CHAPTER-II

SYNTHESIS OF FUROCOUMARINS

CHAPTER - II

SYNTHESIS OF FUROCOUMARINS

Many naturally occurring coumarins contain furan ring system. Furocoumarins occur mainly in psoralea corylifolia, xanthylum flavum or angelica archangelic or bergamot fruit. These furocoumarins can be synthesised by starting with suitably substituted coumarin derivatives and then building up furan ring over it or by building up pyrone ring on hydroxy benzofurans.

Spath,[1] Dean[2,3] and Reppel[4] have written comprehensive reviews about the chemistry of naturally occurring coumarins while Karrer[5] reviewed the furocoumarins that had been isolated.

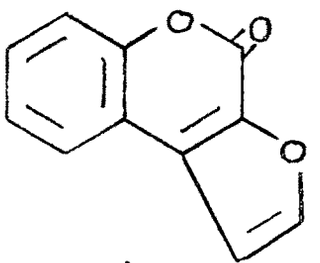
Naturally occuring furocoumarins often possess varied physiological activities. The role of certain plant juices and extractions containing furocoumarins for the treatment of skin lesions such as vitiligo has been known for many years. Juices of various parts of the plants e.g. parsley, celery, fig and parsnip after contact with the skin and exposure to sunlight cause changes on mammalian skin manifested by erythema and increased pigmentation. The discovery of this unique activity of furocoumarins stimulated the research in this area.

PHYSIOLOGICAL ACTIVITIES OF FUROCOUMARINS

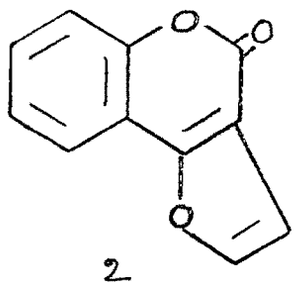
There are eight different isomeric forms of furocoumarins in literature. Out of them only two are found to occur in nature. They are furo(3,2-g)benzopyran-7(H)-one, psoralen (6) and furo(2,3-h)benzopyran-5(H)-one, angelicin (7). The other six isomeric types do not occur in nature but are synthesised.

Furocoumarins of type (6) known as psoralens have received considerable attention due to their therapeutic properties. Psoralen derivatives are used as photochemotherapeutical drugs in PUV-A(Psoralen Ultra Violet-A) therapy of dermatological disorders like psoriasis,[6] vitiligo,[7] atropic eczema[8] and micosis fungoides[9] in tumor stage and also useful tools for studying the structure of nucleic acids in molecular biology.[10-12]

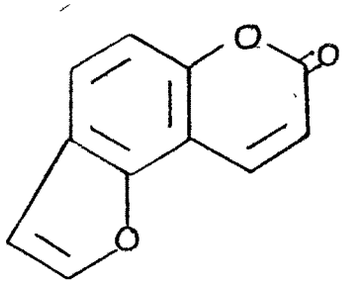
Xanthotoxin or 8-methoxypsoralen (8-MOP) (9) which is a naturally occurring compound is currently the only PUV-A drug in general clinical use. However, it is reported that 8-MOP produces unwarrented side effects in patients.[13] Furthermore 8-MOP in combination with UV-A irradiation has moderate mutagenic properties[14,15] and found to be carcinogic in mice.[16,17]



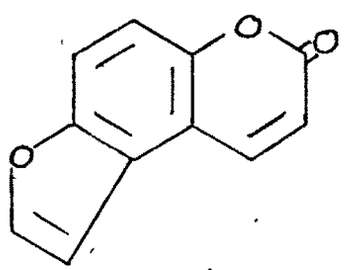
1



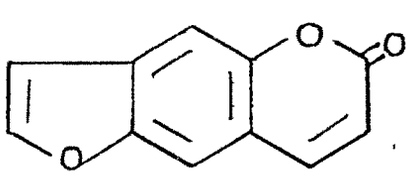
2



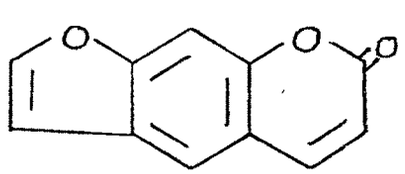
3



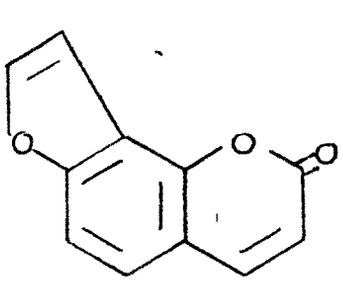
4



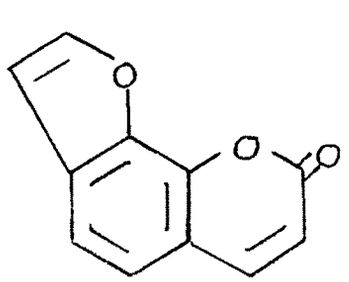
5



6



7



8

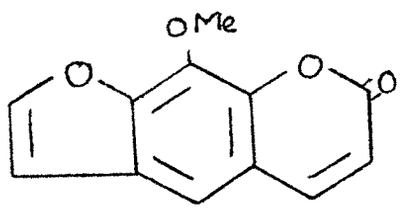
STRUCTURE-ACTIVITY RELATIONSHIP

Kuske[18] found that certain furocoumarins were active agents responsible for the photodermatitis and reported that they showed absorption at 334-366 nm.

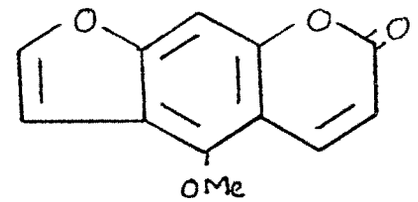
Musazo et al.[19,20] undertook extensive studies to find out the relation between the structure and photodynamic behaviour. They established that under solar or 365 nm UV-radiation, psoralen has the highest activity among the natural coumarins followed by in decreasing order xanthotoxin, (9) bergapten(10) and angelicin(7).

It was reported that the linear furan ring attached to benzopyrone system was necessary for the photosensitizing activity, while the angular furocoumarin exhibits little activity and the introduction of hydroxylfunction at position 5,8 or both delete the activity but however activity is restored by methylation of either but not both of these hydroxyl groups. Pathak and his associates[21] observed that methyl substitution in 4,5' or 8 did not reduce the activity but the activity is lowered by substituting in 3 or 4' positions.

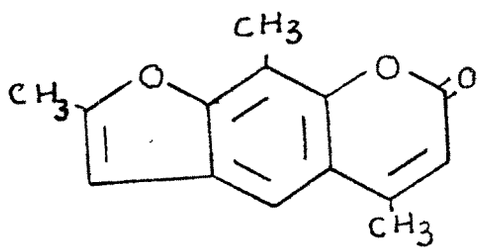
Pathak and Fellman[22] also studied the activity and



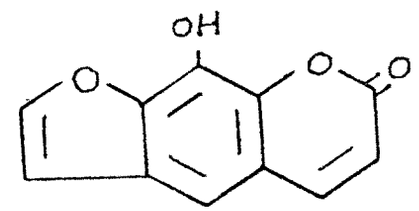
9



10



11



12

fluorescentwave lengths of several furocoumarins and reported that furocoumarins which induced definite photosensitized erythermal response on mammalian skin only showed activation peaks in 340-380 mu region and fluorescent peaks at 420-460 mu. The inactive furocoumarins did not show the specific activity and fluorescent peaks.

MODE OF ACTION

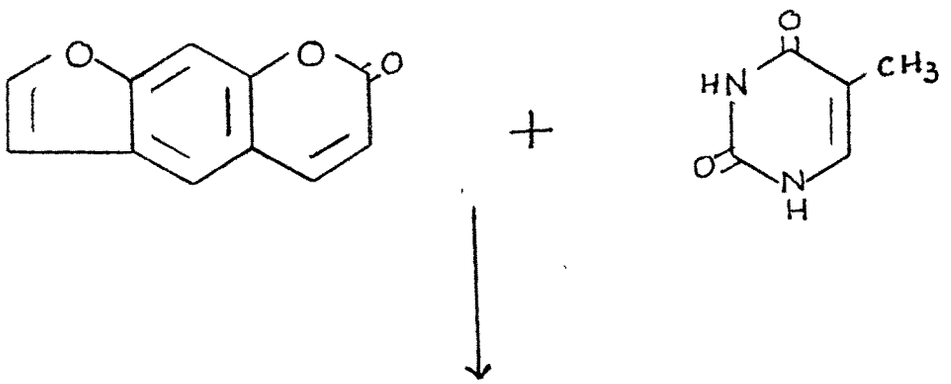
Psoralen [Furo(3,2-g)benzopyran-7(H)-one] (6), 8-methoxy psoralen (8-MOP) (9), 4,5',8-trimethyl psoralen (TMP) (11) are some photodynamically active furocoumarins. From these compounds 8-MOP and TMP are used in photochemotherapy. These compounds are stable in dark, however, under UV-A irradiation they undergo modification. They can act through two mechanisms, (i) the drug, on absorption of light quanta in the UV-visible region is promoted to the electronically excited (singlet) state which may decay to ground state through radiative or non-radiative pathways or (ii) it can be converted to triplet excited state, having a longer life time and has a greater intrensic activity. Triplet stae can also decay to ground state through radiative and non-radiative path ways.

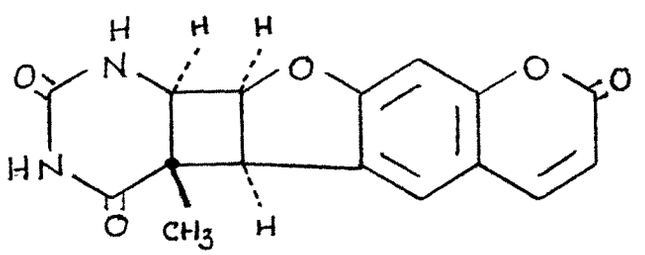
Moore Thomas and Mantogomery[23] studied zerofield splitting parameters (D*) of various furocoumarins in the triplet

state using an optically detected NMR and explained the inactivity of 8-hydroxy psoralen(12) as skinsensitizer, this is due to its anamalous large zero field splitting parameter (D*).

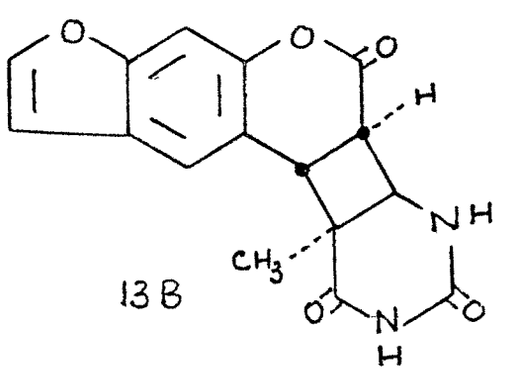
In this, the photoactive psoralen or furocoumarin prior to exposure to the UV-irradiation becomes loosely associated within the strands of DNA of epidermal and dermal cells. When these loosely bound psoralen molecules are photoactivated by UV-A(320-400 nm) irradiation, they form covalent chemical bonds with thyamine bases of DNA(monofunctional adducts). The photo addition involves the formation of cyclobutane bridge beteen the 5,6-double bond of a thyamine base and 3,4 or 4',5' double bond of the psoralen (13A, 13B).

The first photochemical reaction is usually the conjugation of 4',5'-double bond of furan ring with 5,6-double bond of thyamine. This results in the formation of fluorescent adduct which absorbs at 360 nm. Subsequent absorption of a second photon by the mono adduct leads to the formation of additional covalent linkage between the 3,4-double bond of pyrone with the thyamine of the opposite strand(14), thus cross linking the two strands of the double helix.

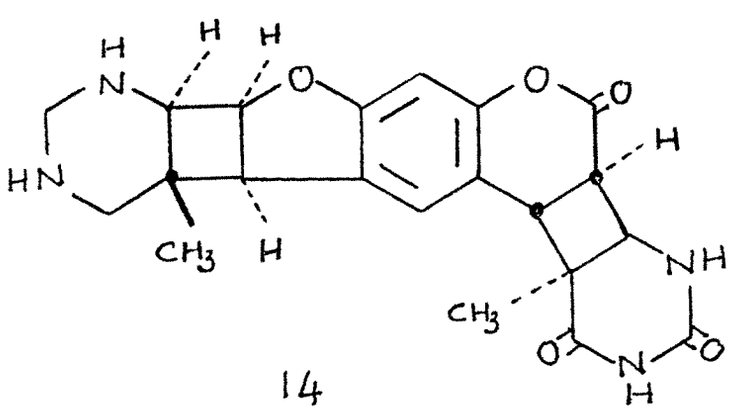




13 A



13 B



14

This light dependent conjugation of psoralen with epidermal DNA leads to the inhibition of DNA synthesis and cell division accounts for the therapeutic behaviour of psoralen to the skin diseases.[24,25]

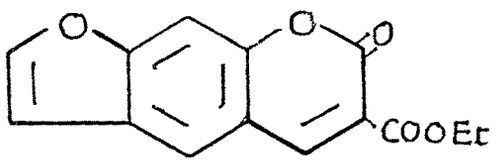
Although at present PUVA is considered best therapeutic treatment for skin diseases but however some undesired side effects are also observed such as skin phototoxicity and possible induction of skin cancer.

This carcinogenic risk in the bifunctional furocoumarins like 8-MOP and TMP initiated search for active but less hazardous psoralens with high binding[26] capacity.

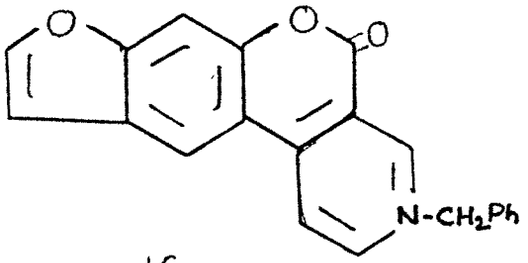
New monofunctional drugs such as 3-carbethoxy psoralen(15) or pyridopsoralen(16), 4,5'-dimethyl angelicin (17), 4,4'-dimethyl angelicin(18) and 5,6'-dimethylangelicin(19), which cannot form interstrand cross linkages with DNA due to steric hindrance, are now widely used for therapeutical treatment.

SYNTHESIS OF FUROCOUMARINS

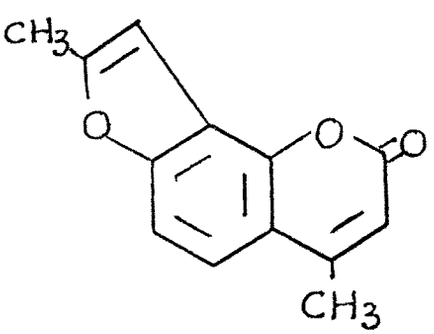
Psoralen and Angelicin occupy a prominent position due to their physiological and therapeutic behaviour. There are many methods described in the literature. The following are some of the important methods to synthesise furocoumarins and their derivatives.



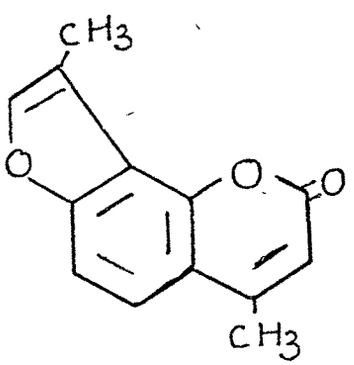
15



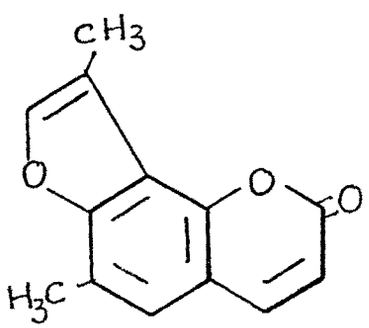
16



17



18



19

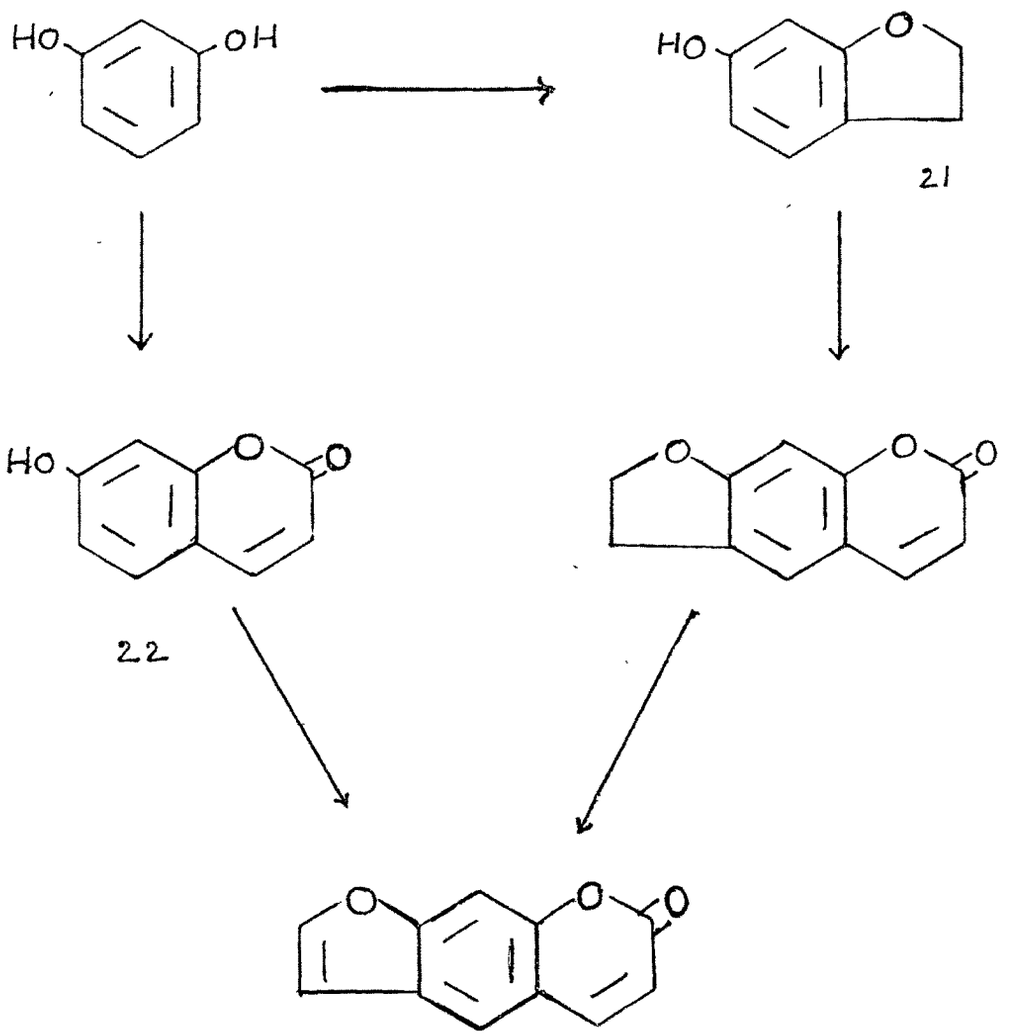
SYNTHESIS OF PSORALEN AND ITS DERIVATIVES

Two routes are available for the synthesis of psoralens i.e. conversion of 6-hydroxycoumaran(21) or through umbelliferone (22). Both of these can be obtained from resorcinol [Scheme-1].

Spath and Pailer[27] carried out the condensation of 6-hydroxy coumaran(21) with malic acid in the presence of con. H_2SO_4 and obtained 2,3-dihydropsoralen(23) which on dehydrogenation with Pd/c gave psoralen(24) [Scheme-2]. Later Horning and Reisner[28] prepared diffferent 5-substituted 2,3-dihydropsoralen derivatives by condensing 6-acetoxy coumaran with a variety of 3-ketonic esters in the presence of con. H_2SO_4. Esse and Chistenson[29] have extended this reaction to obtain 6-alkyl-2,3-dihydro-5-methylpsoralen(26) by condensing appropriate α-alkyl-β-ketonic esters with 6-acetoxycoumaran(25). The main drawback in the method is that the dehydrogenation of dihydropsoralen derivatives(26) with palladised charcoal give poor yields of psoralen derivatives(27) [Scheme-3].

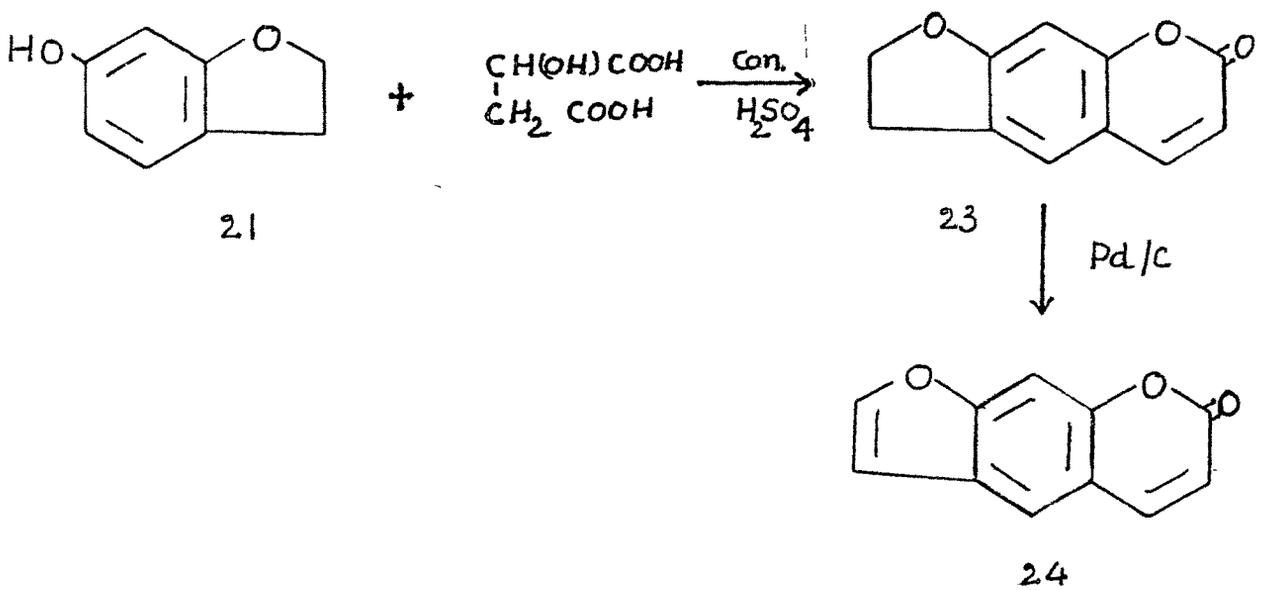
Rodighiero and Antonello[30] synthesised xanthotoxin (8-methoxy psoralen) by first preparing 7-hydroxy-8-methoxy 6-formylcoumarin (28) and then condensing it with ethylbromoacetate to give corresponding ether(29) which was hydrolysed

SCHEME-I



SCHEME-2

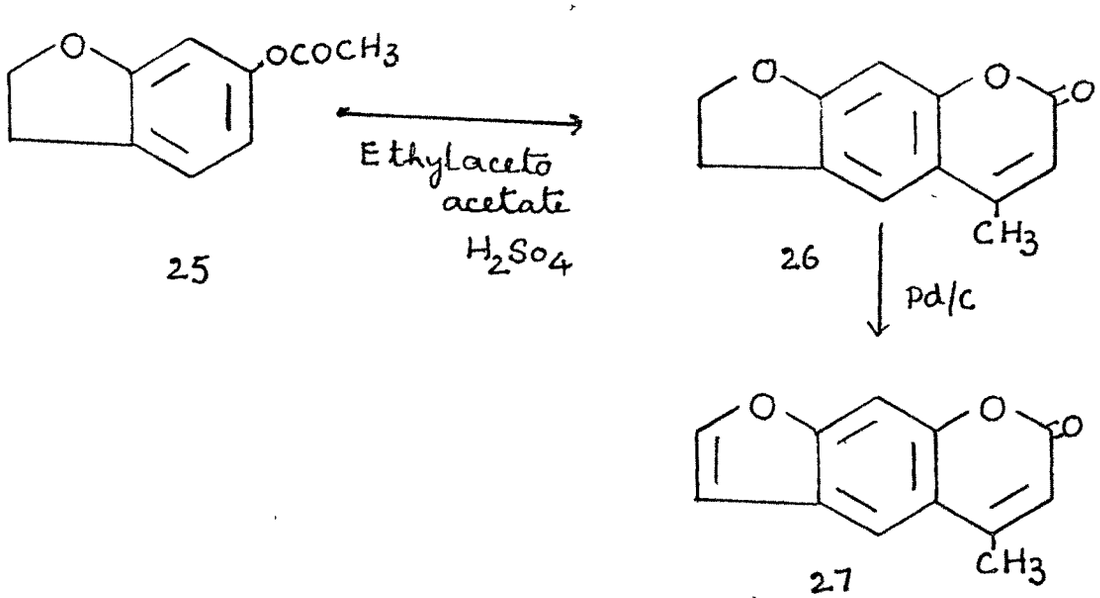
Spath and Pailer[27]



21 23 24

SCHEME-3

Hörning and Reisner[28]



25 26 27

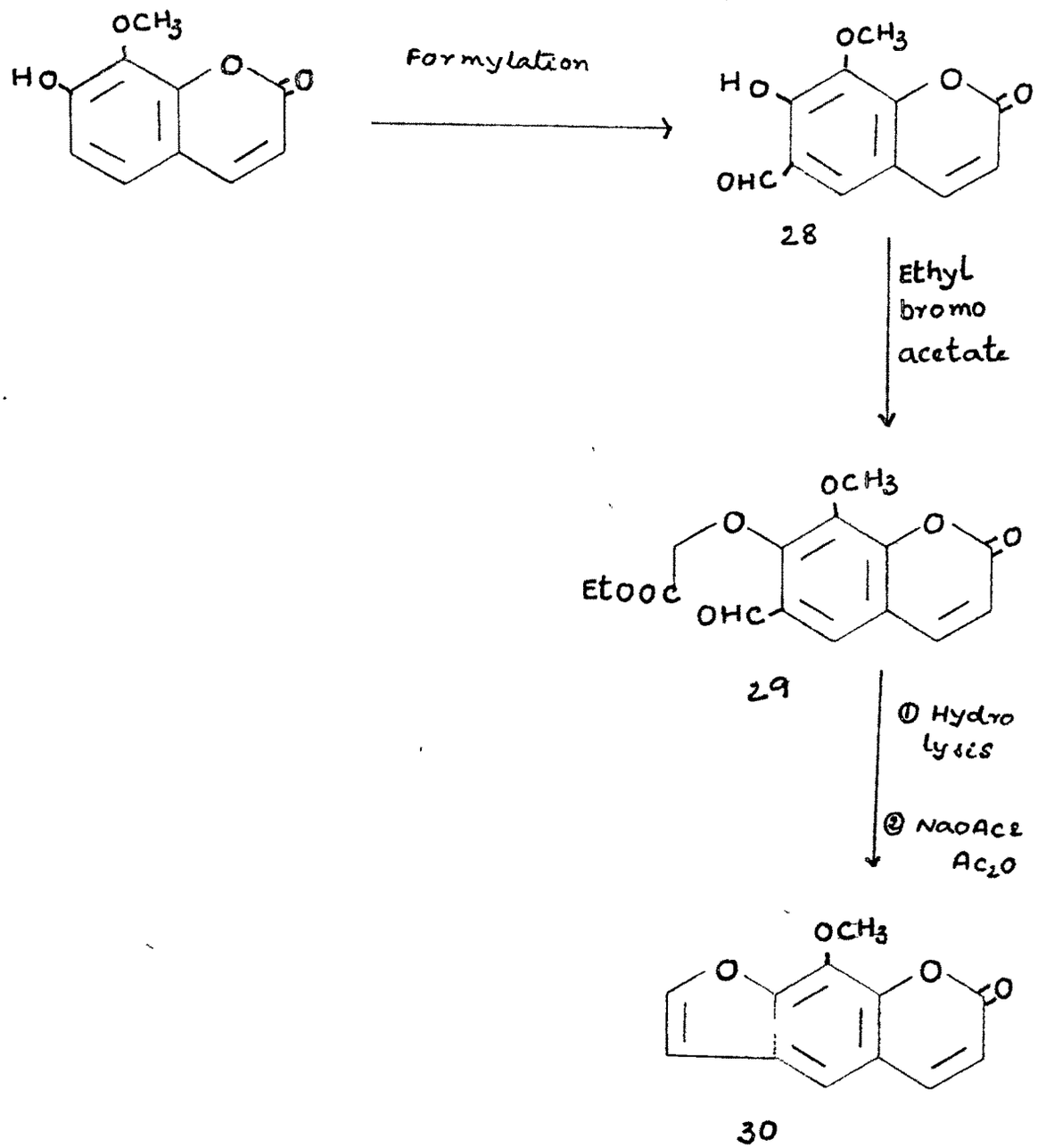
and subjected to cyclisation with sodium acetate and acetic anhydride to make 8-methoxy psoralen(30) [Scheme-4].

However Kaufmann and Worden[31] achieved synthesis of psoralen and 3-methyl psoralen by partially methylating the β-resorcilaldehyde followed by condensation with ethyl bromoacetate to furnish ethyl(2-formyl-5-methoxy-phenoxy) acetate(31). This ester on bromination with Br_2 in acetic acid followed by hydrolysis with alcoholic NaOH and then with sodium acetate and acetic anhydride to make the furan ring, gave 5-bromo-6-methoxy benzofuran(32). Treatment of the bromobenzofuran with butyllithium and N-methylformanilide furnished 5-formyl-6-methoxy benzofuran(33). This was demethylated to the 5-formyl-6-hydroxy benzofuran(34). Condensation of the (34) with diethyl malonate followed by the hydrolysis of ester and decarboxylation with copper bronze gave psoralen. While the Perkin condensation of (34) with sodium propionate and propionic anhydride furnished 3-methyl psoralen [Scheme-5].

Chatterji and Sen[32] also synthesised psoralen and 3-methyl psoralen in a relativelfy good yield from 6-acetoxy-coumaran by condensing with acrylonitrile using $ZnCl_2$ and HCl gas as condensing agents to furnish 2,3,5,6-tetrahydro psoralen (35) which was dehydrogenated using Pd/c to Psoralen

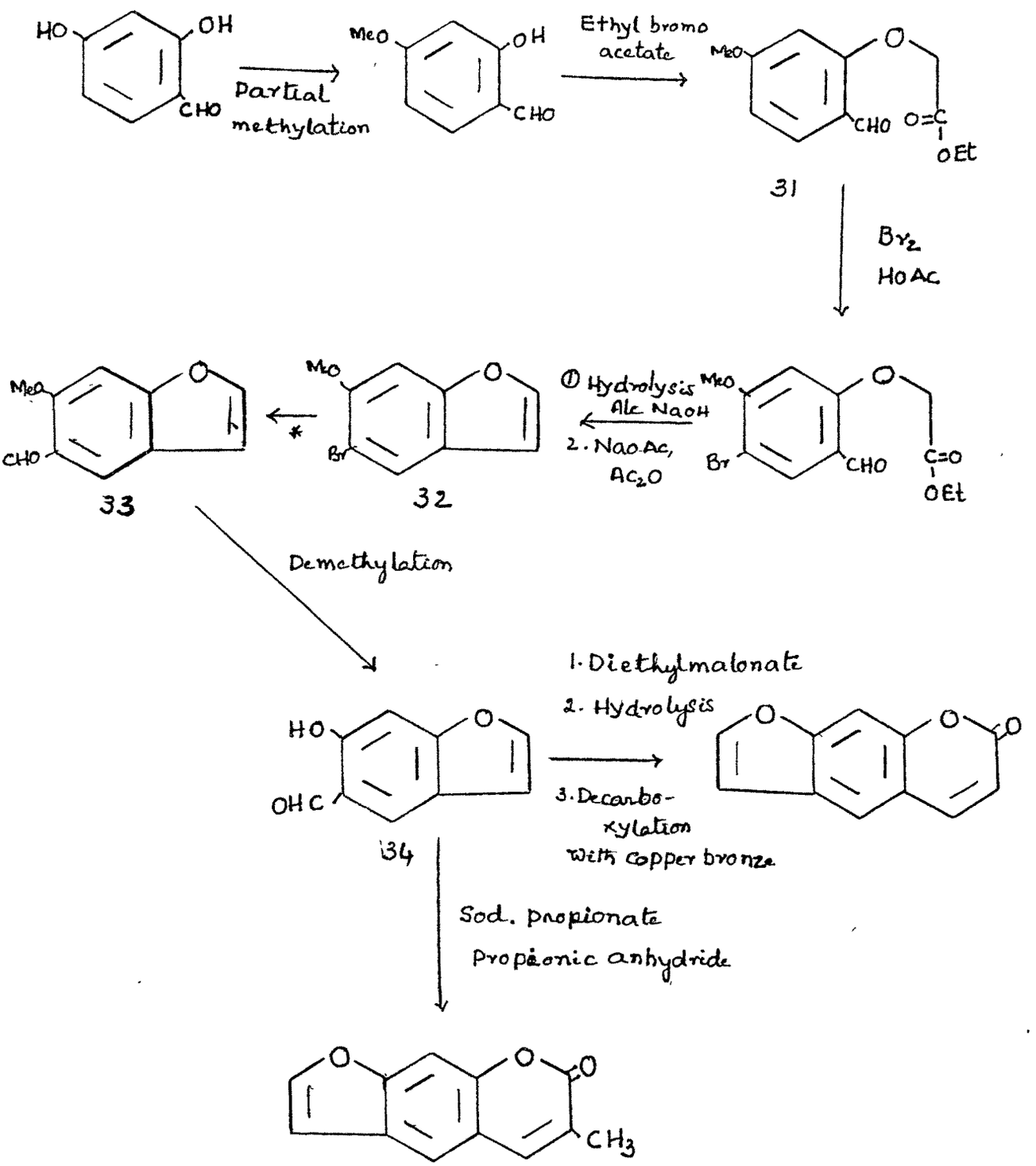
SCHEME-4

Rodighieero and Antonello[30]



SCHEME-5

Kaufmann et al[31]



* butyl lithium and N-methyl formanilide.

[Scheme-6]. 3-Methyl psoralen was also prepared condensing acrylonitrile with 3-methyl-6-hydroxy coumaran.

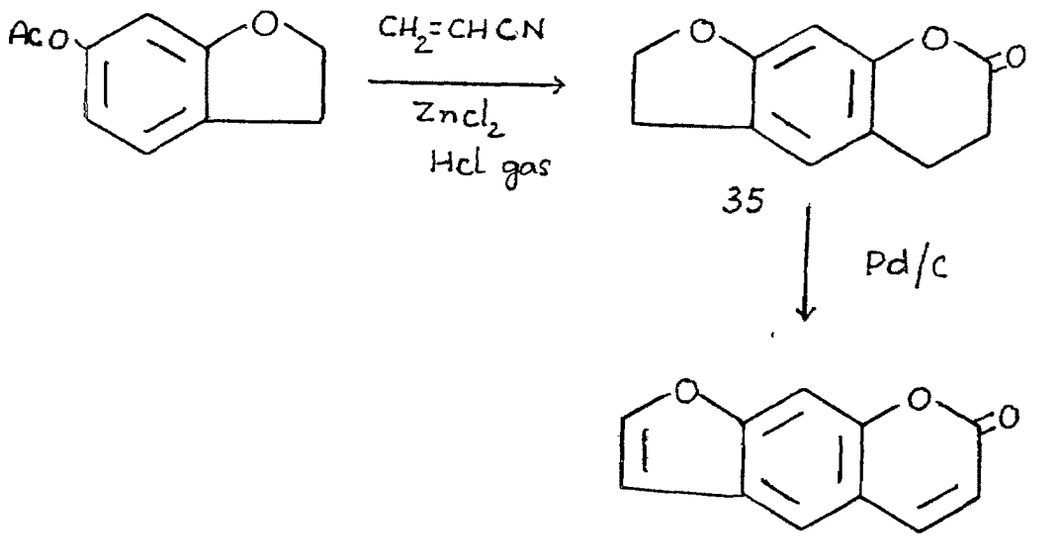
Seshadri and his colleagues[33] synthesised psoralen by using an indirect method of carrying out the thermal rearrangement of 4-allyloxy-2-methoxy benzaldehyde(36) with $AlCl_3$ at 220°. The product 5-allyl-2,4-dihydroxy benzaldehyde (37) was subjected to Perkin reaction to obtain the coumarin derivative(38) which onozonolysis and cyclisation gave psoralen [Scheme-7].

However, Anjanray, Amitabh Gupta and Kalyanmay Sen[34] achieved the synthesis of key compound 6-allylcoumarin for making psoralen from resorcinol in four steps by condensing resorcinol with acrylonitrile in presence of $ZnCl_2$ to give 7-hydroxy-3,4-dihydro coumarin(39). This on allylation and Claisen migration gave the 6-allyl-7-hydroxy-3,4-dihydro-coumarin(40). (40) on dehydrogenation with DDQ in dry benzene gave 6-allyl-7-hydroxy-coumarin (41). [Scheme-8].

Kaufmann[35] prepared 4,5',8-trimethyl psoralen and 5',8-dimethyl psoralen by first carrying out the Claisen rearrangement of 7-allyloxy-4,8-dimethylcoumarin and 7-allyloxy-8-methyl coumarin to 7-hydoxy-6-allyl-4,8-dimethylcoumarin and 7-hydroxy-6-allyl-8-methyl coumarin respectively. These were acetylated, brominated and cyclised to obtain psoralen derivatives [Scheme-9].

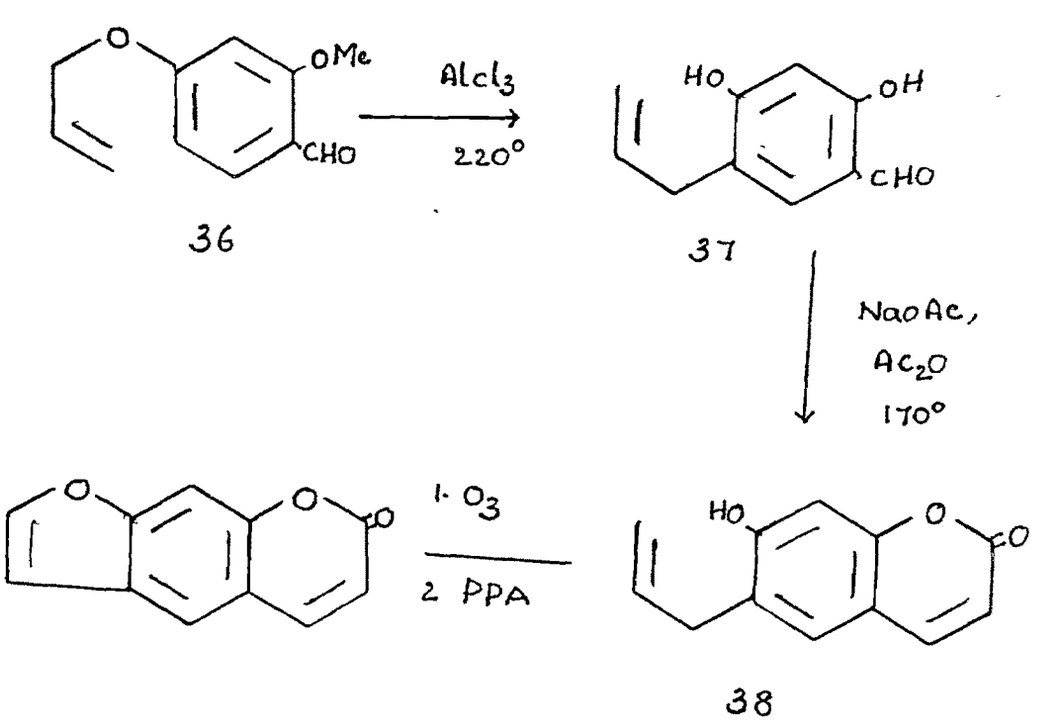
SCHEME-6

Chatterzi and Sen[32]



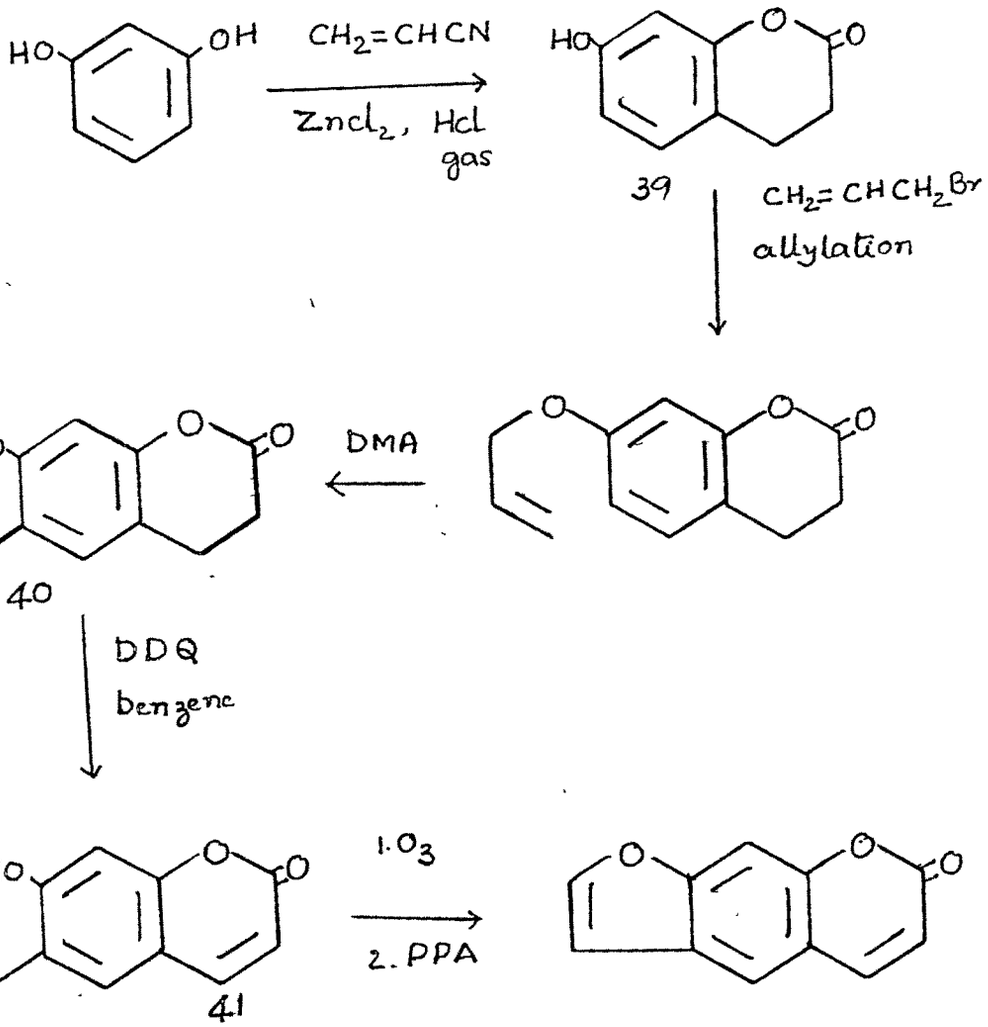
SCHEME-7

Seshadri and coworkers[33]



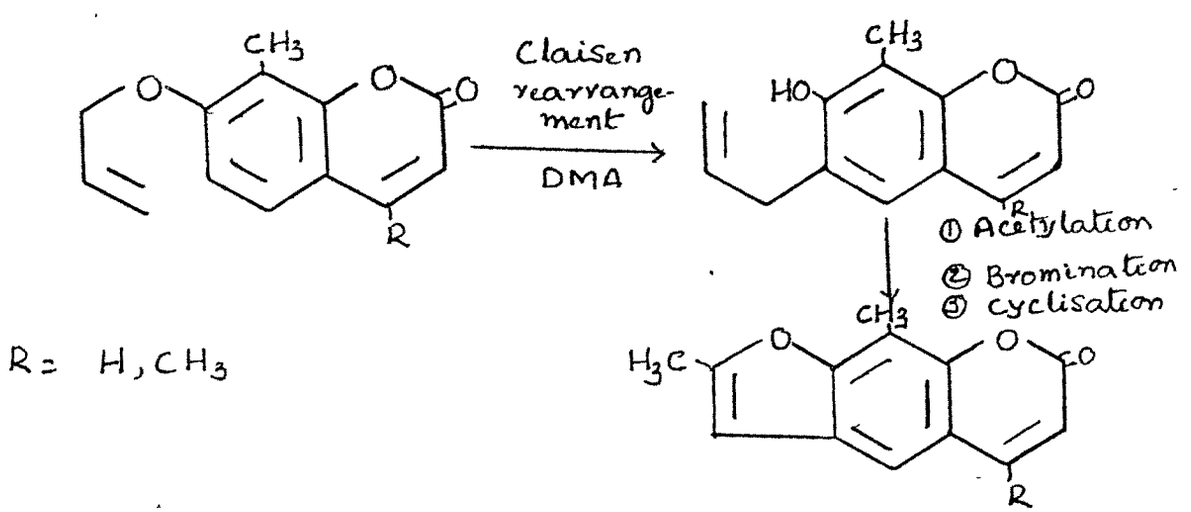
SCHEME-8

K. Sen et al[34]



SCHEME-9

Kaufmann et al[35]



R = H, CH_3

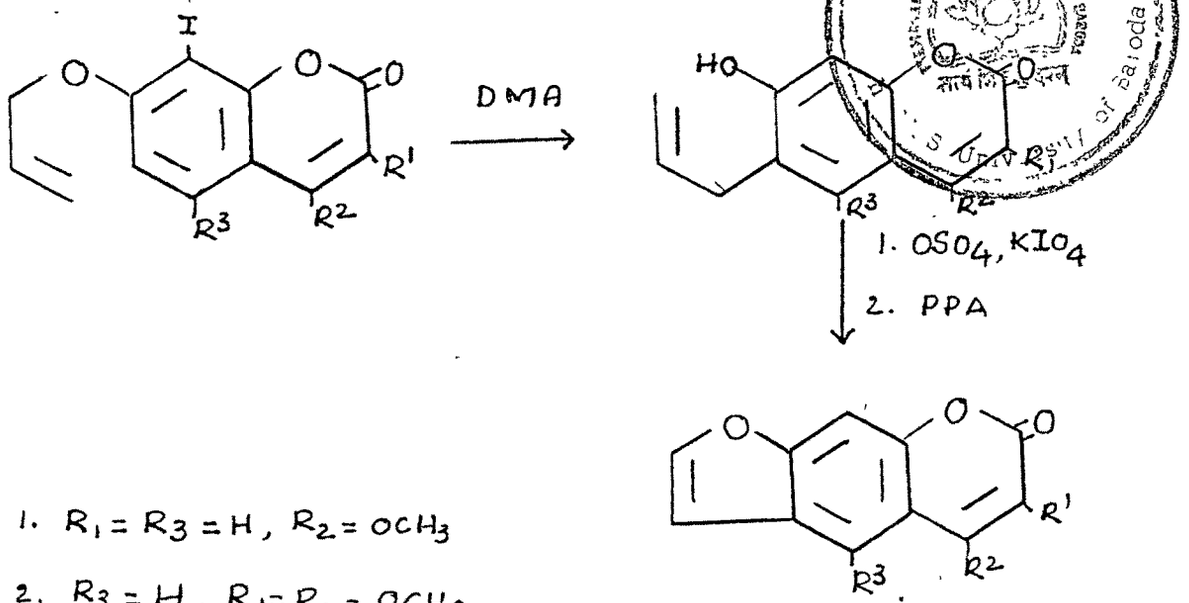
Henry Rapoport[36] also synthesised the above compound in good yields by first carrying out the alkylation of 7-hydroxy-4,8-dimethyl coumarin with 2,3-dichloro-1-propene in DMF/benzene in presence of K_2CO_3 and a catalytic amount of KI to obtain chloroallyl ether (42). This chloroallyl ether on Claisen migration in p-diisopropylbenzene/acetic anhydride gave 7-acetoxy-6-chloroallyl-4,8-dimethyl coumarin (43). (43) on treatment with 70% sulphuric acid produces 4,5',8-trimethyl psoralen. Higher concentrations of sulphuric acid resulted in the formation of dimer of 4,5',8-trimethyl psoralen (44). [Scheme-10].

Ahluwalia and coworkers[37] synthesised 4-methoxy psoralen, 3,4-dimethoxy psoralen, 3,4,5-trimethoxy psoralen conveniently using the method originated by Pardanani and Trivedi by blocking the 8th position with Iodine and subjecting the 7-allyloxy-8-Iodo coumarin to Claisen rearrangement [Scheme-11] followed by oxidation with OSO_4 and KIO_4 and cyclisation with PPA.

Ahluwalia and coworkers[38] also synthesised psoralen derivatives by condensing orthohydroxy ketone with benzoin in presence of PTS followed by Wittig reaction of the resultant diphenylbenzofuran(45) with ethoxy carbonyl methylene

SCHEME-11

V. K. Ahluwalia et al[37]

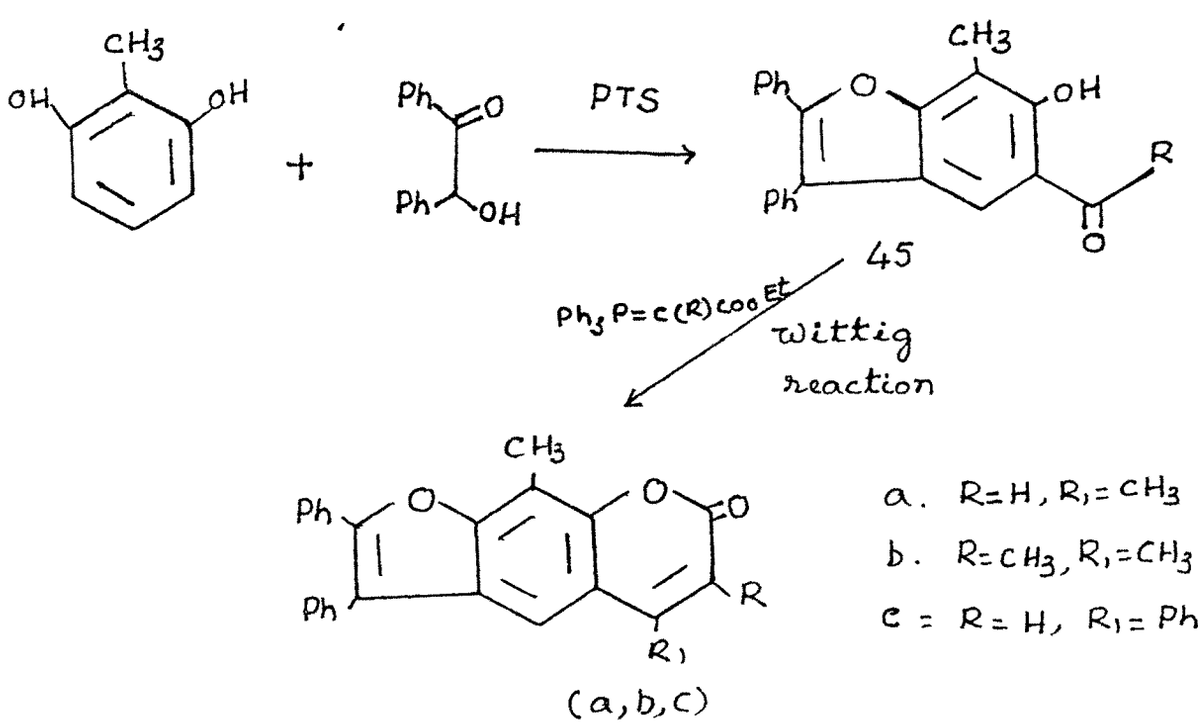


1. $R_1 = R_3 = H$, $R_2 = OCH_3$
2. $R_3 = H$, $R_1 = R_2 = OCH_3$
3. $R_1 = R_2 = R_3 = OCH_3$

(1, 2, 3)

SCHEME - 12

V.K. Ahluwalia coworkers[38]



(a, b, C)

a. $R = H$, $R_1 = CH_3$

b. $R = CH_3$, $R_1 = CH_3$

c = $R = H$, $R_1 = Ph$

(triphenyl)phosphorane or 1-carbethoxy ethylidine(triphenyl) phosphorane [Scheme-12].

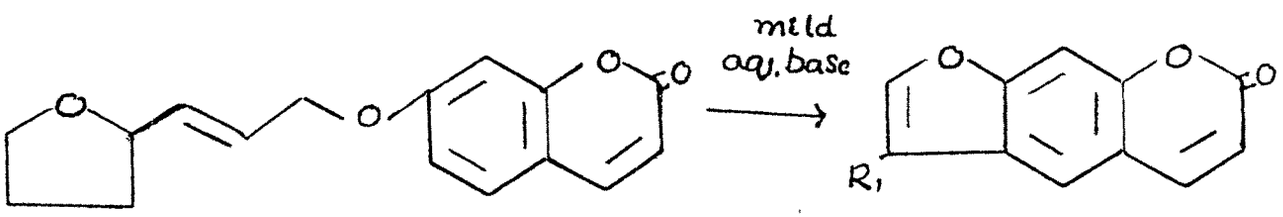
MacLeod and coworkers[39] reported that the naturally occurring coumarin geipavarin(46) on treatment with mild aqueous base was shown to undergo a retro-aldol condensation followed by cyclisation to generate the linear furocoumarin. They used the same base catalysed cyclisation process in the preparation of other linear furocoumarins by condensing first 7-hydroxy coumarin or its 4-methyl derivative with chloro acetone or phenacylbromide to get the ether(47), which on treatment with aqueous KOH for 6 hr. followed by cooling and acidification to yield β-substituted furocoumarin (48).

Unsubstituted psoralen was prepared in 30% yield by similar treatment with aqueous KOH after the ozonolysis of the ether(47) to an aldehyde(49) [Scheme-13].

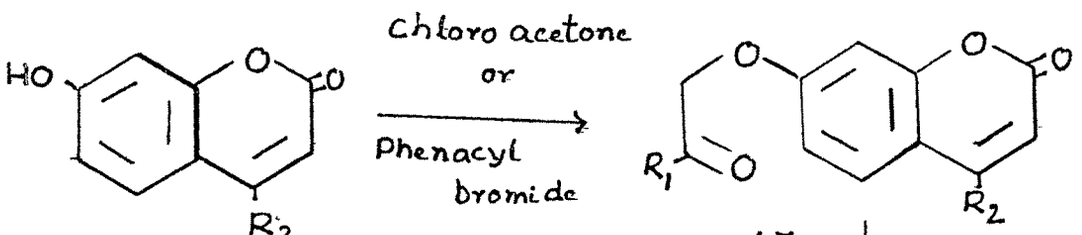
The mechanism of this reaction is described as a type of intramolecular aldol condensation in which the phenoxide ion(a), formed on base hydrolysis of the pyrone ring, promotes attack at the exocyclic carbonyl function through the resonance-stabilised carbanion generated at the position para to the phenoxide ion, viz. a → b. The irreversibility of the process is established by abstraction of the proton

SCHEME-13

Macleod and coworkers[39]



46

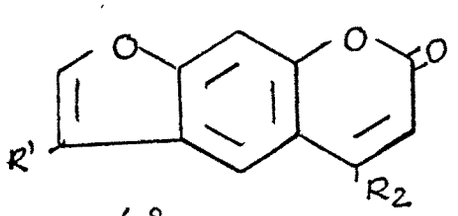


47

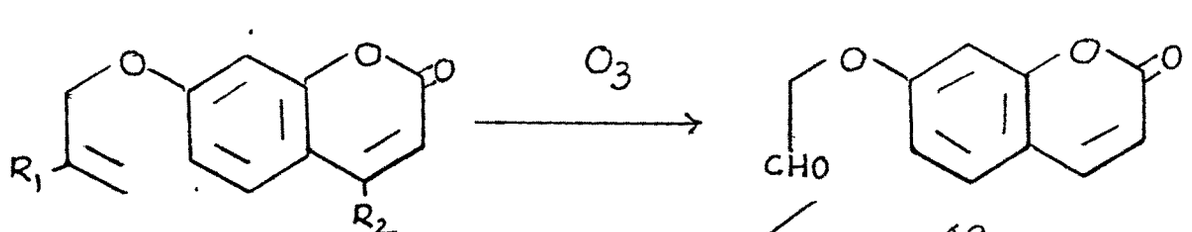
aq. KOH

$R_1 = CH_3, Ph$

$R_2 = H, CH_3$

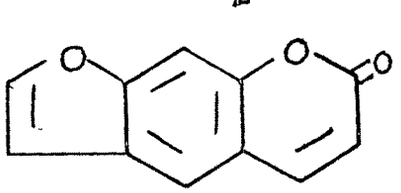


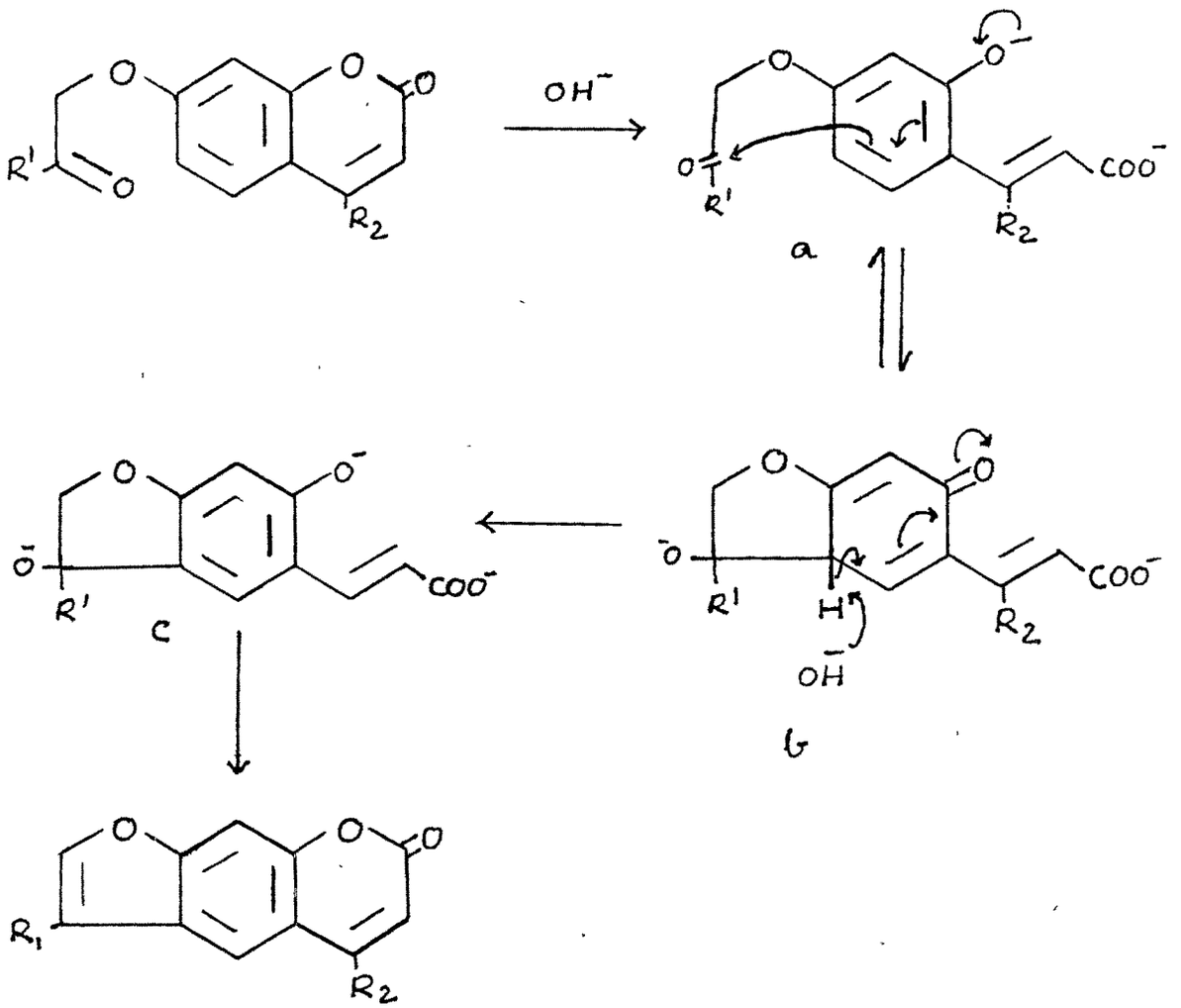
48

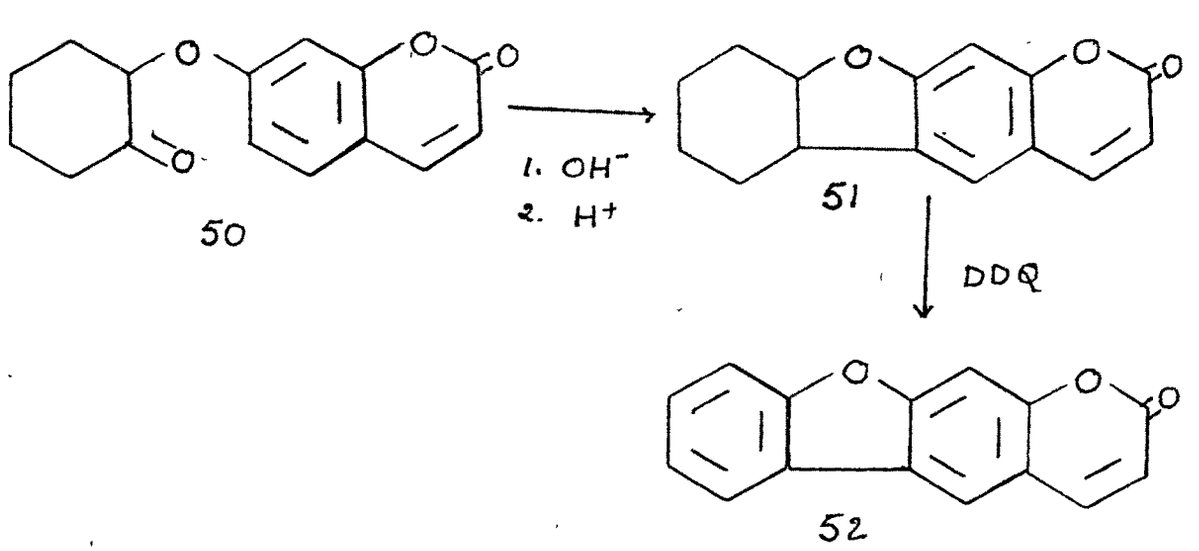


49

0·1N KOH




OH⁻
a
b
c


1. OH⁻
2. H⁺
DDQ
50
51
52

from the newly formed ring junction to regenerate the coumarinic acid salt c. On acidification, the pyrone ring is reformed following protonation of the alkoxy ion, water is spontaneously eliminated from the labile β-hydroxydihydrofuran ring system to give psoralen derivative.

They utilised the same method for preparing dibenzofuran derivatives also by first condensing 2-bromocyclohexanone with 7-hydroxycoumarin to give 7-cyclohexenoloxy coumarin(50) followed by treatment with aqueous KOH under reflux and dehydrogenation of cyclohexenofurobenzopyran(51) to give dibenzofuran derivaive (52).

Guiotto and coworkers[40] synthesised number of tetracyclic furocoumarin derivatives with a linear structure using the principle of MacLeod and coworkers. Methyl groups have been introduced into positions to enhance the photoreactivity of the compounds towards DNA. During the cyclisation of 2-oxo cyclohexenyl ethers (53) of 7-hydroxycoumarin, they observed to give almost exclusively the linear furocoumarins indicating that the 6-position para to the coumarinate ion, is strongly activated with respect to the 8 position ortho to the coumarinate ion. However, trace amounts of angular angelicin type isomer was observed in the crude products. [Scheme-14].

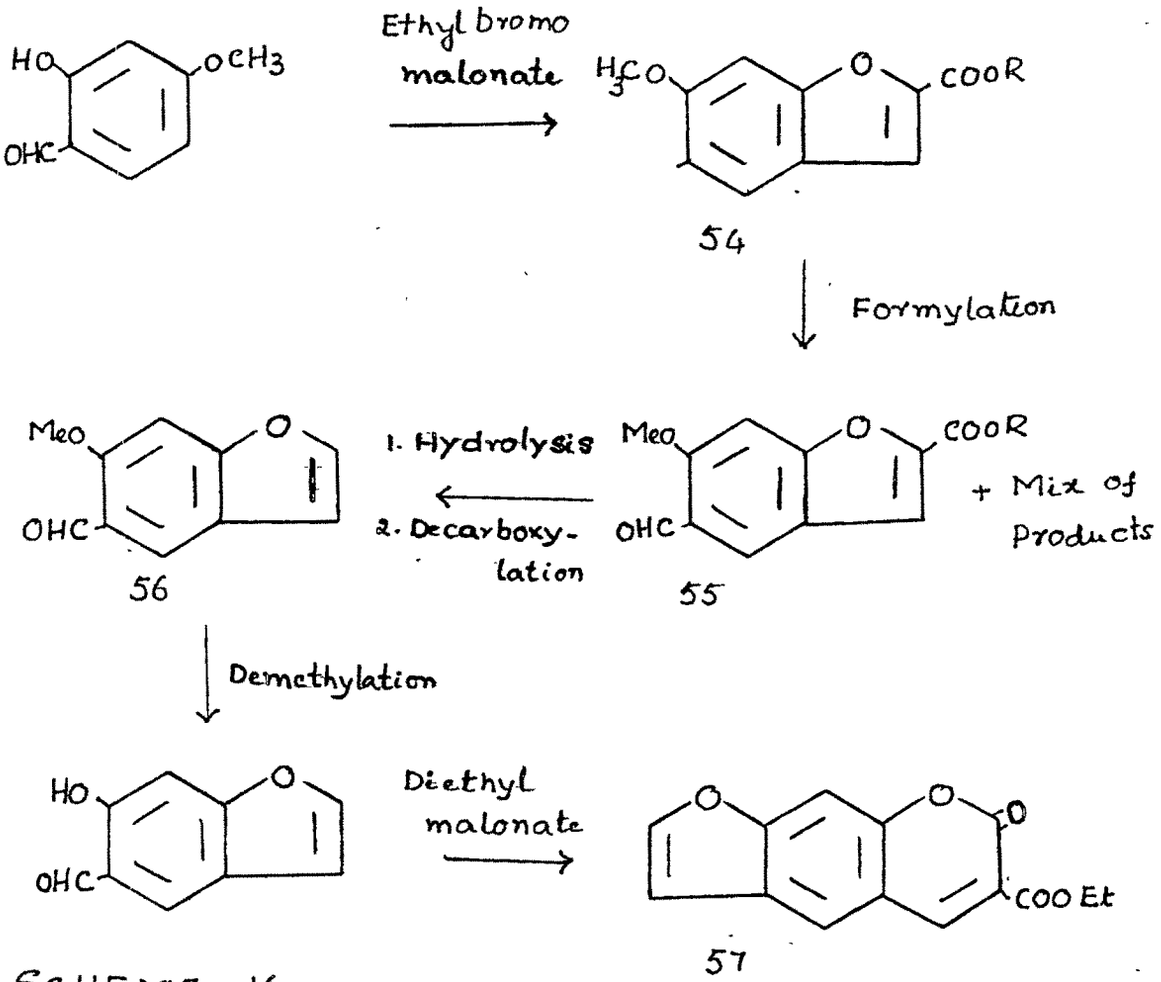
Besagni [41] synthesised more effective non-toxic and non-carcinogenic monofunctional psoralen, reported to exhibit the therapeutic activity as 8-MOP without any local hyper-pigmentation, from 2-hydroxy-4-methoxy benzaldehyde first by condensing with ethylbromomalonate to afford a methoxycoumarilate (54) which on formylation afforded 5-formyl-6-methoxy coumarilate(55). This on subsequent hydrolysis and decarboxylation gave 6-methoxy-5-formyl benzofuran(56). 3-Carbethoxy psoralen (57) is resulted by demethylating 5-formyl-6-methoxy coumarilate(56) followed by condensation with diethylmalonate [Scheme-15].

Besagni[42] also synthesised another monofunctional psoralen 3,4-dipyridopsoralen(60) by condensing 6-acetoxy-7-alkyl-coumaran(58) with 1-benzyl-3-ethoxy carbonyl piperidine-4-one and dehydrogenating the dihydrofuro compound(59) [Scheme-16].

Confalone and Confalone[43] synthesised novel psoralen structurally related to methoxsalen and trioxsalen which are expected to form only monofunctional photo adducts avoiding the potentially mutagenic DNA cross links. Thus 3,4-benzomethoxsalen was synthesised first by condensing resorcinol with α-carbethoxy cyclohexanone in the presence of con. H_2SO_4 to yield tricyclic coumarin(61) which on acetylation gave an acetate(62). A ketone (63) is obtained when (62) is subjected to Fries migration. (63) on allylation with

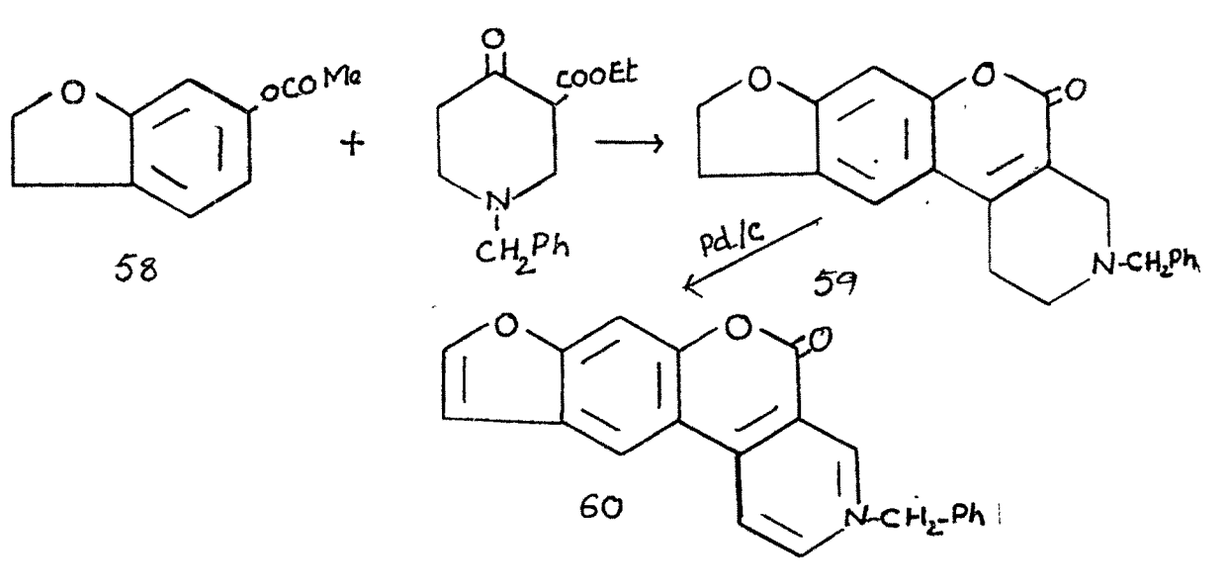
SCHEME - 15

Besagni etal [41]



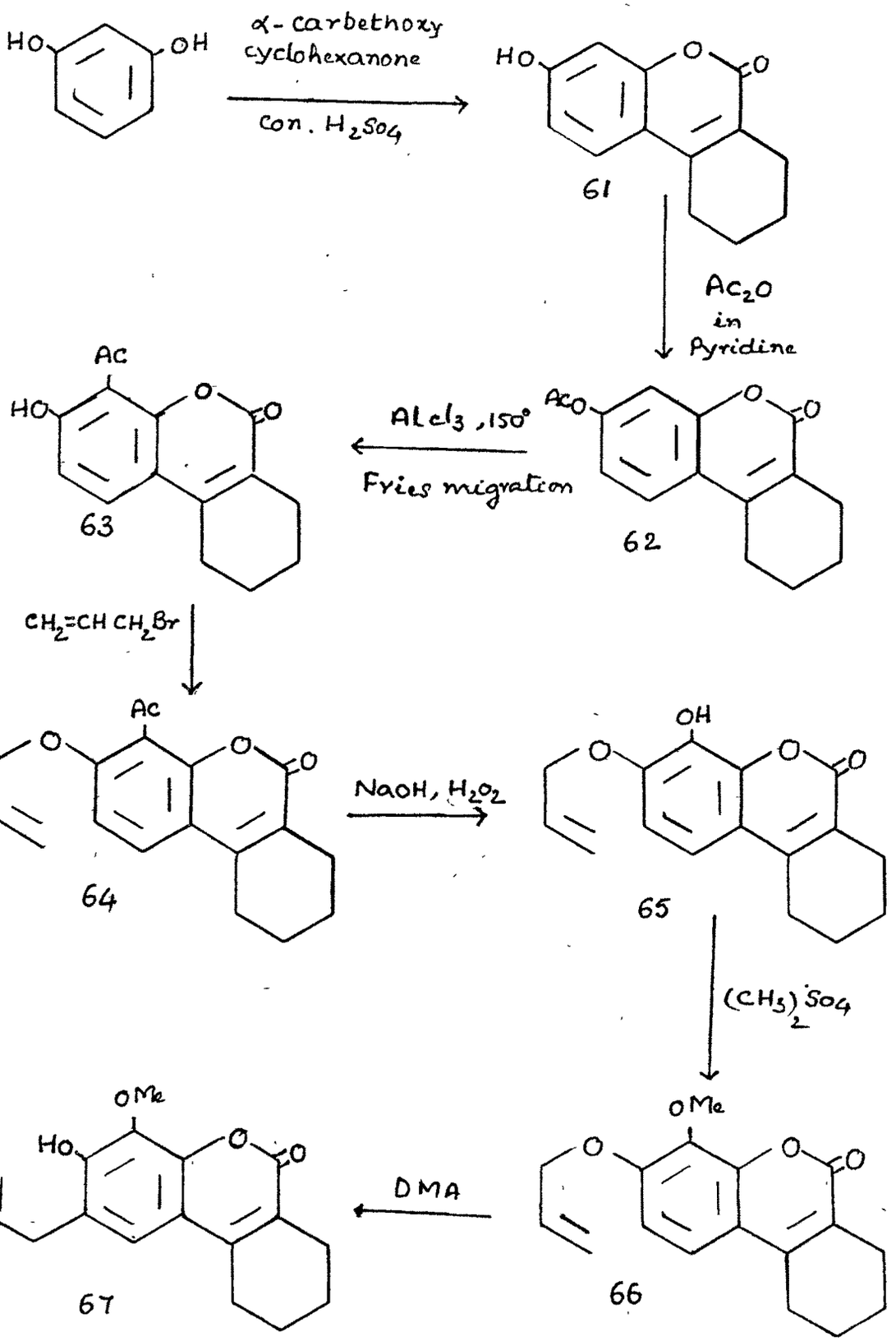
SCHEME - 16

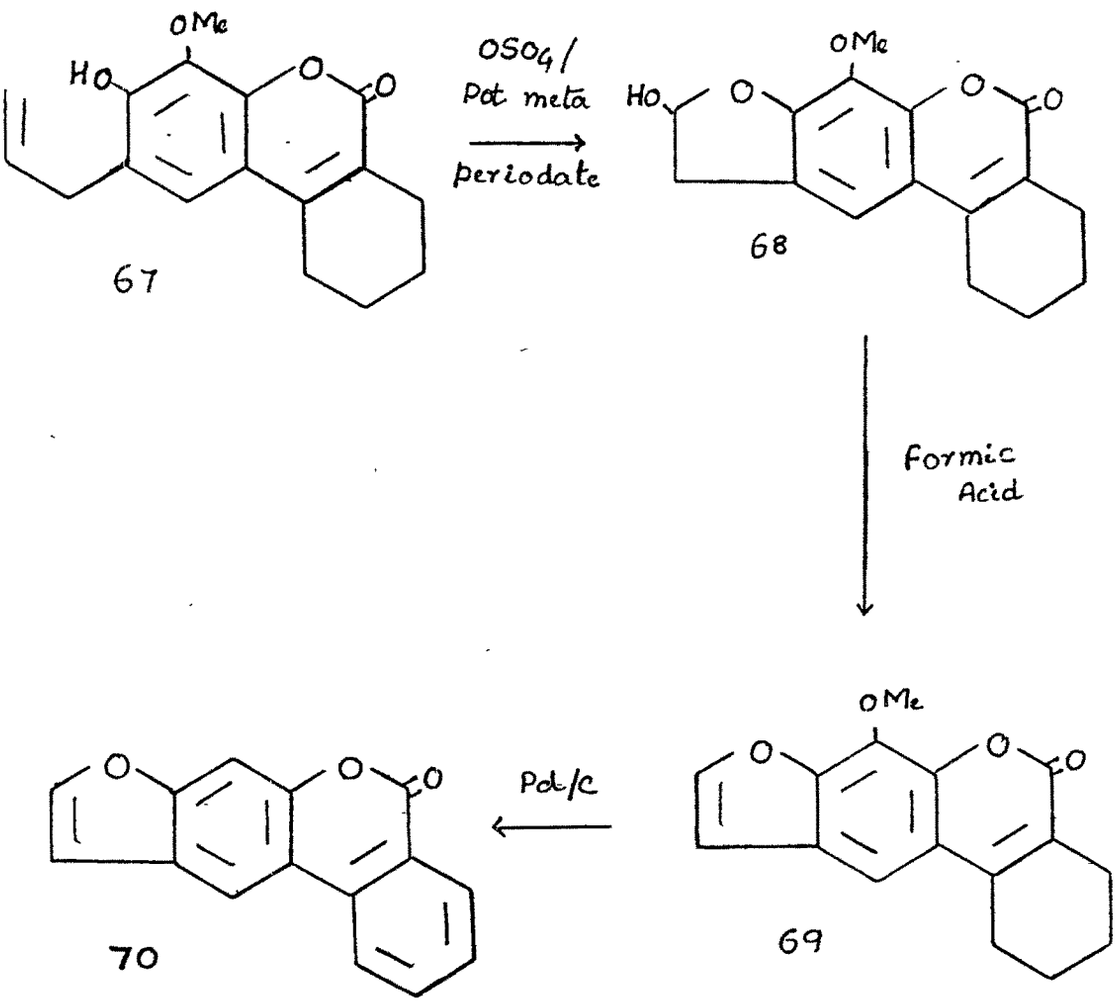
Besagni etal [42]



SCHEME-17

Confalone and Confalone[43]




OMe
HO
O
O
67
OSO4 /
Pot meta
periodate
OMe
HO
O
O
O
68
Formic
Acid
OMe
O
O
O
69
Pd/C
O
O
O
70

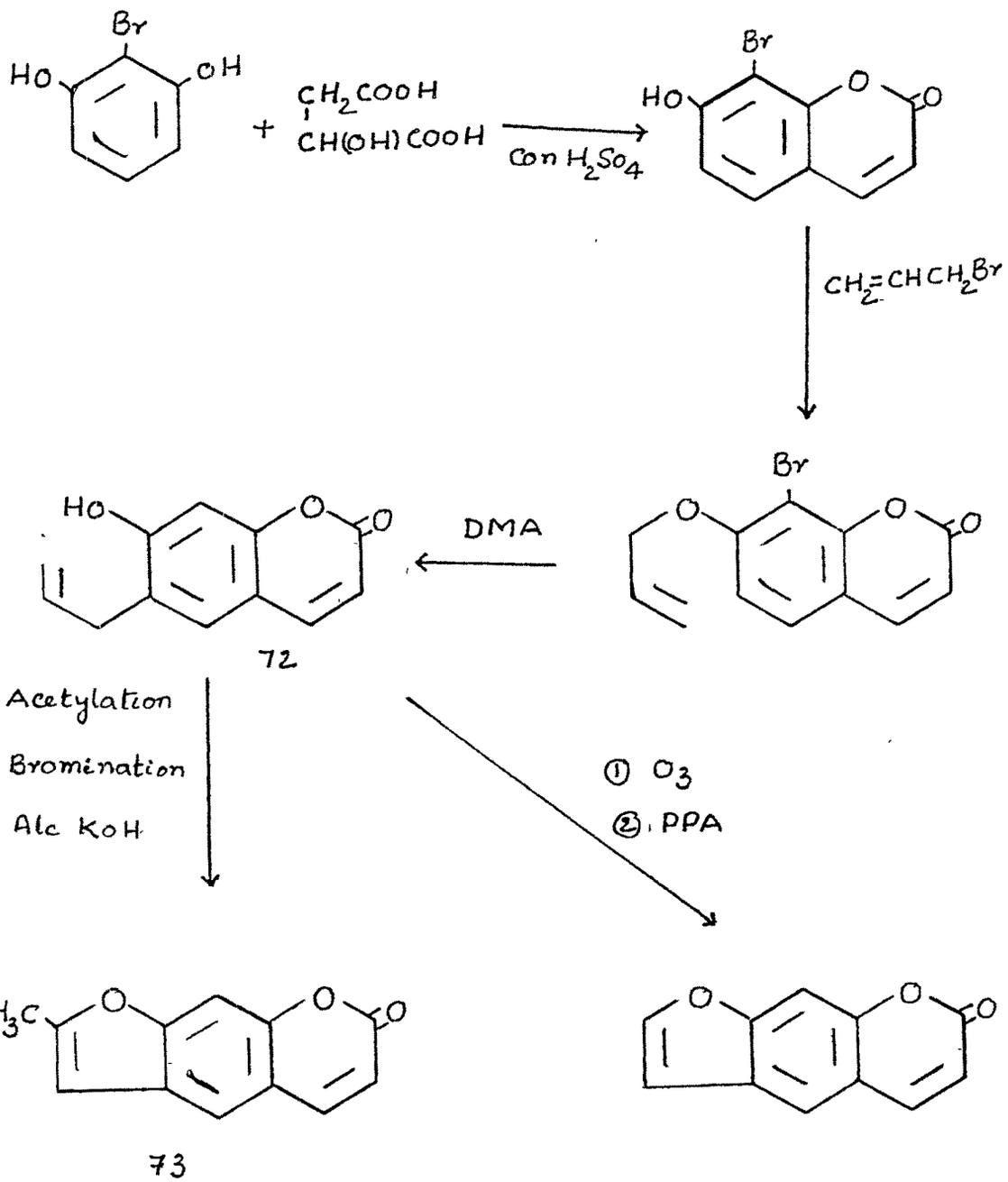
allyl bromide gave an allyloxy derivative (64). This on treatment with basic hydrogen peroxide afforded a hydroxy compound (65). (65) on methylation gave an anisole derivative (66). Claisen migration of (66) afforded an allylphenol (67), which on oxidative cleavage with OSO_4/pot. metaperiodate in a tertiary system yielded a hydroxylated dihydrofuro-coumarin (68), which looses water upon heating with formic acid yielding 3,4-cyclohexano methoxsalen (69). Dehydrogenation of (69) was achieved with Pd/c to give finally 3,4-benzomethoxasalen (70). [Scheme-17]

Pardanani and Trivedi[44] synthesised psoralen and 5'-methylpsoralen by starting with 2-bromoresorcinol which on condensation with malic acid in presene of con. H_2SO_4 gave 7-hydroxy-8-bromocoumarin. This on condensation with allylbromide followed by Claisen rearrangement gave 6-allyl-7-hydroxycoumarin (72), which on ozonolysis followed by cyclisation gave psoralen. (72) on acetylation followed by bromination and cyclisation gave 5'-methyl psoralen (73). [Scheme-18]

Pardanani and Trivedi[45] synthesised alkyl and aryl psoralen derivatives having substituents in 4,4' and 8-positions first by carrying out Pechmann condensation of 2-methyl resorcinol with ethyl benzoylacetate to get 7-hydroxy-4-phenyl-8-methylcoumarin (74), which on acetylation, followed by Fries migration afforded 7-hydroxy-6-acetyl-4-phenyl-8-methyl

SCHEME-18

Pardanani and Trivedi [44]



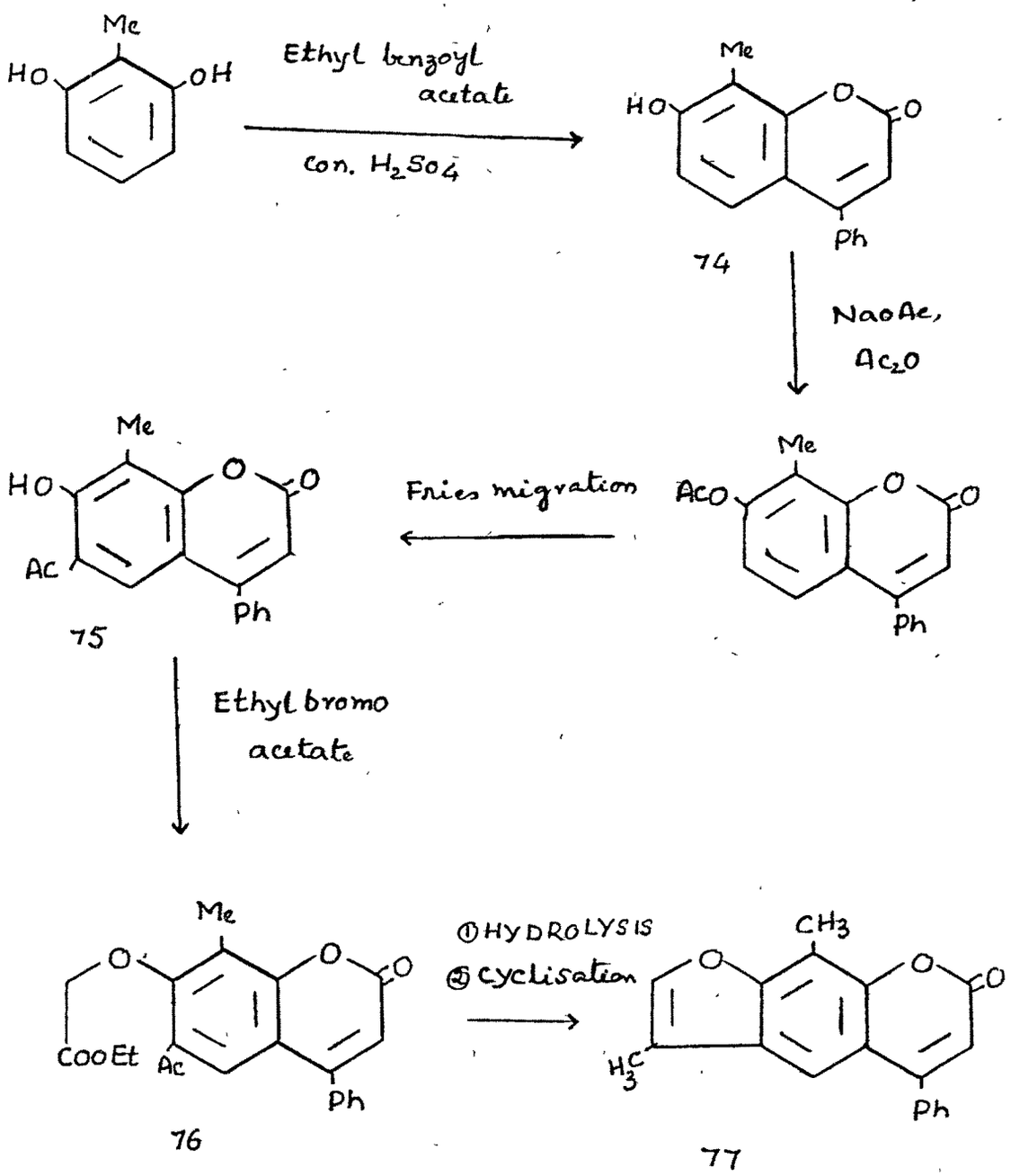
coumarin (75). This when condensed with ethylbromoacetate gave 7-coumarinyloxy acetate (76), which on hydrolysis and subsequent cyclisation with sodium acetate and acetic anhydride gave 4'-methyl-4-phenyl-8-methylpsoralen (77). Similarly 4'-ethyl-4-phenyl-8-methyl and 4,4'-diphenyl-8-methyl psoralen were synthesised from 7-hydroxy-6-propionyl-4-phenyl-8-methyl coumarin and 7-hydroxy-6-benzoyl-4-phenyl-8-methyl coumarin [Scheme-19]. Similar type of psoralens were also synthesised starting with 7-hydroxy-4,8-dimethyl coumarin. (Scheme-19)

Later Pardanani and Trivedi[46] also synthesised 5',8-dimethyl-4-phenyl psoralen by first carrying out the Claisen rearrangement of 7-allyloxy-4-phenyl-8-methyl coumarin to give 7-hydroxy-6-allyl-4-phenyl-8-methyl coumarin (78). This on treatment with con. H_2SO_4 followed by dehydrogenation with Pd/c afforded 5',8-dimethyl-4-phenyl psoralen (79). 4-Phenyl-8-methyl psoralen (80) was prepared by subjecting (78) to ozonolysis followed by cyclisation with ortho phosphoric acid [Scheme-20].

Dholakia and Trivedi[47] synthesised 4-methoxy-5',8-dimethyl psoralen and 4-hydroxy-5',8-dimethyl psoralen by first allylating 2,4-dihydroxy-3-methylacetophenone (81) with allylbromide to 4-allyloxy-2-hydroxy-3-methylacetophenone (82) which on treatment with pulverised sodium and

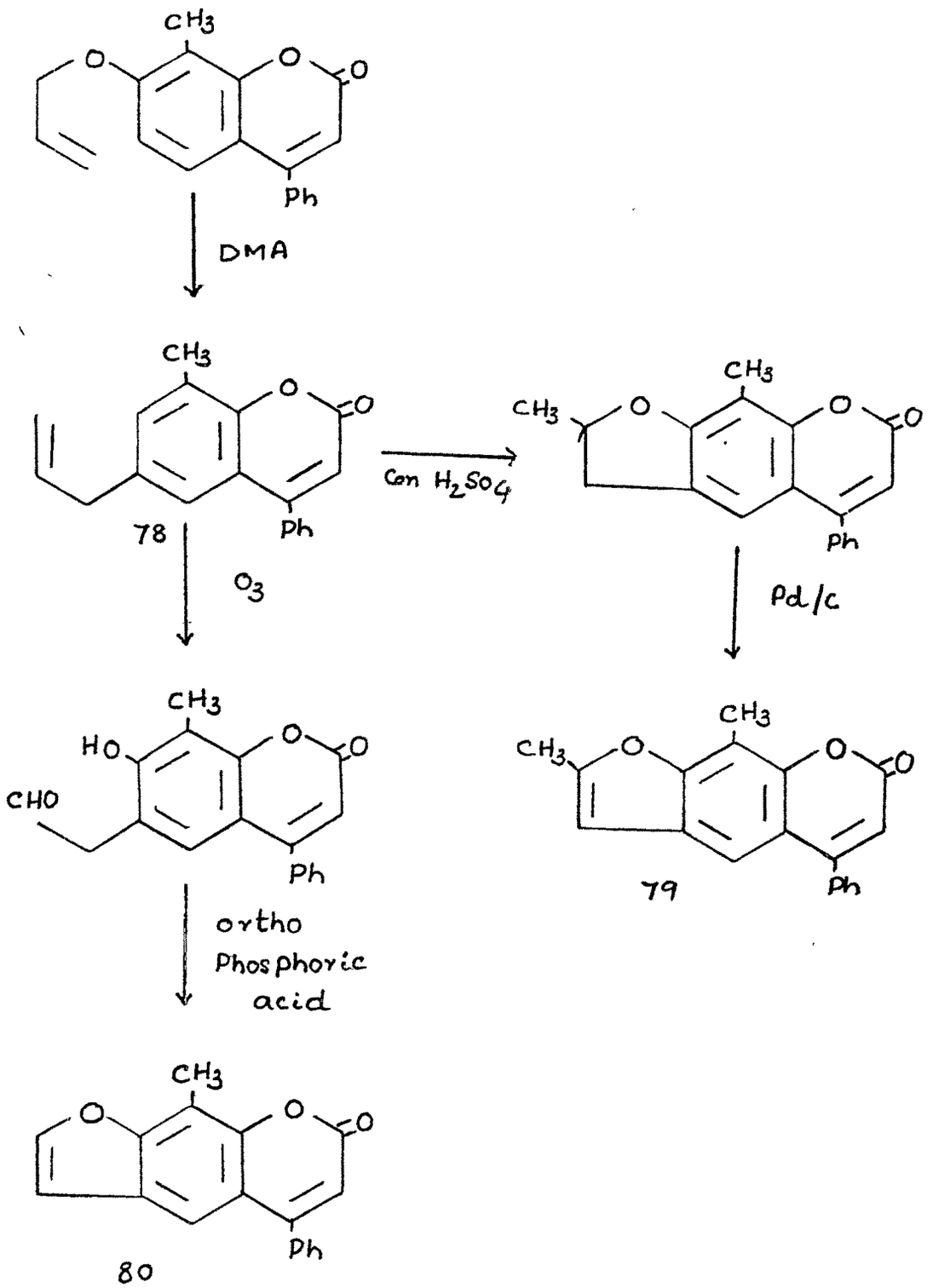
SCHEME - 19

Pardanani and Trivedi [45]



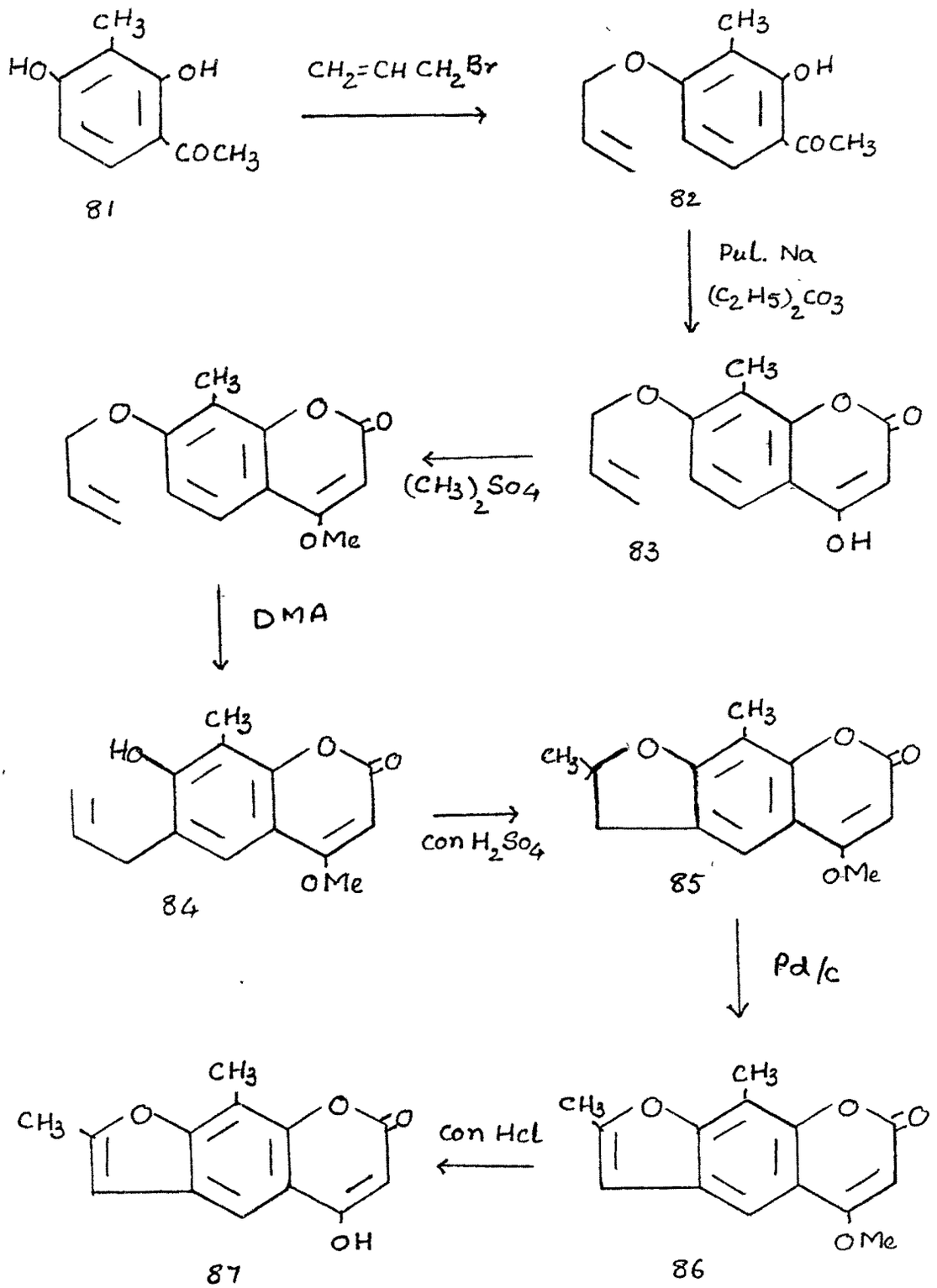
SCHEME-20

Pardanani and Trivedi [46]



SCHEME-21

Dholakia and Trivedi [47]



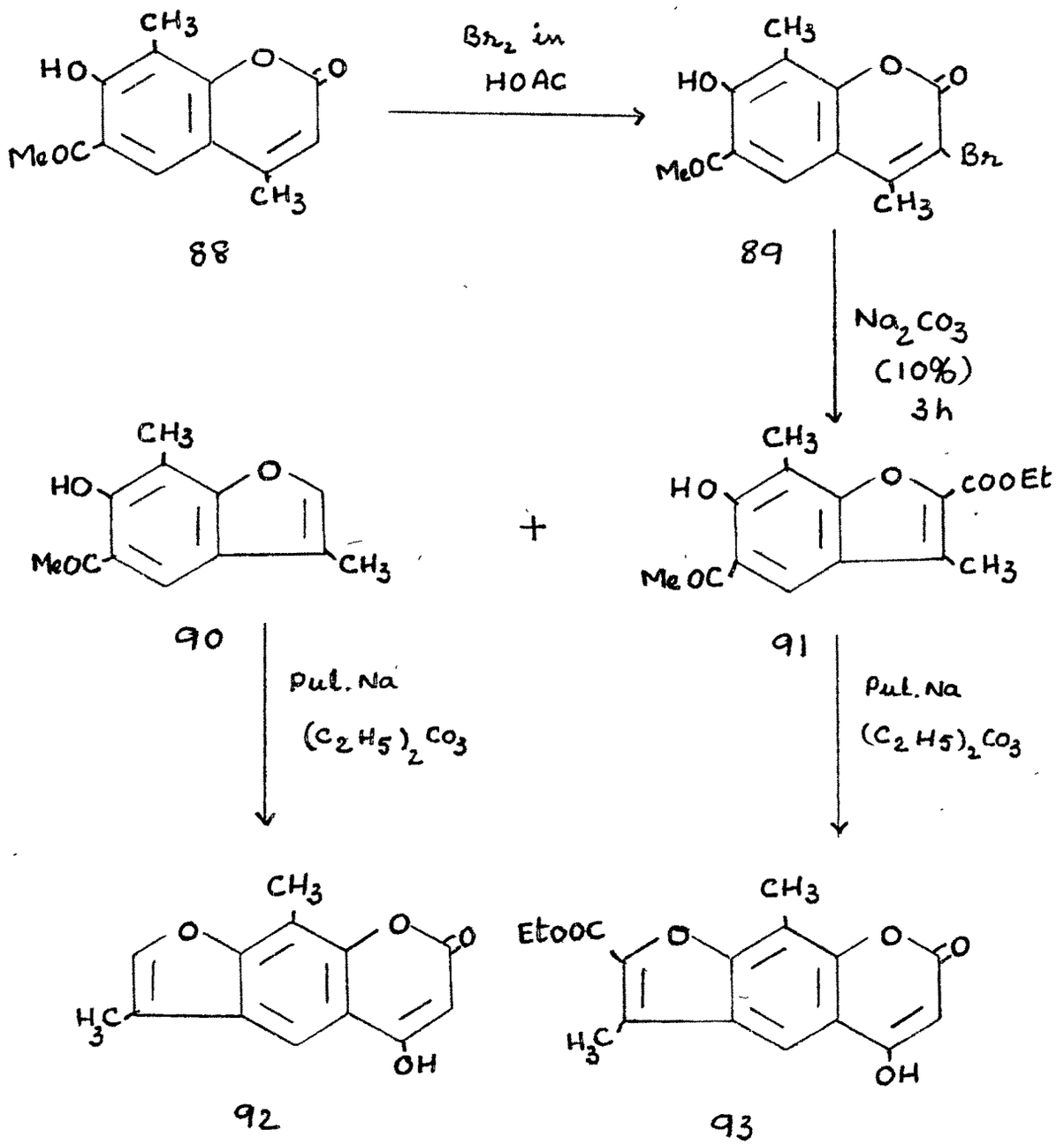
diethyl carbonate gave 4-hydroxy-7-allyloxy-8-methylcoumarin (83). This (83) was methylated and subjected to Claisen rearrangement in DMA to yield 4-methoxy-6-allyl-7-hydroxy-8-methylcoumarin (84). Cyclisation of (84) with con. H_2SO_4 gave 4-methoxy-5',8-dimethyl-4',5'-dihydropsoralen (85), which on dehydrogenation afforded 4-methoxy-5',8-dimethyl psoralen (86). 4-hydroxy-5',8-dimethyl psoralen (87) was obtained when (86) was refluxed with con. HCl. [Scheme-21].

Shaikh and Trivedi[48] also synthesised 4-hydroxy-4',8-dimethyl psoralen derivatives first by brominating the 7-hydroxy-6-acetyl-4,8-dimethyl coumarin (88) to give 3-bromo-7-hydroxy-6-acetyl-4,8-dimethylcoumarin (89) which on hydrolysis gave 6-hydroxy-5-acetyl-3,7-dimethyl benzofuran (90) and its 2-carboxylic acid derivative (91). These (90) and (91) on condensation with pulverised sodium and diethylcarbonate yielded 4-hydroxy-4',8-dimethyl psoralen (92) and 5'-carbethoxy derivative (93) respectively [Scheme-22].

Chandratre and Trivedi[49] synthesised psoralens using intramolecular Wittig reaction and observed that the yields of the psoralens were relatively better than that of the conventional methods.

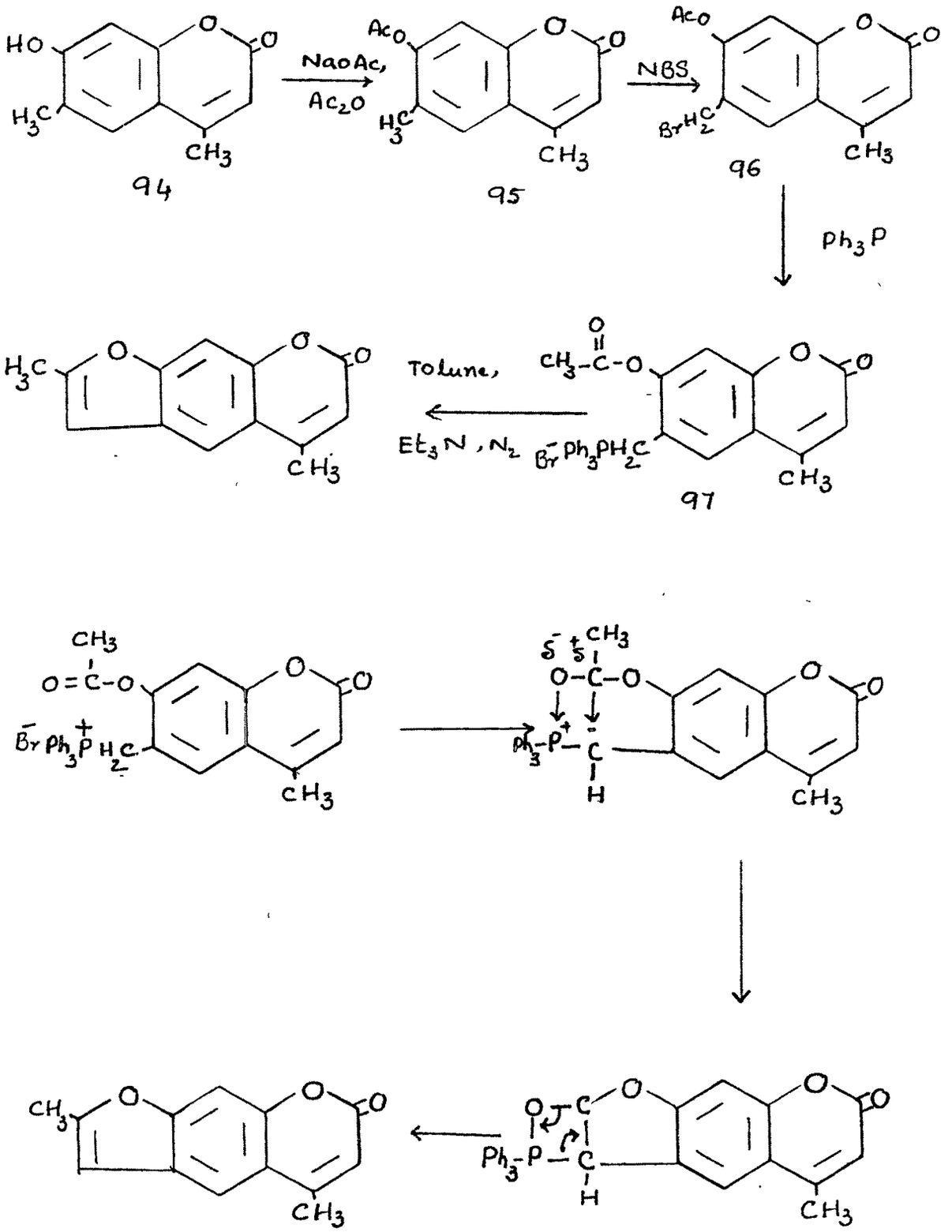
SCHEME - 22

Shaikh and Trivedi[48]



SCHEME-23

Chandratre and Trivedi



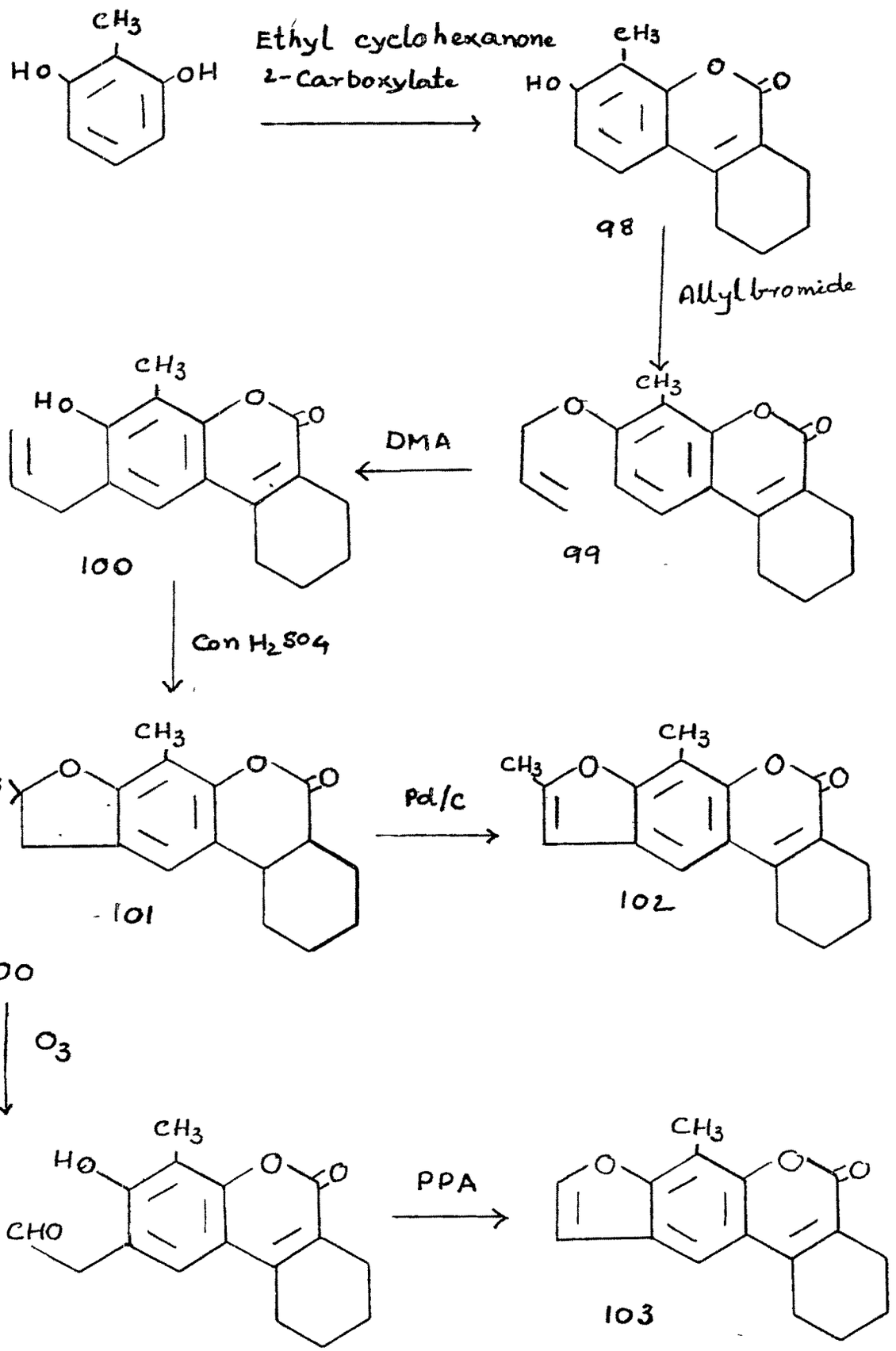
4,5'-Dimethyl psoralen was synthesised first by condensing 4-methyl resorcinol with ethylacetoacetate in presence of con. H_2SO_4 to give 4,6-dimethyl-7-hydroxy coumarin (94), which on acetylation with sodium acetate and acetic anhydride gave 7-acetoxy-4,6-dimethyl coumarin (95). (95) on reaction with N-bromosucinimide in CCl_4 gave 7-acetoxy 6-bromomethyl-4-methyl coumarin (96) which gives a phosphenium salt (97) when it reacts with triphenyl phosphine in dry benzene. (97) underwent Wittig reaction in the presence of triethylamine using nitrogen atmosphere to give 4,5'-dimethylpsoralen [Scheme-23].

Similarly 4-methyl-5'-phenyl psoralen was synthesised by first carrying out benzoylation of 4,6-dimethyl-7-hydroxy coumarin followed by bromination with NBS and intramolecular Wittig reaction.

Shaikh and Trivedi[50] synthesised monofunctional psoralens 3,4-benzopsoralen and 3,4-cyclohexano psoralen by condensing 2-methyl resorcinol with ethylcyclohexanone-2-carboxylate to give a tricyclic coumarin (98) which on allylation gave 7-allyloxy-8-methyl-3,4-cyclohexanocoumarin (99). This on Claisen migration gave 6-allylisomer (100) followed by cyclisation with con. H_2SO_4 afforded dihydrocyclohexano-coumarin (101). Dehydrogenation of (101) with Pd/c in DPE gave the 3,4-benzopsoralen (102). The product (100) on

SCHEME - 24

Shaikh and Trivedi[50]



treatment with OSO_4 and periodate followed by cyclisation with PPA gave 3,4-cyclohexano psoralen (103) [Scheme-24].

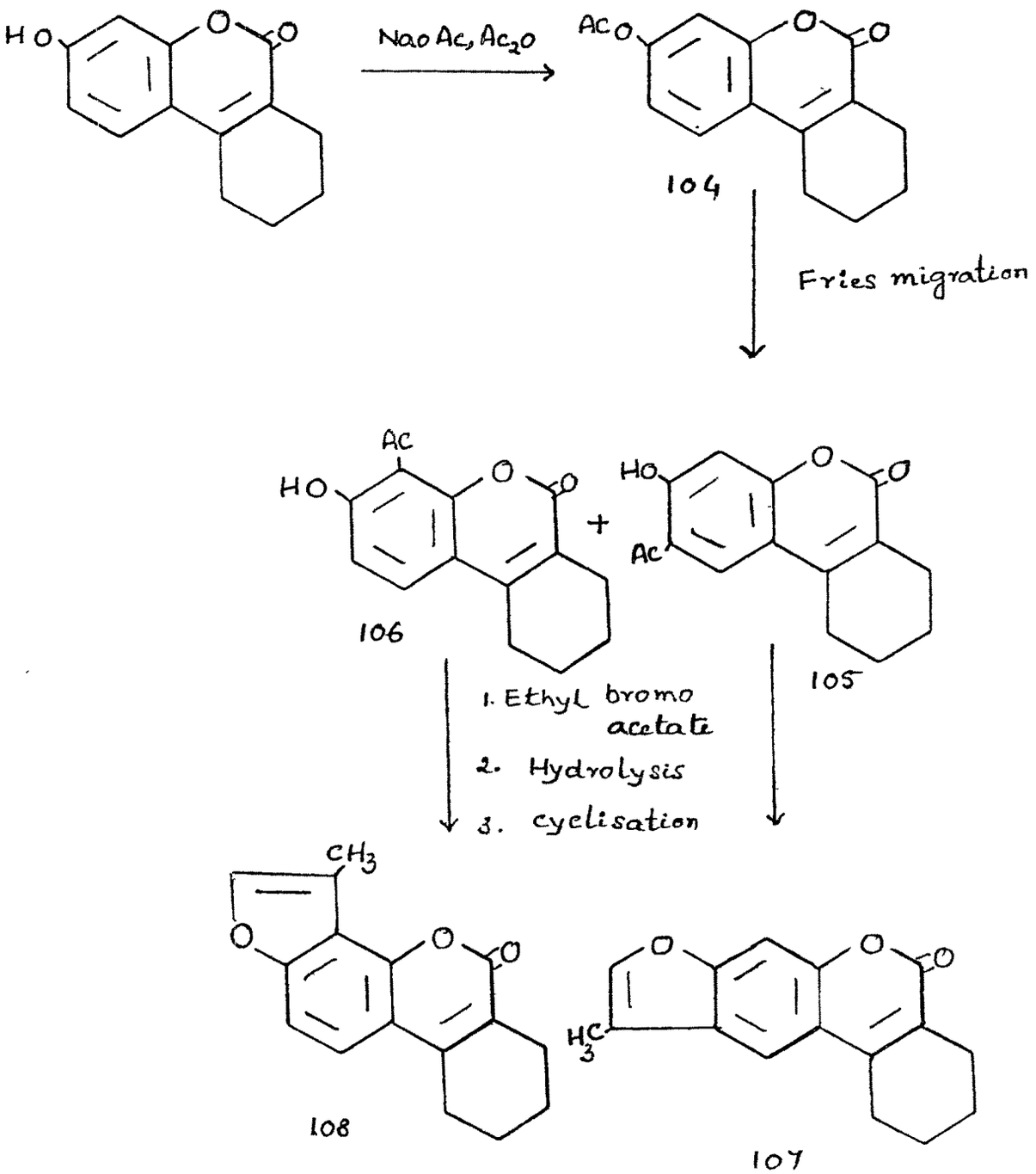
Shaikh and Trivedi also synthesised 3,4-cyclopentano-psoralen by first condensing 2-methyl resorcinol with ethyl cyclopentanone-2-carboxylate followed by allylation, migration, cyclisation and dehydrogenation as described earlier.

Parekh and Trivedi[51] synthesised the monofunctional psoralen 3,4-cyclohexanopsoralen and 3,4-cyclohexanoangelicin by first starting with 7-hydroxy-3,4-cyclohexanocoumarin, which on acetylation gave its acetoxy derivative (104). Fries migration of (104) gave two isomers 6-acetyl-3,4-cyclohexano-7-hydroxy coumarin (105) and 8-acetyl-3,4-cyclohexano-7-hydroxy coumarin (106). Both (105) and (106) on condensation with ethylbromoacetate followed by hydrolysis and cyclisation gave 4'-methyl-3,4-cyclohexano psoralen (107) and 4'-methyl-3,4-cyclohexano angelicin (108) [Scheme-25].

Later Shah and Trivedi[52] synthesised, 3,4-cyclohexano psoralen by condensing 2-bromoresorcinol with ethyl cyclohexanone-2-carboxylate to obtain the bromo substituted coumarin (109) which on allylation gave 7-allyloxy-8-bromo-3,4-cyclohexano coumarin (110). (110) on Claisen migration in DMA

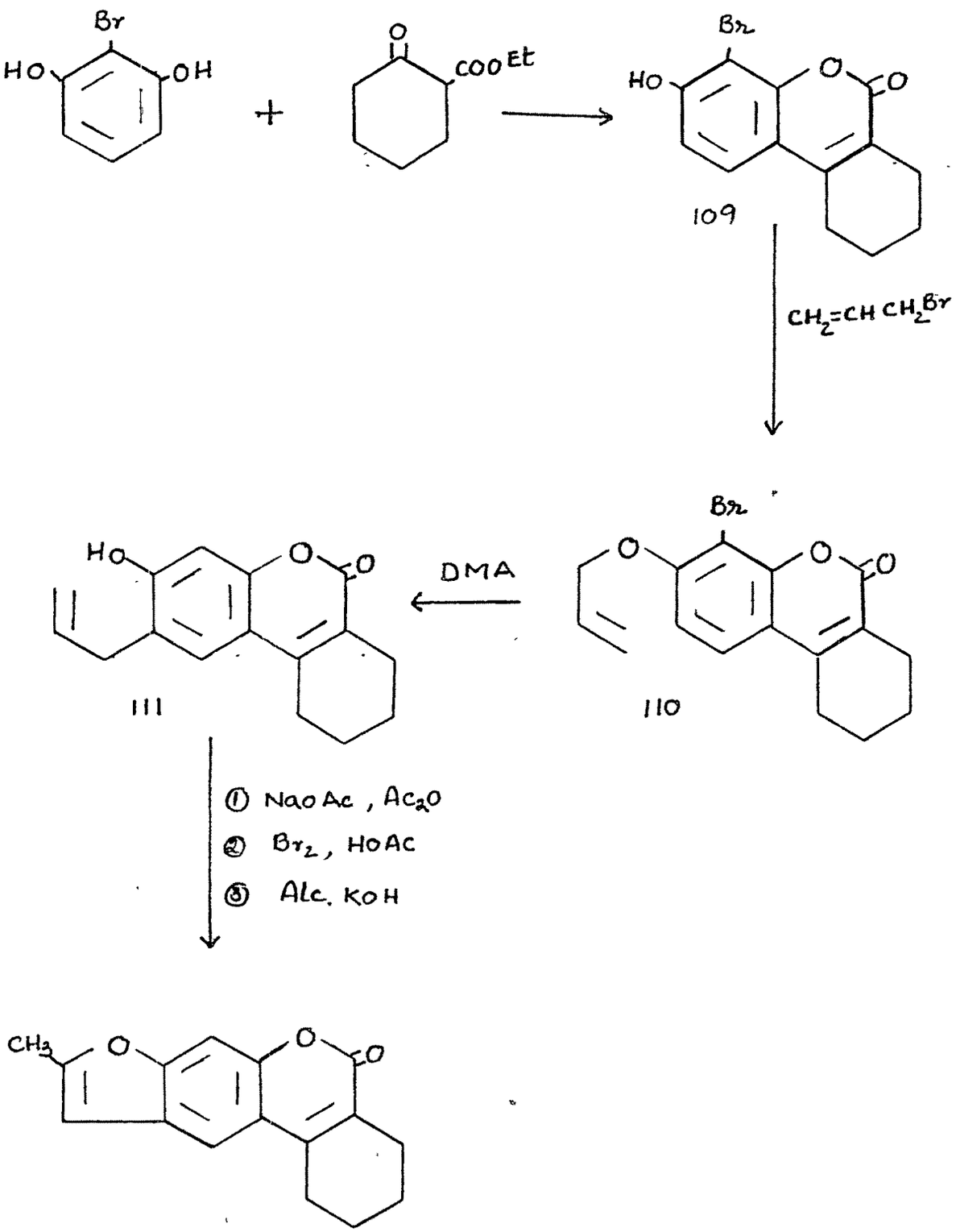
SCHEME-25

Parekh and Trivedi[51]



SCHEME-26

Shah and Trivedi[52]



eliminated the bromine and gave 7-hydroxy-6-allyl-3,4-cyclo-hexano coumarin (111). (111) on actylation with sodium acetate and acetic anhydride followed by bromination and treatment with alcoholic KOH afforded 3,4-cyclohexano-psoralen [Scheme-26].

Desai and Trivedi[53] synthesised 3,4-diphenyl psoralen by carrying out the Claisen migration of 7-allyloxy-8-bromo-3,4-diphenylcoumarin (112) followed by acetylation, bromination and subsequent cyclisation with alcoholic KOH to obtain the 5'-methyl-3,4-diphenyl psoralen (113) [Scheme-27].

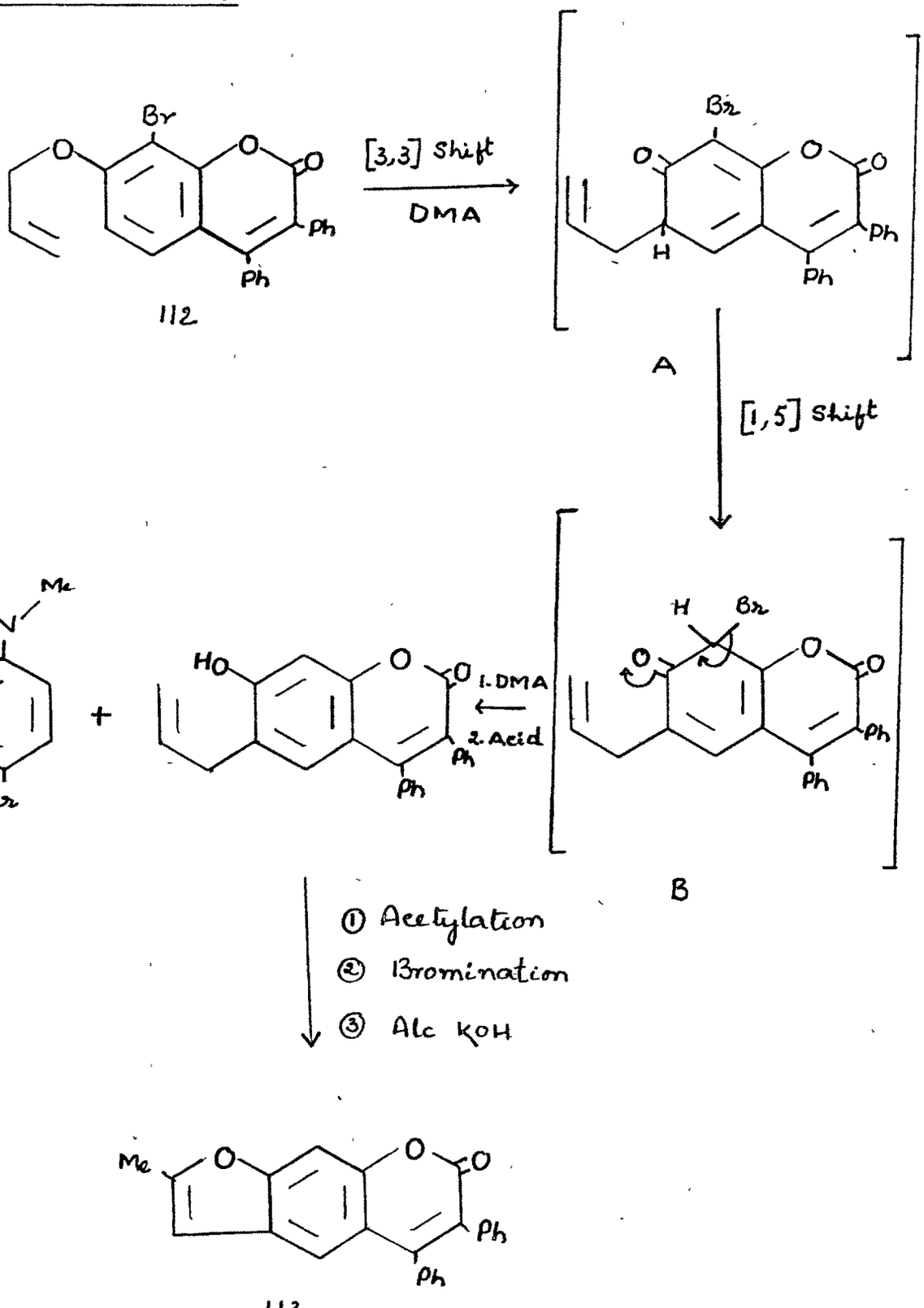
MECHANISM OF THE FORMATION OF 7-HYDROXY-6-ALLYLCOUMARIN DERIVATIVE

7-Allyloxy-8-bromo-3,4-diphenyl coumarin undergoes Claisen rearrangement by (3,3) shift in 6th position to give intermediate (A) which further undergoes(1,5) proton shift to give (B). This in presence of DMA eliminates bromine and finally on acidification forms 6-allyl-7-hydroxy-3,4-diphenylcoumarin, p-bromodimethylaniline being isolated as a side product.

Desai and Trivedi[54] also synthesised purely monofunctional benzofurobenzopyran from 7-hydroxy-4-methyl coumarin condensing first with 2-bromo-cyclohexanone to give 7-(cyclo-

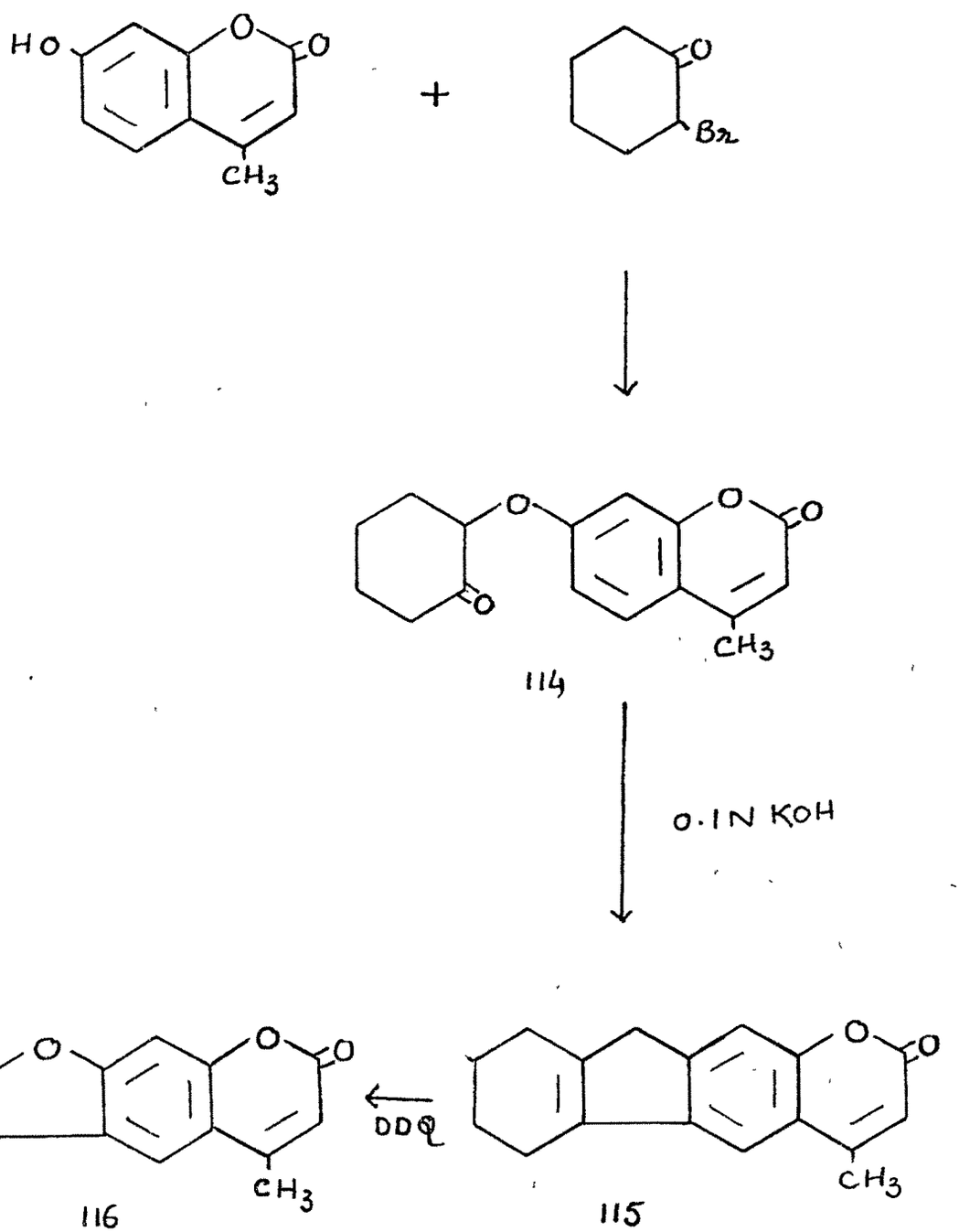
SCHEME-27

Desai and Trivedi[53]



SCHEME - 28

Desai and Trivedi [54]



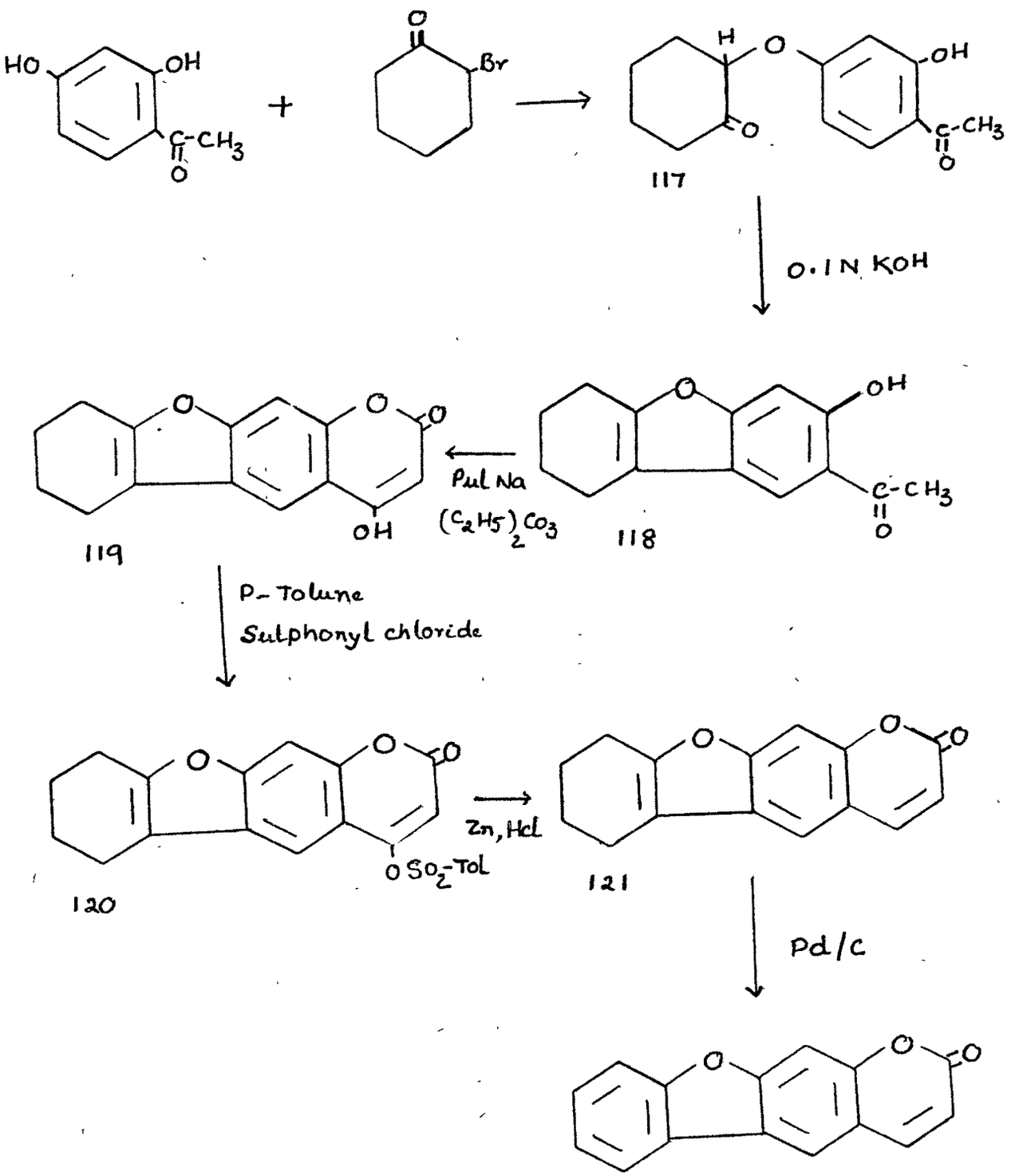
hexan-2-onyloxy)-4-methyl coumarin (114). (114) on cyclisation with alkali furnished 6,7,8,9-tetrahydro-4-methyl-2-oxo-2H-benzofuro(3,2-g)benzopyran (115). This on dehydrogenation with DDQ in drybenzene gave benzofuro(3,2-g)benzopyran (116) [Scheme-28].

Chandratre and Trivedi[55] have also synthesised monofunctional psoralen, 2-oxo-2H-benzofuro(3,2-g)benzopyran bya different route. 2,4-Dihydroxy acetophenone on condensation with 2-bromo cyclohexanone in presence of K_2CO_3 and dry acetone gave 4-cyclohexan-2-onyloxy-2-hydroxy acetophenone (117). This oncyclisation with O.1N KOH gave 5,6,7,8-tetrahydro-2-hydroxy-3-acetyl-dibenzofuran (118) which on condensation with diethyl carbonate in presence of pulverised sodium gave 4-hydroxy-6,7,8,9-tetrahydrobenzofuro(3,2-g) benzopyran-2(H)-one (119). Condensation of the compound with p-toluenesulphonyl chloride in presence of K_2CO_3 in dry acetone gave 6,7,8,9-tetrahydro-4-p-tosyloxy-2-oxo-2H-benzofuro(3,2-g)benzopyran (12O). Reductive detosyloxylation of the compound (12O) by zinc and HCl gave 6,7,8,9-tetrahydro-2-oxo-2H-benzofuro(3,2-g)benzopyran (121). Benzofuro(3,2-g) benzopyran was obtained by dehydrogenation of (121) with palladised charcoal (10%) in diphenyl ether [Scheme-29].

In the recent years alkyl angelicins and its derivatives are used as monofunctional furocoumarins for photochemo-

SCHEME - 29

Chandratre and Trivedi[55]



therapy as the structure of angelicin is angular in nature and does not allow the formation of crosslinkages with DNA.

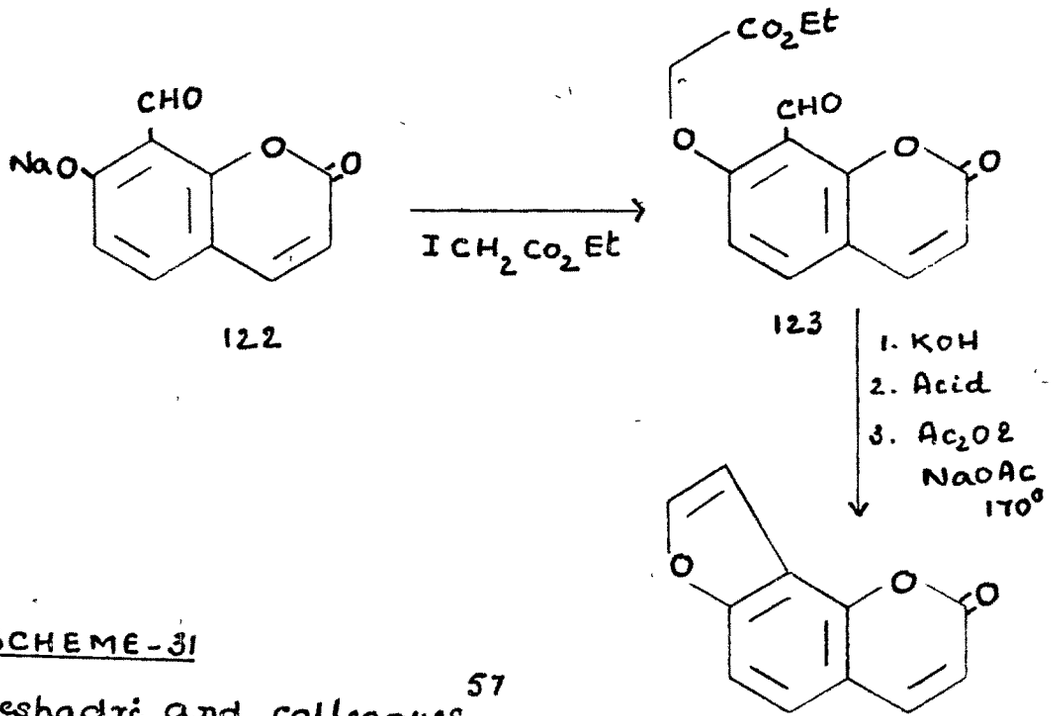
Angelicin is also a naturally occurring furocoumarin and was synthesised first by Spath and Pailer[56] by condensing sodium salt of 8-formyl umbelliferone (122) with iodoacetic ester followed by decarboxylative cyclisation of the phenoxy acetic acid (123) with sodium acetate and acetic anhydride to obtain angelicin, however the yields reported were poor. [Scheme-30]

Seshadri and his colleagues[57] synthesised angelicin in good yield from Claisen rearrangement of 7-alyloxy coumarin (124) which gave 8-allylcoumarin (125). Ozonolysis of 8-allylcoumarin followed by cyclisation with PPA gave the angelicin. [Scheme-31]

Guiotto and coworkers[58] synthesised a series of 6-methyl angelicins carrying a methyl group at 5'-position and without methyl group at 5' position on furan ring by carrying out Claisen migration of 7-allyloxy-4,6-dimethyl-coumarin, 7-allyloxy-5,6-dimethyl coumarin and 7-allyloxy-6-methyl coumarin followed by acetylation and bromination of the 8-allyl coumarin (126) to give corresponding 8-dibromo-propyl derivative. This on cyclisation in alcoholic KOH yielded 5'-methyl angelicins (127).

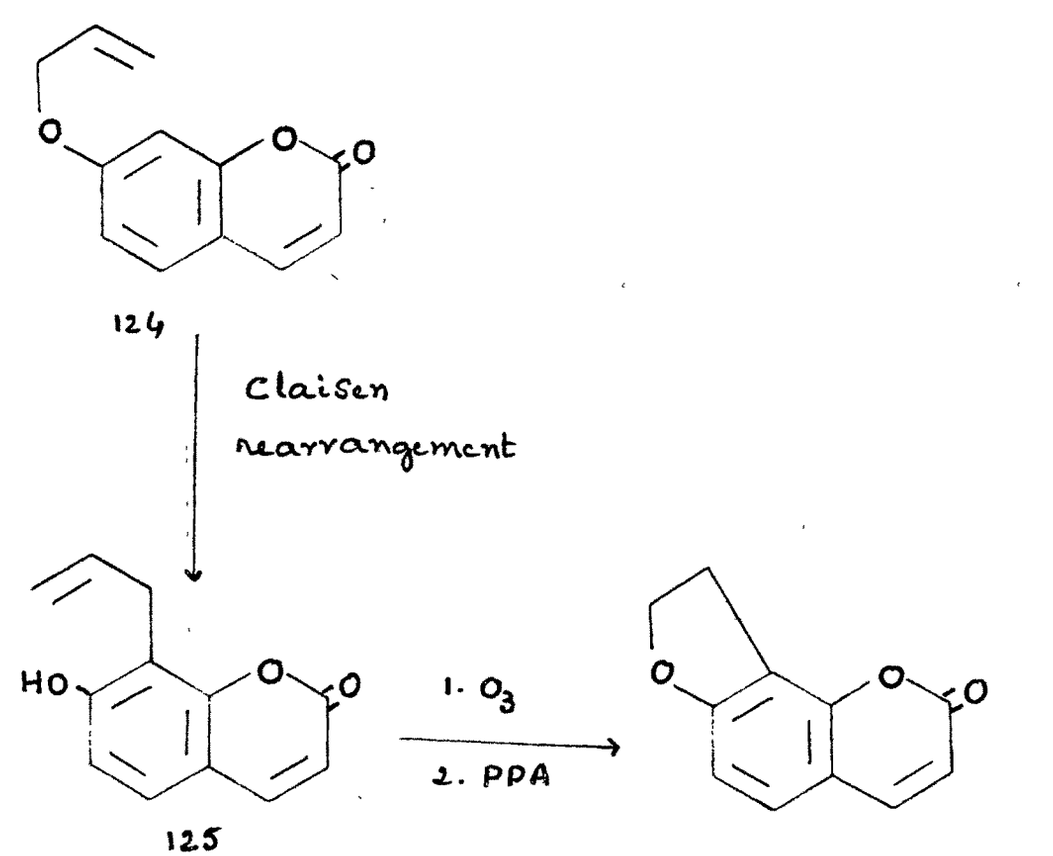
SCHEME-30

Spath and Pailer[56]



SCHEME-31

Seshadri and colleagues[57]



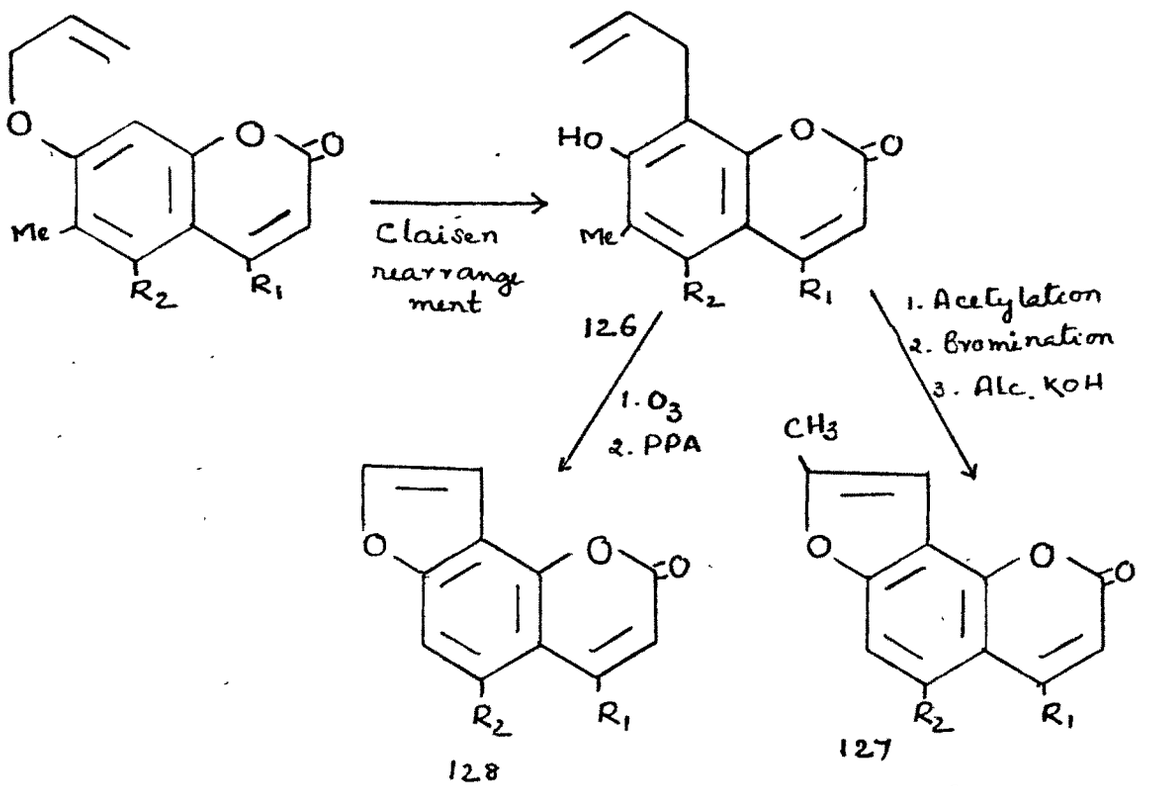
6-Methylangelicins (128) without a methyl group on the furand ring were obtained by cyclisation with phosphoric acid of the 8-coumarinyl acetaldehyde, obtained by ozonolysis of the 8-allylumbelliferone. [Scheme-32] Here the methyl group at 6th position is important so that during migration, there would not be any possibility of forming a linear isomer which subsequently leads to the formation of methyl psoralens which are very effective in inducing the bifunctional photolesions. These 6-methyl-angelicins were observed to show high affinity toward DNA, forming only monoadducts.

Baccichetti and coworkers[59] prepared 4,4',6-trimethyl angelicin, a new monofunctional and a very promising potential agent for the photochemotherapy of psoriasis and reported that it photo-reacts with DNA four times faster than 8-MOP, forming only monoadducts. 4,4',6-Trimethyl angelicin was prepared first by acetylating the 4,6-dimethyl umbelliferone. The acetoxy compound (129) on Fries migration affords 8-acetyl-7-hydroxy-4,6-dimethyl umbelliferone (130) which on treatment with ethyl bromoacetate gave an acetate (131). This gives subsequently an acid on hydrolysis. Title compound 4,4'-6-trimethyl psoralen (132) was obtained by cyclising the free acid accompanied by decarboxylation. [Scheme-33]

Pardanani and Trivedi[60] also synthesised several angelicin derivatives by carrying out the Claisen migration of 7-allyloxy-

SCHEME-32

Guiotta and coworkers[58]



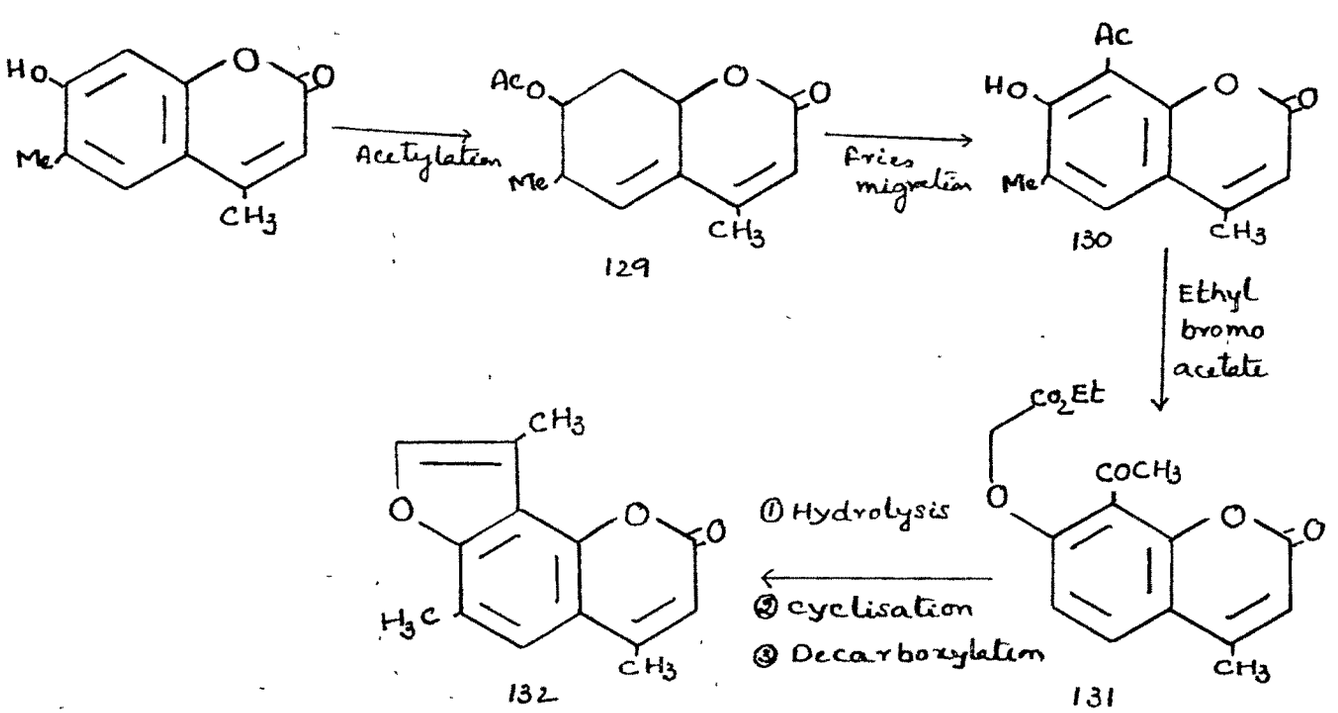
a $R_1 = CH_3$ $R_2 = H$

b $R_1 = H$ $R_2 = CH_3$

c $R_1 = R_2 = H$

SCHEME-33

Baccichette and coworkers[59]



3-phenylcoumarin (133), 7-allyloxy-4-methyl coumarin (134) followed by cyclisation with H_2SO_4 and dehydrogenation with Pd/c to obtain 5'-methyl-3-phenyl psoralen (135) and 5'-methyl-4-methyl psoralen (136). 3-Phenyl psoralen (137) and 4-methyl psoralen (138) were also prepared subjecting the migrated product to ozonolysis followed by cyclisation with orthophosphoric acid [Scheme-34].

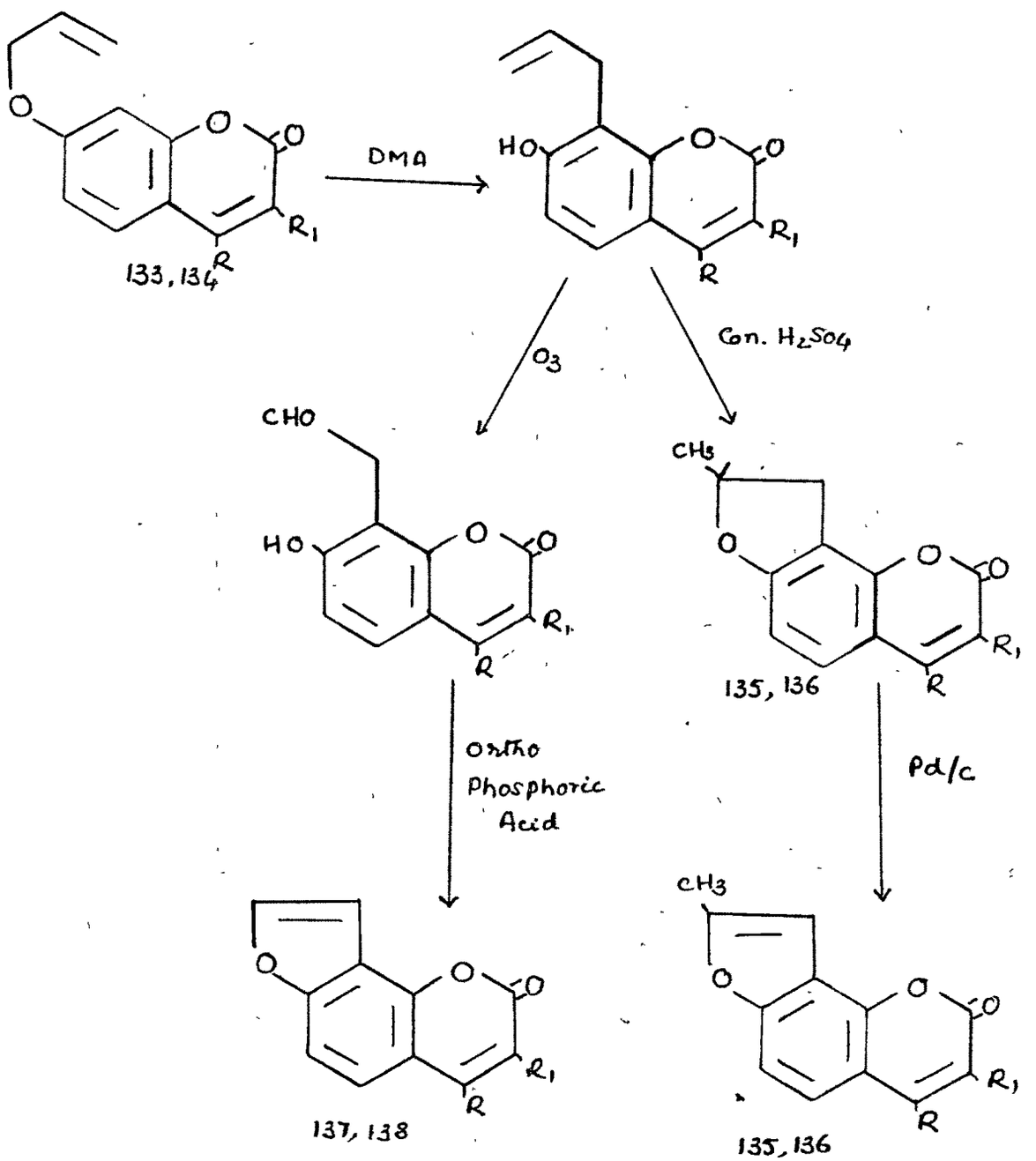
Chandratre and Trivedi[61] synthesised angelicin derivatives also using intramolecular Wittig reaction.

4,5'-Dimethyl angelicin was synthesised first by condensing 2-methylresorcinol with ethyl acetoacetate in con. H_2SO_4 to give 4,8-dimethyl-7-hydroxy coumarin (139) which on acetylation followed by bromination with N-bromosuccinimide in CCl_4 gave 7-acetoxy-8-bromomethyl-4-methylcoumarin (140). This (140) gives a phosphonium salt (141) when it reacts with triphenyl phosphine in dry benzene. (141) undergoes Wittig reaction in presence of triethylamine, nitrogen atmosphere to give 4,5'-dimethyl angelicin [Scheme-35].

4-Methyl-5'-phenyl angelicin was prepared by benzoylation of 4,8-dimethyl-7-hydroxy coumarin followed by bromination with NBS and intramolecular Wittig reaction.

SCHEME-34

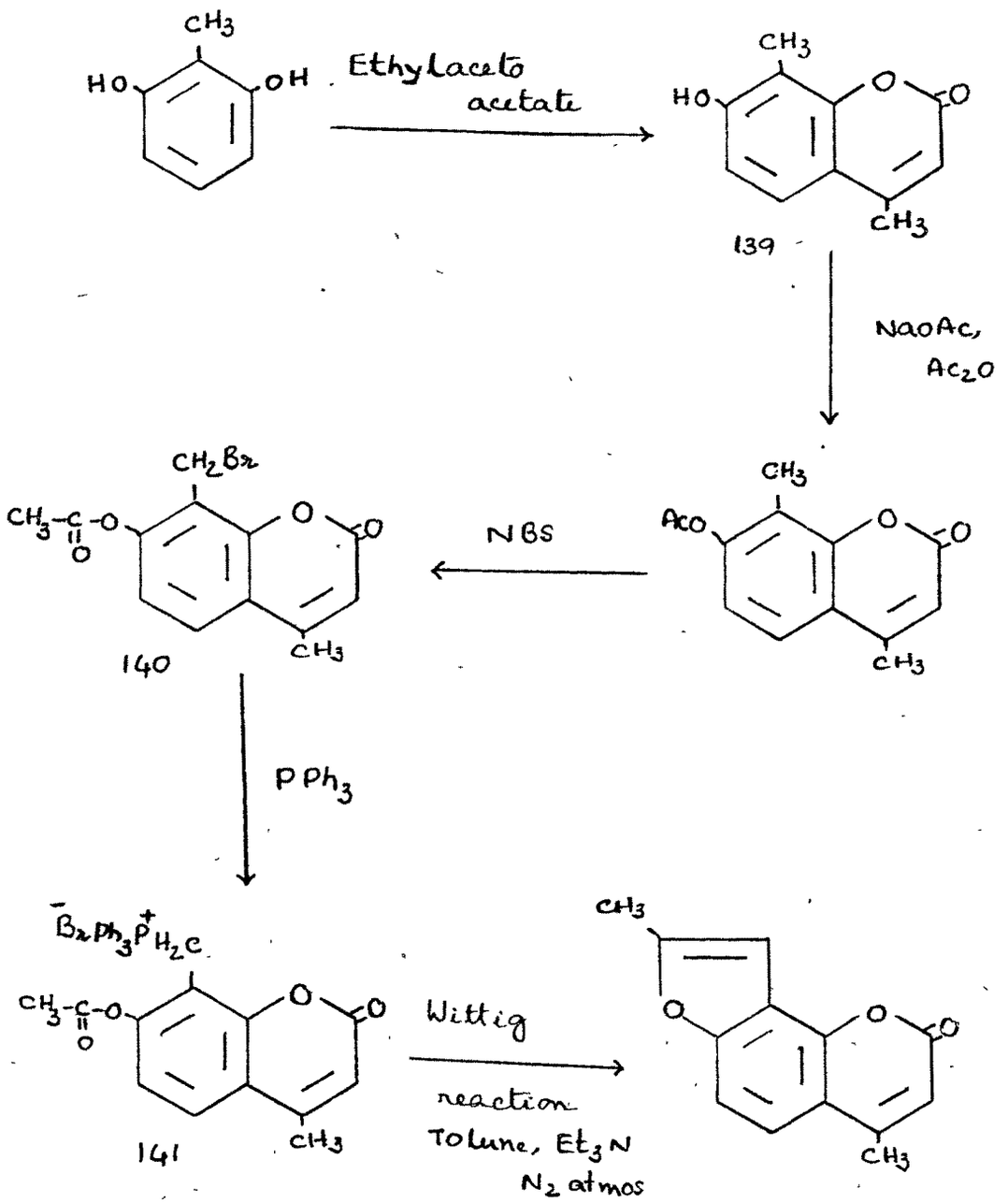
Pardanani and Trivedi[60]



	R	R'
135	H	Ph
136	CH_3	H
137	H	Ph
138	CH_3	H

Scheme – 35

Chandratre and Trivedi



PRESENT WORK

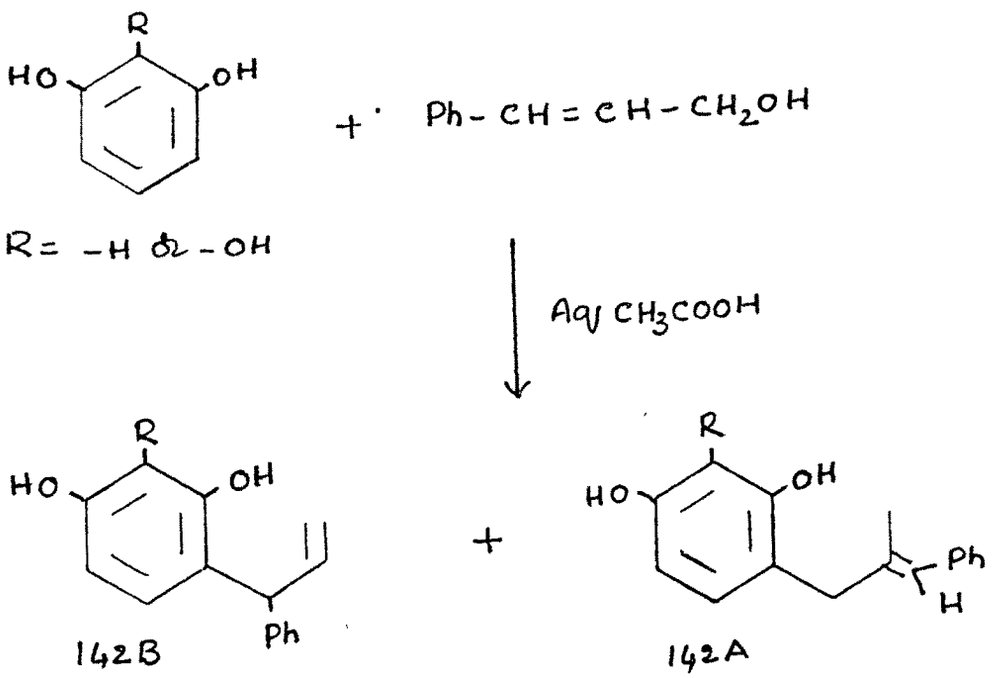
The presence of cinnamyl unit in various forms is found in many naturally occurring polyphenolics. The introduction of cinnamylunit in a polyphenol can be brought in two ways. First method is a direct cinnamylation of phenols with cinnamyl alcohol in the presence of aqueous organic acid such as acetic acid, formic acid etc. Jurd[62] carried out the cinnamylation of phenols such as resorcinol, pyrogallol etc. and obtained benzyl styrene derivatives (142-A, 142-B) [Scheme-36].

The second method involves the o-cinnamylation of polyphenol with cinnamylbromide or chloride in presence of potassium carbonate followed by Claisen migration. Schmid and coworkers[63] carried out a detailed study of Claisen rearrangement of 3'-(aryl substituted) allyl phenol (143) in diethylaniline. 2-(1'-arylallyl)phenols (144) thus obtained are transformed on heating in $PhNEt_2$ into trans-2-aryl-3-methyl coumarans (145) in excellent yields. The same when refluxed under acidic conditions (HBr + HoAc) gave a mixture of 3-aryl-2-methyl coumaran (146), 2-aryl-3-methylcoumaran (147), 2-aryl-2-methyl coumaran (147A) [Scheme-37].

The present work deals with the Claisen rearrangement of 7-cinnamyloxy coumarin and itsderivatives to obtain cinna-

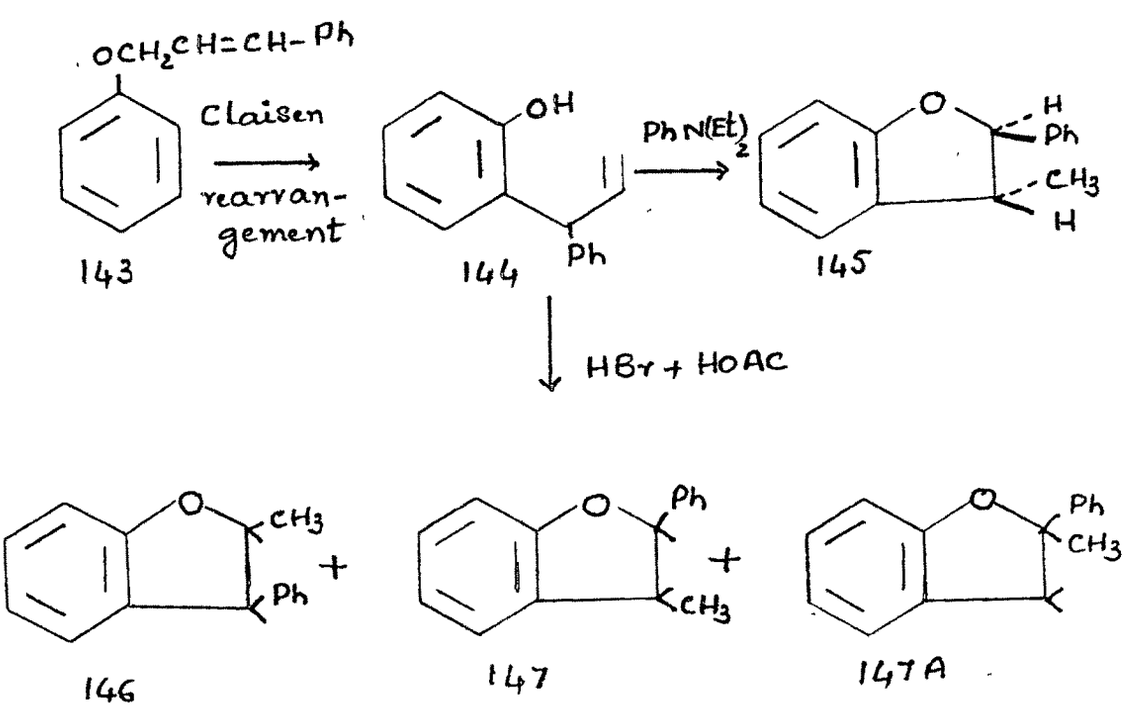
SCHEME-36

Jurd et al[62]



SCHEME-37

Schmid et al[63]



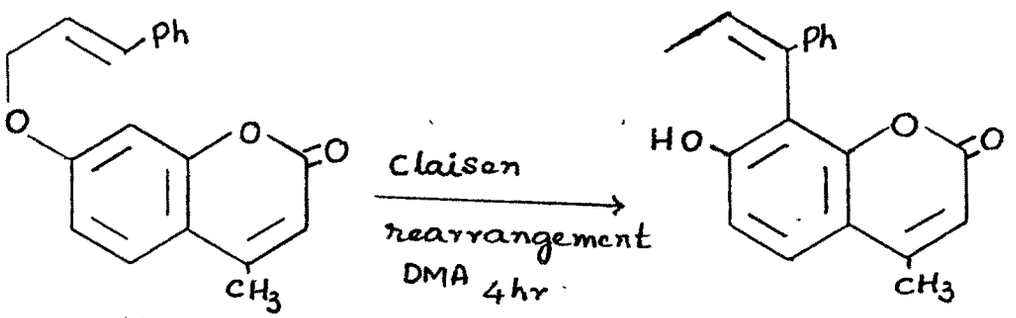
mylcoumarins and their conversion to dihydrofurocoumarins followed by their dehydrogenation to furocoumarins.

Jain and Tuli[64] studied the Claisen rearrangement of 7-cinnamyloxy-4-methylcoumarin (148) and obtained single product 7-hydroxy-4-methyl-8-(1'-phenyl-prop-1'-ene) coumarin (149) m.p. 222-223° when refluxed with DMA for 4 hr. [Scheme-38].

Ahluwalia and coworkers[65] also studied the Claisen rearrangement of the same 7-cinnamyloxy-4-methyl(148) by refluxing it in N,N-dimethylaniline for 24 hr. They isolated two products, one alkali soluble m.p. 223-24°, it was assigned 7-hydroxy-4-methyl-8-(1'-phenylprop-1'-ene)coumarin (149) and the second alkali insoluble product m.p. 230-32° and it was assigned the linear furocoumarin structure as either 4,4'-dimethyl-5'-phenylfuro(2',3':6,7)coumarin (150) or 4,5'-dimethyl-4'-phenylfuro(2',3':6,7)coumarin (151) (Scheme-39] and the former being preferred on the basis of mechanism of migration and on the PMR studies which showed signals at δ 2.42 a doublet J=1.5Hz for three methyl protons at C-4, a singlet at δ 2.51 for three methyl protons at C-4', a quintet at δ 6.18 for vinylic proton at C-3, a broad singlet at δ 7.42 for two aromatic protons at C-5 and C-8 and a singlet at δ 7.50 for five phenyl protons at C-5';

SCHEME - 38

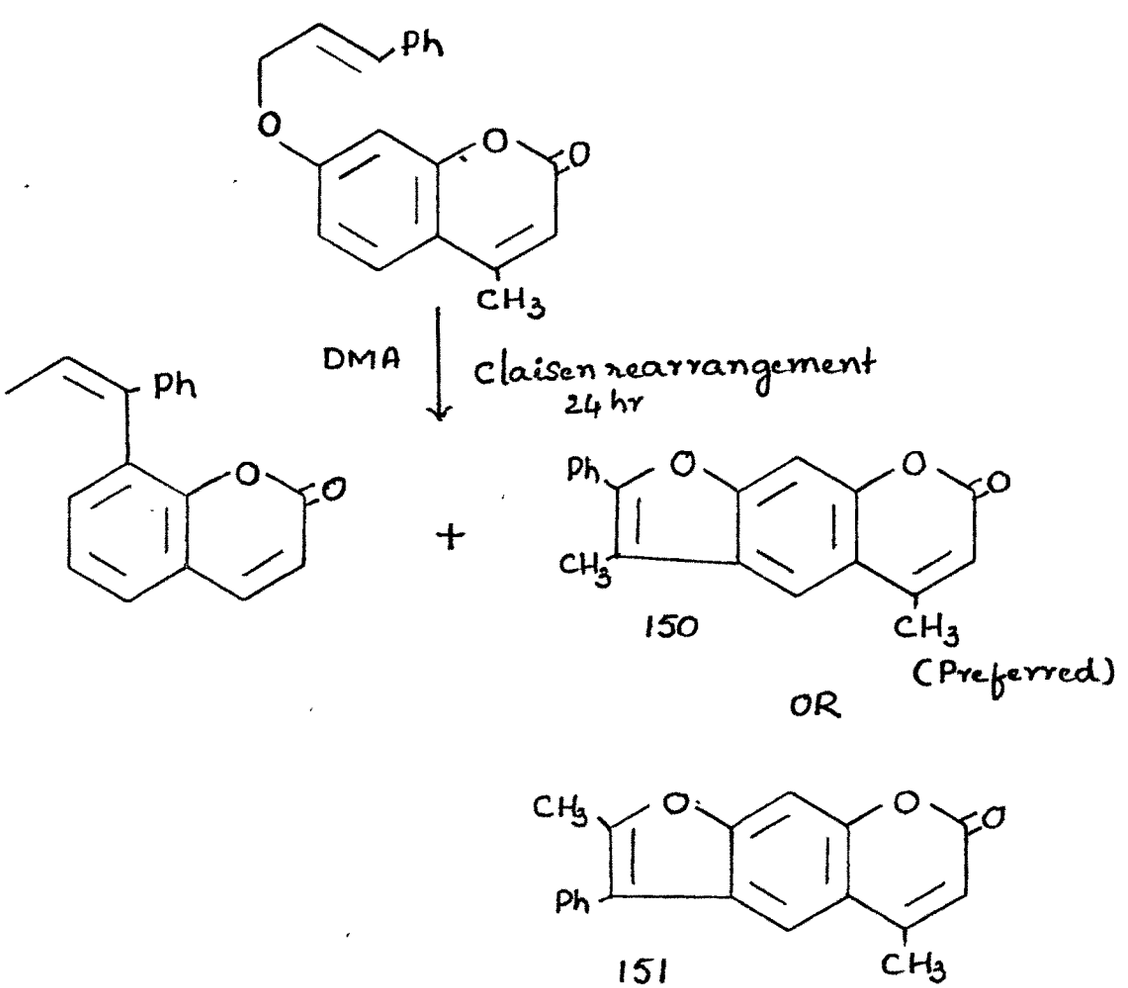
Jain and Tuli [64]



148 149

SCHEME - 39

Ahluwalia et al [65]



The formation of the product (150) having linearly fused furan ring system has created doubts because of the following reasons which could not be answered, (i) it is against the regiospecificity of 7-hydroxy coumarin ring system which normally directs the incoming group to 8-position. (ii) the chemical shift of C_5-H and C_8-H as broad singlet at 7.4 in the PMR spectrum is not consistent with the structure, as the chemical shift of C_5-H and C_8-H in coumarin is separated by at least 0.4 (iii) finally during the Claisen rearrangement, the compound has undergone migration to C-6 position followed by cyclisation and dehydrogenation in a single step. The final step of dehydrogenation is very uncommon in the absence of any driving force in the reaction.

CINNAMYLATION OF 7-HYDROXY-4-METHYLCOUMARIN

In view of the work carried out by Ahluwalia and coworkers, which has developed doubts in the formation of linear furocoumarin, it was thought of interest to reinvestigate the Claisen rearrangement of 7-cinnamyloxy-4-methyl coumarin (148) systematically and to establish the mechanism and structure of the final products obtained in this rearrangement.

7-Hydroxy-4-methylcoumarin was condensed with cinnamylchloride in the presence of fused K_2CO_3 in dry acetone

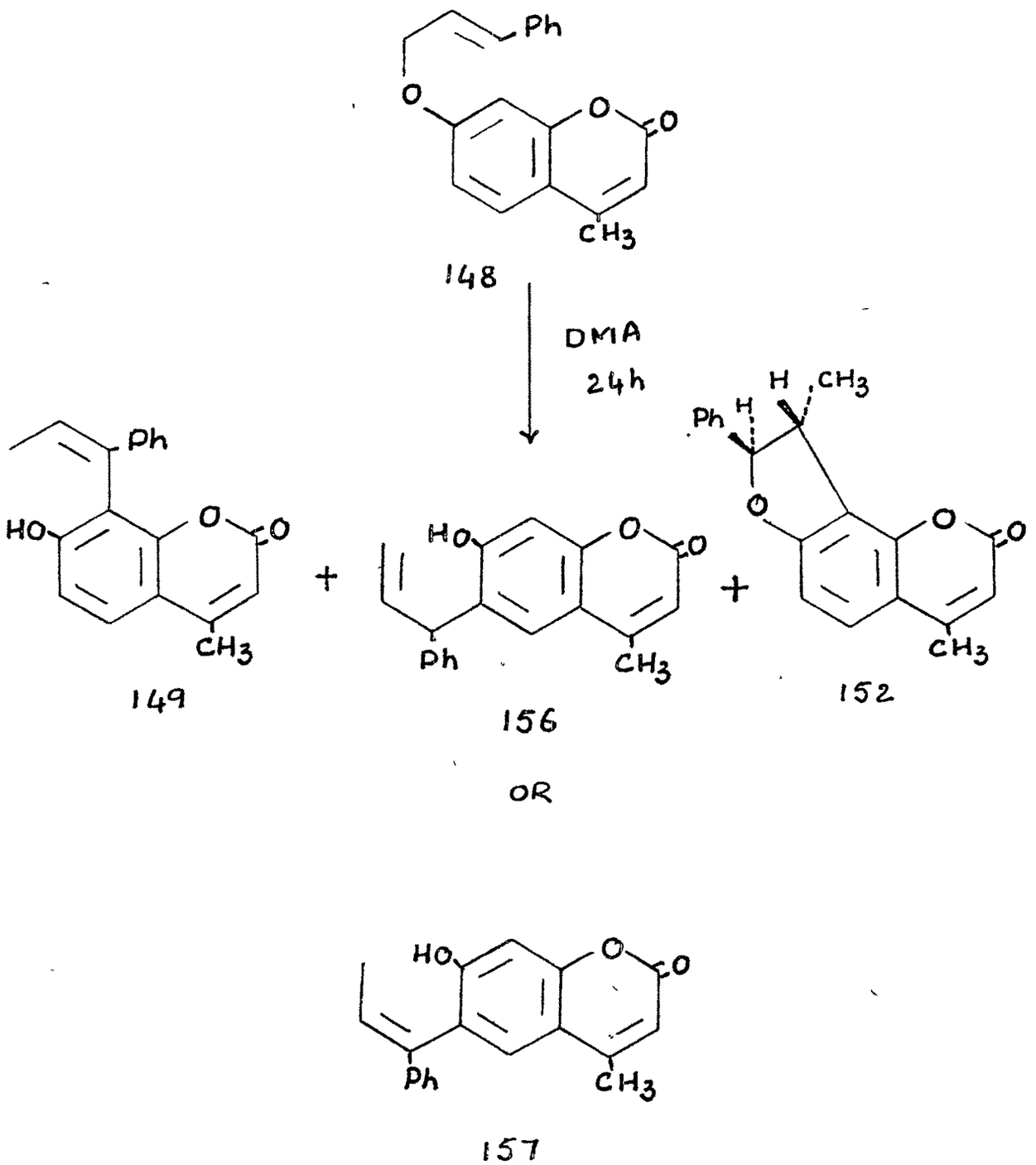
to obtain 7-cinnamyloxy-4-methylcoumarin. On repeating the work of Ahluwalia and coworkers under identical conditions of refluxing 7-cinnamyloxy-4-methylcoumarin in N,N-dimethyl-aniline for 24 hr., three products were obtained, two alkali soluble and one alkali insoluble. The alkali soluble products were separated by preparative TLC [Scheme-40].

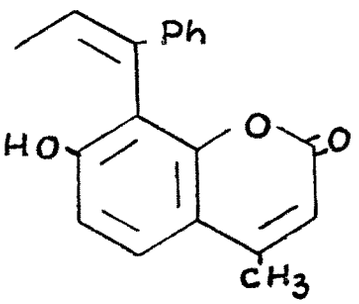
3,7-Dimethyl-2-phenylfuro(2,3-h)benzopyran-5(H)-one (153)

The alkali insoluble product m.p. 136° obtained in the Claisen rearrangement of 7-cinnamyloxy-4-methylcoumarin was totally different from the product m.p. 230-32° from the one reported by Ahluwalia and co-workers, which we failed to isolate it.

The product was assigned trans-3,7-dimethyl-2-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (152), an angular dihydrofurocoumarin on the basis of PMR ($CDCl_3$ + DMSO) which exhibited the following signals at δ 1.6, a doublet J=7Hz for three methyl protons at C-3, a multiplet at δ 3.7 for the proton at C-3, proton at C-2 appeared as a doublet J=7Hz at δ 5.3. Two doublets J=9Hz at δ 6.8 and 7.4 for orthocoupled protons at C-8 and C-9 indicates it is an angular furocoumarin. (Fig. 1)

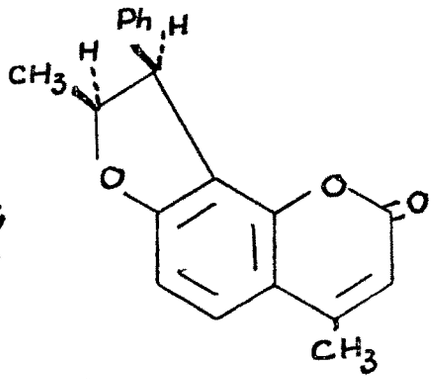
SCHEME-40


Ph
O
O
O
CH3
148
DMA
24h
Ph
HO
O
O
CH3
149
+
HO
O
O
Ph
CH3
156
+
H
CH3
Ph
H
O
O
O
CH3
152
OR
HO
O
O
Ph
CH3
157

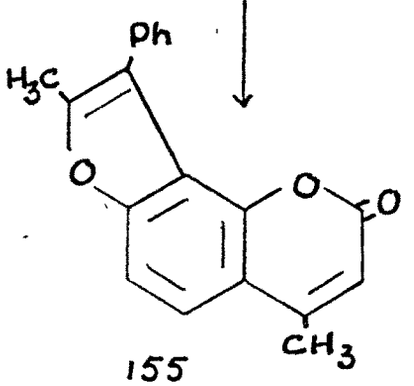


149

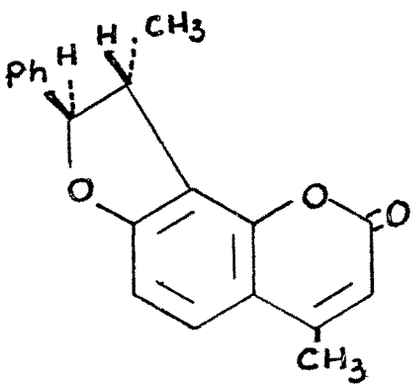
con. H_2SO_4



154

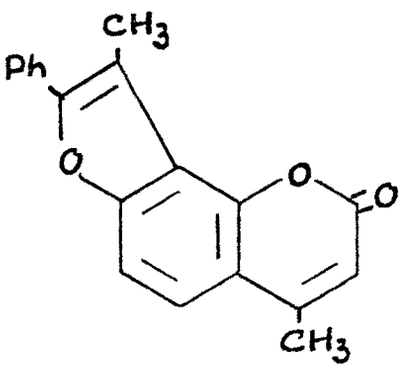


155



152

DDQ



153

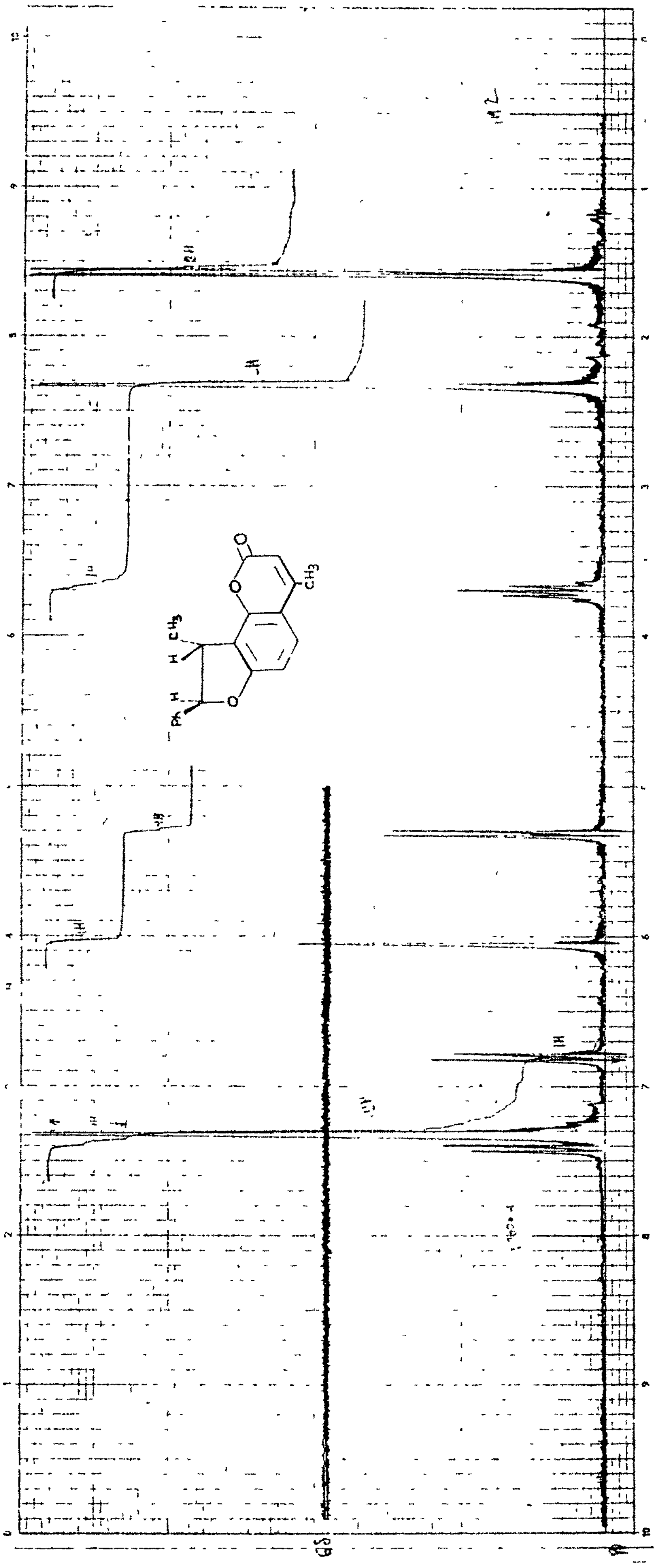


FIG-1

The isomeric structure (155) is eliminated on the basis that the doublet of proton at C-2 appeared down field at δ5.3 in comparison to the proton at C-3 which appeared as a multiplet at δ3.7. If the isomeric structure was present, then the doublet of proton at C-3 would have appeared upfield in comparison with the multiplet of proton at C-2. The isomeric product is prepared from (149) and is discussed later.

The mechanism of formation of the compound is shown in the [Scheme-41].

The Claisen rearrangement of 7-cinnamyloxy-4-methyl-coumarin (148) first yields the normal product (A) by (3,3) shift which undergoes enolisation followed by cyclisation to form cyclopropane intermediate (C) through (1,5) shift which then opens to give trans-3,7-dimethyl-2-phenyl-2,3-dihydro(2,3-h)benzopyran-5(H)-one (152).

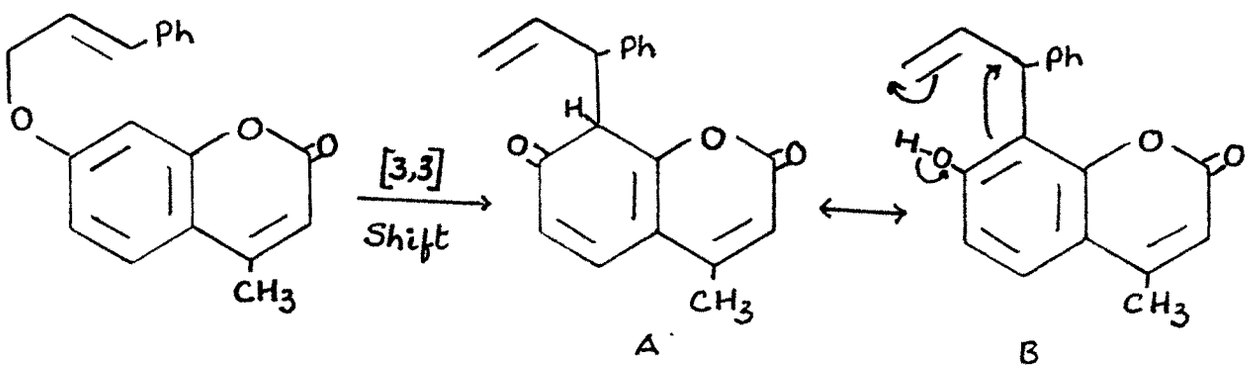
The trans-stereo chemistry of the compound is confirmed by NOE difference spectra.

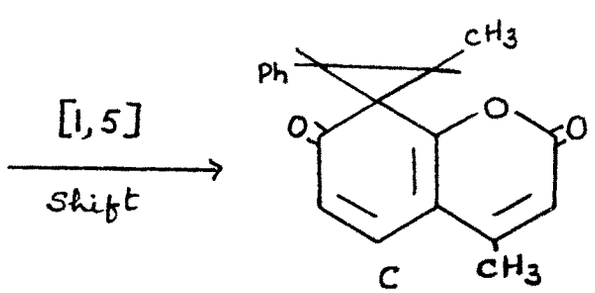
STEREOCHEMISTRY OF 2,3-DIHYDROFUROCOUMARIN-NOE DIFFERENCE SPECTRA -

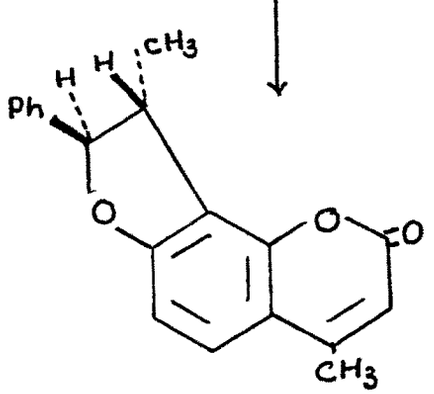
NOES are easily detected by substracting in the computer

SCHEME-41

Mechanism of formation of trans-isomer







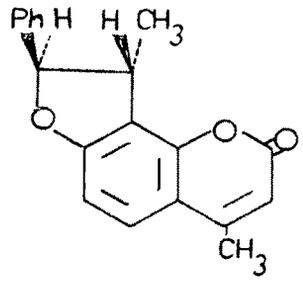
trans-isomer

the normal spectrum from the spectrum taken with the irradiating signal on, and printing the difference between the two spectra. All the uneffected signals simply disappear, and all that appears in the spectrum is the enhancement of the signals of neighbouring protons in the same place. It is easy to detect upto 1% or even less enhancement, with the result that NOES in methyl groups are now quite commonly measurable.

In order to assign the stereochemistry of trans-3,7-dimethyl-2-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one, this technique of NOE difference spectra was applied. Thus the doublet of O-CH-ph at position C-2 when irradiated showed in NOE in the methyl group of about 7% and also in the phenyl protons about 10%, indicating that -H at C-2 is cis to methyl group and trans to hydrogen on position C-3. (Fig. 2)

Dehydrogenation of (152) was carried out with DDQ in drybenzene, gave 3,7-dimethyl-2-phenylfuro(2,3-h)benzopyran 5(H)-one (153). Structure of the compound was confirmed by PMR spectra which showed signals in $CDCl_3$ at δ 2.45, a singlet for three methyl protons at C-7, another singlet at δ 2.7 for three methyl protons at C-3, vinylic proton at C-6 appeared as a singlet at δ 6.2, multiplet at δ 7.3-7.5 for five phenyl protons at C-2 while the orthocoupled protons at C_8 and C_9 doublets overlapped with the phenyl multiplet. (Fig. 3)

Blank -



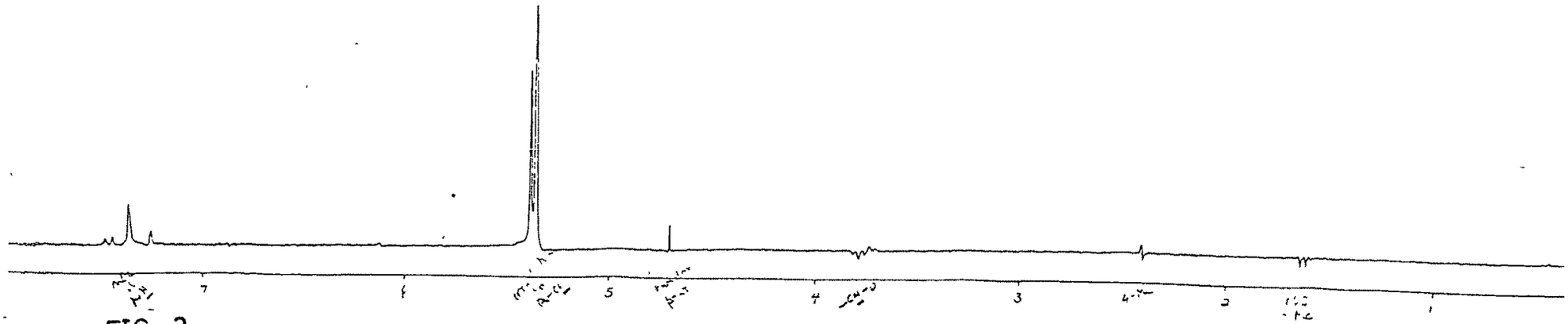


FIG-2

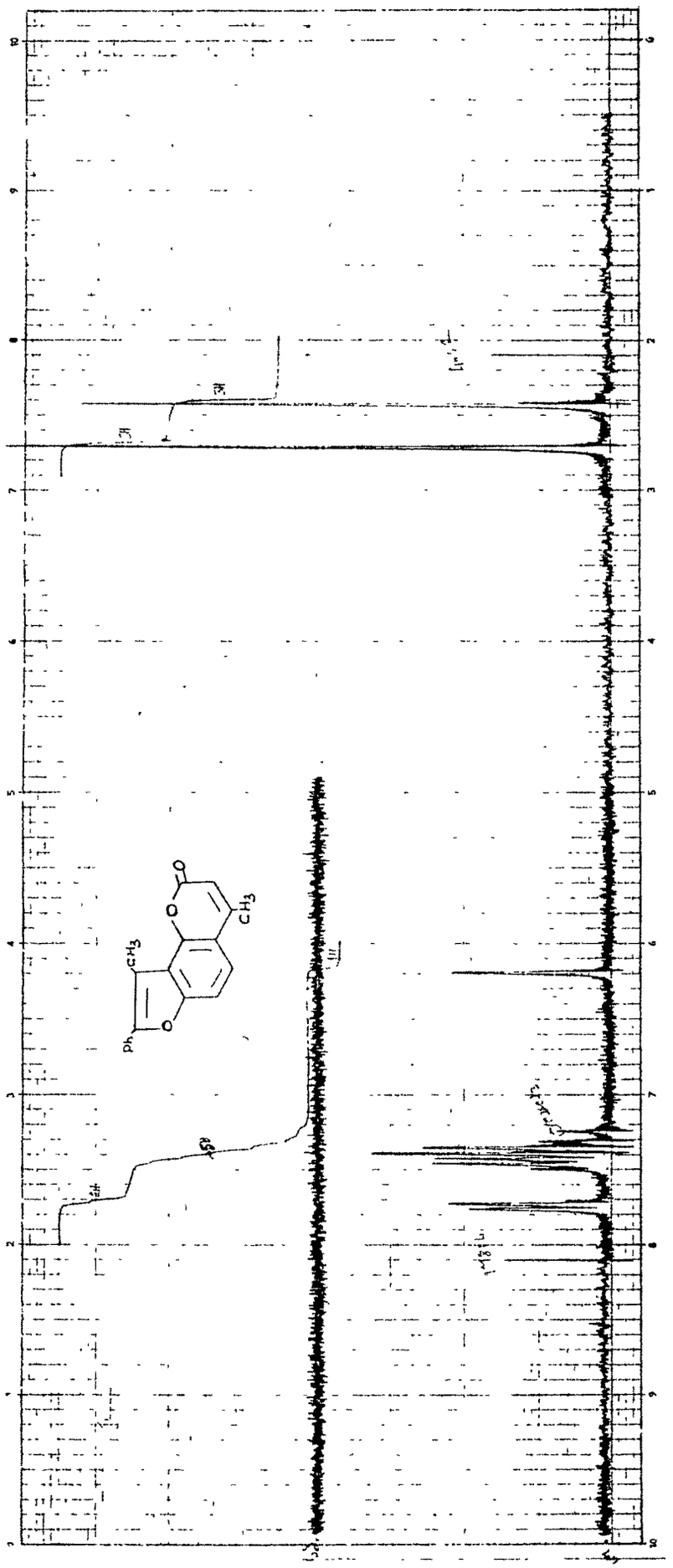


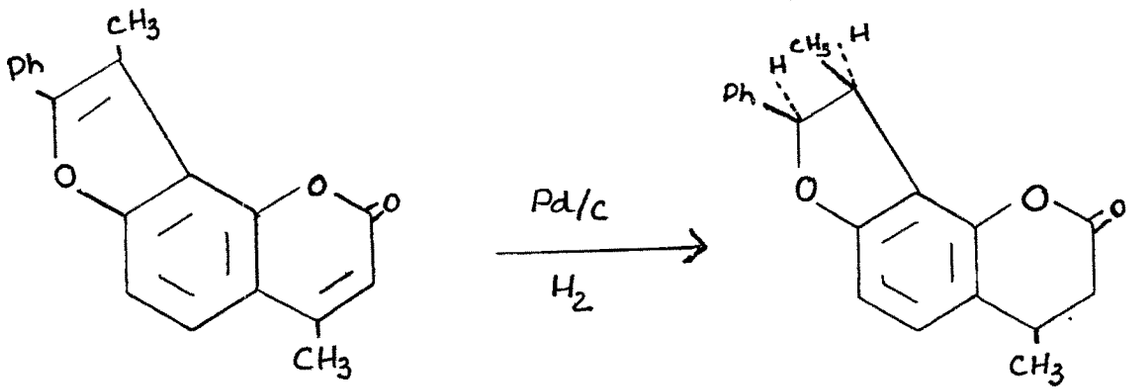
FIG-3

In order to study the stereochemistry of dihydrofuro coumarins, hydrogenation of furocoumarins was carrried out as hydrogenationof furocoumarin with Pd/c would only furnish stereo specifically cis-isomer.

Hydrogenation of (153) was carried out using Pd/c (10%) as catalyst [Scheme-42]. As the compound could not be obtained in the pure form the PMR spectrum of semi-solid was recorded which showed signals in $CDCl_3$ as follows : δ 1.0, a doublet J=7Hz for three methyl protons at C-3, a triplet at δ 1.5 for two protons at C-6, a singlet at δ 2.2 for three methyl protons at C-7, a multiplet for a proton at C-7 appeared at δ 2.7-3.3, another multiplet at δ 3.8 for a proton at C-3, a doublet at δ 5.8 for a proton at C-2. Orthocoupled protons of C-8 and C-9 got mixed up with phenyl protons. (Fig. 4)

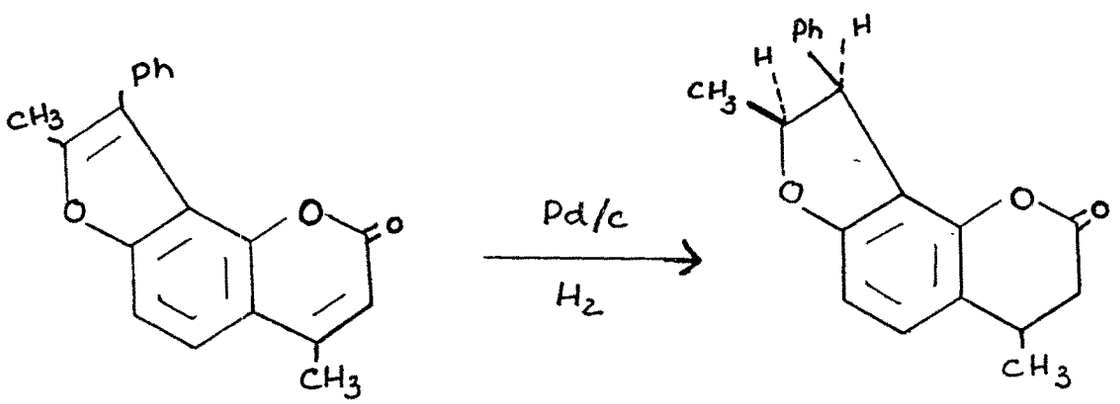
The study of the above spectra makes it clear that the hydrogenation has taken place not only at 2,3 positions but also at 6,7 positions, as it showed a triplet at δ 1.5 and a multiplet at δ 2.7-3.3 corresponding to 6,7 positions. The position of phenyl group and methyl group at C-2 and C-3 respectively were also confirmed by the down field doublet of C-2 proton at δ 5.8.

SCHEME-42



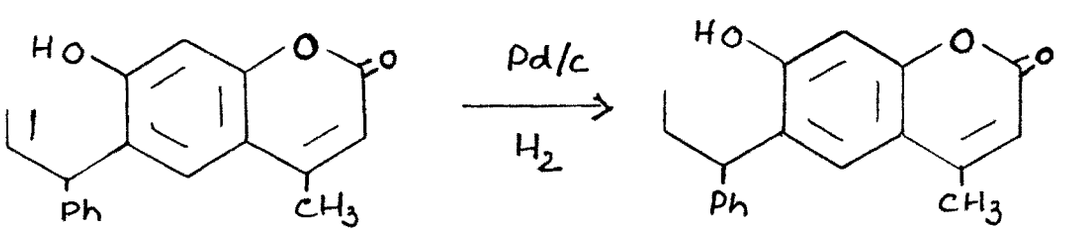
153

SCHEME-43



155

SCHEME-44



156 158

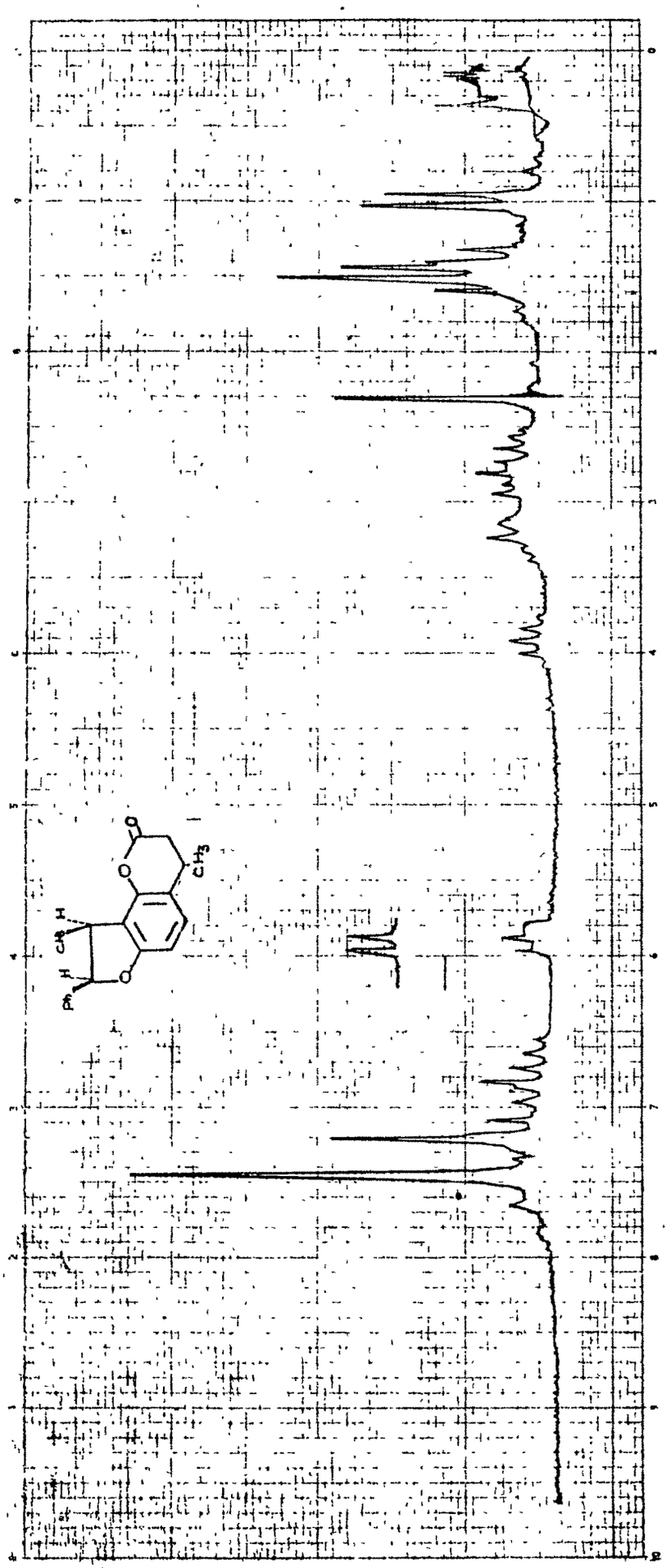


FIG-4

Finally as per the analogy that when a furocoumarin is hydrogenated to make dihydrocoumarin, it gives a cis-isomer. Here as the doublet for three methyl protons at C-3 appeared at δ 1.0, indicates that it is a cis-isomer of dihydrofurocoumarin, methyl group being shielded by the phenyl ring causing the upfield shift from 1.6 to 1.0.

Thus the compound (152) obtained in the Claisen rearrangement is trans-3,7-dimethyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one as it showed a doublet for dihydrofuran ring methyl group at δ 1.6.

2,7-Dimethyl-3-phenylfuro(2,3-h)benzopyran-5(H)-one (155)

The alkali soluble products in the Claisen migration of 7-cinnamyloxy-4-methylcoumarin were isolated by preparative TLC. The product having higher Rf value was assigned 7-hydroxy-4-methyl-8-(1'-phenylprop-1'-ene)coumarin (149), m.p. 220°, a major product, the same as that obtained by Jain et al. and Ahluwalia et al. PMR showed a doublet at δ 1.6 for methyl group in $\underset{\underset{ph}{|}}{CH}=CH-\underline{CH_3}$ at C-8 indicates that the methyl groupis at the terminal position in the cinnamyl unit. Two doublets at δ 6.95 and 7.45 for orthocoupled protons at C-6 and C-5 indicates that the cinnamyl group is migrated to the 8th position. (Fig. 5)

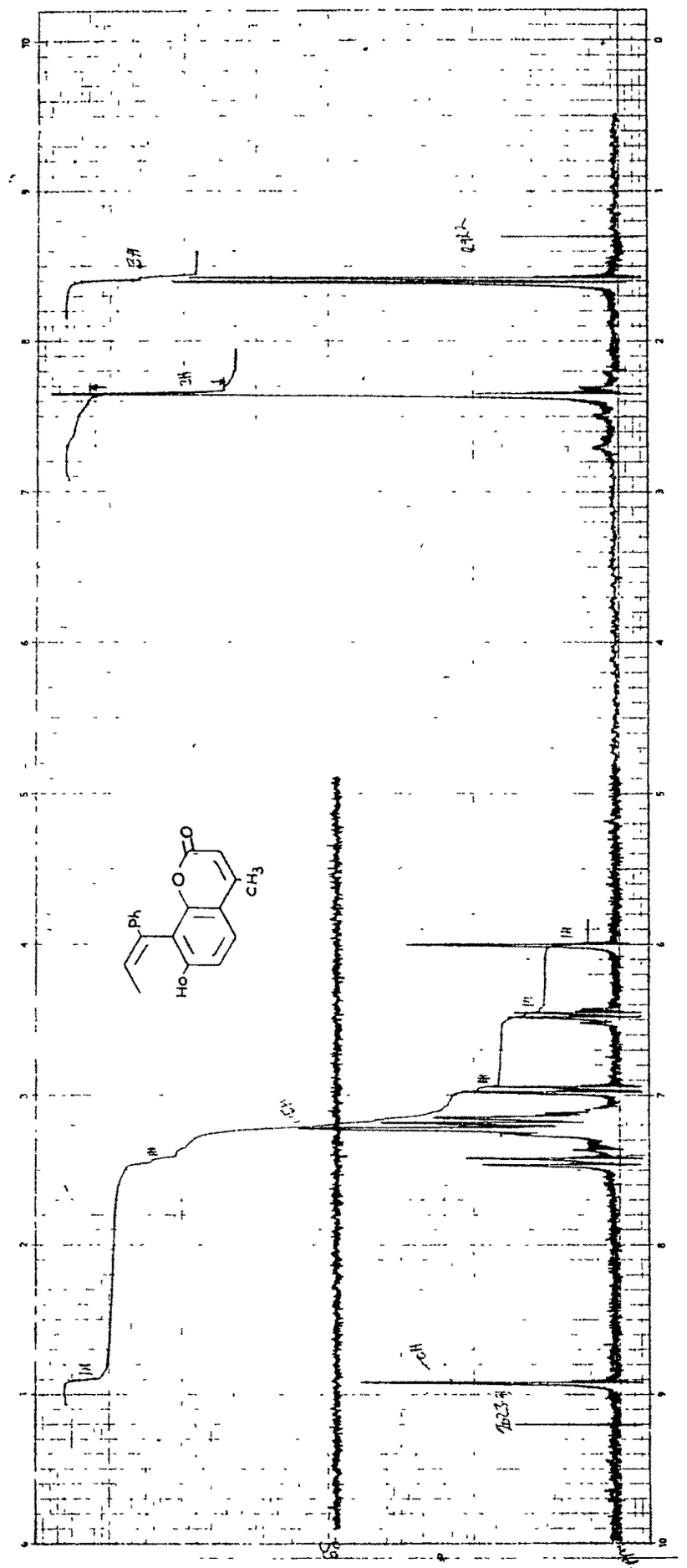


FIG-5

The isomeric cis-2,7-dimethyl-3-phenyl-2,3-dihydro-furo(2,3-h)benzopyran-5(H)-one (154) was obtained when (149) was triturated with con. H_2SO_4. PMR in $CDCl_3$ exhibited signals at δ 1.1 a doublet J=7Hz for methyl protons at C-2, one singlet at δ 2.3 for C-7 methyl protons, doublet J=7Hz at δ 4.65 for a proton at C-3, a multiplet for C-2 proton at δ 5.2. At δ 6.85 and 7.45 two doublets J=9Hz for ortho coupled C-7 and C-8 protons (Fig. 6). PMR showed a upfield shift of doublet here in comparison to the isomer where the phenyl ring is at C-2 it appeared at δ 5.3.

The cis-stereochemistry of the compound (154) was established by NOE studies. The doublet of -CH-Ph at position C-3 was irradiated andthe NOE was observed on C_2-H and also on the proton of the phenyl ring. C_2-Me group showed no NOE at all, thus establishing that the Me and Ph are cis to each other. (Fig. 7)

This is further corroborated by up field shift of C-3 methyl signal at δ 1.1 establishing that the Me group is shielded by the phenyl ring when they are cis to one another.

In case of (152) Me signal appears downfield at δ 1.6 confirming trans-structure

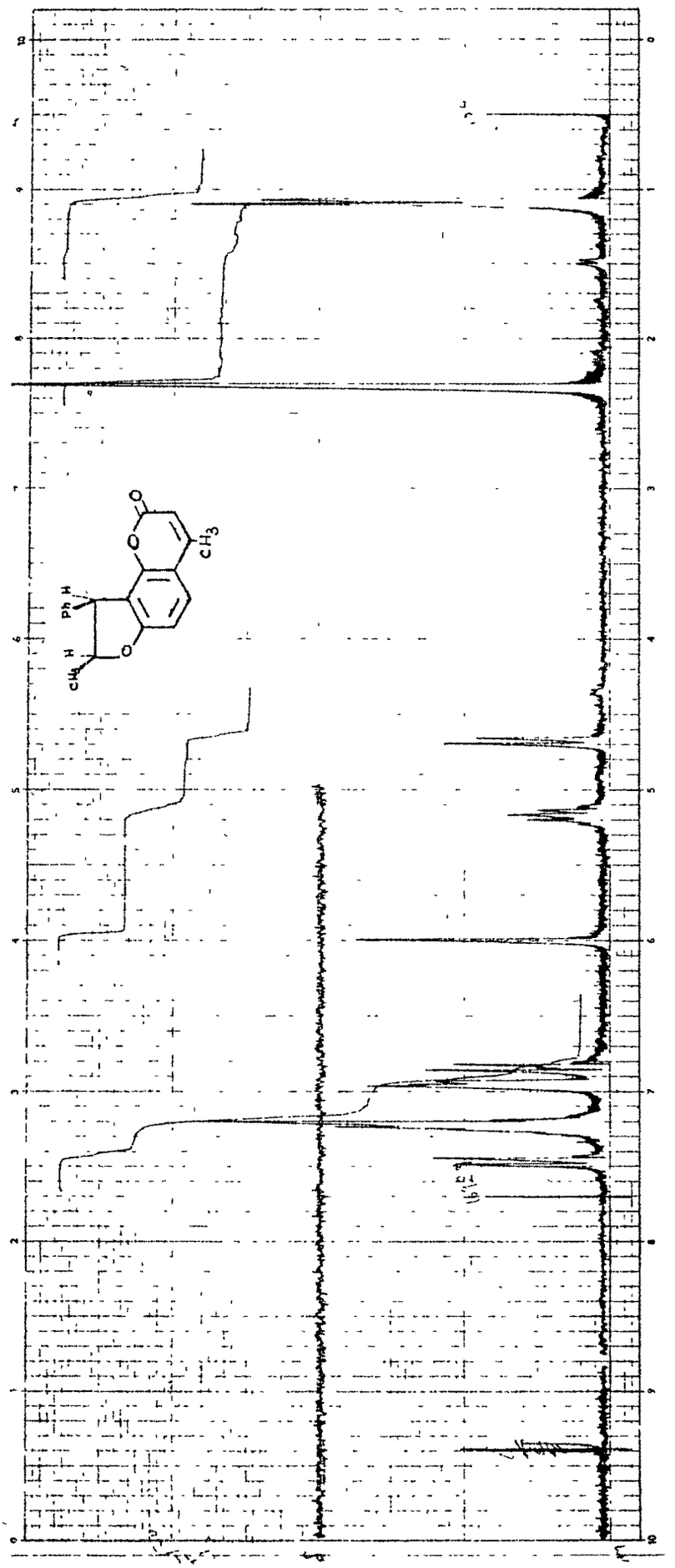


FIG-6

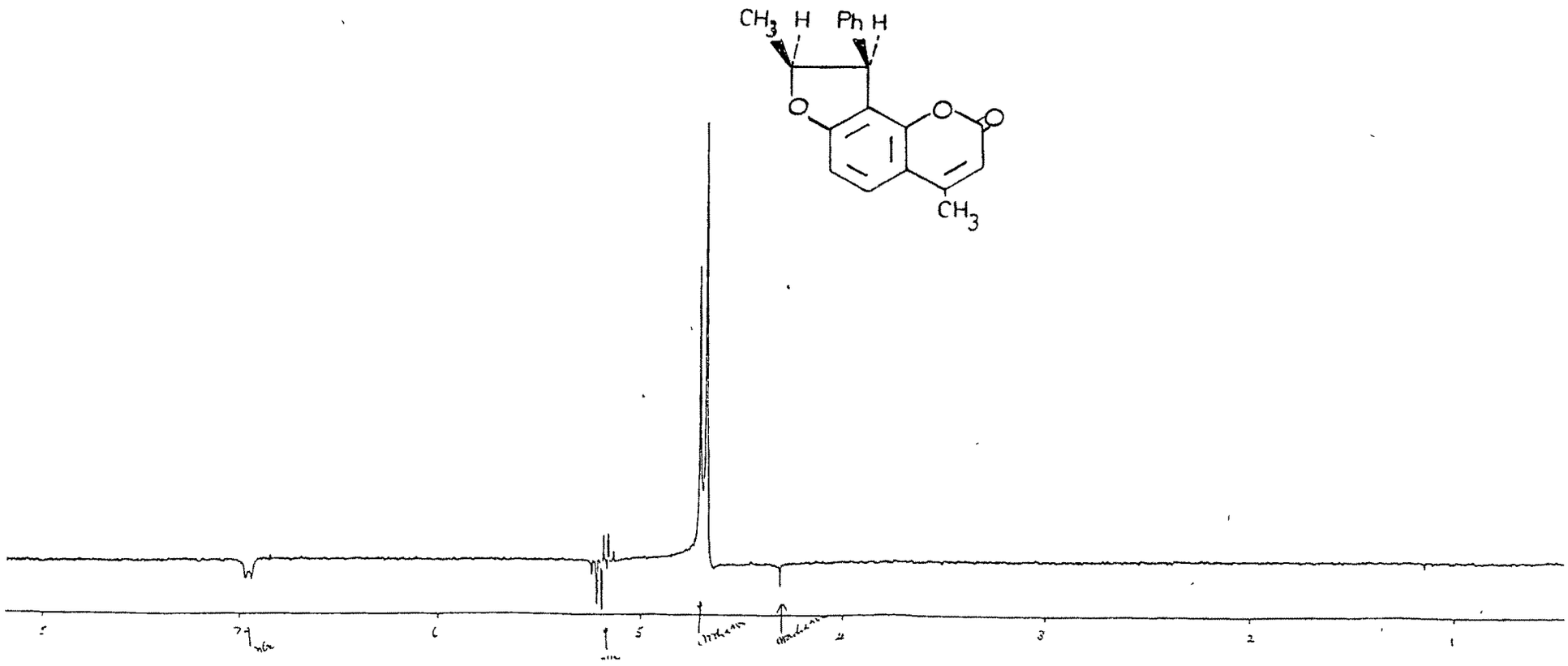


FIG-7

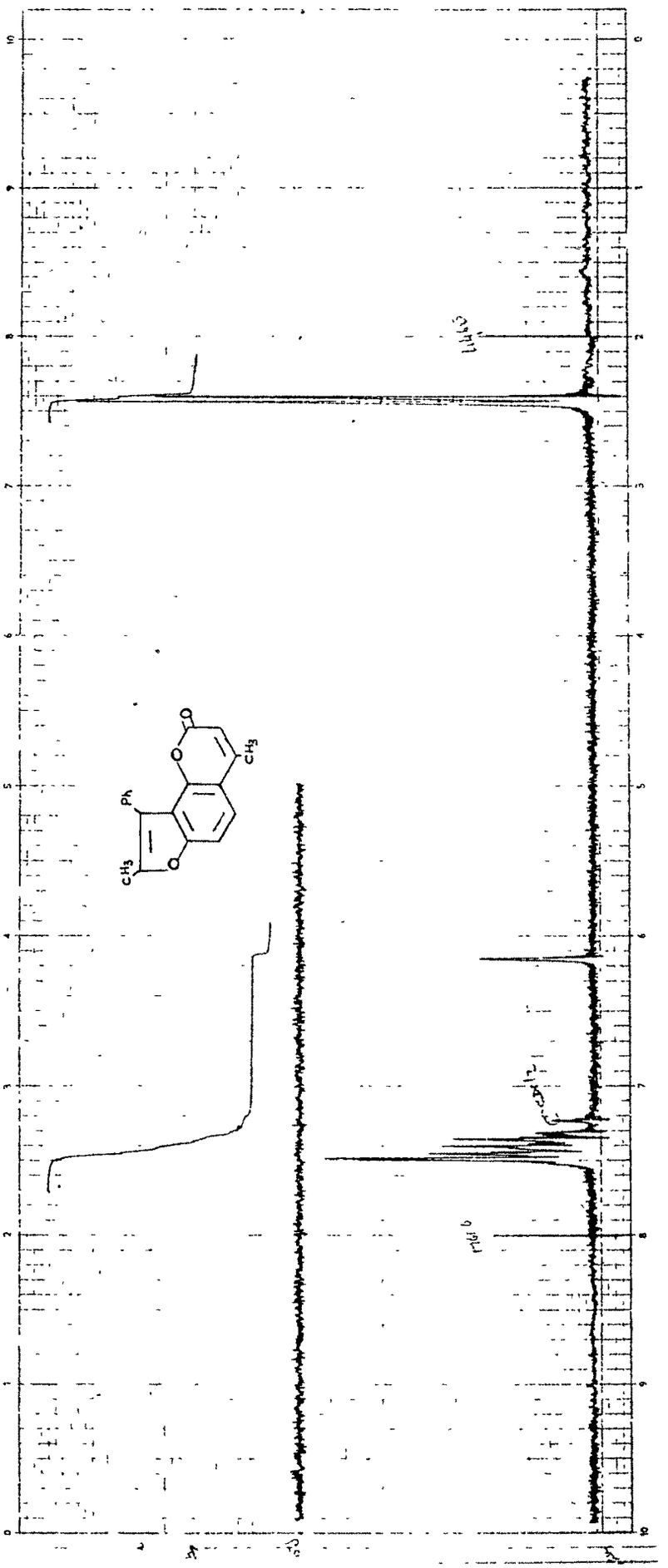


FIG-8

Dehydrogenation of (154) was carried out with DDQ in dry benzene to give isomeric 2,7-dimethyl-3-phenylfuro(2,3-h) benzopyran-5(H)-one (155). The structure of the compound was confirmed by PMR spectrum, which exhibited signals in $CDCl_3$ at δ 2.4, a singlet for three methyl protons at C-7, one more singlet at δ 2.45 for three methyl protons at C-2. Vinylic proton of C-6 appeared as a singlet at δ 6.15. Orthocoupled protons of C-8 and C-9 overlapped with phenylic protons appeared at δ 7.3-7.5. (Fig. 8)

Similarly as earlier the hydrogenation of (155) with Pd/c (10%) was carried out to prepare synthetically the cis-isomer of the dihydrofurocoumarin [Scheme-43]. PMR spectra in $CDCl_3$ showed a doublet at δ 1.1 for C-2 methyl protons, a triplet at δ 1.3 for two protons at C-6, a singlet at δ 2.4 for methyl protons at C-7, amultiplet at δ 2.2-3.1 for a proton at C-7, a doublet at δ 4.4 for proton at C-3 and a multiplet for C-2 proton at δ 5.0.

From the spectra it is understood, as in the earlier case, the hydrogenation has taken place at 2,3 positions and as well as at 6,7 positions. Position of C-2 methyl protons at δ 1.1 reaffirms that it is a cis-isomer.

2,5-Dimethyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (161)

The second alkali soluble product in the Claisen migra-

tion of 7-cinnamyloxy-4-methylcoumarin having lower Rf value was also isolated by preparative TLC as aminor product m.p. 192°, which was not isolated by Jain et al. and Ahluwalia et al. It was assigned 7-hydroxy-4-methyl-6-(1'-phenylprop-2'-ene) coumarin (156) on the basis of PMR spectra in $CDCl_3$ + DMSO. The spectra showed a singlet at δ 2.32 for methyl protons at C-4, a multiplet for three protons at δ 4.9-5.25 in the cinnamyl unit -C(Ph)H-CH=CH_2 at C-6, at δ 6.05 a singlet for C-3 vinylic proton. There is another multiplet at δ 6.3 for a proton in the cinnamyl unit -CH(Ph)-CH=CH_2 at C-6, a singlet at δ 6.85 for C-8 proton and at δ 7.3 there is a multiplet for phenyl ring of the cinnamyl unit at C-6. The other singlet for C-5 proton appeared at δ 7.45 while the exchangeable hydroxy proton at C-7 appeared at δ 9.8. (Fig. 9)

The two singlets at δ 6.85 and 7.45 for the protons at C-8 and C-5 respectively indicates that the migration has taken place in C-6 position. As the PMR does not have any signal for a methyl group, the structure (157) with a terminal methyl group is ruled out.

The position of the double bond in the compound (156) was confirmed by hydrogenating the double bond in the cinnamyl unit by Pd/c (10%) to give 7-hydroxy-6(1'-phenylpropyl)-

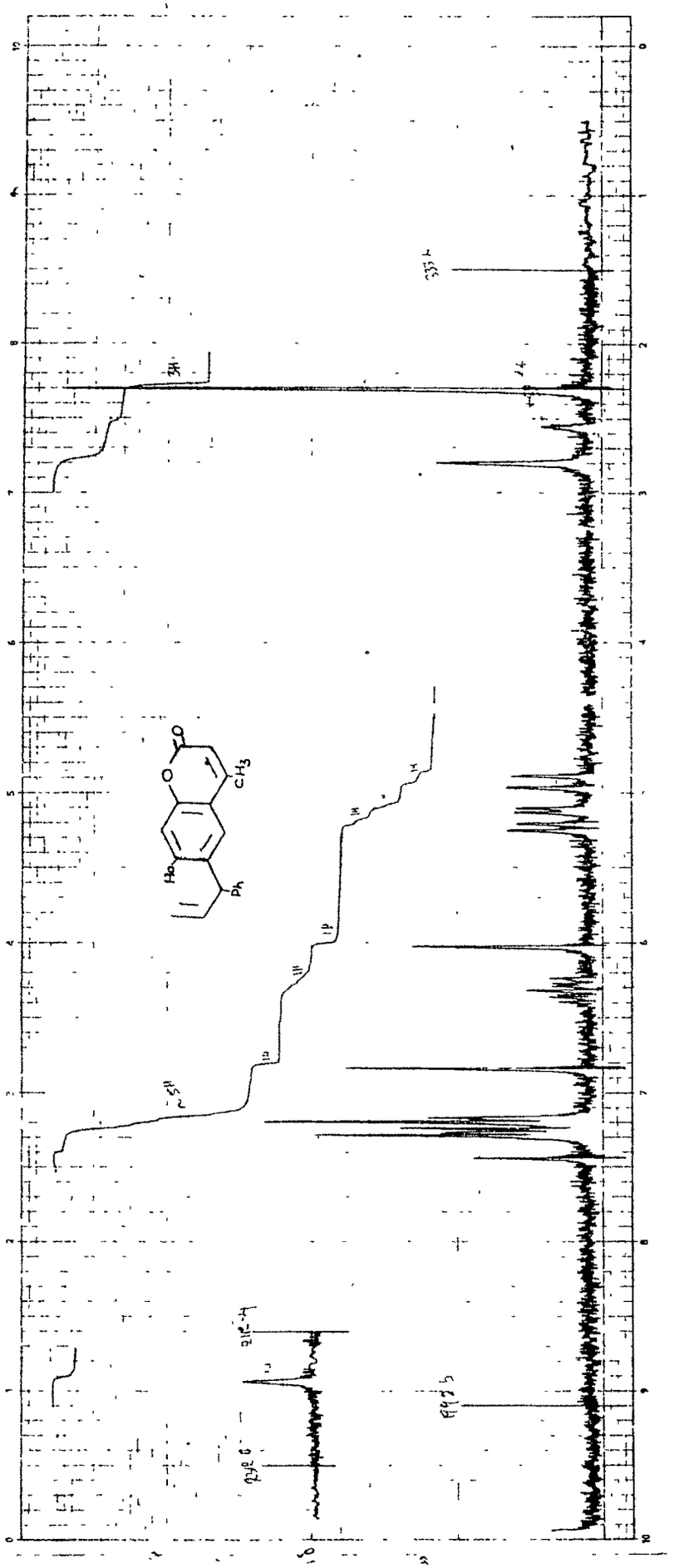


FIG-9

4-methylcoumarin (158) [Scheme-44]. Its PMR showed signals in $CDCl_3$ + DMSO at δ 0.95 a triplet corresponding to the terminal methyl group in the propyl unit at C-6, another multiplet δ 2.1 for two CH_2 protons in C-6 unit, a singlet at δ 2.35 for three methyl protons at C-4, a multiplet for a single proton in the propyl unit $-\underset{\underset{Ph}{|}}{CH}-CH_2-CH_3$ appeared at δ 4.25, at δ 6.05 a singlet for vinylic proton of C-3. Singlets for C-5 proton and C-8 protons appeared at δ 6.8 and 7.35. Phenyl protons in the propyl unit at C-6 showed a singlet at δ 7.25 and while the C_7-OH appeared in the downfield at δ 9.8. The appearence of triplet and multiplet proves that the double bond in the cinnamyl unit is at the terminal position in the compound (156). (Fig. 10)

As the compound (156) is obtained in poor yield the same compound was prepared in better yield by carrying out the Claisen migration of 7-cinnamyloxy-8-Iodo-4-methylcoumarin (159), where 8th position is blocked with iodine, so that the Claisen migration may yield C-6 isomer. The Claisen rearrangement of (159) gave the compound (156), the structure of which was confirmed by comparing the PMR spectra and also its mixed m.p. [Scheme-45].

The compound (156) was triturated with 75% H_2SO_4 to give linear<u>trans</u>-2,5-dimethyl-3-phenyl-2,3-dihydrofuro (3,2-g)

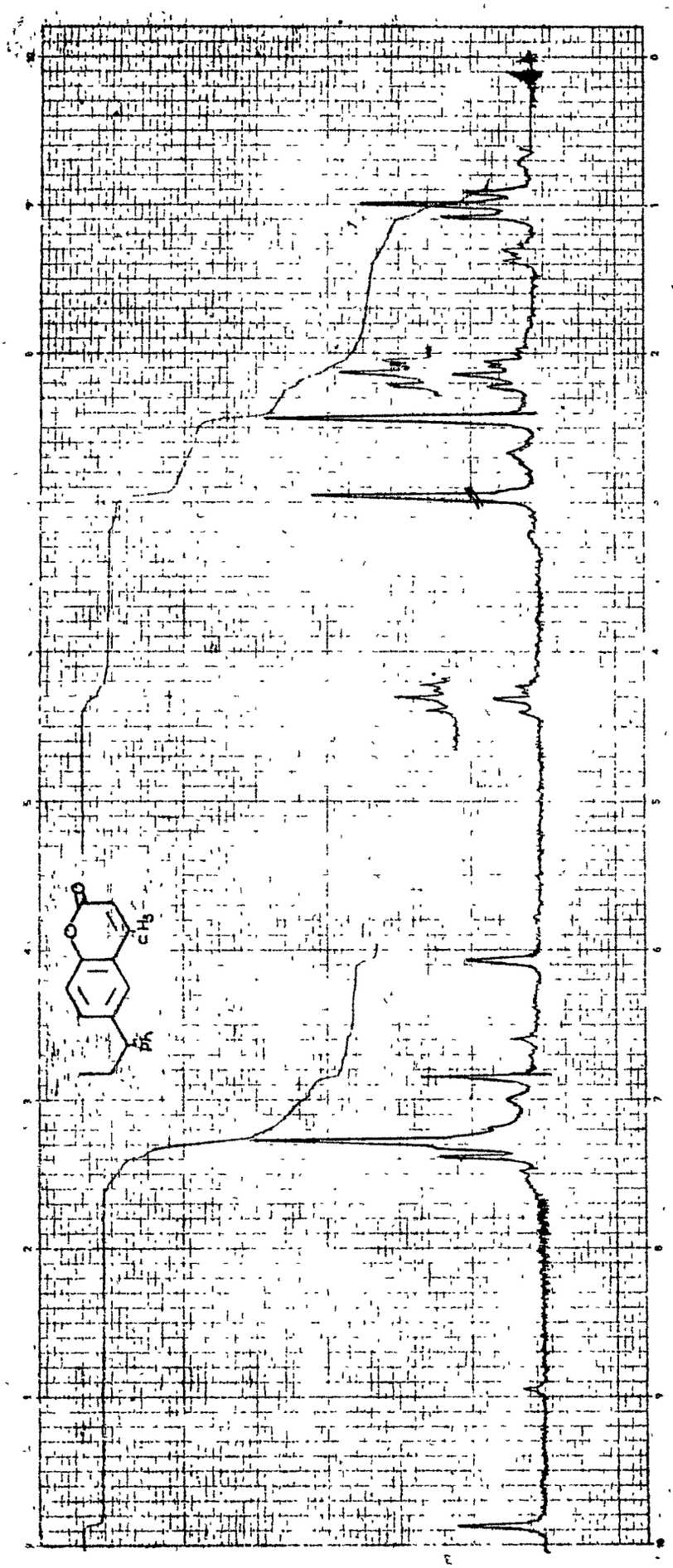
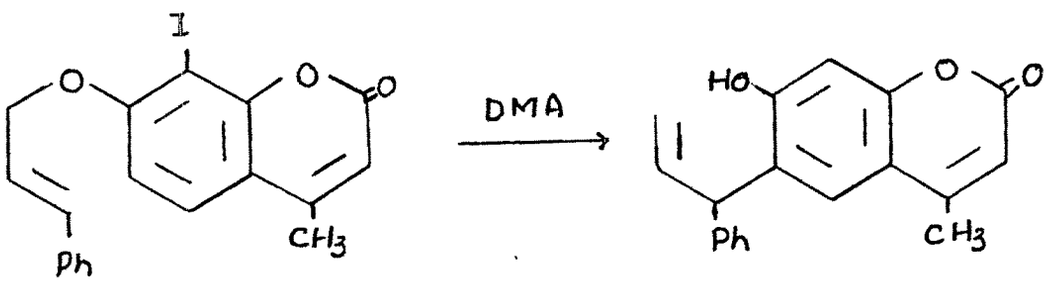


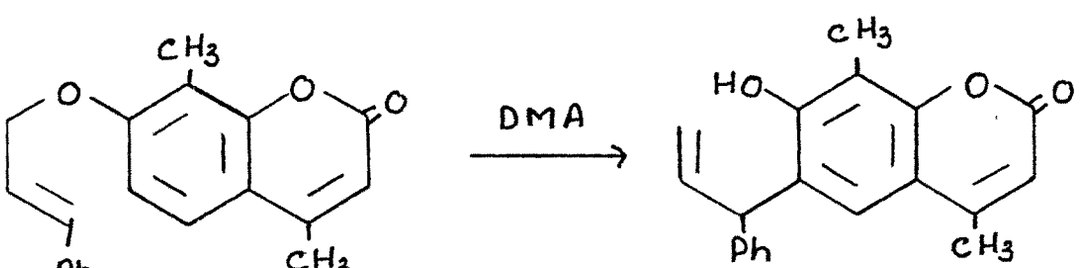
FIG-10

SCHEME - 45

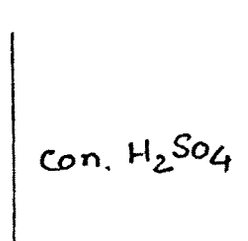


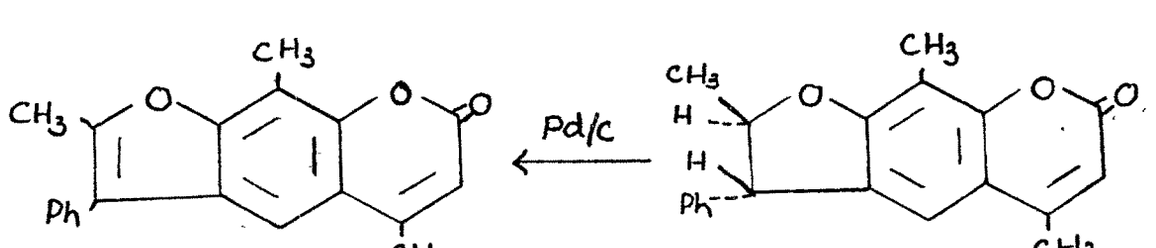
159 156

SCHEME - 46



162 163





165 164

benzopyan-7(H)-one (160). PMR in $CDCl_3$ showed a doublet for C-2 methyl group at δ 1.5 indicate that the Me group and ph ring are trans to each other. The two singlets at δ 6.7 and 7.09 for C-9 and C-4 protons respectively shows that the furan ring is fused linearly, a doublet at δ 4.15 for a proton at C-3 and multiplet at δ 4.8 for a proton at C-2 indicates that methyl group is at C-2 and phenyl ring is at C-3. (Fig. 11)

This compound (160) was dehydrogenated with Pd/c (10%) in diphenyl ether to give 2,5-dimethyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (161). The structure of the compound was proved by PMR spectra, which showed signals in $CDCl_3$ at δ 2.45 a singlet for three methyl protons at C-2, another singlet at δ 2.55 for three methyl protons at C-5, the singlets at δ 7.3 and 7.6 for C-4 and C-9 protons. (Fig. 12)

2,5,9-Trimethyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (165)

7-Hydroxy-4,8-dimethylcoumarin on condensation with cinnamylchloride gave 7-cinnamyloxy-4,8-dimethylcoumarin (162), which when subjected to Claisen rearrangement in N,N-dimethylaniline gave an alkali soluble product 7-hydroxy-6-(1'-phenylprop-2'-ene)coumarin (163). PMR in $CDCl_3$ showed a singlet at δ 2.25 for two methyl groups at C-4 and C-8,

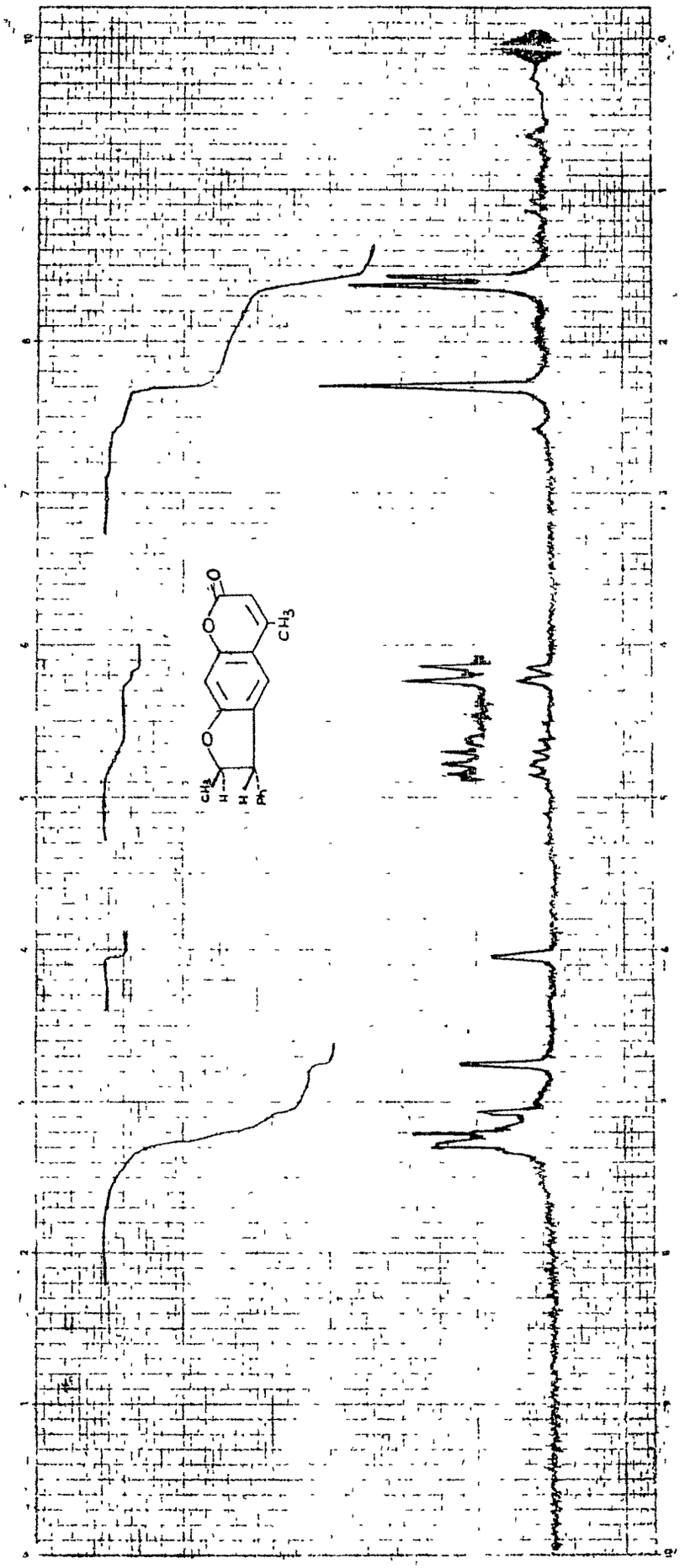


FIG-11

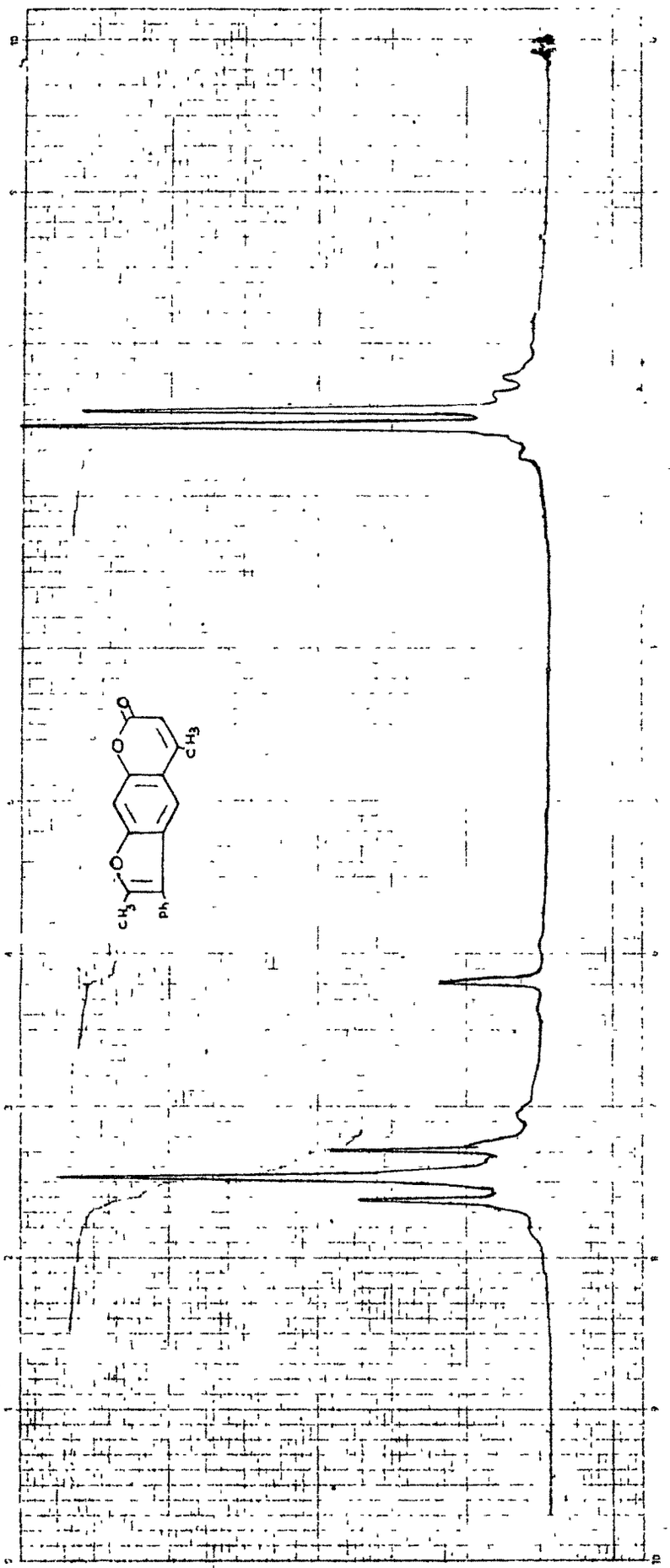


FIG-12

a multiplet at δ 4.9-5.3 corresponding to three protons in the cinnamyl unit -CH(Ph)-CH=CH$_2$ at C-6 and another multiplet at δ 6.1-6.4 for a single proton centered in the cinnamyl unit -CH(Ph)-CH-CH$_2$ at C-6 indicates there is a double bond, only in the terminal position of the cinnamyl unit at C-6 (Fig. 13).

The compound (163) was triturated with con. H_2SO_4 so as to obtain a trans-2,5,9-trimethyl-3-phenyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (164). The structure of the compound was confirmed by PMR spectrum in $CDCl_3$ which showed signals at δ 1.6, a doublet, J=7Hz corresponding to the methyl protons at C-2 indicates that the methyl group is trans to the phenyl group at C-3, doublet at δ 4.2, J=7Hz for C-3 proton and a multiplet at δ 4.7-4.9 for a proton at C-2 shows that the methyl group is at C-2 and the phenyl group is at C-3. Singlet for C-4 proton appeared at δ 6.9 and a multiplet for phenyl protons at C-3 appeared at δ 7.2-7.4. (Fig. 14)

The compound (164) on dehydrogenation with Pd/c (10%) in diphenylether yielded the title compound (165), the structure of which was established by its PMR in $CDCl_3$, exhibited signals at δ 2.4, 2.55 and 2.6 three singlets for C-5, C-2 and C-9 methyl groups respectively. C-4 proton overlapped with phenyl ring multiplet of C-3 appeared at δ 7.4-7.5 [Scheme-46] (Fig. 15)

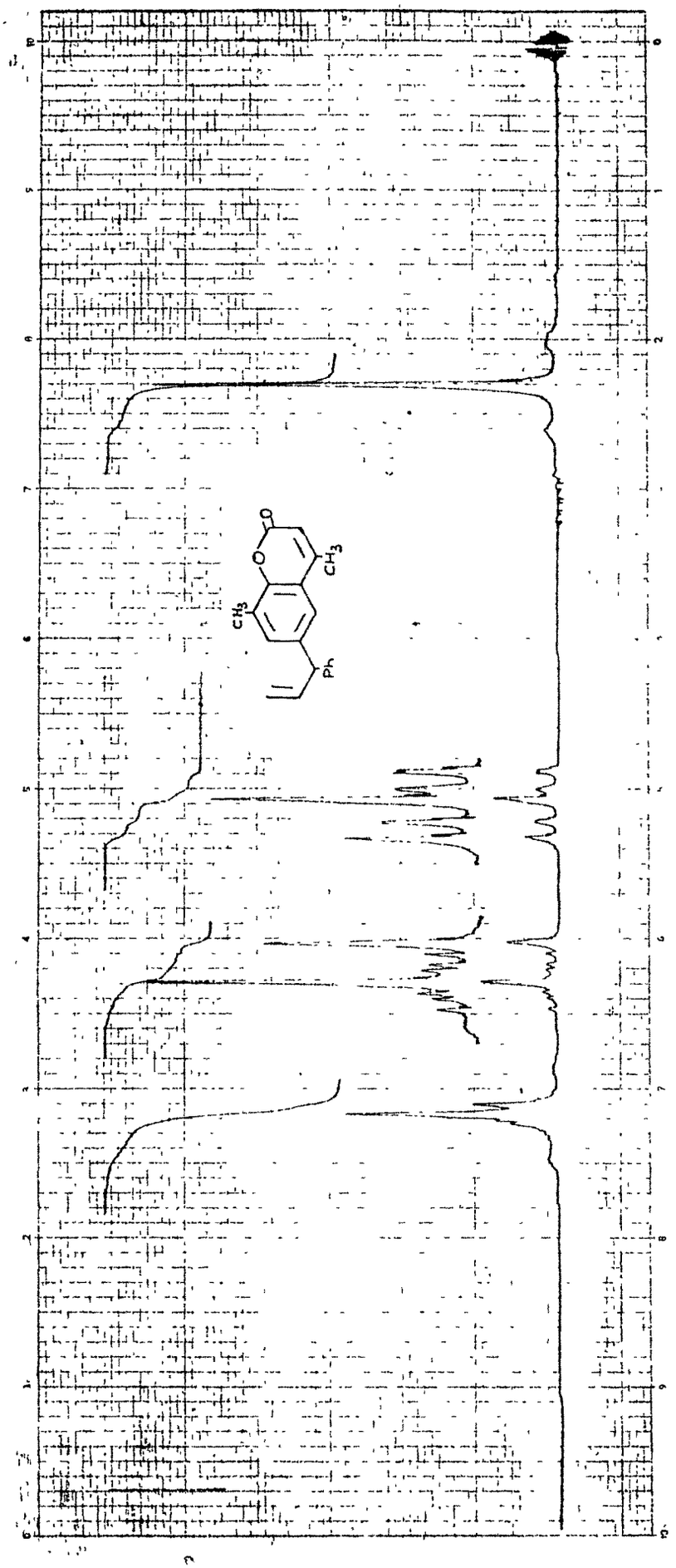


FIG-13

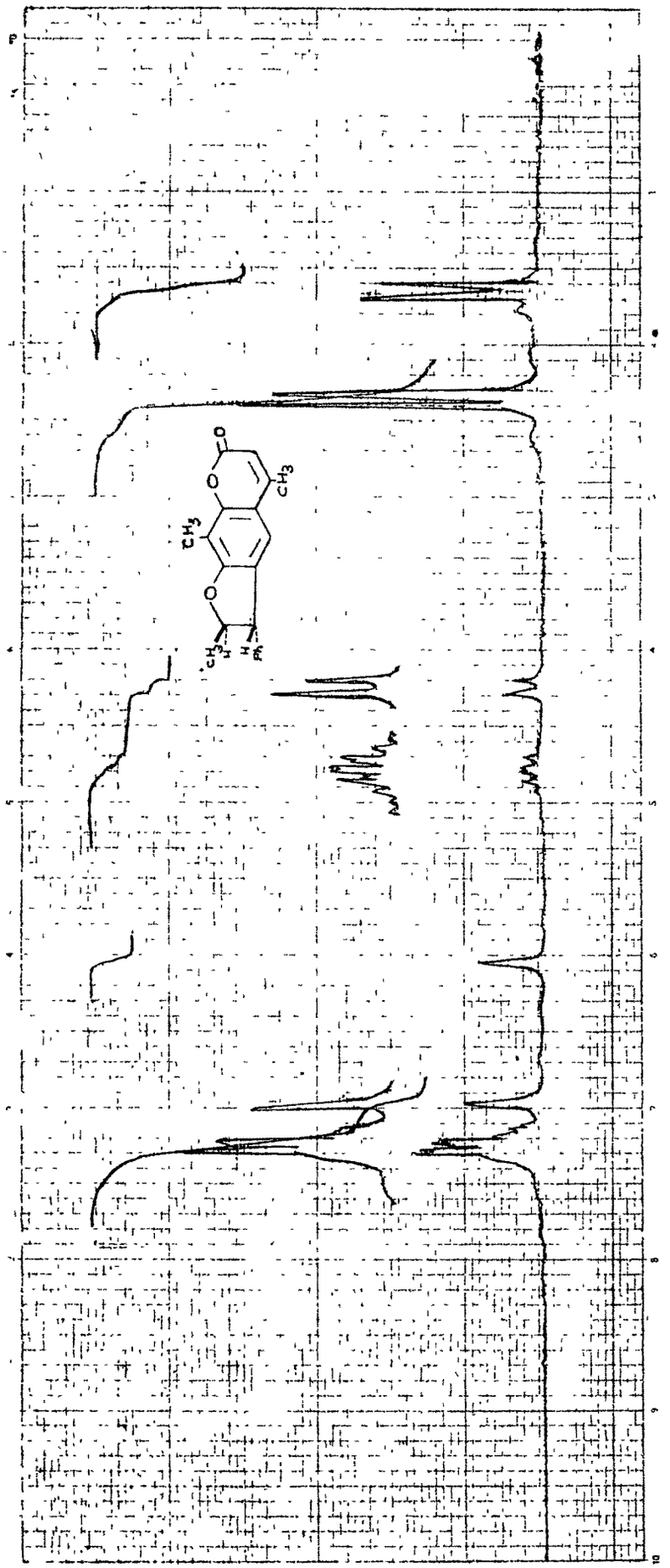


FIG-14

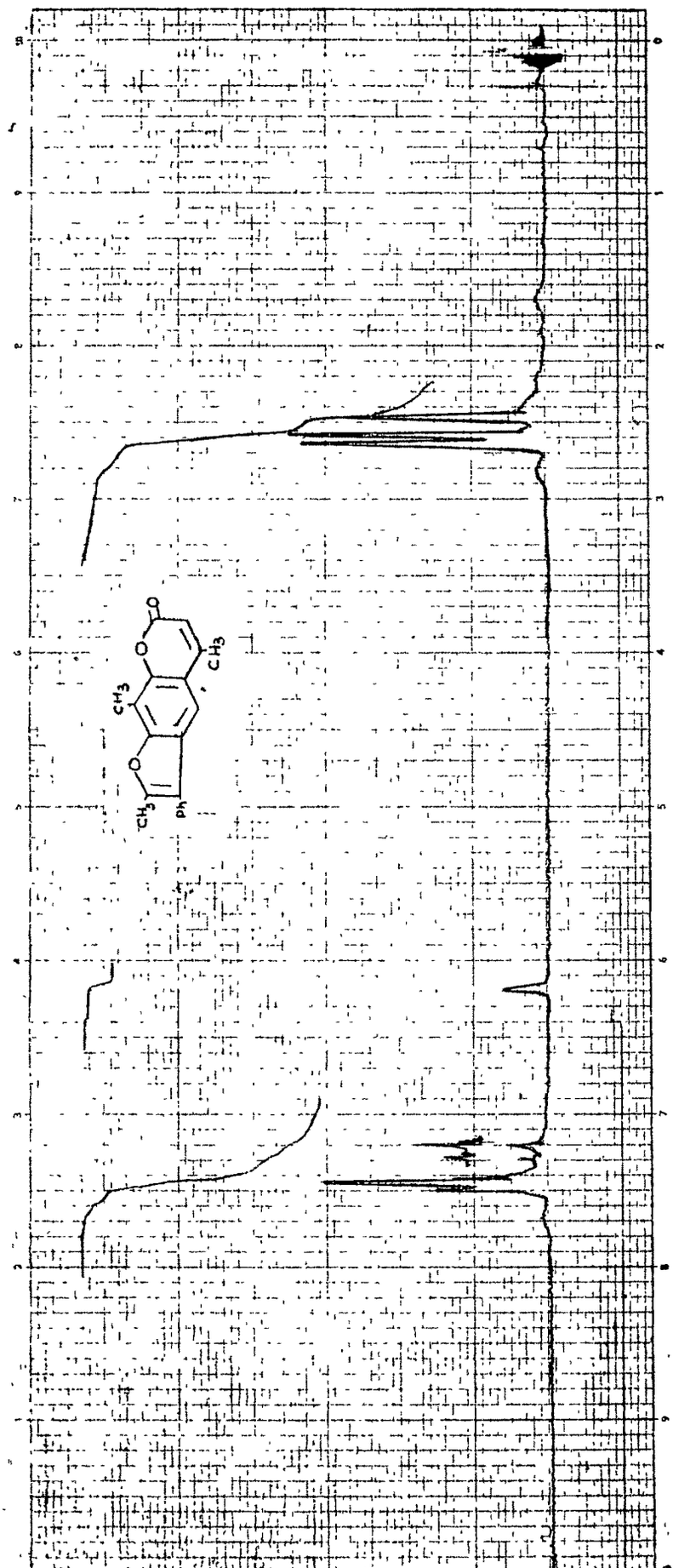


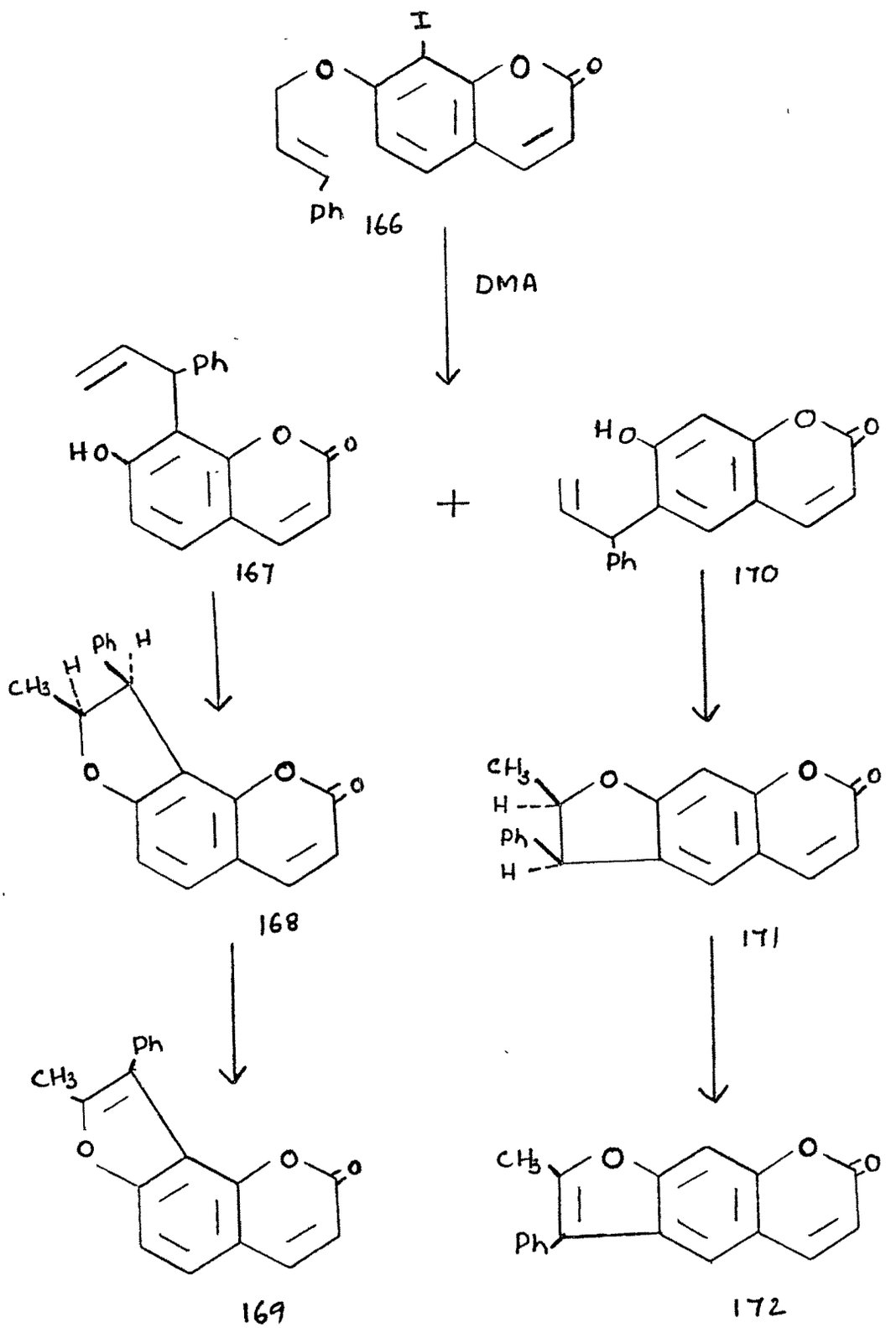
FIG-15

2-Methyl-3-phenylfuro(2,3-h)benzopyran-5(H)-one (169)

7-Hydroxy-8-Iodo-4-methylcoumarin on condensation with cinnamylchloride gave 7-cinnamyloxy-8-Iodo-4-methylcoumarin (166), which when subjected to Claisen rearrangement in refluxing N,N-dimethylaniline gave two alkali soluble products. The two products were separated by preparative column chromatography using benzene as solvent. Benzene fractions (25 ml) were collected and combined after checking with TLC. The product with higher Rf value eluted first with benzene and was assigned 7-hydroxy-8-(1'-phenyl-prop-2'-ene)coumarin (167). PMR showed signals in $CDCl_3$ and few drops of DMSO as follows, a multiplet at δ 5.1-5.5 for three protons in the cinnamyl unit $-\underset{\text{Ph}}{\underset{|}{\underline{C}H}}-CH=\underline{C}H_2$ at C-8, two doublets J=9Hz at δ 6.1 and 7.55 for two orthocoupled protons at C-3 and C-4, another multiplet at δ 6.5-6.8 for single proton in the cinnamyl unit $-\underset{\text{Ph}}{\underset{|}{C}H}-\underline{C}H=CH_2$ at C-8, another doublet for C-6 appeared at δ 6.8 while the signal for C-5 proton merged with the phenyl ring signal, appeared as a multiplet at δ 7.1-7.3, in the cinnamyl unit at C-8 indicated that the migration has taken place at C-8 position. (Fig. 16)

The compound (167) was triturated with con. H_2SO_4 to obtain cis-2-methyl-3-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (168). The structure of the compound was confirmed

SCHEME - 47


I
O
O
O
Ph
166
DMA
Ph
HO
O
O
167
+
HO
O
O
Ph
170
Ph
H
H
CH3
O
O
O
168
CH3
O
O
O
H
Ph
H
171
Ph
CH3
O
O
O
169
CH3
O
O
O
Ph
172

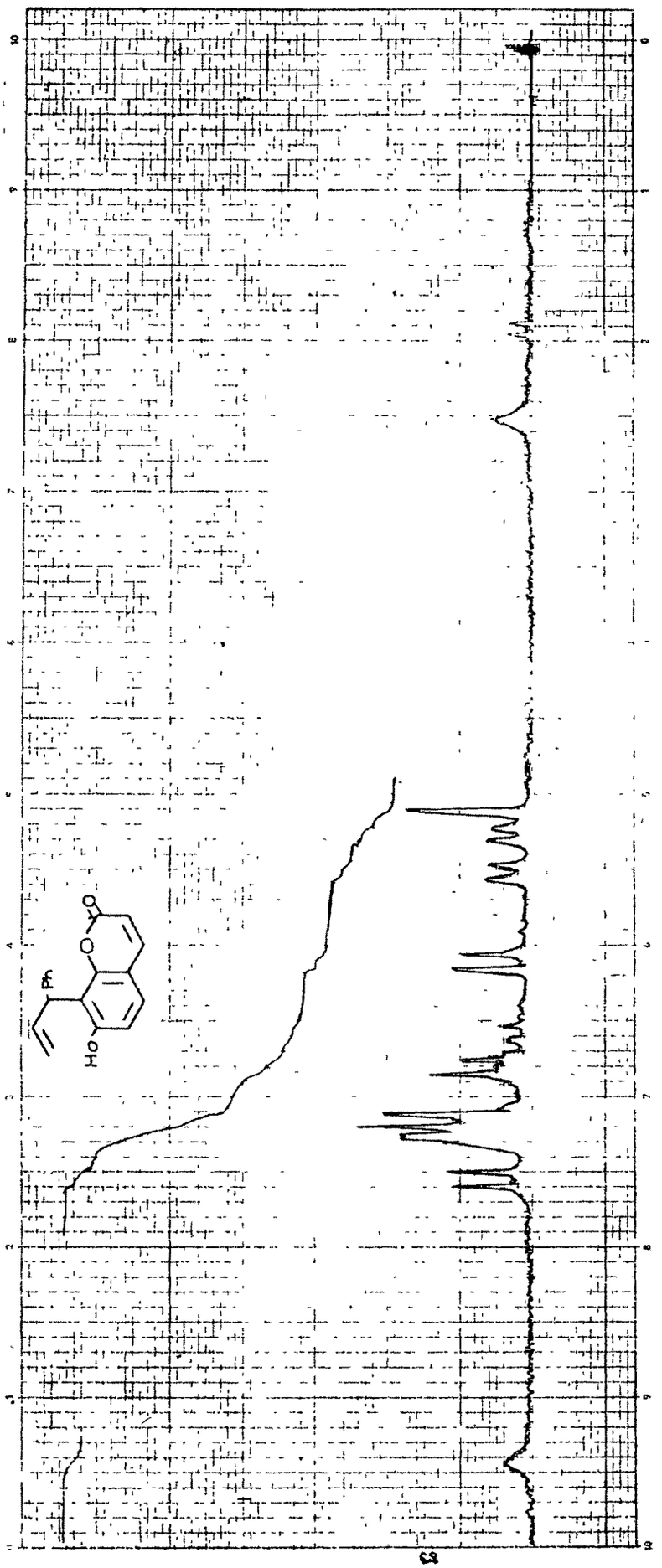


FIG-16

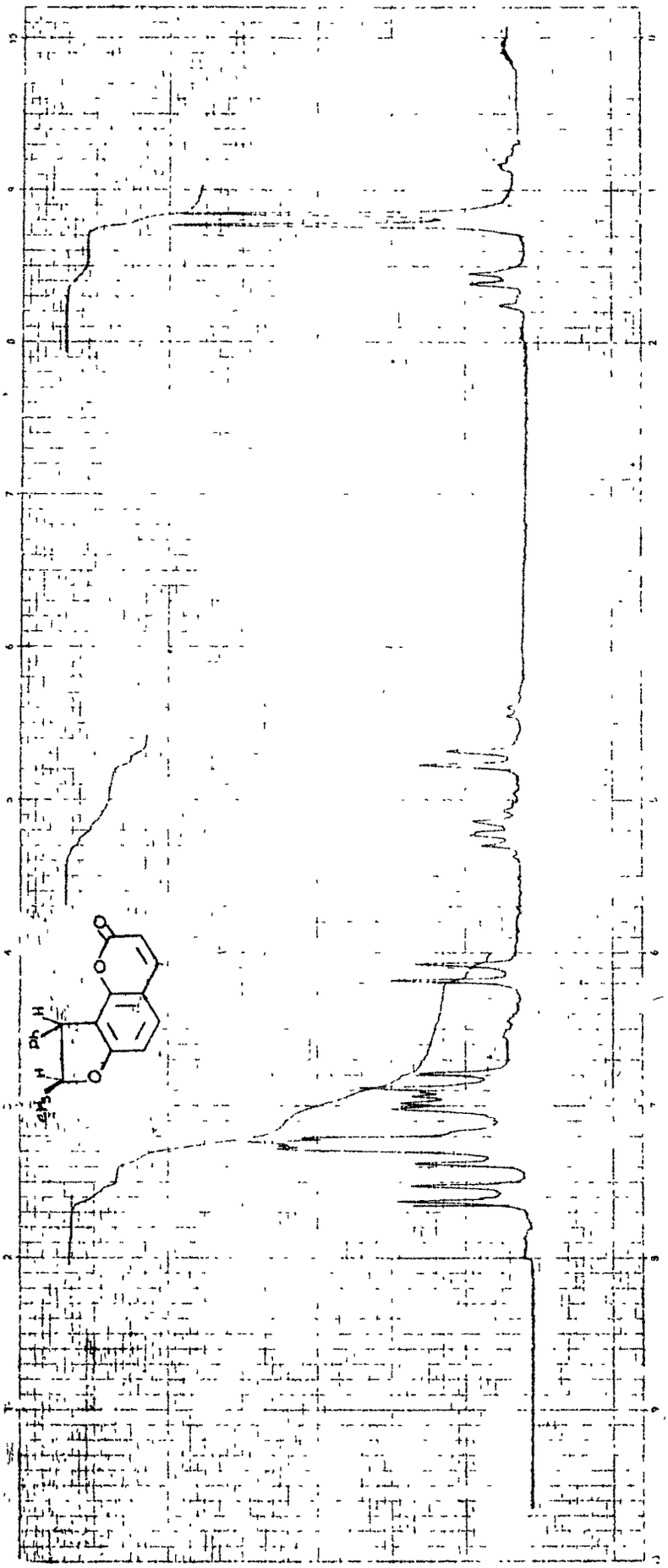


FIG-17

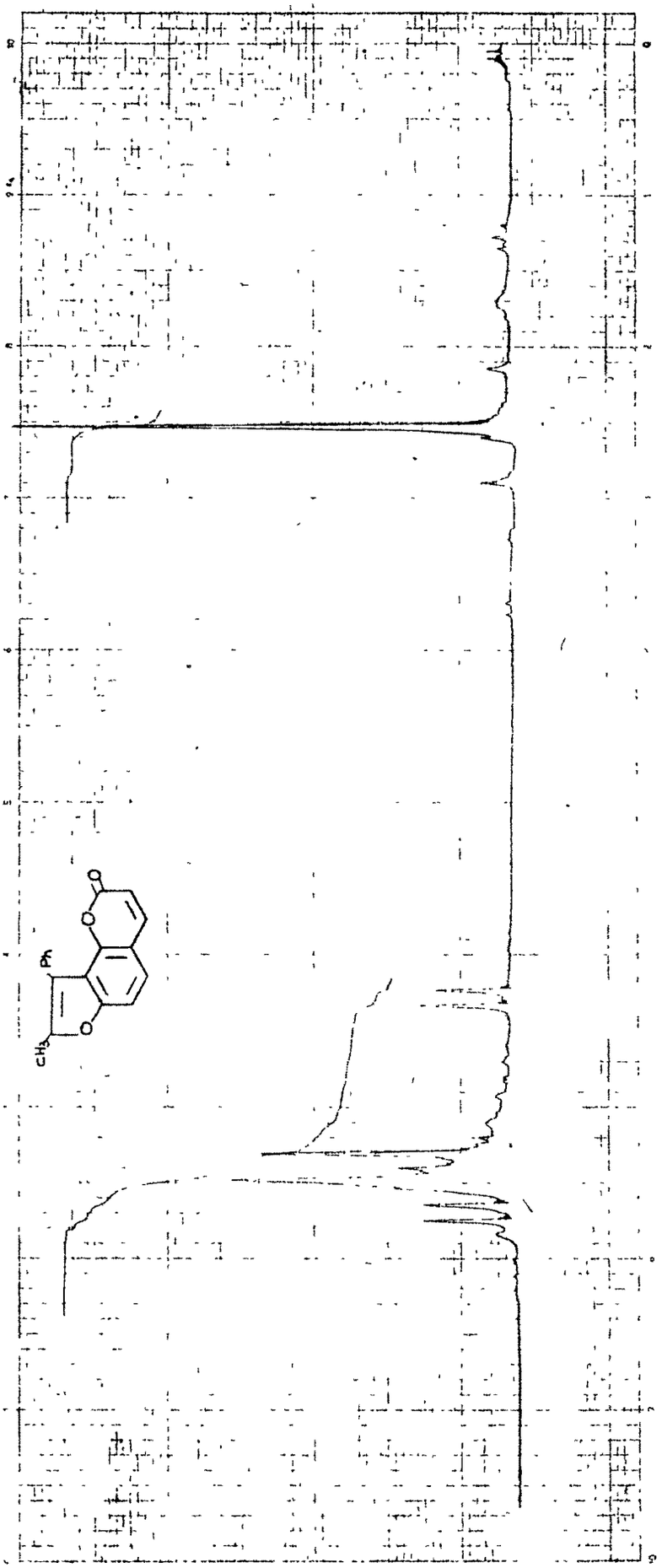


FIG-18

by PMR spectra which showed signals in $CDCl_3$, a doublet, J=7Hz at δ 1.15 for three methyl protons at C-2 indicated that the methyl group is cis to phenyl ring at C-3, a doublet J=7Hz at δ 4.7 for a proton at C-3, a multiplet at 5.1-5.3 for a proton at C-2, two doublets J=9Hz at δ 6.1 and 7.5 for protons at C-6 and C-7, a doublet J=9Hz at δ 6.85 for C-8 proton while the doublet for C-9 merged with the phenyl signal, appeared as a multiplet at δ 6.95-7.35. (Fig. 17)

Compound (168) on dehydrogenation with Pd/c (10%) in diphenyl ether gave the title compound (169). Its PMR showed signals in $CDCl_3$ a singlet at δ 2.5 corresponding to methyl group at C-2. Two doublets, J=9Hz at δ6.25 and 7.65 for C-6 and C-7 protons. Signals of C-8 and C-9 protons merged with the phenyl ring signal at C-3 which appeared at δ 7.25-7.5 [Scheme-47]. (Fig. 18)

2-Methyl-3-phenylfuro[3,2-g]benzopyan-7(H)-one (172)

The second alkali soluble product having lower Rf value was obtained by further eluting the column with benzene. The product was assigned structure 7-hydroxy-6-(1'-phenylprop-2'-ene) coumarin (170) on the basis of PMR which exhibited signals in $CDCl_3$ as a multiplet at δ 4.8-5.3 for three protons in the cinnamylunit $-\underset{Ph}{\underset{|}{CH}}-CH=CH_2$ at C-6, another multiplet

6.1-6.4 for a single proton in the cinnamyl unit -CH--CH-CH=CH at C-6, two doublets, J=9Hz at 6.15 and 7.55 for the protons at C-3 and C-4, two singlets appeared at 7.05 and 7.15 corresponds for the protons at C-5 and C-8 indicates that the migration has taken place at C-6 position and a multiplet appeared at 7.2 for the phenyl ring protons in the cinnamyl unit at C-6. (Fig. 19)

The compound (170) on triturating with con. H_2SO_4 gave cis-2-methyl-3-phenyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (171). PMR in CDCl showed, a doublet J=7Hz at 1.1 for three methyl protons at C-2 indicating that the C-2 methyl group and the phenyl ring at C-3 are cis to one another, a doublet J=7Hz at 4.6 for a proton at C-3 and a multiplet at 5.1-5.3 corresponds to a proton at C-2, two doublets J=9Hz at 6.15 and 7.5 for the protons at C-6 and C-5 respectively, two singlets at 6.8 and 7.1 for the dprotons at C-4 and C-9 while the phenyl protons at C-6 gave multiplet at 7.1 and 7.3. (Fig. 20).

The compound (171) on dehydrogenation with Pd/c (10%) gave the compound 2-methyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (172). The structure of the compound was confirmed by PMR which showed signals in CDCl at 2.5, a singlet for three methyl protons at C-2, two doublets, J=9Hz corresponding to C-6 and C-5 at 6.25 and 7.75, a singlet at 7.3 for a proton at C-4 while C-9 signal merged with the

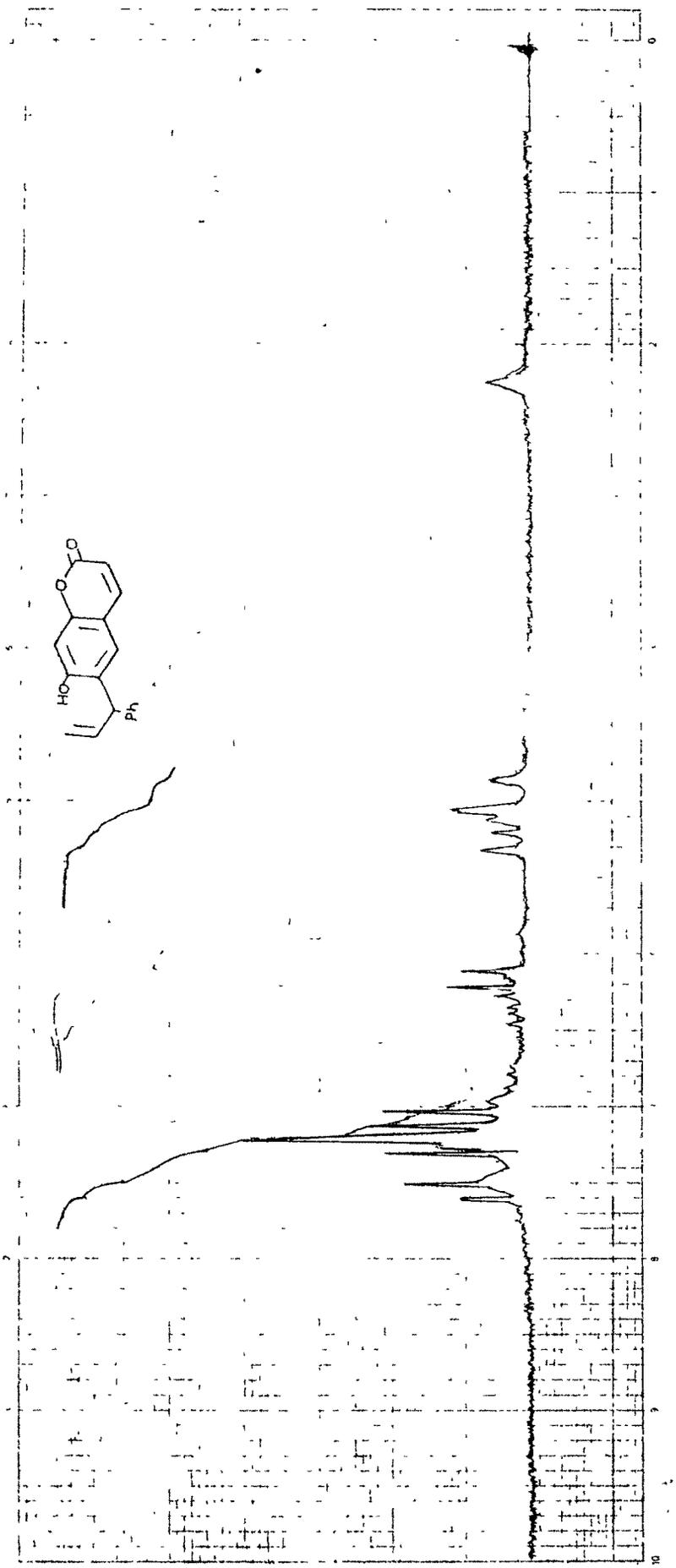


FIG-19

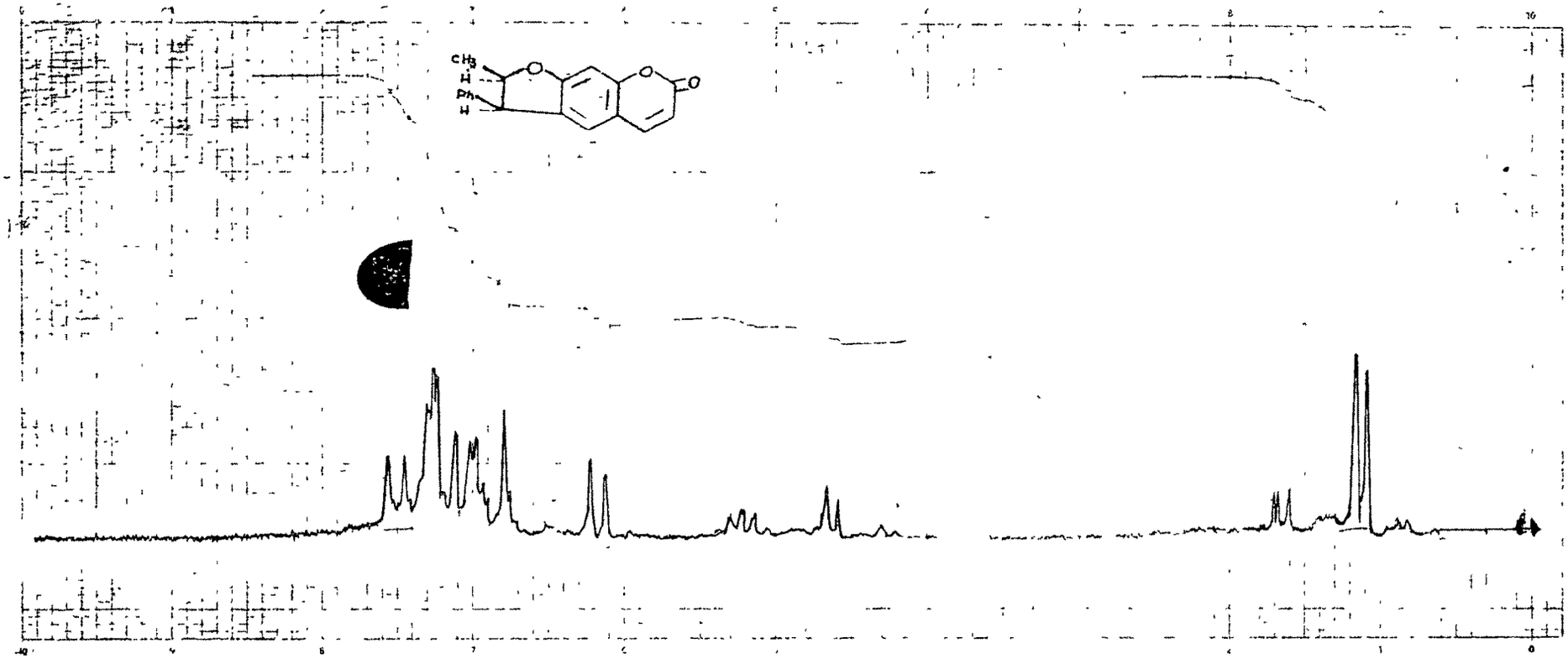


FIG-20

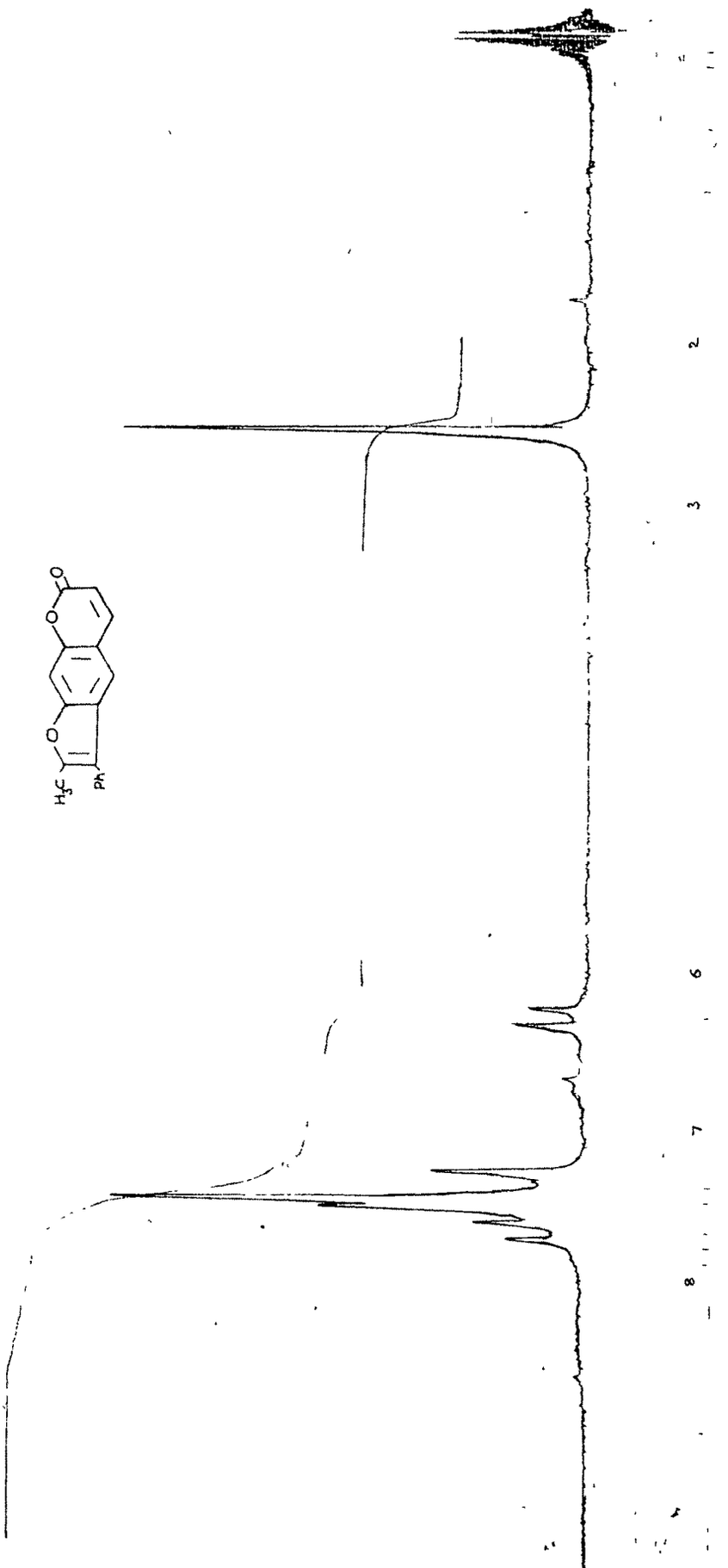


FIG-21

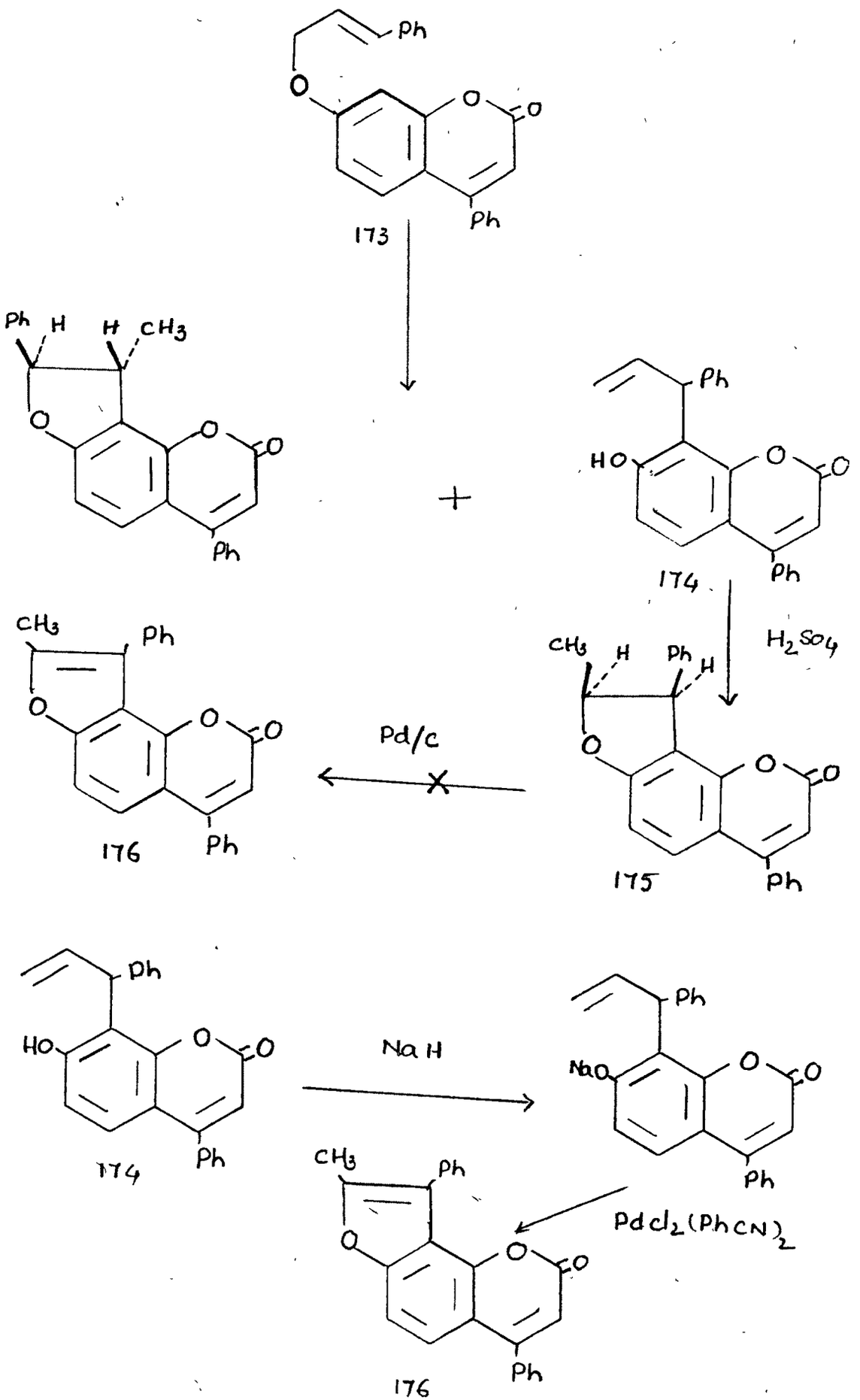
phenyl signal appeared at δ 7.5 [Scheme-47]. (Fig. 21)

2-Methyl-3,7-diphenylfuro(2,3-h)benzopyran-5(H)-one

7-Hydroxy-4-phenylcoumarin on cinnamylation with cinnamylchloride gave 7-cinnamyloxy-4-phenyl coumarin (173) which on Claisen rearrangement in N,N-dimethylaniline gave two products one alkali soluble and another alkali insoluble. The alkali soluble product was identified as 7-hydroxy-4-phenyl-8-(1'-phenylprop-2'-ene)coumarin (174). Its PMR showed signals in $CDCl_3$ and few drops of DMSO at δ 5.1-5.65, a multiplet for the three protons in the cinnamyl unit $-\underset{\underset{Ph}{|}}{CH}-CH=CH_2$ at C-8, a singlet at δ 6.1 for vinylic proton at C-3, a multiplet at δ 6.5-6.8 for single proton in the cinnamyl unit $-\underset{\underset{Ph}{|}}{CH}-CH=CH_2$ at C-8, a doublet, J=9Hz at δ 6.9 for a proton at C-5, while the other doublet for C-6 proton mixed with the signal of the phenyl ring appeared at δ 7.2-7.6. (Fig. 22)

The compound (174) on treatment with Con. H_2SO_4 gave a cis-2-methyl-3,7-diphenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (175). Its PMR exhibited signals in $CDCl_3$ at δ 1.1, a doublet J=7Hz for three methyl protons at C-2 indicate that the methyl group at C-2 and the phenyl group at C-3 are cis to one another, a doublet at δ 4.75 for one

SCHEME-48


Ph
O
O
O
Ph
173
Ph H H CH3
O
O
O
Ph
+
Ph
HO
O
O
Ph
174
H2SO4
CH3
Ph
O
O
O
176
Ph
Pd/C
CH3 H Ph H
O
O
O
175
Ph
Ph
HO
O
O
Ph
174
NaH
Ph
NaO
O
O
Ph
CH3
Ph
O
O
O
Ph
176
PdCl2(PhCN)2

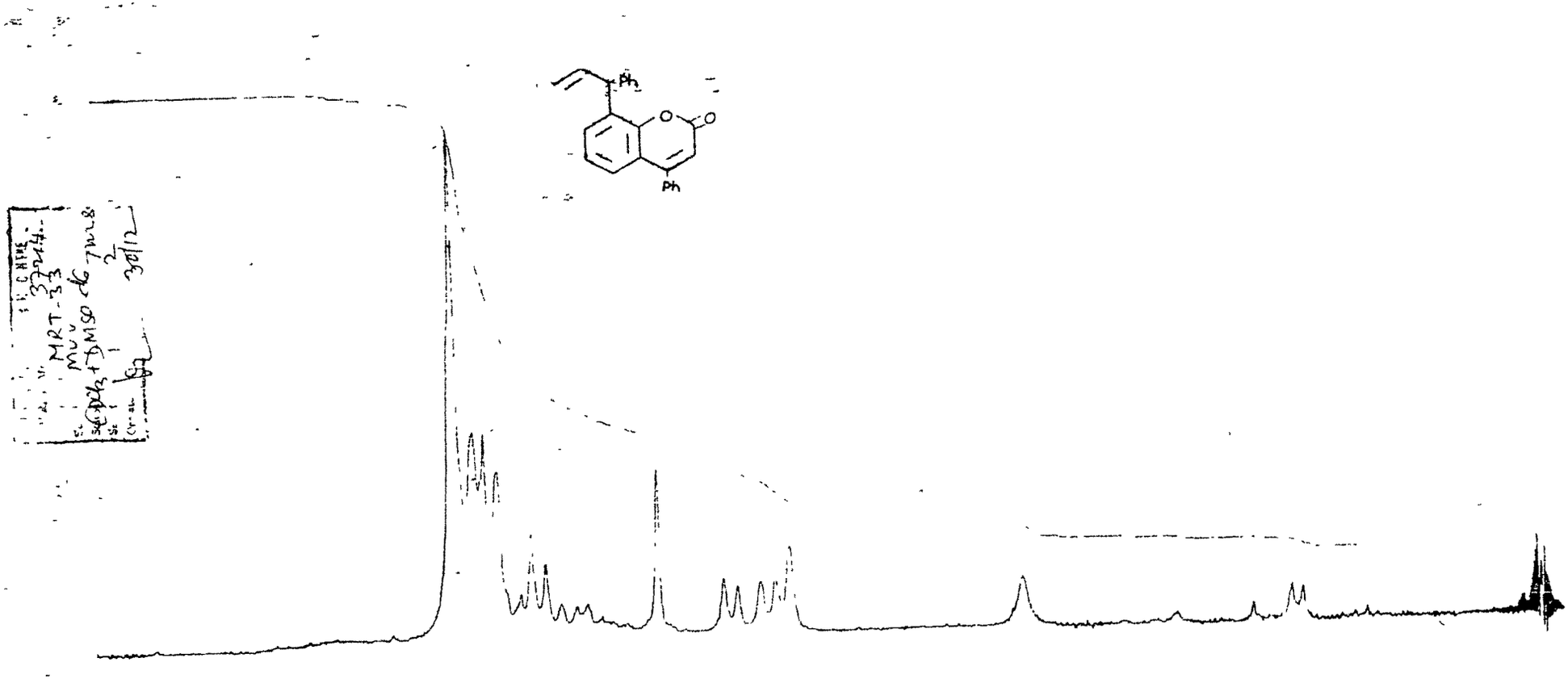


FIG - 22

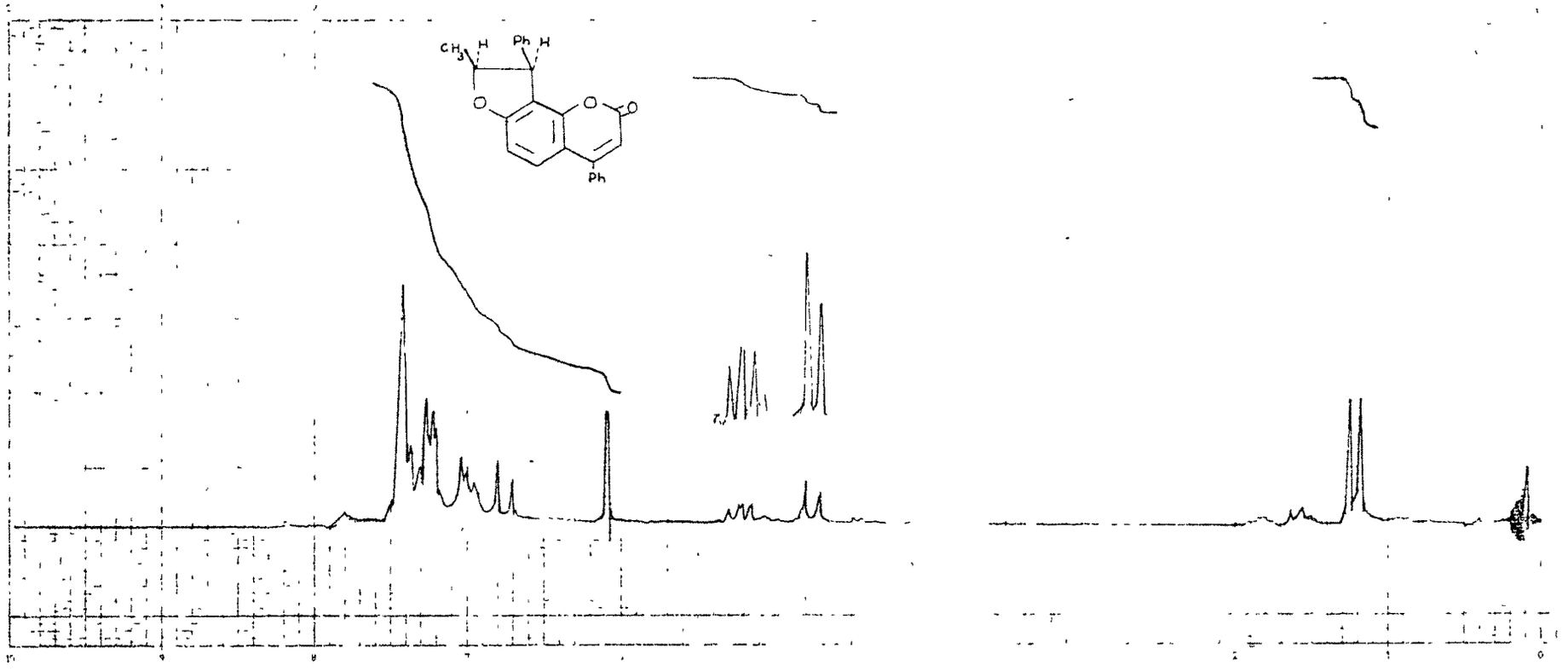


FIG-23

one proton at C-3 and a multiplet at δ 5.1-5.3 for a proton at C-2 indicates -CH-Ph group is at C-3 and -CH-CH_3 group is at C-2, a doublet, J=9Hz appeared at δ 6.75 for C-8 proton while the other doublet for C-9 proton mixed with the signals of the phenyl rings at C-3 and C-7. (Fig. 23)

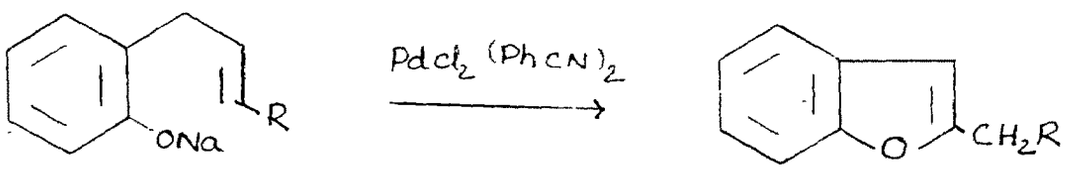
The compound (175) on dehydrogenation with Pd/c in diphenylether did not give the corresponding furocoumarin (176), original being isolated. Hence the furan ring was built up by making use of palladium chloride benzonitrile complex method.

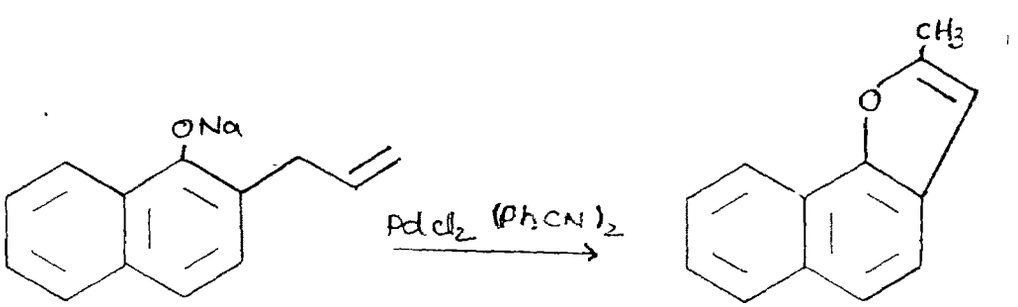
T. Hosokawa et al.[66-68] had prepared benzofuran by the reaction of sodium salt of allylphenols and dichlorobis (benzonitrile)-palladium. They had also prepared different naphthafurans and chromenes using the same method [Scheme-49].

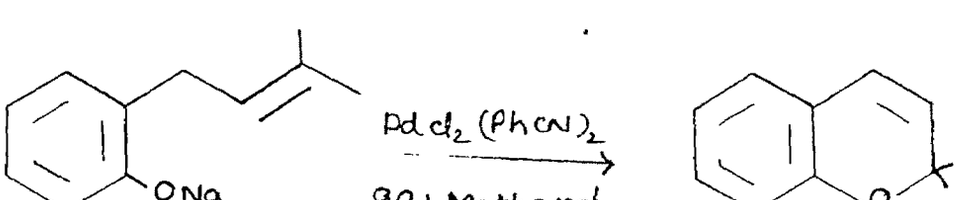
Chandratre and Trivedi[69] also achieved the synthesis of 8-methyl-6-methoxy-1,2,3-trihydrocyclopenta(C) furo(3,2-g) (1)-benzopyran-4-one from the sodium salt of 8-allyl-7-hydroxy-6-methoxy-1,2,3-trihydrocyclopenta(C)-(1)-benzopyran-4-one using the palladium complex. [Scheme-5O]

SCHEME-49

Hosokawa et al[66,67,68]

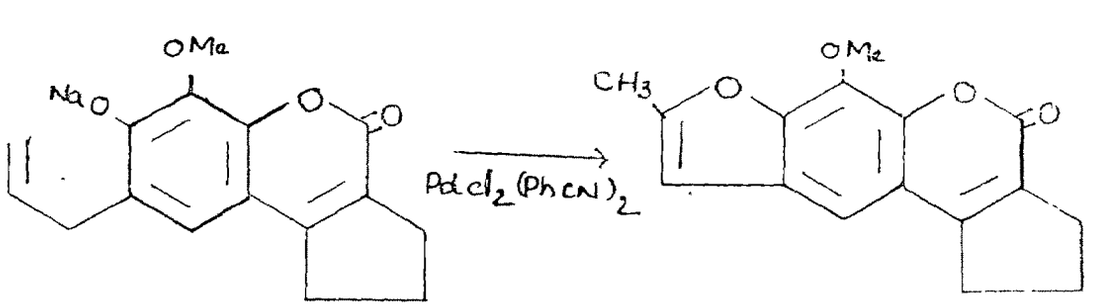






SCHEME-50

Chandratre and Trivedi[69]



2-Methyl-3,7-diphenylfuro(2,3-h)benzopyran-5(H)-one (176) was prepared by refluxing the sodium salt of the compound (174) with dichlorobis (benzonitrile) palladium in dry benzene in a water bath. The structure of the compound was confirmed by PMR specta which exhibited signals in $CDCl_3$ at δ2.55, a singlet for three methyl protons at C-2, another singlet at δ6.25 for vinylic proton at C-6, a multiplet at δ 7.0-7.7 for two phenyl group protons at C-3, C-7 and two orthocoupled protons at C-8 and C-9. (Fig. 24)

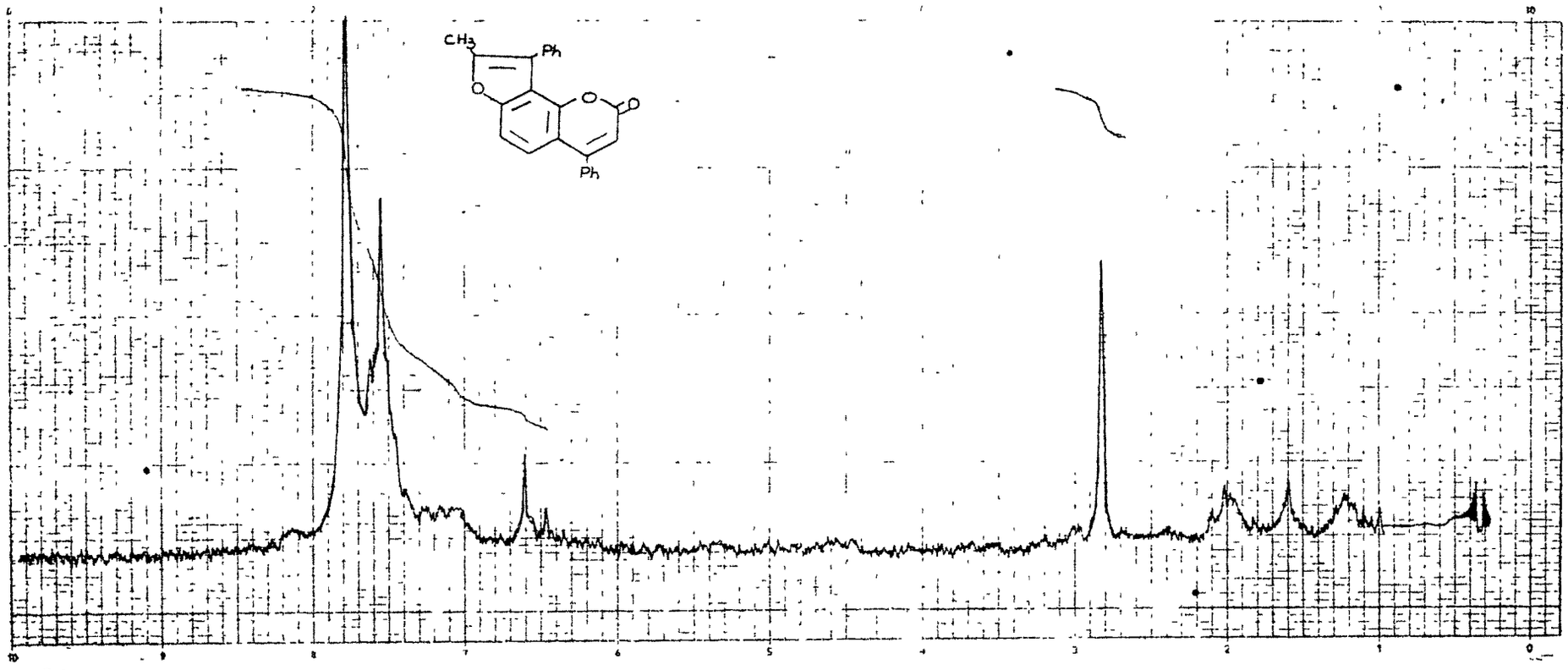


FIG - 24

EXPERIMENTAL

EXPERIMENTAL

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

General Procedure for 7-cinnamyloxy coumarin and its derivatives

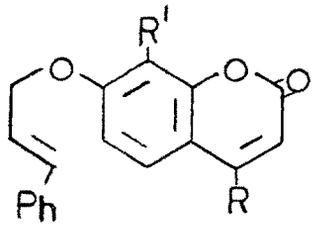
A solution of 7-hydroxy coumarin (0.02 mol) in dry acetone (100 ml) was refluxed with potassium carbonate (15 g), cinnamyl chloride (0.02 mol) and few crystals of potassium iodide on a water bath for 5 hr. The reaction was worked up and the obtained product was treated with dilute alkali to remove the starting material. The product crystallised from ethanol and benzene mixture. The physical properties and analysis of 7-cinnamyloxy derivatives are recorded in Table-1.

trans-3,7-Dimethyl-2-phenyl-2,3-dihydrofuro(2,3-h)benzopyran 5-(H)-one (152)

7-Cinnamyloxy-4-methylcoumarin (1 g) was refluxed with N,N-dimethylaniline (5 ml) for 24 hr. at 210-220°. The reaction mixture was poured into cold dilute HCl and treated with solvent ether. The etheral solution obtained was treated with dilute NaOH to separate the alkali soluble and alkali insoluble fractions. The alkali insoluble fraction

Table - 1

7-Cinnamyloxycoumarin derivatives



Compound No.	Compound/ Mol. Formula	M.p. °C	Yield %	Found/requires C%	H%
148	R=CH_3;R'=H ($C_{19}H_{16}O_3$)	179	75	77.7 78.0	5.4 5.5
159	R=CH_3;R'=I ($C_{19}H_{15}O_3I$)	210	75	55.0 54.5	4.0 3.5
162	R=CH_3;R'=CH_3 ($C_{20}H_{18}O_3$)	196	85	78.5 78.4	6.0 5.8
166	R=H;R'=I ($C_{18}H_{13}O_3I$)	173	70	53.90 53.46	3.6 3.2
173	R=Ph;R'=H ($C_{24}H_{18}O_3$)	184	75	81.1 81.3	5.3 5.1

was evaporated and the residue crystallised from alcohol as colourless crystals (0.2 g), M.p. 136°.

Analysis : Found : C, 78.5% ; H, 5.4%

$C_{19}H_{16}O_3$: requires : C, 78.1% ; H, 5.4%

7-Hydroxy-4-methyl-8-(1'-phenylprop-1'-ene)coumarin (149)

The alkali soluble fraction was acidified with dil. HCl, separated product filtered, dried and checked on TLC. It showed, to be a mixture of two compounds. The two compounds were separated by preparative TLC. The compound with higher Rf. value was assigned structure (149) and crystallised from dilute alcohol (0.3 g), M.p. 220°, Lit. M.p. 223°.

Analysis : Found : C, 77.8% ; H, 5.7%

$C_{19}H_{16}O_3$: requires : C, 78.1% ; H, 5.4%

7-Hydroxy-4-methyl-6-(1'-phenylprop-2'-ene)coumarin (156)

The lower band was collected and extracted with ethanol and recrystallised from dilute alcohol as colourless needles, (0.1 g), M.p. 192°.

Analysis : Found : C, 77.8% ; H, 5.5%

$C_{19}H_{16}O_3$: requires : C, 78.1% ; H, 5.4%

3,7-Dimethyl-2-phenylfuro(2,3-h)benzopyran-5(H)-one (153)

trans-3,7-Dimethyl-2-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (0.5 g) in dry benzene and DDQ (0.5 g) in dry benzene was refluxed on water bath for 8 hr. The reaction mixture was filtered hot and the excess of benzene was removed. On standing crystals separated out. The product was further purified by column chromatography. It crystallised from ethanol as pale pink needles, (0.3 g), M.p. 187°.

Analysis : Found : C, 79.0% ; H, 4.9%

$C_{19}H_{14}O_3$: requires : C, 78.5% ; H, 4.5%

cis-2,7-Dimethyl-3-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (154)

7-Hydroxy-4-methyl-8-(1'-phenylprop-1'-ene)coumarin (0.5 g) was dissolved in 90% H_2SO_4 (1 ml) and the solution was heated on water bath for 5 min. The reaction mixture was poured into cold water. Separated product was filtered and washed with dil. NaOH and distilled water to remove the uncyclised starting compound. The product crystallised from benzene, alcohol mixture (10:1) as colourless needles, (0.4 g), M.p. 154°.

Analysis : Found : C, 77.6% ; H, 5.2%

$C_{19}H_{16}O_3$: requires : C, 78.0% ; H, 5.4%

2,7-Dimethyl-3-phenylfuro(2,3-h)benzopyran-5(H)-one (155)

cis-2,7-Dimethyl-3-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (0.5 g) was dissolved in dry benzene and an equivalent amount of DDQ (0.5 g) in dry benzene was added. The solution mixture was refluxed on water bath for 50 to 60 hr. The reaction mixture was filtered hot and the excess of benzene distilled. The product crystallised from benzene as pale pink needles, (0.2 g), M.p. 226°

Analysis : Found : C, 78.7% ; H, 4.9%

$C_{19}H_{14}O_3$: requires : C, 78.5% ; H, 4.5%

7-Hydroxy-6-(1'-phenylpropyl)-4-methylcoumarin (158)

A solution of 7-hydroxy-6-(1'-phenylprop-2'-ene)-4-methylcoumarin (0.5 g) in ethyl acetate (50 ml) was stirred with Pd/c (10%, 0.5 g) in the atmosphere of H_2 for 4 to 5 hr. The reaction mixture was filtered and the excessof ethyl acetate was distilled. The obtained product was purified by crystallisation which crystallised from alcohol, (0.2 g), M.p. 155°.

Analysis : Found : C, 77.10% ; H, 6.12%

$C_{19}H_{18}O_3$: requires : C, 77.55% ; H, 6.08%

trans-2,5-Dimethyl-3-phenyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (160)

7-Hydroxy-4-methyl-6-(1'-phenylprop-2'-ene)coumarin (0.5 g) was triturated with 75% H_2SO_4 in a water bath for 5 min. The contents were poured on crushed ice, separated product was filtered and washed with dilute sodium hydroxide solution and crystallised from dil. alcohol in colourless needles, (0.4 g), M.p. 154°.

Analysis	:	Found	:	C, 78.4%	;	H, 5.6%
$C_{19}H_{16}O_3$	:	requires	:	C, 78.0%	;	H, 5.4%

2,5-Dimethyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (161)

trans-2,5-Dimethyl-3-phenyl-2,3-dihydrofuro(3,2-g) benzopyran-7(H)-one (0.4 g), palladised charcoal (10% Pd/c) (0.4 g) in diphenyl ether (6 ml) was refluxed for 6 hr. The reaction mixture was filtered hot and the filtrate was cooled and diluted with petroleum ether (40-60°)(5 ml) yellowish compound separated out from the solution and it crystallised from benzene as yellowish shining crystals, (0.2 g), M.p. 185°.

Analysis	:	Found	:	C, 78.9%	;	H, 4.8%
$C_{19}H_{14}O_3$	:	requires	:	C, 78.5%	;	H, 4.5%

7-Hydroxy-4,8-dimethyl-6-(1'-phenylprop-2'-ene)coumarin (163)

7-Cinnamyloxy-4,8-dimethylcoumarin (2 g) was refluxed with N,N-dimethylaniline (15 ml) for 6 hr. The reaction mixture was cooled and poured into ice cold dil. HCl and extracted with solvent ether. The extract was washed with dil. NaOH solution. The alkaline extract on acidification with dil. HCl gave the product, which crystallised from benzene-petroleum ether mixture as light yellow crystals, (1.2 g), M.p. 168°.

Analysis : Found : C, 78.8% ; H, 6.0%

$C_{20}H_{18}O_3$: requires : C, 78.4% ; H, 5.8%

trans-2,5,9-Trimethyl-3-phenyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (164)

7-Hydroxy-4,8-dimethyl-6-(1'-phenylprop-2'-ene) coumarin (0.5 g) was triturated with con. H_2SO_4 (0.5 ml) and heated in water bath for 5 min. The mixture was cooled, poured into crushed ice. Separated product was filtered, washed with dil. NaOH followed by distilled water. It crystallised from benzene-petroleum ether mixture as colourless flakes, (0.3 g), M.p. 159°.

Analysis : Found : C, 78.5% ; H, 6.2%

$C_{20}H_{18}O_3$: requires : C, 78.4% ; H, 5.8%

2,5,9-Trimethyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (165)

A mixture of trans-2,5,9-trimethyl-3-phenyl-2,3-dihydro-furo(3,2-g)benzopyran-7(H)-one (0.5 g) and Pd/c (10%, 0.5 g) in diphenyl ether (8 ml) was refluxed for 5 hr. The mixture was filtered hot, cooled and diluted with pet. ether (5 ml). The separated product was filtered and washed with pet. ether. It crystallised from benzene as yellow shining needles, (0.3 g), M.p. 192°.

Analysis : Found : C, 79.3% ; H, 5.6%

$C_{20}H_{16}O_3$: requires : C, 78.9% ; H, 5.2%

7-Hydroxy-8-(1'-phenylprop-2'-ene)coumarin (167)

7-Hydoxy-8-iodo-coumarin (2.5 g) was refluxed with N,N-dimethylaniline (20 ml) for 5 hr. The reaction mixture was cooled and poured into cold dil. HCl and extracted with solvent ether. Then the extract was washed with dil. NaOH solution. The alkaline extract on acidification with dil. HCl gave solid product which showed on TLC to be a mixture of two compounds. The compounds were separated by preparative column chromatography using benzene as eluent. Small benzene fractions of 25 ml were collected and combined after checking with TLC. The upper spot having higher Rf value was eluted out first and was assigned the structure (167). The compound crystallised from benzene and few drops of alcohol (0.35 g),M.p. 188°.

Analysis : Found : C, 77.85% ; H, 5.18%

$C_{18}H_{14}O_3$: requires : C, 77.69% ; H, 5.03%

7-Hydroxy-6-(1'-phenylprop-2'-ene)coumarin (170)

The second product having lower Rf value was obtained on further eluting the column with benzene. The product crystallised from benzene and few drops of alcohol, (0.4 g) M.p. 130°.

Analysis : Found : C, 77.26% ; H, 5.22%

$C_{18}H_{14}O_3$: requires : C, 77.69% ; H, 5.03%

cis-2-Methyl-3-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (168)

7-Hydroxy-8-(1'-phenylprop-2'-ene)coumarin (0.5 g) was treated with 75% H_2SO_4 (1.0 ml) and heated on water bath for 5 min. The mixture was cooled and poured over crushed ice. Separated product was filtered, washed with dil. NaOH followed by water. The product crystallised from alcohol (0.3 g), M.p. 173°.

Analysis : Found : C, 77.23% ; H, 5.17%

$C_{18}H_{14}O_3$: requires : C, 77.69% ; H, 5.03%

2-Methyl-3-phenylfuro(2,3-h)benzopyran-5(H)-one (169)

2-Methyl-3-phenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (0.5 g) and palladised charcoal (10%, 0.5 g) in diphenylether (8 ml) was refluxed for 6 hr. The reaction mixture was filtered hot and diluted with petroleum ether (40:60) (5 ml). Separated product filtered and washed with hot petroleumether to remove diphenyl ether. The product crystallised from benzene, (0.2 g) M.p.

Analysis : Found : C, 77.83% ; H, 4.38%

$C_{18}H_{12}O_3$: requires : C, 78.26% ; H, 4.34%

cis-2-Methyl-3-phenyl-2,3-dihydrofuro(3,2-g)benzopyran-7(H)-one (171)

7-Hydroxy-6-(1'-phenylprop-2'-ene)coumarin (0.5 g) was treated with 75% H_2SO_4 (1 ml) and heated the mixture on water bath for 5 min. The reaction mixture was cooled and poured over crushed ice. Separated product filtered and washed with dil. NaOH followed by water. The product crystallised from alcohol, (0.3 g), M.p. 170°.

Analysis : Found : C, 77.36% ; H, 5.25%

$C_{18}H_{14}O_3$: requires : C, 77.69% ; H, 5.03%

2-Methyl-3-phenylfuro(3,2-g)benzopyran-7(H)-one (172)

A mixture of 2-methyl-3-phenyl-2,3-dihydrofuro(3,2-g) benzopyran-7(H)-one (0.5 g) and palladised charcoal (10%, 0.5 g) in diphenylether (8 ml) was refluxed for 5 hr. The reaction mixture was filtered hot and diluted with pet. ether (40°-60°) (5 ml). Separated product filtered and crystallised from benzene, (0.3 g), M.p. 170°.

Analysis : Found : C, 78.70% ; H, 4.47%

$C_{18}H_{12}O_3$: requires : C, 78.26% ; H, 4.34%

7-Hydroxy-4-phenyl-8-(1'-phenylprop-2'-ene)coumarin (174)

7-Cinnamyloxy-4-phenylcoumarin (3 g) was refluxed with N,N-dimethylaniline (24 ml) for 5 hr. The reaction mixture was cooled and poured into cold dil. HCl and extracted with solvent ether. The ether extract was then treated with dil. NaOH to separate the alkali soluble and alkali insoluble fractions. The alkali soluble fraction on acidification with HCl gave solid product, which crystallised fro ethyl acetate, (2.0 g), M.p. 240°.

Analysis : Found : C, 81.10% ; H, 5.25%

$C_{24}H_{18}O_3$: requires: C, 81.35% ; H, 5.08%

cis-2-Methyl-3,7-diphenyl-2,3-dihydrofuro(2,3-h)benzopyran-5(H)-one (175)

7-Hydroxy-4-phenyl-8-(1'-phenylprop-2'-ene)coumarin (0.5 g) was triturated with con. H_2SO_4 on a water bath for 5 min. The mixture was then cooled and poured over crushed ice. Separated product was filtered, washed with NaOH and water. The product crystallised from benzene, (0.3 g), M.p. 185°.

Analysis : Found : C, 81.70% ; H, 5.10%

$C_{24}H_{18}O_3$: requires : C, 81.35% ; H, 5.08%

2-Methyl-3,7-diphenylfuro(2,3-h)benzopyran-5(H)-one (176)

7-Hydroxy-4-phenyl-8-(1'-phenylprop-2'-ene)coumarin (0.5 g) was stirred with sodium hydride (0.4 g) in dry ether (50 ml) for 3 to 4 hr. Next day the excess of ether was removed and the sodium salt thus obtained was refluxed with palladiumchloride benzonitrile complex in dry benzene for 3 hr. The reaction mixture was filtered hot and the excess of benzene was removed by distillation. The product could not be purified and hence the same was taken for PMR for assigning the structure.

REFERENCES

1. E. Spath, Chem. Ber., 7OA, 83 (1937).

2. F.M. Dean, Fortschritte der chime organischer Naturstoffe, Vol. 9, Wein Springer, Verlag, Australia, P. 225 (1952).

3. F.M. Dean, Naturally occuring oxygen ring compounds, Butter worth, London, PP. 176-22O (1963).

4. L. Reppel, Pharmazie, 9, 278 (1954).

5. W. Karrer, Konstitution und vorkommen Der Organischem pflangenstoffe, Birkenhauser, Verlag Basil and Stuttgart P. 531 (1958).

6. J.A. Parrish, R.S. Stern, M.A. Pathak and T.B. Fitzpatrick, Photochemistry of skin diseases in the Science of Photo-medicine, New York, 595 (1982).

7. H.H. Roenigk, Jr. Natl. Canc. Inst. Monogr. 66, 179 (1984).

8. M.A. Pathak, B.B. Mosher and T.B. Fitzpatrick, Jr. Natl. Canc. Inst. Monogr, 66, 165 (1984).

9. M. Jaratt, W. Hubler Jr. and W. Panek Dye-light Photo-therapy of Viral, Bacterial and Fungal infections in the Sciene of photomedicine, 595 (1982).

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

11. J.E. Hearst, J. Invert Dermatol, 77, 39 (1981).

12. S.K. Kondoleeom, G.W. Robinson and L.M. Hallick, Virology, 129, 261 (1982).

13. T.F. Anderson and J.J. Vosruhees, Ann. Rev. Pharmacol. Toxicol. 20, 135 (1980).

14. G. Rodighiero and F. Dall'Acqua Photochem. Photobiol, 24, 647 (1976).

15. D. Averbeck and E. Moustacchi, Mutant. Res. 68, 133 (1979).

16. B.G. Bryant, Am. J. Harp Pharm. 37, 814 (1980).

17. Bridge and G. Straurs, Nature (London), 283, 523 (1980).

18. H. Kuske, Dermatologica, 82, 273 (1940).

19. L. Musazo, G. Rodighiero, G.G. Carporale and C. Antonello, Farmaco Ed. Sci., 13, 355 (1958).

20. L. Musazo, G. Rodighiero and F. Santamaria, Z. Naturforsh, 25B, 642 (1970).

21. M.A. Pathak and T.B. Fitzpatrick, J. Invest Dermatol, 32, 509 (1959).

22. M.A. Pathak and J.H. Fellman, Nature 185, 382 (1960).

23. A. Moore Thomas and B. Montgomery Alan, Photochem. Photobiol, 24(1), 83-6 (1976).

24. F. Dall Acqua, S. Marciani and G. Rodighiero, FEBS lettes, 9, 121 (1970).

25. R.S. Cole, Biochem.Biophys. Acta, 217, 30 (1970).

26. T.B. Fitzpatrick, J.A. Parrish and M.A. Pathak, Photo-therapy of Vitiligo sunlight and Man Edited by M.A. Pathak et al., 131-141.

27. E. Spath and M. Pailer, Ber., 67, 1212 (1934).

28. E.C. Horning and D.B. Reisner, J. Am. Chem. Soc., 70, 3619 (1948).

29. R.E. Esse and B.E. Chistenson, J. Org. Chem. 25, 1565 (1960).

30. G. Rodighiero and C. Antonello, Ann. Chim Rome, 46, 960 (1956), Chem. Abstr. 51, 6616 (1957).

31. Leonard R. Worden and Kurt D. Kaufmann, J. Org. Chem., 34, 2311, (1969).

32. Dilipkumar Chatterzi and Kalyanmay Sen, J. Ind. Chem. Soc., Vol. 48, No. 4 (1971).

33. T.R. Seshadri and M.S. Sood, Indian J. Chem. 1, 291 (1963).

34. Anjan Ray, Amitabh Dasgupta and Kalyanmay Sen, Indian J. Chem. Vol. 16B No. 10 PP. 929-30, (1978).

35. K.D. Kaufmann, J. Org. Chem., 26, 117 (1961).

36. Dean R. Bender, John E. Hearst and Henry Rapoport, J. Org. Chem. Vol. 44 No. 15 (1979).

37. V.K. Ahluwalia, Chandra Prakash and R.P. Singh, Aust. J. Chem., 32, 1361-7 (1979).

38. V.K. Ahluwalia, Ranjana Gupta, Manju Grover, Irani Mukherjee and C.H. Khanduri, Ind. J. Chem. Vol. 27B, 1138-39 (1988).

39. J.K. MacLeod and B.R. Worth, Tetrahedron Letters, No.3, PP. 237-240 (1972).

40. P. Rodighiero, M. Palumbo, S. Marciani Magno, P. Manzini, O. Gia, R. Piro and A. Guiotto, J. Heterocyclic. Chem., 23, 1405 (1986).

41. Pierre Queval and Emile Bisagni, Eur.J. Med. Chem.-Chemical Therapeutica, 9, No. 3, P. 335-340 (1974).

42. J. Moron, C.N. Nguyen and E. Bisagni, J. Chem. Soc. Perkin Trans 1, 225 (1983).

43. Pat N. Confalone and Dianne L. Canfalone, Tetrahedran, Vol. 39, No. 8, PP. 1265-71 (1983).

44. N.H. Pardanani and K.N. Trivedi, Curr. Sci., 39, 349 (1970).

45. N.H. Pardanani and K.N. Triedi, Jour. Ind. Chem. Soc. Vol. 46, No. 11 (1969).

46. N.H. Pardanani and K.N. Trivedi, Jour. Ind. Chem.Soc., Vol. 48,No.4 (1971).

47. V.N. Dholakia and K.N. Trivedi, Jour. Ind. Chem. Soc., Vol. 47, 1058 (1970).

48. Y.A. Shaikh and K.N. Trivedi, J. Ind. Chem. Soc., Vol.49 No. 9 (1972).

49. S.P. Chandratre, Ph.D. Thesis, M.S. University of Baroda, Baroda, P. 116 (1989).

50. Y.A. Shaikh and K.N. Trivedi, J. Ind. Chem. Soc., Vol. 51, 755-756 (1974).

51. M.G. Parekh and K.N. Trivedi, Aust. J. Chem., 23, 407-12 (1970).

52. K.R. Shah and K.N. Trivedi, Aust. J. Chem., 27, 1971 (1974).

53. S.M. Desai and K.N. Trivedi, Indian Journal of Chemistry, Vol. 248 PP 47-50 (1985).

54. S.M. Desai and K.N. Trivedi, Asian Journal of Pharmaceutial Sciences, 5,560-67 (1983).

55. S.P. Chandratre ; Ph.D. Thesis, M.S. University of Baroda, Baroda P. 278 (1989).

56. E. Spath and M. Pailer ; Ber. Dtsch. Chem. Ges, 68B, 940 (1935).

57. R. Aneja, S.K. Mukherjee and T.R. Seshadri ; Tetrahedran, 4, 256 (1958).

58. A. Guiotto, P. Rodighiero, P. Manzine, G. Pastorine, F. Bordin, F. Carlassare, D. Vedaldi,F. Dall'Acqua, M. Tamaro, G. Recchia and Cristofolini; Journal of Medicinal Chemistry, 27, 959 (1984).

59. F. Baccichetti, F. Carlassare, F. Bordin, A. Guiotto, P. Rodighiero, D. Vedaldi, M. Tamaro and F. Dall'Acqua Photochemistry and Photobiology ; Vol. 39, No. 4, PP 525-529 (1984).

60. N.H. Pardanani and K.N. Trivedi ; J. Indian Chem.Soc., Vol. 48, No. 4 (1971).

61. S.P. Chandratre ; Ph.D. Thesis, M.S. University of Baroda, Baroda P.114 (1989).

62. L. Jurd ; Tetrahedron, 25, 1407 (1969).

63. E. Schmid, G. Frater, H.J. Hansen and H. Schmid, Helv. Chim. Acta, 55, 1625 (1972).

64. A. A.C. Jain, D.K. Tuli and A. Kumar, Current Science, 46, 839 (1971).

B. A.C. Jain, D.K. Tuli and A. Kumar, Proc. Indian Acad. Sci. 87A, 389 (1978).

65. V.K. Ahluwalia, D. Kumar and Y.K. Gupta, Indian J. Chemistry, 16B, 579 (1978).

66. T. Hosokawa, K. Maeda, K. Koga and I. Mortani, Tetrahedron Letters 10, 739 (1973).

67. T. Hosokawa, H. Ohakata and I. Moritani, Bull. Chem. Soc., Japan, 48, 1533-36 (1975).

68. T. Hosokawa, S. Yamashita, S.I. Murahashi and A. Sonoda, Bull. Chem. Soc. Japan, 49, 3662 (1979).

69. S.P. Chandratre, Ph.D. Thesis, M.S. University of Baroda, Baroda P. 72 (1989).