CHAPTER—II

PART – I

MANNICH REACTION ON SOME HYDROXYCOUMARINS

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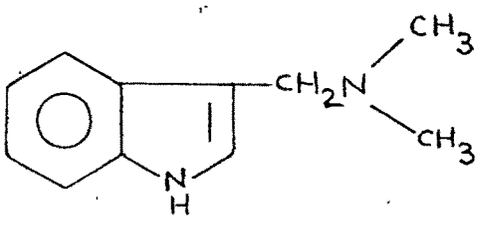
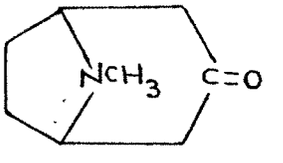
INTRODUCTION

Many alkaloids like Gramine (1) appear to be synthesised in plants through reaction that resembles the Mannich reaction. Recognition of this by R. Robinson led to a synthesis of tropinone (2) that takes place under "physiological conditions" i.e. at room temperature and at a pH near neutrality. Mannich reaction appears to be of central importance in alkaloid biosynthesis. The biosynthetic route that the opium poppy uses to synthesis morphine also involves Mannich - type condensation and is constructed from two moles of tyrosine (3).



(1)



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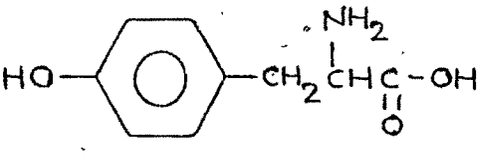


(3)

Mannich reaction, named after Carl Mannich, involves condensation of a carbonyl compound (an enolizable ketone) for exampleacetophenone, with formaldehyde and ammonia or a primary or secondary amine, usually as the hydrochloride. The essential feature of the reaction is the replacement of the active hydrogen atom by an aminomethyl or substituted aminomethyl group. Phenols, ketones, aldehydes, acids, esters, acetylenes, nitrocompounds and heterocyclic ring systems containing either oxygen, nitrogen or sulphur are found to undergo this reaction.

$$C_6H_5COCH_3 + CH_2O + R_2NH.HCl \longrightarrow C_6H_5COCH_2CH_2NR_2.HCl + H_2O$$

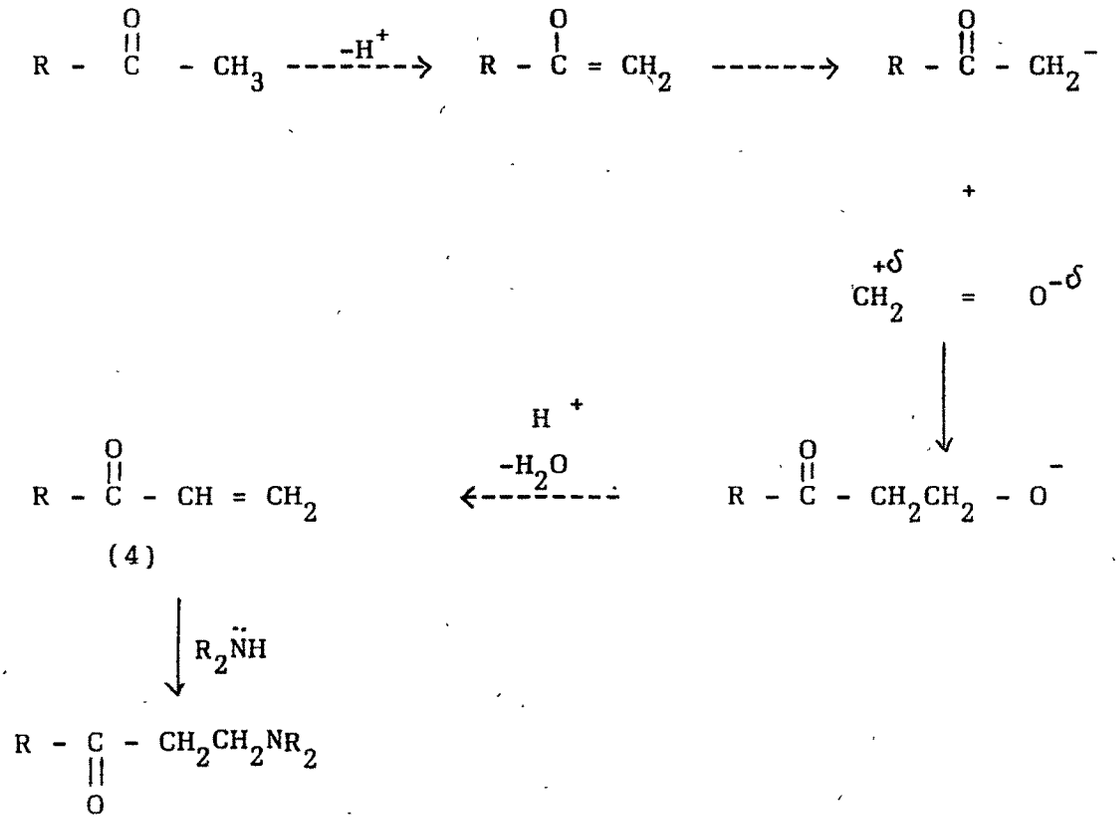
When aqueous formaldehyde is used, the condensation may be carried out with or without solvents. Alcohol and acetic acid have been generally employed. A mixture of equivalent amounts of benzene and nitrobenzene or benzene alone are useful.

Burke and co-workers[1] have used dioxane with very good results. When paraformaldehyde is used, an organic solvent is required. Burkeet al. (loc cit) employed a catalytic quantity of alcoholic potassium hydroxide to effect the depolymerisation of paraformaldehyde. The time limit required for the reaction

depends upon thenature of the compound containing active hydrogen and of the amines or amine salt and upon the boiling point of the solvent employed. Thus, in the reaction of phenols with formaldehyde and primary amines, the reaction is generally completed in about two hours. It is found that the reactionmay be completed within a few minute of refluxing.

MECHANISM :

Dalgliesh[2] suggested a mechanism which involves formation of an α, β-unsaturated ketone (4) that adds ammonia.



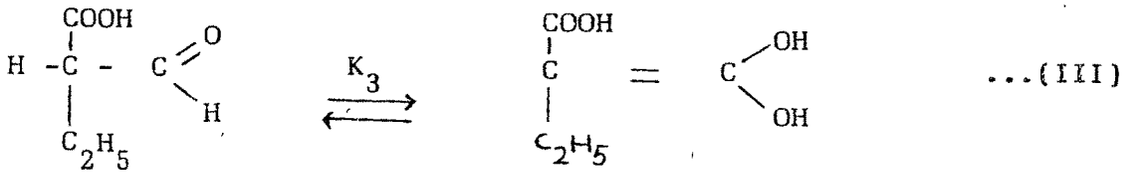
Alexander et al.[3] proposed quite different mechanism for the reaction of compounds containing active methynyl group. They made a Kinetic study of the reaction of ethyl malonic acid with formaldehyde and dimethylamine and based on their results, they proposed a reaction mechanism in which the reaction is considered to be initiated by the reversible addition of dimethylamine and formaldehydeto give dimethyl-aminomethanol. In the presence of an acid HA, a reactive hydrogen bounded addition complex formation (5) is postulated. A properly oriented collision of the complex (6) with ethyl malonic acid, probably in the transitory enol form (7) would produce water, the conjugate base A and a protonated molecule of dimethylaminomethyl malonic acid (8). Reaction of the protonated molecules with the conjugate base A would give the free amino acid (9).

$$CH_2O + (CH_3)_2NH \underset{\longleftarrow}{\xrightarrow{K_1}} (CH_3)_2N.CH_2OH \quad \ldots\ldots (I)$$

(5)

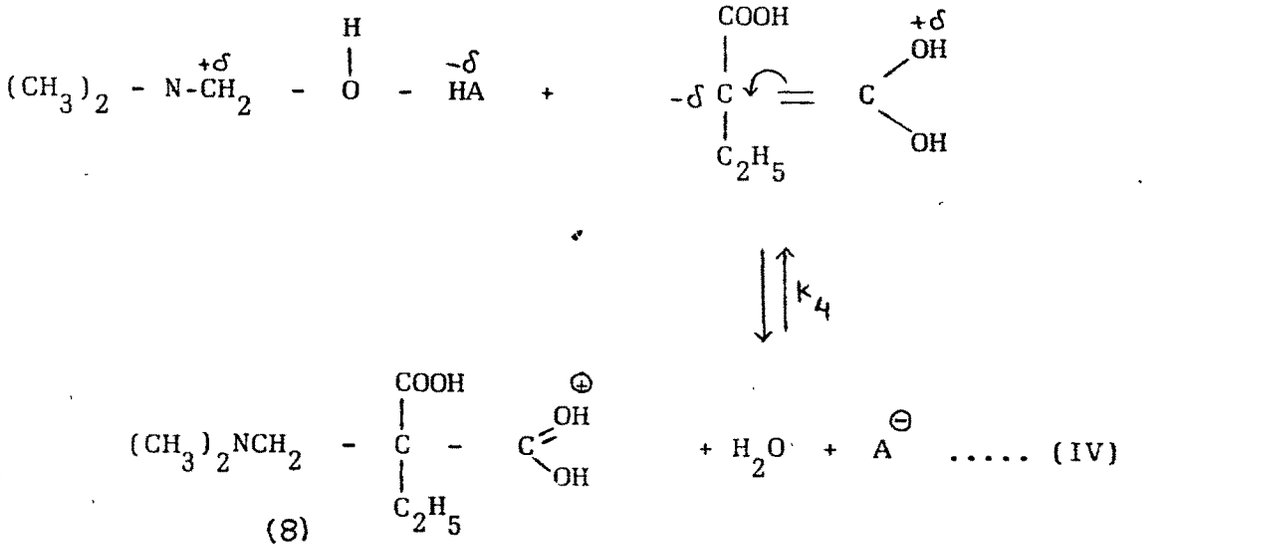
$$(CH_3)_2NCH_2\text{-}\overset{H}{\underset{|}{O}} + HA \underset{\longleftarrow}{\xrightarrow{K_2}} (CH_3)_2N\overset{+\delta}{\text{-}}CH_2\text{-}\overset{H}{\underset{|}{O}}\overset{-\delta}{\text{-}}HA \quad \ldots\ldots (II)$$

(6)



...(III)

(7)



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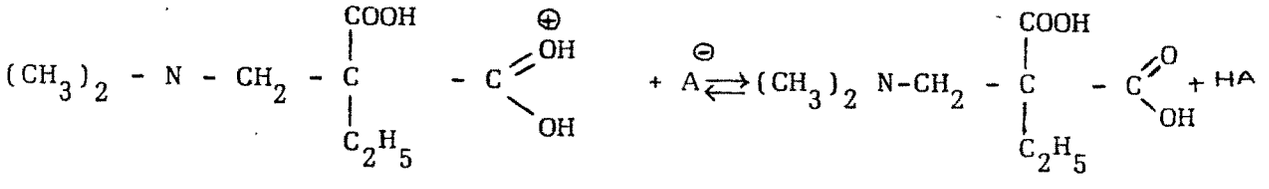
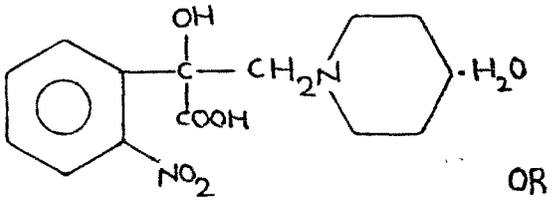
(IV)



(9)

The postulation of enolisation step (III), in the above mechanism was questioned by Grillot et al.[4] They found that in Mannich reactions involving optically active o-nitro mandelic

acids the products formed were also optically active. Thus they argued that lack of racemisation rendered inadmissable the enolisation step postulated above. However, this objection has been cleared by the excellent work of Meinwald et al.[5] who showed that products obtained by Grillot et al.[5] (loc cit) were not the true Mannich bases (10). They considered the products as salts and out of the two possible general structures (11) and (12), they conclusively gave the structure (11) to the products on the results of IR absorption spectra and molecular weight determinations carried out on product from D - O-nitro mandelic acid, formaldehyde and piperidine.



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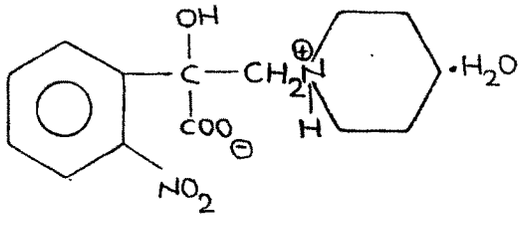

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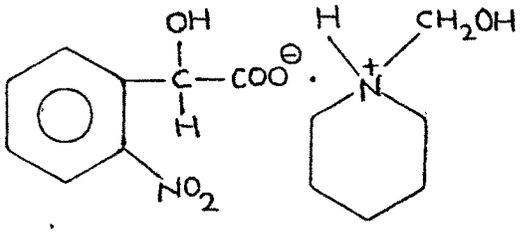

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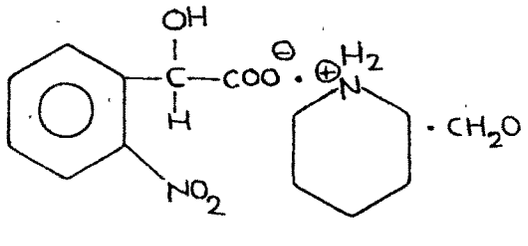
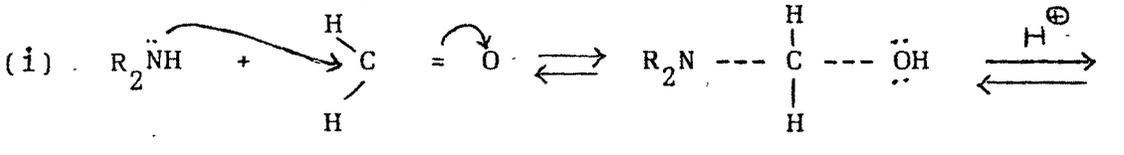
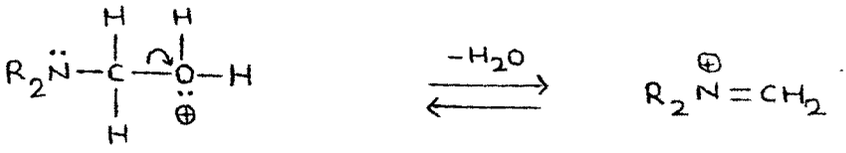


(12)

Liberman and Wagner[6] believe that the Mannich reaction involves a dual catalysis in an amphoteric system in which the cation $R_2\text{-}N\text{-}\overset{\oplus}{C}$ is formed from the condensation products of amine and carbonyl compound and combines finally with the anion of the reactive hydrogen compound. Formation of cation is induced by added acid or by the acidity of the reactive hydrogen compound or both. Formation of the anion is promoted bythe base present or by added alkali or both. The inferences that excessive acid would interfere with the primary condensationof amine and carbonyl compound and would depress the ionisation tendency of the reactive hydrogen compound and that excessive alkali would decrease or prevent the formation of cation $R_2\text{-}N\text{-}\overset{\oplus}{C}$ and therefore obstruct or stop the reaction were supported experimentally. Also the probability that the cation orginates in the alkylidene-bis-amine formed from aldehyde and amine was strengthened by demonstration that methylene-bis-amines, used instead of aldehydes and amines, produced normal yields.

Probable mechanism[7] that appears to operate in neutral or acidic media involves (i) initial reaction of the secondary amine with formaldehyde to yield iminium ion, and (ii) subsequent reaction of the iminium ion with the enol form of the active methylene compound.

(i)




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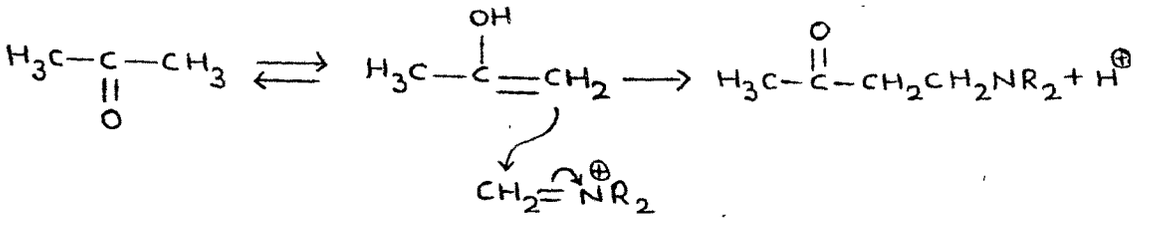
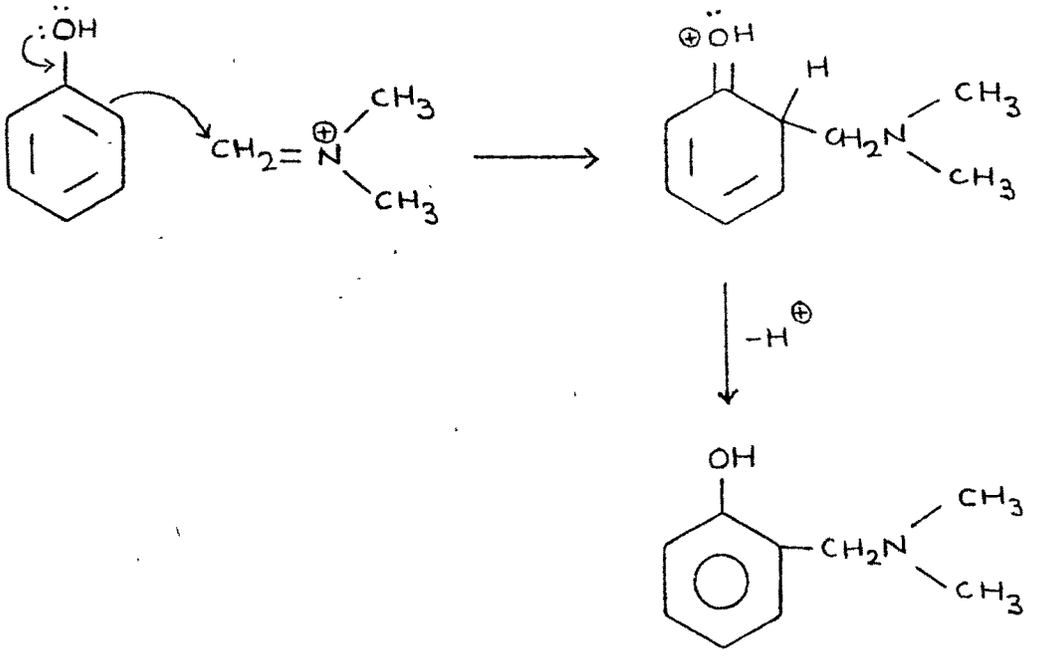




Various types of compounds having reactive hydrogen have been subjected to this reaction. Only a few illustrative reactions are mentioned here.

REACTIONS WITH KETONES :

A primary amine is the first product formed from a Mannich reaction in which ammonia or ammonium salt and formaldehyde react with a ketone. With simple ketones, subsequent action of the primary amines so formed usually leads to the production of secondary amines, salts of which have been isolated and found to be stable, but the free base changes to the tertiary amines.

$$C_6H_5COCH_3 + CH_2O + (CH_3)_2 NH.HCl \xrightarrow[\text{reflux}]{\text{alcohol}}$$

$$C_6H_5COCH_2.CH_2N\ (CH_3)_2.HCl$$

Certain ketonic amines of the type illustrated afford on reduction physiologically active amino alcohols of value in therapy.

REACTION WITH ALDEHYDE :

The α -hydrogen atom of the aldehyde is substituted by a substituted aminomethyl group. A secondary reaction which some times occurs involves the simultaneous introduction of a methylol group on the α-carbon atom.

REACTION WITH ACIDS AND ESTERS :

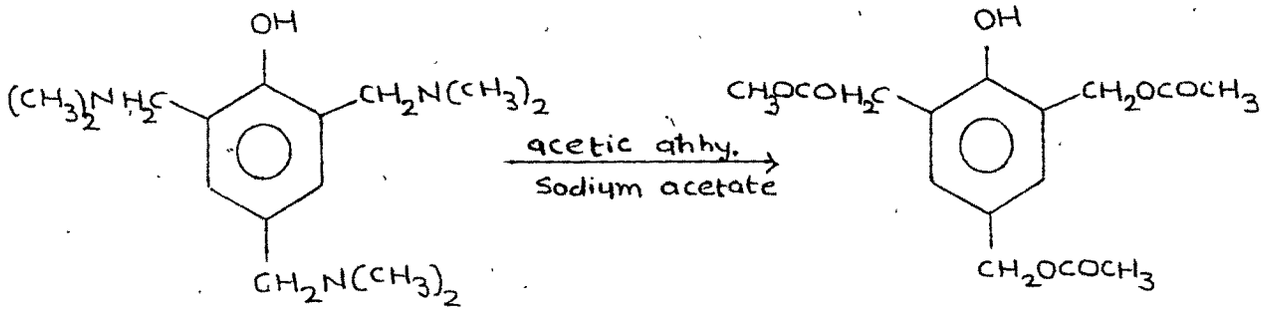
Different acids and esters containing highly reactive hydrogen atoms in the α-position undergo Mannich reaction,

when an acid is employed, the free amine base rather its salt is used.

REACTION WITH PHENOLS :

Decombe[8] has proved that in the Mannich reaction of a phenol with formaldehyde and secondary amines, the resulting dialkyl-aminomethyl group enters the ortho or para position or both and in no case it attaches to oxygen of the hydroxyl group.

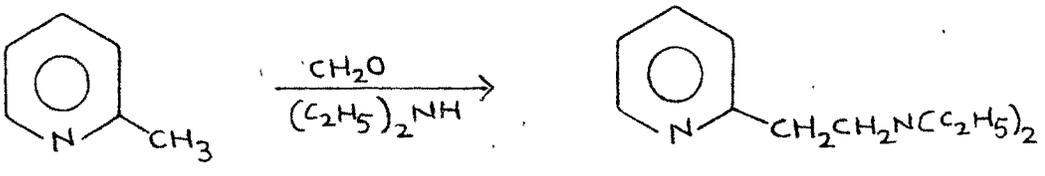
Brusson and co-workers[9] have reported that when phenolic Mannich bases were treated with acetic anhydride, their dimethyl-aminomethyl groups were replaced by acetoxymethyl groups.



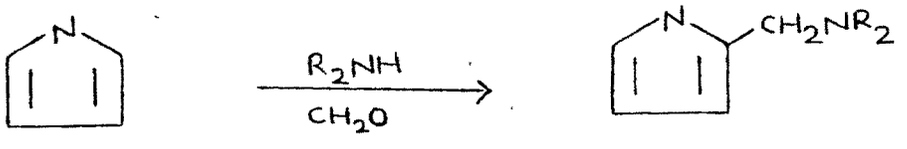
REACTION WITH HETEROCYCLIC COMPOUNDS :

A number of heterocyclic systems containing nitrogen, oxygen or sulphur have been studied. In case of α-picolines

and quinaldines, the hydrogen of the ∝-methyl group is sufficiently reactive to take part in the Mannich reaction. Thus, Tseou and co-workers[10] have reported the formation of 2-(β-diethylaminomethyl) pyridine, when ∝-picoline, formaldehyde and dimethylamine were condensed.

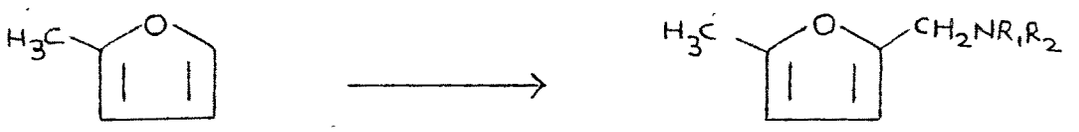


Mannich reaction with pyrrole has been studied by number of workers. Hydrogen on ∝-carbon atom was substituted.



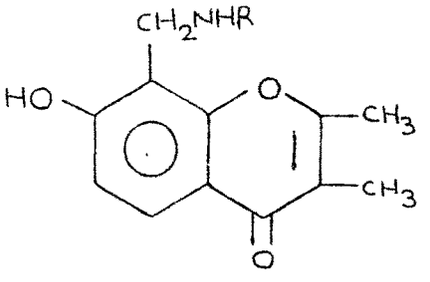
Burke and co-workes[11] have carried out the reaction on several pyrroles with formaldehyde and primary amines.

2-Methyl furan was subjected to Mannich reaction by Nixon and co-workes[12] using formaldehyde, primary and secondary amine.



Wiley[13] carried out Mannich reaction on 6-methoxy-, 6-chloro-, 6-methyl- and 7-methoxychromones with formaldehyde and different secondary amine hydrochlorides and obtained the corresponding 3-(dialkylaminomethyl) chromonehydrochlorides.

P. Da. Re et al.[14] reported the Mannich reaction on 7-hydroxy-2,3-dimethyl (13),2-methyl-3-ethyl (14) and 2-ethyl-3-methylchromones (15) with dimethylamine, diethyl amine, morpholine and piperidine and formalin that gave the corresponding 8-dimethylaminomethyl chromones. Similar results were obtained in the case of 3-methyl-and 3-ethylflavones. These derivatives are reported to act as powerful CNS stimulants especially on the brain steam and have a cardiokinetic and hypertensive action.



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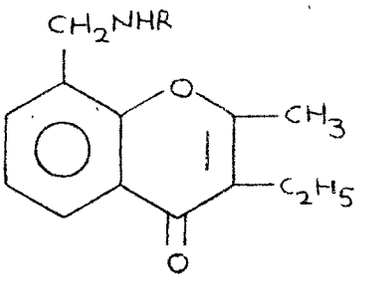

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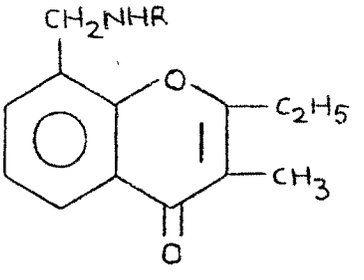
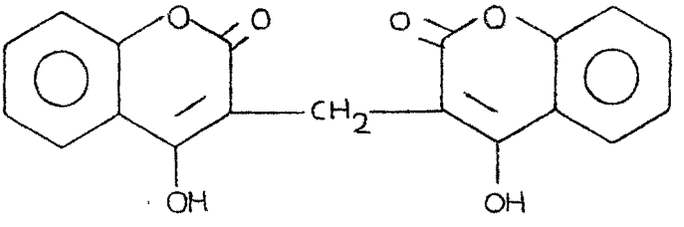


(15)

In recent years Mannich bases have received considerable attention on account of their various therapeutic properties. Some recent research publications on coumarins are briefly reviewed here.

Robertson and Link[15] attempted to prepare Mannich bases from paraformaldehyde and the amine hydrochlorides but failed, instead the bis-product 3,3'-methylene-bis-4-hydroxycoumarin (16) was obtained. Later on they succeeded in preparing a series of 3-substituted aminomethyl-4-hydroxycoumarin (17).



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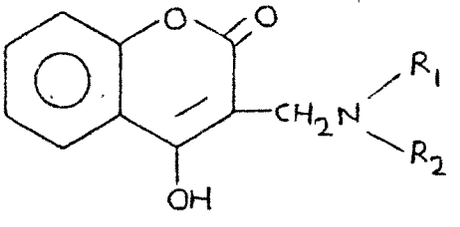
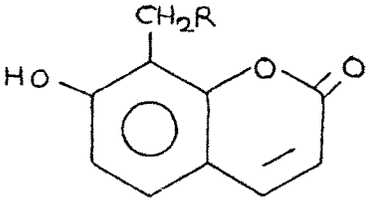


(17)

V.N. Gupta[16] and others reported that Mannich bases synthesized from 7-hydroxycoumarin derivatives with aliphatic amines have been found to have powerful stimulating effect on central nervous system.



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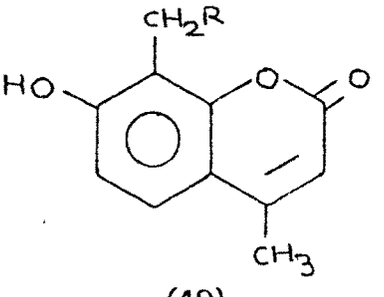
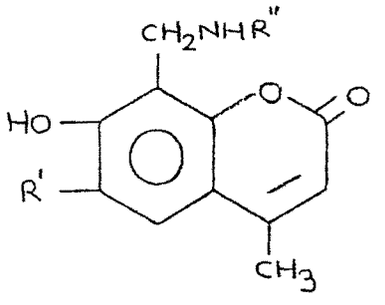


(19)

R.B. Desai[17] studied Mannich reaction on 5-hydroxy-, 6-hydroxy- and 7-hydroxycoumarins with formalin and primary and secondary amines and obtained Mannich bases (20) and also oxazino derivative (21).



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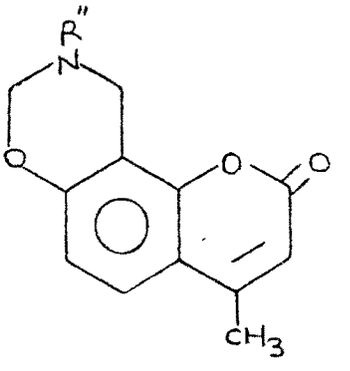
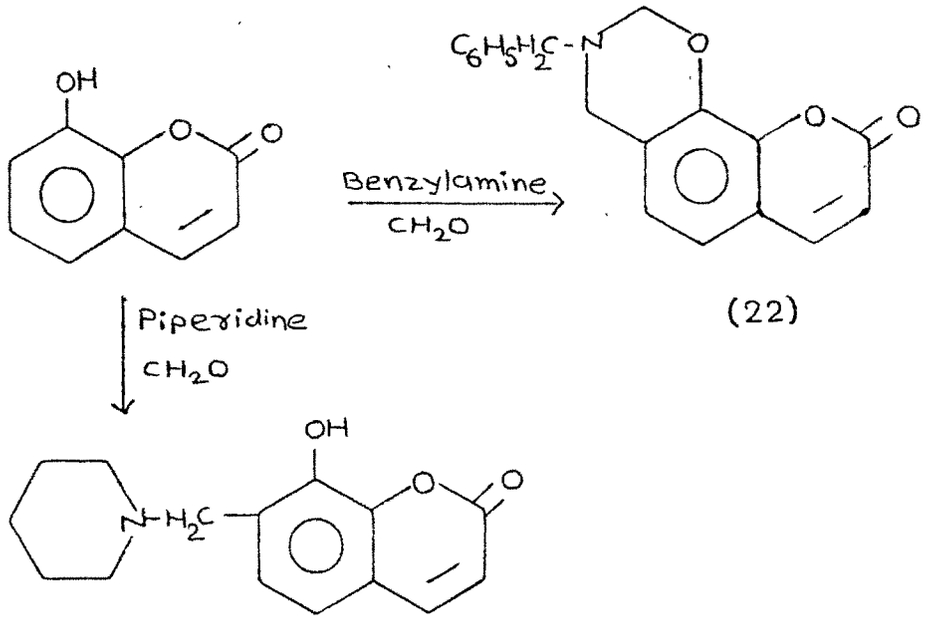


(21)

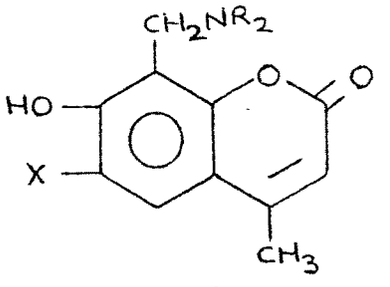
Patel, Mehta and Sethna[18,19] have applied Mannich reaction to 6-hydroxy-, 7-hydroxy-, ethyl-7-hydroxycoumarin-3-carboxylate and 8-hydroxycoumarin and obtained corresponding alkyl amino-methyl and Oxazino derivatives.



(22)

(23)

Satyendrakumar and Shiamsunder[20] prepared Mannich bases (24) from 7-hydroxy-4-methyl-6-chloro- and 7-hydroxy-4-methyl-6-bromocoumarin and studied their CNS stimulating activity.

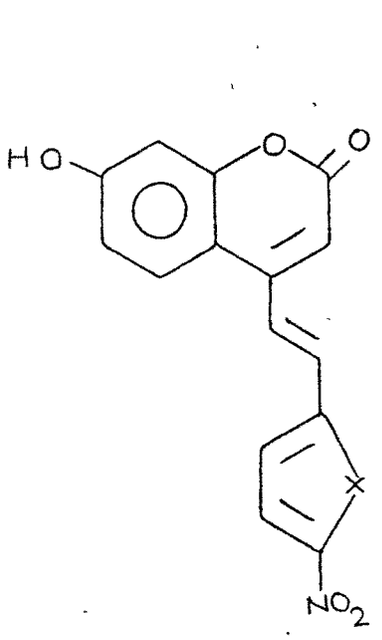


X = Cl, Br

(24)

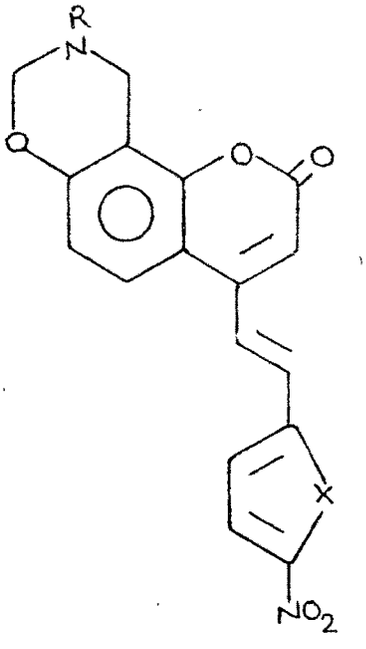
A.K. Agrawal[21] and others synthesied Mannich bases from 7-hydroxy-4-methyl-8-substituted aminomethylcoumarin and tested their antiestrogenic activity. They found that all coumarins possessing approximately LD-50 value of 500->800 mg/kg. antagonised the uterotropic effects ofdimethyl-stilbestrol (DES) in female rats.

D.R. Shridhar and co-workers[22] studied the Mannich reaction on coumarin (25) with different amines and formaldehyde, and they obtained pyranobenzoxazinones (26). They found that the compoundof the type (26) have considerable amebicidal, bactericidal and antitrichomonal activities in vitro but were devoid of such activities in Vivo.



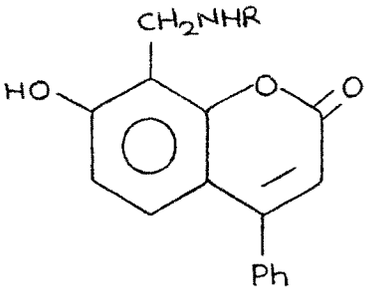
(25)

X = O,S



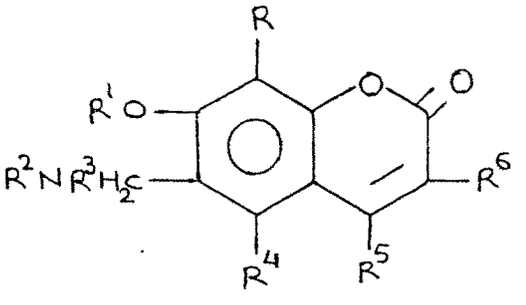
(26)

A. Kameswara Rao, M. Subramanyam Raju and K. Mohana Raju[23] synthesised biologically active Mannich bases from 7-hydroxy-4-phenylcoumarin. They found that 8-morpholinomethyl-7-hydroxy-4-phenylcoumarin and 8-benzylaminomethyl-7-hydroxy-4-phenylcoumarin were more active against S. faelesis and K Pneumoniae. These Mannich bases also exhibited moderate antifungal activity against T. mentagrophytes and Aspergillus famigatus but were inactive against C. Albicans.



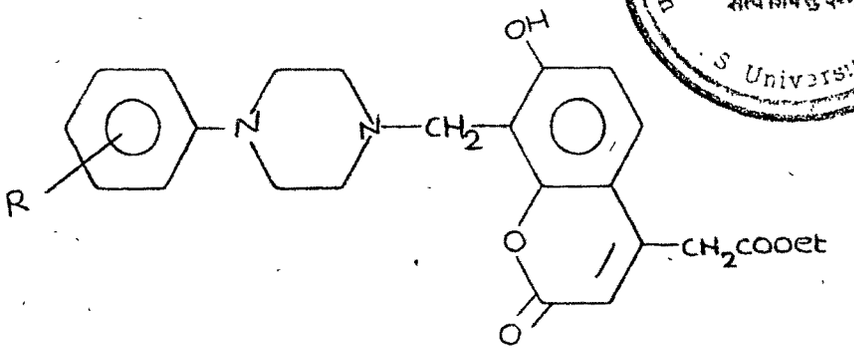
(27)

S.P.A. Fadia[24] prepared substituted 7-hydroxy-6-(aminomethyl)coumarins which inhibited blood platelet aggregation and showed anti-tumor activity.



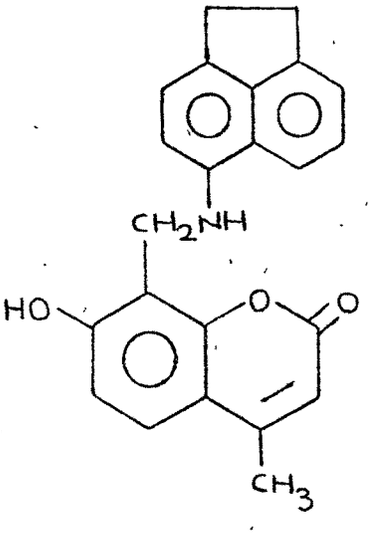
(28)

Mannich bases like 7-hydroxy-8-(1-aryl-piperazinomethyl) coumarin (29), prepared by U.V. Korgaonkar and coworkers[25] showed antiinflammatory activity.



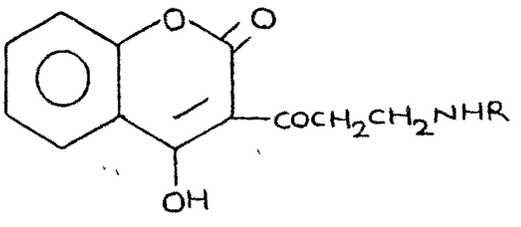
(29)

A.R. Bhat and Shailendrakumar[26] prepared Mannich base of the type (30) from 7-hydroxycoumarin and 5-aminoacenaphthene which was active against gram positive bacteria.



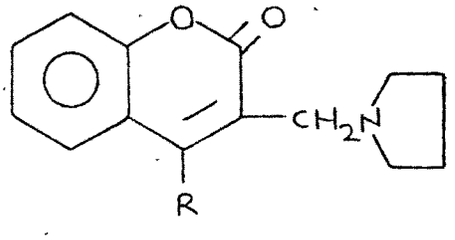
(30)

C-acylcoumarins have also been found to participate in Mannich reaction. S.K. Agrawal and R.C. Saxena[27] synthesised Mannich bases from 4-hydroxy-3-acetylcoumarin. Some of them were found active against Bacillus aureus.

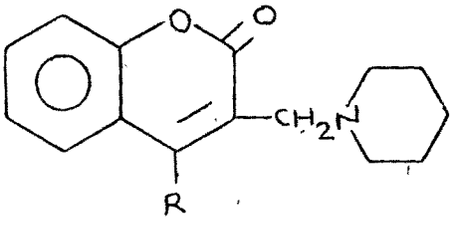


(31)

Mannich reaction of 4-hydroxycoumarin with pyrrolidine and piperidine gave Mannich bases (32) and (33). V.L. Savellev[28] and others suggested that Mannich bases with R = Cl had weak Psychotropic activity.



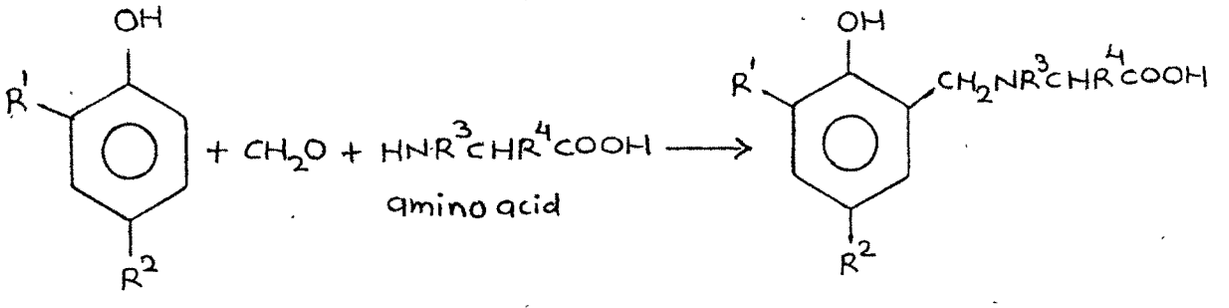
(32)



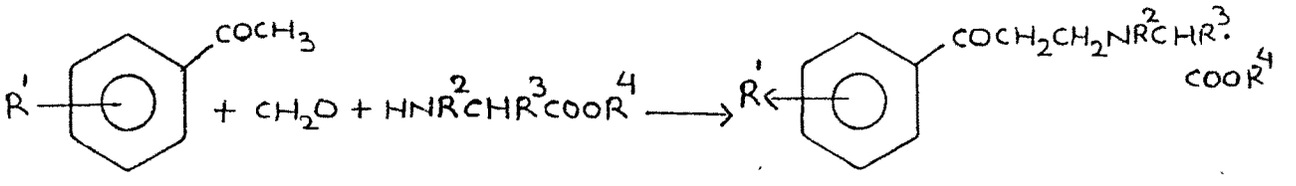
(33)

Recently Short and Ours[29] have shown that aminoacids (34),(35) have been found to participate as the amine component

in the Mannich reaction of substituted phenols instead of usual aliphatic or aromatic amines.

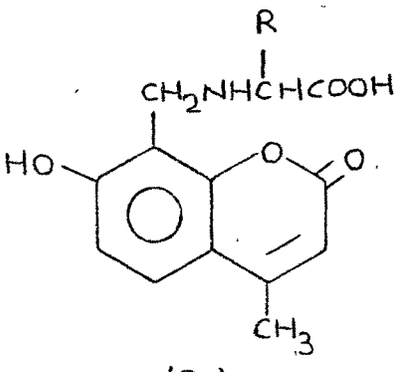


(34)



(35)

R.H. Mehta[30] carried out Mannich reaction of 7-hydroxy-coumarin derivatives with various aminoacids (36) and studied their CNS stimulating activity.



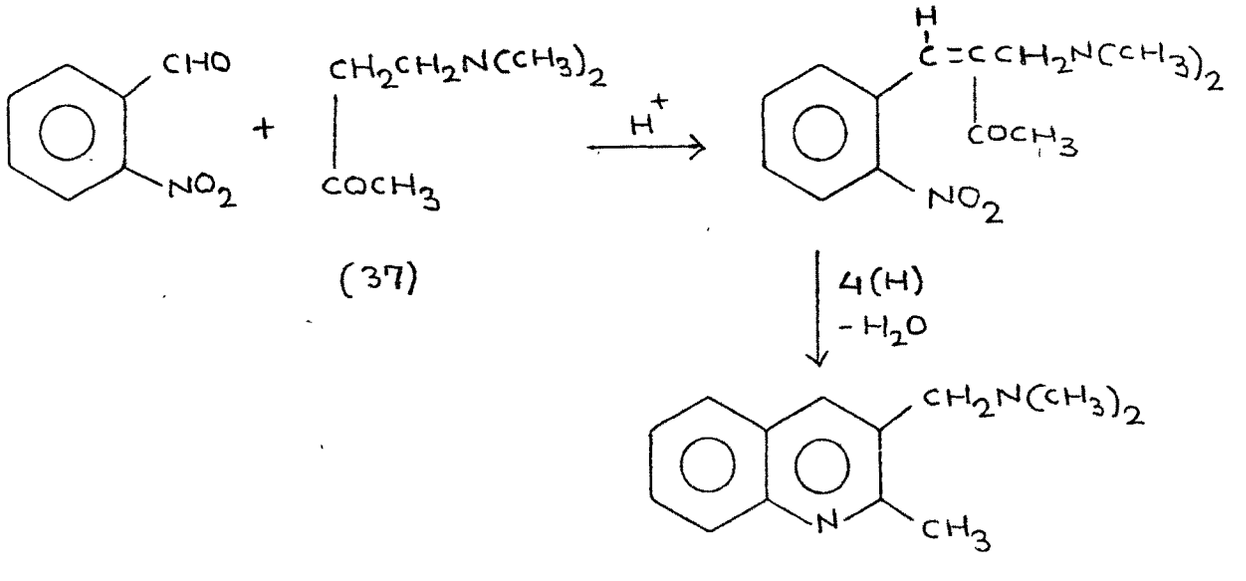
(36)

APPLICATION OF MANNICH REACTION

Recently the Mannich reaction has proved to be an important tool in the Synthetic Chemistry. The resulting products of the Mannich reaction may be further transferred into a variety of compounds. A few of these may be mentioned here. Some of the Mannich bases and their reduction products have proved to be important medicinal agents.

The most useful characteristic property of many of the products obtained in the Mannich reaction, especially those derived from secondary amines, is the decomposition into the amine and unsaturated compound, when subjected to heat or steam distillation.

Mannich et al.[31] found that β-dimethyl aminomethylketone (37) and o-nitrobenzaldehyde reacted to give a product which upon reduction lost water to form a substituted quinoline (38).



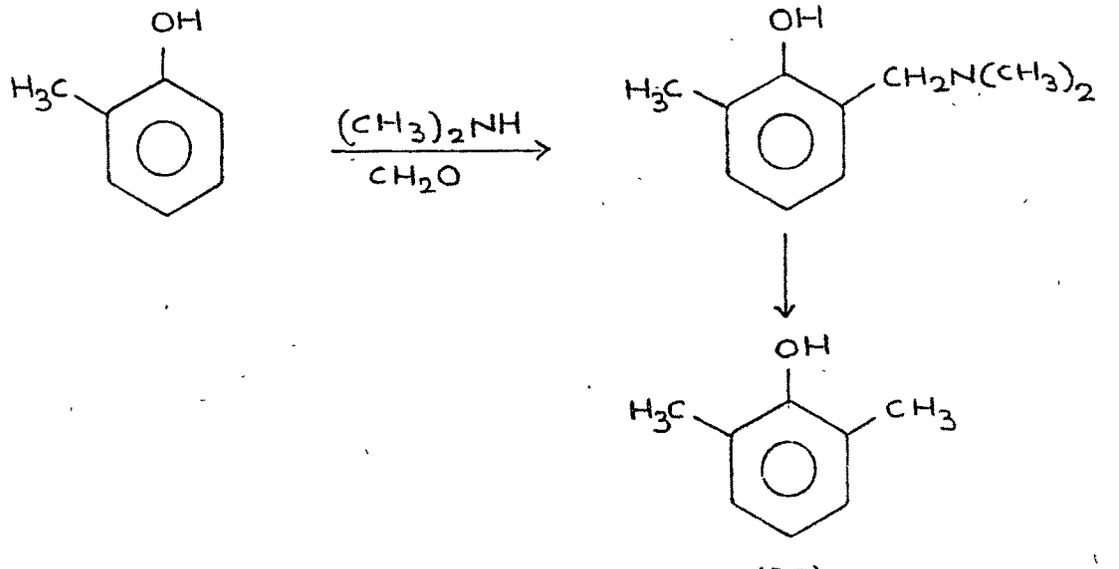
(37)

(38)

Synthesis of aminoalcohols :

The β-substituted aminoketones or aldehydes have been reduced to the corresponding γ-substituted aminoalcohols. Many such aminoalcohols in the form of their esters especially benzoate and p-aminobenzoates have been widely used as local anaesthetics.

Caldwell and Thompson[32] have developed a new method for nuclear methylation of phenols which consists in the hydrogenolysis of the dimethylaminomethyl derivatives obtained by Mannich reaction. On this basis, Callin et al.[33] achieved a practical synthesis of 2,6-xylenol (39).



(39)

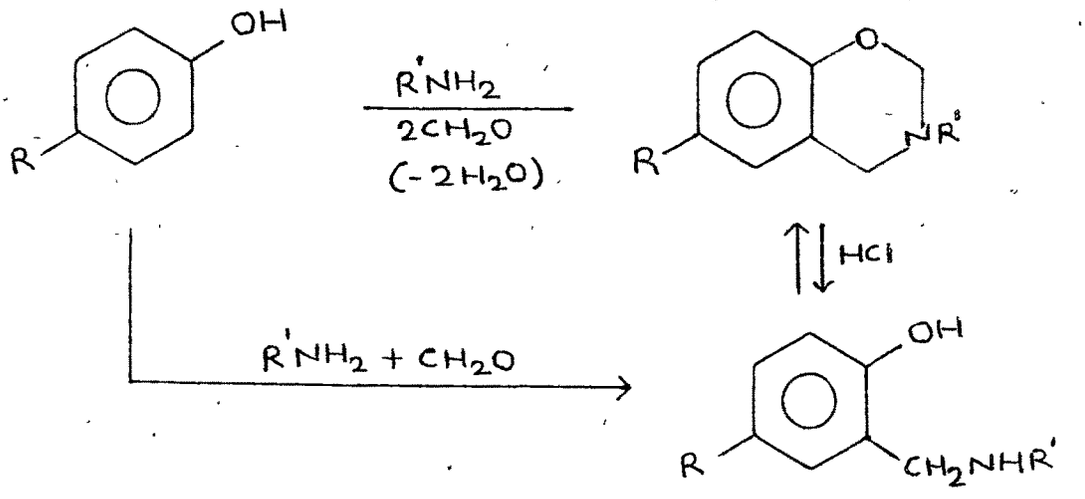
Snyder[34] observed that when Mannich base in acetic acid solution was treated with hexamethylene tetramine the intermediate quaternery salt decomposed to an aldehyde. The interme-

diate quarternary salts were of the type encountered in the Sommelet Synthesis.[35] The conversion of primary and secondary amines to aldehydes by modified Sommelet reaction was described by Graymore et al.[36]

Synthesis of 1,3-Oxazino derivatives :

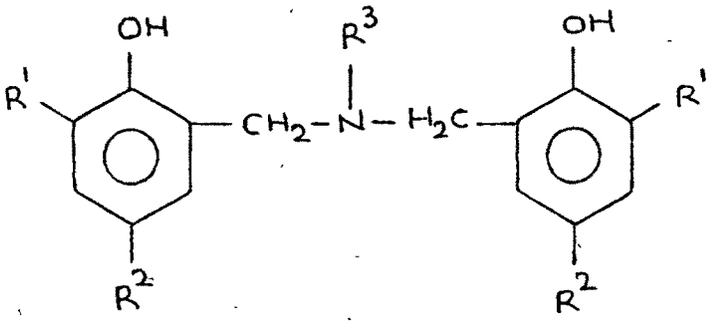
Burke[1] showed that whereas the condensation of equimolar quantities of para substituted phenols with formaldehyde and primary amines gave o-alkylaminomethyl-p-substituted phenols, when the reaction was carried out using phenols, formaldehyde and primary amines in a molar ratio of 1:2:1 respectively, the formation of substituted benzoxazines took place.

These benzoxazines could be prepared alternatively from o-alkylamino-p-substituted phenols by refluxing them with excess of formaldehyde in alcoholic solution in the presence of a basic catalyst such as sodium hydroxide. Benzoxazine derivatives on heating with hydrochloric acid in alcoholic solution decompose readily to give formaldehyde and the corresponding o-alkylaminomethyl-p-substituted phenols (40).



(40)

Burke and coworkers[37] observed that a third kind of product N,N-bis-(2-hydroxybenzyl) alkylamine (41) could be directly obtained.

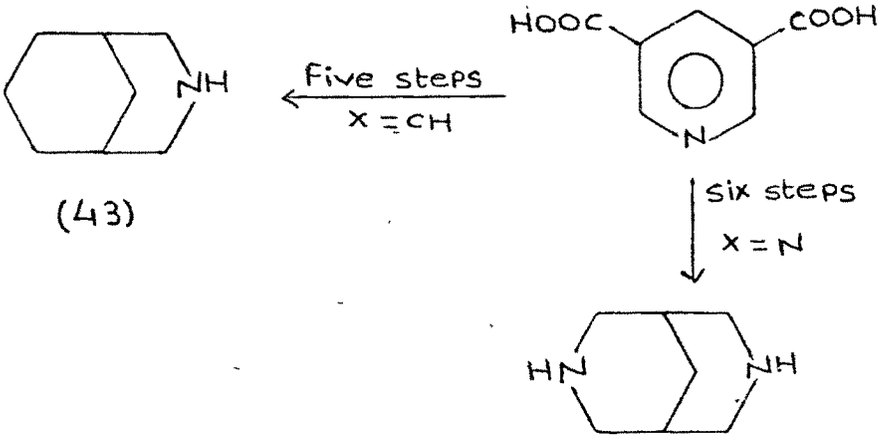


(41)

Synthesis of Bispidine

Petter and Edward[38] synthesised Bispidine (42) using Mannich reaction. Bispidine (42) is used as a ligand in the study of complexation by certain transition metals[39]

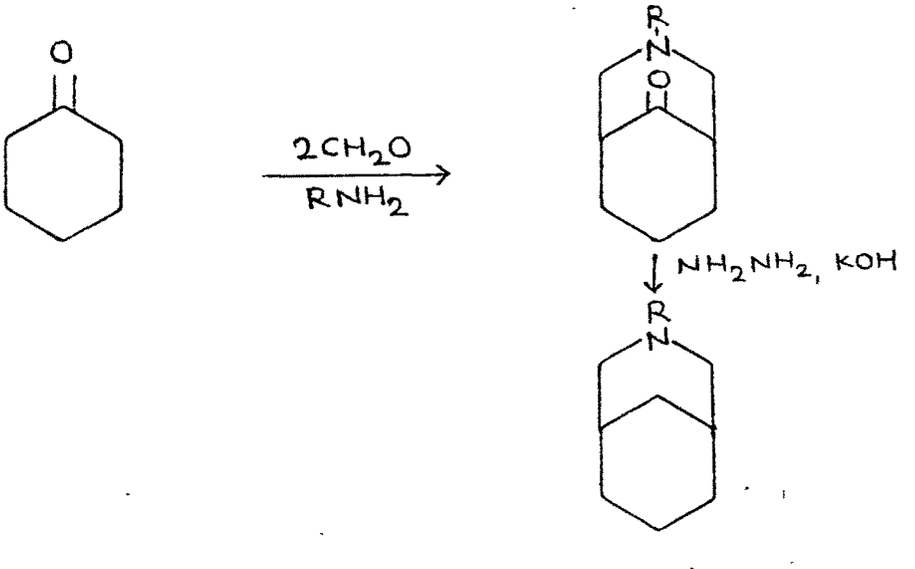
and as an intermediate for the synthesis of pharmacologically active compounds.[40] It was first prepared[41-43] as shown below (X=N)in a manner similar to that initially used[44,45] to prepare its monoazabicyclic counterpart (43) (X=CH).



(43)

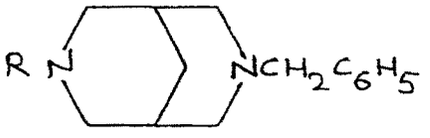
(42)

The alternative route to N-alkyl derivatives of (44) via the initial double Mannich condensation followed by wolff-Kishner reduction of the intermediate amino ketone has been studied by several groups.[46-48] Using this approach they found that N-substituted bispidine (45) may be prepared from N-alkyl-4-piperidones, benzylamine and excess of paraformal-

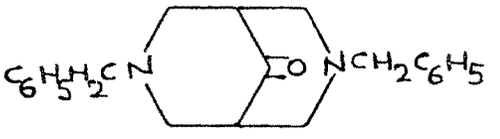


(44)

dehyde.[49] Condensation of N-benzyl-4-piperidone, benzylamine and paraformaldehyde afforded the bicyclic aminoketone (46).



(45)



(46)

PRESENT WORK

The literature survey shows that the Mannich bases of 7-hydroxycoumarin derivatives synthesised with aliphatic, aromatic and heterocyclic amines have been found to have antibacterial activity. On the other hand phenylalanine, methionine and valine are aminoacids essential for mammals. With a view to determine if the common aminoacids will participates in the Mannich reaction involving 7-hydroxy-, 7-hydroxy-5-methyl-, 7-hydroxy-4-methyl-8-acetyl and 7-hydroxy-4-phenyl-coumarins and to explore the possibility of utilising these new Mannich bases as antibacterial agents.

The structures of the Mannich bases synthesised were assigned on the basis of elemental analysis, IR, NMR and mass spectra.

Following IR absorption has been observed in all the Mannich bases prepared during the present work.

3500-3400 cm^{-1}, a broad absorption due to phenolic --OH stretching. A broad strong $\overset{+}{N}H_2$(NH) stretching band in the 3100-2400 cm^{-1} region. The carboxylate ion group (-C$\overset{O}{\underset{O}{<}}$ -) absorbs strongly near 1600-1590 cm^{-1} overlaping aromatic -C=C- stretch at 1600 cm^{-1}. Aliphatic C-H stretch (superimposed on N-H stretch) absorbs at 2960-2850 cm^{-1}.

To support the structures assigned to Mannich bases, some representative compounds and their spectral data is described here.

Some selected compounds were screened for their antimicrobial activity using cup-plate method[50] at 100 ppm and 500 ppm concentration against strains E. coli, S. aureus, S. albus and S.typhosa . Screening report is given in Chapter-IV, Part-II.

Mannich reaction on 7-hydroxy-4-phenylcoumarin : N-(7-hydroxy-4-phenyl-8-coumarinyl) glycine (48a) :

A mixture of 7-hydroxy-4-phenylcoumarin[51] (47), formalin and glycine when reacted gave a product to which N-(7-hydroxy-4-phenyl-8-coumarinyl) glycine structure has been assigned.

The structure of the compound was confirmed by analytical data and following IR and NMR spectra.

The IR (KBr) spectrum showed bands at 3440 (broad), 3180-2400 (broad), 1720 (broad), 1600 (broad) cm^{-1} . (Fig.1)

The NMR spectrum exhibited following signals. (CF_3COOH) δ 4.1, broad singlet, $NHC\underline{H}_2COOH$; δ 4.65, broad singlet, $C\underline{H}_2NH$ protons ; δ 6.2, singlet for a proton at position C-3 of coumarin ring ; δ 6.8, doublet, for a proton at C-6 position (J=9Hz) ; δ 7.4, doublet, for a proton at C-5 position (J=9Hz). Protons of phenyl ring at position C-4 appeared as broad multiplet at δ 7.2. The above NMR did not show the signal of a proton of C-8 position of coumarin ring. This confirmed that substitution has taken place at position C-8 of the coumarin ring (Fig.2)

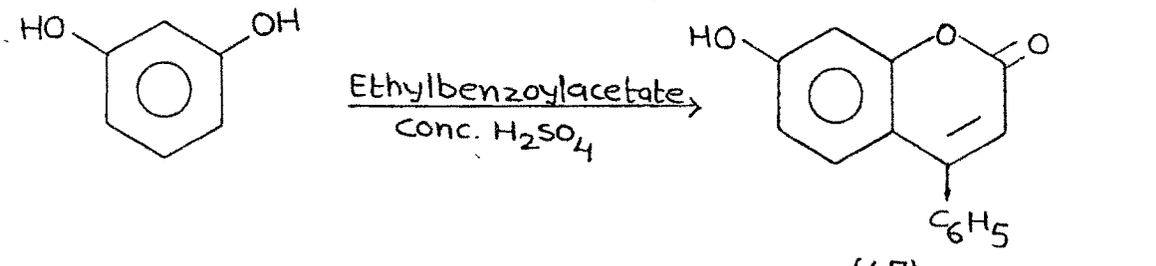
N(7-Hydroxy-4-phenyl-8-coumarinyl)α-alanine (48b) :

7-Hydroxy-4-phenylcoumarin when treated with formalin and α-alanine, gave 8-substituted Mannich base. The structure assigned was established by following IR and NMR spectra.

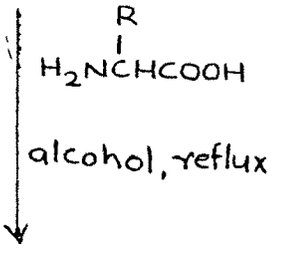
In IR (KBr) spectrum, bands at 3430 (broad), 3160-2400 (broad), 1720 (broad), 1600 (b) cm^{-1} were observed.

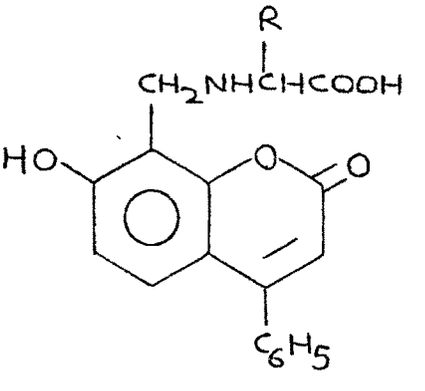
The NMR spectrum exhibited following signals. (CF_3COOH)

Scheme:1



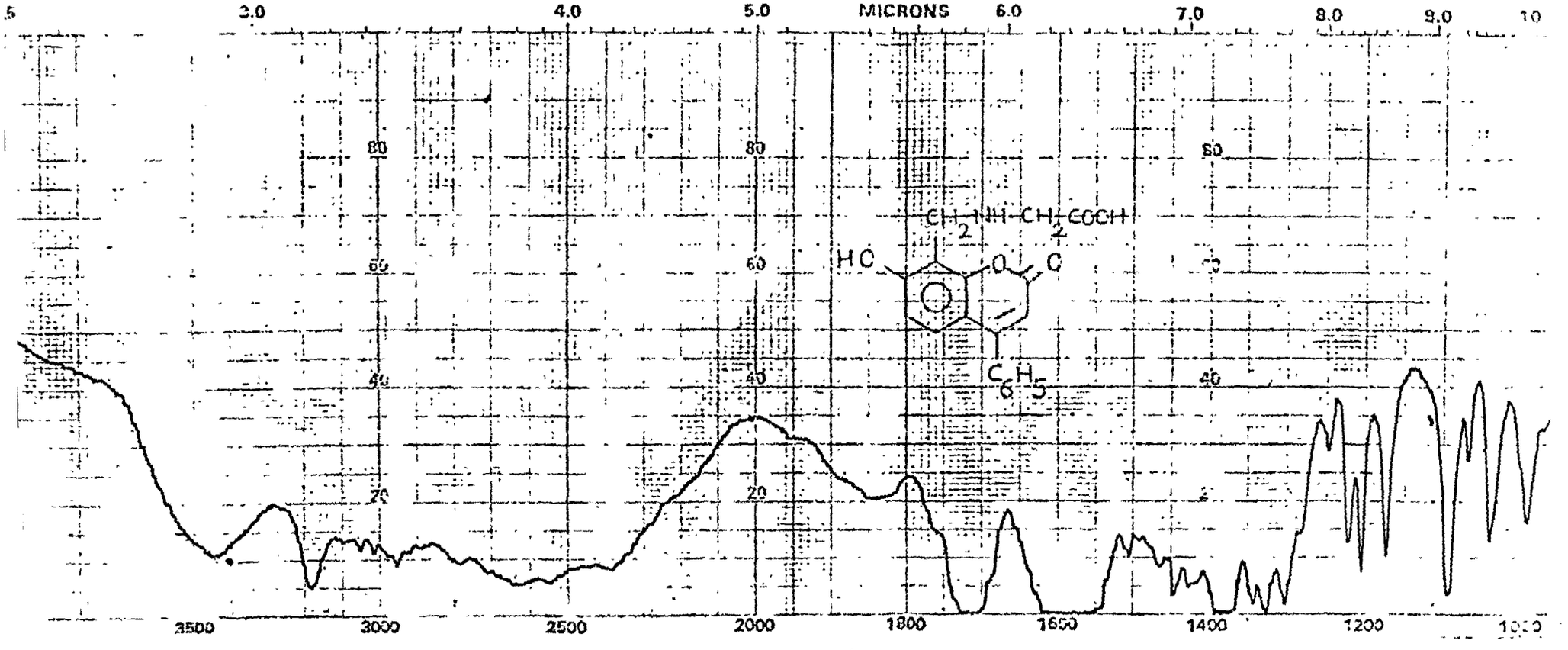
(47)



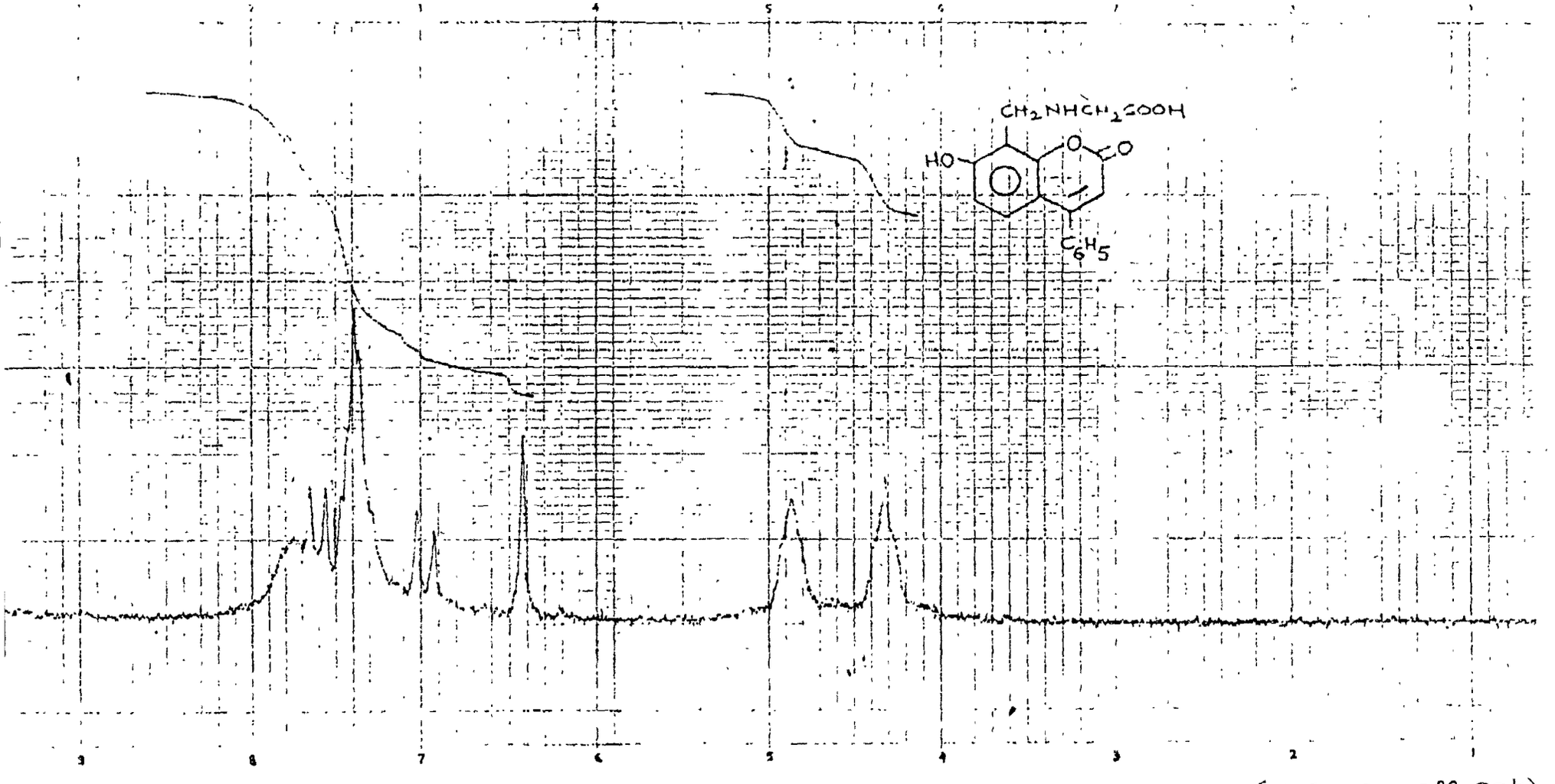


(48)

R = a : -H
b : $-CH_3$
c : $-CH(CH_3)_2$
d : $-CH_2C_6H_5$
e : $-CH_2OH$
f : $-CH_2CH_2SCH_3$


3.0
4.0
5.0
MICRONS
6.0
7.0
8.0
9.0
10
80
60
40
20
3500
3000
2500
2000
1800
1600
1400
1200
HC
O
C
$CH_2NH\text{-}CH_2COCH_3$
C_6H_5

(Fig-1) : 48a



(0.2 ppm off set)

(Fig-2) : 489

δ 1.7, doublet, for methyl group protons of NHCH($C\underline{H}_3$)COOH δ 4.2, multiplet, broad -NHC$\underline{H}$COOH proton ; δ 4.7, broad singlet, $C\underline{H}_2$NH group protons ; δ 6.3, singlet, a proton at C-3 position of coumarin ring ; δ 6.85 doublet of a proton at C-6 position (J=9Hz) ; δ 7.5, doublet of a proton at C-5 position (J=9Hz) ; δ 7.35, multiplet of aromatic protons of phenyl ring at C-4 position. The absence of signal of a proton C-8 of coumarin ring indicates that substitution has taken place at position C-8. (Fig.3)

Other Mannich bases (1 to 6, Table-1) on this nucleus have been synthesised in similar way.

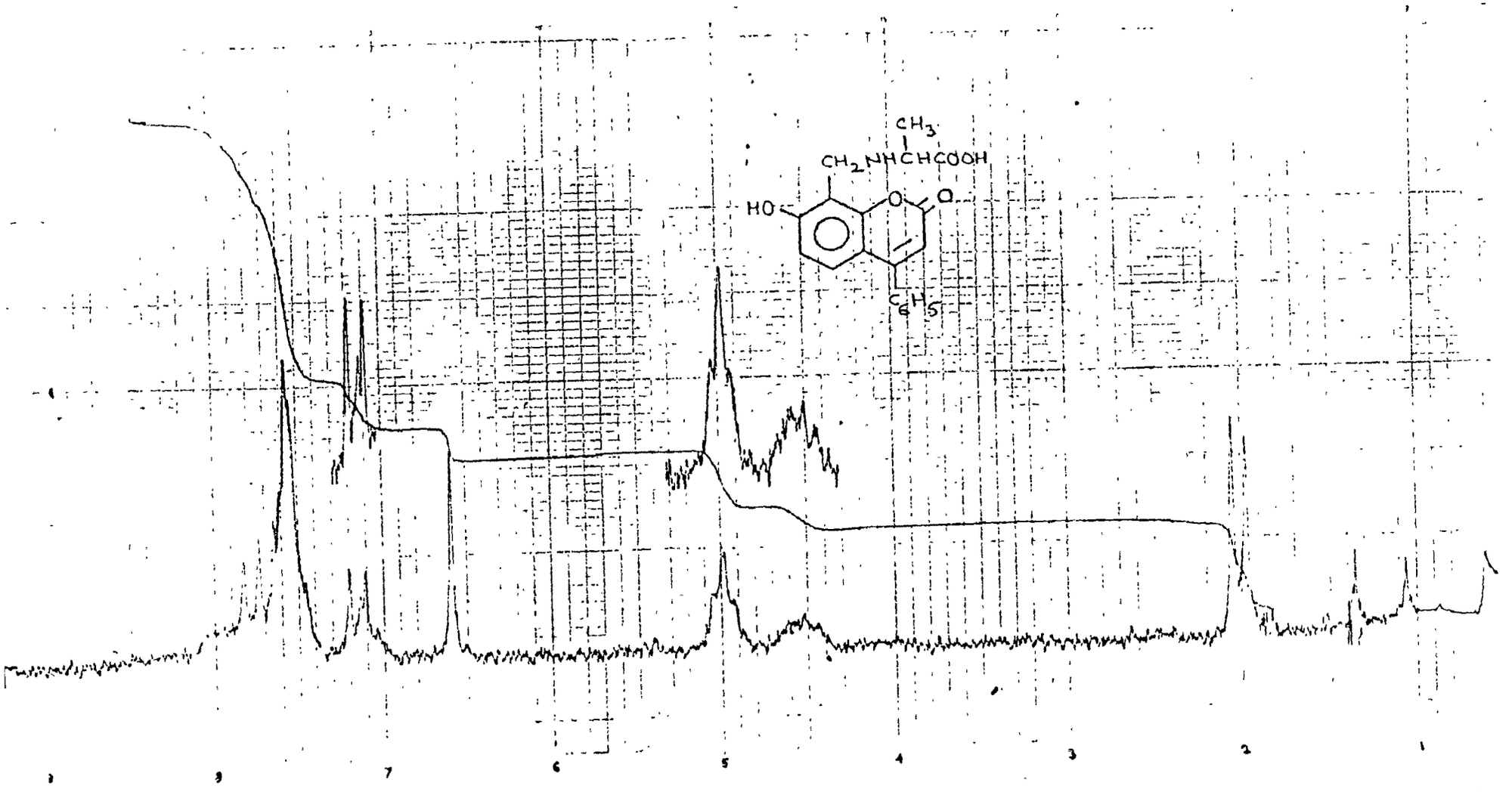
Mannich reaction on 7-hydroxy-5-methyl coumarin :

N(7-hydroxy-5-methyl-8-coumarinyl)α-alanine (50a)

Condensation of 7-hydroxy-5-methylcoumarin[53] (49), formalin and α-alanine gave the Mannich product, which has been assigned N(7-hydroxy-5-methyl-8-coumarinyl)-α-alanine structure. The structure of Mannich compound was confirmed by IR and NMR spectra.

The IR (KBr) spectrum exhibited bands at 3500 (broad), 3000-2300 (broad), 1740, 1600 cm^{-1}.

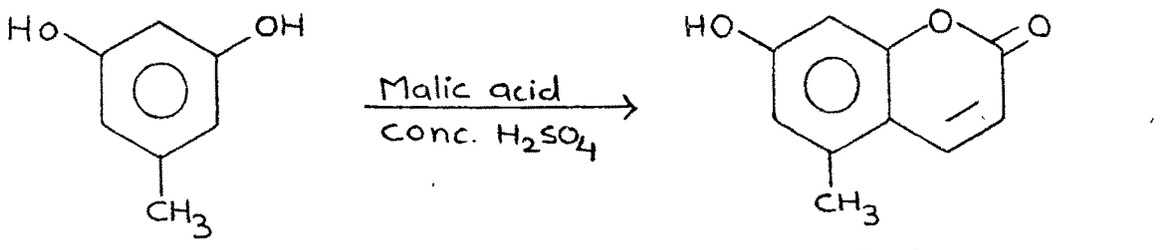
The compound exhibited following signals in NMR spectrum. (CF_3COOH) : δ 1.93, doublet for methyl protons (-NHCH-$C\underline{H}_3$) ;



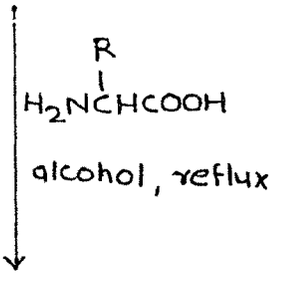
(0·3 PPm off set)

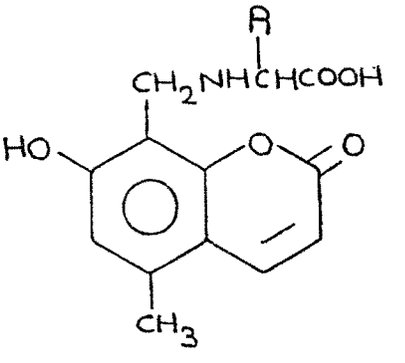
(Fig-3) : 48b

Scheme:2



(49)





(50)

R = a: $-CH_3$

b: $-CH(CH_3)_2$

c: $-CH_2C_6H_5$

d: $-CH_2CH_2SCH_3$

e: Proline

δ 2.6, singlet, for methyl protons attached to coumarin ring at C-5 position ; δ 4.5, broad multiplet for -NH-C<u>H</u>CH_3 ; δ 4.9 broad singlet for -C<u>H</u>$_2$NH- ; δ 6.6, doublet (J=9Hz) , a proton at C-3 position ; δ 8.32, doublet (J=9Hz), a proton at C-4 position of coumarin ring ; δ 7.05, singlet, an aromatic proton at C-6 position ; Signal of C-8 position was not observed indicating that substitution has taken place at C-8 position. (Fig. 4) Other Mannich bases (7 to 11, Table-1) have been synthesised in similar way.

<u>Mannich reaction on 7-hydroxycoumarin :</u>

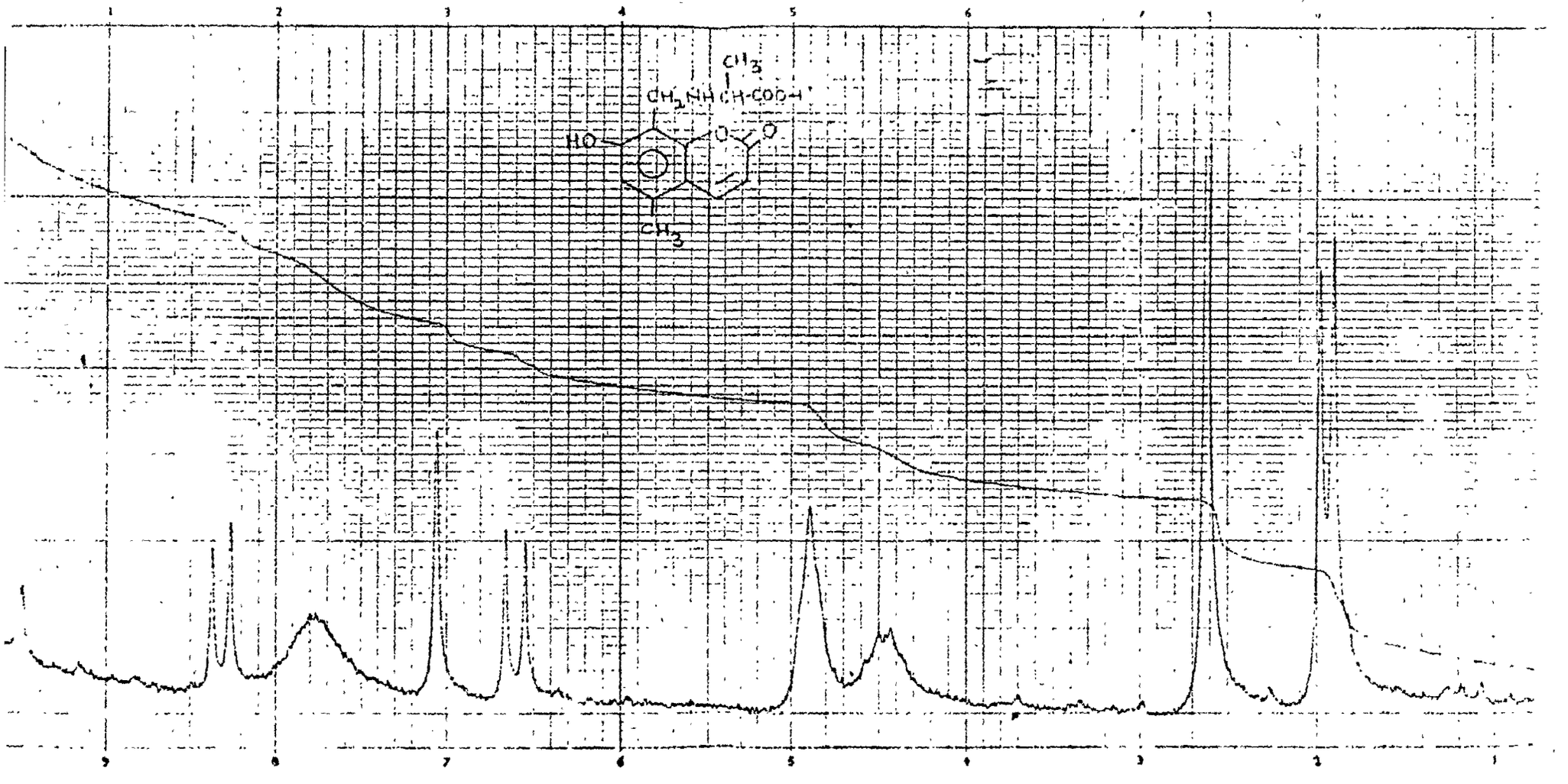
<u>N(7-hydroxy-8-coumarinyl) valine</u> (52b)

7-Hydroxycoumarin [54] (51) when reacted with formalin and valine furnished 8-substituted Mannich base. Its structure has been established as usual by following spectral data.

In IR (KBr) spectra bands at 3425 (broad), 3280-2320 (broad), 1720 (broad), 1600 (broad)cm^{-1} were observed.

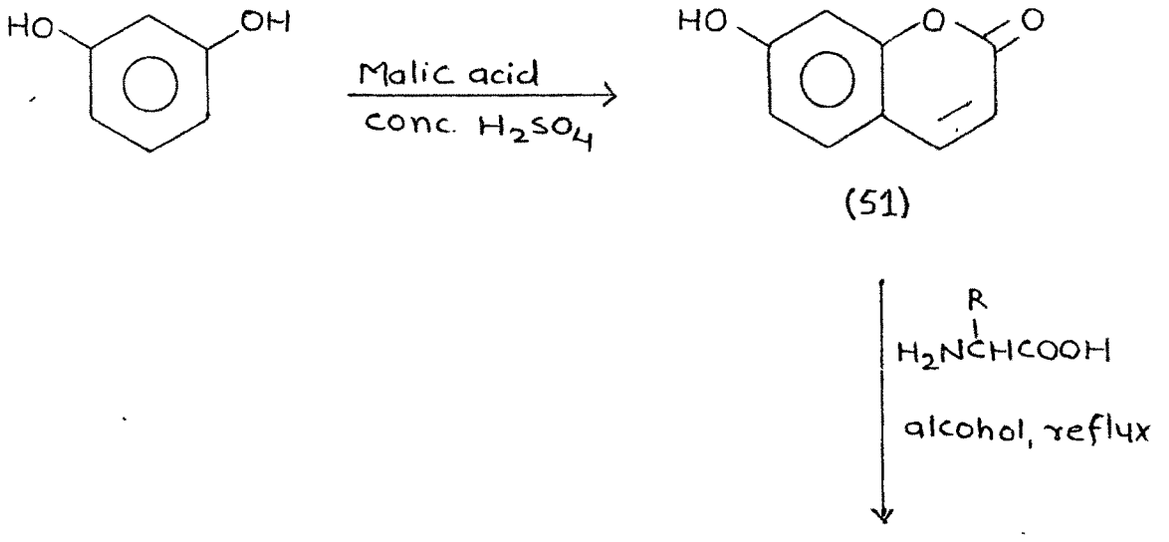
The mass spectrum exhibited signals at m/e : 291 (M^+ ion, 25%), 72 (base peak 100%), 55 (54%). (Fig. 5)

Similarly other Mannich bases (12 to 16, Table-I) have been synthesised.



(Fig·4) : 50a

Scheme : 3



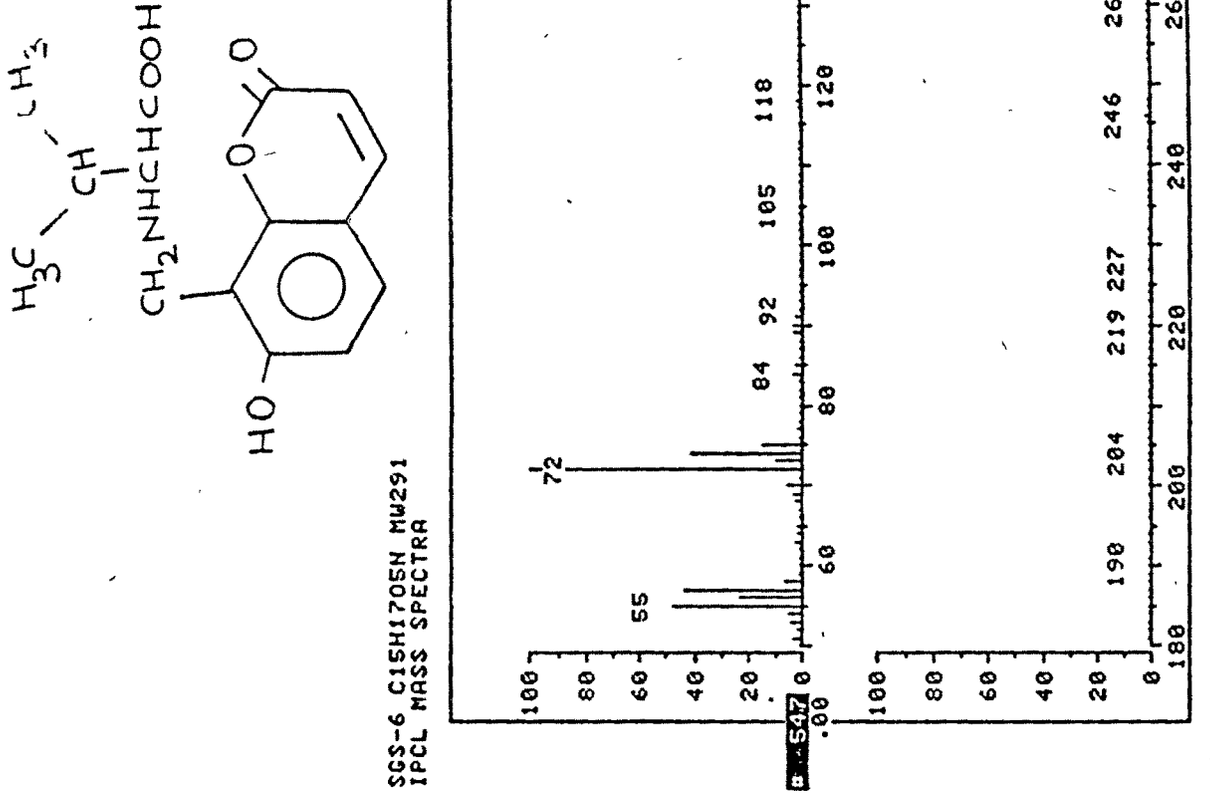
R = a : $-CH_3$

b : $-CH(CH_3)_2$

c : $-CH_2OH$

d : $-CH_2CH_2SCH_3$

e : $-CH_2C_6H_5$



(Fig-5) : 52b

Mannich reaction on 7-hydroxy-4-methyl-8-acetylcoumarin:

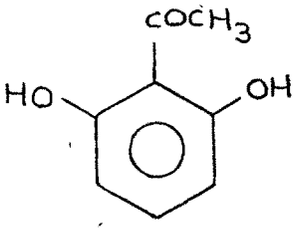
N(7-hydroxy-4-methyl-8-coumarinoylethyl) glycine (54a)

Condensation of 7-hydroxy-4-methyl-8-acetylcoumarin[55] (53) formalin and glycine gave the Mannich base in which substitution took place at α-hydrogen of acetyl group in the side chain. The structure was proved by IR and NMR spectrum.

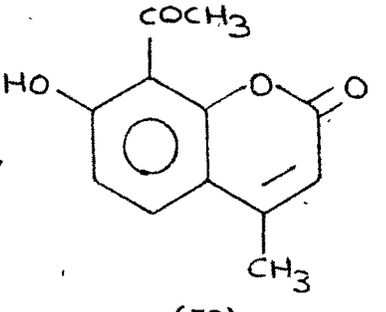
The NMR spectrum, taken in trifluoroacetic acid, exhibited following signals ; δ 2.15, singlet for methyl protons attached to coumarin ring at C-4 position ; δ 2.55-3.5, multiplet, 4H, -CO side chain ; δ 4.15, multiplet, 2H, -CO side chain protons; δ 6.1, singlet, proton at C-3 position ; two doublets (J=9Hz), one at δ 6.75 for a proton at C-6 position and another at δ 7.6 for a proton at C-5 position (Fig. 6)

The NMR of this compound did not show characteristic signal of methyl protons of acetyl group at δ 2.80, instead the signals of glycine moiety were observed. This confirmed that substitution has taken place at α-hydrogen to -CO of acetyl group. (Fig. 6) Other Mannich bases (17 to 22, Table-I) have been synthesised in a similar way.

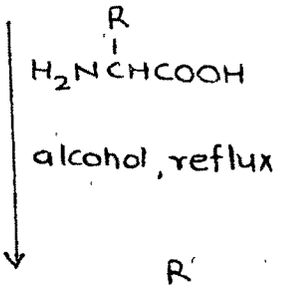
Scheme:4

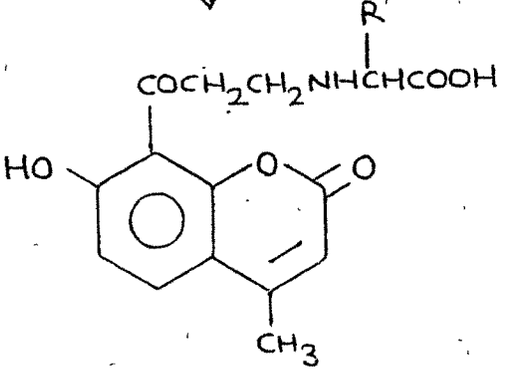


Ethylacetoacetate
$AlCl_3$, nitrobenzene



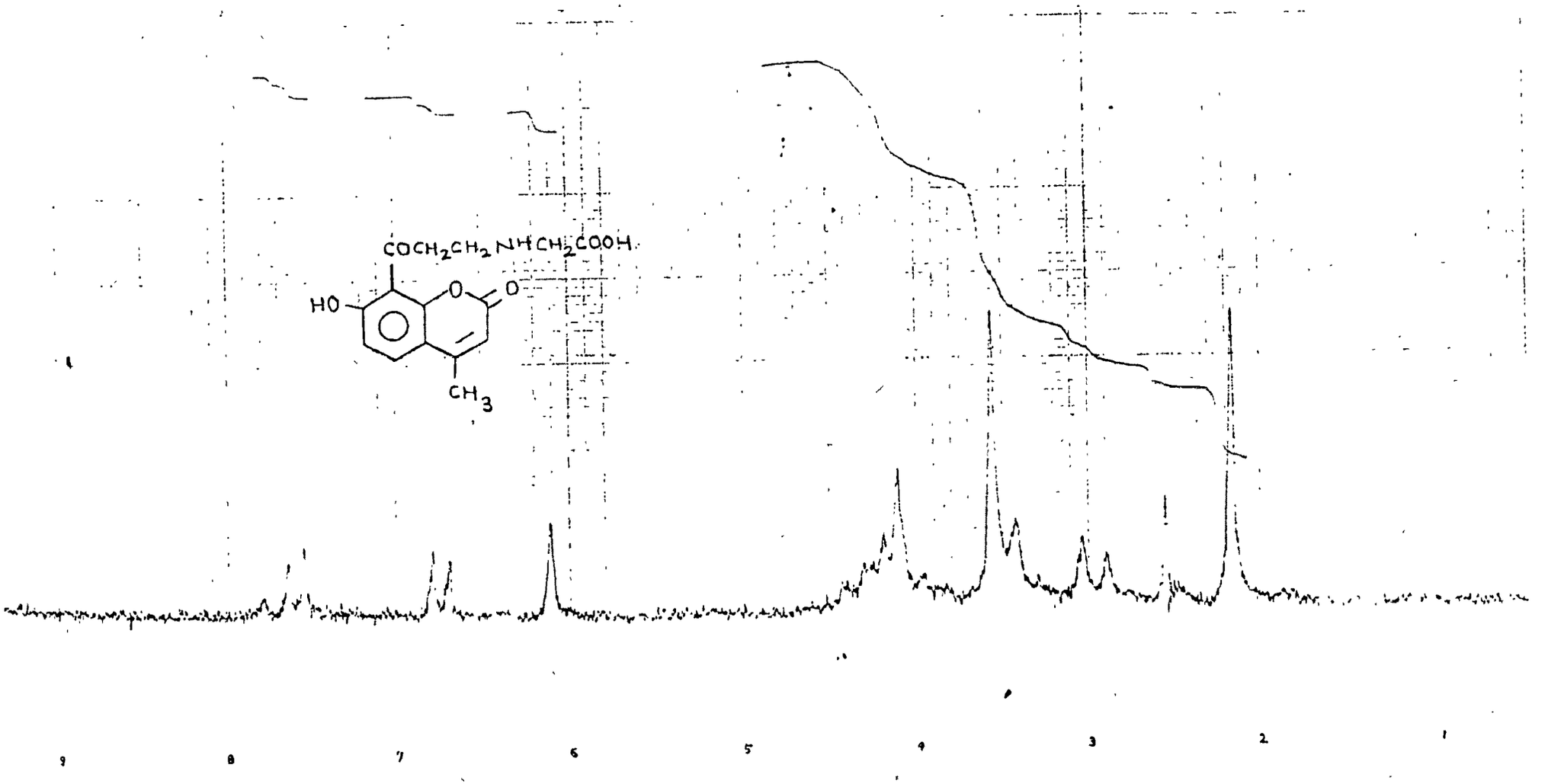
(53)





(54)

R = a: -H
b: $-CH_3$
c: $-CH(CH_3)_2$
d: $-CH_2OH$
e: $-CH_2CH_2SCH_3$
f: $-CH_2C_6H_5$



(Fig-6) : 54a

EXPERIMENTAL

EXPERIMENTAL

All melting points were determined in open capillaries using a paraffin-bath and are uncorrected. Microanalysis of compounds were performed on a Coleman instrument, IR spectra (KBr) were recorded on a Shimadzu 408 Spectrophotometer, NMR spectra were recorded on a Perkin-Elmer R-32 Spectrometer using TMS as the internal standard. Mass spectra were recorded on Gas chromatograph Mass spectrometer, Hewlett packard 5985 at 70 ev.

7-Hydroxy-4-phenylcoumarin[51] (47)

A mixture of ethyl benzoylacetate (3.5 ml), resorcinol (2.2 g) and concentrated sulfuric acid (6 ml) was kept overnight. It was decomposed into ice-cold water and crystallised from alcohol. M.p. 242-44°C, yield 92%.

N-(7-hydroxy-4-phenyl-8-coumarinyl) glycine (48a)

7-Hydroxy-4-phenylcoumarin (1.5 g) in 80% alcohol (50 ml) formalin (1.2 ml) and glycine (0.75 g) were heated on a sand bath. The product was separated within 15 minutes. It was then extracted with alcohol in a soxhlet apparatus to remove unreacted coumarin and crystallised from dimethylformamide. M.p. 246°C(d), yield 65%.

Analysis : Found : C, 66.71 ; H, 4.54 ; N, 4.16%

$C_{18}H_{15}O_5N$: requires : C, 66.46 ; H, 4.62 ; N, 4.31%

N-(7-hydroxy-4-phenyl-8-coumarinyl)∝-alanine (48b)

A mixture of 7-hydroxy-4-phenylcoumarin (1.5 g), ∝-alanine (0.85 g) and formalin (1.2 ml) was refluxed in 80% alcohol (50 ml). The product was separated after 2 hrs. which was extracted with alcohol and crystallised from DMF. M.p. 242°C(d), yield 65%

Analysis : Found : C, 67.70 ; H, 4.87 ; N, 3.73%

$C_{19}H_{17}O_5N$: requires : C, 67.26 ; H, 5.01 ; N, 4.13%

7-Hydroxy-5-methylcoumarin[53] (49)

A mixture of 5-methyl resorcinol (1.0 g), malic acid (1.2 g) and concentrated sulfuric acid (6.0 ml) was heated in an oil bath at 70-80°C for 3 hrs. The product was obtained by decomposing the reaction mixture into ice-cold water. It was crystallised from alcohol. M.p. 248°C, yield 65%.

N-(7-hydroxy-5-methyl-8-coumarinyl)∝-alanine (50a)

7-Hydroxy-5-methylcoumarin (1.6 g) was refluxed with formalin (1.2 ml) and ∝-alanine (0.8 g) in 80% alcohol (20-30 ml) on a sand bath. The product was separated after 2 hrs. It was extracted with alcohol as usual and crystallised from DMF - Benzene mixture, M.p. 245°C, yield 60%.

Analysis : Found : C, 60.20 ; H, 5.71 ; N, 5.10%

$C_{14}H_{15}O_5N$: requires : C, 60.65 ; H, 5.42 ; N, 5.05%

7-Hydroxycoumarin[54] (51)

A mixture of resorcinol (3.0 g), malic acid (2.46 g) and concentrated sulfuric acid (6.1 ml) was heated in an oil bath at 120°C for 1 hr. It was cooled and treated with excess of crushed ice. The product was crystallised from dilute alcohol using decolouring charcoal. M.p. 227-28°C, yield 43%.

N-(7-hydroxy-8-coumarinyl)∝-alanine (52a)

7-Hydroxycoumarin (1.6 g), formalin (1.2 ml) and ∝-alanine (0.9 g) were heated together in 80% alcohol (20-30 ml) for 5 hrs. on a sand bath. The product was separated on cooling which was crystallised from DMF. M.p. 310°C(d), yield 65%.

Analysis	: Found	: C, 58.96	; H, 5.05	; N, 5.14%
$C_{13}H_{13}O_5N$	: requires	: C, 59.31	; H, 4.94	; N, 5.32%

7-Hydroxy-4-methyl-8-acetylcoumarin[55] (53)

A mixture of 2-acetylresorcinol (3.8 g) and ethylaceto-acetate (3.25 g) was added to a solution of anhydrous aluminium chloride (7.0 g) in nitrobenzene (35 ml). It was heated to 125-135°C in an oil bath for 1 hr. (till evolution was negligible). It was crystallised from acetic acid. M.p. 168°, yield 80%.

N-(7-hydroxy-4-methyl-8-coumarinoyl ethyl) glycine (54a)

7-Hydroxy-4-methyl-8-acetylcoumarin (1.0 g), formalin (1.2 ml) and glycine (0.4 g) were refluxed in 80% alcohol (25-30 ml) on a sand bath for 14 hrs. The excess alcohol was distilled off. The oil obtained was scrubed with 1:1 alcohol. It was crystallised from alcohol, M.p. 320°C(d), yield 55%.

Analysis : Found : C, 58.58 ; H, 4.55 ; N, 4.38%

$C_{15}H_{15}O_6N$: requires : C, 59.02 ; H, 4.92 ; N, 4.59%

TABLE-I : ANALYTICAL AND PHYSICAL DATA OF COMPOUNDS (48), (50), (52), (54).

Sr. No.	R	R'	R"	M.P.* °C	Yield %	Molecular Formula	Analysis % Found/(Calcd) C	H	N
1	$-C_6H_5$	H	H	246^{d}(d)	65	$C_{18}H_{15}O_5N$	66.71 (66.46)	4.54 (4.62)	4.16 (4.31)
2	$-C_6H_5$	H	$-CH_3$	242^{d}(d)	65	$C_{19}H_{17}O_5N$	67.70 (67.26)	4.87 (5.01)	3.73 (4.13)
3	$-C_6H_5$	H	$-CH(CH_3)_2$	241^{d}(d)	72	$C_{21}H_{21}O_5N$	68.90 (68.66)	5.32 (5.72)	3.51 (3.81)
4	$-C_6H_5$	H	$-CH_2C_6H_5$	233^{d}(d)	75	$C_{25}H_{21}O_5N$	71.90 (72.29)	5.29 (5.06)	3.71 (3.37)
5	$-C_6H_5$	H	$-CH_2OH$	215^{d}(d)	63	$C_{19}H_{17}O_6N$	64.51 (64.23)	4.96 (4.79)	3.69 (3.94)
6	$-C_6H_5$	H	$-CH_2CH_2SCH_3$	239^{d}(d)	70	$C_{21}H_{21}O_5NS$	63.60 (63.16)	5.39 (5.26)	3.43 (3.51)
7	H	$-CH_3$	$-CH_3$	$245^{(d+b)}$	60	$C_{14}H_{15}O_5N$	60.20 (60.65)	5.71 (5.42)	5.10 (5.05)
8	H	$-CH_3$	$-CH_2CH_2SCH_3$	$270^{d+w}_{(d)}$	62	$C_{16}H_{19}O_5NS$	57.35 (56.97)	5.42 (5.64)	4.45 (4.15)
9	H	$-CH_3$	$-CH_2C_6H_5$	$200^{d+w}_{(d)}$	60	$C_{20}H_{19}O_5N$	67.81 (67.99)	4.97 (5.38)	3.65 (3.97)

cont....

TABLE-I cont...

10	H	$-CH_3$	$-CH(CH_3)_2$	$280^{d+w}_{(d)}$	55	$C_{16}H_{19}O_5N$	62.66 (62.95)	5.95 (6.23)	4.10 (4.59)
11	H	$-CH_3$	Proline	$285^{d}_{(d)}$	55	$C_{16}H_{17}O_5N$	63.82 (63.37)	5.43 (5.61)	4.30 (4.62)
12	H	H	$-CH_3$	$310^{d}_{(d)}$	65	$C_{13}H_{13}O_5N$	58.96 (59.32)	5.05 (4.94)	5.14 (5.32)
13	H	H	$-CH(CH_3)_2$	240^{d}	61	$C_{15}H_{17}O_5N$	62.22 (61.86)	5.73 (5.84)	4.59 (4.81)
14	H	H	$-CH_2OH$	$232^{d}_{(d)}$	50	$C_{13}H_{13}O_6N$	55.70 (55.91)	4.18 (4.66)	4.9 (5.01)
15	H	H	$-CH_2CH_2SCH_3$	$245^{d}_{(d)}$	60	$C_{15}H_{17}O_5NS$	55.34 (55.73)	5.09 (5.26)	4.05 (4.33)
16	H	H	$-CH_2C_6H_5$	237^{d}	66	$C_{19}H_{17}O_5N$	66.81 (67.26)	5.12 (5.01)	3.94 (4.13)
17	-	-	-H	$320^{a}_{(d)}$	55	$C_{15}H_{15}O_6N$	58.58 (59.02)	4.55 (4.92)	4.38 (4.59)
18	-	-	$-CH_3$	285^{d}	51	$C_{16}H_{17}O_6N$	60.06 (60.19)	5.11 (4.39)	3.91 (4.39)
19	-	-	$-CH(CH_3)_2$	$110^{d}_{(d)}$	59	$C_{18}H_{21}O_6N$	62.67 (62.25)	5.84 (6.05)	3.90 (4.03)
20	-	-	$-CH_2OH$	195^{d+b}	50	$C_{16}H_{17}O_7N$	58.86 (59.08)	5.11 (5.23)	3.98 (4.31)
21	-	-	$-CH_2CH_2SCH_3$	220^{d}	55	$C_{18}H_{21}O_6NS$	56.81 (56.99)	5.33 (5.54)	3.28 (3.69)
22	-	-	$-CH_2C_6H_5$	186^{d+b}	60	$C_{22}H_{21}O_6N$	66.71 (66.84)	5.30 (5.32)	3.13 (3.54)

* Crystallisation solvent : d = DMF, b = benzene, a = alcohol, w = water

PART — II

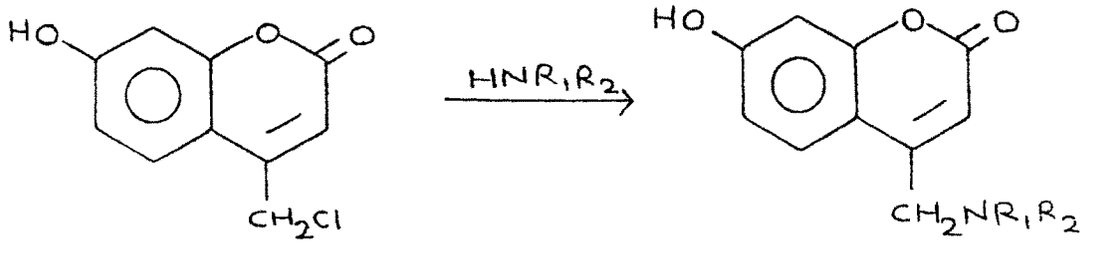
SYNTHESIS OF SOME 8-METHOXY-5-SUBSTITUTED AMINOMETHYLCOUMARINS

PART II : SYNTHESIS OF SOME8-METHOXY-5-SUBSTITUTED-AMINOMETHYLCOUMARINS :

Chloromethyl group can be easily converted into aminomethyl group by treatment with aliphatic or aromatic amines in proper solvents. Thus chloromethyl derivatives have become convenient source for the introduction of aminomethyl group in the organic synthesis.

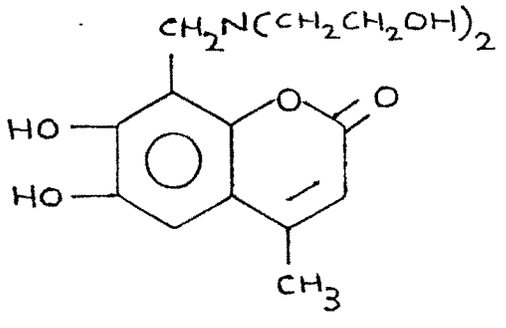
Survey of literature reveals that several research workers have been engaged in the synthesis of aminomethyl derivatives of coumarins obtained via chloromethyl derivative of coumarins and screening them for antimicrobial activity. A brief review of some of these publications is presented here.

S.A. Dause[1] synthesised 4-(tertiary aminomethyl)-7-hydroxycoumarin from 7-hydroxy-4-chloromethylcoumarin which was used as choleretics. They compared the choleretic activity of the compound (1) with that of 4-methyl-umbelliferon.



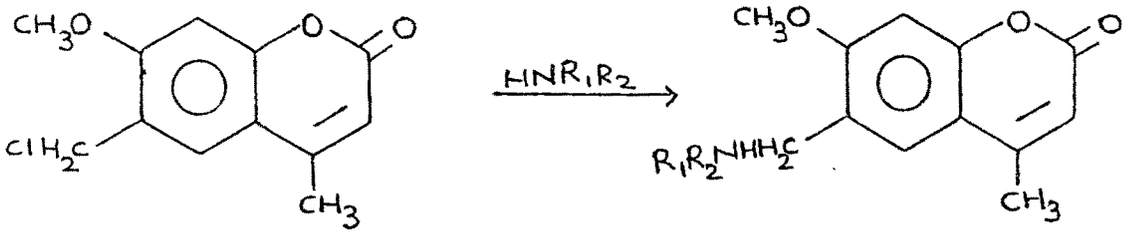
(1)

I.S. Rudakova et al [2] synthesised 8-[[bis-(2-hydroxy-ethyl) amino] methyl]-6,7-dihydroxy-4-methylcoumarin (2) and examined the effect of substituents with p-vitamin activity on the permeability of vessels during burn inflammation. M. P. Gorizentova and A.M. Cherhykh [3] also synthesised same aminomethyl derivative (2). They observed that compound (2) decreased the permeability of liver and thymus tissues of irradiated rats. It also decreased the permeability of the thymus cell nuclei of theanimals of 54 Mn and prevented WT LOSS by the thymus of irradiated animals.

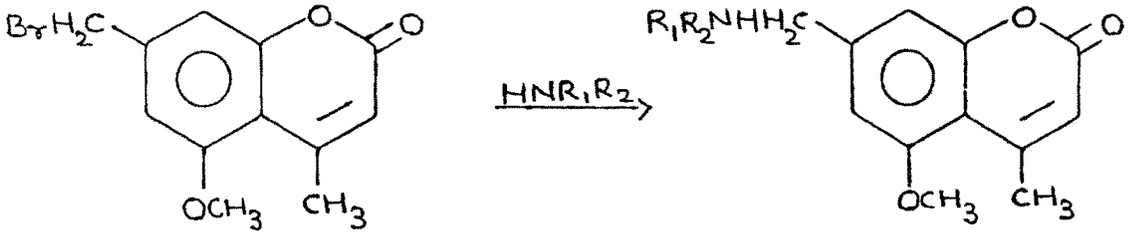


(2)

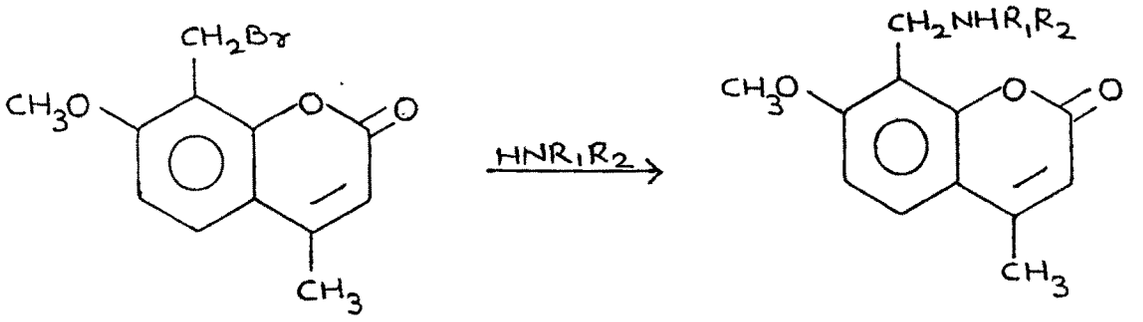
D.O. Shah and K.N. Trivedi [4] synthesised Mannich bases by condensing various amines with 7-methoxy-4-methyl-6-chloro-methylcoumarin (3), 5-methoxy-4-methyl-7-bromomethylcoumarin (4) and 7-methoxy-4-methyl-8-bromomethylcoumarin (5).



(3)



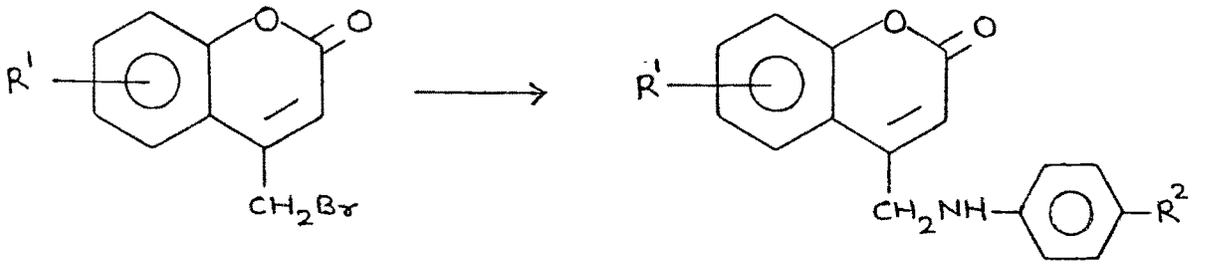
(4)



(5)

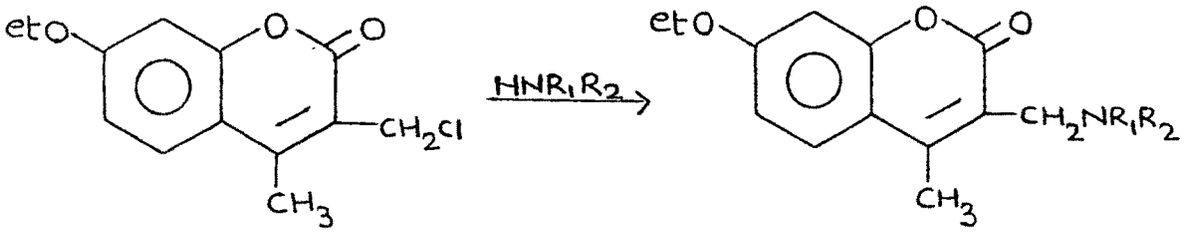
Kulkarni Manohar and D. Vemanna[5] prepared anilinomethyl-coumarin (6) from substituted 4-bromomethyl coumarin. They

found that substituents with R' = 6-methyl-, 7-methoxy-6-chloro, 7-chloro and R^2 = chloro were active against E. coli.



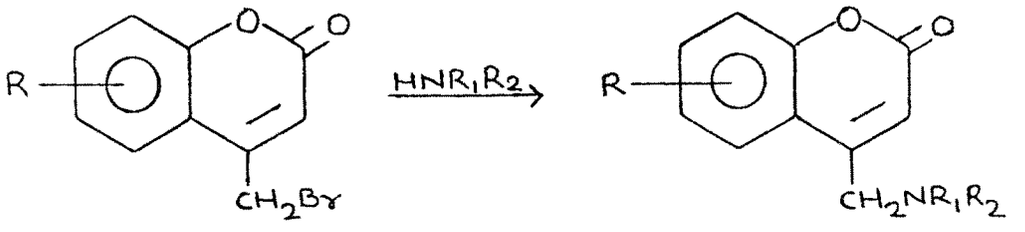
(6)

Recently G. Sailaja, K. Mohana Raju and M. Subramanayam Raju [6] synthesised 7-ethoxy-3-substituted aminomethyl-4-methyl-coumarin (7). They tested all compounds against E. coli, Proteus Vulgaris and K. Pneumoniae at 100 ppm and 500 ppm concentration. They observed that chloromethylated compound and the compound with R_1 = Me and R_2 = ph showed high antibacterial activity whereas morpholino and dimethylaminomethyl derivative showed moderate activity at 100 ppm.



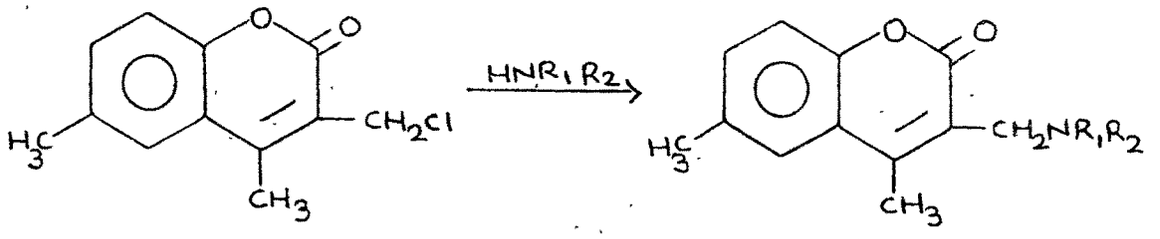
(7)

S. Shrikant Hanmantgad et al.[7] prepared biologically active aminomethyl derivative from 4-bromomethylcoumarin.

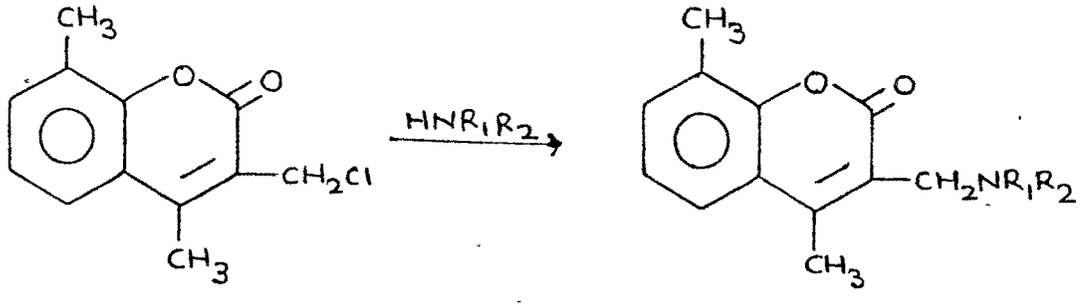


(8)

Most recently M. Nagesam and M. Subramanyam Raju[8-10] synthesised number of 4,6-dimethyl-3-substituted aminomethyl (9) and 3-(picolinyl) aminomethyl coamarins from 4,6-dimethyl-3-chloromethylcoamarin. Most of the compounds showed good inhibition against E. Coli, B. Subtilis and S. aureus in vitro. They also prepared Mannich bases from 4,8-dimethyl-3-chloromethylcoumarin (10) and screened them for antibacterial actiity in vitro against Xanthomonas citri, B. Subtilis, E. Coli and Psuedomonas Viticola using standard drug sulphanilamide. 4,8-dimethylcoumarin and 4,8-dimethyl-3-chloromethylcoumarin also exhibited antibacterial activity. Moreover, they also synthesised Mannich bases from 7-ethoxy-4-chloromethylcoumarin which exhibited antibacterial activity.

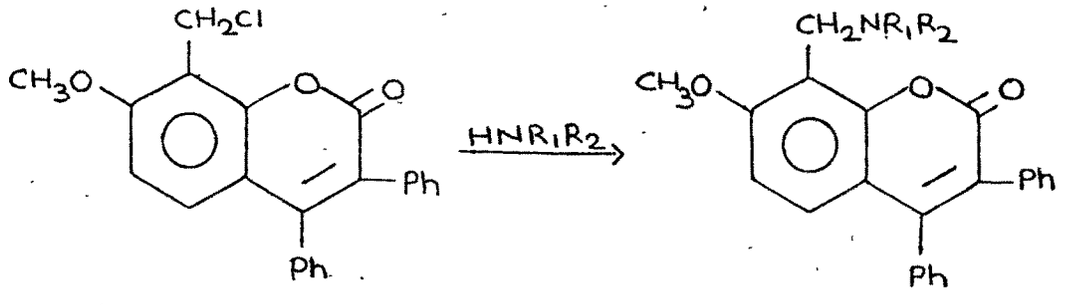


(9)



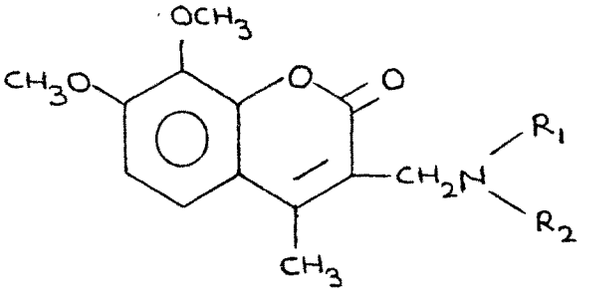
(10)

S.M. Desai[11] prepared 7-methoxy-8-substituted aminomethyl-3,4-diphenylcoumarin (11) from 7-methoxy-8-chloromethyl-3,4-diphenylcoumarin as possible antibacterial agent.



(11)

Rajeev Vyas and R.H. Mehta[12] synthesised 7,8-dimethoxy-3-substituted aminomethyl-4-methylcoumarin derivatives (12) via 7,8-dimethoxy-3-chloromethyl-4-methylcoumarin and reported that number of them have moderate antibacterial activity against E. Coli and S. aureus.



(12)

PRESENT WORK

On survey of literature, it has been found that groups like dimethoxy,[13] aminomethyl,[9] halogen[14] and heterocyclic[15] moieties enhance antibacterial activities. It was therefore thought of interest to synthesise number of 8-methoxy-5-substituted aminomethylcoumarin derivatives. In order to introduce aminomethyl group in the coumarin ring system, a known 8-methoxy-5-chloromethylcoumarin[16] was condensed with various simple and substituted aromatic, alicyclic and heterocyclic primary and secondary amines which furnished new series of 8-methoxy-5-substituted aminomethylcoumarins. Moreover, aminomethyl derivatives synthesised during present work were evaluated for their antibacterial activity.

The structures of the compounds prepared during present study have been established by elemental analysis and spectral data.

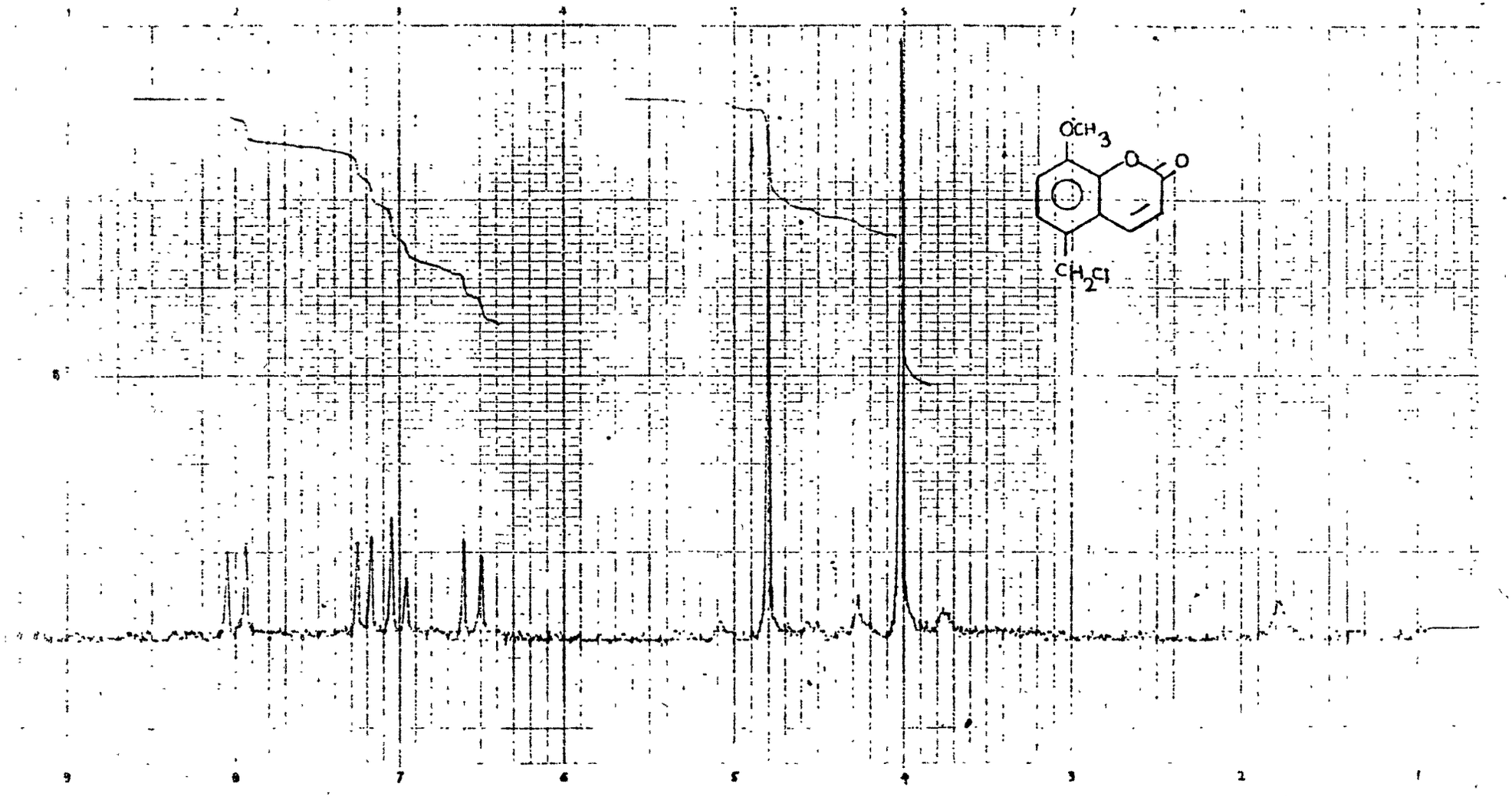
Antimicrobial activity

Some selected compounds were screened for their antimicrobial activity using cup-plate method.[17] Some of them were found active against E. Coli, S. aureus, S.typhosa and B. Subtilis. The detailed screening report is shown in Chapter IV, Part II.

8-Methoxy-5-chloromethylcoumarin[16] (15)

o-Vanilin and malonic acid on Knoevenagel reaction gave 8-methoxycoumarin-3-carboxylic acid[18] (13) which undergoes decarboxylation on treatment with boiling pyridine - hydrochloride to give 8-methoxycoumarin[18] (14). This was subjected to chloromethylation with paraformaldehyde and dry hydrochloric acid gas in presence of zinc chloride as catalyst in glacial acetic acid. It gave 8-methoxy-5-chloromethylcoumarin (15).

The NMR spectrum taken in $CDCl_3$ exhibited singlet of three protons at δ 3.9 for $OC\underline{H}_3$ group at C-8 position ; singlet of two protons at δ 4.7 for $-\underline{CH}_2Cl$ group ; two doublets at δ 6.45 (J=9Hz) and δ 7.9 (J=9Hz) for C-3 and C-4 protons respectively. Another pair of doublet has also been observed in aromatic region at δ 6.9 (C-6 or C-7 protons, J=7Hz) and



(0·1 PPM off set)

Fig-1) : 15

at δ 7.13 (C-7 or C-6 protons, J=7Hz). This confirmed that the chloromethylation has taken place at position C-5 of the coumarin ring. (Fig-1)

General Preparation of 8-methoxy-5-substituted aminomethyl-coumarins (16)

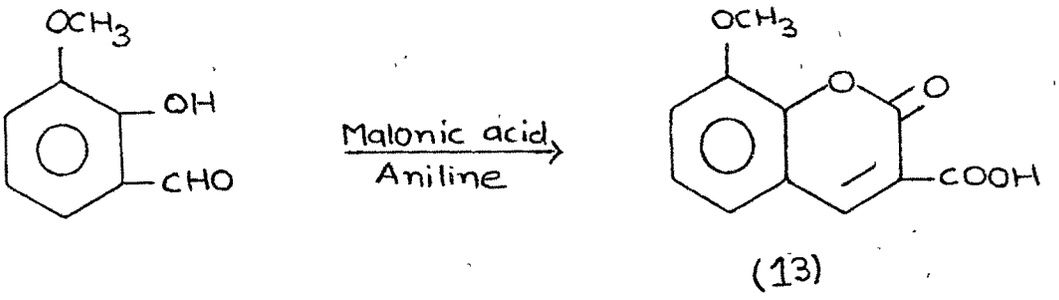
8-Methoxy-5-chloromethylcoumarin on condensation with various simple and substituted aromatic and heterocyclic primary and secondary amines furnished 8-methoxy-5-substituted aminomethylcoumarin (16). Physical data and solvent of crystallisation is exhibited in Table-II. The structures of the compounds were established on the basis of IR, NMR and mass spectra.

General discussion of IR and NMR Spectra

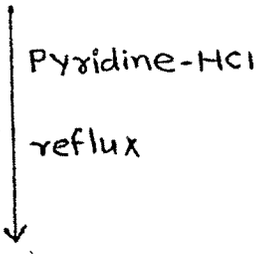
The IR (KBr) spectra of aminomethyl compounds prepared from primary amines (1-20, Table-II) exhibited a weak and sharp band at 3450-3420 cm^{-1} assignable to associated NH group. The IR spectra of all compounds from 1 to 28 exhibited peaks at 2950-2880 (C-H of alkyl), 1730-1705 (lactonic carbonyl of coumarin ring system),[19] 1600-1585 (C=C stretch within aromatic ring), 1390-1175 (C-N) and 1280, 1090 cm^{-1} of (C-O-C).

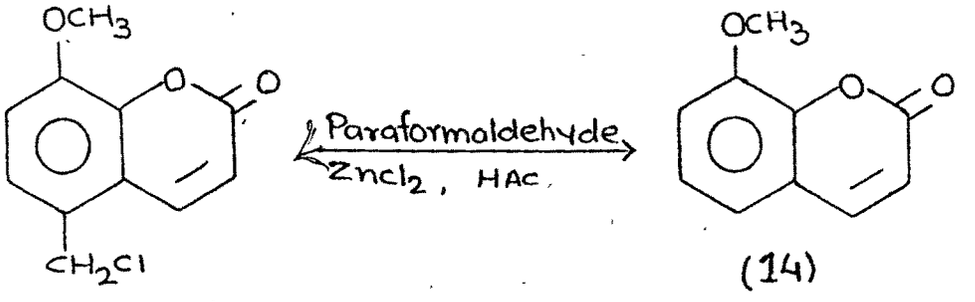
In NMR spectrum, the methylene protons attached to C-5 position of (16) (C_5-CH_2-N) exhibited signal at δ 4.42 while

Scheme:1



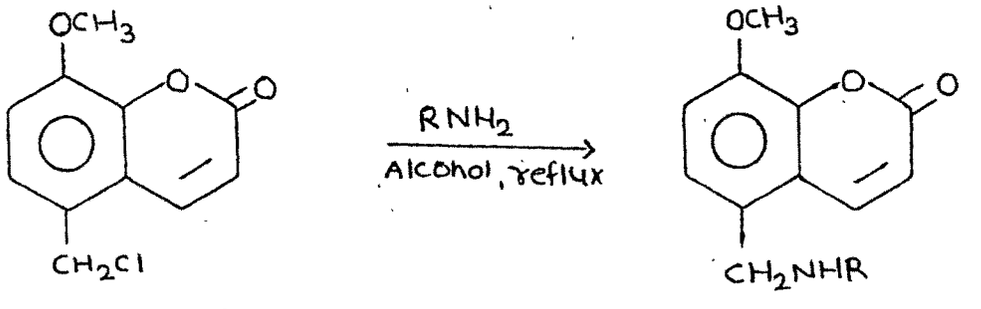
(13)





(15) (14)

Scheme:2



(16)

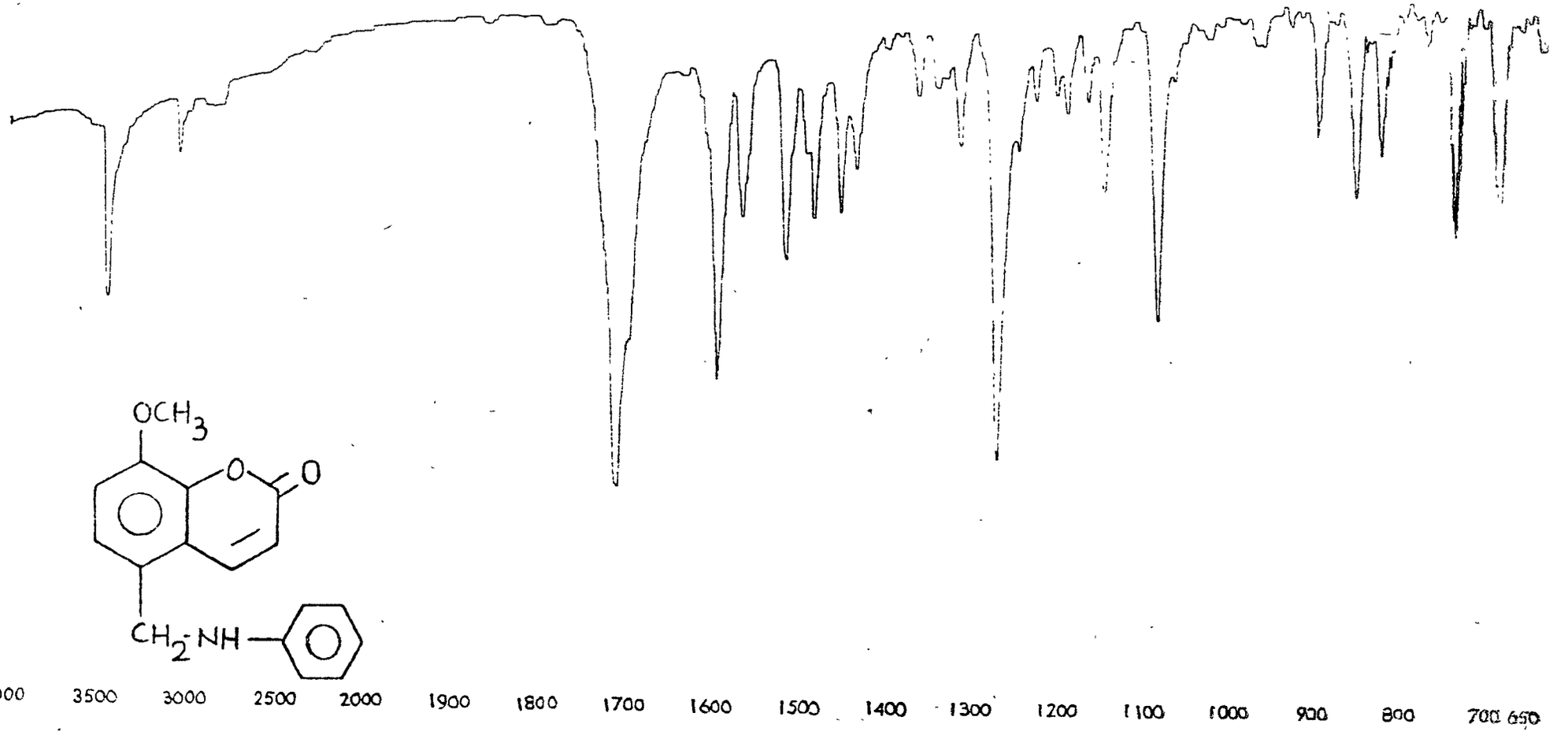
similar signal is observed at δ 4.7 for (15) (C_5-$C\underline{H}_2$-Cl). The low electronegativity of nitrogen atom in comparison to that of chlorine caused upfield shift of the methylene protons in (16) compared to that in (15). Thus, the substitution of aminomethyl group at C-5 position in the coumarin ring system is confirmed by IR and NMR spectra.

8-Methoxy-5-anilinomethylcoumarin (17)

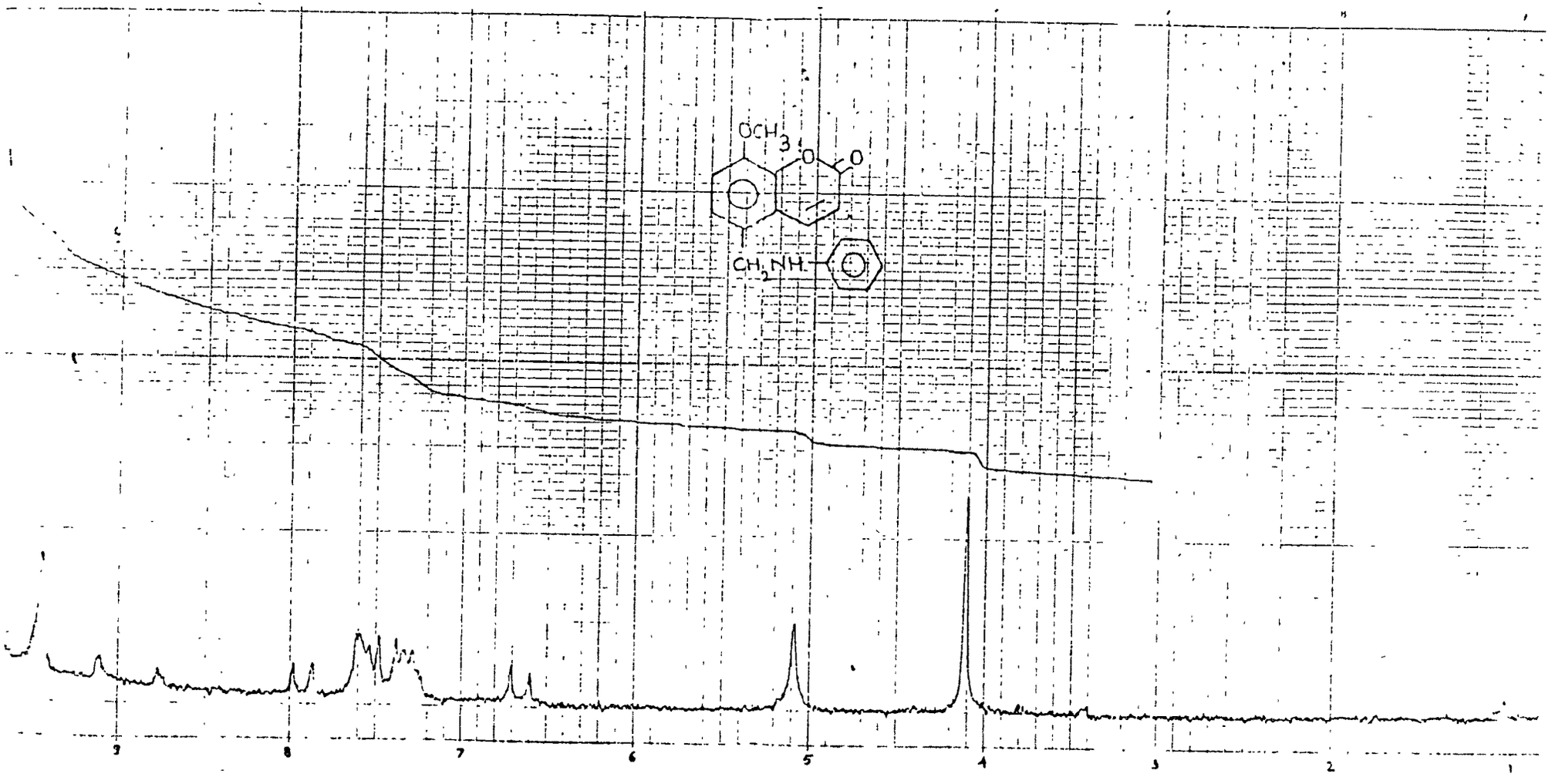
8-Methoxy-5-chloromethylcoumarin was treated with aniline which furnished-5-substituted Mannich base. The structure of the compound was proved by IR, NMR and Mass spectra. The IR (KBr) spectrum exhibited bands at 3450, 1710 (lactonic carbonyl), 1600 (aromatic), 1390-1175, 1280 and 1090 cm^{-1}. (Fig. 2)

The NMR spectrum showed following signals : (CF_3COOH) : Singlet at δ 4.1 for protons of -$OC\underline{H}_3$ group ; singlet at δ 5.1 for -$C\underline{H}_2$NH protons ; pair of doublets at δ 6.65 and δ 7.92 corresponding to the protons at C-3 and C-4 positions respectively. Absorption in the region δ 7.23 - 7.7 corresponds to aromatic protons (Fig. 3)

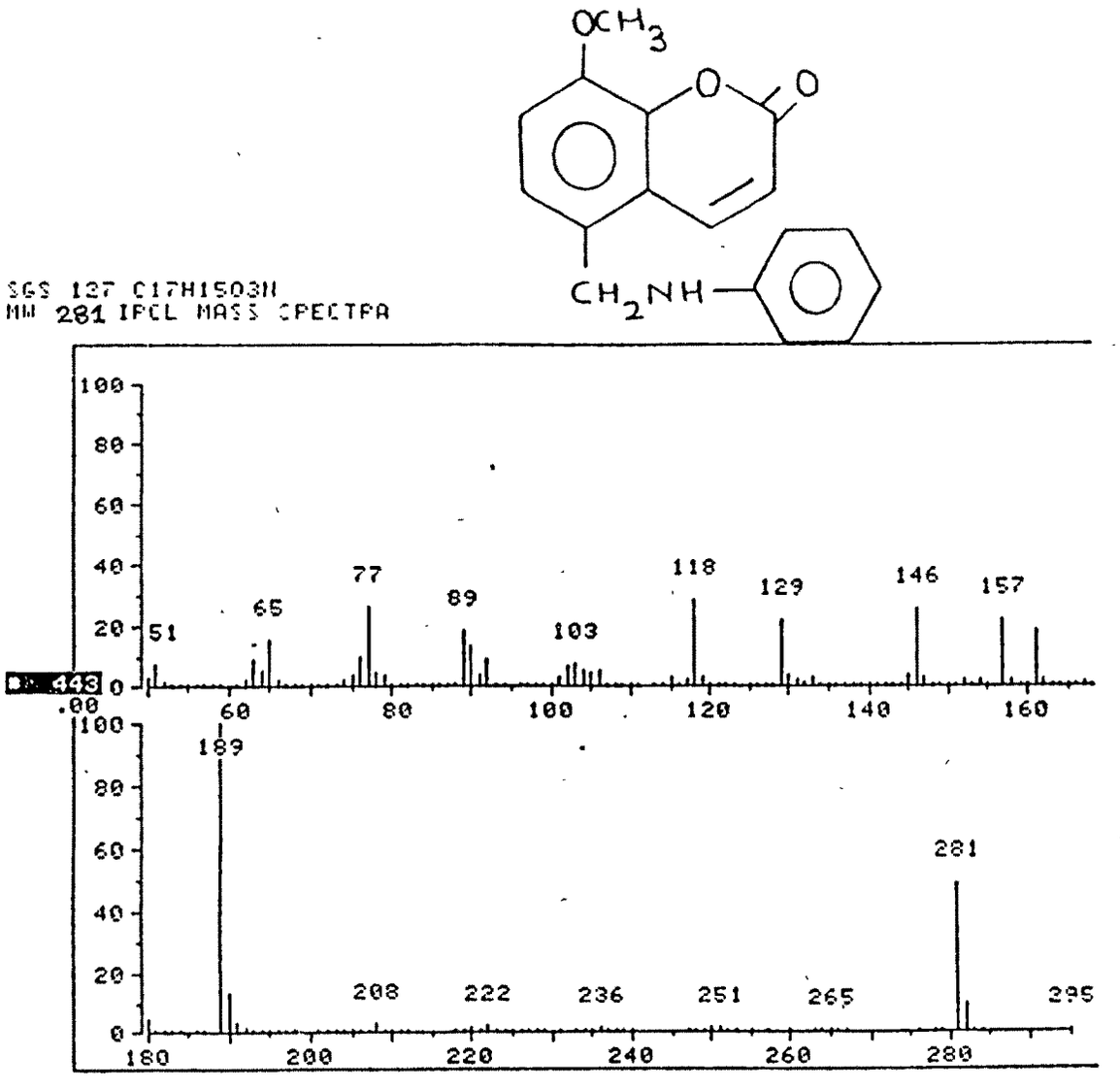
The Mass spectrum exhibited prominent signals at m/e 281 (M^+ ion, 50%), 189 (base peak, 100%), 157 (21%), 146 (25%), 118 (30%) and 77 (28%). (Fig. 4)


OCH3
O
O
CH2 NH
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
650

(Fig - 2) : 17



(Fig - 3) : 17


SGS 127 C17H15O3N
MW 281 IPCL MASS SPECTRA
OCH3
O
O
CH2NH
100
80
60
40
20
0
51
65
77
89
103
118
129
146
157
443
.00
60
80
100
120
140
160
189
208
222
236
251
265
281
295
180
200
220
240
260
280

(Fig-4) : 17

8-Methoxy-5-(o-methyl) anilinomethylcoumarin (18)

Condesation of 8-methoxy-5-chloromethylcoumarin and o-toludine gave a product to which 8-methoxy-5-(o-methyl)-anilino-methylcoumarin structure was assigned.

The following bands were observed in IR (KBr) spectrum.

: 3400, 1725, 1600, 1390-1175, 1280 and 1090 cm^{-1}

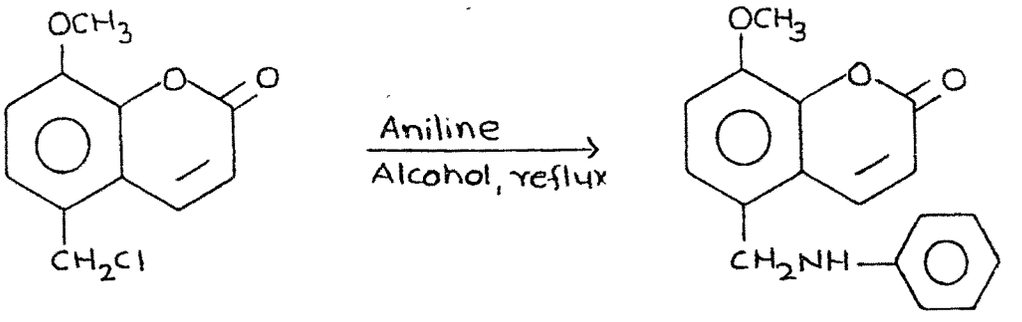
The NMR of the compound taken in $CDCl_3$, exhibited singlet at δ 2.1 for methyl protons of phenyl ring ; singlet at δ 3.94 for protons of $-O\underline{CH}_3$ group ; singlet at δ 4.42 for $C\underline{H}_2NH$ protons. The pair of doublets observed at δ 6.38 (J=9Hz) and δ 7.9 (J=9Hz) corresponds to protons at position C-3 and C-4 of coumarin nucleus. Aromatic protons appeared in the region δ 6.55 - 7.25. (Fig.5)

Thus, the structure of the compound has been confirmed by NMR.

8-Methoxy-5-(p-acetyl) anilinomethylcoumarin (19)

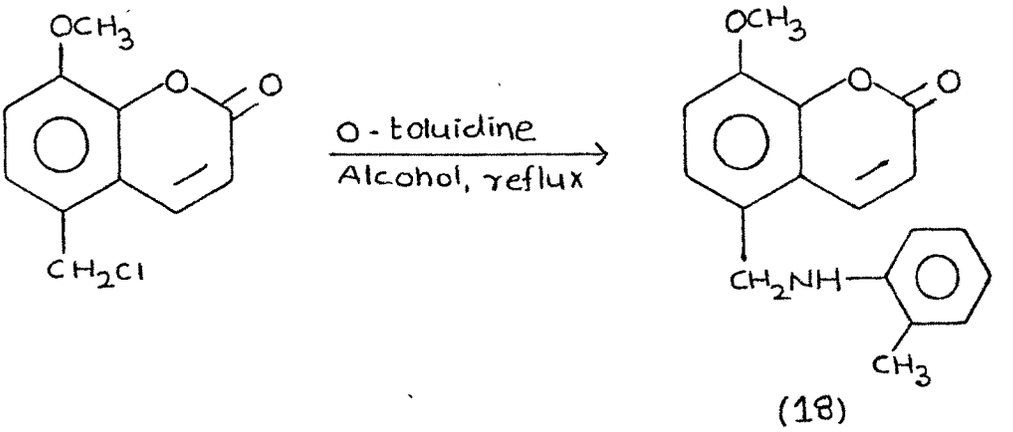
Condensation of 8-methoxy-5-chloromethylcoumarin with p-aminoacetophenone resulted in formation of 8-methoxy-5-(p-acetyl)-anilinomethylcoumarin. The structure of the compound was established by IR and NMR.

Scheme:3



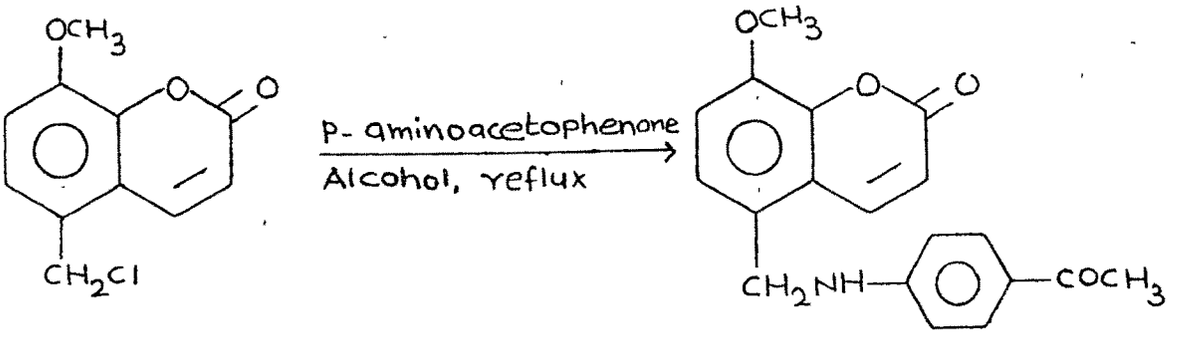
(17)

Scheme:4

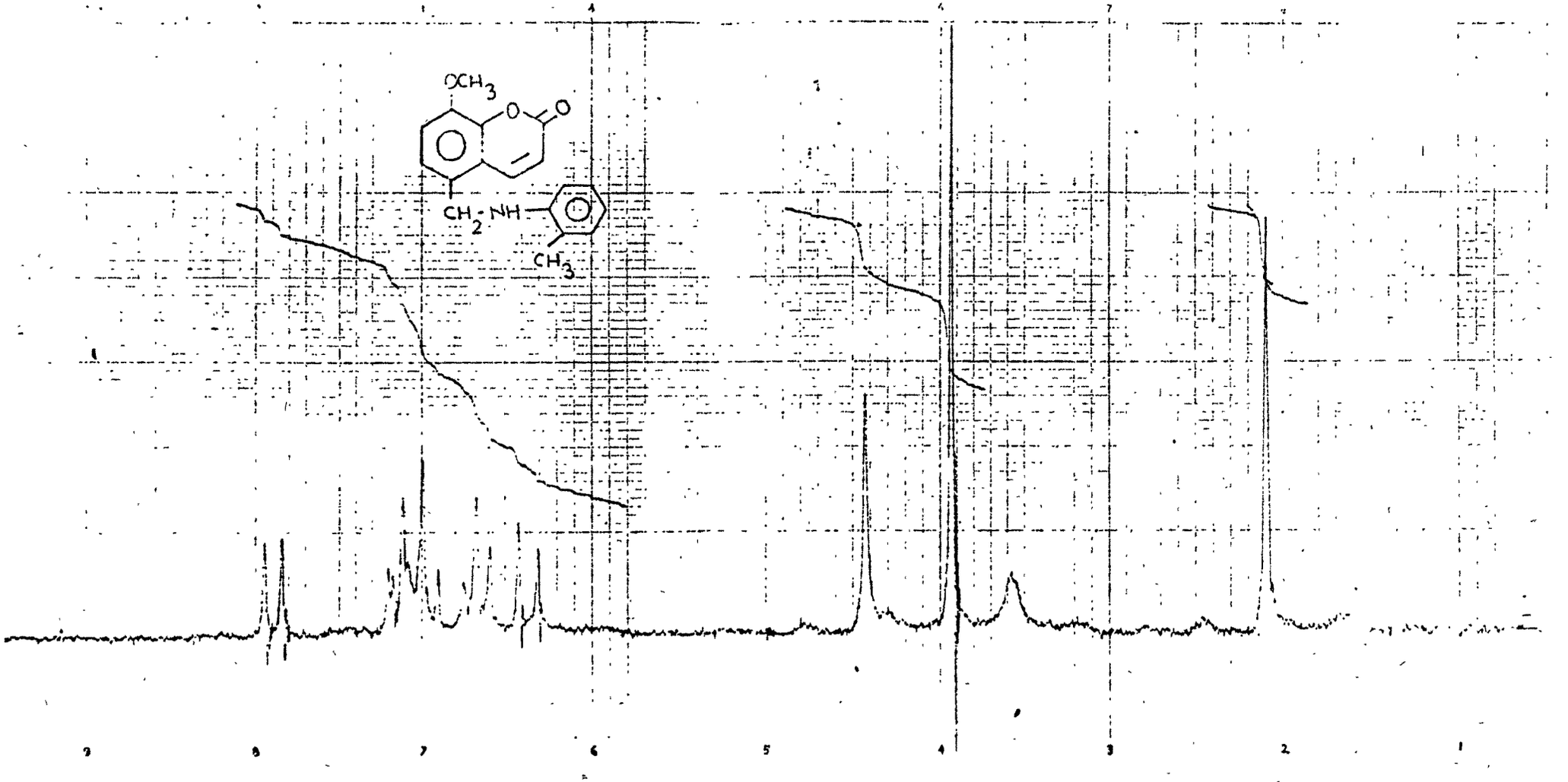


(18)

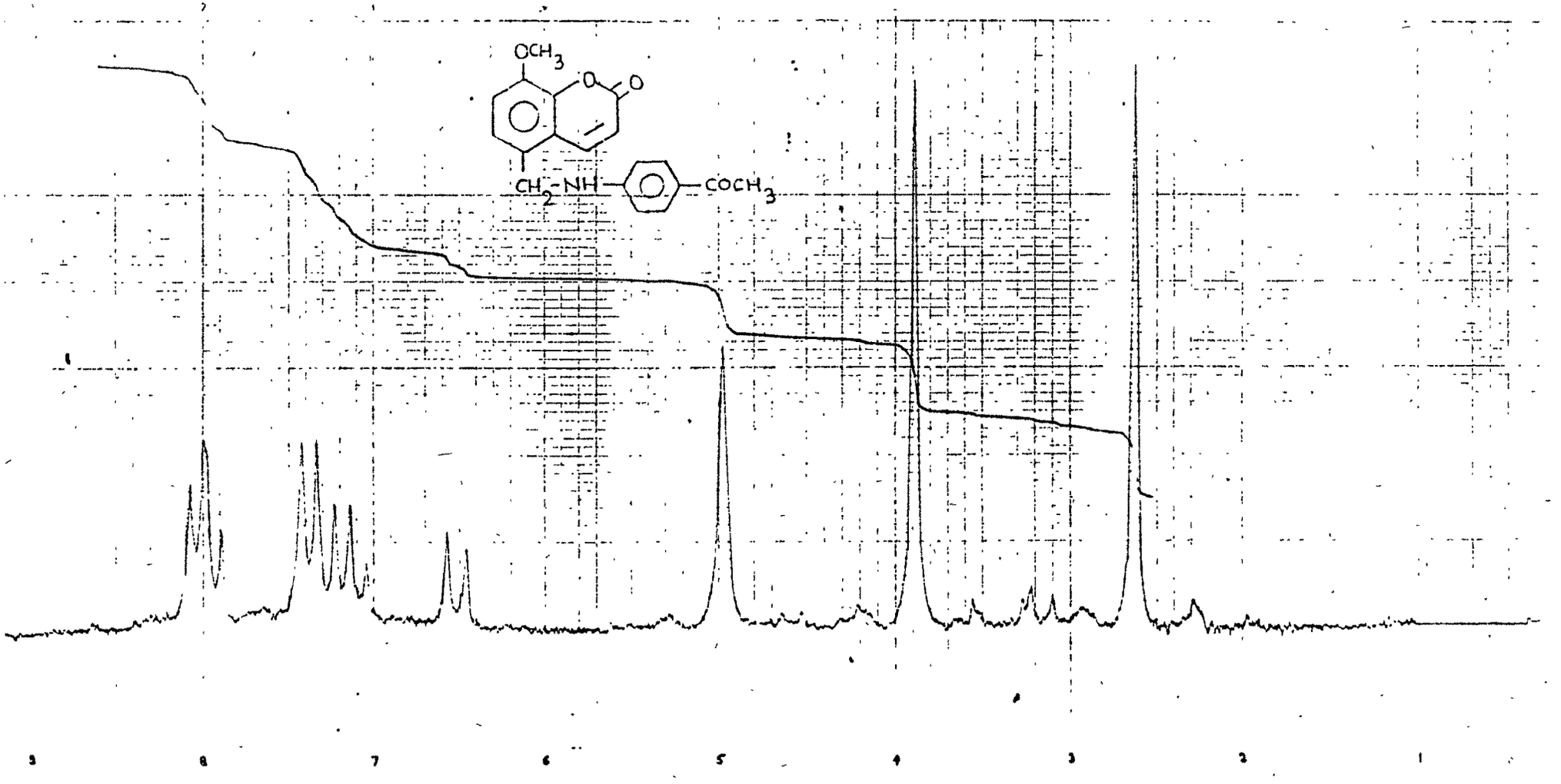
Scheme:5



(19)



(Fig-5) : 18



(Fig-6) : 19

(0·2 PPm off set)

The IR (KBr) spectrum exhibited bands at 3350, 1725, 1280 and 1090 cm^{-1}.

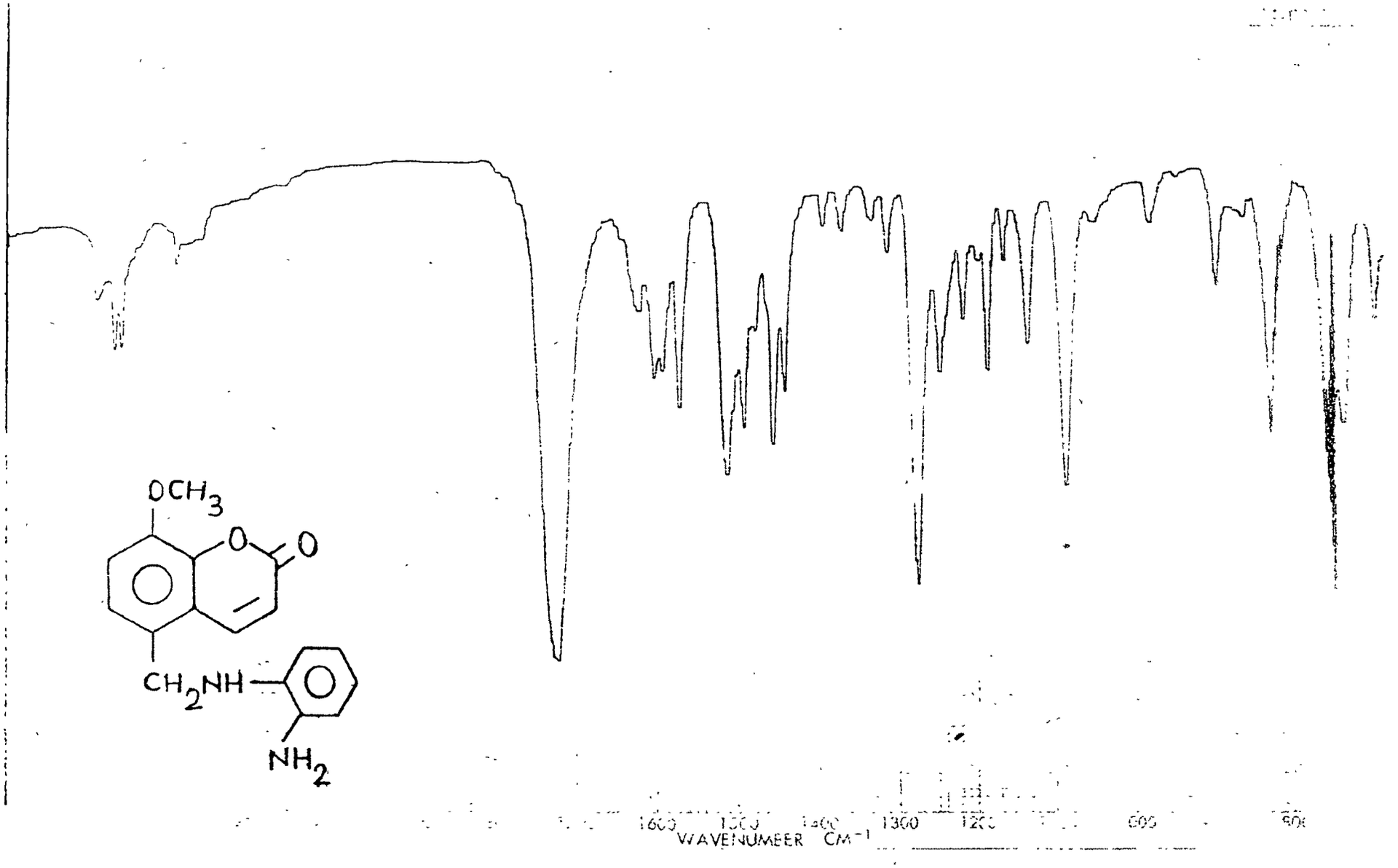
The NMR spectrum (CF_3COOH) showed following signals, Singlet at δ 2.42 of protons $-COCH_3$; singlet at δ 3.7 for methoxy protons ; singlet at δ 4.79 for $-CH_2NH$ protons ; two doublets, one was observed at δ 6.32 and other was found to overlap with the aromatic protons in the region δ 6.8-8.0. (Fig.6)

8-Methoxy-5-(o-amino)anilinomethylcoumarin (20)

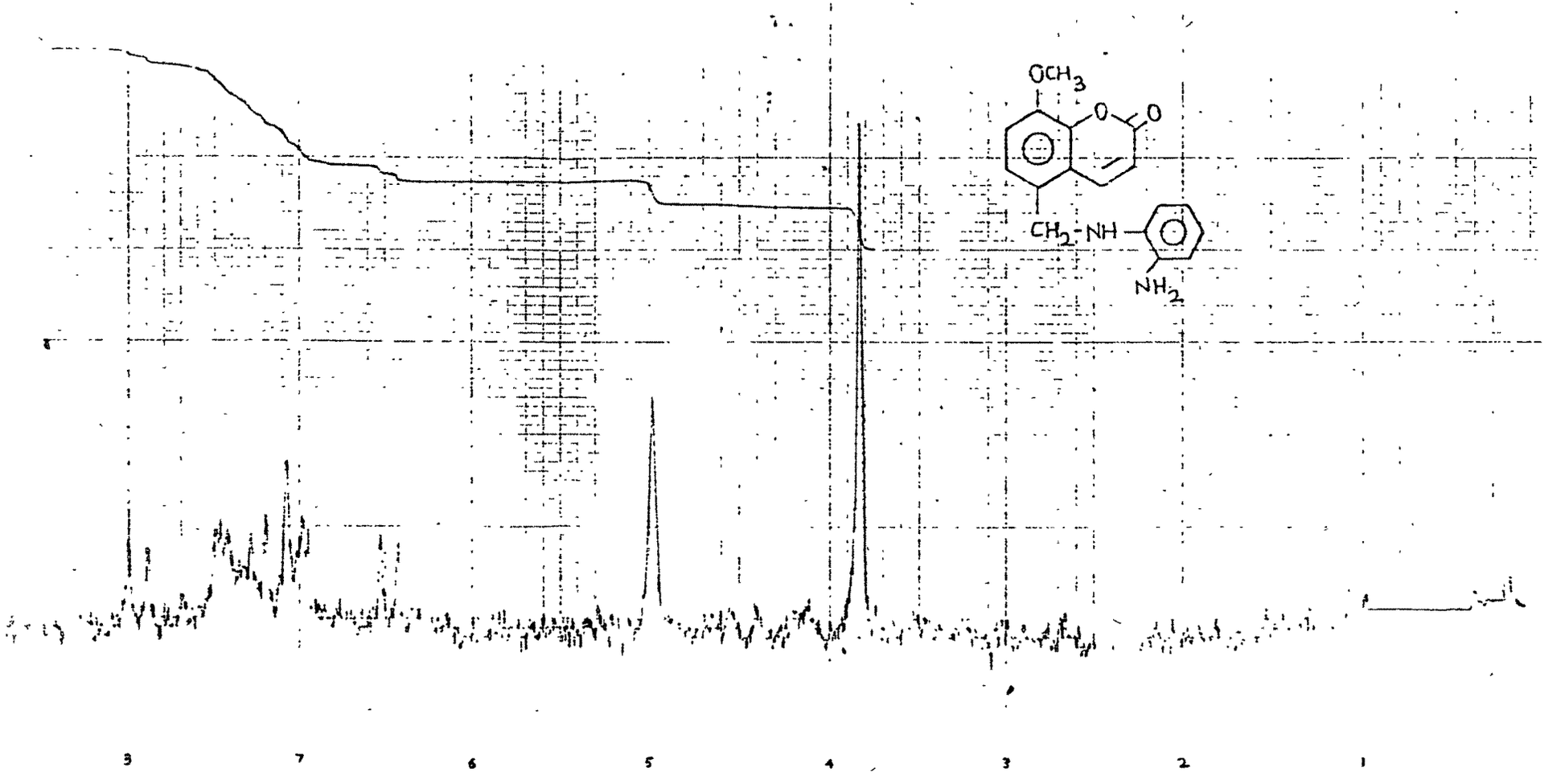
8-Methoxy-5-chloromethylcoumarin was treated with o-o-phenylenediamine which gave the product to which 8-methoxy-5-(o-amino)anilinomethylcoumarin structure has been assigned.

The bands at 3450, 3350-3300, 1725, 1600, 1390 -1175, 1280 and 1090 cm^{-1} were observed in IR (KBr) spectrum (Fig.7)

In NMR spectrum, taken in CF_3COOH, following signals were observed. Singlet at δ 3.62 for $-OCH_3$ protons ; singlet at δ 4.79 for CH_2NH protons ; pair of doublets of protons at position C-3 and C-4 were obsered at δ 6.29 and δ 7.75. In the region δ 6.73-7.32, signals of aromatic protons were observed.(Fig-8) Moreover, Schiff base derivative was also prepared from free -NH group and analysed to confirm the structure. (Chapter-III, Part-I, Table-II).



(Fig-7): 20



(0·2 ppm off set)

Fig-8) : 20

8-Methoxy-5-(p-carbethoxy)anilinomethylcoumarin (21)

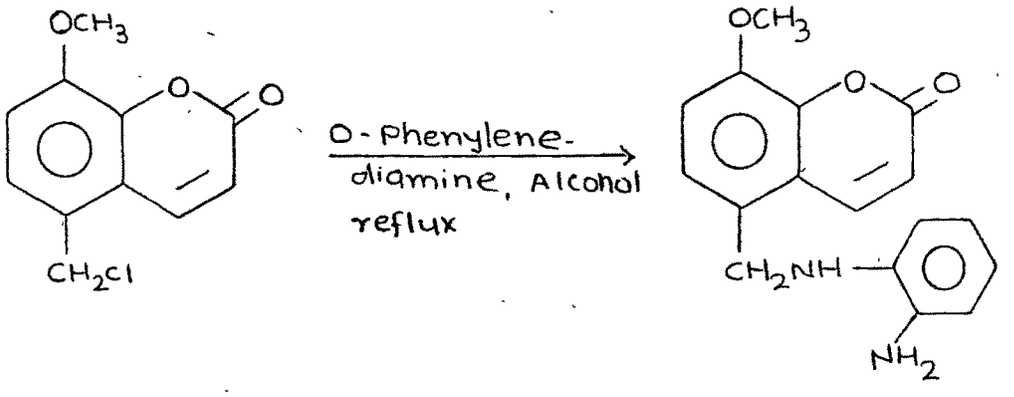
A mixture of 8-methoxy-5-chloromethyl coumarin and ethyl-p-aminobenzoate when reacted, furnished a product to which 8-methoxy-5-(p-carbethoxy)anilinomethylcoumarin structure has been assigned.

The IR spectrum showed following bands : 3350, 1720-1690 (broad), 1600, 1390 - 1175, 1290 and 1080 cm^{-1}.

The NMR spectrum (CF_3COOH) exhibited triplet at δ 1.1 for three protons of $COOCH_2\underline{CH}_3$; singlet at δ 3.65 of OCH_3 protons ; quartet at δ 4.13 of $COO\underline{CH}_2CH_3$ protons ; singlet at δ 4.7 for protons $\underline{CH}_2NH$. Out of two doublets, one was observed at δ 6.29 and other was found to overlap with aromatic protons in the region δ 6.8 - 7.9 (Fig.9). Thus the structure has been confirmed by NMR spectrum.

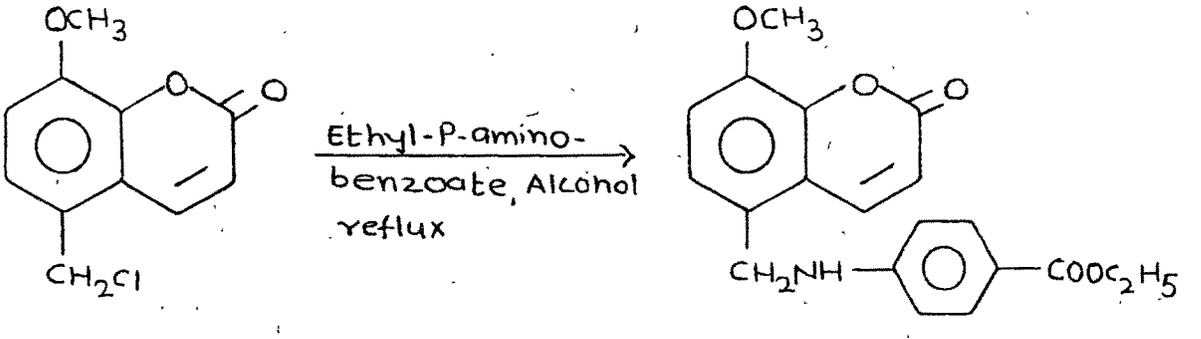
Other aminomethylcoumarin were similarly synthesised. (Table-II).

Scheme : 6

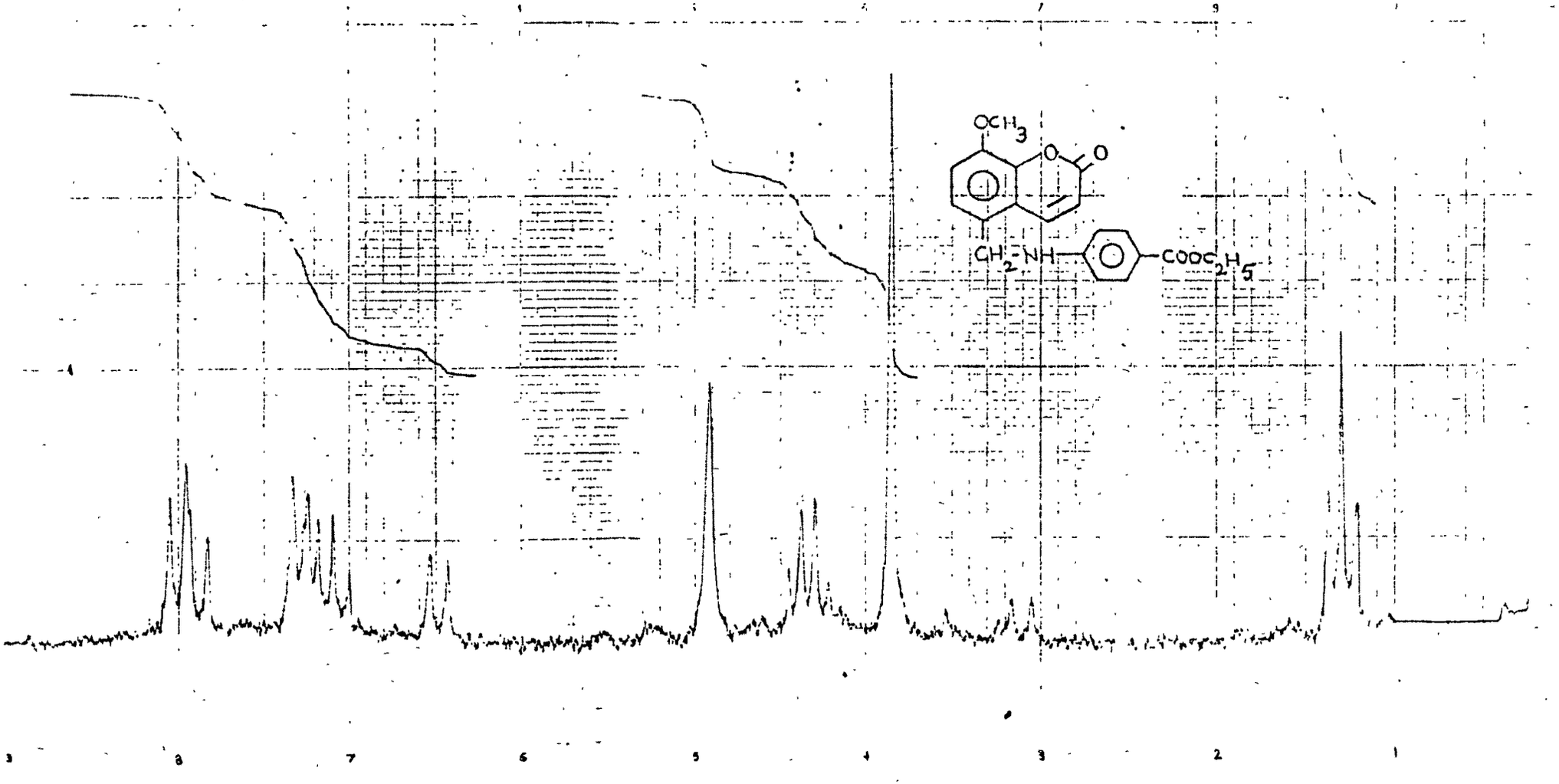


(20)

Scheme : 7



(21)



(Fig-9) : 21

(0.2 ppm off set)

EXPERIMENTAL

EXPERIMENTAL

8-Methoxy-5-chloromethylcoumarin[16] (15)

A mixture of 8-methoxycoumarin (4.0 g), zinc chloride (3.4 g), paraformaldehyde (0.840 g) and dilute glacial acetic acid (125 ml) was stirred at 60-65°C for 2 hrs. While introducing dry hydrochloric acid gas. The product separated on cooling was poured into ice-cold water. It was crystallised from benzene in colourless crystals. M.p. 186°C, yield 75%.

Analysis : Found : C, 59.34 ; H, 4.26%

$C_{11}H_9O_3Cl$: requires : C, 58.93 ; H, 4.02%

8-Methoxy-5-anilinomethylcoumarin (17)

8-Methoxy-5-chlorocoumarin (1.0 g) and aniline (1.0 g) were refluxed in alcohol (15 ml) on a sand bath for 4 hrs. The reaction mixture was concentrated under reduced pressure. The product thus obtained was crystallised from alcohol in light yellow needles, M.p. 190°C, yield 65%.

Analysis : Found : C, 73.00 ; H, 5.31 ; N, 5.44%

$C_{17}H_{15}O_3N$: requires : C, 72.59 ; H, 5.34 ; N, 4.98%

8-Methoxy-5-(o-methyl)anilinomethylcoumarin (18)

8-Methoxy-5-chloromethylcoumarin (1.0 g) was treated with o-toluidine (1.0 g) in alcohol (15-20 ml) for 4-6 hrs.

The excess alcohol was distilled off. The product was crystallisd from alcohol. M.p. 197°C, yield 71%.

Analysis : Found : C, 73.33 ; H, 5.61 ; N, 4.83%

$C_{18}H_{17}O_3N$: requires : C, 73.22 ; H, 5.76 ; N, 4.74%

8-Methoxy-5-(p-acetyl)aminomethylcoumarin (19)

A mixture of 8-methoxy-5-chloromethyl couarin (1.0 g) and p-aminoacetophenone (1.0 g) was refluxed in alcohol (15-20 ml). The product was separated out within 3 hrs. during the reaction. It was filtered and crystallised from DMF-water mixture, M.p. 245°C, yield 65%.

Analysis : Found : C, 70.86 ; H, 5.53 ; N, 4.12%

$C_{19}H_{17}O_4N$: requires : C, 70.58 ; H, 5.26 ; N, 4.33%

8-Methoxy-5-(o-amino) anilinomethylcoumarin (20)

8-Methoxy-5-chloromethyl coumarin (1.0 g) was condensed with o-phenylenediamine (1.0 g) in alcohol (20 - 25 ml). The product was separated within 15 minutes. It was filtered and crystallised from chloroform. M.p. 210°C, yield 72%.

Analysis : Found : C, 68.64 ; H, 5.61 ; N, 9.10%

$C_{17}H_{16}O_3N_2$: requires : C, 68.92 ; H, 5.41 ; N, 9.45%

8-Methoxy-5-(p-carbethoxy) aminomethylcoumarin (21)

Condensation of 8-methoxy-5-chloromethyl coumarin (0.5 g) and ethyl-p-aminobenzoate (0.5 g) in alcohol (15-20 ml) resulted in 5-substituted aminomethylcoumarin. The excess alcohol was distilled off. The product thus obtained was crystallised from 1:1 DMF. M.p. 174°C, yield 56%.

Analysis	:	Found	:	C, 68.01	; H, 5.34	; N, 3.56%
$C_{20}H_{19}O_5N$	:	requires	:	C, 67.99	; H, 5.38	; N, 3.97%

TABLE-II : ANALYTICAL AND PHYSICAL DATA OF 8-METHOXY-5-SUBSTITUTED AMINOMETHYLCOUMARINS

Sr. No.	R_1	R_2	M.P.* °C	Yield %	Molecular Formula	Analysis % Found/(Calcd) C	H	N
1	H	C_6H_5-	190[a]	65	$C_{17}H_{15}O_3N$	73.0 (72.59)	5.31 (5.34)	5.44 (4.98)
2	H	o-CH_3-C_6H_4-	197[a]	71	$C_{18}H_{17}O_3N$	73.33 (73.22)	5.61 (5.76)	4.83 (4.74)
3	H	p-CH_3-C_6H_4-	210[d+w]	61	$C_{18}H_{17}O_3N$	72.8 (73.22)	5.52 (5.76)	4.31 (4.74)
4	H	m-CH_3-C_6H_4-	215[d+w]	55	$C_{18}H_{17}O_3N$	72.80 (73.22)	5.71 (5.76)	4.31 (4.74)
5	H	o-OCH_3-C_6H_4-	184[a]	72	$C_{18}H_{17}O_4N$	69.90 (69.45)	5.59 (5.47)	4.10 (4.5)
6	H	p-OCH_3-C_6H_4-	168[a]	65	$C_{18}H_{17}O_4N$	69.24 (69.45)	5.19 (5.47)	4.19 (4.50)
7	H	-CH_2-C_6H_5	183[d+w]	65	$C_{18}H_{17}O_3N$	73.56 (73.22)	5.26 (5.76)	4.62 (4.74)
8	H	o-Cl-C_6H_4-	204[a+b]	50	$C_{17}H_{14}O_3NCl$	64.19 (64.76)	4.04 (4.44)	3.95 (4.44)

cont....

TABLE-II cont...

9	H	p-Cl-C_6H_4-	185[a+w]	51	$C_{17}H_{14}O_3NCl$	64.61 (64.76)	4.21 (4.44)	4.23 (4.44)
10	H	p-Br-C_6H_4-	205[d+w]	65	$C_{17}H_{14}O_3NBr$	57.05 (56.67)	4.22 (3.89)	4.25 (3.89)
11	H	p-NO_2-C_6H_4-	277-78[d+w]	65	$C_{17}H_{14}O_3N_2$	62.63 (62.57)	4.14 (4.29)	8.47 (8.58)
12	H	m-NO_2-C_6N_4-	265[d+w]	55	$C_{17}H_{14}O_5N_2$	61.97 (62.57)	4.01 (4.29)	8.12 (8.58)
13	H	o-NO_2-C_6H_4-	230[d+w]	71	$C_{17}H_{14}O_5N_2$	63.03 (62.57)	4.57 (4.29)	8.14 (8.59)
14	H	p-$COCH_3$-C_6H_4-	245[d+w]	65	$C_{19}H_{17}O_4N$	70.86 (70.58)	5.53 (5.26)	4.12 (4.33)
15	H	m-$COCH_3$-C_6H_4-	177[d+w]	60	$C_{19}H_{17}O_4N$	70.13 (70.58)	5.05 (5.26)	4.12 (4.33)
16	H	p-NH_2-C_6H_4-	305[d+w]	55	$C_{17}H_{16}O_3N_2$	68.70 (68.92)	4.98 (5.41)	9.31 (9.45)
17	H	o-NH_2-C_6H_4-	210[c]	72	$C_{17}H_{16}O_3N_2$	68.64 (68.92)	5.62 (5.41)	9.10 (9.45)
18	H	β-naphthyl	218[d+w]	55	$C_{21}H_{17}O_3N$	70.91 (71.13)	5.38 (5.13)	4.51 (4.23)

cont....

TABLE-II cont...

19	H	∝-naphthyl	190[a]	52	$C_{21}H_{17}O_3N$	71.28 (71.13)	5.14 (5.13)	4.55 (4.23)
20	H	p-$COOC_2H_5$-C_6H_4	174[d+w]	56	$C_{20}H_{19}O_5N$	68.01 (67.99)	5.35 (5.38)	3.56 (3.97)
21	-C_2H_5	C_6H_5-	169[a]	60	$C_{18}H_{19}O_3N$	72.30 (72.72)	6.13 (6.39)	4.46 (4.71)
22	-C_6H_5	C_6H_5-	185[a+w]	55	$C_{23}H_{19}O_3N$	76.90 (77.31)	5.74 (5.32)	3.45 (3.93)
23	Morpholine		110[a]	55	$C_{15}H_{17}O_4N$	65.25 (65.45)	6.09 (6.19)	5.19 (5.09)
24	N-phenyl piperazine		190[a]	63	$C_{21}H_{22}O_3N_2$	71.90 (72.0)	6.16 (6.29)	7.67 (8.00)
25	2-Methyl piperidine		115[a+w]	60	$C_{17}H_{21}O_3N$	70.91 (71.08)	7.19 (7.32)	4.59 (4.88)
26	4-Methyl piperidine		165[a+w]	60	$C_{17}H_{21}O_3N$	70.65 (71.08)	7.01 (7.32)	4.57 (4.88)
27	H	3,4-Cl_2.C_6H_3-	180[d+w]	70	$C_{17}H_{13}O_3NCl_2$	58.55 (58.45)	4.17 (3.73)	3.95 (4.01)
28	H	2,4-Cl_2-C_6H_3-	235[d+w]	70	$C_{17}H_{13}O_3NCl_2$	58.09 (58.45)	4.02 (3.73)	3.92 (4.01)

* Crystallisation solvent : a = alcohol, b = benzene, c = chloroform, d = DMF, w = water

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