TRANSFORMATION STUDIES OF TERPENOIDS AND NEW SYNTHESIS OF BENZOFUROBENZOFURANS

A THESIS SUBMITTED TO THE

GOA UNIVERSITY

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

IN

CHEMISTRY

BY

BHIWA LADU MALIK M.Sc.

Department of Chemistry

Goa University

Taleigao plateau

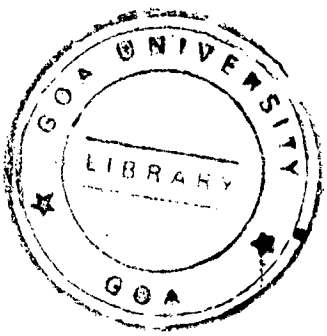
1995

TO

MY PARENTS

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

B. L. Malik
Candidate

C O N T E N T S

GENERAL REMARKS

1. All chart, scheme, table, structure, figure and reference numbers in the chapter refer to that particular chapter only.

2. Organic extracts were dried over anhydrous $MgSO_4$ unless otherwise stated.

3. All melting and boiling points were recorded in degrees celcius and are uncorrected.

4. Petroleum ether refers to the fraction boiling between the range 60^0-80^0.

5. Ether refers to diethyl ether.

6. Silica gel used for column chromatography was of 60-120 mesh size.

7. Thin layer chromatography was done on glass plates coated with TLC grade silica gel with 13% $CaSO_4$ as binder. Visualisation of the plates were done by developing the plates in I_2 chamber, unless otherwise stated.

8. 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.

9. The chemical shift parameters in the ^1H 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 logarithm.

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

ACKNOWLEDGEMENT

I am proud for having the privilege to work with Dr. S. K. Paknikar, Professor and Head, Department of Chemistry, Dean, Faculty of pure sciences of Goa University, as my guide in the course of my research work. I express my deep sense of gratitude to him for his continuous help, valuable and inspiring guidance. This work would not have been completed without his resourcefulness and imaginative approach. I shall be ever grateful to him for the help he has given to me.

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I thank NCL-Poona, IIT-Bombay, Poona University, FDA-Goa for the spectral data made available whenever required. I also thank library staff of NIO-Goa and Pharmacy College, Goa for their constant help.

For spectral data on my samples, I gratefully acknowledge the assistance given by Prof. R. B. Bates, Dr.Ralf Mayer, Prof. Rucker, Dr. Schmaus, Prof. Goldschmidt and Dr. B. Maurer. My special thanks to Mr. Avadhut Dhond and Mr. Netaji Sawant, of A M Computer Academy, Ponda-Goa for efficient and patient typing, to Mr. K. G. Chitari for neat and effective tracing and to Dr. S. P. Kamat for critically doing proof reading.

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Last but not least, I owe a deep sense of gratitude to my wife Mrs. Anjali and sister-in-law Miss Vaishali, other family members, relatives and friends for constant help throughout.

Panaji-Goa

B. L. Malik

CHAPTER ONE

CONTRIBUTION TO SANTONIN CHEMISTRY

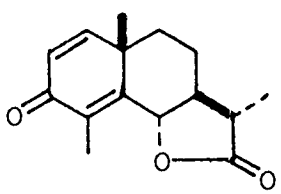
SECTION ONE

CHEMICAL AND MICROBIAL TRANSFORMATIONS OF SANTONIN. September 1986 to March 1994. A REVIEW.

(-)-Santonin (1), the naturally occurring sesquiterpene lactone continues to attract the attention of organic chemists due to its rich chemistry unraveled during the past seven decades. It is perhaps one of the few natural products that has been used extensively by synthetic organic chemists, as a starting material for relay synthesis of other natural products with the objective of establishing the absolute stereochemistry of the unknown ones and conversion into bioactive compounds. Besides, it continues to provide some interesting chemistry in the area of stereochemistry, reaction mechanisms, molecular rearrangements etc. We have been using α-santonin 1 as a starting material for studying its microbial transformation products and supplement the observations by further supporting them by carrying out chemical modifications of 1. It then becomes essential to keep a track of the work done by other investigators. Earlier, we had reviewed[1] the work done on α-santonin 1 during the period January 1980 to August 1986. In this introductory chapter, we have reviewed the work done on transformations of α-santonin 1 reported since September 1986. We feel justified in doing so as the work incorporated in the first chapter of the present thesis is concerned

with our work on this evergreen* natural product. In this section we have now reviewed the work reported during September 1986 to March 1994.

Yamakwa et al.[2] reported synthesis of 8-epiartemisin (2) by chemical as well as microbial transformation of 1. In chemical transformation, introduction of a β-hydroxyl group at C-8 of 1 was achieved via a 8-β-hydroxy compound derived from eudesm-1,4,6-triene-3,8-dione (3), whereas microbial transformation of 1 to 2 was achieved by Aspergillus MIL 5024.



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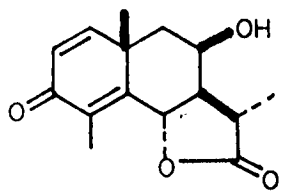

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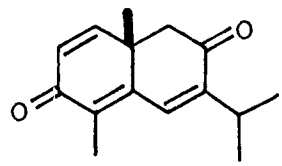

3

These authors also reported[3] microbial hydroxylation of 1 to 4,5 and 6 by using Aspergillus niger MIL 5024 and MIL 5025. Formation of 5 and 6 can be rationalised by acid or base catalysed fragmentation of 9-hydroxysantonin 7 to produce 8 as shown. (Only acid catalysed fragmentation is shown). The intermediate 8 which has not yet been characterised can then give rise

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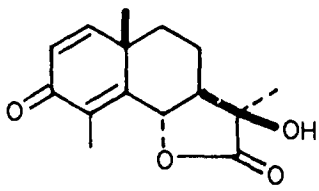
* Not used in the strict dictionary meaning and throughout the presentation in the remaining part santonin refers to α-santonin 1.

to 5 and 6 perhaps via a Cannizzaro reaction.



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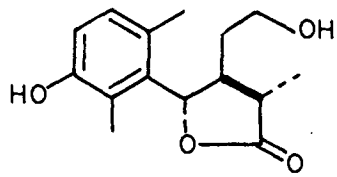

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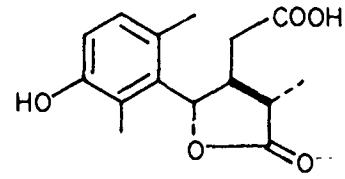

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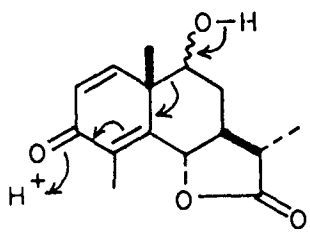
Mavinkurve and co-workers[4] reported microbial transformation of 1 to 11-demethyleudesm-4-ene-3,6-dione (9) by using Pseudomonas strain S (ATCC 43388).



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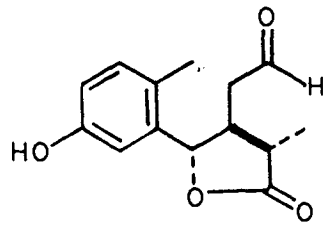

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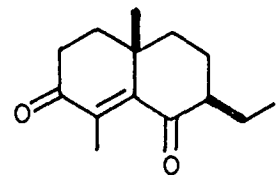
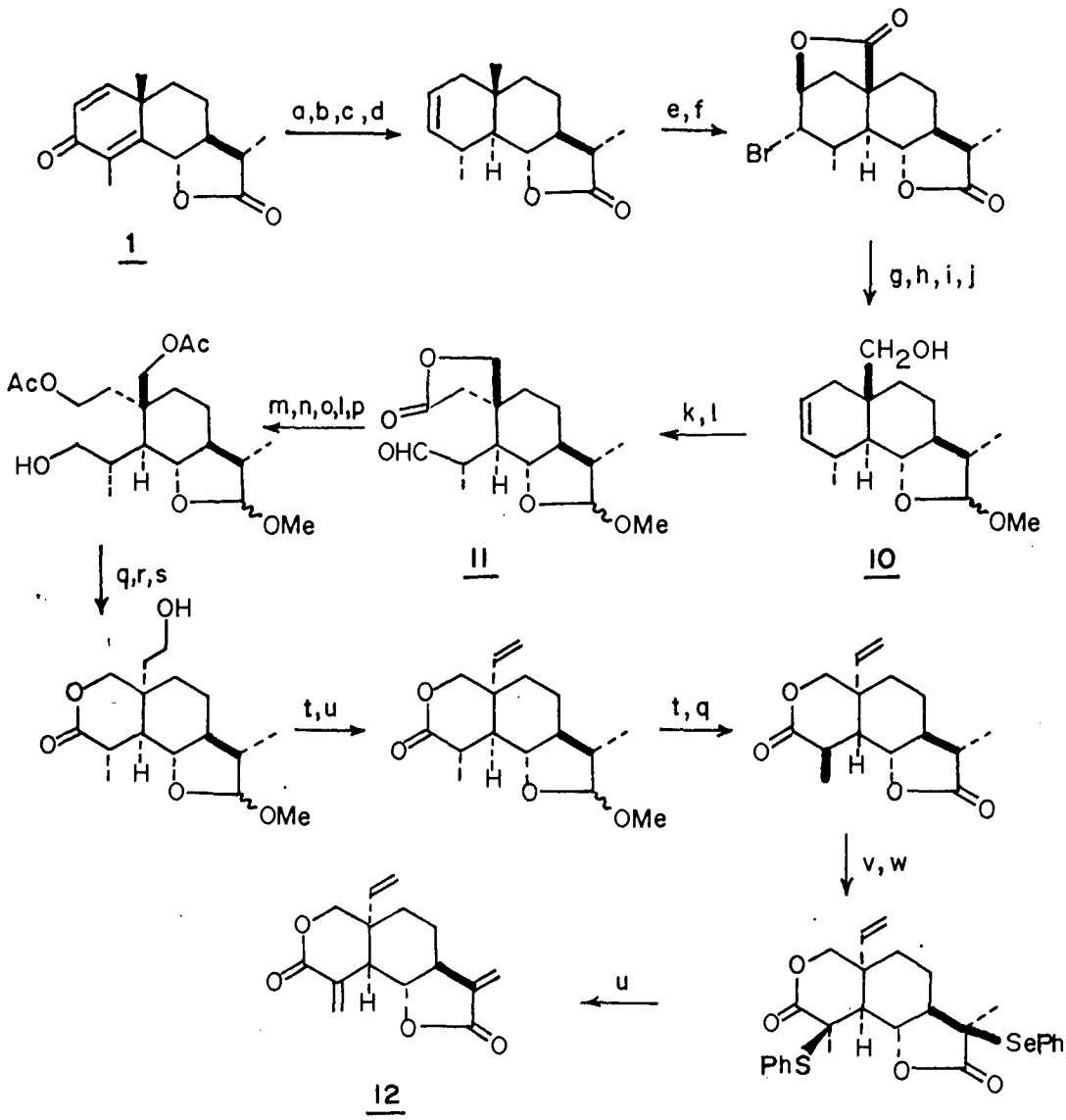


9

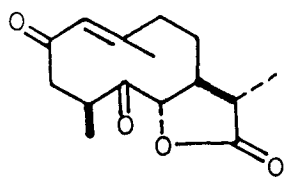
Yoshikoshi and co-workers[5] prepared (+)-8-deoxyvernolepin (12) and related dilactones (Scheme-1.1) from 1. This synthesis was achieved by ozonolysis followed by acetylation of 10 derived from 1 furnished the aldehydolactone 11 which served as a key intermediate. It may be noted that some of these unsaturated lactones were submitted to a preliminary test for antitumar activity. Synthesis of 12 has also been reported by Suarez and co-workers[6].



(a) H_2,Pd-C/Me_2CO; (b) p-TsOH/benzene; (c) Ts-$NHNH_2$/MeOH; (d) Pr^i_2NLi/THF; e) NBS,Me_2SO/H_2O; (f) $Pb(OAc)_4$,I_2,h /cyclohexane; (g) Zn/AcOH; (h) CH_2N_2/ether; (i) Bu^i_2AlH/toluene; (j) $CH(OMe)_3$,p-TsOH/CH_2Cl_2; (k) O_3/CH_2Cl_2;(l) Ac_2O/pyr; (m) $NaBH_4/CH_3OH$; (n) dihydropyran/CH_2Cl_2; (o) $LiAlH_4$/ether; (p) pyridinium toluene p-sulphonate /CH_2Cl_2; (q) Jones reagent; (r) 0.5M aq NaOH; (s) 6M aq HCl; (t) o-$O_2NC_6H_4SeCN$,Bu_3P/THF; (u) 30% H_2O_2/THF; (v) Pr^i_2NLi,Ph_2Se_2/THF; (w) Pr^i_2NLi, Ph_2S_2/THF.

Scheme 1.1

Harpanhalli[7] synthesised (5α,7β,11β-H) - 3,6-dioxo germacr-1-en-12,7-olide (13) from 1. Photolytic skeletal rearrangement of (4α, 6,11-β-H) -5α-hydroxy-2-oxoeudesman-12,6-olide 14 in the presence of HgO-Iodine complex was the key step in this synthesis.



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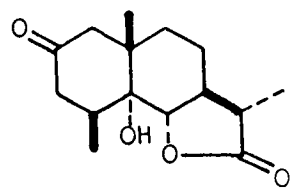
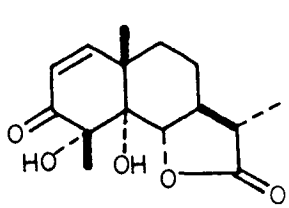


14

4α, 5α-Dihydroxysantonin*(15) and Ethyl-3-oxoeudesma-4,6-diene-12-oate(16) have been characterised as microbial transformation products of 1 by using Pseudomonas Cichorii S[8]. Assigned structures have been confirmed by chemical modification of 1 in our laboratories[1].



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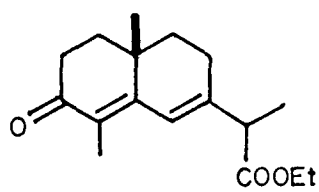
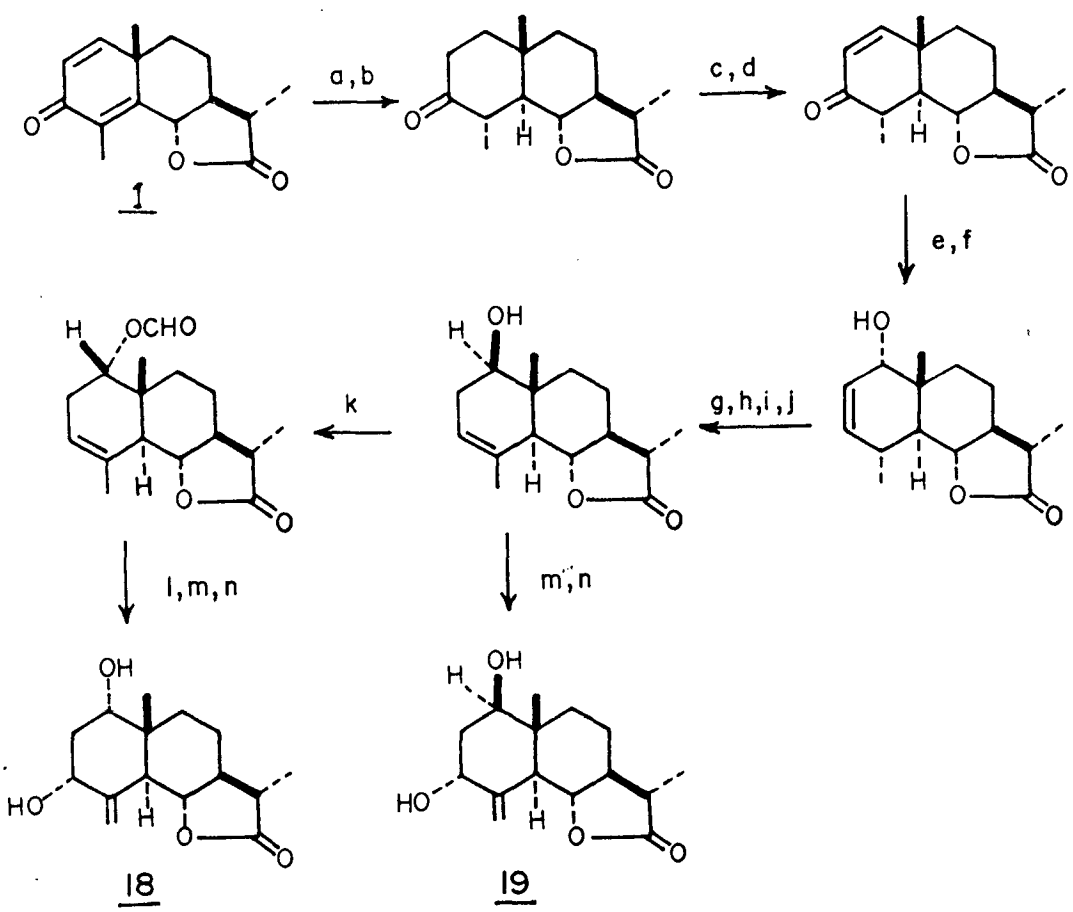


16

* The product has been shown to be 4β,5β-dihydroxysantonin during the present study. (For details see section 4 of this chapter).

Erivanin (18) and its C_1-epimer 19 were prepared[9] (Scheme 1.2) from 1. Application of the Mitsunobu epimerisation procedure[10] on eudesmanic alcohol 17 was the key step in this synthesis.



(a) H_2,Pd-C/Me_2CO; (b) p-TsOH/benzene;

(c) Br_2/CCl_4; (d) LiBr,Li_2CO_3/DMF; (e) 30% H_2O_2/THF;

(f) 85% NH_2NH_2/EtOH/HAc; (g) Jones reagent;

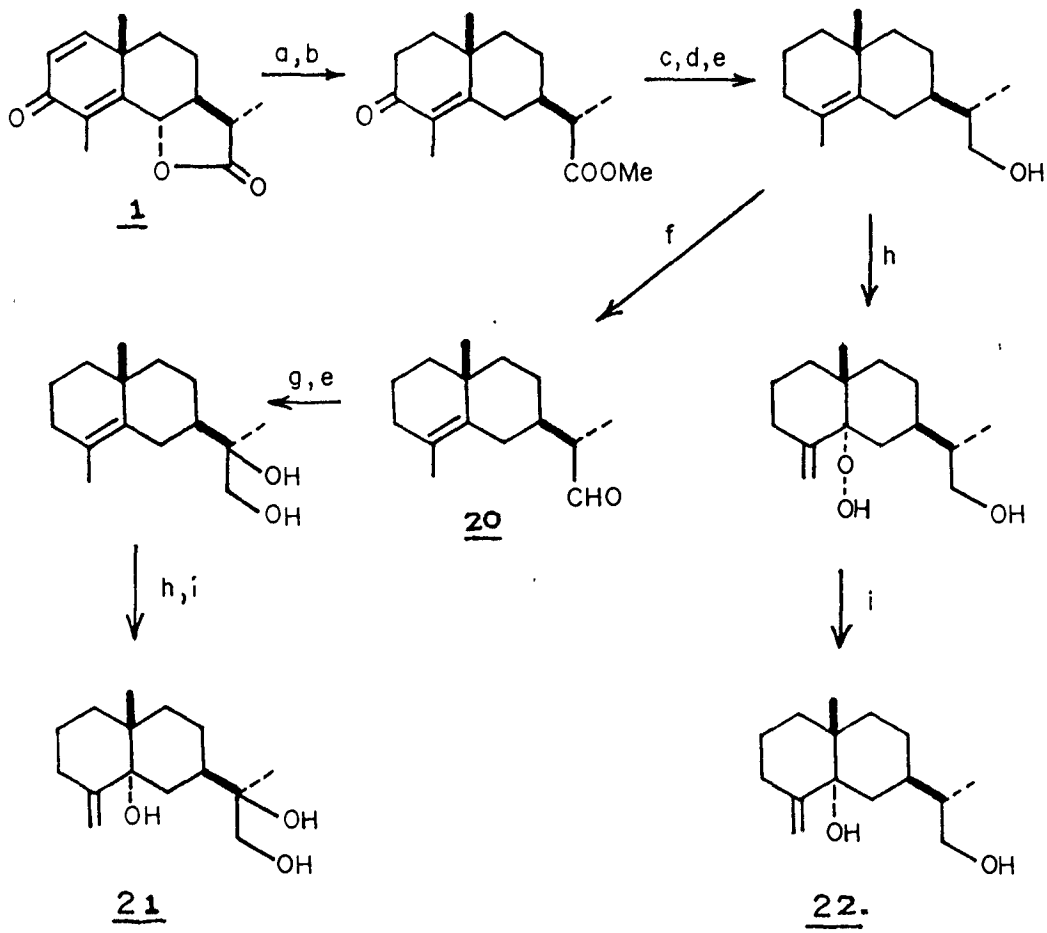
(h) Bromoglycol,p-TsOH; (i) Zn/MeOH; (j) $NaBH_4$/EtOH;

(k) DEAD,$(Ph)_3$P-HCOOH/THF; (l) aq MeOH/HCl;

(m) m-CPBA/CH_2Cl_2;(n) LDA/THF.

Scheme 1.2

Harpanhalli synthesised (Scheme1.3) kudtriol (21) and its 11-deoxy analog 22 from 1 by using Vedejs enolate hydroxylation method[11] on 20 for construction of side chain diol[12].

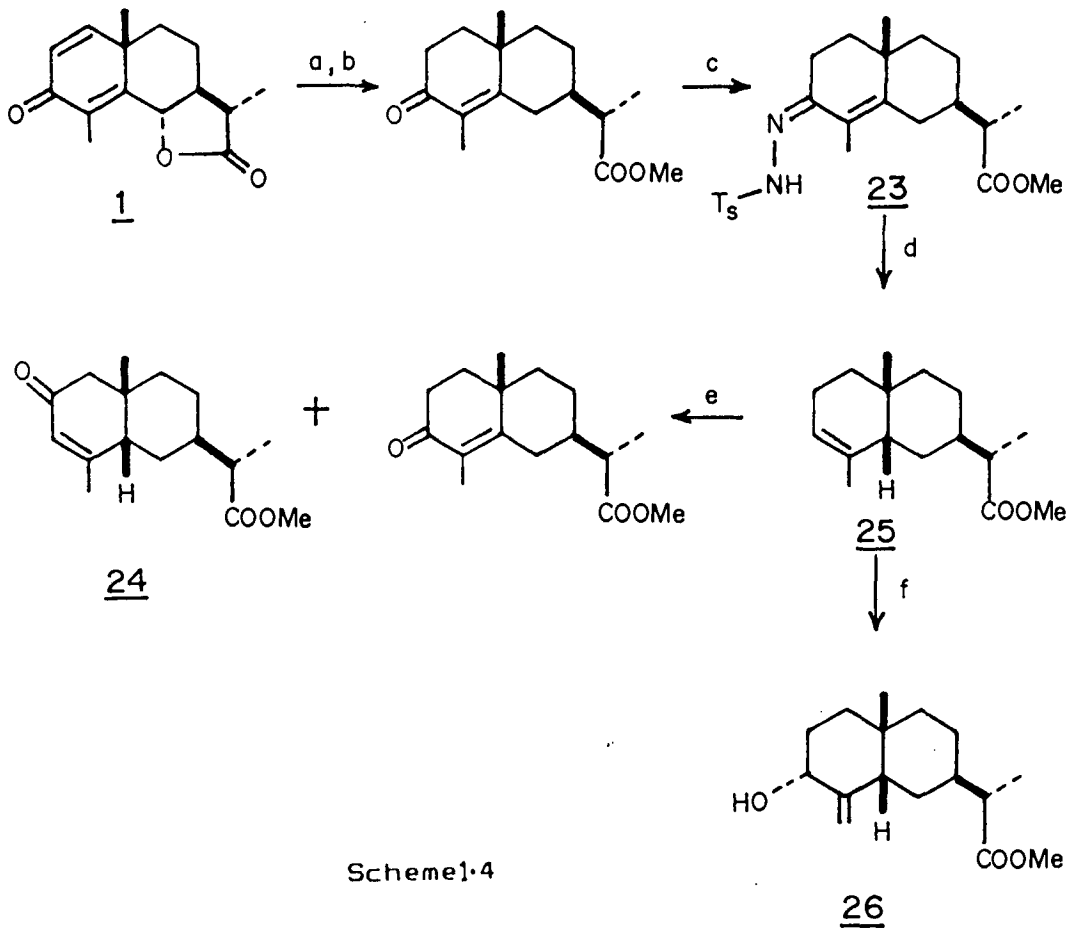


(a) Li-liqNH_3/THF; (b) MeOH/HCl; (c) $(CH_2SH)_2$, BF_3Et_2O/MeOH; (d) Raney Ni/Pr^iOH; (e) DIBAL/THF; (f) CrO_3 supported on silica/CH_2Cl_2; (g) LDA, MoOPH/THF; (h) $^1O_2$,methylene blue/EtOH; (i) $NaBH_4$/EtOH.

Scheme1.3

Transformations of 1 into new intermediates 24, 25 and 26 having cis ring fusion via 23 has also

been reported[13] (Scheme 1.4)



1 23 24 25 26

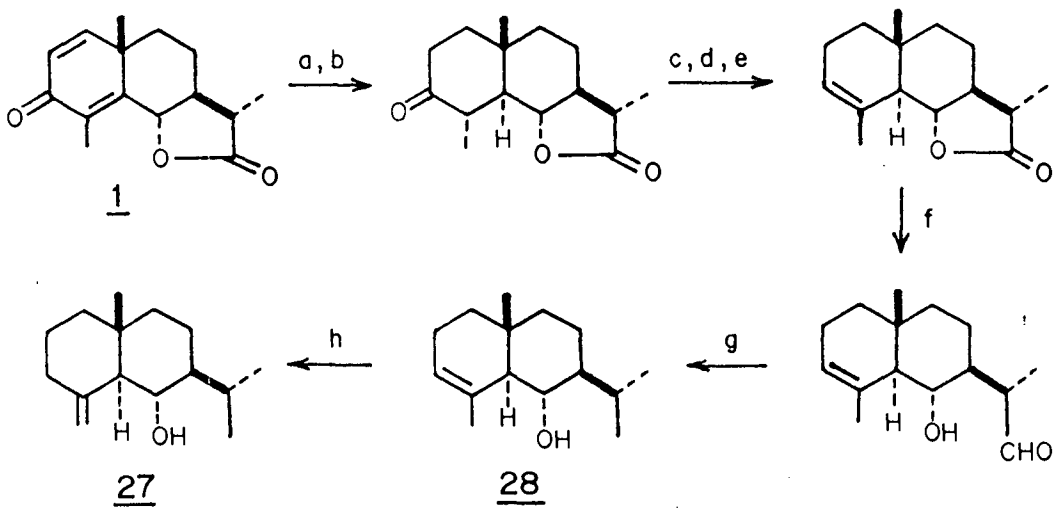
Scheme1·4

(a) Li-liq NH_3/THF; (b) MeOH/HCl; (c) p-$TsNHNH_2$, BF_3Et_2O/THF; (d) catacholborane/THF-NaOAC/H_2O; (e) SeO_2/dioxane; (f) $^1O_2$,methylene blue/EtOH.

Mavinkurve and co-workers[14] found the Pseudomonas species strain S ATCC 43388 utilises 1 by an inducible enzyme system which can be measured by oxygen uptake. Cells grown on acetates and benzoates show negligible oxygen consumption of 1. However, glucose grown cells show rapid induction of 1

indicating that degradation of 1 is regulated by glucose.

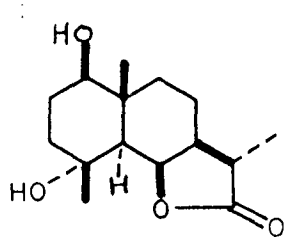
Cardona et al.[15] reported (Scheme 1.5) a new route to the synthesis of (+)-junenol (27) and its isomer (+)-isojunenol (28) from 1.



(a) H_2,Pd-C/Me_2CO; (b) p-TsOH/benzene; (c) $NaBH_4$/EtOH (d) $SOCl_2$/pyr; (e) LiBr-Li_2CO_3/DMF; (f) DIBAL/THF; (g) NH_2NH_2-KOH/DEG; (h) $h\nu$.

Scheme 1.5

Breton et al.[16] reported partial synthesis of 6,12-cis fused lactones from corresponding trans lactones which involves epimerisation at C_6 of santonin 1 to 6-αH-eudesmanolides 29 and 30.



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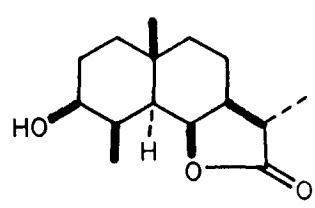
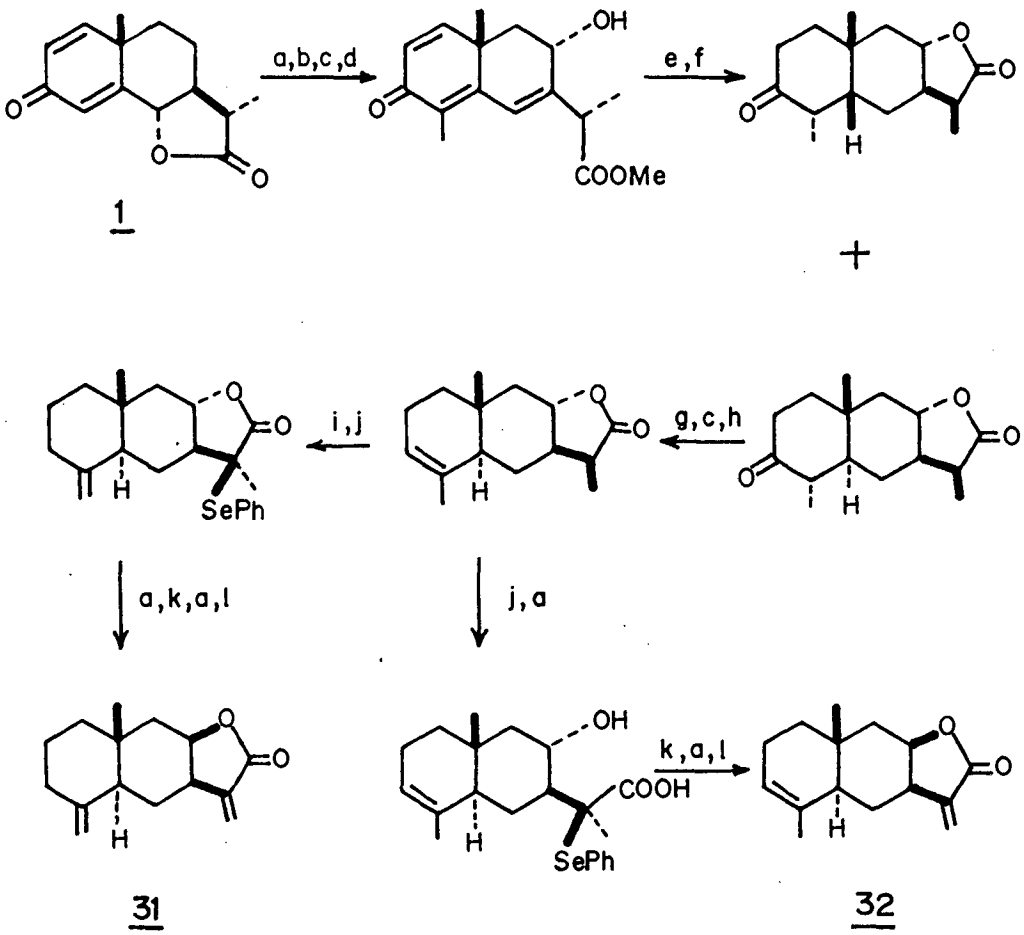


30

Chemical transformation of 1 into (+)-isoalantolactone (31) and (+)-isoalloalantolactone (32), which involves functionality transfer from C_6 to C_8, has been reported[17]. (Scheme1.6)

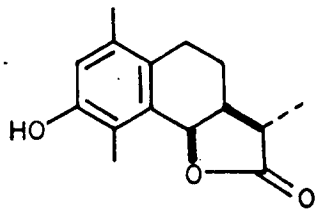


(a) NaOH; (b) MeI; (c) $SOCl_2$/pyr; (d) SeO_2/dioxane; (e) H_2,Pd-C/Me_2CO; (f) p-TsOH/benzene; (g) $NaBH_4$/EtOH; (h) LiBr-Li_2CO_3/DMF; (i) h ν (j) LDA,PhSeCl/THF; (k) CH_3SO_2Cl,Et_3N/THF (l) 30% H_2O_2-AcOH/THF.

Scheme1.6

Investigations were made towards

stereochemistry and relative stabilities of α and β -desmotroposantonins 33 and 34 respectively by Bearden and co-workers using molecular mechanics[18].



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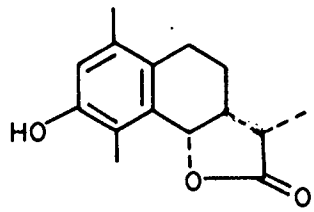

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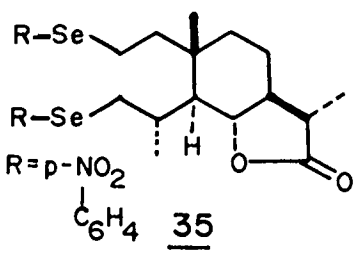
Pedro and co-workers[19] reported synthesis of torrenthin (38) by photooxygenation of dihydrosantamarine (37). Epoxide 36, obtained from 1 via diselenide 35, was the key intermediate in this synthesis.



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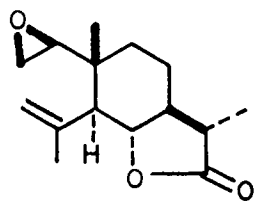

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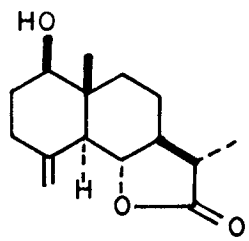

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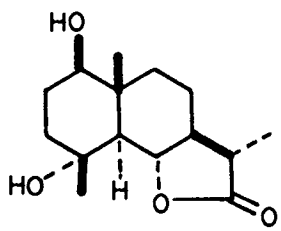

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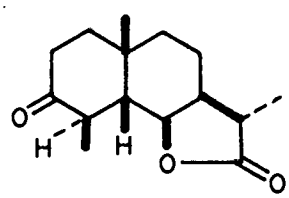

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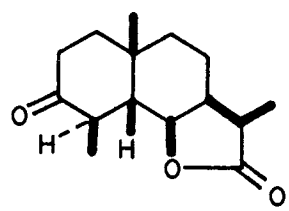
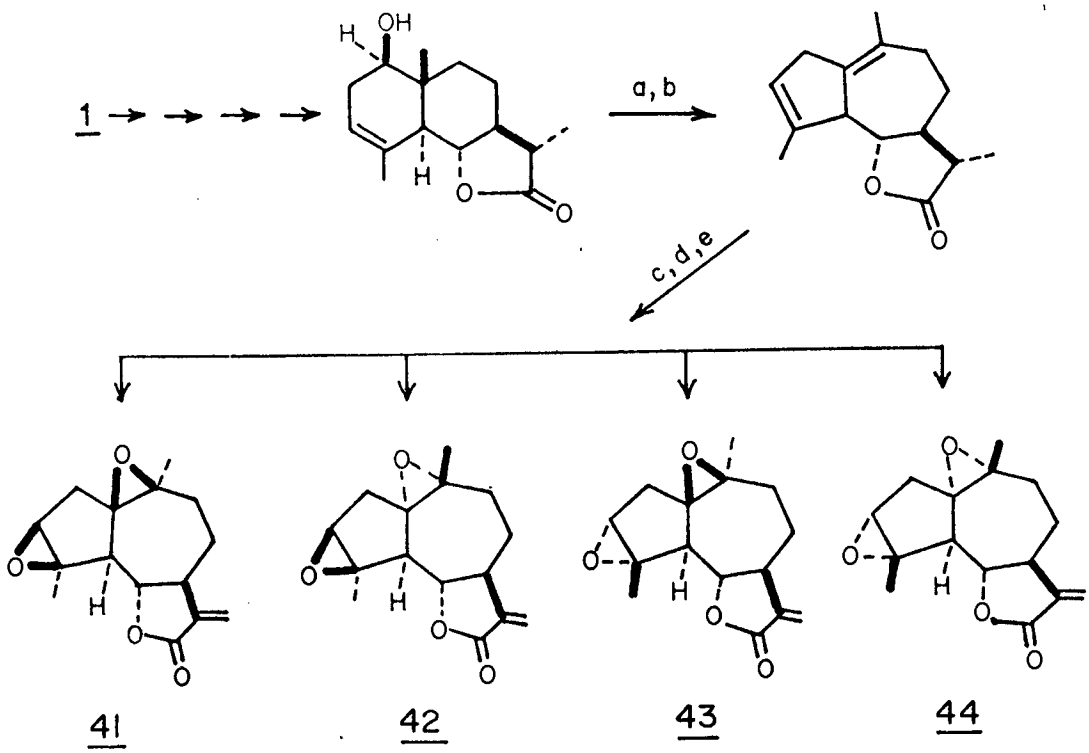


40

The conformations of 4,6α(H),5β-(H)-tetrahydro--α-santonin 39 and 4,6α(H),5β-(H)-tetrahydro-β-santonin 40 were studied[20] by using X-ray analysis and ^{1}H NMR spectral analysis. It was found that 39 exists in a steroidal conformation only in solution whereas 40 exists as a steroidal conformation both in crystalline and in solution.

Ando and Yoshimura[21] synthesised four possible diastereoisomers 41,42,43 and 44 of isoepoxyestafiatin. (Scheme 1.7)

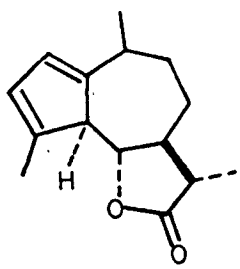


41 42 43 44

(a) CH_3SO_2Cl/pyr; (b) KOAc/AcOH; (c) m-CPBA/$CHCl_3$ (d) LDA,PhSeCl/THF; (e) 30% H_2O_2-AcOH/THF.

Scheme 1.7

The isomeric guainolides 45,46 and 47 are also characterised.



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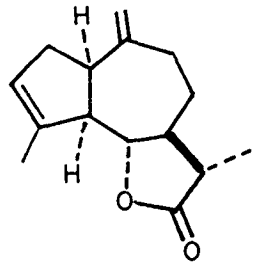

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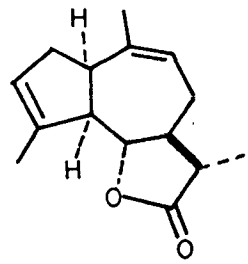

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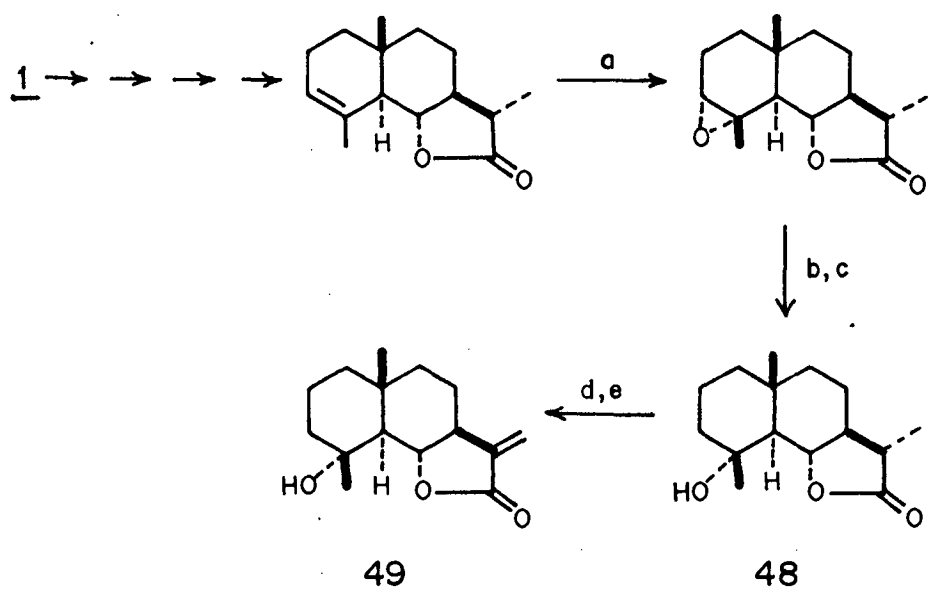
Synthesis of (+)-colartin (48) and (+)-arbusculin (49) from 1 is also reported[22]. (Scheme1.8)



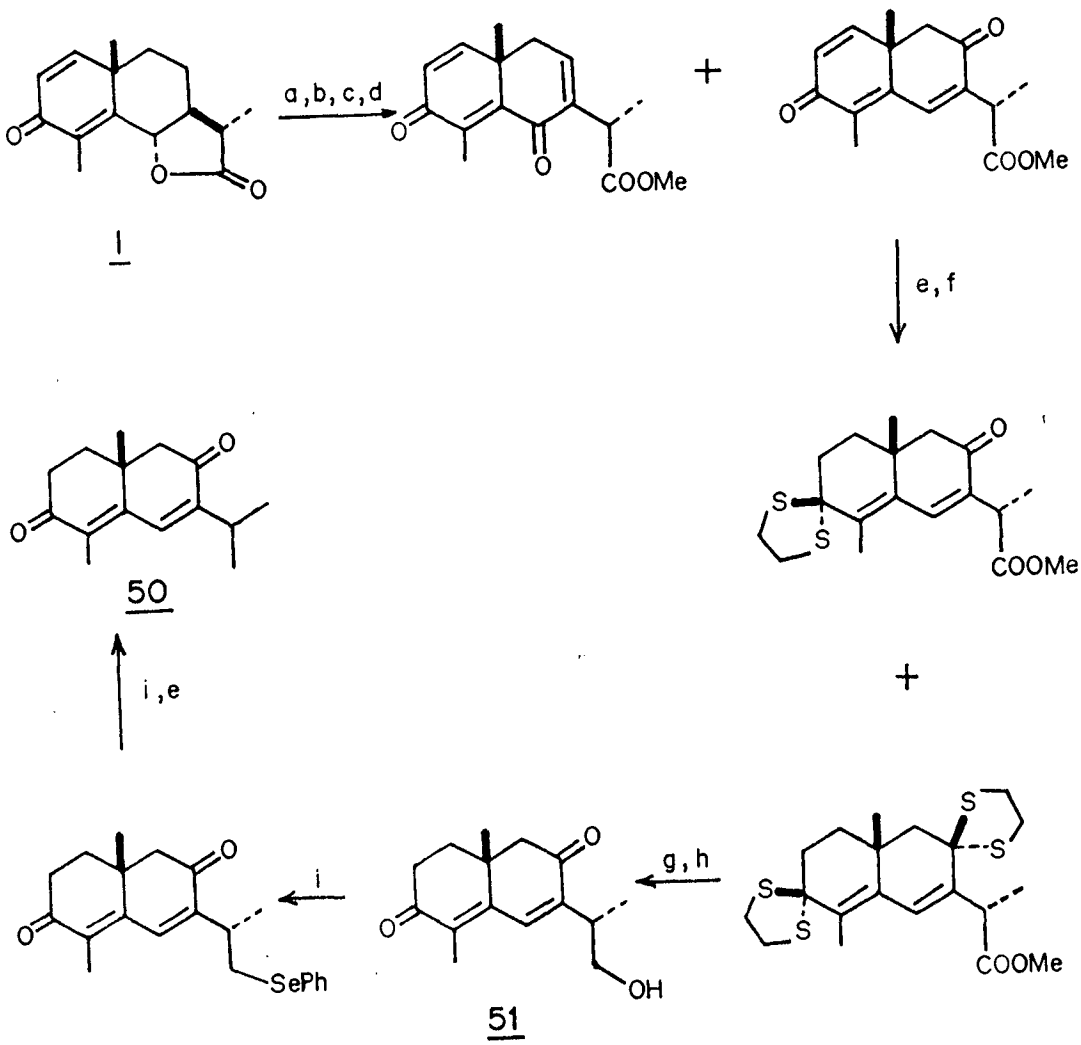
49 48

(a) m-CPBA/CH_2Cl_2; (b) $LiAlH_4$/THF; (c) CrO_3-H_2SO_4/Me_2CO; (d) LDA,PhSeCl/THF; (e) 30% H_2O_2/THF.

Scheme1.8

Pedro and co-workers[23] reported (scheme1.9) synthesis of 8-oxo-β-cyperone (50) and 12-hydroxy-8-

oxo-β-cyperone (51) from 1. The synthesis involves introduction of an 8-oxo-group followed by elaboration of the side chain.



(a) NaOH; (b) MeI; (c) $SOCl_2$/pyr; (d) PCC,NaOAc/CH_2Cl_2; (e) H_2,[$(Ph_3P)_3RhCl$]/toluene;
(f) $(CH_2SH)_2$,BF_3Et_2O/AcOH; (g) $LiAlH_4$/THF;
(h) HIO_4/CH_2Cl_2-MeOH/H_2O; (i) NPSP-Bu_3P/CH_2Cl_2;
(j) H_2O_2/THF.

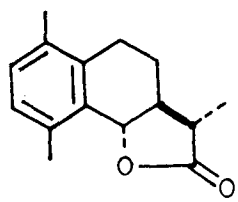
Scheme 1.9

SECTION TWO

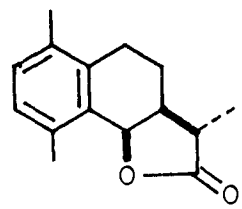
ON THE STRUCTURES OF SANTONONE AND ISOSANTONONE.

Electrolytic reduction[24,25] of santonin 1 in aqueous acetic acid is reported to give a dilactone $C_{30}H_{34}O_4$ called santonone. It was also found that santonone can be obtained by Zn dust reduction of 1 in 50% acetic acid. If 70% acetic acid is used, an isomeric dilactone, isosantonone, is obtained[26]. Isosantonone can also be prepared from santonone by heating it with 70% acetic acid.

Extensive studies on these molecules showed that santonone and isosantonone are related to each other in the same way as hyposantonin 52 and isohyposantonin 53.



52

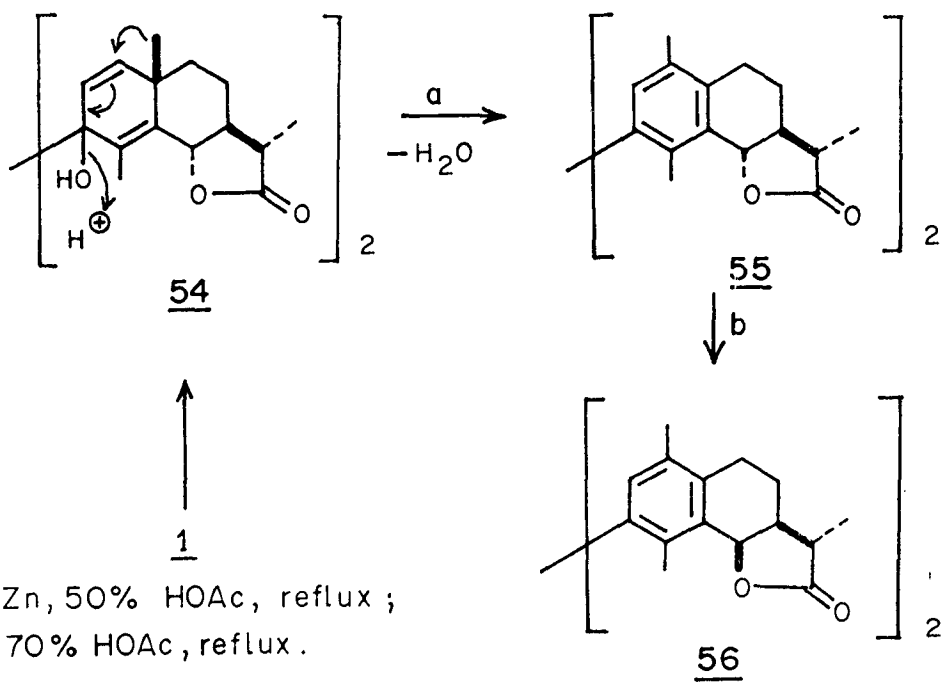


53

The molecular formula of santonone showed that it is presumably formed by dienol-benzene rearrangement of pinacol 54 derived from santonin 1* (Scheme 1.10).

---

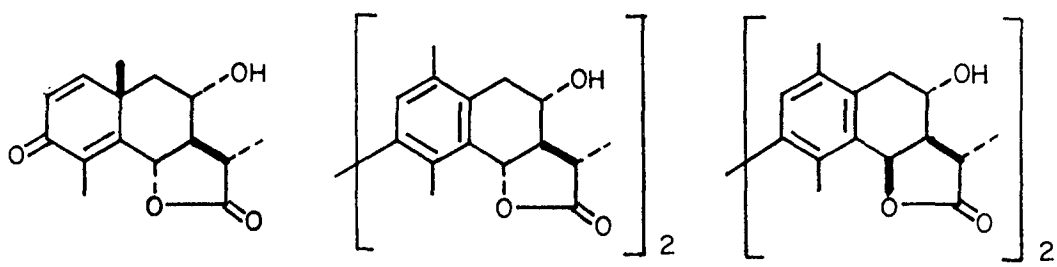
* The structures represented are based on the known stereochemistry of santonin 1 although no stereochemical assignments were made in the original literature. The stereostructures 55 and 56 followed from the proposed relationship of hyposantonin 52 and isohyposantonin 53.



(a) Zn, 50% HOAc, reflux ;
(b) 70% HOAc, reflux.

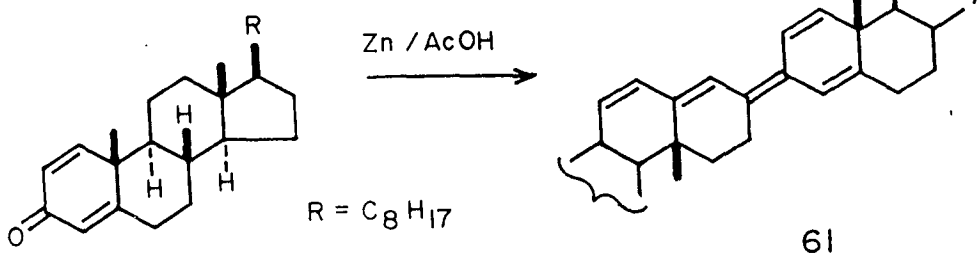
Scheme1.10

Bertolo and Ranfoldi[27] obtained structurally similar products artimisone 58 and isoartimisone 59 which were reported to be formed from artimisin 57 (8-∝-hydroxy-α-santonin) indicating that the transformations reported above are characteristic of the cross conjugated dienone system present in ring A of santonin 1.



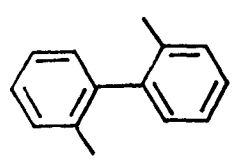
57 58 59

The assigned structures of santonone 55 and isosantonone 56 remained unquestioned till 1962 when some doubts about the validity of the structures were raised by Bladon and Redpath who chose to study similar transformations on the cross conjugated ring A steroid ketone 60[28].



60 61

Since the structure 61 derived from 60 was structurally different from santonone 55 and isosantonone 56 (ring A structural features) Bladon and Redpath repeated the preparation of santonone 55 and measured its UV spectrum (λmax 246nm). While it was consistant with the presence of aromatic ring, the band position differed considerably with that reported for 2,2'-dimethylbiphenyl 62 (λmax 266nm)[29].



62

Bladon and Redpath[28] therefore questioned the validity of the structures 55 and 56 assigned to santonone and isosantonone respectively. The concluding remarks of their reinvestigation are quoted below.

" Reduction of santonin 1, which has the similar cross-conjugated dienone system, with zinc and acetic acid is reported to give the bimolecular santonone 55[24,25]. The light absorption [λmax(in chloroform) 246, 274mμ (ϵ 7624, 3015) (hitherto unreported)] is consistant with an aromatised structure but is different from that of 2,2'-dimethylbiphenyl. The behaviour of santonin and the steroids 1,4-diene-3-ones on bimolecular reduction is clearly different and structure of santonone is worthy of reinvestigation".

Interestingly it appears that their suggestion remained unnoticed as we could find no report on further reinvestigation work until 1988 when we initiated the present study*.

Our interest in the chemistry of santonin 1 led us to undertake reinvestigation of the structures assigned to santonone and isosantonone. This looked particularly attractive as modern spectroscopic techniques would settle the structures of santonone 55 and Isosantonone

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* To the best of our knowledge, no reinvestigation appeared until August 1994.

56 beyond any doubt. The experimental details of the preparation of 55 or 56 could not be obtained from chemical abstracts and we had to resort to some other literature procedure which involved the use of Zn–AcOH. Though the yields were not highly satisfactory, we could obtain santonone 55 and isosantonone 56 in quantities sufficient to record the spectral data.

(IR,UV, ^{1}H, ^{13}C NMR and MS). It may be noted that the spectral data besides UV were not recorded before and are hence presented here. The spectral analysis presented below unambiguously confirmed the gross structures previously assigned to santonone and isosantonone and the stereochemistry expected and represented by 55 and 56 respectively on the basis of their structural relationship to hyposantonin 52 and isohyposantonin 53.

Santonone, m.p. 226^{0}, $[\alpha]_{D}$ $+82.3^{0}$, $C_{30}H_{34}O_{4}$ (M^{+} 458) exhibited an absorption maximum at λ 245nm in the UV region (Fig 1.1) as reported by Bladon and Redpath. Its IR spectrum (Fig 1.2) showed an intense carbonyl band at $1780cm^{-1}$ indicating the presence of a γ-lactone group. Absence of any other band in the carbonyl region clearly showed that the ring A has been structurally modified as expected. However the IR spectrum did not show any bands due to an aromatic ring though its presence was seen beyond doubt on the basis of ^{1}H and ^{13}C NMR data. The ^{1}H NMR spectrum of santonone 55 (Fig 1.3) showed signals for a secondary methyl

(1.31, d, J=7.5 Hz) two methyl groups attached to the benzenoid ring (2.20 and 2.23) and a one proton singlet at 6.90 due to an aromatic hydrogen at C_2. The C_6 methine hydrogen appeared as a doublet at 5.10 (J=9 Hz) and the J value indicated that the hydrogens attached to C_6 and C_7 are both diaxial. Moreover the downfield chemical shift of the C_6 hydrogen when compared to that of santonin 1 confirmed that the ring A has been aromatised.

The ^{13}C NMR spectrum (Fig 1.4) showed, as expected, three quertets, two triplets, four doublets and six singlets showing a total of 15 signals. The molecular formula $C_{30}H_{34}O_4$ and only 15 signals in the ^{13}C NMR spectrum conclusively showed that santonone is a symmetrical dimer and can be represented by stereostructure 55. The assignments of ^{13}C chemical shifts are shown in Table 1.1. Though the mass spectrum (Fig 1.5) showed a peak at m/z 229 due to the cleavage of the C_3-C_3' bond, it was not the major mode of fragmentation. Besides the molecular ion at m/z 458, the base peak was observed at m/z 443 ($M^{+\cdot}-CH_3$) and the other significant peaks were at 414($M^{+\cdot}-CO_2$), 399(m/z 414-CH_3), 385(m/z 399-CH_2), 355(m/z 399-CO_2) and 311. The fragment ion at 311 appears due to the loss of the $C_3H_4O_2$ fragment from both sides together with a proton. While the mass spectra of santonone 55 and isosantonone 56 are quite similar, as expected considering their stereoisomeric relationship,

the base peak was observed at m/z 87($C_4H_7O_2$) for isosantonone 56 (Fig1.8) as opposed to the base peak at m/z 443 in the case of santonone 55. The origin of the

Table 1.1

^{13}C NMR (250 MHz, $CDCl_3$) data for santonone 55

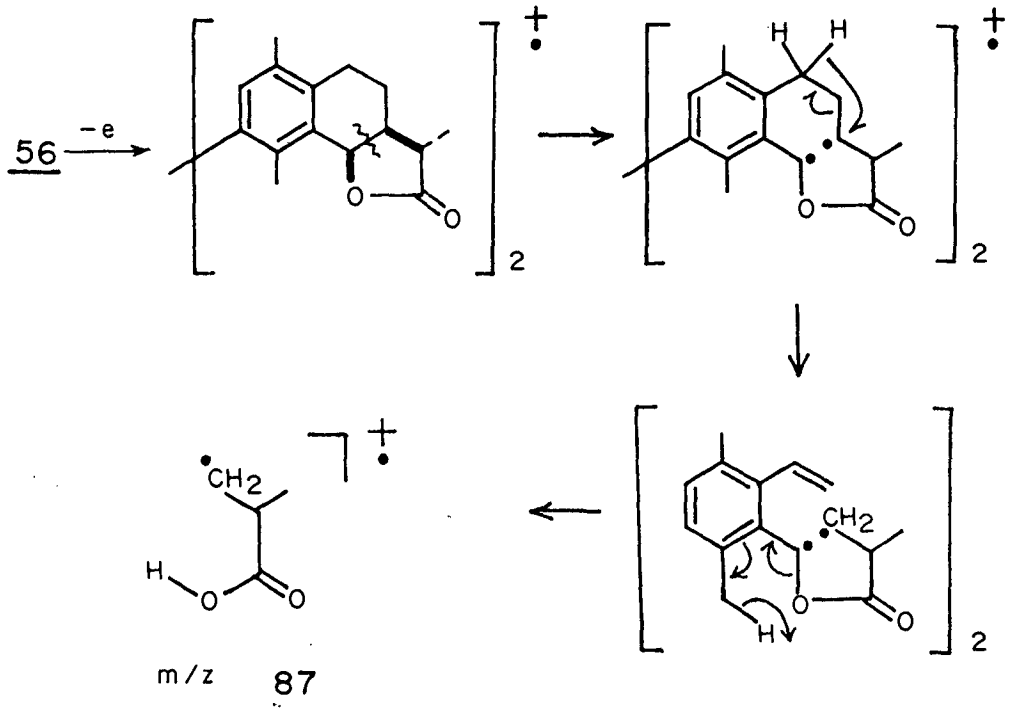
Carbon	Chemical shift	Multiplicity
C-1	132.9*	s
C-2	131.0*	d
C-3	140.2	s
C-4	133.1*	s
C-5	133.6*	s
C-6	082.2	d
C-7	041.0	d
C-8	022.9	t
C-9	027.7	t
C-10	133.8*	s
C-11	049.1	d
C-12	179.3	s
C_1-$\underline{C}H_3$	018.0**	q
C_4-$\underline{C}H_3$	019.7**	q
C_{11}-$\underline{C}H_3$	012.3	q

* assignments may be interchanged.

** assignments may be interchanged.

base peak at m/z 87 is rationalised in terms of

fragmentation process is shown in Scheme* 1.11.



Scheme1·11

The spectral data presented above conclusively established that santonone is represented by structure 55 and confirmed the gross structure assigned earlier.

Only one question remains to be answered. The observed difference in the UV spectrum of santonone 55 and 2,2′-dimethylbiphenyl 62. This may be due to non coplanarity of the model compound 62.

---

* A mass spectral study of santonin 1 and its derivatives has been reported by Yoshi and co-workers[30]. The mass spectrum of hyposantonin 52 is reproduced but no report on the mass spectral fragmentation of isohyposantonin 53 is available and hence it is not possible to make any comparison with the base peak observed at m/z 87 in the case of isosantonone 56.

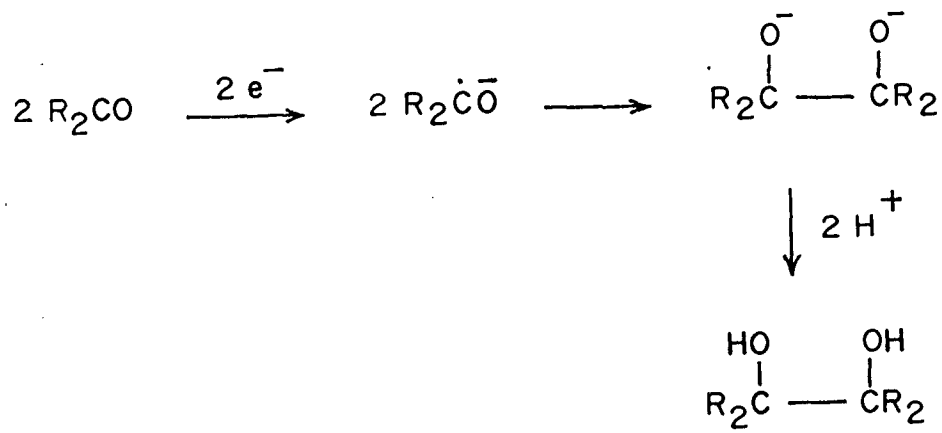
Isosantonone 56 m.p. 276^{0} decomposition, (lit.[25] 280^{0} with decomposition), $[\alpha]_D$ -161.80^{0}, $C_{30}H_{34}O_4$ (M^+ 458) could be obtained as reported by epimerisation at C_6 of santonone 55 by heating it with 70% aqueous acetic acid. The IR spectrum (Fig 1.6) showed an intense band at 1780cm^{-1} due to a lactone grouping. The major difference between the ^{1}H NMR spectrum of 56 (Fig 1.7) and that of santonone 55 is the chemical shift of C_6-H which appeared as a doublet at 5.64 with a coupling constant of 5 Hz which clearly indicates that isosantonone is the C_6 epimer of santonone 55. It was reported earlier that santonone 55 and isosantonone 56 have the same relationship as hyposantonin 52 $[\alpha]_D$ +32.70^{0} (benzene) to isohyposantonin 53 $[\alpha]_D$ -70.30 (benzene). The observed change in the sign of optical rotation in going from plus to minus is also observed in the corresponding pair santonone 55 and isosantonone 56[31].

The data presented above clearly confirm the literature structures for santonone and isosantonone and in addition establish the stereochemistry of these santonin derived molecules.

SECTION THREE

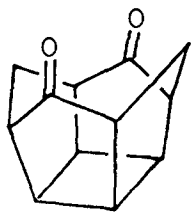
REACTIONS OF SANTONIN AND SANTONIC ACID WITH Zn–HCl–ETHER.

The coupling of ketones to give pinacols via radical anions has been widely employed in organic synthesis. The radical anion intermediates can be generated photochemically or by using a variety of metals such as zinc, aluminium, magnesium etc, commonly as amalgams[32]. The normal process of coupling via radical anions is shown in Scheme 1.12.



Scheme 1.12

We were interested in the preparation of santonone (55) and isosantonone (56) from santonin 1. The pinacol 54 derived by coupling of santonin C_3 carbonyl is considered to be an intermediate in the above transformation but has not been characterised before. Though we could prepare 55 and 56 and collect spectral data for confirmation of assigned structures, we were not happy with the yields and were thus looking for a better method. The reported formation of pinacol 64 from the diketone 63 in excellent yields, (74%) suggested that the experimental conditions (Zn-HCl-ether,0°) used by Paquette and co-workers[33] might be



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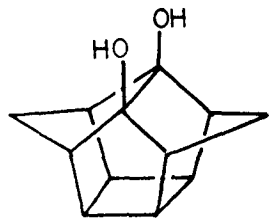

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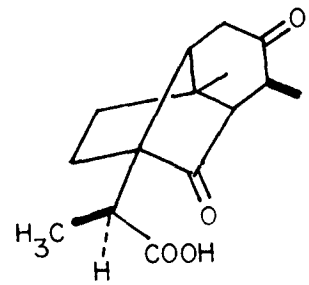


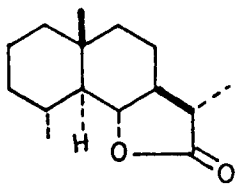
65

suitable for improving the yields of 55 and 56 from santonin 1. We therefore subjected santonin 1 to these reaction conditions but were surprised to note the total absence of either 55 or 56 in the reaction product which, after careful purification by column chromatography, afforded two crystalline compounds besides unchanged santonin 1. The characterisation of these compounds forms the subject matter of this section. As an extension of this study we have studied the reaction of santonic acid (65) with Zn-HCl-ether and the results obtained are also presented.

Thus, santonin 1 on treatment with Zn-HCl-ether at 0^{o} for two hours afforded, after usual workup and chromatography over silica gel, two crystalline compounds, A (18.9%), m. p. 154^{o} and B (28.6%), m. p. 152^{o} besides a small quantity of santonin 1 (24.3%).

Compound A, $C_{15}H_{24}O_2$ showed the presence of a band at 1770 cm^{-1} in its IR spectrum (Fig 1.9) but bands due to the conjugated carbonyl group of santonin 1 were absent. Its ^{1}H NMR spectrum (Fig 1.10) was more informative, showing the presence of two secondary

methyl groups, a tertiary methyl and no olefinic hydrogens. This data clearly showed that compound A must be one of the known derivatives of santonin 1, viz. deoxytetrahydro-α-santonin (66) unambiguously confirmed by Co-TLC, spectral comparison and mixture melting point determination.



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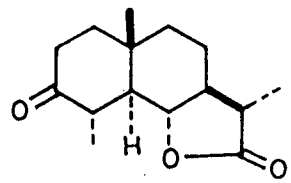

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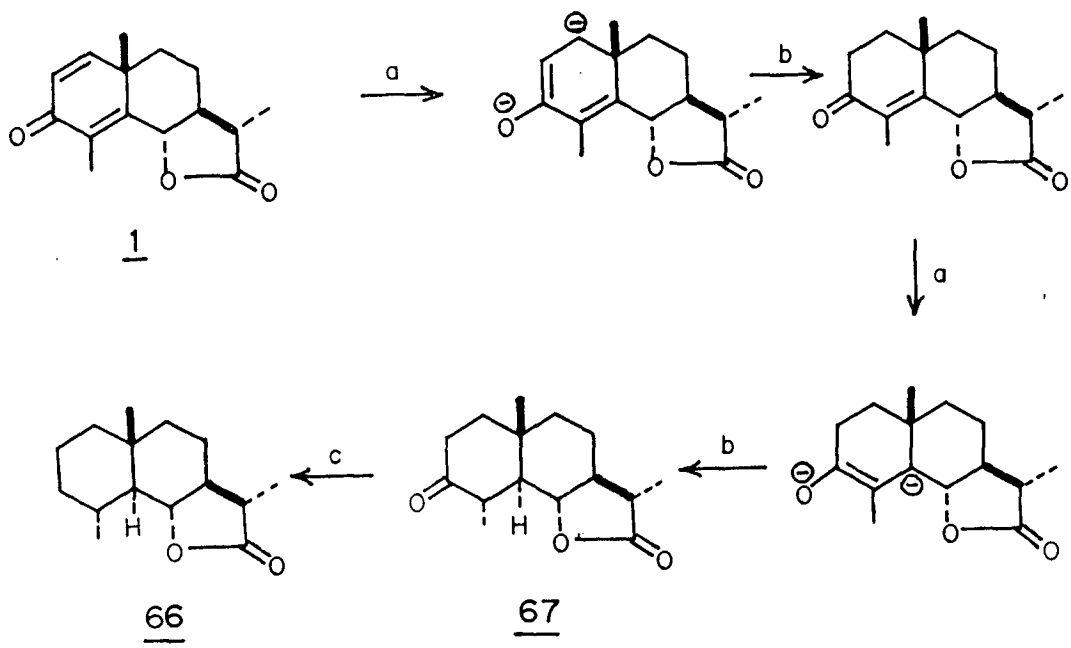
The IR spectrum (Fig 1.11) of compound B, $C_{15}H_{22}O_3$ showed an intense band at 1770 cm^{-1} due to the γ-lactone grouping and another intense band at 1700cm^{-1} indicating the presence of a ketone in a saturated 6 membered ring. This was further confirmed by the absence of olefinic protons in its ^1H NMR spectrum, (Fig 1.12) but the presence of two secondary methyls, a tertiary methyl and the intact trans-fused γ-lactone of the original molecule. The melting point, IR and ^1H NMR spectra suggested compound B to be α-tetrahydrosantonin (67) and its identity was established by preparation of an authentic sample of α-tetrahydrosantonin using a known procedure[34].

The saturation of both the double bonds of santonin 1 to produce 66 and 67 can be explained by the mechanism shown in Scheme 1.13



(a) $2e^-$; (b) H^+, tautomerisation; (c) Clemmensen reduction.

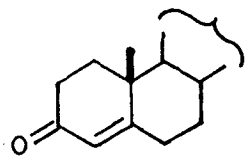
Scheme 1.13

A careful literature search showed that Yamamura and co-workers[35] had earlier obtained similar results while studying the reactions of cholestenone 68 with Zn-HCl-ether system. In fact, Paquette and co-workers[33] had adopted the experimental conditions of Yamamura and co-workers[35] for the preparation of pinacol 64 reported earlier. Since the ketone carbonyl groups of

cholestenone 68 and other model compounds were converted into methylene groups under mild conditions, Yamamura and co-workers[35] named their reaction a "modified" Clemmensen reduction.

The major difference between the results obtained during the present study and those reported by Paquette and co-workers[33] is that no pinacol and the products derived from it could be detected. The reported good yields of pinacol 64 from 63 must therefore be due to the proximity of the two carbonyl groups in 63, which favors the intramolecular reaction.

In order to confirm the above explanation, we chose to study the reaction of santonic acid (65) with 5% Na-Hg in NaOH[36] which is known to produce pinacol 69. Moreover, (65) is readily accessible[37] from 1 by reaction with NaOH. Here we anticipated the



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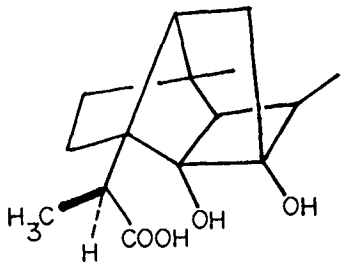

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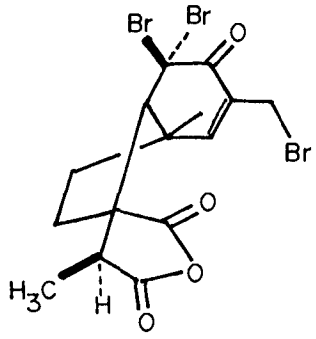

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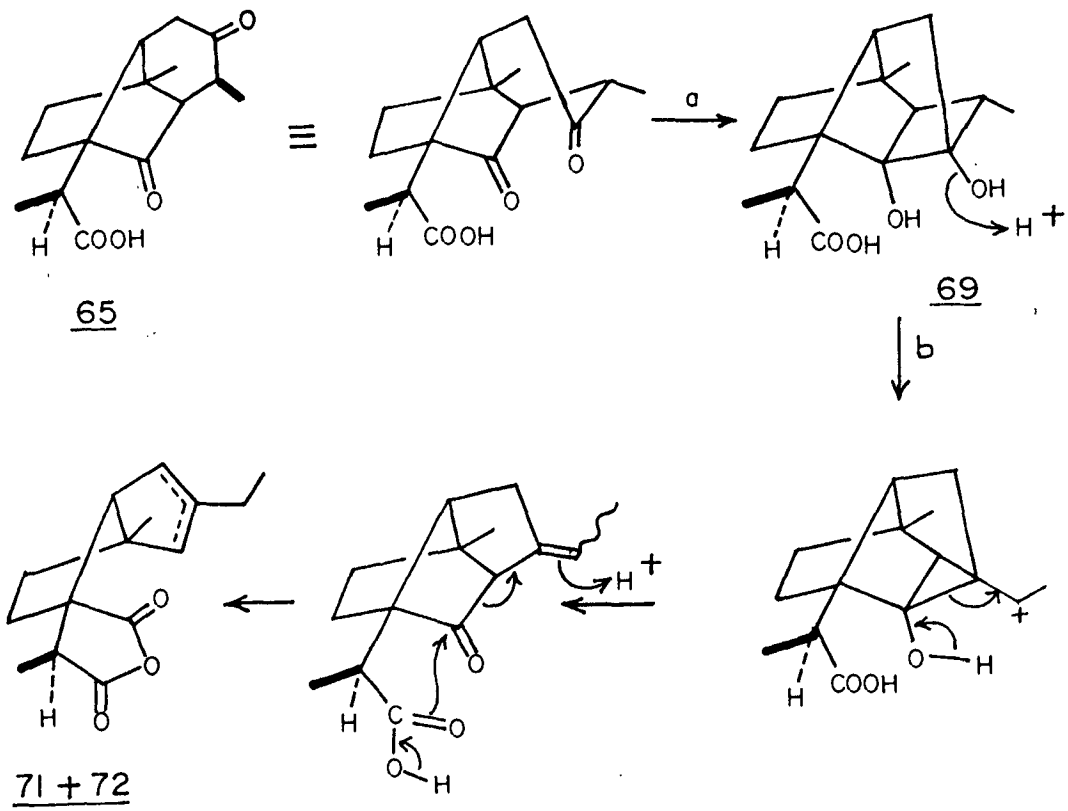
formation of products derived from acid catalysed reaction of 69, which were not expected to survive under the strong acidic conditions (Scheme 1.14). The results obtained show that the

reaction did proceed as anticipated and the end product after purification obtained as a viscous colorless liquid which showed a single spot on TLC using different solvent systems. Spectral analysis,



(a) Zn-HCl/ether; (b) H^+.

Scheme 1.14

particularly ^1H and ^{13}C NMR showed it to be a mixture and this was further confirmed by GC MS* which showed it to be a 60:40 mixture of two compounds having the same molecular formulae, $C_{15}H_{20}O_3$ (M^+ 248).

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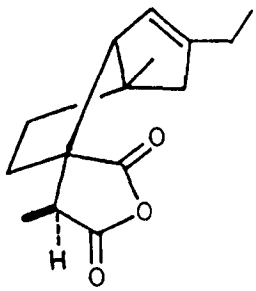
* We thank Dr. Bruno Maurer for GC MS analysis and confirming our structural assignments.



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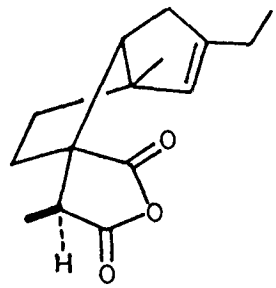

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The twin infrared absorption bands at 1835 and 1780 cm^{-1} together with the higher intensity of a later band (Fig 1.13) indicated the presence of a substituted succinic anhydride. In fact these carbonyl positions were almost the same as observed by us in the IR spectrum of another substituted succinic anhydride 70 derived from santonic acid (65) on reaction with Br_2 in wet chloroform.

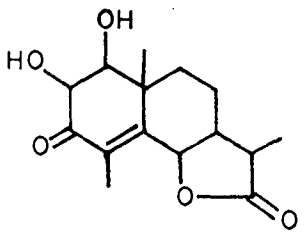
Its ^{13}C NMR spectrum (APT) showed the presence of 5 quartets, 8 triplets, 6 doublets and 9 singlets, thus further confirming it to be a mixture of two C_{15} compounds. (Chemical shifts are given in the experimental section). Its ^{1}H NMR spectrum (Fig 1.14) showed a triplet at 1.0 (3H, J = 7Hz, $\underline{CH_3}-CH_2-$), two singlets at 1.18 and 1.20 together integrating for three hydrogens ($\underline{CH_3}-\overset{c}{\underset{c}{C}}-C-$), a doublet at 1.35 (3H, J = 7Hz, $\underline{CH_3}-CH-C=O$) a complex pattern in the region 1.4 to 2.6, a broadened singlet at 2.78 (allylic H), two signals at 4.92 (broadened singlet)

and 5.09 (singlet) together integrating for one olefinic proton. The relative heights of the signals showed it to be a mixture (60:40) of two compounds 71 and 72 and these differ in the position of the C=C double bond. We assume that the configuration at C_{11} has not changed during the transformation.

SECTION FOUR

REINVESTIGATION OF $KMnO_4$ OXIDATION REACTION OF SANTONIN

Oxidation of santonin 1 with potassium permanganate was studied first by Anjeli and Marino[38] who obtained a product $C_{15}H_{20}O_5$, m.p. 261°and considered to have constitution 73[25]. During their elegant studies in the structures of various derivatives of santonin 1, Hendrickson and Bogard[39] suggested that the dihydroxysantonin reported by Anjeli and Marino should be represented by structure 74. This assignment was



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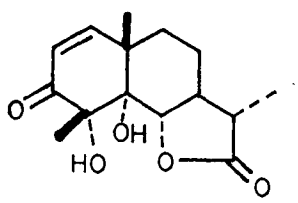


74

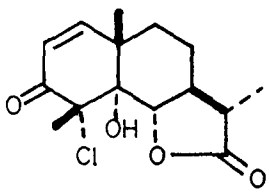
based on the basis of the higher reactivity of the 4,5 olefinic linkage and approach of the reagent from the less hindered α-face. It may be noted that Hendrickson and Bogard[39] did not reinvestigate the products derived from $KMnO_4$ oxidation of santonin 1. Their stereochemical assignments as shown in 74 looked convincing and remained unquestioned till recently.

Mavinkurve and co-workers[8] have shown that microbial oxidation of santonin 1 results in the formation of 4,5-α-dihydroxysantonin, m.p. 220°. In order to confirm the configuration at C_4 and C_5 of this dihydroxy derivative the $KMnO_4$ oxidation of santonin 1

was reinvestigated in our laboratories and it was conclusively established that 4,5-dihydroxysantonin obtained in this reaction is identical with the microbial oxidation product and has m.p. 220° and not 261° as reported earlier. The stereochemistry as shown in 74 was accepted as suggested by Hendrickson and Bogard[39].

Present study

Hendrickson and Bogard had assigned structure 75 to santonin chlorohydrin. Subsequently Takayanagi et al. revised the structure of santonin chlorohydrin from 75 to 76a (R = H) on the basis of X-ray analysis of the corresponding methoxy derivative 76b (R = CH_3)[40].



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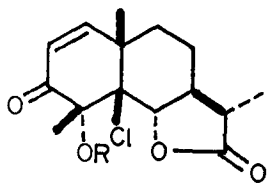

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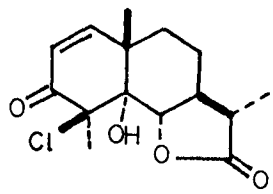


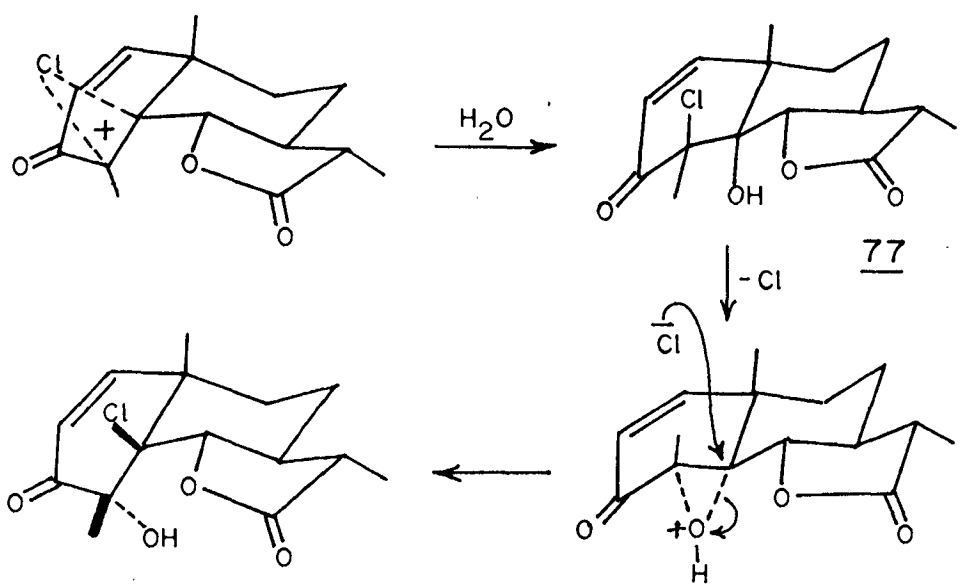
77

76a, (R = H)

76b, (R = CH_3)

The revision of the structure of santonin chlorohydrin as shown in 76a shows that the chloronium ion is formed on the β-face contrary to earlier claims based on the assumption that the α-face of

santonin is less hindered*. Addition of water to the intermediate chloronium ion would be expected to take place from the α-face and at C_5 resulting in the over all formation of chlorohydrin**77 as the first product of the reaction; this is then transformed to 76a which is apparently more stable than 77 due to the absence of 1,3-diaxial interactions with the angular methyl group. The proposed mechanistic pathway of conversion of santonin 1 into santonin chlorohydrin is shown in Scheme 1.15. It would be of interest to see whether santonin-α-isochlorohydrin 77 is converted to 76a under the same experimental conditions.

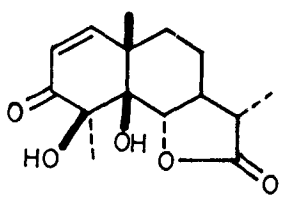


Scheme 1.15

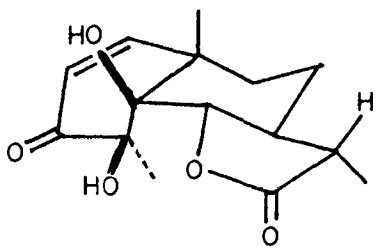
* Attack of the reagent occurs from below, owing to steric hindrance by the angular methyl group, which moreover in the steroid series leads to the same result[39].

** In fact this structure has been assigned to santonin-α-isochlorohydrin[39].

These observations led us to believe that the stereochemical assignment made earlier for the diol obtained by $KMnO_4$ oxidation of santonin 1 may also be an error and warrant further investigation either by nOe studies or X-ray crystallographic analysis. Based on the unambiguous stereochemical assignment of α-santonin chlorohydrin as shown in 76a, the $KMnO_4$ oxidation product would in all probability be represented by structure 78. The spectral data recorded on the sample, m. p. 220° prepared following the procedure of Naik[1] was identical with those recorded earlier. The nOe experiment turned out to be rewarding and as anticipated the hydroxy groups at C_4 and C_5 were found to have β-configuration as shown in 78 by nOe studies which showed 17% nOe in H_7 on irradiation of C_4 methyl group. Inspection of molecular models of 78 shows that H_7 is close to C_4 methyl group only when the hydroxyl groups at C_4 and C_5 are in the β-configuration as shown in the conformational formula 78a. Examination of molecular models of 1 further



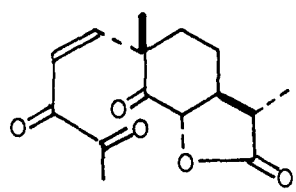
78



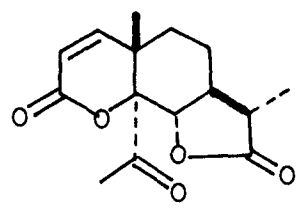
78a

shows hindrance from C_{10} methyl on the β-face, whereas the 9-methylene and C_6 oxygen shields the α-face.

The more interesting result of the present study is the structure 80, assigned to the higher melting (268^0) and less polar product, which further represents a new molecular rearrangement of santonin 1. The higher melting compound, $C_{15}H_{18}O_5$ was assigned the tentative structure 79 on the basis of ^1H NMR and its formation by lead tetraacetate cleavage of 74. Failure to give a quinoxaline derivative under a variety of experimental conditions and total recovery of the starting material on attempted hydrogenation of the C_1-C_2 double bond raised doubts about the correctness of the assigned structure. Further, ^1H NMR and ^{13}C NMR spectral studies (for assignments see Tables 1.2 and 1.3) conclusively established the structure to be 80.



79



80

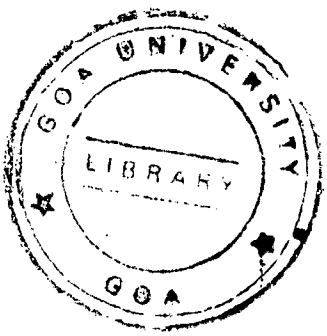
Table1-2

^{1}H NMR(500 MHz, $CDCl_3$) data for 78 and 80

	compound	
Proton	78	80
H-1	6.37,d,10.3	6.92,d,9.6
H-2	6.02,d,10.9	5.85,d,9.6
H-6	4.22,d,12.0	4.38,d,11.1
H-7	2.31,m	1.95,qd,12.1,3.9
H-8α	2.02,dq,13.1,3.5	1.97,m
H-8	1.66,qd,12.2,4.1	1.63,qd,13.3,4.5
H-9α	1.91,td,13.6,4.4	2.77,td,13.1,4.4
H-9	1.82,dt,14.2,3.5	1.68,ddd,13.1,4.5,1.5
H-11	2.31,m	2.36,dq,13.4,6.8
4-CH_3	1.54,s	2.30,s
10-CH_3	1.38,s	1.31,s
11-CH_3	1.28,d,6.6	1.22,d,6.8
-OH	4.01,s & 4.19,s	——

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

B. L. Malik
Candidate

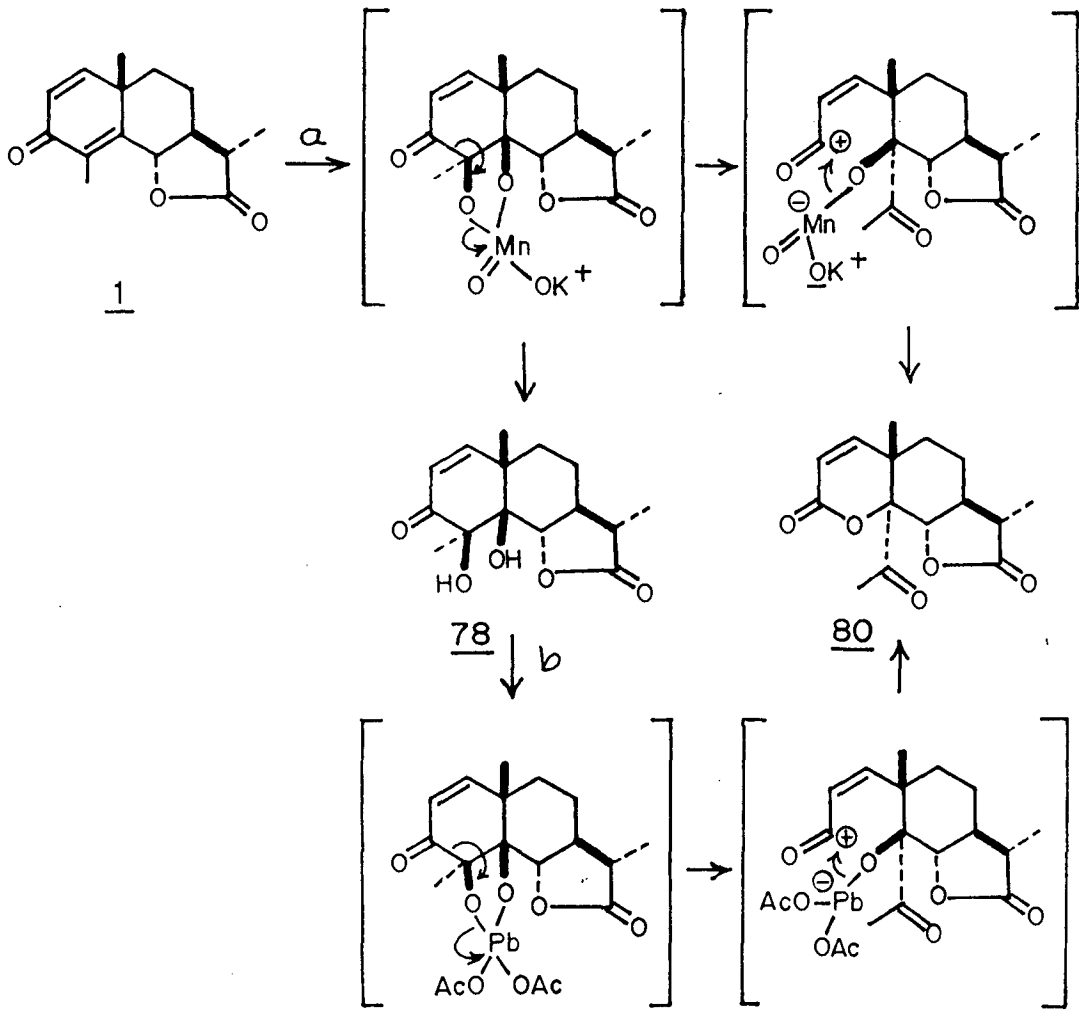
Table 1.3

^{13}C NMR (250 MHz, $CDCl_3$) data for 80 & 1

Carbon	81	1*
C-1	158.5,d	155.1,d
C-2	118.7,d	125.9,d
C-3	162.0,s	186.0,s
C-4	208.3,s	128.4,s
C-5	090.1,d	151.5,s
C-6	078.6,d	081.5,d
C-7	045.6,d	054.0,d
C-8	022.1,t	023.3,t
C-9	031.4,t	039.3,t
C-10	041.6,s	041.7,s
C-11	041.0,d	041.2,d
C-12	177.0,s	177.4,s
C_4-$\underline{C}H_3$	031.9,q	010.9,q
C_{10}-$\underline{C}H_3$	023.1,q	025.3,q
C_{11}-$\underline{C}H_3$	012.3,q	012.5,q

* based on reference[41]

A rational mechanism is proposed to explain the formation of 80 from 1 involving an unprecedented cleavage of a cyclic manganate ester intermediate. Lead tetraacetate cleavage of 78 must also involve a similar abnormal cleavage of the cyclic lead ester intermediate. (Scheme 1.16)



(a) $KMnO_4$/pyr; (b) $Pb(OAc)_4$/benzene.

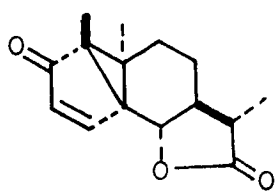
Scheme 1.16

The present study has thus clearly established the stereostructures of the $KMnO_4$ oxidation products of santonin 1. It is now essential to reinvestigate the products obtained by ozonolysis of santonin 1 and 4,5-β-dihydroxysantonin ($KMnO_4$ oxidation product) as these are expected to clarify the discrepancies which still exist in the literature. Work in this direction has already been initiated.

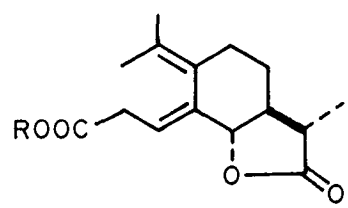
SECTION FIVE

PHOTOCHEMICAL REACTIONS OF SANTONIN IN METHYL, ETHYL AND ISOPROPYL ALCOHOL.

Studies on the photochemical rearrangements of santonin were initiated by Cannizzaro and Gucci[42] over a century ago. These authors observed that, when exposed to sunlight for several weeks or irradiated through pyrex container, a neutral solution of santonin 1 in ethanol yields the dienoid ester photosantonin* and another crystalline substance, $C_{17}H_{24}O_4$, m.p. 153°. While the main photoproducts lumisantonin (81)[43,44] and photosantonic acid (82)[45] were fully characterised through the extensive efforts of different groups, we did not find any report on the second compound reported by Cannizzaro and Gucci[42]. It was therefore considered worthwhile to study the photoreaction of santonin 1 in different alcohols by exposure to sunlight** and if possible re-obtain and characterised the unknown compound, m.p. 153° (santonin $\xrightarrow[EtOH]{h\nu}$ compound, m.p. 153°).



81



82, R = H,
83, R = Et
84, R = Me

---

* Ethyl ester of photosantonic acid 83.

** It was observed that santonin undergoes photo conversion by exposure to sunlight for 8 to 10 hrs. during April & May.

Exposure of an ethanolic solution (1%) of santonin 1 to sunlight and monitoring the reaction by TLC, it was observed that conversion is complete after 10 hrs. Removal of ethanol and chemical separation into neutral and acidic parts gave two products, i) a neutral viscous oil and ii) a crystalline acid, m.p. 149-50^{0}. We failed to obtain the previously reported crystalline natural compound and could not isolate any single pure substance from the neutral fraction. The spectral data on the acidic compound (IR, ^{1}H NMR, ^{13}C NMR) fully established its identity with photosantonic acid (82). While the literature[45] records a 60 MHz ^{1}H NMR spectrum of photosantonic acid, we were able to record a 300 MHz spectrum and identify and assign the various signals with the help of $^{1}H^{1}H$ COSY and $^{1}H^{13}C$ HETCOR spectra. In addition to the confirmation of the previous assignments, the present study helped us to assign the (E)-configuration of the C_2-C_8 double bond. The assignments are given in Table 1.4. When the photoreaction was carried out in methanol, workup of the reaction product (10 hrs, TLC monitoring) indicated that practically no acidic compound is formed. The neutral portion contained two components which could be separated by careful chromatography over silica gel. The first component, a viscous liquid, showed signs of solidification but could not be obtained in a crystalline form*. The ^{1}H NMR

* TLC in different solvent systems indicated it to be homogeneous.

TABLE 1.4

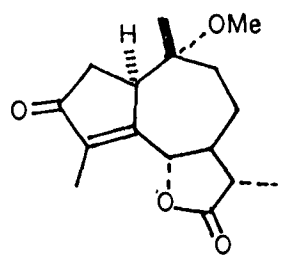
^1H NMR of photosantonic acid 82 in $CDCl_3$, 300 MHz.

Chemical shift 'δ'	No of hydrogens	multiplicity J (in Hz)	Assignment
4.12	1	dd	H-3
1.7 - 1.85	2	m(complex)	H-4 and H-6β
2.03	1	dq	H-5α
1.34	1	td	H-5β
2.80	1		H-6α
5.66	1	ddd	H-8
2.99	2	m(complex)	H-9α and H-9β
2.33	1	q(6.5)	H-11
1.23	3	d(6.5)	11-CH_3
1.76	3		7-CH_3 (a)
1.63	3		7-CH_3 (b)

carboxyl hydrogen not given.

spectrum (Fig 1.20) showed a striking similarity to the ^1H NMR spectrum of photosantonic acid (82) except for an additional three proton singlet at 3.7 ppm and the absence of the acidic proton (no signal above 10.00 ppm). This clearly showed that the product is methylphotosantonate (84) (methyl ester of photosantonic acid). The formation of the ethyl ester was observed earlier and hence this was the expected product of the reaction.

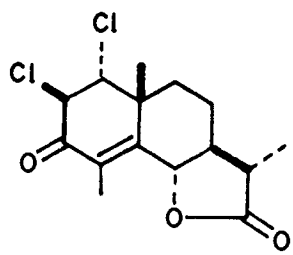
The second neutral compound, m.p. 152-53^0 obtained in this reaction has not been previously reported and analysed for $C_{16}H_{22}O_4$, clearly showing addition of methanol has taken place (structure 85). Moreover, this was further evident from its ^1H NMR spectrum (Fig 1.21) which showed the absence of the C_1-C_2 olefinic linkage present in santonin and a new 3 proton singlet at 3.21



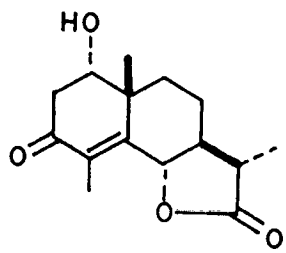
85-b

The ^{13}C NMR spectral data collected after the submission of thesis shows only one doublet at 81.3 obviously due to C-6. The presence of a singlet at 78.0 shows that methoxy group is attached to a quarternary carbon. Structure 85b is therefore assigned to it.

double bond and appearance of a methoxy group can be rationalised in terms of a photo-Michael reaction. Inspection of the molecular model (see conformation 85a) clearly shows that the observed shielding is possible only if C_1-OCH_3 is α and axial. This is further confirmed by the observation that W ½ H of the C_1 methine is 9 Hz. These results thus indicate that the reagent adds from the α-face and is in contrast to our findings concerning the $KMnO_4$ oxidation of santonin 1 (Section 4, Chapter 1) where the reagent adds from the β-face. Obviously, in this latter reaction the hindrance is due to the C_6 oxygen and the C_9 methylene group. One can therefore safely conclude that in the case of santonin 1 reagents can add either to the α or the β-face of the molecule depending on the reaction site i. e. C_1-C_2 olefinic linkage or C_4-C_5 olefinic linkage. In further support to this conclusion, the structure assigned to 1,2-dichloro-α-santonin (86) is understandable. The chloronium ion is formed on the α face followed by diaxial opening resulting in the formation of the dichloro derivative 86.



86



87

While the compound 85 has not been previously reported a structurally close analogue, dehydroisoerivanin (87), has been isolated from the plant species Balsamita major DESF (compositae)[50].

The photoreaction of santonin 1 using isopropyl alcohol as solvent was also studied. Chromatographic separation on silica gel afforded, besides unreacted 1, a viscous oil and two crystalline solids, m.p. 153-54^{0} and 147-48^{0} in order of their elution. The IR spectrum of the viscous liquid which could not be fully characterised showed bands at 1790 and 1730 due to lactone and ester carbonyl groups respectively and is assumed to be the isopropyl ester of photosantonic acid. The most polar compound m.p. 147-48^{0} was conclusively identified as photosantonic acid (82). But the most important observation of this study was the characterisation (IR, Fig 1.22, ^{1}H-NMR and m.p.) of compound m.p. 153-54^{0} as lumisantonin (81). While santonin 1 ⟶ lumisantonin (81) has proved to be typical of cyclohexa-2,5-dienones, and Van Tamelen and others have explained the formation of photosantonic acid (82) via the intermediacy of lumisantonin (81), previous studies have failed to isolate lumisantonin (81) and its isolation in our present study is of special interest. It may be noted that lumisantonin (81) could be isolated only when santonin 1 was exposed to sunlight in isopropyl alcohol. Monitoring of the photoreaction by TLC shows the appearance of the spot

corresponding to lumisantonin (81) which gradually disappears to produce new spots corresponding to photosantonic acid (82) and its ester. Lumisantonin (81) is therefore an intermediate in the photo transformation of santonin 1 to photosantonic acid (82).

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

Activation of Zn dust[51]

Commercial Zn powder was activated by washing with 2% hydrochloric acid for 5 minutes followed by an excess of water, ethanol, AR acetone and dry ether. Activated Zn powder so obtained was heated in an oven at 100^{0} for 15 minutes and used immediately.

Preparation of santonone 55

A 50% solution of glacial acetic acid (30 mL) was introduced into a three necked round bottomed flask (250 mL) equipped with a reflux condenser and a mercury sealed mechanical stirrer. It was heated in an oil bath at 100^{0} and to this hot solution was added a mixture of santonin 1 (1.0 g, 0.004 moles) and activated Zn (1.307 g, 0.02 moles) over a period of 30 minutes with vigorous stirring. After addition of Zn was complete the mixture was stirred for additional 4.5 hours at bath temperature and allowed to stand overnight. The separated yellowish solid was filtered, washed several times with water to remove acetic acid completely. Recrystallization from aqueous ethanol gave 55; 0.215 g; 21.5%; m.p. 226^{0} (lit.[25] $222-23^{0}$); $[\alpha]_{D}$ $+82.3^{0}$.

UV, $CHCl_3$, (Fig. 1.1), λmax 245nm.

IR, Nujol, (Fig. 1.2), bands at;

2950, 1780, 1475, 1340, 1185, 1150, 1130, 1030, 1010 and 900 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 1.3), 90 MHz, signals at;

1.31 (3H, d, J = 7.5 Hz, C_{11}-CH_3),

2.20 (3H, s, C_1-CH_3),

2.23 (3H, s, C_4-CH_3),

5.10 (1H, d, J = 9.0 Hz, C_6-H),

6.90 (1H, s, C_2-H).

^{13}C NMR, $CDCl_3$,(Fig. 1.4), 250 MHz,

See Table 1.1.

MS, (Fig. 1.5), major peaks at;

m/z 458 (M^+), 443 (100%), 414, 399, 385, 369, 355, 341, 325, 311, 297, 283, 273, 259, 243, 229, 215, 203 ,185, 171, 165, 156, 149, 133, 121, 115, 105, 97, 91, 83, 69 and 55.

Isomerisation of santonone 55 to isosantonone 56.

A mixture of santonone 55 (0.025g, 0.0545 moles) and 70% glacial acetic acid (5 mL) was refluxed in an oil bath for a period of 5 hours. After cooling, the acetic acid was neutralized by saturated $NaHCO_3$ solution (8 mL) and extracted with ether (3 x 10 mL). Combined ether extracts were washed with water (2x10 mL) and dried. Evaporation of ether gave a yellowish sticky solid which was filtered through a small silica gel column to give a white solid 56; 0.016 g; 64%; m.p. 276^{o} decomposition (lit.[25] 280^{o} decomposition); $[\alpha]_D$-161.8^{o}.

IR, Nujol, (Fig. 1.6), bands at:

2950, 1780, 1475, 1235, 1195, 1165, 1125, 990 and 950 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 1.7), 250 MHz, signals at:

1.42 (3H, d, J = 7.5 Hz, C_{11}-CH_3),

2.14 (3H, s, C_1-CH_3),

2.26 (s, 3H, C_4-CH_3),

5.64 (1H, d, J = 5 Hz, C_6-H),

6.92 (s, 1H, C_2-H).

MS, (Fig. 1.8), major peaks at:

m/z 458(M^+), 443, 423, 414, 399, 385, 369, 355, 341, 325, 311, 297, 283, 273, 257, 243, 229, 215, 192, 183, 170, 163, 156, 149, 141, 133, 115, 105, 97, 91, 87 (100%), 83, 69 and 55.

Reaction of santonin 1 with Zn-HCl-ether.

Dry ether (25 mL) was introduced into a round bottomed flask (100 mL) equipped with a $CaCl_2$ drying tube and saturated with dry HCl gas at 0°. Santonin 1 (1.0g, 0.004 moles) was then added and dissolved by stirring. To this cold solution was added, in portions with stirring, activated[51] Zn powder (1.308g, 0.02 moles) over a period of one hour. After complete addition of Zn the resulting mixture was stirred at 0° for another hour and at room temperature for an additional one hour. The reaction mixture was then poured into crushed ice while stirring, made alkaline by adding solid Na_2CO_3 (4.0 g) and extracted with ether (4 x 15 mL). The combined ether extracts were washed

with water (2 x 10 mL) and dried. Evaporation of the ether afforded a yellowish solid (0.868 g) which was chromatographed over silica gel.

The fractions eluted with ether-petroleum ether (20:80) followed by concentration furnished 66; 0.189 g; 18.9 %. Recrystallization from aqueous ethanol yielded shiny crystals; m.p. 153° (lit.[52] 154°).

IR, Nujol, (Fig. 1.9), bands at:

2920, 2840, 1770, 1380, 1200, 1175, 1120, 1010 and 990 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 1.10), 90 MHz, signals at:

0.9 (3H, s, C_{10}-CH_3),

1.0 (3H, d, J = 7.5 Hz, C_4-CH_3),

1.23 (3H, d, J = 7 Hz, C_{11}-CH_3),

3.85 (m, 1H).

Further elution of the column with ether-petroleum ether (30:70) followed by concentration furnished 67; 0.286 g; 28.6 %. Crystallization from aqueous ethanol gave white crystals; m.p. 152° (lit.[34] 153°).

IR, Nujol, (Fig. 1.11), bands at:

2920, 2840, 1770, 1700, 1380, 1210, 1150, 1020 & 990 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 1.12), 90 MHz, signals at:

1.17 (3H, s, C_{10}-CH3),

1.24 (3H, d, J = 7 Hz, C_{11}-CH_3),

1.27 (3H, d, J = 7 Hz, C_4-CH_3),

3.8 (1H, t).

Further elution of the column with ether-petroleum

ether (35:65) followed by concentration furnished 1; 0.243g; 24.3%; m.p. and mixed m.p. 172°.

Preparation of santonic acid 65

Santonic acid 65 was prepared from santonin 1 (5g, 0.02 moles) following the literature[37] procedure to furnish 2.53 g of yellowish crystals; 50.6%; m.p.166° (lit.[37] 165°).

Reaction of santonic acid 65 with Zn-HCl-ether

Reaction of santonic acid 65 (0.54g, 0.00216 moles) with activated Zn (0.708g, 0.108 moles) in dry ether (20 mL) saturated with dry HCl gas was carried out as previously reported (see above). Usual workup furnished a yellow liquid (0.390g) which was distilled under reduced pressure to give a colorless liquid, 0.37g; 68.5% which was identified as a mixture of 71 and 72.

IR, Neat, (Fig 1.13), bands at;

2950, 1835, 1780, 1380, 1335, 1210 and 930 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig 1.14), 360 MHz, signals at:

1.0 (3H, t, J = 7 Hz, CH_3-CH_2-),

1.18, 1.20 (3H, s, CH_3-C(-C)(-C)-C each),

1.35 (3H, d, J = 7 Hz, CH_3-CH-C(=O)-O),

2.78 (1H, s, -CH=C(-)-CH_2),

3.07, 3.11 (1H, q, J = 7 Hz, CH_3-CH(-)-C(=O)-O each),

4.92, 5.09 (1H, bs, >C=C(H)- each).

^{13}C NMR, $CDCl_3$, 250 MHz:

five quartets at, 10.0, 11.1, 12.2, 26.8 and 28.5.

eight triplets at, 23.6, 24.1, 35.4, 36.5, 37.3, 37.6, 39.3 and 50.7.

six doublets at, 44.4, 45.6, 51.5, 61.6, 118.6 and 130.4.

nine singlets at, 50.0, 58.4, 60.0, 60.7, 143.2, 149.4, 173.2, 173.6 and 173.9.

$KMnO_4$-pyridine oxidation of santonin 1

Oxidation of santonin 1 (1.0g, 0.004 moles) in freshly distilled pyridine (5 mL, 0.619 moles) was carried out according to the reported[1] procedure to furnish a brown sticky mass (0.738g) which was chromatographed over silica gel. Fractions eluted with benzene on concentration gave 80 as a white crystalline solid; 0.35 g; 35% ; m.p. 268^0 (lit.[1] 268^0).

IR, KBr, (Fig 1.15), bands at:

3000, 1790, 1736, 1721, 1468, 1250, 1177, 1140, 1107, 1073, 1040, 961, 912, 820, 794 and 784 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig 1.16), 500 MHz signals at:

See Table 1.2.

^{13}C NMR, $CDCl_3$, (Fig 1.17), 250 MHz :

five singlets at 41.6, 90.1, 162.0, 177.0, and 208.3.

five doublets at 41.0, 45.6, 78.6, 118.7 and 158.5.

two triplets at 22.1 and 31.4.

three quartets at 12.3, 23.1 and 31.9.

Further elution of the column with ethyl acetate - benzene (5 : 95) followed by concentration furnished 78; 0.156g; 15.6%. Recrystallisation from benzene yielded white needles, m.p. 220^0(lit.[1] 220^0).

IR, Nujol, (Fig 1.18), bands at:

3570, 3475, 2970, 2870, 1775, 1685, 1463, 1265, 1140, 1110, 1025, and 820 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig 1.19), 500 MHz signals at:

See Table 1.2.

Photochemical reactions of santonin 1

General procedure

1% solution of santonin 1 in different alcohols were exposed to bright sunlight (in the month of April-May) for 8 to 10 hrs while periodically monitoring the progress of the reaction using TLC. Alcohols were removed by distillation and the residue was separated chemically and/or by column chromatography.

Photochemical reaction of 1 with ethanol

In two conical flasks (100 mL each) was dissolved santonin 1 (0.25g, 0.001 moles) in absolute ethanol (25 mL). The flasks were exposed to sunlight with occasional shaking. The progress of the reaction was periodically monitored by TLC. After 10 hrs the flasks were removed, the two fractions were combined and ethanol was removed by distillation to furnish a yellow viscous liquid (0.427g). This liquid was dissolved in ether (25 mL) and extracted with saturated $NaHCO_3$

solution (3 x 10 mL) followed by water (2 x 10 mL). Bicarbonate and water extracts were combined, acidified with dilute HCl and extracted with ether (3 x 15 mL). Combined ether extracts were washed with water (10 mL) and dried. Evaporation of solvent ether afforded a yellowish sticky mass (0.089g) which was chromatographed over silica gel. Elution with ethyl acetate-petroleum ether (20:80) followed by concentration gave colorless needles of 82. 0.038 g; 7.0%; m.p. 149-50^{o} (lit.[45] 152-54^{o}).

IR, Nujol, bands at :

3000-3500 (broad), 2980, 2940, 2900, 1760, 1700, 1440, 1130, 1000, 790 and 760cm^{-1}.

^{1}H NMR, $CDCl_3$, 300 MHz, signals at :

See Table 1.4.

^{13}C NMR, $CDCl_3$,

five singlets at 127.45, 130.82, 140.09, 177.59 and 178.44.

four doublets at 42.24, 54.22, 83.31 and 110.28.

three triplets at 27.48, 30.44 and 33.80.

three quartets at 12.52, 22.03 and 22.20.

Further elution of the column with petroleum ether-ethyl acetate (70:30) gave a yellowish liquid (0.032g) which was not characterised.

Neutral ether extracts were dried and ether was removed to give a yellowish viscous liquid (0.386g) which was chromatographed over silica gel. Elution with petroleum ether-benzene (95:5) followed by

concentration gave a colorless viscous liquid (0.282g) which was not characterised.

Photochemical reaction of santonin 1 in methanol

Santonin 1 (1.0g, 0.004 moles) was dissolved in AR grade methanol (100 mL) and exposed to sunlight as before. Removal of methanol gave yellow liquid (0.973g) which was chromatographed over silica gel. Elution with petroleum ether - benzene (50:50) followed by concentration afforded 84 as a colorless liquid; 0.629 g; 57%.

IR, Neat, bands at :

3000, 2940, 1780, 1730, 1450, 1370, 1310, 1180, 1100, 1000 and 780 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 1.20), 90 MHz, signals at :

1.19 (3H, d, J = 7 Hz, $C_{11}-CH_3$),

1.6 (3H, d, J = 2 Hz, $CH_3-\overset{|}{C}=\overset{|}{C}-$),

1.74 (3H, s , $CH_3-\overset{|}{C}=\overset{|}{C}-$),

2.33 (m, 1H, $C_{11}-H$),

2.94 (2H, m),

3.7 (3H, s, $-\overset{|}{C}-O-CH_3$),

4.11 (1H, d, d, J = 10 Hz and 2 Hz, C_3-H),

5.66 (1H, m, C_8-H).

Elution of the column with benzene-ethyl acetate (90:10) followed by concentration gave unreacted santonin 1 (0.086 g) identified by co-TLC, m.p. and mixed m.p. 170-71^0.

Elution of the column with benzene-ethyl acetate (70:30) followed by concentration gave 85 as a colorless

liquid (0.083g). This liquid was warmed with ether (15 mL) and stored in the refrigerator overnight to yield colorless needles; 0.218g; 19.3%; m.p. 152-53^{0}.

IR, Nujol, bands at :

2990, 2860 (broad) 1785, 1690, 1625, 1470, 1400, 1390, 1340, 1300, 1200, 1180 & 1000 cm^{-1}

^{1}H NMR, $CDCl_3$, (Fig 1.21), 300 MHz, signals at:

0.86 (3H, s, $C_{10}-CH_3$),

1.27 (3H, d, J = 7.5 Hz, $C_{11}-CH_3$),

1.4 (1H, m, C_7-H),

1.87 (3H, s, C_4-CH_3),

1.98 -2.14 (4H, m, C_8 and C_9-H, each),

3.21 (3H, s, $-\overset{|}{C}-\overset{|}{C}OCH_3$),

3.35 (1H, m, C_1-H),

4.81 (1H, d, J = 11 Hz. with further fine splitting, C_6-H).

Photochemical reaction of santonin 1 with isopropyl alcohol.

Santonin 1 (1.0g, 0.004 moles) was dissolved in isopropyl alcohol (100 mL) and exposed to sunlight as before. After 8 hrs, when the reaction was complete (TLC), the solvent alcohol was removed to give a yellow viscous liquid (0.886 g) which was chromatographed over silica gel. Elution with benzene followed by concentration gave a colorless viscous liquid; 0.545g which was not fully characterised .

IR, CCl_4, bands at :

3000, 2940, 1790, 1730, 1100, 1000 & 780 cm^{-1}

Elution of the column with benzene-ethyl acetate (99:1) followed by concentration gave a yellow solid which was recrystallised from a petroleum ether-ether mixture to give yellowish needles of 81; 0.043 g; 4.3%; m.p. 153-54^{0} (lit.[43] 154-55^{0}).

IR, Nujol, (Fig. 1.22), bands at :

2960-2840 (broad), 1775, 1720, 1470, 1400,

1200, 1180, 1160, 1100, 1040, 1010 & 850 cm^{-1}.

Elution of the column with benzene-ethyl acetate (90:10) gave yellow crystals of 1 (0.018 g), m.p. and mixed m.p. 170^{0}.

Further elution of the column with benzene-ethyl acetate (85:15) followed by concentration gave a solid which was recrystallised from a mixture of petroleum ether-benzene to give colorless needles of 82; 0.106g; 9.8%; m.p. 148-49^{0} (lit.[45] 152-53^{0}).

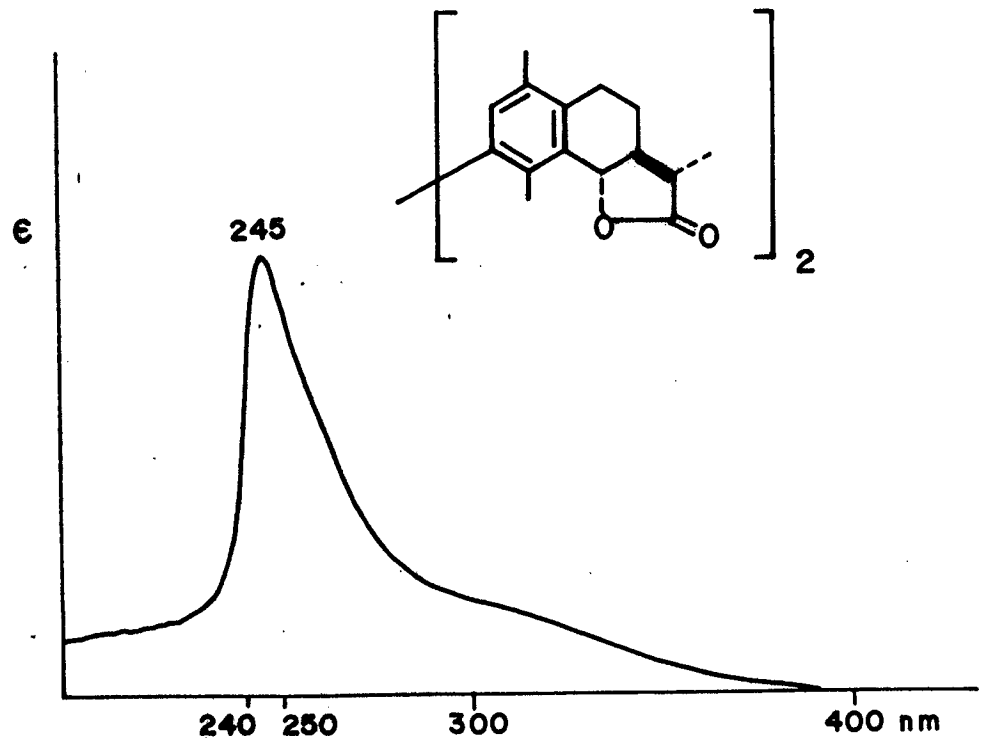


Fig. I.I UV Spectrum of 55

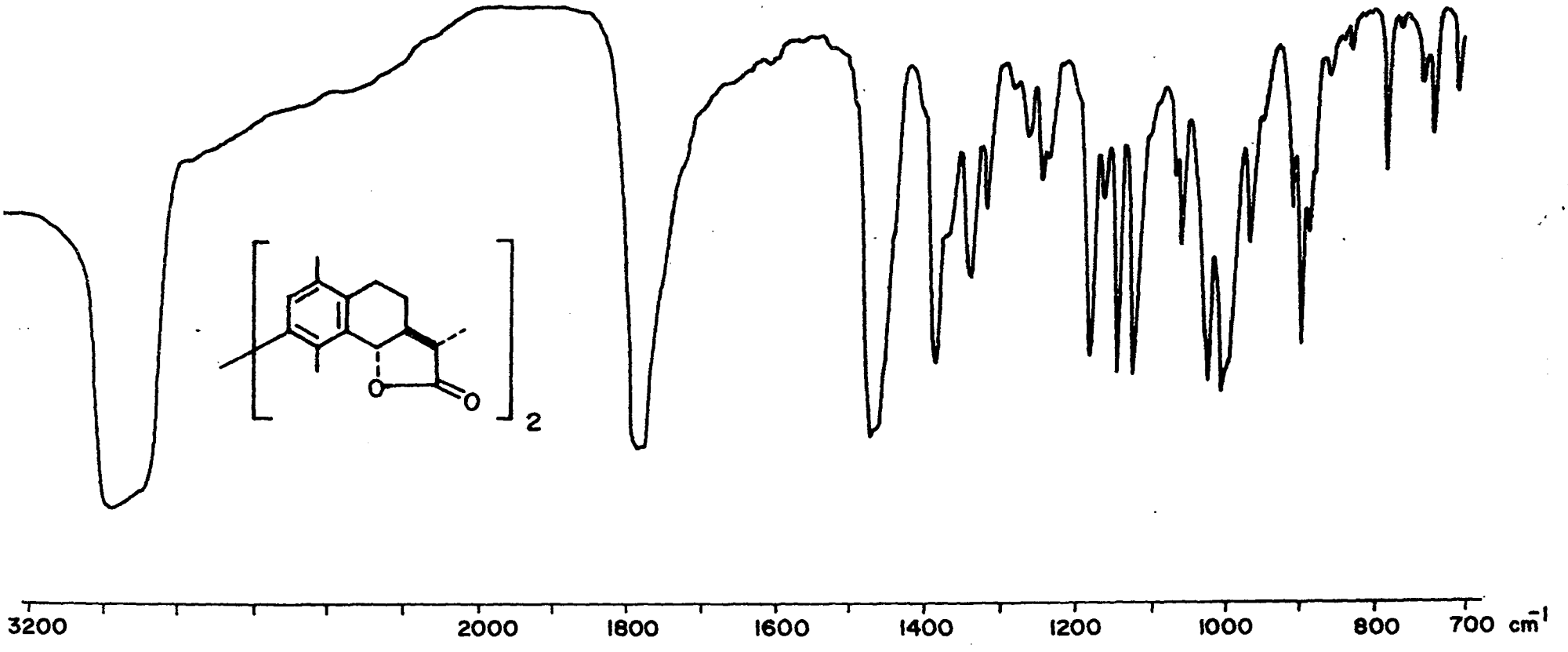


Fig. I.2 IR Spectrum of 55

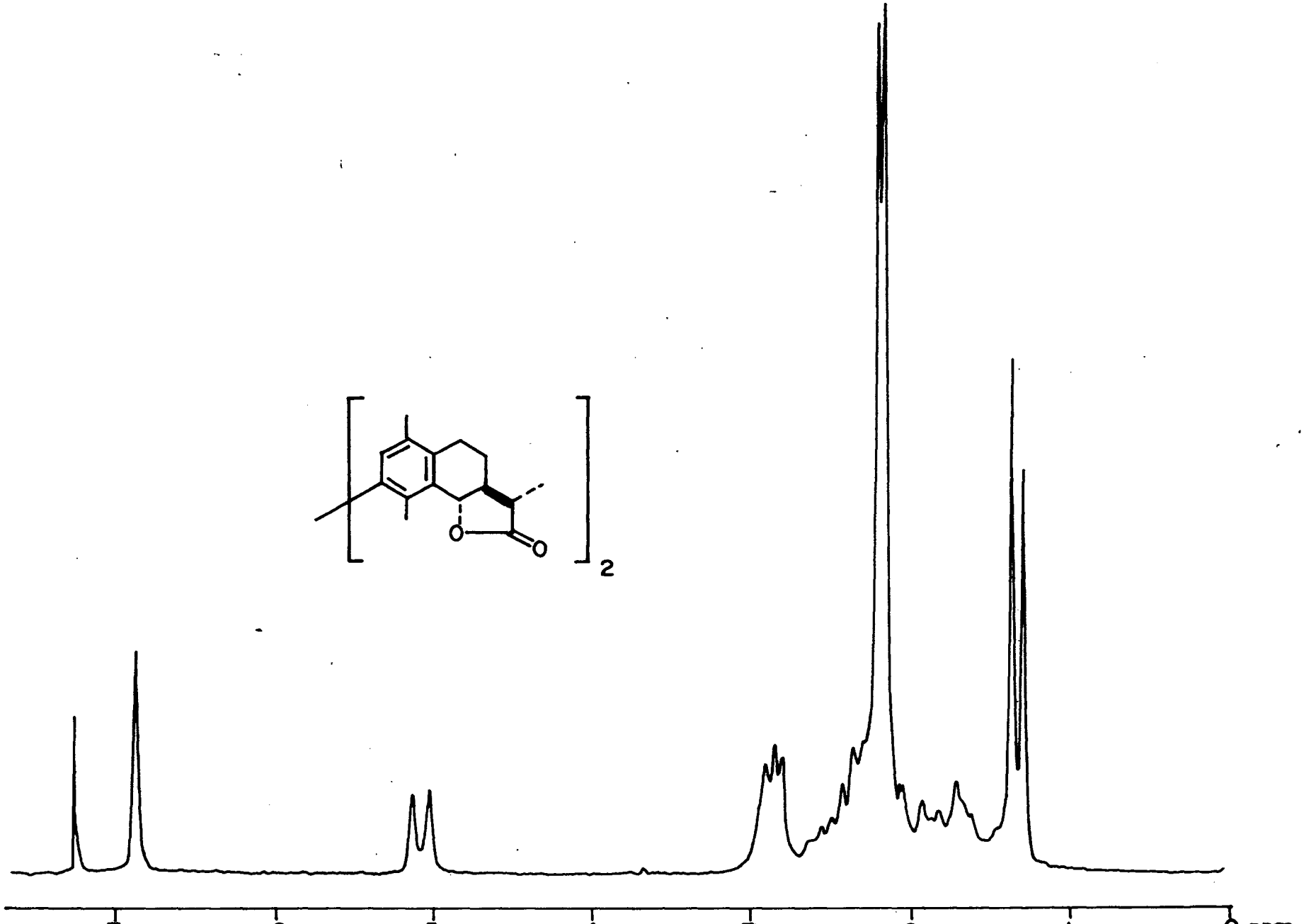


Fig. 1.3 ^{1}H NMR Spectrum of 55

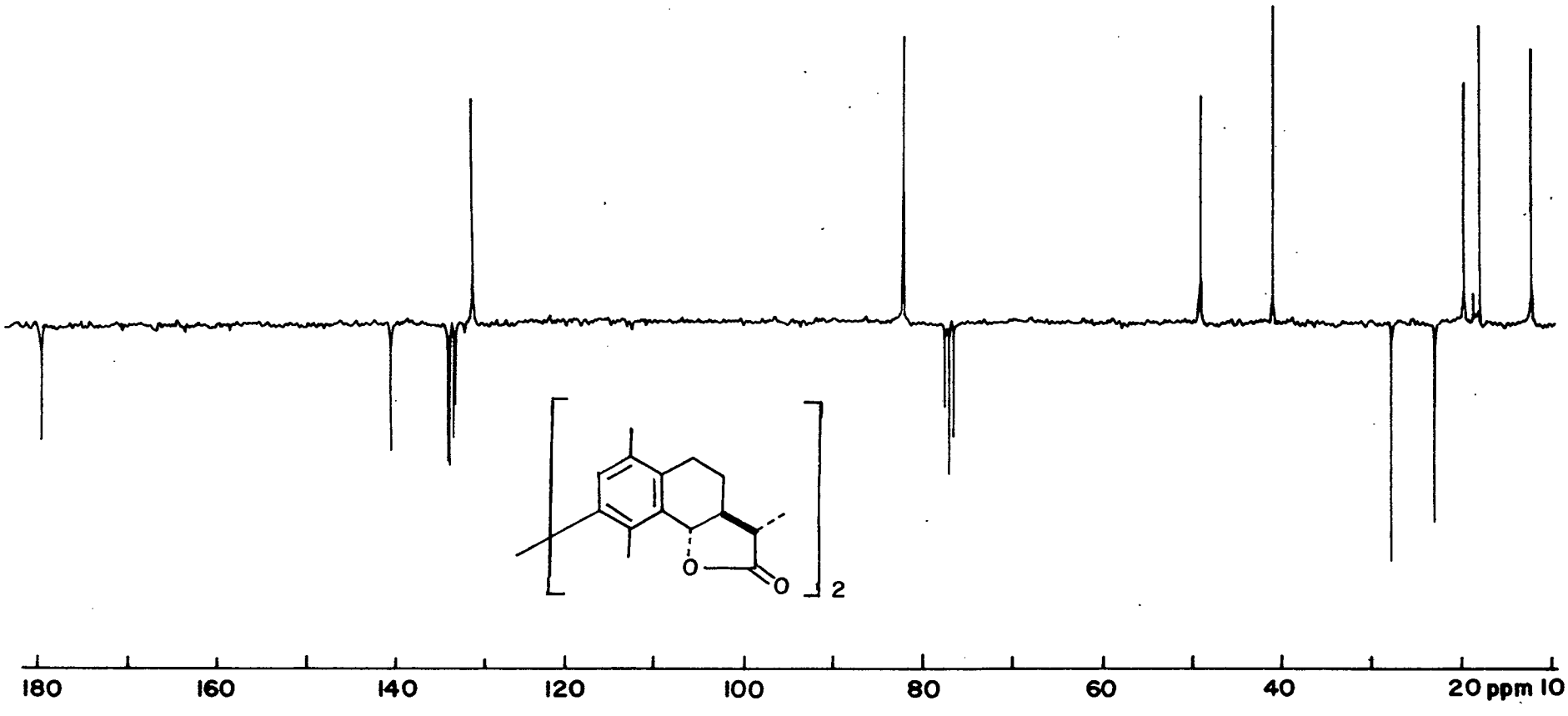


Fig 1.4 APT ^{13}C NMR Spectrum of 55

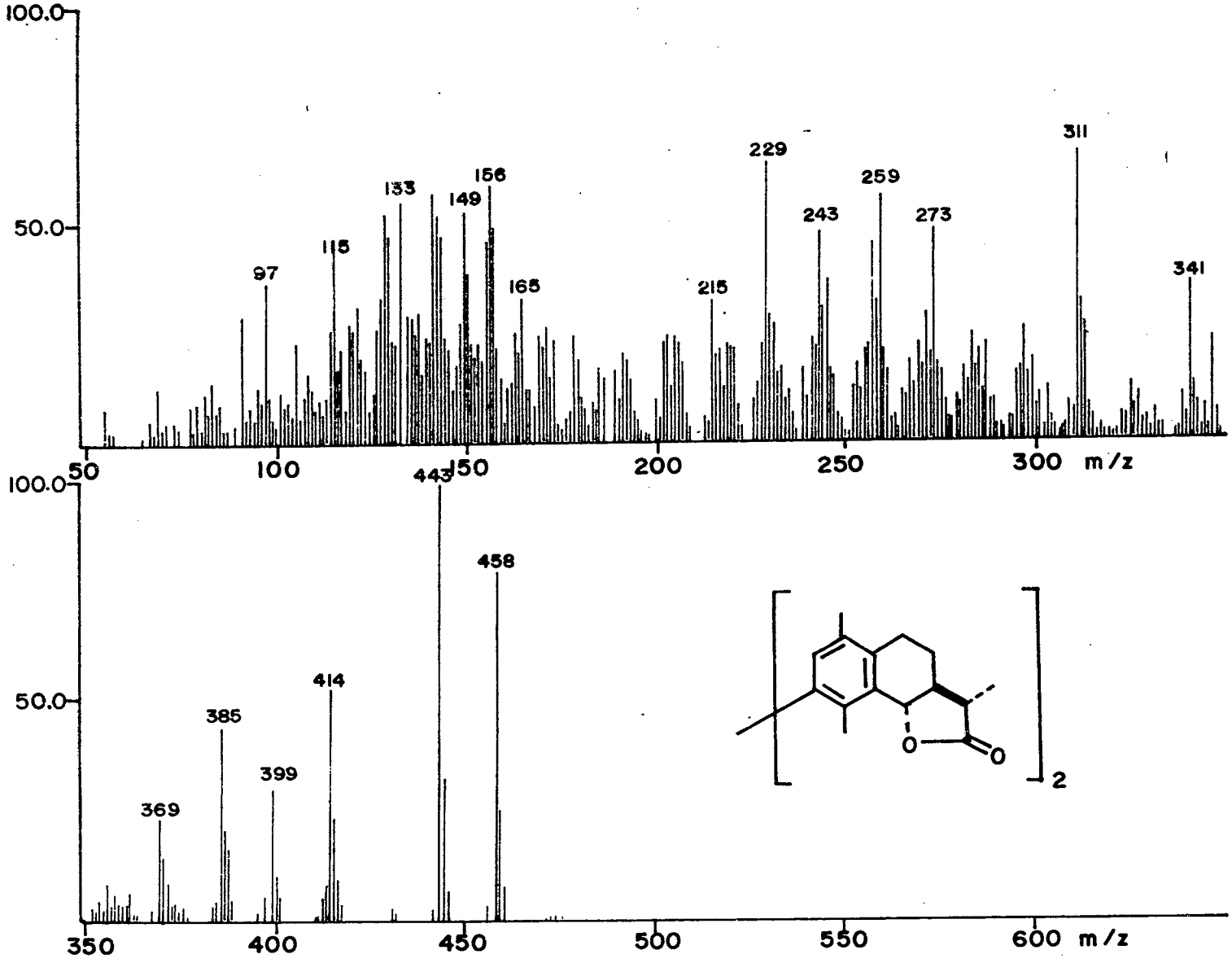


Fig. 1.5 Mass spectrum of 55

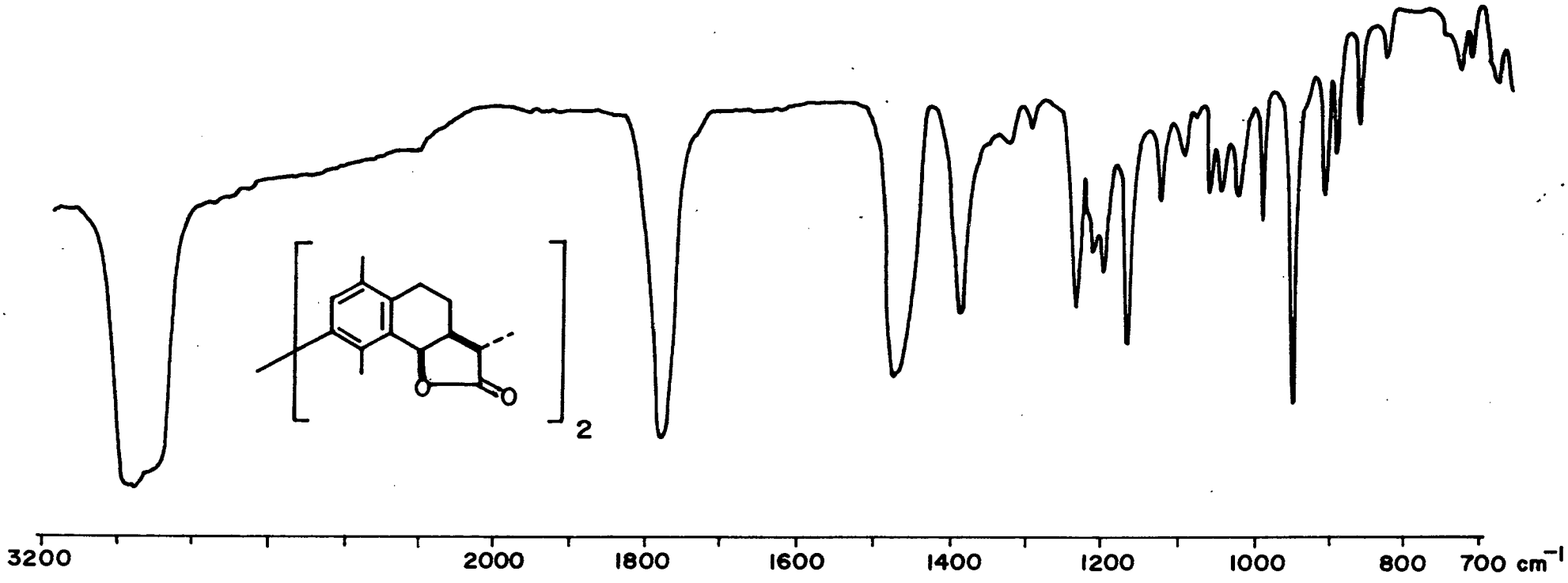


Fig. I.6 IR Spectrum of 56

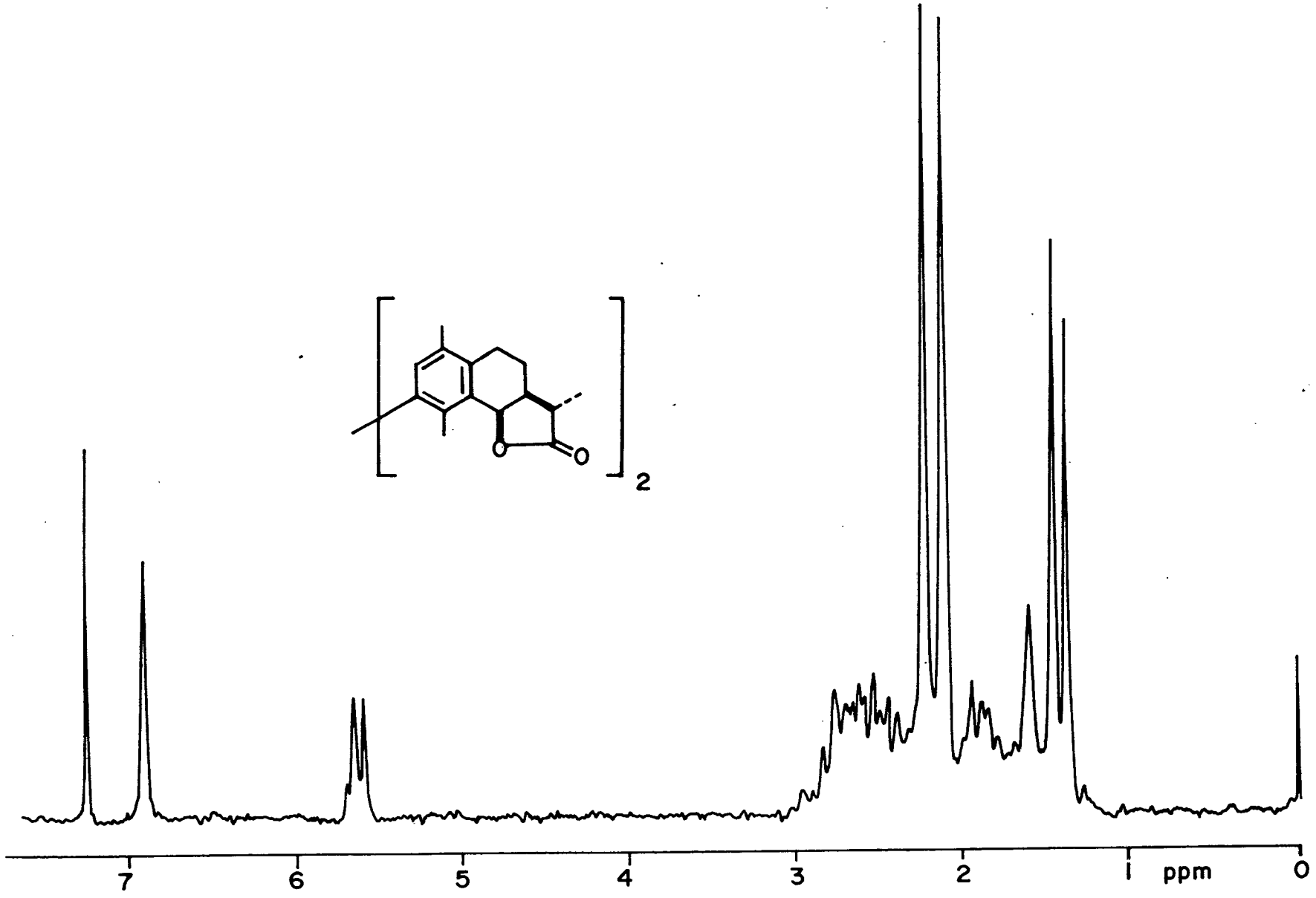


Fig. I.7 ^{1}H NMR Spectrum of 56

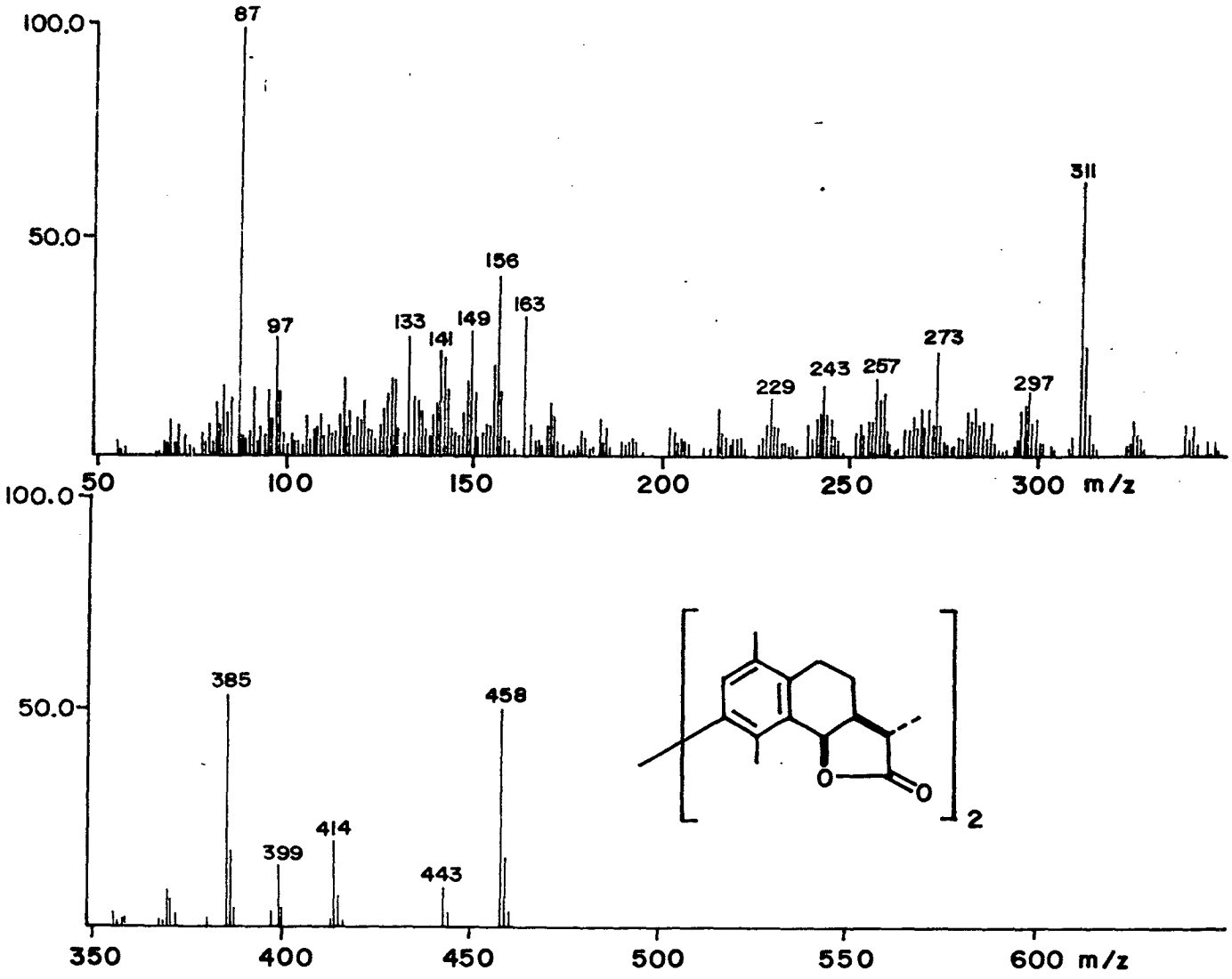


Fig. 1.8 Mass spectrum of 56

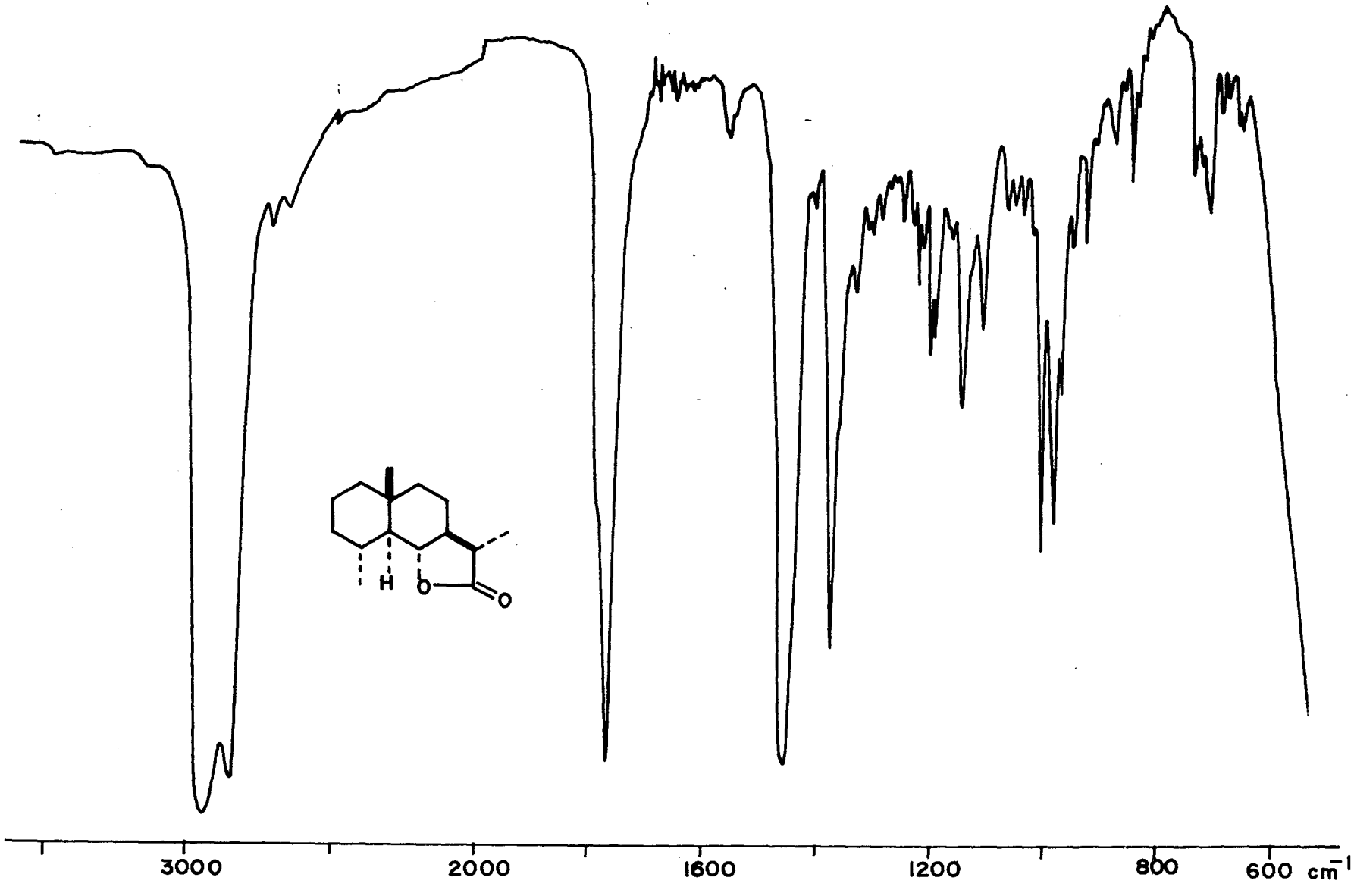


Fig. 1.9 IR spectrum of 66

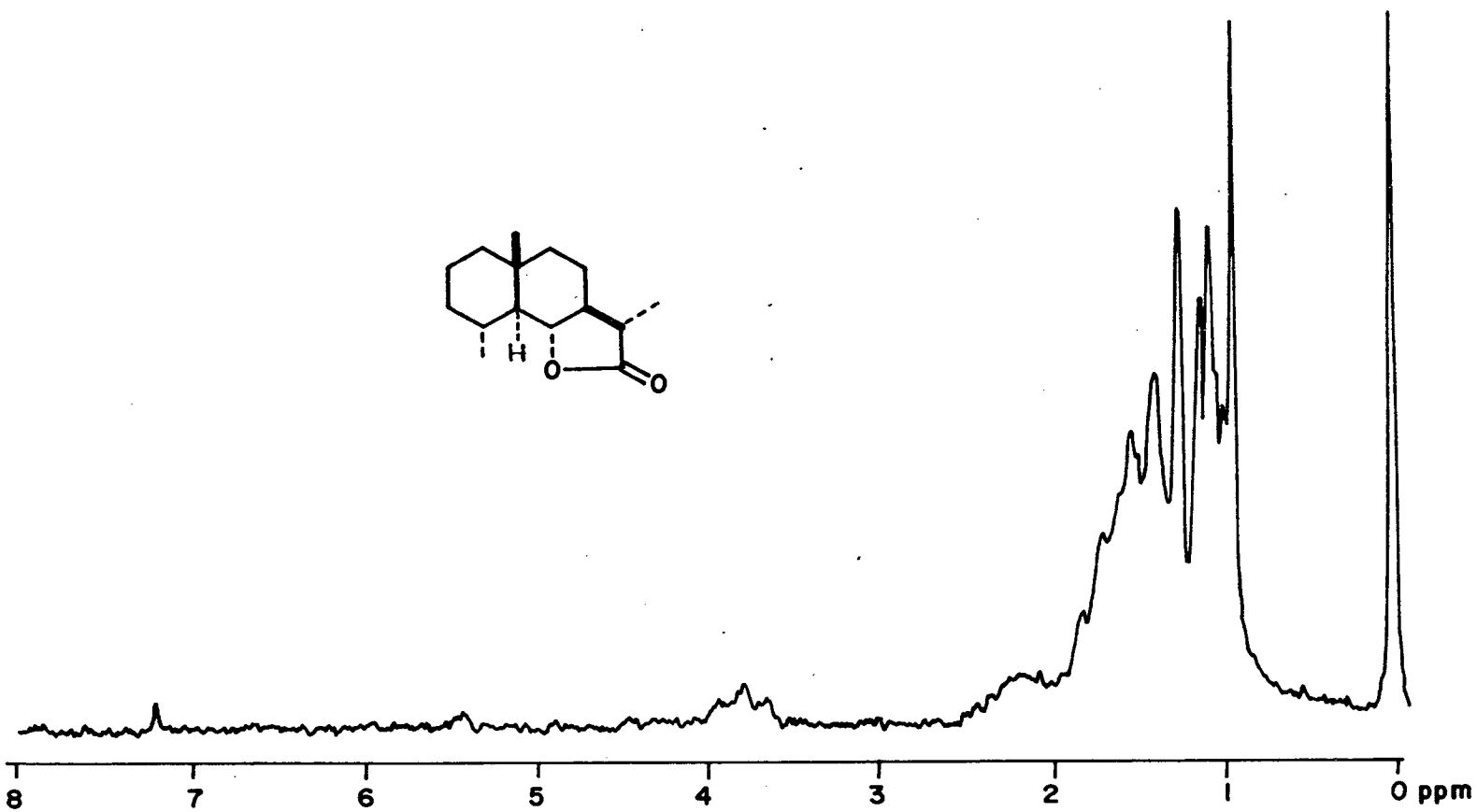


Fig. 1.10 ^{1}H NMR spectrum of 66

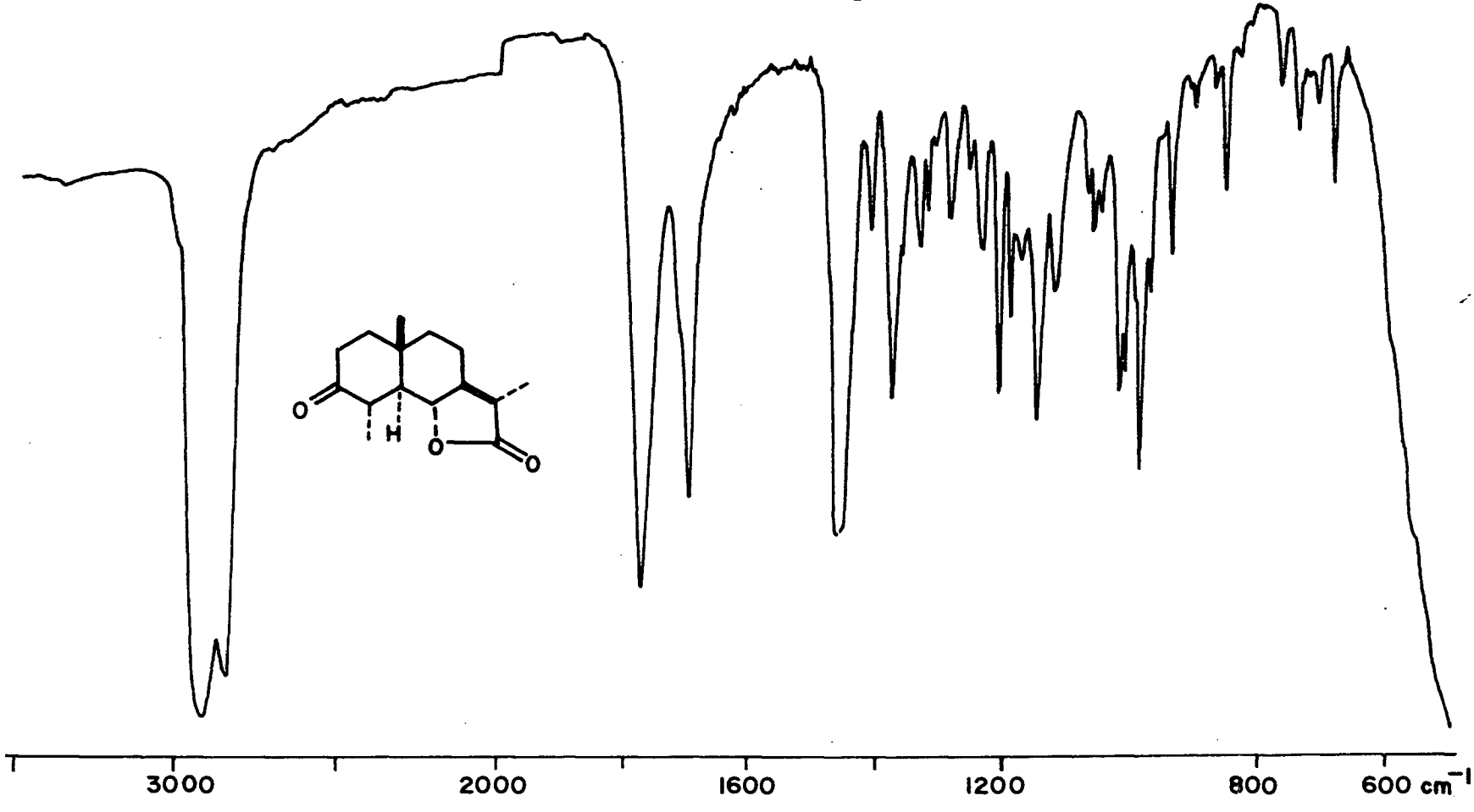


Fig. I.11 IR spectrum of 67

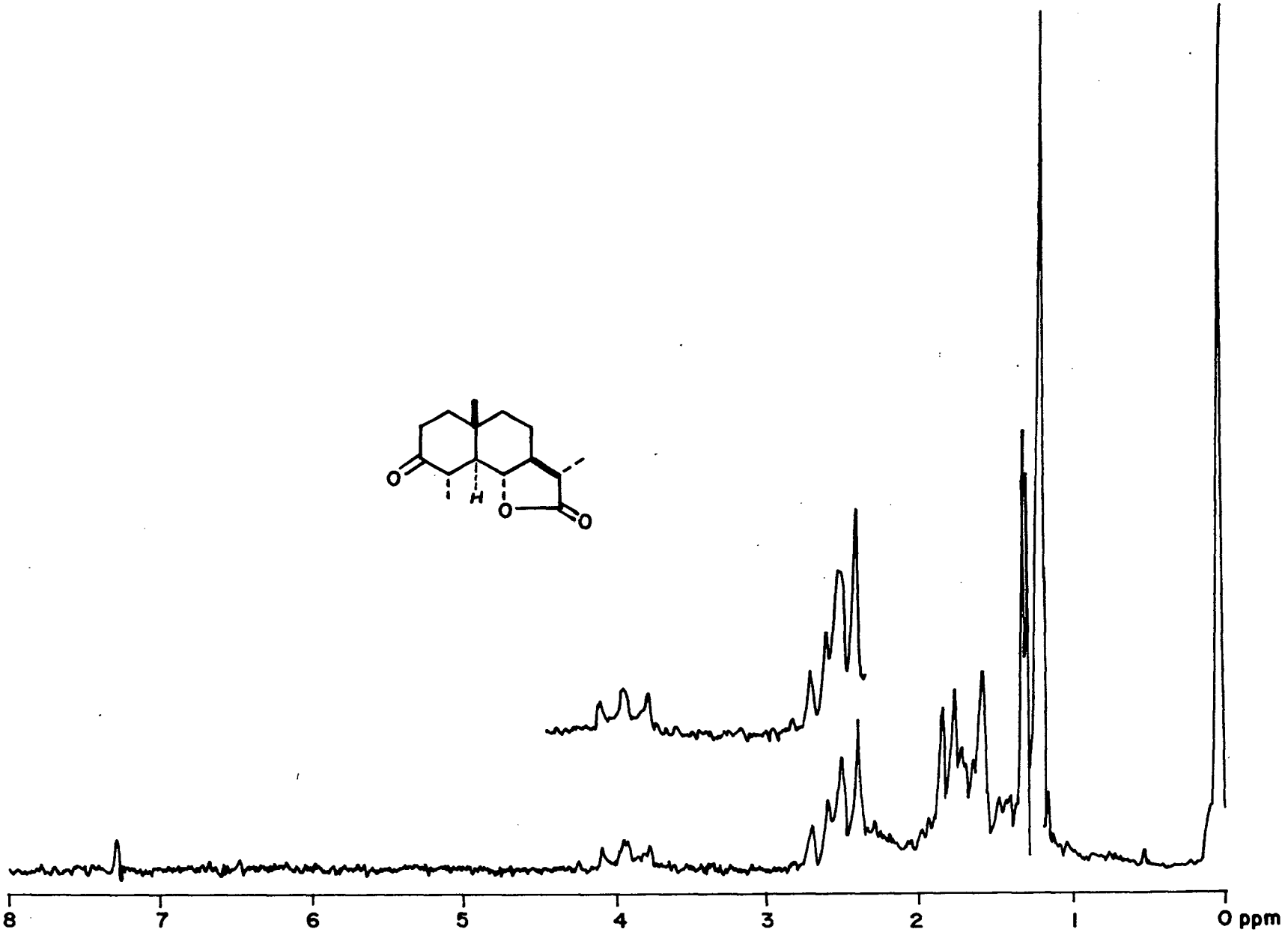


Fig. 1.12 ^{1}H NMR spectrum of 67

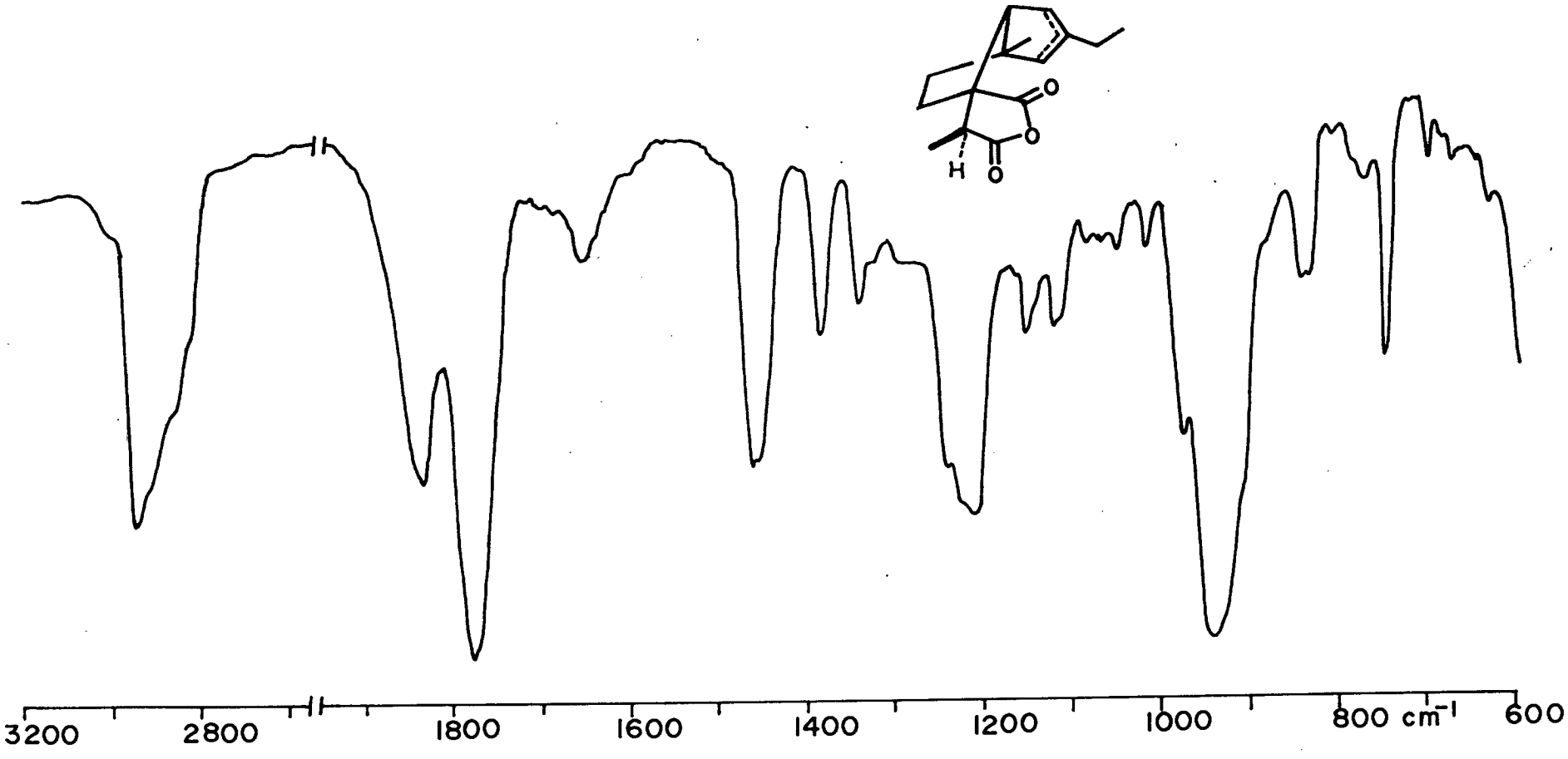


Fig. 1.13 IR spectrum of mixture of 71 & 72

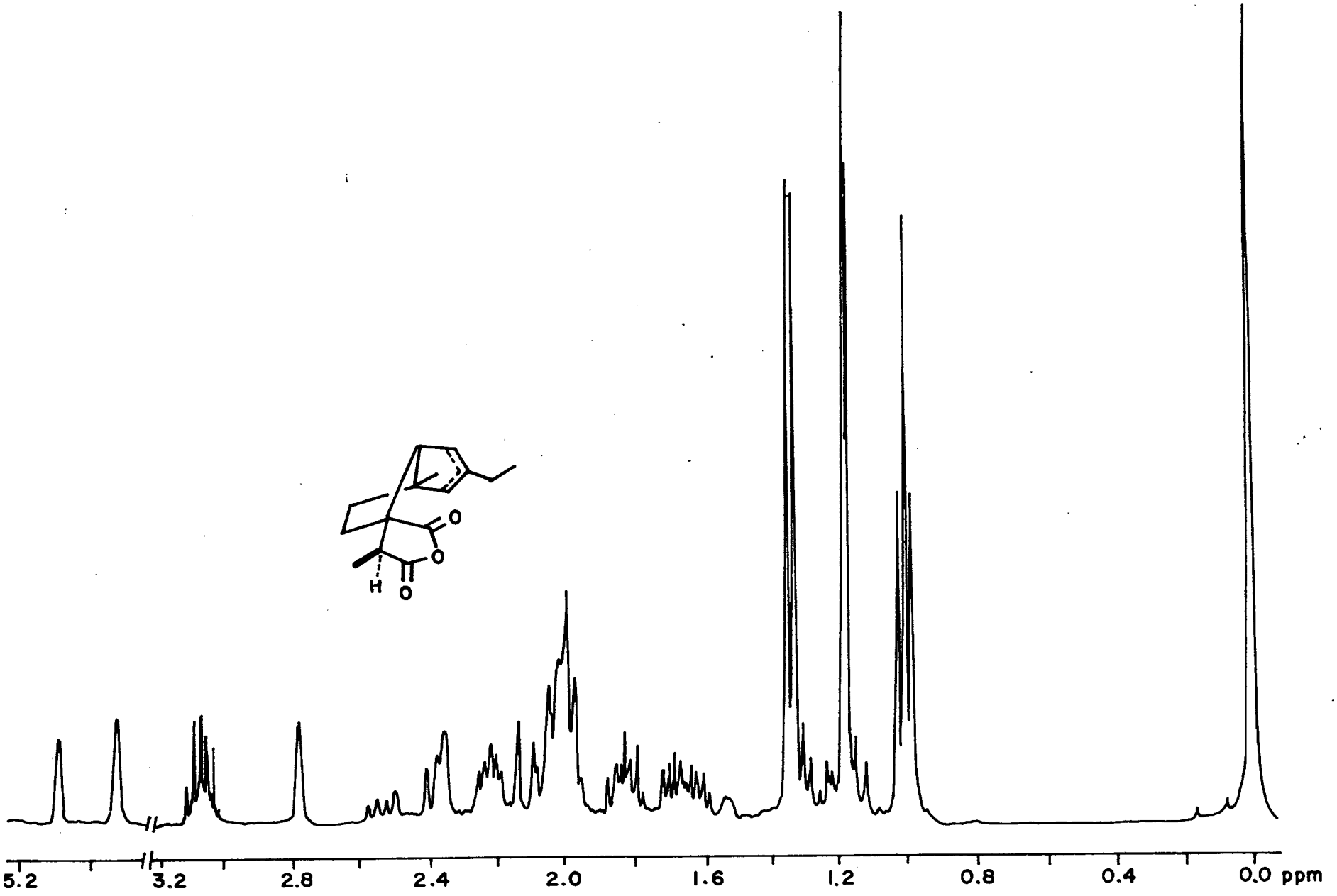


Fig. 1.14 ^{1}H NMR spectrum of mixture of 71 & 72

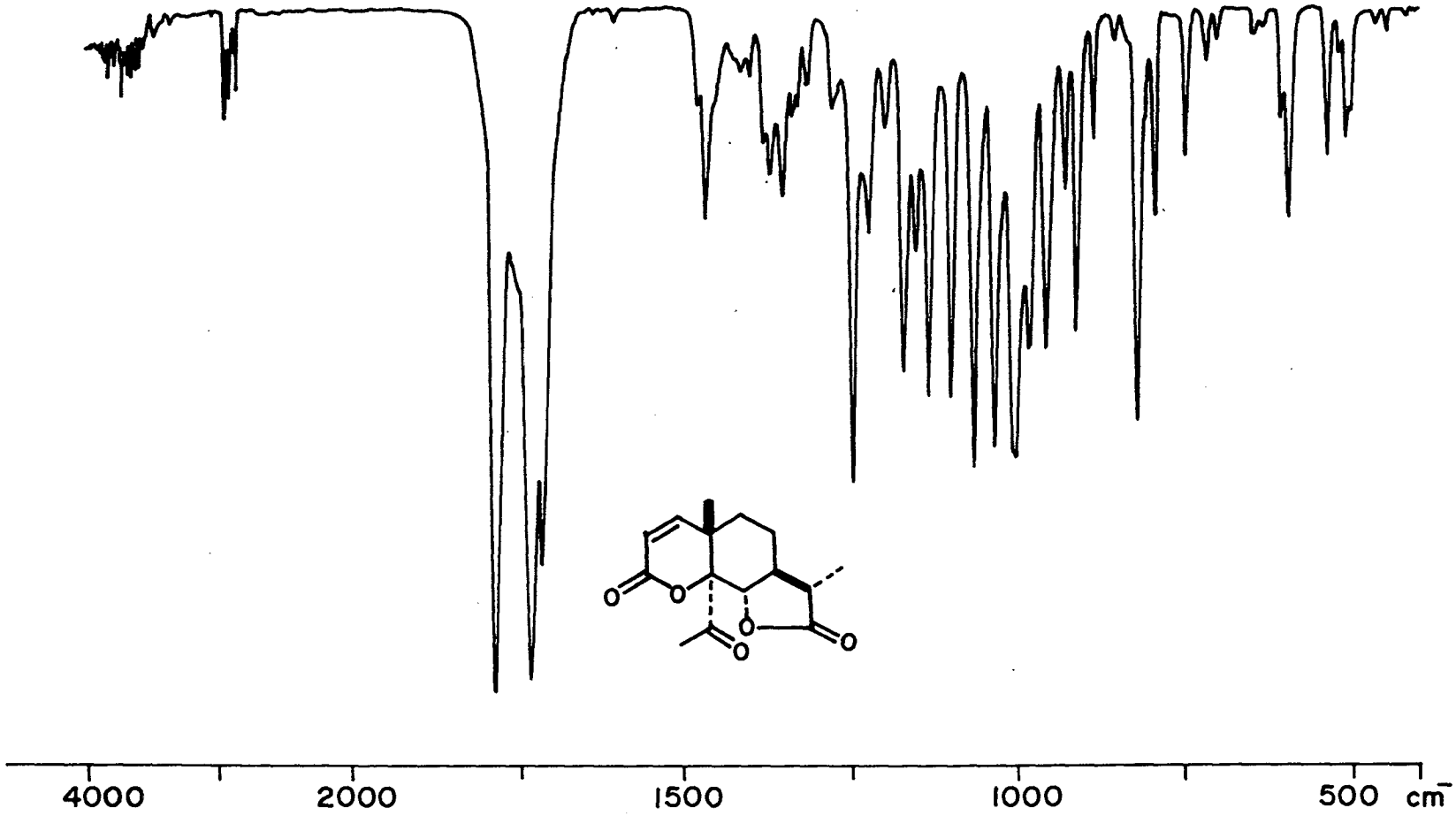


Fig. I.15 IR spectrum of 80

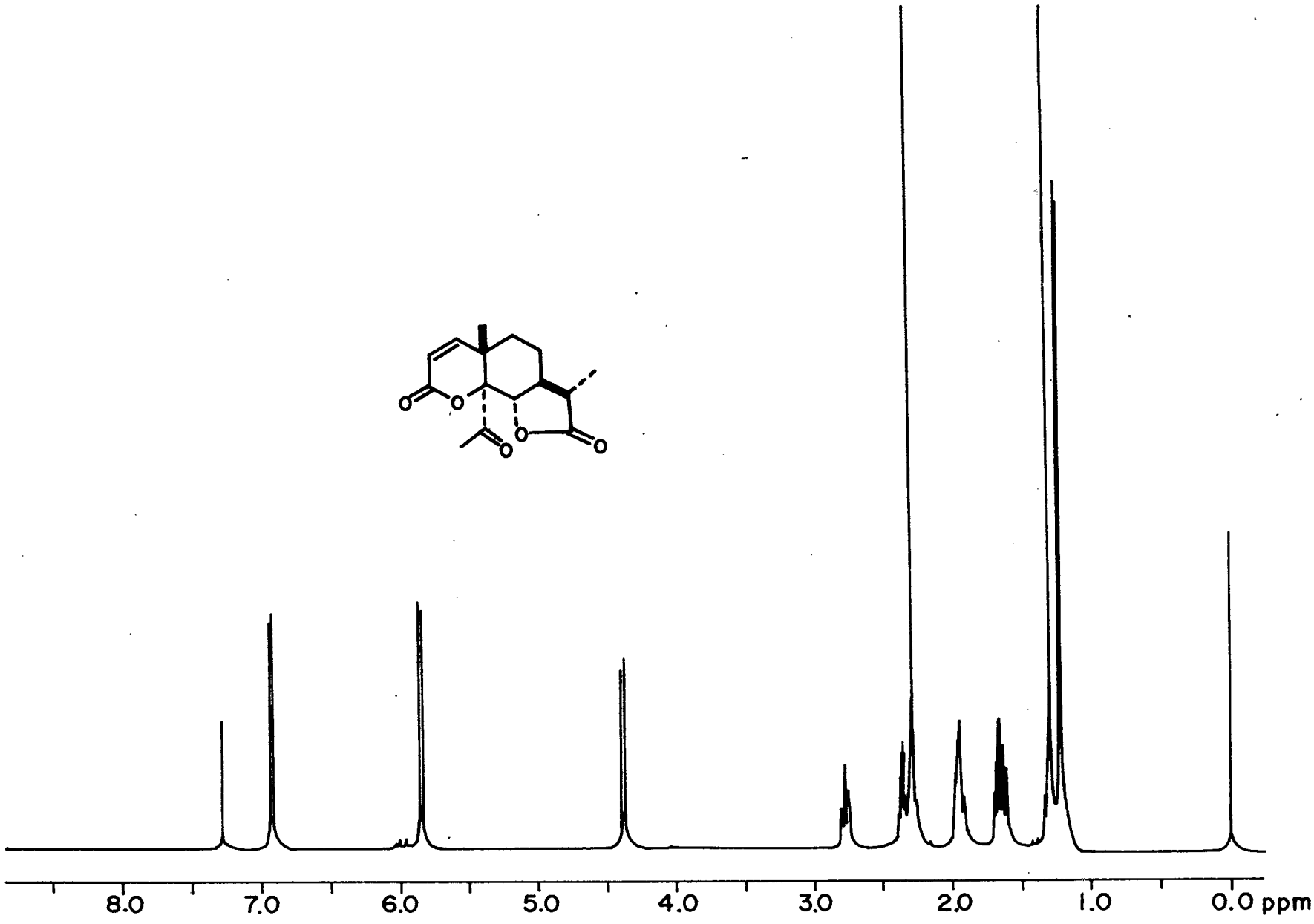


Fig. 1.16 ^{1}H NMR spectrum of 80

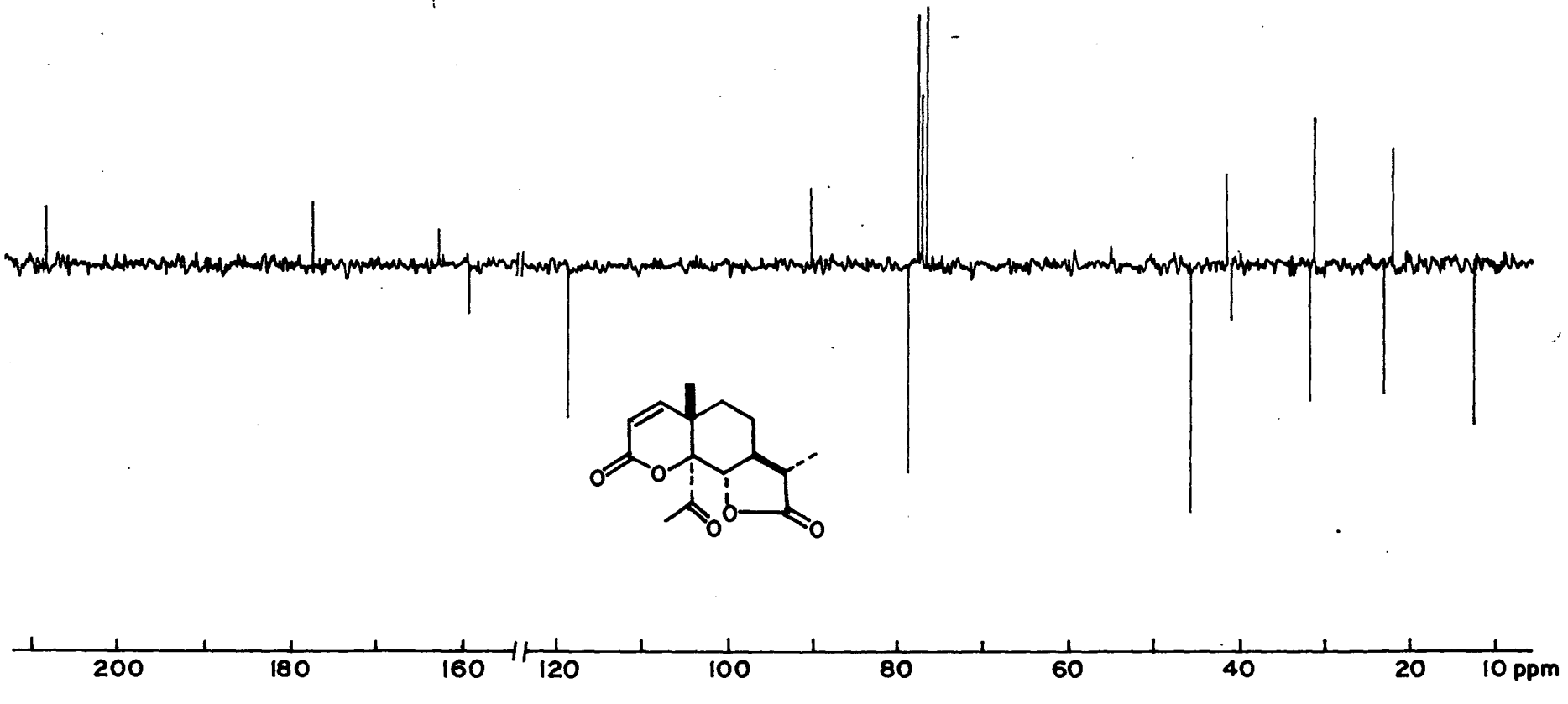


Fig 1.17 APT ^{13}C NMR spectrum of 80

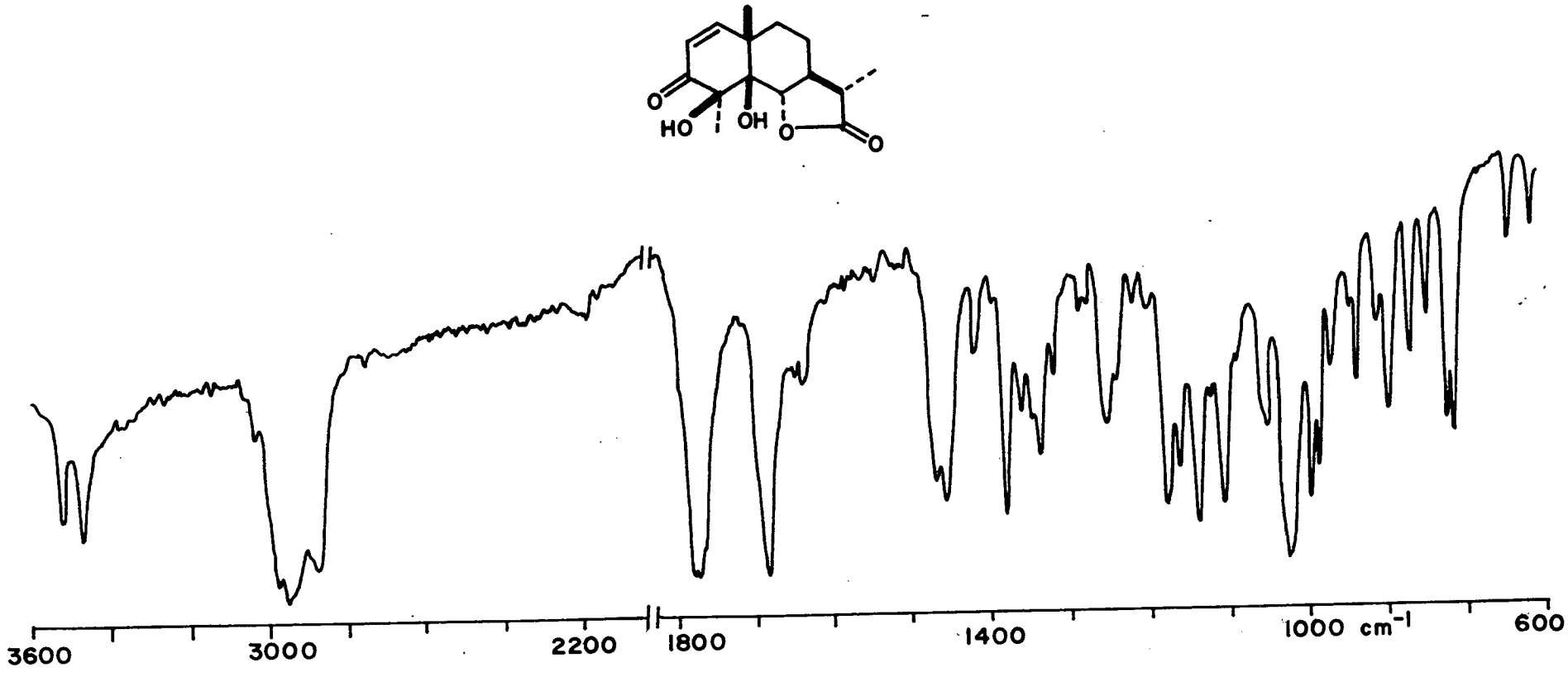


Fig. 1.18 IR spectrum of 78

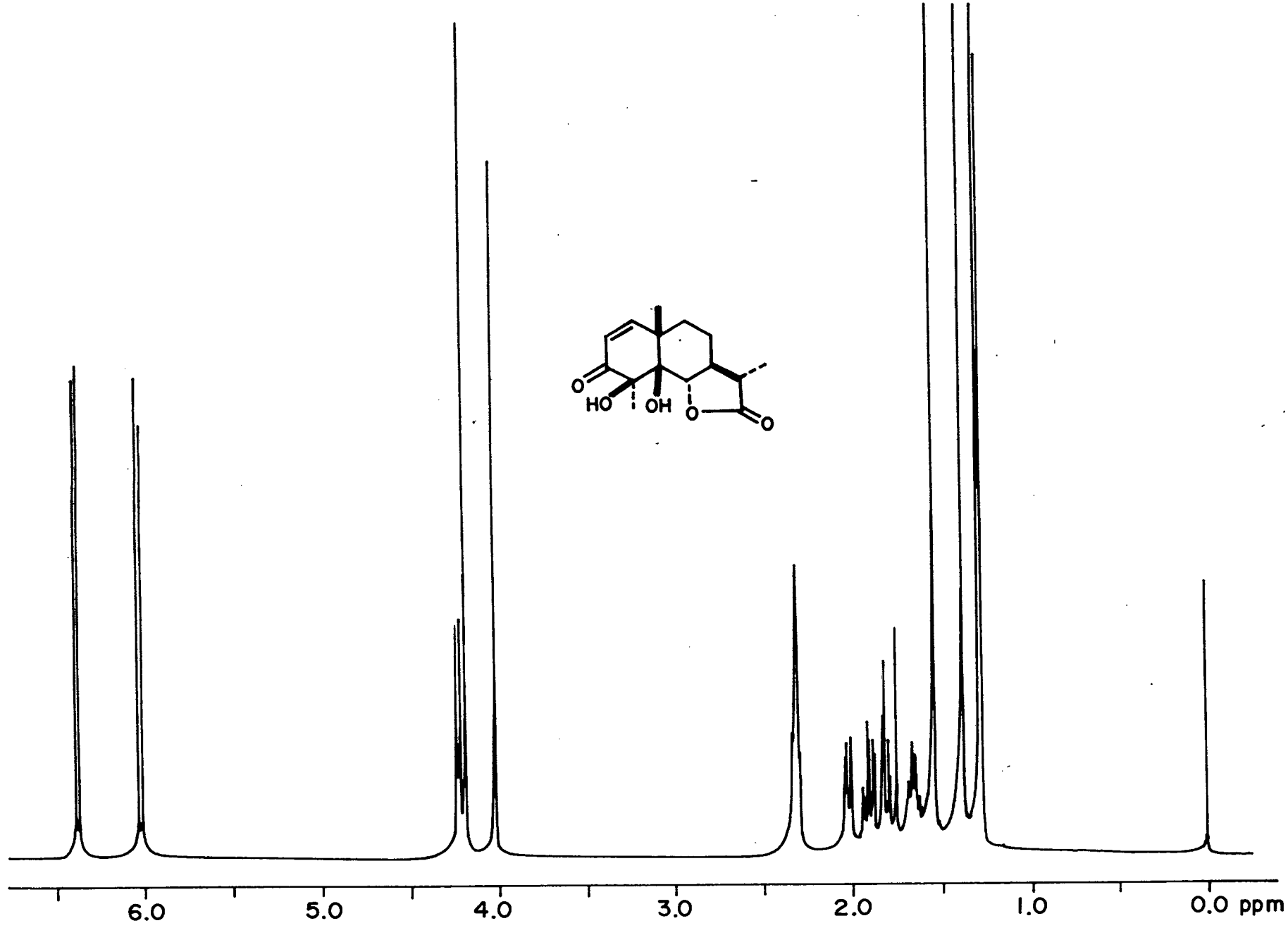


Fig. 1.19 ^{1}H NMR spectrum of 78

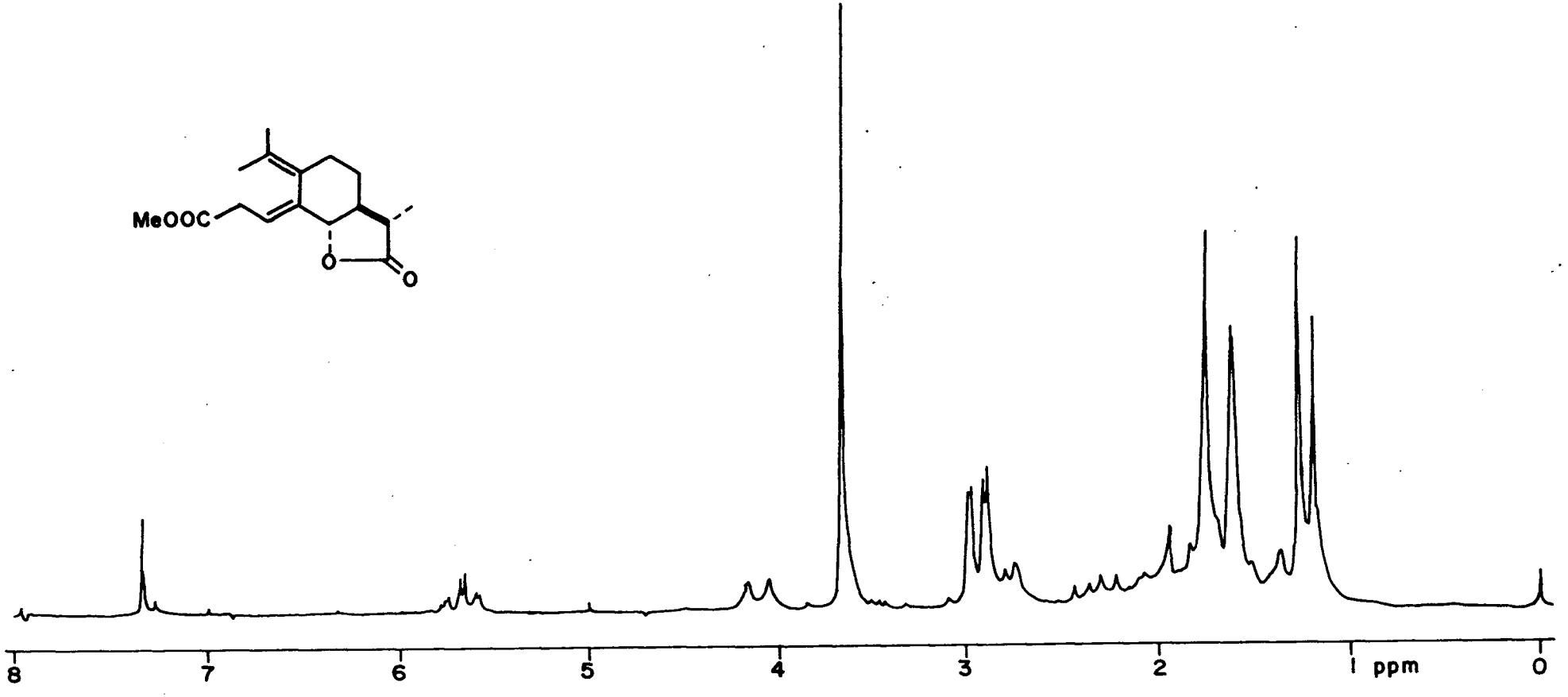


Fig. 1.20 ^{1}H NMR spectrum of 84

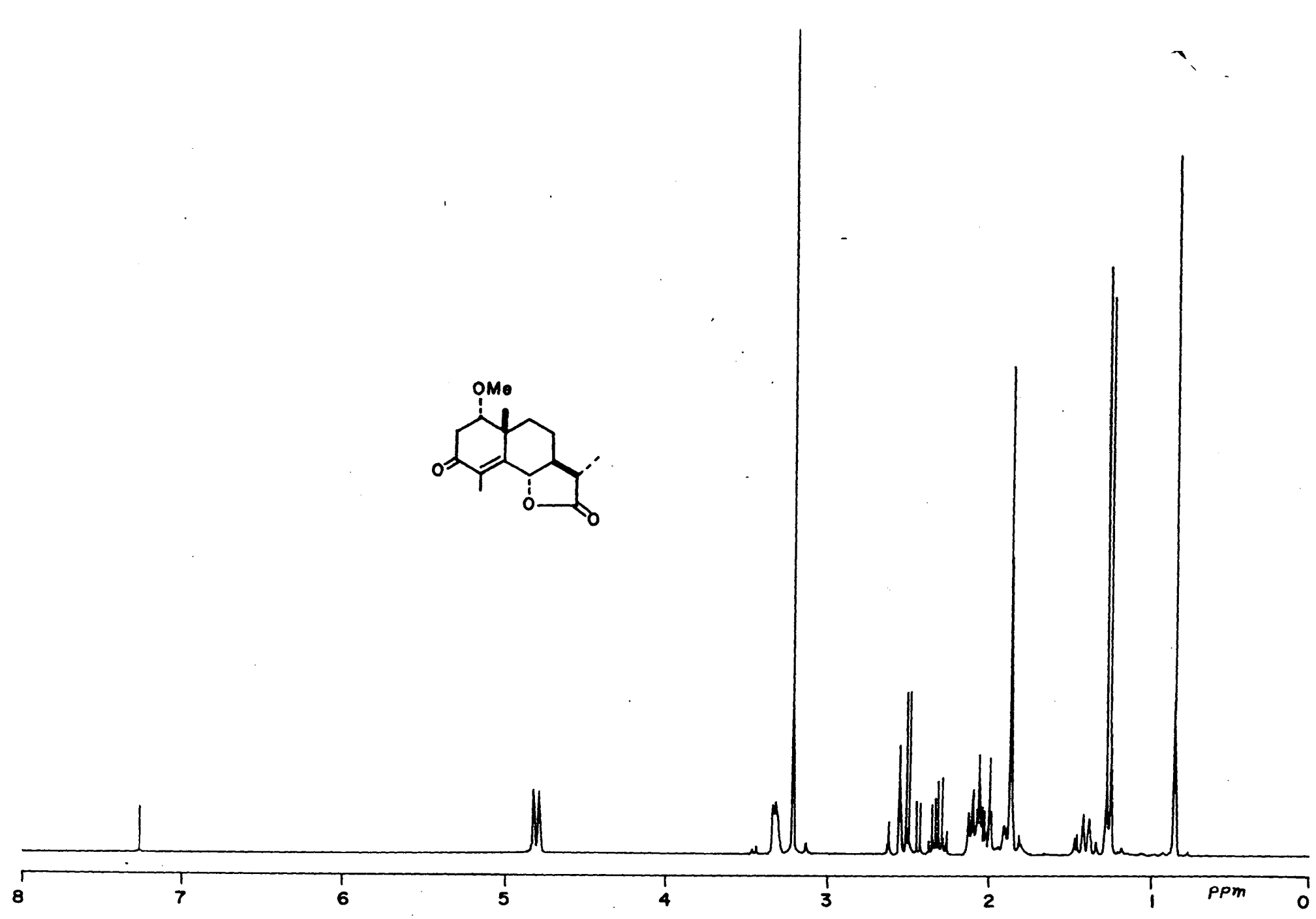


Fig. 1.21 ^{1}H NMR spectrum of 85

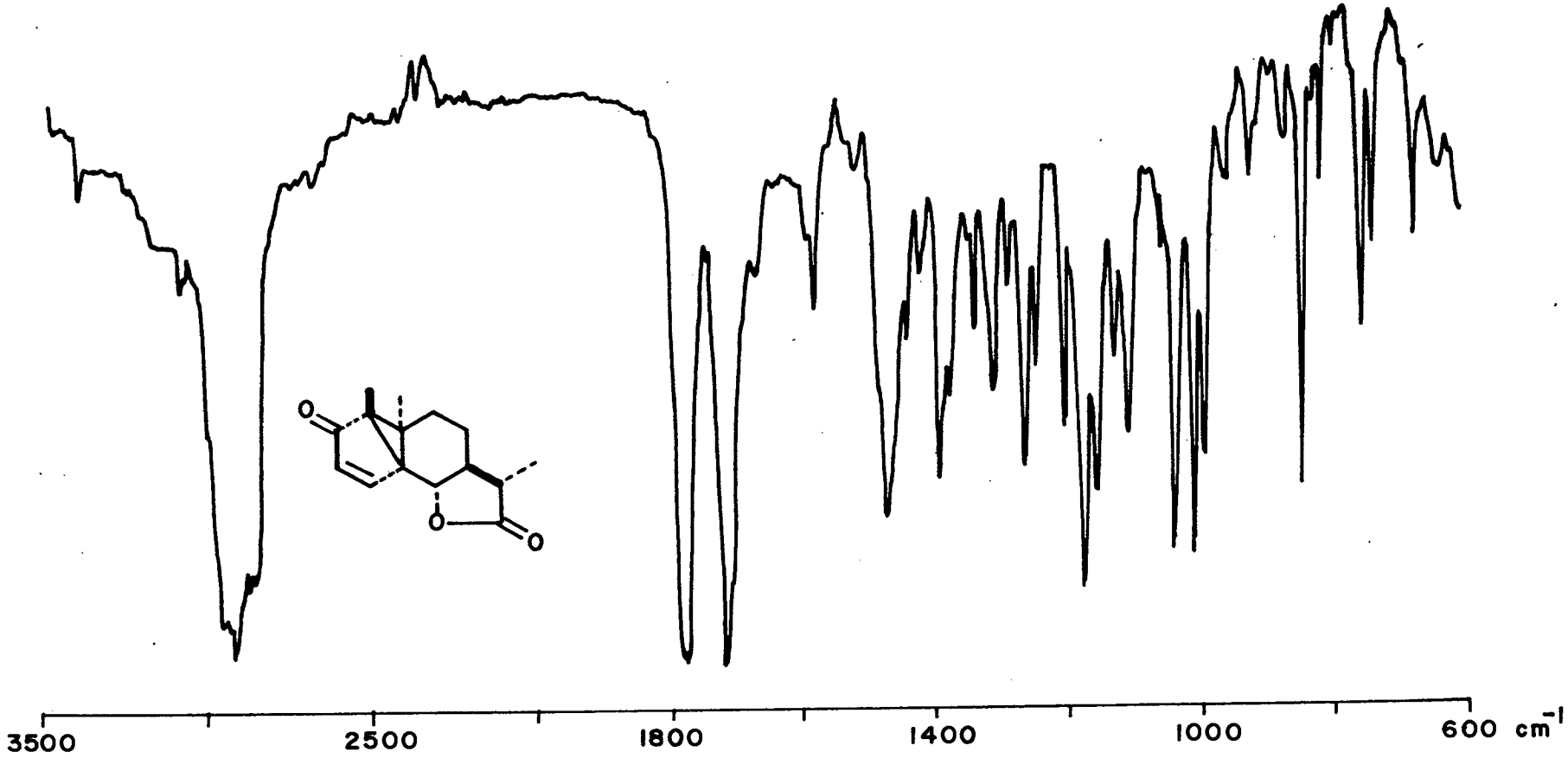


Fig. 1.22 IR spectrum of 81

R E F E R E N C E S

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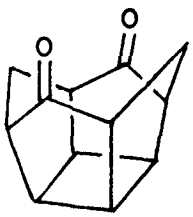
CHAPTER TWO

REACTIONS OF ARYL-KETONES WITH Zn-HCl-ETHER SYSTEM, A NEW SYNTHESIS OF BENZOFUROBENZOFURANS

Based on the reported formation[1] of pinacol 2 from the diketone 1 in good yield (74%), we studied the reaction of santonin 3 under identical experimental conditions (Zn-HCl-ether, 0^{o}) in the hope that the pinacol 4 derived from bimolecular condensation of 3 would undergo dienol-benzene rearrangement and afford a mixture of santonone 5 and isosantonone 6*. The outcome of this study has already been described in section 2, chapter 1.



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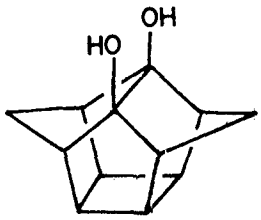

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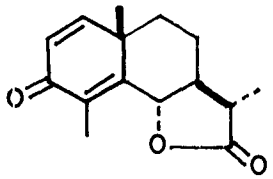

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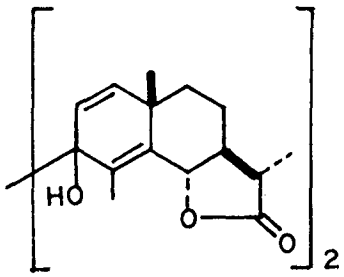

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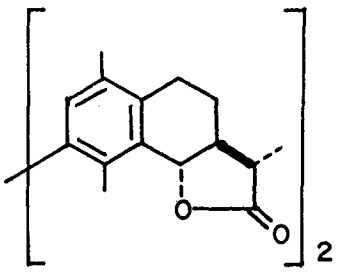

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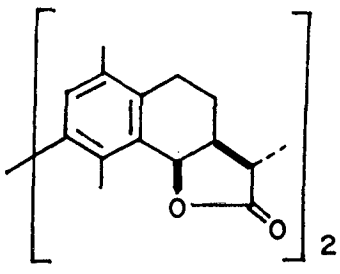

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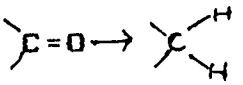
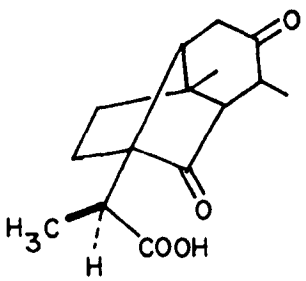
* The numbering of the compounds are different from those given for the same compounds in Chapter 1 of this thesis.

Yamamura and co-workers[2] were the first to study the reaction of ketones with the Zn-HCl-ether system at 0° and observed that  conversion takes place quite efficiently and named it a modified Clemmensen reduction. Our results on santonin 3 using the modified Clemmensen reduction matched well with their observations and those using santonic acid 7 as substrate were also as expected. In connection with other studies from our laboratories[3], we had failed to obtain 9 from 8 using normal Clemmensen reduction conditions and hence considered it worthwhile to subject 8 to the modified Clemmensen reduction conditions. The results obtained led us to study as substrates



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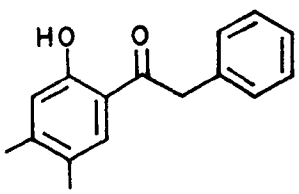

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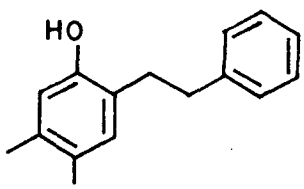
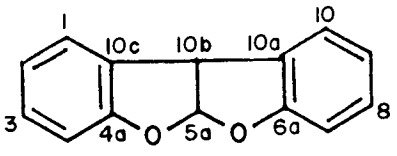


9

several o-hydroxy acetophenone derivatives and other compounds having structurally similar features. We found that the products obtained are benzofurobenzofuran derivatives and that this procedure can be considered as a new general method for the synthesis of this group of heterocyclic compounds. The details of this work are presented in this chapter.

Benzofuro[2,3-b]benzofuran 10 and benzofuro [3,2-b]benzofuran 11 are the two basic skeletons of this heterocyclic system.



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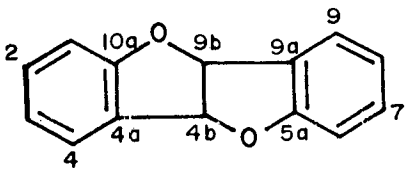


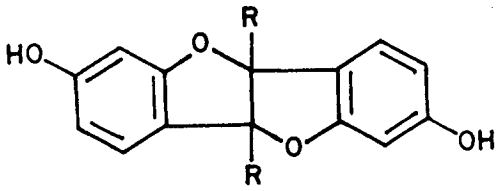
11

Before describing the details of our new synthesis, it is instructive to present the previously known synthetic routes to benzofurobenzofurans and various reports of their formation in certain organic reactions.

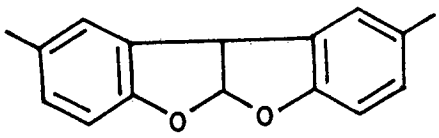
Compounds which are presently known as benzofurobenzofurans were earlier called as coumaranocoumarans and the first account of their preparation appeared in 1937 when Baker and McGowan[4] reported the condensation of phenols with 1,2-dicarbonyl compounds in the presence of sulfuric acid.

Niederel and Nagel[5] carried out further studies using resorcinol as the phenolic substrate and diacetyl and benzil as the 1,2-dicarbonyl compounds. They showed that the products of these reactions were benzofuro[3,2-b]benzofurans 12 and 13.

Sisido, Nozaki and Iwako[6] also investigated the reaction of diacetyl with phenols and showed that the



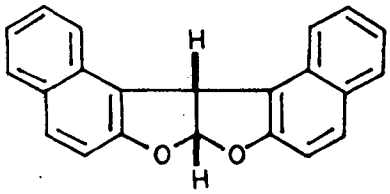
12 , R = Me
13 , R =Ph



14

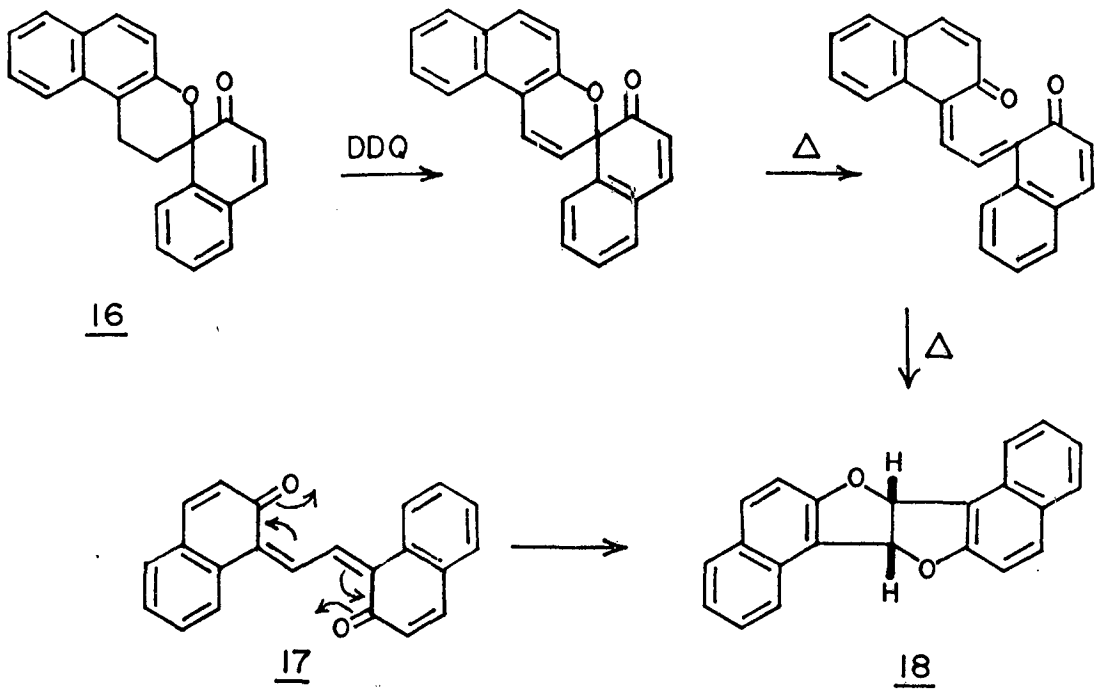
products derived from m and p-cresols are pinacols and benzofuro[3,2-b] benzofurans. The intermediate pinacols obtained can be separately transformed into the latter products under appropriate dehydrating conditions (AcOH, H_2SO_4, AcOH-H_2SO_4 mixture).

Thyagarajan, Balsubramanian and Bhima Rao[7] reinvestigated the condensation of p-cresol with glyoxal and found that the product is benzofuro[2,3-b] benzofurans 14 (acetal structure). Though their conclusions regarding the structures were correct, Coxworth[8] studied these reactions in further detail, particularly with the aid of high resolution ^1H NMR spectra. He showed that the hydrogens located at C_{10b} and C_{5a} can be easily distinguished, the former is observed as a doublet (J= 6-7 Hz) in the region 4.8-5.4 ppm while the latter is a doublet (J= 6-7 Hz) in the region 6.8 - 7.0 ppm, which incidentally falls in the aromatic region and was not identified by Thyagarajan *et al.*[7]. During this study, Coxworth[8] was able to show that the structure of the product from the reaction between β-naphthol and glyoxal is represented by 15.



15

During their study on the oxidation of 1,2-naphthaquinone-1-methide dimer 16 with DDQ, Kasturi and Jayaraman[9] reported the formation of 18 and explained its origin as shown in Scheme 2.1. In order to explain the formation of 18 in a better way, we prefer transoid structure 17 for the bismethide intermediate.

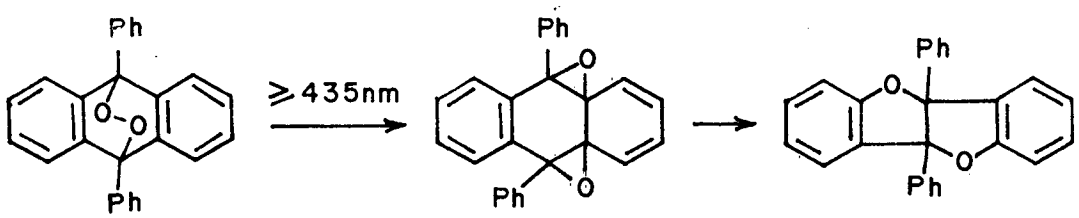


16 17 18

Scheme 2.1

Kasturi and Jayaraman[9] reported that the melting point 255-56^0 of their compound 18 is distinctly different from the one reported by Merlini and co-workers[10] for the same compound prepared by a different route (m.p. 232-33^0). The reported melting point matches well with that reported for 15 and it is likely that the structure of the compound reported by the Italian workers[10] is the acetal structure 15.

In another study, Rigaudy, Scribe and Breliere[11] observed that photolysis of the 9,10-endoperoxide of 9,10-diphenylanthracene 19 results in the formation of benzofuro[3,2-b]benzofuran 21 via the isomeric diepoxide 20 as shown in Scheme 2.2.

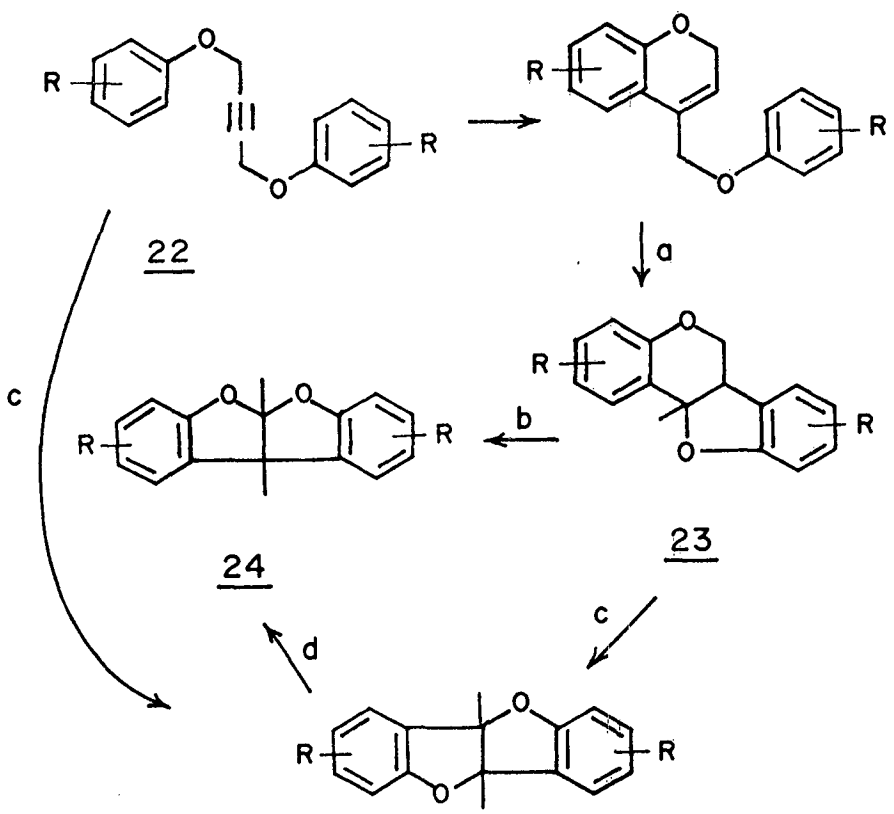


19 20 21

Scheme 2.2

The thermal rearrangement of 1,4-diaryloxy-2-butynes 22 has been studied independently by three groups[12-14]. It has been conclusively established that two sequential Claisen rearrangements are involved and the products obtained were proved to be 11a-methylpterocarpanes 23 which in turn could be transformed into substituted benzofuro[2,3-b]benzofuran 24 and benzofuro[3,2-b]benzofuran 25. Balasubramanian

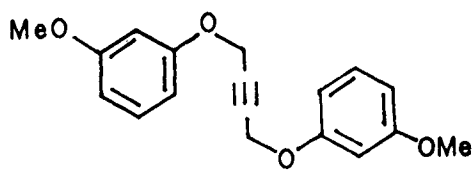
and co-workers[12] showed that if the thermal rearrangement of 22 is carried out in the presence of solvents such as N,N-diethylamine, quinoline, diphenyl ether or polyethylene glycol-200, then benzofurobenzofurans can be obtained directly. Bates and Jones[13] showed that if the Claisen rearrangements of 22 are catalysed by acids, the products obtained are benzofurobenzopyran and benzofuro[3,2-b]benzofurans.



(a) N,N-DEA, ; (b) N,N-DEA, PTS, ; (c) N,N-DEA,NH_4CL; (d) acid catalysis.

Scheme 2.3

Kiehlmann and co-workers[14] studied the Claisen rearrangement of 1,4-bis(m-methoxyphenoxy)-2-butyne 26 and observed the formation of benzofurobenzopyrans which on reaction with $AlCl_3$ gave benzofuro[3,2-b]benzofurans and benzofuro[2,3-b]benzofurans. The results of these investigations are summarised in Scheme 2.3.



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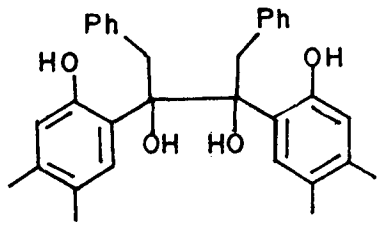
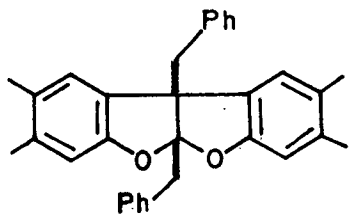


27

As mentioned earlier the 2-phenacetyl-4,5-dimethylphenol 8 was treated with Zn-HCl-ether at 0^o for 2 hrs. From the crude reaction product, we could isolate two pure compounds A & B having melting points 233^o and $195-96^o$ respectively. Purification of compound A was facilitated due to its insolubility in petroleum ether. Compound A analysed for $C_{32}H_{30}O_2$, (M^+ 446) and devoid of any absorption due to carbonyl or hydroxyl groups in its IR spectrum (Fig. 2.1). The two oxygen functions were considered to be present as ether linkages. The molecular formula clearly showed the involvement of two molecules of 8 in this reaction. Pinacolisation of ketones under Clemmensen conditions has precedent and it became clear that the compound A is derived by loss of two molecules of H_2O from the pinacol 27. Two possible

structures 28 & 29 were therefore considered for compound A.



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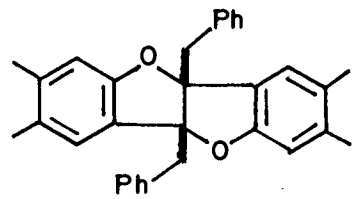
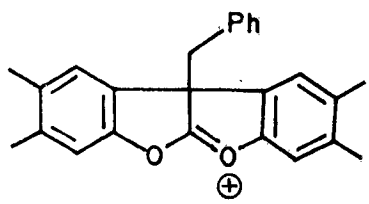


29

The ^{1}H NMR spectrum (Fig. 2.2) of compound A showed singlets due to aromatic methyls at 2.23 & 2.24, two benzylic methylenes as singlets at 3.32 & 3.56 indicating the attachment of benzylic groups to quaternary carbons, two singlets at 6.73 & 6.93 due to aromatic hydrogens of a 1,2,4,5-tetrasubstituted aromatic ring. In addition, the expected signals due to monosubstituted phenyl rings were observed in the region 7-7.5 ppm. The most important feature of the ^{1}H NMR spectrum was the two distinct singlets (2H each) due to the benzylic methylenes which immediately ruled out structure 29 for compound A as the two methylenes are identical in 29 and should have identical chemical shift. Moreover, compound 29 should show only 14 signals in the ^{13}C NMR spectrum.

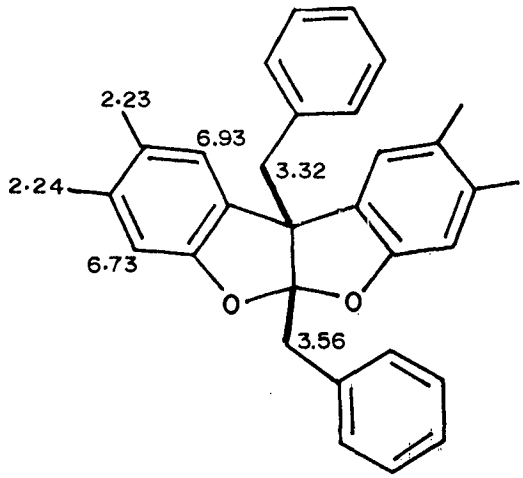
^{13}C NMR spectrum (Fig. 2.3) of compound A showed two quartets (19.8 & 20.5), two triplets (40.1 & 40.3), eight doublets (111.3, 124.8, 126.6, 126.7, 127.7,

127.8, 130.8 & 130.9) and eight singlets (60.5, 124.1, 129.0, 129.3, 134.9, 136.6, 137.5 & 155.8). The two singlets at 60.5 and 124.1 clearly support the ketal structure 28 for compound A. The mass spectrum of compound A showed, besides the molecular ion peak at m/z 446, the base peak at m/z 355 ($M^{+\cdot}-C_6H_5CH_2$) and certainly corresponds to fragment ion 30. For the sake of clarity the ^1H & ^{13}C chemical shift assignments are shown separetely on two structures in chart 2.1.

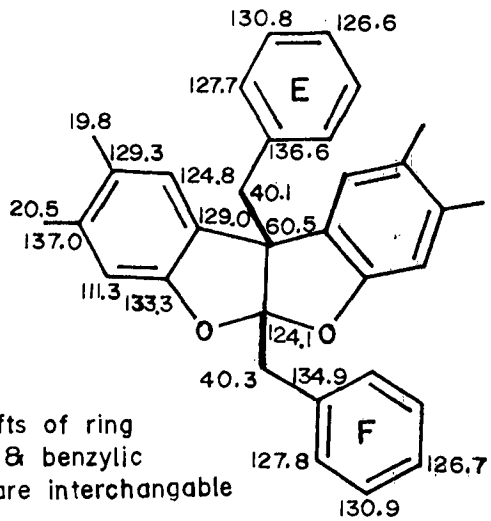


30

The more polar compound B, m.p. 195-96° was found to have molecular formula $C_{32}H_{30}O_2$ ($M^{+\cdot}$446) and and thus isomeric with compound A. The major difference being the presence of a hydroxyl functionality (band at 3320 cm^{-1} in its IR spectrum, Fig. 2.4). In contrast to the ^1H NMR of compound A, compound B in its ^1H NMR spectrum (Fig. 2.5) showed singlets due to methyl groups (1.76, 2.17, 2.18, 2.19) an AB quartet (3.21 & 3.59, J = 14.2 Hz) due to benzylic methylene group and six singlets (1H each) at 3.78 (bs), 4.60, 5.58 (exchangeable -OH), 6.63, 6.68 & 7.1 ppm. The ^1H NMR spectrum also showed a complex



^{1}H NMR assignments of 28



Chemical shifts of ring carbons E,F & benzylic methylenes are interchangable

^{13}C NMR assignments of 28

Chart 2.1

pattern in the region 6.9-7.4 ppm accounting for the remaining aromatic hydrogens.

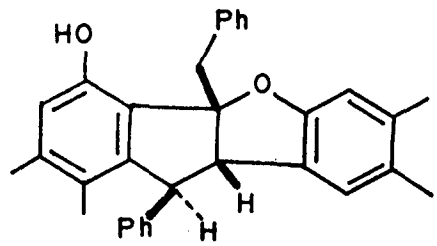
The ^{13}C NMR spectrum (Fig. 2.6) of compound B showed four quartets (15.10, 19.37, 19.99, 20.19), one triplet (43.11), eleven doublets (56.68, 59.13, 111.28, 117.43, 125.42, 126.25, 126.44, 127.50, 128.12, 128.56, 130.41)

twelve singlets (100.90, 125.58, 127.45, 127.89, 128.68, 136.38, 136.81, 139.65, 142.58, 143.28, 150.66 & 155.87)

The FAB mass spectrum (Fig 2.7) of compound B showed MH^+ at m/z 447 from which the peak at m/z 446 corresponds to the molecular weight and its molecular formula $C_{32}H_{30}O_2$. Other significant fragment ions were observed at m/z 355 (100%), 325, 281, 267, 221, 207, 191 & 147.

The spectral data taken together suggest that compound B contains only one Ph-CH_2- group, a free phenolic hydroxyl and 18 sites of unsaturation. The presence of four aromatic rings accounts for 16 sites of unsaturation and hence besides four aromatic rings, compound B must contain two additional rings. Considering the structure of compound A at least one of the rings will be furan ring and the remaining one is likely to be carbocyclic ring.

Mechanistic considerations (Scheme 2.4) which can account for the formation of compound A & B in the same reaction and the spectral data suggest structure 31 for compound B.



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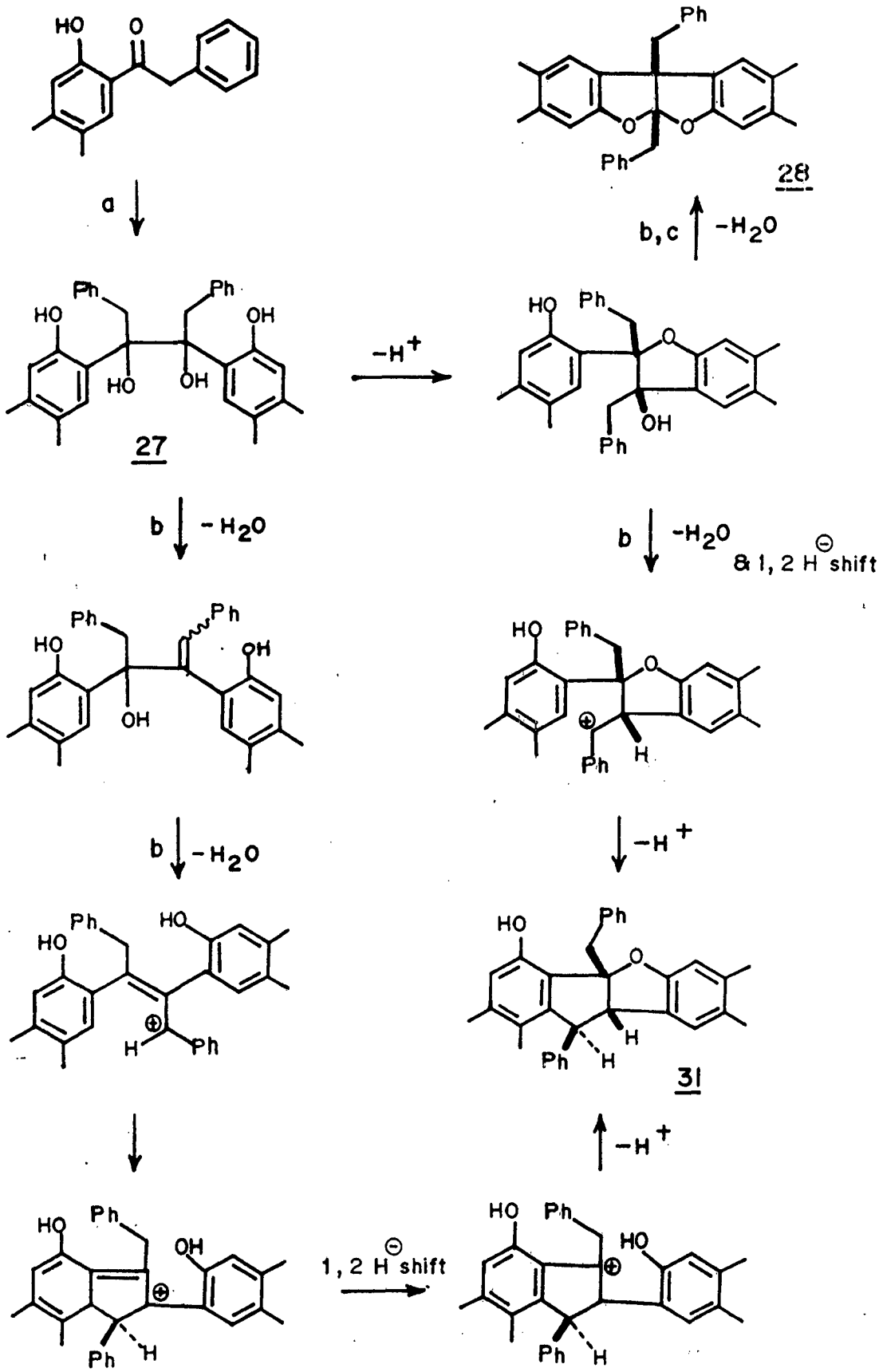
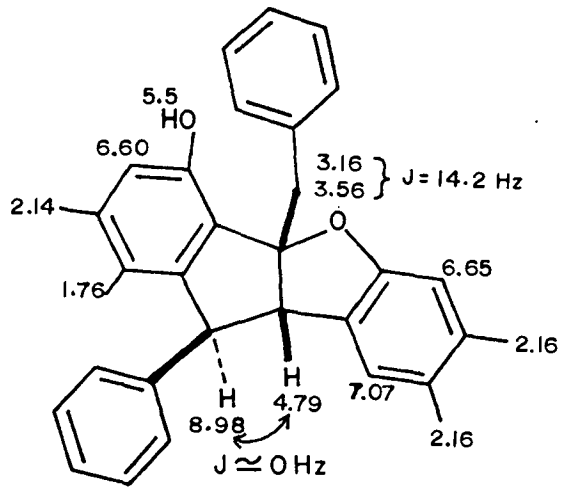


(a) Zn – HCl – ether, 0° (b) H^+ (c) aryl migration

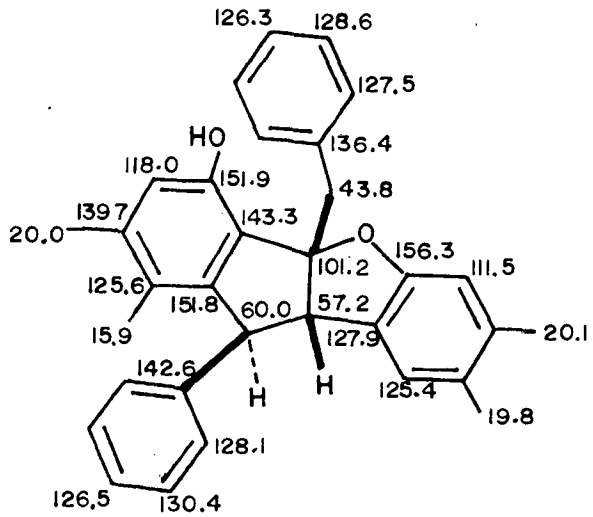
Scheme - 2.4

The most characteristic features of the ^{1}H and ^{13}C NMR spectra of 31 are i) shielding of one of the aromatic methyls (^{1}H NMR 1.76 ppm, ^{13}C NMR 15.9 ppm), ii) the chemical shift 4.66 of one of the hydrogens is unusually far downfield and, though the neighboring carbon carries a hydrogen, is observed as a singlet. Examination of molecular models showed that these unusual spectral features can be explained if the compound B possesses the stereochemistry as shown in Chart 2.2. The observed shielding of the methyl group of ring A is understandable as it comes in the shielding zone of the phenyl group (ring E). The chemical shift of bis-benzylic hydrogen (4.60 ppm) and its singlet nature can be explained due to its near coplanarity with three aromatic rings and ($\simeq$) 90^{o} dihedral angle with the hydrogen attached to the adjacent carbon. The ^{1}H and ^{13}C assignments are shown in chart 2.2.

The results described above not only unravel interesting chemistry but lead us to believe that the carbocation having structure 32 can be generated in a one pot operation as shown in Scheme 2.5 and it should have potential applicability as a general procedure for the synthesis of substituted benzofuro[2,3-b]benzofurans 10 and benzofuro[3,2-b]benzofurans 11.



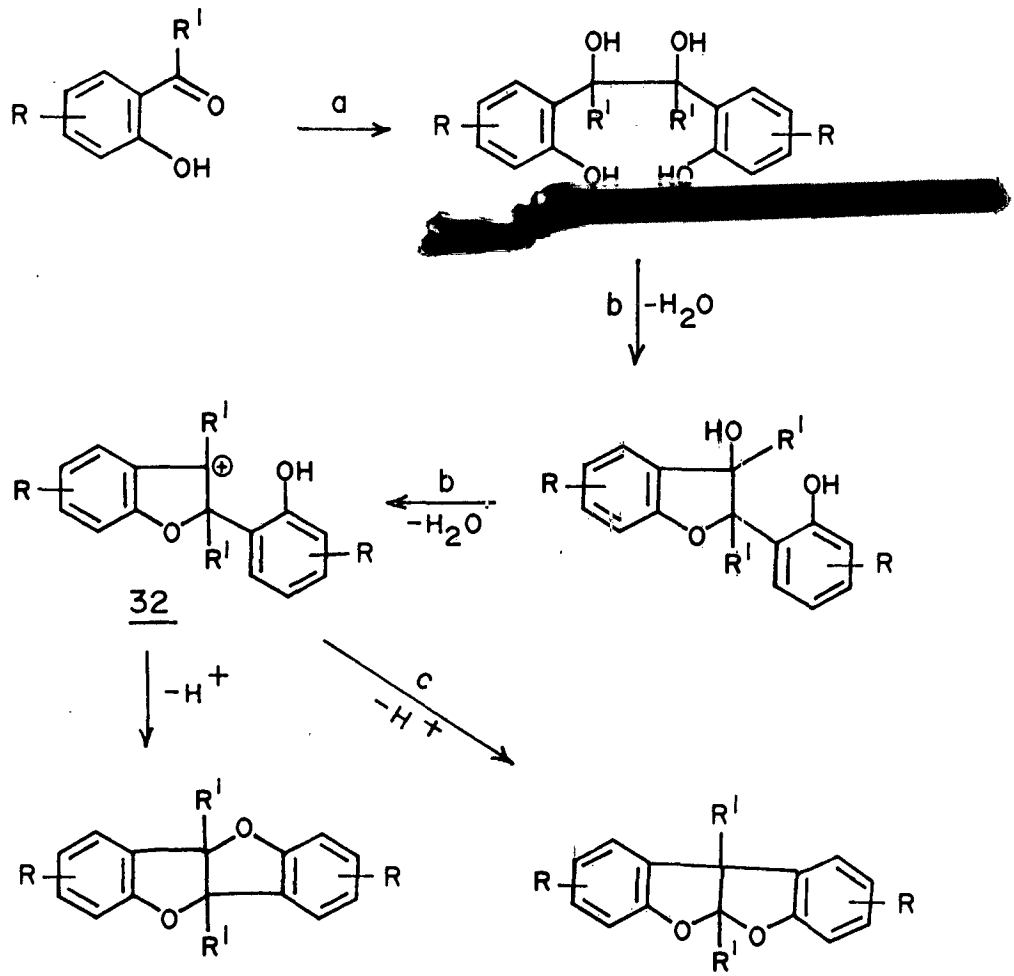
^{1}H NMR assignments of 31



^{13}C NMR assignments of 31

Chart 2.2

The carbocation intermediate 32 (Scheme 2.5) is the same as the one generated in the acid catalysed Claisen rearrangements of 1,4-bis aryloxy-2-butynes 22 presented earlier (Scheme 2.3). The starting materials, ortho-acylated phenols can be easily prepared by Fries rearrangement of the corresponding phenol esters. We

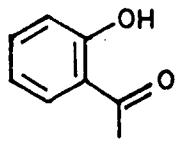


(a) Zn-HCl-ether, 0°; (b) H^+; (c) [1,2] aryl migration.

Scheme 2.5

have selected methyl or methoxy substituted phenols for the preparation of esters and subjected them to Fries rearrangement under conditions which favor the ortho-

acylated phenols. Compounds 33 to 36 were thus prepared during the present study and then subjected to reaction with Zn-HCl-ether at 0^{o} for 2 hrs. and the reaction product in each case was isolated/purified by column chromatography.



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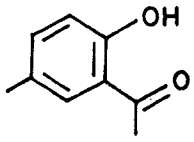

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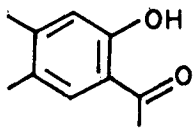

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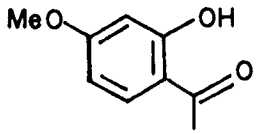
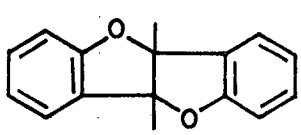


36

Spectral analysis on the individual compounds obtained during this present study confirmed our expectations and benzofurobenzofurans, previously known and unknown were fully characterised. For the sake of brevity the starting materials used and products characterised are listed below. Spectral data are presented in the experimental section. IR and NMR spectra of some of the representative compounds are reproduced and in other cases presented in the experimental section.

o-Hydroxyacetophenone 33 on treatment with Zn-HCl-ether was expected to yield two products,



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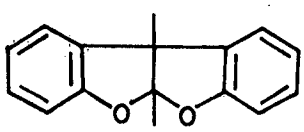
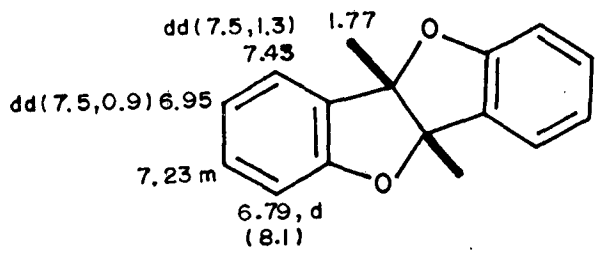
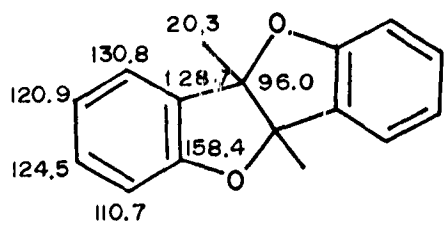


38

4b,9b-dimethyl benzofuro[3,2-b]benzofuran 37 and 5b, 10b-dimethyl benzofuro[2,3-b]benzofuran 38. However 33 gave a single isolable product C, m.p. 122-23° which was identified as 37 from its ^{1}H and ^{13}C NMR spectral data. Assignments are shown in Chart 2.3 .



^{1}H NMR assignments of 37

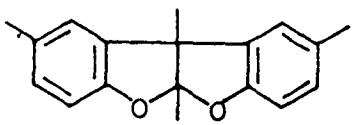


^{13}C NMR assignments of 37

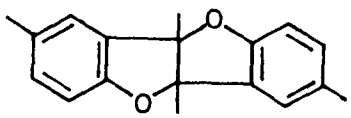
Chart 2.3

2-Hydroxy-5-methyl acetophenone 34 on reaction with Zn-HCl-ether at 0° for 2 hrs, gave five products, D (4%), m.p. 203-4°, E (8%), m.p. 154-55°, F (5.9%), m.p. 181-82°, G (4.7%), m.p. 124-25° and a colorless liquid H. Compound D, m.p. 203-4° turned out to be a single compound by spectral analysis and, by virtue of the two singlets at 56.6 and 124.7 in its ^{13}C NMR spectrum (Fig. 2.9) and also by inspection of the ^{1}H NMR (Fig. 2.8) data, it was identified as 2,5a,9,10b-tetramethyl benzofuro [2,3-b]benzofuran 39.

Compound E, m.p. 154-55°* was proved to be a 2:3 mixture of 2,5a,9,10b-tetramethyl benzofuro [2,3-b] benzofuran 39 and 2,4b,7,9b-tetramethyl benzofuro [3,2-b] benzofuran 40 on the basis of ^{1}H NMR and further supported by the ^{13}C NMR spectrum.



39



40

Compound F, m.p. 181-82°* was once again found to be a mixture of ketal 39 and ether 40 from the spectral analysis but in 1:1 proportion.

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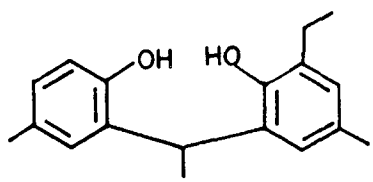
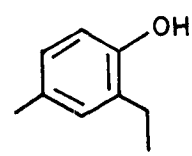
* Melting points were not very sharp.

The ^{1}H and ^{13}C NMR (Fig. 2.10 and 2.11) of compound G, $C_{18}H_{22}O_2$, m.p. 124-25° showed that it does not possess a benzofurobenzofuran skeleton but contains $2CH_3-CH_2-Ar$ (1.19, 3H, t, J = 7.5 Hz), $Ar-\overset{CH_3}{\underset{|}{C}}H-Ar$ (1.63, 3H, d, J = 7.1 Hz) and two closely spaced aromatic methyl groups (2.26 and 2.27, singlets, 3H each). The corresponding benzylic methylene and methines were observed as multiplet centered at 2.56 and a one proton quartet (J = 7.1 Hz) at 4.56 ppm. Two broad singlets at 5.77 and 5.87 were certainly due to phenolic hydroxyl hydrogens (D_2O exchangeable). The five aromatic hydrogens could be grouped under two sets, three belonging to a 1,2,4 substitution pattern and the remaining to a 1,2,3,5-tetrasubstituted benzene ring. The spectral data could be accommodated by structure 41 for compound G. Incidentally, the liquid compound H obtained in this reaction could not be completely characterised but appears to be 2-ethyl,4-methyl phenol 42, the normal Clemmensen reduction product of 34.



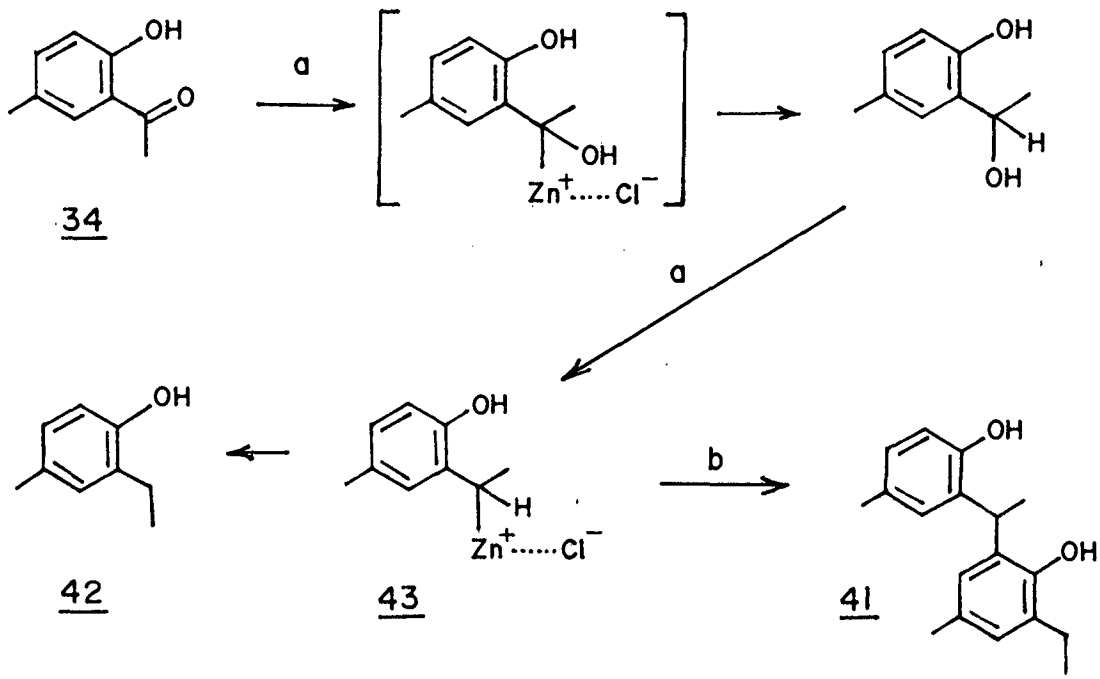
41



42

It therefore appears that an intermediate 43 in the

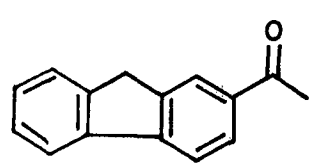
normal Clemmensen reduction of 34 is reacting with 42 by a Friedal-Crafts reaction as shown in Scheme 2.6. The intermediates shown in Scheme 2.6 are based on the elegant work of Minabe and co-workers[15] concerning the



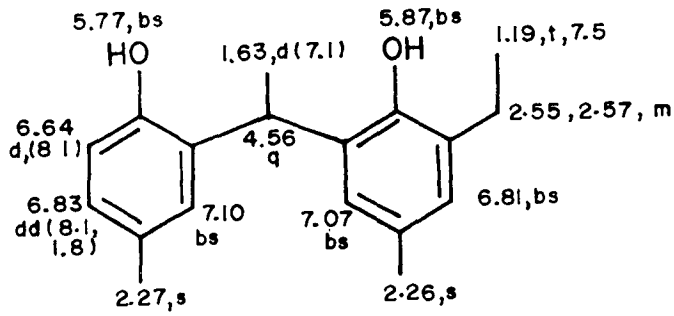
(a) Zn-HCl-ether,0^O; (b) 2-ethyl-4-methyl phenol 42.

Scheme 2.6

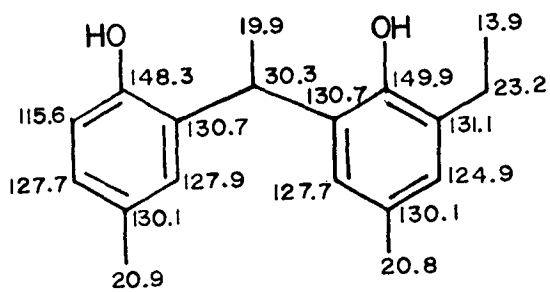
Clemmensen reduction of 2-acetylfluorene 44 where the structures of the intermediates proposed were determined by labelling studies. The NMR assignments are shown separately in Chart 2.4.



44



^{1}H NMR assignments of 41



^{13}C NMR assignments of 41

Chart 2.4

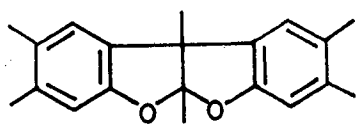
It may be noted that all attempts to obtain a pure sample of 2,4b,7,9b- tetramethyl benzofuro[3,2-b] benzofuran 40, either by chromatography or repeated crystallization of some of the fractions containing 40, failed.

When 2-acetyl-4,5-dimethyl phenol 35 was subjected to modified Clemmensen reduction conditions only one product, compound I, m.p. 233-34^{0} could be obtained in pure form, particularly due to its insolubility in petroleum ether and repeated crystallization from ethanol. The petroleum ether soluble products have not yet been isolated in pure form and have thus not been characterised.

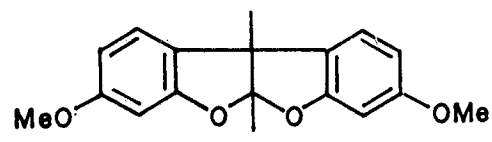
The compound I, m.p. 233-34^{0}, was identified as the ketal, 2,3,5a,8,9,10b-hexamethyl benzofuro[2,3-b] benzofuran 45 by analysis of the ^{1}H and ^{13}C NMR spectra and assignments are shown in Chart 2.5.

2-Hydroxy-4-methoxy acetophenone 36 when subjected to Zn-HCl-ether at 0^{0} for 2 hrs. and following the normal isolation procedure gave only one substance, compound J, m.p. 147^{0} in pure form. The other products are yet to be characterised.

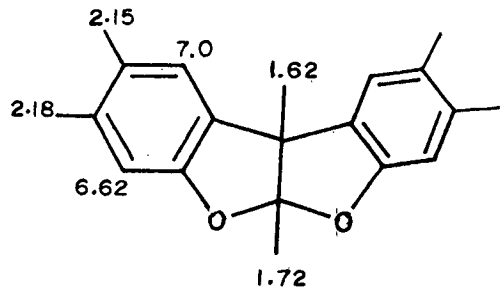
Compound J, m.p. 147^{0} turned out to be 3,8-dimethoxy-5a,10b-dimethyl benzofuro[2,3-b]benzofuran 46.



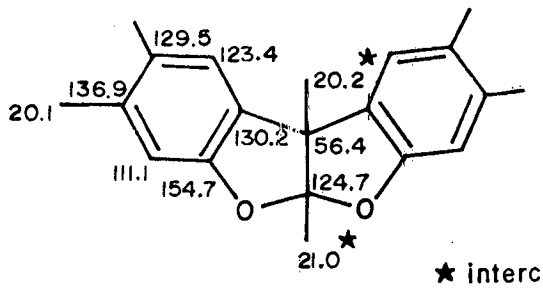
45



46



^{1}H NMR assignments of 45

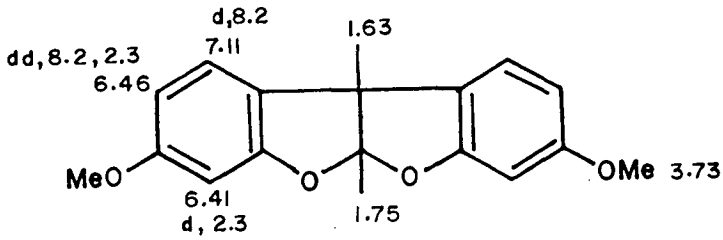


^{13}C NMR assignments of 45

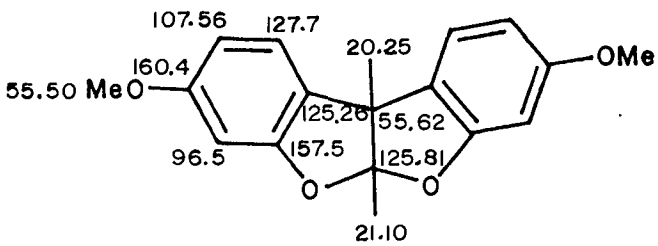
Chart 2.5

The ^{1}H and ^{13}C NMR assignments are shown in Chart 2.6.

The results presented above show that ketals, i.e. benzofuro[2,3-b]benzofurans, appear to be the major products in these reactions, formed by pinacol-pinacolone rearrangement of the initially formed pinacol under the strongly acidic conditions. The pinacolone can then



^{1}H NMR assignments of 46



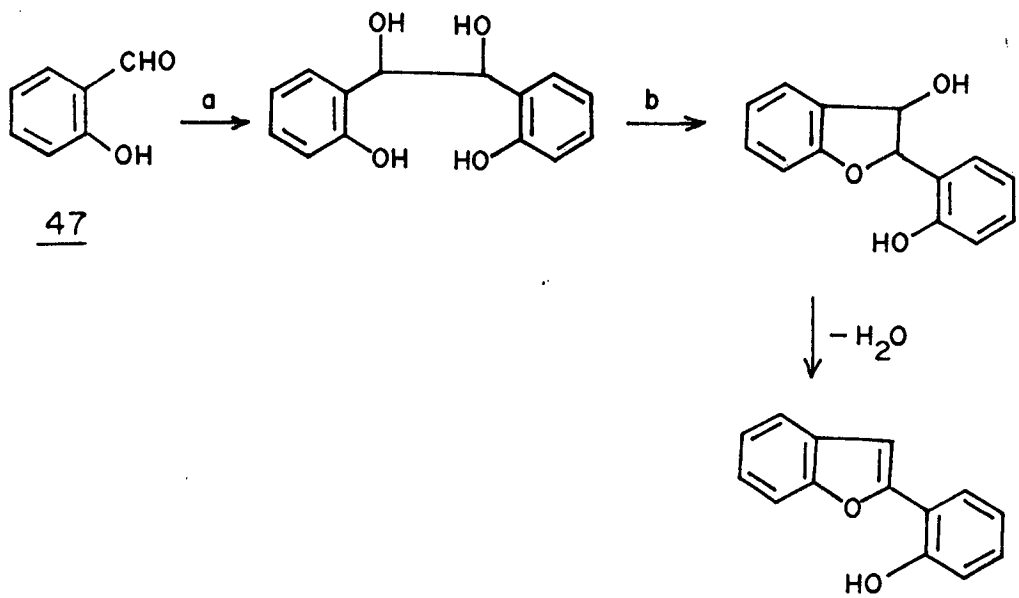
^{13}C NMR assignments of 46

Chart 2.6

form the observed benzofuro[2,3-b]benzofurans because of the ideally substituted phenolic hydroxyls for internal ketal formation.

We envisaged a simple preparation of the basic compounds of this series viz. benzofuro[2,3-b]benzofuran 10 and benzofuro[3,2-b]benzofuran 11 by replacing the

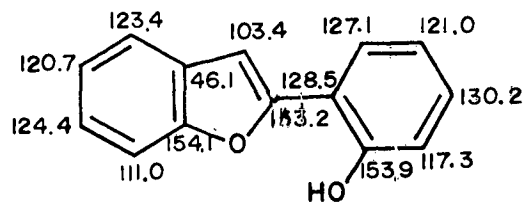
acetophenone derivatives by salicylaldehyde 47. However, the only product which we could obtain in this reaction, compound K, m.p. 98-99^{0} showed the presence of a hydroxyl hydrogen (3300cm^{-1}) in its IR spectrum (Fig.2.12). The ^{13}C NMR spectra (Chart 2.7 for assignments) showed it to be 2-(2-hydroxyphenyl) benzofuran 48 and its formation can be rationalised as shown in Scheme 2.7.



(a) Zn-HCl-ether,0^{0}; (b) H^{+}.

Scheme 2.7

The results obtained during this study of the reaction of o-hydroxyacetophenone and its derivatives with Zn-HCl-ether system clearly demonstrate that intermolecular pinacolisation is a major pathway and the final products are derived from further acid catalysed

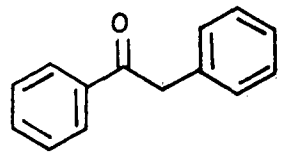


^{13}C NMR assignments of 48

Chart 2.7

reactions of the initially formed pinacols. The observed formation of benzofurobenzofurans is due to the appropriately placed phenolic hydroxy groups with respect to the vicinal glycol functionality. Simple acetophenone or its derivatives without an ortho hydroxy group should then yield pinacols and/or further acid catalysed transformation products. Pinacols were not isolated in any of the foregoing reactions.

Stocker and Kern[16] studied the ultraviolet promoted bimolecular reduction of benzyl phenyl ketone (deoxybenzoin) 49 and fully characterised the diastereomeric pinacols, meso 1,2,3,4-tetraphenyl-2,3-butane diol 50 and dl-1,2,3,4-tetraphenyl-2,3-butane diol 51. They further showed that the ^{1}H NMR of 50 and 51 were sufficiently different and can be used as a convenient means of distinguishing between them. It was therefore of interest to study the reaction of benzyl phenyl ketone 49 with Zn-HCl-ether at 0^{o} and



49

characterise the products. Thus benzyl phenyl ketone 49 was treated with Zn-HCl-ether at 0^{0} for 2 hrs. Usual workup and chromatography afforded three products, compound L, m.p. 213^{0}, compound M, m.p. $159-60^{0}$ and compound N, m.p. 52^{0}.

The ^{1}H NMR data of compound L, m.p. 213^{0} was identical with that reported for meso-1,2,3,4-tetraphenyl-2,3-butane diol 50 (lit[16]. m.p. 213^{0}). Its ^{13}C NMR spectrum* showed one triplet (42.2), six doublets (126.4, 126.9, 127.2, 128.0, 128.4 & 130.8) and three singlets (81.3, 136.2 & 142.5).

Compound M was found to be a 3:1 mixture of dl-1,2,3,4-tetraphenylbutane diol 51 and corresponding meso isomer 50. Further purification gave almost pure isomer, m.p. 170^{0}. However we did not obtain any ^{1}H or ^{13}C-NMR data as we considered it unnecessary.

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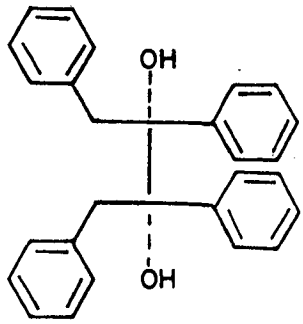
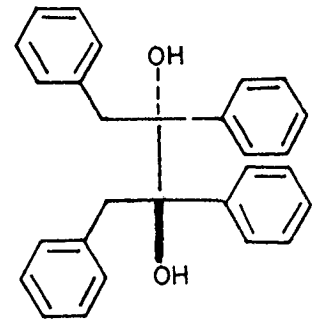
* To the best of our knowledge ^{13}C NMR data has not been recorded before.

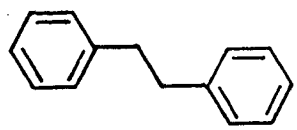


50

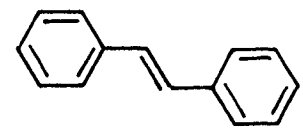


51

Compound N, m.p. 52^{0} was also found to be a 3:1 mixture 1,2-diphenyl ethane 52, the normal Clemmensen reduction product and trans-stilbene 53 whose presence could be inferred by the characteristic signal for the vinylic hydrogens at 7.11 ppm.



52



53

In the above reaction we were unable to characterise any product arising from the pinacol-pinacolone rearrangement.

We have not made any effort to optimise the experimental conditions but it would be instructive to

study this reaction in more detail and with a variety of substrates*.

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* Instrumental facilities are not available at our laboratories and the spectral data were obtained on several samples through the courtesy of Prof. R. B. Bates and Mrs Sriyani Caldera. The author thanks them for the spectral data and valuable help in interpretation. The work will be published jointly. Prof. G. Rucker and Dr. R. Mayer also supplied spectral data on some samples.

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

Preparation of 2-phenacetyl-4,5-dimethyl phenol 8 .

Compound 8 was prepared following a literature procedure[17].

Reaction of 8 with Zn-HCl-ether at 0°.

2-Phenacetyl-4,5-dimethyl phenol 8 (1.0g, 0.00416 moles) was reacted with activated Zn (1.359g, 0.0208 moles) using dry ether saturated with HCl gas at 0° as previously described [Chapter 1, section 3]. Usual workup gave orange solid (0.824g) which was successively washed with petroleum ether and recrystallized from aqueous ethanol to give 28; 0.228 g; 12.5 %; m.p. 233-34°.

IR, KBr, (Fig. 2.1), bands at :

3040, 3020, 2920, 1620, 1600, 1480, 1450, 1270, 1180, 860, 8720 and 700 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 2.2), 200 MHz

and

^{13}C NMR, $CDCl_3$, (Fig. 2.3), 250 MHz.

For assignments see Chart 2.1

MS, major peaks at :

m/z 446(100%), 355 and 264.

The petroleum ether soluble yellow liquid (0.329g) was chromatographed over silica gel. Fractions eluted with petroleum ether-ethyl acetate (95:5) followed by concentaration gave a white solid which was recrystallized from ethanol to give 31; 0.133g;

7.3 %; m.p. 195-96°.

IR, KBr, (Fig. 2.4), bands at :

3320, 2950, 1600, 1300, 1270, 1110, 1000, 850 and 700cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 2.5), 200 MHz

and

^{13}C NMR, $CDCl_3$, (Fig. 2.6), 250 MHz.

For assignments see Chart 2.2.

MS, (Fig.2.7), major peaks at :

m/z, 446, 355 (100%), 325, 281, 267, 221, 207, 191 and 147.

Preparation of 33, 34, 35 and 36

General procedure :

The compounds 33 to 36 were prepared by Fries rearrangement of the corresponding phenol esters by using high temperatures followed by chromatographic separation.

Reaction of 33 with Zn-HCl-ether at 0°.

Reaction of o-hydroxy acetophenone 33 (1.0g, 0.00735 moles) with activated Zn (2.402g, 0.0367 moles) afforded a dark brown residue (0.937g) which was chromatographed over silica gel. Elution of the column with petroleum ether-ether (99:1) followed by concentration gave a yellowish solid which on repeated crystallization from aqueous ethanol afforded 37; 0.434g; 24.8%; m.p. 122-23° (lit.[18] 126-29°).

IR, Nujol, bands at :

3049, 2975, 1594, 1479, 1461, 1267, 1239, 1086,

998, 752 and 745 cm^{-1}.

^{1}H NMR, $CDCl_3$, 200 MHz

and

^{13}C NMR, $CDCl_3$, 250 MHz.

For assignments see Chart 2.3.

Reaction of 34 (1.0g, 0.0068 moles) with activated Zn (2.223g, 0.034 moles) afforded a yellowish solid (0.836g) which was washed with petroleum ether to give a white solid which upon recrystallization from aqueous ethanol yielded 39 ; 0.076g; 4%; m.p. 203-4°.

IR, Nujol, bands at :

3300, 2980, 2950, 2930, 1600, 1580, 1260, 1080, 900 and 800cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 2.8), 200 MHz, signals at:

1.67 (3H, s, C_{10b}-CH_3),

1.76 (3H, s, C_{5a}-CH_3),

2.31 (3H, s, C_2-CH_3), 6.73 (1H, d, J=8.5 Hz),

6.93 (1H, m, C_3-H),

7.09 (1H, s, C_1-H).

^{13}C NMR, $CDCl_3$, (Fig. 2.9), 250 MHz,

five singlet at 56.6, 124.7, 130.9, 132.6 and 154.3.

three doublets at 109.5, 123.1 and 128.8.

three quartets at 20.3, 20.96 and 20.99.

The petroleum ether soluble portion (0.728g) was chromatographed over silica gel. Elution of the column with petroleum ether-ether (98:2) followed by concentration gave a colourless liquid (0.036g) which is

yet to be characterised but appears to be 2-ethyl-4-methyl phenol 42.

Elution with petroleum ether-ether (96:4) followed by concentration gave a colourless solid (0.102g) which was found to be a 1:1 mixture of 39 and 40.

Elution with petroleum ether-ether (95:5) followed by concentration yielded a solid (0.143g) which was also found to be a 2:3 mixture of 39 and 40.

Elution with petroleum ether-ether (94:6) followed by concentration gave 41 as a colorless solid; 0.085g; 4.7% ; m.p. 124-25°.

IR, Nujol, bands at :

3193, 3026, 2981, 2929, 1505, 1462,

1213 and 812 cm^{-1}.

^{1}H NMR, $CDCl_3$, (Fig. 2.10), 200 MHz

and

^{13}C NMR, $CDCl_3$, (Fig. 2.11), 250 MHz,

For assignments see Chart 2.4.

Reaction of 35 (1.0g, 0.00607 moles) with activated Zn (1.972g, 0.03035 moles) afforded a brown solid (0.832g) which was washed successively with petroleum ether to give a white solid which, upon recrystallization from aqueous ethanol, yielded 45; 0.1429g; 8.0%; m.p. 233-34°.

IR, Nujol, bands at :

3000-2860 (broad), 1660, 1610, 1510, 1290, 1250,

1085, 1030, 915, 850 and 775cm^{-1}.

^{1}H NMR, $CDCl_3$, 200 MHz

and

^{13}C NMR, $CDCl_3$, 250 MHz.

For assignments see Chart 2.5.

Reaction of freshly distilled 36 (1.0g, 0.00602 moles) with activated Zn (1.969g, 0.03012 moles) yielded a dark brown liquid (0.932g) which was chromatographed over silica gel. Elution of the column with petroleum ether-benzene (95:5) followed by concentration afforded a solid which upon recrystallization from ethanol yielded 46; 0.132g; 7.0%; m.p. 147°.

IR, KBr, bands at :

2921, 2852, 1622, 1604, 1501, 1445, 1292, 1196, 1160, 1076, 1059 and 949cm^{-1}.

^{1}H NMR, $CDCl_3$, 200 MHz

and

^{13}C NMR, $CDCl_3$, 250 MHz.

For assignments see Chart 2.6.

Reaction of freshly distilled 47 (1.0g, 0.00819 moles) with activated Zn (2.675g, 0.0041 moles) afforded a dark brown liquid (0.884g) which was chromatographed over silica gel. Elution of the column with petroleum ether-benzene (80:20) followed by concentration afforded a yellowish solid which upon recrystallization from ethanol yielded colourless needles of 48; 0.153 g; 9.0%; m.p. 98-99°.

IR, Nujol, (Fig 2.12), bands at :

3300, 2940, 2860, 1460, 1080, 1030 and 830 cm^{-1}.

^{13}C NMR, $CDCl_3$, 250 MHz.

For assignments see Chart 2.7.

Preparation of benzyl phenyl ketone 49

Benzyl phenyl ketone 49 was prepared by following a reported procedure[19]. Reaction of benzyl phenyl ketone 49 (1.0g; 0.0051 moles) with activated Zn (1.678g, 0.02551 moles)-HCl-ether at 0^{o} afforded a petroleum ether insoluble solid which upon recrystallization from ethanol yielded colorless crystals of 50; 0.1g; 5.4%; m.p. 210-13^{o} (lit.[16] m.p. 213-14^{o}).

IR, Nujol, bands at :

3400 (broad), 2940, 2880, 1650, 1470,

1400 and 1080cm^{-1}.

^{1}H NMR, $CDCl_3$, 200 MHz, signals at:

2.24 (2H, s, 2-OH),

2.94, 3.00 and 3.66, 3.71 (2H, s, each),

6.75, 7.04 and 7.26 (5H, m, each),

7.48 (5H, m).

^{13}C NMR, $CDCl_3$, 250 MHz:

one triplet at 42.2,

six doublets at 126.4, 126.9, 127.2,

128.0, 128.4 and 130.8,

three singlets at 81.3, 136.2 and 142.5.

The petroleum ether soluble yellow liquid (0.678g) was chromatographed over silica gel. Fractions eluted with petroleum ether followed by concentration yielded a white solid which was recrystallized from aqueous

ethanol to give a white solid (0.205g) which was found by ^{1}H-NMR to be a 3:1 mixture of 52 and 53. Elution of the column with benzene followed by concentration afforded a colourless liquid which, on keeping for 24 hours solidified. Recrystallization from petroleum ether afforded white needles (0.024g) m.p. 158-59 ^{o} which was found to be a mixture of 50 and 51 on the basis of ^{1}H NMR.

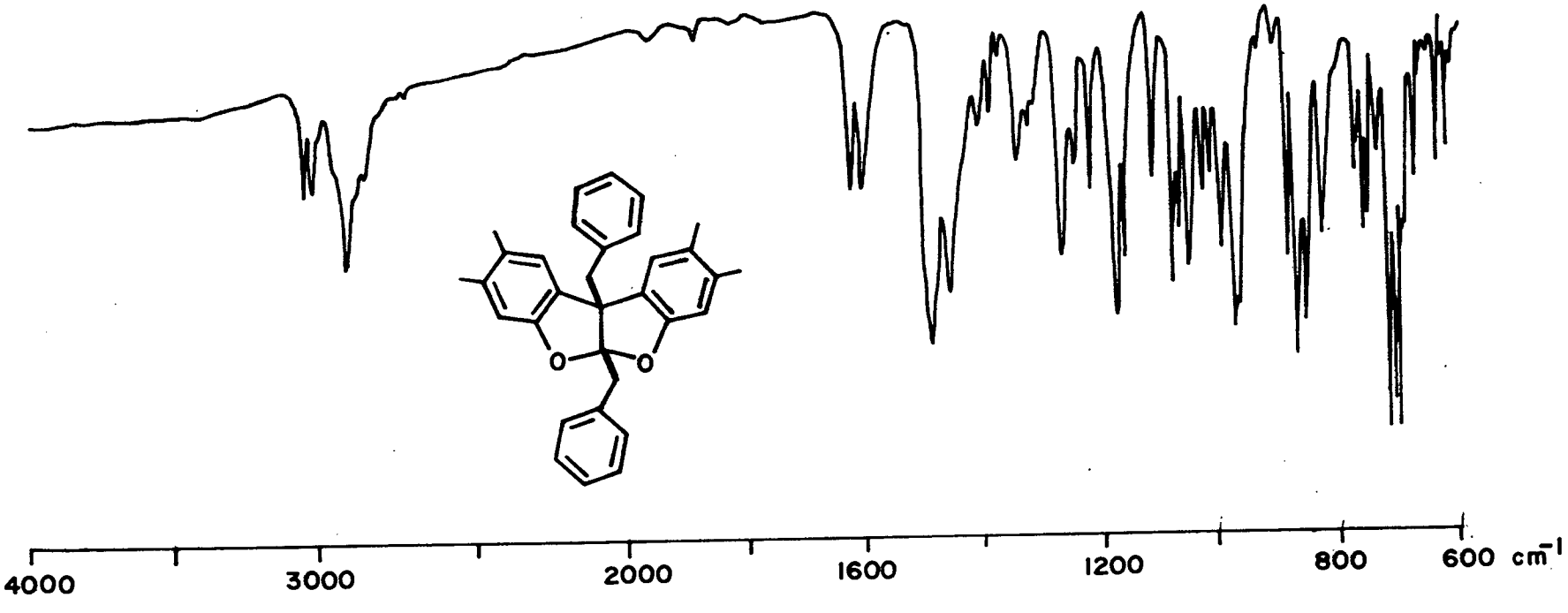

Fig. 2.1 IR spectrum of 28

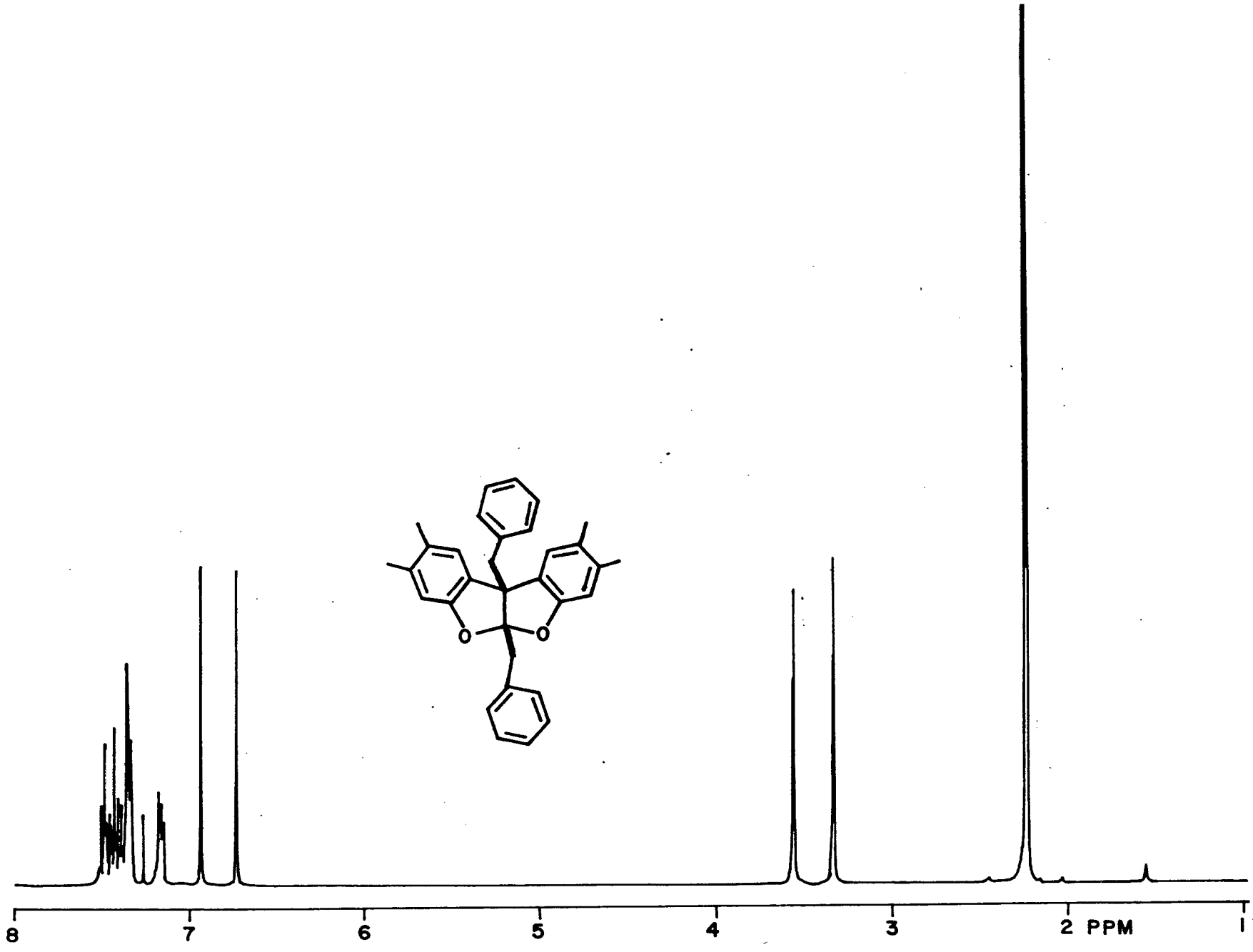

Fig. 2.2 ^{1}H NMR spectrum of 28

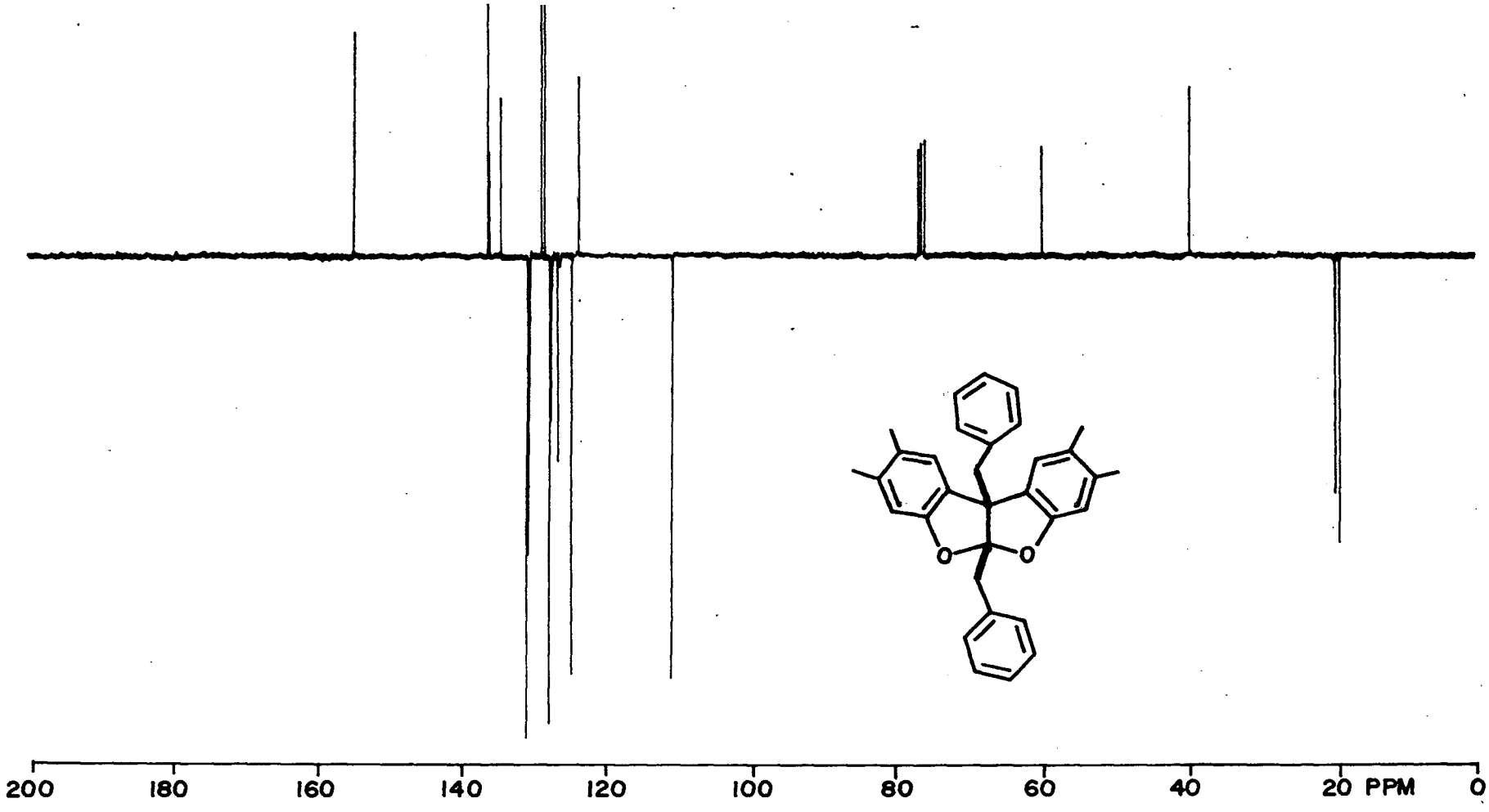

Fig. 2.3 APT ^{13}C NMR spectrum of 28

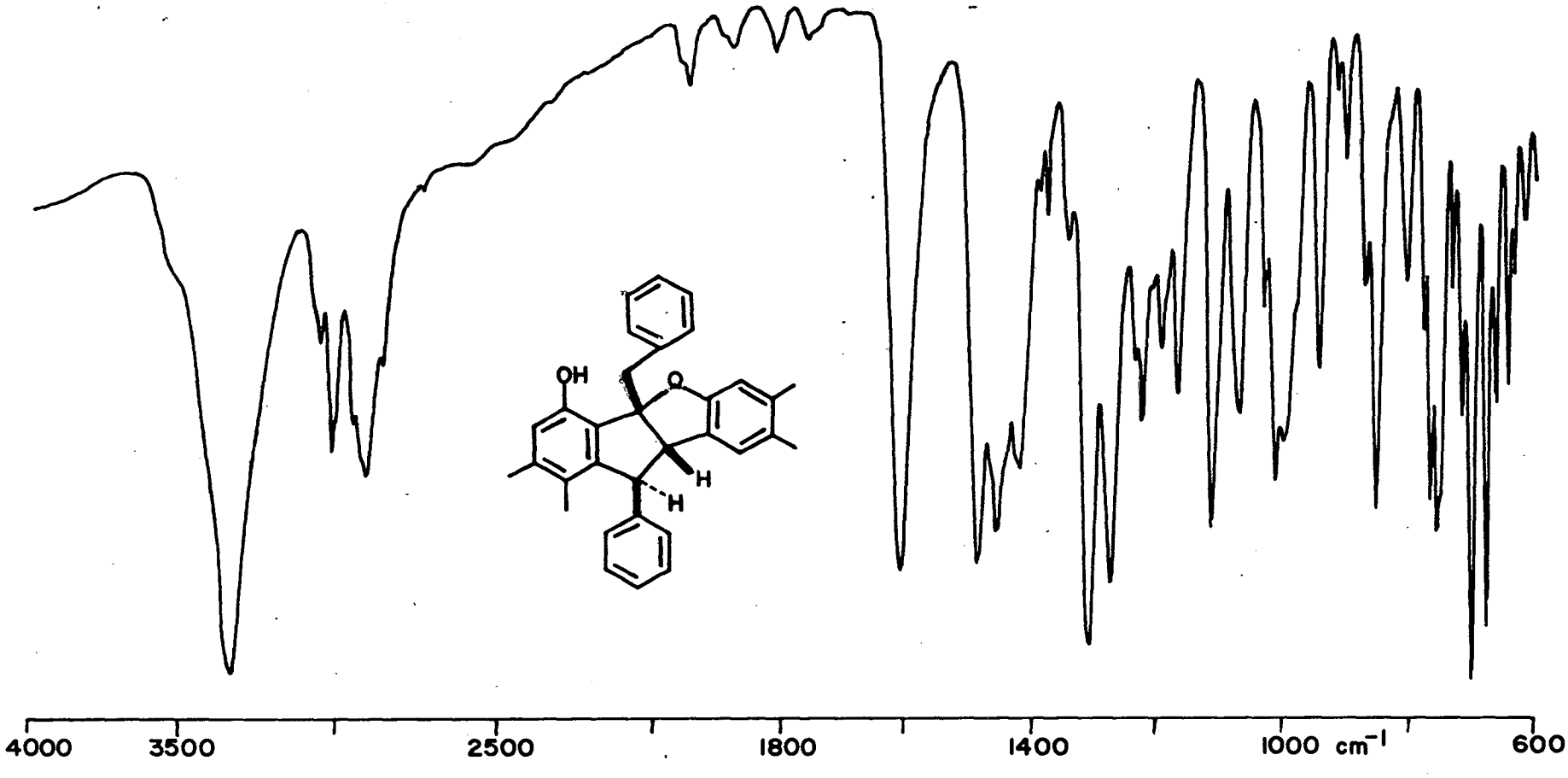

Fig. 2.4 IR spectrum of 31

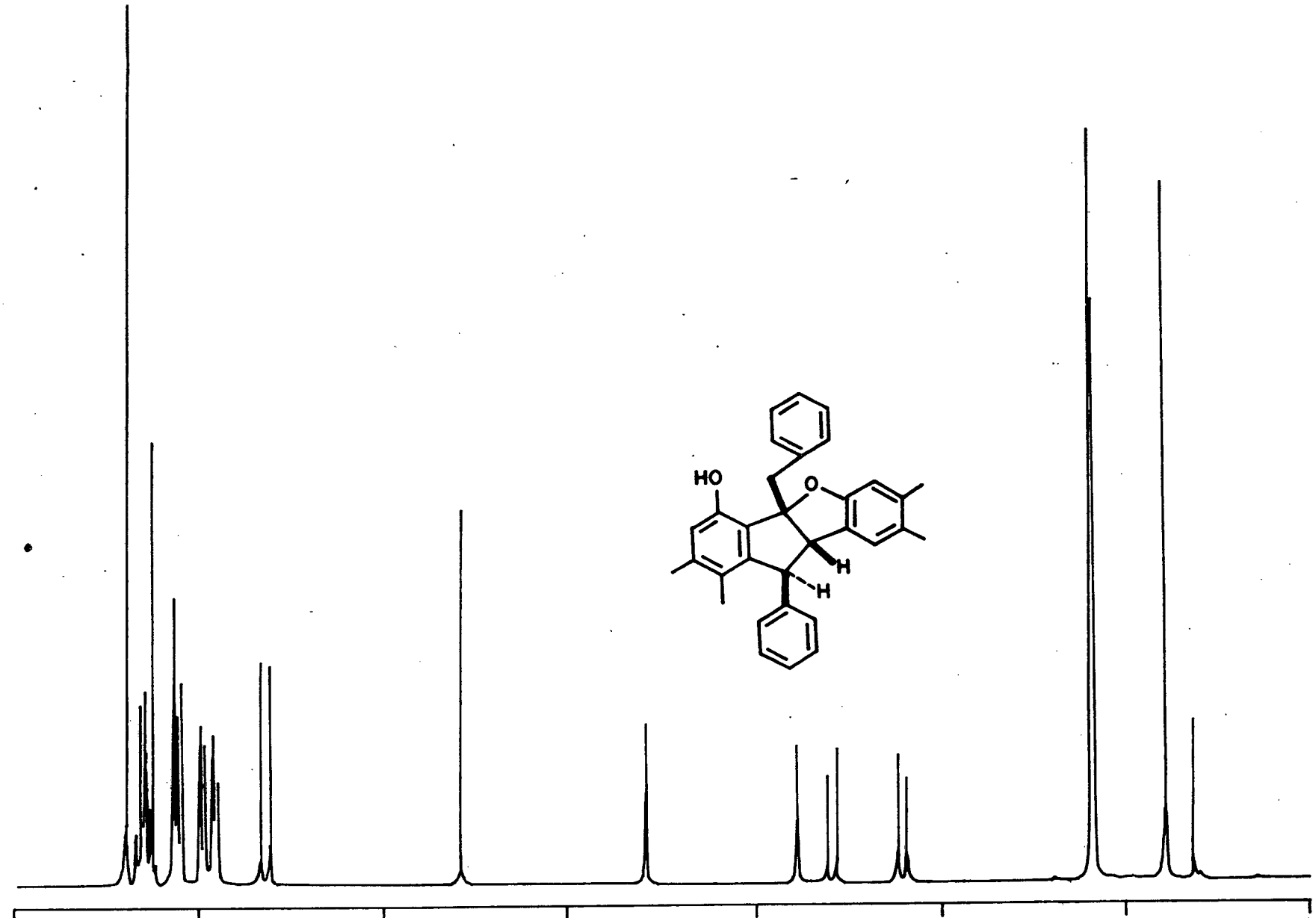

Fig. 2.5 ^{1}H NMR spectrum of 31

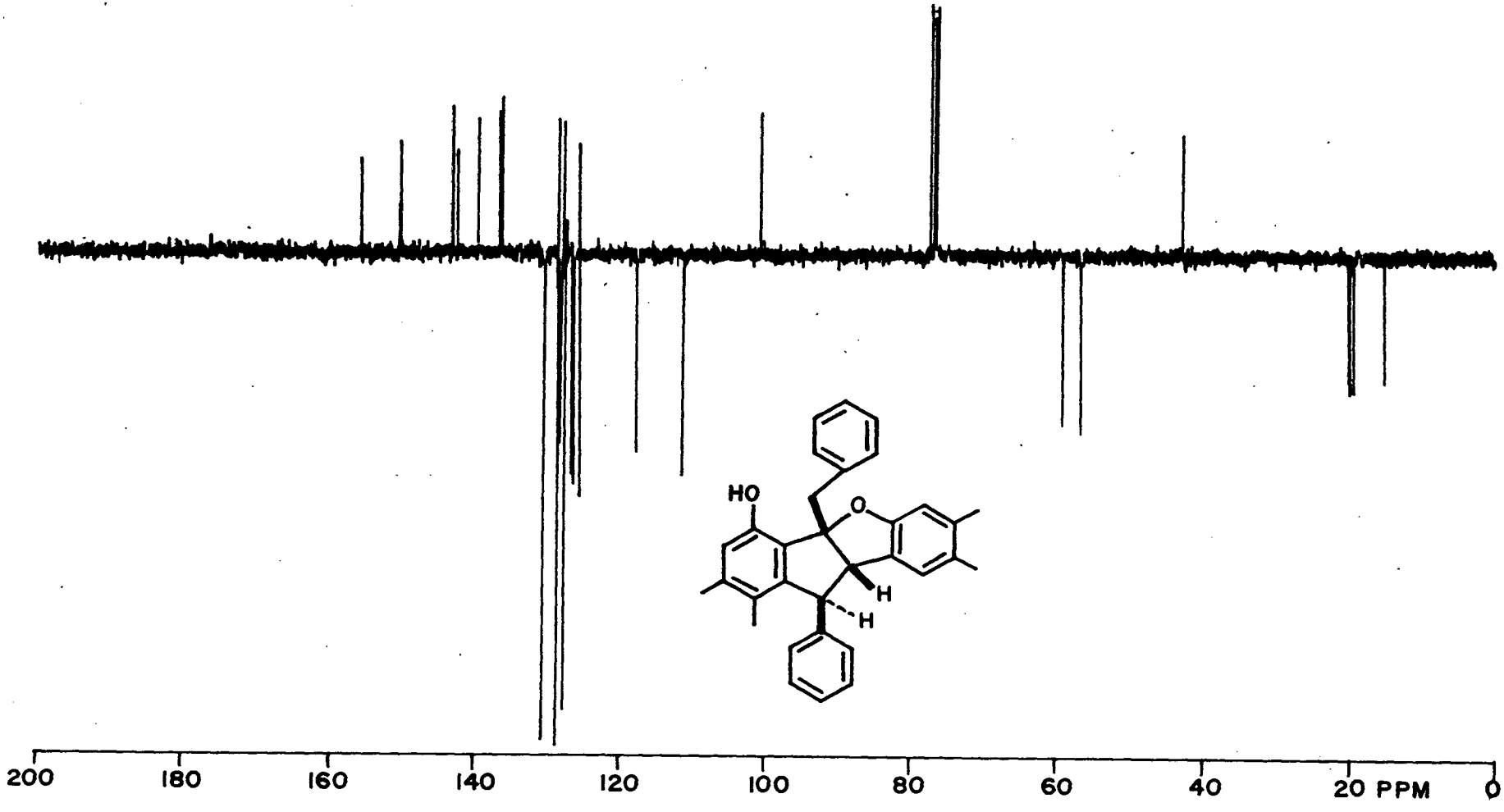

Fig. 2.6 APT ^{13}C NMR of 31

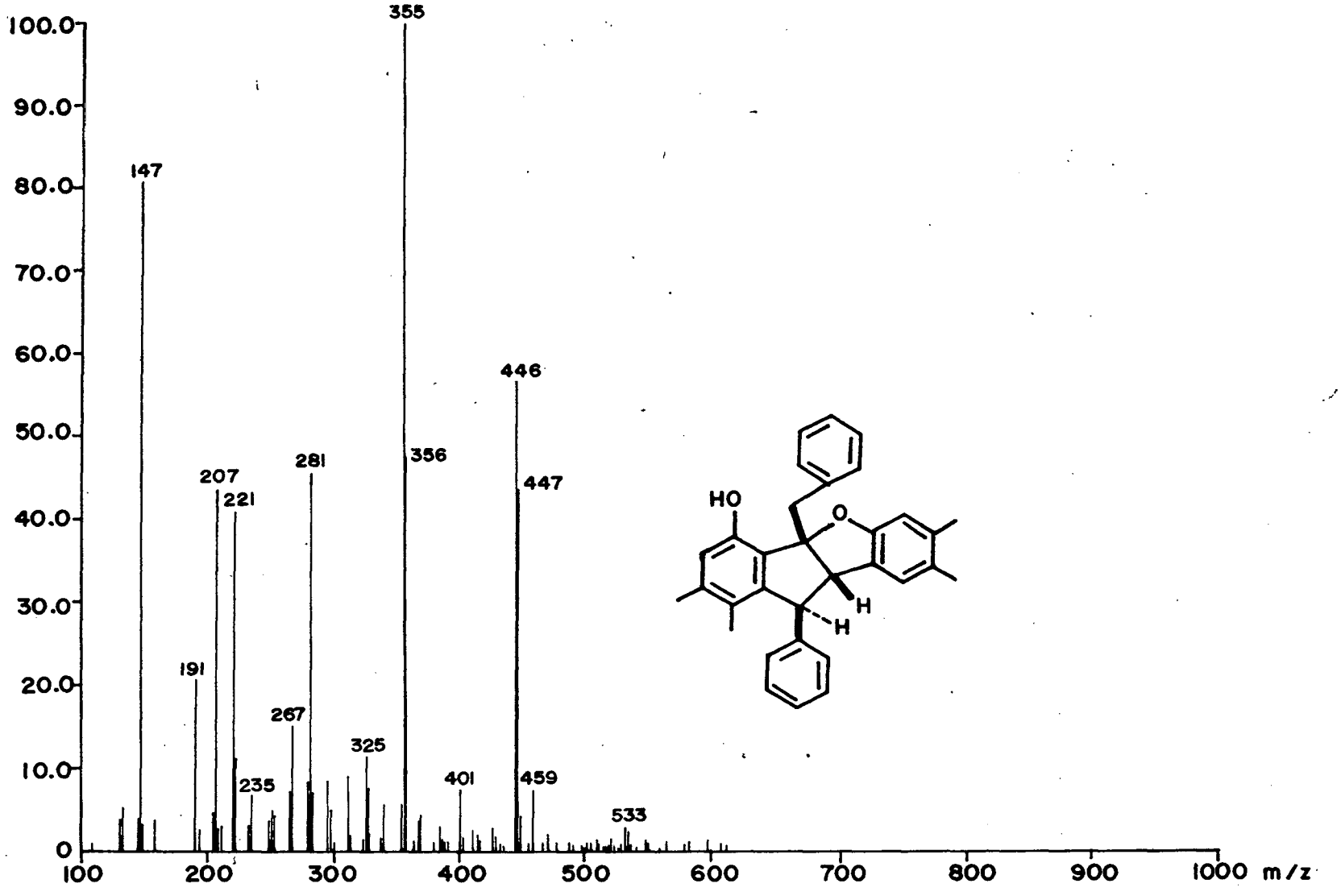

Fig. 2.7 Mass spectrum of 31

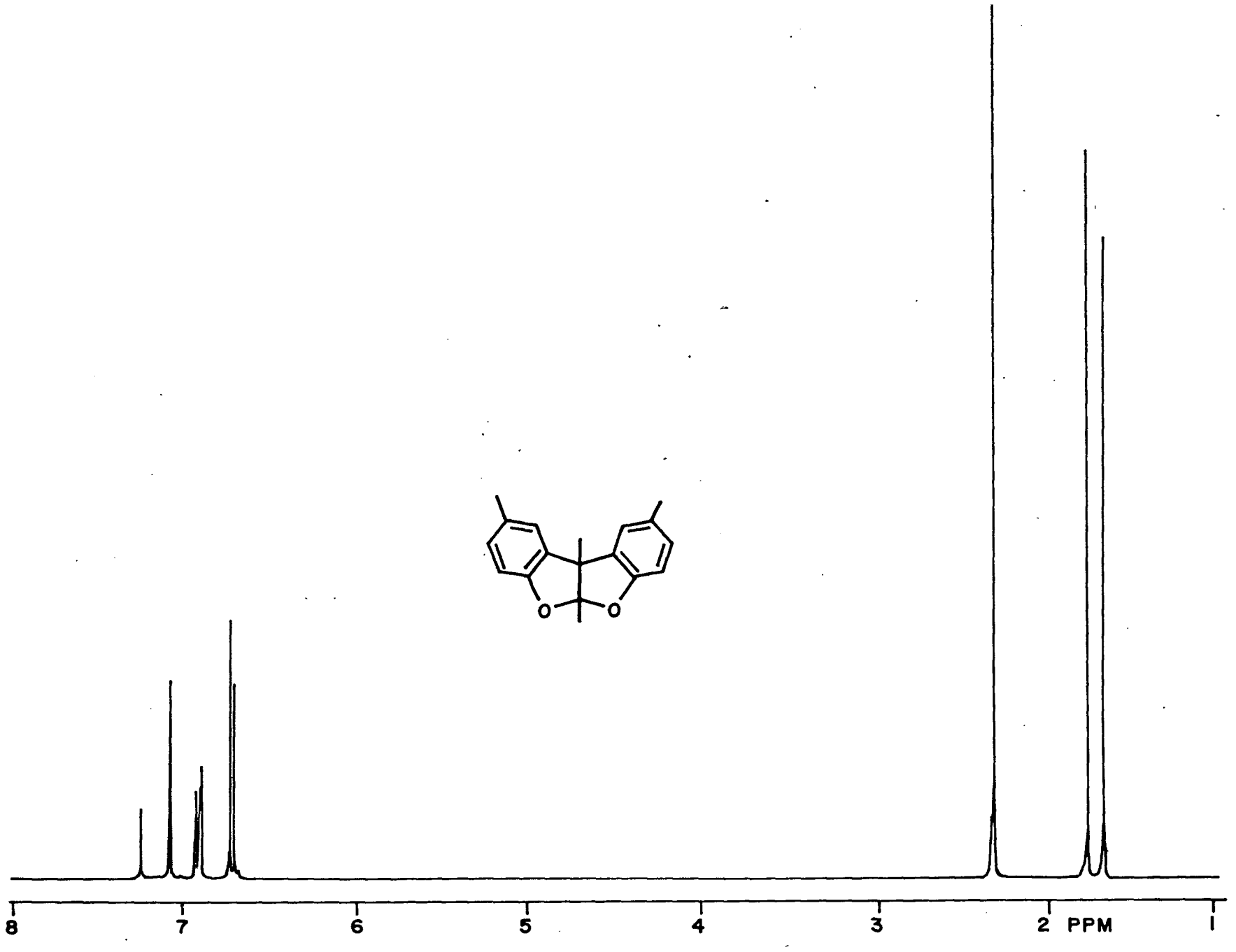

Fig. 2.8 ^{1}H NMR spectrum of 39

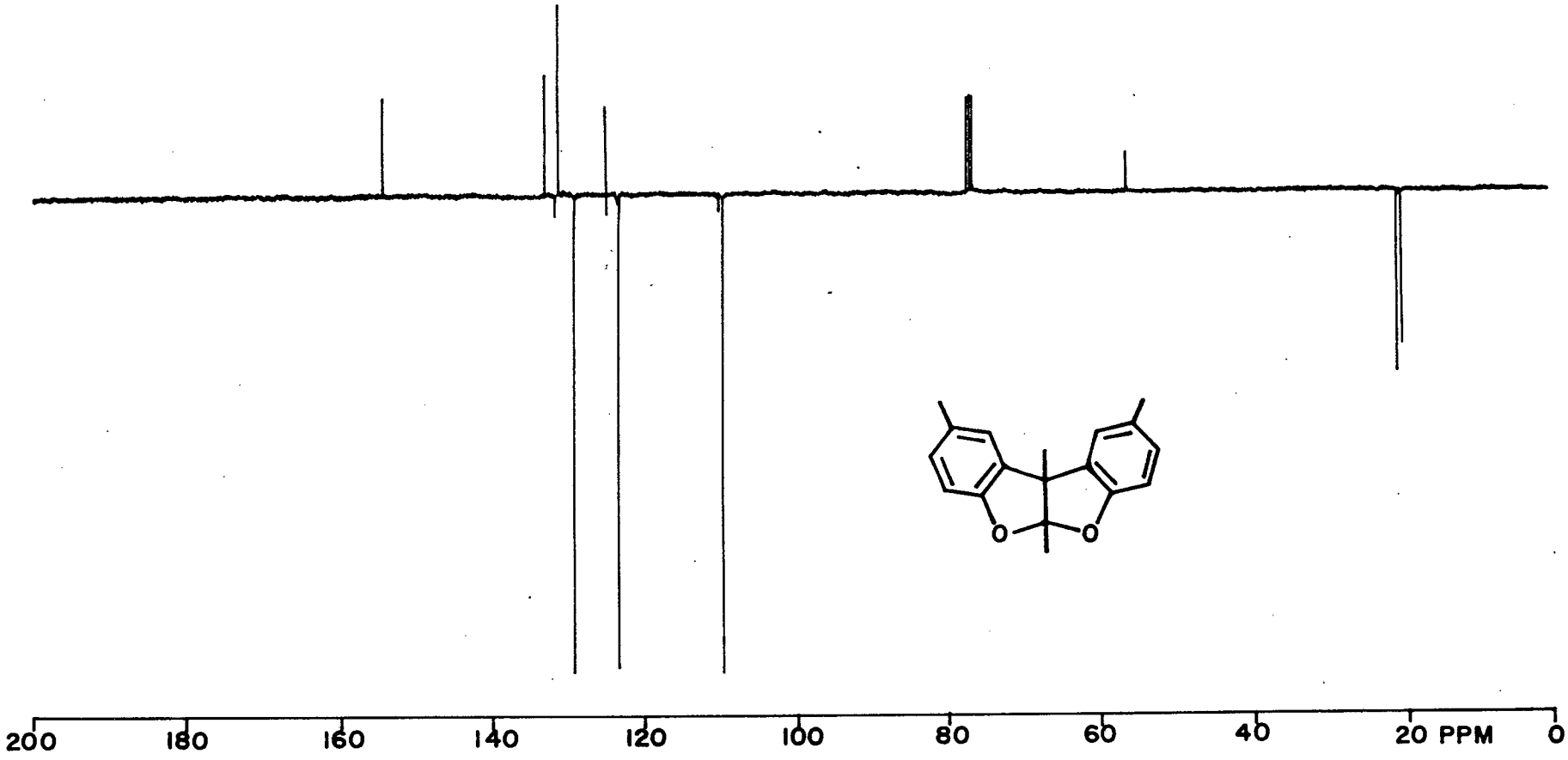

Fig. 2.9 APT ^{13}C NMR spectrum of 39

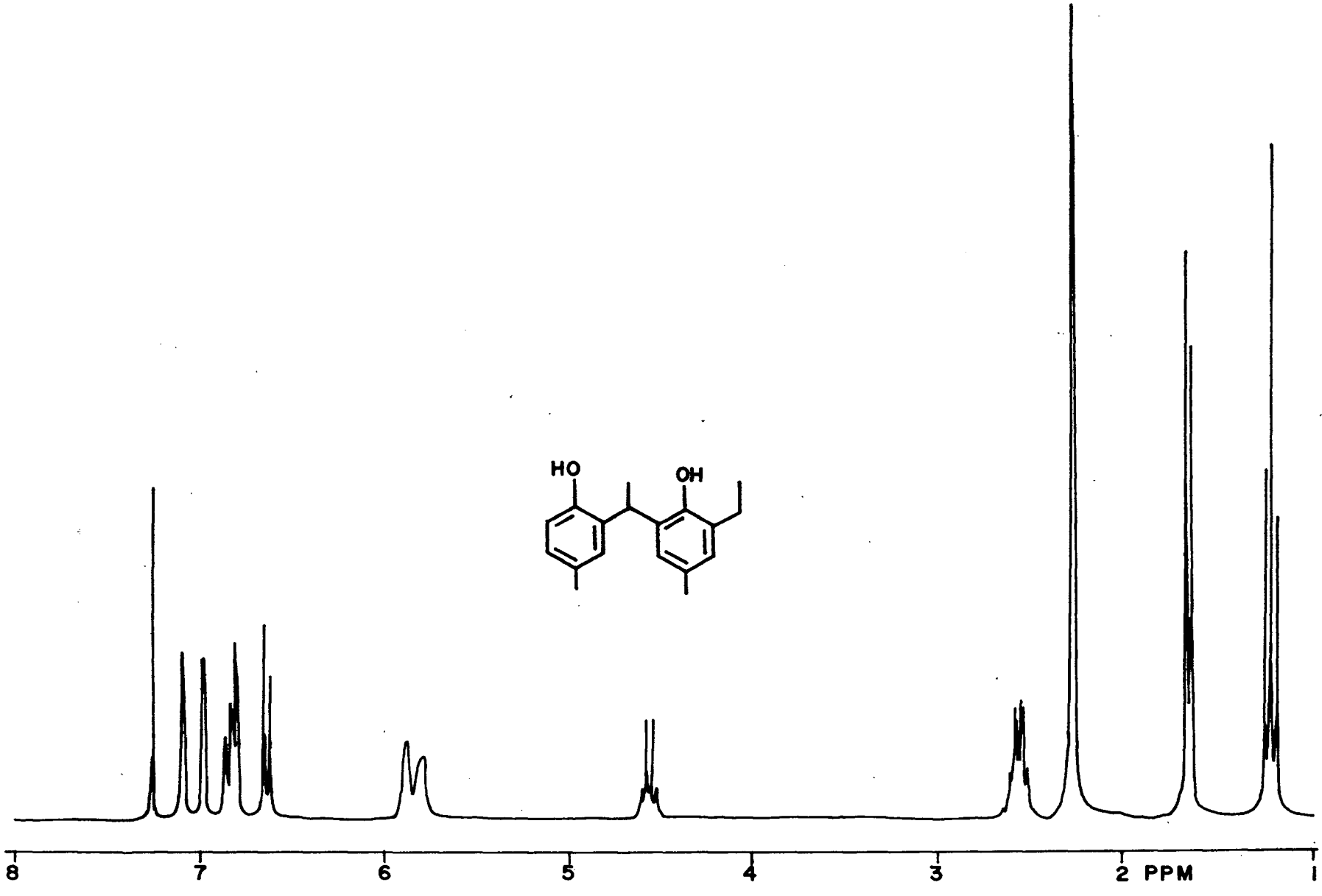

Fig. 2.10 ^{1}H NMR spectrum of 41

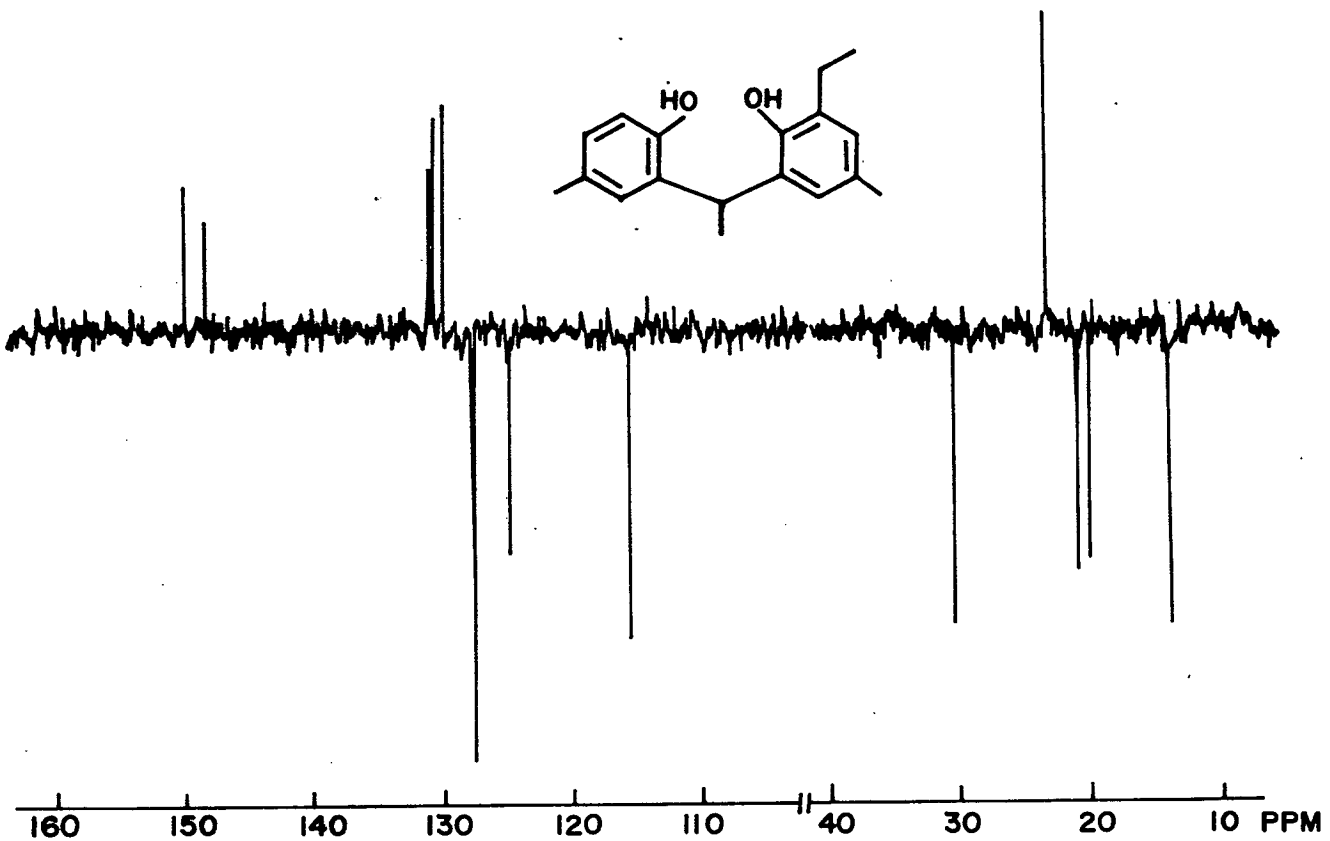

Fig. 2.11 APT ^{13}C NMR spectrum of 41

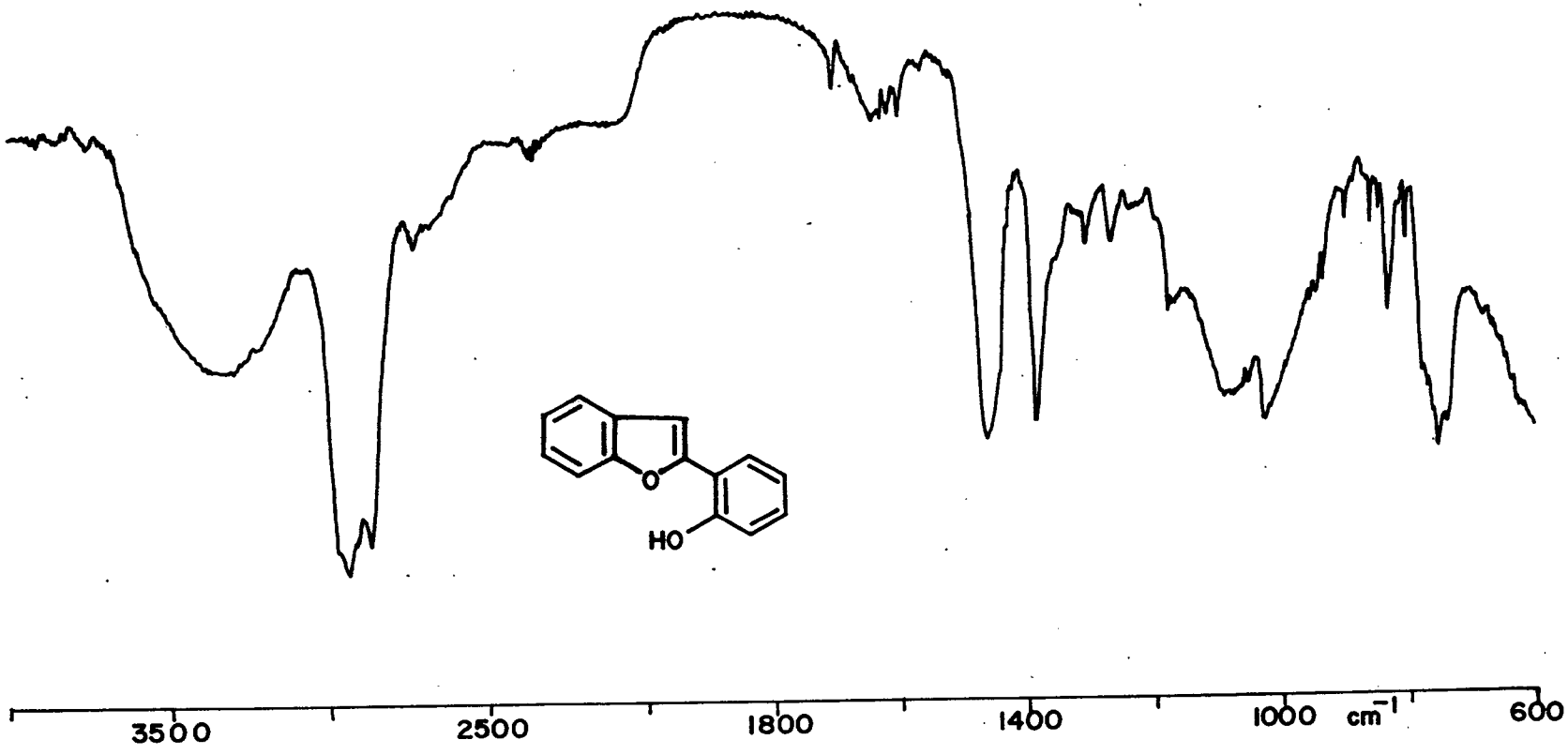

Fig. 2.12 IR spectrum of 48

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CHAPTER THREE

STRUCTURAL AND SYNTHETIC STUDIES ON SOME NATURAL PRODUCTS.

SECTION ONE

p-NITROBENZOIC ACID, A NEW REAGENT FOR INTERCONVERSION OF LONGIFOLENE AND LONGICYCLENE.

The chemistry of logifolene 1, the well known chemical constituent of Indian turpentine oil (Pinus Longifolia Roxb) has richly contributed to the understanding of some deep seated molecular rearrangements involving carbocations. This abundantly available raw material has also been converted to other isomeric compounds and used successfully for the commercial preparation of some perfumery compounds.

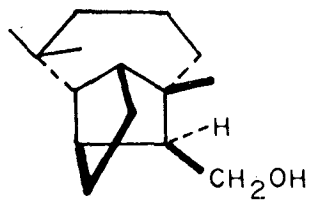
1

2

Alloisolongifolene 2 is a comparatively recently characterised isomer of longifolene 1. Nayak and co-workers[1] prepared it by treatment of longifolene 1 with specific catalysts such as bromoacetic acid and iodoacetic acid. In fact this isomer of longifolene was first obtained by Zeiss and Arakawa[2] by reaction of isolongifolol 3 with $KHSO_4$ but remained uncharacterised till 1983, when Kamat and Paknikar[3] established its equivalence to the alloisolongifolene of Nayak and co-workers and favored structure 2 as opposed to structure 4 suggested by Nayak and co-workers[4]. X-ray analysis unambiguously established structure 2 for

alloisolongifolene.

Nayak and co-workers carried out further



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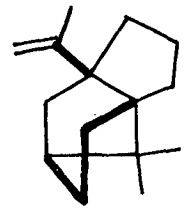

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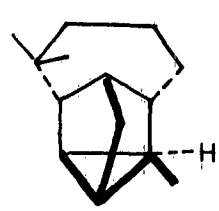
transformations on this new isomer and showed that, like longifolene, alloisolongifolene can also serve as a good starting material for the preparation of valuable odorants. Considering the pK_a values of bromoacetic acid (2.90) and idoacetic acid (3.16), we selected p-nitrobenzoic acid (3.43) as a possible catalyst for isomerisation of longifolene 1 in the hope of preparing alloisolongifolene 2 by a new method. It will be seen from the results presented in this section that we did not observe the formation of alloisolongifolene 2 but instead resulted in the generation of an equilibrium mixture of longicyclene 5 and longifolene 1, thus providing a new method for the conversion of longifolene to longicyclene.



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Reaction of longifolene 1 with p-nitrobenzoic acid under different experimental conditions (Table 3.1) led to a mixture of which one component was found to be the starting hydrocarbon* and a new

Table 3.1

No.	Catalyst	Quantity w/w Cat:1	Reaction Temperature/Time	% Products
1.	p-Nitro benzoic acid	1:1	260-70°, 1 hr.	1 (27.1) 6 (66.7)
2.	p-Nitro benzoic acid	1:10	200-210°, 3 hrs.	1 (77.18) 5 (22.1)
3.	p-Nitro benzoic acid	1:10	260-70°, 2 hrs.	1 (73.04) 5 (26.92)
4.	picric acid	1:2.5	200°, 3 hrs.	1 (26.3) 6 (67.9)

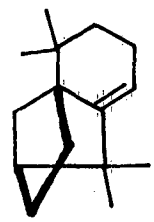
The GLC analysis were carried out at 100° on a TFAP column using a FID detector.

hydrocarbon not identical with alloisologifolene 2

This observation was based on using authentic reference sample of alloisolongifolene 2 for GLC studies. It will be seen from the table that isolongifolene 6 is formed only when the catalyst to longifolene ratio is kept as 1:1 (entry 1) and using picric acid as a catalyst (entry 4). Considerable decrease (ten fold) in the quantity of the catalyst (entries 2 and 3) resulted in the formation of an

* We did not measure the specific rotation of the recovered longifolene but longifolene is known to racemise under acidic conditions[5]

equilibrium mixture containing longifolene 1 and a new hydrocarbon having lower retention time (Rt 1.76) than isolongifolene (Rt 1.98).



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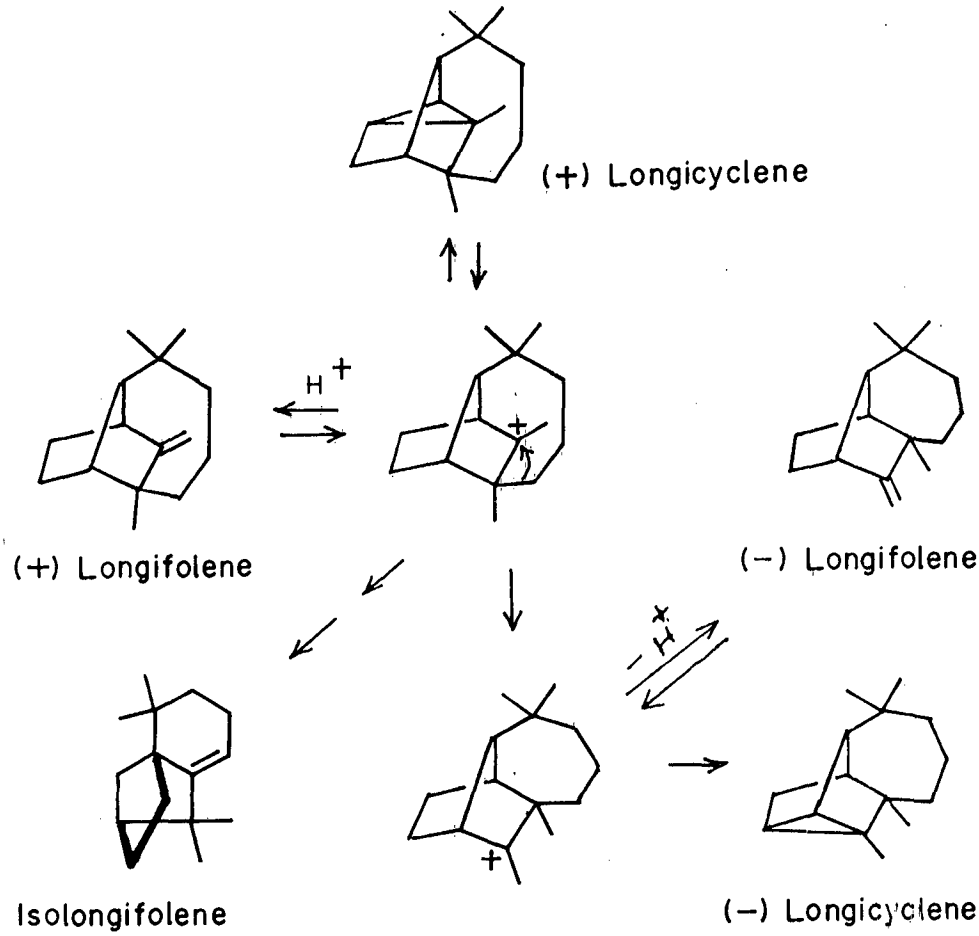
Isolation of this new hydrocarbon (Rt 1.76) was possible using $AgNO_3$ impregnated silica gel for chromatography. The spectral data ^1H NMR and IR (Fig 3.1) conclusively established its identity with longicyclene 5, the tetracyclic sesquiterpene of Indian turpentine oil. The most interesting features of this study was that the longicyclene 5 obtained was optically active, $[\alpha]_D$ $+23^0$. In this context it is desirable to present in brief the previous reports on the conversion of longifolene 1 into longicyclene 5.

In 1964, Sukh Dev and co-workers[6] reported that when longifolene is treated with cupric-acetate in refluxing acetic acid, a three component equilibrium mixture of isomeric sesquiterpene is established between longifolene 1 (51%), longicyclene 5 (29%,) and isolongifolene 6 (15%). The longifolene 1 recovered in this reaction was found to be racemic and this presumably takes place by the pathway shown. (Scheme 3.1).

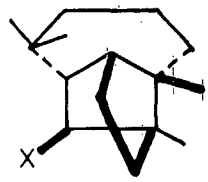
Bhattacharyya and co-workers[7] reported conversion

of longifolene 1 in to longicyclene 5 via



Scheme 3.1

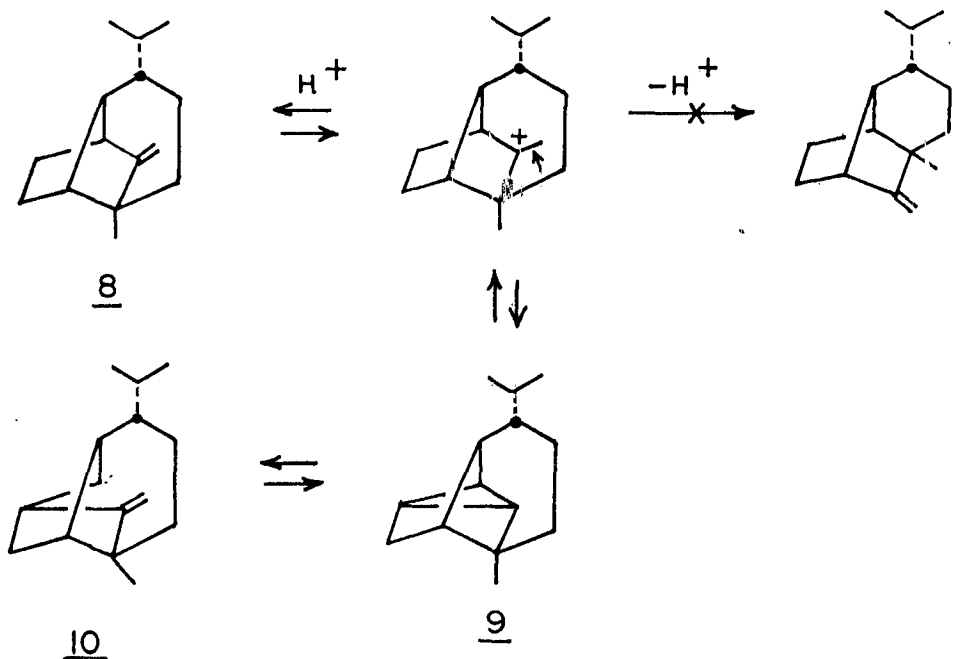
longibornyl chloride 7a. It was observed that reaction of longibornyl chloride 7a with NaOAc-AcOH produces a mixture of longifolene 1 (80%), longicyclene 5 (8%) and isolongifolene 6 (12%). On the other hand if longibornyl bromide 7b is refluxed with aqueous ethanolic KOH, it gives a equilibrium mixture of longicyclene 5 (26%) and longifolene 1 (74%). Since no optical rotations are reported, it is not possible to establish if racemisation also occurs during this equilibration.



7a X = Cl

7b X = Br

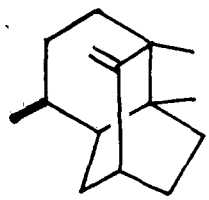
The method developed by Sukh Dev and co-workers[6] has been successfully used by McMurry[5] in the acid catalysed conversion of sativene 8. He observed that sativene 8 on treatment with $Cu(OAc)_2$ in refluxing HOAc is rearranged to an equilibrium mixture of recovered sativene 8 (7%), cyclosativene 9 (32%) and isosativene 10 (61%). (Scheme 3.2). Since sativene 8 contains an additional chiral center, the products obtained here are optically active.



Scheme 3.2

The cupric acetate-acetic acid reagent was also used

by Lawrence and co-workers[8] for conversion of seychellene 11 into cycloseychellene 12.



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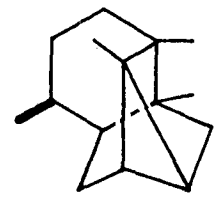

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Sukh Dev and co-workers[9] have shown that longifolene 1, when treated with H_3PO_4-dioxane produces isolongifolene 6 via longicyclene 5. The formation of isolongifolene 6 with a higher concentration of catalyst (Entry 1, Table 3.1) is therefore understandable.

We also carried out acid catalysed transformation of 1 using picric acid (1.02) as a catalyst (Entry 4, Table 3.1). The reaction product was found to be a mixture of longifolene 1 and isolongifolene 6. In this case also the GLC showed the total absence of alloisologifolene 2.

p-Nitrobenzoic acid, used by us in the longifolene→ longicyclene conversion, appears to be equally good reagent for the equilibration of unsaturated terpenes of the structural type described above and moreover this reagent produces optically active longicyclene 5 in contrast to the results obtained with cupric acetate-acetic acid. The results of the present study are summarised in Scheme 3.1. The characteristic feature of

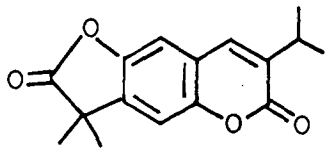
this equilibration reaction is isolation of longicyclene 5 without racemisation.

SECTION TWO

ONE POT SYNTHESIS OF 4-METHYL-7-HYDROXY-8-ISOPROPYL AND 4-METHYL-7-HYDROXY-6,8-DIISOPROPYL-COUMARINS FROM DIISOPROPOXYRESORCINOL.

Among the naturally occurring coumarins[10,11] the three containing both isopropyl and methyl substituents 13, 14 and 15 can be regarded as a rare group of natural products.

Though these are listed under naturally occurring coumarins, these compounds are in fact degraded terpenoids. The synthesis of one of the degraded sesquiterpenes 16 listed under naturally occurring coumarins has been recently reported from our laboratory.



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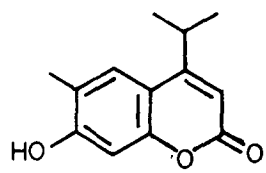

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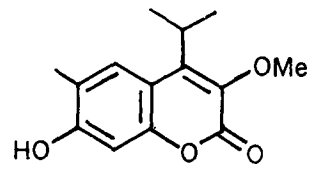

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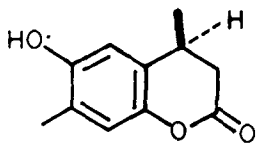
Recently it was observed by us that resorcinol dimethylether on treatment with ethyl acetoacetate under Pechmann conditions gave 4-methyl-7-methoxycoumarin[12]. This observation appeared to be interesting from a mechanistic viewpoint and led us to undertake the preparation of diisopropoxyresorcinol 17 and study its reaction with ethyl acetoacetate under Pechmann conditions. The logical expected outcome of this strategy was the formation of 4-methyl-7-isopropoxycoumarin 18. Under

these experimental conditions the isopropoxy group



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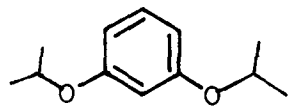

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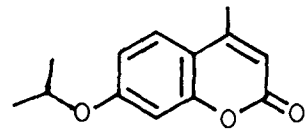

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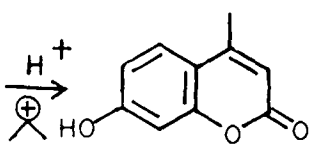
would undergo cleavage to produce 4-methyl-7-hydroxycoumarin 19. The compound 18 would generate 4-methyl-7-hydroxycoumarin 19 and the isopropyl carbocation formed in turn would react at the C_6 or C_8 position giving 4-methyl-6-isopropyl-7-hydroxycoumarin 20 or 4-methyl-7-hydroxy-8-isopropylcoumarin 21.



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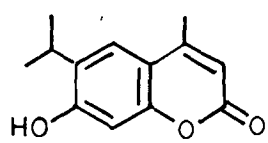

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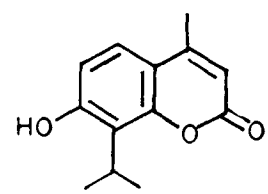


21

A literature survey indicated that though a large number of 4-methyl substituted coumarins were prepared, coumarins 20 and 21 have not been reported.

Diisopropoxyresorcinol 17 was prepared[13] by reaction of the dianion derived from resorcinol and isopropyl bromide. The other product, monoisopropoxyresorcinol formed in this reaction was removed chemically. The spectral characteristics (IR & ^{1}H NMR) of 17 were consistent with the structure and are

given in the experimental section.

Treatment of 17 with ethyl acetoacetate in the presence of conc. H_2SO_4 for six hours followed by usual workup and chromatography over silica gel produced three substances A (23.15%), B (13.7%) and C (4%). (Fluorescent spots on TLC plate when observed under UV). These compounds could be isolated in pure form, compound A, m.p. 174^0, compound B, m.p. 225^0 and compound C, m.p. $180-81^0$.

The spectral data and m.p. recorded on the most polar compound C (IR, ^1H and ^{13}C-NMR spectrum[14] and Mass spectrum) conclusively established its identity with 4-methyl-7-hydroxycoumarin 19, further confirmed by mixed melting point[15] determination with an authentic sample of 19.

Formation of 19 showed that cleavage of the 7-isopropylether took place as anticipated and further indicated that the other two compounds would be 6- and 8-isopropyl substituted coumarins 20 and 21. The possibility of an isopropyl substituent at C_3 was also considered. Compound B, $C_{13}H_{14}O_3$ (M^+ 218), m.p. 225^0 showed in its IR spectrum (Fig 3.2) the presence of an hydroxyl group and coumarin carbonyl group. Its ^1H NMR spectrum (Fig 3.3) was more informative and showed the presence of an isopropyl group 1.39 (d, 6H, J = 7.3 Hz) as expected. The presence of C_3-H, 6.09 (s, 1H) showed that the isopropyl group is attached to the benzenoid ring. The appearance of two doublets (1H,

each, J = 8.6 Hz) at 6.82 and 7.42 clearly established the substitution pattern and the compound B, was assigned the structure, 4-methyl-7-hydroxy-8-isopropylcoumarin 21. The ^{13}C NMR data (Fig 3.4) was fully consistent with the assigned structure 21 and the assignments are shown in Table 3.2.

Table 3.2

Compound B

Carbon	Chemical shift	Multiplicity
C_2	162.95	s
C_3	110.99	d
C_4	155.07	s
C_5	121.34	d
C_6	114.26	d
C_7	160.30	s
C_8	122.07	s
C_9	154.31	s
C_4 methyl	018.83	q
C_8 isopropyl	020.79, 020.79	q,q
H->C	025.25	d
C_6 isopropyl	———	——
H->C	———	——

Compound A, m.p. 174^0 showed the composition, $C_{16}H_{20}O_3$ (M^+ 260). A pair of doublets at 1.27 and 1.42 (J = 7 Hz) integrating for 6H each indicated the presence of two isopropyl groups, singlets at 2.44 (3H)

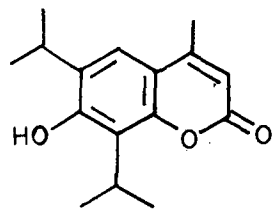
and 6.1 (1H) in its ^1H NMR (Fig 3.5) clearly established 3-unsubstituted 4-methylcoumarin structure suggesting that both the isopropyl groups are located on the aromatic ring. The lone singlet (1H) at 7.31 is due to C_5-H and hence the structure 22 was assigned to compound A. As expected the ^1H NMR spectrum also showed two one proton multiplates at 3.32 and 3.71 due to the methines of the isopropyl groups and a broad singlet at 4.8 due to phenolic OH. The ^{13}C NMR spectrum (Fig 3.6) of compound A showed 5 quartets, 4 doublets and 7 singlets. The chemical shifts and assignments are shown in Table 3.3.

Table 3.3

Compound A

Carbon	Chemical shift	Multiplicity
C_2	164.04	s
C_3	111.18	d
C_4	156.52	s
C_5	120.39	d
C_6	134.59	s
C_7	157.05	s
C_8	123.22	s
C_9	152.71	s
C_4 methyl	018.95	q
C_8 isopropyl	021.09, 021.09	q,q
H->C	026.20	d
C_6 isopropyl	023.31, 023.31	q,q
H->C	028.11	d

In conclusion, we have found that the reaction of diisopropoxyresorcinol 17 with ethyl acetoacetate in the presence of conc. H_2SO_4 (Pechman conditions) affords 4-methyl-7-hydroxycoumarin 19, 4-methyl-7-hydroxy-8-isopropylcoumarin 21 and 4-methyl-7-hydroxy-6,8-diisopropylcoumarin 22. These synthetic coumarins will be tested for their biological activities. It is proposed to prepare 4-methyl-7-isopropoxycoumarin 18 from 19 and study its reaction with conc. H_2SO_4. We expect to obtain isopropyl substituted coumarins 20 and 21 from this reaction*



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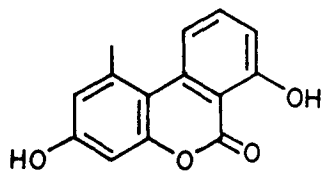
* The reaction of monoisopropoxyresorcinol with ethyl acetoacetate in the presence of conc. H_2SO_4 also resulted in the formation of coumarins 19, 21 and 22[16].

SECTION THREE

A NEW SYNTHESIS OF 6-METHYL-7-METHOXYCOUMARIN.

The plants belonging to the families Umbellifarae and Rutaceae have been shown to produce a variety of oxygenated, barring few exceptions, coumarins and of those which contain three or more oxygen atoms, one of them is always at C_7. C-Methylated coumarins are not so uncommon but such naturally occurring coumarins are not large in number and the methyl group in most cases is situated at C_4 of the coumarin skeleton. In a few cases such as 23, 24 and 25 the methyl group is



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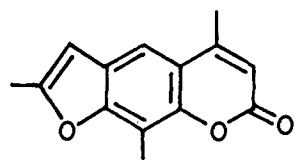

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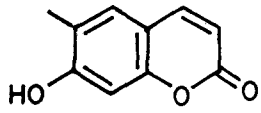
attached to the benzenoid ring. Sharma and Sharma[17] reported the isolation and characterisation of 6-methyl-7-hydroxy and 6-methyl-7-methoxycoumarin 25 and 26 respectively from the seeds of Trachyspernum Roxburghianum (DC) Craib (Umbellifarae). The assigned structures were based on spectral studies and chemical conversion of 25 into 26 by methylation with dimethylsulphate in the presence of K_2CO_3.



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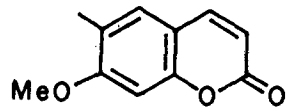
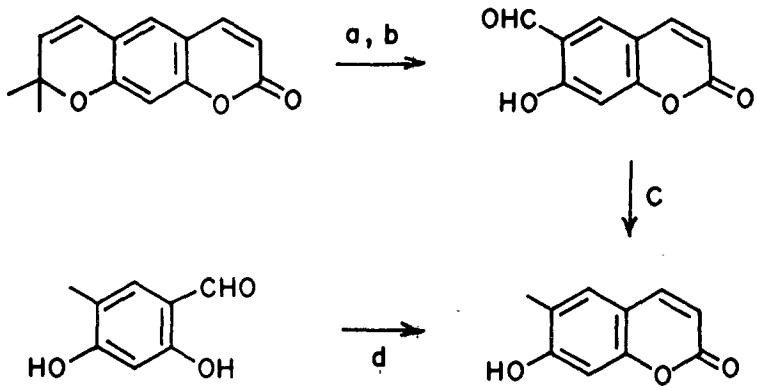


26

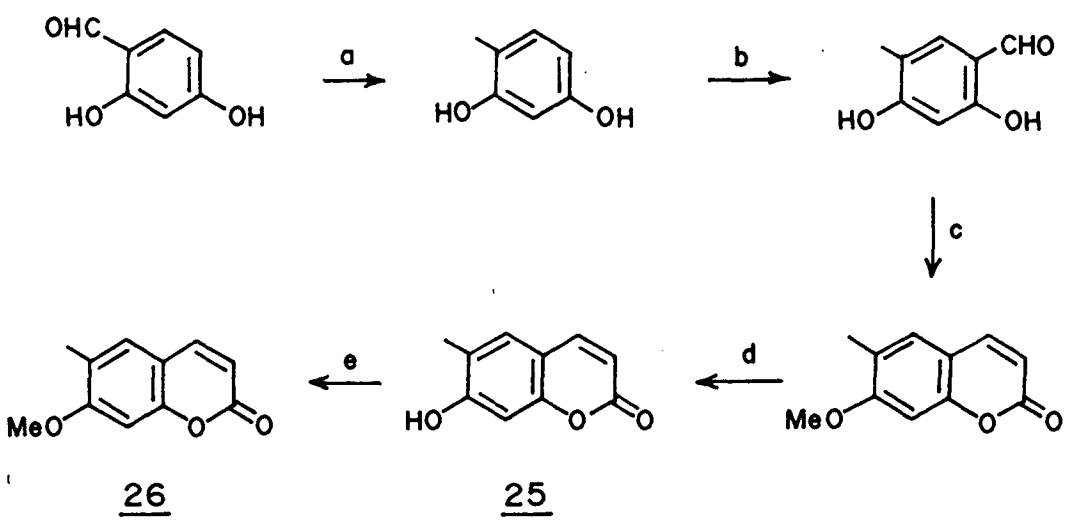
Prior to the isolation of these coumarins in 1980, 25 and 26 were known in the literature as synthetic compounds. In 1982, Mali and co-workers[18] reported yet another synthesis utilizing a Wittig reaction on the appropriately substituted salicylaldehyde. The previously known synthetic routes are depicted[19,20] in Schemes 3.3, 3.4 and 3.5.



25

(a) $O_3/CHCl_3$; (b) $O_2/CHCl_3$; (c) H_2-Pd/C;
(d) $(CH_3CO)_2O$, CH_3COONa.

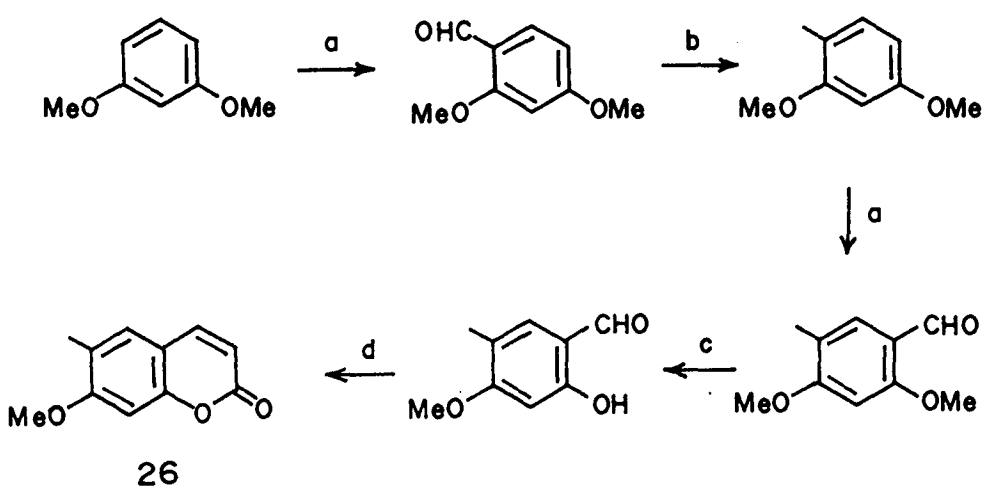
Scheme 3.3



26 25

(a) $Zn-HCl/C_2H_5OH$; (b) HCN, $HCl-AlCl_3/H_2O$; (c) $(CH_3CO)_2O$ - CH_3COONa; (d) EtOH-HCl; (e) $(CH_3)_2SO_4-K_2CO_3/(CH_3)_2CO$.

Scheme 3.4



26

(a) $POCl_3-HCONMe_2$; (b) NH_2NH_2-KOH/DEG; (c) $AlCl_3/CH_2Cl_2$; (d) $Ph_3P=CHCOOEt$.

Scheme 3.5

This section describes a new and simple synthesis of 6-methyl-7-methoxycoumarin 26.

Most of the synthetic routes to coumarins involve the use of salicylaldehyde derivatives and in all the previously reported synthesis of 26, 2,4-dihydroxy-5-methyl benzaldehyde was the key intermediate. In the Perkin coumarin synthesis[21-23] salicylaldehyde or substituted salicylaldehydes are treated with malonic acid in the presence of acetic anhydride and sodium acetate. This well known method suffers from the inherent drawbacks of the preparation of the requisite o-hydroxybenzaldehydes and in some cases the yields are poor. Improvements in the yields were reported by (i) addition of a small quantity of iodine,[24] (ii) replacing NaOAc with triethylamine,[25] (iii) heating of o-hydroxybenzaldehydes with either 1,1-dimorpholinoethane[26] or 1-dimethylamino-1-ethoxyethene[27] and (iv) use of the Wittig reaction[18].

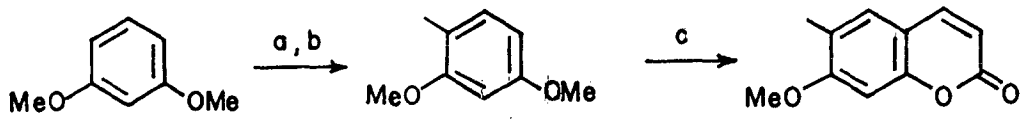
A milder two step synthesis involves reaction of o-hydroxybenzaldehydes with malonic acid in the presence of pyridine and aniline at room temperature followed by decarboxylation[28-31] of coumarin-3-carboxylic acid. Similarly, Knoevenagel condensation of o-hydroxybenzaldehyde with diethyl malonate in pyridine followed by hydrolysis and decarboxylation gives coumarin[32,33].

To overcome the problems associated with

obtaining suitable o-hydroxybenzaldehydes, Pechmann reported[34] an alternative method in which a phenol is heated with malic acid and sulphuric acid at $\simeq 120^0$ until gas evolution is complete. This method has also been further modified by the use of blocking α-hydroxy carboxylic functionality of malic acid . Four carbon chain of malic acid is then transformed to phenols to obtain coumarins.

Recently we found that resorcinol dimethylether when treated with ethyl acetoacetate in presence of conc.H_2SO_4, 7-methoxycoumarin is obtained in good yield[12]. This prompted us to study the reaction of 2,4-dimethoxytoluene with malic acid in presence of conc. H_2SO_4 where we envisaged a new synthetic route to 6-methyl-7-methoxycoumarin 26.

2,4-Dimethoxytoluene 27 was obtained by Vilsmeier formylation (Scheme 3.6) with dimethyl-formamide and phosphoryl chloride followed by Wolff-Kishner reduction of the formylation product viz.



27 26

(a) $POCl_3$-$HCON(CH_3)_2$; (b) NH_2NH_2-KOH/DEG; (c) malic acid/conc.H_2SO_4.

Scheme 3.6

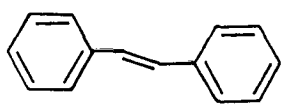
2,4-dimethoxybenzaldehyde. The spectral data (IR, ^{1}H NMR) recorded on 27 were consistent with the structure. Heating of 27 with malic acid in presence of conc. H_2SO_4 at 100^0 for 2 hours followed by usual workup and chromatography yielded a crystalline substance, m.p. $132-34^0$ which was found to be identical in all respects with 6-methyl-7-methoxycoumarin 26. It may be noted that the yield (1.3%) of the final step was not good but the present synthesis is shorter and can be considered as further modification of the Pechmann coumarin synthesis. We did not make any efforts to optimise the experimental conditions in order to improve the yield but we believe that further studies with different aryl ethers and malic acid using conc. H_2SO_4 as a catalyst would prove fruitful. The major portion of the reaction is bicarbonate soluble and still remains to be characterised.

SECTION FOUR

REVISED STRUCTURE OF ALBOCTALOL, AND SYNTHESIS OF ITS OCTAMETHYL ETHER.

Stilbenoids represent a small group of natural products which include the parent hydrocarbon E-stilbene 28, its hydroxylated derivatives and their oligomers. Some of these hydroxylated stilbenes are isoprenylated. Bibenzyls, phenyldihydroisocoumarins and phenanthrols are also included in this group.

Besides the unsubstituted E-stilbene 28 which is known to occur in *Alnus sieboldiana*[35,36] and *Petiveria alliacea*[37], its oxygenated derivatives in the form of free hydroxyls or O-glycosides are of common occurrence and over thirty such compounds have been fully characterised. One of the most common hydroxylated stilbene is resveratrol 29 [(E)-3,4',5-trihydroxystilbene] a phytoalexin isolated from grape wine (*Vitis vinifera*)[38] and the groundnut (*Arachis hypogea*)[39]. Isoprenylated resveratrol 30 is known to be a constituent of *Arachis hypogea*[40]. In recent years resveratrol 29 and its oligomers have received considerable attention because of their antibacterial



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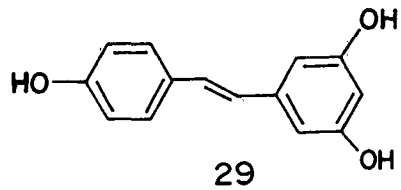

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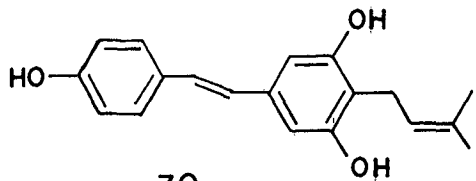
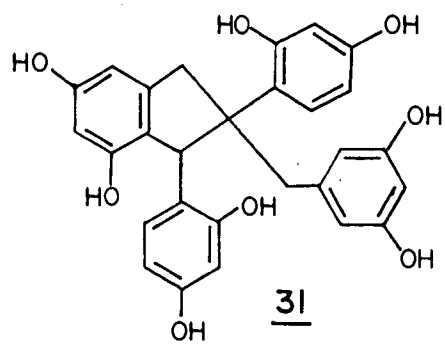


30

and antifungal[41] activities. During the past 40 years, dimers, trimers and tetramers of resveratrol have been fully characterised. Some representative structures belonging to stilbenoids are presented in Chart 3.1.

In 1976, Deshpande et al.[42] reported the isolation and characterisation of several interesting and novel constituents of Morus alba(family Moraceae). Among these, the structure 31 assigned to the optically active polyphenol, alboctalol attracted our attention for two reasons, i) its proposed biogenetic origin (Scheme 3.7) involving pinacol type coupling of hydroxylated deoxybenzoin 32 and further acid catalysed transformations, ii) oxyresveratrol 33 is present in large quantities in the heartwood of Morus alba and the molecular weight, 488 of alboctalol is exactly double that of oxyresveratrol 33.



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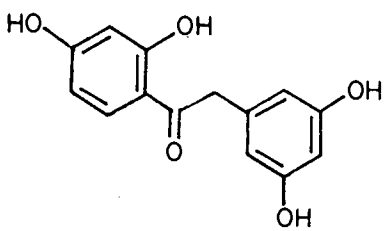

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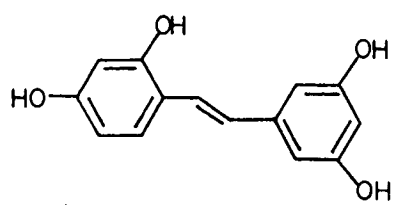

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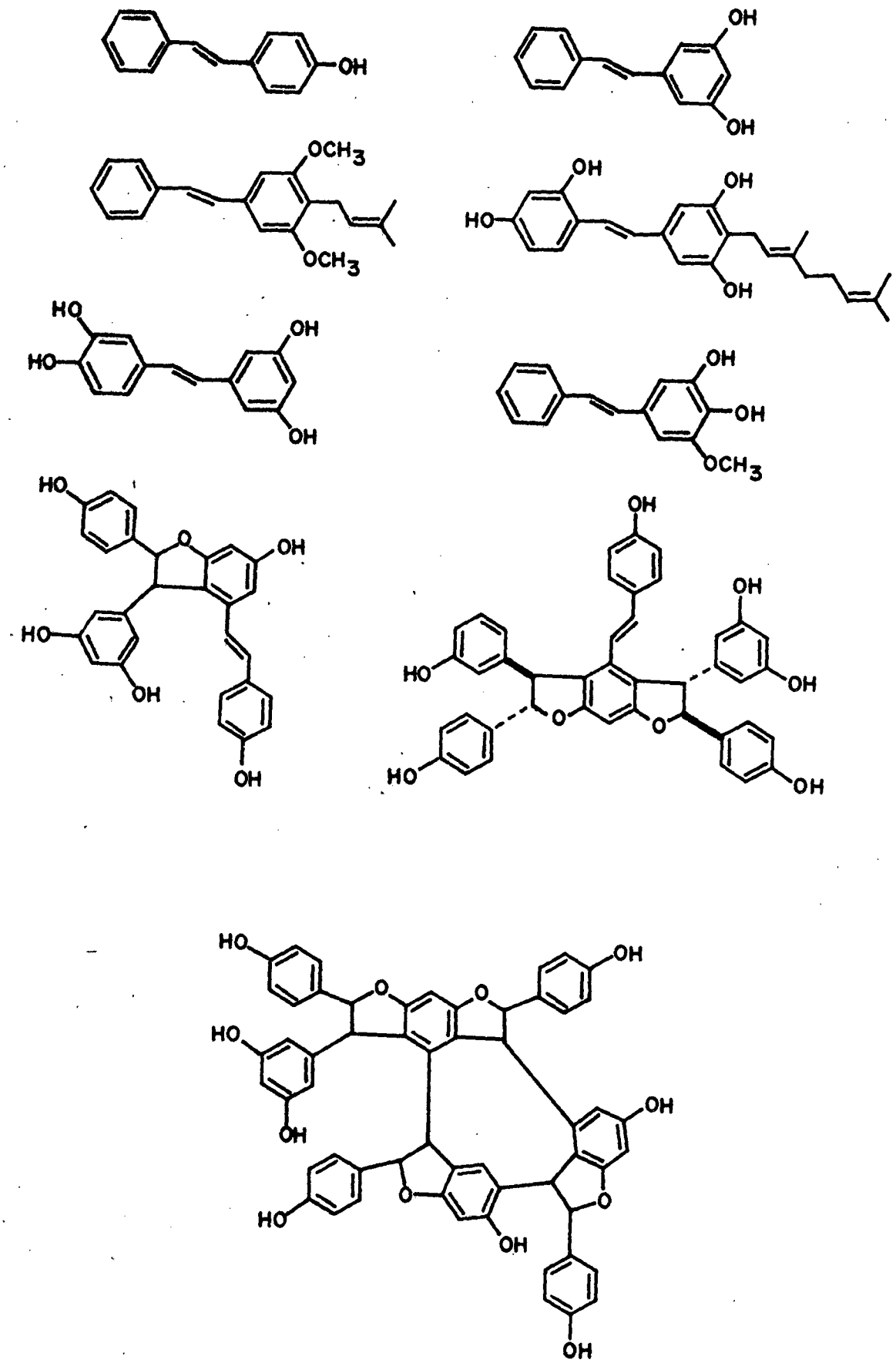
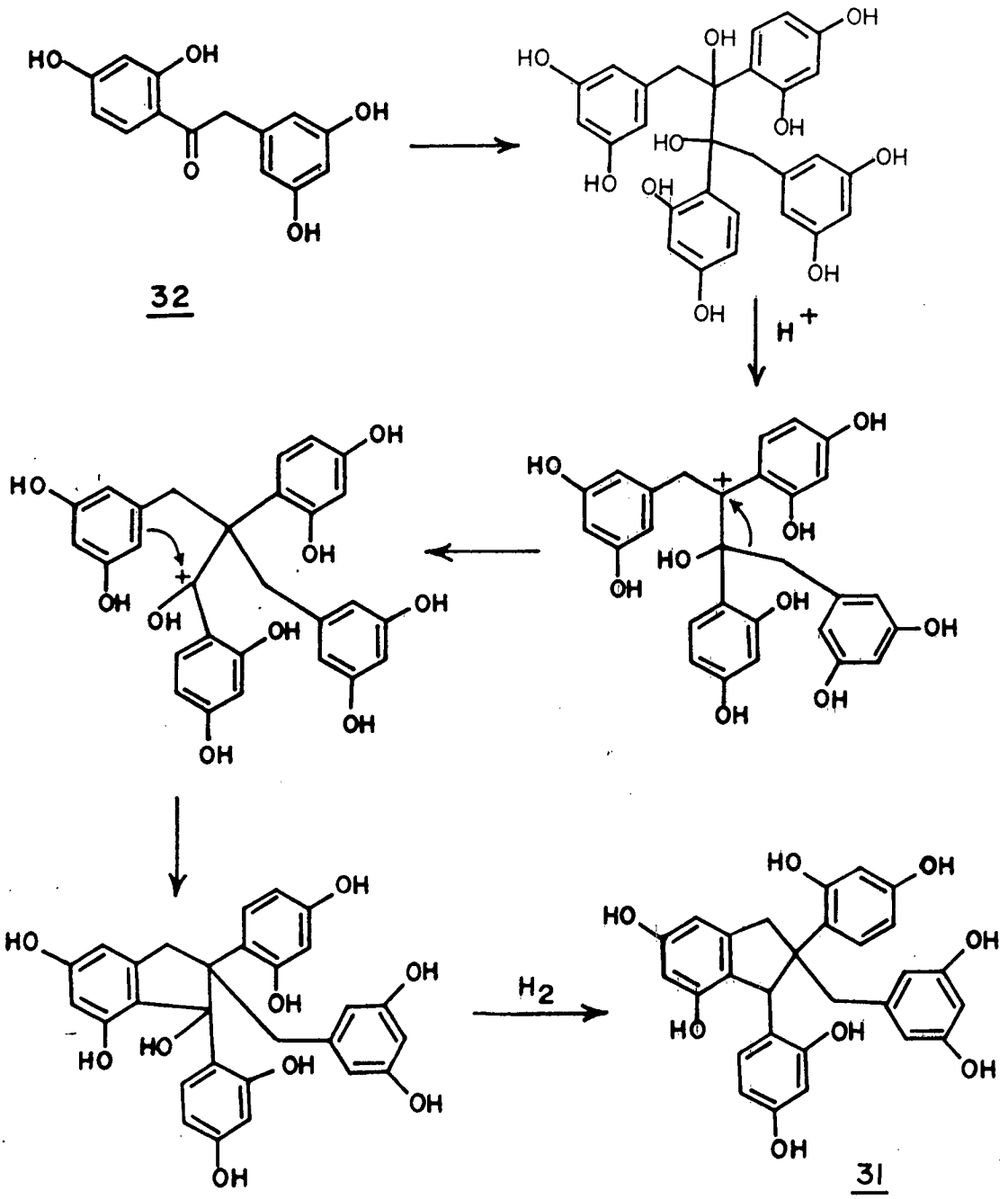


Chart 3.1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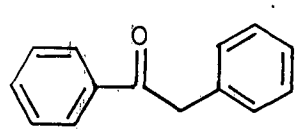
OH
31

Scheme 3.7

Our experience* showed that o-hydroxyacetophenone and its derivatives including benzyl phenyl ketone 34 when treated with Zn-HCl-ether at 0^{o} undergo intermolecular condensation via the radical anion intermediates which are transformed into further acid catalysed products.



34

Therefore, we realised that the biogenetic pathway proposed by Deshpande et al.[42] (Scheme 3.7) could be simulated in the laboratory if we treat hydroxylated benzyl phenyl ketone 32 with Zn-HCl-ether at 0^{o}. The outcome of this simple experiment would then be a biomimetic synthesis of a product, structurally related to alboctalol 31. We also realised that the proposed reduction in the ultimate step (Scheme 3.7) would not be possible under our experimental conditions but the desired intermediate product if obtained could be transformed into alboctalol by using standard reactions. This attractive possibility of achieving a biomimetic synthesis of alboctalol led us to study its reported chemistry[42] in greater detail.

Alboctalol, itself, could not be isolated in pure form but was purified via formation of its octamethyl ether derivative, $C_{36}H_{40}O_8$

* details are given in Chapter 2 of this thesis.

(M^+ 600), m.p. 168-9°, $[\alpha]_D$ +8.13°($CHCl_3$). It also gave a crystalline acetate, $C_{44}H_{40}O_6$, m.p. 143-45° (benzene : hexane).

The ^1H NMR spectral data collected on the octamethyl ether and octaacetyl derivative obtained from natural alboctalol are reported in Table 3.4*

Careful scrutiny of the spectral data along with the co-occurrence of oxyresveratrol 33 in substantial amounts raised certain doubts about the correctness of the assigned structure. Moreover, the positions of the hydroxyl groups rested totally depended on biogenetic considerations and hence the assigned structure 31 requires further support through additional spectral analysis and, if possible, by synthesis.

Since the dimers, trimers and tetramers of resveratrol are known[43] to be natural products (Chart 3.1), it appeared probable to us that alboctalol isolated by Deshpande et al. would turnout to be a dimer of oxyresveratrol 33. This consideration received further support from the observations of Battersby and Binks[44] who found that 3,4,3',4'-tetramethoxystilbene 35 forms a dimer 36 when heated under reflux with phosphoric anhydride in toluene. Moreover, the preparation and natural occurrence of dimers 40, 41,

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* Reported in the Ph. D. thesis of Smt. P. V. Wakharkar, University of Poona, 1974. We thank Dr. V. H. Deshpande for the xerox copies of the relevant part of the thesis.

Table 3.4

NMR spectrum of alboctaloloctamethylether in $CDCl_3$.

Chemical shift	Multiplicity	No of H	Assignment
3.37-3.83	not resolved	9	aromatic
4.25.4.3	meta coupled doublet J=2 cps or 2 singlets	2	aromatic
5.17	singlet	1	-CH
6.2-6.65		24	$-OCH_3)_8$
7.15-7.35	m	4	$-CH_2)_2$

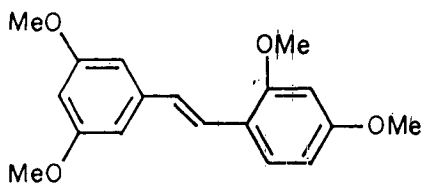
NMR spectrum of alboctaloloctaacetate in $CDCl_3$

3.05-3.5	m (n.r.)	9	aromatic
3.85	meta coupled d J=2 cps or 2.5	2	aromatic
5,45	s	1	-CH
6.7-7.1	2m.	4	$-CH_2)_2$
7.7-8.4		24	$-COCH_3)_8$

Alboctaloloctamethylether in $CDCl_3$ $-OCH_3$) at	Alboctaloloctamethylether in benzene $-OCH_3$) at
6.2	6.44
6.22	6.52
6.3	6.6
6.4	6.78
6.55	6.85
6.6	----

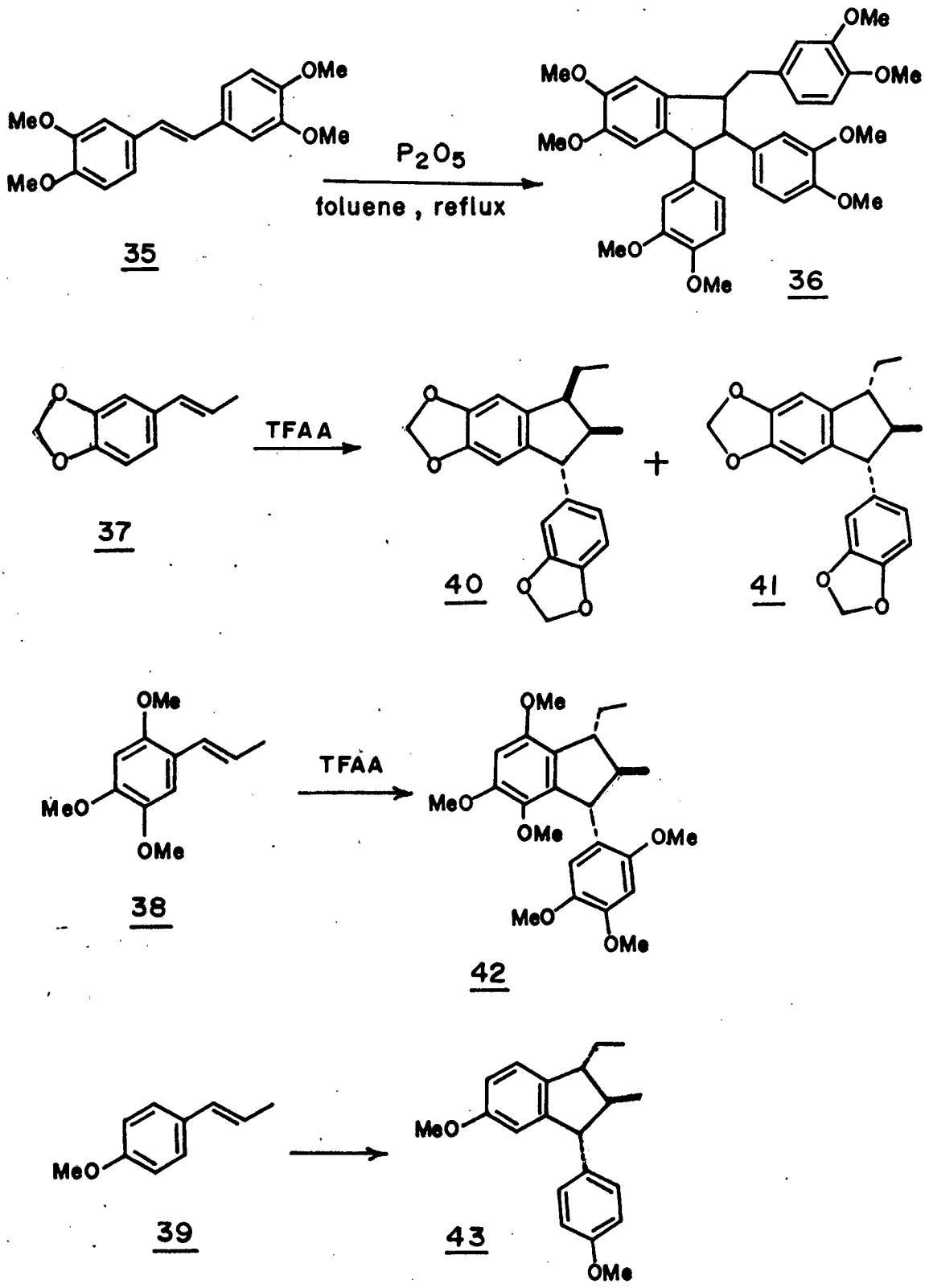
42 & 43 of aryl propenes such as isosafrole 37[45], asarone 38[45] and anethole 39[46] have been well established (Chart 3.2). We therefore considered it worthwhile to inspect the published data in terms of a dimeric oxyresveratrol structure for alboctalol. Since the octamethylether and octaacetyl derivatives are well characterised, we chose to study the dimerisation of the tetramethyl derivative of oxyresveratrol 33 following the conditions reported by other investigators[44-46].

For the present study we required authentic samples of alboctaloloctamethylether and tetramethylether of E-2,4,3',5'-tetramethoxystilbene 44



44

(oxyresveratrol tetramethylether) as reference samples. As mentioned earlier, the isolation and structure assignment of alboctalol was reported in 1976 and the availability of these reference materials was rather doubtful. Fortunately, Dr.Deshpande had preserved the samples and though only crude impure alboctalol was available, oxyresveratroltetramethylether still remained in a highly crystalline form and showed no deterioration after 16 years. Availability of these samples made our job easier and eventually led us to the correct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37
40
41
TFAA
38
42
39
43

Chart 3.2

structure assignment of alboctaloloctamethylether and its synthesis by acid catalysed dimerisation of oxyresveratroltetramethylether.

The crude alboctalol (50 mg) was subjected to methylation using dimethyl sulphate and NaOH. The methylated product on chromatography over silica gel afforded a crystalline solid (10 mg), m.p. 168-69^0 (benzene : petroleum ether)(lit.[42] 168-69^0). The IR spectrum of this material matched perfectly with the one recorded earlier on alboctaloloctamethylether. The compound was then subjected to spectral analysis and the outcome of these experiments is presented below.

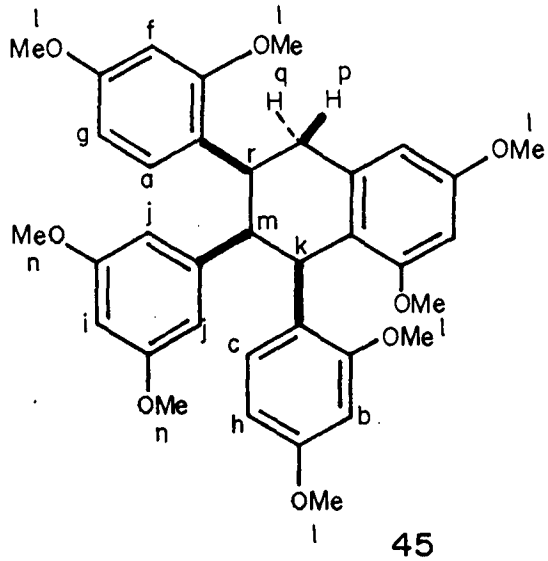
The 300 MHz ^{1}H NMR spectrum (Fig 3.7) of alboctaloloctamethylether obtained during the present study not only confirmed most of the previous observations but it was possible to make assignments (Table 3.5) for all the protons as the signals were well separated and suggested that the previous assignments needs revision. The observed one proton singlet at 4.84 was previously assigned to the doubly benzylic methine with neighboring carbon fully substituted and the remaining four aliphatic protons (2.7 to 3.3 region) were not resolved properly and considered to be due to two methylene groups. The present reinvestigation showed that the five aliphatic hydrogens belong to the saturated part of a substituted tetralin having dimethoxyphenyl substituents in the 5, 6 and 7 positions. The doubly benzylic methine at C_5 appears as

Table 3.5

^1H NMR Chemical shifts of alboctaloloctamethylether, $CDCl_3$

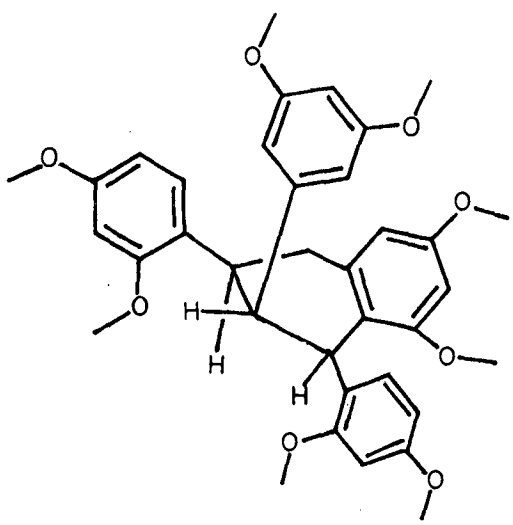
Chemical shifts	multiplicity (J in parenthesis)	No of hydrogens	Assignment
2.64	dd (16.8,4.1)	1	q
2.85	dd (16.8,14.4)	1	p
3.27	d (2.9)	1	r
3.39	s	3	l
3.46	s	6	n
3.60	s	3	l
3.72	m	1	m
3.73	s	3	l
3.79	s	3	l
3.80	s	3	l
3.83	s	3	l
4.84	s	1	k
5.74	d (2.3)	2	j
6.20		1	i
6.27	dd (8.4,2.4)	1	h
6.33	dd (8.4,2.4)	1	g
6.34	d (2.4)	1	f
6.35	d (2.5)	1	d or e
6.36	d (2.5)	1	d or e
6.46	d (8.4)	1	c
6.54	d (2.4)	1	b
6.56	d (8.4)	1	a

a singlet, as the dihedral angle between C_5-H (designated as k, structure 45) and C_6-H (designated as m) is 90°. The multiplicity and coupling constants observed for hydrogens designated as m, r , p and q showed that all the three dimethoxyphenyl substituents are cis to each other indicating the stereo structure 45



45

for alboctaloloctamethylether. Examination of a molecular model of 45 suggested that all the data fits well with the conformational structure 46 for alboctaloloctamethylether. This also explains the



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observed shielding of the aromatic hydrogen (j, Table 3.5) and methoxy group of the dimethoxyphenyl ring attached to C_6 of the basic tetralin skeleton.

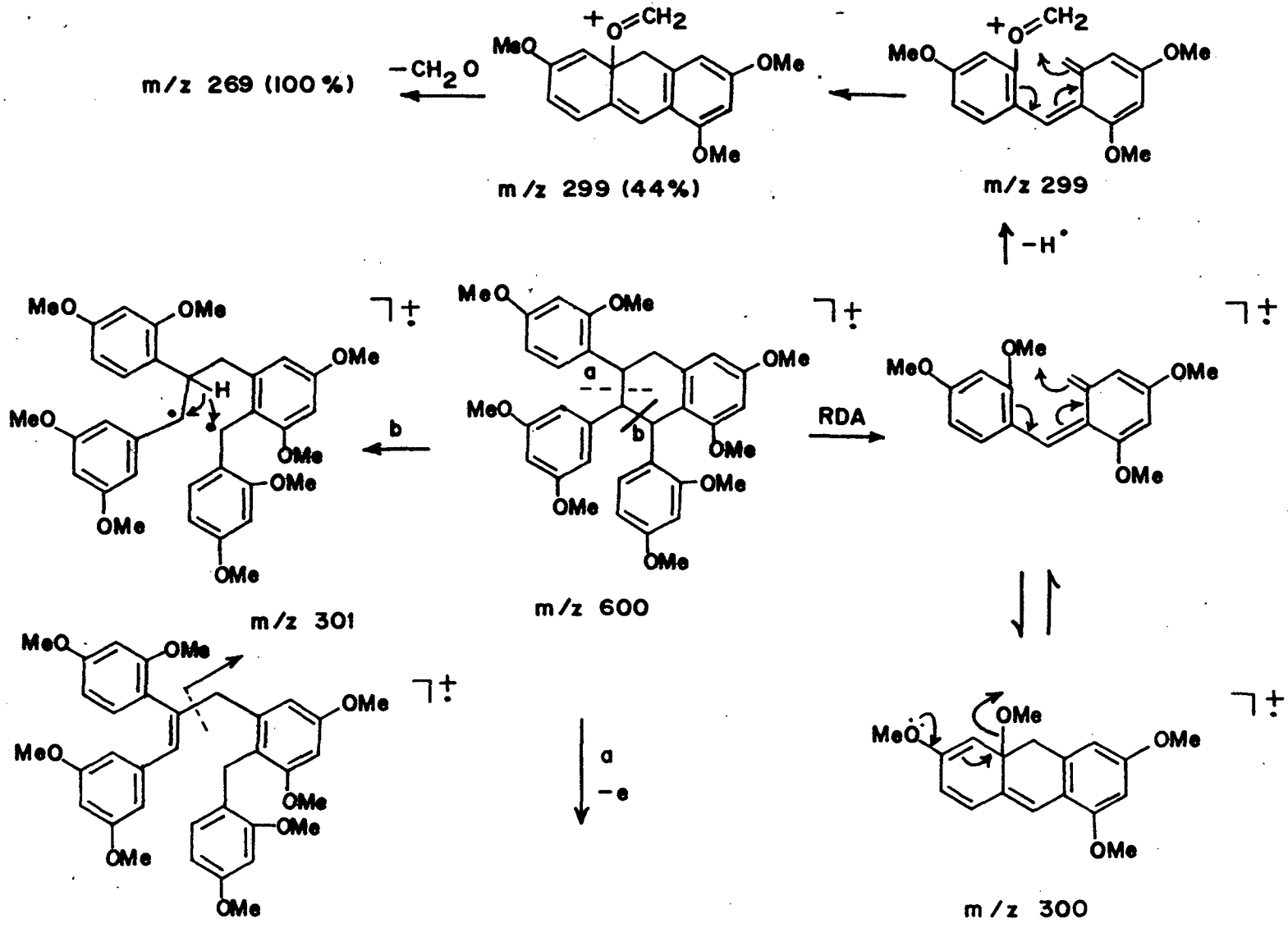
The ^{13}C NMR spectrum (Fig 3.8) of alboctalol-octamethylether, which has not previously been reported showed quartets at 54.8, 55.0, 55.2, 55.3, 56.6 and 57.7 ppm of which the signals at 54.8 and 55.3 were of double intensity indicating overlap of the signals and accounted for eight methoxy groups. The lone triplet at 29.9 ppm clearly indicated the presence of only one methylene group. In all twelve doublets were observed at 31.0, 37.9, 48.0, 97.0, 98.1, 98.3, 98.4, 102.8, 104.3, 107.1, 128.1 and 129.2 ppm. The first three of these corresponded to benzylic $>C-H$ (C_7,C_6 and C_5 respectively) and the remaining belong to the aromatic carbons bearing a hydrogen atom. It also showed ten singlets due to quaternary carbons at 119.3, 125.0, 128.8, 140.6, 145.0, 157.7, 157.9, 158.5, 158.6 and 159.2. The last five signals have been assigned to the quaternary carbon atoms carrying methoxy substituents and since only five and not eight are observed, again at least three of them correspond to two quaternary carbons. The most important feature of the ^{13}C NMR spectrum of alboctaloloctamethylether is the presence of only one triplet and not two as expected for the previously assigned structure and therefore raise doubts about its correctness.

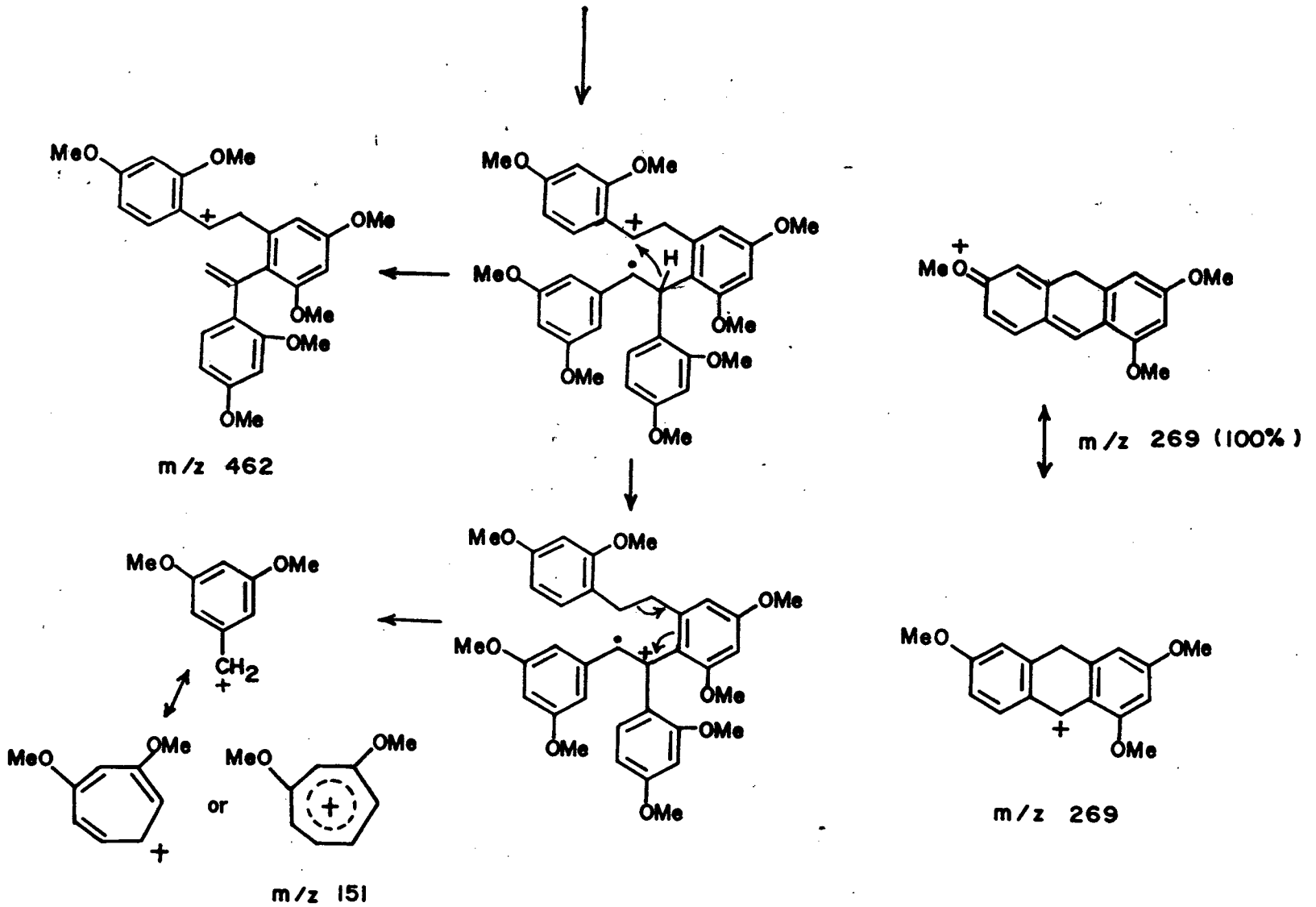
The ^{1}H and ^{13}C NMR spectra conclusively established the structure of alboctaloloctamethylether including its stereochemistry as shown in 45. Moreover, the mass spectral fragmentation pattern can easily be interpreted in terms of structure 45. The possible mode of major fragmentation and the likely structures for the major fragment ions are shown in Scheme 3.8.

Having established the structure of alboctaloloctamethylether as shown in 45 and the previous reports on the dimerisation of 3,4,3',4',-tetramethoxystilbene 35, and aryl propenes isosafrole 37, asarone 38 and anethole 39, we envisaged a straightforward synthesis of 45 by acid catalysed dimerisation of E-2,4,3',5'-tetramethoxystilbene 44. Mechanistically, this acid catalysed dimerisation looked very attractive, particularly due to the expected participation of the properly substituted aromatic methoxy groups in stabilising the intermediate carbocations. (Scheme 3.9)

There are several known methods for the synthesis of symmetrical and unsymmetrical stilbenes. These methods are reviewed by Becker[47]. There are five[48-52] more reports of the methods of stilbene synthesis since the appearance of Backer's review.

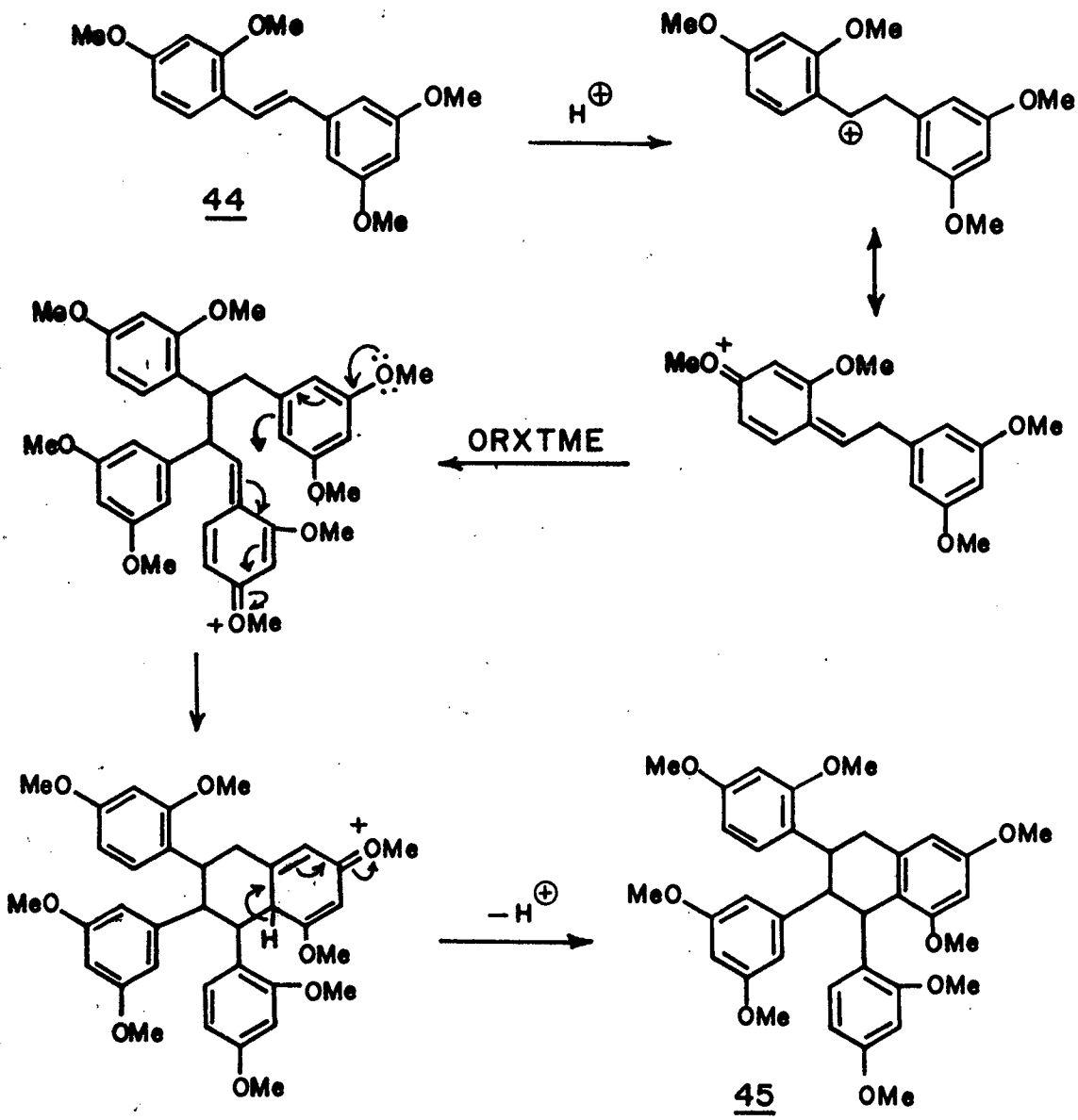
The commercially available 3,5-dihydroxybenzoic acid 47 was selected as a starting material and was converted into the desired intermediate 3,5-dimethoxy methyl benzoate 48 by methylation with dimethyl


m/z 269 (100 %)
−CH2O
m/z 299 (44%)
m/z 299
−H•
m/z 301
b
m/z 600
a
b
RDA
m/z 300
a
−e



Mass spectral fragmentation of albactalol octomethyl ether 45

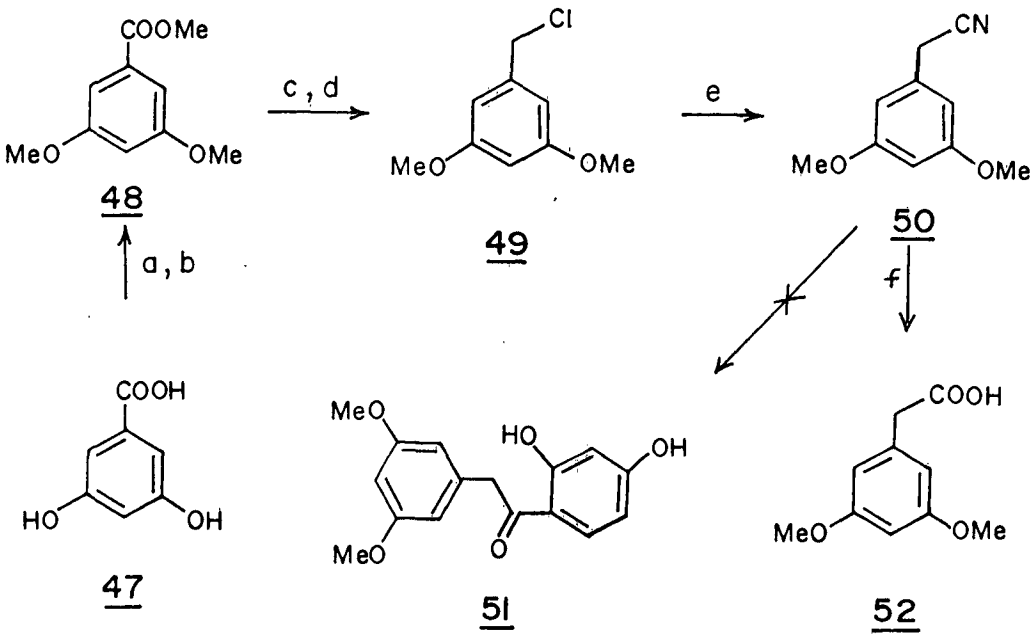
Scheme 3.8



★ ORXTME – Oxyresveratroltetramethyl ether

Scheme 3.9

sulphate in the presence of NaOH followed by Ficher esterification with MeOH, conc. H_2SO_4. The product had spectral data consistent with its structure. The ester 48 was transformed into 3,5-dimethoxybenzyl chloride 49 which afforded 3,5-dimethoxybenzyl cyanide* on reaction with KCN in aqueous EtOH. The reaction of 3,5-dimethoxybenzyl cyanide with resorcinol in the presence of $HCl/ZnCl_2$, ether at 0^0 [53] did not produce the desired acylated resorcinol derivative 51 but resulted in the formation of 3,5-dimethoxyphenylacetic acid 52, m.p. 104^0 (lit.[54] $102-3^0$) (Scheme 3.10).



(a) $(CH_3)_2SO_4$, NaOH; (b) CH_3OH, H_2SO_4; (c) $LiAlH_4$/ether; (d) $SOCl_2$, pyr/ether; (e) KCN/aq EtOH; (f) Resorcinol, $ZnCl_2$, HCl gas/ether.

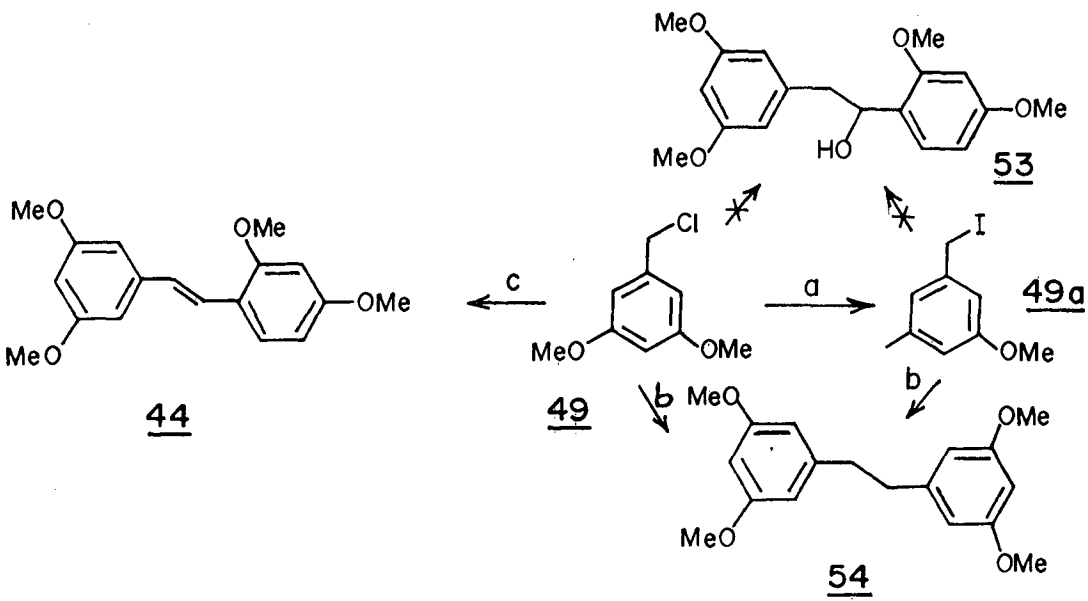
Scheme 3.10

---

* The spectral data obtained (for details see experimental) was consistent with its structure.

Evidently under the experimental conditions used the nitrile 50 had hydrolysed.

The addition of an aryl Grignard compound to an aromatic aldehyde followed by dehydration of the resulting alcohol is one of the known methods[47] of stilbene synthesis. The Grignard reagent prepared from 3,5-dimethoxybenzyl chloride with Mg in dry ether was reacted with 2,4-dimethoxybenzaldehyde and the reaction product worked up in the usual manner. Chromatography over silica gel yielded a crystalline compound in the initial fractions and was found to be the major product. The product, m.p. 93-95^{0} was not the desired alcohol 53 but was shown by spectral analysis to be 1,2-bis-(3,5-dimethoxyphenyl) ethane 54 (Scheme 3.11).



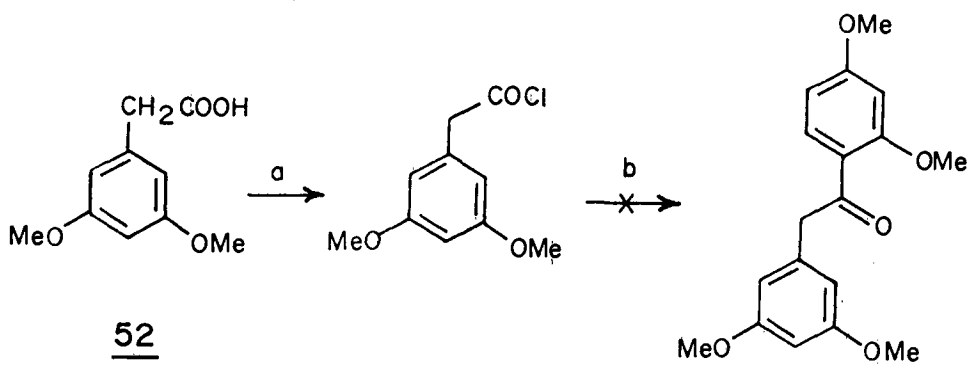
(a) NaI/CH_3COCH_3; (b) 2,4-dimethoxybenzaldehyde,Mg/ether

(c) Ph_3P,K-tert butoxide, 2,4-dimethoxybenzaldehyde/ethe

Scheme 3.11

The compound 54 is evidently formed by dimerisation of 3,5-dimethoxyphenylmagnesium chloride. Such Wurtz coupling condensations have been reported[55-57] before and various instances are known where it was found to be the major, if not the exclusive reaction pathway. The Grignard reagent prepared from 3,5-dimethoxybenzyl iodide and its reaction with 2,4-dimethoxybenzaldehyde also resulted in the formation of 54 (Scheme 3.11).

3,5-Dimethoxyphenylacetic acid 52 obtained earlier as an undesired product was converted into the corresponding acid chloride by reaction with $SOCl_2$ and was immediately reacted with 1,3-dimethoxybenzene in the presence of anhydrous aluminum chloride using nitrobenzene as a solvent (Scheme 3.12). Once again the



52

(a) $SOCl_2$, pyr/ether; (b) 1,3-dimethoxybenzene, anhydrous $AlCl_3$/nitrobenzene.

Scheme 3.12

reaction did not proceed as desired and the only product which could be characterised was 3,5-dimethoxyphenyl acetic acid, evidently formed by hydrolysis of

the acid chloride during workup. Failure of this simple and straight-forward Friedel-Crafts acylation reaction cannot be explained except for doubting the quality of the $AlCl_3$ used.

After making several unsuccessful attempts to synthesize the seemingly simple 2,4,3',5' tetramethoxy stilbene 44 required for the synthesis of alboctaloloctamethylether 45, finally we met with success, this time by the reaction of Wittig reagent prepared from 3,5-dimethoxybenzyl chloride and 2,4-dimethoxybenzaldehyde (Scheme 3.11). The reaction product was a mixture (TLC) but availability of the reference material helped us to obtain the desired compound by column chromatography. The product obtained was a crystalline material, m.p. 83-84^0 (lit.[58] 84^0) and was found to be identical in all respects with 2,4,3',5'-tetramethoxy stilbene 44.

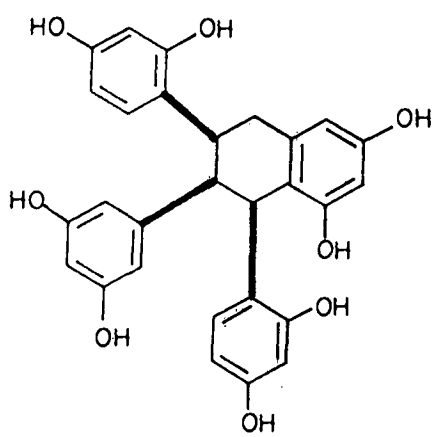
Several experimental procedures are available for the dimerisation[44-46] of stilbenes. However, none of the reported experimental procedures when used for 44 gave us alboctaloloctamethylether 45. Since only a limited quantity of 44 was available, each time the reaction was carried out with only few mg and the reaction was monitored by TLC using the reference target molecule. When 44 was kept in contact with dry ether saturated with dry HCl for 4 hours at 0^0 a spot corresponding to the target molecule finally appeared. Repetition of the reaction with a somewhat larger quantity of 44 (200 mg)

followed by column chromatography afforded a crystalline compound, m.p. 168^{0} (4.0%) which was proved to be identical with alboctaloloctamethylether (IR, ^{1}H & ^{13}C NMR spectra). We have not made any efforts to characterise other products of this reaction.

By this successful synthesis, we have conclusively demonstrated that alboctalol 55 is a dimer of oxyresveratrol 33 as anticipated at the outset of this reinvestigation.

Biogenesis

Alboctaloloctamethylether 45 prepared by methylation of alboctalol with dimethyl sulphate and NaOH is reported to be optically active, $[\alpha]_{D}$ +8.13^{0} (c,0.53% in $CHCl_3$). It therefore follows that alboctalol 55 itself must be optically active. However, the biogenesis of alboctalol 55 involves dimerisation of oxyresveratrol 33, then alboctalol should be optically inactive. The observed optical activity would then indicate that the



55

biogenesis of alboctalol does not involve acid catalysed dimerisation of oxyresveratrol 33. Though we do not have any proof or even an indirect support by way of a report on the isolation of an optically active derivative of oxyresveratrol 33, it is tempting to propose a logical explanation which would account for the observed optical activity of alboctalol 55. Since a number of glycosidic stilbenes occur naturally (Chart 3.3) we believe that the optical activity of alboctalol is due to enzyme catalysed * dimerisation of

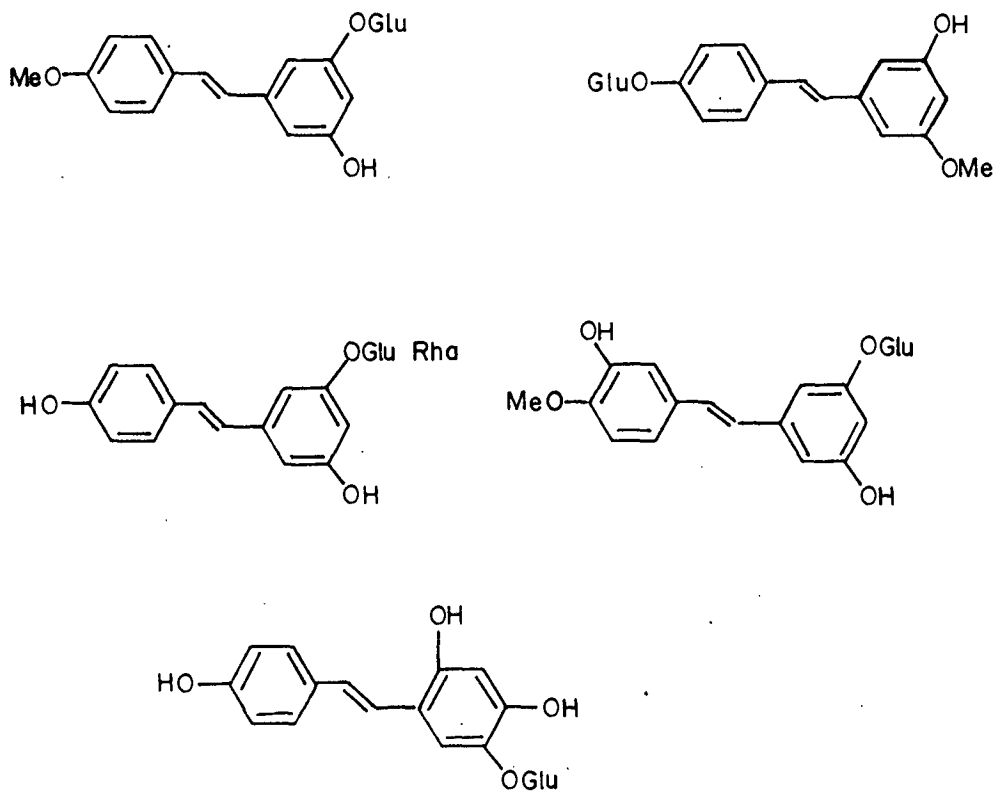
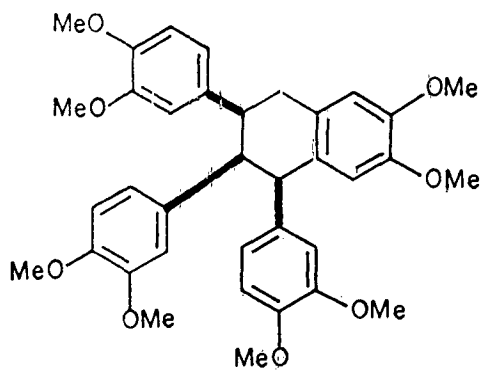


Chart 3.3

* Involving either ionic or radical intermediates.

a glycosidic derivative of alboctalol followed by enzymic hydrolysis. Dimerisation results in the creation of three chiral centers and hydrolysis of the glycosidic linkage (after dimerisation) would then afford the optically active alboctalol. The stereochemistry shown in 55 is only relative and the absolute configuration remains to be established.

While 3,4,3′,4′-tetramethoxystilbene 35 can give an aryl indane dimer 36 as suggested by Battersby and Binks;[44] there is every possibility of dimerisation analogous to what we observed in the case of acid catalysed dimerisation of 2,4,3′,5′-tetramethoxystilbene 44 to alboctaloloctamethylether 45 (Scheme 3.9) and Battersby's dimer may have a alternative structure 56. It may be noted that no NMR spectra were recorded on Battersby's dimer and it seems worthwhile to obtain the dimer again in order to ascertain the structure beyond doubt.



56

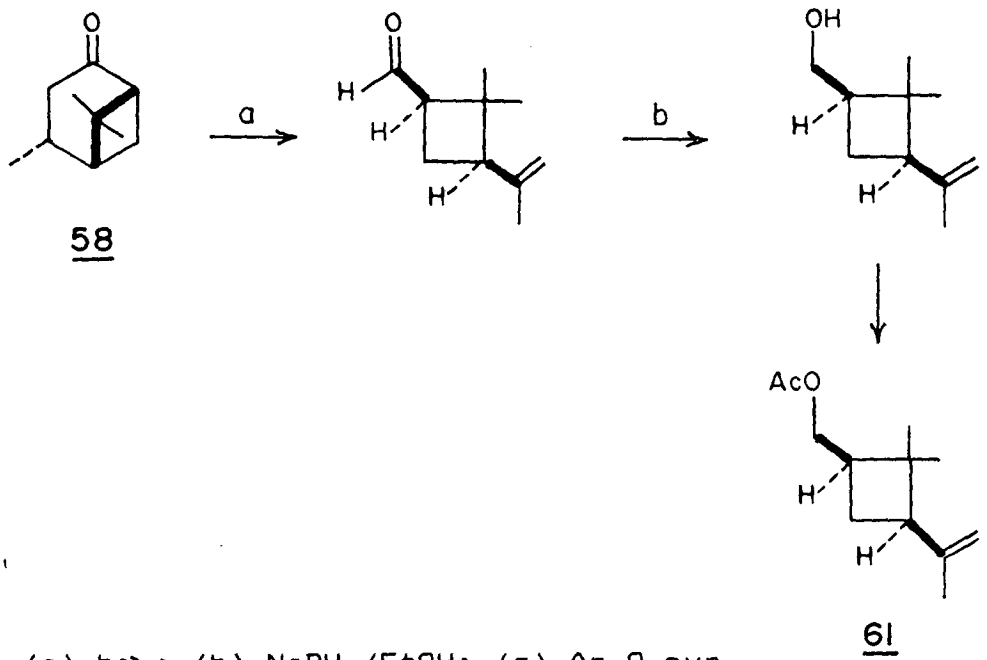
SECTION FIVE

INVESTIGATIONS TOWARDS SYNTHESIS OF CIS-PLANOCOCCYL ACETATE.

In 1981, Bierl-Leonhardt and co-workers[59] isolated the sex pheromone of the citrus mealybug Planococcus citri (Risso) and identified it as (+)-(1R)-cis-2,2-dimethyl-3-isopropenylcyclobutanemethanol acetate 61. This pheromone is commonly known as (+)-cis-planococcyl acetate and known to damage several crops and, more importantly, damage citrus fruits. The field tests[60-63] showed that planococcyl acetate is a potent attractant for the male insect and if available in quantity, may serve as an insecticide to control this pest. The efforts made in synthesising this sex pheromone are therefore understandable.

The four membered ring with a gem-dimethyl substituent is the main structural feature of planococcyl acetate 61 and the previously known synthesis makes use of (+)-α-pinene 57 as the starting material. (+)-Verbanone 58[64-66] obtained from (+)-α-pinene was transformed into planococcyl acetate 61 (Scheme 3.13).

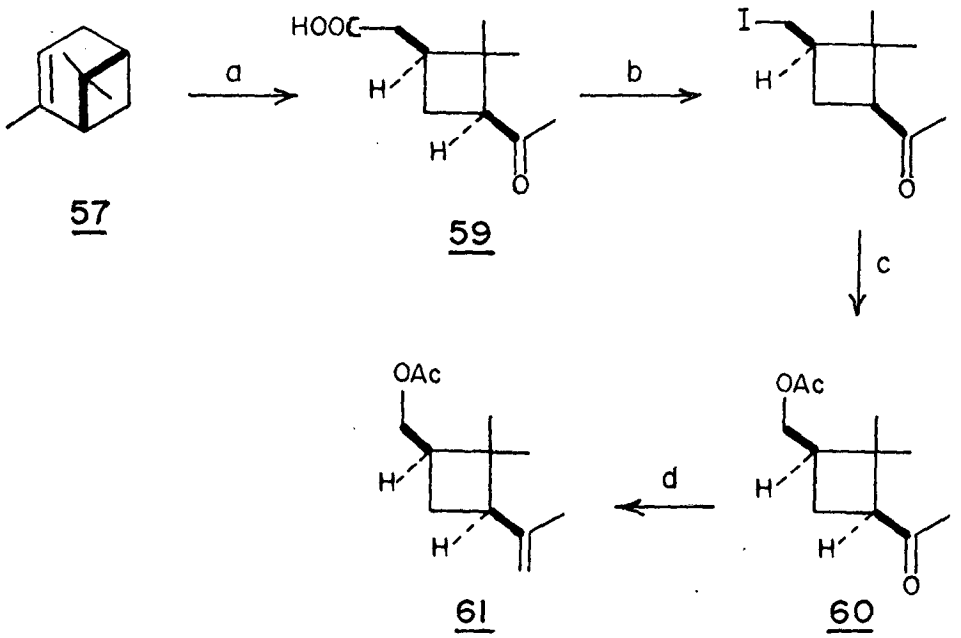
Wolk and Goldschmidt[67] reported a short stereoselective synthesis of 61 based on oxidative decarboxylation of (+)-cis-pinonic acid 59 by a Cristol-Firth variation of the Hunsdiecker reaction[68-70]. This synthesis is certainly very attractive and involves only four steps from the commercial available α-pinene 57 (Scheme 3.14). Based on our experience with oxidative decarboxylation[71] of carboxylic acids with lead



58 61

(a) hν ; (b) $NaBH_4$/EtOH; (c) Ac_2O,pyr.

Scheme 3.13



57 59 60 61

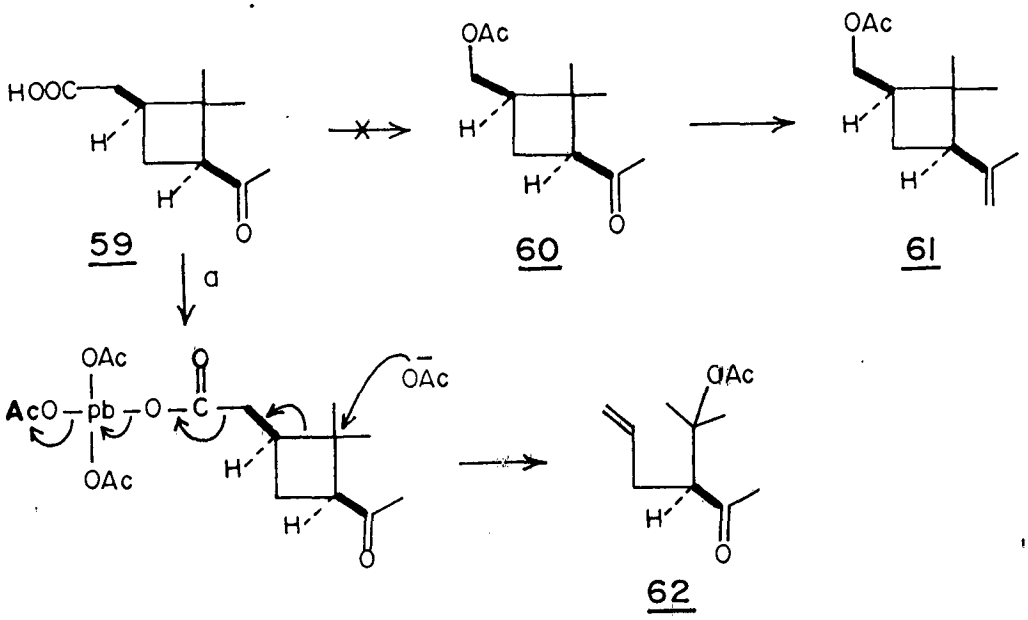
(a) $KMnO_4$,$(NH_4)_2SO_4$/H_2O; (b) I_2,HgO,hν /CCl_4;

(c) $(H_3C)_4NOAc$/DMF; (d) $(C_6H_5)_3P{=}CH_2$,n-BuLi/THF.

Scheme 3.14

tetraacetate, we envisaged a short and alternative

synthesis of (+)-planococcyl acetate 61 via cis-pinononyl acetate 60 as shown in Scheme 3.15.



(a) $Pb(OAc)_4$, Cupric acetate, pyr/benzene.

Scheme 3.15

(+)-cis-Pinonic acid 59 was obtained in good yield by $KMnO_4$ oxidation of α-pinene 57 following the literature procedure[67]. Kochi decarboxylation[72] of 59 gave a mixture of three products (TLC) and the IR spectrum of the crude product showed the presence of an acetoxyl function (band at 1735 cm^{-1}) as well as the aliphatic carbonyl of the starting material (1715 cm^{-1}). Sharp bands at 3080, 1640, 990 and 910 cm^{-1} indicated the unsaturated monosubstituted olefinic linkage. Attempted isolation of individual components was not totally successful but the major compound could be isolated and characterised as 62. Its IR spectrum (Fig 3.9) showed bands at 1735 (acetoxy grouping), 1715 (methyl keto functionality). Sharp bands at 3080,

1640, 990 and 910 cm^{-1} showed the presence of monosubstituted olefinic linkage. Further support to these structural features came from its ^1H NMR which showed four singlets (3 protons each) at 1.48, 1.50 (acetoxy isopropyl), 1.98 ($-O-\overset{O}{\overset{\|}{C}}-CH_3$), 2.18 ($-\overset{O}{\overset{\|}{C}}-CH_3$), a one proton multiplate centered at 3.26 and a 3 proton multiplate in the region 4.9 to 5.8 ppm ($-CH=CH_2$).

The structural features derived from the above spectral data are consistent with the structure 62 for the major product. The formation of 62 can be rationalised mechanistically as shown in Scheme 3.15.

The IR spectrum of the second component, although not obtained in a high state of purity, was devoid of any bands due to olefinic linkage and was initially considered to be the desired cis-pinononyl acetate 60. However, nonidentity of the spectral data with those recorded on authentic 60* clearly showed that the second component is different from 60. It has not been possible to assign any structure to this product so far.

After studying the Kochi[72] reaction on cis-pinonic acid 59 reported in this section, we learnt from Prof. Goldschimdt that this reaction had been studied by this group independently but in view of not obtaining the desired intermediate, 60 they did

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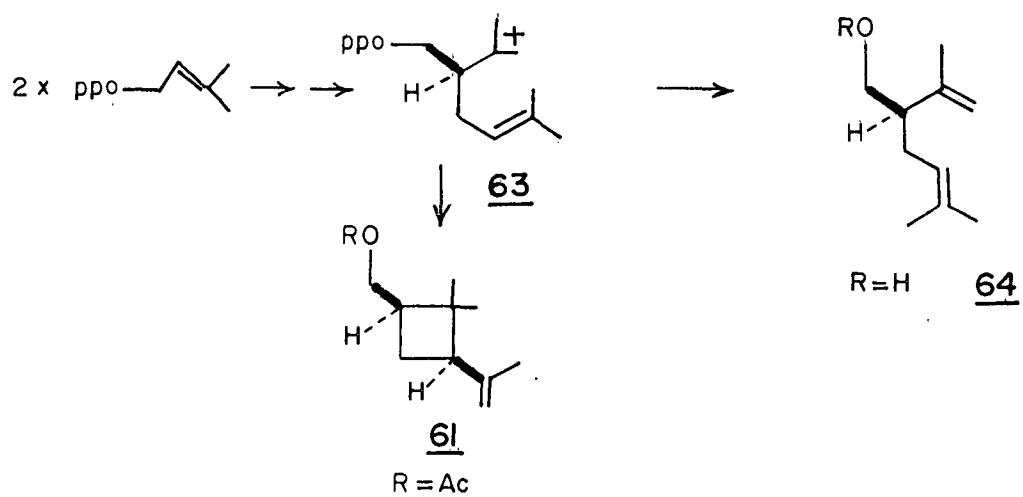
* Copies of IR and ^1H NMR of 60 were kindly made available by Prof. Goldschimdt.

not further study the reaction in spite of having spectral data (^{1}H NMR) of the products formed. It is of interest that their spectral data turned out to be identical to ours.

Though the structure assigned to cis-planococcyl acetate 61 has been confirmed by two independent syntheses, there is no reference to its biogenetic origin so far. The cyclobutane ring with a gem-dimethyl substituent, resembles the corresponding structural unit of α and β-pinene. However, we believe that cis planococcyl acetate 61 is biogenetically derived by cyclisation of the carbocation 63, which also is capable of producing lavandulol 64 and its acetyl derivative by proton elimination, hydrolysis and acetylation (Scheme 3.16). It would be of interest to attempt a biomimetic synthesis of 61 by generating the carbocation 63 from a suitable precursor.



Scheme 3.16

EXPERIMENTAL

Reactions of longifolene 1 with p-nitrobenzoic acid and picric acid.

General procedure

Varying amounts of p-nitrobenzoic acid were heated with longifolene 1 at different temperatures (Table 3.1). The dark brown liquid obtained in each case was extracted with ether. Combined ether extracts were washed with saturated $NaHCO_3$ followed by water and dried. After removing ether the resulting dark brown liquid was purified by using $AgNO_3$ impregnated silica gel for chromatography and subjected to GLC analysis.

Isolation of longicyclene 5

The reaction product obtained in the case of reaction of longifolene 1 with p-nitrobenzoic acid (Entry 2 and 3, Table 3.1) was chromatographed over $AgNO_3$ impregnated silica gel (20%). Elution of the column with petroleum ether furnished longicyclene 5 besides unchanged logifolene 1.

IR, Neat, (Fig 3.1), bands at:

3150, 3000 (broad), 1500, 1420, 1405, 1320, 1210, 975, 885 and 770 cm^{-1}.

Similar reaction of longifolene 1 with picric acid, followed by chromatography and GLC analysis showed the presence of isolongifolene 6 and longifolene 1 (Entry 4, Table 3.1).

Preparation of diisopropoxyrisorcinol 17

Methanol (30 mL) was introduced into a two necked

round bottomed flask (100 mL) equipped with a reflux condenser and cooled in ice water. To this cold methanol, was added in small portions freshly cut sodium metal (1.39g, 0.055 moles). After complete dissolution of the metal, to the resulting sodium methoxide was added resorcinol (5.5g, 0.05 moles) in methanol (10 mL) followed by freshly distilled isopropyl bromide (9.0g, 0.075 moles) in methanol (10 mL). This mixture was refluxed gently in an oil bath for three hours, cooled and diluted with water (50 mL). The resulting solution was acidified with conc. HCl and extracted with ether (4 x 20 mL). The combined ether extracts were washed with water (2 x 15 mL), 2N NaOH (4 x 15 mL) followed by water (2 x 10 mL) and dried. Removal of ether gave a yellowish liquid (1.6g) which was eluted through a small silica gel column followed by distillation under reduced pressure to give colorless liquid 17; 1.2g; 21.80%.

IR, Neat, bands at:

2920, 2880, 1570, 1465, 1370, 1320, 1270, 1250, 1175, 1100, 1000, 935 and 675 cm^{-1}.

^{1}H NMR, $CDCl_3$, 90 MHz, signals at:

1.24 (6H, d, J = 6 Hz, $-CH-(CH_3)_2$),

1.26 (6H, d, J = 6 Hz, $-CH-(CH_3)_2$),

4.49 (2H, m, 2 X $-CH-(CH_3)_2$),

6.48 -6.62 (2H, m, Ar-H),

7.24 (1H, t, J = 8 Hz, Ar-H).

The alkali portion was acidified with conc. HCl and extracted with ether (4 x 20 mL). The combined ether

extracts were washed with water (2 x10 mL) and dried. Removal of ether furnished a dark brown liquid (2.692g) which upon distillation under reduced pressure furnished yellowish liquid (2.496g) which was identified as 3-isopropoxyphenol; 45.4%.

IR, Neat, bands at:

3425, 3020, 1640, 1530, 1500, 1320, 1180, 1020, and 710 cm^{-1}.

^1H NMR, $CDCl_3$, 60 MHz, signals at:

1.4 (6H, d, J = 6 Hz, $-CH(CH_3)_2$),

4.5 (1H , m , $-CH(CH_3)_2$),

6.2 (bs, 1H , -OH),

6.4 - 7.3 (4H, m , Ar-H).

Reaction of diisopropoxyresorcinol 17 with ethyl acetoacetate in cold conc. H_2SO_4.

Concentrated H_2SO_4 (5.6 mL) was cooled in ice-salt bath. To this cold acid was added dropwise with constant stirring a mixture of diisopropoxyresorcinol 17 (0.95g, 0.00559 moles) and freshly distilled ethyl acetoacetate (0.727g, 0.00559 moles) over a period of 40 minutes. After addition was complete the reaction mixture was stirred at room temperature for six hours and poured into crushed ice while stirring. The aqueous layer was extracted with $CHCl_3$ (4 x 15 mL). The combined $CHCl_3$ extracts were washed with saturated $NaHCO_3$ (3 x 10 mL) followed by water (2 x 10 mL) and dried. Removal of $CHCl_3$ gave a brown solid (0.634g) which was chromatographed over silica gel.

The fractions eluted with petroleum ether-benzene (50 : 50) followed by concentration gave a white solid, which on recrystallization from petroleum ether benzene mixture afforded 22; 0.22g; 23.15%; m.p. 174°.

IR, Nujol, bands at:

3438, 2922, 1704, 1602, 1563, 1376,1311, 1194, 1116 and 1052 cm^{-1}.

^{1}H NMR, CD_3OD, (Fig 3.5), 300 MHz,

^{13}C NMR , CD_3OD, (Fig. 3.6), 75 MHz

and

Mass spectrum. For assignments see Table 3.6.

Further elution of the column with petroleum ether benzene (40 : 60) followed by concentration gave a white solid which upon recrystallization from petroleum ether ethyl acetate mixture yielded 21; 0.13g; 13.7%; m.p. 226°.

IR, Nujol, (Fig 3.2), bands at:

3329, 2923, 1691, 1599, 1568, 1389, 1353, 1301, 1083, 1047 and 840^{-1}.

^{1}H NMR, CD_3OD, (Fig. 3.3), 300 MHz,

^{13}C NMR, CD_3OD, (Fig 3.4), 75 MHz

and

MASS spectrum. For assignments see Table 3.6.

Further elution of the column with ether followed by concentration gave a yellowish solid which upon recrystallization from a petroleum ether-ethyl acetate

Comp. and Structure	m. p.^{O}C and Mol.For	Mass m/z (%)	^{1}H NMR (CD_3OD)	^{13}C NMR (CD_3OD)
22, A	174^{O} $C_{16}H_{20}O_3$	260 (98.3) 245 (100) 203 (85) 175 (13.3) 128 (13.3) 115 (14) 77 (10.8) 43 (13.3)	1.27 (6H,d,J=7.0) 1.42 (6H,d,J=7.0) 2.44 (3H,s) 3.32 (1H,m) 3.71 (1H,m) 4.80 (1H,6s) 7.31 (1H,s)	164.04 (s, C_2), 111.18 (d, C_3) 156.62 (s, C_4 120.39 (d, C_5) 134.59 (s, C_6), 157.05 (s, C_7) 123.22 (s, C_8), 152.71 (s,C_9) 114.57 (s, C_{10}), 18.95 (q,C_4CH_3) 23.31 (2 x q, C_6 ipr CH_3) 28.11 (d,C_6 ipr$\underline{C}$H) 21.09 (2 x q, C_8 ipr$\underline{C}$H) 26.20 (d, C_8 ipr $\underline{C}$H)
21, B	226^{O} $C_{13}H_{14}O_3$	218 (32.5) 203 (100) 175 (13.7) 147 (6.2) 55 (8.7) 41 (10)	1.39 (6H,d,J=7.3) 2.41 (3H, s) 3.75 (1H,m) 4.78 (1H,bs) 6.09 (1H,d,J=8.6) 6.82 (1H,d,J=8.6)	162.95 (s,C_2) 110.99 (d, C_3) 155.70 (s,C_4) 121.34 (d, C_5) 114.26 (d,C_6), 160.30(s, C_7) 122.07 (s,C_8), 154.31 (s, C_9) 113.68 (s,C_{10}), 18.83 (q,C_4 CH_3 20.79 (2 x q ipr CH_3) 25.29 (d, ipr $\underline{C}$H)
19, C *	181^{O} $C_{10}H_8O_3$	176 (100) 176 (83.3) 120 (10) 91 (16.6) 65 (7.2) 39 (7.2),	2.41 (3H,d,J=1.02) 4.81 (1H,bs), 6.08 (1H, bs) 6.69 (1H, d, J=2.3) 6.81 (1H,dd,J=8.7,2.3) 7.57 (1H, D, J=8.7)	163.01 (s,C_2), 110.30 (d, C_3) 155.94 (s, C_4), 127.44 (d, C_5) 114.38 (d, C_6), 163.88 (s, C_7) 103.54 (d, C_8) 156.55 (s, C_9) 113.93 (s,C_{10}), 18.65 (q,C_4 CH_3)

^{1}H NMR, ^{13}C NMR and Mass spectral assignments of 19, 21 and 22.

* ^{13}C NMR spectral data on 19 has been recorded earlier[14].

Table 3.6

mixture gave 19; 0.038g, 4.0%, m.p. 180-81^{0} (lit.[15] 186^{0}).

^{1}H NMR, CD_3OD, 300 MHz,

^{13}C NMR, CD_3OD, 75 MHz

and

Mass spectrum. For assignments See Table 3.6.

Preparation of 2,4-dimethoxybenzaldehyde,

A mixture of 1,3-dimethoxybenzene (1.5g, 0.012 moles) and distilled N,N-dimethylformamide (1.22g, 0.016 moles) was cooled using ice salt mixture. To this cold mixture was added dropwise with stirring freshly distilled $POCl_3$ (2.46g, 0.016 moles) over a period of 0.5 hour. After complete addition of $POCl_3$ the mixture was heated in an oil bath at 110^{0} for six hours and poured into crushed ice while stirring. The separated solid was filtered, washed with water (5 x 15 mL) and recrystallized from petroleum ether to give white needles; 1.70g; 94.2%; m.p. 71-72^{0} (lit.[73] 71^{0}).

Preparation of 2,4-dimethoxytoluene 27

A mixture of 2,4-dimethoxybenzaldehyde (1.3g, 0.00783 moles), diethylene glycol (8 mL), hydrazine hydrate (0.8 mL) and KOH (1.044g) were introduced into a round bottomed flask (100 mL) fitted with a reflux condenser and warmed on a water bath till the KOH had completely dissolved. It was then refluxed on a heating mantal for six hours. The cooled reaction mixture was poured into water and extracted with ether (3 x 20 mL).

The combined ether extracts were washed with water (2 x 10 mL) and dried. Removal of ether gave a yellowish liquid (0.94g) which was eluted through a small silica gel column to afford a colorless liquid; 27; 70.7%.

IR, Neat, bands at :

3030, 2970, 2860, 1630, 1600, 1520, 1300, 1220, 1170, 1150 and 1060 cm^{-1}.

^{1}H NMR, $CDCl_3$, 60 MHz, signals at :

2.13 (3H, s, $-CH_3$),

3.78 (6H, s, 2 x $-OCH_3$),

6.3 (2H, s, Ar-H),

7.0 (1H, d, J = 8 Hz, Ar-H).

Reaction of 2,4-dimethoxytoluene 27 with malic acid in presence of conc.H_2SO_4

2,4-Dimethoxytoluene 27 (1.0g, 0.00657 moles) and malic acid (0.881g, 0.00657 moles) were mixed in a round bottomed flask fitted with a reflux condenser. To this mixture was added dropwise with stirring conc. H_2SO_4 (0.8 mL) at room temperature over a period of 15 minutes. After complete addition of conc. H_2SO_4 the mixture was maintained at 100^0 using an oil bath. To this hot solution was added oleum (0.6 mL) in three portions of 0.2 mL each and the mixture was stirred at 100^0 for two hours. The cooled reaction mixture was poured into crushed ice and kept in the refrigerator. Twenty four hours later the cold mixture was extracted with ethyl acetate (5 x 25 mL). The combined ethyl acetate extracts were washed with saturated $NaHCO_3$ (4 x

15 mL), followed by water (2 x 10 mL) and dried. Removal of ethyl acetate furnished a dark-red liquid (0.128g) which was chromatographed over silica gel. Elution of the column with petroleum ether-benzene (50:50) followed by concentration afforded 26. Recrystallization from petroleum ether gave yellowish needles; 0.014g; 1.3%; m.p. 132-34^{0} (lit.[17,18] m.p. 135-36^{0}).

IR, Nujol, bands at:

3060, 3020, 2940, 1760, 1730, 1620, 1510, 1420, 1390, 1380, 1260, 1210, 1150, 1130, 1070, 1020, 980, 850, 810, 790, 750 and 710 cm^{-1}.

^{1}H NMR, $CDCl_3$, 200 MHz, signals at:

2.23 (3H, s, C_6-CH_3),

2.89 (3H, s, C_7-OCH_3),

6.21 (1H, d, J = 6.5 Hz, C_3-H),

6.76 (1H, s, C_8-H),

7.20 (1H, s, C_5-H),

7.58 (1H, d, J = 6.5 Hz, C_4-H).

Bicarbonate extracts were neutralised by 2N HCl and extracted with ether (3 x 15 mL). The combined ether extracts were dried and ether was removed to give a dark syrupy liquid (1.5g) which was not characterised.

Attempted preparation of 44

3,5-Dimethoxybenzoic acid

A mixture of 3,5-dihydroxybenzoic acid 47 (4.0g, 0.026 moles) and ethanol (20 mL) was introduced into a two necked round bottomed flask (100 mL) fitted with a reflux condenser and heated using a water bath until the

acid dissolved completely. To this hot solution was added with shaking a solution of NaOH (2.7g) in water (7 mL) followed by freshly distilled dimethyl sulphate (7.87g, 5.9 mL, 0.0624 moles) over a period of 30 minutes. After complete addition of dimethyl sulphate the reaction mixture was made alkaline by further addition of NaOH (0.8g) in water (1.5 mL). The reaction mixture was refluxed for six hours, cooled and excess of ethanol was removed by distillation. The dark brown liquid so obtained was acidified with 2N HCl. The separated solid was filtered in vacuo, washed with water (3 x 10 mL) and recrystallised from water to give brownish needles; 4.0g; 84.6%; m.p. 181-82^{0} (lit.[74] 185-86^{0}).

3,5-Dimethoxymethyl benzoate 48

A mixture of 3,5-dimethoxybenzoic acid (4.0g, 0.0212 moles), methanol (20 mL) and conc. H_2SO_4 (0.4 mL) was refluxed in a round bottomed flask (100 mL) for 16 hours. After cooling, the mixture was extracted with ether (4 x 25 mL). The combined ether extracts were washed with saturated $NaHCO_3$ (3 x 10 mL) followed by water (2 x 10 mL) and dried. Removal of ether followed by distillation under reduced pressure afforded 48 as a colorless liquid; 4.120g; 94.7%.

3,5-Dimethoxybenzyl chloride 49

Lithium aluminium hydride (2.086g, 0.0549 moles) was placed in dry ether (30 mL) in a two necked round bottomed flask (100 mL) equipped with a dropping funnel,

a reflux condenser and $CaCl_2$ drying tube. To this suspension was added with constant stirring 3,5-dimethoxymethyl benzoate 48 (4.12g, 0.0208 moles) in dry ether (25 mL) over a period of 45 minutes. After complete addition of ester the total mixture was stirred overnight at room temperature. Excess of LAH was carefully decomposed by adding acetone (10 mL) in small portions with cooling. The resulting solution was transferred to a separating funnel, the organic layer was separated and the residue was washed with ether (3 x 15 mL). Combined ether extracts were washed with water (2 x 10 mL) and dried. Removal of solvent ether followed by distillation under reduced pressure yielded 3,5-dimethoxybenzyl alcohol as a colorless liquid; 3.215g; 91.8%.

A mixture of freshly distilled thionyl chloride (4.76g, 3.2 mL, 0.04 moles) in dry ether (30 mL) and dry pyridine (0.25 mL) was introduced into a two necked round bottomed flask (250 mL) fitted with a dropping funnel and a $CaCl_2$ drying tube. To this mixture was added with stirring distilled 3,5-dimethoxybenzyl alcohol (3.2g, 0.019 moles) in dry ether (50 mL) over a period of 30 minutes. After the addition of alcohol, the reaction mixture was stirred for three hours at room temperature and poured into crushed ice while stirring. The ether layer was separated and the aqueous layer was extracted with ether (4 x 25 mL). The combined ether extracts were washed with dilute HCl (2 x 10 mL)

followed by water (2 x 15 mL) and dried. Removal of ether gave a gray colored solid which was recrystallised from petroleum ether to give white shiny crystals of 49; 2.638g; 74.1%; m.p. 43-44^{0} (lit.[75] 46-48^{0}).

3,5-Dimthoxybenzyl cyanide 50

Potassium cyanide (1.159g, 0.0178 moles) was dissolved in distilled water (1.2 mL) in a round bottomed flask (50 mL) equipped with a reflux condenser. To this solution was added 3,5-dimethoxybenzyl chloride 49 (2.6g, 0.0139 moles) in ethanol (5 mL). The resulting mixture was refluxed in a water bath for four hours. On cooling, the alcohol was decanted off carefully and the KCl formed was washed with ethanol (3 x 10 mL). Ethanol layers were mixed and concentrated to give a yellow liquid which upon elution through a silica gel column gave 50 as a colorless liquid*; 2.29g; 93%.

IR, Nujol, bands at:

2920, 2840, 2250, 1610, 1420, 1310, 1290, 1220, 1180, 1080, 1030, 950, 850, 830, 725 and 680 cm^{-1}.

^{1}H NMR, $CDCl_3$, 90 MHz, signals at:

4.1 (2H, s, $-CH_2CN$),

4.25 (6H, s, 2 x $-OCH_3$),

7.25 (3H, m, C_2,C_4,C_5-H).

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* It solidified after storage for a few days.

Reaction of 3,5-dimethoxybenzyl cyanide 50 with resorcinol

3,5-Dimethoxybenzyl cyanide 50 (1.0g, 0.00534 moles), freshly distilled resorcinol (0.295g, 0.00267 moles), dry ether (10 mL) and anhydrous $ZnCl_2$ (0.068g, 0.490 mmoles) were placed in a two necked round bottomed flask (50 mL) fitted with a wide gas inlet tube and $CaCl_2$ drying tube. The flask was cooled in an ice-salt mixture and a rapid stream of dry HCl gas was passed through the solution for two hours with occasional shaking. The flask was kept in the refrigerator for 24 hours and again dry HCl was passed into the pale orange mixture for a further two hours. The flask was stoppered and kept in the refrigerator for three more days. The ether layer was decanted off, the residue was washed with dry ether (2 x 10 mL), refluxed with water (25 mL) for two hours and allowed to stand overnight. The pale yellow crystals were filtered and dried; 0.6g; 54.2%; m.p. 104^{0} (lit.[54] $102-3^{0}$). This was characterised as 52 by IR and ^{1}H NMR data.

IR, Nujol, bands at:

3000 to 3400 (broad), 2960, 2860, 1720, 1610, 1230, 1170, 1085 and 800 cm^{-1}.

^{1}H NMR, $CDCl_3$, 60 MHz, signals at :

3.55 (2H, s, $-CH_2-C-OH$),

3.75 (6H, s, 2 x $-OCH_3$),

6.35 (3H, s, C_2,C_4,C_6-H).

Reaction of 3,5-dimethoxybenzyl chloride 49 and 2,4-dimethoxybenzaldehyde.

Activated Mg turnings (0.102 g, 0.00425 moles) in dry ether (20 mL) were placed in a two necked round bottomed flask (100 mL) equipped with a reflux condenser, a dropping funnel and a $CaCl_2$ drying tube. To this mixture was added a small iodine crystal followed by 3,5-dimethoxybenzyl chloride 49 (0.8g, 0.00427 moles) in dry ether (25 mL) while stirring over a period of 30 minutes. After complete addition of 49, the resulting Grignard reagent was stirred at room temperature for one hour. To this Grignard reagent was added with stirring 2,4-dimethoxybenzaldehyde (0.71g, 0.00427 moles) in dry ether (10 mL) over a period of 30 minutes. The resulting mixture so obtained was stirred overnight at room temperature and refluxed gently for three hours. On cooling, ethyl acetate (10 mL) was added while stirring and the mixture was refluxed gently on a water bath for one hour in order to complete the reaction and poured into crushed ice containing 2N H_2SO_4 (5 mL). The ether layer was separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined ether extracts were washed with water (2 x 10 mL) and dried. Removal of ether afforded a yellow liquid (1.024g) which was chromatographed over silica gel. Elution with petroleum ether-benzene (80 : 20) followed by concentration gave a white solid, 0.835g; 64.7%; m.p. 93-94^0 which was

characterised as 54.

IR, Nujol, bands at :

2960, 2880, 1600, 1470, 1320, 1280, 1220, 1200, 1150, 1080, 950, 860, 810 and 700cm^{-1}.

^{1}H NMR, $CDCl_3$, 60 MHz, signals at:

2.3 (4H, s, 2 x $-CH_2-$),

3.75 (12H, s, 3 x $-OCH_3$),

6.35 (6H, s, Ar-H).

Preparation of 3,5-dimethoxybenzyl iodide 49a

Sodium iodide (2.58g, 0.0173 moles) was dissolved in dry acetone (20 mL) in a two necked round bottomed flask (100 mL) fitted with a reflux condenser, a dropping funnel and a $CaCl_2$ drying tube. To this solution was added dropwise while stirring, 3,5-dimethoxybenzyl chloride 49 (3.208g, 0.0172 moles) in acetone (20 mL) over a period of 30 minutes. After complete addition of 49, the resulting mixture was refluxed in a water bath for two hours. Acetone layer was removed by decantation and the white solid in the flask was washed with dry acetone (3 x 10 mL). The combined acetone fractions after drying were removed to give a yellowish solid which upon recrystallisation from methanol gave a white solid which was characterised as 49a; 3.08g; 64.5%; m.p. 65-68^{0}.

IR, Nujol, bands at:

2940, 2860, 1600, 1440, 1340, 1210, 1170, 1160, 950, 870, 860, 830, and 700cm^{-1}.

Grignard reaction of 3,5-dimethoxybenzyl iodide

and 2,4-dimethoxybenzaldehyde gave 54; m.p. 93-95°.

Preparation of 3,5-dimethoxyphenyl acetyl chloride

3,5-Dimethoxyphenyl acetic acid 52 (1.9g, 0.00968 moles) was introduced into a round bottomed flask (50 mL) equipped with a $CaCl_2$ drying tube. To this was added freshly distilled thionyl chloride (1.371g, 0.84 mL, 0.01152 moles) in small portions with occasional shaking. After the addition, resulting mixture was kept overnight and distilled under reduced pressure to give 3,5-dimethoxyphenyl acetyl chloride as a colorless liquid; 1.258g; 59.9%.

Reaction of 3,5-dimethoxyphenyl acetyl chloride with dimethoxyresorcinol

3,5-Dimethoxyphenyl acetyl chloride (1.2g, 0.00558 moles), anhydrous $AlCl_3$ (0.745g, 0.00558 moles) and freshly distilled nitrobenzene (4 mL) were mixed together in a two necked round bottomed flask (50 mL) equipped with a dropping funnel. To this mixture was added, while stirring, dimethoxyresorcinol (0.746g, 0.00602 moles) in nitrobenzene (2 mL) over a period of 15 minutes. The reaction mixture was further stirred overnight at room temperature and nitrobenzene was removed by steam distillation. The residual aqueous layer was extracted with ether (3 x 15 mL). The combined ether extracts were washed with water (2 x 10 mL) and dried. Removal of ether gave a white solid (0.8360g) which was found to be identical with 52; m.p. 104°.

Preparation of 44 by using Wittig reaction

A mixture of triphenyl phosphine (0.352g, 0.00134 moles), 3,5-dimethoxybenzyl chloride (0.25g, 0.00133 moles) and dry benzene (10 mL) were introduced into a round bottomed flask (50 mL) equipped with a reflux condenser, and refluxed in an oil bath for three hours. On cooling, benzene was removed by decantation and the white solid obtained was washed with dry benzene (2 x 10 mL) and dried to give triphenyl-3,5-dimethoxy benzyl phosphonium chloride; 0.566g; 82.8%.

The above salt (0.56g, 0.0013 moles) and dry ether (10 mL) were introduced into a three necked round bottomed flask (100 mL) equipped with a dropping funnel, a $CaCl_2$ drying tube and an inlet tube for passing N_2 gas. To this solution was added dropwise with stirring under the nitrogen atmosphere potassium-tert-butoxide prepared by dissolving freshly cut potassium metal (0.053g, 0.00134 moles) in tert-butanol (10 mL) over a period of 15 minutes. The resulting orange solution was stirred at room temperature for an additional 15 minutes and to this was added dropwise while stirring a solution of 2,4-dimethoxybenzaldehyde (0.225g, 0.00136 moles) in dry ether (15 mL) over a period of 20 minutes. The reaction mixture was then stirred for additional 1 hour and poured into crushed ice while stirring. The ether layer was separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined ether extracts were

washed with water (2 x 10 mL) and dried. Removal of ether afforded yellow oil (0.386g) which was chromatographed over silica gel. Elution with petroleum ether-benzene (90:10) followed by concentration gave 54 as a colorless liquid, 0.214g (TLC). Further elution of the column with petroleum ether-benzene (80 : 20) followed by concentration gave a white crystalline solid, 44; 0.042g; 10.3%; m.p. 83-84^{0} (lit.[58] 84^{0}).

IR, KBr; bands at:

2979, 2870, 1593, 1513, 1459, 1430, 1325, 1295, 1201, 1158, 1110, 1063, 1034, 969 and 820 cm^{-1}.

^{1}H NMR, $CDCl_3$, 90 MHz : was found to be identical with that reported by Vakharker*

Methylation of alboctalol 55.

Crude alboctalol 55 (0.05g, 0.102 mmoles) was dissolved in ethanol (5 mL) by heating in a two necked round bottomed flask (50 mL) equipped with reflux condensor. To this hot solution was added NaOH (0.2g) in H_2O (2mL) followed by freshly distilled dimethyl sulphate (2mL). The mixture was further made alkaline by adding NaOH (0.10g) in H_2O (0.5 mL) and refluxed for 1½ hours. After removing excess of ethanol the dark brown liquid was extracted with ether (3 x 10 mL). The combined ether extracts were washed with 2N NaOH (2 x 10 mL) followed by water (10 mL) and dried. Removal of ether gave a colourless solid which upon

*Smt. P. V. Vakharker, Ph.D. Thesis, University of Poona, 1974.

recrystallisation from benzene afforded white needles of 45; 0.010 g; 16.4%; m.p.168° (lit.[42] 168°).

Attempted dimerisation of 2,4,3',5'-tetramethoxystilbene 44

In presence of phosphorus pentoxide in refluxing toluene

2,4,3',5'-Tetramethoxystilbene 44 (0.15g, 0.5m moles and dry toluene (15 mL) were introduced into a two necked round bottomed flask (50 mL) equipped with a reflux condenser and a $CaCl_2$ drying tube. To this solution was added phosphorus pentoxide* (1.5g, 0.0105 moles) and the mixture was refluxed on a heating mantal for 5 hours. The resulting mixture was cooled and poured into crushed ice while stirring. Toluene was separated and washed with an excess of HCl (5 x 10 mL), HCl extracts were mixed with the main aqueous solution which was then extracted with ethyl acetate (3 x 15 mL). Toluene and ethyl acetate extracts were combined together, washed with water (2 x 10 mL) and dried. Removal of solvent gave a yellow oil, 0.123g, 41.0% which was found to be identical (TLC) with 44.

In presence of p-TSA in refluxing benzene.

2,4,3',5'-Tetramethoxystilbene (0.1g, 0.34mmoles), p-toluenesulphonic acid (0.005g, 0.0263 mmoles) and dry benzene (10 mL) were mixed together in a two necked round bottomed flask (50 mL) equipped with a reflux

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* Exposed to air for approximately 1 minute.

condenser and a $CaCl_2$ drying tube. The mixture was refluxed in an oil bath for 6 hours. Removal of benzene gave a yellow oil which was eluted through a small silica gel column to give a colorless liquid (0.084g) identical (TLC) with 44.

In presence of trifluoroacetic acid (TFAA)

To a solution of trifluoroacetic acid (0.5 mL) in dry $CHCl_3$ (4.5 mL) was added 2,4,3',5'-tetramethoxy stilbene (0.1g, 0.34 mmoles) in a round bottomed flask (25 mL) fitted with a $CaCl_2$ drying tube. The solution, which immediately gave a bright pink color, was allowed to stand at room temperature for 3 days. The product formed was dissolved in CH_2Cl_2 and eluted through a small silica gel column. Removal of CH_2Cl_2 gave a colorless solid; 0.078g identical (TLC) with 44.

In presence of dry ether saturated with dry HCl gas

Dry ether (25 mL) was introduced into a two necked round bottomed flask (100 mL) fitted with wide gas inlet tube and a $CaCl_2$ drying tube. The flask was cooled in an ice salt mixture and dry HCl gas was bubbled through until saturation was complete. 2,4,3',5'-Tetramethoxy stilbene 44 (0.2g, 0.68 mmoles) was added and the reaction mixture was stirred at 0^0 for 2 hours followed by an additional 2 hours at room temperature and then poured into crushed ice while stirring. The aqueous layer was neutralised with solid Na_2CO_3 and extracted with ether (3 x 20 mL). The combined ether extracts were washed with water (15 mL) and dried. Removal of ether

gave a pink colored liquid, (0.164g) which was chromatographed over silica gel. Elution with petroleum ether-ethyl acetate (75 : 25) followed by concentration gave 45 as white solid; 0.012g; 4.0%; m.p. 166-68^0 (lit.[42] m.p. 168^0).

IR, KBr, bands at:

2943, 1608, 1550, 1455, 1390, 1292, 1208, 1158, 1045 and 838 cm^{-1}.

^{1}H NMR, $CDCl_3$, 200 MHz, (Fig. 3.7) :

See Table 3.5.

^{13}C NMR, $CDCl_3$, 250 MHz, (Fig. 3.8), peaks at :

eight quartets at 2 x 54.8, 55.0, 55.2, 2 x 55.3, 55.6 and 55.7,

one triplet at 29.9,

fourteen doublets at 31.0, 37.9, 48.0, 97.0, 98.1, 98.3, 2 x 98.4, 102.8, 103.1, 104.2, 107.1, 128.1 and 129,

thirteen singlets at 119.3, 125.0, 128.8, 140.6, 145.0, 157.7, 157.9, 158.5, 158.6, 3 x 159.2 and 158.9.

preparation of (+)-Cis-pinonic acid 59.

(+)-Cis-pinonic acid 59 was prepared following a literature procedure[67].

Lead tetraacetate decarboxylation of 59

Decarboxylation of 59 (4.0g, 0.217 moles) with excess lead tetraacetate (15.0g, 0.0338 moles) in the presence of cupric acetate (1.257g, 0.0069 moles), dry pyridine (0.812g, 0.78 mL, 0.0096 moles) and dry benzene

(150 mL) was carried out according to the reported procedure[71] to give a yellowish liquid (2.136g) which was chromatographed over silica gel. Elution of the column with petroleum ether-ethyl acetate (90:10) followed by concentration gave a colorless liquid (0.836g) which on distillation under reduced pressure gave a pure colorless liquid; 62 ; (0.526g).

IR, Neat, (Fig. 3.9), bands at :

3080, 2995, 2950, 1725, 1670, 1430,1370, 1220, 1150, 1010 & 910 cm^{-1}.

^{1}H NMR, $CDCl_3$, 90 MHz, signals at :

1.48 and 1.50 (3H, s, each, $-\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{C}}}}-OCH_3$),

1.98 (3H, s, $-O-\overset{O}{\overset{\|}{C}}-CH_3$),

2.18 (3H, s, $-\overset{O}{\overset{\|}{C}}-CH_3$),

3.26 (1H, m),

4.9-5.8 (3H, m, $-\overset{|}{C}H-CH_2-$).

Further elution of the column with petroleum ether-ethyl acetate (80:20) gave another colorless liquid (0.736g). The spectral data (IR and ^{1}H NMR) indicated it not to be the desired cis-pinononyl acetate 60.

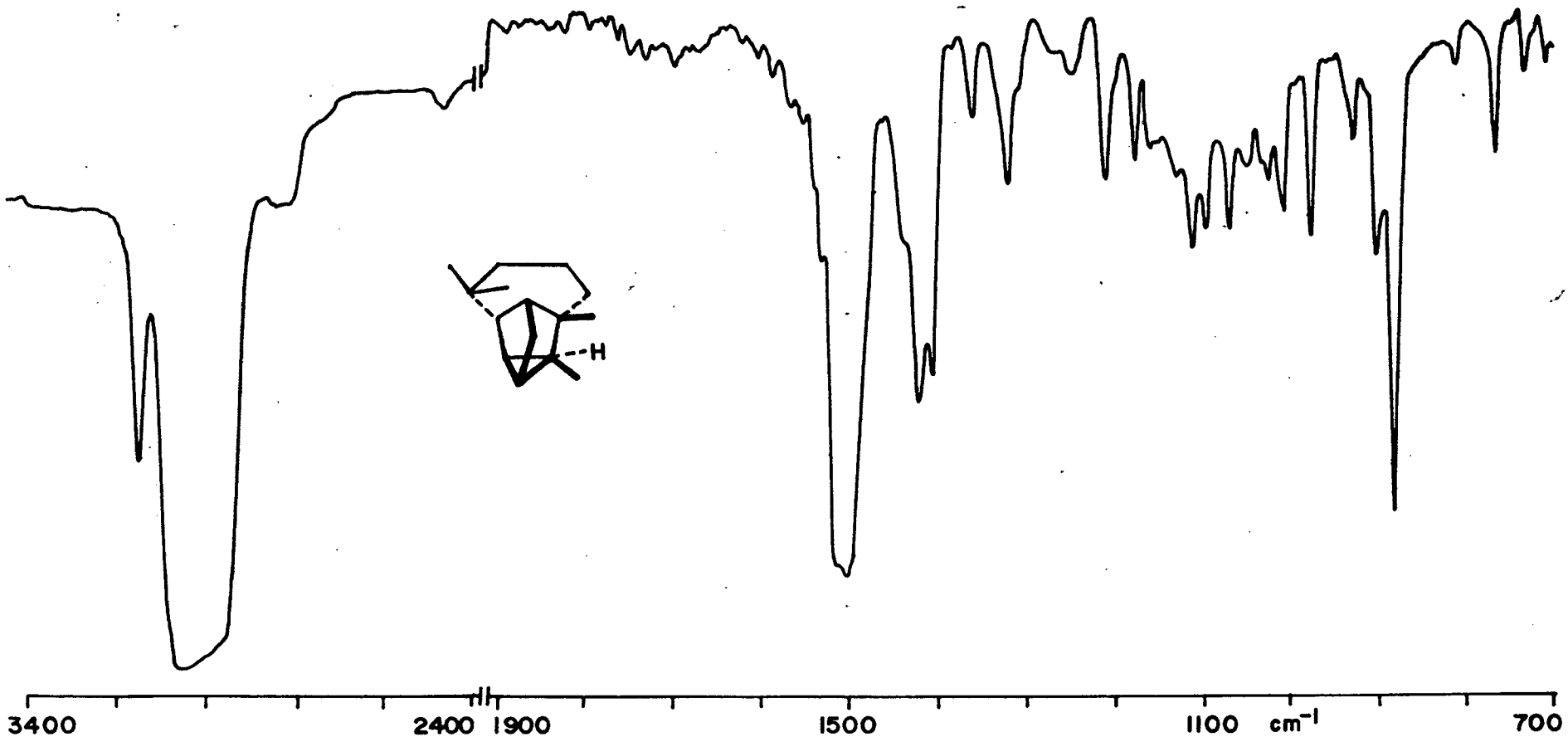

Fig. 3.1 IR spectrum of 5

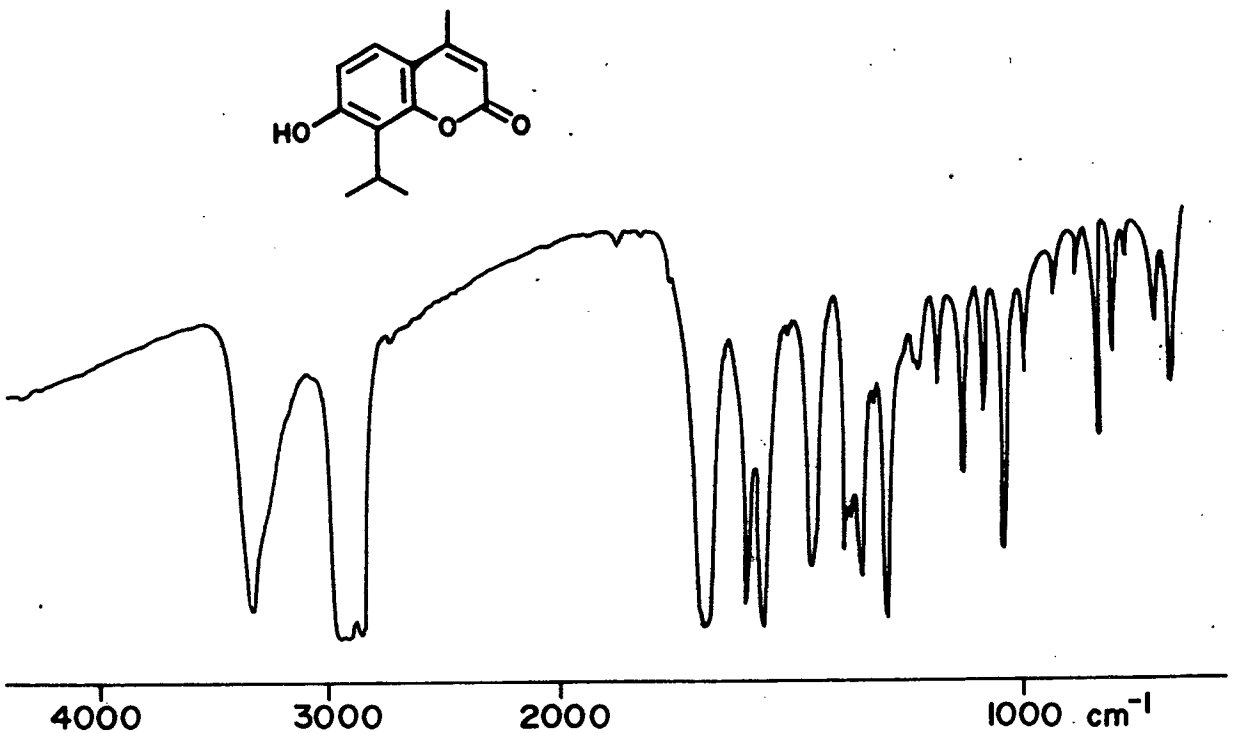

Fig. 3.2 IR Spectrum of 21

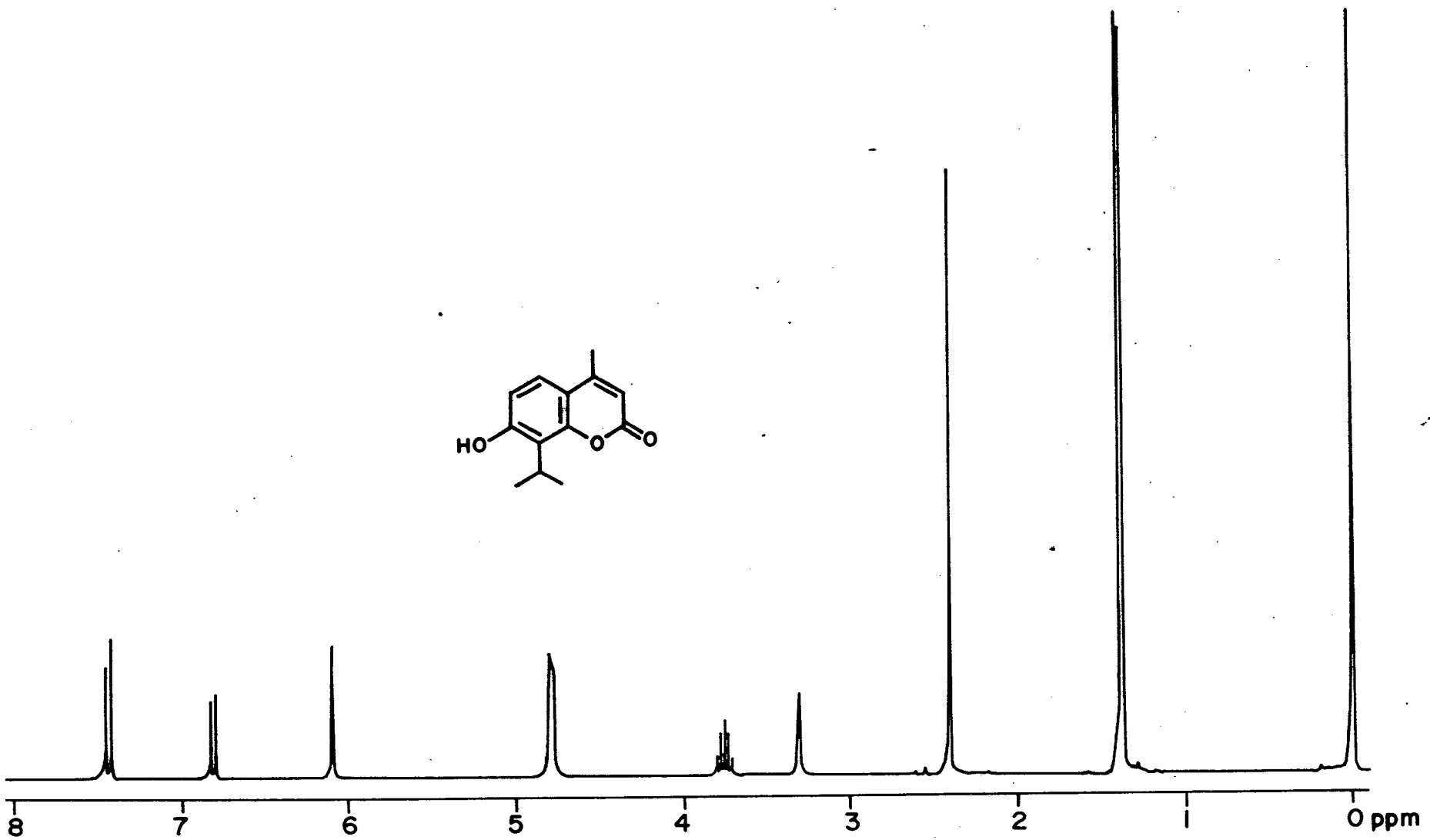

Fig. 3.3 ^{1}H NMR Spectrum of 21

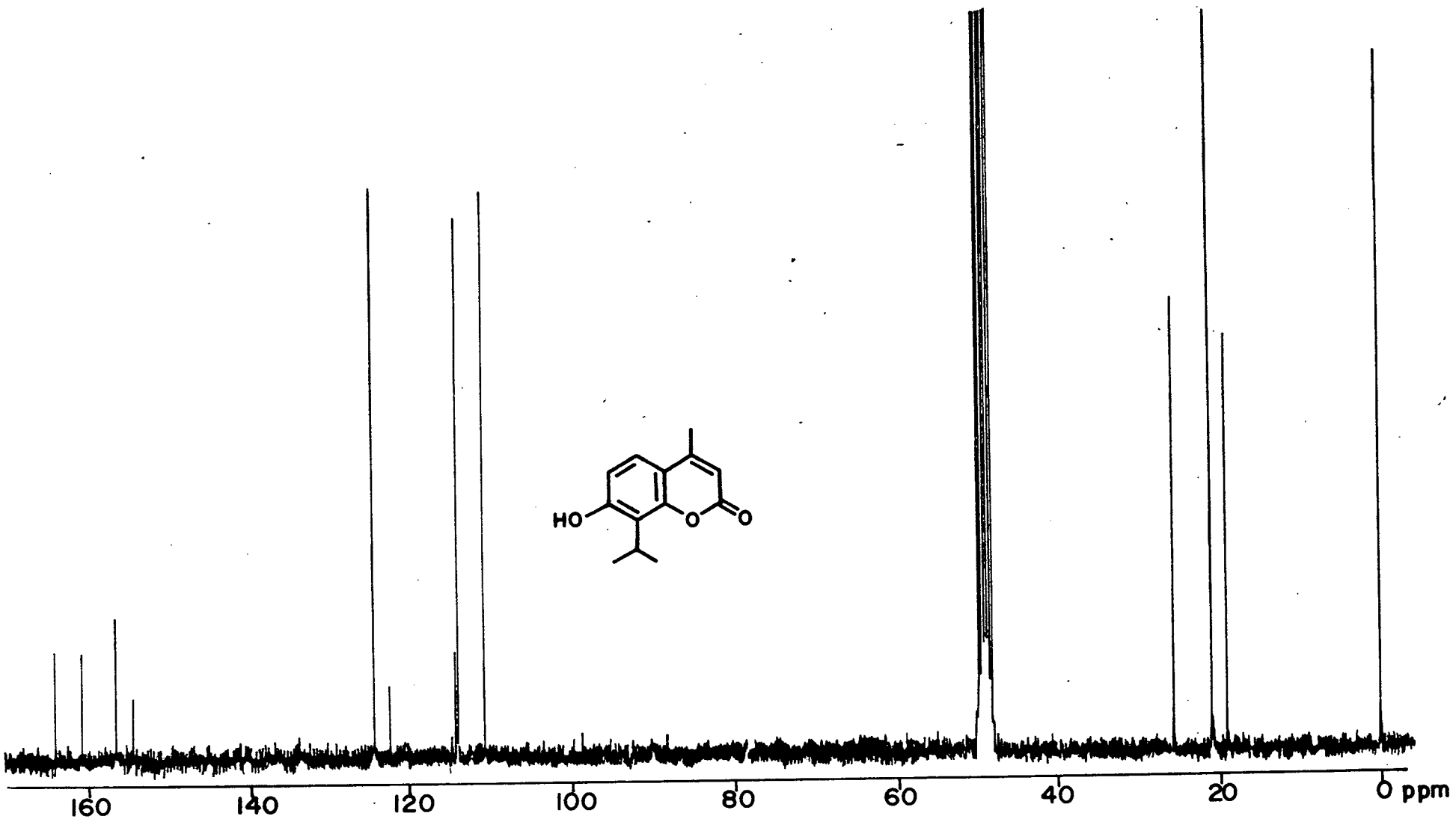

Fig. 3.4 ^{13}C NMR Spectrum of 21

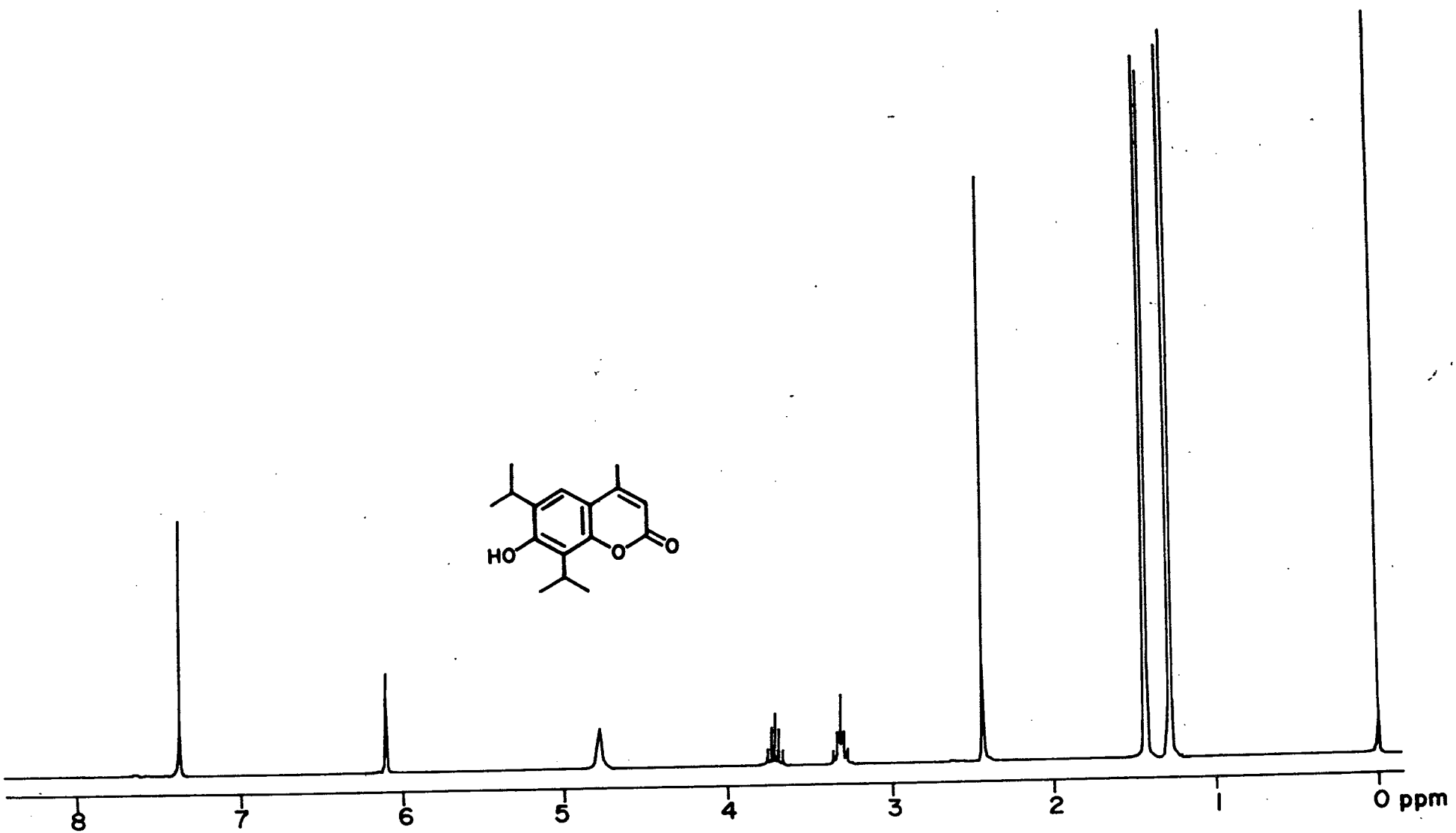

Fig. 3.5 ^{1}H NMR Spectrum of 22

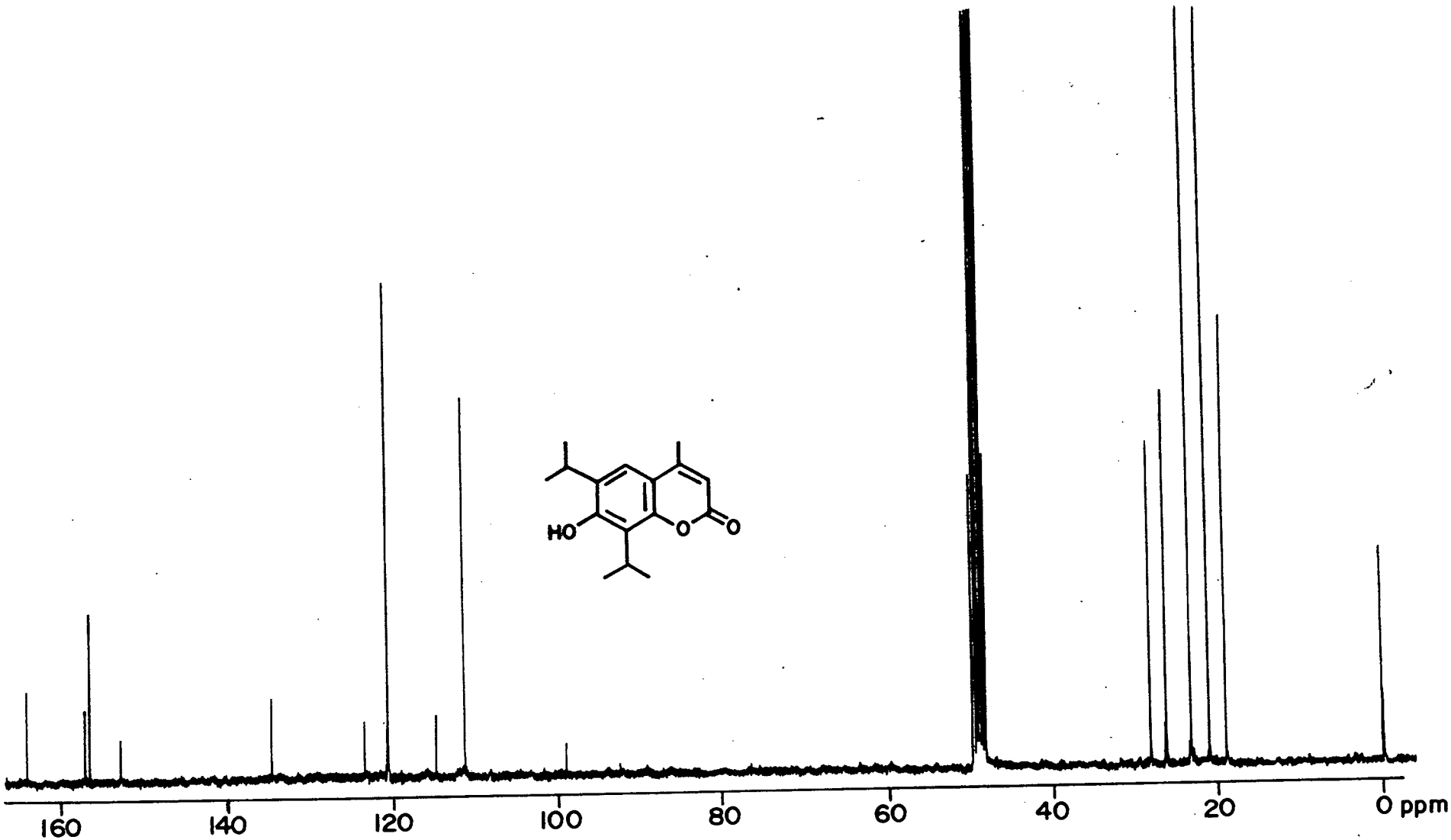

Fig. 3.6 ^{13}C NMR Spectrum of 22

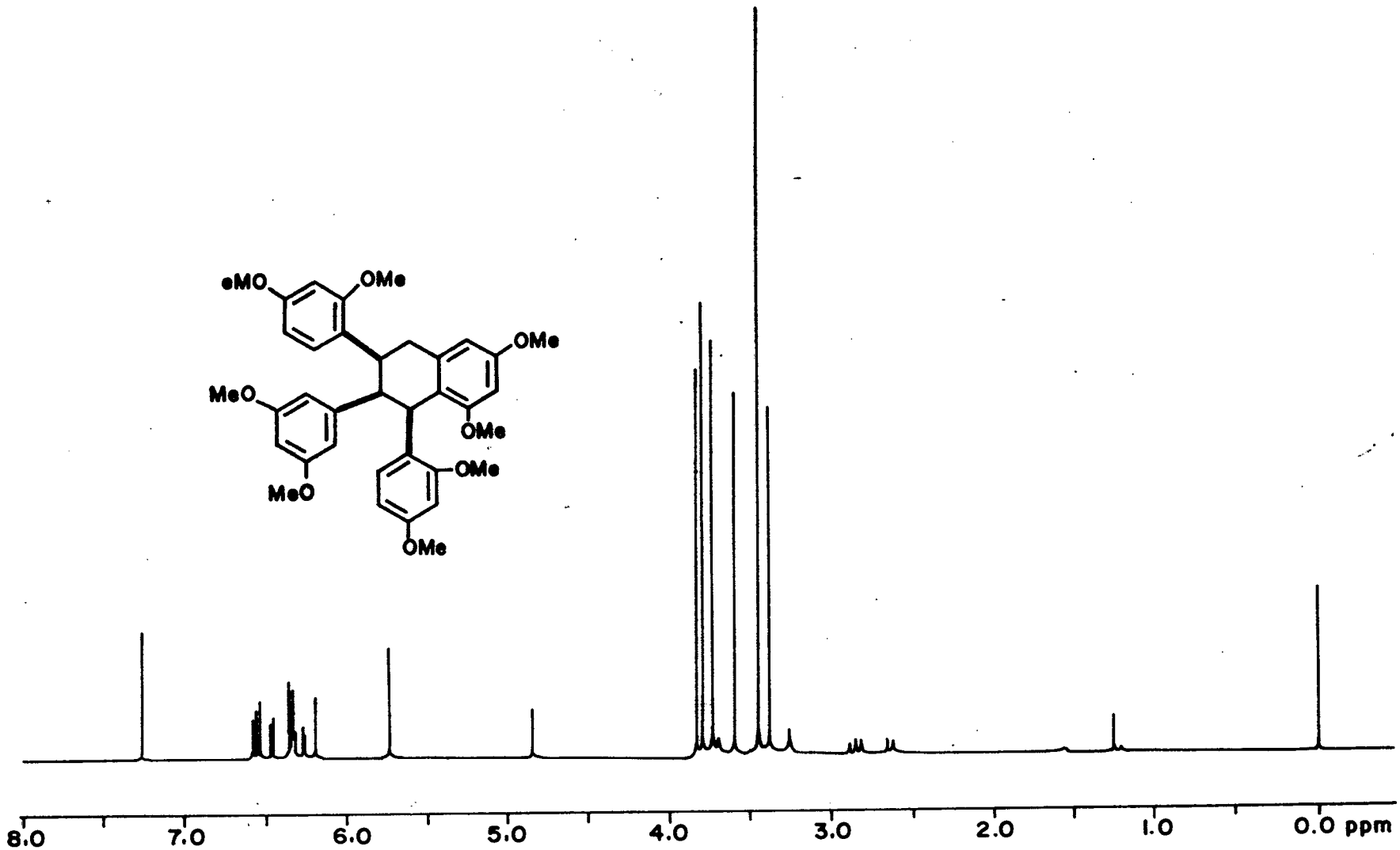

Fig. 3.7 ^{1}H NMR spectrum of 45

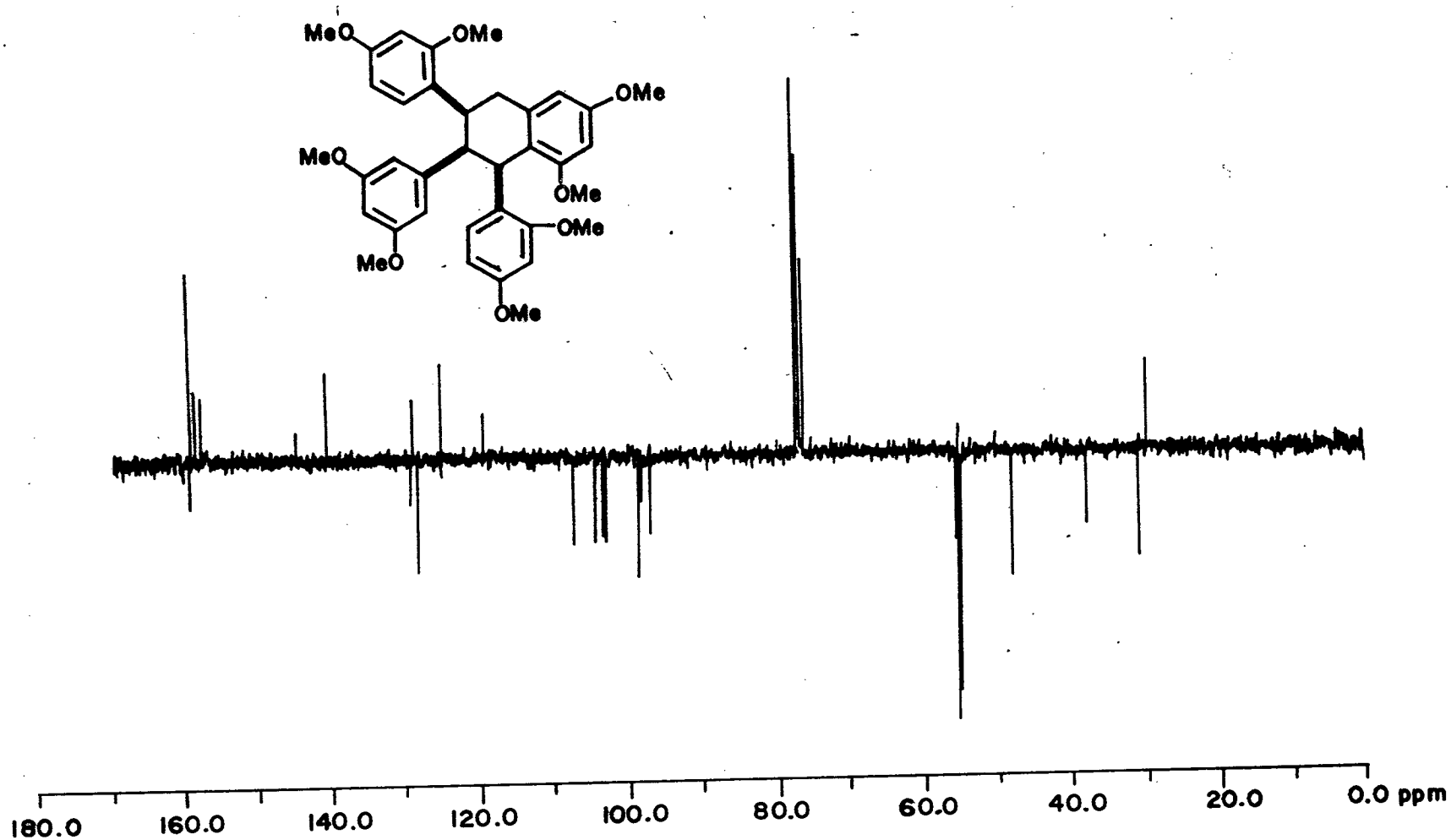

Fig. 3.8 APT ^{13}C NMR spectrum of 45

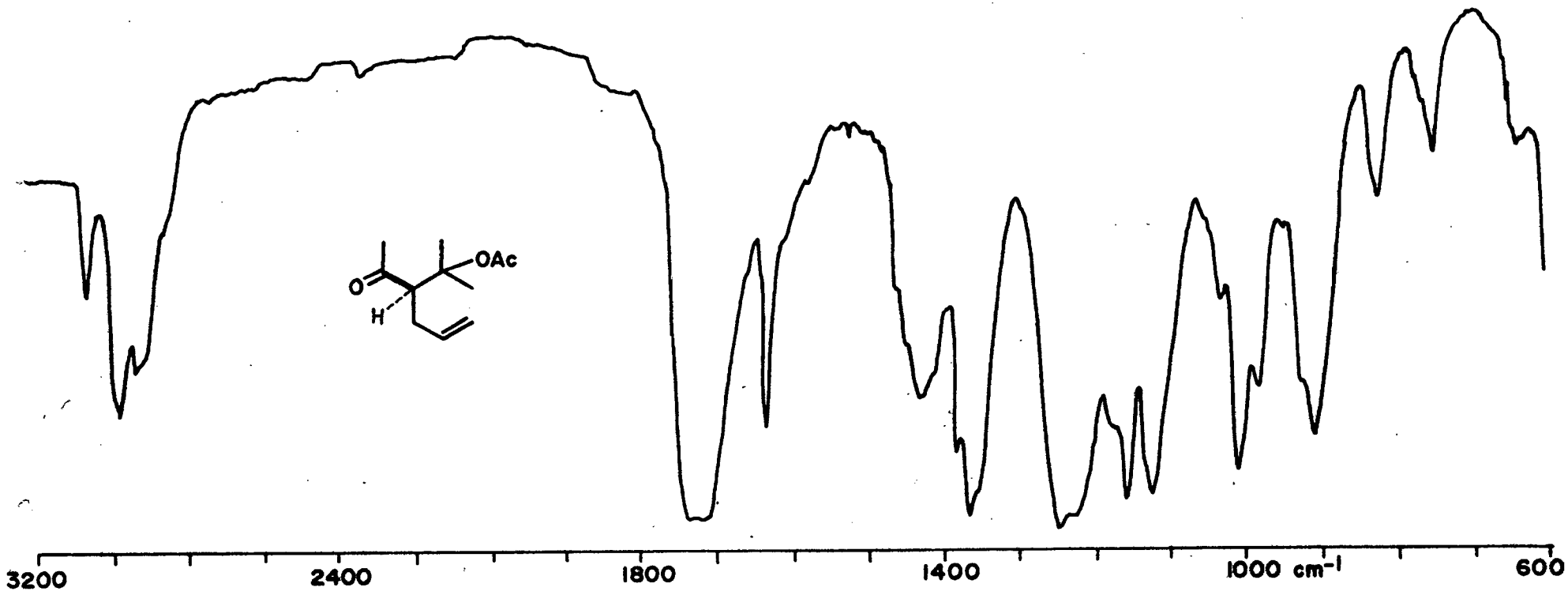

Fig. 3.9 IR spectrum of 62

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S U M M A R Y*

The thesis is divided into three chapters .

Chapter-1 : Contribution to santonin chemistry.

Chapter one is further subdivided into five sections.

Section-1 : Chemical and microbial transformations of santonin. September 1986 to March 1994. A review.

The work reported in the first chapter concerns some new chemistry of santonin and its derivatives and hence a brief literature survey on the chemistry of santonin published during September 1986 to March 1994 is presented in section one. This is a supplement to the literature survey on santonin chemistry reported earlier from this laboratory[1].

Section-2 : On the structures of santonone 2 and isosantonone 3.

The correctness of the assigned structures 2 and 3 to santonone and isosantonone respectively obtained by reaction of santonin 1 with Zn and acetic acid, was questioned by Redpath and co-workers on the basis of the deviation of the observed UV maxima of santonone (λmax 246nm) from that of model compound 2,2'-dimetylbiphenyl 4 (λ max 266nm). It was therefore considered worthwhile to prepare santonone and isosantonone by a reported

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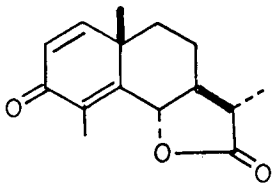
* The structure numbers of the compounds and reference numbers are not the same as they appear in the respective sections of Chapters 1 to 3.

literature procedure[3] and confirm the previous structural assignments or otherwise by analysis of the spectral data (IR, UV, ^{1}H & ^{13}C NMR). The ^{1}H and ^{13}C NMR



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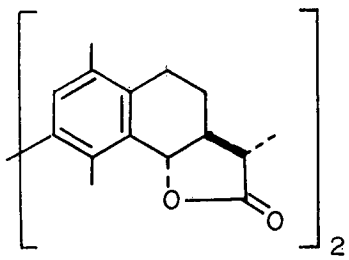

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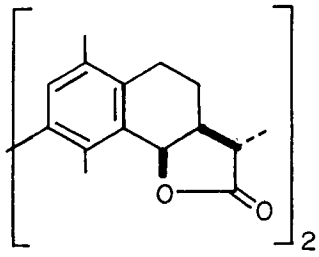

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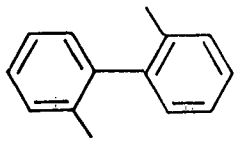

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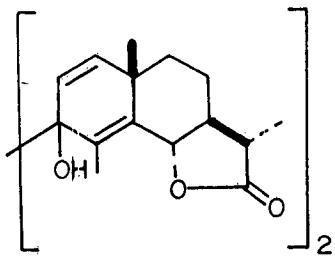

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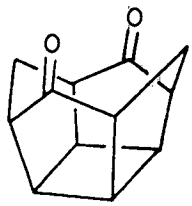
data, recorded for the first time, unambiguously confirm the previously assigned structures 2 and 3 to santonone and isosantonone respectively. Santonone and isosantonone are presumably formed by dehydration of corresponding pinacol 5 which could not be isolated. The results are incorporated in this section.

Section-3 : Reactions of santonin and santonic acid with Zn-HCl-ether.

Non-availability of the exact procedure for the preparation of santonone and isosantonone (Section-2) resulted in the isolation of these compounds in poor

yield. Paquette and co-workers reported that an excellent yield of pinacol 7 was obtained by reaction of ketone 6 with Zn-HCl-ether under very mild conditions[4].



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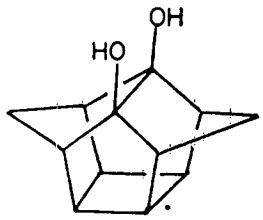

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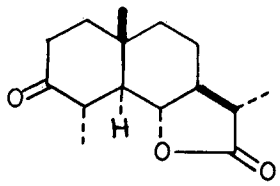

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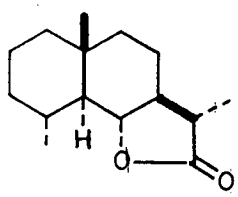

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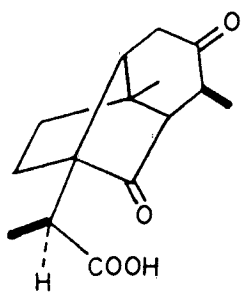

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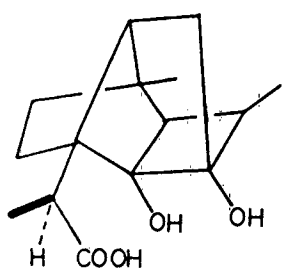

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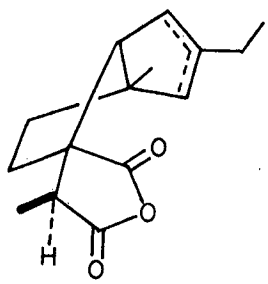

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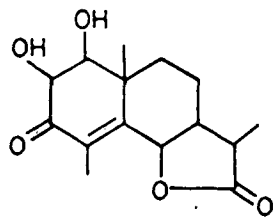
We envisaged preparation of santonone and isosantonone from santonin 1 under these experimental conditions. However santonin 1 failed to undergo bimolecular condensation but yielded tetrahydro-α-santonin 8 and deoxytetrahydro-α-santonin 9. A literature survey showed that similar observations were made by Yamamura and

co-workers on cholestenone under identical reaction conditions[5]. Since intermolecular pinacolisation failed to give the expected 2 and 3 via pinacol 5 it was then of interest to see whether intramolecular pinacolisation is favored under these experimental conditions. Santonic acid 10, which is known to give pinacol[6], was then chosen as a substrate. Under these experimental conditions santonic acid 10 gave a mixture of anhydrides 12, formation of which can be explained by further acid catalysed rearrangement of the initially formed pinacol 11.

Section-4 : Reinvestigation of the $KMnO_4$ oxidation reaction of santonin.

The potassium permanganate oxidation of santonin 1 was originally studied by Angeli and Marino[7] who reported the formation of dihydroxy-α-santonin (m.p. 261^0) having structure 13. Though the reaction was not reinvestigated, Hendrickson and Bogared[8] suggested that the 4,5-olefinic linkage was more reactive and approach of the reagent from the less hindered α-face, should afford 4α,5α-dihydroxy-α-santonin 14 . Our reinvestigation has shown that the melting point of 14 is 220^0 and not 261^0 as reported earlier. Besides 14, $KMnO_4$-pyridine oxidation of 1 gives another compound having m.p. 268^0. The revision of the stereochemistry of α-santonin-chlorohydrin from 15 to 16 suggested further studies on 4,5-dihydroxy-α-santonin 14, particularly concerning the stereochemical assignments. The products

of $KMnO_4$ oxidation were thus subjected to further scrutiny which showed that dihydroxy-α-santonin and the product having m.p. 268^0 should be represented by stereostructures 17 and 18 respectively.



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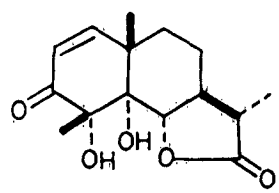

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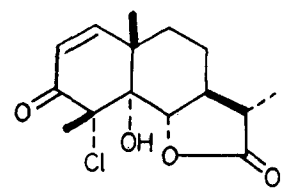

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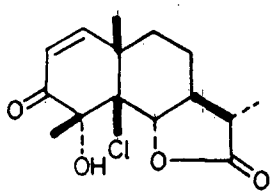

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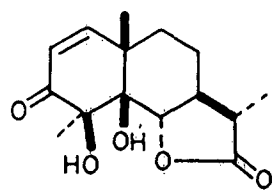

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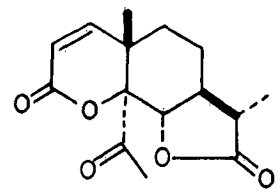

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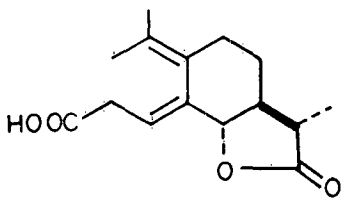
Section-5 : Photochemical reactions of santonin in ethyl, methyl and isopropyl alcohol.

Exposure of an ethanolic solution of santonin 1 to sunlight was reported to produce photosantonic acid and another uncharacterised product. The structure 19 was assigned to photosantonic acid by Van Tamelen and co-workers[9]. In the present study photochemical transformations of santonin 1 using different alcohols

have been investigated and the products obtained have



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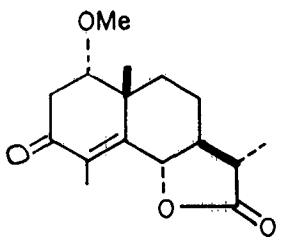

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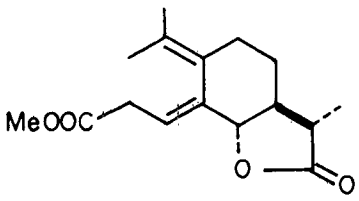

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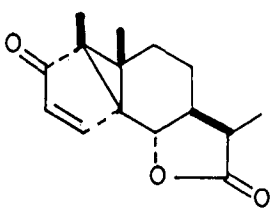

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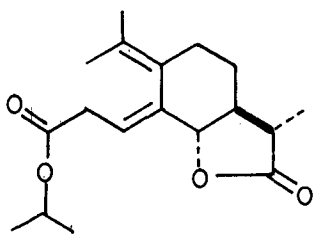

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been characterised. Methanolic solution of santonin 1 on exposure to sunlight gave two products which were separated by chromatography and assigned structures 20 and 21. On the other hand replacing methanol by isopropyl alcohol afforded three products which could be separated by chromatography. Structures 19, 22, and 23 have been assigned by spectral analysis and the results of this investigation are included in this section.

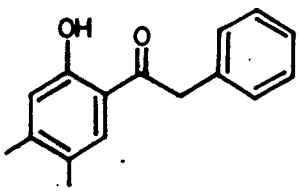
CHAPTER-2 : Reactions of aryl-ketones with Zn-HCl-ether system. A new synthesis of benzofurobenzofurans.

In continuation of the work reported in Chapter-1, several aryl-ketones were subjected to reaction with the Zn-HCL-ether system originally used by Yamamura and co-workers[10]. These authors referred to this reaction as a modified Clemmensen reduction. In another investigation it was observed that the phenolic ketone 24 failed to give deoxy-phenol 25 under normal Clemmensen conditions. This led us to study the reaction of 24 using the Zn-HCL-ether system. The products 26 and 27 obtained in this reaction clearly showed that bimolecular reduction at the metal surface (pinacolisation) is a predominant path and the acidic conditions result in rearrangement of the initially formed pinacols. Several o-hydroxy-acetophenone derivatives 28-31 were subjected to this reaction conditions and the products formed, 34-39, were isolated and characterised by spectral analysis. Under these experimental conditions, salicylaldehyde 32 gave 40 as the major product. Benzyl phenyl ketone 33, on the other hand, gave pinacols 41 and 42 besides bibenzyl 43 and stilbene 44.

CHAPTER-3 : Structural and synthetic studies on some natural products.

Section-1: p-Nitrobenzoic acid, a new reagent for interconversion of longifolene and longicyclene.

In 1984, Shitole et. al,[11] reported isomerisation



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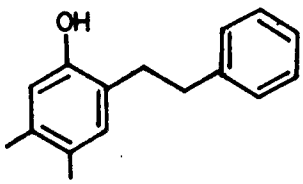

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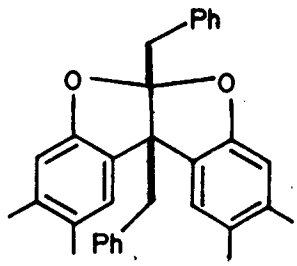

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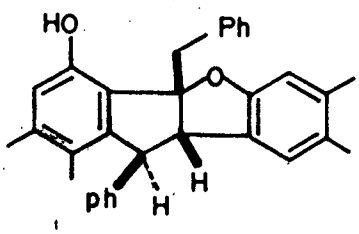

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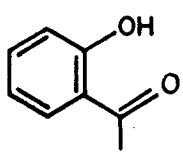

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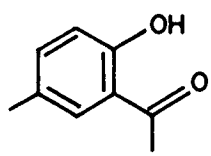

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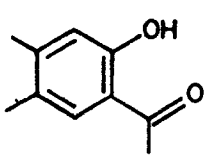

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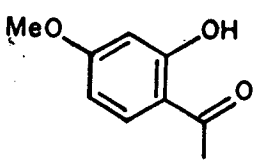

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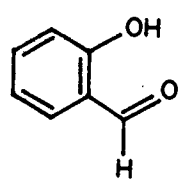

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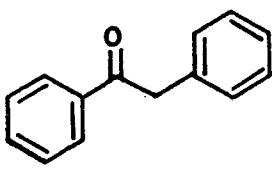

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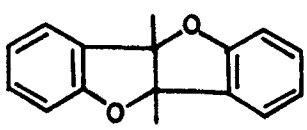

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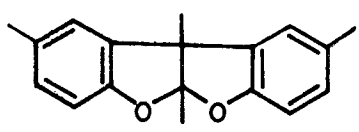

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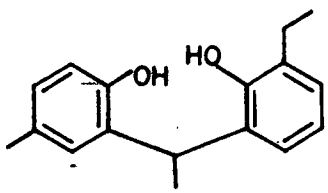

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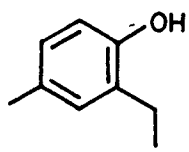

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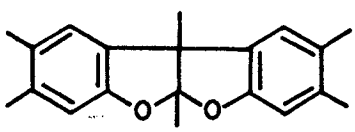

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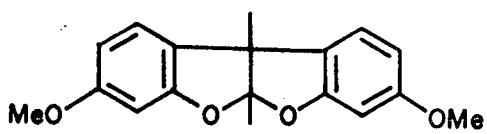

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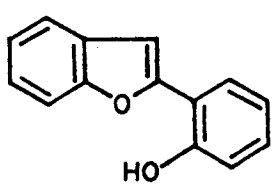

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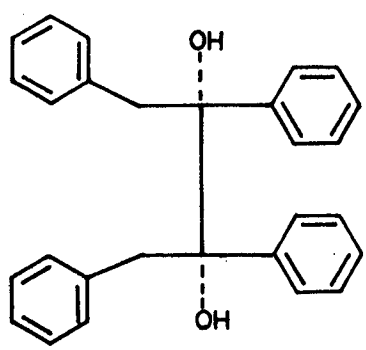

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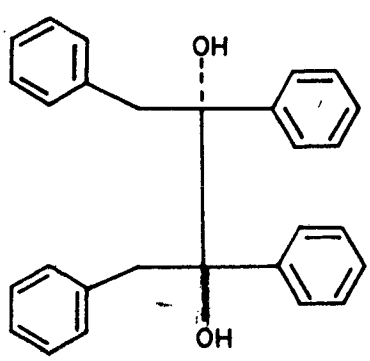

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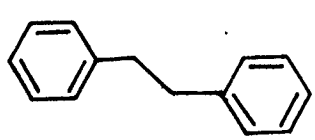

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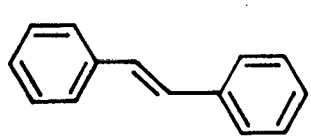

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of longifolene 45 to a new isomer alloisolongifolene 46 by using specific catalysts such as bromo and iodo acetic acid (pKa 2.9 and 3.16 respectively). Since some of the derivatives of alloisolongifolene 46 were found to be useful in perfumery, it was of interest to study

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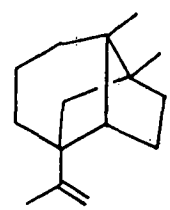

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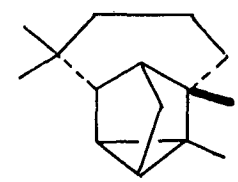

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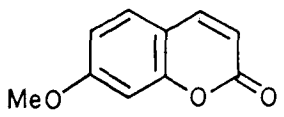
the reaction of longifolene 45 with other acids having comparable pKa values. p-Nitrobenzoic acid (pKa 3.4) was thus chosen as a catalyst and its reaction with longifolene 45 was studied. Alloisolongifolene 46 was not found to be present in the reaction product, which was proved to be a mixture of longifolene 45 and longicyclene 47. Pure 47 was isolated by chromatography over $AgNO_3$ impregnated silica gel and characterised by its spectral data.

Section-2 : One pot synthesis of 4-methyl-7-hydroxy-8-isopropyl and 4-methyl-7-hydroxy-6,8-diisopropoxy coumarins from diisopropoxyresorcinol.

Reaction of phenols with ethylacetoacetate in the presence of sulphuric acid to yield 4-methylcoumarins is commonly known as the Pechmann condensation[12] and, since its discovery, has been used for the synthesis of a large number of coumarins. Limye[13] reported the reaction

of methyl and ethyl ethers of phenols with ethyl acetoacetate in the presence of H_2SO_4 and reported the formation of β-methyl-p-methoxy and p-ethoxy cinnamic acids along with some partially characterised products.



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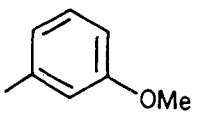

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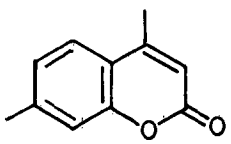

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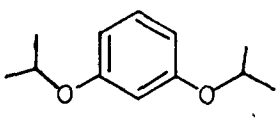

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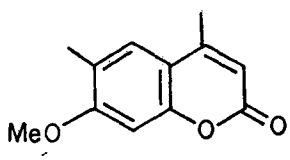

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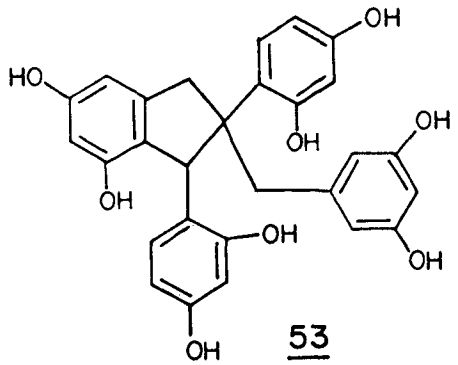
This reaction was further studied in our laboratory using 1,3-dimethoxy phenol and it was found that the major reaction product was 7-methoxycoumarin 48. This result is very interesting from a mechanistic point of view and hence the results were confirmed by repetition of the experiment. As expected the reaction of 3-methoxytoluene 49 with ethyl acetoacetate in the presence of H_2SO_4 yielded 4,7-dimethylcoumarin 50. To study the generality of this reaction, diisopropoxyresorcinol 51 was treated with acetoacetic ester under the same experimental conditions to give 5,7-diisopropyl-4-methylcoumarin and



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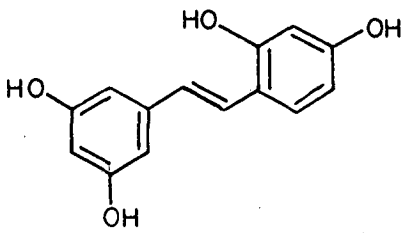

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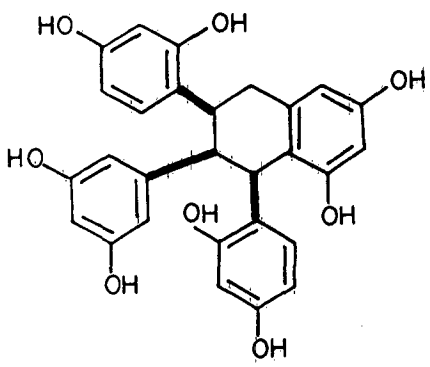

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Section-5 : Reinvestigation of the synthesis of cis-planococcyl acetate.

Bierl-Lenhardt et.al.[17] isolated (+)-cis-planococcyl-acetate, 58 a sex pheromone from citrus mealybug, Planococcus citri (Risso). Goldschmidt reported conversion of (+)-α-pinene 56 into (+)-cis-planococcyl acetate 58 via a Hunsdiecker decarboxylation of (+)-cis-pinonic acid 57[18]. The reaction of this carboxylic acid with lead tetraacetate with added pyridine and $CuSO_4$ in dry benzene results in decarboxylation to form an olefin and / or an acetate[19].

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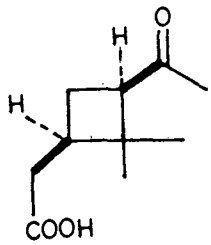

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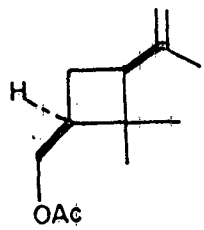

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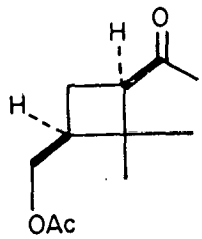

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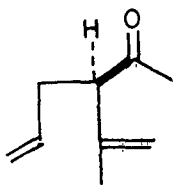

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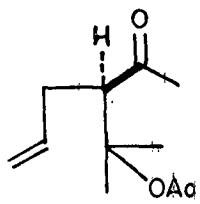

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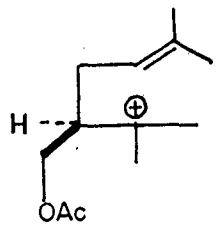

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It seemed to us that a Kochi reaction of (+)-cis-pinonic acid 57 should give ketoacetate 59 as one of the products, which in turn could be transformed into 58. Cis-pinonic acid 57, prepared by $KMnO_4$ oxidation of α-pinene 56, when subjected to Kochi reaction, gave two products 60 and 61 which have been characterised by spectral analysis. As anticipated, we did obtain an acetoxy compound but not the desired one. This section also presents a hypothetical biogenetic pathway for (+)-cis-planococcyl acetate 58 and our attempts to generate the carbocation 62, in an effort to synthesise 58 biomimetically.

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