Chapter IV

Section I

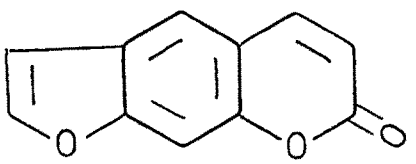
SYNTHESIS OF BENZOFURO BENZO - γ - PYRONES

Benzofuran derivatives are known to exhibit diverse physiological properties.[1-3] Furochromones like Khellin and Visnagin are also well known for their pharmacological activity.[4-11] In view of these reports it was thought of to construct benzofuran ring on benzo-γ-pyrones like chromones and chromanones. The benzofurobenzo-γ-pyrones thus obtained may have pronounced physiological activities.

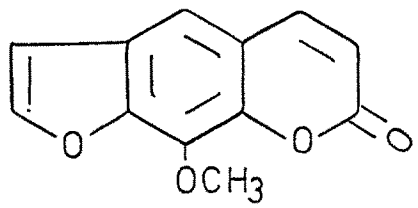
Psoralen (1) and its derivatives has received considerable attention on account of their therapeutic properties. e.g. Xanthotoxin (2) is a fish poison[12] and possess molluscidal activity.[13] Musajo and co-workers[14,15] have observed that Psoralen derivatives are photodynamically active.

It was found that naturally occuring benzofurocoumarins are reported to possess estrogenic[16] insecticial[17] and antibacterial[18] activities and are also known to play an important role as phytolaxins.[19]

J.K. MacLeod and Worth[20] synthesised linear furocoumarin-Psoralene (1) by carrying out etherification of 7-hydroxycoumarin with allyl bromide, followed by ozonolysis and followed by cyclisation with alkali. They[20] extended the above method to prepare dibenzofuran derivatives by condensing 2-bromocyclohexanone with 7-hydroxycoumarin (3) followed by treatment

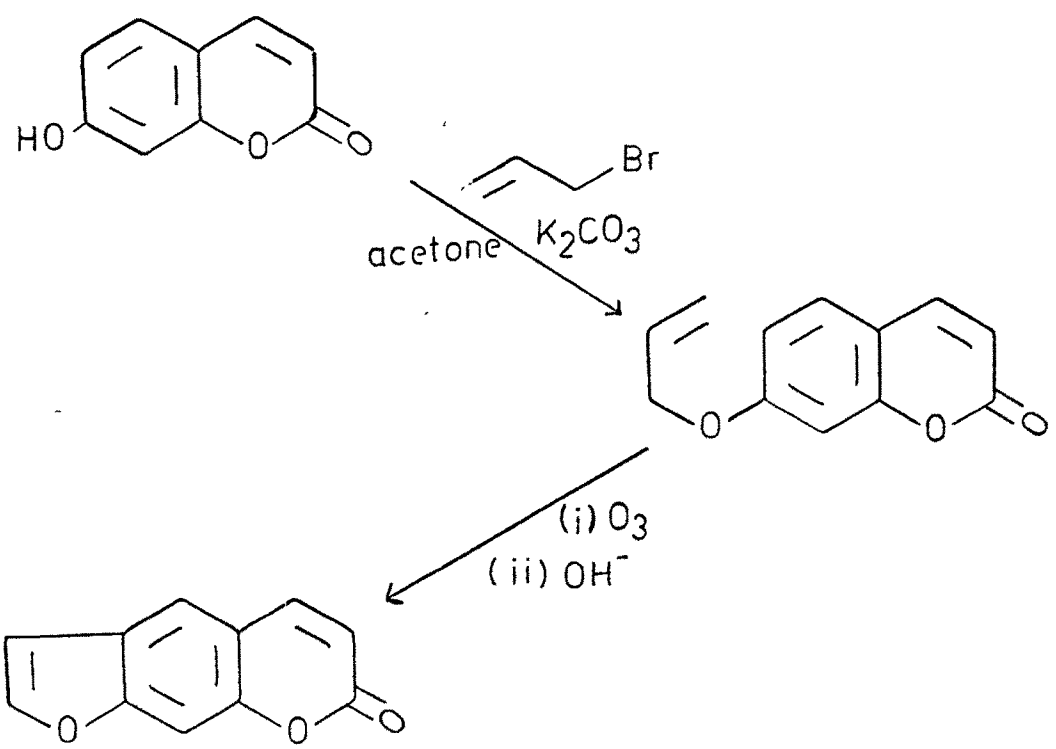


1



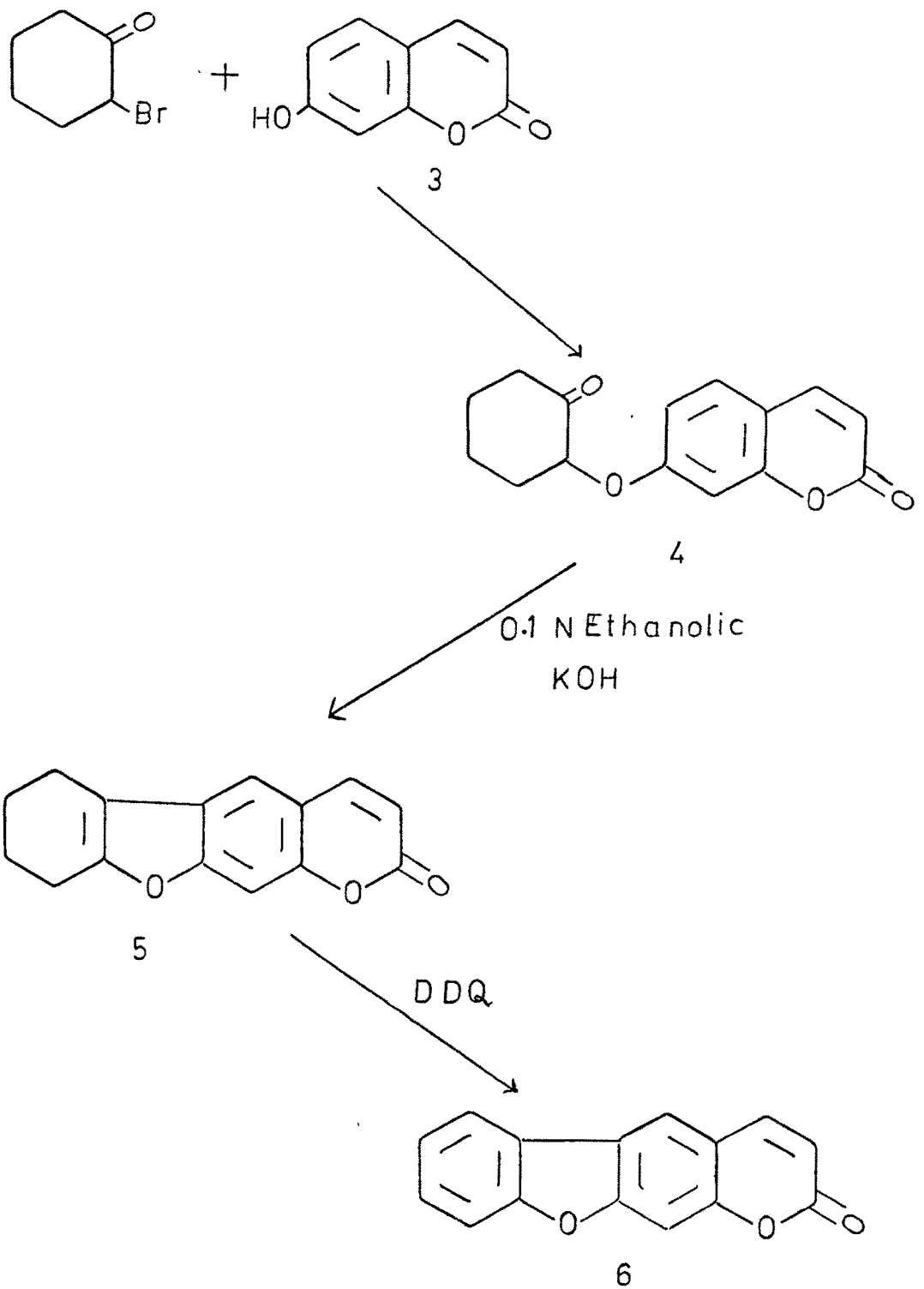
2

Macleod and coworkers[20]



1

SCHEME-I



with aqueous KOH under reflux. This product (5) was readily dehydrogenated to 2H-benzofuro [3,2-g]-1-benzopyran-2-one (6) after cyclization (Scheme-I).

Using this procedure K. Lingeshwara Rao[21] prepared (8) from (7). Ahluwalia and coworkers[22] synthesised methyl derivatives of benzofurocoumarins by alkylation of hydroxycoumarins with 2-bromocyclohexanone followed by cyclization of the resulting compound with polyphosphoric acid (PPA) or alcoholic KOH and subsequent dehydrogenation with DDQ (Scheme-II & III).

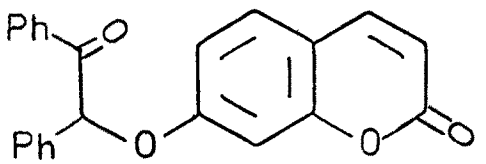
Rodhighiero and coworkers[23] also synthesized methyl derivatives of tetrahydrobenzofuro and benzofurocoumarins starting from appropriate hydroxycoumarins on which the tetrahydrobenzofuro and benzofuro moiety was built up, methyl groups have been introduced into position which look most promising for the photoreactivity of the compound towards DNA (Scheme-IV).

Ahluwalia, Adhikari and Singh[24] carried out similar type of synthesis on benzo- γ -pyrones for the first time. They condensed 2-bromocyclohexanones with 7-hydroxy-5-methoxy flavones and obtained corresponding benzofuroflavones (9-13).

Present Work

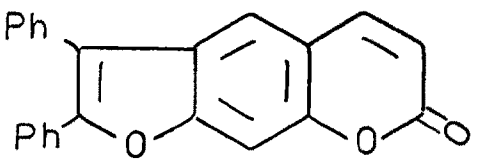
Desai and Trivedi[25] reported the synthesis of 2H-benzofuro (3,2-g)-[1]-benzopyran-2-one derivatives by condensing the different hydroxycoumarins with 2-bromocyclohexanone followed

Lingeshwara rao and coworkers[21]



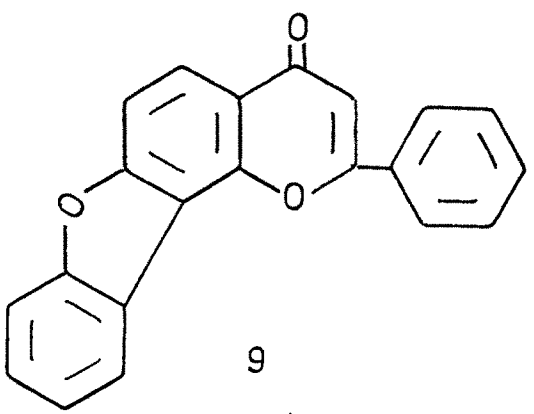
7

0·1 N alc. KOH

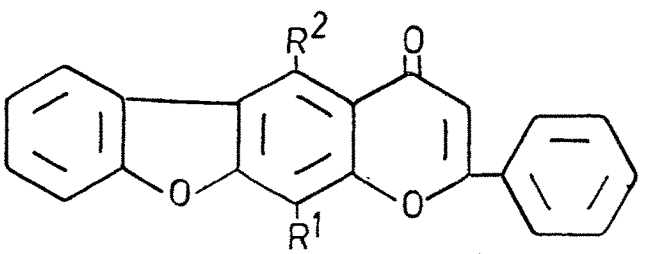


8

Ahluwalia, Adhikari and Singh[24]



9



10,11,12,13

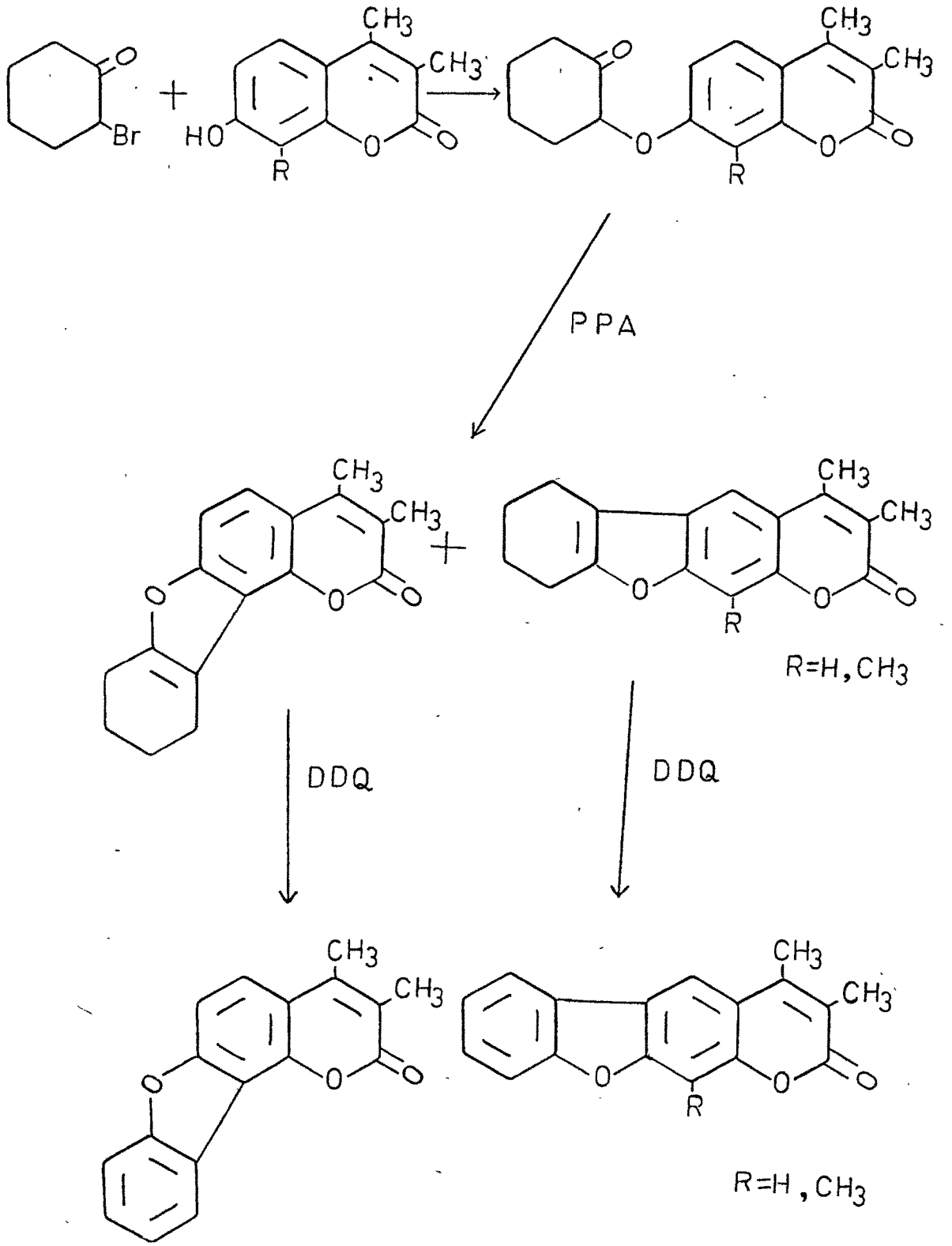
10. $R^1=R^2=H$

11. $R^1=H, R^2=OH$

12. $R^1=CH_3, R^2=H$

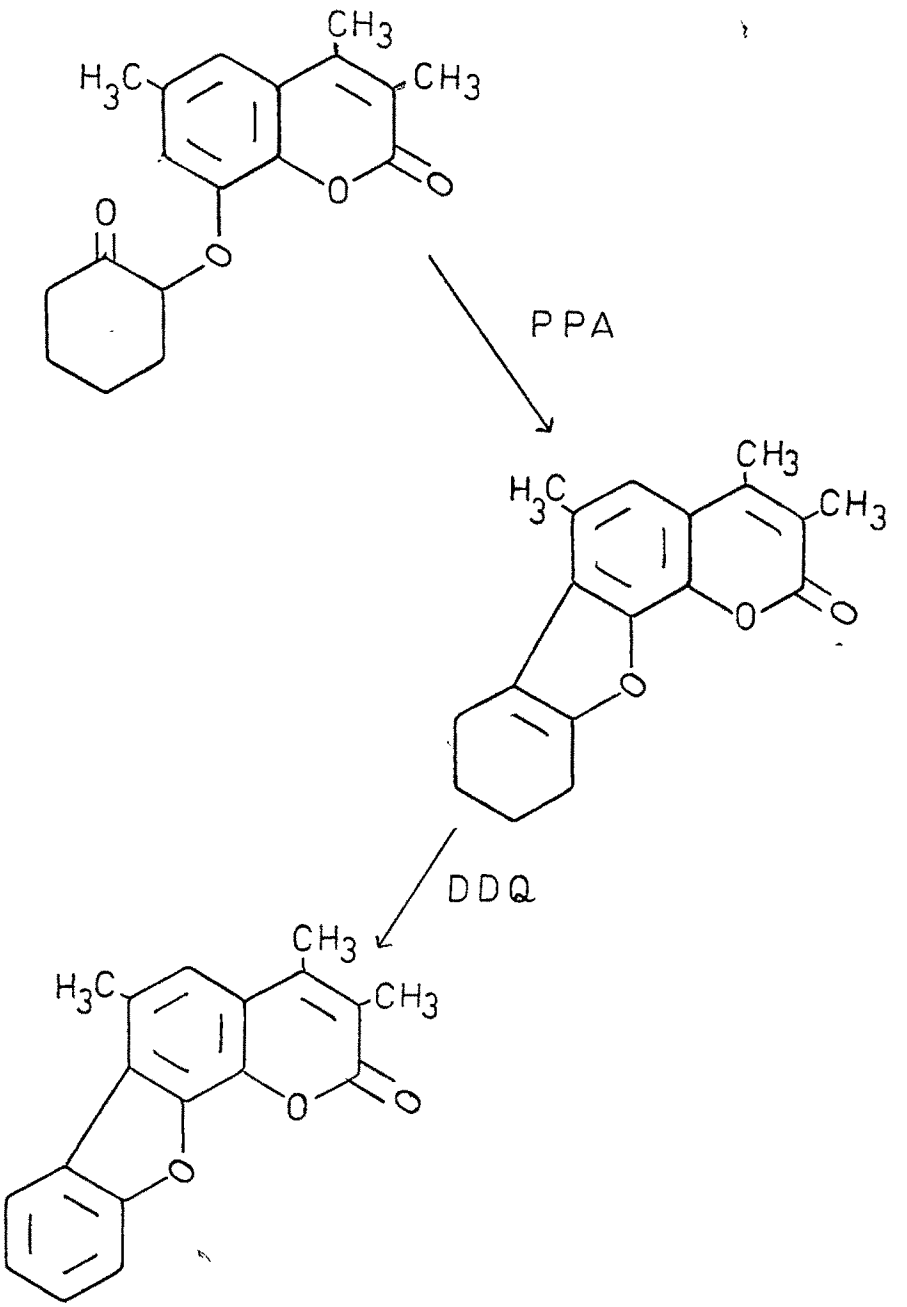
13. $R^1=H, R^2=OCH_3$

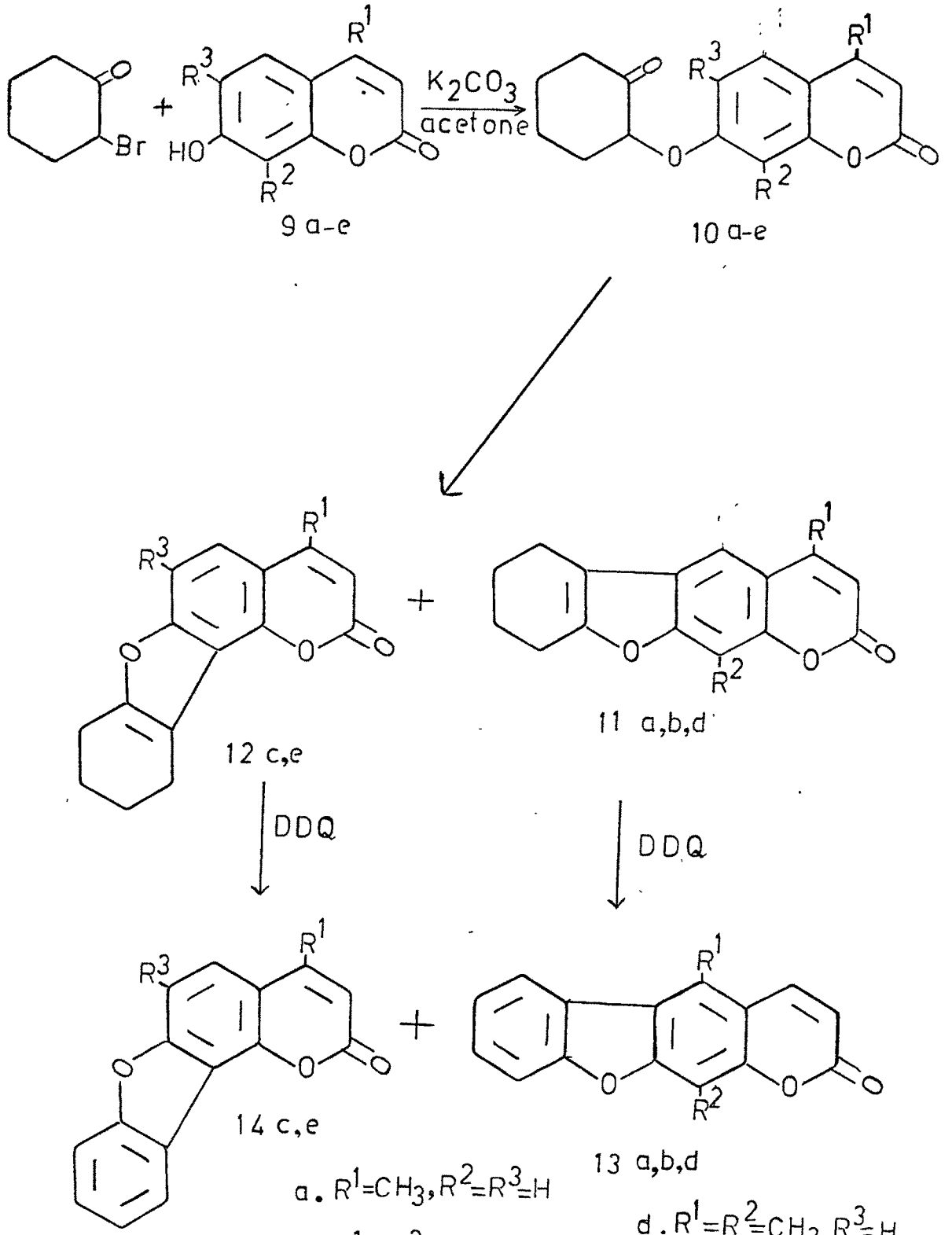
Ahluwalia and coworkers[22]



SCHEME - II

SCHEME-III




K2CO3
acetone
9 a-e
10 a-e
12 c,e
11 a,b,d
DDQ
DDQ
14 c,e
13 a,b,d
a. R1=CH3, R2=R3=H
b. R1=R2=R3=H
c. R1=R2=H, R3=CH3
d. R1=R2=CH3 R3=H
e. R1=R3=CH3 R2=H

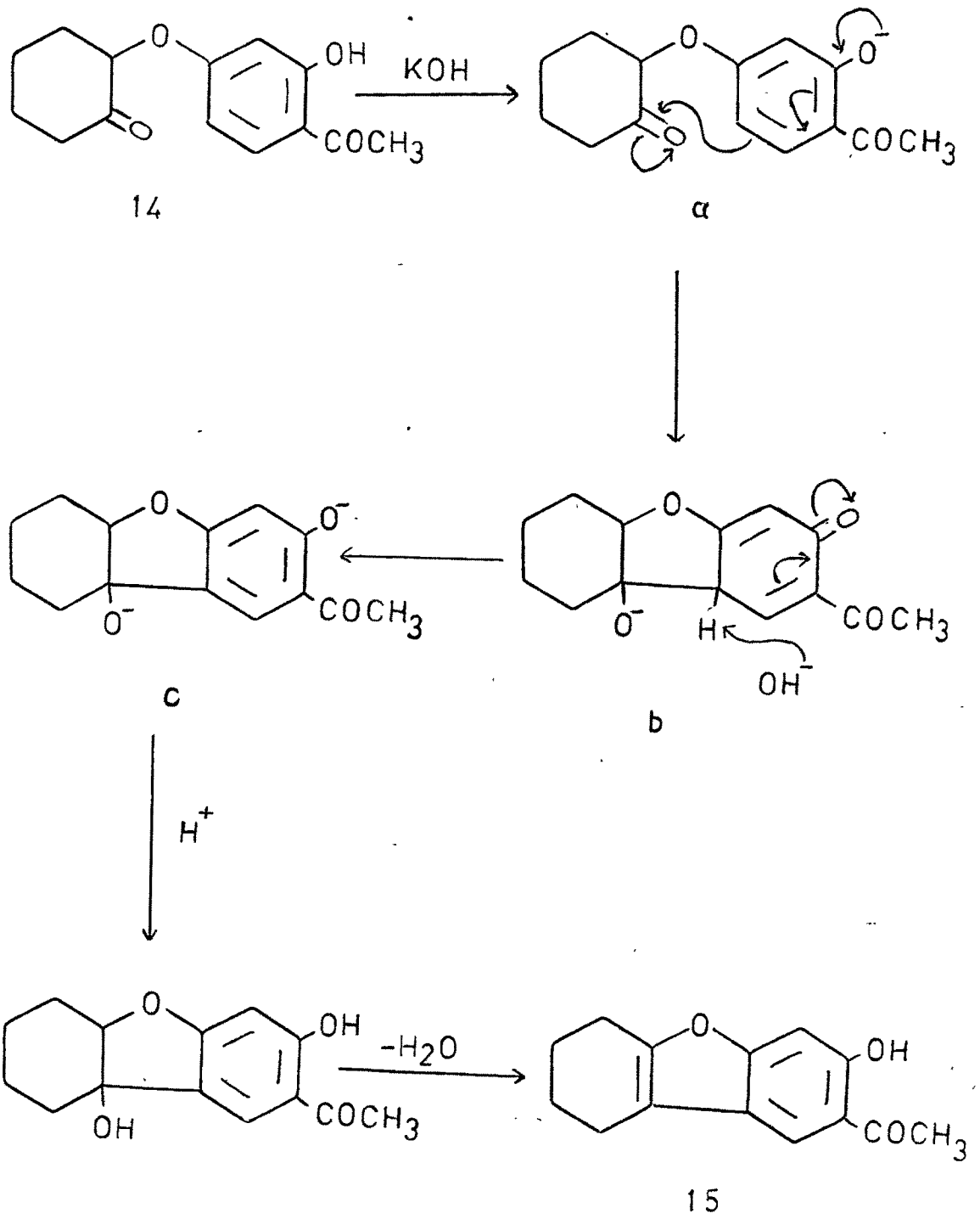
SCHEME - IV

by cyclisation of the ether with mild alkali. This work is now extended to different hydroxychromones and hydroxychromanones to synthesize different benzfurobenzo-γ-pyrones.

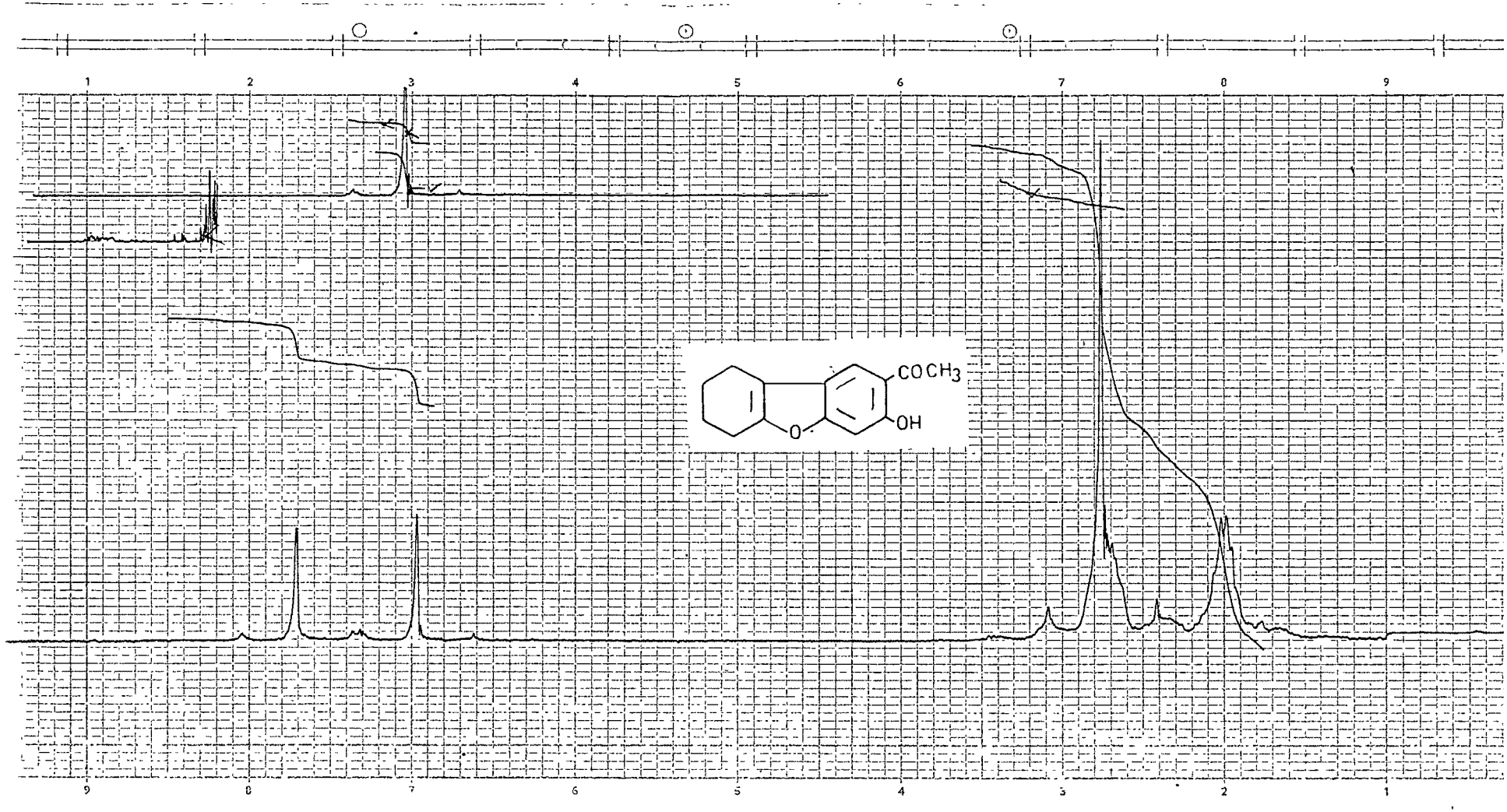
4H-Benzofuro (3,2-g)-[1]-benzopyran-4-one (18)

Resacetophenone on condensation with 2-bromocyclohexanone in presence of anhydrous potassium carbonate gave the ether 4-(cyclohexan-2-onyloxy)-2-hydroxyacetophenone (14). The ether (14) was cyclized by refluxing with 0.1N alcoholic potassium hydroxide[20] to furnish 5,6,7,8-tetrahydro-2-hydroxy-3-acetyl dibenzofuran (15). NMR spectra of (15) exhibited singlet at δ 7.55 for one proton at C-4, singlet at 6.8 for one protonat C-1, singlet at 2.6 for three hydrogens of $-COCH_3$ group at C-3 and two multiplets at 2.6 and 1.85 for 4 x 2H methylene protons of cyclohexanone ring ; the peak for -OH group appeared at 12.4. Mechanism of this reaction (Scheme-V) can be described as aldol type of condensation in which the phenoxide ion (a) formed due to the alkali, favours the attack at exocyclic carbonyl function through resonance stabilized carbanion, generated at the para position to phenoxide in viz. (a) ---- (b). This is irreversible process because proton at the nearby formed ring junction is immediately abstracted by the base to regenerate the phenoxide ion (c). On acidification the alkoxide ion is protonated, water being eliminated spontaneously from the labile 3-hydroxydibenzofuran system to give (15).

MECHANISM



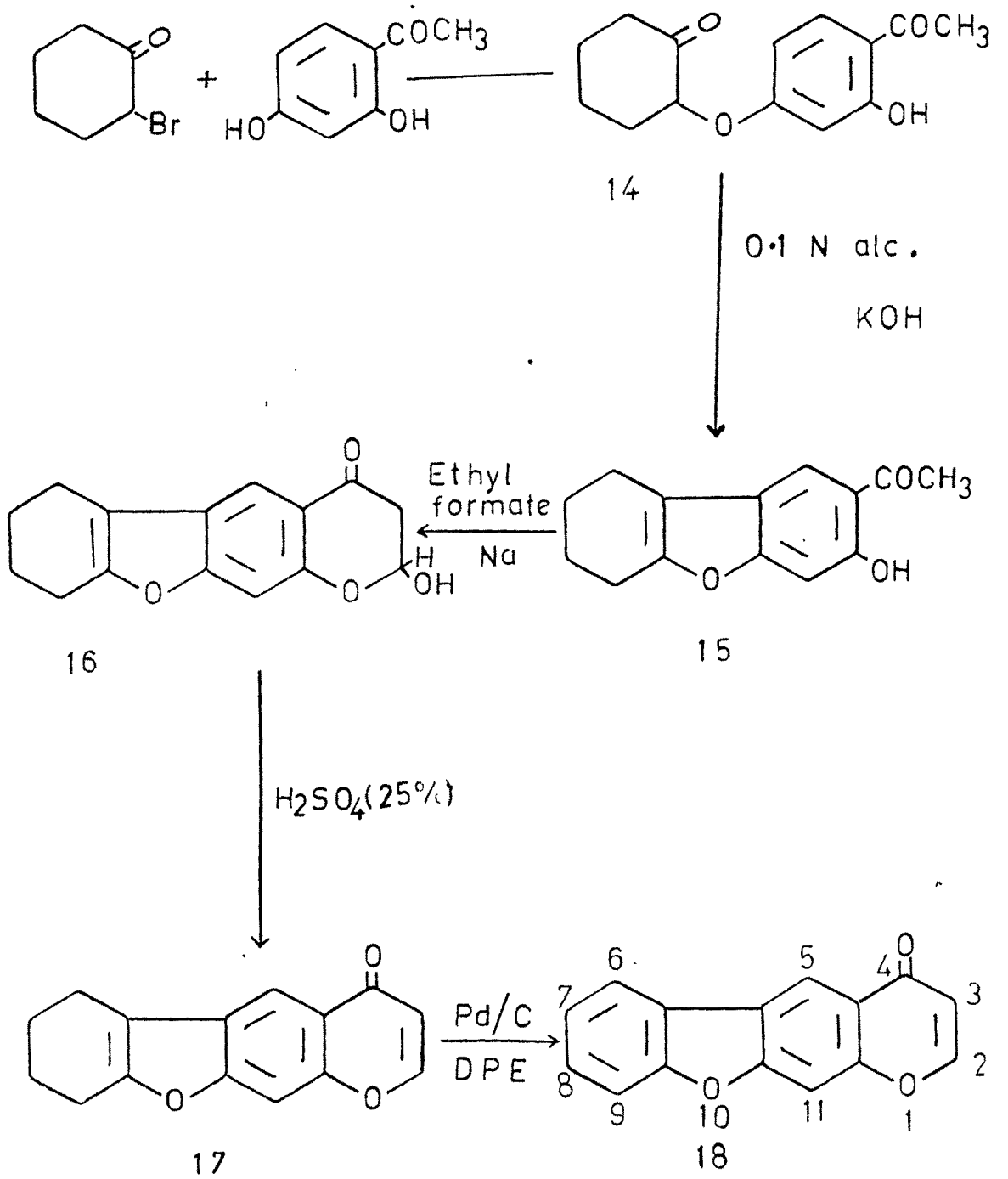
SCHEME -V



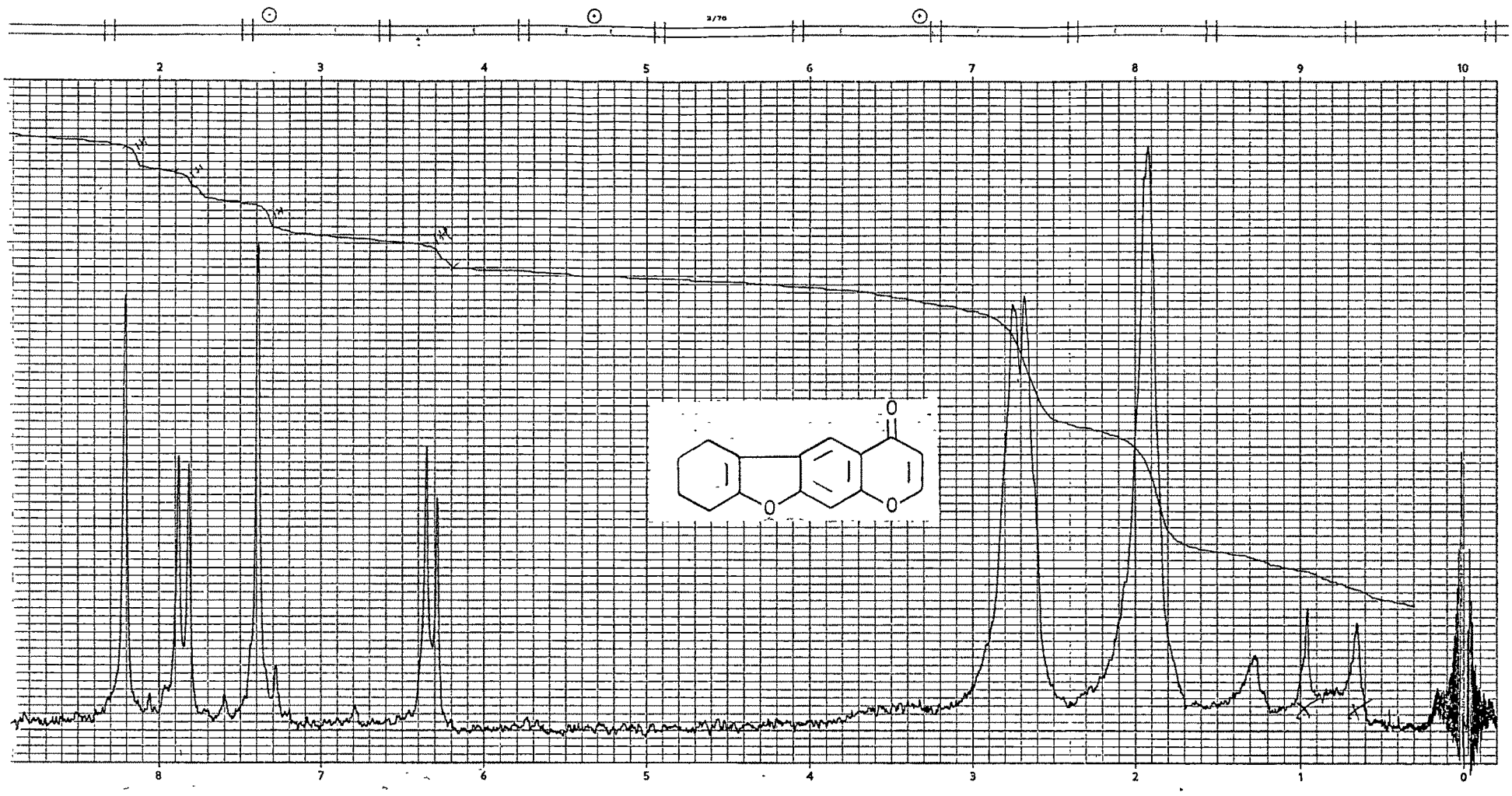
(15) on condensation[27] with ethylformate in presence of pulverized sodium gave 2-hydroxy-2,3,6,7,8,9-hexahydro-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (16) which on subsequent dehydration with dil. H_2SO_4 (1(25)%) gave 6,7,8,9-tetrahydro-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (17), the structure (17) was confirmed by pmr spectra which showed two singlets at δ 8.2 and 7.4 for two aromatic protons at C-5 and C-11 respectively, two multiplets at 2.7 and 1.9 for 4 x 2H methylene protons of cyclohexanone ring, two doublets at 7.85 and 6.30, J=6Hz for two protons at C-2 and C-3 respectiely. (17) was then dehydrogenated with palladised charcoal in refluxing diphenyl ether to 4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (18) (Scheme-VI) the structure (18) was confirmed by pmr spectra which showed two singlets at δ 8.7 and 7.5 for two protons at C-5 and C-11 respectively ; two doublets at 7.9 and 6.35, J=6Hz for two protons at C-2 and C-3 respectively and one multiplet at 7.0-7.3 for four protons aromatic protons.

11-Methyl-4H-1-benzofuro [3,2-g]-benzopyran-4-one (23)

2,4-Dihydroxy-3-methylacetophenone on condensation with 2-bromocyclohexanone in acetone in presence of anhydrous potassium carbonate gave the ether 4-(cyclohexan-2-onyloxy)-2-hydroxy-3-methyl acetophenone (19). The ether (19) was cyclized by refluxing with 0.1N alcoholic potassium hydroxide[20] to furnish 5,6,7,8-tetrahydro-1-methyl-2-hydroxy-3-acetyl dibenzofuran (20), pmr spectra of (20) showed singlet at δ 7.45 for one aromatic proton at C-4, another two singlets at 2.65 and


COCH3
Br
HO
OH
14
0·1 N alc.
KOH
Ethyl
formate
Na
H
OH
16
15
H2SO4(25%)
Pd/C
DPE
17
18

SCHEME-VI



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SPECTRUM Nº	
DATE	
OPERATOR	
SAMPLE Nº	RR-132
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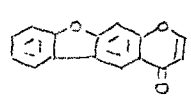
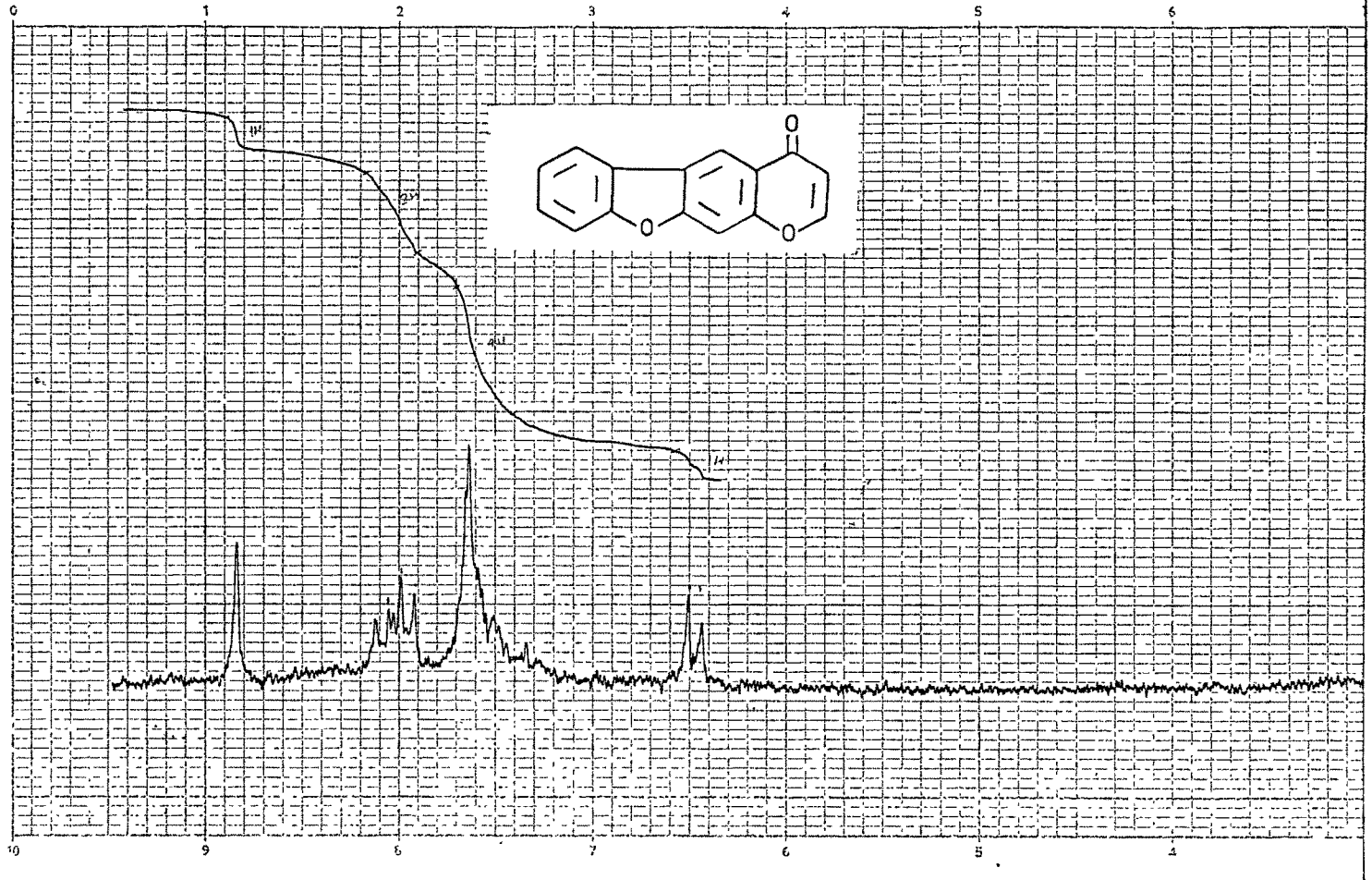


^{1}H	60	90	MHz
^{19}F	56.4	84.6	MHz

SOLVENT	C_6D_6
CONC	
TEMPERATURE	
REF STD	
LOCK SIGNAL	
SWEEP RANGE	
SWEEP TIME	
FILTER	
OFFSET	
H_1 LEVEL	
SENSITIVITY	8



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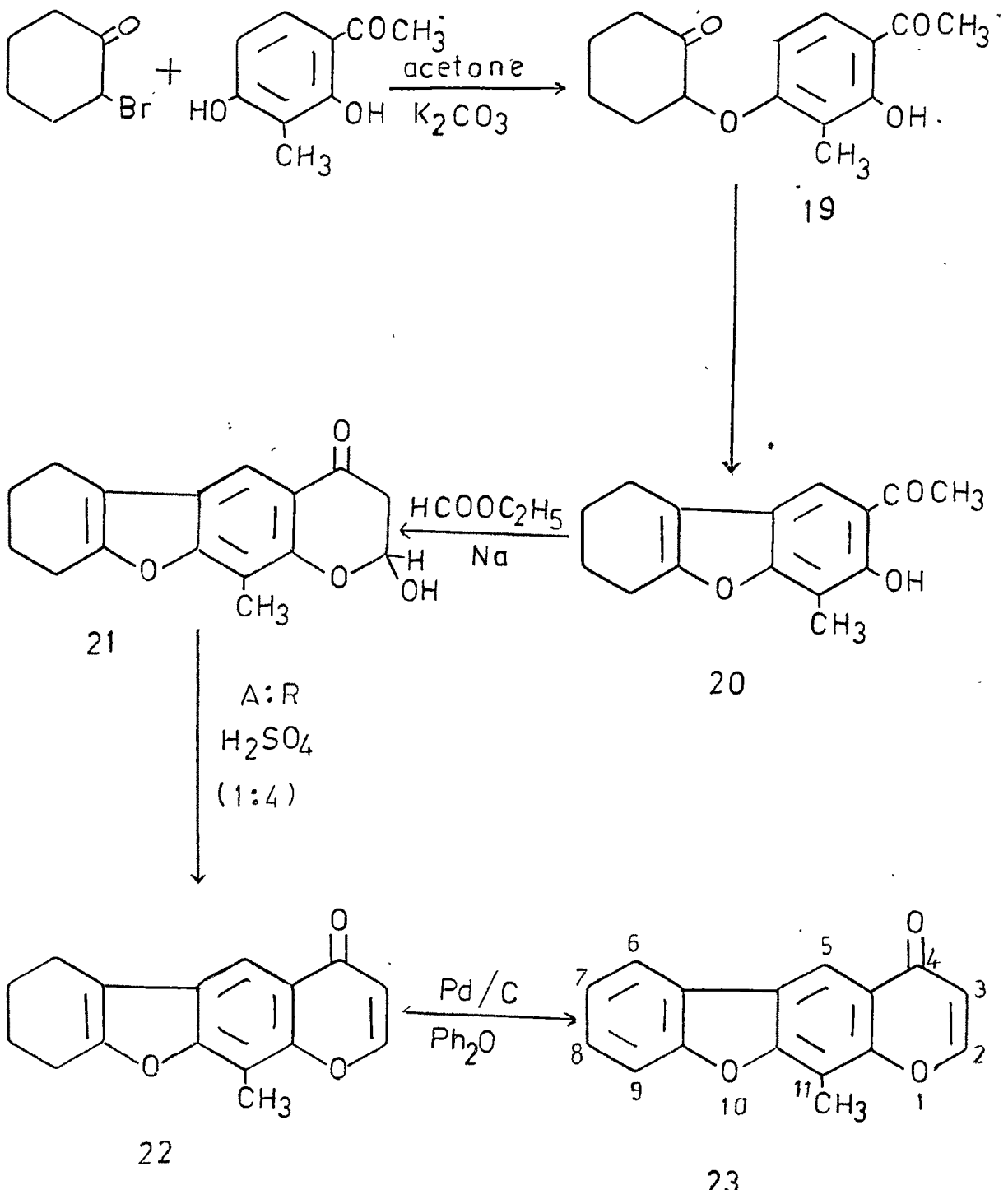
143

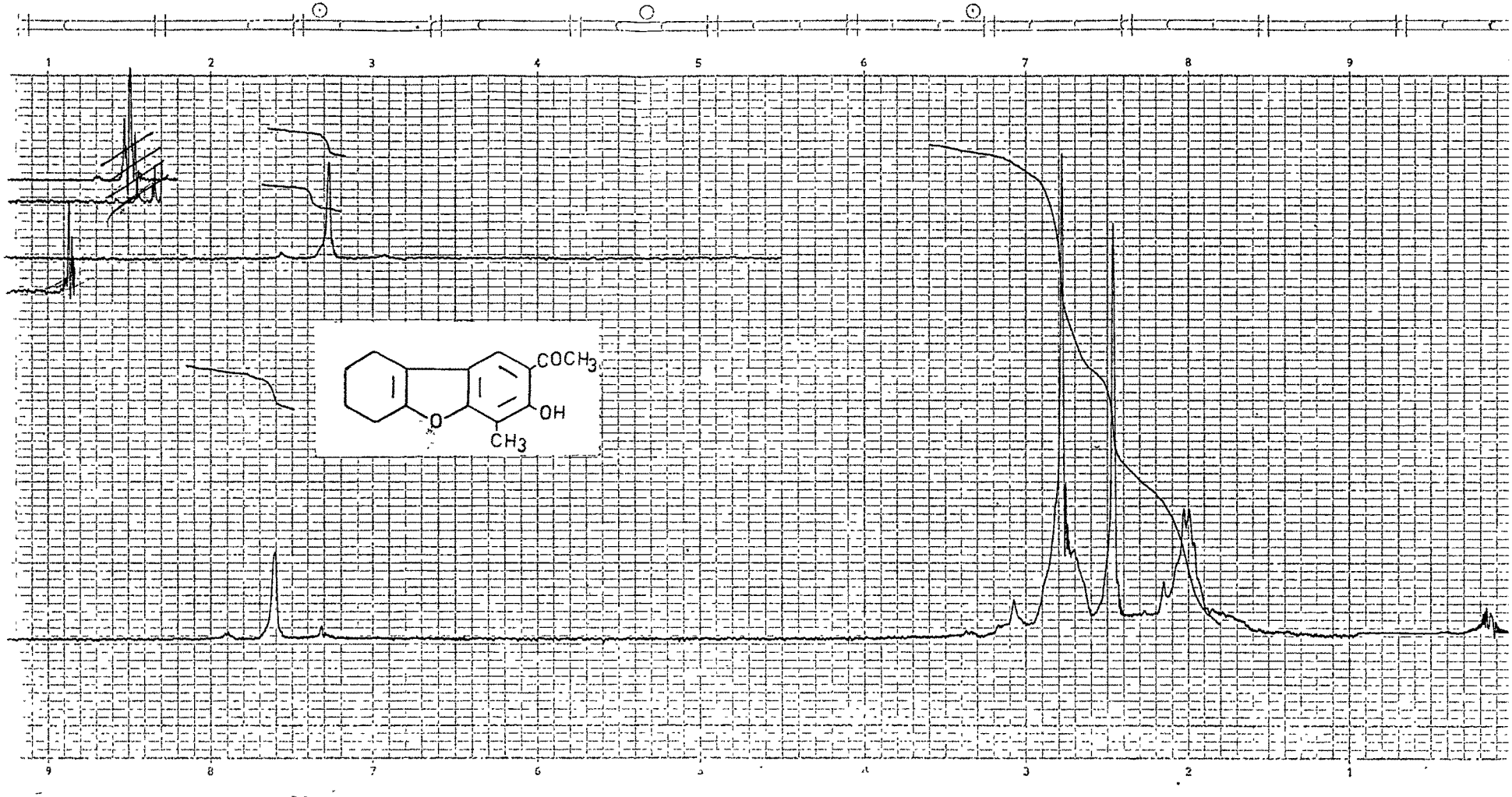
2.3 for $-COCH_3$ group at C-3 and methyl group at C-1 respectively, two multiplets at 2.6 and 1.85 for 4 x 2H methylene protons of cyclohexene ring, and one singlet at 12.4 for -OH group at C-2. (20) on condensation with pulverized sodium metal and ethylformate gave 2-hydroxy-2,3,6,7,8,9-hexa hydro-11-methyl-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (21), which on subsequent dehydration with H_2SO_4 (25%) gave 6,7,8,9-tetrahydro-11-methyl-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (22), the structure (22) was confirmed by pmr spectra which showed singlet at δ 8.5 for one proton at C-5, two doublets at 7.8 and 6.3 J=6Hz for two protons at C-2 and C-3 respectively, singlet at 2.45 for three protons of methyl group at C-11 and two multiplets at 2.65 and 1.9 for 4 x 2H methylene protons of cyclohexane ring. (22) was thendehydrogenated with palladised charcol in refluxing diphenyl ether to gave 11-methyl-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (23). (Scheme-VII) the structure (23) was confirmed by pmr spectra which showed singlet at 8.5 for one aromatic proton at C-5, two doublets at 7.85 and 6.3, J=6Hz for two protons at C-2 and C-3 respectively, one multiplet at 7.8 - 7.3 for four aromatic protons and singlet at 2.65 for three protons of methyl group at C-11.

<u>2,2-Dimethyl-2,3-dihydro-4H-benzofuro-(3,2-g)-[1]-benzopyran-4-one</u> (26)

7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one (24) on condensation with 2-bromocyclohexanone furnished ether


COCH3
acetone
K2CO3
Br
HO
OH
CH3
O
19
HCOOC2H5
Na
H
OH
21
20
A:R
H2SO4
(1:4)
22
Pd/C
Ph2O
23

SCHEME-VII



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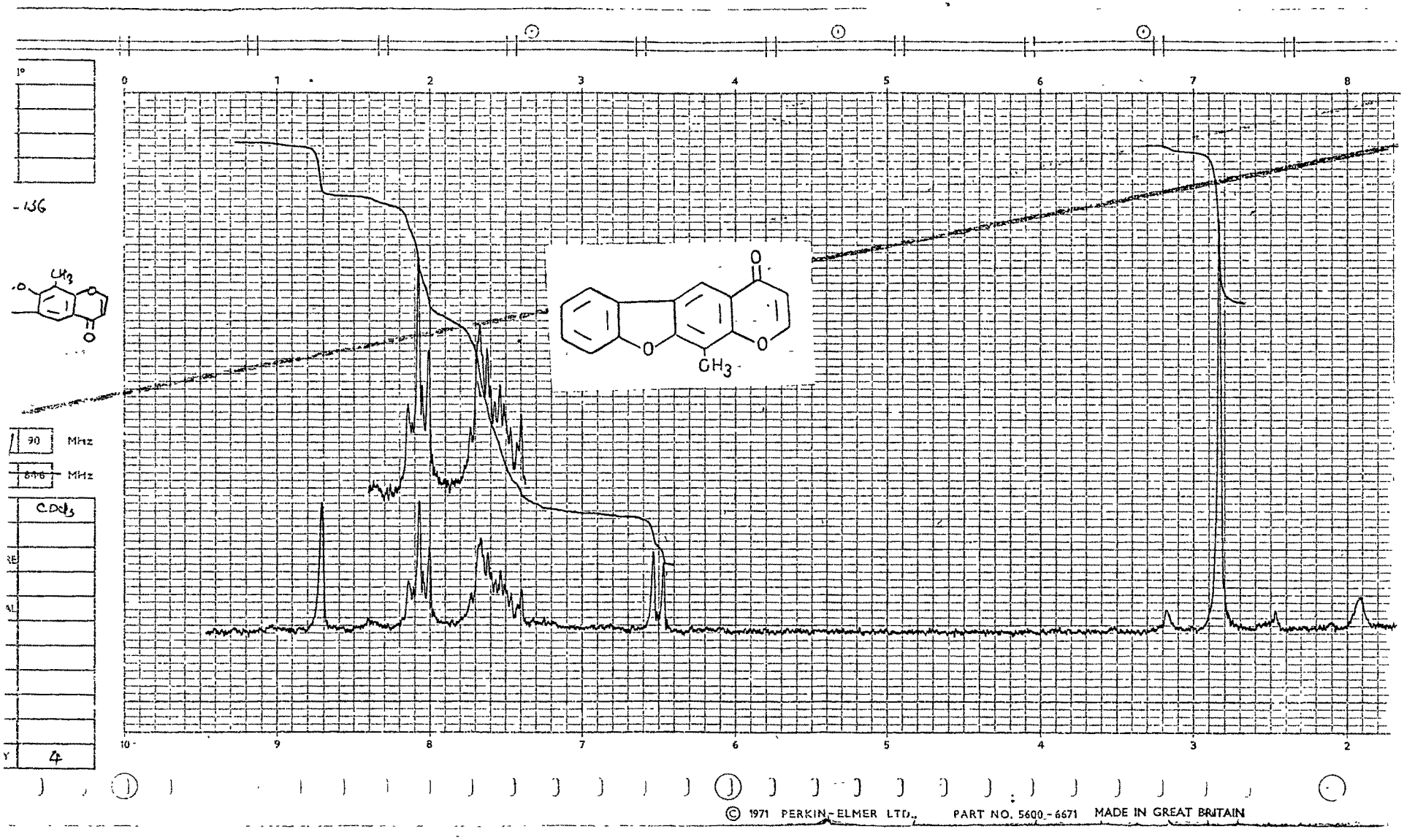
-136
90 MHz
CDCl3
4
0 1 2 3 4 5 6 7 8
10 9 8 7 6 5 4 3 2
O
O
O
CH3
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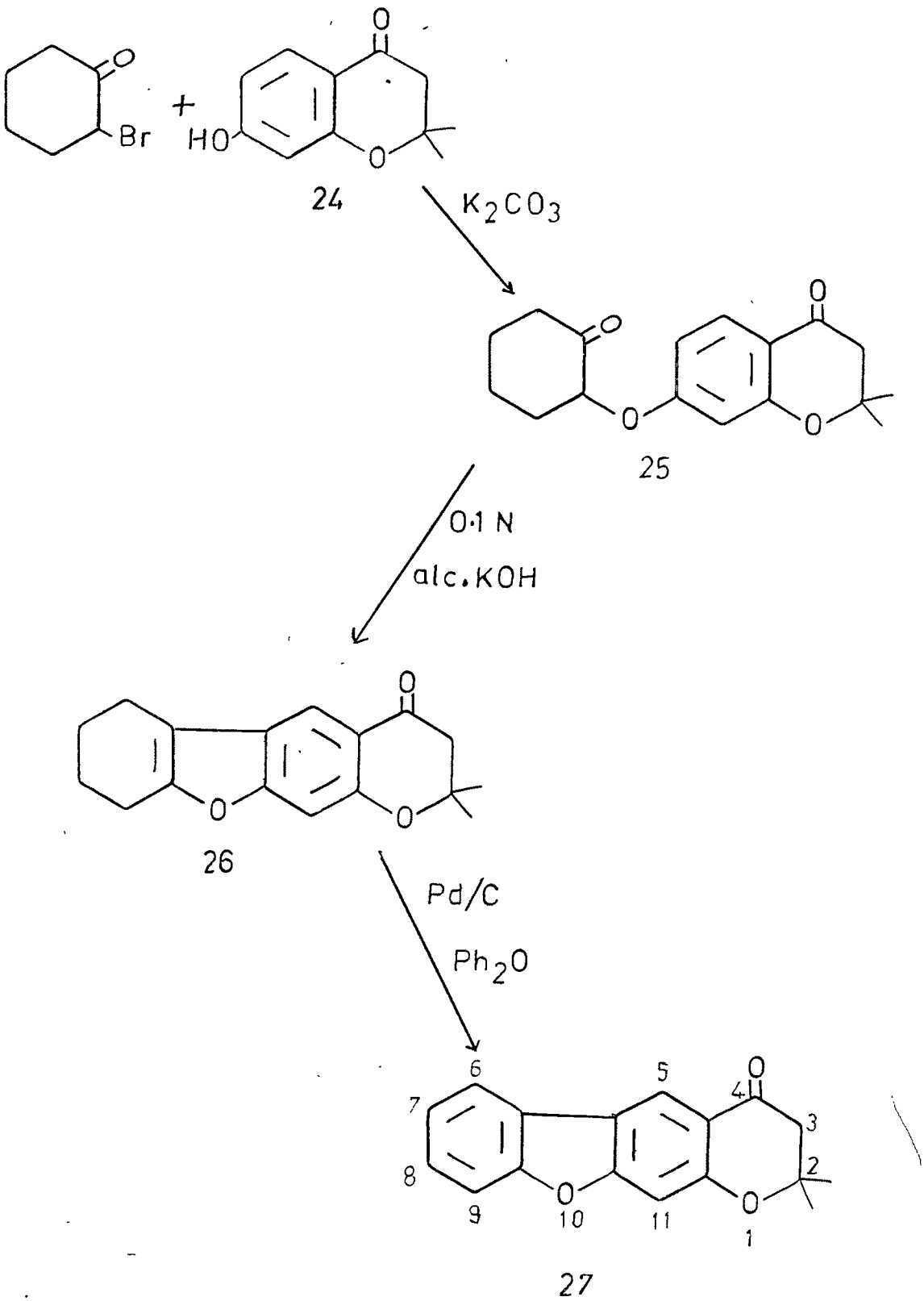
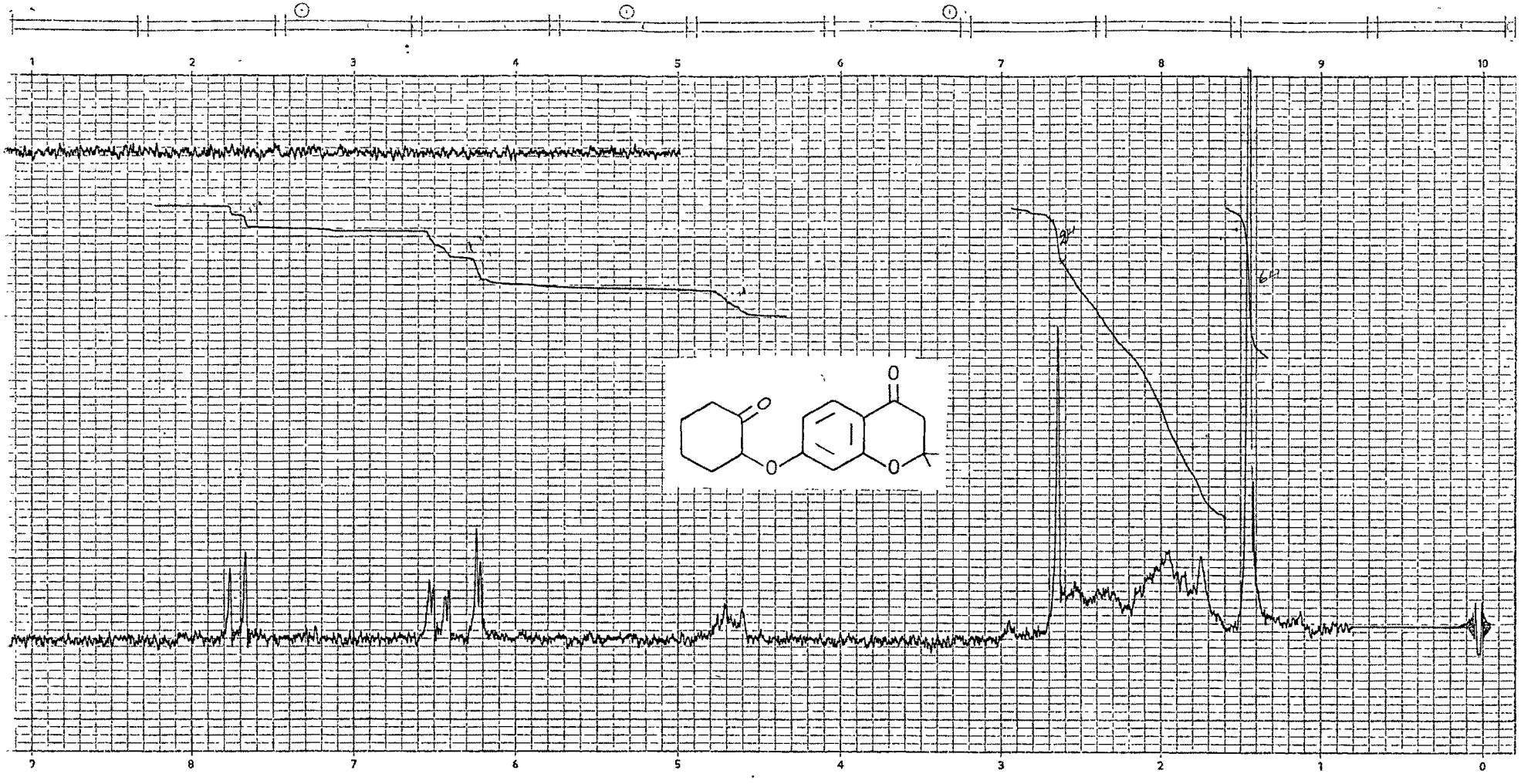
7-(Cyclohexan-2-onyloxy)-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one (25), the structure of ether (25) was proved by pmr spectra which showed doublet at δ 7.65 J=9Hz for one proton at C-5, double doublet J=9,2Hz for one proton at C-6, another doublet at 6.2, J=2Hz (m-coupling) for one proton at C-8, one multiplet at 4.6 for one proton of cyclohexane ring adjecent to carbonyl group, two multiplet at 2.5 and 1.9 for 4 x 2H methylene protons of cyclohexane ring and two singlets at 2.6 and 1.4 for two protons at C-3 and six protons of 2 x CH_3 group at C-2 respectively. (25) was cyclized with O.1N alcoholic KOH to 2,2-dimethyl-2,3,6,7,8,9-hexahydro-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (26), the structure (26) was confirmed by pmr spectra which showed two singlets at δ 7.85 and 6.9 for two protons at C-5 and C-11 respectively, singlet at 2.75 for two protons at C-3, one singlet at 1.45 for six protons of two methyl groups at C-2 ; two mutiplets at 2.65 and 1.85 for 4 x 2H of four methylene protons of cyclohexane ring. (26) was then dehydrogenated with palladised charcol in refluxing diphenyl ether to 2,2-dimethyl-2,3-dihydro-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (27) (Scheme-VIII), the structure (27) was confirmed by pmr which showed two singlets at δ 8.4 and 7.0 for two protons at C-5 & C-11 respectively, two siglets at 1.6 and 1.5 each for three protons of two methyl groups at C-2, singlet at 2.8 for two protons at C-3, double doublet, J=9,2Hz, at 7.85 for one proton at C-6', multiplet at 7.6-7.1 for three aromatic protons at C-7, C-8 and C-9.

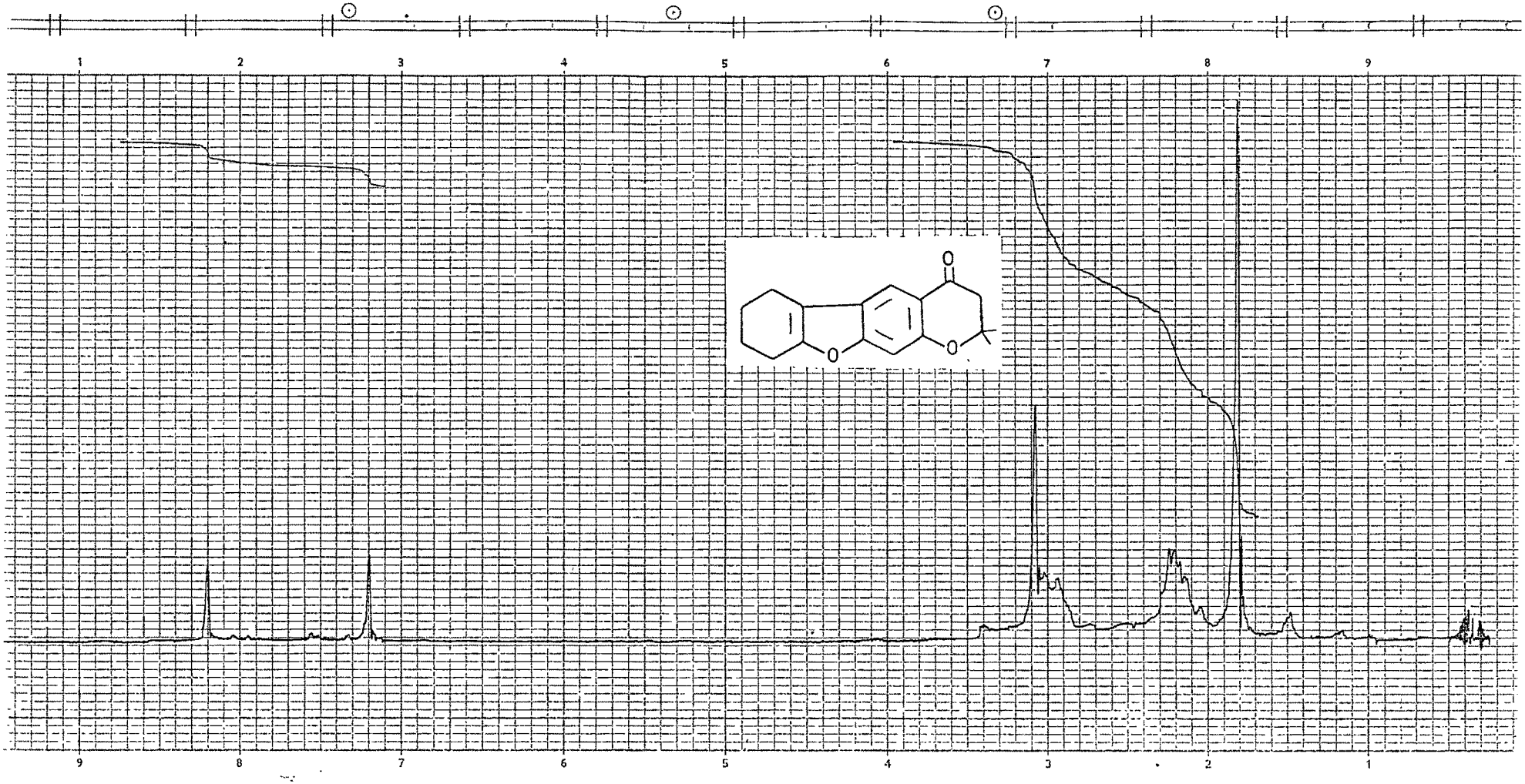
2,2,11-Trimethyl-2,3-dihydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (31)

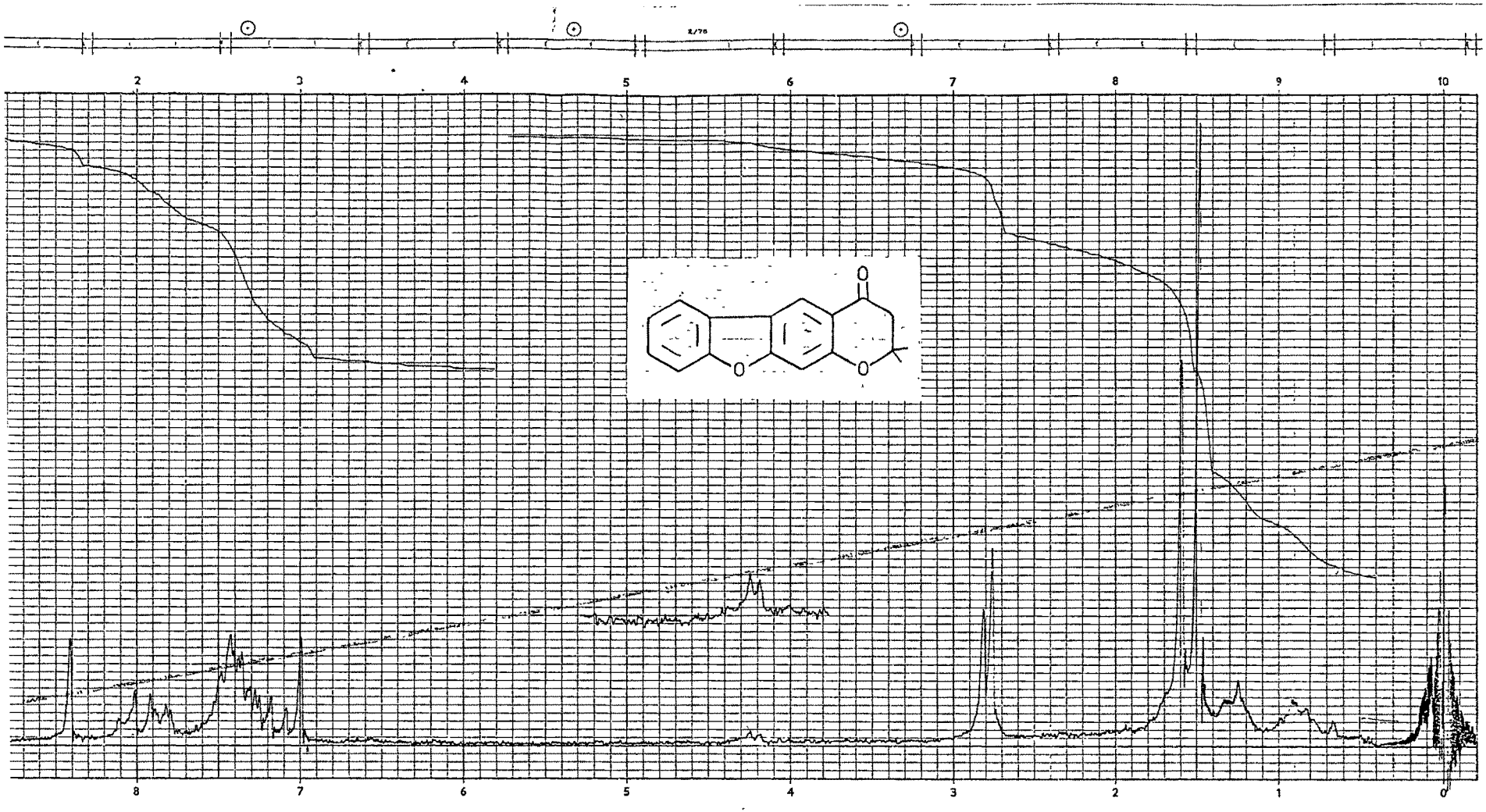
7-Hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-1-benzopyran-4-one

SCHEME-VIII









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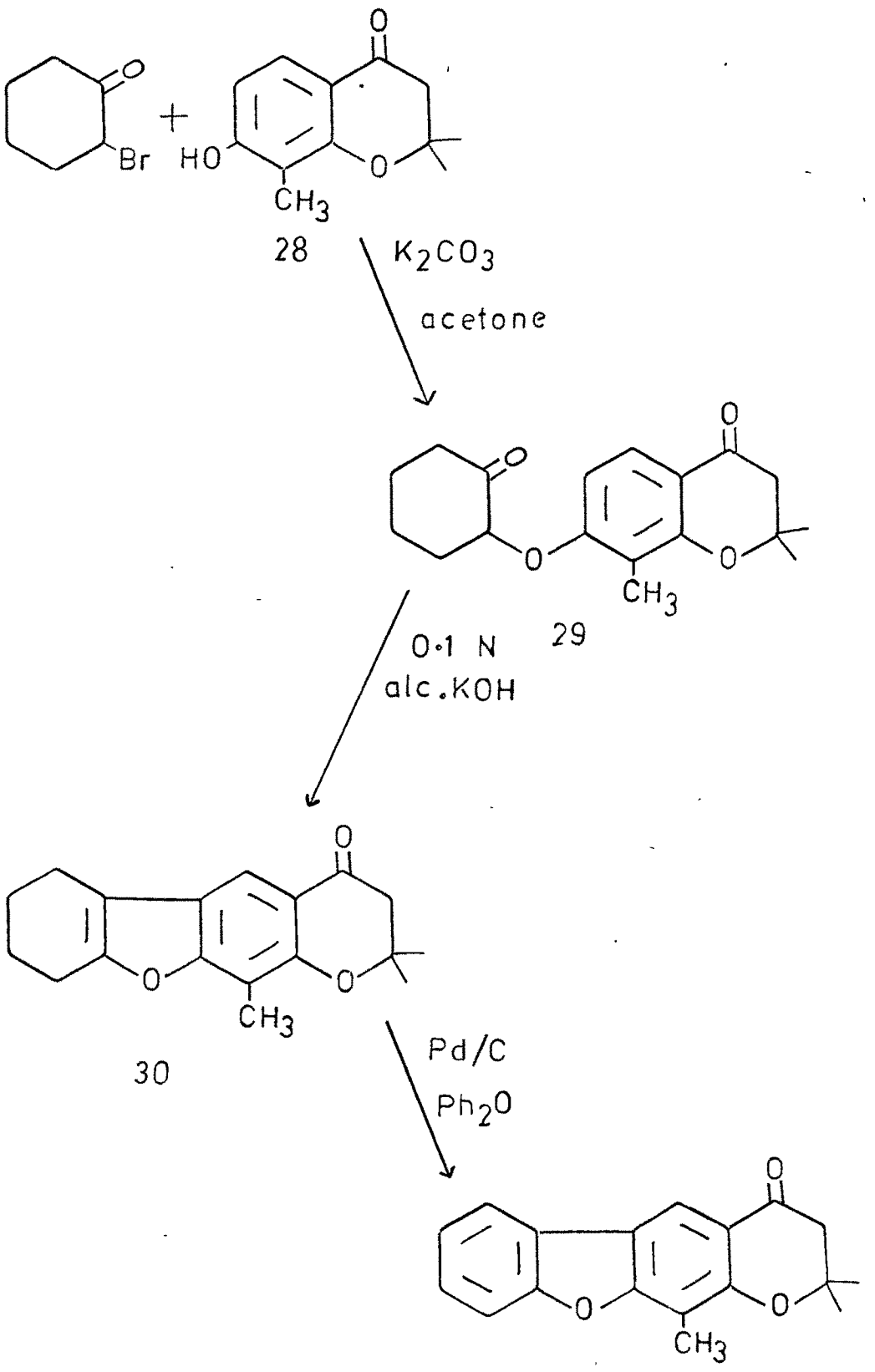
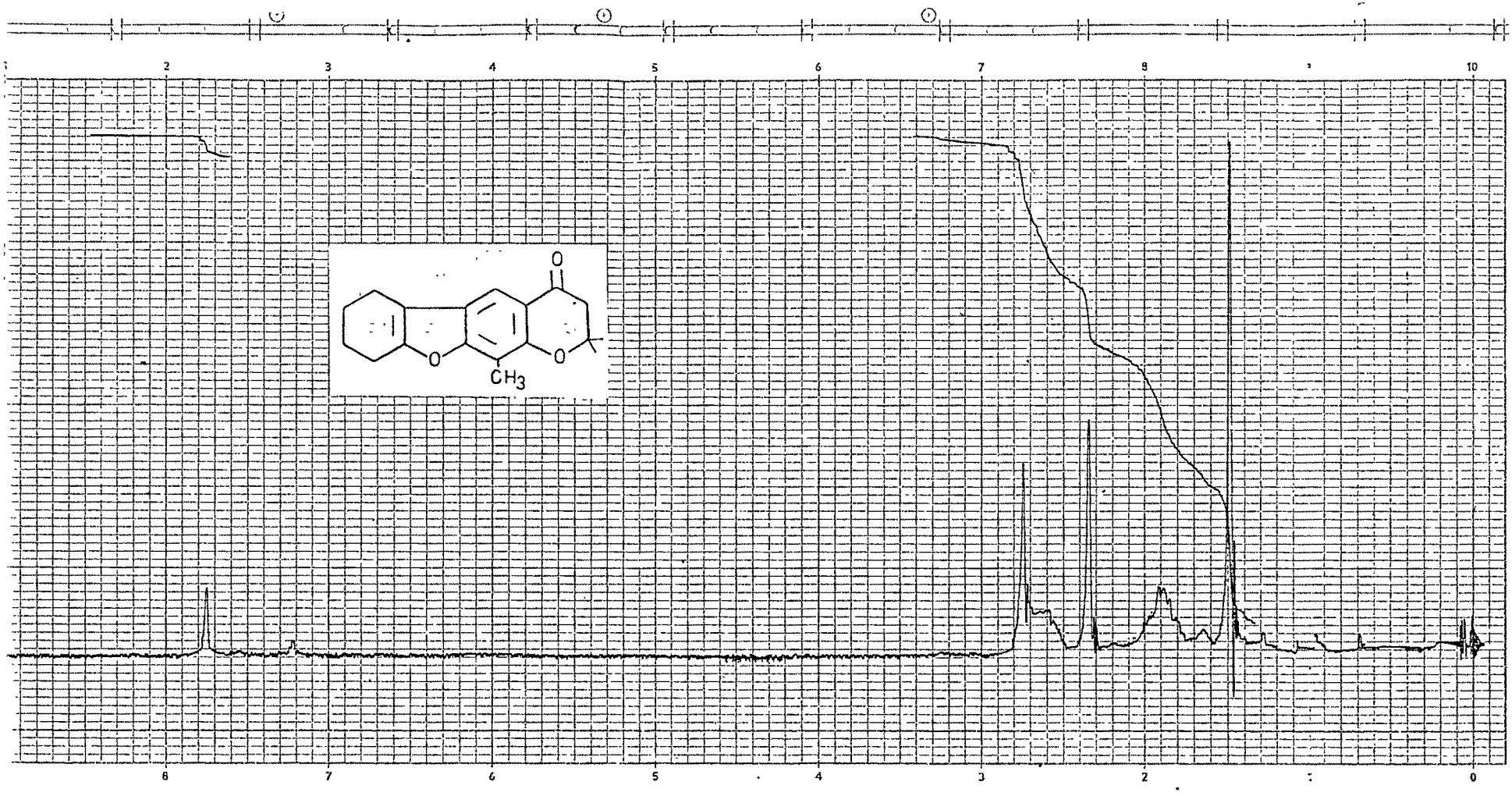
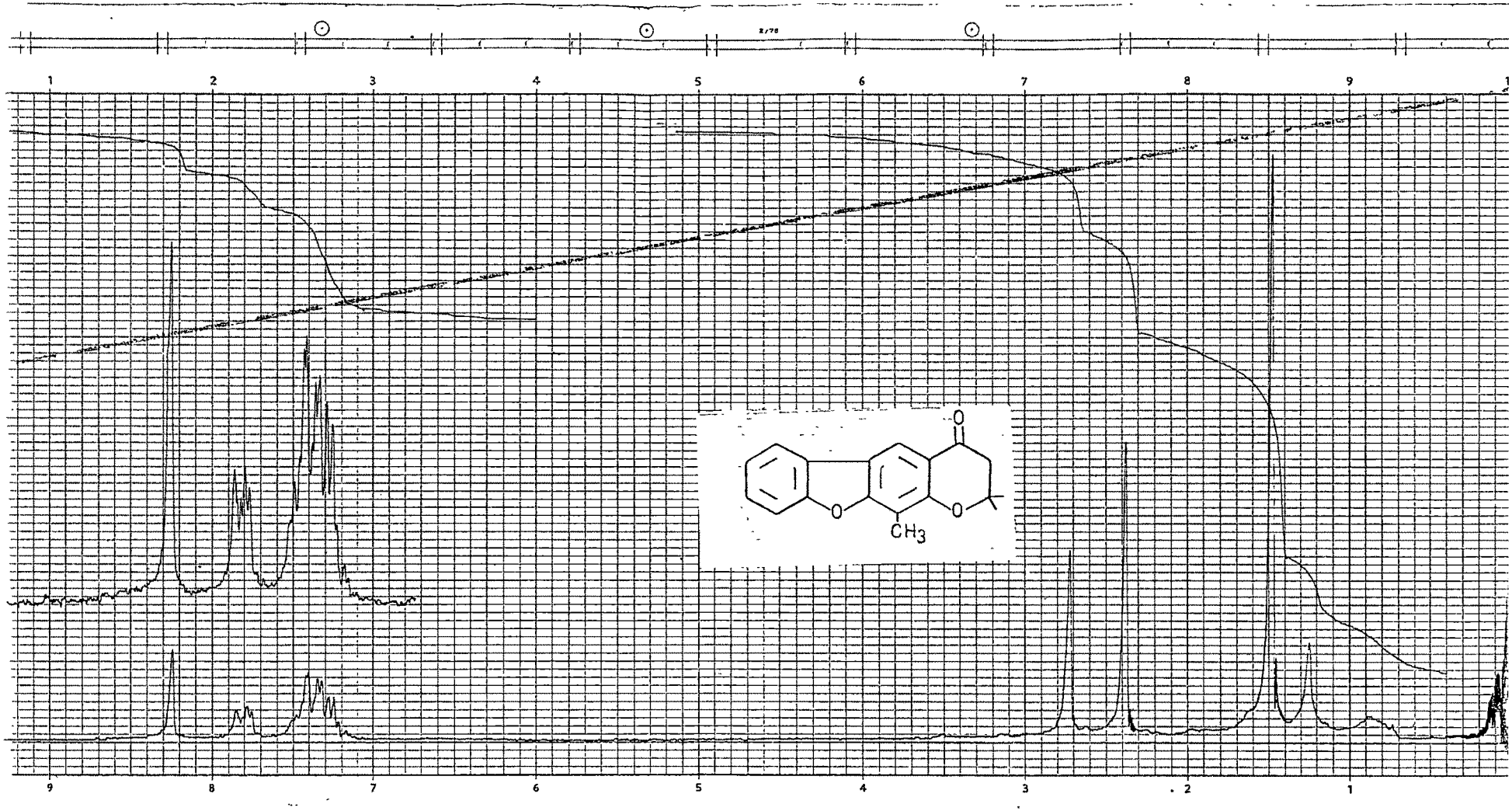
(28) is synthesized by condensation between 2-methyl resorcinl and 3,3-dimethylacrylic acid in presence of $ZnCl_2$ and $POCl_3$ which on condensation with 2-bromocyclohexanone in presence of K_2CO_3 furnished ether 7-(cyclohexan-2-onyloxy)-2,2,8-trimethyl-2,3-dihydro-4H-1-benzopyran-4-one (29), the structure of ether (29) was proved by pmr spectra which shows two doublets at δ 7.6 and 6.3, J=9Hz for two protons at C-5 and C-6 respectively, one triplet at 4.7 for one proton of cyclohexanone ring adjacent to carbonyl group, singlet at 2.6 for two protons at C-3, singlet at 2.1 for three protons of methyl group at C-8and singlet at 1.4 for six protons for 2 x CH_3 groups at C-2, two multiplets at 2.6 and 1.7 for 4 x 2H of four methylenes protons of cyclohexane ring. (29) was cyclized by refluxing with O.1N alcoholic KOH to 2,2,11-trimethyl-2,3,6,7,8,9-hexahydro 4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (3O), the structure (3O) was confirmed by pmr spectra which showed singlet at δ 7.7 for one proton at C-5, singlet at 2.7 for two protons at C-3, singlet at 2.3 for three protons of methyl group at C-11 and singlet at 1.45 for six hydrogens of two methyl group at C-2, two multiplets at 2.6 and 1.85 for 4 x 2H methylene protons ofcyclohexane ring, the compound (3O) was then dehydrogenated by palladised charcol in refluxing diphenyl ether to give 2,2,11-trimethyl-2,3-dihydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (31) (Scheme-IX), the structure (31) was confirmed by pmr spectra which shows singlet at δ 8.25 for

one proton at C-5, double doublet at 7.8, J=8,2Hz for one proton at C-6, multiplet at 7.5-7.25 multiplet at 7.25 three protons at C-7, C-8 and C-9, singlet at 2.75 for two protons at C-3, singlet at 2.35 for three protons of methyl group at C-4 and another singlet at 1.45 for six protons of two methyl groups at C-2.

SCHEME-IX







EXPERIMENTAL

M.ps. are uncorrected. NMR spectra were recorded on Perkin-Elmer R-32 90MHz spectrometer with TMS as internal standard in $CDCl_3$, the column chromatography was done with silica gel, mesh size 60-120.

4-(Cyclohexan-2-onyloxy)-2-hydroxyacetophenone (14)

A mixture of resacetophenone (0.02 mole, 3.04 g), 2-bromocyclohexanone (0.02 mole, 3.5 g), dry acetone (150 ml) and freshly ignited potassium carbonate (10.0 g) was refluxed for 10 h. on waterbath, reaction mixture was cooled and filtered and excess of solvent was removed to obtain 4-(cyclohexan-2-onyloxy)-2-hydroxy acetophenone (14), crystallised from benzene and petroleum ether (1:1). M.p. 136°C.

Analysis	:	Found	:	C, 67.92%	;	H, 6.47%
$C_{14}H_{16}O_4$	:	requires	:	C, 67.74%	;	H, 6.45%

5,6,7,8-tetrahydro-2-hydroxy-3-acetyldibenzofuran (15)

4-(Cyclohexan-2-onyloxy)-2-hydroxyacetophenone (14) (1 g) was treated with alcoholic potassium hydroxide (0.1N, 400 ml) and refluxed for 8 h. excess of solvent was removed and product separated on acidification with dil. HCl, separated product crystallized from mixture of benzene and petroleum ether (2:1), m.p. 183°C, yield 0.4 g. 43.15%.

Analysis	:	Found	:	C, 73.00%	;	H, 6.32%
$C_{14}H_{14}O_3$	:	requires	:	C, 73.04%	;	H, 6.09%

2-Hydroxy-2,3,6,7,8,9-hexahydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (16)

On finely pulverized sodium (1 g), a solution of (15)

(1 g) and ethylformate (10 ml) in dry solvent ether (25 ml) was added slowly and next day reaction mixture was poured over ice, the aqueous solution separated and acidified with dil. acetic acid. The separated product was crystallized from mixture of benzene and petroleum ether (2:1) as 2-hydroxy-2,3-6,7,8,9-hexahydro-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (16). M.p. 165°C, yield 0.9 g, 80.36%.

Analysis	:	Found	:	C, 69.81%	;	H, 5.65%
$C_{15}H_{14}O_4$	:	requires	:	C, 69.76%	;	H, 5.43%

6,7,8,9-Tetrahydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (17)

Compound (16) (500 mg) was taken in 40 ml of H_2SO_4 (25%) and heated on waterbath at 60°C for 2 hours. Reaction mixture was cooled and extracted with solvent ether; ethereal layer on evaporation gave (17) which was crystallized from benzene and petroleum ether (1:1). M.p. 145°C, yield 350 mg, 75.27%.

Analysis	:	Found	:	C, 74.55%	;	H, 5.26%
$C_{15}H_{12}O_8$	:	requires	:	C, 75.00%	;	H, 5.00%

4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (18)

(17) (300 mg) and 10% palladised charcol (300 mg) was taken in diphenyl ether (20 ml) and refluxed for 10 h.; reaction mixture was filtered hot and diphenyl ether was removed by steam distillation, crude product separated was purified

by column chromatography, elution with mixture of pet. ether and benzene (1:1) gave (18). M.p. 207°C, yield 0.070 g, 23.73%.

4-Cyclohexan-2-onyloxy)-2-hydroxy-3-methylacetophenone (19)

A mixture of 2,4-dihydroxy-3-methylacetophenone (0.02 mole, 3.36 g), 2-bromocyclohexanone (0.02 mole, 3.5 g) dry acetone (150 ml) and freshly ignited potassium carbonate (10.0 g) wasrefluxed for 10 h. on waterbath. Reaction mixture was cooled and filtered, excess of solvent was removed to obtain 4-(cyclohexan-2-onyloxy)-2-hydroxy-3-methylacetophenone (19), crystallised from mixture of benzene and petroleum ether (1:1). M.p. 125°C.

Analysis : Found : C, 69.12% ; H, 6.99%

$C_{15}H_{18}O_4$: requires : C, 68.70% ; H, 6.87%

5,6,7,8-Tetrahydro-1-methyl-2-hydroxy-3-acetyl-dibenzofuran (20)

4-(Cyclohexan-2-onyloxy)-2-hydroxy-3-methylacetophenone (19) (1 g) was treated with alcoholic potassium hydroxide (0.1N, 400 ml) and refluxed for 8 h. excess of solvent was removed and product separated on acidification with dil. HCl solution, product crystalized from mixture of benzene and petroleum ether (2:1). M.p. 146°C, yield 0.4 g, 43.01%.

Analysis : Found : C, 74.16% ; H, 6.96%

$C_{15}H_{16}O_3$: requires : C, 73.77% ; H, 6.56%

2-hydroxy-11-methyl-2,3,6,7,8,9-hexahydro-4H-benzofuro (3,2-g)-[1]-benzopyran-4-one (21)

To finely pulverized sodium (1 g) a solution of (20) (1 g)

and ethylformate (10 ml)in dry solvent ether (25 ml) was added slowly and allowed reaction to commence, Nextday reaction mixture was poured over ice, the aqueous solution separated was acidified with dil. acetic acid. The separated solid was crystallized from mixture ofbenzene and petroleum ether (2:1) to give (21). M.p. 169°C, yield, 0.85 g, 75.6%

Analysis : Found : C, 74.80% ; H, 6.19%

$C_{16}H_{16}O_4$; requires : C, 75.00% ; H, 6.25%

11-Methyl-6,7,8,9-tetrahydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (22)

Compound (21) (500 mg) was taken in 40 ml of A.R. H_2SO_4 (25%) and heated on a waterbath at 60°C for 2 hours. The reaction mixture was cooled and extracted with solvent ether, ethereallayer on evaporation gave (22), which was crystallized from benzene and petroleum ether (1:1). M.p. 177°C, yield 0.33 g, 70.66%.

Analysis : Found : C, 75.11% ; H, 5.90%

$C_{16}H_{14}O_3$: requires : C, 75.95% ; H, 5.51%

11-Methyl-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (23)

(22) (300 mg) and 10% palladised charcol (300 mg) was taken in diphenyl ether (20 ml) and refluxed for 10 h., Reaction mixture was filtered hotand diphenyl ether was removed by steam distillation, the separated crude product was purified

by column chromatography, elution with mixture of pet. ether and benzene (1:1) gave (23). M.p. 218°C, yield 0.075 g, 25.86%.

Analysis	:	Found	:	C, 76.43%	;	H, 3.86%
$C_{16}H_{10}O_3$	:	requires	:	C, 76.8%	;	H, 4.0%

7-(Cyclohexan-2-onyloxy)-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one (25)

A mixture of 7-hydroxy-2,2-dimethyl-2,3-dihydro-4H-1-benzopyran-4-one (0.02 mole, 3.84 g), 2-bromocyclohexanone (0.02 mole, 3.5 g), dry acetone (150 ml) and freshly ignited potassium carbonate (10.0 g) was refluxed for 10h. on waterbath reaction mixture was cooled and filtered, excess of solvent was removed to obtain (25), it was crystallized from benzene and petroleum ether (1:2). M.p. 121°C, yield 4.6 g, 79.86%.

Analysis	:	Found	:	C, 70.41%	;	H, 6.83%
$C_{17}H_{20}O_4$	:	requires	:	C, 70.83%	;	H, 6.94%

2,2-Dimethyl-2,3,6,7,8,9-hexahydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (26)

(25) (1.5 g) was treated with alcoholic potassium hydroxide (0.1N, 600 ml) and refluxed for 8 h., excess of solvent was removed and product separated on acidification with dil. HCl the separated product was crystallized from mixture of petroleum ether and benzene (2:1). M.p. 105°C, yield 0.6 g, 42.67%.

Analysis : Found : C, 75.84% ; H, 7.11%

$C_{17}H_{18}O_3$: requires : C, 75.56% ; H, 6.67%

2,2-Dimethyl-2,3-dihydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (27)

(26) (300 mg) and 10% palladised charcol (300 mg) was taken in diphenyl ether (20 ml) and refluxed for 10 h. Reaction mixture was filtered hot and diphenyl ether was removed by steam distillation. Crude product ~~separated~~ was purified by column chromatography, elution with mixture of petroleum ether and benzene (1:1) gave (27). M.p. 96°C, yield 0.06 g, 20.3%.

7-(Cyclohexan-2-onyloxy)-2,2,8-trimethyl-2,3-dihydro-4H-1-benzopyran-4-one (29)

A mixture of 7-hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (28) (0.02 mole, 4.12 g), 2-bromocyclohexanone (0.02 mole, 3.5 g), dry acetone (150 ml) and freshly ignited potassium carbonate (10.0 g) was refluxed for 10 h. on waterbath, Reaction mixture was cooled and filtered, excess of solvent was removed to obtain (29), it was crystallized from benzene and petroleum ether (1:2). M.p. 127°C, yield 4.8 g, 79.47%.

Analysis : Found : C, 71.55% ; H, 7.50%

$C_{18}H_{22}O_4$: requires : C, 71.53% ; H, 7.28%

2,2,11-Trimethyl-2,3,6,7,8,9-hexahydro-4H-benzofuro(3,2-g)-[1]-benzopyran-4-one (30)

(29) (1.5 g) was treated with alcoholic potassium hydroxide (0.1N, 600 ml) and refluxed for 8 h. excess of solvent was removed and acidified with dil. HCl. The separated product crystallized from mixture of petroleum ether and benzene (2:1) as (30). M.p. 109°C, Yield 0.6 g, 42.53%.

Analysis	:	Found	:	C, 75.68%	;	H, 7.50%
$C_{18}H_{20}O_3$	:	requires	:	C, 76.06%	;	H, 7.04%

2,2,11-Trimethyl-2,3-dihydro-4H-benzofuro(3,2g)-[1]-benzopyran-4-one (31)

(30) (300 mg) and 10% palladised charcol (300 mg) was taken in diphenyl ether (20 ml) and refluxed for 10 hours. Reaction mixture was filtered hot and diphenyl ether was removed by steam distillation, the crude product was purified by column chromatography, elution with mixture of petroleum ether and benzene (1:1) gave (31). M.p. 86°C, yield 0.065 g, 21.98%

Analysis	:	Found	:	C, 76.72%	;	H, 6.19%
$C_{18}H_{16}O_3$	:	requires	:	C, 77.14%	;	H, 5.71%

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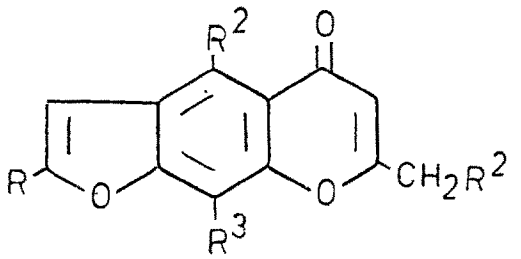
Section II

SYNTHESIS OF FUROCHROMANONES

Furochromones or Furobenzopyrones,[1,2] occour mainly in the fruits and seeds of Ammi Visnaga L., are of the linear type and are limited in number. Khellin (1), Khellinol (2), Ammiol (3), Visnagin (4), Khellinin (5) Khellol (6) and Visammiol (7) are important furochromones isolated from the natural products. Some of them and other linear as well as angular type of furochromones have been studied synthetically by many groups of workers.[3-13]

Physiological activity

Khellin (1) has pronounced physiological activities. It has selective antispasmodic effect upon ureter,[14-15] gall bladder[16] and bile duct.[17] A bronchodilating action of (1) has beend reported.[18,19] It is used as potent coronary vasodilator[20-22] and in whooping cough. Khellin has been used for a variety of pharmacological indications including hypertension, renal and biliary cholic and stomach disorders. The recent discovery of Khellin's lipid altering activity in man and antiatheroscierotic activity in animal models has renewed interest in Khellin and analogues.[23] Recently Khellin was employed for the photochemotherapy of Vitiligo,[24,25] an idiopatic disease characterized by the lack of pigmentation of some areas of human skin. It has been demonstrated that Khellin, unlike psoralene, is not phototoxic and consequently, the treatment by sunlight is considerably safe.



1. $R=R^2=H$, $R^1=R^3=OCH_3$

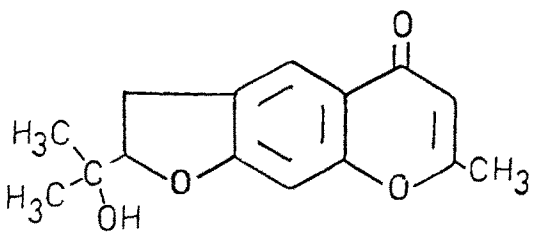
2. $R=R^2=H$, $R^1=OH$, $R^3=OCH_3$

3 $R=H$, $R^2=OH$, $R^1=R^3=OCH_3$

4 $R=R^2=R^3=H$, $R^1=OCH_3$

5 $R=R^3=H$, $R^1=OCH_3$, $R^2=OC_6H_{11}O_5$

6 $R=R^3=H$, $R^1=OCH_3$, $R^2=OH$

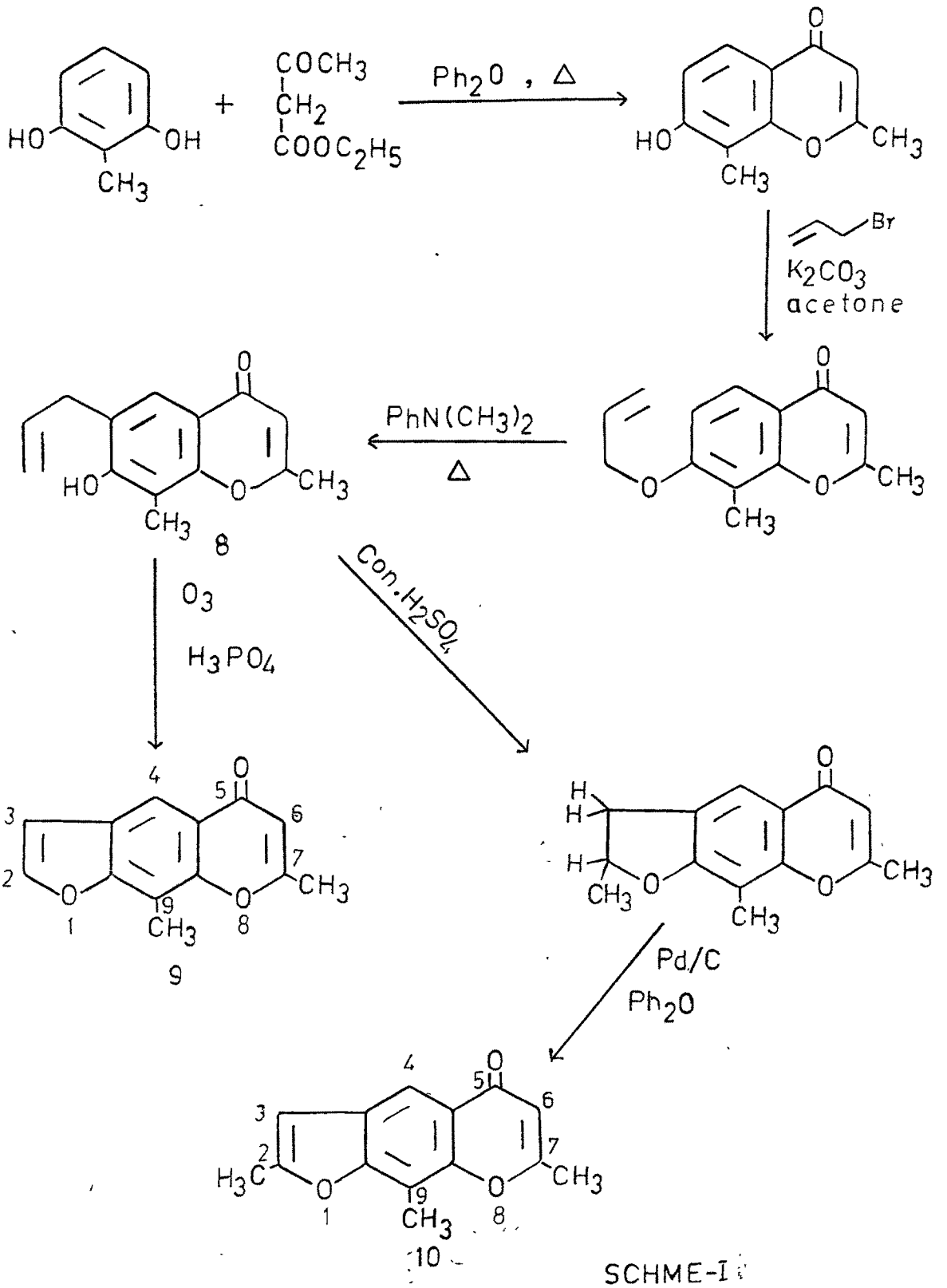
7. 

Khellol glucoside, Khellinin (5) exerts a stimulating action on the heart and increases the coronary flow. It is not converted into the khellin in digestive track or in the body tissue.[26] Schonberg and Sina[27] studied antispasmodic activity of a number of furochromones with the relation to their chemical constitutions.

Pardanani and Trivedi[8] have synthesized linear furochromones from 2,8-dimethyl-7-hydroxychromone which was obtained by thermal condensation of 2-methyl-[illegible]-resorcinol with ethylacetoacetate in diphenyl ether,[28] followed by allylation and Claisen rearrangement gave 2,8-dimethyl-6-allyl-7-hydroxy chromones (8). This on ozonolysis followed by cyclization with ortho phosphoric acid gave 2,9-dimethyl-5H-furo(3,2-g) benzopyran-8-one (9), while allyl derivatives on cyclization with con. H_2SO_4 followed by dehydrogenation afforded 2,7,9-trimethyl-5H-furo(3,2-g)benzopyran-5-one (10) [Scheme-I].

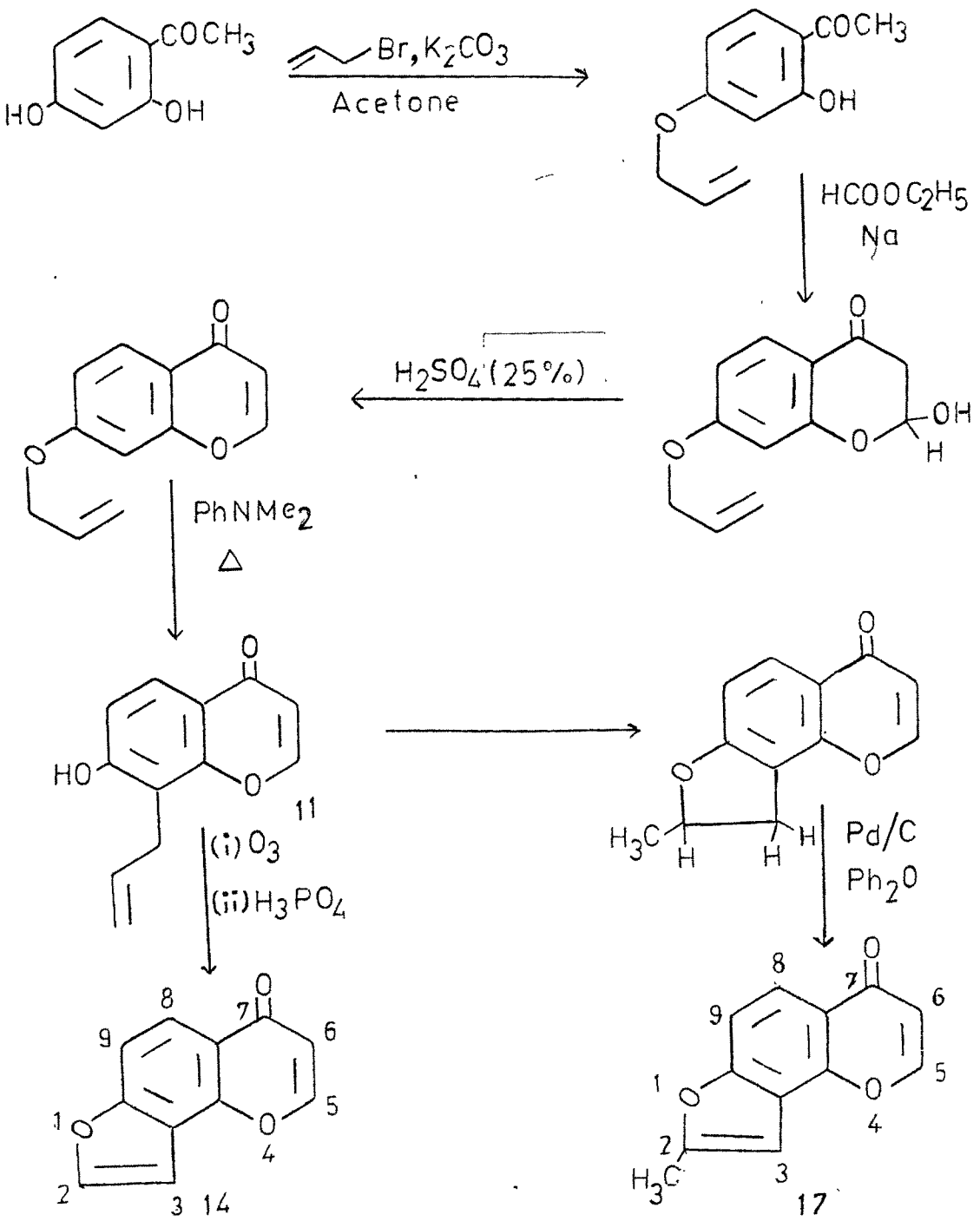
Patolia and Trivedi[29] have synthesized angular furochromones unsubstituted at γ-pyrone ring. Resacetophenone, 2,5-Dihydroxy acetophenone and 2,5-dihydroxy-4-methylacetophenone on allylation gave 4-allyloxy and 5-allyloxy derivatives respectively. This allyloxy derivatives on condensation with ethyl formate in presence of pulverized sodium followed by dehydration with H_2SO_4 gave 7-allyloxychromone, 6-allyloxy chromone and 6-allyloxy-7-methylchromone. This on Claisen

Pardanani and Trivedi[8]

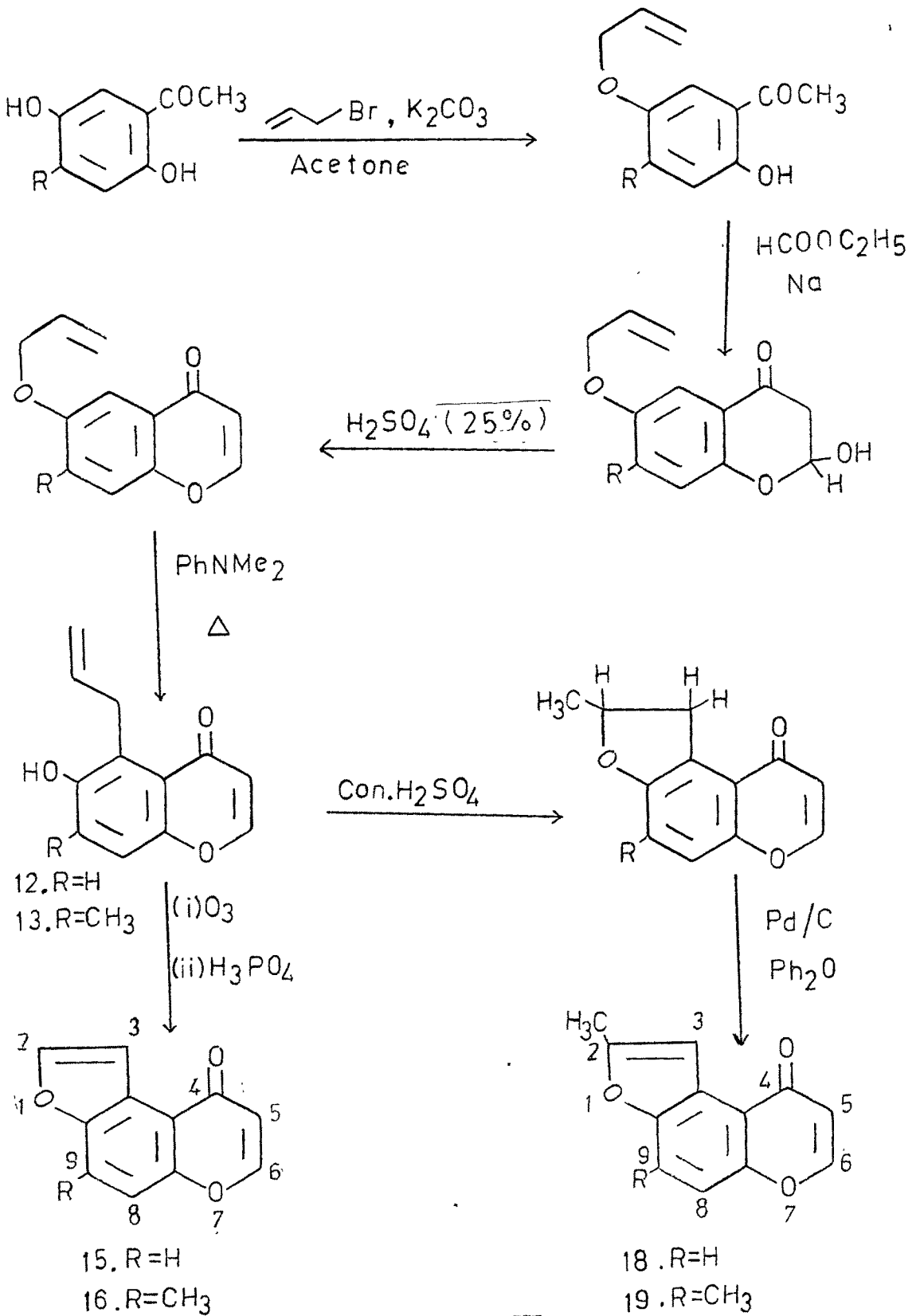


SCHME-I

Patolia and Trivedi[29]



SCHEME-II


HO
COCH3
R
OH
Br , K2CO3
Acetone
HCOOC2H5
Na
H2SO4 (25%)
PhNMe2
△
Con.H2SO4
(i)O3
(ii)H3PO4
Pd/C
Ph2O
12.R=H
13.R=CH3
15. R=H
16.R=CH3
18 .R=H
19 .R=CH3

SCHEME-III

rearrangement in refluxing N,N-dimethylaniline gave 8-allyl (11) and 5-allyl (12), (13) derivatives respectively. This on ozonolysis followed by cyclization with ortho phosphoric acid gave 7H-furo(2,3-h)benzopyran-7-one (14), 4H-furo(3,2-f) benzopyran-4-one (15) and 9-methyl-4H-furo(3,2-f)benzopyran-4-one (16) respectivey. While 8-allyl (11) and 5-allyl (12) & (13) derivatives on cyclization with con. H_2SO_4 followed by dehydrogenation with palladised charcol in refluxing diphenyl ether afforded 2-methyl-7H-furo(2,3-h)benzopyran-7-one (17), 2-methyl-4H-furo(3,2-f)benzopyran-4-one (18) and 2,9-dimethyl-4H-furo(3,2-f)benzopyran-4-one (19) respectively [Scheme-II & III].

Present work

As there was no report on the synthesis of furochromanones the work on furochromones[8,9] has been now extended for the synthesis of furochromanones.

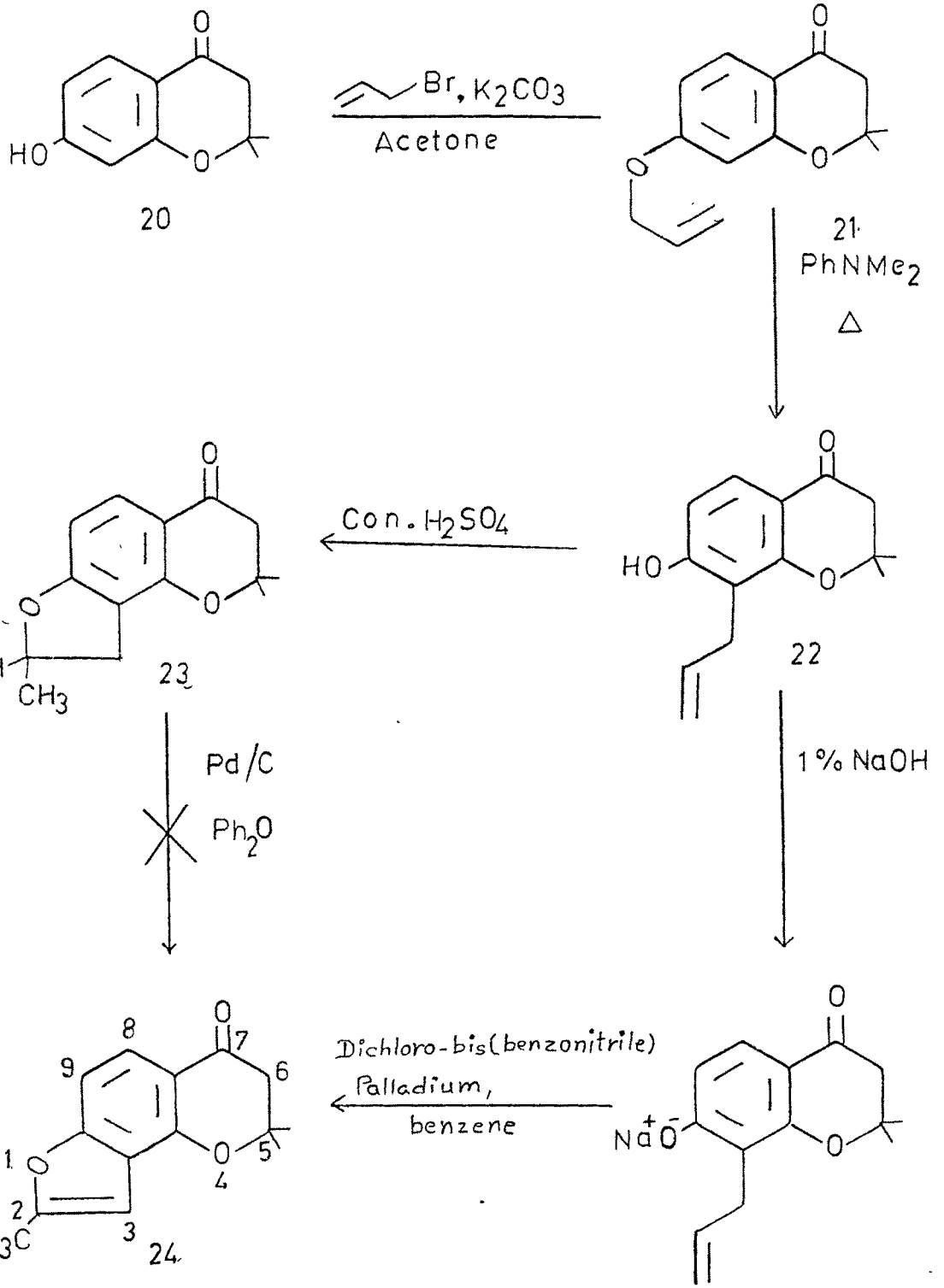
Synthesis of 2,5,5-trimethyl-5,6-dihydro-7H-furo (2,3-h)benzopyran-7-one (25)

7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one[30] (20) on allylation with allylbromide in presence of fused potassium carbonate in dry acetone gave 7-allyloxy-2,3-dimethyl-2,3-dihydro-4H-benzopyran-4-one (21) which where subjected to Claisen rearrangement furnished 8-allyl-7-hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (22), (22) on tituration with 80% H_2SO_4 furnished 2,5,5-trimethyl-2,3,5,6-tetrahydro-

7H-furo(2,3-h)benzopyran-7-one (23), the structure of which was established by it's pmr spectrum ($CDCl_3$) which showed following signals : double doublets for two geminal protons at C-3, one at δ 2.7 (j=18Hz,8Hz) and another at 3.2 (J=18, 8Hz) ; the signal for the proton at C-2 appeared as multiplet at 5.0 ; while the protons at C-8 and C-9 appeared as doublets (J=9Hz) at 7.6 and 6.3 respectively, the methyl group at C-2 appeared as doublet (J=8Hz) at 1.45 ; two methyl groups at C-5 appeared as singlet at 1.5 and methylene protons at C-6 appeared as singlet at 2.65. Dehydrogenation of (23) with 10% palladised charcol in refluxing diphenyl ether failed to give dehydrogenated product (24). In order to synthesize 2,5,5-trimethyl-5,6-dihydro-7H-furo (2,3-h)-benzopyran-7-one (24), sodium salt of (22) when treated with dichlorobis (benzonitrile) palladium complex[31-35] in refluxing benzene furnished (24). The structure (24) was established by pmr spectrum ($CDCl_3$) which showed following signals ; the doublets (J=9Hz) at δ 7.7 and 6.95 for protons at C-8 and C-9 respectively singlet at 2.75 for methylene protons at C-6 ; singlet at 2.45 for three protons of methyl group at C-2 and singlet at 1.5 for six protons of two methyl groups at C-5. [Scheme-IV]

Synthesis of 2,7,7,9-Tetramethyl-6,7-dihydro-5H-furo(3,2-g) benzopyran-5-one (29)

7-Hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one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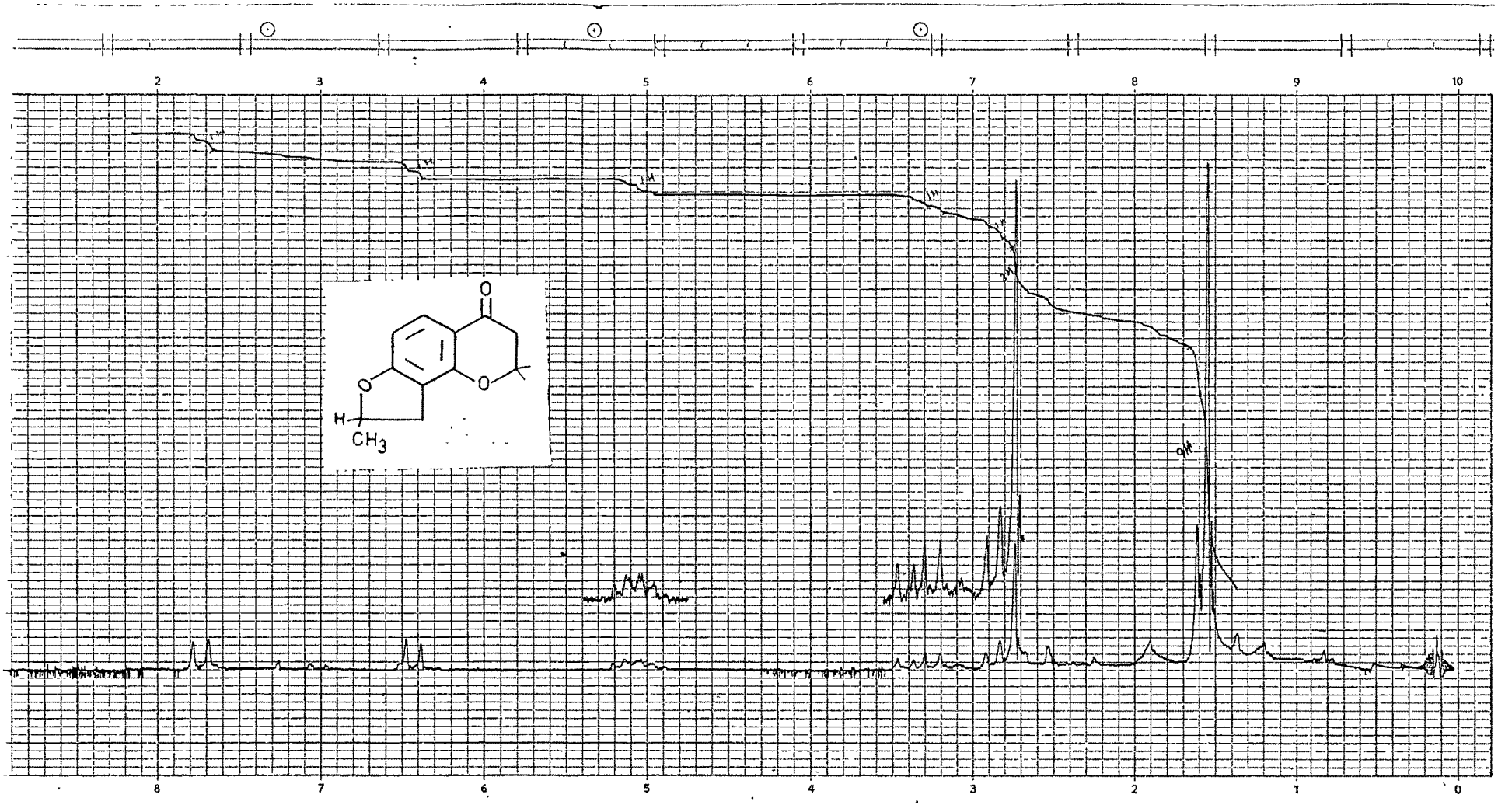
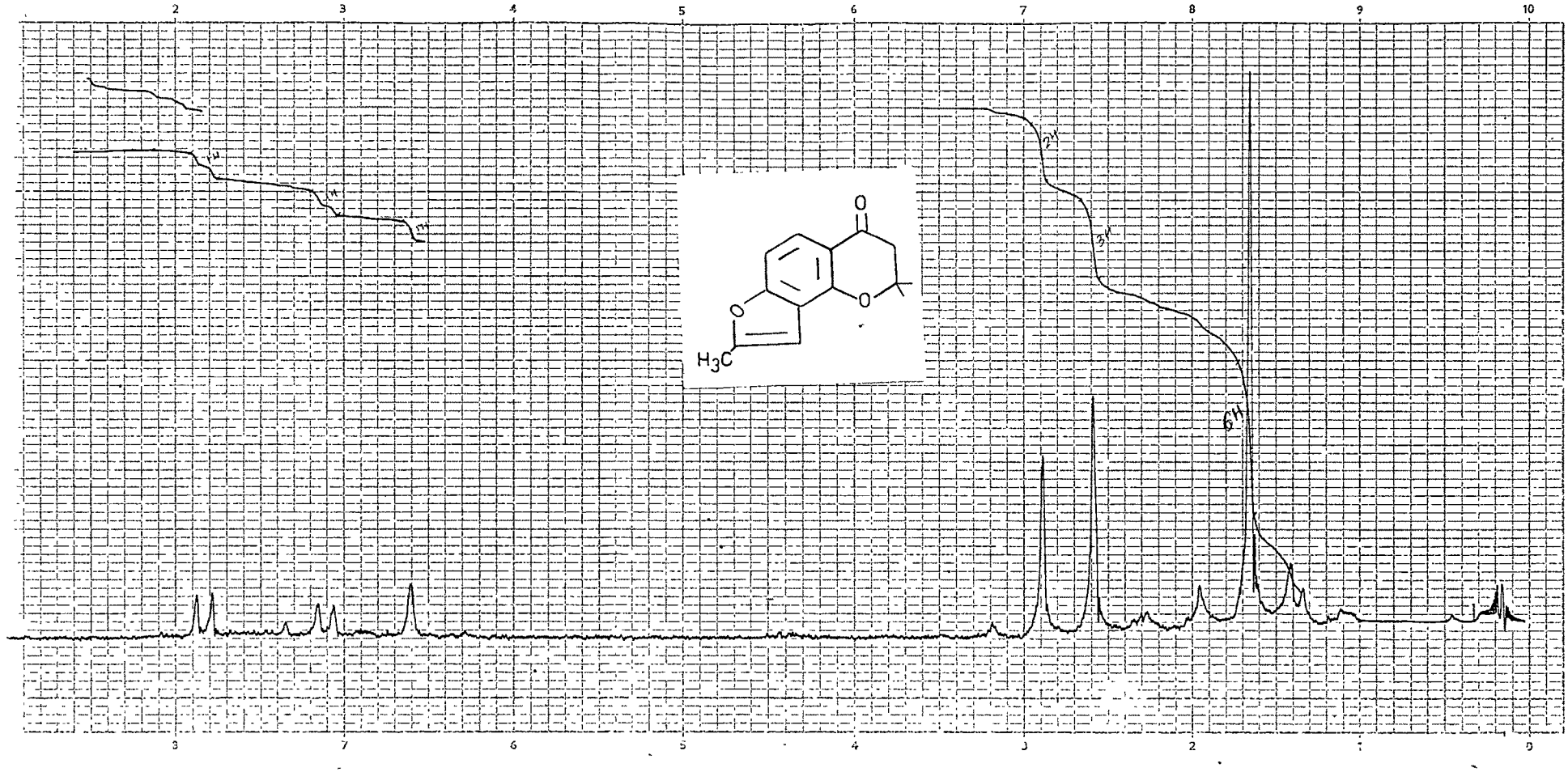
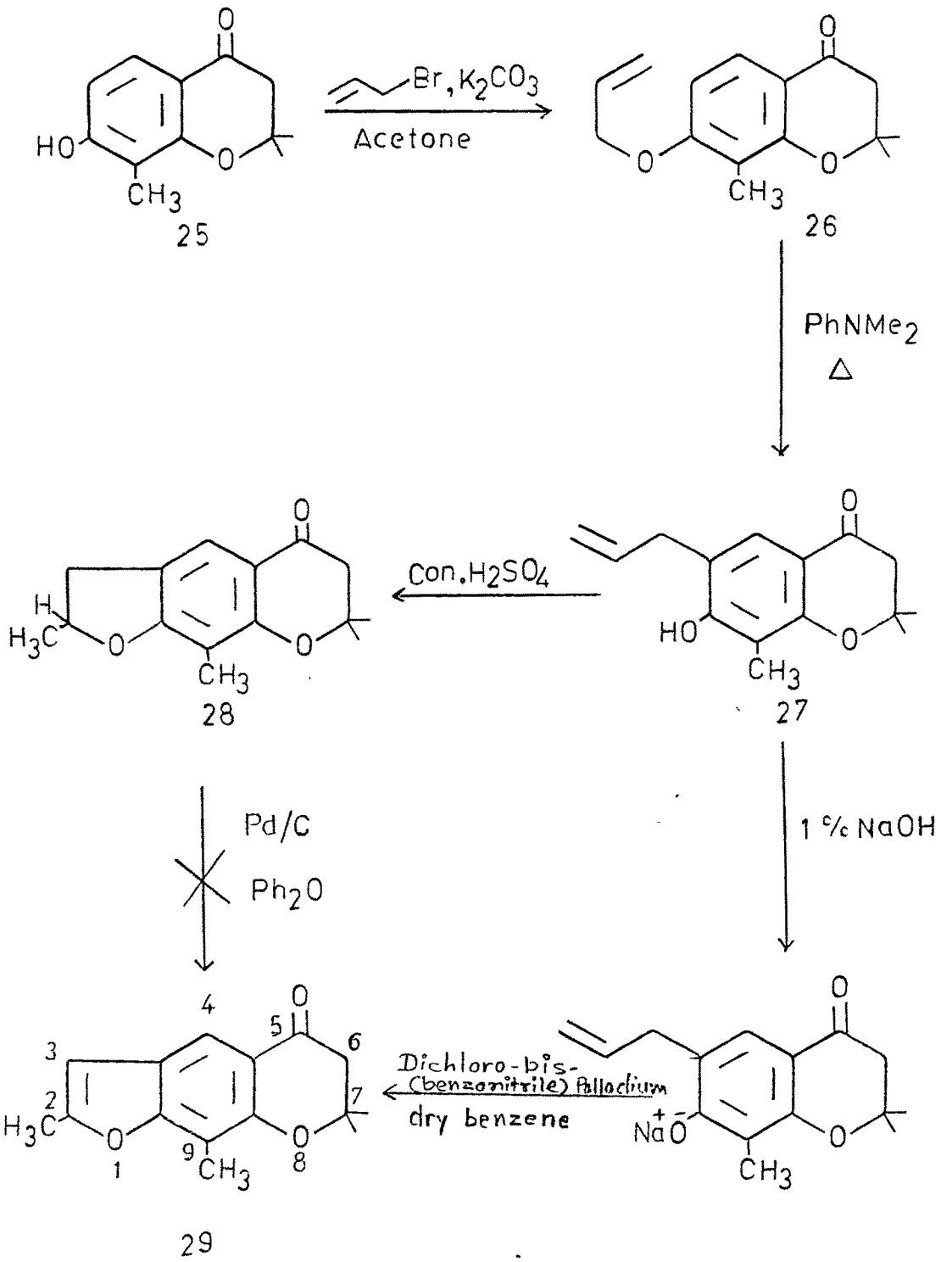
20
Br, K2CO3
Acetone
21
PhNMe2
△
22
HO
1% NaOH
Con. H2SO4
23
H
CH3
Pd/C
Ph2O
Dichloro-bis(benzonitrile)
Palladium,
benzene
24
H3C
Na+O-

SCHEME-IV

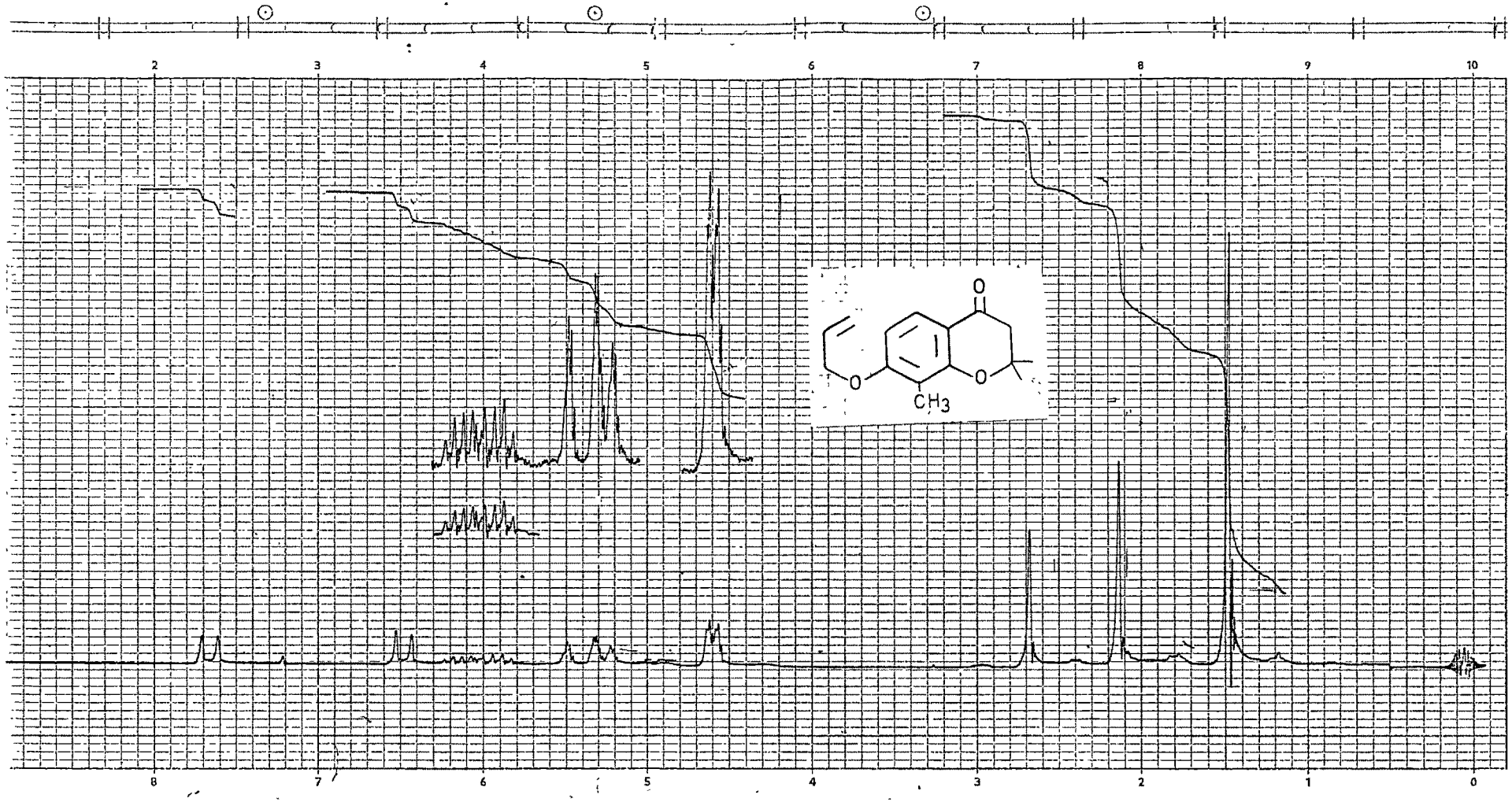


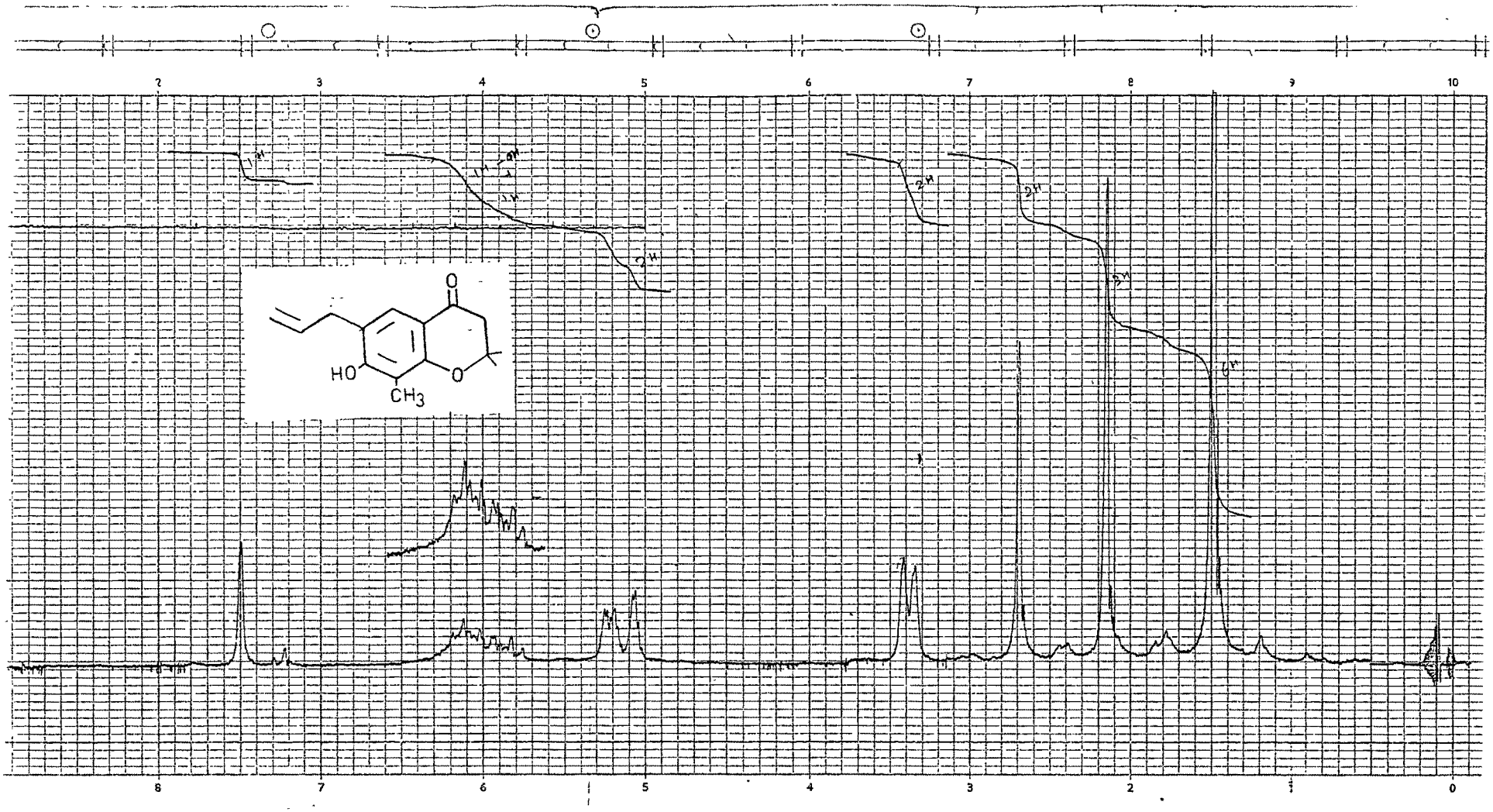


(25) was synthesized from 2-methyl resorcinol by same method as that of (20). (25) on alkylation with allylbromide in presence of fused potassium carbonate in dry acetone gave 7-allyloxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (26), the structure of which was established by pmr spectrum ($CDCl_3$) which showed following signals : two doublets (J=9Hz) at δ 7.6 and 6.4 for two protons at C-5 and C-6 respectively, multiplet at 6.15-5.8 for one proton of allyl group ($-O-CH_2-\underline{CH}=CH_2$) ; double doublet (J=16,2Hz) at 5.3 for terminal methylene proton of allyl group ($-O-CH_2-CH=\underline{CH_2}$) ; three singlets at 2.65, 2.1 and 1.45, for two methylene protons at C-3, for three protons of methyl group at C-2 and six protons of two methyl groups at C-8. (26), on Claisen rearrangement in refluxing N,N-dimethylaniline afforded 7-hydroxy-6-allyl-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (27), the structure of (27) was established by pmr spectrum ($CDCl_3$) which showed following signals : δ 7.4, singlet for one proton at C-5 ; one broad multiplet for two protons at 6.2-5.8 for one proton of allyl group ($-O-CH_2-\underline{CH}=CH_2$) and -OH group at C-7 ; double doublet (J=16,2Hz) at 5.1 for the terminal methylene protons of allyl group ($-O-CH_2-CH=\underline{CH_2}$), doublet (J=8Hz) at 3.3 for methylene protons of allyl group ($-\underline{CH_2}-CH=CH_2$) ; three singlets at 2.6, 2.05 and 1.4 for two methylene protons at C-3, methyl group at C-8 and for six protons of two methyl groups at C-2. (27) on tituration with 80% H_2SO_4 furnished 2,7,7,9-tetramethyl-2,3,6,7-tetra-


HO
O
CH3
25
Br, K2CO3
Acetone
26
PhNMe2
△
27
Con. H2SO4
28
Pd/C
Ph2O
1 % NaOH
Dichloro-bis-
(benzonitrile) Palladium
dry benzene
29

SCHEME-V

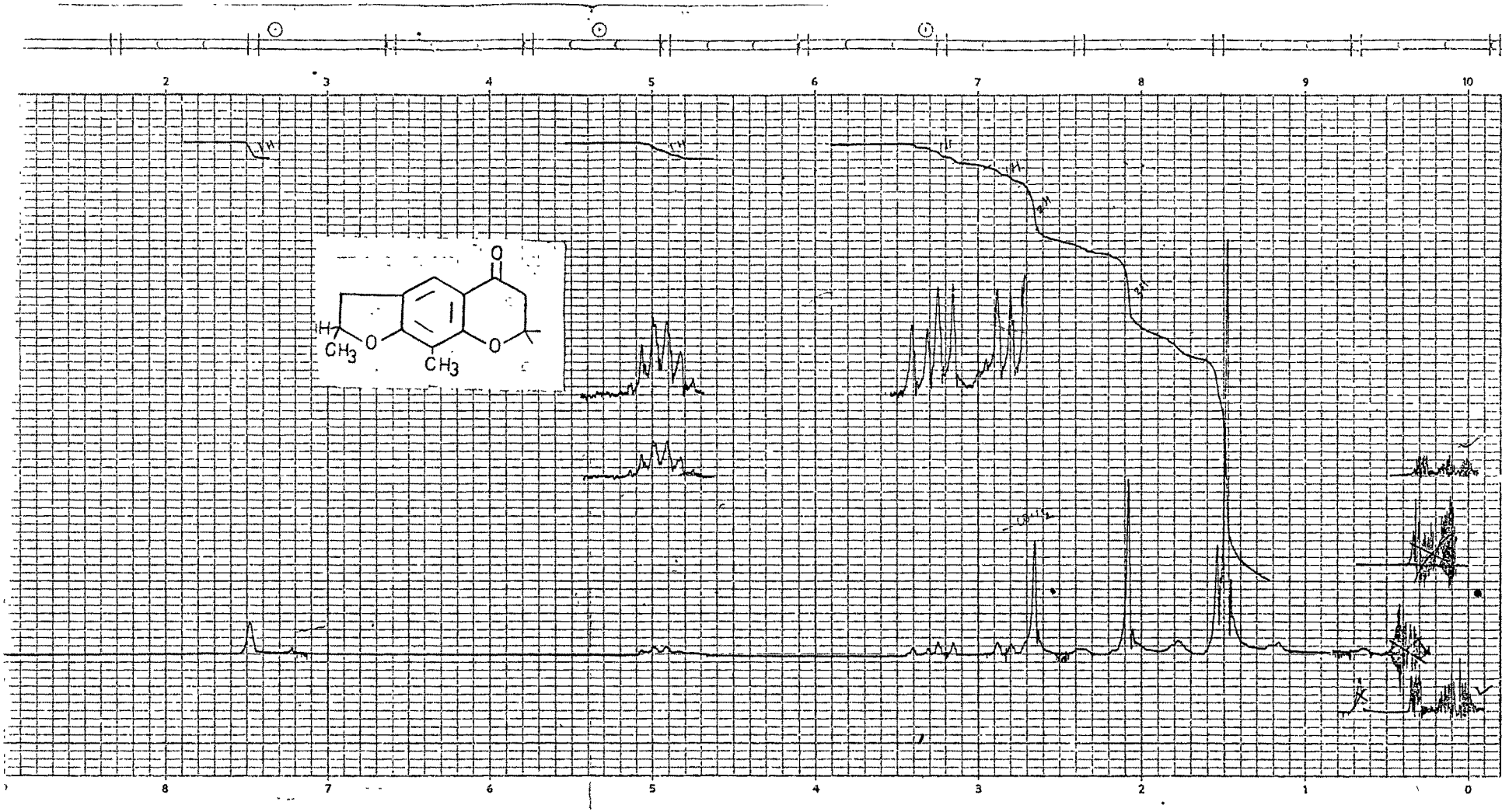


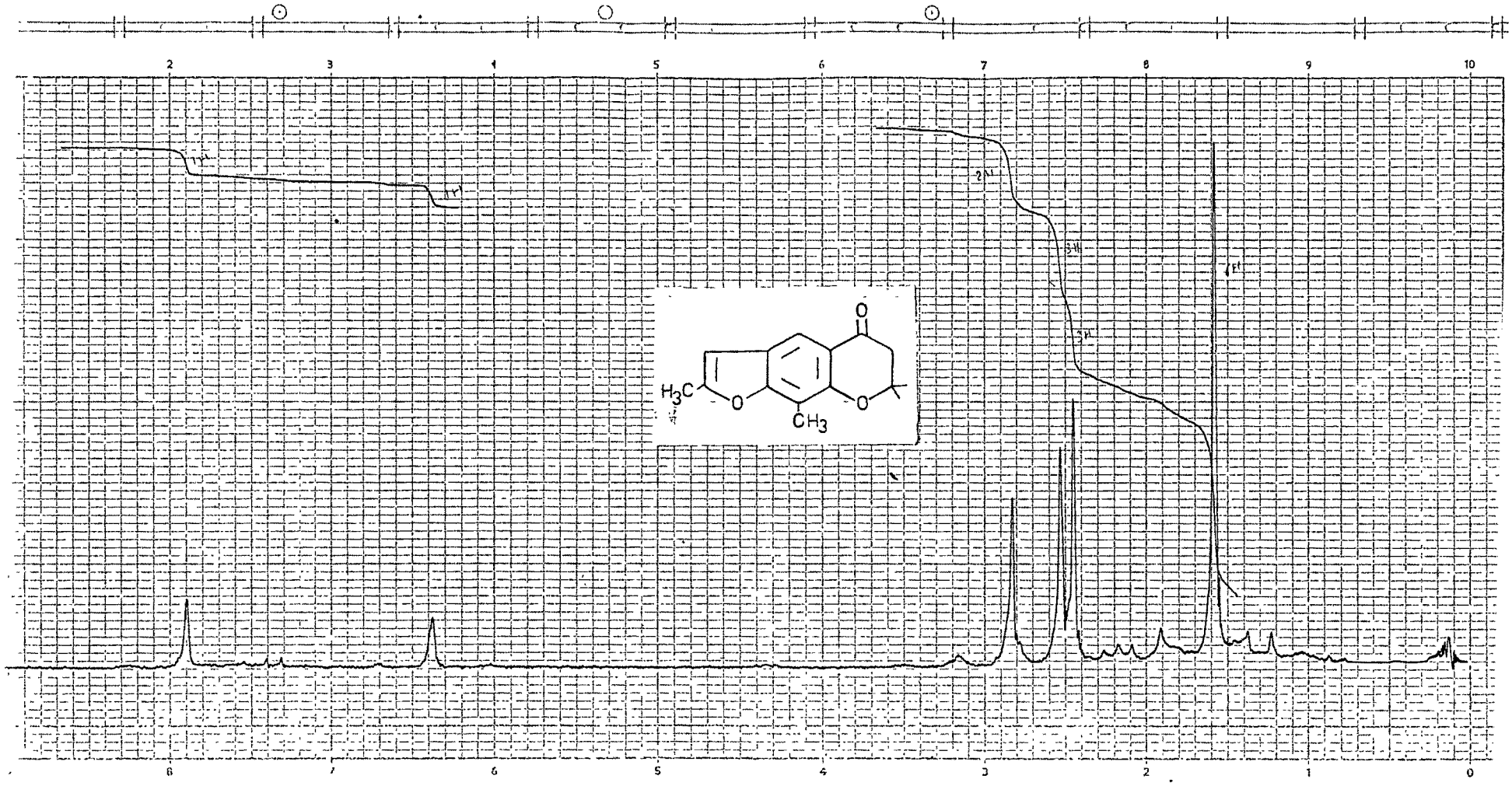


hydro-5H-furo(3,2-g)benzopyran-5-one (28), the structure (28) was confirmed by pmr spectrum ($CDCl_3$) which exhibited following signals : δ 7.4, singlet for one proton at C-4; 4.85, multiplet for one proton at C-2 ; double doublet for two geminal protons at C-3, one at 3.2 (J=18,8Hz) and another at 2.7(J=18,8Hz) ; doublet (J=8Hz) at 1.5 for methyl group at C-2 ; three singlets at 2.6, 2.05 and 1.45 for two methylene protons at C-6, three proton of methyl group at C-9 and for six protons of two methyl groups at C-7. Dehydrogenation of (28) with 10% palladised charcol in refluxing diphenylether failed to give required product (29). In order to synthesize (29) , sodium salt of (27) when treated with dichloro-bis(benzonitrile) palladium complex [31-35] in refluxing benzene gave 2,7,7,9-tetramethyl-6,7-dihydro-5H-furo(3,2-g)benzopyran-5-one (29). Structure (29) was confirmed by pmr spectra ($CDCl_3$) which exhibited following signals δ 7.8, singlet for one proton at C-4 ; 6.3, singlet for one proton on furan ring at C-3 ; 2.75, singlet for two methylene protons at C-6 ; 2.5, singlet for three protons of methyl group at C-2 ; and singlet at 1.45 for six protons of two methyl groups at C-7. [Scheme-V]

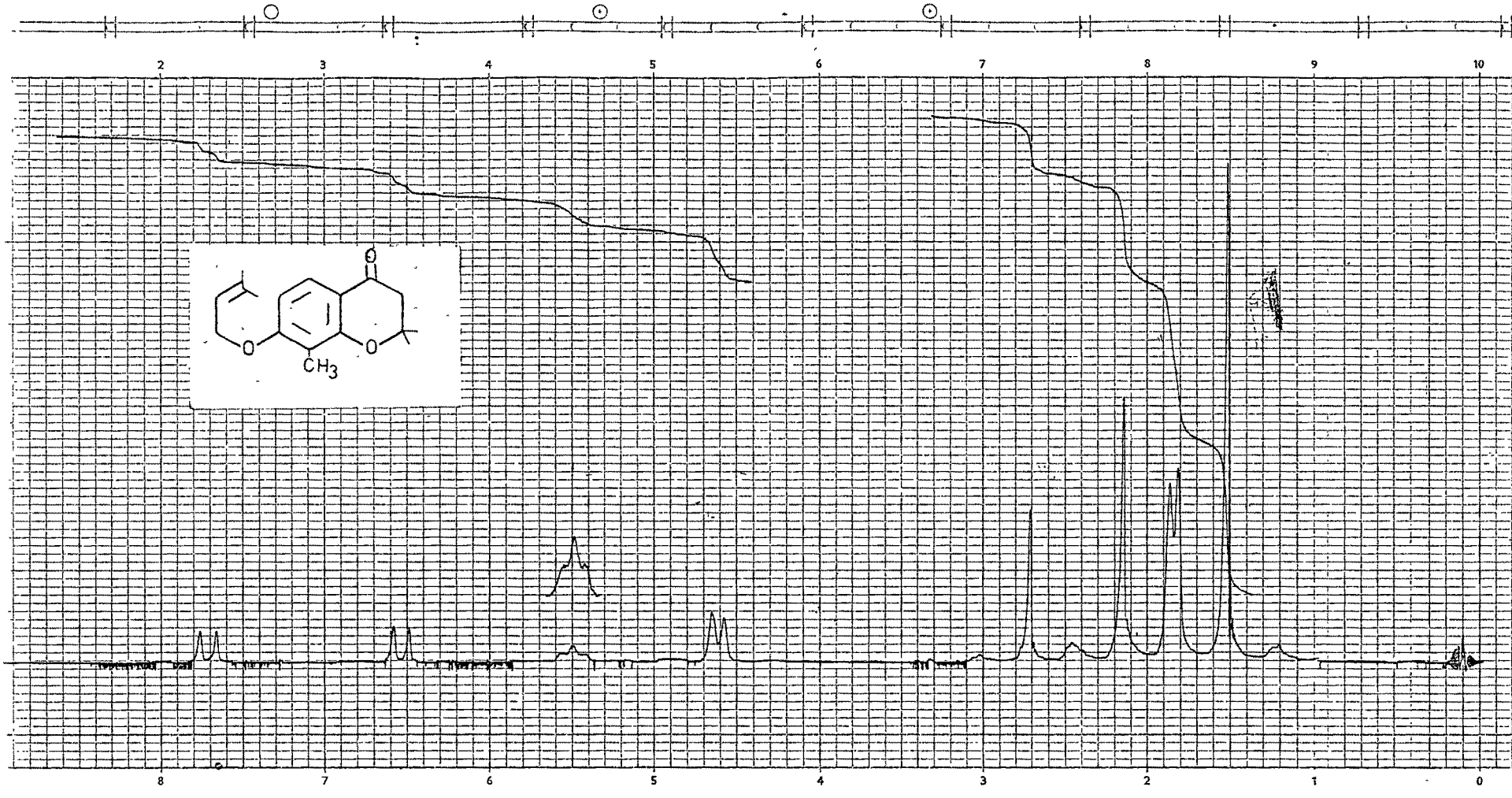
Synthesis of 2,2,3,7,7,9-Hexamethyl-2,3,6,7-tetrahydro-5H-furo(3,2-g)benzopyran-5-one (32)

7-(3'-methyl-but-2'-enyloxy-2,2,8-trimethyl-2,3-dihydro-



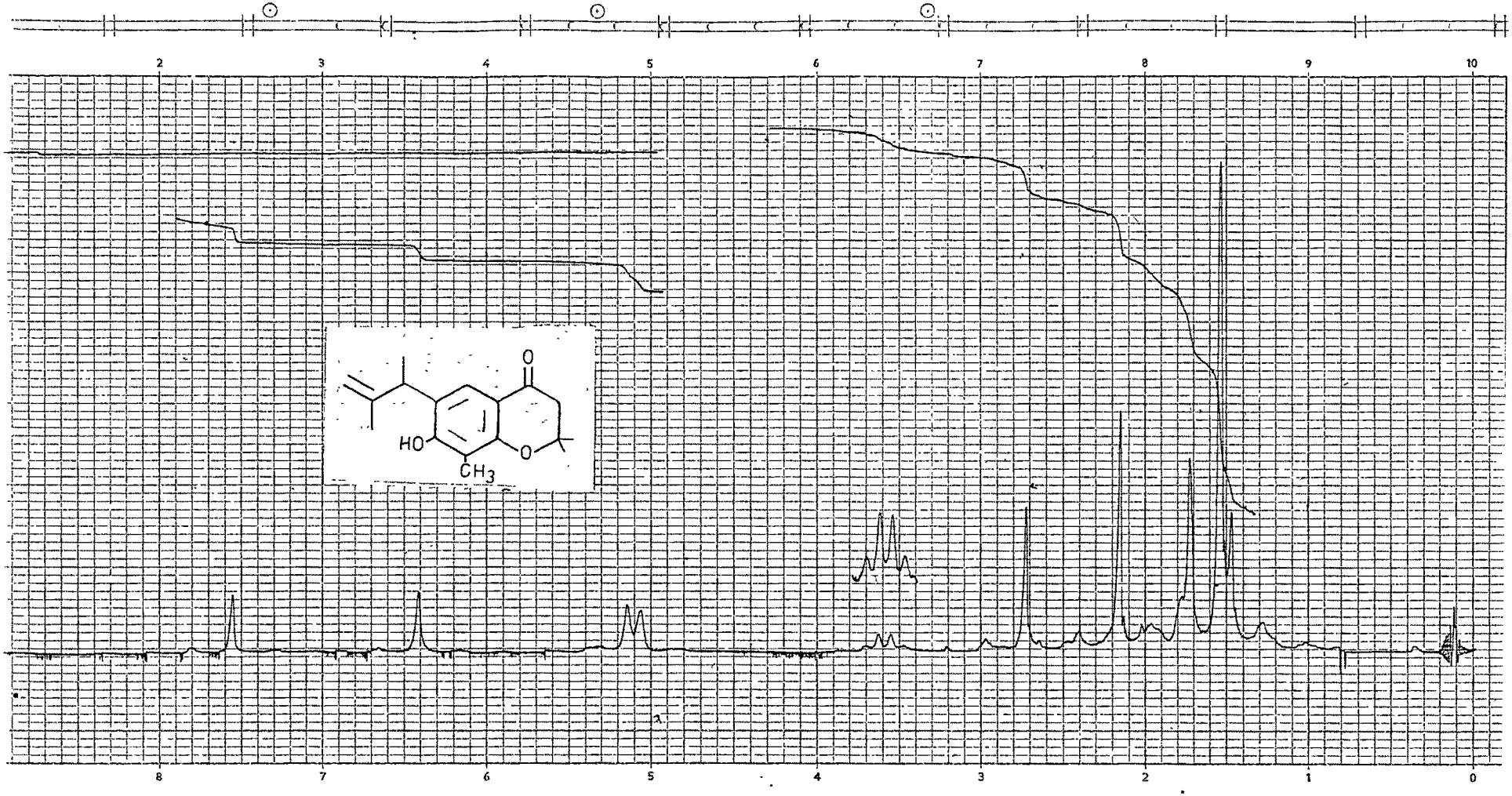


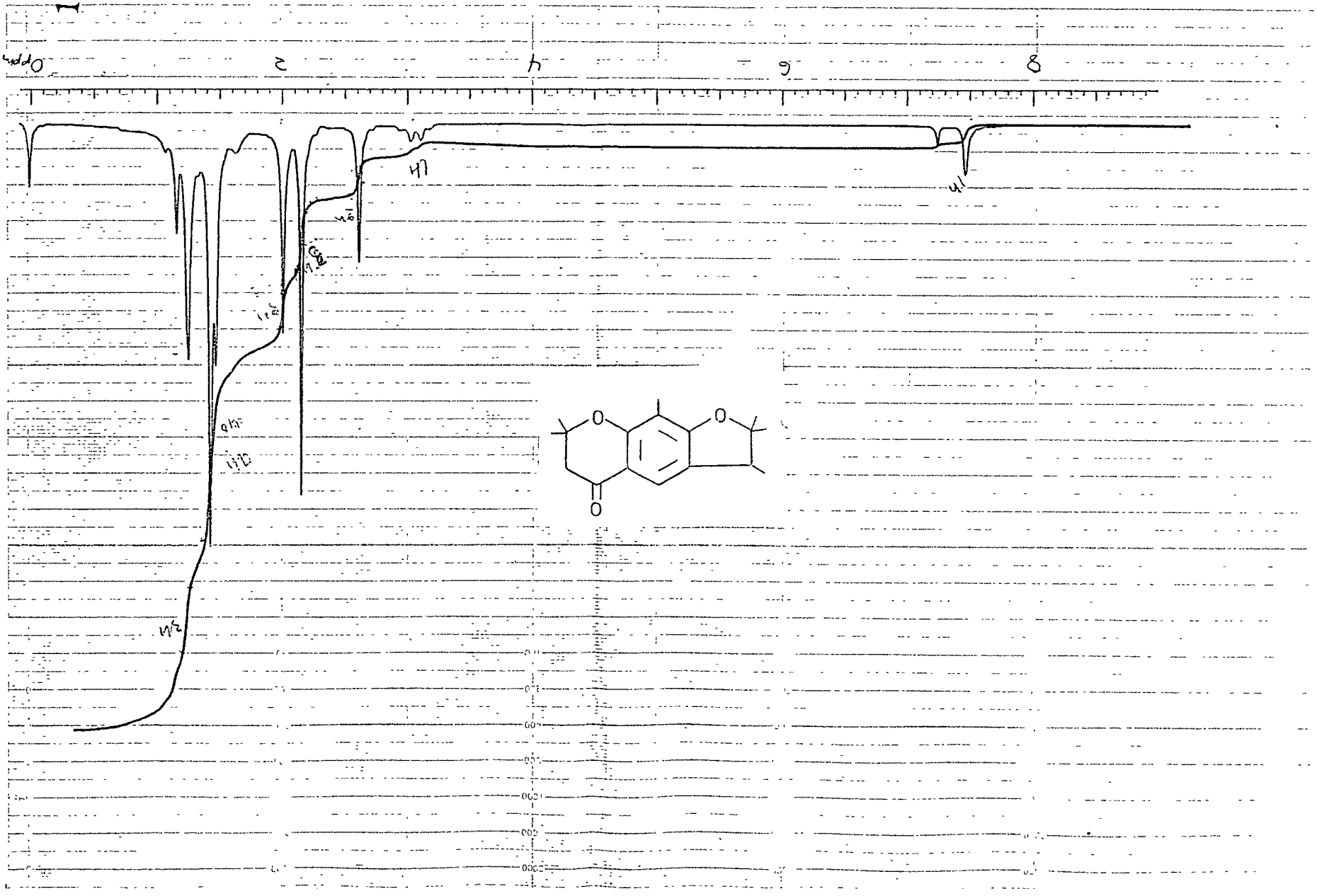
4H-benzopyran-4-one (30) was prepared by condensing (25) with 1-bromo-3-methyl-but-2-ene in presence of fused potassium carbonate in dry acetone. (30), on Claisen rearrangement in refluxing N,N-dimethylaniline gave the abnormal product 7-hydroxy-6-(1',2'-dimethyl-2-propenyl)-2,2,8-trimethyl- 2,3-dihydro-4H-benzopyran-4-one (31), the structure (31) was established by it's pmr spectrum ($CDCl_3$) which showed following signals δ 7.45, singlet for one proton at C-5, singlet at 6.3 for one proton of -OH group at C-7 which disappears on exchange with D_2O, two singlets at 5.05 and 4.95 for two vinylic protons of allyl side chain ($-\underset{CH_3}{\underset{|}{CH}}-\underset{CH_3}{\underset{|}{C}}=\underline{CH_2}$) quartet at 3.5 for one allylic proton of allyl side chain ($-\underset{CH_3}{\underset{|}{\underline{CH}}}-\overset{CH_3}{\overset{|}{C}}=CH_2$), singlet at 2.6 for two methylene protons at C-3 ; singlet at 2.05 for three protons of methyl group at C-8 ; singlet at 1.7 for three protons of methyl group on allyl chain ($-CH-\overset{\underline{CH_3}}{\overset{|}{C}}=CH_2$) ; singlet at 1.45 for six protons of two methyl groups at C-2 and singlet at 1.35 for three protons of homo-allylic methyl group on allyl chain ($-\underset{\underline{CH_3}}{\underset{|}{CH}}-\overset{CH_3}{\overset{|}{C}}=CH$). (31) on tituration with H_2SO_4 (80%) gave 2,2,3,7,7,9-Hexamethyl-2,3,6,7-tetrahydro-5H-furo(3,2-g)benzopyran-5-one (32), the structure (32) was established by it's pmr spectrum ($CDCl_3$) which shows following signals : δ 7.45, singlet for one proton at C-4 ; 3.04, quartet for one proton at C-3 ; 2.6, singlet for three protons of methyl group at C-9 ; singlet at 2.0

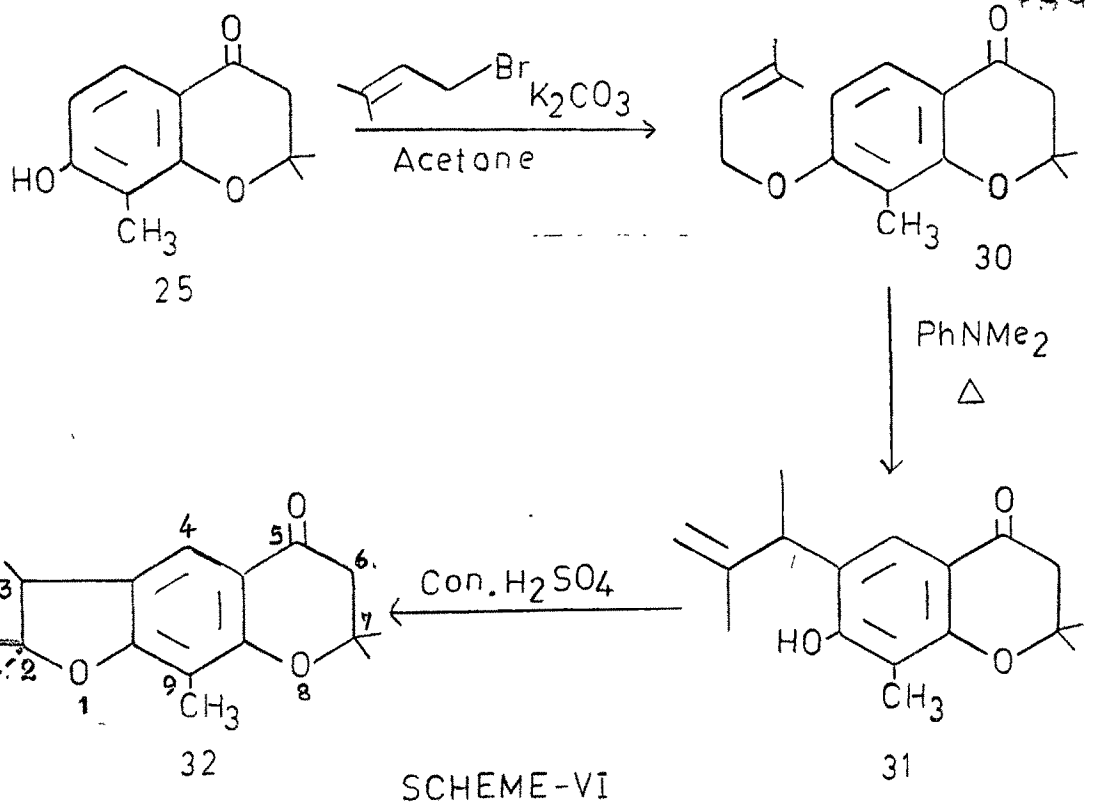


for three protons of axial methyl group at C-2 and singlet at 1.45 for nine protons, three protons of equatorial methyl group at C-2 and six protons of two methyl groups at C-7, doublet at 1.25 for three protons of methyl group at C-3 [Scheme-VI]

In order to synthesise pyranochromanones, Claisen rearrangement of propargyl or 1,1-dimethyl propargyl ether of respective hydroxychromanones was carried out. Propargyl or 1,1-dimethyl propargyl ether can be prepared by refluxing a mixture of phenol and propargyl bromide or 2-methyl-2-chloro-but-3-yne in acetone in presence of KI and K_2CO_3. It's rearrangement in N,N-dimethylaniline give pyranochromanone. This method is developed by Iwai and Ide[36] and probably it is the best method for preparing chromenes in high yields. Thus Evodionol methyl ether (33) is prepared in 80% yield.[Scheme-VII) Zsindely and Schmid[37] have established that the reaction is variant of the Claisen allylic rearrangement. Mukerjee, Sarkar and Seshadri[38] synthesised Iso-encecalin (34) and encecalin (35) by adopting the similar route. Resacetophenone was converted to corresponding ether which was further subjected to cyclization and methylation to furnish iso-encecalin (34) and encecalin (35). Thermal cyclization in refluxing DMA produced. different products [Scheme-VIII]. Same method is applied to synthesize pyranobenzo- γ -pyrones by several other groups of research workers.[39-42]

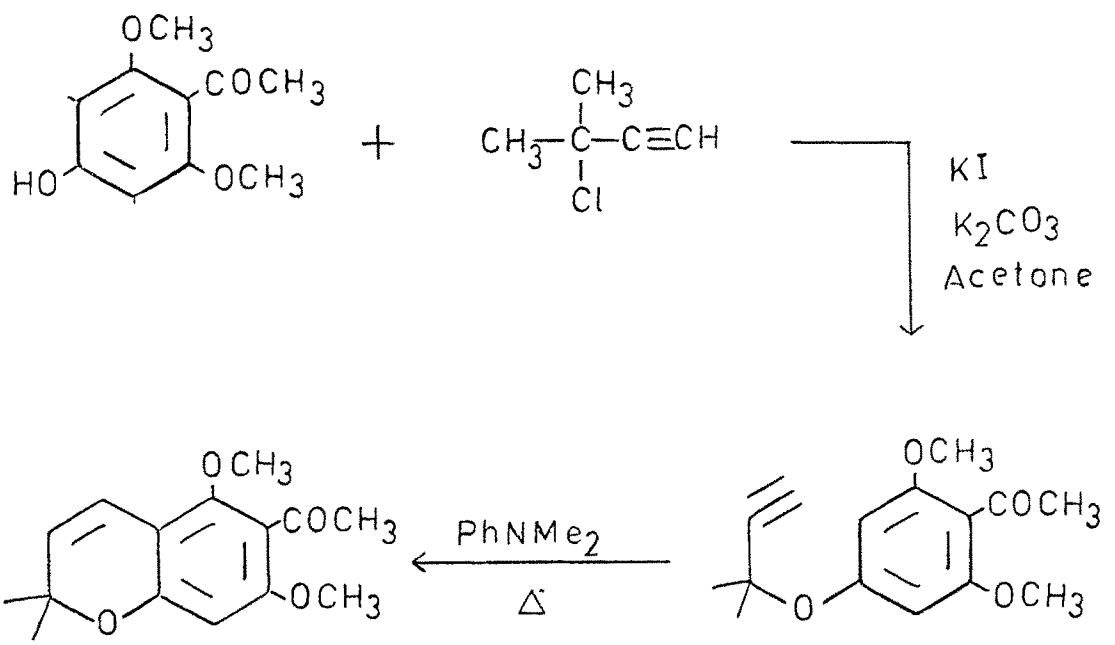



8
6
4
2
0ppm
1H
1H
2H
2H
3H
3H
O
O
O



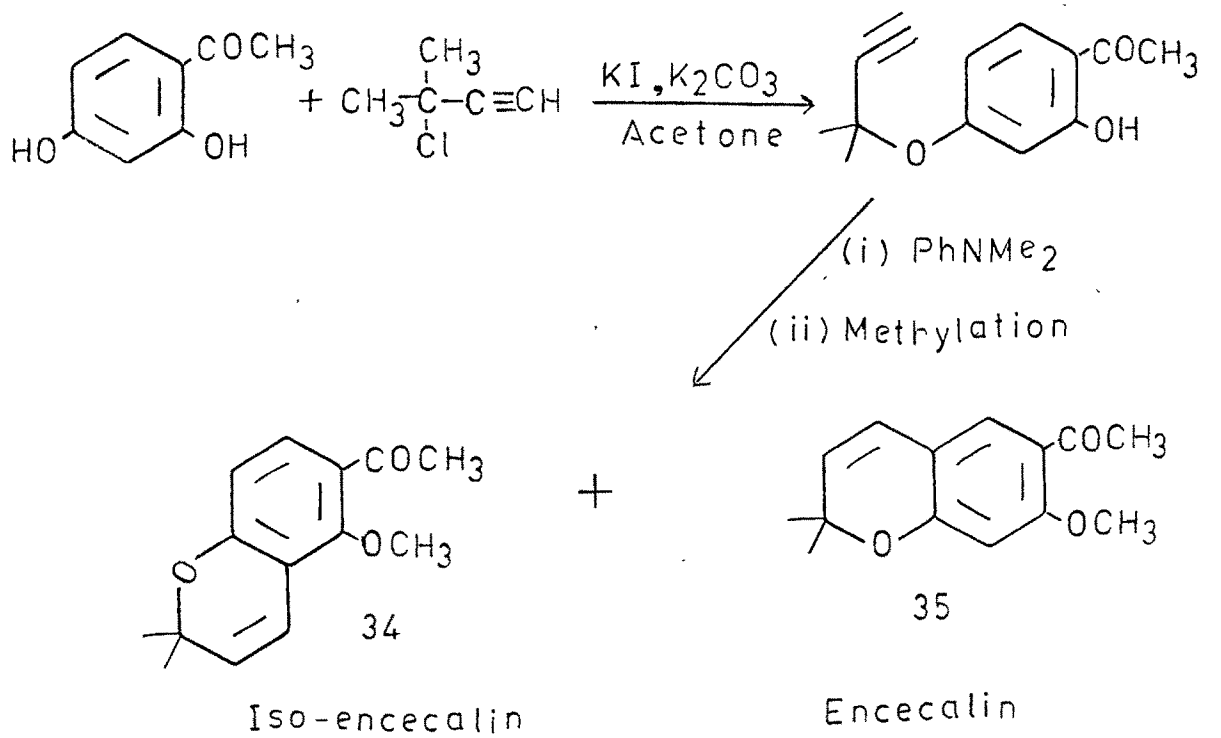
SCHEME-VI

Iwai and Ide[36]

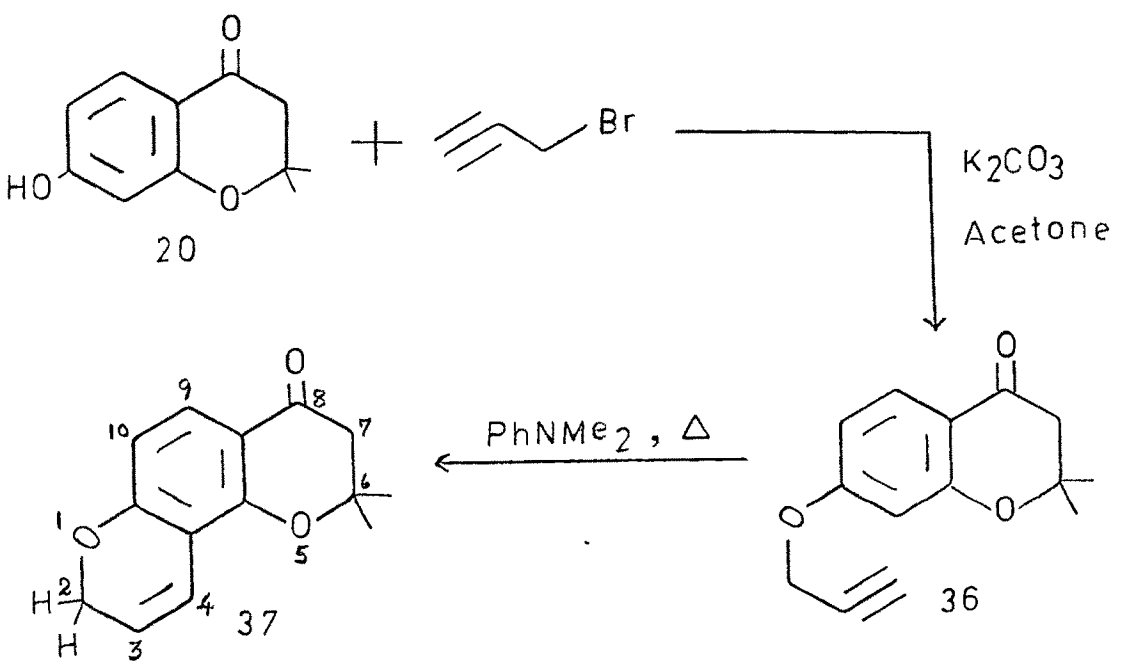


SCHEME-VII

Seshadri and coworkers[38]



SCHEME-VIII



SCHEME-IX

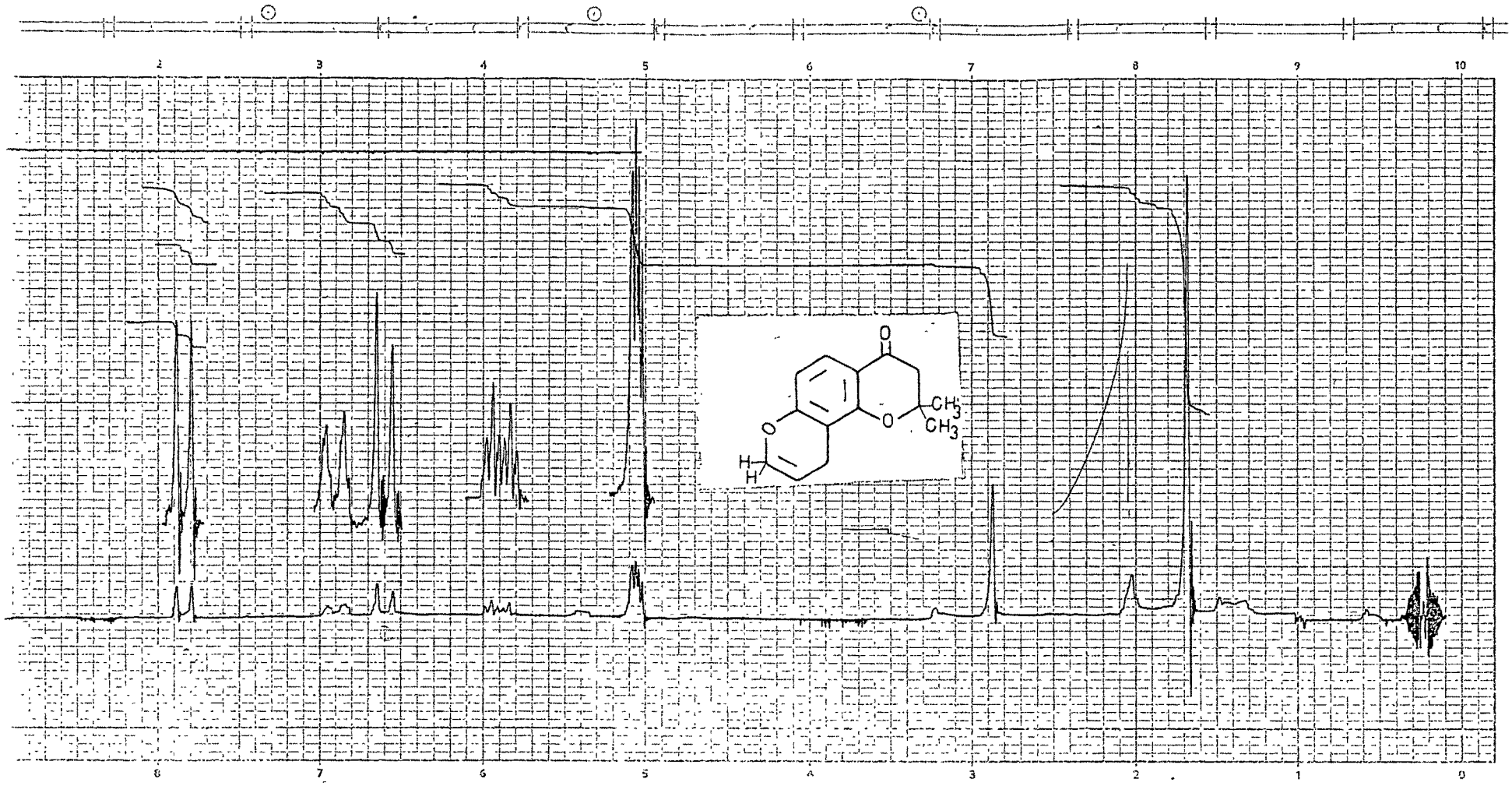
In continuation of the work done by Joshi, Patel and Trivedi,[43] the Claisen rearrangement of propargyl ether of chromanones is carried out.

6,6-Dimethyl-6,7-dihydro-8H-pyrano(2,3-h)benzopyran-8-one (37)

7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (20) was condensed with propargyl bromide in presence of fused potassium carbonate by refluxing the mixture in dry acetone. On working up the reaction mixture pure 7-(3-prop-2-ynyloxy)-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (36) was obtained. Ether (36), when subjected to Claisen rearrangement by refluxing in N,N-dimethylaniline for 6 h. gave 6,6-dimethyl-6,7-dihydro-8H-pyrano(2,3-h)benzopyran-8-one (37). Structure (37) was assigned on the basis of pmr spectrum which exhibited following signals : δ 7.65, doublet, J=9Hz for one proton at C-9, doublet at 6.7, J=10Hz for one proton at C-4, doublet at 6.4, J=9Hz for one proton at C-10, multiplet at 5.7 for one proton at C-3, multiplet at 4.85, for two protons at C-2, singlet at 2.65 for two methylene protons at C-7, singlet at 1.45 for six protons of two methyl groups at C-6.[Scheme-IX]

2,2,6,6-Tetramethyl-6,7-dihydro-8H-pyrano(2,3-h)benzopyran-8-one (39)

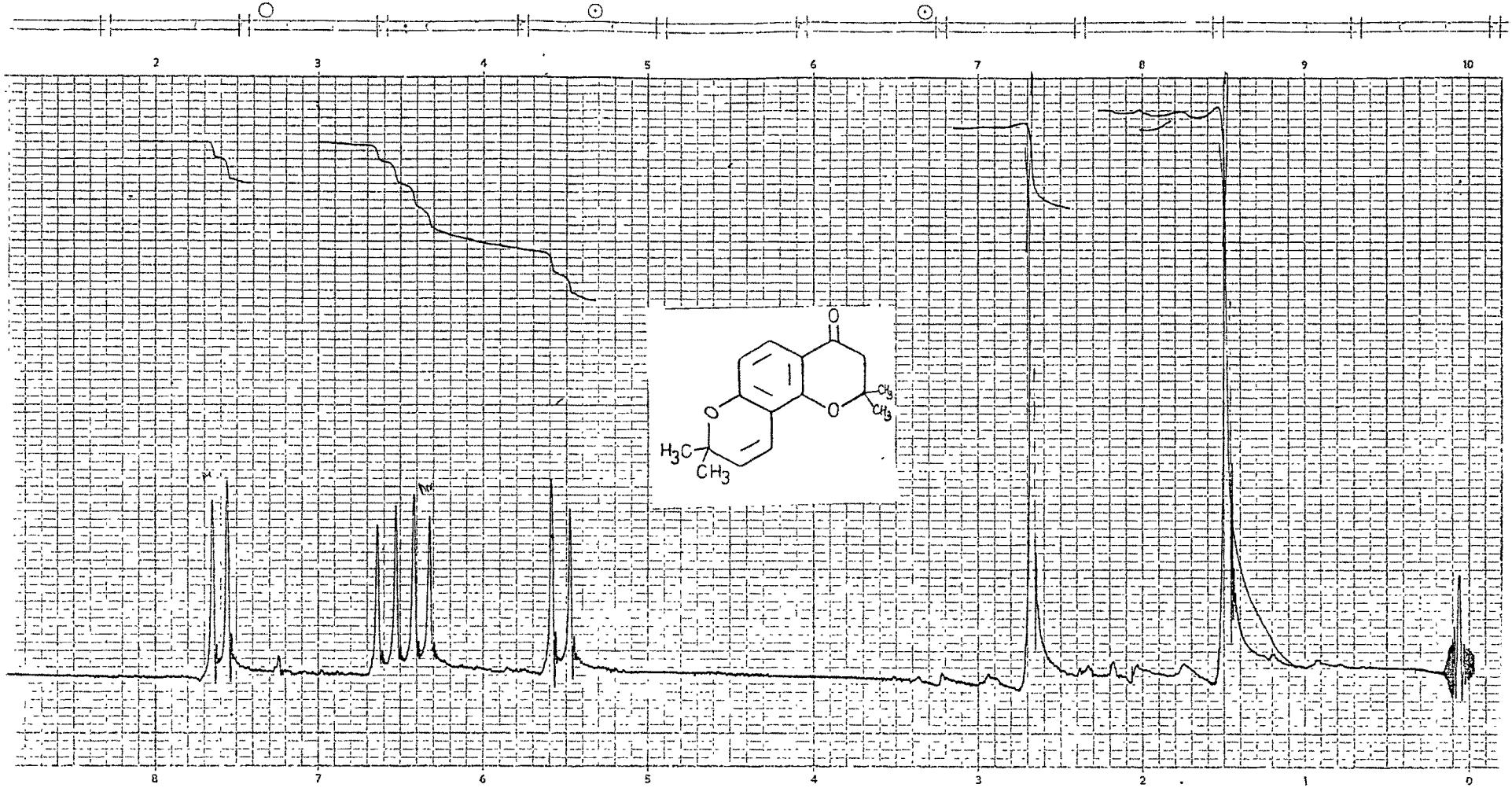
7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (20) was condensed with 3-chloro-3-methylbut-1-yne in presence

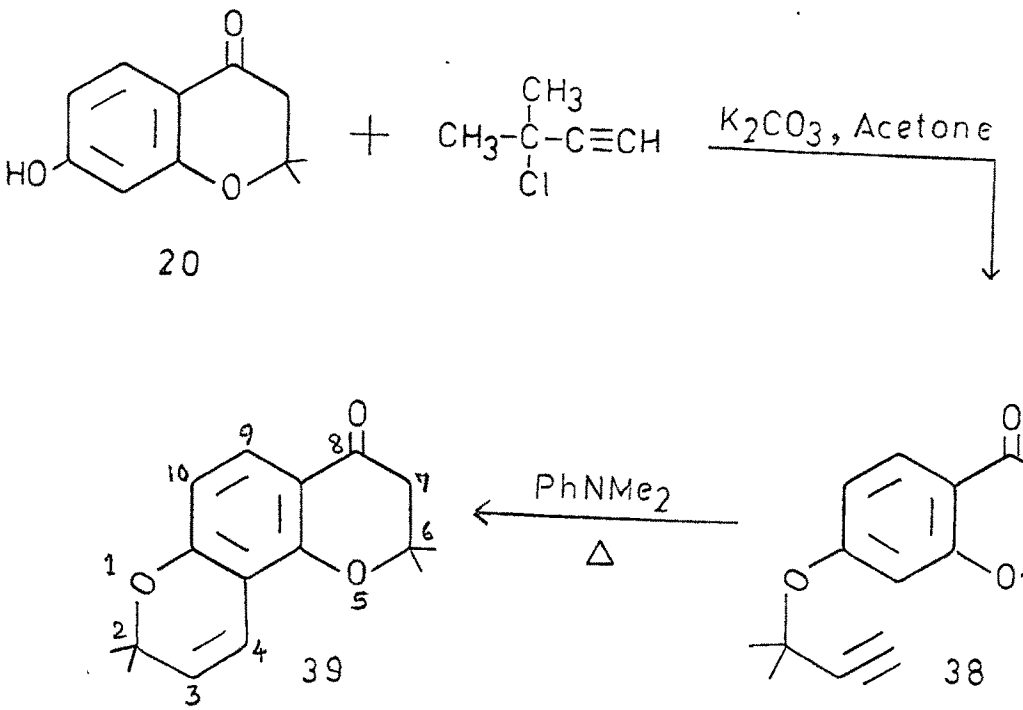


of fused potassium carbonate and few crystals of potassium iodide by refluxing the mixture in dry acetone. In working up the reaction mixture pure 7-(1',1'-dimethyl-prop-2-ynyloxy), 2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (38) was obtained. Ether (38), when subjected to Claisen rearrangement by refluxing in N,N-dimethylaniline for 6 h. gave 2,2,6,6-tetramethyl-6,7-dihydro-8H-pyrano (2,3-h)benzopyran-8-one (39). Structure (39) was assigned on the basis of pmr spectrum which exhibited following signals : δ 7.6, doublet, J=9Hz, for one proton at C-9 : doublet at 6.5, J=10Hz for one protonat C-4 : doublet at 6.3, J=9Hz for one proton at C-10 ; doublet at 5.45, J=10Hz for one proton at C-3 ; singlet at 2.6 for two methylene protons at C-7 ; and singlet at 1.5 for six protons of two methyl group at C-6 [Scheme-X]

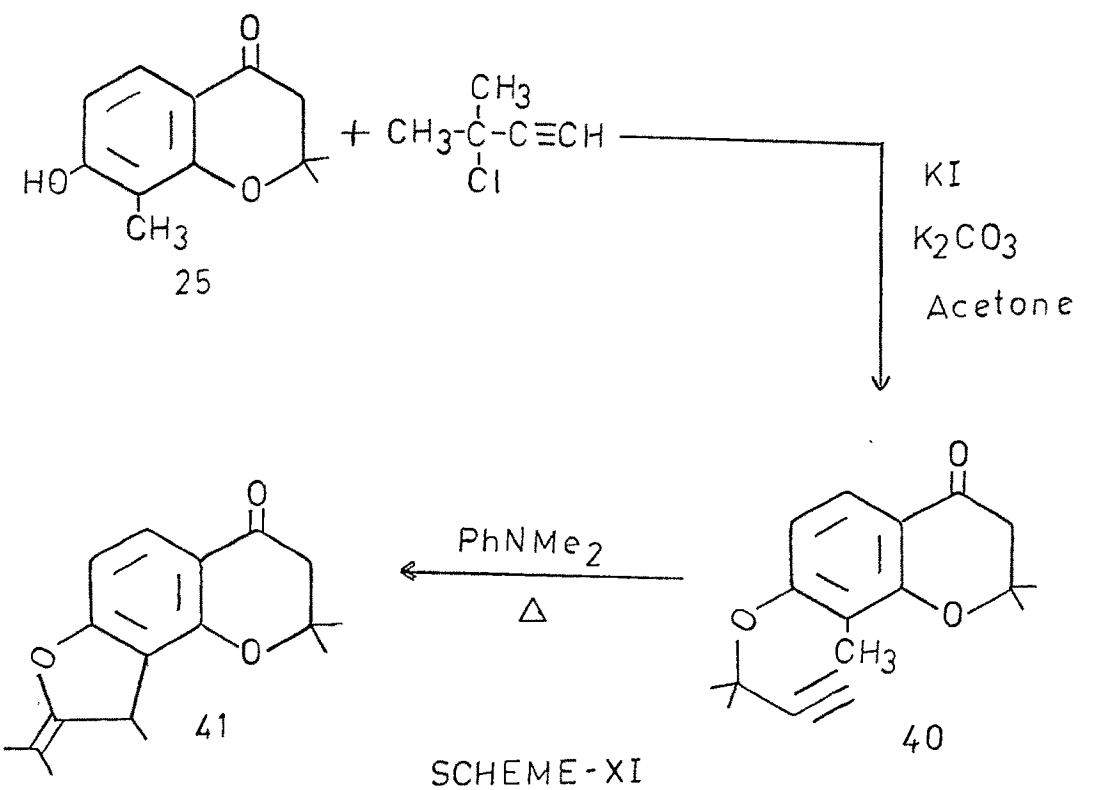
Synthesis of 1,2,3,5,6,7-Hexahydro-1,1,3,5,5-pentamethylcyclo-penta(2,3-h) [2H,7H]-benzopyran-2,7-dione (42)

7-Hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (25) 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-prop-2-ynyloxy)-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (40) was obtained. Structure (40) was assigned on the basis of pmr spectrum which exhibited following signals ($CDCl_3$) : δ 7.6, doublet J=9Hz, for one proton at C-5 ;





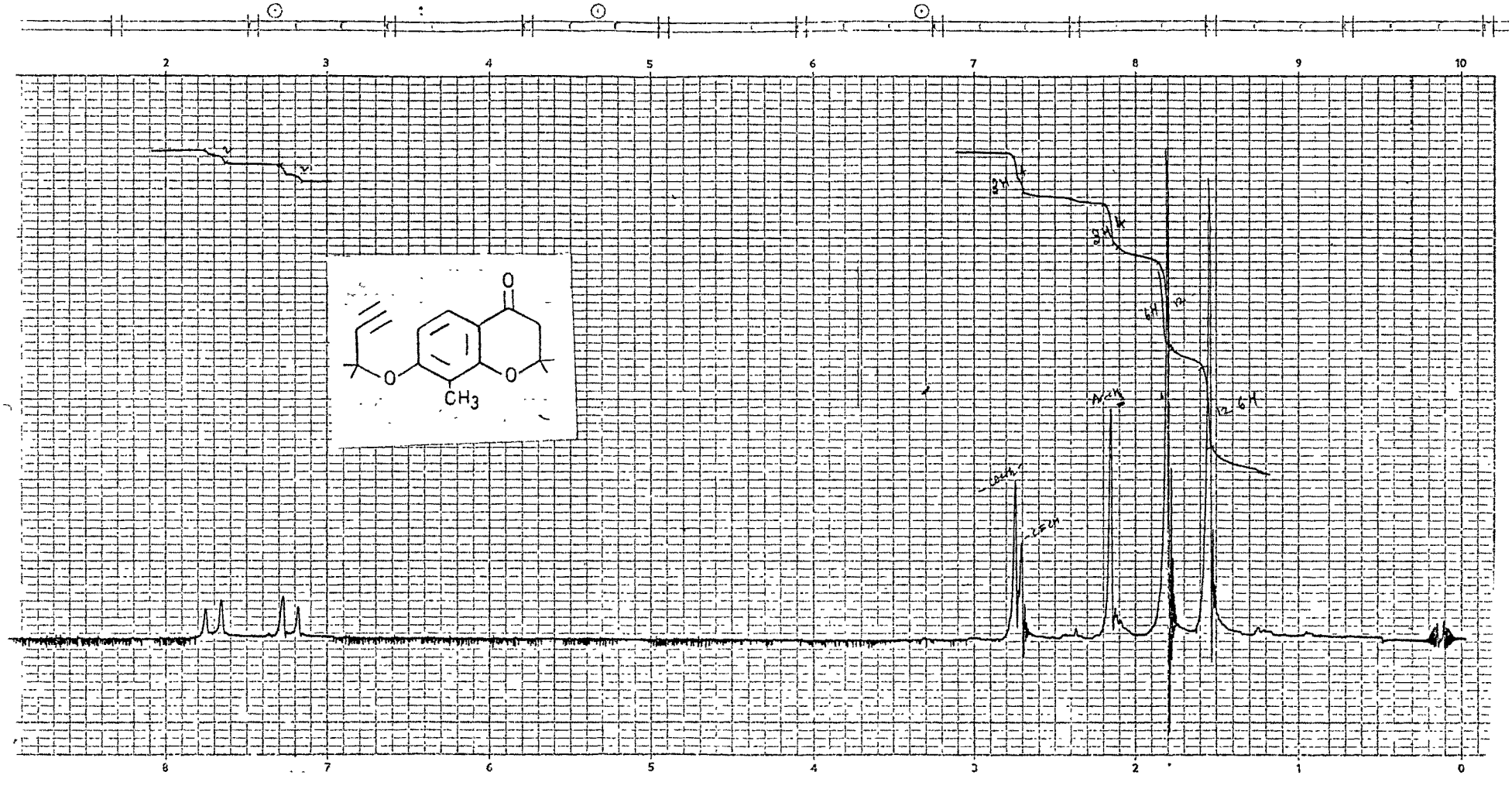
SCHEME-X

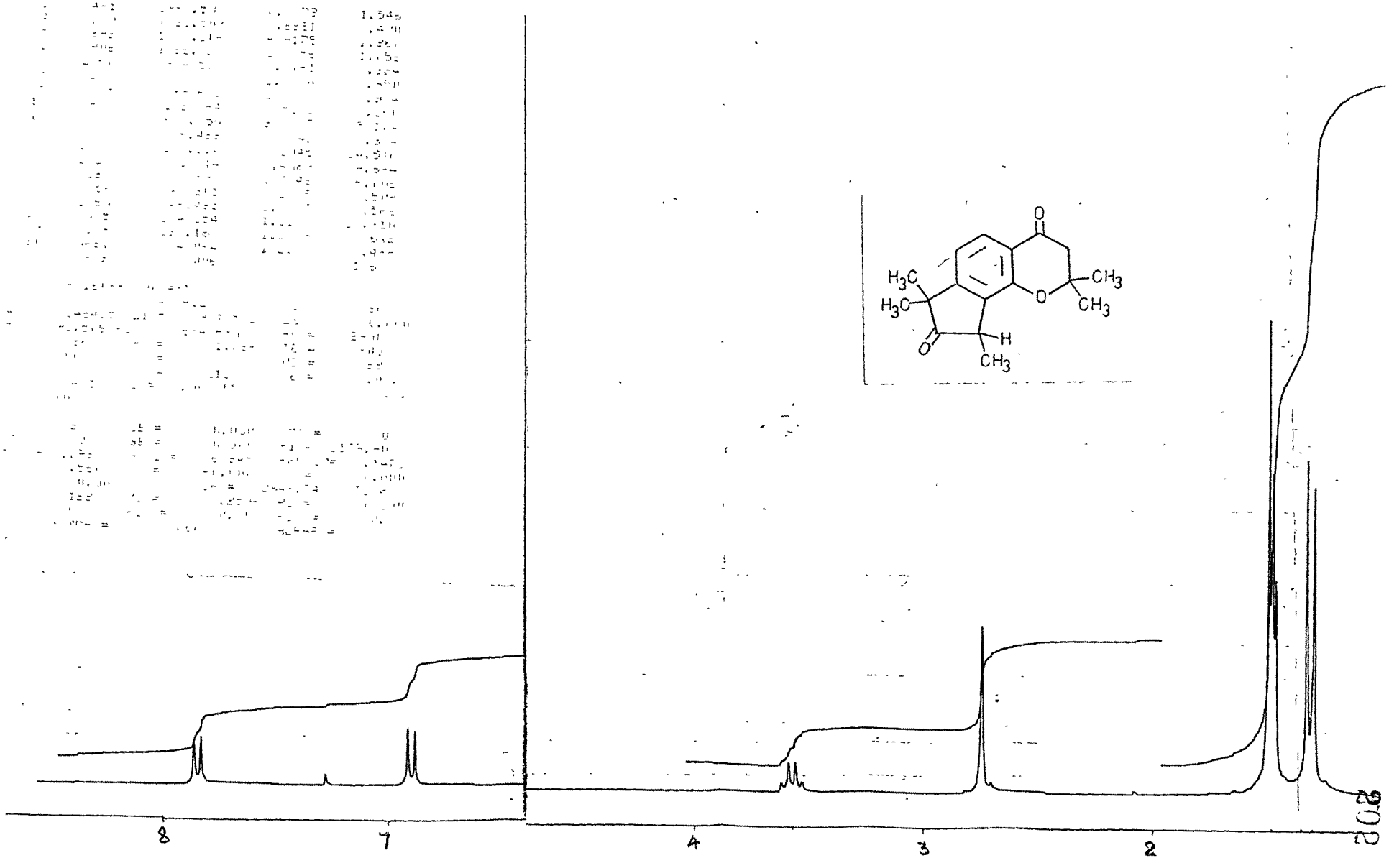


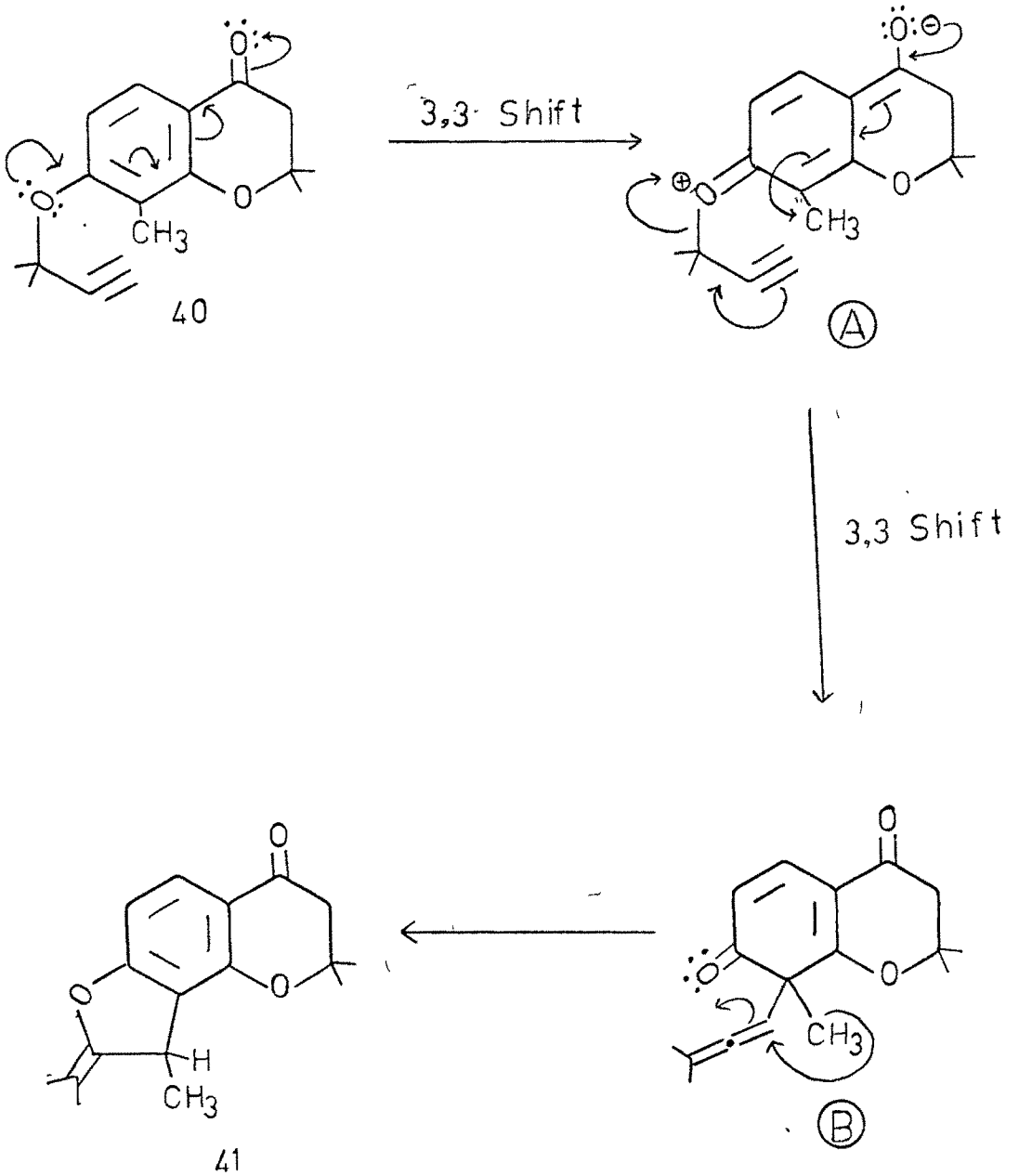
SCHEME-XI

doublet at 6.15 J=9Hz, for one proton at C-6 ; singlet at 2.65 for two methylene protons at C-3 ; singlet at 2.6 for one acetylenic proton, singlet at 2.05, for three protons of methyl group at C-8, singlet at 1.7 for six protons of two methyl group of alkyne side chain and singlet at 1.45 for six protons of two methyl groups at C-2. Ether (40) was subjected to Claisen rearrangement by refluxing in N,N-dimethylaniline for 6 hrs. On working up it gave a novel product (41). [Scheme-XI] which exhibited the following signals in pmr spectrum (250.13 MHz, $CDCl_3$) ; δ 7,85, doublet, J=9Hz, for one proton at C-8 ; doublet at 6.9, J=9Hz, for one proton at C-9 ; quartet at 3.55, J=9Hz for one proton at C-3 ; singlet at 2.7 for two methylene protons at C-6 doublet at 1.5, J=9Hz for three protons of methyl group at C-3 ; singlet at 1.48 for six protons of two methyl groups at C-5 and two singlets at 1.3 and 1.25 for two methyl groups of 2',2'-dimethyl methylene group C-2. 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-3,5,5-trimethyl-2,3,5,6-tetrahydrofuro(2,3-h)benzopyran-7-one (41).

The formation of (41) can be explained by the mechanism suggested in the [Scheme-XII].



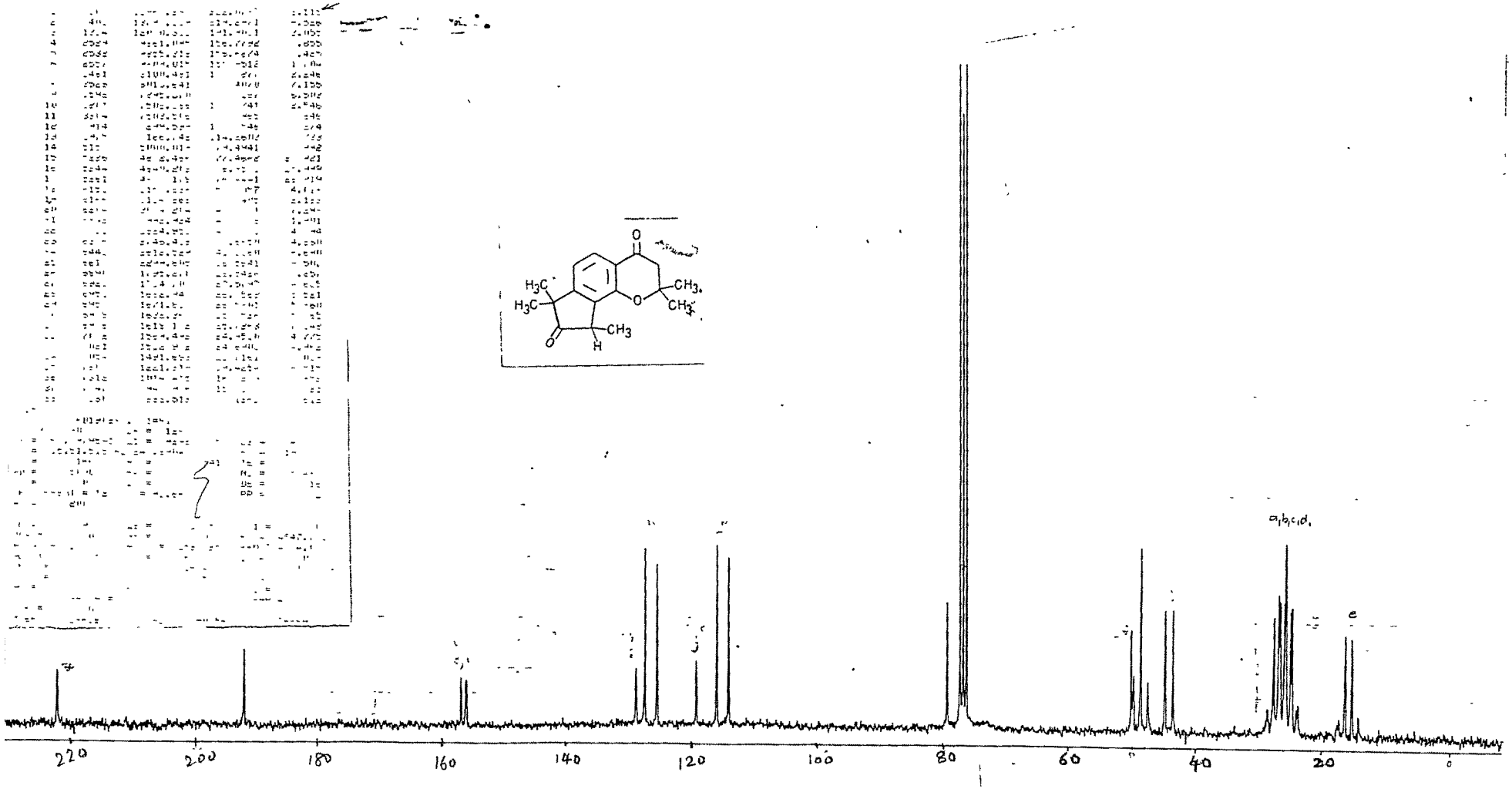

O
H3C
CH3
H3C
O
CH3
O
H
CH3
8
7
4
3
2
0.0



SCHEME-XII

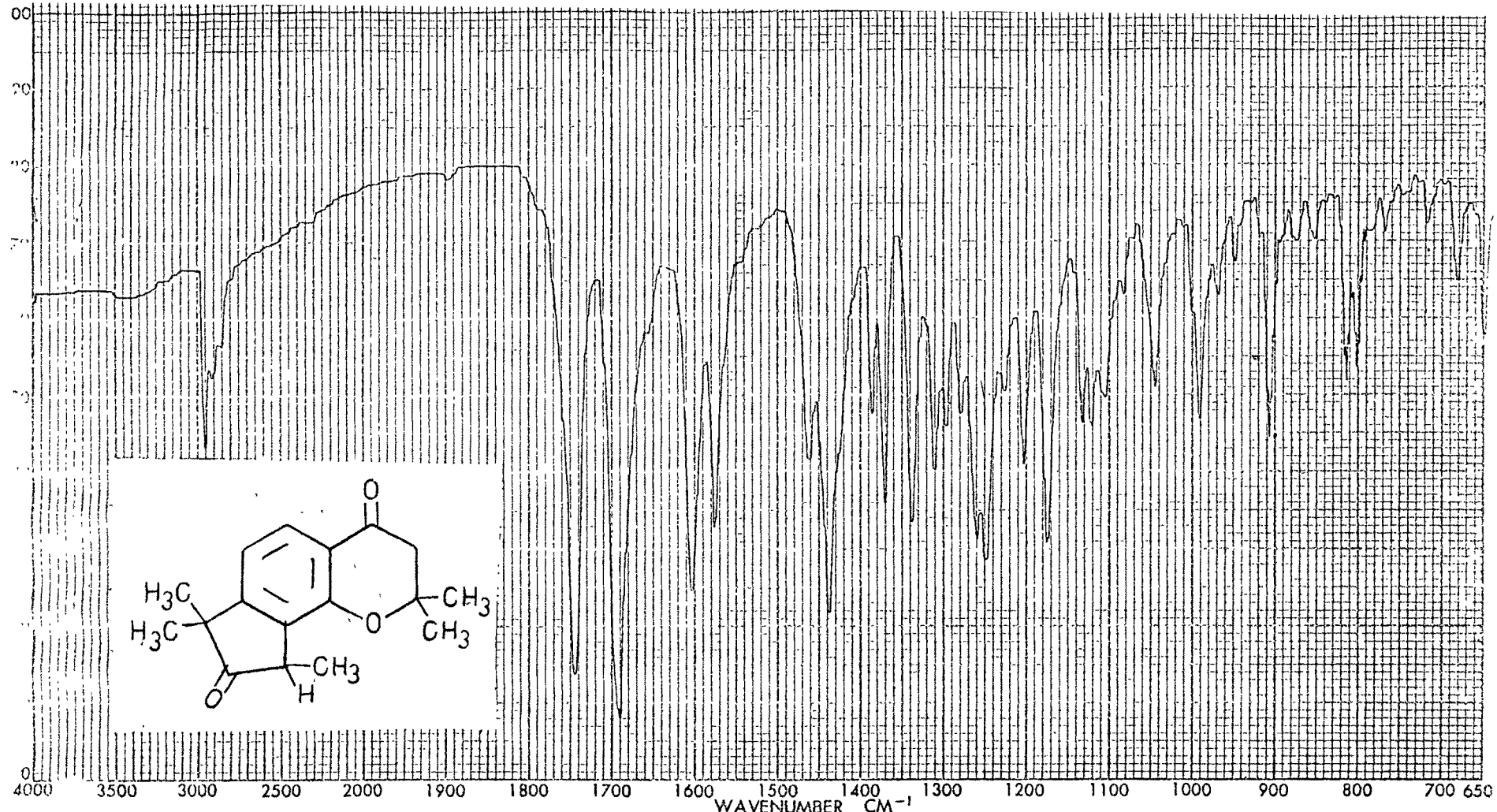
The driving force in the compound (40) is the carbonyl group at C-4, which attract the electron from oxygen of the ether, thus creating positive charge on phenolic oxygen and negative charge the carbonyl oxygen as shown in structure (A). On Claisen rearrangement, the 3,3-dimethylpropargyl group migrates to regiospecific position 8 and collapses into allene system (B). This is supported by the fact that proton at C-8 exhibited doublet of 9Hz otherwise it would have shown a singlet only. The system present in structure (B) can easily undergo Woodward-Hoffmann allowed 2S + 2S + 2S sigmatropic shift with the migration of methyl group to the furan ring system giving compound (41).

C^{13} NMR (62.89MHz, $CDCl_3$) of (41) showed five quartets at δ 16.0, 24, 25, 27, 27 for five methyl carbons, one at C-3 ; two at C-1 and two at C-5 respectively, doublet for $-CH-CH_3$ group was observed at 43, triplet at 49 was observed for methylene carbon at C-6 and a singlet at 50 and 79 was observed for two methyl carbons at C-1, and C-5 respectively, singlets for aromatic carbons at C-8, C-8a, C-9, C-11 was observed at 128.0, 119.0, 115.0 and 126.0, other aromatic carbons at C-10 and C-11a appears in downfield region at 158.0 and 156.0, surprisingly it showed two singlets in the downfield carbonyl region one at 191.0 and other at 222.0. The former can be assigned to the carbonyl group


O
H3C
CH3
H3C
O
CH3
CH3
H
a,b,c,d
e
220
200
180
160
140
120
100
80
60
40
20
0

of γ -pyrone ring system while the second could be assigned to a overcrowded carbonyl group in the cyclopentanone ring system. This observation for the presence of second carbonyl group was confirmed by it's IR spectrum which showed two bands one at 1690 cm^{-1} for carbonyl group of the γ -pyrone ring system and the other at 1742 cm^{-1} for the carbonyl group in the cyclopentene ring system. Based on this observation, the structure (41) is now revised to 1,2,3,5,6,7-hexahydro-1,1,3,5,5-pentamethylcyclopenta (2,3-h)- [2H,7H]-benzopyran-2,7-dione (42), which satisfies all the spectral data-PMR, C^{13} NMR and IR. The mechanism for the revised structure can be formulated as given in the [Scheme-XIII].

(40) on Claisen rearrangement gives cyclohexadienone structure (B), the propargyl system collapsing into allene system. This structure cannot undergo aromatization as there is no proton on the neighbouring carbon atom. Hence, it undergoes intramolecular Diel-Alder reaction to give a tricyclic ring system as shown in the structure (C). Cyclopropane ring system, being highly unstable, undergoes ring opening to give the intermediate (D) and finally to structure (42). 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 ofthe ether chain in the final structure, β and γ carbon of side chain have



SPECTRUM NO.	PHASE Solid	THICKNESS	REMARKS	DATE
SAMPLE RR-65	SOLVENT KBr disc	REFERENCE		OPERATOR
	CONCENTRATION	SCAN TIME		

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PART NO. 200-91506
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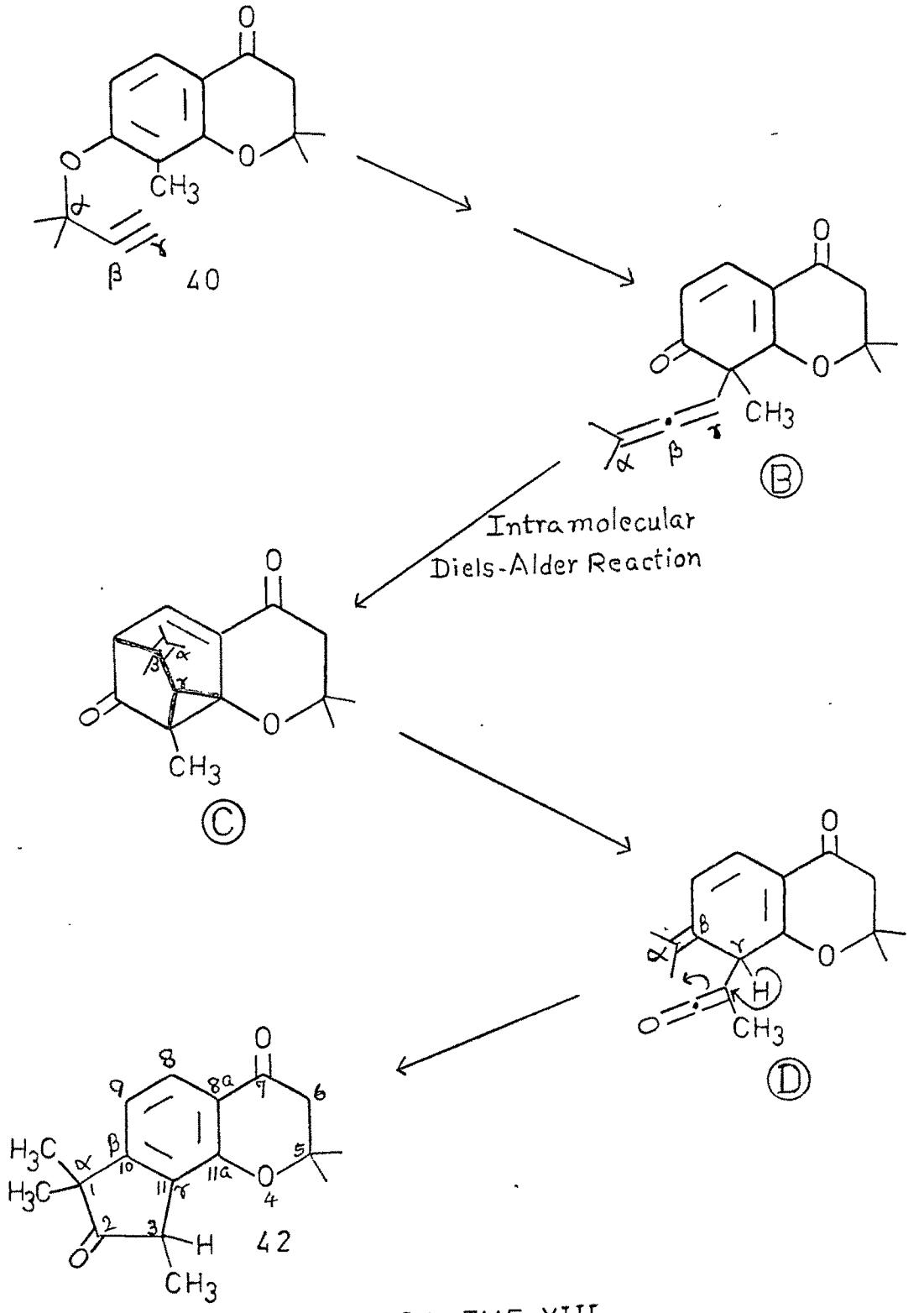
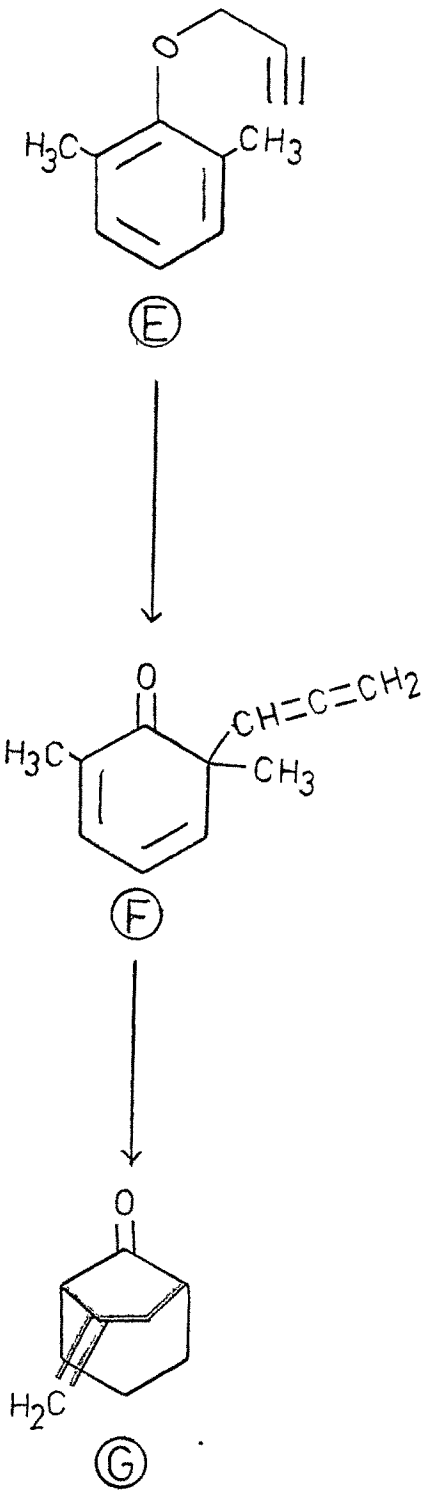


SCHEME-XIII

now become the part of the new benzene ring and the carbon carrying the gem-dimethyl group becomes the part of cyclopentanone ring system.

Zsindely and Schmid[37] have made similar observation in the Claisen rearrangement of 2,6-dimethylphenyl propargyl ether and have suggested the formation of tricyclic ketone (G). In fact they reported that this tricyclic ketone can be converted to 2-Indanones, but no details are given.[44] [Scheme-XIV]



SCHEME-XIV

EXPERIMENTAL

EXPERIMENTAL

M.Ps. are uncorrected. pmr spectra were recorded on Perkin-Elmer R-32 90MHz spectrometer and 250.13MHz spectrometer using TMS as an internal standard. IR spectra were recorded on Shimadzu IR-408 spectrophotometer. Silica gel used for column chromatography with mesh size 60-120.

7-Allyloxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (21)

7-Hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (20) (1.9 gm, 0.01 mole), allyl bromide (1.2 gm, 0.01 mole) and anhyhdrous potassium carbonate (10 gm) were taken in dry acetone (100 ml) and refluxed for 6 hrs. on waterbath, ~~then~~ Reaction mixture was allowed to cool and poured in water, the separated oil was extracted with solvent ether, etheral layer was washed with aq. NaOH (2%) and [illegible] evaporated to give 7-allyloxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (21) as oil, which was directly taken for next step.

7-Hydroxy-8-allyl-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (22)

(21) from previous step was taken in 50 ml of freshly distilled N,N-dimethylaniline and refluxed for 8 hrs, [illegible] reaction mixture was cooled and poured in cold dil. HCl, the solid separated was filtered and crystallised from benzene as white crystals, M.p. 124°C.

Analysis : Found : C, 72.55% ; H, 6.98%

$C_{14}H_{16}O_3$: requires : C, 72.41% ; H, 6.89%

2,5,5-Trimethyl-2,3,5,6-tetrahydro-7H-furo(2,3-h)benzopyran-7-one (23)

7-Hydroxy-8-allyl-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (23) (800 mg) was titurated with sulphuric acid (80%, 10 ml) in a waterbath for 10 minutes, the contents were poured on crushed ice, the separated product was filtered and washed with dil. sodium hydroxide solution. It crystallised from mixture of benzene and petroleum ether (1:1) as white needles. M.p. 92°C, yield 500 gm, 62.5%.

Analysis : Found : C, 72.63% ; H, 6.61%

$C_{14}H_{16}O_3$: requires : C, 72.41% : H, 6.89%

2,5,5-Trimethyl-5,6-dihydro-7H-furo(2,3-h)benzopyran-7-one (24)

Sodium salt of 7-hydroxy-8-allyl-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one was prepared by dissolving 1.0 gm of (22) in 1% NaOH (18 ml) and the aq. solution was evaporated. The sodium salt of (22) (0.254 gm, 0.001 mole) was suspended in benzene (200 ml), dichloro-bis (benzonitrile) palladium (0.001 mole, .383 gm) was added and stirred at room temperature for 1/2 hr. The suspension became red color during the stirring,

it was refluxed for 2 h. when the palladium metal separated out and the solution turned colourless, palladium was filtered, the filtrate concentrated and the product chromatographed on silica gel. Elution with pet. ether (60-80°C) gave benzonitrile and subsequent elution with benzene gave 2,5,5-trimethyl-5,6-dihydro-7H-furo(2,3-h)benzopyran-7-one (24). It crystallised from mixture of pet. ether and benzene (1:2) as light yellow crystals. M.p. 124°C, yield 0.080 gm, 34.5%.

Analysis	:	Found	:	C, 72.71%	;	H, 6.46%
$C_{14}H_{14}O_3$	:	requires	:	C, 73.04%	;	H, 6.09%

7-Allyloxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (26)

7-Hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (25) (2.04 g, 0.01 mole), allyl bromide (1.2 g., 0.01 mole) and anhydrous potassiu carbonate (10 gm) were taken in dry acetone (100 ml) and refluxed on waterbath for 6 h., the reaction mixture was allowed to cool and poured in water, the separated solid was filtered and washed with dil. sodium hydroxide solution to give (26). It crystallised from pet. ether as white crystals. M.p. 74°C, yield : 1.8 gm, 73.8%.

Analysis	:	Found	:	C, 73.21%	;	H, 6.93%
$C_{15}H_{18}O_3$	:	requires	:	C, 73.17%	;	H, 7.32%

7-Hydroxy-6-allyl-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (27)

(26) (1 gm) was taken in N,N-dimethylaniline (5 ml) and refluxed for 8 h., the reaction mfixture was cooled and poured in ice cold dil. HCl, the separated solid was filtered and crystallized from benzene

. M.p. 145°C, yield 800 mg, 80%

Analysis : Found : C, 72.79% ; H, 6.84%

$C_{15}H_{18}O_3$: requires : C, 73.17% ; H, 7.32%

2,7,7,9-Tetramethyl-2,3,6,7-tetrahydro-5H-furo-(3,2-g)benzopyran-5-one (28)

(27) (800 mg) was triturated with sulphuric acid (80%, 10 ml in a waterbath for 10 minutes, the contents was poured into crushed ice, the separated product was filtered and washed with di. sodium hydroxide solution, it cryst-allized from mixture of benzene and pet. ether (1:1) to give (28). M.p. 79°C, yield 450 mg, 56.2%.

Analysis : Found : C, 72.16% ; H, 6.98%

$C_{15}H_{18}O_3$: requires : C, 73.17% ; H, 7.32%

2,7,7,9-Tetramethyl-6,7-dihydro-5H-furo(3,2-g)benzopyran-5-one (29)

Sodium salt of 7-hydroxy-6-allyl-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (27) was prepared by dissolving 1.0 gm of (27) in 1% NaOH (20 ml) and then aq. solution was evaporated. The sodium salt of (34) (.270 g, 0.001

mole) was suspended in benzene (200 ml), dichloro-bis(benzonitrile) palladium (0.001 mole, .383 g) was added and stirred at room temperature for 1/2 hr. The suspension became clear and intense red colour developed during stirring, it was refluxed for 2 hr. when the palladium metal separated out and the solution turned colourless. Palladium was filtered, the filtrate was concentrated and the product chromatographed on silica gel. Elution with pet. ether (60-80°C) gave benzonitrile and susbsequent elution with benzene gave 2,7,7,9-tetramethyl-6,7-tetrahydro-5H-furo(3,2-g)benzopyran-5-one (29). It crystallised from mixture of pet. ether and benzene (1:2) as light yellow crystals of (29). M.p. 186°C, yield 0.1 g, 41.3%

7-(3'-methyl-but-2-enyl)oxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (30)

A mixture of 7-hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (25) (1.92 g., 0.01 mole), prenyl bromide (1.5 gm., 0.01 mole) and anhydrous potassium carbonate (10 g) was refluxed in dry acetone (100 ml) in waterbath for 8 hr. The reaction mixture poured into cold water, separated solid filtered, washed with dilute sodium hydroxide solution. The product (30) crystallized from pet. ether. M.p. 95°C, yield 2.1 gm, 76.6%.

Analysis	:	Found	:	C, 74.32%	;	H, 7.85%
$C_{17}H_{22}O_3$	:	requires	;	C, 74.45%	;	H, 8.03%

7-Hydroxy-6-(1',2'-dimethyl-2-propenyl)2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (31)

7-Prenyloxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (30) (1 gm) was refluxed with N,N-dimethylaniline (5ml) for 8 hr. The reaction mixture poured in cold dil. HCl,

the separated solid was filtered and crystallized from benzene + petroleum ether mixture (1:2). M.p. 117°C, yield 750 mg, 75%.

Analysis	:	Found	:	C, 74.89%	;	H, 8.04%
$C_{17}H_{22}O_3$	:	requires	:	C, 74.45%	;	H, 8.03%

2,2,3,7,7,9-Hexamethyl-2,3,6,7-tetrahydro-5H-furo(3,2-g)-benzopyran-5-one (32)

(31) (700 mg) was titurated with 80% H_2SO_4 (4 ml) and heated on waterbath for 15 minutes. The content was poured on crushed ice, separated product filtered and washed with dilute sodium hydroxide solution. Residue crystallized from pet. ether to give (32). M.p. 94°C, yield 500 mg, 66.7%.

Analysis	:	Found	:	C, 74.00%	;	H, 7.55%
$C_{17}H_{22}O_3$	:	requires	:	C, 74.45%	;	H, 8.03%

7-(3-prop-2-ynyloxy)-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (36)

A mixture of 7-hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (20) (1.92 gm, 0.01 mole), propargyl bromide (1.2 gm, 0.01 mole), fused potassium carbonate (10 gm) was refluxed in dry acetone (100 ml) in waterbath for 10 hr. The reaction mixture poured into cold water, the separated product filtered and washed with dilute alkali solution to remove any unreacted material. It crystallized from pet. ether to give (36). M.p. 61°C, yield 2.0 gm, 86.9%.

Analysis : Found : C, 73.14% ; H, 6.33%

$C_{14}H_{14}O_3$: requires : C, 73.04% ; H, 6.08%

6,6-Dimethyl-6,7-dihydro-8H-pyrano(2,3-h)benzopyran-8-one (37)

(36) (1.0 g) was refluxed with N,N-dimethylaniline (10 ml) for 6 hrs. The reaction mixture poured in cold dil. HCl, the separated solid was filtered and crystallised from pet. ether. M.p. 97°C, yield 550 mg, 55%.

Analysis : Found : C, 72.61% ; H, 6.43%

$C_{14}H_{14}O_3$: requires : C, 73.04% ; H, 6.09%

7-(1',1'-dimethylprop-2-ynyloxy)-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (38)

A mixture of 7-hydroxy-2,2-dimethyl-2,3-dihydro-4H-benzopyran-4-one (20) (1.9 gm, 0.01 mole) 3-chloro-3-methyl-but-1-yne (1.1 gm), fused plotassium carbonate (10 gm) and few crystals of potassium iodide was refluxed in dry acetone (100 ml) in waterbath for 10 hr. The reaction mixture poured into cold water, the separated product filtered and washed with dilute alkali solution to remove any unreacted material, it was directly taken for next step.

2,2,6,6-Dimethyl-2,3-dihydro-8H-pyrano(2,3-h)benzopyran-8-one (39)

The crude product (38) was refluxed with N,N-dimethyl-aniline for 6 hr. The reaction mixture poured in cold dil.

HCl, the separated solid was filtered and crystallised from pet. ether. M.p. 99-100°C.

Analysis : Found : C, 74.40% ; H, 7.22%

$C_{16}H_{18}O_3$: requires : C, 74.42% ; H, 6.97%

7-(1',1'-dimethyl-prop-2-ynyloxy)-2,2,8-trimethyl-2,3-dihydro 4H-benzopyran-4-one (40)

A mixture of 7-hydroxy-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (25) (2.05 gm, 0.01 mole), 3-chloro-3-methyl-but-1'-yne (1.1 gm, 0.01 mole) fused potassium carbonate (10 gm) and few crystals of potassium iodide was refluxed in dry acetone (100 ml) on waterbath for 10 hr. The reaction mixture poured into cold water, the separated product filtered and washed with dilute alkali solution to remove any unreacted material, it crystallised from pet. ether. M.p. 74°C, yield 2.2 gm, 80.9%

Analysis : Found : C, 74.59% ; H, 7.19%

$C_{17}H_{20}O_3$: requires : C, 75.00% ; H, 7.35%

Migration of (40) in N,N-dimethylaniline

7-(1',1-dimethyl-3'-prop-2-ynyloxy)-2,2,8-trimethyl-2,3-dihydro-4H-benzopyran-4-one (40) (1.0 gm) was refluxed in N,N-dimethylaniline (10 ml) for 6 hr then reaction mixture was cooled and poured into mixture of crushed ice and con.

HCl, the crude solid separated was purified by column chromatography. On elution with pet. ether gave (42). It was crystallised from pet.ether. M.p. 131°C,yield 450 mg, 45%.

Analysis	:	Found	:	C, 74.57%	;	H, 7.09%
$C_{17}H_{20}O_3$	:	requires	:	C, 75.00%	;	H, 7.35%

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