CHAPTER-III

SYNTHESIS OF AMINOMETHYL FUROCOUMARINS

CHAPTER - III

SYNTHESIS OF AMINOMETHYLFUROCOUMARINS

In the previous chapter, the occurrence, synthesis and properties of furocoumarins and in particular the photochemotherapeutic behaviour of psoralen have been discussed in detail. It is well known that psoralen derivatives are commonly used as photochemotherapeutic drugs in the PUV-A (Psoralen Ultraviolet-A) therapy of dermatological disorders like Psoriasis, vitiligo, atopic eczema and micosis fungoides in the tumor stage and also as tools for studying the structure of nucleic acids in molecular biology. These psoralens when photoreact with nucleic acids, DNA in particular, form both mono and diadducts.

Currently 8-methoxy psoralen(8-MOP) which is also a naturally occurring compound, is mainly used in the PUV-A therapy. But it is reported that 8-MOP in combination with UV-irradiation produces unwarrented side effects like inflamation of skin, skintoxicity and at times skin cancer.

These undesired side effects are believed to be mainly due to the formation of cross-linkages in DNA. Therefore, it was felt that monoaddition would be safer to overcome the problems encountered with 8-MOP and so now a days scien-

tists are in very much search for furocoumarins which will have only monoaddition having a high photoreactivity with DNA.

Thus it was achieved in the case of psoralens by introducing an electron withdrawing group at C-3 position such as carboethoxy, cyno etc. in order to reduce the photoreactivity of one of the sites in particular the 3,4 double bond to prevent the formation of double adduct (cross-linkages). But in all these cases the cross-linkages formed to limited extent and some times not formed at all and besides, the binding capacity to DNA becomes very low in comparison with 8-MOP.

Later Song et al.[1] demonstrated in psoralen there are two photoreactive sites namely the 3,4 double bond of the pyronic ring and the 4',5' double bond of the furan ring and in singlet excited state the excitation energy is uniformly distributed in the whole molecule while in the triplet state it is concentrated in the 3,4 double bond, therefore, the latter is the most photo-reactive site in the molecule. In fact, it has been found that when psoralen molecules are free in solution and photoreact with small molecules (for instance pyrimidine bases) only 3,4-cycloadducts are formed. It is, therefore, undesirable to insert in the

C-3 position a strong electron withdrawing group like carbo-ethoxy group which cancels out the photoreactivity of the 3,4-double bond and reduce considerably the photobinding capacity with DNA.

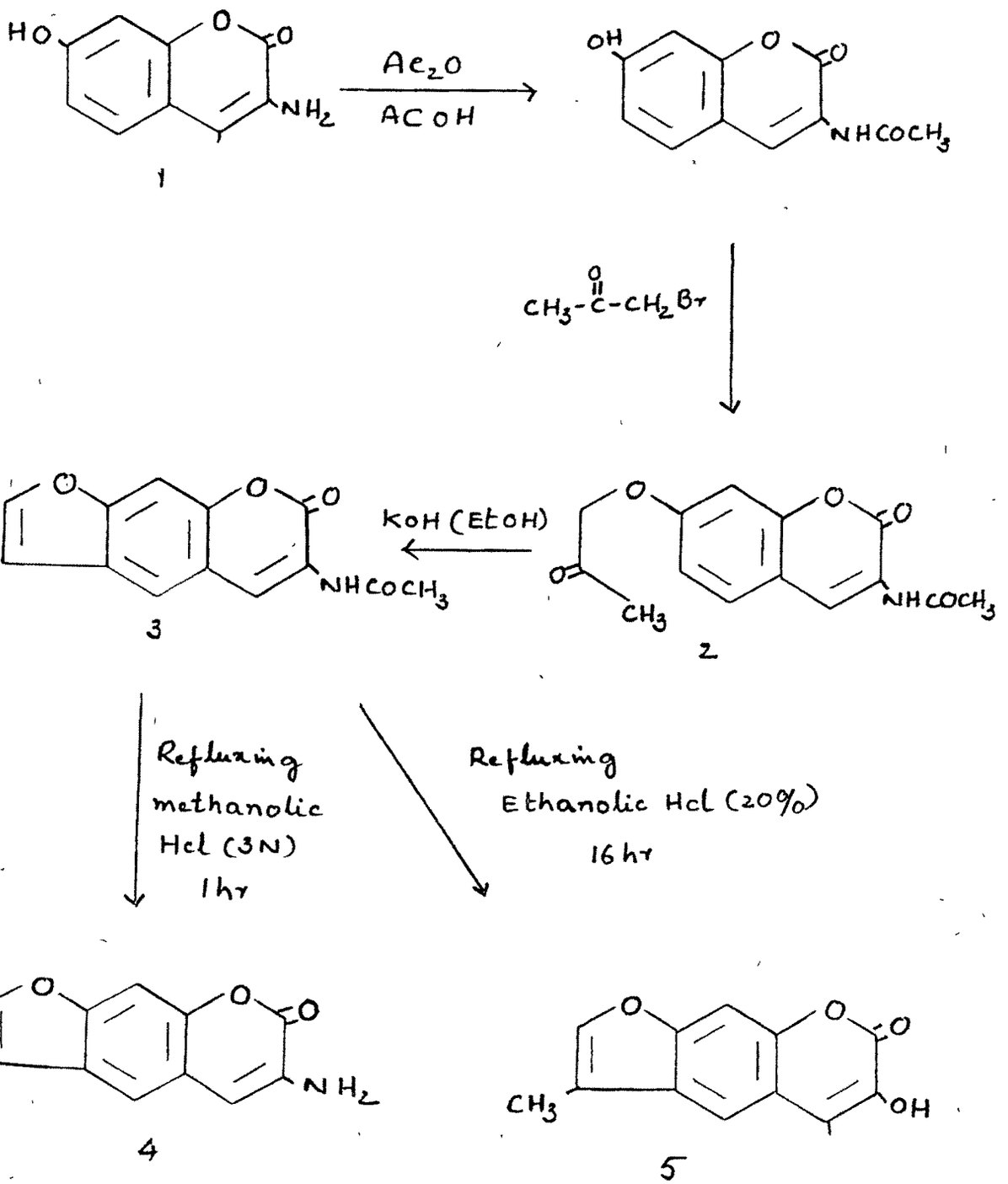
Antonello and coworkers[2] synthesised new psoralen derivatives containing an electron donating group at 3-position, such as 3-amino and 3-hydroxy instead of electron withdrawing groups and observed very high photobinding capacity to DNA compared to 8-MOP and lack of capacity to form cross-linkages.

3-Amino and 3-hydroxy psoralens are synthesised by first acetylating the 3-amino-7-hydroxy coumarin (1) followed by condensation with bromoacetone to give 3-acetyl amido-7-acetonyloxy coumarin (2) which on cyclisation with alcoholic KOH gave 3-acetylamido-4'-methylpsoralen (3). 3-Amino-4'-methylpsoralen (4) is obtained when (3) is hydrolysed by refluxing it in methyl alcohol with 3N HCl for 1 hr. while the 3-hydroxy-4'-methylpsoralen (5) is obtained when (3) is refluxed for 16 hr. with ethanolic HCl (20%) [Scheme-1].

Rapoport and coworkers[3] synthesised psoralens having a haloalkyl, hydroxyalkyl, alkoxyalkyl and aminoalkyl groups at 4'-position on furan ring from trioxsalen (6) by first treating with $ClCH_2OMe$ to give chloromethyl compound (7).

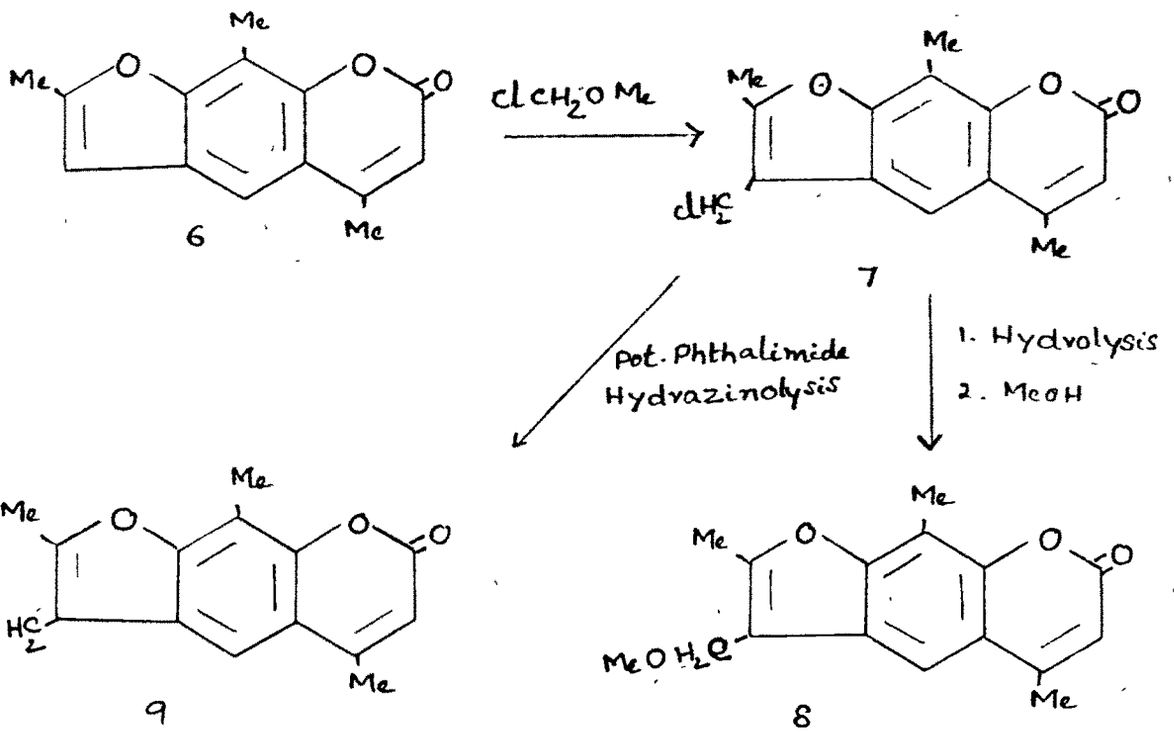
SCHEME-I

Antonello and coworkers[2]



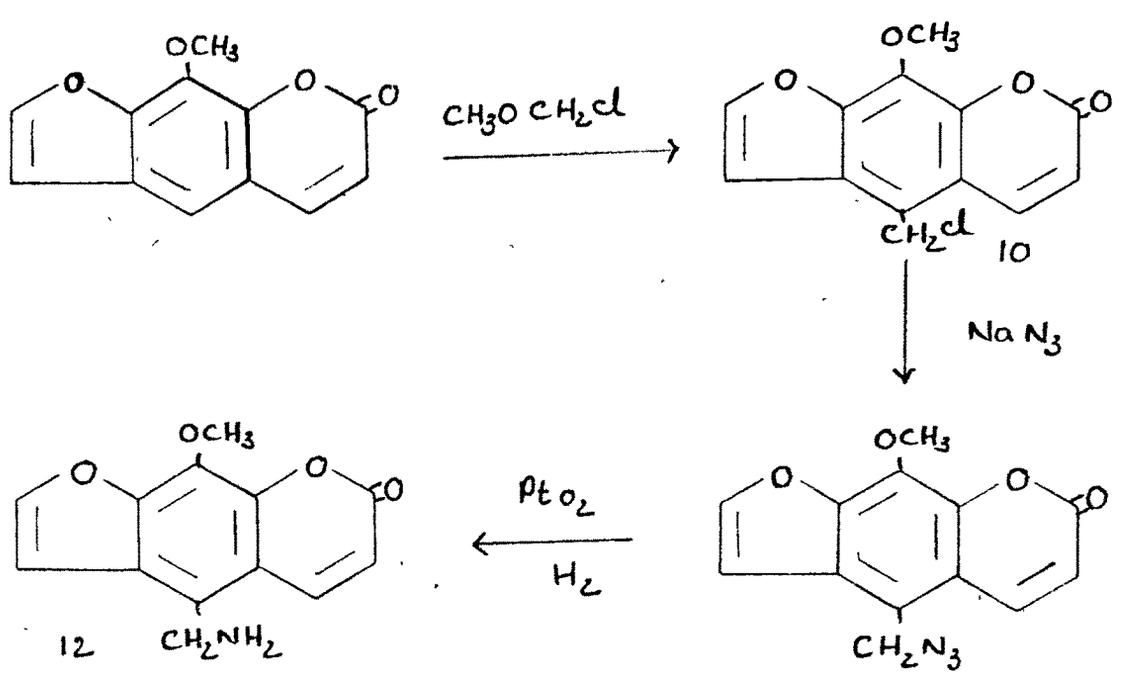
SCHEME – 2

Rapoport et al[3]



SCHEME – 3

Buchardt et al[4]



Alkoxyalkyl (8) is obtained by treating the chloromethyl (7) compound with MeOH. Aminomethyl psoralens (9) are obtained by phthalimidation followed by hydrazinolysis. [Scheme-2]

They 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 inactivation of viruses and in photochemotherapy of psoriasis.

While Buchardt et al.[4] synthesised 5-aminomethyl-8-methoxypsoralen, since 8-MOP is by far felt most important clinical drug and as an attempt to prepare hydrophilic derivative of the compound 8-MOP, they condensed 8-MOP with chloromethylmethyl ether in acetic acid to give 5-chloromethyl derivative (10). This chloromethyl derivative (10) on refluxing with NaN_3 gave 5-azidomethyl derivative (11) followed by reduction by catalytic hydrogination in methanol using PtO_2 as catalyst afforded 5-aminomethyl-8-methoxypsoralen (12). [Scheme-3]

In view of the activity of bergapten and isopempinillin Hishmat and coworkers[5] studied the acylaminomethylation of 4-hydroxybergapten and 4-hydroxyisopimpinillin with different N-hydroxymethylcarboxamides to give corresponding 3-acylaminomethyl derivatives (12). Acid hydrolysis of these

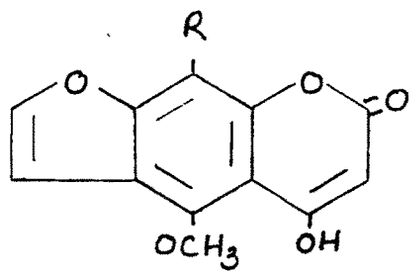
acylaminomethyl compounds (12) gave 3-aminomethyl derivatives (13). [Scheme-4]

Hishmat and coworkers[6] also synthesised 4-aminomethyl xanthotoxin and 4-aminoimperatorin (15) by condensing 4-chloromethylxanthotoxin or imperatorin (14) with different heterocyclic amines with a view to study the photosensitizing activity as well as tuberculostatic and antibacterial activity. [Scheme-5]

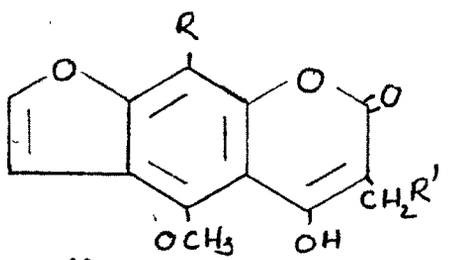
Kaufmann and coworkers[7] attempted to synthesise 8-aminomethylpsoralen and 8-aminomethyl-4-methylpsoralen by chloromethylating the 8-methyl and 4,8-dimethyl psoralen, but it gave mixture of compounds. Vilsmeir formylation with $POCl_3$ and DMF at an elevated temperature gave good yields of 4'-formyl-8-methylpsoralen which indicated the 4'-position is preferred for electrophilic attack. As the yields are not encouraging at larger scale, this method of synthesising aminomethyl psoralens was discontinued. They discovered bromination of 8-methyl and 4,8-dimethyl psoralen with N-bromosucinimide in the presence of benzoylperoxide which give primarily 8-bromomethylpsoralen (16). Hence this method was used for making 8-aminomethylpsoralen (17) by condensing first (16) with pot. phthalimide followed by hydrazinolysis.

SCHEME-4

Hishmat et al[5]

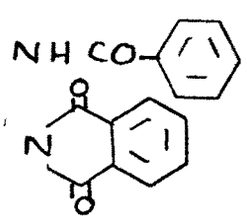


Acylamino-methylation →

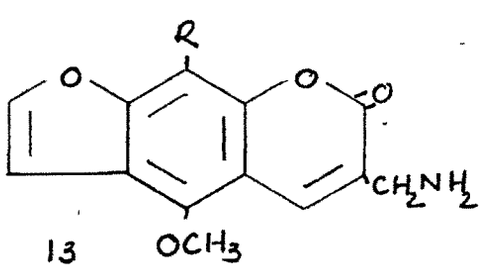


12

$R = H, OCH_3$

$R_1 =$ 

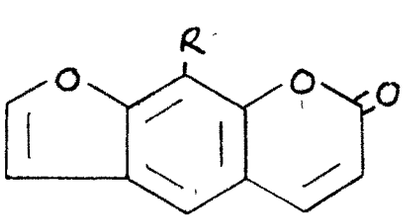
↓ Con HCl, 140°, 10hr



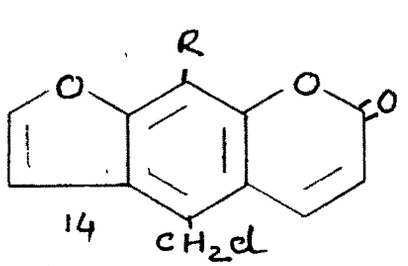
13

SCHEME-5

Hishmat et al[6]

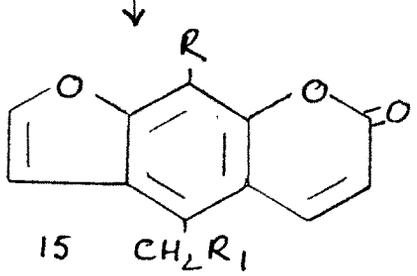


chloromethylation →



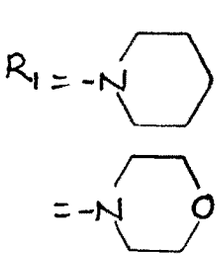
14

↓ cyclic Secondary amines



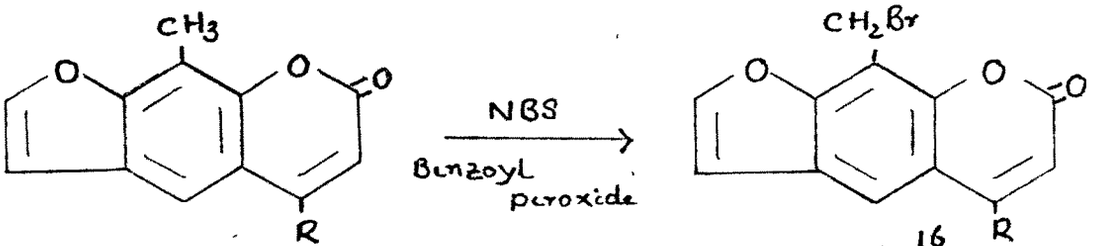
15

$R = OCH_3, OCH_2CH{=}CH\langle^{CH_3}_{CH_3}$

$R_1 =$ 

SCHEME-6

Kaufmann et al[7]

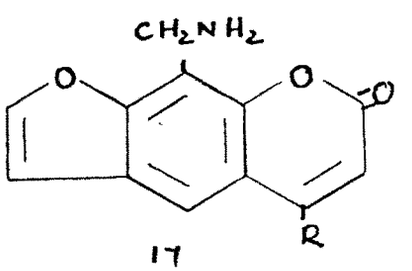


16

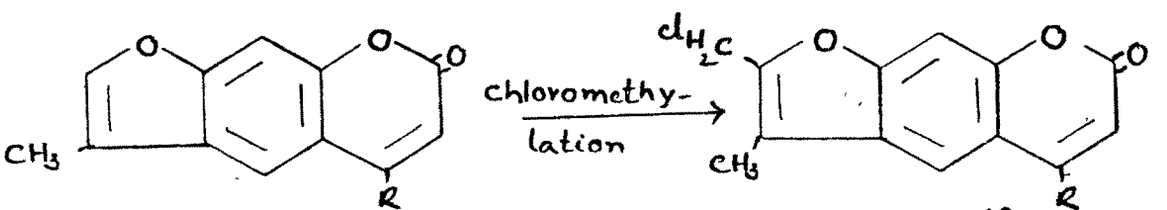
R = H, CH_3

① Pot. Phthalimide

② Hydrazinolysis



17

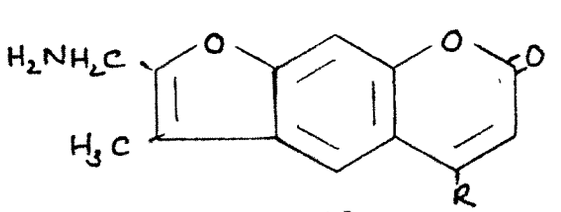


18

R = H, CH_3

1. Pot. Phthalimide

2. Hydrazinolysis



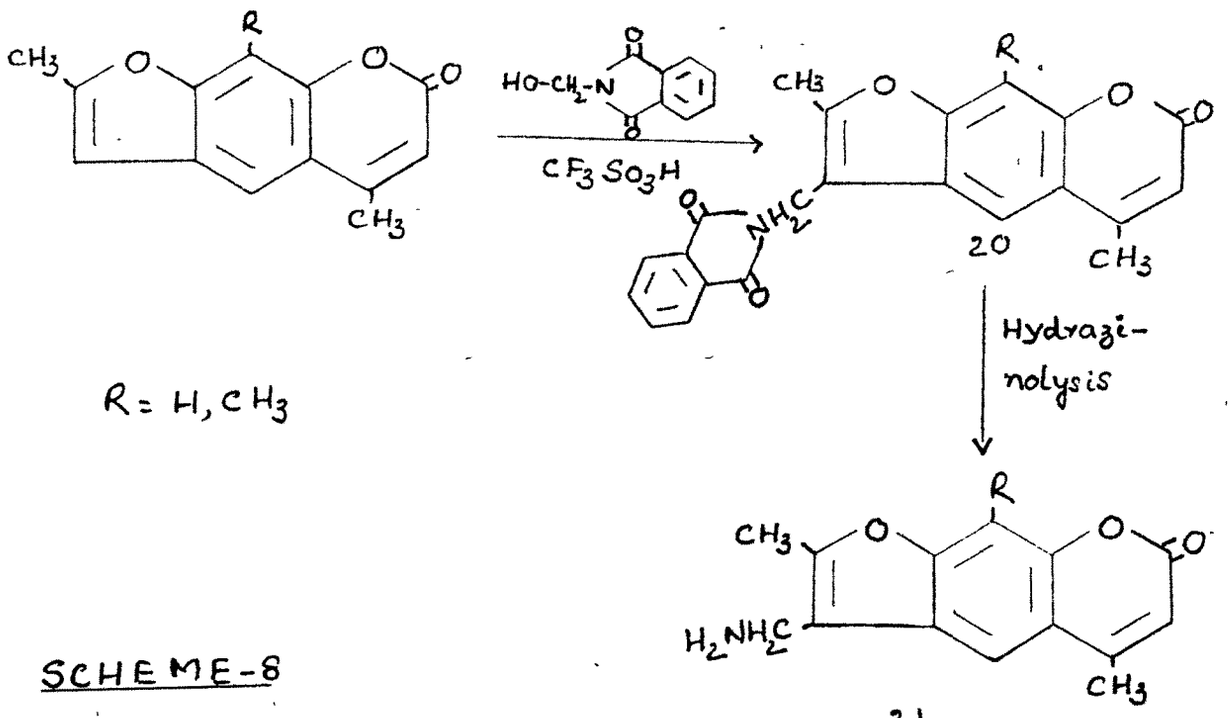
19

They also synthesised 5'-aminomethy psoralens (19) from the hypothesis, since 4'-position is more reactive towards electrophilic attack in 4-methyl and 4,8-dimethyl psoralen and when 4'-position is blocked the preferential attack would be 5' for chloromethylation. On this basis 5'-chloromethyl derivatives of psoralen were synthesised by keeping a methyl substituent at 4'-position. Thus 4'-methyl psoralen and 4,4'-dimethy psoralen on chloromethylation gave 5'-chloromethyl derivative (18) which on phthalimidation followed by hydrazinolysis afforded (19), [Scheme-6]. They reported these compounds had outstanding dermal photosensitizing activity and were useful in phototherapeutic treatment of psoriasis.

Heindel et al.[8] synthesised aminomethyl psoralens having substitution on the furan ring by electrophilic substitution of N-hydroxymethyl phthalimide followed by hydrazinolysis. Thus 4,5'-dimethyl psoralen and 4,5',8-trimethyl psoralen on phthalimidomethylation gave phthalimidomethyl psoralen (20), which on subsequent hydrazinolysis gave aminomethyl psoralens (21). [Scheme-7] Although the method is very attractive with 60-70% yields, but the methoxy, hydroxy groups containing psoralens undergo multisite electrophilic substitution by the phthalimidomethyl group.

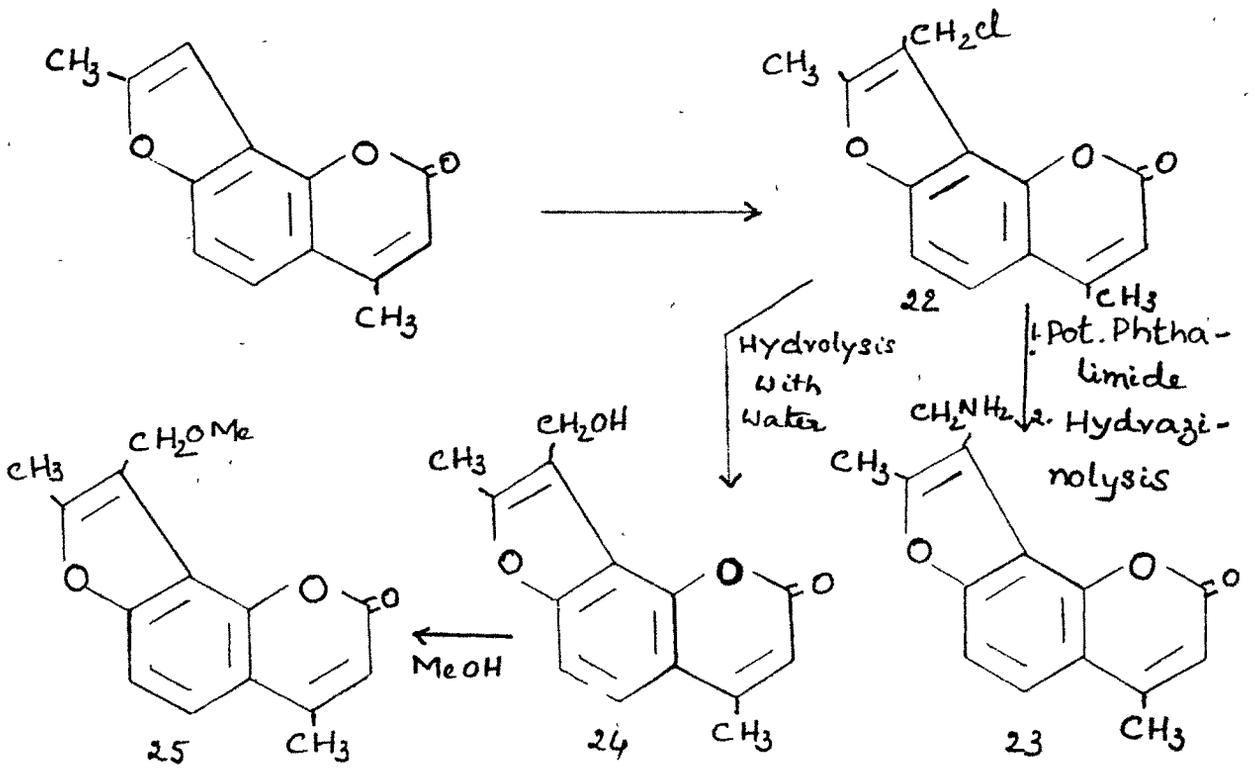
SCHEME-7

Heindel et al[8]



SCHEME-8

Dall' Acqua et al



In contrast it was reported that angilicin exhibited good phototherapeutical behaviour and the activity was also enhanced by the introduction of one or two methyl groups in the molecule. But surprisingly it augmented the hydrophobic character and lowered the solubility in water than that of parent angelicin. A dramatic increase of the affinity toward the DNA was marked by the introduction of aminomethyl group, a polar group in the 4'-position of 4,5'-dimethylangelicin.

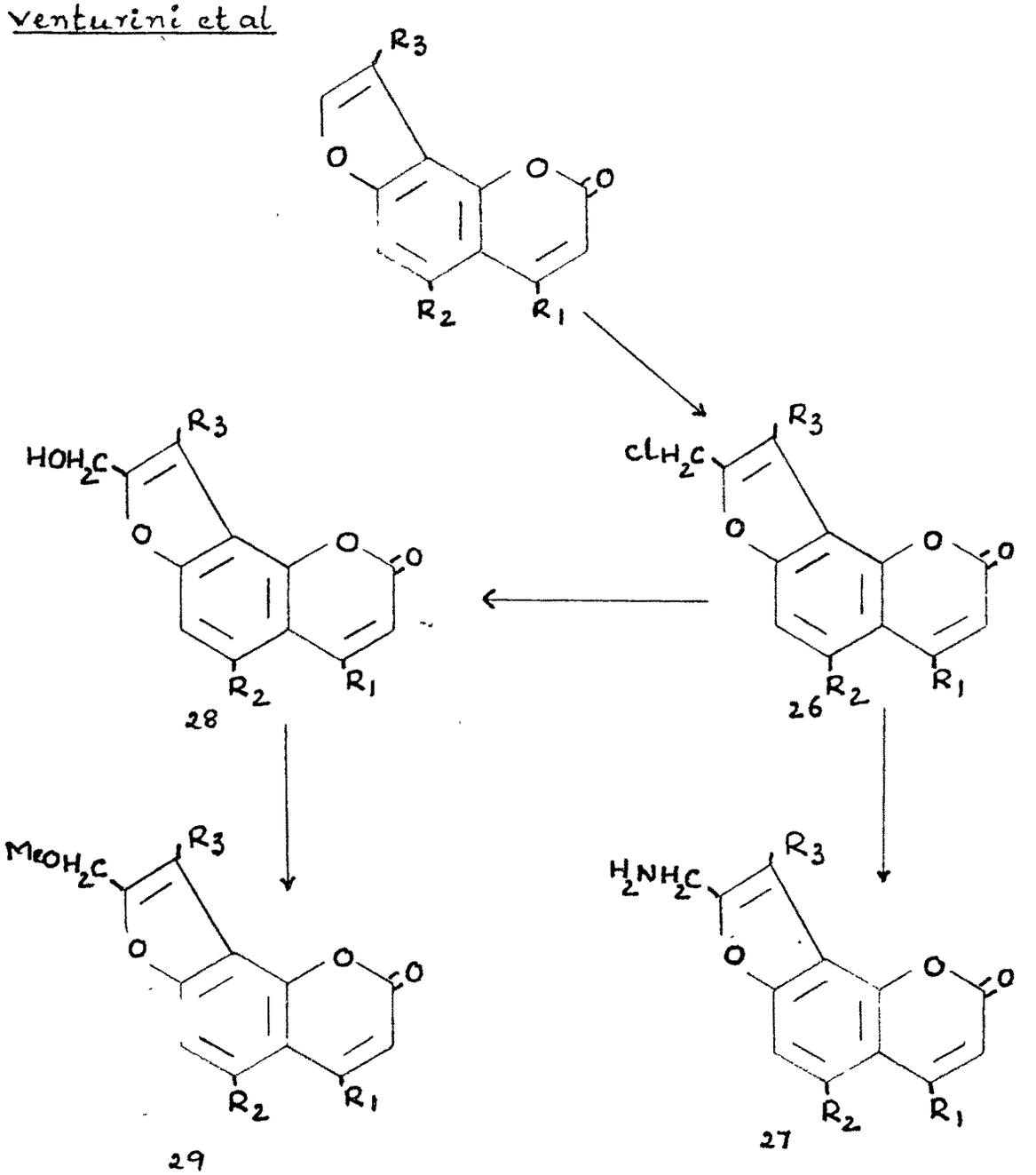
Dall' Acqua et al.[9] synthesised new derivatives of 4,5'-dimethylangelicin carrying hydroxymethyl, methoxymethyl and aminomethyl groups at 4'-position with an aim of modifying the lipophilic character of 4,5'-dimethyl angelicin.

Thus aminomethyl derivative (23) was prepared by first carrying out the chloromethylation of 4,5'-dimethylangelicin to give a chloromethyl derivative (22) followed by phthalimidation and hydrazinolysis with hydrazine hydrate. Hydroxymethyl derivative (24) was prepared by the hydrolysis of chloromethyl derivative (22). (24) on methylation afforded (25). [Scheme-8]

While Venturini et al.[10] synthesised 5'-aminomethyl, 5-hydroxymethyl and 5'-methylhydroxymethyl derivatives of

SCHEME-9

Venturini et al[10]



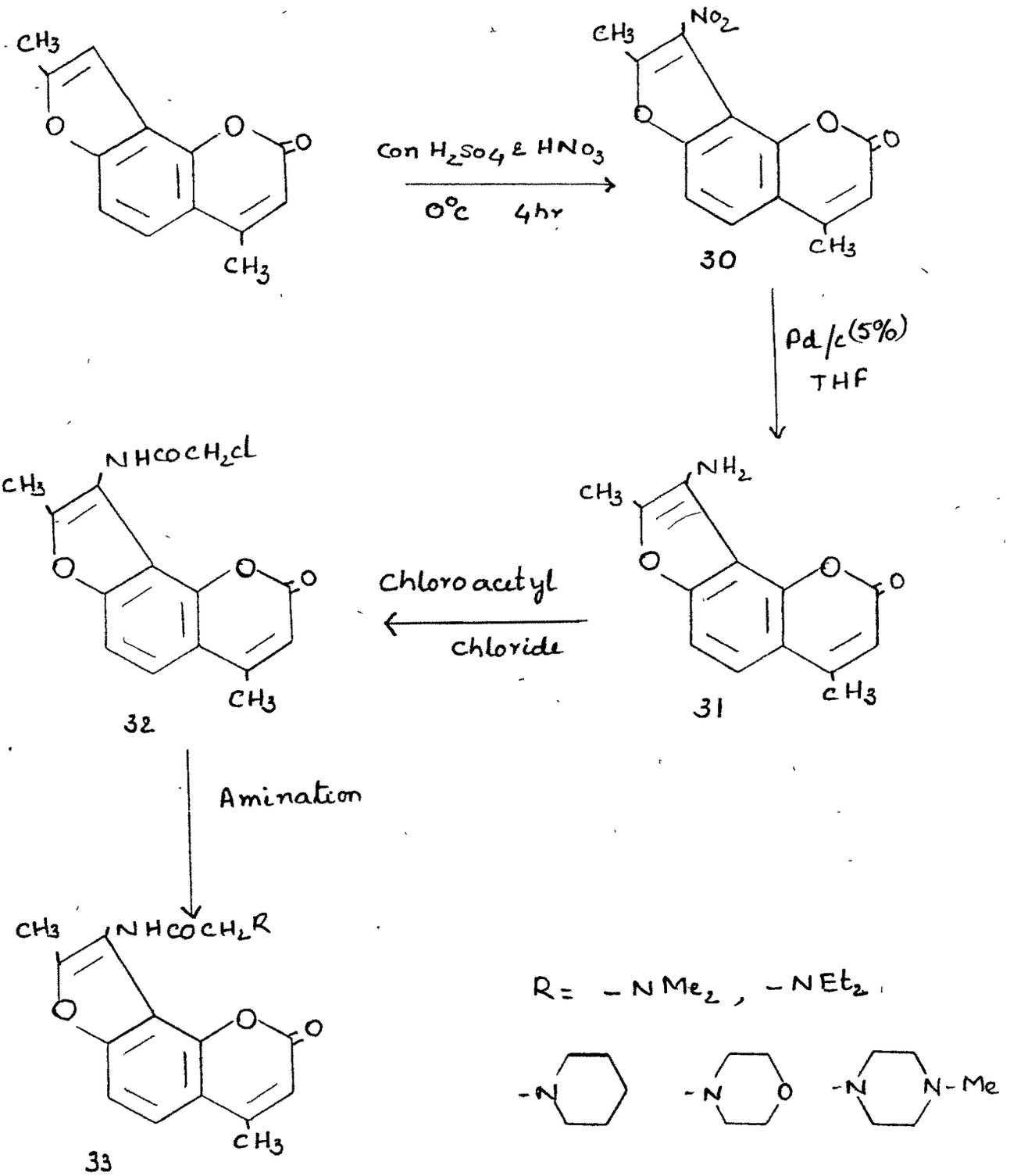
$R_1 = R_2 = R_3 =$ H or Me

substituted angelicins by first carrying out the chloromethylation to give chloromethyl derivative (26), which on phthalimidation and hydrazinolysis gave amino methyl derivative (27). (26) on hydrolysis yielded hydroxymethyl derivative (28). Methoxymethyl derivative (29) was obtained on methylation of (28). [Scheme-9] They also reported that these compounds inhibit cell division and lack skin toxicity. They also tested the mutagenic activity of the compounds with or without near UV-radiation in salmonellatyphimurium strains.

Piero Valenti et al.[11] have prepared N-substituted 4,5'-dimethyl angelicin glycinamides in four steps by carrying out first the nitration of 4,5'-dimethylangelicin which normally takes place in position 4' of furan ring yielding 4'-nitro intermediate (30). This on reduction resulted the 4'-aminoangelicin (31), which on amidation with chloroacetylchloride furnished chloroacetylimide derivative (32) of 4,5'-dimethylangelicin which on condensation with different secondary amines gave the titled glycinamide derivatives (33). [Scheme-10] These compounds possess good activity in surface, infiltration and conduction anæsthesia, in particular the piperidine derivative shows greater anaesthetic potency and lower acute toxicity than the reference standard lidocaine. These are possessing weak photosensitizing activity under UV-irradiation at 365 nm.

SCHEME - ID

Valenti et al [11]

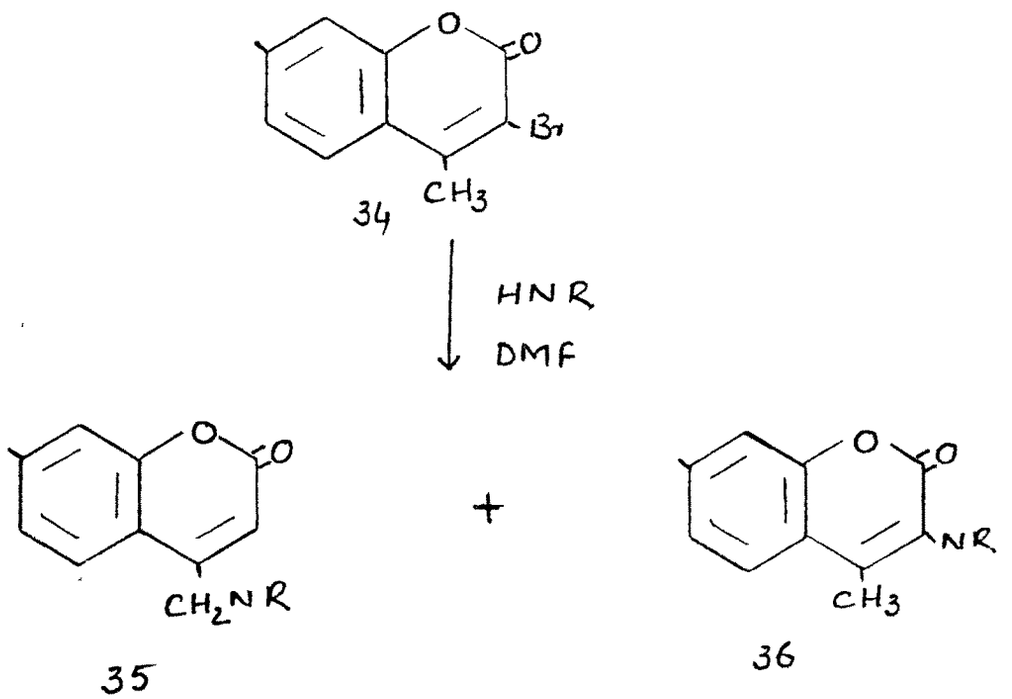


It is observed in all earlier procedures, mostly a three step method involving chloromethylation and displacement of chlorineby potassium phthalimide followed by hydrazinolysis and sometimes hydrolysis of acetyl amide group was employed. But many a times these methods produce poor yields. Hence in order to obtain good yields of aminomethylfurocoumarin, a new method has been developed.

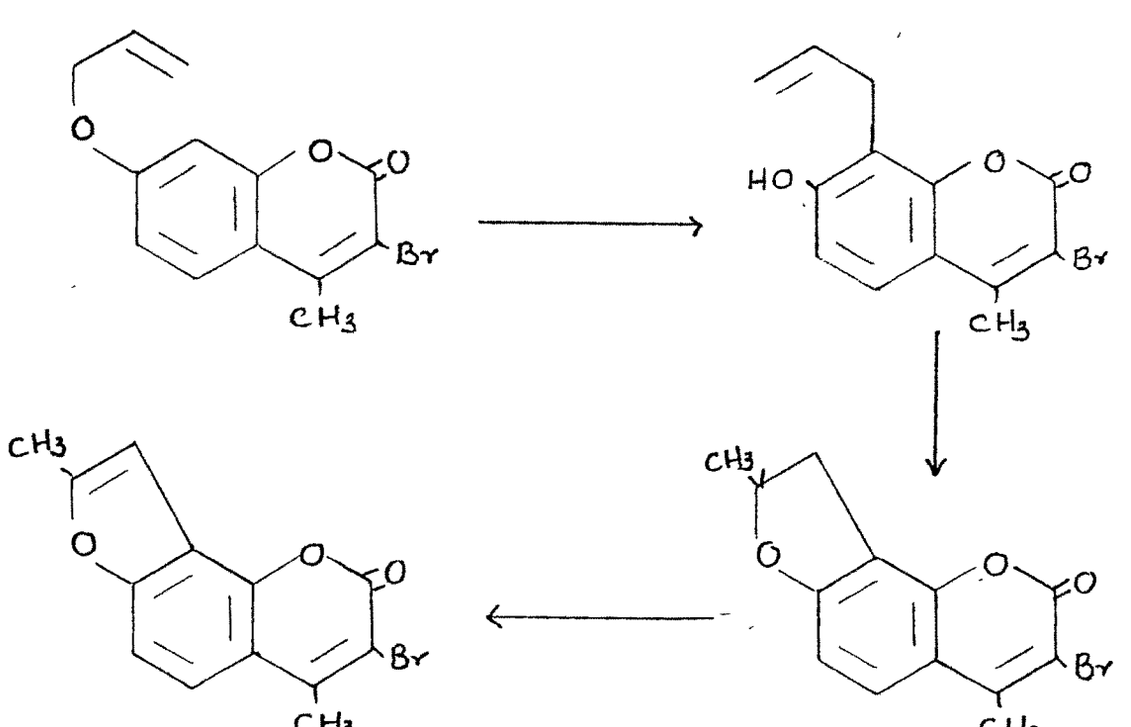
Paradkar and coworkers[13] reported a novel synthesis of 4-aminomethyl coumarin (35) by condensing 3-bromo-4-methyl coumarin (34) with secondary amines using dimethylformamide as solvent. A normal expected product, 3-aminocoumarin derivative was also obtained (35). [Scheme-11] This method is now utilized for the attempted synthesis of aminomethyl psoralen and angelicin over here.

SCHEME-11

Paradkar et al[13]



SCHEME-12



PRESENT WORK

4,5'-Dimethylangelicin or psoralen are photodynamically active furocoumarins. In the present work one of the methyl groups is transformed to aminomethyl group to make it hydrophilic in nature.

Thus in order to carry out the synthesis of 4-aminomethyl angelicin derivatives using the procedure of Paradkar and coworkers, it was necessary to synthesise 6-bromo-2,7-dimethylfuro(2,3-h)benzopyran-5(H)-one (42). Three routes were attempted to synthesise (42). In the first route it was decided to carry out the Claisen rearrangement of 7-allyloxy-3-bromo-4-methylcoumarin followed by ring closure and dehydrogenation. [Scheme-12]

3-Bromo-7-hydroxy-4-methylcoumarin (37) was first allylated with allylbromide in presence of anhydrous potassium carbonate in acetone to give 7-allyloxy-3-bromo-4-methylcoumarin (38) which when subjected to Claisen rearrangement in dimethylaniline gave 8-allyl-7-hydroxy-4-methylcoumarin (39), bromine being eliminated during the course of the reaction. The structure of the compound (39) was confirmed by taking the mixed m.p. with the authentic sample.

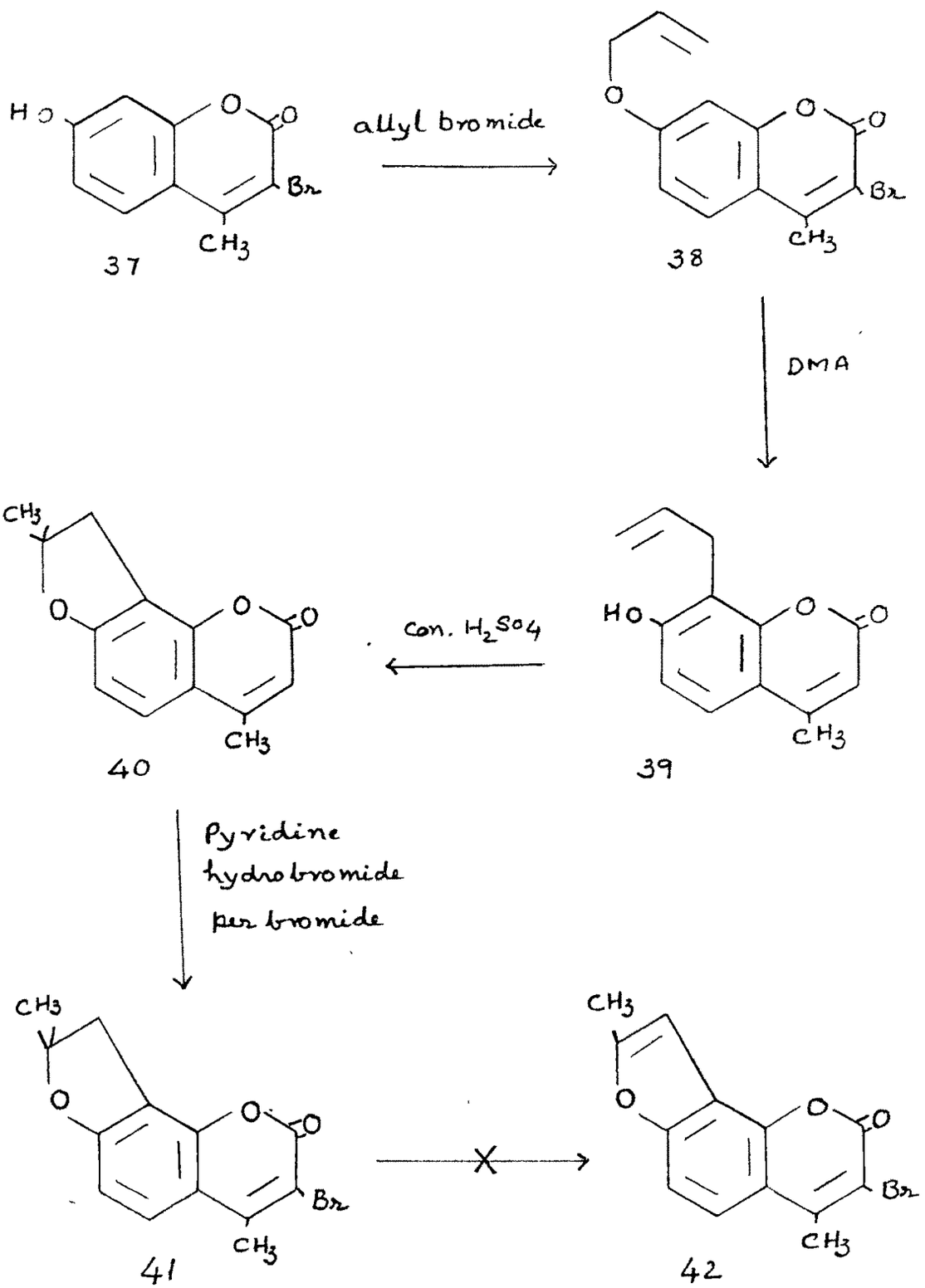
As this route failed, it was decided to introduce bromine

at the later stage of reaction sequence. Thus 8-allyl-7-hydroxy-4-methylcoumarin (39) was cyclised with con. H_2SO_4 to give 2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (40) which onbromination with pyridinehydrobromideperbromide gave 6-bromo-2,7-dimethyl-2,3-dihydrofuro(2-,3-h) benzopyran-5(H)-one (41). The structure of the compound (41) was confirmed by PMR spectra which exhibited signals in $CDCl_3$ at δ1.55, a doublet, J=7Hz for three methyl protons at C-2, a multiplet at δ2.85-3.65 for two protons at C-3 and another multiplet at δ 5.15 for single proton at C-2, two doublets, J=9Hz at δ 6.7 and 7.4 for the orthocoupled protons of C-9 and C-8. The absence of signal for the C-6 proton around δ6.1 indicated that bromine has entered at position C-6.(Fig. 1)

Dehydrogenation of (41) with Pd/c (10%) in refluxing diphenylether gave the known 2,7-dimethyl-2,3-dihydrofuro(2,3-h) benzopyran-5(H)-one (40) bromine being eliminated in the course of the reaction. The structure of the compound was confirmed by taking the mixed m.p. with authentic sample of (40).

As this route also failed, it was, decided to condense directly 6-bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (41) with secondary amines using dimethylformamide as solvent according to Paradkar et al. and then to dehydro-

SCHEME - 13


allyl bromide
DMA
Con. H_2SO_4
Pyridine
hydrobromide
per bromide
37
38
39
40
41
42

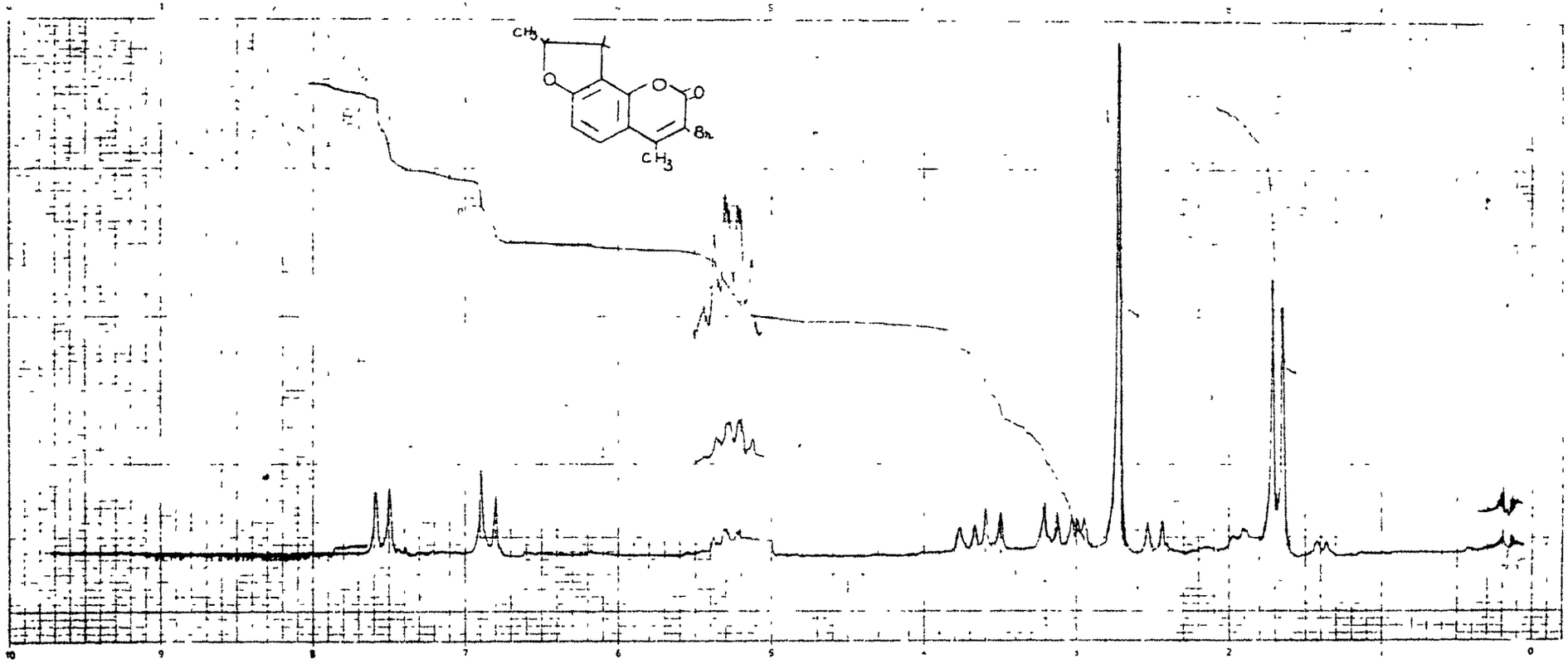


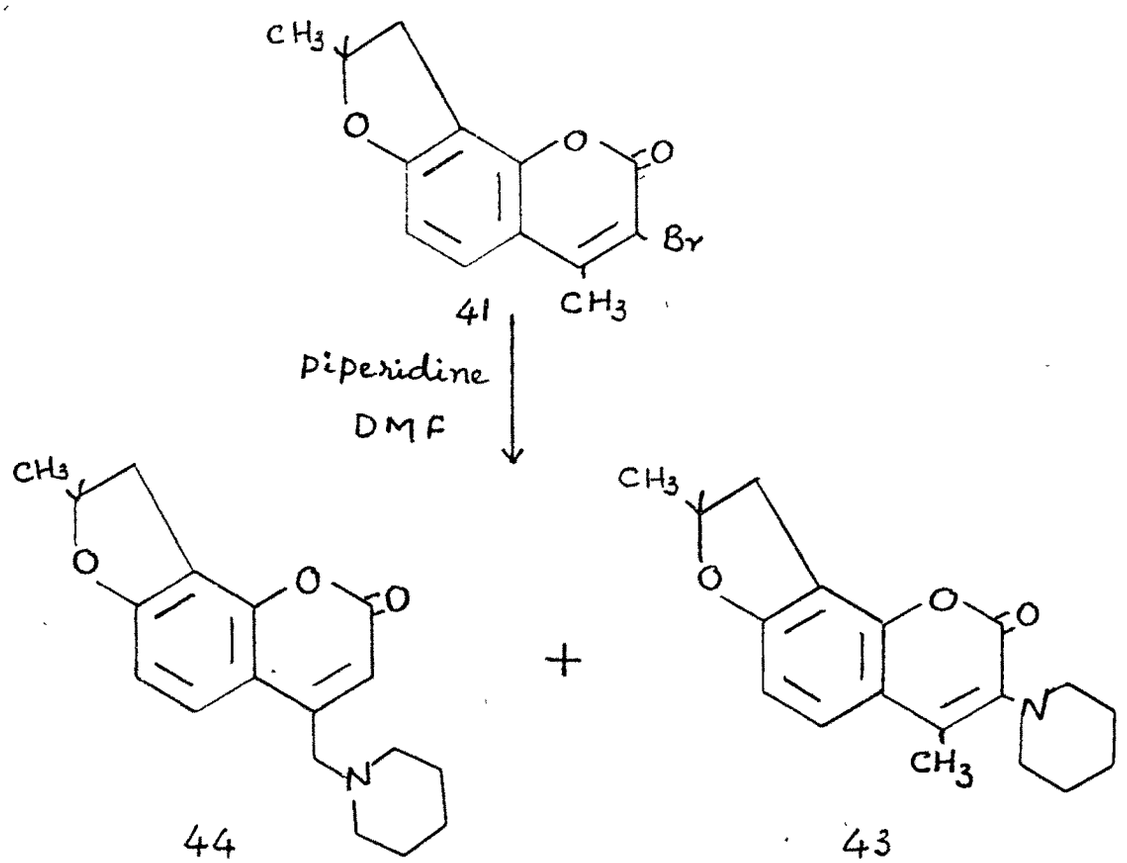
FIG-1

genate amino compound in refluxing diphenylether with Pd/c. [Scheme-13]

2,7-Dimethyl-6-piperidinyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (43)

6-Bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (41) when condensed with piperidine using N,N-dimethylformamide as solvent gave two products [Scheme-14]. The product having higher Rf value was eluted out first with benzene fraction and was assigned 2,7-dimethyl-6-piperidinyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (43). Its PMR showed signals in $CDCl_3$ at δ 1.55, a doublet, J=7Hz for three methyl protons at C-2, a broad singlet at δ 1.65 for three terminal methylene groups of six protons in piperidine ring at C-6, a singlet at δ 2.45 for three protons at C-7. There is another multiplet at δ 3.0 for the two remaining methylene groups of four protons adjacent to nitrogen in the piperidine ring at C-6. Two multiplets at δ 2.9-3.6 and at δ 5.1 corresponding to the two protons at C-3 and one proton at C-2 respectively. The absence of signal for C-6 vinylic proton confirms that the piperidine got substituted at C-6 position. Singlet at δ 2.45 for three methyl protons at C-7 indicates the methyl group is intact. (Fig. 2)

SCHEME - 14



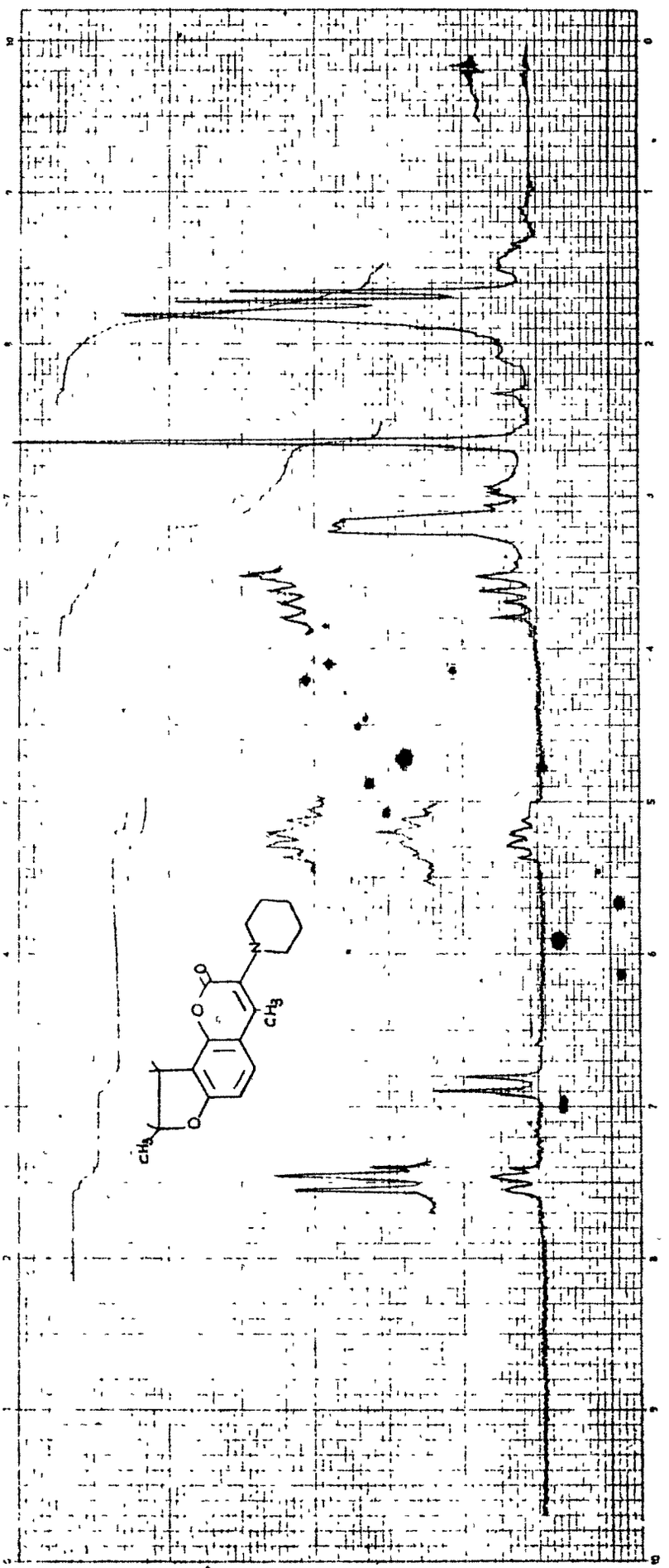


FIG-2

2-Methyl-7-piperidinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (44)

The second product obtained, on condensation of (41) with piperidine in DMF solvent, having lower Rf value, eluted out with chloroform was assigned 2-Methyl-7-piperidinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (44). The structure of the compound was confirmed by PMR spectra in $CDCl_3$ which exhibited the signals at δ 1.55, a doublet, J=7Hz for three methyl protons at C-2, a broad singlet at δ 1.65 for six protons of terminal three methylene groups in piperidine ring at C-7, another broad singlet at δ 2.45 for the remaining two methylene groups of four protons adjacent to nitrogen in the piperidine ring, a multiplet at δ 2.8-3.4 for two protons at C-3, a singlet at δ 3.5 for two protons at C-7, another multiplet for single proton at δ 5.1 at C-2. A singlet at δ 6.3 for vinylic proton at C-6 and two doublets J=9Hz for C-9 and C-8 protons at δ 6.7 and 7.65. (Fig. 3)

The presence of vinylic proton signal at δ 6.3 and the absence of methyl group signal at δ 2.45 and appearence of a signal at δ 3.5 for two protons of methylene group indicates that the piperidine got substituted in the methyl group forming piperidinomethyl group.

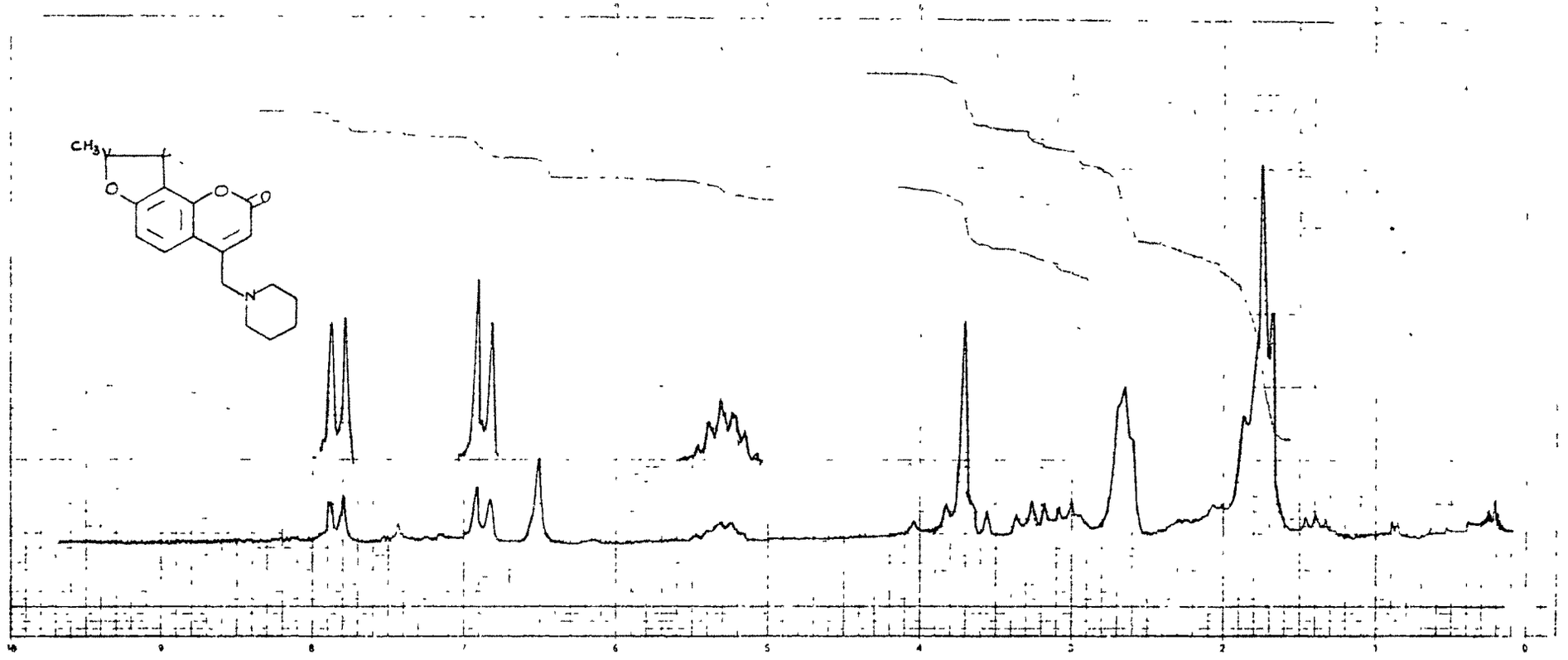


FIG-3

The mechanism of formation of (44) is outlined in Scheme-15.

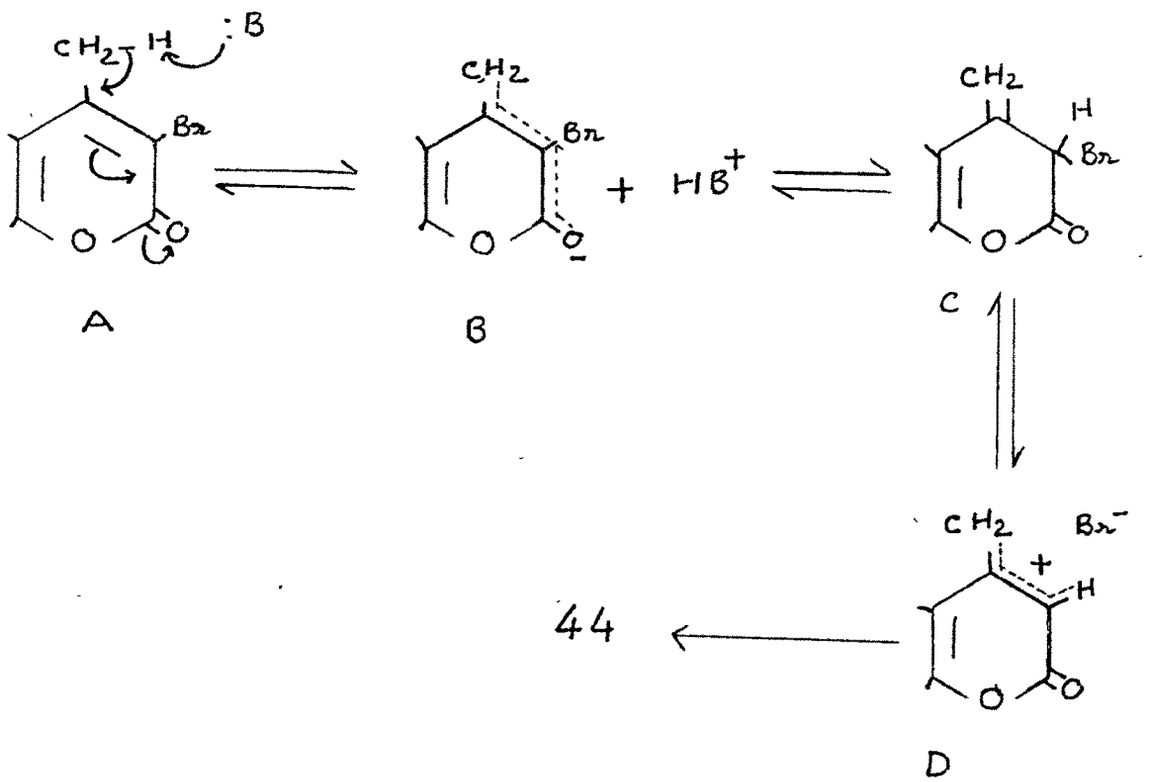
The unexpected product requires migration of one hydrogen from Me to 3-position and of Br from 3-position to the Me group. The reagent/solvent mixture is both basic(piperidine) and highly ionising (DMF). SP^2-C. Br links are very difficult to break, so it is proposed that the structure (A) undergoes a base catalysed prototropic shift to the structure (C) through (B). Now the 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 unexpected (44).

In a similar way, condensation of (41) with other secondary amines like morpholine, N-methylpiperzine and N-phenylpiperizine was carried out. In all these three condensation only one product such as 2-methyl-7-morpholinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (45), 2-methyl-7-methylpiperizinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (46) and 2-methyl-7-phenylpiperzinomethyl-2,3-dihydrofuro(2,3-h) benzopyran-5(H)-one (47) were respectively obtained. The structure of all the compounds were confirmed by PMR and analysis.

These aminomethyl dihydrofurocoumarins were subjected to dehydrogenation with DDQ in dry benzene, DDQ in dioxan

SCHEME - 15

Mechanism of formation of 44

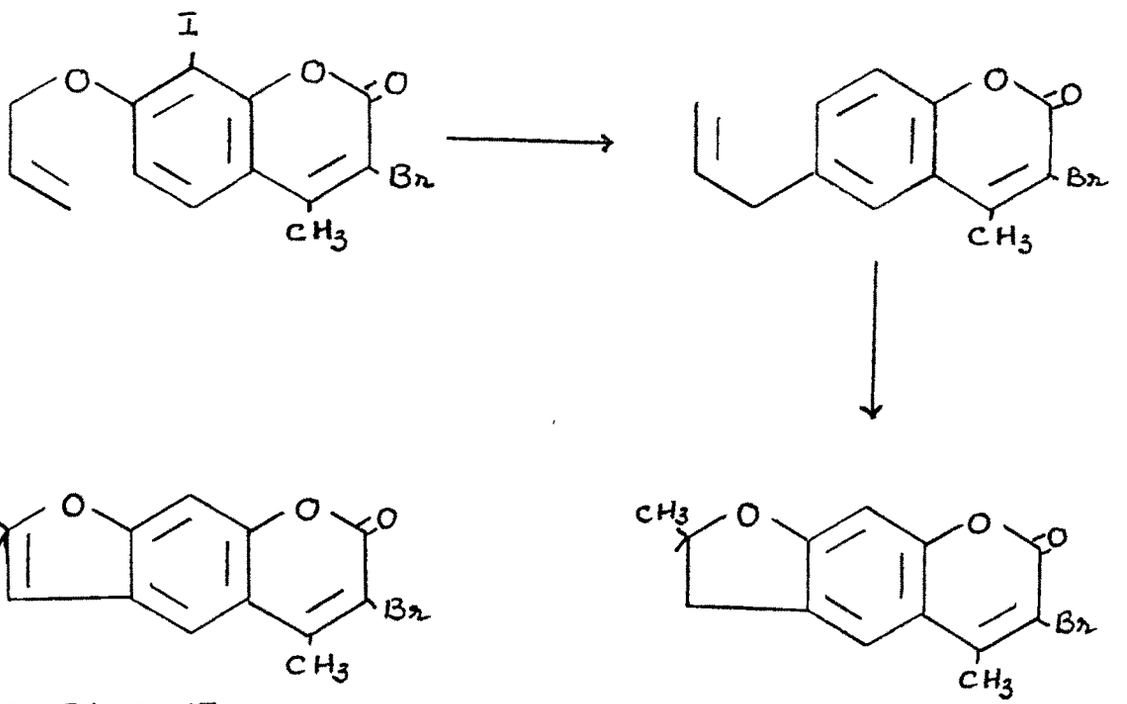


and Pd/c in diphenyl ether. No dehydrogenation occurred with DDQ while with Pd/c in DPE it underwent hydrogenolysis at position 7 giving the known 2,7-dimethyl-2,3-dihydrofuro (2,3-h)benzopyran-5(H)-one (40). The structure of the compound was confirmed by mixed m.p. with authentic sample.

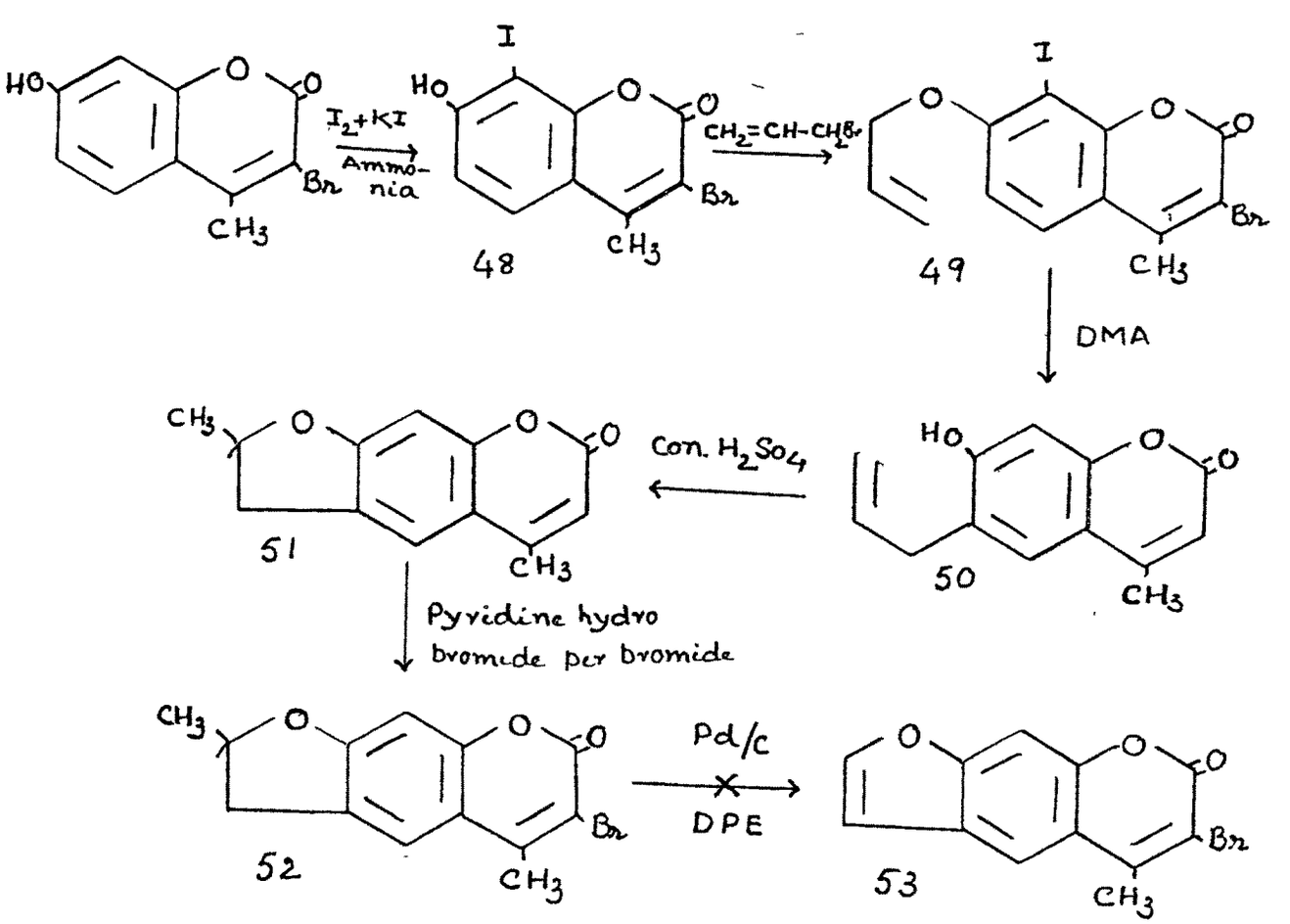
To synthesise 4-aminomethyl psoralen deivatives using the procedure of Paradkar and coworkers, it was necessary to synthesise 6-bromo-2,5-dimethylfuro(3,2-g)benzopyran-7(H)-one (53). Three routes were attempted in this case also. Initially it was decided to carryout the Claisen rearrangement of 3-bromo-7-allyloxy-8-iodo-4-methylcoumarin which enables to give 3-bromo-6-allyl-4-methylcoumarin followed by cyclisation and dehydrogenation to yield 6-bromo-2,5-dimethylfuro(3,2-g)benzopyran-7(H)-one (53). [Scheme-16]

3-Bromo-7-hydroxy-4-methylcoumarin was iodinated with iodine and potassium iodide in ammonia to give 3-bromo-7-hydroxy-8-iodo-4-methylcoumarin (48) which on allylation with allylbromide gave 3-bromo-7-allyloxy-8-iodo-4-methylcoumarin (49). This on Claisen rearrangement in N,N-dimethylaniline gave the known 7-hydroxy-6-allyl-4-methylcoumarin (50), both bromine and iodine were eliminated during the course of the reaction ; the same product was also obtained by Pardanani and Trivedi[14] when 7-allyloxy-8-bromo-4-methyl coumarin subjected to Claisen rearrangement. The structure of compound was confirmed by taking mixed m.p. with the authentic sample.

SCHEME - 16



SCHEME - 17



As this route failed, it was decided to introduce bromine at the later stage. Thus 6-allyl-7-hydroxy-4-methylcoumarin (50) obtained by known procedure was cyclised with con. H_2SO_4 to give 2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (51). This on bromination with pyridinehydrobromideperbromide in acetic acid gave 6-bromo-2,5-dimethyl-2,3-dihydrofuro (3,2-g)benzopyran-7(H)-one (52). The structure of the compound was confirmed by PMR spectra which exhibited signals in CDCl at 1.55 a doublet, J=7Hz for three methyl protons at C-2, a singlet at 2.6 for three methyl protons at C-5, two multiplets at 2.9-3.6 and at 5.1 corresponding to two protons at C-3 and one proton at C-2 respectively and two singlets at 6.65 and 7.35 for C-4 and C-9 protons.

Dehydrogenation of (52) with Pd/c in diphenylether gave the known 2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (51). The structure of the compound was confirmed by taking the mixed m.p. with the authentic sample. [Scheme-17]

As this route also failed, it was decided to condense 6-bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one with different secondary amines, using dimethylformamide as solvent and then to dehydrogenate it with Pd/c (10%) in refluxing diphenylether.

2,5-Dimethyl-6-piperidinyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (54)

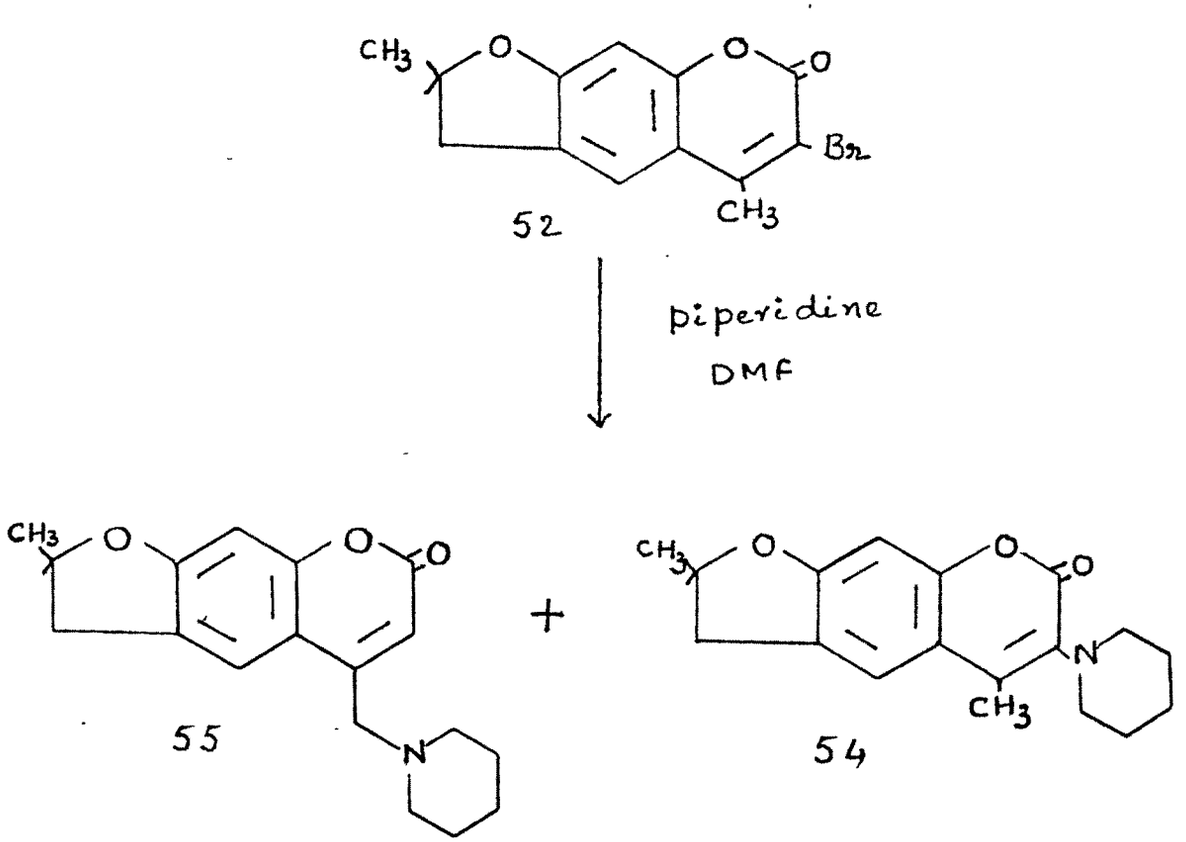
6-Bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-

7(H)-one (52) on condensation with piperidine using N,N-dimethylformamide as solvent as in the earlier, gave two products [Scheme-18]. The products were isolated using column chromatography. The product having higher Rf value was eluted out with benzene and was identified 2,5-dimethyl-6-piperidinyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (54). The structure of the compound was confirmed by PMR in $CDCl_3$ δ 1.55 a doublet, J=7Hz for three methyl protons at C-2, at δ 1.6 a broad peak for six protons of three terminal methylene groups in piperidine ring at C-6, a singlet at δ 2.45 for three methyl protons at C-5, another broad peak at δ 3.0 for four protons of two methylene groups close to nitrogen in the piperidine, at δ 3.1-3.5, a multiplet for two protons at C-3, another multiplet at δ 5.0 for one proton at C-2 and two singlets for C-4 and C-9 protons at δ6.6 and 7.25 respectively. (Fig. 4)

2-Methyl-5-piperidinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (55)

The second product of the condensation of (52) with piperidine having lower Rf value was eluted out with chloroform and was assigned 2-methyl-5-piperidinomethyl 2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (55). The structure of the compound was confirmed by PMR in $CDCl_3$ which exhibited a doublet, J=7Hz at δ 1.5 for three methyl protons at C-2,

SCHEME – 18



52

55

54

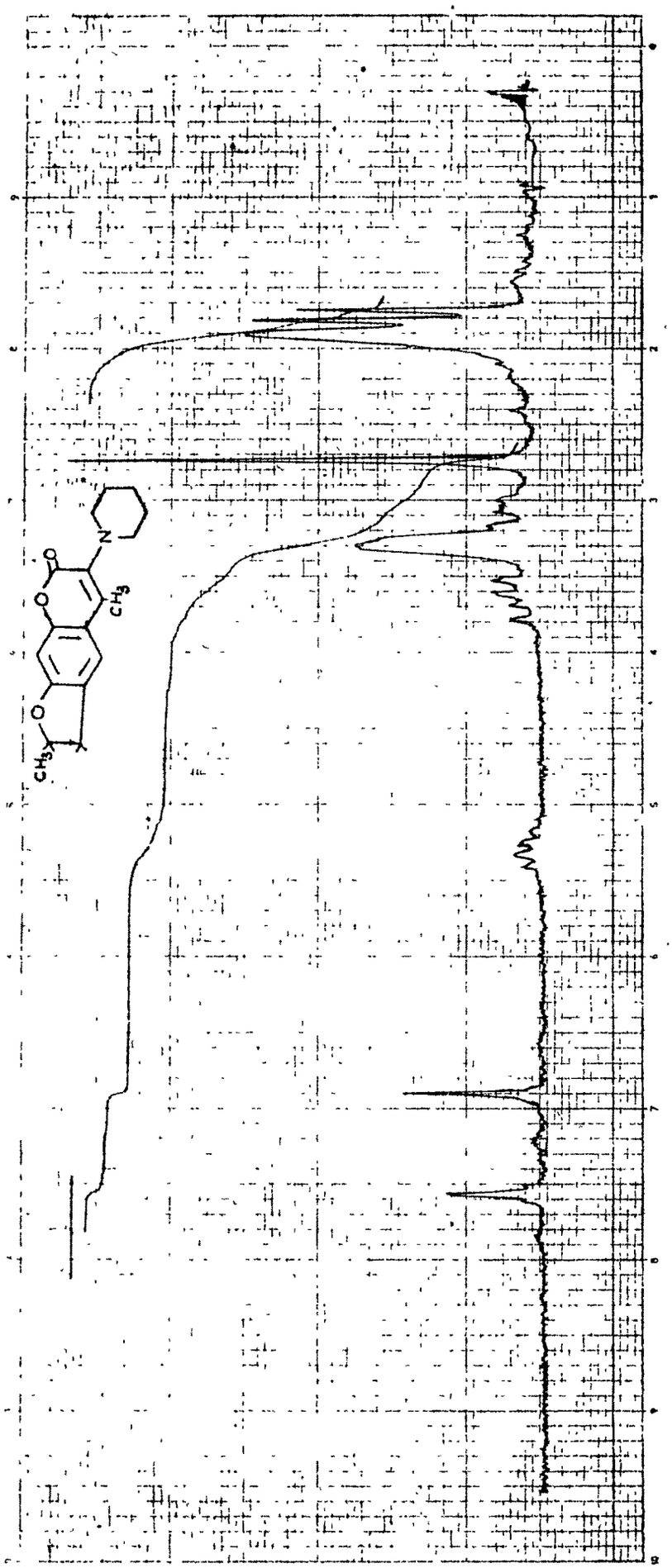


FIG-4

a multiplet for 6 protons at δ1.6 for three terminal methylene groups in the piperidine ring, another multiplet at δ2.45 for four protons of two methylene groups close to nitrogen in the piperidine ring,a multiplet at δ2.7-3.35 for two protons at C-3, a singlet at δ3.5 for methylene group of C-5, at δ 5.05 a multiplet for one proton at C-2, vinylic proton of C-5 appeared as a singlet at δ 6.25 while the protons at C-4 and C-9 showed singlets at δ 6.65 and 7.55 respectively. (Fig. 5)

Similar condensation of (52) with morpholine N-methylpiperzine and N-phenylpiperzine gave only 2-methyl-7-morpholinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (56), 2-methyl-7-methyl piperzinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (57) and 2-methyl-7-phenylpiperzinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (58) respectively. The structure of all the compounds were confirmed by PMR and analysis.

These aminomethyl dihydrofuro coumarins were also subjected to dehydrogenation with DDQ in dry benzene, DDQ in dioxan and Pd/c in diphenylether. Dehydrogenation had not taken place with DDQ but it underwent hydrogenolysis at position 5 with Pd/c in diphenylether giving known 2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (51). The structure

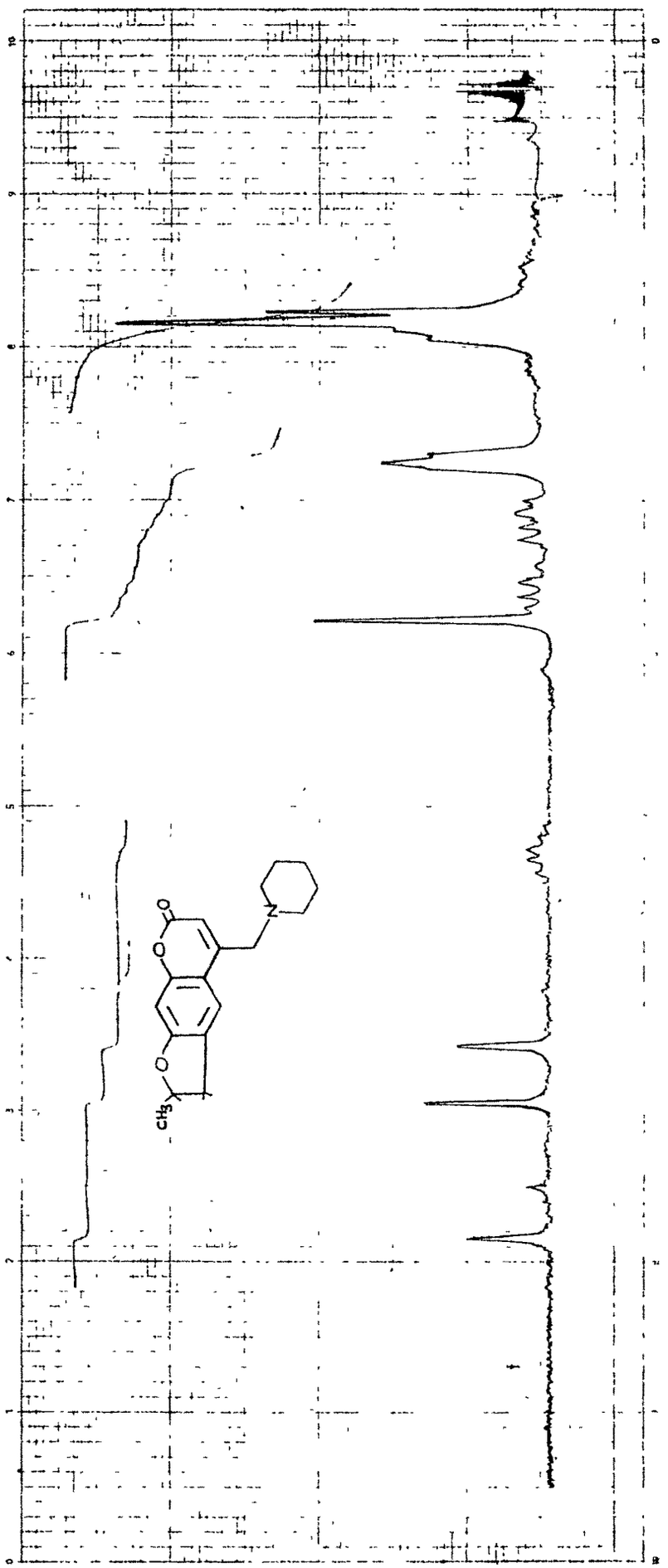


FIG-5

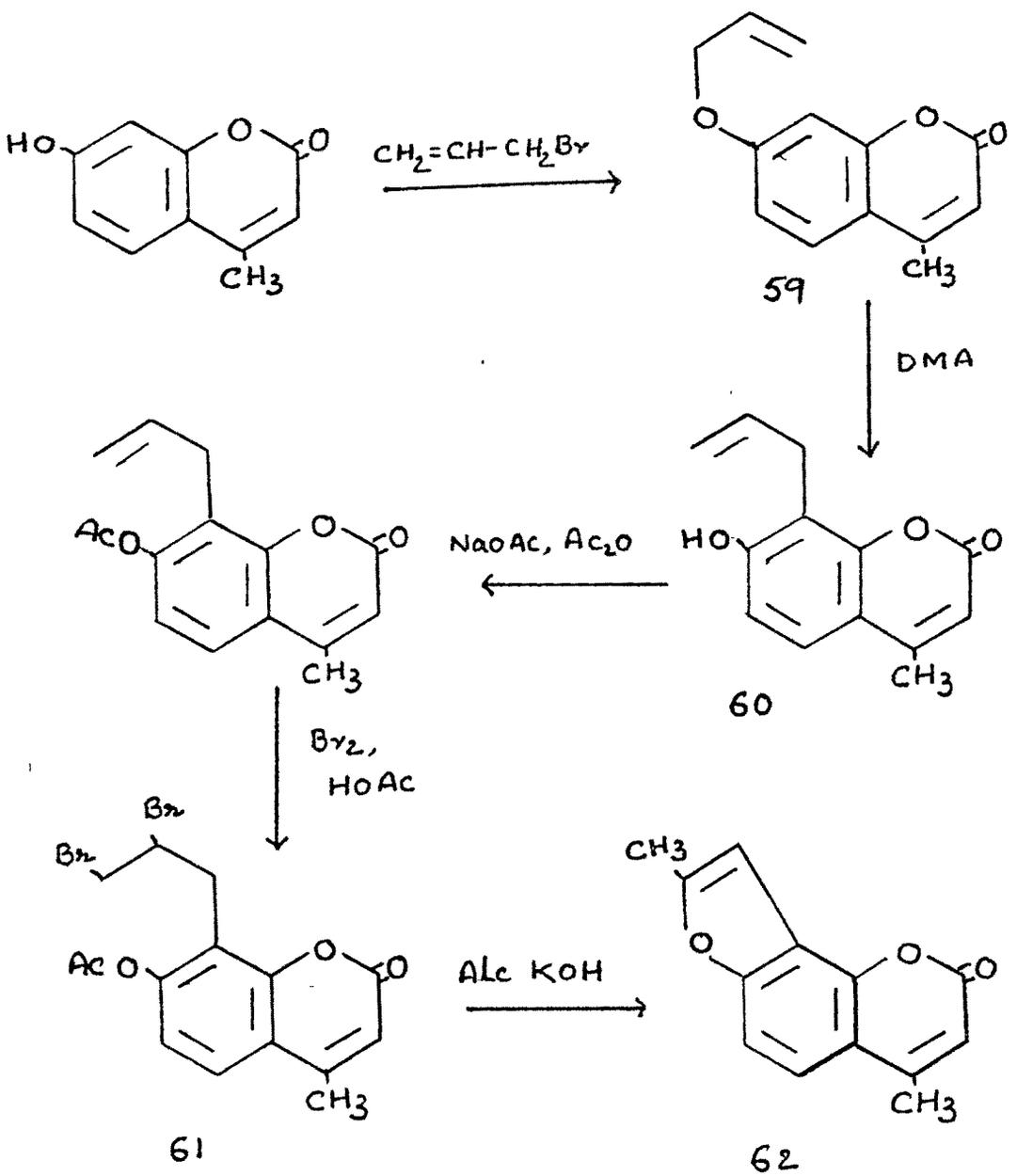
of the compound was confirmed by mixed m.p. with authentic sample.

As the above approach for the synthesis angelicinamines and psoralenamines failed to give respective compounds, it was thought of interest to study the bromination of 2,7-dimethylfuro(2,3-g)benzopyran-5(H)-one and 2,5-dimethylfuro (3,2-g)benzopyran-7(H)-one.

2,7-Dimethylfuro(2,3-h)benzopyran-5(H)-one (62)

The above dimethylangelicin was prepared by first allylating the 7-hydroxy-4-methylcoumarin with allylbromide to give 7-allyloxy-4-methylcoumarin (59) which on Claisen migration in refluxing dimethylaniline gave 8-allyl-7-hydroxy-4-methylcoumarin (60). (60) on acetylation followed by bromination across the double bond in the allyl group, with bromine in acetic acid furnished 8-dibromopropyl-7-acetoxy-4-methylcoumarin (61). 2,7-Dimethylfuro(2,3-h) benzopyran-5(H)-one (62) was obtained on cyclisation of (61) with alcoholic KOH [Scheme-19]. PMR of the compound showed signals in $CDCl_3$ at δ 2.4 and δ 2.45 two singlets for the methyl groups at C-2 and C-7, a singlet at δ 6.15 for vinylic proton at C-6 and another singlet at δ 6.6 for a proton at C-3. Two doublets at δ 7.2 and 7.35 for C-8 and C-9. (Fig. 6)

SCHEME - 19


HO
O
O
CH3
CH2=CH-CH2Br
59
DMA
60
HO
NaOAc, Ac2O
AcO
Br2,
HOAc
61
Br
Br
AcO
Alc KOH
62
CH3

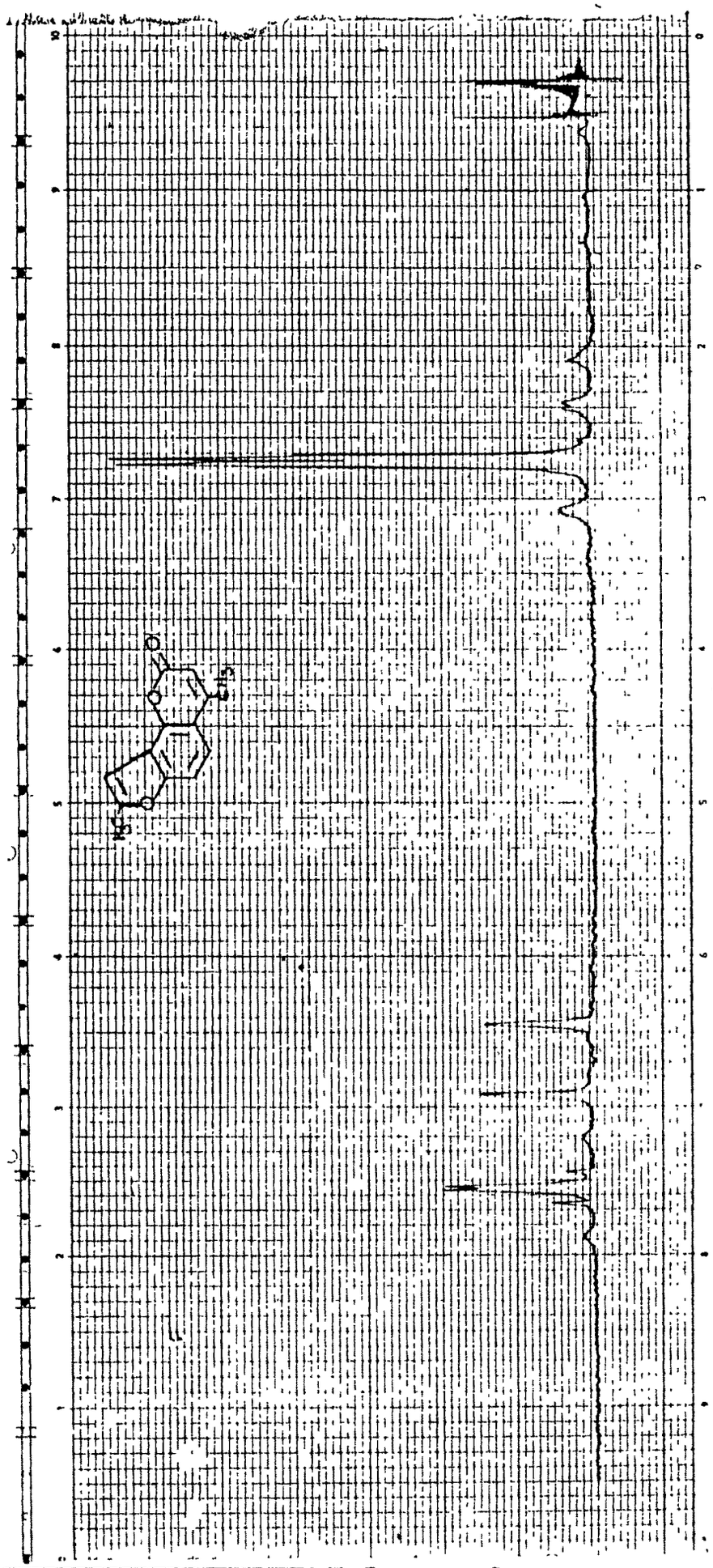


FIG-6

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (63)

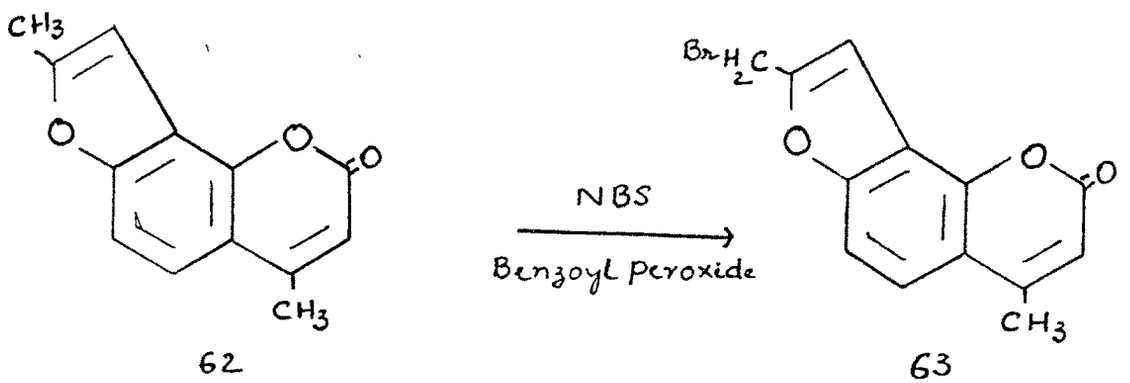
Bromination of (62) was carried out with bromine in chloroform, bromine in acetic acid and with pyridine hydrobromide perbromide in acetic acid. But in all these attempts bromination did not take place. Therefore, (62) was brominated with N-Bromosucinimide in CCl_4 using benzoyl peroxide as the reaction initiator. The reaction mixture was refluxed under 200W bulb for 8 hr. It was filtered hot and the product was taken over silica gel to obtain pure 2-bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (63). [Scheme-20)

The PMR spectrum of (63) in $CDCl_3$ exhibited signals at δ 2.45, a singlet for the methyl proton at C-7, a singlet at δ 4.55 for two protons of methylene at C-2, another singlet at δ 6.2 for vinylic proton at C-6, and C-3 proton appeared at δ 7.0 while the orthocoupled protons of C-8 and C-9 showed doublets, J=9Hz at δ 7.3 and 7.45 respectively. (Fig. 7)

As the methyl groups of position 2 and 7 in structure (62) showed almost identical chemical shifts, it was difficult to find out which methyl group has undergone bromination.

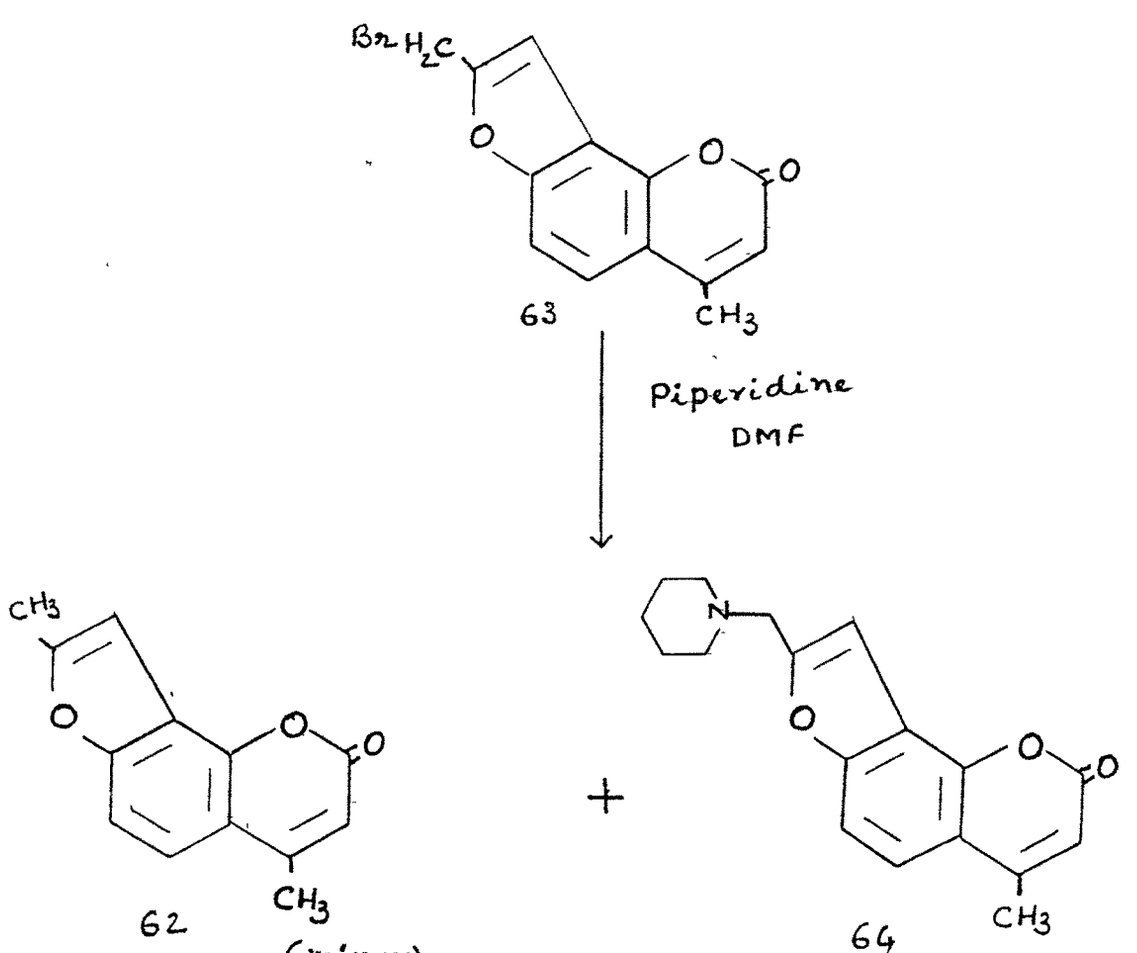
^{13}C NMR of (62) showed distinct chemical shifts for the two methyl groups, C-2 methyl group appeared at δ 14 and

SCHEME-20



62 63

SCHEME-21



62 (minor) 64

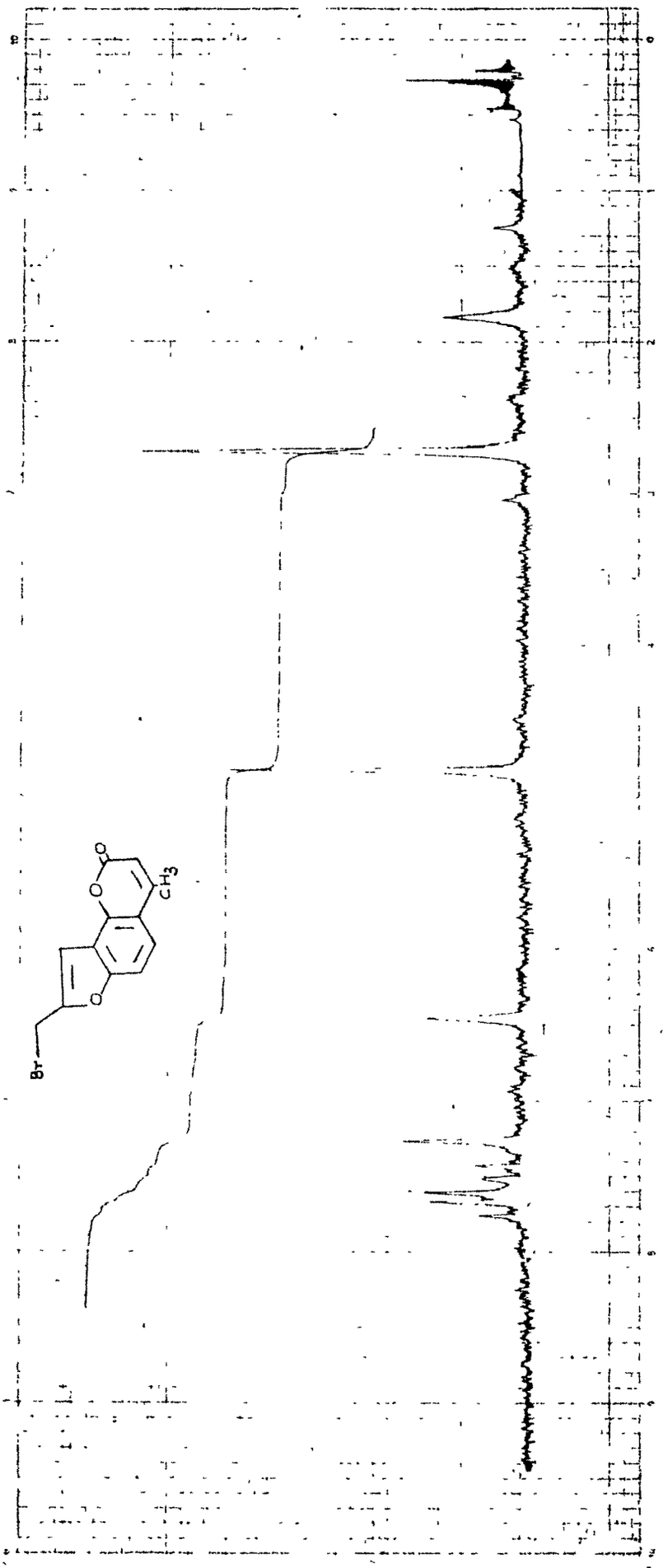


FIG-7

C-7 methyl group appeared at δ 19 and after bromination C-2 methyl group at δ14 disappeared instead it showed a signal at δ 22.2 for C-2 methylene group, whereas C-7 methyl group remained stationary, indicating that methyl group at C-2 was brominated. (Fig. 8)

Besides ^{13}C NMR data, a close look at the chemical shifts of C_6-H and C_3-H in both the PMR spectrum of (62) and (63) indicated that the chemical shifts of C_6-H is almost stationary while C_3-H suffers a downfiled shift from δ6.6 to δ 7.0 after bromination. This downfield shift is significant and establishes that the bromination has taken place at C-2 position only.

2-Piperidinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (64)

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (63) on condensation with piperidine using N.N-dimethylformamide as solvent gave 2-piperidinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (64) and small amount of (62), that is 2,7-dimethylfuro(2,3-h)benzopyran-5(H)-one. [Scheme-21] These products were separated by column chromatography. The initial benzene elutions gave (62). The product (64) was obtained on further eluting the column with chloroform. The structure of (62) was confirmed by m.p., m.m.p., TLC, analysis and PMR.

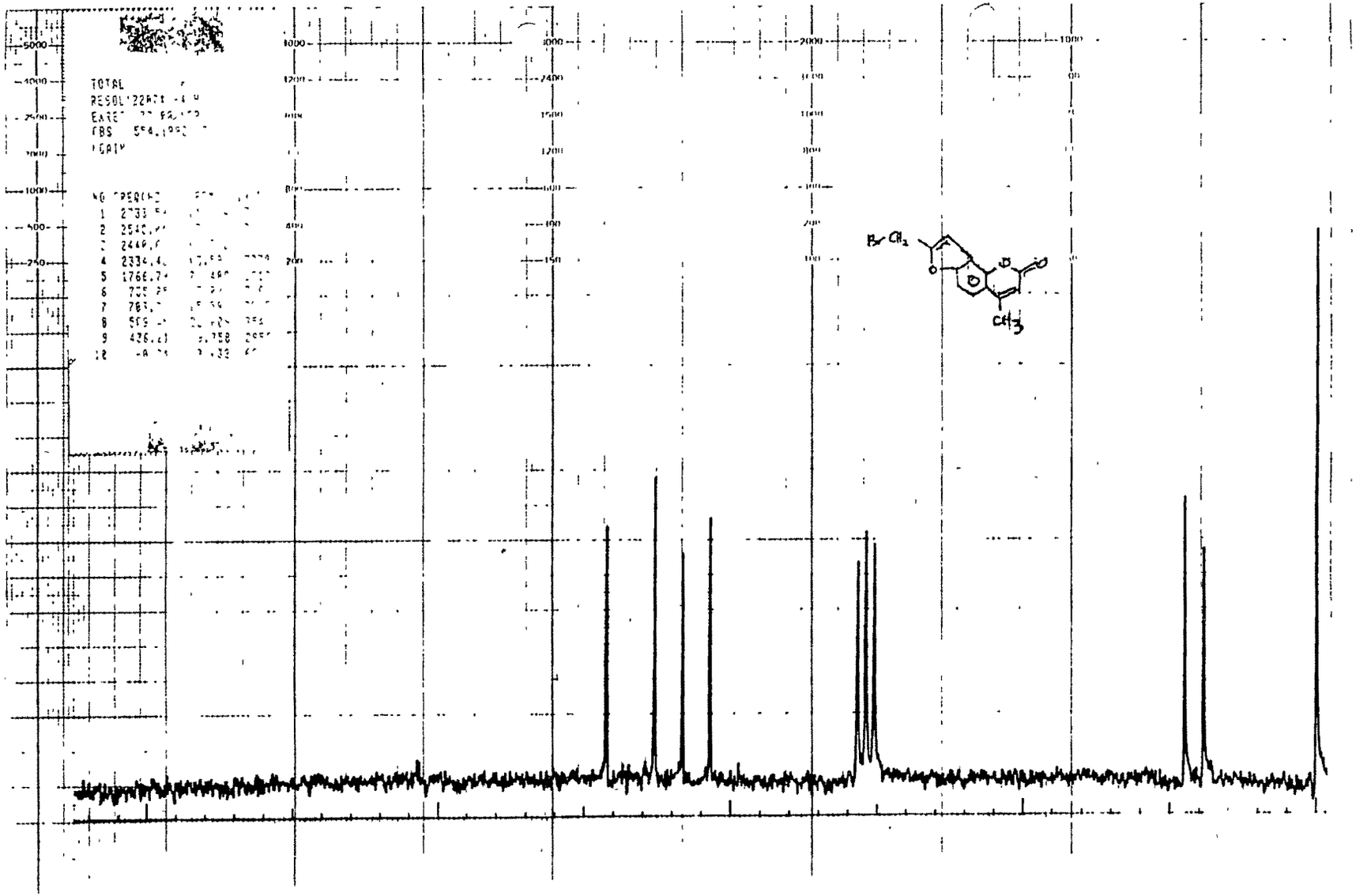


FIG-8

PMR of (64) showed signals in $CDCl_3$ at δ 1.55 a multiplet for 6 protons of three terminal methylene groups in piperidine ring at C-2, a singlet at δ2.5 for methyl group at C-7, a broad singlet at δ 2.55 for 4 protons of two methylene groups adjacent to nitrogen in piperidine ring, a singlet at δ 3.65 for two protons of the C-2 methylene group, there is a singlet for vinylic proton of C-6 at δ 6.2 and the two doublets of C_8 and C_9 protons appeared at δ 7.3 and 7.4 respectively. (Fig. 9)

Similarly 2-bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (63) was condensed with different cyclic secondary amines like morpholine, N-methyl piperazine and N-phenylpiperazine to yield 2-morpholinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (65), 2-methylpiperazinomethyl-7-methylfuro (2,3-h)benzopyran-5(H)-one (66) and 2-phenylpiperzinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (67) respectively. While (63) on condensation with open chain secondary amines diethanolamine, diethlamine gave 2-diethanolaminomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (68). (Fig. 10) and 2-diethylaminomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (69).

2,5-Dimethylfuro(3,2-g)benzopyran-7(H)-one (74)

Linearfurocoumarin, 4,5'-dimethylpsoralen was prepared

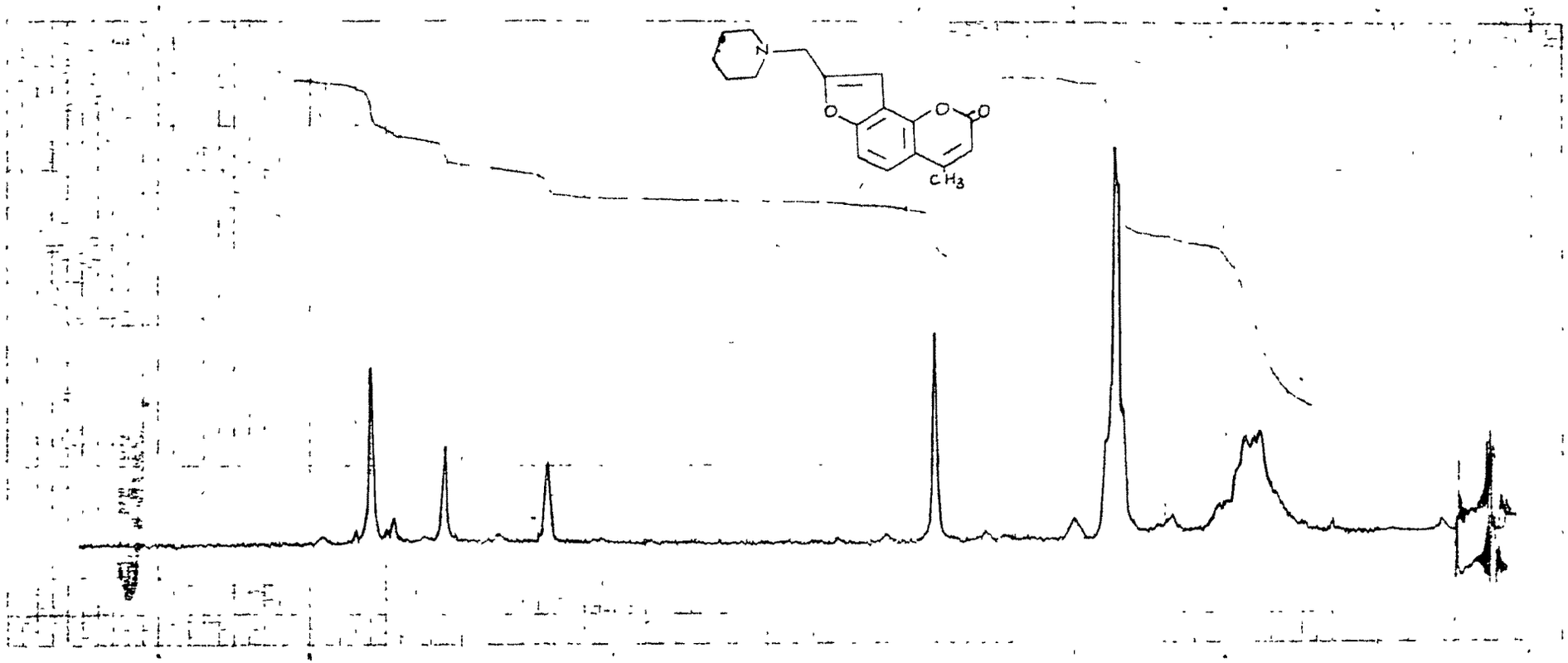


FIG-9

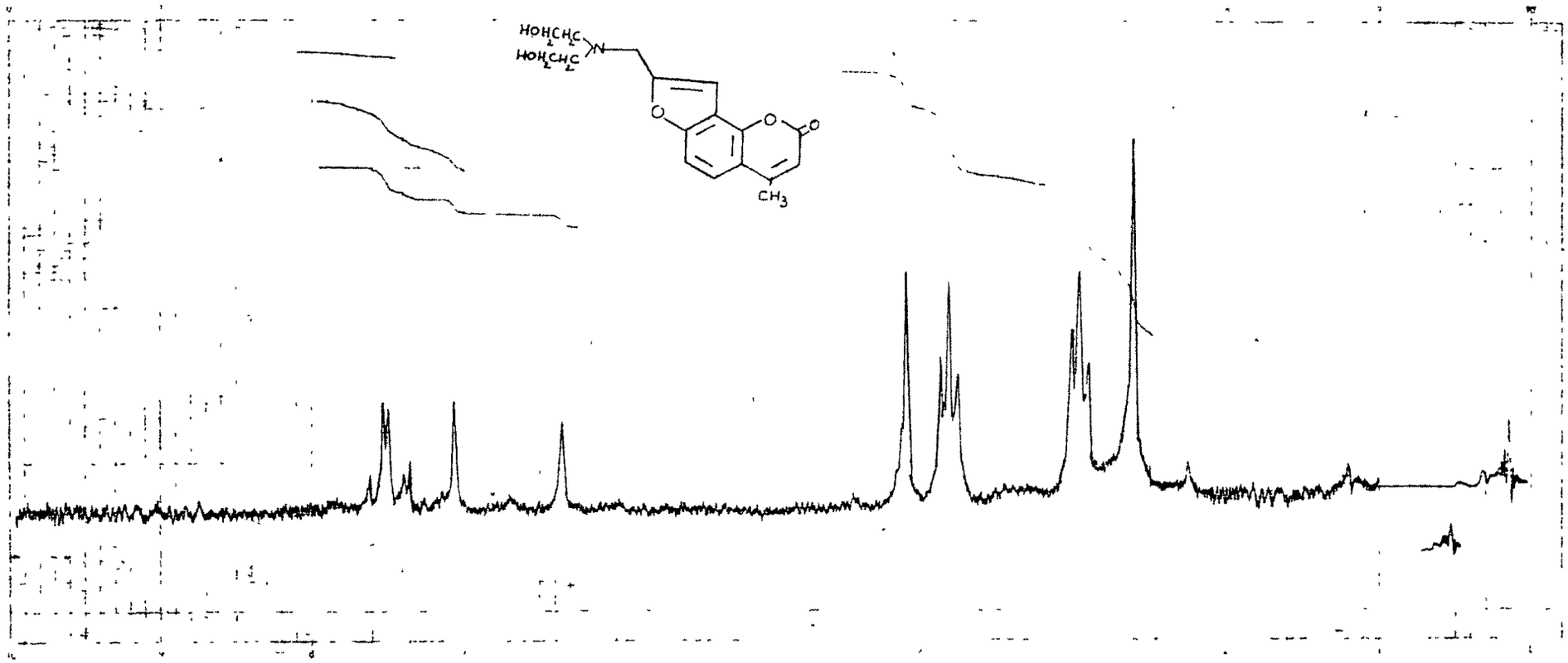


FIG-10

207

by first iodinating the 7-hydroxy-4-methylcoumarin to give 7-hydroxy-8-iodo-4-methylcoumarin (70), which on allylation with allylbromide gave 7-allyloxy-8-iodo-4-methylcoumarin (71). (71) on Claisen rearrangement in DMA gave 6-allyl-7-hydroxy-4-methylcoumarin (72). This (72) on acetylation followed by bromination furnished 6-dibromopropyl-7-acetyl-4-methylcoumarin (73). 2,5-Dimethylfuro(3,2-g)benzopyran-7(H)-one (74) was obtained on cyclisation of the dibromo compound (73) with alcoholic KOH. The structure of the compound was confirmed by its PMR in $CDCl_3$. [Scheme-22] (Fig. 11)

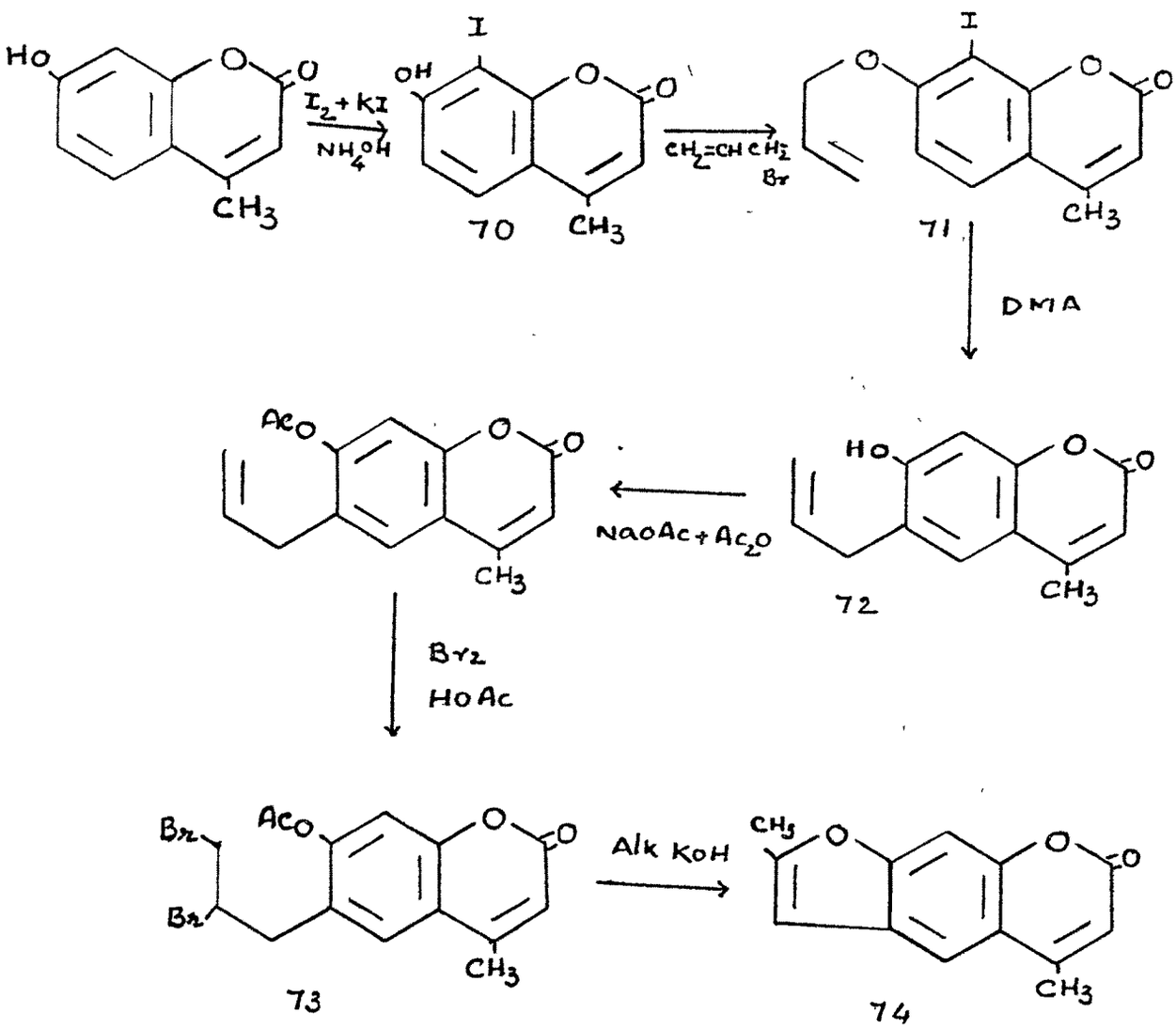
2-Bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (75)

Bromination of 2,5-dimethylfuro(3,2-g)benzopyran-7(H)-one (74) with NBS in CCl_4 in the presence of benzoyl peroxide gave 2-bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (75) [scheme-23]. As it is difficult to know where the bromination has taken place by PMR, the structure of the compound was confirmed by ^{13}C-NMR spectra which showed the presence of C_5-CH_3 group at δ 19 and C_2-CH_2 group at δ 22.3. (Fig. 12 & 13)

2-Piperidinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (76)

2-Bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one on condensation with piperidine using dimethylformamide as

SCHEME-22


HO
O
O
CH3
I2 + KI
NH4OH
I
OH
70
CH2=CH CH2
Br
71
DMA
AcO
NaOAc + Ac2O
72
Br2
HOAc
Br
Br
73
Alk KOH
CH3
74

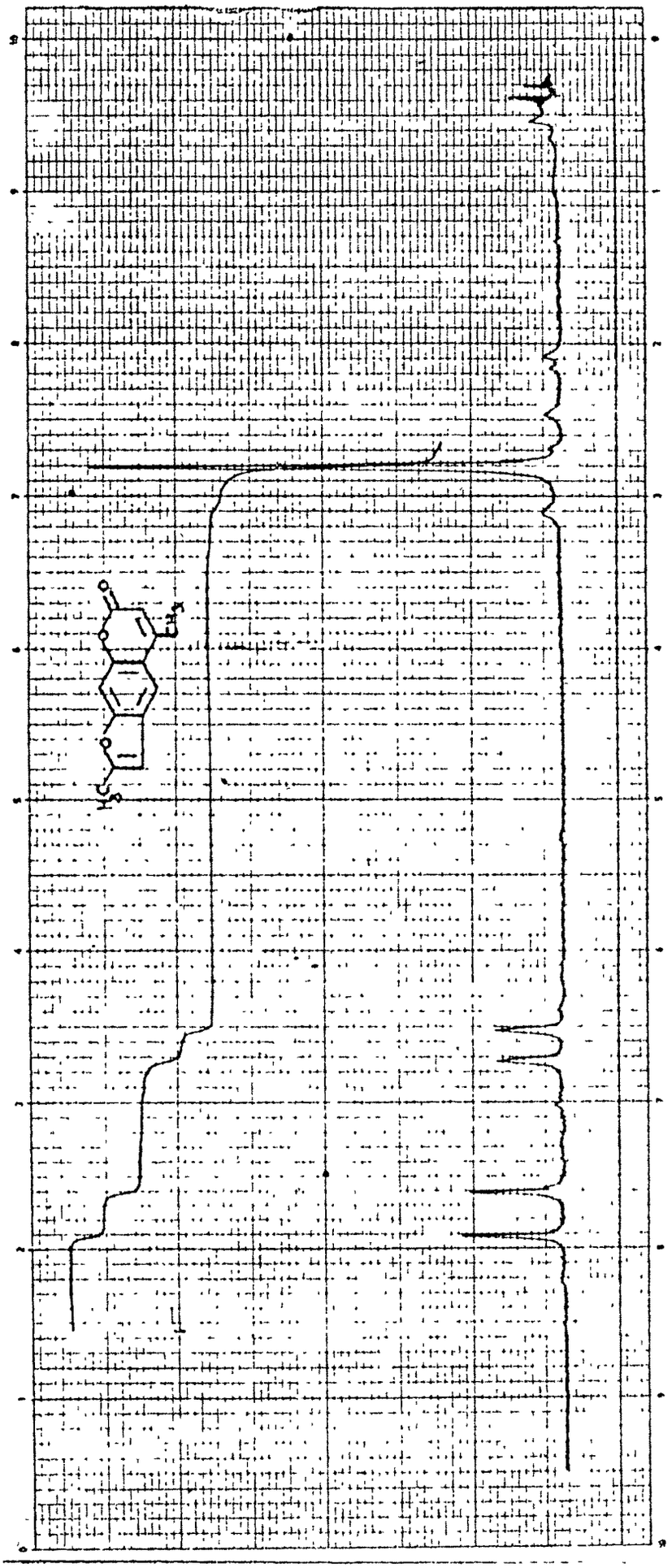
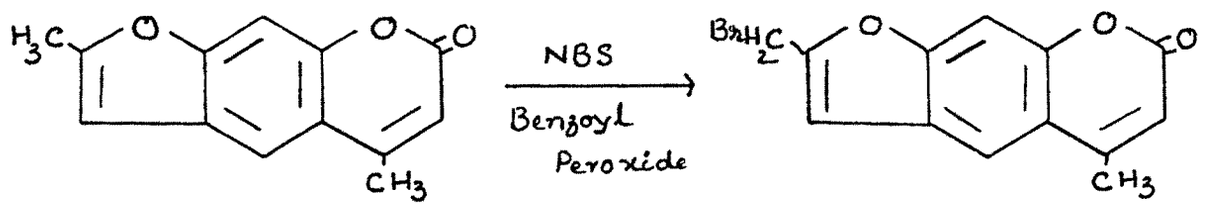


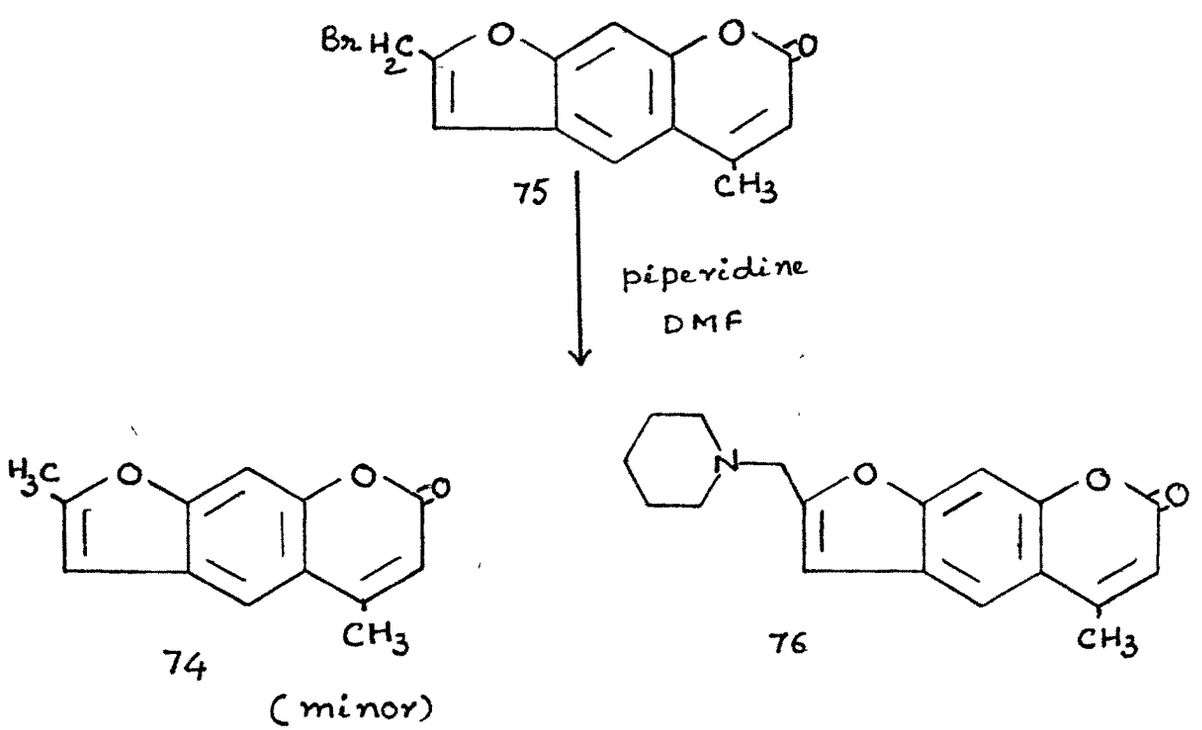
FIG-11

SCHEME – 23



74 75

SCHEME – 24



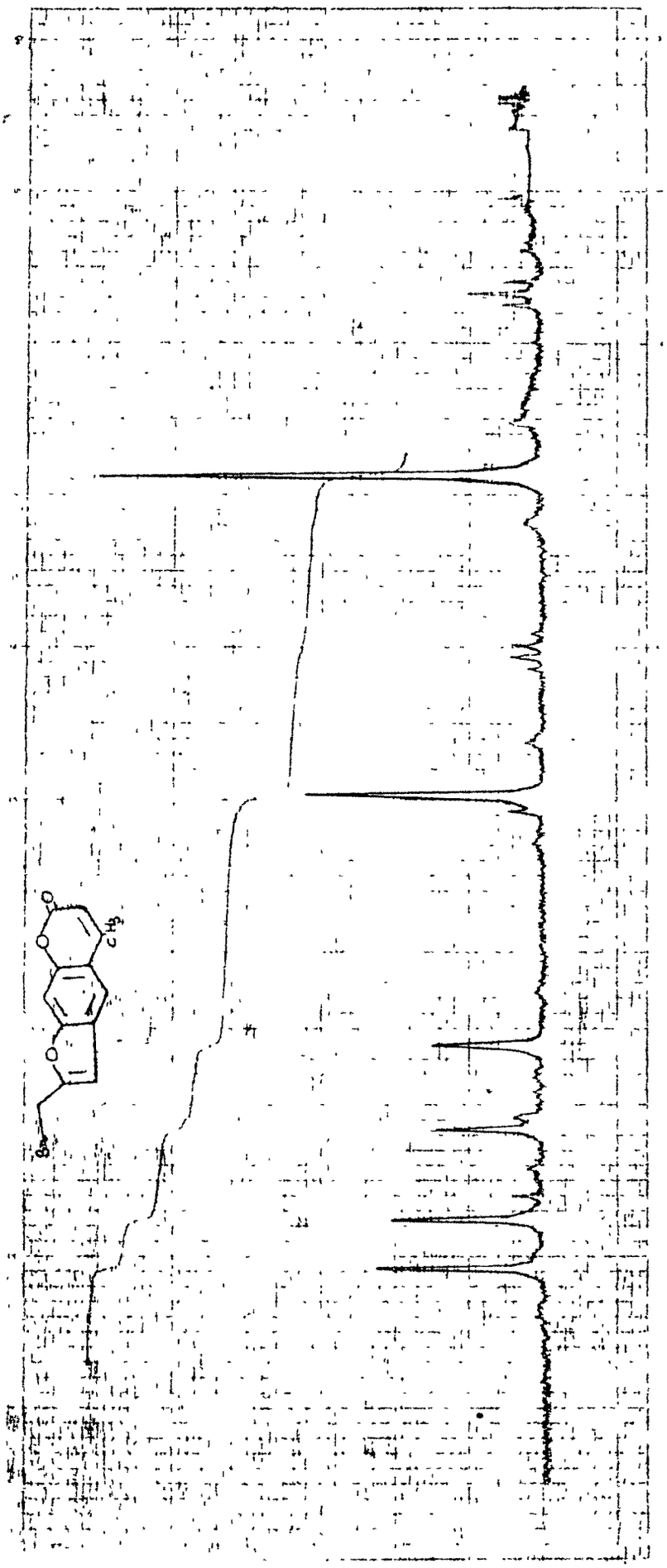


FIG-12

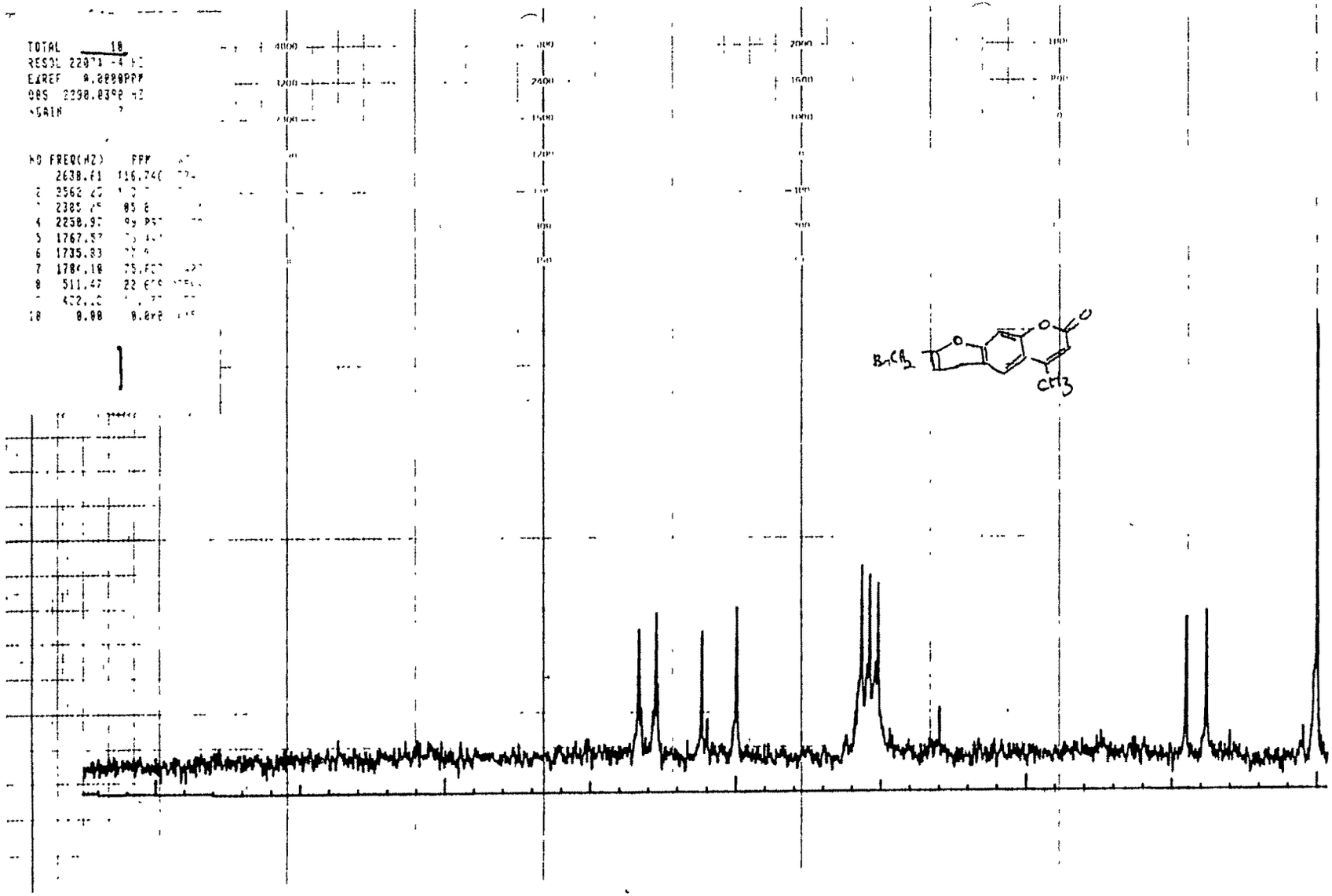


FIG-13

CDCl3

13 C

10,000

11/2/89

212

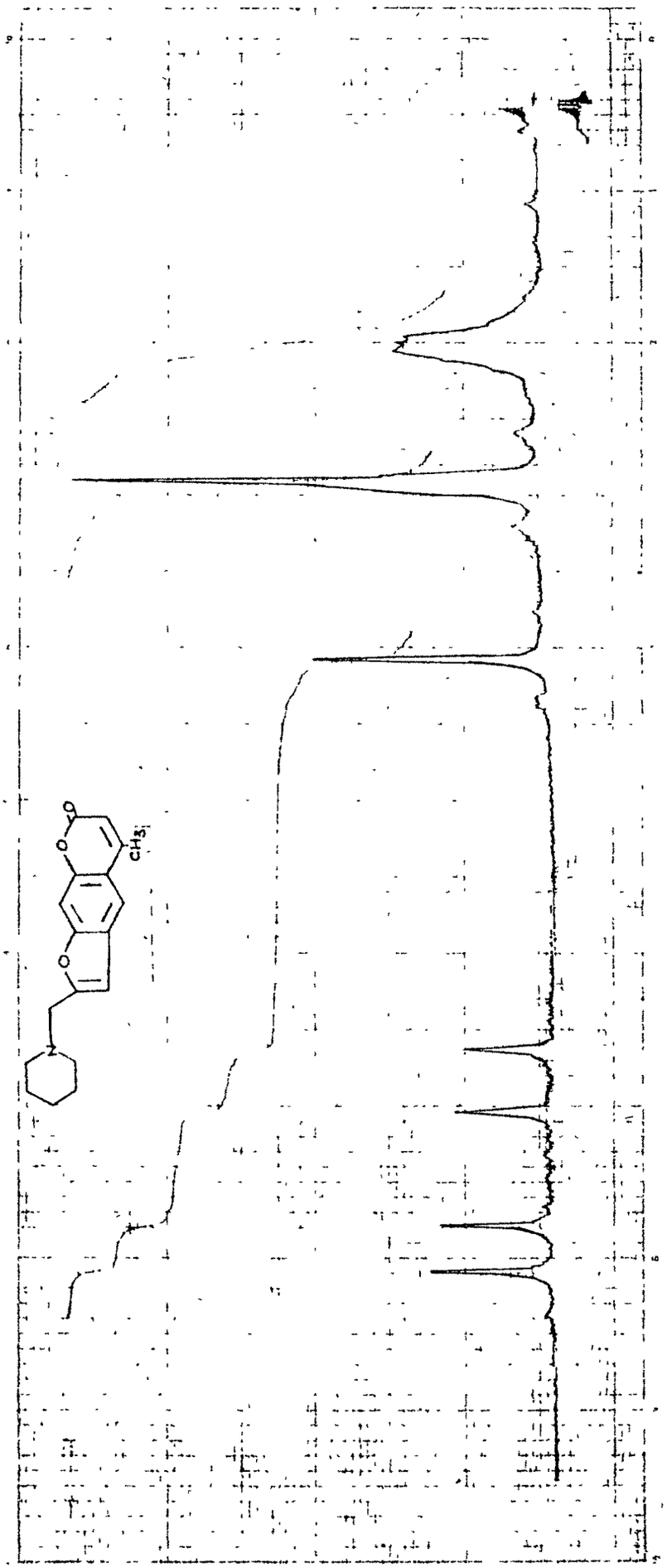


FIG-14

solvent gave 2-piperidinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (76) and small amount of 2,5-dimethylfuro(3,2-g)benzopyran-7(H)-one (74). The structure of (74) was confirmed by m.p., m.m.p. and PMR. [Scheme-24]

The PMR of (76) showed signals in $CDCl_3$ at δ 1.6, a multiplet for 6 protons of three CH_2 groups of piperidine at C-2, δ 2.5, a singlet for three methyl protons at C-5, at δ 2.55, a multiplet for 4 protons of two methylene groups of piperidine at C-2, at δ 3.7, a singlet for two protons of CH_2 at C-2, C-6 vinyic proton showed singlet at δ 6.25, another singlet of C-3 at δ 6.65. Singlets corresponding to C-4 and C-9 appeared at δ 7.4 and 7.7. (Fig. 14)

Similarly 2-bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one was condensed with different secondary cyclic amines like morpholine, N-methylpiperzine and N-phenylpiperzine to obtain corresponding 2-morpholinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (77), 2-piperzinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (78) and 2-phenylpiperzinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (79) respectively.

EXPERIMENTAL

EXPERIMENTAL

All melting points are uncorrected. PMR spectra recorded on Perkin-Elmer R-32 Spectrometer (90 MHz) using TMS as internal standard.

6-Bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (41)

A solution of 2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (2 g) in 25 ml of acetic acid was stirred with pyridinehydrobromide perbromide (3 g) for about 1 hr. Then the solution mixture was left over night. Next day the solution mixture was poured over ice water. The obtained product was purified bycrystallisation from alcohol (1.5 g) m.p. 156°.

Analysis	: Found	: C, 53.26%	; H, 4.09%
$C_{13}H_{11}O_3Br$	: requires	: C, 52.81%	; H, 3.72%

2,7-Dimethyl-6-piperidinyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (43)

A mixture of 6-bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h) benzopyran-5(H)-one (1.2 g) (0.004 mol), piperidine (1.4 ml, 0.016 mol) in N,N-dimethylformamide was refluxed for 30 min. The mixture was cooled and poured over 150 ml ice

water. The separated solid was filtered and subjected to column chromatography.(43) eluted out in the benzene fraction in poor yield and crystallised from ethanol (0.2 g), m.p. 124°.

Analysis : Found : C, 71.89% ; H, 7.12% ; N, 4.73%

$C_{18}H_{21}O_3N$: requires : C, 72.24% ; H, 7.02% ; N, 4.68%

2-Methyl-7-piperidinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (44)

The above product was obtained on eluting the column with chloroform and crystallised from ethanol (0.6 g), m.p. 120°.

Analysis : Found : C, 72.68% ; H, 7.14% ; N, 5.04%

$C_{18}H_{21}O_3N$: requires : C, 72.24% ; H, 7.02% ; N, 4.68%

2-Methyl-7-morphilinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (45)

6-Bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (1.2 g, 0.004 mol) and morpholine (1.6 ml, 0.016 mol), in 10 ml of N,N-dimethylformamide was refluxed for 30 min. The reaction was worked up as described earlier. It gave only 2-methyl-7-morpholinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one and crystallised from alcohol (0.7 g), m.p. 114°.

Analysis : Found : C, 68.14% ; H, 6.38% ; N, 4.25%

$C_{17}H_{19}O_4N$: requires : C, 67.77% ; H, 6.33% ; N, 4.65%

PMR($CDCl_3$) : δ1.5(d, J=7Hz, 3H, CH_3 at C-2) ; 2.5(m, 4H, CH_2 x 2 of morpholine close to N at C-7) ; 2.85-3.45(m, 2H, at C-3), 3.55(s, 2H, CH_2 at C-7) ; 3.7(m, 4H, CH_2 x 2 of morpholine close to O at C-7) ; 5.1(m, 1H at C-2) ; 6.3(s, 1H at C-6) ; 6.65(d, J=9Hz, 1H at C-8) ; 7.6(d, J=9Hz, 1H at C-9).

2-Methyl-7-methylpiperzinomethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (46)

6-Bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (0.8 g), N-methylpiperzine (1 ml) in 8 ml of N,N-dimethylformamide was refluxed for 30 min. The reaction gave only (46) and crystallised from alcohol (0.3 g), M.p. 118°.

Analysis : Found : C, 68.48% ; H, 6.87% ; N, 9.30%

$C_{18}H_{22}O_3N_2$: requires : C, 68.47% ; H, 7.00% ; N, 8.91%

PMR($CDCl_3$) : δ1.5(d, J=7Hz, 3H, CH_3 at C-2), 2.3(s, 3H, N-Me at C-7) ; 2.5(b, 8H, CH_2 x 4 of piperizine at C-7) ; 2.85-3.45 (m, 2H at C-3) ; 3.55(s, 2H, CH_2 at C-7), 5.05(m, 1H at C-2) ; 6.3(s, 1H at C-6) ; 6.65(d, J=9Hz, 1H at C-8), 7.55(d, J=9Hz, 1H at C-9).

2-Methyl -7-phenylpiperzinomethyl-2,3-dihydrofuro(2,3-h) benzopyran-5(H)-one (47)

A mixture of 6-bromo-2,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (1.2 g), N-phenylpiperzine (2.7 ml), in 10 ml of DMF was refluxed for 30 min. The reaction was worked up as usual. It gave only (47) and crystallised from alcohol (1.1 g). M.p. 158°.

Analysis : Found : C, 73.88% ; H, 6.81% ; N, 7.24%

$C_{23}H_{24}O_3N_2$: requires : C, 73.40% ; H, 6.38% ; N, 7.44%

PMR ($CDCl_3$) : δ 1.5(d, J=7Hz, 3H, CH_3 at C-2), 2.65(m, 4H, CH_2 x 2 of piperzine close to N at C-7) ; 3.2(m, 4H, CH_2 x 2 of piperzine close to N-Ph at C-7) ; 2.8-3.45(m, 2H at C-3) ; 3.5(s, 2H at C-7), 5.05(m, 1H at C-2), 6.3(s, 1H at C-6), 6.65 (d, J=9Hz, 1H, at C-8) ; 6.8-7.3(m, 5H, phenyl at C-7), 7.6(d, J=9Hz, 1H at C-9).

6-Bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (52)

2,5-Dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (2 g) in 25 ml of acetic acid was stirred with pyridine hydrobromide perbromide (3 g) for about 1 hr. Then the solution was left overnight. The other day the solution mixture was poured over ice water. The obtained product

was purified by crystallisation from alcohol (1.5 g) M.p. 174°.

Analysis : Found : C, 53.16% ; H, 4.11%

$C_{13}H_{11}O_3Br$: requires : C, 52.81% ; H, 3.72%

2,5-Dimethyl-6-piperidinyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (54)

A mixture of 6-bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g) benzopyran-7(H)-one (0.6 g), pipyridine (0.7 ml) in 5 ml of N,N-dimethylformamide was refluxed for 30 min. The reaction was worked up as usual. The obtained product showed to be a mixture of two compounds. The compound having higher Rf value eluted out with benzene fraction and was crystallised from ethanol (0.1 g), M.p. 162°.

Analysis : Found : C, 71.80% ; H, 6.68% ; N, 5.03%

$C_{18}H_{21}O_3N$: requires : C, 72.24% ; H, 7.02% ; N, 4.68%

2-Methyl-5-piperidinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (55)

The above product was obtained on further eluting the column with chloroform. The product crystallised from ethanol (0.3 g), M.p. 134°.

Analysis : Found : C, 71.80% ; H, 7.07% ; N, 4.45%

$C_{18}H_{21}O_3N$: requires : C, 72.24% ; H, 7.02% ; N, 4.68%

2-Methyl-5-morpholinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (56)

A mixture of 6-bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g) benzopyran-7(H)-one (0.6 g), morpholine (0.8 ml) in 5 ml of DMF was refluxed for 30 min. The reaction was worked up as earlier. The reaction gave only (56) the product crystallised from alcohol (0.3 g), M.p. 175°.

Analysis : Found : C, 68.21% ; H, 6.44% ; N, 4.24%

$C_{17}H_{19}O_4N$: requires : C, 67.77% ; H, 6.33% ; N, 4.65%

PMR ($CDCl_3$) : δ 1.5(d, J=7Hz, 3H, CH_3 at C-2), 2.55(m, 4H, CH_2 x 2 morpholine close to N at C-5), 2.8-3.4(m, 2H at C-3), 3.55(s, 2H, CH_2 at C-5); 3.7(m, 4H, CH_2 x 2 close to O in the morpholine at C-5), 5.0(m, 1H at C-2), 6.35(s, 1H at C-6) ; 6.65(s, 1H at C-4), 7.5(s, 1H at C-9).

2-Methyl-5-methylpiperzinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (57)

8-Bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (0.6 g) and N-methylpiperzine (0.7 ml) in 5 ml of DMF was refluxed on sand bath for 30 min. The reaction was worked up as usual which gave only (57). The compound crystallised from benzene and few drops of petroleum ether (40-60°) (0.2 g)., M.p. 162°.

Analysis : Found : C, 68.64% ; H, 6.95% ; N, 8.61%

$C_{18}H_{22}O_3N_2$: requires : C, 68.47% ; H, 7.00% ; N, 8.91%

PMR($CDCl_3$) : δ 1.5(d, J=7Hz, 3H, CH_3 at C-2) ; 2.3(s, 3H, N-Me at C-5); 2.55(b, 8H, CH_2 x 4 of piperzine at C-5), 2.6-3.5(m, 2H at C-3) ; 3.55(s, 2H, CH_2 at C-5) ; 5.05(m, 1H at C-2), 6.3(s, 1H at C-6) ; 6.65(s, 1H at C-4); 7.5(s, 1H at C-9).

2-Methyl-5-phenylpiperzinomethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (58)

6-Bromo-2,5-dimethyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (0.6 g) and N-phenylpiperzine (1.4 ml) in 5 ml of DMF was refluxed for 30 min. The reaction was worked up as usual which gave only (58). The compound crystallised from alcohol (0.6 g), m.p. 195°.

Analysis : Found : C, 73.81% ; H, 6.58% ; N, 7.01%

$C_{23}H_{24}O_3N_2$: requires : C, 73.40% ; H, 6.38% ; N, 7.44%

PMR($CDCl_3$) : δ 1.45(d, J=7Hz, 3H, CH_3 at C-2) ; 2.7(m, 4H, CH_2 x 2 of piperzine close to N at C-5) ; 3.2(m, 4H, CH_2 x 2 of piperzine close to N-Ph at C-5), 2.8-3.5(m, 2H at C-3), 3.55 (s, 2H, CH_2 at C-5) ; 6.25(s, 1H, at C-6) ; 6.6(s, 1H at C-4).

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (63)

2,7-Dimethylfuro(2,3-h)benzopyran-5(H)-one (2.0 g), N-bromosuccinimide (1.8 g) and a pinch of benzoyl peroxide in 50 ml of CCl_4 was refluxed under 200 W bulb for 8 hr. The solution was filtered hot and the excess of CCl_4 was distilled. The product obtained was purified by column chromatography and crystallised from alcohol (1.2 g), m.p. 210°.

Analysis : Found : C, 52.95% ; H, 3.29%

$C_{13}H_9O_3Br$: requires : C, 53.24% ; H, 3.07%

2-Piperdinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (64)

A mixture of 2-bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (0.6 g, 0.002 mol), piperidine (0.7 ml) in N,N-dimethylformamide (5 ml) was refluxed for 40 min. The mixture was cooled and poured over ice water. The separated solid was filtered and subjected to column chromatography, 2-bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one after loosing bromine during condensation gave 2,7-dimethylfuro-(2,3-h)benzopyran-5(H)-one, in poor yield when eluted with benzene, while the 2-piperidinomethyl derivative was obtained on elution with chloroform. The compound crystallised from ethanol (0.3 g), M.p. 145°.

Analysis : Found : C, 72.35% ; H, 6.44% ; N, 4.43%

$C_{18}H_{19}O_3N$: requires : C, 72.72% ; H, 6.36% ; N, 4.71%

2-Morpholinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (65)

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (0.6g, 0.002 mol), morpholine (0.8 ml, 0.008 mol) in N,N-dimethylformamide (5 ml) was refluxed for 40 min. The reaction was worked up as usual. On column chromatography 2,7-dimethylfuro coumarin eluted out with benzene in poor yield while the morpholinomethyl derivative obtained on eluting the column with chloroform. The product crystallised from alcohol, (0.3 g), M.p. 180°.

Analysis : Found : C, 67.60% ; H, 6.16% ; N, 4.51%

$C_{17}H_{17}O_4N$: requires : C, 68.22% ; H, 5.68% ; N, 4.68%

PMR($CDCl_3$) : δ 2.5(s, 3H, CH_3 at C-7); 2.65(m, 4H, CH_2 x 2, of morpholine close to N at C-2); 3.70(m, 4H, CH_2 x 2 of morpholine close to O at C-2); 3.8(s, 2H, CH_2 at C-2) ; 6.2(s, 1H at C-6) ; 6.9(s, 1H at C-3), 7.3(d, J=9Hz, 1H at C-8) ; 7.45 (d, J=9Hz, 1H at C-9).

2-N-Methylpiperzinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (66)

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (0.6 g, 0.002 mol) and N-methylpiperzine (0.7 ml, 0.008 mol)

in dimethylformamide (5 ml) was refluxed for 40 min. The reaction was worked up as usual. The product on column chromatography gave 2,7-dimethylfurocoumarin in poor yields with benzene fraction while the methylpiperzinomethyl derivative was obtained with chloroform elution, which crystallised from ethanol (0.2 g), m.p. 200°.

Analysis : Found : C, 69.63% ; H, 6.72% ; N, 8.45%

$C_{18}H_{20}N_2O_3$: requires : C, 69.23% ; H, 6.41% ; N, 8.97%

PMR($CDCl_3$) : δ2.3(s, 3H, N-Me, at C-2) ; 2.45(s, 3H, CH_3 at C-7) ; 2.55(m, 8H, CH_2 x 4 of piperzine at C-2) ; 3.7(s, 2H, CH_2 at C-2) ; 6.2(s, 1H at C-6) ; 6.9(s, 1H at C-3) ; 7.3(d, J=9Hz, 1H at C-8) ; 7.4(d, J=9Hz, 1H at C-9).

2-N-Phenylpiperzinomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (67)

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (0.6 g, 0.002 mol), N-phenylpiperzine (1.35 ml, 0.008 mol) in DMF (5 ml) was refluxed for 40 min. The reaction was worked up as usual. Small amount of 2,7-dimethylfurocoumarin was also obtained along with phenylpiperzinomethyl derivative which crystallised from ethanol (0.5 g), M.p. 209°

Analysis : Found : C, 73.07% ; H, 6.31% ; N, 7.19%

$C_{23}H_{22}O_3N_2$: requires : C, 73.52% ; H, 5.85% ; N, 7.48%

PMR($CDCl_3$) : δ 2.45(s, 3H, CH_3 at C-7) ; 2.7(m, 4H, CH_2 x 2 of piperzine close to N at C-2), 3.20(m, 4H, CH_2 x 2 of piperzine close to N-Ph at C-2) ; 3.75(s, 2H, CH_2 at C-2) ; 6.2(s, 1H at C-6) ; 6.8(s, 1H at C-3) ; 6.9-7.15(m, 5H, N-Ph at C-2) ; 7.3(d, J=9Hz, 1H at C-8); 7.4(d, J=9Hz, 1H at C-9).

2-Diethanolaminomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (68)

2-Bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (0.6 g, 0.002 mol), diethanolamine (0.85 ml, 0.008 mol) in dimethylformamide (5 ml) was refluxed for 40 min. The reaction was worked up as usual. The product obtained crystallised from ethanol (0.3 g), M.p. 128°

Analysis : Found : C, 64.65% ; H, 6.39% ; N, 4.05%

$C_{17}H_{19}O_5N$: requires : C, 64.35% ; H, 5.99% ; N, 4.41%

PMR($CDCl_3$) : δ 2.45(s, 3H, CH_3 at C-7), 2.8(t, 4H, CH_2 x 2 of diethanol close to N at C-2) ; 3.65(t, 4H, CH_2 x 2 of diethanol close to OH at C-2), 3.95(s, 2H, CH_2 at C-2) ; 6.2 (s, 1H at C-6) ; 6.9(s, 1H at C-3) ; 7.3(d, J=9Hz, 1H at C-8) 7.45(d, J=9Hz, 1H at C-9).

2-Diethylaminomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (69)

The above compound was also prepared by refluxing 2-bromomethyl-7-methylfuro(2,3-h)benzopyran-5(H)-one (0.6 g)

and diethylamine (0.6 ml) in DMF for 40 min. The reaction mixture wascooled and poured over ice water. Separated product filtered and dried. Product crystallised from ethanol (0.4 g) M.p. 95°

Analysis : Found : C, 71.21% ; H, 7.02% ; N, 4.45%

$C_{17}H_{19}O_3N$: requires : C, 71.57% ; H, 6.66% ; N, 4.91%

PMR($CDCl_3$) : δ1.25(t, 6H, CH_3 x 2 of diethyl at C-2); 2.6(s, 3H, CH_3 at C-7) ; 2.7(q, 4H, CH_2 x 2 of diethyl at C-2) ; 3.95 (s, 2H, CH_2 at C-2) ; 6.3(s, 1H at C-6) ; 7.0(s, 1H at C-3) ; 7.45(d, J=9Hz, 1H at C-8) ; 7.55(d, J=9Hz, 1H at C-9).

2-Bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (75)

The above compound was also synthesised in a similar way as (63). 2,5-Dimethylfuro(3,2-g)benzopyran-7(H)-one (2.0 g), N-bromosucinimide (1.8 g) and pinch of benzoyl peroxide in 50 ml of CCl_4 was refluxed under 200W bulb for 8hr. The reaction was worked up as described earlier. The obtained product was purified by crystallisation from alcohol (1.2 g), M.p. 170°.

Analysis : Found : C, 52.85% ; H, 3.50%

$C_{13}H_9O_3Br$: requires : C, 53.24% ; H, 3.07%

2-Piperidinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (76)

2-Bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one

(0.6 g) was refluxed in DMF (5 ml) with piperidine (0.7 ml) for 40 min. The reaction mixture was cooled and poured over ice water. The separated product on column chromatography gave small amounts of 2,5-dimethylfuro(3,2-g)benzopyran-7(H)-one which eluted out in the benzene fraction while the compound (76) eluted with chloroform. The product crystallised from ethanol (0.1 g), M.p. 150°.

Analysis : Found : C, 72.30% ; H, 6.06% ; N, 4.36%

$C_{18}H_{19}O_3N$: requires : C, 72.72% ; H, 6.36% ; N, 4.71%

2-Morpholinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (77)

2-Bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (0.6 g) was refluxed in DMF (5 ml) with morpholine (0.8 ml) for 40 min. The reaction was worked up as usual. Small amount of 2,5-dimethylfurocoumarin was also obtained along with (77). Product crystallised from alcohol (0.3 g), M.p. 182°.

Analysis : Found : C, 68.32% ; H, 5.55% ; N, 5.11%

$C_{17}H_{17}O_4N$: requires : C, 68.22% ; H, 5.68% ; N, 4.68%

PMR($CDCl_3$) : δ 2.5(s, 3H, CH_3 at C-5) ;2.6(m, 4H, CH_2 x 2 of morpholine close to N at C-2) ; 3.7(s, 2H, CH_2 at C-2) ; 3.8(m, 4H, CH_2 x 2 of morpholine close to O at C-2) ; 6.25(s, 1H at C-6) ; 6.65(s, 1H at C-3) ; 7.4(s, 1H at C-4) ; 7.7(s, 1H at C-9).

2-N-Methylpiperzinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (78)

A mixture of 2-bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (0.6 g), N-methylpiperizine (0.7 ml) in DMF (5 ml) was refluxed for 40 min. The reaction was worked up as usual. 2,5-Dimethylfuro coumarin was also obtained in small quantities along with the product (78), which crystallised from benzene (0.2 g), M.p. 160°.

Analysis : Found : C, 69.69% ; H, 6.05% ; N, 9.38%

$C_{18}H_{20}O_3N_2$: requires : C, 69.23% ; H, 6.41% ; N, 8.97%

PMR($CDCl_3$) : δ 2.3(s, 3H, N-Me at C-2); 2.5(s, 3H, CH_3 at C-5) 2.6(m, 8H, CH_2 x 4 of piperzine at C-2) ; 3.75(s, 2H, CH_2 at C-2) ; 6.25(s, 1H at C-6) ; 6.65(s, 1H at C-3) ; 7.4(s, 1H at C-4) ; 7.65(s, 1H at C-9).

2-N-Phenylpiperzinomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (79)

2-Bromomethyl-5-methylfuro(3,2-g)benzopyran-7(H)-one (0.6 g), N-phenylpiperzine (1.4 ml) in DMF (5 ml) was refluxed for 40 min. The reaction was worked up as usual. Small amount of 2,5-dimethylfurocoumarin was also obtained along with (79). It crystallised from the mixture of alcohol and benzene (0.5 g), M.p. 193°

Analysis : Found : C, 73.29% ; H, 5.72% ; N, 7.57%

$C_{23}H_{22}O_3N_2$: requires : C, 73.52% ; H, 5.85% ; N, 7.48%

PMR($CDCl_3$) : δ 2.45(s, 3H, CH_3 at C-5) ; 2.7(m, 4H, CH_2 x 2 of piperzine close to N at C-2) ; 3.2(m, 4H, CH_2 x 2 of piperzine close to N-Ph at C-2) ; 3.7(s, 2H, CH_2 at C-2) ; 6.2(s, 1H at C-6) ; 6.6(s, 1H at C-3) ; 6.75-7.15(m, 5H, N-Ph at C-2) 7.35(s, 1H at C-4) ; 7.65(s, 1H at C-9).

REFERENCES

1. P.S. Song and K.J. Tapley, Photochem. Photobiol, 29, 1177 (1979).

2. C. Antonello, S. Marciani Magno, O. Gia, O. Baessato and M. Palumbo ; IL Farmaco Ed. Sc. Vol. 36 PP. 566-584 (1981).

3. J.E. Hearst, H. Rapoport, S. Isaacs and J. Shen Che-kun ; Biochem 16, 1058 (1977).

4. J.B. Hansen and Ole Buchardt, Tetrahedran Letters, Vol.22 No. 19 PP. 1847 (1981).

5. Orchidee H. Hismat and Khairia, M.A. Khalil ; Indian Journal of Chemistry, Vol. 7 No. 4, PP 411-412 (1969).

6. Orchidee H., Hismat, Abdel-karim, M.N. Gohar, Mohamed N.M. Khodeir and Mohamed S. Yousef ; Ind. J. Chem. Vol. 18B PP. 386-87 (1979).

7. K.D. Kaufmann, D.J. Erb, J.M. Blok, R.W. Carlson, D.J. Knoechel, L.McBride and T. Zeitlow ; J.Heterocyclic Chem. 19, 1051 (1982).

8. N.D. Heindel, Mridula Chowdari, J. Ressner and N. Foster; J. Heterocyclic Chem. 22, 73 (1985).

9. F. Dall'Acqua, D. Vedaldi, S. Caffieri, A. Guiotto, P. Rodighiero, F. Baccichetti, F. Carlassare and F. Bordin ; J. Med. Chem., 24, 178-184 (1981).

10. S. Venturini and M. Tamaro ; Mutat Res. 88 (1), 17-22 (1981).

11. P. Valenti, P. Montanari, G. Scapini, R.P. Giusti and L. Cima ; Arch. Pharm(Weinheim) 313, 449-453 (1980).

12. F. Bordin, F. Baccichetti, F. Carlassare, M. Peron, F. Dall'Acqua, D. Vedaldi, A. Guiotto, P.Rodighiero ; and M. Pathak ; IL FARMACO-Ed. Sc. Vol. 36 fasc 7 PP. 506-518 (1981).

13. R.M. Kelkar, V.K. Joshi and M.V. Paradkar ; Synthesis No. 3, 214-216 (1986).

14. N.H. Pardanani and K.N. Trivedi, Australian Journal of Chemistry 25, 1537 (1972).