CHAPTER-IV

SYNTHESIS OF BENZOFUROBENZOPYRANS

AYAPIN AND DIOXO-BENZO-DIPYRAN

CARBOXYLIC ACIDS

CHAPTER -IV

SYNTHESIS OF BENZOFUROBENZOPYRANS, AYAPIN AND DIOXO-BENZO-DIPYRAN CARBOXYLIC ACIDS

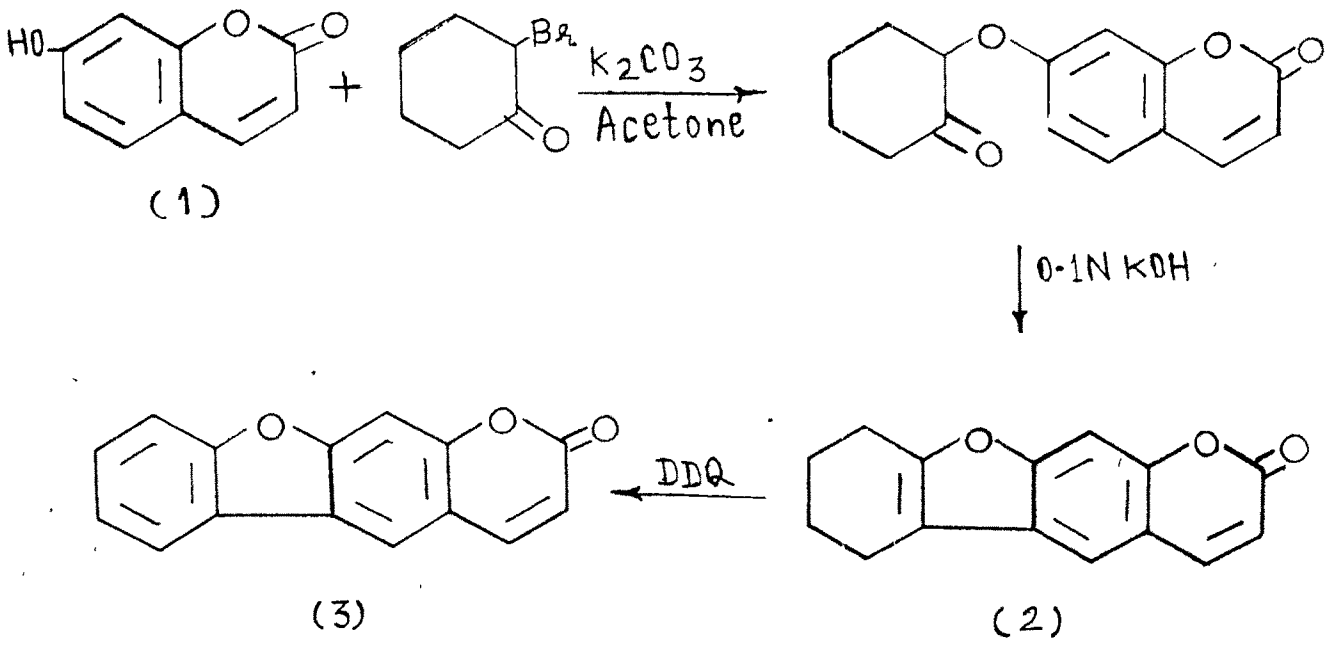
Benzofurocoumarins occur in nature and are well known for their estrogenic,[1] insecticidal,[2] antibacterial[3] activities. They play important role as phytoalexins.[4] Therefore, it was thought of interest to synthesise benzofurobenzopyran derivatives.

Macleod[5] [illegible] prepared dibenzofuran derivative by condensing 2-bromocyclohexanone with 7-hydroxy coumarin (1), followed by treatment with aq. KOH under reflux to give (2), which was readily dehydrogenated to give -benzofuro (3,2-g) (1)-benzopyran-2(H)-one (3). [Scheme-1]

Ahluwalia and coworkers[6] [illegible] synthesised 8-aryl-7-phenyl-benzofuro (3,2-g)[1]-benzopyran-9(H)-one (7). They [illegible] condensed 2-bromocyclohexanone with 2,4-dihydroxy-benzophenone (4) which gave (5) which was further condensed with phenyl-acetylchloride under the conditions of phase transfer catalysis to give (6). This was cyclised in alcoholic KOH and was further dehydrogenated with DDQ to give (7). [Scheme-2]

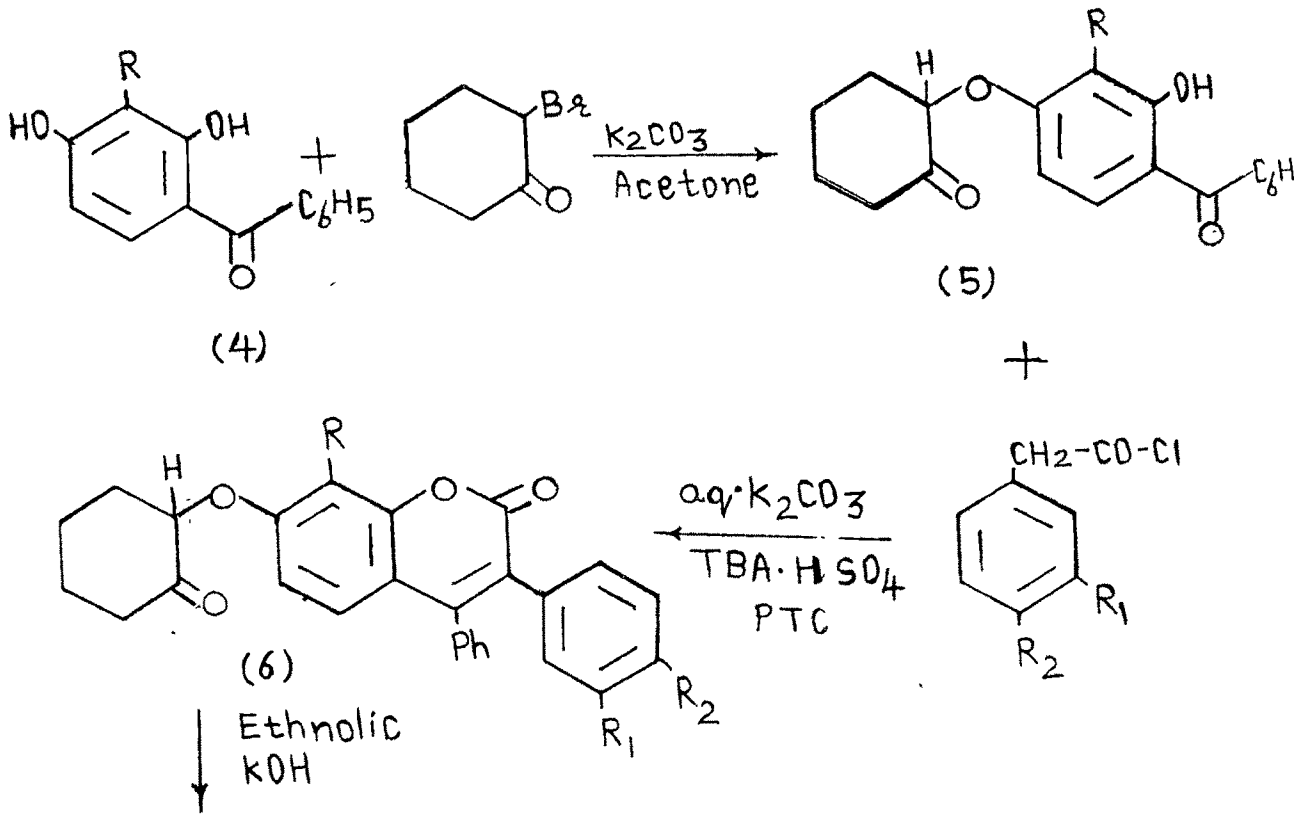
Desai and Trivedi[7] reported the synthesis of 2-oxo-2H-

Scheme - 1 Macleod et al[5]

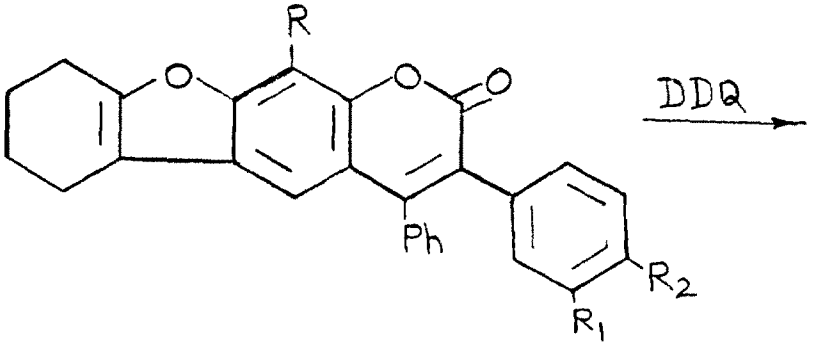


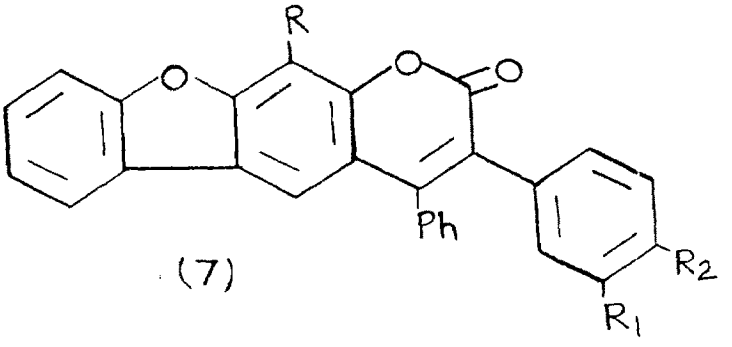
(1) (2) (3)

Scheme - 2 Ahluwalia and Coworkers[6]



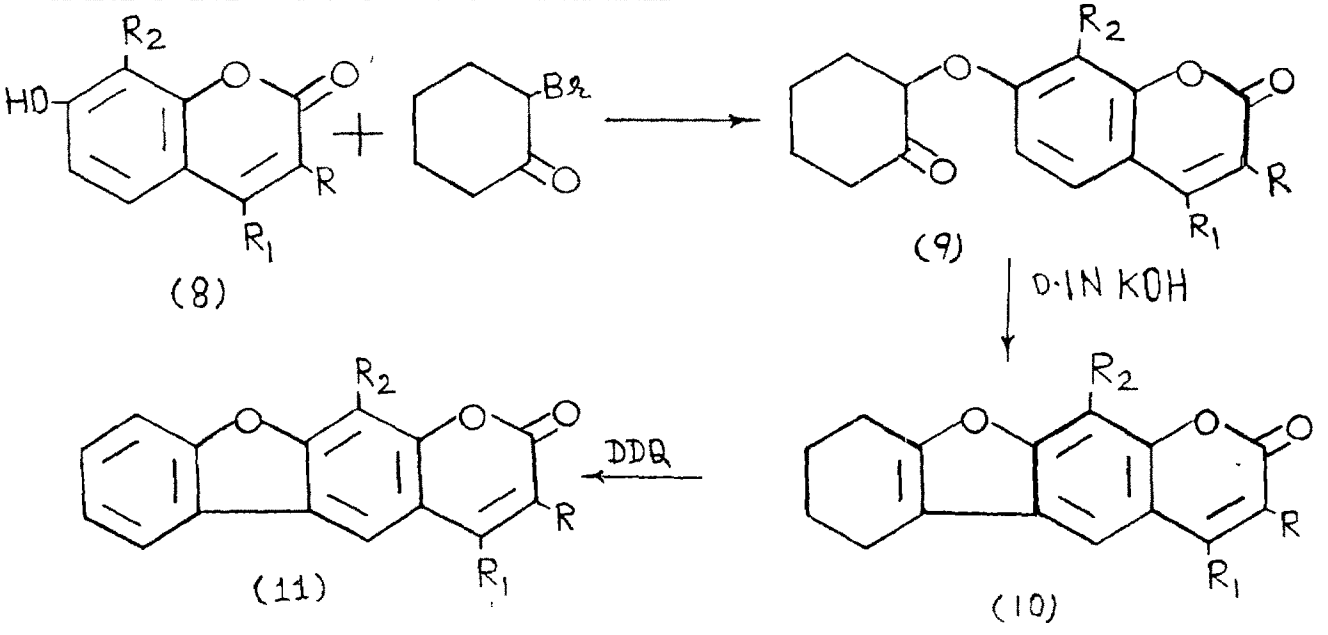
(4) (5) (6)





(7)

Scheme - 3 Desai and Trivedi[7]



II(a) R = H , $R_1 = R_2 = CH_3$

II(b) $R = R_2 = H$, $R_1 = C_6H_5$

II(c) $R = R_1 = C_6H_5$, $R_2 = H$

benzofuro(3,2-g)-benzopyran-derivatives (11) by condensing different 7-hydroxycoumarins (8) with 2-bromocyclohexanone which gave (9). This was cyclised with O.1N alcoholic KOH followed by dehydrogenation with DDQ gave (11). [Scheme-3].

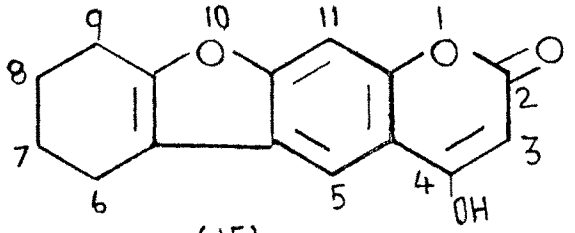
PRESENT WORK

Synthesis of 2-oxo-2H-benzofuro(3,2-g)-benzopyran (18)

Synthesis of 6,7,8,9-tetrahydro-4-hydroxy-2-oxo-2H-benzofuro(3,2-g)-benzopyran (15) prepared from 2,4-dihydroxy acetophenone (12) is described on page No. 224-231 (Scheme-4)

Compound (15) when refluxed with p-toluenesulfonylchloride in presence of anhydrous potassium carbonate in dry acetone gave 6,7,8,9-tetrahydro-4-p-tosyloxy-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (16). The structure of this compound was assigned on the basis of PMR spectra of this compound taken in (DMSO-d_6) (Fig. 1). The broad multiplet at δ 1.6-2.0 indicated four protons at C-7 and C-8. Singlet at δ 2.3 indicated $-CH_3$ group of tosyl ring. Multiplet at δ 2.4-2.8 indicated four protons at C-6 and C-9. Singlet at δ 6.2 indicated proton at C-3. Two doublets at δ 7.05 and 7.9 J=9Hz indicated two protons at C-2' and C-3'. Two doublets at δ 7.3 and 7.55, J=9Hz indicated two protons at C-5' and C-6'. Two singlets at δ 7.45 and 7.75 indicated two protons at C-5 and C-11.

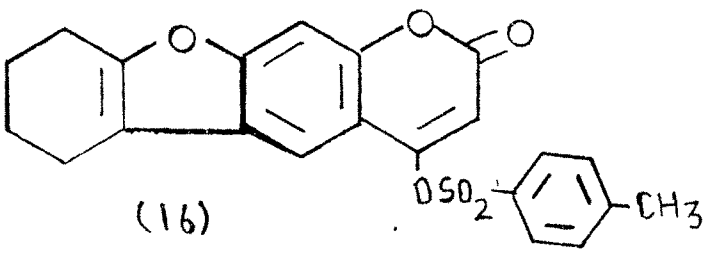
Scheme-4



(15)

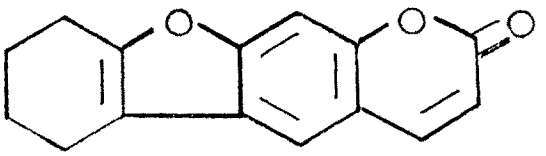
p-Tosylchloride

K_2CO_3, Acetone



(16)

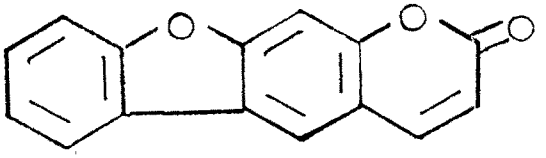
Zn/HCl



(17)

Pd/C, Ph_2O

Δ



(18)

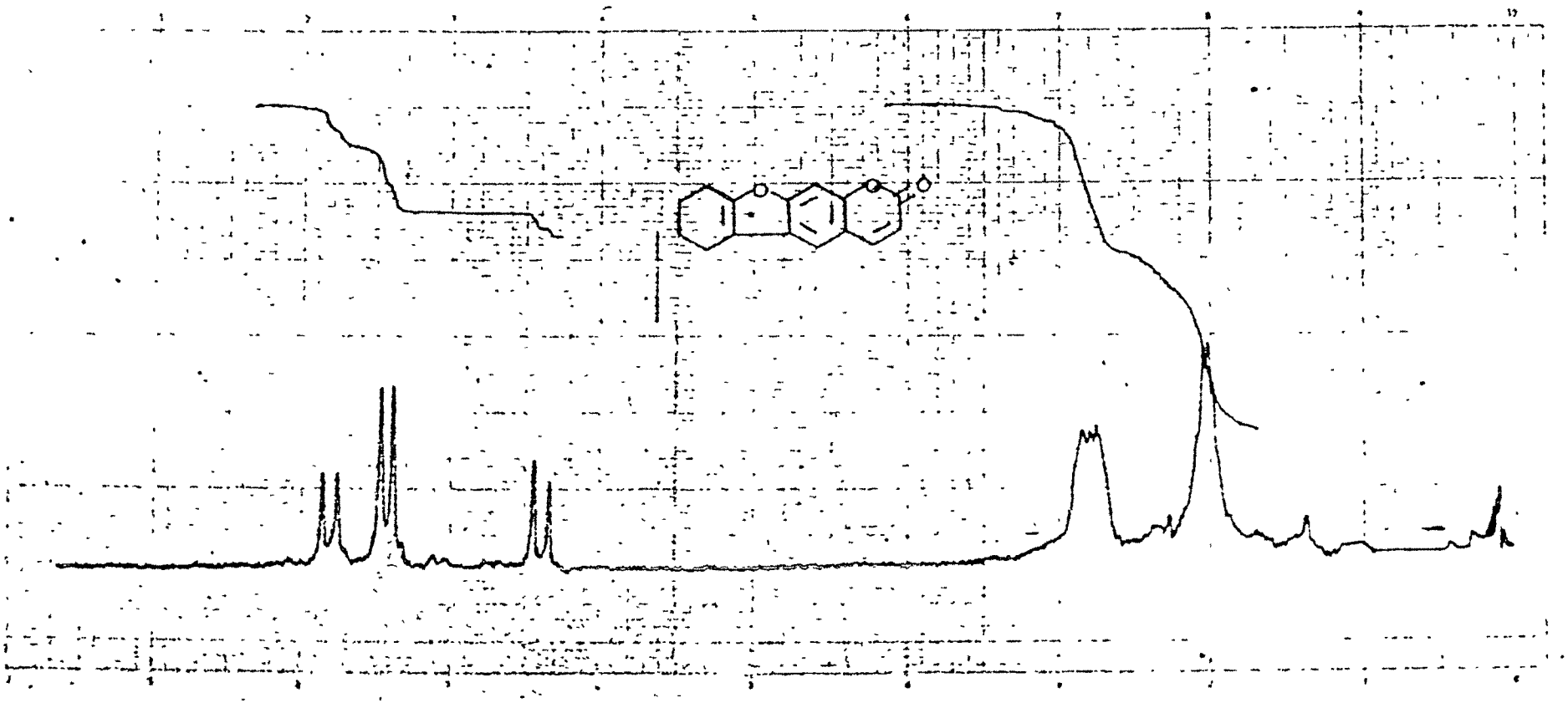
(fig-1): 6,7,8,9-tetrahydro-4-p-tosyloxy-2-oxo-2H-benzofuro(3,2-g) benzopyran. (16)

Reductive detosyloxylation[8] of compound (16) by zinc dust and hydrochloric acid gave 6,7,8,9-tetrahydro-2-oxo-2H-benzofuro(3,2-g)-benzopyran (17). The structure of this compound was assigned on the basis of its PMR spectrum taken in ($CDCl_3$) (Fig. 2). The multiplet at δ 1.7-2.1 indicated four protons at C-7 and C-8. The another multiplet at δ δ 2.4-2.8 indicated four protons at C-6 and C-9. The two doublets at δ 6.25 and 7.75, J=9Hz indicated orthocoupling of two protons at C-3 and C-4. Two singlets at δ 7.25 and 7.32 indicated two protons at C-11 and C-5. Compound (17) when refluxed in diphenylether with palladised charcoal (10%) gave 2-oxo-2H-benzofuro-(3,2-g)-benzopyran (18). The structure of this compound was assigned on the basis of its PMR spectrum taken in ($CDCl_3$) (Fig. 3). The doublet at δ 6.35, J=9Hz indicated proton at C-3. The another doublet is mixed with other signals of aromatic protons. The broad multiplet from δ 7.2-8.0 indicated all remaining aromatic protons.

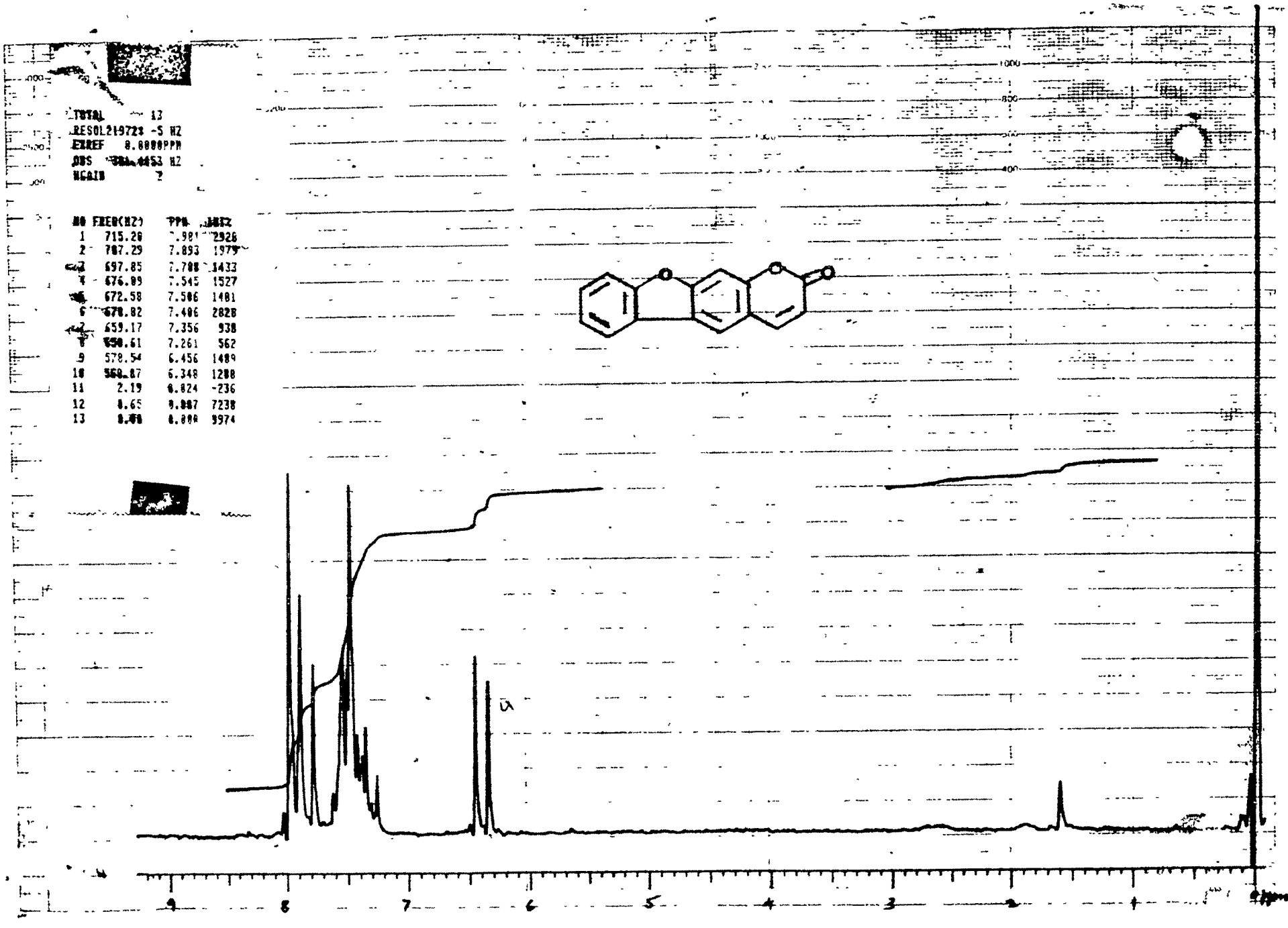
Synthesis of 11-methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (25)

Synthesis of 6,7,8,9-tetrahydro-4-hydroxy-11-methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (22) prepared from 2,4-dihydroxy-3-methylacetophenone (19) is described on page No. 235 - 239

Compound (22) was then refluxed with p-toluenesulfo-

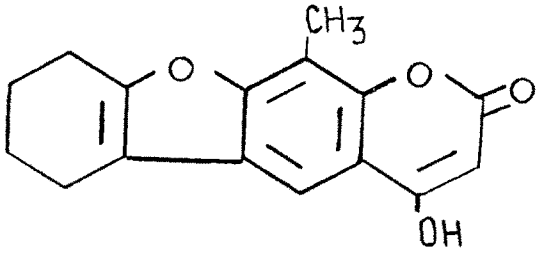


(fig-2): 6,7,8,9-tetrahydro-2-oxo-2H-benzofuro(3,2-g)-benzopyran.(17)



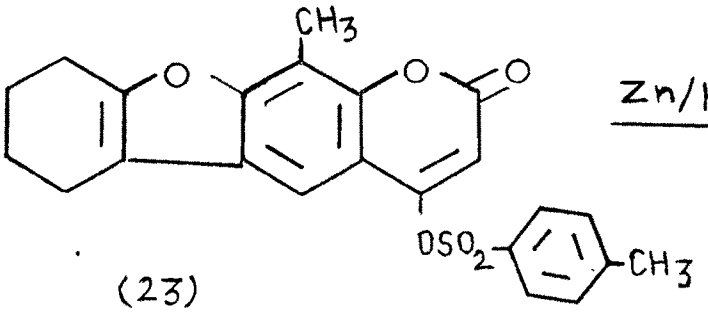
(fig-3): 2-OXO-2H-benzofuro-(3, 2-g)-benzopyran. (18).

Scheme-5



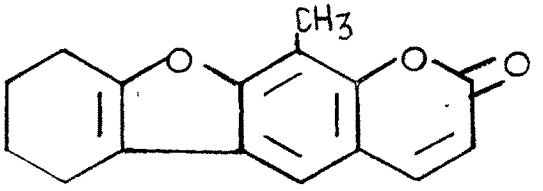
Et_2CO_3 / Pul Na →

(22)



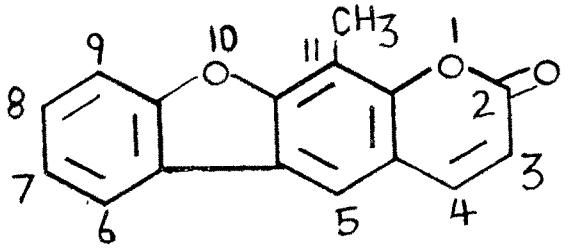
Zn/HCl →

(23)



Pd/C, Ph_2O / Δ →

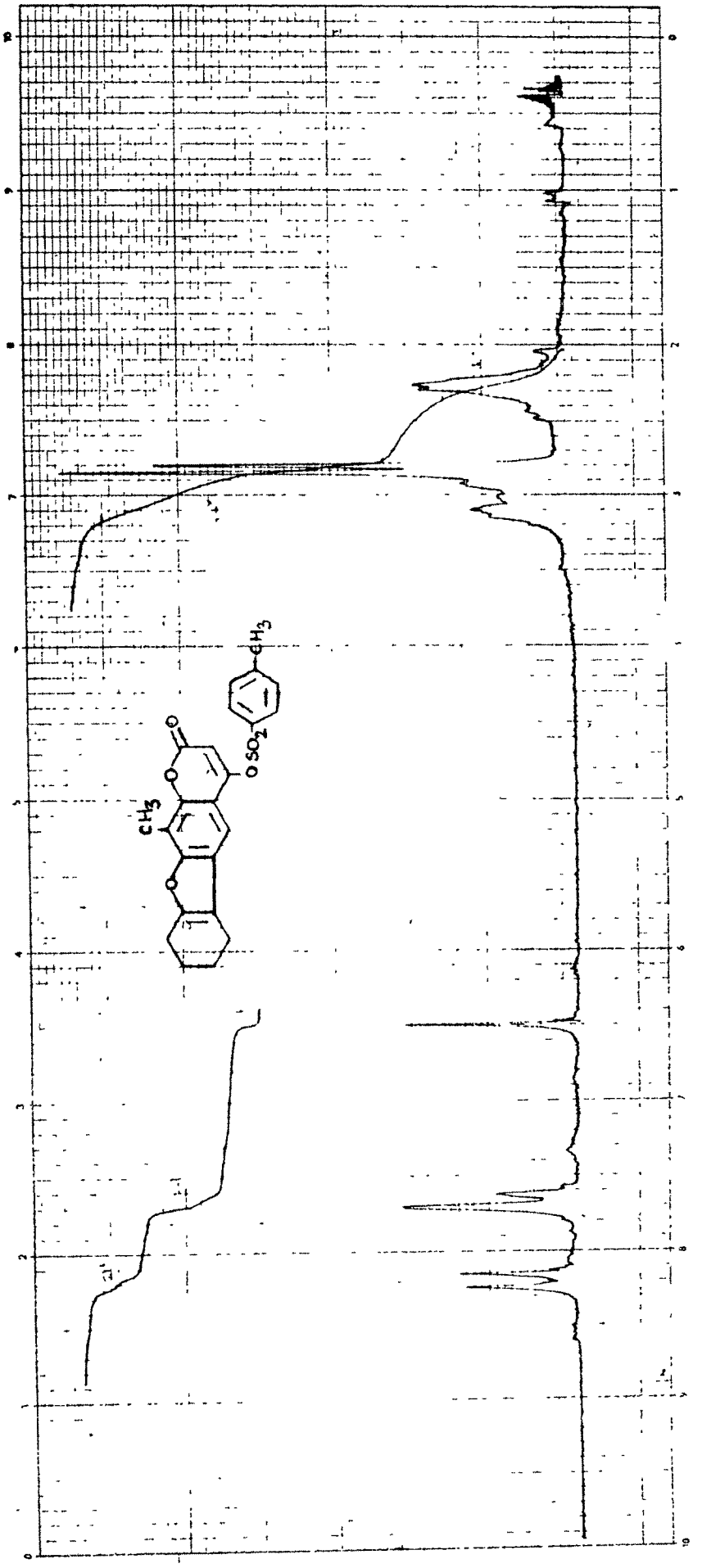
(24)



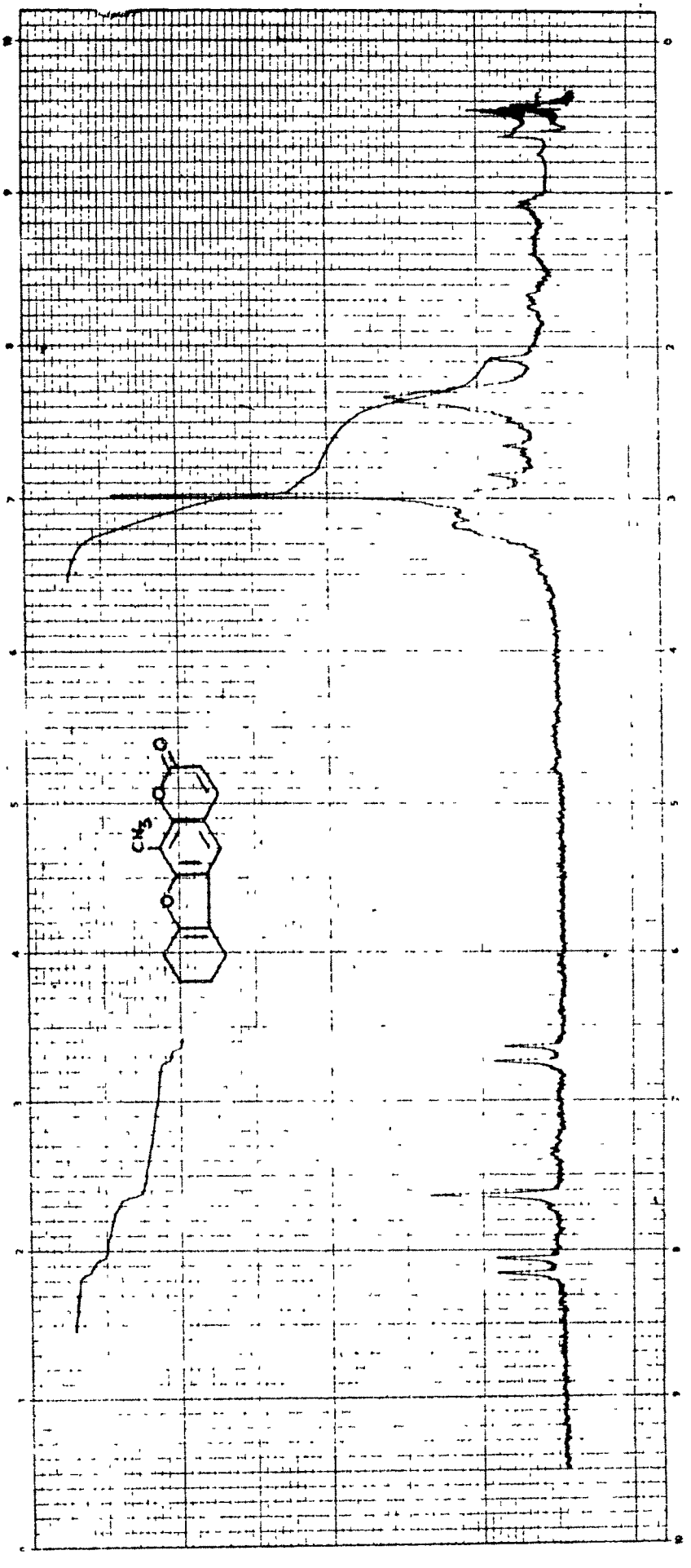
(25)

nylchloride in presence of anhydrous potassium crbonate in dry acetone gave 6,7,8,9-tetrahydro-4-(p-toluenesulfonyloxy) 11-methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (23). (scheme-5) The structure of this compound was established by its PMR spectrum taken in ($CDCl_3$) (Fig. 4). Multiplet at δ 1.65-2.1 indicated four protons at C-7 and C-8. Two singlets at δ2.55 indicated two $-CH_3$ groups. The multiplet at δ2.4-2.8 indicated 4 protons at C-6 and C-9. Singlet at δ 6.15 indicated proton at C-3. The singlet at δ 7.35 indicated proton at C-5. The another singlet at δ 7.4 indicated two protons at C-2' and C-3'. Singlet at δ7.8 indicated proton at C-5' and another singlet at δ 7.9 indicated proton at C-6'.

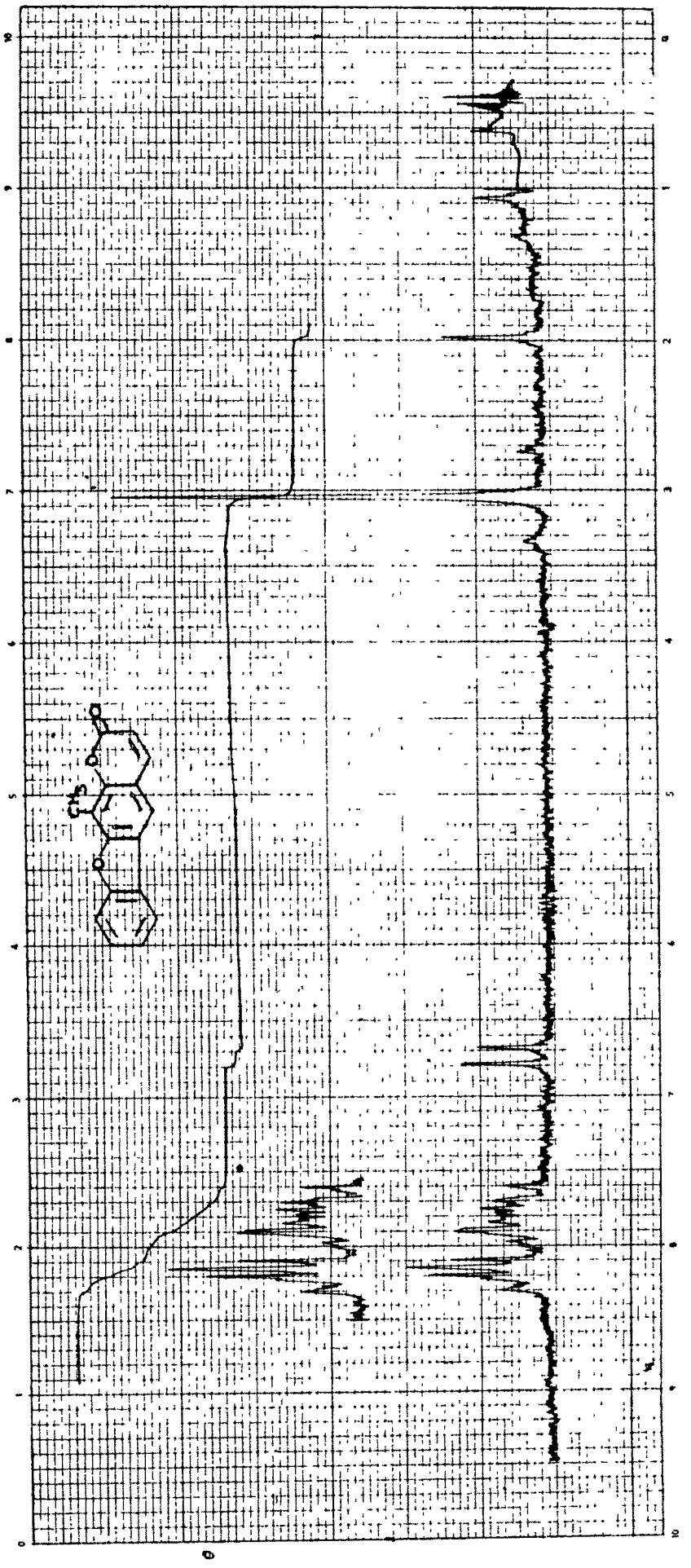
Compound (23) on reductive detosyloxylation[8] with zinc dust and HCl gave 6,7,8,9-tetrahydro-11-methyl-2-oxo-2H-benzofuro (3,2-g)-benzopyran (24). The structure of this compound was assigned on the basis of its PMR spectrum taken in ($CDCl_3$) (Fig. 5). Multiplet from δ 1.6-2.0 indicated four protons at C-7 and C-8. The another multiplet from δ2.4-2.85 indicated four protons at C-6 and C-9. Singlet at δ 2.55 indicated $-CH_3$ group at C-11. Two doublets at δ6.3 and 7.8, J=9Hz indicated orthocoupling of two protons at C-3 and C-4. Singlet at δ 7.25 indicated aromatic proton at C-5. Compound (24) was refluxed with palladised charcoal (10%) in diphenylether gave 11-methyl-2-oxo-2H-benzofuro-



(fig-4) : 6,7,8,9- tetrahydro-4-p- tosyloxy-11-methyl-2-oxo- 2H- benzofuro-
(3,2-g)- benzopyran. (23)



(Fig-5) : 6, 7, 8, 9 - tetrahydro - 11 - methyl - 2 - oxo - 2H - benzofuro (3, 2 - g) - benzopyran. (24)



(Fig-6): 11-Methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (25).

(3,2-g)-benzopyran (25) [Scheme-5]. The structure of this compound was established by PMR spectrum taken in ($CDCl_3$) (Fig. 6). The signals are as follows : Singlet at δ 2.6 indicated $-CH_3$ at C-11. The doublet at δ 6.3, J=9Hz indicated orthocoupling of proton at C-3. Multiplet from δ 7.1-7.9 indicated all remaining aromatic protons.

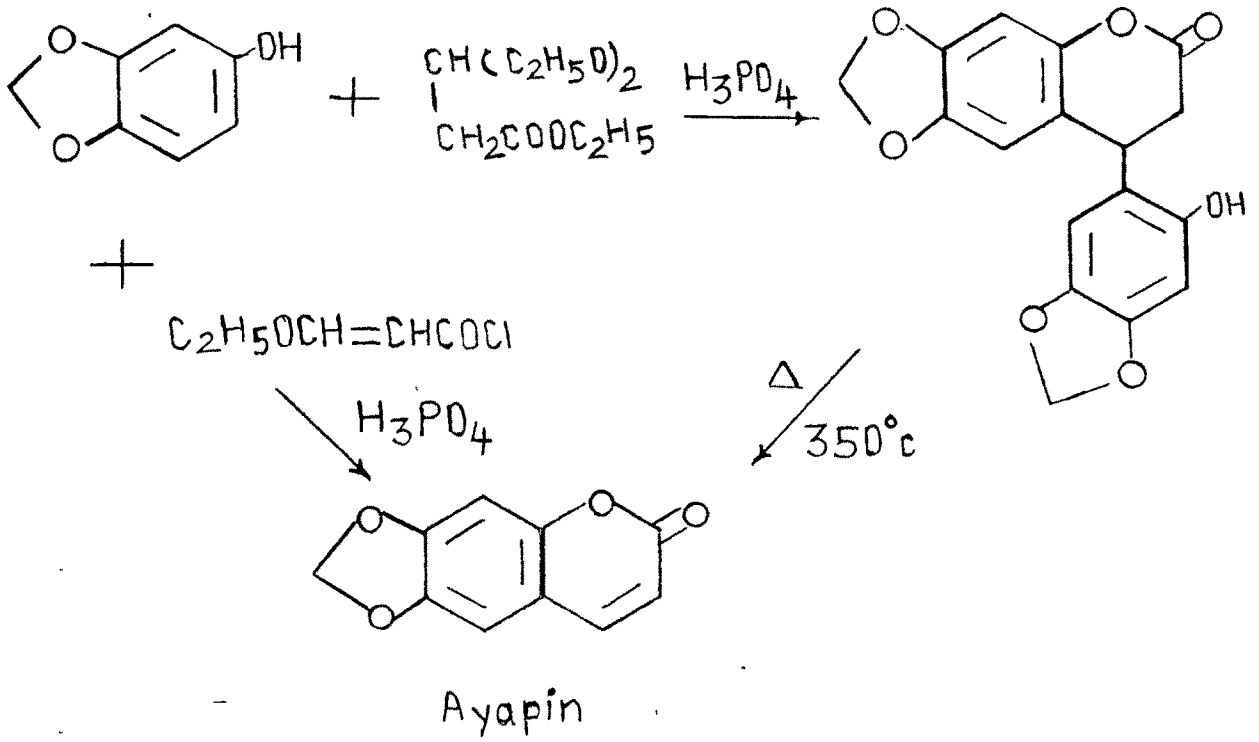
Synthesis of Ayapin (34) and 4-chloroayapin (37)

Ayapin is naturally occuring coumarin which exhibits hemostatic[9] and antibiotic[10] activities. Three methods are reported[11] in literature for the synthesis of ayapin.

Crosby and coworkers[12] reported the synthesis of ayapin from 3,4-methylnedioxy phenol which on reaction with ethyl 3,3-diethoxypropionate and phosphoric acid gave 3,4-dihydro-4-(3',4'-methylenedioxy-6'-hydroxyphenyl)-6,7-methylenedioxy coumarin which on heating at 350°C gave ayapin. 3,4-Methylene-dioxyphenol on reaction with 3-ethoxy acrylylchloride and phosphoric acid gave ayapin directly. [Scheme-6]

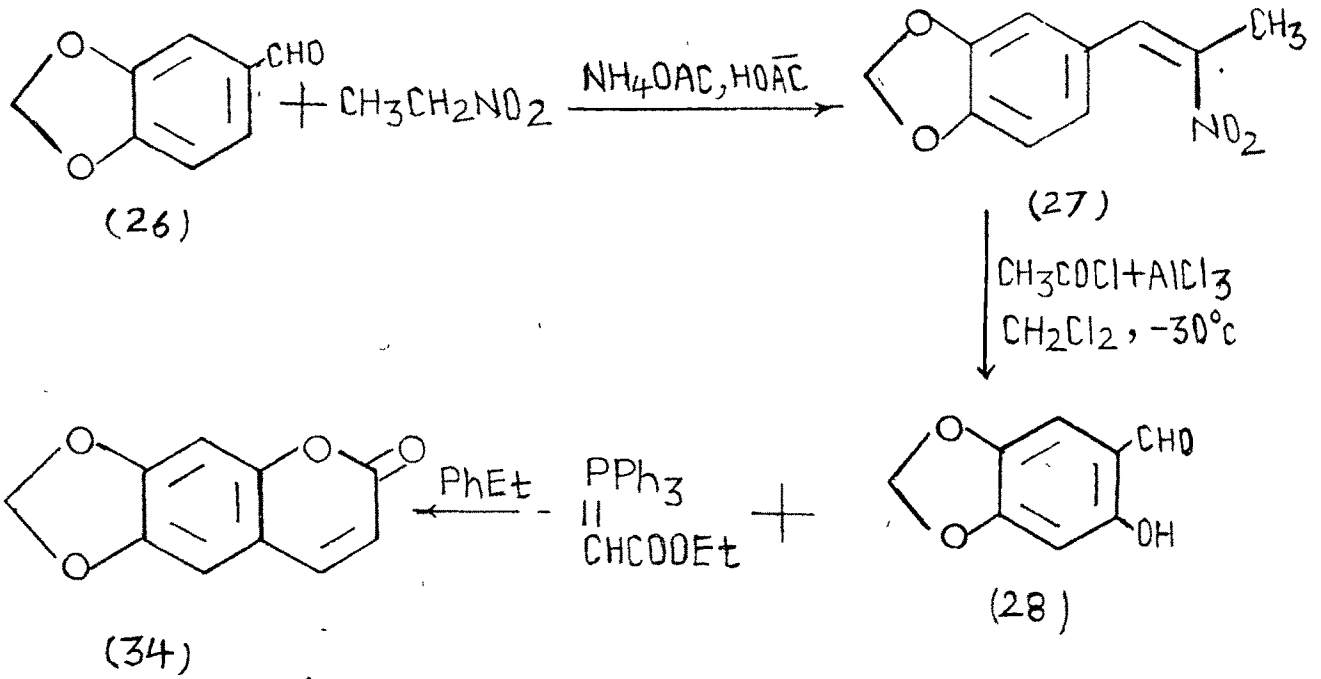
Kelkar and coworkers[13] synthesised ayapin by starting with piperonal (26) which was converted to β-methyl-β-nitro-styrene (27) using nitroethane and ammonium acetate. (27) was converted to 2-hydroxy-4,5-methylenedioxy benzaldehyde (28) by the reaction of acetyl chloride and aluminium chloride at -30°C. It was then converted to ayapin by intramolecular Wittig reaction using the corresponding ylide. [Scheme-6]

Scheme - 6 Crosby and Coworkers[12]



Ayapin

Scheme - 6 Kelkar and Coworkers[13]

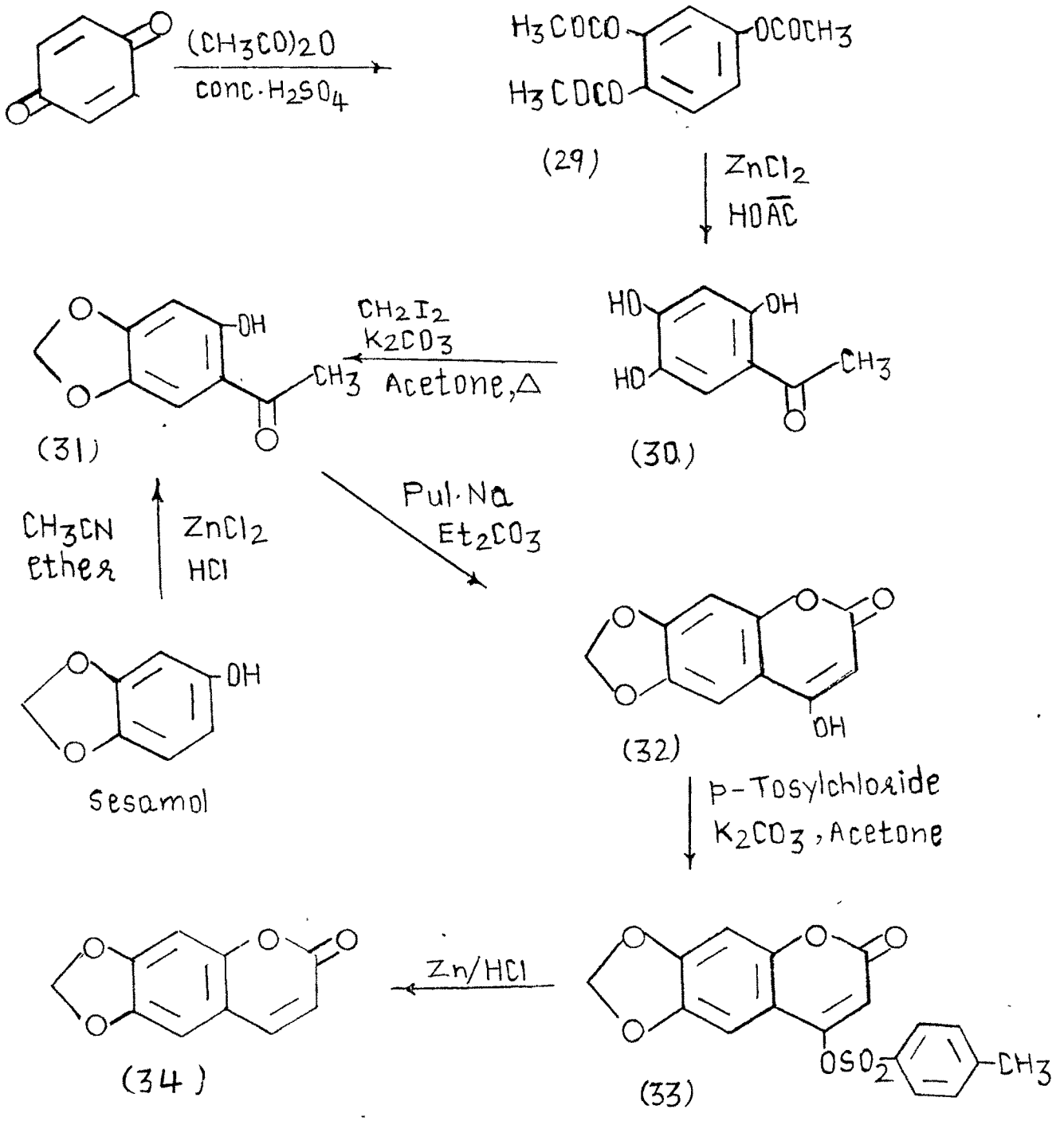


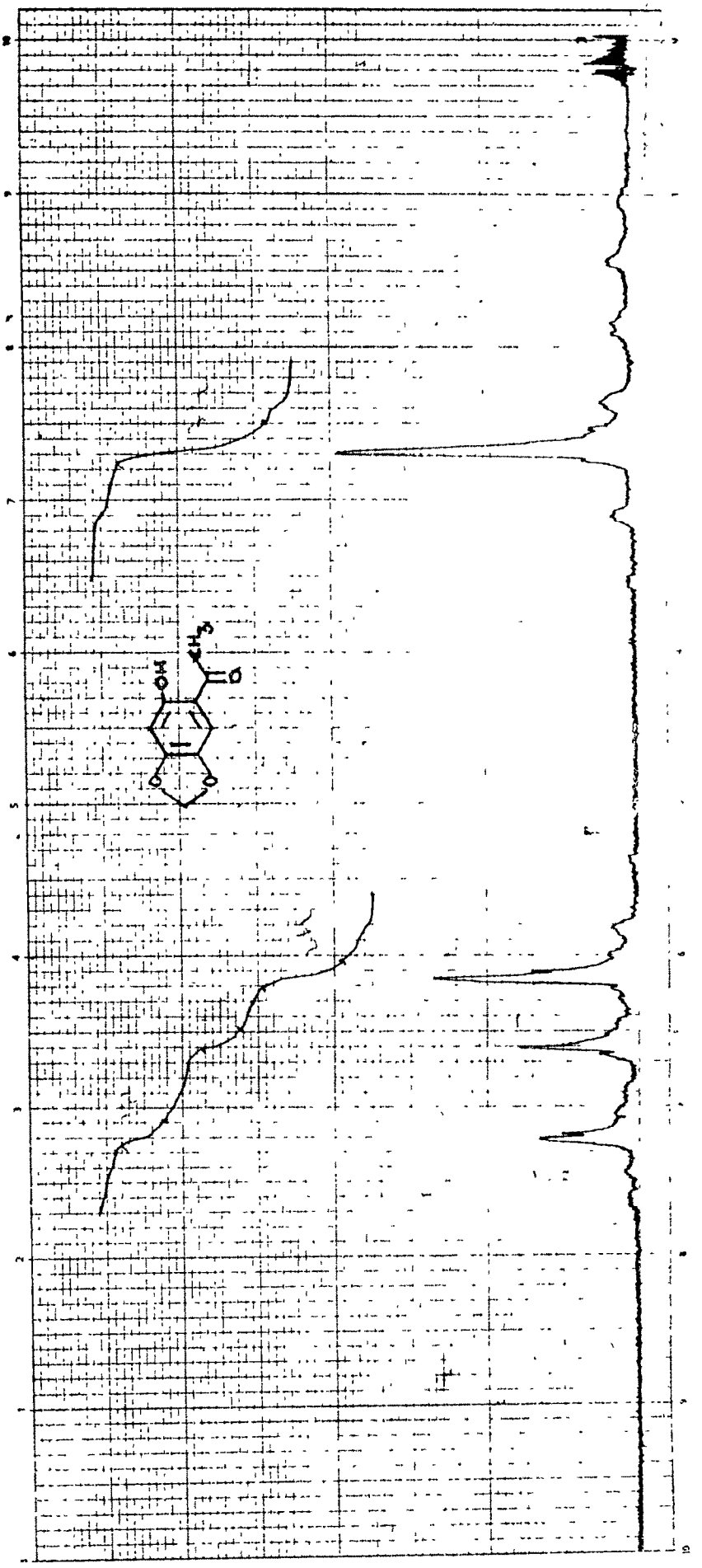
To synthesise ayapin the technique of preparing unsaturated coumarin ring by tosylation followed by reductive detosyloxylation of 6,7-methylenedioxy-4-hydroxy coumarin, is used.

Benzoquinone on acetylation with acetic anhydride and conc. sulfuric acid gave hydroxyhydroquinone triacetate (29). This when refluxed with zinc chloride and acetic acid gave 2,4,5-trihydroxyacetophenone (30). This was condensed with diiodomethane in presence of anhydrous potassium carbonate and dry acetone to give 4,5-methylenedioxy-2-hydroxyacetophenone (31) [Scheme-7], which was also prepared from sesamol by Hoesch method.[14] The structure of this compound was established by its PMR spectrum taken in ($CDCl_3$) (Fig. 7). Singlet for 3H at δ 2.45 indicated -$COCH_3$ group. Singlet at δ 5.9 is for methylenedioxy group while singlet at δ 6.3 is for aromatic proton at C-3 and singlet at δ 7.05 indicated aromatic protons at C-6.

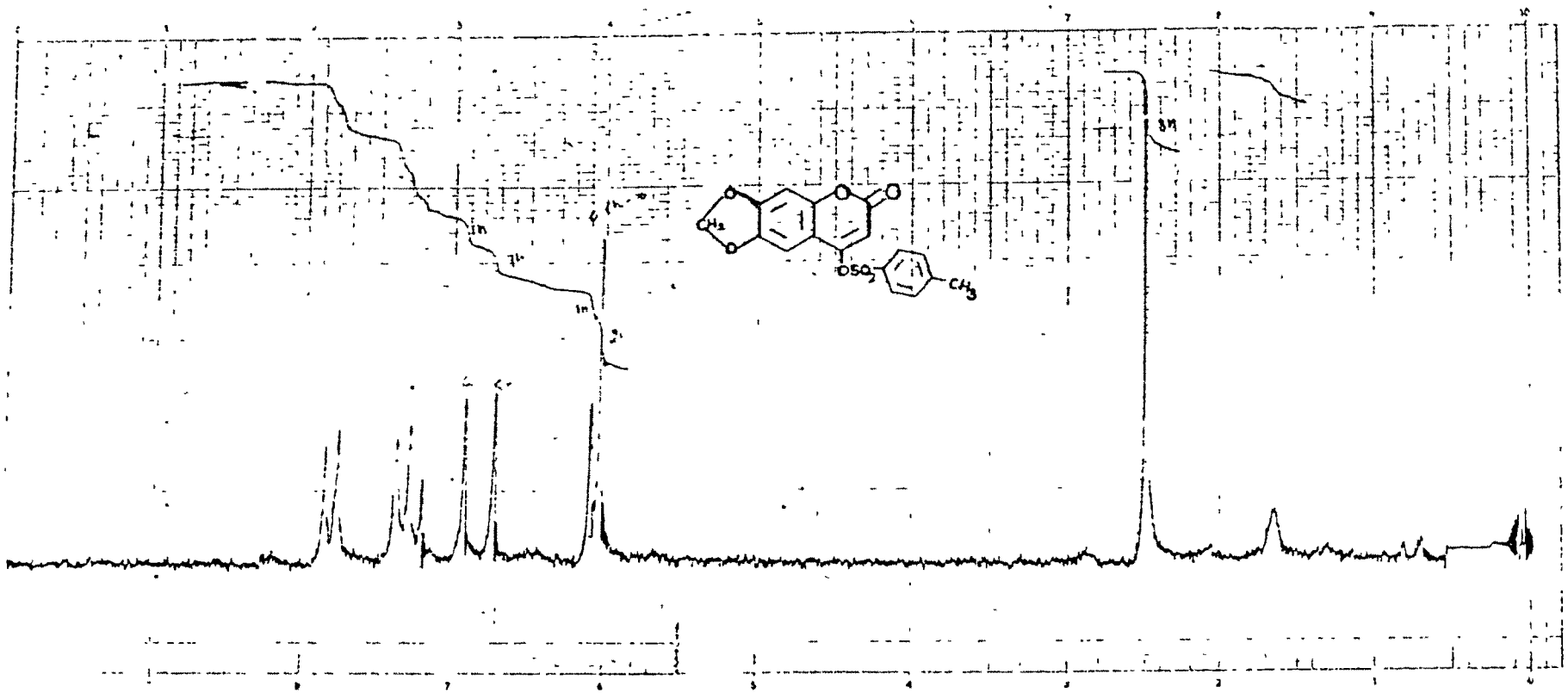
Compound (31) was condensed with diethylcarbonate in presence of pulverised Na to give 4-hydroxy-6,7-methylenedioxy-2-oxo-2H-benzopyran (32). This when condensed with p-toluenesulfonylchloride in presence of anhydrous potassium carbonate and dry acetone gave 4-(p-toluenesulfonyloxy)-6,7-methylenedioxy-2-oxo-2H-benzopyran (33). The structure of this compound was assigned on the fbasis of its PMR spectrum taken in ($CDCl_3$) (Fig. 8). Singlet at δ 2.45 is for -CH_3 group of tosyl ring. Singlet at δ 5.9 is for -O-CH_2-O- group. The singlet at δ 6.05 is for proton at C-3. Two singlets at δ 6.7 and δ6.85 are for protons at C-8 and C-6. The doublet at δ7.28 J=9Hz is for

Scheme - 7


(CH3CO)2O
conc.H2SO4
H3COCO
OCOCH3
H3COCO
(29)
ZnCl2
HOAc
HO
OH
HO
CH3
(30)
CH2I2
K2CO3
Acetone,Δ
OH
CH3
(31)
Pul.Na
Et2CO3
CH3CN
Ether
ZnCl2
HCl
OH
Sesamol
OH
(32)
p-Tosylchloride
K2CO3, Acetone
Zn/HCl
OSO2
CH3
(33)
(34)



(Fig-7): 4,5-methylenedioxy-2-hydroxy acetophenone (31).



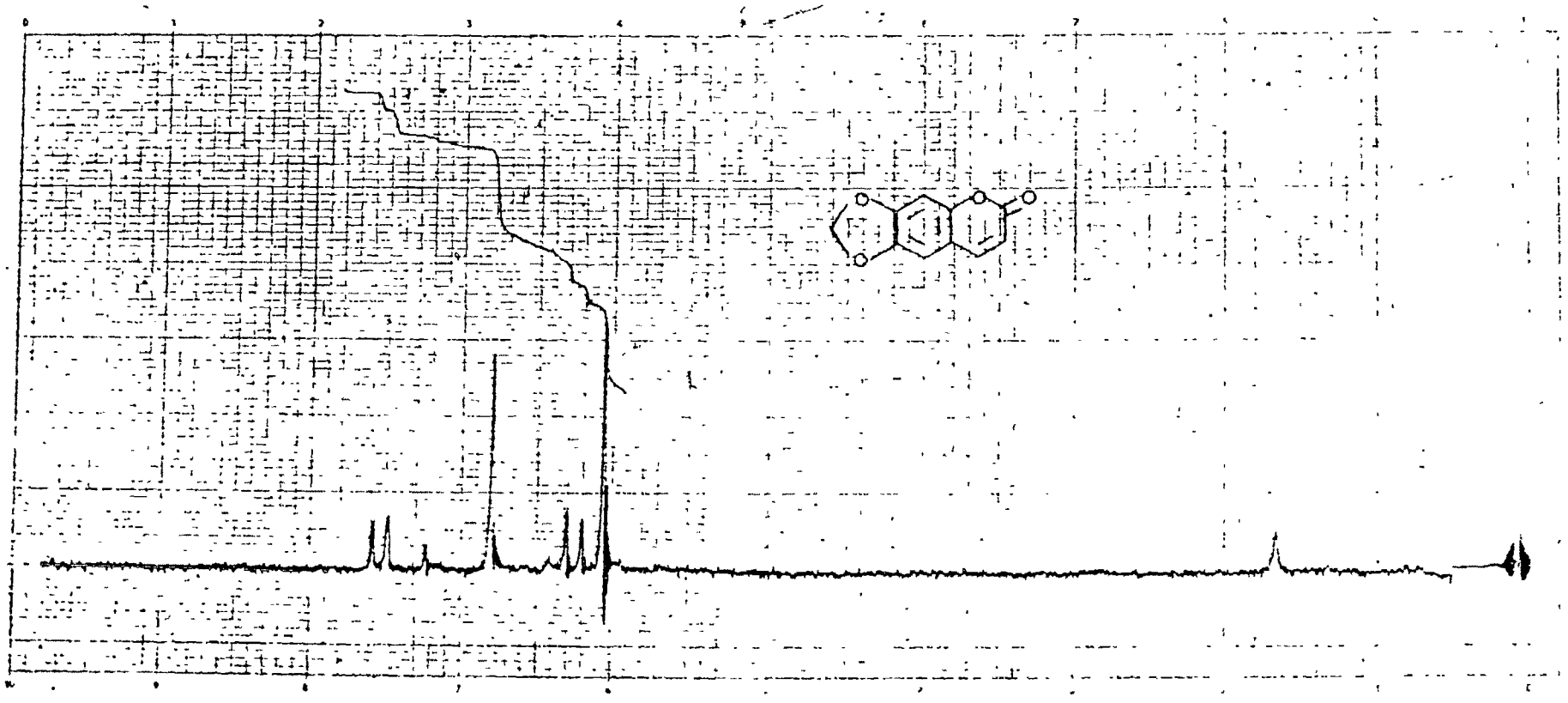
(fig-8): 4-p-tosyloxy-6,7-methylenedioxy-2-oxo-2H-benzopyran (33)

proton at C-2' and C-3'. The another doublet at δ 7.75 is for proton at C-5' and C-6'.

Reductive detosyloxylation of compound (33) was done by zinc dust and HCl to give 6,7-methylenedioxy-2-oxo-2H-benzopyran (34) or ayapin, the naturally occuring coumarin. The structure of this compound was assigned on the basis of its PMR spectrum taken in ($CDCl_3$) (Fig. 9). The signals are as follows : Singlet at δ 6.0 is for $-O-CH_2-O-$ group. The doublet at δ 6.2, J=9Hz is for proton at C-3. The another doublet at δ 7.5, J=9Hz indicated orthocupled proton at C-4. Singlet at δ 6.75 indicated two protons at C-5 and C-8.

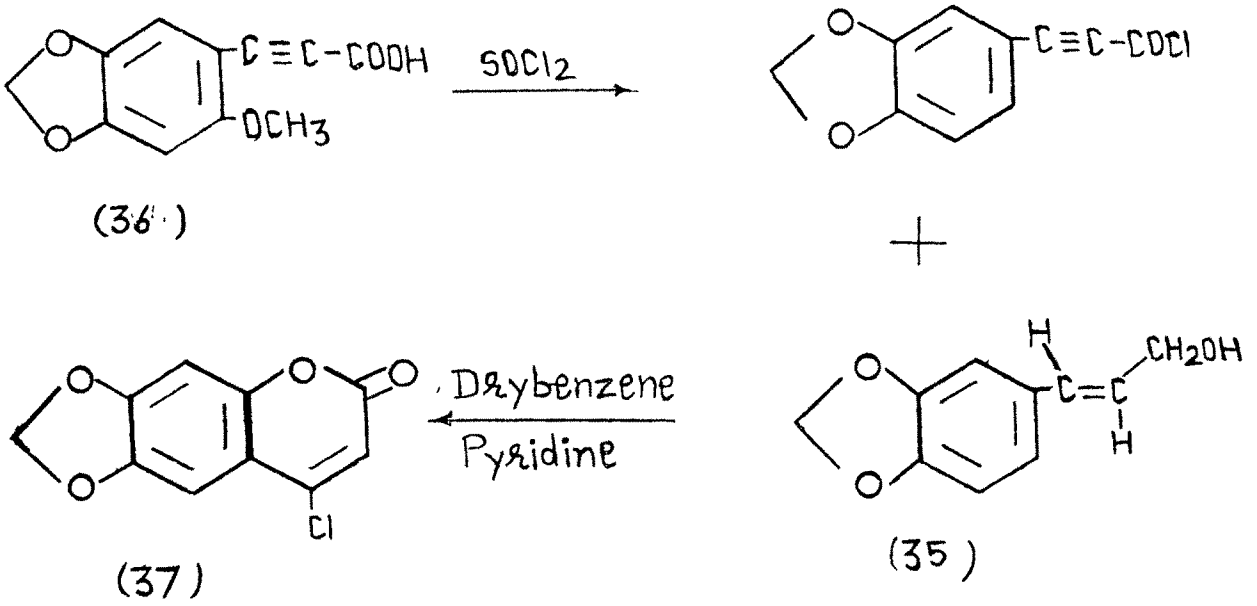
Satyanarayan and coworkers[15] obtained 4-chloro ayapin (37) during the esterification of trans-3,4-dimethoxy cinnamyl alcohol (35) with 2-methoxy-4,5-methylenedioxy phenylpropionic acid (36) [Scheme-8]. They converted acid (36) to acid chloride by refluxing with thionyl chloride and this acid chloride was refluxed with alcohol (35) which surprisingly gave (37). It was therefore thought of interest to prepare 4-chloroayapin by an independent route from the corresponding 4-hydroxy coumarin.

6,7-Methylenedioxy-4-hydroxy-2-oxo-2H-benzopyran (32) was refluxed with phosphorusoxychloride, whichd gave 4-chloro-ayapin (37) [Scheme-9]. The structure of this compound was assigned on the basis of PMR spectrum taken in ($CDCl_3$) (Fig.10) The singlet at δ 6.0 is for $-O-CH_2-O-$ group. The another singlet at δ 6.35 indicated proton at C-3. Two singlets at δ 6.75 and δ 7.1 indicated protons at C-8 and C-5 respectively.

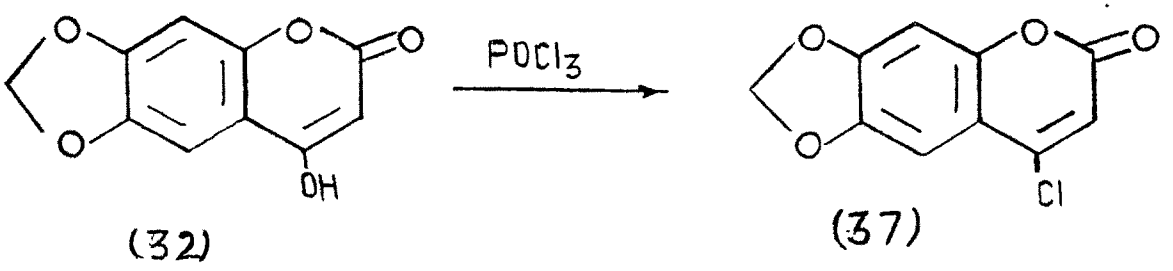


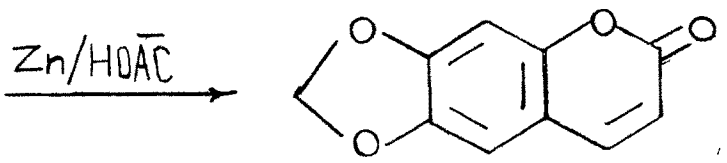
(fig-9): 6,7-methylenedioxy-2-oxo-2H-benzopyran (34)
OR Ayapin.

Scheme-8 Satyanarayan and Coworkers[15]

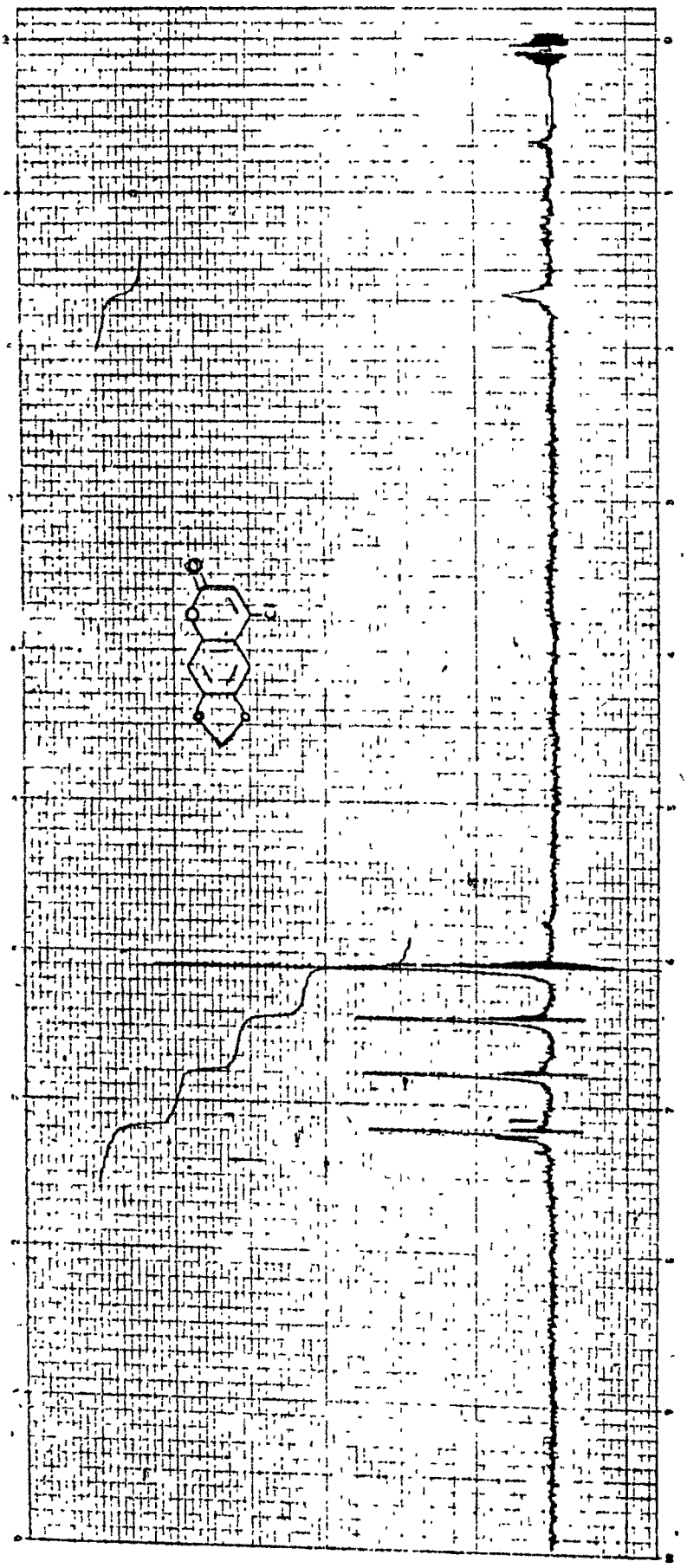


Scheme-9





(34)



(fig-10): 4-chloroayapin. (37).

Compound (37) when refluxed with zinc dust and acetic acid gave ayapin (34). The m.p. and m.m.p. of compound (34) obtained by both methods were same. [Scheme-19]

Synthesis of dipyran-carboxylic acids

Disodium cromoglycate (D.S.C.G.) is clinically useful antiallergic agent particularly for bronchial asthama. It is thought to inhibit the release of mediators like histamine, several kinins etc. of immediate hypersensitivity reactions.[16]

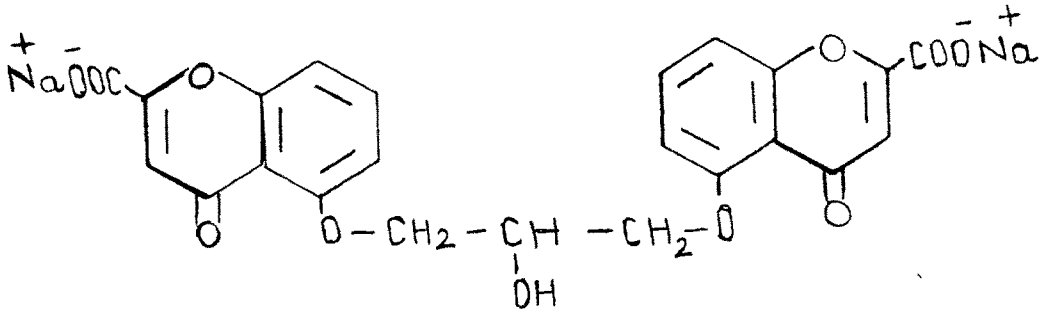
Vercauteren[17] reported the use of activated alkynes for condensing it with tryptamine in Pictel-Spengler synthesis of tetrahydro-β-carbolines which involves acid catalysed ring closure. Srimannarayana and coworkers[18] have synthesised 4,10-dioxo-2-phenyl-4H-10H-benzo (1,2-b : 3,4-b')dipyran-8-carboxylic acid (39) from 7-hydroxy flavones (38) [Scheme-10] using dimethylacetylenedicarboxylate (DMAD).

Present work

Synthesis of different dioxo-benzo-dipyran-8-carboxylic acids is achieved by condensing different hydroxycoumarins with dimethylacetylene dicarboxylate (DMAD).

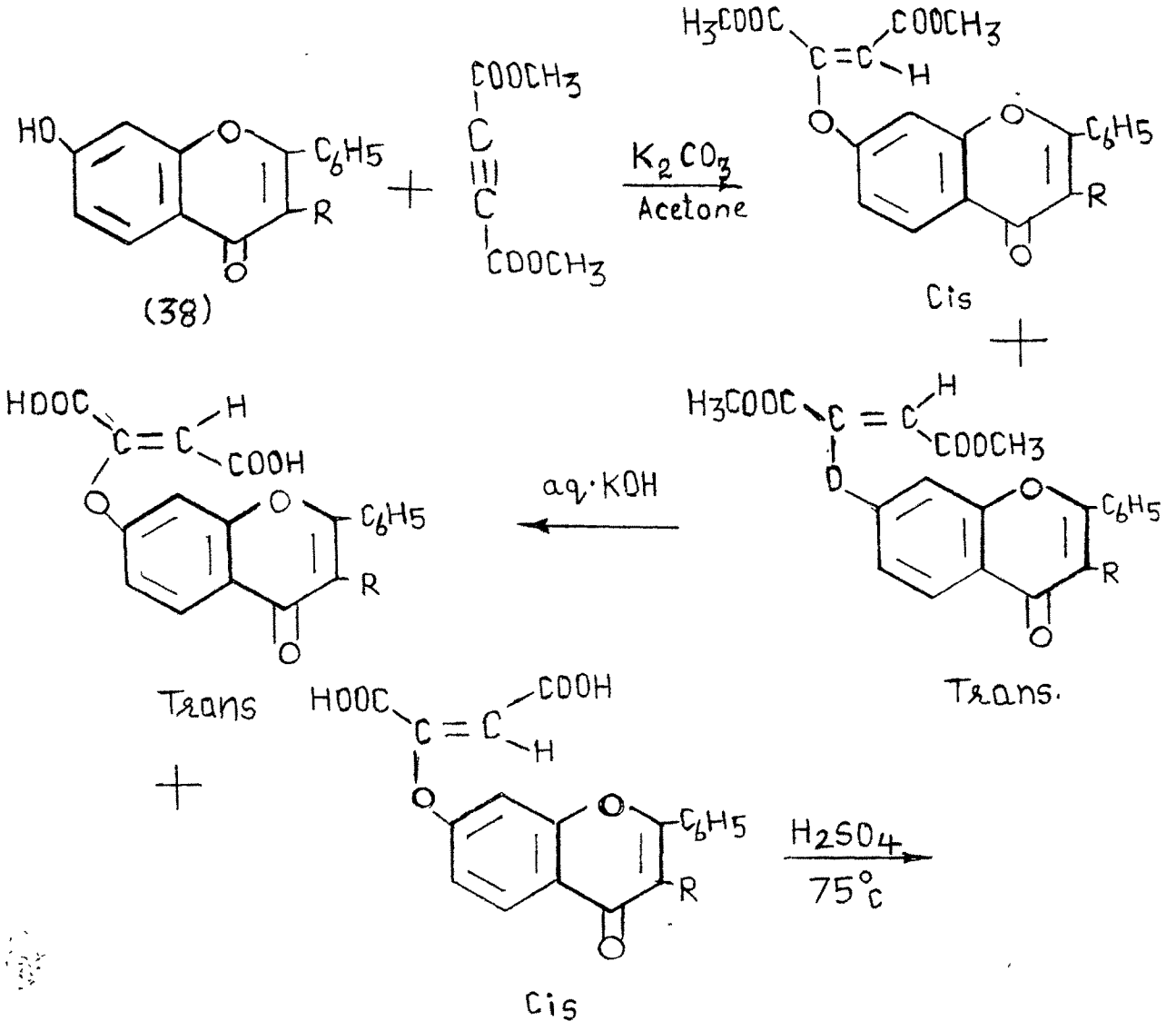
Synthesis of methylester of 2,10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b')-dipyran-8-carboxylic acid (44)

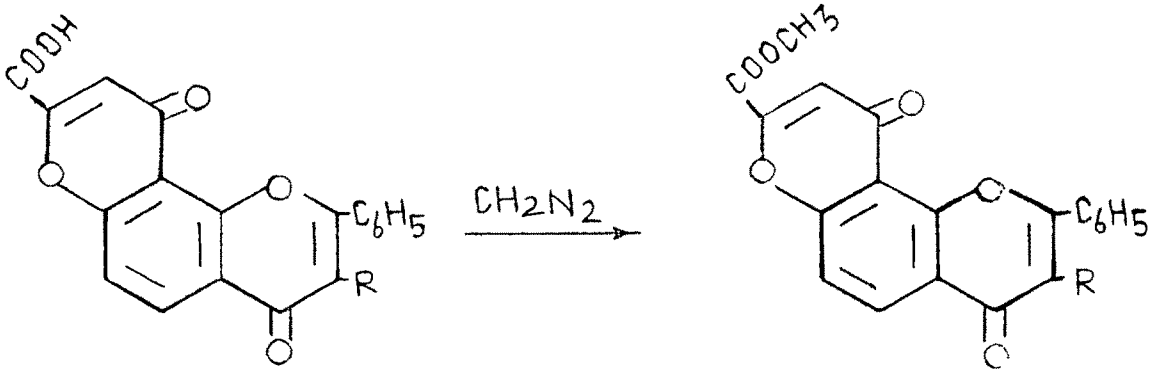
7-Hydroxy-4-methyl coumarin (40) was condensed with



Disodium Chromoglycate

Scheme-10 Srimannarayan and Coworkers[18]





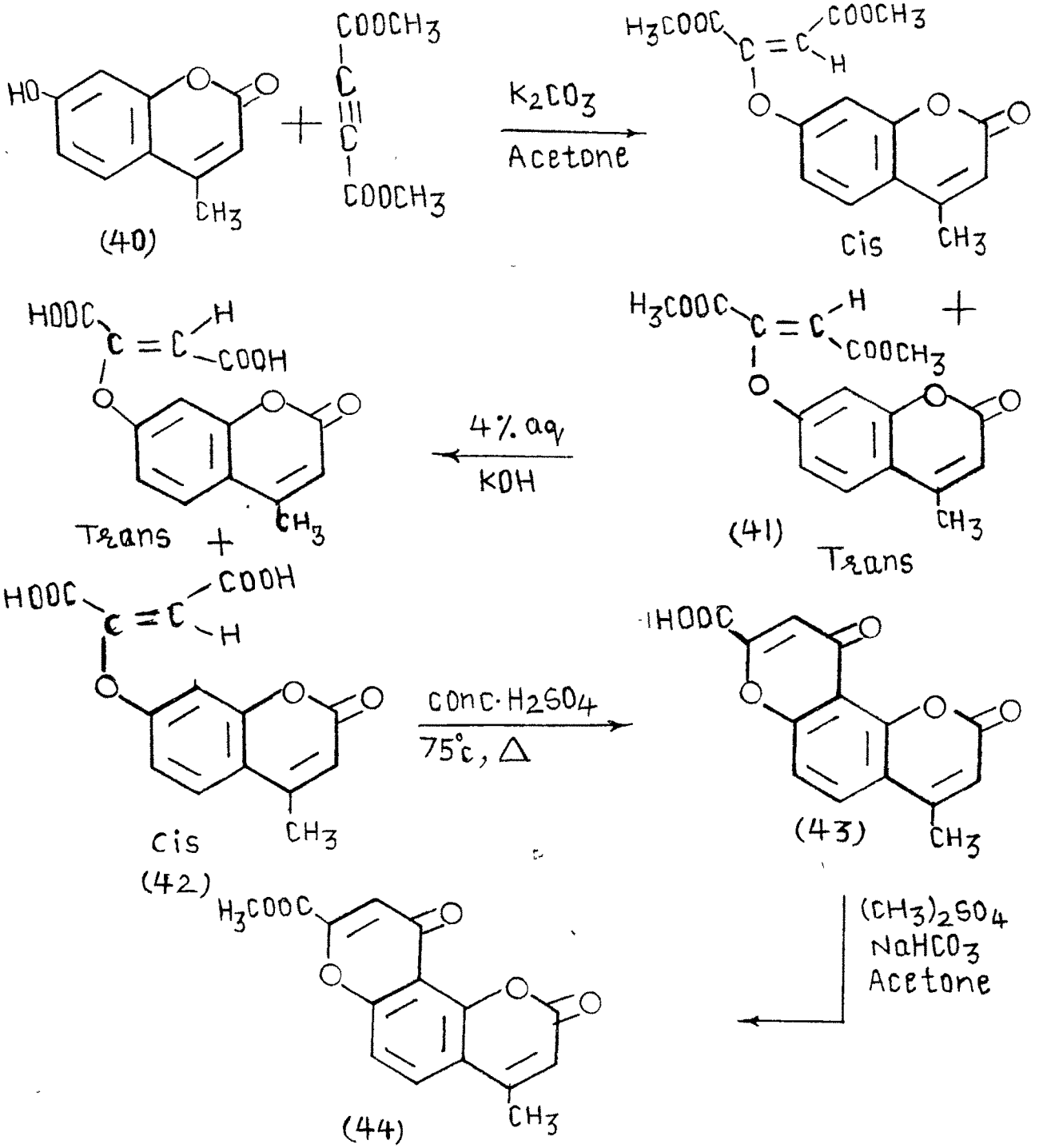
(39.)

DMAD in presence of anhydrous potassium carbonate and dry acetone. The adduct (41) obtained was found to be a mixture of Cis-trans isomers as revealed by its PMR spectra. It was not possible to separate these isomers either by column chromatography or by preparative TLC method. George[19] and Srimannarayana and coworkers[18] also could not separate the Cis-trans isomer of the adducts obtained by condensing phenols with DMAD. The IR spectra of compound (41) showed band at 1710 cm^{-1} & 1760 cm^{-1} for ester group (Fig. 18).

Mild hydrolysis of the adduct (41) in aq. potassiumhydroxide (4%) at room temperature furnished the corresponding mixture of Cis-and trans-dicarboxylic acid (42) which also could not be separated into cis and trans isomers. The IR of this compound showed band at 1710 - 1730 cm^{-1} for carbonyl group of acid and broad band at 2500 - 3000 cm^{-1} for -OH of carboxylic acid (Fig. 19).

Compound (42) was cyclised in the presence of sulfuric acid at 75°C to give 2,10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b')-dipyran-8-carboxylic acid (43) [Scheme-11]. The structure of this compound was established by its PMR spectrum taken in (TFA) (Fig. 20) which showed singlet at δ 2.67 for $-CH_3$ at C-4. The singlet at δ 6.4 is for proton at C-3. The another singlet at δ 7.53 is for proton at C-9. Two doublets at δ 7.8 and 8.28, J=9Hz indicated orthocoupling

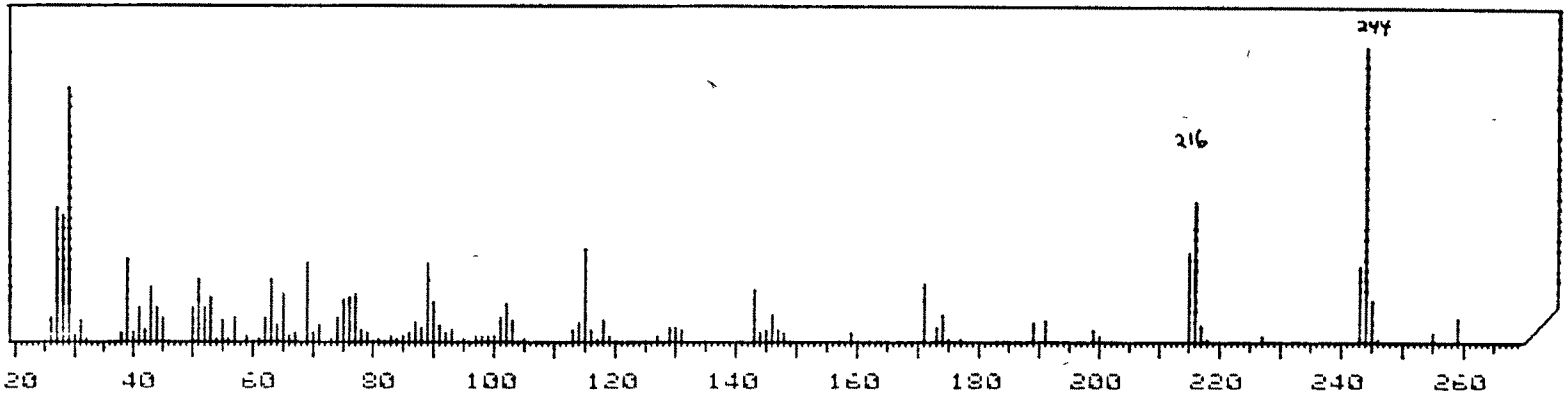
Scheme-II

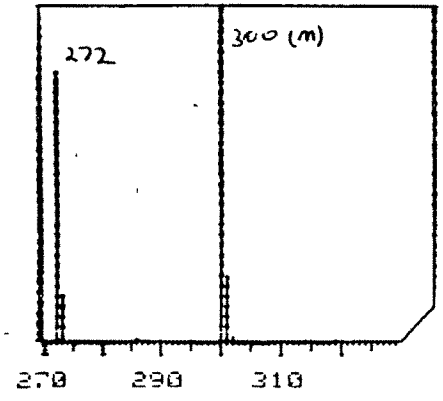

HO
CH3
(40)
COOCH3
COOCH3
K2CO3
Acetone
H3COOC
COOCH3
H
Cis
CH3
HOOC
H
COOH
Trans
4% aq
KOH
H3COOC
H
COOCH3
(41)
Trans
HOOC
COOH
H
Cis
(42)
conc·H2SO4
75°c, Δ
HOOC
(43)
(CH3)2SO4
NaHCO3
Acetone
H3COOC
(44)

FILENAME:RL0147.11
COMMENT:SP 134

MODE: EI
EJ: 70 GAIN: 2.1
II TEMP: 275 ICHN SPEED: .8
DI TEMP: 140

DATA	R.T.	PEAK	MASS RANGE	BASE PEAK	TOTAL	RAW-	B.G.
9	.4	134	25- 369	71000(| 300)	931073	0-	0
		132	25- 319	71000(| 300)	930239	0-	0





(fig-11): Methyl ester of 2, 10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b')-dipyran-8-carboxylic acid. (44).

of two protons at C-5 and C-6. Singlet at δ 8.7 indicated -COOH proton. The IR spectra showed bands at 1630 - 1650 cm^{-1} for C=O of chromone. The band at 1700 - 1720 cm^{-1} is for C=O of coumarin and acid. The band at 2500 - 3400 cm^{-1} is for -OH of -COOH group.

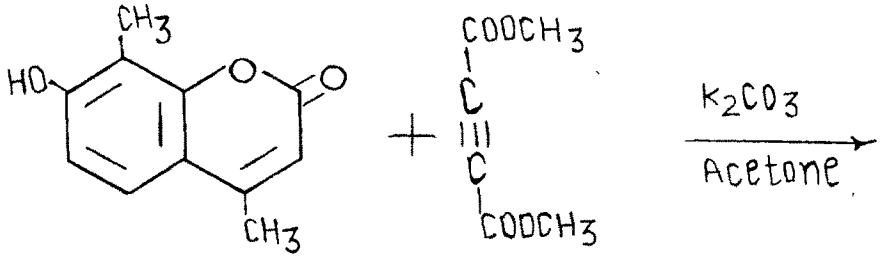
Compound (43) was methylated with dimethylsulfate in presence of sodium bicarbonate and dry acetone to give methyl-ester of 2,10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b') dipyran-8-carboxylic acid (44). The structure of this compound was assigned on the basis of elemental analysis and mass spectra whichexhibited the molecular ion peak at m/e 300. (Fig. 11)

Synthesis of 2,6-dioxo-4,10-dimethyl-2H-6H-benzo(1,2-b : 4,5-b') dipyran-8-carboxylic acid (48)

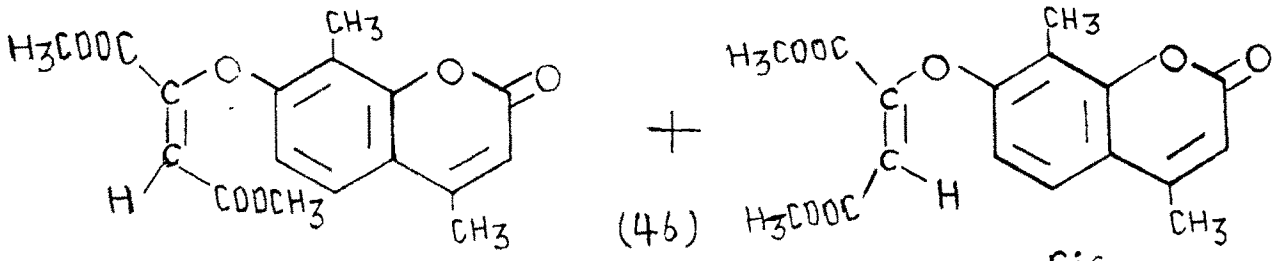
7-Hydroxy-4,8-dimethyl coumarin (45) was condensed with DMAD in presence of anhydrous potassium carbonate and dry acetone to give adduct (46) which was a mixture of Cis-trans isomers. The IR spectra showed band at 1720-1760 cm^{-1} for ester and >C=O of coumarin ring. The band at 2995 cm^{-1} is for ethylenic proton (Fig. 12). (scheme-12)

Compound (46) on mild hydrolysis with 4% aq. potassium hydroxide gave the mixture of corresponding cis-trans acid

- Scheme - 12

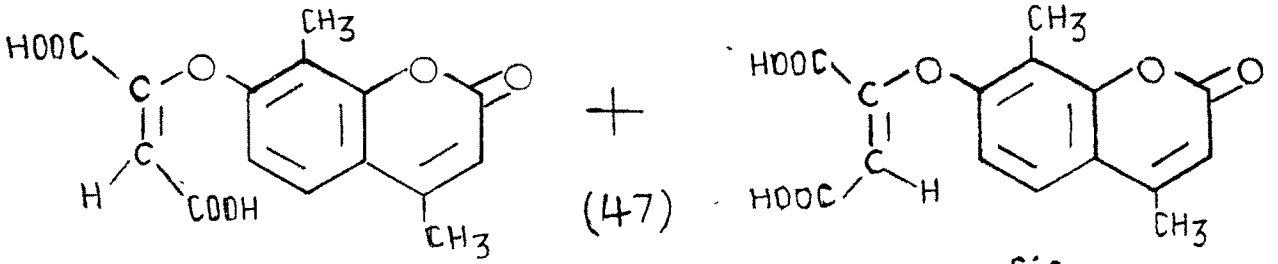


(45)



Trans (46) Cis

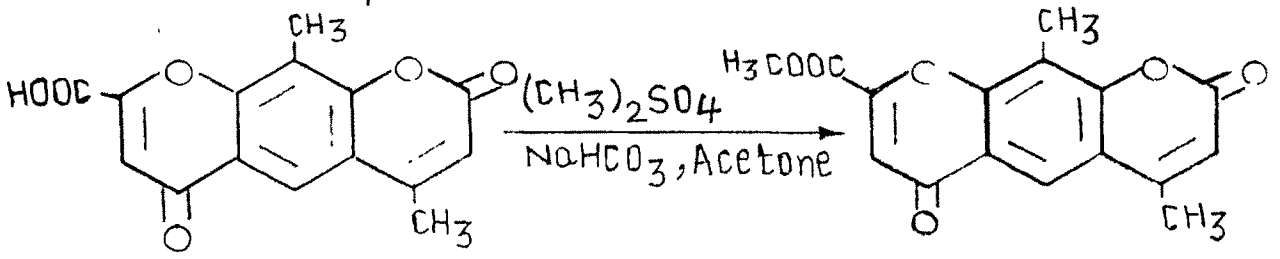
4% aq. KOH



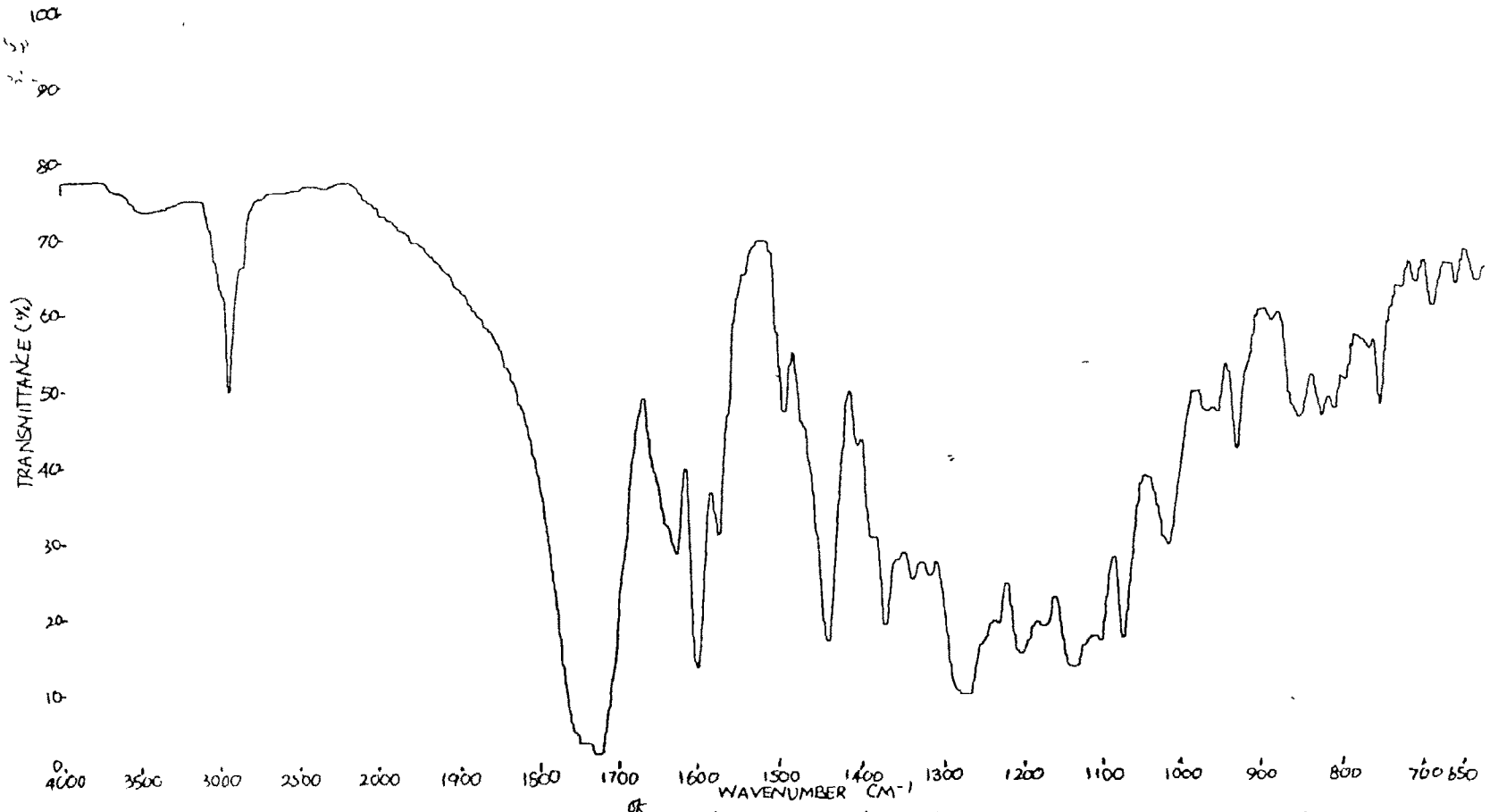
Trans (47) Cis

Conc. H_2SO_4

75°C



(48) (49)



(fig-12): Adduct of 7-hydroxy-4,8-dimethylcoumarin with DMAD (46)

3c-125

(47). The IR spectra of this compound showed broad band at 1700 - 1750 cm^{-1} for >C=O of acid and >C=O of coumarin ring. The broad band at 2400-3100 cm^{-1} indicated -OH of -COOH group (Fig. 13). Compound (47) on cyclisation in conc. H_2SO_4 at 75°C gave 2,6-dioxo-4,10-dimethyl-2H-6H-benzo(1,2-b : 4,5-b') dipyran-8-carboxylic acid (48) [Scheme-12]. The structure of this compound was assigned on the basis of elemental analysis and IR spectra (Fig. 14). The band at 1660 cm^{-1}, is of >C=O of chromone ring, at 1720 cm^{-1} is for >C=O of carboxylic acid and at 1760 cm^{-1} is for >C=O of coumarin ring. The methylester of compound (48) was prepared by condensation with dimethylsulfate in presence of sodium bicarbonate and dry acetone to give methylester of 2,6-dioxo-4,10-dimethyl-2H-6H-benzo (1,2-b : 4,5-b')-dipyran-8-carboxylic acid (49).

Synthesis of 2,5-dioxo-4-methyl-2H-5H-benzo(1,2-b-: 3,4-b')-dipyran-7-carboxylic acid (53)

6-Hydroxy-4-methyl coumarin (50) was condensed with DMAD inpresence of anhydrous potassium carbonate and dry acetone to give adduct (51), which was mixture of cis-trans isomers. The IR spectra of this compound exhibited broad band at 1720 - 1760 cm^{-1} for >C=O of ester and coumarin ring. The sharp band at 2995 cm^{-1} is for ethylenic proton (Fig. 15).

Mild hydrolysis of (51) in 5% aq. potassium hydroxide gave

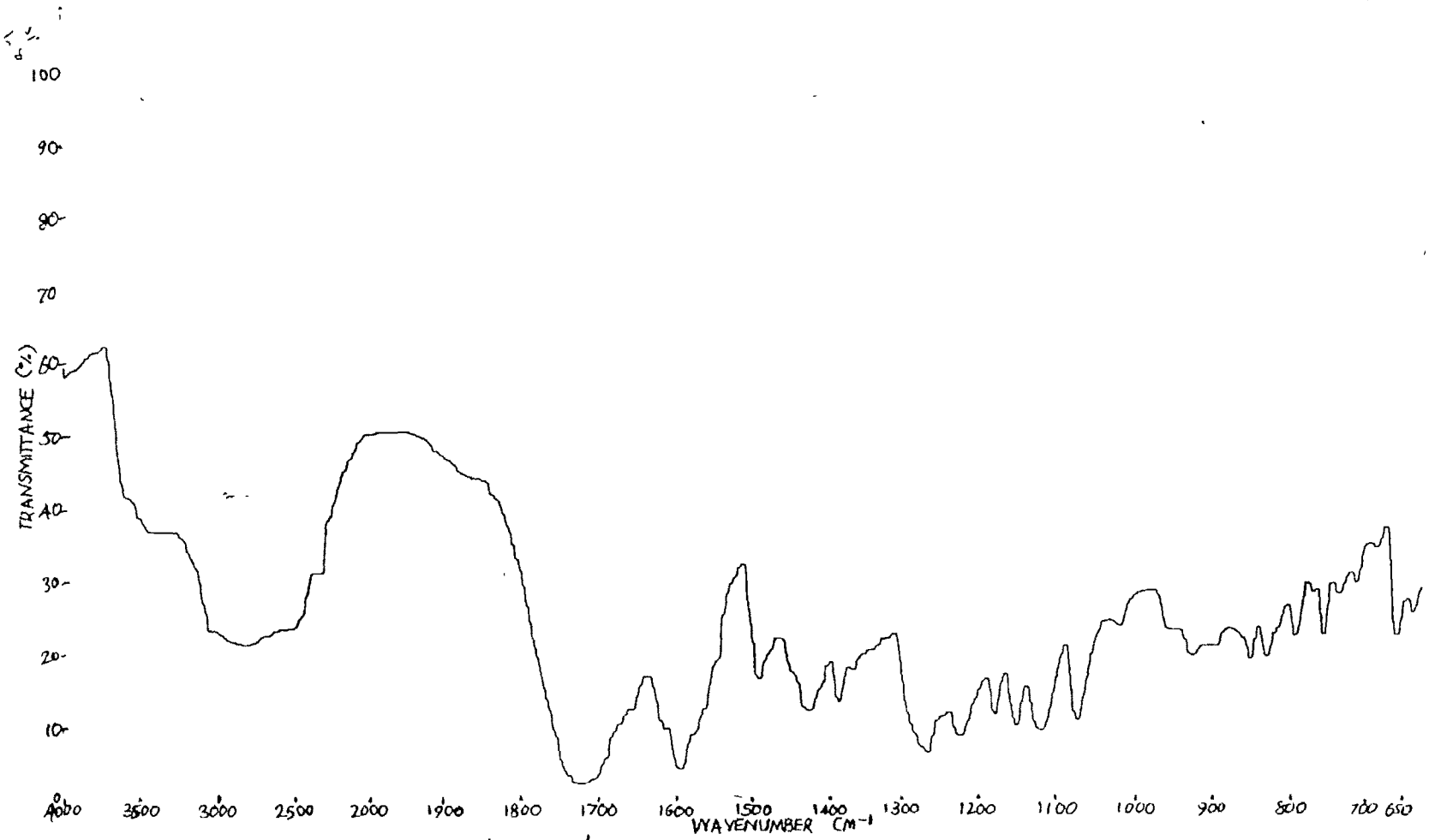
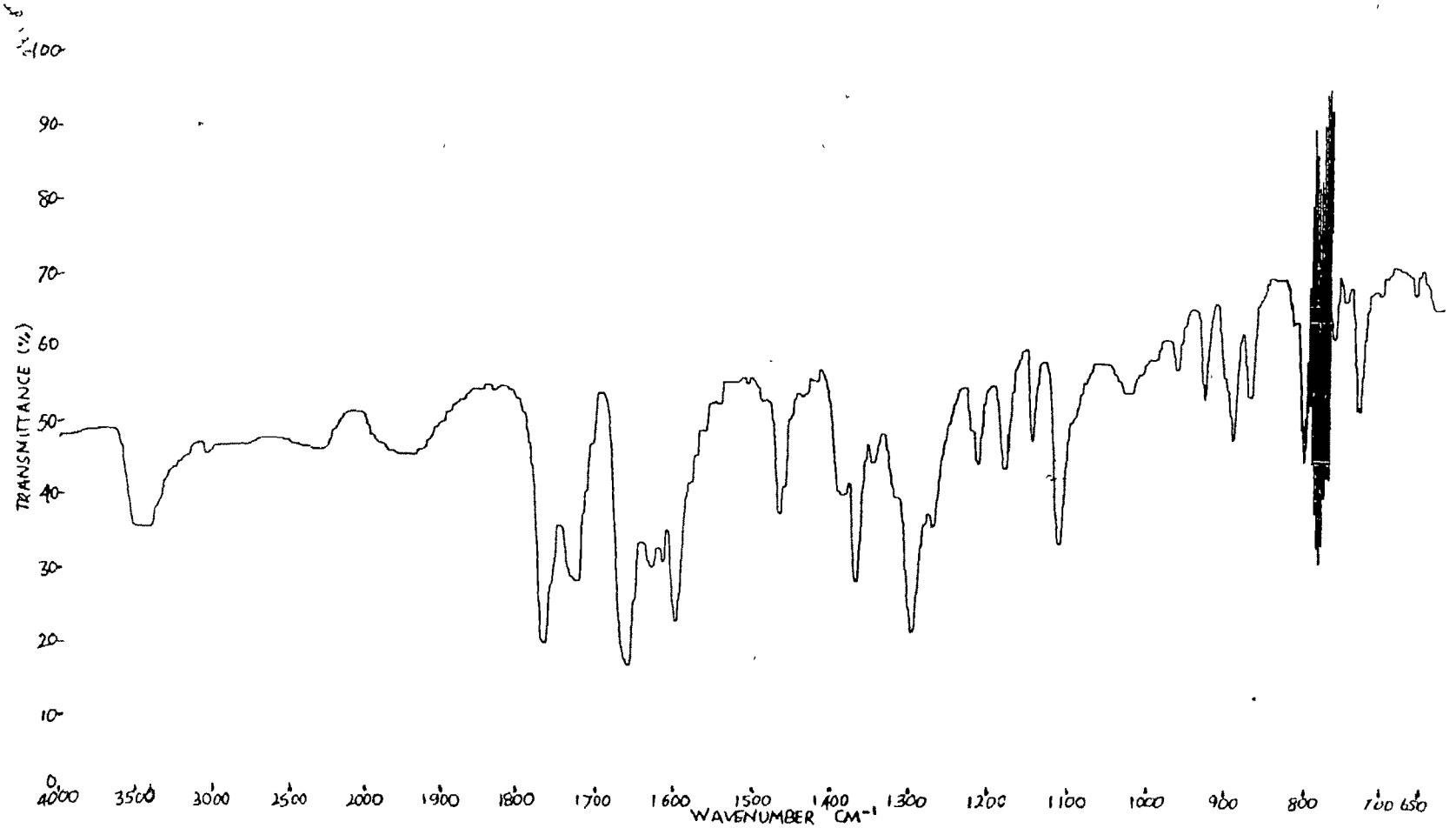
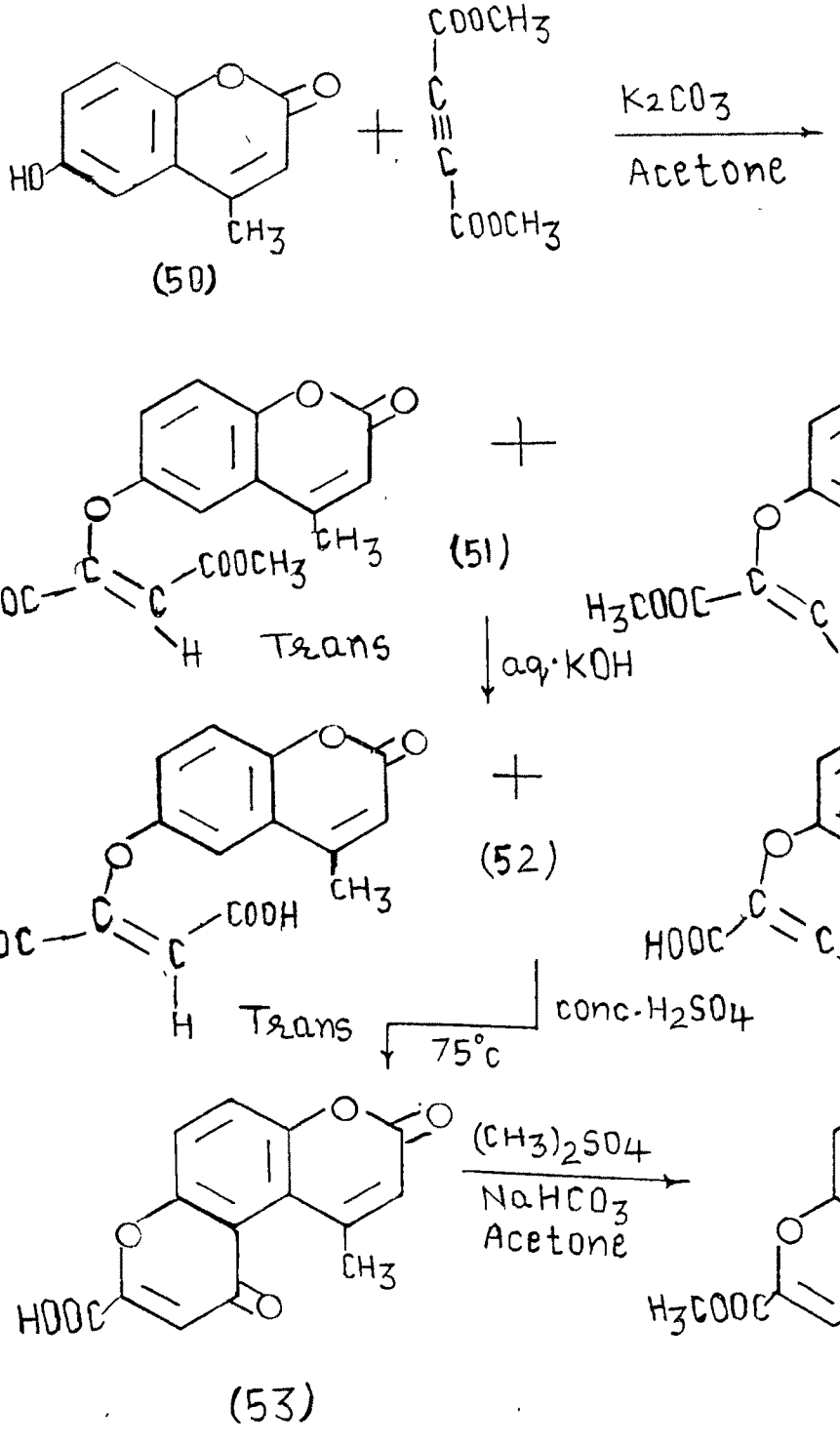


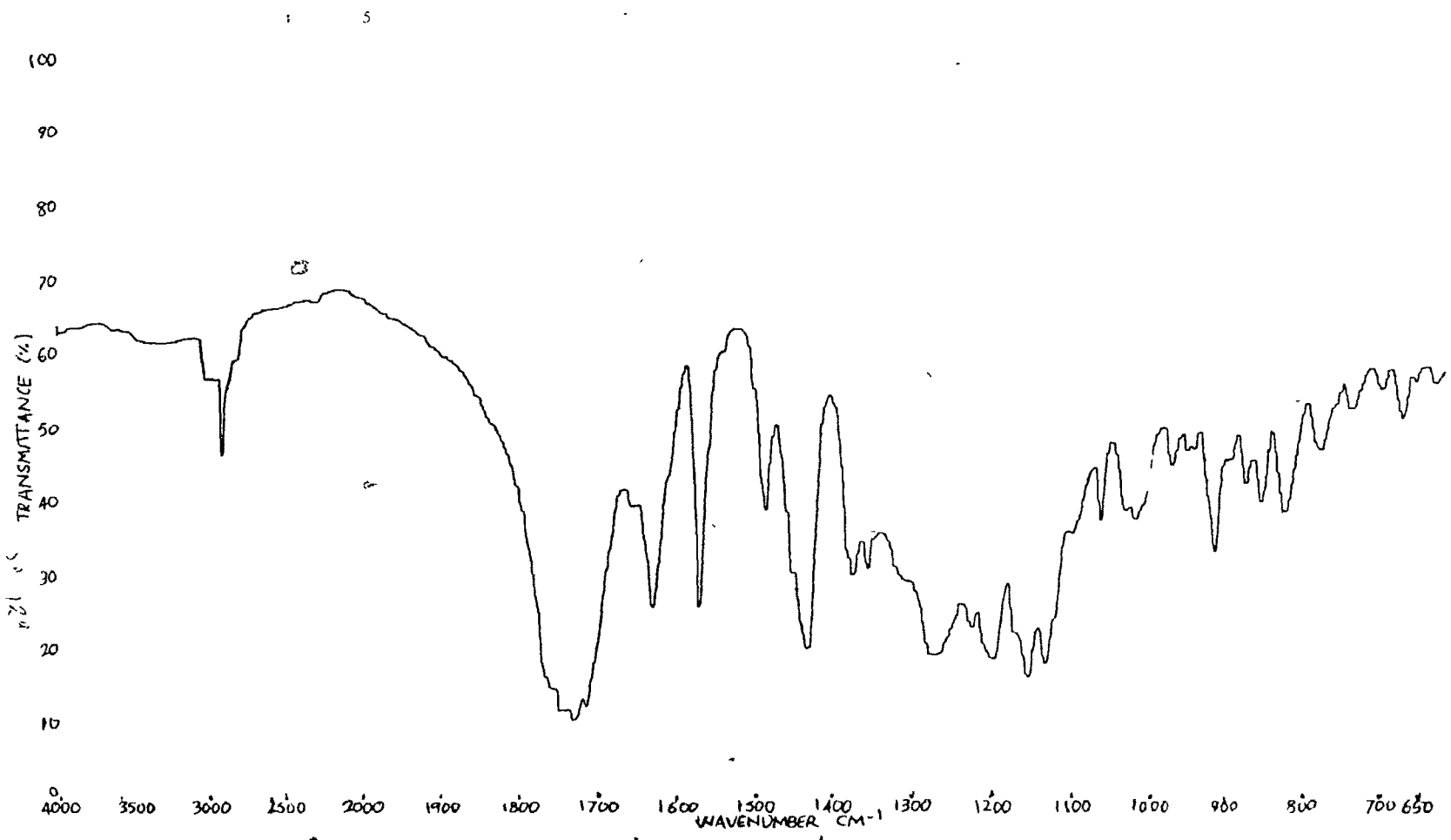
Fig-13): Dicarboxylic acid (47)



(fig-14) : 2,6-dioxo-4,10-dimethyl-2H-6H-benzo (1,2-b : 4,5-b') dipyran-8-carboxylic acid (48)

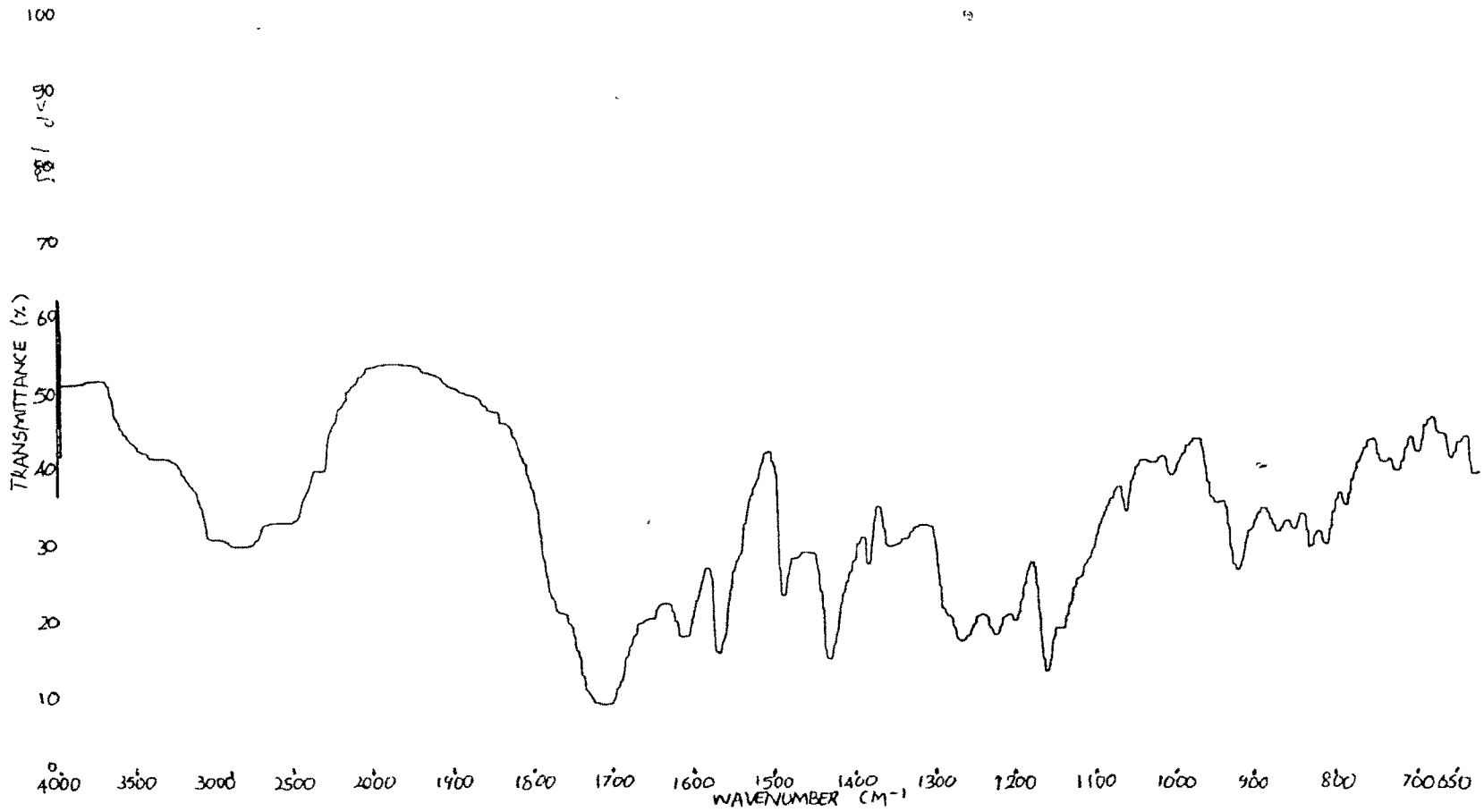
Scheme - 13


HO
CH3
(50)
COOCH3
COOCH3
K2CO3
Acetone
H3COOC
COOCH3
H
Trans
(51)
Cis
aq. KOH
HOOC
COOH
(52)
conc. H2SO4
75°C
(CH3)2SO4
NaHCO3
Acetone
(53)
(54)

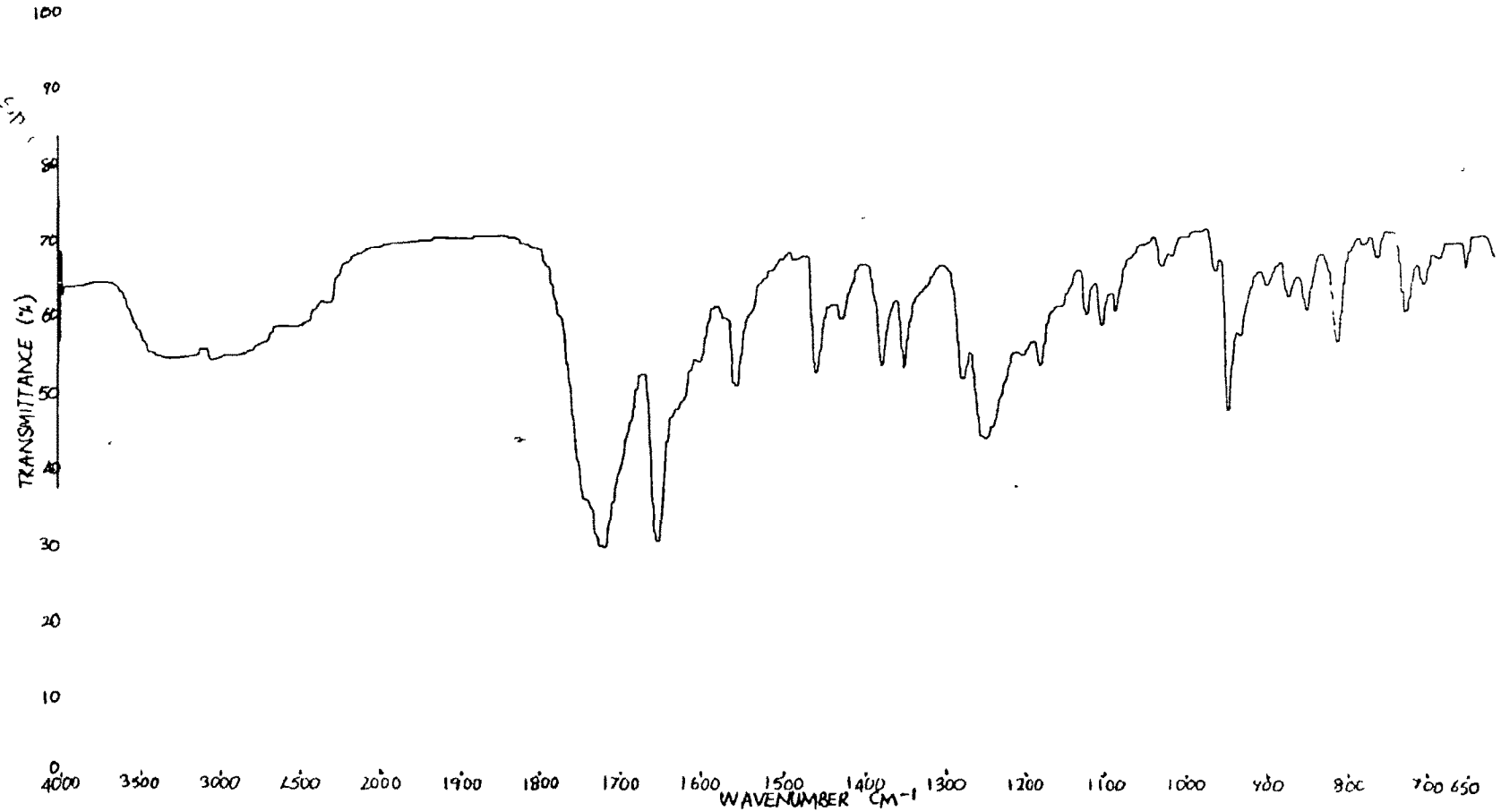


(fig-15): Adduct of 6-hydroxy-4-methylcoumarin and DMAD (51)

the corresponding acid (52) which is also a mixture of cis-trans isomers. The structure of this compound was assigned on the basis of elemental analysis and IR spectra (Fig. 16). The IR spectra showed the bands at 1700 - 1720 cm^{-1} and 1740 cm^{-1} for >C=O of carboxylic acid and coumarin ring. The broad band at 2500 - 3100 cm^{-1} is for -OH of -COOH group. Compound (52) on cyclisation with conc. H_2SO_4 gave 2,5-dioxo-4-methyl-2H-5H-benzo (1,2-b : 3,4-b')-dipyran-7-carboxylic acid (53) [Scheme-13] (Fig. 17). The IR spectra showed band at 1660 cm^{-1} for >C=O of chromone ring, at 1720 cm^{-1} for >C=O of coumarin ring and at 2500 - 3500 cm^{-1} is for -OH of carboxylic acid. This compound on methylation with dimethyl-sulfate in presence of sodium bicarbonate and dry acetone gave the methylester of 2,5-dioxo-4-methyl-2H-5H-benzo (1,2-b : 3,4-b')-dipyran-7-carboxylic acid (54).



(fig-16): Dicarboxylic acid of adduct. (52)
(51)



(fig-17) : 2,5-dioxo-4-methyl-2H-5H-benzo-(1,2-6 : 3,4-b')-dipyran 7-carboxylic acid (53)

EXPERIMENTAL

E X P E R I M E N T A L

All melting points are uncorrected. PMR spectra recorded on Perkin-Elmer R-32 Spectrometer (90 MHz) using TMS as internal standard. IR spectra recorded on Schimadzu Spectrometer R-40 using KBr pallet technique. Silica gel used for column chromatography with mesh size 60-120.

6,7,8,9-Tetrahydro-4-hydroxy2-oxo-2H-benzofuro-(3,2-g)-benzopyran (15)

5,6,7,8-Tetrahydro-2-hydroxy-3-acetyl-dibenzofuran (1.0 g) dissolved in diethyl carbonate (10.0 ml) was added slowly to pulverised sodium (2.0 g) and heated in waterbath for 10 hrs. Alcohol was added to decompose unreacted Na metal and poured into ice-cold water. It was acidified with conc. HCl. The product ~~obtained was~~ crystallised from alcohol. M.p. 280°C. Yield (0.8 g).

Analysis	:	Found	:	C, 70.09%	;	H, 4.97%
$C_{15}H_{12}O_4$	:	requires	:	C, 70.33%	;	H, 4.69%

6,7,8,9-Tetrahydro-4-p-tosyloxy-2-oxo-2H-benzofuro (3,2-g)-benzopyran (16)

A mixture of 6,7,8,9-tetrahydro-4-hydroxy-2-oxo-2H-benzofuro (3,2-g)-benzopyran (1.0 g), p-toluenesulfonylchloride (1.0 g)

and anhydrous potassium carbonate (4.0 g) was refluxed in dry acetone (100 ml) for 14 hrs. It was worked out as usual. The solid obtained was washed with sodium bicarbonate several times. It was purified by column chromatography using benzene as eluent, it crystallised from benzene. M.p. 211°C, yield (0.8 g).

Analysis	:	Found	:	C, 64.80%	;	H, 4.50%
$C_{22}H_{18}O_6S$	:	requires	:	C, 64.39%	;	H, 4.39%

6,7,8,9-Tetrahydro-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (17)

6,7,8,9-Tetrahydro-4-p-tosyloxy-2-oxo-2H-benzofuro(3,2-g)-benzopyran (1.0 g) was dissolved in benzene-alcohol (1:10) mixture (400 ml). To this zinc dust (3.0 g) and conc. HCl (10 ml) were added and refluxed on sandbath for 1 hr. The excess of benzene-alcohol mixture was distilled out & filtered and poured over ice (30 g). The oil obtained was extracted with ether and purified by preparative TLC using benzene as running solvent. It crystallised from benzene. M.p. 150°C, Yield (0.2 g).

Analysis	:	Found	:	C, 75.40%	;	H, 5.15%
$C_{15}H_{12}O_3$	:	requires	:	C, 75.00%	;	H, 5.00%

2-Oxo-2H-benzofuro-(3,2-g)-benzopyran (18)

6,7,8,9-Tetrahydro-2-oxo-2H-benzofuro-(3,2-g)-benzopyran

(0.2 g) was dissolved in dry benzene and DDQ (0.4 g) dissolved in dry benzene was added to it and refluxed for 6 hrs. It was filtered, excess of benzene distilled out and the remaining benzene was passed through silica gel. The product was crystallised from benzene. M.p. 207°C, Yield (0.1 g).

Analysis : Found : C, 76.05% ; H, 3.44%

$C_{15}H_8O_3$: requires : C, 76.28% ; H, 3.39%

6,7,8,9-Tetrahydro-4-hydroxy-11-methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (22)

Compound (21) (1.0 g) dissolved in diethylcarbonate (10 ml) was added slowly to the pulverised Na (2.0 g) and heated in waterbath for 8 hrs. Alcohol was added to decompose unreacted Na and then poured into ice. It was acidified with conc. HCl. The product obtained was crystallised from ethanol. M.p. 301°C, Yield (0.8 g).

Analysis : Found : C, 70.93% ; H, 4.70%

$C_{16}H_{14}O_4$: requires : C, 71.11% ; H, 5.19%

6,7,8,9-Tetrahydro-4-p-tosyloxy-11-methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyan (23)

A mixture of 6,7,8,9-tetrahydro-4-hydroxy-11-methyl-2-oxo-2H-benzofuro (3,2-g)-benzopyran (1.0 g),p-toluenesulfonylchloride

(1.0 g) and anhydrous potassium cabonate (4.0 g) was taken in dry acetone (100 ml) and refluxed for 14 hrs. It was worked out as usual. The product was purified by column chromatography using benzene. It was crystallised from benzene. M.p. 227°C, Yield (0.85 g).

Analysis	:	Found	:	C, 65.49%	;	H, 4.57%
$C_{23}H_{20}O_6S$	:	requires	:	C, 65.09%	;	H, 4.72%

6,7,8,9-Tetrahydro-11-methyl-2-oxo-2H-benzofuro (3,2-g)-benzopyran (24)

Compound (23) (1.0 g) was dissolved in benzene-alcohol (1:10) mixture (400 ml) and zinc dust (3.0 g) and conc. HCl (15 ml) were added to it and refluxed for one hr. The excess of benzene-alcohol mixture was distilled out and filtered and then poured into ice (30 g). The oil obtained was extracted with ether. It was purified by column chromatogaphy using benzene, crystallised from benzene. M.p. 168°C, Yield (0.3 g).

Analysis	:	Found	:	C, 75.10%	;	H, 5.77%
$C_{16}H_{14}O_3$	:	requires	:	C, 75.59%	;	H, 5.51%

11-Methyl-2-oxo-2H-benzofuro-(3,2-g)-benzopyran (25)

A mixture of 6,7,8,9-tetrahydro-11-methyl-2-oxo-2H-benzo-

furo (3,2-g)-benzopyran (0.3 g) and palladised charcoal (10%) (0.25 g) was refluxed in diphenylether (5.0 ml) for 12 hrs. It was filtered hot and poured into pet. ether. It crystallised from benzene. M.p. 226°C, Yield (0.18 g).

Analysis	:	Found	:	C, 75.95%	;	H, 4.37%
$C_{16}H_{10}O_3$	:	requires	:	C, 76.00%	;	H, 4.00%

2,4,5-Trihydroxy-actophenone (30)

A mixture of hydroxyhydroquinonetriacetate (30.0 g), anhydrous zinc chloride (45.0 g) and acetic acid (45.0 g) was heated for 20 minutes. It was then poured inot (1:1) ice cold HCl. The solid obtained was filtered and filtrate was extracted with ether. The combine product crystallised from hot water. M.p. 202°C, Yield (6.0 g).

Analysis	;	Found	:	C, 57.60%	;	H, 4.77%
$C_8H_8O_4$	:	requires	:	C, 57.14%	;	H, 4.76%

4,5-Methylenedioxy-2-hydroxy-acetophenone (31)

A mixture of 2,4,5-trihydroxy acetophenone (1.7 g), anhydrous potassium carbonate (7.0 g) and diiodomethane (0.8 ml) was refluxed in dry acetone (100 ml) for 16 hrs. It was worked out as usual. The product obtained was filtered and extracted with benzene. On evaporation of benzene gave the product, which was crystallised from pet. ether. M.p. 112°C, Yield (1.0 g).

Analysis	:	Found	:	C, 60.45%	;	H, 5.06%
$C_9H_8O_4$	:	requires	:	C, 60.00%	;	H, 4.44%

4,5-Methylene-dioxy-2-hydroxy-acetophenone by Hoesch method (31)

To a mixture of Sesamol (6.0 g), anhydrous zinc chloride (3.0 g), dry ether (30.0 ml) and freshly distilled acetonitrile (3.0 ml), dry HCl gas was passed at 0-5°C till the solution becomes saturated (4-5 hrs). It was kept overnight for 2 days and then solvent ether was removed. Water was added to the pasty material obtained. The water extract was neutralise slowly with liq. NH_3. It was then heated on wire gauze for 15 minutes. The solid obtained was filtered and crystallised from pet. ether. The m.p. and m.m.p. were same as obtained earlier, i.e. 112°C, Yield (1.0 g).

4-Hydroxy-6,7-methylenedioxy-2-oxo-2H-benzopyran (32)

4,5-Methylenedioxy-2-hydroxy-acetophenone (1.0 g), dissolved in diethylcarbonate (5.0 ml) was added slowly to the pulverised Na (1.0 g) and then little excess of diethyl-carbonate was added and heated for 4-5 hrs in waterbath. Alcohol was added to remove unreacted Na metal and then poured into ice-cold water. The product obtained was treated with sodiumbicarbonate and filtered, filtrate acidified with conc. HCl. The product crystallised from ethanol. M.p. 290°C, Yield (1.1 g).

Analysis	:	Found	:	C, 57.99%	;	H, 3.41%
$C_{10}H_6O_5$	:	requires	:	C, 58.25%	;	H, 2.91%

4-Tosyloxy-6,7-methylenedioxy-2-oxo-2H-benzopyran (33)

A mixture of 4-hydroxy-6,7-methylenedioxy-2-oxo-2H-benzo-pyran (2.0 g) p-toluenesulfonylchloride (2.0 g) and anhydrous potassium carbonate (8.0 g) was refluxed in dry acetone (100 ml) for 8 hrs. It was worked out as usual. The product obtained was filtered and washed with sodium bicarbonate to remove unreacted compound. It was purified by column chroma-tography, using benzene. It crystallised from benzene. M.p. 180°C, Yield (1.5 g).

Analysis	:	Found	:	C, 56.96%	;	H, 3.81%
$C_{17}H_{12}O_7S$	:	requires	:	C, 56.67%	;	H, 3.33%

6,7-Methylenedioxy-2-oxo-2H-benzopyran or Ayapin (34)

4-p-Tosyloxy-6,7-methylenedioxy-2-oxo-2H-benzopyran (1.0 g) was dissolved in ethanol (100 ml). To this zinc dust (3.0 g) and conc. HCl (15 ml) were added and refluxed for one hr. The excess of alcohol was distilled out and it was filtered hot and poured over ice (30 g). The oil obtained was extracted with ether, purified by preparative TLC using benzene. It crystallised from benzene. M.p. sublimes 170-172°C, M.p. 223°C under cover slide (Lit.[13] m.p. 225 under cover slide, sublimes 170°C). Yield (0.3 g).

Analysis : Found : C, 62.76% ; H, 3.53%

$C_{10}H_6O_4$: requires : C, 63.16% ; H, 3.16%

4-Chloro ayapin (37)

A mixture of 6,7-methylenedioxy-4-hydroxy-2-oxo-2H-benzopyran (1.0 g) and phosphorusoxychloride (4-5 ml) was refluxed for 6 hrs. It was poured in ice cold water. The product obtained was purified by preparative TLC using benzene. It crystallised from benzene. M.p. 183-184°C (Lit.[15] m.p. 179-80°C), Yield (0.4 g).

Analysis : Found : C, 54.00% ; H, 2.70%

$C_{10}H_5O_4Cl$: requires : C, 53.48% ; H, 2.23%

Ayapin from 4-chloroayapin

4-Chloro ayapin (0.5 g), zinc dust (1.0 g) and acetic acid (15 ml) were heated for 30 minutes. It was filtered and then poured over ice. The product obtained was purified by preparative TLC using benzene. It showed blue fluoroscence in UV light. Crystallised from benzene. It showed same m.p. 170-172°C and m.m.p. as compound (34) obtained earlier.

7-Hydroxy-4-methyl-benzopyran-2-one + Dimethylacetylene - dicarboxylate (41)

To a mixture of 7-hydroxy-4-methyl-benzopyran-2-one (3.4 g) and anhydrous potassium carbonate (3.0 g) in dry acetone (150 ml) a solution of DMAD (3.0 g) in acetone (25 ml) was added slowly with stirring during 3 hr. at room temperature. It was stired further for 8 hr. The reaction mixture was filtered, concentrated and extracted with ether (3 x 300 ml). The etheral solution was washed with aq. NaOH and water dried, and solvent was removed to give pale yellow solid, which crystallised from benzene. M.p. 98°C, Yield (2.0g)

Analysis : Found : C, 59.96% ; H, 4.79%

$C_{16}H_{14}O_7$: requires : C, 60.39% ; H, 4.40%

Hydrolysis of Adduct (41), (42)

The adduct (41) (2.0 g) was stirred with potassium hydro-

xide (4%) (200 ml) for 3 hr. and left overnight at room temperature. The alkaline solution was washed with ether to remove unhydrolysed ester. It was then acidified with conc. HCl and then extracted with ether. On evaporation of ether, the product was obtained. It crystallised from ethanol. M.p. 205°C, Yield (1.0 g).

Analysis	:	Found	:	C, 57.69%	;	H, 3.91%
$C_{14}H_{10}O_7$	:	requires	:	C, 57.93%	;	H, 3.45%

2,10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b')-dipyran-8-carboxylic acid (43)

The dicarboxylic acid (1.0 g) was treated with conc. H_2SO_4 (10 ml) and heated at 75°C for 1 hr. The reaction mixture was cooled to 5°C and poured over crushed ice (30 g) and left overnight. The solid separated was filtered, dried and crystallised from ethanol. M.p. 270°C, Yield (0.5 g).

Analysis	:	Found	:	C, 61.31%	;	H, 3.41%
$C_{14}H_8O_6$	:	requires	:	C, 61.76%	;	H, 2.94%

Methylester of 2,10-dioxo-4-methyl-2H-10H-benzo (1,2-b : 5,6-b')-dipyran-8-carboxylic acid (44)

A mixture of compound (44) (0.5 g), sodium bicarbonate (2.0 g) and dimethyl sulfate (0.4 ml) was refluxed in dry

acetone (30 ml) for 6 hrs. It was worked out as usual. The product obtained was filtered, dried and crystallised from ethanol. M.p. decomposes at 230°C, Yield (0.3 g).

Analysis : Found : C, 63.40% ; H, 3.94%

$C_{15}H_{10}O_6$: requires : C, 62.93% ; H, 3.50%

7-Hydroxy-4,8-dimethyl-benzopyran-2-one + dimethylacetylene-dicarboxylate (46)

To a mixture of 4,8-dimethyl-7-hydroxy-benzopyran-2-one (3.0 g) anhydrous potassium carbonate (3.0 g) in dry acetone (150 ml), a solution of DMAD (2.9 g) in dry acetone (25 ml) was added slowly with stirring during 3 hrs at room temperature. It was stirred further for 8 hrs. The reaction mixture was filtered, concentrate and extracted with ether (3 x 300 ml). The etheral solution was washed with aq. NaOH andwater, dried and solvent was removed to give pale yellow solid ; which crystallised from benzene. It was a mixture of cis-trans isomers. M.p. 70°C, Yield (2.0 g).

Hydrolysis of Adduct (46) = (47)

The adduct (46) (2.0 g) was stirred with aq. potassium hydroxide (4%) (200 ml) for 3 hrs. and left overnight at room temperature. The alkaline solution was washed with ether to remove unhydrolysed ester. It was then acidified with conc. HCl and extracted with ether. On evaporation

of ether, the product obtained was crystallised from ethanol. M.p. 200°C decomposes, Yield (1.0 g).

Analysis	:	Found	:	C, 59.00%	;	H, 4.11%
$C_{15}H_{11}O_7$	:	requires	:	C, 59.41%	;	H, 3.63%

2,6-Dioxo-4,10-dimethyl-2H-6H-benzo (1,2-b : 4,5-b')-dipyran-8-carboxylic acid (48)

The dicarboxylic acidmixture (1.0 g) was treated with conc. H_2SO_4 (10 ml) and kept at 75°C for 1 hr. The reaction mixture was cooled to 5°C and poured over crushed ice (30 g) and left overnight. The solid separated was filtered, dried and crystallised from ethanol. M.p. 289°C, Yield (0.5 g)

Analysis	:	Found	:	C, 62.50%	;	H, 3.88%
$C_{15}H_{10}O_6$	:	requires	:	C, 62.94%	;	H, 3.50%

Methylester of 2,6-dioxo-4,10-dimethyl-2H-6H-benzo (1,2-b : 4,5-b')-dipyran-8-carboxylic acid (49)

A mixture of compound (48) (0.5 g), sodium bicarbonate (2.0 g) and dimethyl sulfate (0.4 ml) was refluxed in dry acetone (30 ml) for 6 hrs. It was worked out as usual. The product obtained was filtered, dried and crystallised from ethanol. M.p. 148°C, Yield (0.155 g).

Analysis : Found : C, 63.86% ; H, 4.51%

$C_{10}H_{12}O_6$: requires : C, 64.00% ; H, 4.00%

6-Hydroxy-4-methyl-benzopyran-2-one + DMAD (51)

To a mixture of 6-hydroxy-4-methyl coumarin (3.4 g) and anhydrous potassium carbonate (3.0 g) in dry acetone (150 ml), a solution of DMAD (3.0 g) in dry acetone (25 ml) was added slowly with stiring during 3 hr. at room temperature. The reaction mixture was stirred further 8 hrs. It was filtered concentrated and extracted with ether (3 x 300 ml). The etheral solution was washed with aq. NaOH and water, dried and evaporated to give solid which crystallised from benzene. M.p. 75°C, mixture of cis-trans isomer, yield (1.8g).

Analysis : Found : C, 59.97% ; H, 4.90%

$C_{16}H_{14}O_7$: requires : C, 60.38% ; H, 4.40%

Hydrolysis of adduct (51) = (52)

The adduct (51) (2.0 g) was stired with aq. potassium hydroxide 4% (200 ml) for 3 hrs. and left overnight at room temperature. The alkaline solution was washed with ether to remove unhydrolysed ester. It was acidified with conc. HCl and extracted with ether. The product was obtained on evaporation of solvent and crystallised from ethanol. M.p. 165°C, Yield (1.0 g).

Analysis : Found : C, 57.68% ; H, 3.84%

$C_{14}H_{10}O_7$: requires : C, 57.93% ; H, 3.45%

2,5-Dioxo-4-methyl-2H-5H-benzo (1,2-b : 3,4-b')-dipyran-7 carboxylic acid (53)

The dicarboxylic acid (1.0 g) was treated with conc. H_2SO_4 (10 ml) and heated at 75°C for 1 hr. The reaction mixture was cooled to 5°C and poured into crushed ice (30 g) and left overnight. The solid separated was filtered, dried and crystallised from ethanol. M.p. 265°C decomposes. Yield (0.45 g).

Analysis : Found : C, 61.28% ; H, 3.45%

$C_{14}H_8O_6$: requires : C, 61.76% ; H, 2.94%

Methyl ester of 2,5-dioxo-4-methyl-2H,5H benzo (1,2-b : 3,4-b')-dipyran-7-carboxylic acid (54)

A mixture of compound (53) (0.5 g), sodium bicarbonate (2.0 g) and dimethyl sulfate (0.4 ml) was refluxed in dry acetone (30 ml) for 6 hrs. It was worked out as usual. The product obtained was filtered, dried and crystallised from ethanol. M.p. 120°C, Yield (0.35 g).

Analysis : Found : C, 63.28% ; H, 4.01%

$C_{15}H_{10}O_6$: requires : C, 62.94% ; H, 3.50%

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