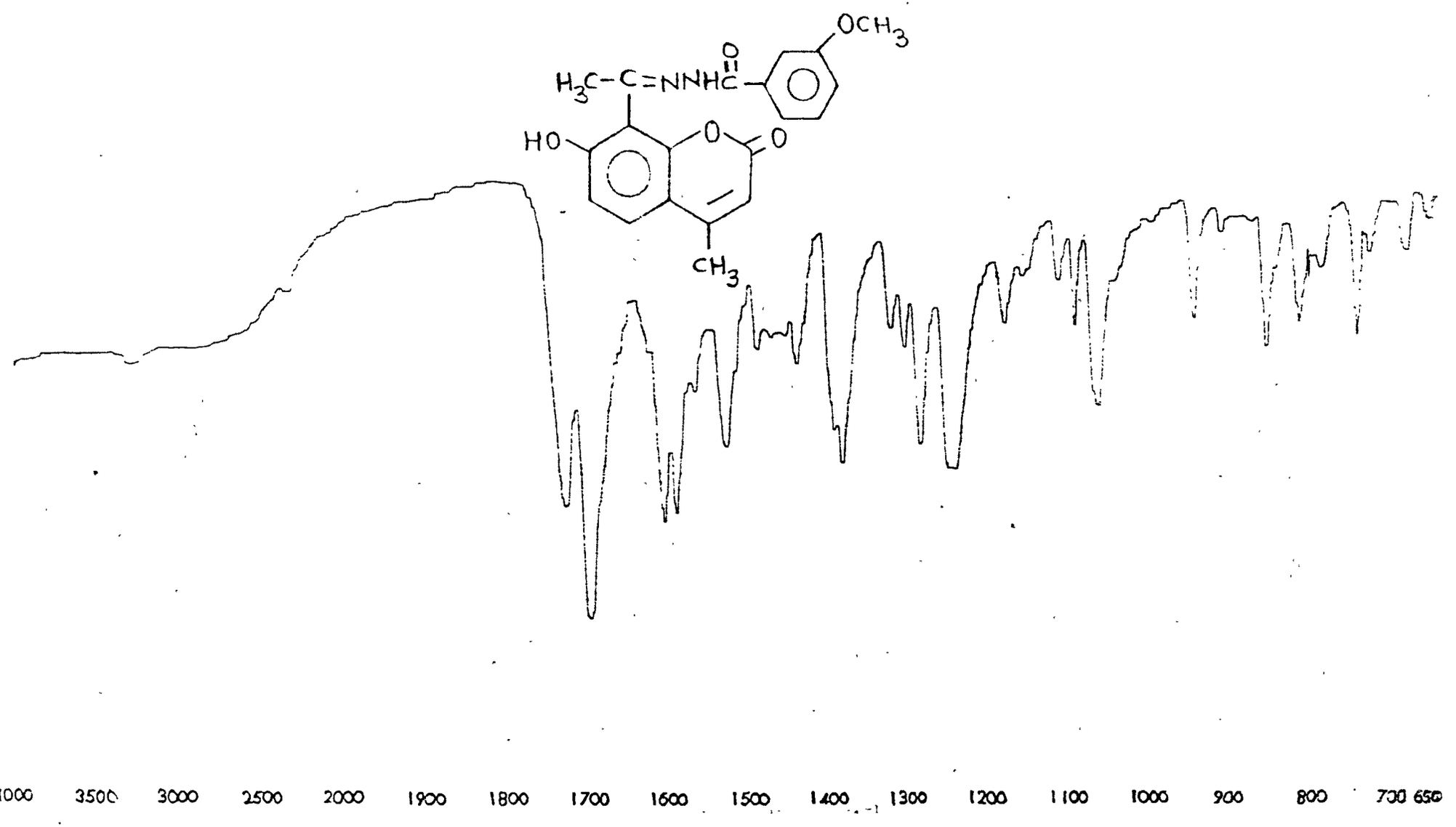
(7-Hydroxy-4-methylcoumarin-8-yl)-ethyldiene-m'-anisic acid hydrazone (32, Table-IV, 1)

Condensation of 7-hydroxy-4-methyl-8-acetylcoumarin and m -anisic acid hydrazide gave a product as usual. The product obtained was characterised by following spectral information.

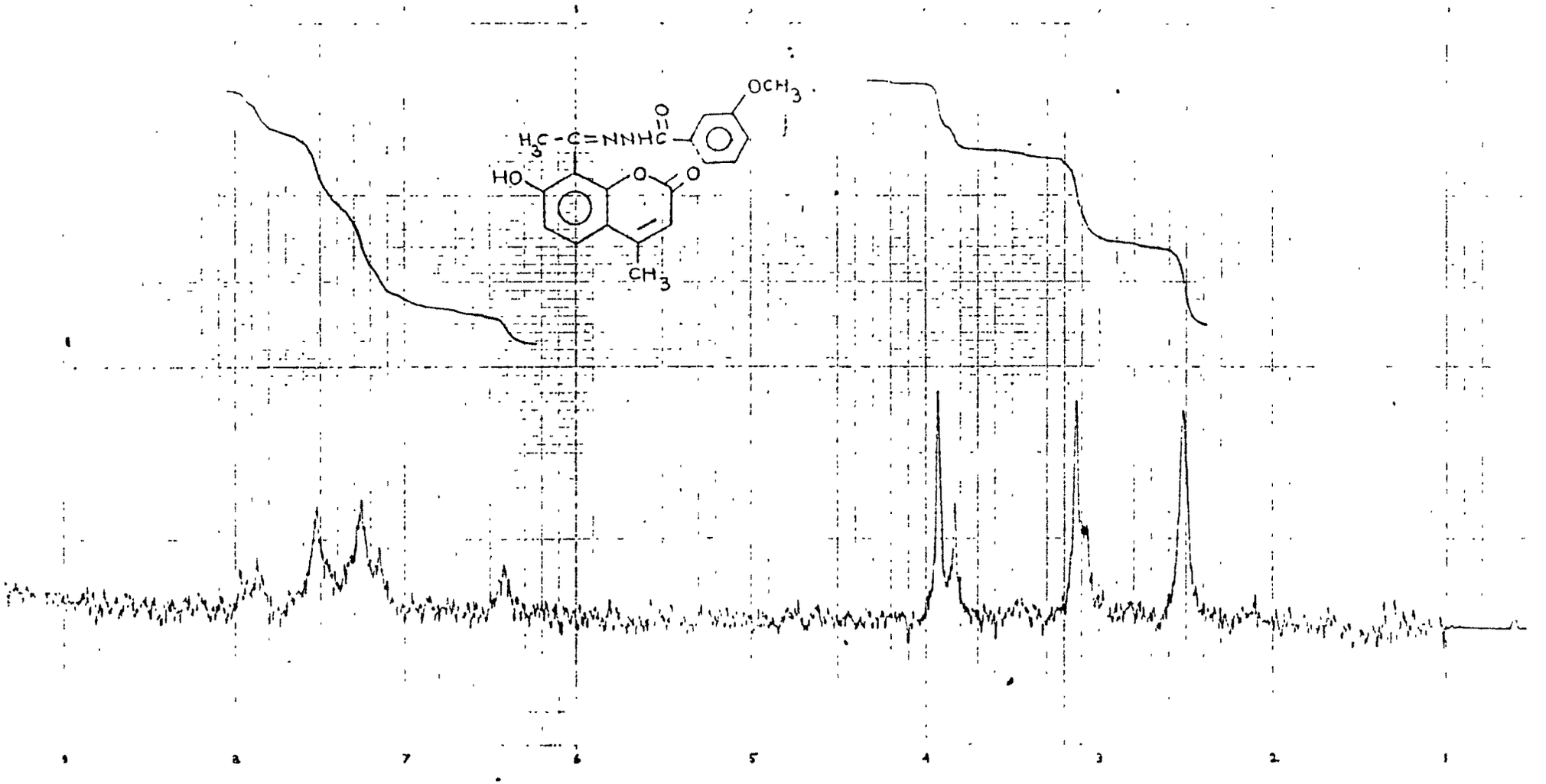
The IR spectrum exhibited bands at 3350 - 3200 (broad, OH and NH stretching), 1730 - 1700 (lactonic C=O and NHCO), 1530 (C=N) cm^{-1} (Fig.13).

The NMR spectrum (CF_3COOH) exhibited signals at δ 2.2, singlet, methyl protons at C-4 position of coumarin ring δ 2.9, singlet, methyl protons at C-8 position (=C-CH_3) ; singlet at δ 3.7 appeared as two peaks partially resolved (difference 0.03 δ) for methoxy protons ; δ 6.2, singlet of proton at C-3 position of coumarin ring ; multiplet in the region δ 6.9-7.7 for aromatic protons (Fig.14).

Mass spectrum exhibited following fragments :
m/e : 366 (M^+ ion, 20%), 135 (base peak, 100%), 107 (25%),

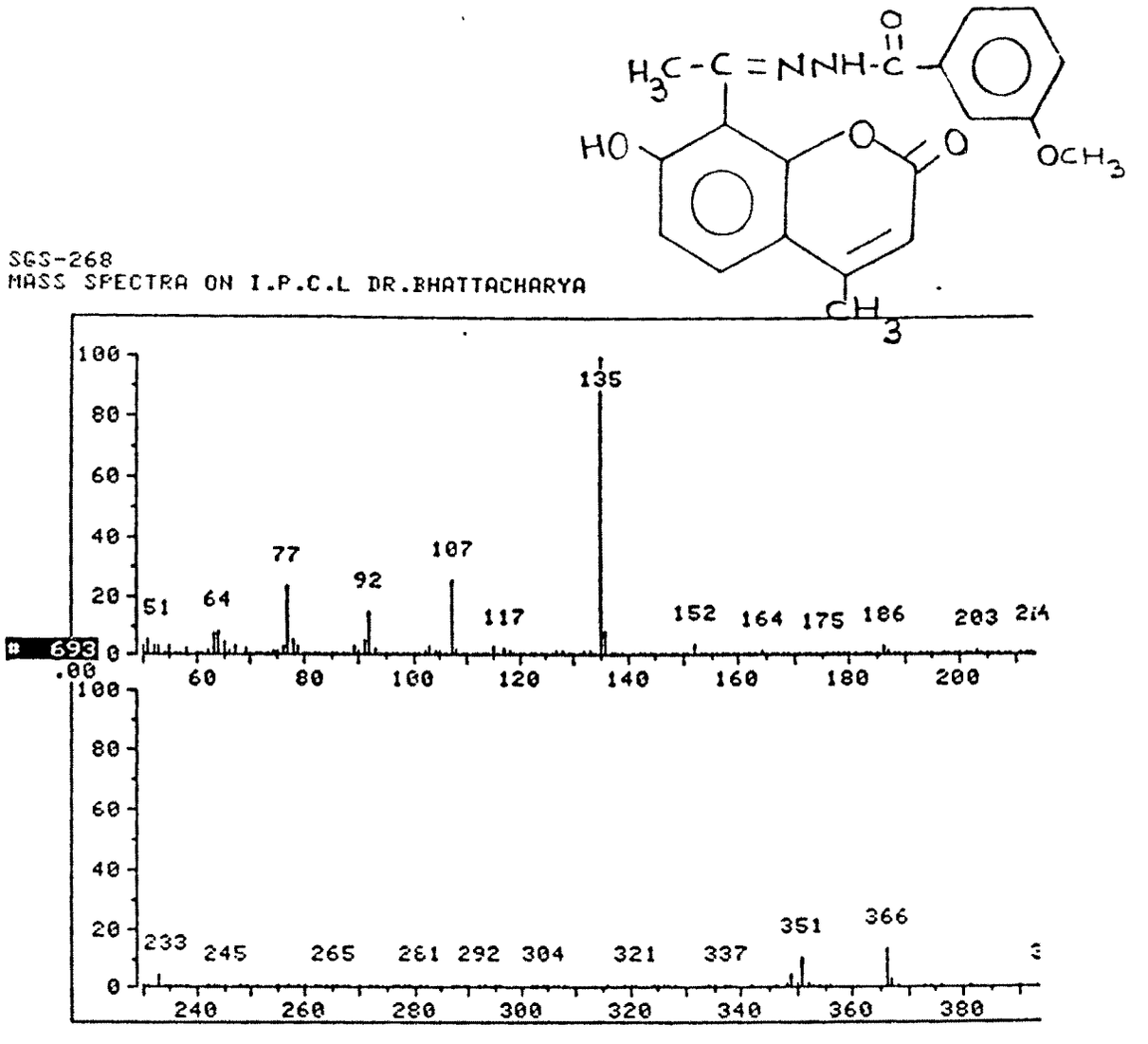


(Fig-13) : 32, Table-IV, 1



(0.3 ppm off set)

(Fig - 15) : 32, Table - IV, 1



(Fig - 15) : 32, Table - IV, 1

77 (22%). (Fig. 15). Thus the structure was confirmed by nmr and mass spectra.

(7-Hydroxy-4-methylcoumarin-8-yl)-ethyldiene-p'-chlorobenzoic acid hydrazone (32, Table-IV, 3)

The condensation of 7-hydroxy-4-methyl-8-acetylcoumarin with p-chloro benzoic acid hydrazide gave above iminomethyl derivative, whose structure was supported by spectral data.

The bands at 3450 - 3000 (broad), 1730 - 1705 (broad), 1590 cm^{-1} were observed in the IR spectrum.

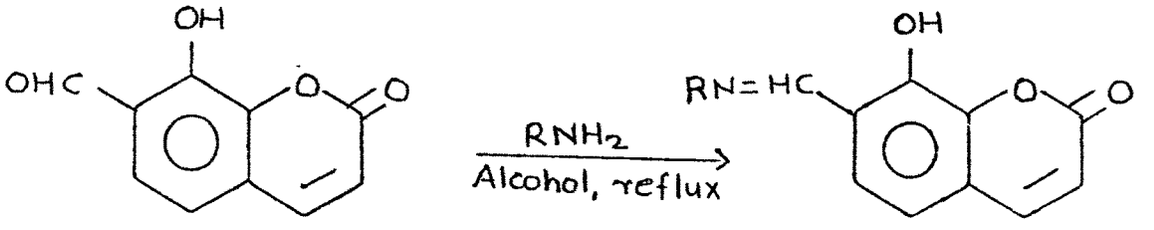
The assigned structure was confirmed by following NMR spectra (CF_3COOH) singlet at δ 2.25, for methyl protons at C-4 position of coumarin ring ; singlet at δ 2.85 for $=C-CH_3$ protons appeared as two peaks partially resolved (difference 0.01 δ) ; δ 6.2, singlet for proton at C-3 position of coumarin ring ; aromatic protons appeared as multiplet in the region δ 7.1-7.8 (Fig.16).

Other hydrazones were synthesised by condensing 7-hydroxy-4-methyl-8-acetylcoumarin and various substituted acid hydrazides in a similar way (32, Table-IV, 1-5).

Antimicrobial activity

Some selected compounds from each series were tested

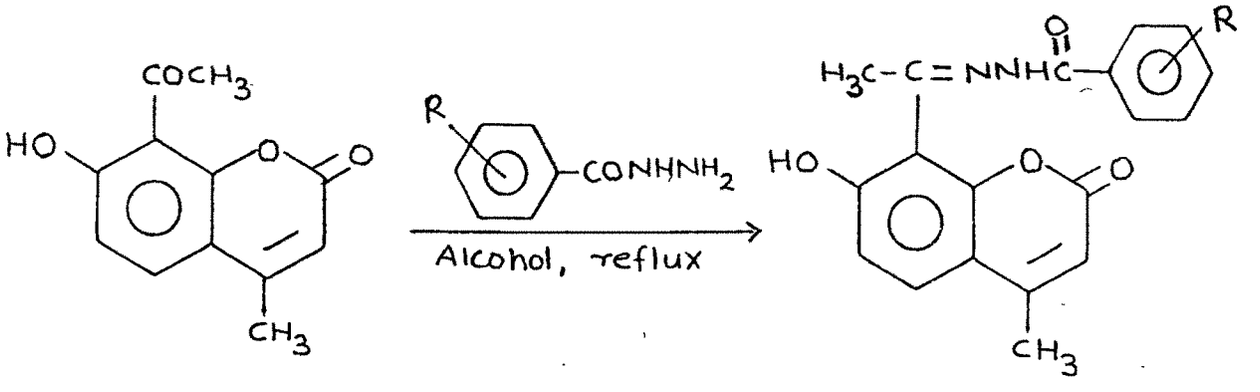
Scheme:3



(31)

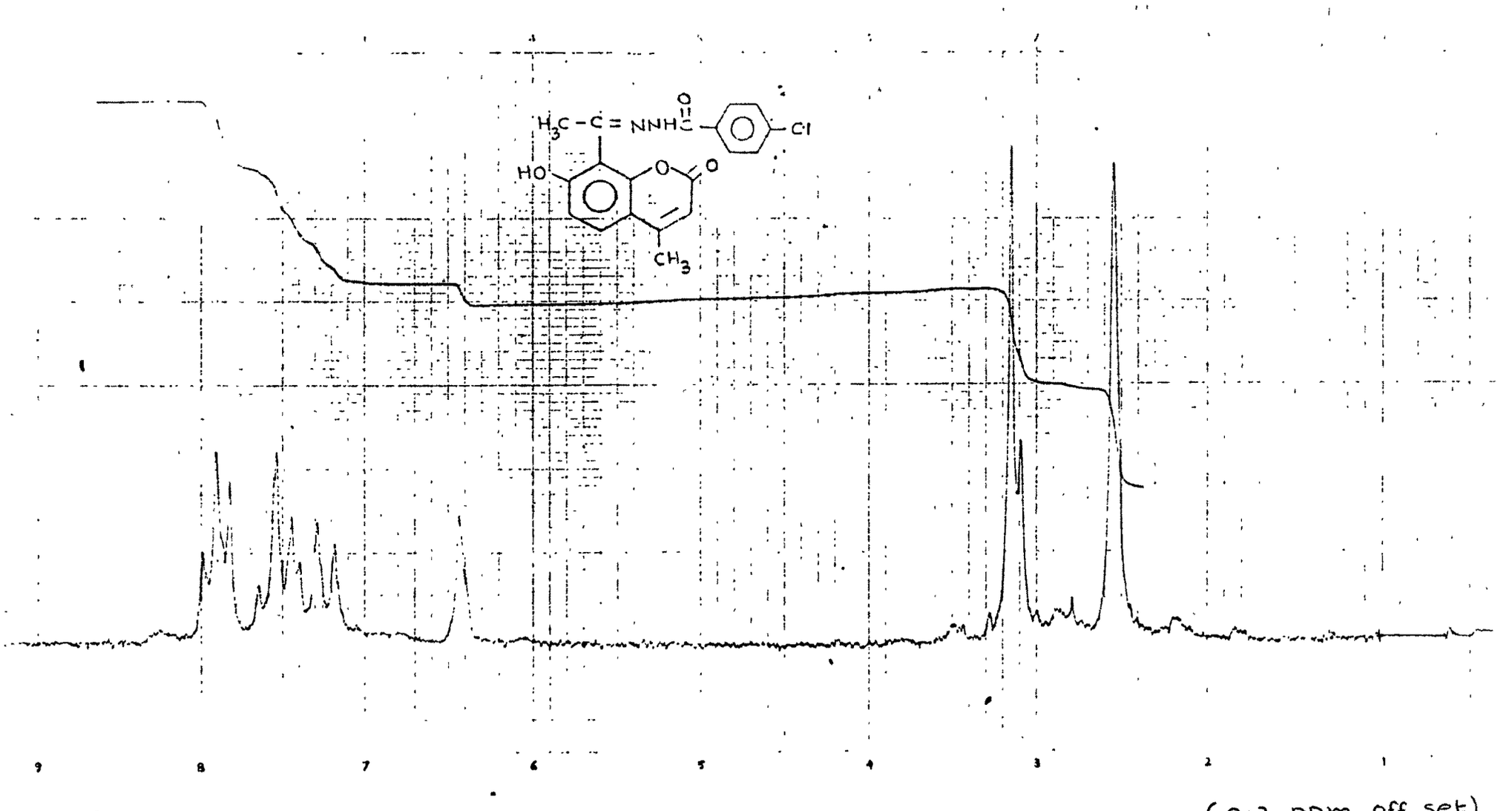
Table - III, 1-4

Scheme:4



(32)

Table - IV, 1-5



(0·3 ppm off set)

(Fig - 16) : 32, Table - IV, 3

EXPERIMENTAL

against E. coli, S. aureus, S. albus and B. subtilis using cup-plate method[77] at concentration 100 and 500 ppm. Some of them showed moderate to good activity. The detailed screening report is given in Chapter-IV, Part-II.

EXPERIMENTAL

All melting points are uncorrected. Microanalysis of compounds were performed ona Coleman instrument, IR spectra (KBr) were taken on a Shimadzu 408 spectrophotometer, NMR spectra were reocrded on a Perkin Elmer R-32 Spectrometer using TMS as the internal standard. Mass spectra were recorded on GCMS Model Hewlett Packard 5985 U.S.A. analysed at 70 ev.

8-Methoxy-5-formylcoumarin (28)

A mixture of 8-methoxy-5-chloromethylcoumarin (1.0 g) and hexamine (5.0 g) was refluxed in chloroform (20 - 25 ml) on a steam bath for 2 h. The separated product was refluxed in acetic acid (20%, 50 ml) on a steam bath for 4 h. The product separated during the reaction was crystallised from 1:1 glacial acetic acid in light yellow needles, M.p. 218°C, yield 75-80%.

Analysis	: Found	: C, 46.59	;	H, 3.61%
$C_{11}H_8O_4$	: requires	: C, 46.71	;	H, 3.92%

N-(8-methoxy-5-coumarilidine)-p'-methylbenzoic acid hydrazone

(29, Table-I, 4)

8-Methoxy-5-formylcoumarin (0.1 g) and p-methyl benzoic acid hydrazide (0.1 g) were refluxed in absolute alcohol (50 ml) with few drops of glacial acetic acid on a sand bath. The yellow product was separated out within 15 miniuts. It was filtered and crystallised from DMF - water mixture in yellow needles. M.p. 233°C, yield 80%.

Analysis : Found : C, 66.56 ; H, 4.19 ; N, 7.79%

$C_{19}H_{16}O_5N$: requires : C, 66.66 ; H, 4.67 ; N, 8.18%

N-(8-methoxy-5-coumarilidine)-p'-nitro benzoic acid hydrazone

(29, Table-I, 7)

A mixture of 8-methoxy-5-formyl coumarin (0.1 g) and p -nitrobenzoic acid hydrazide (0.1 g) was refluxed in absolute alcohol (50 ml) with few drops of glacial acetic acid. The product was separated out within half an hour during the reaction. It was crystallised from DMF - water mixture in yellow needles, M.p. 304°C, yield 73%.

Analysis : Found : C, 58.84 ; H, 3.95 ; N, 10.98%

$C_{18}H_{13}O_6N_3$: requires : C, 58.86 ; H, 3.54 ; N, 11.44%

TABLE - I : ANALYTICAL AND PHYSICAL DATA OF N-(8-METHOXY-5-COUMARILIDINE)-SUBSTITUTED BENZOIC ACID HYDRAZONES (29)

Sr. No.	R	M.P.* °C	Yield %	Molecular Formula	Analysis % Found /(Calcd) C	H	N
1	-m-OCH_3	233^{d+w}	80	$C_{19}H_{16}O_5N_2$	66.56 (66.67)	4.19 (4.68)	7.79 (8.19)
2	-p-OCH_3	242^{d+w}	75	$C_{19}H_{16}O_5N_2$	66.51 (66.67)	4.23 (4.69)	7.99 (8.19)
3	-m-CH_3	275^{d+w}	81	$C_{19}H_{16}O_4N_2$	67.66 (67.86)	4.53 (4.76)	8.01 (8.33)
4	-p-CH_3	257^{d+w}	75	$C_{19}H_{16}O_4N_2$	65.56 (67.86)	5.17 (4.76)	8.11 (8.33)
5	-o-NO_2	293^{d+w}	86	$C_{18}H_{13}O_6N_3$	58.71 (58.86)	3.13 (3.54)	11.10 (11.44)
6	-m-NO_2	214^{d+w}	75	$C_{18}H_{13}O_6N_3$	58.53 (58.86)	3.43 (3.54)	10.96 (11.44)
7	-p-NO_2	304^{d+w}	73	$C_{18}H_{13}O_6N_3$	58.84 (58.86)	3.95 (3.54)	10.98 (11.44)

cont..

Table - I cont....

8.	-o-Cl	225^{d+w}	85	$C_{18}H_{13}O_4N_2Cl$	60.51 (60.67)	3.23 (3.65)	7.67 (7.87)
9.	-p-Cl	257^{d+w}	80	$C_{18}H_{13}O_4N_2Cl$	60.32 (60.67)	3.40 (3.65)	7.62 (7.87)
10.	-m-Br	222^{d+w}	82	$C_{18}H_{13}O_4N_2Br$	54.31 (53.87)	3.70 (3.24)	6.53 (6.98)
11.	-p-OH	285^{d+w}	85	$C_{18}H_{14}O_5N_2$	63.73 (63.91)	4.04 (4.14)	8.1 (8.28)
12.	-p-NH_2	278^{d+w}	89	$C_{18}H_{15}O_4N_3$	63.75 (64.09)	4.32 (4.45)	12.1 (12.46)
13.	-Thiosemicarbazide	275^{d+w}	75	$C_{12}H_{11}O_3N_3S$	52.20 (51.99)	4.45 (3.97)	15.51 (15.16)
14.	-Semicarbazide hydrochloride	$>300^{d}$	75	$C_{12}H_{11}O_4N_3$	55.65 (55.17)	4.51 (4.21)	15.64 (16.09)

---

* Solvent of crystallisation : d = DMF ; w = Water

8-Methoxy-5-[o-(N-5'-bromo-salicylidine)]anilinomethyl coumarin (3O, Table-II, 1O)

A mixture of 8-methoxy-5-(o-amino)-anilinomethyl coumarin (O.2 g) (2O, Chapter-II, Part-II), and 5-bromo salicylaldehyde (O.2 g) was heated in absolute alcohol (5O ml) for 7-8 h. The excess alcohol was removed by vacuum distillation. The product was obtained on cooling and it crystallised from DMF - water mixture, M.p. 213°C, yield 65%.

Analysis : Found : C, 6O.33 ; H, 3.96 ; N, 5.84%

$C_{24}H_{19}O_4N_2Br$: requires : C, 6O.12 ; H, 4.39 ; N, 5.7O%

8-Methoxy-5-[o-(N-piperonalidine)] anilinomethyl coumarin (3O, Table-II, 12)

8-Methoxy-5-(o-amino)-anilinomethyl coumarin (O.2 g) piperonal (O.2 g) and absolute alcohol (5O ml) were heated under reflux for 7-8 h. The product was obtained on removal of excess of solvent which was crystallised from DMF - alcohol mixture, M.p. 242°C, yield 75%

Analysis : Found : C, 69.74 ; H, 4.54 ; N, 6.37%

$C_{25}H_{2O}O_5N_2$: requires : C, 7O.O9 ; H, 4.67 ; N, 6.54%

TABLE - II : ANALYTICAL AND PHYSICAL DATA OF 8-METHOXY-5-[o-(N-arylidine)]-anilino-methyl coumarin (30)

Sr. No.	R	M.p.* °C	Yield %	Molecular formula	Analysis % Found/(Calcd)		
					C	H	N
1.	CH_3 -	266^{d+w}	65	$C_{19}H_{18}O_3N_2$	70.51 (70.81)	5.63 (5.59)	8.17 (8.69)
2.	p-CH_2-C_6H_4-	235^{a}	60	$C_{25}H_{22}O_3N_2$	74.91 (75.38)	5.41 (5.53)	6.88 (7.04)
3.	p-OCH_3-C_6H_4-	177^{a+b}	60	$C_{25}H_{22}O_4N_2$	71.98 (72.46)	5.30 (5.31)	6.32 (6.76)
4.	2,3-$(OCH_3)_2$-C_6H_3-	234^{d+w}	60	$C_{26}H_{24}O_5N_2$	67.69 (67.24)	4.98 (5.17)	6.44 (6.03)
5.	o-NO_2-C_6H_4-	210^{d+w}	80	$C_{24}H_{19}O_5N_3$	66.67 (67.13)	4.59 (9.65)	9.65 (9.79)
6.	m-NO_2-C_6H_4-	225^{d+w}	73	$C_{24}H_{19}O_5N_3$	66.71 (67.13)	4.23 (4.43)	9.96 (9.79)
7.	p-NO_2-C_6H_4-	272^{d+w}	75	$C_{24}H_{19}O_5N_3$	66.92 (67.13)	4.13 (4.43)	9.38 (9.79)

cont.....

TABLE - II Cont...

8.	o-OH-C_6H_4-	228[a+d]	60	$C_{24}H_{20}O_4N_2$	72.08 (72.00)	4.76 (5.00)	6.62 (7.00)
9.	p-OH-C_6H_4-	278[d+w]	73	$C_{29}H_{20}O_4N_2$	71.90 (72.00)	5.12 (5.00)	6.74 (7.00)
10.	2-OH-5-Br-C_6H_3-	213[d+w]	65	$C_{24}H_{19}O_4N_2Br$	60.33 (60.13)	3.97 (4.39)	5.85 (5.70)
11.	p-Cl-C_6H_4-	285[d+w]	57	$C_{24}H_{19}O_3N_2Cl$	68.49 (68.89)	4.92 (4.55)	6.62 (6.69)
12.	Piperonal	242[a+d]	75	$C_{25}H_{20}O_5N_2$	69.74 (70.09)	4.54 (4.67)	6.37 (6.54)

* Solvent of crystallisation : a = alcohol,
b = benzene,
d = DMF
w = water

7-(Phenyl iminomethyl)-8-hydroxy coumarin (31, Table-III, 1)

A mixture of 8-hydroxy-7-formylcoumarin (0.1 g) and aniline (0.1 g) was refluxed in alcohol (50 ml) with few drops of glacial acetic acid for 6 h. The product obtained on cooling was crystallised from alcoholin orange colour crystals. M.p. 209°C, yield 85%.

Analysis : Found : C, 72.63 ; H, 4.34 ; N, 4.85%

$C_{16}H_{11}O_3N$: requires : C, 72.45 ; H, 4.15 ; N, 5.28%

(7-Hydroxy-4-methylcoumarin-8-yl) ethylidene-m-anisic acid hydrazone (32, Table-IV, 1)

A mixture of 7-hydroxy-4-methyl-8-acetylcoumarin (0.2 g) and m -anisic acid hydrazide (0.2 g) was refluxed in alcohol (50 ml) with few drops of glacial acetic acid on a sand bath. The product was separated within half an hour and crystallised from 1:1 DMF. M.p. 235°C, yield 75%.

Analysis : Found : C, 65.74 ; H, 5.31 ; N, 7.15%

$C_{20}H_{18}O_5N_2$: requires : C, 65.57 ; H, 4.91 ; N, 7.65%

(7-Hydroxy-4-methyl coumarin-8-yl) ethylidine-p'-chlorobenzoic acid hydrazone (32, Table-IV, 3)

7-hydroxy-4-methyl-8-acetylcoumarin (0.2 g)

was treated with p -chloro benzoic acid hydrazide (0.2 g) in alcohol (50 ml) with few drops of glacial acetic acid. The product was separated out within half an hour. It was filtered and crystallised from DMF - water mixture, M.p. 283°C, yield 80%

Analysis	: Found	: C, 61.67	; H, 4.50	; N, 7.27%
$C_{19}H_{15}O_4N_2Cl$	: requires	: C, 61.62	; H, 4.05	; N, 7.56%

TABLE - III : ANALYTICAL AND PHYSICAL DATA OF 7-(ARYLIMINOMETHYL)-8-HYDROXY COUMARIN (31)

Sr. No.	R	M.P.* °C	Yield %	Molecular formula	Analysis % Found (Calcd) C	H	N
1	C_6H_5-	209[a]	85	$C_{16}H_{11}O_3N$	72.63 (72.45)	4.34 (4.15)	4.86 (5.28)
2	p-Br-C_6H_4-	218[a+w]	85	$C_{16}H_{10}O_3NBr$	55.50 (55.81)	2.70 (2.91)	4.57 (4.07)
3	p-NO_2-C_6H_4-	232[a+d]	80	$C_{16}H_{10}O_5N_3$	61.35 (61.94)	3.44 (3.23)	8.91 (9.03)
4	o-Cl-NHCO-C_6H_4-	235[a+w]	75	$C_{17}H_{11}O_4N_2Cl$	59.33 (59.65)	3.48 (3.22)	7.96 (8.19)

* Solvent of crystallisation : a = alcohol,
d = DMF
w = water

TABLE - IV : ANALYTICAL AND PHYSICAL DATA OF (7-HYDROXY-4-METHYL-8-YL)-SUBSTITUTED BENZOIC ACID HYDRAZONES (32)

Sr. No.	R	M.P.* °C	Yield %	Molecular Formula	Analysis % found/(calcd) C	H	N
1	-m-OCH_3	235^{d+w}	75	$C_{20}H_{18}O_5N_2$	65.74 (65.57)	5.31 (4.92)	7.16 (7.65)
2	-m-Br	284^{d+w}	81	$C_{19}H_{15}O_4N_2Br$	54.82 (54.94)	3.97 (3.61)	6.52 (6.75)
3	-p-Cl	283^{d+w}	80	$C_{19}H_{15}O_4N_2Cl$	61.67 (61.62)	4.51 (4.05)	7.23 (7.57)
4	-p-OH	300^{d+w}	65	$C_{19}H_{16}O_5N_2$	64.53 (64.77)	4.12 (4.55)	7.81 (7.96)
5	-p-NH_2	277^{d+w}	75	$C_{18}H_{17}O_4N_3$	64.16 (63.72)	5.37 (5.02)	11.90 (12.39)

* Solvent of crystallisation : d = DMF
w = water

PART – II

SYNTHESIS OF SOME OXADIAZOLYL COUMARINS AND HYDRAZIDES OF COUMARIN DERIVATIVES

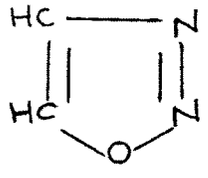
CHAPTER - III

PART-II : SYNTHESIS OF OXADIAZOLYLCOUMARINS AND HYDRAZIDES OF COUMARIN DERIVATIVES

OXADIAZOLES

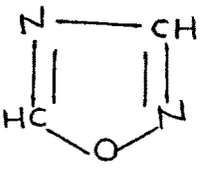
INTRODUCTION

There are four types of oxadiazoles, each of the four oxadiazole rings contains two carbon atoms, two nitrogen atoms and one oxygen atom.



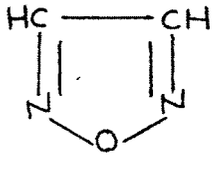
(1)

1,2,3-Oxadiazole
(diazoxide)



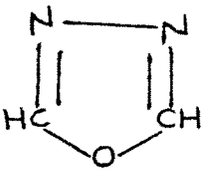
(2)

1,2,4-Oxadiazole
(azoxime)



(3)

1,2,5-Oxadiazole
(azoxazole) (furazan)



(4)

1,3,4-Oxadiazole
(Oxadiazole)(Oxybiazole)

Most derivatives of 1,2,3-oxadiazole appear to be isomeric ∝-diazocarbonyl compounds. Natural products with oxadiazole rings are unknown.

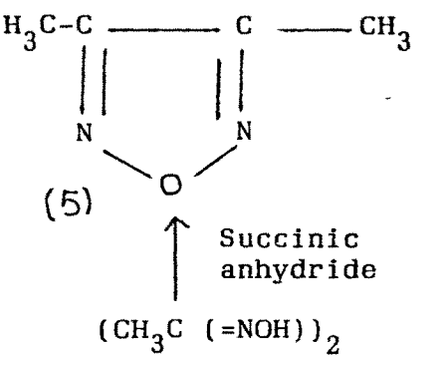
1,2,5-OXADIAZOLES (FURAZAN)

PREPARATIONS

(1) Dehydration of Glyoximes

Furazans (5), (6) have been obtained when glyoximes are heated with water,[1] aqueous ammonia or sodium hydroxide,[2] urea,[3] acetic[4] or succinic anhydride[5] or phosphorous oxychloride.[6] Other acid dehydrating agents appear to be unsuccessful[5] and the action of phosphorous oxychloride on glyoximes has brought about the formation of 1,2,4-oxadiazoles.[7] Other methods include the treatment of either ∝ or β-benzil dioxime with copper sulfate[8] or prolonged exposure of ∝-benzil dioxime in dilute alkali to tropical sunlight.[9] Glyoxime diesters may be transformed by alkali[10,11] or by steam distillation[12] into furazans (7). Furazans can also be obtained from the combination of hydroxylamine or 1,2-dicarbonyl derivatives.[13]

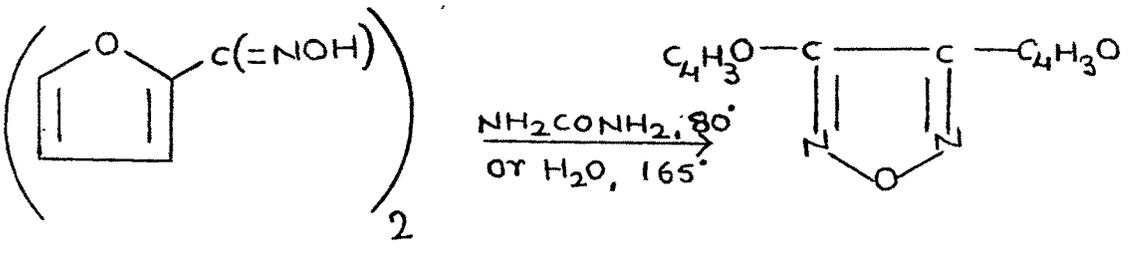
$(CH_3C(=NOH))_2 \xrightarrow[\text{or NaOH}]{NH_4OH} \underset{160°C}{}$



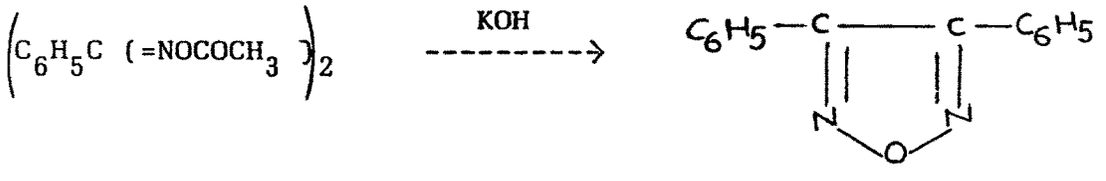
(5)

Succinic anhydride

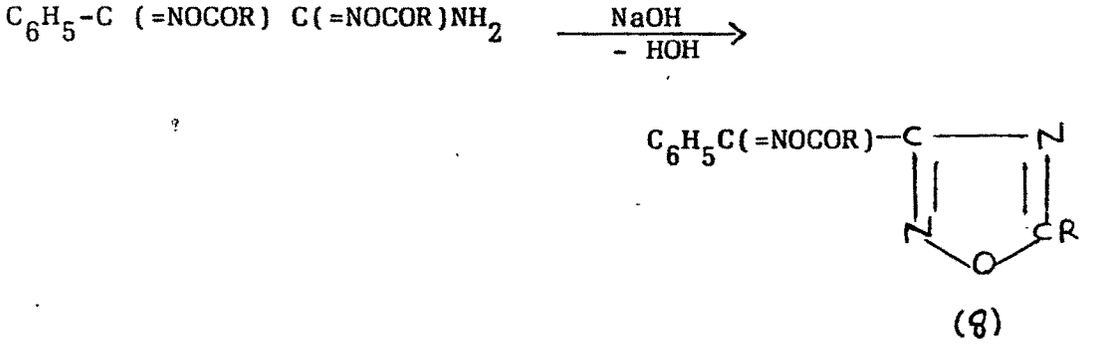
$(CH_3C(=NOH))_2$



(6)

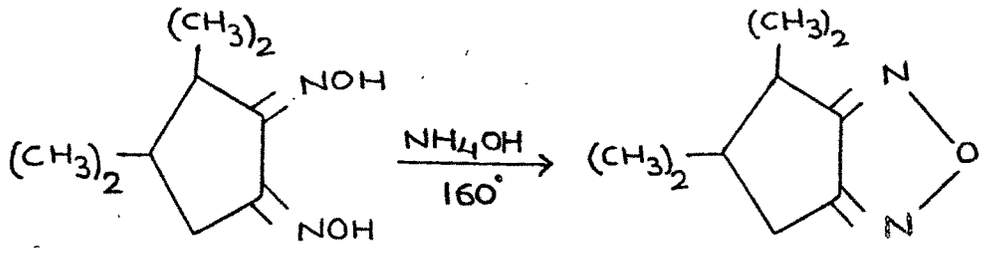


(7)



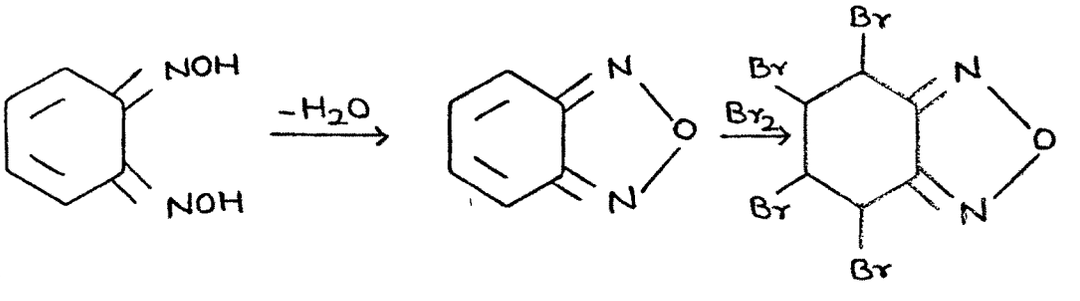
(8)

Dehydration of the dioxime (9) into the furazan (10) occur in presence of ammonia[14] in which furazan ring is fused to a nonaromatic five-membered ring.



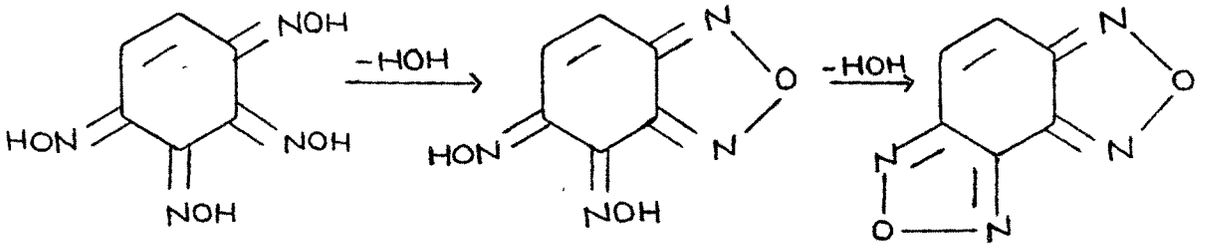
(9) (10)

Tetrabromotetramethylenefuran (12) has been obtained from benzofurazan (11) and bromine.[15]

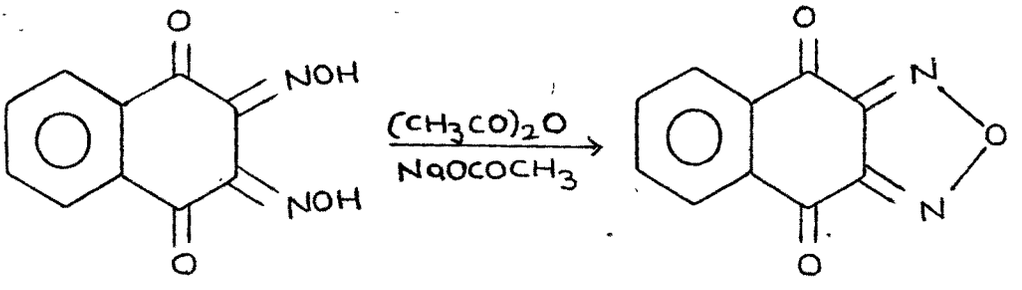


(11) (12)

Dehydrogenation with acetic anhydride transforms the tetraoxime (13) into the angular tricyclic furazan (14)[16] and the dioxime (15) of tetraketotetrahydronaphthalene into the furazan (16).[4]

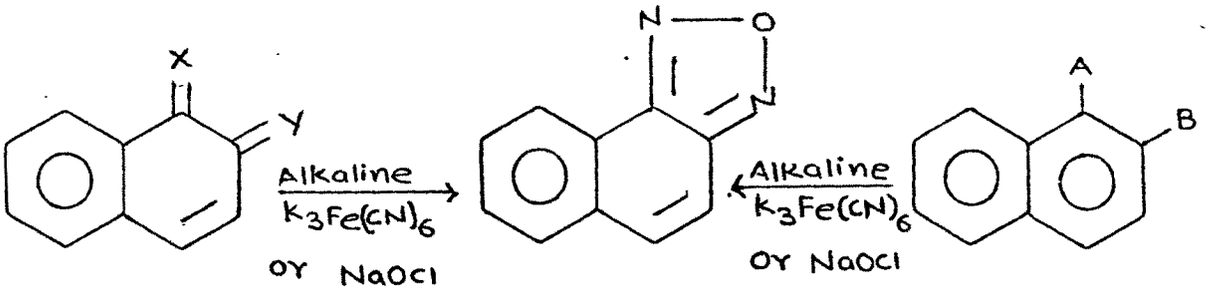


(13) (14)



(15) (16)

Alkaline ferricyanide or hypochlorite oxidation of both 1-nitroso-2-amino- and 1-amino-2-nitroso-naphthalene leads to the same furazan (17).[17,18]



(17)

X = NOH Y = NH

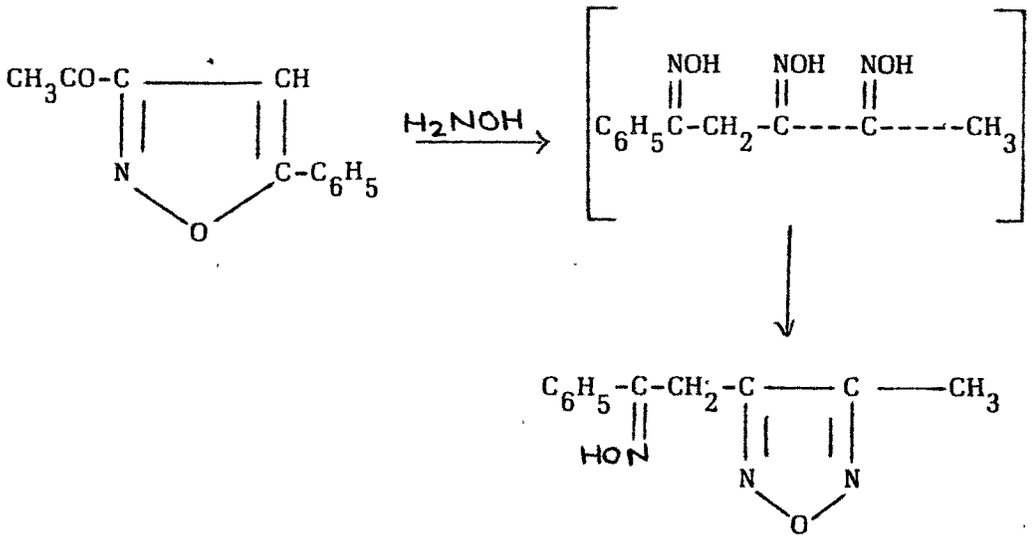
X = NH Y = NOH

A=NO, B = NH_2

A=NH_2, B = NO

(2) Ring Transformations

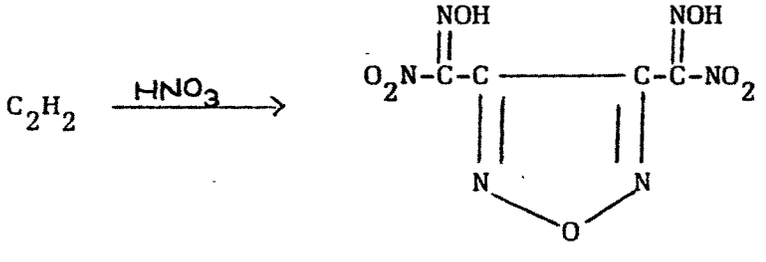
Certain acylisoxazole undergo ring opening followed by furazan formation (18) on treatment with alkaline hydroxylamine.[19]



(18)

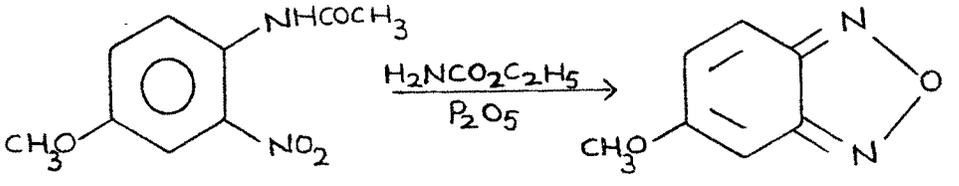
(3) Miscellaneous Methods

In addition to isoxazoles from acetylene and nitric acid in the presence of acetone, it has been found that reaction of acetylene with nitric acid leads to furazans, one of which may be furazandinitrolic acid (19).[20]



(19)

5-Methoxybenzofurazan (20) prepared by the treatment of 2-nitro-4-methoxyacetanilide with ethyl carbamate and phosphorus pentoxide in boiling xylene.[21]



(20)

PHYSICAL PROPERTIES

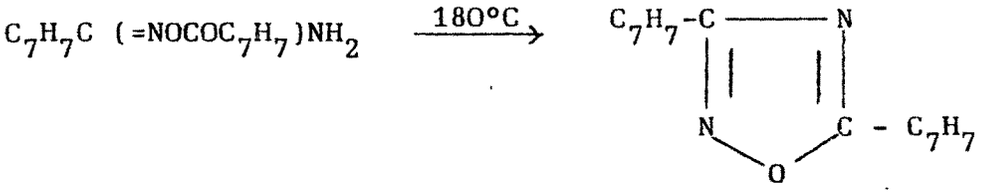
The IR absorption[22] of the ring allows a band at 1380 cm^{-1} to be characteristic of the pentatomic nucleus. A Furazan band at 1570 cm^{-1} is assigned to the five membered ring. A band at 1030 cm^{-1} found in 1,2,4- and 1,3,4-oxadiazoles but not in furazans is attributed to the C-O bond. Furazan absorption in the region 1430 to 1385 cm^{-1} has been assigned the N-O bond.[23]

1,2,4-OXADIAZOLES

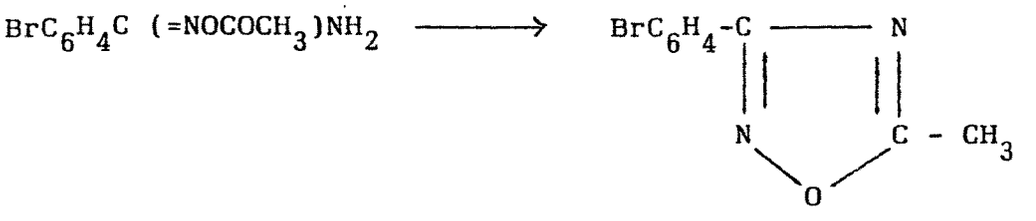
PREPARATIONS

(1) Pyrolysis of amidoximes and their esters

A more general preparation for certain disubstituted 1,2,4-oxadiazoles is found in the pyrolysis of amidoxime esters. e.g. the o-toluic ester of o-tolylamidoxime gives 3,5-di (o-tolyl) 1,2,4-oxadiazole (21)[24] and the acetate ester of p-bromobenzamidoxime gives 3-(p-bromophenyl)-5-methyl-1,2,4-oxadiazole (22).[25]

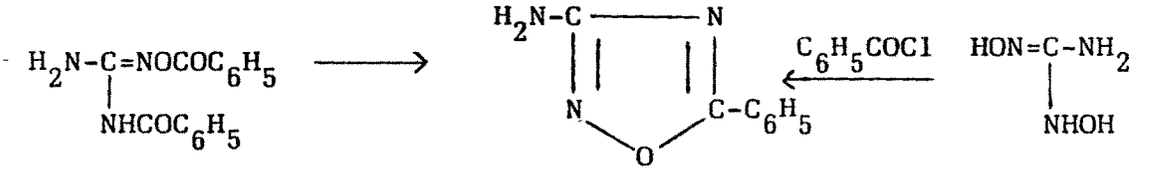


(21)



(22)

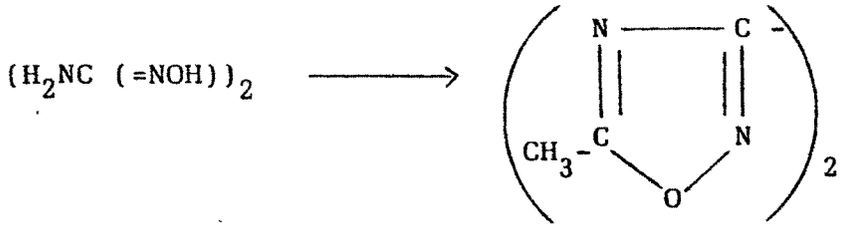
An unequivocal synthesis of 3-amino-5-phenyl-1,2,4-oxadiazole (23) consists in the treatment of dihydroxyguanidine hydrobromide with benzoyl chloride and sodium bicarbonate.[26,27] The same product is obtained on hydrolysis of N, o-dibenzoylhydroxyguanidine.[27]



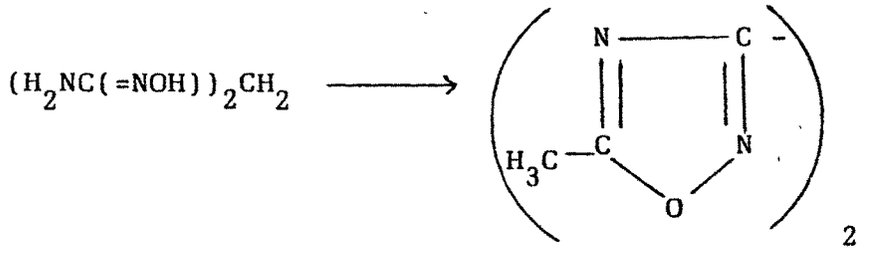
(23)

Aliphatic amidoxime like mandelamidoxime with acetic anhydride,[28] acetamidoxime with benzoyl chloride[29] and malonic

monoamidoxime with benzoic acid[30] give the expected oxadiazoles(24), (25).



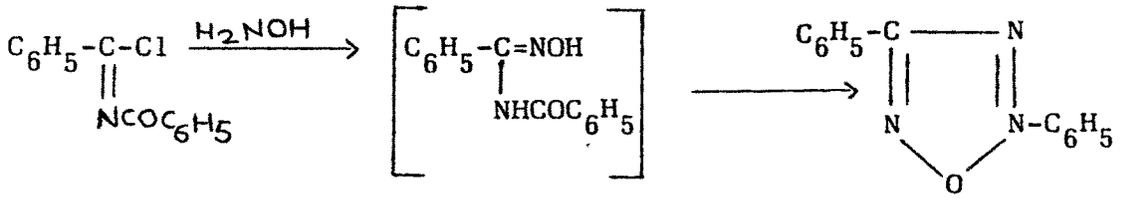
(24)



(25)

(2) Ring closure of monoximes of diacylamides

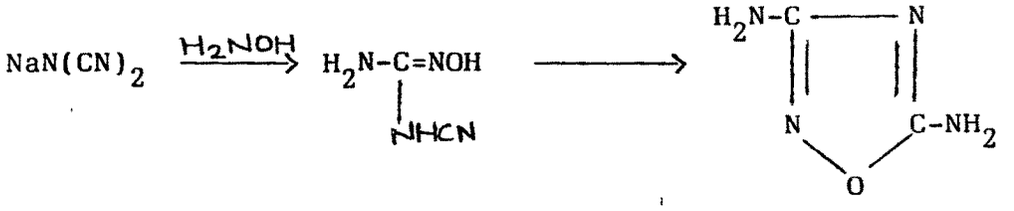
The imidyl chloride of dibenzamide with hydroxylamine gives 3,5-diphenyl-1,2,4-oxadiazole (26).[31]



(26)

A probable intermediate is an oxime of dibenzamide.

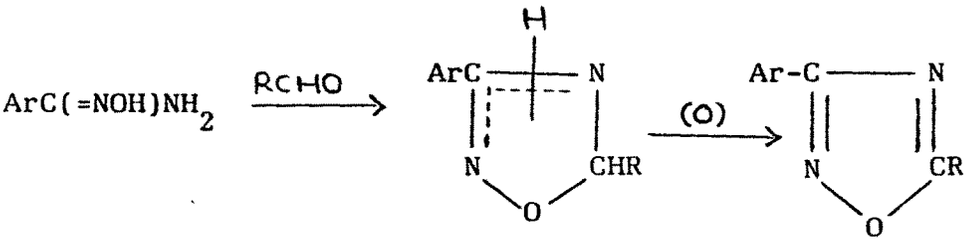
An oxime of a diacylamide may be an intermediate in the preparation of diamino 1,2,4-oxadiazole (27) from sodium dicyanamide and hydroxylamine.[32]



(27)

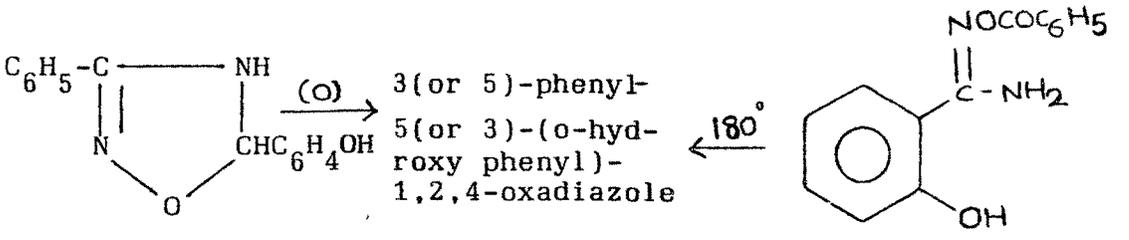
(3) Oxidation of 1,2,4-oxadiazolines

Aromatic amidoximes have been condensed with acetaldehyde[33-37] propionaldehyde,[38] isobutyraldehyde,[38] phenylacetaldehyde[38] and salicylaldehyde[38] to give dihydro-1,2,4-oxadiazoles. α, β-Dichloroethyl ether may be substituted for acetaldehyde.[38] The products are oxidised with permanganate to 3,5-disubstituted 1,2,4-oxadiazoles (28).



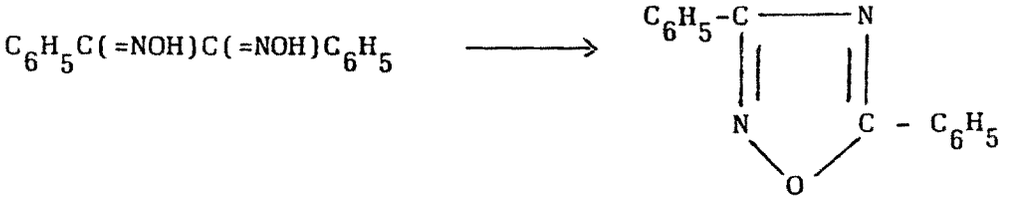
(28)

It is reported that the same oxadiazole results from the oxidation of condensation product from benzamidoxime and salicylaldehyde[38] and from heating the oxime benzoate ester of salicylamidoxime.[39]



(4) Dehydration with rearrangement of glyoximes

In polyphosphoric acid, ∝-benzildioxime gives predominantly diphenyl 1,2,4-oxadiazole (29). Other reagents which transform ∝-benzildioxime into diphenyl-1,2,4-oxadiazole include sulfuric acid, hydrogen chloride in acetic acid, phosphorus pentoxide in benzené and phosphorus pentachloride or pentabromide or phosphorus oxychloride.[40]

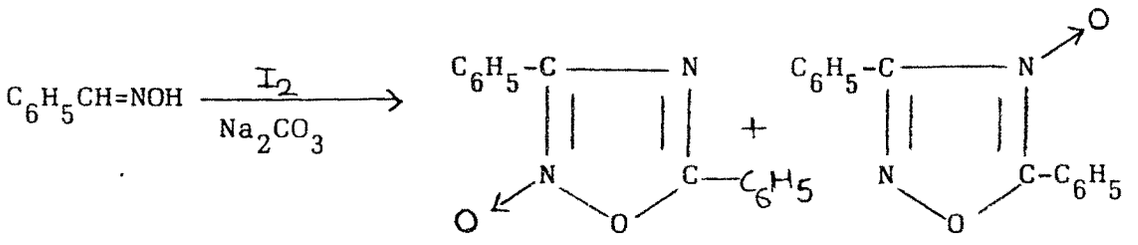


(29)

In the presence of phosphorus oxychloride, phenylaminoglyoxime gives 3-phenyl-5-amino-1,2,4-oxadiazole.[6,7]

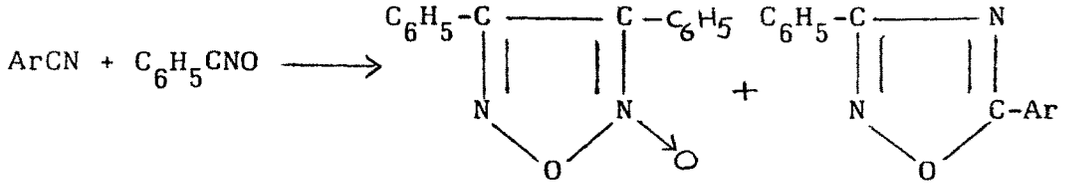
(5) Addition of nitrile oxides of nitriles

Iodine in aqueous sodium carbonate transforms benzaldoxime into the two isomeric N-oxide derivatives of 3,5-diphenyl-1,2,4-oxadiazole-3-oxide.[41] One of which (30) is obtainedfrom the ammonium salt of benzonitrosolic acid in nitric or hydrochloric acid.[42]



(30)

The combination of benzonitrile oxide and an aromatic nitrile in ether leads to the formation of diphenylfuroxan (31) and 3-phenyl-5-aryl-1,2,4-oxadiazole (32).[43]



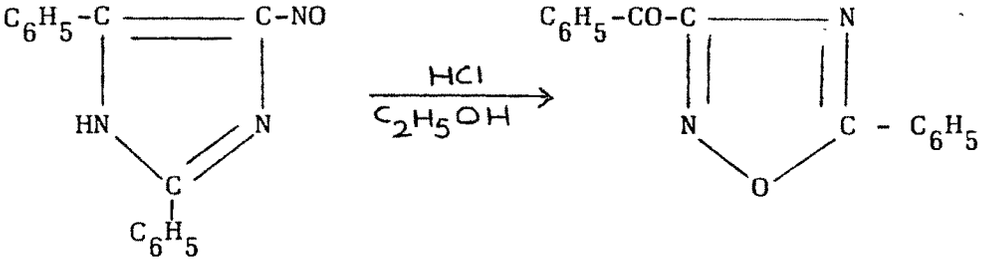
(31) (32)

The transformation of aromatic aldoximes into 3,5-diaryl-1,2,4-oxadiazoles by alkyl nitrites,[44] monopersulfuric acid,[45] alkaline ferricyanide[46] or alkaline hypochlorite.[47]

(6) Ring transformations

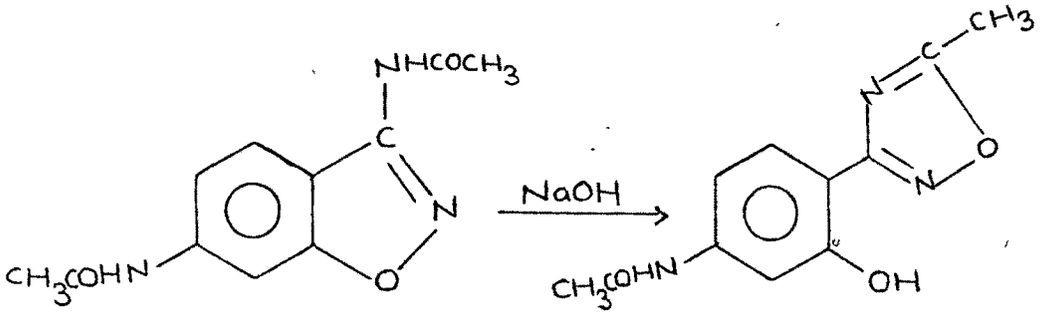
The rings which enter into reactions leading to the formation of 1,2,4-oxadiazole are imidazoles, isoxazoles, pyrroles and pyrimidines.

In alcoholic hydrochloric acid, 2,5 (or 4) diphenyl-4- (or 5)-nitrosoimidazole (33) is changed into 3-benzoyl-5-phenyl-1,2,4-oxadiazole (34).[48]



(33) (34)

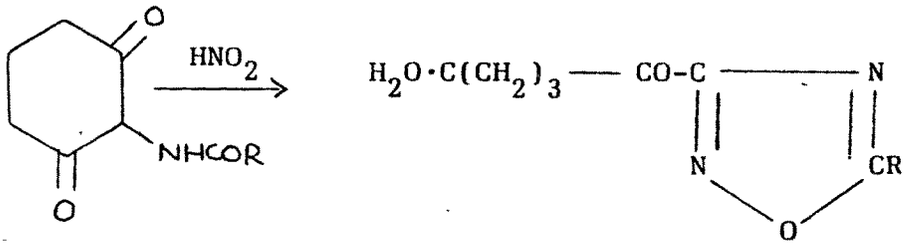
From 3,6-diacetamidobenzisoxazole (35) in sodium hydroxide solution 3-(2-hydroxy-4-acetamidophenyl)-5-methyl-1,2,4-oxadiazole (36) has been obtained.[49]



(35) (36)

(7) Miscellaneous preparations

Nitrous acid transforms N-acyl derivatives of 2-amino-1,3-cyclohexanedione (37) into 3-(ω-carboxybutyryl)-5-substituted 1,2,4-oxadiazole (38).[50]



(37) (38)

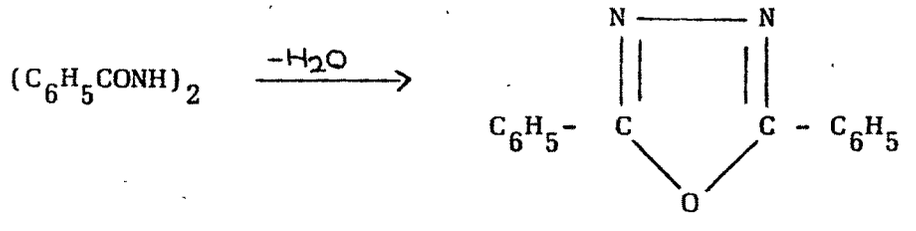
A combination of β-phenylhydroxylamine acetaldehyde and benzaldehyde in sodium hydroxide solution gives the N-phenyl nitrone of cinamaldehyde. This combines with phenyl isocyanate to give 2,4-diphenyl-3-styryl-5-keto-tetrahydro-1,2,4-oxadiazole.[51]

1,3,4-OXADIAZOLES

PREPARATIONS

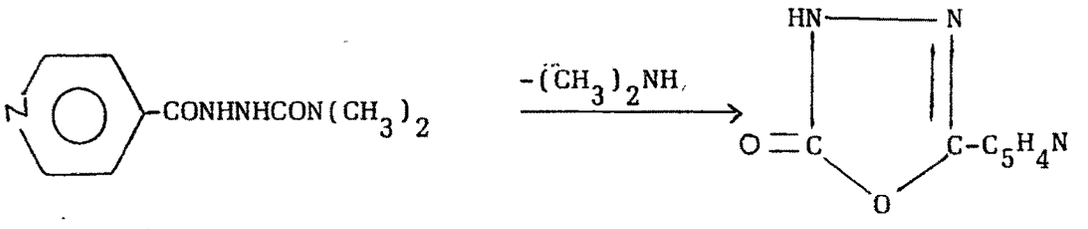
(1) Dehydration of 1,2-Diacylhydrazines[52]

Cyclodehydration of dibenzoylhydrazine gives 2,5-diphenyl-1,3,4-oxadiazoles (39).[53]



(38)

In refluxing pyridine 4,4-dimethyl-1-isonicotinyl-semicarbazide gives 5-(4-pyridyl)-1,3,4-oxadiazol -2(3H)-one (40).[54]

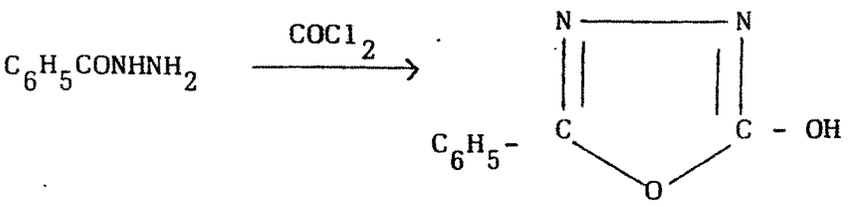


(40)

Dehydrating agents including chlorosulfonic acid,[55] sulfuryl chloride,[55] phosphorus pentoxide, p-toluenesulfonic acid,[55] tosyl chloride,[55] thionyl chloride,[56] phosphorus oxychloride,[56,57] zinc chloride,[58] organic acid anhydrides[59] phosphorus pentachloride[60] and sulfuric acid[61] have been successful in bringing about the formation of 1,3,4-oxadiazole rings.

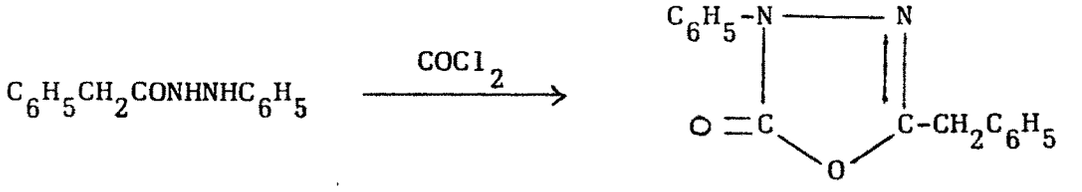
(2) Hydrazides and Phosgene

Hydroxy-1,3,4-oxadiazoles or 3-substituted-1,3,4-oxadiazoles-2 are obtained from appropriate hydrazides and phosgene. Benzoyl hydrazide and phosgene in chloroform give 2-phenyl-5-hydroxy-1,3,4-oxadiazole (41).[62,63] Similarly, aromatic, heterocyclic[64] or alkyl[65] groups may be substituted at the 2-position in 5-hydroxy-1,3,4-oxadiazoles.



(41)

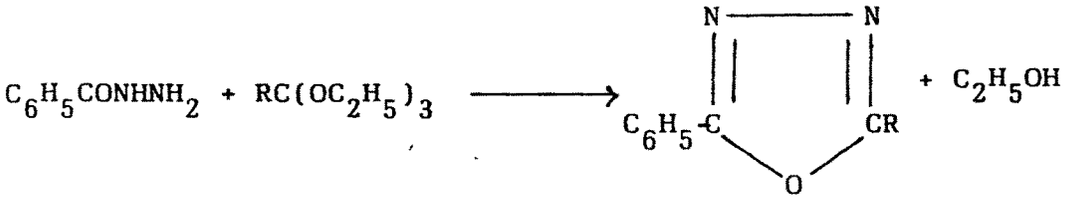
Substituted hydrazides with phosgene give 3-substituted-1,3,4-oxadiazolones, e.g. from the phenylhydrazide of phenylacetic acid, 3-phenyl-5-benzyl-1,3,4-oxadiazolone-2 is obtained (42).[66,67]



(42)

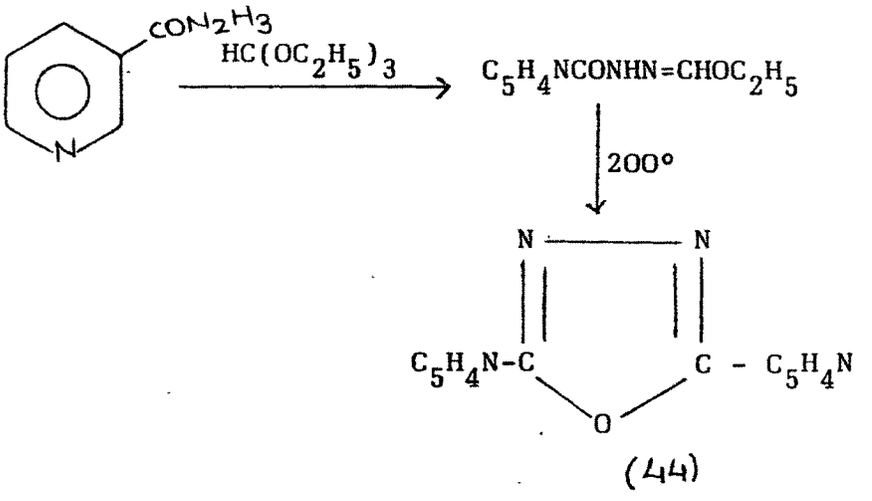
(3) Ortho esters and aryl carboxylic acid hydrazides

Monosubstituted 1,3,4-oxadiazoles may be prepared by the condensation of an aromatic carboxylic acid hydrazide with excess ethyl orthoformate.[68]



(43)

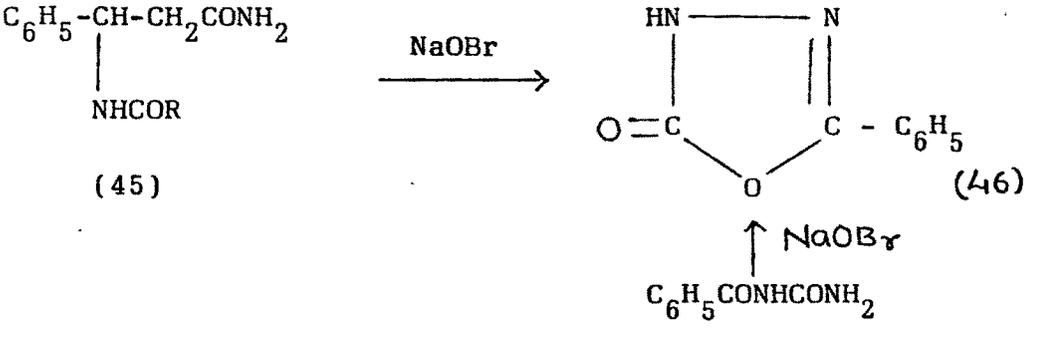
From higher ortho esters corresponding 2-alkyl-5-aryl-1,3,4-oxadiazoles are obtained.[68] (43).



(44)

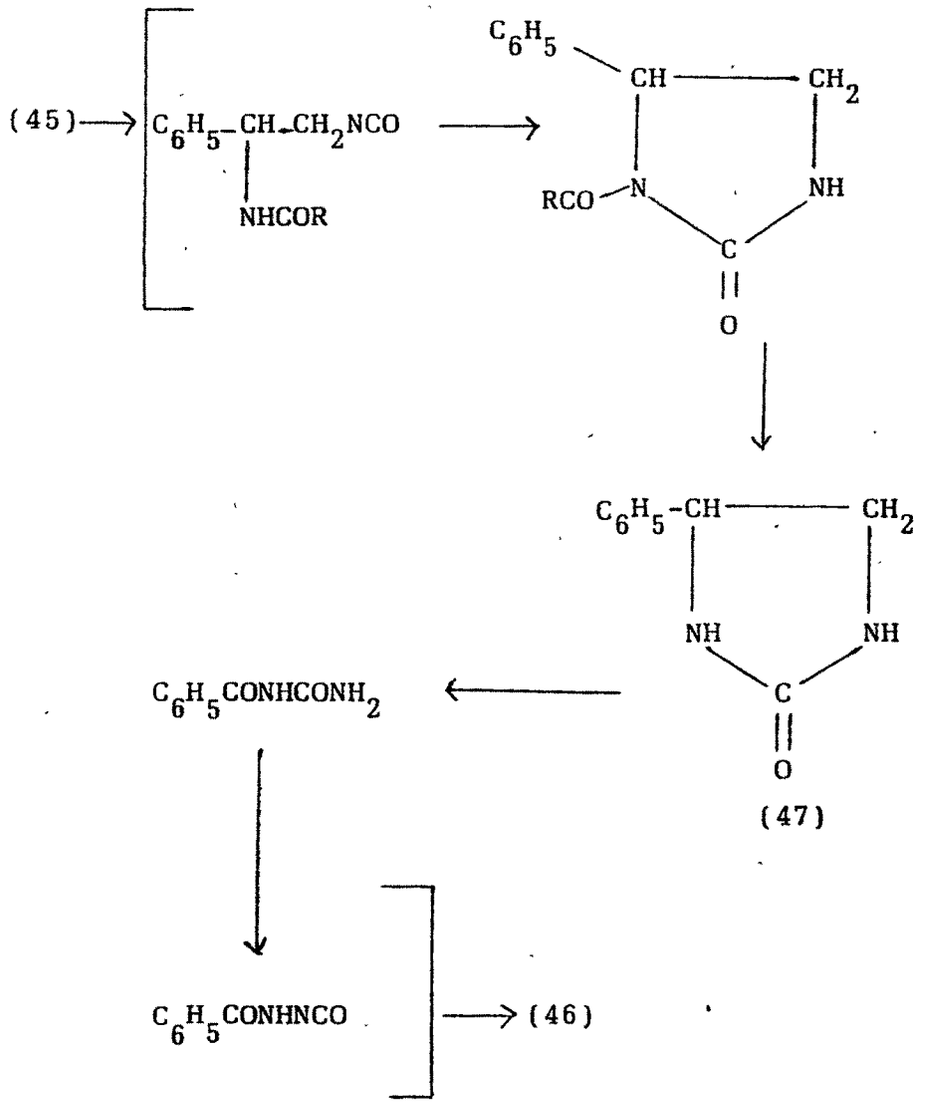
(4) Hofmann-reaction on amides of N-acyl-β-aryl-β-alanines

Alkaline hypobromite transforms the amide N-acyl-β-phenyl-β-alanine into 5-phenyl-1,3,4-oxadiazol-2(3H)-one (40) identical with the product of the hypobromite reaction with benzoylurea.[69]



(45) (46)

The product (46) was obtained from the Hofmann reaction with (47).[69]

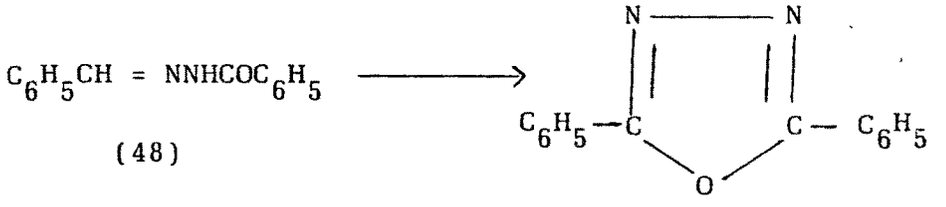


(47)

(5) Oxidation of hydrazones

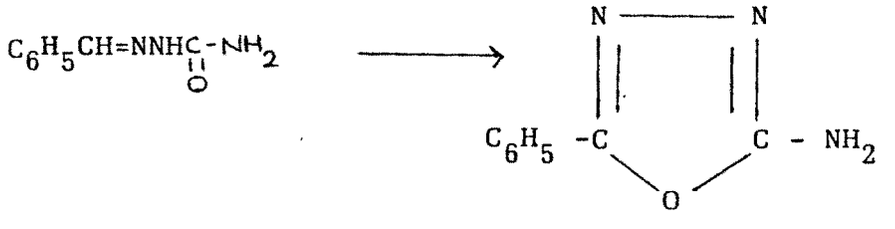
An alkaline solution of both potassium ferricyanide and isoamyl nitrite will transform benzoylhydrazone of benzaldehyde (48) into a 2,5-diphenyl-

1,3,4-oxadiazole (49).[70]



(48) (49)

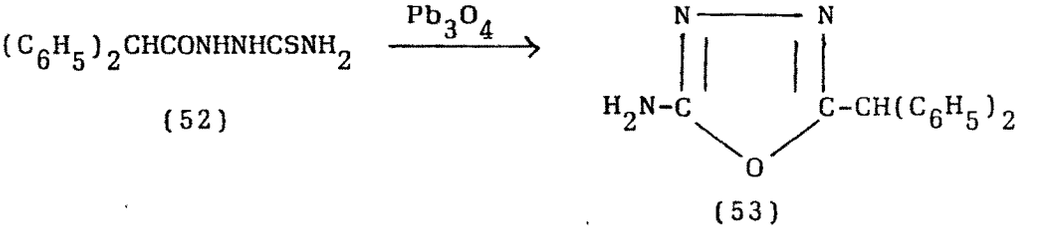
The product from benzaldehyde semicarbazone (50) & sodium hypoiodite or hypobromite is 2-amino-5-phenyl-1,3,4-oxadiazole (51).[71]



(50) (51)

(6) Acylthiosemicarbazides

In the presence of lead or mercury oxide certain acylthiosemicarbazides (52) lose the elements of hydrogen sulfide as ring closuer to a 1,3,4-oxadiazole (53).[72]

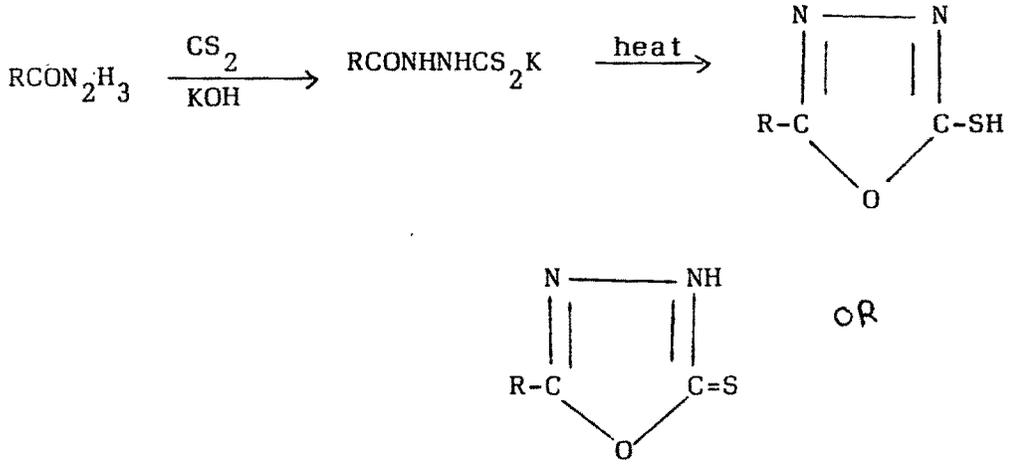


(52) (53)

A similar ring closure has been observed with potassium hydroxide[73] and hydrochloric acid.[74]

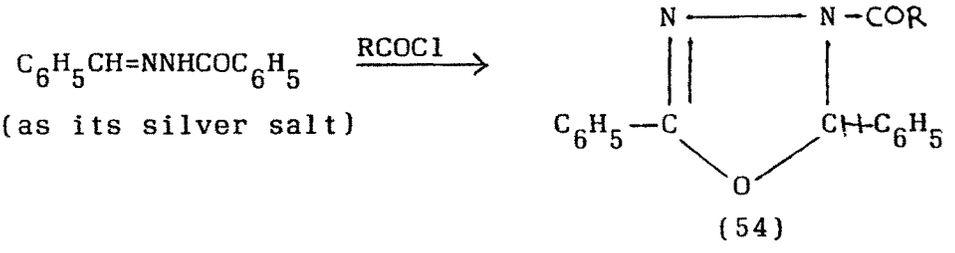
(7) Carboxylic acid hydrazides with carbon bisulfide

Hoggarth observed the formation of 2-substituted 1,3,4-oxadiazole-5-thiols on heating the potassium salts of 3-aroyldithiocarbazates.[75]



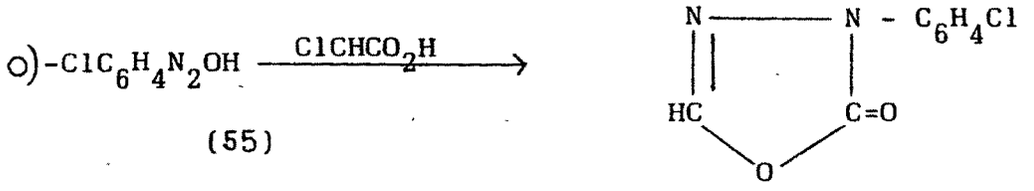
(8) Dihydro-1,3,4-oxadiazoles

Treatment of the silver salt of benzaldehyde benzoylhydrazone with acetyl or benzoyl chloride in an inert solvent gives a 2,5-diphenyl-4,5-dihydro-4-acyl-1,3,4-oxadiazole (54).[76]



(54)

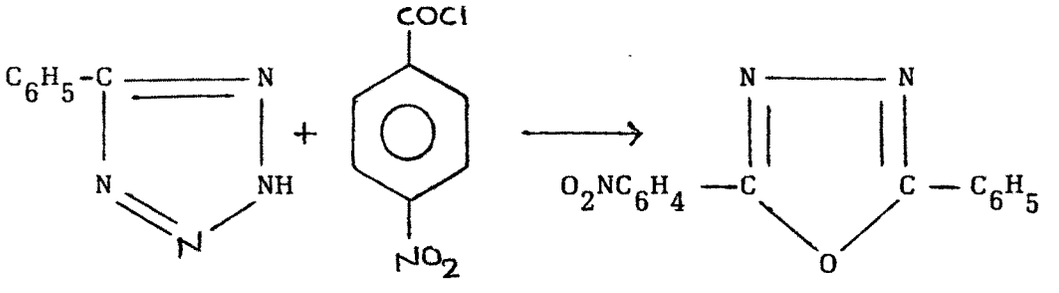
Diazotised o-chloroaniline (55) combines with chloromalonic acid in an alkaline medium to give 2,3-dihydro-2-keto-3-(o-chlorophenyl)-1,3,4-oxadiazole (56).[77]



(55) (56)

(9) Other preparations

From phenyltetrazole and p-nitrobenzoyl chloride in pyridine, 2-(p-nitrophenyl)-5-phenyl-1,3,4-oxadiazole(57) has been obtained.[78]



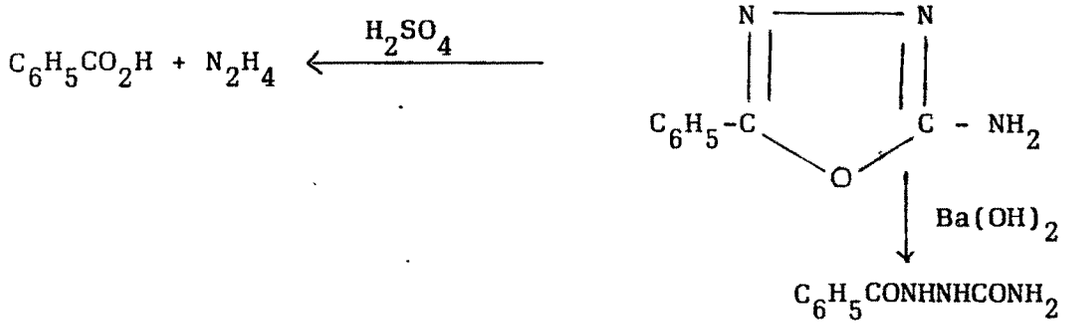
(57)

Reactions with Ring Cleavage

Many 1,3,4-oxadiazoles are easily cleaved by alkali into hydrazine derivatives.[79] Milder conditions with barium hydroxide,[80] sodium carbonate,[67] hydrazine in methanol,[64] aniline[64,79] alcohlic ammonia[65] or potassium hydroxide[81]

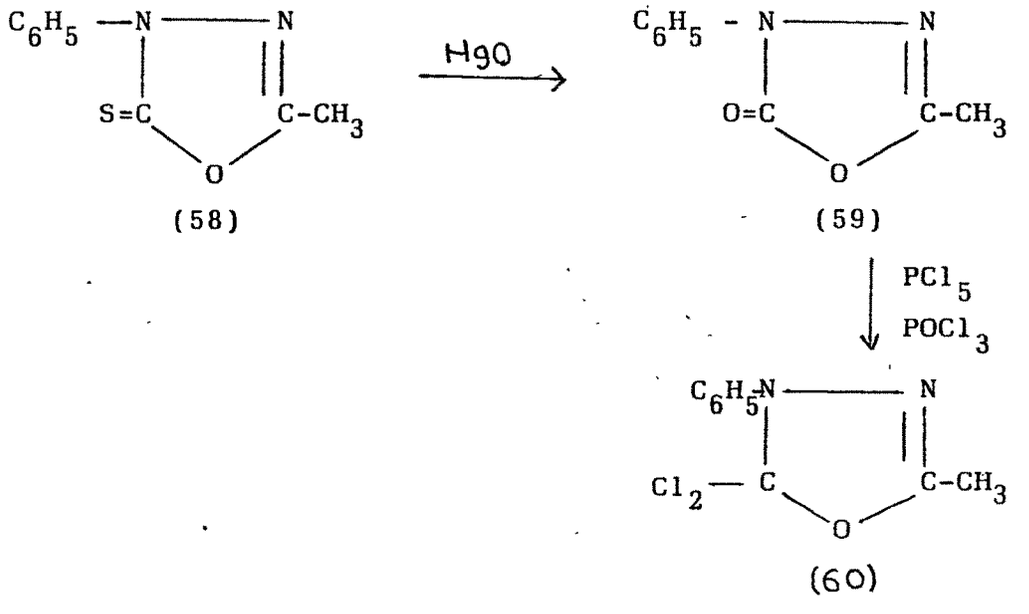
allow isolation of hydrazides and more vigorous conditions with sodium ethoxide or potassium hydroxide[58.67] give hydrazine or an alkyl or aryl derivative of hydrazine.

Prolonged treatment with concentrated hydrochloric acid degrades dialkyl 1,3,4-triazoles[82] and in dilute sulfuric acid, 2-amino-5-phenyl-1,3,4-oxadiazole is degraded into hydrazine and benzoic acid.[80]



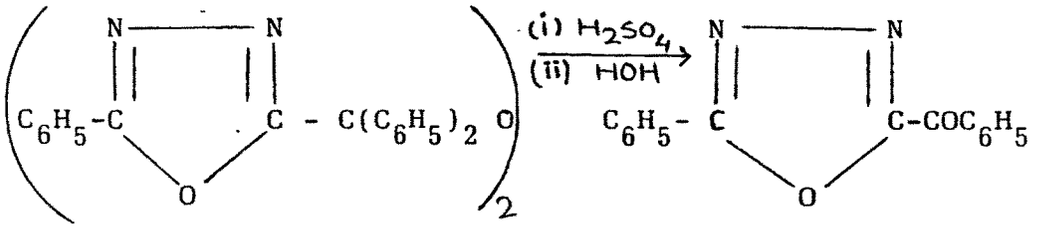
REACTIONS WITHOUT RING CLEAVAGE

Mercuric oxide changes oxadiazoline thiones (58) into corresponding oxadiazolones (59).[67] The oxadiazolone (59) reacts with phosphorus pentachloride withd the formation of the corresponding gem-dichloride (60).[83]



(58) (59) (60)

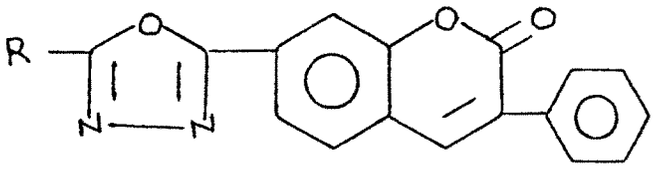
The peroxide when treated with sulfuric acid and then with water, is changed into 2-phenyl-5-benzoyl-1,3,4-oxadiazole (61) which may be reduced to mandelic and benzoic acids with zinc amalgam.[84]



(61)

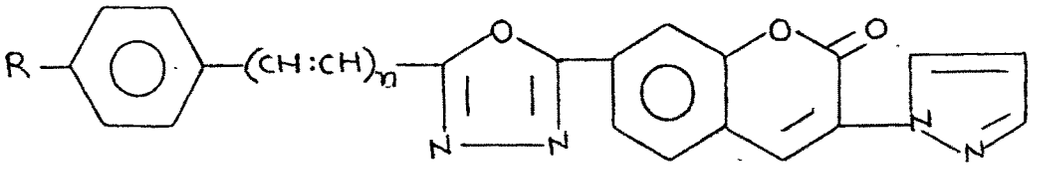
USES

Certain anthraquinone vat dyes are 1,3,4-oxadiazole derivatives.[85,87] Phenylbiphenyl-oxadiazole has been used in scintillation counting for B^{10} disintegration.[86] 7-(1,3,4-oxadiazole-2-yl)-3-phenyl coumarin (62)[87] could be used as optical whitenes. It could be incorporated in polyamides, poly-(ethylene tetraphthalate) or polyporpylene before spinning into fibers or they can be applied to polyesters, polyamides or poly (vinylchloride) fabricsby dyeing.



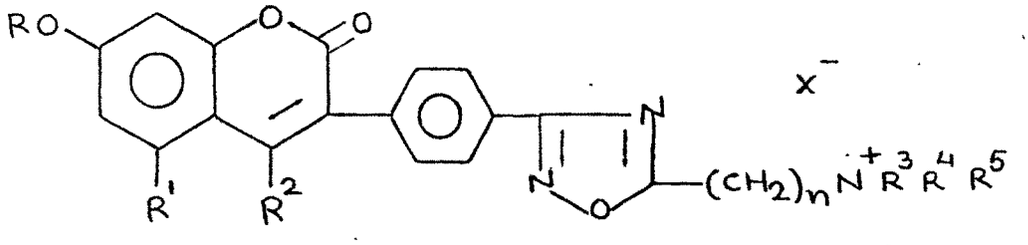
(62)

7-Oxadiazolyl coumarins[88] (63) had been reported as fluorescent whitening agents for poly(ethylene terephthalate), poly(vinyl chloride), cellulose acetate and poly-propylene fibers.



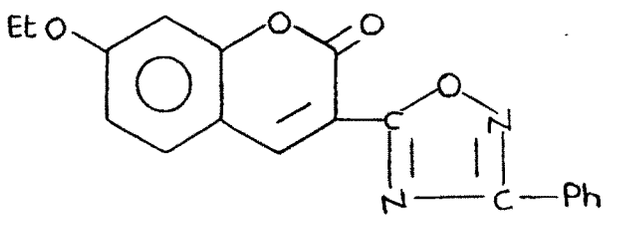
(63)

Davison Hugh et al.[89,90] synthesised 3-[4-(1,2,4-oxadiazolyl)phenyl] coumarin cationic fluorescent whiteners (64) which were used as chlorite bleach-stable fluorescent whiteners for acrylic and cellulose triacetate fibers.

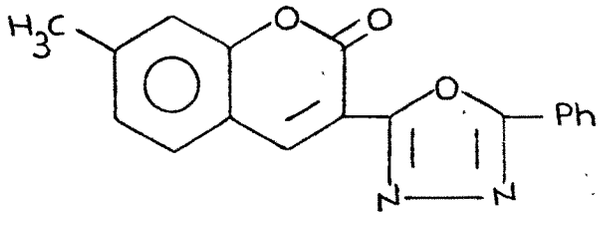


(64)

They also synthesised 7-ethoxy-(3-phenyl-1,2,4-oxadiazole-5-yl)coumarin (65) and 7-methyl- (5-phenyl-1,3,4-oxadiazole-2-yl) coumarin (66).

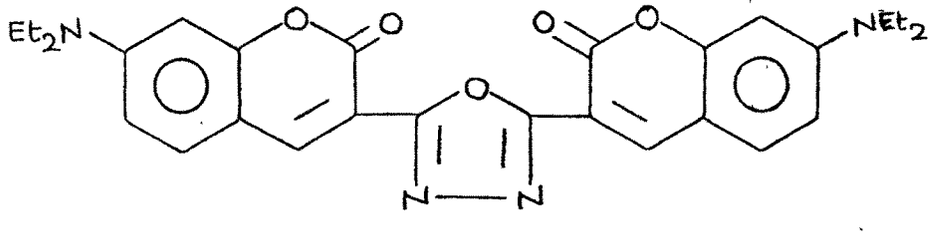


(65)

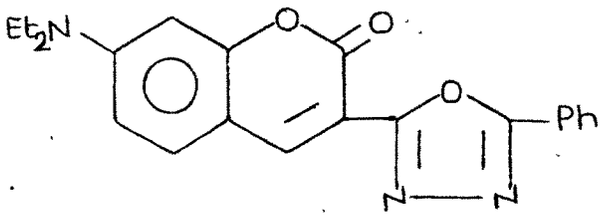


(66)

Schwander Hansrudolf[91] prepared oxadiazoylcoumarin dyes (67) and (68) which were used for dyeing polyester fibers light and sublimation fast brilliant greenish yellow shades.

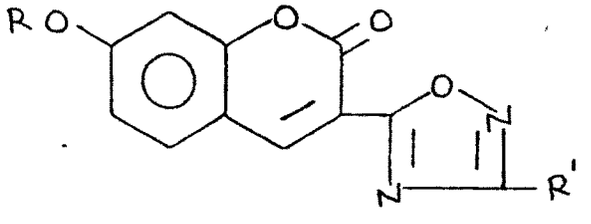


(67)



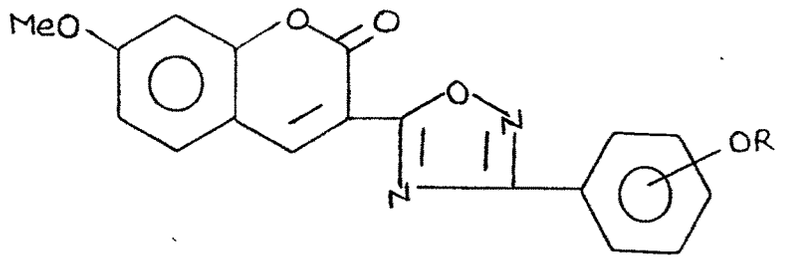
(68)

Domerque Annick [92,93] synthesised various oxadiazolyl-coumarin derivatives (69) from p-vanilline and Et-3-phenyl-1,2,4-oxadiazole-5-acetate which were used as fluorescent whiteners.



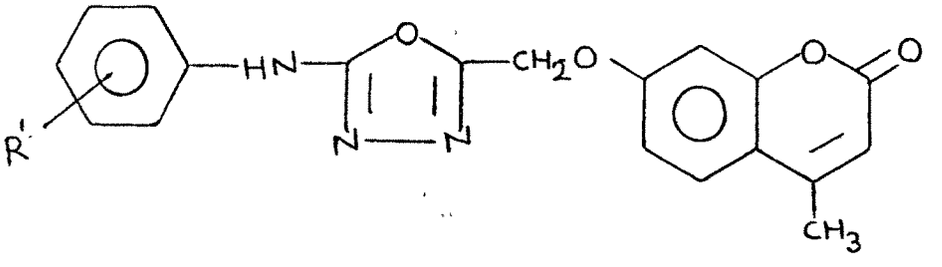
(69)

He also synthesised oxadiazolylcoumarin derivatives (70) by condensation of 3-(chloroformyl)-7-methoxycoumarin with $ROC_6H_4C(:NOH)NH_2$ which was used to whiten polyester fibers.



(70)

A.K. Sen Gupta and Coworkers[94] synthesised 2-aryl-amino-5-[((4-methyl-2-oxa-2H-1-benzopyran)7-yl)oxy]-1,3,4-oxadiazoles (71) which were found to be active against S. aureus. They reported that substitution of oxadiazole moiety with 4-methyl-7-coumarinyloxy moiety showed remarkable activity against bacteria. Moreover these compounds possessed good antifungal activity against fungi A Spergillus niger, Chaetomium globosum, Fusarium celmonum, Pullularia Pullulans, Cladospenium Spp. and Trichodrma Viridi.



(71)

PRESENT WORK

Sen Gupta and Coworkers[94] hae observed that subtitution of oxadiazole moiety with the 4-methyl-7-coumarinyloxy moiety showed remarkable activity against bacteria. Others[95] have also reported that heterocyclic compounds having six or five membered ring have diversed biological activities. Keeping above observations in mind, a number of oxadiazolyl coumarins have been synthesised to study if the products could display and enhance any biological properties.

In the beginning of this Chapter, synthesis and characterization of some oxadiazolyl coumarins have been described. It includes :

(i) Oxadiazolylcoumarins from 8-methoxycoumarin-3-carboxylic acid and various substituted benzoic acid hydrazides.

(ii) The same above oxadiazolylcoumarins were prepared by different route. First, the condensation of 8-methoxycoumarin-3-carbonylchloride with various acid dhydrazides and the resulting products have been characterised. These were then cyclised into oxadiazolyl-coumarins.

(iii) Some oxadiazolylcoumarins also have been prepared by condensation of acid chloride of 8-methoxycoumarin-3-carboxylic acid and 2-aryl-5-amino-1,3,4-oxadiazoles.

In the later part of this chapter, synthesis of hydrazides

by condensation of 8-methoxy-5-chloromethylcoumarin with substituted benzoic acid hydrazides and their characterisation have been described.

2-Aryl-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole from 8-methoxycoumarin-3-carboxylic acid and substituted benzoic acid hydrazides (73, Table-I, 1-14)

Method-I

General Preparation

A mixture of 8-methoxycoumarin-3-carboxylic acid, various substituted benzoic acid hydrazides and phosphorus oxychloride was condensed to obtain 2-aryl-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole. To support the structure assigned, some spectral data of individiaual compounds is described here.

2-(p-chlorophenyl)-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole (73, Table-I, 6)

8-Methoxy-5-bromocoumarin-3-carboxylic acid(72)required in the above synthesis was prepared by treating 8-methoxy-coumarin-3-carboxylic acid with liquid bromine in acetic acid. The structure of the compound was proved by NMR spectra.

The NMR spectrum (CF_3COOH) exhibited signals at δ 3.88, singlet, OCH_3 protons ; δ 7.1, doublet (J=9Hz) of proton at C-7 position ; δ 7.5, doublet (J=9Hz) of proton at C-6 position ; δ 9.2, singlet, proton at C-4 position. (Fig-1)

A mixture of 8-methoxy-5-bromocoumarin-3-carboxylic acid and p-chlorobenzoic acid hydrazide was treated with phosphorus oxychloride to obtain above 1,3,4-oxadiazole deriative.

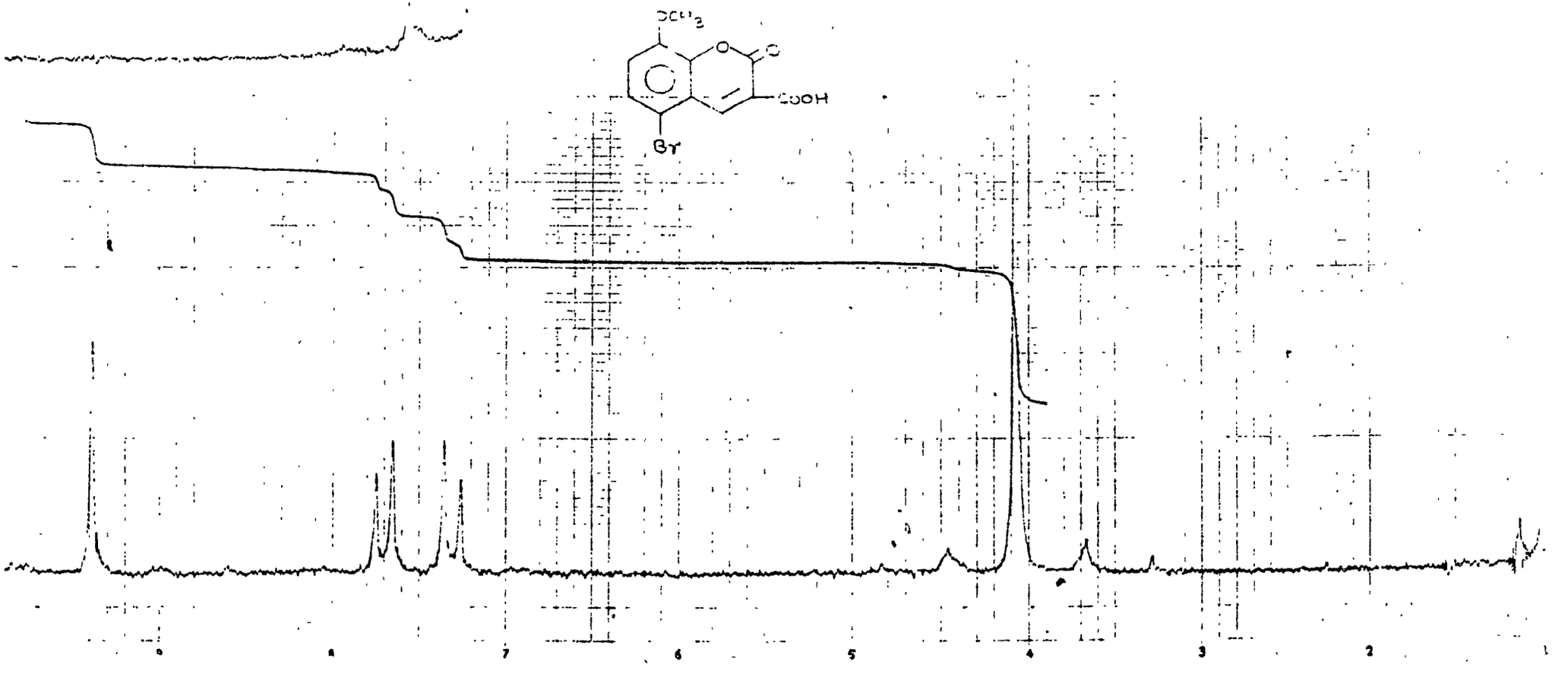
The IR (KBr) spectrum exhibited bands at 1755-1735 (C=O of coumarin ring), 1600 (C=C stretching) 1590 (C=N stretching), 1290 and 1100 (C-O-C) cm^{-1} were observed. (Fig.2)

The NMR spectra (CF_3COOH) showed singlet at δ 3.7 for OCH_3 protons of coumarin ring at C-8 position ; Aromatic protons appeared as multiplet in the region δ 6.9-7.9 ; proton at C-4 position appeared as singlet at δ 9.0 (Fig. 3)

From the above spectral data and analytical data, the structure assigned has been established.

2-(o-nitrophenyl)-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole (73, Table-I, 1)

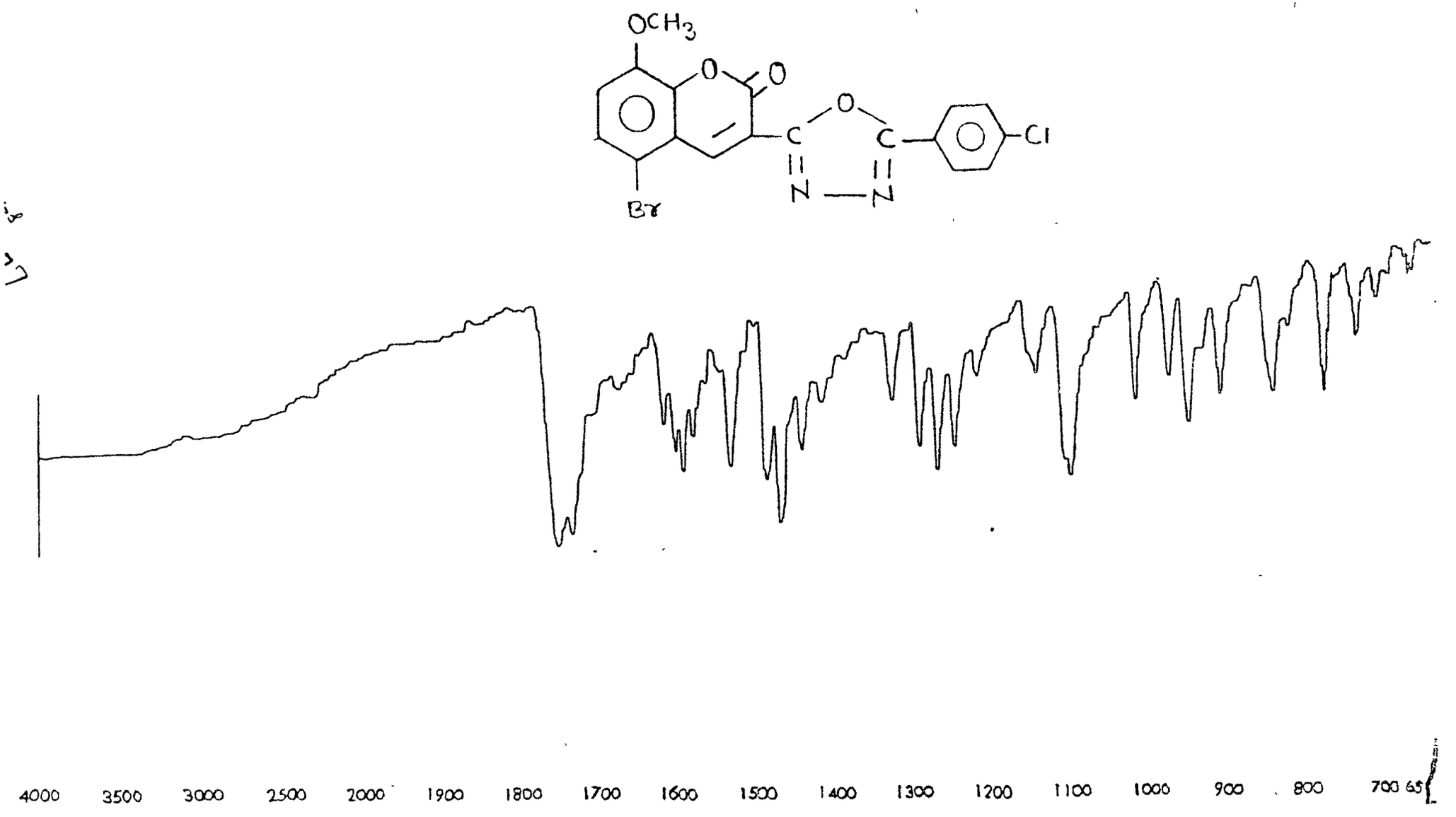
8-Methoxycoumarin-3-carboxylic acid, o-nitro benzoic



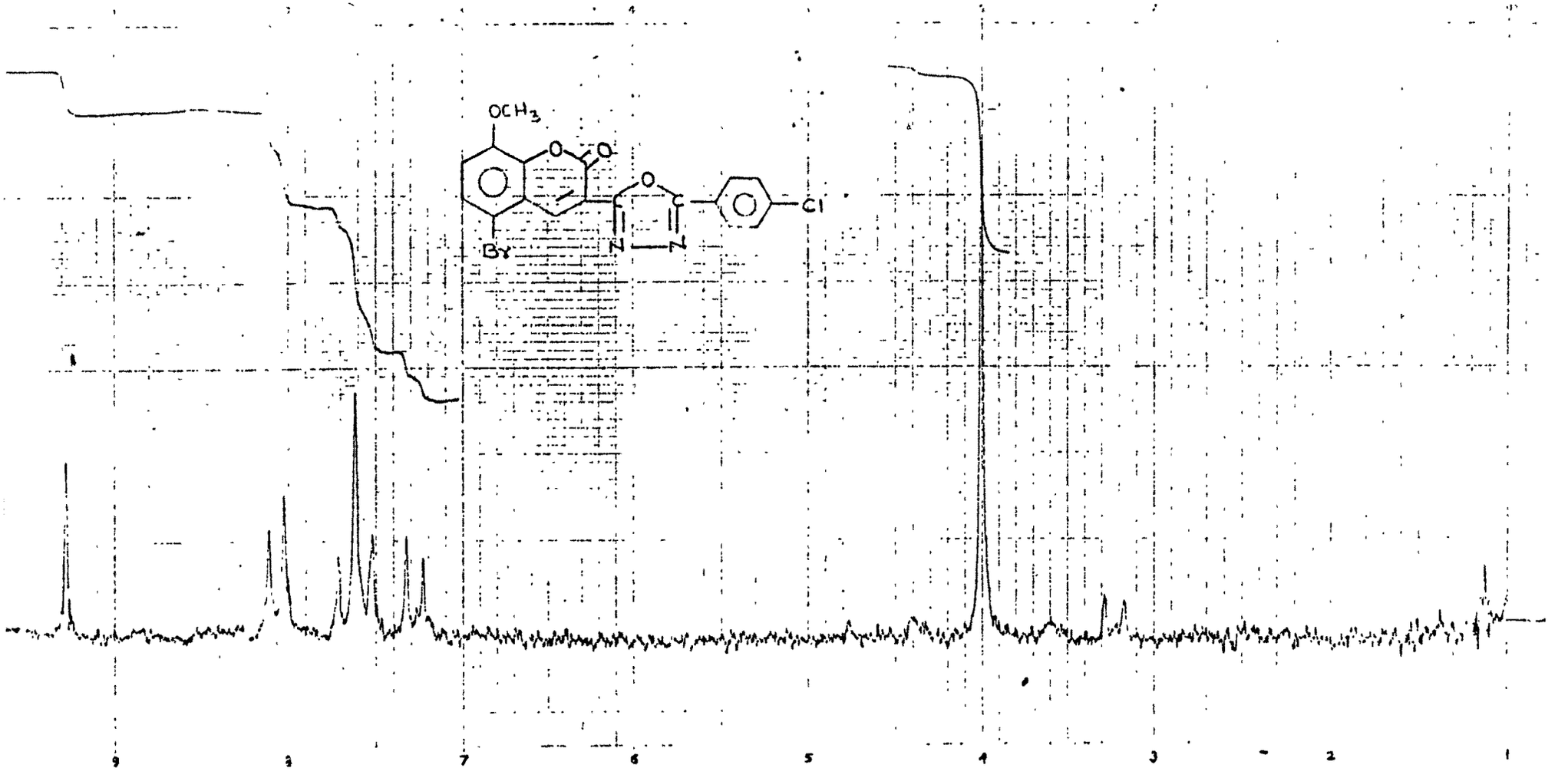
(Fig - 1) : 72

(0·3 ppm off set)

602



(Fig- 2) : 73, Table-I, 6



(Fig - 3) : 73, Table - I, 6

(0.3 ppm off set)

acid hydrazide and phosphorus oxychloride were refluxed to obtain above coumarinyl 1,3,4-oxadiazole derivative. The structure was established by IR and Mass spectrum.

The IR (KBr) exhibited strong bands at 1765-1740, 1610, 1580, 1285 and 1100 cm^{-1}.

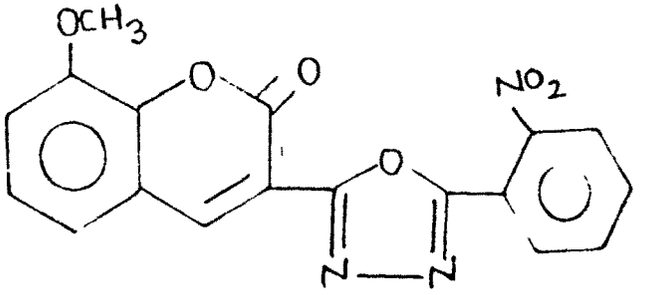
The Mass spectra showed following fragmentation. m/e : 365 (M^+ ion, 35%), 203 (base peak, 100%), 134 (20%), 104 (27%), 76 (19%). (Fig. 4).

2-Aryl-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole from 8-methoxy-3-coumarinoyl substituted benzoic acid hydrazide (73)

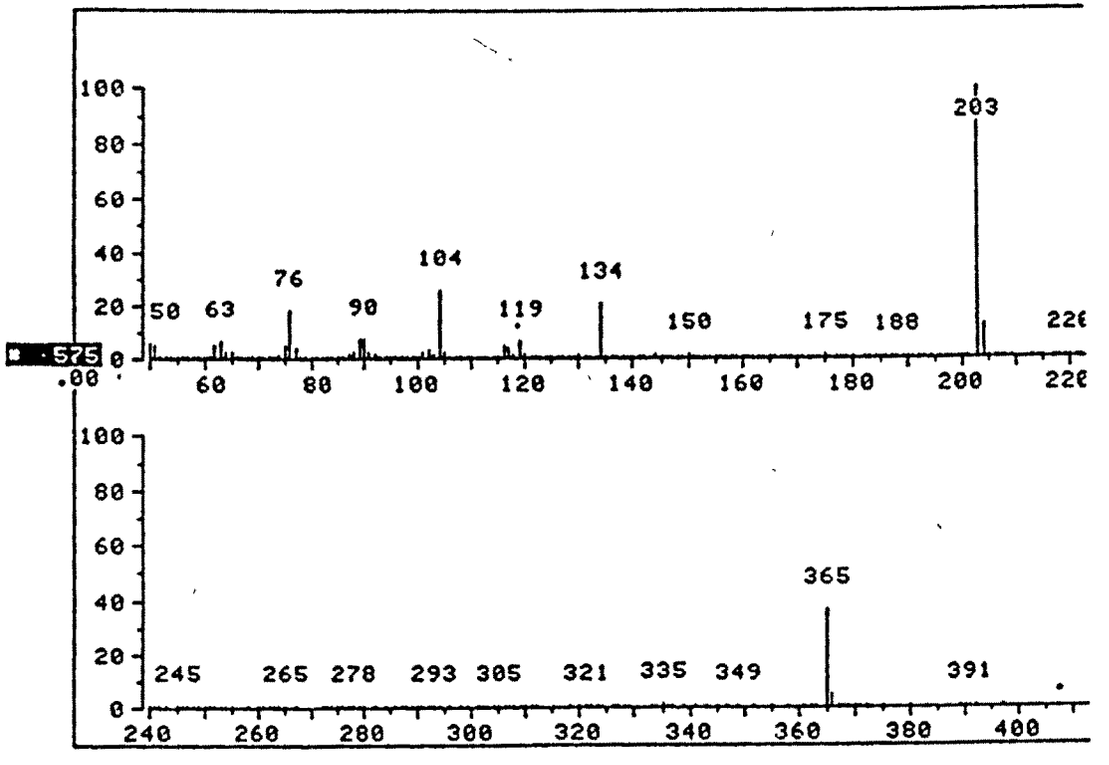
Method - 2

General preparation

Acid chloride of 8-methoxycoumarin-3-carboxylic acid and substituted benzoic acid hydrazides were stirred in ether to obtain 8-methoxy-3-coumarinoyl substituted benzoic acid hydrazides (74, Table-II, 1-14). These were then refluxed in phosphorus oxychloride, when they cyclised into corresponding 1,3,4-oxadiazole derivatives. (73, Table-I, 1-14). The mixed melting point of the above oxadiazoles and the oxadiazoles obtained from 8-methoxycoumarin-3-carboxylic



SGS-279 MW 365 C18H11O6N3
IPCL MASS SPECTRA 5:2:90



(Fig - 4) : 73, Table - I, 1

acid and substituted benzoic acid hydrazides (Method-I) did not depress. The identity was further established by their superimposible IR spectra.

8-Methoxy-3-coumarinoyl-substituted benzoic acid hydrazide (74, Table-II, 1-14)

General Method of Preparation

Acid chloride of 8-methoxycoumarin-3-carboxylic acid and substituted benzoic acid hydrazides were stirred in ether to obtain 8-methoxy-3-coumarinoyl-substituted benzoic acid hydrazide. To support the structure assigned, some spectral data of individual compounds are described here.

8-Methoxy-3-coumarinoyl-m-methyl benzoic acid hydrazide : (74, Table-II, 1)

A mixture of acid chloride of 8-methoxy coumarin-3-carboxylic acid and m-methyl benzoic acid hydrazide were stirred in ether to obtain above coumarinoyl hydrazide. The structure of the compound was characterised by following spectral data.

Th IR (KBr) spectrum, bands at 3300-3150 (NH stretching), 1720-1700 (lactonic carbonyl and NHCO), 1610-1600 (C=C) aromatic ring stretching), 1280 and 1100 (C-O-C) cm^{-1} were observed. (Fig. 5).

NMR spectrum exhibited following signals :
(CF_3COOH) : Singlet of methyl protons of phenyl ring appeared at δ 2.01 ; another singlet appeared at δ 3.7 for protons of methoxy group of coumarin nucleus ; aromatic protons appeared as multiplet in the region δ 6.8-7.5 ; δ 8.78, singlet for proton at C-4 position. (Fig. 6).

Mass spectra exhibited following fragments :
m/e : 352 (M^+ ion, 25%), 203 (15%), 119 (base peak, 100%), 91 (30%), 65 (10%), (Fig. 7).

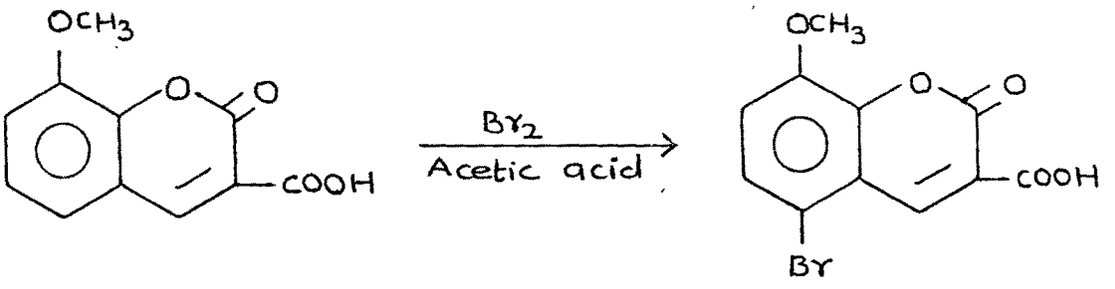
8-Methoxy-3-coumarinoyl-o-chloro benzoic acid hydrazide :
(74, Table-II, 5)

A mixture of 8-methoxycoumarin-3-carbonyl chloride and o-chlorobenzoic acid hydrazide was stirred in ether to obtain a product to which 8-methoxy-3-coumarinoyl-o-chloro-benzoic acid hydrazide structure was assigned.

The IR spectrum exhibited bands at 3300-3150, 1730-1700 and 1620-1600, 1275 and 1100 cm^{-1}.

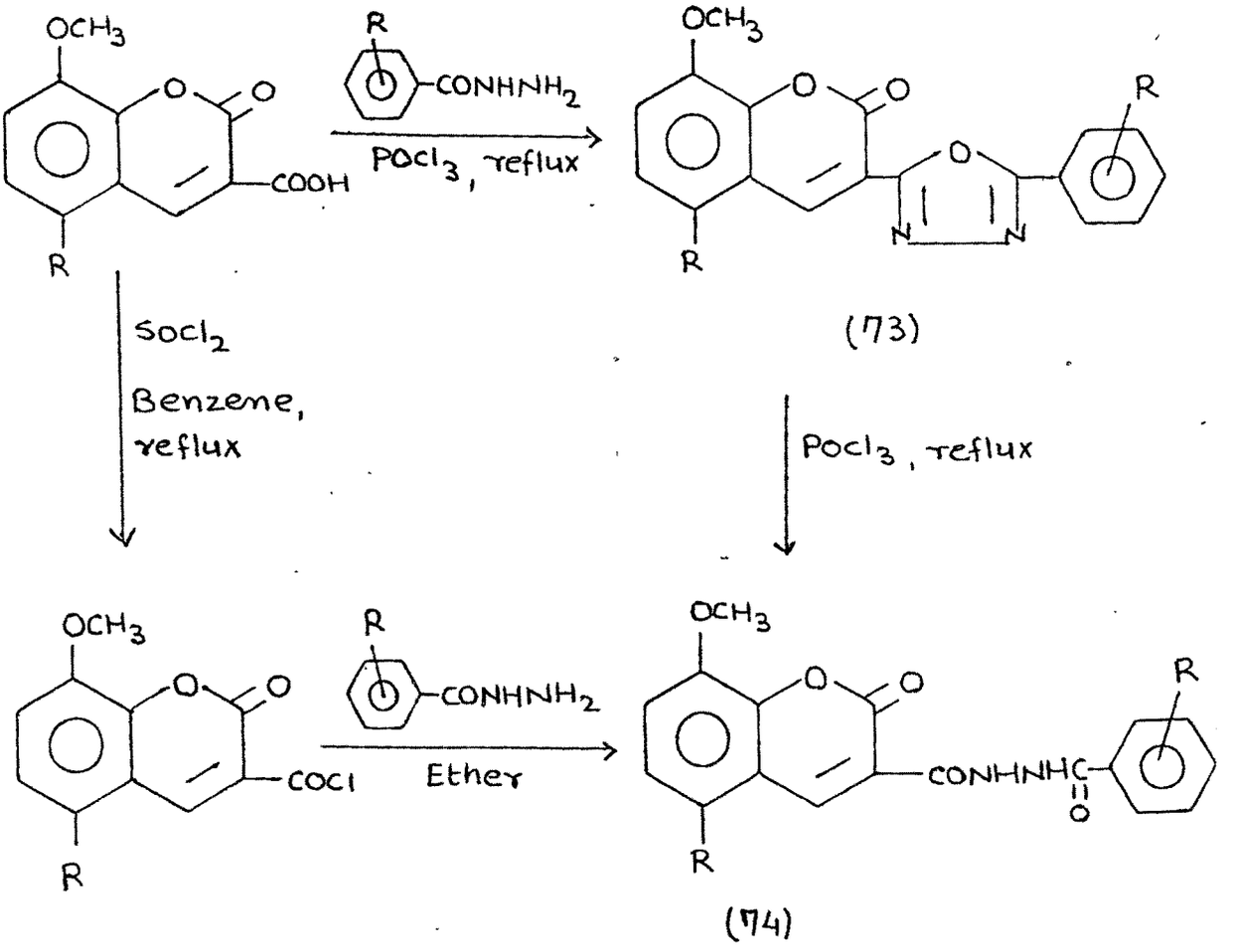
The NMR spectrum (CF_3COOH) exhibited following signals:
δ 3.7, singlet, $OC\underline{H}_3$ protons of coumarin nucleus ; aromatic protons appeared as multiplet in the region δ 6.7-7.4 ;

Scheme:1



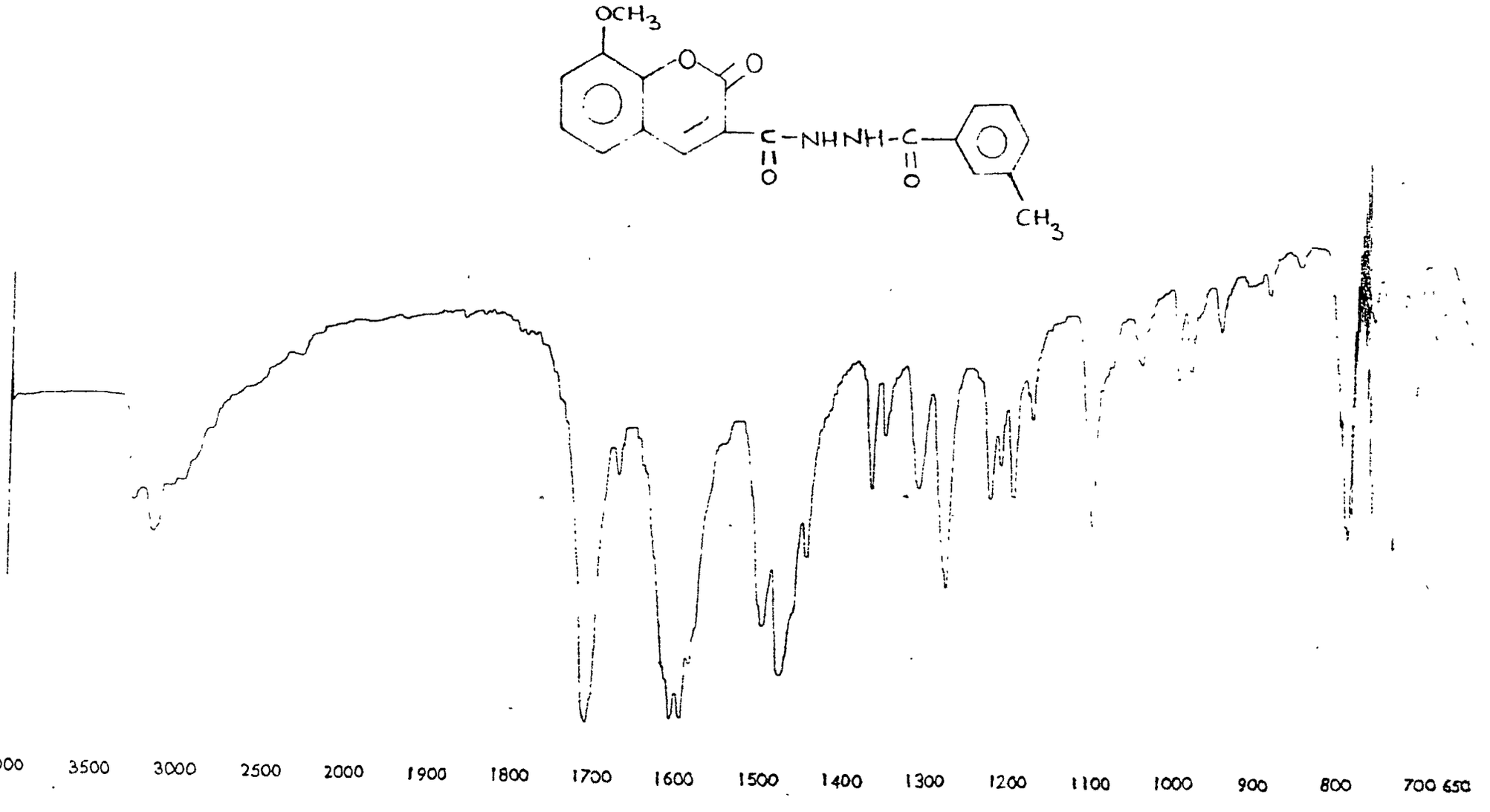
(72)

Scheme:2

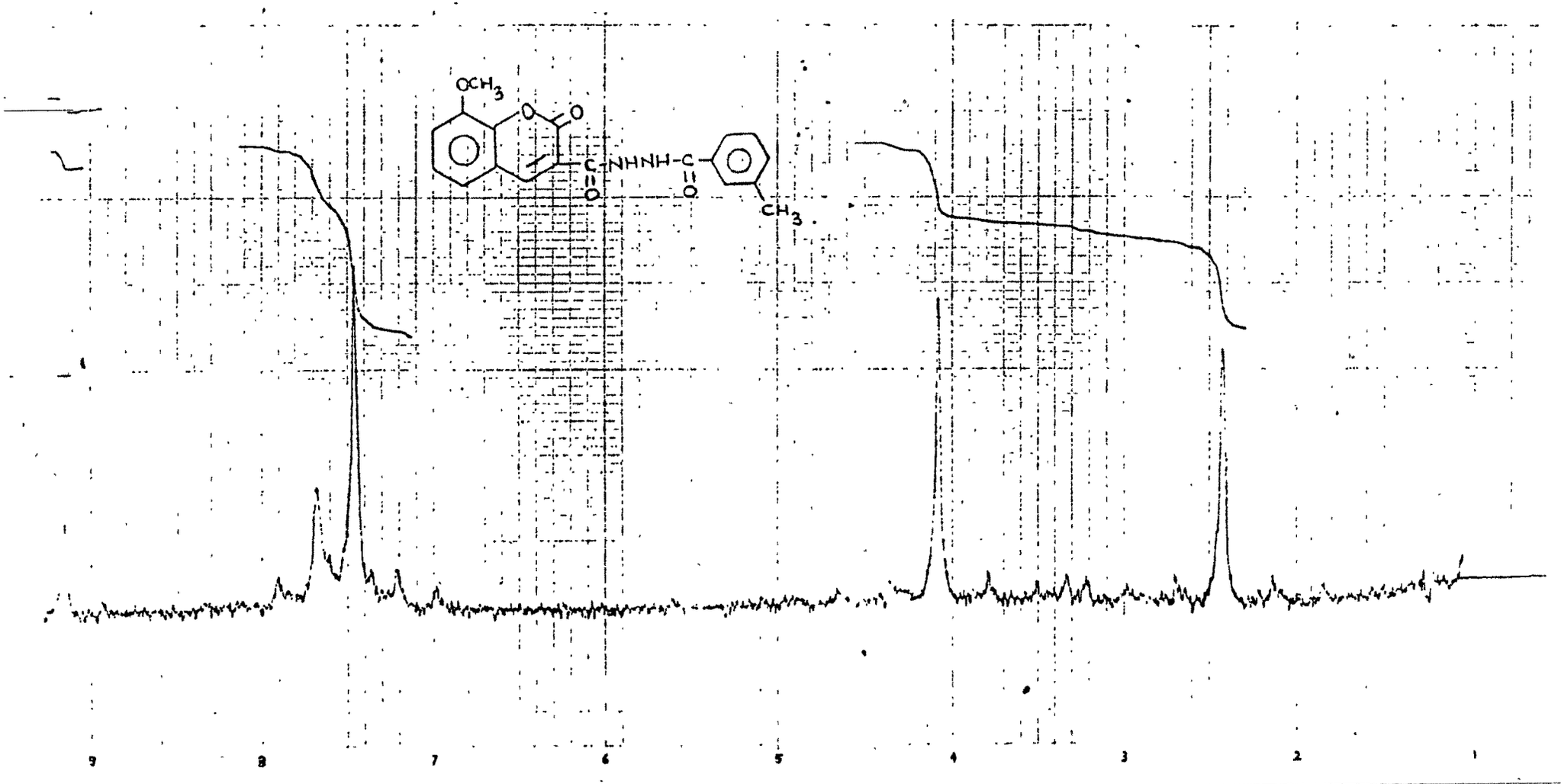


(73)

(74)

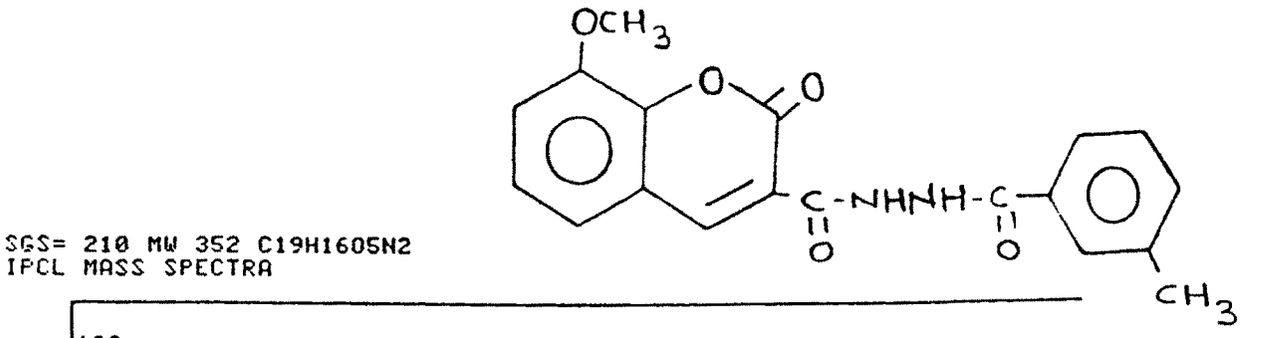


(Fig - 5): 74, Table - II, 1

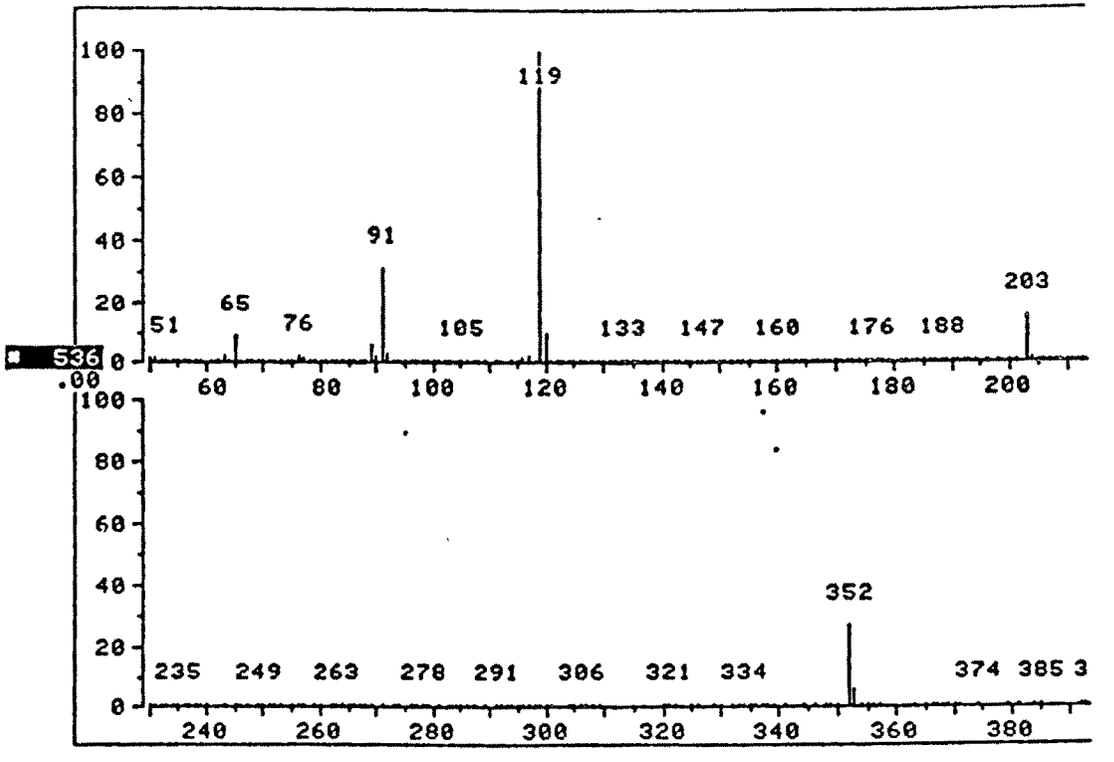


(0.4 ppm off set)

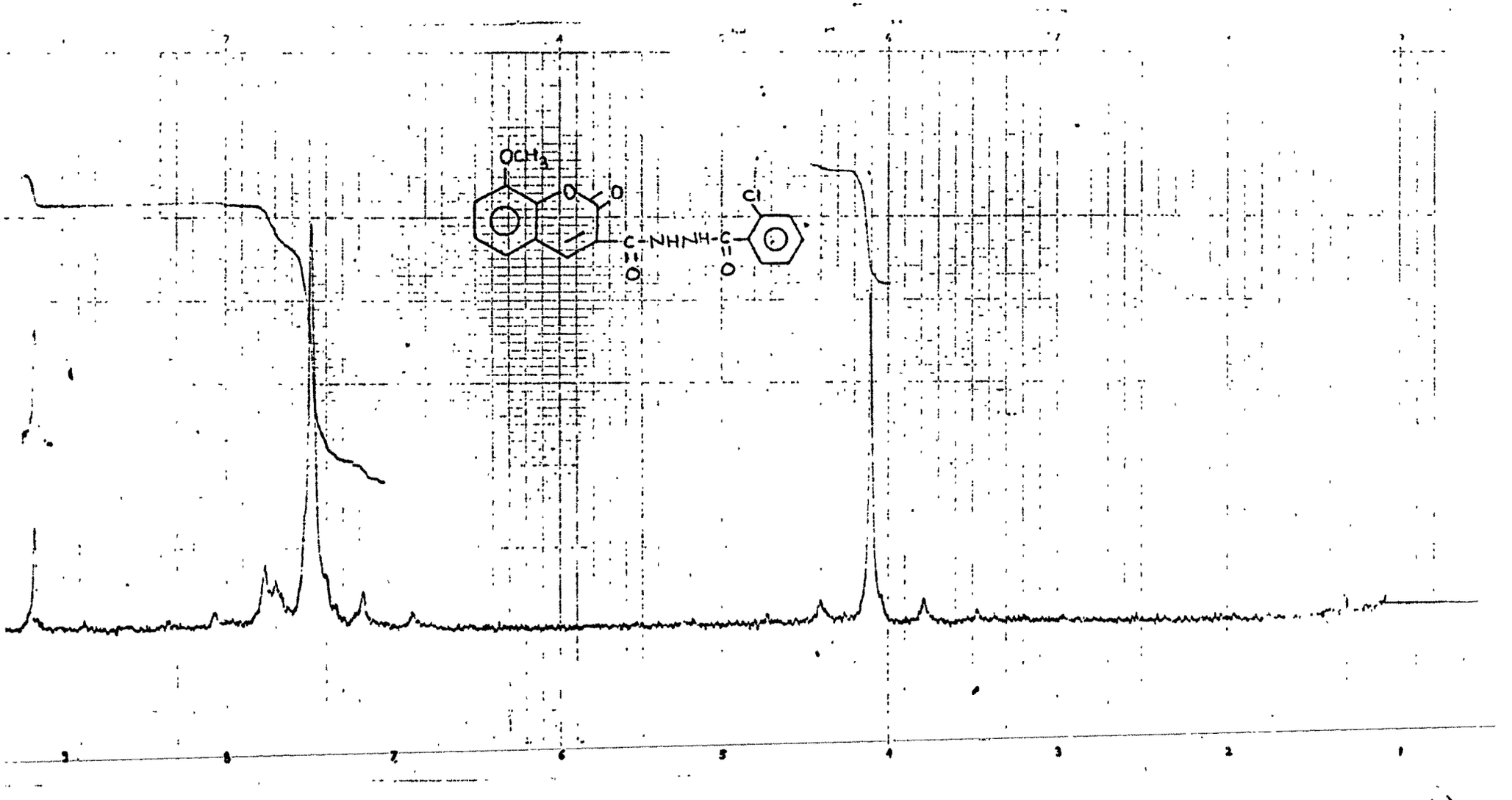
(Fig. 6): 74, Table-II.1



SGS= 210 MW 352 C19H16O5N2
IPCL MASS SPECTRA



(Fig-7) : 74, Table-II, 1



(Fig - 8) : 74, Table - II, 5

(0.4 ppm off set)

singlet at δ 8.8, for proton at C-4 position. (Fig. 8).

Thus the structure of the above compound was confirmed by IR and NMR spectra.

Similarly other coumarinoyl hydrazides were prepared (Table-II, 1-14).

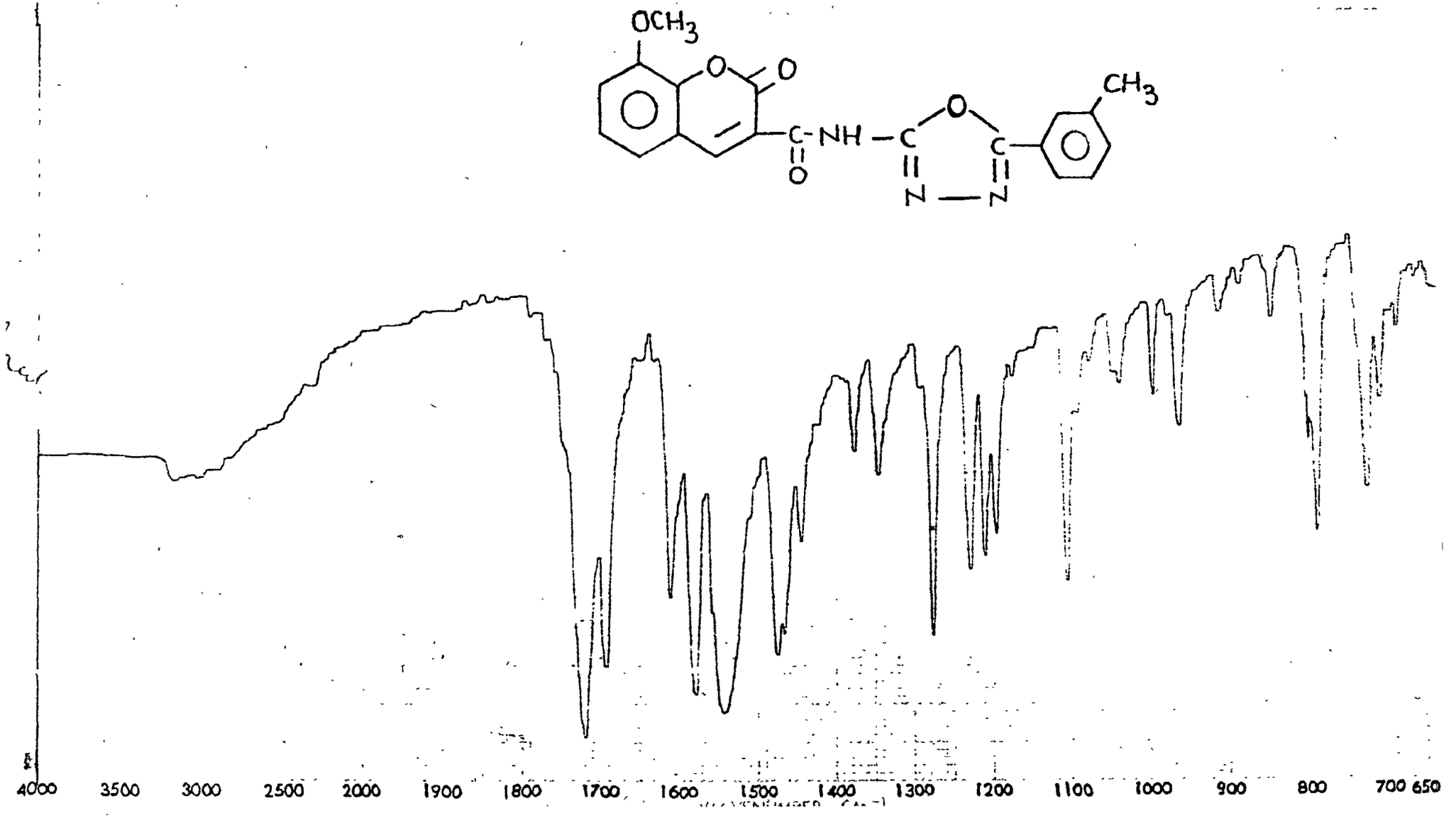
2-(m-methylphenyl)-5-(8'-methoxycoumarin-3'-carboxamido)-1,3,4-oxadiazole (76, Table-III, 1)

2-(m-methylphenyl)-5-amino-1,3,4-oxadiazole (75)[96] and acid chloride of 8-methoxycoumarin-3-carboxylic acid were reacted to obtain 2-(m-methylphenyl)-5-(8'-methoxycoumarin-3'-carboxamido)-1,3,4-oxadiazole.

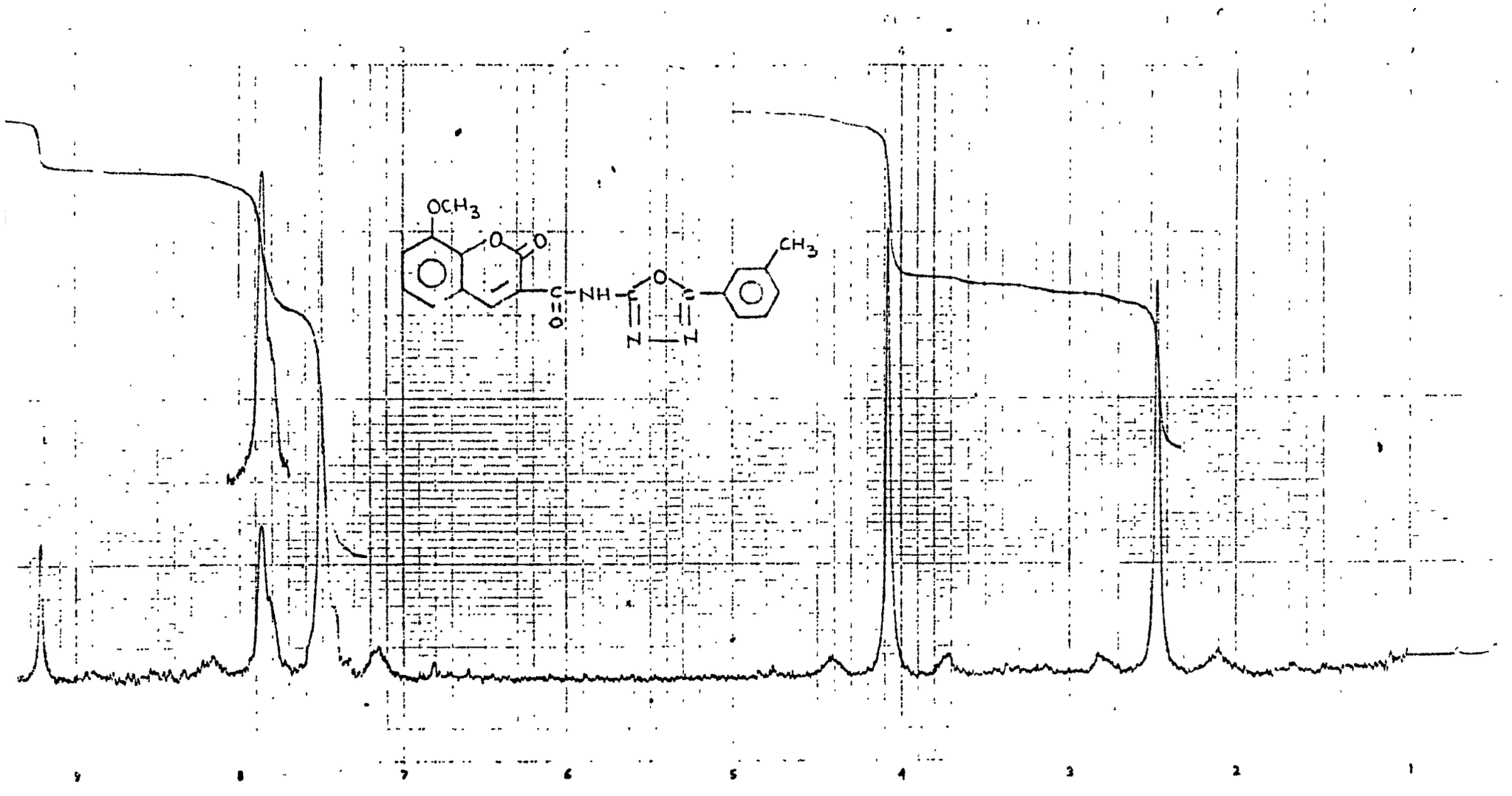
The IR (KBr) spectrum showed following bands :

νmax 3200 (NH stretching), 1720 (C=O, lactonic carbonyl), 1695 (C=O of CONH), 1610 (C=C, aromatic), 1580 (C=N), 1280 and 1105 (C-O-C) cm^{-1} (Fig. 9).

The NMR spectrum, taken in CF_3COOH, exhibited singlet at δ 2.16 for methyl protons of phenyl ring ; δ 3.78, singlet, protons of methoxy group of coumarin ring ; aromatic protons appeared as multiplet in the region δ 7.0-7.65 ; δ 8.92, singlet, a proton at C-4 position (fig. 10).



(Fig - 9) : 76, Table - III, 1



(Fig-10): 76, Table-III, 1

(0·3 ppm off set)

2-(m-Methoxyphenyl)-5-(8'-methoxycoumarin-3'-carboxamido)-1,3,4-oxadiazole (76, Table-III, 2)

The above carboxamido-1,3,4-oxadiazole was obtained by condensing 2-(m-methoxy phenyl)-5-amino-1,3,4-oxadiazole (75)[96] and acid chloride of 8-methoxycoumarin-3-carboxylic acid. The structure was confirmed by following NMR spectrum.

The NMR spectrum (CF_3COOH) exhibited signals at δ 3.61, singlet, OCH_3 protons of phenyl ring ; δ 3.7, singlet, OCH_3 protons of coumarin nucleus ; δ 6.8-7.4, multiplet, aromatic protons ; δ 8.88, singlet, proton at C-4 position of coumarin ring. (Fig. 11).

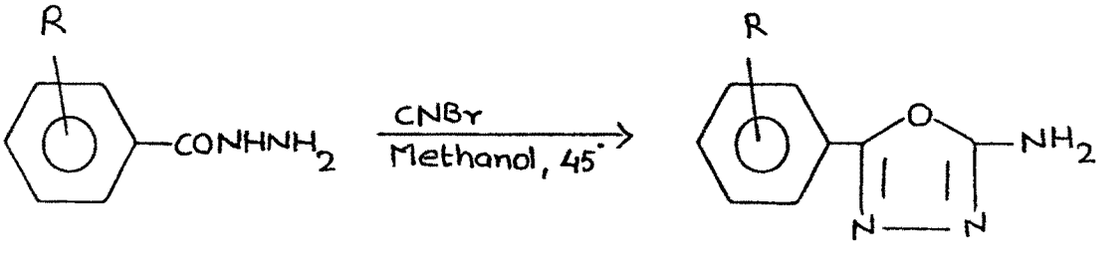
Similarly other carboxamido-1,3,4-oxadiazoles were prepared (75, Table-III, 1-4).

ANTIMICROBIAL ACTIVITY

Some selected compounds were tested against E. Coli, S. aureus, S. albus and B. subtilis using cup-plate method at concentration 100 and 500 ppm. Some of the oxadiazole derivatives showed moderate to good activity. The detailed screening report is given in Chapter-IV, Part-II.

The hydrazide derivatives obtained from coumarin carbonyl chloride did not show any antimicrobial activity, as there is no proper solvents for testing. They precipitated out at testing tempeature.

Scheme:3



(75)

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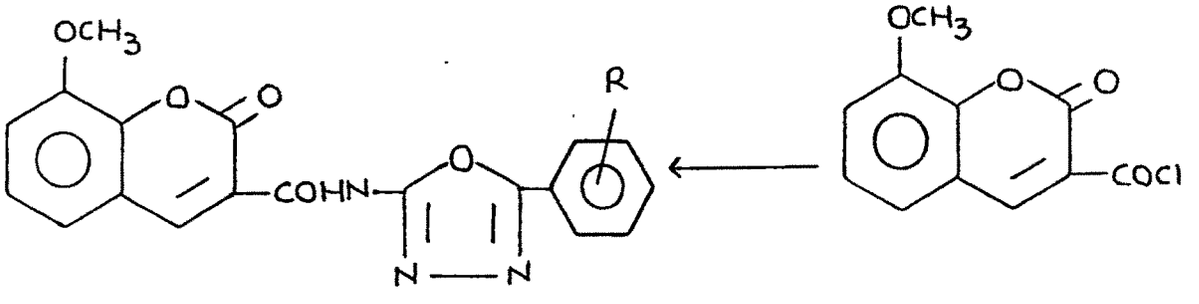
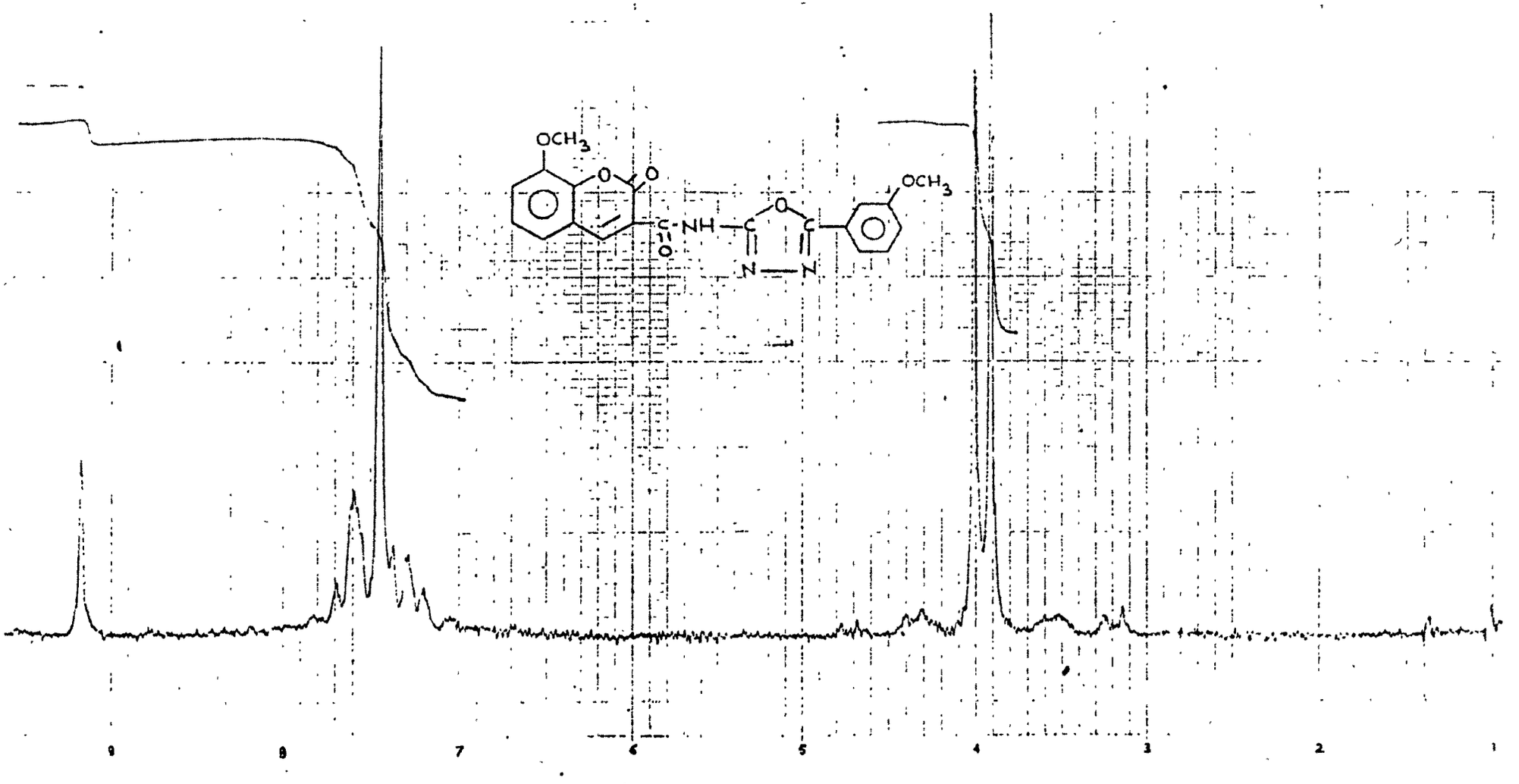


(76)



(Fig-11): 76, Table-III, 2

(0.2 ppm off set)

EXPERIMENTAL

EXPERIMENTAL

8-Methoxy-5-bromocoumarin-3-carboxylic acid (72)

8-Methoxycoumarin-3-carboxylic acid (3.0 g) dissolved in 20 ml of glacial acetic acid was treated in cold with a solution of Br_2 (3.0 g) in 4 ml of glacial acetic acid. The clear solution was poured into ice cold water. The resulting solid was crystallised from diluted acetic acid, M.p. 230°C, yield90%

Analysis : Found : C, 44.01 ; H, 2.12%

$C_{11}H_7O_5Br$: requires : C, 44.15 ; H, 2.34%

Method-1

2-(p-Chlorophenyl)-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole (73, Table-I, 6)

A mixture of 8-methoxy-5-bromocoumarin-3-carboxylic acid (0.02 mole) and p-chlorobenzoic acid hydrazide (0.01 mole) was refluxed in $POCl_3$ (5.0 ml) on a water bath for 5 hrs. The reaction mixture then poured into ice-cold water and crystallised from alcohol-DMF mixture, M.p. 254°C, yield 65%.

Analysis : Found : C, 49.94 ; H, 2.75 ; N, 6.84%

$C_{18}H_{10}O_4N_2BrCl$: requires : C, 49.88 ; H, 2.31 ; N, 6.47%

2-(o-Nitrophenyl)-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole (73, Table-I, 1)

8-Methoxycoumarin-3-carboxylic acid (0.02 mole), o-nitro

TABLE-I : ANALYTICAL AND PHYSICAL DATA OF 2-ARYL-5-(8'-METHOXY-3'-COUMARINYL)-1,3,4-OXADIAZOLE (73)

Sr. No.	R	R_1	M.p.* °C	Yield %	Molecular Formula	Analysis % Found/(Calcd) C	H	N
1	H	o-NO_2-	270^{d+w}	65	$C_{18}H_{11}O_6N_3$	59.40 (59.18)	3.37 (3.01)	11.10 (11.51)
2	H	m-NO_2-	290^{d+w}	60	$C_{18}H_{11}O_6N_3$	59.63 (59.18)	2.83 (3.01)	11.22 (11.51)
3	H	p-NO_2-	$>300^{dm}$	60	$C_{18}H_{11}O_6N_3$	59.60 (59.18)	3.20 (3.01)	11.12 (11.51)
4	Br	p-NO_2-	$>300^{d+w}_{(d)}$	65	$C_{18}H_{10}O_6N_3Br$	48.24 (48.65)	2.03 (2.25)	9.32 (9.46)
5	H	o-Cl-	175^{a+d}	70	$C_{18}H_{11}O_4N_2Cl$	60.78 (61.02)	3.56 (3.11)	7.63 (7.91)
6	Br	p-Cl-	254^{a+d}	65	$C_{18}H_{10}O_4N_2BrCl$	49.94 (49.88)	2.75 (2.31)	6.84 (6.47)
7	Br	m-Br-	$320^{a+d}_{(d)}$	65	$C_{18}H_{10}O_4N_2Br_2$	45.02 (45.19)	2.47 (2.09)	5.61 (5.86)
8	H	m-CH_3-	224^{d+w}	65	$C_{19}H_{14}O_4N_2$	68.0 (68.26)	3.91 (4.19)	7.94 (8.38)
9	H	p-CH_3-	264^{d+w}	60	$C_{19}H_{14}O_4N_2$	68.53 (68.26)	4.06 (4.19)	8.1 (8.38)
10	H	m-OCH_3-	225^{d+w}	70	$C_{19}H_{14}O_5N_2$	64.93 (65.14)	3.9 (4.0)	8.03 (8.0)

cont...

Table-I cont...

11	H	p-NH_2-	310^{d}	60	$C_{18}H_{13}O_4N_3$	64.27 (64.48)	4.09 (3.88)	12.32 (12.51)
12	H	p-OH-	>300^{dm}	55	$C_{18}H_{12}O_5N_2$	64.18 (64.29)	3.30 (3.57)	8.02 (8.33)
13	H	Isoniazide	>300^{dm}	50	$C_{17}H_{11}O_4N_3$	63.14 (63.55)	3.21 (3.43)	12.9 (13.08)
14	Br	Isoniazide	>300$^{dm}_{(d)}$	50	$C_{17}H_{10}O_4N_3Br$	49.4 (49.76)	2.31 (2.44)	10.1 (10.24)

---

* Solvent of Crystallisation = a = alcohol
d = DMF
dm = DMSO
w = Water

benzoic acid hydrazide (0.01 mole) and $POCl_3$ (5.0 ml) were refluxed on a water bath for 5 hrs. The reaction mixture was poured into ice-cold water. The resulting solid was crystallised from 1:1 DMF. M.p. 290°C, yield 60%.

Analysis : Found : C, 59.63 ; H, 2.83 ; N, 11.22%

$C_{18}H_{11}O_6N_3$: requires : C, 59.18 ; H, 3.01 ; N, 11.51%

2-(Aryl)-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole (73)

Method-2

8-Methoxycoumarin-3-carbonyl chloride (0.5 g) and substituted benzoic acid hydrazides (0.5 g) were stirred in ether (30 ml) for 2 hrs. The separated 8-methoxy-3-coumarinoyl substituted benzoic acid hydrazides were filtered and crystallised from proper solvents. These were then refluxed in $POCl_3$ (5.0 ml) on a water bath for 5 hrs. which were cyclised into 2-(aryl)-5-(8'-methoxy-3'-coumarinyl)-1,3,4-oxadiazole. The reaction mixture was then poured into ice-cold water and crystallised from proper solvents.

8-Methoxy-3-coumarinoyl-m-methyl benzoic acid hydrazide : (74, Table-II, 1)

A mixture of acid chloride of 8-methoxy coumarin-3-carboxylic acid (0.01 mole) and m-methyl benzoic acid hydrazide

TABLE-II : ANALYTICAL AND PHYSICAL DATA OF 8-METHOXY-3-COUMARINYL SUBSTITUTED BENZOIC ACID HYDRAZIDE (74)

Sr. No.	R	R_1	M.P.* °C	Yield %	Molecular Formula	Analysis % Found/(Calcd) C	H	N
1	H	m-CH_3-	248^{d+w}	91	$C_{19}H_{16}O_5N_2$	66.31 (66.77)	4.66 (4.55)	7.66 (7.96)
2	H	p-CH_3-	253^{d+w}	90	$C_{19}H_{16}O_5N_2$	66.42 (66.77)	4.32 (4.55)	7.74 (7.96)
3	H	m-OCH_3-	221^{d+w}	85	$C_{19}H_{16}O_6N_2$	61.48 (61.96)	4.22 (4.35)	7.37 (7.61)
4	H	p-OCH_3-	246^{d+w}	84	$C_{19}H_{16}O_6N_2$	62.40 (61.96)	4.74 (4.35)	7.34 (7.61)
5	H	o-Cl	274^{d}	80	$C_{18}H_{13}O_5N_2Cl$	57.46 (58.07)	3.63 (3.49)	7.49 (7.53)
6	H	p-Cl-	268^{d+w}	82	$C_{18}H_{13}O_5N_2Cl$	58.47 (58.06)	3.52 (3.49)	7.0 (7.53)

Cont....

TABLE - II Cont.....

7	H	m-Br-	268[d]	75	$C_{18}H_{13}O_5N_2Br$	51.45 (51.79)	3.43 (3.12)	7.08 (6.72)
8	H	o-NO_2-	306[d+w]	73	$C_{18}H_{13}O_7N_3$	55.98 (56.39)	3.86 (3.39)	10.61 (10.97)
9	H	m-NO_2-	288[d+w]	70	$C_{18}H_{13}O_7N_3$	56.76 (56.39)	3.81 (3.39)	10.64 (10.97)
10	H	p-NO_2-	306[d+w]	70	$C_{18}H_{13}O_7N_3$	56.80 (56.39)	3.83 (3.39)	10.82 (10.97)
11	H	p-OH-	304[d]	72	$C_{18}H_{14}O_6N_2$	61.43 (61.02)	3.92 (3.96)	7.98 (7.91)
12	H	p-NH_2-	>300[d]	70	$C_{18}H_{15}O_5N_3$	61.20 (61.18)	4.07 (4.25)	11.62 (11.89)
13	Br	p-Cl-	264[d+w]	75	$C_{18}H_{12}O_5N_2BrCl$	47.64 (47.89)	3.05 (2.66)	6.29 (6.21)
14	Br	m-Br-	165[d+w]	75	$C_{18}H_{12}O_5N_2Br_2$	43.11 (43.55)	2.91 (2.42)	5.47 (5.65)

* Solvent of crystallisation : d = DMF

w = water

(O.O1 mole) were stirred in ether (5O ml) for 2 hrs. The resulting solid was crystallised from 1:1 DMF
M.p. 248°C, yield 91%.

Analysis : Found : C, 66.31 ; H, 4.66 ; N, 7.66%
$C_{19}H_{16}O_5N_2$: requires : C, 66.77 ; H, 4.55 ; N, 7.96%

8-Methoxy-3-coumarinoyl-o-chloro benzoic acid hydrazide :
(74, Table-II, 5)

A mixture of 8-methoxycoumarin-3-carbonyl chloride (O.O1 mole) and o-chlorobenzoic acid hydrazide (O.O1 mole) was stirred in ether (5O ml). The resulting solid was purified by repeated crystallisation from 1:1 DMF
M.p. 274°C, yield 8O%.

Analysis : Found : C, 57.46 ; H, 3.63 ; N, 7.49%
$C_{18}H_{13}O_5N_2Cl$: requires : C, 58.O6 ; H, 3.49 ; N, 7.53%

2-(m-Methylphenyl)-5-(8'-methoxycoumarin-3'-carboxamido)-1,3,4-oxadiazole (76, Table-III, 1)

A mixture of 2-(m-methylphendyl)-5-amino-1,3,4-oxadiazole[1O1] (O.O1 mole) and acid chloride of 8-methoxycoumarin-3-carboxylic acid (O.O1 mole) was refluxed in pyridine (1.O ml) on an oil bath at 12O°C for 3 hrs. The reaction mixture

was then poured into large excess of water. The resulting solid was crystallised from 1:1 DMF.

M.p. 236°C, yield 80%.

Analysis	:	Found	:	C, 63.18	; H, 4.29	; N, 11.35%
$C_{20}H_{15}O_5N_3$	:	requires	:	C, 63.66	; H, 3.98	; N, 11.14%

2-(m-Methoxyphenyl)-5-(8'-methoxycoumarin-3'-carboxamido)-1,3,4-oxadiazole (76, Table-III, 2)

2-(m-methoxyphenyl)-5-amino-1,3,4-oxadiazole[101] (0.01 mole), acid chloride of 8-methoxycoumarin-3-carboxylic acid (0.01 mole) and pyridine (1.0 ml) were refluxed on an oil bath at 120°C for 3 hrs. It was then treated with dilute hydrochloric acid and crystallised from 1:1 dimethyl formamide.

M.p. 220°C, yield 75%.

Analysis	:	Found	:	C, 60.7	; H, 3.61	; N, 10.42%
$C_{20}H_{15}O_6N_3$	:	requires	:	C, 61.07	; H, 3.82	; N, 10.69%

TABLE - III : ANALYTICAL AND PHYSICAL DATA OF 2-ARYL-5-(8'-METHOXY-COUMARIN-3-CARBOXAMIDO)-1,3,4-OXADIAZOLE (76)

Sr.No.	R	M.P.* °C	Yield %	Molecular Formula	Analysis % Found/(Calcd) C	H	N
1	m-CH_3-	236^{d+w}	80	$C_{20}H_{15}O_5N_3$	63.18 (63.66)	4.29 (3.98)	11.35 (11.14)
2	m-OCH_3-	220^{d+w}	75	$C_{20}H_{15}O_6N_3$	60.7 (61.07)	3.61 (3.82)	10.42 (10.69)
3	m-NO_2-	268^{a}	75	$C_{19}H_{12}O_7N_4$	55.52 (55.88)	3.33 (2.94)	13.51 (13.73)
4	p-Cl-	290^{d+w}	73	$C_{19}H_{12}O_5N_3Cl$	57.19 (57.43)	3.45 (5.03)	10.11 (10.58)

* Solvent of crystallisation : a = alcohol
d = DMF
w = water

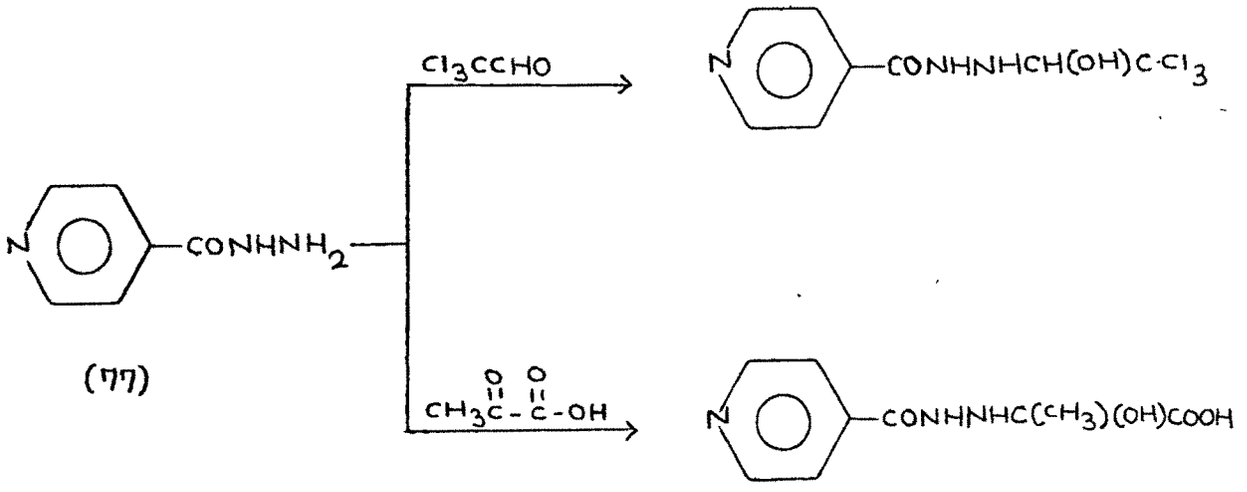
HYDRAZIDES :

Introduction

Isonicotinic acid hydrazide (Isoniazide) (77), known since 1912, is specifically, antimycobacterial at low (0.05 µg/ml) concentration,[97] but it is not active against saprophytic mycobacteria. It was bactericidal even at its MIC for growing bacilli, but did not affect resting cells.[98] When administered orally or subcutaneously, it produced a remarkable suppression of experimental tuberculosis in mice guinea pigs and rabits.[99,100] and removed tuberculin sensitivity in monkeys, indicating eradication.[101]

The very high activity and relatively low toxicity of isoniazide prompted the synthesis of an extremely large number of structural analogs by many groups of workers. A small number of compounds had high activity. Some because of convension in Vivo to isoniazide.

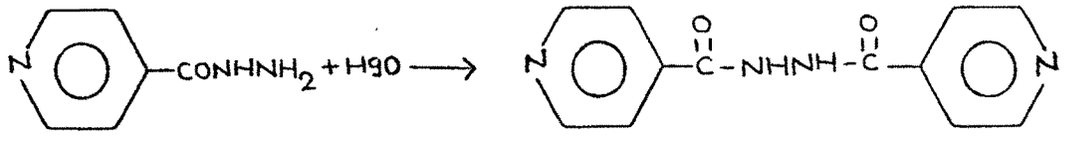
H.L. Yale and co-workers[102] reported the tuberculosis activity of acid hydrazides. They synthesised various hydrazides of heterocyclic acid like substituted isonicotinic acid.



(77)

Diacyl hydrazine derivatives were prepared by the reaction of an acid hydrazide with an acid chloride or acid anhydride or by the reaction of an acid chloride with hydrazine.

1,2-Bis-(isonicotinyl)-hydrazine (78) was prepared by the oxidation of isonicotinic acid hydrazide with mercuric oxide.

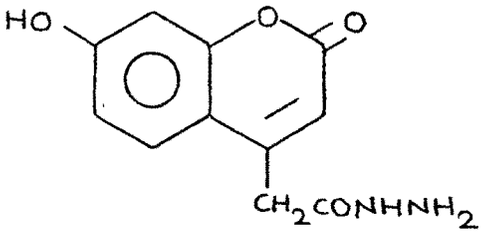


(78)

$+ N_2 + 2H_2O + 2Hg$

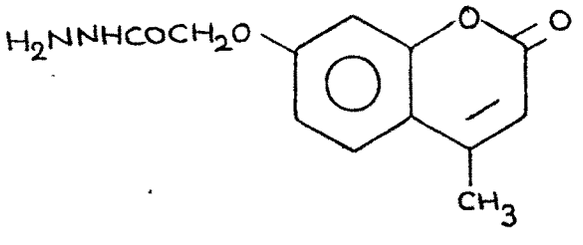
A.R. Parikh et al.[103] reported antibacterial activity of 2-amino-5-(4'-pyridyl)-1,3,4-oxadiazole which was prepared from isoniazide. This hydrazide was also used as intermediate for preparing other biologically active heterocyclic compounds.

Krejcoves Jiri and coworkers[104] synthesised 4-(7-hydroxy-coumarinyl) acetic acid hydrazides (79) from methyl-4-(7-acetoxycoumarinyl) acetate which showed luminescent properties.



(79)

A.K. Sen Gupta and coworkers[94] prepared (4-methyl-7-coumarinyloxy) acetic acid hydrazide (80) as an intermediate for biologically active heterocyclic compounds.



(80)

Present Work

As observed in the literature references, a large number of hydrazides reported have antitubercular, antibacterial and pesticial[105] properties. On the other hand, several

coumarin derivatives are found to have various biological activities.[106] It was therefore, thought meaningful to prepare hydrazides of coumarin derivatives and to examine if the products could exhibit and augment antimicrobial properties.

(8-Methoxy-5-coumarinomethyl)-substituted benzoic acid hydrazide (81)

General Method

A mixture of 8-methoxy-5-chloromethyl coumarin and various substituted benzoic acid hydrazide was condensed to give (8-methoxy-5-coumarinomethyl)-substituted benzoic acid hydrazides. The structures were confirmed by spectral analysis.

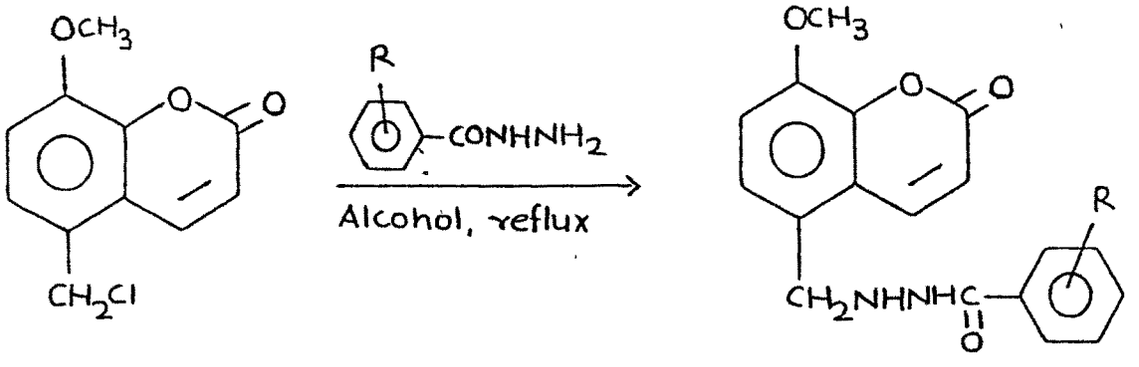
(8-Methoxy-5-coumarinomethyl)-p-methyl-benzoic acid hydrazide (81, Table-IV, 2)

8-Methoxy-5-chloromethyl coumarin and p-methyl benzoic acid hydrazide were reacted to furnish above hydrazide.

The IR (KBr) spectrum exhibited bands at 3200-3000 (NH), 1740-1720 (C=O of lactone and NHCO), 1600 (C=C aromatic), 1280 and 1085 (C-O-C) cm^{-1}. (Fig. 1).

The NMR spectrum (CF_3COOH) exhibited following signals δ 2.11, singlet, $-CH_3$ protons of phenyl ring ; δ 3.7, singlet, OCH_3 protons of coumarin ring at C-8 position ; δ 5.12, singlet,

Scheme:4



(81)

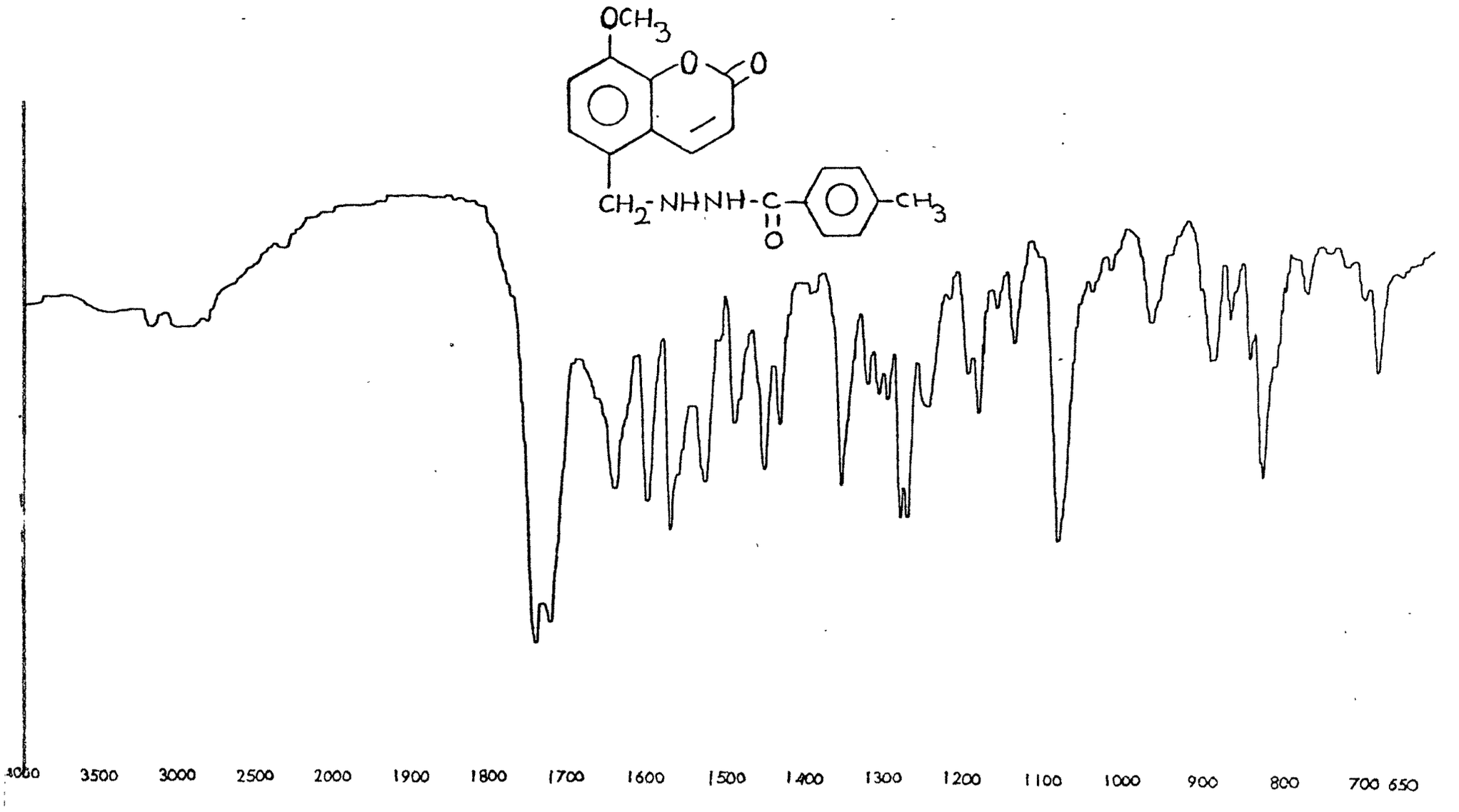
$\underline{CH}_2$ protons of $-CH_2NH$; a pair of doublet (J=9Hz) appeared at δ 6.49 and δ 8.15 for protons at C-3 and C-4 position of coumarin ring respectively. Aromatic protons appeared as multiplet in the region δ 6.85-7.4 (Fig. 2).

This NMR data confirmed the structure of the above compound.

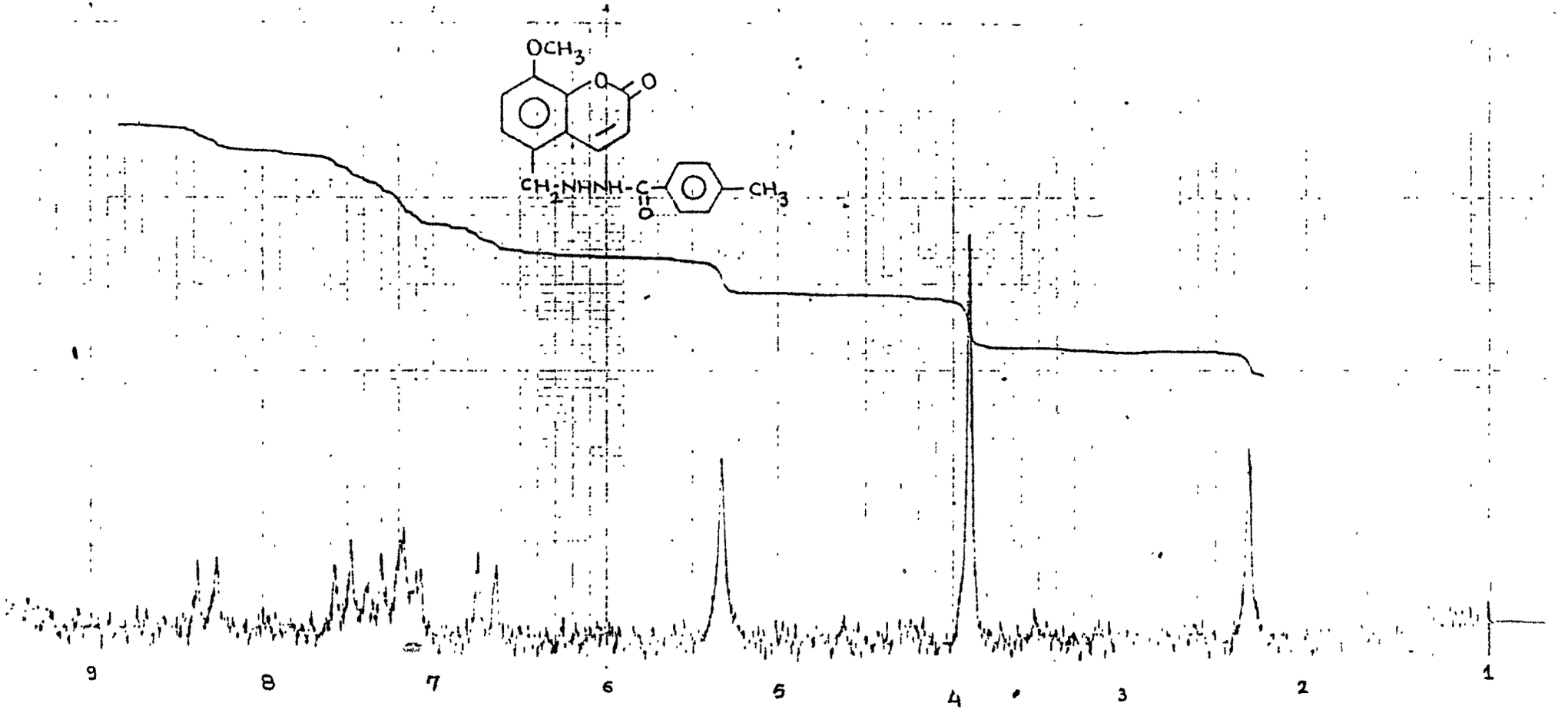
Similarly, other coumarinomethyl substituted benzoic acid hydrazides were prepared (81, Table-IV, 1-12).

Antimicrobial Activity

Some of the selected compounds were tested for their antimicrobial activity using cup-late method. They did not show any activity as they precipitated out of solution at testing temperature.



(Fig - 1) : 81, Table - IV, 2



(Fig - 2) : 81, Table - IV, 2

(0·2 PPm off set)

EXPERIMENTAL

(8-Methoxy-5-coumarinomethyl)-p-methyl benzoic acid hydrazide (81, Table-IV, 2)

A mixture of 8-methoxy-5-chloromethyl coumarin (0.01 mole) and p-methyl benzoic acid hydrazide (0.01 mole) was refluxed in absolute alcohol (30 ml) on a sand bath for 6-8 hr. The excess of alcohol was removed by distillation. The resulting solid was crystallised from 1:1 alcohol, M.p. 240°C, yield 65%.

Analysis	:	Found	:	C, 67.41	; H, 5.18	; N, 7.86%
$C_{19}H_{18}O_4N_2$	:	requires	:	C, 67.46	; H, 5.33	; N, 8.28%

TABLE - IV : ANALYTICAL AND PHYSICAL DATA OF (8-METHOXY-5-COUMARINOMETHYL) SUBSTITUTED BENZOIC ACID HYDRAZIDE (81)

Sr. No.	R	M.P.* °C	Yield %	Molecular Formula	Analysis % Found/(Calcd) C	H	N
1	m-CH_3-	233^{d+w}	65	$C_{19}H_{18}O_4N_2$	66.32 (67.46)	5.01 (5.33)	8.11 (8.28)
2	p-CH_3-	240^{a+w}	65	$C_{19}H_{18}O_4N_2$	67.41 (67.46)	5.18 (5.33)	7.86 (8.28)
3	m-OCH_3-	176^{a+w}	70	$C_{19}H_{18}O_5N_2$	64.53 (64.41)	5.41 (5.09)	8.08 (7.91)
4	p-OCH_3-	240^{d+w}	72	$C_{19}H_{18}O_5N_2$	64.82 (64.40)	4.94 (5.08)	7.63 (7.90)
5	o-Cl-	202^{a+b}	71	$C_{18}H_{15}O_4N_2Cl$	60.12 (60.34)	4.07 (4.19)	7.62 (7.82)
6	p-Cl-	229^{a}	63	$C_{18}H_{15}O_4N_2Cl$	60.01 (60.34)	4.18 (4.19)	8.24 (7.82)

cont.....

TABLE - IV cont....

7	m-Br-	249[a+b]	60	$C_{18}H_{15}O_4N_2Br$	53.4 (53.59)	3.31 (3.72)	6.82 (6.95)
8	o-NO_2-	185[a+w]	75	$C_{18}H_{15}O_6N_3$	58.2 (58.54)	3.95 (4.07)	11.11 (11.38)
9	m-NO_2-	215[a]	70	$C_{18}H_{15}O_6N_3$	58.11 (58.54)	4.39 (4.07)	11.12 (11.38)
10	p-NO_2-	254[d+w]	72	$C_{18}H_{15}O_6N_3$	58.30 (58.54)	3.95 (4.07)	11.1 (11.38)
11	p-OH-	240[a]	62	$C_{18}H_{16}O_5N_2$	63.22 (63.53)	4.42 (4.71)	7.94 (8.24)
12	p-NH_2-	245[d]	55	$C_{18}H_{17}O_4N_3$	63.39 (63.72)	4.9 (5.01)	12.06 (12.39)

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* Solvent of crystallisation : a = alcohol,
b = benzene,
d = DMF
w = water

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