chapter - II

synthesis of pyranoisoflavones

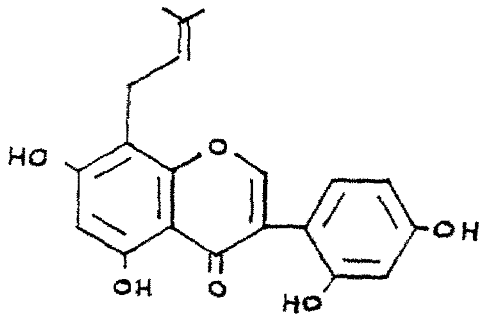
CHAPTER - II

Synthesis of Pyranoisoflavone

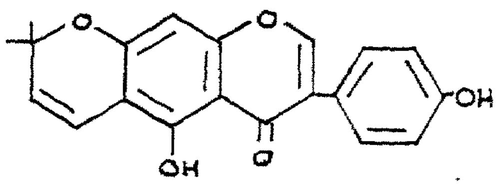
Most of the naturally occuring Isoflavones have been shown to possess a prenyl unit either in open chain form or as a hetero oxygen ring viz. pyran fused linearly or angularly to the isoflavone ring system. eg 2,3-dehydrokievitone, Alpinum isoflavone and Derrone are the examples for the same. In certain isoflavones, both pyran ring as well as prenyl side chain are present. eg. Osajin, Derrubone, Warangalone etc.

Many routes for the synthesis of prenylated isoflavanoids have been developed by different workers. Jain, Lal and Seshadri[1] carried out nuclear prenylation of 2,4-dihydroxy acetophenone (1) with prenyl bromide in basic conditions such as methanolic potash and obtained a mixture of three products viz. 3-C-prenyl (2), 3,5-di-C-prenyl (3) and 4-o-prenylresacetophenone (4) derivatives, while 2-methyl-5,7-dihydroxychromone (5) gave 7-o-prenyl derivative (6), 6,8-di-C-prenyl (7) and 6-prenyl derivative (8) which was identical with peucenin. (8), on treatment with formic acid gave (9) (Scheme-I).

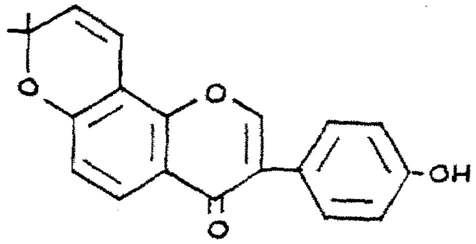
Similar reaction was carried out by Jain & coworkers[2] on 2,4-dihydroxy phenylbenzyl ketone (10) and obtained



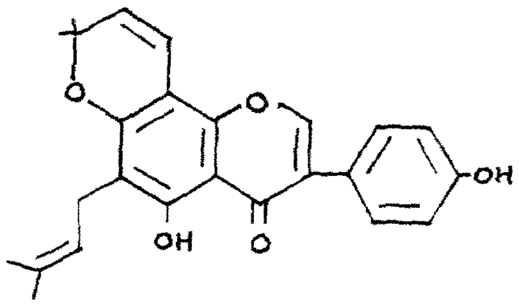
2,3 - Dehydrokievitone



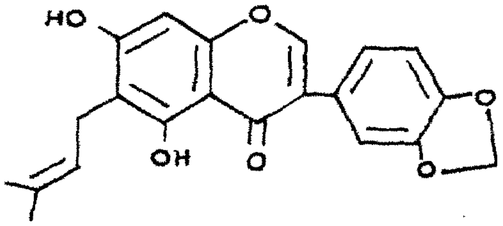
Alpinum isoflavone



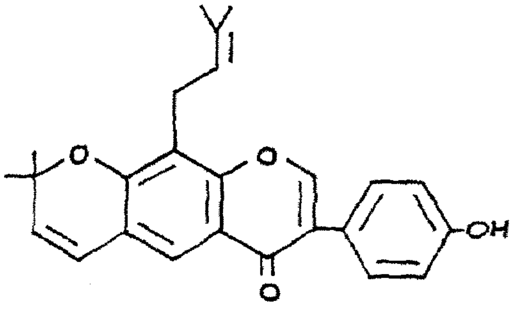
Derrone



Osajin

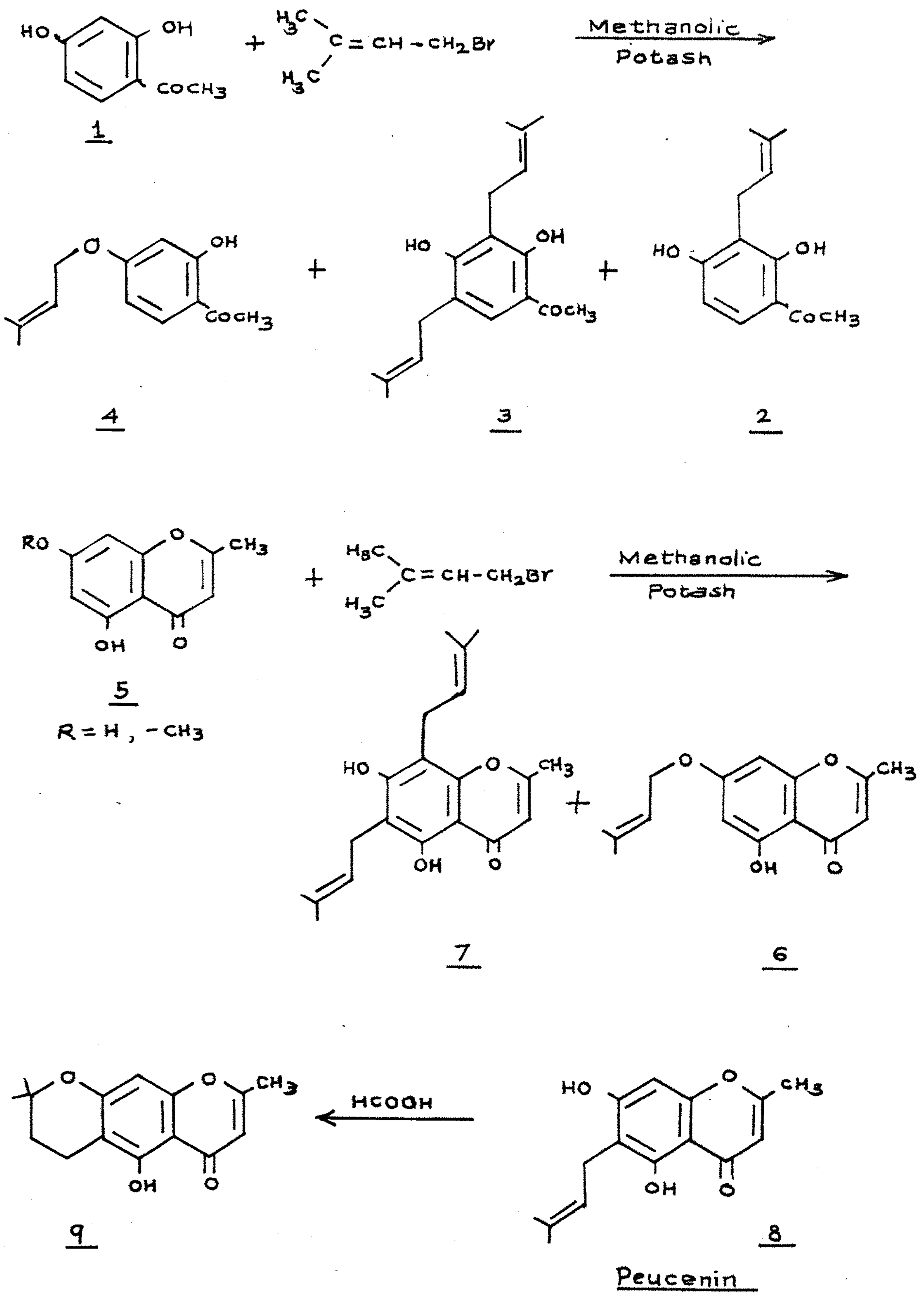


Derrubone



Warangalone

Scheme I : Jain, Lal & Seshadri[1]



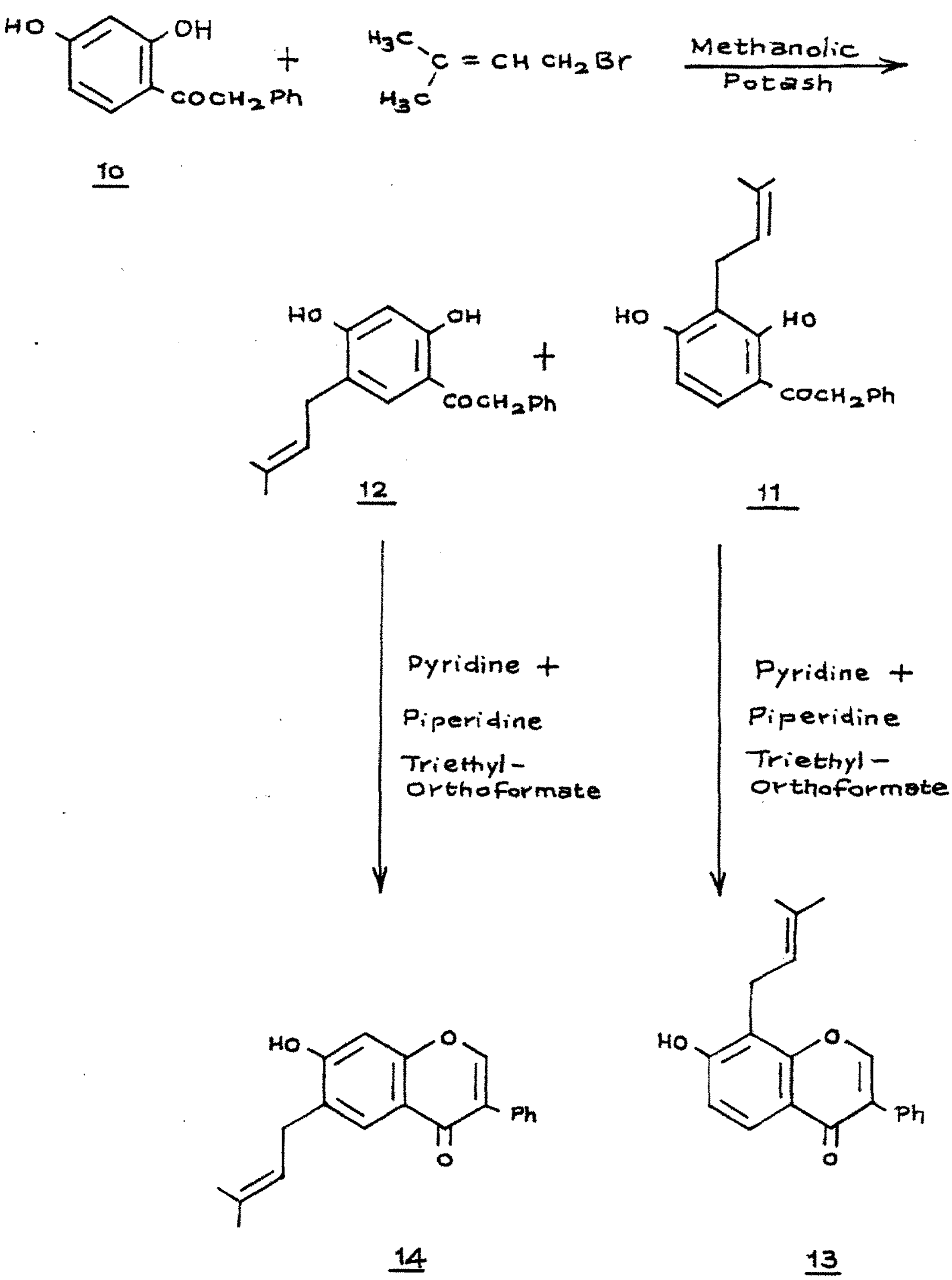
a mixture of 3-C-prenylated (11) and 5-C-prenylated 2,4-dihydroxy phenylbenzyl ketone (12), (11) and (12) on condensation with triethylorthoformate in the presence of pyridine and piperidine formed the corresponding C-prenylated isoflavones (13) and (14) (Scheme-II).

The second method for the synthesis of prenylated isoflavones consisted of condensation of polyphenolics with 2-methyl-but-3-ene-2-ol in acidic medium such as boron trifluoride etherate. Bohlman and Kleine[3] used this reagent for introducing a prenyl unit in hydroquinone to get 2-prenyl hydroquinone which could be converted to naturally occuring prenyl benzoquinone by mild oxidation with Ag_2O.

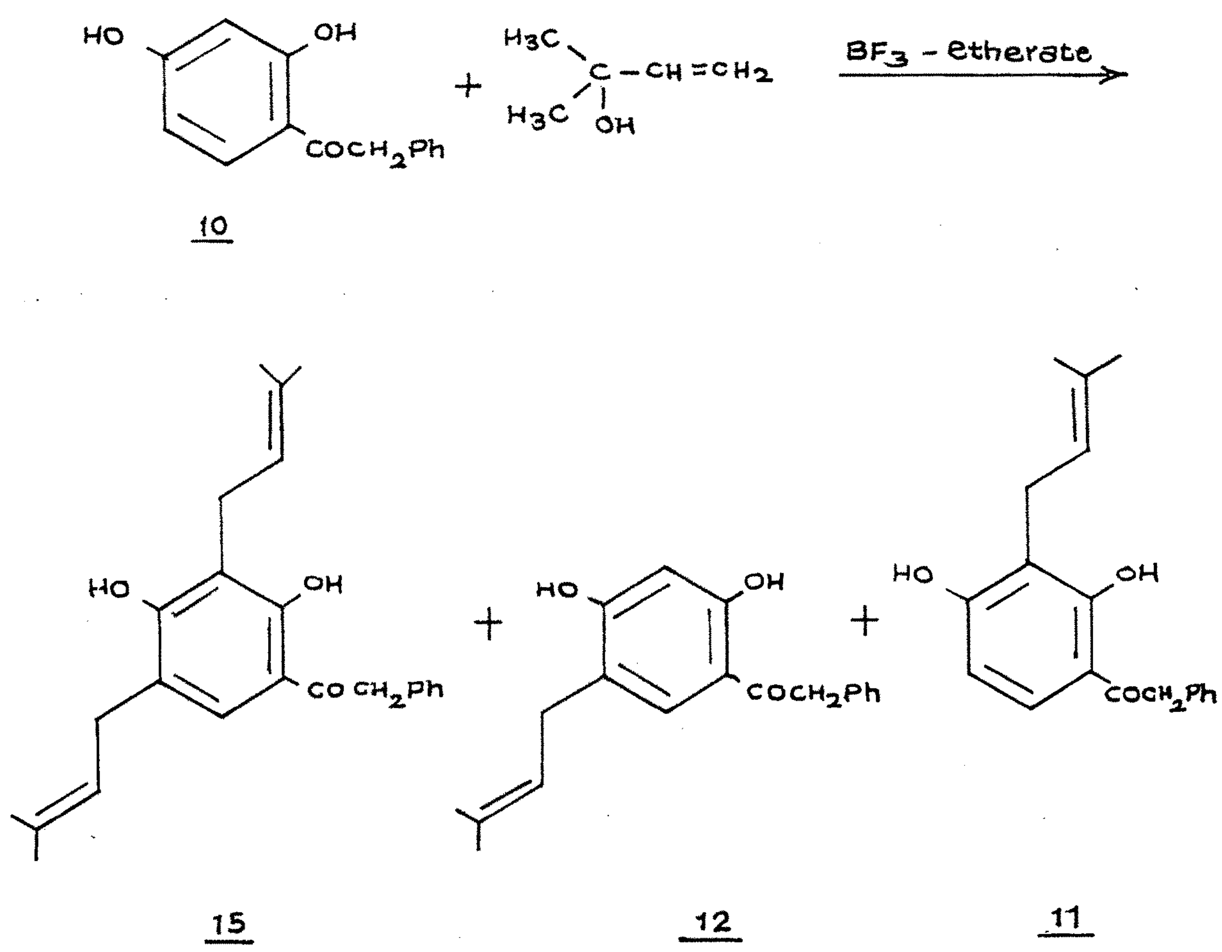
Jain and coworkers[4] condensed 2-methyl-3-butene-2-ol with 2,4-dihydroxy phenylbenzyl ketone (10) in the presence of boron trifluoride etherate and obtained a mixture of 3-C-prenyl- (11) 5-C-prenyl- (12) and 3,5-di-C-prenyl- 2,4-dihydroxy phenylbenzyl ketone (15).(Scheme-III)

These C-prenylated derivatives were cyclized to corresponding pyran derivatives by heating with formic acid. Refluxing these C-prenylated derivatives with DDQ in dry benzene directly gave the corresponding chromene derivatives. Conversion of these pyran derivatives to corresponding isoflavones was effected by treatment with sodium and ethyl formate.

Scheme II : Jain et al [2]



Scheme III : Jain and coworkers[4]



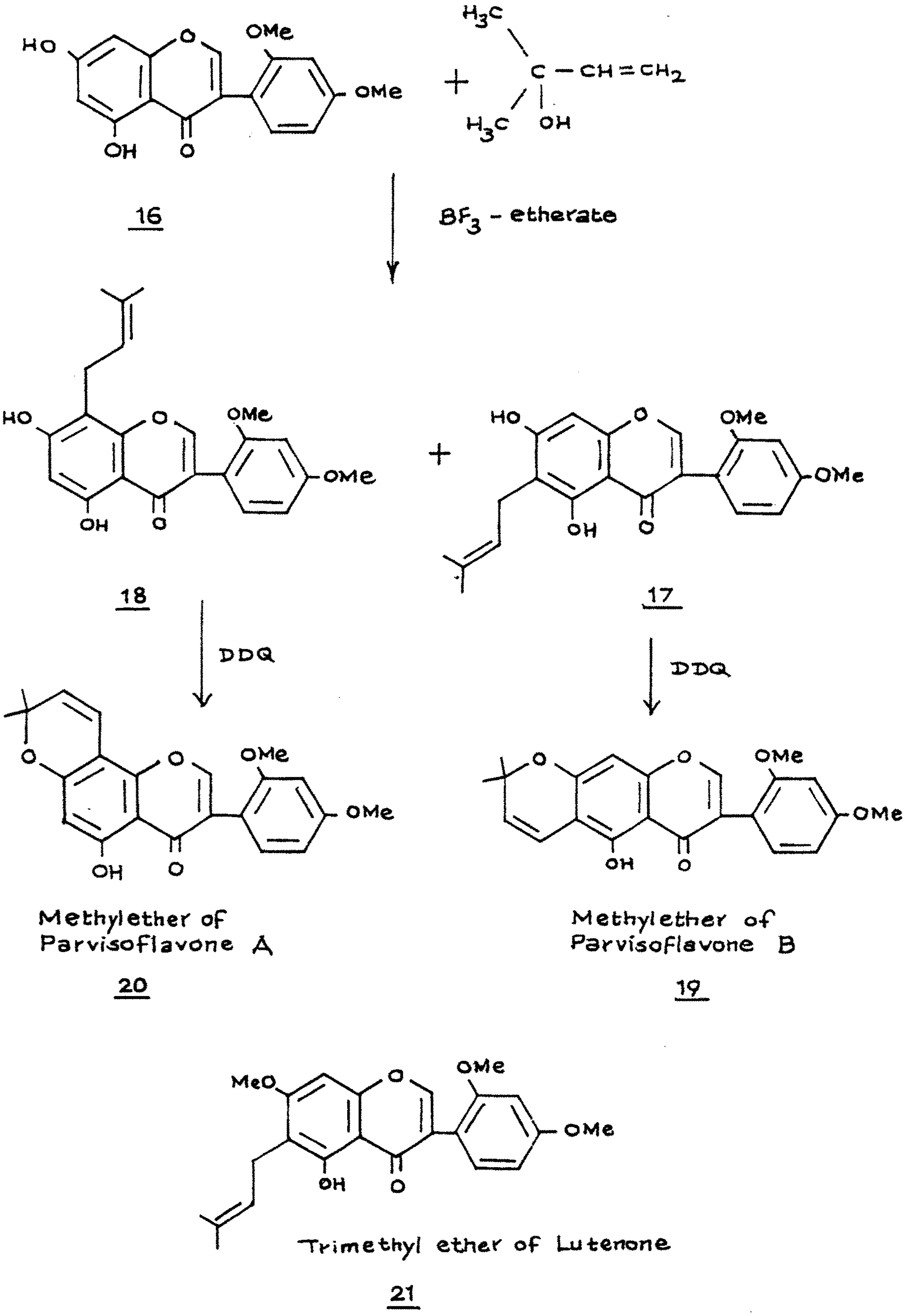
Using this procedure, Jain, Kumar and Gupta[5] synthesized trimethyl ethers of Lutenone (21), Parvisoflavone-A (20) and Parvisoflavone-B (19). 2,4'-Dimethoxy 5,7-dihydroxy isoflavone (16) on condensation with 2-methylbut-3-ene-2-ol in presence of boron trifluoride etherate gave a mixture of 6-C-prenyl- (17) and 8-C-prenyl derivatives (18), which on cyclization with DDQ furnished (19) and (20) respectively (Scheme-IV). Methylation of 6-C-prenylisoflavone (17) at 7-OH group gave trimethyl ether of Lutenone (21).

The same group of workers[6,7] synthesized dimethyl ether of Auriculasin (26) and pomiferin (27), starting from orobol dimethyl ether (22). Nuclear prenylation of (22) with prenylbromide in the presence of sodium methoxide in methanol gave corresponding 6,8-di-C,C-prenyl- (23), 6-C-prenyl- (24) and 7-o-prenyl- (25) derivatives. (23), on cyclization with DDQ gave (26) and (27) (Scheme-V).

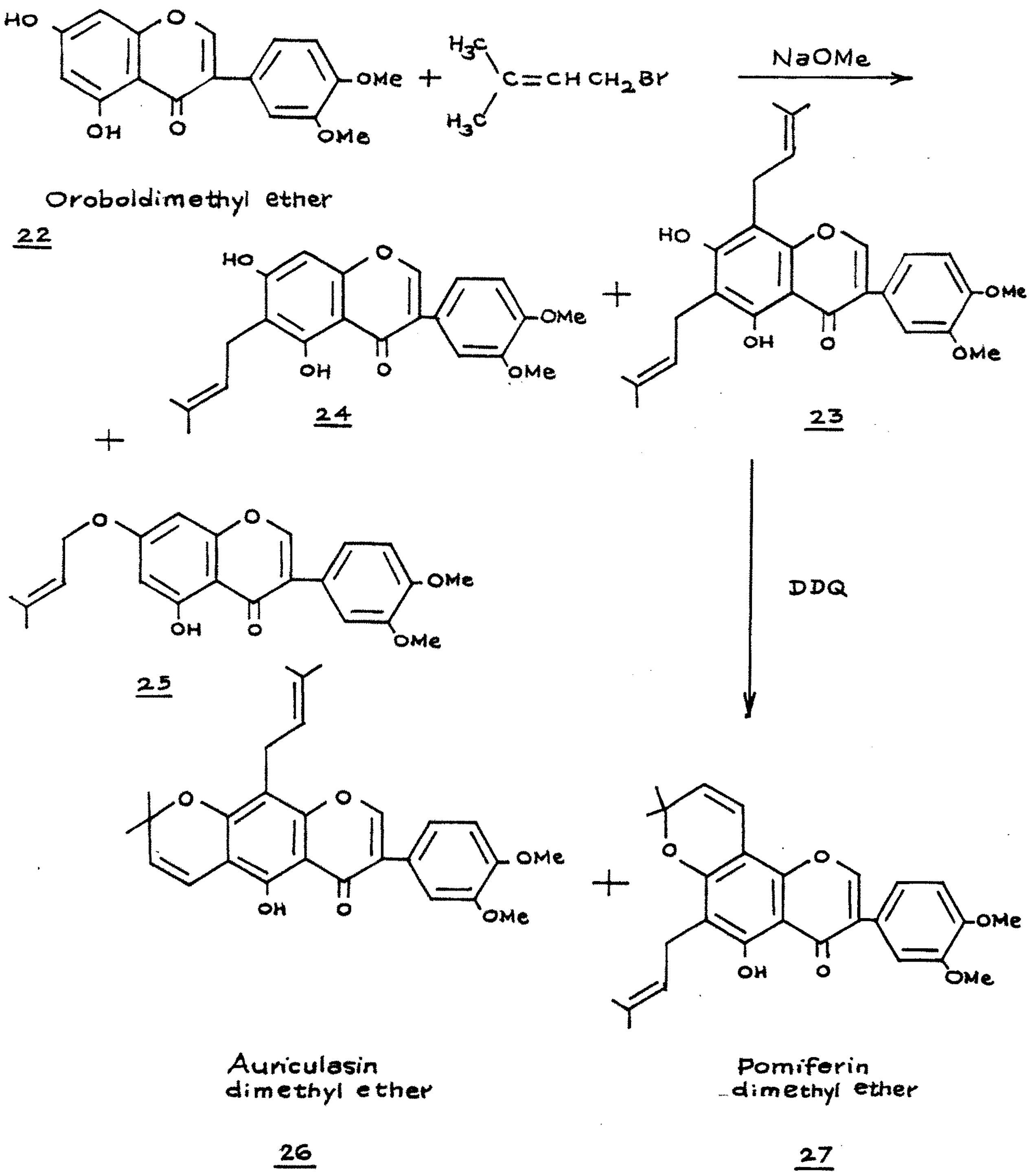
Jain and coworkers[8] prenylated 5,7-dihydroxy isoflavone with prenyl bromide in the presence of methanolic sodium methoxide and synthesized 4'-methylether of Osajin and Warangalone by above route.

Third approach for the synthesis of prenylated isoflavone was to carry out the Claisen rearrangement of the prenyl ether of hydroxy isoflavones. Jain and Tuli [9] carried out the Claisen rearrangement of 7-prenyloxy

Scheme IV : Jain, Kumar and Gupta[5]



Scheme V : Jain, Kumar and Gupta[6,7]



isoflavone (28) in refluxing dimethylaniline and obtained 2,3,3-trimethyldihydrofuro (2,3-h) benzopyran-[7H]-one (29). (Scheme-VI)

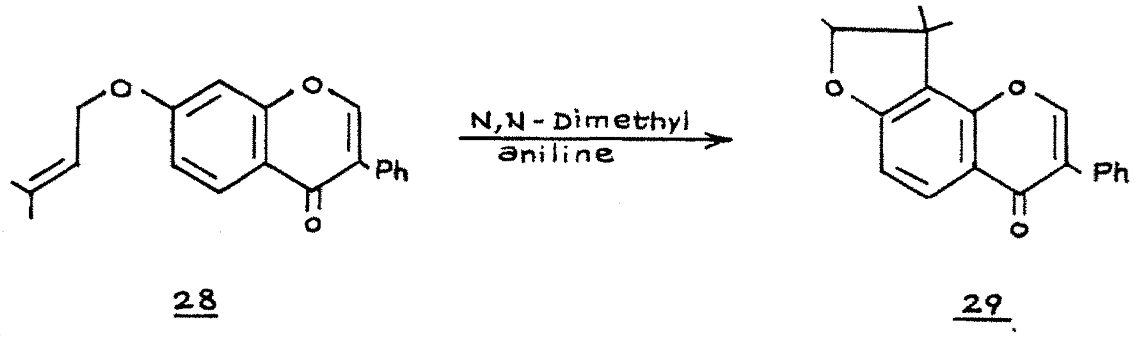
They also observed that 3',4'-dimethoxy-5,7-dihydroxy isoflavone (30) when prenylated with prenyl bromide in the presence of K_2CO_3 and acetone gave its 7-prenyloxy derivative (31) which on Claisen rearrangement in N,N-dimethylaniline gave a mixture of angular (32) as well as linear (33) dihydrofuro isoflavones.[10] (Scheme-VII).

The fourth approach to prepare the prenylated isoflavone in its pyran from consisted of first preparing the 1,1-dimethyl propargyl ether by refluxing a mixture of phenol and 2-methyl-2-chloro-but-3-yne in acetone in the presence of KI and K_2CO_3 followed by its rearrangement in boiling dimethyl aniline. This method is developed by Iwai and Ide[11] and probably it is the best method for preparing chromenes in high yields.

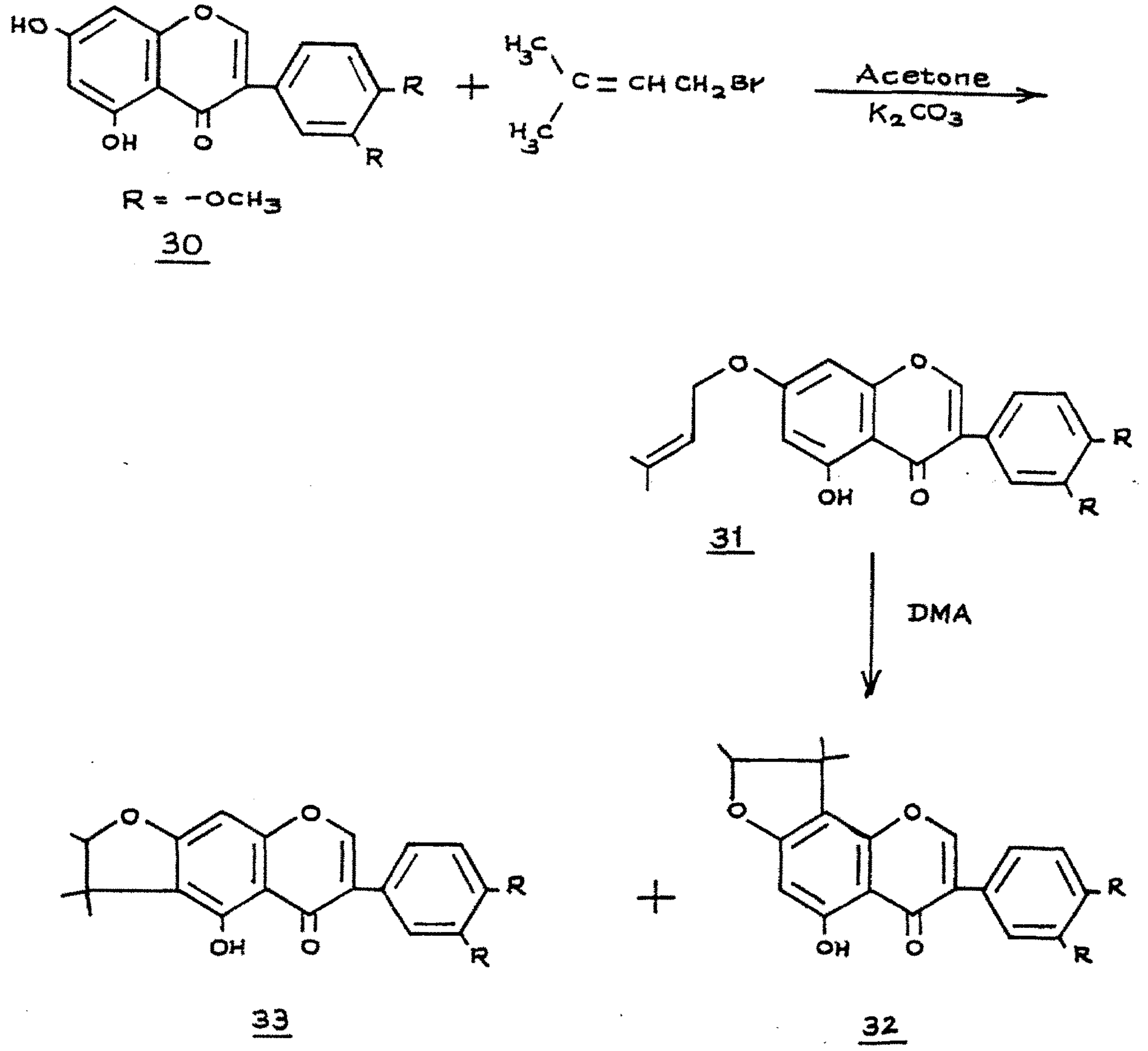
Thus Evodionol methylether (34) is prepared in 80% yield.[11] (Scheme-VIII)

Zsindel y and Schmid[12] have established that the reaction is varient of the Claisen allylic rearrangement. Mukerjee, Sarkar and Seshadri[13] synthesized iso-encecalin and encecallin by adopting the similar route. Resaceto-

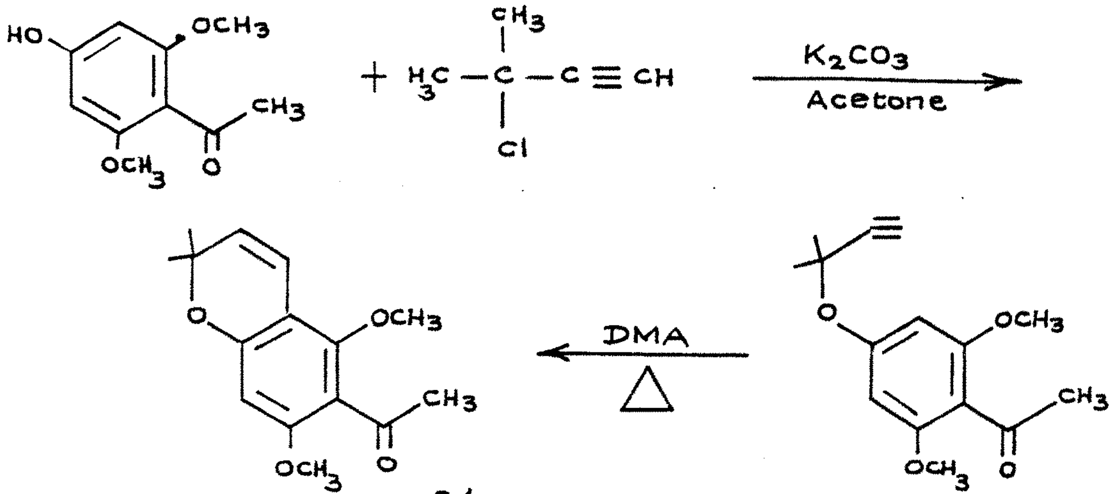
Scheme VI : Jain et al[9]



Scheme VII : Jain and Coworkers[10]



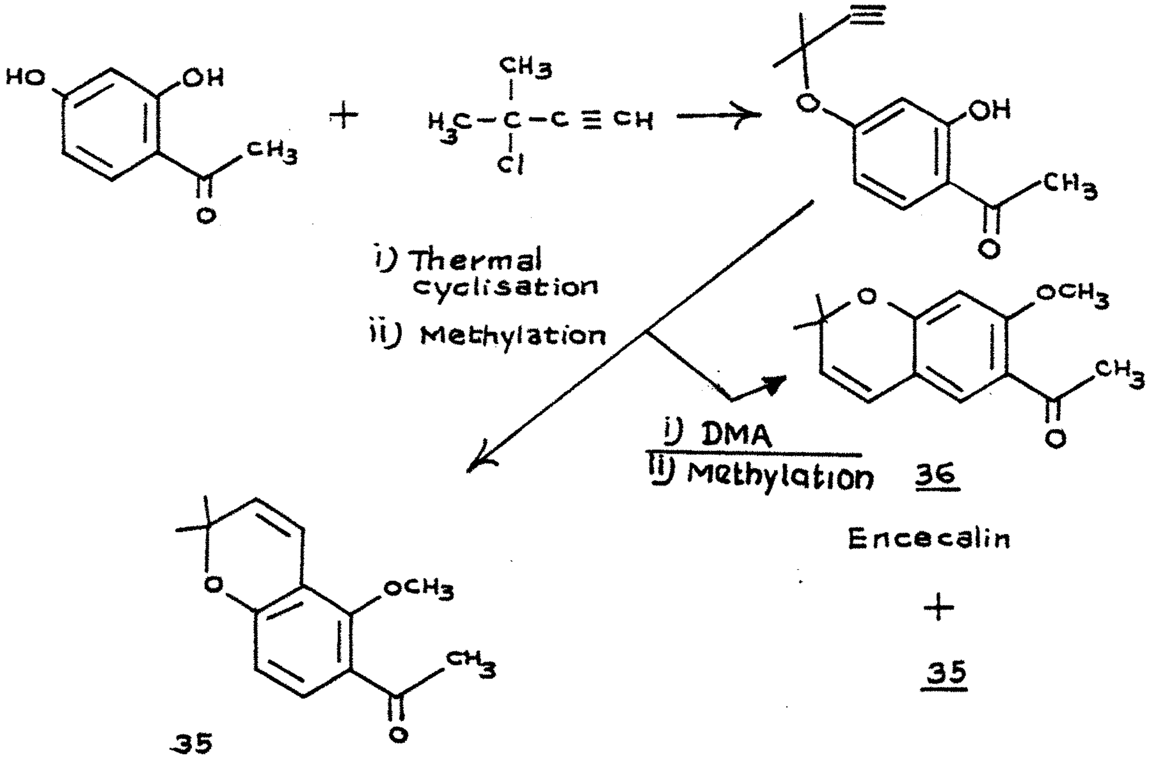
Scheme VIII :



34

Evodionol methyl ether

Scheme IX : Mukerjee, Sarkar and Seshadri[13]



36

Encecalin

+

35

35

iso - encecalin

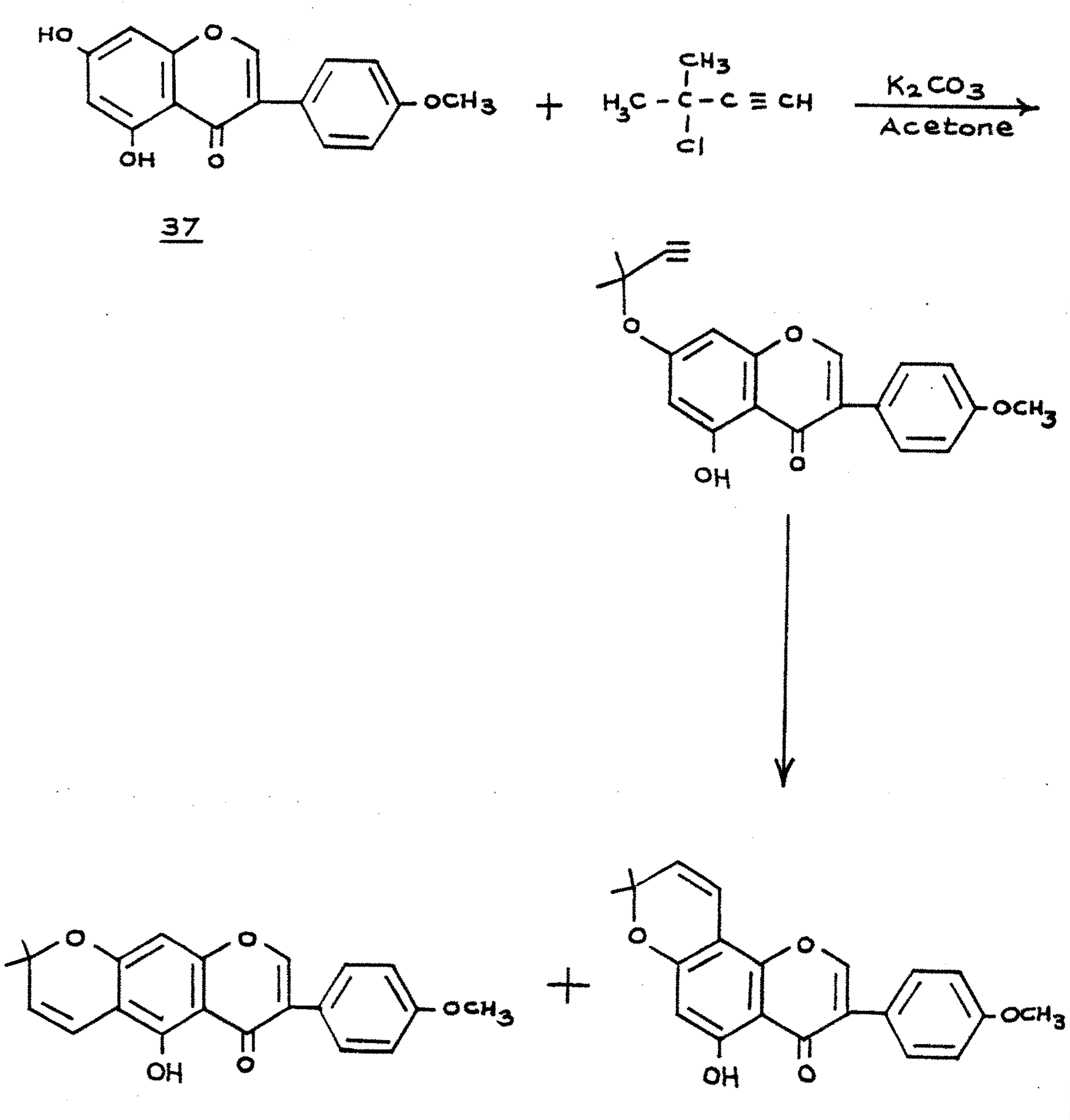
phenone was converted to corresponding ether which was further subjected to cyclization and methylation to furnish iso-encecalin (35) and encecalin (36). Thermal cyclization and cyclization in refluxing DMA produced different product. (Scheme-IX).

Seshadri and cowcrkers[14] studied the different mode of the reactions to furnish linear and angular products. They observed that rearrangement of ether of resacetophenone, flavones and isoflavones always results in the formation of two isomers irrespective of the group of polyphenols used. 5,7-Dihydroxy-4'-methoxyisoflavone (37) gave angular (38) and linear isoflavone (39).(Scheme-X)

Jain, Tuli and Khazanchi[15] carried out the rearrangement of propargyl ether of 5,7-dihydroxy-3',4'-dimethoxy isoflavone (30), with N,N-dimethylaniline and obtained linear (40) as well as angular product (41). (Scheme-XI).

The same group of workers [16] started with 7-hydroxy-4'-methoxy isoflavone (42) and condensed it with 2-chloro-2-methyl-3-but-yne to obtain 7-(1,1-dimethyl-3-prop-2-ynyloxy) 4'-methoxy isoflavone (43) and rearrangement of ether gave angular 6,6"-dimethyl-4'-methoxy pyrano (2",3":7,8) isoflavone only (44). (Scheme-XII).

Scheme X : Seshadri and coworkers[14]

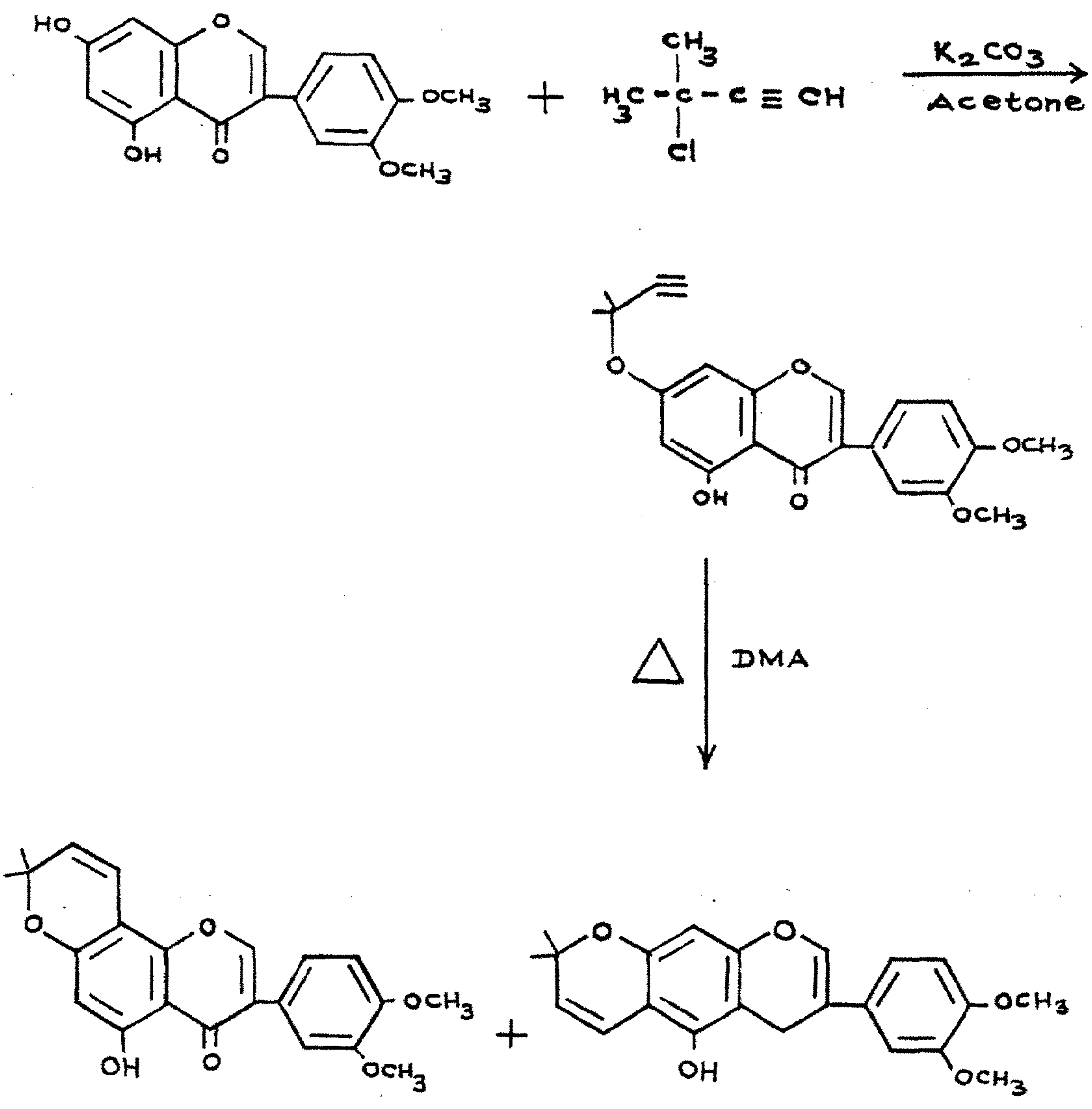


37

39

38

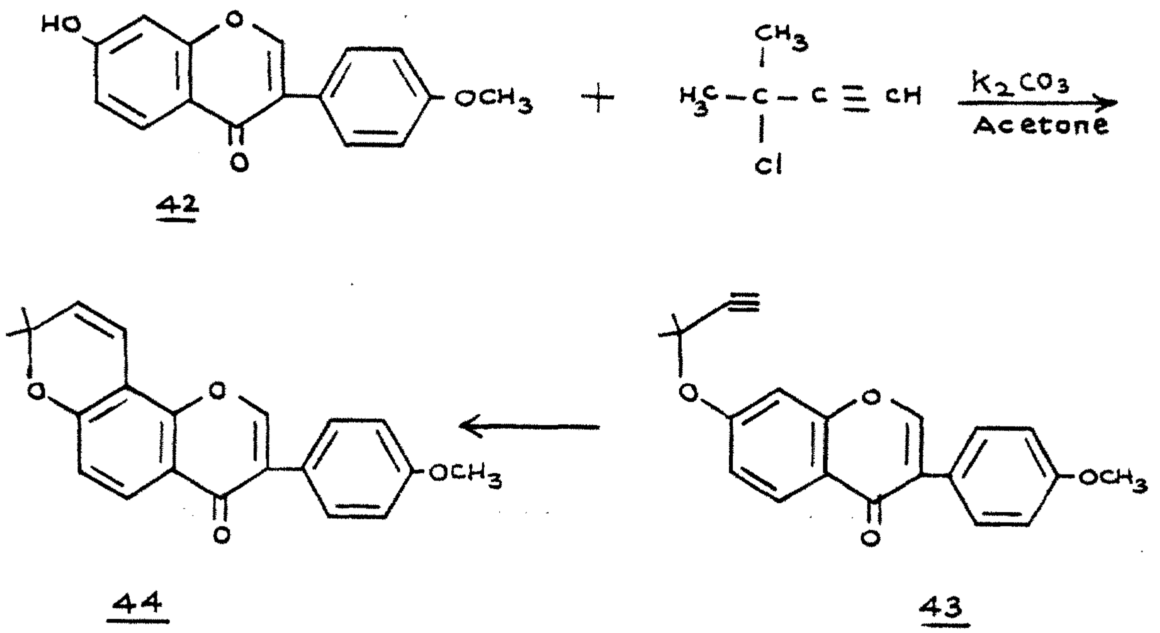
Scheme XI : Jain et al[15]



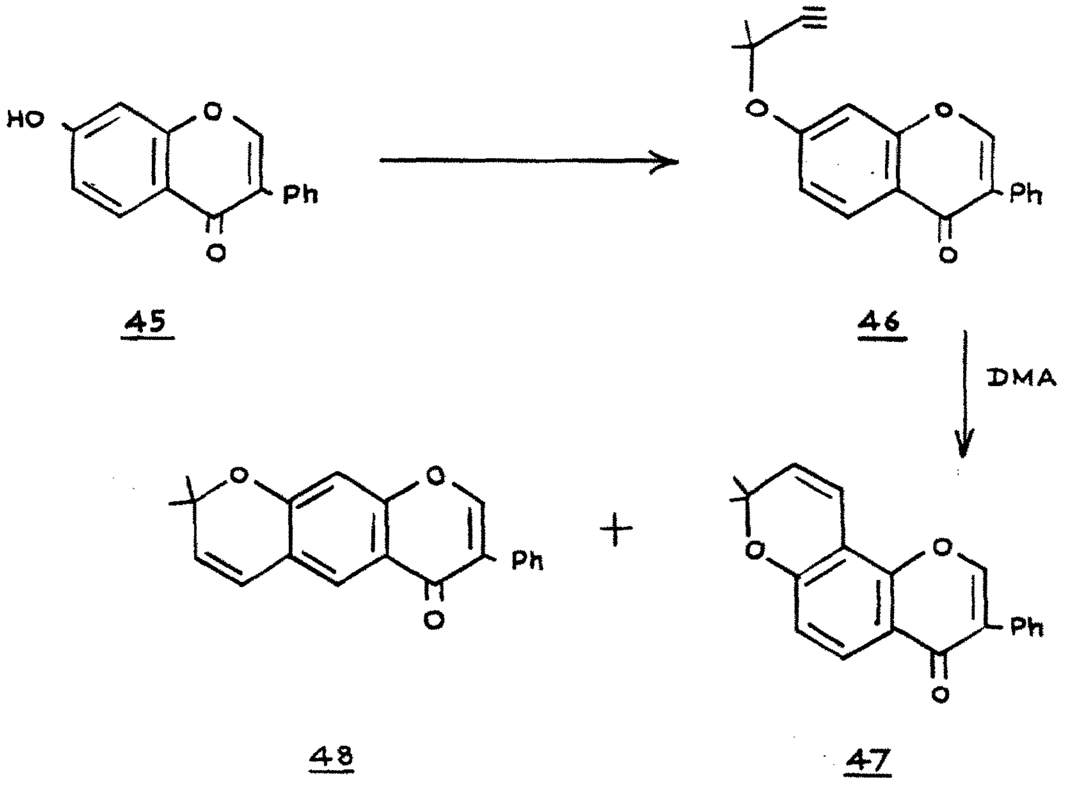
41

40

Scheme XII : Jain et al[16]



Scheme XIII : Jain et al[17]



They[17] also reported that the condensation of 7-hydroxy isoflavone (45) with 2-chloro-2-methyl-3-butyne gave the ether (46) which on rearrangement in dimethylaniline furnished both angular as well as linear pyrano isoflavones (47) and (48). (Scheme-XIII).

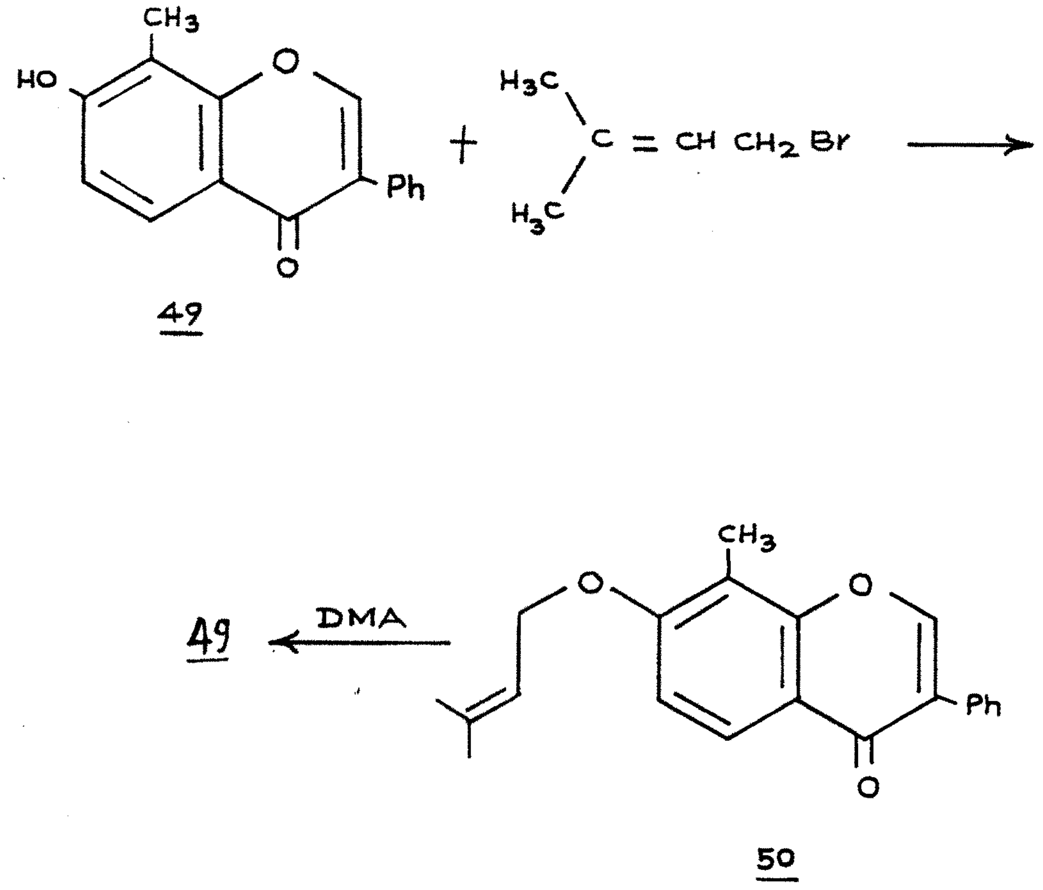
PRESENT WORK

The present work deals with the Claisen rearrangement of 7-prenyloxy-8-methylisoflavone and C-prenylation of 2,4-dihydroxy-3-methylphenyl benzylketone and their conversion to corresponding pyrano isoflavones. Novel products were obtained during the Claisen rearrangement of 7-(1,1-dimethyl prop-2-nyloxy)-8-methyl, 8-allyl and 8-cinnamyl isoflavone derivatives.

o-Prenylation of 7-hydroxy-8-methylisoflavone (49)

7-(3'-methyl-but-2'-enyl)oxy-8-methyl isoflavone (50) was prepared by condensing 7-hydroxy-8-methylisoflavone (49) with 3,3-dimethylallylbromide in the presence of anhydrous potassium carbonate in dry acetone (50) on Claisen rearrangement in N,N-dimethylaniline gave the product which was found to be identical with 7-hydroxy-8-methylisoflavone, indicatingthat deprenylation took place during the reaction. Similar deprenylation was also observed when (50) was refluxed with decalin in the

Scheme XIV



presence of few crystals of zinc chloride or o-dichlorobenzene, dimethylaniline with butyric anhydride, sodium acetate and acetic anhydride. (Scheme-XIV)

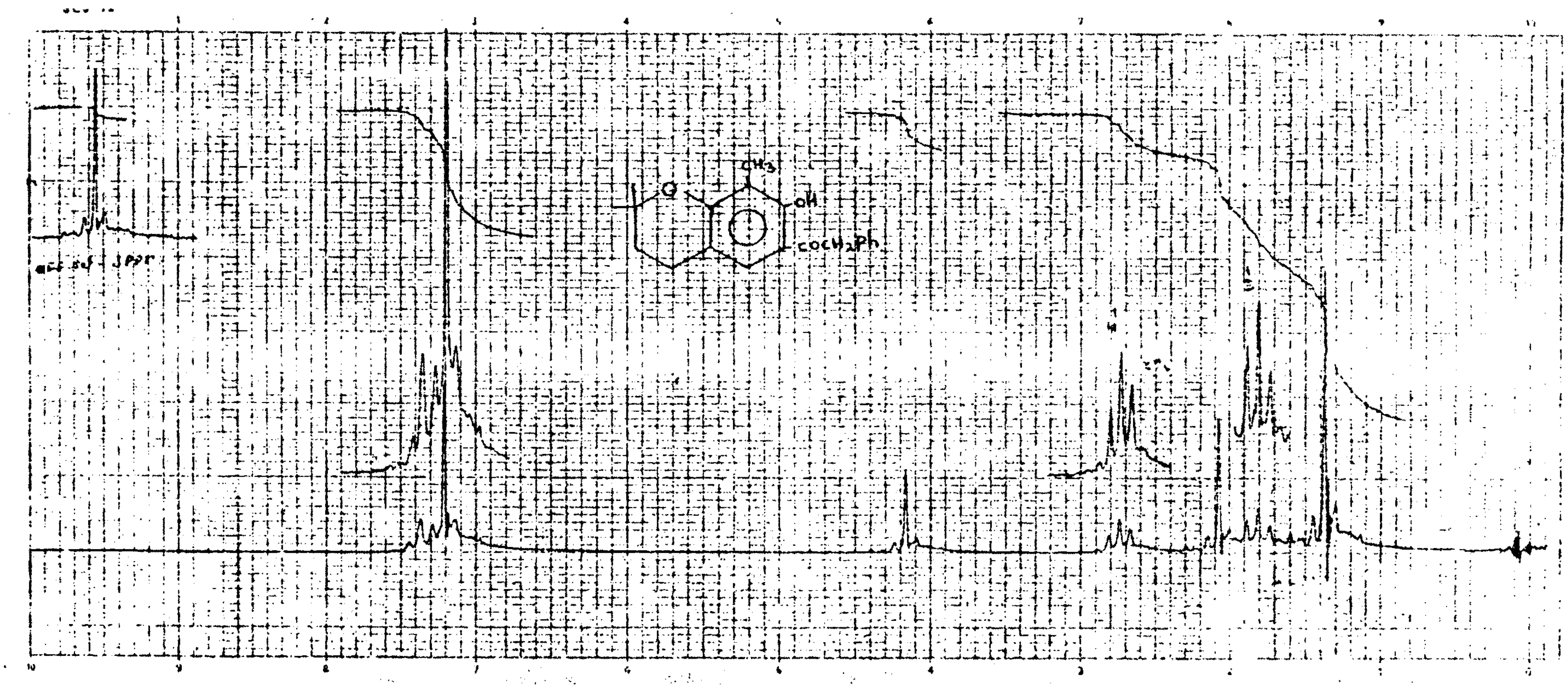
As the above approach failed, C-prenylation of 2,4-dihydroxy-3-methyl prenylbenzyl ketone was next tried in acidic condition.

C-prenylation of 2,4-dihydroxy-3-methyl phenylbenzyl ketone (51)

2,4-Dihydroxy-3-methyl-phenylbenzyl ketone (51) dissolved in dry dioxan was condensed with 2-methyl-but-3-ene-2-ol in the presence of boron trifluoride etherate at room temperature. Reaction mixture showed several spots on TLC and so it was subjected to column chromatography.

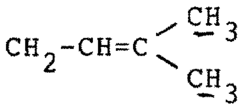
Fraction A :

Elution with light petroleum ether (40-60°C) gave 7-hydroxy-8-methyl-6-phenylacetyl-2,2-dimethylchroman (52). The structure of this compound was established by PMR spectrum which exhibited following signals ($CDCl_3$) ; δ 1.3, singlet for six protons of two methyl groups of pyran ring at C-2 position ; 1.8, triplet, J=8Hz, for two protons at C-3 ; 2.0, singlet for three protons of methyl group at C-8 ; 2.7, triplet, J=8Hz, two protons at C-4 ; 4.1, singlet, 2H, $-COCH_2Ph$; 7.2 - 7.3, multiplet



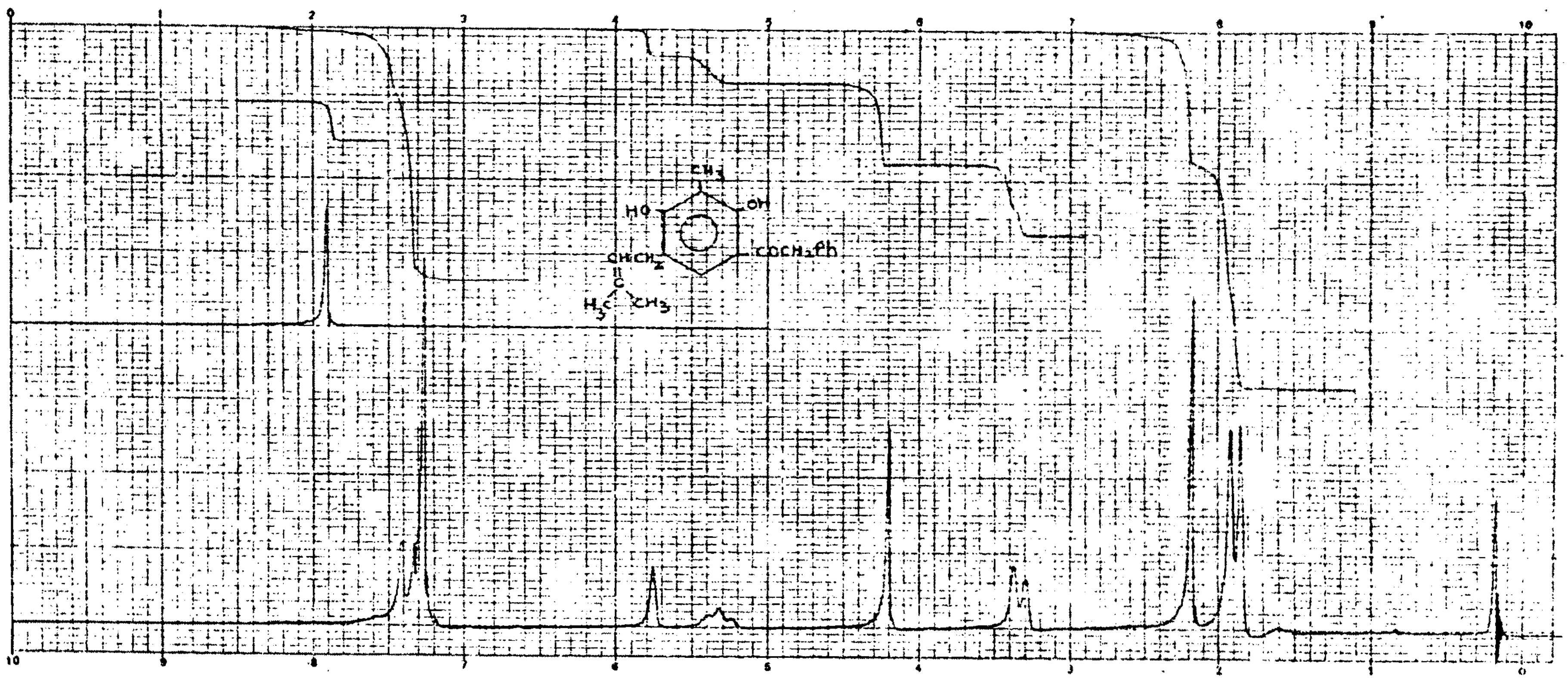
7-Hydroxy-8-methyl-6-phenylacetyl-2,2-dimethylchroman (52) (Fig.1) for 6H, aromatic protons of -COCH$_2$Ph ; 10.4, singlet, -OH group at C-7. (Fig.1)

Fraction B :

Elution with benzene gave the product 2,4-dihydroxy-3-methyl-5-(3'-methyl-but-2'-enyl)phenylbenzyl ketone (53). It showed following signals in PMR spectrum (CDCl$_3$) ; δ 1.65 and 1.7, two closely spaced singlets for two methyl groups of side chain,  $CH_2\text{-}CH{=}C\begin{smallmatrix}\nearrow CH_3\\ \searrow CH_3\end{smallmatrix}$; another singlet for methyl group at C-3 appeared at 2.0 ; methylene protons attached to aromatic nucleus appeared at 3.15 as doublet with coupling constant J=8Hz, Ar-CH$_2$- ; another methylene protons Ar-COCH$_{22}$Ph appeared as singlet at 4.0 ; vinylic proton of the side chain appeared as multiplet at 5.1, = CH-CH$_2$-Ph ; 5.6, singlet for one proton of -OH group at C-4 ; five aromatic protons gave multiplet at 7.1 ; one aromatic proton at C-6 appeared as singlet at 7.2; hydroxyl proton at C-2 appeared as downfield singlet at 12.7. (Fig.2) C-prenylated ketone (53), when refluxed with formic acid furnished chroman derivative (52).

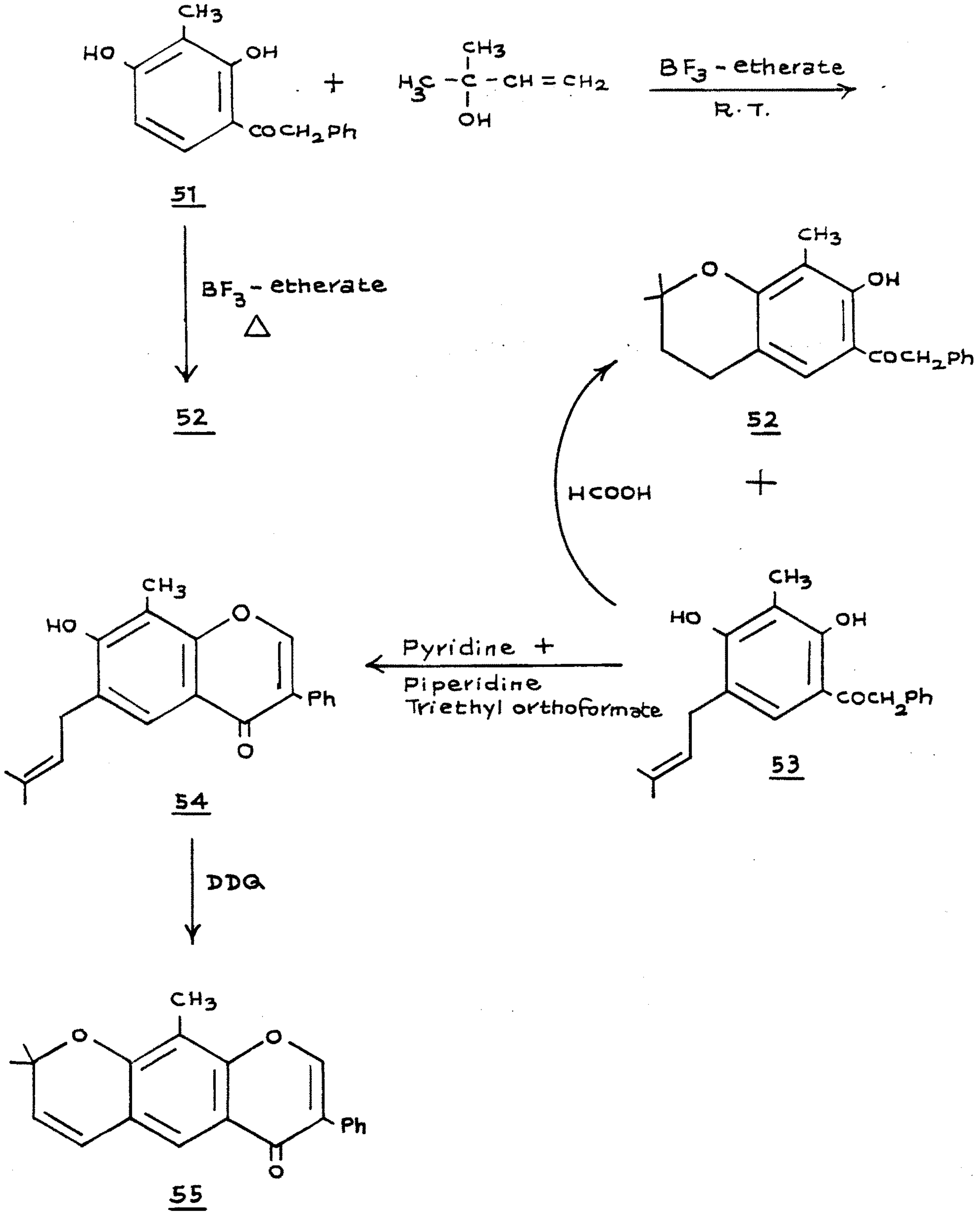
Better yields were obtained when the above reaction was carried out at higher temperature. (Scheme-XV).

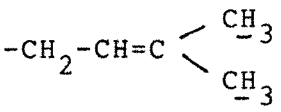
When 2,4-dihydroxy-3-methyl-4-(3-methyl-but-2-enyl)

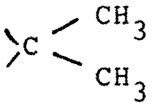


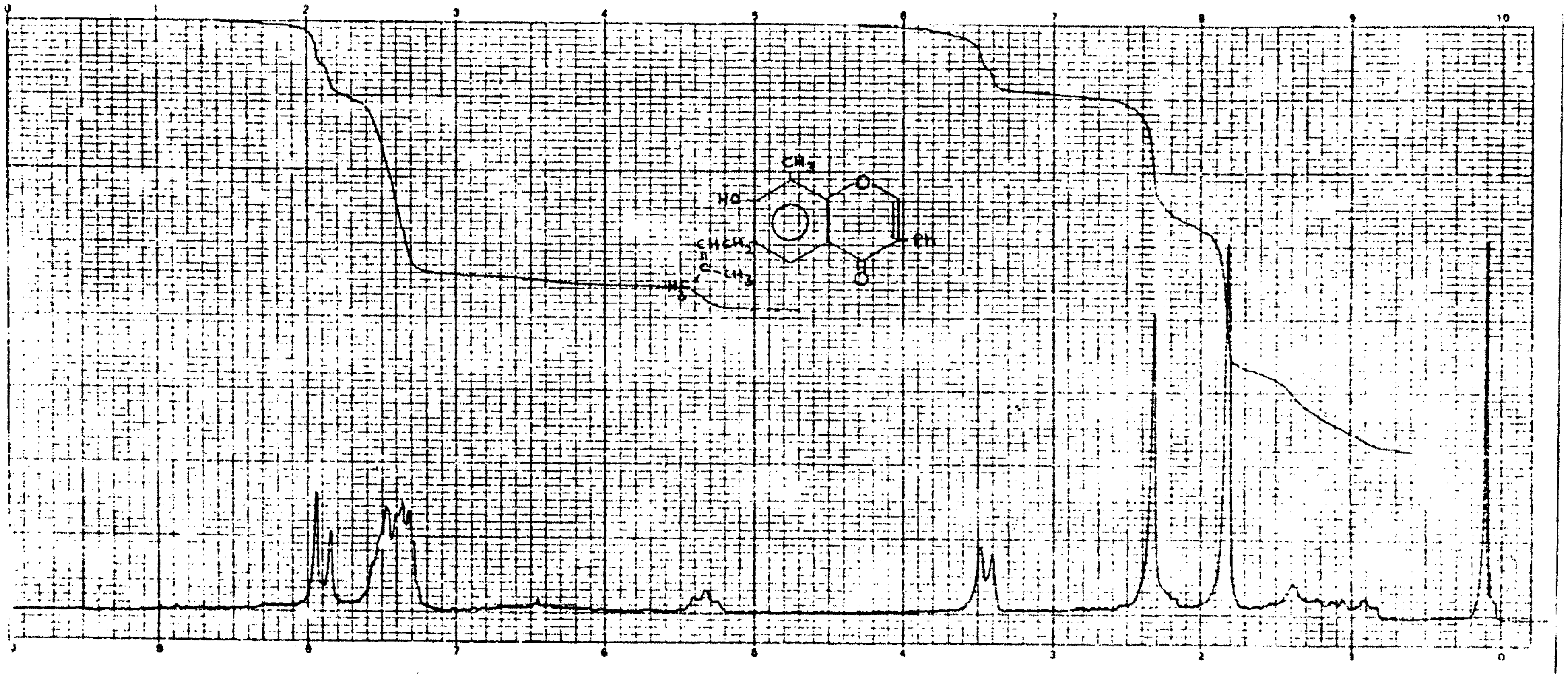
2,4-Dihydroxy-3-methyl-5-(3 -methyl-but-2 -enyl) phenyl benzylketone (53)(Fig. 2)

Scheme XV

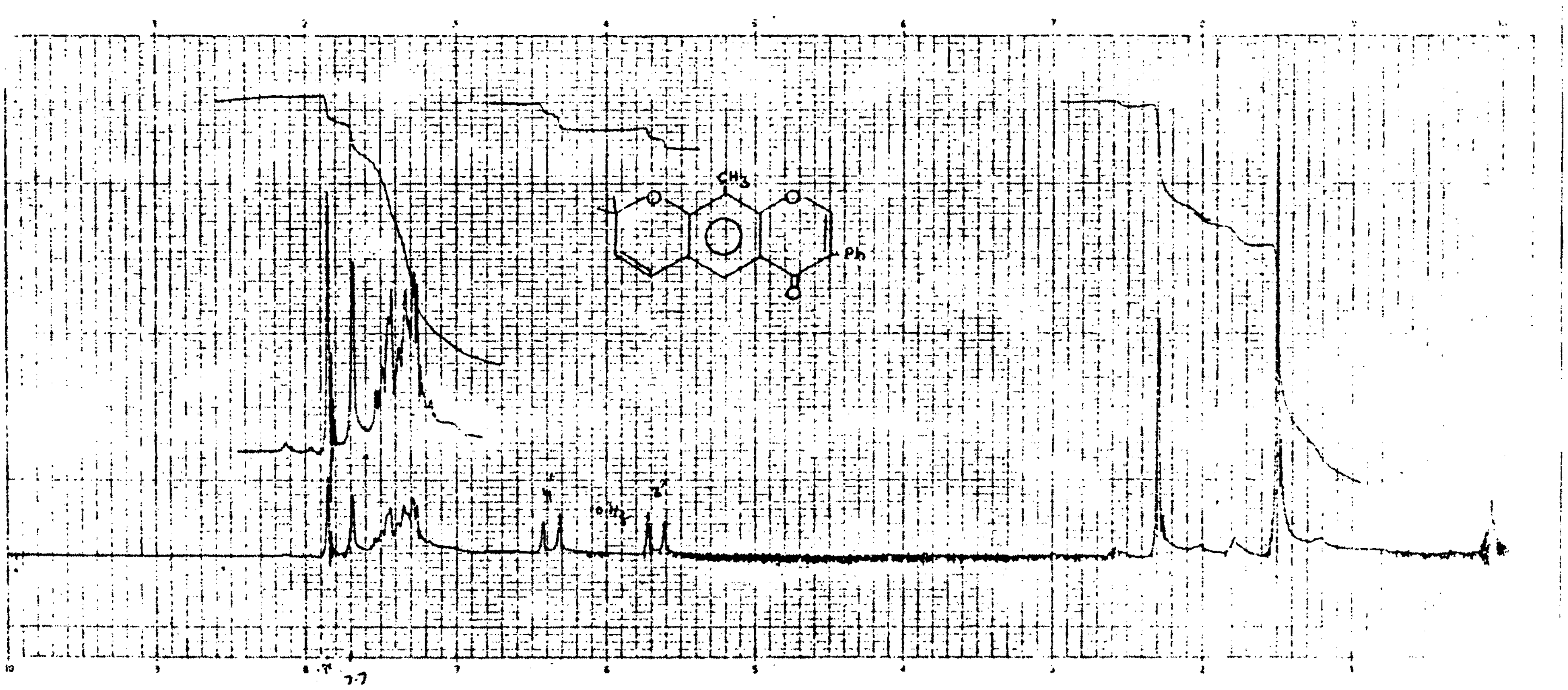

CH3
HO
OH
COCH2Ph
51
+
CH3
H3C - C - CH = CH2
OH
BF3 - etherate
R.T.
BF3 - etherate
Δ
52
CH3
O
OH
COCH2Ph
52
HCOOH
+
CH3
HO
OH
COCH2Ph
53
Pyridine +
Piperidine
Triethyl orthoformate
CH3
HO
O
Ph
O
54
DDQ
CH3
O
O
Ph
O
55

phenylbenzyl ketone (53) was refluxed with the mixture of pyridine/piperidine and triethylorthoformate, it furnished 7-hydroxy-6-(3-methyl-but-2-enyl)-8-methyl isoflavone (54), structure of which was confirmed by PMR spectrum which showed following signals. (CDCl$_3$) : δ 1.7, singlet, 6H,  $-CH_2-CH=C\langle^{CH_3}_{CH_3}$ at C-6 ; 2.2, singlet, 3H, methyl group at C-8 ; 3.35, doublet, J=8Hz, 2H, -CH -Ar at C-6 ; 5.2, multiplet, 1H, vinylic proton in the side chain ; 7.2-7.4, multiplet, 5H, aromatic protons ; 7.75, singlet, 1H at C-5 and 7.85, singlet, 1H at C-2.(Fig.3)

Cyclodehydrogenation of (54) was effected when it was refluxed with DDQ in dry benzene. It furnished 8,8,10-trimethyl-3-phenylpyrano (2,3-g)-1-benzopyran-[4H]-one (55). Structure of (55) was established by PMR spectrum which exhibited following signals :
(CDCl$_3$) : δ 1.5, singlet, 6H,  $>C\langle^{CH_3}_{CH_3}$ at C-8 ; 2.3, singlet, 3H, $-CH_3$ at C-10 ; 5.7, doublet, J=10Hz, 1H at C-7 6.4, doublet, J=10Hz, 1H at C-6 ; 7.4, multiplet, 5H, aromatic protons ; 7.7, singlet, 1H, C-5 ; 7.85, singlet, 1H at C-2.(fig 4) (52), when condensed with sodium and ethylformate gave 6,7-dihydro-8,8,10-trimethyl-3-phenylpyrano (2,3-g) -1-benzopyran-[4H]-one (56), which exhibited following signals in PMR spectrum (CDCl$_3$) : δ 1.4, singlet, 6H,

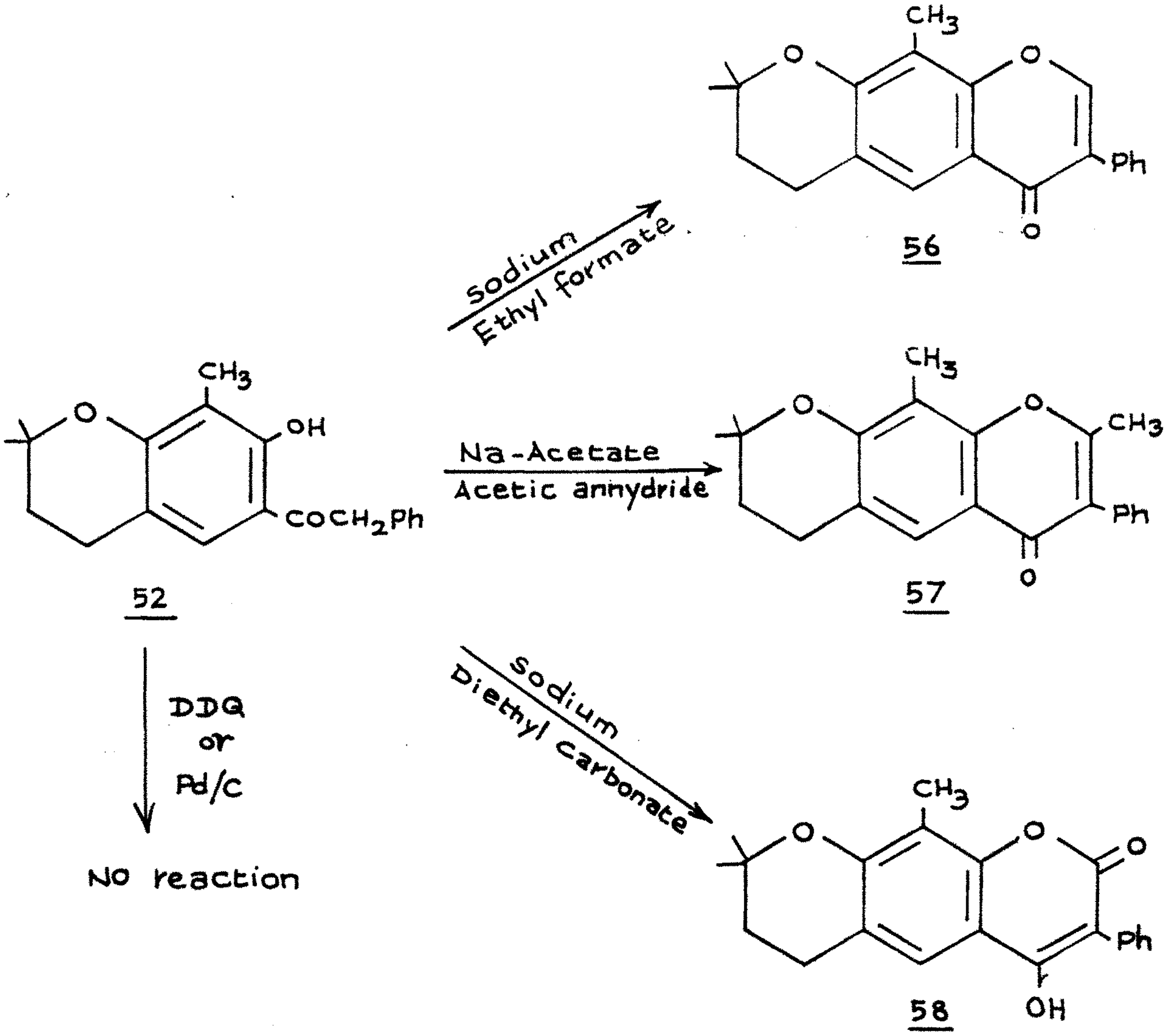


7-Hydroxy-6-(3 -methyl-but-2 -enyl)-8-methylisoflavone (54) (Fig.3)



8,8,10-Trimethyl-3-phenylpyrano (2,3-g)-1-benzopyran-(4H)-one (55) (Fig. 4)

Scheme XVI :

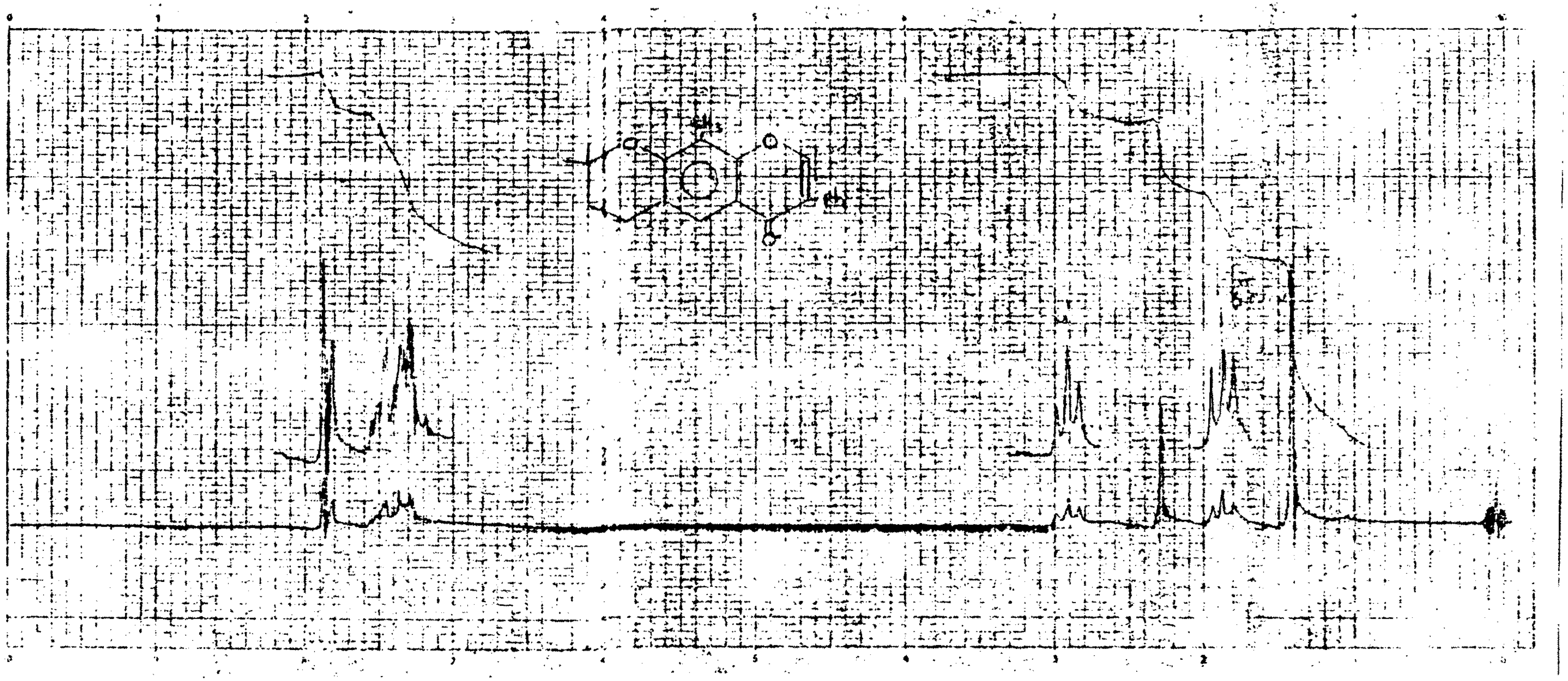


CH3
OH
COCH2Ph
52
Sodium
Ethyl formate
CH3
Ph
56
Na-Acetate
Acetic anhydride
CH3
CH3
Ph
57
Sodium
Diethyl carbonate
CH3
Ph
OH
58
DDQ
or
Pd/C
No reaction

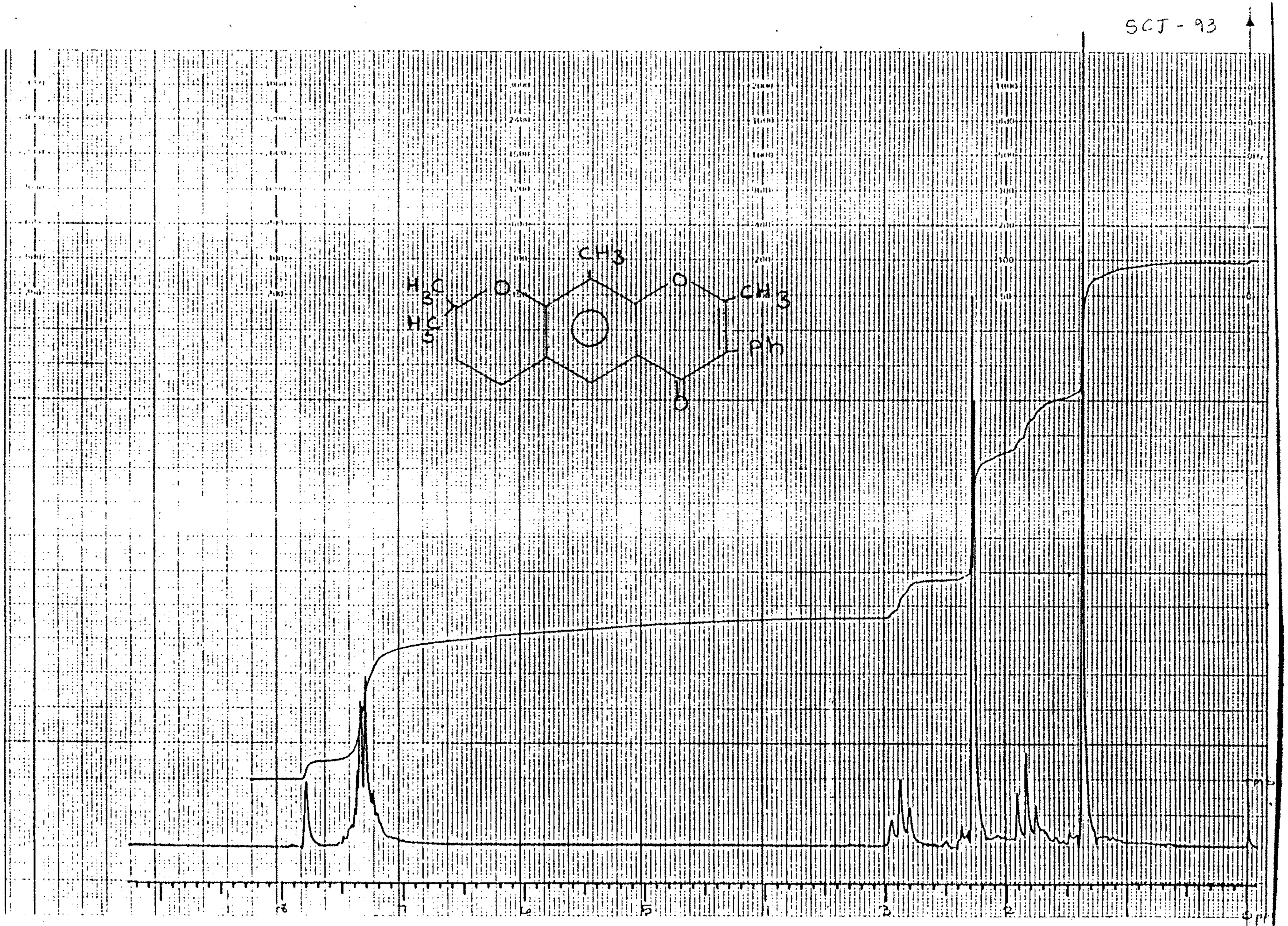
$>C{<}^{CH_3}_{CH_3}$ at C-8 ; 1.9, triplet, J=8Hz, 2H, $-CH_2-$ at C-6 ; 7.3, multiplet, 5H, aromatic protons ; 7.8, singlet, 1H, C_5-H ; 7.9, singlet, 1H, C_2-H. (Fig 5)

Further, (52) when condensed with sodium acetate and acetic anhydride gave 6,7-dihydro-2,8,8,10-tetramethyl-3-phenylpyrano (2,3-g)-1-benzopyran-(4H)-one (57). The structure was established by PMR spectrum exhibited signals at ($CDCl_3$) : δ 1.4, singlet, 6H, $>C{<}^{CH_3}_{CH_3}$ groups at C-8 ; 2.3, singlet, 6H, two methyl groups at C-2 and C-10 ; 1.8, triplet, J=8Hz, 2H at C-7 ; 2.8, triplet, J=8Hz, 2H at C-6 ; 7.3, multiplet, 5H, aromatic protons ; 7.8, singlet, 1H at C-5. (Fig.6)

6,7-Dihydro-8,8,10-trimethyl-4-hydroxy-3-phenyl pyrano (2,3-g)-1-benzopyran-(2H)-one (58) was synthesized from (52) by condensing it with pulverized sodium and diethyl carbonate.[19] On workinhg up the reaction mixture, the compound (58) exhibited following signals in PMR spectrum ($CDCl_3$) : δ 1.4,singlet, 6H, two methyl groups at C-8 2.2 singlet, 3H, $-CH_3$ group at C-10 ; 1.8, triplet, J=8Hz, 2H, $-CH_2-$ group at C-7 ; 2.8, triplet, J=8Hz, 2H, $-CH_2-$ group at C-6 ; 7.3, multiplet, 5H, aromatic protons ; 7.5, singlet, 1H at C-5. (Fig.7)

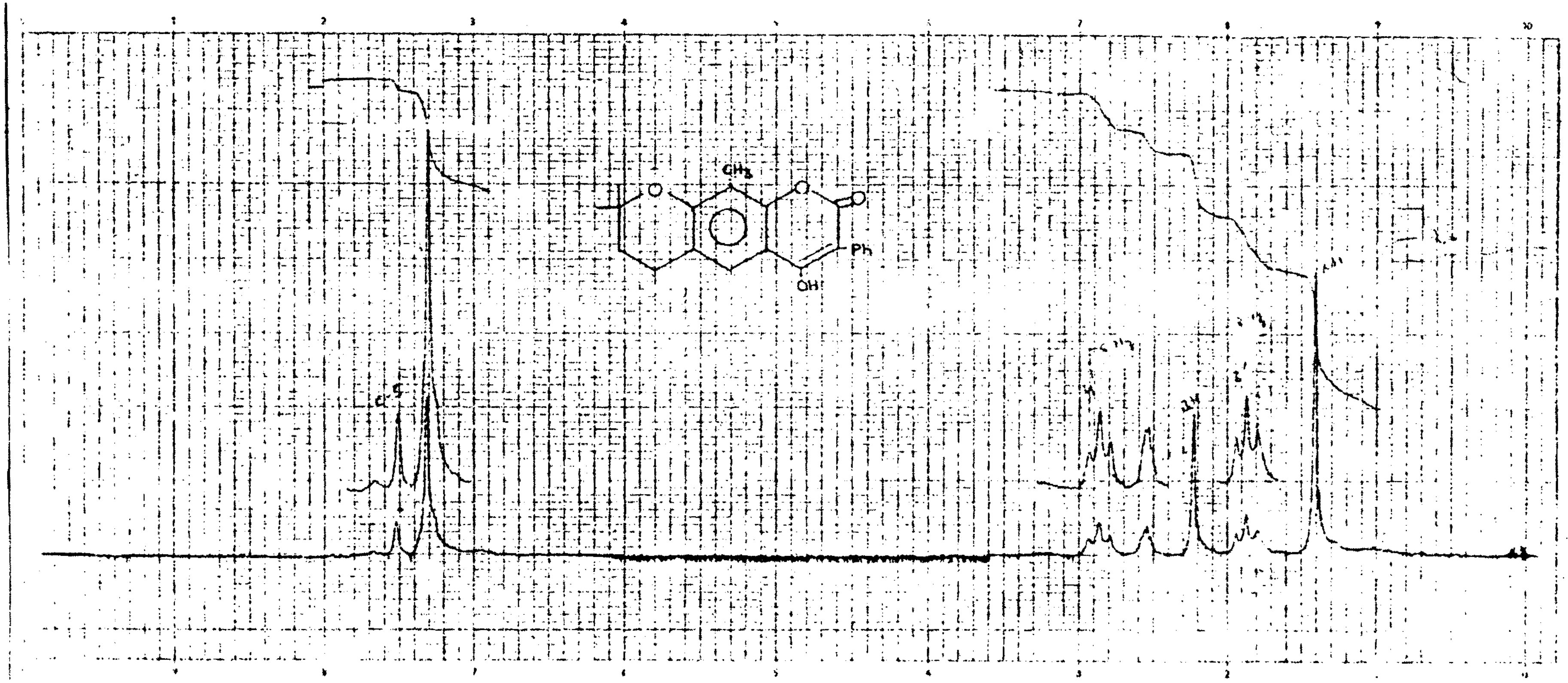


6,7-Dihydro-8,8,10-trimethyl-3-phenylpyrano(2,3-g)-1-benzopyran-(4H)-one (56) (Fig.5)



6,7-Dihydro-2,8,8,10-tetramethyl-3-phenylpyrano (2,3-g)-1-benzopyran-(4H)-one (57)

(Fig. 6)



6,7-Dihydro-8,8,10-trimethyl-4-hydroxy-3-phenylpyrano(2,3-g)-1-benzopyran-(2H)-one (58)

(Fig. 7)

(52) could not be dehydrogenated with DDQ or Pd/C. (Scheme-XVI)

Synthesis of 1,2,3,7-tetrahydro-1,1,3-trimethyl-6-phenyl cyclopenta-(2,3-h)[2H,7H]-benzopyran-2,7dione (63) and 8,8,10-trimethyl-3-phenylpyrano (2,3,-g)-1-benzopyran-[4H]-one (62)

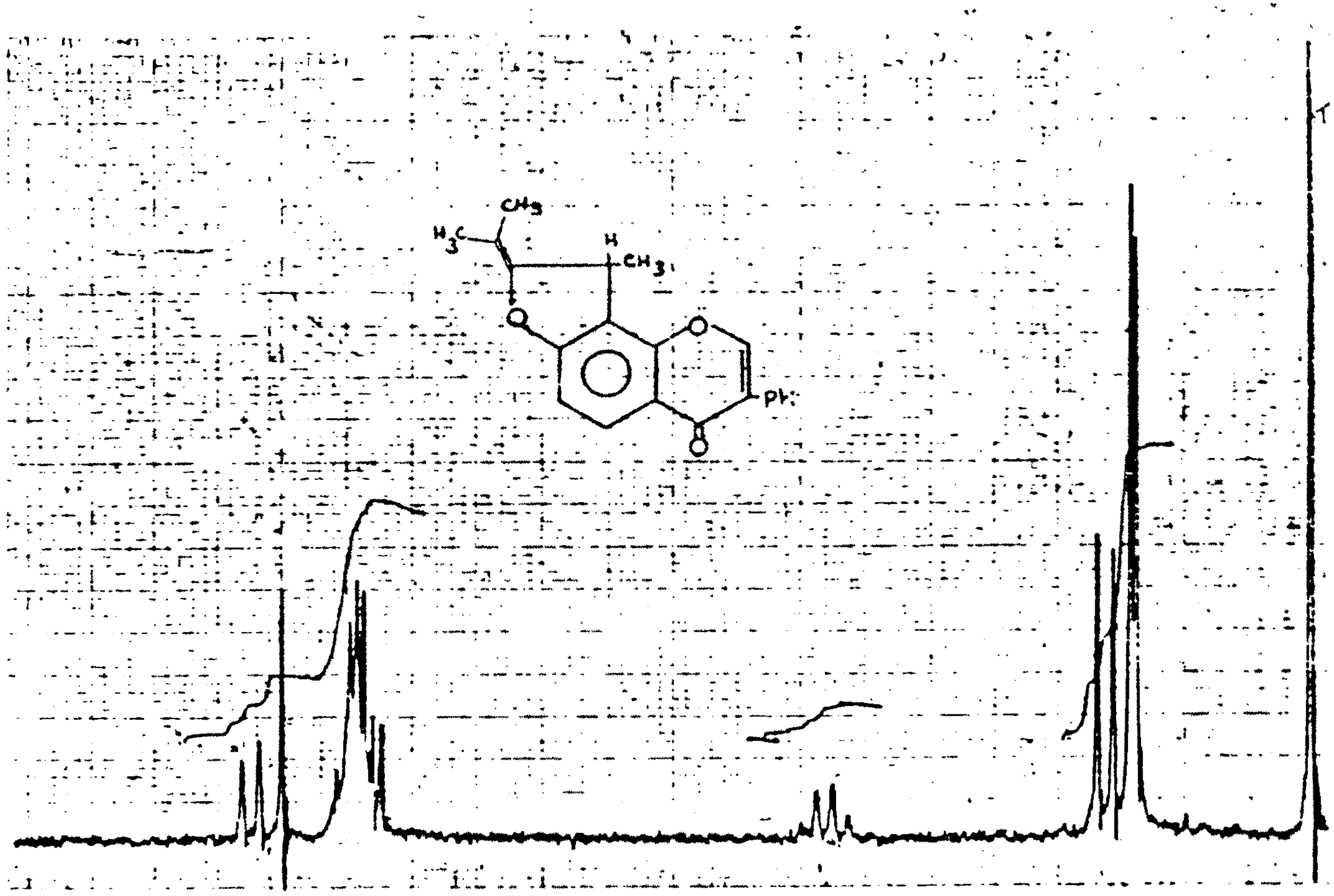
7-Hydroxy-8-methylisoflavone (59) was condensed with 3-chloro-3-methylbut-1-yne in the presence of fused potassium carbonate and a few crystals of potassium iodide by refluxing the mixture in dry acetone. On working up the reaction mixture, pure 7-(1,1-dimethyl-3-prop-2-ynyloxy)-8-methyl isoflavone (60) was obtained. (Scheme-XVII) Structure of (60) was assigned on the basis of PMR spectrum which exhibited following signals ($CDCl_3$) : δ 1.6, singlet, 6H, 2x-CH_3 groups of side chain ; another singlet at 2.2 for 3H, -CH_3 group Ar-CH_3 ; acetylenic proton showed a singlet at 2.5 ; 7.2 - 7.6, multiplet for six aromatic protons ; 7.9, singlet, 1H at C-2 ; 8.0, doublet, J=9Hz, 1H at C-5. IR spectrum showed band at 3200 cm^{-1} for terminal alkyne group. Ether (60) was subjected to Claisen rearrangement by refluxing it in N,N-dimethylaniline for 5 hrs. On working up the reaction mixture the crude product showed two spots on TLC and so it was subjected to column chromatography. On eluting the column with petroleum ether product (61) was isolated. On further elution with benzene an impure product was obtained in poor yield. This was purified by subjecting it to preparative TLC using benzene as the solvent to furnish (62).

Product A :

The product (61) with light yellow fluorescence was isolated in small quantity exhibited the following signals in PMR spectrum ($CDCl_3$) : δ 1.38 and 1.4, two singlets for two methyl group at C-2 ; 1.65, doublet, J=9Hz, 3H, $-CH_3$ at C-3 ; 3.8, quartet, J==9Hz, 1H at C-3 7.5 - 7.7, multiplet, 6H, aromatic protons ; 8.25, doublet, J=9Hz, 1H at C-8 ; 8.0, singlet, 1H at C-5. This pattern of PMR spectrum suggested that usual dimethyl pyran ring is absent and instead a novel type of ring system is present in the structure of this compound. It was tentatively assigned structure 2,2-dimethylmethylene-3-methyl-6-phenyl-2,3,4-trihydrofuro (2,3-h) benzopyran-7-one (61). (Fig.8)

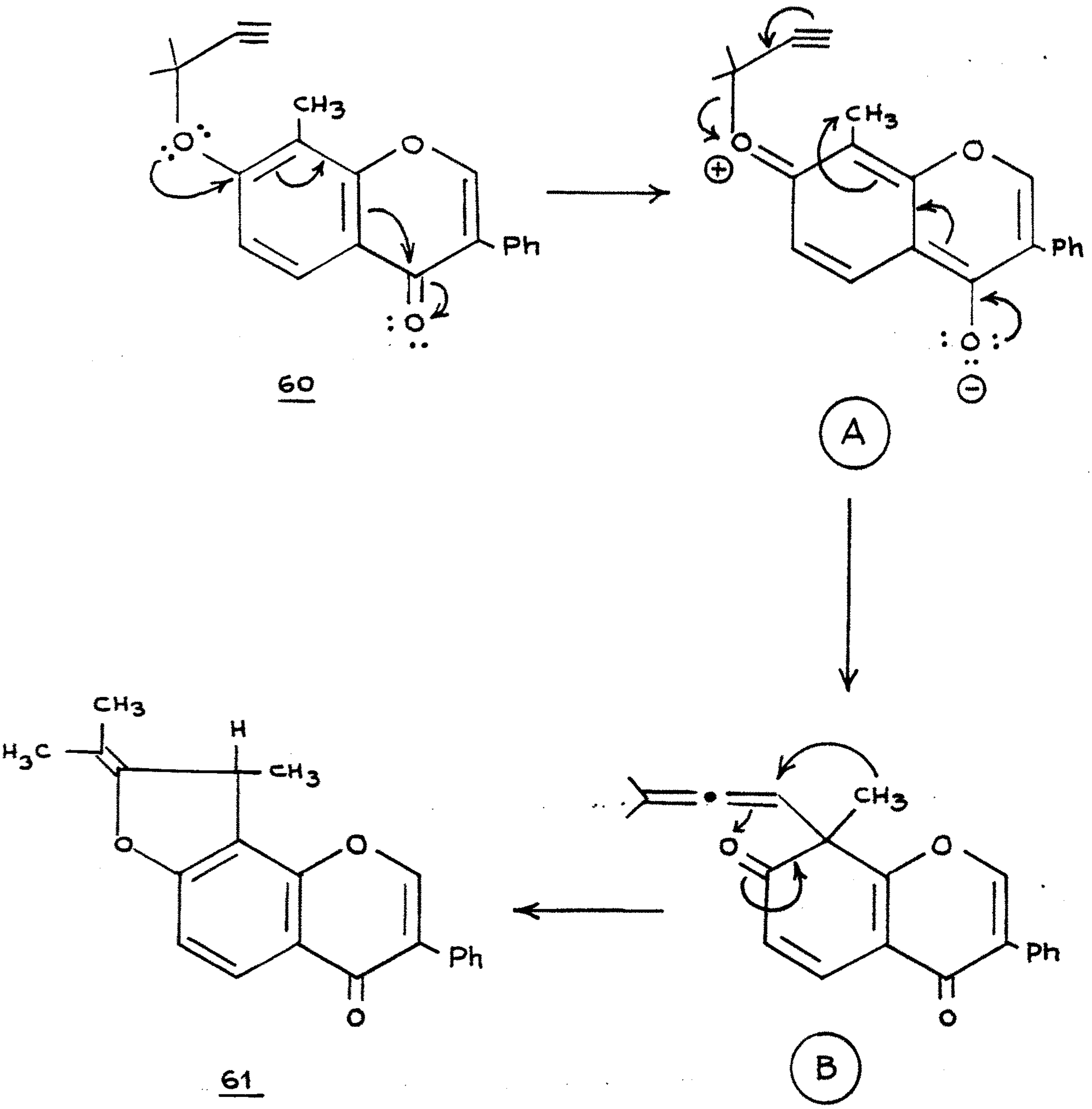
The formulation of (61) can be explained by the mechanism suggested in the (Scheme-XVIII).

The driving force in compound (60) is the carbonyl group at position 4 which attract the electron from oxygen of the ether, thus creating positive charge on phenolic oxygen and negative charge on the carbonyl oxygen as shown

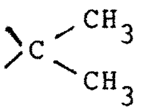


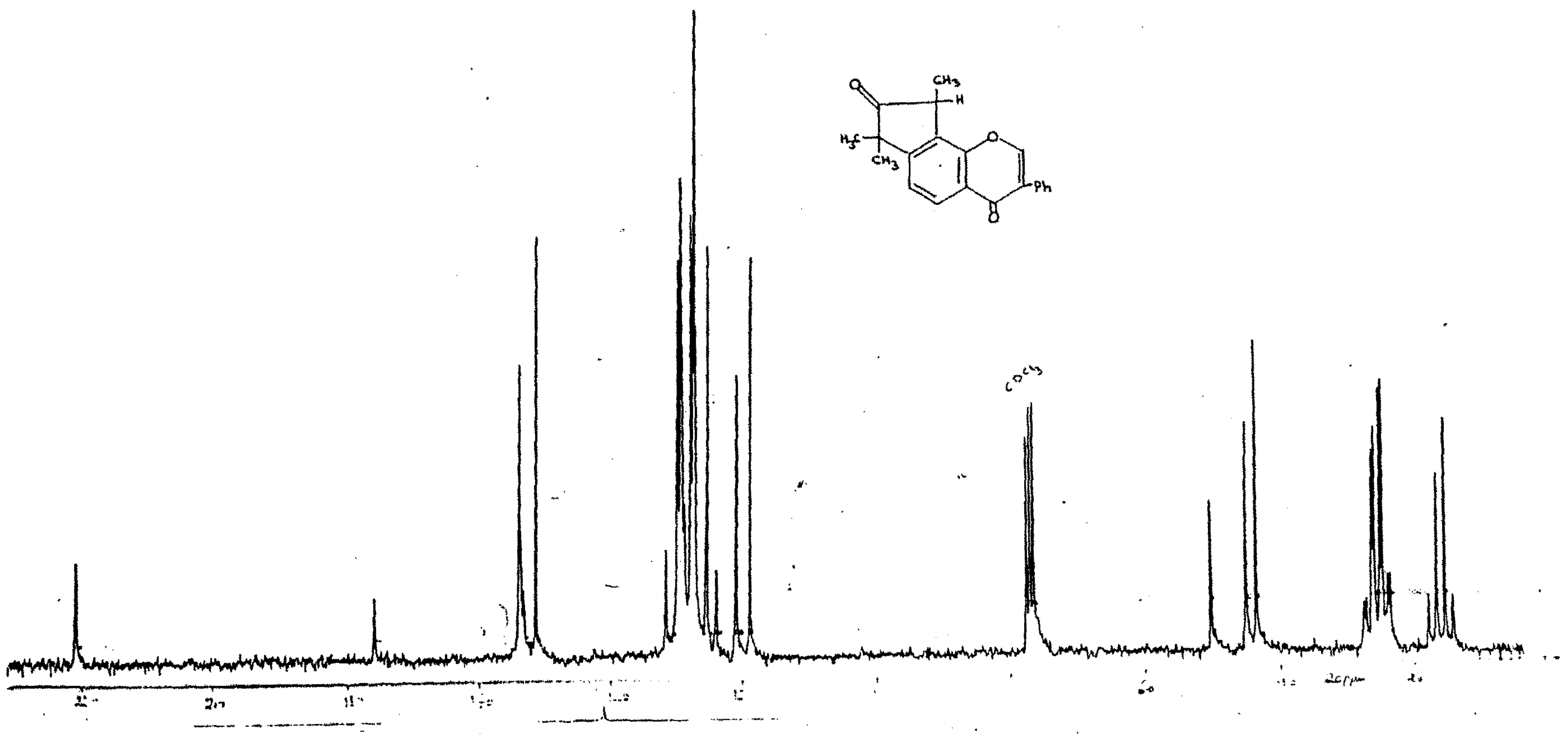
2,2-Dimethyl methylene-3-methyl-6-phenyl-2,3,4-trihydro furo (2,3-h) benzopyran-(7H)-8ne (61) (Fig. 8)

Scheme XVIII



in structure (A). On Claisen rearrangement, the 3,3-dimethyl propargyl group migrates to regiospecific position 8 and collapses into a allene system (B). This is supported by the fact that proton at position C-8 exhibited doublet of 9Hz otherwise it would have shown a singlet only. The system present in structure (B) can easily undergo Woodward - Hoffman allowed 2S + 2S + 2S sigmatropic shift with the migration of methyl group to the furan ring system giving compound (61).

^{13}C NMR of (61) showed three quartets at δ 15.9, 25.3 and 25.3 for three methyl carbons, one at C-3 and two at C-1. A doublet for $-CH-CH_3$ group was observed at 44 and a singlet at 50 was observed for  $>C(CH_3)_2$ group at C-1. Singlets, for aromatic carbons C-6, C-10, C-11 and C-1' was observed at 123.8, 125.4, 126.3 and 131.5. One downfield doublet and a singlet for C-5 and C-11a was observed at 152.4 and 153.5 respectively. Other aromatic carbons appear as doublets at 128.1, 128.3 and 128.9. Surprisingly it showed two singlets in the downfield carbonyl region, one at 175.8 and other at 220.8. The former can be assigned to the carbonyl group of γ -pyran ring system, while the second could be assigned to a overcrowded carbonyl group in the cyclopentane ring system. (Fig.9) This observation for



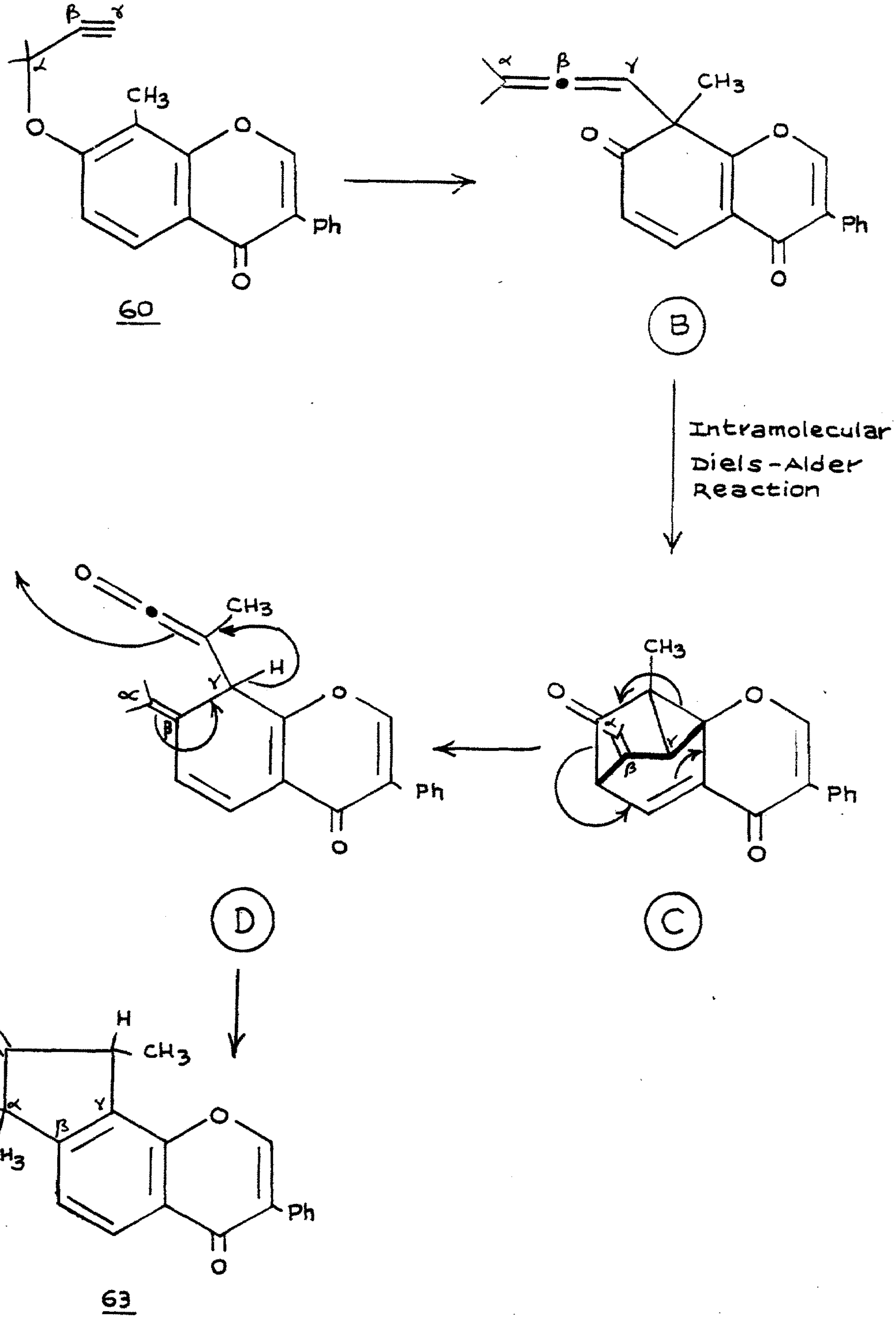
C^{12} n m r 1,2,3,7-Tetrahydro-1,1,3,5-tetramethyl-6-phenyl cyclopenta-[2H,7H]-benzopyran-2,7-dione (68)

(Fig.9)

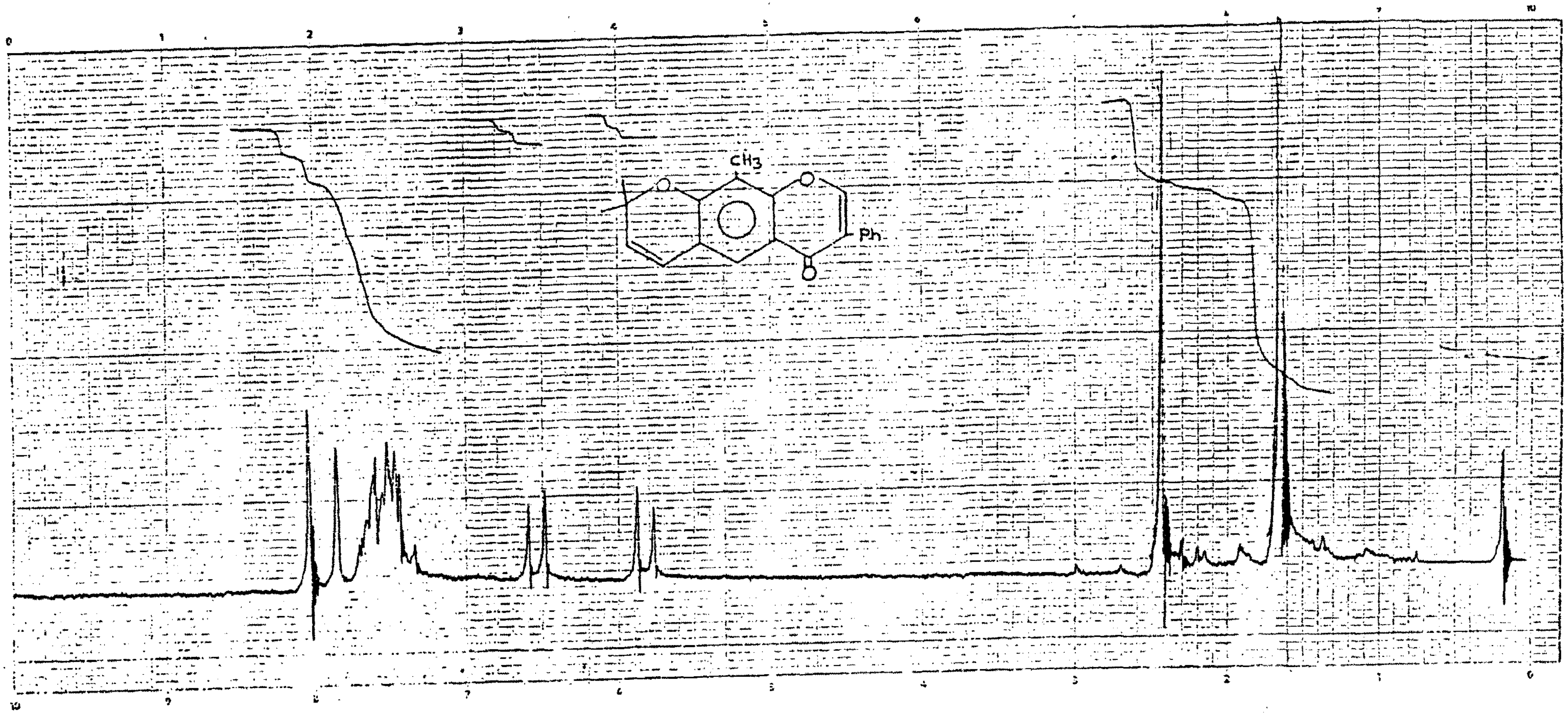
the presence of second carbonyl group was confirmed by its IR spectrum which showed two bands, one at 1640 cm^{-1} for carbonyl group of the γ-pyran ring system annd the other at 1740 cm^{-1} for the carbonyl group in the cyclopentene ring system. Based on this observation, the structure (61) is now revised to structure 1,2,3,7-tetrahydro-1,1,3-trimethyl-6-phenylcyclopenta(2,3-h)[2H,7H]-benzopyran — 2,7-dione (63), which satisfies all the spectral data - PMR, C^{13} NMR and IR. The mechanism fort he revised structure can be formulated as given in the (Scheme-XVIV).

(60), on Claisen rearrangement gives cyclohexadienone structure (B), the propargyl system collapsing into allene system. This structure can not undergo aromatization as there is no proton on the neighbouring carbon atom. Hence, it undergoes intramolecular Diels-Alder reaction to give a tricyclic ring sysem as shown in structure (C). Cyclopropane ring system, being highly unstable, undergoes ring opening to give the intermediate (D) and finally to structure (63). Thus this mechanism involves four thermally allowed six-electron concerted reaction. The metamorphosis of the structural change can be visualized by assigning α, β and γ nomenclature to carbon atom of the ether chain. In the final structure, β and γ carbon of side chain have now become the part of new benzene

Scheme XVIV

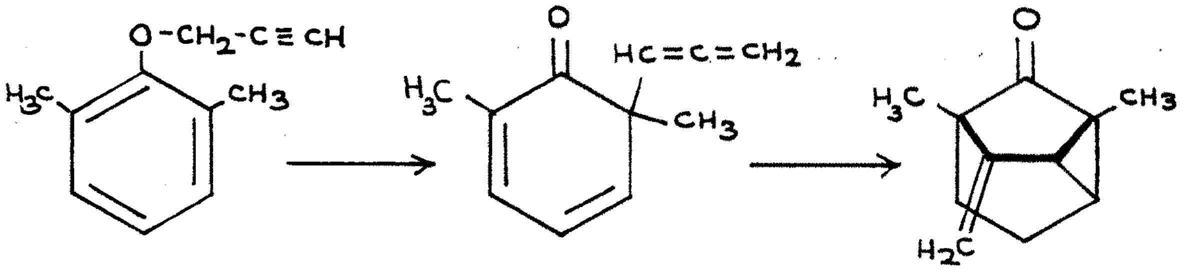


α
β
γ
CH3
O
Ph
60
B
Intramolecular Diels-Alder Reaction
C
D
H
H3C
63



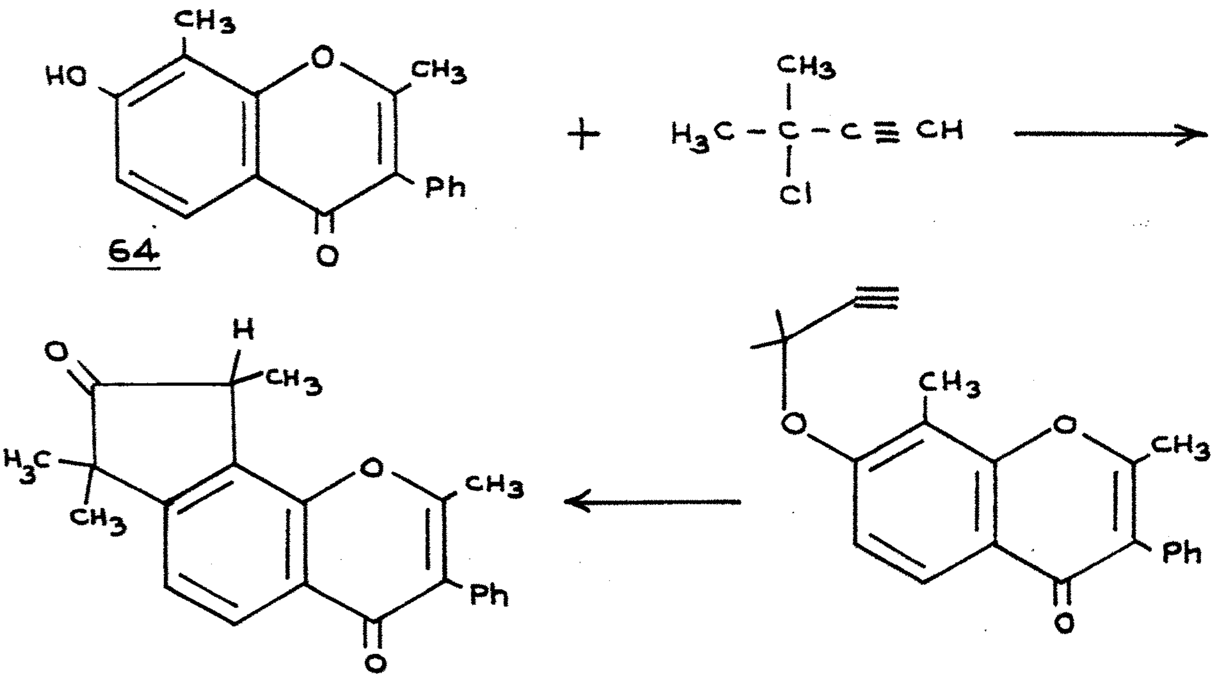
8,8,10-Trimethyl-3-phenylpyrano (2,3-g)-1-benzopyran-[4H]-one (62) (Fig. 10)

Scheme XX : Zsindely and Schmid[12]



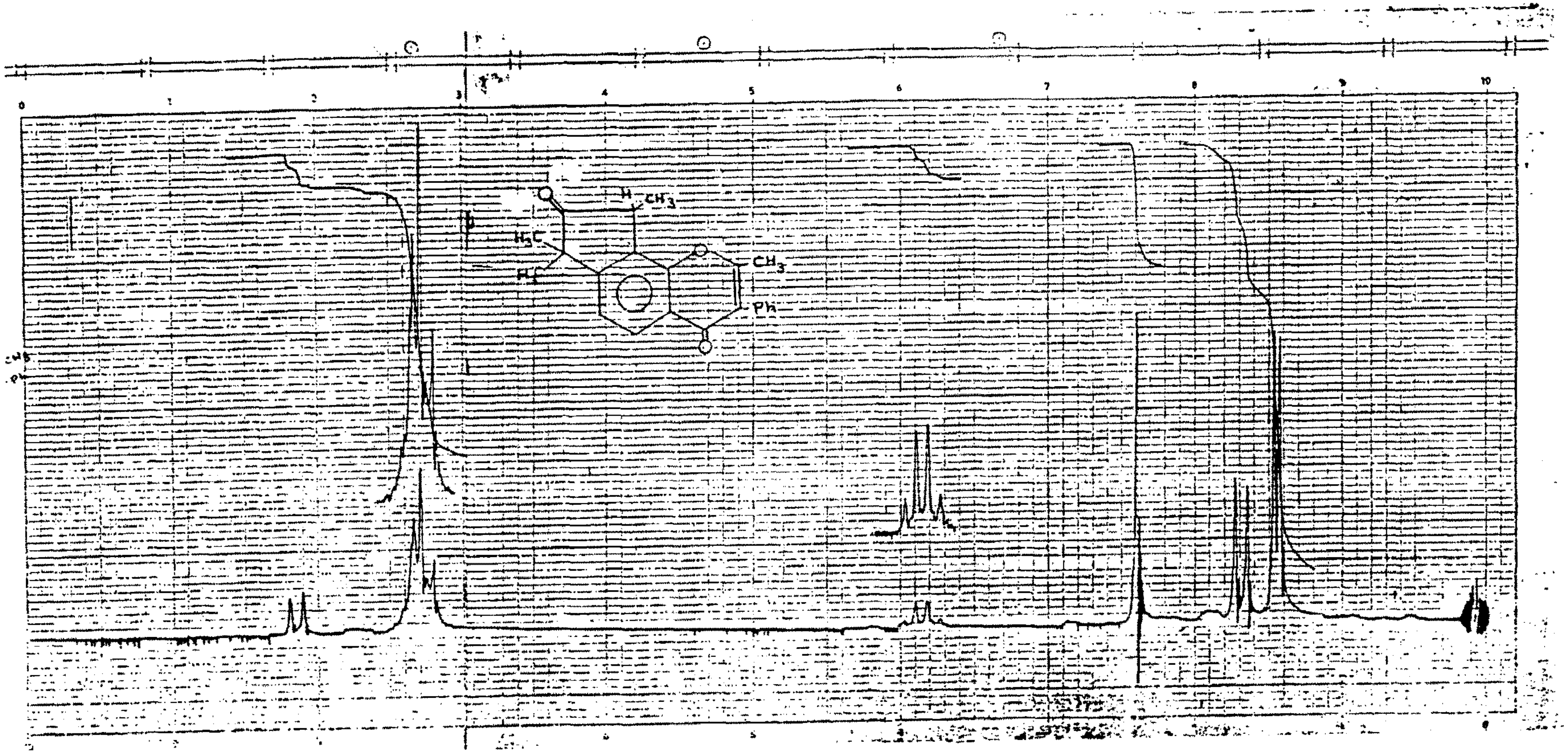
E F G

Scheme XXI



64

66 65



1,2,3,7-Tetrahydro-1,1,3,5-tetramethyl-6-phenyl cyclopenta-[2H,7H]-benzopyran-2,7-dione (66)

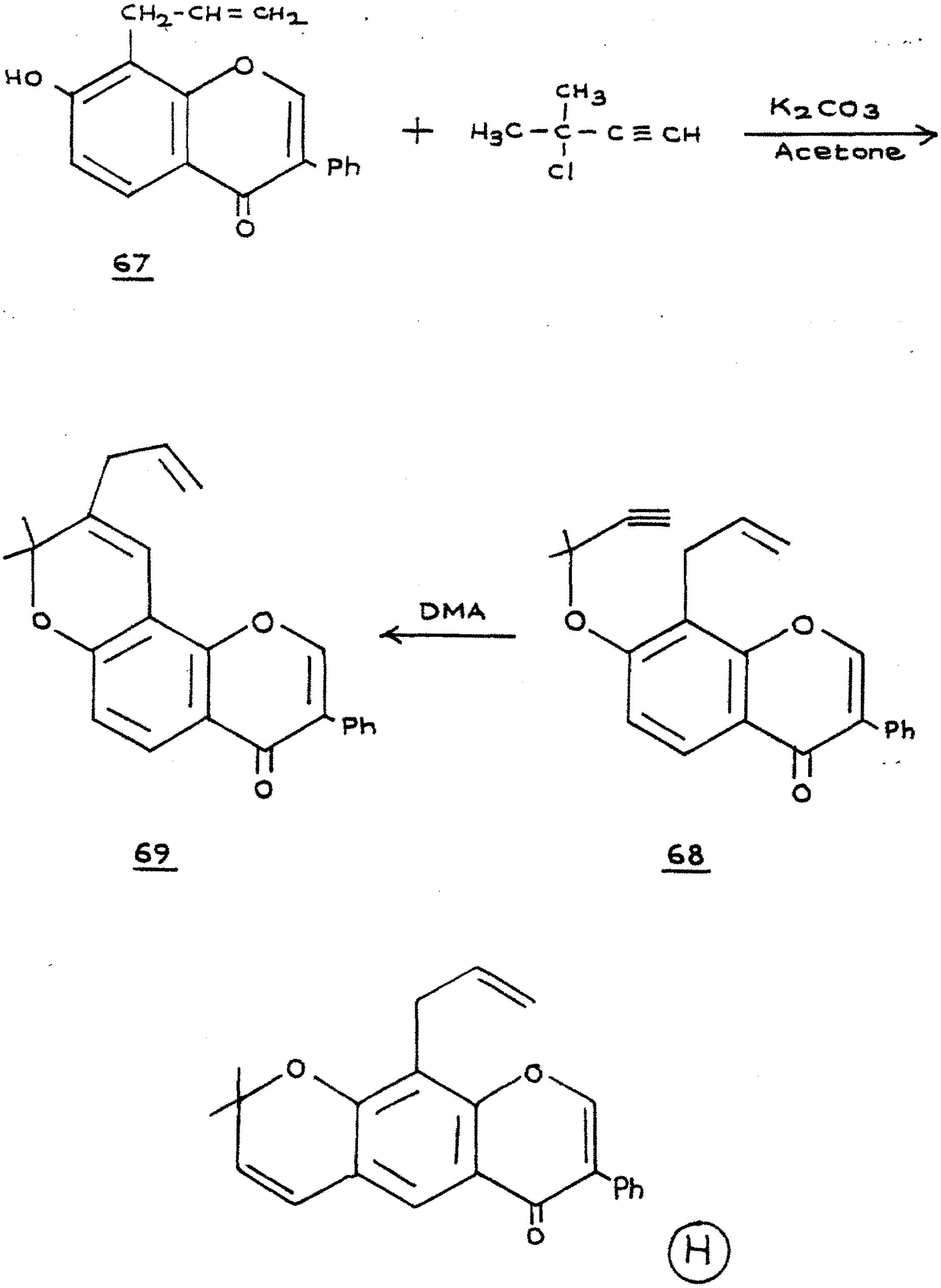
(Fig. 11)

J=9Hz, 1H at C-8. (fig 11) Further the compound (66) showed two bands in the carbonyl region one at 1620 cm^{-1} for γ-pyran carbonyl group while another at 1750 cm^{-1} for cyclopentenone carbonyl group. Thus on the basis of the PMR and IR spectra and also in analogy with compound (66) the structure 1,2,3,7-tetrahydro-1,1,3,5-tetramethyl-6-phenylcyclopenta-(2,3-h)[2H,7H]-benzopyran-2,7-dione is assigned to compound (66). (Scheme-XXI).

Synthesis of 2,2-dimethyl-7-phenyl-3-(Prop-2-enyl) pyrano (2,3-h)-[1]-benzopyran-(8H)-one (69)

7-Hydroxy-8-allylisoflavone (67), obtained from Claisen rearrangement of 7-allyloxyisoflavone was refluxed with 3-chloro-3-methylbut-1-yne in the presence of anhydrous potassium carbonate, potassium iodide and dry acetone as solvent. On working up of the reaction mixture, 7-(1,1-dimethyl-prop-2-ynyloxy)-8-allyl isoflavone (68) was obtained. It exhibited following signals in nmr ($CDCl_3$) δ 1,75, singlet, 6H, 2x-CH_3 groups at C-2 ; 2.7, singlet 1H, -C≡CH ; 3.6, doublet, J=8Hz, 2H, -CH_2-Ph ; 5.0,multiplet 2H, -CH_2- in the allyl side chain ; 6.0, multiplet, 1H, H_2C=CH-CH_2- ; 7.4, multiplet, 5H, aromatic protons. In the downfield region there are two doublets due to ortho coupling with coupling const J=9Hz each. One at 7.65 for proton at C-6 while other at 8.05 for proton at C-5. 7.9, singlet, 1H at C-2. (Scheme-XXII).

Scheme XXII



67

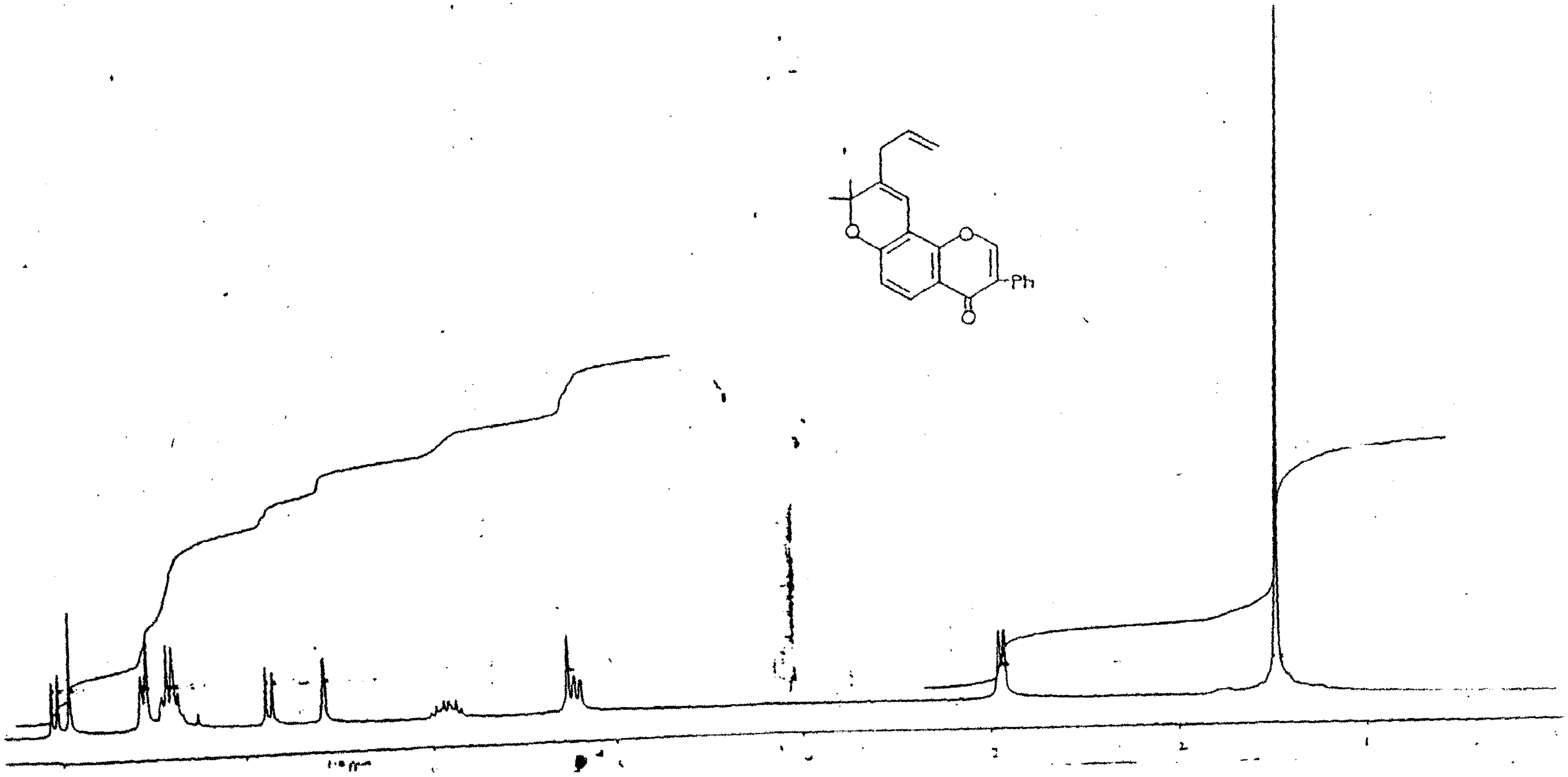
69

68

Ⓗ

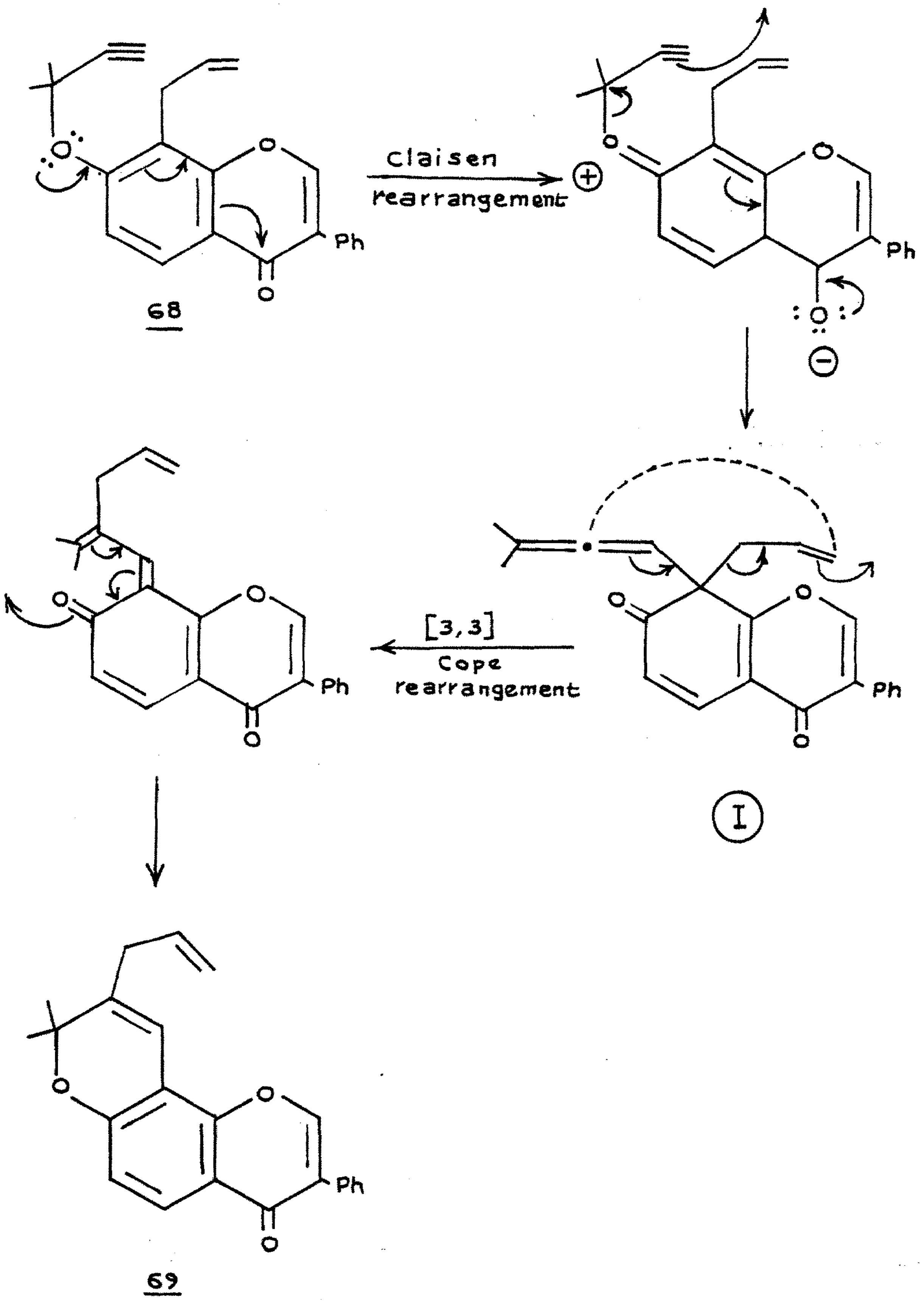
(68), was subjected to Claisen rearrangement by refluxing in N,N-dimethylaniline for 3 hr. On working up of reaction mixture single product was obtained and it was purified by passing through a column of silica gel using benzene as eluent. The product is assigned 2,2-dimethyl-7-phenyl-3-(prop-2-enyl)pyrano (2,3-h)-1-benzopyran-(8H)-one (69) structure on the basis of pmr spectrum ($CDCl_3$) : 1.4, singlet, 6H, 2x-CH_3 groups at C-2 ; 2.85, doublet, J=8Hz, 2H, -CH_2-CH=CH_2 at C-3 ; 5.1, multiplet, 2H, -CH_2-CH=CH_2 at C-3 ; 5.8,multiplet, 1H, -CH_2-CH=CH_2 ; 6.5, singlet, 1H at C-4 ; 6.7, doublet, J=9Hz, 1H at C-10 ; 7.1-7.5, multiplet, 5H, aromatic protons 7.8, singlet, 1H at C-6 ; 7.9, doublet, J=9Hz, 1H at C-9. The expected product (H) having 10-allyl-8,8-dimethyl-3-phenylpyrano (2,3-9) benzopyran-(4H)-one structure is eliminated because it did not show the expected two doublets around 6-7 with coupling constant J=10Hz and also the downfield singlet of the proton at C-5. The fact that it showed two doublets at δ 7.9 and 6.7 indicated that the migration has taken place on C-8 and not at C-6 of the isoflavone ring system. The mechanism for the formation of compound (69) is shown in (Scheme-XXIII). (Fig. 12)

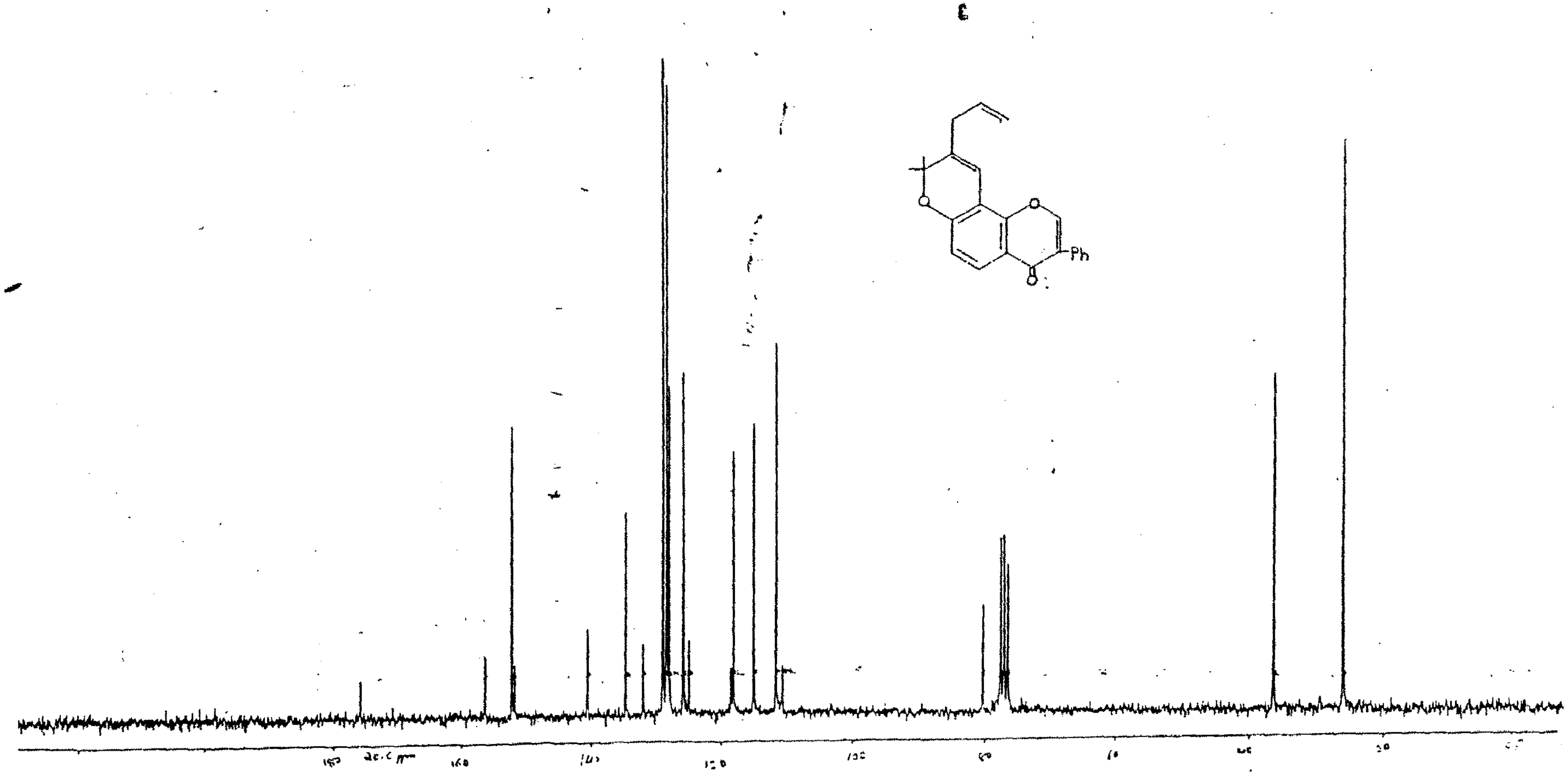
Here the Claisen migration first takes place on C-8 position, the acetylenic side chain collapsing to allenic



2,2-Dimethyl-7-phenyl-3-(prop-2-enyl)pyrano (2,3-h)-1-benzopyran-[8H]-one (69) (Fig. 12)

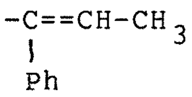
Scheme XXIII



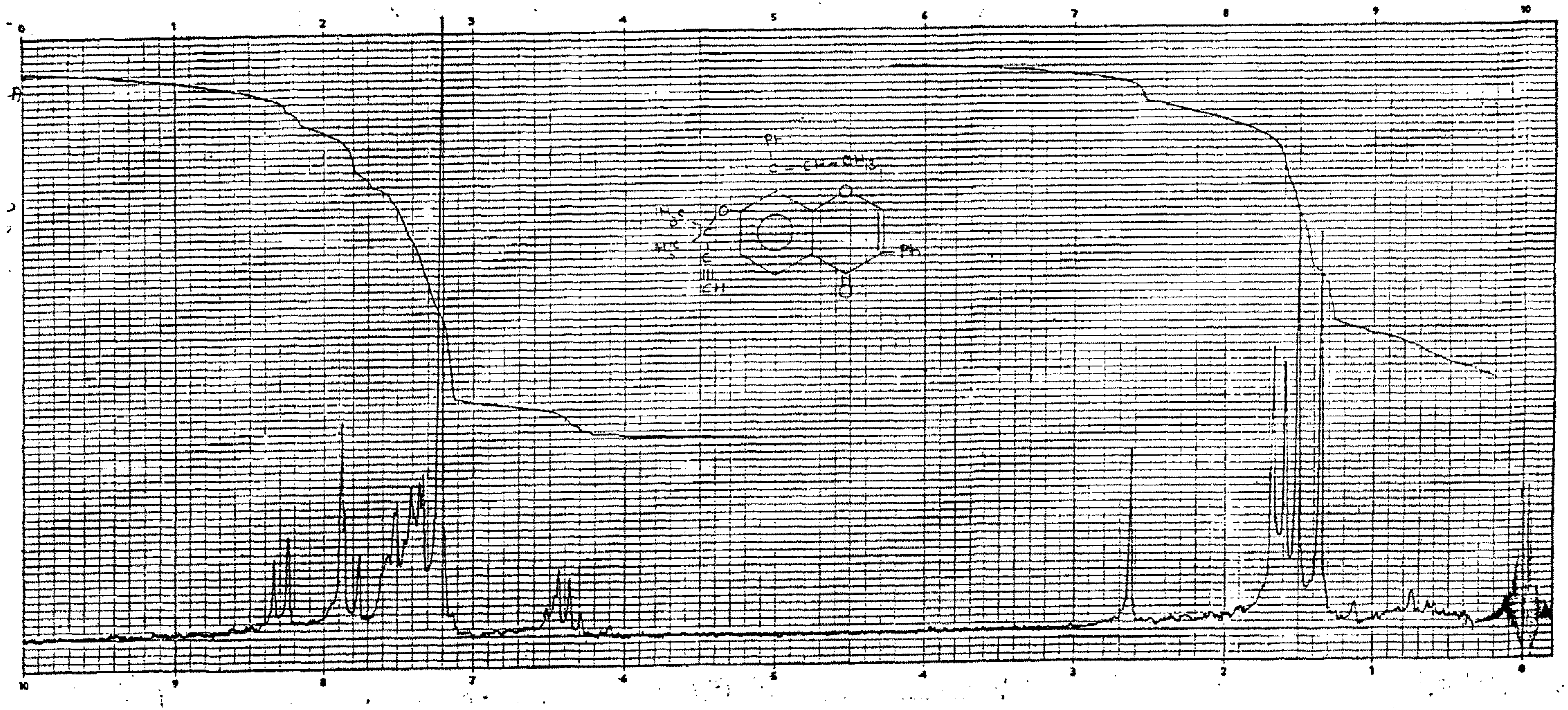


2,2-Dimethyl-7-phenyl-3-(prop-2-enyl)pyrano (2,3-h)-1-benzopyran-[8H]-one (69) (Fig.13)

C^{13} NMR

was condensed with 3-chloro-3-methyl-but-1-yne, anhydrous potassium carbonate, potassium iodide and refluxed in dry acetone solvent. On working up of the reaction mixture a single product was obtained. It was assigned 7-(1,1-dimethyl-prop-2-ynyloxy)-3-phenyl-8-(1-phenyl-prop-2-ene) benzopyran (4H)-one (71), structure on the basis of pmr spectrum ($CDCl_3$) : δ 1.35 and 1.5, two singlets for two methyl groups of side chain ; 1.65, doublet J=7Hz, 3H, $-CH_3$ group of the side chain $-C=CH-CH_3$. This doublet for methyl group indicates that the terminal double band present at position C-8 in the starting compound has undergone a prototopic rearrangement to 1st carbon of propylene side chain. Thus methylene $= CH_2$ has converted to $-CH_3$ due to double bond isomerization. This reaction occurs due to presence of weak alkali K_2CO_3 in the reaction mixture in which substance is heated for a very long period. Acetylenic proton appears as a singlet at 2.6 ; 6.4, multiplet for single vinylic proton  $-\underset{Ph}{\underset{|}{C}}{==}CH-CH_3$; 7.2-7.8, multiplet for eleven aromatic protons. 7.9, singlet, 1H at C-2 ; 8.3, doublet, J=9Hz, 1H at C-5. (Fig. 14)

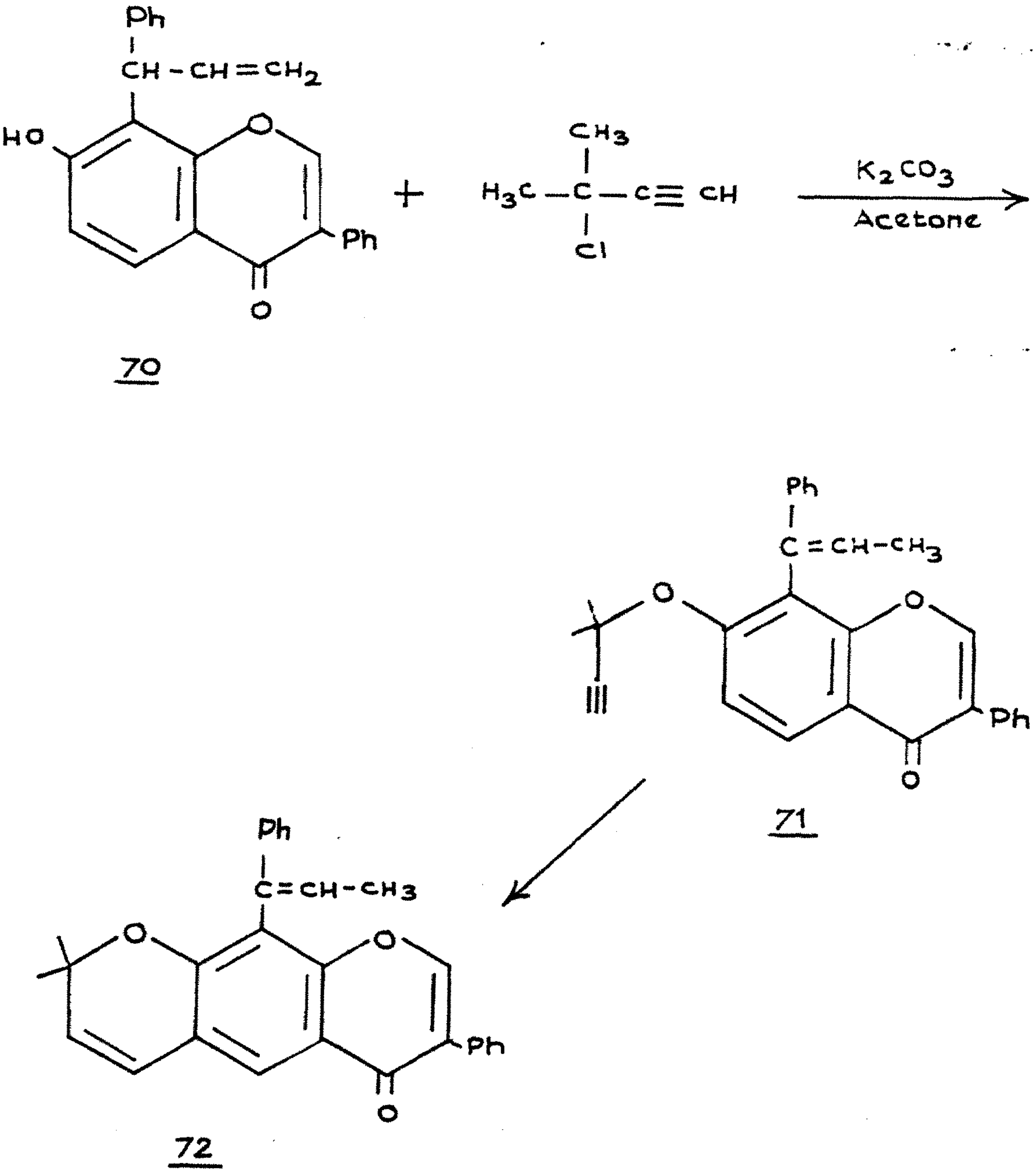
(71) was subjected to Claisen rearrangement by refluxing in N,N-dimethylaniline. Reaction mixture was worked up as before. The product obtained was assigned 2,2-dimethyl-7-phenyl-10-(1-phenyl-prop-1-enyl)pyrano (2,3-g)-



7-(1,1-dimethyl-prop-2-ynyloxy)-3-phenyl-8-(1-phenyl-prop-2-ene)benzopyran-[4H]-one (71)

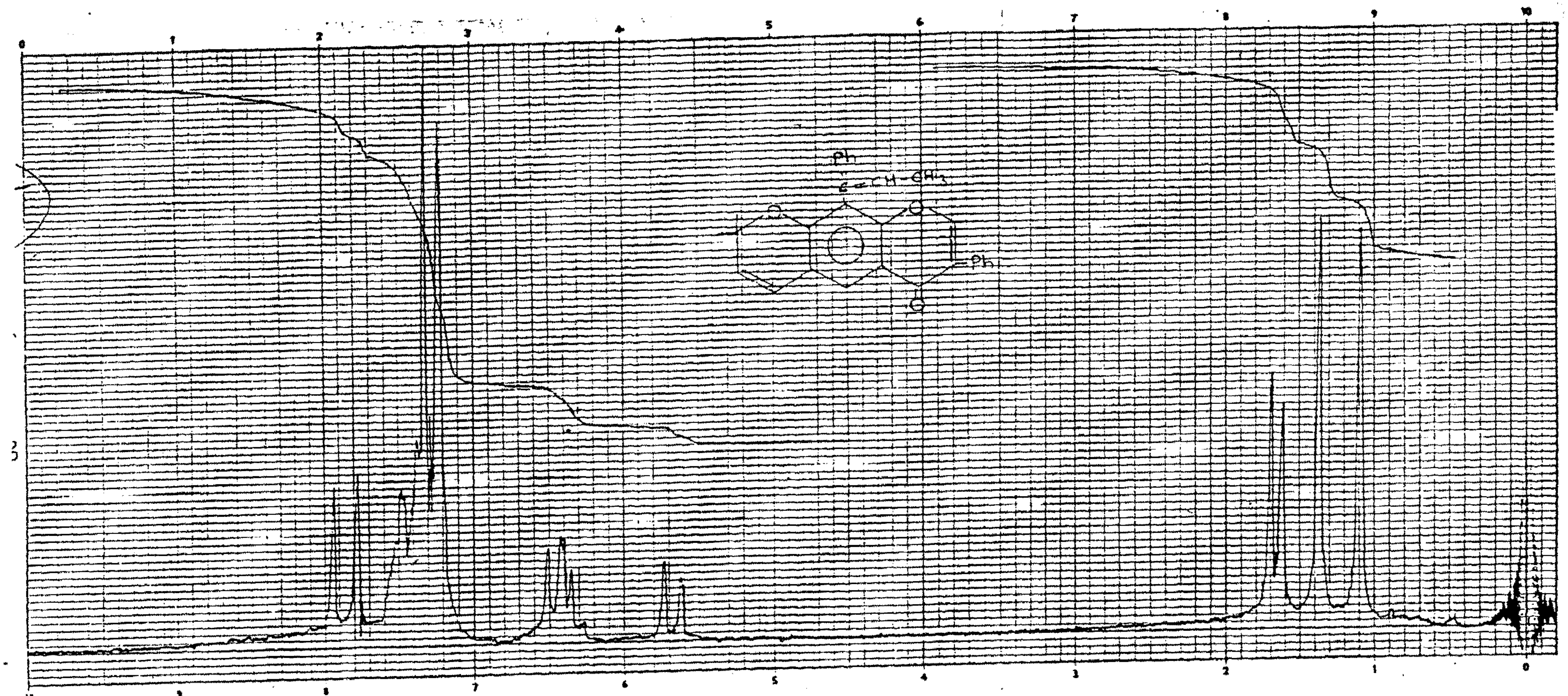
(Fig. 14)

Scheme XXIV


Ph
CH-CH=CH2
HO
O
Ph
O
70
CH3
H3C
C
C≡CH
Cl
K2CO3
Acetone
Ph
C=CH-CH3
O
O
Ph
O
71
Ph
C=CH-CH3
O
O
Ph
O
72

1-benzopyran-[6H]-one (72) structure on the basis of pmr spectrum ($CDCl_3$) : δ 1.1 and 1.35, two singlets for six protons of two methyl group at C-2 ; 1.65, doublet, J=9Hz, $-CH_3$ group at the terminal position of side chain $-\underset{\substack{| \\ Ph}}{C}=CH-CH_3$ at C-10 ; 5.7, doublet, J=9Hz, 1H at C-3 ; 6.4, multiplet 2H, the signal of the proton at C-4 has overlapped with signals of $=CH-CH_3$ group in the side chain ; 7.2 - 7.5, 10H, aromatic protons multiplet ; 7.8, singlet, 1H at C-8 ; 7.95, singlet, 1H at C-5. (Fig. 15)

The singlet at δ 7.95 for the proton at C-5 indicated that the ring closer has taken place at 6th position of the isoflavone ring system and not at the 8th position as has been observed in previous two cases. (Scheme-XXIV)



2,2-Dimethyl-7-phenyl-10-(1-phenyl-prop-1-enyl)pyrano (2,3-g)-1-benzopyran-[6H]-one (72)

(Fig. 15)

experimental

EXPERIMENTAL

All melting points are uncorrected. PMR spectrum recorded on Perkin-Elmer R-32 Spectrometer, (90 MHz) using TMS as internal standard. Silica gel used for column chromatography with mesh-size 60 - 120.

7-(3'-methyl-but-2'-enyl)oxy-8-methyl isoflavone (50)

A mixture of 7-hydroxy-8-methylisoflavone (49) (2.5 2-methylbut-3-ene-2-bromide (1.5 ml) and anhydrous potassium carbonate (8 gm) was refluxed in dry acetone (300 ml) fo5r 12 hrs. The reaction mixture was poured into water, the separated product filtered and washed with dilute sodium hydroxide solution to remove any unreacted compound. The product crystallized from benzene. M.p. 110°C, Yield 2.5 g, 80%.

Analysis : Found : C, 79.2 ; H, 5.8
$C_{21}H_{20}O_3$: requires : C, 78.7 ; H, 6.2%

Claisen migration of (50)

7-(3'-methylbut-2'-enyl)oxy-8-methylisoflavone (50) (1 gm) was refluxed with N,N-dimethylaniline (7 ml) for 8 hr. The reaction mixture was poured in cold dil. HCl and extracted with solvent ether, ethanol extract washed dilute sodium hydroxide solution and then with water.

Alkali solution on acidification with conc. HCl gave product. It was crystallized from benzene + ethanol, m.p. 253° Rf value on TLC plate is similar to 7-hydroxy-8-methylisoflavone m.p. and m.m.p. with authentic sample are identical.

C-Prenylation of 2,4-dihydroxy-3-methyl phenylbenzyl ketone (51) R.T.

To an ice-cooled solution of 2,4-dihydroxy-3-methyl phenylbenzyl ketone (51) (3 gm) in dry dioxan (15 ml) was slowly added BF_3 - etherate (1.25 ml) followed by 2-methyl-but-3-ene-2 ol (3.4 ml) in dioxan (10 ml) in one lot. The resulting mixture was stirred for 4 hr at room temperature, diluted with solvent ether (150 ml), washed with ice-cooled 1% Na_2CO_3 solution and finally with water. The alkaline solution gave unchanged 2,4-dihydroxy-3-methyl phenylbenzyl ketone. The etheral extract was dried and examined on TLC when it shows two spots. It was therefore subjected to column chromatography.

Fraction A :

Petroleum ether used as eluent which gave 7-hydroxy-8-methyl-6-phenylacetyl-2,2-dimethylchroman (52). It crystallized from benzene. M.p. 155°, yield 1 g.

Analysis : Found : C, 77.8 ; H, 7.3

$C_{20}H_{22}O_3$: requires : C, 77.5 ; H, 7.0%

Fraction B :

Benzene was eluted to furnish 2,4-dihydroxy-3-methyl-4-(3'-methyl-but-2'-enyl) phenylbenzyl ketone (53). It crystallized from petroleum ether. M.p. 114-5°, yield 0.5 g.

Analysis : Found : C, 77.9 ; H, 6.6
$C_{20}H_{22}O_3$: requires : C, 77.4 ; H, 7.0%

C-Prenylation of 2,4-Dihydroxy-3-methyl phenylbenzyl ketone (51) (High temperature)

The modification made in the above c-prenylation process is that the stirring was carried out with refluxing temperature of dioxan solvent. It was refluxed for 4 hr, diluted with solvent ether (150 ml), washed with ice-cooled 1% aqueous Na_2CO_3 solution and with water. The alkaline solution gave unchanged 2,4-dihydroxy-3-methyl-phenylbenzyl ketone. The etheral extract dried and subjected to column chromatography.

Only one product was obtained with petroleum ether as eluent viz. 7-Hydroxy-8-methyl-6-phenylacetyl-2,2-dimethylchroman (52). M.p. 155°C, Yield 1.5 g.

7-Hydroxy-8-methyl-6-phenylacetyl-2,2-dimethylchroman (52)

1 gm of 2,4-dihydroxy-3-methyl-4-(3'-methyl-but-2'enyl)

phenylbenzyl ketone (53) in formic acid (10 ml) was heated on steam bath for 1 hr. The reaction mixture was poured over crushed ice, the solid filtered and crystallized from petroleum ether. M.p. 155°C, yield 1.7 g. It was identical with (52) in all respects.

7-Hydroxy-6-(3-methyl-but-2-enyl)-8-methyl isoflavone (54)

2,4-Dihydroxy-3-methyl-4-(3'-methyl-but-2'-enyl) phenylbenzyl ketone (53) (1 gm), dry pyridine (5 ml), piperidine (0.5 ml) and redistilled triethyl orthoformate (3 ml) were refluxed together for 8 hr and the reaction mixture left overnight. Next day it was decomposed in ice and conc. HCl mixture. Solid separated, filtered, dried and crystallized from benzene. M.p. 148°C, yield 0.6 g.

Analysis	:	Found	:	C, 79.1 ;H, 5.8
$C_{21}H_{20}O_3$	:	requires	:	C, 88.7 ; H, 6.2%

8,8,10-Trimethyl-3-phenylpyrano (2,3,-g)-1-benzopyran-[4H]-one (55)

A mixture of (54), (0.7 g) & DDQ (0.7 g) were refluxed in dry benzene (120 ml) on steam bath for 1 hr. Reaction mixture filtered hot and excess of solvent distilled off. Solid obtained was passed through column of silica gel using benzene as eluent. It crystallized from petroleum ether. M.p. 136°C, yield0.5 g.

Analysis : Found : C, 79.2 ; H, 5.4

$C_{21}H_{18}O_3$: requires : C, 79.2 ; H, 5.6%

6,7-Dihydro-8,8,10-trimethyl-3-phenyl pyrano (2,3-g)-1-benzopyran-[4H]-one (56)

7-Hydroxy-8-methyl-6-phenylacetyl 2,2-dimethylchroman (52), (1.5 g) in redistilled ethyl formate (40 ml) was gradually added to finely pulverized sodium (1.5 g). A vigorous reaction took place which was complete within about 4 hrs. A brownish coloured mixture was cautiously poured into ice and dil. HCl. A brownish-yellow semi solid, which soon solidifies, separated. It was filtered, dried and purified by passing through the column of silica gel, using benzene as eluent. It crystallized from benzene. M.p. 177-8°, yield 0.3 g.

Analdysis : Found : C, 79.1 ; H, 6.2

$C_{21}H_{20}O_3$: requires : C, 78.7 ; H, 6.2%

6,7-Dihydro-2,8,8,10-tetramethyl-3-phenylpyrao (2,3-g)-1-benzopyran-[4H]-one (57)

A solution of 7-Hydroxy-8-methyl-6-phenylacetyl-2,2-dimethylchroman (52) (1.5 g) in freshly distilled diethyl carbonate (10 ml) was added slowly over finely pulverized sodidum (1.5 g). The mixture was refluxed for 5 hr. Then cooled and poured over crushed ice. Next day solid separated, filtered and dried. It crystallized from benzene to furnish (58). M.p. 207°, yield 0.4 g.

Analysis : Found : C, 75.4 ; H, 5.8

$C_{21}H_{20}O_4$: requires : C, 75.0 ; H, 5.9%

7-(1,1-dimethyl-3-prop-2-ynyloxy)-8-methyl isoflavone (60)

A mixture of 7-hydroxy-8-methyl isoflavone (59) (4g) 3-chloro-3-methyl-but-1-yne (2 ml), anhydrous potassium carbonate (12 gm) and few crystals of potassium iodide was refluxed in dry acetone as solvent for 72 hrs. After every 10 hrs, 1 ml of fresh reagent was added, to the reaction mixture. After reaction is over, it was poured in cold water. Next day solid separated. It was filtered and dried. It crystallized from benzene to obtain pure (60). M.p. 150°, yield 1 g.

Analysis : Found : C, 79.34 ; H, 5.5

$C_{21}H_{18}O_3$: requires : C, 79.24 ; H, 5.6%

Migration of (60) in DMA

7-(1,1-dimethyl-3-prop-2-ynyloxy)-8-methylisoflavone (60) (1 gm) was refluxed in N,N-dimethylaniline (7 ml) for

5 hr. Reaction mixture was cooled and poured into mixture of crushed ice and conc. HCl. Solid was separated which on inspection on TLC gave two spots. It was subjected to column chromatography.

Fraction A :

Light petroleum ether was eluted to obtain compound with light yellow fluorescence. It was crystallized from benzene + pet. ether to furnish 1,2,3,7-tetrahydro-1,1,3-trimethyl-6-phenylcyclopenta-[2H,7H]-benzopyran-2,7-dione (63). M.p. 165°, yield 125 mg.

Analysis	:	Found	: C, 79.62 ; H, 5.4
$C_{21}H_{18}O_3$	:	requires	: C, 79.24 ; H, 5.6%

Fraction B :

Benzene was eluted to obtain the solid which further purified by preparative TLC giving product in traces. It has bluish white fluorescence, crystallized from petrolem ether furnishing 8,8,10-trimethyl-3-phenylpyrano (2,3-g) -1-benzopyran-[4H]-one (62). M.p. 136-40°, yield 30 mg.

Analysis	:	Found	: C, 78.86 ; H, 6.03
$C_{21}H_{18}O_3$	:	requires	: C, 79.24 ; H, 5.66%

7-(1,1-dimethyl-3-prop-2-ynyloxy)-2,8-dimethyl isoflavone (65)

A mixture of 7-hydroxy-2,8-dimethyl isoflavone (64) (6 gm), 3-chloro-3-methyl-but-1-yne (3 ml), anhydrous potassium carbonate (15 gm) and few crystals of KI was refluxed in dry acetone for 72 - 75 hrs. After each 10 hrs. 1 ml of fresh reagent was added. Reaction mixture was poured over crushed ice and left overnight. Next day solid separated. It crystallized from benzene to obtain (65). M.p. 125°, yield 2 g.

Analysis : Found : C, 79.9 ; H, 5.8
$C_{22}H_{20}O_3$: requires : C, 79.5 ; H, 6.0%

1,2,3,7-Tetrahydro-1,1,3,5-tetramethyl-6-phenylisoflavone Cyclopenta-[2H,7H]-benzopyran-2,7-dione (66)

1 gm of 7-(1,1-dimethyl-3-prop-2-ynyloxy)-2,8-dimethyl isoflavone (65) was refluxed with N,N-dimethylandiline (7 ml) for 8 hr. Reaction mixture was cooled and poured over crushed ice and conc. HCl mixture. Solid was separated filtered and dried. Inspection on TLC gave only one spot. It was purified by passing through the column of silica-gel and crystallized from benzene + light petroleum ether to furnish (66). M.p. 165°, yield 300 mg.

Analysis : Found : C, 79.9 ; H, 5.79

$C_{22}H_{20}O_3$: requires : C, 79.5 ; H, 6. 2%

7-(1,1-dimethyl-prop-2-ynyloxy)-8-allyl isoflavone (68)

A mixture of 7-hydroxy-8-allyl isoflavone (67) (2gm) 3-chloro-3-methyl-but-1-yne (2 ml), anhydrous potassium carbonate (7 gm) potassium iodide in N,N-dimethyl formamide as solvent was refluxed with stirring for 25 hrs. 0.5 ml of fresh reagent was added after interval of 6 hrs. Reaction mixture was cooled, filtered and excess of solvent was distilled off. It was poured over crushed ice, solid separated was crystallized from benzene to furnish (68) M.p. 138°, yield 1 g.

Analysis : Found : C, 80.7 ; H, 5.97

$C_{23}H_{20}O_3$: requires : C, 80.2 ; H, 5.8%

2,2-Dimethyl-7-phenyl-3-(prop-2-enyl)pyrano (2,3-h)-[1]-benzopyran-[8H]-one (69)

1 gm of 7-(1,1-dimethyl-prop-2-ynyloxy)-8-allyl-isoflavone (68) was refluxed with N,N-dimethylaniline (7 ml) for 3 hrs. Reaction mixture was cooled and poured into mixture of crushed ice and conc. HCl. Solid was separated, filtered and dried. It was purified by passing

through the column of silica gel using benzene as eluent. It crystallized from benzene + petroleum ether to furnish (69). M.p. 165°, yield 250 mg.

Analysis : Found : C, 80.9 ; H, 5.59
$C_{23}H_{19}O_3$: requires : C, 80.46; H, 5.5%

7-(1,1-dimethyl-prop-2-ynyloxy)-3-phenyl-8-(1-phenyl prop-2-ene)benzopyran-[4H]-one (71)

A mixture of 7-hydroxy-8-cinnamyl isoflavone (70) (2 gm), 3-chloro-3-methyl but-1-yne (2 ml), anhydrous potassium carbonate (7 gm) & potassium iodide was refluxed with stirring in N,N-dimethyl formamide for 25 hrs. 0.5 ml of fresh reagent was added after interval of 6 hrs. Reaction mixture was cooled, filtered and excess of solvent was distilled off. It was poured over crushed ice, solid separated, filterd and dried. It crystallized from benzene to obtain (71). M.p. 160°, yield 1.2 g.

Analysis : Found : C, 82.4 ; H, 5.6
$C_{29}H_{24}O_3$: requires : C, 82.8 ; H, 5.7%

2,2-Dimethyl-7-phenyl-10(1-phenyl Prop-1-enyl)pyrano (2,3-g)-1-benzopyran-[6H]-one (72)

1 gm of 7-(1,1-dimethyl Prop-2-ynyloxy)-3-phenyl 8-(1-phenyl prop-2-ene)benzopyran-[4H]-one (71) was refluxed with N,N-dimethylaniline (7 ml) for 8 hr. Reaction mixture was cooled and poured into mixture of crushed ice and Conc. HCl. Solid obtained was filtered dried and crystallized from benzene to furnish 2,2-dimethyl-7-phenyl-10-(1-phenyl prop-1-enyl) pyrano (2,3-g)-1-benzopyran-[6H]-one (72). M.p. 161-2°, yield 400 mg.

Analysis : Found : C, 82.43 ; H, 5.8

$C_{29}H_{24}O_3$: requires : C, 82.85 ; H, 5.7%

References

1. A.C. Jain, P. Lal, & T.R. Seshadri, Ind. J. Chem., 7, 1072 (1969).

2. A.C. Jain, & D.K. Tuli, Curr. Sci., 41(3), 486-7, (1972)

3. F. Bohlman and K.M. Kleine, Chem. Ber, 99, 885 (1966).

4. A.C. Jain and S.M. Jain, Tetrahedron, 28, 981 (1972).

5. A.C. Jain, A. Kumar, & R.C. Gupta, Ind. J. Chem., 16B, 613 (1978).

6. A.C. Jain, D.K. Tuli, & R.C. Gupta, Ind. J. Chem., 16B, 7, 611-13 (1978).

7. A.C. Jain, D.K. Tuli, & R.C. Gupta, J. Org. Chem. 43, 3446, 18 (1978).

8. A.C. Jain, P. Lal, & T.R. Seshadri, Tetrahedron, 26, 1977-88 (1970).

9. A.C. Jain, & D.K. Tuli, Curr. Sci., 47, 682-3, (1978).

10. A.C. Jain, D.K. Tuli, & R. Khazanchi, Ind. J. Chem., 16B, 973-6 (1978).

11. I. Iwai, & J. Ide, Chem. Pharm. Bull. (Japan), 10, 926 (1962) ; 11, 1042 (1963).

12. Zsindely and H. Schmid, Helv. Chem. Acta., 51, 1510 51, 1510 (1968).

13. S.K. Mukerjee, S.C. Sarkar, & T.R. Seshadri, Ind. J.Chem., 8, 861 (1970).

14. B.S. Bajwa, P. Lal & T.R. Seshadri, <u>Ind. J. Chem.</u>, 9, 17 (1971).

15. A.C. Jain, D.K.Tuli & R. Khazanchi, <u>Ind. J. Chem.</u>, 17B, 123-6 (1979).

16. A.C. Jain, R.C. Gupta & D.K. Tuli, <u>Natl. Acad. Sci. Lett.</u> 1(2), 65 (1978).

17. A.C. Jain, R.C. Gupta & D.K. Tuli, <u>Proc. Ind. Natl. Sci. Acad.</u> A, 45(1), 9-96 (1979).

18. H.J. Hansen and H. Schmid, <u>Chimica</u> ; 24, 89 (1970).

19. J. Boyd and A. Robertson, <u>J. Chem. Soc.</u>, 174 (1948).