CHAPTER IV : SECTION 1

SYNTHESIS OF AMINOMETHYLFUROBENZOPYRONES

INTRODUCTION

In the previous chapters the occurrence, syntheses and properties of furocoumarins have been discussed in detail. It is well known that some of the naturally occurring psoralens (e.g. 8-MOP, TMP) are widely used in photochemotherapy of the wide spread dermatological disorders and also their action therapy as due to irreversible photoaddition of the drug to DNA. Later Issacs *et al.*[1] in their report proposed that by increasing the affinity and photoreactivity of a drug towards DNA, the efficiency of the therapy could be improved. Thus they attempted the synthesis of aminomethyl psoralen and reported that it not only has superior photoreactivity towards DNA and RNA than before but also increased the hydrophilic nature of the drug.

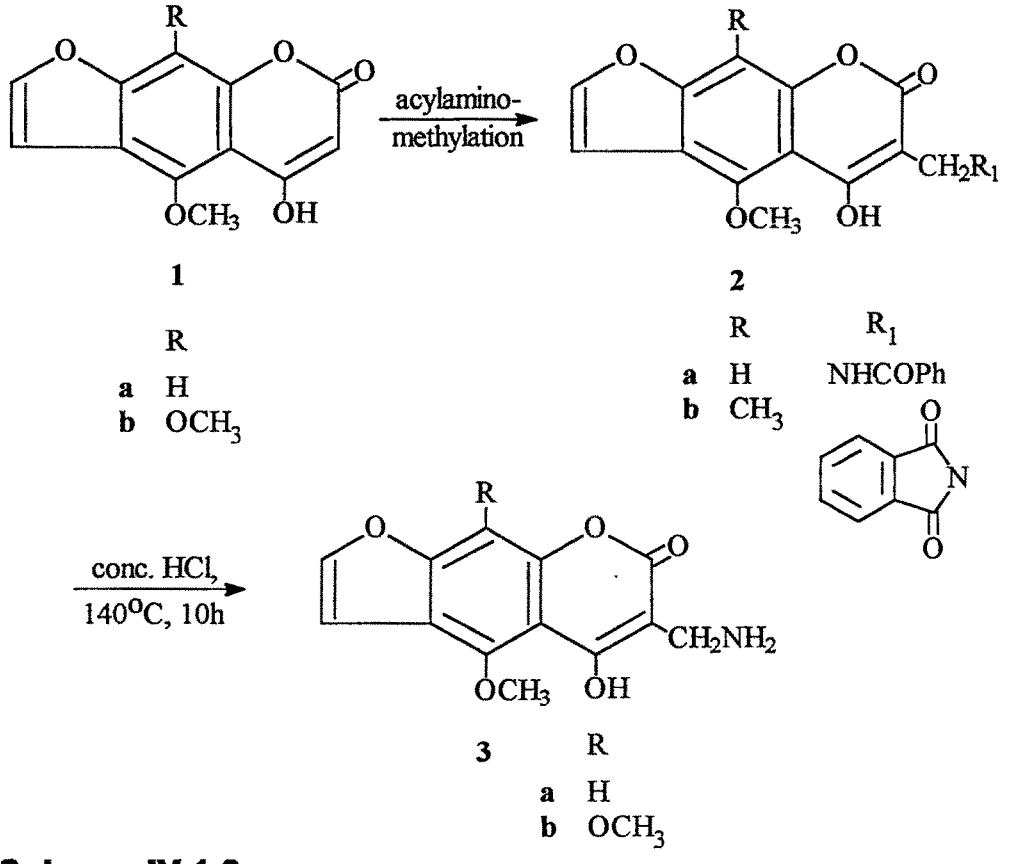
Some of the synthetic methods to prepare aminomethyl furobenzopyron and its derivatives are discussed here.

Hismat *et al.*[2] studied the acylaminomethylation of 4-hydroxybergapten (1a) and 4-hydroxyisopimpinillin (1b) with different N-hydroxymethyl carboxamides to give corresponding 3-acylaminomethyl derivatives **2a,b**. Acid hydrolysis of **2a,b** gave 3-aminomethyl derivatives **3a,b**. **[Scheme IV.1.1]**

Hansen *et al.*[3] reported the synthesis of 5-aminomethyl-8-methoxypsoralen (7), since 8-MOP is by far felt most important clinical drug and as an attempt to prepare hydrophilic derivative of 8-MOP, they condensed 8-MOP (4) with chloromethyl methyl ether in acetic acid to afford 5-chloromethyl derivative **5**. This on refluxing with NaN_3 gave 5-azidomethyl derivative **6** followed by reduction by catalytic hydrogenation in methanol using PtO_2 as catalyst resulted in the formation of 7. **[Scheme IV.1.2]**

While Isaacs *et al.*[1] synthesized psoralens having a haloalkyl, hydroxyalkyl, alkoxyalkyl and aminoalkyl groups at 4′-position of furan ring from trioxsalen (8) by first treating with $ClCH_2OCH_3$ to give chloromethyl product **9**, which on hydrolysis and subsequent treatment with methanol yielded

Scheme IV.1.1



1

	R
a	H
b	OCH_3

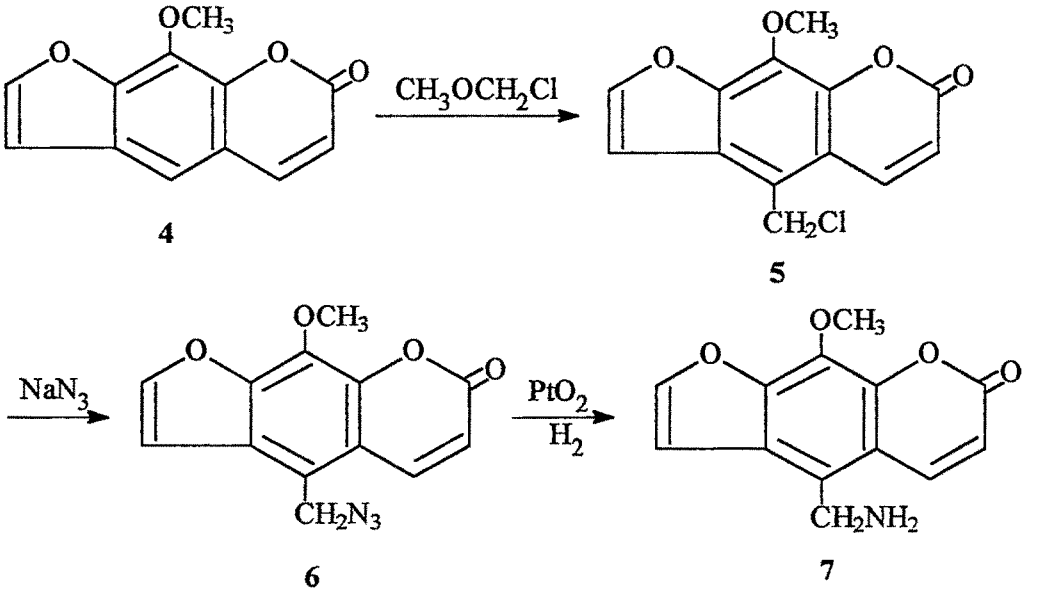
2

	R	R_1
a	H	NHCOPh
b	CH_3	

3

	R
a	H
b	OCH_3

Scheme IV.1.2



4

5

6

7

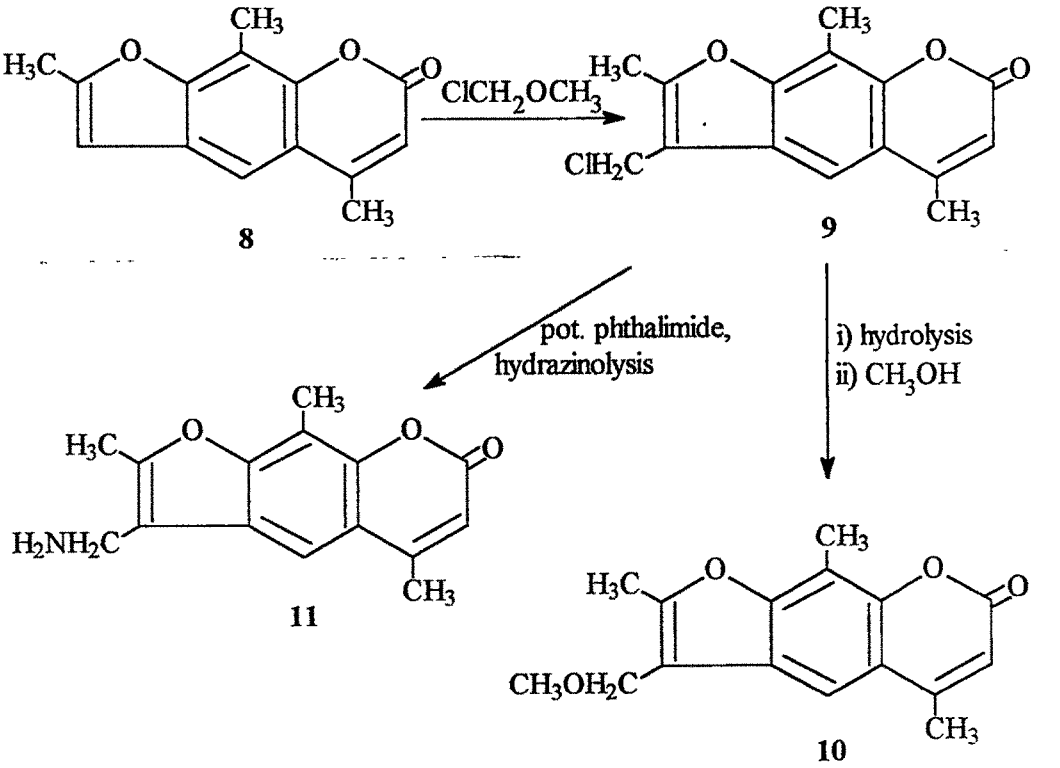
alkoxyalkyl derivative **10**. Whereas aminomethyl psoralens **11** were obtained by phthalimidation followed by hydrazinolysis. **[Scheme IV.1.3]**

They also reported that these compounds exhibit high solubility in aqueous solutions and low dissociation constants from DNA and also are good inhibitors of RNA in the activation of viruses as well as in photochemotherapy of psoriasis.

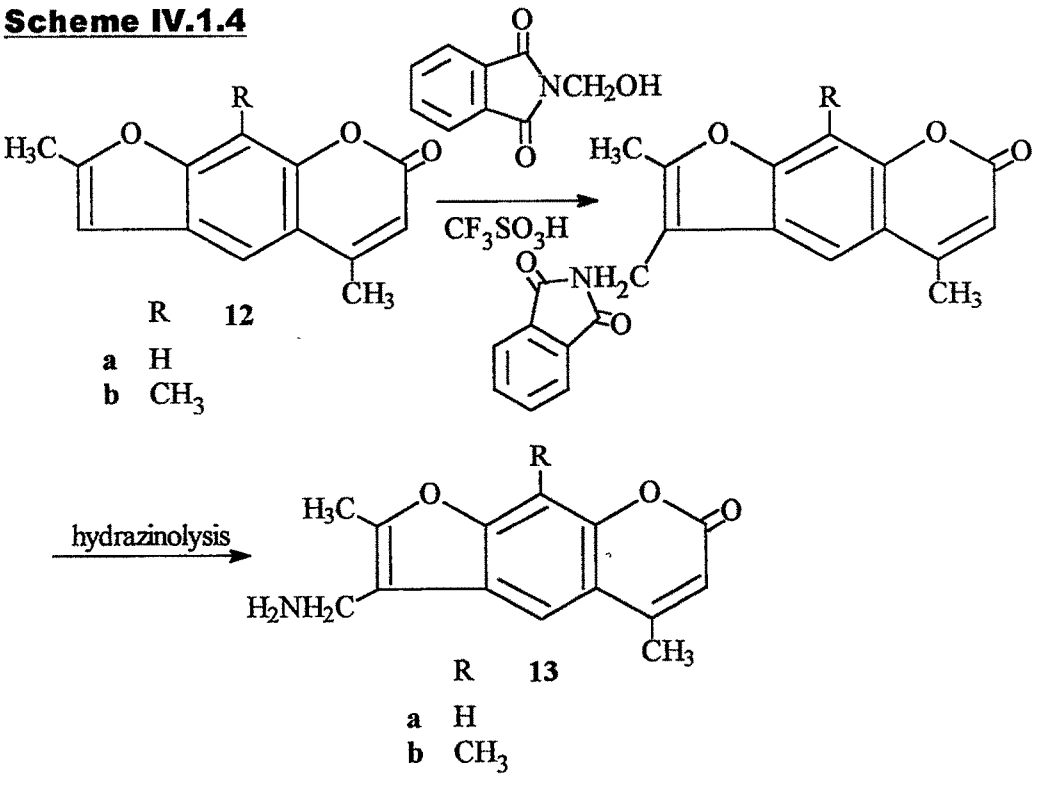
Heindel and coworkers[4] synthesized aminomethylpsoralens **13a,b** by electrophilic substitution of N-hydroxymethylphthalimide on the furan ring of psoralens **12a,b** followed by hydrazinolysis. Although the method is very attractive with 60-70% yields, but methoxy, hydroxy groups containing psoralens undergo multisite electrophilic substitution by the phthalimidomethyl group. **[Scheme IV.1.4]**

Rao and Trivedi[5] reported some 4-aminomethyldihydroangelicin derivatives by using method of Kelkar *et al.*[6]. 3-Bromo7-hydroxy-4-methyl coumarin (14) was first allylated to give allyloxy derivative **15** followed by Claisen rearrangement with refluxing DMA to afford **16**, which on cyclization with conc. H_2SO_4 furnished 2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (17). Bromination with pyridinehydrobromideperbromide gave 6-bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (18). **18** when condensed with piperidine using DMF as solvent produced two products; 2,7-dimethyl-6-piperidinyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (19) and 2-methyl-7-piperidinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one (20). **[Scheme IV.1.5]**

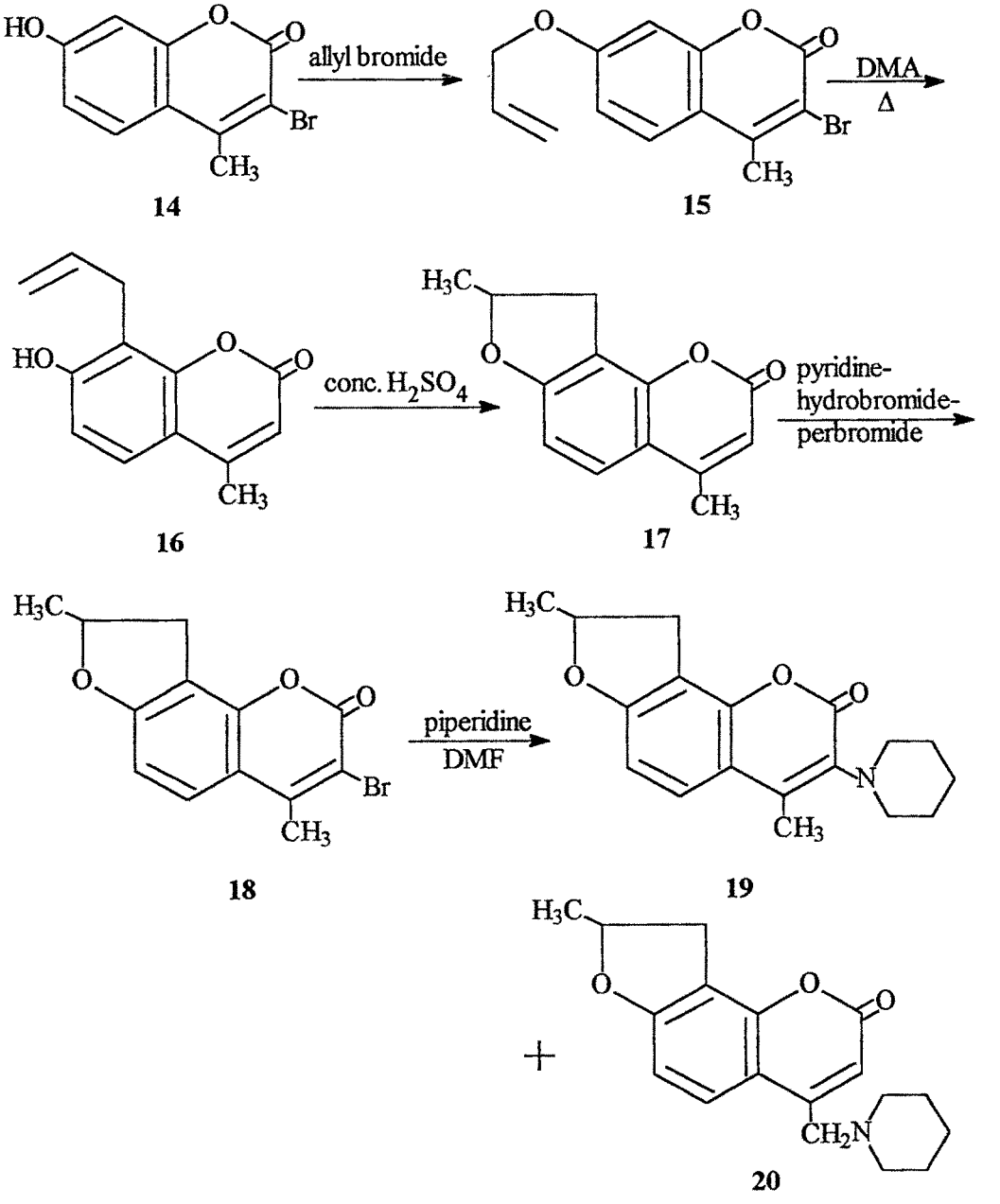
Scheme IV.1.3



Scheme IV.1.4



Scheme IV.1.5

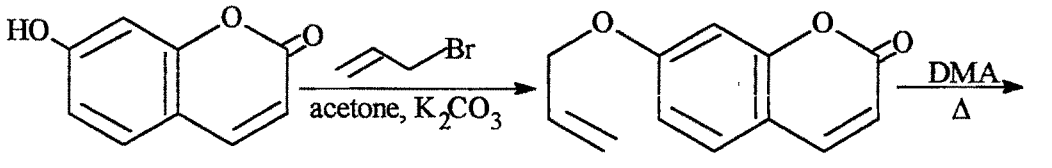

HO
O
O
Br
CH3
allyl bromide
DMA
Δ
14
15
conc. H2SO4
H3C
pyridine-
hydrobromide-
perbromide
16
17
piperidine
DMF
N
18
19
CH2N
20

PRESENT WORK

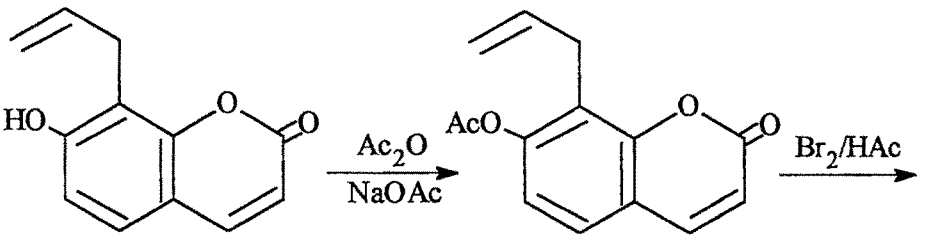
In the present work, the methyl group of the furobenzopyrone derivative is transformed in to an aminomethyl derivative to enhance its hydrophilic character. 4′-Aminomethyl- and 5′-aminomethyl- psoralens are reported to have good photodynamic behaviour for viral inactivation[7], in dermal photosensitization[8], in photochemotherapy against L_{1210} Lukemia in mice[9], in photoactivated DNA binding[1] and in the treatment of dermatological disorders[10,11]. As a result, the penetration of the compound into skin during topical application improves and efficiency of the therapy will be increased.

2-Piperidinomethylfuro(2,3-h)benzopyran-5H-one (28) was prepared by first allylating the 7-hydroxybenzopyran-2H-one (21) with allylbromide to give 7-allyloxybenzopyran-2H-one (22), which on Claisen migration in boiling DMA gave 7-hydroxy-8-allylbenzopyran-2H-one (23). **23** on acetylation gave acetoxy derivative **24** followed by bromination across the double bond in the allyl side chain with bromine in acetic acid furnished 7-acetoxy-8-(2′,3′-dibromopropyl) benzopyran-2H-one (25). Cyclodebromination of **25** with ethanolic KOH resulted in the formation of 2-methylfuro(2,3-h)benzopyran-5H-one (26). The methylangelicin **26** when treated with NBS in carbon tetrachloride in the presence of benzoylperoxide yielded its bromomethyl derivative. **[Scheme IV.1.6]** The structure was confirmed by elemental analysis, IR and PMR spectra as 2-bromomethylfuro(2,3-h)benzopyran-5H-one (27). Its IR spectrum showed absorption band at 1732cm^{-1} for >CO of lactone **[Fig. IV.1.1]** while the PMR exhibited signals at δ 4.70, a singlet for methylene group protons of -C$\underline{H_2}$Br at C-2; a doublet at 6.40, J = 9Hz for a proton at C-6; singlet at 7.20 for a proton at C-3; two doublets at 7.40, J = 8.5Hz and 7.55, J = 8.5Hz for each one proton at C-9 and C-8 respectively and another doublet at 7.80, J = 9Hz for a proton at C-7. **[Fig. IV.1.2]** **27** was then

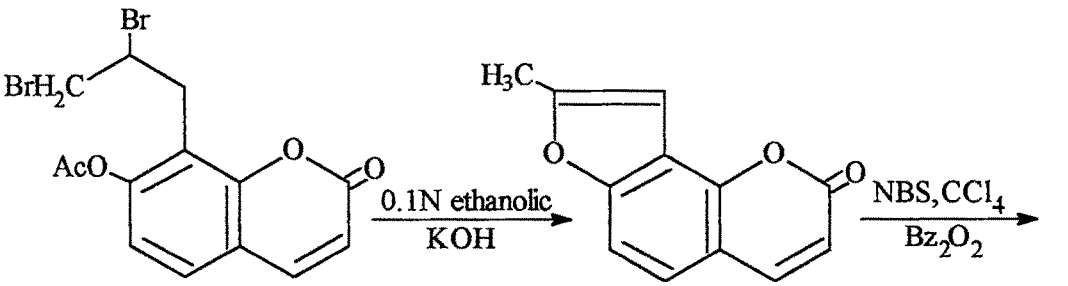
Scheme IV.1.6



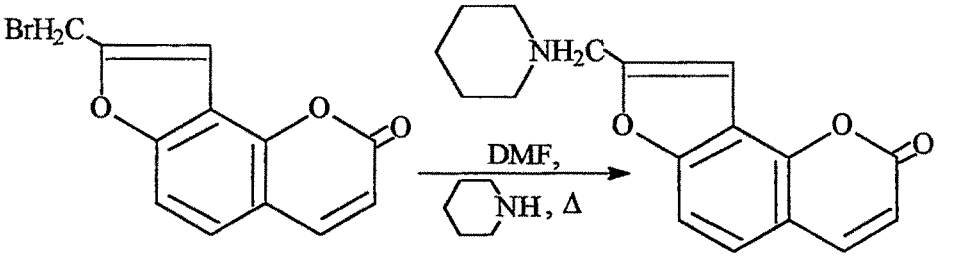
21 **22**



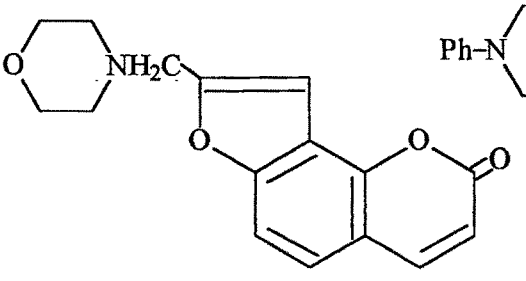
23 **24**



25 **26**



27 **28**



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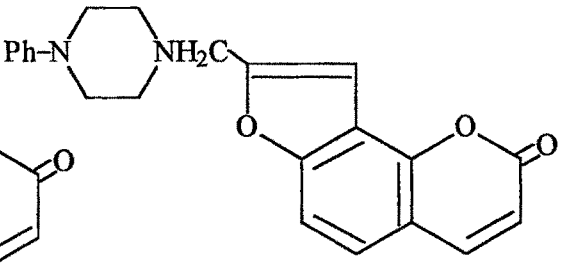

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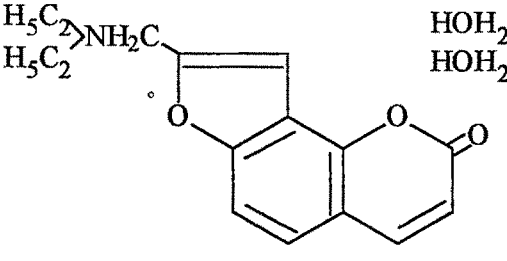

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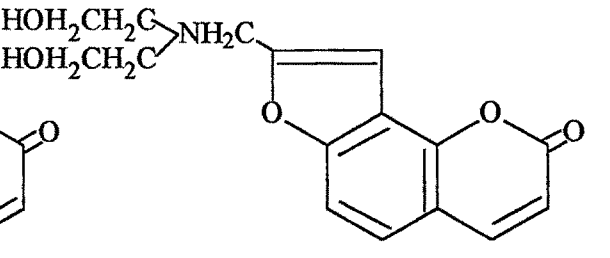

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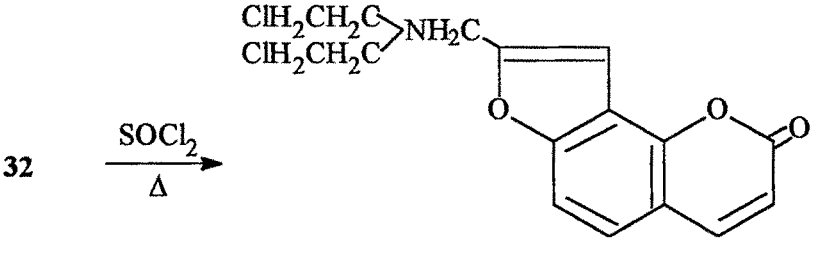

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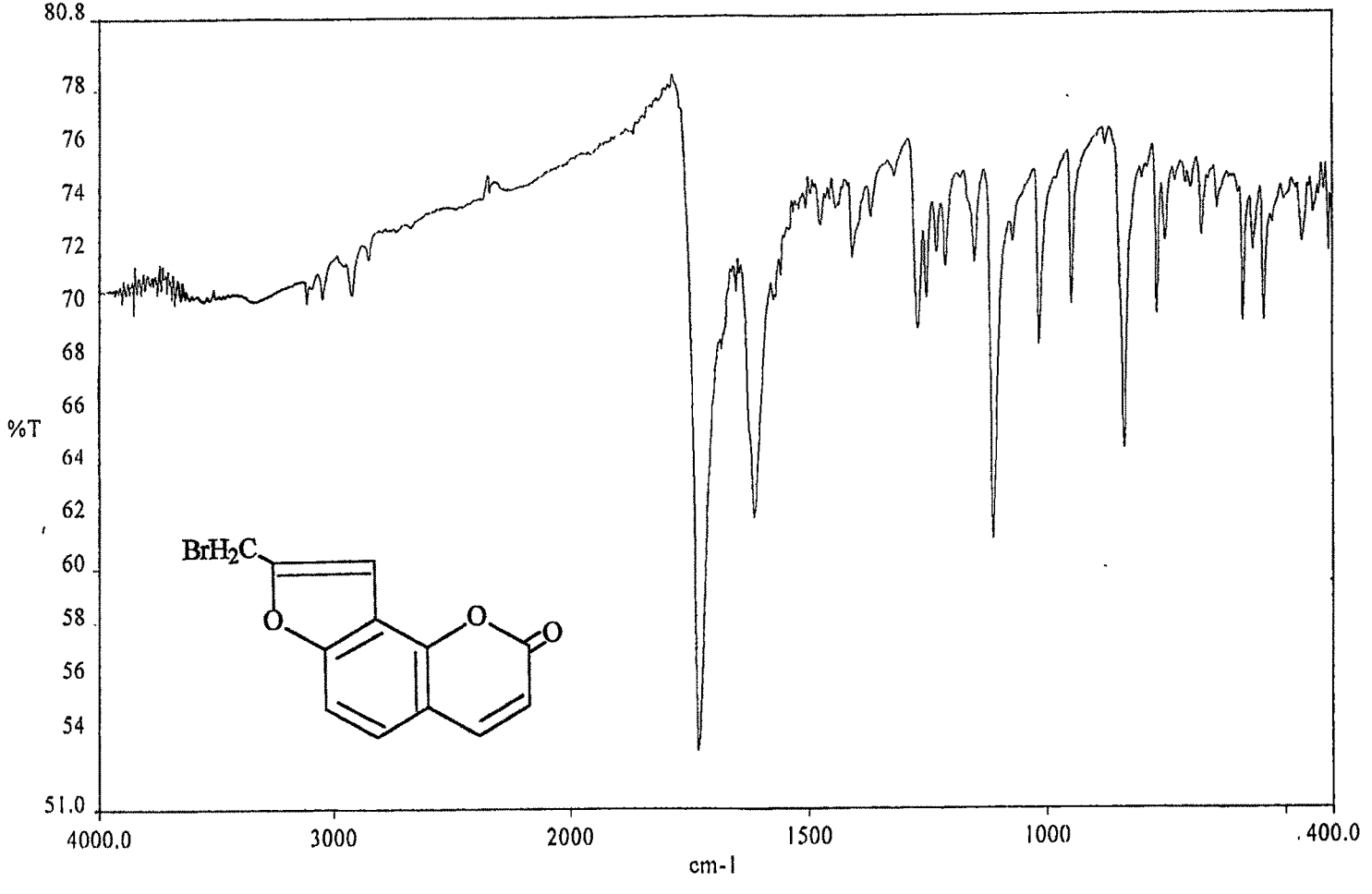

80.8
78
76
74
72
70
68
66
64
62
60
58
56
54
51.0
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
BrH2C
O
O
O

Fig. IV.1.1

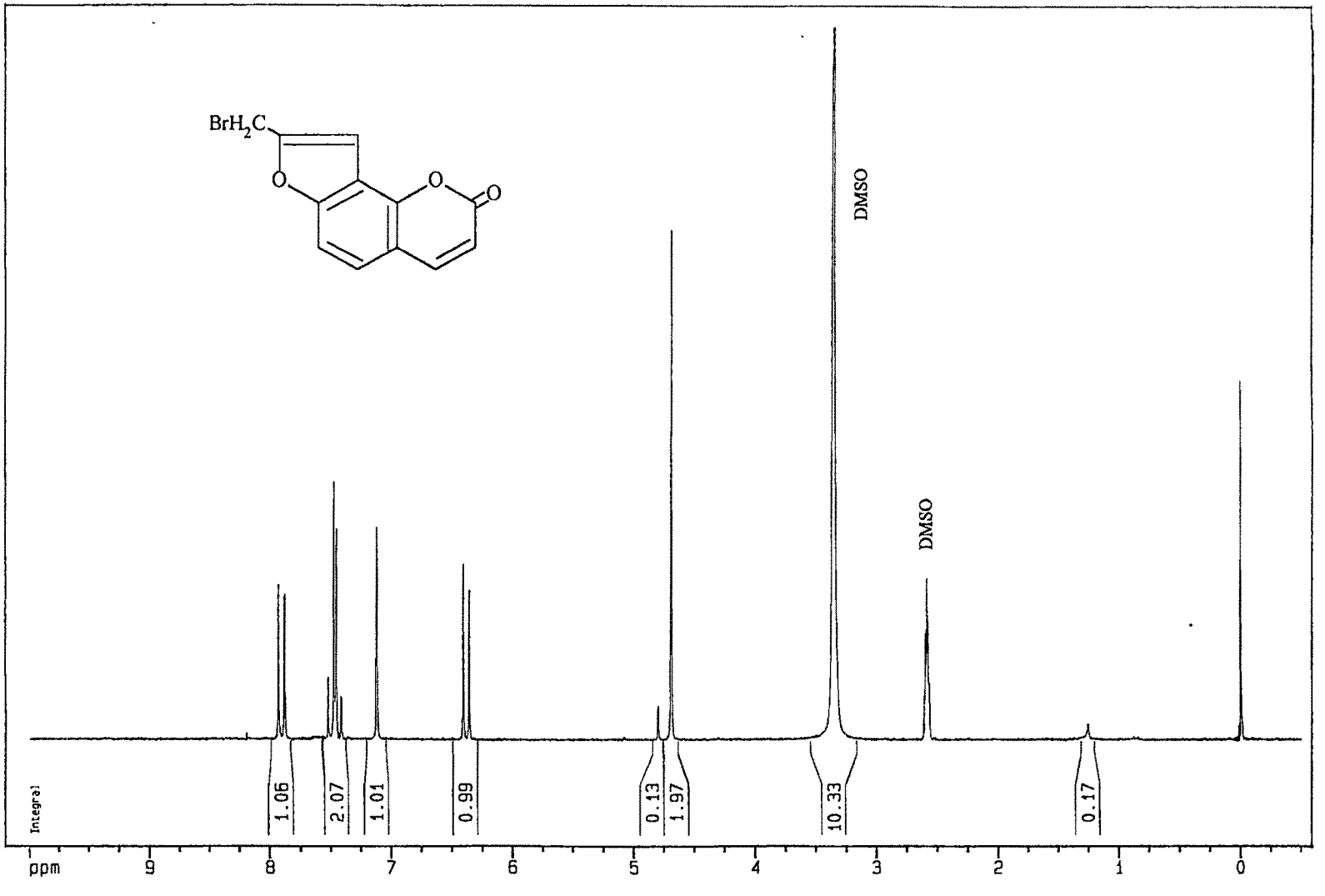
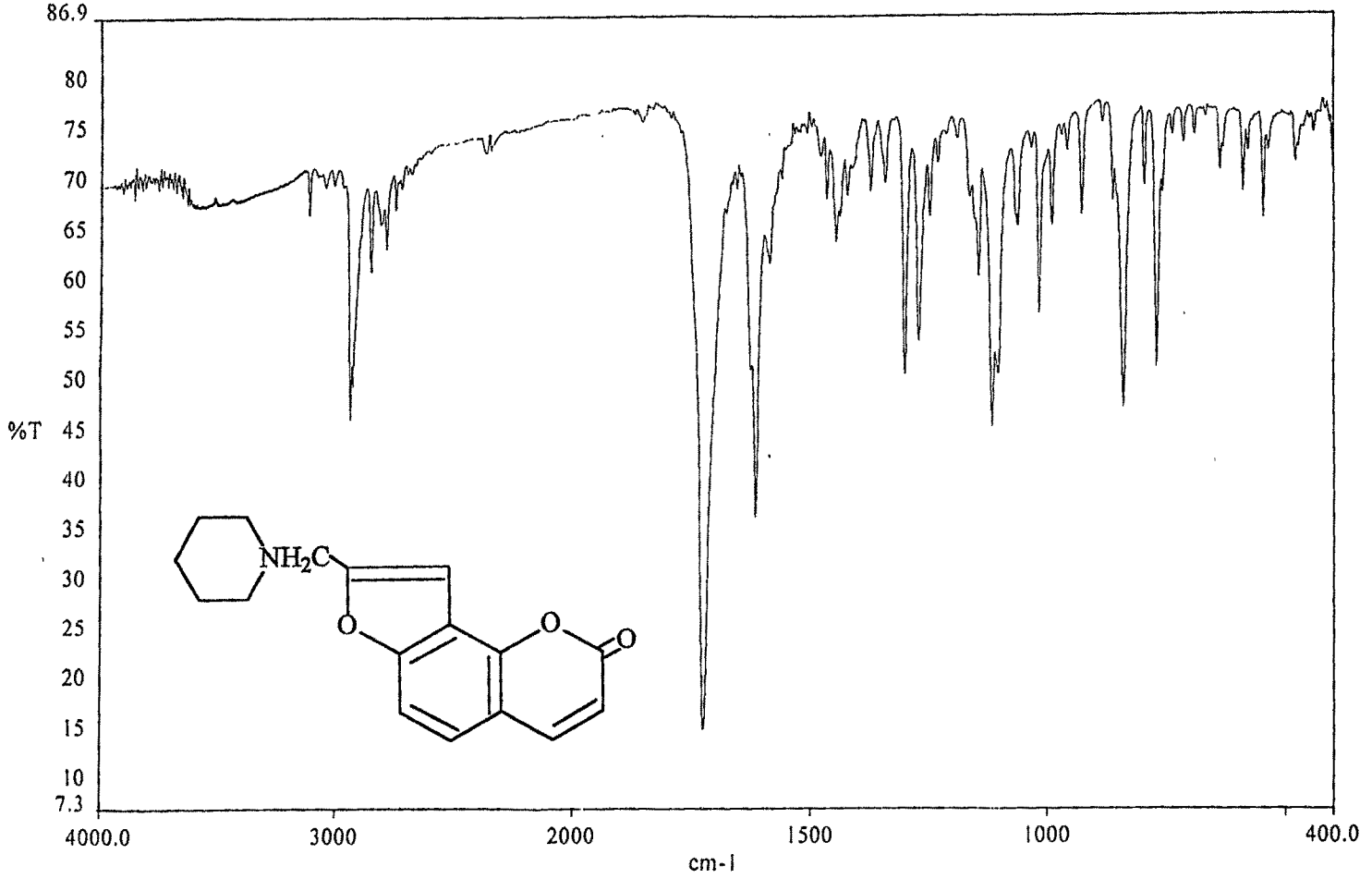

BrH2C
O
O
O
DMSO
DMSO
Integral
1.06
2.07
1.01
0.99
0.13
1.97
10.33
0.17
ppm
9
8
7
6
5
4
3
2
1
0

Fig. IV.1.2

condensed with piperidine in DMF, gave its piperidinomethyl derivative **28**, which was confirmed by elemental analysis, IR and PMR spectra. Its IR spectrum showed absorption band in KBr at 1725cm^{-1} for >CO of lactone **[Fig. IV.1.3]** while the PMR signals in $CDCl_3$ appeared at δ 1.70, a multiplet for six protons of three methylene groups in the piperidine ring away from N at C-2; another multiplet at 2.60 for four protons of two methylene groups in the piperidine ring attached to N at C-2; a singlet at 3.65 for two protons at C-2; a doublet at 6.35, J = 9Hz for a proton at C-6; another singlet at 6.85 for a proton at C-3; a multiplet at 7.25 for two protons at C-9 and C-8 and a doublet appeared at 7.75, J = 9Hz for a proton at C-7. **[Fig. IV.1.4]**

Similarly cyclic secondary amines like morpholine, N-phenylpiperazine and aliphatic secondary amines such as diethylamine, diethanolamine were also condensed using DMF as a solvent with above bromomethyl product **27** to get their corresponding aminomethyl derivatives **29-32**. Chlorination of diethanolamine condensed product **32** was also carried out with thionylchloride to prepare nitrogen mustard **33**.

2-Morpholinomethylfuro(3,2-g)benzopyran-7H-one (41) was prepared by first iodinating 7-hydroxybenzopyran-2H-one (21) with iodine and potassium iodide in liq. NH_3 to give 7-hydroxy-8-iodobenzopyran-2H-one (34). **34** on allylation with allylbromide furnished 7-allyloxy-8-iodobenzopyran-2H-one (35). **35** on Claisen rearrangement produced 7-hydroxy-6-allylbenzopyran-2H-one (36), which was acetylated to form acetoxy derivative **37**. Bromination of **37** resulted in the formation of dibromo derivative **38**, which on subsequent cyclodebromination produced 2-methylfuro(3,2-g)benzopyran-7H-one (39). **[Scheme IV.1.7]** Bromination of methyl group was carried out with NBS using CCl_4 as a medium to prepare 2-bromomethylfuro(3,2-g)benzopyran-7H-one (40), which was confirmed by elemental analysis, IR and PMR data. Its IR spectrum showed band in KBr at1734cm^{-1} for >CO of lactone **[Fig. IV.1.5]** while the PMR exhibited signals in $CDCl_3$ at δ 4.65, a singlet for two methylene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80
75
70
65
60
55
50
%T 45
40
35
30
25
20
15
10
7.3
4000.0
3000
2000
1500
1000
400.0
cm-1
NH2C
O
O
O

Fig. IV.1.3

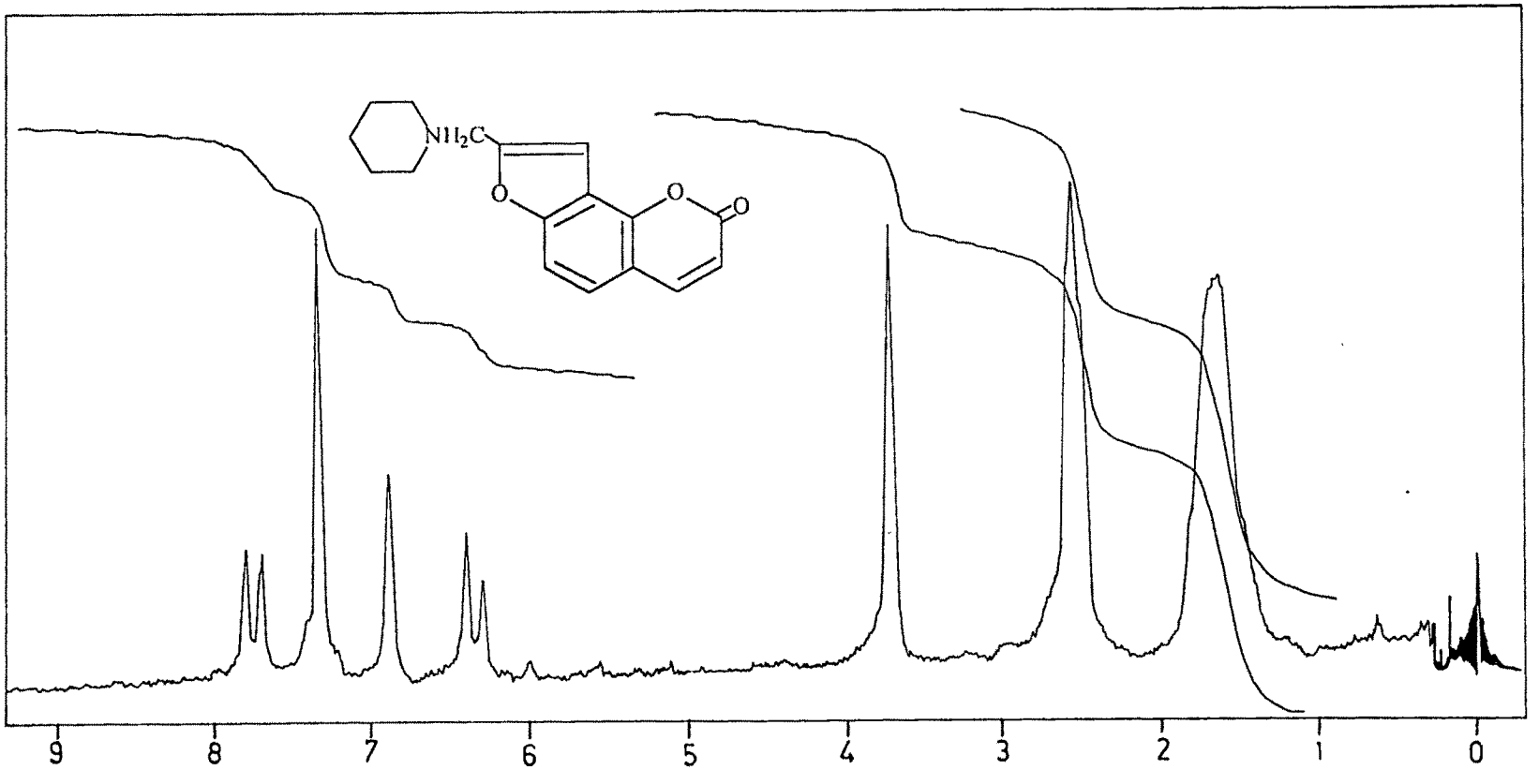
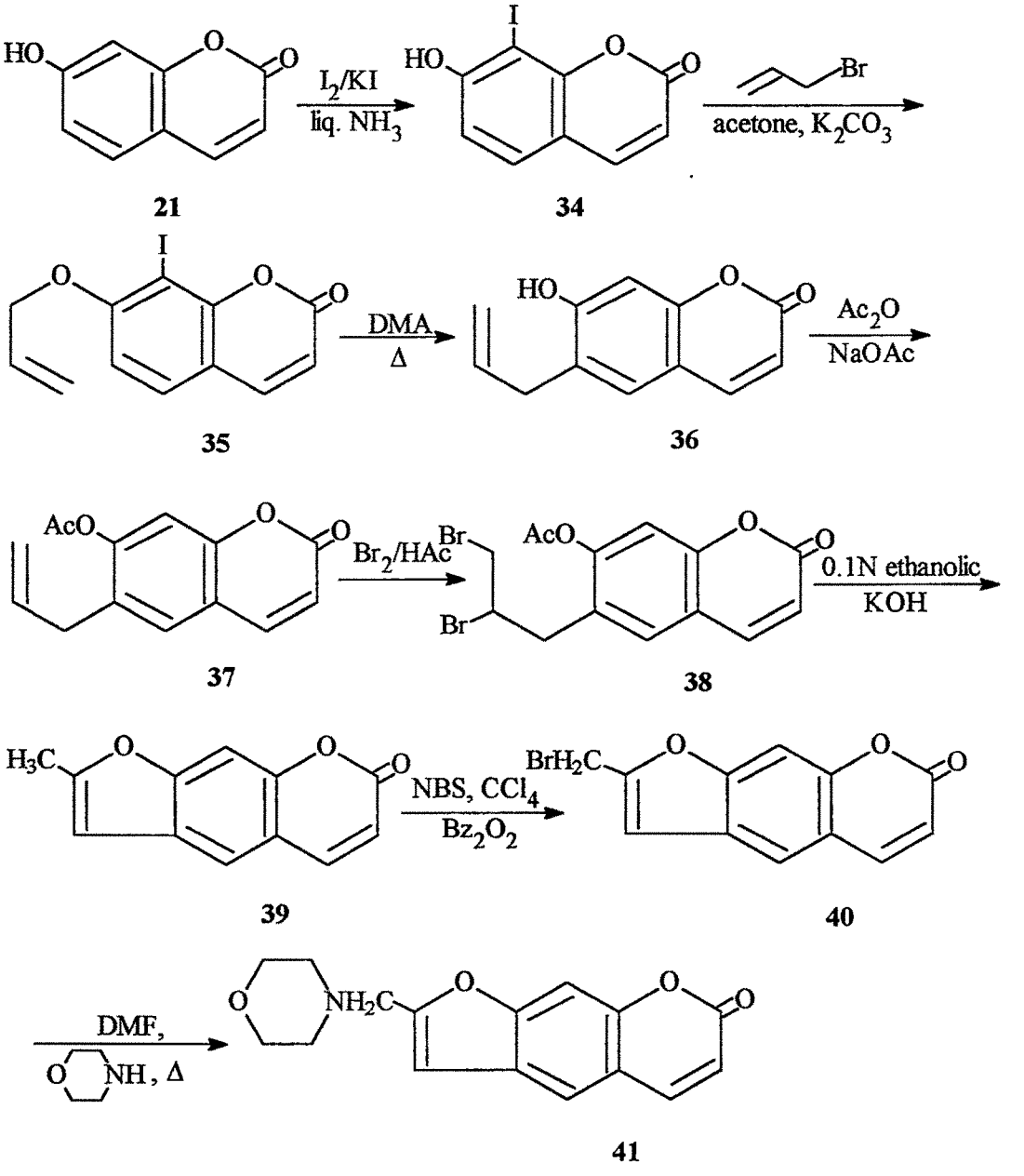
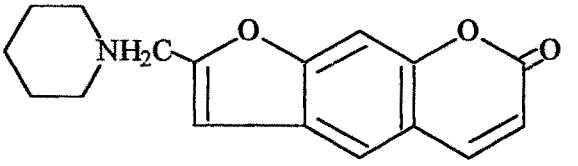


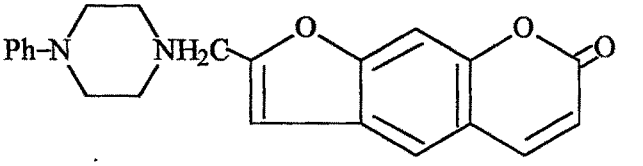
Fig. IV.1.4

Scheme IV.1.7


HO
O
O
I2/KI
liq. NH3
I
Br
acetone, K2CO3
21
34
DMA
Δ
Ac2O
NaOAc
35
36
AcO
Br2/HAc
Br
0.1N ethanolic
KOH
37
38
H3C
NBS, CCl4
Bz2O2
BrH2C
39
40
DMF,
NH, Δ
NH2C
41



42



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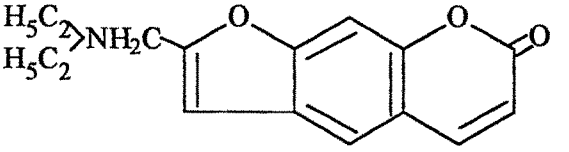

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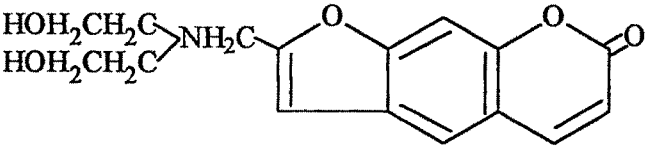
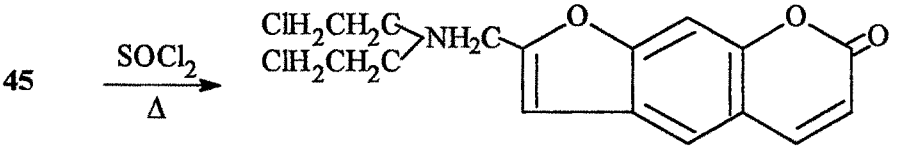


45



46

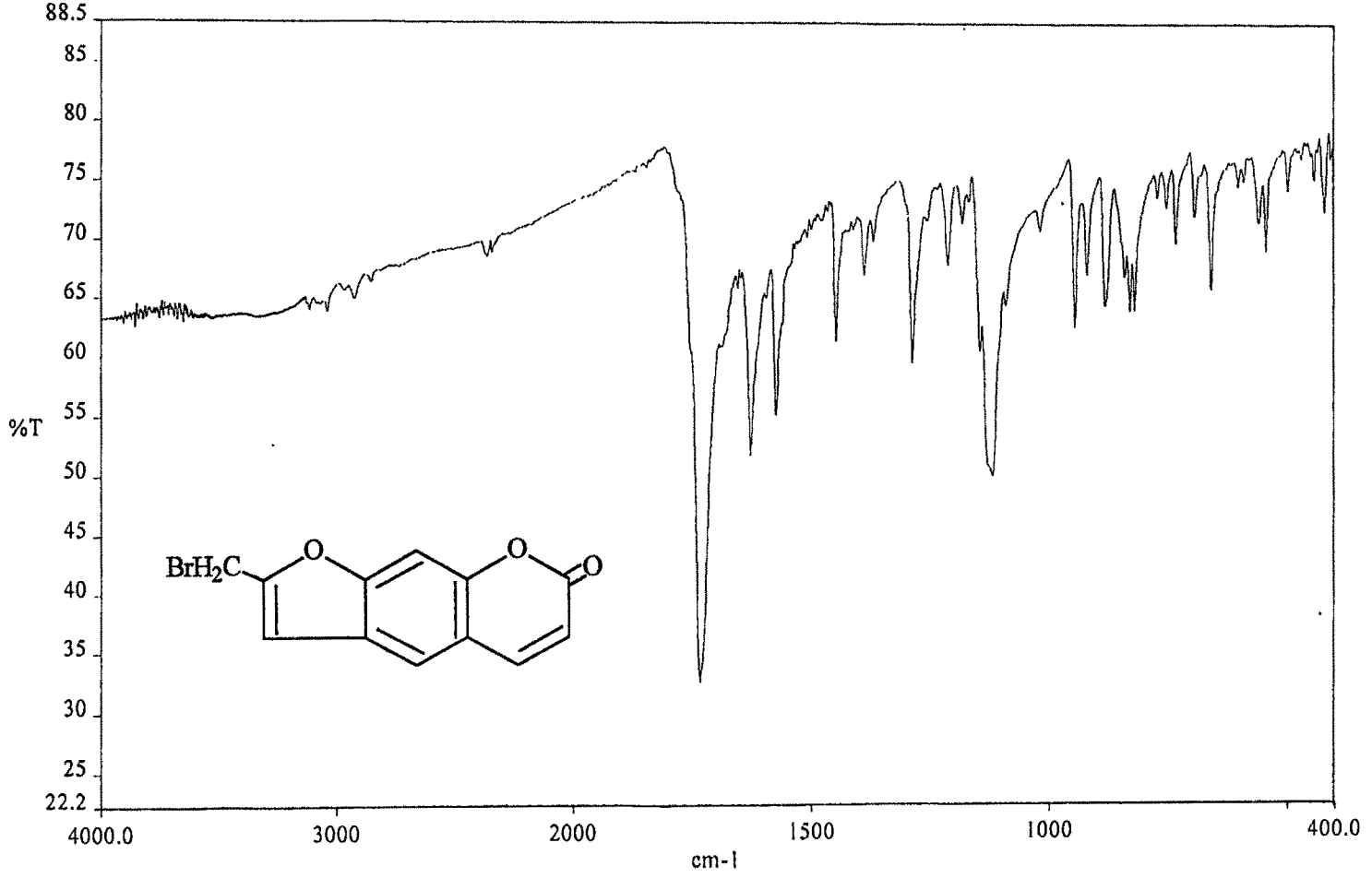

88.5
85
80
75
70
65
60
55
%T
50
45
40
35
30
25
22.2
4000.0
3000
2000
1500
1000
400.0
cm-1
BrH2C
O
O
O

Fig. IV.1.5

group protons of -$\underline{CH_2}$Br at C-2; doublet at 6.30, J = 9Hz for a proton at C-6; three singlets at 6.85, 7.40 and 7.70 for each one proton at C-3, C-4 and C-9 respectively and a doublet at 7.85, J = 9Hz for a proton at C-5. **[Fig. IV.1.6]** **40** was then condensed with morpholine in DMF, gave its morpholinomethyl derivative **41**, which was confirmed by elemental analysis, IR and PMR spectra. Its IR spectrum showed band in KBr at 1716cm^{-1} due to >CO of lactone **[Fig. IV.1.7]** while the PMR signals in $CDCl_3$ appeared at δ 2.50, a broad singlet for four protons of methylene groups in the morpholine ring attached to N at C-2; another broad singlet at 3.75 for six protons of two methylene groups in the morpholine ring and one methylene group at C-2; a doublet at 6.25, J = 9Hz for a proton at C-6; three singlets at 6.60, 7.35 and 7.55 for each one proton at C-3, C-4 and C-9 and a doublet appeared at 7.75, J = 9Hz for a proton at C-5. **[Fig. IV.1.8]**

Similarly secondary cyclic amines like piperidine, N-phenylpiperazine and aliphatic amines like diethylamine, diethanolamine were also condensed with above bromomethyl product **40** to get their corresponding aminomethyl derivatives **42-45**. Nitrogen mustard **46** was also prepared by chlorination of diethanolamine reaction product **44** with $SOCl_2$ in a convenient way.

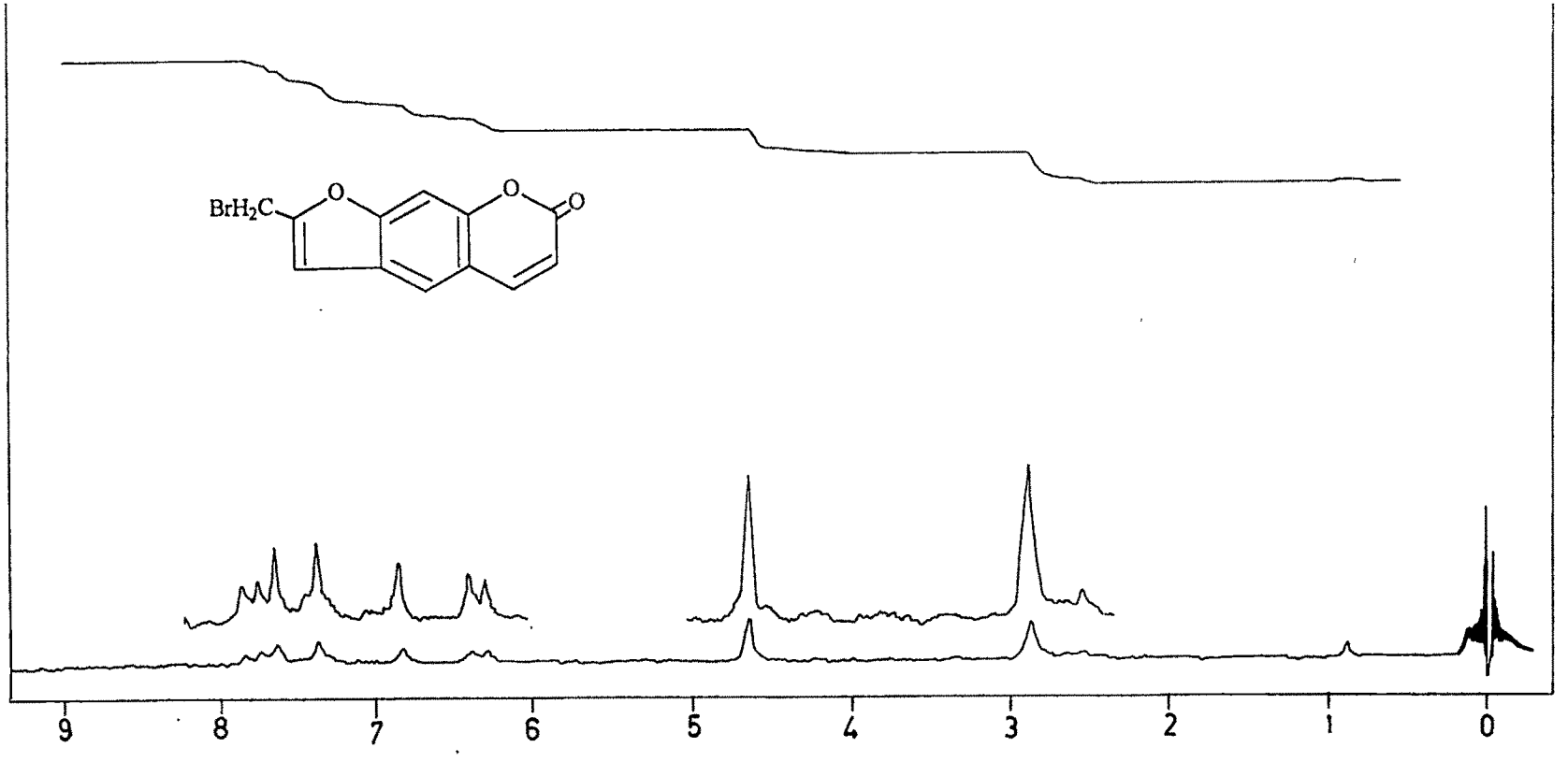
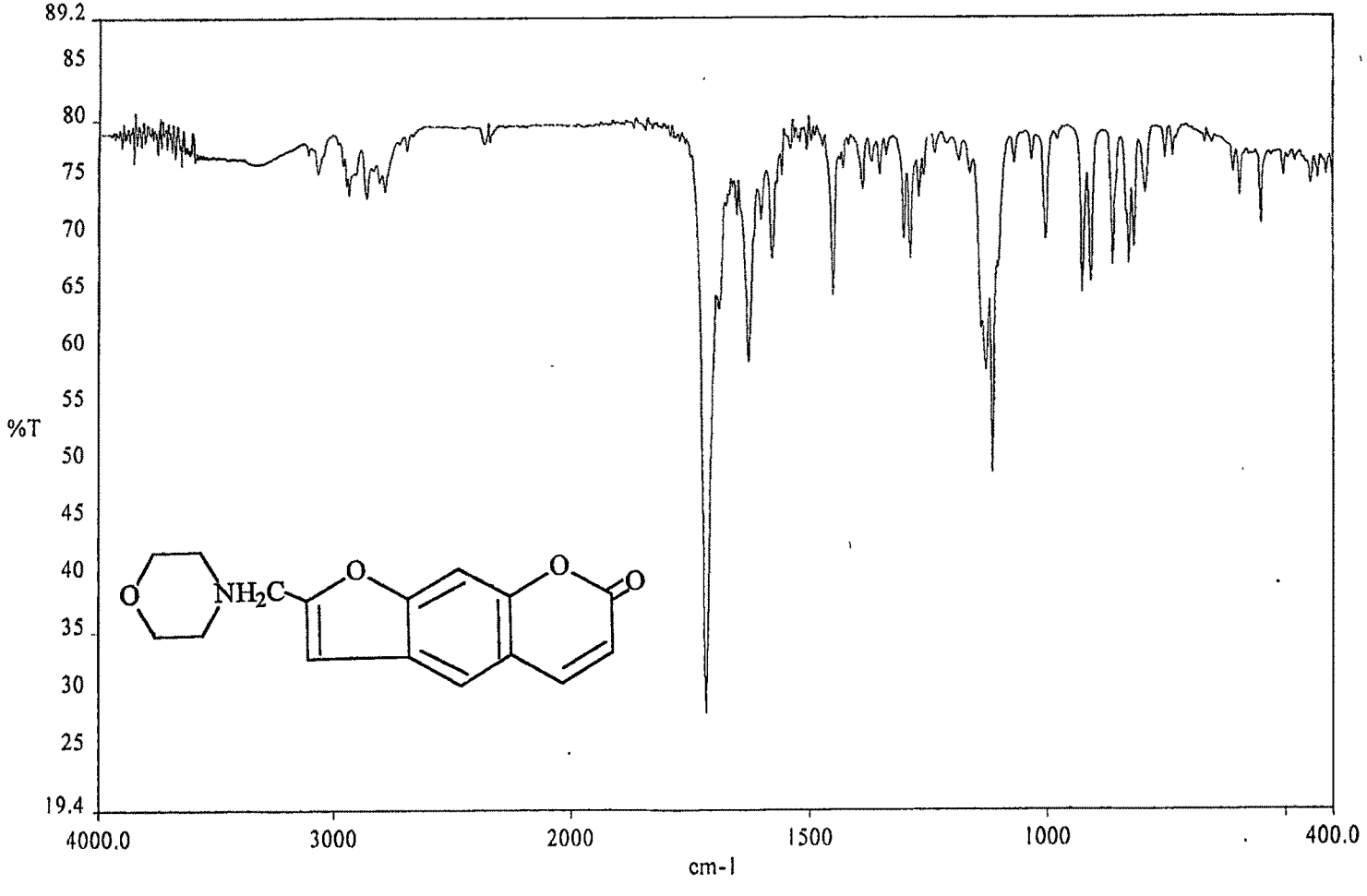


Fig. IV.1.6


89.2
85
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65
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%T
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45
40
35
30
25
19.4
4000.0
3000
2000
1500
1000
400.0
cm-1
O
NH2C
O
O
O

Fig. IV.1.7

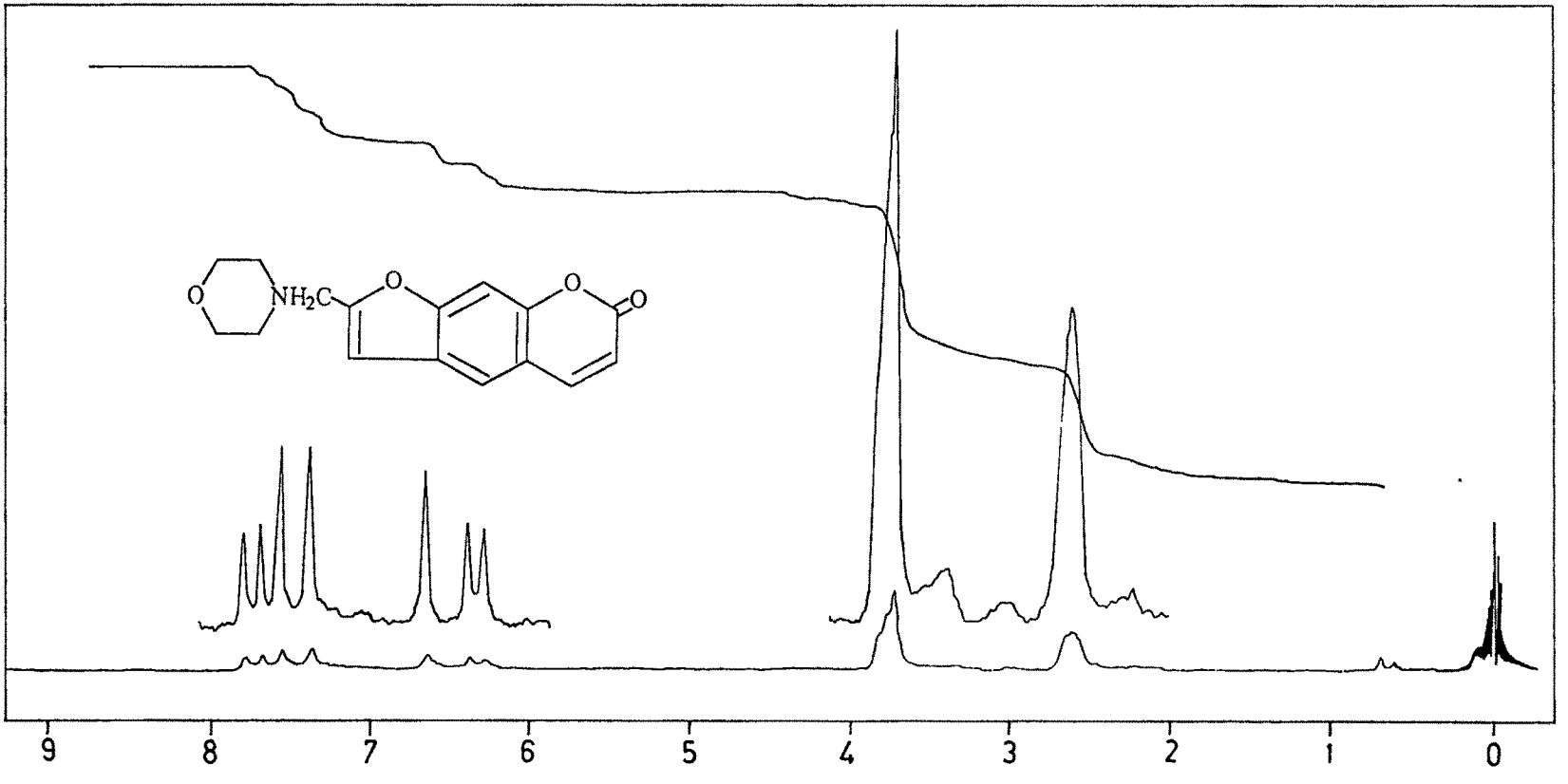

Fig. IV.1.8

EXPERIMENTAL

^{1}H-NMR spectra were recorded on Bruker 200MHz or Perkin-Elmer 90MHz spectrophotometer. Chemical shifts are relative to tetramethylsilane. Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (Spectrum RX 1). Melting points were taken by capillary method and are uncorrected. Elemental analyses were carried out on Perkin-Elmer C,H,N,S analyzer (Model 2400).

7-Allyloxybenzopyran-2H-one (22):

7-Hydroxybenzopyran-2H-one (5g, 30.8mmol) was dissolved in dry acetone (90ml) and freshly prepared K_2CO_3 (15g, 0.11mole), allylbromide (3.8ml, 30.8mmol) were added and refluxed the contents on waterbath for 6h. Excess of acetone was removed and the mixture was poured onto crushed ice. Separated solid was filtered off and treated with dilute alkali to remove unreacted starting compound and the product was recrystallized from ethanol as pale pink crystals (5.3g, 85.5%), m.p. 80°C.

Analysis	:	Found	:	C, 71.41%; H, 4.72%
$C_{12}H_{10}O_3$	:	Requires	:	C, 71.29%; H, 4.95%

7-Hydroxy-8-allylbenzopyran-2H-one (23):

7-Allyloxybenzopyran-2H-one (2g, 9.9mmol) in N,N-dimethylaniline (14ml) was refluxed at 200°C for 5.5h. The reaction mixture was poured in to ice-cold HCl. Separated solid was stirred with dilute alkali for 5min. to give alkali soluble product, which was acidified and recrystallized from ethanol as colourless needles (1.2g, 60.0%), m.p. 164°C.

Analysis	:	Found	:	C, 71.42%; H, 4.99%
$C_{12}H_{10}O_3$	:	Requires	:	C, 71.29%; H, 4.95%

7-Acetoxy-8-allylbenzopyran-2H-one (24):

A homogeneous mixture of 7-hydroxy-8-allylbenzopyran-2H-one (5g, 24.7mmol) and fused sodium acetate (15g, 0.18mole) was heated with acetic anhydride (8.0ml, 78.4mmol) on steambath at 100°C for 6h. It was poured into cold water and separated solid was treated with dilute alkali and the product was recrystallized from ethanol as colourless needles (4.7g, 78.3%), m.p. 101°C.

Analysis	:	Found	:	C, 68.71%; H, 4.84%
$C_{14}H_{12}O_4$	:	Requires	:	C, 68.85%; H, 4.92%

7-Acetoxy-8-(2′,3′-dibromopropyl)benzopyran-2H-one (25):

7-Acetoxy-8-allylbenzopyran-2H-one (5g, 20.4mmol) was dissolved in acetic acid (20ml). Bromine in acetic acid (3.3g, 20.4mmol) was added dropwise from addition funnel to the above solution with constant stirring. After the addition, the content was stirred for further 1h and left overnight. It was then dropped into cold water. Obtained solid was filtered and the product was recrystallized from ethanol to get pale pink crystals (7g, 84.3%), m.p. 225°C.

Analysis	:	Found	:	C, 41.29%; H, 3.13%
$C_{14}H_{12}O_4Br_2$	:	Requires	:	C, 41.58%; H, 2.97%

2-Methylfuro(2,3-h)benzopyran-5H-one (26):

7-Acetoxy-8-(2′,3′-dibromopropyl)benzopyran-2H-one (5g, 12.4mmol) was refluxed with 0.1N ethanolic KOH (6.9g KOH in 173ml ethanol) for 2h. After the reaction excess ethanol was distilled off and remaining mixture dropped into 3N HCl to get product. It was then filtered, dried and recrystallized from benzene as yellow needles (1.8g, 72.9%), m.p. 154°C. [lit.[12] m.p. 153-4°C]

Analysis	:	Found	:	C, 72.12%; H, 3.92%
$C_{12}H_8O_3$	:	Requires	:	C, 72.00%; H, 4.00%

2-Bromomethylfuro(2,3-h)benzopyran-5H-one (27):

2-Methylfuro(2,3-h)benzopyran-5H-one (2.0g, 10mmol), freshly prepared N-bromosuccinimide (1.8g, 10mmol) and a pinch of benzoyl peroxide were refluxed in CCl_4 (80ml) under 200W tungsten bulb for 16h. When the reaction got over excess of CCl_4 was distilled out and remaining solution left for evaporation. Obtained product was purified by column chromatography using benzene as eluent and recrystallized from benzene as pale yellow needles (2.1g, 75.3%), m.p. 235°C.

Analysis : Found : C, 51.42%; H, 2.61%

$C_{12}H_7O_3Br$: Requires : C, 51.61%; H, 2.51%

IR(KBr) cm^{-1} : 3080, 2989, 2952, 1732, 1616, 1254, 1114

General procedure for 2-aminomethylfuro(2,3-h)benzopyran-5H-ones (28-32):

2-Bromomethylfuro(2,3-h)benzopyran-5H-one (0.3g, 1.1mmol) and secondary amine (4.3mmol) were refluxed in N,N-dimethylformamide (8ml) for 55min.. The mixture was cooled and poured over the crushed ice. The solid separated was purified by column chromatography using $CHCl_3$ and CH_3OH (75:25) mixture as an eluent to get aminomethyl product and recrystallized.

2-Piperidinomethylfuro(2,3-h)benzopyran-5H-one (28):

m.p. 146°C (ethanol) ; yield 0.22g, 73.3%

Analysis : Found : C, 71.91%; H, 6.12%; N, 4.71%

$C_{17}H_{17}O_3N$: Requires : C, 72.08%; H, 6.01%; N, 4.95%

IR(KBr) cm^{-1} : 3075, 2985, 2957, 1725, 1615, 1118

2-Morpholinomethylfuro(2,3-h)benzopyran-5H-one (29):

m.p. 162°C (benzene) ; yield 0.20g, 66.7%

Analysis : Found : C, 67.21%; H, 5.50%; N, 4.82%

$C_{16}H_{15}O_4N$: Requires : C, 67.37%; H, 5.26%; N, 4.91%

PMR ($CDCl_3$): δ 2.65 (m, 4H of 2x-CH_2- in the morpholine ring attached to N at C-2); 3.80 (m, 6H of 2x-CH_2- in the morpholine ring attached to O and -CH_2- at C-2); 6.40 (d, J = 9Hz, 1H at C-6); 6.95 (s, 1H at C-3); 7.25-7.45 (m, 2H at C-9 and C-8); 7.80 (d, J = 9Hz, 1H at C-7)

2-N-Phenylpiperazinomethylfuro(2,3-h)benzopyran-5H-one (30):

m.p. 156°C (benzene) ; yield 0.25g, 65.8%

Analysis : Found : C, 73.15%; H, 5.22%; N, 7.95%

$C_{22}H_{20}O_3N_2$: Requires : C, 73.33%; H, 5.55%; N, 7.78%

IR(KBr) cm^{-1} : 3080, 2972, 2941, 1730, 1617, 1599, 1115

2-N,N-Diethylaminomethylfuro(2,3-h)benzopyran-5H-one (31):

m.p. 110°C (benzene) ; yield 0.23g, 79.3%

Analysis : Found : C, 70.68%; H, 6.35%; N, 5.04%

$C_{16}H_{17}O_3N$: Requires : C, 70.85%; H, 6.27%; N, 5.17%

IR(KBr) cm^{-1} : 3071, 2975, 2946, 1722, 1614, 1115

2-N,N-Diethanolaminomethylfuro(2,3-h)benzopyran-5H-one (32):

m.p. 132°C (benzene) ; yield 0.26g, 81.2%

Analysis : Found : C, 63.18%; H, 5.47%; N, 4.71%

$C_{16}H_{17}O_5N$: Requires : C, 63.37%; H, 5.61%; N, 4.62%

PMR ($CDCl_3$): δ 2.80 (t, 4H of 2x-CH_2- attached to N at C-2); 3.70 (t, 4H of 2x-CH_2- attached to -OH group at C-2); 3.95 (s, 2H of -CH_2- at C-2); 6.40 (d, J = 9.5Hz, 1H at C-6); 6.95 (s, 1H at C-3); 7.35 (d, J = 9Hz, 1H at C-9); 7.40 (d, J = 9Hz, 1H at C-8); 7.85 (d, J = 9Hz, 1H at C-7)

2-N,N-Bis(2-chloroethyl)aminomethylfuro(2,3-h)benzopyran-5H-one (33):

2-N,N-Diethanolaminomethylfuro(2,3-h)benzopyran-5H-one (0.15g, 0.49mmol) was refluxed with excess of thionylchloride (1.0ml) for 1h on waterbath. After the reaction excess $SOCl_2$ was removed and separated product

on recrystallization with benzene and ethanol mixture gave yellow needles (0.11g, 64.7%), m.p. 210°C.

Analysis : Found : C, 56.38%; H, 4.29%; N, 4.02%

$C_{16}H_{15}O_3NCl_2$: Requires : C, 56.47%; H, 4.41%; N, 4.12%

IR(KBr) cm^{-1} : 3074, 2971, 2949, 1729, 1618, 1121

7-Hydroxy-8-iodobenzopyran-2H-one (34):

Dissolved 7-hydroxybenzopyran-2H-one (10g, 0.06mole) in a diluted liq. NH_3 (62ml liq. NH_3 in 188ml H_2O) and added previously made iodine solution (15.6g, 0.06mole I_2 and 31.2g, 0.19mole KI in 10ml H_2O) dropwise through addition funnel with constant stirring. After the addition, stirring was continued for 1h. It was then poured into ice-cold H_2SO_4 and separated product was filtered, dried and recrystallized from ethanol (15.5g, 87.1%), m.p. 268°C.

Analysis : Found : C, 37.14%; H, 1.56%

$C_9H_5O_3I$: Requires : C, 37.50%; H, 1.74%

7-Allyloxy-8-iodobenzopyran-2H-one (35):

7-Hydroxy-8-iodobenzopyran-2H-one (5g, 17.3mmol) in dry acetone (150ml) was refluxed with anhydrous K_2CO_3 (15g, 0.11mole) and allylbromide (2.1ml, 17.3mmol) for 24h. on waterbath. The reaction was worked out as usual and obtained product was purified by column chromatography using mixture of petroleum ether and benzene (50:50), which recrystallized finally from benzene and petroleum ether mixture as yellow orange needles (4.2g, 73.8%), m.p. 158°C.

Analysis : Found : C, 43.77%; H, 2.89%

$C_{12}H_9O_3I$: Requires : C, 43.90%; H, 2.74%

7-Hydroxy-6-allylbenzopyran-2H-one (36):

7-Allyloxy-8-iodobenzopyran-2H-one (3g, 9.1mmol) was refluxed in N,N-DMA (18ml) for 5.5h. Undesired p-N,N-dimethyliodobenzene, a side

product, which deposited at the bottom of the condensor was discarded after regular intervals. Then the reaction mixture was cooled and dropped into cold HCl. Separated solid was stirred with dilute alkali and acidified the alkali solution with dilute HCl to give **34**, which was purified by column chromatography using benzene as eluent and recrystallized from benzene as colourless crystals (1.2g, 64.9%), m.p. 149°C.

Analysis	:	Found	:	C, 71.14%; H, 4.79%
$C_{12}H_{10}O_3$	:	Requires	:	C, 71.29%; H, 4.95%

7-Acetoxy-6-allylbenzopyran-2H-one (37):

An intimate mixture of 7-hydroxy-6-allylbenzopyran-2H-one (5g, 0.02mole) and fused sodium acetate (15g, 0.18mole) was taken in acetic anhydride (8ml, 0.08mole) and heated on the steambath for 6h. After the reaction, the mixture was poured into cold water and the separated product was recrystallized from benzene (4.8g, 79.6%), m.p. 110°C.

Analysis	:	Found	:	C, 68.67%; H, 4.99%
$C_{14}H_{12}O_4$	:	Requires	:	C, 68.85%; H, 4.92%

7-Acetoxy-6-(2′,3′-dibromopropyl)benzopyran-2H-one (38):

7-Acetoxy-6-allylbenzopyran-2H-one (5g, 20.5mmol) in acetic acid (20ml) was stirred with bromine in acetic acid (3.3g, 20.5mmol), added through the addition funnel dropwise. After the completion of addition, continued stirring for further 1h and left the flask overnight. It was poured in ice cold water and separated product was filtered and recrystallized from ethanol (6.8g, 81.9%), m.p. 190°C.

Analysis	:	Found	:	C, 41.25%; H, 2.53%
$C_{14}H_{12}O_4Br_2$	:	Requires	:	C, 41.58%; H, 2.97%

2-Methylfuro(3,2-g)benzopyran-7H-one (39):

7-Acetoxy-6-(2′,3′-dibromopropyl)benzopyran-2H-one (5g, 12.4mmol) was refluxed with 0.1N ethanolic KOH (6.9g KOH in 173ml ethanol) for 2h. Excess solvent was removed and the mixture was dropped into 3N HCl to get product, which was filtered and recrystallized from benzene (1.7g, 68.8%), m.p. 155°C.

Analysis : Found : C, 72.21%; H, 4.17%

$C_{12}H_8O_3$: Requires : C, 72.00%; H, 4.00%

2-Bromomethylfuro(3,2-g)benzopyran-7H-one (40):

2-Methylfuro(3,2-g)benzopyran-7H-one (2.0g, 10mmol) and freshly prepared NBS (1.8g, 10mmol) in distilled CCl_4 (80ml) were refluxed under 200W-tungsten lamp for 16h by adding benzoyl peroxide. After reaction got over, excess of CCl_4 was distilled out and remaining left for evaporation. Obtained product was purified by column chromatography with benzene as eluent and recrystallized from the same solvent (1.9g, 68.1%), m.p. 162°C.

Analysis : Found : C, 51.53%; H, 2.32%

$C_{12}H_7O_3Br$: Requires : C, 51.61%; H, 2.51%

IR(KBr) cm^{-1} : 3073, 2991, 2942, 1734, 1627, 1118

General procedure for 2-aminomethylfuro(3,2-g)benzopyran-7H-ones (41-45):

2-Bromomethylfuro(2,3-h)benzopyran-5H-one (0.3g, 1.1mmol) and secondary amine (4.3mmol) were refluxed in DMF (8ml) for 55min.. The reaction mixture was cooled and poured over the crushed ice. Separated solid was purified by column chromatography using $CHCl_3$ and CH_3OH (75:25) mixture to give desired aminomethyl product and recrystallized.

2-Morpholinomethylfuro(3,2-g)benzopyran-7H-one (41):

m.p. 164°C (ethanol) ; yield 0.21g, 70.0%

Analysis : Found : C, 67.12%; H, 5.01%; N, 4.78%

$C_{16}H_{15}O_4N$: Requires : C, 67.37%; H, 5.26%; N, 4.91%

IR(KBr) cm^{-1} : 3069, 2981, 2940, 1716, 1629, 1116

2-Piperidinomethylfuro(3,2-g)benzopyran-7H-one (42):

m.p. 120°C (benzene) ; yield 0.21g, 70.0%

Analysis : Found : C, 72.21%; H, 5.82%; N, 4.87%

$C_{17}H_{17}O_3N$: Requires : C, 72.08%; H, 6.01%; N, 4.95%

IR(KBr) cm^{-1} : 3068, 2983, 2939, 1717, 1628, 1128

2-N-Phenylpiperazinomethylfuro(3,2-g)benzopyran-7H-one (41):

m.p. 182°C (ethanol) ; yield 0.29g, 76.3%

Analysis : Found : C, 73.45%; H, 5.68%; N, 7.52%

$C_{22}H_{20}O_3N_2$: Requires : C, 73.33%; H, 5.55%; N, 7.78%

IR(KBr) cm^{-1} : 3071, 2985, 2934, 1730, 1630, 1597, 1125

PMR ($CDCl_3$): δ 2.70 (m, 4H of 2x-CH_2- in the piperazine ring attached to N at C-2); 3.25 (m, 4H of 2x-CH_2- in the piperazine ring attached to N-phenyl group at C-2); 3.75 (s, 2H of -CH_2- at C-2); 6.35 (d, J = 9.2Hz, 1H at C-6); 6.70 (s, 1H at C-3); 6.85-7.30 (m, 5H of phenyl ring attached to N); 7.45 (s, 1H at C-4); 7.60 (s, 1H at C-9); 7.80 (d, J = 9.2Hz, 1H at C-5)

2-N,N-Diethylaminomethylfuro(3,2-g)benzopyran-7H-one (44):

m.p. 118°C (ethanol) ; yield 0.23g, 79.3%

Analysis : Found : C, 70.61%; H, 6.45%; N, 5.21%

$C_{16}H_{17}O_3N$: Requires : C, 70.85%; H, 6.27%; N, 5.17%

2-N,N-Diethanolaminomethylfuro(3,2-g)benzopyran-7H-one (45):

m.p. 140°C (ethanol) ; yield 0.26g, 81.2%

Analysis : Found : C, 63.22%; H, 5.49%; N, 4.78%

$C_{16}H_{17}O_5N$: Requires : C, 63.37%; H, 5.61%; N, 4.62%

IR(KBr) cm^{-1} : 3374, 3071, 2985, 2935, 1729, 1631, 1137

PMR ($CDCl_3$): δ 2.70 (bs, 4H of 2x-CH_2- attached to N at C-2); 3.60 (bs, 4H of 2x-CH_2- attached to -OH group at C-2); 3.90 (s, 2H of -CH_2- at C-2); 6.25 (d, J = 9.5Hz, 1H at C-6); 6.65 (s, 1H at C-3); 7.25 (s, 1H at C-4); 7.55 (s, 1H at C-9); 7.85 (d, J = 9Hz, 1H at C-5)

2-N,N-Bis(2-chloroethyl)aminomethylfuro(3,2-g)benzopyran-7H-one (46):

2-N,N-Diethanolaminomethylfuro(2,3-h)benzopyran-5H-one (0.15g, 0.49mmol) was refluxed with excess of $SOCl_2$ (1.0ml) for 1h on waterbath. After the reaction, excess of $SOCl_2$ was removed and separated product on recrystallization with benzene and ethanol mixture gave yellow needles (0.10g, 58.8%), m.p. 221°C.

Analysis : Found : C, 55.94%; H, 4.12%; N, 4.43%

$C_{16}H_{15}O_3NCl_2$: Requires : C, 56.47%; H, 4.41%; N, 4.12%

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Chapter IV : Section 2

Synthesis of Schiff Bases

INTRODUCTION

Coumarins are widely distributed in nature exhibiting various physiological properties. Many natural and synthetic derivatives of coumarins have found a place in therapy such as anticoagulants[1,2], antibiotics[3-5] etc.. 3-Aminocoumarins which are generally prepared by the condensation of salicylaldehyde derivatives with amino acid derivatives[6,7] have acquired special place due to their pronounced analgesic and sedative properties. Not only that its derivatives with amino acid and platinum possess antibacterial properties. The Schiff bases, which are formed with aldehydes have fungicidal, viricidal properties. Therefore looking at the useful properties of 3-aminocoumarins and their Schiff bases it was thought to review the various methods followed earlier to synthesize these compounds.

Kumar *et al.*[6] synthesized 3-(α-arylazo-benzylideneamino/furfurylidene-amino)coumarins **4a,b** and studied the anti-inflammatory activity by condensing salicylaldehyde with N-acetylglycine in the presence of acetic anhydride and piperidine to give 3-acetylaminocoumarin (1), which on deacetylation afforded 3-aminocoumarin (2). Condensation of **2** with different aromatic aldehydes in absolute ethanol produced 3-arylideneaminocoumarins **3a,b** which underwent coupling reaction with arenediazonium chlorides to yield **4a,b**. They also suggested that o-hydroxyphenyl group directly attached to the azomethine carbon enhances the anti-inflammatory activity compared to other substituents, such as p-N,N-dimethylaminophenyl and furfuryl groups. **[Scheme IV.2.1]**

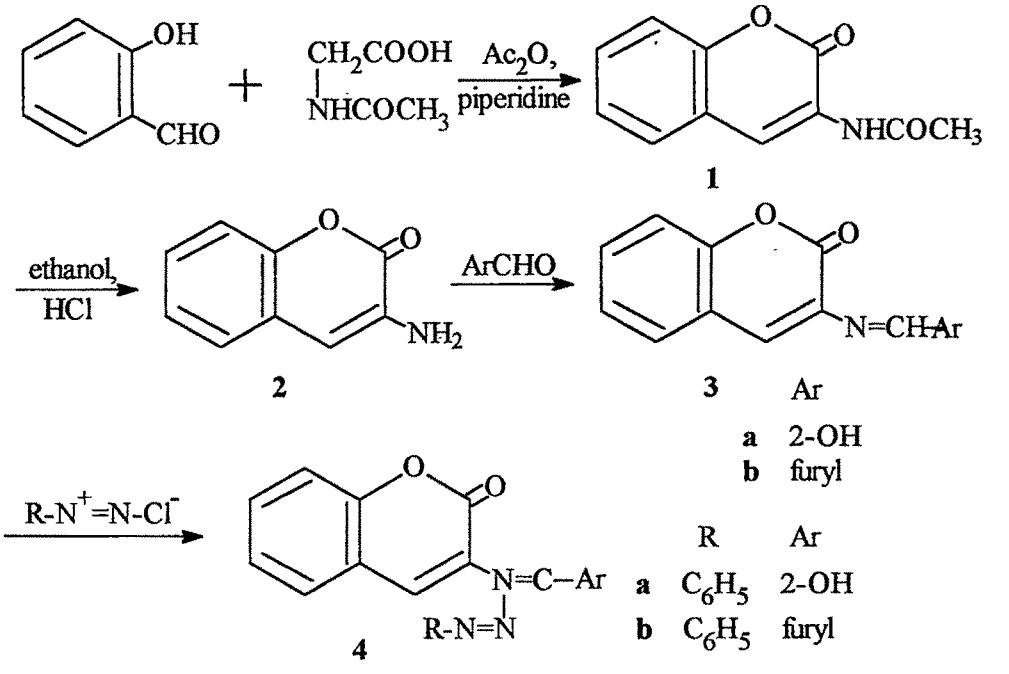
Desai *et al.*[8] synthesized various Schiff bases from 7-n-butoxy-3-amino coumarin (7) and found that some of them were moderately active as antibacterial agents. 7-Acetoxy-3-acetamidocoumarin (5), which was prepared by the condensation of resorcilaldehyde and acetylglycine in the presence of acetic anhydride and sodium acetate, on butylation gave 7-n-butoxy-3-acetamido coumarin (6). **6** on acid hydrolysis with conc. H_2SO_4 in ethanol afforded amino

derivative 7, which on condensation with different aldehydes furnished Schiff bases **8a,b**. **[Scheme IV.2.2]**

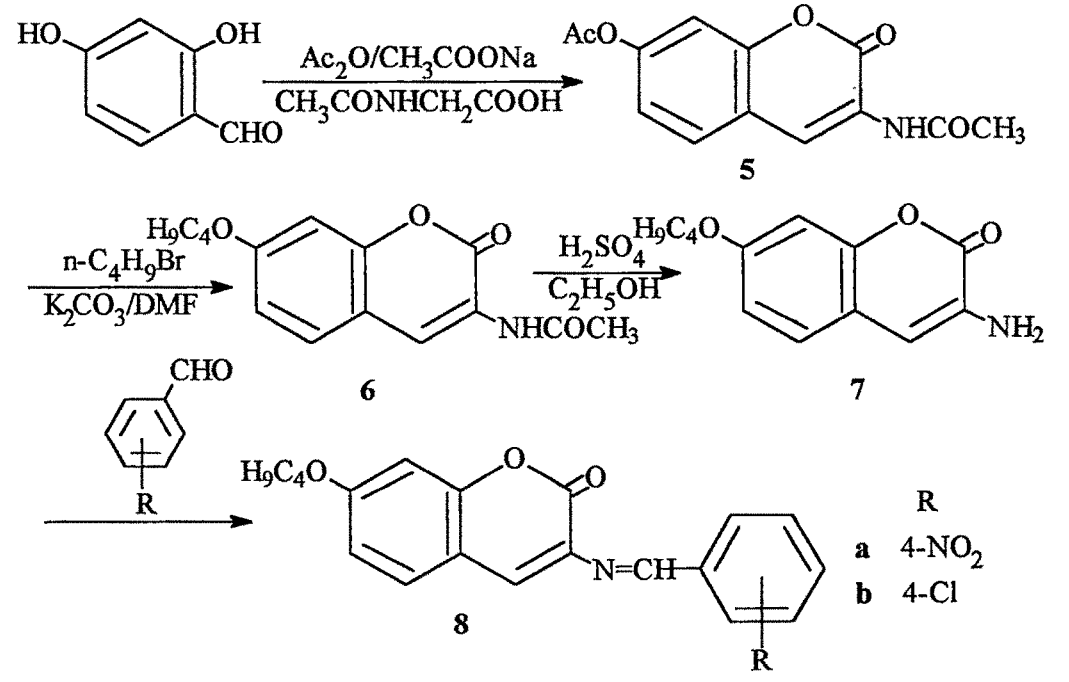
While Kokotos *et al.*[9] obtained the Schiff base of 3-aminocoumarin **10** in a single step by the condensation of ethylester of glycinehydrochloride (9) with salicylaldehyde in the presence of triethylamine. **[Scheme IV.2.3]**

Corrie[10] utilized convenient direct Pechmann condensation of 3-dimethyl aminophenol (11) and ethyl-2-acetamido-3-oxobutyrate (12) to give directly 3-acetamidocoumarin **13** in modest yields which is readily converted into 3-aminocoumarin **14a,b** and maleimide derivative **15**. **[Scheme IV.2.4]**

Scheme IV.2.1

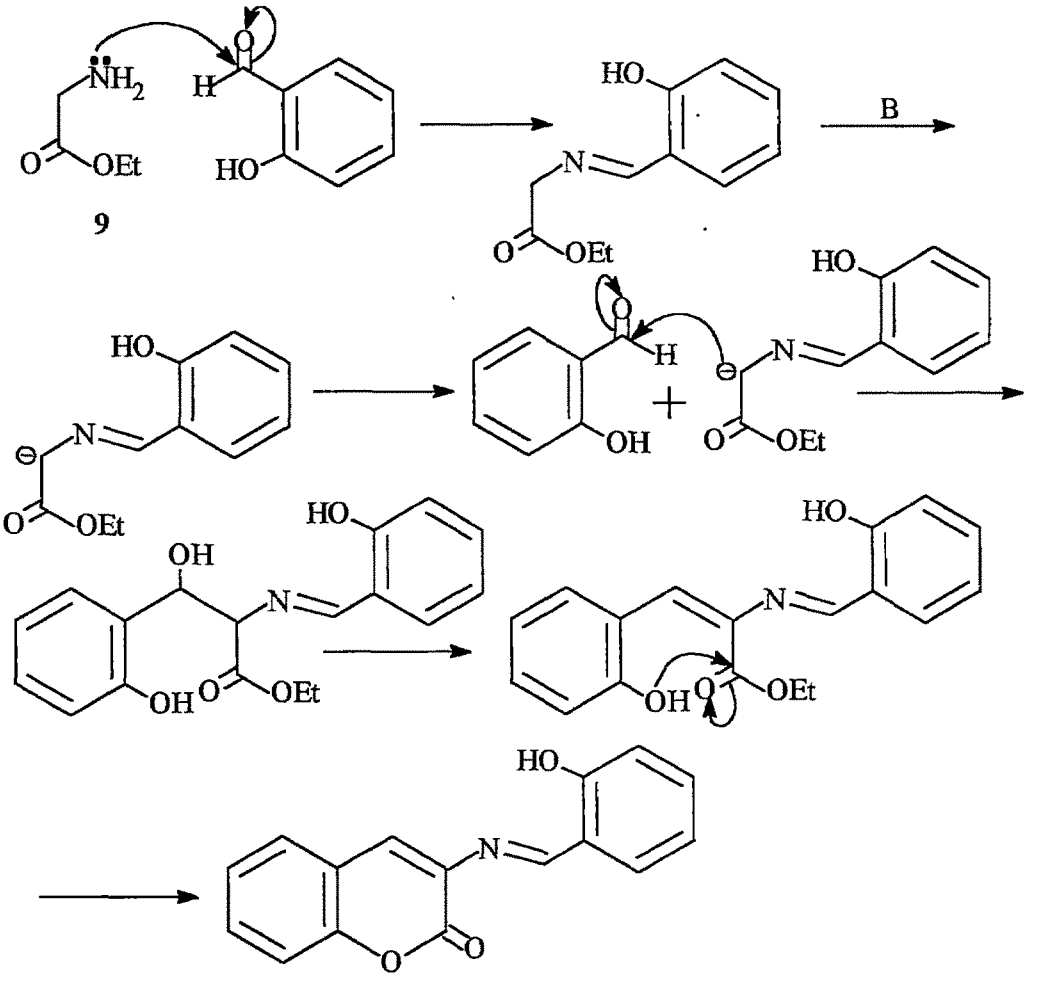


Scheme IV.2.2

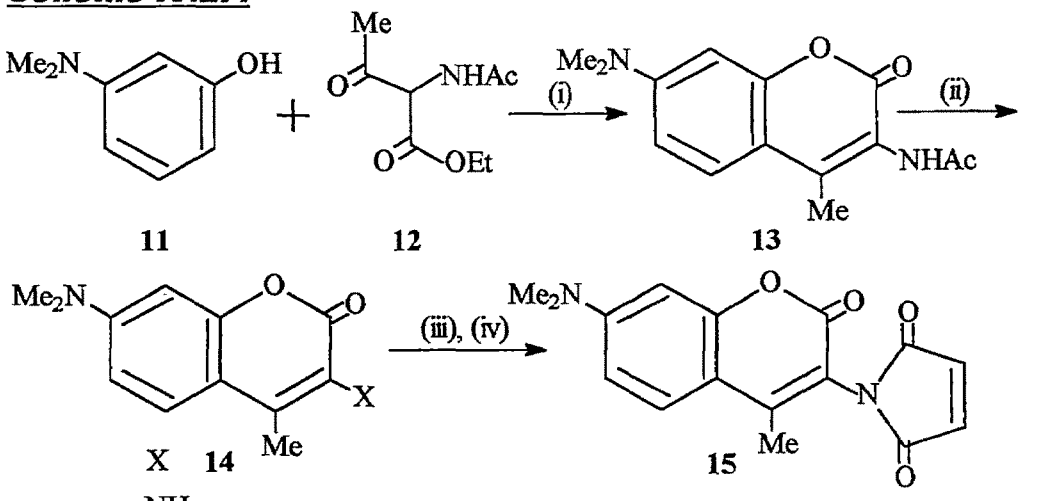


Scheme IV.2.3

Mechanism for the formation of Schiff base



Scheme IV.2.4



a NH_2
b OH

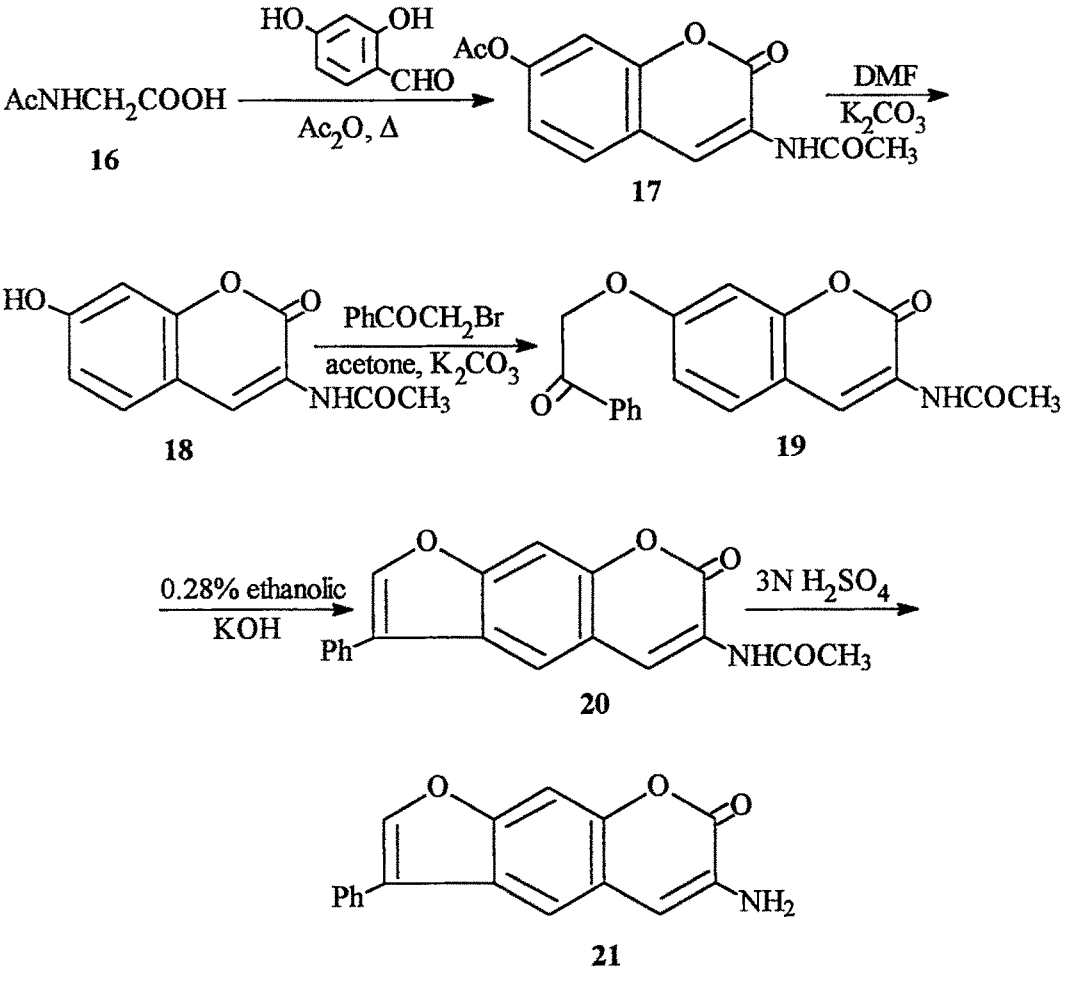
(i) $ZnCl_2$-EtOH; (ii) conc. HCl; (iii) maleic anhydride-$CHCl_3$; (iv) Ac_2O-NaOAc

PRESENT WORK

Presence of azomethine (-CH=N) linkage in the Schiff bases has been reported for long time to be responsible for exhibiting or enhancing the antibacterial activity and also it was found that Schiff bases derived from 3-aminocoumarin possess antibacterial, antifungal and anthelmintic activity. Hence in order to have potent antibacterial agent, efforts have been made to prepare Schiff bases using furobenzopyrone system.

Synthesis of 3-phenyl-6-(4′-nitrophenyliminomethyl)furo(3,2-g) benzopyran-7H-one (22) was carried out from 7-acetoxy-3-acetamido benzopyran-2H-one (17), which was prepared by condensation of acetyl glycine (16) and 2,4-dihydroxybenzaldehyde using acetic anhydride and sodium acetate, was first deacetylated to 7-hydroxy-6-acetamidobenzopyran-2H-one (18) by heating with anhydrous K_2CO_3 and DMF solvent. Phenacylation of **18** with phenacylbromide in dry acetone using fused K_2CO_3 gave 7-phenacyloxy-3-acetamidobenzopyran-2H-one (19) in a satisfactory yield, which on subsequent cyclization with ethanolic KOH afforded 3-phenyl-6-acetamidofuro(3,2-g) benzopyran-7H-one (20). Hydrolysis of acetamido group was achieved by heating **20** with H_2SO_4 and methanol mixture to get 3-phenyl-6-aminofuro(3,2-g) benzopyran-7H-one (21). **[Scheme IV.2.5]** Its structure was established on the basis of elemental analysis, IR which showed absorption bands in KBr at 3468 and 1710cm^{-1} due to amino group and >CO of lactone respectively **[Fig. IV.2.1]** and PMR spectrum as it exhibited signals in $CDCl_3$ at δ 4.20, a broad singlet for two protons of amino group at C-6; a singlet at 6.80 for proton at C-2; a multiplet at 7.40-7.75 for seven protons of phenyl group at C-3 overlapped with protons at C-4 and C-9 and a singlet at 7.85 for proton at C-5. **[Fig. IV.2.2]** **21** was condensed with p-nitrobenzaldehyde using benzene and piperidine as a catalyst to afford 3-phenyl-6-(4′-nitrophenyliminomethyl)

Scheme IV.2.5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AcO
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DMF
K2CO3
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17
HO
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acetone, K2CO3
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Ph
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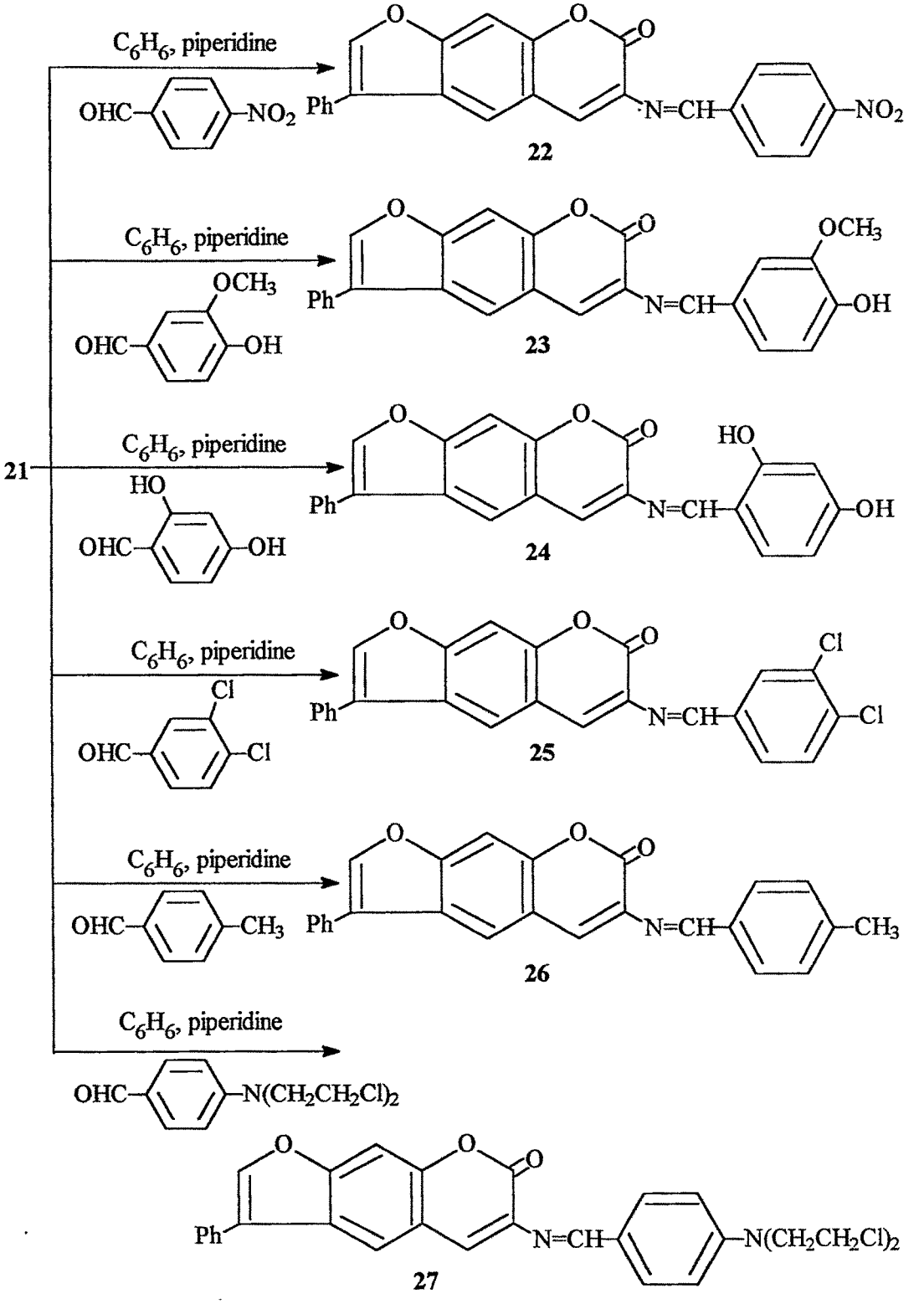
20
Ph
NH2
21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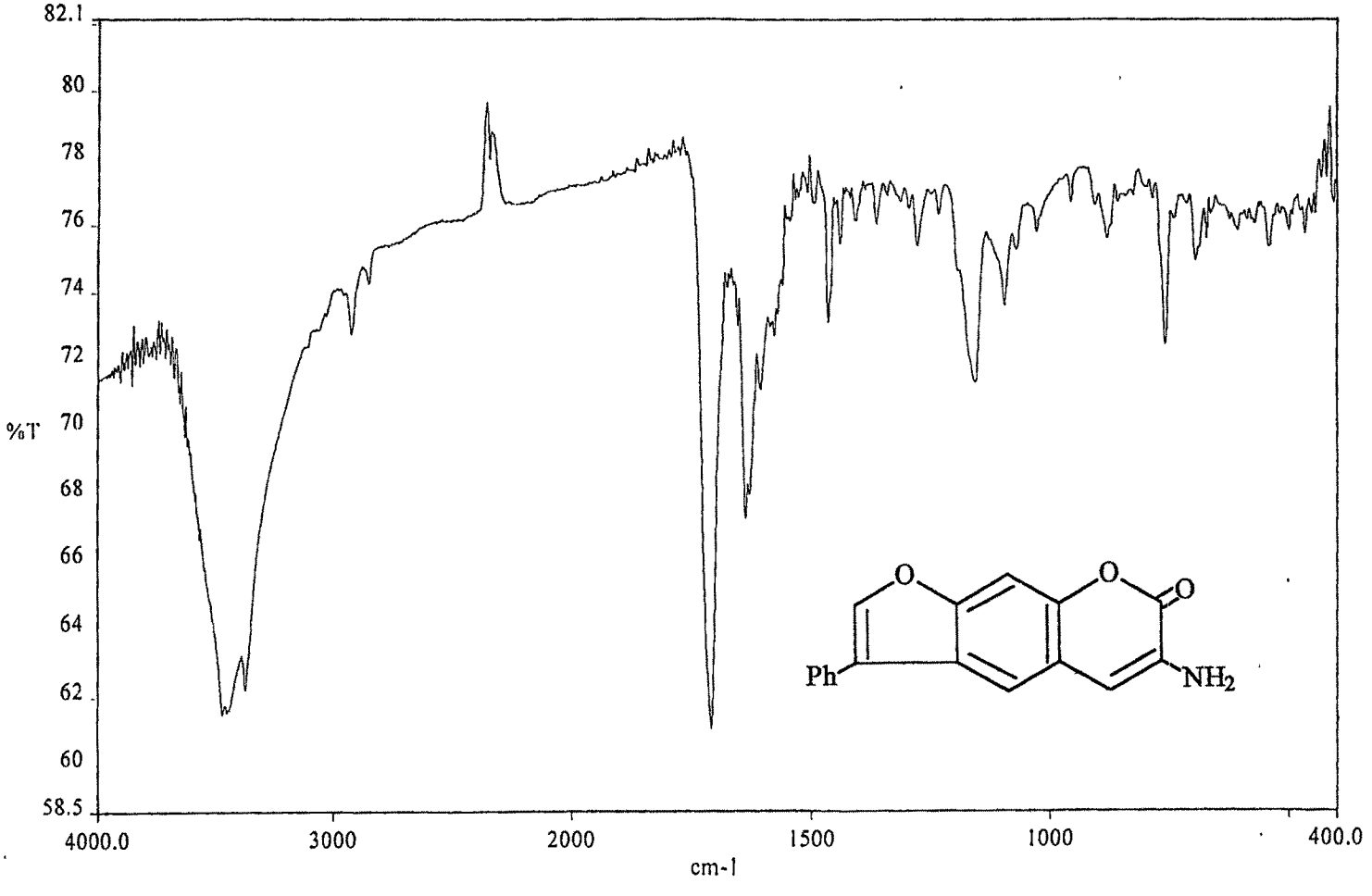
OH
23
HO
24
Cl
25
CH3
26
N(CH2CH2Cl)2
27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78
76
74
72
%T 70
68
66
64
62
60
58.5
4000.0
3000
2000
1500
1000
400.0
cm-1
O
O
O
Ph
NH2

Fig. IV.2.1

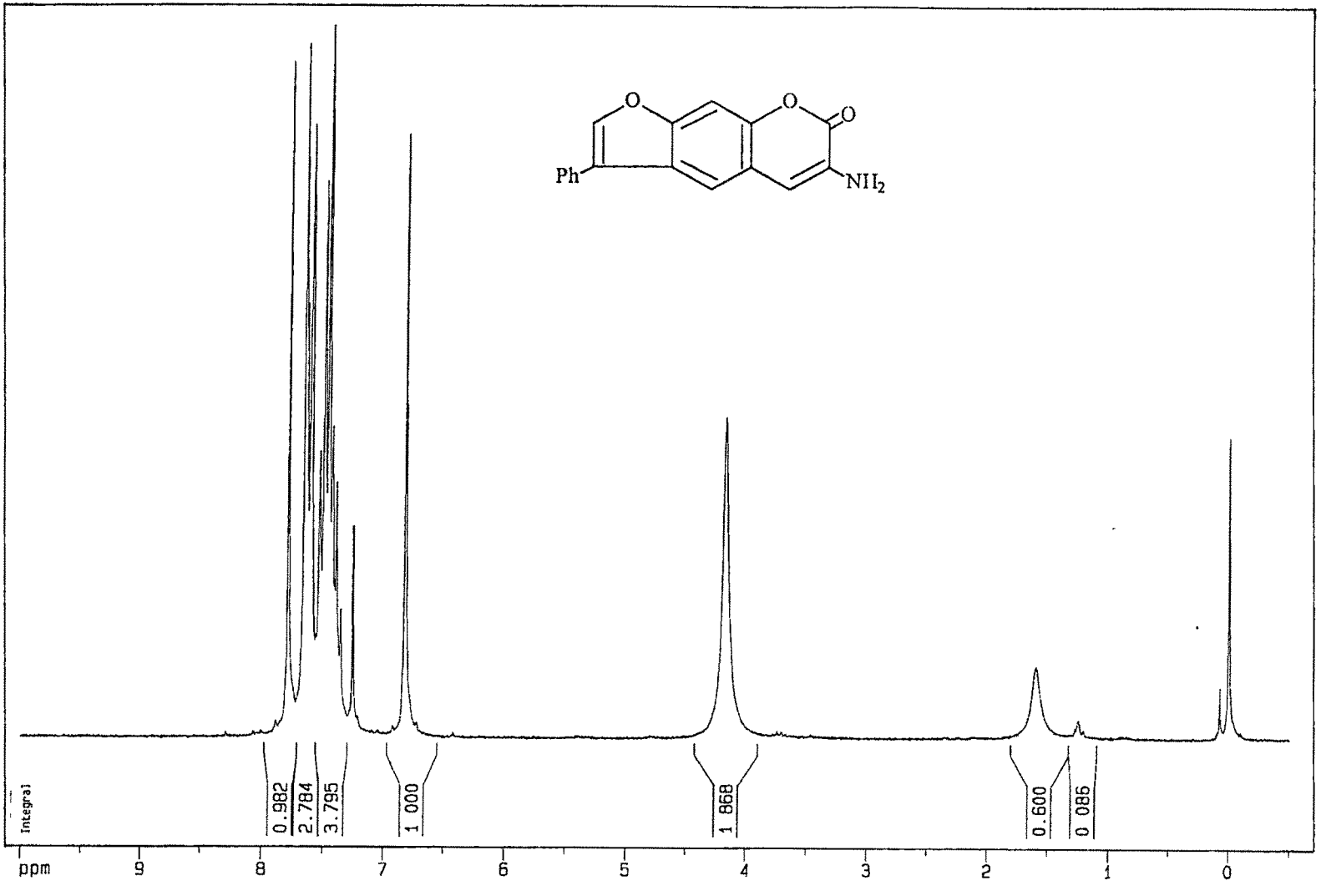

O
O
O
Ph
NH2
Integral
0.982
2.784
3.795
1.000
1.868
0.600
0.086
ppm
9
8
7
6
5
4
3
2
1
0

Fig. IV.2.2

furo(3,2-g)benzopyran-7H-one (22), which was confirmed by the elemental analysis, IR and PMR data. IR spectrum showed bands in KBr at 1720 and 1630cm^{-1} due to >CO of lactone and C=N linkage **[Fig. IV.2.3]** while PMR spectrum exhibited signals in $CDCl_3$ at δ 7.40-7.60, a multiplet for six protons of phenyl group at C-3 overlapped with proton at C-2; a singlet at 7.85 for proton at C-4; a broad singlet at 8.00 for two protons at C-5 and C-9; a doublet at 8.10, J = 8.8Hz for two protons at C-2′ and C-6′; another doublet at 8.35, J = 8.8Hz for two protons at C-3′ and C-5′ and a singlet at 9.55 for proton of -N=C<u>H</u> at C-6. **[Fig. IV.2.4]**

Similarly other aldehydes such as p-vanillin, 2,4-dihydroxybenzaldehyde, 3,4-dichlorobenzaldehyde and p-methylbenzaldehyde were condensed with **21** to make corresponding Schiff bases **23-26**. Nitrogen mustard 3-phenyl-6-[4′-(N,N-bis(2-chloroethyl)amino)phenyliminomethyl]furo(3,2-g)benzopyran-7H-one (27) was also achieved by treating **21** with p-[N,N-bis(2-chloroethyl)amino-benzaldehyde under the same reaction conditions, which was confirmed by its elemental analysis, IR and PMR spectral data. Two absorption bands in KBr observed at 1718 and 1630cm^{-1} due to >CO of lactone and C=N linkage respectively **[Fig. IV.2.5]** while its PMR signals in $CDCl_3$ appeared as multiplet at δ 3.60-3.75 for four protons of two methylene groups adjacent to N in -N($C\underline{H}_2CH_2Cl)_2$ chain; another multiplet at 3.80-3.90 for four protons of two methylene groups adjacent to Cl in -N($CH_2C\underline{H}_2Cl)_2$ chain; a doublet at 6.75 for two protons at C-2′ and C-6′; a multiplet at 7.40-7.85 for five protons of phenyl group at C-3 overlapped with protons at C-2, C-4, C-9 and two protons at C-3′ and C-5′; a singlet at 7.90 for proton at C-5 and another singlet at 9.00 for a proton of -N=C<u>H</u> at C-6. **[Fig. IV.2.6]**

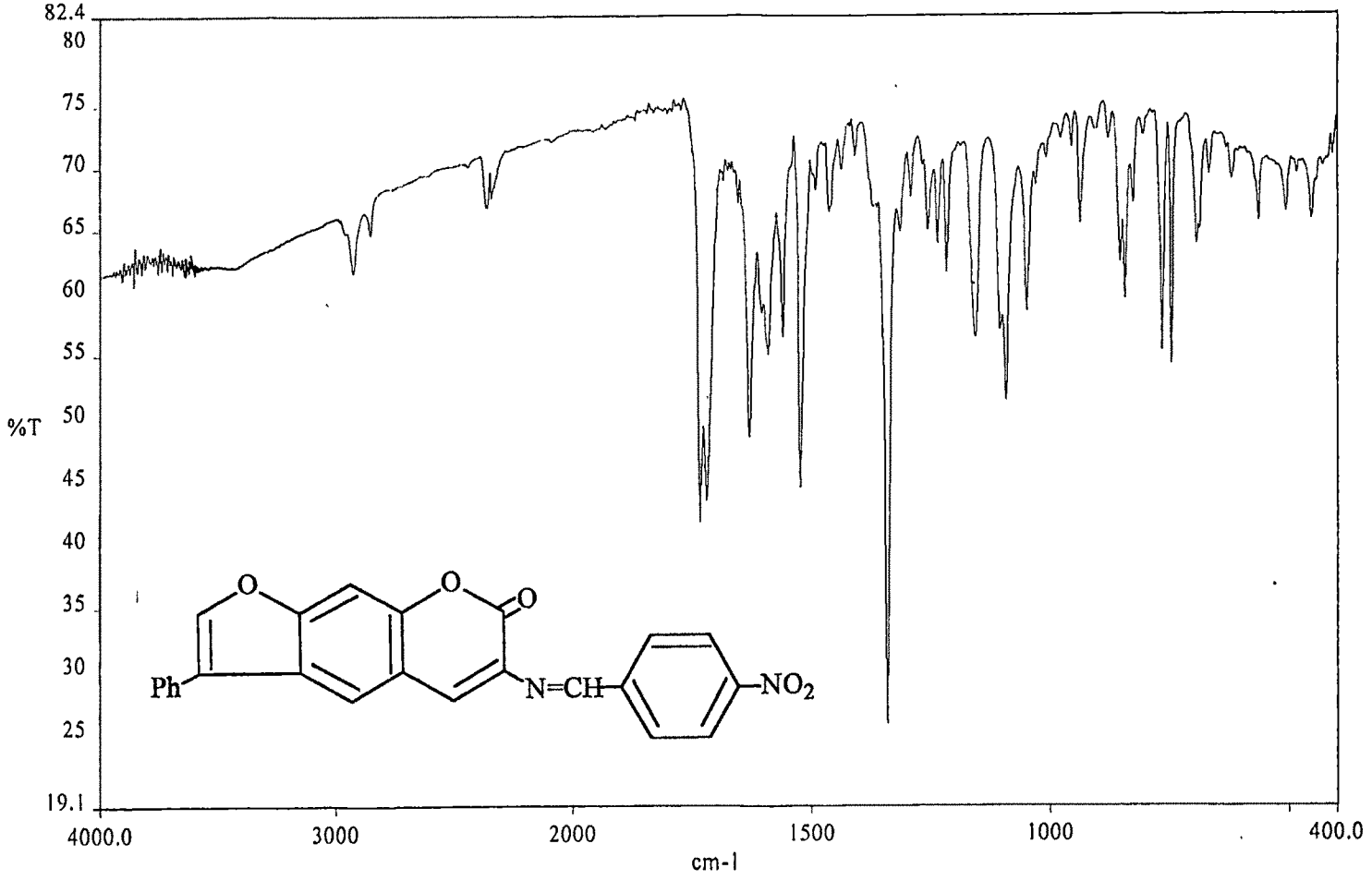
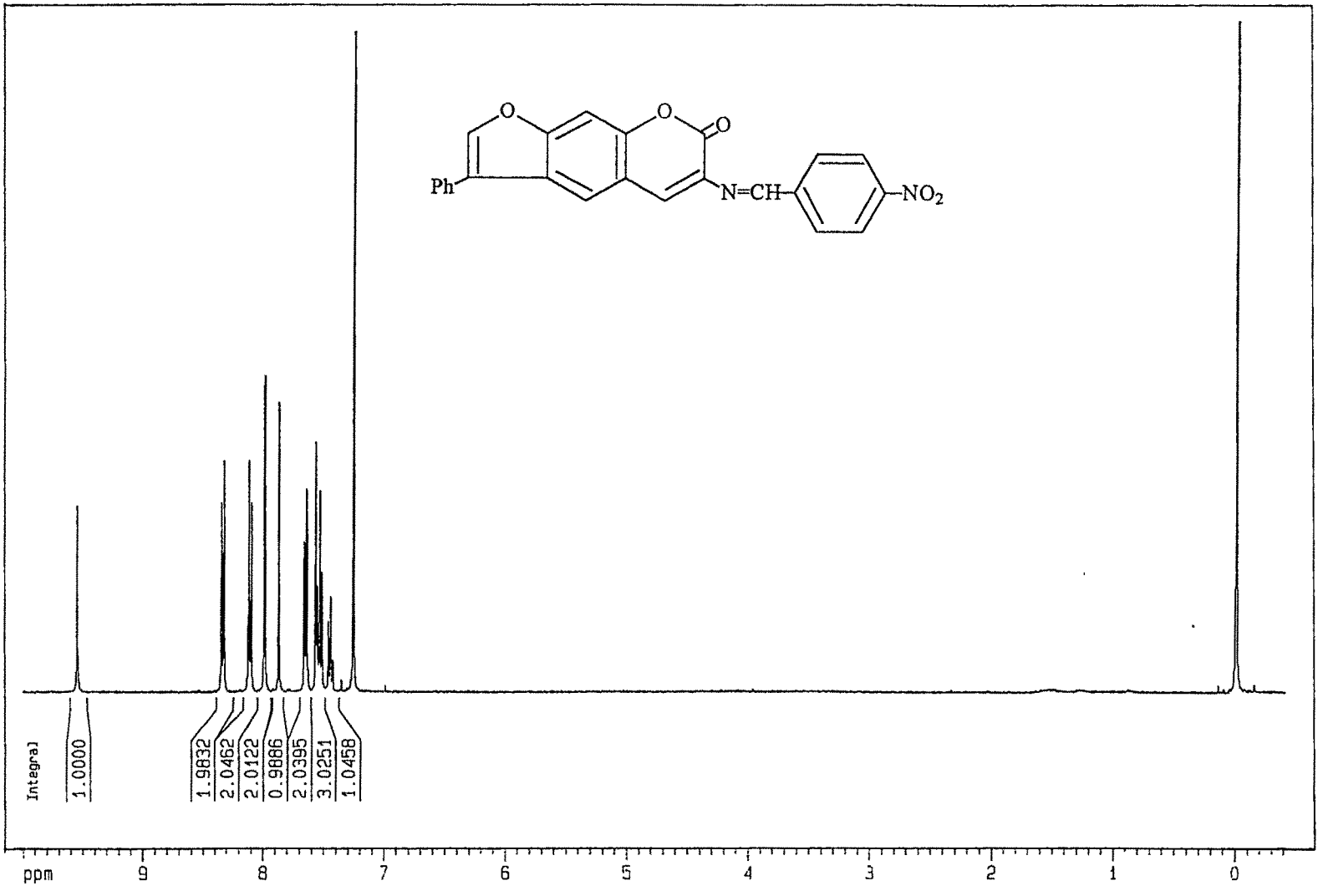

82.4
80
75
70
65
60
55
50
45
40
35
30
25
19.1
%T
4000.0
3000
2000
1500
1000
400.0
cm-1
O
O
O
Ph
N=CH
NO2

Fig. IV.2.3


Ph
O
O
O
N=CH
NO2
Integral
1.0000
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2.0462
2.0122
0.9886
2.0395
3.0251
1.0458
ppm
9
8
7
6
5
4
3
2
1
0

Fig. IV.2.4

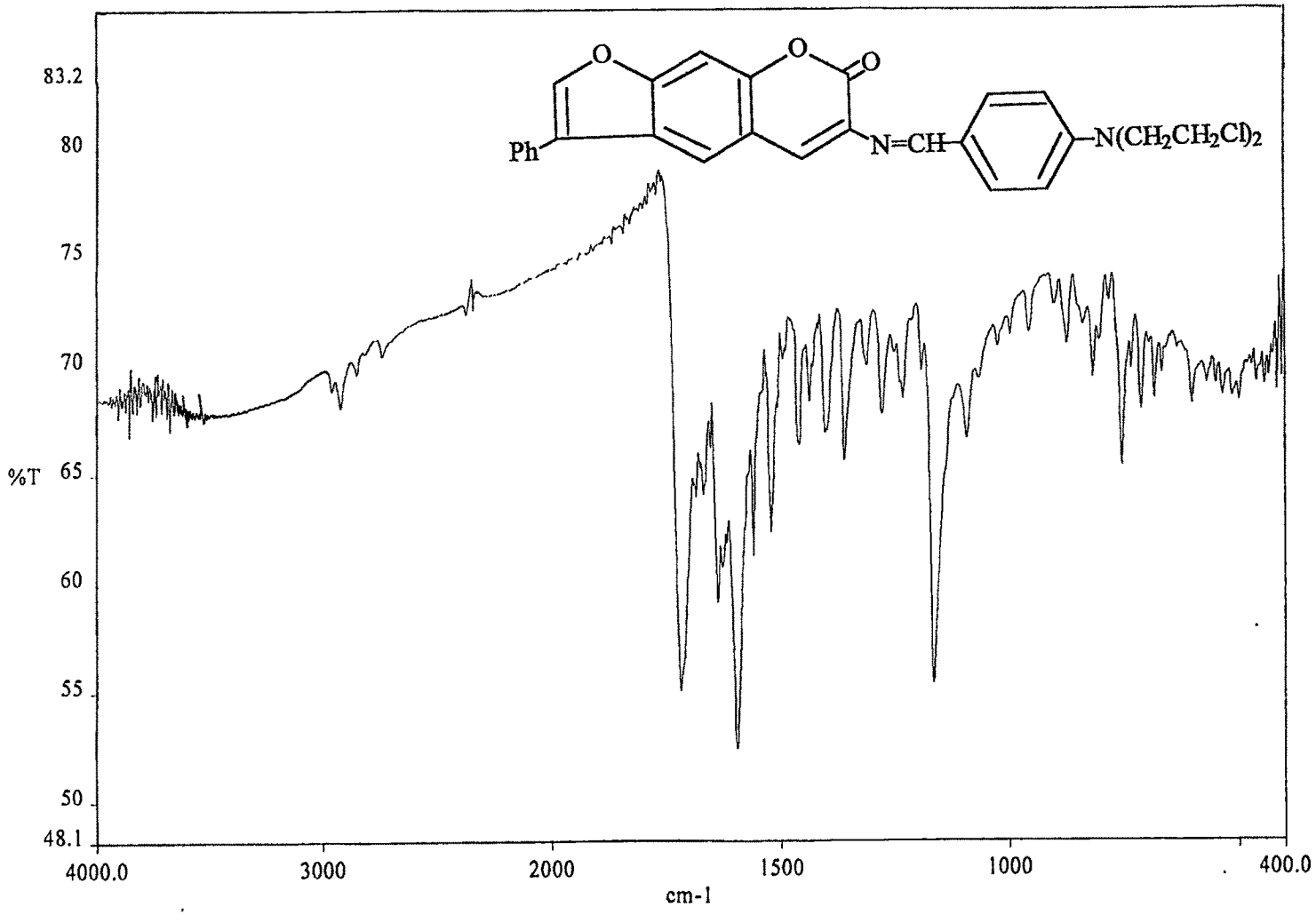
83.2
80
75
70
%T 65
60
55
50
48.1
4000.0
3000
2000
1500
1000
400.0
cm-1
Ph
O
O
O
N=CH
N(CH2CH2Cl)2

Fig. IV.2.5

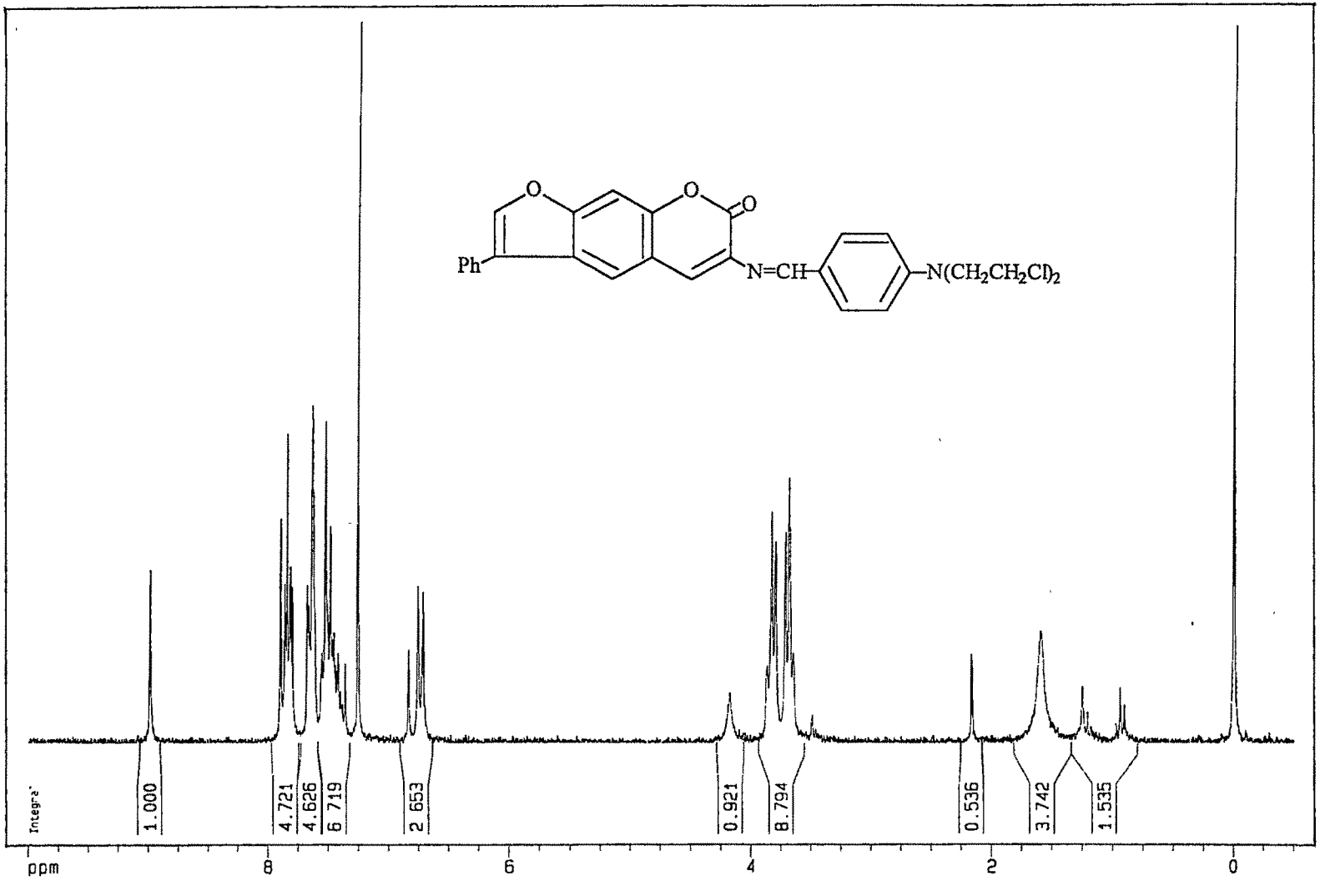
Ph
O
O
O
N=CH
N(CH2CH2Cl)2
1.000
4.721
4.626
6.719
2.653
0.921
8.794
0.536
3.742
1.535
ppm
8
6
4
2
0

Fig. IV.2.6

EXPERIMENTAL

Melting points were determined by open capillary method and are uncorrected. Elemental analyses were performed on Perkin-Elmer C,H,N,S analyzer (Model 2400). Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (Spectrum RX 1). ^{1}H-NMR spectra were recorded on Bruker 200MHz or Perkin-Elmer 90MHz spectrophotometer. Chemical shifts are relative to tetramethylsilane.

7-Acetoxy-3-acetamidobenzopyran-2H-one (17):

A homogeneous mixture of acetylglycine (5g, 42.7mmol), 2,4-dihydroxy benzaldehyde (5.2g, 37.6mmol) and anhydrous sodium acetate (8g, 97.5mmol) was heated in acetic anhydride (15ml, 0.15mole) on steambath for 6h. The reaction mixture was then poured into ice cold water. Separated solid was filtered and recrystallized from dilute ethanol to give **17** as pale yellow floppy needles (6.7g, 70.8%), m.p. 241-2°C.

Analysis	:	Found	:	C, 59.71%; H, 4.38%; N, 5.12%
$C_{13}H_{11}O_5N$	:	Requires	:	C, 59.77%; H, 4.21%; N, 5.36%

7-Hydroxy-3-acetamidobenzopyran-2H-one (18):

7-Acetoxy-3-acetamidobenzopyran-2H-one (5g, 19.1mmol) in dry DMF (35ml) was heated with anhydrous K_2CO_3 (12g, 86.9mmol) on steambath for 5h. It was then poured into ice water after testing with dilute alkali. Separated product was filtered and recrystallized from mixture of ethanol and benzene (3.8g, 90.4%), m.p. 287°C.

Analysis	:	Found	:	C, 60.52%; H, 3.91%; N, 6.11%
$C_{11}H_9O_4N$	:	Requires	:	C, 60.27%; H, 4.11%; N, 6.39%

7-Phenacyloxy-3-acetamidobenzopyran-2H-one (19):

7-Hydroxy-3-acetamidobenzopyran-2H-one (5g, 22.8mmol) in dry acetone (150ml) was refluxed with phenacylbromide (4.6g, 22.8mmol) and fused K_2CO_3 (12.0g, 86.9mmol) on waterbath for 7h. After the reaction, excess acetone was removed and the mixture was poured onto crushed ice. The product obtained was filtered and recrystallized from ethanol (5.3g, 68.8%), m.p. 224°C.

Analysis : Found : C, 67.47%; H, 4.37%; N, 4.29%

$C_{19}H_{15}O_5N$: Requires : C, 67.66%; H, 4.45%; N, 4.15%

3-Phenyl-6-acetamidofuro(3,2-g)benzopyran-7H-one (20):

7-Phenacyloxy-3-acetamidobenzopyran-2H-one (2.5g, 7.4mmol) was refluxed in ethanolic KOH (0.28%, 0.56g KOH in 200ml ethanol) for 3h. Excess ethanol was distilled off after the reaction and the mixture was dropped into 3N HCl. Obtained product was filtered and recrystallized from ethanol as orange-yellow needles (1.4g, 59.1%), m.p. 256°C.

Analysis : Found : C, 71.63%; H, 4.31%; N, 4.57%

$C_{19}H_{13}O_4N$: Requires : C, 71.47%; H, 4.07%; N, 4.39%

3-Phenyl-6-aminofuro(3,2-g)benzopyran-7H-one (21):

3-Phenyl-6-acetamidofuro(3,2-g)benzopyran-7H-one (2g, 6.3mmol) was refluxed in a mixture of methanol (60ml) and conc. H_2SO_4 (3ml) for 1h. It was dropped into ice cold water to give solid, which was filtered and recrystallized from ethanol to give **21** as pale orange crystals (1.2g, 69.0%), m.p. 164°C.

Analysis : Found : C, 73.87%; H, 3.82%; N, 5.19%

$C_{17}H_{11}O_3N$: Requires : C, 73.64%; H, 3.97%; N, 5.05%

IR(KBr) cm^{-1} : 3468, 2927, 1710, 1637

General procedure for 3-phenyl-6-(substitutedphenyliminomethylfuro(3,2-g) benzopyran-7H-ones (22-27):

3-Phenyl-6-aminofuro(3,2-g)benzopyran-7H-one (0.3g, 1.1mmol) in dry benzene (30ml) was refluxed with aldehyde (1.1mmol) and few drops of piperidine for 5h using dean-steark apparatus. After the reaction, excess of solvent was removed and the mixture was left for evaporation to give solid. The product was purified by column chromatography using benzene as eluent and recrystallized.

3-Phenyl-6-(4′-nitrophenyliminomethyl)furo(3,2-g)benzopyran-7H-one (22):

m.p. 255°C (benzene) ; yield 0.32g, 72.7%

Analysis : Found : C, 70.11%; H, 3.72%; N, 6.69%

$C_{24}H_{14}O_5N_2$: Requires : C, 70.24%; H, 3.41%; N, 6.83%

IR(KBr) cm^{-1} : 2925, 1720, 1630, 1590, 1523, 1341

3-Phenyl-6-(4′-hydroxy-3-methoxyphenyliminomethyl)furo(3,2-g) benzopyran-7H-one (23):

m.p. 146°C (ethanol) ; yield 0.33g, 75.0%

Analysis : Found : C, 73.12%; H, 4.02%; N, 3.26%

$C_{25}H_{17}O_5N$: Requires : C, 72.99%; H, 4.14%; N, 3.41%

IR(KBr) cm^{-1} : 3440, 2932, 1718, 1629, 1591, 1513

PMR ($CDCl_3$): δ 4.00 (s, 3H of -OCH_3 at C-3′); 7.00 (d, 1H at C-5′); 7.30 (s, 1H at C-2); 7.40-7.65 (m, 7H of Phenyl group at C-3 overlapped with protons at C-4 and C-9); 7.75-7.85 (m, 2H at C-2′ and C-6′); 7.90 (s, 1H at C-5); 9.00 (s, 1H of -N=C<u>H</u> at C-6)

3-Phenyl-6-(2′,4′-dihydroxyphenyliminomethyl)furo(3,2-g)benzopyran-7H-one (24):

m.p. >300°C (ethanol) ; yield 0.30g, 69.8%

Analysis : Found : C, 72.34%; H, 3.61%; N, 3.68%

$C_{24}H_{15}O_5N$: Requires : C, 72.54%; H, 3.78%; N, 3.53%

IR(KBr) cm^{-1} : 3434, 2925, 1710, 1625, 1499

3-Phenyl-6-(3′,4′-dichlorophenyliminomethyl)furo(3,2-g)benzopyran-7H-one (25):

m.p. 224°C (ethanol) ; yield 0.36g, 76.6%

Analysis : Found : C, 66.73%; H, 3.23%; N, 3.14%

$C_{24}H_{13}O_3NCl_2$: Requires : C, 66.36%; H, 2.99%; N, 3.22%

PMR ($CDCl_3$+DMSO): δ 7.45-7.95 (m, 8H of phenyl group at C-3 overlapped with protons at C-2, C-4 and C-9); 8.10-8.20 (m, 2H at C-2′ and C-6′); 8.35 (s, 1H at C-5′); 8.50 (s, 1H at C-5); 9.10 (s, 1H of -N=CH at C-6)

3-Phenyl-6-(4′-methylphenyliminomethyl)furo(3,2-g)benzopyran-7H-one (26):

m.p. 190°C (ethanol) ; yield 0.28g, 68.3%

Analysis : Found : C, 79.02%; H, 4.12%; N, 3.51%

$C_{25}H_{17}O_3N$: Requires : C, 79.16%; H, 4.48%; N, 3.69%

IR(KBr) cm^{-1} : 2927, 1735, 1628, 1596, 1508

3-Phenyl-6-[4′-(N,N-bis(2-chloroethyl)amino)phenyliminomethyl]furo(3,2-g) benzopyran-7H-one (27):

m.p. 185°C (ethanol) ; yield 0.39g, 70.9%

Analysis : Found : C, 66.79%; H, 4.12%; N, 5.39%

$C_{28}H_{22}O_3N_2Cl_2$: Requires : C, 66.53%; H, 4.36%; N, 5.54%

IR(KBr) cm^{-1} : 2928, 1718, 1630, 1594, 755

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Chapter IV : Section 3

Synthesis of Benzaldazines

INTRODUCTION

In the present endeavour, it was proposed to prepare hydrazide of ethylbenzopyran-2H-one-3-carboxylate with hydrazine and to condense subsequently with mustard compounds to afford nitrogen mustards, which are known to be anticancerous agents. When the above was attempted in refluxing ethanol, after usual work up, it was noticed to yield a different unexpected product.

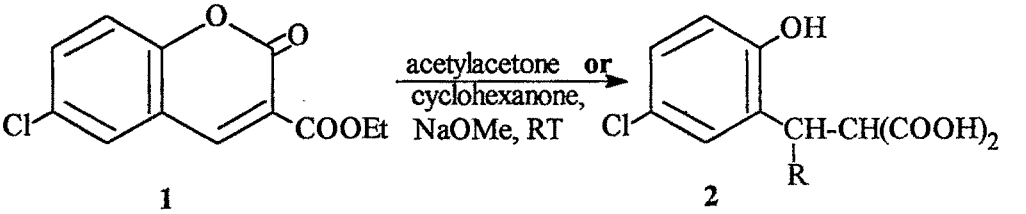
Although opening of pyrone ring is a well-known phenomena in the base catalyzed reactions, Seshadri *et al.*[1] observed that benzopyran-2H-ones containing an electron withdrawing group at position 3 are good acceptors in Michael reactions.

Hassan *et al.*[2] carried out base catalyzed reactions on such nucleus to add acetyl acetone, cyclohexanone etc. through Michael reaction at room temperature and noticed opening of pyrone ring during the process. Acetyl acetone or cyclohexanone when added to 6-chloro-3-carboethoxycoumarin (1) at room temperature in the presence of sodium methoxide base, a cleavage in pyrone ring was observed giving [α-(2′,4′-pentanedion-3′-yl)-5-chlorosalicyl]malonic acid (2a) and [α-(2′-oxocyclohexyl)-5-chlorosalicyl]malonic acid (2b). **[Scheme IV.3.1]**

Whereas Bojilova *et al.*[3,4] established such reactions by carrying out the addition of nitromethane to esters under the action of potassium fluoride and ethanol. In this reaction nitromethane was added to esters **3a** or N,N-dialkylamides **3b** of 2-oxo-2H-1-benzopyran-3-carboxylicacid at room temperature under above conditions to give Michael adducts, diesters of 2-carboxy-3-(2-hydroxyphenyl)-4-nitrobutyricacid **4a** or ethyl esters of 2-(N,N-dialkylcarbamoyl)-3-(2-hydroxyphenyl)-4-nitrobutyricacid **4b**. **[Scheme IV.3.2]**

Recently Mitra and coworkers[5] intend to exploit the nucleophilicity of the position 3 in 4-hydroxycoumarin with an electrophile like 3-carboethoxy coumarin through Michael reaction in order to synthesize anti HIV agents. An equimolecular mixture of 4-hydroxycoumarin (5) and 3-carboethoxy coumarin (6) was refluxed in pyridine under the nitrogen atmosphere to get 6-(4-hydroxy-coumarin-3-yl)-6H,7H-benzopyrano[3,2-c][1]benzopyran-7-one (7). **[Scheme IV.3.3]**

Scheme IV.3.1



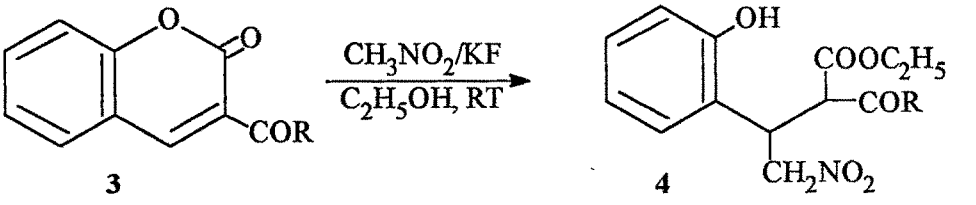
1 2

R

a $CH(COCH_3)_2$

b 2-oxocyclohexyl

Scheme IV.3.2



3 4

R

a OC_2H_5

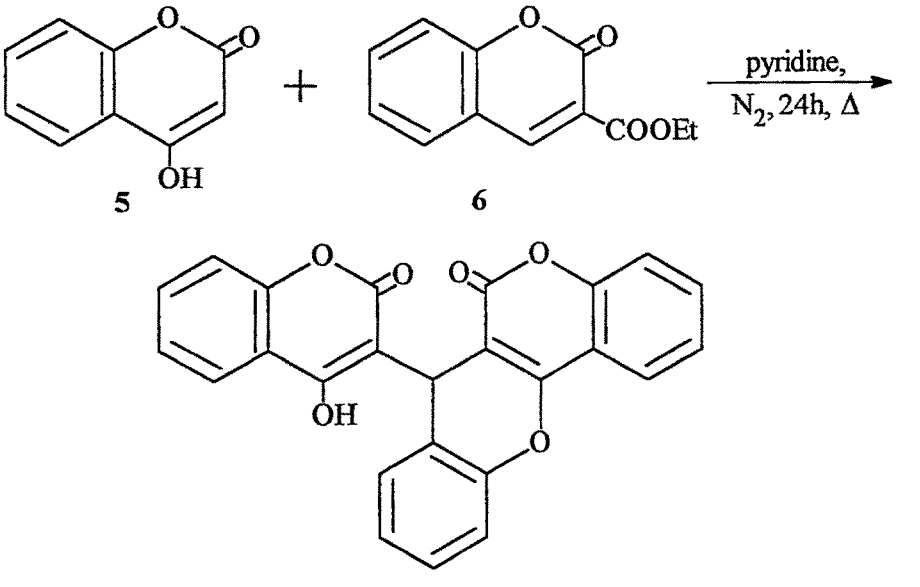
b NH_2

R

a OC_2H_5

b NH_2

Scheme IV.3.3



5 6

7

PRESENT WORK

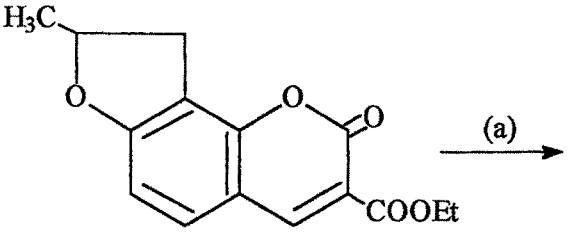
In the present work a novel cleavage in the pyrone ring system was observed when such base catalyzed Michael type reaction was attempted with hydrazine, affording exclusively benzaldazine derivatives.

2,2′-Dihydroxy-4,4′-dimethyl-3,4,3′,4′-tetrahydrodifuro(2,3-f) benzaldazine (9) was prepared from ethyl-2-methyl-2,3-dihydrofuro(2,3-h) benzopyran-5H-one-6-carboxylate (8) with hydrazine in refluxing ethanol. After usual work up, reaction afforded a product of yellowish needles, which was found soluble in dilute alkali. **[Scheme IV.3.4]** Its structure was established on the basis of elemental analysis suggesting empirical formula as $C_{10}H_{10}O_2N$, IR, PMR and mass spectral data. Two absorption bands in KBr appeared at 3434 and 1616cm^{-1} for hydroxyl group and C=N linkage respectively **[Fig. IV.3.1]** while the PMR spectrum of the product exhibited signals in $CDCl_3$ at δ 1.50, a doublet for three methyl protons at C-4; two multiplets at 2.80 and 3.30 for two methylene protons at C-3; another multiplet at 5.00 for a proton at C-4. All the above signals indicate that the dihydrofuran ring is very much intact. Two doublets at δ 6.35 and 7.05 for two ortho coupled protons of benzene ring and finally a singlet at 8.50 for -CH=N at C-1. **[Fig. IV.3.2]**

The mass spectrum of the product m/z at 352 confirms the molecular formula as $C_{10}H_{10}O_2N \times 2 = C_{20}H_{20}O_4N_2$ (MW = 352) and its structure as 2,2′-dihydroxy-4,4′-dimethyl-3,4,3′,4′-tetrahydrodifuro(2,3-f)benzaldazine (9) **[Fig. IV.3.3]** which exhibited peaks at m/z: 352(M^+), 335, 176, 162 (base peak,100%), 148, 132, 121, 103, 97, 91, 85, 77, 69, 57.

Similarly, reactions of ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate (10a) and 7-allyloxy-3-cyanobenzopyran-2H-one (10b) with hydrazine in refluxing ethanol were carried out to understand the formation of product. The

Scheme IV.3.4



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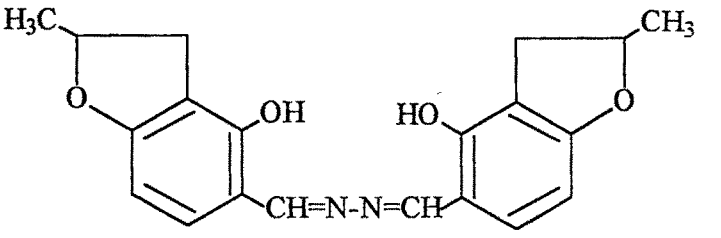

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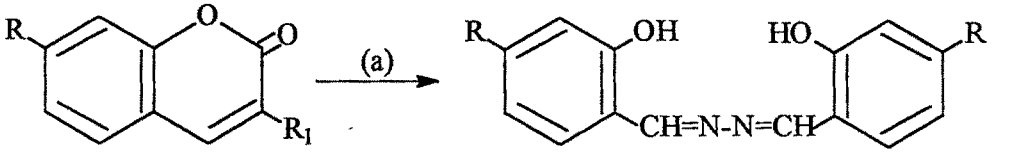


10 **11**

	R	R_1
a	O	COOEt
b	O	CN
c	H	$COCH_3$
d	H	COOEt

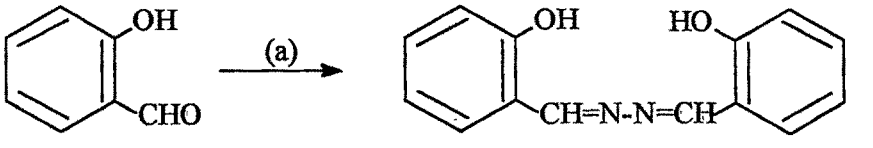
R

a O

a O

b H

b H



12 **11b**

(a) NH_2NH_2, C_2H_5OH, Δ

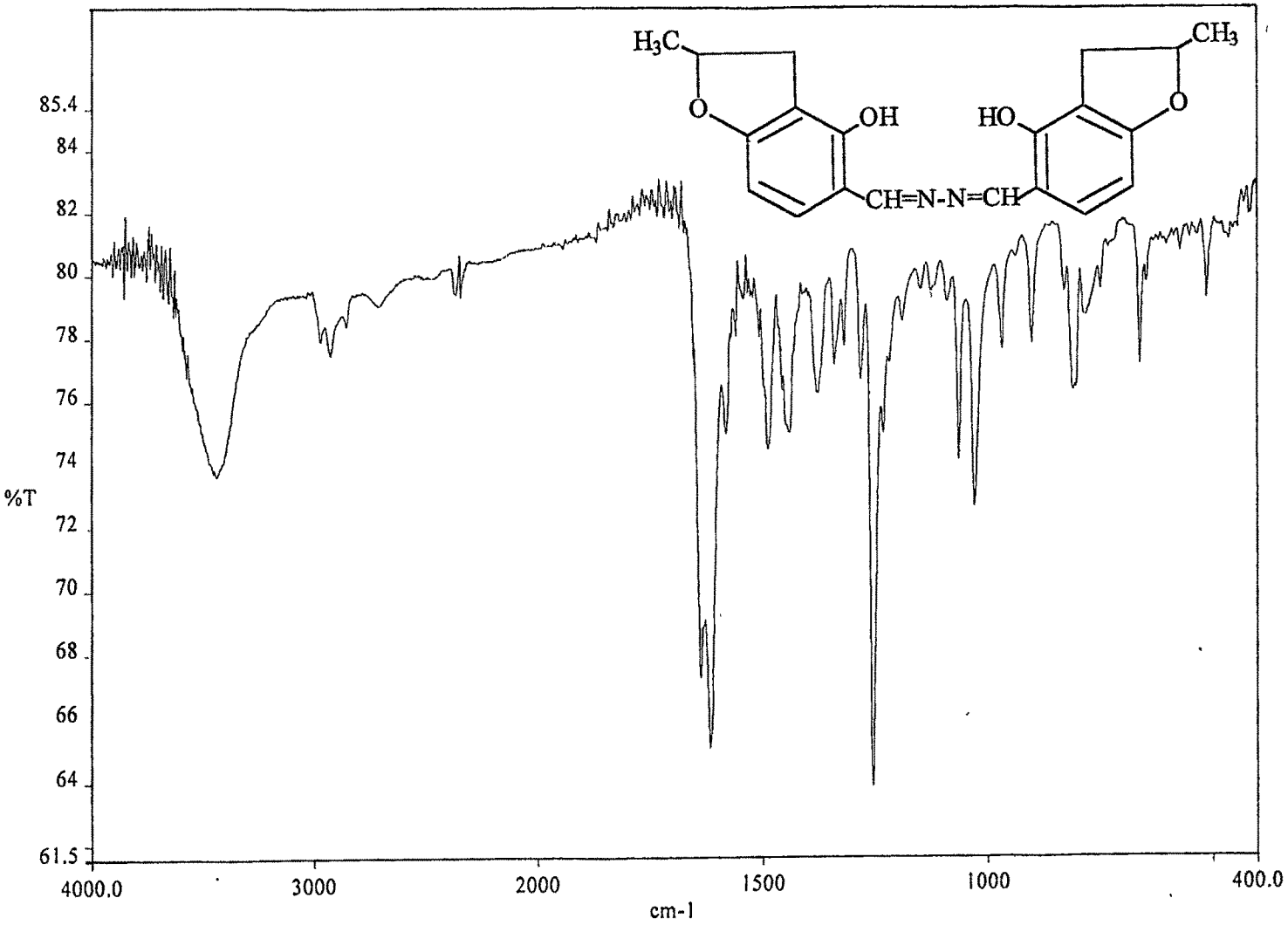

H3C
O
OH
CH=N-N=CH
HO
CH3
O
85.4
84
82
80
78
76
74
%T
72
70
68
66
64
61.5
4000.0
3000
2000
1500
1000
400.0
cm-1

Fig. IV.3.1

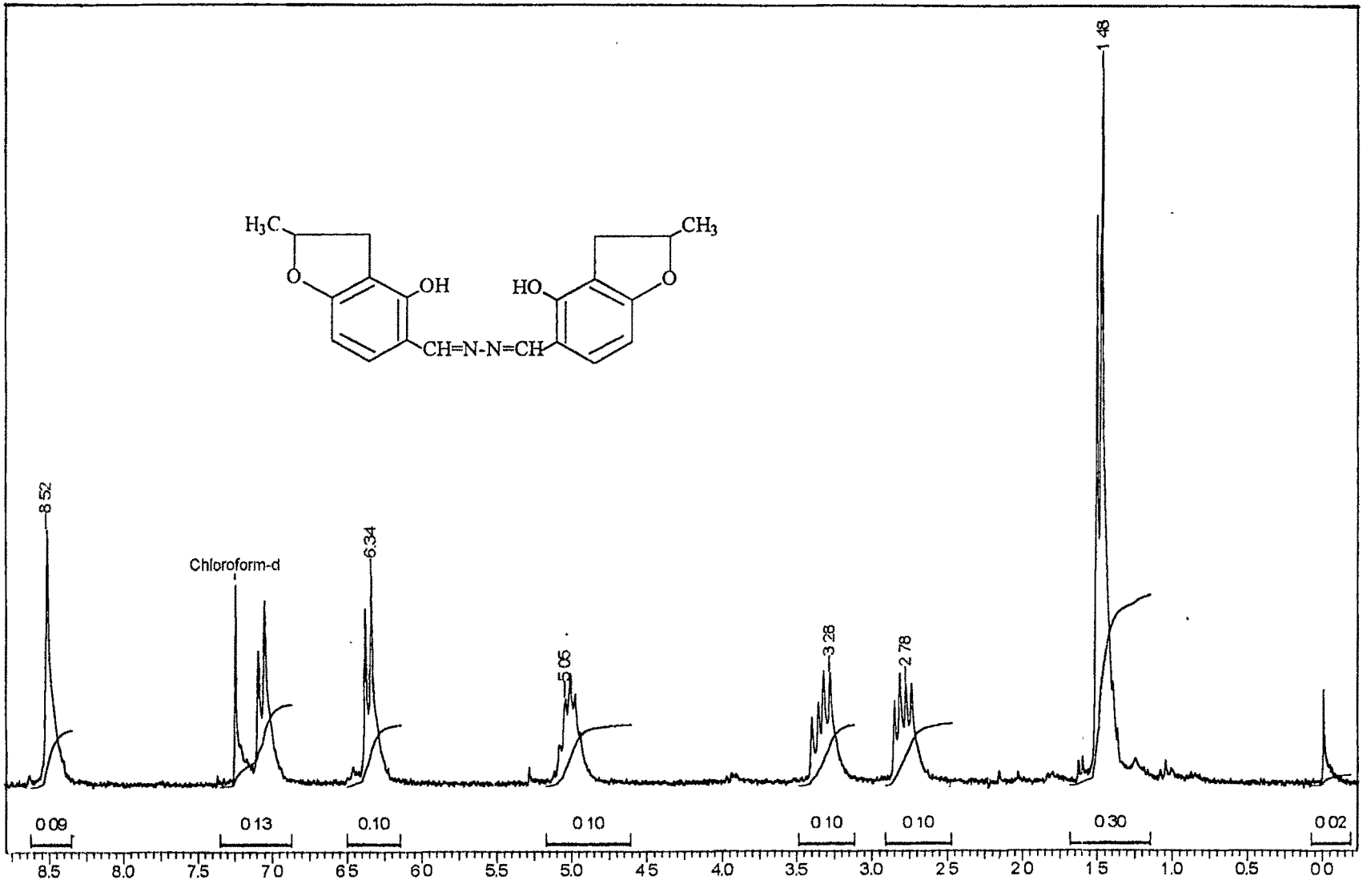
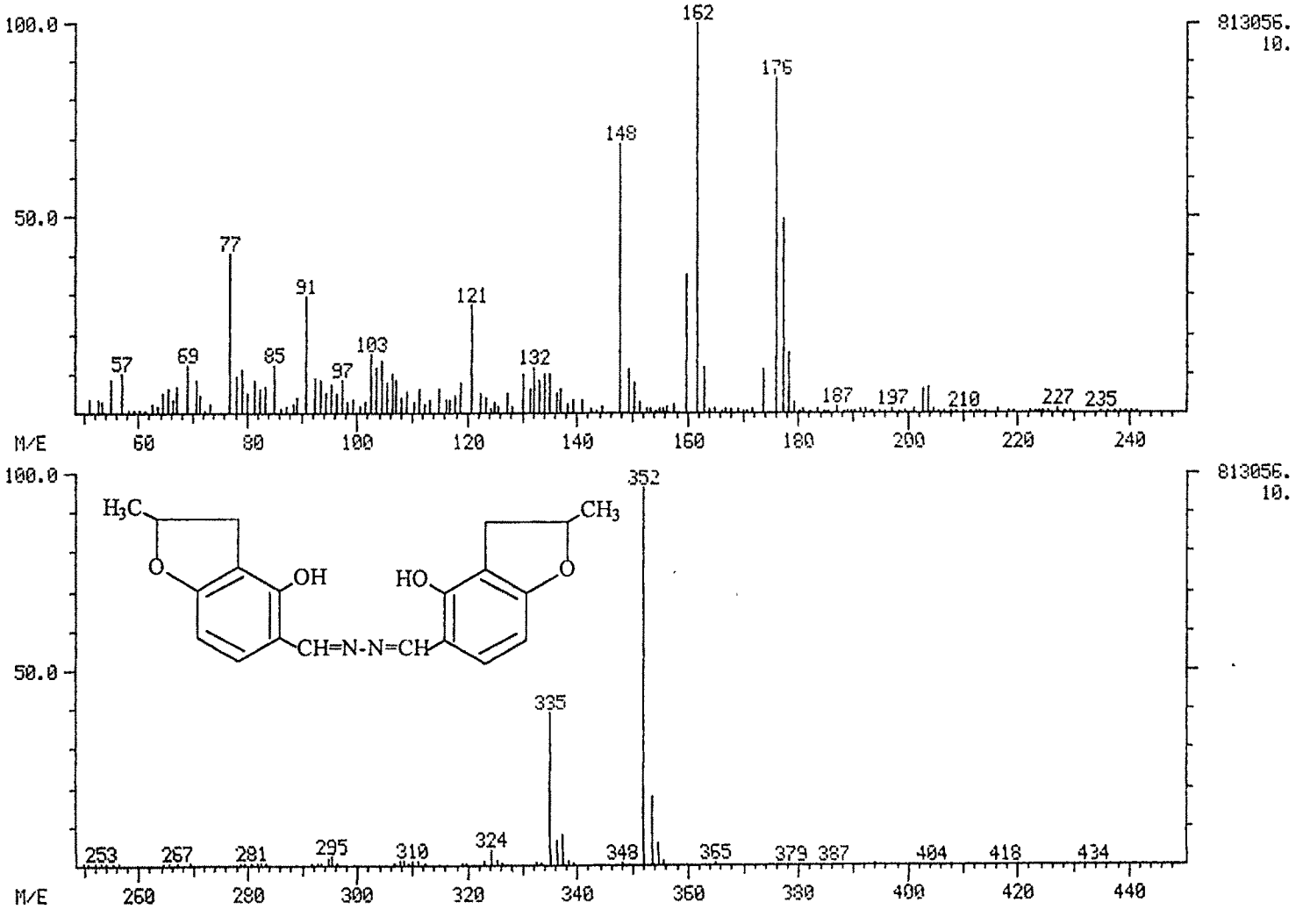

H3C
CH3
OH
HO
O
O
CH=N-N=CH
8.52
Chloroform-d
6.34
5.05
3.28
2.78
1.48
0.09
0.13
0.10
0.10
0.10
0.10
0.30
0.02
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

Fig. IV.3.2


100.0
50.0
M/E
813056.
10.
162
175
148
77
91
121
57
69
85
97
103
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187
197
210
227
235
60
80
100
120
140
160
180
200
220
240
H_3C
CH_3
OH
HO
O
O
CH=N-N=CH
352
335
253
267
281
295
310
324
348
365
379
387
404
418
434
260
280
300
320
340
360
380
400
420
440

Fig. IV.3.3

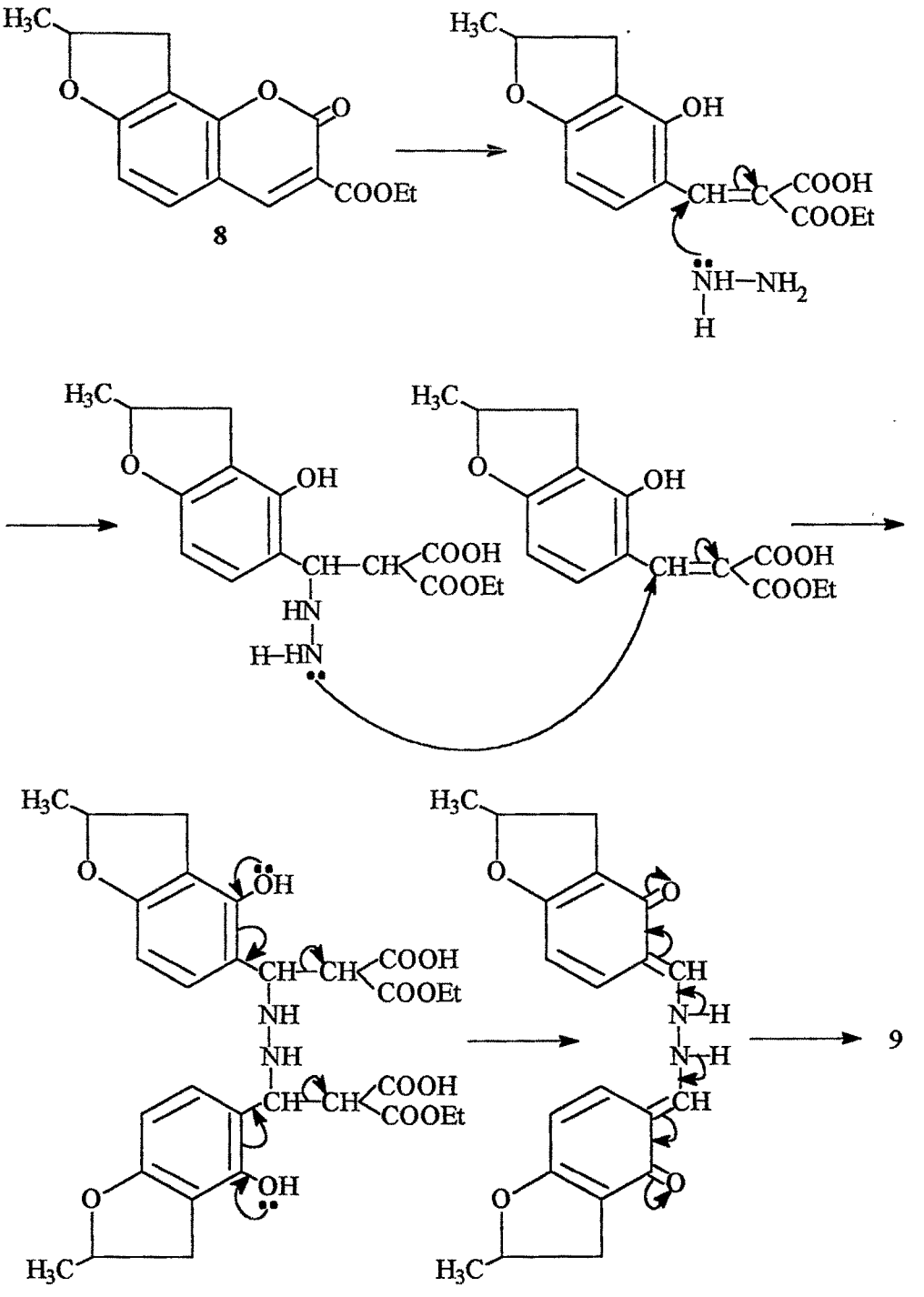
structure of the products were established through m.p., mmp, elemental analysis, IR and PMR spectra as 2,2′-dihydroxy-4,4′-diallyloxybenzaldazine (11a). In both the cases same product was obtained.

An independent reaction of salicylaldehyde (12) with hydrazine in refluxing ethanol was also studied. The mmp of the product 2,2′-dihydroxy benzaldazine (11b) and the products, which resulted from ethylbenzopyran-2H-one-3-carboxylate (10c) and 3-acetylbenzopyran-2H-one (10d) under similar conditions, was taken and found no depression in the melting points suggest that all the three products **11b** prepared from different starting compounds are identical.

All these observations revealed that the reaction gives same type of benzaldazine derivative with benzopyrone ring system, irrespective of electron withdrawing substituents such as -COOEt, -$COCH_3$ or -CN at position 3.

The plausible mechanism is explained in which the benzopyrone ring initially gets opened as known in the base catalyzed reactions, giving a α-carboethoxycinnamicacid derivative. This derivative on nucleophilic attack (Michael type reaction) by an amino group of hydrazine gives a hydrazido derivative, which subsequently reacts with second molecule of cinnamic acid derivative forming a dimeric compound. The elimination of monoethylmalonic acid is facilitated by the movement of lone pair of electron on oxygen, which resulted in the formation of **9** by rearomatization.

Mechanism:



EXPERIMENTAL

^{1}H-NMR spectra were recorded on Bruker 200MHz or Perkin-Elmer 90MHz spectrophotometer. Chemical shifts are relative to tetramethylsilane. Infrared spectra were recorded on Perkin-Elmer FT-IR spectrometer (Spectrum RX 1). Melting points were obtained by open capillary method and are uncorrected. Elemental analyses were carried out on Perkin-Elmer C,H,N,S analyzer (Model 2400). Mass spectrum was taken on MAT 1020B-70ev mass spectrometer.

General procedure for benzaldazine derivatives (9,11a,b):

3-Substituted benzopyrone derivative (3.6mmol) in ethanol (25ml) was refluxed with hydrazine (98%, 5.4mmol) for 5h. After the reaction, excess of solvent was removed and the product was filtered and recrystallized.

Reaction of Ethyl-2,3-dihydrofuro(2,3-h)benzopyran-5H-one-6-carboxylate (8) with hydrazine:

m.p. 229-30°C (ethanol) ; yield, 85.0 %

Analysis : Found : C, 68.05%; H, 5.52%; N, 7.87%

$C_{20}H_{20}O_4N_2$: Requires : C, 68.18%; H, 5.68%; N, 7.95%

IR(KBr) cm^{-1} : 3434, 2927, 1616, 1490, 1255

Reaction of Ethyl-7-allyloxybenzopyran-2H-one-3-carboxylate (10a) with hydrazine:

m.p. 162-3°C (ethanol) ; yield, 82.0%

Analysis : Found : C, 68.10%; H, 5.61%; N, 7.83%

$C_{20}H_{20}O_4N_2$: Requires : C, 68.18%; H, 5.68%; N, 7.95%

IR(KBr) cm^{-1} : 3433, 2925, 1618, 1498, 1279

PMR($CDCl_3$): δ 4.49 (d, 2H of -$OC\underline{H}_2CH=CH_2$); 5.20-5.43 (m, 2H of -$OCH_2CH=C\underline{H}_2$); 5.85-5.91 (m, 1H of -$OCH_2C\underline{H}=CH_2$); 6.44 (m, 2H at C-5 and

C-3); 7.15 (d, 1H at C-6); 8.49 (s, 1H of -CH=N at C-1); 11.41 (s, 1H of -OH at C-2)

Reaction of 7-Allyloxy-3-cyanobenzopyran-2H-one (10b) with hydrazine:

m.p. 163°C (ethanol) ; yield, 83.2%

Analysis : Found : C, 68.13%; H, 5.64%; N, 7.82%

$C_{20}H_{20}O_4N_2$: Requires : C, 68.18%; H, 5.68%; N, 7.95%

Reaction of Ethyl benzopyran-2H-one-3-carboxylate (10c) with hydrazine:

m.p. 215°C (ethanol) ; yield, 80.8%

Analysis : Found : C, 70.12%; H, 5.08%; N, 11.59%

$C_{14}H_{12}O_2N_2$: Requires : C, 70.00%; H, 5.00%; N, 11.67%

IR(KBr) cm^{-1} : 3436, 2924, 1625, 1488, 1278

Reaction of 3-Acetylbenzopyran-2H-one (10d) with hydrazine:

m.p. 216-17°C (ethanol) ; yield, 79.5%

Analysis : Found : C, 70.07%; H, 5.04%; N, 11.57%

$C_{14}H_{12}O_2N_2$: Requires : C, 70.00%; H, 5.00%; N, 11.67%

Reaction of 2-Hydroxybenzaldehyde (12) with hydrazine:

m.p. 216°C (ethanol) ; yield, 89.1%

Analysis : Found : C, 70.12%; H, 5.11%; N, 11.54%

$C_{14}H_{12}O_2N_2$: Requires : C, 70.00%; H, 5.00%; N, 11.67%

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