Chapter - III
Part - I
Synthesis of Schiff bases of coumarin derivatives

SYNTHESIS OF SCHIFF BASES OF COUMARIN DERIVATIVES

INTRODUCTION

Recognition of the toxic effects of aflatoxin dates from 1960, when a disease named turkey X disease ravaged turkey flocks, with the resulting deaths of over 100000 birds in England. The origin of the disease was shown due to consumption of ground nut meal contaminated by a mould, containing a diverse array of toxins as reported by British workers. Early studies of Dikens and Jones[1,2] who determined the carcinogenic effects of a number of lactones and consistently found that carcinogenesis is associated with α, β-unsaturated lactones with four- , five and six membered rings. These authors have shown that presence of such stuctured features in AFB_1 could be responsible for the carcinogenic action of the toxins.

Schiff base formation

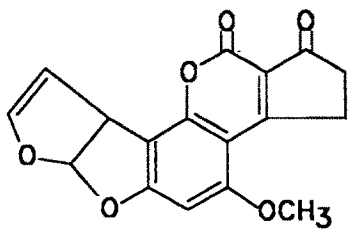
Chipley[3] and coworkers found that several protiolytic enzymes liberated a peptide (or amino acid) conjugate of AFB_{2a} after treatment by these enzymes of tissue extracts from chicken fed AFB_1. It was hypothesized that AFB_{2a} cleaves to form dialdehyde derivatives which form schiff bases with free amino groups of the microsomal proteins (scheme, after Patterson[4]). This may be the nature of the ultimate carcinogen formed from aflatoxins (Scheme - 1).

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 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 $CH_3CH_2CH(CH_3)\text{-}CH_2\text{-}CH_2\text{-}C(CH_3) = NC_2H_5$ is named N-2(4-methyl heptylidene) 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

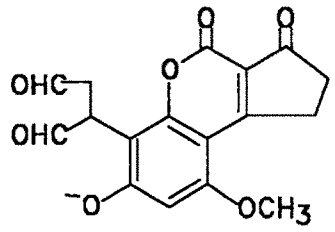
Certain imines are known to be liquid crystals.[5,6] Some imines have also been noted to exhibit phototrophy and thermotropy.

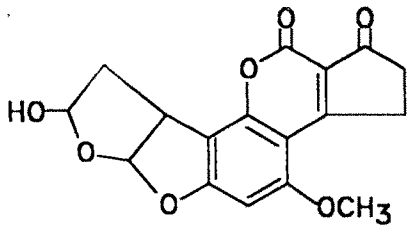
SCHEME–1



AFB1

NADPH–dependent microsomal enzymes

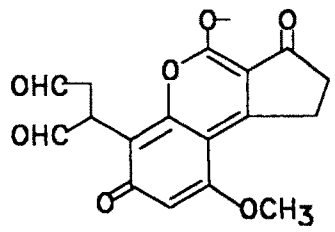


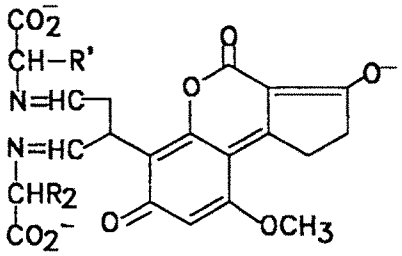


AF_{B2a}

resonancehybrids

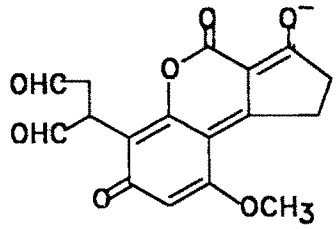
atPH 7or above





Hypothetical Schiff base

Covalent bonding to aminoacids and proteins



UV and visible spectra of imines depend on substituents. In IR of imines (of the type $R_2C=NH$), all dialkyl kitimines absorbed in the region from 6.08 to 6.10μ 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

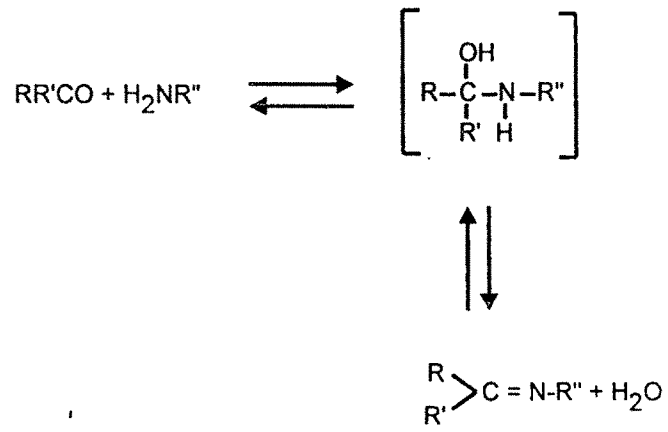
1 Reaction of aldehydes and ketones with Amines

The most common method for preparing imines is the reaction of aldehydes and ketons with amines. This reactions was first discovered by Schiff[7] and imines are often referred to as schiff bases (1).

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 it is formed.

Hammett[8] proposed that acids protonate the carbonyl group to give a carbonium ion which adds to the amine in 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[9] 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[10] (2). Similarly, tertiary aldehyde as neopentaldehyde and ammonia gives N-neopentylidine neopentylamine (3) and t-butylcyanide (4).



(1)

$$(CH_3)_2\,CHCHO + NH_3 \rightarrow [(CH_3)_2\,CHCH=N]_2\,CHCH\,(CH_3)_2$$

$$\downarrow$$

$$(CH_3)_2\,CHCH=NCH_2CH\,(CH_3)_2 + NH_3$$

(2)

$$(CH_3)_3\,CCHO + NH_3 \rightarrow [(CH_3)_3\,CCH=N]_2\,CHC\,(CH_3)_2$$

$$\downarrow$$

$$(CH_3)_3\,CCH=NCH_2C\,(CH_3)_3 + (CH_3)_3\,CCN$$

(3) (4)

2. Reaction of Nitrites with Organometallic Compounds

Moureau and Mignonac[11] were the first to add an aryl or alkyl Grignard to an arylcyanide to obtain after careful hydrolysis at - 15°C treatment with hydrochloric acid and finally with ammonia the ketimine (5).

3 Reaction of Carbon-nitrogen double bond Compound with Organometallics

Busch[12,13] 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. (6)

Montagne[14] later found that anilides which may be regarded as C-hydroxyimines, react with alkyl or aryl Grignards to give the corresponding imines (7).

Grammatickis[15] has also found that oximes of aromatic aldehydes react with Grignard to give as the predominant product the benzylamine of the Grignard with the ketimines (8) as the secondary product.

4 Dehydrogenation of Amines

Ritter[16] 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 (9). Secondary amines which are prepared from phenols, hexamethylenetetramine and 2-ethoxyethanol, are readily dehydrogenated to the imines (10) by heating hexamethylenetetraamine in acetic acid.[17]

5 Reaction of Phenols and Phenol ethers with nitriles

Hoesch and Houben[18-20] found that phenols or their ethers react with alkyl or aryl cynides in ether when catalysed by hydrochloric acid and or zinc chloride to give ketimines (11). The reaction works readily for dihydroxy compounds or monoethers where the groups are meta to one another.

6. Reduction of Carbon-Nitrogen Compounds

Oxime of aliphatic and aromatic ketones can be reduced with hydrogen and nickel under pressure to give ketimines[21] (12).

Nitriles when hydrogenated over nickel or platinum catalysts can give imines[22] (13).

$$C_6H_5CN + C_6H_5MgBr \longrightarrow C_6H_5C(=NMgBr)C_6H_5 \xrightarrow{H_2O/H^+} (C_6H_5)_2C = NH$$

(5)

$$C_6H_5\,C(Cl) = NAr + RMgX \longrightarrow C_6H_5\,C(R) = NAr$$

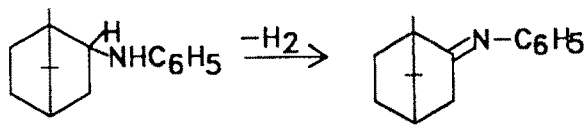
(6)

$$C_2H_5MgBr + PrCONHC_6H_5 \longrightarrow PrC(C_2H_5) = N\text{-}C_6H_5$$

(7)

$$ArCH = N\text{-}OH + RMgX \longrightarrow ArCHNHR + ArC(R) = NH$$

(8)



(9)

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

(10)

Lithiumaluminiumhydride in tetrahydrofuran has been found to reduce aromatic nitriles to give imine (14).

Nitriles also can be reduced to imines with stannous chloride in ethylacetate containing hydrochloric acid.[23]

β α
α-Nitrotyrenes can be reduced with Lithiumaluminium hydride to imine[24] (15).

7. Reaction of Nitroso compounds with active hydrogen compounds

The reaction of active hydrogen compounds with nitroso compounds formed imines (16).

8 Reaction of metal amides

An alkali metal or calcium salt of primary amines reacts with aromatic ketones to give imines[25] (17).

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[26] (18).

9 Miscellaneous Methods

Imines react with other amines to give the exchange products[27,28] e g. (19) gives (20). Also (21) reacts with diphenethyl formamidine in dioxane to give[29] (22)

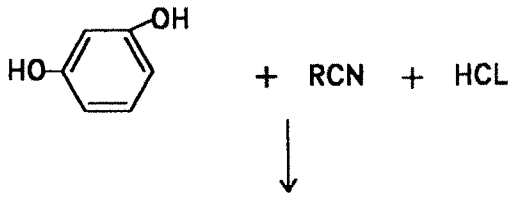
Secondary nitroalkanes react with primary amines to give imine[30] (23).

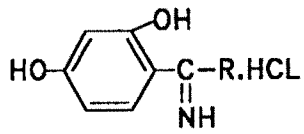
α-aminoacids react with sodium hypochlorite to give the chloramine intermediate which decomposes with the elimination of carbon dioxide and sodium chloride to give the imine[31](24).

ADDITION REACTIONS OF IMINES

1 Addition of Water

Reddelien and Danilof[32] 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.[33]





(11)

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

(12)

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

(13)

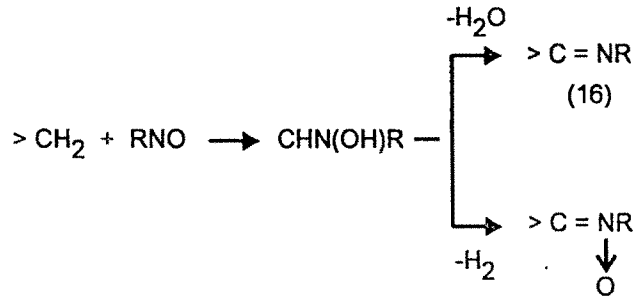
$$RCH = NH + R\,CH_2NH_2 \longrightarrow RCH_2NHCH_2R + NH_3$$

$$C_6H_5CN \xrightarrow{LiAlH_4} C_6H_5CH_2NH_2 + C_6H_5CH_2N = CHC_6H_5 + NH_3$$

(14)

$$C_6H_5CH = CHNO_2 \longrightarrow C_6H_5CH_2CH = NH$$

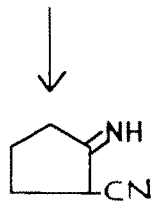
(15)



$$(C_6H_5)_2CO + C_6H_5NHNa \longrightarrow (C_6H_5)_2C=NC_6H_5$$

(17)

$$NC(CH_2)_4CN + NaNR_2$$



(18)

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

(19) (20)

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 with the acid catalysed dehydration of the carbinol intermediate 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 aldamines give the secondary amines by a platinum catalytic reduction.[34] Aliphatic ketimines are also reduced to secondary amines by platinum catalysts.[35,36] Other catalysts such as nickel copper chromite and 1000 psi of hydrogen also reduce imines.

Mailhe[37] reduced n-benzylideneaniline and N-isobutylidene aniline over nickel by vapour phase hydrogenations.

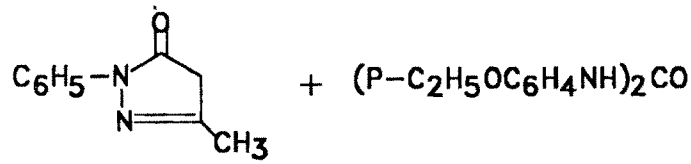
There are many chemical reagents which will reduce imines. Most of the reagents that are used to reduce ketones and aldehydes will reduce imines e.g. sodium and refluxing alcohol,[38,39] sodium amalgam, zinc and acetic acid,[40] magnesium in methanol,[41] lithiumaluminiumhydride[42-44] sodiumaluminiumhydride, sodiumborohydride in methanol.[45] The imino group can be selectively reduced in the presence of other groups such as nitro, chloro, methoxy and hydroxyl with sodiumborohydride.[46,47]

3 Addition of Primary Amines

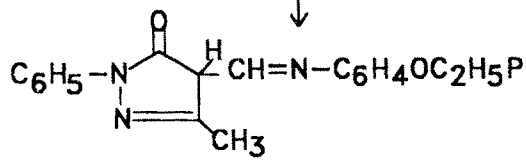
The addition of primary and secondary amines take place just as water adds to imines. The intermediate 1, 1-diamino alkane (25) is not stable and in the case of secondary amines no reaction occurs because determination of this (25) can only give the starting material. The exchange reaction, in the case of primary amines was first used by Reddelien[48] to obtain imines (26).

4 Addition of active hydrogen compounds

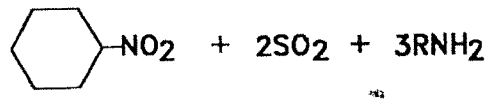
Numerous compounds containing an active hydrogen add to the imines (27) in the manner shown here to give (28).

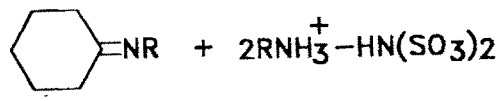


(21)

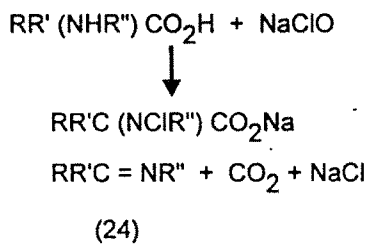


(22)

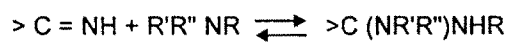




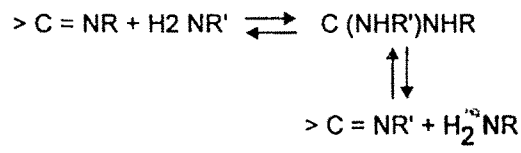
(23)


RR' (NHR") CO_2H + NaClO
RR'C (NClR") CO_2Na
RR'C = NR" + CO_2 + NaCl

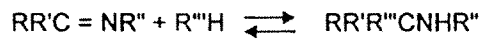
(24)


> C = NH + R'R" NR
>C (NR'R")NHR

(25)


> C = NR + H2 NR'
C (NHR')NHR
> C = NR' + $H_2^{\oplus}$NR

(26)


RR'C = NR" + R'"H
RR'R'"CNHR"

(27) (28)

Imines derived from aliphatic aldehydes and ketons which contain an α-hydrogen undergo aldol condensation e.g. N-2-propylideneaniline reacts with itself in the prresence of hydrogen chloride to give 2,2-4-trimethyl hydroquinoline (29). This involves an aldol condensation, cyclisation and deamination.[49-51]

Most of the addition reaction 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.

MISCELLANEOUS REACTIONS OF IMINES

1 Reactions involving ring formation

When N-benzylidene propylamine is treated with hydrocyanic acid 1-propyl-6-phenyl-2,4-diketohexahydrocynidene is obtained[52] while phenyl isocynate and N-benzylideneethylamine[53] react to give (30).

Snyder[54,55] has found that N-2-ethylhexen-2-ylideneaniline 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 (31).

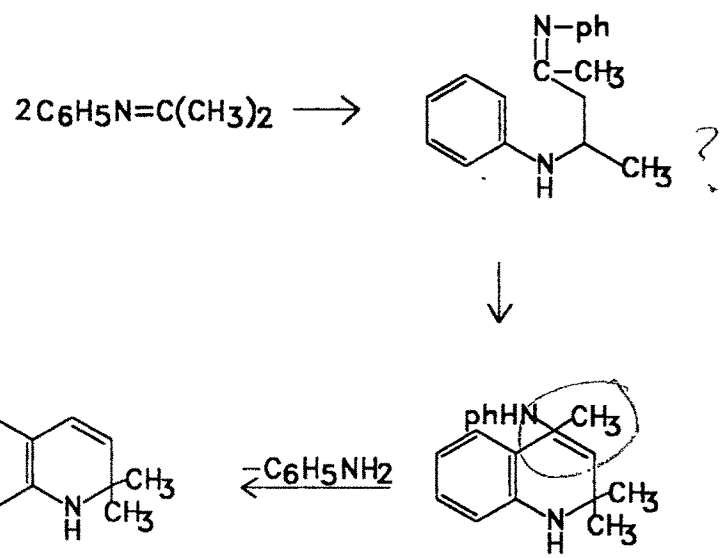
1,2-Diaminonaphthalene reacts with excess benzaldehyde to give the monoimine 2-N-benzylidene-1, 2-diaminonaphthalene. In the presence of hydrochloric acid, N-benzyl-C-phenylnaphth (1,2) imidazole (32) is formed.[40]

An improved Pomeranz-Fritsch isoquinoline synthesis utilizes N-2, 2'-ethoxy-ethylidene benzylamine which is cyclised with sulfuric acid. Polyphosphoric acid and phosphoryl chloride are also effective catalysts and the thienylideneamine can also be cyclised.[56,57] It furnished (33).

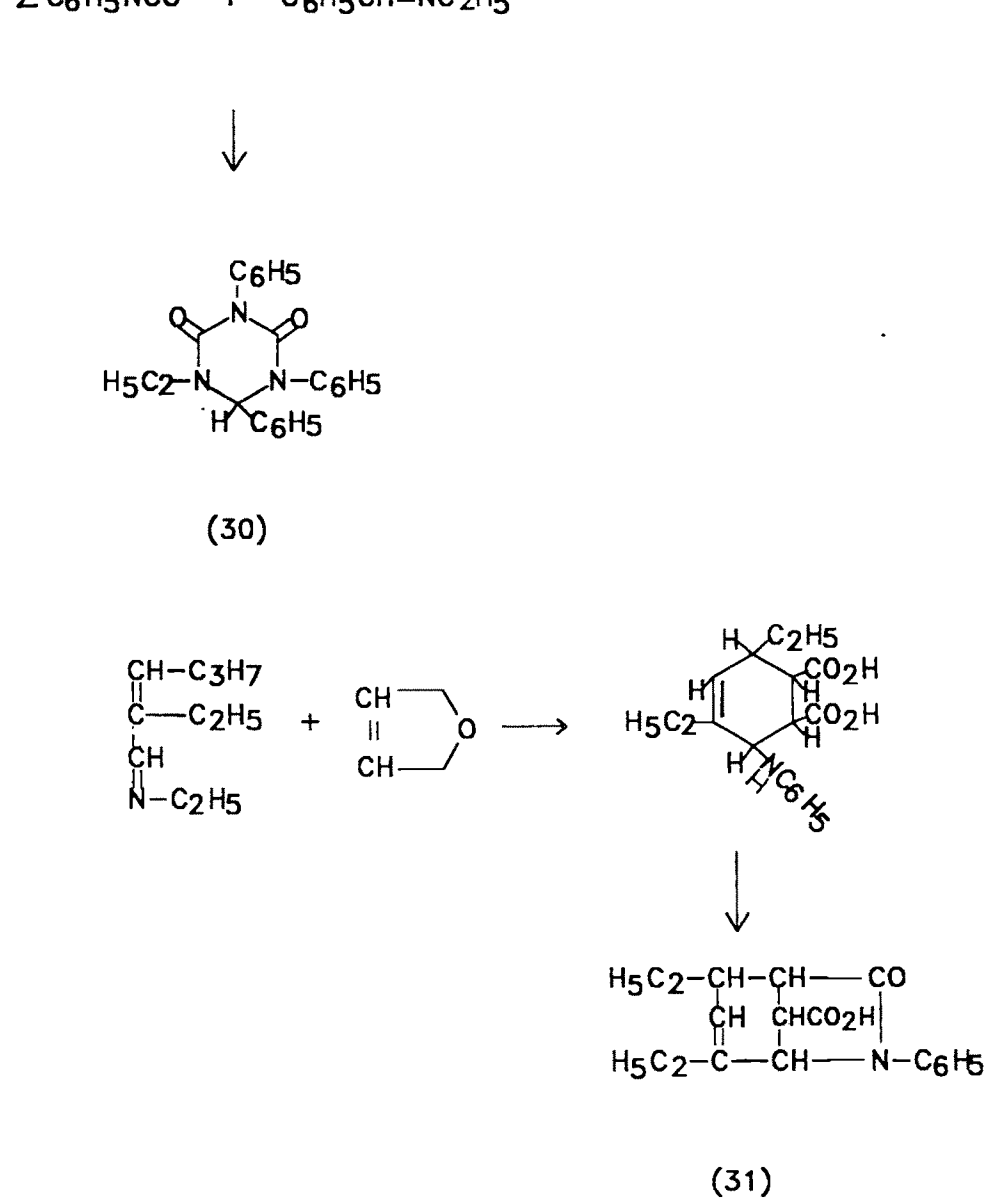
N-Nitrobenzylidene-o-phenylenediamines are oxidised with leadtetraacetate to give the nitro-substituted benzoxazoles[58,59] (34).

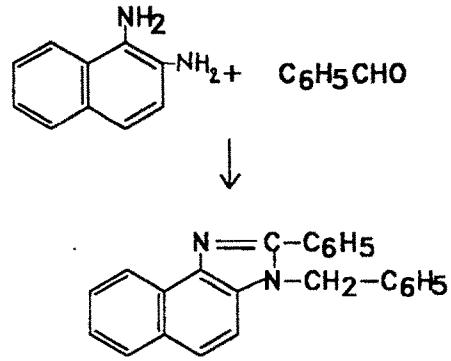
N-Benzylideneaniline and sulfur at 280°C gives 2-phenylbenzathiazole[60] (35).

The imines of β-oxoacid ester, β-diketones and β-oxoaldehydes are cyclised to β-hydroxypyrroles[61] (36).


2C6H5N=C(CH3)2
N–ph
C–CH3
CH3
N
H
?
phHN
CH3
CH3
CH3
N
H
−C6H5NH2
CH3
CH3
N
H

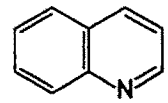
(29)


2 C6H5NCO + C6H5CH=NC2H5
C6H5
H5C2
C6H5
H
C6H5
(30)
CH-C3H7
C-C2H5
CH
N-C2H5
CH
O
CH
H
C2H5
CO2H
H5C2
CO2H
H
C6H5
H5C2-CH-CH-CO
CH CHCO2H
H5C2-C-CH-N-C6H5
(31)

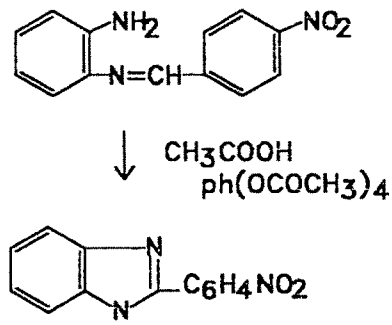


(32)

$C_6H_5CH_2N{=}CHCH[OC_2H_5]_2$



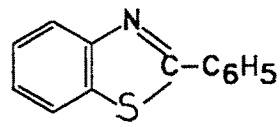
(33)



(34)

$C_6H_5CH{=}NC_6H_5 + S$

↓

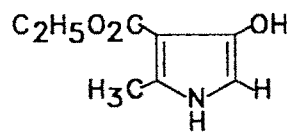


(35)

$C_2H_5O_2CCH_2C(CH_3){=}NCH_2CO_2C_2H_5$

$+ C_2H_5ONa$

↓ $(C_2H_5)_2O/0°$



(36)

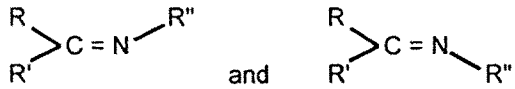
N-Benzylidene-2-phenylaniline (37) is cyclised in stannic chloride in refluxing o-dichlorobenzene or with phosphorous pentachloride in trichlorobenzene to give (38).

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 salicyldehyde complex with metals[62], with Cu^{++} they form complex (39).

Syn-anti Isomerization of Imines

The fact that imines posses a double bond suggests that geometric isomers should be possible like (40) and (41).

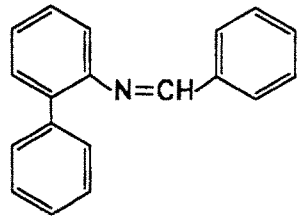


(40) and (41)

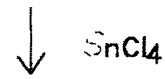
N-salicylidene-p-carbethoxy aniline was found to exist as yellow needles which melt at 145°C. These needles when exposed to light are converted to orange-red needles which melt at 259°C.[63] This was attributed to the isolation of the syn and anti isomers of this compound.

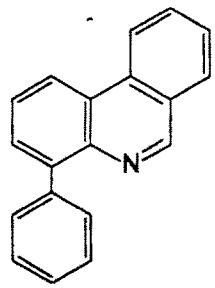
Aliphatic and aromatic imines, including N-salicylidene-p–carbethoxyaniline, were investigated in the ultraviolet and visible regions before and after illumination with ultraviolet light for 5-6 hours. All of the imines investigated showed no difference in the absorption spectra. Consequently no isomerisation was noted, and it was concluded that all the materials tested exist in the antiform.[64]

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

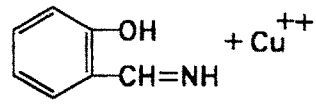


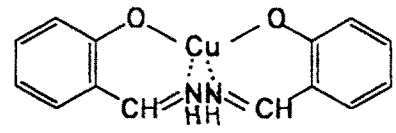
(37)





(38)



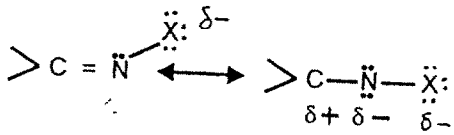


(39)

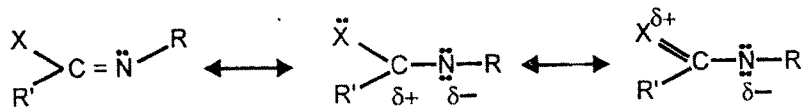
Curtin and Hausser[65] are the first workers to demonstrate that imines are capable of existing in syn and anti isomer forms. They have measured the rate of isomerisation of the imine obtained from p-nitro- or p-chlorobenzophenone dichloride and methyl amine. Crystalline p-chlorobenzophenone methylamine exists as the syn 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 show an equilibrium of syn and anti isomers as determined by nuclear magnetic resonance spectroscopy. Mutarotations of substituted N-benzylidene benzylamines in the pure state and in solution have been used to suggest syn-anti isomerisation.

Imines cannot be isolated in both syn and anti forms due to the ease of free rotations 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,[66] 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 charges in the following resonance structures.



This would give the imino group more double bond character that 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[67-68]. These groups could facilitate the polarisation of the imines group by their resonance contribution.



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

C.Antonello and G.Baretta[69] synthesised azomethines (42), (43) 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.

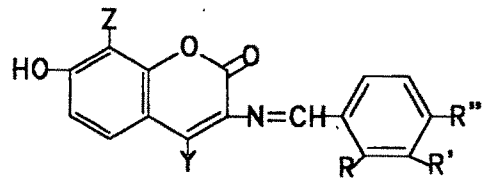
Datta and Daniels[70] prepared semicarbazones, p-nitrobenzoyl hydrazones and isonicotinoyl hydrazones from unsubstituted and 3-substituted-4-phenyl-2-oxo-3-butenoic acid and 6-formyl-1-2-benzopyrone. They measured the toxicities and in vitro antitubercular activities. They found that three isonicotinoyl hydrazones showed antitubercular activity.

Trkovnik et al[71,72] synthesised azomethines (44), (45) and (46) from 6-and 8-aminocoumarin and 3-amino-4-hydroxy-6-chlorocoumarin.

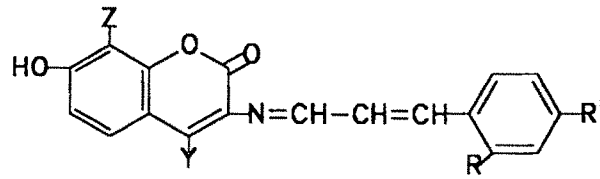
Bobarevic Blanka, Trkovnik Mladen and V.Knez[73] obtained hydrazones (47), (48) from 3-formyl-4-hydroxy-6-bromocoumarin and hydrazinehydrate and phenylhydrazine hydrate.

Strakov and co-workers[74] synthesised schiff bases (49) from 3-acetyl-4-hydroxycoumarin and various primary amines.

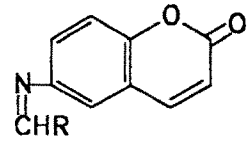
Shridhar et al[75] prepared different nitrones (50), (51) by condensing 4-formyl-7-methoxy- and 3-formyl (or acetyl)-4-hydroxy-7-methoxycoumarin with HONHR or



(42)



(43)



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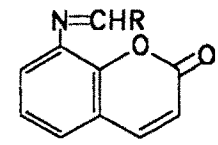

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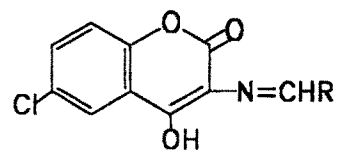

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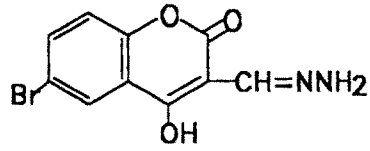

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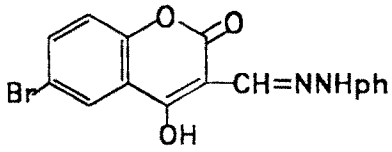

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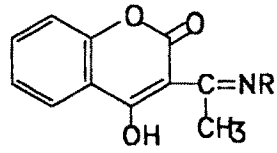

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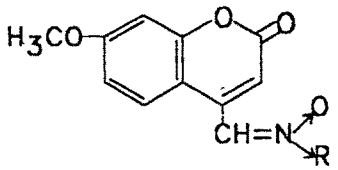

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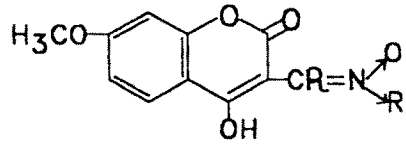


(51)

HONHR1. It was found that N-alkyl/aryl nitrones derived from someheteroarometic system were found as bactericides, fungicides and antiprotozoal agents.

Shridhar, Vishwakarma and Bhujanga[76] synthesised schiff bases (52) from 4-formyl-7-methoxycoumarin and appropriate amines. Schiff bases derived from 2,4-dichloroaniline, semicarbazide and N-amino-morpholine were found to posses antibacterial, antifungal amebicidal and anthelmintic activities.

Veerabhadraian Uadarapu Rao, Vedeela Rajeswar Rao, Tadeplay Venkata Padmanbha[77] prepared schiff bases (53). Reactions of (53) with $HSCH_2CO_2H$ and $ClCH_2CO_2H$ gives (54) and (55) respectively.

Rajeev Vyas and R.H. Mehta[78] synthesised 8-methoxycoumarin-3-carboxy-o-(N-benzylidene)aniline (56) and studied their antibacterial activity.

Sonal Shah, Rajeev Vyas and R.H.Mehta[79] synthesised various schiff bases (57), (58),(59) and (60) from 8-hydroxy, and 8-methoxycoumarin derivatives, some of them were found active against S.aureus and S.albus.

Prasad K. Rajendra and Darbarwar Malleswar[80] have prepared 6,8-substituted-3-aminocoumarin derivative (61) and synthesised schiff bases (62) from it

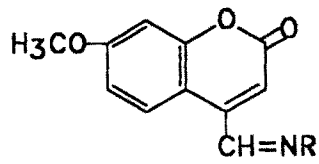
Gursoy Aysel, Karali Nilgun, Otuk Gulten[81] have synthesised (63) and (64) from 3-acetylcoumarin which showed significant antibacterial, antifungal insecticidal and herbicidal activity.

C.D.Lakkannaur, V.D.Anklekar and K.V.Kulkarni[82] carried out schiff base synthesis of (65) starting from 6-methyl-4-chloromethyl coumarin.

H.C.Sharma and N.K.Chudgar[83] prepared schiff bases (66) from 3-aminocoumarin and studied their liquid crystaline properties.

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



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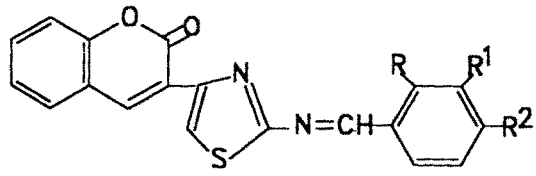

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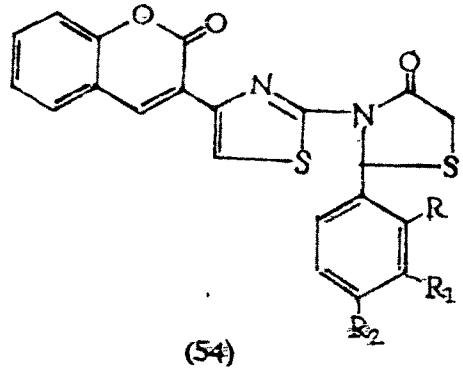

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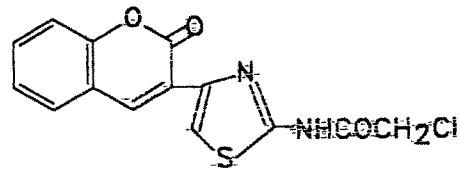

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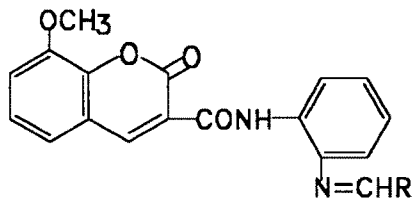
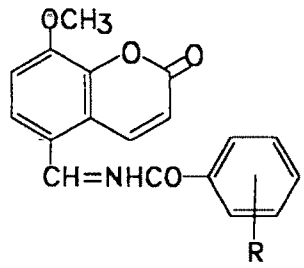
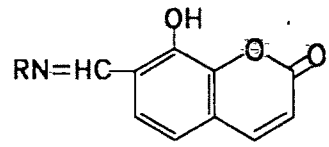

OCH3
O
O
CONH
N=CHR

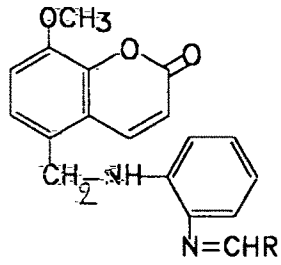
(56)


OCH3
O
O
CH=NHCO
R

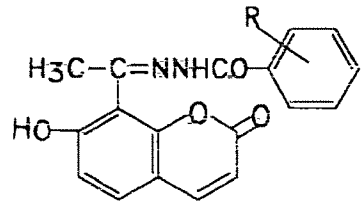
(57)


OH
RN=HC
O
O

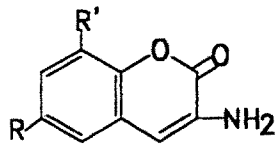
(58)


OCH3
O
O
CH2-NH
N=CHR

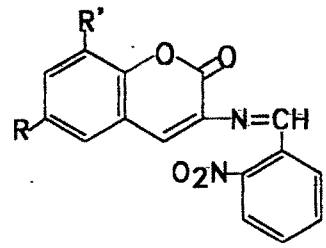
(59)


R
H3C-C=NNHCO
HO
O
O

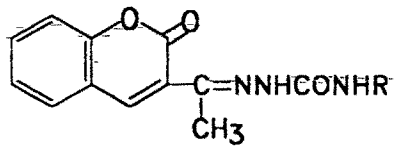
(60)



(61)



(62)



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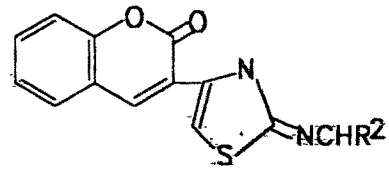

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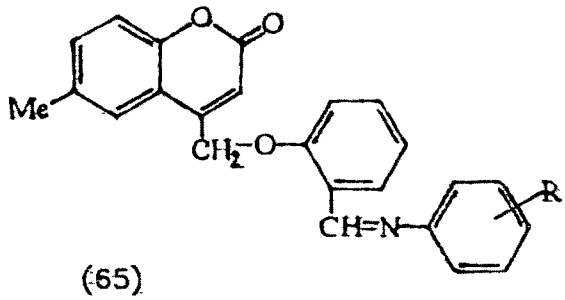

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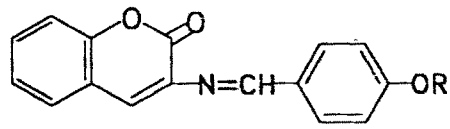


(66)

from various coumarin derivatives like 7,8-dimethoxy-3-(3'acetylphenyl aminomethyl)-4-methylcoumarin, 7,8-dimethoxy-3-(4'-acetylphenyl aminomethyl)-4-methylcoumarin, 7,8-dihydroxy-6-formyl-4-methylcoumarin,6'-hydroxy-5'formyl-4-methyl-7,8 benzocoumarin and 7-n-butoxy-3-aminocoumarin with various substituted benzoic acid hydrazides and primary aromatic amines.

7,8-Dimethoxy-3-[3'-yl-ethylidene-(2"-nitrobenzoic acid hydrazide)-phenyl aminomethyl] -4-methyl coumarin (70, Table - 1,2) (Scheme - 1).

A mixture of 7,8-dimethoxy-3-(3'-acetylphenylaminomethyl)-4-methylcoumarin[85] (69) and 2-nitrobenzoic acid hydrazide was refluxed with few drops of glacial acetic acid which gave the product to which 7,8-dimethoxy-3-[3'-yl-ethylidene (2"nitro benzoic acid hydrazide)-phenylaminomethyl]-4-methylcoumarin structure was assigned. The structure was confirmed by following spectral data.

The IR spectra (KBr) showed bands at 3400 cm^{-1} for NH, 1730 cm^{-1} for lactonic C=O, 1600 cm^{-1} for aromatic C=C ring stretch, 1670 cm^{-1} amide band I, 1560 cm^{-1} amide band II, 1390 cm^{-1} C=N and 1100 cm^{-1} for C-O-C linkage (Fig.1).

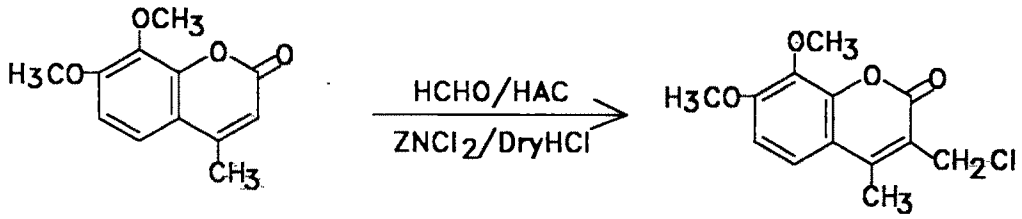
The PMR spectra in CF_3COOH exhibited a singlet at δ 2.3 for three protons of methyl group at C-4 overlapping a singlet at δ 2.6 for three protons of other methyl group i.e. =C-CH_3; a singlet at δ 3.8 for six protons of two methoxy groups at C-7 and C-8, a singlet at δ 4.8 for two protons of methylene group, CH_2NH; a doublet at δ 6 75 for one proton at C-6; a doublet at δ 7.9 for one proton at C-5 overlapping a multiplet obtained for rest of the aromatic protons between δ 7.1-7.7 (Fig.2).

Other Schiff bases (Table - 1, 1-7) on this coumarin moiety were synthesised in similar way.

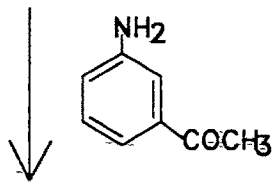
7,8-Dimethoxy-3[4'-yl-ethylidene(2"-nitro benzoic acid hydrazide)phenylaminomethyl]-4-methyl coumarin (72, Table - 2, 3) (Scheme - 2).

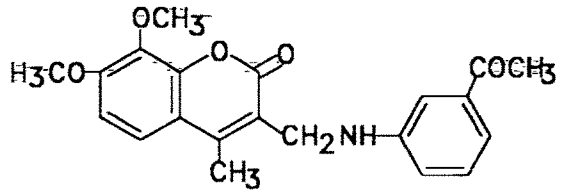
A mixture of 7,8-dimethoxy-3-(4'-acetylphenylaminomethyl)-4-methylcoumarin[85] (71) and 2-nitrobenzoic acid hydrazide was refluxed in absolute alcohol with few drops of glacial acetic acid which furnished the product to which 7,8-dimethoxy-3[4'-yl-ethylidene(2"-nitrobenzoic acid hydrazide)phenylaminomethyl]-4-methylcoumarin structure was assigned.

Scheme - 1

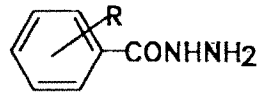


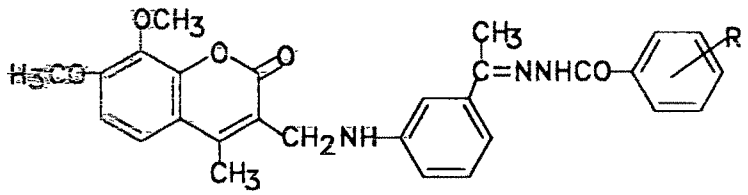
(67) (68)





(69)





(70, Table–1, 1 - 7)

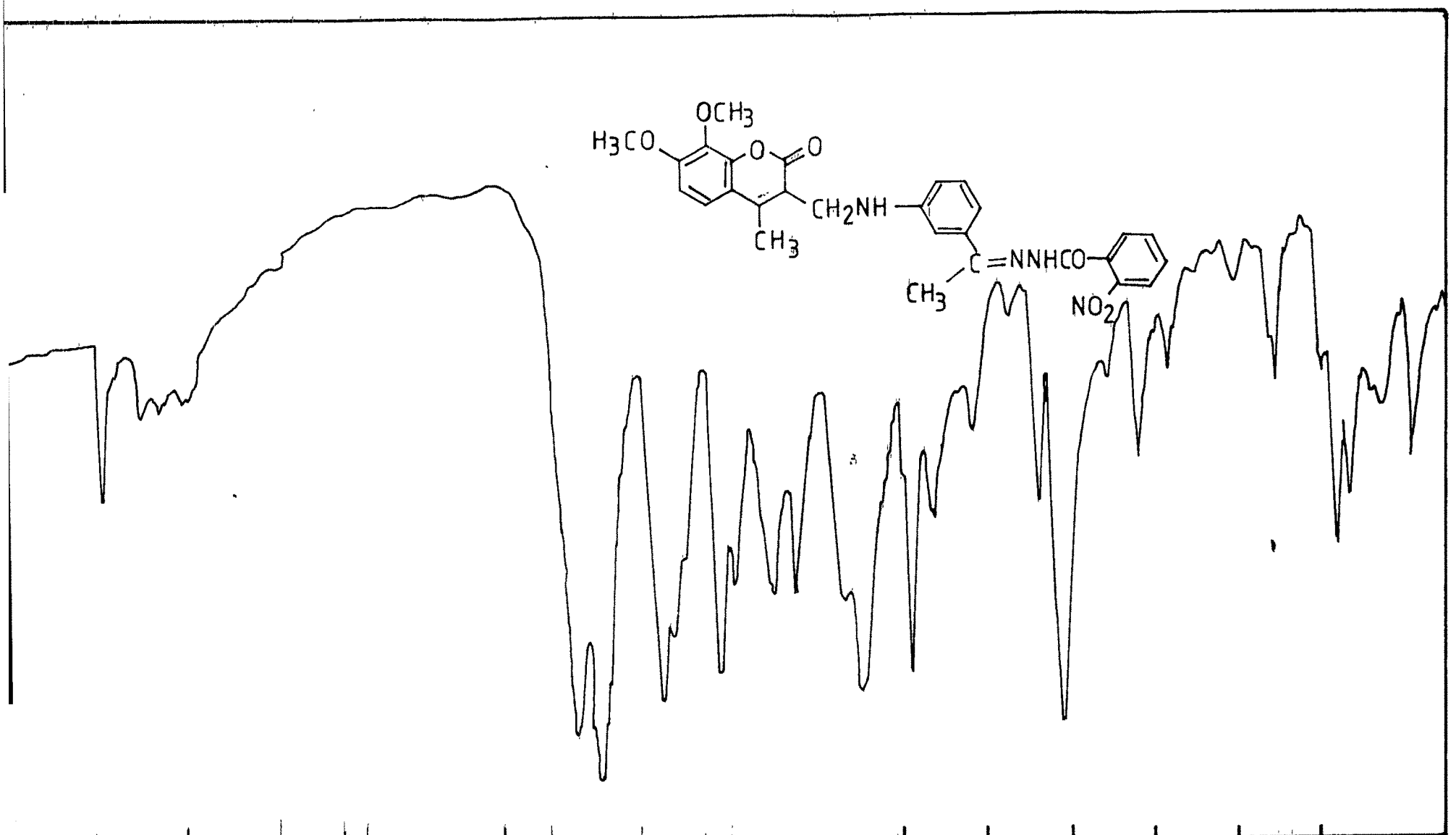

OCH3
H3CO
O
O
CH2NH
CH3
C=NNHCO
CH3
NO2
3000
2000
1800
1600
1400
1200
1000
800
Wavenumber cm-1

FIG.1

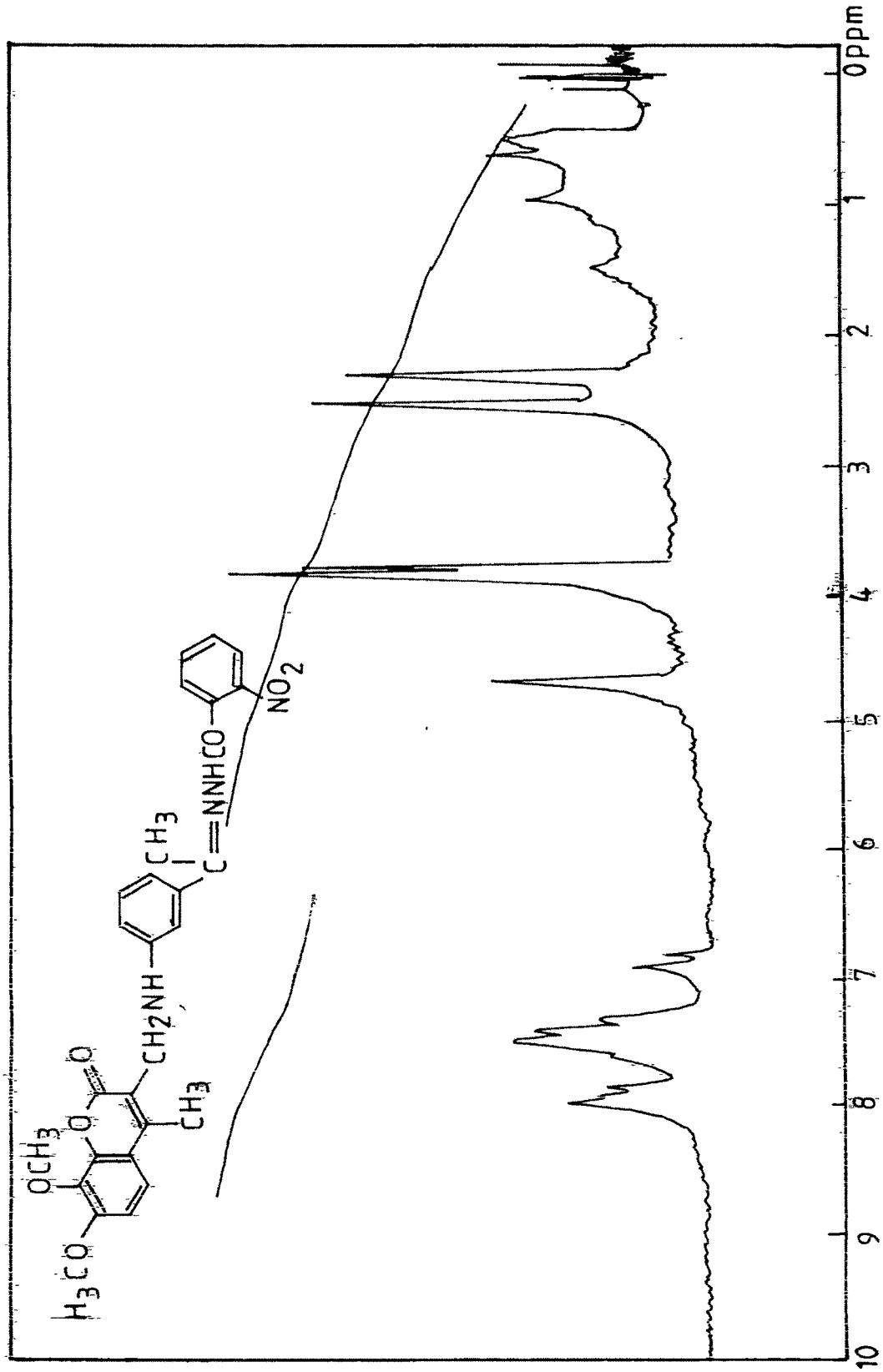
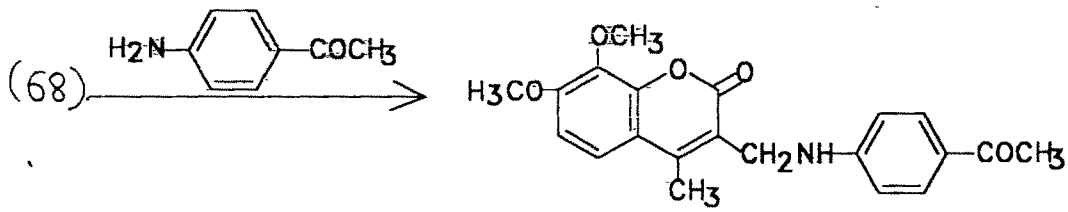
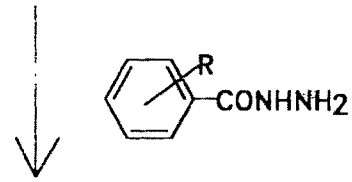


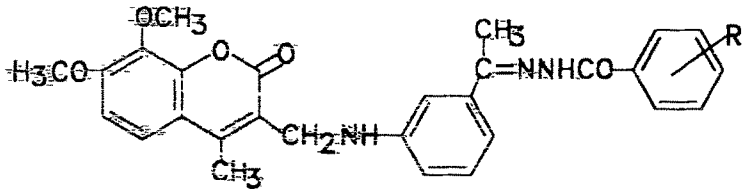
FIG. 2

Scheme--2



(71)





(72, Table-2, 1-6)

The structure of this compound was established on the basis of IR, PMR and Mass spectra.

The IR spectrum (KBr) showed following bands at 3450 cm^{-1} for NH, 1700 cm^{-1} for lactonic C=O, 1600 cm^{-1} for aromatic C=C, 1660 cm^{-1} for amide band I, 1530 cm^{-1} for amide band II, 1370 cm^{-1} for C=N and 1100 cm^{-1} for C-O-C linkage (Fig. 3).

The PMR spectra in CF_3COOH exhibited a singlet at δ 2.25 for three protons of methyl group at C-4 overlapping a singlet at δ 2.8 for three protons of other methyl group i e. =C-C$\underline{H}_3$; a singlet at δ 3.95 for six protons of two methoxy groups at C-7 and C-8; a singlet at δ 4.9 for two protons of methylene group C$\underline{H}_2$-NH; a doublet at δ 7 1 for one proton at C-6; a doublet at δ 8.05 for one proton at C-5 and a multiplet between δ 7.4-7.8 for rest of the aromatic protons (Fig.4).

The Mass spectra of this compound showed following m/z peaks; 530 (M^+, 11 6%) and 233 (Base peak, 100%) (Fig.5)

All other Schiff bases (Table - 2, 1-6) on this moiety were prepared in same way

7,8-Dihydroxy-6-(4'-methyl phenyl iminomethyl)-4-methylcoumarin (75, Table - 3, 1) (Scheme - 3).

When 7,8-dihydroxy-6-formylcoumarin[86] (74) was condensed with p-toluidine in glacial acetic acid, gave a product which was assigned 7,8-dihydroxy-6-(4'-methylphenyl iminomethyl)-4-methylcoumarin structure. This was charecterised on the basis of following spectral data.

The IR spectra (Nujol) showed following bands at 1700 cm^{-1} for lactonic C=O, 1610 cm^{-1} for aromatic C=C, 1580 cm^{-1} for C=N and 1050 cm^{-1} for C-O-C linkage (Fig 6)

The PMR spectra in CF_3COOH exhibited a singlet at δ 2.35 for three protons of methyl group at C-4 overlapping a singlet at δ 2.55 for three protons of methyl group of p-toluidine moiety; a singlet at δ 6.45 for one proton at C-3; a multiplet between δ 7.23-7.6 for aromatic protons; a singlet at δ 7.9 for one proton at C-5 and a singlet at δ 9.05 for one proton of =C-$\underline{H}$ (Fig. 7).

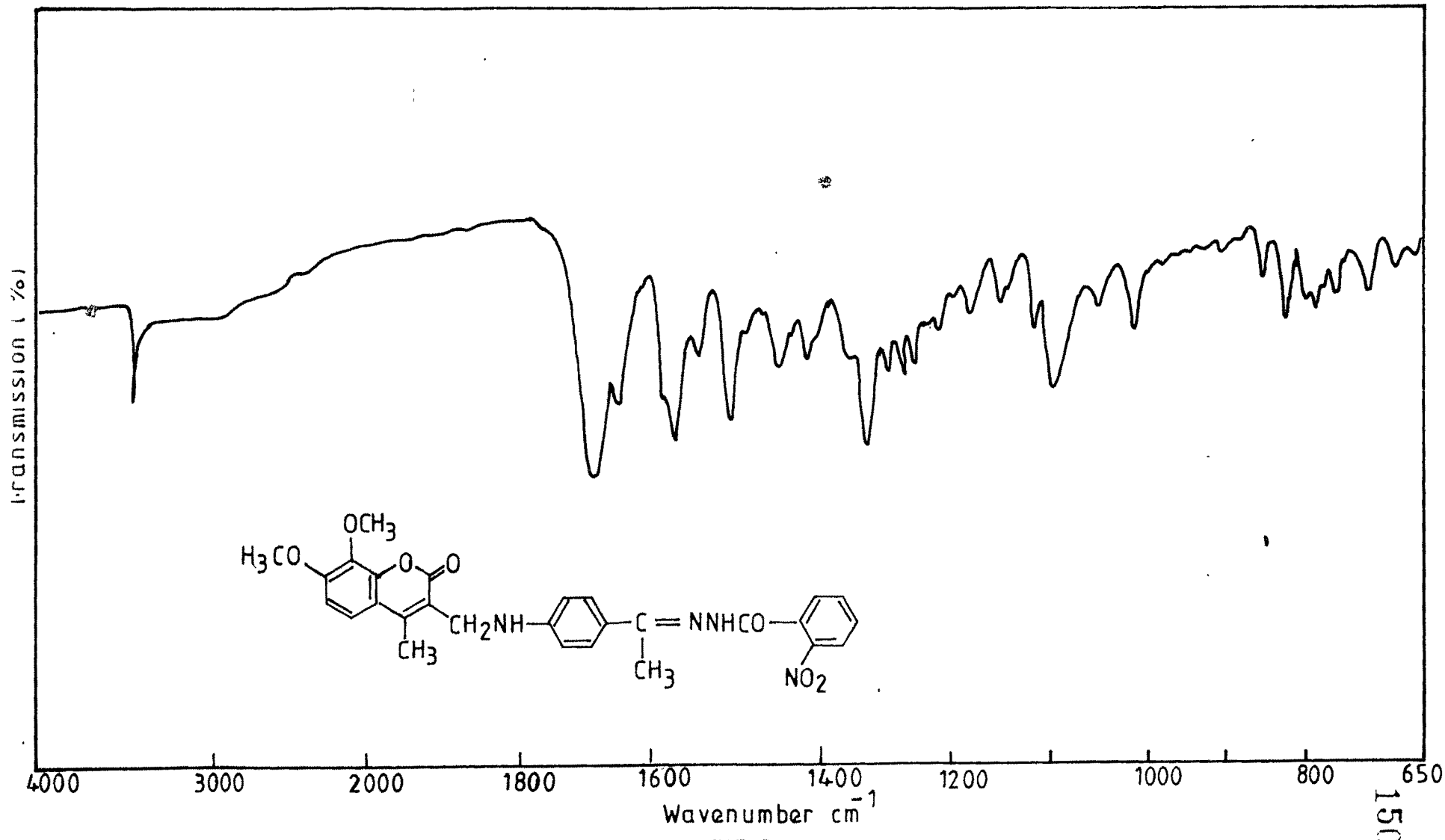

Transmission (%)
OCH3
H3CO
O
O
CH2NH
C = NNHCO
CH3
CH3
NO2
4000
3000
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm-1

FIG 3

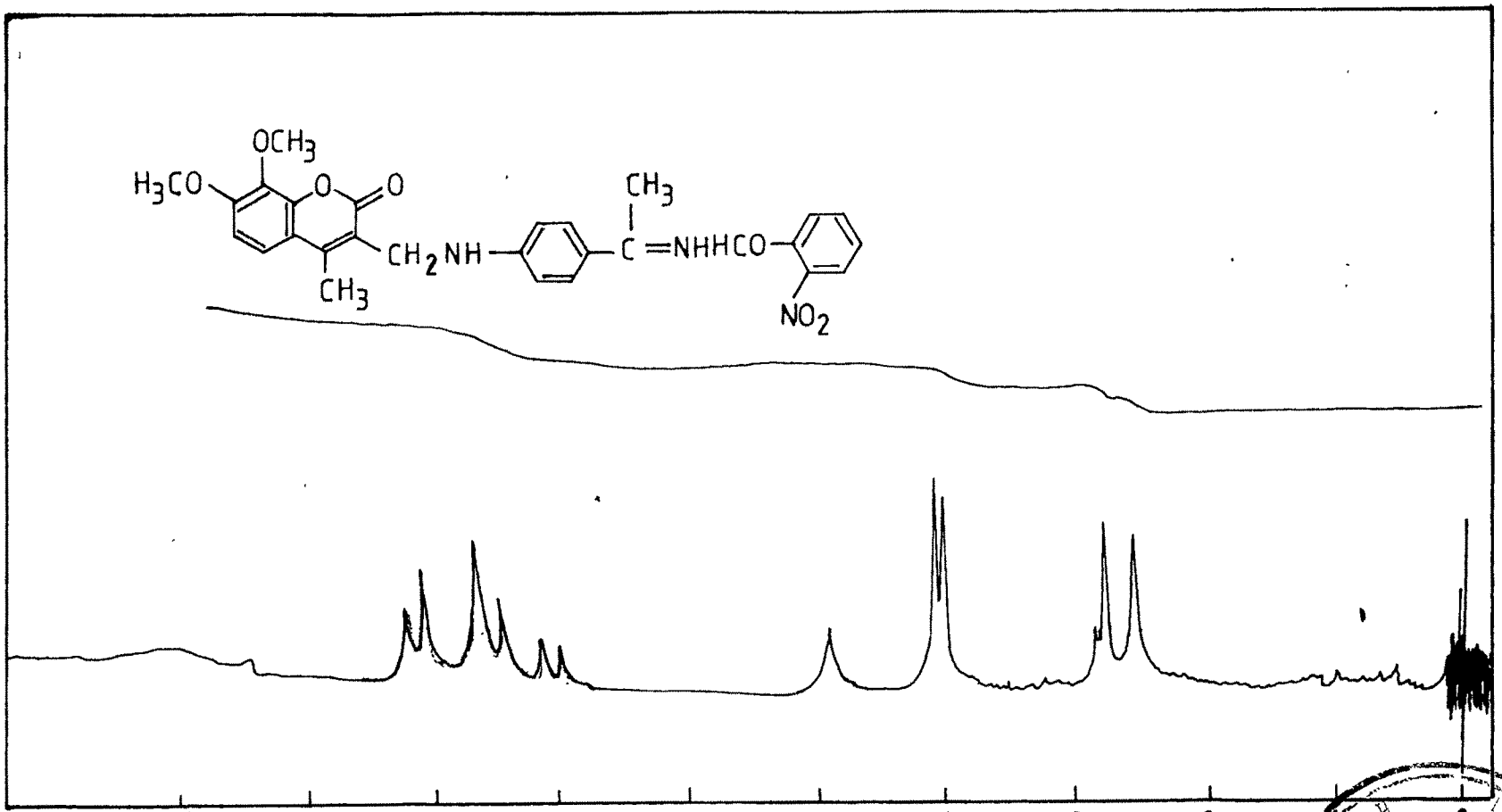


FIG. 4

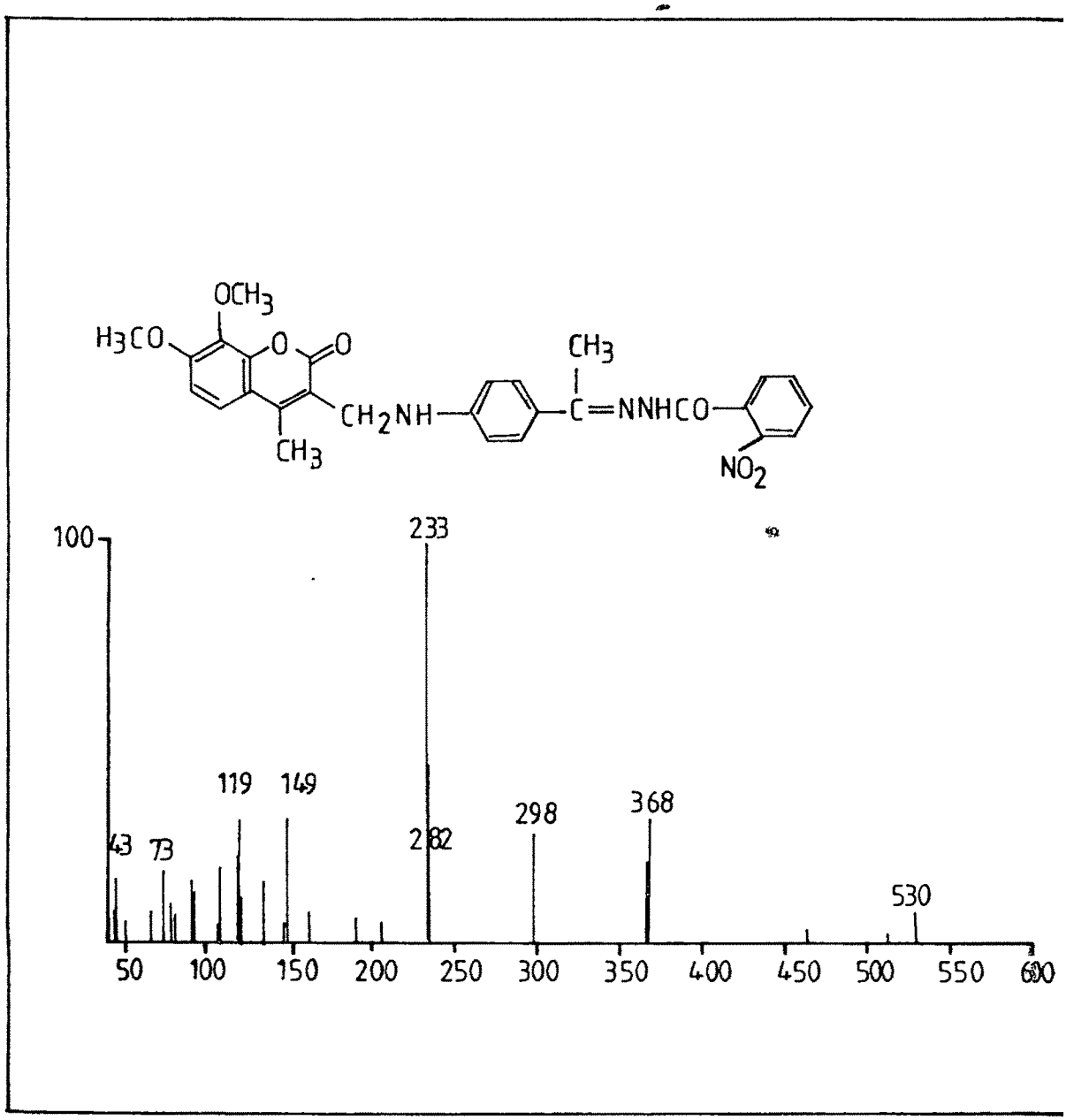

OCH3
H3CO
O
O
CH3
CH2NH
C=NNHCO
CH3
NO2
100
233
119
149
43
73
282
298
368
530
50
100
150
200
250
300
350
400
450
500
550
600

FIG. 5

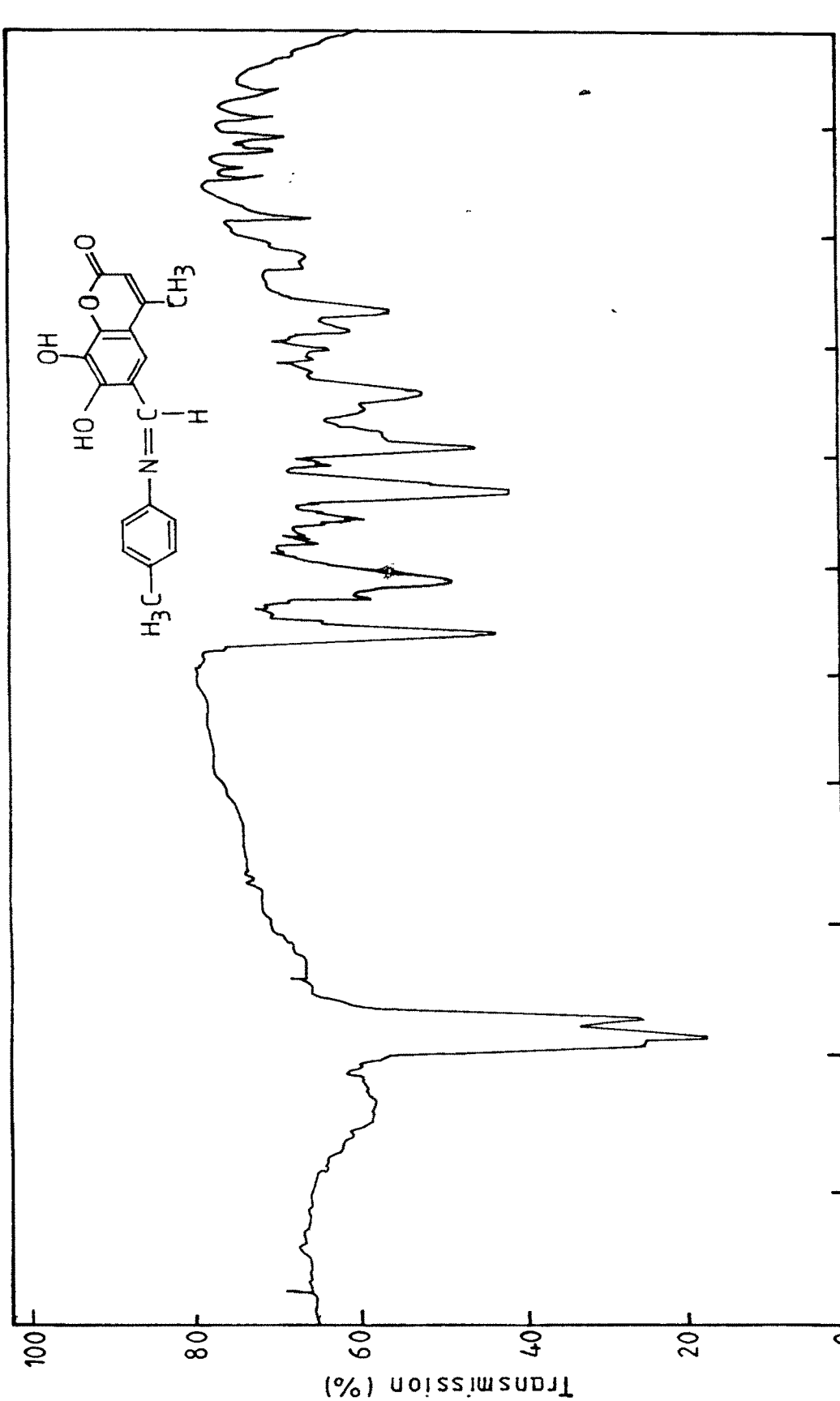

Transmission (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm⁻¹
OH
HO
O
O
CH3
N=C
H
H3C

FIG. 6

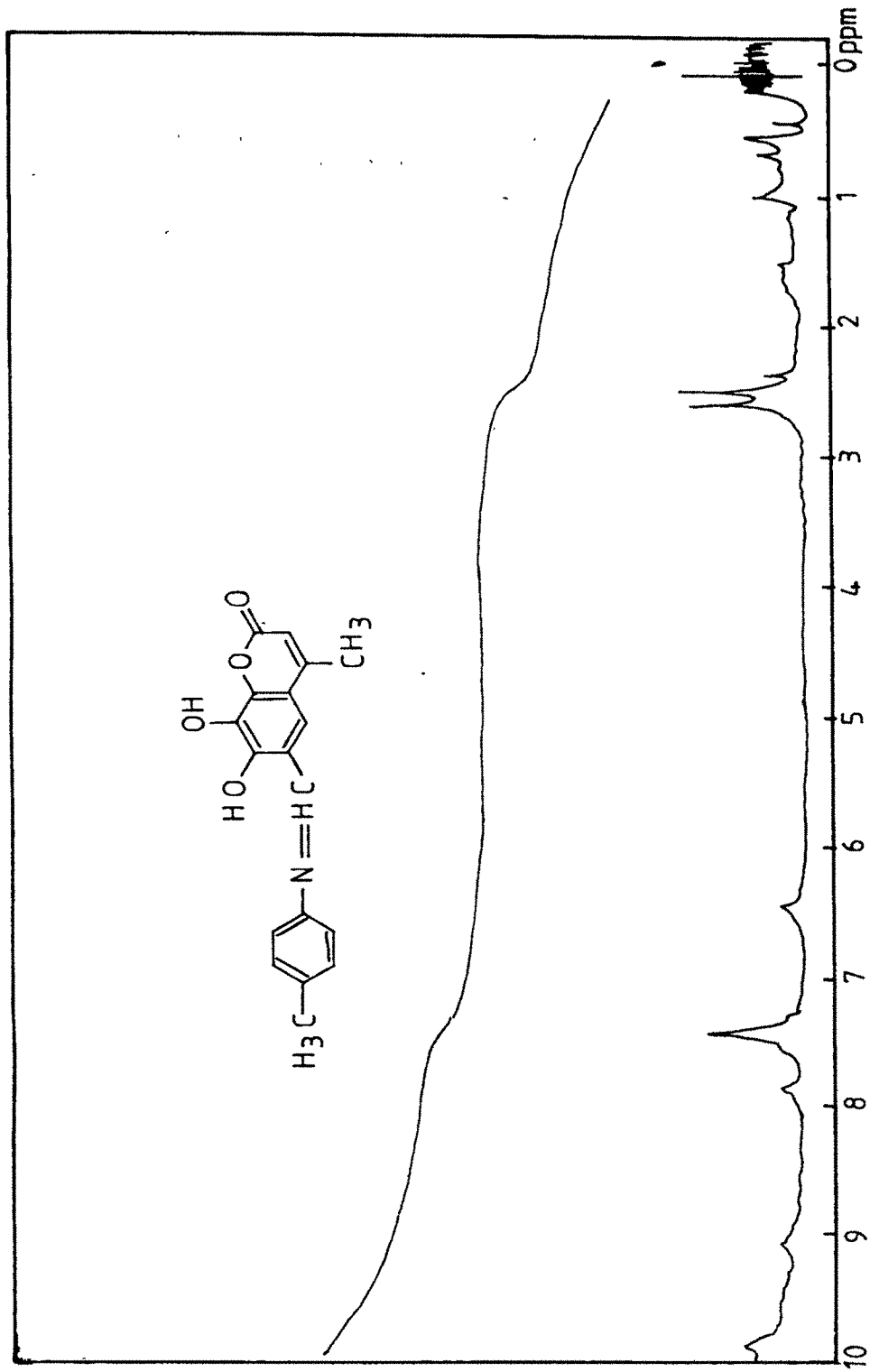


FIG. 7

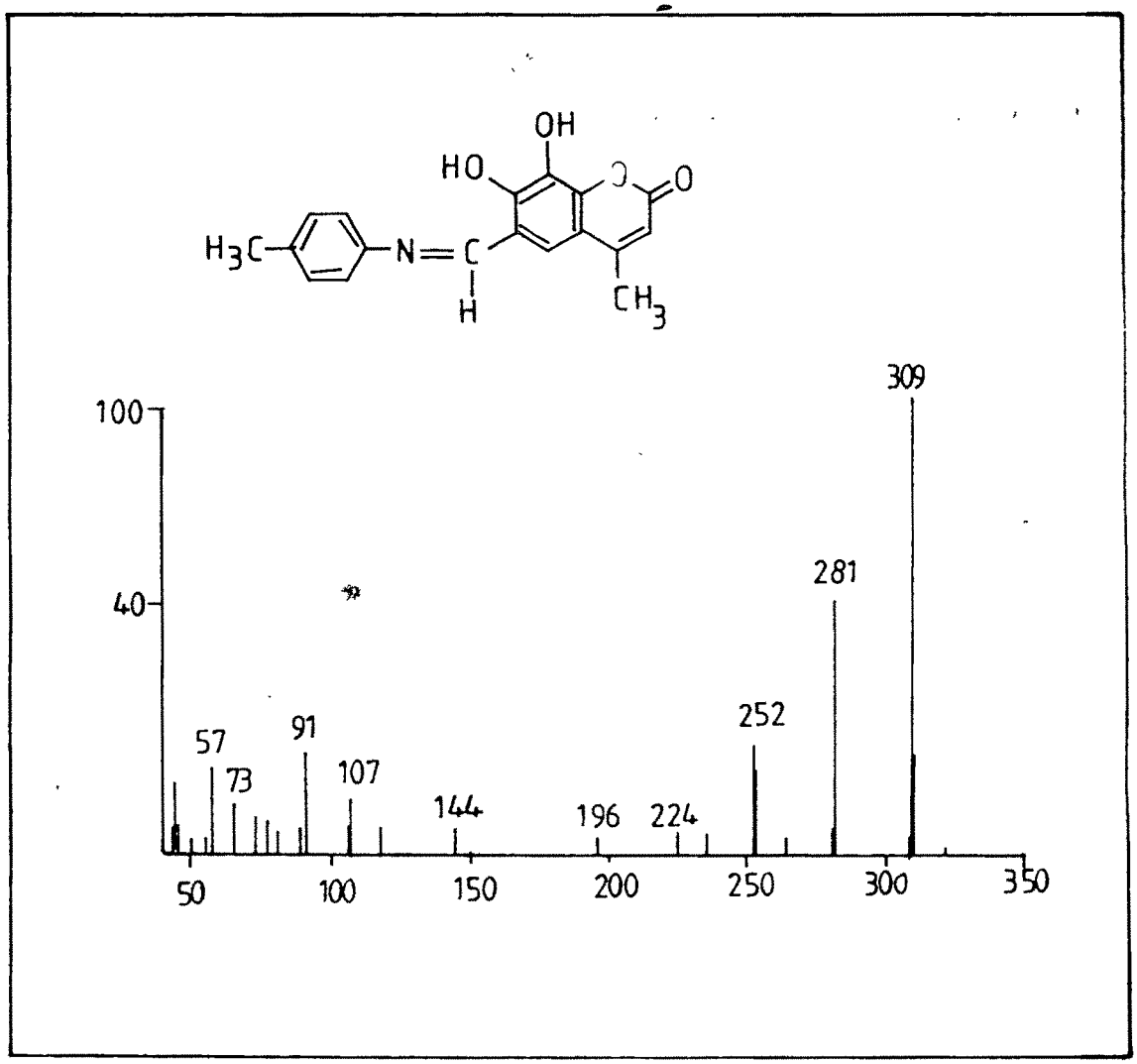

OH
HO
O
O
H3C
N
C
H
CH3
100
40
309
281
252
91
57
73
107
144
196
224
50
100
150
200
250
300
350

FIG. 8

The Mass spectra showed following peak m/z, 309 (M^+ ion and it is also a base peak, 100%) (Fig.8).

All other Schiff bases (Table - 3, 1-4) on the same nucleus were prepared in similar way.

6'-Hydroxy-5'-(4"methyl phenyl iminomethyl)-4-methyl-7,8 benzocoumarin (79, Table - 4,7) (Scheme - 4).

When 6'-hydroxy-5'-formyl-4-methyl-7,8 benzocoumarin[86] (78) was condensed with p-toluidine in glacial acetic acid, it gave the product which was assigned 6'-hydroxy-5'-(4"-methyl phenyl iminomethyl)-4-methyl 7,8 benzocoumarin structure. It was established on the basis of following data.

The IR spectra (in KBr) exhibited bands at 1730 cm^{-1} for lactonic C=O, 1600 cm^{-1} for aromatic C=C, 1380 cm^{-1} for C=N and 1000 cm^{-1} for C-O-C linkage (Fig.9).

The PMR spectra in CF_3COOH exhibited a singlet at δ 2.35 for three protons of methyl group at C-4; a singlet at δ 2.70 for three protons of methyl group of p-toluidine moiety; a singlet at δ 6 80 for one proton at C-3; a multiplet at δ 7.3-8 5 for aromatic protons and a singlet at δ 9.05 for one proton of =C-H (Fig.10).

6'-Hydroxy-5'(3",4"-dichloro phenyl iminomethyl)-4-methylcoumarin (79, Table - 4,6).

A mixture of 6'-hydroxy-5'-formyl-7,8-benzocoumarin and 3,4-dichloroaniline was refluxed in glacialacetic acid. The separated product was assigned 6'-hydroxy-5'-(3"-4"dichloro phenyl iminomethyl)-4-methyl-7, 8-benzocoumarin structure.

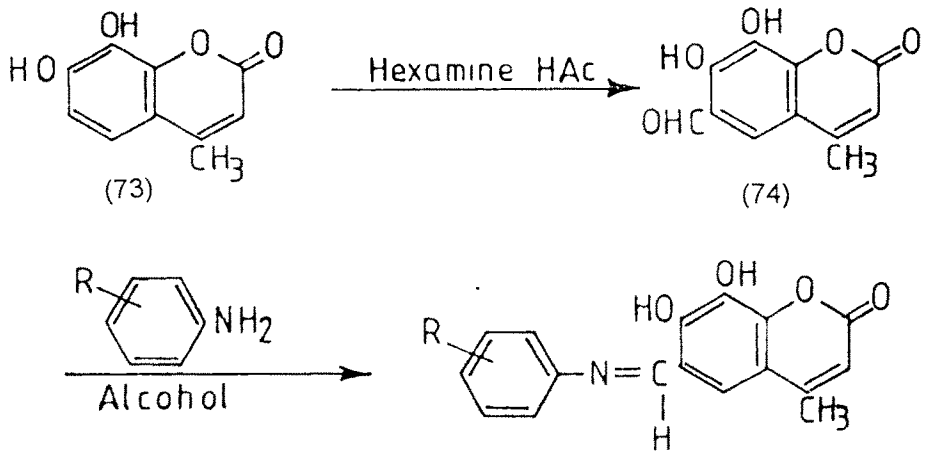
The structure was established on the basis of mass spectra which exhibited following peaks m/z, 398 (M^+, 18.6%) and 149 (Base Peak, 100%) (Fig. 11).

All other Schiff bases (Table - 4, 1-10) were prepared in same way.

7-n-Butoxy-3-(4'-nitro phenyl iminomethyl) coumarin (83, Table - 5, 1) (Scheme - 5).

A mixture of 7-n-butoxy-3-aminocoumarin (82) and 4-nitro benzaldehyde was refluxed in ethylalcohol with few drops of glacial acetic acid.The product separated was assigned 7-n-butoxy-3-(4'-nitro phenyl iminomethyl) coumarin structure. This was assigned on the basis of IR and PMR spectral data

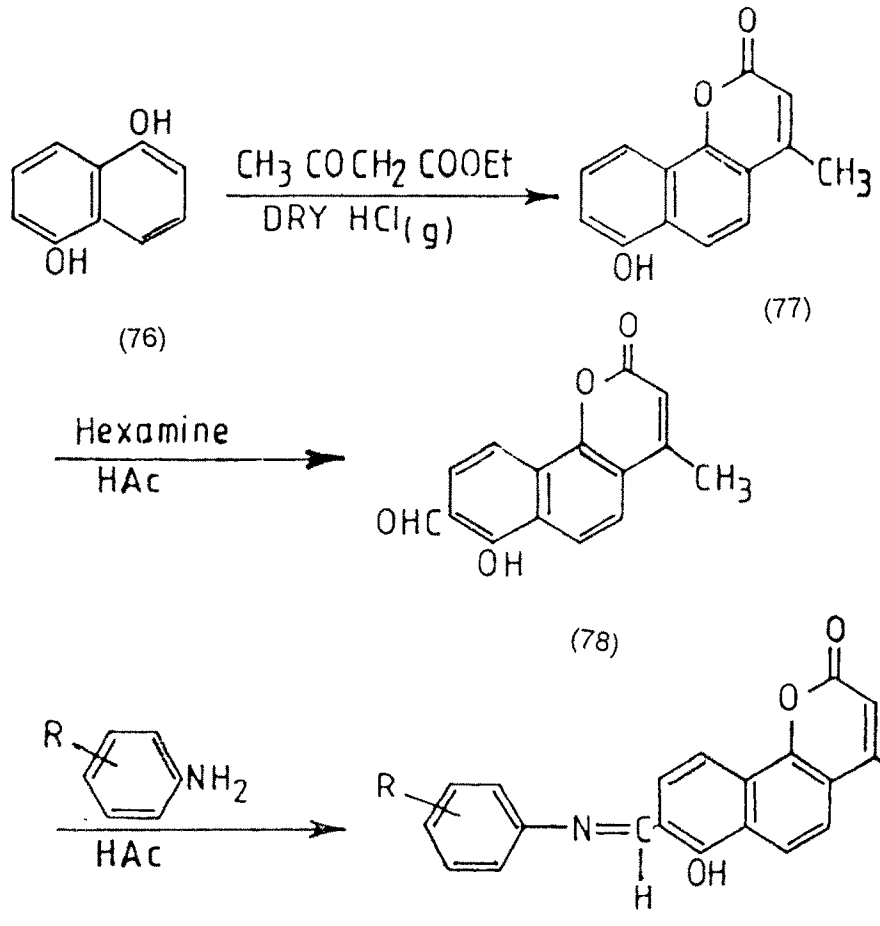
Scheme - 3



(73) (74)

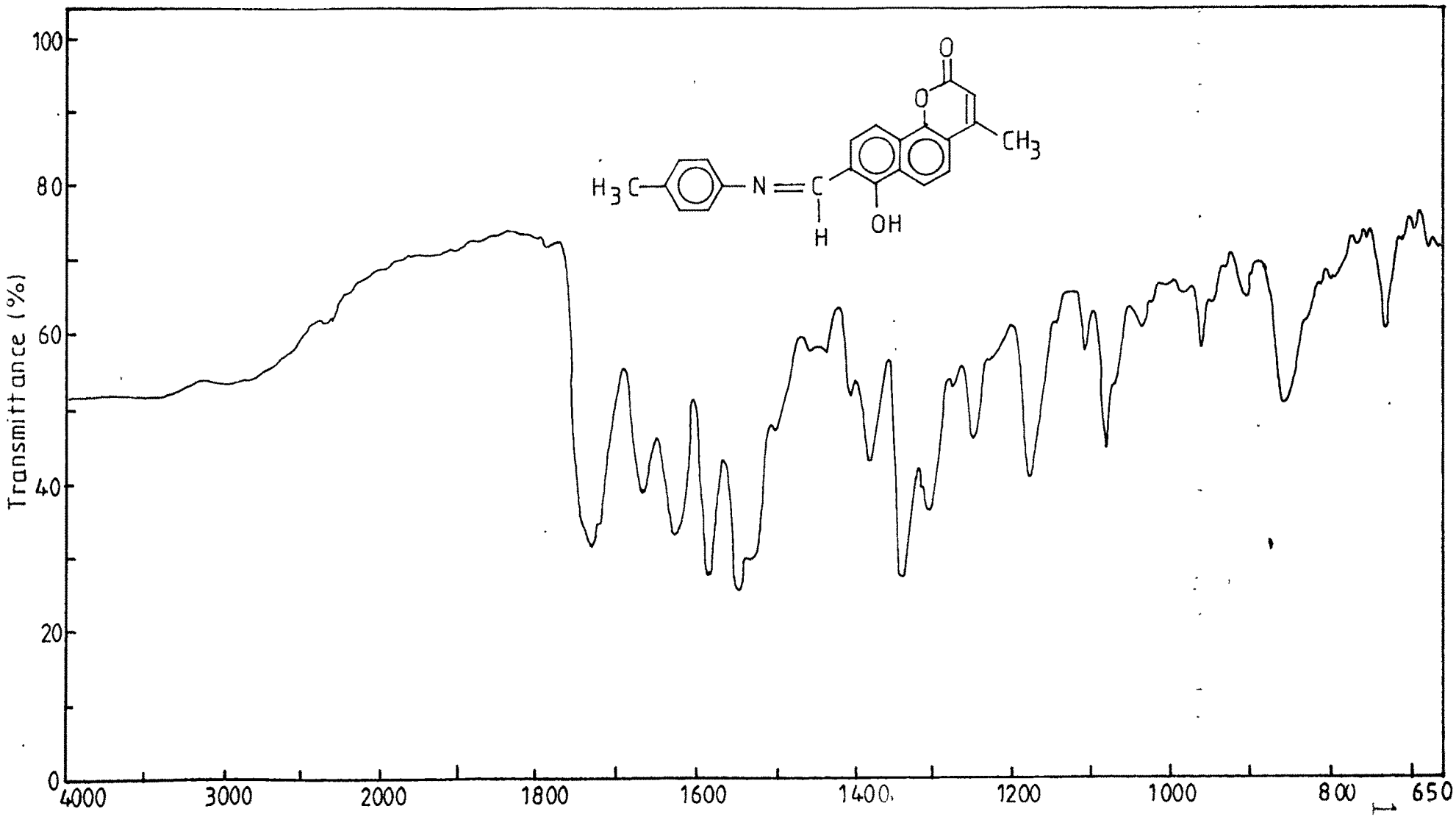
(75, Table - 3, 1-4)

Scheme - 4



(76) (77) (78)

(79, Table - 4, 1-10)


100
80
60
40
20
0
Transmittance (%)
4000
3000
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm⁻¹
O
O
CH3
H3C
N
C
H
OH
FIG. 9

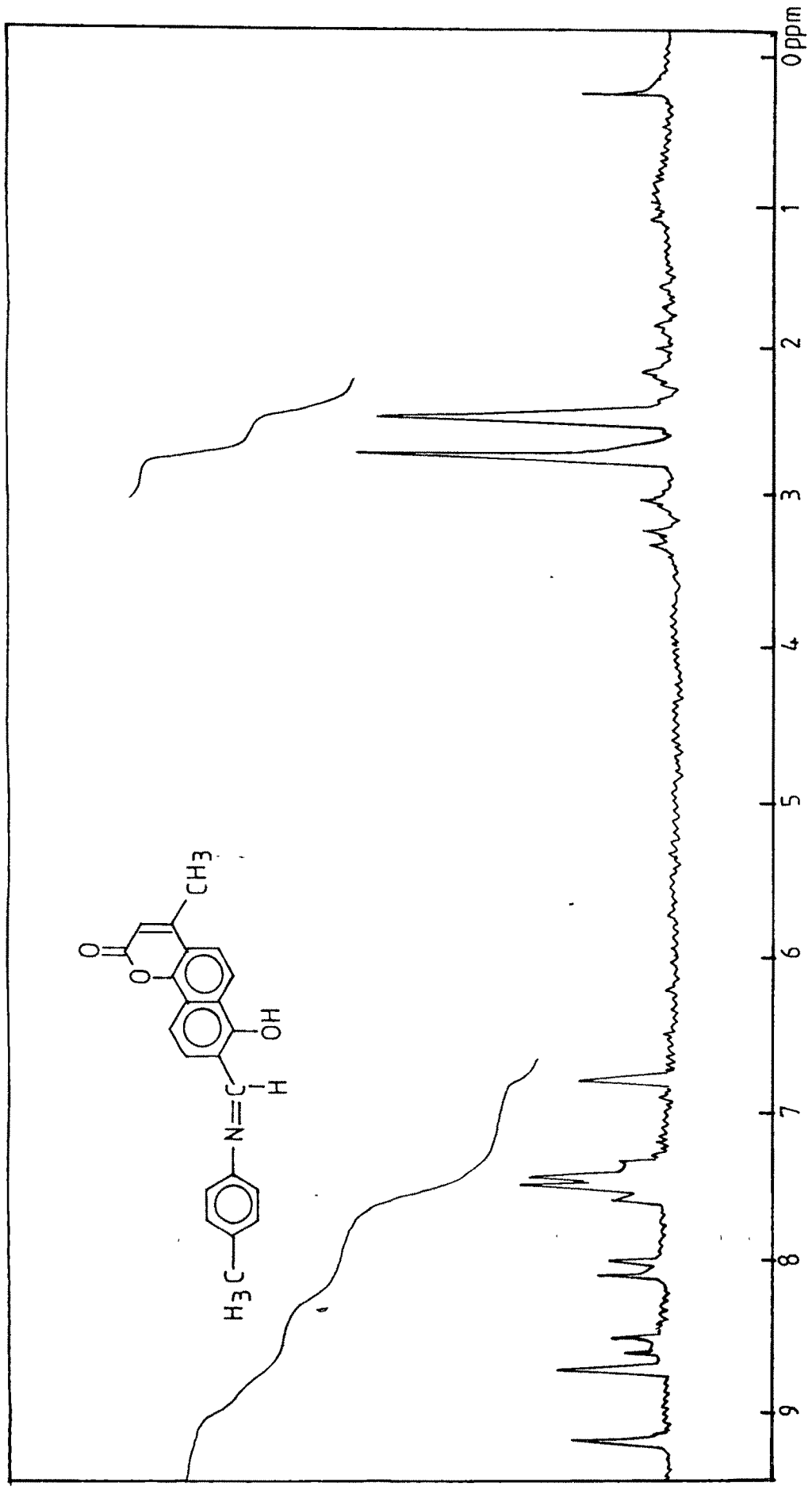


FIG. 10

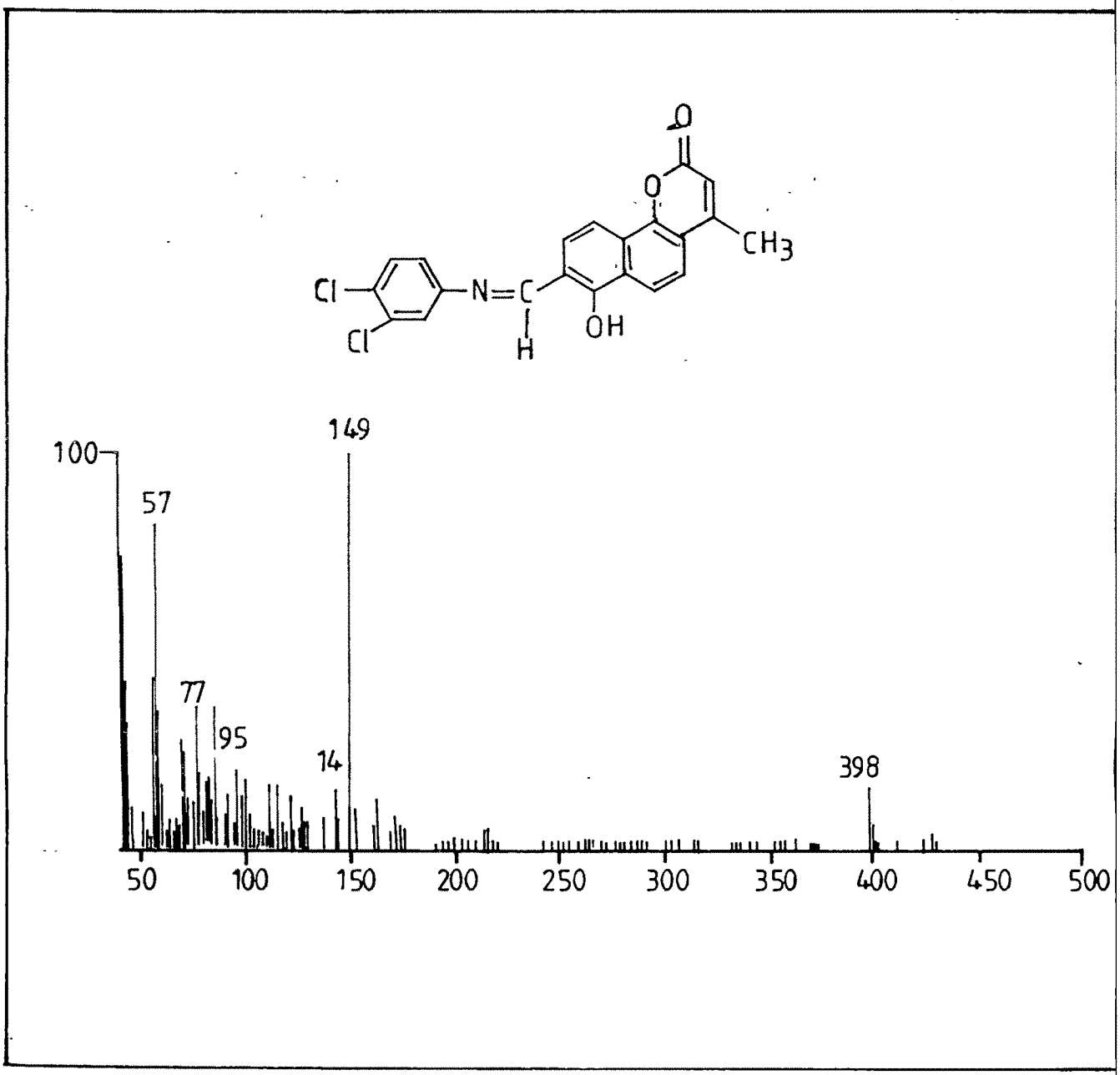

O
O
CH3
Cl
Cl
N=C
H
OH
100
57
149
77
95
14
398
50
100
150
200
250
300
350
400
450
500

FIG. 11

The IR (KBr) exhibited bands at 1720 cm^{-1} for lactonic C=O, 1610 cm^{-1} for aromatic C=C, 1380 cm^{-1} for C=N and 1100 cm^{-1} for C-O-C linkage (Fig. 12).

The PMR spectrum in $CDCl_3$ exhibited a triplet at δ 1.0 for three protons of methyl group of OC_4H_9 at C-7, $OCH_2CH_2CH_2\underline{CH_3}$; a multiplet at δ 1.55 for two protons of methylene group at C-7, $OCH_2CH_2\underline{CH_2}CH_3$; a multiplet at δ 1.89 for two protons of methylene group at C-7, $OCH_2\underline{CH_2}CH_2CH_3$; a triplet at δ 4.05 for two methylene protons attached to oxygen at C-7, $O\underline{CH_2}CH_2CH_2CH_3$; a multiplet at δ 6.8 - 8 29 for aromatic protons; a singlet at δ 7.75 for one proton at C-4; and a singlet at δ 9.5 for one proton i.e. = C-H (Fig.13).

7-n-Butoxy-3-(3'-nitro phenyl iminomethyl)coumarin (83, Table - 5, 2)

When 7-n-butoxy-3-aminocoumarin was condensed with 3-nitro benzaldehyde gave a product which was assigned as 7-n-butoxy-3-(3'-nitro phenyl iminomethyl)coumarin.

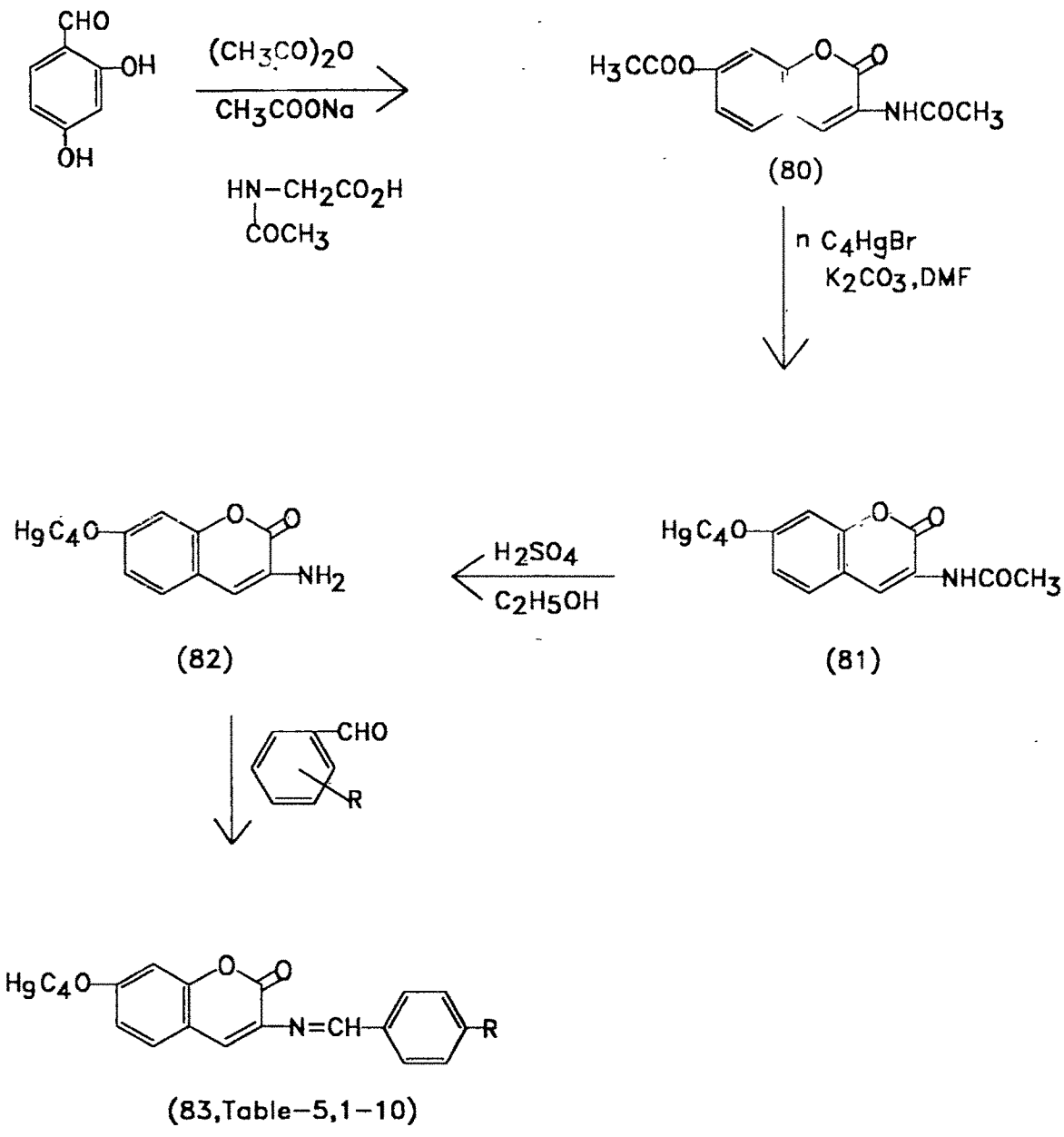
The structure was characterised by its mass spectral data. Which exhibited peaks at m/z 366 (M^+, 2.1%) and 177 (Base Peak, 100%) (Fig.14).

All other Schiff bases (Table - 5, 1-10) on this same nucleus were synthesised in similar way.

Antibacterial Activity

All the Schiff bases were tested for their antibacterial activity using cup-plate method against strains E. coli and S. aureus at 100 and 500 ppm concentrations. The results are mentioned in chapter V.

Scheme - 5



(83,Table–5,1–10)

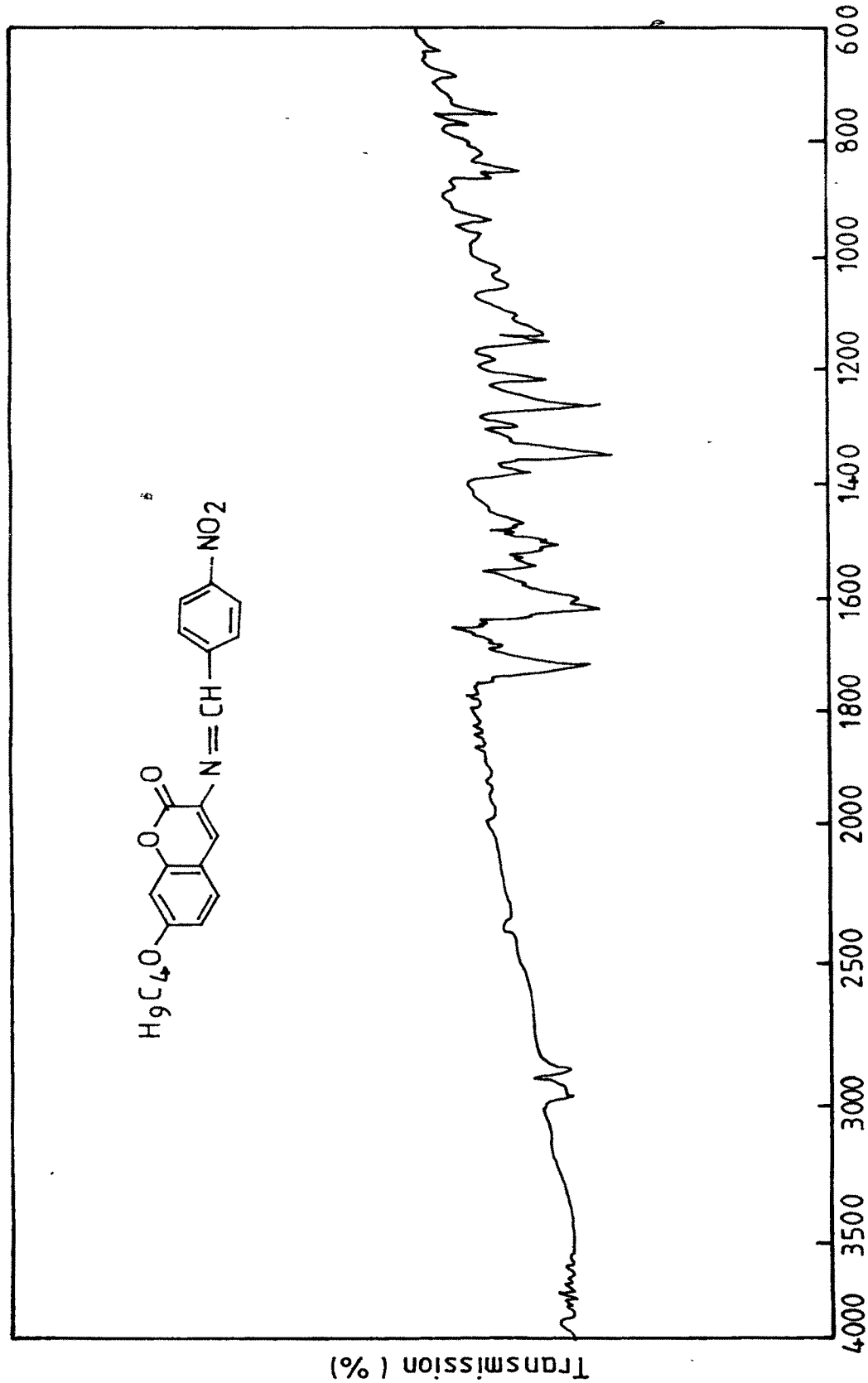

Transmission (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm⁻¹
O
O
N=CH
NO2
H9C4O

FIG 12

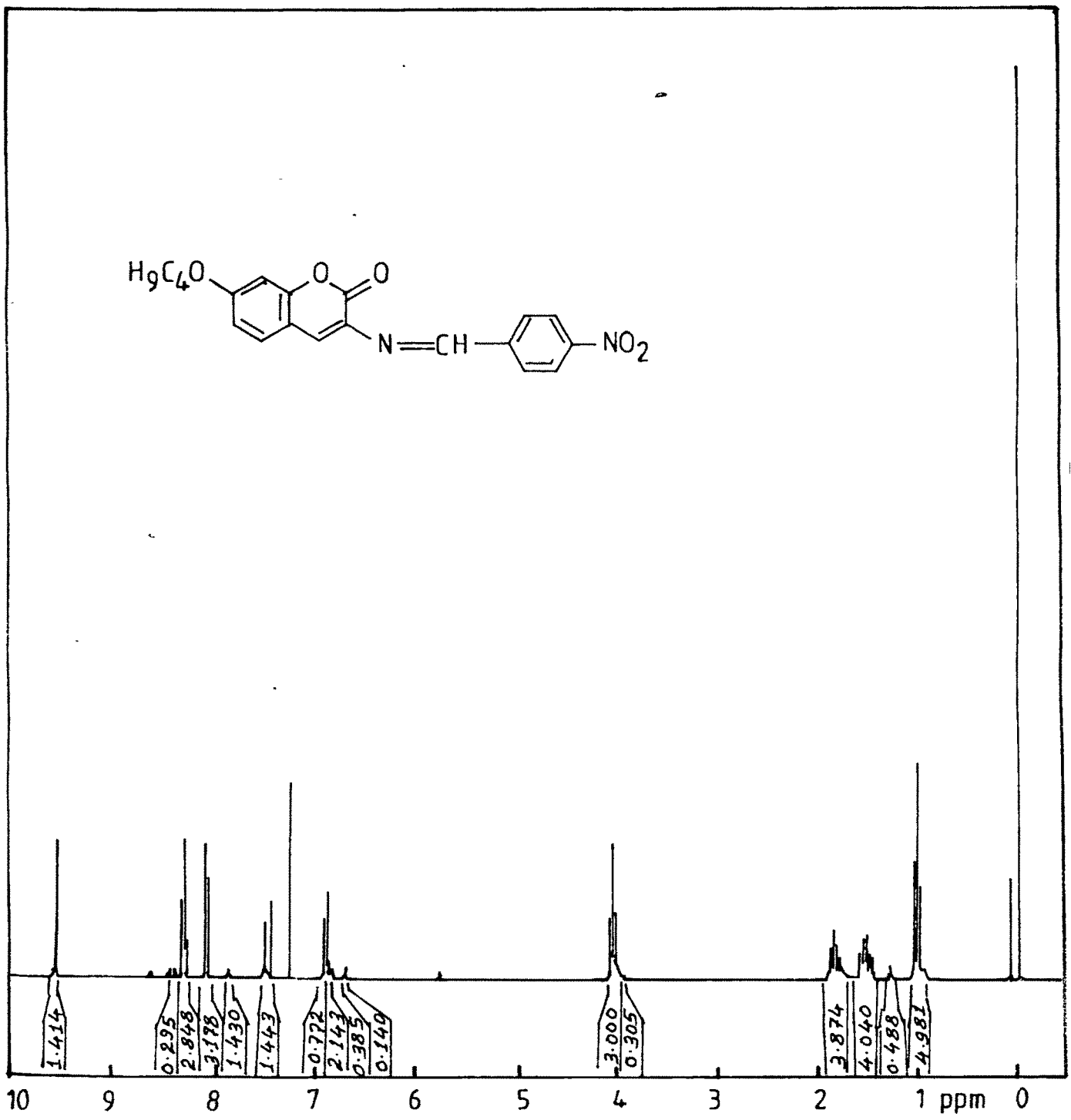

H_9C_4O
O
O
N=CH
NO_2
1.414
0.295
2.848
3.178
1.430
1.443
0.772
2.143
0.385
0.140
3.000
0.305
3.874
4.040
0.488
4.981
10
9
8
7
6
5
4
3
2
1 ppm
0

FIG. 13

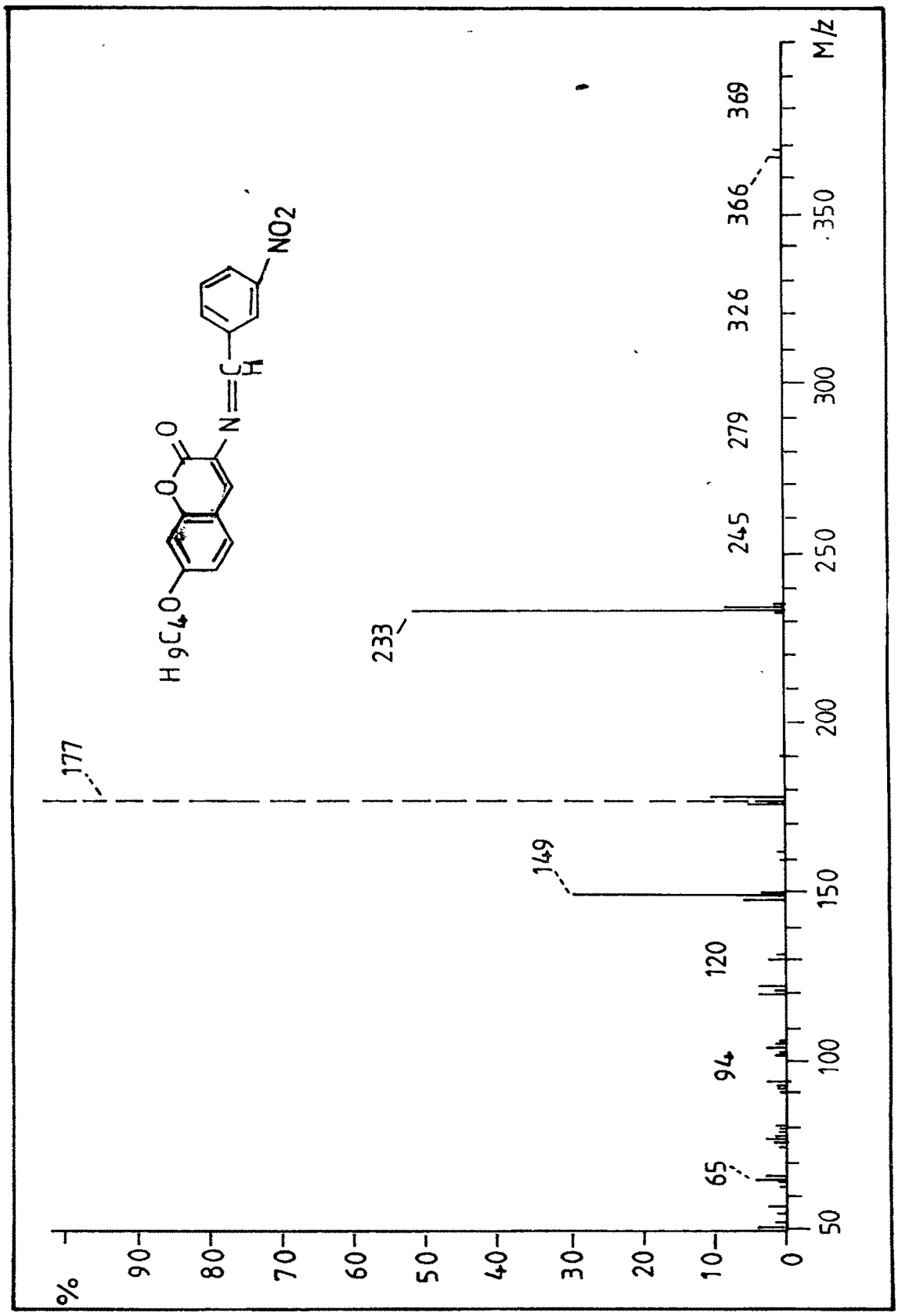

%
90
80
70
60
50
40
30
20
10
0
50
65
94
100
120
149
150
177
200
233
245
250
279
300
326
350
366
369
M/z
H_9C_4O
O
O
N
C
H
NO_2

FIG. 14

Experimental

Melting points were determined in open capillaries and were uncorrected. Microanalyses were performed on a Coleman instrument. IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. PMR spectra were recorded on Perkin Elmer R-32 spectrometer at 90 MHz and dpx spectrometer at 200 MHz using tetramethyl silane as the internal standard and chemical shifts are measured in δ ppm .The homogenity and purity were tested by TLC using silica gel G.

7,8-Dimethoxy-3-chloromethyl-4-methylcoumarin[84] (68)

A mixture of 7,8-dimethoxy-4-methylcoumarin (0.02 mol) in minimum quantity of acetic acid (80%) and paraformaldehyde (0.02 mol) was treated with hydrogen chloride gas at 60-70°C on a water bath for 1 hr and mixture was left overnight. Next day the product which separated out on dilution with water was filtered, washed with alcohol and crystallised from benzene, M.p. 140-141°C, Yield 36%.

7,8-Dimethoxy-3-(3'-acetylphenyl aminomethyl) 4-methyl coumarin[85] (69)

A mixture of (68) (0.01 mol) and 3-acetylaniline (0.01 mol) was dissolved in absolute alcohol and than refluxed on a waterbath for 2 hrs. The separated product was crystallised from ethylalcohol, M.p. 180°C, Yield 60%

7,8-Dimethoxy-3-[3'-yl-ethylidene(2"-nitrobenzoic acid hydrazide) phenylaminomethyl] -4-methyl coumarin (70, Table - 1,2).

A mixture of 7,8 dimethoxy-3-(3'acetylphenylaminomethyl)-4-methylcoumarin (3.67 g, 0.01 mol) and 2-nitrobenzoic acid hydrazide (1.01 g, 0.01 mol) in 50 ml ethylalcohol (95%) with few drops of glacial acetic acid was refluxed on a sandbath for 1 hr. The separated solid was crystallised from DMF. M.p. 254°C, Yield 60%.

Analysis	:	Found	:	C, 63.53;	H, 5.33; N, 10.21%
$C_{28}H_{26}O_7N_4$	:	Required	:	C, 63.39;	H, 4.90; N, 10.56%

7,8-Dimethoxy-3-(4'-acetylphenylaminomethyl)4-methylcoumarin[85] (71)

A mixture of (68) (0.01 ml) and 4-acetylaniline (0.01 ml) was refluxed in absolute alcohol for 2 hrs. on a waterbath. The separated product was worked up as usual, M.p. 210°C, Yield 62%.

7,8-Dimethoxy-3[4'-yl-ethylidene(2"-nitro benzoic acid hydrazide)phenylaminomethyl]-4-methylcoumarin (72, Table - 2,3).

7,8-Dimethoxy-3-(4'-acetyl phenyl aminomethyl)-4-methylcoumarin (3.69 g, 0.01 mol) was refluxed with 2-nitro benzoic acid hydrazide (1.81 g, 0.01 mol) in 50 ml rectified spirit with few drops of glacial acitic acid. The mixture was refluxed on a sandbath for 1 hr. The separated product was purified by crystalisation using DMF. M.p. 284°C (d), Yield 55%.

Analysis	:	Found	:	C, 63.38;	H, 5.31; N, 10.26%
$C_{28}H_{26}O_7N_4$	:	Required	:	C, 63.39;	H, 4.90; N, 10.56%

7,8-Dihydroxy-6-formyl-4-methylcoumarin[86] (74)

7,8-Dihydroxy-4-methylcoumarin (1.92gm,0.01 mol) and hexamethylene-tetramine (5.62 g, 0.04 mol) in glacial acetic acid (50 ml) were heated on a steam bath for 7 hrs. Then 10 ml hydrochloric acid (1:1) was added and refluxed for more 2 hrs. The product (77) was obtained by extracting with ether. Then it was crystallised from 1:1 acetic acid.

7,8-Dihydroxy-6-(4'-phenyl imino methyl)4-methylcoumarin (75, Table - 3,1)

7,8-Dihydroxy-6-formyl-4-methyl coumarin (2.20 g, 0.01 mol) was dissolved in 20 ml ethylalcohol (95%). To this 4-methylaniline (1.07 g, 0.01 mol) dissolved in 5-6 ml ethylalcohol was added. This mixture was refluxed on a sandbath for 1.5 hr. The excess of solvent was removed by distillation and the remaining liquid was cooled in fridge for 2-3 hrs. The scarlet red solid separated on cooling was filtered, washed with ethylalcohol and crystallised from DMF + WATER. M.p. 255°C, Yield 65%.

Analysis	:	Found	:	C, 70.40;	H, 4.38; N, 4.73%
$C_{18}H_5O_4N$	:	Required	:	C, 69.90;	H, 4.85; N, 4.53%

6'-Hydroxy-4-methyl-7,8-benzocoumarin[87] (77)

Hydrogenchloride gas was led into a cooled mixture of 1,5 dihydroxy naphthalene (4.0g), ethylacetoacetate (10.0g) and 40 ml ethylalcohol, temperature rose to 30°C, reaction completed after 1.5 hrs. The separated product was crystallised from pyridine. M.p. 299-302°C, Yield 4.9 g.

6'-Hydroxy-5'-formyl-4-methyl 7,8 benzocoumarin[86] (78)

6'-Hydroxy-4-methyl-7,8-benzocoumarin (2.6g,0.01 mol) and hexamethylene tetramine (5.62 g 0.04 mol) in glacial acetic acid (50 ml) were heated on a steambath for 7 hrs. Hydrochloric acid (1:1) was then added (15 ml) and the heating continued for 2 hrs. The product (78) was obtained on extraction with ether, crystallised from acetic acid. M.p. = 265-67°C, Yield 30 %

6'-Hydroxy-5'-(4"-methyl phenyl iminomethyl)-4-methyl-7,8 benzocoumarin (79, Table - 4,7)

A mixture of 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin (2.30 g, 0.01 mol) and 4-methylaniline (1.07 g, 0.01 mol) in 10-12 ml glacial acetic acid was refluxed on a sandbath for 30 minutes. The separated solid was filtered washed with glacial acetic acid, dried and crystallied from DMF + WATER. M.p. 310°C, Yield 40%.

Analysis	:	Found	:	C, 76.79;	H, 5.15, N, 3.72%
$C_{22}H_{17}O_3N$	:	Required	:	C, 76.90;	H, 4.95; N, 4.08%

6'-Hydroxy-5'-(3"-4"-dichlorophenyliminomethyl)-4-methyl-7,8 benzocoumarin (79, Table 4,6)

A mixture of 6'-hydroxy-5'-formyl-4-methyl-7,8-benzocoumarin (2.30 g, 0.01 mol) and 3,4-dichloroaniline (1.62 g, 0.01 mol) in 10 ml glacial acetic acid was refluxed on a sandbath for 30 minutes. The separated product was worked out as usual. M.p. 310°C, Yield 40%.

Analysis	:	Found	:	C, 63.66;	H,2.91; N, 4.05%
$C_{21}H_{13}O_3NCl_2$	:	Required	:	C, 63.31;	H, 3.26; N, 3 51%

Acetyl Glycine

A mixture of glycine (40 g) and water (150 ml) was taken in 500 ml conical flask and stirred vigorously till the solid dissolves completely. Then acetic anhydride (80 ml) was added in portion with constant stirring. The mixture was kept overnight. Solid separated was filtered, washed with ice-cold water, dried. M.p. 207-8°C, Yield 94%

7-Acetoxy-3-acetamidocoumarin[83] (80)

2,4-Dihydroxy benzaldehyde (5.0 g), acetic anhydride (8.0 ml), acetyl glycine (4.5 g) and fused sodium acetate (3.0 g) were taken in 100 ml round bottom flask. It was refluxed on a steam bath for 4-5 hrs, cooled and decomposed to ice-cold water. The solid separated was washed and crystallised from ethylalcohol. M.p. 230-31°C, Yield 65%.

7-n-Butoxy-3-acetamidocoumarin (81)

7-Acetoxy-3-acetamidocoumarin (0.01 mol) was dissolved in 20 ml dry DMF Dry, anhydrous potassium carbonate (0.015 mol) and n-butyl bromide (0.012 mol) was added to it. This mixture was refluxed on a steam bath for 12-14 hrs. Then it was decomposed by ice-water. The solid separated was filtered washed and crystallised from ethylalcohol. M.p. 198°C, Yield 50-60%.

7-n-Butoxy-3-aminocoumarin (82)

7-n-Butoxy-3-acetamidocoumarin (2.75 g, 0.01 mol) was dissolved in 25 ml ethylalcohol (95%) taken in 250 ml conical flask. To this, 2 ml. concentrated sulfuric acid mixed with 5 ml ethylalcohol (95%) was added. This mixture was heated on a sandbath for 35-40 minutes. It was cooled to room temperature and treated with saturated solution of sodiumbicarbonate. The solid separated was filtered, washed with water and crystallised from mixture of ethylalcohol and water. M.p 99-101°C, Yield 60-65%.

7-n-Butoxy-3-(4'-nitrophenyliminomethyl) coumarin (83, Table - 5,1)

A mixture of 7-n-butoxy-3-aminocoumarin (2.33 g, 0 01 mol), 4-nitrobenzaldehyde (1.51 g, 0.01 mol) in 50 ml ethylalcohol (95%) with 2-3 drops of glacial acetic acid was refluxed for 4 hrs. The excess of solvent was removed by distillation, on cooling to room temperature, solid was separated which was filtered and dried. Then it was subjected to column chromatography and eluted with benzene solvent. Solid obtained after chromatography was crystallised using mixture of benzene petroleum ether. M.p. 148-49°C, Yield 70%.

Analysis	:	Found	:	C, 65.10;	H, 5.18; N, 7.32%
$C_{20}H_{18}O_5N_2$	:	Required	:	C, 65.57;	H, 4.91; N, 7 65%

7-n-Butoxy-3-(3'-nitro phenyl iminomethyl)coumarin (83, Table - 5,2)

7-n-Butoxy-3-aminocoumarin (2.33 g, 0.01 mol) was refluxed with 3-nitrobenzal dehyde (1.51 g., 0.01 mol) in 50 ml. ethylalcohol (95%) with few drops of glacial acetic acid. The excess of solvent was removed by distillation. The solid product was separated out after 2-3 hrs. on cooling. It was dried and subjected to column chromatography using silica Gel, eluting with benzene. Solid obtained after column chromatography was again purified by crystallisation. M.p. 98-99°C, Yield 73%.

Analysis	:	Found	:	C, 65.50;	H, 5.12; N, 8.05%
$C_{20}H_{18}O_5N_2$	:	Required	:	C, 65.57;	H, 4.91; N, 7.65%

Table - 1. Analytical and Physical Data of Compounds (70)

Sr. No.	R	M.P.* in°C	% Yield	Molecular Formula	Elemental Analysis Found / Required		
					%C	%H	%N
1	3-CH_3	200^{D+W}	57	$C_{29}H_{29}O5N_3$	69.34 69.73	6.00 5.81	8.10 8.41
2	2-NO_2	252^{D}	60	$C_{28}H_{26}O_7N_4$	63.53 63.39	5.33 4.90	10.21 10.56
3	3-Br	195^{D}	60	$C_{28}H_{26}O_5N_3Br$	59.83 59.57	4.91 4.60	7.41 7.44
4	4-OH	262^{D+W}	55	$C_{28}H_{27}O_6N_3$	67.45 67.06	5.19 5.38	7.90 8.38
5	2-Cl	$165D^{+W}$	55	$C_{28}H_{26}O_5N_3Cl$	64.71 64.73	5.40 5.00	7.65 8.09
6	3-Cl	196^{D}	65	$C_{28}H_{26}O_5N_3Cl$	65.11 64.73	4.79 5.00	7.89 8.09
7	4-Cl	208^{D+W}	65	$C_{28}H_{26}O_5N_3Cl$	64.43 64.73	5.29 5.00	8.39 8.09

* Solvent of crystallisation, D = DMF, W = Water

Table - 2. Analytical and Physical Data of Compounds (72)

Sr. No.	R	M.P.* in °C	% Yield	Molecular Formula	Elemental Analysis Found / Required		
					%C	%H	%N
1	3-CH_3	184^{D+W}	60	$C_{29}H_{29}O_5N_3$	69.42 69.73	5.55 5.81	8.14 8.41
2	3-OCH_3	280^{D}	58	$C_{29}H_{29}O_6N_3$	67.52 67.57	5.93 5.63	7.98 8.15
3	2-NO_2	290^{D}	55	$C_{28}H_{26}O_7N_4$	63.38 63.39	5.31 4.90	10.26 10.56
4	3-Br	200^{B}	50	$C_{28}H_{26}O_5N_3Br$	59.22 59.57	4.51 4.60	7.12 7.44
5	4-Cl	266^{D}	60	$C_{28}H_{26}O_5N_3Br$	64.50 64.73	5.33 5.00	7.86 8.09
6	2-Cl	276^{D+W}	70	$C_{28}H_{26}O_5N_3Cl$	65.19 64.73	5.21 5.00	8.27 8.09

* Solvent of crystallisation D = DMF, W = Water, B = Benzene

Table - 3. Analytical and Physical Data of Compounds (75)

Sr. No.	R	M.P.* in°C	% Yield	Molecular Formula	Elemental Analysis Found / Required		
					%C	%H	%N
1	4-CH_3	255^{D+W}	65	$C_{18}H_{15}O_4N$	70.40 69.90	4.38 4.85	4.73 4.53
2	4-$COOC_2H_5$	255^{D+W}	75	$C_{20}H_{17}O_6N$	65.19 65.39	3.95 4.63	3.48 3.81
3	3,4-Cl_2	215^{D+W}	70	$C_{17}H_{11}O_4NCl_2$	56.36 56.04	3.48 3 02	4.23 3.84
4	2,4-Cl_2	245^{D+W}	65	$C_{17}H_{11}O_4NCl_2$	56.41 56.04	2.98 3.02	3.48 3.84

* Solvent of crystallisation D = DMF, W = Water

Table - 4. Analytical and Physical Data of Compounds (79)

Sr. No.	R	M.P.* in °C	% Yield	Molecular Formula	Elemental Analysis Found / Required		
					%C	%H	%N
1	H	> 310d[D]	60	$C_{21}H_{15}O_3N$	76.59 76.21	4.55 4.91	4.25 3.86
2	4-Br	> 300d[D]	70	$C_{21}H_{14}O_3NBr$	62.13 61.76	3.76 3.43	3.02 3.43
3	4-NO_2	> 310d[D+W]	65	$C_{21}H_{14}O_5N_2$	65.37 65.15	3.74 4.32	8.48 8.93
4	3-NO_2	> 300d[D+W]	50	$C_{21}H_{14}O_5N_2$	64.98 65.15	4.65 4.32	9.12 8.93
5	2,4-Cl_2	> 300d[D+W]	60	$C_{21}H_{13}O_3NCl_2$	63.65 63.31	3.59 3.26	3.36 3.51
6	3,4-Cl_2	> 310d[D]	65	$C_{21}H_{13}O_3NCl_2$	63.66 63.31	2.91 3.26	4.05 3.51
7	4-CH_3	> 310d[D+W]	65	$C_{22}H_{17}O_3N$	76.79 76.90	5.15 4.95	3.72 4.08
8	4-$COOC_2H_5$	275[D]	55	$C_{24}H_{19}O_5N$	71.56 71.82	5.12 4.73	3.34 3.49
9	1-Naphthyl	> 300d[D]	45	$C_{25}H_{17}O_3N$	79.35 79.15	4.78 4.45	3.52 3.69
10	2-Naphthyl	> 300d[D]	40	$C_{25}H_{17}O_3N$	78.86 79.15	3.13 4.45	3.91 3.69

* Solvent of crystallisation D = DMF, W = Water

Table - 5. : Analytical and Physical Data of Compounds (83)

Sr. No.	R	M.P.* in°C	% Yield	Molecular Formula	Elemental Analysis Found / Required		
					%C	%H	%N
1	4-NO_2	$148\text{-}49^{B+P}$	70	$C_{20}H_{18}O_5N_2$	65.10 65.57	5.18 4.91	7.32 7.65
2	3-NO_2	$98\text{-}99^{B+P}$	72	$C_{20}H_{18}O_5N_2$	65.50 65.57	5.12 4.91	8.05 7.65
3	2-NO_2	155^{B+P}	60	$C_{20}H_{18}O_5N_2$	65.31 65.57	5.23 4.91	7.87 7.65
4	2,4-Cl_2	140^{B}	70	$C_{20}H_{17}O_3NCl_2$	61.32 61.53	4.59 4.35	3.41 3.58
5	3,4-Cl_2	135^{B}	68	$C_{20}H_{17}O_3NCl_2$	61.25 61.53	4.01 4.35	3.83 3.58
6	4-Cl	125^{B+P}	60	$C_{20}H_{18}O_3NCl$	67.79 67.60	5.39 5.07	4.12 3.97
7	3-Cl	96^{B}	58	$C_{20}H_{18}O_3NCl$	67.82 67.60	5.21 5.07	3.75 3.94
8	2-Cl	109^{B}	55	$C_{20}H_{18}O_3NCl$	67.50 67.60	4.86 5.07	3.82 3.94
9	4-CH_3	176^{B+P}	60	$C_{21}H_{21}O_3N$	75.55 75.22	6.61 6.26	4.40 4.17
10	3-OCH_3	172^{B+P}	62	$C_{21}H_{21}O_4N$	71.38 71.79	5.45 5.98	3.71 3.98

* Solvent of crystallisation, B = Benzene, P = Petroleum ether

Chapter - III
Part - II
Synthesis of oxadiazolylcoumarins and hydrazides of coumarin derivatives

SYNTHESIS OF OXADIAZOLYLCOUMARINS AND HYDRAZIDES OF COUMARIN DERIVATIVES

OXADIAZOLES

INTRODUCTION

There are four types of oxadiazoles, each of the four oxadiazole rings contain two carbon atoms, two nitrogen atoms and one oxygen atom. They are 1,2,3 oxadiazole (diazoxide) (1); 1,2,4 oxadiazole (azoxime) (2); 1,2,5 oxadiazole (azoxazole, furazan) (3) and 1,3,4 oxadiazole (oxadiazole,oxybiazole) (4).

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

1,2,5-OXADIAZOLES (FURAZAN)

PREPARATIONS

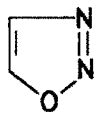
1 Dehydration of Glyoximes

Furazans (5), (6) have been obtained when glyoximes are heated with water,[1] aqueous ammonia or soidum 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 α or β-benzil dioxime with copper sulfate[8] or prolonged exposure of α-benzil dioxime in dilute alkali to tropical sunlight. Glyoxime diesters may be transformed by alkali[10,11] or by steam distillation[12] into furazans. Furazans can also be obtained from the combination of hydroxylamine or 1,2-dicarbonyl derivatives.[13]

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.

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

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]



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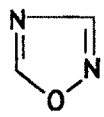

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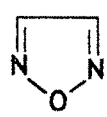

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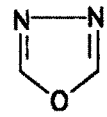

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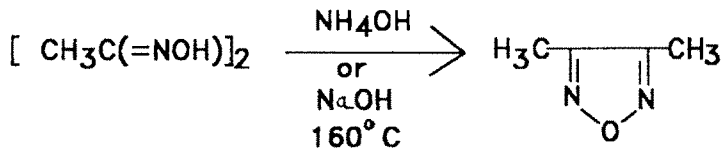
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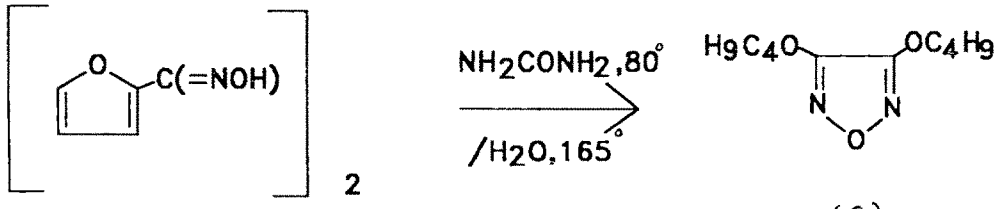
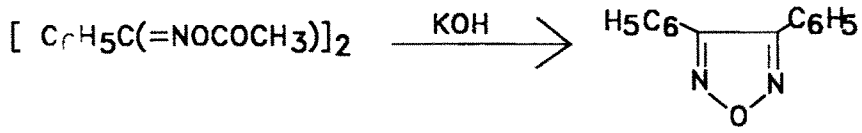
NH4OH
or
NaOH
160° C
H3C
CH3
N
O
N

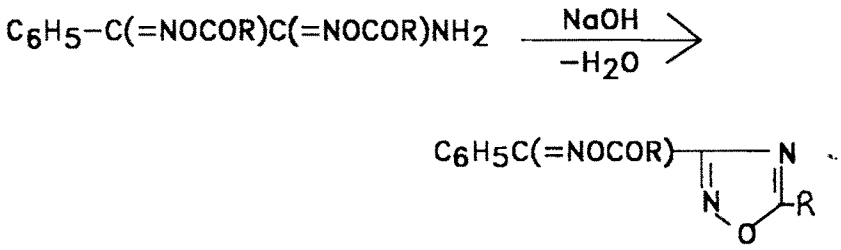
(5)


O
C(=NOH)
2
NH2CONH2,80°
/H2O,165°
H9C4O
OC4H9
N
O
N

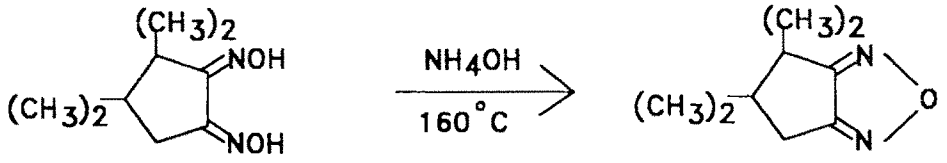
(6)


[C6H5C(=NOCOCH3)]2
KOH
H5C6
C6H5
N
O
N

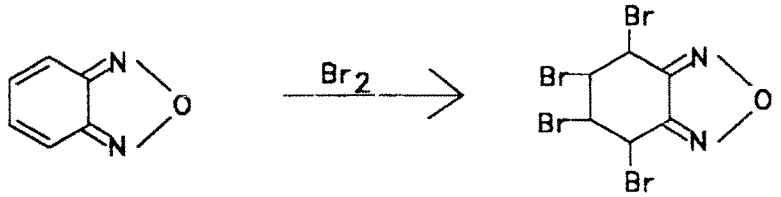
(7)


C6H5-C(=NOCOR)C(=NOCOR)NH2
NaOH
-H2O
C6H5C(=NOCOR)
N
N
O
R

(8)


(CH3)2
NOH
(CH3)2
NOH
NH4OH
160°C
(CH3)2
N
O
(CH3)2
N

(9) (10)


N
O
N
Br2
Br
Br
Br
N
O
N
Br

(11) (12)

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]

2. Ring Transformations

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

PHYSICAL PROPERTIES

The IR absorption[20] 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-0 bond. Furazan absorption in the region 1430 to 1385 cm^{-1} has been assigned the N-O bond.[21]

1,2,4-OXADIAZOLES

PREPARATIONS

1. Pyrolysis of Amidoximes and their esters

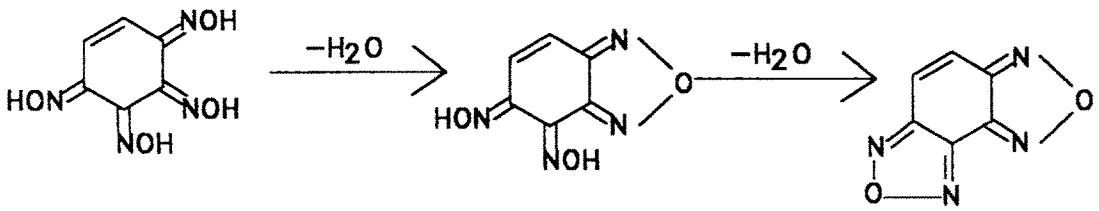
A more general preparation for certain disubstituted 1,2,4-oxadiazoles is found in the pyrolysis of amidoxime esters. E.g. the o-toluic ester of o-tolylamidoxime gives 3,5-di (o-tolyl) 1,2,4-oxadiazole (19)[22] and the acetate ester of p-bromobenzamidoxime gives 3-(p-bromophenyl)-5-methyl-1,2,4-oxadiazole (20) [23]

An unequivocal synthesis of 3-amino-5-phenyl-1,2,4-oxadiazole (21) consists in the treatment of dihydroxyguanidine hydrobromide with benzoyl chloride and sodium bicarbonate.[24,25] The same product is obtained on hydrolysis of N, o-dibenzoyl-hydroxyguanidine.[25]

Aliphatic amidoxime like mandelamidoxime with acetic anhydride,[26] acetamidoxime with benzoyl chloride[27] and malonic monoamidoxime with benzoic acid[28] give the expected oxadiazoles (22),(23).

2. Ring Closure of Monoximes of diacylamides

The imidyl chloride of dibenzamide with hydroxylamine gives 3,5-diphenyl-1,2,4-oxadiazole (24).[29] A probable intermediate is an oxime of dibenzamide.



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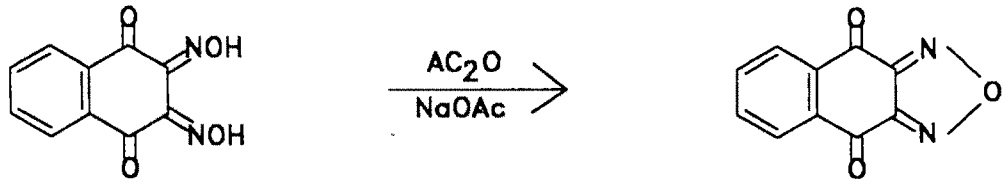
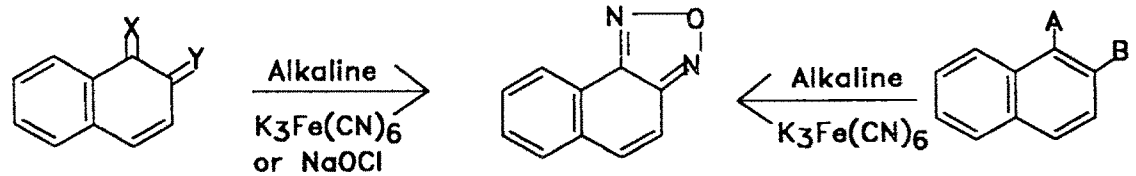


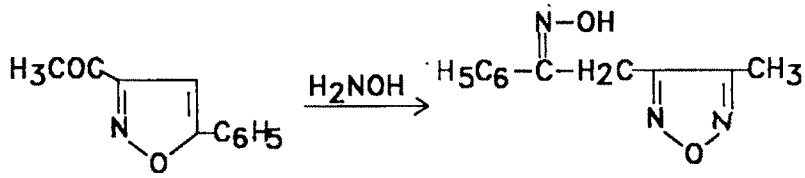
(15) (16)



X=NOH,Y=NH
X=NH, Y=NOH

(17)

A=NO,B=NH2
A=NH2,B=NO



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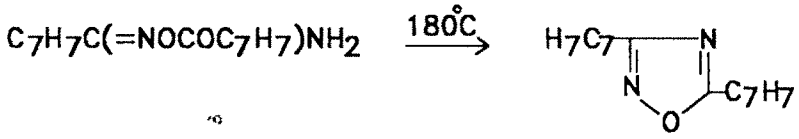

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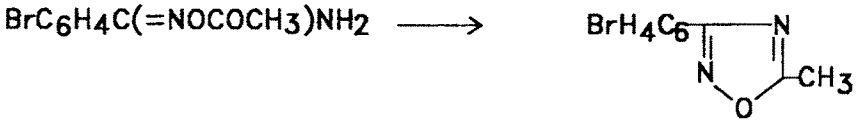

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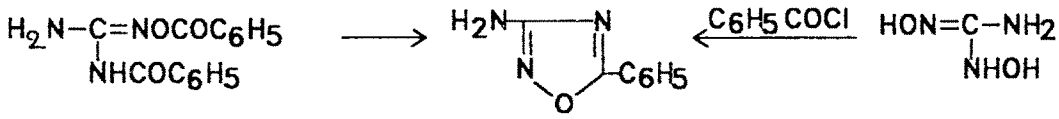


(21)

An oxime of a diacylamide may be an intermediate in the preparation of diamino 1,2,4-oxadiazole (25) from sodium dicyanamide and hydroxylamine.[30]

3. Oxidation of 1,2,4-oxadiazolines

Aromatic amidoximes have been condensed with acetaldehyde[31-35] propionaldehyde,[36] isobutyraldehyde,[36] phenyl-acetaldehyde[36] and salicylaldehyde[36] to give dihydro-1,2,4-oxadiazoles. α, β-Dichloroethyl ether may be substituted for acetaldehyde.[36] The products are oxidised with permanganate to 3,5-disubstituted 1,2,4-oxadiazoles (26).

It is reported that the same oxadiazole results from the oxidation of condensation product from benzamidoxime and salicylaldehyde[36] and from heating the oxime benzoate ester of salicylamidoxime.[37]

1,3,4-OXADIAZOLES

PREPARATIONS

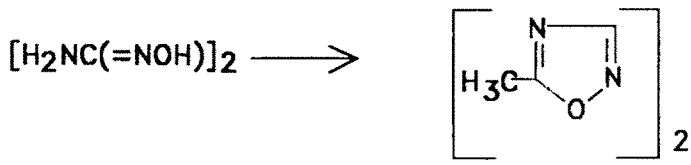
1 Dehydration of 1,2-diacylhydrazines[38]

Cyclodehydration of dibenzoylhydrazine gives 2,5-diphenyl-1,3,4-oxadiazoles (27).[39] In refluxing pyridine 4,4-dimethyl-1-isonicotinyl-semicarbazide gives 5-(4-pyridyl)-1,3,4-oxadiazole -2(3H)-one (28).[40]

Dehydrating agents including chlorosulfonic acid,[41] sulfuryl chloride,[41] phosphorus pentoxide, p-toluenesulfonic acid,[41] tosyl chloride,[41] thionyl chloride,[42] phosphorus oxychloride,[42,43] zinc chloride,[44] organic acid anhydrides[45] phosphorus pentachloride[46] and sulfuric acid[47] 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 (29).[48,49] Similarly, aromatic, heterocyclic[50] or alkyl[51] groups may be substituted at the 2-position in 5-hydroxy-1,3,4-oxadiazoles.



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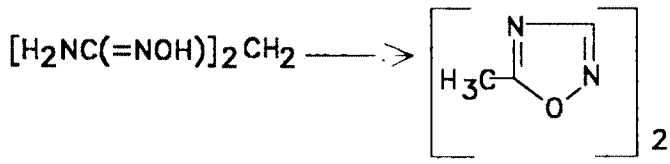

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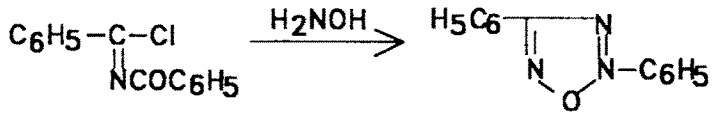

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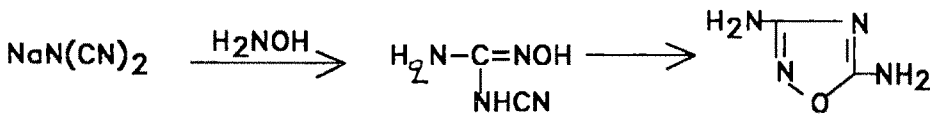

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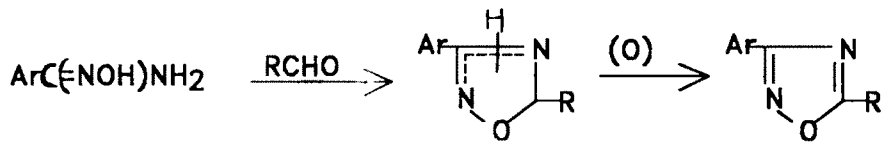

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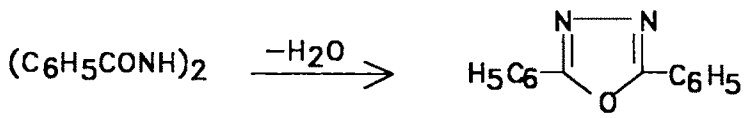

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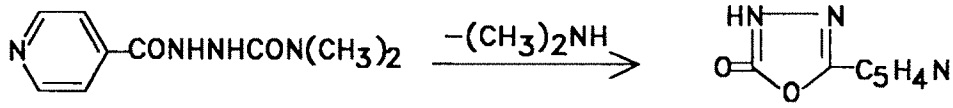

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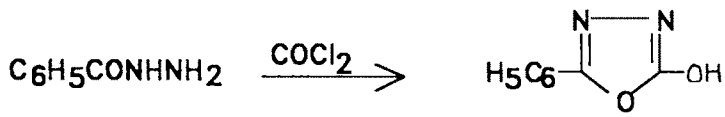


(29)

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 (30).[52,53]

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 [54] From higher ortho esters corresponding 2-alkyl-5-aryl-1,3,4-oxadiazoles are obtained. (31).[54]

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 (28) identical with the product of the hypobromite reaction with benzoylurea.[55]

The product (34) was obtained from the Hofmann reaction with (35).[55]

5 Oxidation of hydrazones

An alkaline solution of both potassium ferri-cyanide and isoamyl nitrite will transform benzoyl-hydrazone of benzaldehyde (36) into a 2,5-disphenyl-1,3,4-oxadiazole (37).[56]

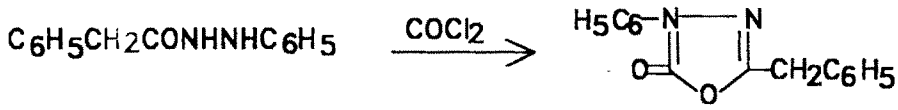
The product from benzaldehyde semicarbazome (38) and sodium hypoiodite or hypobromite is 2-amino-5-phenyl-1,3,4-oxadiazole (39).[57]

6 Acylthiosemicarbazides

In the presence of lead or mercury oxide certain acylthiosemicarbazides (40) lose the elements of hydrogen sulfide as ring closuer to a 1,3,4-oxadiazole (41).[58] A similar ring closure has been observed with potassium hydroxide[59] and hydrochloric acid [60]

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 (42).[61]



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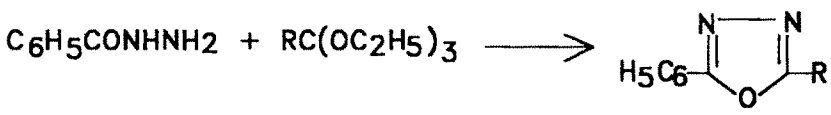

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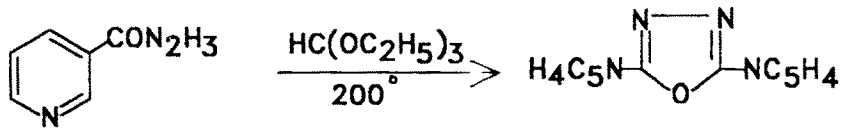

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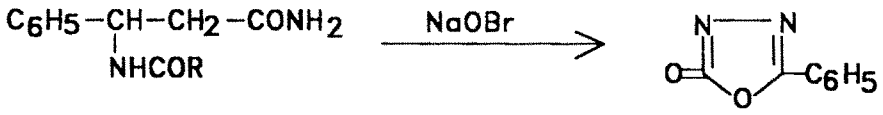
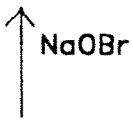
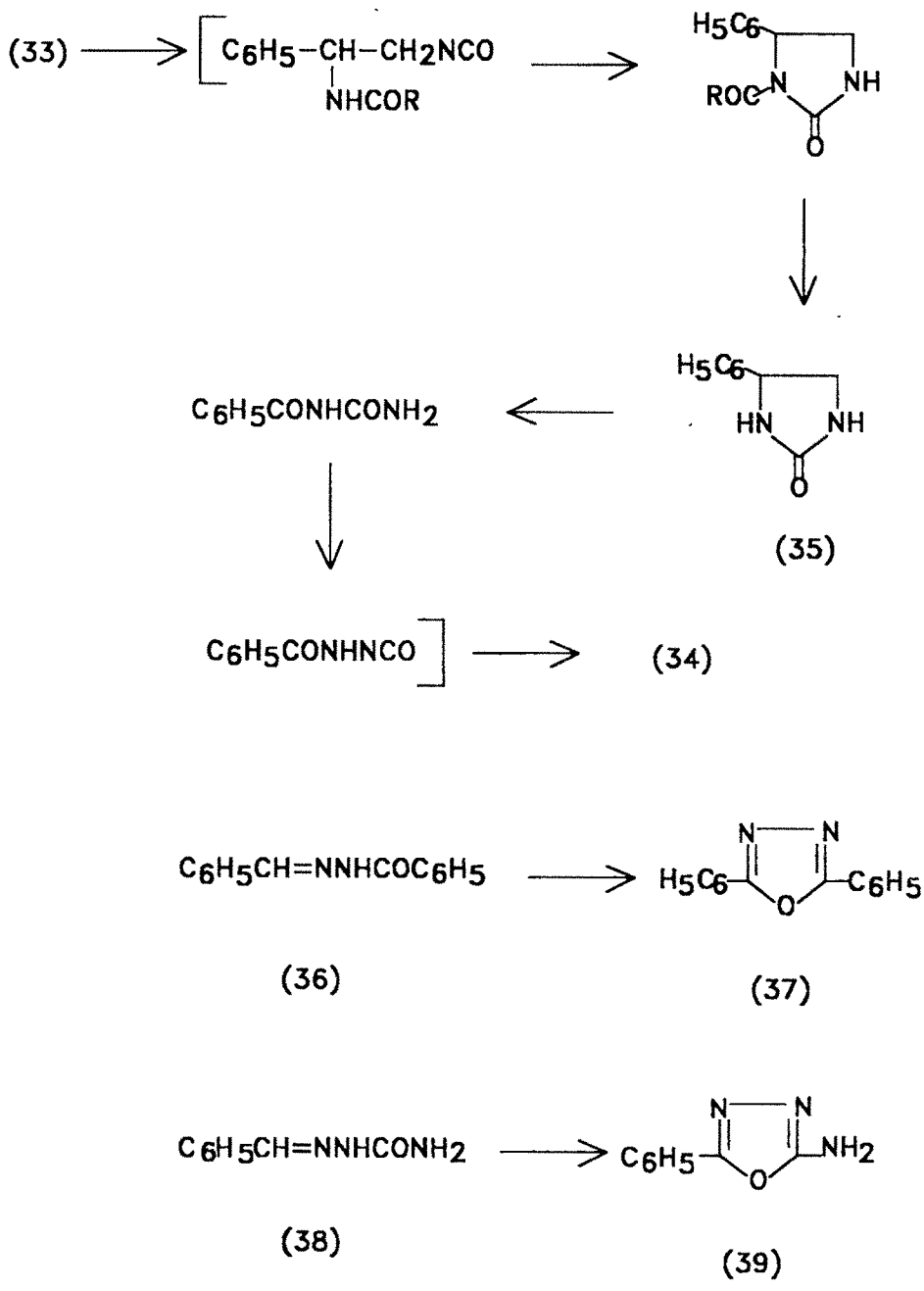


(33)

(34)




(33)
C6H5–CH–CH2NCO
NHCOR
H5C6
ROC
N
NH
O
H5C6
HN
NH
O
(35)
C6H5CONHCONH2
C6H5CONHNCO
(34)
C6H5CH=NNHCOC6H5
(36)
N
N
H5C6
O
C6H5
(37)
C6H5CH=NNHCONH2
(38)
N
N
C6H5
O
NH2
(39)

8. Dihydro-1,3,4-oxadiazoles

Treatment of the silver salt of benzaldehyde benzoyl-hydrazone with acetyl or benzoyl chloride in an inert solvent gives a 2,5-diphenyl-4,5-dihydro-4-acyl-1,3,4-oxadiazole (43).[62] Diazotised o-chloroaniline (44) combines with chloromalonic acid in an alkaline medium to give 2,3-dihydro-2-keto-3-(o-chlorophenyl)-1,3,4-oxadiazole (45).[63]

Applications

Literature survey shows that certain anthraquinone vat dyes are 1,3,4-oxadiazole derivatives.[64,66] Phenylbiphenyl-oxadiazole has been used in scintillation counting for β disintegration.[65] 7-(1,3,4-oxadiazole-2-yl)-3-phenyl coumarin (46)[66] could be used as optical whitener. 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) fabrics by dyeing.

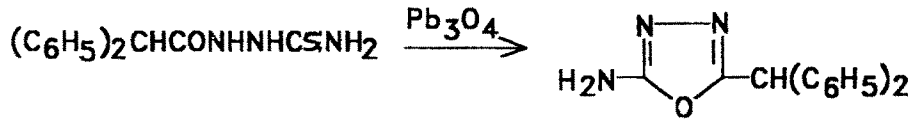
7-Oxadiazolyl coumarins[67] (47) had been reported as fluorescent whitening agents for poly(ethylene terephthalate), poly(vinyl chloride), cellulose acetate and poly-propylene fibers.

Davison Hugh et al[68,69] synthesised 3-[4-(1,2,4-oxadiazolyl)phenyl] coumarin cationic fluorescent whiteners (48) which were used as chlorite bleach-stable fluorescent whiteners for acrylic and cellulose triacetate fibers.

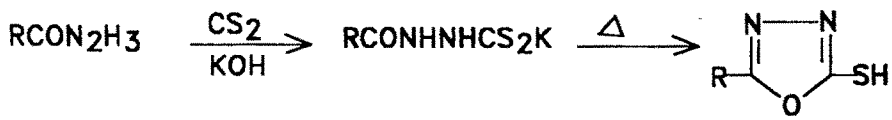
They also synthesised 7-ethoxy-(3-phenyl-1,2,4-oxadiazole-5-yl) coumarin (49) and 7-methyl-(5-phenyl-1,3,4-oxadiazole-2-yl) coumarin (50).

Schwander Hansrudolf[70] prepared oxadiazoylcoumarin dyes (51) and (52) which were used for dyeing polyester fibers light and sublimation fast brilliant greenish yellow shades.

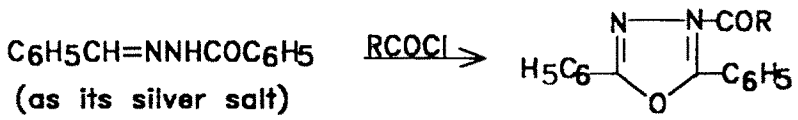
Domerque Annick[71,72] synthesised various oxadiazolylcoumarin derivatives (53) from p-vanilline and Et-3-phenyl-1,2,4-oxadiazole-5-acetate which were used as fluorescent whiteners.



(40) (41)



(42)



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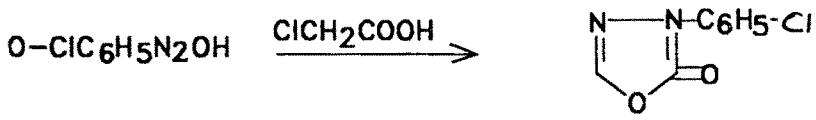

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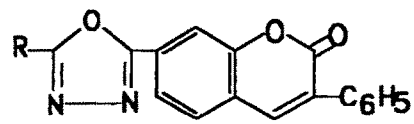

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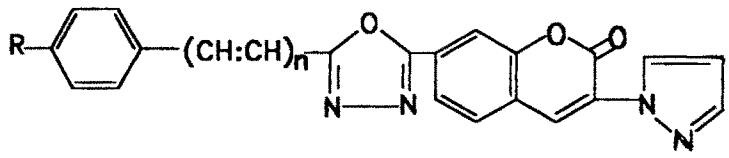

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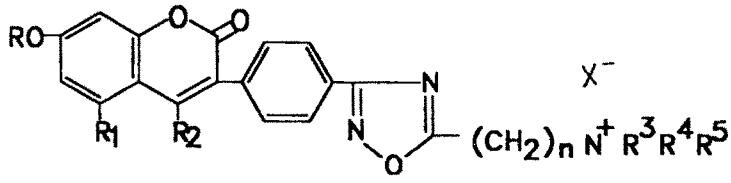

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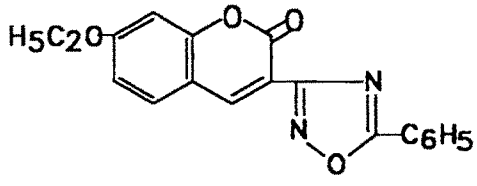


(49)

He also synthesised oxadiazolylcoumarin derivatives (54) by condensation of 3-(chloroformyl)-7-methoxycoumarin with $ROC_6H_4C(:NOH)NH_2$ which was used to whiten polyester fibers.

A.K. Sen Gupta and Coworkers[73] synthesised 2-aryl-amino-5-[((4-methyl-2-oxa-2H-1-benzopyran)7-yl)oxy]-1,3,4-oxadiazoles (55) 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.

Badran M.M., El-Gendy A.A., Soliman L.N. and El.AssiHR[74] reported sythesis of 1,3,4 oxadiazoles (56) of coumarin.

Sonal Shah and R.H. Mehta[75] condensed 8-methoxy-coumarin-3-carbonyl chloride with various benzoic acid hydrazides to obtain (57) which were cyclised to get 1,3,4-oxadiazole derivatives (58). Some of them were found active against E.coli, S.aureus and S.Typhosa.

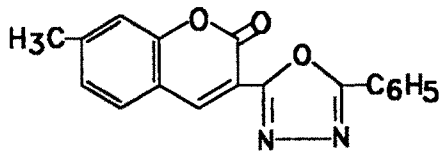
Present work

Literature survey reveals that a large number of substituted hydrazides including heterocyclic compounds having five or six membered rings and possess various bilogical activities.[76-80] Hence it was thought of interest to prepare a number of hydrazides and oxadiazolyl coumarins and to evaluate their antibacterial activity. Here condensation of 8-methoxy-5-bromocoumarin-3-carbonyl chloride with various substituted benzoic acid hydrazide is described.

1-Aryl-4-(8'-methoxy-5'-bromo-3'-coumarinyl)-2,3-diaza-1,4-dioxobutane
(61, Table -1, 1-9)

General Method of Preparation

A mixture of 8-methoxy-5-bromocoumarin-3-carbonyl chloride and substituted benzoic acid hydrazides was stirred in ether for 3-4hrs to get above product.



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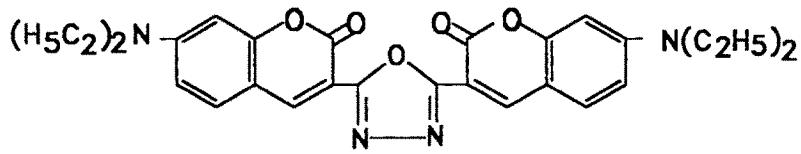

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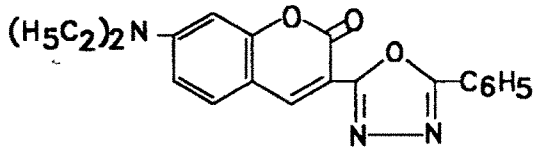

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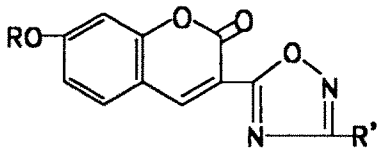

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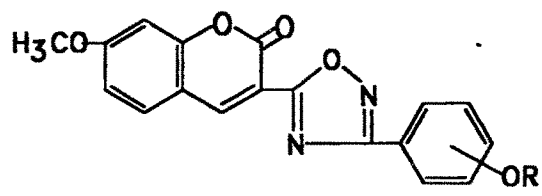

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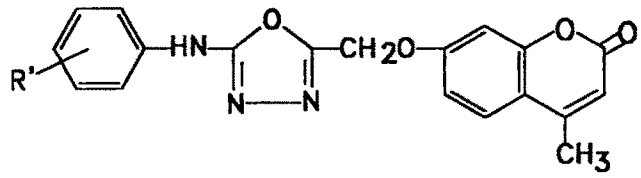

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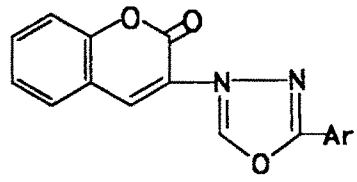

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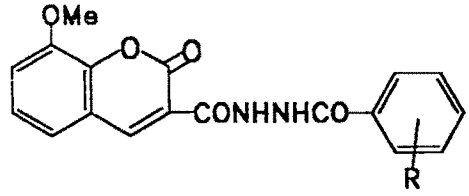

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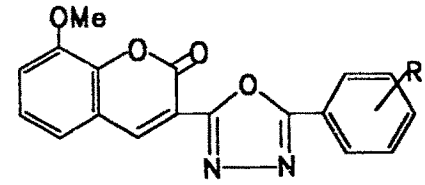

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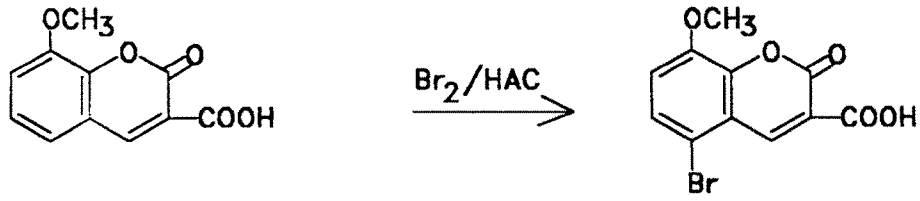

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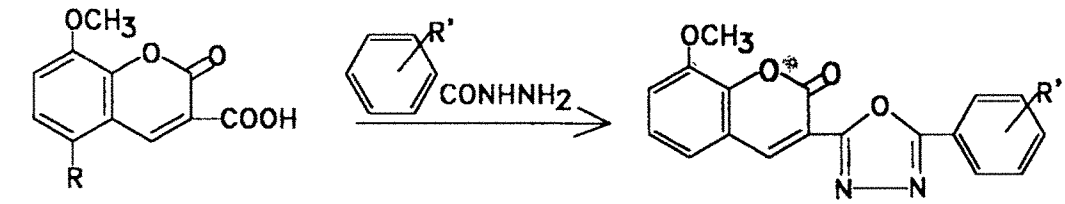
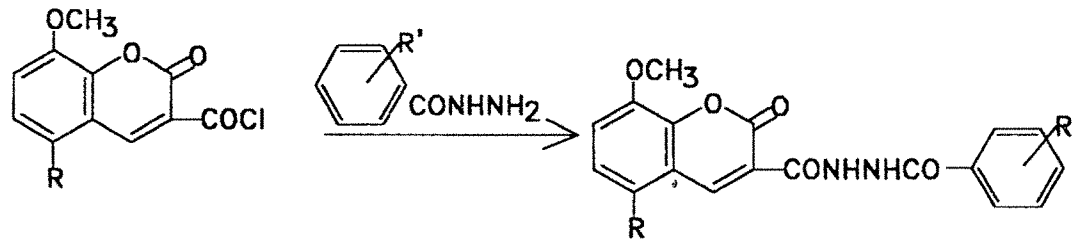


(62, Table - 2, 1-6)

Reflux | $SOCl_2$
↓ Benzene

$POCl_3$, Reflux



(61, Table - 1, 1-9)

1-(4"-Methylphenyl)-4-(8'-methoxy-5'-bromo-3'-coumarinyl)-2,3-diaza-1,4-dioxobutane (61, Table - 1, 1).

8-Methoxy-5-bromocoumarin-3-carbonyl chloride was condensed with p-toluic hydrazide in dry ether to get this product. The structure assigned was established on the basis of IR, PMR and mass spectral data.

In IR (KBr) spectrum bands at 3300-3150cm^{-1} (NH stretching), 1720-1700 cm^{-1} (lactonic carbonyl and CONH), 1600 cm^{-1} (aromatic C=C), 1280 and 1100 cm^{-1} (C-O-C, ether linkage) were observed (Fig. 1).

The PMR spectrum (CF_3COOH) showed a singlet at δ 2.3 for three protons of methyl group of p-toluic moiety; another singlet appeared at δ 4.0 for three protons of methoxy group at C-8. In aromatic region, one doublet at δ 7.1 (J=9Hz) for C-7 proton; another at δ 7.5 for C-6 proton (J=9Hz). Other two doublets at δ 7.2 (J=9Hz) and at δ 7.7 (J=9Hz) were observed for four aromatic protons of p-toluichydrazide component and one singlet at δ 9.1 was observed for C-4 proton (Fig. 2).

The mass spectra exhibited following peaks m/z, 430 (M^+, 41.56%); 432 (M+2, 41.17%) and 119 (Base peak, 100%) (Fig. 3).

Other substituted benzoic acid hydrazides were condensed in similar way (Table - 1, 1-9).

2-Aryl-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole (62, Table - 2, 1-6).

General Praparation

Method I

A mixture of 8-methoxy-5-bromocoumarin-3-carboxylic acid and phosphorus oxychloride was refluxed to obtain 2-aryl-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole.

Method 2

8-Methoxy-5-bromocoumarin-3-carboxylic acid was converted into 8-methoxy-5-bromocoumarin-3-carbonyl chloride using thionylchloride in benzene. This acidchloride was condensed with various substituted benzoic acid hydrazides to obtain,1-aryl-4-(8'-methoxy-5'-bromo-3'-coumarinyl)-2,3diaza-1,4-dioxobutane. These were then refluxed in phosphoruous oxychloride, when they cyclised into

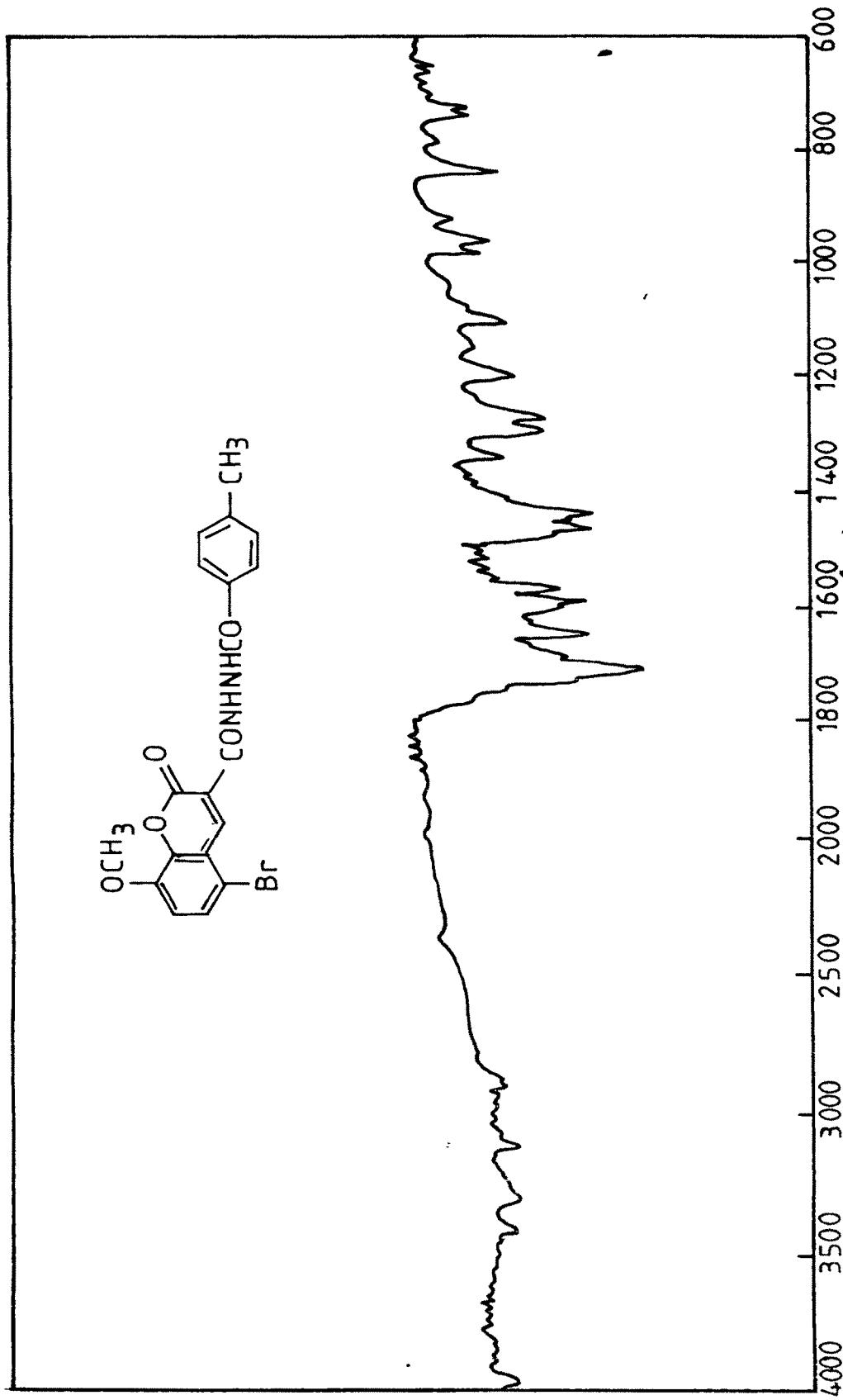

Transmission (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm⁻¹
OCH3
O
O
CONHNHCO
CH3
Br

FIG. 1

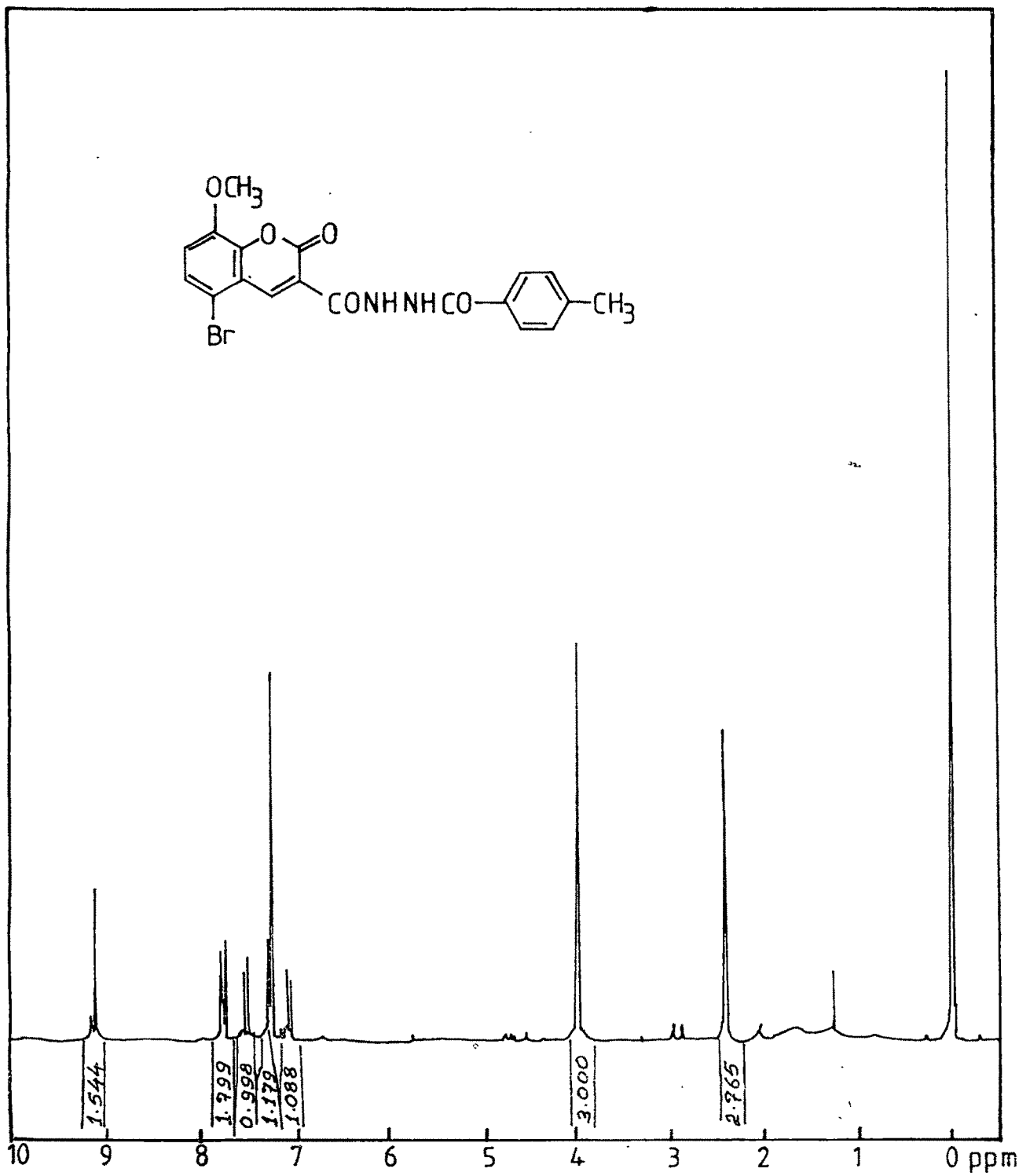

OCH3
O
O
CONHNHCO
CH3
Br
1.544
1.999
0.998
1.179
1.088
3.000
2.765
10
9
8
7
6
5
4
3
2
1
0 ppm

FIG. 2

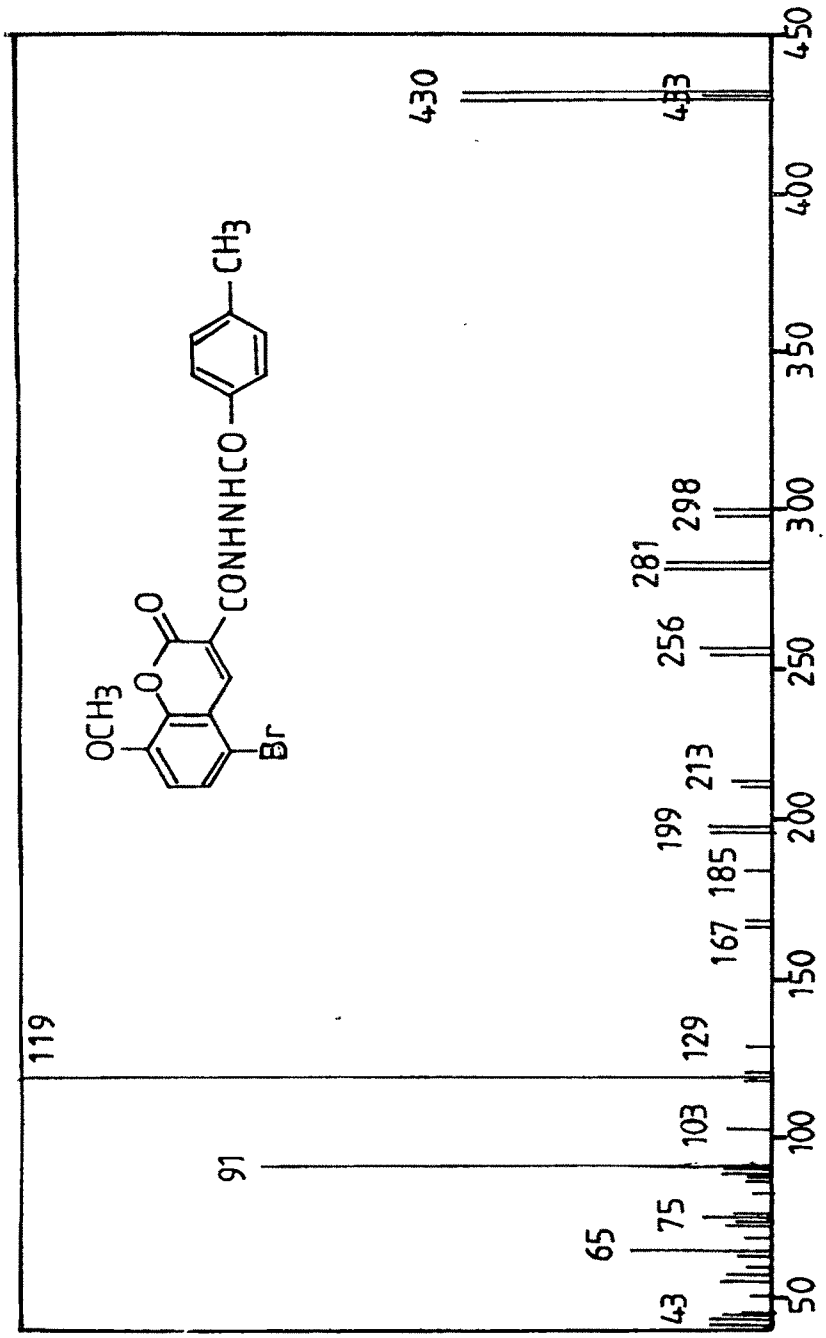

OCH3
O
O
CONHNHCO
CH3
Br
119
91
65
75
43
103
129
167
185
199
213
256
281
298
430
433
50
100
150
200
250
300
350
400
450

FIG. 3

corresponding 1,3,4-oxadiazole derivatives. The mixed melting point of above oxadiazoles and the oxadiazoles obtained by method I did not depress.

2-(2"-Chlorophenyl)-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole (62, Table - 2, 1)

8-Methoxy-5-bromocoumarin-3-carboxylic acid and o-chlorobenzoic acid hydrazide were m ed and treated with phosphorous oxychloride to obtain above 2-(2"-chlorophenyl)-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole. It was also prepared by method 2, as mentioned above. The structure assigned was established by IR and PMR spectra.

In IR (KBr) band at 1755-1735 cm^{-1} (lactonic carbonyl), 1600 cm^{-1} (C=C stretching), 1590 cm^{-1} (C=N stretching), 1285 and 1100 cm^{-1} (C-O-C) were observed (Fig. 4).

The PMR spectrum (CF_3COOH) showed following signals, a singlet at δ 4.0 for three protons of methoxy group at C-8 and in aromatic region one doublet at δ 7.1 for C-7 proton another doublet at δ 8.0 for C-6 proton and a multiplet at δ 7.4 - 7.8 for aromatic protons of phenyl ring, also a singlet for C-4 proton at δ 9.2 (Fig. 5).

Other compounds were synthesised in same way (Table - 2, 1-6).

Antibacterial Activity

All the synthesised compounds were tested at 100 and 500 ppm concentrations for their antibacterial activity against strains E. coli and S aureus using cup-plate method.

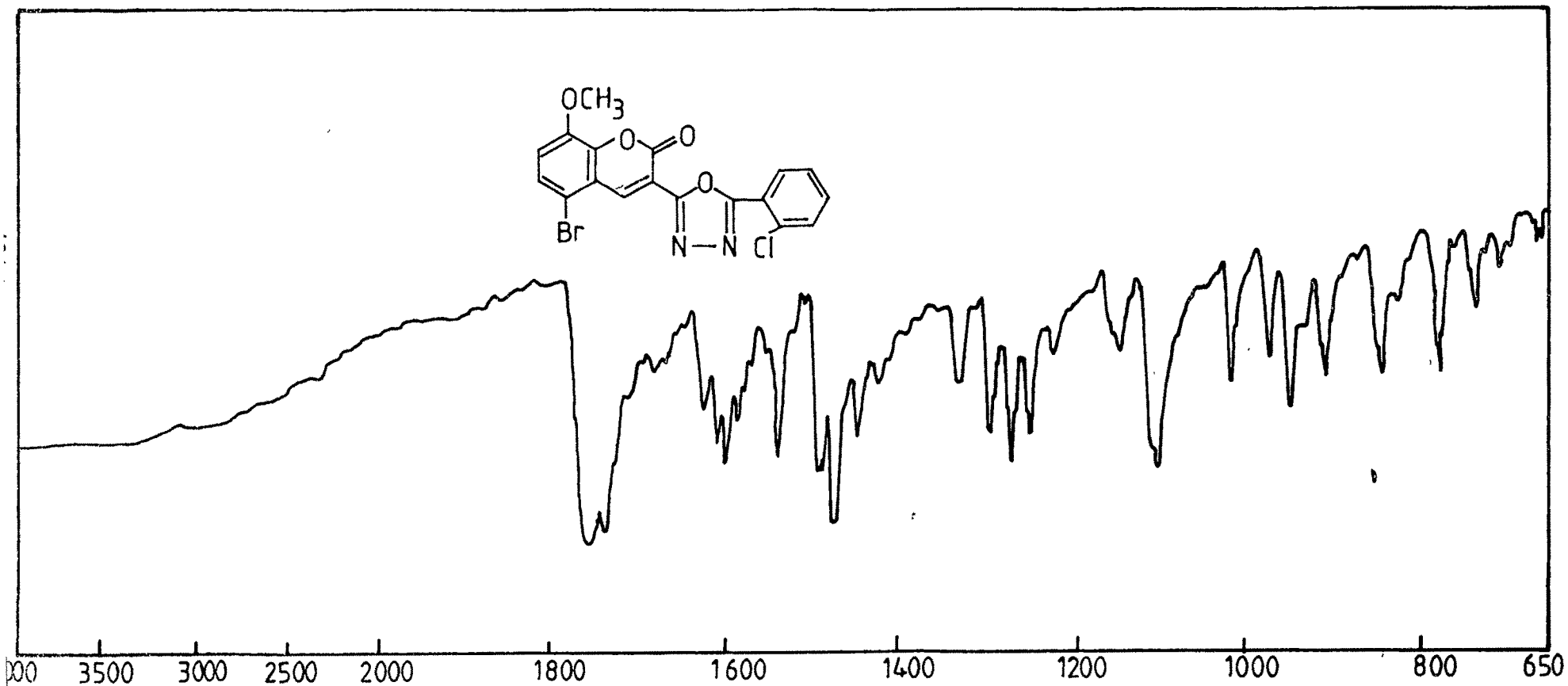

OCH3
O
O
O
Br
N—N
Cl
000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
650
Wavenumber cm-1

FIG. 4

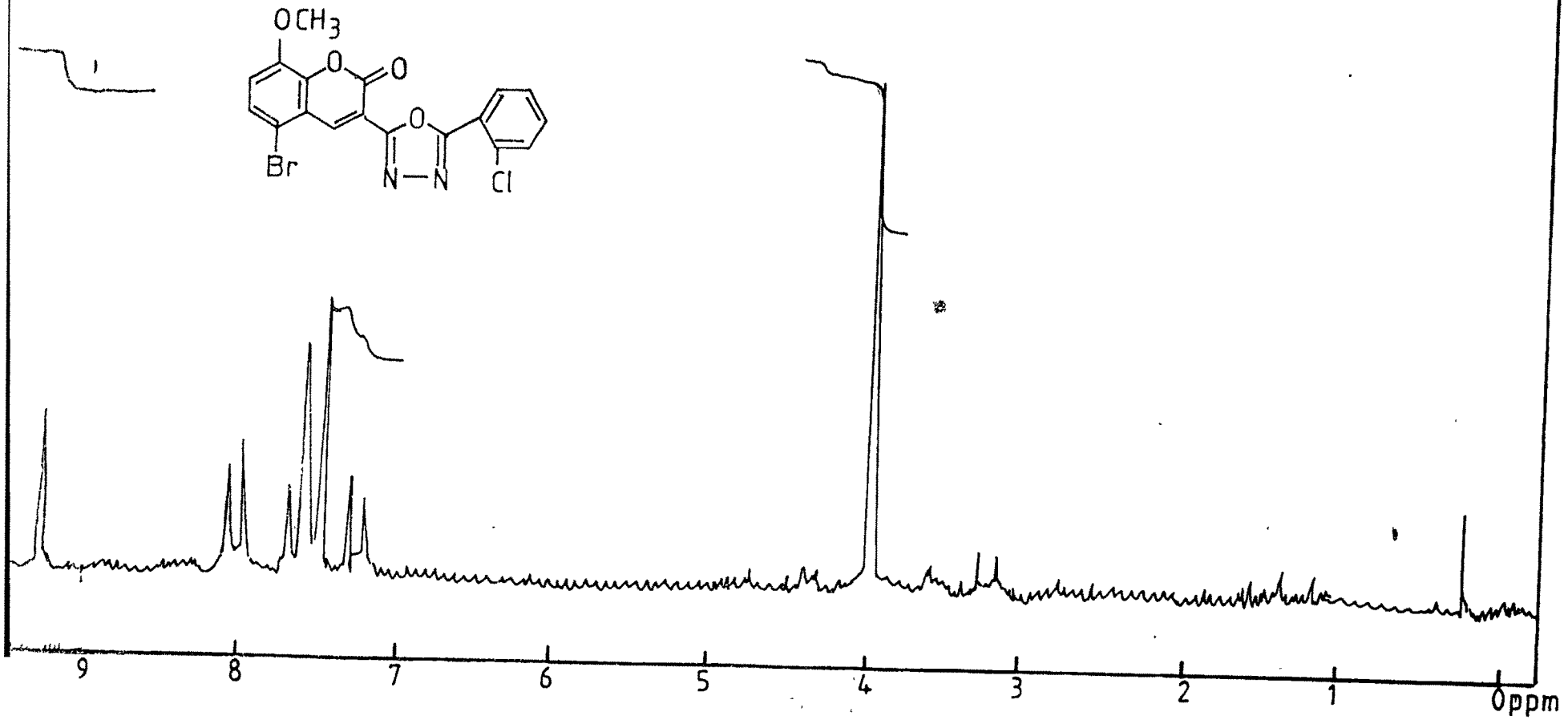


FIG. 5

Experimental

8-Methoxy-5-bromocoumarin-3-carboxylic acid[81] (60)

8-Methoxycoumarin-3-carboxylic acid (3.0g) dissolved in 20ml of glacial acetic acid was treated in cold with a solution of Bromine (3.0g) in 4 ml of glacial acetic acid The clear solution was poured into ice water. The resulting solid was crystallised from dilute acetic acid M.p. 230°C, Yield 90%.

1-(4"-Methylphenyl)-4-(8'-methoxy-5'-bromo-3'-coumarinyl)-2,3-diaza-1, 4-di-oxobutane (61, Table - 1, 1)

A mixture of 8-methoxy-5-bromocoumarin-3-carbonylchloride (0.01 mole) and p-toluic hydrazide (0.01 mol) was stirred in dry, diethylether (50-60ml) for 3 hrs. The resulting solid was crystallised from 1:1 DMF. M.p. 250°C, Yield 75%.

Analysis	: Found	:	C, 52.56;	H, 3 23;	N, 6 88%
$C_{19}H_{15}O_5N_2Br$	: Required	:	C, 52.90,	H, 3.48;	N, 6.49%

2-(2"-Chlorophenyl)-5-(8'-methoxy-5'-bromo-3'-coumarinyl)-1,3,4-oxadiazole (62, Table - 2, 1)

Method - I

A mixture of 8-methoxy-5-bromocoumarin-3-carboxylic acid (0.02 mol) and o-chloro benzoic acid hydrazide (0.01 mole) was refluxed in $POCl_3$ (5.0 ml) on a steambath for 5 hrs The reaction mixture then poured into ice-cold water and then crystallised from 1:1 DMF M.p. °C, Yield 61%.

Analysis	: Found	:	C, 49 43;	H, 1.98;	N, 6 91%
$C_{18}H_{10}O_4N_2BrCl$	. Required	:	C, 49.88,	H, 2.30;	N, 6 46%

Method - II

8-Methoxy-5-bromocoumarin-3-carbonylchloride (0.01 mol) and 2-chlorobenzoic acidhydrazide (0.01 mol) was stirred in ether (50-60 ml) for 3 hrs The separated product was filtered, dried and refluxed in $POCl_3$ (5.0 ml) on a steambath for 5 hrs Then it was poured into ice-cold water and separated product was filtered washed and crystallised from 1:1 DMF.

Table - 1. Analytical and Physical Data of Compounds (61)

Sr. No.	R	R'	M.P.* in °C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
						%C	%H	%N
1.	Br	4-CH_3	256^{D+W}	75	$C_{19}H_{15}O_5N_2Br$	52.56 52.90	3.21 3.48	6.88 6.49
2.	Br	2-NO_2	212^{D+W}	65	$C_{18}H_{12}O_7N_3Br$	46.26 46.75	3.12 2.59	9.46 9.09
3.	Br	3-NO_2	258^{D}	60	$C_{18}H_{12}O_7N_3Br$	47.12 46.75	3.09 2.59	8.88 9.09
4	Br	4-NO_2	278^{D+W}	69	$C_{18}H_{12}O_7N_3Br$	46.95 46.75	2.91 2.59	9.39 9.09
5.	Br	2-Cl	248^{D+A}	70	$C_{18}H_{12}O_5N_2BrCl$	47.44 47.84	3.15 2.65	6.61 6.20
6	Br	3-OCH_3	222^{D+A}	62	$C_{19}H_{15}O_6N_2Br$	50.60 51.00	3.75 3.35	6.55 6.26
7	Br	4-OCH_3	$206\text{-}08^{D+W}$	55	$C_{19}H_{15}O_6N_2Br$	50.82 51.00	3.11 3.35	6.05 6.26
8.	Br	H	183^{D+W}	60	$C_{18}H_{13}O_5N_2Br$	51.52 51.79	2.92 3.11	7.15 6.71
9	H	H	202^{D+W}	57	$C_{18}H_{14}O_5N_2$	64.37 63.90	4.23 4.14	8.58 8.28

Solvent of crystallisation, A = Alcohol, D = DMF, W = Water

Table - 2. Analytical and Physical Data of Compounds (62)

Sr. No.	R	R'	M.P.* in ^{o}C	%Yield	Molecular Formula	Elemental Analysis Found / Required		
						%C	%H	%N
1.	Br	2-Cl	255^{D+W}	61	$C_{18}H_{10}O_4N_2BrCl$	49.59 49.88	1.98 2.30	6.91 6.46
2.	Br	2-NO_2	250^{D+W}	52	$C_{18}H_{10}O_6N_3Br$	48.50 48.64	2.47 2.25	9.43 9.45
3.	Br	3-OCH_3	180^{D+W}	55	$C_{19}H_{13}O_5N_2Br$	53.42 53.14	3.46 3.03	6.98 6.52
4.	Br	4-CH_3	$259\text{-}60^{D}$	60	$C_{19}H_{13}O_4N_2Br$	55.48 55.20	2.85 3.14	6.90 6.77
5.	Br	3-NO_2	265^{D+W}	58	$C_{18}H_{10}O_6N_3Br$	48.39 48.64	2.47 2.25	8.97 9.45
6.	H	H	221^{D+W}	50	$C_{18}H_{12}O_4N_2$	67.37 67.50	3.80 3.75	8.43 8.75

Solvent of crystallisation, D = DMF, W = Water

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