Chapter III

SYNTHESIS OF FUROCHROMENES

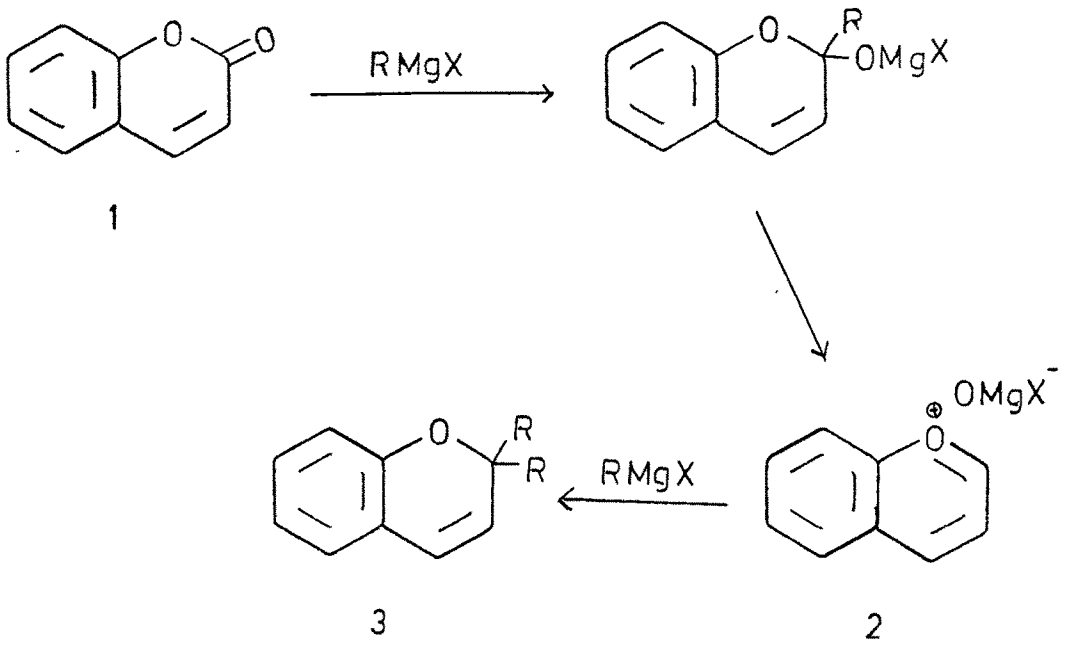
2H-1-Benzopyrans are very well known due to their natural occurrence and their biological properties. In the 2H-1-benzopyran series, the only known isolable natural products are 2,2-disubstituted 2H-1-benzopyran, primarily 2,2-dimethyl substituted resulting from the combination of a phenol and an isoprene unit. The chemical methods for structural identification of 2H-1-benzopyrans are degradation and/or synthesis. A number of papers [1-3] on acetyl substituted natural products containing 2H-1-benzopyrans describe oxidation with permanganate or osmium tetroxide[4] if permanganate fails, followed by pyrolysis to give a known substituted hydroxyacetophenone. Other reagents and reactions sometime used in structural identification are (a) hydrogenation to easy recognizable chroman[5] (b) alkalifusion to give salicylic acid derivative and acetic acid[6] and (c) reaction with dimethyl acetylene dicarboxylate which produces acetone as a product when 2H-1-benzopyrans are present.[7] In more recent papers the most straight forward method of identification has been spectroscopy.

2H-1-benzopyrans are synthesized by variety of methods. Some of the important methods are described here.

(A) Grignard Reagents on Coumarin

In one of the earliest method employed for the preparation of 2,2-disubstituted 2H-1-benzopyrans, an alkylmagnesium halide was allowed to react with a coumarin[8] (1).

Grignard reagent on coumarin[8,9,10]



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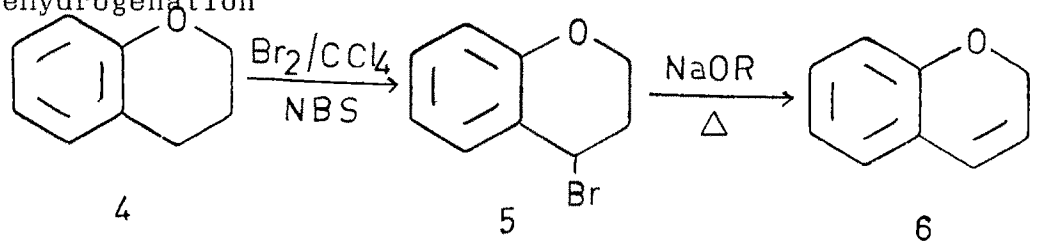
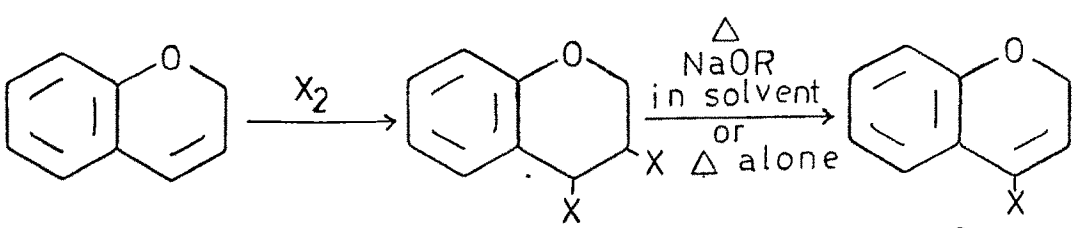
Dehydrogenation[11,12]



4 5 6



6 7 8

X=Br, Cl

Other catalysts (and yields) employed for the dehydration of chromanols are : dimethyl sulphate at 175° (58%),[15] alumina at 160° (70%), anhydrous potassium bisulphite at 120° (33-93%)[16,17] naphthalene sulphonic acid in boiling toluene (88-90%),[18] P_2O_5 at 80° under vacuum[19] and $POCl_3$ in benzene and pyridine at 85° (67%).[20] Dehydration has been also accomplished by employing acetic anhydride in pyridine (46-62%)[21] or in two steps by acetylating the carbinol and then acetate pyrolysis at 350° (89%).[15] Chromans with alkoxy or 4-N-substituted alkylcarbamate group (12), on treatment in refluxing acetic acid with a trace of HCl also gives 2H-1-benzopyrans (13).[22]

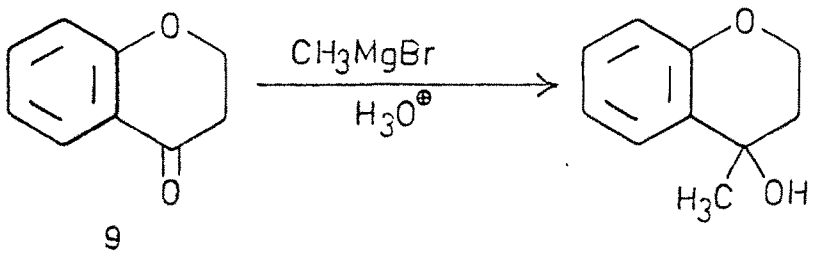
(D) From α, β-unsaturated aldehydes or their precursors

α, β-Unsaturated aldehyde or precursors of α, β-unsaturated aldehyde 3-hydroxy-3-methylbutanal dimethyl acetal (15) when treated with 10% hydrochloric acid,[23] or with pyridine hydrochloride and a phenol (14) gave 2H-1-benzopyrans. Products (16) and (17) were obtained in 3% yield.

(E) From Isobutylene or its precursors

Isobutylenes and 2-chloro-2-methylpentane (which can be readily dehydrohalogenated to 2-methyl-2-butene) react with salisaldehyde (18) in the presence of silica-alumina (150°C) or $ZnCl_2$ (75°) respectively, to give the corresponding 2H-1-benzopyran.[25] The reaction probably involves electrophilic attack of the carbonium ion on the olefin to give a

Dehydration[13,14]



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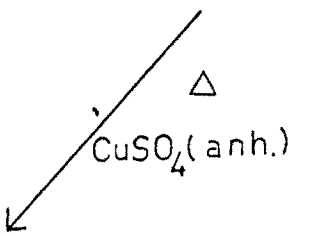

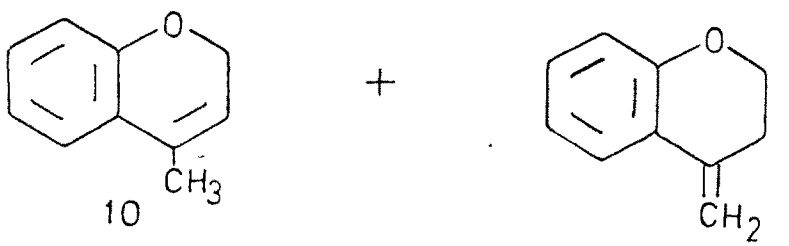

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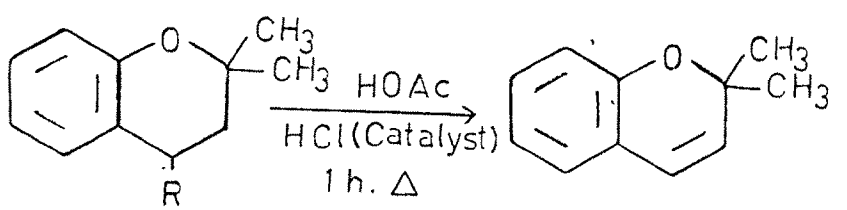
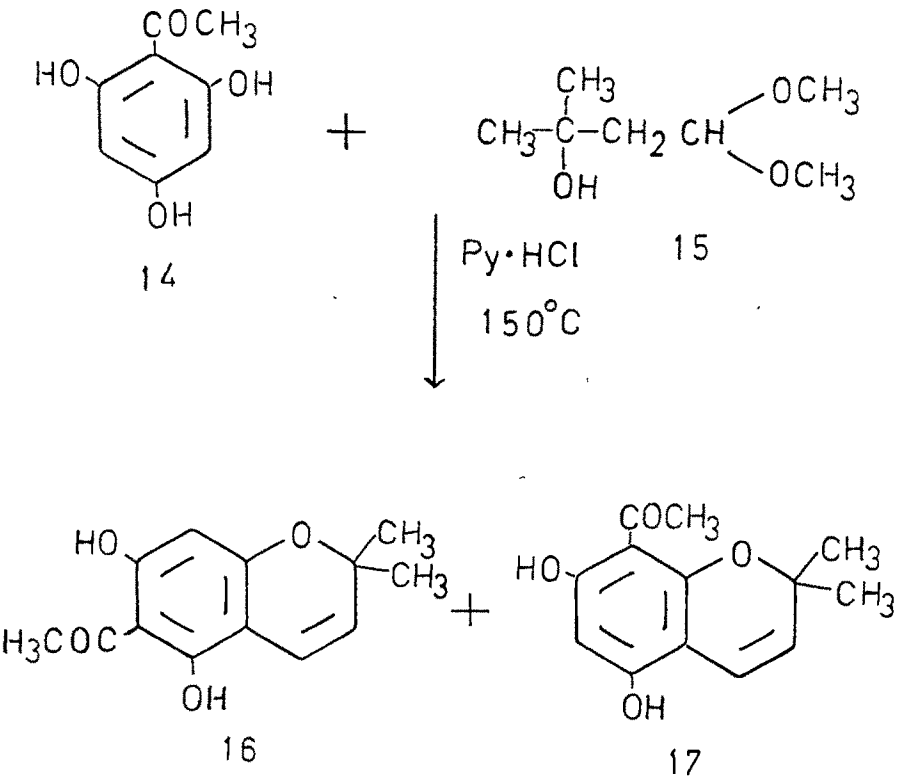


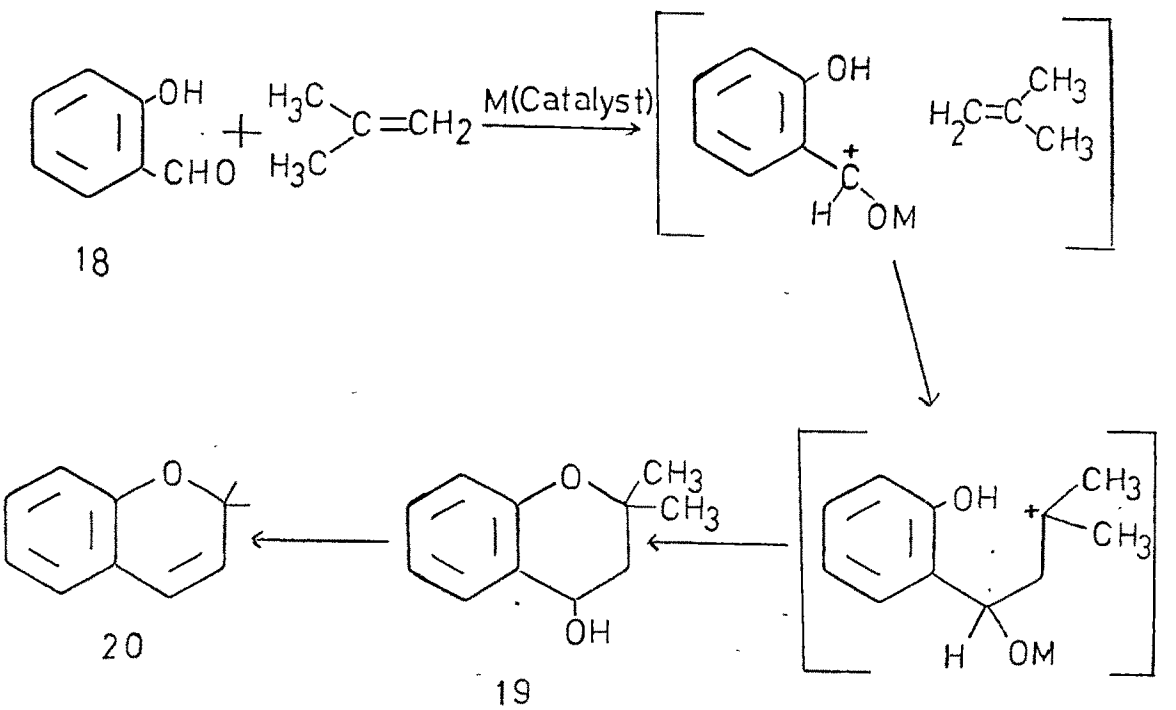
12 13

Where $R = NHCOOC_2H_5$

From ∝, β-unsaturated aldehydes or their precursors[23,24]



From Isobutylene or its precurosrs[25]



chromanol (19) which is then dehydrated to the desired product (20).

(F) Aldol-Type Condensation

The reaction of the sodium salt of salicaldehyde (21) and 2-chloro-1-nitropropane (22) was found to give the saturated alcohol (23) and the 2-methyl-3-nitro-2H-1-benzopyran (24) (35%).[26]

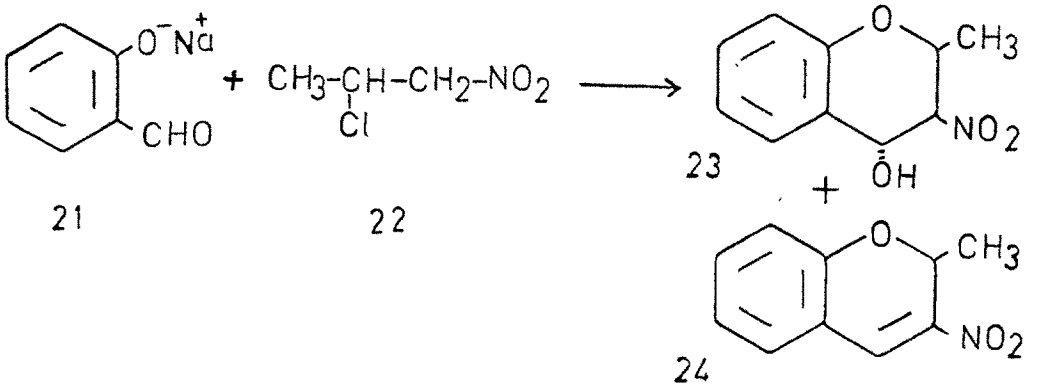
(G) Chromene-3-carboxamide and 3-Cyanochromenes

Condensation of salicaldehyde (18) and acrylonitrile (25) in the presence of 20% NaOH reported by Taylor[27] to yield 4-hydroxy-3-cyanochromene (26) which on dehydration and partial hydrolysis gave chromene-3-carboxamide (27) have same m.p. as reported for 4-hydroxy-3-cyanochroman (26).

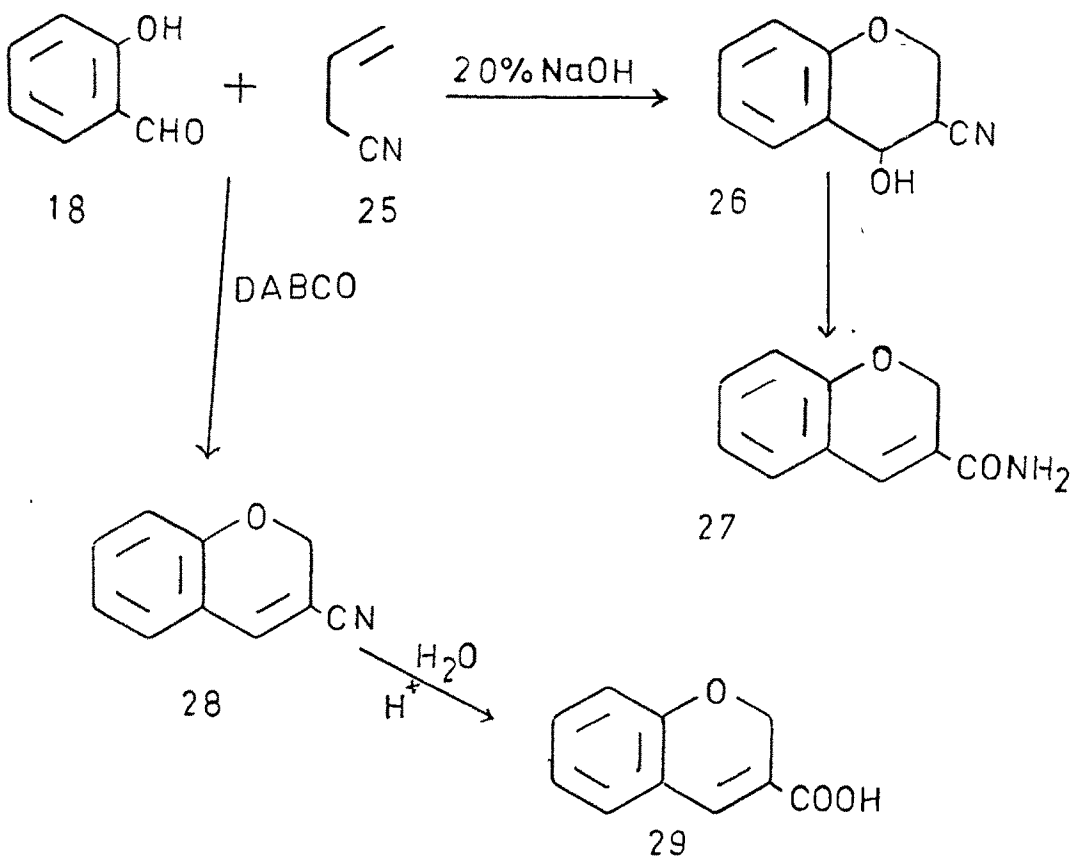
The use of 1,4-diazobicyclo [2,2,2] octane (DABCO)[28] in the condensation of (18) and (25) gave excellent yield of 3-cyano-chromene (28) which on alkaline hydrolysis gave chromene-3-carboxylic acids (29).

Trivedi and co-workers[29] prepared 2-Aryl-3-nitro chromene (32) by condensing salicaldehyde (18) and 3-nitro-styrene (30) in the presence of triethylamine, and found them as analogues to 2-alkyl-3-nitrochromenes which shows antimicrobial activity.[30]

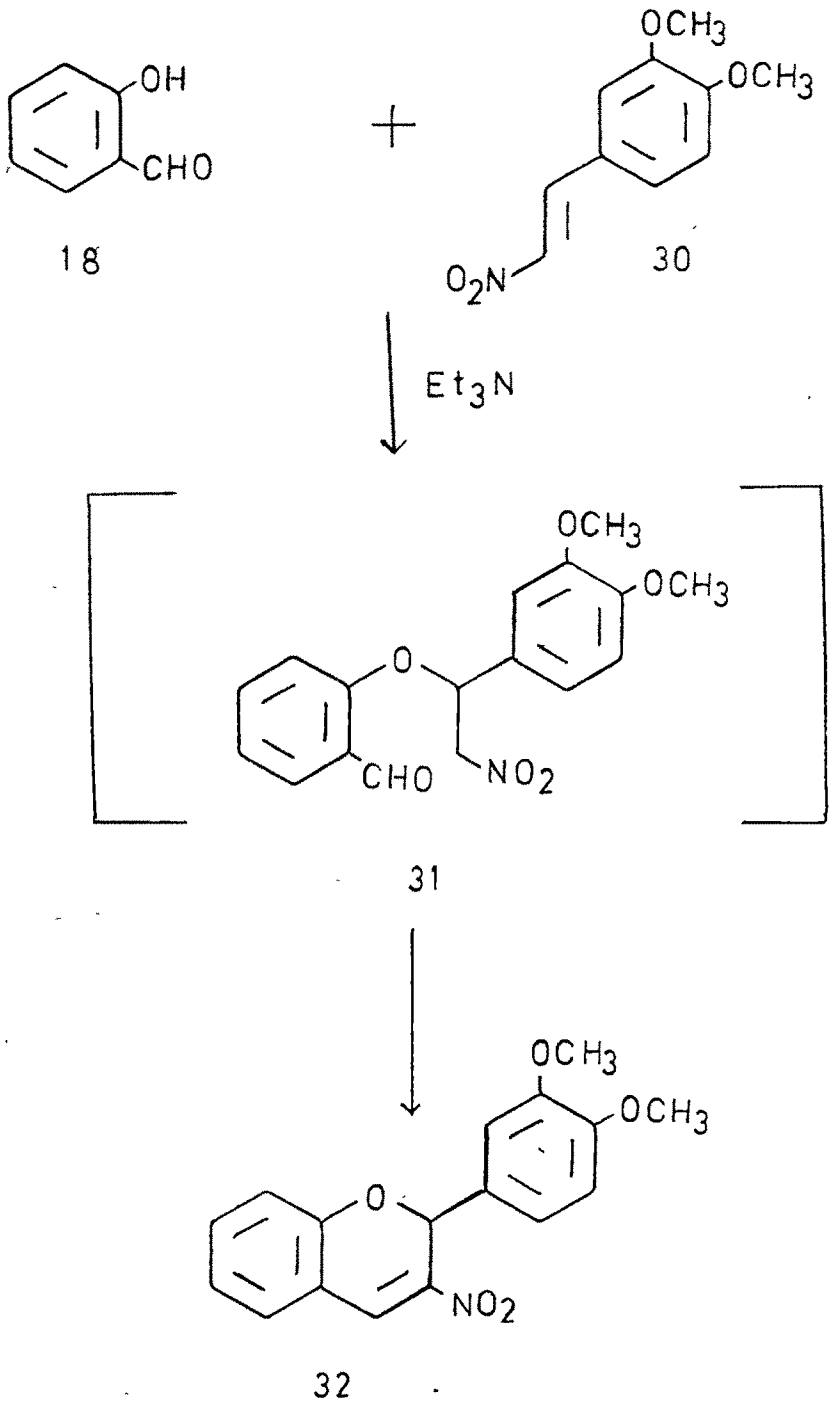
Aldol-Type Condensation[26]



Chromene-3-carboxamide and 3-Cyanochromenes[27,28]



Trivedi and Coworkers[29,30]



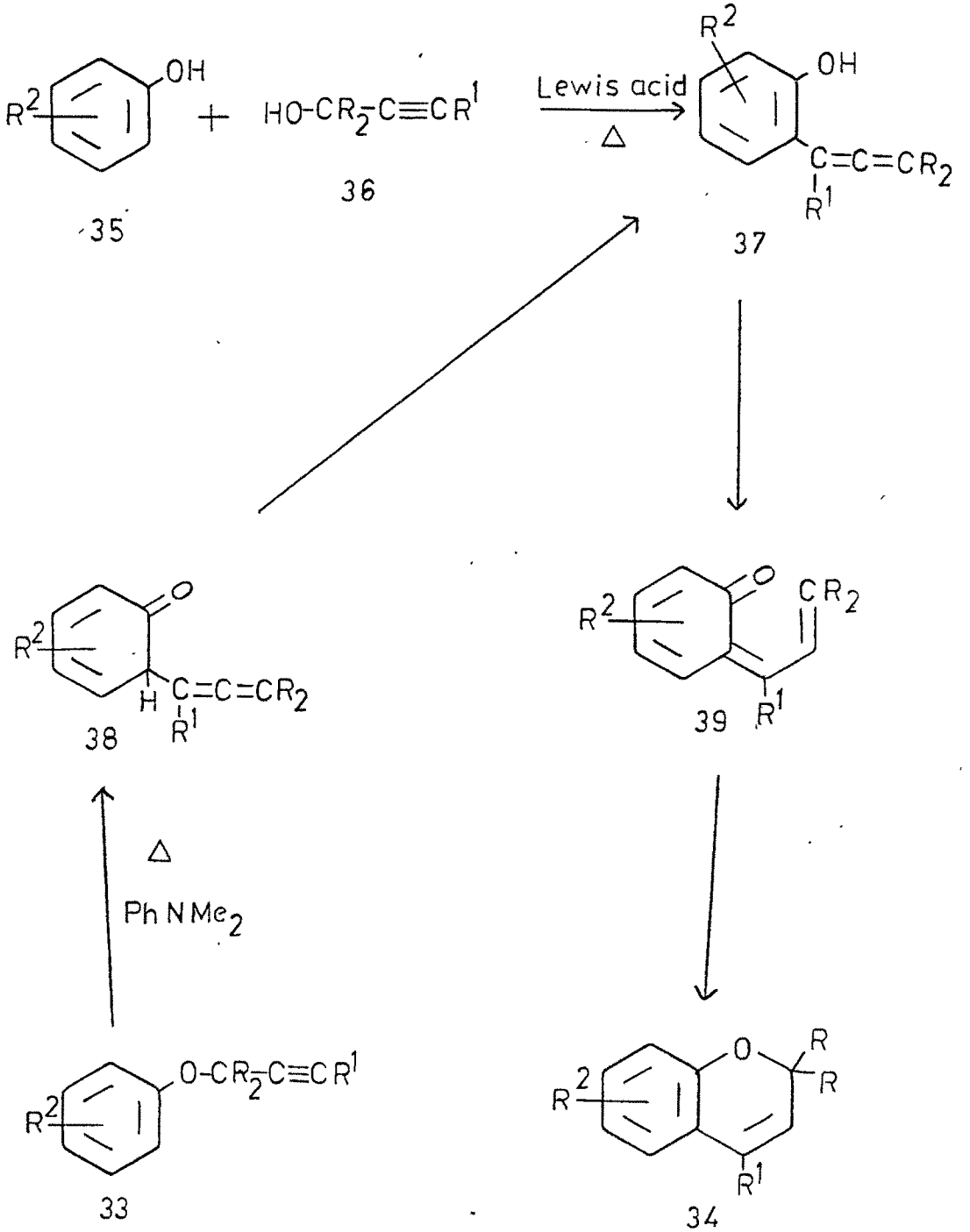
They employed the method of Sakakibara[31] to prepare 2-Aryl-3-nitrochromenes (32) which comprises of the condensation of salicaldehyde with 3-nitrostyrenes in the presence of triethylamine, which proceeds from the intermediate (31).

(H) Thermal rearrangements

The reaction of propargyl phenyl ethers (33) under the influence of refluxing N,N-diethylaniline [32-37] (210-230°C) gives benzopyrans (34). The yields of the thermal rearrangement range from 12 to 48%, whene R=R'=H (33),[37] Where R=H, R'=CH_2OH or CH_2OAc in (33), the yields were reported to be greater than 90%.[35] A number of reports on the acid-catalyzed reactions of phenols (35) with propargyl alcohols (36) lead one to believe that the corresponding allenes (37) might be the intermediate [38-41] on the path to the appropriate benzopyrans (34).[32] Most of the yield reported for the acid-catalyzed reactions are less than 10%.

The mechanism involves a 3,3-sigmatropic rearrangement (33-38) followed by isomerization to the tautomer (37) or (39). The latter rapidly undergoes an electrocyclic rearrangement to the benzopyran (34).[32] A variety of 2,2-dimethyl-2H-1-benzopyrans have beend prepared in high yields (80-95%) by refluxing the appropriate propargyl phenyl ethers (33) with N,N-diethylaniline. Natural products such as ageratochromene, Lapachenol, and evodionol methyl ether have been prepared in this manner.[35]

Mechanism of Thermal rearrangements[32]



(I) Ylide reactions

Cardillo, Merlini and Servi[42] synthesized 2,2-dimethyl substituted 2H-1-benzopyrans by allowing a ylide of 2-butenyl-3-methyltriphenylphosphonium salts (41) to react with benzo-naphtho- and phenanthro orthoquinones by way of methylenequinone as shown in the sequence.

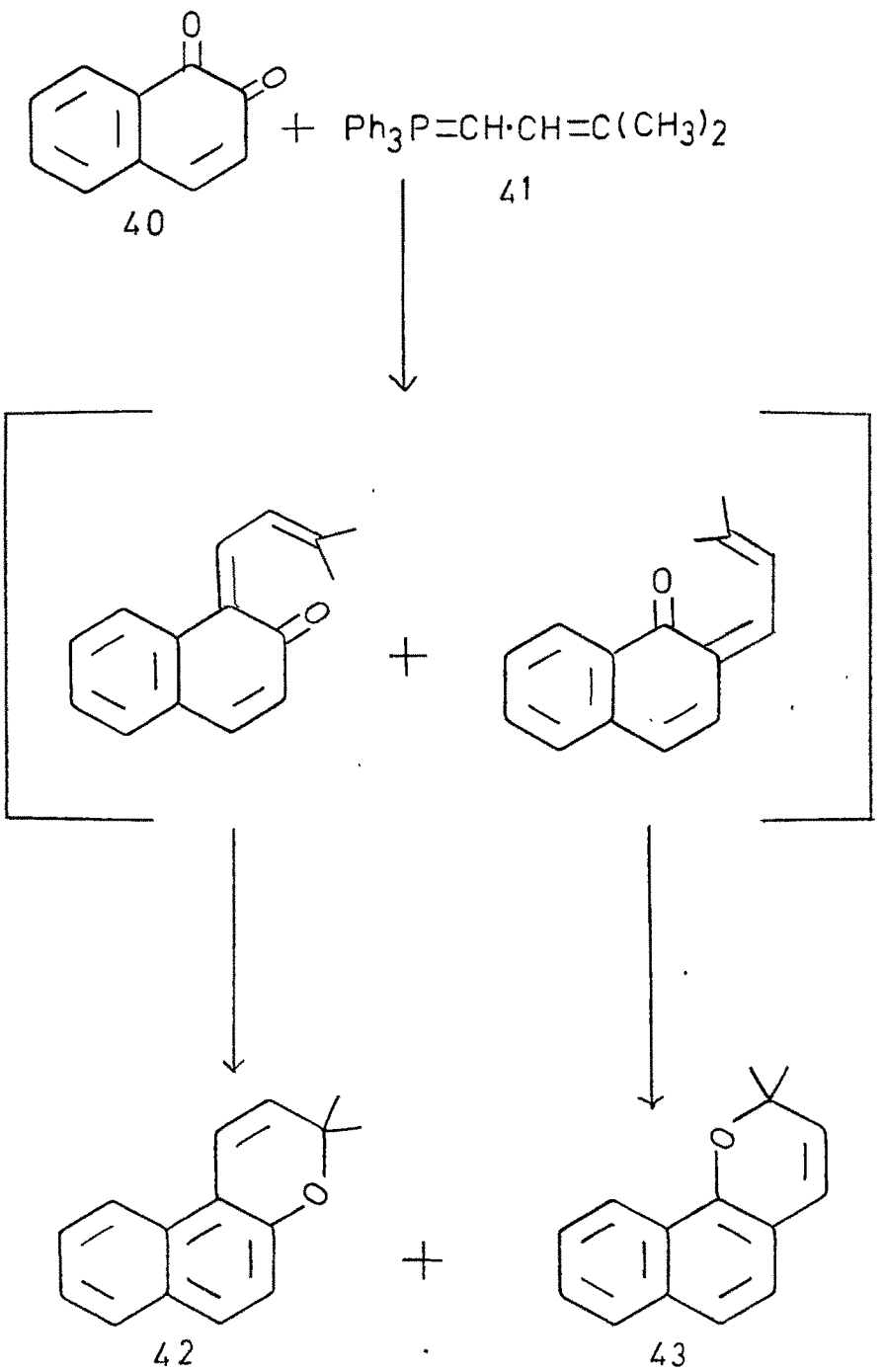
Chromenes are also synthesized from salicaldehyde derivatives using ylides. The sodium salt of salicaldehyde derivative itself acts as base initiating a Wittig reaction in dimethylformamide as solvent. e.g. synthesis of grinimbine (44) an alkaloid found with mahanimbine in Murraya Koenigin,[43] ; Schweiger[44,45] postulated a general ring synthesis employing a vinyl triphenylphosphorium bromide derivatives and salicaldehyde to give 2H-1-benzopyran derivatives (45 a,b).

(J) Dehydrogenation by 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)

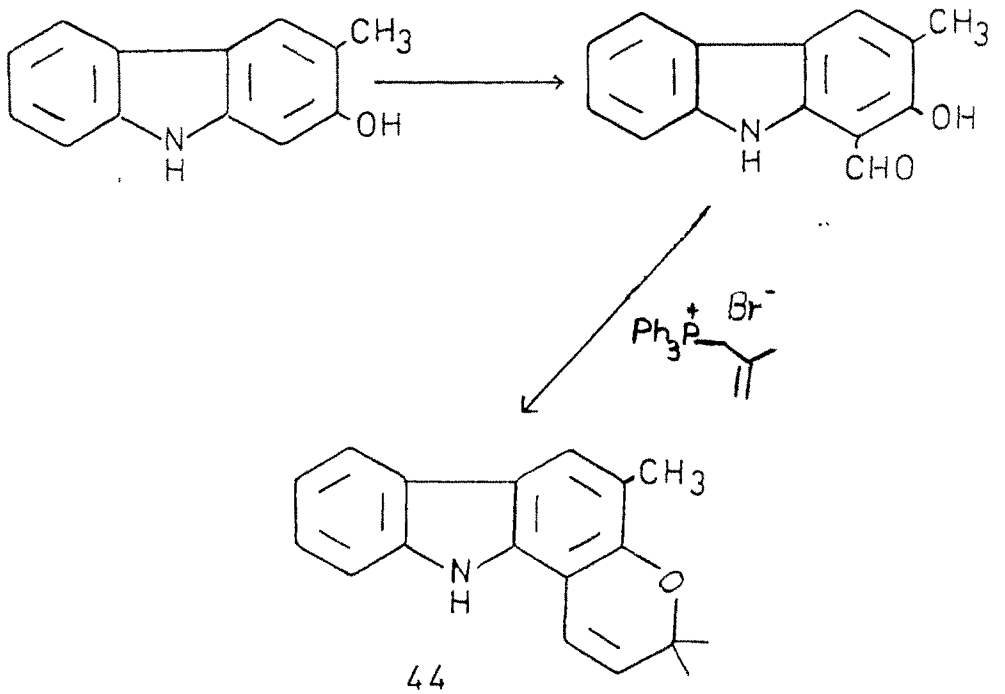
A number of group of workers[46-49] have employed DDQ to prepare 2H-1-benzopyrans (49) from various o-substituted phenol such as (46), (47) and (48) in which R and R' are not hydrogens.

The ratio of DDQ to the phenol was 1:1 for (46) and (47) and 2:1 for (48). Yields for this type of reactions generally ranged from 40-50% for simple molecules. The mechanism of conversion of phenol (46) to benzo-

Ylide reaction[42]

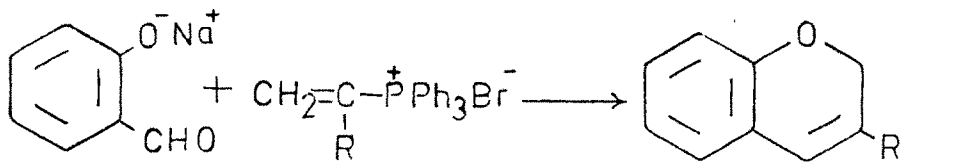


Ylide reaction[44,45]



44

Scheweiger[44,45]



45 a, R=H

b, R=CH_3

pyran (49) is thought to involve a hydride transfer to DDQ forming the intermediate carbonium ion (50), Abstraction of proton from (50) would lead to the o-quinone molecules (51) which rapidly close to benzopyran (49).[46,50]

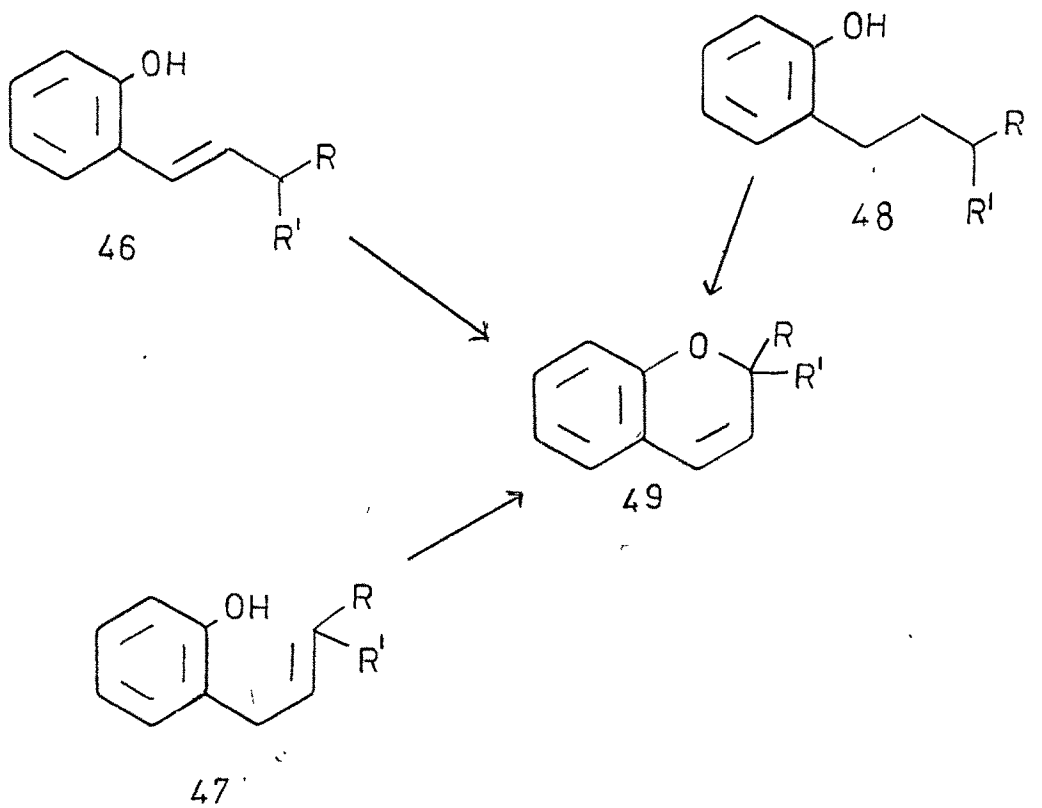
It has been shown that 3,4-dihydro-2H-1-benzopyans may also be converted to the corresponding 2H-1-benzopyrans by the DDQ, for example the conversion of the chroman (52) to the natural product alloevodionol (53)[49] in 40-50% yield.

(K) 4-Chlorochromenes

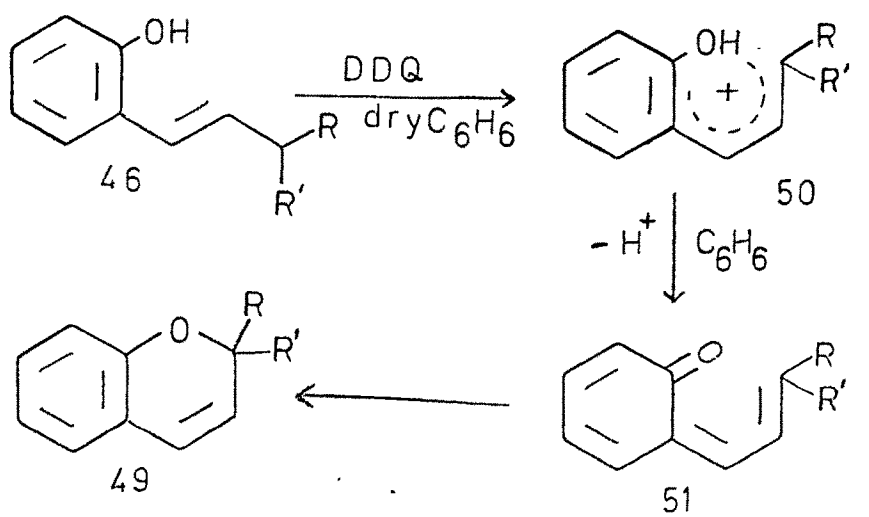
In one very recent paper[51] a number of 4-chloro chromenes and chromanones were synthesized from γ-chloro propargyl aryl ethers proceeding through Claisen rearrangement, depending upon the solvent of choice.

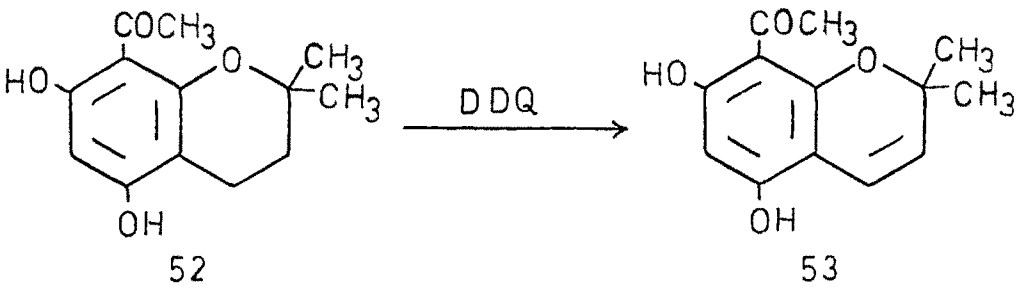
4,6-Dichloro-2,2-dimethyl-2H-1-benzopyran (56a) and 6-Methoxy-4-chloro-2,2-dimethyl-2H-1benzopyran (56b) were synthesized by refluxing respective γ-chloropropargyl aryl ethers (55a & b) in N,N-dimethylaniline (DEA) for 5 minutes, but the same γ-chloropropargyl aryl ethers (55a & b) in refluxing ethylene glycol (EG) for 5 minutes furnished 6-chloro-2,2-dimethyl-2,3-dihydro-4-oxo-4H-1-benzopyran (57a) and 6-Methoxy-2,2-dimethyl-2,3-dihydro-4-oxo-4H-1-benzopyran (57b). γ-chloropropargyl aryl ethers were synthesized from the corresponding lithium salts of arylpropargyl ethers with p-toluenesulphonyl chloride.

Dehydrogenation-by-DDQ[46-49]



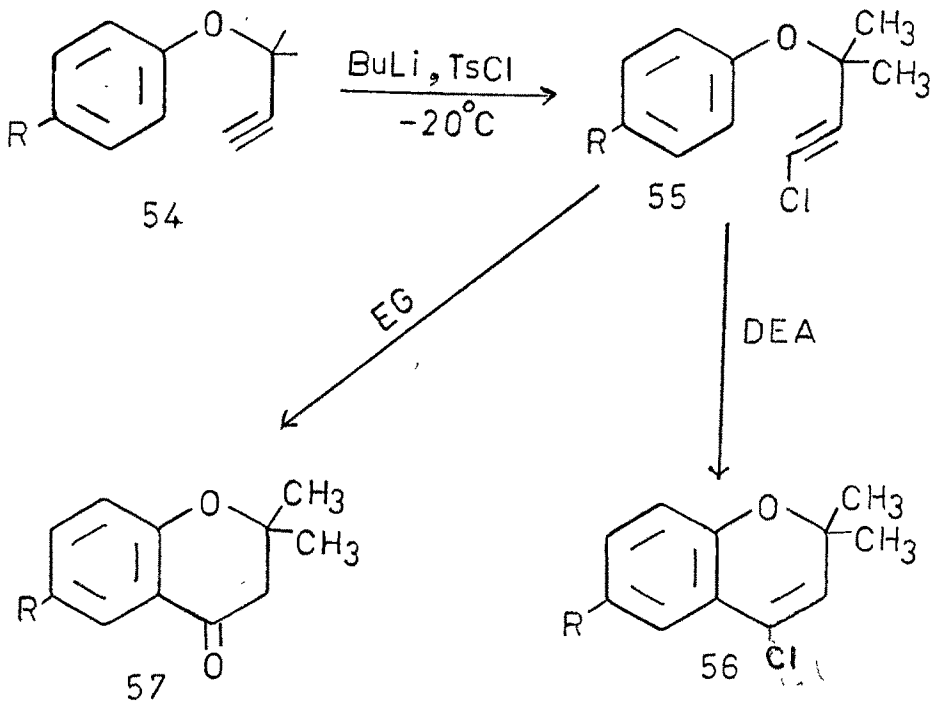
Mechanism





52 53

4-Chlorochromenes[51]



54 55 56 57

a. R=Cl
b. R=CH_3

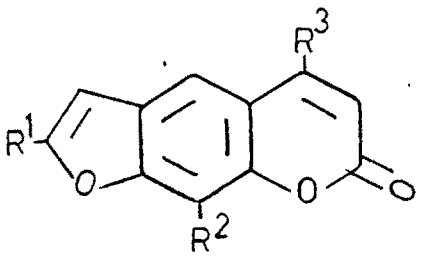
Furochromenes are analogus to the furocoumarins. The biological activity of linear furocoumarins known as psoralene have been known for many years. 8-Methoxypsoralene (58) and the trimethyl analogue, trioxasalene (59) are effective photochemotherapeutic agents in treatment of Psoriasis.[52] While 7-methoxyallopsoralene (60) and 4,7-dimethylallopsoralene (61) form monoadduct with DNA thereby showing antiproliferative effects.[53]

Renee et al.[54] synthesized linear as well as angular furochromene derivatives by condensing different o-hydroxyformyl benzofurans with acrolein, crotonaldehyde etc.

Furochromenes (63) and (64) (R^5=R^7=H, CH_3, R^6=CHO, Ac) were prepared by condensing benzofurans (62) (R^1=R^4=Me, H, R^2, R^3=OH, CHO) with Cl CH_2COCH_3, $ClCH_2CN$, $ClCH_2COOEt$, CH_2=CH-CHO, CH_3-CH=CH-CHO, CH_2=CH_2=CH-$COCH_3$, CH_3-CH=CH-$COCH_3$.

They also synthesized the furochromenes (65,66) derivatives by starting with o-hydroxyformyl derivatives of 2,2-dimethyl-2H-1-benzopyran and then built up furan ring on it.[55] They found these furochromenes as potential photosensitizers and as such they are pharmacochemical analogues of some natural furanocoumarins.

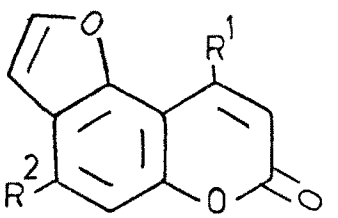
Averback et al[56] reported that linear as well as angular furochromenes that are double methylated or non-methylated



58,59

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

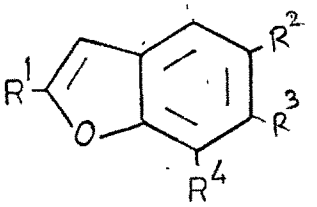
59. $R^1=R^2=R^3=OCH_3$



60,61

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

61. $R^1=R^2=CH_3$



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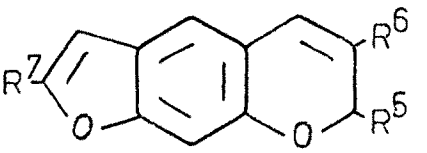

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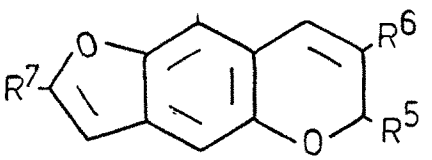

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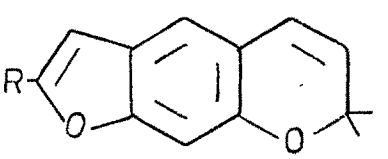

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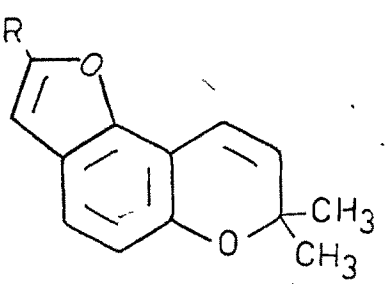


66

In 65&66

R= $COOCH_3$, COOH, H, CHO

$COCH_3$, CN, NO_2

at the pyran ring and substituted at the furan ring by a --CHO, $-COCH_3$, -COOH, -COOEt, -CN or $-NO_2$ groups in the photobiological experiments performed with the yeast Saccharomyces cerevisiae exhibited a photoactivity on cell survial comparable to that of furocoumarins used in photochemotherapy as well as strong capacity for inducing cytoplasmic petite mutants.

In view of these pharmaco-chemical activity of furochromenes, it was thought of interest to synthesize linear as well as angular furochromenes derivatives, starting from different o-hydroxy acyl or formyl derivatives of 2,2-dimethyl-2H-1-benzopyran and then building up furan ring by treatment with either diethylbromomalonate or ethyl bromoacetate.

Present work

In present workf synthesis of following furochromene derivatives are achieved.

(a) 2,2,6-Trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid

(b) 2,2,6,9-Tetramethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid

(c) Ethyl-2,2,9-trimethylfuro [3,2-g]-2H-1-benzopyran-7-carboxylate

(d) 2,2,7-Trimethyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid

(e) 2,2-Dimethyl-7-phenyl- furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid

(f) 2,2,7-Trimethyl-furo [2,3-f]-2H-1-benzopyran

(g) 2,2-Dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran

(a) 2,2,6-Trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (72)

Resacetophenone on C-prenylation [57] with 2-Methyl-but-3-ene-2-ol in presence of $BF_3.Et_2O$ in dry dioxan gave a mixture of 3,5-diprenyl-2,4-dihydroxyacetophenone (67), 3-prenyl-2,4-dihydroxy acetophenone (68) and 5-prenyl-2,4-dihydroxy acetophenone (69). 5-prenyl-2,4-dihydroxy acetophenone was then cyclized with formicacid to 7-hydroxy-6-acetyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (70) which on condensation with diethylbromomalonate in presence of K_2CO_3 gave directly 2,2,6-trimethyl-3,4-dihydro furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (71). The structure (71) was established by pmr spectra. Pmr spectra of (71) showed singlet at δ 1.4 for geminal dimethyl groups at C-2, two triplets at 1.8 and 2.75, J=8Hz for two methylene groups at C-3 and C-4 respectively, two singlets at 6.2 and 7.3 for two aromatic protons at C-9 & C-5 respectively

Fellenberg[9] found that on allowing one equivalent of Grignard reagents to react with coumarin (1) pyrylium chloride (2) was isolated after neutralization with HCl. (2) on further reaction with RMgX gave chromene (3). The solvents most commonly employed in this reaction are anhydrous diethyl ether, benzene or anisole. The time of reaction usually varies from two to four hours and the temperatures from 15° to 100°C.[10]

(B) Dehydrohalogenation

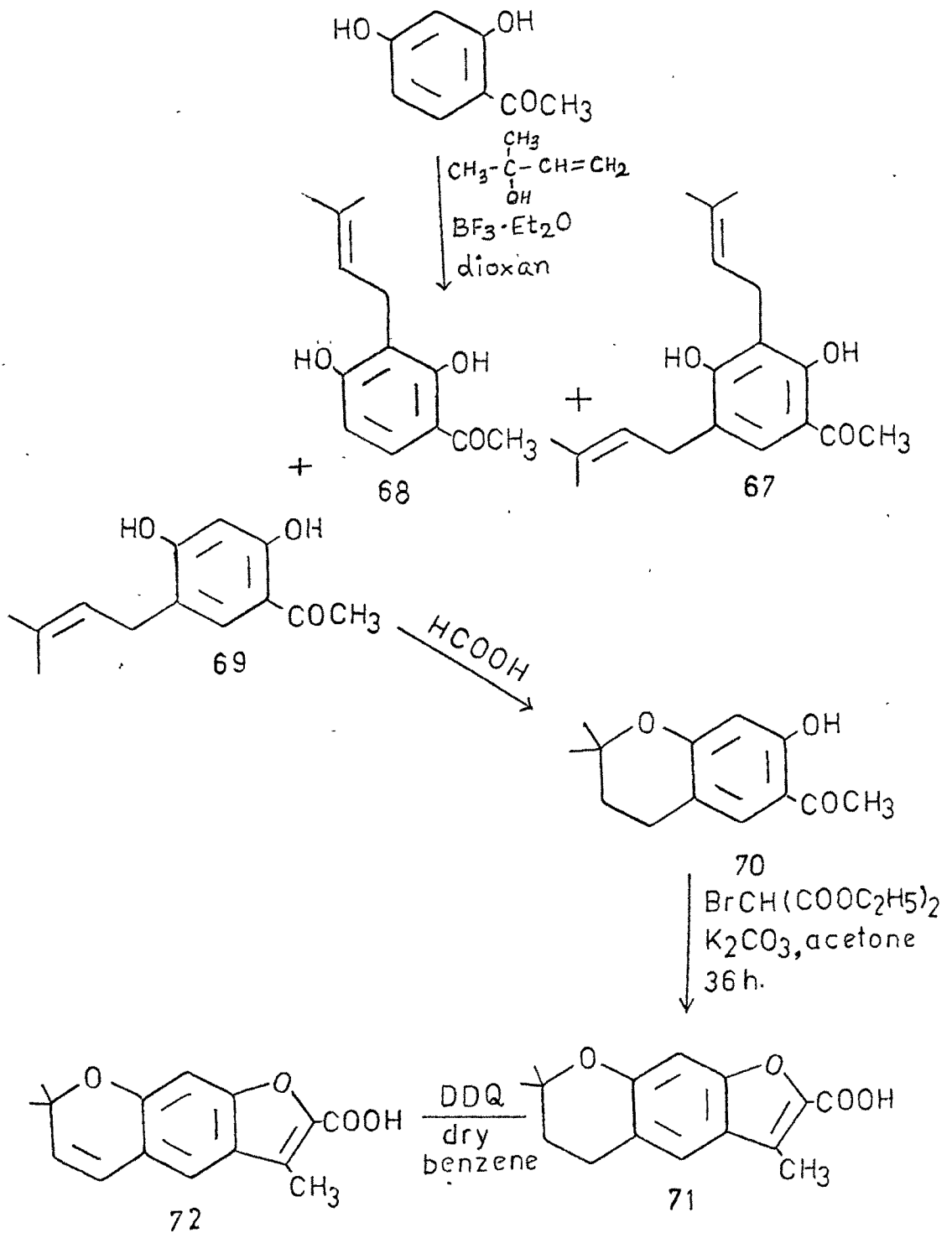
The halogenation of chromans (4) has been accomplished by using iodine in CCl_4 or N-bromosuccinimide (NBS) as the halogenating agent.[11] Distillation of halochromans (5) over sodium alkoxide or treatment with alkoxide in benzene under reflux yield 2H-1-benzopyran (6).

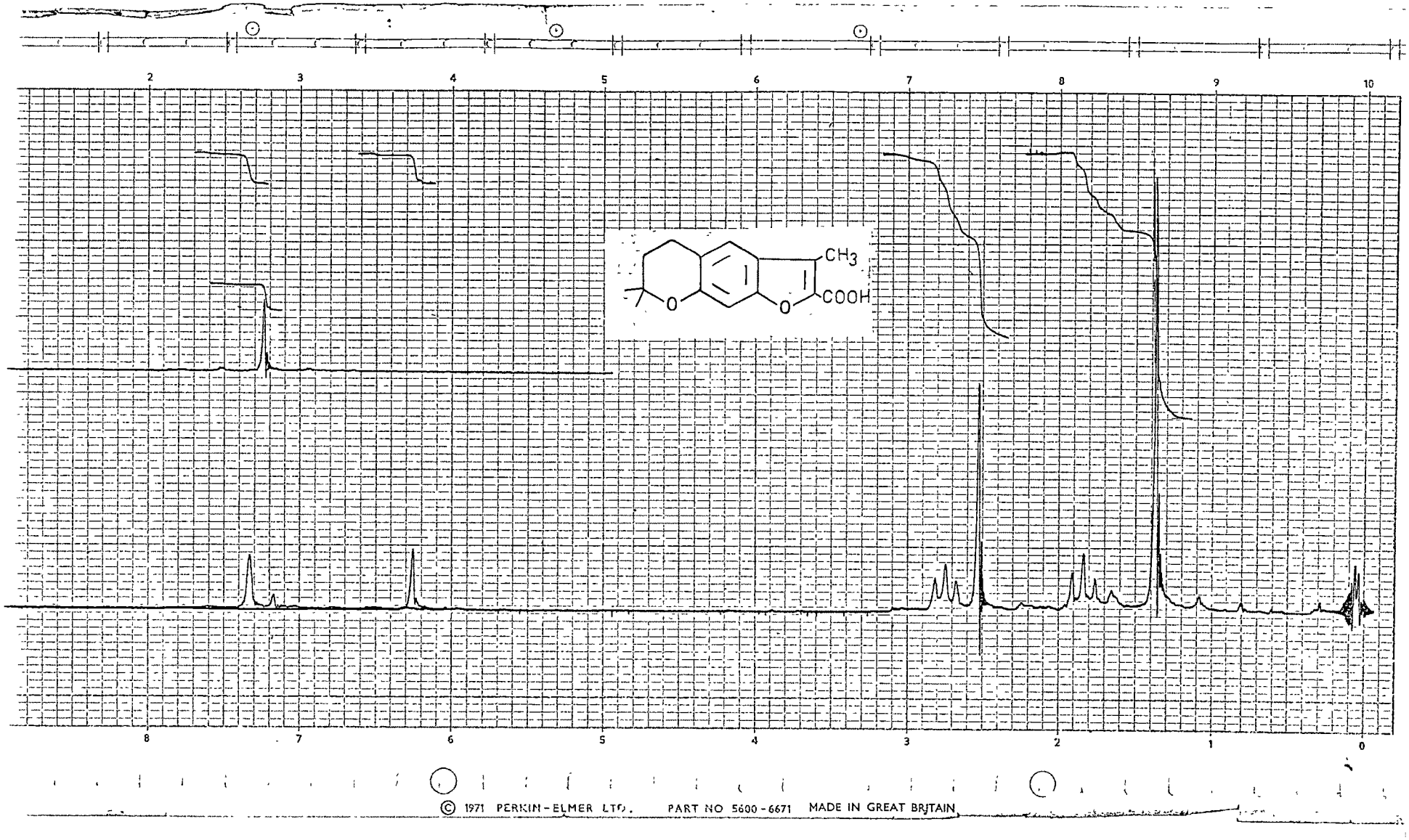
The dehydrohalogenation of 3,4-dihalochromans (7) prepared from the corresponding 2H-1-benzopyrans (6) with halogen, is usually accomplished by reacting the chroman (7) with sodium alkoxide in a solvent under reflux.[12] Sometime heat alone (150-190°C) is sufficient for dehydrohalogenation to give the corresponding 4-halo-2H-1-benzopyran[10] (8).

(C) Dehydration

The treatment of chromanones (9) with Grignard reagents followed by dehydration has been used to prepare 2H-1-benzopyrans [13-14] (10). Copper sulphate at 150-60°C give yields of 58 to 100%, In this reaction, alkylidene chroman derivatives (11) arise as side products.[14]

SCHEME-I

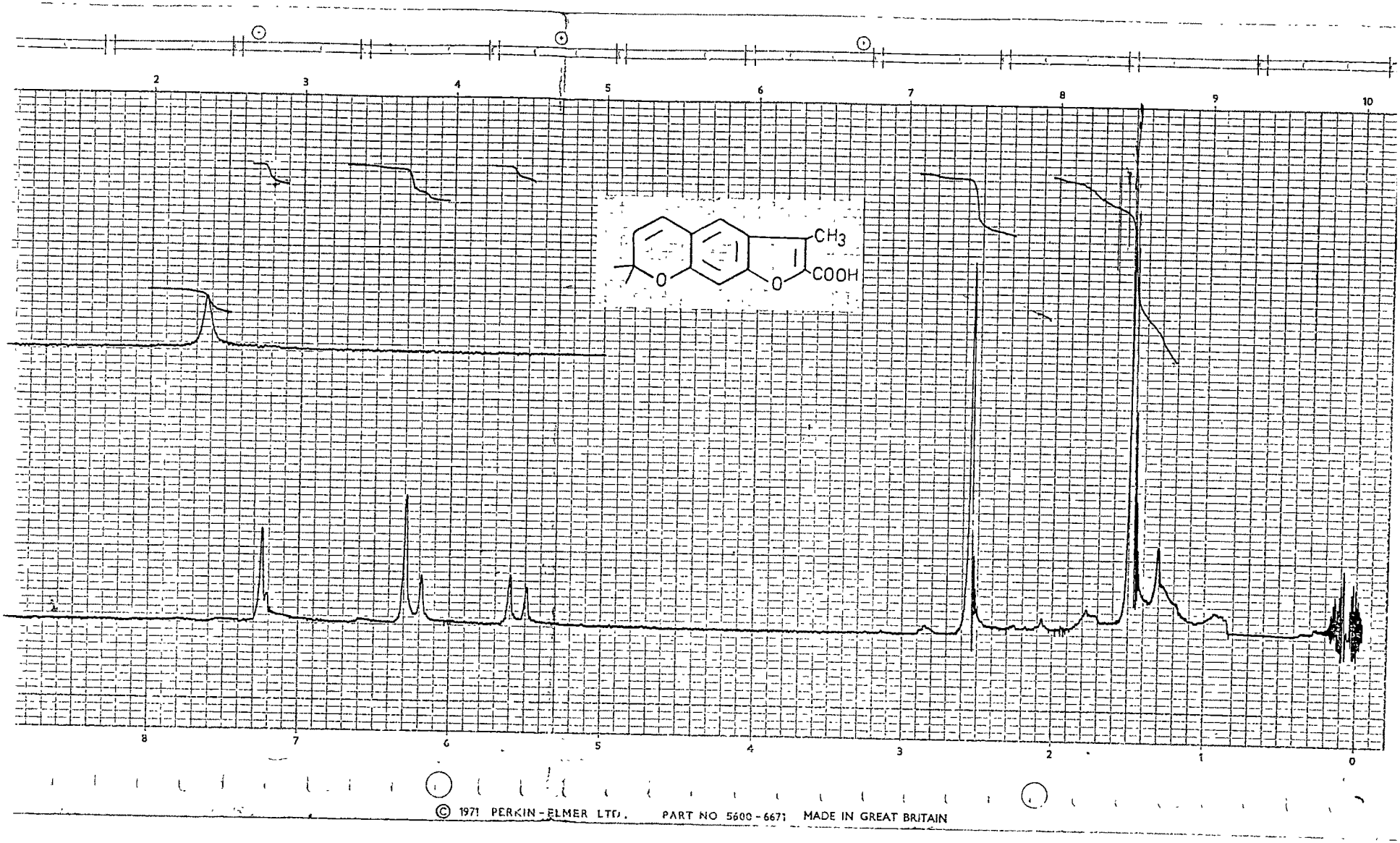

HO
OH
COCH3
CH3-C(CH3)(OH)-CH=CH2
BF3·Et2O
dioxan
68
67
69
HCOOH
70
BrCH(COOC2H5)2
K2CO3, acetone
36 h.
DDQ
dry
benzene
COOH
CH3
71
72



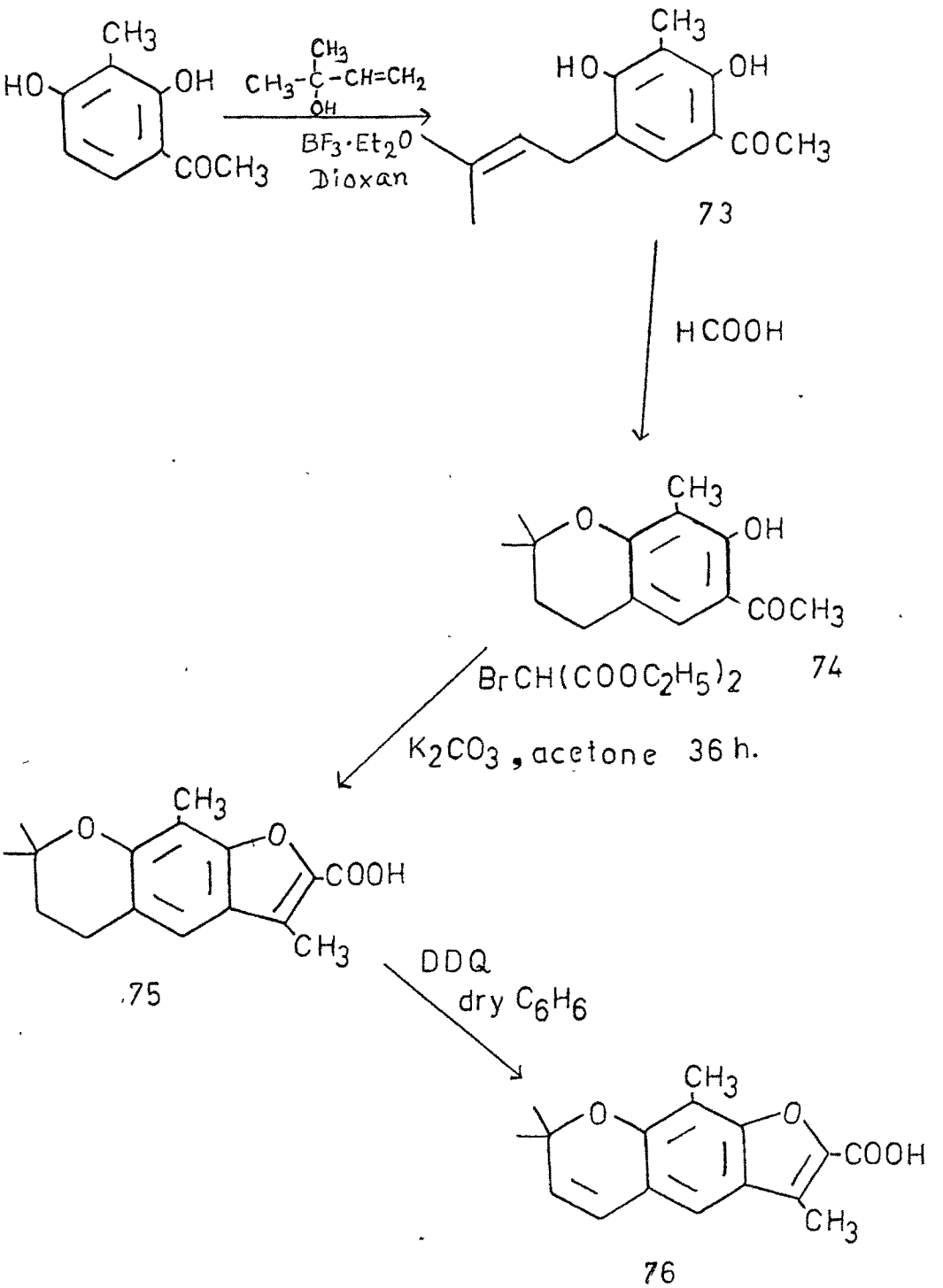
One singlet at 2.5 for $-CH_3$ group at C-6 and one singlet at 12.0 for -COOH group at C-7. Dehydrogenation of (71) was carried out with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in refluxing benzene to give 2,2,6-trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (72), the structure (72) was established by pmr spectra, which showed singlet at δ 1.4 for geminal dimethyl grous at C-2, two doublets at 5.5 and 6.2, J=10Hz for two protons at C-3 and C-4 respectively, two singlets at 6.3 and 7.2 for two aromatic protons at C-9 and C-5 respectively, one singlet at 2.4 for methyl groups at C-6 and one singlet at 12.6 for -COOH group at C-7. (Scheme-I)

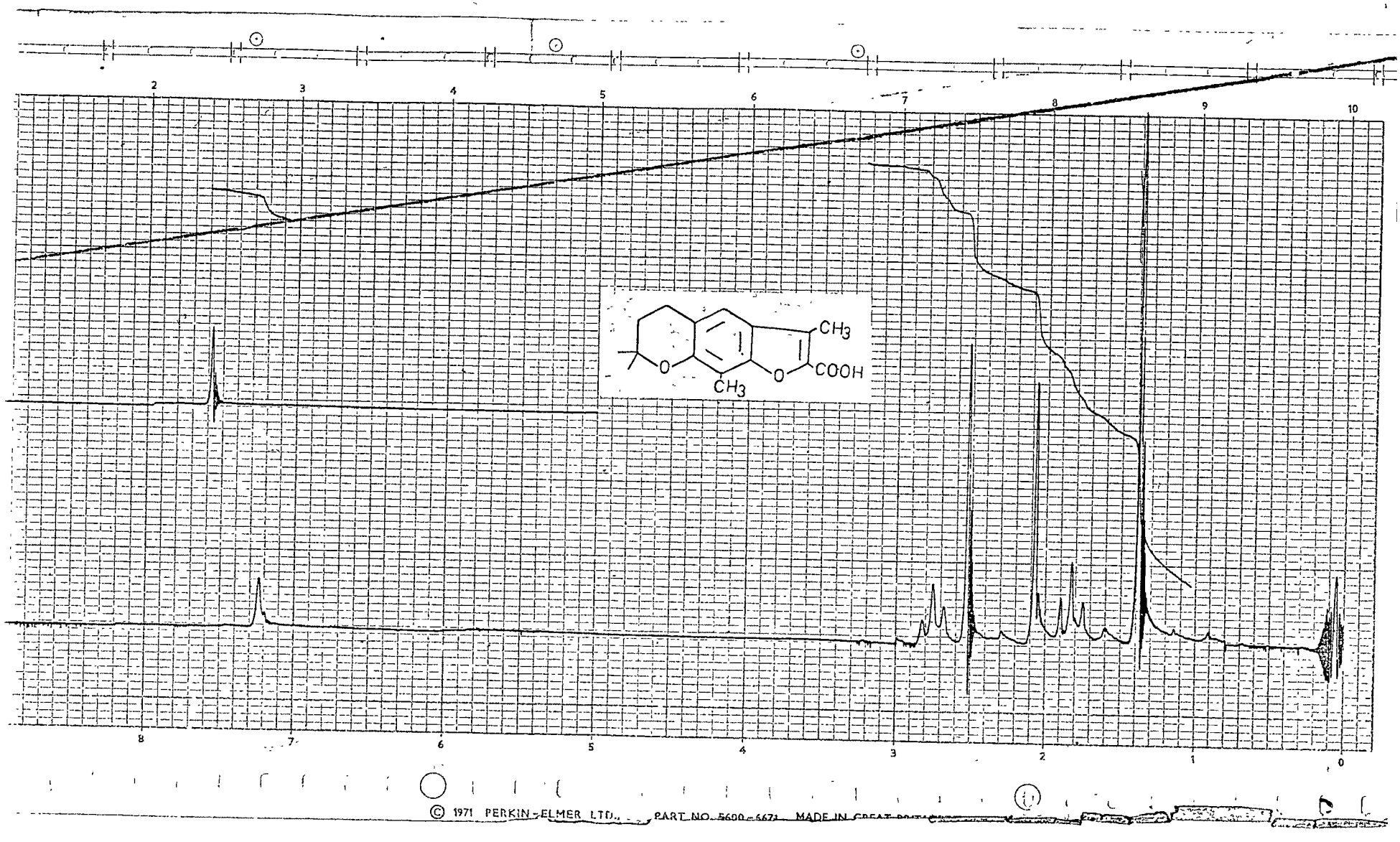
(b) 2,2,6,9-Tetramethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (76)

2,4-Dihydroxy-3-methyl acetophenone 3 on C-prenylation with 2-methyl-but-3-ene-2-ol in dry dioxan in presence of $BF_3.Et_2O$ gave 5-prenyl-2,4-dihydroxy-3-methyl acetophenone (73). (73) was then cyclized with formic acid[58] to 7-hydroxy-6-acetyl-2,2,8-trimethyl-3,4-dihydro-2H-1-benzopyran (74) which on condensation with diethylbromomalonate in presence of K_2CO_3 gave directly 2,2,6,9-tetramethyl-3,4-dihydro-furo [3,2-g] -2H-1-benzopyran-7-carboxylic acid (75), the structure (75) was established by pmr spectra which showed singlet at δ 1.4 for geminal dimethyl groups at C-2, two triplets at 1.8 and 2.7, J=8Hz for two methylene groups at C-3 and C-4 respectively, one singlet at 7.2 for one proton at C-5, two singlets for three protons at 2.0 and 2.5 for two methyl groups at C-9



SCHEME-II

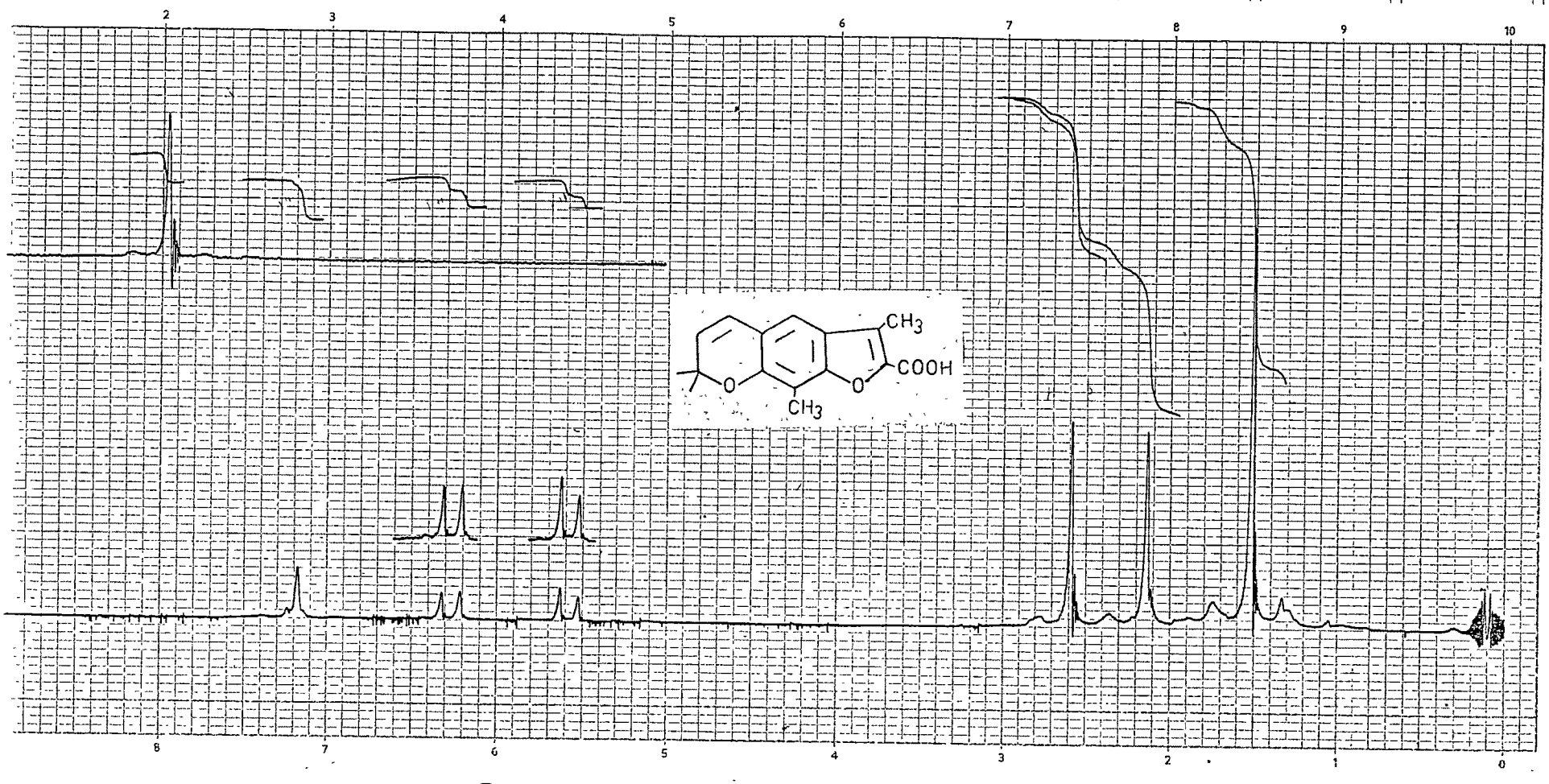

CH3
HO
OH
COCH3
CH3
CH3-C-CH=CH2
OH
BF3·Et2O
Dioxan
73
HCOOH
74
BrCH(COOC2H5)2
K2CO3, acetone 36 h.
75
DDQ
dry C6H6
76
O
COOH



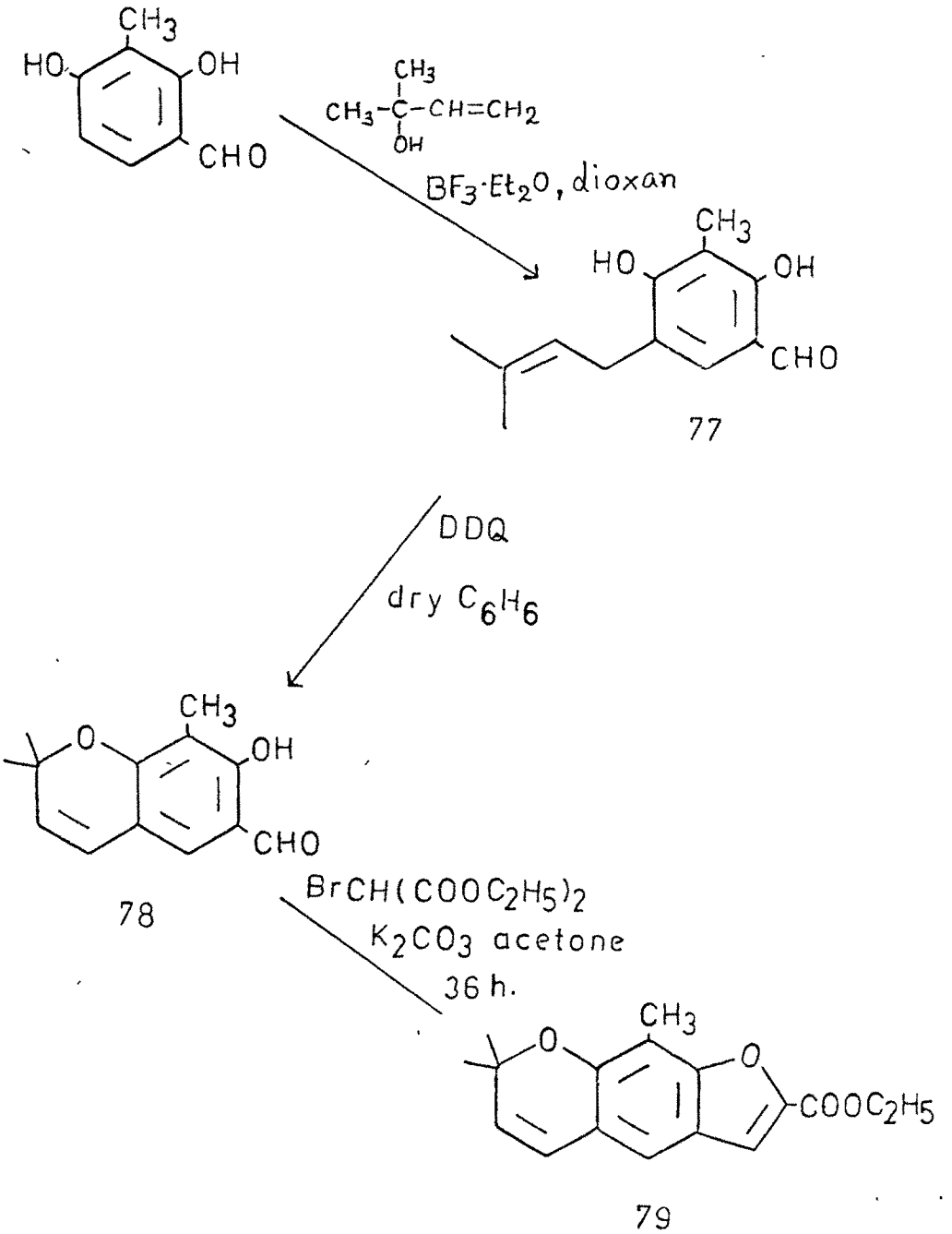
and C-6 and one singlet at 12.5 for -COOH group at C-7. Dehydrogenation of (75) was carried out with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene to gave 2,2,6,9-tetramethyl- furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (76), the structure (76) was established by pmr spectra which showed singlet at δ 1.4 for geminal dimethyl groups at C-2 two doublets at 5.5 and 6.2, J=10Hz for two protons at C-3 and C-4 respectively, one singlet at 7.1 for one aromatic proton at C-5, two singlets for three protons at 2.1 and 2.4 for two methyl groups at C-9 and C-6 respectively and one singlet at 12.9 for -COOH group at C-7. (Scheme-II)

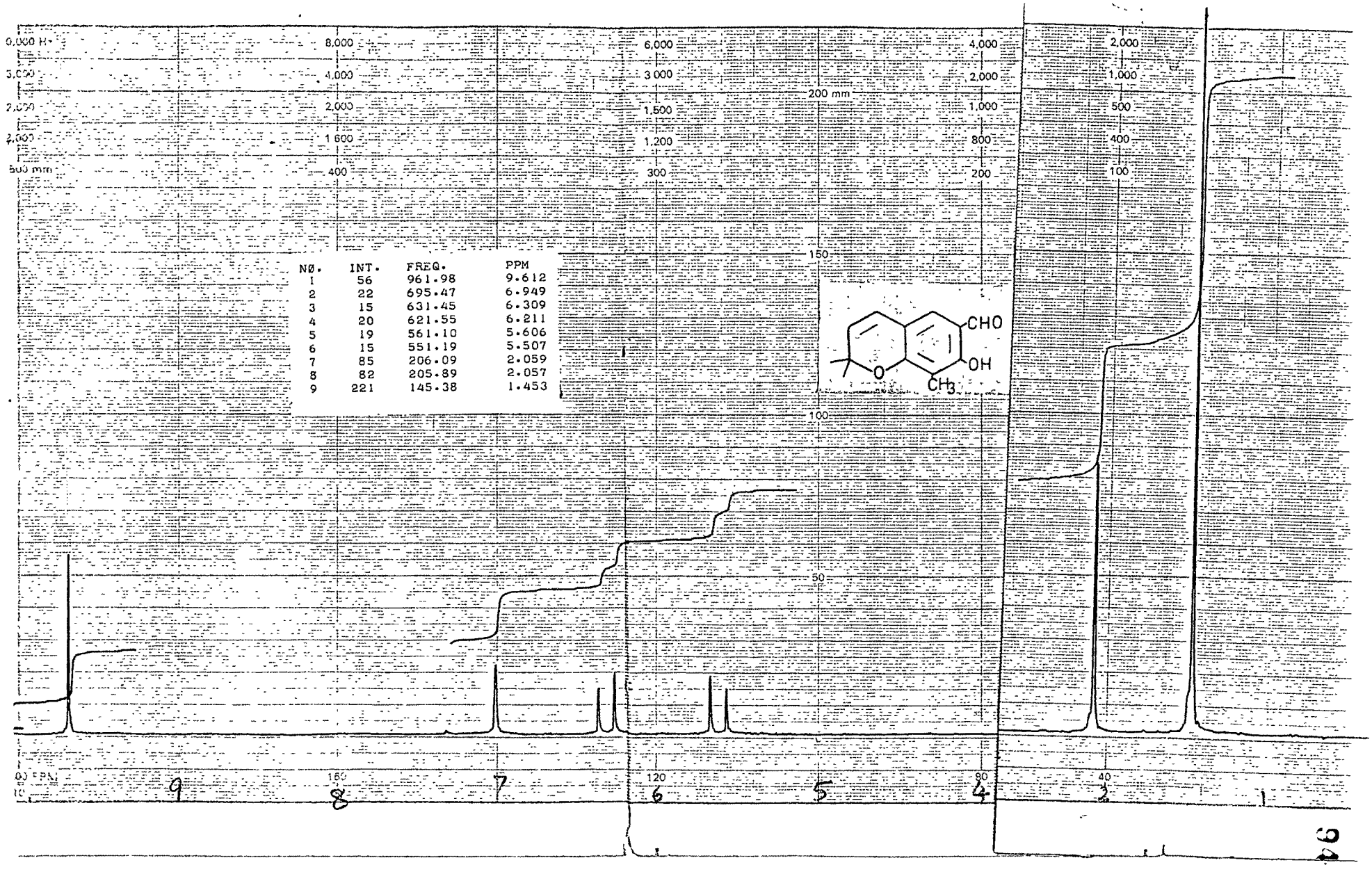
(C) Ethyl-2,2,9-trimethyl- furo [3,2-g]-2H-1-benzopyran-7-carboxylate (79)

2,4-Dihydroxy-3-methyl benzaldehyde, on C-prenylation with 2-methyl-but-3-ene-2-ol in presence of $BF_3.Et_2O$ afford 2,4-dihydroxy-3-methyl-5-prenyl benzaldehyde (77) which was cyclodehydrogenated with DDQ to gave 7-hydroxy-2,2,8-trimethyl-2H-1-benzopyran-6-carboxaldehyde (78). The structure (78) was confirmed by pmr spectra of (78) (220 MHz/$CDCl_3$) which showed singlet at δ 1.45 for geminal dimethyl groups at C-2 two doublets at 5.6 and 6.3, J=10Hz for two protons at C-3 and C-4 respectively, one singlet at 2.1 for one methyl group at C-8, one singlet at 7.0 for one aromatic proton at C-5 and one singlet at 9.65 for one aldehydic proton. (78) on condensation with diethylbromomalonate in dry acetone in



SCHEME-III

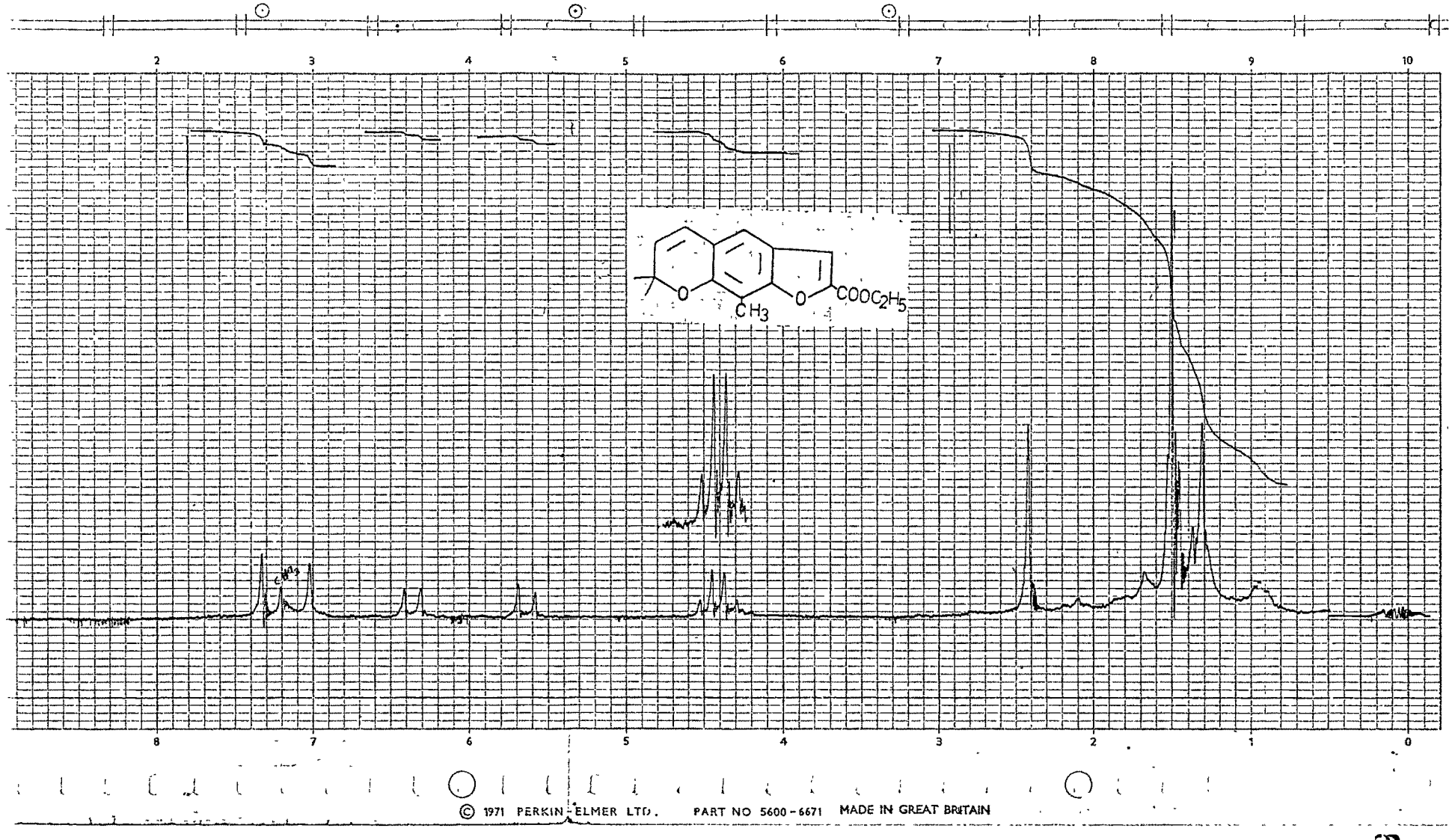

CH3
HO
OH
CHO
CH3
CH3-C-CH=CH2
OH
BF3·Et2O, dioxan
77
DDQ
dry C6H6
78
BrCH(COOC2H5)2
K2CO3 acetone
36 h.
COOC2H5
79


NØ. INT. FREQ. PPM
1 56 961.98 9.612
2 22 695.47 6.949
3 15 631.45 6.309
4 20 621.55 6.211
5 19 561.10 5.606
6 15 551.19 5.507
7 85 206.09 2.059
8 82 205.89 2.057
9 221 145.38 1.453
CHO
OH
O
CH3
200 mm
150
100
50
9
8
7
6
5
4
3
1

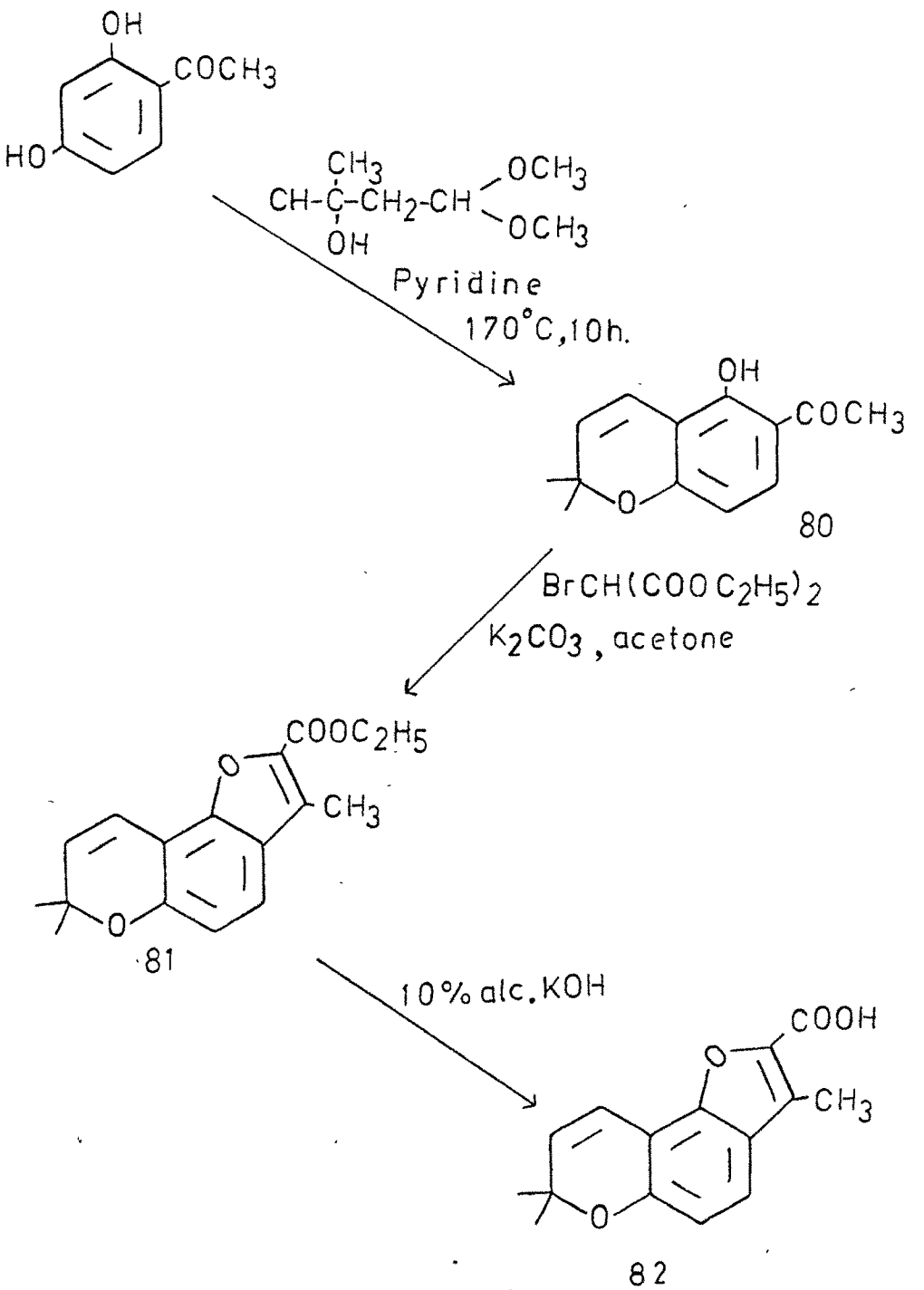
presence of K_2CO_3 gave ethyl-2,2,9-trimethyl- furo [3,2-g]-2H-1-benzopyran-6-carboxylate (79), the structure (79) was confirmed by pmr spectra which showed a triplet for three protons at δ 1.2, J=8Hz, for methyl group of ester, one quartet for two protons at 4.3 for methylene group of ester, singlet at 1.4 for geminal dimethyl groups at C-2, two doublets at 5.5 and 6.25, J=10Hz for two protons at C-3 and C-4 and two singlet at 6.95 and 7.3 for two protons at C-6 (furan ring) and C-5 (aromatic) respectively. The quantity of this ester was so poor that further hydrolysis and decarboxylation to furochromene could not be carried out. (Scheme-III)

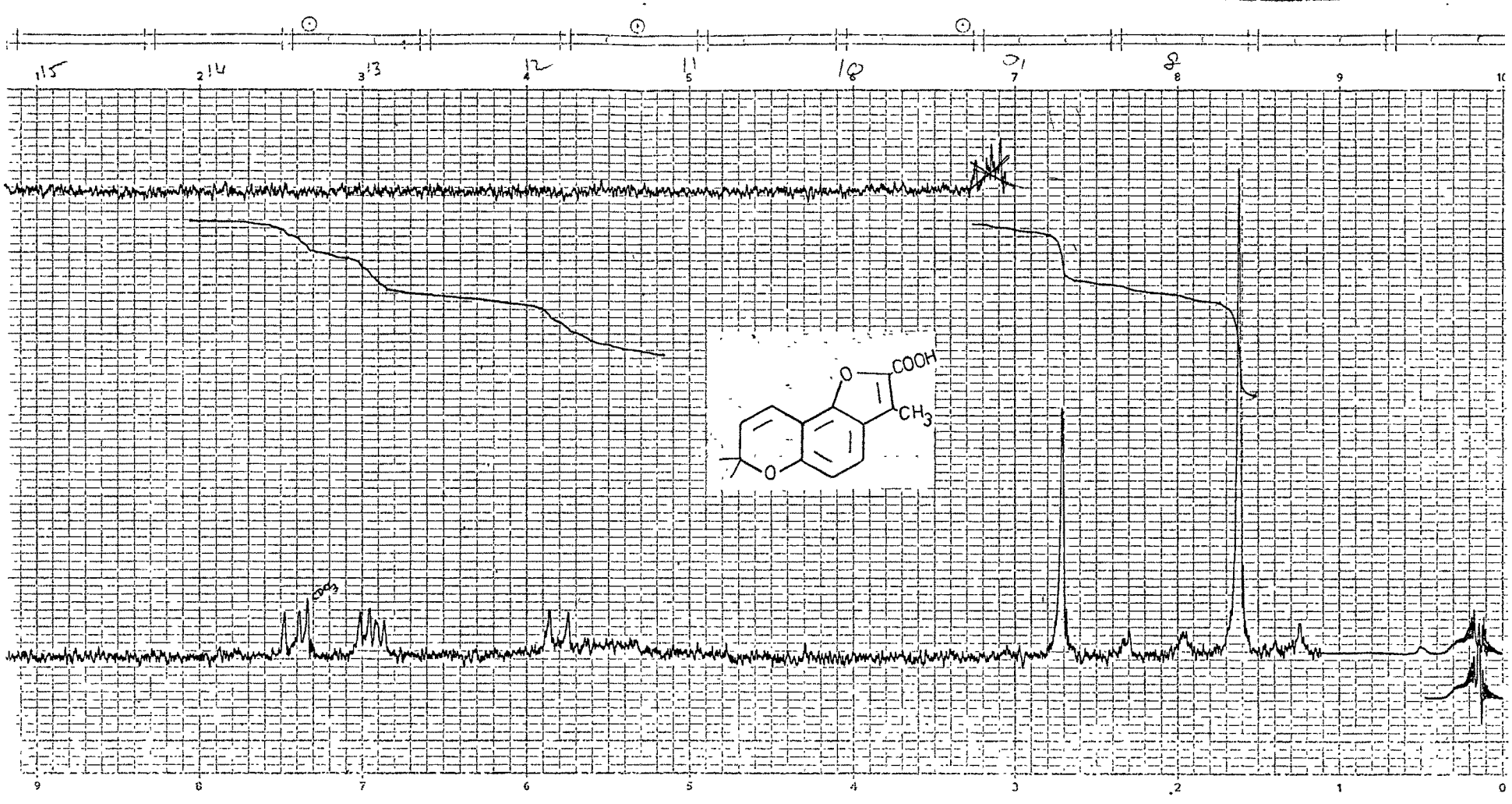
(d) 2,2,7-Trimethyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (82)

5-Hydroxy-6-acetyl-2,2-dimethyl-2H-1-benzopyran[59] (80) was prepared by condensation of resacetophenone with hydroxy isovaleraldehyde dimethyl acetal in presence of pyridine. (80) was then condensed with diethylbromomalonate in presence of K_2CO_3 to give ethyl-2,2,7-trimethyl-furo [2,3-f]-2H-1-bebnzopyran-6-carboxylate (81) which on alkaline hydrolysis afforded 2,2,7-trimethyl- furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (82) soluble in aq. $NaHCO_3$, structure (82) was confirmed by pmr and IR spectra. IR spectra (KBr disc) showed a band at 1690 cm^{-1} for carbonyl group of acid. Pmr spectra of (82) showed singlet at 1.5 for geminal dimethyl group at C-2, singlet at 2.6 for methyl group at C-7, two doublets at 5.65 and 6.85, J=10Hz,

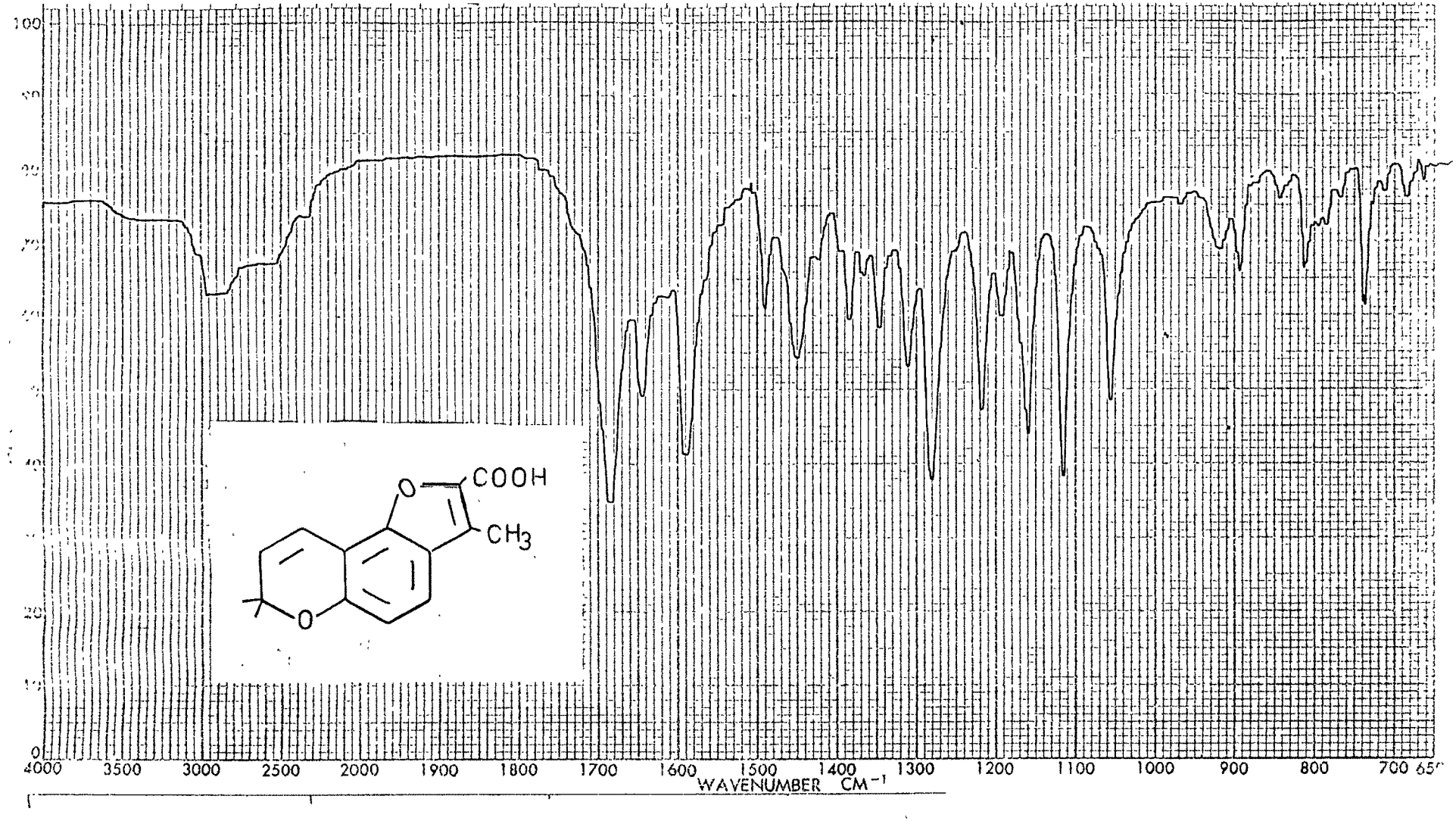


SCHEME-IV


OH
COCH3
HO
CH3
CH-C-CH2-CH
OH
OCH3
OCH3
Pyridine
170°C,10h.
OH
COCH3
O
80
BrCH(COOC2H5)2
K2CO3, acetone
COOC2H5
O
CH3
O
81
10% alc.KOH
COOH
O
CH3
O
82



 PART NO 5600-6671 MADE IN GREAT BRITAIN


100
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM⁻¹
COOH
CH3
O
O

for two protons at C-3 and C-4 respectively, two doublets at 6.7 and 7.3, J=9Hz for two aromatic protons at C-8 and C-9 respectively. (Scheme-IV)

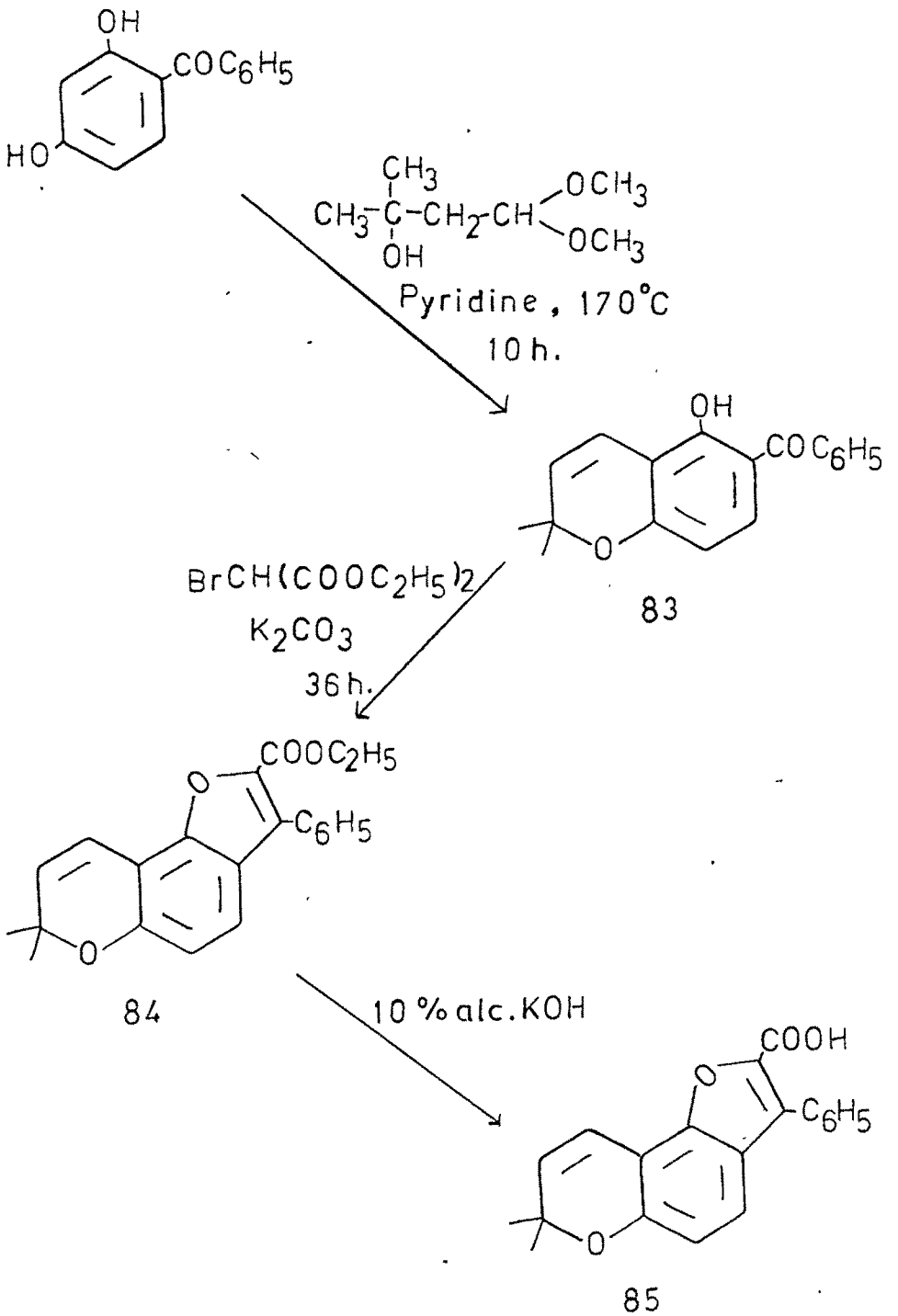
(e) 2,2-Dimethyl-7-phenyl furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (85)

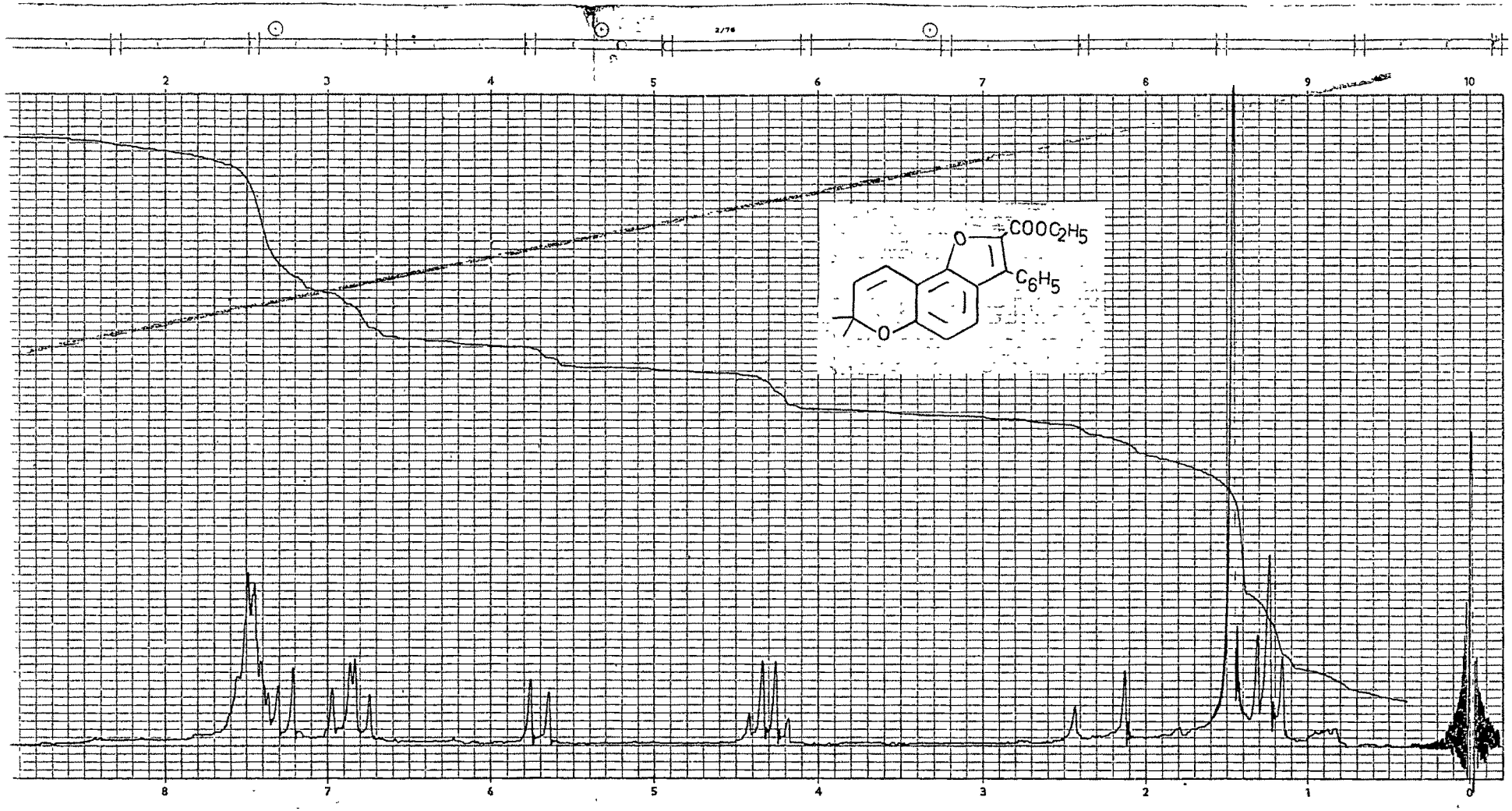
2,4-Dihydroxybenzophenone on condensation with hydroxy isovaleraldehyde dimethylacetal in presence of pyridine gave 5-hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran (83) which on condensation with diethylbromomalonate in presence of K_2CO_3 gave ethyl-2,2-dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylate (84). Structure (84) was confirmed by pmr spectra which showed triplet at δ 1.25, J=8Hz for three protons of methyl group of ester, one quartet for two protons at 4.3, J=8Hz for methylene group of ester, one singlet for six protons at 1.5 for two methyl groups at C-2, two doublets at 5.7 and 6.9, J=10Hz for two protons at C-3 and C-4 respectively two doublets at 6.8 and 7.25, J=9Hz for two protons at C-8 and C-9 respectively and one multiplet for five protons at 7.25 for phenyl group at C-7. (84) on alkaline hydrolysis afforded 2,2-dimethyl-7-phenyl furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (85) soluble in aq. $NaHCO_3$. The structure (85) was proved by IR spectra which shows a band at 1690 cm^{-1} for carbonyl group of -COOH. (Scheme-V).

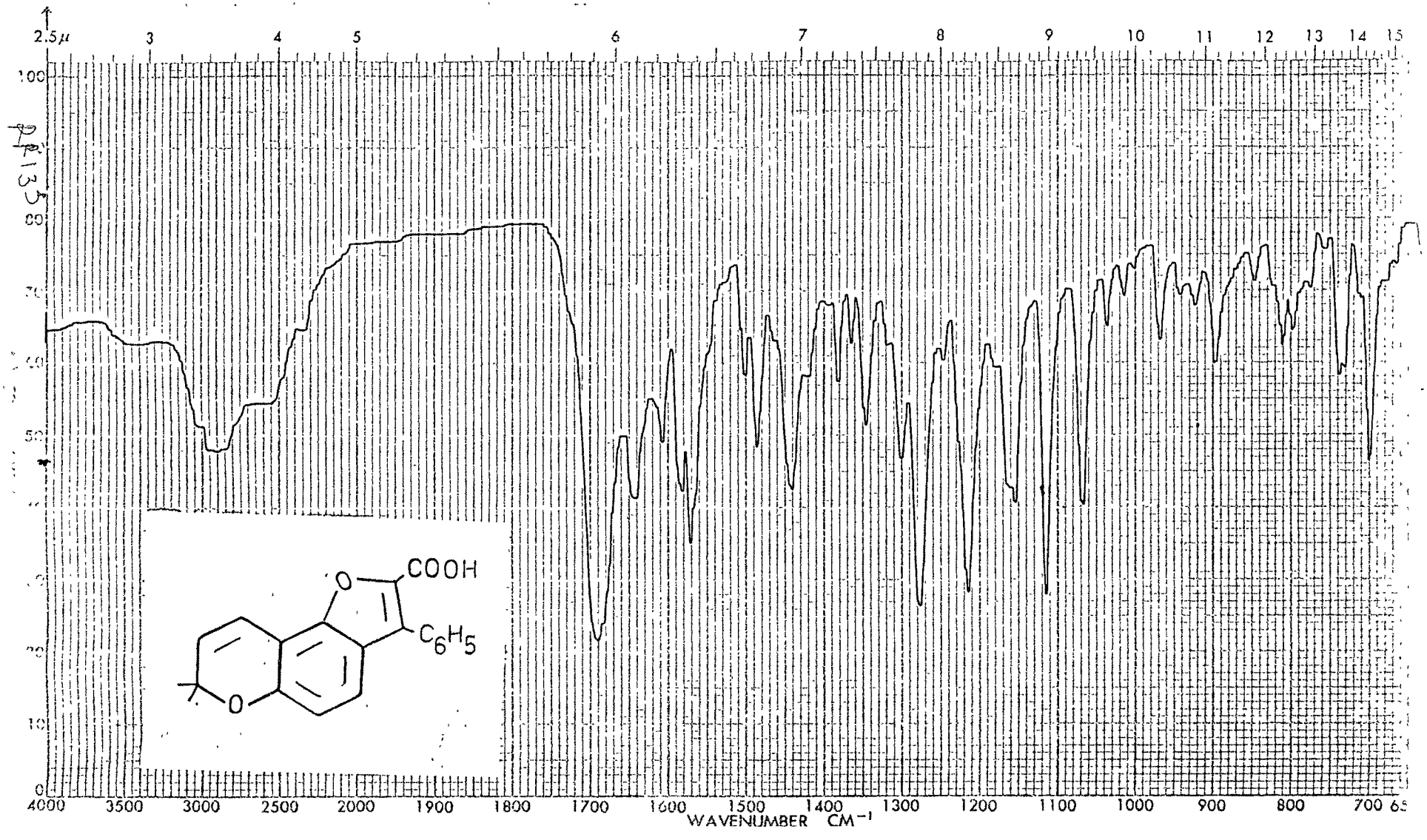
(f) 2,2,7-Trimethyl-furo [2,3-f]-2H-1-benzopyran (88)

5-Hydroxy-6-acetyl-2,2-dimethyl-2H-1-benzopyran (80)[59] when

SCHEME-V


OH
COC6H5
HO
CH3
CH3-C-CH2-CH
OH
OCH3
OCH3
Pyridine, 170°C
10 h.
OH
COC6H5
O
83
BrCH(COOC2H5)2
K2CO3
36 h.
COOC2H5
O
C6H5
O
84
10 % alc. KOH
COOH
O
C6H5
O
85




2.5μ
3
4
5
6
7
8
9
10
11
12
13
14
15
100
80
60
40
20
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
650
WAVENUMBER CM⁻¹
COOH
O
O
C6H5

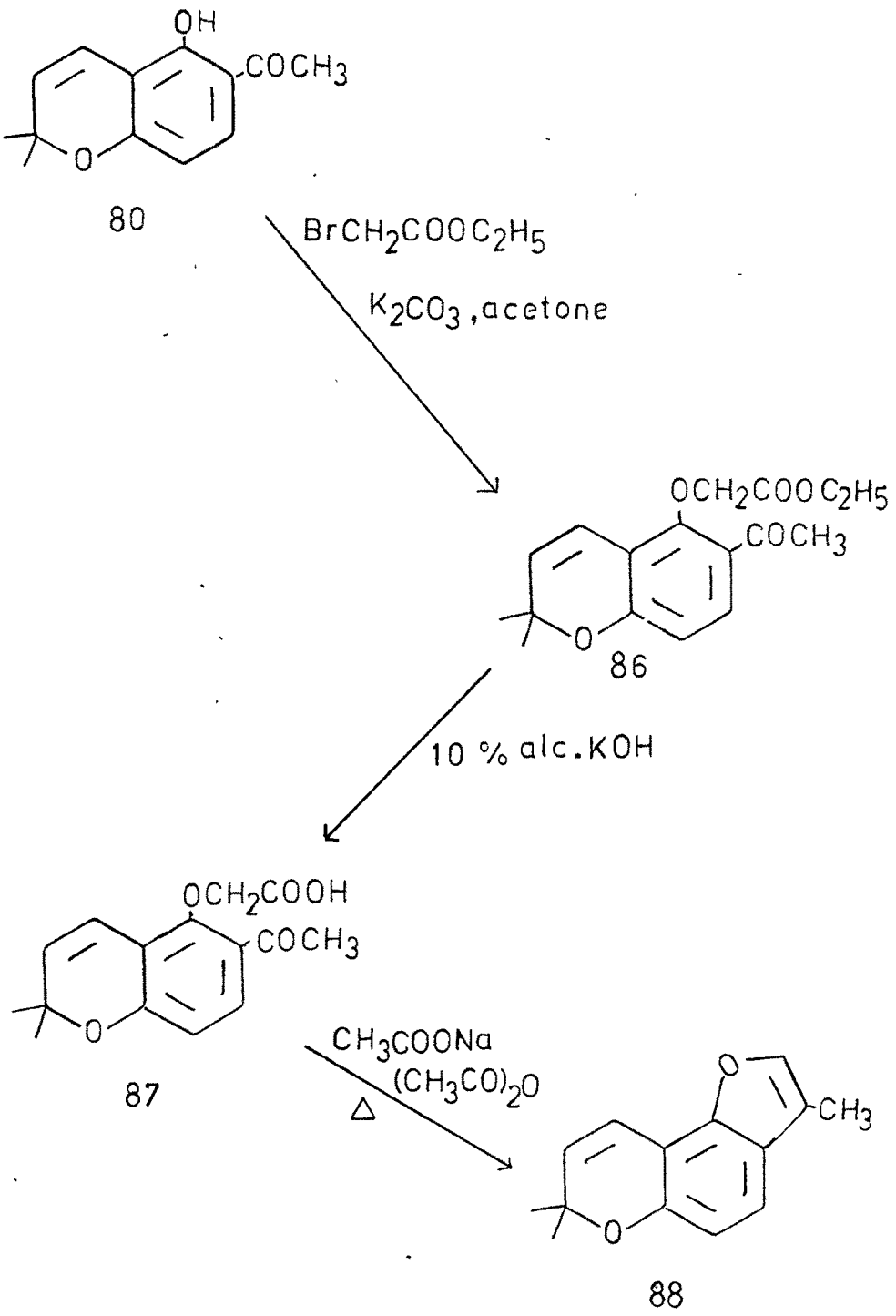
P#135

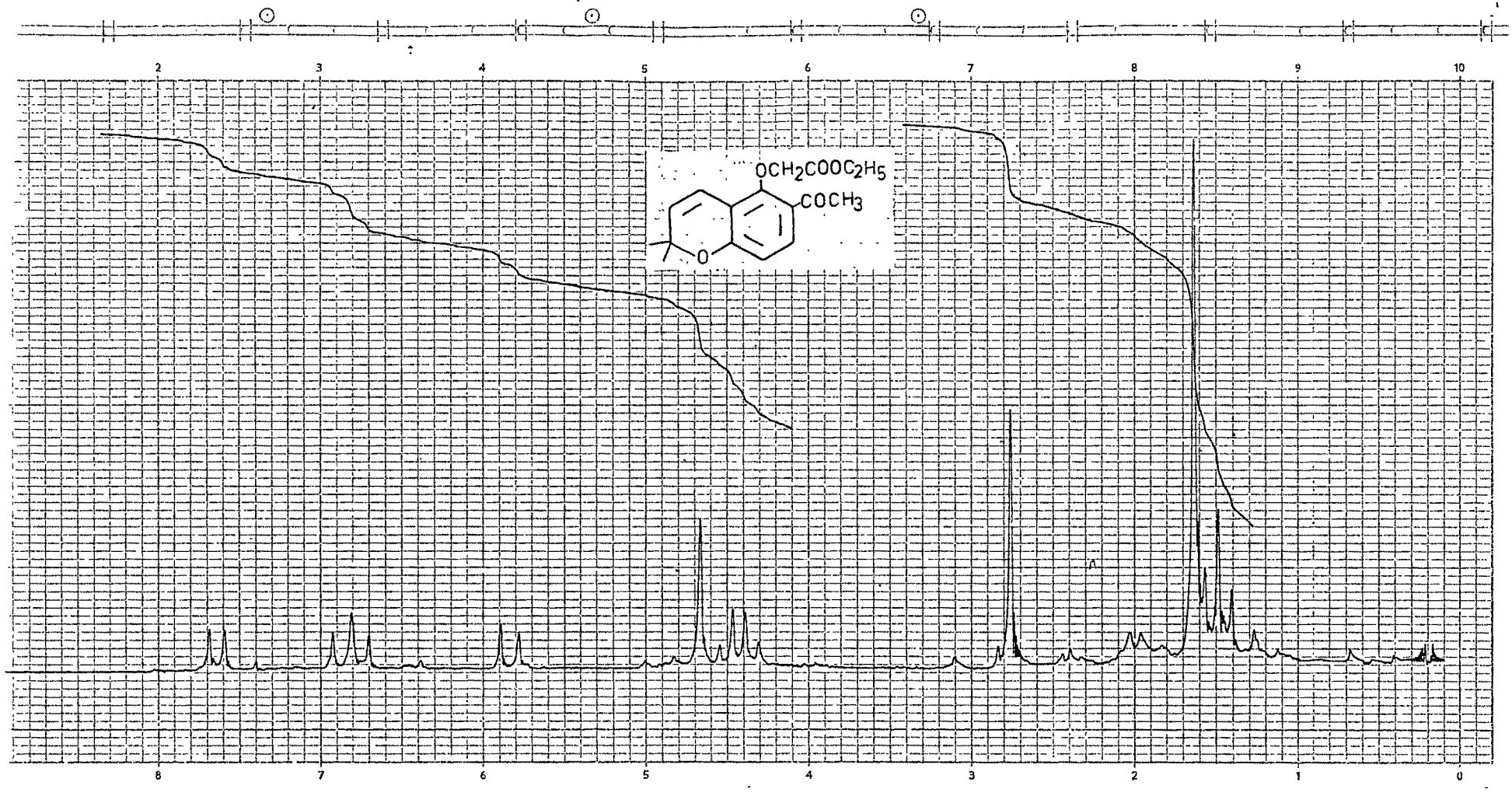
condensed with ethylbromoacetate in presence of K_2CO_3 gave ethyl-6-acetyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetate (86). Structure (86) was confirmed by pmr spectra which showed a triplet at δ 1.3, J=8Hz for three hydrogens of methyl group of ester, one quartet at 4.2, J=8Hz for two protons of methylene group of ester, singlet at 1.5 for two geminal methyl groups at C-2, singlet at 2.6 for $-COCH_3$ group, two doublets at 5.7 and 6.8, J=10Hz for two protons at C-3 and C-4 respectively, two singlets at 6.5 and 7.4, J=9Hz for two protons at C-7 and C-8 respectively. (86) on alkaline hydrolysis afforded 6-acetyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetic acid (87) which was cyclized with sodium acetate and acetic anhydride to furnish 2,2,7-trimethyl furo [2,3-f]-2H-1-benzopyran (88). Structure (88) was confirmed by pmr spectra which showed singlet at δ 1.4 for two geminal methyl groups at C-2, singlet at 2.2 for methyl group at C-7, two doublets at 5.5 and 6.7, J=10Hz for two protons at C-3 and C-4 respectively, two doublets at 6.6 and 7.1, J=9Hz for two protons at C-8 and C-9 respectively and singlet at 7.2 for one proton at C-6. (Scheme-VI)

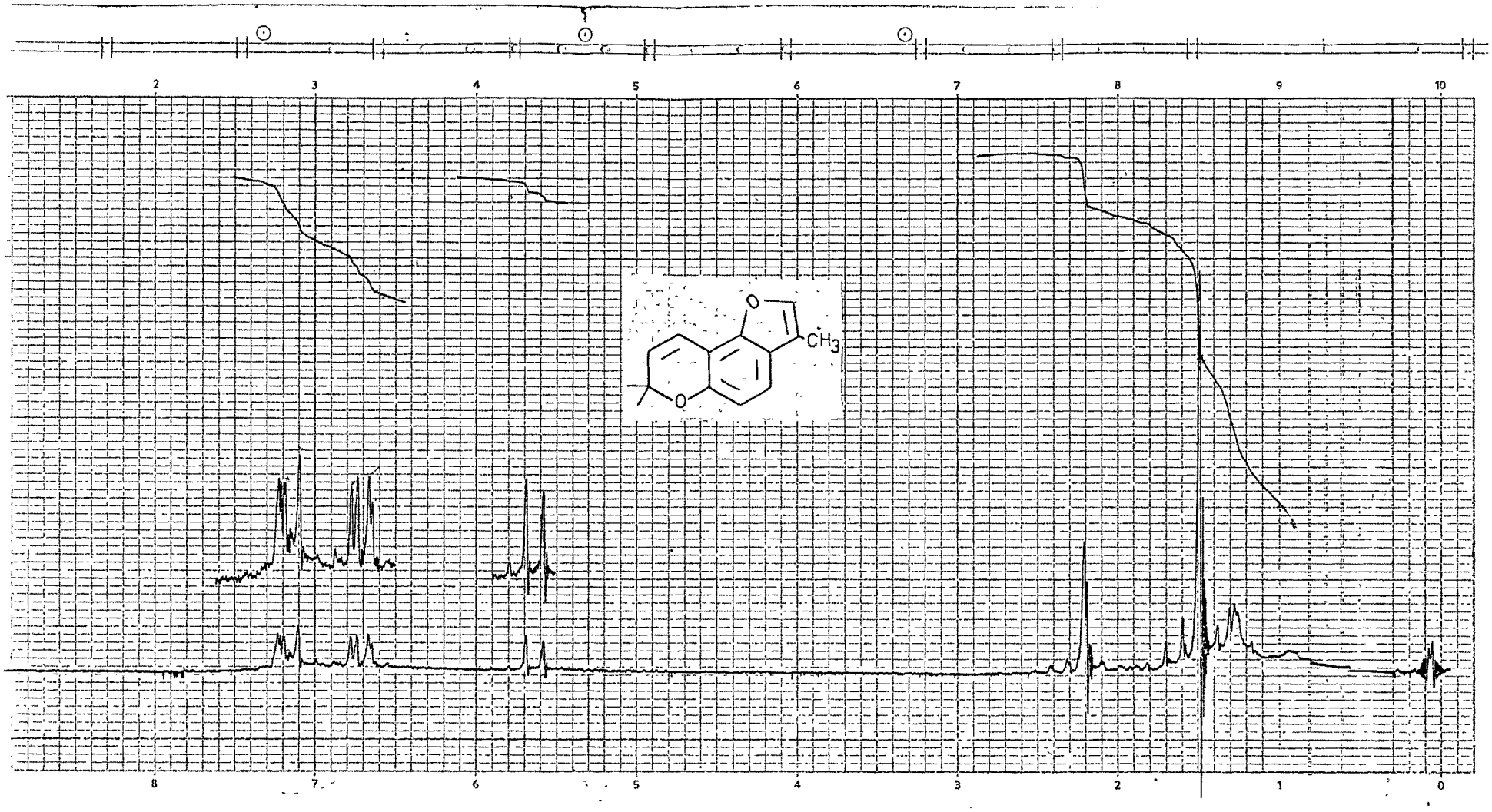
(g) 2,2-Dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran (91)

5-Hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran (83) on condensation with ethyl bromoacetate in presence of K_2CO_3 gave ethyl-6-benzoyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetate (89), structure (89) was confirmed by pmr spectra which showed triplet at δ 1.2 for three porotons of methyl group of ester,

SCHEME -VI

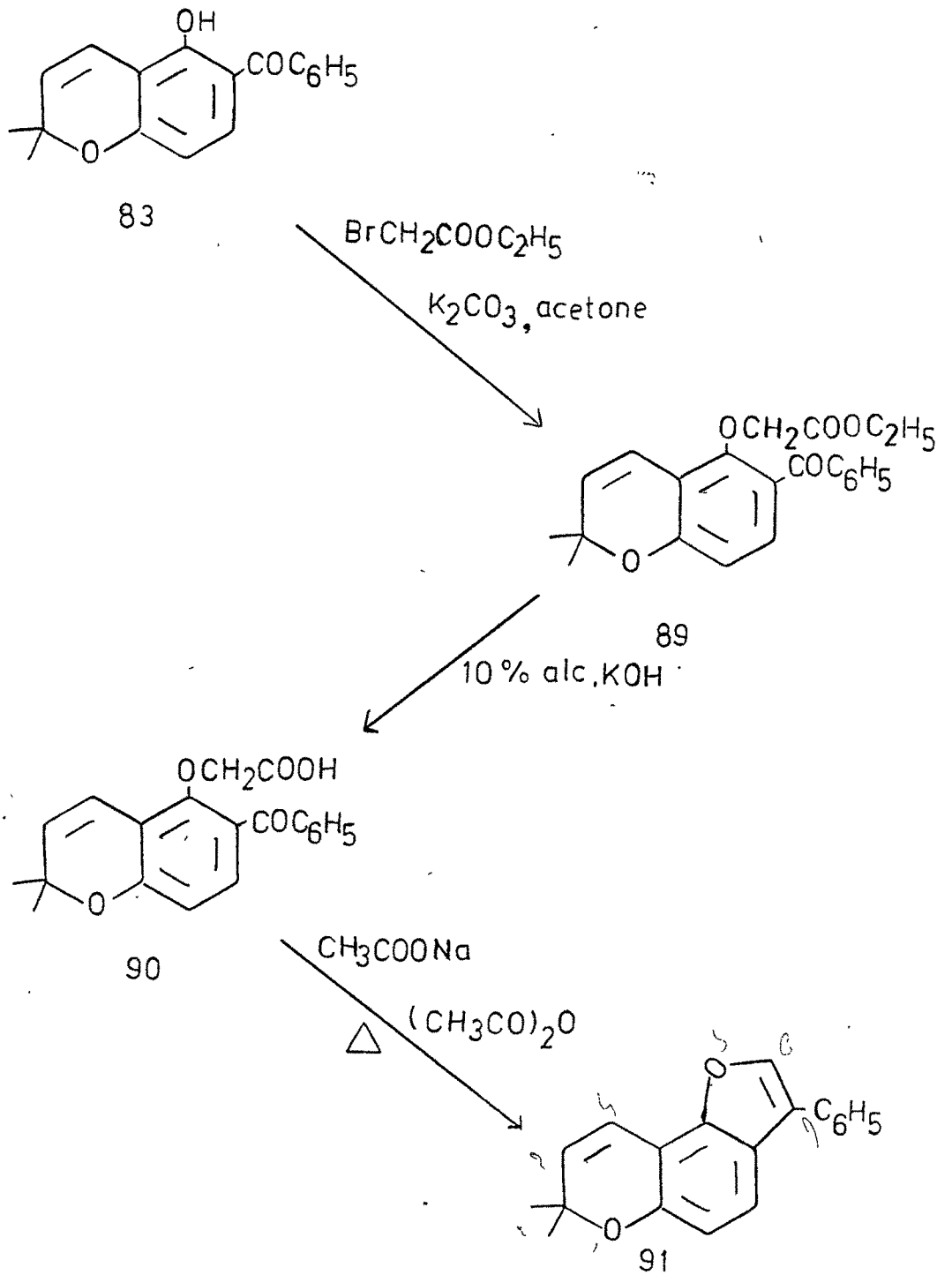

OH
COCH3
O
80
BrCH2COOC2H5
K2CO3, acetone
OCH2COOC2H5
COCH3
O
86
10 % alc. KOH
OCH2COOH
COCH3
O
87
CH3COONa
(CH3CO)2O
Δ
O
CH3
O
88

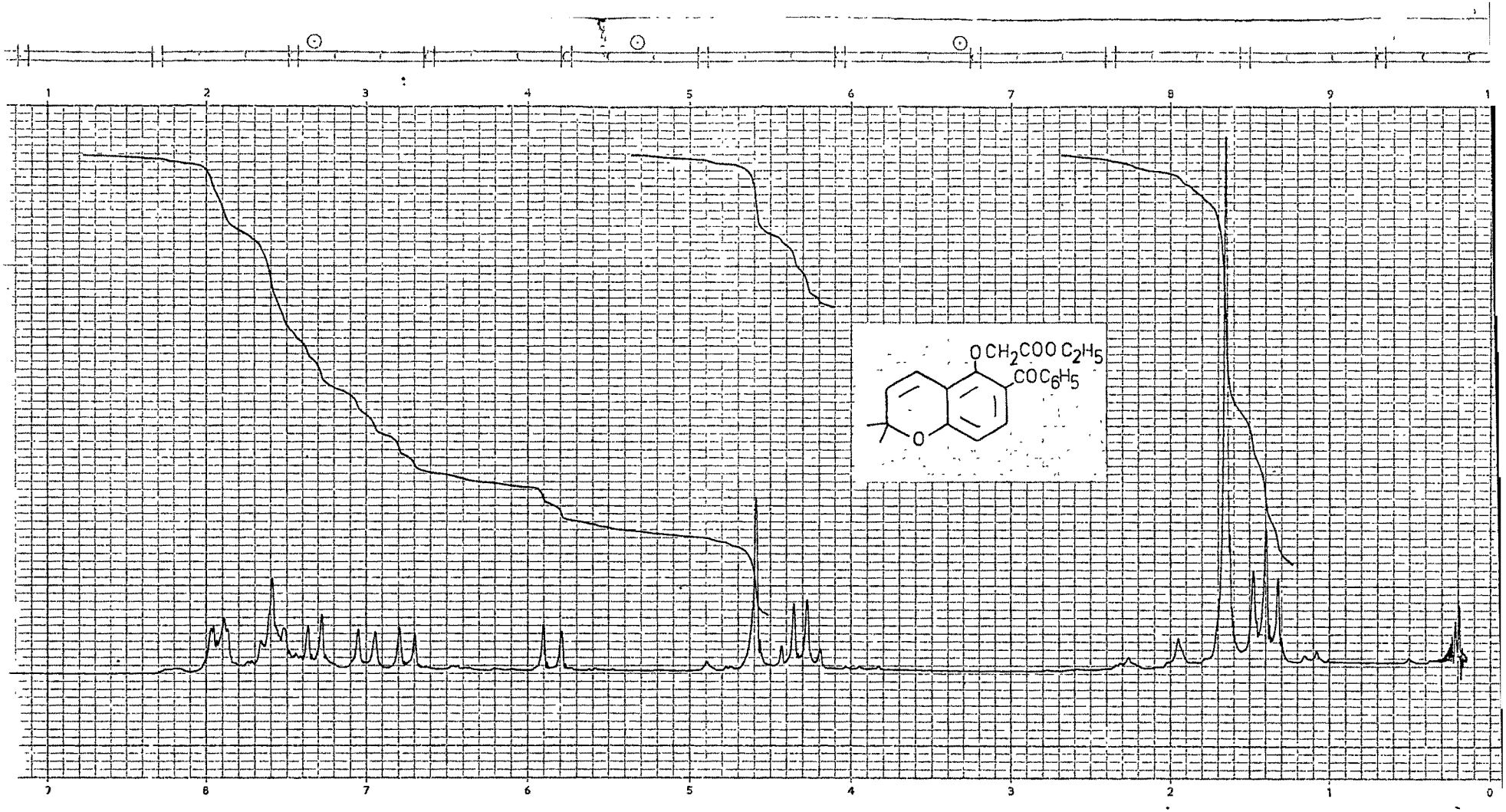


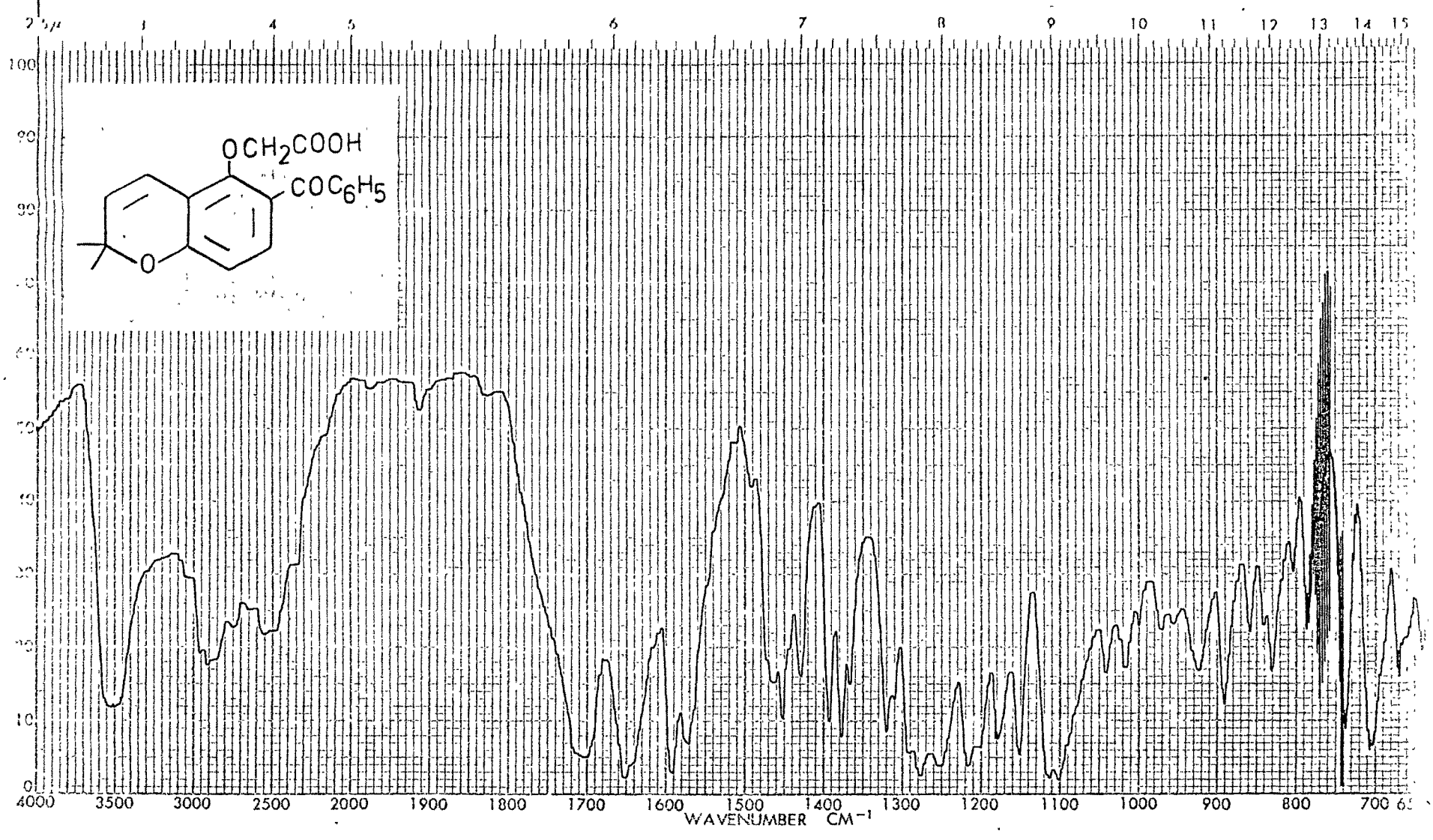


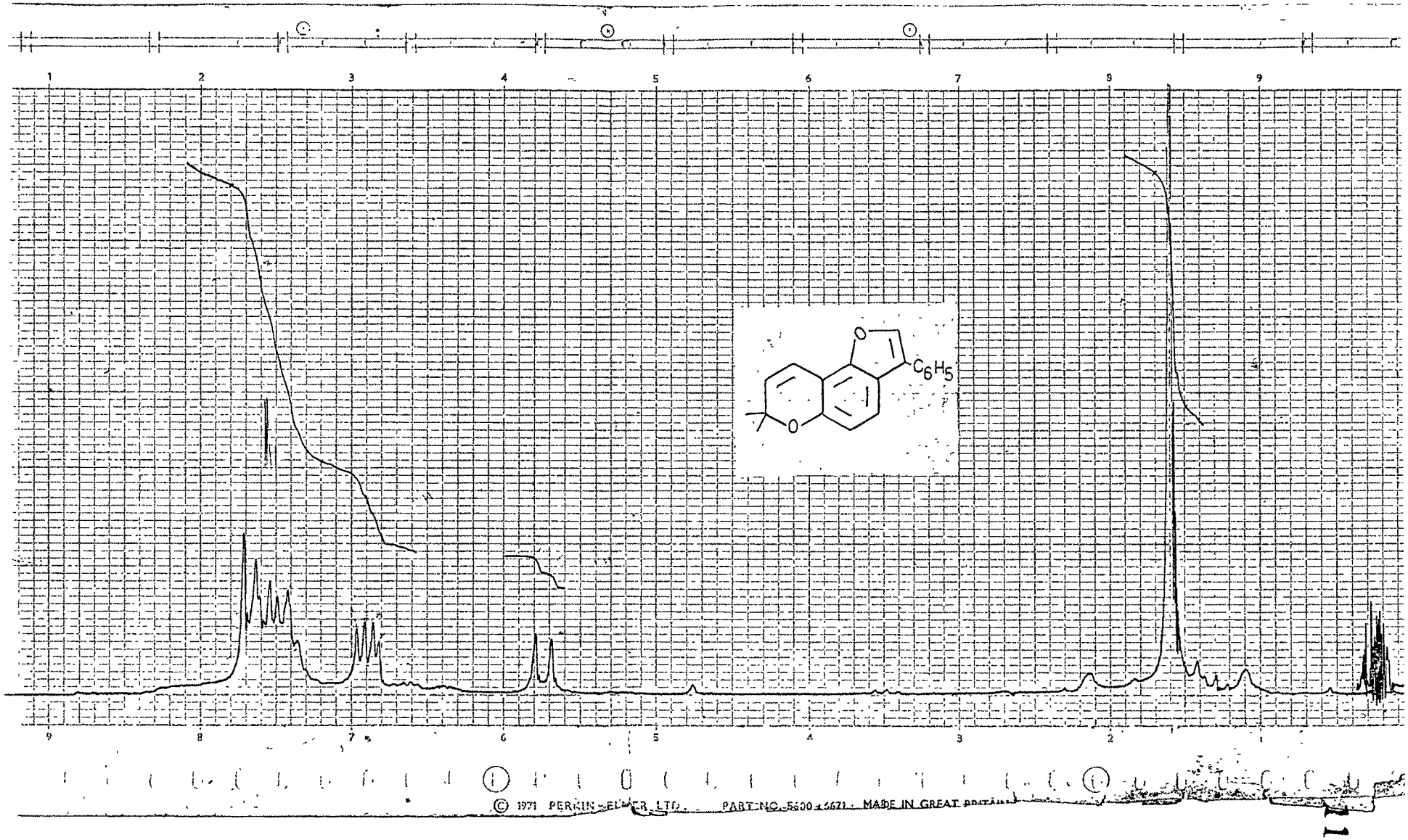
quartet at 4.2 for two protons of methylene group of ester singlet at 1.5 for two dimethyl groups at C-2, two singlets at 5.7 and 6.8, J=10Hz for two protons at C-3 and C-4 respectively, two singlets at 6.55 and 7.2, J=9Hz for two protons at C-7 and C-8 respectively, one multiplet at 7.4-7.7 for five protons of benzoyl group. (89) on alkaline hydrolysis afforded 6-benzoyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetic acid (90) which shows IR bands at 1710 cm^{-1} for cabonyl group and 3500 cm^{-1} for -OH group of acid. (90) was cyclized with NaOAc - Ac_2O to furnish 2,2-dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran (91), the structure (91) was confirmed by pmr spectra which showed singlet at δ 1.4 for two geminal dimethyl group at C-2, two doublets at 5.55 and 6.70, J=10Hz for two protons at C-3 and C-4 respectively, two doublets at 6.6 and 7.25,J=9Hz for two protons at C-8 and C-9 respectively, one multiplet at 7.5 for five aromatic protons of phenyl group at C-7. (Scheme-VII)

SCHEME-VII


OH
COC6H5
83
BrCH2COOC2H5
K2CO3, acetone
OCH2COOC2H5
COC6H5
89
10% alc. KOH
OCH2COOH
COC6H5
90
CH3COONa
(CH3CO)2O
△
C6H5
91




OCH2COOH
COC6H5
O
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM⁻¹



EXPERIMENTAL

M.ps. are uncorrected.NMR spectra were recorded on Perkin Elmer 90 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on Shimadzu Model No. 408. Silica gel used for column chromatography with mesh size 60-120.

Prenylation of Resacetophenone[57]

To a stirred solution (2.2 g) of resacetophenone in dry dioxan (8.0 ml), added gradually (0.6 ml) $BF_3.Et_2O$ at room temperature when the solution acquired a pink colour to this add a solutin of 2-methyl-but-3-ene-2-ol (1.0 ml) in dry dioxan (5 ml) and the whole is stirred for 1 hr at room temperature. After dilution with moist ether (100 ml), wash the solution with water (3 x 50 ml) thus discharging the colour, the solution is then extracted with 1% Na_2CO_3 which on acidification gave unreacted resacetophenone. The remaining etheral solution on examination by TLC (solvent $CHCl_3$) showed the presence of three spots, hence it was subjected to column chromatography and column eluted successively with (i) benzene : pet. ether (1:3) (ii) Benzene : light pet. ether (1:1) (iii) Benzene : pet ether (2:1) giving following three main fractions :

Fraction A : crystallized from light pet. ether yielding 3,5-diprenyl-2,4-dihydroxy acetophenone (67) 120 mg. m.p. 109-110°C.

Fraction B : crystallized from benzene giving 3-prenyl-2,4-dihydroxy acetophenone (68) 310 mg. m.p. 155-56°C.

Fraction C : as colourless plates (310 mg) m.p. 144-45°C of 5-prenyl-2,4-dihydroxy acetophenone (69).

7-Hydroxy-6-acetyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (70)

200 mg of (69) in formic acid (3 ml) was heated on a steambath for 1 hr. The yellow solution thus obstained was cooled and poured over ice and the solid product filtered, crystallized from light pet. ether as colourless needles. M.p. 119-20°C,[57] yield 170 mg.

2,2,6-Trimethyl-3,4-dihydro furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (71)

A mixture of 7-hydroxy-6-acetyl-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran (70) (1.1 g, 0.005 mole), diethylbromomalonate (1.2 g., 0.005 mole) and anhydrous K_2CO_3 (5 g) in dry acetone (100 ml) refluxed on a water bath for 36 h. concentrated and poured in ice cold water, the separated solid was filtered and crystallized from mixture of pet. ether (60-80°) & benzene (1:2), m.p. 111°C, yield 0.65 g. (52%).

Analysis : Found : C, 69.02% ; H, 6.42%

$C_{15}H_{16}O_4$: requires : C, 69.23% ; H, 6.15%

2,2,6-Trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (72)

To above compound (71) (0.520 g., 0.002 mole) dissolved

in dry benzene (30 ml), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was added and refluxed for 48 h. The hot reaction mixture was filtered and benzene distilled off. The residue was column chromatographed on silica gel, elution withmixture of pet. ether and benzene (2:1) gave 2,2,6-trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid as yellow coloured needles. M.p. 73°C, yield 0.16 g (31%).

Analysis	:	Found	:	C, 69.20%	;	H, 5.46%
$C_{15}H_{14}O_4$	:	requires	:	C, 69.66%	;	H, 5.42%

Preparation of 2,4-Dihydroxy-3-methyl-5-prenyl acetophenone (73)

To a stirred solution of 2,4-dihydroxy-3-methyl acetophenone (1.2 g) in dry dioxan (10 ml) was added to a solution of 2-Methyl-but-3-ene-2-ol(0.6 g) in dioxan (5 ml) in presence of $BF_3.Et_2O$ (0.5 ml) and the whole solution was stirred for 1 hr. at room temperature. The solution was then diluted with ether and the etheral layer was washed with water (3 x 100 ml) to discharge the colour. The solution was then washed with Na_2CO_3 (10%) (2 x 50 ml) which on acidification gave unreacted 2,4-dihydroxy-3-methyl acetophenone (0.5 g). The etheral solution onexamination by Tlc ($CHCl_3$) showed the presence of two spots. This was then subjected to column chromatography over silica gel and the column was eluted successively by benzene : pet. ether (80 : 20) and benzene - EtOAc (80 : 20). Fraction I gave a 2,4-dihydroxy-3-methyl-5-prenyl resacetophenone (0.4 g) (73) crystallized from benzene : pet. ether

mixture (1:1).M.p. 117-18°C.[58] Fraction II gave unreacted ketone.

7-Hydroxy-6-acetyl-2,2,8-trimethyl-3,4-dihydro-2H-1-benzopyran (74)

200 mg. of (73) in formic acid (3 ml) was heated on a steambath for 1 hr. The yellow solution thus obtained was cooled and poured over ice and the solid product filtered, crystallized from light pet. ether as colourless needles of (74). M.p. 119-20°C,[58] yield 170 mg.

2,2,6,9-Tetramethyl-3,4-dihydro furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (75)

A mixture of 7-hydroxy-6-acetyl-2,2,8-trimethyl-3,4-dihydro-2H-1-benzopyran (74) (1.2 g, 0.005 mole), diethylbromomalonate (1.2 g, 0.005 mole) and anhydrous K_2CO_3 (5 g) in dry acetone (100 ml) was refluxed for 36 h. in a water bath, concentrated and poured in cold water, the separated solid was filtered and crystallized from mixture of pet. ether (60-80°)/benzene (1:2) as light yellow needles of (75). M.p.115°C, yield 0.74 g. (55.5%).

Analysis : Found : C, 71.08% ; H, 7.27%

$C_{16}H_{18}O_4$: requires : C, 71.52% ; H, 7.28%

2,2,6,9-Tetramethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (76)

To above compound (75) (0.54 g, 0.002 mole) dissolved in

dry benzene (30 ml), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.5 g) was added and refluxed for 48 hr. The hot reaction mixture was filtered and benzene was distilled off, the residue was column chromatographed on silica gel, on elution with pet. ether : benzene (2:1) gave 2,2,6,9-tetramethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylic acid (76) as yellow coloured needles. M.p. 81°C, yield 0.12 g. (21.5%).

Analysis : Found : C, 71.00% ; H, 5.32%

$C_{16}H_{16}O_4$: requires : C, 70.59% ; H, 5.28%

2,4-Dihydroxy-3-methyl-5-prenylbenzaldehyde (77)

A mixture of 2,4-dihydroxy-3-methylbenzaldehyde (1.5 g, 0.01 mole), $BF_3.Et_2O$ (0.6 ml) and 2-Methyl-but-3-ene-2-ol (1.0 ml) in dry dioxan (20 ml) was stirred for 2 hrs. The solution was diluted with ether (50 ml) then it is washed three times with water and two times with aq. Na_2CO_3, solvent ether on evaporation gave a solid which on crystallization from pet. ether : benzene (1:1) gave 2,4-dihydroxy-2-methyl-5-prenylbenzaldehyde (77) as white crystals. M.p. 121°C, yield 1.0 g. (45.5%).

7-Hydroxy-2,2,8-trimethyl-2H-1-benzopyran-6-carboxaldehyde (78)

A mixture of 2,4-dihydroxy-3-methyl-5-prenylbenzaldehyde (0.55 g, 0.0025 mole) (77), 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.5 g) in dry benzene (20 ml) refluxed on steam

bath for 0.5 hr. and filtered hot and evaporated, the residue obtained was column chromatographed on silica gel, elution with pet. ether (69-80°) gave 7-hydroxy-2,2,8-trimethyl-2H-1-benzopyran-6-carboxaldehyde (7g) as yellow crystals. M.p. 70°C, yield 0.22 g (40.4%).

Analysis	:	Found	:	C, 71.55%	;	H, 5.96%
$C_{13}H_{14}O_3$	:	requires	:	C, 71.10%	;	H, 6.42%

Ethyl-2,2,9-trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylate (7g)

A mixture of 7-hydroxy-2,2,8-trimethyl-2H-1-benzopyran-6-carboxaldehyde (7g) (1.1 g., 0.005 mole), diethylbromomalonate (1.2 g, 0.005 mole), anhydrous K_2CO_3 (5 g) in dry acetone (100 ml) refluxed for 36 h. on a water bath, concentrated and poured into cold water, the separated oil was extracted with solvent ether, etheral layer washed with dil. aq. NaOH and evaporated to gave a crude oil which was purified by column chromatographed, on elution with pet. ether gave ethyl 2,2,9-trimethyl-furo [3,2-g]-2H-1-benzopyran-7-carboxylate (7g) as liquid.

Ethyl-2,2,7-trimethyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylate (8g)

A mixture of 5-hydroxy-6-acetyl-2,2-dimethyl-2H-1-benzopyran (8g) (1.1 g., 0.005 mole), diethyl bromomalonate (1.2 g, 0.005 mole) anhydrous K_2CO_3 (5 g) in dry acetone (100 ml)

refluxed for 36 hr. in a waterbath concentated and poured into waterbath, etheral layer washed with dil. NaOH solution and evaporated to gave a crude oil which was column chromatographed, elution with pet. ether gave ethyl-2,2,7-trimethyl-furo [2,3-f]-2H-1-benzopyran (81) as liquid.

2,2,7-Trimethyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (82)

Compound (81) was dissolved in 10% ethanolic KOH (50 ml) and kept at room temperature for two days and then acidified, the separated solid crystallized from benzene - pet. ether (1:1) to get 2,2,7-trimethyl-furo [2,3-f]-4H-1-benzopyran-6-carboxylic acid (82). M.p. 224°C.

Analysis	:	Found	:	C, 70.16%	;	H, 5.87%
$C_{15}H_{14}O_4$	:	requires	:	C, 69.76%	;	H, 5.43%

5-Hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran (83)

2,4-Dihydroxybenzophenone (4.3 g., 0.02 mole) and dry pyridine (2.0 ml) where heated and stirred to 170°C, hydroxy-isovalaraldehyde dimethyl acetal (2.22 g., 0.015 mole) was added during 1 hr. and the heating was continued for 6 h. additional acetal (1.68 g., 0.01 mole) was added and the reaction was continued further for 5 h. the mixture evaporated to dryness and the residue was chromatographed on silica gel, the column, on elution with pet. ether : benzene (2:1) gave 5-hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran (83). M.p. 106°C, yield 2.0 g (55.55%).

Analysis	:	Found	:	C, 77.52%	;	H, 5.36%
$C_{18}H_{16}O_3$	:	requires	:	C, 77.14%	;	H, 5.71%

Ethyl-2,2-dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylate (84)

A mixture of (83) (1.4 g., 0.005 mole), diethyl bromomalonate (1.2 g., 0.005 mole), anhydrous K_2CO_3 (5 g) in dry acetone (100 ml) refluxed for 36 hr. on a waterbath, concentrated and poured into water, the separated solid crystallised from pet. ether : benzene (1:1) to give yellow coloured crystals of ethyl-2,2-dimethyl-7-phenyl-furo-[2,3-f]-2H-1-benzopyran-6-carboxylate (84). M.p. 98°C, yield 0.75 g. (43%)

Analysis ; Found : C, 75.16% ; H, 5.83%

$C_{22}H_{20}O_4$: requires : C, 74.71% ; H, 5.75%

2,2-Dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (85)

Compound (84) was dissolved in 10% ethanolic KOH (50 ml) and kept at room temp. for two days and then acidified. The separated solid crystallized from benzene : pet. ether (2:1) to get 2,2-dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran-6-carboxylic acid (85). M.p. 203°C,

Analysis : Found : C, 74.65% ; H, 5.26%

$C_{20}H_{16}O_4$: requires : C, 75.00% ; H, 5.00%

Ethyl-6-acetyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetate (86)

A mixture of 5-hydroxy-6-acetyl-2,2-dimethyl-2H-1-benzopyran (80) (2.18 g., 0.01 mole), ethylbromo acetate (1.7 g., 0.01 mole) and anhydrous K_2CO_3 (10 g) in dry acetone (100 ml) was refluxed for 8 h. on a waterbath, concentrated and

poured into water, the oil obtained was extracted with solvent ether, washed with dil. NaOH solution, dried over anhydrous Na_2SO_4 and evaporated to obtain ethyl-6-acetyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetate (8_6) as an oil.

6-Acetyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetic acid (87)

The crude oil (8_6) obtained in above process was dissolved in 10% ethanolic KOH (50 ml) and left overnight at room temperature it was acidified with dil. HCl, , the separated solid was taken directlyfor the next reaction as it was difficult to purify.

2,2,7-Trimethyl-furo [2,3-f]-2H-1-benzopyran (88)

A mixture of (87) (0.55 g., 0.002 mole),fused NaOAc (0.5 g) and freshly distilled acetic anhydride (3 ml) was refluxed in an oilbath for 6 h. The cold reaction mixture was poured in ice, the oil separated was extracted with solvent ether, etheral layer washed with dil.$NaHCO_3$ to remove unreacted acid. It was dried over anhydrous Na_2SO_4 and evaporated to get the crude oil which was purified bycolumn chromatographed on silica gel, elution with pet. ether gave 2,2,7-trimethyl-furo [2,3-f]-2H-1-benzopyran (88) as liquid. It was characterized by PMR spectrum.

Ethyl-6-benzoyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetate (89)

A mixture of 5-hydroxy-6-benzoyl-2,2-dimethyl-2H-1-benzopyran (83) (1.4 g., 0.005 mole), ethyl bromoacetate (0.85 g.,

0.005 mole) and anhydrous K_2CO_3 (10 g.) in dry acetone (100 ml) was refluxed for 8 h. on a waterbath, the oil obtained was extracted with solvent ether, washed with dil. NaOH solution and dried over anhydrous Na_2SO_4 and evaporated to obtain ethyl-6-benzoyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetate (88) as an oil.

6-Benzoyl-2,2-dimethyl-2H-1-benzopyran-5-oxyacetic acid (90)

The oil (89) was dissolved in 10% ethanolic KOH (50 ml) and left overnight at room temperature, It was acidified with dil. HCl, the separated solid (90) was taken directly for the next step.

2,2-Dimethyl-7-phenyl-furo [2,3-f]-2H-1-benzopyran (91)

A mixture of (90) (0.65 g., 0.002 mole), fused NaOAc (0.7 g) and freshly distilled acetic anhydride (4 ml) was refluxed in an oilbath for 6 h. The cold reaction mixture was poured on ice, the oil separated was extracted with solvent ether, etheral layer dried over anhydrous Na_2SO_4 and evaporated to get the crude oil which was purified by column chromatography, pet. ether fraction gave 2,2-dimethyl-7-phenyl-furo [2,3-f] 2H-1-benzopyran (91) as liquid. It was characterized by PMR s spectrum.

References

1. M.E. Baldwin, I.R.C. Bick, A.A. Kozmak and J.R. Price, Tetrahedron, 16, 206 (1961).

2. S.E. Wright, J. Chem. Soc., 2005 (1948).

3. M.H. Sutherland, Univ. Queensl. Pap., Dept. Chem. 1, No. 35 (1949). Chem. Abstr., 44, 1230d (1950)

4. A.R. Alertsen, Acta. Chem. Scand., 9, 1725 (1955).

5. D.R. Taylor and J.A. Wright, Phytochemistry, 10, 1665 (1971).

6. G. Cardillo, L. Merlini and R. Mondelli, Tetrahedron, 24, 497 (1968).

7. W. Sundermann and M.H. Simatupang, Chem. Ber., 97, 588 (1964).

8. K.D. Kirby and M.H. Sutherland, Aust. J. Chem., 9, 411 (1956).

9. H. Decker and T. Fellenberg, Justus Liebigs Ann. Chem., 356, 281 (1907)

10. W.R. Thompson and R.K. Razdan, S. Afr. Patent, 6802, 269 (1968) Chem. Abstr., 70, 68161d (1969).

11. P. Maitte, Ann. Chim. (Paris), 9, 431 (1954) ; Chem. Absr. 49, 6829i (1955).

12. H. Hofmann and G. Salbeck, Chem. Ber. 104, 168 (1971).

13. J. Colonge and A. Guyot, Bull. Soc. Chim. Fr., 325 (1958).

14. F. Baranton, G. Fontaine and P. Maitee, Bull. Soc. Chim. Fr., 4203 (1968).

15. W.E. Parham and L.D. Huestis, J. Am. Chem. Soc., 84, 813 (1962).

16. J.R. Hlubeck, E. Ritchie and W.C. Taylor, Aust. J. Chem., 24, 2347 (1971).

17. G. Canalini, I. Degani, R. Fochi and G. Spunta, Ann. Chim. (Rome), 57, 1045 (1967) ; Chem.Abstr., 69, 2789q (1968).

18. J. Nickl, Chem. Ber., 92, 1989 (1959).

19. K. Auwers and F. Krollpfeieffer, Chem. Ber., 47, 2585 (1914).

20. W. Baker and J. Walker, J. Chem. Soc., 646 (1935).

21. R.W.H.O'Donnell, F.P. Reed, and A. Robertson, J. Chem. Soc., 419 (1936).

22. R. Metten and G. Miller, Chem. Ber., 97, 682 (1964).

23. S.P. Starkov and L.V. Glushova, Khim. Geterotskil. Soedin., 16 (1968) ; Chem. Abstr., 69, 77054e (1968).

24. W.H. Donnelly and P.V.R. Shannon, J. Chem. Soc., D, 76 (1971).

25. J.T. Arrigo, U.S. Patent, 2,987,525 ; Chem. Abstr., 56, 3460i (1961).

26. G.B. Bachman and H.A. Levine, J. Am. Chem. Soc., 70, 599 (1948).

27. Taylor H.V., and Tomlinson M.L., J. Chem. Soc., 2754 (1950).

28. Gupta R.C., Pratap R. Prasad, C.R. Anand Ind. J. Chem., 21B, 344 (1982).

29. Deshpande S.R., Mathur H.H. and Trivedi G.K., Ind. J. Chem., 22B, 168 (1983).

30. Rene L, Blanco L, Royer R, Cavier R and Lemonie J.R., Eur. J. Med. Chem. Chim. Ther(Jr), 12 385 (1977) ; Chem. Abstr., 87, 19469u (1977).

31. Sakakibara T, Koezaka M and Sudoh R., Bull. Chem. Soc. Japan, 51, 3095 (1978).

32. J. Zsindely and H. Schmid, Helv. Chim. Acta, 51, 1510 (1968).

33. B.S. Thyagrajan, K.K. Balasubramanian and R.B. Rao, Tetrahedron, 23, 1893 (1967).

34. Y. Besace, I. Marszak and J. Naisse, Bull. Soc. Chim. Fr. 2275 (1971).

35. J. Hlubucek, E. Ritchie and W.C. Taylor, Tetrahedron Lett., 1369 (1969).

36. I. Iwai and S. Iwade, Jap. Patent, 22587 (1963) ; Chem. Abstr., 60, 2910e (1964).

37. I. Iwai and J. Ide, Chem. Pharm. Bull. (Tokyo), 11. 1042 (1963).

38. J. Nickl., Chem. Ber., 91, 1372 (1958).

39. G. Cardillo and L. Merlini, Gazz. Chim. Ital., 98, 191 (1968) ; Chem. Abstr., 69, 43735k (1968).

40. F. Hofmann-La Roche and Co., A.G. Brit. Patent, 877960 (1960) ; Chem. Abstr., 56, 7282 (1962).

41. H. Pendse, R. Rnegg, G. Ryser, U.S. Patent, 3,004,040 (1960) ; Chem. Abstr., 56, 8693d (1962).

42. G. Cardillo, L. Merlini and S. Servi, Ann. Chim. (Rome), 60, 564 (1970) ; Chem. Abstr., 74, 42254u (1971).

43. N.S. Narazimhan, M.V. Paradkar and A.M. Gokhale, Tetrahedron Lett., 1664 (1970).

44. E.E. Scheizer, J. Am. Chem. Soc., 86, 2744 (1964).

45. E.E. Scheizer, A.T. Wehmann and D.M. Nycz, J. Org. Chem., 38, 1583 (1964).

46. G. Cardillo, R. Cricchio and L. Merlini, Tetrahedron, 27, 1875 (1971).

47. A.C. Jain and M.K. Zutshi, Tetrahedron Lett., 3179 (1971).

48. I.M. Campbell, C.H. Calzadilla and N.J. McCorkindale, Tetrahedron Lett., 5107 (1966).

49. G. Cardillo, R. Cricchio, and L. Merlini, Tetrahedron, 24, 4825 (1968).

50. A.B. Turner, Quat. Rev.(London), 18, 347 (1964).

51. G. Ariamala and K.K. Balasubramanian, Tetrahedron Lett., 29, 3487 (1988).

52. Parrish J.A., Fitzpatrick T.B., Tenechaum G. and Pathak M.A., New Eng. J. Med. 291, 1207 (1974).

53. Vedaldi D, Dall'Aqua F., Caporale G.A., Guttio A., Baccichetti, F., Bordin, F., and Pathak M.A., Formaco Ed. Sci., 38, 826 (1983).

54. Rene L., Bussion J.P., Royer R. and Averback D.,Eur. J. Med. Chem. Chim. Ther., 12, 13 (1977).

55. Rene L., Falques M., Royer R., J. Heterocyclic Chem., 17, 1149 (1980).

56. Averback D., Moradi M., Falques M., Rene L., and Royer R., Eur. J. Med. Chem. Chim. Ther., 18, 15 (1983).

57. A.C. Jain, Pyraelal and T.R. Seshadri Ind. J. Chem., 7, 1072 (1969).

58. R.R. Shah and Trivedi K.N., J. Ind. Chem. Soc., 56, 995 (1979).

59. Bandarnayake W.M., Crombie L., Whiting D.A., J. Chem. Soc. (C) 811 (1971).