Chapter - II

Part - I

Synthesis of some 7,8-dimethoxy-4-aminomethylcoumarins

SYNTHESIS OF SOME 7,8 DIMETHOXY-4-AMINOMETHYLCOUMARINS

Chloromethyl or bromomethyl group can be easily converted into aminomethyl group by treatment with aliphatic, aromatic or heterocyclic amines in appropriate solvents. Thus chloromethyl or bromomethyl derivatives have become convenient source for the introduction of aminomethyl group in the synthetic organic chemistry.

The past 25 years or so have witnessed an enormous increase in research publications in the field of coumarins particularly with respect to biological activity. A brief review of some of these is presented here.

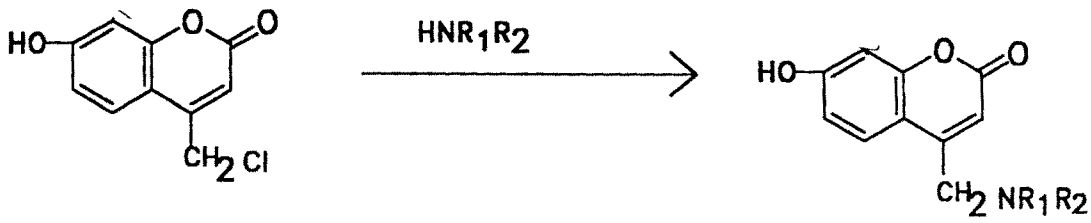
S.A. Dause[1] synthesised 4-(tertiary aminomethyl)-7-hydroxycoumarin from 7-hydroxy-4-chloromethylcoumarin which was used as choleretics. They compared the choleretic activity of the compound (1) with that of 4-methyl umbelliferone.

I.S. Rudakova et al[2] synthesised 8-[bis-(2-hydroxyethyl)]aminomethyl-6, 7-dihydroxy-4-methylcoumarin (2) and examined the effect of substituents with P-vitamin activity on the permeability of vessels during burn inflamation. M. P Gorizentova and A. M. Cherhykh[3] also synthesised same aminomethyl derivatives (2). They observed that compound (2) decreased the permeability of liver and thymus tissues of irradiated rats.

D.O. Shah and K.N. Trivedi[4] synthesised some aminomethylcoumarin derivatives by condensing various amines with 7-methoxy-4-methyl-6-chloromethylcoumarin, with 5-methoxy-4-methyl-7-bromomethylcoumarin and 7-methoxy-4-methyl-8-bromomethyl coumarin and obtained corrosponding aminomethyl derivatives (3), (4) and (5) respectively.

Manohar Kulkarni and D. Vemanna[5] prepared anilinomethylcoumarins (6) from substituted 4-bromomethylcoumarin. They found that substituent with R'=6-methyl-, 7-methoxy-6-chloro-, 7-chloro and R_2 = chloro were active against E.coli.

G.Sailaja, K.Mohana Raju and M. Subramanayam Raju[6] synthesised 7-ethoxy-3-substitutedaminomethyl-4-methylcoumarin (7). They tested all compounds against E. coli, Proteus Vulgaris and K.Pneumoniae at 100 ppm and 500 ppm concentrations. They observed that chloromethylated compound and the compound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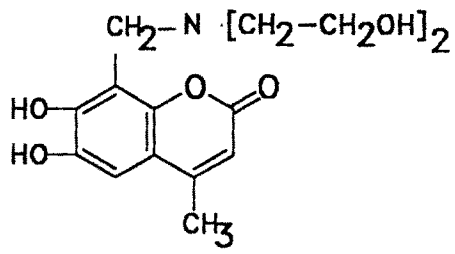
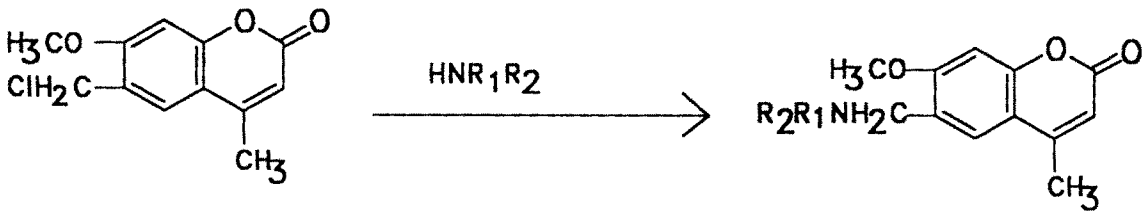
O
O
CH2 Cl
HNR1R2
HO
O
O
CH2 NR1R2

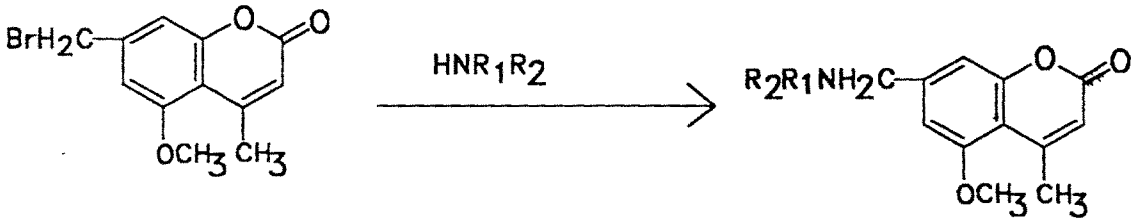
(1)


CH2–N [CH2–CH2OH]2
HO
HO
O
O
CH3

(2)


H3CO
ClH2C
O
O
CH3
HNR1R2
H3CO
R2R1NH2C
O
O
CH3

(3)


BrH2C
O
O
OCH3
CH3
HNR1R2
R2R1NH2C
O
O
OCH3
CH3

(4)

with R_1 = CH_3 and R_2=C_6H_5 showed high antibacterial activity where as morpholino and dimethylaminomethy derivatives showed moderate activity at 100 ppm.

S.Shrikant Hanmantgud et al[7] prepared bilogically active aminomethyl derivatives from 4-bromomethylcoumarin to give (8).

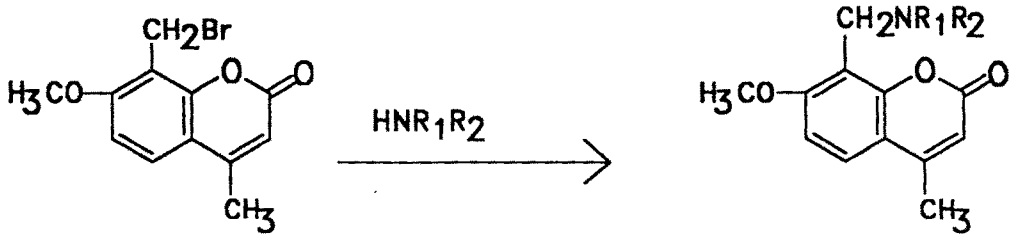
M.Nagesam and M.Subramanyam Raju[8-10] synthesised number of 4,6-dimethyl-3-substitutedaminomethylcoumarin (9) and 3-(picolinyl) aminomethylcoumarins from 4,6-dimethyl-3-chloromethylcoumarin. Most of the compounds showed good inhibition against E.coli, B.Subtilis and S.aureus in vitro. They also prepared some aminomethyl derivatives (10) from 4,8-dimethyl-3-chloromethylcoumarin and screend them for antibacterial activity in vitro against Xanthomonascitri, 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.

S.M. Desai[11] prepared 7-methoxy-8-substitutedaminomethyl-3,4-diphenyl coumarin (11) from 7-methoxy-8-chloromethyl-3,4-diphenylcoumarin as possible antibacterial agents.

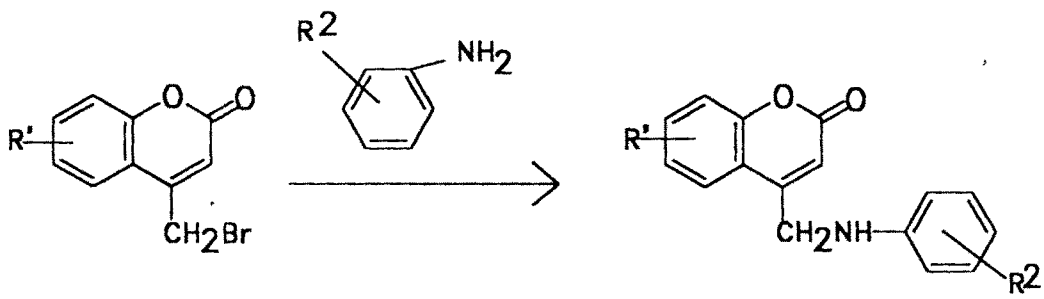
Rajeev Vyas and R.H.Mehta[12] synthesised 7,8-dimethoxy-3-substitutedaminomethyl-4-methylcoumarin derivatives (12) via 7,8-dimethoxy-3-chloromethyl-4-methylcoumarin and reported that number of them have moderate antibacterial activity against E.coli and S.aureus.

Sonal Shah and R.H.Mehta[13] reported synthesis of 8-methoxy-5-aminomethyl coumarin compounds (13). They were screened for antibacterial activity. Some of them were found active against E.coli, S. aureus, S.Thyphosa and B.Subtilis.

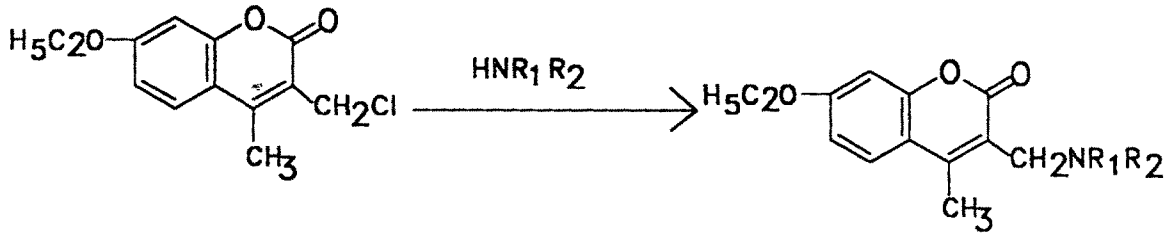
M. V. Paradkar et al[14] reported a novel synthesis of 4-aminomethylcoumarins (14) They had condensed 3-bromo-4-methylcoumarin derivatives with secondary amines and furnished a novel product i.e. 4-aminomethylcoumarin derivative (14) along with 3-amino coumarin derivative (15).


CH2Br
H3CO
O
O
CH3
HNR1R2
CH2NR1R2
H3CO
O
O
CH3

(5)


R2
NH2
R'
O
O
CH2Br
R'
O
O
CH2NH
R2

(6)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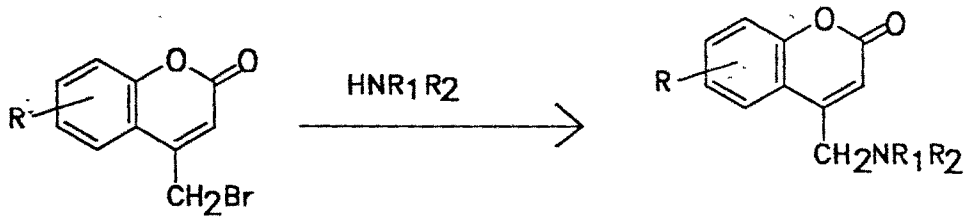
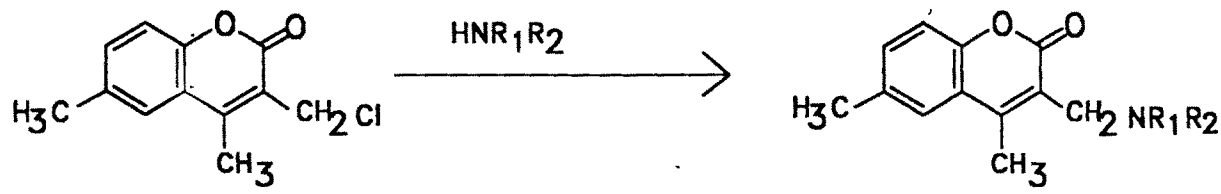
O
O
CH2Cl
CH3
HNR1R2
H5C2O
O
O
CH2NR1R2
CH3

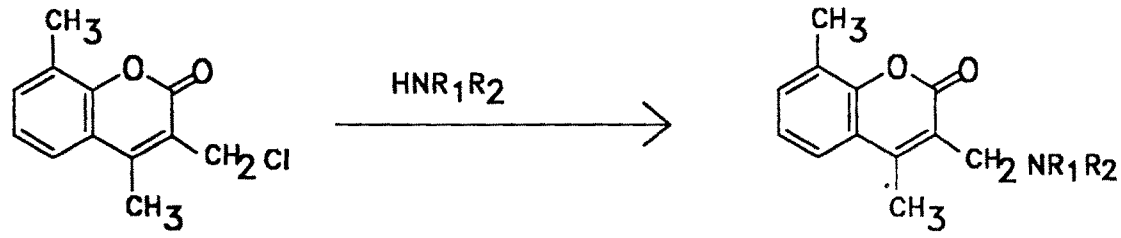
(7)


R
O
O
CH2Br
HNR1R2
R
O
O
CH2NR1R2

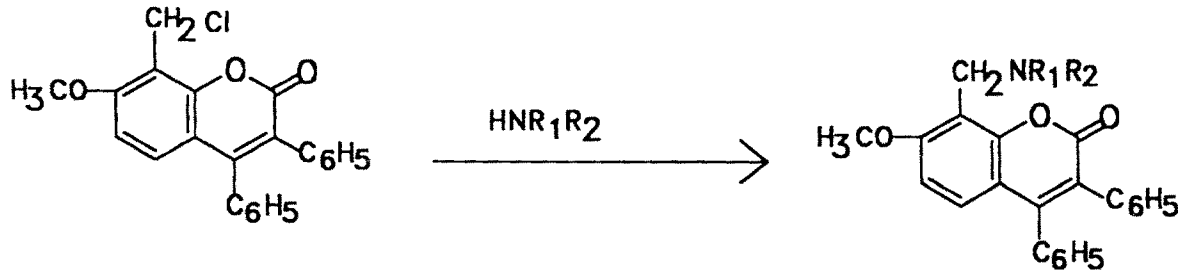
(8)


HNR1R2
H3C
CH2 Cl
CH3
CH2 NR1R2

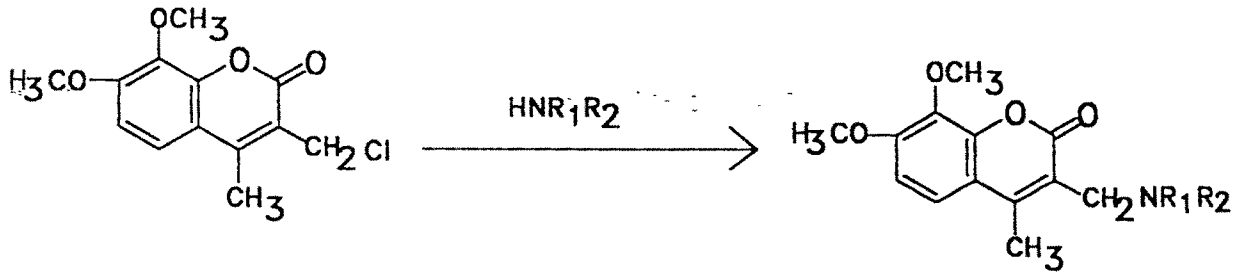
(9)


CH3
HNR1R2
CH2 Cl
CH3
CH2 NR1R2

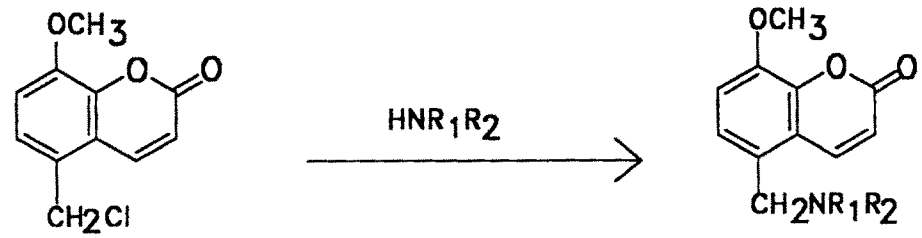
(10)


CH2 Cl
H3CO
C6H5
C6H5
HNR1R2
CH2 NR1R2

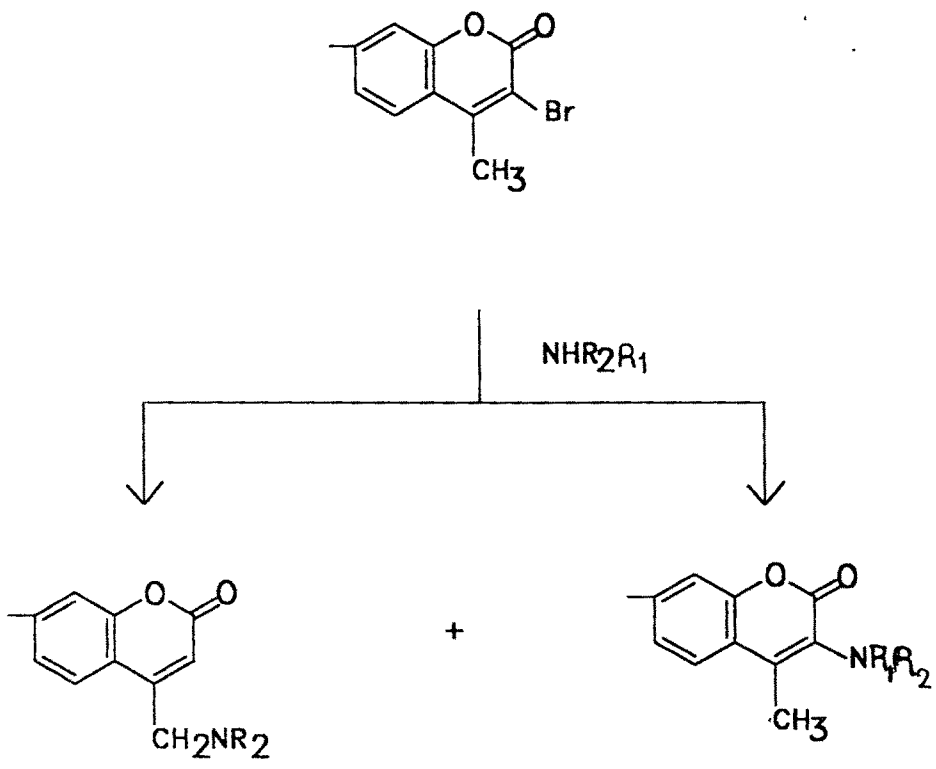
(11)


OCH3
H3CO
CH2 Cl
CH3
HNR1R2
CH2 NR1R2

(12)


OCH3
O
O
CH2Cl
HNR1R2
OCH3
O
O
CH2NR1R2

(13)


O
O
Br
CH3
NHR2R1
O
O
CH2NR2
+
O
O
NR1R2
CH3

(14) (15)

S.S. Madhava Rao and K.N. Trivedi[15] reported some 4-aminomethyl dihydroangelicin derivatives using the procedure of Paradkar and coworkers. They showed condensation of 3-bromo-4,8-dimethyl-8,9-dihydrofuro [2,3-h] benzopyran 2(H)-one (16) with piperidine using DMF as solvent, gave two products (i) 8-methyl-4-piperidinomethyl 8,9-dihydrofuro [2,3-h] benzopyran-2(H)-one (17) and (ii) 4,8-dimethyl -3-piperidinyl-8,9-dihydrofuro [2,3-h] benzopyran-2(H)-one (18).

They have observed that when other secondary amines like morpholine, N-phenyl piperazine, 4-methylpiperidine were condensed with (16), only 4-aminomethyl coumarin derivative was obtained.

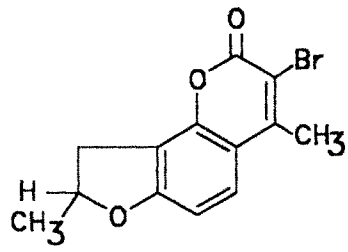
They have also established mechanism for formation unusual product (17) from (16). This unexpected product needs migration of one hydrogen from CH_3 group to 3-position and migration of Br from 3-position to the CH_3 group. The regent/solvent mixture is both basic (piperidine) and highly ionising (DMF). SP^2-C.Br links are very difficult to break, so it is proposed that the structure (A) undergoes a based catalysed prototropic shift to the structure (C) through (B). Now structure (C) has SP^3-C.Br link which is easily ionised giving allylic cation (D) which can add piperidine at 4-methylene to give the product (17). (Scheme - 1).

They have also reported[16] bromination of 2,7-dimethyl furo [2,3-h] benzopyran-5(H)-one (19) with N-bromosuccinimide which gave 2-bromomethyl-7-methyl furo [2,3-h] benzopyran-5(H) one (20). This (20) was converted into 2-aminomethyl derivatives (21).

Present Work

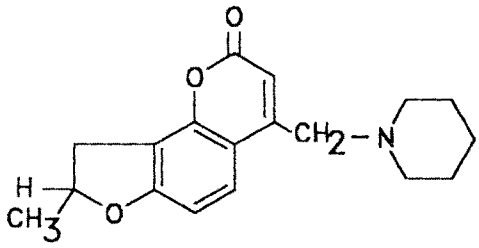
Above survey of earlier research publications on coumarin compounds reveals that they have remarkable potential to act as antimicrobial agents. Moreover it has been observed that groups like dimethoxy[17], aminomethyl[9], halogen[18] and heterocyclic moieties[19] enhance antibacterial activity of coumarins. It was therefore decided to undertake synthesis of number of 7,8-dimethoxy-4-substitutedaminomethylcoumarin derivatives and to evaluate them for their antibacterial activity.

In order to introduce aminomethyl group in coumarin ring system, we have utilised two different approaches.

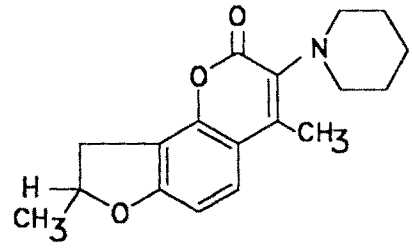


(16)

DMF,Piperidine, △



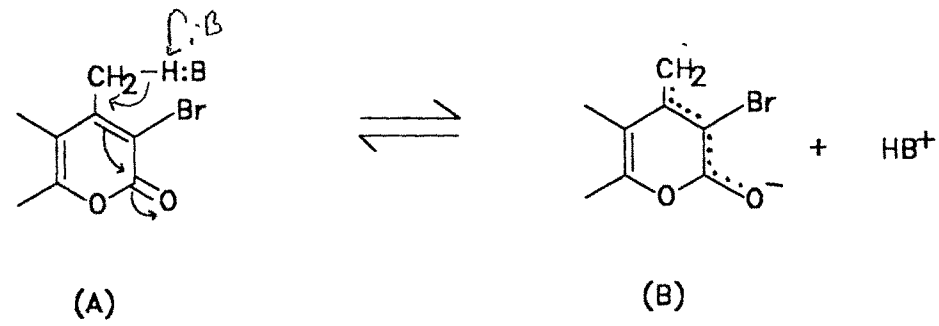
+



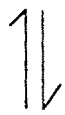
(17)

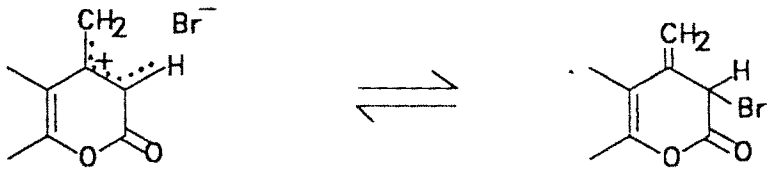
(18)

Scheme - 1

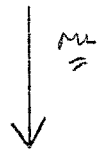


(A) (B)

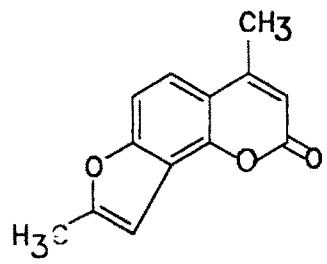




(D) (C)

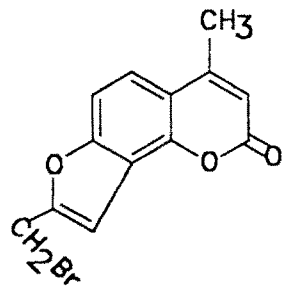


(17)



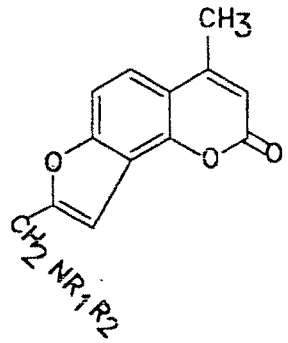
(19)

NBS,Benzoylperoxide



(20)

HNR_1R_2



(21)

In first approach, a known 7,8-dimethoxy-3-bromo-4-methylcoumarin was condensed with some secondary amines which gave 7,8-dimethoxy-4-aminomethylcoumarins. Here when piperidine was used as amine, two products were isolated while other secondary amines furnished only single product.

In second approach, 7,8-dimethoxy-4-methylcoumarin was prepared and then brominated using N-bromosuccinimide which furnished 7,8-dimethoxy-4-bromomethyl coumarin (31). This when condensed with secondary amines, gave products identical with those obtained by the first approach. Moreover this (31) was also condensed with different primary aromatic amines.

7,8-Dimethoxy-3-bromo-4-methylcoumarin (25) (Scheme 2)

Pyragallol (22) on Pechmann condensation[20] with ethylacetoacetate and concentrated sulfuric acid gave 7,8-dihydroxy-4-methylcoumarin (23), which was methylated using dimethyl sulfate in dry acetone and potasium carbonate to get 7,8-dimethoxy-4-methyl coumarin[21] (24). This when treated with bromine in acetic acid, undergoes nuclear bromination[22] to obtain 7,8-dimethoxy-3-bromo-4-methylcoumarin (25)

The PMR spectrum of (25) in $CDCl_3$ exhibited, a singlet at δ 2.2 for three protons of methyl group at C-4 position, a singlet at δ 4.0 for six protons of two methoxy groups at C-7 and C-8 position, a doublet at δ 6.9 (J = 9Hz) and a doublet at δ 7.5 (J = 9Hz) for C-6 and C-5 protons respectively (Fig. 1).

Condensation of 7,8-dimethoxy-3-bromo-4-methylcoumarin (25) with secondary amines[15].

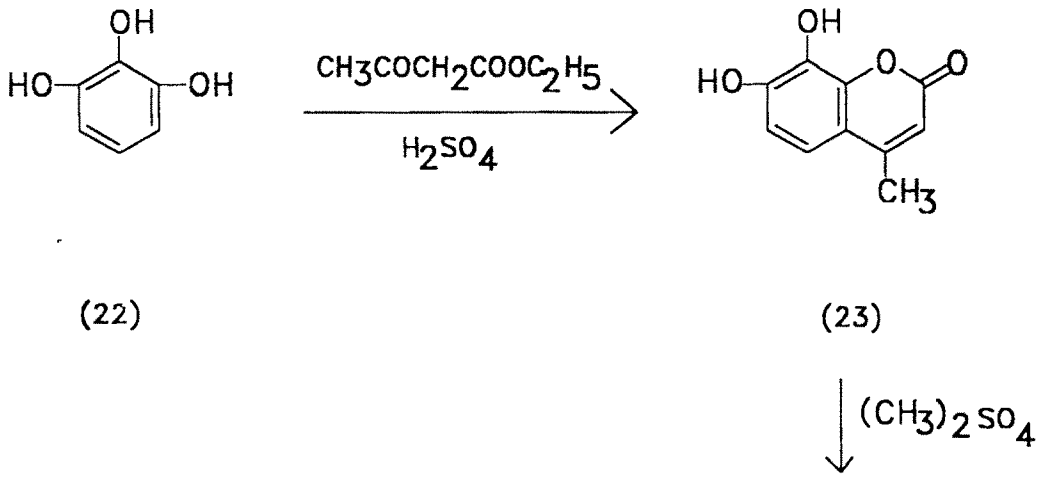
(a) Condensation with Piperidine (Scheme - 3)

(i) 7,8-Dimethoxy-3-piperidinyl-4-methylcoumarin (26)

When 7,8-dimethoxy-3-bromo-4-methylcoumarin (25) was condensed with piperidine using N, N-dimethylformamide as solvent gave two products.

These two products were separated by column chromatography. The product having higher Rf value was eluted out first with benzene fraction and was assigned 7 8-dimethoxy-3-piperidinyl-4-methylcoumarin structure (26). The structure was

Scheme - 2



(22) (23) (24) (25)

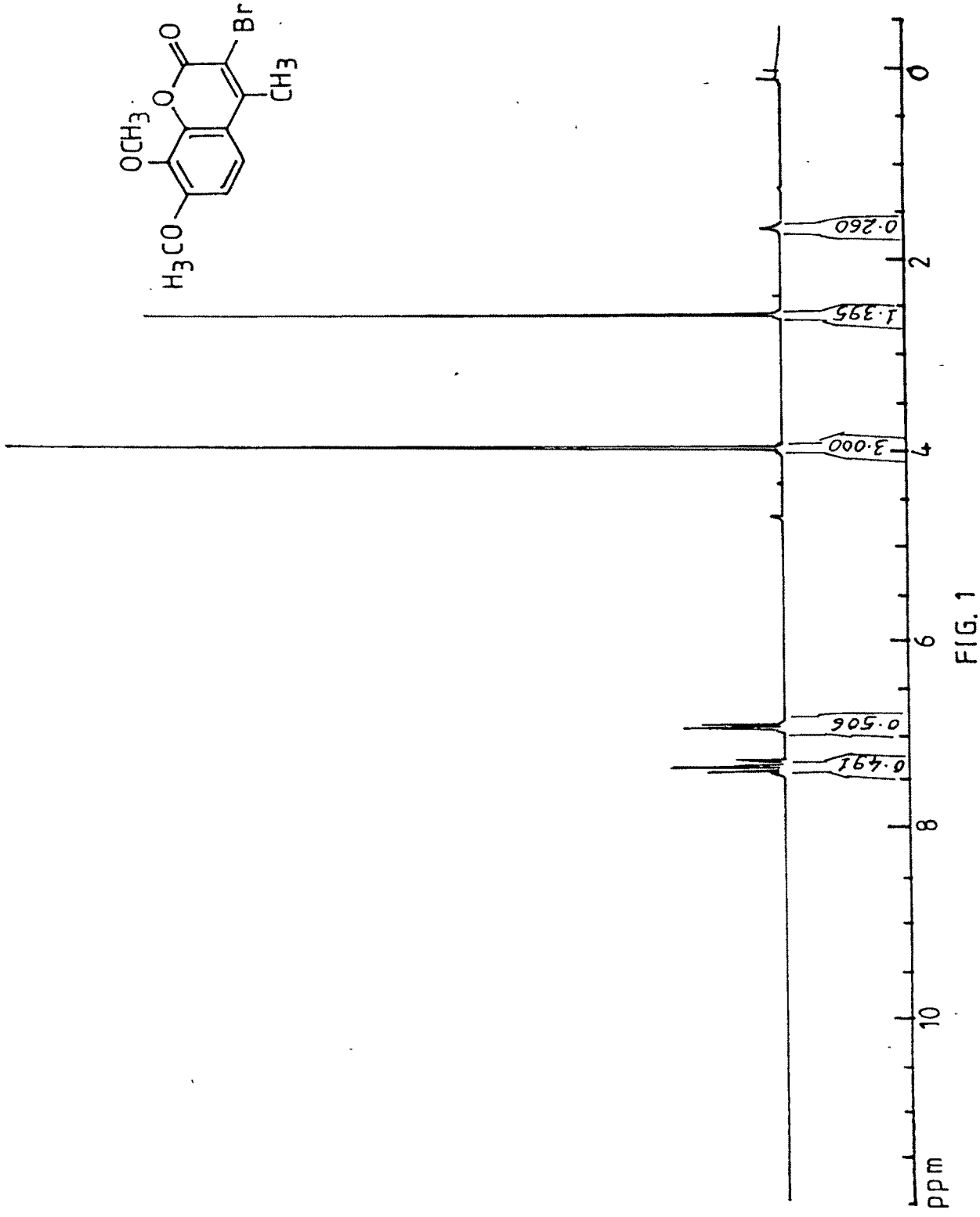


FIG. 1

established by PMR spectra in $CDCl_3$ exhibited a broad singlet at δ 1.55 for three terminal methylene groups of six protons in piperidine ring at C-3; a singlet at δ 2.4 for three protons of methyl group at C-4; another broad singlet at δ 3.0 for two remaining methylene groups of four protons adjacents to nitrogen in the piperidine ring at C-3; one singlet at δ 4.0 for six protons of two methoxy groups at C-7 and C-8 and two doublets in aromatic region, one at δ 6.7 (J=9Hz) for one proton at C-6 and another at δ 7.2 (J = 9Hz) for one proton at C-5 (Fig. 2).

The absence of signal of C-3-H (vinylic proton) confirms that the piperidine moiety got substituted at C-3 position. Also, the singlet at δ 2.4 for methyl group at C-4 indicates that methyl group at C-4 remains intact.

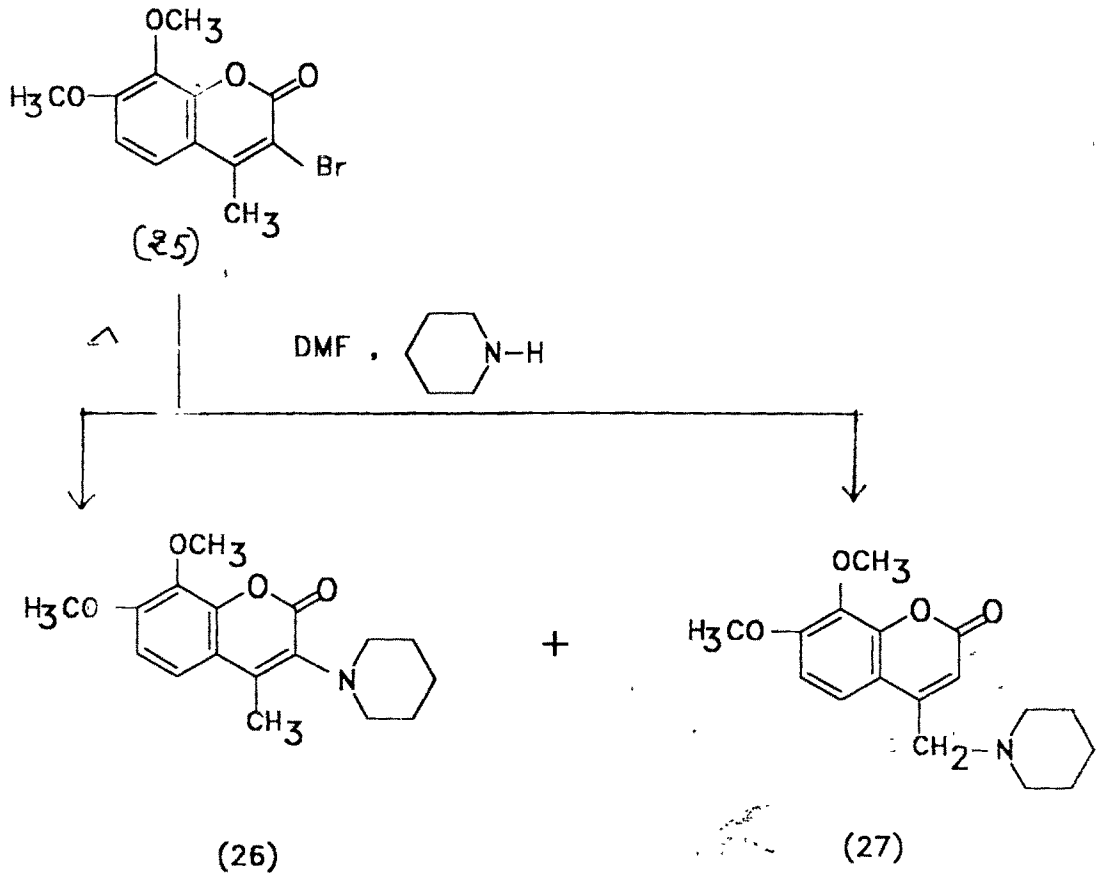
ii) 7,8-Dimethoxy 4-piperidinomethylcoumarin (27)

The second product obtained on condensation of (25) with piperidine in DMF solvent, having lower Rf value, eluted out with mixture of chloroform methanol (97:3 ratio) was assigned 7,8-dimethoxy-4-piperidinomethyl coumarin structure (27).

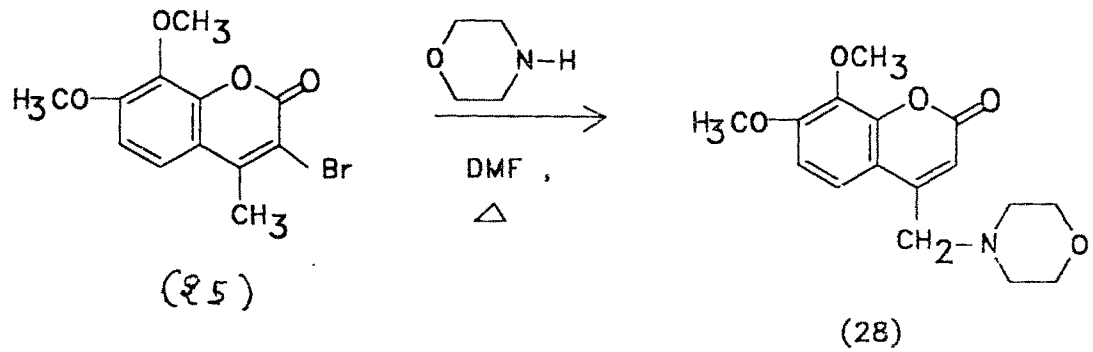
The structure of this compound was established by PMR spectrum. It showed in $CDCl_3$ following signals, a multiplet at δ 1.54 -1.65 for six protons of three terminal methylene groups in piperidine ring; another multiplet at δ 2.42 - 2.46 for four protons of other two methylene groups adjacent to nitrogen in piperidine ring; a singlet at δ 3 5 for two protons of methylene groups attached to C-4; a singlet at δ 4.0 for six protons of two methoxy groups at C-7 and C-8 positions. A singlet at δ 6.4 for C-3-H (vinylic proton) and two doublets at δ 6.8 (J = 9Hz) and 7.5 (J = 9Hz) for C-6 and C-5 protons respectively (Fig. 3)

The presence of vinylic proton signal at δ 6.4 and absence of methyl group signal at δ 2.4 and also presence of signal at δ 3.5 for two protons of methylene group attached to C-4 position indicate that piperidine got substituted in the methyl group at C-4 forming piperidinomethyl group.

SCHEME–3



SCHEME–4



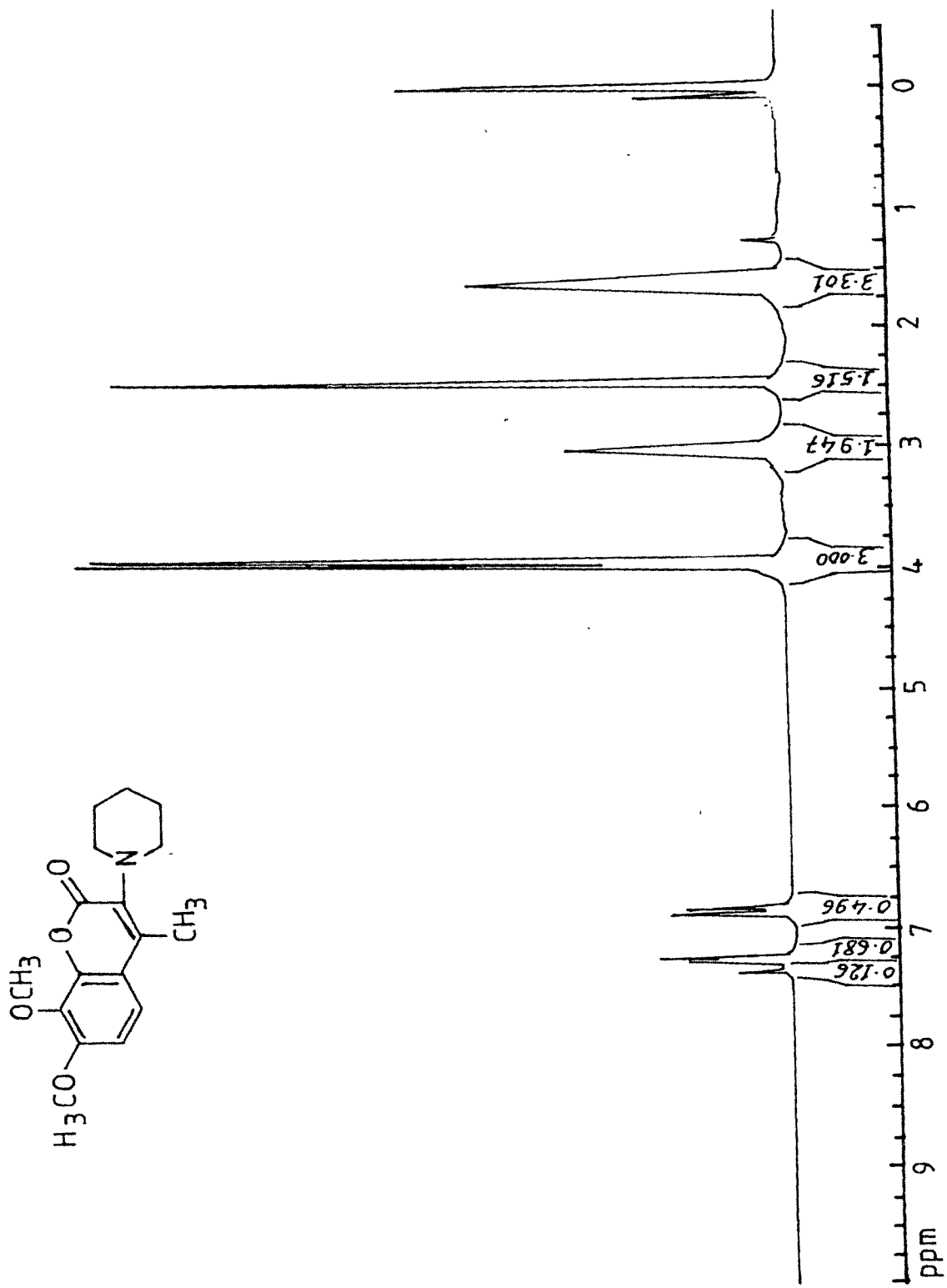

3.301
1.516
1.947
3.000
0.496
0.681
0.126
ppm
0
1
2
3
4
5
6
7
8
9
O
O
N
O
CH3
OCH3
H3CO

FIG. 2.

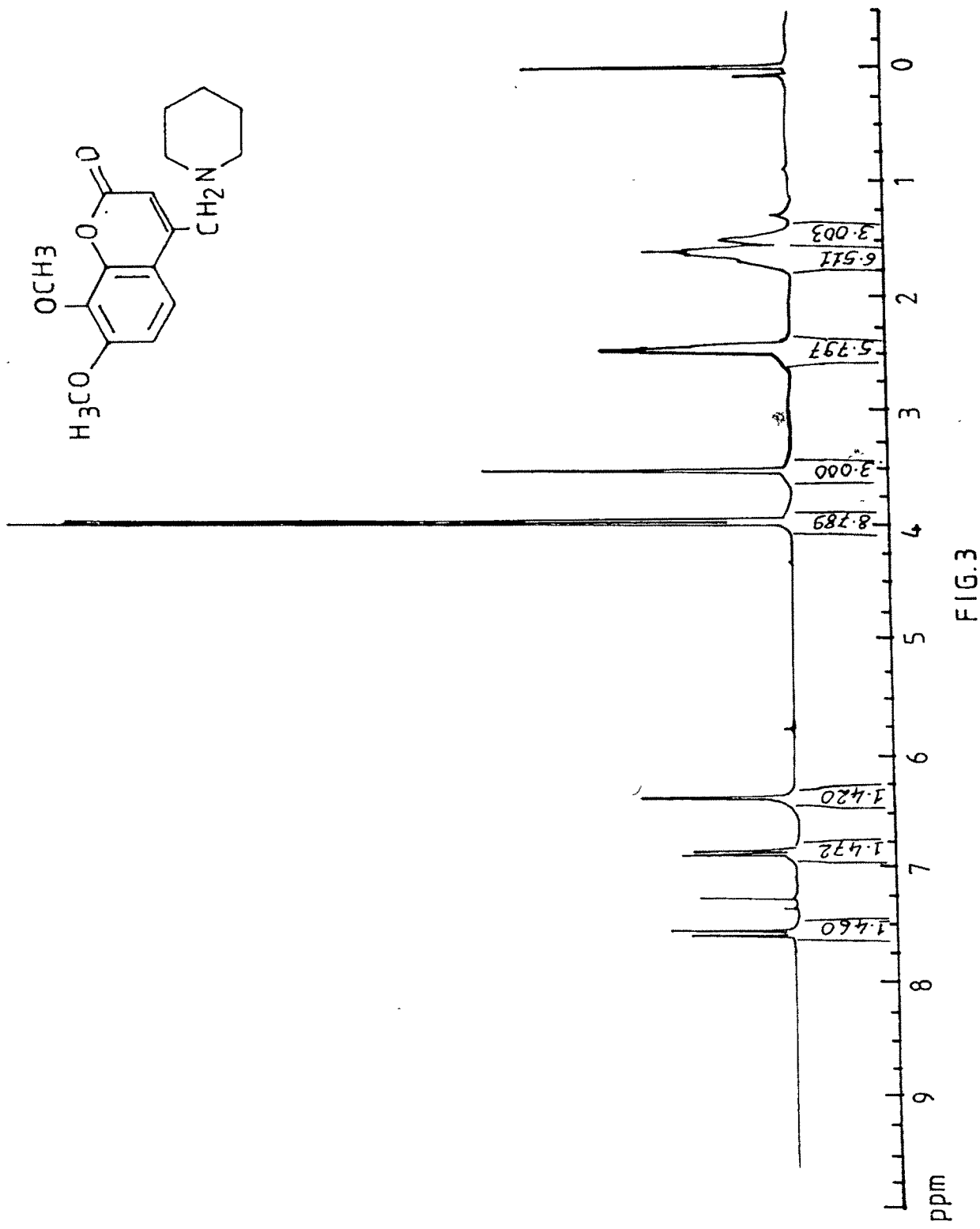

OCH3
H3CO
O
O
CH2N
ppm
0
1
2
3
4
5
6
7
8
9
3.003
6.511
5.397
3.000
8.789
1.420
1.472
1.460

FIG.3

b) Condensation of (25) with morpholine (Scheme - 4)

7,8-Dimethoxy-4-morpholinomethylcoumarin (28)

When 7,8-dimethoxy-3-bromo-4-methylcoumarin was condensed with morpholine in DMF solvent, it furnished a single product to which 7,8-dimethoxy-4-morpholinomethyl coumarin structure was assigned. The structure was confirmed by PMR spectrum In $CDCl_3$ it exhibited following signals; a multiplet at δ 2.55 for four protons of two methylene groups adjacent to nitrogen of morpholine ring; other multiplet at δ 3.7 for four protons of remaining two methylene groups adjacent to oxygen of morpholine ring; a signlet at δ 3.6 for two protons of methylene group attached to C-4 position. A singlet at δ 4.0 for six protons of two methoxy groups at C-7 and C-8, a singlet at δ 6.3 for C-3-H (vinylic proton); two doublets in aromatic region, one at δ 6 8 (J = 9Hz) and other at δ 7.5 (J = 9Hz) for C-6 and C-5 protons respectively (Fig 4).

The absence of signal for methyl protons and appearence of signal for methylene protons at δ 3.6, moreover, singlet for vinylic proton at δ 6.4 for C-3-H strongly indicate that morpholine moiety got substituted in methyl group at C-4 position forming morpholinomethyl group.

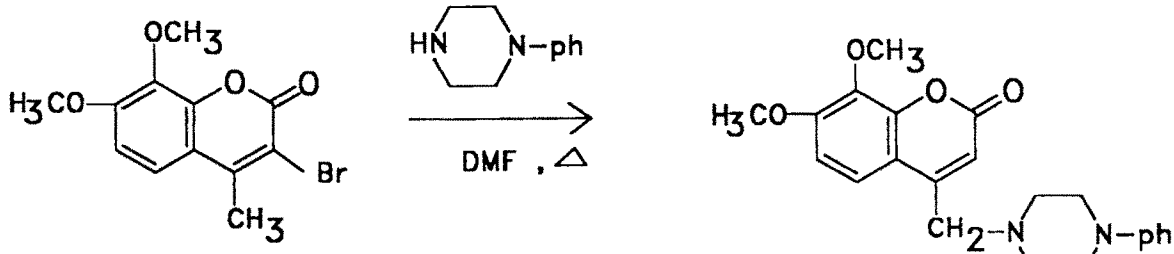
c) Condensation of (25) with N-phenylpiperazine (Scheme - 5)

7,8-Dimethoxy-4-(N-phenyl)-piperazinomethylcoumarin (29)

When (25) was condensed with N-phenylpiperazine, it also furnished a single product (29). The IR (KBr) spectra of (29) exhibited bands at 2900-2810 cm^{-1} for C-H of alkyl, 1710 cm^{-1} for lactonic carbonyl of coumarin ring system, 1600 cm^{-1} for aromatic C=C stretching, 1390-1175 cm^{-1} for C-N and 1285 and 1090 cm^{-1} for C-O-C linkage (Fig. 5).

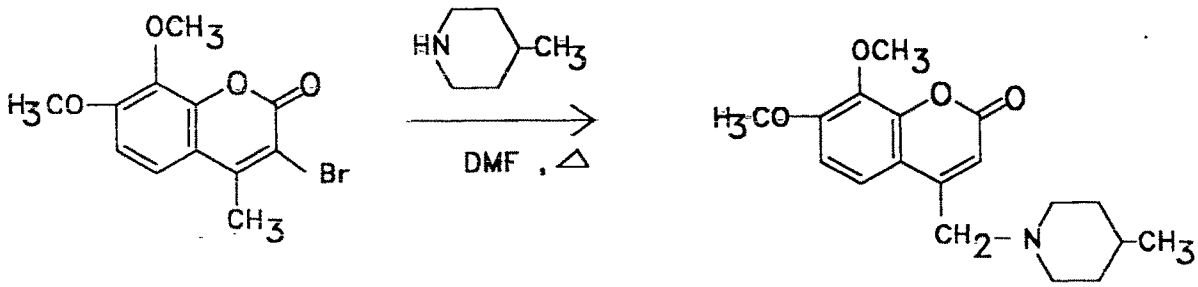
The PMR spectrum of this showed following signals in $CDCl_3$, a multiplet at δ 2 7 for four methylene protons of two methylene groups attached to the nitrogen which is attached to methylene at C-4; another multiplet at δ 3.2 for four protons of other two methylene groups of N-phenypiperazine. A singlet at δ 3.85 for two protons of methylene group attached to C-4; a singlet at δ 4.0 for six protons of two methoxy groups at C-7 and C-8; a singlet at δ 6.4 for one proton at C-3; a multiplet at δ 6 8 for aromatic protons of N-phenylpiperazine component; a multiplet at δ 7 2 - 7 3 for

SCHEME–5



(25) (29)

SCHEME–6



(25) (30)

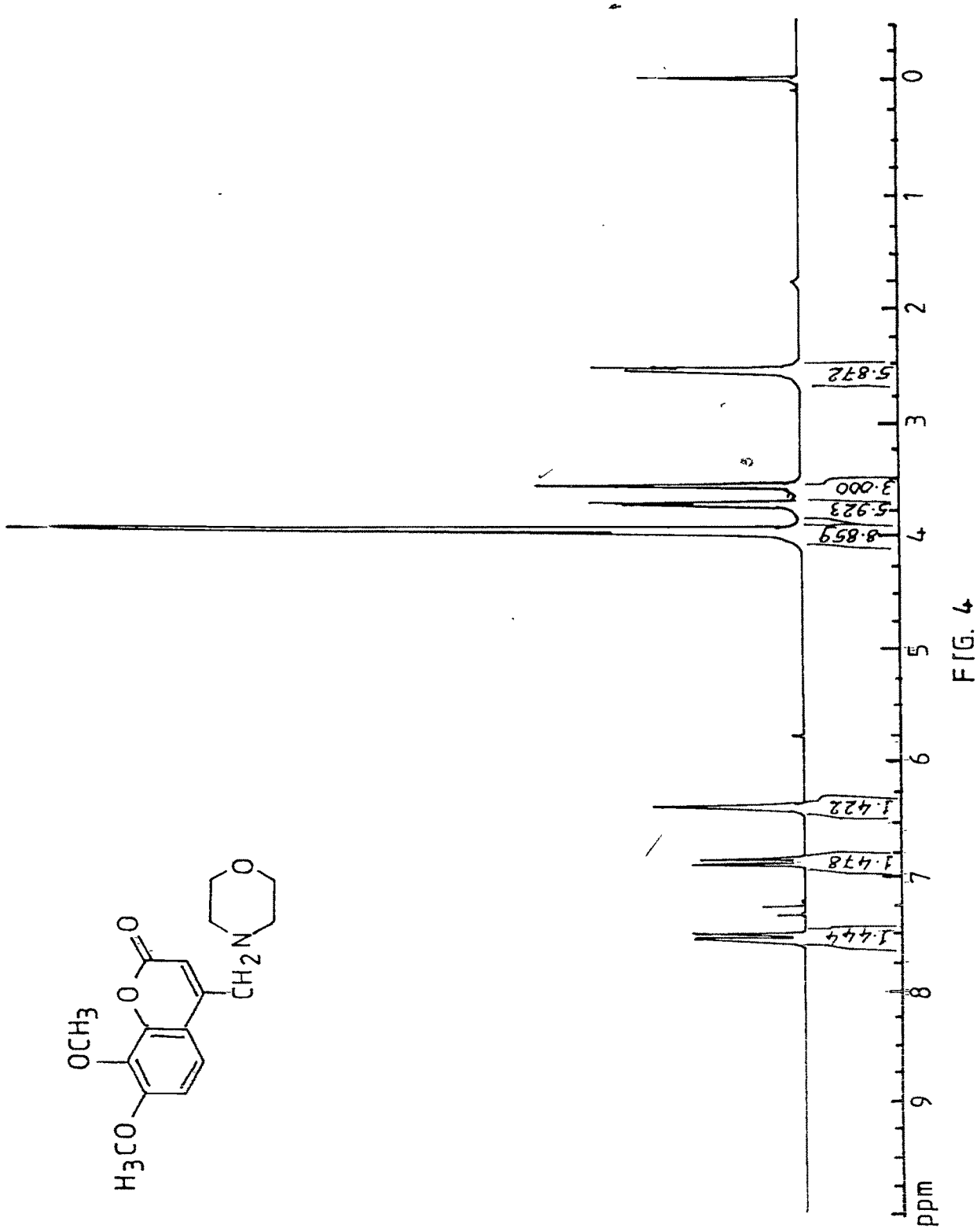

5.872
3.000
5.923
8.859
1.422
1.478
1.446
ppm
0
1
2
3
4
5
6
7
8
9
O
O
O
CH2
N
OCH3
H3CO

FIG. 4

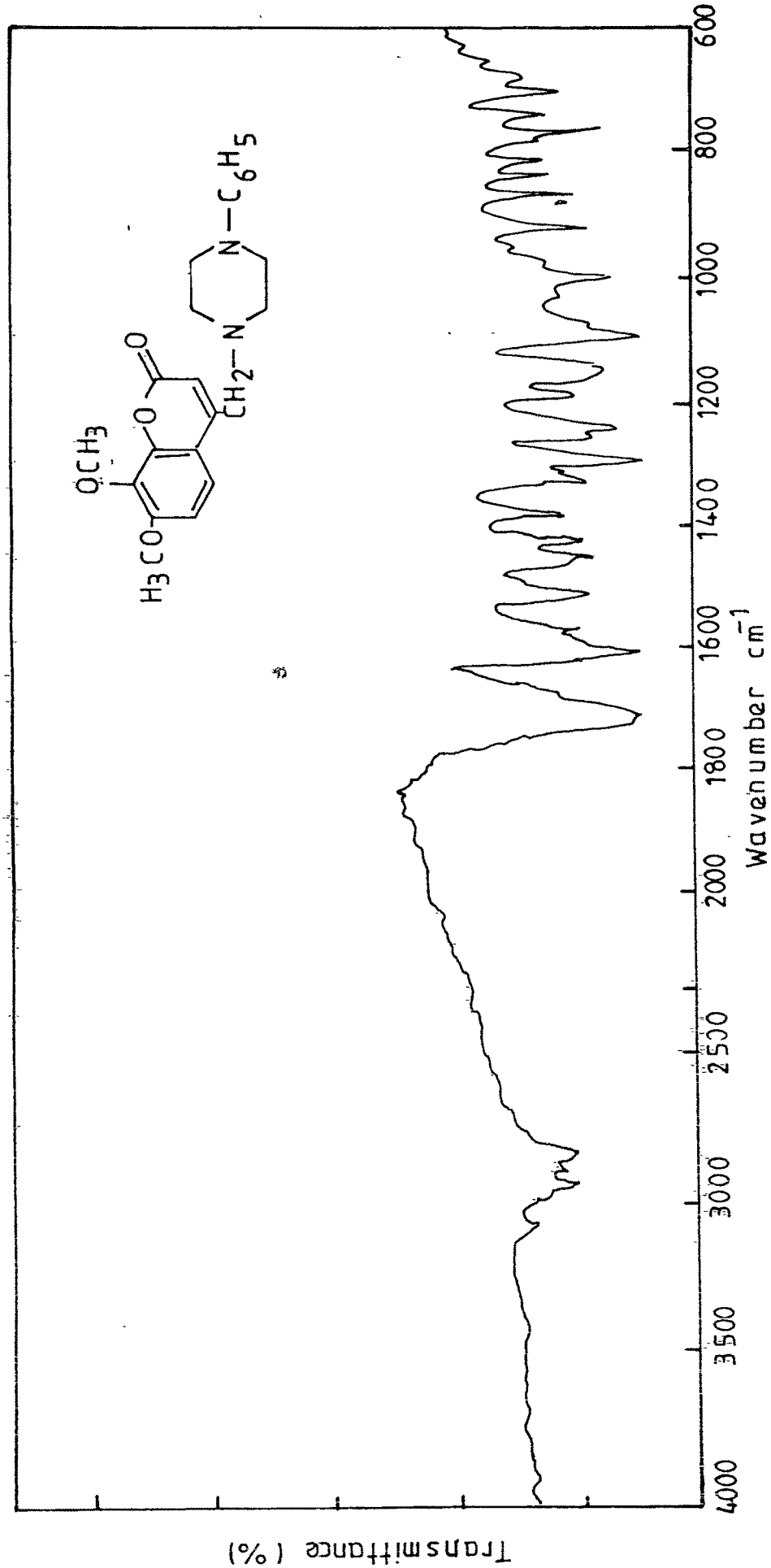

Transmittance (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm⁻¹
OCH3
H3CO
O
O
CH2—N
N—C6H5

FIG.5

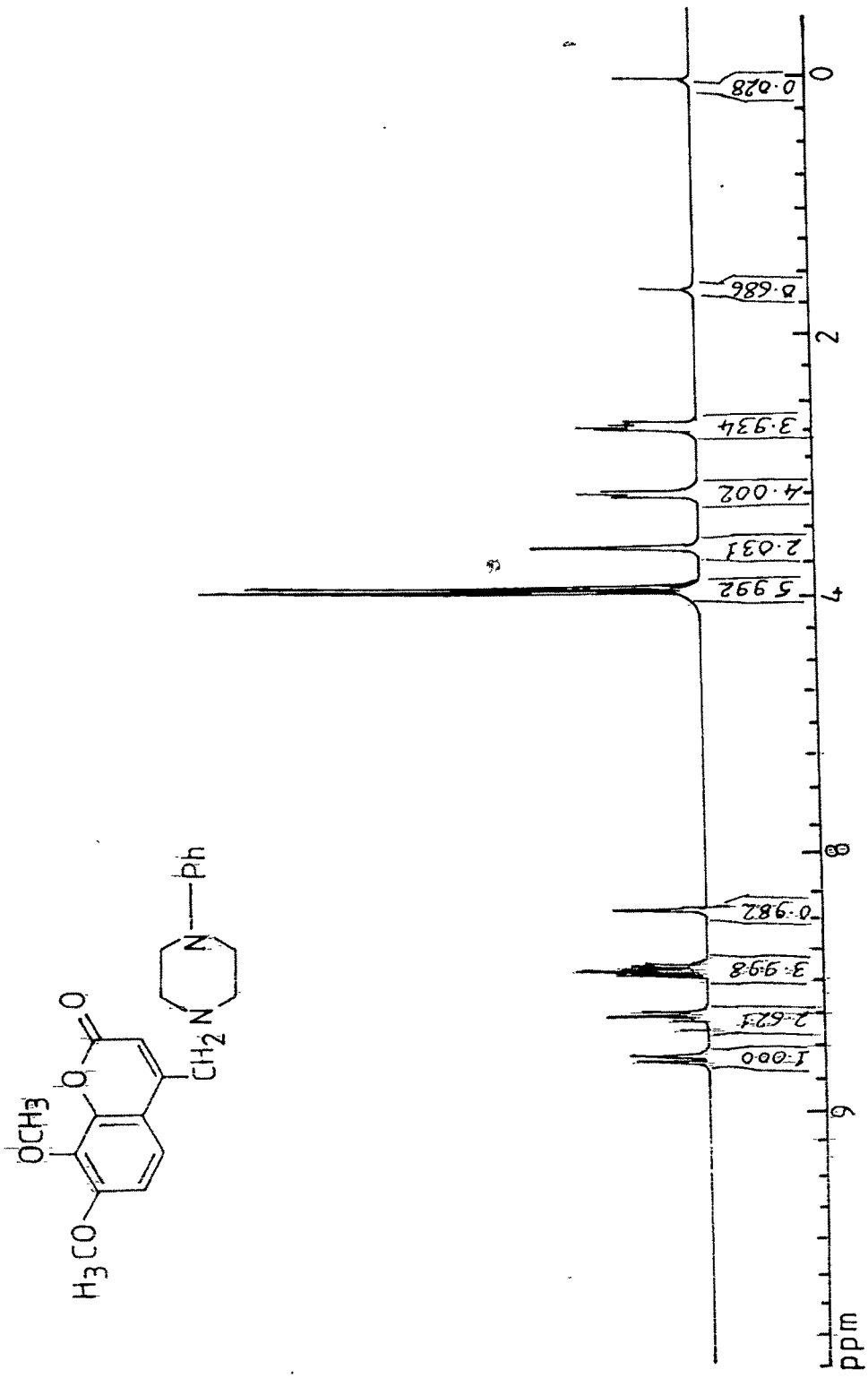

0.628
8.686
3.934
4.002
2.031
5.992
0.982
3.998
2.627
1.000
0
2
4
6
8
ppm
Ph
N
N
CH2
O
O
OCH3
H3CO

FIG.6

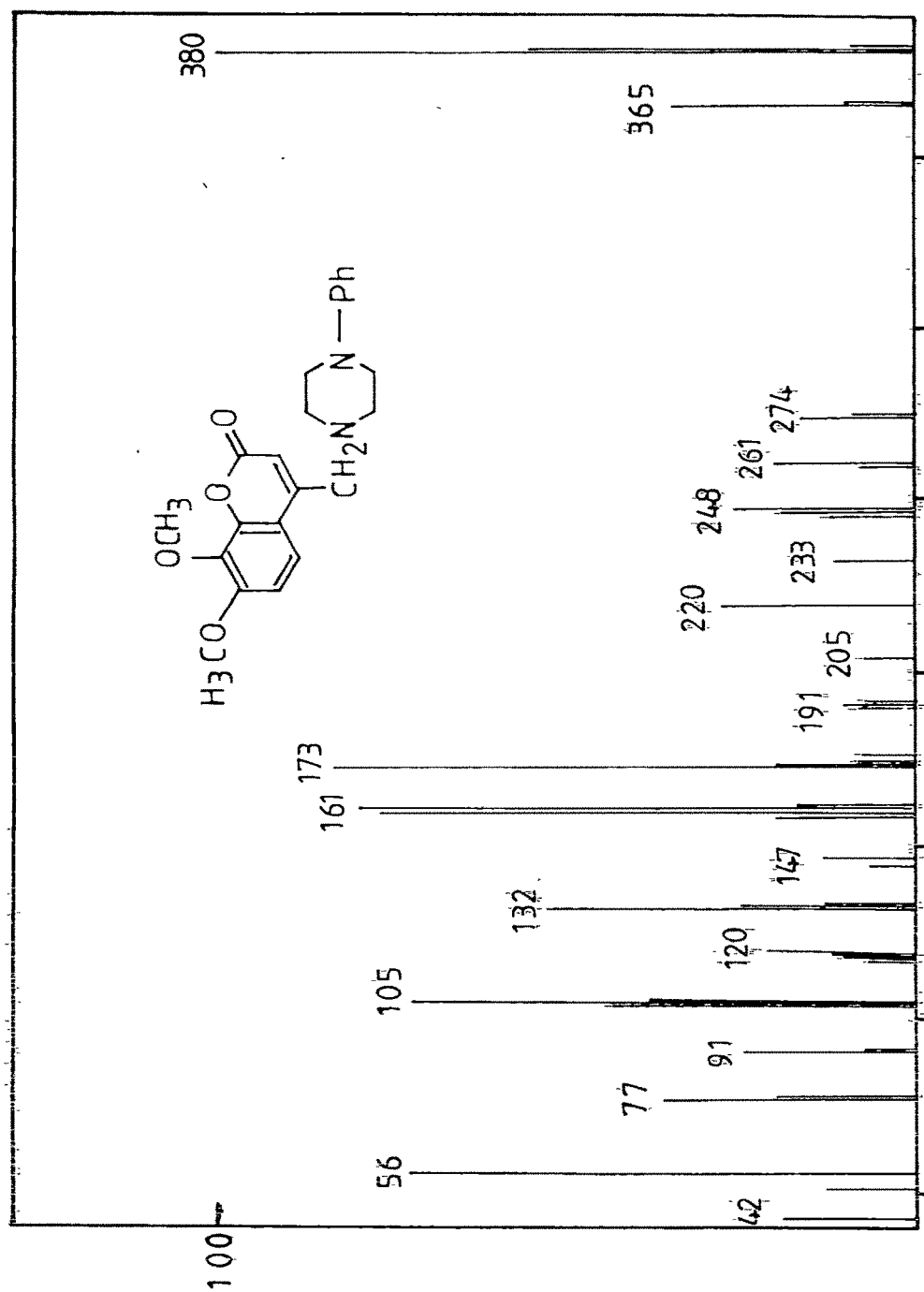

380
365
350
300
250
200
150
100
50
100
56
77
91
105
120
132
147
161
173
191
205
220
233
248
261
274
OCH3
O
O
CH2N
N
Ph
H3CO

FIG. 7

aromatic protons of N-phenylpiperazine merged with a doublet of one proton at C-6 and a doublet at δ 7.55 for one proton at C-5 (Fig. 6).

The Mass spectra of this compound exhibited prominent peak at m/z 380 (M+ ion and it is also a base peak, 100%) (Fig. 7).

d) Condensation of (25) with 4-methylpiperidine (Scheme - 6)

Similarly 4-methylpiperidine was condensed with (25) which also gave a single product to which 7,8-dimethoxy-4-(4'-methyl) piperidinomethylcoumarin (30) structure has been assigned.

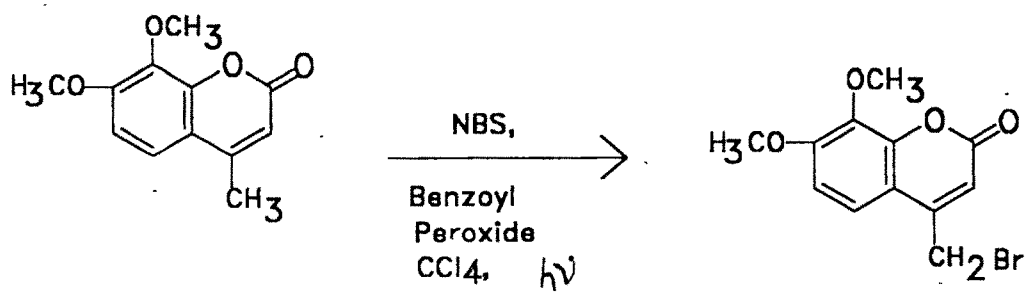
The second approach was applied to prepare following aminomethyl derivatives from bromomethylcoumarin.

7,8-Dimethoxy-4-bromomethylcoumarin (31) (Scheme - 7)

7,8-Dimethoxy-4-methylcoumarin (24) was subjected[16] to bromination with N-bromosucinimide in carbontetrachloride solvent using benzoylperoxide as initiator under 200 w.bulb which furnished the product, to which 7,8-dimethoxy-4-bromomethylcoumarin (31) structure was assigned. It was confirmed by its PMR spectrum in $CDCl_3$, which showed following signals; a singlet at δ 4.0 for six protons of two methoxy groups at C-7 and C-8; a singlet at δ 4.4 for two protons of methylene group attached to C-4; another singlet at δ 6.25 for one proton at C-3 (vinylic proton) and two doublets at δ 6.9 and δ 7.35 for C-6 and C-5 protons respectively (Fig. 8).

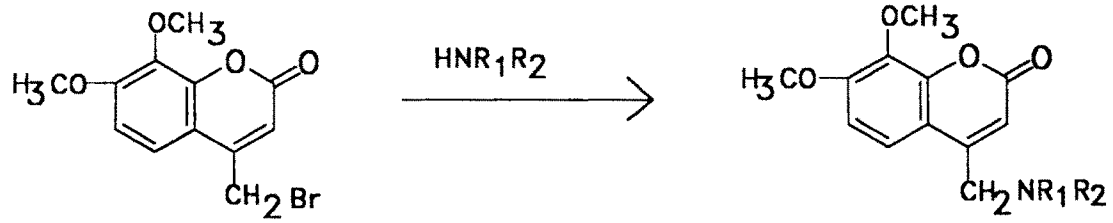
The absence of signal for methyl group at C-4 and instead of this a new signal for methylene group at δ 4.4 as well as presence of vinylic proton at C-3 indicates that bromine has replaced one proton of CH_3 group at C-4 and formed bromomethyl i.e. CH_2Br group.

SCHEME–7



(31)

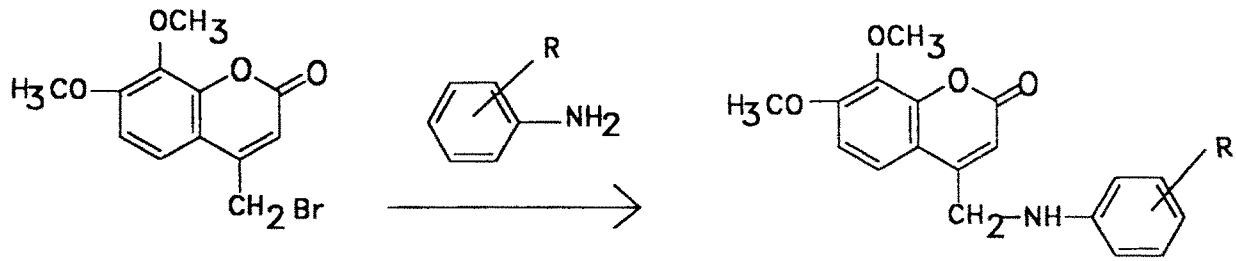
SCHEME–8



(31)

(27),(28),(29),(30)

SCHEME–9



(31)

(32)

Table–1

(1 to 11)

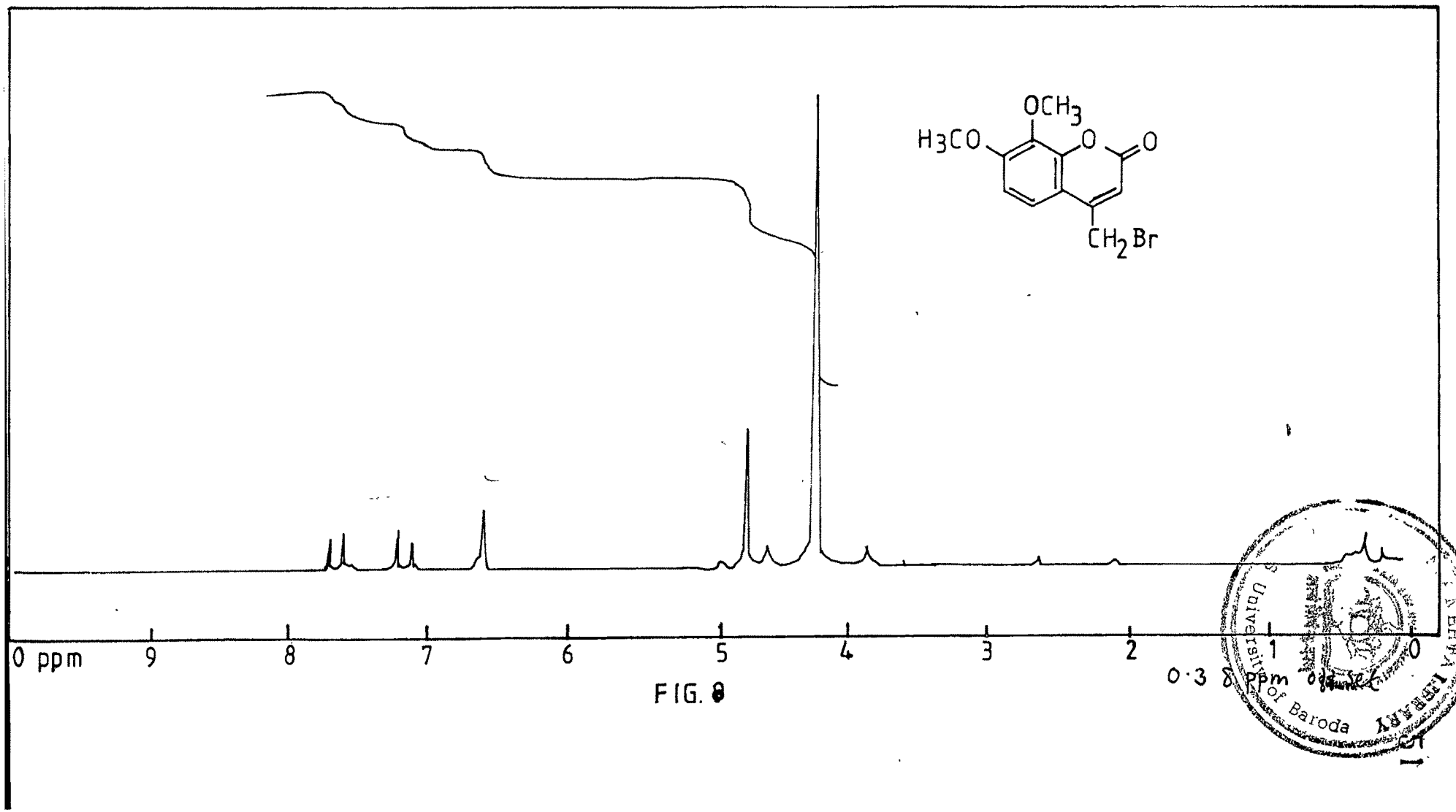


FIG. 8

Condensation of 7,8-dimethoxy-4-bromomethylcoumarin (31) with secondary amines (Scheme - 8)

When (31) was condensed with piperidine, morpholine, N-phenylpiperazine and 4-methylpiperidine, it gave 7,8-dimethoxy-4-piperidinomethylcoumarin, 7,8-dimethoxy-4-morpholinomethylcoumarin, 7,8-dimethoxy-4-(N-phenyl) piperazino-methylcoumarin and 7,8-dimethoxy-4-(4'-methyl)piperidinomethylcoumarin respectively. These products were found identical with (27), (28), (29) and (30) respectively. Identity was established on the basis of mixed melting points, PMR and IR spectral data.

Condensation of 7,8-dimethoxy-4-bromomethylcoumarin (31) with N-phenylpiperazine (29)

A mixture of (31) and N-phenylpiperazine was refluxed in alcohol for 3-4 hrs The excess of solvent was removed by distillation and product was obtained on cooling It was purified by crystallisation.

The IR (KBr) spectra of this compound exhibited bands at 2900 - 2810 cm^{-1} for C-H of alkyl, 1710 cm^{-1} for lactonic carbonyl of coumarin ring, 1600 cm^{-1} for aromatic C=C, 1390-1175 cm^{-1} for C-N and 1285, 1090 cm^{-1} for C-O-C linkage (Fig 9)

The PMR spectrum of this exhibited following signals in $CDCl_3$; a multiplet at δ 2 6 for four protons of two methylene groups attached to the nitrogen which is attached to the CH_2 group at C-4; a multiplet at δ 3.2 for four protons of rest of two methylene groups of N-phenylpiperazine moiety; a singlet at δ 3.66 for two protons of methylene groups attached to C-4; a singlet at δ 3.9 for six protons of two methoxy groups at C-7 and C-8. In aromatic region a singlet at δ 6.4 for C-3 proton; a multiplet between δ 6.7-7 for aromatic protons, also a multiplet between δ 7.1-7.3 for rest of the aromatic protons of N-phenylpiperazine component merged with a doublet of C-6 proton and a doublet at δ 7.6 for C-5 proton (Fig. 10).

The above result indicates that condensation of 7,8-dimethoxy-3-bromo-4-methylcoumarin (25) with secondary amines and condensation of 7,8-dimethoxy-4-bromomethyl coumarin (31) with secondary amines gave the same products.

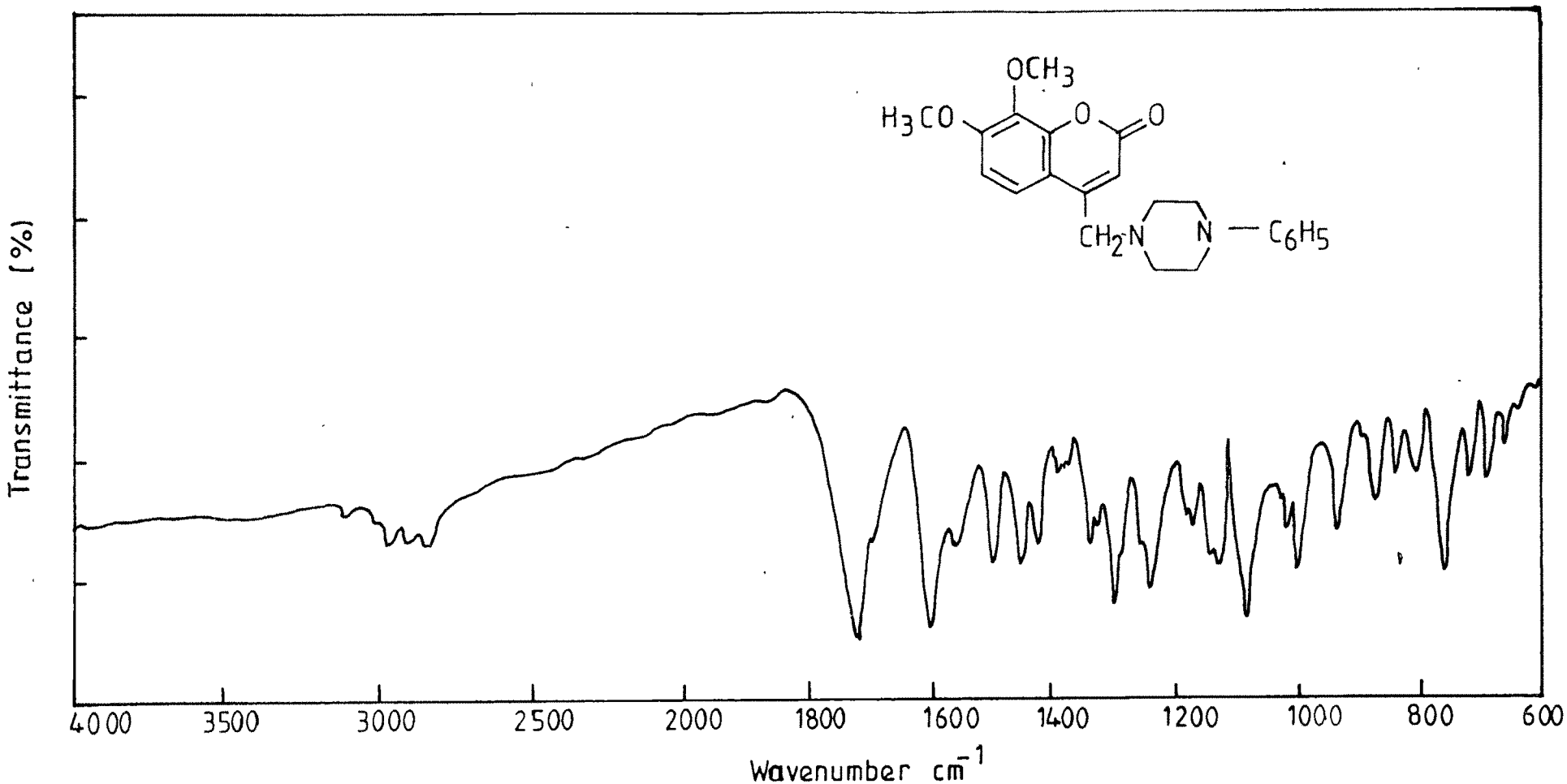
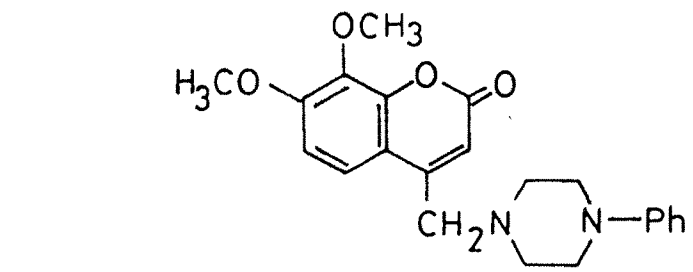

OCH3
H3CO
O
O
CH2N
N
C6H5
Transmittance (%)
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm-1

FIG. 9



VIA Bromomethyl

FIG. 10

Condensation of 7,8-dimethoxy-4-bromomethylcoumarin (31) with primary aromatic amines (Scheme - 9)

7,8-Dimethoxy-4-substituted anilinomethylcoumarin

The condensation of (31) with various primary aromatic amines in alcohol furnished the product to which 7,8-dimethoxy-4-substitutedanilinomethylcoumarin was assigned. Physical data and solvent of crystallisation has been given in Table - 1 (Experimental section). The structures of the compounds were established on the basis of IR, PMR and mass spectral data.

The IR (KBr) spectra of aminomethyl compounds from primary aromatic amines (compound No.1-11, Table -1) exhibited a weak and sharp band at 3450-3420 cm^{-1} assignable to associated NH group. These compounds exhibited bands at 2950-2880 cm^{-1} for C-H of alkyl, at 1730-1705 cm^{-1} for lactonic C=O of coumarin ring system, at 1600-1585 cm^{-1} for C=C stretch within aromatic ring, at 1390-1175 cm^{-1} for C-N and 1280, 1090 cm^{-1} for C-O-C linkage.

7,8-Dimethoxy-4-(2'-methy) anilinomethylcoumarin (32, Table - 1, 1)

7,8-Dimethoxy-4-bromomethylcoumarin (31) was condensed with o-toluidine, which gave the above product. Its structure has been characterised on the basis of IR, PMR and mass spectral data.

The IR spectrum (KBr) showed bands at 3400, 2950, 1700, 1610, 1370 - 1175, 1280 and 1100 cm^{-1} (Fig. 11).

The PMR spectrum in ($CDCl_3$ + DMSO) exhibited following signals; a singlet at δ 2.24 for three protons of methyl group of o-toluidine moiety; a singlet at δ 3 98 for six protons of two methoxy groups at C-7 and C-8; a broad singlet at δ 4.5 for two methylene protons attached to C-4; a singlet at δ 6.29 for one proton at C-3; a multiplet in region of δ 6.38-6.64 for aromatic protons of o-toluidine function; a multiplet at δ 7.05 for aromatic protons with merged a doublet of C-6 proton; a doublet at δ 7.44 for one proton at C-5 and a singlet at δ 7.56 for NH-proton (Fig 12).

The Mass spectra of the above compound exhibited following prominent peaks at m/z; 325 (100%, Base peak and M^+ ion), 120 (50%), 177 (48%) (Fig. 13).

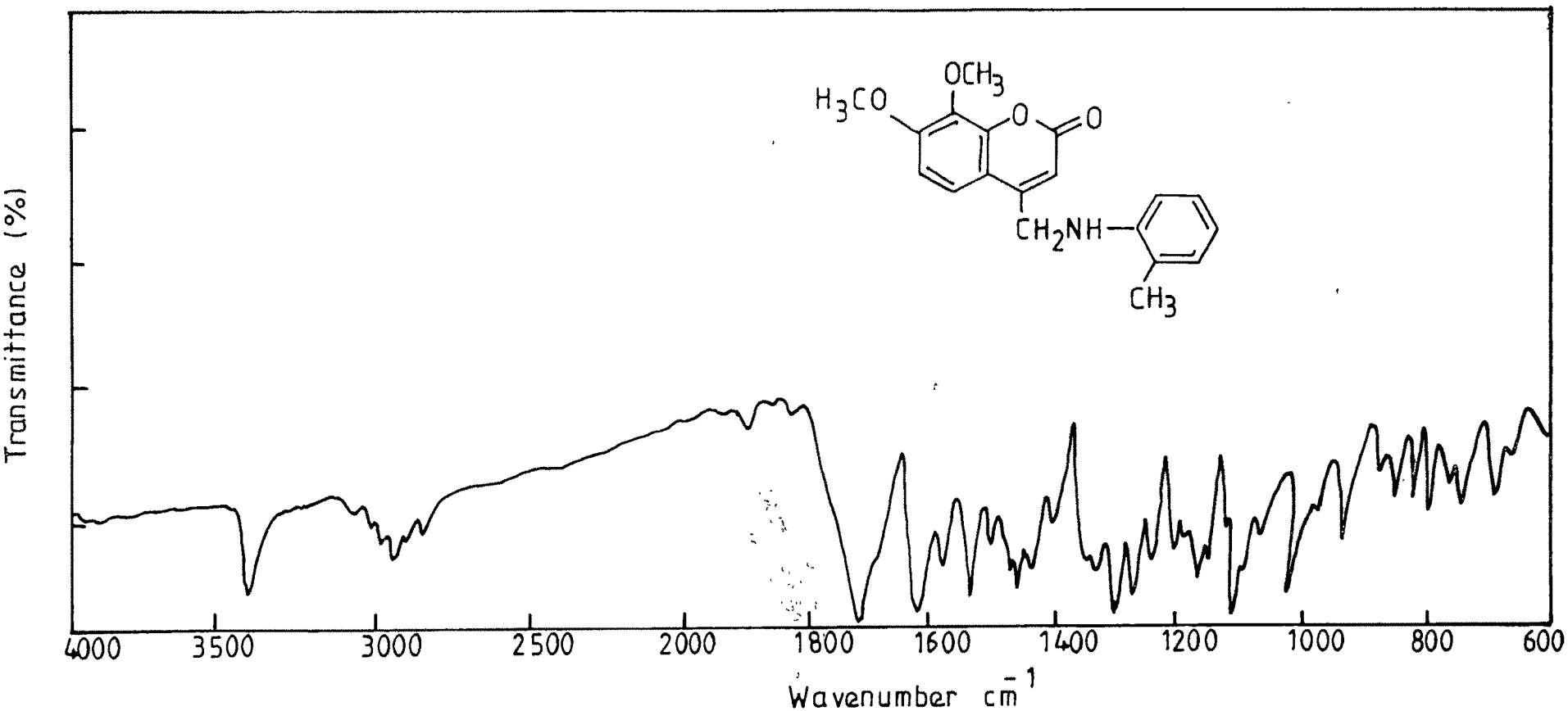
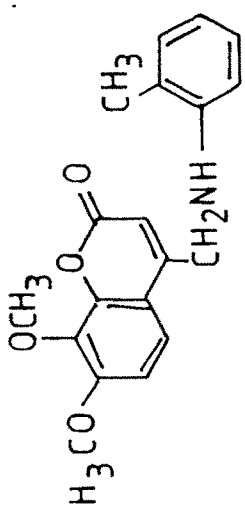

Transmittance (%)
H_3CO
OCH_3
O
O
CH_2NH
CH_3
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
Wavenumber cm^{-1}

FIG. 11


CH3
O
CH2NH
OCH3
O
H3CO

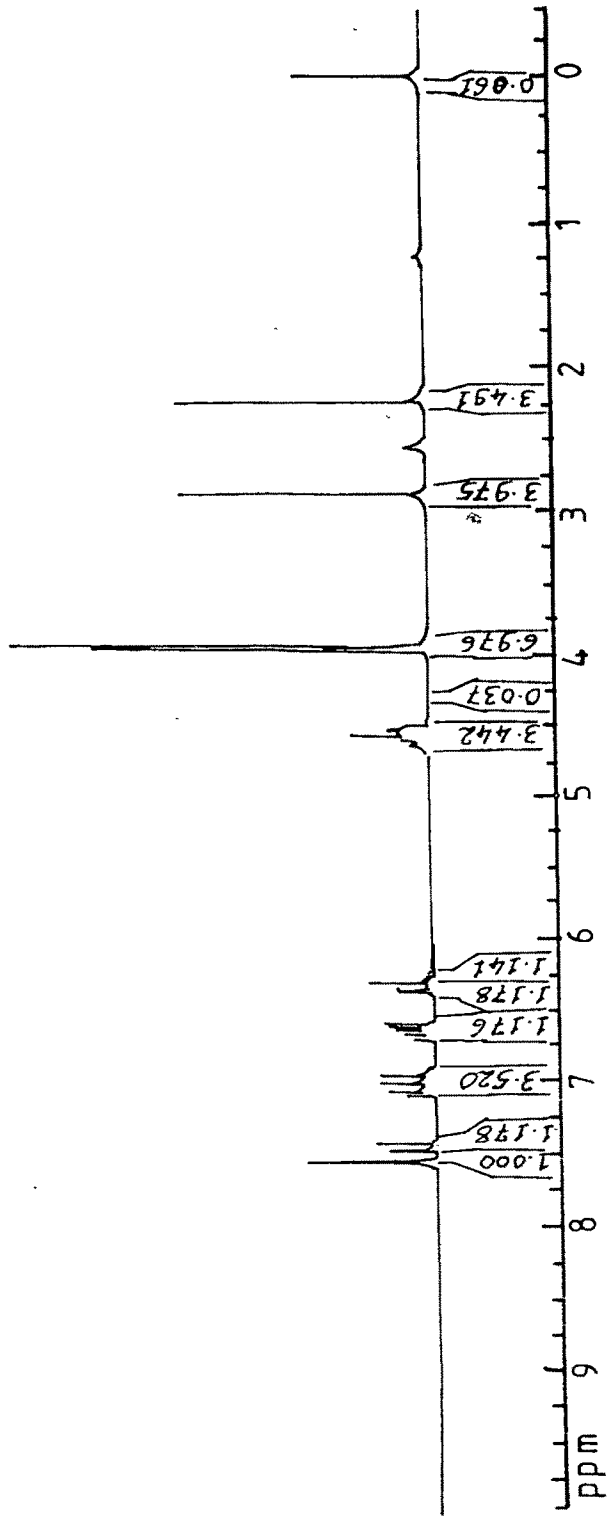

0.061
3.491
3.975
6.936
0.037
3.442
1.141
1.178
1.176
3.520
1.178
1.000
0
1
2
3
4
5
6
7
8
9
ppm

FIG. 12

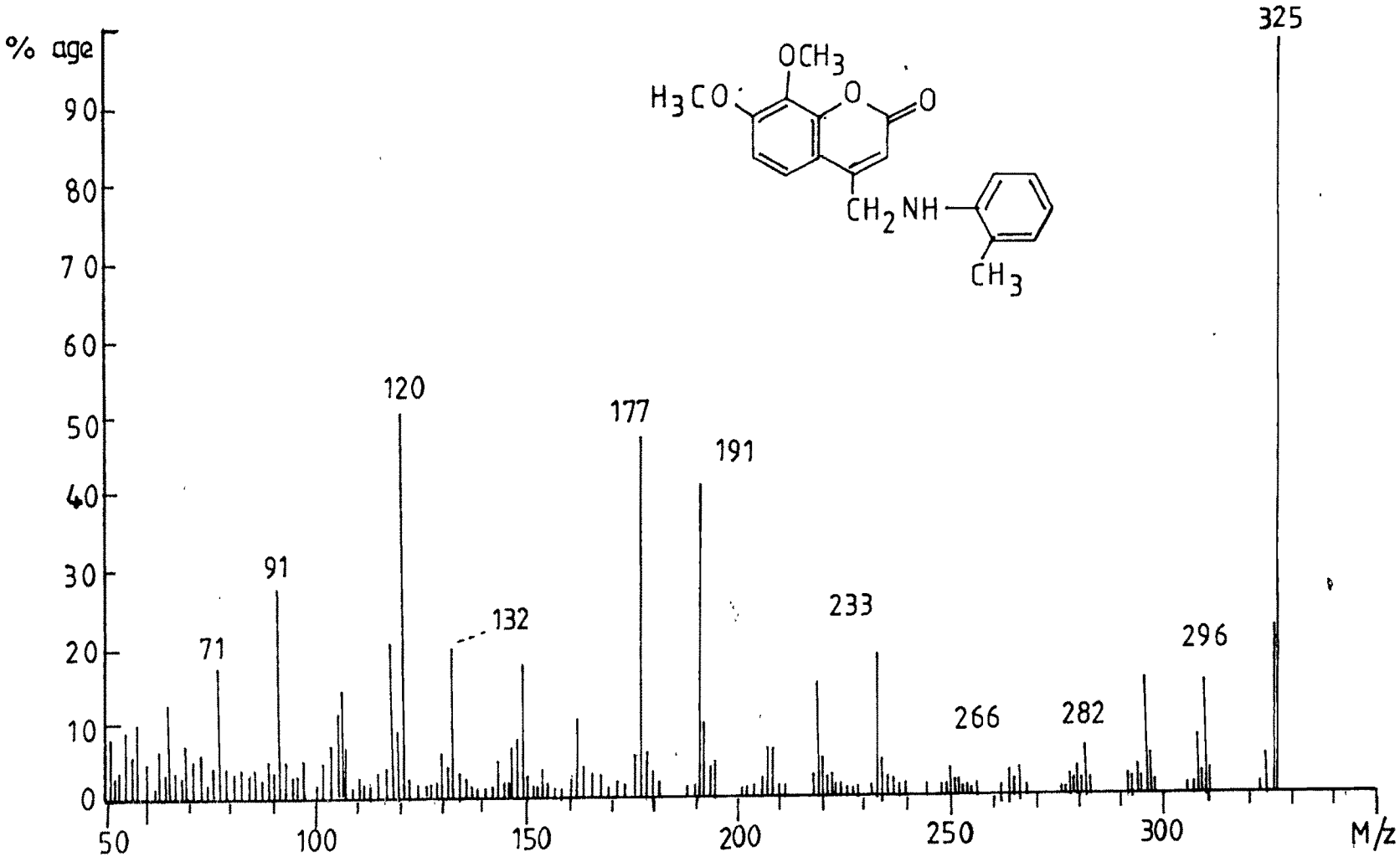

% age
90
80
70
60
50
40
30
20
10
0
50
100
150
200
250
300
M/z
325
120
177
191
91
71
132
233
296
266
282
OCH3
H3CO
O
O
CH2 NH
CH3

FIG.13

Antibacterial Activity

All the above compounds synthesised during present work were screened for their antibacterial activity using cup-plate[23] method against E. coli and S. aureus at 100 and 500 ppm concentrations. The details are mentioned in chapter V.

Experimental

All the m.p.s were uncorrected. PMR spectra were recorded on Perkin-Elmer R-32 spectrometer at 90 MHz and on dpx 200 spectrometer at 200 MHz using Tetramethyl silane as internal standard and chemical shifts were recorded in δ ppm.

7,8-Dihydroxy-4-methylcoumarin[20] (23)

Pyragallol (1.3 g), ethylacetoacetate (1.3 ml) and concentrated sulfuric acid (1.3 ml) were mixed and kept overnight. Then reaction mixture was poured into ice-water. Separated solid was filtered and crystallised from dilute alcohol. M.p. 235, Yield 40%.

7,8-Dimethoxy-4-methylcoumarin[21] (24)

7,8-Dihydroxy-4-methylcoumarin (1.9 g) was dissolved in 100 ml dry acetone. To this, potassiumcarbonate (anhydrous, 5.0g) followed by dimethylsulfate (2.4 ml) was added. This was refluxed for 7-8 hrs. Then it was decomposed by cold water. The solid product, separated out was washed with dilute NaOH to remove unreacted (23). It was crystallised from dilute acetic acid. M.p 132°C, Yield 30%.

7,8-Dimethoxy-3-bromo-4-methylcoumarin[22] (25)

7,8-Dimethoxy-4-methylcoumarin (2.2g, 0.01 mol) was dissolved in 10-15 ml acetic acid, to which solution of bromine (0.55 ml, 0.01 mol) in 5 ml, acetic acid was added. This mixture was stirred for 30 minutes. Then it was added to ice-water. Solid separated was filtered washed with water and crystallised from dilute alcohol M.p. 165-66°C, Yield 40%.

7,8-Dimethoxy-3-piperidinyl-4-methylcoumarin (26) and 7,8-dimethoxy-4-piperidinomethyl coumarin (27)

A mixture of 7,8-dimethoxy-3-bromo-4-methylcoumarin (1.2g, 0.004 mol) and piperidine (1.4 ml, 0.016 mol) in N,N-dimethylformamide (10 ml) was refluxed for 30 minutes on the sand bath. Then it was cooled and poured to ice-water (150 ml). The solid separated was filtered and dried and subjected to column chromatography (using silica). First product (26) eluted in the benzene fraction. Then it was crystallised from mixture of benzene and petroleum ether. M.p. 165°C, Yield 30%.

Analysis	:	Found	:	C, 67.11,	H, 7.42; N, 4.28%
$C_{17}H_{21}O_4N$	:	Required	:	C, 67.32;	H, 6.93; N, 4.62%

The second product (27) was obtained on eluting the above column with mixture of chloroform and methanol (97:3 ratio) and crystallised from mixture of benzene and petroleum ether. M.p. 87-89°C, Yield 45%.

Analysis	:	Found	:	C, 67.10;	H, 7.33; N, 4.46%
$C_{17}H_{21}O_4N$	:	Required	:	C, 67.32;	H, 6.93; N, 4.62%

7,8-Dimethoxy-4-morpholinomethylcoumarin (28)

A mixture of (25) (1.2g, 0.004 mol), morpholine (1.4ml, 0.016 mol) in 10 ml of DMF was refluxed for 30 minutes, cooled, dried and subjected to column chromatography, only one product was obtained, on eluting the column with mixture of chloroform and methanol (97:3 ratio). Then it was crystallised from mixture of benzene and petroleum ether. M.p. 142°C, Yield 40%.

Analysis	:	Found	:	C, 63.21	H, 6.31; N, 4.38%
$C_{16}H_{19}O_5N$	:	Required	:	C, 62.95;	H, 6.22; N, 4.59%

7,8-Dimethoxy-4-(N-phenyl) piperazinomethylcoumarin (29)

A mixture of (25) (1.2g, 0.004mol), N-phenylpiperazine (2.6 ml, 0.016 mol) in 10 ml DMF was refluxed for 30 minutes. It was cooled and poured to 100 ml ice-cold water filtered dried and subjected to column chromatography. The only one product was isolated while eluting with benzene. It was crystallised from mixture of benzene and petroleum ether. M.p. 180°C, Yield 60%.

Analysis	:	Found	:	C, 69.45;	H, 6.64; N, 7.77%
$C_{22}H_{24}O_4N_2$	:	Required	:	C, 69.47;	H, 6.31; N, 7 36%

7,8-Dimethoxy-4-(4'-methyl)piperidinomethylcoumarin (30)

(25) (1.2 g, 0.004 mol) was treated with 4-methylpiperidine (1.6ml, 0.016mol) in 10 ml DMF. This was refluxed for 30 minutes. The product was worked up as usual. It was subjected to column chromatography and on eluting with benzene,

product (30) was obtained. Then it was crystallised from mixture of benzene and petroleum ether. M.p. 104°C, Yield 30%.

Analysis	:	Found	:	C, 68.11;	H, 7.42; N, 4.63%
$C_{18}H_{23}O_4N$	:	Required	:	C, 68.43;	H, 7.25; N, 4.41%

7,8-Dimethoxy-4-bromomethylcoumarin (31)

7,8-Dimethoxy-4-methylcoumarin. (0.01 mol) was dissolved in 100 ml of carbontetrachloride to which N-bromosuccinimide (0.01 mol) was added, followed by a pinch of benzoyl peroxide. It was refluxed under 200 w bulb for 16 hrs. Then it was cooled to room temperature and it was filtered and then excess of solvent was distilled and it was again cooled. The separated solid was filtered and subjected to column chromatography. On eluting with benzene, this product was obtained. It was crystallised from mixture of benzene and petroleum ether. M.p. 118°C, Yield 55%.

Analysis	:	Found	:	C, 48.42;	H, 3.94%
$C_{12}H_{11}O_4Br$	:	Required	:	C, 48.16;	H, 3.67%

7,8-Dimethoxy-4-(N-phenyl)piperazinomethylcoumarin (29)

A mixture of (31) (1.2g, 0.004mol) and N-phenylpiperazine (2.6ml, 0.016 mol) was refluxed in 30-35 ml of alcohol for 3-4 hrs. The excess of solvent was removed by distillation, and separated product was crystallised from mixture of benzene and petroleum ether M.p. 180°C, Yield 60%. Other secondary amines were condensed in similar way.

7,8-Dimethoxy-4-(2'-methyl)-anilinomethyl-coumarin (32, Table - 1, 1)

A mixture of (31) (1.2g, 0.004 mol) and o-toluidine (1.7ml, 0.016 mol) was refluxed in 30-35 ml of alcohol. The excess of solvent was distilled and then it was cooled. The separated product was crystillised from DMF. M.p. 208°C, Yield 70%.

Analysis	:	Found	:	C, 69.89;	H, 6.13; N, 4.11%
$C_{19}H_{19}O_4N$	:	Required	:	C, 70.15;	H, 5.84; N, 4.30%

Table - 1. Analytical and Physical Data of Compounds (32)

Sr. No.	R	M.P.* in °C	% Yield	Molecular Formula	Elemental Analysis Found / Required		
					%C	%H	%N
1	2-CH_3	208^{D+A}	70	$C_{19}H_{19}O_4N$	69.89 70.15	6.13 5.84	4.11 4.30
2	3-CH_3	205^{D+A}	60	$C_{19}H_{19}O_4N$	70.42 70.15	5.71 5.84	4.05 4.30
3	4-CH_3	180^{A+W}	65	$C_{19}H_{19}O_4N$	70.31 70.15	5.73 5.84	3.98 4.30
4	3-$COCH_3$	184^{A}	69	$C_{20}H_{19}O_5N$	68.10 67.98	5.79 5.38	4.12 3.96
5	4-$COCH_3$	218^{A+W}	70	$C_{20}H_{19}O_5N$	67.86 67.98	5.19 5.38	3.89 3.96
6	4-$COOC_2H_5$	190^{A+W}	72	$C_{21}H_{21}O_6N$	65.36 65.79	5.79 5.48	3.64 3.65
7	3,4-Cl_2	222^{A}	70	$C_{18}H_{15}O_4NCi_2$	56.64 56.84	3.81 3.94	3.91 3.68
8	4-Br	211^{A}	60	$C_{18}H_{16}O_4NBr$	55.67 55.38	4.08 4.10	3.51 3.58
9	4-NO_2	230^{D+W}	55	$C_{18}H_{16}O_6N_2$	60.55 60.67	4.32 4.49	7.71 7.86
10	H	245^{D+W}	70	$C_{18}H_{17}O_4N$	69.10 69.45	5.82 5.46	4.82 4.50
11	2-Naphthyl	205^{A}	55	$C_{22}H_{19}O_4N$	73.4 73.13	5.79 5.26	4.12 3.85

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

Chapter - II
Part - II
Mannich Reaction on some hydroxycoumarins

MANNICH REACTION ON SOME HYDROXYCOUMARINS

INTRODUCTION

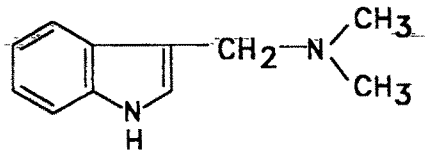
Mannich reaction appears to be of central importance in alkoloid biosynthesis. The biosynthetic route that the opium poppy uses to systhesise morphine also involves Mannich-type condensation and is constructed from two moles of tyrosine.

Many alkoloids like Gramine (1) appear to be synthesised in plants through reaction that resembles 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 . A rough outline of the biosynthesis of lupinine (3) alkoloid system from amino acid lysine is also illustreted here . Mannich reaction, named after Carl Mannich, involves condensation of a 'carbonyl compound (an enolizable ketone) for example, acetophenone, 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, sulphur, phosphorous or arsenic are found to undergo this reaction (Scheme--1).

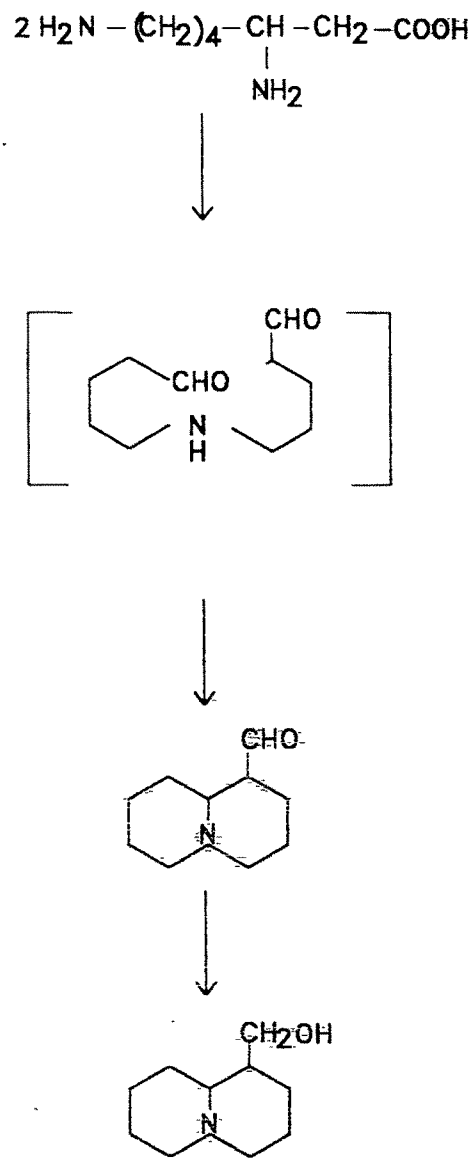
When aqueous formaldehyde is used, the condensation may be carried out with or without solvents. Alcohol and acetic acid have been generally employed . A mixture of equivalent amounts of benzene and nitrobenzene or benzene alone are useful.

Burke and co-workers[1] have used dioxane with very good results. When paraformaldehyde is used, an organic solvent is required . Burke et al (loc cit) employed catalytic quantity of alcoholic potassium hydroxide to effect the depolymerisation of paraformaldehyde. The time limit required for the reaction depends upon the nature 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 reaction may be completed within a few minutes of refluxing.



(1)

(2)



(3)

MECHANISM

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

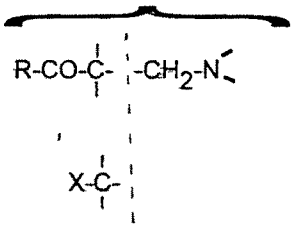
Alexander et al[3] proposed quite different mechanism for the reaction of compounds containing active methylene group. They made a kinetic study of the reaction of ethyl malonic acid with formaldehyde and dimethylamine and based on their results, they proposed a reaction mechanism in which the reaction is considered to be initiated by the reversible addition of dimethylamine and formaldehyde to 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 ethylmalonic acid, probably in the 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) (Scheme - 3).

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 recemisation 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 (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.

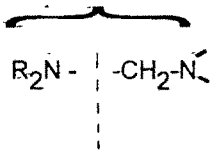
Liberman and Wagner[6] believe that the Mannich reaction involves a dual catalysis in an amphoteric system in which the cation R_2-N-C^+ is formed from the condensation products of amine and carbonyl compound and combines finally with the anion of the reactive hydrogen compound. Formation of cation is induced by added acid or by the acidity of the reactive hydrogen compound or both. Formation of the anion is promoted by the base present or by added alkali or both. The inferences that excessive acid would interfere with the primary condensation of amine and carbonyl compound and would depress the ionisation tendency of the reactive hydrogen compound and that excessive alkali would decrease or prevent the

SCHEME - 1

C-Mannich base

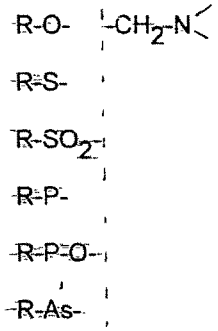


N-Mannich base



[X = N-heteroaromatic ring, carboxy-, nitrogroup .....]

O, S, P and As Mannich bases



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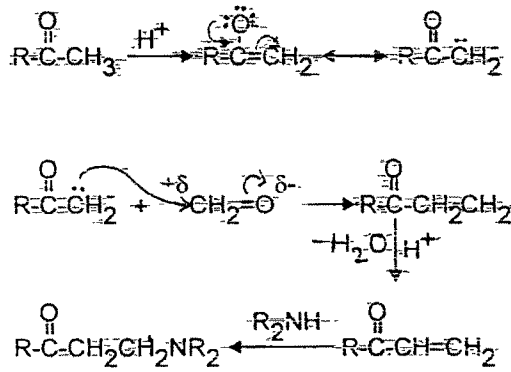
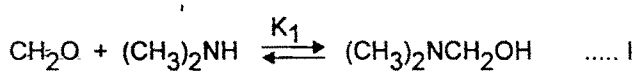
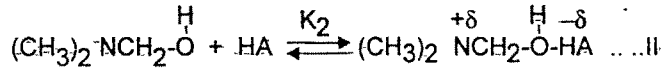


SCHEME–3



(5)



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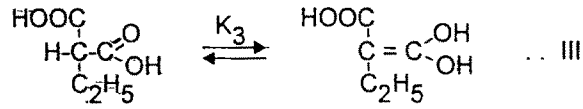

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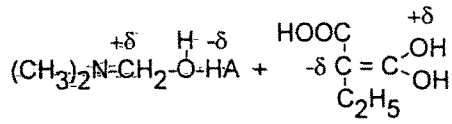
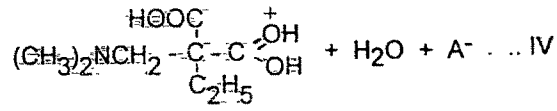
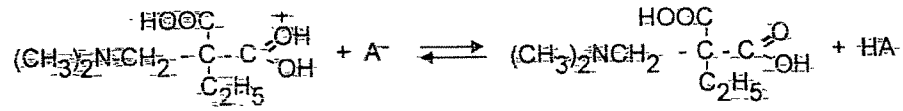




(8)



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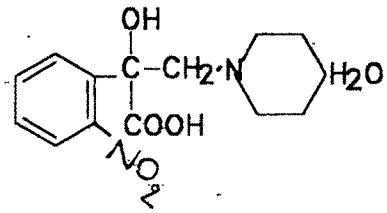
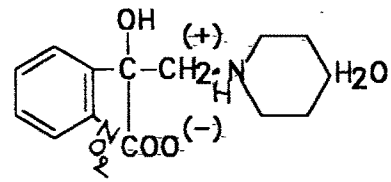


OR



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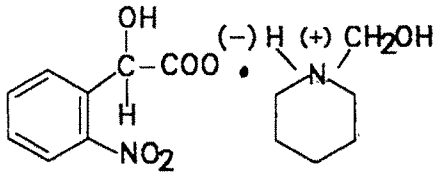

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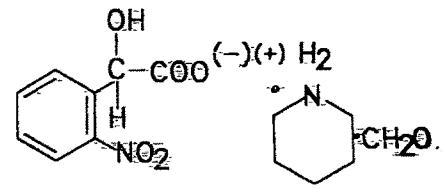


(12)

formation of cation R_2-N-C^+ and therefore obstruct or stop the reaction were supported experimentally. Also the probability that the cation originates in the alkylidene-bis-amine formed from aldenyde 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 imiuium ion with the enol form of the active methylene compound (Scheme - 4).

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

REACTION 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 (Scheme - 5).

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

REACTION WITH ALDEHYDES

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

REACTION WITH ACIDS AND ESTERS

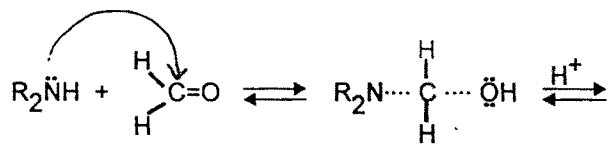
Different acids and esters containing highly reactive hydrogen atoms in the α-position undergo Mannich reaction, when an acid is employed, the free amine base rather its salt is used.

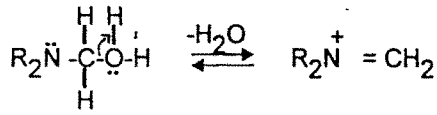
REACTION WITH PHENOLS

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.

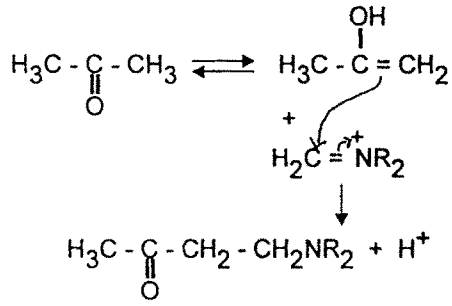
SCHEME - 4

(i)

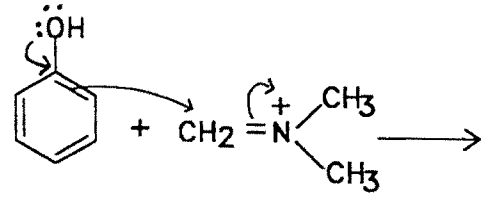


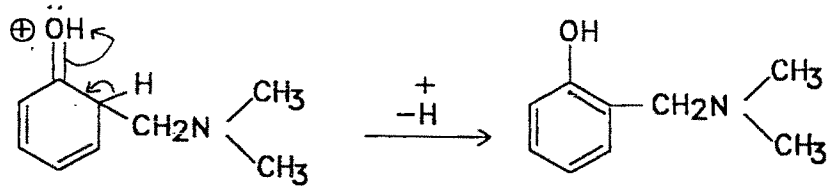


(ii)



(iii)





Brusson and coworkers[9] have reported that when phenolic Mannich bases were treated with acetic anhydride, their dimethyl-aminomethyl groups were replaced by acetoxymethyl groups (Scheme - 6).

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 α-methyl group is sufficiently reactive to take part in the Mannich reaction. Thus, Tseou and coworkers[10] have reported the formation of 2-(β-diethyl aminomethyl) pyridine, when α-picoline, formaldehyde and dimethylamine were condensed (Scheme - 7). Mannich reaction with pyrrole has been studied by number of workers. Hydrogen on α-carbon atom was substituted (Scheme - 8).

Burke and coworkers[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-workers[12] using formaldehyde, primary amine and secondary amine.

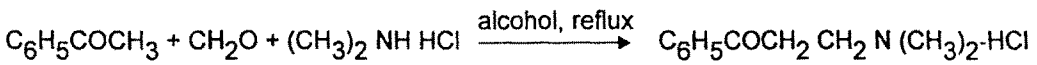
In recent years Mannich bases have received considerable attention on account of their various therapeutic properties. Some recent research publications on Mannich bases from coumarins have been briefly reviewed here

Robertson and Link[13] attempted to prepare Mannich bases from paraformaldehyde and the amine hydrochlorides but failed, instead the bis-product 3,3' methylene-bis-4-hydroxycoumarin (13) was obtained . Later on they succeeded in preparing a series of 3-substituted aminomethyl-4-hydroxy coumarin (14).

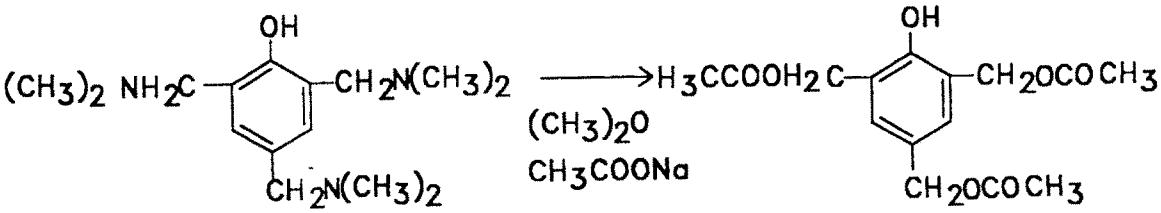
V.N.Gupta[14] and others reported that Mannich bases synthsized from 7-hydroxycoumarin derivatives (15), (16) with aliphatic amines have been found to have powerful stimulating effect on central nervous system.

R.B.Desai[15] studied Mannich reaction on 5-hydroxy-, 6-hydroxy and 7-hydroxy coumarins with formalin and primary and secondary amines and obtained Mannich bases (17) and also oxazino derivatives.(18).

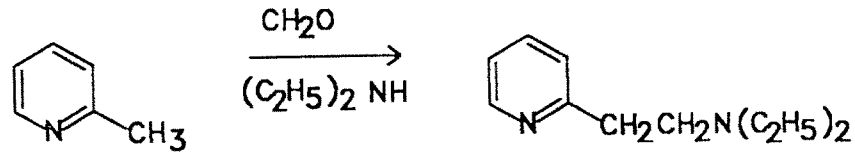
SCHEME - 5



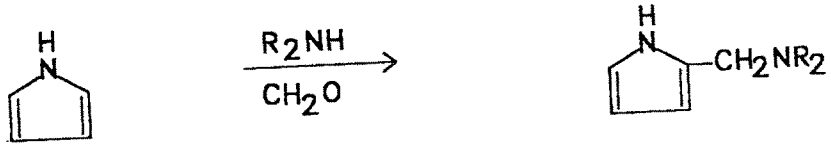
SCHEME–6

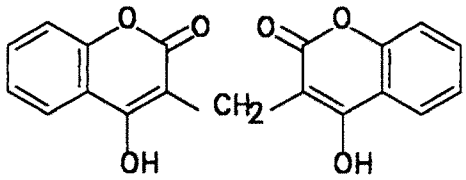


SCHEME–7



SCHEME–8





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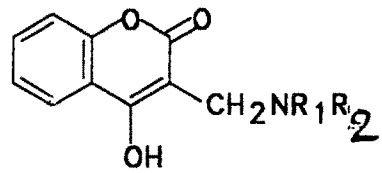

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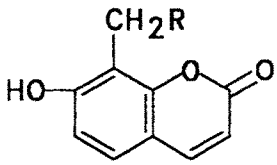
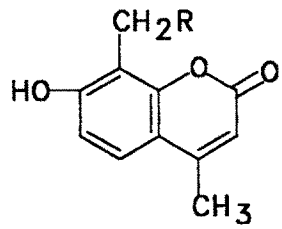


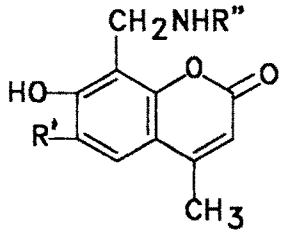
R = aminomethyl

(15)



R = aminomethyl

(16)



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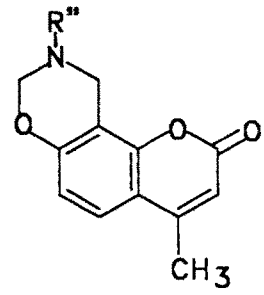


(18)

Patel, Mehta and Sethna[16,17] have applied Mannich reaction to 6-hydroxy-, 7-hydroxy-, ethyl-7-hydroxycoumarin-3-carboxylate and 8-hydroxycoumarin and obtained corresponding alkyl aminomethyl (19) and oxazino derivatives (20).

Satyendrakumar and Shiamsunder[18] prepared Mannich bases (21) from 7-hydroxy-4-methyl-6-chloro- and 7-hydroxy-4-methyl-6-bromocoumarin and studied their CNS stimulating activity.

A.K. Agrawal[19] and others synthesised Mannich bases, 7-hydroxy-4-methyl-8-substitutedaminomethylcoumarin and tested their antiestrogenic activity. They found that all coumarins possessing approximately LD-50 value of 500-800 mg/kg. antagonised the uterotropic effects of dimethyl stilbestrol (DES) in female rats

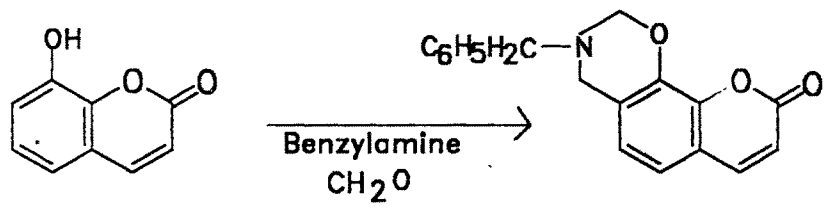
D.R. Shridhar[20] and coworkers studied the Mannich reaction on coumarin (22) with different amines and formaldehyde, and they obtained pyranobenz-oxazinones(23). They found that compound of type (23) have considerable amebicidal, antibacterial and antitrichomonal activities in vitro but were devoid of such activities in vivo.

A. Kameswara Rao, M. Subramanyam Raju and K.Mohana Raju[21] 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-phenyl coumarin were more active against S faelesis and K Pneumoniae. These Mannich bases (24) also exhibited moderate antifungal activity against T. mentagrophytes and Aspergillus famigatus but were inactive against C.Albicans.

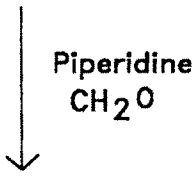
S.P.A Fadia[22] prepared substituted 7-hydroxy-6-(aminomethyl)coumarins (25) which inhibited blood platelet aggregation and showed anti-tumor activity.

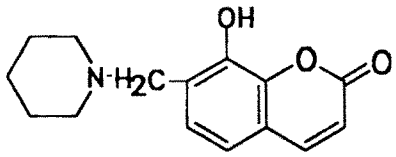
Mannich bases like 7-hydroxy-8-(1-aryl-piperazinomethyl)coumarin (26), prepared by U.V. Korgaonkar and coworkers[23] showed antiinflammatory activity.

A.R. Bhat and Shailendrakumar[24] prepared Mannich base of the type (27) from 7-hydroxycoumarin and 5-aminoacenaphthene which was active against gram positive bacteria.

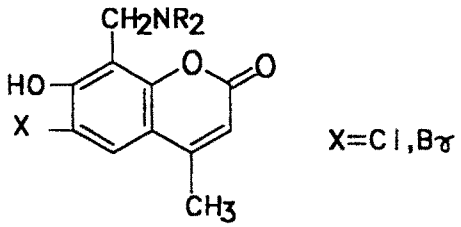

OH
O
O
C6H5H2C—N
O
O
O
Benzylamine
CH2O

(20)

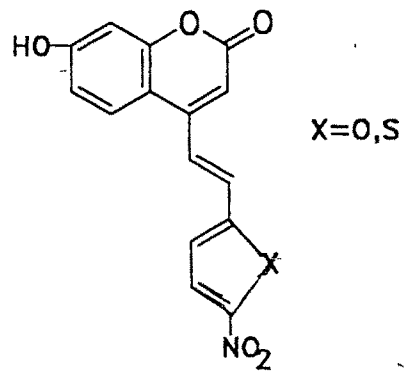

Piperidine
CH2O


OH
N-H2C
O
O

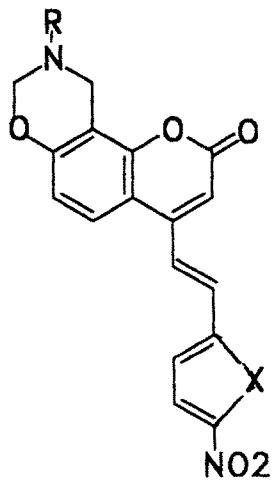
(19)


CH2NR2
HO
X
O
O
CH3
X=Cl,Br

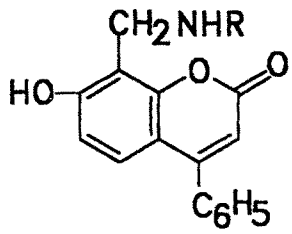
(21)


HO
O
O
X=O,S
X
NO2

(22)



(23)



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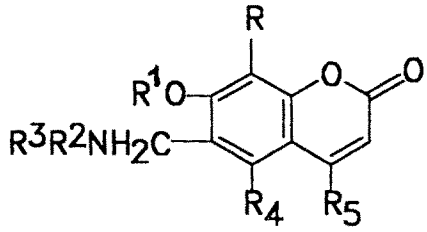

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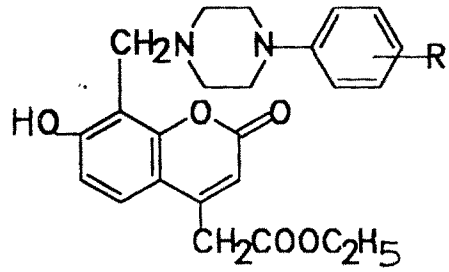

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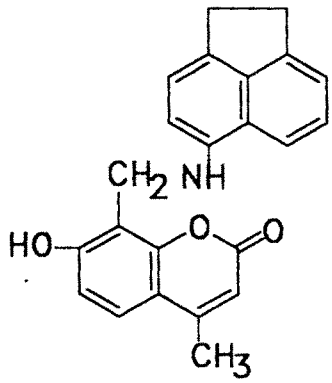

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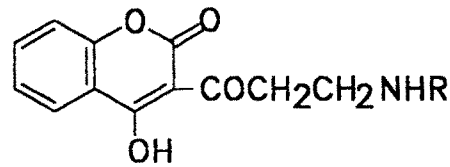


(28)

C-acylcoumarins have also been found to participate in Mannich reaction. S.K.Agrawal and R.C. Saxena[25] synthesised Mannich bases from 4-hydroxy-3-acetyl coumarin (28). Some of them were found active against Bacillus aureus.

Mannich reaction of 4-hydroxycoumarin with pyrrolidine and piperidine gave Mannich bases (29) and (30). V.L. Savellev[26] and others suggested that Mannich bases with R=Cl had weak Psychotropic activity.

M.M. Budran et al[27] carried out Mannich reaction on 7-hydroxy-4-methylcoumarin and obtained some novel piperazinyl coumarins (31) and tested for antiallergic activity.

P. Eswarian, M. Nagesam and M.S. Raju[28] have synthesised 7,8-(3'-substituted-4'-dihydro) m-oxazino-4-methylcoumarins (32) and tested them for antimicrobial activity.

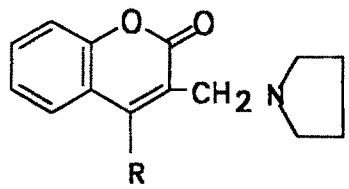
M. Nagesam, K.M. Raju and M.S. Raju[29] have synthesised 2H, 5H, 3,4 dihydro-8- and 9-methyl[1] benzopyrano [3,4-e] 1,3 oxazino-5-ones (33) and studied their biological activity. R_2 = 4-Cl-Ph, 4-Br-Ph, 4-Tolul were more active as antibacterial and antifungal agents.

J.N. Gadre and Prasad K. Raote[30] have prepared Mannich bases of 7-hydroxy coumarin derivatives (34) and m-oxazinoderivatives (35) using piperazine derivatives Some of them were found active against B. subtilis and S. typhosa.

M. Nagesam and M.S. Raju[31] have prepared N-substituted-m-oxazino-4-methyl -2H-1-benzopyran-2-ones (36).

J.N. Gadre and Dhubhashi Vaman[32] prepared m-oxazino derivatives (37) from 3-bromo-4-methylumbelliferone with various primary and secondary amines with formalin and tested for antibacterial activity.

J.N. Gadre, M.R. Khanolkar and Prasad K. Raote[33] also synthesised 5-(substituted amino methyl)-6-hydroxycoumarin (38) and tested for antibacterial activity.



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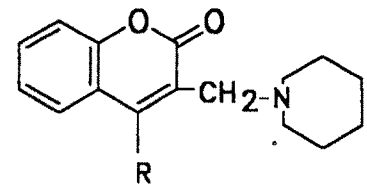

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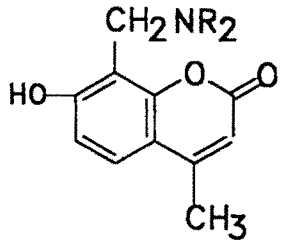

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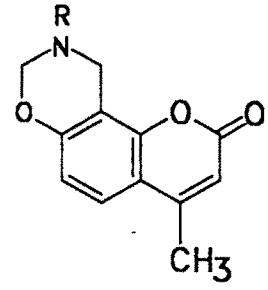

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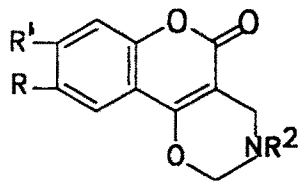

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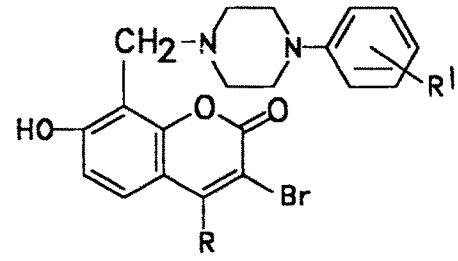


(34)

S.B. Bhavsar, D.V. Mane, D.B. Shinde, M.S. Shingare, A.S. Deokate and L.V. Gangwane[34] have synthesised 8-[(6'-sub1'-3'-benzothiazol-2'-yl)aminomethyl] substituted hydroxycoumarin (39) by Mannich reaction of substituted hydroxy coumarin with 2-aminobenzothiazole . They were found active against Alternaria brussicide, Fusarium udam, S.aureus and E.coli.

Jehane A.A. Miky, Salen Nadia M, Shmeiss Nadia A.M.M.[35,36] have prepared 4-aminomethyl derivatives (40) via Mannich reaction on 3-hydroxy coumarin derivatives.

Short and Ours[37] have shown that aminoacids have been found to participate as the amine component in the Mannich reaction of substituted phenols instead of usual aliphatic or aromatic amines, (41) and (42) were synthesised by them condensing aminoacids with formaldehyde and phenols

R.H. Mehta[38] carried out Mannich reaction on 7-hydroxycoumarin derivatives with formalin and various aminoacids to get Mannich products (43) and studied their CNS stimulating activity.

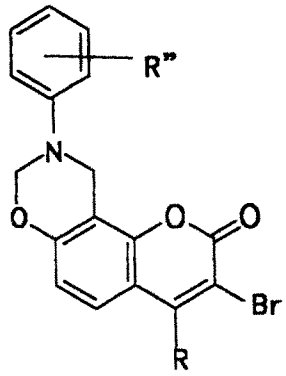
Sonal Shah , R. Vyas and R. H. Mehta[39] carried out Mannich reaction on 7-hydroxy-4-methyl-, 7-hydroxy-4-phenyl-, 7-hydroxy-5-methyl, and 7-hydroxycoumarin with different DL-aminoacids and formalin and obtained Mannich products (44). Some of them were found active against S.typhosa and S.albus.

J.N. Garde and Prasad K. Raote[40] have synthesised Mannich bases (45) from umbelliferone derivatives incorporating essential aminoacids. They were found active against S. aureus and E. coli.

J.N. Gadre, N.K. Shetty and Prasad S. Raote[41] prepared Mannich bases (46) from 4- [2-(4- methoxyphenyl)vinyl]-7-hydroxycoumarin with various aminoacids. They also condensed substituteed piperazines and other secondary amines.

APPLICATIONS OF MANNICH REACTION

Recently 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



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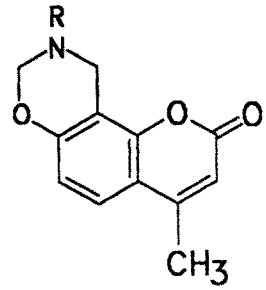

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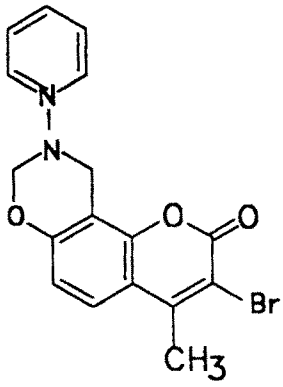

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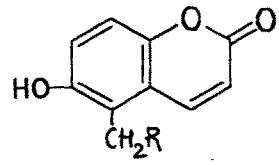
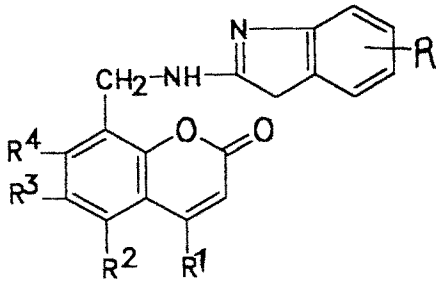
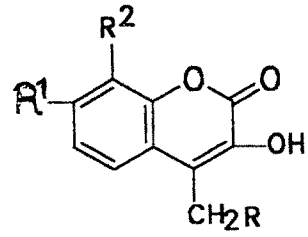


R = aminomethyl

(38)

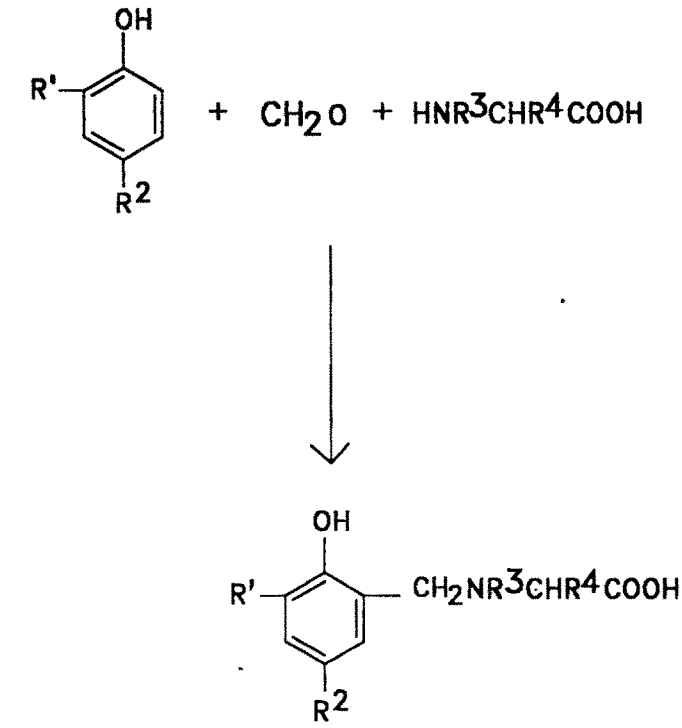


(39)

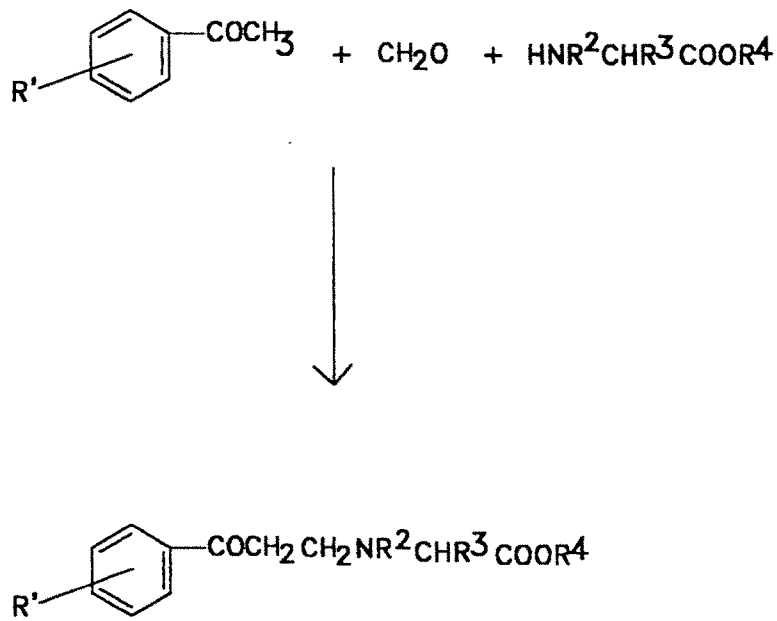


R = aminomethyl

(40)


OH
R'
R2
+ CH2O + HNR3CHR4COOH
OH
R'
CH2NR3CHR4COOH
R2

(41)


COCH3
R'
+ CH2O + HNR2CHR3COOR4
COCH2CH2NR2CHR3COOR4
R'

(42)

Mannich bases and their reduction products have proved to be important medicinal agents.

Mannich et al[42] found that β-dimethyl aminomethyl ketone (47) and ortho-nitrobenzaldehyde reacted to give a product which upon reduction, lost water to form a substituted quinoline (48).

SYNTHESIS OF AMINOALCOHOLS

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

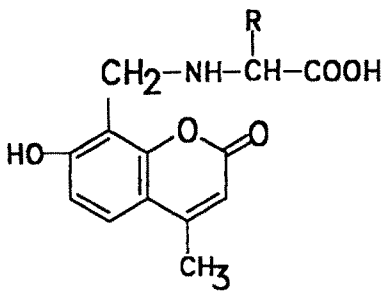
Caldwell and Thompson[43] have developed a new method for nuclear methylation of phenols which consist in the hydrogenolysis of the dimethylaminomethyl derivatives obtained by Mannich reaction. On this basis Callin et al[44] achived a practical synthesis of 2, 6-xylenol (49).

Snyder[45] observed that when Mannich base in acetic acid solution was treated with hexamethylenetetramine the intermediate quaternery salt decompose to an aldehyde. The intermediate quarternary salts were of the type encountered in Sommelet synthesis[46]. The conversion of primary and secondary amines to aldehydes by modified Sommelet reaction was described by Graymore et al.[47]

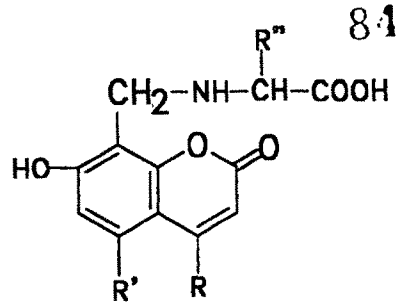
SYNTHESIS OF 1, 3-OXAZINO DERIVATIVES

Burke[1] showed that where as the condensation of equimolar quantities of parasubstituted 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.

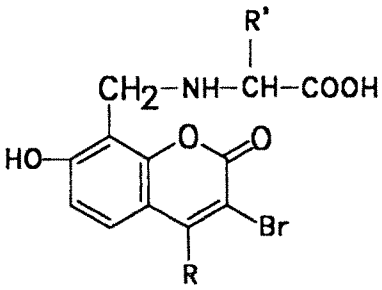
These benzoxazines could be prepared alternatively, from o-alkylamino-p-substituted phenols by refluxing them with excess of formaldehyde in alcoholic solution in the presence of a basic catalyst such as sodium hydroxide. Benzoxazine derivatives on heating with hydrochloric acid in alcoholic solution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



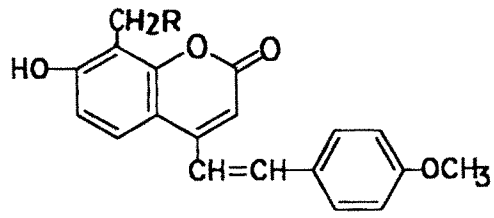
(43)



(44)

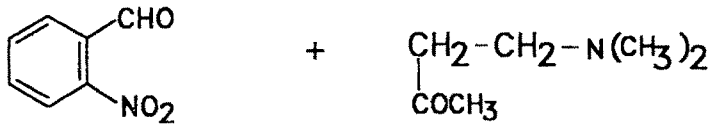


(45)

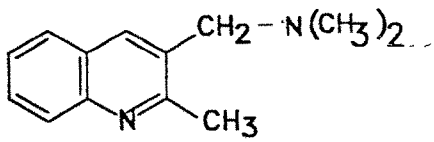


R = aminomethyl

(46)



(47)



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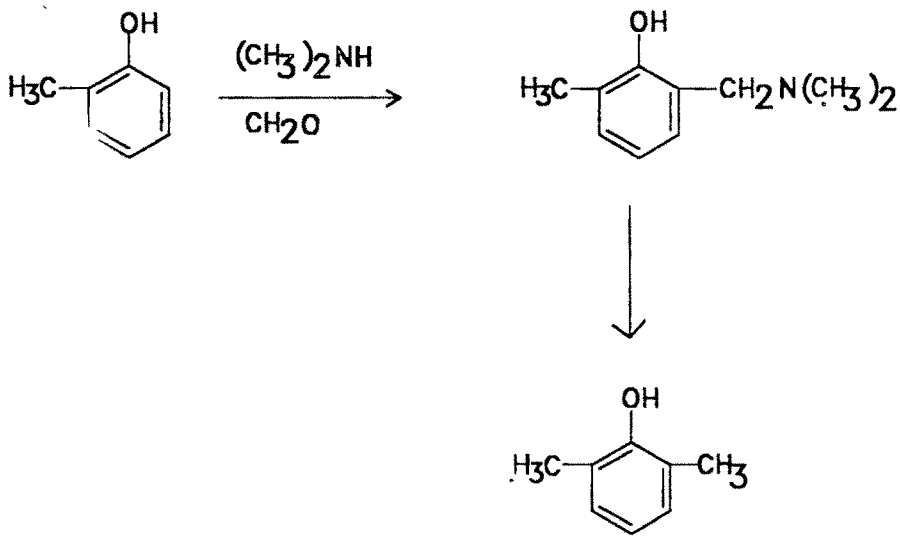
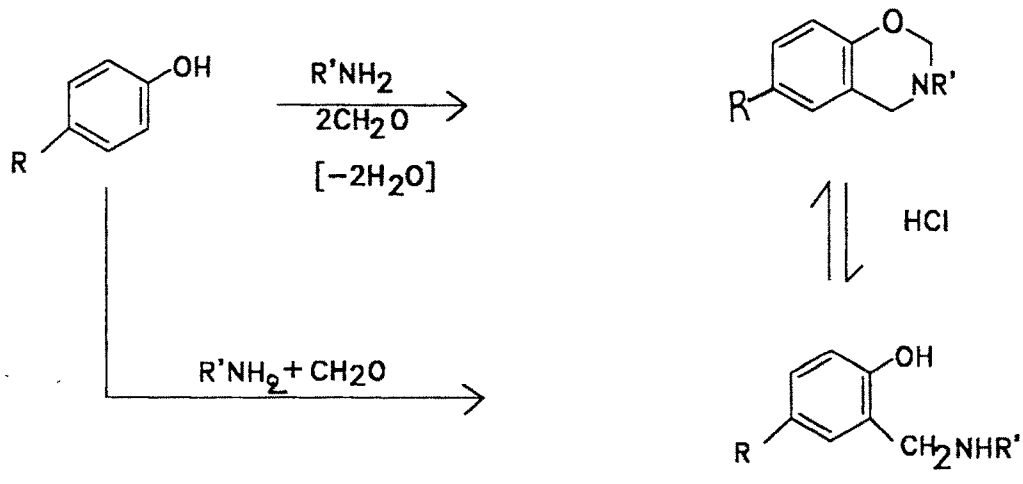

OH
H3C
(CH3)2NH
CH2O
OH
H3C
CH2N(CH3)2
OH
H3C
CH3

(49)


OH
R
R'NH2
2CH2O
[−2H2O]
O
R
NR'
HCl
R'NH2+CH2O
OH
R
CH2NHR'

(50)

to give formaldehyde and the corrosponding o-alkylaminomethyl-p-substituted phenols (50).

Burke and coworkers[48] observed that a third kind of product N, N-bis-(2-hydroxy benzyl) alkylamine (51) could be directly obtained.

SYNTHESIS OF COMPLEXES

Petter and Edward[49] synthesised a bicyclic ring system called Bispidine (52) using Mannich reaction. Bispidine is used as a ligand in the study of complexation by certain transition metals[50] and as an intermediate for the synthesis of pharmacologically active compounds.[51] The possibility of complex formation by Mannich bases has been widely investigated in connection with potential technological applications. Phosphorous Mannich bases have also provided the object of many investigations. A significant example of this class is reported here[52] i e. synthesis of complex (54) from (53).

SYNTHESIS OF POLYMERS

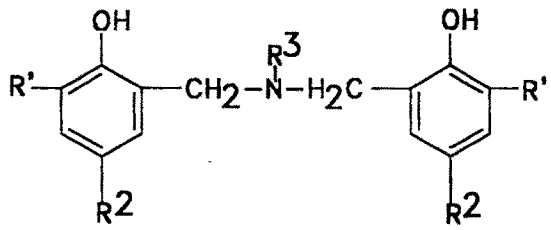
Mannich bases have been submitted to step polymerization.[53] The interesting polymerization of diallylamino Mannich bases (55) leading to poly-pyrrolidines (56) is shown here.

Since the early studies of Mannich reactions, Mannich bases have become important tools for the synthesis of new compounds[54]. Mannich bases can be either directly employed or used as intermediates. The most important application of these compounds is in pharmaceutical chemistry. Research on antineoplastic drugs analgesics, antibiotics etc.,[55-63] including labelled molecules[64-67] has received particular attention. In recent years a comparable importance has been developed by the technological applications of Mannich bases in polymer chemistry[68] with respect to paints and surface active agents.

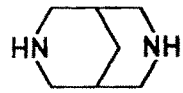
Reviews have also been devoted to study of Mannich bases including the use of aminoacids in aminomethylation.[69]

PRESENT WORK

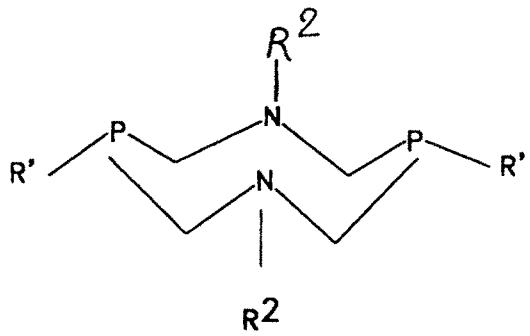
The literature survey shows that the Mannich bases of 7-hydroxycoumarin derivatives synthesised with aliphatic, aromatic and heterocyclic amines or aminoacids have been found to have antibacterial activity.


OH
R'
CH2
N
H2C
OH
R'
R3
R2
R2

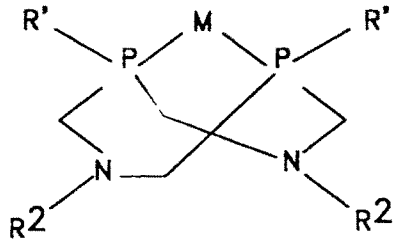
(51)


HN
NH

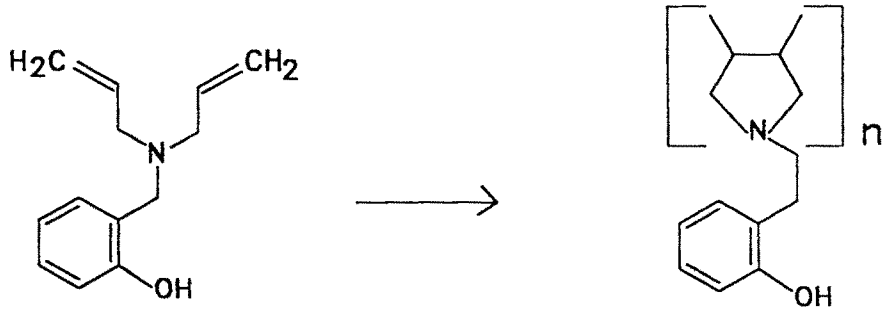
(52)


R2
P
N
P
R'
R'
N
R2

(53)


R'
M
R'
P
P
N
N
R2
R2

(54)


H2C
CH2
N
OH
n
N
OH

(56)

The present work is undertaken to synthesise Mannich products involving 7-hydroxy-, 7-hydroxy-4-methyl and 7-hydroxy-4-phenylcoumarins, formaldehyde and optically active L-aminoacids as amine componant and to explore the possibility of utilising these new Mannich products as antibacterial agents.

All the synthesised compounds were screened for their antibacterial activity by cup-plate[70] method at 100 and 500 ppm concentration against strains Escherichia coli and S. Bacillus.

The structures of the number of Mannich compounds synthesised were assigned on the basis of their elemental analysis, IR, PMR and Mass spectral data The specific rotations were also determined.

The following IR absorption bands have been observed in all the Mannich compounds prepared during the present work. They display 3500-3400 cm^{-1}, a broad absorption due to phenolic -OH stretching. A broad strong -NH stretching band in the 3100-2400 cm^{-1} region, 1725-1690 cm^{-1}, a broad band due to coumarin lactone. The carboxylate ion group 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 mentioned.

Mannich reaction on 7-hydroxycoumarin (Scheme - 1)

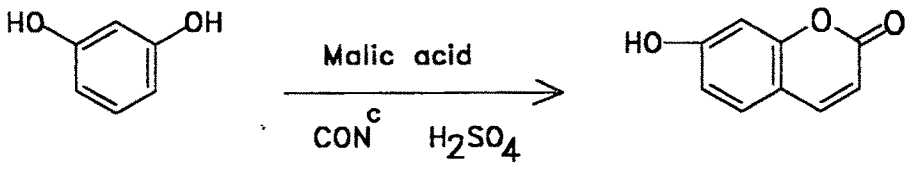
N-(7-hydroxy-8-coumarinyl)L-alanine (59, Table - 1, 1)

7-Hydroxycoumarin[71-72] (58) when reacted with formalin and L-alanine furnished 8-substituted Mannich product. The structure was confirmed by following spectral data.

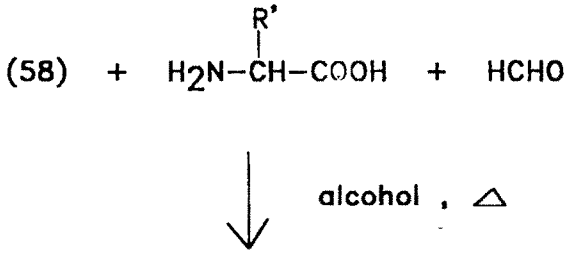
In IR (KBr) spectra following bands were observed, 3450 (broad), 3100, 2950, 1720 and 1600-1510 (broad) cm^{-1} (Fig 1).

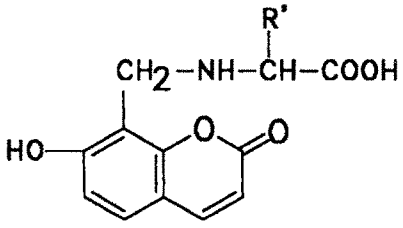
The PMR spectrum in CF_3COOH exhibited a doublet at δ1.7 for three protons of methyl group of alanine part CH_3-CH-COOH; a multiplet at δ 4.35 for one proton of

SCHEME–1



(57) (58)





(59)

(Table–1,1 to 6)

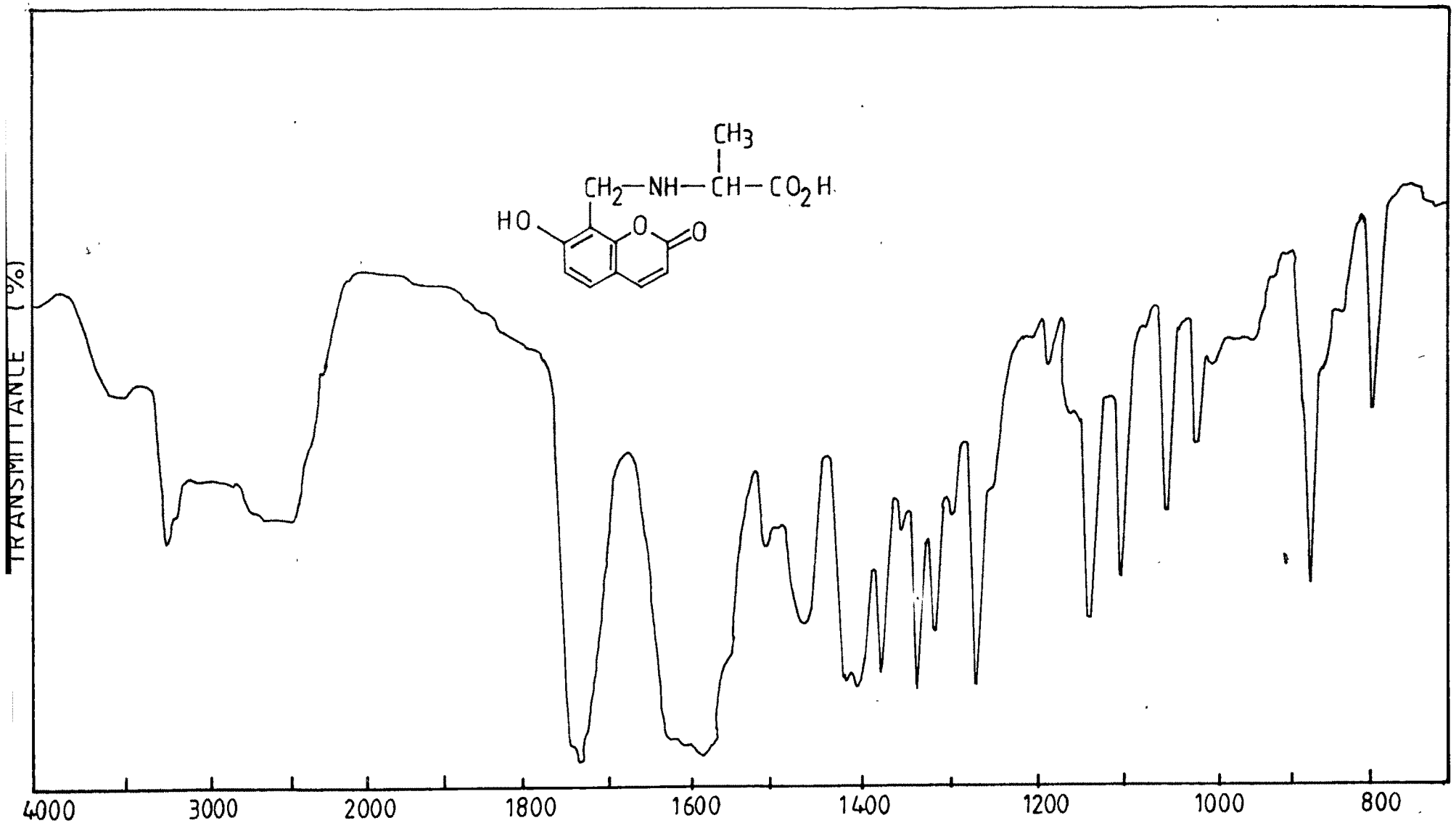

CH3
CH2—NH—CH—CO2H
HO
O
O
TRANSMITTANCE (%)
4000
3000
2000
1800
1600
1400
1200
1000
800
WAVENUMBER CM-1

FIG.1

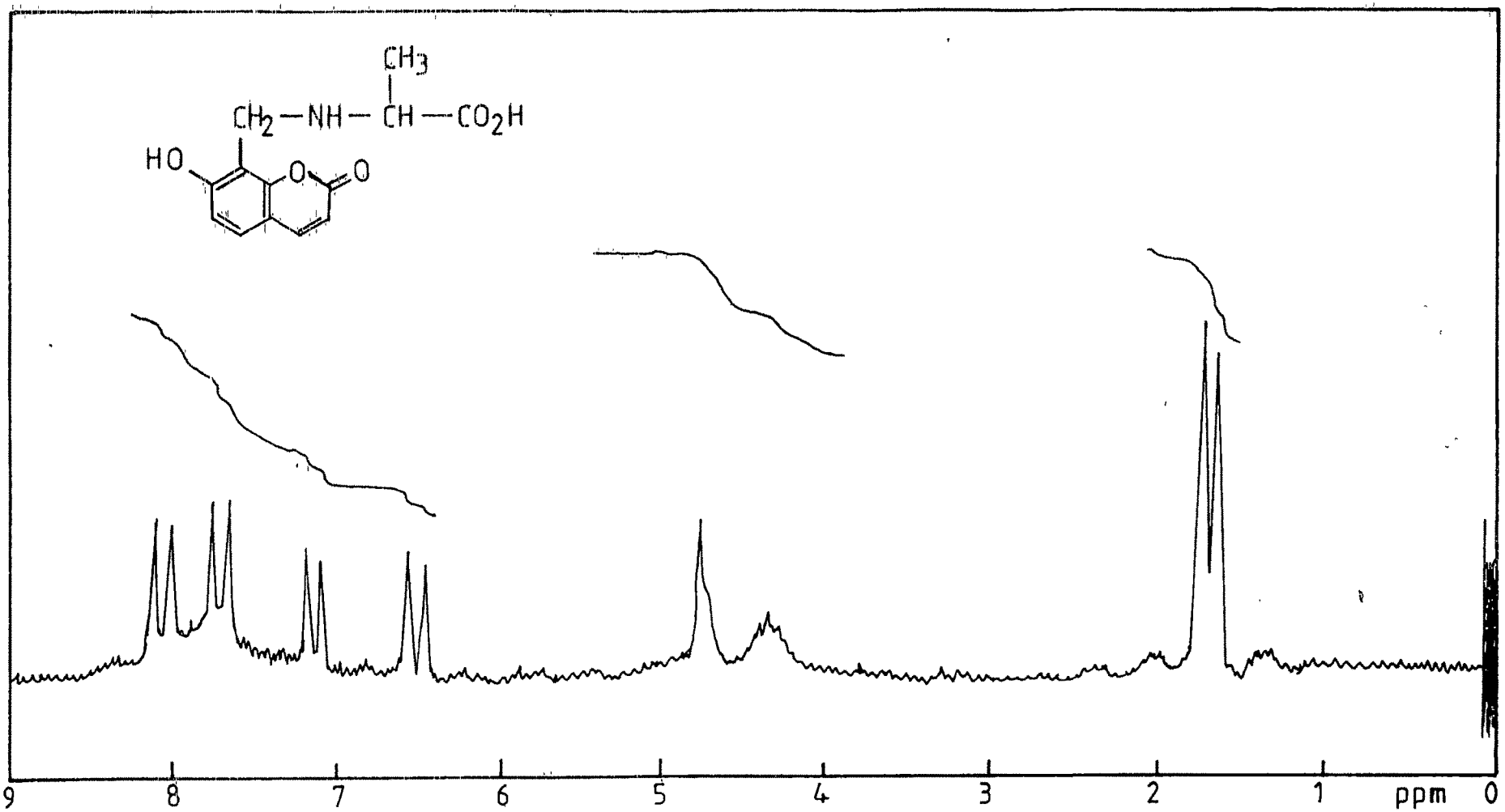


FIG. 2

NH-C<u>H</u>-COOH; a broad singlet at δ 4.78 for two protons of -C<u>H</u>$_2$ -NH; a doublet at δ 6 5 for one proton at C-3 position (J=10Hz); a doublet at δ 7.15 for one proton at C-6 position (J=10Hz); a doublet at δ 7.72 for one proton at C-4 position (J=10Hz) and a doublet at δ 8.08 for one proton at C-5 position (J=10Hz) (Fig. 2). The absence of signal for C-8 position indicates that substitution has taken place at C-8 position only.

<u>N-(7-Hydroxy-8-coumarinyl)-L-methionine</u> (59, Table - 1, 2)

7-Hydroxycoumarin when treated with formalin and L-methionine it gave 8-substituted Mannich product. The structure is confirmed by PMR spectrum.

It showed in CF_3COOH, a singlet at δ 2.0 for three protons of methyl group of methionine part, CH_2-S-C<u>H</u>$_3$; a multiplet at δ 2.35 for two protons of methylene group of methionine part, C<u>H</u>$_2$-CH_2-S-CH_3; a multiplet at δ 2.70 for other two protons of methylene group nearer to sulphur atom of methionine part, CH_2-C<u>H</u>$_2$-S-CH_3; a multiplet at δ 4.3 for one proton attached with carboxylate group of methionine, NH-C<u>H</u>-COOH; a broad singlet at δ 4.8 for two methylene protons C<u>H</u>$_2$-NH; a doublet at δ 6 5 for one proton attached with C-3 position (J=10Hz); a doublet at δ 7.65 for one proton at C-4 position (J=10Hz); a doublet at δ 7.10 for one proton at C-6 position (J=8Hz) and a doublet at δ 8.00 for one proton at C-5 position (J=8Hz) (Fig. 3)

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

Mannich reaction on 7-hydroxy-4-methylcoumarin (Scheme - 2)

<u>N-(7-hydroxy-4-methyl-8-coumarinyl) L-alanine</u> (61, Table - 1, 7)

Condensation of 7-hydroxy-4-methylcoumarin[73] (60), formalin and L-alanine gave the Mannich product which has been assigned N-(7-hydroxy-4-methyl-8-coumarinyl)-L-alanine structure. This structure is confirmed by IR and PMR spectra.

The IR (KBr) spectrum exhibited bands at 3450(broad), 3100(broad), 2950, 1720 and 1600-1510(broad) cm^{-1}. (Fig. 4).

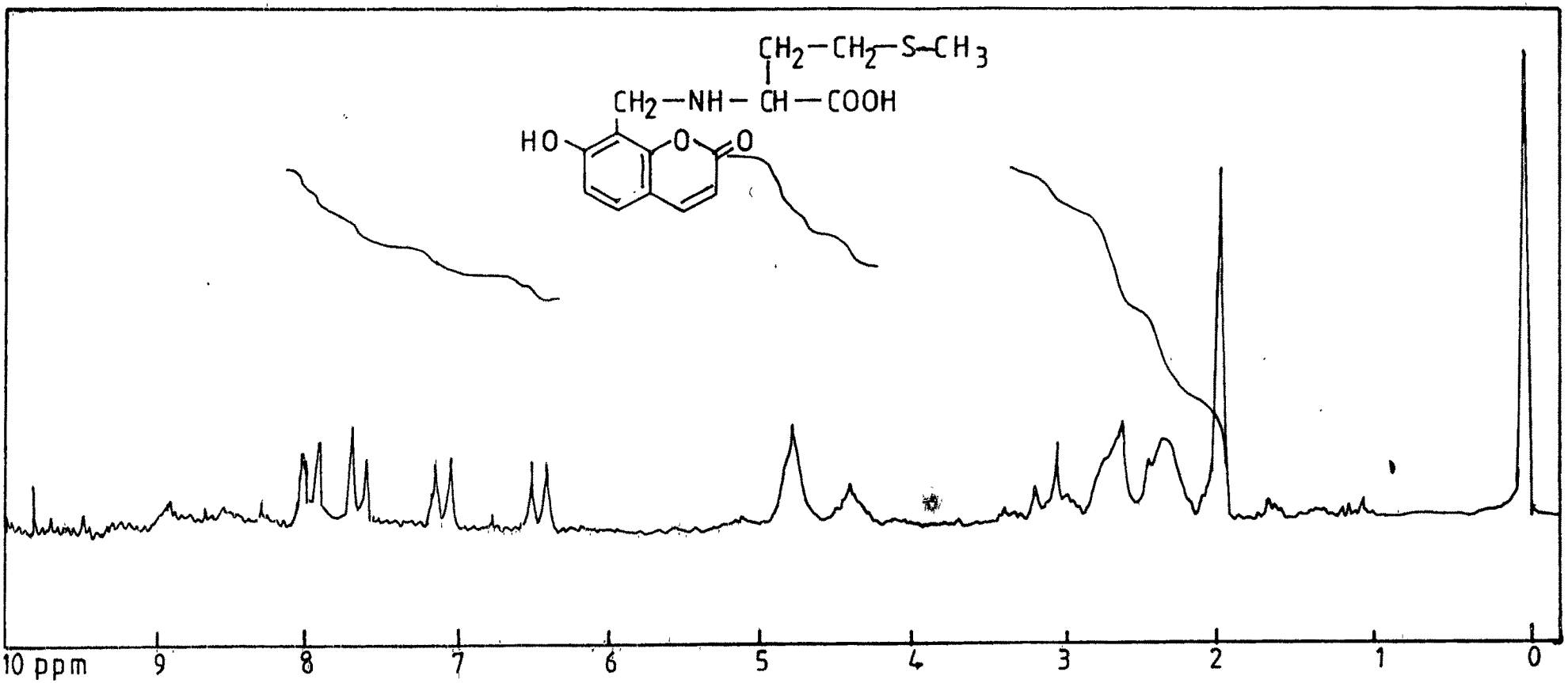
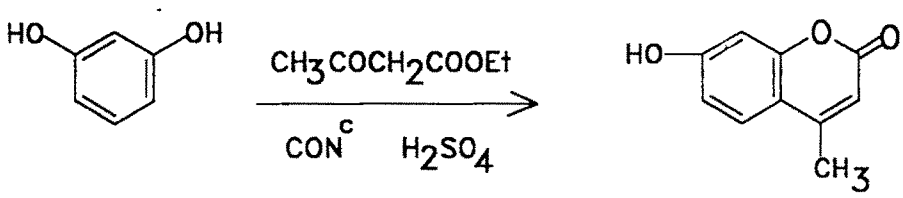
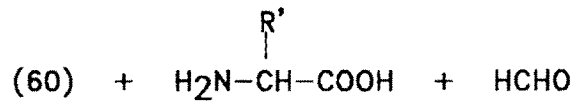


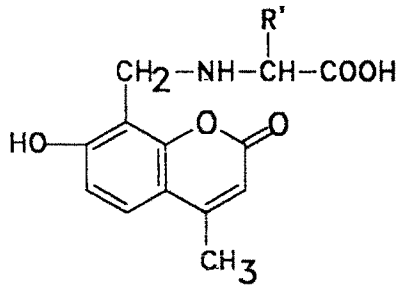
FIG. 3

SCHEME–2



(60)





(61)

(Table–1,7 to 14)

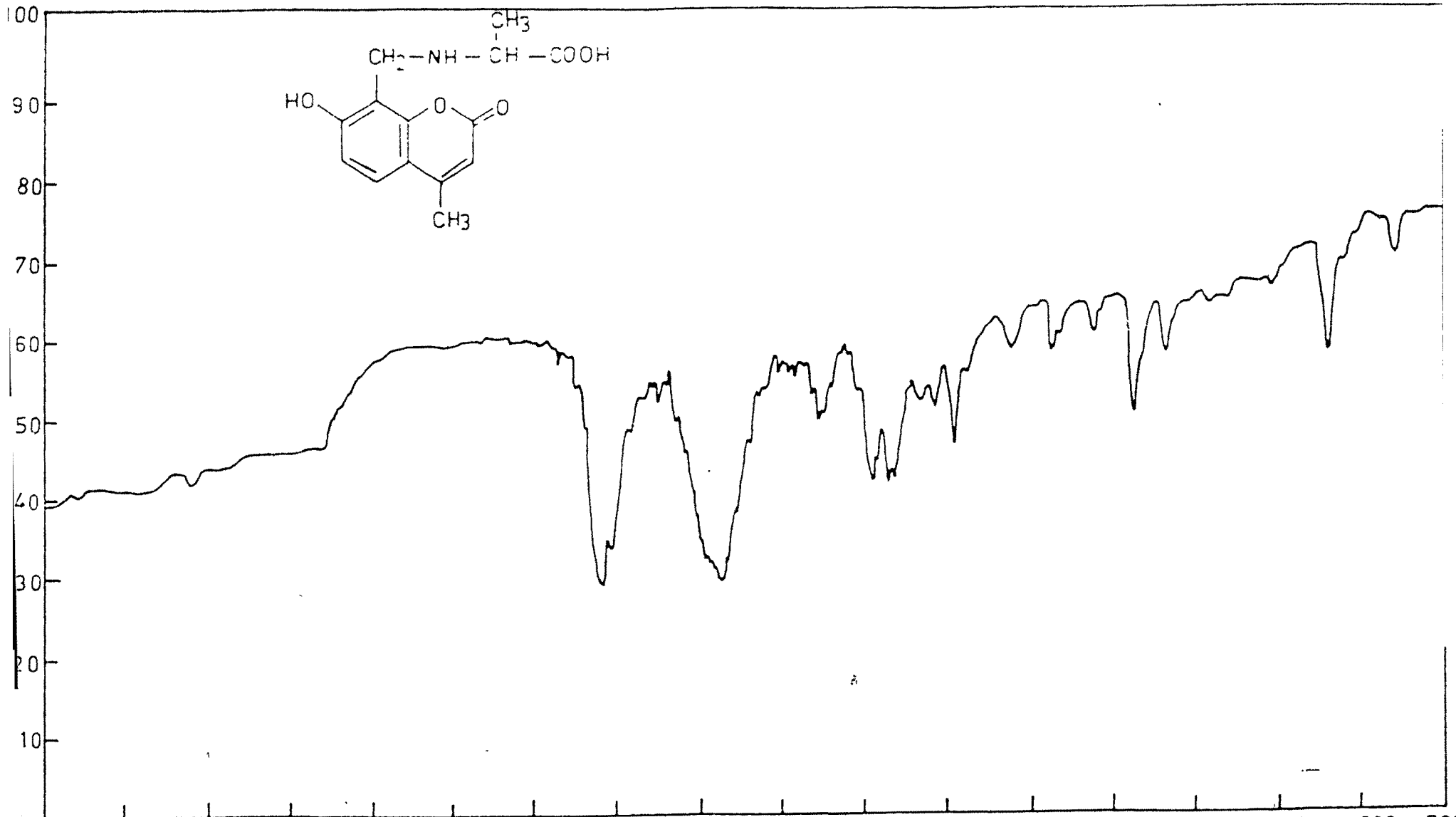

100
90
80
70
60
50
40
30
20
10
CH3
CH2—NH—CH—COOH
HO
O
O
CH3
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM-1

Fig 4

FIG. 4

The PMR spectrum in CF_3COOH exhibited a doublet at δ 1.5 for three protons of methyl group of NH-CH-C<u>H</u>$_3$; a singlet at δ 2.2 for three protons of methyl group at C-4; a multiplet at δ 4.05 for one proton for NH-C<u>H</u>-CH_3 proton; a broad singlet at δ 4 5 due to C<u>H</u>$_2$-NH; a singlet at δ 6.1 for one proton at C-3 position; a doublet at δ 6.8 for one proton at C-6 position (J=10Hz); a doublet at δ 7.5 for one proton at C-5 position (J=10Hz) (Fig. 5). Signal of C-8 position was not observed indicates that substitution took place at C-8 position.

<u>N-(7-Hydroxy-4-methyl-8-coumarinyl) L-methionine</u> (61, Table - 1,8)

Condensation of 7-hydroxy-4-methylcoumarin with formalin and L-methionine gave the Mannich product which has been assigned N-(7-hydroxy-4-methyl-8-coumarinyl) L-methionine structure which was confirmed by PMR spectrum which in CF_3COOH exhibited a singlet at δ 1.85 for three protons of methyl group of methionine component; a singlet at δ 2.25 for three protons of methyl group at C-4 position; a multiplet at δ 2.55 for two protons of methylene group, C<u>H</u>$_2$-CH_2-S-CH_3; a multiplet at δ 2.9 for two protons of methylene group attached with sulphur atom of methionine part, CH_2-C<u>H</u>$_2$-S-CH_3; a multiplet at δ 4.25 for one proton i.e. NH-C<u>H</u>-COOH; a broad singlet at δ 4.6 for two protons of methylene group attached with nitrogen C<u>H</u>$_2$-NH; a singlet at δ 6.2 for one proton at C-3 position; a doublet at δ 6.9 for one proton at C-6 position (J=10Hz) and a doublet at δ 7.6 due to a proton at C-5 position (J=10 Hz) (Fig. 6).

<u>N-(7-Hydroxy-4-methyl-8-coumarinyl)L-valine</u> (61, Table - 1, 9)

When 7-hydroxy-4-methylcoumarin was allowed to react with formalin and L-valine gave the product which has been assigned N-(7-hydroxy-4-methyl-8-coumarinyl)L-valine. Its structure was confirmed by Mass spectral data. The mass spectra showed following peaks m/z; 305 (M^+, 5%), 149 (30%), 72 (base peak, 100%) and 57 (80%) (Fig. 7).

Other Mannich products (7 to 14) on this coumarin moiety have been synthesised by same method.

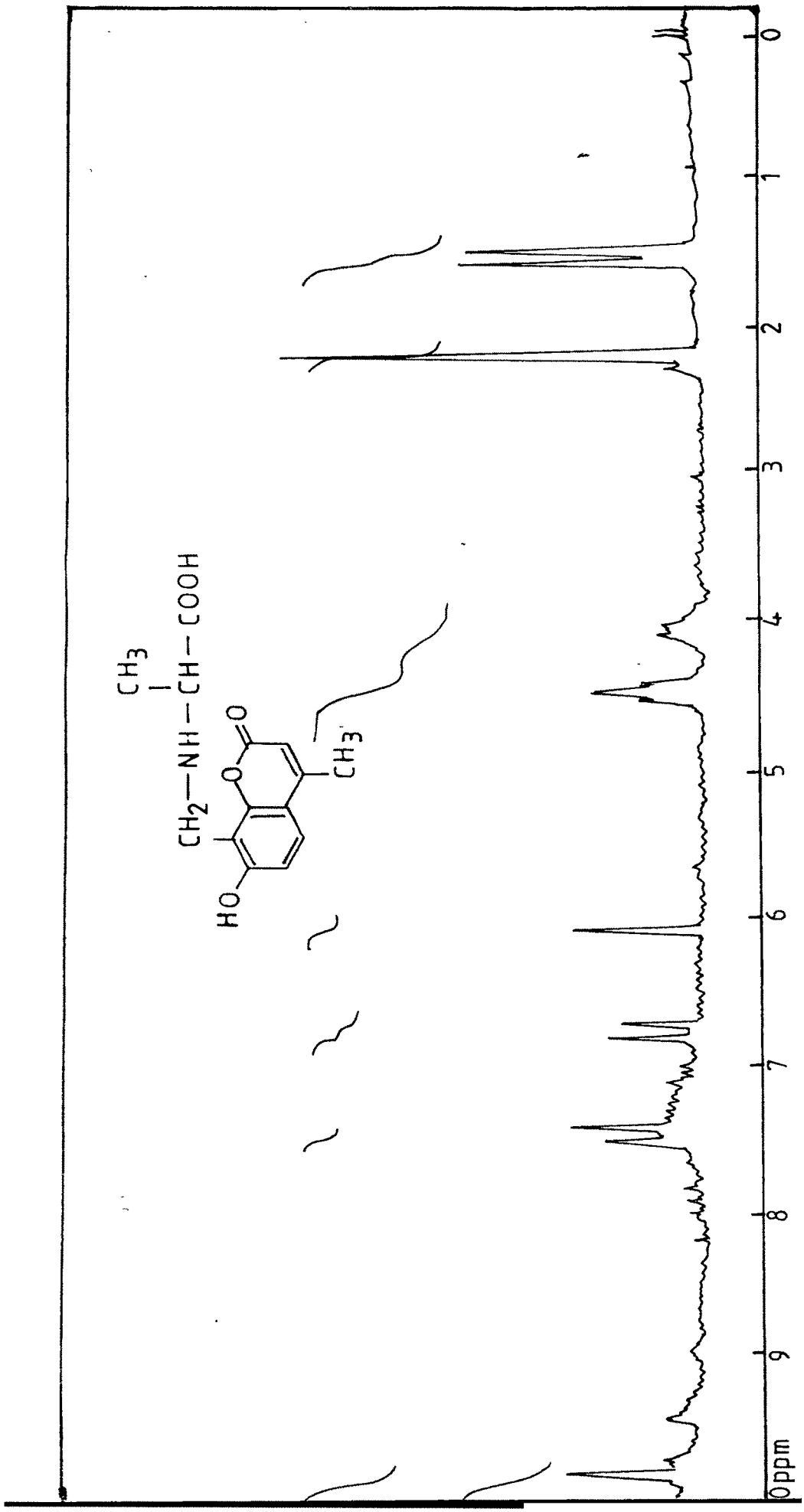


FIG. 5

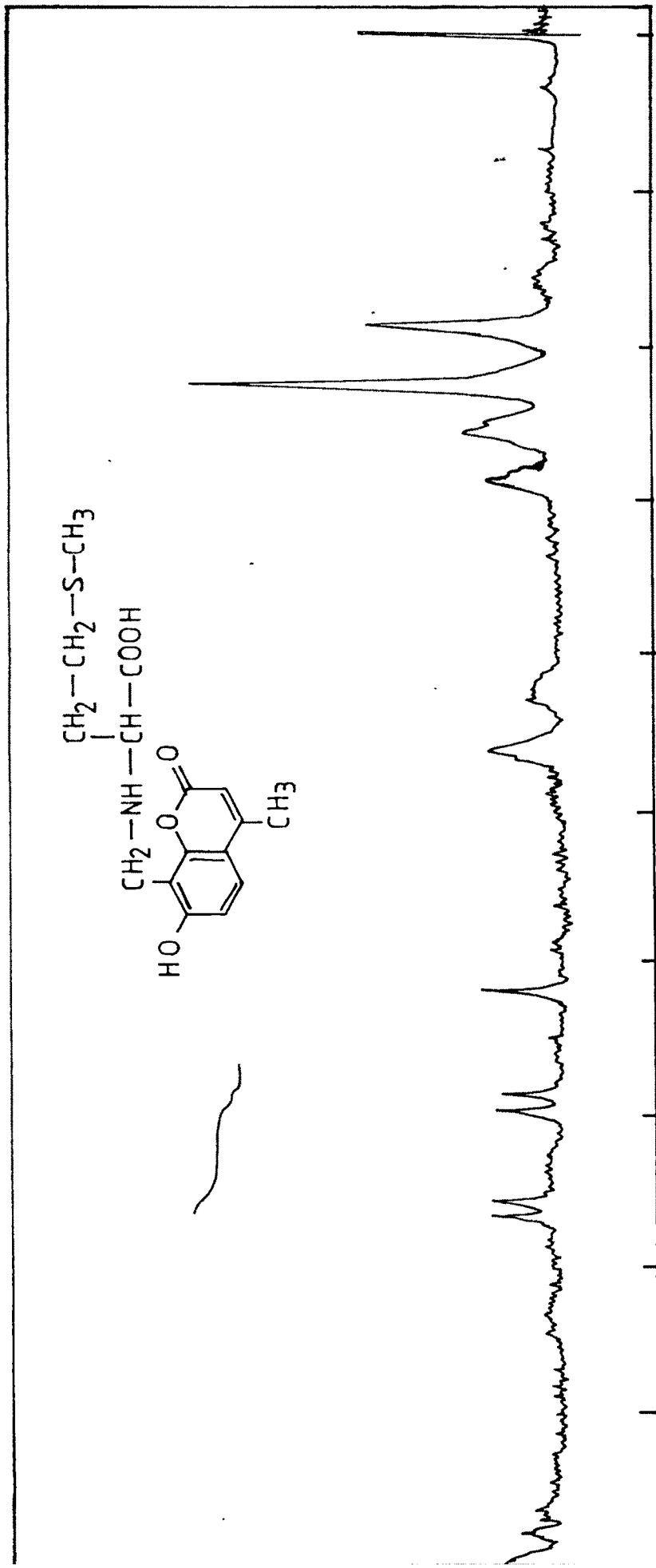


FIG.6

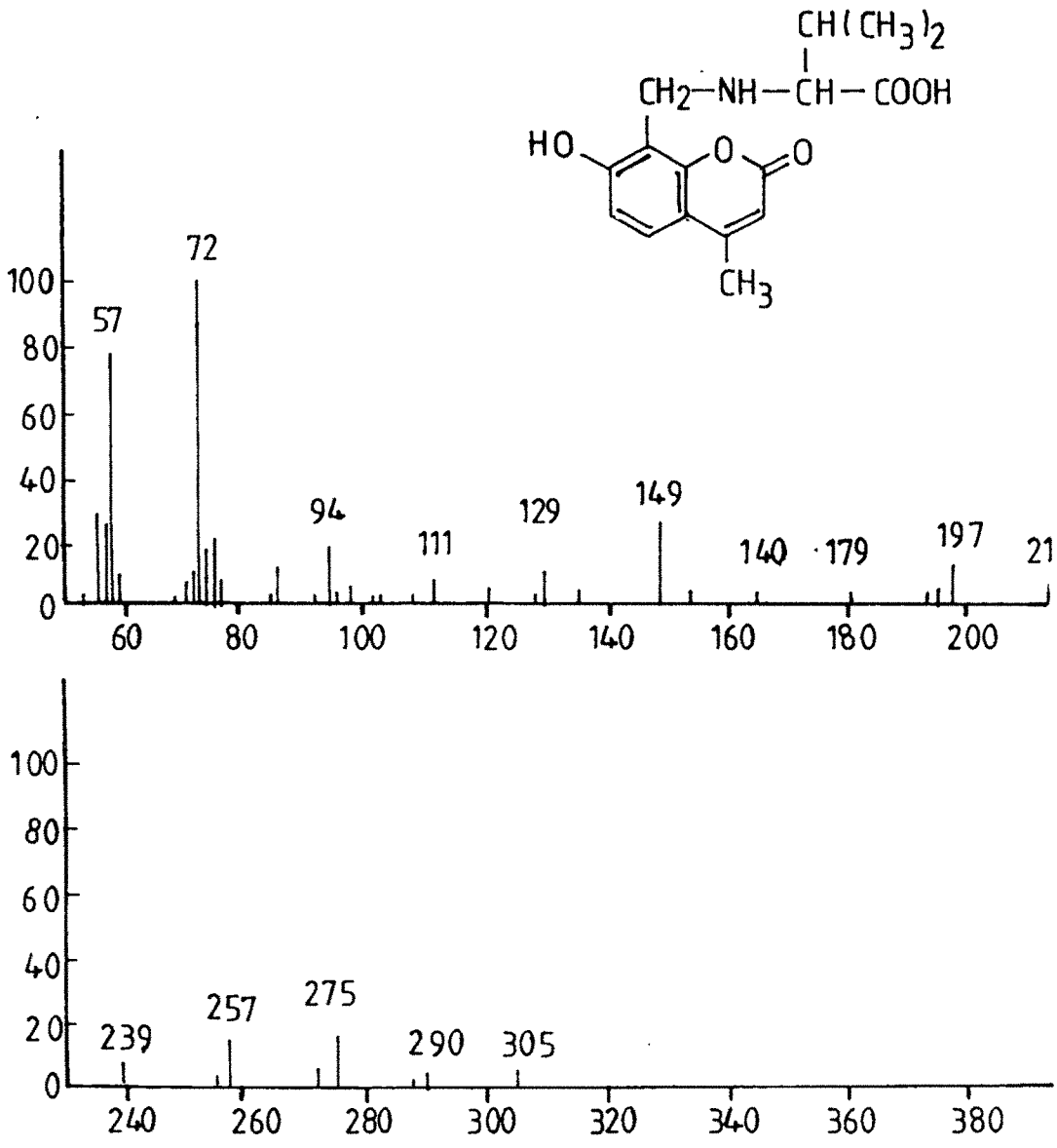

CH(CH3)2
CH2—NH—CH—COOH
HO
O
O
CH3
100
80
60
40
20
0
57
72
94
111
129
149
140
179
197
21
60
80
100
120
140
160
180
200
100
80
60
40
20
0
239
257
275
290
305
240
260
280
300
320
340
360
380

FIG. 7

Mannich reaction on 7-Hydroxy-4-phenylcoumarin (Scheme - 3)

N-(7-hydroxy-4-phenyl-8-coumarinyl) L-alanine (63, Table - 1, 15)

A mixture of 7-hydroxy-4-phenylcoumarin[74] (62), formalin and L-alanine when reacted, gave the product, which was assigned as N-(7-hydroxy-4-phenyl-8-coumarinyl) L-alanine structure. This structure was confirmed by following IR and PMR data.

The IR (KBr) spectrum, showed bands at 3500 (broad), 3150-2900 (broad), 1720 (broad) and 1600 cm^{-1} (Fig. 8).

The PMR spectrum in CF_3COOH exhibited a doublet at δ 1.6 for three protons of methyl group of alanine, $NHCH(C\underline{H})_3COOH$; a multiplet at δ 4.6 for one proton of CH attached with nitrogen NH-C<u>H</u>-COOH; a broad singlet at δ 5.0 for methylene protons -$C\underline{H}_2$-NH; a singlet at δ 6.25 for one proton at C-3 position of coumarin ring; a doublet at δ 6.8 of one proton at C-6 position (J=9Hz); a multiplet at δ 7.2-7.4 for aromatic protons of phenyl ring at C-4 position and a doublet at δ 7.5 for one proton at C-5 position (J=9Hz) (Fig. 9). The absence of signal of a proton at C-8 of coumarin ring indicates that substitution has taken place at C-8 position.

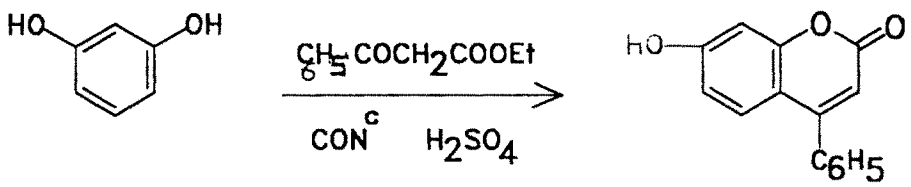
N-(7-hydroxy-4-phenyl-8-coumarinyl) L-methionine (63, Table - 1, 16)

7-hydroxy-4-phenylcoumarin when treated with formalin and L-methionine, gave 8-substituted Mannich product. The structure assigned was established by IR, PMR and Mass spectral data.

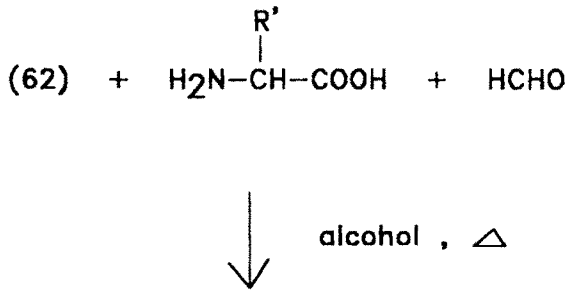
In IR (KBr) spectra bands were observed at 3450 (broad band), 3200-2900 (broad), 1720 (broad) and 1600 cm^{-1} (Fig. 10).

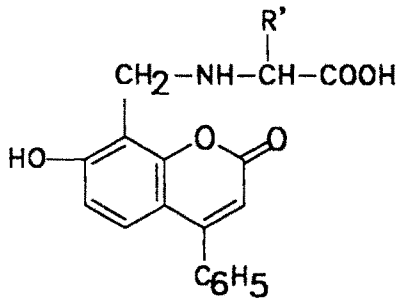
The PMR spectrum in CF_3COOH exhibited a singlet at δ 2.1 for methyl group protons of methionine part, CH_2-S-$C\underline{H}_3$; a multiplet at δ 2.3 due to methylene protons of $C\underline{H}_2$-CH_2-S-CH_3; a multiplet at δ 2.65 for methylene protons attached to sulphur, CH_2-$C\underline{H}_2$-S-CH_3; a multiplet at δ 4.5 for NH-C<u>H</u>-COOH; a broad singlet at δ 4.75 due to two protons of $C\underline{H}_2$-NH; a singlet at δ 6.32 due to one proton at C-3 position; a

SCHEME–3



(62)





(63)

(Table–1,15 to 18)

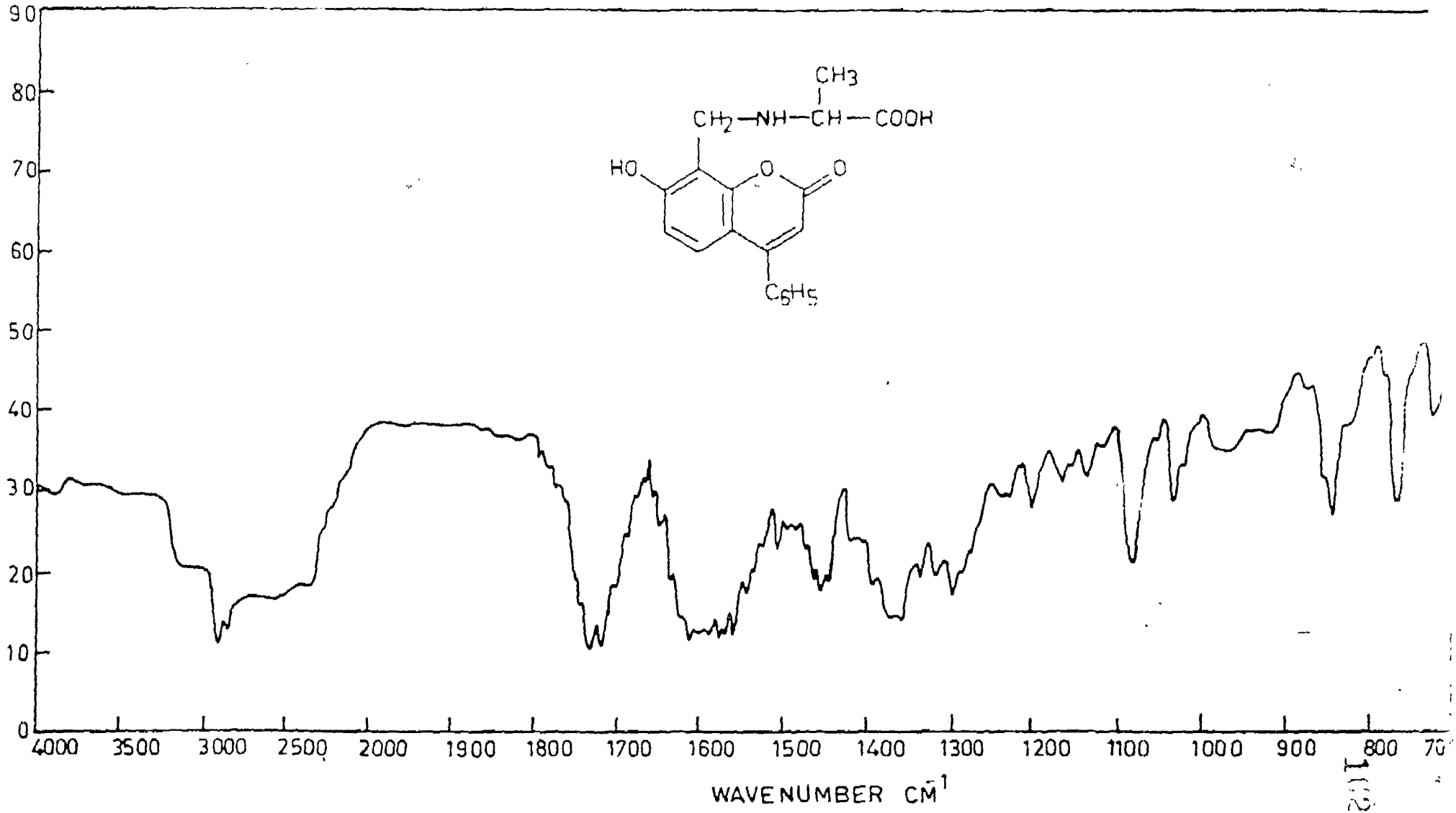
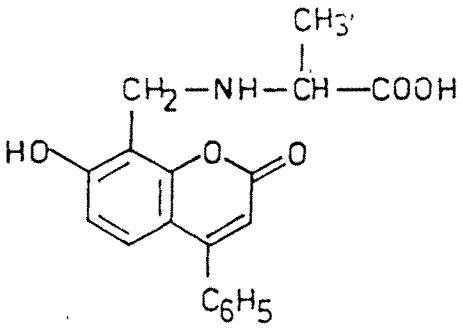

90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
WAVENUMBER CM⁻¹
CH3
CH2—NH—CH—COOH
HO
O
O
C6H5

FIG. 8



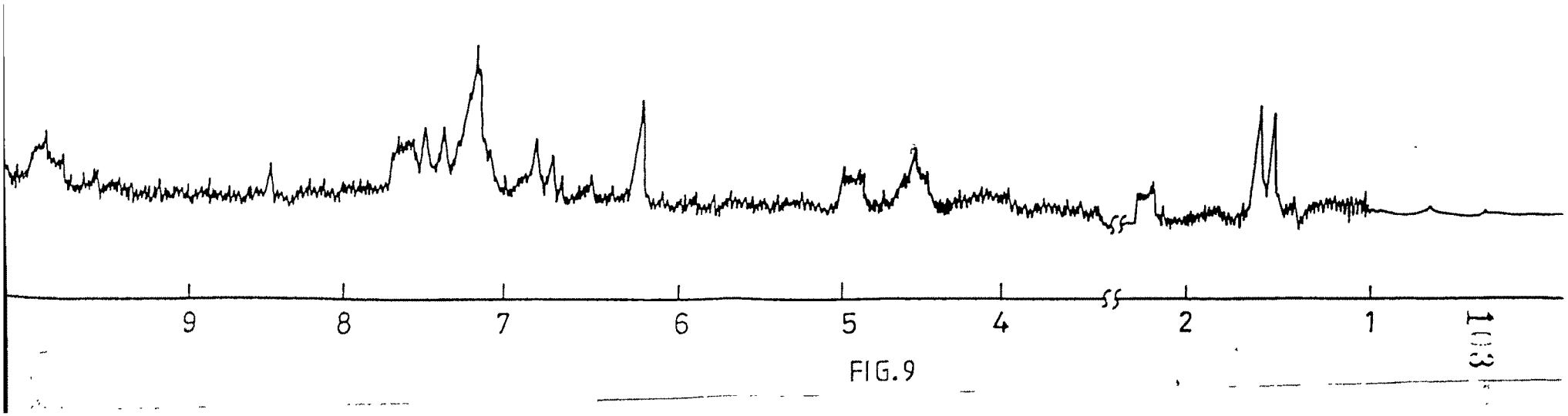


FIG.9

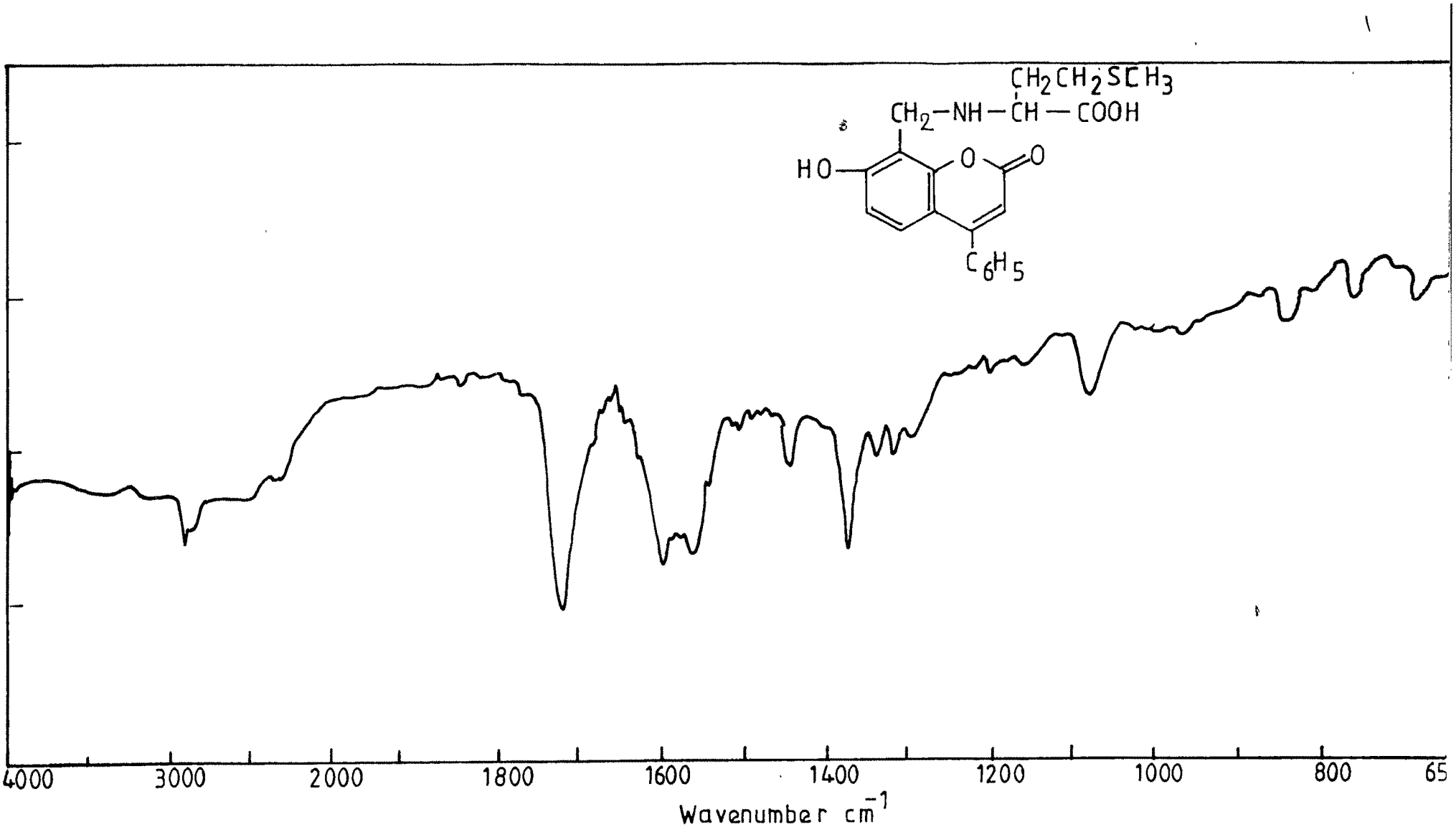

CH2CH2SCH3
CH2—NH—CH—COOH
HO
O
O
C6H5
4000
3000
2000
1800
1600
1400
1200
1000
800
65
Wavenumber cm-1

FIG. 10

doublet at δ 6.9 for one proton at position C-6 (J=10Hz); a doublet at δ 7.6 due to a proton at C-5 position (J=10Hz) and a broad singlet at δ 7.30 due to phenyl ring at C-4 position (Fig. 11).

The mass spectra exhibited peaks at following m/z; 399 (M^+, 10%), 129 (base peak, 100%) (Fig. 12).

Other Mannich products (15-18) on the same coumarin derivative have been synthesised in similar way.

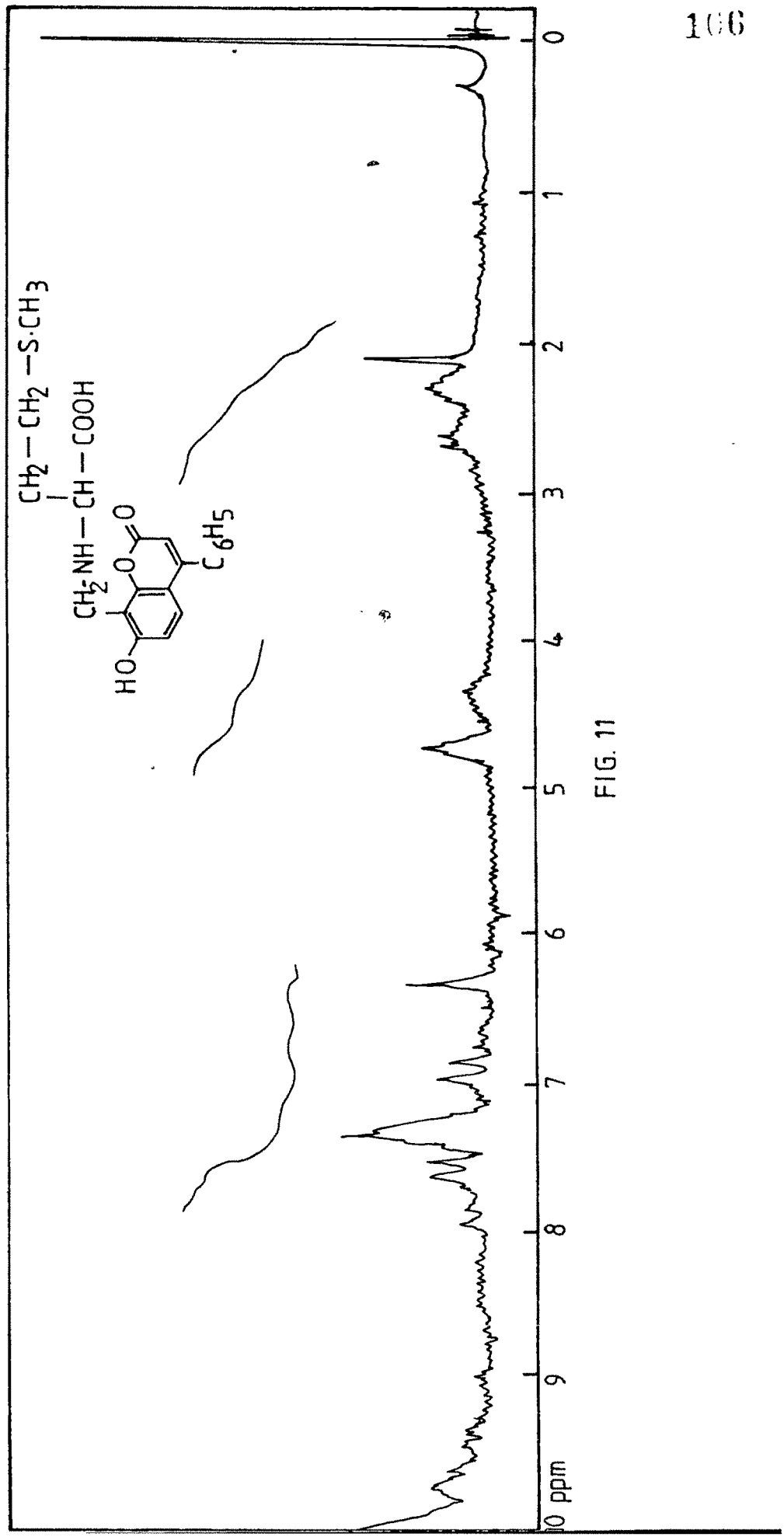


FIG. 11

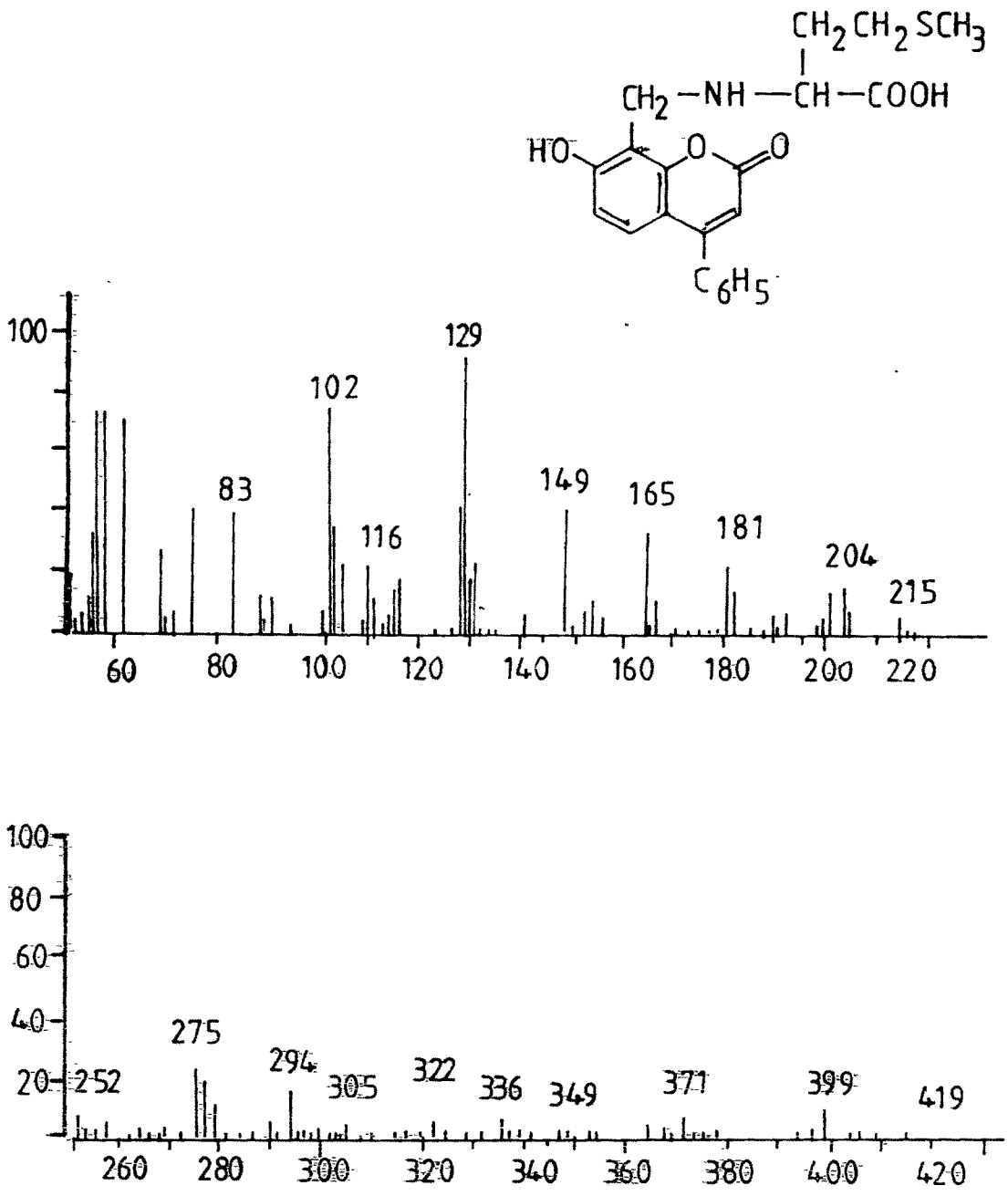

CH2CH2SCH3
CH2—NH—CH—COOH
HO
O
O
C6H5
100
129
102
83
149
165
116
181
204
215
60
80
100
120
140
160
180
200
220
100
80
60
40
20
275
294
252
305
322
336
349
371
399
419
260
280
300
320
340
360
380
400
420

FIG. 12

Experimental

All the melting points were determined in open capillaries using a paraffin bath and were uncorrected. Microanglysis of compounds were performed on a coleman instrument. IR spectra (KBr) were recorded on a shimadzu 408 spectrophotometer. PMR spectra were recorded on a Perkin-Elmer R-32 spectrometer using TMS as a internal standard. Mass spectra were recorded on Gas chromatograph Mass spectrometer Hewlett 5985 at 70 ev. Specific rotations were carried out on Jesso-Dip 370.2V digital polarimeter.

7-Hydroxycoumarin[71-72] (58)

A mixture of resorcinol (3.0 g), malic acid (2.46g) and concentrated sulfuric acid (6.1 ml)was heated on an oil-bath at 120°C for 1-1.5 hrs., till all the carbondioxide evolved off, it was cooled and treated with excess of crushed ice. The product was crystallised from dilute alcohol using decolouring charcol. M.p. 227-228°C, Yield 43%.

N-(7-Hydroxy-8-coumarinyl) L-alanine (59, Table - 1, 1)

7-hydroxycoumarin (1.62 g, 0.01 mol), L-alanine (0.89 g, 0.01 mol) and formalin (1.2 ml) in ethylalcohol were refluxed on the waterbath for 3 hrs The separated product was filtered, washed with water, dried and extracted with ethanol in soxhlet apparatus and finally crystallised from DMF. M.p. 250°C, Yield 70%

Analysis	:	Found	:	C, 59.20;	H, 5.26; N, 4.92%
$C_{13}H_{13}O_5N$	:	Required	:	C, 59.31;	H, 4.94; N, 5.32%

N-(7-Hydroxy-8-coumarinyl) L-methionine (59, Table - 1, 2)

7-hydroxycoumarin (1.62 g, 0.01 mol), L-methionine (1.49 g, 0.01 mol) formalin (1.2 ml) were mixed in 15-20 ml ethyl alcohol and refluxed for 3.5-4 hrs. Then the solid Mannich Product was filtered and washed with water to remove unreacted aminoacid and then extracted with hot alcohol using soxhlet apparatus to remove unreacted coumarin then it was purified by crystallisation using DMF. M.p. 230°C, Yield 75%.

Analysis	:	Found	:	C, 55.68;	H, 5.52; N, 4.51%
$C_{15}H_{17}O_5NS$	:	Required	:	C, 55.72;	H, 5.26; N, 4.33%

7-Hydroxy-4-methylcoumarin[73] (60)

Resorcinol (1.10 g, 0.01 mol), ethylacetoacetate (1.13 ml, 0.01 mol) and concentrated sulfuric acid (3.0 ml) were mixed and this was heated at 70°C on a water bath for 1 hr. The syrup obtained was poured into 200 ml ice water, filtered, washed and crystallised from 1:1 acetic acid. M.p. 179°C, Yield 80%

N-(7-Hydroxy-4-methyl-8-coumarinyl) L-alanine (61, Table - 1, 7)

7-hydroxy-4-methylcoumarin (1.76 g, 0.01 mol), L-alanine (0.89 gm, 0.01 mol), and formalin (1.2 ml) were taken in 15-20 ml ethanol (80%) and refluxed on a water bath for 4 hrs. The separated product was filtered and washed with water extracted with hot alcohol, dried and crystalised from DMF M.p. 248-50°C, Yield 70%

Analysis	:	Found	:	C, 61.11;	H, 5.88; N, 4.68%
$C_{14}H_{15}O_5N$	:	Required	:	C, 60.64;	H, 5.41; N, 5.05%

N-(7-hydroxy-4-methyl-8-coumarinyl) L-methionine (61, Table - 1, 8)

A mixture of 7-hydroxy-4-methylcoumarin (1.76 g, 0.01 mol) was dissolved in alcohol. To this, solution of L-methionine (1.49 g, 0.01 mol) in distilled water was added, followed by formalin (1.2 ml). The reaction mixture was refluxed on a water bath for 4 hrs. The separated product was worked out as usual. M.p. 264-65°C, Yield 80%.

Analysis	:	Found	:	C, 56.57;	H, 5.05; N, 4.46%
$C_{15}H_{19}O_5NS$	:	Required	:	C, 56.97;	H, 5.06; N, 4.15%

N-(7-hydroxy-4-methyl-8-coumarinyl) L-valine (61, Table - 1, 9)

A mixture of 7-hydroxy-4-methylcoumarin (1.76 g, 0.01 mol), L-valine (1.12 g, 0.01 mol) and formalin (1.2 ml) were mixed in 20 ml ethanol and refluxed for 3 hrs. The product separated was filtered and worked out as usual. M.p. 248°C, Yield 80%.

Analysis	:	Found	:	C, 62.52;	H, 6.61; N, 4.73%
$C_{16}H_{19}O_5N$	:	Required	:	C, 62.95;	H, 6.22; N, 4.59%

7-Hydroxy-4-phenylcoumarin[74] (62)

A mixture of ehtylbenzoylacetate (1.19 ml, 0.01 mol), resorcinol (1.10 g, 0.01 mol) and concentrated sulfuric acid (3.0 ml) was kept overnight. It was poured into ice-cold water. The separated product was filtered and crystallised from ethanol. M.p. 242-44°C, Yield 92%

N-(7-hydroxy-4-phenyl-8-coumarinyl)L-alanine (63, Table - 1, 15).

7-hydroxy-4-phenylcoumarin (2.38 g, 0.01 mol) was dissolved in 15 ml ethylalcohol, L-alanine (0.89 g, 0.01 mol) dissolved in distilled water was added to it, followed by formalin (1.2 ml). The reaction mixture was refluxed on a water bath for 3-4 hrs. The product separated during the reflux was then filtered, washed with water and extracted with hot ethanol using soxhlet apparatus M.p. 268°C, Yield 75%.

Analysis	:	Found	:	C, 67.70;	H, 5.49; N, 3.72%
$C_{19}H_{17}O_5N$	:	Required	:	C, 67.25;	H, 5.01; N, 4.12%

N-(7-hydroxy-4-phenyl-8-coumarinyl) L-methionine (63, Table - 1, 16)

7-hydroxy-4-phenylcoumarin (2.38 g, 0.01 mol), L-methionine (1.49 g, 0.01 mol) and formalin (1.2 ml) were mixed in 80% ethanol for 3-4 hrs. The separated product was worked out as usual. M.p. 243-44°C, Yield 75%.

Analysis	:	Found	:	C, 63.60;	H, 5.50; N, 3.16%
$C_{21}H_{21}O_5NS$	:	Required	:	C, 63.15;	H, 5.20; N, 3.50%

Table - 1. : Analytical and Physical Data of Compounds (59) (61) & (63)

Sr. No.	R	R'	M.P. in °C	Yield	Molecular Formula	Elemental Analysis Found / Required			Specific Rotation $[\alpha]_{25}^{D}$
						%C	%H	%N	
1.	H	CH_3	250	70	$C_{13}H_{13}O_5N$	59.20 59.31	5.26 4.94	4.92 5.32	+ 3.6014°
2.	H	$CH_2CH_2SCH_3$	230	75	$C_{15}H_{17}O_5NS$	55.68 55.72	5.52 5.26	4.51 4.33	+ 1.2005°
3.	H	$CH_2C_6H_5$	210	70	$C_{19}H_{17}O_5N$	66.80 67.25	5.01 5.01	4.61 4.12	+6.020°
4.	H	$CH(CH_3)_2$	240-42	75	$C_{15}H_{17}O_5N$	61.40 61.85	6.26 5.84	4.07 4.81	+25.210°
5.	H	$CH_2CH(CH_3)_2$	212-14	80	$C_{16}H_{19}O_5N$	62.50 62.95	6.57 6.27	4.82 4.59	+84.330°
6.	H	CH_2OH	221	65	$C_{13}H_{13}O_6N$	55.43 55.91	5.09 4.65	4.87 5.01	-24.090°
7.	CH_3	CH_3	248-50	70	$C_{14}H_{15}O_5N$	61.11 60.64	5.88 5.41	4.68 5.05	-1.2005°
8.	CH_3	$CH_2CH_2SCH_3$	264-65	80	$C_{16}H_{19}O_5NS$	56.57 59.97	5.65 5.63	4.46 4.15	+2.401°
9.	CH_3	$CH(CH_3)_2$	248	80	$C_{16}H_{19}O_5N$	62.52 62.98	6.61 6.22	4.73 4.59	+13.2050°

(contd..) Analytical and Physical Data of Compounds (59) (61) & (63)

Sr. No.	R	R'	M.P. in °C	Yield	Molecular Formula	Elemental Analysis Found / Required			Specific Rotation $[\alpha]_{25}^{D}$
						%C	%H	%N	
10.	CH_3	$CH_2C_6H_5$	235	75	$C_{20}H_{19}O_5N$	67.71 67.98	5.33 5.38	3.60 3.90	-1.2005°
11.	CH_3	$CH_2CH(CH3)2$	242-43	80	$C_{17}H_{21}O_5N$	64.34 63.94	6.20 6.58	4.59 4.38	+12.040°
12.	CH_3	CH_2OH	249-50	75	$C_{14}H_{15}O_6N$	57.57 57.33	5.85 5.11	5.05 4.77	-2.4010°
13.	CH_3	$CH(OH)CH_3$	245	60	$C_{15}H_{17}O_6N$	58.16 58.63	5.99 5.53	4.18 4.56	+12.040°
14.	CH_3	sarcosin	207-9	70	$C_{14}H_{15}O_5N$	60.95 60.64	5.14 5.41	5.22 5.05	No chiral centre
15.	C_6H_5	CH_3	268-70	75	$C_{19}H_{17}O_5N$	67.70 67.25	5.49 5.01	3.72 4.12	+7.2029°
16.	C_6H_5	$CH_2CH_2SCH_3$	243-44	75	$C_{21}H_{21}O_5NS$	63.60 63.15	5.50 5.20	3.16 3.50	+12.005°
17.	C_6H_5	$CH_2C_6H_5$	245-46	70	$C_{25}H_{21}O_5N$	72.19 72.28	5.01 5.06	2.97 3.37	-6.0024°
18.	C_6H_5	$CH(CH_3)_2$	256-60	80	$C_{21}H_{21}O_5N$	69.08 68.66	6.19 5.70	3.40 3.81	+10.8040°

All the compounds were crystallised from DMF

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