IN LOVING MEMORY

OF MY BROTHER

ARVIND

STATEMENT REQUIRED TO BE SUBMITTED UNDER ORDINANCE 19.8 OF THE GOA UNIVERSITY

No part of this Thesis has been submitted for a degree or diploma or other academic award. The literature concerning the problems investigated has been surveyed and all the necessary references are incorporated in this Thesis. The experimental work has been carried out independently and due acknowledgement has been made wherever outside facilities have been availed of.

(S. K. Paknikar)
Research Guide

(K. K. Nadkarni)
Candidate

CONTENTS

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I shall be failing in my duty if I do not mention unstinted co-operation extended,keen interest shown and tireless efforts taken by Dr.C. G. Naik in this endeavour of mine.

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The most important people I leave until last my mother and my father without whom none of this would have been possible.

GENERAL REMARKS

1. All chart, scheme, table, structure, figure and reference numbers in a part refer to that particular part only.
2. Organic extracts were dried over anhydrous Na_2SO_4 unless otherwise stated.
3. All melting and boiling points were recorded in degrees celsius and are uncorrected.
4. Petroleum-ether refers to the fraction boiling between the range 60°-80°.
5. Silica gel used for column chromatography was of 60-120 mesh size and was activated at 110° for 5 hours before use.
6. Thin layer chromatography was done on glass plates coated with 0.25 mm. layer of TLC grade silica gel with 13% $CaSO_4$ as binder. Visualisation of the plates was done by developing the plates in I_2 chamber, unless otherwise stated.
7. Spectral data on compounds were mainly obtained through the courtesy of various institutions. No details of individual instruments are therefore given. These have been suitably acknowledged.

8. The chemical shift parameters in the ^{1}H nmr and ^{13}C nmr spectra are expressed in 'δ' ppm, with TMS as the internal standard. IR absorption bands are expressed in cm^{-1}. UV absorption signals are expressed in nm. with the molecular extinction coefficient in logarithum.

9. All known compounds were identified by direct comparison of spectral data and physical constants reported in literature. Molecular formulae of the compounds were assigned on the basis of the molecular weight as obained by mass spectrometry or elemental analysis.

10. The ^{1}H nmr spectra presented are obtained in the normal form and the J values reported are of the resolved form.

INTRODUCTION

Coumarins, structurally known as 2H-1-benzopyran-2-ones are widely distributed in plant kingdom. They are the secondary metabolites present in living organisms. They are found in abundance in the Angiosperms but are comparatively rare in Gymnosperms and Lower plants. Some are also obtained from micro — organisms. Umbelliferae, Rutaceae, Leguminosae are among the important families representing the coumarin containing plants.

Since the isolation of simple coumarin by Vogel[1] in 1820 several other coumarin derivatives are similarly isolated and are classified into simple, furanocoumarins, pyranocoumarins and coumarins substituted in the heterocyclic ring. The chemistry of these coumarins have been the subject of several monographs[2] and review articles. Many of these coumarins possess a wide range of physiological activity[3] such as anticoagulant, antitumor, antibiotic hepatotoxicity and carcinogenicity. A variety of coumarins find a wide range of applications industrially[4] such as fluorescent brightning agents, optical bleaching agents etc. Some may even be used as insecticides and pesticides.

The 7-hydroxy coumarin commonly known as Umbelliferone has often been regarded as the basic unit both structurally and biogenetically of the more complex coumarins. The simple coumarin nucleus has been shown to be derived from a phenyl propanoid precursor (C_6-C_3 unit).

A large number of methods[5] for the synthesis of coumarins are known in literature. Amongst them Pechmann condensation is the most commonly used method. Prior to the Pechmann condensation coumarins were mainly synthesised by the Perkin reaction. The methods employed make use of either phenols or salicylaldehydes. Many phenols are commercially available. If required, they can be made available from aromatic aldehydes and ketones by Baeyer-Villiger oxidation followed by hydrolysis.

In 1986, Talapatra and co-workers[6] reported that the reaction of p-methoxy cinnamic acid and resorcinol in the presence of PPA gave 7-methoxy coumarin. They visualised an oxidative biogenetic type self condensation of p-methoxy cinnamic acid to 7-methoxy coumarin. The mechanism proposed by these authors (Scheme-1) bears a close analogy to the biogenesis of 7-methoxy coumarin from p-methoxy cinnamic acid. On going

research work in our laboratory on the reaction of phenols with acids in the presence of PPA drew our attention to this report of Talapatra and co-workers.

The Scheme-1 though looked attractive is less likely based on the previous reports that in a acid catalysed conjugate addition of a phenol to conjugated carbonyl compounds, a new carbon-carbon bond is formed which is para or ortho with respect to the phenolic hydoxyl. No report of addition with the formation of phenol ether is available.

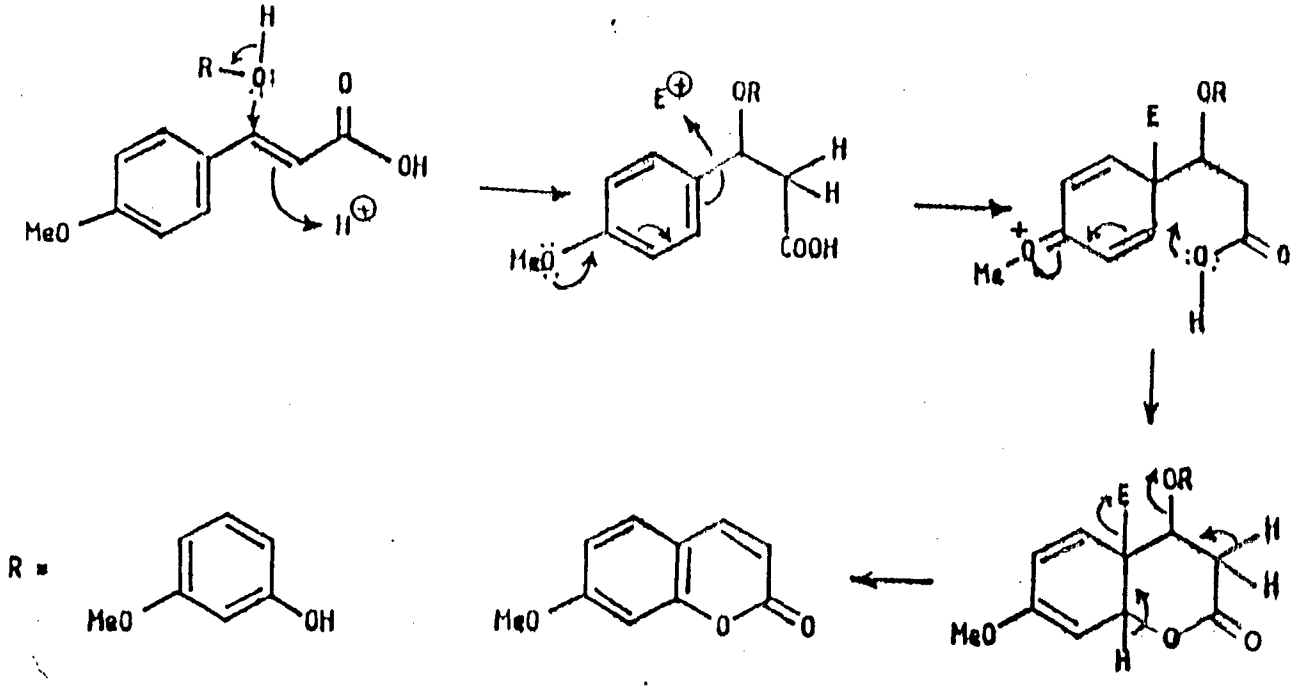
We, therefore, had every reason to believe that the aromatic ring of 7-methoxy coumarin formed in the above reaction must originate from 3-methoxy phenol used in the condensation reaction. We[7], therefore, proposed an alternative mechanism (Scheme-2) which nicely accounts for the observations of Talapatra and co-workers.

The most noteworthy feature of this mechanism is that it envisages the fact that the aromatic ring of the coumarin originates from the phenol and the remaining three carbons of the α-pyrone ring come from the p-methoxy cinnamic acid i.e. it is in fact a transfer of a C-3 unit from the p-methoxy cinnamic acid on to the C-6 unit of the phenol in the presence of PPA.

Further investigations on these lines confirmed the hypothesis and several natural and synthetic coumarins could be obtained by using different phenols and different derivatives of cinnamic acid.

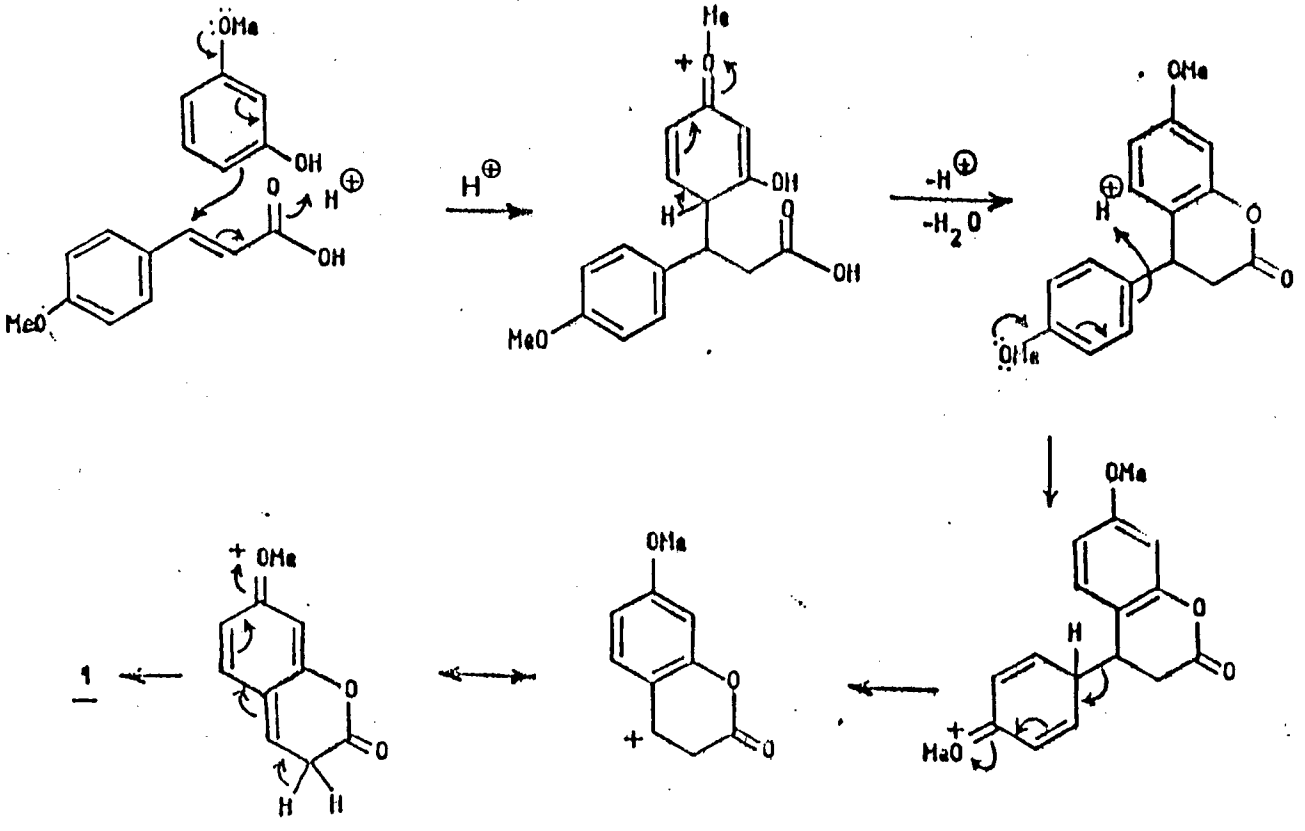
PRESENT STUDY

The present investigation was undertaken to find out the scope and limitations of this method. The structural features of phenols which yield the coumarins or the intermediate 3,4-dihydro-4-aryl coumarins when reacted with p-methoxy cinnamic acid in the presence of PPA and other reagents and the generality of this reaction for the synthesis of naturally and non-naturally occurring coumarins forms the subject matter of the present Thesis.


H
R
O
O
OH
MeO
H⊕
E⊕
OR
H
H
COOH
MeO
E
OR
Me
O
O
H
R =
MeO
OH
MeO
O
O
E
OR
H
H
MeO
O
O
H

1

Scheme - 1



Scheme - 2

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P A R T - I

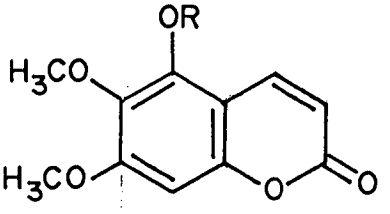
CHAPTER - 1

SECTION - 1

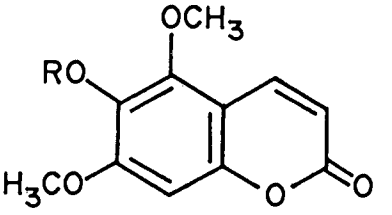
A NEW SYNTHESIS OF 5,7-DIMETHOXY-6-HYDROXY COUMARIN (FRAXINOL)

1.1 A NEW SYNTHESIS OF 5,7-DIMETHOXY-6-HYDROXY COUMARIN (2a. FRAXINOL)

A large number of coumarins having different types of oxygenation pattern have been found to occur in nature. These contain a small group having 5,6,7,-tri-oxygenated pattern having all the possible combinations of a free hydroxyl functionality with the remaining two substituents as methoxy groups. These combinations are shown in Chart-1 (R=H).

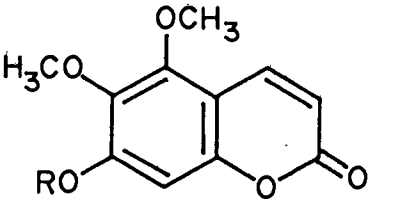


1



2

a) R = H
b) R = β-D-glucosyl
c) R = CH_3



3

Chart-1

It is also observed that the free hydroxyl coumarin (aglycone) usually co-occours with the corresponding glucoside. e.g. Chart-1 (R=β-D-glucosyl).

It may be noted that 5,6,7 -trimethoxy coumarin (1c, R=CH_3) is also a natural product and has been isolated from Pelargonium reniforme by Wagner and co--workers[1]. The synthesis of the 5,6,7-trimethoxy coumarin is comparatively straightforward and besides its previously known synthetic routes, we have recently reported a new synthesis of 5,6,7-trimethoxy coumarin by reaction of 3,4,5-trimethoxy phenol with p-methoxy cinnamic acid in the presence of polyphosphoric acid[2]. In principle selective demethylation of 5,6,7-trimethoxy coumarin should result in the formation of 1a, 2a, and 3a. However, in practice the selective demethylation poses practical difficulties. In this section a new synthesis of 5,7-dimethoxy-6-hydroxy coumarin (2a, fraxinol) is reported as a further extension of our coumarin synthesis.

Fraxinol (2a), was isolated by Späth and Sienkiewiczowa from Fraxinus excelsior[3]. Subsequently, fraxinol was also isolated from other species of the genus Fraxinus[4] and from Prunus domestica[5]. The assigned structure has been confirmed by synthesis by four independent routes which are depicted in Scheme-1. The first method[3] involves the preparation of salicylaldehyde derivative 4 which on Perkin condensation affords fraxinol (2a). The second route[6] uses the 5,7-

dimethoxy coumarin (5) as a starting material. The desired 6-hydroxy group is introduced by coumarin ring opening in alkaline medium followed by Elb's persulfate oxidation and ring closure. In the third method[7], the furocoumarin bergapten (6) has been transformed into apoxanthoxyletin (7) by oxidative elimination of the α-carbon atom of the furan ring. The formyl group of 8 is then transformed into fraxinol by Baeyer-Villiger oxidation. The last and chronologically the most recent synthesis is due to Wagner and Bladt[8] who used phloroglucinaldehyde (9) as the starting material and introduction of 6-hydroxy substituent by Biginelli's method (Scheme-1, method IV). These authors reported the spectral data on fraxinol for the first time.

It seemed to us that reaction of 2,6-dimethoxy-p-hydroquinone (10) with p-methoxy cinnamic acid in the presence of PPA should afford fraxinol (2a) in a single step.

The synthesis of fraxinol (2a) reported in sequel is further simplification of the route reported by Späth and Sienkiewiczowa[3] who used 2,6-dimethoxy-p-hydroquinone (10) as one of the intermediates. We, however, prepared this compound by a different route. 1,3,5-Trimethoxybenzene (11) on oxidation with 30%

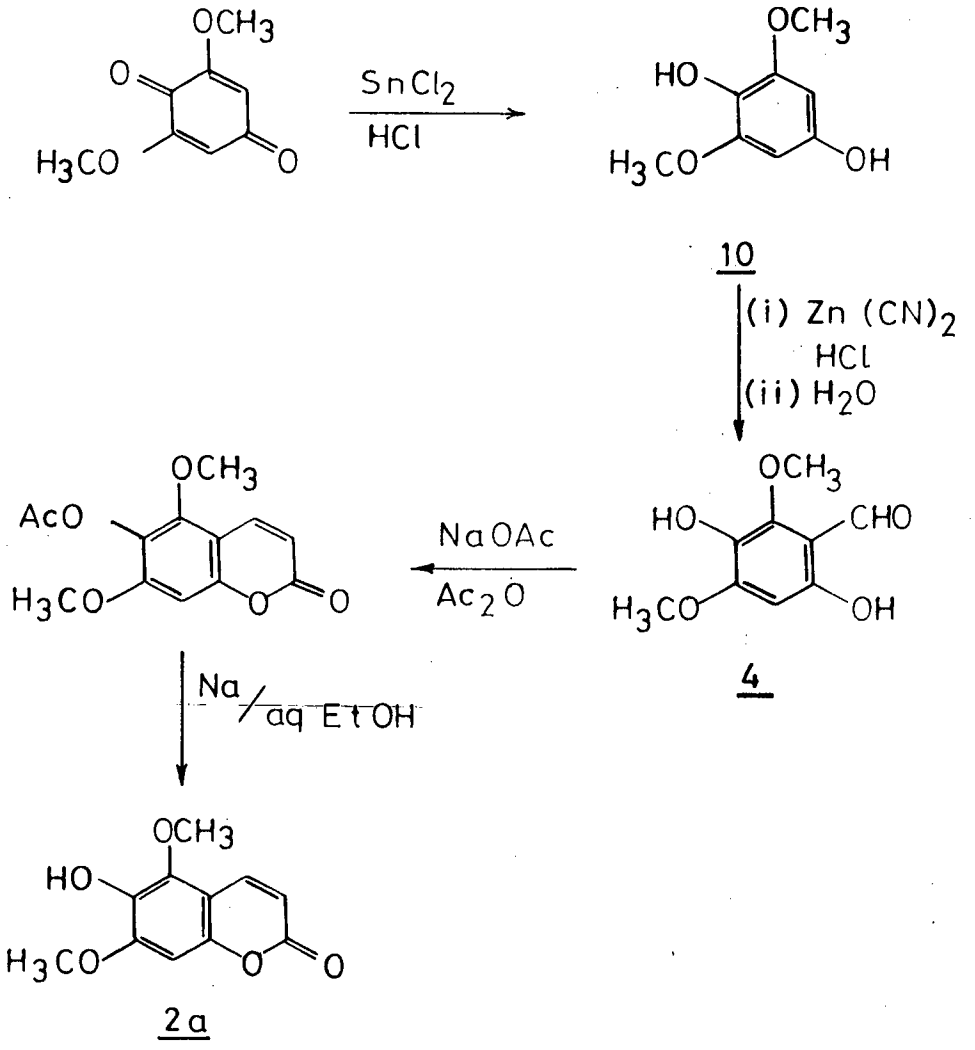
nitric acid in ethanol[9a] gave 2,6-dimethoxy-p-benzoquinone (12), melting point as reported in literature[3] but in poor yield (6%). The yield could be increased considerably (67%) when oxidation of 11 was carried out in CrO_3-aq.AcOH(80%) reagent[9b]. The product obtained showed identical spectral and physical properties reported for 12. The desired 2,6-dimethoxy-p-hydroquinone (10), m.p. 169° was then obtained in excellent yield by subjecting 12 to catalytic hydrogenation over Pd-C (10%) in chloroform*. Identity was established by comparison of melting point (lit.[3] m.p.166-67°; lit.[10] m.p. 159-60°) and IR spectrum kindly supplied by Professor H. Otsuka, School of Medicine, Institute of Pharmaceutical Sciences, Hiroshima University, Hiroshima, Japan.

Firstly, reaction of 10 with p-methoxy cinnamic acid in the presence of PPA at 70° for 4 hours gave after purification by filtration through a silica gel column and recrystallisation from benzene - petroleum-ether a pure compound, m.p. 171° identical with fraxinol. The whole sequence is shown in Scheme-2.

---

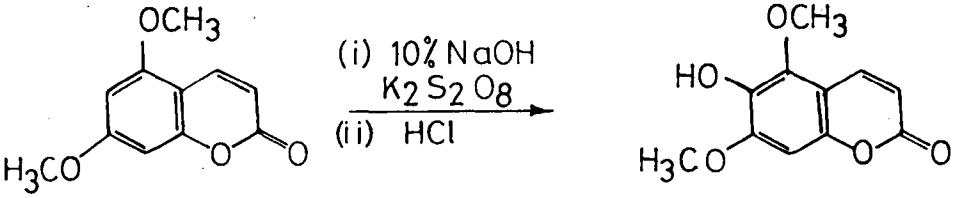
* 2,6-dimethoxy-p-hydroquinone is easily soluble in water and hence its preparation by other methods of reduction where its isolation requires extraction with organic solvents results in considerable loss.

Method I : Späth's synthesis[3]



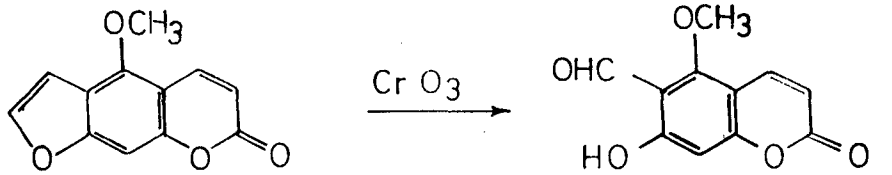
Scheme – 1

Method II: Dalvi's synthesis[6].

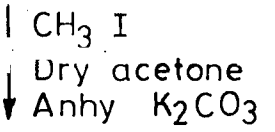


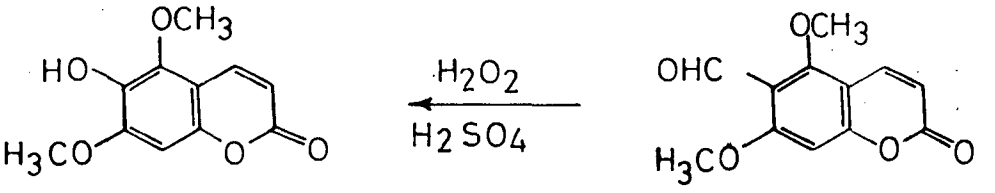
5 2a

Method III: Schönberg's synthesis[7]



6 7

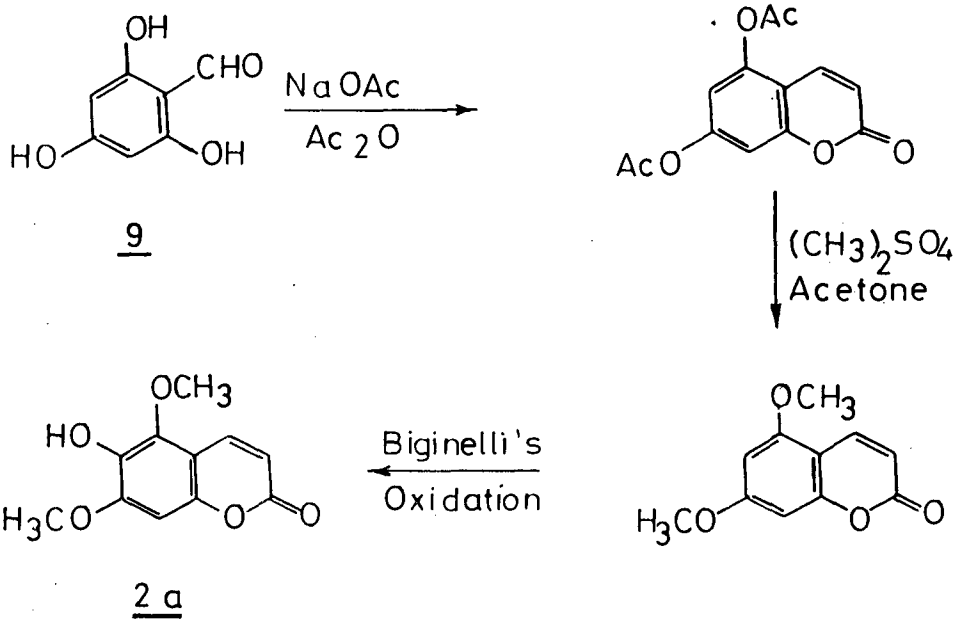




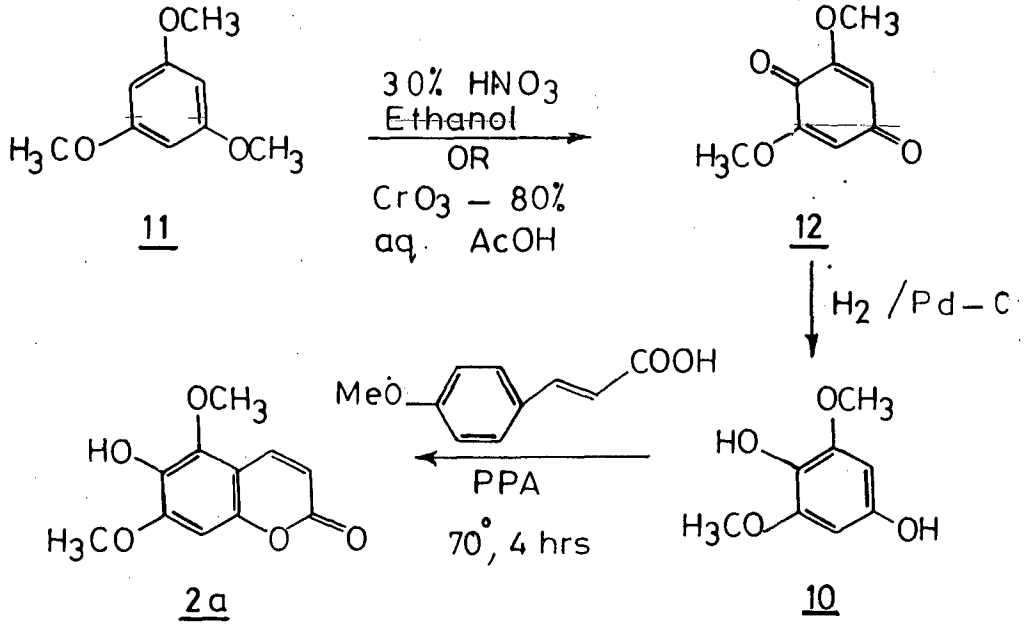
2a 8

Scheme-1

Method IV : Wagner's synthesis[8]

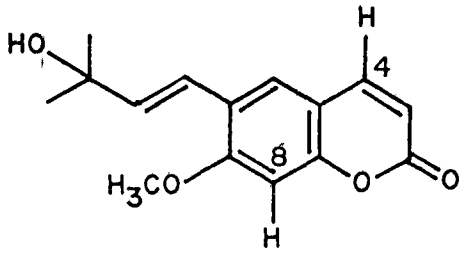


Scheme – 1



Scheme – 2

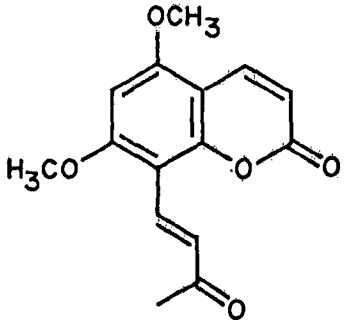
A literature survey on previous work on fraxinol (2a) (isolation and synthesis) was mainly done during the period when the present day spectroscopic methods were not available. As mentioned earlier the spectral data (uv, ^{1}H nmr) on fraxinol was reported by Wagner and Bladt[8] and our synthetic sample showed spectral data (uv, ^{1}H nmr) virtually identical as reported by them, thus establishing identity of our synthetic compound with fraxinol(2a). The characteristic feature of the ^{1}H nmr spectrum (fig. 4) is the long range coupling (J=0.5Hz) observed between C_4-H and C_8-H further establishing 5,6,7-substitution pattern. In fact when the spectrum is well resolved as in our case, it can be taken as a proof for the coumarin to be unsubstituted at C_4 and C_8 positions. Such conclusions nave been drawn before in case of suberenol (13)[11].



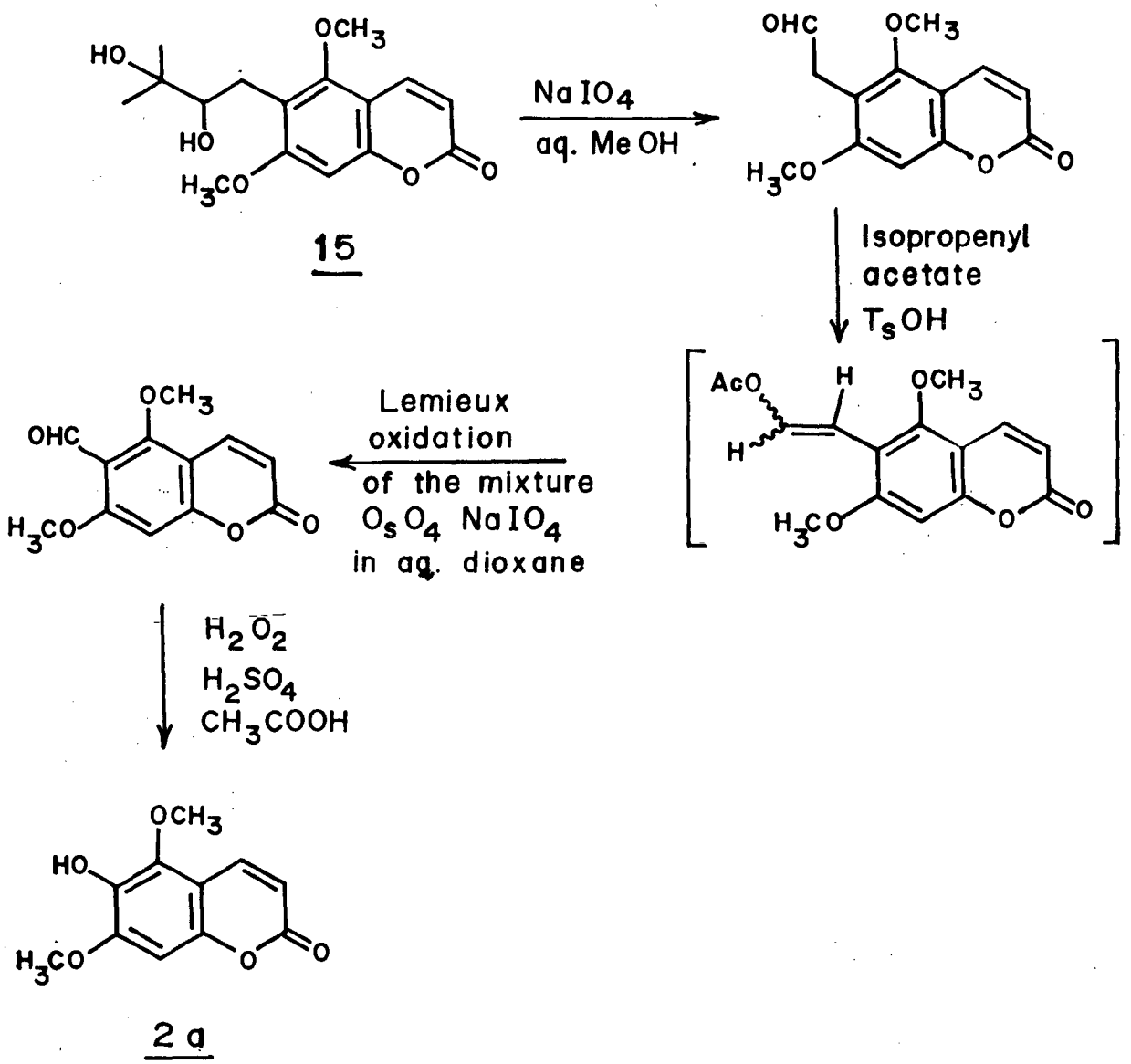
13

In 1977, Nagarajan and Parmar[5] reported the isolation of fraxinol (2a) from Prunus domestica (Rosaceae). However, the spectral data reported by them, though similar shows some differences in the uv absorption maxima and ^1H nmr chemical shifts. This discrepancy raises doubts about identification of their natural product as fraxinol (2a) and warrants further close scrutiny.

In 1983, Ishii and co-workers[12] during their work on the structure determination of naturally occurring coumarin toddalenone (14), proposed a route for the synthesis of fraxinol (2a). The route as depicted in Scheme-3 uses toddalolactone (15), a major component of Toddalia asiatica as the starting material. However, they do not provide any spectral data on their synthetic fraxinol which could be used for comparison.



14


HO
OCH3
HO
H3CO
O
O
15
NaIO4
aq. MeOH
OHC
OCH3
H3CO
O
O
Isopropenyl
acetate
TsOH
AcO
H
H
OCH3
H3CO
O
O
Lemieux
oxidation
of the mixture
OsO4 NaIO4
in aq. dioxane
OHC
OCH3
H3CO
O
O
H2O2
H2SO4
CH3COOH
HO
OCH3
H3CO
O
O
2a

Scheme -3

P A R T - I

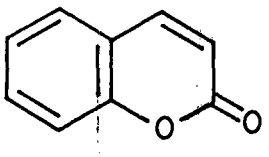
CHAPTER - 1

SECTION - 2

A NEW SYNTHESIS OF 6-HYDROXY-7-METHOXY COUMARIN (ISOSCOPOLETIN)

1.2 A NEW SYNTHESIS OF 6-HYDROXY-7-METHOXY COUMARIN (18a, ISOSCOPOLETIN)

A large number of oxygen heterocyclic compounds are known in the living kingdom[14] and coumarins constitute an important group amongst them. Since the isolation of the parent compound coumarin (16) from natural sources several other coumarin derivatives[15] have been isolated with the passage of time. It is indeed interesting that all naturally occurring coumarins except the coumarin (16) and the 4-methyl thio-5-methyl coumarin (17)[16] are oxygenated at one or more of the six available positions (C-3 to C-8).



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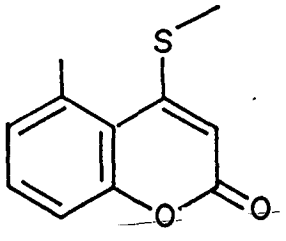
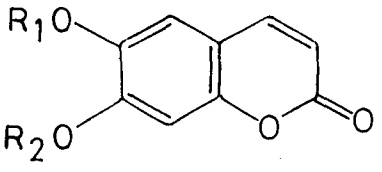


17

The 6,7-dioxygenated coumarins constitute a small group among coumarins. some typical examples having a free hydroxyl either at C-6 or C-7 are shown in Chart-2

Synthesis of 6,7-dimethoxy coumarin (19, scoparone) has been achieved in our laboratory by reaction of 3,4-dimethoxy phenol (20) with p-methoxy cinnamic acid in the presence of PPA. While selective mono-



18

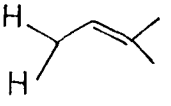
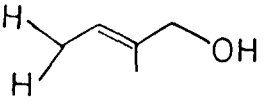
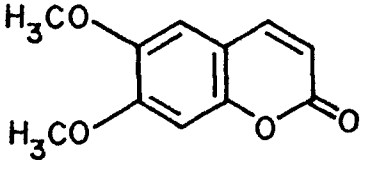
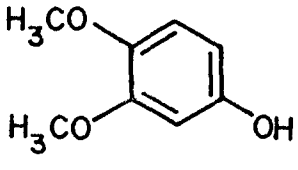
	R_1	R_2
a)	H	CH_3
b)	H	
c)	H	β-D-glucosyl
d)	H	6^1 ← β-D-apiosyl → β-D-glucosyl
e)	H	
f)	CH_3	H
g)	β-D-glucosyl	H
h)	Rutinosyl	H

Chart – 2

-demethylation[17] of scoparone (19) should afford 6-hydroxy-7-methoxy coumarin (18a, isoscopoletin) and/or 7-hydroxy-6-methoxy coumarin (18f). However, as indicated in Part-I, Chapter 1.1 such selective demethylations have practical difficulties unless the methoxy group is in close proximity with a carbonyl group. Alternatively selective mono-methylation of 6,7--dihydroxy coumarin (21, esculetin) should afford isoscopoletin (18a) and/ or scopoletin (18f). However, such partial mono-methylations have generated trace amounts of the other methylated product[18] also. We envisaged a new synthesis of 6-hydroxy-7-methoxy coumarin (18a, isoscopoletin) as an extention of our method by treatment of 2-methoxy-1,4-hydroquinone (24) with [illegible]-methoxy cinnamic acid in the presence of PPA.



19



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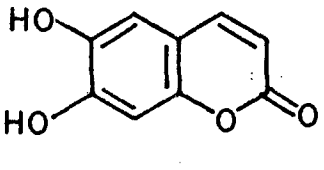


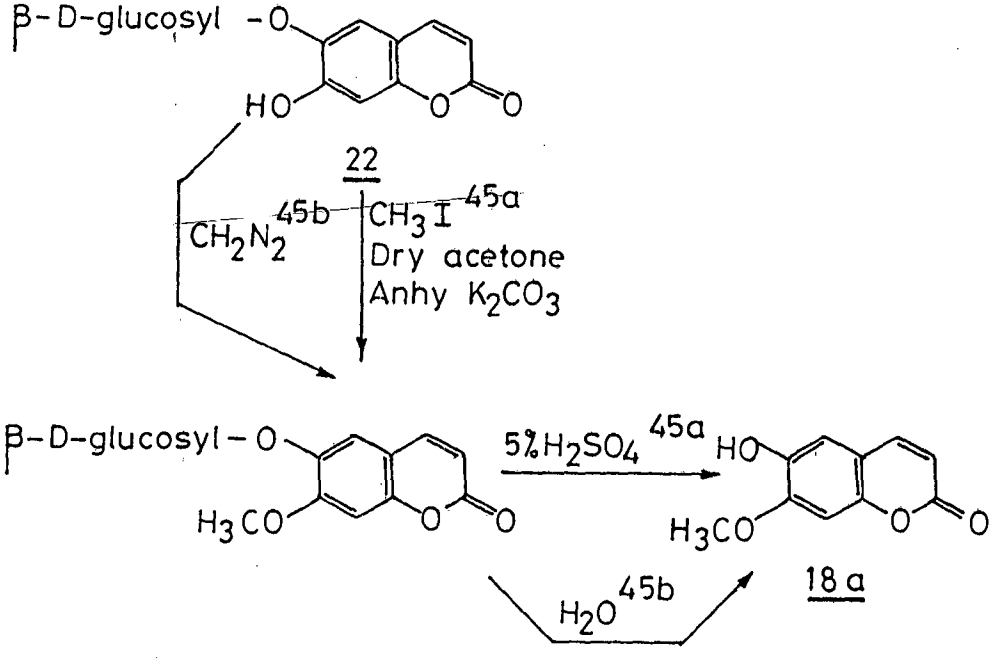
21

Isoscopoletin (18a) was first isolated by Hahn from Artemisia messerschmidiana[19]. Subsequently its isolation from several other sources such as Artemisia tridentata[20], Artemisia scoparia[21], Artemisia

capillaris[22], Solanum melongena[23], Angelica pachycarpa[24], Melia azedarach[25], Convolvulus aevranisis[26], Afraegle paniculata[27], Randia nilotica[28], Diospyros kaki[29], Haplophyllum bungei[30], Coronilla elegans[31], Olea capensis[32], Chloranthaceae japonicus[33], Anagyris foetida[34], Gundelia tournefortii[35], Aesculus turbinata[36], Achillea biebershteinia[37], Achillea krasheninnikovii[37], Phaseolus aureus[38], Hydvotis chrysotricha[39], Bupleurum fruticescens[40], Vernonia scorpioides[41], Tripetaleia paniculata[42], Skimmia malanocarpa[43], and Skimmia laureola[44] has been reported. The assigned structure has been confirmed by its synthesis by seven independent routes. The method due to Head and Robertson[45a] as well as Seka and Kallir[45b] was the first method reported and employs a preformed coumarin, esculin (22). The second method[46] uses 2,5--dihydroxy-4-methoxy benzaldehyde (23) which on Perkin condensation gives isoscopoletin (18a). In the third method[47] 2-methoxy-1,4-hydroquinone (24) is the starting material. The three carbons of the α-pyrone ring are introduced using ethyl-β,β-diethoxy propionate or the acid chloride derived from β-ethoxy acrylic acid. The fourth route[48] utilises condensation of 2,5-dihydroxy-4--methoxy benzaldehyde (23) with malonic acid with simultaneous decarboxylation and cyclisation to

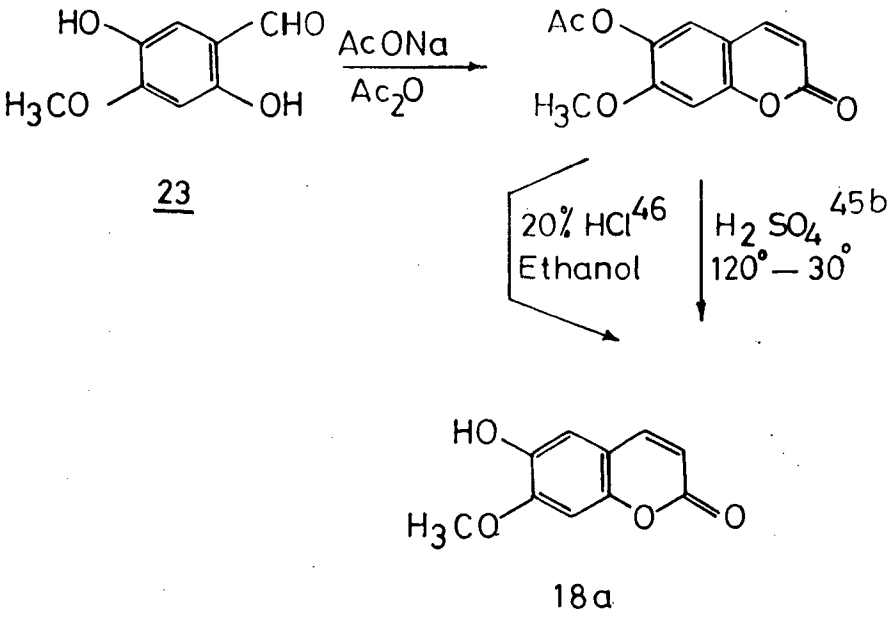
isoscopoletin (18a). In the fifth route[49] isoscopoletin (18a) was obtained from methyl ether of umbelliferone (25) by Elb's persulfate oxidation. In 1983, Xiaotian et al.[50] reported the transformation of esculetin (21) into isoscopoletin (18a). In 1992, Ishii and co-workers[51] reported yet another synthetic route to isoscopoletin (18a) starting with vanillin (26). All these synthetic routes to isoscopoletin (18a) are depicted in Scheme-4.

Method I : Head's synthesis[45a] and
Seka's synthesis[45b]



Scheme—4

Method II : Seka's synthesis[45b] and
Joshi's synthesis[46]

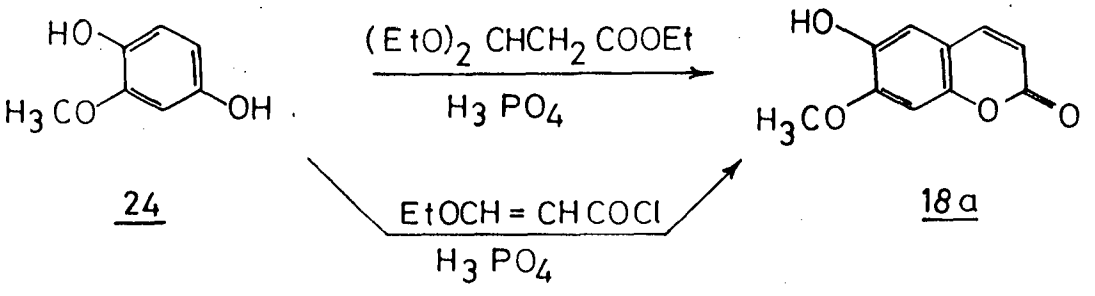


23

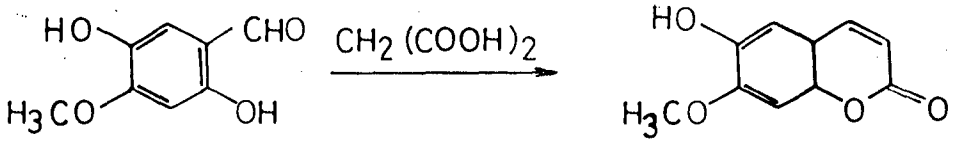
18a

Scheme — 4

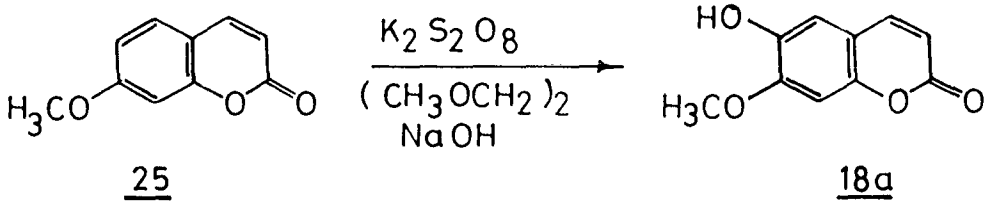
Method III : Crosby's synthesis[47]



Method IV : Thakur's synthesis[48]

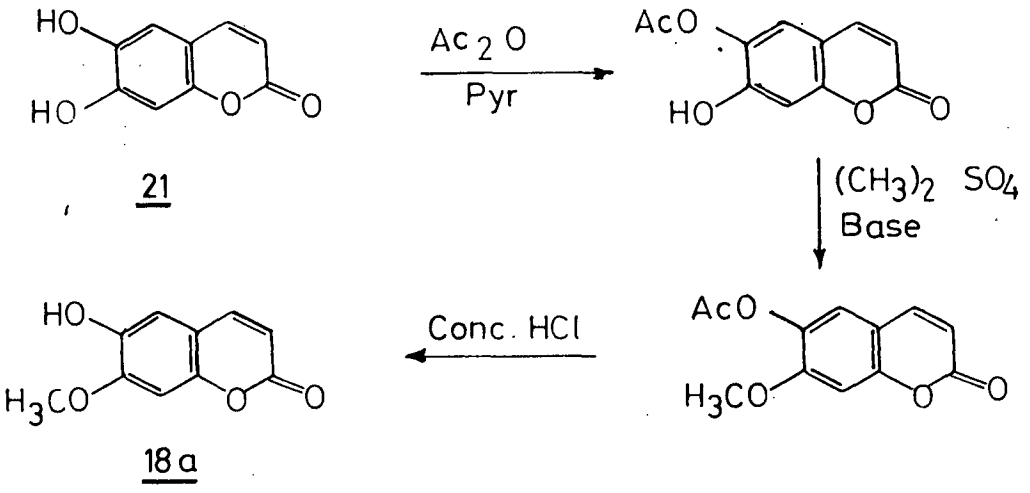


Method V : Bower's synthesis[49a] and
Thakur's synthesis[49b]

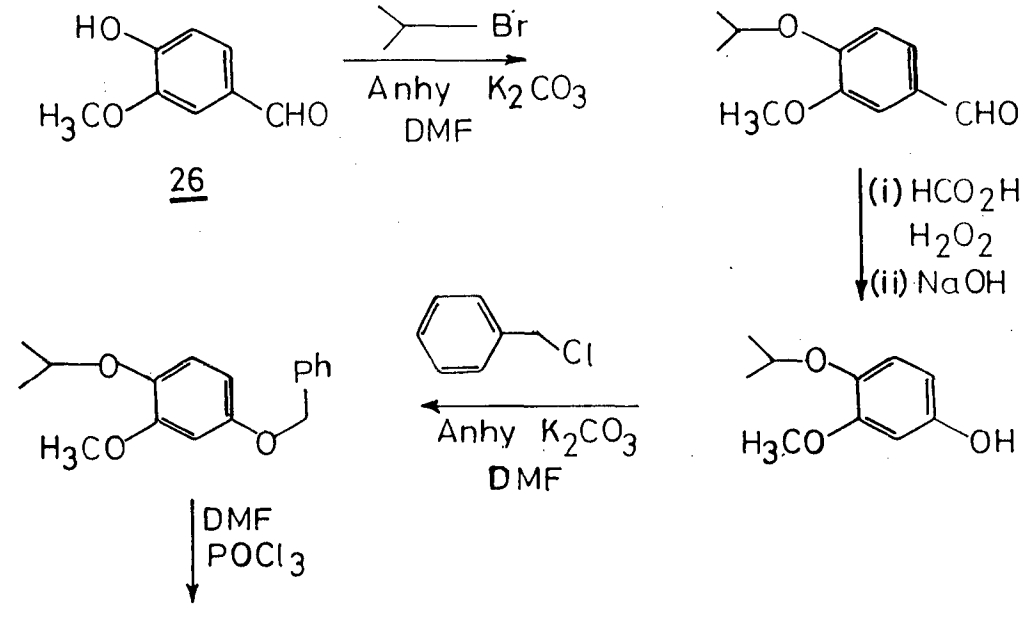


Scheme — 4

Method VI : Xiaotian's synthesis[50]



Method VII : Ishii's synthesis[51]



Scheme – 4

On the basis of our previous observations, we anticipated the formation of isoscopoletin (18a) by the reaction of 2-methoxy-1,4-hydroquinone (24) with p-methoxy cinnamic acid in the presence of PPA. The desired 2-methoxy-1,4-hydroquinone (24) was obtained in good yield by Dakin oxidation of vanillin (26). Reaction of 24 with p-methoxy cinnamic acid in the presence of polyphosphoric acid at 70° for 4 hours gave after purification by silica gel column chromatography and recrystallisation from chloroform - petroleum-ether a pure compound, m.p.180° (lit.[20] m.p. 185°, lit.[23] m.p.185-87°, lit.[32] m.p. 187-90°) identified as isoscopoletin (18a). The yield of the pure product 18a is, however, comparatively low (18%). It may be noted that ^{1}H nmr spectral data of isoscopoletin (18a) measured in different solvents is available in the literature. However, the chemical shifts measured in the same solvent e.g.$CDCl_3$ by different groups are not identical. As indicated earlier the values for our synthetic product agree with those reported by Ishii and co-workers[51].

In this reaction, we obtained another product, m.p. 205° which is yet to be characterised.

P A R T - I

CHAPTER - 1

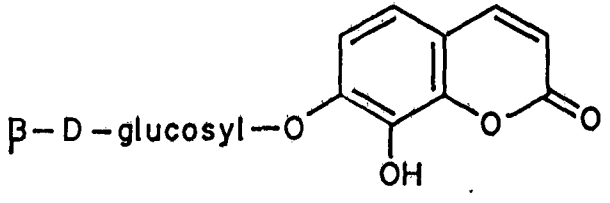
SECTION - 3

7-METHOXY-8-HYDROXY COUMARIN

A NEW SYNTHESIS

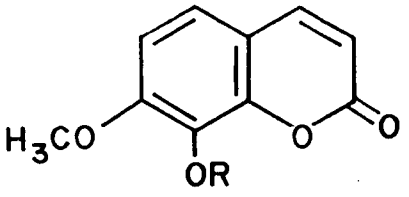
1.3 7-METHOXY-8-HYDROXY COUMARIN (28a) : A NEW SYNTHESIS

The glycoside originally isolated by Vauquelin[55] from Daphne alpina in 1812, was characterised by Wessely and Sturm[56] as 7-β-D-glucosyloxy-8-hydroxy coumarin (27) in 1930 and was called by trivial name daphnin[57] This may be considered as the first member of 7,8-dioxygenated coumarin. With the advancement of improved isolation methods and modern sophisticated techniques for structure determination several other members representing 7,8-dioxygenated coumarins have been well characterised.



27

Among this group, the coumarins having a methoxy group at C-7 and a hydroxy or an alkoxy group at C-8 position derived from natural sources[58] are listed in Chart-3.



28

R

a) H

b) CH_3

c) $CH_2-CH_2-CH(CH_3)-CH_2OH$

d) $CH_2-CH(OH)-C(CH_3)=CH_2$

e) $CH_2-CH=C-(CH_3)_2$

f) $CH_2-CH(O)-C-(CH_3)_2$

g) $CH_2-CH(OH)-C(OH)-(CH_3)_2$

h) $CH_2-CH_2-C(=CH_2)-CH_2-CH_2-CH(O)-C-(CH_3)_2$

i) $CH_2-CH_2-C(=CH_2)-CH_2-CH_2-CH(OH)-C(OH)-(CH_3)_2$

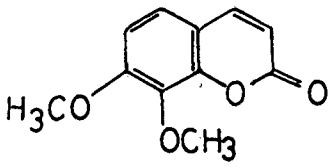
Chart - 3

7-Methoxy-8-hydroxy coumarin (28a) was first isolated by Herz and co-workers[58a] from Artemisia dracunculoides in 1970. Subsequently Gray and co-workers[58f] isolated it from Coleonema calycinum. Practical selective methylation of C-7 hydroxyl of 7,8-dihydroxy coumarin to obtain 7-methoxy-8-hydroxy coumarin is difficult[59]. However, selective demethylation of 7,8-dimethoxy coumarin (28b) has been reported[59] to give good yield of 7-methoxy-8-hydroxy coumarin (28a) which constitute a simple method of its synthesis.

There are two other independent routes in addition to selective demethylation of 28b. One of these[60] involves the Perkin condensation of the salicylaldehyde derivative 31 which inturn was obtained by Baeyer-Villiger oxidation and subsequent hydrolysis followed by formylation of o-vanillin (29). The other route[61] uses the preformed coumarin, 7-methoxy-8-acetyl coumarin (32) which on Dakin reaction yields the desired 7-methoxy-8-hydroxy coumarin (28a). These three routes are depicted in Scheme-5.

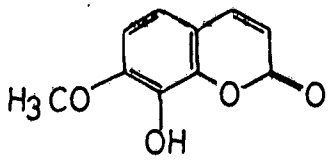
To gain credance to our synthesis of coumarins substituted in the aromatic ring we envisaged the preparation of 28a by reaction of 2-hydroxy-3-methoxy phenol (30) and p-methoxycinnamic acid in the presence of PPA.

Method I : Dean's synthesis [59]



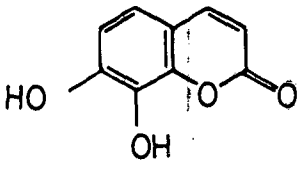
28b

dil. H_2SO_4, 70°, 14 hrs

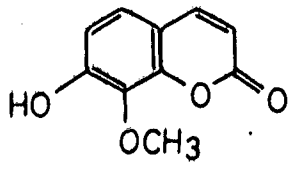


28a

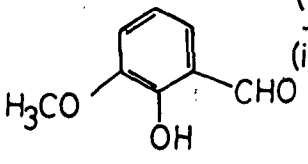
+



and

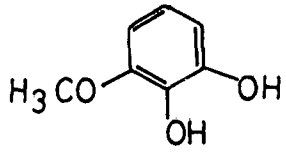


Method II : Mauthner's synthesis [60]



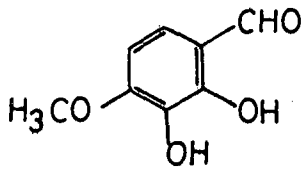
29

(i) B.V. Oxidn
(ii) KOH / HOH



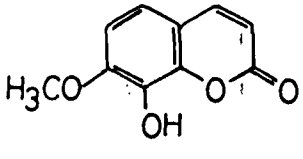
30

Formylation



31

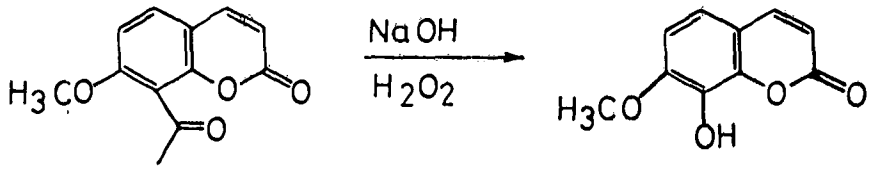
Ac_2O
AcONa



28a

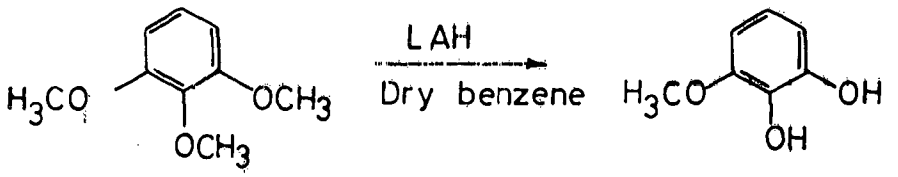
Scheme – 5

Method III : Ahluwalia's synthesis[61]

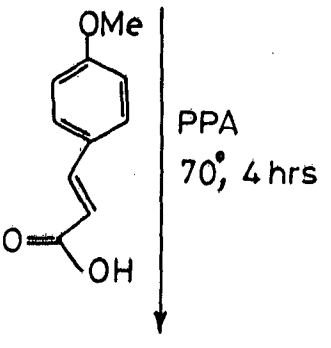


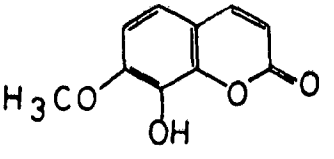
32 28a

Scheme – 5



33 30





28a

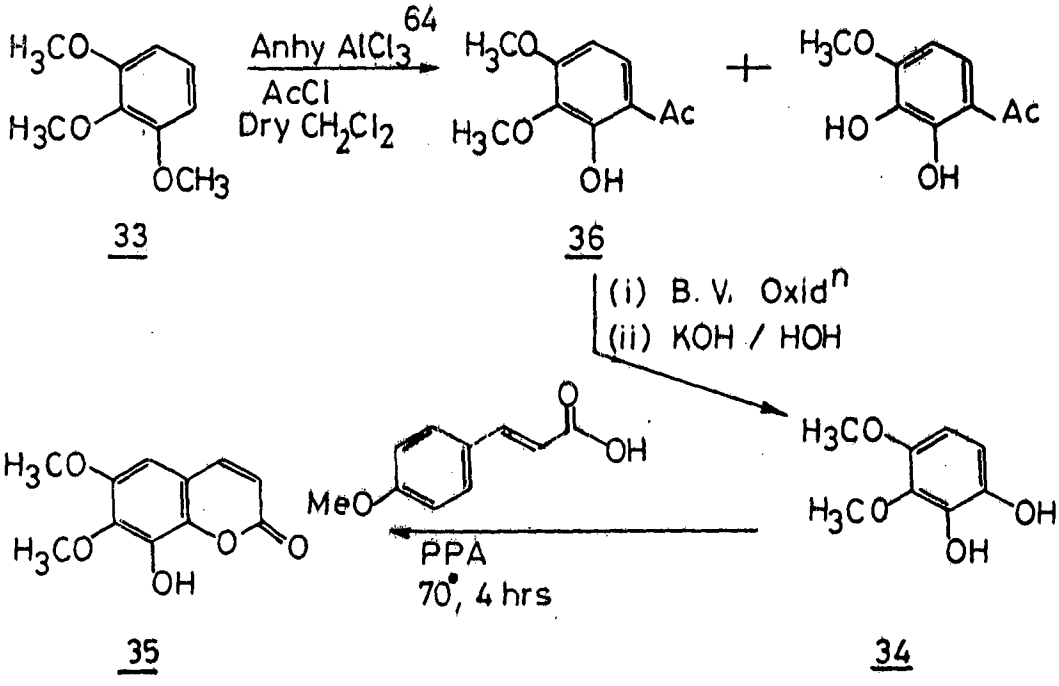
Scheme – 6

We did obtain the desired coumarin in this reaction as anticipated and firmly believe that the present synthesis of 7-methoxy-8-hydroxy coumarin (28a) (Scheme-6) is much more simple than the route adopted by Mauthner[60] who also used 2-hydroxy-3--methoxy phenol (30) as one of the intermediates. We prepared 30 by an independent route. 1,2,3-Trimethoxybenzene (33) on selective demethylation[62] with lithium aluminium hydride in dry benzene gave the desired 2-hydroxy-3-methoxy phenol (30) in good yield. However, in our hands this compound was obtained as a viscous liquid even on column chromatography and purification by distillation (lit.[63] m.p. 38-41°). The spectral comparison unambiguously established identity of our compound with 30. Finally, the reaction of 30 with p-methoxy cinnamic acid in the presence of PPA at 70° for 4 hours gave after column chromatography and recrystallisation from benzene, a pure compound m.p. 173° identified as 7-methoxy-8-hydroxy coumarin (28a).

The ^{1}H nmr spectrum recorded on our synthetic sample 28a was found to be virtually identical with the one reported by Dean and co-workers[59] as well as Gray and co-workers[58f]. It may be noted that there are certain discrepances in the reported ^{1}H nmr chemical shifts for the same coumarin by Herz and co-workers[58a].

The second synthesis of 7-methoxy-8-hydroxy coumarin (28a) described in sequel was not a planned one, but as it happens in any experimental research it came to us as a surprise. We were interested in the synthesis of 6,7--dimethoxy-8-hydroxy coumarin (35) and the phenol required for this purpose was the catechol derivative 34. Based on the literature precedent[64] we planned the synthesis of 35 as shown in Scheme-7.

Reaction of 1,2,3-trimethoxybenzene (33) with acetyl chloride and anhydrous aluminium chloride in dry methylene chloride gave two products purified by column chromatography having melting points 113° and 132° in order of their polarity (TLC). The reported[65] melting point of 2-hydroxy-3,4-dimethoxy acetophenone (36) is 83° which made clear that we are handling substances other than 36. Incidentally on an earlier occasion we had carried out methylation of gallacetophenone a known substance and prepared by Nencki reaction[66] on pyrogallol. The product m.p. 113°, had identical TLC behaviour with one of the compounds (less polar substance, m.p.113°) prepared by acylation of 1,2,3-trimethoxybenzene (33). We took for granted that the reported m.p. 83° of 36 is an error and subjected the product having melting point 113° to Baeyer Villiger oxidation followed by hydrolysis. Crystalline compound m.p. 131°


Anhy AlCl3
AcCl
Dry CH2Cl2
64
H3CO
H3CO
OCH3
Ac
OH
HO
33
36
(i) B. V. Oxidn
(ii) KOH / HOH
MeO
OH
PPA
70°, 4 hrs
O
35
34

Scheme – 7

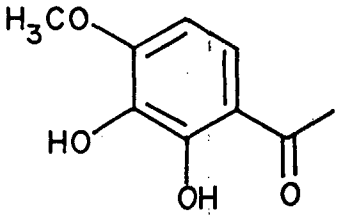
obtained in this reaction was different from the starting material. Assuming that it was 34* we subjected it to reaction with p-methoxy cinnamic acid in the presence of PPA . To our surprise the coumarin formed in this reaction showed m.p. 173° and proved to be identical with 7-methoxy-8-hydroxy coumarin (28a). The identity could be established without difficulty as we had spectral data and authentic sample of this coumarin as described in earlier part of this section.

Identification of the coumarin as 7-methoxy-8--hydroxy coumarin (28a) in the above reaction made it clear that the phenol used in its reaction with p-methoxy cinnamic acid in the presence of PPA cannot be catechol derivative 34 but must have a different structure. It became then essential to characterise it by routine spectral analysis. We were in for further interesting data. The ^1H nmr of compound m.p. 131° showed the following data : δ ($CDCl_3$) 2.57, s, 3H, $-\overset{O}{\overset{\|}{C}}-CH_3$; 3.96, s, 3H, Ar-$OCH_3$; 5.52, s, 1H, Ar-OH; 6.50, d (J=10 Hz), 1H, Ar-H; 7.32, d (J=10 Hz), 1H, Ar-H; 12.48, s, 1H, Ar-OH chelated.

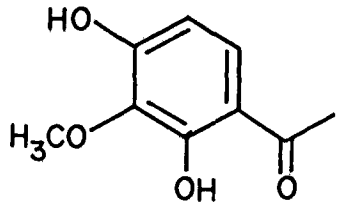
---

* Based on the general outcome of B.V.Oxidation and hydrolysis.

The above spectral data suggested structures 37 and 38 for the compound used in the reaction with p-methoxy cinnamic acid. This makes clear that the Baeyer--Villiger oxidation didn't proceed as expected but one of the methoxy group got demethylated. There are no literature precedents on the demethylation of $-OCH_3$ groups under Baeyer-Villiger conditions. The question then arises how 7-methoxy-8-hydroxy coumarin is formed. The simplest explanation which we would like to offer is assignment of structure 37 to the product used for the reaction with p-methoxy cinnamic acid. Retro Friedel-Craft reaction on acetophenone derivative 37 then yields 2-hydroxy-3-methoxy phenol (30) which in turn gets transformed into the coumarin 28a by the well established method.



37



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PART - I

CHAPTER - (2)

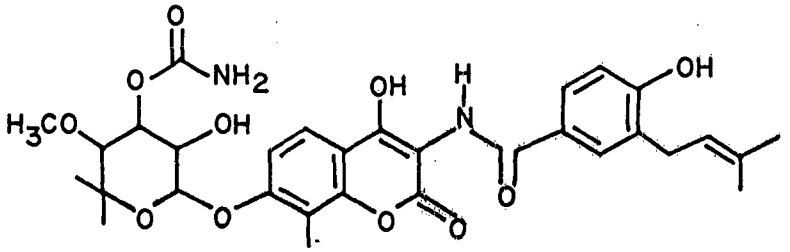
SECTION - 1

4-HYDROXY-5-METHYL COUMARIN

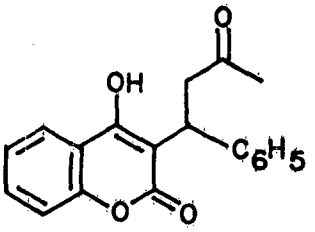
A NEW SYNTHESIS

2.1 4-HYDROXY-5-METHYL COUMARIN (41a) : A NEW SYNTHESIS

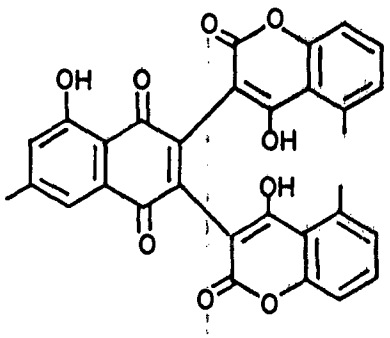
4-Hydroxy coumarins form an important group among substituted naturally occurring coumarins. These coumarin derivatives have been isolated and characterised from higher plants and owe their importance mainly due to anticoagulant effects associated with them. Some of the important members of this group having medicinal properties such as antifungal, anticoagulant, estrogenic etc. are as shown in Chart-4.



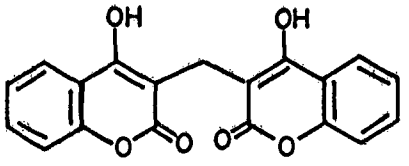
Novobiocin



Warfarin



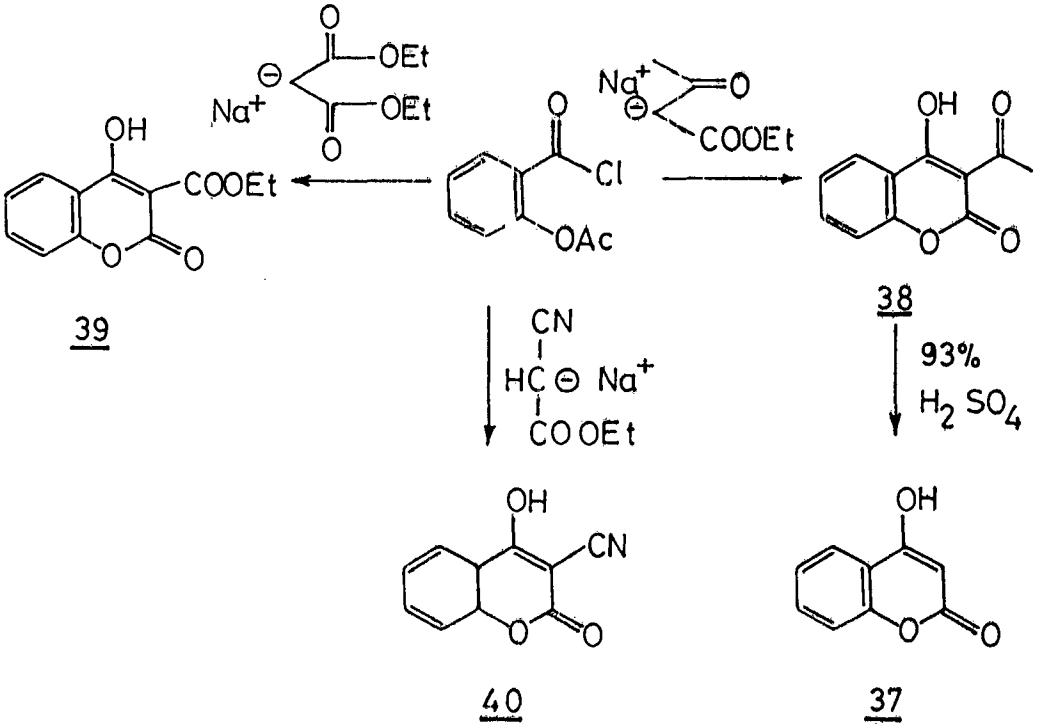
Ismailin



Dicoumarol

Chart-4

In view of the reported medicinal properties, synthetic routes to the parent coumarin belonging to this group viz.4-hydroxy coumarin (37) were developed by different groups. While a general method for the synthesis of 3-substituted 4-hydroxy coumarins by condensation of o-acetoxy benzoyl chloride with sodium salts of ethyl aceto acetate, diethyl malonate and ethyl cyano acetate to produce 3-acetyl, 3-carboethoxy and 3-cyano coumarins (38,39,& 40) respectively was reported by Anschutz[67] as early as 1908, the parent coumarin 37 was available only by indirect method i.e. by removal of the 3-substituent as shown in Scheme-8.

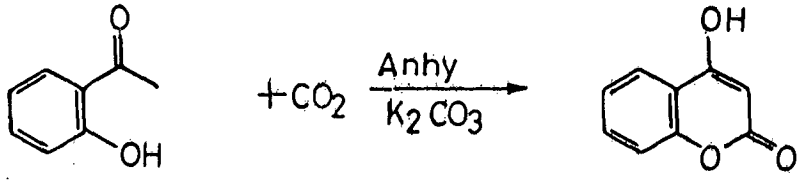


Scheme-8

After a gap of almost five decades, several routes for the direct preparation of 4-hydroxy coumarin (37) were reported mainly during the years 1960-1961. These routes are summarised in Scheme-9. It may be noted that only the route (viii, Scheme-9) is the most recent one.

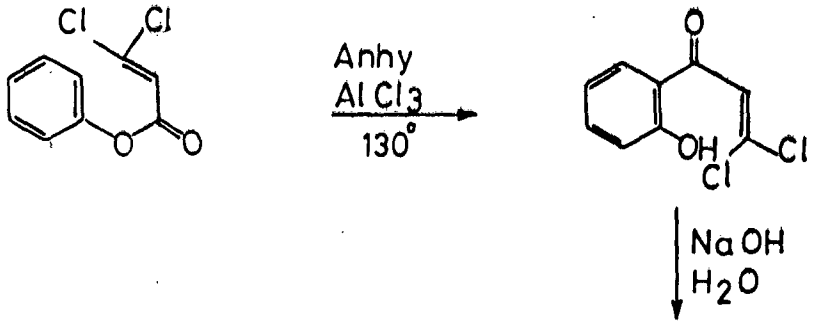
With the advent of modern isolation techniques, spectroscopic methods for structure elucidation and search for bio-active substances of natural origin, a large number of natural products have been isolated and characterised during the past 30 years. Even among the coumarins, the number of naturally occurring coumarins has increased to such an extent that it became necessary to put them together in the form of a book entitled "The naturally occurring coumaris"[15] which deals with all aspects of coumarins followed by an equally exhaustive review article[76] updating the information upto the end of 1989.

A cursory look at the tabulated information in the above two references would show that a very large number of derivatives of 4-hydroxy coumarins have been isolated and characterised (Chart-4A). Among this group, 4-hydroxy-5-methyl coumarin (41a) and further modifications of this disubstituted coumarin attracted our attention for two reasons: (i) our own interest in coumarin synthesis and (ii) previous identification of

(I) 

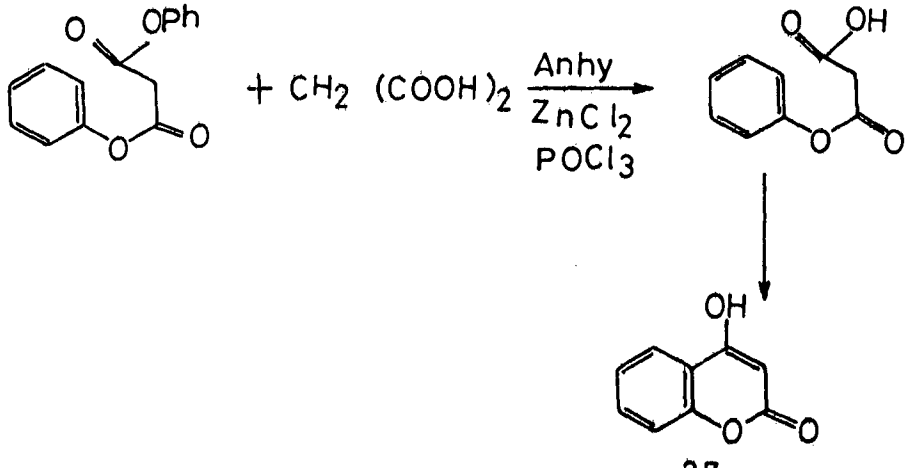
37

(Ref. 68)

(II) 

37

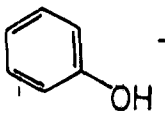
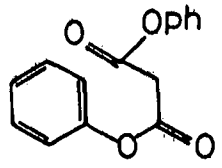
(Ref. 69)

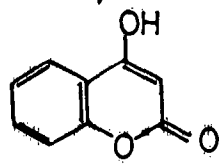
(III) 

37

(Ref. 70)

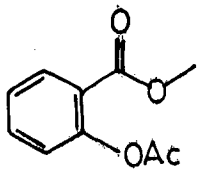
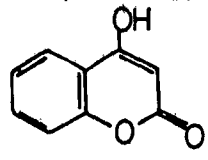
Scheme–9

(IV) 2  + $CH_2(COOH)_2$ $\xrightarrow{POCl_3}$ 

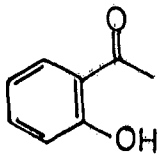
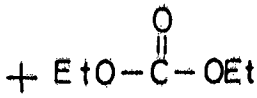
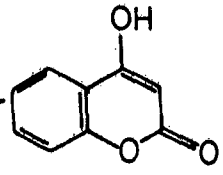


37

(Ref. 70,71)

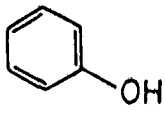
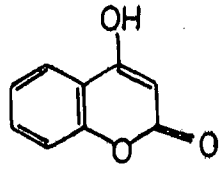
(V)  $\xrightarrow[\text{liq. Paraffin}]{Na}$ $\xrightarrow[240^\circ]{}$ 

(Ref. 72)

(VI)  +  $\xrightarrow{Na}$ 

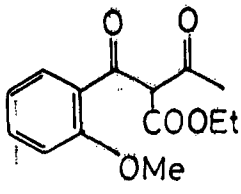
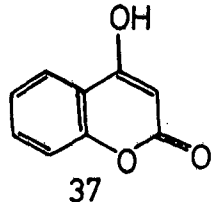
37

(Ref. 73)

(VII)  + $CH_2(COOH)_2$ $\xrightarrow[POCl_3]{\text{Fused } ZnCl_2}$ $\xrightarrow{60-75^\circ}$ 

37

(Ref. 74)

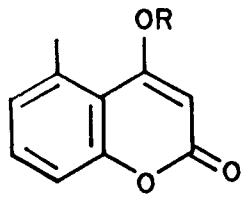
(VIII)  $\xrightarrow[AlCl_3]{Anhy}$ 

37

(Ref. 75)

Scheme - 9

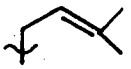
* only representative examples are given



41

R = (a) H

(b) CH_3

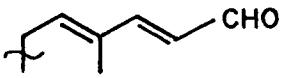
(c) 

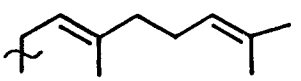
(d) β-D-glucosyl

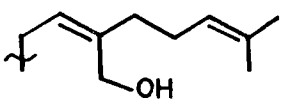
(e) Rutinosyl

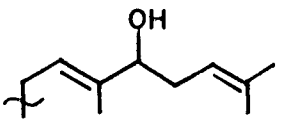
(f) Cellobiosyl

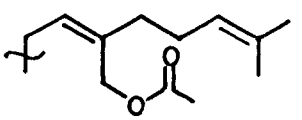
(g) Gentiobiosyl

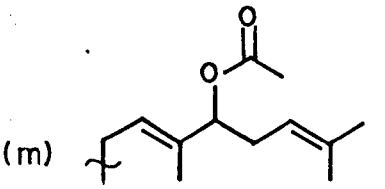
(h) 

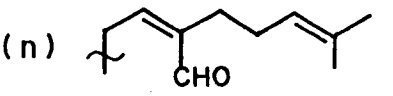
(i) 

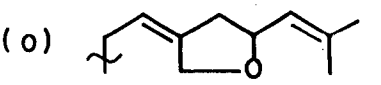
(j) 

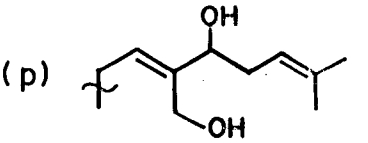
(k) 

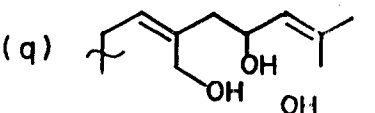
(l) 

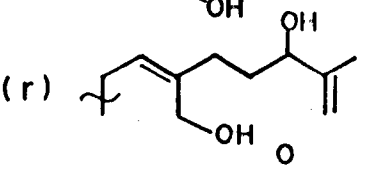
(m) 

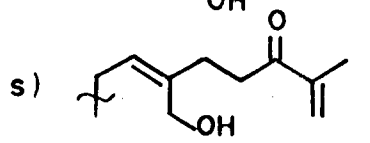
(n) 

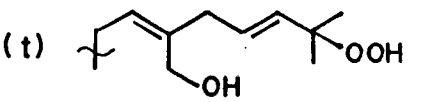
(o) 

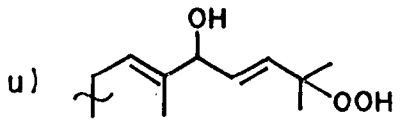
(p) 

(q) 

(r) 

(s) 

(t) 

(u) 

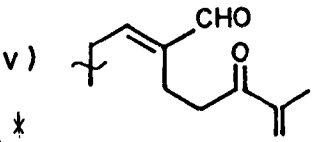
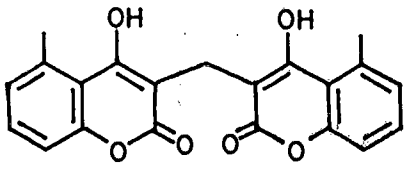
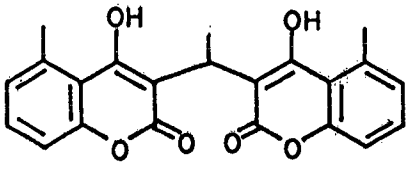
(v) 

Chart – 4A*

two unidentified compounds isolated from Diospyros kaki Thumb and D. kaki varsylvestris Makino[77] as 42 and 43 from our laboratory.[78] Identity of one of these unidentified products, earlier isolated by Natori and co-workers[77] from D. kaki with 42 was unambiguously established by direct spectral comparison and physical constants. The second unknown compound was shown to possess structure 43 and being a naturally occurring substance a synthetic support seemed desirable.*



42

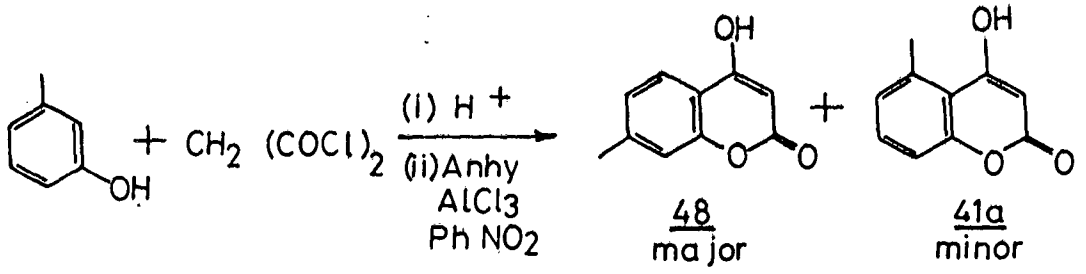


43

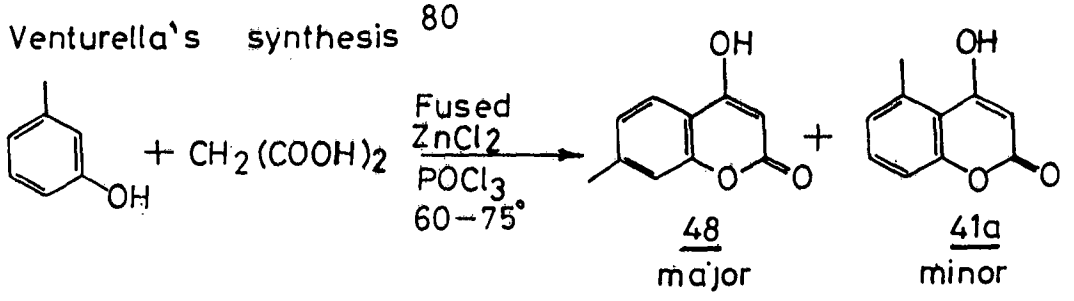
A literature survey of the previously known synthetic methods for 4-hydroxy-6-methyl coumarin (41a) are depicted in Scheme- 10. As expected these were mearly the application of previously known methods and m-cresol and its derivatives (Scheme-10) were used to obtain the desired coumarin 41a.

* The results were sent for publication but the referees insisted on the confirmation of the structure by synthesis before it is accepted for publication.

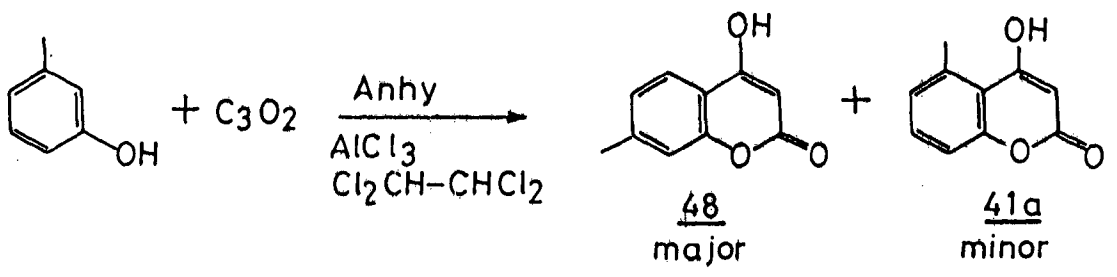
(I) Matsui's synthesis[79]



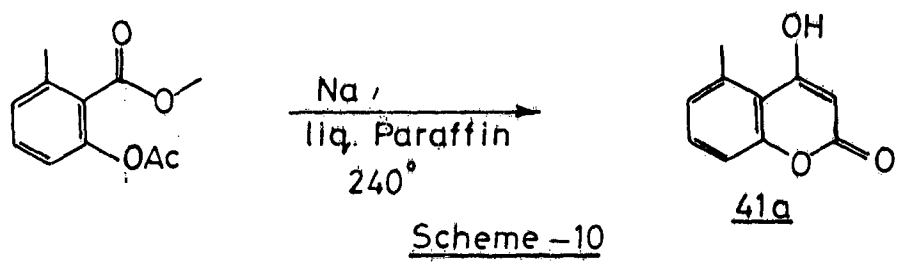
(II) Venturella's synthesis[80]



(III) Tsutsumi's synthesis[81]

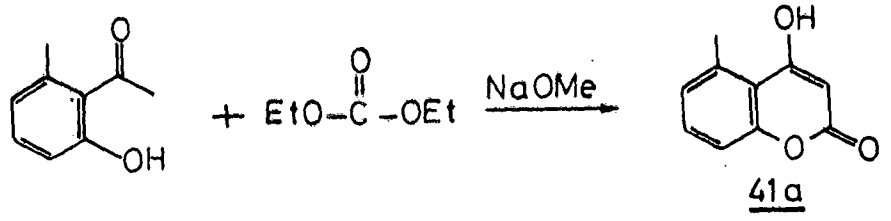


(IV) Okogun's synthesis[82]



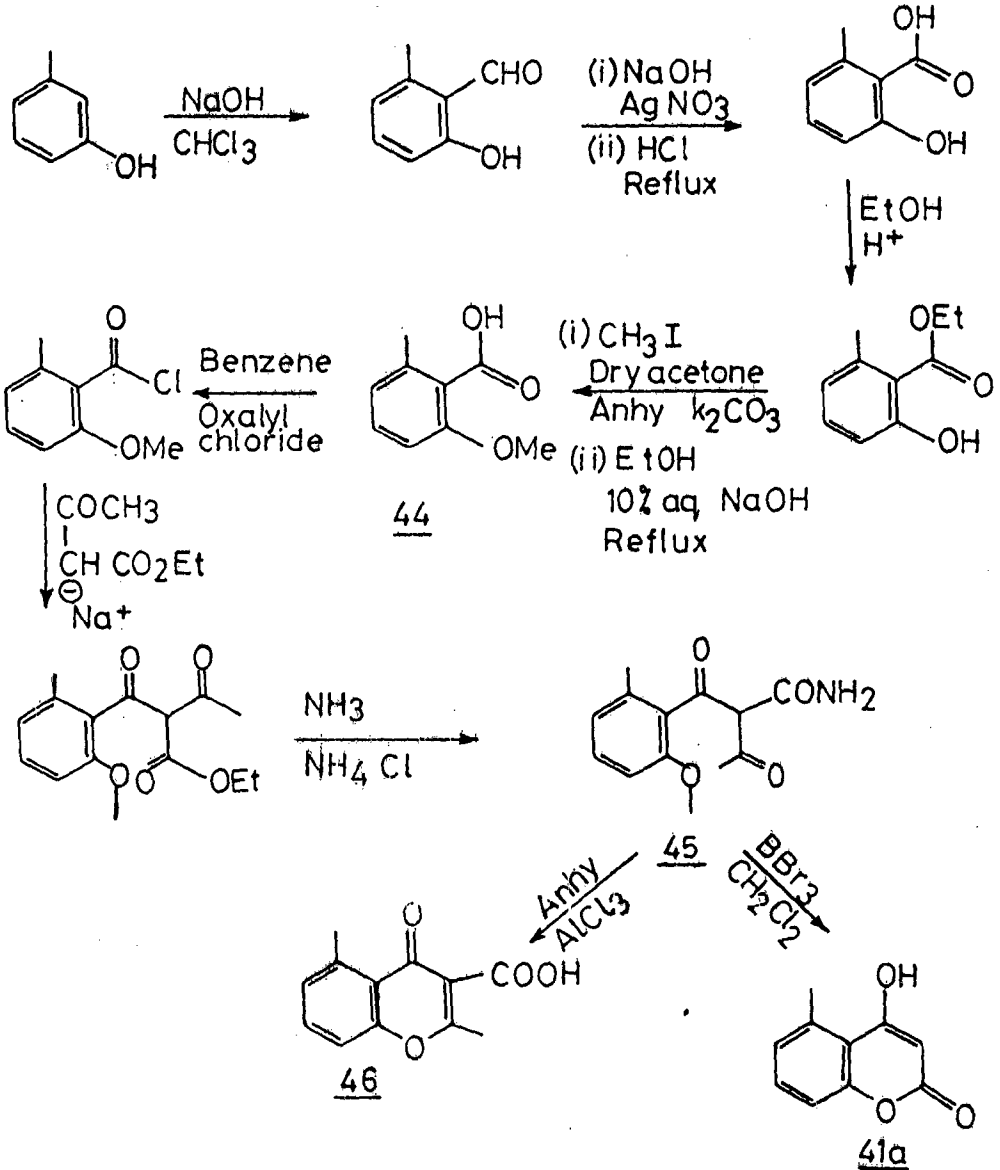
Scheme –10

(V) Boyd's synthesis[73a]



41a

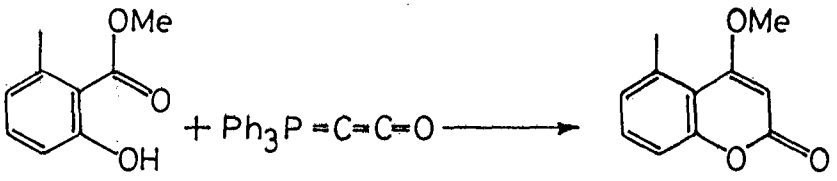
Scheme –10



Scheme –11

The most recent method of Chatterjea and co-workers[75] (Scheme-11) uses 2-methoxy-6-methyl benzoic acid (44) (prepared by six steps from m-cresol) as shown. The interesting feature of this sequence is the reported conversion of the intermediate 45 to 41a by boron tribromide in methylene chloride. These authors further observed that replacement of BBr_3 by $AlCl_3$ results in the formation of 2,5-dimethyl-chromone-3-carboxylic acid (46). Nickisch and co-workers[83] prepared 4-methoxy-5-methyl coumarin (47) by application of intramolecular Wittig reaction as shown in Scheme-12.

Nickisch's synthesis [83]

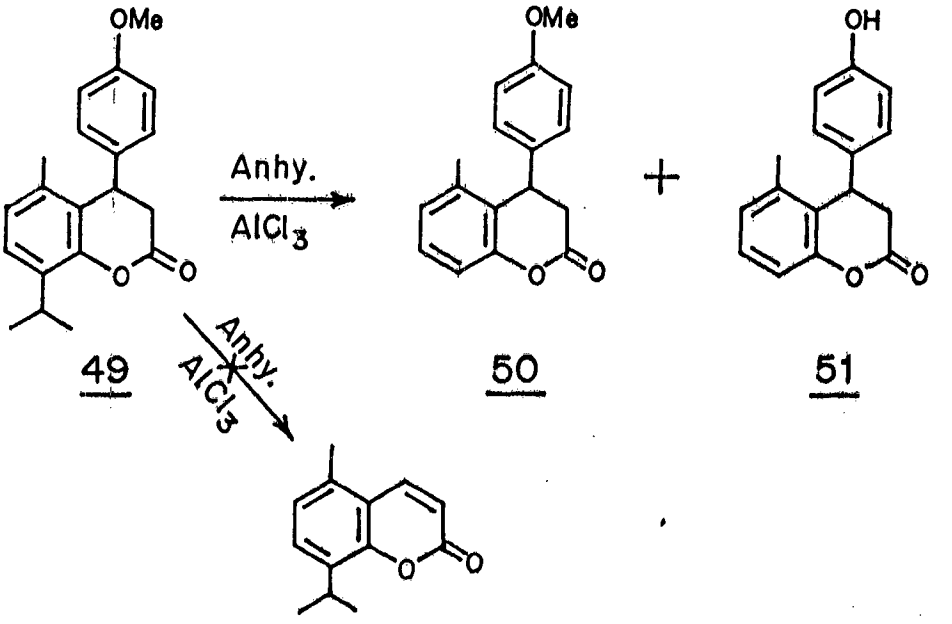


47

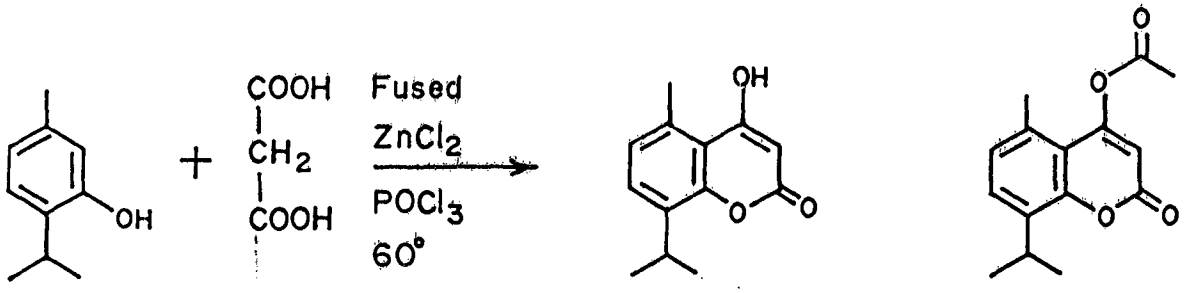
Scheme-12

The major drawback in the above methods where m-cresol is used as a starting material, the desired 4-hydroxy-5-methyl coumarin (41a) is always formed as a minor compound and its separation from 4-hydroxy-7--methyl coumarin (48) is very tedious. In other cases, preparation of the intermediates from m-cresol requires several steps. These shortcomings in the known methods and our requirement of 41a for the preparation of 43 prompted us to explore a new synthetic route for 41a. We have now synthesised 41a by an entirely new method and the results are described in the following few pages.

We had observed earlier that attempted dearylation of 49 with anhydrous $AlCl_3$ resulted in the loss of isopropyl substituent and the reaction product contained a mixture of 50 and 51 (for details, see Part-II, Chapter 4.2).



This suggested the use of thymol (52) as the starting material for the preparation of 41a. We were encouraged to see the reported[74] preparation of 4-hydroxy-5-methyl-8-isopropyl coumarin (53) by reaction of thymol (52) with malonic acid in the presence of anhydrous zinc chloride and phosphorus oxychloride. The assigned structure 53 was only tentative and not supported by spectral analysis. We thought of preparation of 53 by this method, confirm the structure by spectral analysis and then subject it to reaction with anhydrous $AlCl_3$ where we anticipated the loss of isopropyl group thus leading to the desired 4-hydroxy-5-methyl coumarin (41a). Repeatition of the known reaction sequence posed no special problems and the product obtained had melting point 223° as reported by Shah and co-workers[74]. Measurement of the ^1H nmr spectrum, however, posed some practical difficulties due to its poor solubility but the spectrum clearly showed the presence of isopropyl group confirming the assigned structure 53.



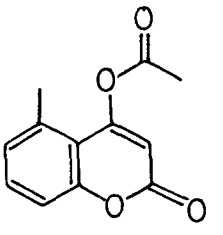
52 53 54

In order to confirm the above findings, coumarin 53 was subjected to treatment with acetic anhydride-pyridine according to the procedure of Ahluwalia and co-workers[85]. In this reaction we obtained three compounds A, B, and C having melting points 125°, 198° and 165° respectively. The ^1H nmr spectrum ($CDCl_3$) of compound "A" showed it to be a mixture of at least two compounds and was not investigated further. The ^1H nmr spectrum of compound "B", m.p. 198° showed the presence of isopropyl group (1.27, 6H,d,J=7Hz), acetyl group (2.43, 3H,d,J=1Hz), Ar-CH_3 (2.76, 3H,d,J=1Hz), benzylic methine (3.63, 1H,quintet,J=7Hz), vinyl hydrogen (6.34, 1H,q,J=1Hz) and a pair of doublets for the remaining two aromatic hydrogens (7.15 and 7.50, 1H each,J=8 Hz). Structure 54 is assigned to compound "B". The downfield shift of the aromatic methyl group is highly characteristic of 5-methyl coumarins with an -OR substituent at C-4 position (peri effect). The spectral data on compound "C" could not be collected due to paucity of the sample.

4-Hydroxy-5-methyl-8-isopropyl coumarin (53) thus obtained was heated with anhydrous aluminium chloride in chlorobenzene at 95° for one hour. The purified product, m.p.235° obtained by recrystallisation from ethanol, was identified as 4-hydroxy-5-methyl coumarin

(41a) by a direct comparison with an authentic sample.*

On attempted acetylation with acetic anhydride-pyridine 41a gave two products (m.p. 225° and 208°). Based on the previous reports, formation of two compounds under these experimental conditions is not surprising. The major product having melting point 225° has been assigned structure 55 on the basis of spectral data (for details see experimental section).



55

The present synthetic method offers distinct advantages over previous methods and the coumarin 41a can be obtained in sufficient quantities from the commercially available starting material, viz. thymol (52). It may be noted that in our synthesis, isopropyl group of thymol functions as a protecting group thus yielding 41a without contamination of 48, the major product obtained in other methods starting from m-cresol. In conclusion, we claim to have developed a new synthetic route to 4-hydroxy-5-methyl coumarin.

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* An authentic sample of 4-hydroxy-5-methyl coumarin 41a was supplied by Prof. T. Inoue, Faculty of Pharmaceutical Sciences, Hoshi University, Tokyo 142, Japan.

P A R T - I

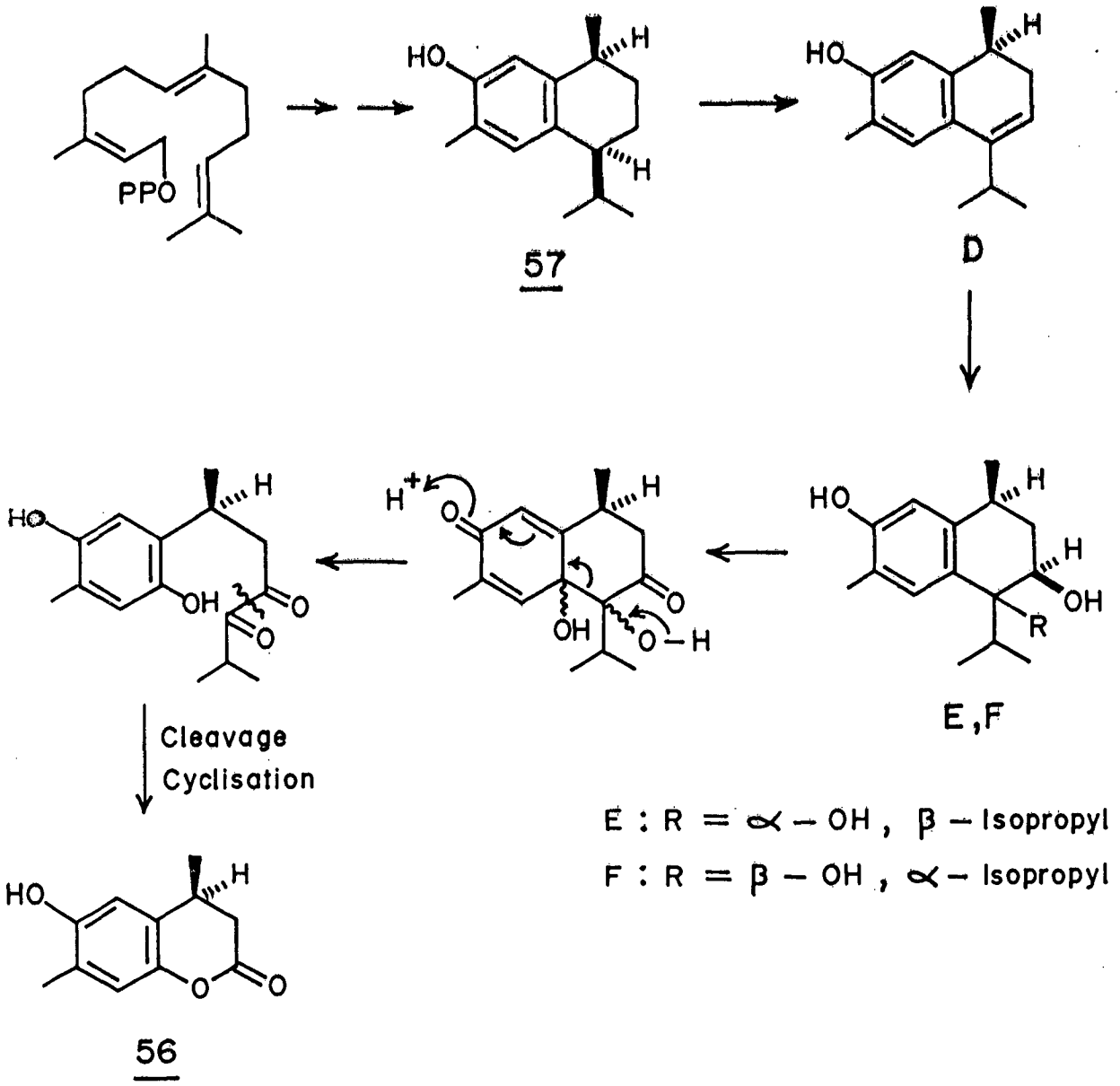
CHAPTER - 2

SECTION - 2

SYNTHESIS OF 6-HYDROXY-3,4-DIHYDRO-4,7-DIMETHYL-BENZO-1-PYRAN-2-ONE, A TETRANORSESQUITERPENOID

2.2 SYNTHESIS OF 6-HYDROXY-3,4-DIHYDRO-4,7-DIMETHYL BENZO-1-PYRAN-2-ONE, A TETRANORSESQUITERPENOID

Although 4-methyl coumarin and its derivatives have been synthetically known for over a century[15], very few of the naturally occurring coumarins possess a 4-methyl substituent[76]. The recent isolation and characterisation of (-)-6-hydroxy-3,4-dihydro-4,7-dimethyl coumarin (56) by Cambie and co-workers from Heritiera.ornithocephala[86] (Fam sterculiaceae) is perhaps the first representative of naturally occurring 3,4-dihydro coumarins and is likely to have a terpenoid biosynthetic origin rather than the customary biosynthetic derivation from a phenylpropanoid precursor[15]. Because of our continued interest in modified terpenoids, the structural features present in 56 attracted our attention. Though the structure assigned seemed unambiguous, a synthetic proof was considered desirable. In this section, we report a synthetic confirmation to the assigned structure 56. We also propose a detailed biogenetic pathway which accounts for its co-occurrence with cis-7-hydroxy calamenene (57) and explain how four carbon atoms of the sesquiterpenoid precursor 57 are eliminated resulting in the formation of 56. The hypothetical biogenetic pathway (Scheme-13) is mechanistically sound and has literature precedents which lend further support to the



E : R = ∝ – OH , β – Isopropyl

F : R = β – OH , ∝ – Isopropyl

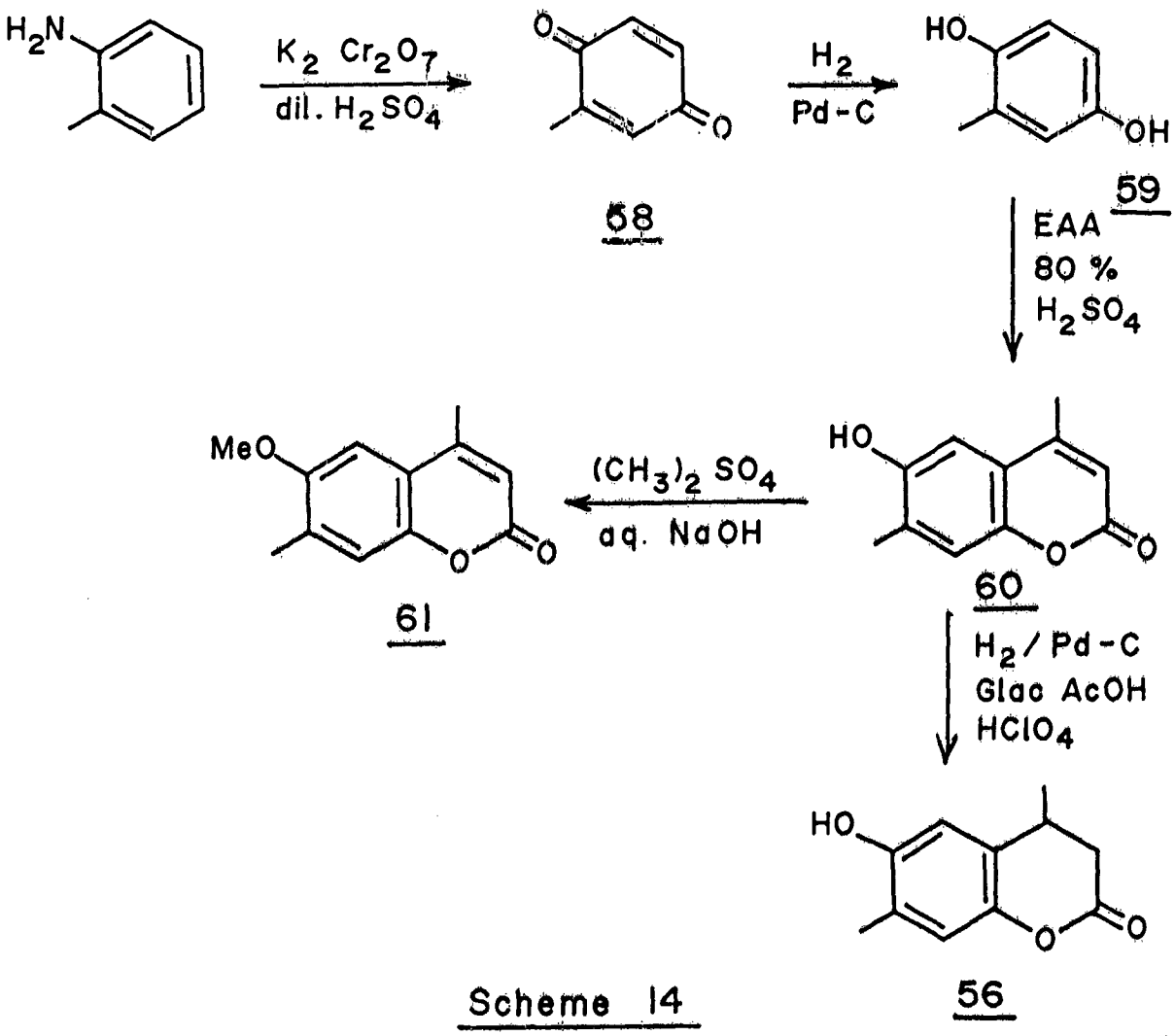
Scheme – 13

biosynthetic transformation of a normal sesquiterpenoid. Compound 56 represents the first member of tetranorsesquiterpenoid group.

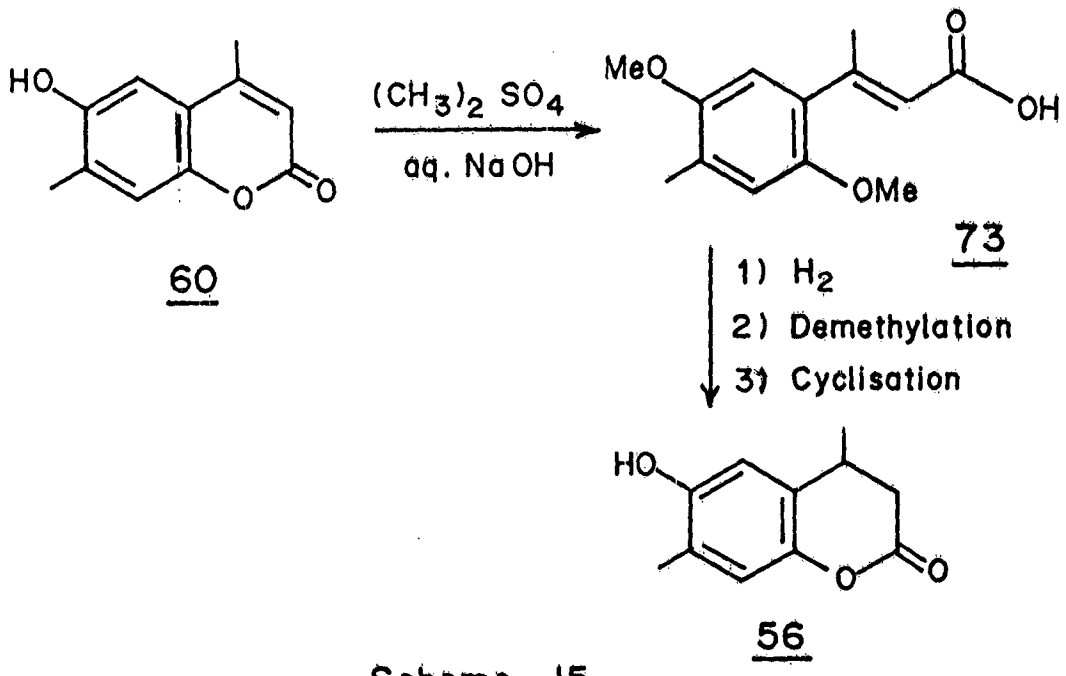
2-Methyl-p-benzoquinone (58), prepared by the CrO_3 oxidation of o-toluidine[87] was converted into 2-methyl--p-hydroquinone (59) by catalytic hydrogenation over Pd--C in ethyl acetate. The hydroquinone 59 was condensed with ethyl aceto acetate under Pechmann conditions[88] to yield 6-hydroxy-4,7-dimethyl coumarin (60) (Scheme-14). The spectral data (MS, ^1H nmr) previously not recorded in the literature confirmed the structure assigned.

Saturation of 3,4-double bond of 60 proved to be unusually difficult mainly because of its poor solubility in normal organic solvents and also the known inertness of the 3,4-double bond of coumarins towards hydrogenation[15].

Methylative ring opening [89a] of coumarin 60 followed by hydrogenation, demethylation and ring closure was expected to yield 56 as depicted in Scheme-15. However, reaction of 60 with NaOH and $(CH_3)_2SO_4$ (Scheme-14) failed to give the ring opened product 73 but gave a crystalline compound m.p. 160° which was identified as methyl ether 61 of 60 on the basis of ^1H nmr analysis. Failure to get the ring opened o-methoxy-β-methyl


H2N
K2 Cr2O7
dil. H2SO4
O
O
H2
Pd-C
HO
OH
58
59
EAA
80 %
H2SO4
HO
O
O
60
(CH3)2 SO4
aq. NaOH
MeO
O
O
61
H2 / Pd-C
Glac AcOH
HClO4
HO
O
O
56

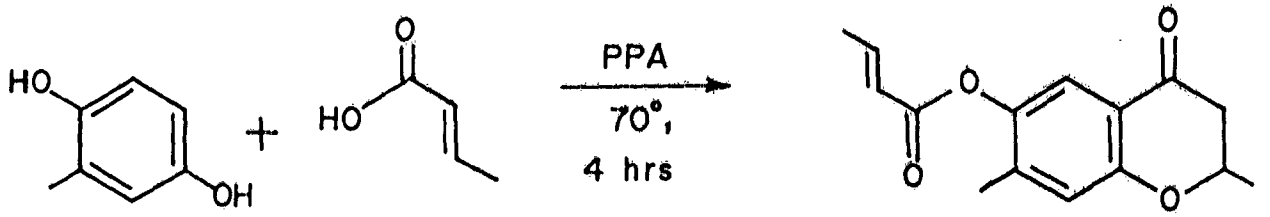
Scheme 14


HO
O
O
60
(CH3)2 SO4
aq. NaOH
MeO
OMe
O
OH
73
1) H2
2) Demethylation
3) Cyclisation
HO
O
O
56

Scheme –15

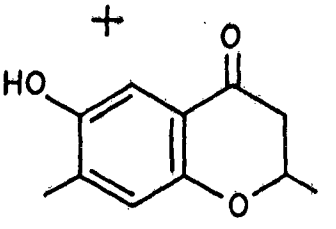
cinnamic acid derivative 73 is somewhat surprising as this method has been used before by other investigators. Neverthless there are reports in literature[89b] wherein under such experimental conditions methyl ether of the corresponding coumarin has also been formed. The desired dihydro derivative 56 (Scheme-14) could be obtained as a crystalline solid m.p. 142° by carrying out the catalytic hydrogenation of 60 over 10% Pd-C at 90° in glacial acetic acid containing traces of perchloric acid[15,90]. The synthetic coumarin 56 was found to have identical spectral data when compared to those recorded on the natural sample.

Gupta et al.[91] reported the preparation of 5-, 6- and 7-hydroxy-3,4-dihydro coumarins by reaction of corresponding phenols with methyl acrylate in the presence of anhydrous aluminium chloride and dry HCl. These authors further observed that hydroquinone failed to react under these conditions. An attempt to synthesise the title compound 56 by the reaction of 2-methyl-p--hydroquinone (59) with methyl crotonate in the presence of anhydrous $AlCl_3$ and dry HCl did not produce any encouraging result and the starting phenol was recovered unchanged(TLC, m.p., m.m.p.). Our successful approach for the synthesis of coumarins with PPA[2] together with previous reports of condensation of phenols with



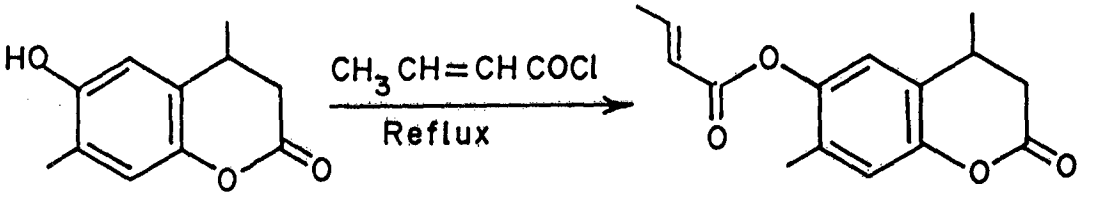
59

62



63

Scheme-16



56

64

Scheme-17

crotonic acid[92] prompted us to investigate the reaction of 2-methyl-p-hydroquinone (59) with crotonic acid in the presence of PPA at 70°. Under these conditions two compounds 62 and 63 having melting points 119° and 184° respectively were obtained as shown in Scheme-16.

Examination of the ^1H nmr spectrum of compound 62 revealed the presence of vinyl methyl at δ 1.98 (3H, dd, J=7 & 1.75Hz), a vinyl proton at δ 6.05 (1H, dq, J=15.5 & 1.75Hz), another vinyl proton multiplet at δ 7.2 (1H) clearly indicating the presence of crotyl ester side chain. The presence of [-O-$\overset{1}{C}$H(CH_3)-CH_2-CO-Ar] grouping could be seen from the secondary methyl doublet at δ 1.50 (3H, J=6.5Hz), a two proton doublet at δ 2.64 (2H) and a multiplet at δ 4.57 (1H) corresponding to the C-2 hydrogen. The two aromatic protons appeared as singlets at δ 6.85 and 7.52 having a 1,4 relationship and an aromatic methyl group singlet at δ 2.17(3H). These chemical shifts were consistent with the structure 6-crotyloxy-2,3-dihydro-2,7-dimethyl benzo-1-pyran-4-one (62). In order to support the assigned structure 62, crotyl ester 64 of coumarin 56 was prepared (Scheme-17). As anticipated, esters 62 and 64 were found to be different.

Compound 63 was analysed for $C_{11}H_{12}O_3$. Its ^1H nmr spectrum (for chemical shifts refer experimental section). lacked the signals due to the crotyl ester side chain, but showed the presence of $-O-\overset{|}{C}H(CH_3)-CH_2-$ CO-Ar grouping, two aromatic protons in 1,4 position and a phenolic proton. These facts are consistent with the structure 6-hydroxy-2,3-dihydro-2,7-dimethyl benzo-1--pyran-4-one (63). Formation of benzo-1-pyran-4-one derivatives by reaction of 2,3- and 2,5-dimethyl phenols with crotonic acid in the presence of PPA has been reported by Merchant and Joshi[92a].

The biosynthesis of 56 is thought to involve 7-hydroxy calamenene (57) as an intermediate. The sequence of events leading finally to the loss of four carbon atoms most likely involves oxidative cleavage process (Scheme-13). It is of interest to note that the compounds D, E and F have been reported to co-occur in the soft coral Lemnalia cervicornis[93].

P A R T - I

CHAPTER - 2

SECTION - 3

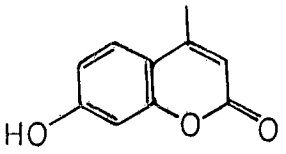
A STRAIGHTFORWARD SYNTHESIS OF 4-METHYL-6,7-METHYLENEDIOXY COUMARIN (4-METHYL AYAPIN) : COMMENTS ON THE STRUCTURE OF $C_{11}H_8O_4$ ISOLATED FROM *ACHILLEA SCHISCHKINII*

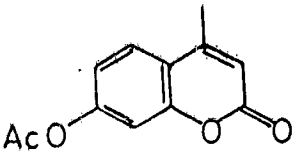
2.3 A STRAIGHTFORWARD SYNTHESIS OF 4-METHYL-6,7-METHYLENEDIOXY COUMARIN (4-METHYL AYAPIN) : COMMENTS ON THE STRUCTURE OF $C_{11}H_8O_4$ ISOLATED FROM ACHILLEA SCHISCHKINII SONS (FAM. COMPOSITAE)

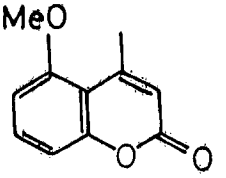
While the number of naturally occurring coumarins having a substituent at C-3 or C-4 position and those having both these positions substituted has increased during the past few years, their percentage with respect to coumarins unsubstituted at C-3 and C-4 positions is still very meagre. Naturally occurring 4-methyl coumarins are listed in Chart-5. In contrast to the requirements for the synthesis of 3,4-unsubstituted coumarins, synthesis of 4-methyl coumarins has been the most straightforward and usually done by Pechmann condensation.

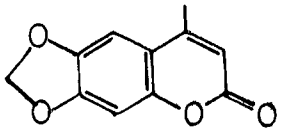
Ulubelen and co-workers[94] reported the isolation and characterisation of a new coumarin, viz. 4-methyl--6,7-methylenedioxy coumarin (65, 4-methyl ayapin) from the ether-petrol extract of the aerial part of Achillea schischkinii sons (Fam compositae) along with some known flavanoids and 6-methoxy-7-hydroxy coumarin (18f, scopoletin) & 6,7-dimethoxy coumarin (19, scoparon). The structure assignment of 65 was mainly based on ^1H nmr data (assignments are shown) and further supported by characteristic uv and mass spectral fragmentation pattern.

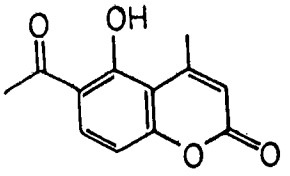
* only representative examples are given

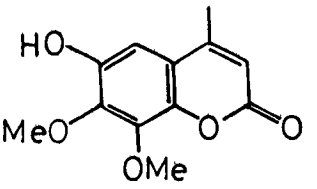




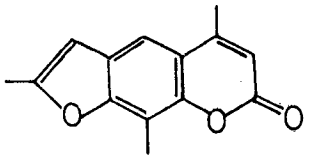


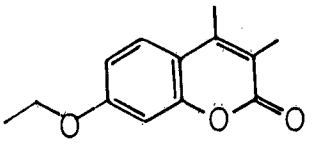


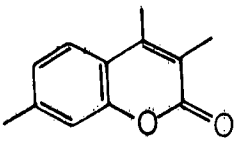




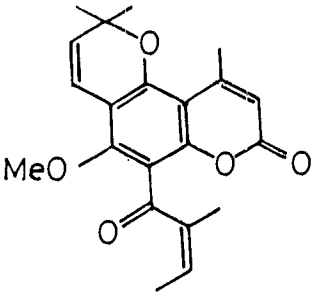
Troupin



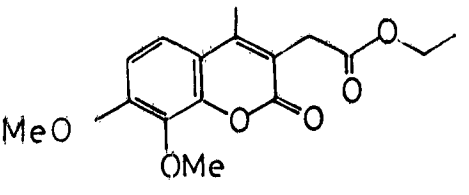




Trigoforin

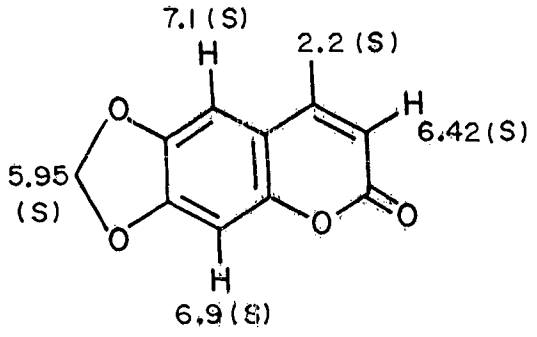


Oblongulide

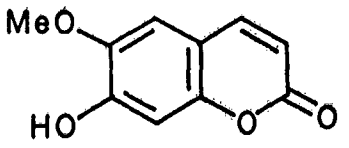


Trigocoumarin

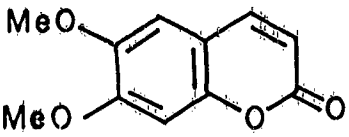
Chart – 5*



65 Natural



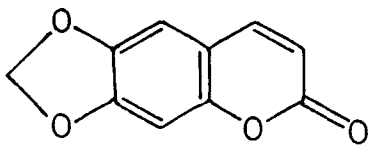
18 f



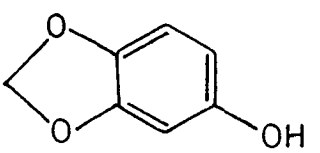
19

Ulubelen and co-workers did not report the confirmation of their assignment by synthesis or refered to any literature report describing its synthesis.

In the course of our coumarin synthesis by transfer of the C-3 unit of p-methoxy cinnamic acid to phenols, we had synthesised ayapin (66) starting from sesamol (67). Since some quantity of sesamol was still available, we thought of preparing 65 by a straightforward synthesis by Pechmann condensation. There was no difficulty in getting the desired synthetic 65, but to our surprise, the spectral data collected on our synthetic 65 and those reported on natural 65 differed considerably thus casting doubts about the correctness of the assigned structure 65 to the coumarin of Achillea schischkinii sons. The results obtained during this study are reported in this section.



66



67

Sesamol(67), and ethyl aceto acetate were reacted in the presence of sulfuric acid (80%) and normal work-up afforded after purification by column chromatography a crystalline solid, m.p. 180°. Its IR spectrum ($CHCl_3$) showed carbonyl absorption at 1695 cm^{-1}. In nujol mull the carbonyl absorption was observed as twin bands at 1720 and 1700 cm^{-1}. Its UV spectrum (MeOH) showed absorption maxima at 234, 289 and 343 nm. The ^1H nmr spectrum ($CDCl_3$) showed a doublet atδ2.35 (3H, J=1.8Hz; C_4- methyl), a quartet atδ 6.15 (1H, J=1.8Hz; C_3- H), a two proton singlet atδ6.05 (-O-CH_2-O-) and two one proton singlets atδ6.80 and 6.95 (Ar-H).

The ^1H nmr and uv spectra measured on our synthetic sample 65 showed differences when compared to the corresponding data on the natural product. Unfortunately no IR was recorded on the natural product and hence IR spectral comparison was not possible. However, it was clear that the synthetic compound m.p. 180°

prepared by us was not identical with the coumarin (4--methyl ayapin) isolated by Ulubelen and co-workers from A. schischkinii*. The non identity than raises the question- what is the correct structure of the natural product? In order to get the answer we decided to look into the available data more carefully and collect additional data on our synthetic sample so that we can at least be sure of the structure of the synthetic product.

When phenols are condensed with ethyl aceto acetate in the presence of sulfuric acid the product is usually the corresponding 4-methyl coumarin. However, there are scanty reports about the formation of chromones as the minor products. We should, therefore, consider structures 68-71 for the synthetic compound m.p. 180°.

Structures 69 and 71 could be eliminated on the basis of ^{1}H nmr data presented above.

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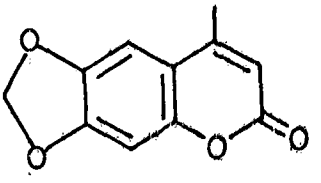
* We thank Prof. A. Ulubelen for confirming the non-identity of the synthetic and natural product and also providing copies of the spectra of natural product and measuring IR, ^{1}H nmr and ^{13}C nmr spectra on our synthetic product.



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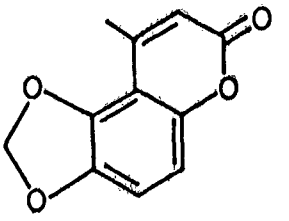

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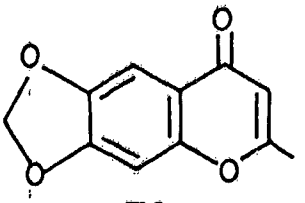

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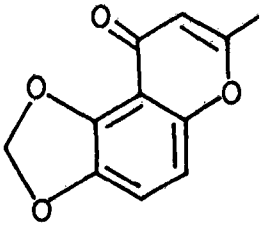


71

In the case of 4-methyl coumarins, H-3 resonates at 6.15 and when the spectrum is well resolved (as in our case) H-3 appears as a quartet and the C-4 methyl as a doublet (J=1.5-2.0 Hz). Similarly in 6,7-disubstituted coumarins, H-5 and H-8 appear as singlets with H-5 downfield as compared to the chemical shift of H-8.

In the case of 2-methyl chromones,[95,96] the IR carbonyl is expected to be in the region of 1635-70 cm^{-1} In addition the chemical shift of C_5-H will be in the region 7.8-8.6 ppm[97a].

In the ^{13}C nmr spectrum the position of the signal due to the carbonyl carbon of benzopyran-2-ones and benzopyran-4-ones may prove to be of some diagnostic value to distinguish them from each other. From the

several examples listed in Table-1, it can be concluded that the carbonyl carbon signal in benzopyran-4-ones is in the region 175-183 ppm[97]; while the corresponding ^{13}C signal of benzopyan-2-ones is found in the region 159-163 ppm[98].

The ^{13}C nmr spectrum of our synthetic sample m.p.180° showed one quartet (19.15), one triplet (102.28), three doublets (98.33, 102.1, and 112.19) and six singlets (113.78, 144.86, 150.50, 150.91, 152.40 and 161.23). The chemical shift of the carbonyl carbon (161.23) shows that it fits well with that of benzopyran-2-ones and hence we conclude that our synthetic sample is 4-methyl-6,7-methylenedioxy coumarin (65, 4-methyl ayapin).

As indicated before, a very large number of 4-methyl coumarins have been synthesised and characterised by the application of Pechmann condensation. Although Ulubelen and co-workers did not refer to any literature report describing the physical constant/ spectral data on 4-methyl-6,7-methylenedioxy coumarin (65, 4-methyl ayapin), we were able to trace a literature report (through chemical abstracts) which is covered under a Japanese patent[99] and describes the preparation of 65 and its 3-nitro derivative. Unfortunately, chemical

Table – I

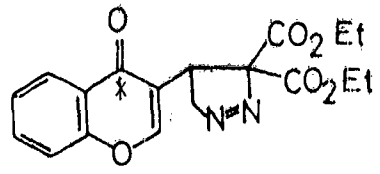
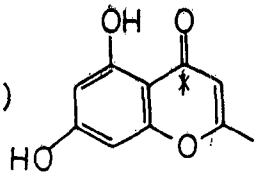
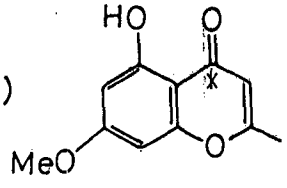
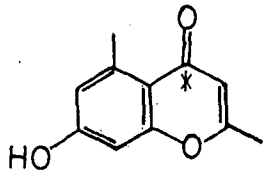
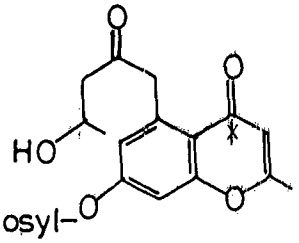
Compound	Chemical shift of the carbonyl carbon* in ^{13}C nmr spectrum	Reference
1) 	175·9	97a
3,3-Diethoxycarbonyl-4-{4-oxo-4H-1-benzopyran-3-yl}-1-Pyrazoline		
2) 	182·62 181·70	97b 97c
2-Methyl-5,7-dihydroxy chromone		
3) 	182·46	97b
2-Methyl-5-hydroxy-7-methoxy chromone		
4) 	178·4	97d
2,5-Dimethyl-7-hydroxy-chromone		
5) 	177·6	97d
β-D-glucosyl-O 2-Methyl-5{2'-oxo-4'-hydroxy pentyl}-7-hydroxy chromone-7-O-β-D-gluco-Pyranoside		

Table – 1 (Cont.)

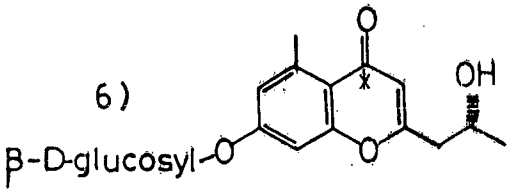
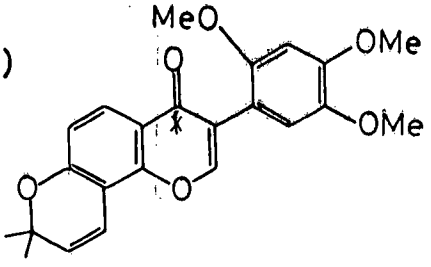
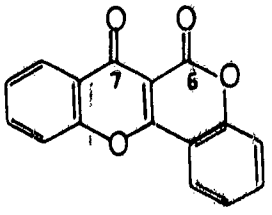
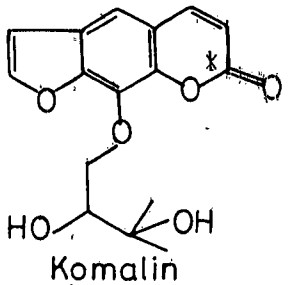
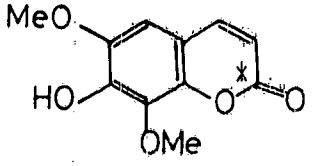
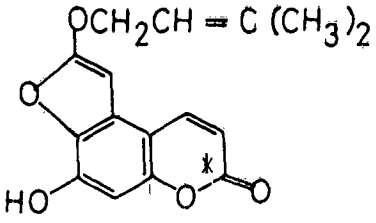
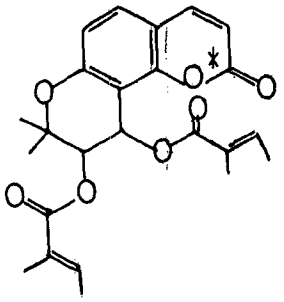
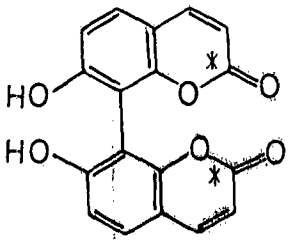
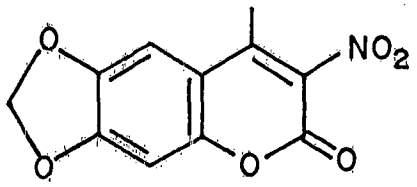
Compound	Chemical shift of the carbonyl carbon* in ^{13}C nmr spectrum	Reference
6)  β-D-glucosyl-O 2{2'-Hydroxypropyl}5-methyl-7-hydroxy chromone 7-O-β-D-glucopyranoside	178·1	97d
7)  Lonchocarpusone	175·8	97e
8)  Frutinone A (chromanocoumarin)	C_6 – 156 C_7 – 173	97f
9)  Komalin	160·10	98a
10)  6, 8 – Dimethoxy – 7 – hydroxycoumarin	160·77	98b

Table – I (Cont.)

	Compound	Chemical shift of the carbonyl carbon* in ^{13}C nmr Spectrum	Reference
11)	 Pyracanthin B	162·7	98c
12)	 3', 4'-Diangeloyl – cis – Khellactone	159·67	98d
13)		160·88	98e

abstracts do not refer to their melting points or spectral data*. In order to support our assignment, it seemed desirable to prepare a nitro derivative of our synthetic coumarin and characterise it by spectral analysis. Following the experimental conditions reported by Parham and Traynelis[100] for nitration of coumarins, we obtained a crystalline yellow nitro derivative 72 of 65. Its ^1H nmr spectrum (D_5-pyridine) showed the presence of olefinic methyl, δ(2.37, s, 3H), methylenedioxy, δ (6.20, s, 2H) and two one ar-H singlets at δ6.99 and 7.29. This clearly indicates that $-NO_2$ group is introduced at C-3 position of the coumarin ring system.



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The unambiguous establishment of structure 65 for our synthetic product necessitates structural modification for the A.schischkinii natural product, $C_{11}H_8O_4$ isolated by Ulubelen and co-workers.

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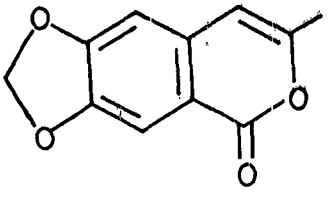
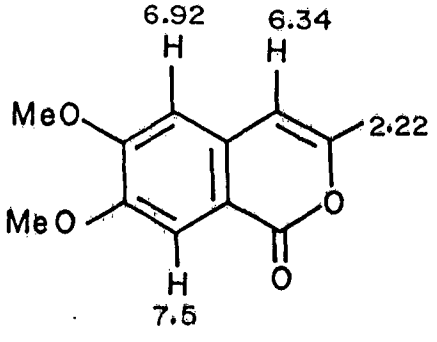
* We failed to get any information from the Japanese workers as the postal address available in chemical abstract is not sufficient and our letter did not reach the concerned investigators.

The ^1H nmr data recorded on the natural product is inconsistent with the alternative coumarin structure 69 or the chromone structure 70. The C-3 hydrogen of 2-methyl chromone derivative has been shown to have chemical shift δ5.94, while the olefinic proton of the natural product is reported to resonate at δ6.42. We are now left with only one theoretical possibility that the natural product may be an isocoumarin having structure 73. It may be noted that the chemical shifts of the structurally related isocoumarin 74 show close agreement with those reported[101] on the natural product. This, however, is only a tentative conclusion and requires further evidence to support this assignment. Efforts are being made in this direction.



73



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EXPERIMENTAL

General procedure for the preparation of polyphosphoric acid (PPA) : A solution of polyphosphoric acid (PPA) was prepared by stirring a mixture of P_2O_5 (10.0 g, 70 mmole) and 85% orthophosphoric acid (7 mL) in an oil bath at 110° using an overhead stirrer under anhydrous conditions until a free flowing clear solution was obtained. This was then cooled to 70°.

1,3,5-Trimethoxybenzene (11, Phloroglucinol trimethyl ether) : Anhydrous K_2CO_3 (11.0 g, 80 mmole) was added to a solution of commercial grade 1,3,5-trihydroxy-benzene (phloroglucinol, 3.0 g, 24 mmole) in dry acetone (22.5 mL). To this slurry was added freshly distilled dimethyl sulfate (7.8 mL, 80 mmole) while stirring with an overhead stirrer over a period of 1 hour. The reaction mixture was then refluxed for 24 hours with simultaneous stirring. This was then cooled and filtered. The residual K_2CO_3 was washed with acetone and filtered. Evaporation of the solvent from the combined filtrates gave a brown solid. Chromatography on silica gel using petroleum-ether : benzene (80:20) gave a white solid. Recrystallisation from petroleum-ether gave

white needles of 11(3.0 g, 75%), m.p.52°. (lit.[13] m.p. 54-5°).

IR (νmax, nujol) : 1655, 1630, 1620, 1475, 1390, 1355, 1335, 1210, 1200, 1160, 1075, 950, 820, 785. cm^{-1}.

2,6-Dimethoxy-p-benzoquinone (12) : Oxidation of 1,3,5--trimethoxybenzene (11) using

(A) Nitric acid : 30% HNO_3 (26 mL) was added to a solution of 1,3,5-trimethoxy benzene (11, 2.6 g, 16 mmole) in ethanol (26 mL). The reaction mixture was heated on a steam bath for 2.5 hours, cooled and extracted with $CHCl_3$ till aqueous layer was colourless. The $CHCl_3$ extracts were washed successively with water, 5% $NaHCO_3$ and sat. brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a solid which was recrystallised from petroleum-ether to give the starting compound, 1,3.5-trimethoxy benzene (11, 1.8 g, 70%) (identified by TLC, m.p., m.m.p., and IR). The coloured aqueous phase (washings) was, therefore, extracted with $CHCl_3$ till colourless. The $CHCl_3$ extracts were dried over anhydrous $MgSO_4$. Evaporation of the solvent gave 2,6-dimethoxy-p-benzoquinone (12), an yellow solid recrystallised from EtOAc as yellow needles (0.15 g, 6%), m.p. 250-52°.[lit.[3] m.p 255°(d)].

(B) Chromium trioxide in 80% aqueous acetic acid : 1,3,5-Trimethoxy benzene (11, 1.8 g, 11 mmole) recov-

ered in the above method (A) was dissolved in 80% aqueous acetic acid (10 mL). To this solution was added in slow portions a solution of chromium trioxide (3.6 g, 36 mmole) in 80% aqueous acetic acid (5 mL). The reaction became violent and an yellow solid separated out. The reaction mixture was allowed to cool to room temperature. The solid obtained was filtered under suction, washed with cold water and dried in an oven at 120°. Recrystallisation from EtOAc gave yellow needles of 12 (1.2 g, 67%), m.p. 252° identical (TLC, m.p., m.m.p., and IR) with (12) obtained in method (A).

IR (νmax, nujol) : 1710, 1655, 1650, 1615, 1520,1470, 1460, 1385, 1335, 1260, 1110, 1040, 1010, 865, 835, 810,760, 705. cm^{-1}.

2,6-Dimethoxy-p-hydroquinone (10) : Reduction of 2,6-dimethoxy-p-benzoquinone (12) using

(A) Hydrogen over Pd-C in dioxane : 2,6-Dimethoxy-p-benzoquinone(12, 0.3 g, 1.8 mmole) was dissolved in dioxane (35 mL) and hydrogenated over 5% Pd-C (0.15 g) for 4 hours. After filtration through a bed of charcoal, the catalyst-charcoal bed was washed with dioxane. The combined filtrates were evaporated to give a solid. Purification by repeated recrystallisation from benzene-EtOAc gave two compounds melting points 171° and 257°.

Except for IR* of compound m.p. 171° no other data was recorded on these two compounds.

IR (νmax,KBr) : 3410, 1690, 1645, 1450, 1370,1345,1325, 1285, 1250, 1235, 1185, 1100, 1020, 985, 975, 915, 860,835,810, 730. cm^{-1}

(B) Hydrogen over Pd-C in chloroform : 2,6-Dimethoxy-p-benzoquinone (12, 0.15 g, 0.9 mmole) was dissolved in $CHCl_3$ (20 mL) and hydrogenated over 5% Pd-C (0.07 g) for 4 hours. The solid obtained after usual work up was recrystallised from benzene-EtOAc to give silvery white flakes of 2,6-dimethoxy-p-hydroquinone* (10, 0.14 g, 92%), m.p. 169°. (lit.[3] m.p. 166-67°.,lit.[10] m.p. 159-60°).

IR (νmax, KBr) (Fig.1) : 3320, 1640, 1610, 1525, 1485, 1465,1445, 1370, 1220, 1185, 1140, 1110, 985, 910, 810, 795, 725. cm^{-1}

5,7-Dimethoxy-6-hydroxy coumarin (2a, fraxinol) : 2,6-Dimethoxy-p-hydroquinone (10, 0.09 g, 0.5 mmole) followed by p-methoxy cinnamic acid (0.09 g, 0.5 mmole) were added to PPA at 70° and the solution stirred at

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* The IR of 2,6-dimethoxy-p-hydroquinone (10) obtained in method (B) was superimposable on the IR of 2,6-dimethoxy-p-hydroquinone supplied by Prof. H. Otsuka. However, the IR of the compound m.p. 171° obtained in method (A) differed considerably.

70^{o} for 4 hours. The reaction mixture was then cooled to room temperature and poured over crushed ice (50 g). This was kept overnight and then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a solid which was chromatographed on silica gel using benzene-EtOAc (96:4) as an eluent to give 5,7-dimethoxy-6-hydroxy coumarin (2a fraxinol). Recrystallisation from benzene - petroleum-ether gave whitish needles (0.06 g, 51%), m.p. 171^{o}. (lit.[8] m.p. $171-73^{o}$).

UV (λmax, MeOH) (Fig.2) : 209 nm (log ϵ= 4.80), 231nm (log ϵ= 4.47), 310nm (log ϵ= 4.34).

IR (νmax, KBr) (Fig.3) : 3390, 1710, 1625, 1565, 1510, 1390, 1325, 1280,1185, 1140, 1115, 1080, 1015, 960, 930, 885, 820, 810. cm^{-1}.

^{1}H nmr (300 MHz, $CDCl_3$, δ) (Fig.4) : 3.95 (3H, s, $-OCH_3$) ; 4.03 (3H, s, $-OCH_3$) ; 5.46 (1H, s,-OH ; D_2O exchangeable) ; 6.27 (1H, d, J=10 Hz, C_3-H) ; 6.63 (1H, s, C_8-H) ; 7.95 (1H, d, J=10 Hz, C_4-H).

2-Methoxy-1,4-hydroquinone (24) : To a solution of vanillin (26, 1.0 g, 6.5 mmole) in 2N NaOH (7 mL) was added 3% H_2O_2 (10 mL) slowly with stirring over a period of 30 minutes and the reaction mixture was magnetically

stirred for 17 hours. Acidified with dil. HCl and extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a viscous liquid. Chromatography on silica gel using benzene:EtOAc (95:5) as an eluent gave a liquid which solidified on cooling. Recrystallisation from chloroform - petroleum-ether gave 24 as white needles. (0.5 g, 54%), m.p. 82°. (lit.[52] m.p. 84°).

IR (νmax, nujol) (Fig.5) : 3360, 1630, 1520, 1500, 1460, 1390, 1305,1260, 1230, 1200, 1155, 1120, 1040, 955, 830, 800, 730. cm^{-1}.

6-Hydroxy-7-methoxy coumarin (18a, Isoscopoletin) : 2-Methoxy-1,4-hydroquinone (24, 0.2 g, 1.4 mmole) followed by p-methoxy cinnamic acid (0.225 g, 1.4 mmole) were added to PPA at 70° and the solution stirred at 70° for 4 hours. The reaction mixture was then cooled to room temperature and poured over crushed ice (50 g). This was kept overnight and then extacted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a viscous liquid which was chomatographed on silica gel and eluted with benzene:EtOAc (98:2) to give a solid. Recrystallisation from chloroform - petroleum-ether afforded white needles, m.p. 205°. Further elution with benzene:EtOAc

(95:5) gave another solid recrystallised from chloroform petroleum-ether as white needles of 18a (0.5 g, 18%), m.p. 180° (lit.[20] mp. 185°).

IR (νmax, KBr) (Fig.6) : 3400, 1700, 1640, 1560, 1520, 1470, 1440,1390, 1300, 1270, 1250, 1200, 1140, 1100, 1050, 1000, 940, 860,820. cm^{-1}.

^1H nmr (300MHz, $CDCl_3$, δ) (Fig.7) : 3.98 (3H, s, $-OCH_3$); 5.58 (1H, s, -OH); 6.29 (1H, d, J=10 Hz, C_3-H); 6.83 (1H, s, C_8-H); 6.97 (1H, s, C_5-H); 7.60 (1H, d, J=10 Hz, C_4-H).

1,2,3-Trimethoxy benzene (33, Pyrogallol trimethyl ether) : Anhydrous K_2CO_3 (11.0 g, 80 mmole) was added to a solution of commercial grade 1,2,3-trihydroxy benzene (pyrogallol, 3.0 g, 24 mmole) in dry acetone (22.5 mL). To this slurry was added freshly distilled dimethyl sulfate (7.8 mL, 80 mmole) while stirring with an overhead stirrer over a period of 1 hour. The reaction mixture was then refluxed for 24 hours with simultaneous stirring. This was cooled and filtered. The residual K_2CO_3 was washed with acetone and filtered. Evaporation of the solvent from the combined filtrates gave a brown solid. Chromatography on silica gel using petroleum-ether : benzene (80:20) gave a white solid. Recrystallisation from petroleum-ether gave white need-

les of 33 (3.0 g, 75%), m.p. 48°. (lit.[63] m.p. 47°).

2-Hydroxy-3-methoxy phenol (30) : To a well stirred solution of $LiAlH_4$ (0.48 g, 12 mmole) in dry benzene 15 mL) was added a solution of 1,2,3-trimethoxybenzene (1.0 g, 6 mmole) in dry benzene (10 mL) over a period of 30 minutes. The reaction mixture was then refluxed for 6 hours and kept overnight at room tempeature. 2N HCl was added slowly with stirring till a clear solution resulted. This was extracted with diethyl ether. The ether extracts were washed with sat. brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a viscous liquid which was chromatographed on silica gel using petroleum-ether : EtOAc (98:2) as an eluent to give an oil which was distilled under reduced pressure to give 30 as a colourless oil (0.6 g, 72%) (lit.[63] mp.38-41°).

IR (ν max, neat) (Fig.8) : 3380, 1630, 1525, 1490, 1455, 1370, 1305,1260, 1225, 1180, 1090, 940, 830, 770, 720, 710.cm $^{-1}$.

7-Methoxy-8-hydroxy coumarin (28a) : 2-Hydroxy-3-methoxy phenol (30, 0.12 g, 0.9 mmole) followed by p-methoxy cinnamic acid (0.16 g, 0.9 mmole) were added to PPA at 70° and the solution was stirred at 70° for 4 hours. The reaction mixture was then cooled to room temperature

and poured over crushed ice (50 g). This was kept overnight and then extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a viscous liquid. Chromatography on silica gel using petroleum-ether : EtOAc (96:4) as an eluent gave a white solid. Recrystallisation from benzene furnished white needles of 28a (0.095 g, 57%), m.p. 173° (lit.[59] m.p. 173-74°).

IR (ν max, nujol) (Fig.9) : 3400, 1710, 1625, 1510, 1470, 1385, 1295,1210, 1160, 1135, 1085, 1050, 970, 830, 760, 705. cm^{-1}.

^1H nmr (300MHz, $CDCl_3$,δ) (Fig.10) : 3.98 (3H, s, $-OCH_3$); 5.76 (1H, s,-OH); 6.27 (1H, d, J=9.5 Hz, C_3-H); 6.87 (1H, d,J=9.5 Hz, C_6-H); 7.02 (1H, d, J=9.5 Hz, C_5-H); 7.64 (1H, d, J=9.5 Hz, C_4-H)

Mass m/e (rel.int.) (Fig.11) : [M^+] 192 (100), 177(11), 164 (11), 149 (42), 136 (6), 121 (19), 105 (12), 93(11), 79(4), 65 (42), 51 (14), 44 (1), 39 (22).

Reaction of 1,2,3-trimethoxybenzene (33) with acetyl chloride in the presence of $AlCl_3$:To an ice cold solution of 1,2,3-trimethoxybenzene (33, 1.0 g, 6 mmole) in dry CH_2Cl_2 (10 mL) was added anhydrous $AlCl_3$ (1.29 g,

9.7 mmole) and acetyl chloride (0.7 mL, 9 mmole). The reaction mixture was refluxed for 48 hours. After cooling to room temperature this was carefully acidified with dil. HCl and extracted with CH_2Cl_2. The organic phase was then extracted with 10%NaOH and the alkaline extracts were acidified with conc. HCl. The acidified aqueous phase was extracted with CH_2Cl_2. The CH_2Cl_2 extracts were washed with sat. brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a viscous liquid which was chromatographed on silica gel to give two fractions. The first fraction eluted out with petroleum-ether : EtOAc (90:10) on evaporation of the solvent gave a solid which on recrystallisation from petroleum-ether melted at 113° (0.8 g). The second fraction eluted out with petroleum-ether : EtOAc (88:12) also gave a solid which on recrystallisation from benzene melted at 132° (0.08g).

Reaction of above solid m.p.113° with m-chloroperbenzoic acid (attempted Baeyer-Villiger oxidation) followed by alkaline hydrolysis : A solution of m-chloroperbenzoic acid (1.0 g, 5.8 mmole) in $CHCl_3$ (9 mL) was added to a solution of the above solid m.p 113° (1.14 g.) in CH_2Cl_2 (2 mL). The reaction mixture was magnetically stirred overnight. 10% $Na_2S_2O_4$ (3 mL) was then added to this and stirred for another 45 minutes.

The organic phase was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with sat. brine and dried. The residue obtained on evaporation of the solvent was dissolved in MeOH (3 mL). The solution formed was cooled in ice and to this was added 5% KOH (8 mL) slowly with stirring. The reaction mixture was magnetically stirred overnight, acidified with conc. HCl while cooling in ice and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine and dried. Evaporation of the solvent gave a solid which was chromatographed on silica gel using benzene:EtOAc (95:5) to give a solid. Recrystallisation from $CHCl_3$ - petoleum-ether gave whitish needles (0.25 g), m.p. 131°.

^1H nmr (90MHz, $CDCl_3$, δ) (Fig.12) : 2.57 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$); 3.96 (3H, s, Ar-$OCH_3$); 5.52 (1H, s, Ar-OH); 6.50 (1H, d, J=10 Hz); 7.32 (1H, d, J=10 Hz); 12.48 (1H, s, Ar-OH, chelated)

Formation of 7-methoxy-8-hydroxy coumarin (28a) : Reaction of above compound m.p.131° with p-methoxy cinnamic acid in the presence of PPA : The above compound m.p.131°(0.1 g, 0.55 mmole) followed by p-methoxy cinnamic acid (0.1 g, 0.56 mmole) were added to PPA at 70° and the solution was stirred at 70° for 4 hours.

The reaction mixture was then cooled to room temperature and poured over crushed ice (50 g). This was then kept overnight and extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a viscous liqid. Chromatography on silica gel using benzene:EtOAc (90:10) as an eluent gave a solid which was recrystallised from $CHCl_3$ - petroleum-ether to give white needles of 28a (0.025 g, 23%), m.p. 173° (lit.[59] m.p.173-74°).

For IR, ^1H nmr and Mass refer fig. nos. 9, 10 and 11 respectively.

2,3,4-Trihydroxy acetophenone (Gallacetophenone) : Freshly fused and powdered $ZnCl_2$ (2.8 g, 21 mmole) was dissolved by heating at 135-40° in glacial acetic acid (3.8 mL). To this was added acetic anhydride (4.0 g, 37 mmole) and freshly distilled 1,2,3-trihydroxybenzene (5.0 g, 40 mmole) in one lot. The reaction mixture was heated at 140-45°. for 45 minutes with frequent and vigorous shaking. Unused acetic acid and Ac_2O was removed by distillation under reduced pressure. The red-brown cake was broken up by water (30 mL) with stirring and cooling in ice water. The solid was filtered over suction, washed with cold water and dried at 120° in an oven. Recrystallisation from ethyl alcohol gave

whitish needles (3.7 g, 55%), m.p. 169° (lit.[66] m.p.171-72°).

IR ($\sqrt{}$max, nujol) : 3430, 3340, 1610, 1455, 1375, 1315, 1290,1240, 1200, 1165, 1035, 975, 900, 805. cm^{-1}.

Methylation of gallacetophenone : Anhydrous K_2CO_3 (3.0 g, 22 mmole) was added to a solution of gallacetophenone (2.0 g, 12 mmole) in dry acetone (30 mL). To this slurry was added freshly distilled dimethyl sulfate (2.26 mL, 23 mmole) while stirring with an overhead stirrer over a period of 1 hour. The reaction mixture was then refluxed for 24 hours with simultaneous stirring. This was cooled to room temperature and filtered. The residual K_2CO_3 was washed with acetone and filtered. Evaporation of the solvent from the combined filtrates gave a brown liquid. This was washed with 10% $NaHCO_3$ and extracted with diethyl ether. The ether extracts were washed with sat. brine and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave a liquid which was chromatographed on silica gel using petroleum-ether : EtOAc (90:10) to give a solid. Recrystallisation from petroleum-ether gave whitish needles (0.4 g), m.p. 113°.

4-Hydroxy-5-methyl-8-isopropyl coumarin (53) : A mixture of thymol (52, 3.75 g, 25 mmole), malonic acid (2.5 g, 24 mmole), anhydrous zinc chloride (9.8 g, 70 mmole) and phosphorus oxychloride (6.5 mL, 70 mmole) was stirred with an overhead stirrer at 60-65° for 35 hours under anhydrous conditions. The reaction mixture was cooled to room temperature, decomposed with ice and water and allowed to stand. The resulting crude solid was filtered under suction, dissolved in 10% Na_2CO_3 and acidified with dil. HCl. This was then extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a sticky solid which was chromatographed on silica gel using benzene:EtOAc (75:25) to give the coumarin 53. Recrystallisation from ethanol gave whitish needles of 53 (2.3 g, 42%), m.p. 223° (lit.[74] m.p. 223°).

4-Acetoxy-5-methyl-8-isopropyl coumarin (54) : To a solution of 4-hydroxy-5-methyl-8-isopropyl-coumarin (53, 0.1 g, 45 mmole) in dry pyridine (2 mL) was added Ac_2O (3 mL, 32 mmole). The reaction mixture was refluxed in an oil bath for 5 hours, cooled to room temperature and kept overnight. This was then extracted with diethyl ether. The ether extracts were washed successively with 2N HCl, 2N Na_2CO_3 and water and dried. Evaporation of the solvent gave a viscous liquid which was

chromatographed on silica gel to give two fractions. The first fraction eluted out with benzene:EtOAc (97:3) was a solid recrystallised from petroleum-ether to give whitish needles, m.p.165°. No data was recorded on this compound due to very small quantity obtained and as such could not be identified. The second fraction eluted out with benzene:EtOAc (50:50) was also a solid. Recrystallisation from $CHCl_3$ – petroleum-ether gave whitish needles of 54 (0.03 g, 25%), m.p. 198°.

^1H nmr (300MHz, $CDCl_3$, δ) (Fig.13) : 1.27 (6H, d, J=7 Hz, CH_3-$\underset{|}{C}H$-CH_3); 2.43 (3H, d, J=1 Hz, -O-CO-CH_3); 2.76 (3H, d, J=1 Hz, -CH_3); 3.63 (1H, quintet, J=7 Hz, -$\underset{|}{C}H$-); 6.34 (1H, q, J=1 Hz); 7.15 (1H, d, J=8 Hz); 7.50 (1H, d, J=8 Hz)

The HCl washings of the ether extracts on standing overnight gave a red coloured solid which was filtered under suction and dried at 120° in an oven. Chromatography on silica gel using petroleum-ether gave a pale yellow solid which was recrystallised from petroleum-ether to give whitish needles (0.025 g),m.p. 125°. Its ^1H nmr indicated it to be a mixture of at least two compounds. It showed TLC pattern identical to the least polar compound m.p. 165° obtained from the ether extracts.

4-Hydroxy-5-methyl coumarin (41a) : To chlorobenzene (24 mL) was added 4-hydroxy-5-methyl-8-isopropyl coumarin (53, 0.8 g, 3.6 mmole). To this was added finely powdered anhydrous $AlCl_3$ (2.4 g, 18 mmole). The reaction mixture was then heated on an oil bath at 95° for 1 hour. Cooled and poured over crushed ice (50 g) containing dil. HCl. This was extracted with EtOAc. The organic phase was then extracted with sat. $NaHCO_3$ (3x10 mL). Acidification of the $NaHCO_3$ layer with dil. HCl gave a solid which was filtered under suction, dried in an oven at 120° and recrystallised from ethanol to give white needles of 41a, m.p. 235°. (lit.[80] m.p. 232-33°).

UV (λ max, MeOH) (Fig.14) : 206 nm ($\log \epsilon = 4.65$), 289 nm ($\log \epsilon = 4.32$)

Acetylation of 4-Hydroxy-5-methyl coumarin (41a) : To solution of 4-hydroxy-5-methyl coumarin (41a, 0.1 g, .55 mmole) in dry pyridine (2 mL) was added Ac_2O (3 mL, 32 mmole) and the reaction mixture was refluxed at 140° while monitoring the progress of the reaction over TLC after every 30 minutes. The reaction was stopped after 2 hours, cooled to room temperature and kept overnight. This was then extracted with diethyl ether. The ether extracts were washed successively with dil. HCl, sat. Na_2CO_3 and water and dried. Evaporation of

the solvent gave a viscous liquid which was chromatographed on silica gel using benzene:EtOAc (99:1) to give a solid. Recrystallisation from $CHCl_3$ - petroleum-ether gave white needles, m.p. 208°.

The HCl washings of the ether extracts on standing overnight gave a red coloured solid which was filtered under suction and dried in an oven at 120°. Recrystallisation from ethanol gave an yellow crystalline solid which on further recrystallistion from $CHCl_3$-petroleum-ether gave white needles 55, m.p. 225°.

^1H nmr (90 MHz, $CDCl_3$,δ) : (Fig.32) : 2.48 (3H, s, -O-CO-CH_3); 2.80 (3H, s, -CH_3); 6.37 (1H, s, C_3-H);7.14-7.66 (3H, m, ar-H).

2-Methyl-p-benzoquinone (58) : Conc. H_2SO_4 (8.0 g) was added slowly to water (30 mL) with stirring and cooling. O-toluidine (1.0 g, 9.2 mmole) was added to this diluted H_2SO_4 with magnetic stirring and cooling in ice. To this solution was added powdered $K_2Cr_2O_7$ (1.0 g, 3.4 mmole) in portions over a period of 1 hour; taking care that the temperature does not exceed 10°. The reaction mixture was kept overnight. Further $K_2Cr_2O_7$ (1.6 g, 5.5 mmole) was added under the same previous conditions. The reaction mixture was allowed to stand for 5 hours and extracted with diethyl ether. The ether extracts were washed with sat. brine and dried. Evaporation of the solvent gave a greenish solid recrystallised from petroleum-ether to give yellow needles of 58 (0.75 g, 66%), m.p. 67° (lit.[87] m.p.67°).

2-Methyl-p-hydroquinone (59) : 2-Methyl-p-benzoquinone (58, 0.61 g, 5 mmole) was dissolved in EtOAc (30 mL) and hydrogenated over 5% Pd-C (0.65 g) at room temperature until absorption of H_2 ceased (4 hours). After filtration through a bed of charcoal the catalyst charcoal bed was washed with EtOAc (2x10 mL). Evaporation of the solvent from the combined organic fractions gave a solid recrystallised from benzene to give white needles of 59 (0.6 g,96%), m.p. 126°.

Formation of 6-hydroxy-2,3-dihydro-2,7-dimethyl chromone (63) and 6-crotyloxy-2,3-dihydro-2,7-dimethyl chromone (62) : Reaction of 2-methyl-p-hydroquinone (59) with crotonic acid in the presence of PPA : 2-Methyl-p-hydroquinone (59, 0.42 g,3.4 mmole) followed by crotonic acid (0.29 g, 3.4 mmole) was added to PPA at 70° and the solution was stirred at 70° for 4 hours. The reaction mixture was cooled to room temperature and poured over crushed ice (100 g). This was kept overnight. The solid obtained was suction filtered and found to be a mixture of two compounds (TLC). The filtrate was extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a liquid from which the more polar component, 6-hydroxy-2,3-dihydro-2,7-dimethyl chromone (63) was precipitated out by the addition of petroleum-ether. Recrystallisation from benzene - petroleum-ether gave white needles of (63, 0.062 g, 10%), m.p. 184°.

IR (ν max, KBr) (Fig.15) : 3390, 1685, 1625, 1470, 1435, 1400, 1365, 1260,1210, 1110, 1065, 1045, 1030, 940, 875, 815, 755. cm^{-1}.

^1H nmr (80 MHz, $CDCl_3$, δ) (Fig.16) : 1.48 (3H, d, J=7 Hz, $-\overset{|}{C}H-CH_3$);2.24 (3H, s, $Ar-CH_3$); 2.60 (2H, d, J=9 Hz, $O=\overset{|}{C}-CH_2-$); 4.54 (1H, m, $-\overset{|}{C}H-CH_3$); 5.60 (1H, s, -OH);

6.76 (1H, s, Ar-H); 7.28 (1H, s, Ar-H);

Elemental analysis : Found: C, 68.48; H, 6.34; $C_{11}H_{12}O_3$
Requires: C,68.75; H,6.25

Concentration of the petroleum-ether soluble portion (motherliquor) gave a viscous liquid. Chromatography on silica gel using benzene:EtOAc (99:1) gave a solid. Recrystallisation from petroleum-ether gave white needles of(62, 0.035 g, 4%), m.p. 119°.

IR (νmax, KBr) (Fig.17) : 1745, 1695, 1665, 1635, 1495, 1455, 1395, 1315, 1260, 1205, 1165, 1105, 1045, 980, 895, 865, 820 cm^{-1}.

^1H nmr (300 MHz, $CDCl_3$,δ) (Fig.18) : 1.50 (3H, d, J=6.5 Hz,-CH-CH_3); 1.98 (3H, dd, J=7 & 1.75 Hz, -CH=CH-CH_3); 2.17 (3H, s, Ar-CH_3); 2.64 (2H, d,J=7 Hz, -CO-CH_2-); 4.57 (1H, m, -CH-CH_3); 6.05 (1H, dq,J= 15.5 & 1.75 Hz, -CH=CH-CH_3); 6.85 (1H, s, Ar-H); 7.20 (1H, m, -CH=CH-CH_3); 7.52 (1H, s, Ar-H)

6-Hydroxy-4,7-dimethyl coumarin (60) : To a thoroughly cooled and well stirred mixture of 2-methyl-p-hydroquinone (59, 0.5 g, 4 mmole) and ethyl aceto acetate (0.53 g, 4 mmole) was added 80% H_2SO_4 (2.5 mL) over a period of 1 hour. The temperature was not

allowed to rise above 5° during the addition. The reaction mixture was further stirred for 24 hours at room temperature. It was poured over ice water (30 mL) and the solid formed was filtered over suction, dried at 120° and recrystallised from ethanol using activated charcoal to give shining white needles of 60 (0.55 g, 72%), m.p. 210° (lit.[88] m.p. 208°).

IR (νmax, KBr) (Fig.19) : 3177, 1662, 1567, 1418, 1271, 1207, 1167, 1015,939, 894, 860. cm^{-1}.

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.20) : 2.34 (3H, s, $-CH_3$); 2.37 (3H, s, $-CH_3$); 4.90 (1H, s); 6.24 (1H, br s, -OH); 6.95 (1H, s, Ar-H); 7.12 (1H, s, Ar-H)

Mass m/e (rel. int.) (Fig.21) : M^+ 190 (80), 162 (70), 161 (100).

Formation of 6-methoxy-4,7-dimethyl coumarin (61) : An attempted lactone ring opening reaction of the coumarin 60 : 6-Hydroxy-4,7-dimethyl coumarin (60, 0.19 g, 1 mmole) was dissolved in 1% NaOH (2.5 mL) by heating on a steam bath. Further 2N NaOH was added and heating continued till a clear solution resulted. This was cooled to room temperature and to this solution was added freshly distilled $(CH_3)_2SO_4$ (1 mL,10 mmole) while magnetically stirring over a period of 2 hours. Care

was taken not to allow the temperature to rise above 50° during the addition. The reaction mixture was then stirred for 1 hour with the temperature not rising above 50°. The resulting solution was cooled to room temperature and acidified with dil.HCl with cooling in ice. This was then extracted with CH_2Cl_2. The CH_2Cl_2 extracts were successively washed with $NaHCO_3$ and water and dried. Evaporation of the solvent gave a solid which was chromatographed on silica gel to give two fractions. The first fraction eluted out with benzene:EtOAc (95:5) was a solid. Recrystallisation from $CHCl_3$ - petroleum-ether gave white needles of 61 (0.060 g, 29%), m.p.160°. Further elution with benzene-EtOAc (92:8) also gave a solid. Recrystallisation from ethanol gave white needles (0.125 g), m.p.210° and identical with the starting coumarin 60 (TLC, m.p., m.m.p.).

IR (νmax, nujol) (Fig.22) : 1740, 1570, 1510, 1470, 1420, 1390, 1280,1250, 1230, 1200, 1180, 1070, 1040, 930, 900, 860. cm^{-1}.

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.23) :2.32 (3H, s, $-CH_3$); 2.44 (3H, s, $-CH_3$); 3.92 (3H, s, $-OCH_3$); 6.20 (1H,s); 6.84 (1H, s); 7.08 (1H, s).

6-Hydroxy-3,4-dihydro-4,7-dimethyl coumarin (56) : A solution of 6-hydroxy-4,7-dimethyl coumarin (60, 0.304 g, 1.6 mmole) in glacial AcOH (30 mL) containing 70% $HClO_4$ (10 drops) was hydrogenated at 90° using 5% Pd-C (0.1 g) until absorption of H_2 had ceased (3 hours). After filtration through a bed of charcoal the catalyst charcoal bed was washed with AcOH. Practically all AcOH was distilled out and the residue was neutralised with solid $NaHCO_3$. This was then extracted with diethyl ether. The ether extracts were washed with sat. brine and dried. Evaporation of the solvent gave a solid which was chromatographed on silica gel using benzene:EtOAc (95:5) to give 56. Recrystallisation from EtOAc - petroleum-ether gave whitish needles of 56 (0.19 g, 62%), m.p. 142-3°.

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.24) : 1.23 (3H, d, J= 7Hz, -CH-CH_3); 2.20 (3H,s, Ar-CH_3); 2.50 (1H, dd, J=16 & 8 Hz, -CO-CH_2-); 2.78 (1H, dd, J= 16 & 6 Hz, -CO-CH_2-); 3.06 (1H, m, -CH-CH_3); 4.95 (1H, s,-OH); 6.62 (1H, s, Ar-H); 6.80 (1H, s, Ar-H)

Preparation of Crotonyl chloride from Crotonic acid : Crotonic acid (4.3 g, 50 mmole) was heated in an oil bath at 100°. To this was added dropwise redistilled thionyl chloride (5 mL,67 mmole) over a period of 45

minutes with intermittent shaking. The reaction mixture was refluxed for 30 minutes, cooled and distilled. Crotonyl chloride distilled out at 120-30°.

6-Crotyloxy-3,4-dihydro-4,7-dimethyl coumarin (64) : A mixture of 6-hydroxy-3,4-dihydro-4,7-dimethylcoumarin (56, 0.1 g, 0.52 mmole) and crotonyl chloride (0.06 g, 0.57 mmole) was heated under reflux at 100° on an oil bath for 2 hours. The reaction mixture was then cooled to room temperature and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with 2N NaOH and water and dried. Evaporation of the solvent gave a viscous liquid which was chromatographed on silica gel using benzene and subsequently distilled under reduced pressure to give an oil of Crotyl ester 64, (0.08 g, 64%).

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig 25) : 1.32 (3H, d, J=6.5 Hz, $-\overset{1}{C}H-CH_3$); 2.04 (3H, d, J=6.5 Hz, $-CH=CH-CH_3$); 2.18 (3H, s, $Ar-CH_3$); 2.70 (2H, m, $-CO-CH_2-$); 3.12 (1H, m, $-\overset{1}{C}H-CH_3$) 6.13 (1H, s, $-CH=CH-CH_3$) 6.32 (1H, s, Ar-H) 7.1 (1H, s, Ar-H) 7.4 (1H, m, $-CH=CH-CH_3$).

4-Methyl-6,7-methylenedioxy coumarin (65, 4-Methyl ayapin) : To a thoroughly cooled and well stirred mixture of sesamol (67 0.28 g, 2 mmole) and ethyl aceto acetate (0.26 g, 2 mmole) was added 80% H_2SO_4 (1.2 mL)

over a period of 1 hour. The temperature was not allowed to rise above 5° during the addition. The reaction mixture was further stirred for 24 hours at room temperature. This was then poured over ice water and the solid obtained was suction filtered. The solid was dried at 120° in an oven and chromatographed on silica gel using benzene:EtOAc(95:5)as an eluent to give a solid. Recrystallisation from $CHCl_3$ - petroleum-ether gave whitish needles of 65, (0.27 g, 66%), m.p. 180°.

UV (λmax, MeOH) (Fig.26) : 343 nm (log ε = 3.9), 289 nm (log ε = 3.4), 234 nm (log ε = 4.0).

IR (νmax, $CHCl_3$) (Fig.27) : 1695, 1580, 1500, 1440, 1390, 1340, 1260,1210, 1140, 1120, 1040, 940, 920, 880, 800. cm^{-1}

IR (νmax, nujol) (Fig.28) : 1720, 1700, 1635, 1600, 1515, 1450, 1430,1410, 1360, 1280, 1230, 1160, 1130,1055, 955, 940, 900, 850, 820,760. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.29) : 2.35 (3H, d, J=1.8 Hz, $-CH_3$); 6.05(2H, s, $-O-CH_2-O-$);6.15 (1H, q, J=1.8Hz, C_3-H);6.80 (1H, s, C_8-H);6.95 (1H, s, C_5-H).

^{13}C nmr ($CDCl_3$,δ)(Fig.30) : 19.15 (q), 98.33 (d), 102.10 (d), 102.28 (t),112.19 (d), 113.78 (s), 144.86 (s), 150.50 (s), 150.91 (s),152.40 (s), 161.23 (s).

3-Nitro-4-methyl-6,7-methylenedioxy coumarin (72, 3-Nitro (4-methyl avapin) : A nitrating solution was prepared by mixing conc. HNO_3 (3.15 mL), powdered urea (0.05 g), and glacial acetic acid (5 mL). To a solution of 4-methyl-6,7-methylenedioxy coumarin (65, 0.1 g, 0.5 mmole) in Ac_2O (5 mL) was added slowly while stirring the above nitrating mixture (2 mL) at room temperature. The progress of the reaction was monitored by TLC after every 10 minutes. After 1 hour the reaction mixture was poured into water (10 mL) and extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a solid which was chromatographed over silica gel and eluted with benzene to give an yellow solid. Recrystallisation from acetone - petroleum-ether gave yellow needles of 72 (0.045 g, 37%) m.p.247° (d).

^1H nmr (300 MHz, C_5D_5N,δ)(Fig.31) : 2.37 (3H, s, $-CH_3$) 6.20 (2H, s, $-O-CH_2-O-$); 6.99 (1H, s, C_8- H); 7.29 (1H, s, C_5-H)

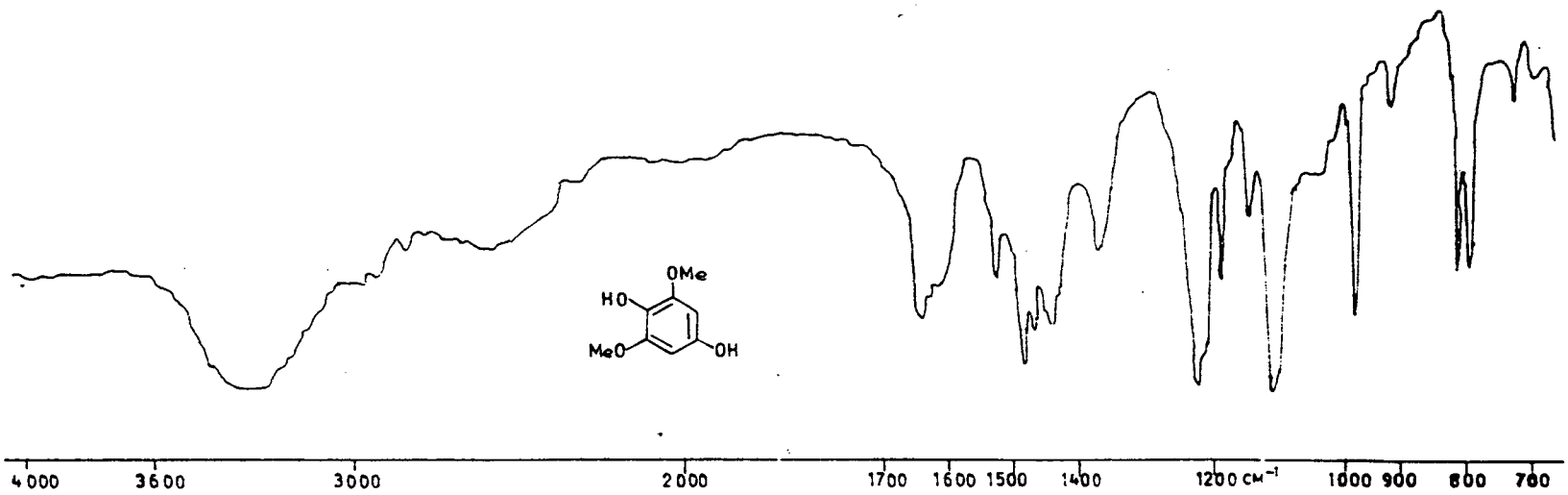

Fig. 1 IR SPECTRUM OF (10)

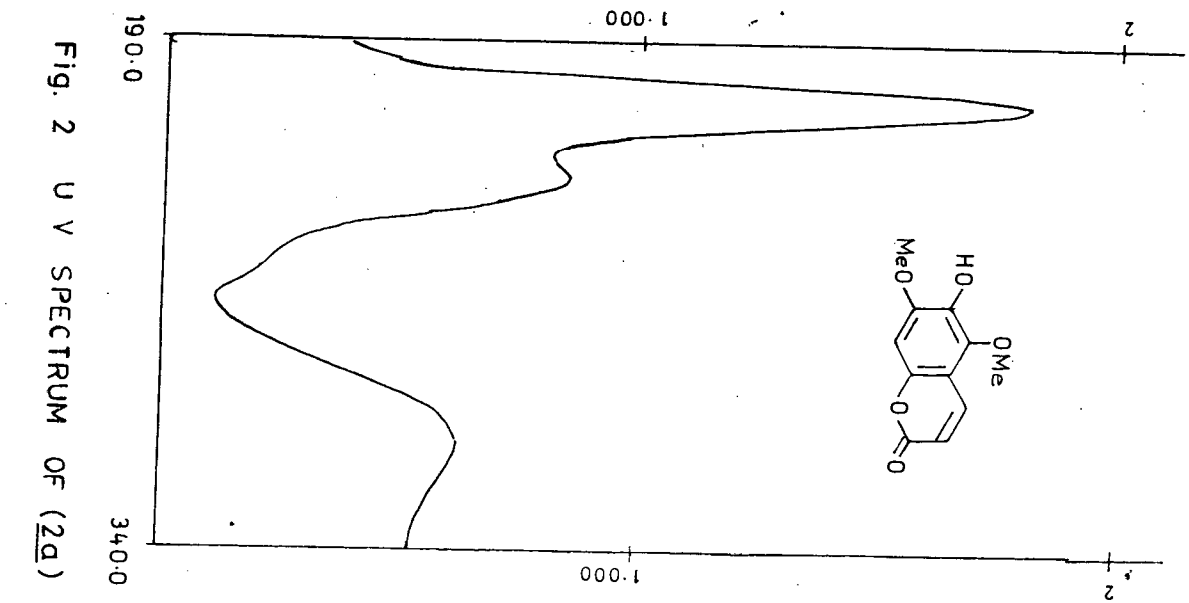

Fig. 2 U V SPECTRUM OF (2a)

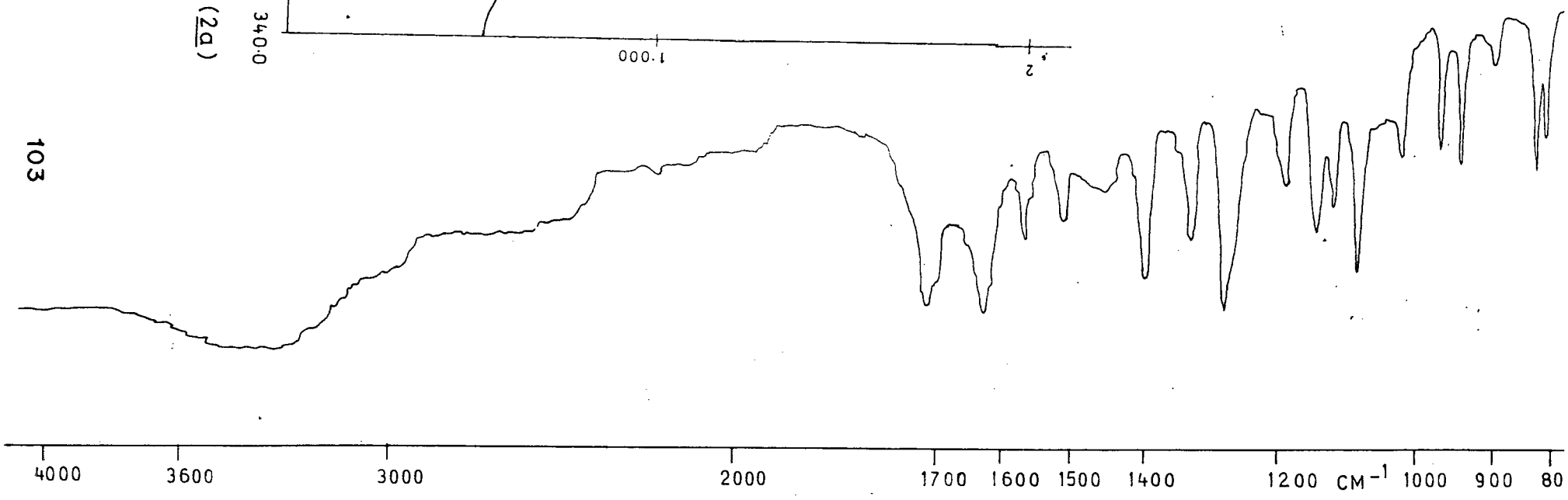

Fig. 3 IR SPECTRUM OF (2a)

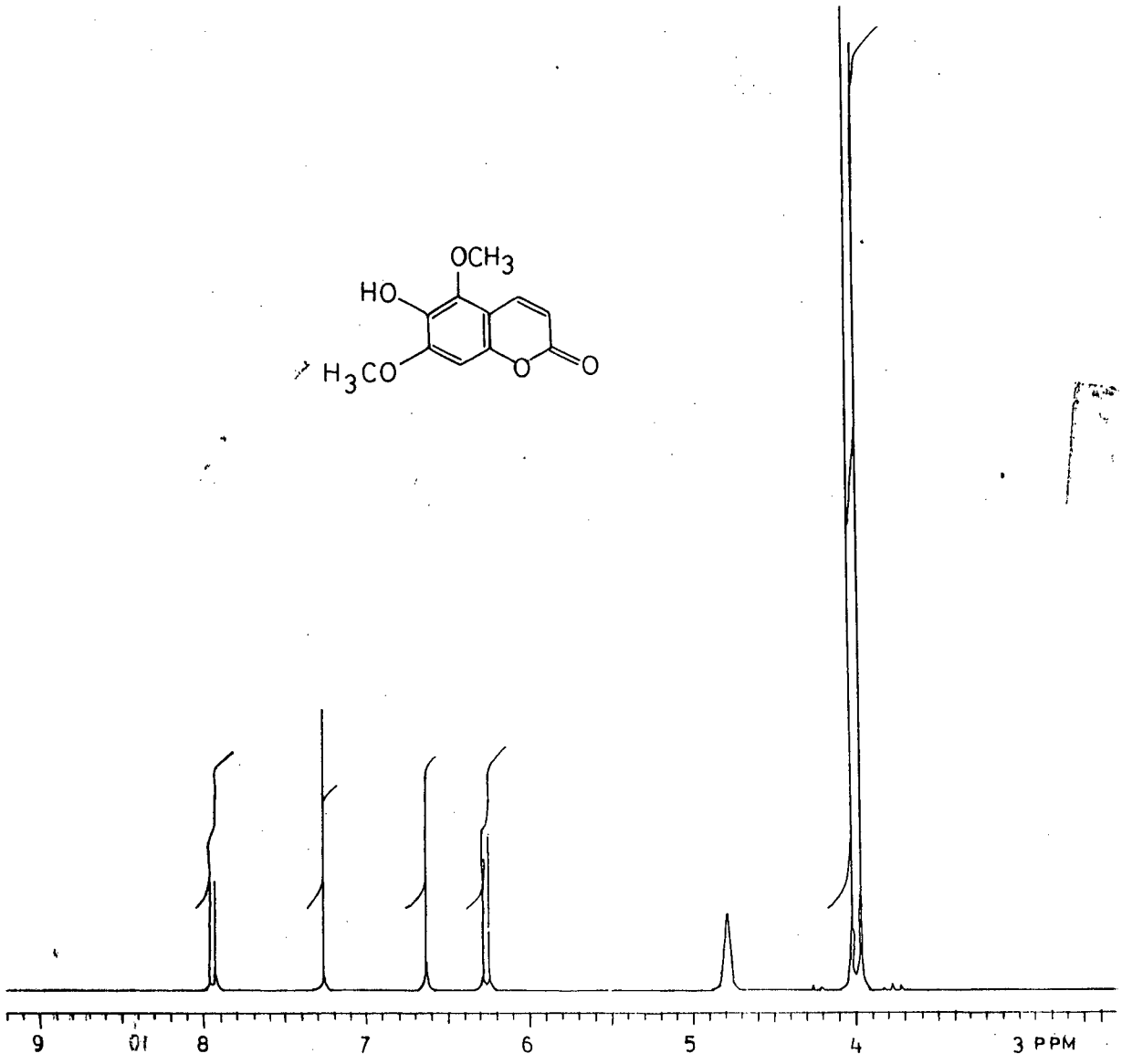

Fig. 4 ^{1}HNMR (D_2O) SPECTRUM OF (2a)

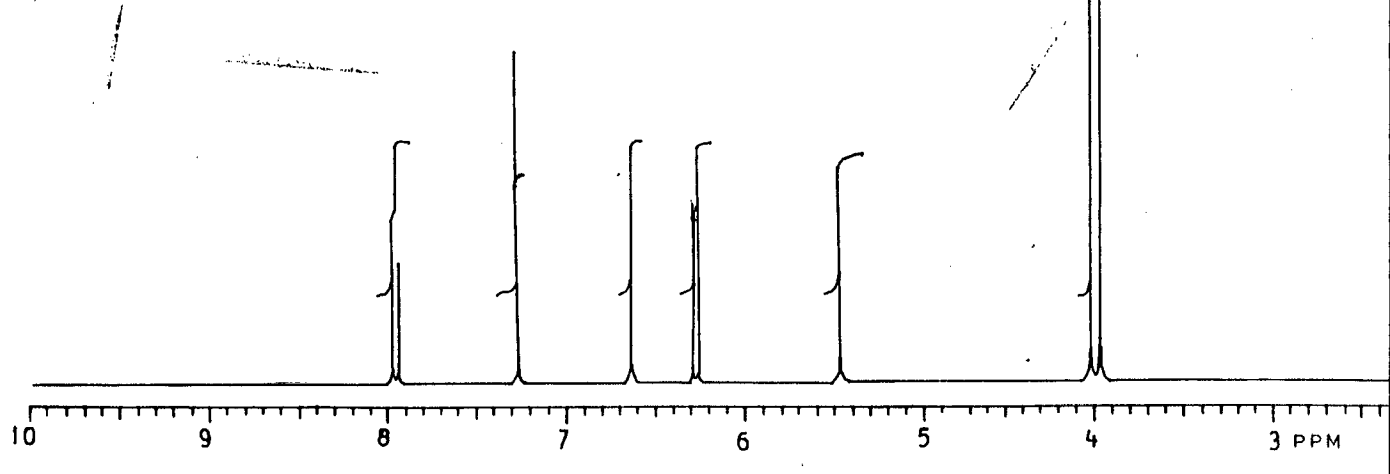

Fig. 4 ^{1}HNMR SPECTRUM OF (2a)

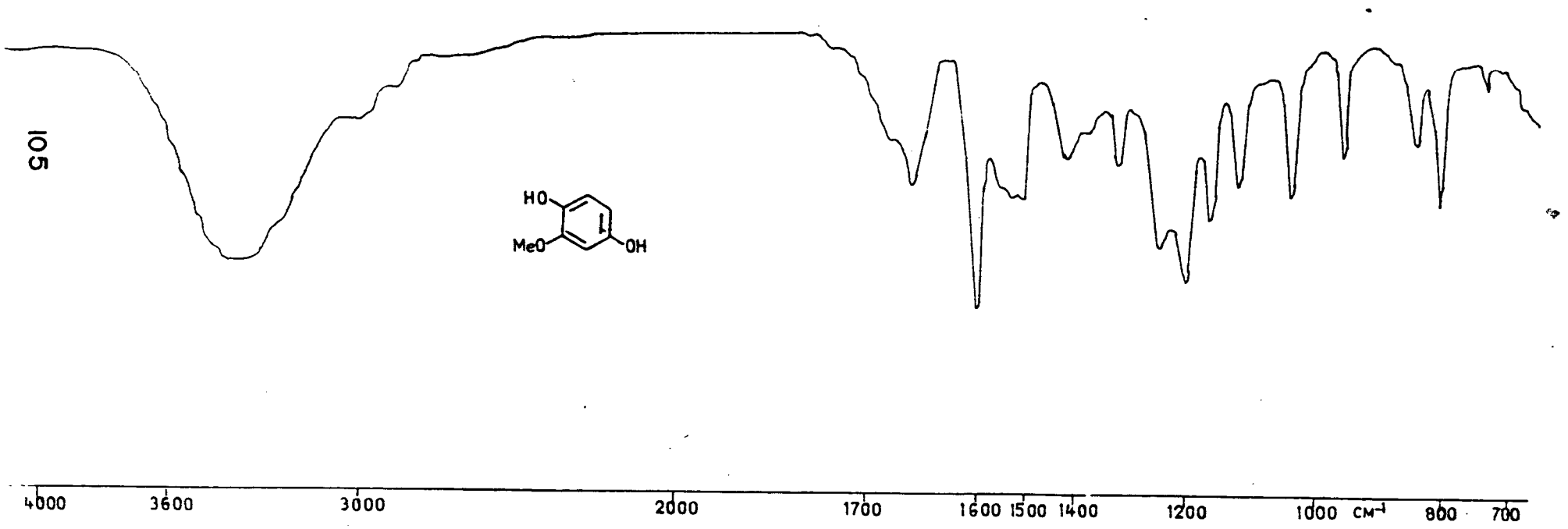

Fig. 5 IR SPECTRUM OF (24)

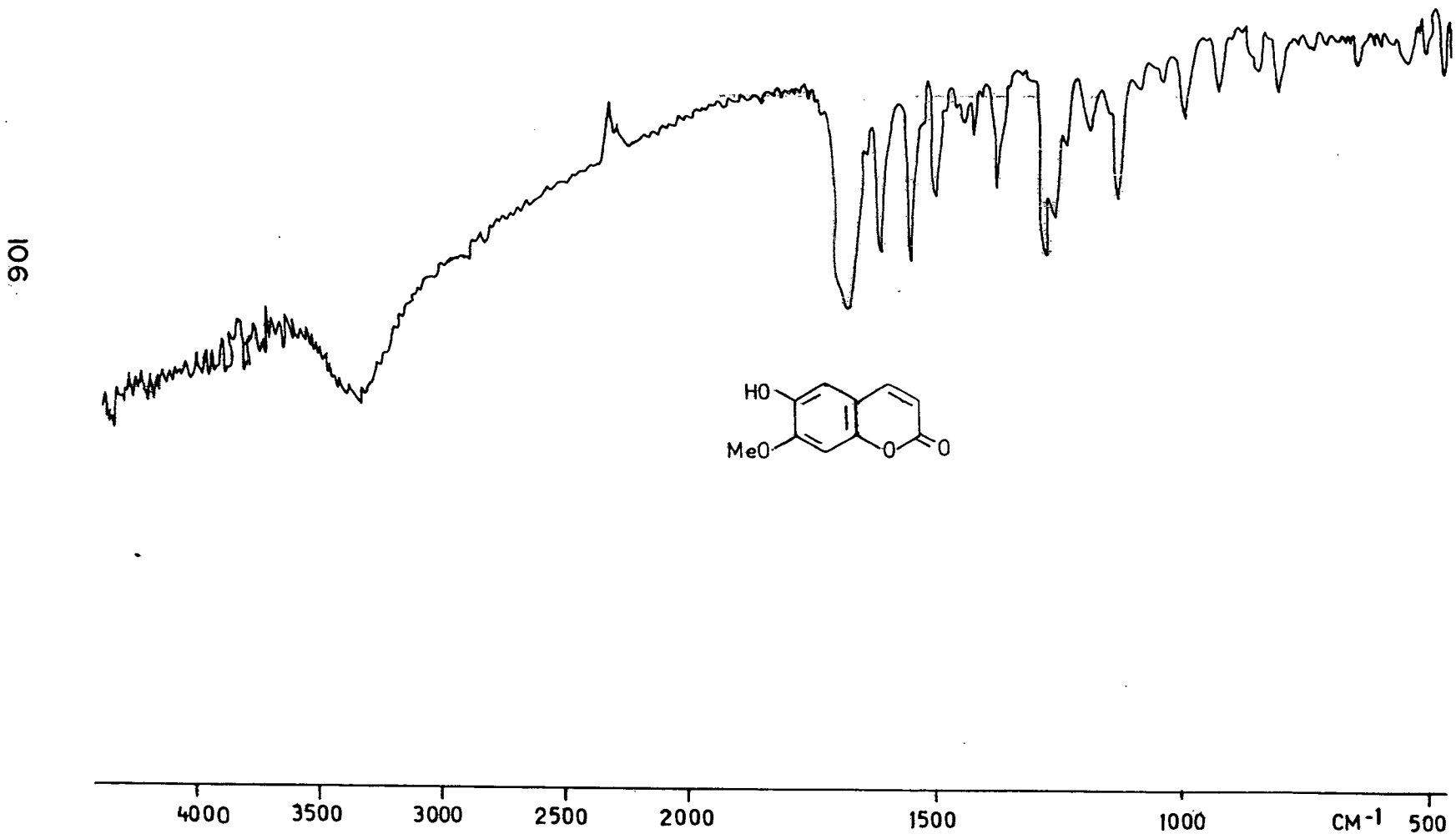

Fig. 6 IR SPECTRUM OF (18a)

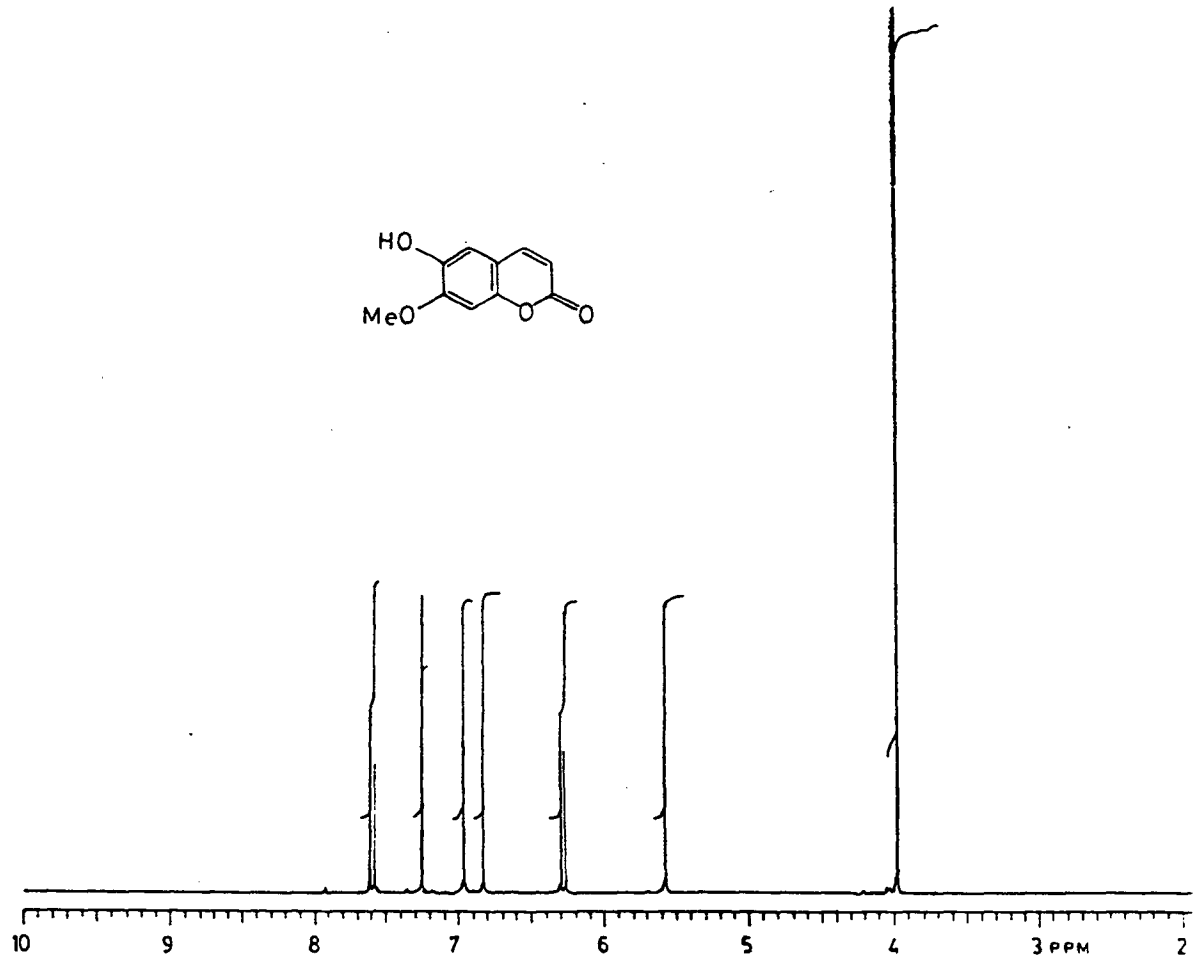

Fig. 7 ^{1}HNMR SPECTRUM OF (18a)

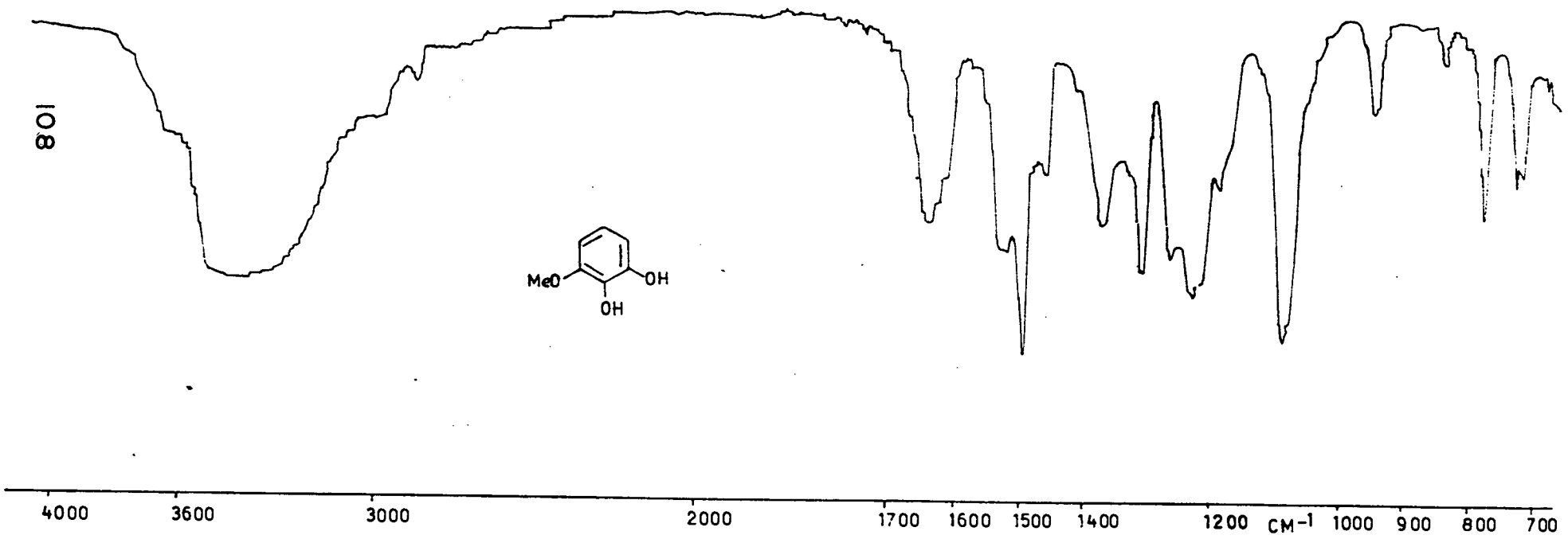

Fig. 8 IR SPECTRUM OF (30)

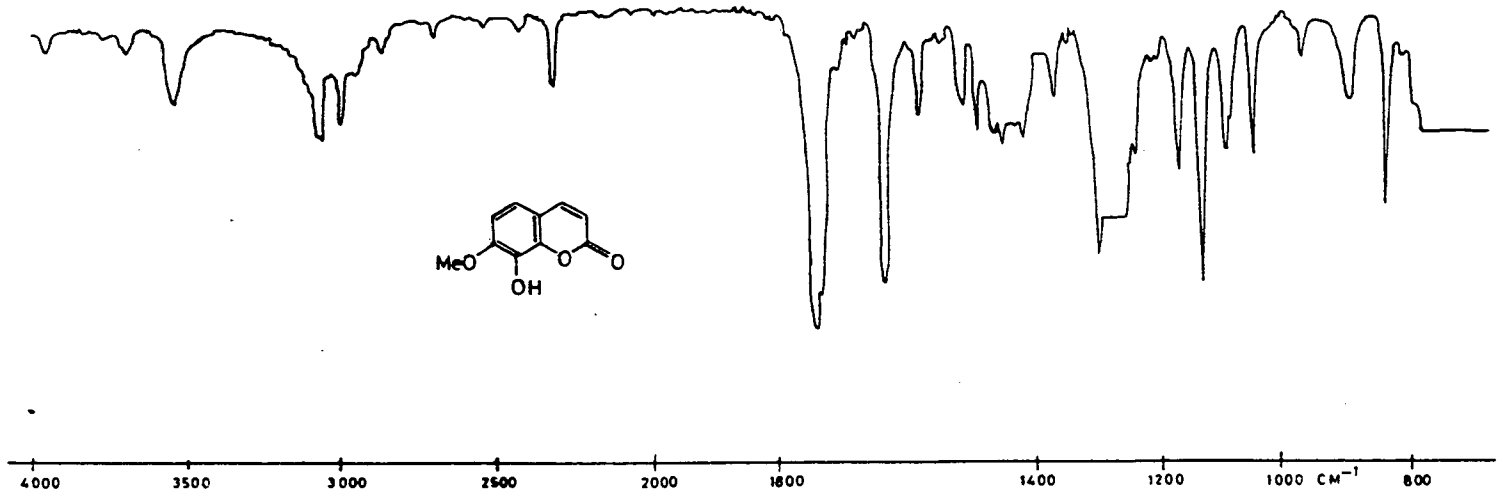

Fig. 9 IR SPECTRUM OF (28a)

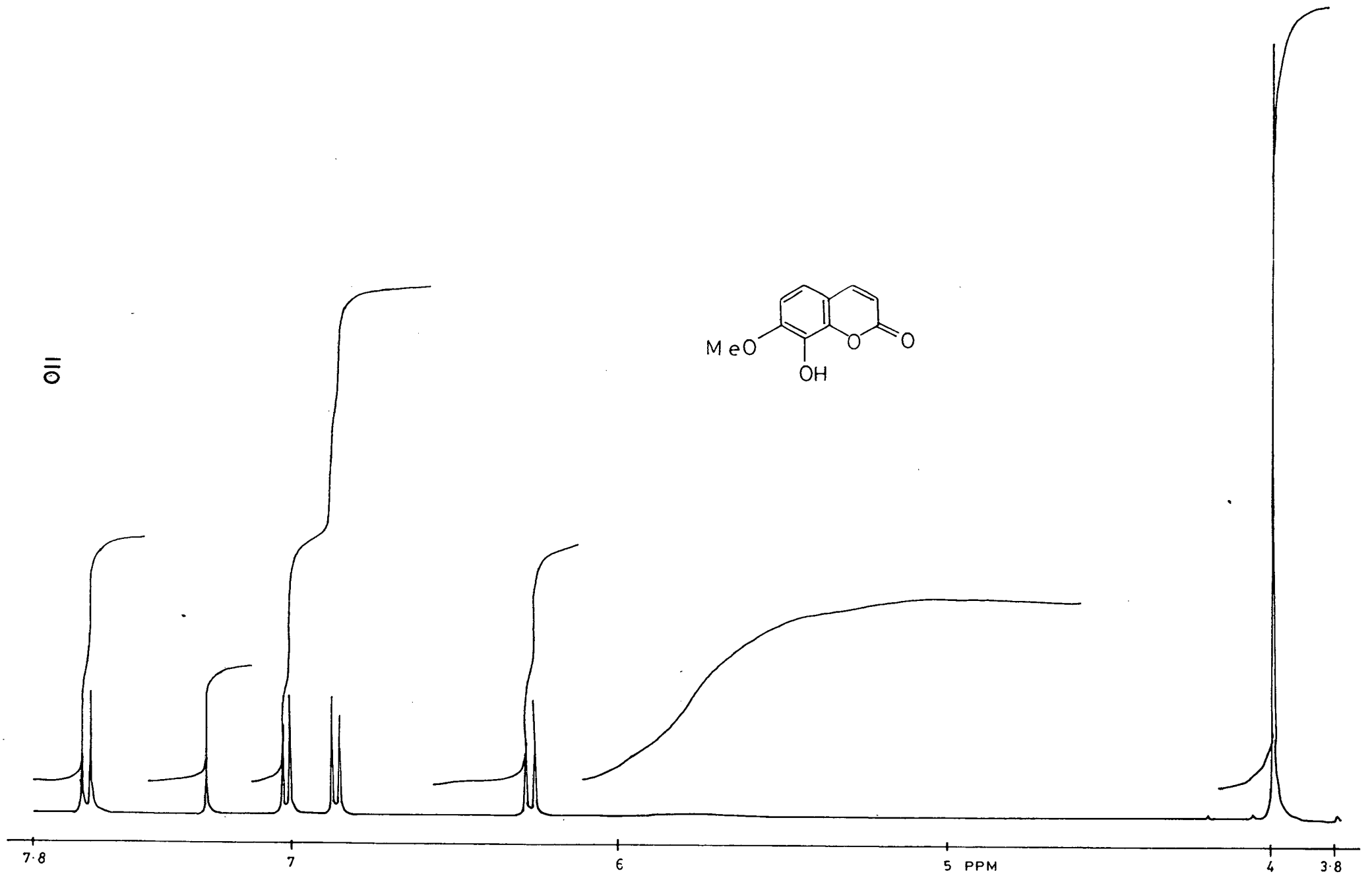

Fig. 10 ^{1}H NMR SPECTRUM OF (28a)

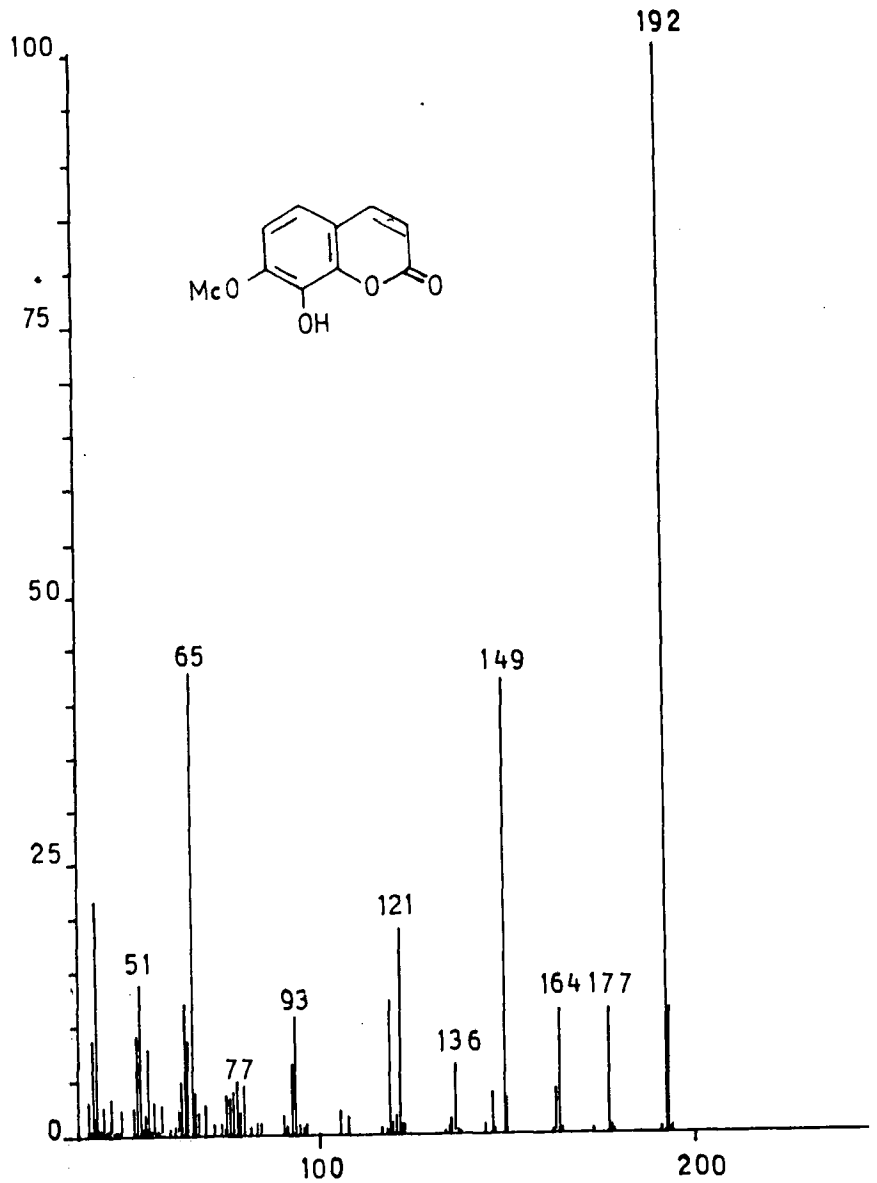

Fig. 11 MASS SPECTRUM OF (28a)

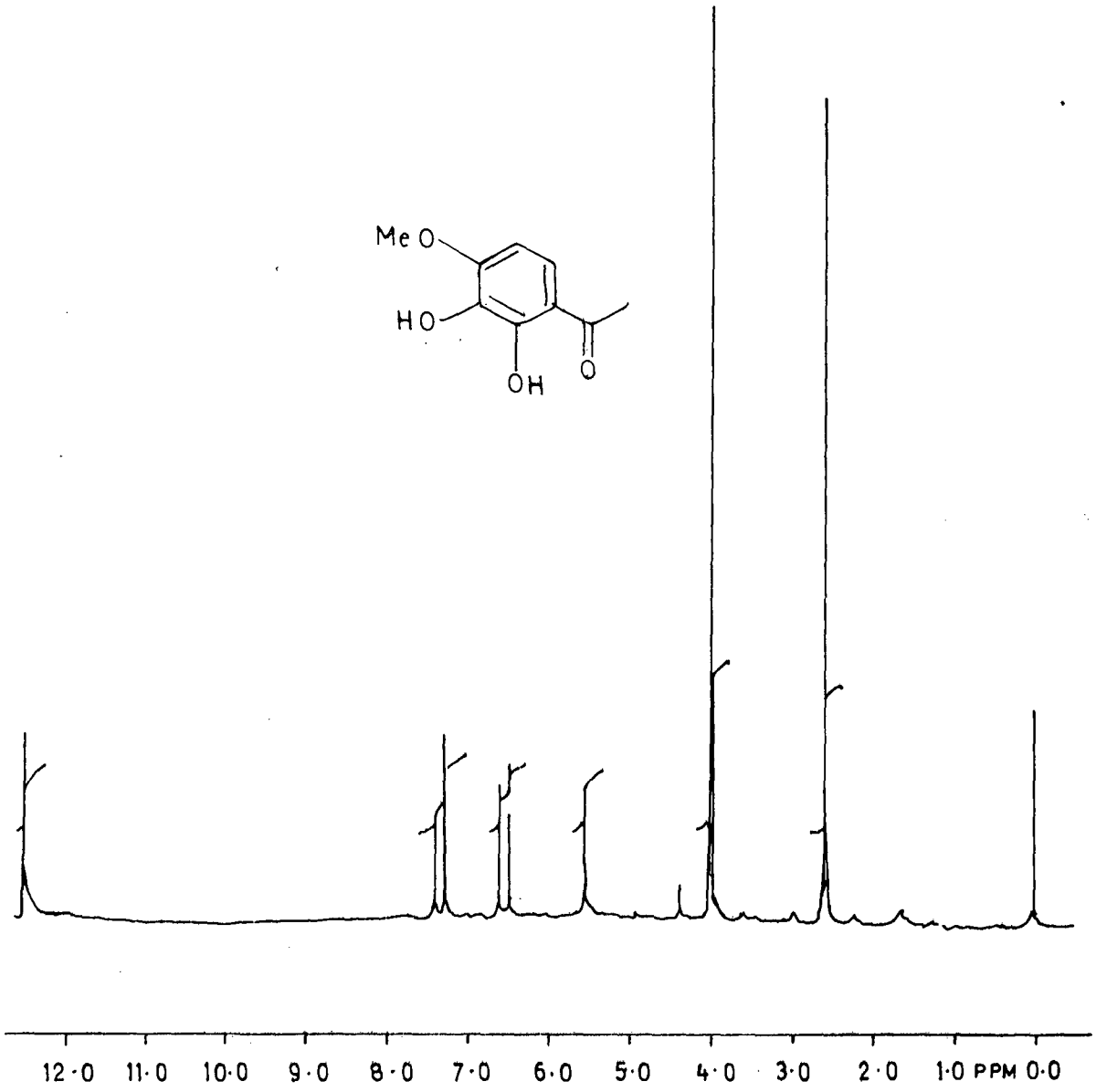

Fig. 12 ^{1}H NMR SPECTRUM OF (37)

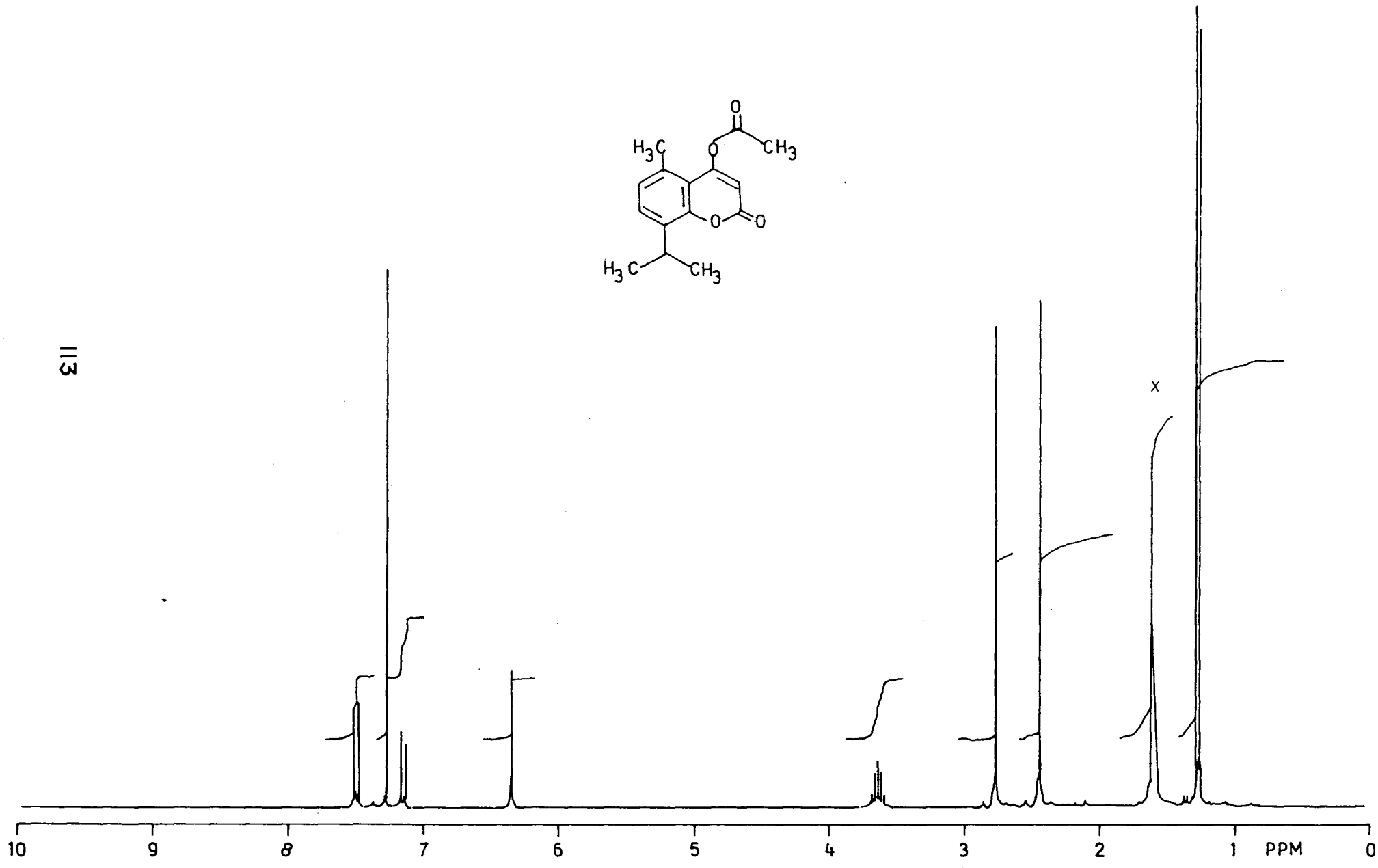

Fig. 13 ^{1}H NMR SPECTRUM OF (54)

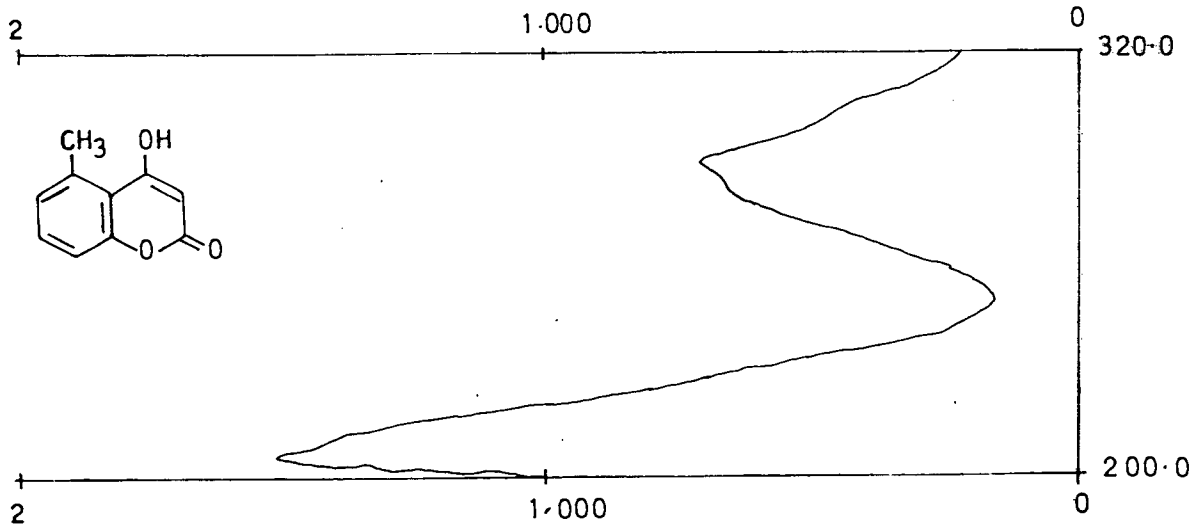

Fig. 14 UV SPECTRUM OF (41a)

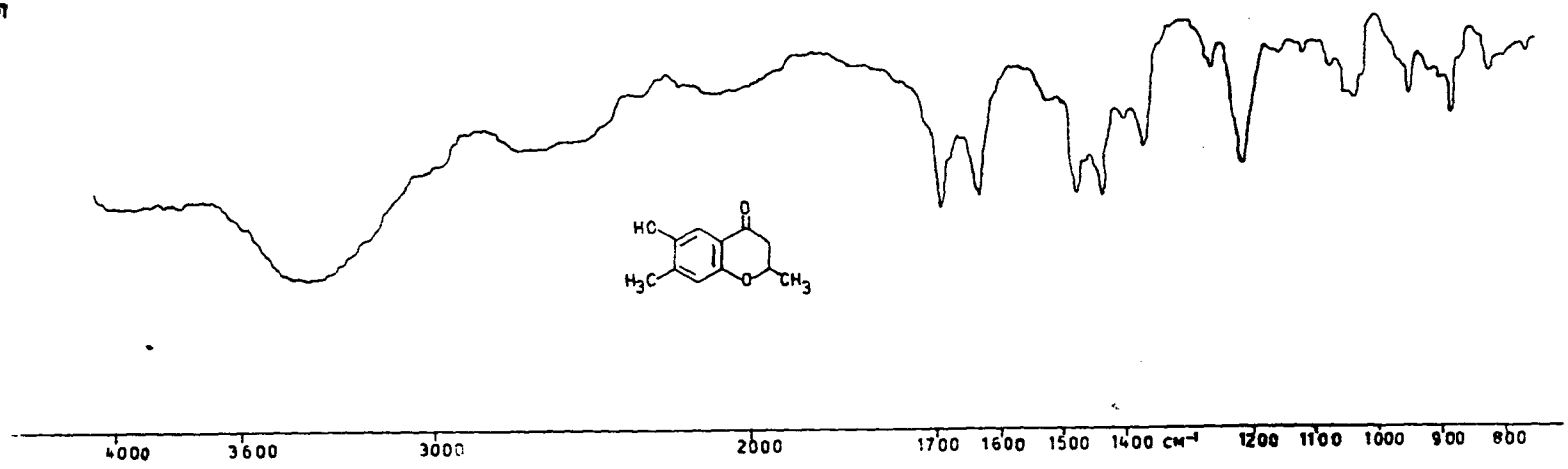

Fig. 15 IR SPECTRUM OF (63)

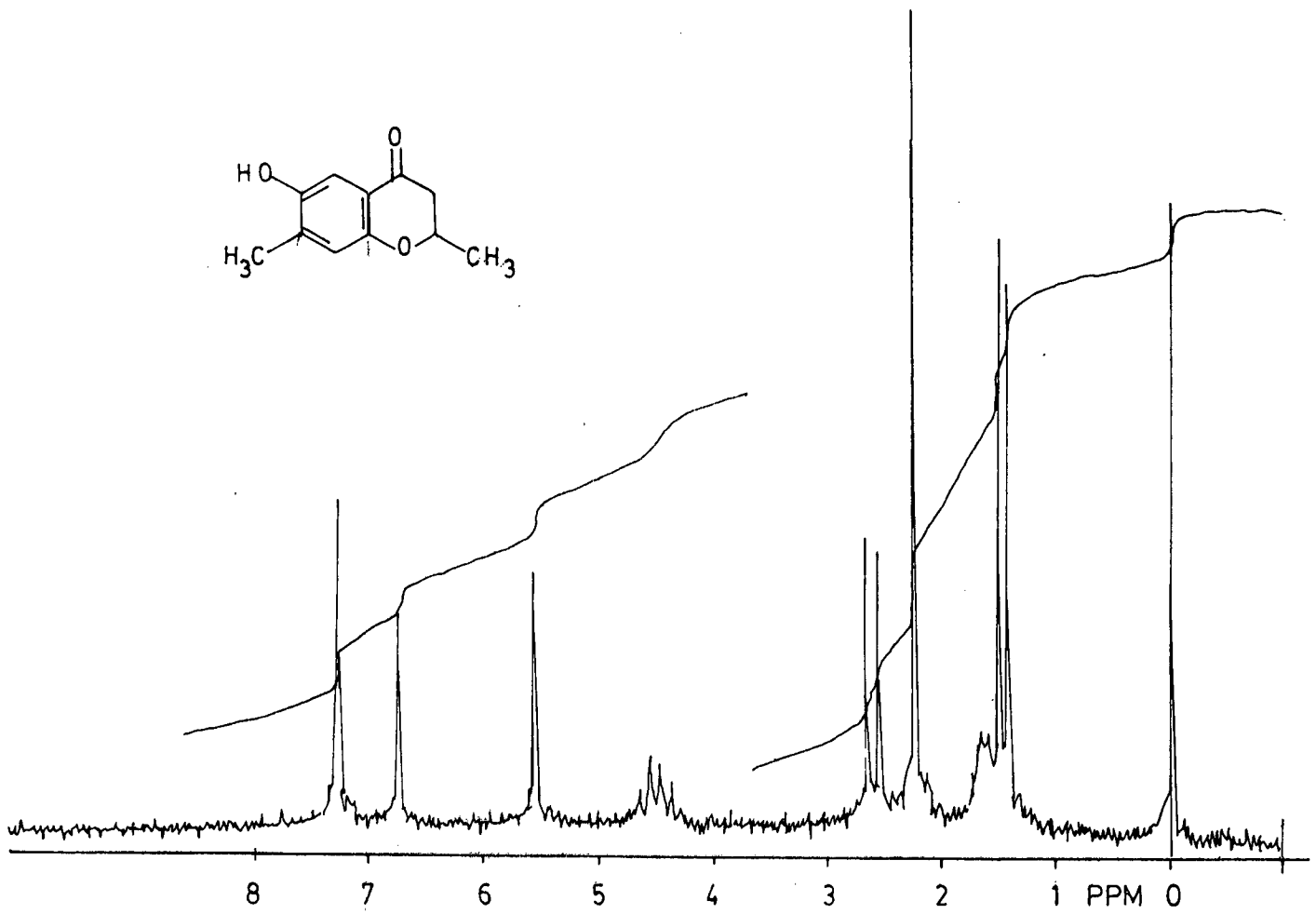

Fig. 16 ^{1}HNMR SPECTRUM OF (63)

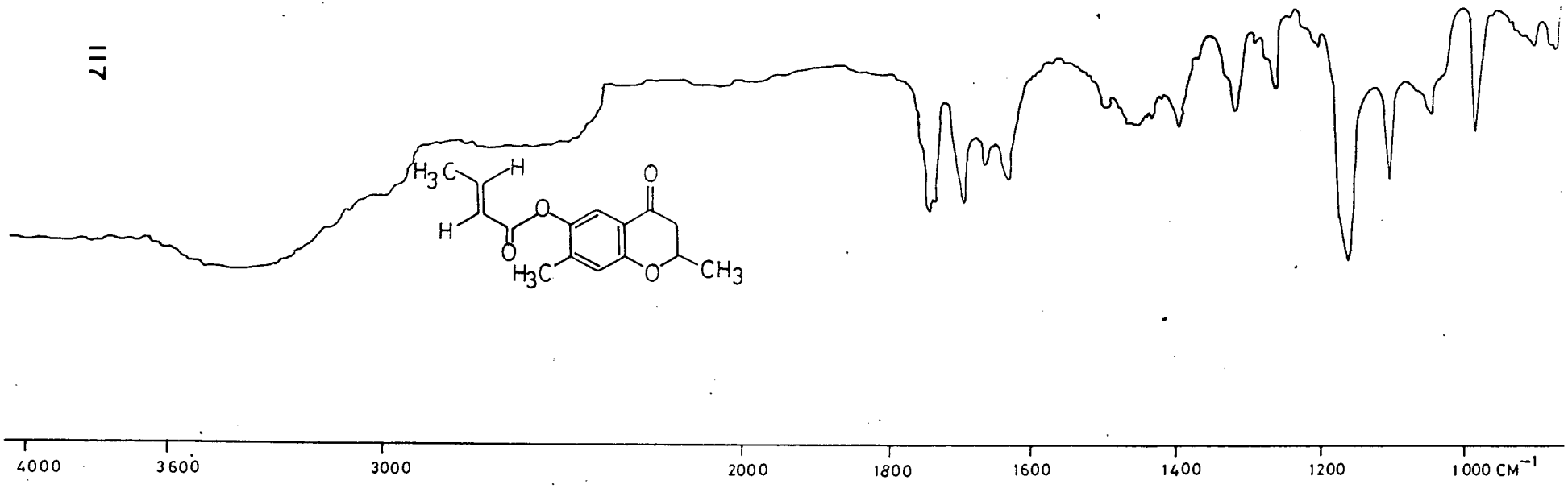

Fig. 17 IR SPECTRUM OF (62)

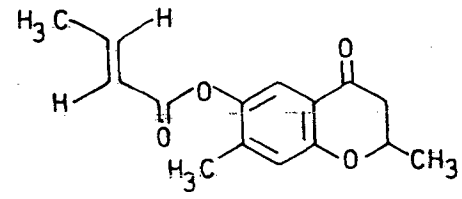

Fig. 18 ^{1}H NMR SPECTRUM OF(62)

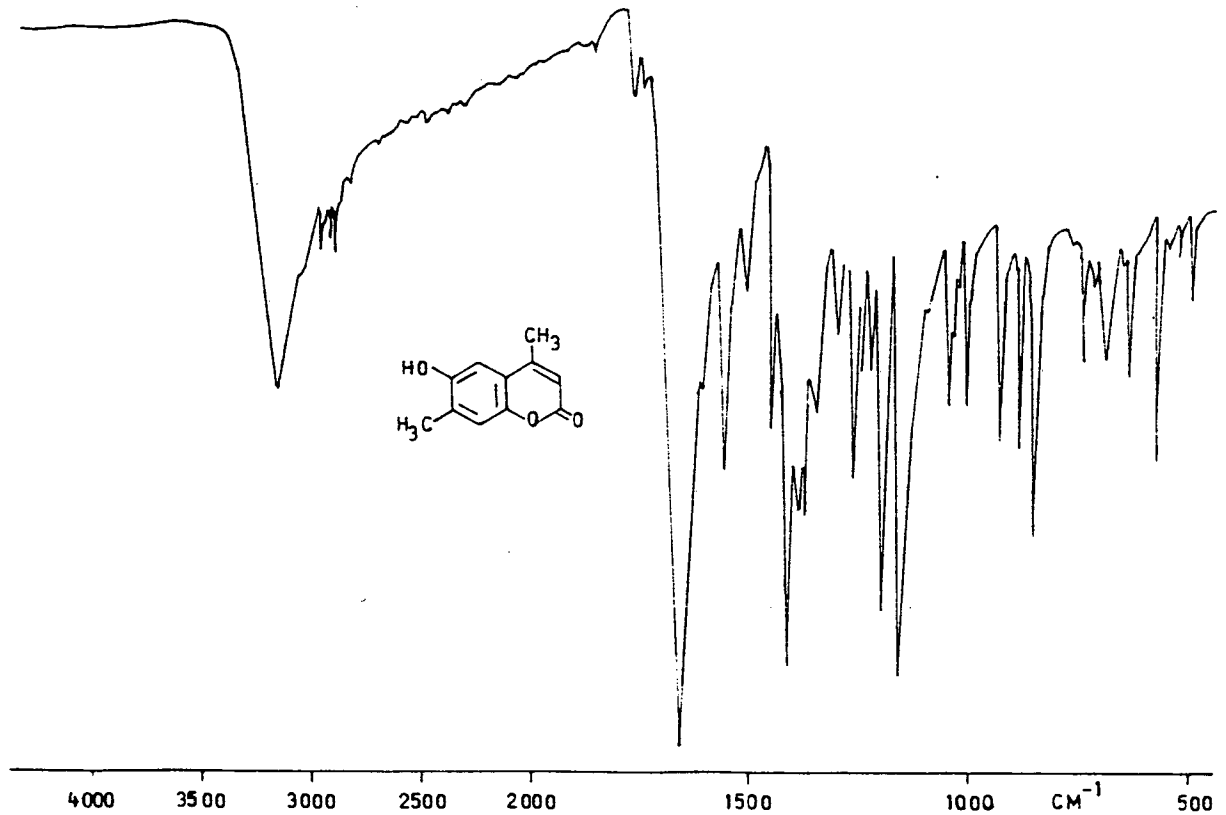

Fig. 19 IR SPECTRUM OF (60)

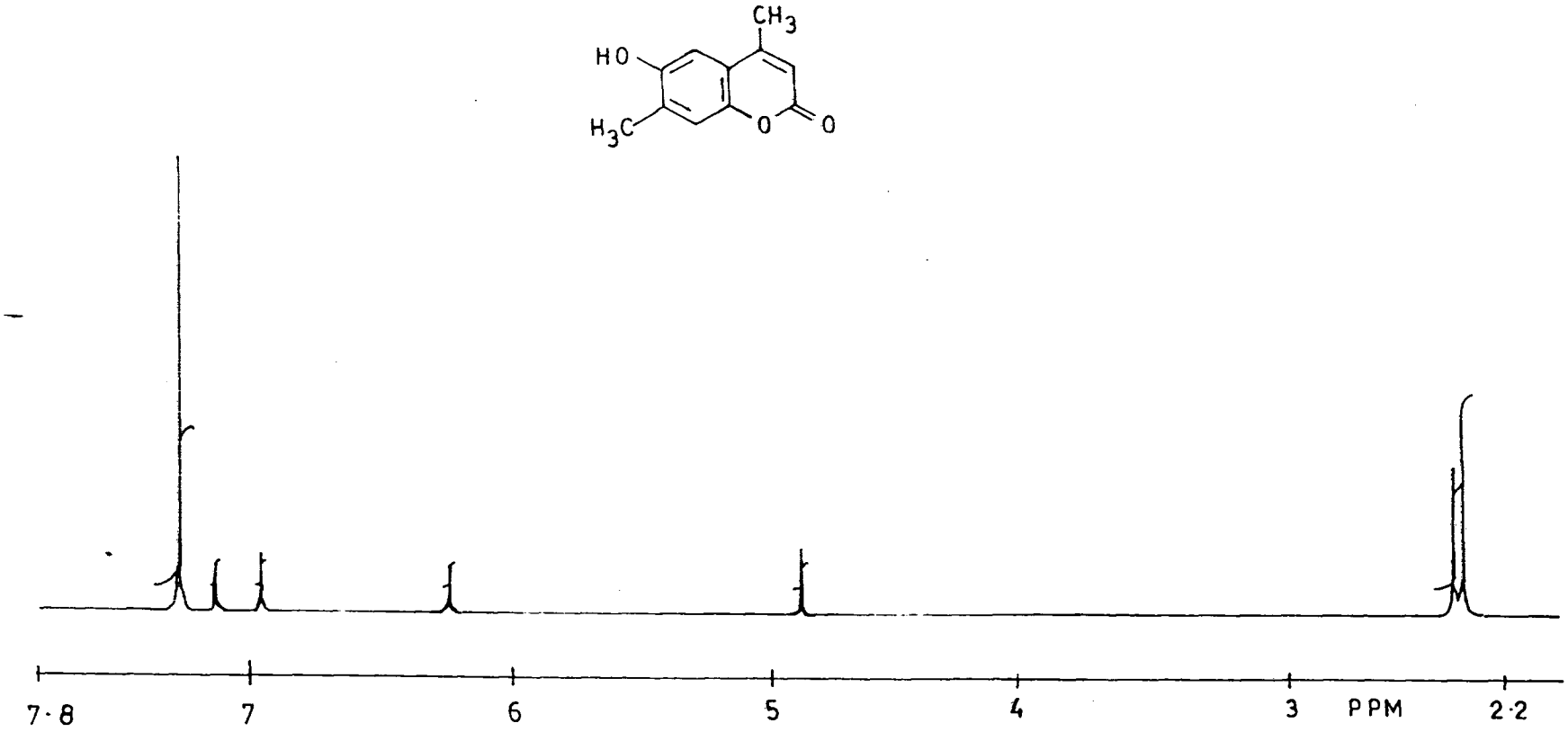

Fig. 20 ^{1}HNMR SPECTRUM OF (60)

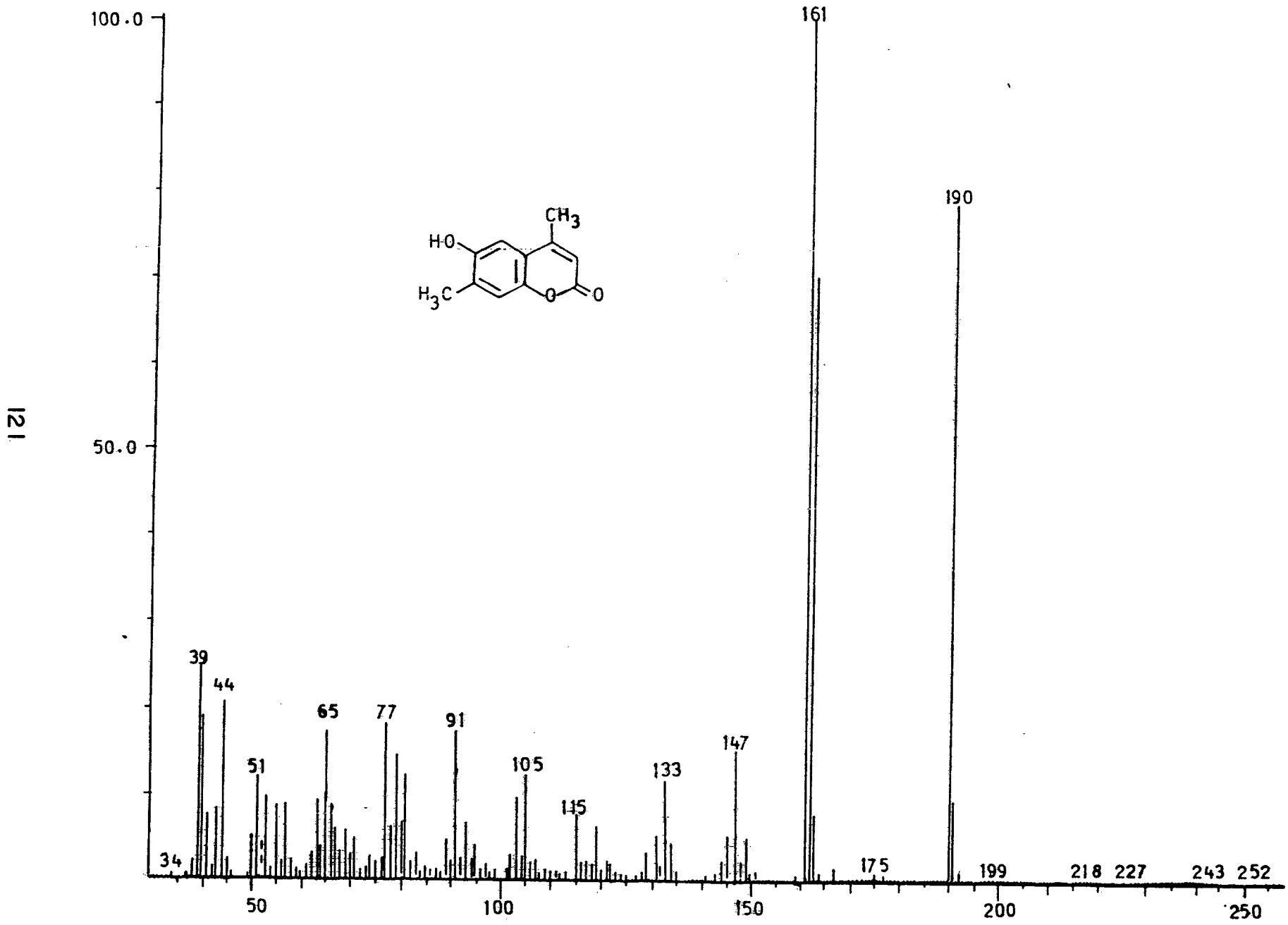

Fig. 21 MASS SPECTRUM OF (60)

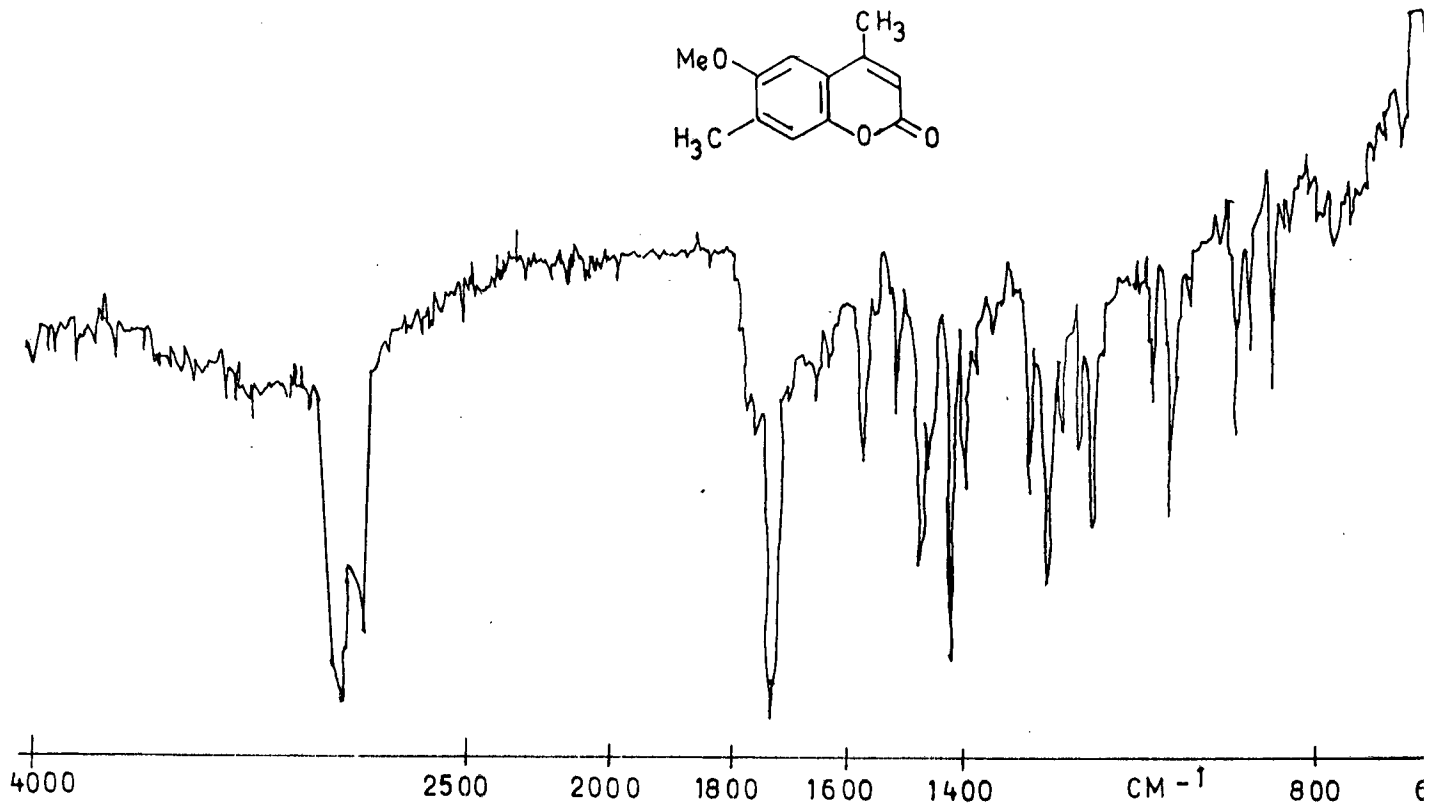

Fig. 22 IR SPECTRUM OF (61)

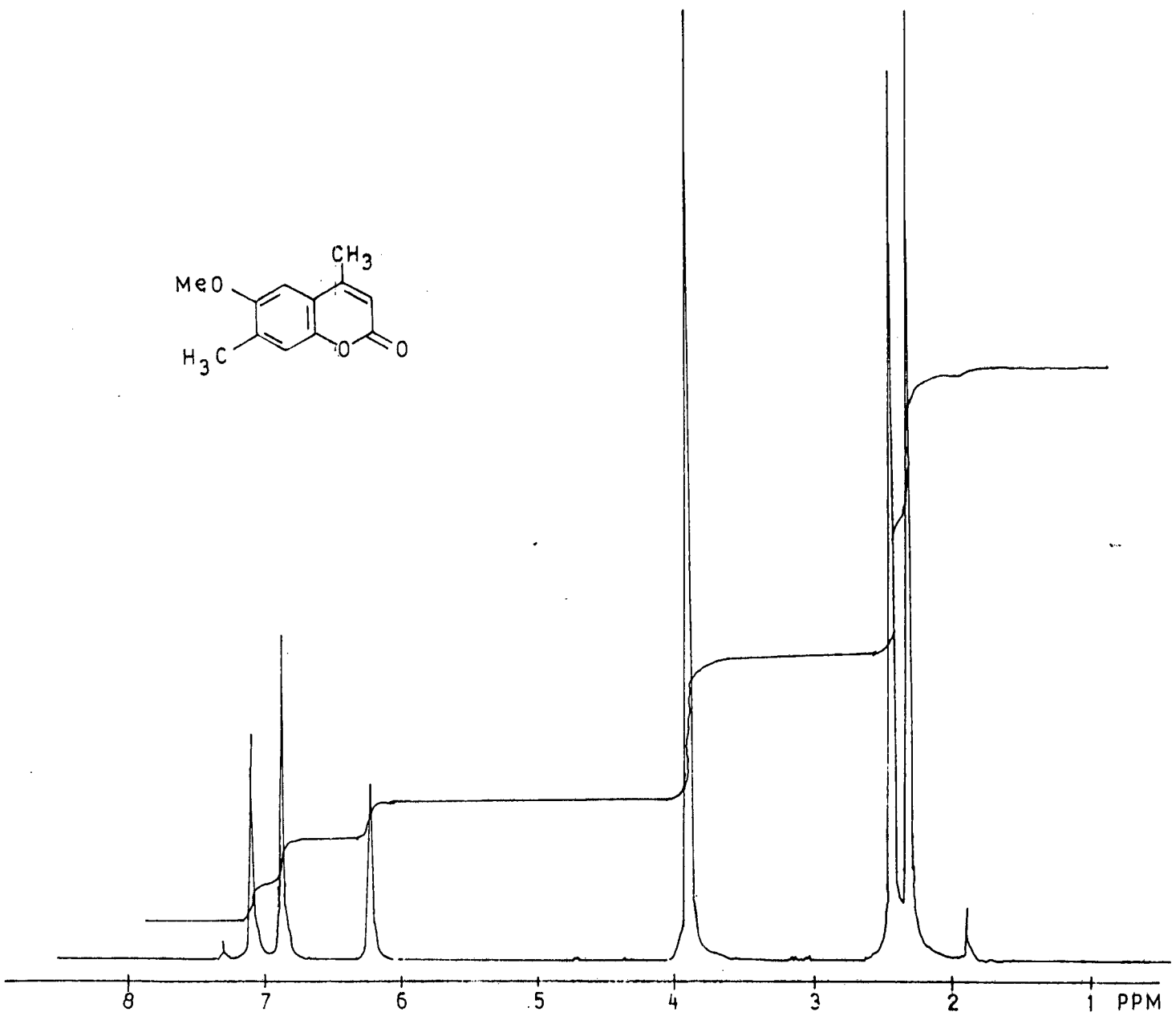

Fig. 23 ^{1}HNMR SPECTRUM OF (61)

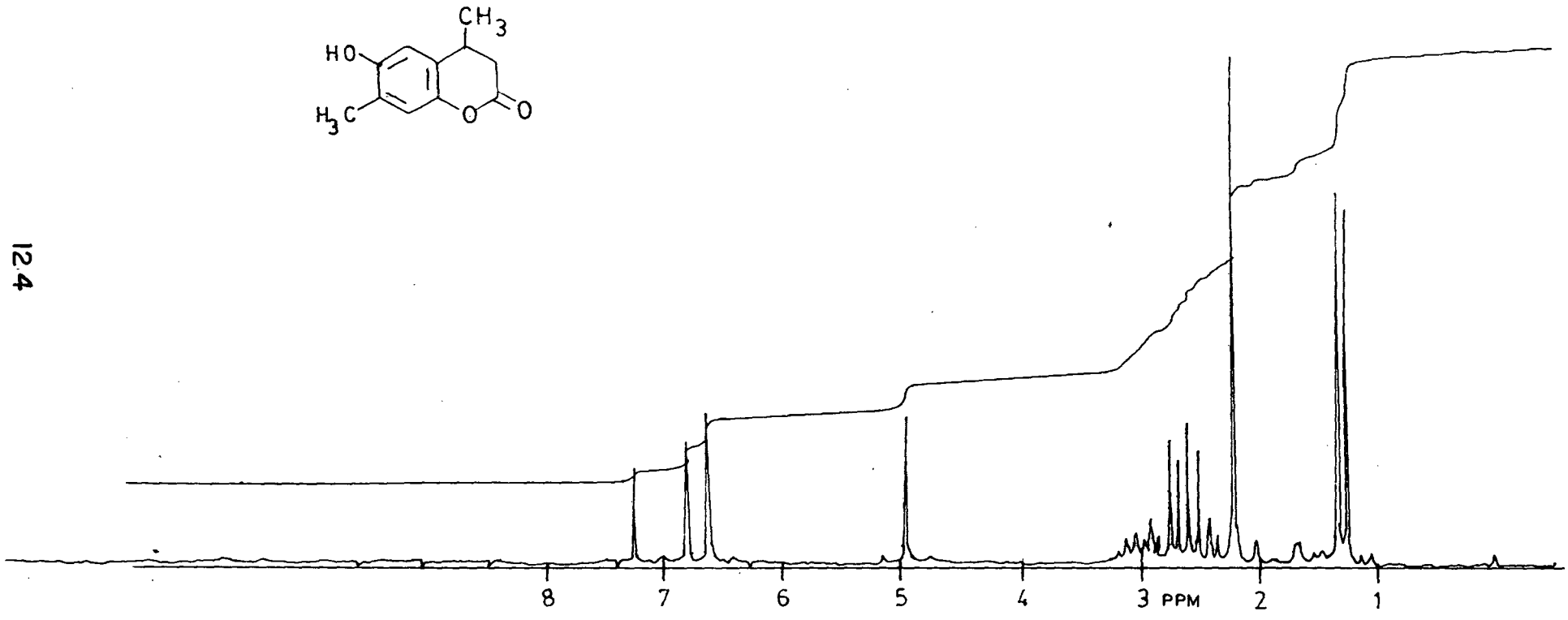

Fig. 24 ^{1}HNMR SPECTRUM OF (56)

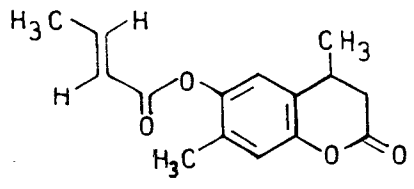

Fig. 25 ^{1}HNMR SPECTRUM OF (64)

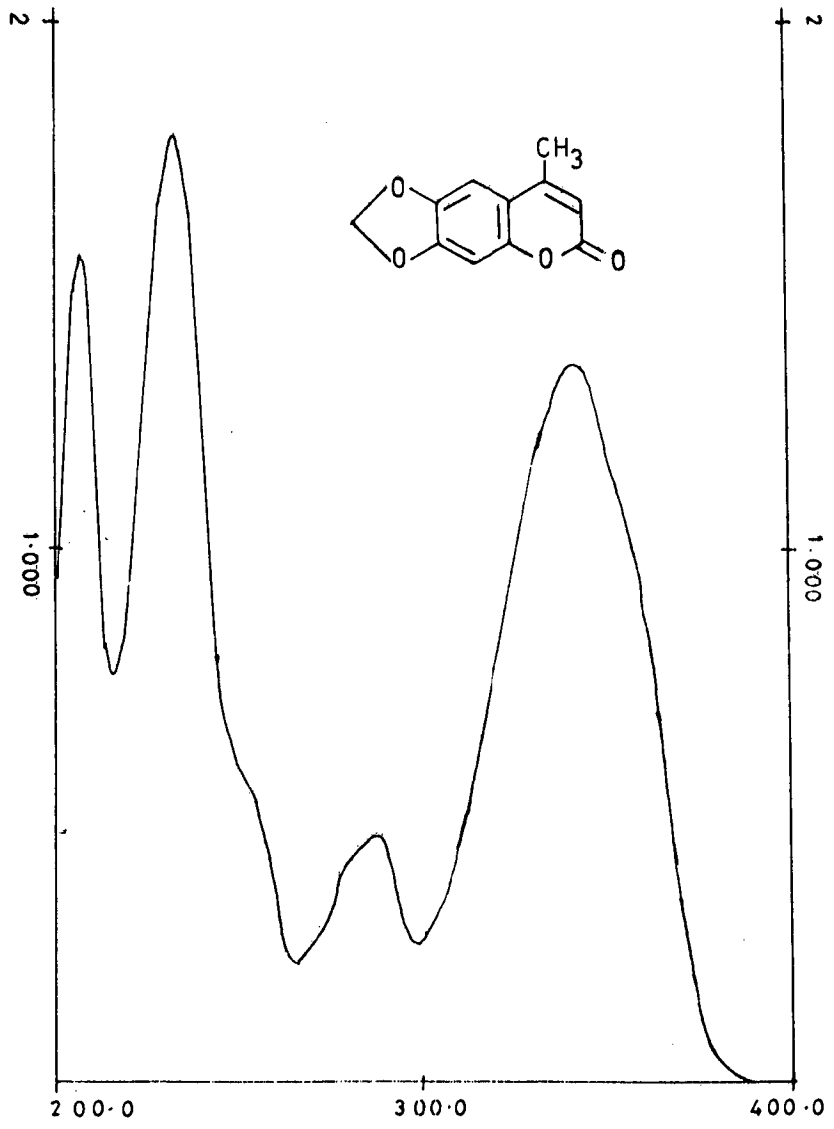

Fig. 26 U V SPECTRUM OF (65)

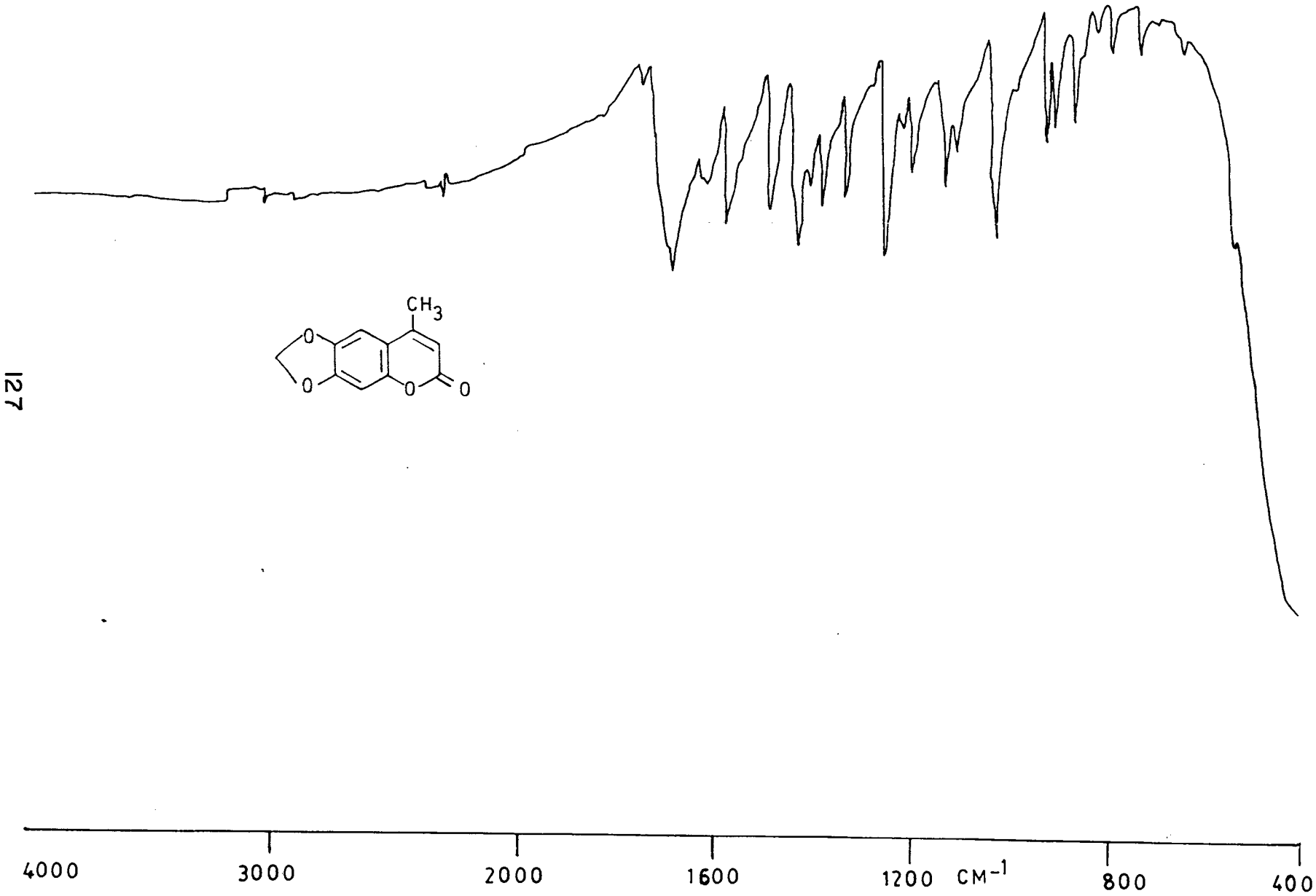

Fig. 27 IR SPECTRUM OF (65) in ($CHCl_3$)

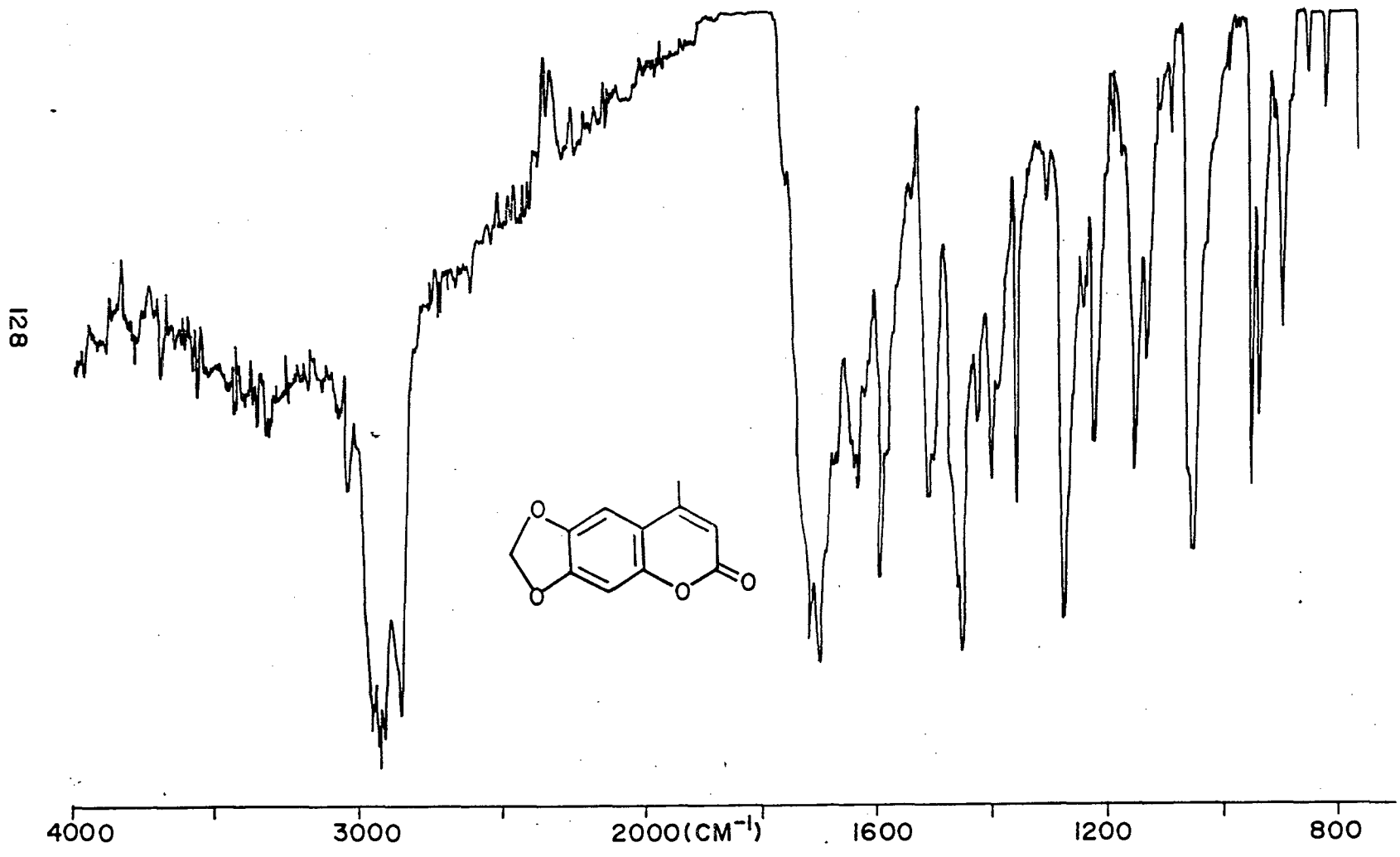

Fig. 28 IR SPECTRUM OF (65)in (Nujol)

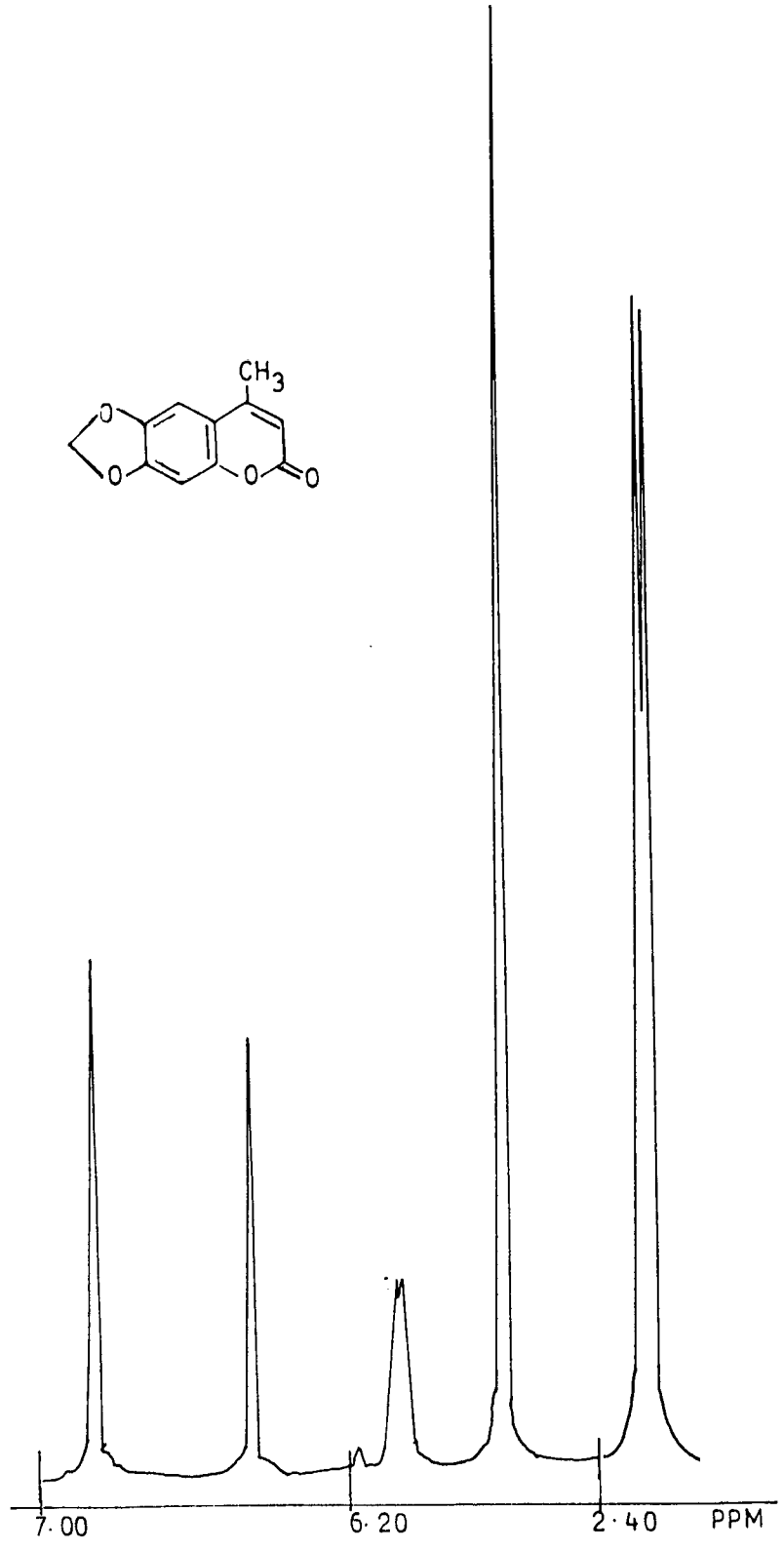

Fig. 29 ^{1}H NMR SPECTRUM OF (65)

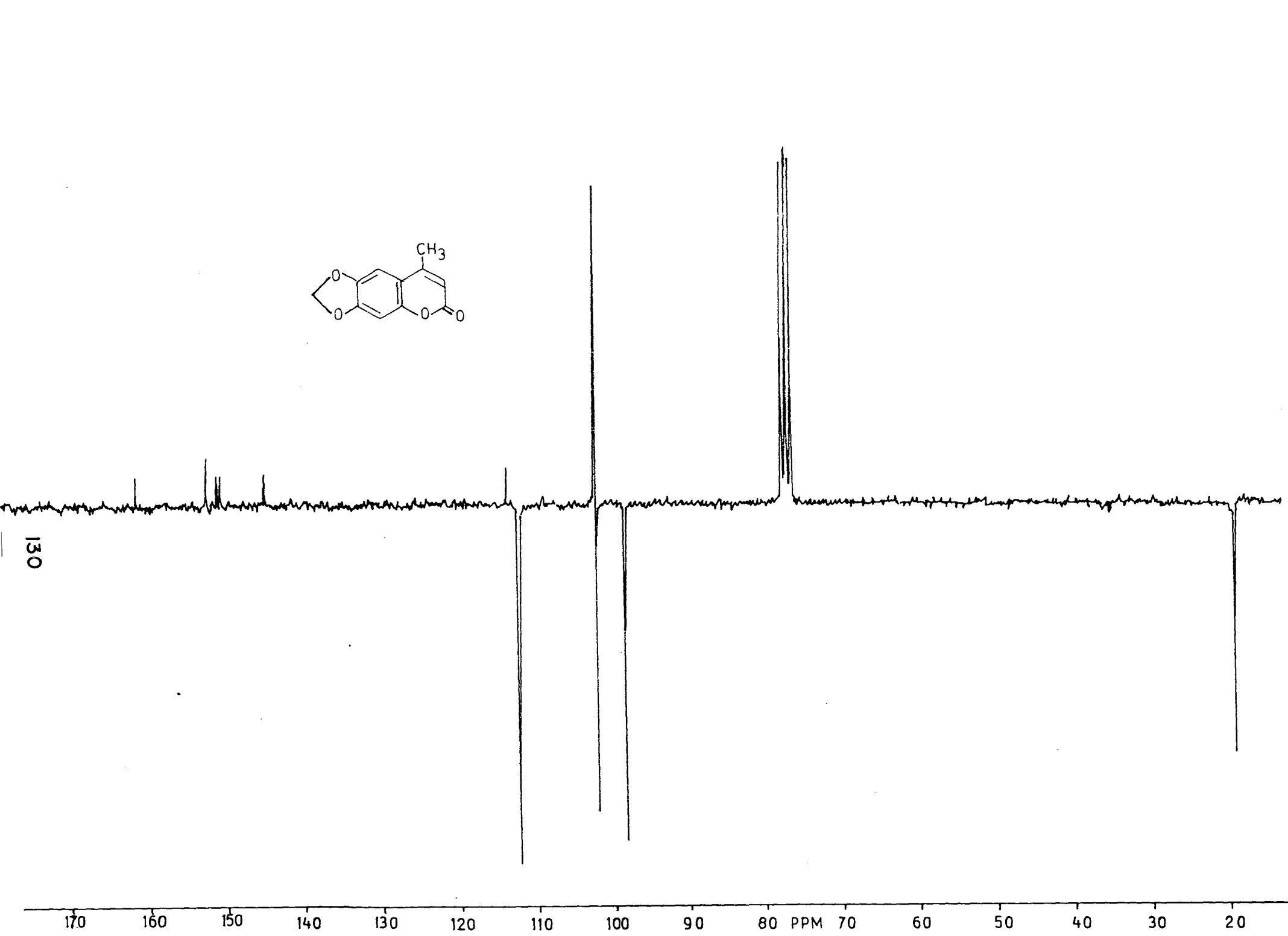

Fig 30 ^{13}C NMR SPECTRUM OF (65)

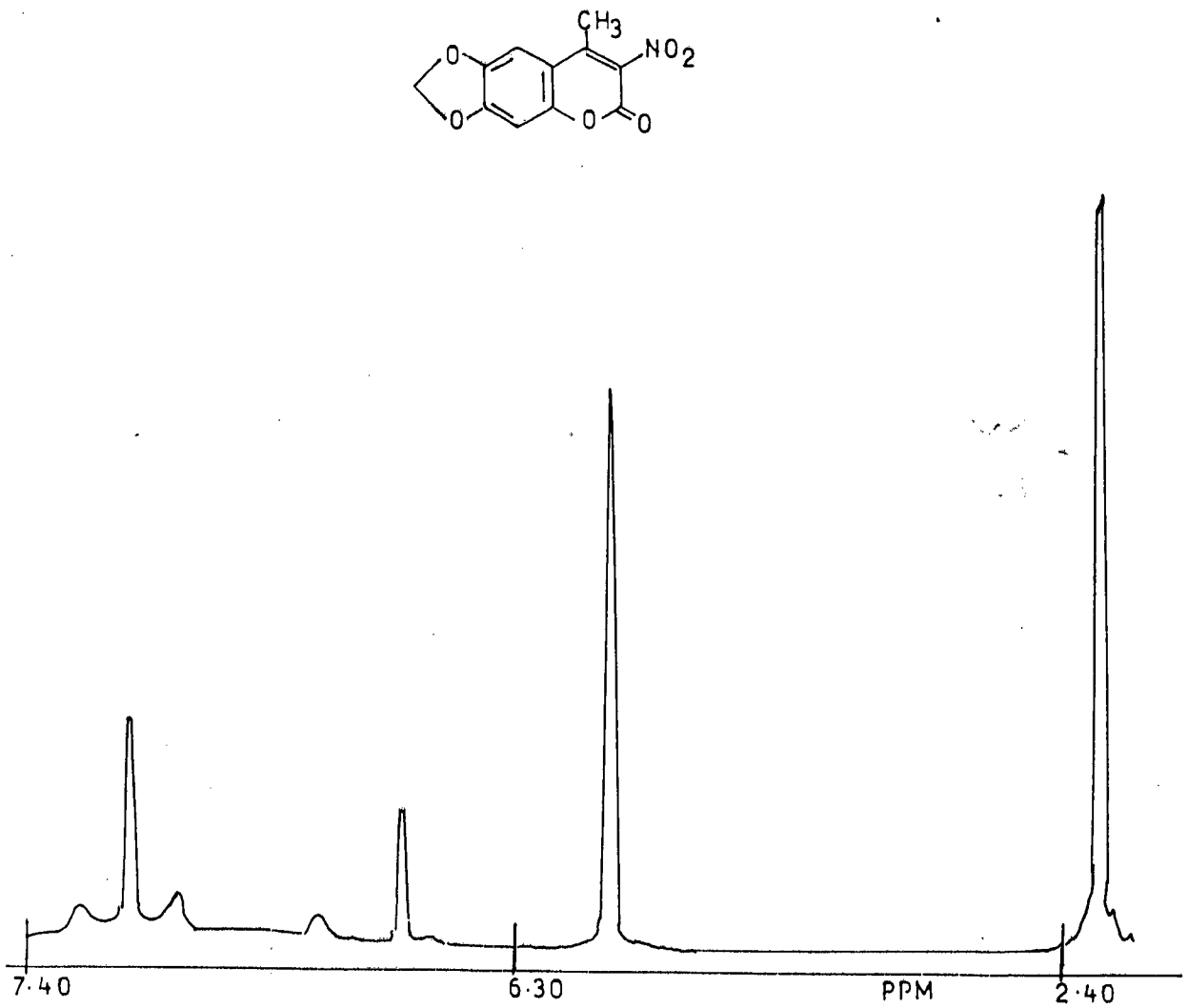

Fig. 31 ^{1}H NMR SPECTRUM OF (72)

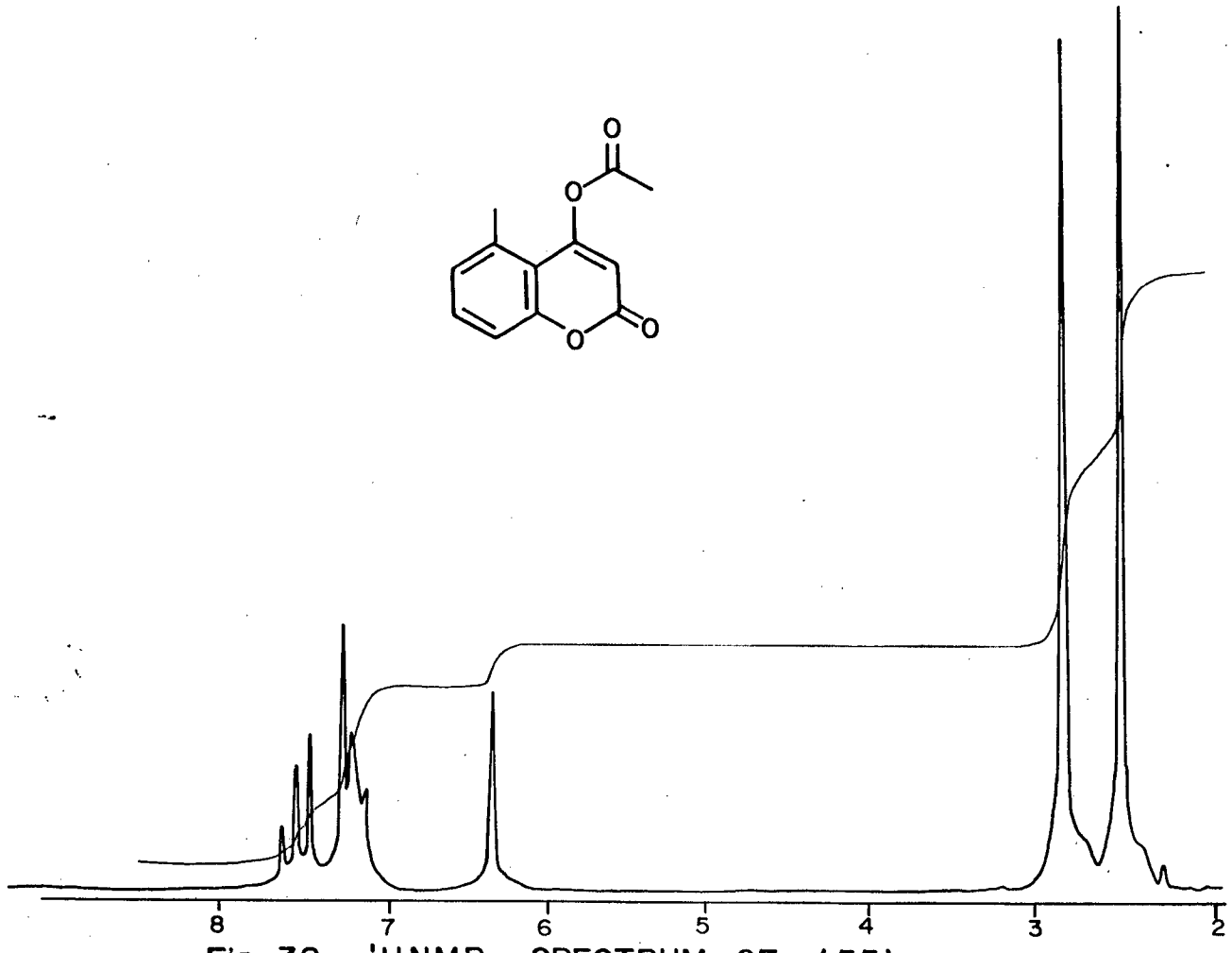

Fig. 32 'HNMR SPECTRUM OF (55)

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P A R T - II

CHAPTER - 3

SECTION - 1

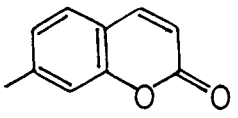
SYNTHESIS OF 7-METHYL, 6,7-DIMETHYL AND 7,8-DIMETHYL COUMARINS

3.1 SYNTHESIS OF 7-METHYL, 6,7-DIMETHYL, AND 7,8-DIMETHYL COUMARINS :

Compared to the total number of natural coumarins only a few are known to possess a methyl substituent on the aromatic ring (Chart-1). Practically all these compounds are oxygenated at C_7 and/or C_4. Alkylated coumarins without an oxygen function at C_7 and/or C_4 have been prepared by condensation of cresols, xylenols with malic acid in the presence of H_2SO_4 or PPA.[1] Similarly synthetic coumarins having methyl substituent/s on the aromatic ring and also at C_4 position are known (Chart-2). In this section a new preparation of (i) 7-methyl, (ii) 6,7-dimethyl and (iii) 7,8-dimethyl coumarins is reported.

Condensation of m-cresol with p-methoxy cinnamic acid in the presence of PPA at 70°C for 4 hours, gave after usual work up and purification by column chromatography, a crystalline solid m.p. 126°C (lit[2]. m.p. 124-26°C) and was identified as 7-methyl coumarin (1). Under identical experimental conditions 3,4-dimethyl phenol (2) and 2,3-dimethyl phenol (3) gave coumarins 4 and 5 respectively. These were characterised by spectral data

which is presented in Tables-1 and 2. In the reaction of 3,4-dimethyl phenol, the coumarin 4 was accompanied by the intermediate 6. The spectral data were found to be consistent with its formulation as 6.



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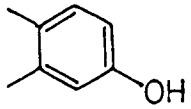

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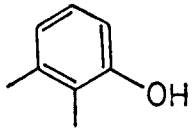

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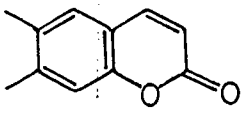

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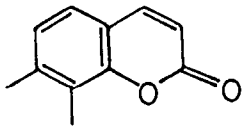

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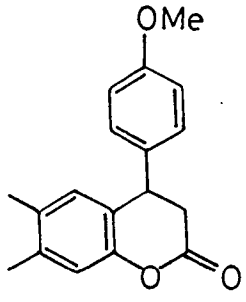


6

Although the new method developed cannot be claimed to be superior to the previously known methods, it does confirm the generality of our new method of coumarin synthesis.[3]

* only representative examples are given

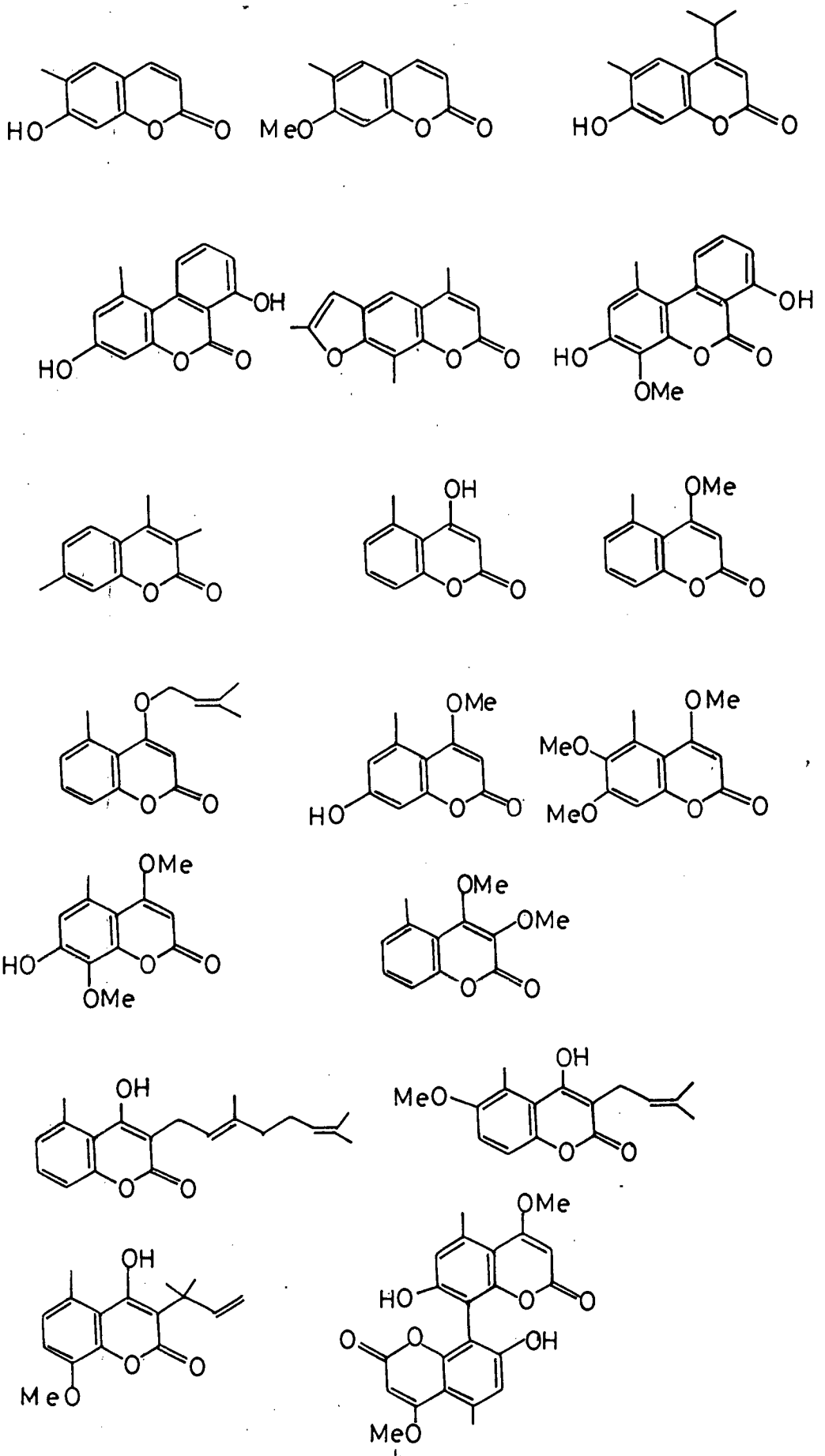


Chart – 1*

* only representative examples are given

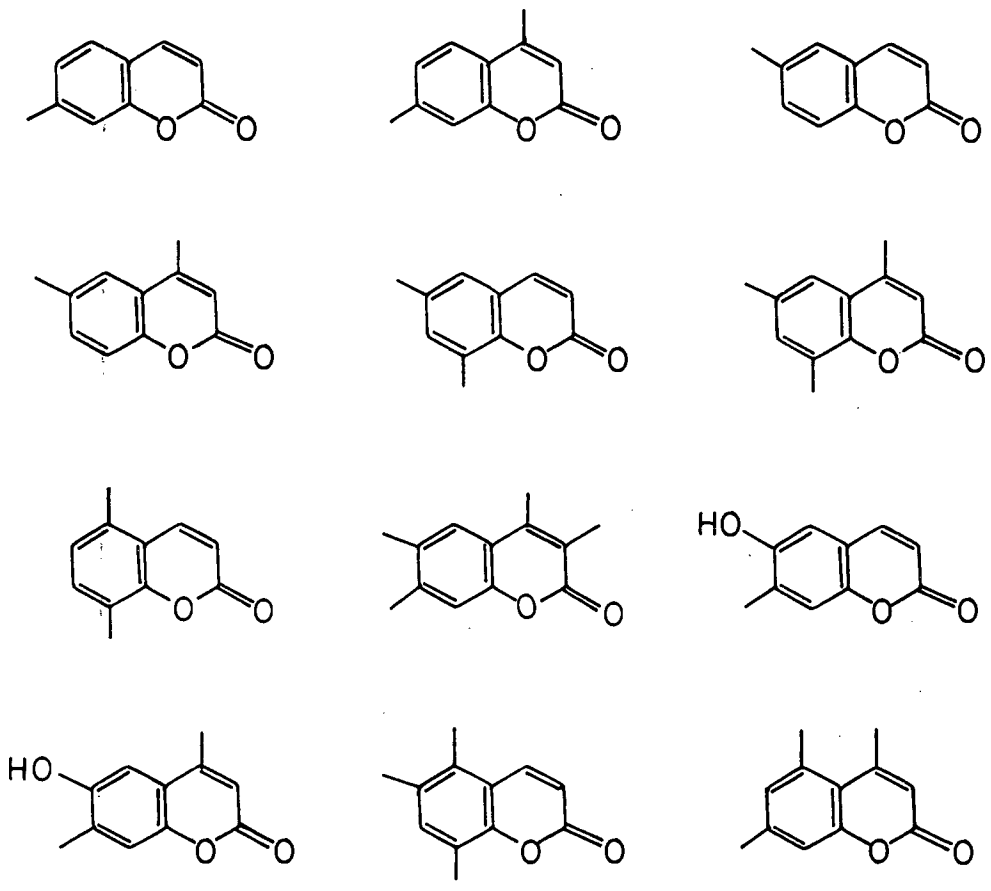


Chart – 2*

Table – 1

Compound	IR ν max. cm^{-1}	^{1}H nmr δ ppm ($CDCl_3$)
1	1725 (Nujol)	2·452 (3H, s, $C_7-C\underline{H}_3$)
		6·352 (1H, d, J=9·5Hz, C_3-H)
		7·09 (1H, dd, J=8 & 2Hz, C_6-H)
		7·142 (1H, dd, J=2 & 0·4Hz, C_8-H)
		7·360 (1H, d, J=8Hz, C_5-H)
		7·668 (1H, dd, J=9·5 & 0·4Hz, C_4-H)
4	1725 (Nujol)	2·293* (3H, s, $C_6-C\underline{H}_3$)
		2·342* (3H, s, $C_7-C\underline{H}_3$)
		6·330 (1H, d, J=9·5Hz, C_3-H)
		7·10 (1H, s, C_5-H)
		7·21 (1H, d, J=0·4Hz, C_8-H)
		7·623 (1H, dd, J=9·5 & 0·4Hz, C_4-H)
5	1730 (KBr)	2·38[a] (3H, s, $C_8-C\underline{H}_3$)
		2·42[a] (3H, s, $C_7-C\underline{H}_3$)
		6·34 (1H, d, J=10Hz, C_3-H)
		7·08 (1H, d, J=8Hz, C_6-H)
		7·22 (1H, d, J=8Hz, C_5-H)
		7·66 (1H, d, J=10Hz, C_4-H)

*, a: values may be interchanged

Table-2 ^{13}C Chemical shifts $CDCl_3$

(in δ, ppm) of methyl coumarins 1 and 4

Carbon Number	1 (multiplicity)	4 (multiplicity)
2	160·75 (s)	160·98 (s)
3	115·12 (d)	115·08 (d)
4	143·01 (d)	142·95 (d)
5	127.15 (d)	127 54 (d)
6	125·24 (d)	132·79 (s)
7	142·75 (s)	141·55 (s)
8	116·73 (d)	117·05 (d)
4a	116·12 (s)	116·26 (s)
8a	153·83 (s)	152·12 (s)
$6-CH_3$	———	18·80[a] (q)
$7-CH_3$	21·43 (q)	19·97[a] (q)

a : assignments may be interchanged

P A R T - II

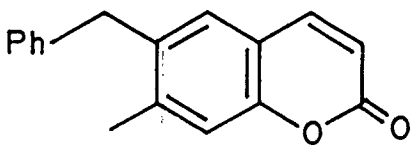
CHAPTER - 3

SECTION = 2

ATTEMPTED PREPARATION OF 6-BENZYL-7-METHYL COUMARIN

3.2 ATTEMPTED PREPARATION OF 6-BENZYL-7-METHYL COUMARIN.

Several benzylated flavanoids[4-6] have been found to be biologically active compounds. In view of our current interest in the synthesis of natural and non-natural coumarins, it seemed worthwhile to prepare some benzylated coumarins and study their biological properties. It was observed by us that 3,4-dimethyl phenol(2) on reaction with p-methoxy cinnamic acid in the presence of PPA gives 6,7-dimethyl coumarin (4). (Part-II, Chapter 3.1). Based on these observations it seemed possible to prepare 6-benzyl-7-methyl coumarin (7) under identical experimental conditions mentioned above by replacing 2 by 3-methyl-4-benzyl phenol (8).



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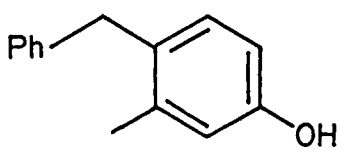
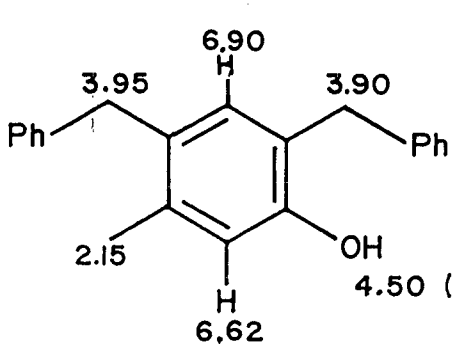


8

In order to prepare 8, m-cresol was heated with benzyl chloride at reflux temperature for 8

hours. The reaction product on chromatography over silica gel gave two crystalline substances A and B having melting points 95° and 109° respectively. The IR spectrum of compound m.p. 109° showed the presence of hydroxyl group as desired. Its ^1H nmr spectrum, however, showed it to be dibenzylated m-cresol 9. The assignments are as shown.

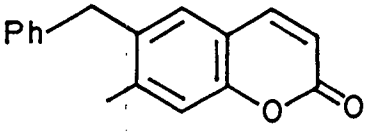


9

A literature search indicated that monobenzylated and dibenzylated m-cresol 8 and 9 respectively have been prepared before by Huston and Houk*,[7]. The compound having higher melting point (109°) compared well with the literature value (lit. m.p. 106-107°[7]). The lower melting point compound (m.p. 95°) corresponded to 3-methyl-4-benzyl phenol (lit. m.p. 93-94°[7]). It was, there

*Experimental procedure used by these authors was different than our method of preparation.

fore, subjected to the treatment with p-methoxy cinnamic acid in the presence of PPA at 70° for 4 hours. Surprisingly, no compound having either structure 7 or 10 could be isolated from the reaction mixture. The reasons for failure to get 7 or 10 are not clear. It may be possible to get the desired coumarin 7 by carrying out PPA reaction at higher temperatures. However, no attempt has been made so far in this direction. It would be interesting to see whether 11 can be obtained by using TFA as catalyst or using our own method[8,9] for preparing 3,4-dihydro-4-aryl coumarins (12). Preparation of 7 would then be possible by using dearylation procedure of Manimaran and Ramakrishnan[10].



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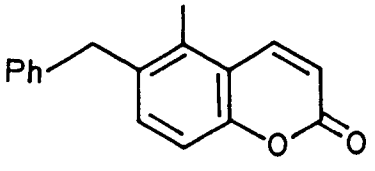

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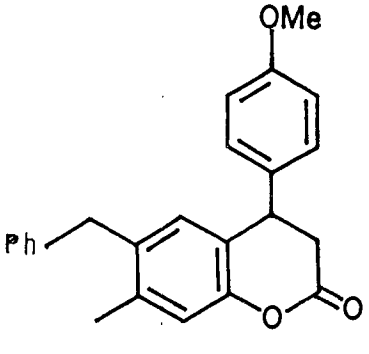

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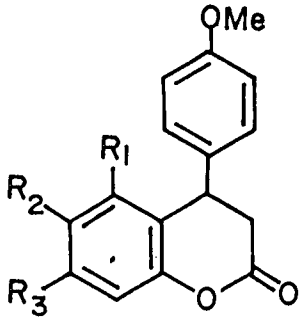


12

PART - II

CHAPTER - 3

SECTION - 3

A SIMPLE AND CONVENIENT SYNTHESIS OF 6-METHOXY-7-ETHOXY COUMARIN

3.3 A SIMPLE AND CONVENIENT SYNTHESIS OF 6-METHOXY-7-ETHOXY COUMARIN

Although the natural occurence of 6-hydroxy-7-methoxy coumarin (13, isoscopoletin) and 6-methoxy-7-hydroxy coumarin (14, scopoletin) is known, there is no report so far on the natural occurence of the corresponding ethyl ether derivatives. However, ethyl ether 15 of 13 has been prepared before and well characterised[11]. In view of the absence of any previous synthesis of 16, we thought it worthwhile to prepare it using our coumarin synthesis. The phenol required for this purpose could be prepared by the sequence shown (Scheme-1). The starting material, 3-ethoxy-4-hydroxy benzaldehyde (commercially known as ethyl vanillin*) (17) was methylated with anhydrous K_2CO_3, $(CH_3)_2SO_4$ to give 3-ethoxy-4-methoxy benzaldehyde (18), m.p.52° which when subjected to Baeyer-Villiger oxidation followed by hydrolysis gave the desired phenol 19, m.p.81°.

3-Ethoxy-4-methoxy phenol (19) on reaction with p-methoxy cinnamic acid at 70° for 4 hours in the presence of PPA gave a viscous liquid which on chromatography with silica gel and elution with EtOAc:Benzene (5:95) gave a solid $C_{12}H_{12}O_4$, m.p. 143° (crystallised from

---

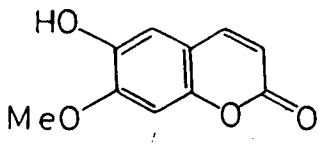
* We thank Reckitt & Colman of India Ltd. for a gift sample of Ethyl vanillin

benzene - petroleum-ether). The IR spectrum showed a band at 1715 cm^{-1} characteristic of α -benzopyrone grouping. Its ^1H nmr spectrum showed the presence of all the characteristic signals expected on the basis of structure 16. The ^1H nmr data and assignments are given in Table-3.

Table-3 ^1H nmr (in δ ppm, $CDCl_3$) for 16

Proton	Chemical shift 'δ'
$-O-CH_2-CH_3$	1.47, t (J=7 Hz)
$-O-CH_3$	3.88, s
$-CH_2-CH_3$	4.11, q (J=7 Hz)
C_3-H	6.30, d (J=9 Hz)
C_5-H	6.82, s
C_8-H	6.82, s
C_4-H	7.63, d (J=9 Hz)

The present work further demonstrates the synthetic utility of the coumarin synthesis developed by us. We have no doubt that it would be possible to synthesise ethyl ether of isoscopoletin by carrying out the analogous sequence of reactions starting from vanillin.



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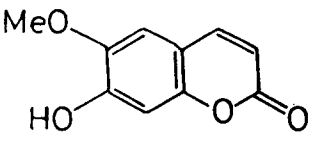

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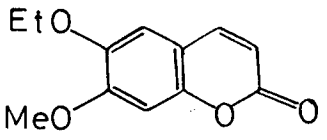

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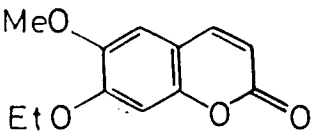

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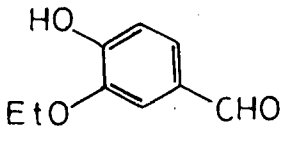

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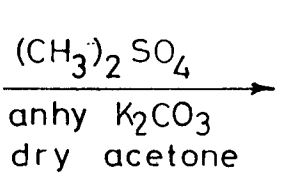
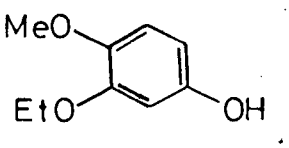


18

(i) Baeyer–villiger oxidn

(ii) KOH/HOH



19

Scheme – 1

P A R T - II

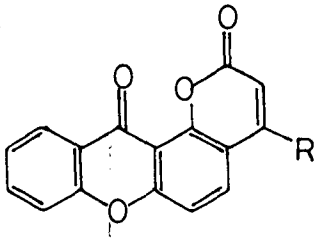
CHAPTER - 3

SECTION - 4

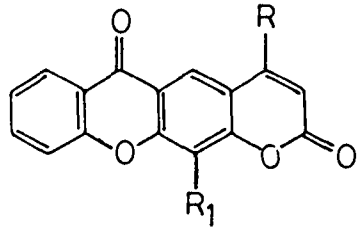
EXPERIMENTS DIRECTED TOWARDS THE SYNTHESIS OF PYRANO [2,3-a] XANTHONE : SYNTHESIS OF PYRANO [2,3-a] XANTHENE

3.4 EXPERIMENTS DIRECTED TOWARDS THE SYNTHESIS OF PYRANO [2,3-a] XANTHONE : SYNTHESIS OF PYRANO [2,3-a] XANTHENE

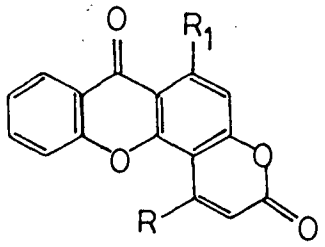
Although a large variation of structural types in naturally occurring coumarins is known, we haven't come across any report on the natural occurence of pyranoxanthones (xanthano coumarins) having basic skeleton 20a(R=H), 20b(R=R_1=H) and 20c(R=R_1=H)



20a



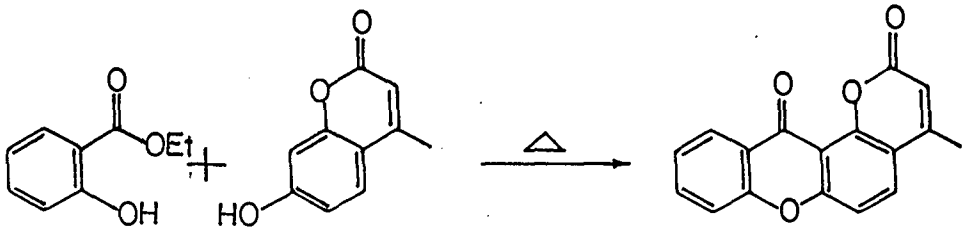
20b



20c

There are, however, some reports of synthesis of derivatives of 20a(R=CH_3), 20b(R=R_1=CH_3) and 20c(R=R_1=CH_3) in order to find out biological activity if any, resulting out of combination of xanthone nucleus coupled to a coumarin ring system. Patolia and Trivedi[12] reported obtaining 20a(R=CH_3) by means of

heating 7-hydroxy-4-methyl coumarin with ethyl salicylate (9-15 hours) in diphenyl ether (Scheme-2).



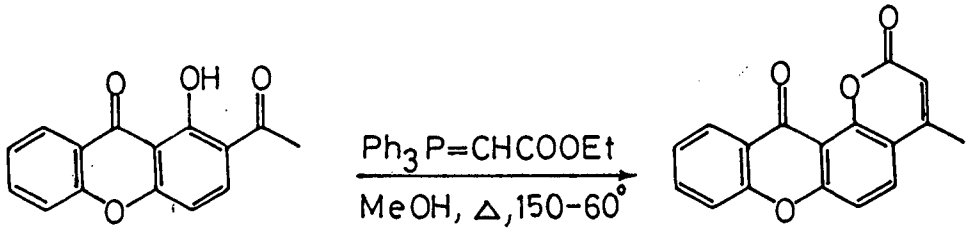
21

m. p. 280°
no spectral data
given (Ref. 12)

Scheme—2

In connection with our work involving thermal reactions of salol, we attempted the preparation of 20a(R=CH_3), by heating salol and 7-hydroxy-4-methyl coumarin (21) with or without diphenyl ether. In all the experiments carried out so far we failed to isolate any product identical with the one reported by Patolia and Trivedi. Identical observations were made independently by Paradkar and co-workers*. However, Kondedeshmukah and Paradkar[13] reported the preparation of 20a(R=CH_3) by using Wittig synthesis of coumarins on appropriately synthesised starting compound, viz. 1-hydroxy-2-acetyl-xanthone(22) (Scheme-3). There exists some discrepancy in reported melting points of 20a(R=CH_3), m.p.[12] 280°, m.p.[13] 259°. Kondedeshmukah and Paradker have also synthesised 20b(R=R_1=H)[14].

* Dr. M. V. Paradkar, personal communication.

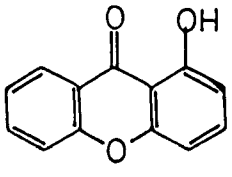


22

m.p. 259°
^{1}Hnmr ($CDCl_3$)
given (Ref. 13)

Scheme-3

By using our coumarin synthesis, we thought of preparing the parent pyranoxanthone 20a(R=H) by reaction of 1-hydroxy xanthone (23) with p-methoxy cinnamic acid in the presence of PPA. The reaction, however, was not successful and the starting materials were practically recovered quantitatively. 3-hydroxy xanthone (24) also failed to give any pyranoxanthone under these



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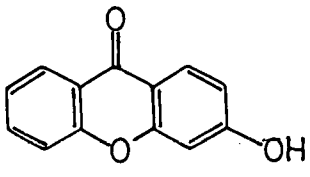

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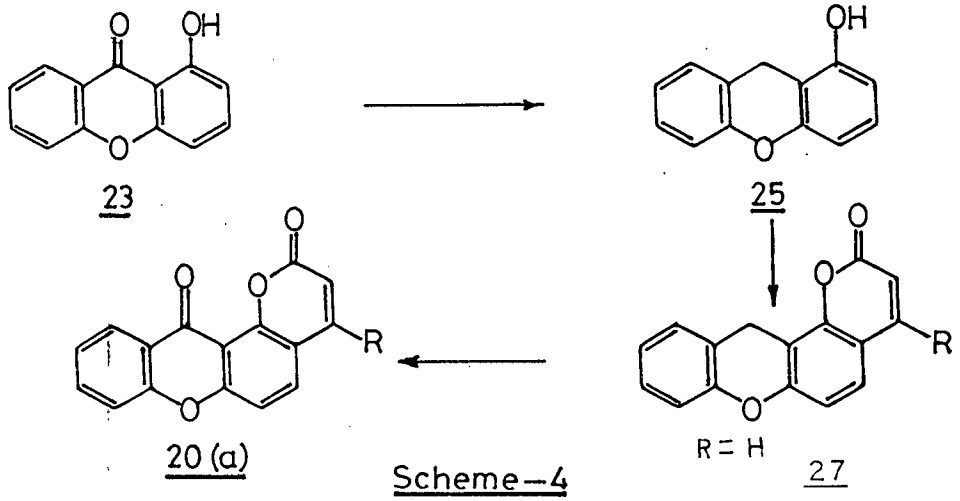
experimental conditions. It has been already reported before that pyranoxanthone derivatives are not obtainable by the Pechmann[15] or the Simonis[16] reaction.

These observations made before by other investigators led us to believe that the xanthone carbonyl may be deactivating the substrate used for Pechmann condensation. If true, it seemed possible to synthesise the desired pyranoxanthone 20a(R=H) by suitable modifications as shown in Scheme-4.

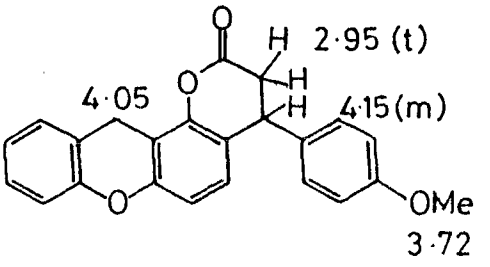


Scheme—4

1-Hydroxy xanthene(25) required for this synthesis was prepared by reductive conversion of xanthone carbonyl to methylene group by reaction of 1-hydroxy xanthone (23) (prepared by literature procedure[17]) with $LiAlH_4$/ether. The spectral data and physical constants matched well with those previously reported. Reaction of 1-hydroxy xanthene (25) with p-methoxy cinnamic acid in the presence of PPA gave after usual work up and purification by column chromatography three componds D, E and F having melting points 150°, 170° and 209° respectively in increasing order of polarity. Compound 'D'(m.p. 150°) was proved to be 1-hydroxy xanthone(23)

by comparison (TLC; m.p., m.m.p., IR) with an authentic specimen. Formation of 23 can be explained as air oxidation of 25.

The compound 'E'(m.p. 170°) analysed for $C_{23}H_{18}O_4$ and showed in its IR spectrum a band at 1780 cm^{-1} indicating it to be the intermediate 26. This conclusion was further confirmed by examining its ^1H nmr spectrum which was consistent with its formulation as 26. The assignments are as shown.



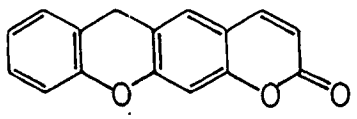
ar— H m 6·6 to 7·3

26

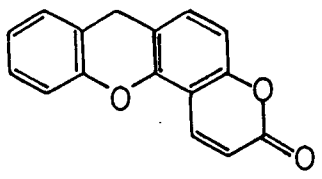
The most polar compound 'F'(m.p. 209°) was proved to be the desired pyranoxanthene 27. Its IR and ^1H nmr fully supported its formulation as 27. There are several reports of oxidation of xanthenes ⟶ xanthones Conversion of 27 to pyranoxanthone 20a(R=H) should pose no difficulty but has not been achieved

so far as the intermediate 27 obtained during the present study was just sufficient for collecting spectral data on it.

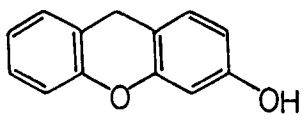
Attempted preparation of 28a and/or 28b by the reaction of 3-hydroxy xanthene (29) with p-methoxy cinnamic acid in the presence of PPA gave only 3-hydroxy xanthone (24) identified by comparison (TLC, m.p., m.m.p.) with an authentic sample and we could not detect the formation of 28a or 28b.



28a



28b



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P A R T - II

CHAPTER - 3

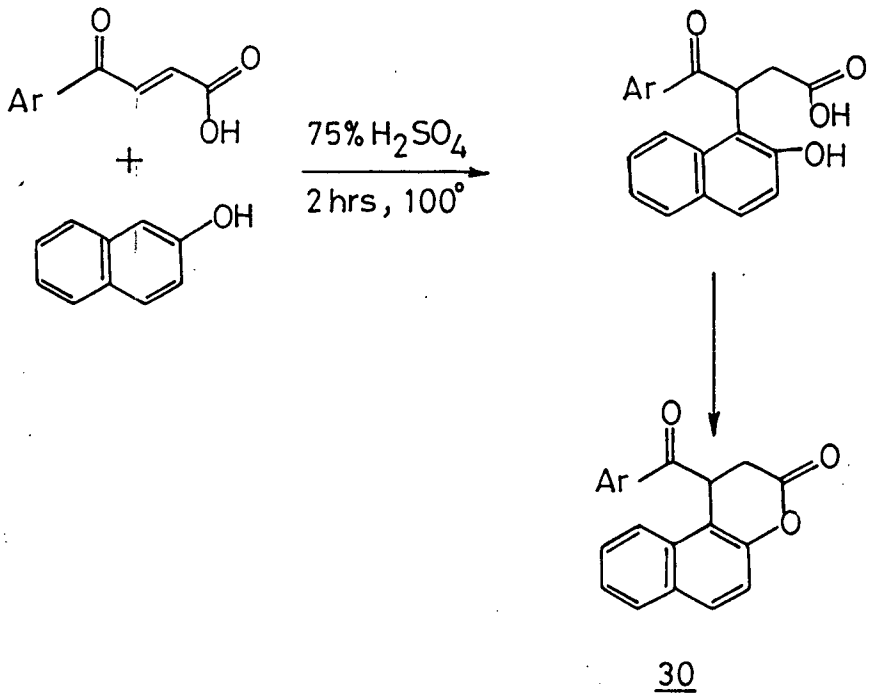
SECTION - 5

A CONVENIENT SYNTHESIS OF NATURALLY AND NON-NATURALLY OCCURRING COUMARINS : REPLACEMENT OF PPA BY 75% H_2SO_4

3.5 A CONVENIENT SYNTHESIS OF NATURALLY AND NON-NATURALLY OCCURRING COUMARINS : REPLACEMENT OF PPA BY 75% H_2SO_4.

A new synthesis of coumarins involving transfer of a C-3 unit of p-methoxy cinnamic acid on to phenols in the presence of PPA has been described in earlier sections. (Part-I, Chapter 1.1 to 1.3 and Part-II, Chapter 3.1 to 3.4). There have been inherent drawbacks in carrying out reactions with PPA. Several alternate procedures have been shown to be better than those involving the use of PPA, such as replacement of polyphosphoric acid by methanesulfonic acid. We were interested in developing a further simpler method for coumarin synthesis where we can transfer C-3 unit of p-methoxy cinnamic acid on to phenols under experimental conditions other than PPA. Several combinations were tried (e.g. Dioxane/BF_3, BF_3-etherate/THF) but the results were not encouraging. Surprisingly we could arrive at the solution under a much more simple, inexpensive and straightforward process. The process involves heating a mixture of phenol and p-methoxy cinnamic acid with 75% H_2SO_4 for 2 hours on steam bath. It is of interest to note that under these experimental conditions Shiba and co-workers[18] obtained

4-aroyl-5,6-benzocoumarins(30) by condensing βnaphthol and aroyl acrylic acids. These investigators did not observe the formation of 5,6-benzocoumarin (31) in these reactions (Scheme-5).

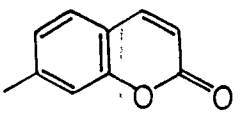


30

Scheme-5

The coumarins prepared by this procedure are (i) 7-methyl coumarin (1), (ii) 6,7-dimethyl coumarin(4), (iii) 7,8-dimethyl coumarin (5), (iv) 5,6-benzocoumarin (31), (v) 7-methoxy coumarin (32) (vi) 5,7-dimethoxy-6-hydroxy coumarin (33,

fraxinol), and (vii) 6,7-methylenedioxy coumarin (34, ayapin). Coumarins (i) to (vii) were identified by routine techniques (IR, m.p., m.m.p., CO-TLC with reference samples prepared by us earlier). The reaction involving phenols 35 and 36 with methoxy and methylenedioxy groups respectively resulted in the formation of tarry materials but the formation of fraxinol (33) and ayapin (34) could be established unambiguously by CO-TLC under different solvent systems and by short-wave UV illumination.



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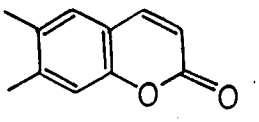

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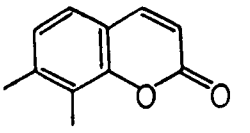

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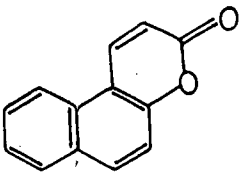

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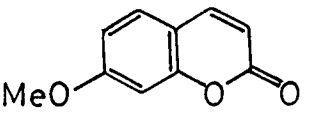

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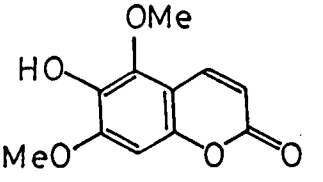

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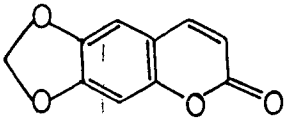

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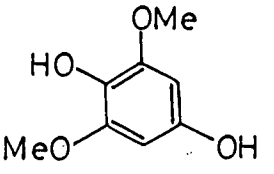

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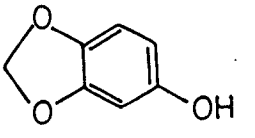


36

The interesting feature of this method is the insitu dearylation of 4-(p-methoxyphenyl)-3,4-dihydro coumarins yielding the coumarins as end products. Previously dearylations were observed when PPA or $AlCl_3$/chlorobenzene was used.

In conclusion, we claim that we have developed yet another simple procedure for the synthesis of coumarins where transfer of C-3 unit of p-methoxy cinnamic acid on to phenols is shown to occur in presence of 75% H_2SO_4 and heating the mixture on steam bath for 2 hours.*

---

* Since all the coumarins reported in this section were previously characterised no details regarding their spectral properties are presented.

P A R T - II

CHAPTER - 4

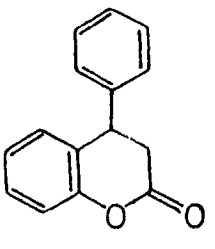
SECTION - 1

SYNTHESIS OF SOME NON-NATURALLY OCCURRING 3,4-DIHYDRO-4-(P-METHOXYPHENYL) COUMARINS

4.1 SYNTHESIS OF SOME NON-NATURALLY OCCURRING 3,4- DIHYDRO-4-(P-METHOXY PHENYL)- COUMARINS :

While several 4-aryl coumarins (Chart-3) are known to occur naturally, there is no report so far on the isolation of 3,4-dihydro-4-aryl-coumarins as natural products. There are , however, some reports of characterisation of 3,4-dihydro-4-aryl coumarins as intermediates in the synthesis of coumarins.

Simpson and Israelstum[19] were the first to confirm the formation of 3,4-dihydro-4-phenyl coumarin (37) by heating equimolar quantities of cinnamic acid and phenol for 30 minutes at 130-40°C in the presence of conc.H_2SO_4. They also reported the formation of 37 by refluxing phenyl cinnamate with 70% H_2SO_4 for 30 minutes.



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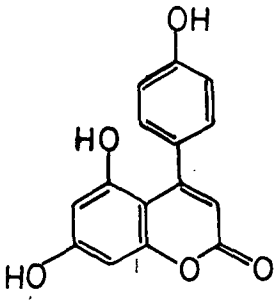
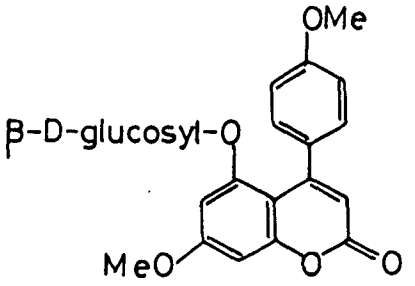


Nivegin
(Ref. 31)



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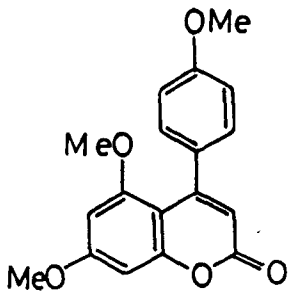
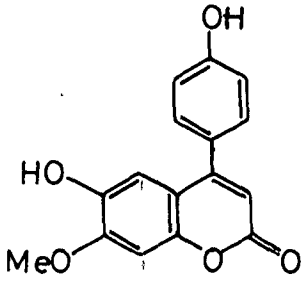
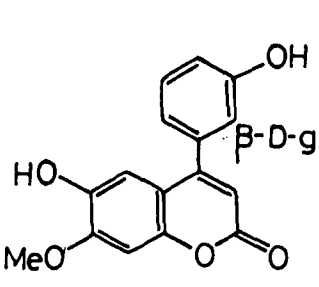


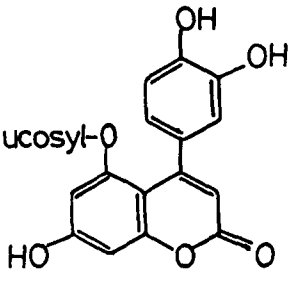
(Ref 33,34)



Melanettin
(Ref. 35, 36)



Stevenin
(Ref. 37, 38)



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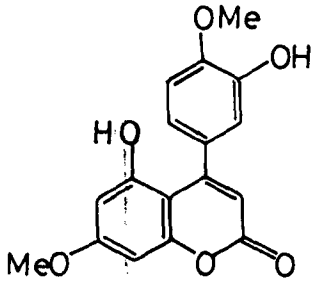

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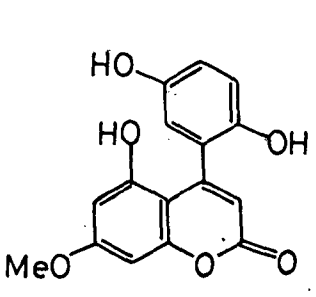

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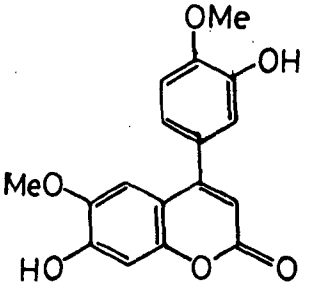

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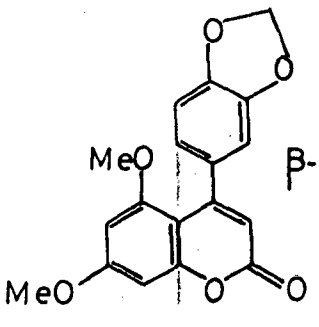
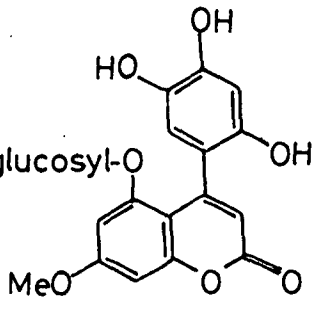


(Ref. 33, 42)



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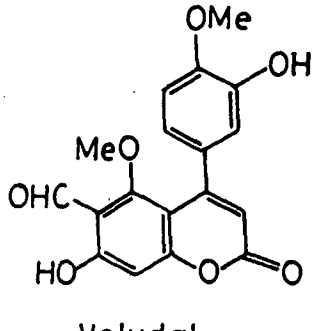


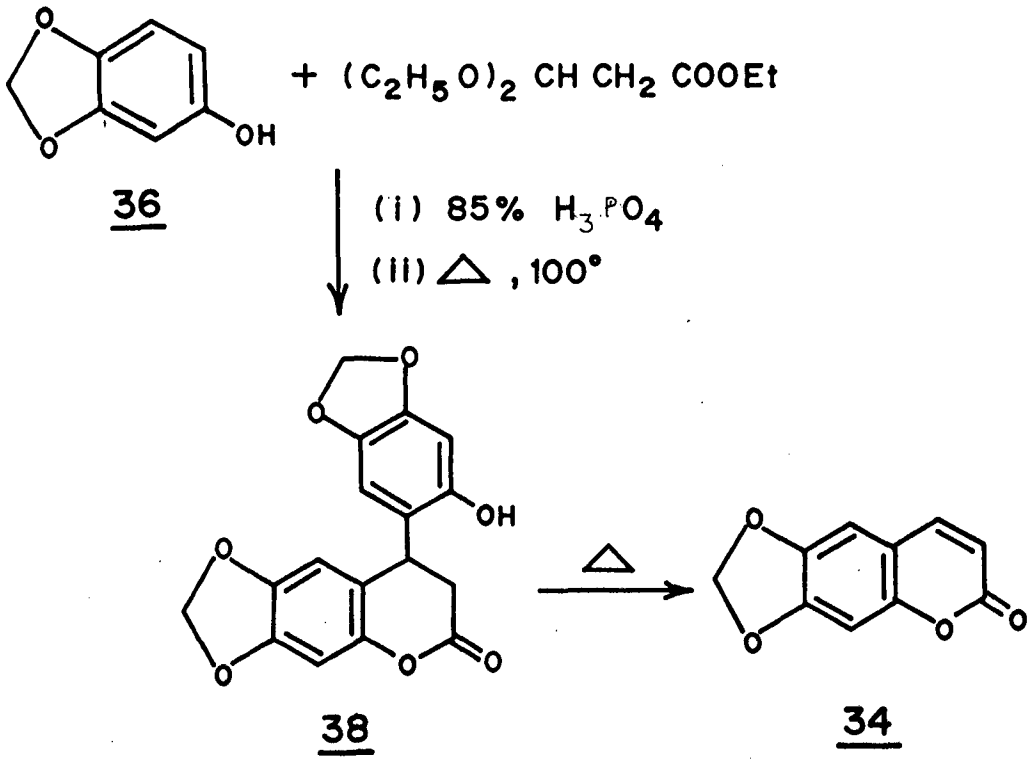
Voludal
(Ref. 44)

Chart-3*

* Only some representative examples are listed

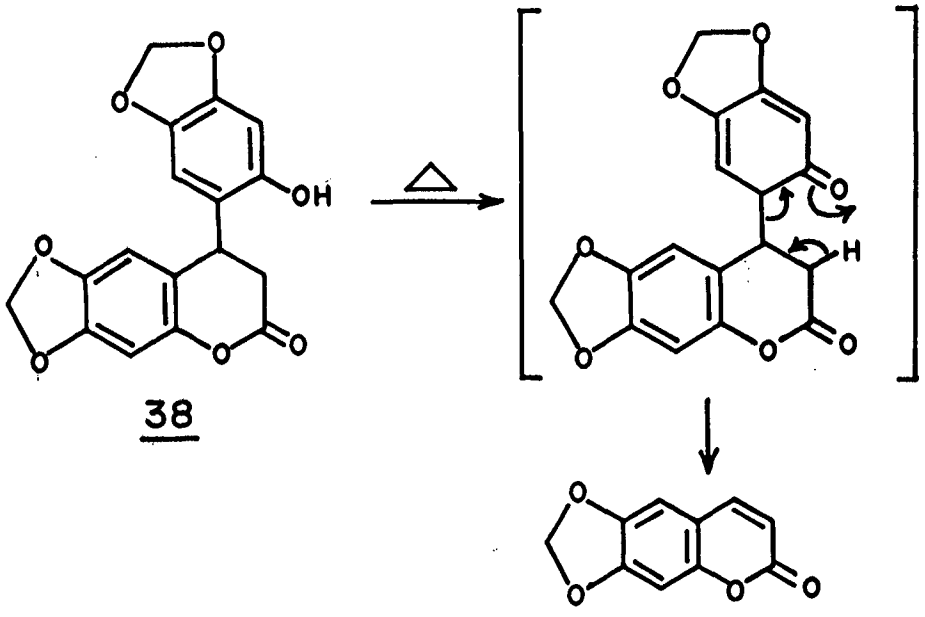
In 1962, Crosby and Berthhold[20] observed the formation of 3,4-dihydro-4-(3′,4′-methylene dioxy-6′-hydroxy phenyl)-6,7-methylene dioxy coumarin (38) when 3,4-methylene dioxy phenol (36) and ethyl 3,3-diethoxy propionate were added to 85% phosphoric acid at room temperature followed by heating on steam bath for 1 hour (Scheme-6). Formation of 38 was considered to be the result of Michael addition of 3,4-methylene dioxy phenol (36) to the initially formed ayapin (34).

These authors further made an interesting observation that 38 formed ayapin (34) when heated in vaccuo above its melting point. Thermal dearylation which is observed in this case appears to be specific for this coumarin and the position of the phenolic hydroxyl group is very important for the thermal dearylation. Though Crosby and Berthhold did not comment on its mechanism, a rational mechanism has been proposed for this reaction (scheme-7).



36 38 34

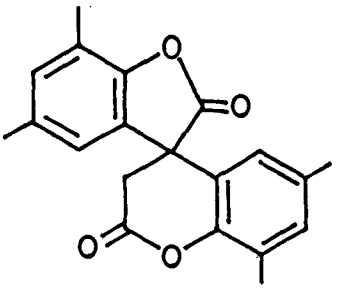
Scheme-6



38 34

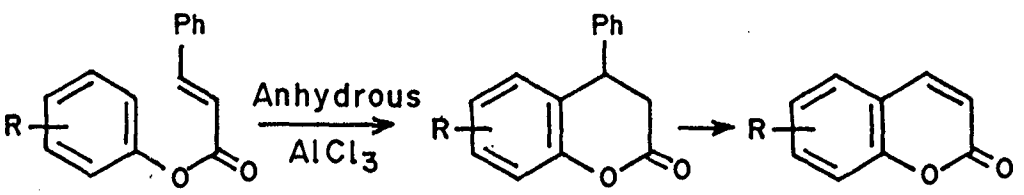
Scheme-7

Smith and Bealor[21] observed that reaction of two moles of 2,4-xylenol with one mole of diethyl keto succinate and dilactonisation results in the formation of the γ-δ-spirodilactone 39. Isolation



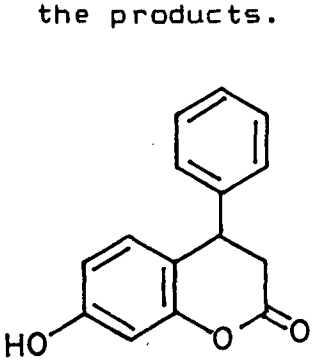
39

of 3,4-dihydro-4-aryl coumarins as intermediates was also reported by Manimaran and Ramakrishnan[10] during their coumarin synthesis by the condensation of cinnamoyl derivatives of phenols with anhydrous aluminium chloride (scheme-8). These 3,4-dihydro-4-aryl coumarins have been shown to undergo dearylation on further heating with anhydrous $AlCl_3$ in chlorobenzene at 95°.



Scheme-8

Ramana and Kudav[22] reported the formation of 7-hydroxy-3,4-dihydro-4-phenyl coumarin (40) in the reaction of N-formamido-3-phenyl-2-propanamide with resorcinol in the presence of PPA at 130° for 5 hours. Lastly the publication of Talapatra and co-workers[23] which led to our coumarin synthesis also describes the formation of 7-methoxy-3,4-dihydro-4-(p-methoxyphenyl)coumarin (41) as one of the products.



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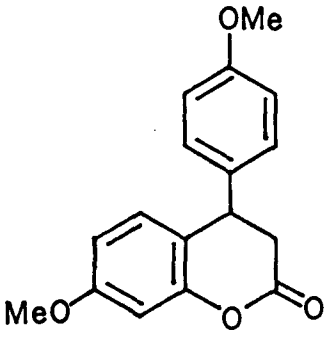

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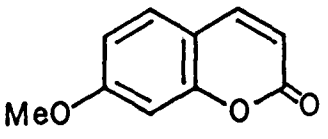


32

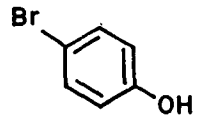
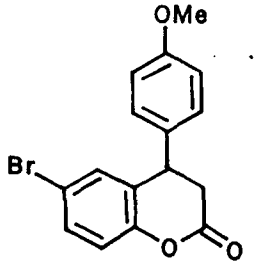
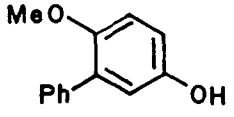
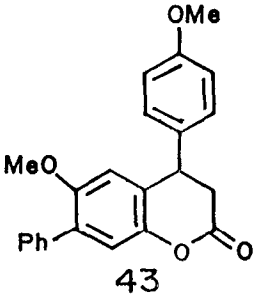
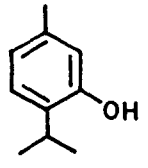
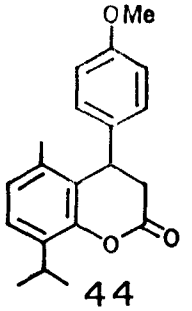
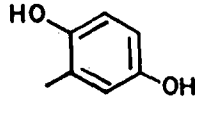
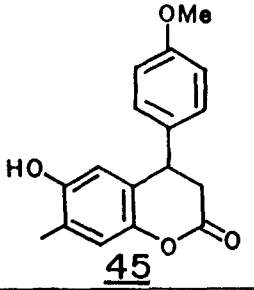
Very recently, Kirtany[24] on the basis of reinterpretation of the published spectral data has shown that the reaction of phenols with cinnamic acids in the presence of trifluoroacetic acid (TFA) yield 3,4-dihydro-4-aryl coumarins and not benzofuranones as proposed earlier by Chaturvedi and Mulchandani[25].

As mentioned before several 4-aryl coumarins have been isolated as natural products. In principle, introduction of C_3-C_4 double bond (dehy-

drogenation) in the 3,4-dihydro-4-aryl coumarins should be possible using quinones such as DDQ, chloranil etc. thus providing an alternative method of synthesis of 4-aryl coumarins.

While clarifying the mechanism of the formation of 7-methoxy coumarin (32) in the reaction of 3-methoxy phenol and p-methoxy cinnamic acid in the presence of PPA we had proposed that 3,4-dihydro-4-aryl coumarins are obligatory intermediates and further dearylation of these intermediates finally results in the formation of coumarins[3]. In the course of our studies we could isolate 3,4-dihydro-4-(p-methoxy phenyl) coumarins only or accompanied by the corresponding coumarins in few cases having different substituents on the benzenoid ring. The details of this work where only 3,4-dihydro-4-aryl coumarins were formed are reported in this section. The reactions wherein both the intermediates and coumarins were formed and characterised are reported under a separate section (Part-II, Chapter 3.1 and 3.4). The compounds obtained during this study are listed in (Table-4). 3,4-dihydro-4-aryl coumarins could be easily distinguished from the corresponding couma-

Table-4*

Phenol	Acid	Product	m.p.	Ref.
		 42	147°	Present study
	〃	 43	161°	〃
	〃	 44	115°	〃
	〃	 45	163°	〃

* All the reactions were carried out in the presence of PPA at 70° for 4 hours

rins by the absence of characteristic fluorescence under short-wave UV illumination, presence of infra red carbonyl band around 1770 cm^{-1} and presence of ^{1}H nmr signals for the grouping ar-CH-CH$_2$-C(=O)-O-. Whenever these 3,4-dihydro-4-aryl coumarins were accompanied by the corresponding coumarins, the Rf value and blue fluorescence on the TLC plate was of great help in their identification.

The 3,4-Dihydro -4-aryl coumarins obtained during the present studies were characterised by spectral analysis (Table-5).

Table – 5

Compound	IR ν_{max} cm^{-1}	^{1}H nmr ($CDCl_3$) δ ppm
42	1780[a]	3·071 (2H, d, J=7Hz, $-\underset{1}{CH}-C\underline{H}_2-$) 3·91 (3H, S, $-OC\underline{H}_3$) 4·37 (1H, t, J=7Hz, $\underset{1}{C\underline{H}}-CH_2-$) 7.00–7.627 (7H, m, Ar–H)
43	1770[b]	2·98 (1H, dd, J= 7·5& 14Hz, C_3-Ha) 3·083 (1H, dd, J=6 & 14Hz, C_3-Hb) 3·66 (3H, s, $-OC\underline{H}_3$) 3·82 (3H, s, $-OC\underline{H}_3$) 4·32 (1H, dd, J=6 & 7·5Hz, C_4-H) 6·56 (1H, d, J=0·5Hz, Ar – H.) 6·91 (2H, d, J=9Hz, $C_{3'}-H$ & $C_{5'}-H^s$) 7·13 (1H, s, Ar – H) 7·14 (2H, d, J=9Hz, $C_{2'}-H$ & $C_{6'}-H^s$) 7·32–7·54 (5H, m, Ar–H)

a: in nujol
b: in KBr

Table - 5 (contd.)

Compound	IR ν_{max} cm^{-1}	^1H nmr ($CDCl_3$) δ ppm
44	1770[a]	1·22 (3H, d, J = 7Hz, $CH_3-\underset{|}{C}H-CH_3$) 1·28 (3H, d, J = 7Hz, $CH_3-\underset{|}{C}H-CH_3$) 2·11 (3H, s, $-CH_3$) 2·97 (2H, d, J = 5Hz, $-\underset{|}{C}H-CH_2$) 3·42 (1H, quintet, J = 7Hz, $CH_3-\underset{|}{C}H-CH_3$) 3·71 (3H, s, $-OCH_3$) 4·33 (1H, t, J = 5Hz, $-\underset{|}{C}H-CH_2-$) 6·71–7·233 (6H, m, Ar–H)
45	1750[b]	2·26 (3H, s, $-CH_3$) 3·00 (2H, m, $-\underset{|}{C}H-CH_2$) 3·88 (3H, s, $-OCH_3$) 4·29 (1H, t, J = 6·4Hz, $-\underset{|}{C}H-CH_2-$) 4·84 (1H, s, $-OH$) 6·48 (1H, s, Ar–H) 6·96–7·54 (5H, m, Ar–H)

a: in nujol
b: in KBr

P A R T - II

CHAPTER - 4

SECTION - 2

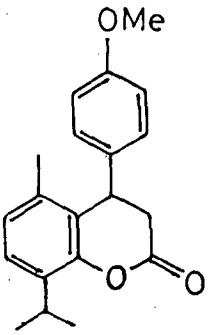
REACTION OF 5-METHYL-8-ISOPROPYL-4(P-METHOXYPHENYL)-3,4-DIHYDRO COUMARIN WITH $AlCl_3$ IN CHLOROBENZENE

4.2 REACTION OF 5-METHYL-8-ISOPROPYL-4-(P-METHOXY PHENYL)-3,4-DIHYDRO COUMARIN WITH $AlCl_3$ IN CHLORO-BENZENE:

In 1975, Manimaran and Ramakrishnan[26] showed that the reaction of phenyl cinnamates with anhydrous $AlCl_3$ either neat or in chlorobenzene affords coumarins via insitu dearylation of 3,4-dihydro-4-aryl coumarins. The solvent used (chlorobenzene) plays a very important role as no dearylation was observed when chlorobenzene was replaced by carbontetrachloride. This method of dearylation of 3,4-dihydro-4-aryl coumarins has been used by us successfully to prepare substituted coumarins.

During the course of present investigation, we had prepared 5-methyl-8-isopropyl-3,4-dihydro--4-(p-methoxyphenyl) coumarin (44). By using the dearylation method of Manimaran and Ramakrishnan[10] we thought of preparing 5-methyl-8-isopropyl coumarin (46) from 44. Treatment of 44 with anhydrous $AlCl_3$ in chlorobenzene, however, did not afford the desired coumarin 46, but the reaction product was found to be a mixture of two compounds X, m.p. 100°C and Y, m.p. 184°C.

The IR spectrum of compound 'X', m.p.100°C showed the presence of carbonyl band at 1770 cm^{-1} indicating that the 4-aryl substituent is still intact but the product is certainly different from 44 (IR, TLC, m.p.). Its ^1H nmr was found to be more useful and showed the absence of isopropyl substituent. Such elimination of isopropyl substituents has been observed before by other investigators[27,28] under these experimental conditions. The ^1H nmr data (Table-6) clearly showed structure 47 for 'X'. The structure assigned was further confirmed by ^{13}C nmr data (assignments are as shown).



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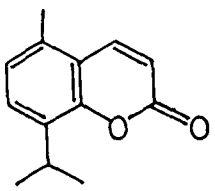

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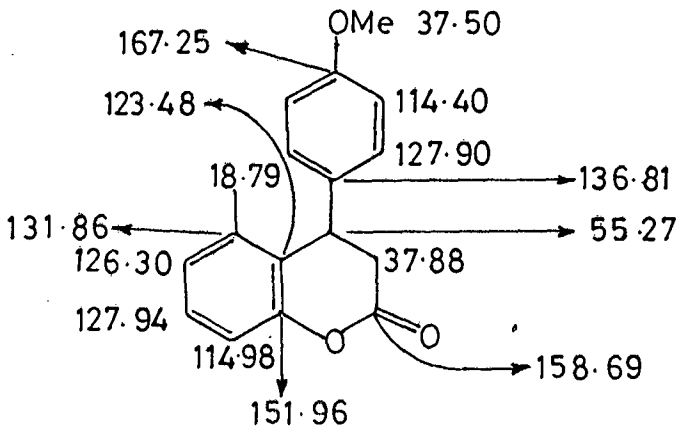


47

Table – 6

^1H nmr ($CDCl_3$) for compound 47

Proton	δ ppm
$C_5 - C\underline{H}_3$	2·192, s
$C_3 - 2H$	3·02, m
$C_4' - OC\underline{H}_3$	3·752, s
$C_4 - H$	4·365, dd, J=6 & 3 Hz
$C_3' - H$	6·80, d, J = 9Hz
$C_5' - H$	6·80, d, J = 9Hz
$C_2' - H$	6·98, d, J=9Hz
$C_6' - H$	6·98, d, J= 9Hz
ar – H	6·95 – 7·25, m

The second compound, the higher melting point and the polar substance having m.p.184°C was assigned structure 48 on the basis of ^{1}H nmr (Table-7) spectral analysis and further supported by its ^{13}C nmr spectra (refer experimental section).

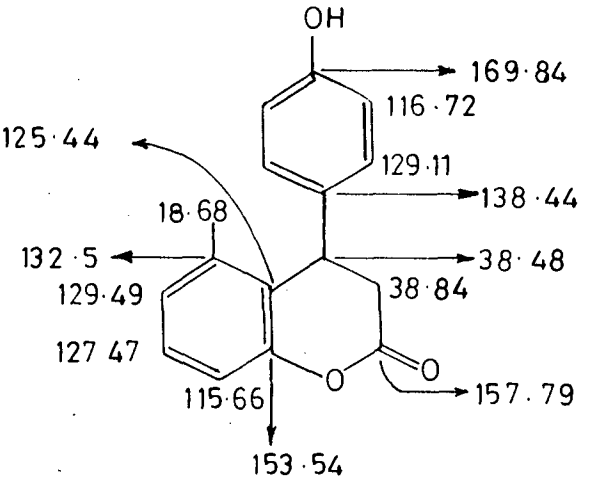
While Manimaran and Ramakrishnan[10] observed dearylation of the 4-aryl substituent of 3,4-dihydro-4-aryl coumarins in the presence of anhydrous $AlCl_3$ in chlorobenzene, the observations of the present study clearly show that elimination of isopropyl substituent takes place in preference to dearylation. The demethylation of the 4'-methoxy substituent rather than dearylation after the elimination of isopropyl substituent appears to be interesting. Isolation of 48 is important from mechanistic point of view as in all the previous studies cleavage of the alkoxy substituent has not been reported. It is quite likely that dearylation is preceded by demethylation the net elimination being the phenol and not anisole. However, we do not have any evidence in support or otherwise of this pathway at this stage.

Table - 7

^1H nmr ($CDCl_3$) for compound 48

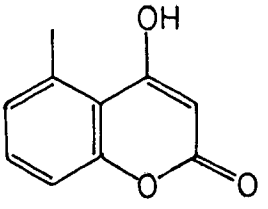
Proton	δ ppm
$C_5 - C\underline{H}_3$	2·17 , s
$C_3 -$ Ha	2·89, dd, J=2·5 & 16 Hz
$C_3 -$ Hb	3·11, dd, J=7 & 16 Hz
$C_4 -$ H	4·45, dd, J=2·5 & 7Hz
$C_4' -$ O<u>H</u>	4·87, s
C_3' & C_5'–2H	6·67, d, J=9Hz
C_2' & C_6'–2H	6·84, d, J=9Hz
ar – H	6·95 – 7·25, m

^{13}C nmr ($CDCl_3$) for compound 48



48

The deisopropylation observed in the present study has been used by us successfully to develop a new improved synthesis of 4-hydroxy-5-methyl coumarin using the isopropyl substituent of thymol as blocking group. Deblocking takes place under the experimental conditions used and provides a better method for the synthesis of 41a. The details have been incorporated in this Thesis (Part-I, Chapter 2.1).



41a

PART - II

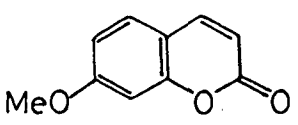
CHAPTER - 4

SECTION - 3

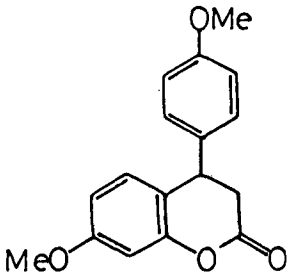
A SIMPLE ONE STEP PREPARATION OF 3,4-DIHYDRO -4(P-METHOXYPHENYL) COUMARINS

4.3 A SIMPLE ONE-STEP PREPARATION OF 3,4-DIHYDRO-4-(P-METHOXY PHENYL) COUMARINS :

We had suggested earlier that the reaction of phenols with p-methoxy cinnamic acid in the presence of PPA gives coumarins as a result of insitu dearylation of the 3,4-dihydro-4-aryl coumarin intermediates (Part-I, Chapter-1.1). Isolation of these intermediates in certain cases was taken as an additional proof in support of our mechanism. It was of interest to see whether we can find out experimental conditions where we can stop the reaction yielding only 3,4-dihydro- 4-aryl coumarins. Variation of temperatures and the reaction periods in the PPA reaction did not yield any encouraging results. In fact in one case where Talapatra et al.[23] had reported the formation of 7-methoxy-4-(p-methoxy phenyl)-3,4-dihydro coumarin (41), we obtained directly 7-methoxy coumarin (32) even when the reaction time was reduced to 30 minutes in place of 4 hours. In a similar way, our attempt to prepare 5,7-dimethoxy-4-(p-methoxy phenyl)-3,4-dihydro coumarin (49) by the reaction of phloroglucinol dimethyl ether (50) and p-methoxy cinnamic acid in the presence of PPA at 70° for 15 minutes failed to give the desired product 49 and we obtained only 5,7-dimethoxy coumarin (51). Lowering



32



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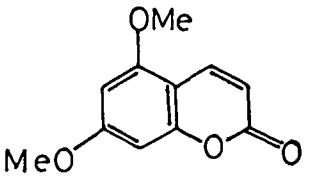

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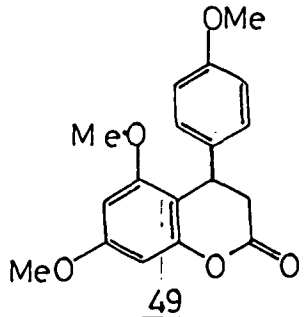

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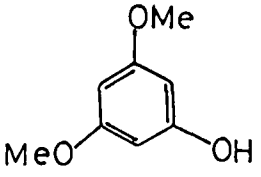
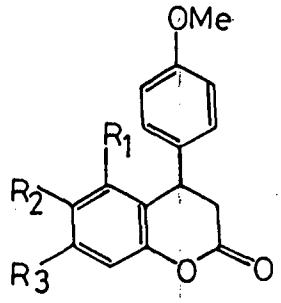


50

the temperatures in the case of PPA poses practical difficulties because of the viscosity of the reaction mixture. We, therefore, considered to carry out the reaction of phenols with p-methoxy cinnamic acid using the Pechmann reaction conditions. Considering the poor solubility of p-methoxy cinnamic acid in aqueous medium, we selected dioxane as co-solvent and carried out the reaction at room temperature for 2 hours. Under these conditions it was found that besides unchanged p-methoxy cinnamic acid only 3,4-dihydro-4-(p-methoxy phenyl) coumarins were formed. We could not detect any dearylation product (absence of any fluorescent spot on TLC, UV visualisation).

The reaction of four phenols viz. 3,4,5-trimethoxy phenol, resorcinol monomethyl ether, m-cresol, and 3,4-methylenedioxy phenol (sesamol) yielding the corresponding 3,4-dihydro-4-(p-methoxy phenyl) coumarins is

described in this section. Besides finding out suitable experimental conditions to yield the intermediates 12a-12d, the other purpose of this investigation was



12

a : $R_1 = R_2 = R_3 = OMe$

b : $R_1 = R_2 = H$; $R_3 = OMe$

c : $R_1 = R_2 = H$; $R_3 = Me$

d : $R_1 = H$; $R_2\,R_3 = -O-CH_2-O-$

that these intermediates can be converted by further oxidation (dehydrogenation) with DDQ or equivalent to 4-aryl coumarins. It may be mentioned here that several 4-aryl coumarins have been isolated as natural products and hence synthesis of this group of naturally occurring coumarins would be possible by a relatively simple and new method. Few representative naturally occurring 4-aryl coumarins are shown in Chart-3(Part-II, Chapter 4.1).

The general procedure is as follows. To an equimolar mixture of phenol and p-methoxy cinnamic acid dissolved in minimum volume of dioxane, 75% H_2SO_4 is

added and the resultant solution is stirred vigorously at room temperature for 2 hours. The reaction mixture is then poured over crushed ice and extracted with $CHCl_3$ or EtOAc. Removal of organic solvent after drying over anhydrous Na_2SO_4 followed by chromatography gives the 3,4-dihydro-4-(p-methoxyphenyl) coumarin (with different substituents on the aromatic ring depending on the structure of phenol used).

By using this procedure we have prepared the dihydrocoumarins 12a to 12d. All these have been characterised by spectral analysis (IR, ^1H nmr) further supplemented by molecular weight determination either by mass spectrometry or elemental analysis. The spectral details are presented in Table-8. We were able to collect ^{13}C nmr data on 12c which is fully consistent with the assigned structure.

After completion of this work, we came across a paper by Chaturvedi and Mulchandani[25] reporting the condensation of phenols and cinnamic acids in the presence of trifluoroacetic acid. These authors characterised the products of this reaction as 2-(3H)-benzofuranones 52. In a recent communication the spectral data has been reinterpreted by Kirtany[24] and the products have been shown to be 3,4-dihydro-4-aryl coum-

Table–8

Compound	IR $\nu_{max}^{cm^{-1}}$	^{1}H nmr ($CDCl_3$) δ ppm
12a	1780 (nujol)	2·95 (2H, d, J=4Hz, $-\underset{1}{C}H-C\underline{H}_2-$)
		3·65 (3H, s, $-OC\underline{H}_3$)
		3·73 (3H, s, $-OC\underline{H}_3$)
		3·81 (3H, s, $-OC\underline{H}_3$)
		3·85 (3H, s, $-OC\underline{H}_3$)
		4·50 (1H, t, J=4Hz, $-\underset{1}{C}\underline{H}-CH_2-$)
		6·48 (1H, s, C_8-H)
		6·78 (2H, d, J= 8Hz, C_3'&$C_5'-H^s$)
		7·00 (2H, d, J=8Hz, C_2'&$C_6'-H^s$)
12b	1780 (nujol)	2·95 (1H, dd, J=8 & 14Hz, C_3-Ha)
		3·04 (1H, dd, J=6 & 14Hz, C_3-Hb)
		3·79 (3H, s, $-OC\underline{H}_3$)
		3·81 (3H, s, $-OC\underline{H}_3$)
		4·24 (1H, dd, J=6 & 8Hz, $\underset{1}{C}\underline{H}-CH_2-$)
		6·62 (1H, d, J= 2·5 Hz, C_8-H)
		6·66 (1H, dd, J=2·5 & 9Hz, C_6-H)
		6·87 (3H, d, J=9Hz, C_5, C_3'& $C_5'-H$)
		7·065 (2H, d, J=9Hz, C_2'&$C_6'-H$)

Table-8 (contd.)

Compound	IR $\nu_{max}^{cm^{-1}}$	^{1}H nmr ($CDCl_3$) δ ppm
12c	1770 (nujol)	2·35 (3H, s, $-C\underline{H}_3$)
		2·95 (1H, dd, J=8 & 15·5 Hz, C_3-Ha)
		3·029 (1H, dd, J=6 & 15·5 Hz, C_3-Hb)
		3·79 (3H, s, $-O\,C\underline{H}_3$)
		4·25 (1H, t, J=6 Hz, $-C_1\underline{H}-CH_2-$)
		6·83-7·25 (7H, m, Ar-H)
12d	1760 (nujol)	3·007 (1H, dd, J=8 & 16Hz, C_3-Ha)
		3·06 (1H, dd, J=6 & 16 Hz, C_3-Hb)
		4·05 (3H, s, $-OC\underline{H}_3$)
		4·24 (1H, t, J=6Hz, $-C_1\underline{H}-CH_2-$)
		6·57 (2H, s, $-O-C\underline{H}_2-O-$)
		6·79 (1H, s, C_8-H)
		6·92 (1H, s, C_5-H)
		7·04 (2H, d, J=9Hz, C_3' & C_5'-H)
		7·13 (2H, d, J=9Hz, C_5' & C_6'-H)

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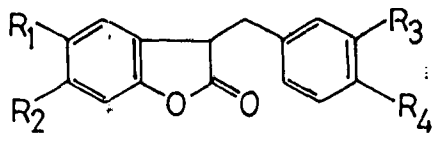

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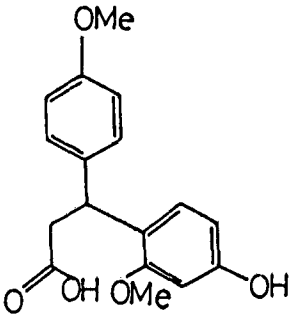
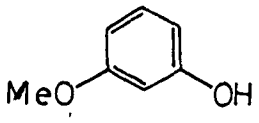


53



54

It may be mentioned that the acidic portion though mainly contained the unchanged p-methoxy cinnamic acid, we could isolate and characterise ββ-(2-methoxy-4-hydroxyphenyl)-p-methoxyphenyl propionic acid (53) in the reaction of 3-methoxy phenol (54) and p-methoxy cinnamic acid. The isolation of this can be explained by formation of a new C-C bond, p- with respect to phenolic hydroxyl and o- to the methoxy substituent of 54 in an alternate mode of conjugate addition.

Because of the simplicity and inexpensive nature of the reagents used compared to TFA, our procedure is superior to that of Chaturvedi and Mulchandani[25] and we believe that it can serve as a general method for the preparation of additional compounds of this group. We

are currently engaged in developing a further simpler method for the synthesis of 3,4-dihydro-4-aryl coumarins.

P A R T - II

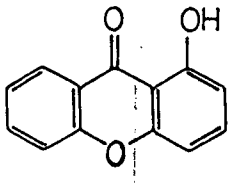
CHAPTER - 4

SECTION - 4

REACTION OF 3- AND 5-HYDROXYBENZISOXAZOLES AND 2-ACETYL RESORCINOL WITH P-METHOXY CINNAMIC ACID IN THE PRESENCE OF PPA

4.4 REACTION OF 3-AND 5- HYDROXY BENZISOXAZOLES AND 2-ACETYL RESORCINOL WITH P-METHOXY CINNAMIC ACID IN THE PRESENCE OF PPA

In connection with our studies towards preparation of pyranoxanthones (xanthano coumarins), it was observed that 1-hydroxy xanthone (23) and 3-hydroxy xanthone (24) do not produce the corresponding pyranoxanthones 20a(R=H) and 20b(R=R_1=H) and/or 20c(R=R_1=H) respectively when condensed with p-methoxy cinnamic acid



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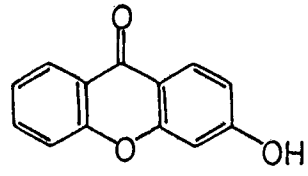

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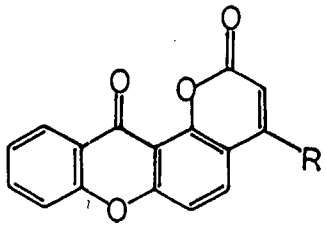
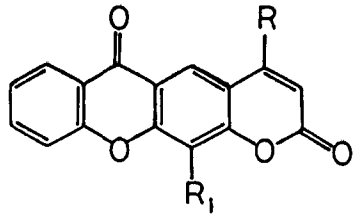
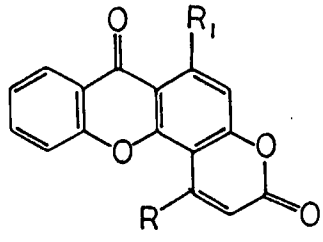


20a

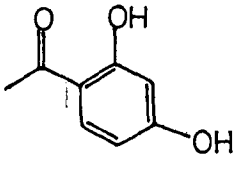


20b



20c

in the presence of PPA. Similarly phenols with electron withdrawing substituents are found to be inert and do not give either 3,4-dihydro-4-aryl coumarins or the coumarins when reacted with p-methoxy cinnamic acid in the presence of PPA. In this connection the previous observation from this laboratory seemed of particular interest because, resacetophenone (55) gave 5-hydroxy-6-acetyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin (56) on reaction with p-methoxy cinnamic acid in the presence of PPA at 70° for 4 hours. Resacetophenone (55) is also reported to react with ethyl aceto acetate (57) in the presence of conc. H_2SO_4 to give 4-methyl-5-hydroxy-6-acetyl coumarin (58).



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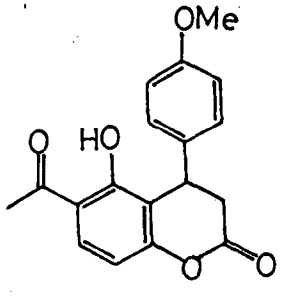

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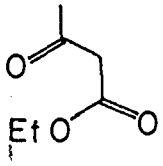

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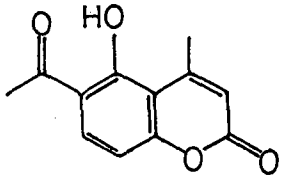
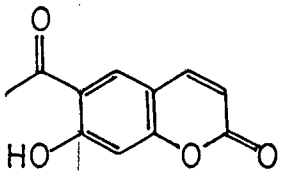
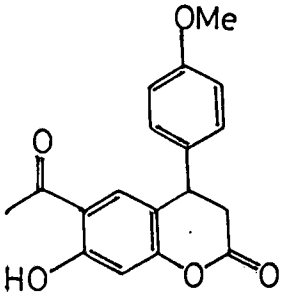


58

These two reactions show that the new C-C bond is formed ortho to both phenolic hydroxyls and meta with respect to the acyl group. It was, therefore, of interest to see whether protecting together the o-hydroxy acetophenone grouping in any form and then subjecting the product for condensation with p-methoxy cinnamic acid would afford 6-acetyl-7-hydroxy coumarin (59) or the intermediate 60.



59



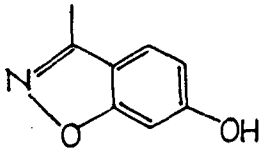
60

Literature survey indicated that o-hydroxy acetophenone oximes on treatment with base afford isoxazoles. Although under acid conditions, isoxazoles are expected to revert back to o-hydroxy acetophenone (via oxime intermediates) or produce the corresponding Beckmann rearrangement product/s we still considered it worthwhile to study the reaction of isoxazoles 61 and 62 with p-methoxy cinnamic acid in the presence of PPA. The products formed in the above reaction were expected to throw light on the reactivity of hydroxy benzisoxazoles

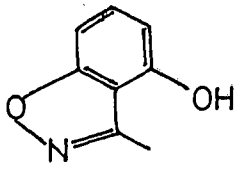
when compared to the resacetophenone (55) and 2-acetyl resorcinol (63).

Isoxazoles 61 and 62 were prepared by reaction of oximes of resacetophenone and 2-acetyl resorcinol with KOH using literature procedure[30] and characterised by their physical constants.

Treatment of isoxazole 61 with p-methoxy cinnamic acid in the presence of PPA gave only 5-hydroxy-6-acetyl-4-(p-methoxyphenyl)-3,4-dihydro coumarin (56) with trace quantities of other compounds (TLC). The purified



61



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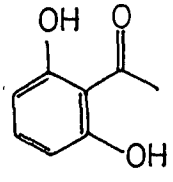
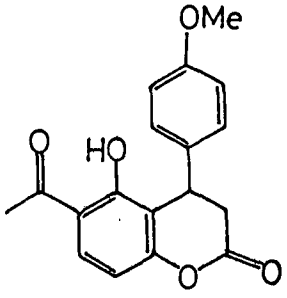


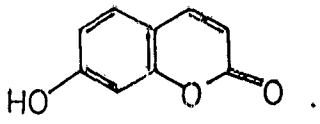
63



56

product m.p. 177° was found to be identical in all respects with 56 prepared earlier by using resacetophenone as starting material. Formation of only 56 clearly shows that isoxazole 61 first gives resacetophenone which inturn reacts with p-methoxy cinnamic acid in the manner observed earlier. The reaction of 3-hydroxy benzisoxazole 62 under identical experimental conditions gave a crystalline product m.p. 155° which is yet to be characterised.

In the case of reaction using 2-acetyl resorcinol as starting material, the product m.p. 228°, did not contain the acetyl grouping indicating the initial loss of {-CO-CH_3 group prior to or after the formation of coumarin. The product of the reaction turned out to be 7-hydroxy coumarin (64). since dearylation also takes place, in all probability the loss of {-CO-CH_3 group takes place prior to the condensation with p-methoxy cinnamic acid. In short 2-acetyl resorcinol gets converted to resorcinol first by a retro-Friedel-Crafts acylation reaction and then follows the normal course. Talapatra and Co-workers have reported the formation of 7-hydroxy coumarin (64) in the reaction of resorcinol and p-methoxy cinnamic acid under the above reaction conditions.[23]



64

In conclusion, we can state that blocking of o-hydroxy acetophenone grouping by converting it into isoxazole derivative is not useful in the above condensation reactions. The alternative method for the preparation of 59 appears to be the preparation of 6-ethyl--7-hydroxy coumarin and then oxidation of the Ar-CH_2CH_3 to Ar-CO-CH_3 by known oxidation methods*.

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* Paradkar and co-workers have observed this conversion in excellent yields (>90%) by oxidation with CAN^{14}.

EXPERIMENTAL

Synthesis of coumarins by the condensation of phenols and p-methoxy cinnamic acid in the presence of PPA.

General Procedure

A solution of polyphosphoric acid (PPA) was prepared by stirring a mixture of P_2O_5 (10.0 g, 70 mmole) and 85% orthophosphoric acid (7 mL) in an oil bath at 110° using an overhead stirrer under anhydrous conditions until a free flowing clear solution was obtained. This was then cooled to 70°.

An appropriate phenol (1 mmole) and p-methoxy cinnamic acid (1 mmole) were then added in quick succession to the above solution of PPA and the resulting solution was stirred at 70° for 4 hours. The reaction mixture was then cooled to room temperature and poured over crushed ice (50 g). This was kept overnight and then extracted with $CHCl_3$ or EtOAc. The organic extracts were washed with sat. brine and dried. Evaporation of the solvent gave a viscous liquid which was chromatographed on silica gel using benzene containing increasing amounts of EtOAc to give several fractions which were monitored by TLC, the plates visualised under

short wave UV illumination. The fractions containing the coumarins and the 3,4-dihydro coumarins were combined separately and concentrated. The solid coumarins were recrystallised from benzene - petroleum-ether or $CHCl_3$ - petroleum-ether.

Spectral data of individual coumarins synthesised by the above method

7-Methyl coumarin (1) : 54%, m.p. 126°. (lit.[2] m.p.124-26°).

IR (ν max, nujol) : 1725, 1710, 1635, 1485, 1395, 1150, 1125, 905, 865, 830, 770. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.1) : 2.452 (3H, s, $-CH_3$); 6.352 (1H, d, J=9.5 HZ, C_3-H); 7.09 (1H, dd, J=8 & 2 HZ, C_6-H); 7.142 (1H, dd, J=2 & 0.4 Hz, C_8-H); 7.360 (1H, d, J=8 Hz, C_5-H); 7.668 (1H, dd, J=9.5 & 0.4 Hz, C_4-H).

^{13}C nmr (300 MHz, $CDCl_3$, δ) ppm; (multiplicity) (Fig.2) :21.43 (q), 115.12 (d), 116.12 (s), 116.73 (d), 125.24 (d), 127.15 (d), 142.75 (s), 143.01 (d), 153.83 (s), 160.75 (s)

6,7-Dimethyl coumarin (4) : 55%, m.p. 153°.

IR (ν max, nujol) : 1725, 1635, 1570, 1475, 1395,1280, 1260, 1205, 1130, 1030, 925, 890, 875, 850, 790. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.3) : 2.293 (3H, s, $-CH_3$); 2.342 (3H, s, $-CH_3$); 6.330 (1H, d, J=9.5 Hz, C_3--H); 7.10 (1H, s, C_5-H); 7.21 (1H, d, J=0.4 Hz,C_8-H); 7.623 (1H, dd, J=9.5 & 0.4 Hz, C_4-H)

^{13}C nmr (300 MHz, $CDCl_3$, δ) ppm; (multiplicity) (Fig. 4) : 18.80 (q), 19.97 (q), 115.08 (d), 116.26 (s), 117.05 (d), 127.54 (d), 132.79 (s), 141:55 (s), 142.95 (d), 152.12 (s), 160.98 (s)

6,7-Dimethyl-3,4-dihydro-4-(p-methoxy phenyl) coumarin (6) : 14%, m.p. 116°

IR (ν max, nujol) : 1770, 1530, 1480, 1420, 1395, 1330, 1265, 1190, 1155, 1060, 1045, 980, 920 900, 835. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.5) : 2.171 (3H, s, $-CH_3$); 2,285 (3H, s, $-CH_3$); 3.00 (2H, d, J=6.4 Hz, $-\overset{1}{C}H-CH_2-$); 3.827 (3H, s, $-OCH_3$); 4.285 (1H, m, $-\overset{1}{C}H-CH_2-$); 6.855-7.370 (6H, m, ar-H)

7,8-Dimethyl coumarin (5) : 59%, m.p. 134°.

IR (ν_{max}, KBr) : 1730, 1620, 1575, 1430, 1395, 1280, 1255, 1190, 1165, 1135, 1090, 1050, 945, 860, 845, 830, 815, 765, 705 cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig. 6) : 2.38 (3H, s, $-CH_3$); 2.42 (3H, s, $-CH_3$); 6.34 (1H, d, J=10 Hz, C_3-H); 7.08 (1H, d, J=8 Hz, C_6-H); 7.22 (1H, d, J=8 Hz, C_5-H); 7.66 (1H, d, J=10 Hz, C_4-H)

3-Methyl-4-benzyl (8) and 3-methyl-4,6-dibenzyl phenol (9) from m-cresol : A mixture of benzyl chloride (1.15 mL, 10 mmole) and m-cresol (1.10 mL, 10 mmole) was refluxed for 8 hours while monitoring the progress of the reaction on TLC after every 1 hour. The reaction mixture was then cooled to room temperature and extracted with diethyl ether. The ether extracts were washed with 2N NaOH (3x25 mL), water and sat. brine and dried. Evaporation of the solvent gave a gummy liquid which was chromatographed on silica gel using benzene as an eluent to give an oil. The oil was distilled under reduced pressure. The distillate on standing at room temperature for over 20 days gave a solid. Recrystallisation from benzene - petroleum-ether gave white needles of 8 (0.12 g, 10%), m.p. 95°. (lit[7]. mp.93-94°).

IR (ν max, KBr) (Fig.7) : 3300, 1610, 1590, 1510, 1500, 1470, 1455, 1360, 1320, 1315 1295, 1260, 1215, 1190, 1160, 1100, 1080, 1030, 1010, 960,950, 940, 860, 820, 780, 730, 700. cm^{-1}

^1H nmr (60 MHz, $CDCl_3$, δ) (Fig.8) : 2.25 (3H, s, $-CH_3$); 3.95 (2H, s, ar-CH_2-ar); 4.63 (1H, s, -OH); 6.65 (1H, s, C_2-H); 6.8-7.5 (7H, m, ar-H)

The undistilled portion of the oil on cooling to room temperature generated solid which on recrystallisation from $CHCl_3$ - petroleum-ether afforded 9 as white needles (0.820 g, 54%), m.p. 109°.(lit.[7] m.p.106-107°).

IR (ν max, KBr) (Fig.9) : 3475, 1600, 1580, 1500, 1450, 1440, 1415, 1340, 1290, 1260, 1220, 1180, 1140, 1060, 1020, 940, 880, 860, 840, 780, 740, 720, 700.cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.10) : 2.15 (3H, s, CH_3); 3.90 (2H, s, ar-CH_2-ar); 3.945 (2H, s, ar-CH_2-ar); 4.50(1H, s, -OH, D_2O exchangeable); 6.62 (1H, s, C_5-H); 6.90 (1H, s, C_2-H); 7.09-7.31 (10H, m, ar-H)

3-Ethoxy-4-methoxy-benzaldehyde (18) from ethyl vanillin:

Anydrous K_2CO_3 (1.66 g, 12 mmole) was added to a solution of commercial grade ethyl vanillin (17, 2.0 g, 12 mmole) in dry acetone (20 mL). To this slurry was

added freshly distilled $(CH_3)_2SO_4$ (1.15 mL, 16 mmole) while stirring with an overhead stirrer over a period of 1 hour. The reaction mixture was then refluxed for 15 hours with simultaneous stirring and monitoring the progress of the reaction on TLC after every 1 hour. Since no change was observed on TLC, after 15 hours of stirring, 10% methanolic KOH[45] (0.5 mL) was added to the reaction mixture and it was stirred while refluxing for another 10 hours. This was then cooled and filtered. The residual K_2CO_3 was washed with acetone and filtered. Evaporation of the solvent from the combined filtrates gave a viscous liquid which was chromatographed on silica gel using petroleum-ether : benzene (75:25) to give a white solid. Recrystallisation from petroleum-ether afforded white needles of 18 (1.4 g, 65%), m.p.52°.

IR (ν max, nujol) : 1705, 1610, 1615, 1600, 1530, 1480, 1455, 1405, 1285, 1260, 1175, 1150, 1050, 1035, 905, 870, 820, 785, 755. cm^{-1}

Further elution using benzene:EtOAc (95:5) gave another white solid which was recrystallised from petroleum-ether to give white needles (0.5 g), m.p. 95°

IR (νmax, nujol) : 1725, 1680, 1660, 1635, 1610, 1535, 1475, 1460, 1445, 1375, 1275, 1245, 1175, 1150, 1115,

1050, 1030, 1020,985, 890, 815, 805, 785, 760. cm^{-1}

3-Ethoxy-4-methoxy phenol 19 : 3-Ethoxy-4-methoxy benzaldehyde (18, 0.8 g, 4.5 mmole) was dissolved in CH_2Cl_2 (2 mL). To this was added freshly prepared perbenzoic acid[46] (1.2 g, 8 mmole) in $CHCl_3$ (5 mL). The reaction mixture was magnetically stirred overnight. 10% $Na_2S_2O_4$ (3 mL) was then added to this and stirred for another 45 minutes. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with sat. brine and dried. The residue obtained on evaporation of solvent was dissolved in MeOH (3 mL). The solution formed was cooled in ice and to this was added 5% KOH (8 mL) slowly with stirring. The reaction mixture was magnetically stirred overnight, acidified with conc. HCl while cooling in ice and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine and dried. Evaporation of solvent gave a solid which was chromatographed on silica gel using petroleum-ether:benzene (50:50) to give a solid. Recrystallisation from EtOAc gave white needles (1 g) identified as benzoic acid (TLC, m.p., m.m.p., IR). Further elution with benzene gave another solid which on recrystallisation from benzene afforded white needles of 19 (0.23 g, 31%), m.p. 81°. (lit.[11] b.p.

175°; crystals from water gives a hydrate m.p. 92°).

IR (ν max, nujol) (Fig.11) : 3550, 3180, 1625, 1530, 1480, 1395, 1330, 1300, 1265, 1240, 1200, 1180, 1135, 1050, 1030, 995, 905, 830, 815, 780, 725. cm^{-1}.

6-Methoxy-7-ethoxy coumarin 16 : A mixture of 3-ethoxy-4-methoxy phenol (19, 0.166 g, 1 mmole) and p-methoxy cinnamic acid (0.178 g, 1 mmole) was stirred in PPA at 70° for 4 hours. Usual work up and purification by chromatography on silica gel using benzene:EtOAc (95:5) gave a solid which on recrystallisation from benzene afforded whitish needles of 16 (0.08 g, 31%), m.p. 143°.

IR (νmax, nujol) (Fig.12) : 1715, 1625, 1570, 1530, 1475, 1435, 1400, 1290, 1260, 1205, 1180, 1150, 1100, 1045, 1025, 935, 920, 885, 815. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.13) : 1.47 (3H, t, J=7 Hz, CH_3-CH_2-O-); 3.88 (3H, s, -OCH_3); 4.11 (2H, q, J=7 Hz, -CH_3-CH_2-); 6.30 (1H, d, J=9 Hz, C_3-H); 6.82 (2H, s, C_8-H & C_5-H); 7.63 (1H, d, J=9 Hz C_4-H).

1-Hydroxy xanthone (23) and 3-hydroxy xanthone (24) : A mixture of salol (4.28 g, 20 mmole) and resorcinol (2.2 g, 20 mmole) was pyrolysed at 325°. The reaction product obtained was cooled dissolved in benzene and then washed with sat. $NaHCO_3$ and water and finally

extracted with 2N NaOH. The alkali extract on acidification with dil. HCl gave 3-hydroxy xanthone which was recrystallised from ethanol using activated charcoal to give whitish needles of 24 (1.80 g, 43%), m.p. 248°.

IR (ν max, nujol) : 3140, 1650, 1620, 1570, 1520, 1485, 1460, 1385, 1345, 1320, 1285, 1265, 1230, 1215, 1185, 1165, 1120, 1110, 975, 930, 855, 825, 775, 750,700. cm^{-1}

The organic phase was washed with sat. brine and dried. Evaporation of the solvent gave a viscous liquid which was chromatographed on silica gel using petroleum-ether:benzene (70:30) to give a yellow solid. Recrystallisation from benzene - petroleum-ether afforded yellow needles of 23 (0.76 g, 19%), m.p. 150°.

IR (ν max, nujol) : 1650, 1620, 1580, 1490, 1470, 1385, 1360, 1340, 1295, 1245, 1220, 1180, 1160, 1120, 1065, 1050, 1020, 965, 935, 875, 865, 820, 810, 785, 775, 765, 730. cm^{-1}

1-Hydroxy xanthene (25) : To a stirring solution of $LiAlH_4$ (0.76 g, 20 mmole) in sodium dried diethyl ether (50 mL) was added a solution of 1-hydroxy xanthone (23, 0.97 g,4.5 mmole) in sodium dried benzene (30 mL) over a period of 30 minutes. The reaction mixture was refluxed

for 3 hours and left overnight at room temperature. 10% cold NH_4Cl was then added slowly with stirring till a clear solution resulted and organic layer separated out. The residue was extracted with petroleum-ether. The combined extracts and organic phase were washed with sat. brine and dried. Green solid obtained after evaporation of the solvent was chromatographed on silica gel using petroleum-ether - benzene (50:50) as an eluent to give colourless solid. Recrystallisation from benzene - petroleum-ether gave white needles of 25 (0.55 g, 60%), m.p. 145°.

IR (ν_{max}, KBr) : 3460-3140, 1645, 1625, 1595, 1520, 1505, 1485, 1470, 1440, 1420, 1355, 1325, 1295, 1265, 1190, 1165, 1155, 1115, 1040, 1020, 970, 930, 890, 875, 785, 760, 720. cm^{-1}

Pyrano [2,3-a] xanthene 27 : A mixture of 1-hydroxy xanthene (25, 0.198 g, 1 mmole) and p-methoxy cinnamic acid (0.178 g, 1 mmole) was stirred in PPA at 70° for 4 hours. Usual work up and purification by chromatography on silica gel gave three fractions. The first fraction eluted out using petroleum-ether - benzene (50:50) was a yellow solid recrystallised from benzene to give yellow needles of 23 (0.018 g, 8%), m.p. 150°, identified by comparison (TLC, m.p., m.m.p., IR) with an authentic

sample prepared earlier. The second fraction was eluted out with benzene as a white solid which on recrystallisation from benzene - petroleum-ether afforded white needles of 26 (0.067 g, 18%), m.p. 170°.

IR (ν max, KBr) (Fig.14) : 1780, 1625, 1590, 1525, 1495, 1455, 1370, 1320, 1285, 1270, 1245, 1210, 1190, 1180, 1145, 1115, 1060, 1035, 1005, 975, 930, 885, 855, 830,815. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.15) : 2.95 (2H, t, J=6.4 Hz, -CH-CH_2-); 3.72 (3H, s, -OCH_3); 4.05 (2H, s, -CH_2-); 4.15 (1H, m,-CH-CH_2); 6.64-7.32 (10H, m, ar-H).

The third fraction eluted out with benzene:EtOAc (98:2) was also a solid. Recrystallisation from acetone afforded white needles of 27 (0.04 g, 17%), m.p. 209°.

IR (ν max, nujol) (Fig.16) : 1730, 1685, 1615,1520, 1495, 1470, 1415, 1385, 1370, 1315, 1265, 1225, 1175, 1115, 1065, 1035, 1000, 980, 950, 940, 885, 850, 835, 810,760, 750. cm^{-1}

^1H nmr ($CDCl_3$, δ) (Fig.17) : 4.2 (2H, s, -CH_2-); 6.3 (1H, d, J=9 Hz, C_3-H); 6.96 (1H, d, J=8 Hz, C_6-H); 7.02-7.24 (4H, m, ar-H); 7.31 (1H, d, J=8 Hz, C_5-H); 7.64 (1H, d, J=9 Hz, C_4-H).

3-Acetoxy xanthone : 3-Hydroxy xanthone (24, 0.95 g, 4.5 mmole) was dissolved in dry pyridine (10 mL). To this was added Ac_2O (10 mL, 10 mmole). The reaction mixture was refluxed for 6 hours and kept overnight at room temperature. This was then extracted with diethyl ether. The ether extracts were washed successively with 5% HCl (3x20 mL), 2N Na_2CO_3 (3x10 mL), water (2x20 mL) and dried. Evaporation of the solvent gave a solid which was recrystallised from benzene to give silvery white flakes of 3-acetoxy xanthone (0.91 g, 80%), m.p. 160°.

IR (ν max, nujol) : 1760, 1665, 1615, 1475, 1440, 1385, 1325, 1255, 1205, 1150, 1105, 1030, 1015, 985, 930, 905, 865, 835, 795, 775, 760. cm^{-1}

3-Hydroxy xanthene 29 : To a stirring solution of $LiAlH_4$ (0.28 g, 7.3 mmole) in sodium dried diethyl ether (15 mL) was added a solution of 3-acetoxy xanthone (0.82 g, 3.2 mmole) in sodium dried benzene (40 mL) slowly over a period of 30 minutes. The reaction mixture was refluxed for 8 hours. Cold 10% NH_4Cl was then added slowly with stirring followed by cold dil. HCl till the solution became clear. This was extracted with diethyl ether. The ether extracts were washed with sat. brine and dried. Evaporation of the solvent gave a red coloured

solid which was chromatographed on silica gel using benzene:EtOAc (99:1) to give a white solid. Recrystallisation from benzene - petroleum-ether gave white needles of 29 (0.4 g, 62%) m.p. 126°.

IR (ν max, nujol) : 3570, 1640, 1620, 1595, 1525, 1505, 1475, 1395, 1325, 1250, 1155, 1125, 1105, 1085, 990, 885, 870, 855, 815, 765, 755, 705. cm^{-1}

3-Acetoxy xanthene 66 : Ac_2O (0.04 mL, 0.4 mmole) was added to a solution of 3-hydroxy xanthene (29, 0.035 g, 0.18 mmole) in dry pyridine (0.4 mL). The reaction mixture was refluxed on an oil bath for 3 hours and left overnight at room temperature. Usual work up gave a shining solid. Recrystallisation from benzene - petroleum-ether afforded silvery white crystals of 66 (0.03 g, 75%), m.p. 121°.

IR (ν max, nujol) : 1755, 1610, 1585, 1495, 1465, 1380, 1310, 1285, 1265, 1220, 1190, 1135, 1110, 1095, 1080, 1015, 980, 910, 815, 755. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig. 18) : 2.25 (3H, s, -O--CO-CH_3); 4.0 (2H, s, -CH_2-); 6.76-7.32 (7H, m, ar-H).

Synthesis of coumarins by reaction of phenols and p-methoxy cinnamic acid in the presence of 75% H_2SO_4.

General procedure : 75% H_2SO_4 (3.2 mL) was added in one lot to a mixture of appropriate phenol (1 mmole) and p-methoxy cinnamic acid (1 mmole). The reaction mixture was then heated on a steam bath for two hours with intermittent shaking. This was cooled and poured into cold water (8 mL). The solid obtained was suction filtered and dried in an oven at 120°. It was recrystallised either from benzene - petroleum-ether or $CHCl_3$ - petroleum-ether.

Data of individual coumarins synthesised by the above method.

7-Methyl coumarin (1) : 63%, m.p. 126°.
For ^1H nmr and ^{13}C nmr refer Fig.nos. 1 and 2

6,7-Dimethyl coumarin (4) : 60%, m.p. 150°.
For ^1H nmr and ^{13}C nmr refer Fig. nos. 3 and 4

7,8-Dimethyl coumarin (5) : 60%, m.p. 132°.
For ^1H nmr refer Fig. no. 6

5,6-Benzocoumarin (31)* : 55%, m.p. 118°.

7-Methoxy coumarin (32)* : 50%, m.p. 117°.

Synthesis of 3,4-dihydro-4-(p-methoxyphenyl) coumarin by reaction of phenols and p-methoxy cinnamic acid in the presence of PPA.

General procedure : Refer the general procedure for the synthesis of coumarins by reaction of phenols and p-methoxy cinnamic acid in the presence of PPA

Data of individual 3,4-dihydro-4-(p-methoxyphenyl) coumarin synthesised by the above method.

6-bromo-3,4-dihydro-4-(p-methoxyphenyl) coumarin (42) : 30%, m.p. 147°.

IR (ν_{max}, nujol) : 1780, 1530, 1490, 1420, 1395, 1275, 1235, 1195, 1150, 1130, 1080, 1040, 1025, 900, 885, 850, 825, 770. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.19) : 3.07 (2H, d, J=7 Hz, -CH-CH_2-); 3.91 (3H, s, -OCH_3); 4.37 (1H, t, J=7 Hz, -CH-CH_2-); 7.00-7.627 (7H, m, ar-H).

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*These coumarins were identified by (CO-TLC, m.m.p., and IR) comparison with the corresponding synthetic samples prepared in our laboratory by reaction of β-naphthol and resorcinol monomethyl ether respectively with p-methoxy cinnamic acid in the presence of PPA.

6-Methoxy-7-phenyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin (43) : 33%, m.p. 161°.

IR (ν max, KBr) (Fig.20) : 1770, 1615, 1520, 1490, 1470, 1410, 1260, 1230, 1190, 1180, 1145, 1110, 1025, 945, 905, 885, 850, 830, 810, 765. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.21) : 2.98 (1H, dd, J=7.5 & 14 Hz, C_3-H_a); 3.083 (1H, dd, J= 6 & 14 Hz, C_3-H_b); 3.66 (3H, s, $-OCH_3$); 3.82 (3H, s, $-OCH_3$); 4.32 (1H, dd, J =6 & 7.5 Hz, $-\overset{|}{C}H-CH_2-$); 6.56 (1H, d, J=0.5 Hz, C_8-H); 6.91 (2H, d, J=9 Hz, C_3' and C_5'-H^s); 7.13 (1H, s, ar-H) 7.14 (2H, d, J=9 Hz, C_2' and C_6'-H^s); 7.32-7.54 (5H, m, ar-H)

5-Methyl-8-isopropyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin (44) : 25%, m.p. 115°.

IR (ν max, nujol) (Fig.22) : 1770, 1610, 1585, 1515, 1495, 1465, 1425, 1385, 1350, 1290, 1250, 1175, 1135, 1065, 1035, 980, 965, 950, 880, 855, 825, 810, 775, 750, 705. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ)(Fig.23) : 1.22 (3H, d, J=7 Hz, $CH_3-\overset{|}{C}H-CH_3$); 1.28 (3H, d, J=7 Hz, $CH_3-\overset{|}{C}H-CH_3$); 2.11 (3H, s, $-CH_3$); 2.97 (2H, d, J=5 Hz, $-\overset{|}{C}H-CH_2$); 3.42 (1H; quintet, J=7 Hz, $CH_3-\overset{|}{C}H-CH_3$); 3.71 (3H, s, $-OCH_3$); 4.33 (1H, t, J=5 Hz, $-\overset{|}{C}H-CH_2$); 6.71-7.233 (6H, m, ar-H)

6-Hydroxy-7-methyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin (45) : 35%, m.p.163°.

IR (νmax, KBr) : 3660-3220, 1750, 1620, 1590, 1520, 1425, 1320, 1270, 1185, 1160, 1110, 1035, 965, 920, 875, 835, 815, 785, 760. cm^{-1}

^1H nmr (90 MHz, $CDCl_3$, δ) (Fig.24) : 2.26 (3H, s, $-CH_3$); 3.00 (2H, m, $-\overset{|}{C}H-CH_2-$) 3.88 (3H, s, $-OCH_3$); 4.292 (1H, t, J=6.4 Hz, $-\overset{|}{C}H-CH_2-$); 4.84 (1H, s, -OH); 6.48 (1H, s, ar-H) 6.96- 7.542 (5H, m, ar-H)

Acetylation of 2-phenyl phenol : Ac_2O (8 mL, 75mmole) was added to a solution of 2-phenyl phenol (5 g, 30 mmole) in dry pyridine (10 mL). The reaction mixture was refluxed for 6 hours and left overnight at room temperature. This was extracted with diethyl ether. The ether extracts were washed successively with 5% HCl, 2N Na_2CO_3, water and dried. Evaporation of the solvent gave a liquid which was chromatographed on silica gel using benzene as an eluent to give an oil, 2-phenyl phenol acetate.

IR (νmax, neat) : 1775, 1490, 1450, 1385, 1230, 1190, 1115, 1055, 1015, 915, 830, 785, 765, 745, 705. cm^{-1}

Fries reaction on 2-phenyl phenol acetate : 2-phenyl phenol acetate (3.4 g, 16 mmole) was mixed with finely crushed anhydrous $AlCl_3$ (3.4 g, 26 mmole) and heated at 130°for 3 hours. The reaction mixture was then cooled and quenched with dil. HCl (50 mL) and left overnight. The solid obtained was suction filtered and washed with water. Chromatography on silica gel using benzene as an eluent gave a liquid. Further elution using benzene:EtOAc (80:20) gave a solid which was recrystallised from EtOAc to give white needles of 2-phenyl-4-acetyl phenol (2.2 g, 65%), m.p. 170°. (lit.[47] m.p 172-3°.

IR (ν max, nujol) : 3210, 1675, 1600, 1485, 1405, 1300, 1260, 1160, 985, 830, 790, 710. cm^{-1}

Methylation of 2-phenyl-4-acetyl phenol : Anhydrous K_2CO_3 (1.5 g, 10 mmole) was added to a solution of 2-phenyl-4-acetyl phenol (2.2 g, 10 mmole) in dry acetone (10 mL). To this slurry was added freshy distilled $(CH_3)_2SO_4$ (1.5 mL, 16 mmole). The reaction mixture was refluxed for 8 hours while simultaneous stirring. This was then cooled and filtered. The residual K_2CO_3 was washed with acetone and filtered. Evaporation of the solvent from the combined filtrates gave a brown solid. Chromatography on silica gel using benzene:EtOAc (95:5)

IR (ν max, neat) : 3560-3120, 1605, 1575, 1495, 1465, 1435, 1310, 1275, 1230, 1200, 1175, 1130, 1040, 1030, 895, 870, 810, 770, 745, 720, 710, 700.cm^{-1}

5-Methyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin 47 and 5-methyl-3,4-dihydro-4-(p-hydroxyphenyl) coumarin 48: To chlorobenzene (8 mL) was added 5-methyl-8-isopropyl-3,4-dihydro-4-(p-methoxyphenyl)coumarin (44 0.3 g, 0.96 mmole). To this was added finely powdered anhydrous $AlCl_3$ (0.75 g, 5.6 mmole). The reaction mixture was then heated on an oil bath at 95° for 1 hour. This was cooled, poured over crushed ice (20 g) containing dil. HCl and extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a viscous liquid which was chromatographed on silica gel using petroleum-ether - benzene (80:20) to give a solid. Recrystallisation from petroleum-ether gave white needles of 47 (0.07 g, 27%), m.p. 100°.

IR (ν max, nujol) (Fig.25) : 1770, 1600, 1570, 1500, 1450, 1360, 1270, 1240, 1170, 1120, 1010, 960, 880, 830, 760, 740. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ)(Fig.26) : 2.192 (3H, s, $-CH_3$); 3.02 (2H, m, $-\overset{1}{C}H-CH_2-$); 3.752 (3H, s, $-OCH_3$); 4.365 (1H, dd, J=6 & 3 Hz, $-\overset{1}{C}H-CH_2-$); 6.8 (2H, d, J=9

Hz, C_3' & C_5'-H^s); 6.98 (2H, d, J=9 Hz, C_2' & C_6'-H^s); 6.95-7.25 (3H, m, ar-H)

^{13}C nmr ($CDCl_3$, δ) (Fig.27) : 18.79 (q), 37 50 (q), 37.88 (t), 55.27 (d) 114.4 (d), 114.98 (d), 123.48 (s),126.30 (d), 127.90 (d), 127.94 (d), 131.86 (s), 136.81(s), 151.96 (s), 158.69 (s), 167.25 (s).

Further elution with benzene:EtOAc (96:4) gave a viscous liquid which solidified on addition of petroleum-ether and on recrystallisation from EtOAc - petroleum-ether gave white needles of 48 (0.04 g, 16%), m.p. 184°.

IR (ν max, nujol) (Fig.28) ; 3240, 1740, 1610, 1570, 1510, 1450, 1370, 1340, 1260, 1240, 1170, 1150, 1100, 1030, 960, 890, 840, 820, 780, 750, 720. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.29) : 2.17 (3H, s, $-CH_3$); 2.89 (1H, dd, J=2.5 & 16 Hz, C_3-H_a) 3.11 (1H, dd, 7 & 16 Hz,C_3-H_b); 4.45 (1H, dd, J=2.5 & 7 Hz, $-\underset{|}{CH}-CH_2$); 4.87 (1H, s, -OH); 6.67 (2H, d, J=9 Hz, C_3' & C_5'-H^s); 6.845 (2H, d, J=9 Hz, C_2' & C_6'-H^s); 6.95-7.25 (3H, m, ar-H)

^{13}C nmr ($CDCl_3$, δ) (Fig.30) : 18.68 (q), 38.48 (d), 38.84 (t), 115.66 (d), 116.72 (d), 125.44 (s), 127.47(d), 129.11 (d), 129.49 (d), 132.5 (s), 138.44 (s), 153.54 (s), 157.79 (s), 169.84 (s).

Synthesis of 3,4-dihydro-4-(p-methoxyphenyl) coumarins by reaction of phenols and p-methoxy cinnamic acid in the presence of 75% H_2SO_4-dioxane.

General procedure : p-methoxy cinnamic acid (1 mmole) was first dissolved in minimum volume of dioxane. To this solution was then added an appropriate phenol (1 mmole) and 75% H_2SO_4 in quick succession. The reaction mixture was stirred for 2 hours at room temperature and poured into cold water. This was extracted with EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a semi solid which was chromatographed on silica gel using benzene containing increasing amounts of EtOAc. The various fractions collected were monitored by TLC, the plates visualised by developing in I_2 chamber. The fractions containing the 3,4-dihydro coumarin were combined and concentrated. The solid 3,4-dihydro coumarins were recrystallised from $CHCl_3$ - petroleum-ether. In the reaction of resorcinol monomethyl ether and m-cresol along with the 3,4-dihydro coumarin, fractions containing an acid were collected separately and concentrated. The solid acids* were recrystallised from $CHCl_3$ - petroleum-ether.

* The solid acid m.p.134° obtained in the reaction of m-cresol by the above method is yet to be characterised.

Spectral data of individual 3,4-dihydro coumarins and β,β-(2-methoxy-4-hydroxyphenyl)-p-methoxyphenyl propionic acid synthesised by the above method.

5,6,7-Trimethoxy-3,4-dihydro-4-(p-methoxyphenyl) coumarin 12a : 23%, m.p. 91°.

IR (ν_{max}, nujol) (Fig.31) : 1780, 1620, 1520, 1500, 1470, 1440, 1420, 1390, 1340, 1310, 1290, 1260, 1240, 1190, 1140, 1110, 1040,1010, 990, 980,950, 940, 910, 880, 840, 800. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.32) : 2.95 (2H, d, J=4 Hz, -CH-CH_2-); 3.65 (3H, s, $-OCH_3$); 3.73 (3H, s, $-OCH_3$); 3.81 (3H, s, $-OCH_3$); 3.85 (3H, s, $-OCH_3$); 4.50 (1H, t, J=4 Hz, -CH-CH_2-); 6.48 (1H, s, C_8-H); 6.78 (2H, d, J=8 Hz, C_3' & C_5'-H^s); 7.00 (2H, d, J=8 Hz, C_2' & C_6'-H^s).

^{13}C nmr ($CDCl_3$, δ) (Fig.33) : C_2-158.66 (s), C_3-34.65 (t), C_4-37.39 (d), C_5-133.75 (s), C_6-147.60 (s), C_7-150.48 (s), C_8-96.77 (d), C_{4a}-111.29 (s), C_{8a}-153.57 (s), C_1'-138.96 (s), C_2' & C_6'-127.78 (d), C_3' & C_5'-114.29 (d), C_4'-167.57 (s), $-OCH_3$-61.13 (q), $-OCH_3$-60.97 (q), $-OCH_3$-56.11 (q), $-OCH_3$-55.22 (q).

Elemental analysis : Found: C, 66.31; H, 5.79; $C_{19}H_{20}O_6$
Requires: C, 66.27; H, 5.81.

7-Methoxy-3,4-dihydro-4-(p-methoxyphenyl) coumarin 12b: 21%, m.p. 134°.

IR (ν max, nujol) : 1780, 1630,1620, 1600, 1520, 1470, 1450, 1390, 1340, 1330 , 1300, 1270, 1250, 1230, 1200, 1190, 1170, 1140, 1120, 1050, 990, 980, 900, 860, 840, 830. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.34) : 2.95 (1H, dd, J=8 & 14 Hz, C_3-H_a); 3.04 (1H, dd, J=6 & 14 Hz, C_3-H_b); 3.79 (3H, s, $-OCH_3$); 3.81 (3H, s, $-OCH_3$); 4.24 (1H, dd, J=6 & 8 Hz, $-\overset{1}{C}H-CH_2-$); 6.62 (1H, d, J=2.5 Hz, C_8-H); 6.66 (1H, dd, J=2.5 & 9 Hz, C_6-H); 6.87 (3H, d, J=9 Hz C_5, C_3' & C_5'-H^s); 7.065 (2H, d, J=9 Hz, C_2' & C_6'-H^s).

7-Methyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin 12c: 29%, m.p. 87°.

IR (νmax, nujol) (Fig.35) : 1770, 1630, 1620, 1590, 1520, 1470, 1430, 1390, 1350, 1340, 1320, 1300, 1290, 1260, 1230, 1200, 1190, 1150, 1120, 1040, 990, 980, 950 900, 890, 860, 840, 830, 750, 700. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.36) : 2.35 (3H, s, $-CH_3$); 2.95 (1H, dd, J=8 & 15.5 Hz, C_3-H_a); 3.029 (1H, dd, J=6 & 15.5 Hz, C_3-H_b); 3.79 (3H, s, $-OCH_3$); 4.25 (1H, t, J=6 Hz, $-\overset{1}{C}H-CH_2-$); 6.83-7.25 (7H, m, ar-H).

Elemental analysis : Found: C, 75.70; H, 6.06; $C_{17}H_{16}O_3$

Requires : C,76.10; H, 5.9

6,7-Methylenedioxy-3,4-dihydro-4-(p-methoxyphenyl) coumarin 12d : 23%, m.p.130°.

IR (ν max,nujol) (Fig.37) : 1760, 1610, 1580, 1510, 1480, 1440, 1380, 1340, 1240, 1180, 1140, 1080, 1040, 970, 940, 900, 860, 830, 750, 730. cm^{-1}

^1H nmr ($CDCl_3$, δ) (Fig.38) : 3.007 (1H, dd, J=8 & 16 Hz, C_3-H_a); 3.06 (1H, dd, J=6 & 16 Hz, C_3-H_b); 4.05 (3H, s, $-OCH_3$); 4.24 (1H, t, J=6 Hz, $-\underset{|}{C}H-CH_2-$); 6.57 (2H, s, $-O-CH_2-O-$); 6.79 (1H, s, C_8-H); 6.92 (1H, s, C_5-H); 7.04 (2H, d, J=9 Hz, C_3' & C_5'-H^s); 7.13 (2H, d, J=9 Hz, C_5' & C_6'-H^s)

Elemental analysis : Found: C, 68.33; H,4.74; $C_{17}H_{14}O_5$

Requires: C, 68.45; H,4.69

β,β-(2-Methoxy-4-hydroxyphenyl)-p-methoxyphenyl propionic acid 53 : 24%, m.p. 145°.

IR (ν max, nujol) (Fig.39) : 3400, 1700, 1620, 1610, 1520, 1480, 1390, 1340, 1320, 1280, 1230, 1200, 1190, 1160, 1130, 1040, 980, 840, 830, 820. cm^{-1}

^1H nmr (300 MHz, $CDCl_3$, δ) (Fig.40) : 2.95 (1H, dd, J=8 & 15 Hz, α-C-H_a); 3.03 (1H, dd, J=7 & 15 Hz, α-C-H_b); 3.73 (3H, s, $-OCH_3$); 3.76 (3H, s, $-OCH_3$); 4.75 (1H, dd, J=7 & 8 Hz, $-\dot{C}H-CH_2-$); 6.29 (1H, d, J=2.5 Hz, C_3-H); 6.34 (1H, dd, J=2.5 & 8 Hz, C_5-H); 6.8 (2H, d, J=9 Hz, C_3, C_5,-H^s); 6.91 (1H, d, J=8 Hz, C_6-H); 7.16 (2H, d, J=9 Hz, C_2, and C_6,-H^s

Elemental analysis : Found: C, 66.74; H, 5.67; $C_{17}H_{18}O_5$
Requires: C, 67.55; H, 5.9

3,4,5-Trimethoxy phenol from 3,4,5-trimethoxy benzaldehyde : To a solution of 3,4,5-trimethoxy benzaldehyde (1 g, 5.1 mmole) in CH_2Cl_2 (2 mL)was added a solution of m-chloroperbenzoic acid (1.5 g, 8 mmole) in $CHCl_3$ (9 mL). The reaction mixture was magnetically stirred overnight. 10% $Na_2S_2O_4$ (3 mL) was added to this and stirred for another 45 minutes. The organic phase was separated and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with sat. brine and dried. The residue obtained after evaporation of the solvent was dissolved in MeOH (3 mL). The solution formed was cooled in ice and to this was added 5% KOH (8 mL) slowly with stirring. The reaction mixture was magnetically stirred overnight, acidified

with conc. HCl while cooling in ice and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with sat. brine and dried. Evaporation of the solvent gave a solid which was chromatographed on silica gel using benzene:EtOAc (90:10) to give a solid. Recrystallisation from $CHCl_3$ - petroleum-ether gave white needles of 3,4,5-trimethoxy phenol (0.3 g, 32%), m.p.148°.

4-Methyl-7-hydroxy coumarin : A solution of freshly distilled resorcinol (2 g, 18 mmole) in ethyl aceto acetate (2.6 mL, 20 mmole) was added slowly while stirring to ice cold conc. H_2SO_4 (20 mL). The temperature was not allowed to rise above 10° during the addition. The reaction mixture was stirred for 2 hours and left at room temperature for 18 hours. It was then poured while stirring vigorously into a mixture of crushed ice (40 g) and water (60 mL). The solid obtained was suction filtered and washed with cold water. This was dissolved in 5% NaOH (30 mL) and reprecipitated with 2M H_2SO_4. This solid was suction filtered, dried at 120° in an oven and recrystallised from ethanol to give white needles of 4-methyl-7-hydroxy coumarin (1.8 g, 70%), m.p. 185°. (lit.[48] m.p. 185-6°).

4-Methyl-7-acetoxy coumarin : 4-Methyl-7-hydroxy coumarin (1.2 g, 6.8 mmole) was dissolved in dry pyridine (20 mL). To this was added Ac_2O (1.7 mL, 17 mmole). The reaction mixture was refluxed for 1 hour, cooled and poured into cold water. The solid formed was suction filtered, dried at 120° in an oven and recrystallised from $CHCl_3$ - petroleum-ether to give white needles of 4-methyl-7-acetoxy coumarin (1.2 g, 81%), m.p. 150°. (lit.[48] m.p.150°.)

4-Methyl-7-hydroxy-8-acetyl coumarin : 4-Methyl-7-acetoxy coumarin (0.9 g, 4 mmole) was intimately mixed with anydrous $AlCl_3$ (2.7 g, 20 mmole) and heated rapidly at 130°. Heating was continued slowly to 175° over a period of 2 hours. The reaction mixture was then cooled, quenched with dil.HCl (20 mL) and ice (2 g) and kept overnight at room temperature. The solid formed was suction filtered and chromatographed on silica gel using petroleum-ether:CH_2Cl_2 (70:30) to give a white solid which was recrystallised from $CHCl_3$ - petroleum-ether to afford white needles of 4-methyl-7-hydroxy-8-acetyl coumarin (0.7 g, 77%), m.p. 168°. (lit.[49] m.p.168°)

2-Acetyl resorcinol : 4-Methyl-7-hydroxy-8-acetyl coumarin (0.29 g, 1.3 mmole) was boiled with NaOH (0.1 g, 2.5 mmole) in water (2.5 mL). The reaction mixture was then cooled and acidified with dil. HCl. The solid thus obtained was suction filtered, dried at 120° and recrystallised from $CHCl_3$ - petroleum-ether to afford white needles of 2-acetyl resorcinol (0.13g, 64%), m.p. 157°.(lit.[50] m.p.157°)

PPA reaction of 2-acetyl resorcinol and p-methoxy cinnamic acid : A mixture of 2-acetyl resorcinol (0.2 g, 1.3 mmole) and p-methoxy cinnamic acid (0.235 g, 1.3 mmole) was stirred in PPA at 70° for 4 hours. Usual work up in EtOAc gave a viscous liquid which was chromatographed on silica gel using benzene:EtOAc (92:8) to give a solid. Recrystallisation from EtOAc-petroleum ether gave white needles of 64 (0.05 g, 23%), m.p. 229° identified by comparison (TLC, m.p., m.m.p.) with 7-hydroxy coumarin prepared from resorcinol and malic acid under pechmann conditions.

7-Hydroxy coumarin : A mixture of commercial grade resorcinol (1.5 g, 13 mmole) malic acid (1.25 g, 9.3 mmole) and conc H_2SO_4 (3ml) was heated at 120° till effervescence ceased. The reaction mixture was cooled and poured over crushed ice. This was extracted with

EtOAc. The EtOAc extracts were washed with sat. brine and dried. Evaporation of the solvent gave a solid which on recrystallisation from EtOAc - petroleum-ether afforded white needles of 7-hydroxy coumarin (1 g, 45%), m.p. 228°.

Oxime of 2-acetyl resorcinol : 2-acetyl resorcinol (0.75 g, 5 mmole) was added to a solution of hydroxylamine hydrochloride (0.75 g, 10 mmole) and sodium acetate (1 g, 12 mmole) in water (2ml). To this was added methanol (3ml) and the reaction mixture was refluxed for 3 hours. This was then cooled, methanol removed under reduced pressure and extracted with EtOAc. The EtOAc extracts were washed with sat.brine and dried. Evaporation of the solvent gave a solid which was chromatographed on silica gel using benzene:EtOAc (95:5) to give a pale yellow solid. Recrystallisation from chloroform - petroleum-ether gave whitish needles of 2-acetyl resorcinol oxime (0.45 g, 54%), m.p 175° (lit.[30] m.p. 177°).

Isoxazole 62 from 2-acetyl resorcinol oxime : To a solution of 2-acetyl resorcinol oxime (0.6 g, 3.3 mmole) in methanol (36ml,1:1) was added 85% KOH (0.237g) and the reaction mixture was refluxed for 24 hours. This was cooled, methanol was removed in vacuo and the

residual solution was made strongly basic by adding excess of 2N alkali. This was extracted with EtOAc. The aqueous phase was acidified with dil. HCl and the product was extracted with EtOAc. The EtOAc extracts were washed with water and dried . Evaporation of the solvent gave a red solid which was chromatographed on silica gel using benzene:EtOAc (95:5) as an eluent to give pale yellow solid. Recrystallisation from EtOAc - petroleum-ether gave whitish needles ofisoxazole 62 (0.3 g, 56%), m.p.219^{o} (lit.^{30} m.p. 219-21^{o}).

PPA reaction of isoxazole 62 and p-methoxy cinnamic acid:

A mixture of isoxazole 62 (0.14 g, 0.9 mmole) and p-methoxy cinnamic acid (0.17 g, 0.9 mmole) was stirred in PPA at 70^{o} for 4 hours. Usual work up in EtOAc gave a semi solid which was chromatographed on silica gel using benzene as an eluent to give a solid which was recrystallised from $CHCl_3$ - petroleum-ether to give whitish needles (0.08g), m.p. 155^{o}.

Resacetophenone from resorcinol : A mixture of freshly distilled resorcinol (4 g, 36 mmole), anhydrous zinc chloride (4 g, 29 mmole) and acetic anhydride (5.6 mL, 59 mmole) was refluxed for 30 minutes. The reaction mixture was then cooled and poured into dil. HCl (40 mL) while stirring. The solid obtained was suction filtered

recrystallised from $CHCl_3$ - petroleum-ether to give white needles of 56 (0.1 g, 22%), m.p 177° identified by comparison (TLC, m.p., m.m.p.) with an authentic sample prepared earlier in our laboratory by reaction of resacetophenone and p-methoxy cinnamic acid in the presence of PPA.

^1H nmr ($CDCl_3$, δ) (Fig.41) : 2.62 (3H, s, $-CO-CH_3$); 3.06 (2H, d, J=5 Hz, $-\overset{|}{C}H-CH_2-$); 3.77 (3H, s, $-OCH_3$); 4.69 (1H, t, J=5 Hz, $-\overset{|}{C}H-CH_2-$); 6.71 (2H, d, J=11 Hz, C_3' & $C_5'-H^S$); 6.82 (1H, d, J=10.5 Hz, C_8-H); 7.11 (1H, d, J=10.5 Hz, C_7-H); 7.74 (2H, d, J=11 Hz, C_2' & $C_6'-H^S$); 12.36 (1H, s, Ar-OH Chelated).

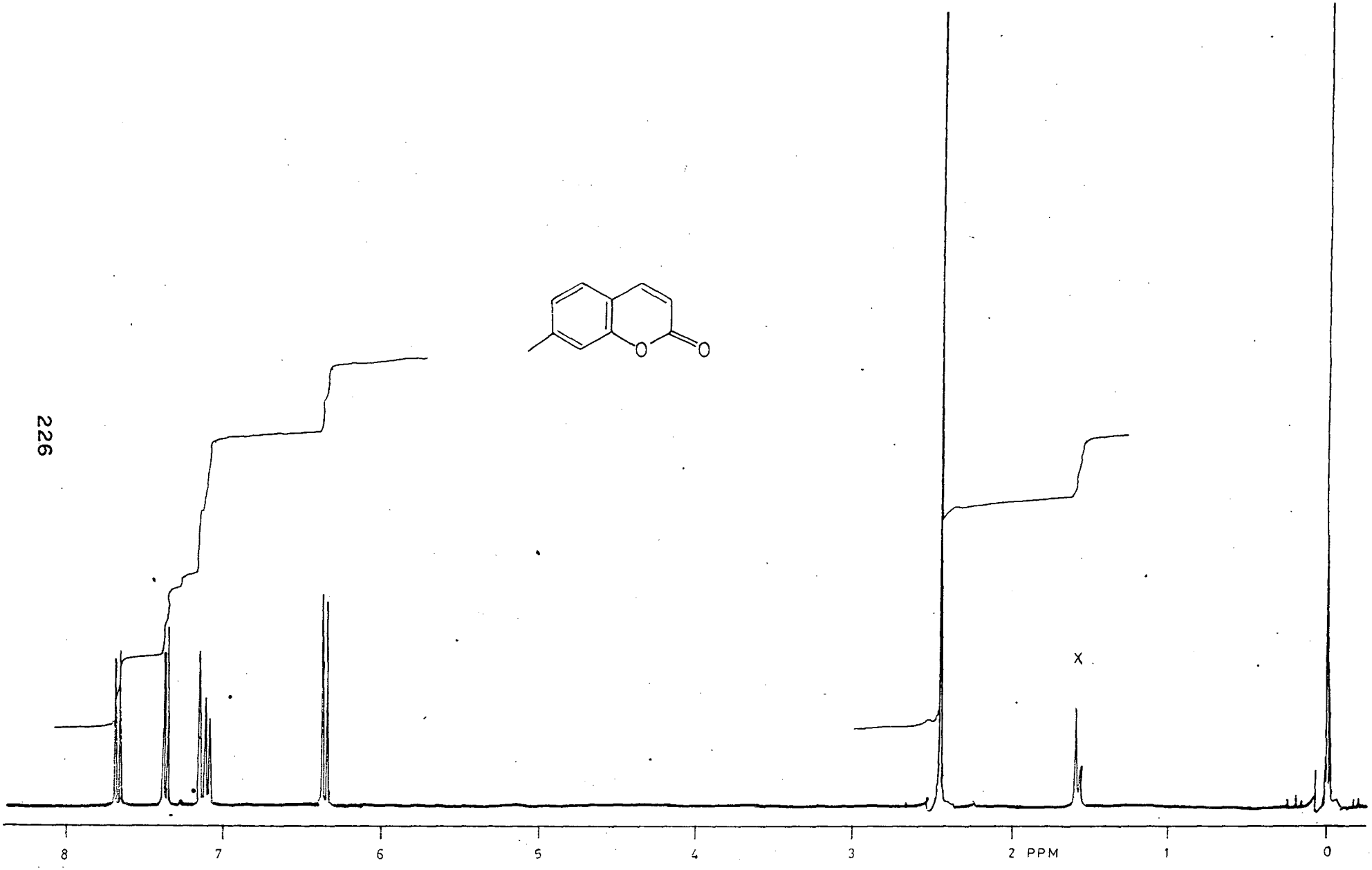

Fig. 1 ^{1}H NMR SPECTRUM OF (1)

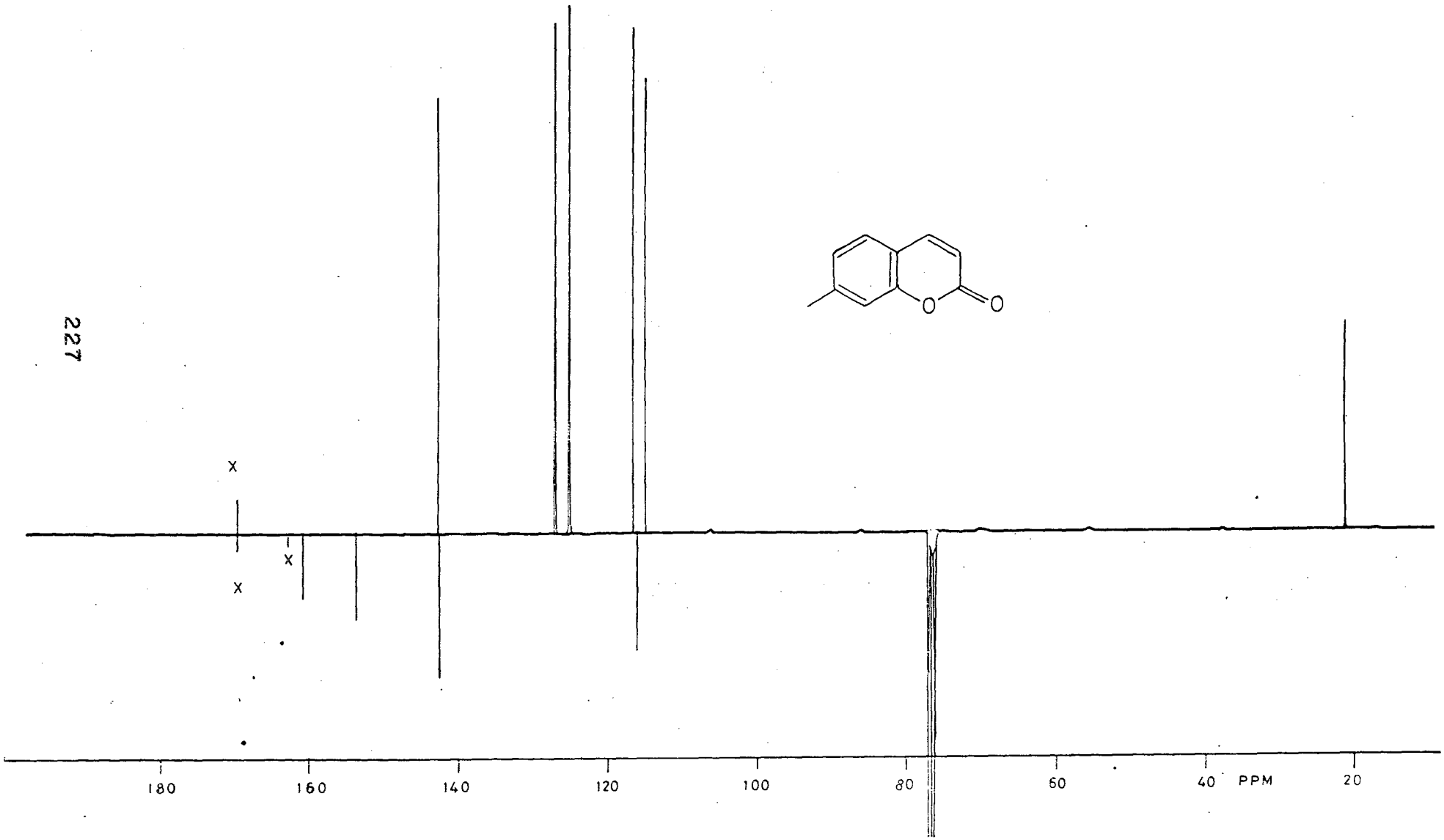

Fig. 2 ^{13}C NMR SPECTRUM OF (1)

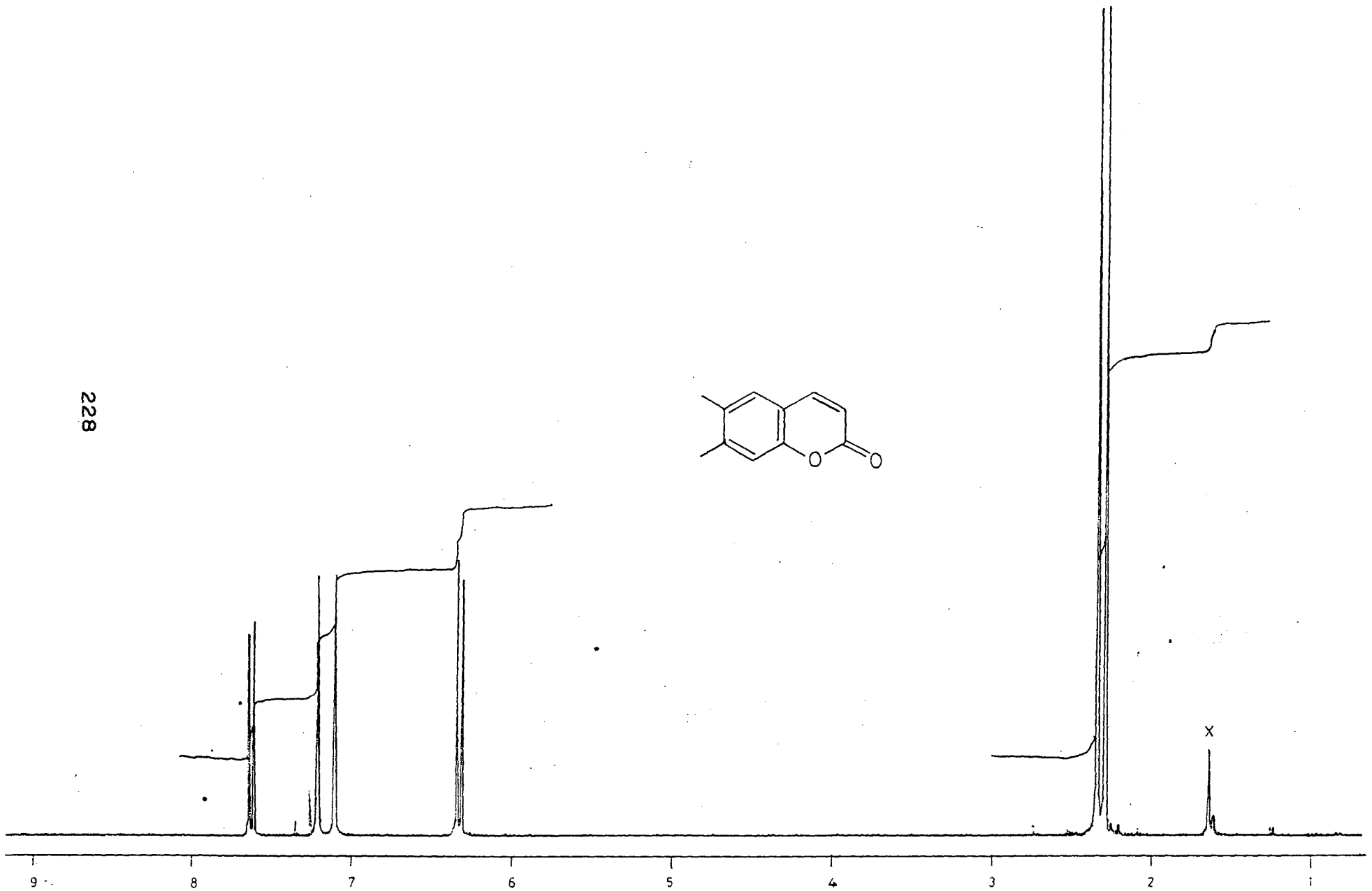

Fig. 3 ^{1}H NMR SPECTRUM OF (4)

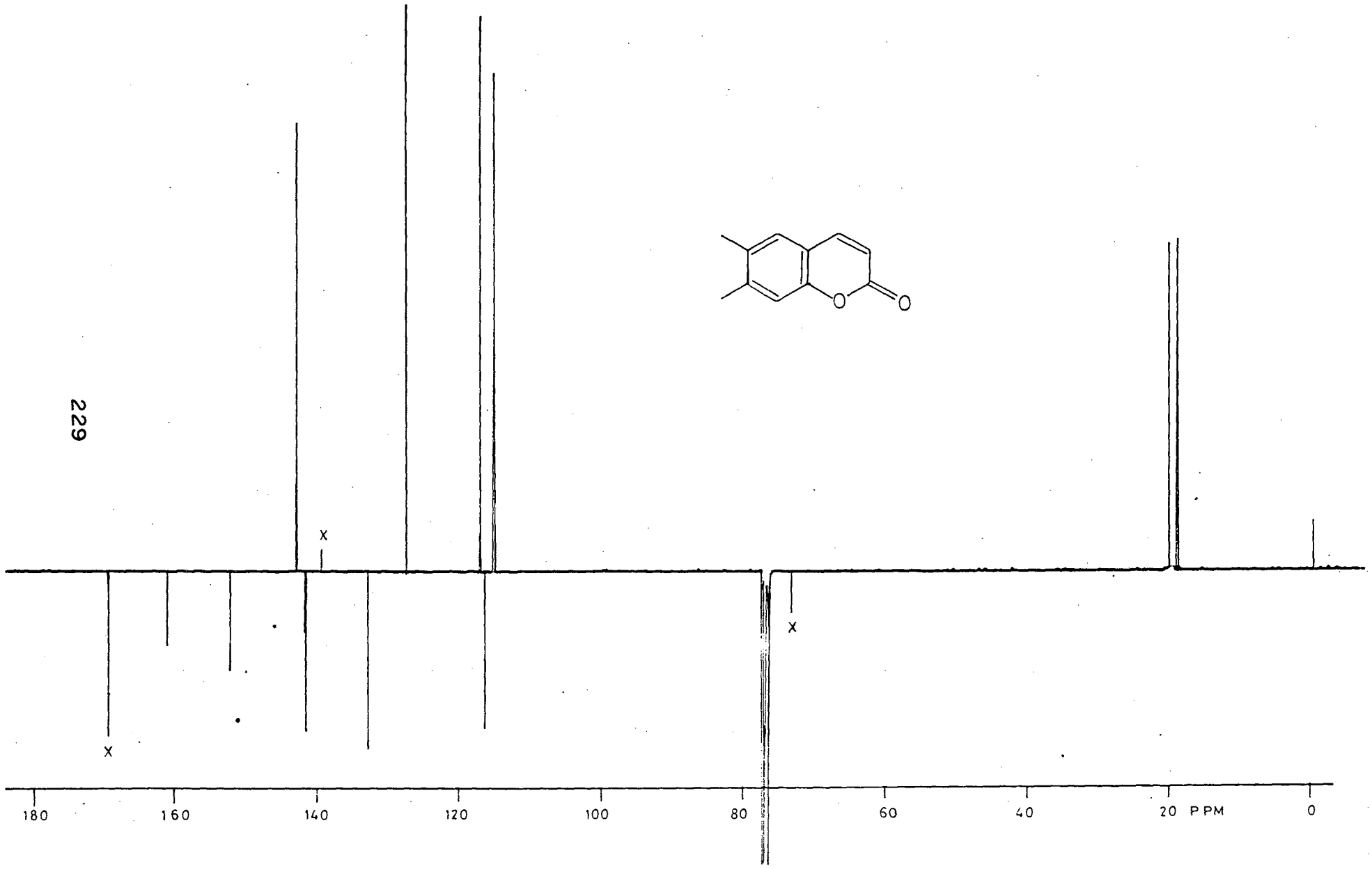

Fig. 4 ^{13}C NMR SPECTRUM OF (4)

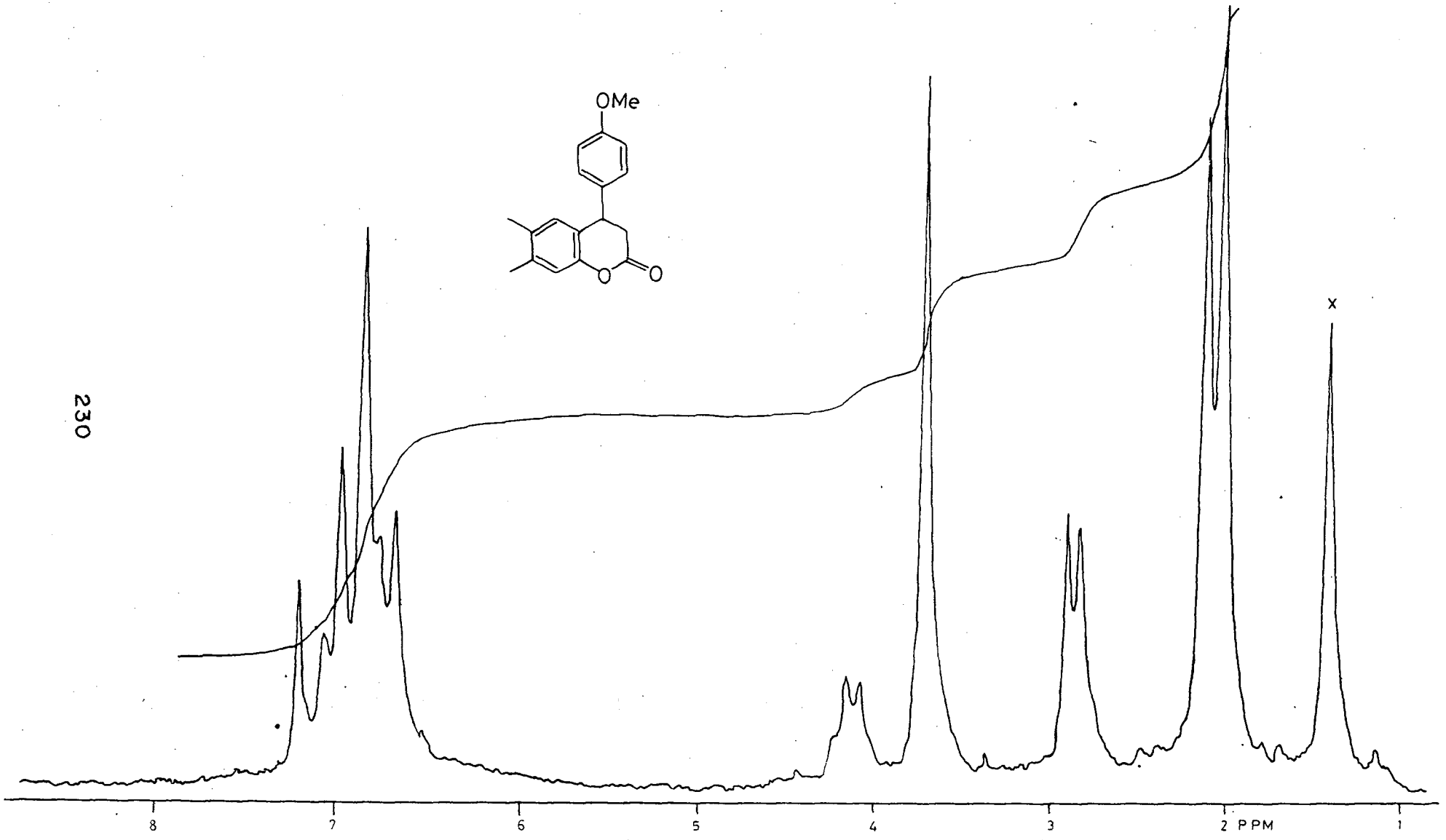

Fig. 5 ^{1}H NMR SPECTRUM OF (6)

Fig. 6 ^{1}H NMR SPECTRUM OF (5)

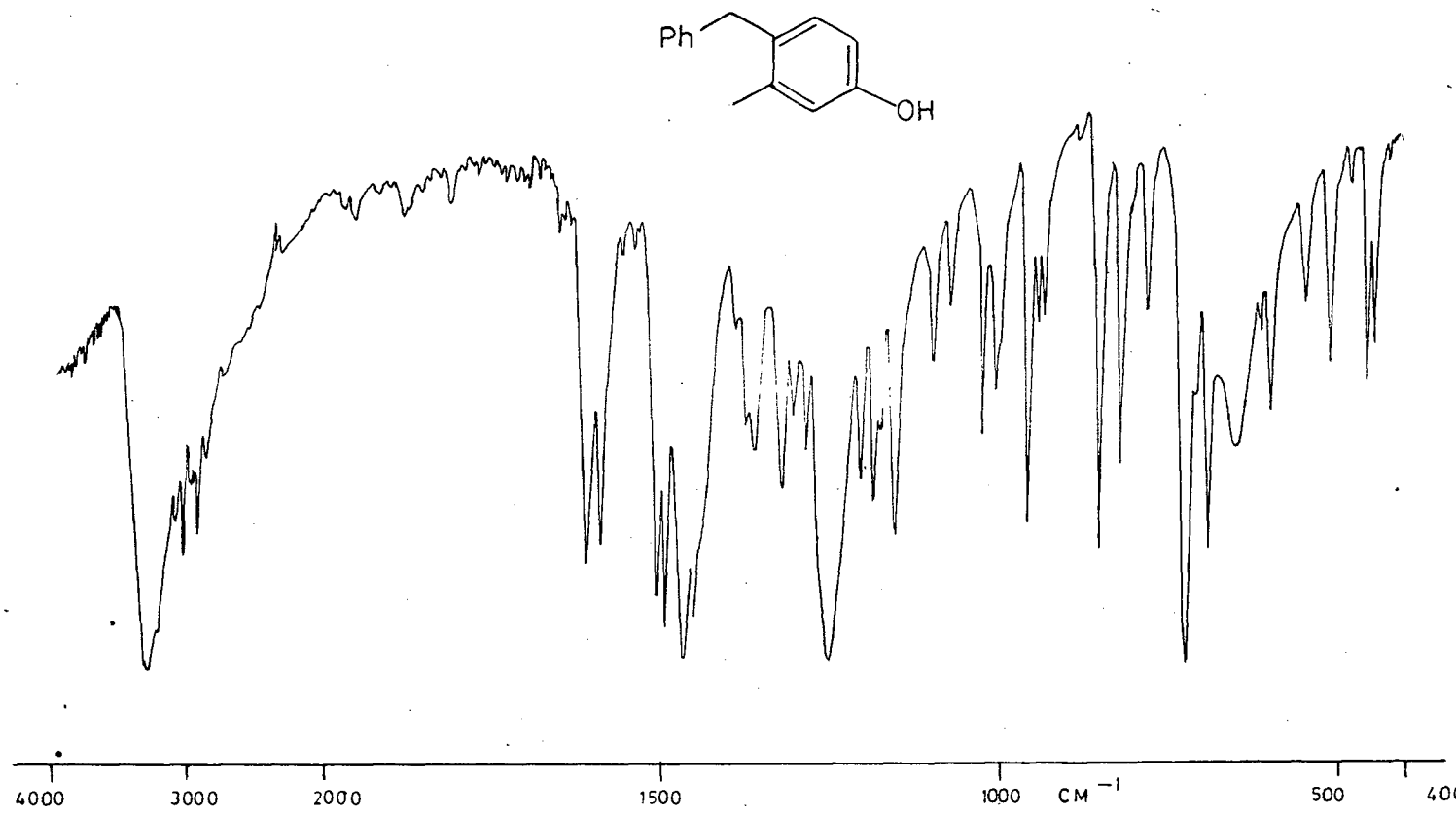

Fig. 7 IR SPECTRUM OF (8)

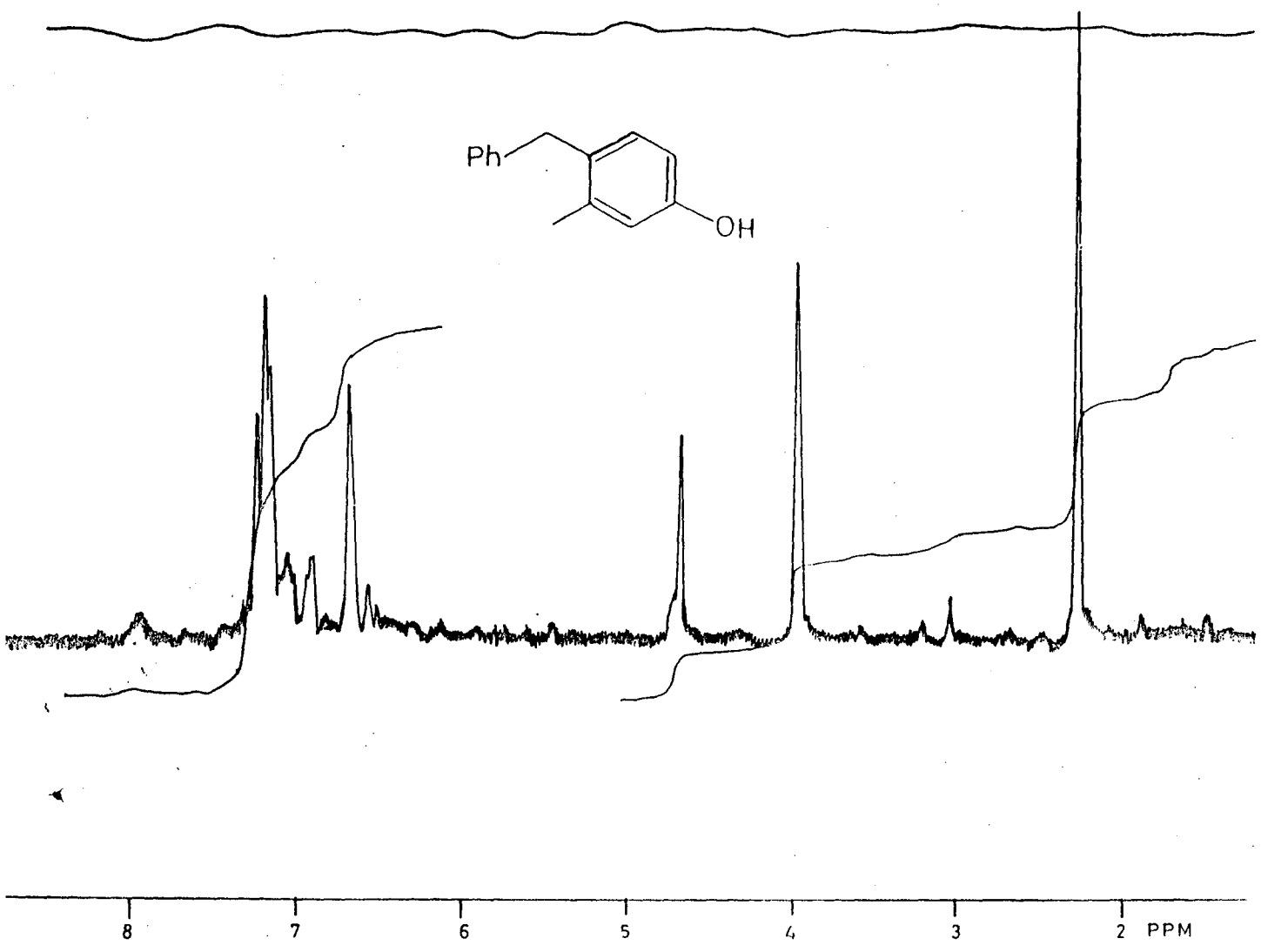

Fig. 8 ^{1}H NMR SPECTRUM OF (8)

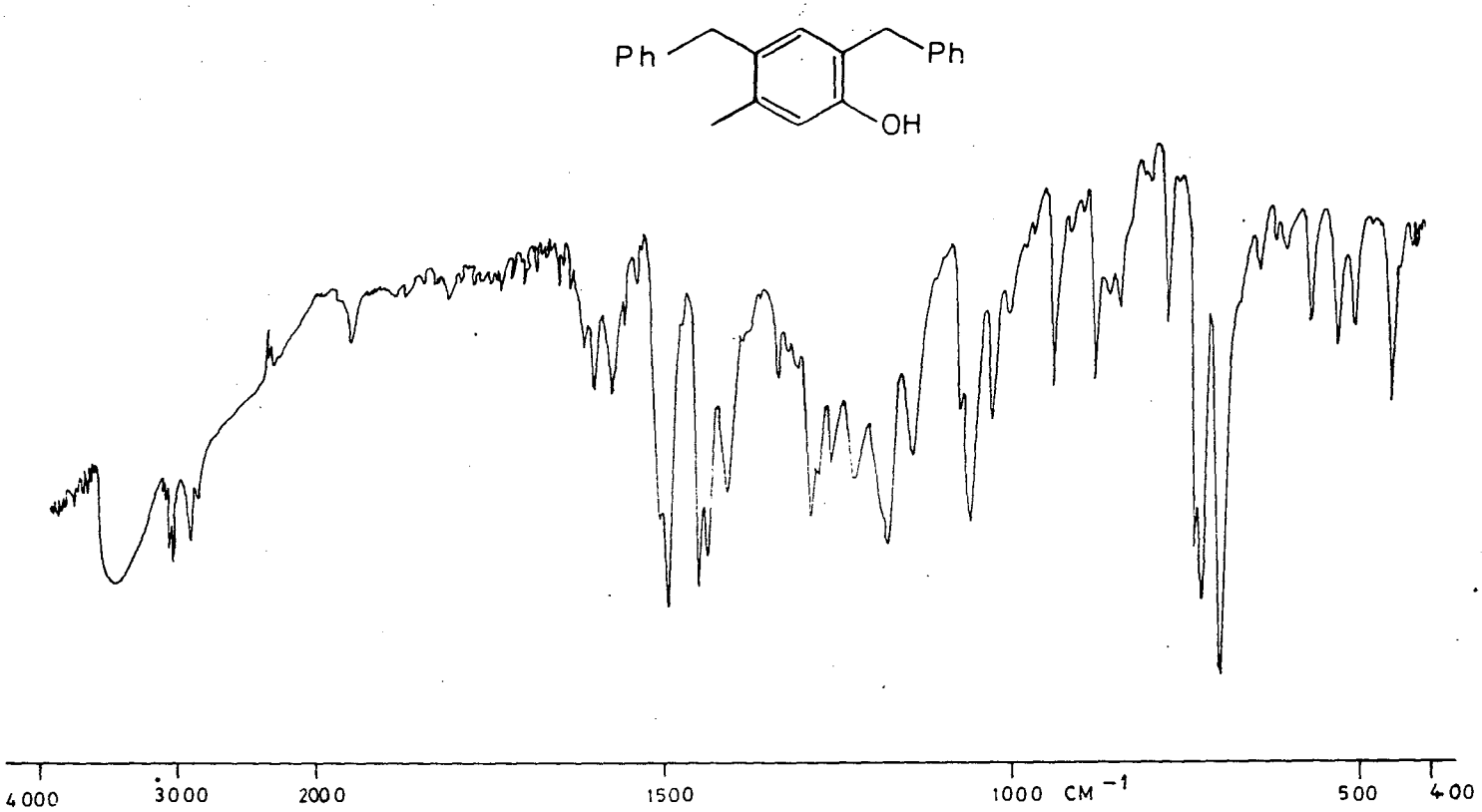

Fig. 9 IR SPECTRUM OF (9)

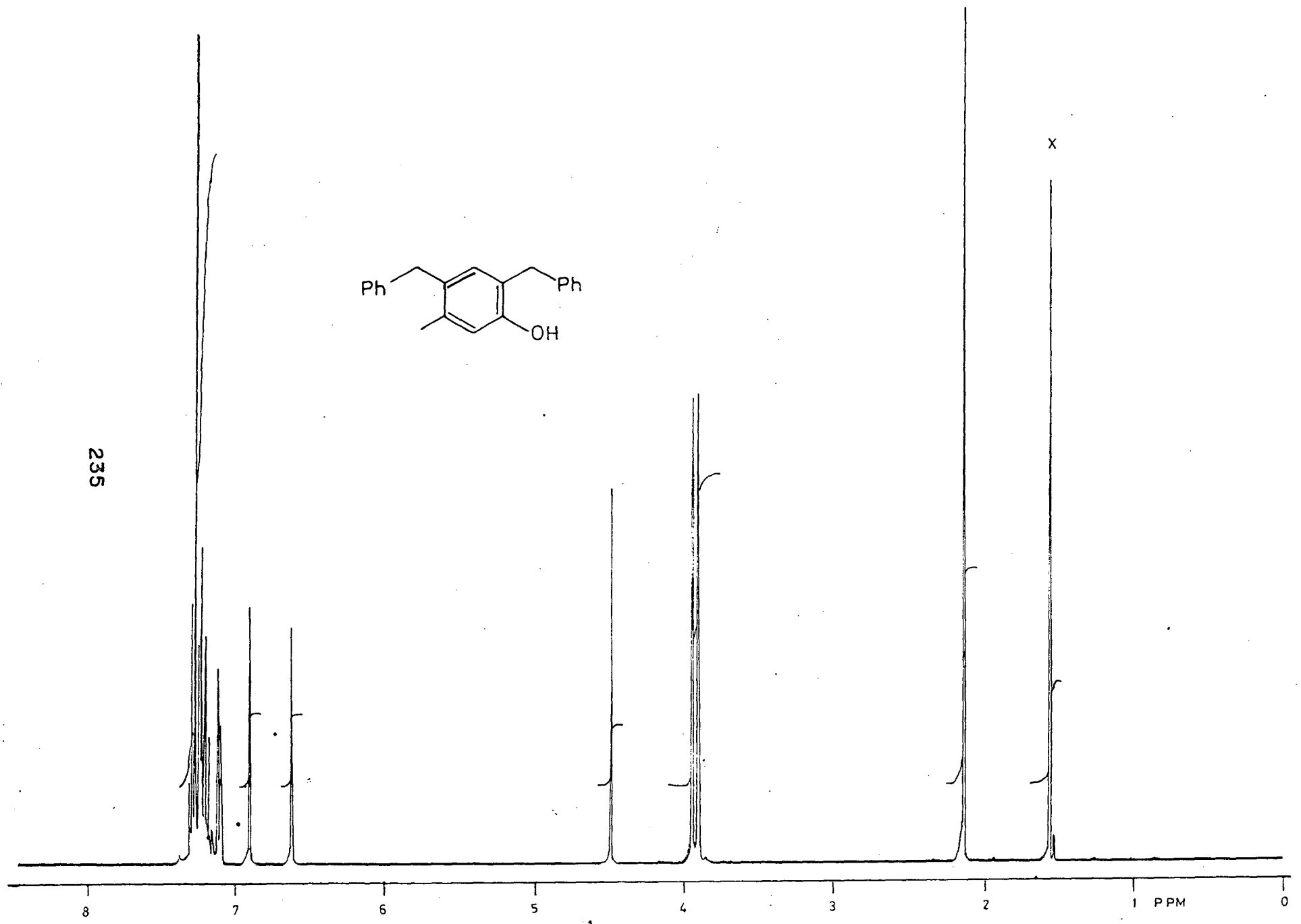

Fig. 10 ^{1}H NMR SPECTRUM OF (9)

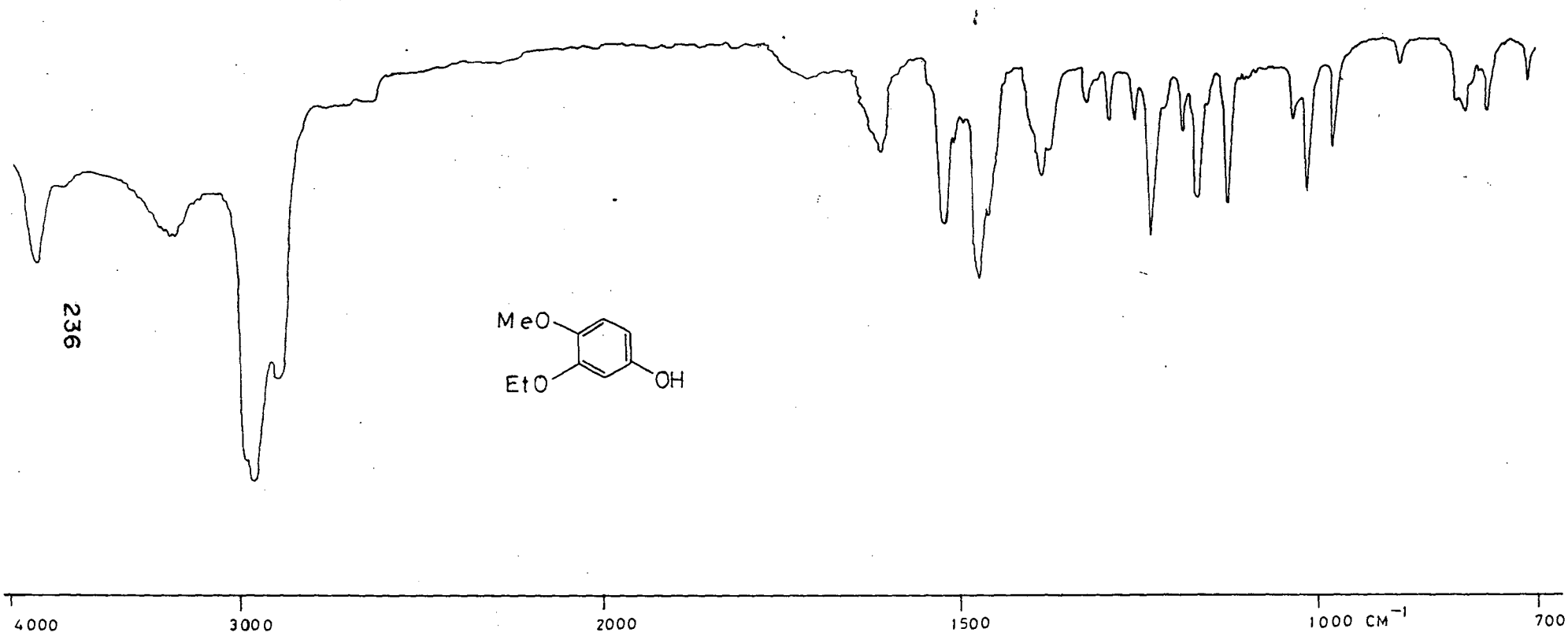

Fig. 11 IR SPECTRUM OF (19)

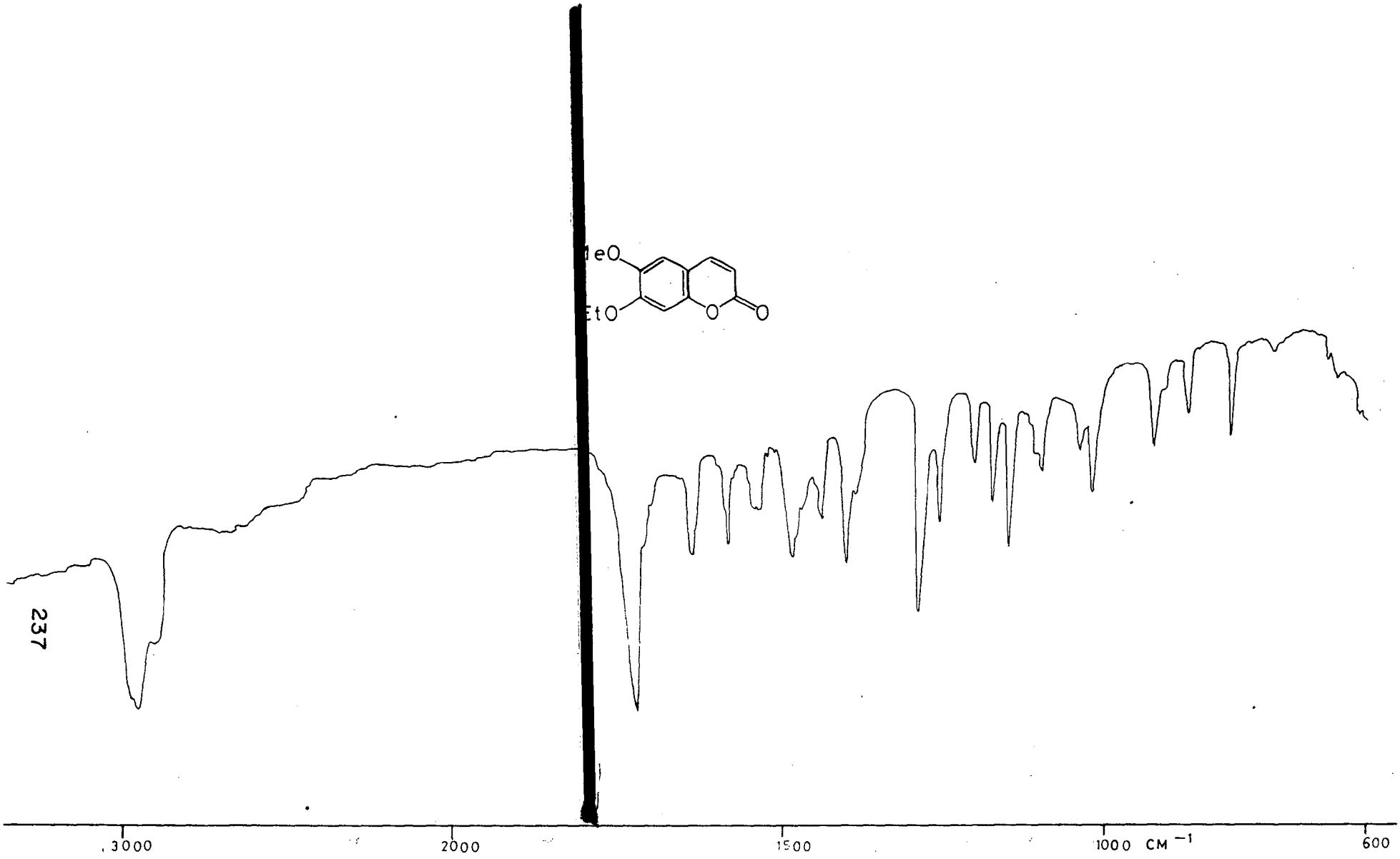

Fig. 12 IR SPECTRUM OF (16)

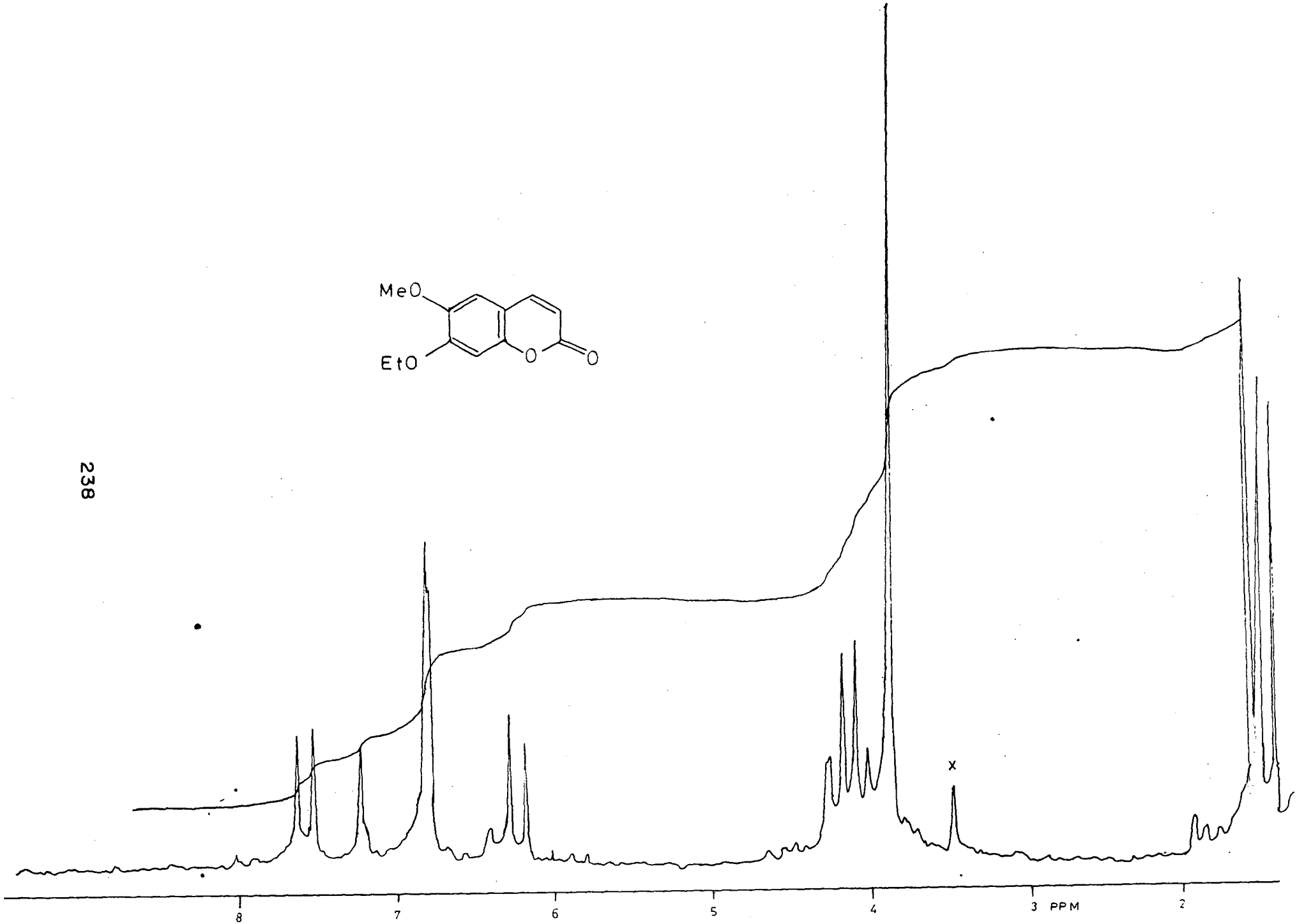

Fig. 13 ^{1}H NMR SPECTRUM OF (16)

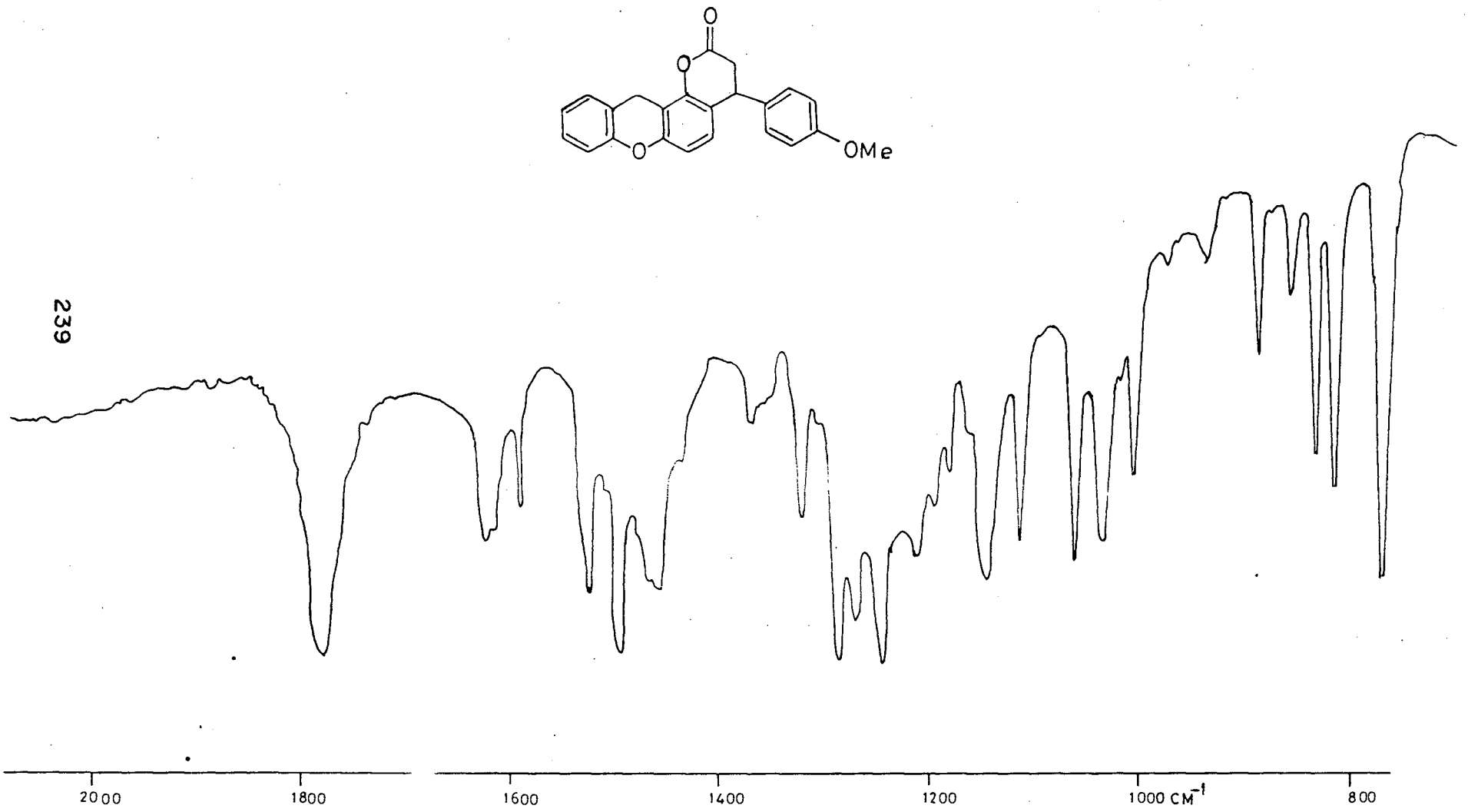

Fig. 14 IR SPECTRUM OF (26)

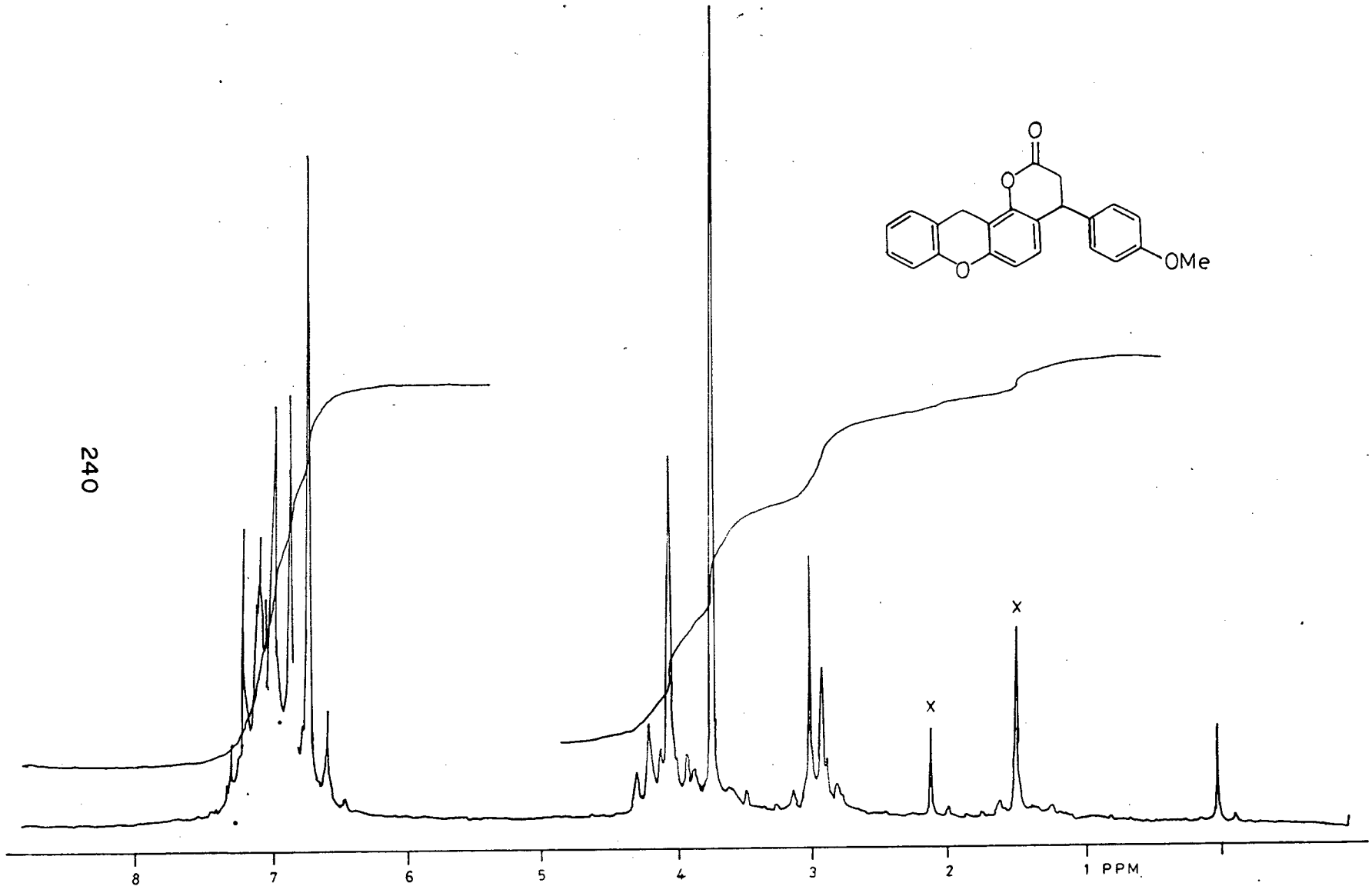

Fig. 15 ^{1}H NMR SPECTRUM OF (26)

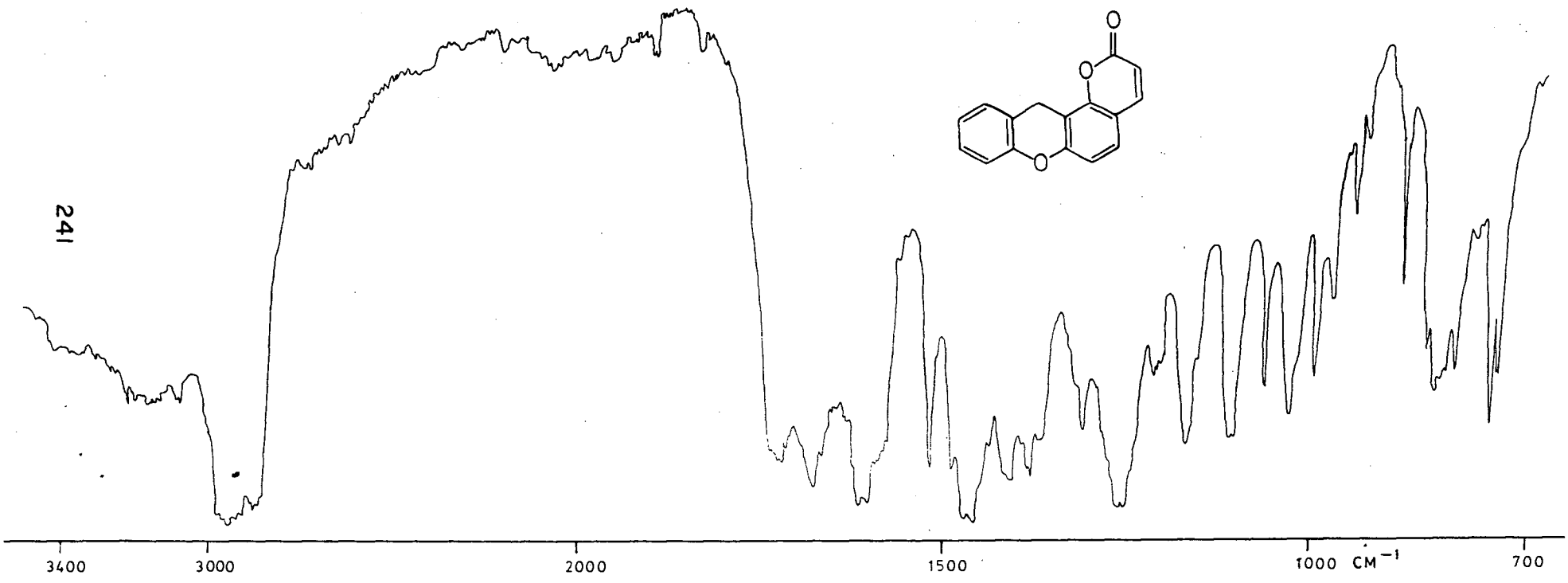

Fig. 16 IR SPECTRUM OF (27)

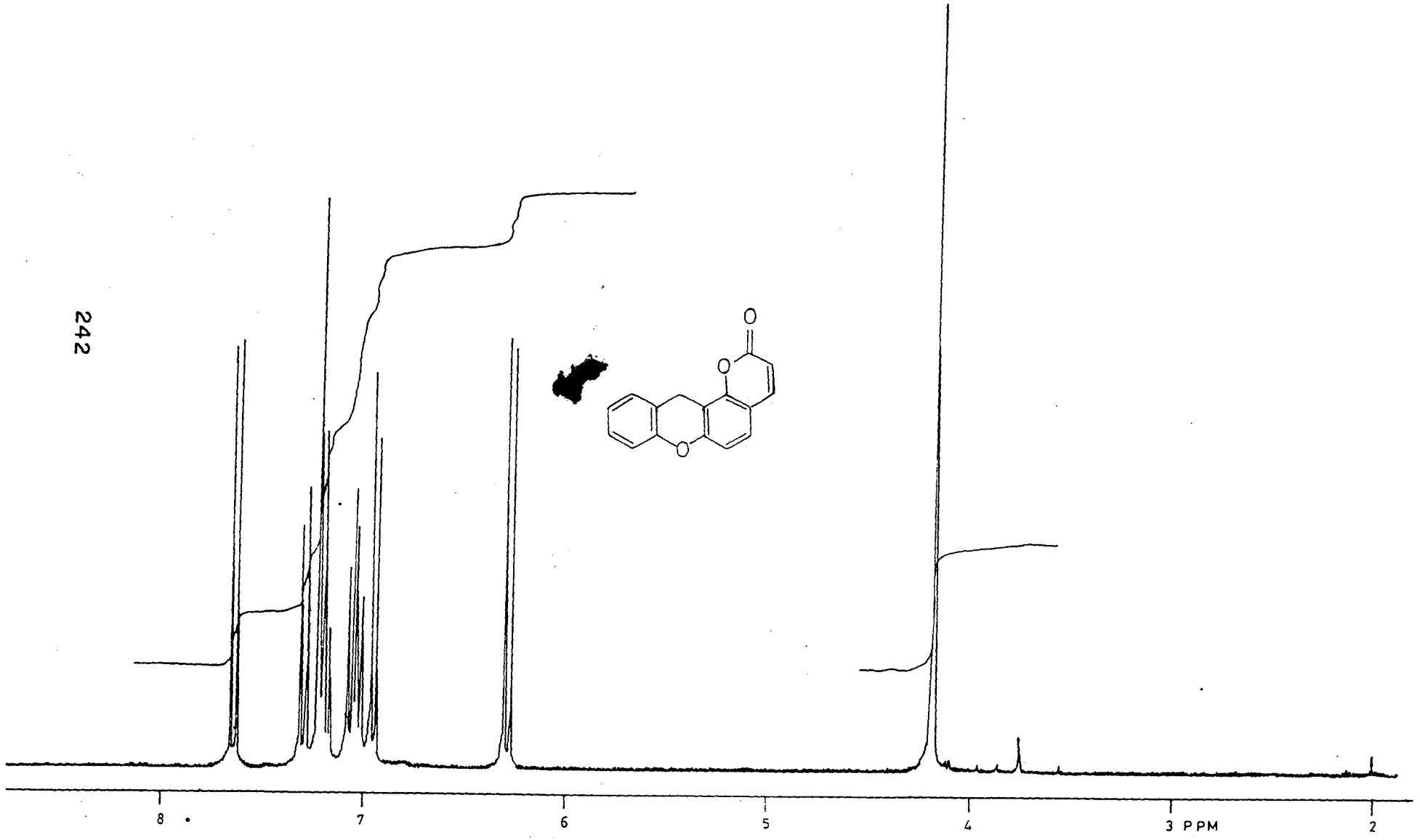

Fig. 17 ^{1}H NMR SPECTRUM OF (27)

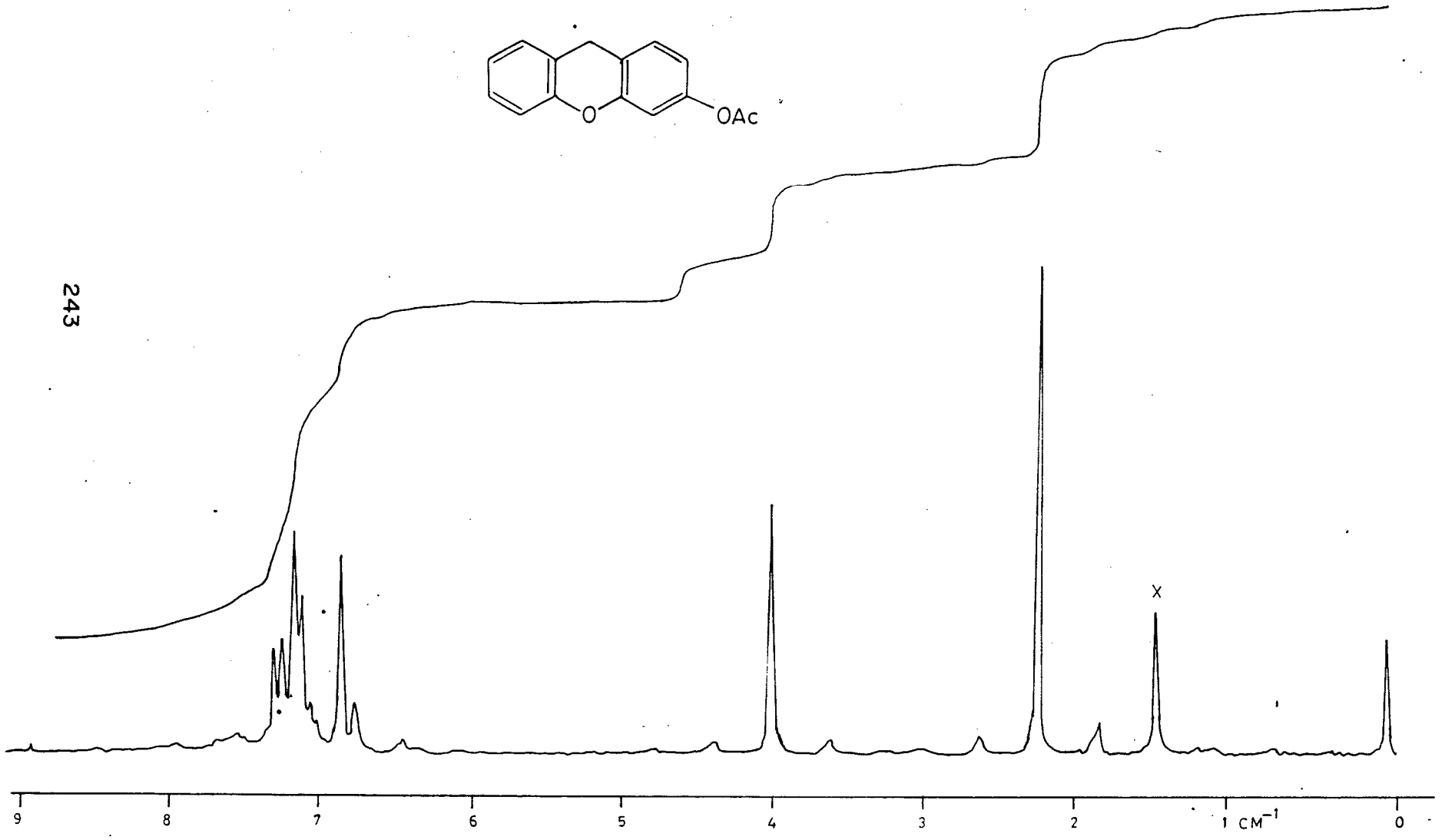

Fig. 18 ^{1}H NMR SPECTRUM OF (66)

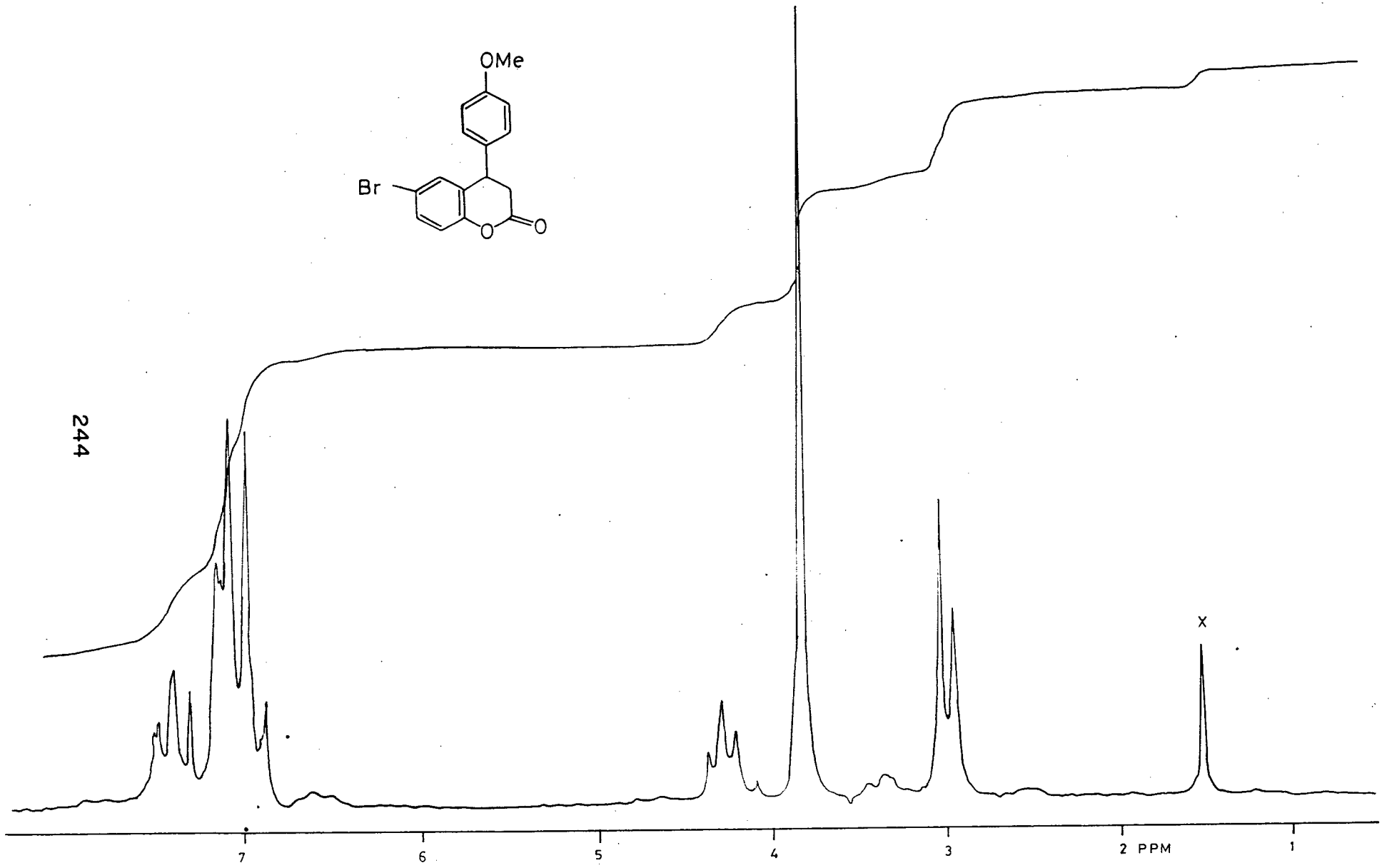

Fig. 19 ^{1}H NMR SPECTRUM OF (42)

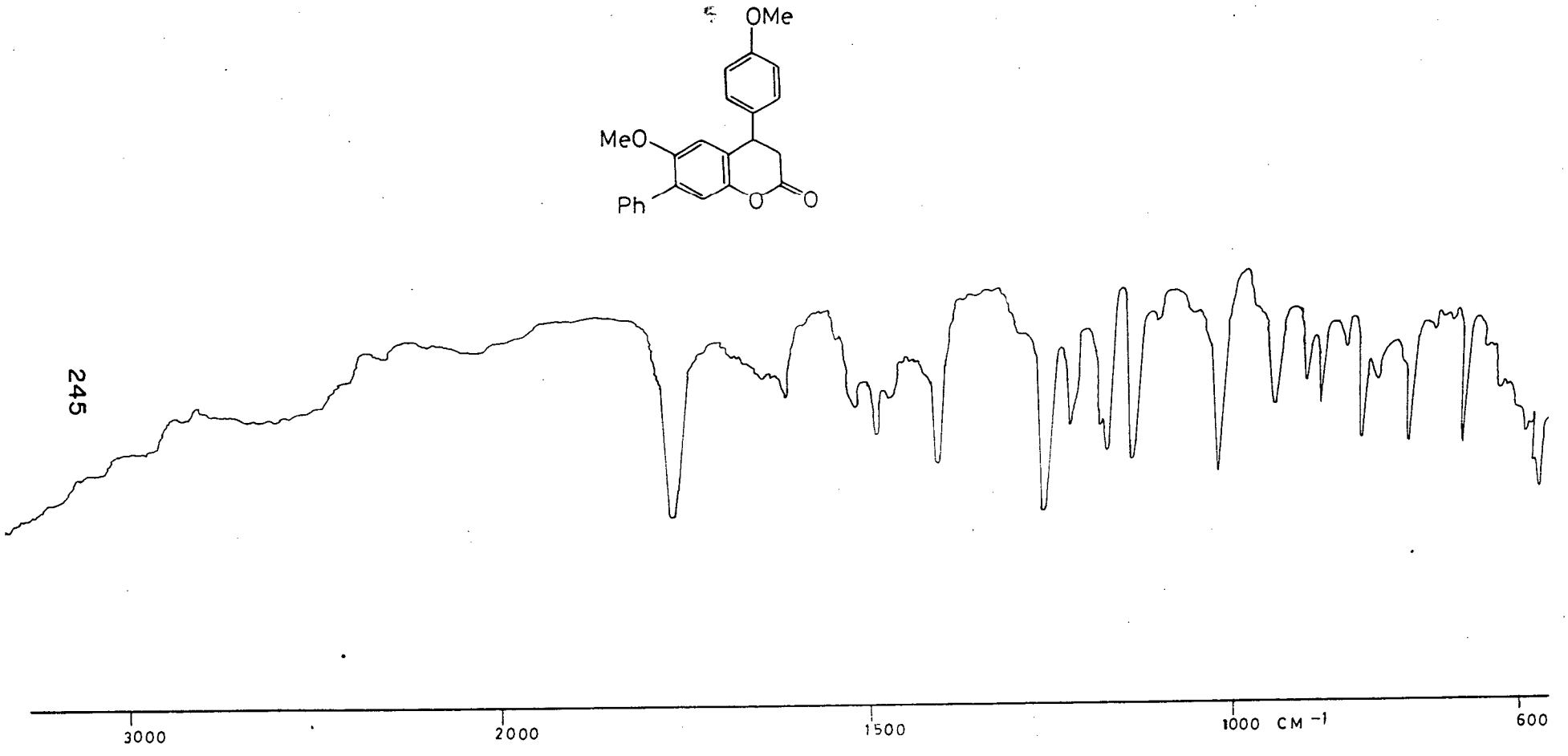

Fig. 20 IR SPECTRUM OF (43)

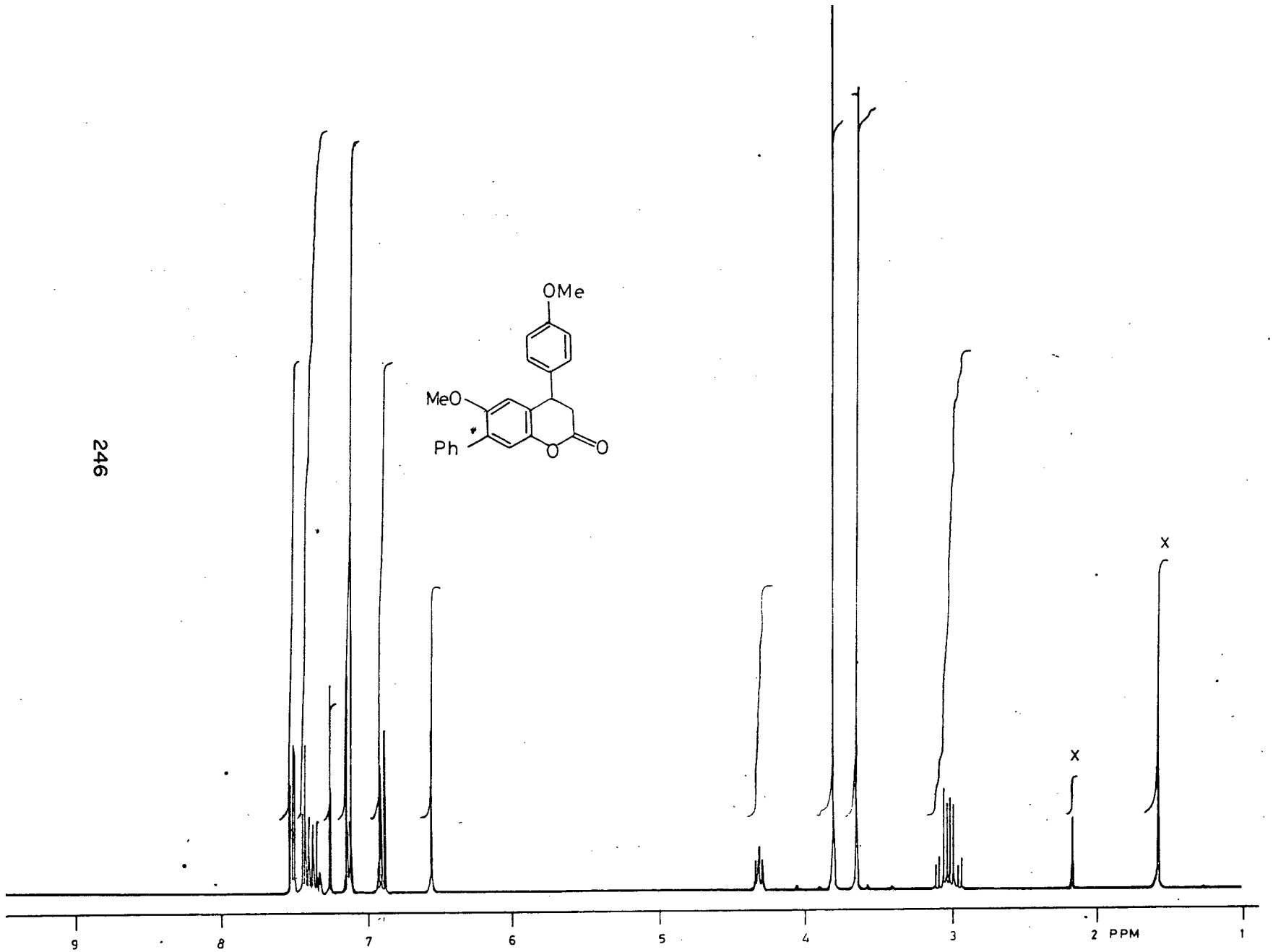

Fig. 21 ^{1}H NMR SPECTRUM OF (43)

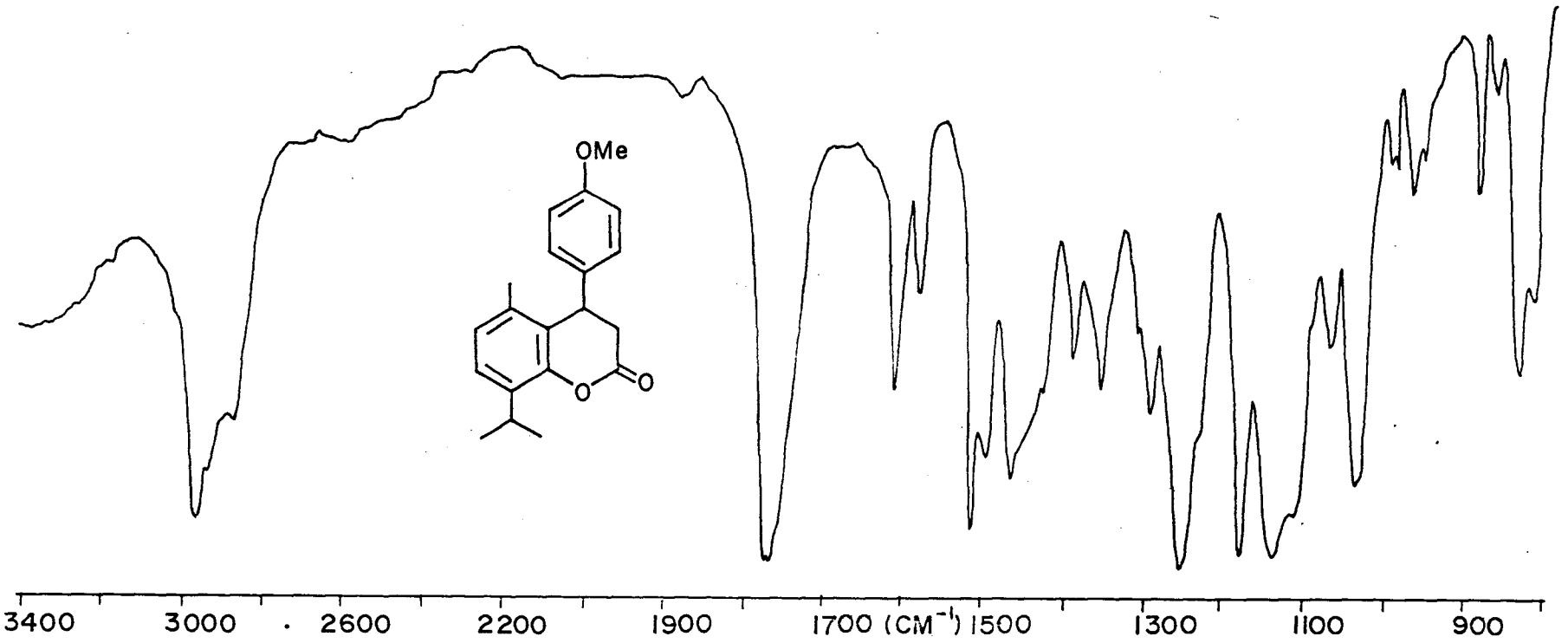

Fig. 22 IR SPECTRUM OF (44)

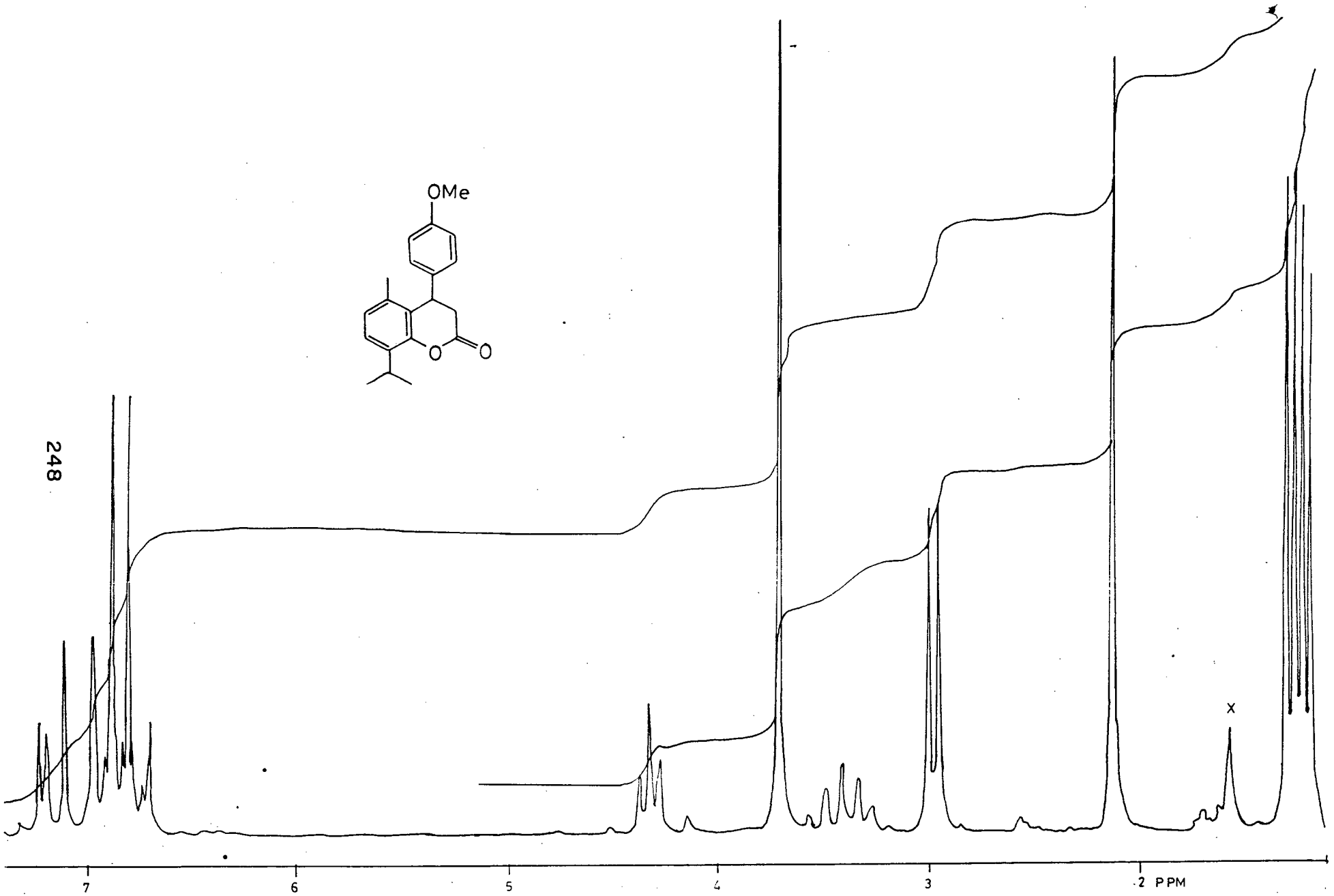

Fig. 23 ^{1}H NMR SPECTRUM OF (44)

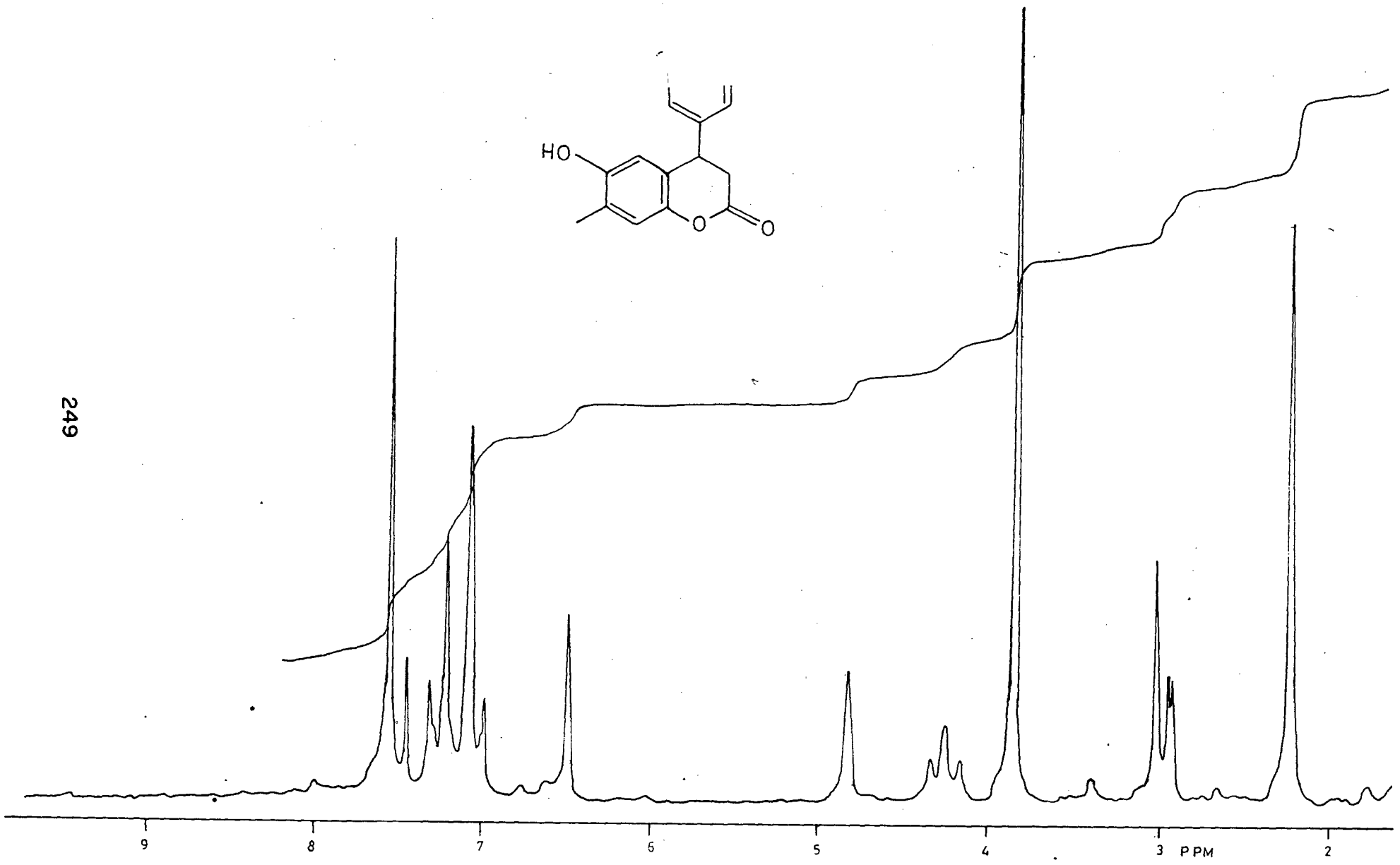

Fig. 24 ^{1}H NMR SPECTRUM OF (45)

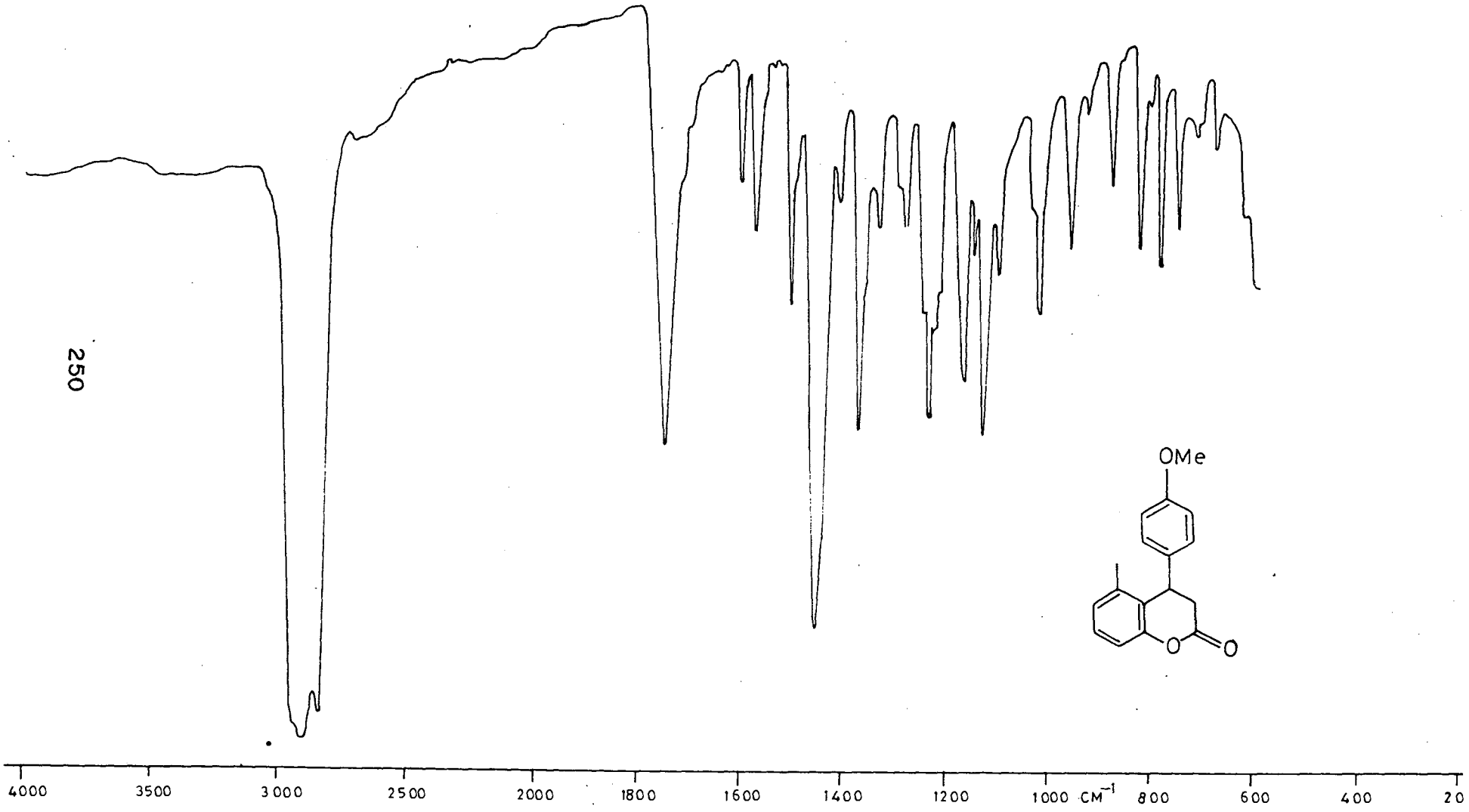

Fig. 25 IR SPECTRUM OF (47)

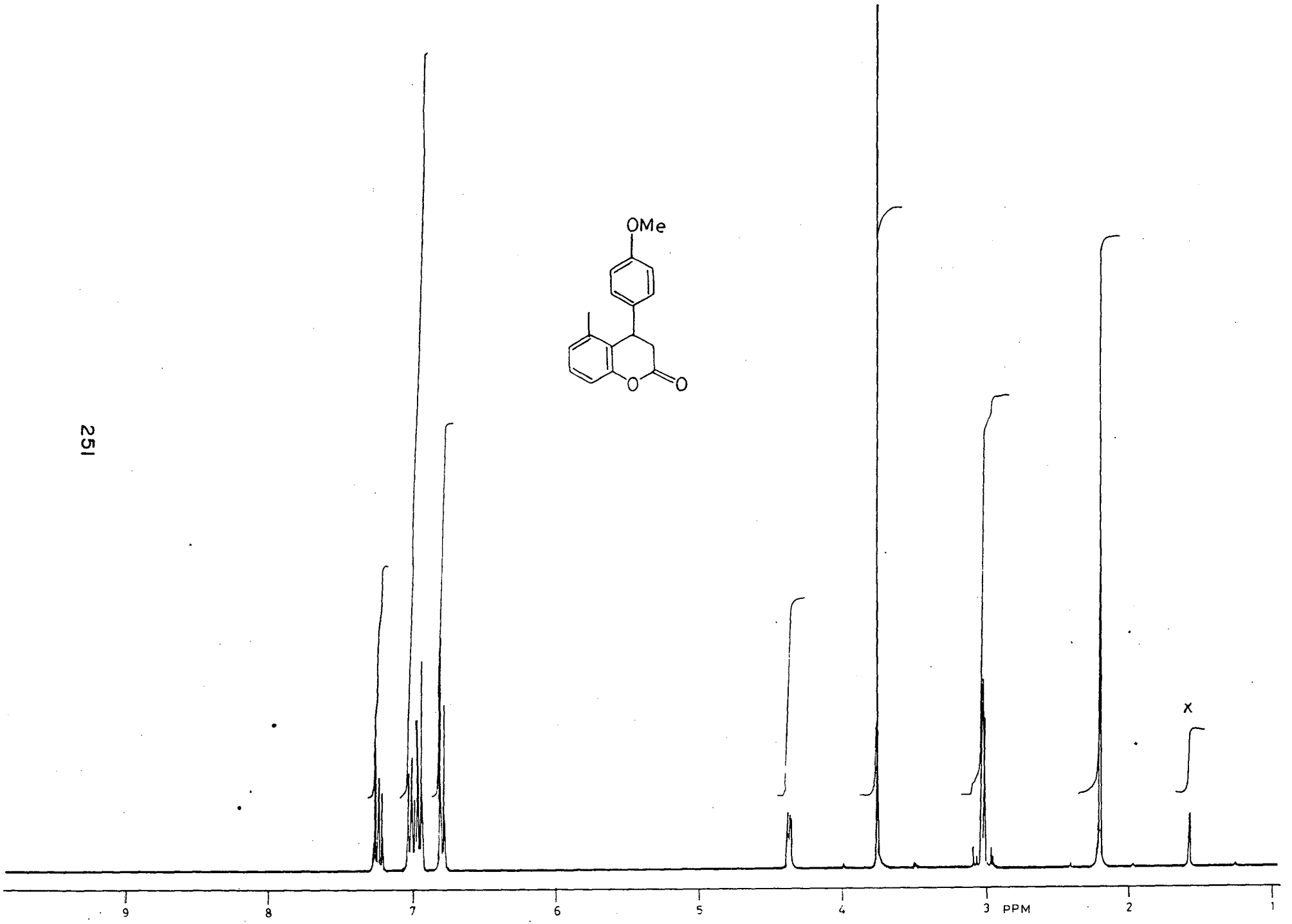

Fig. 26 ^{1}H NMR SPECTRUM OF (47)

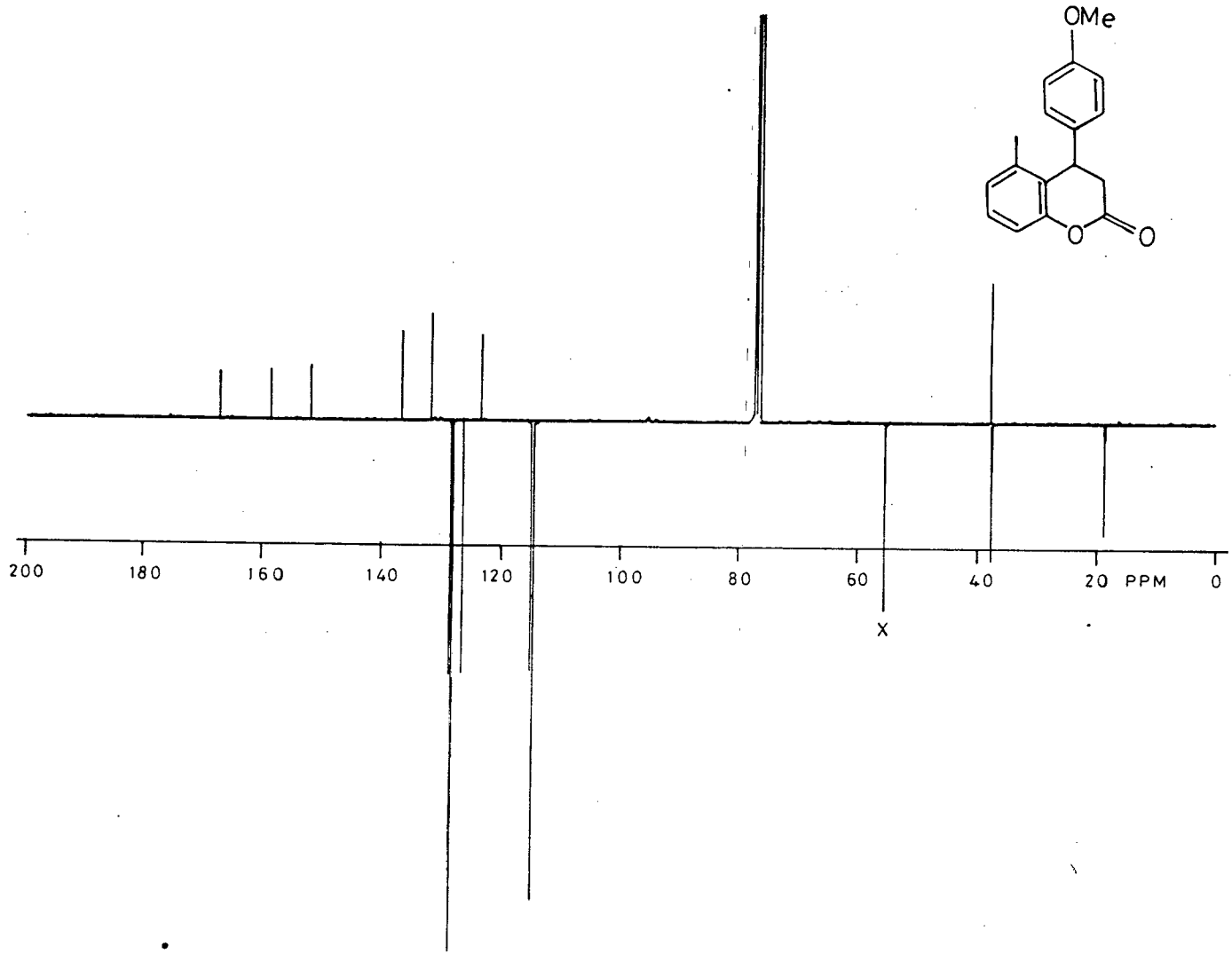

Fig. 27 ^{13}C NMR SPECTRUM OF (47)

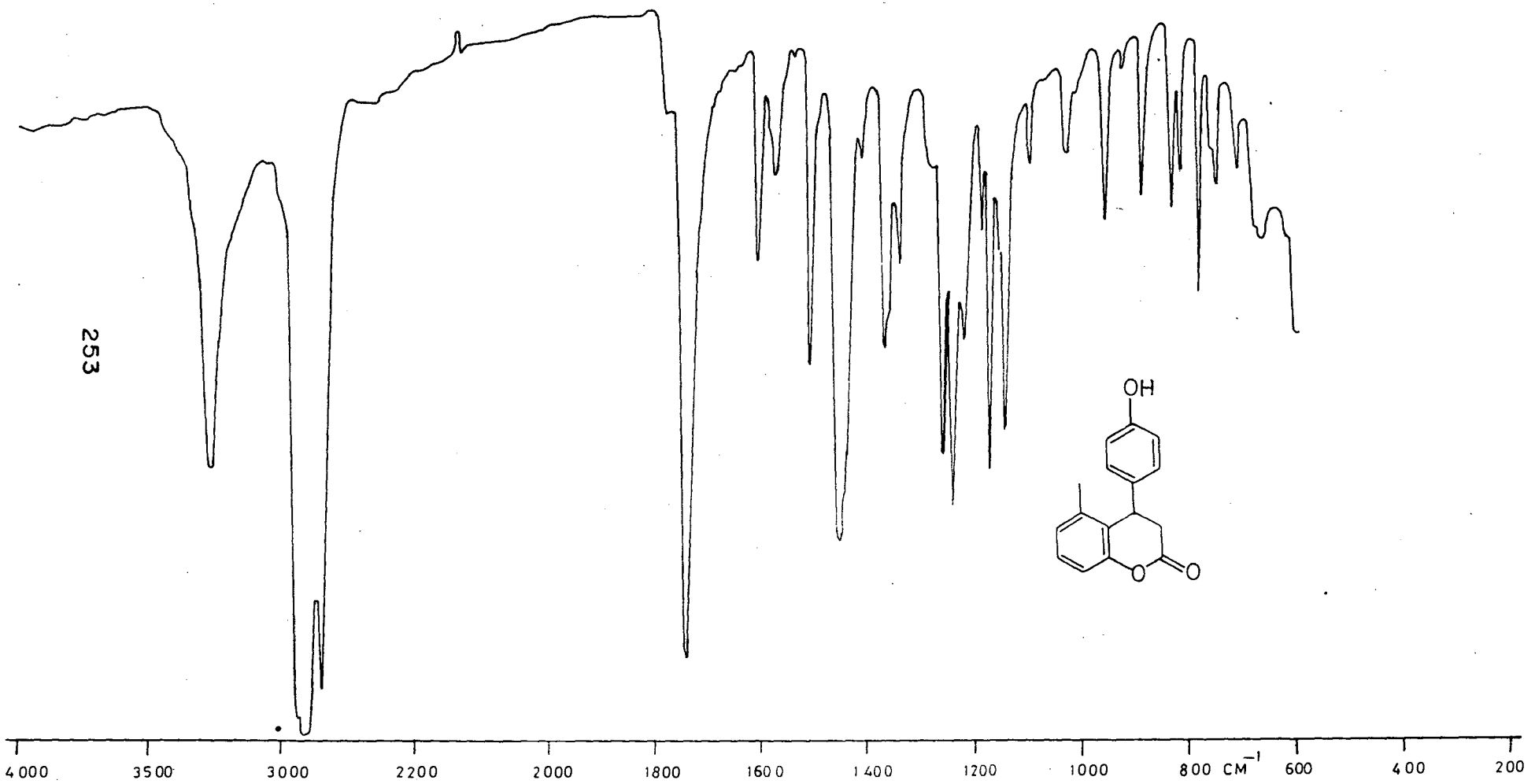

Fig. 28 IR SPECTRUM OF (48)

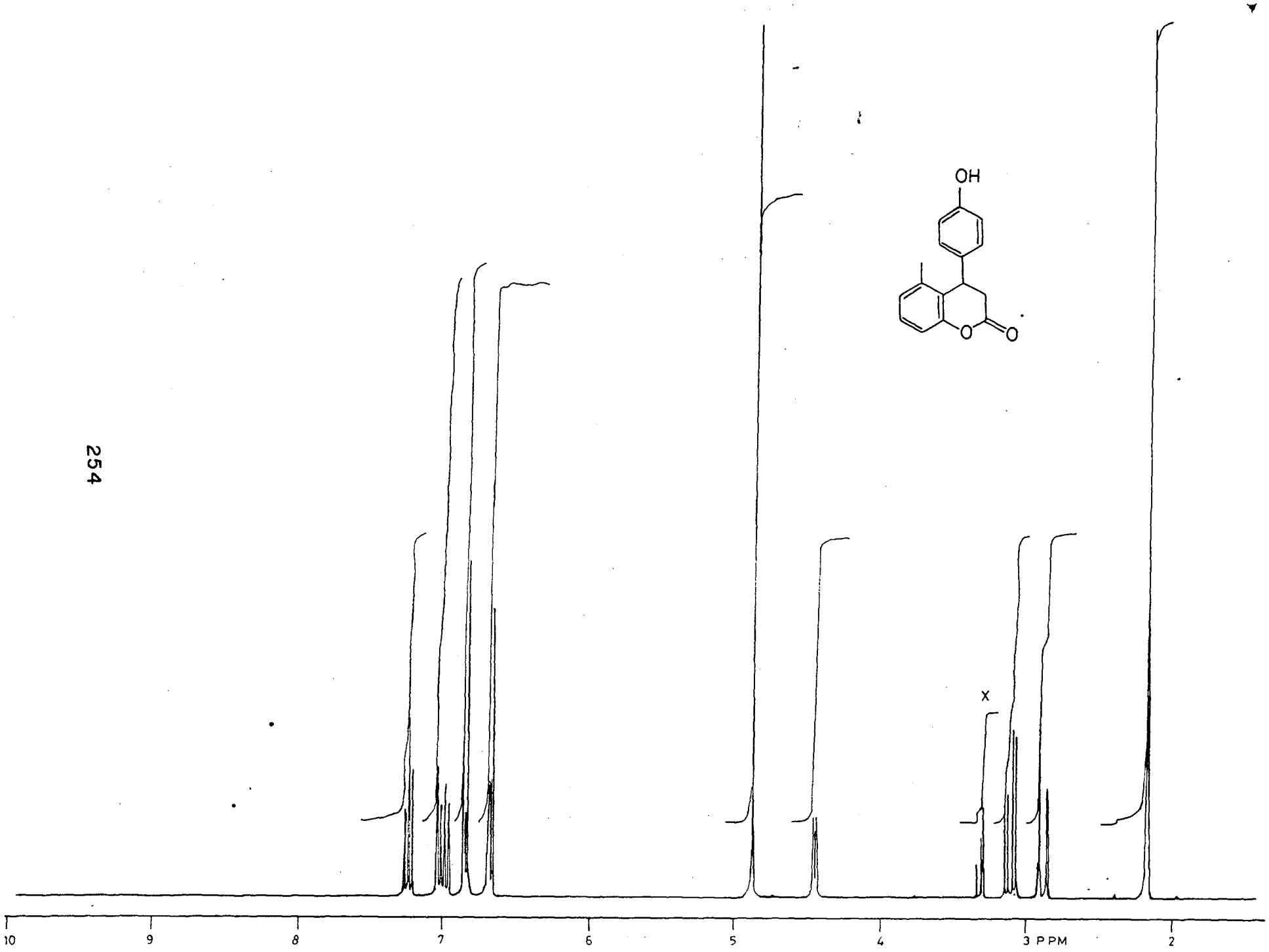

Fig. 29 ^{1}H NMR SPECTRUM OF (48)

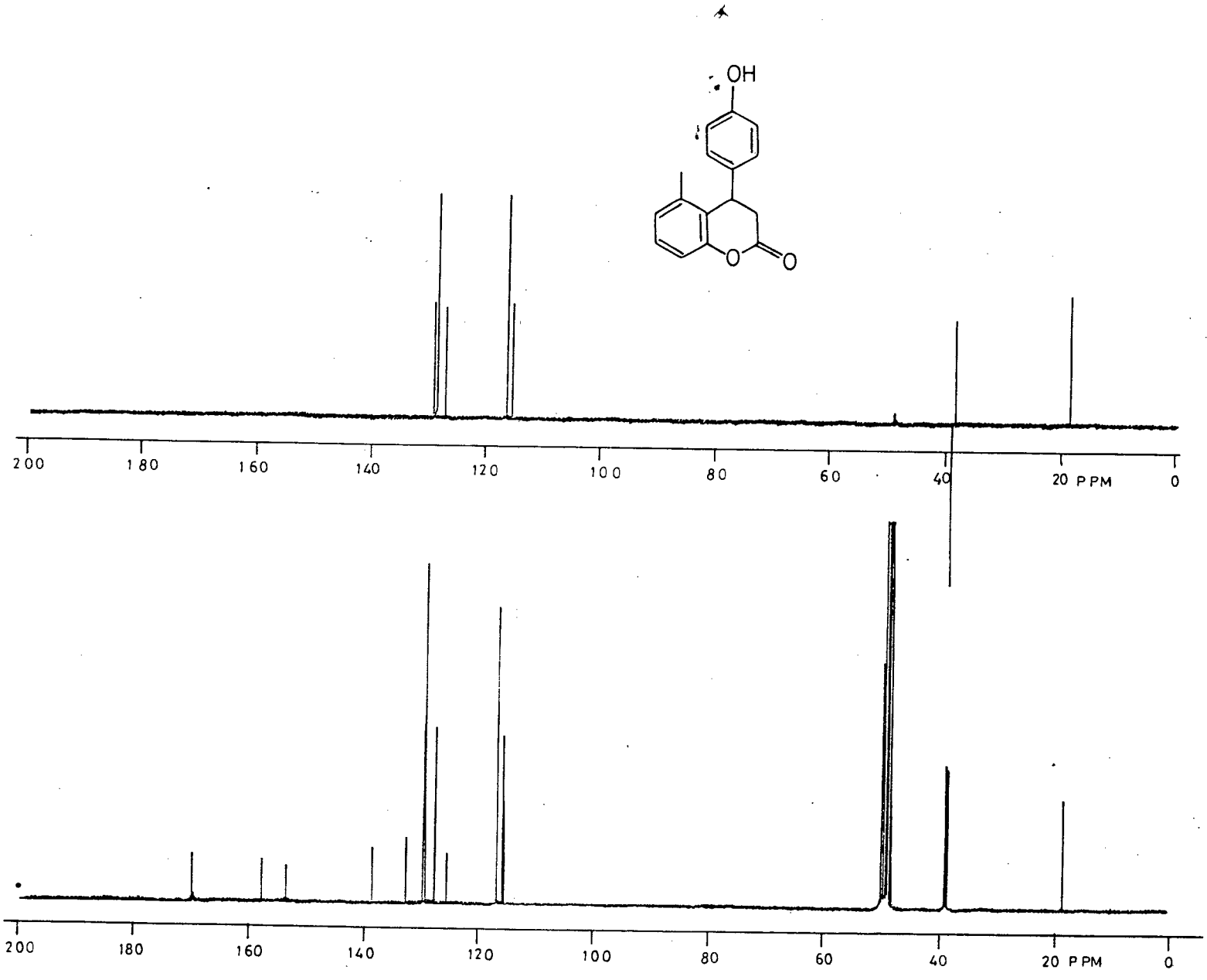

Fig. 30 ^{13}C NMR SPECTRUM OF (48)

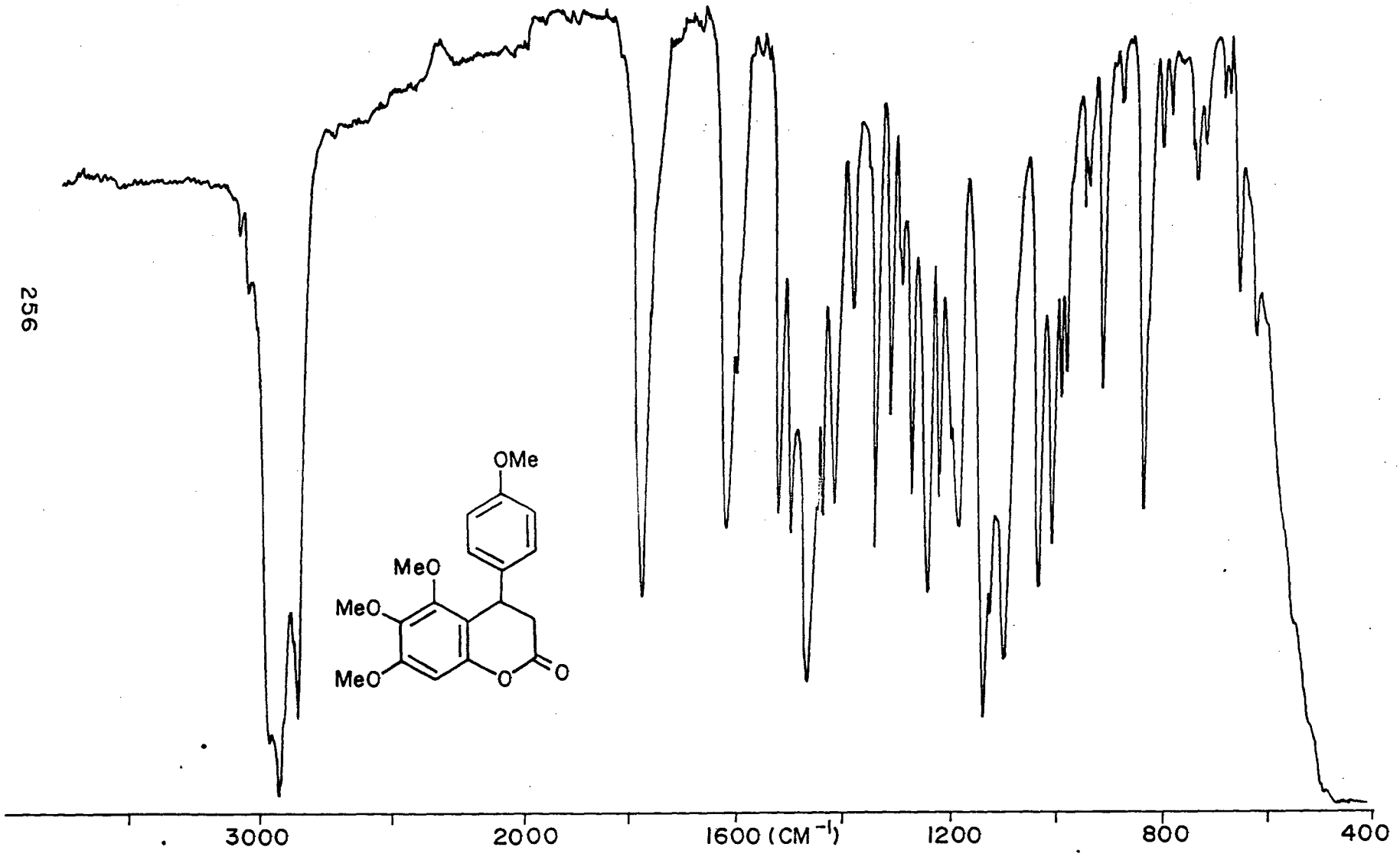

Fig. 31 IR SPECTRUM OF (12a)

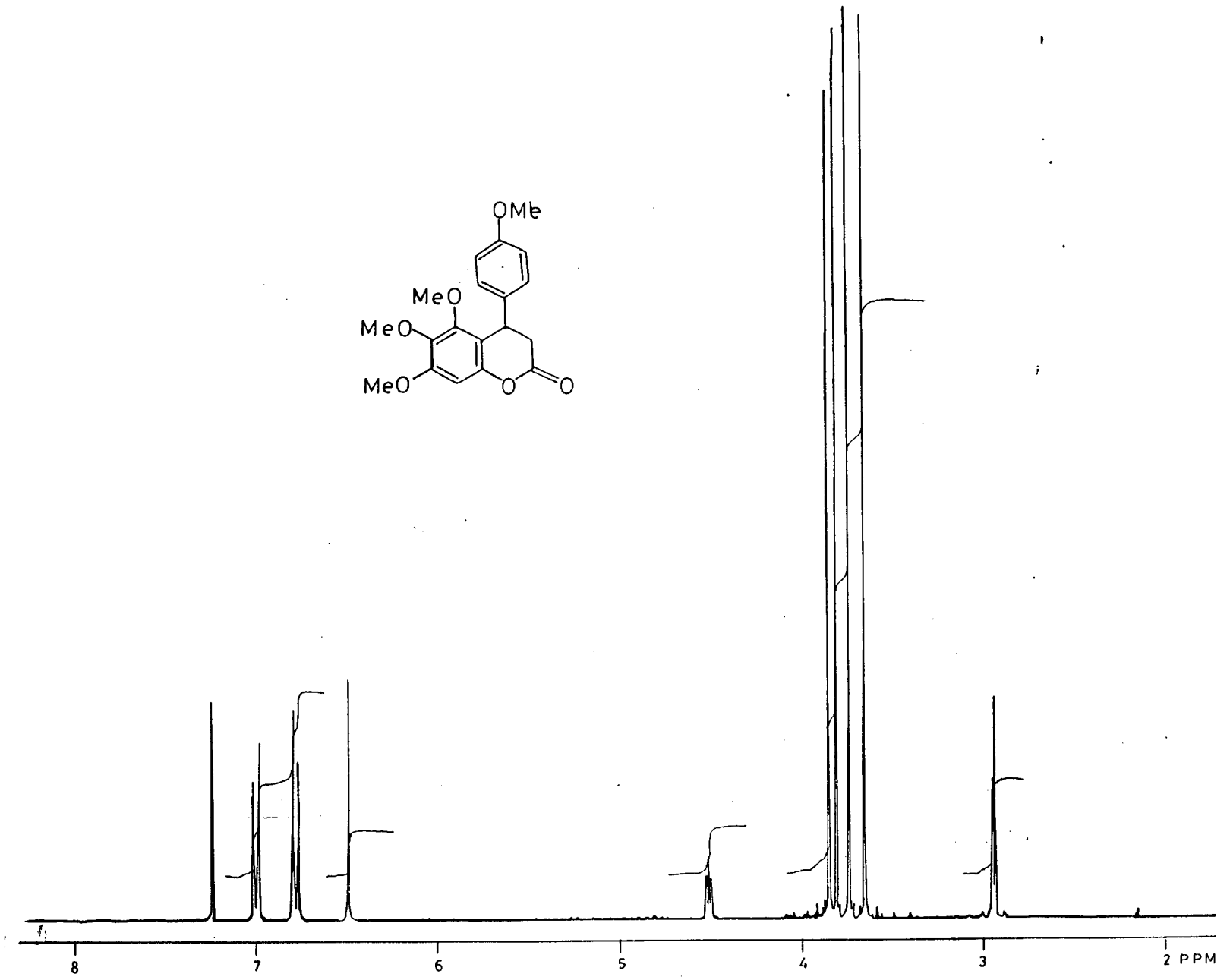

Fig. 32 ^{1}H NMR SPECTRUM OF (12a)

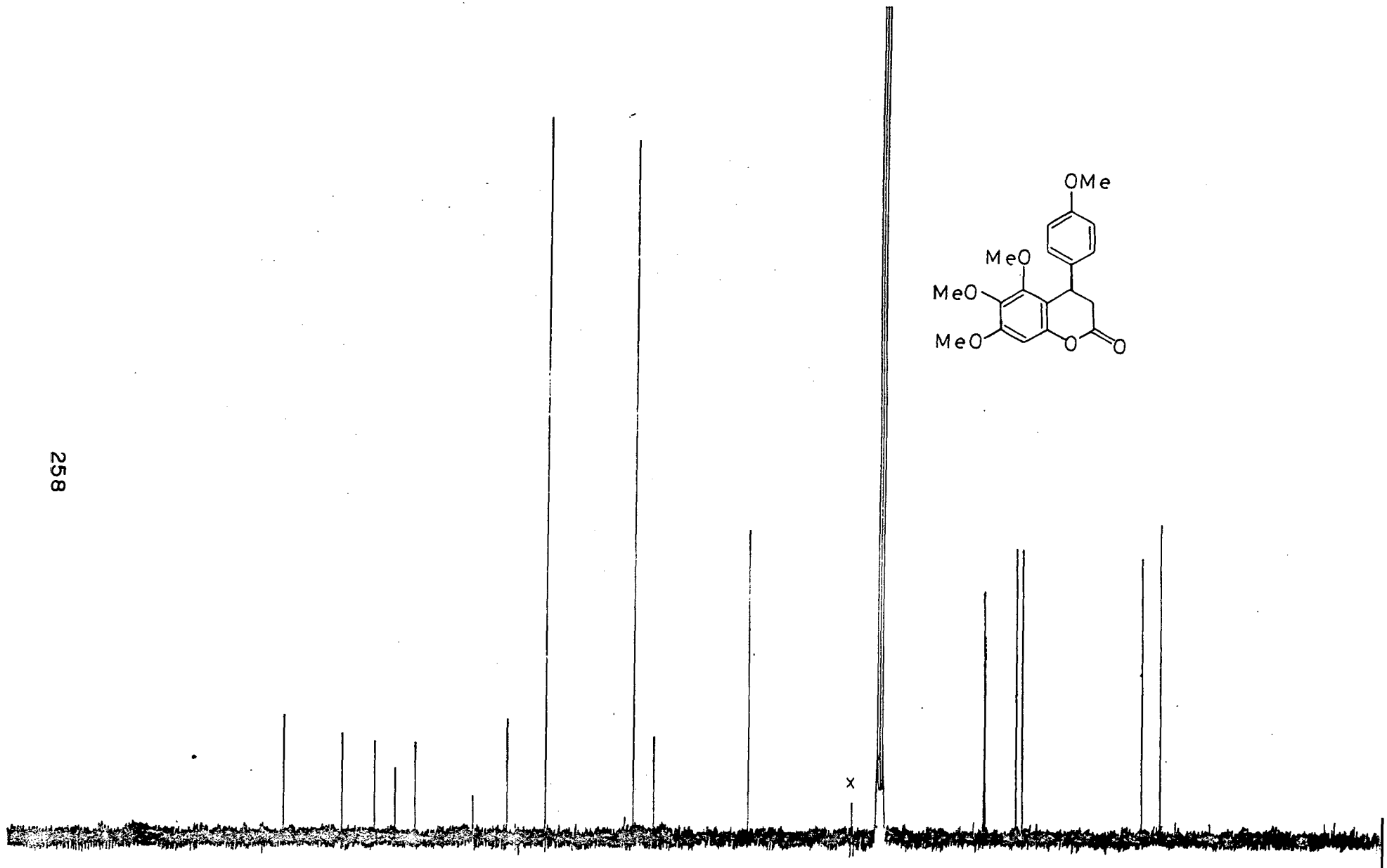

Fig. 33 ^{13}C NMR SPECTRUM OF (12a)

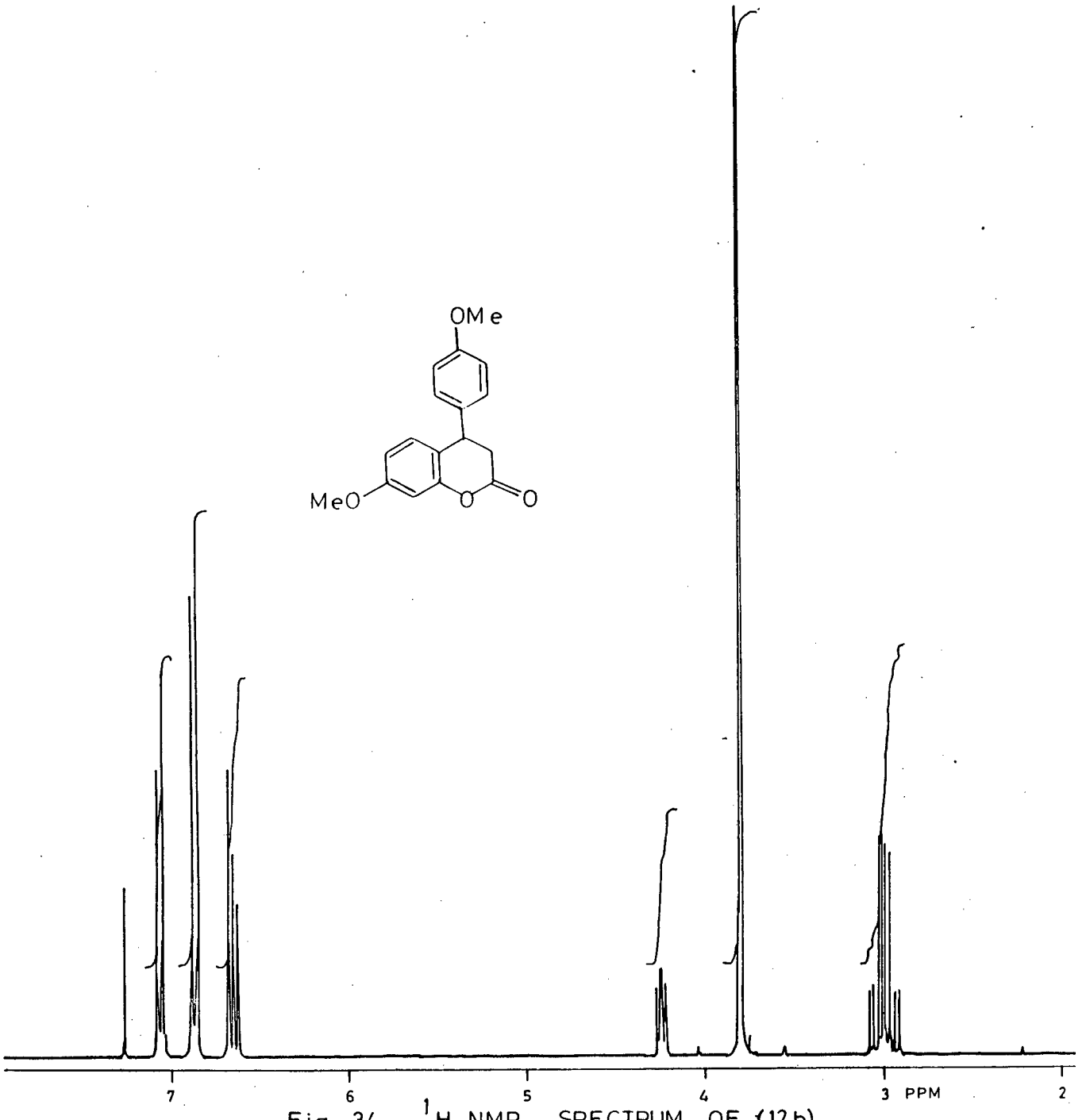

Fig. 34 ^{1}H NMR SPECTRUM OF (12b)

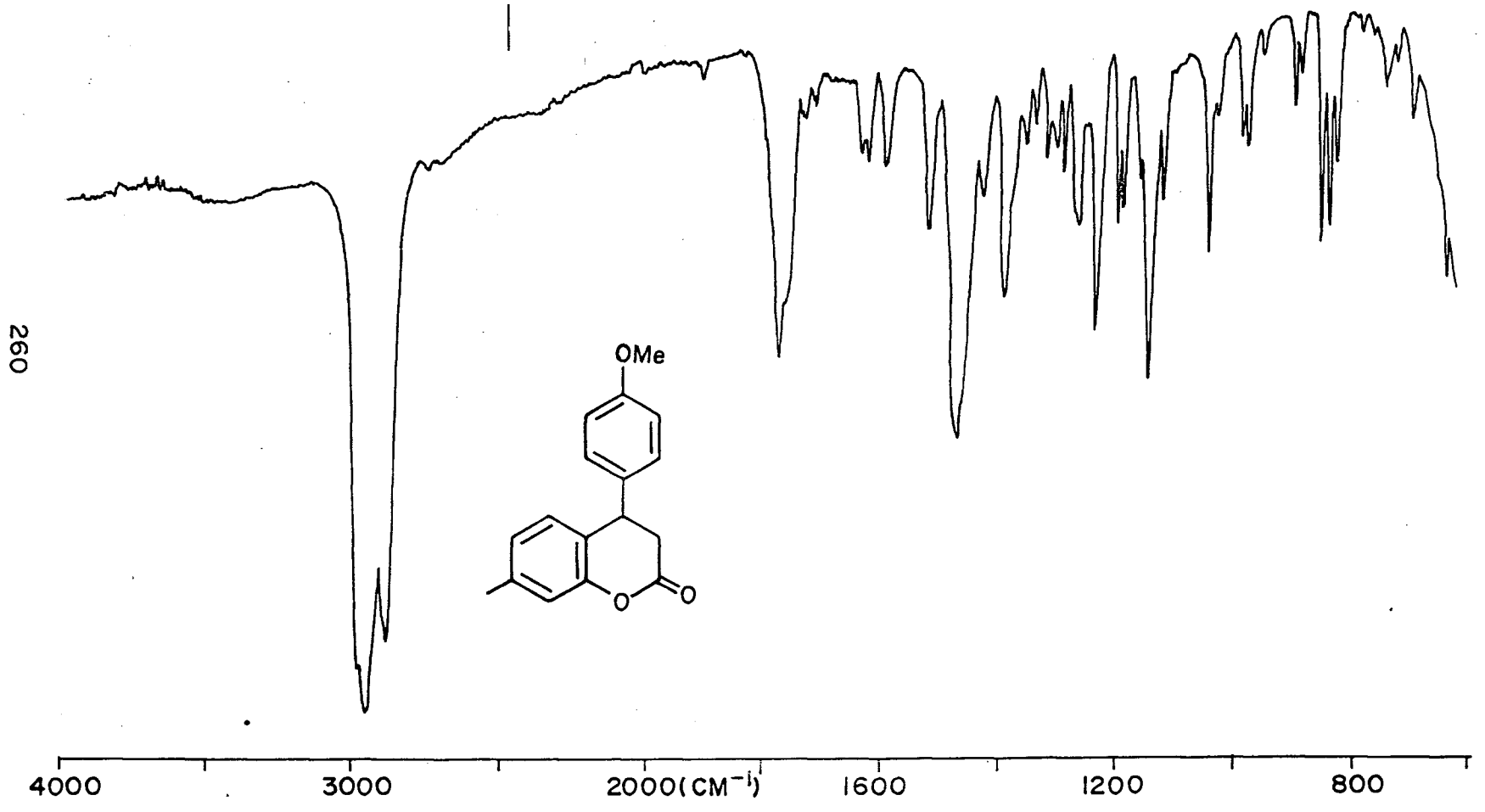

Fig. 35 IR SPECTRUM OF (12c)

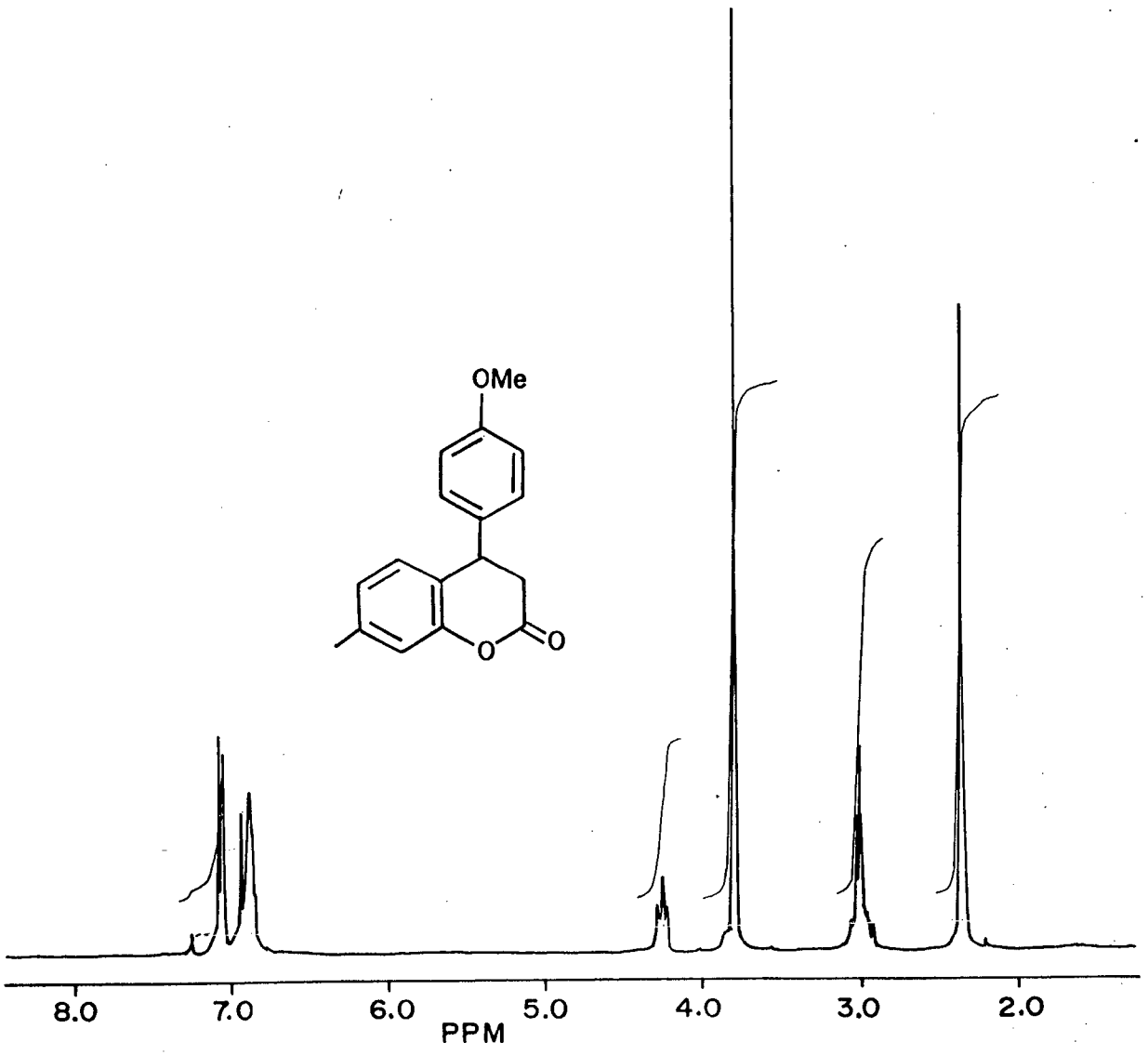

Fig. 36 ^{1}H NMR SPECTRUM OF (12c)

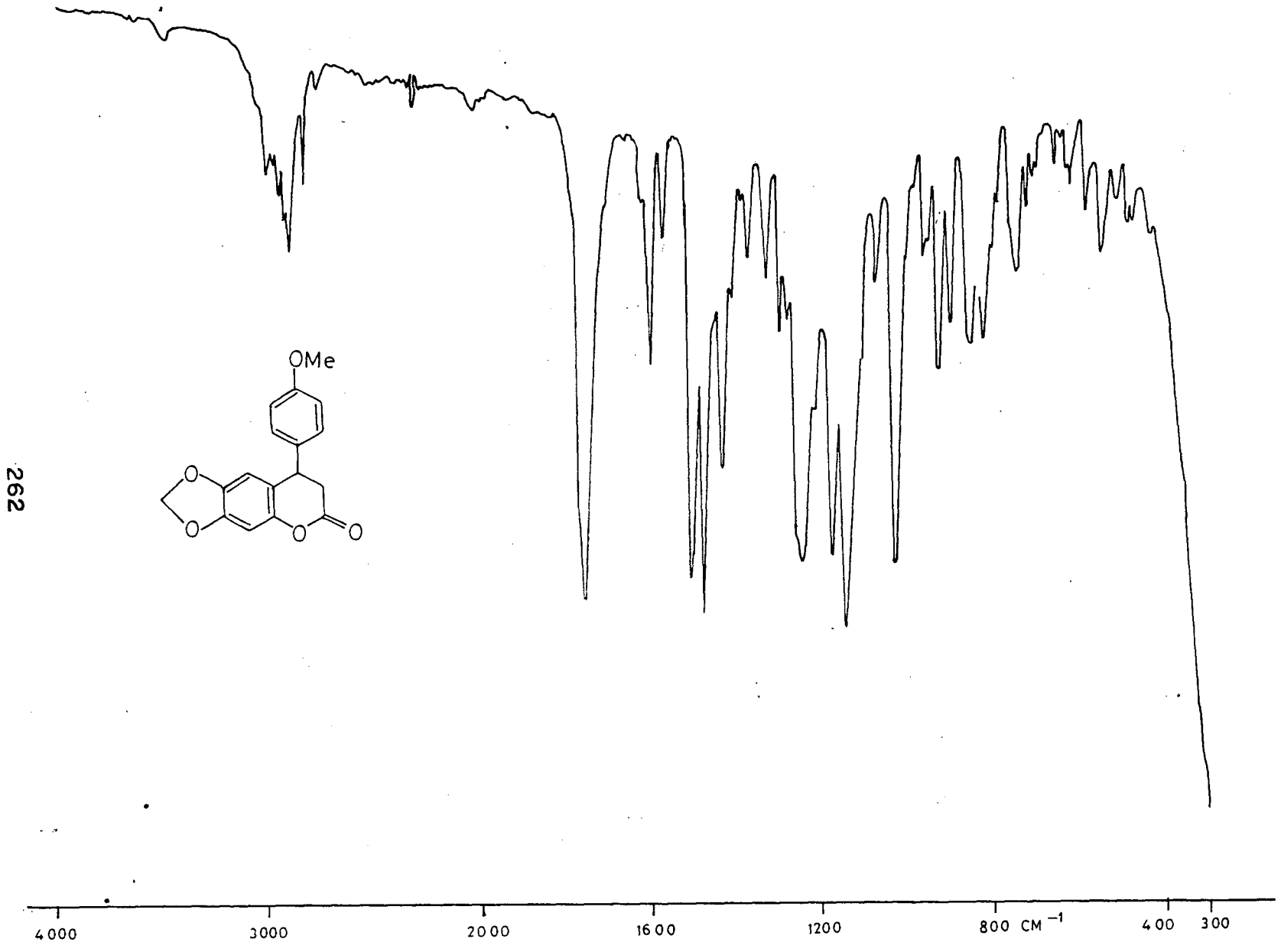

Fig. 37 IR SPECTRUM OF (12d)

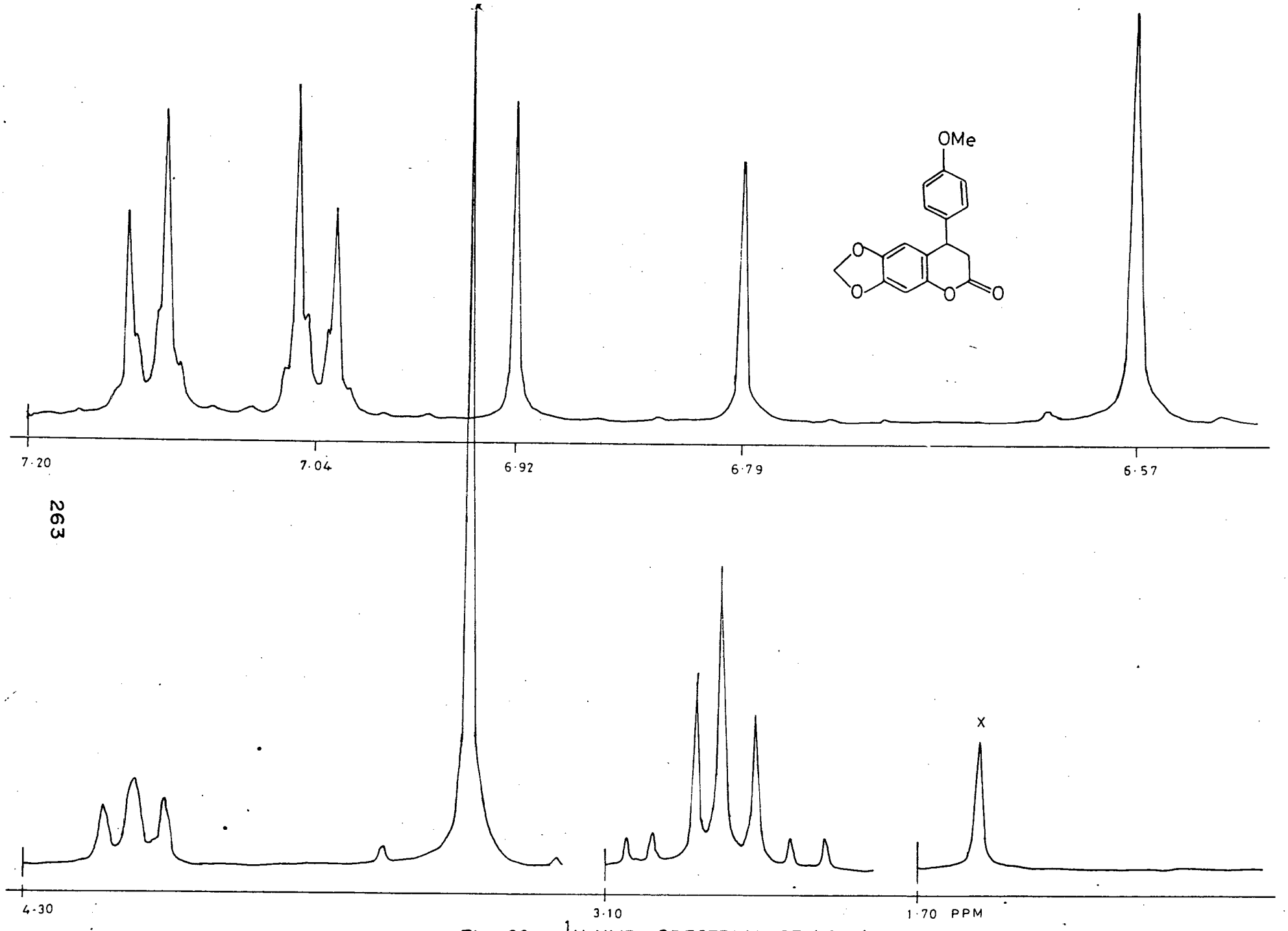

Fig. 38 ^{1}H NMR SPECTRUM OF (12d)

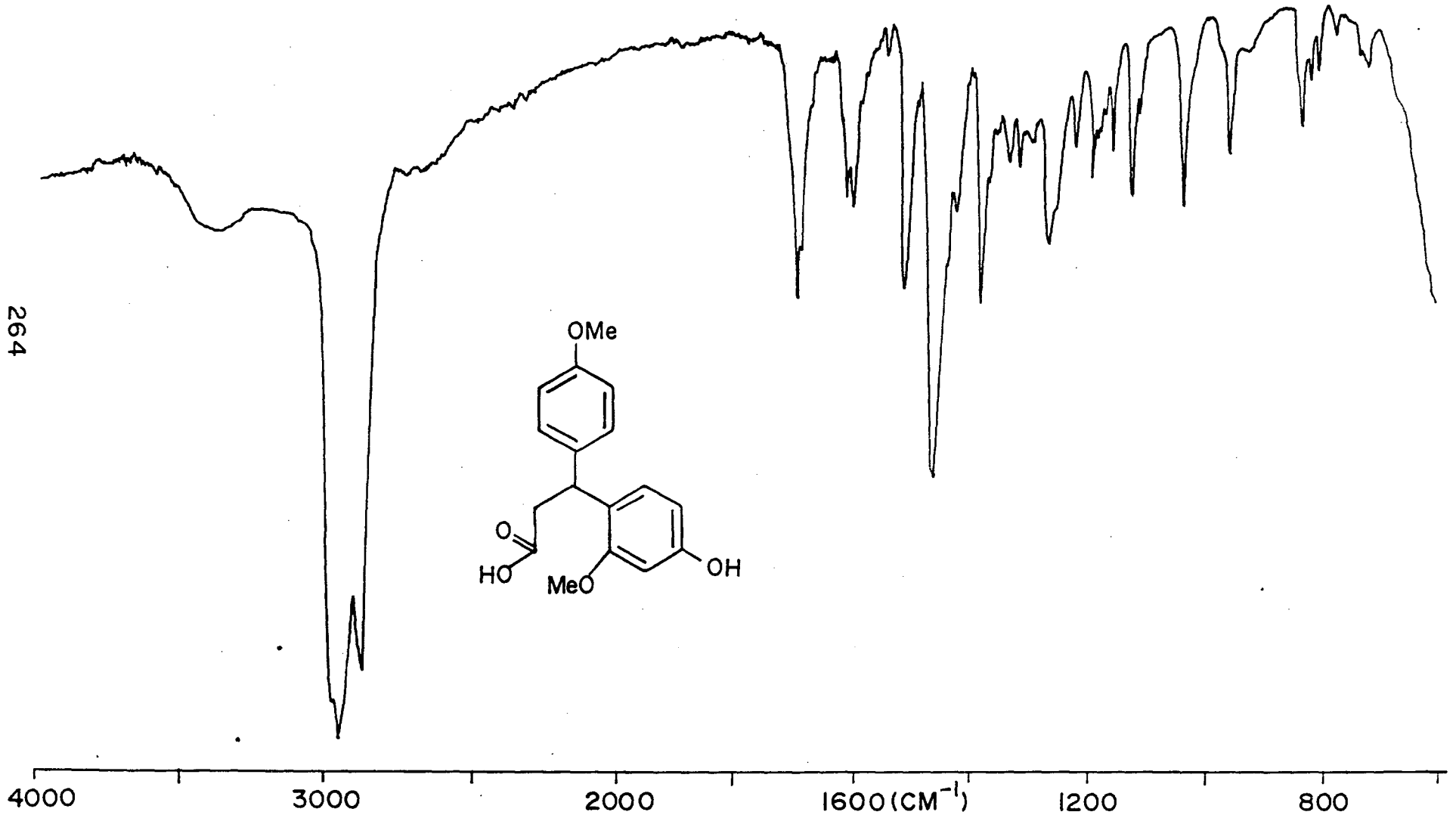

Fig. 39 IR SPECTRUM OF (53)

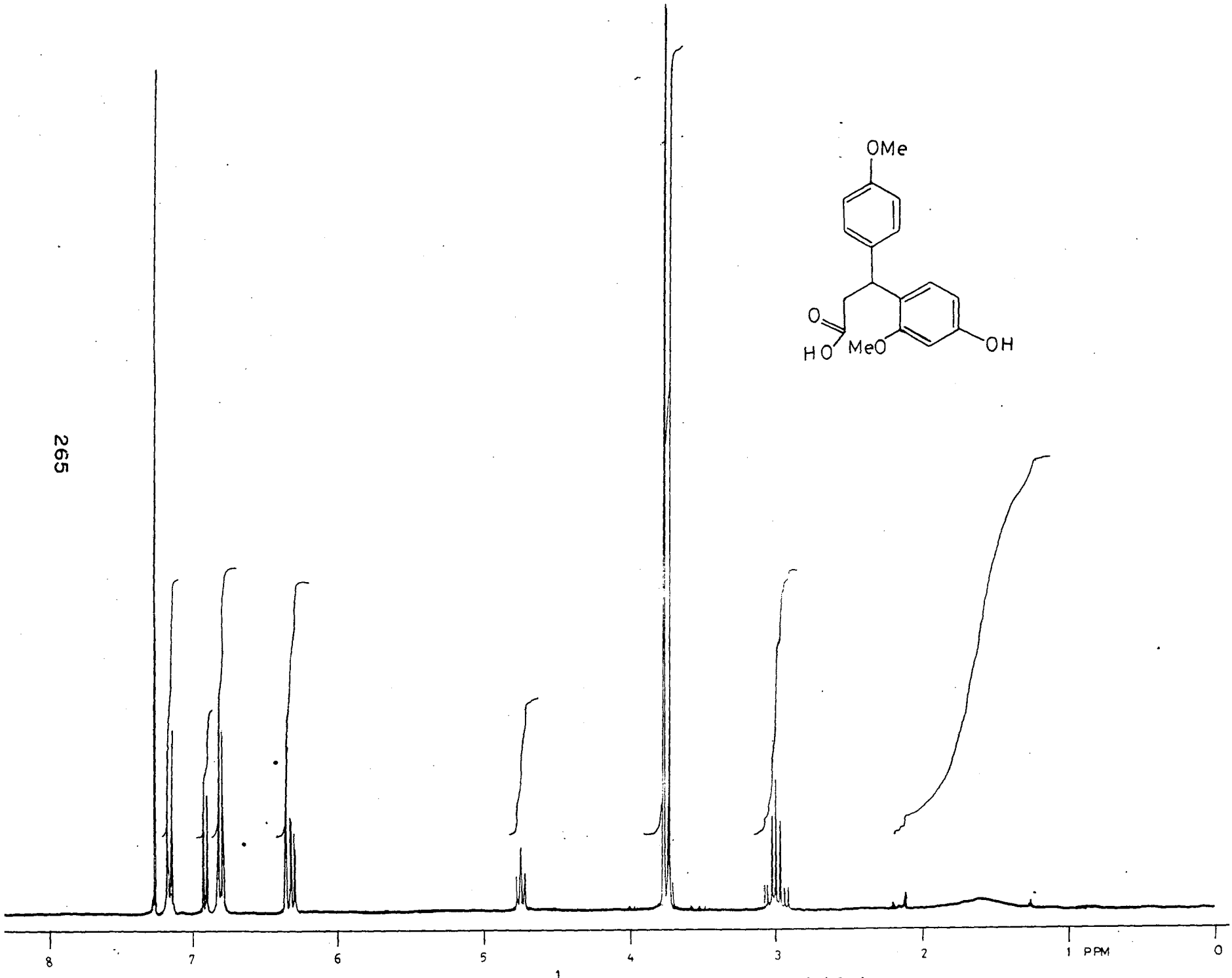

Fig. 40 ^{1}H NMR SPECTRUM OF (53)

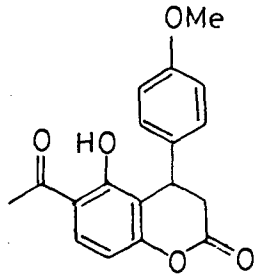

Fig. 41 ^{1}H NMR SPECTRUM OF (56)

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SUMMARY

The Thesis is divided into two parts

Part I : This contains the synthesis of naturally occurring coumarins and is classified into two chapters.

Chapter 1 : It deals with the synthesis of natural coumarins by the transfer of C_3- unit of p-methoxy cinnamic acid onto phenols using PPA. Most of the naturally occurring coumarins have a oxygen functionality at C_7. In our methodology we have observed that a meta-oxygen functionality in the phenol assists the reaction and further the same functionality appears at C_7 of the coumarin nucleus. Following naturally occurring coumarins have been synthesised and the details are incorporated sectionwise.

Section-1: It describes a new synthesis of 5,7 dimethoxy-6-hydroxy coumarin commonly known as fraxinol. The present synthesis is much shorter compared to the previous synthetic routes.

Section-2: This deals with the synthesis of 6-hydroxy-7-methoxy coumarin (isoscopoletin), a coumarin first isolated from Artemisia messerschmidiana (compositae) having biological activity. The present synthesis is an extension of our new coumarin synthesis

and makes use of 2-methoxy-1,4-hydroquinone as the starting material.

Section-3: A natural product isolated from Artemisia dracunculoids (compositae) has been shown to be 7-methoxy-8-hydroxy coumarin on the basis of spectral analysis. The assigned structure is now confirmed by a straight forward synthesis.

Chapter 2 : This chapter includes the synthesis of 4-substituted naturally occurring coumarins and is sub-divided into three sections. Each section describes the synthesis of one naturally occurring coumarin.

Section-1: This deals with the synthesis of 4-hydroxy-5-methyl coumarin, a naturally occurring coumarin having antibacterial activity.

Our interest in the synthesis of this coumarin was two fold. Firstly, because it is a natural product and secondly a large number of other natural products having medicinal value could be synthesised from it.

The present method offers a special advantage over previous synthetic routes where 4-hydroxy-7-methyl coumarin has been always found to be major product. In our synthesis 4-hydroxy-7-methyl-coumarin is not formed at all.

The isopropyl group of the starting phenol, thymol served as a blocking group thus yielding only 4-hydroxy-5-methyl-coumarin after deisopropylation with $AlCl_3$ in chlorobenzene.

The product obtained on acetylation of 4-hydroxy-5-methyl-8-isopropyl coumarin has also been fully characterised.

Section 2: This describes the synthesis of (±) 6-hydroxy-3,4-dihydro-4,7-dimethyl coumarin, a naturally occurring coumarin isolated by Cambie and co-workers in its laevorotatory form from the heart wood of Heritiera ornithocephda (Fam sterculiaceae). In view of its structural similarity with its congener cis-7-hydroxy calamenene they suggested that these compounds may share a common biogenetic precursor. Because of our continued interest in modified terpenoids, the structural features present in this coumarin attracted our attention and a straightforward synthesis of 6-hydroxy-3,4-dihydro-4,7-dimethyl coumarin has been achieved. A detailed biosynthetic scheme depicting the manner in which the four carbon atoms of a sesquiterpene precursor are lost is also presented.

Section 3: This incorporates the synthesis of 4-methyl-6,7-methylenedioxy coumarin from 3,4-methylenedioxy phenol (sesamol) and ethyl aceto acetate using pechmann conditions. The method exclusively gives 4-methyl-6,7-methylenedioxy coumarin. The synthetic coumarin was found to have different physical & spectral properties than those reported on the natural product. The structure assigned to the natural product isolated from Achillea schischkinii by Ulubelen and co-workers therefore needs revision. A tentative structure is proposed for the natural product.

Part II

In order to study the generality of our coumarin synthesis, a large number of non naturally occurring coumarins have been synthesised and characterised. Formation of 4-aryl-3,4 -dihydro coumarin as intermediate is established beyond doubt. It is observed that in some cases only 4-aryl-3,4-dihydrocoumarins are formed while in some reactions 3,4-unsubstituted coumarins are exclusive products. This part is divided into two chapters.

The individual chapters are further subdivided into sections inorder to have continuity in presentation.

Chapter 3 : It describes the synthesis of three methyl substituted coumarins viz 7-methyl;6,7-dimethyl and 7,8-dimethyl coumarins. 6,7-Dimethyl-3,4-dihydro-4-(p-methoxyphenyl) coumarin has also been characterised **(section-1)**.

Benzylated flavanoids have been found to be biologically active compounds. However, naturally occurring benzylated coumarins are yet unknown. An attempted synthesis of 6-benzyl-7-methyl coumarin is described in **(section-2)**.

A convenient synthesis of 6-methoxy-7-ethoxy coumarin is reported in **(section-3)**.

Xanthanocoumarins are yet to be discovered as natural products but there are scanty reports about the synthesis of few representatives of this group. Experiments directed towards synthesis of compound of this group using our C_3-transfer coumarin synthesis are incorporated in **(section-4)**.

Considering the practical difficulties in handling PPA, the reaction of phenols with p-methoxy cinnamic acids were carried out by replacing PPA by 75% H_2SO_4 and the results obtained are presented in **(section-5)**.

Chapter 4 : This deals with the synthesis of 3,4-dihydro-4-(p-methoxyphenyl) coumarins that are considered as intermediates in the reaction of phenols with p-methoxy cinnamic acid using either PPA or 75% H_2SO_4-dioxane reagents.

Various 4-(p-methoxyphenyl)-3,4-dihydrocoumarins have been obtained and their characterisation by special methods is described. These were found to be the only products when 75% H_2SO_4 -dioxane combination was used in place of PPA.

Contrary to the finding of previous investigators, no dearylation was observed when 5-methyl-8-isopropyl-4-(p-methoxyphenyl)-3,4-dihydrocoumarin was treated with anhydrous $AlCl_3$ in dry chlorobenzene. Only deisopropylation was observed and the results are presented.