SYNTHESIS OF TERPENES AND SOME TRANSFORMATIONS OF SMALL MEMBERED RING COMPOUNDS

T H E S I S

Submitted to the University of Poona
for the degree of Doctor of Philosophy
in Chemistry

By

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C O N T E N T S

CHAPTER 3

CHAPTER 4

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. IR spectra were recorded as liquid film or nujol mull on Perkin-Elmer Infracord spectrophotometer - model 137B.
3. PMR spectra were recorded on a Varian A-60 and Varian T-60 spectrometers using TMS as internal standard.
4. Pet. ether refers to the fraction boiling between 60°-80°.
5. All extracts were finally dried over anhydrous sodium sulphate.
6. TLC were carried out on silica gel, made in this laboratory, plates being prepared by spreading the aqueous slurry, drying at room temperature and finally activating at 100°C for ten minutes.
7. 'Alumina' refers to neutral alumina made in this laboratory.
8. Microanalyses were carried out in the micro analytical section of the laboratory

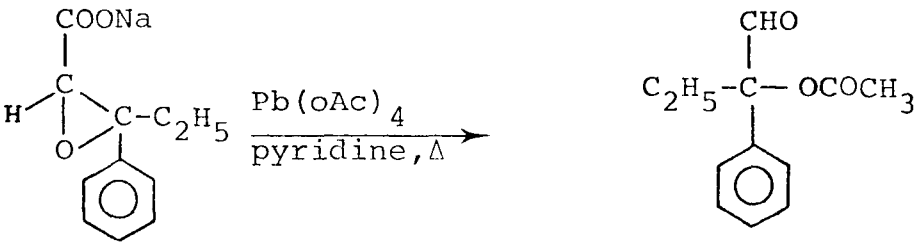
CHAPTER 1

ACTION OF LEAD (IV) ACETATE ON SODIUM GLYCIDATES: A CONVENIENT ROUTE FOR THE PREPARATION OF α-ACETOXY-ALDEHYDES

1.1. SUMMARY

α-Acetoxy aldehydes were obtained by the action of lead (IV) acetate, on sodium glycidates, in the presence of pyridine.

This can be exemplified by the conversion of sodium glycidate (1b) to α-acetoxy aldehyde (1).



(1b) (1)

1.2 INTRODUCTION

The synthesis of aldehydes and ketones possessing electronegative groups (such as -OH, -Cl, -Br, and -OAc) on the α carbon atom has received considerable attention. This has led to the formulation of several methods for the synthesis of this class of compounds. A brief review of some of these methods is presented below.

(1) By the action of dichloromethyl lithium on ketones

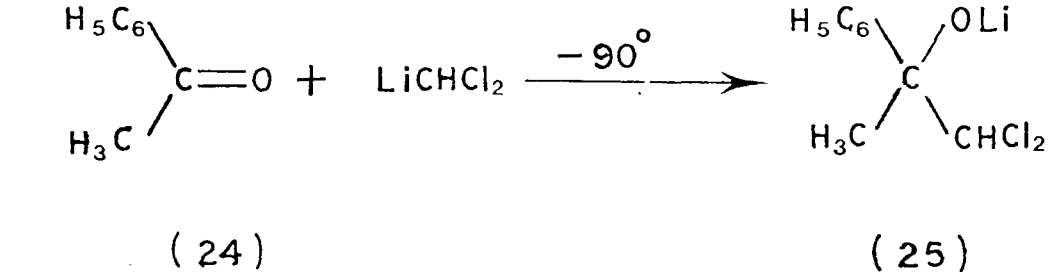
Synthesis of several aldehydes with the α position substituted with chlorine or hydroxyl group were carried out by Köbrich and Werner[1] using this reaction.

Addition of dichloromethyl lithium on acetophenone at low temperature (-90°) furnished (25) which on hydrolysis in THF solvent and after refluxing for one or two hours yielded the α-chloro-α-phenyl-propanaldehyde (27). The carbinol obtained (25) was stable up to +20°, which after loss of LiCl was found to furnish α-chloroepoxide (26). Epoxide (26) was thus found to be the intermediate in the formation of α-chloroaldehyde (27). (See scheme 1, chart 1.)

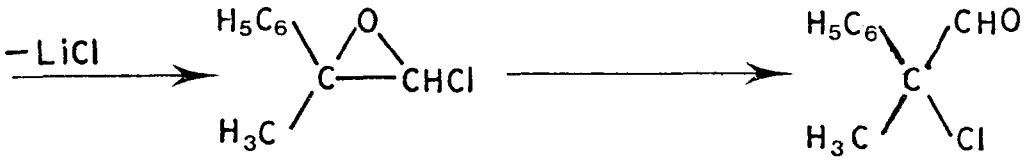
In modification of this method by Köbrich and co-workers[2], the lithium alkyl derivatives were converted to the corresponding trimethyl silyl ether; using $(CH_3)_3SiCl$. These compounds readily rearranged to the α-chloro oxiranes or α-chloro aldehydes.

CHART I

SCHEME 1

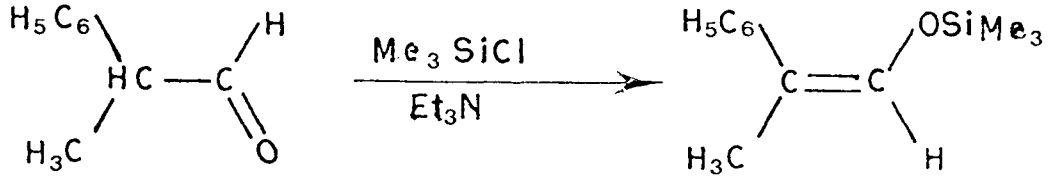


(24) (25)

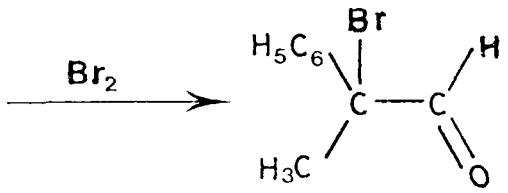


(26) (27)

SCHEME 2



(28)



(30)

(2) By halogenation of the aldehyde enol ethers or esters

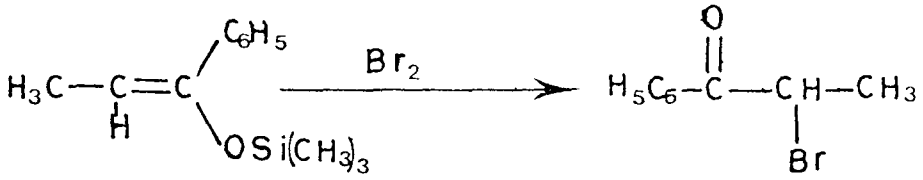
(a) Aldehydes themselves undergo α-halogenation only with difficulty. However, their enol ethers or esters may be halogenated at the α-position with greater ease. This is generally true for all α-halogenations of carbonyl compounds.

Enol silyl ethers undergo rapid addition of halogen to afford α-halo aldehyde. Since the silyl enol ethers are readily generated from aldehydes in high yields, this method provides a simple route for the preparation of α-halo aldehydes[3]. Carbonyl compounds were converted to their enol silyl ethers by reaction with $ClSiMe_3$ and Et_3N in DMF. Enol silyl ethers were found to react instantaneously with one equivalent of bromine in CCl_4 at room temperature. The product was isolated by evaporating solvent and trimethyl bromosilane (b.p. 85°). (See scheme 2, chart 1).

This technique is applicable to a wide range of aldehydes as well as ketones. Particularly noteworthy the bromination at α-position of adelhydes in presence of double bond. α-chloro aldehydes are obtained by using Cl_2 in presence of Br_2.

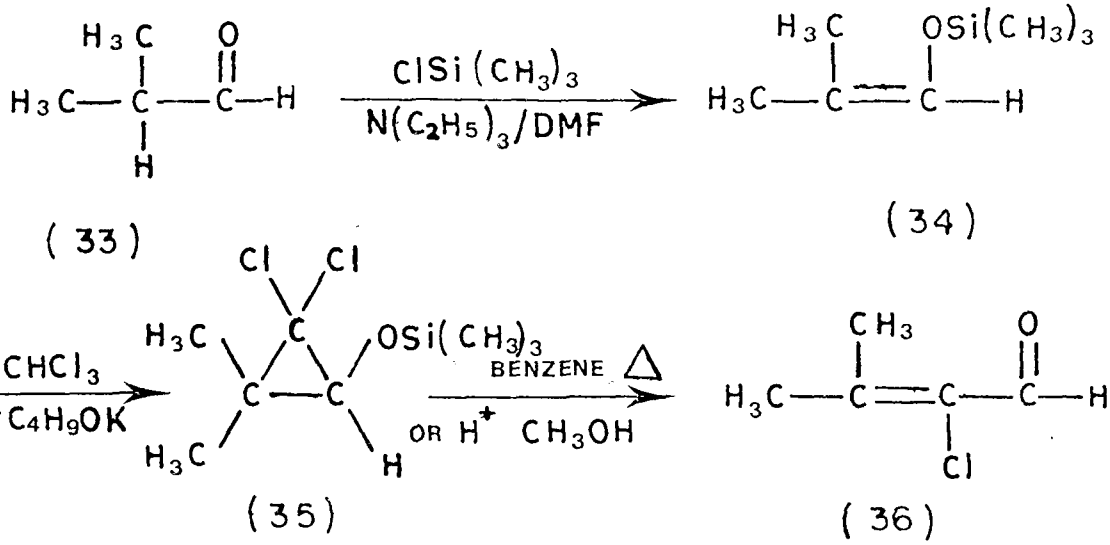
The use of enol silyl ethers for bromination of ketones is demonstrated by quantitative conversion of silyl enol ether (31) to α-bromopropiophenone (32). (See chart 2)

CHART 2



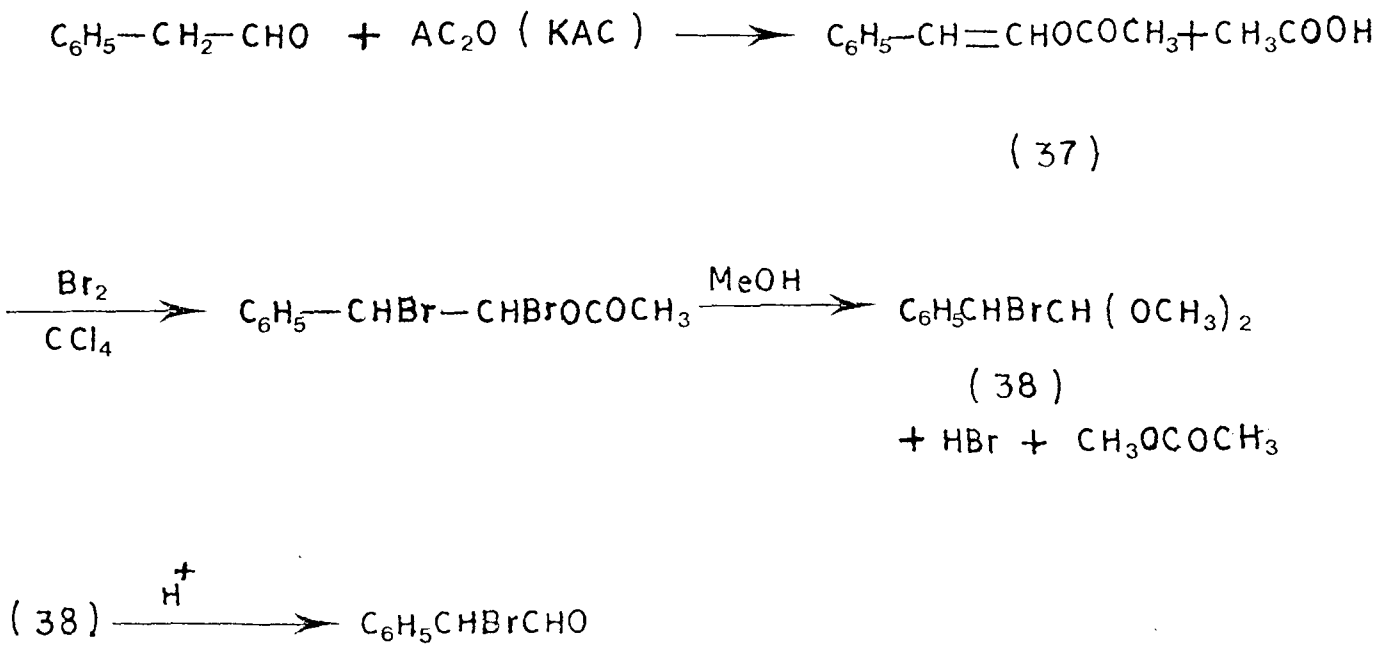
(31) (32)

SCHEME 3



(33) (34) (35) (36)

SCHEME 4



(37) (38)

(b) Amice et al[4] improved the preparation of α-halo, α-β unsaturated compounds by using enol silyl ethers instead of enol ethyl ethers.

This method can be exemplified as given in (Scheme 3, chart 2)

The reaction of enol silyl ether (34) with dihalocarbene affords, 1,1 dichloro-2-siloxy-3,3 dimethyl cyclopropane (35). (35) readily undergoes elimination of halo trimethyl silane when refluxed with benzene, to give α-chloro, α-β unsaturated aldehyde (36) in very high yield and in fast reaction.

(3) By bromination of enol acetates

It is well known that enols add bromine very rapidly and although aldehydes do not exist in enolic forms in appreciable quantities, it is possible to prepare stable enol acetates. Paul[5] has reported that addition of bromine to the double bond of an enol acetate would be rapid and resulting compound would undergo alcoholysis with great facility to give bromoacetals on treatment with alcohol. This can be exemplified as given in (scheme 4, chart 2).

The enol acetate (37) was prepared in usual manner by boiling phenylacetaldehyde with aceticanhydride and potassium acetate. Addition of bromine to enol acetate (37) proceeds rapidly and smoothly in cold CCl_4 solution. Upon adding excess of methanol to brominated mixture and allowing it to

stand for 2-3 days, dimethyl acetal (38) was obtained in good yield. Hydrolysis of dimethyl acetal by boiling with acid gave α-bromoaldehyde.

(4) α-Acetoxy aldehydes from α-halo aldehydes

Riehl et al[6] reported a new method for synthesis of α-acetoxy aldehydes.

α-acetoxy aldehyde (41) was obtained in 60% yield without isomerization to the acetoxy ketone (see scheme 5, chart 3).

Aldehyde (39) on treatment with stoichiometric amount of $BF_3 \cdot OEt_2$ and lead tetra-acetate in benzene solution at <50° for one or two hours, furnished α-acetoxy aldehyde (41). An ionic mechanism was postulated consisting of slow enol formation and rapid reaction with $Pb(OAc)_4$. Initial attack of OAc was followed by formation of epoxide ring.

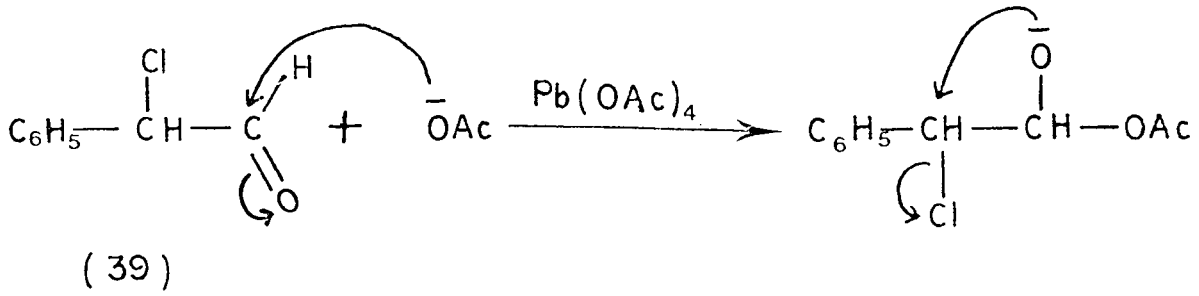
(5) By using glycidonitriles

Stork et al[7] developed a method for preparation of glycidonitriles and transformed them into α-haloacyl compounds (see scheme 6, chart 3).

Glycidonitrile (42) was obtained from cyclohexanone and α-chloroacetonitrile. Treatment of (42) with anhydrous HCl in dry ether at 0° led to a stable chlorocyanohydrin (43). It was possible to transform (43) to desired chloroketone (44) in 93% yield by shaking with cold 5% sodium hydroxide solution for 30 seconds.

CHART 3

SCHEME 5



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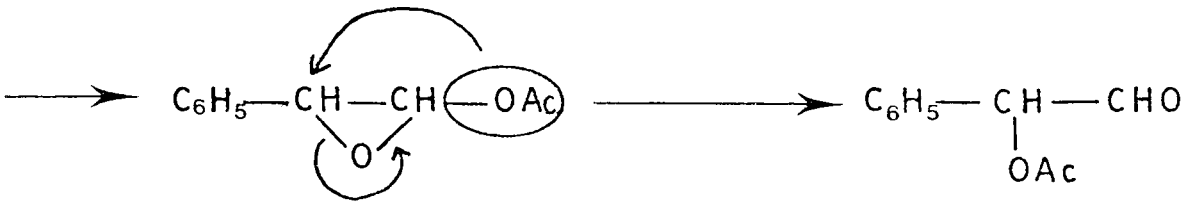
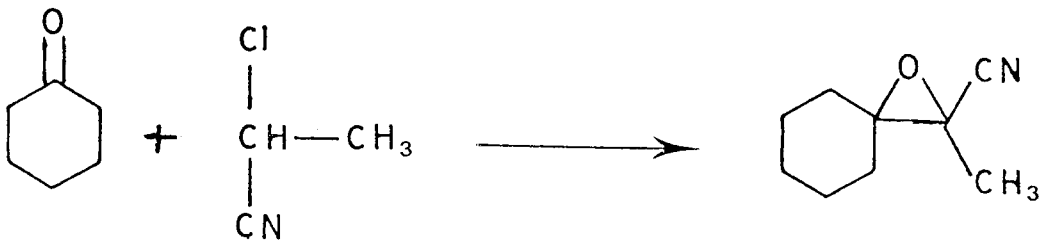
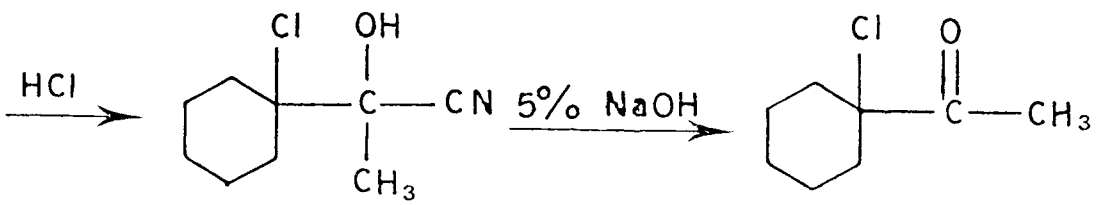


(40) (41)

SCHEME 6



(42)



(43) (44)

(6) By thermal rearrangement of epoxide

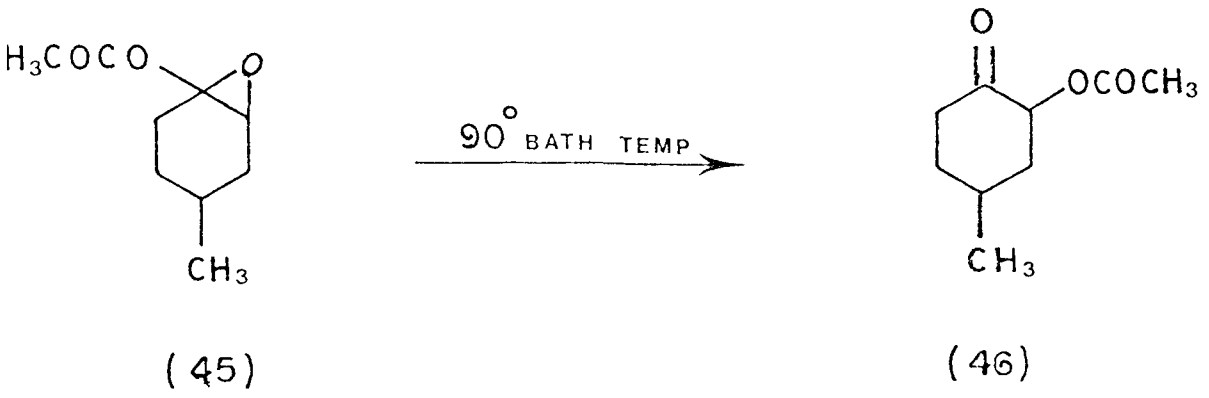
Draper and co-workers[8] reported that when the epoxide (45) was heated at 90° bath temperature it underwent a rearrangement to give α-acetoxy ketone (46). Further report was that when a mixture of 1-acetoxy-4-methyl cyclohexane oxide (45) and 1-propionoxy cyclohexane oxide (47) was allowed to undergo thermal rearrangement no cross products were formed. The rate of rearrangement of (47) was shown to be approximately 2.5 times as fast as that of (45). This establishes the rearrangement as an intramolecular 1, 2 migration of the acyloxy group (see scheme 7, chart 4).

Similar type of rearrangement was found to be taking place when sodium glycidates were treated with lead tetra acetate in presence of pyridine. Thus sodium glycidate (1b) furnished α-acetoxy aldehyde (1) by thermal rearrangement of acyloxy group. The details of the reaction will be discussed later in this chapter.

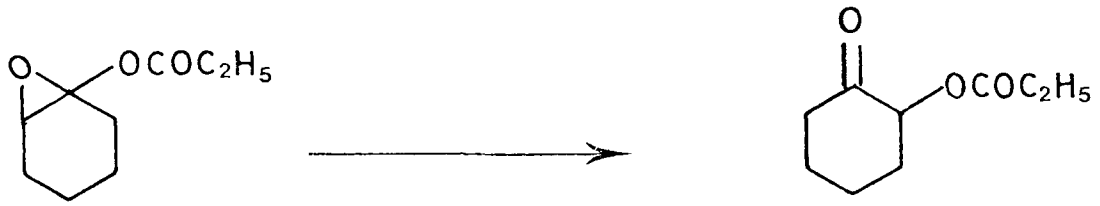
There are a number of reports in the literature in which α-acetoxy epoxides rearrange thermally to yield α-acetoxy aldehydes or ketones. For example 3β-20-Diacetoxy-9α-11β-dichloro-16β methyl $\Delta^{17(20)}$pregnane oxide (49) has been isolated and found to rearrange[9] to ketoacetate (50) by thermal reaction (see chart 4).

CHART 4

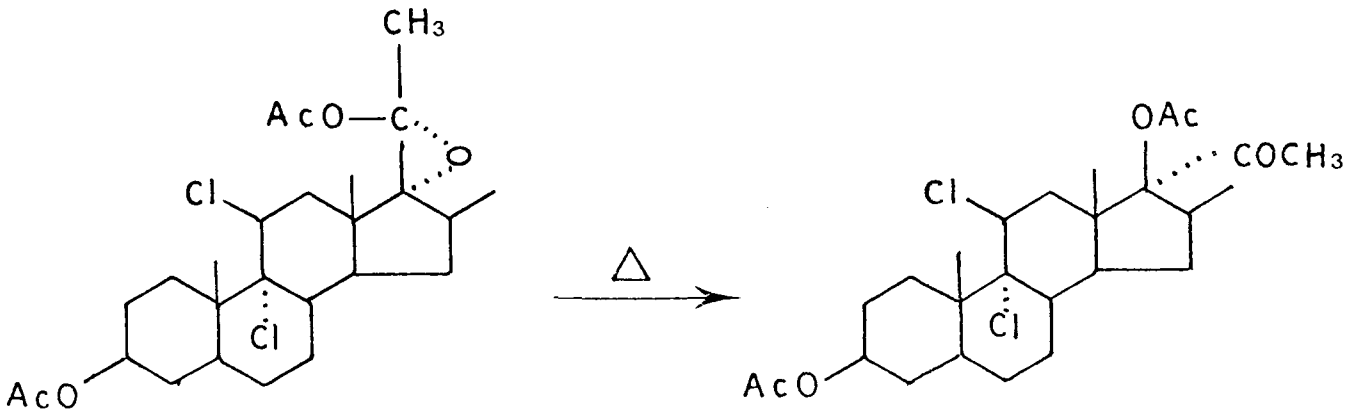
SCHEME 7



(45) (46)



(47) (48)



(49) (50)

1.3. PRESENT WORK

One of the objectives during our investigations was the synthesis of naturally occurring[10,11] thymol derivatives (7) and (8) (see chart 5). The aldehyde (9) appeared to be a good intermediate for the synthesis of (7) and (8).

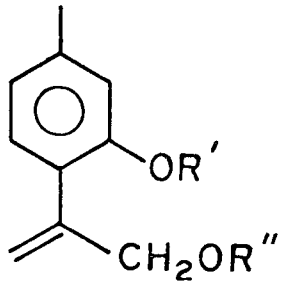
A possible route for the synthesis of (9) would be through the aldehydes (10), (11), (12), and (13). (see chart 5). As these aldehydes possess electronegative group on the α-carbon, it can be visualized that they may undergo ready elimination of HX (X=Br, OH, OAc or Cl) to give (9). Therefore a project was undertaken to devise a synthetic route for substituted aldehydes, having a suitable electronegative group on the carbon atom α- to the aldehyde group*.

A convenient route for the preparation of α-acetoxy aldehydes has been developed starting from glycidic esters.

Glycidic esters were obtained by the well known Darzens glycidic ester synthesis. In essence, the method involves the condensation of aldehyde or ketone with α halo ester in presence of a base, which is frequently sodium ethoxide or sodium amide.

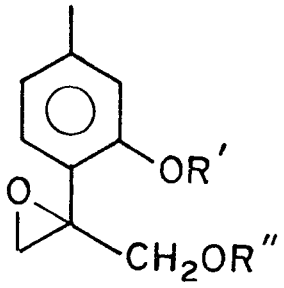
*The known methods for synthesis of α-bromo, α-chloro, and α-hydroxy aldehydes have been reviewed earlier.

CHART (5)

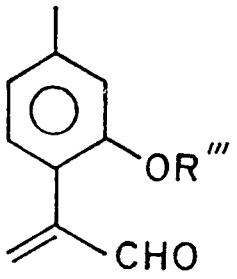


(7)

R' = R'' = CO CH(CH3)2

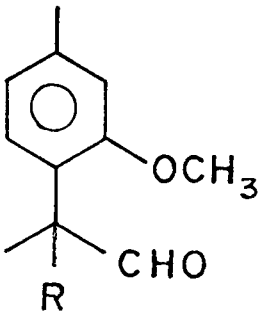


(8)



(9)

R''' = CH3

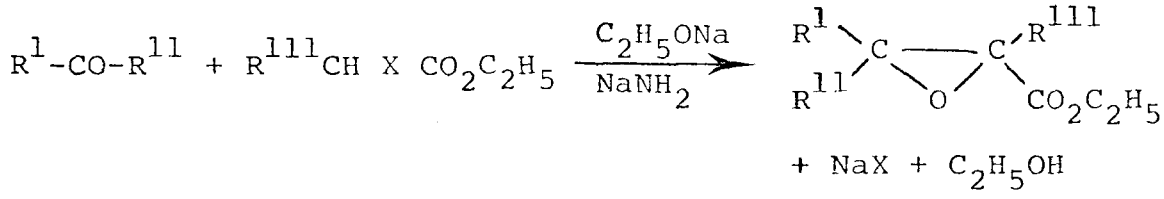


R = Br (10)

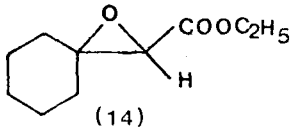
R = OH (11)

R = OAc (12)

R = Cl (13)



The first synthesis of glycidic ester was performed by Erlenmeyer[12], who obtained ethyl-β-phenyl-α, β-epoxy propionate by condensing benzaldehyde with ethylchloroacetate, in presence of sodium metal. Darzens developed and generalized this reaction by using sodium ethoxide as condensing agent. This was further modified by Johnson et.al[13] by using potassium t butoxide as condensing agent. For example, when a solution of the alkoxide in t-butanol was slowly added to a solution of cyclohexanone and ethylchloroacetate in t-butanol at 10-15°, the glycidic ester (14) was obtained in 83% yield. Thus using potassium-tert-butoxide afforded good yields of the glycidic ester.

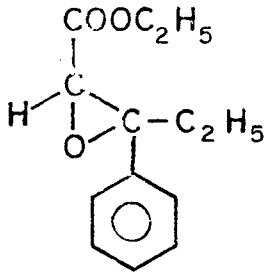


(14)

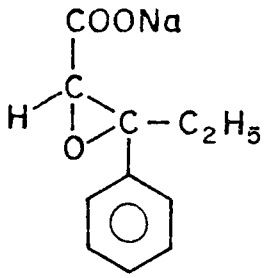
The mechanism of glycidic ester formation probably involves the addition of the enolate of the halo ester to the carbonyl group of the aldehyde or ketone followed by an intramolecular nucleophilic displacement on carbon. The basic condensing agent acts to convert the halo ester to its enolate[13].

The glycidic esters 1a→6a (see chart 6) are known compounds[14]. They were prepared as exemplified by the preparation of (1a). (1a) was prepared by condensing propiophenone

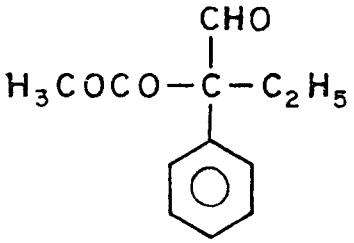
CHART (6)



(1a)



(1b)



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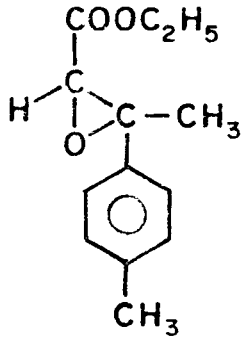
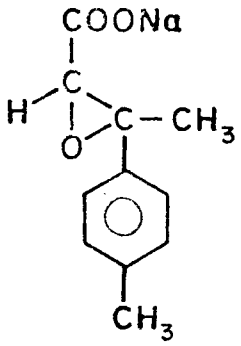


(2a)



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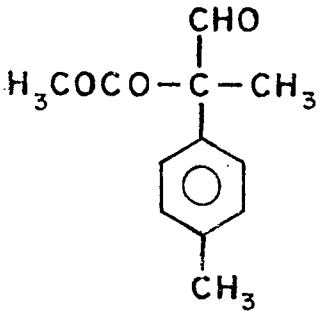

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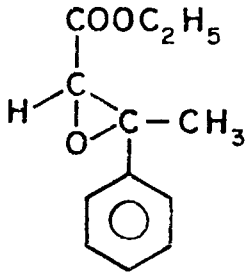
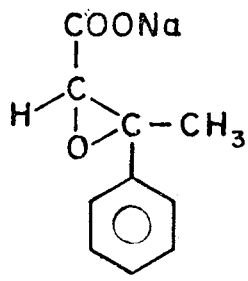


(3a)



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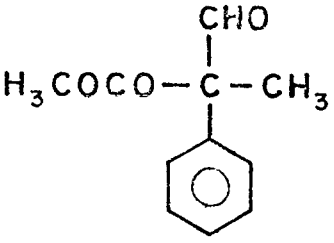

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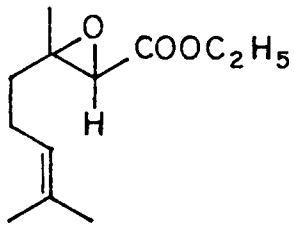
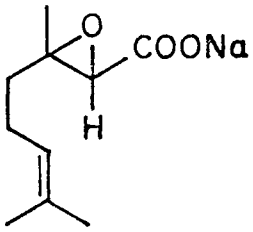


(4 a)



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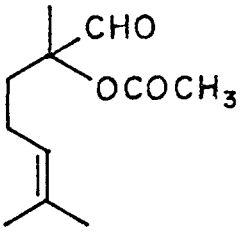

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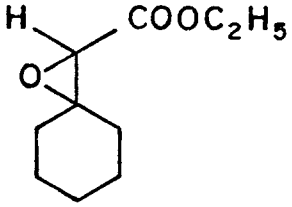

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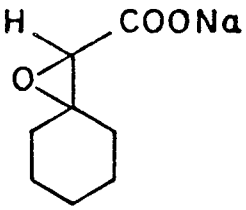

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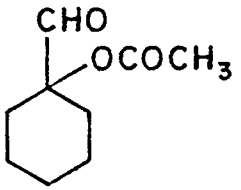

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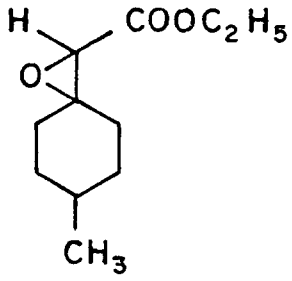

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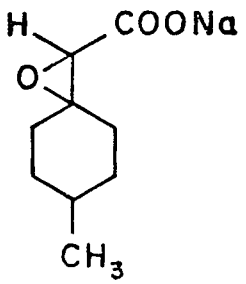

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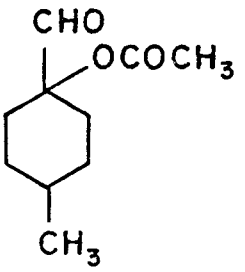
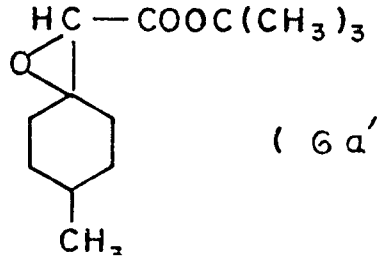


(6)



(6 a′)

and ethylchloroacetate in presence of potassium-tert-butoxide.

The glycidic esters (2a→6a) were prepared by condensing the suitable carbonyl compound with ethyl chloroacetate under similar conditions.
(p.s. experimental part)*. The glycidic esters obtained were identified as required compounds from their IR and PMR spectra. Glycidic ester (1a) showed a band at 5.7μ in IR due to ester carbonyl stretching. Its PMR spectrum showed signals for cis and trans isomers. It showed signals at 4.26 and 3.8 (two quartets due to ester CH_2), 3.6, 3.3 (singlets due to oxirane proton), 1.36δ, 0.95δ (triplets due to ester methyl group).

The product obtained from 4-methyl cyclohexanone and ethyl chloroacetate was found to be the mixture of (6a) and ($6a^1$). No serious attempts were made for separation of this mixture because both esters (6a) and ($6a^1$) were expected to give same sodium salt (6b).

*It is reported in the literature[15] that (3a) was obtained in 62% yield on condensing acetophenone and ethylchloroacetate in presence of sodium amide.

Condensation of 6-methyl-5-heptene-2-one and ethylchloroacetate in presence of sodium ethoxide at -5° is reported to give the glycidic ester (6a)[16]

Johnson et al[17] have devised a method for the preparation of the sodium salt of glycidic acid. Thus ethyl glycidate when treated with one equivalent of sodium in ethanol followed by exactly one equivalent of water afforded the sodium glycidate.

The sodium salt (1b) was prepared following similar conditions. It was obtained as a mixture of diastereoisomers. Literature reports opening of the epoxide ring of the glycidic ester in presence of a base. However it was found to be intact in (1b) as shown by oxirane proton signals at 3.6 and 3.3δ in its PMR spectrum.

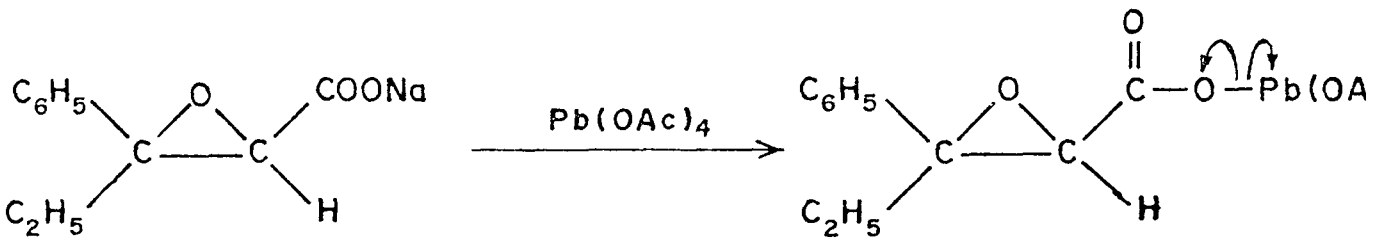
The sodium salts (2b→6b) (chart 6) were prepared similarly and characterized spectroscopically.

It was now left to convert the sodium glycidates to the corresponding α-acetoxyaldehydes. The reagent of choice was lead (IV) acetate. It was anticipated that when the sodium salt (1a) was treated with lead (IV) acetate under suitable conditions, the α-acetoxy aldehyde (1) would be obtained.

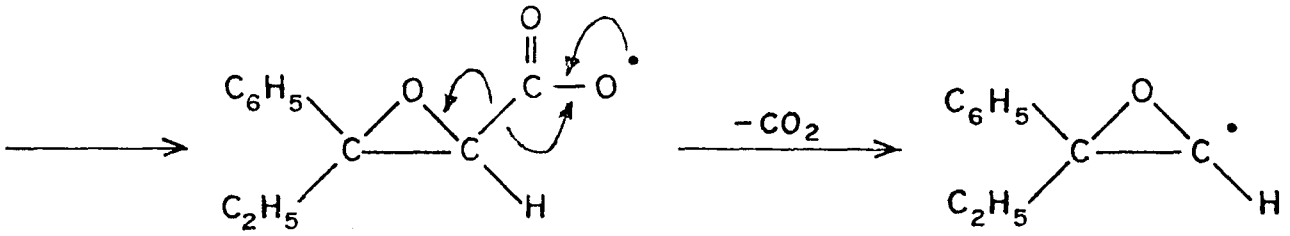
The formation of (1) from (1b) could proceed through the lead (IV) ester (21). The lead (IV) ester (21) could decompose to furnish the radical (22) (chart 7).

More recent studies[18] have indicated that thermal or photolytic decomposition of a lead (IV) ester may lead to

CHART (7)

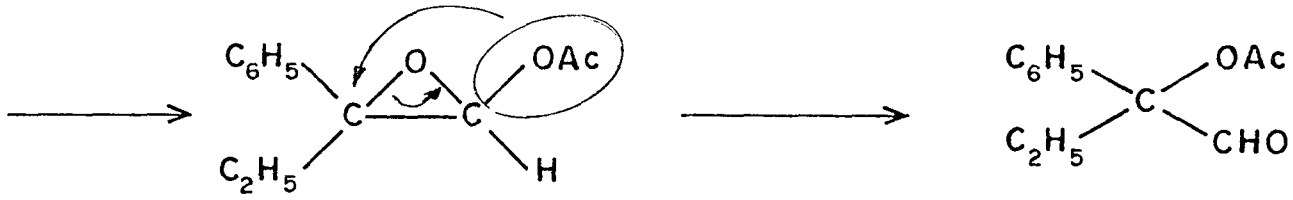


(1b) (21)



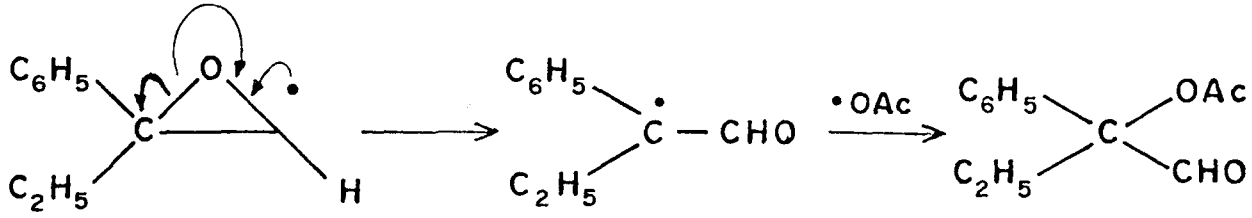
+ •Pb(OAc)3 (18)

(22)



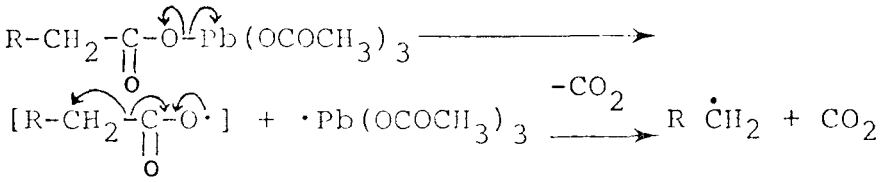
(19) (I)

ALTERNATE PATHWAY



(18) (20) (I)

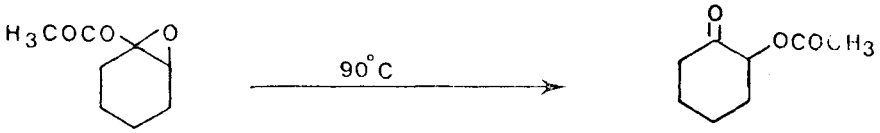
a transient acyloxy radical. Rapid decarboxylation of this acyloxy radical would lead to the formation of an alkyl radical, e.g.



On similar lines the formation of the oxiranyl radical (18) from (1b) can be explained as given in the (chart 7).

The oxiranyl radical (18) could then undergo substitution with ·OAc to give the acetoxy oxirane (19).

It is well known in the literature[19] that oxiranes with α-acetoxy groups readily rearrange on heating to the α-substituted carbonyl compounds e.g.



Analogously (19) may rearrange to yield the aldehyde (1) (chart 7).

Alternatively the radical (18) might first rearrange to the radical (20) and then react with the acetoxy radical to give the same aldehyde (1) (chart 7).

The reaction between lead (IV) acetate and the sodium salt (1b) was carried out in benzene at reflux temperature, in presence of catalytic amounts of pyridine. The anticipated α-acetoxy aldehyde (1) was obtained after workup.

The structure of (1) was confirmed by its IR and PMR spectra. The IR spectrum exhibited bands at 3.67μ (aldehyde C-H stretching), and 5.78 and 8.05μ (due to acetate

group). The PMR spectrum (fig. 1) exhibited signals at 9.35δ (1H singlet due to the aldehyde proton), 2.23δ(3H singlet due to acetate methyl).

The aldehyde (1) furnished a semicarbazone which was characterized by elemental analysis.

Five more α-acetoxy aldehydes (1→6) (chart 6) were synthesized following the similar sequence of reactions. The structures of all these compounds have been confirmed by spectroscopy and analysis (see figs. 2-6).

CHART (8)

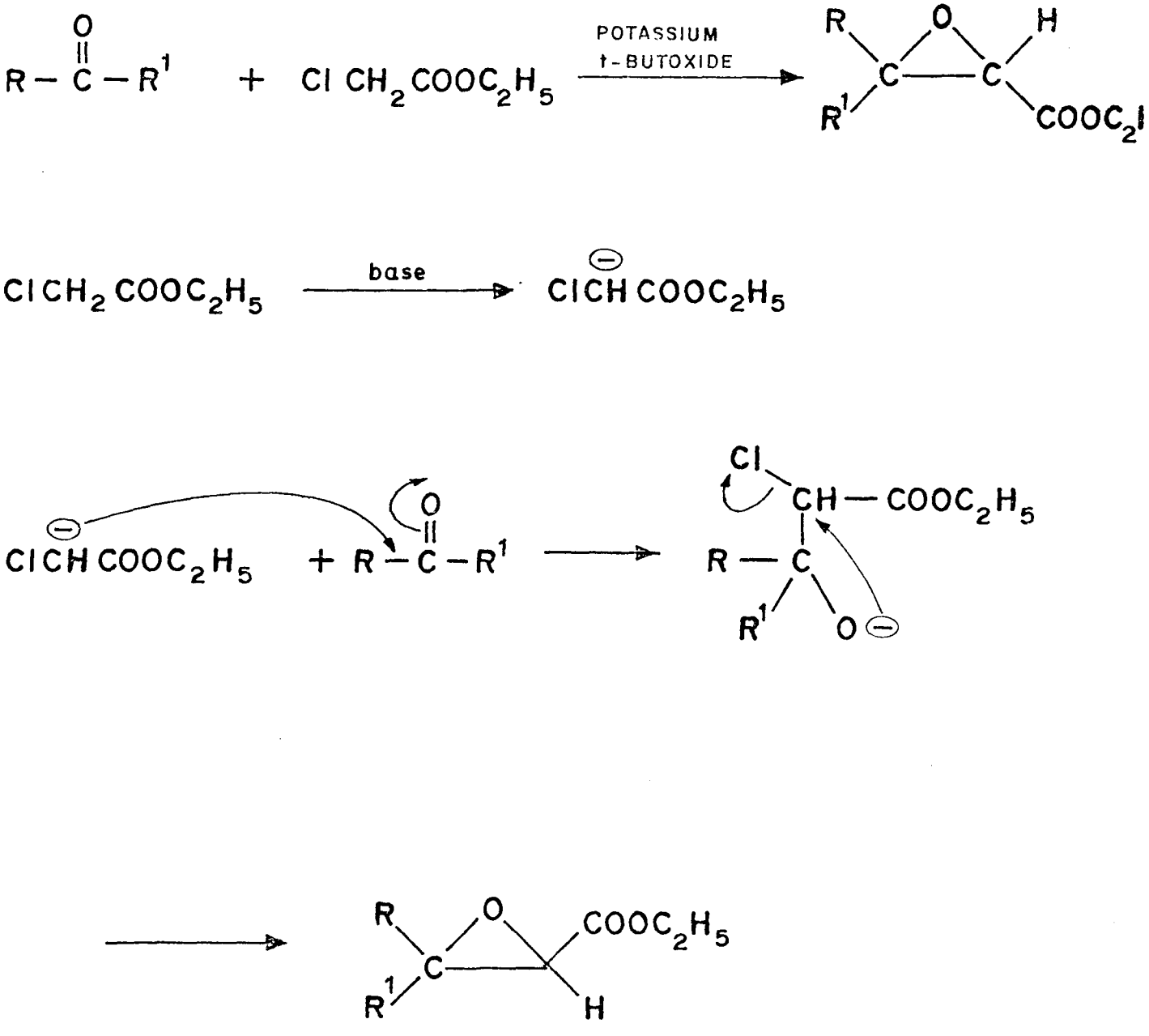
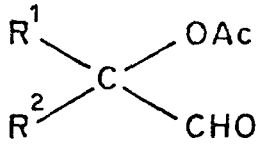
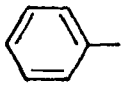
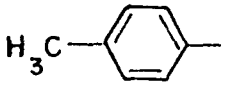
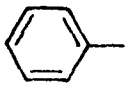
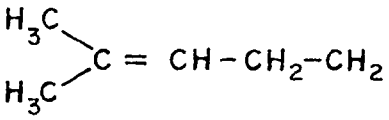


CHART (9)



(23)

23	R^1	R^2	YIELD %	B.P./torr.	SEMICARBAZON m.p
1	C_2H_5		56	170-175°/30	186°
2	CH_3		35	165-170°/30	215°
3	CH_3		50	150-155/°30	205°
4	CH_3		45	140-145°/60	140°
5	$-(CH_2)_5-$		35	140-145°/70	190°
6	$-CH_2-CH_2-CH(CH_3)-CH_2-CH_2-$		40	180-185°/55	201°

1.4. EXPERIMENTAL

1) 2-Acetoxy-2-phenyl butanal (1)

Ethyl ester (1a) of 2-ethyl-2-phenyl oxirane carboxylic acid was prepared from propiophenone and ethyl chloroacetate according to the method given in the literature[17].

b.p. $_{10mm}$ 140-142°C; literature[15] reports b.p. $_{12mm}$ 150°.

IR Spectrum (liquid film) showed bands at 5.7μ (-C=O) stretching.

PMR Spectrum (CCl_4) showed signals for cis and trans isomers at δ=7.3 (S, 5H, aromatic H), 4.26, 3.8 (two quartets, 2H, J=7Hz, ester $-CH_2-CH_3$), 3.6, 3.33 (two singlets, 1H, oxirane H·), 2.0 (q, 2H, $-CH_2-CH_3$), 1.36, 0.95 (two triplets, 3H, J=7Hz, ester $-CH_2-CH_3$).

(1a) was transformed to its sodium salt (1b) as follows:

To the ice cooled solution of sodium ethoxide prepared by dissolving sodium (0.53 g, 0.023 mol) in absolute alcohol (15 ml), was added (1a) (5.0 g, 0.023 mol), dropwise and with stirring. Addition of water (0.4 ml, 0.023 mol) furnished sodium salt (4.7 g) which was separated by filtration.

A mixture of sodium salt (1b) (2.14 g, 10 m mol), pyridine (1.58 g, 20 m mol), lead (IV) acetate (8.86 g, 20 m mol), and benzene (75 ml) was stirred under nitrogen for 0.5 hrs. at room temperature and under reflux for 5 hrs. The reaction mixture was cooled to room temperature, treated with

ethylene glycol to decompose excess of lead (IV) acetate and then washed with water, dilute hydrochloric acid and again with water. The benzene layer was separated, dried (Na_2SO_4), solvent distilled off and the residue was vacuum distilled to furnish acetoxy aldehyde (1).

(Yield: 1.15 g.) b.p. $\overset{\text{(bath)}}{30\text{ mm}}$ 170-175°

IR Spectrum (liquid film) showed bands at 3.67μ (C-H stretching. 5.78 and 8.05μ (acetate $-\overset{O}{\overset{\|}{C}}-$).

PMR Spectrum (CCl_4) showed signals at δ=9.35 (S, 1H, -CO-H), 7.32 (m, 5H, aromatic), 2.32 (q, 2H, $-CH_2-CH_3$, J=7Hz), 2.23 (S, 3H, $-O-CO-CH_3$), 0.68 (t, 3H, J=7Hz, $-CH_2-CH_3$).

2) Semicarbazone derivative of acetoxy aldehyde (1)

To a solution of semicarbazide hydrochloride (0.17 g, 2.6 m mol) and sodium acetate (0.13 g) in water (2 ml) was added acetoxy aldehyde (1) (0.30 g, 2.12 m mol). Slight turbidity appeared which was discharged by adding alcohol (2 ml). Solution was warmed on water bath for few minutes and allowed to cool at room temperature. Separated semicarbazone was filtered, washed (H_2O), then with cold alcohol and dried. Crystallized from alcohol. m.p. - 186°.

Analysis

Found: C, 59.34; H, 6.46; N, 16.19

$C_{13}H_{17}N_3O_3$ requires: C, 59.30; H, 6.51; N, 15.96%

3) 2-Acetoxy-2-(4-methylphenyl) propanal (2)

Ethyl ester (2a) was prepared as reported in the literature[17].

IR Spectrum (liquid film) showed band at 5.7μ (-C=O stretching).

PMR Spectrum (CCl_4) showed signals for cis and trans isomers at δ=7.2 (m, 4H, aromatic H), 4.33, 3.86 (two quartets, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 3.5, 3.26 (two S, 1H, oxirane H), 2.36 (S, 3H, CH_3 on benzene ring), 1.76 (S, 3H, methyl on oxirane), 1.35, 0.9 (two t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

Sodium salt of (2a) was prepared as described earlier.

A mixture of sodium salt (2b) (2.5 g, 0.047 mol), pyridine (1.85 g, 0.940 mol), lead (IV) acetate (10.35 g, 0.094 mol), and benzene (70 ml) was treated as described earlier.

The residue was vacuum distilled.

(Yield: 0.842 g, 35%) b.p. $\overset{\text{(bath)}}{30\text{ mm}}$ 165-170°

IR Spectrum (liquid film) showed bands at 5.75μ, 8.1μ (acetate -C=O group), 5.98 (-C-H stretching of aldehyde).

PRM Spectrum (CCl_4) showed bands at δ=9.32 (S, 1H, $-\overset{O}{\overset{\|}{C}}-\underline{H}$), 7.25 (m, 4H, aromatic), 2.37 (S, 3H, CH_3 on benzene ring), 2.2 (S, 3H, -O-CO $C\underline{H}_3$), 1.79 (S, 3H, $Ph-\overset{OAc}{\overset{|}{\underset{CHO}{\underset{|}{C}}}}-C\underline{H}_3$).

4) Semicarbazone derivative of acetoxy aldehyde (2)

Semicarbazone of acetoxyaldehyde was prepared as described earlier.

m.p.: 215°

Mass spectrum showed M^+ peak at 263. M^+ calculated for $C_{13}H_{17}N_3O_3$ = 263.

5) 2-Acetoxy-2-phenyl propanal (3)

Ethyl ester (3a) of 2-methyl-2-phenyl-oxirane carboxylic acid was prepared by method reported in the literature[17]. b.p. $_{4\ mm}$ 120-125° [literature reports b.p. $_{3mm}$ 111-114°]

IR Spectrum (liquid film) showed band at 5.7μ (-C=O stretching).

PMR Spectrum (CCl_4) showed signals for cis and trans isomers at δ=7.5-7 (m, 5H, aromatic H), 4.23 (q, 2H J=7Hz, $-C\underline{H}_2-CH_3$), 3.8 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 1.76 (d, 3H, J=3Hz, methyl on oxirane), 1.26 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 0.83 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

A mixture of sodium salt (3a) (5.00 g, 0.025 mol), pyridine (3.9 g, 0.05 mol), lead (IV) acetate (22.1 g, 0.050 mol) and benzene (150 ml) was treated as described earlier.

The residue was vacuum distilled at 150-155° (bath temperature) at 30 mm. (Yield: 2.4 g, 50%).

IR Spectrum (liquid film) showed bands at 3.65μ (C-H stretching), 5.78μ, (acetate group), 5.95μ (aldehyde-$\overset{O}{\overset{\|}{C}}$-stretching).

PMR Spectrum (CCl_4) showed signals at δ=9.4 (S, 1H, $-\overset{O}{\overset{\|}{C}}-H$), 7.4 (m, 5H, aromatic), 2.26 (S, 3H, $-O-CO-C\underline{H}_3$), 1.9 (S, 3H, $Ph-\overset{OAc}{\overset{|}{\underset{CHO}{\underset{|}{C}}}}-CH_3$)

Semicarbazone of acetoxy aldehyde (3) was prepared as described earlier. m.p. 205°C.

6) 2-Acetoxy-2,6 dimethyl, hept-5-en-al (4)

Ethyl ester (4a) was prepared as reported in the literature[17].

b.p. $\overset{(bath)}{30mm}$ 190-200°C. (literature reports b.p. $\overset{117°C)}{5mm}$

IR Spectrum (liquid film) showed band at 5.8μ (ester $-\overset{O}{\overset{\|}{C}}-$ stretching).

PMR Spectrum (CCl_4) showed signals at δ=5.1 (t, 1H, proton on double bond), 4.23 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 3.2 (d, 1H, oxirane H), 1.76 (S, 3H, methyl on double bond), 1.66 (S, 3H, methyl on double bond), 1.4 (t, 3H, J=7Hz, $-CH_3-C\underline{H}_3$)

Sodium salt of (4a) was prepared as described earlier.

A mixture of sodium salt (4b) (2.2 g, 0.01 mol), pyridine (1.68 g, 0.02 mol), lead (IV) acetate (9.4 g, 0.02 mol) and benzene (75 ml) was treated in similar manner as given earlier.

The residue was vacuum distilled at 140-145° (bath temperature at 60 mm).

(Yield: 0.95 g, 45%)

IR Spectrum (liquid film) showed band at 5.8μ ($-\overset{O}{\overset{\|}{C}}-$ stretching.)

PMR Spectrum (CCl_4) showed signals at δ=9.6 (S, 1H, $-\overset{O}{\overset{\|}{C}}-H$),

5.1 (t, 1H, vinyl H), 2.18 (S, 3H, -OCO-$\underline{CH_3}$), 1.75 (S, 6H, methyl groups on double bond), 1.45 (S, 3H, -O-CO-$\underline{CH_3}$).

Semicarbazone of acetoxy aldehyde (4) was prepared as given earlier.

m.p. 140°C.

Analysis

Found: C, 56.55; H, 8.5; N, 16.51

$C_{12}H_{21}O_3N_3$ requires: C, 56.45; H, 8.29; N, 16.46%.

7) 1-Acetoxy cyclohexane carboxaldehyde (5)

Ethyl ester (5a) was prepared according to the method given in literature.

b.p. $_{13\ mm}$ 120-124°C, (literature reports b.p.$_{27mm}$ 134-137°C.

IR Spectrum (liquid film) showed band at 5.7μ (ester $-\overset{O}{\overset{\|}{C}}-$ stretching).

PMR Spectrum (CCl_4) showed signals at δ=4.16 (q, 2H, J=7Hz, -$\underline{CH_2}$-CH_3), 3.1 (S, 1H, oxirane H), 1.3 (t, 3H, J=7Hz, -CH_2-CH_3).

Sodium salt (5b) of ester (5a) was prepared as described earlier.

A mixture of sodium salt (5b) (2.0 g, 0.011 mol), pyridine (1.77, 0.02 mol), lead (IV) acetate (9.95 g, 0.02 mol), and benzene (75 ml) was treated as described earlier.

The residue was vacuum distilled at 140-150° (bath temperature) at 70 mm. (Yield: 0.66 g, 35%.)

IR Spectrum (liquid film) showed band at 5.7μ (-C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=9.45 (S, 1H, -C-H), 2.19 (S, 3H, -OCO-CH_3), 1.7 (m, 10H, methylene protons).

Semicarbazone of acetoxy aldehyde was prepared which had m.p. 190°C (literature reports m.p. 193°C).

8) 1-Acetoxy-4-methyl-cyclohexane carboxaldehyde (6)

Ethyl ester (6a) was prepared as reported in literature[17].

IR Spectrum (liquid film) showed band at 5.7μ (ester -C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=4.5-4.3 (two quartets, 2H, J=7Hz, -CH_2-CH_3), 3.23 and 3.13 (d, 1H, oxirane proton), 1.33 (t, 3H, J=7Hz, -CH_2-CH_3).

Sodium salt (6b) was prepared as described earlier.

A mixture of sodium salt (6b), (2.0 g, 0.010 mol), pyridine (1.64 g, 0.02 m mol), lead (IV) acetate (9.20 g, 0.02 mol) and benzene (75 ml) was treated as described earlier.

The residue was vacuum distilled at 180-185° (bath temperature) at 55 mm. (Yield: 0.76 g, 40%).

IR Spectrum (liquid film) showed bands at 3.75μ (aldehyde -C-H stretching).

PMR Spectrum (CCl_4) showed signals at δ=9.4 (S, 1H, -C-H), 2.2 (S, 3H, -O-C-CH_3), 1.1 (d, 3H, CH_3 on cyclohexane ring).

Semicarbazene of acetoxy aldehyde (6) was prepared as given earlier. m.p. 201°C.

Analysis

Found: N, 23.23 $C_{11}H_{19}N_3O_3$ requires: N, 23.2%.

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1.6 FIGURES

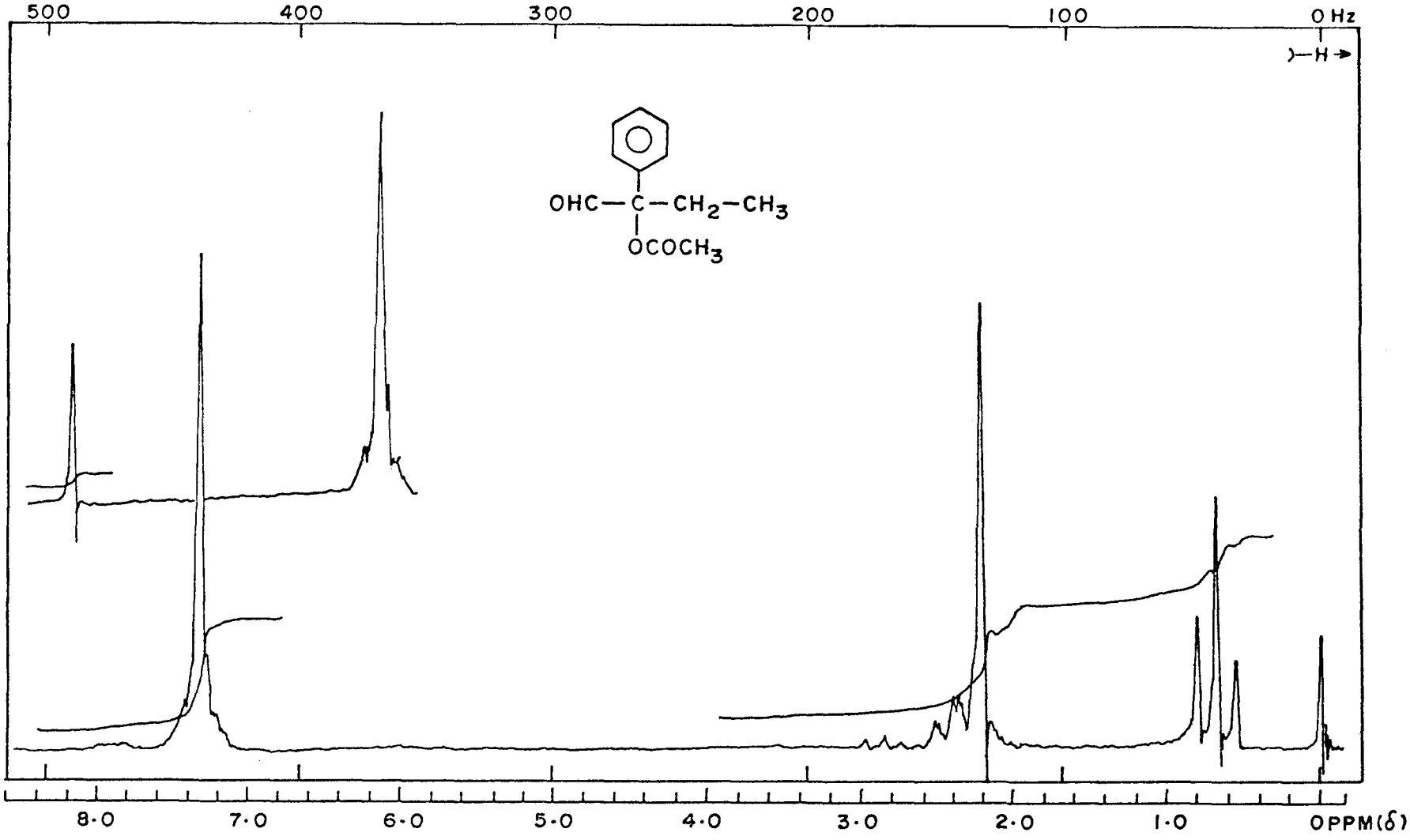


FIG. 1 PMR SPECTRUM OF 2-ACETOXY-2-PHENYL BUTANAL (I)

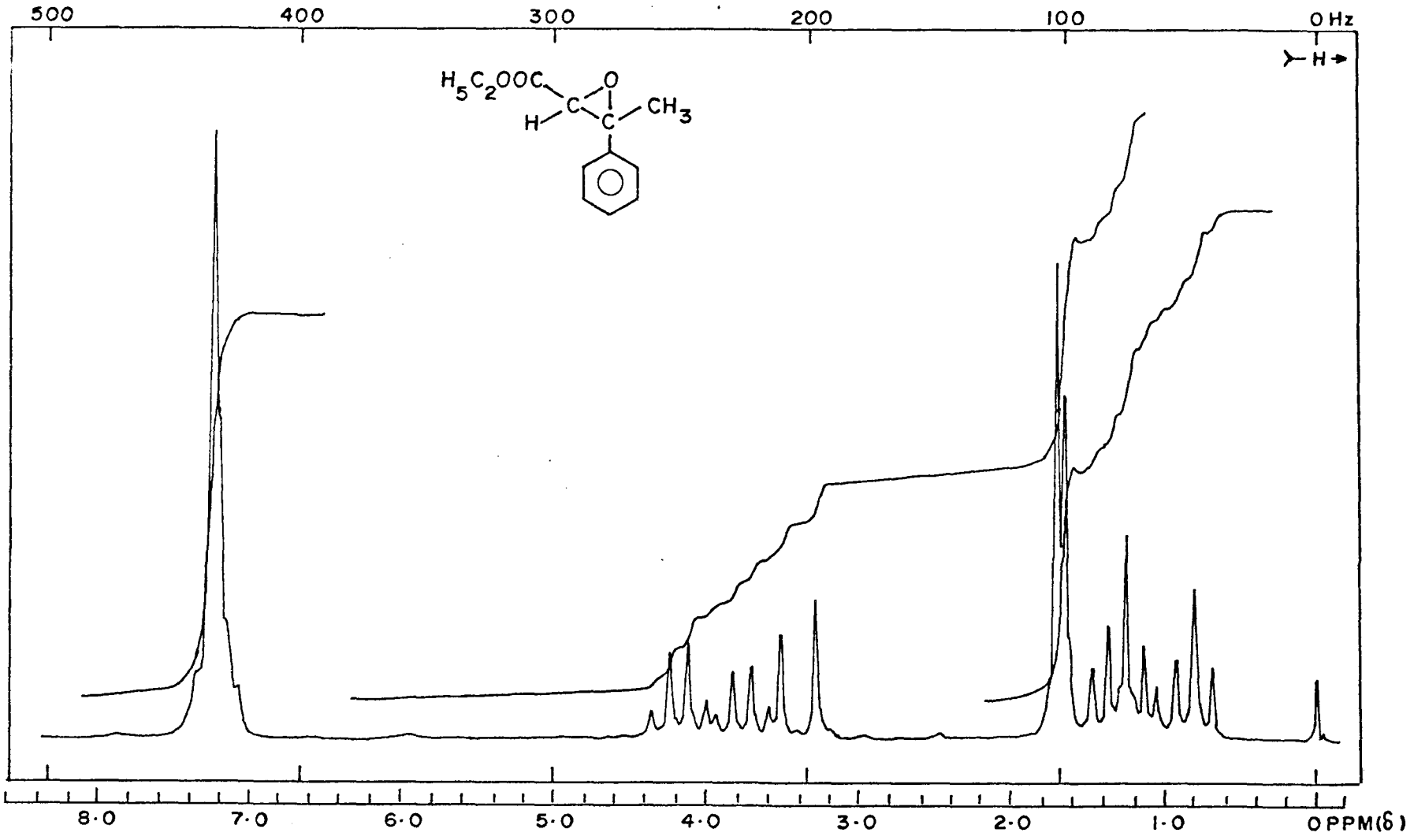


FIG.2 PMR SPECTRUM OF ETHYL-2-METHYL-2-PHENYL OXIRANE CARBOXYLATE (3a)

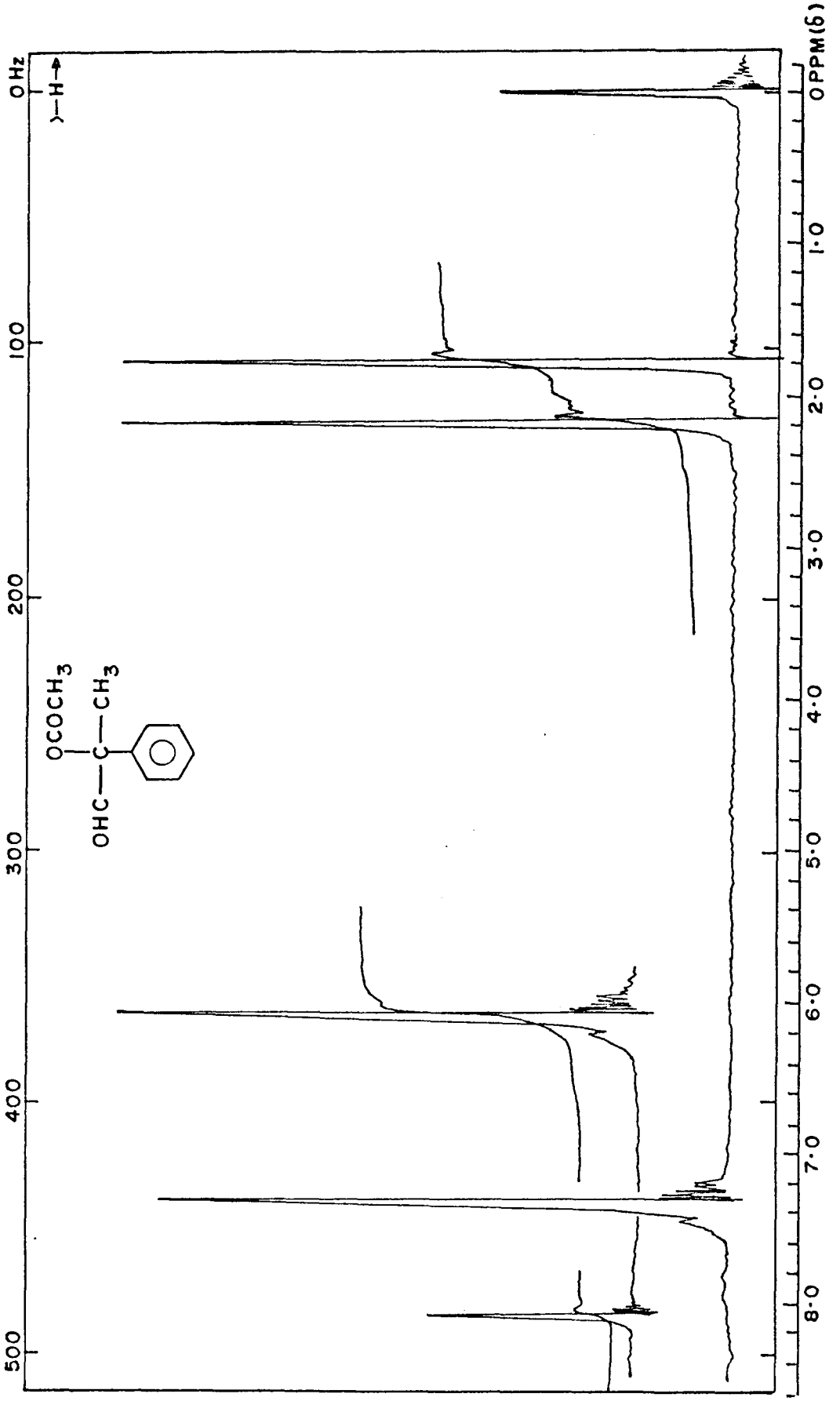


FIG.3 PMR SPECTRUM OF 2-ACETOXY-2-PHENYL PROPANAL(3)

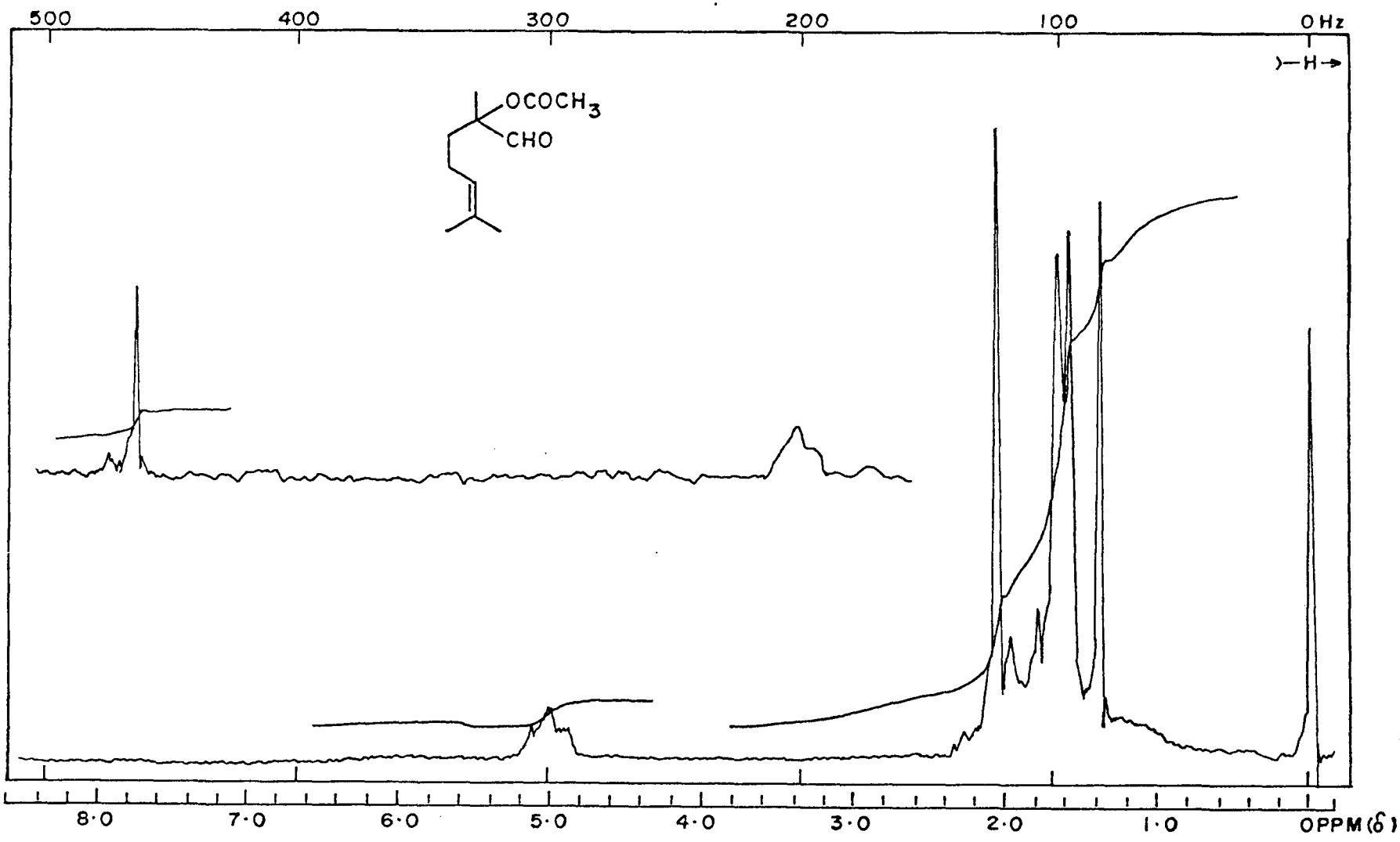


FIG. 4 PMR SPECTRUM OF 2-ACETOXY-2,6 DIMETHYL, HEPT-5-EN-1-AL(4)

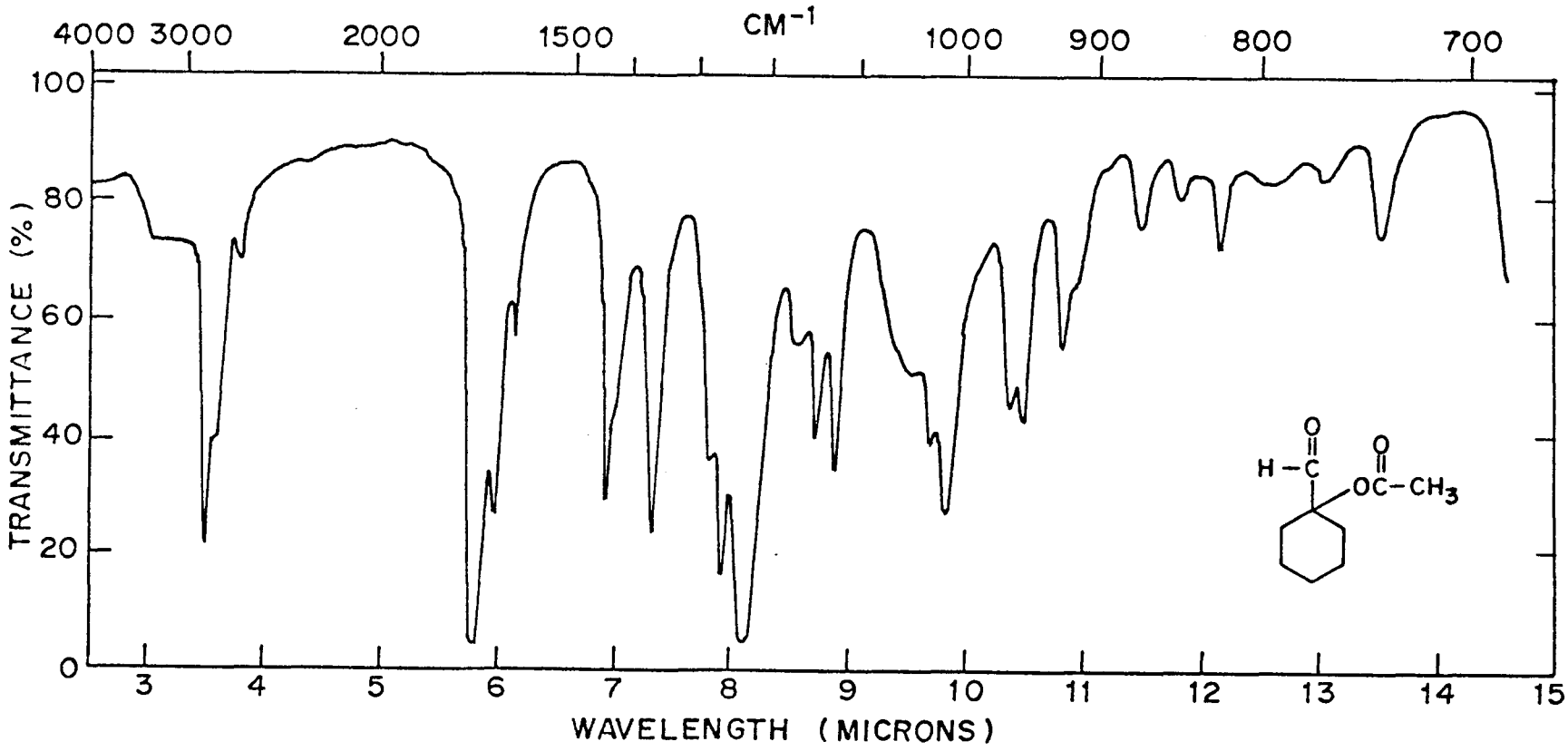
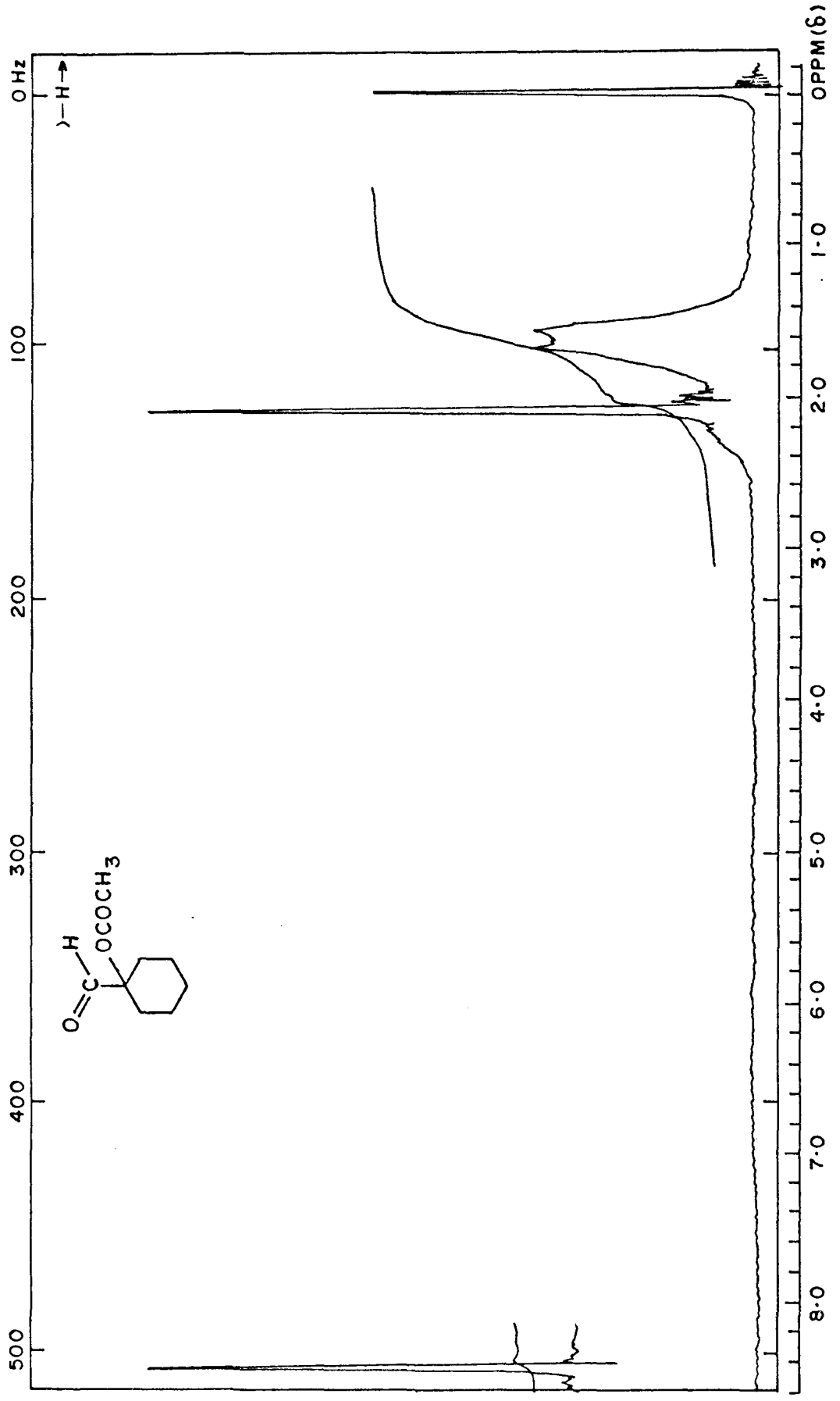


FIG. 5 IR SPECTRUM OF 1-ACETOXY CYCLOHEXANE CARBOXALDEHYDE (5)



FIG·6 PMR SPECTRUM OF 1-ACETOXY CYCLOHEXANE CARBOXALDEHYDE (5)

Th. 5319

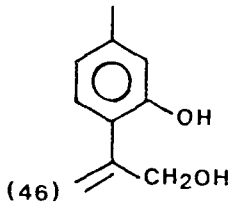
CHAPTER 2

1) SYNTHESIS OF 2-(2-HYDROXY-4-METHYLPHENYL) PROP-2-EN-1-OL DIISOBUTYRATE AND 2-HYDROXYMETHYL-2-(2-HYDROXY-4-METHYLPHENYL)-OXIRANE DIISOBUTYRATE.

2) TRANSFORMATIONS OF 2-(2-ACETOXY-5-METHYLPHENYL)-1-PROPENE AND 2-(2-ACETOXY PHENYL)-1-PROPENE.

2.1 SUMMARY

The synthesis of naturally occurring thymol derivatives, diisobutyrate (25) and oxirane (27), from diol (46), is presented.



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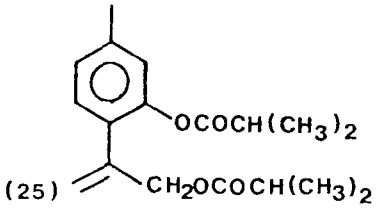

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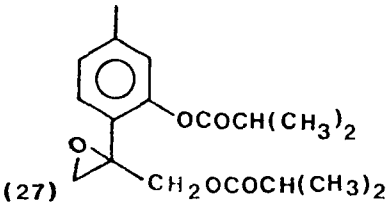
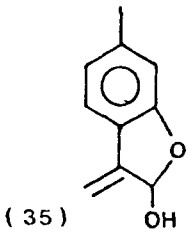


(27)

Also described here is the synthesis of benzofuranol derivatives (4) and (32), which are structurally related to the naturally occurring benzofuranol (35) possessing antineoplastic activity.



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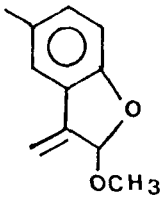

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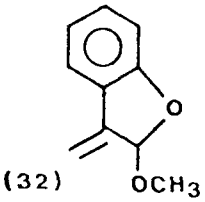
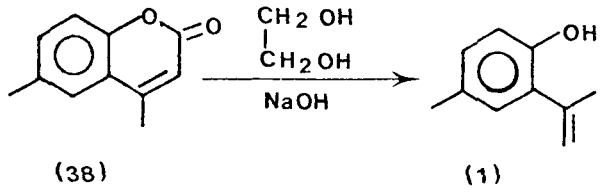


(32)

A convenient route for the preparation of ortho isopropenyl phenols is also presented. This can be exemplified by conversion of coumarin (38) to o-isopropenyl phenol (1). It is suggested that the quinone methide (40) is an intermediate in the transformation of (38) to (1).

Some interesting transformations of aldehydes (3), (31), and (8) are also presented.



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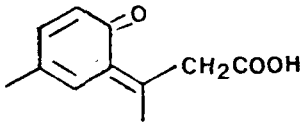

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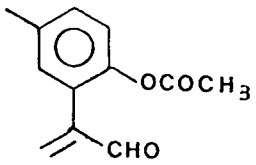

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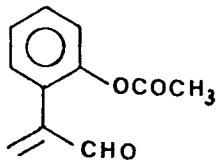

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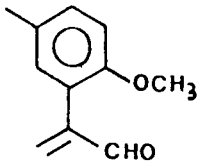


(8)

2.2. INTRODUCTION

Ortho isopropenyl phenols are important intermediates in the preparation of naturally occurring thymol derivatives. For example, 2-(2-hydroxy-4-methyl phenyl)-prop-1-ene (43), is an intermediate in the synthesis* of naturally occurring benzofuranol (35). Acylation of (43) furnished acetate (44) which was converted to aldehyde (45) by SeO_2 oxidation. Alkaline saponification of (45) with sodium hydroxide in methanol gave methyl ether of benzofuranol (35) Demethylation of methyl ether of (35) furnished (35), as reported in the literature[1]. (See chart 1). Benzofuranol (35) exhibits strong nematicidal action in vitro.

Similarly the synthesis of compounds (4), (5), (32), (33), which are structurally related to naturally occurring thymol derivative (35), involves o-isopropenyl phenols as intermediates.

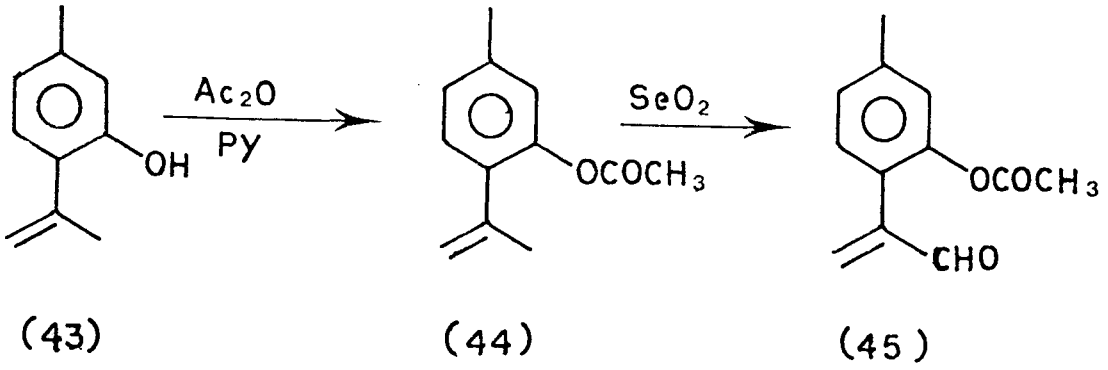
Several methods are available for the synthesis of o-isopropenyl phenols. A brief review of some of these methods is presented here.

(1) Dehydration method.

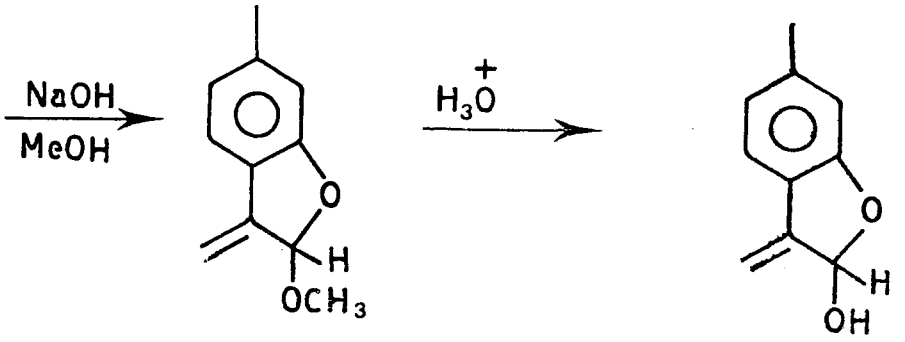
4-Chloro-2-isopropenyl phenol was prepared by W. Baker

*The synthesis of (35) has been carried out in NCL by Divakar and Rao. The synthesis has also been achieved by Bohlmann et.al.[1] employing a different route.

CHART I



(43) (44) (45)



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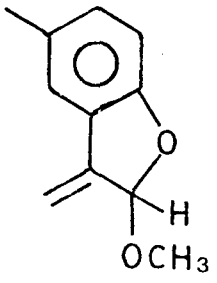

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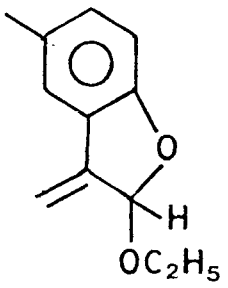

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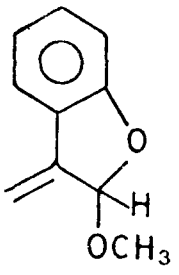

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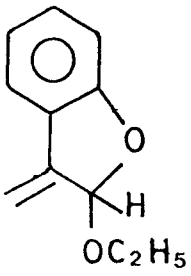


(33)

et.al.[2] starting from methyl 5-chloro salicylate.

The isopropenyl compound (56) cannot be obtained by direct condensation of p-chloro phenol with acetone owing to the weak reactivity of aromatic nuclei. It was, therefore, prepared by treating sodium salt of 5-chloro salicylate with methyl magnesium iodide. The resulting alcohol (55) was then dehydrated by heat to furnish required isopropenyl phenol (56). (See scheme 1, chart 1). 4-Bromo-2-isopropenyl phenol was also prepared by same route.

(2) o-Isopropenyl phenols by opening of aromatic-o-heterocycles.

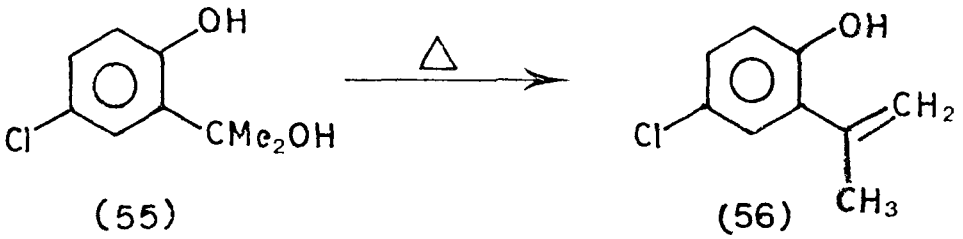
The method reported by J. Gripenberg et.al.[3] involved ring opening of aromatic o-heterocycles by sodium in pyridine. This method can be illustrated by the synthesis of 2-(2-hydroxy phenyl)-prop-2-ene (58) starting from 3-methyl-2,3 dihydrobenzofuran (57). (See scheme 2, chart 2).

(3) o-Isopropenyl phenols by catalytic dehydrogenation of alkyl phenols.

A.A. Balandin et.al.[4] observed that when the dehydrogenation of o-isopropyl phenol was carried out at 500-600° over Cu-Cr oxide catalyst, product was found to retain the phenolic group. The products obtained were isopropenyl phenol, H_2, CH_4, C_2H_4, C_2H_6, and C_3H_6. The catalysts were not poisoned by the products and retain the activity for long periods.

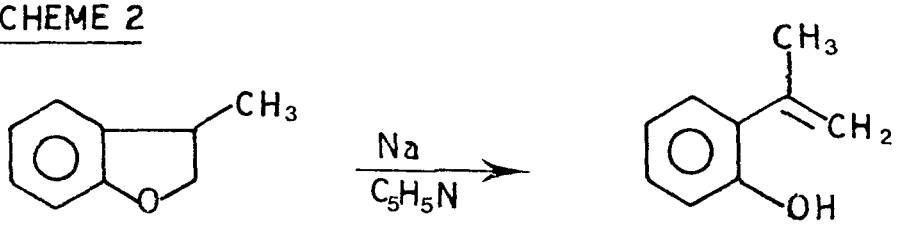
CHART 2

SCHEME 1



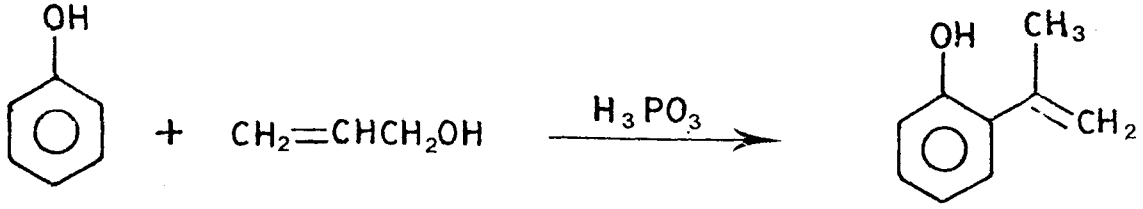
(55) (56)

SCHEME 2

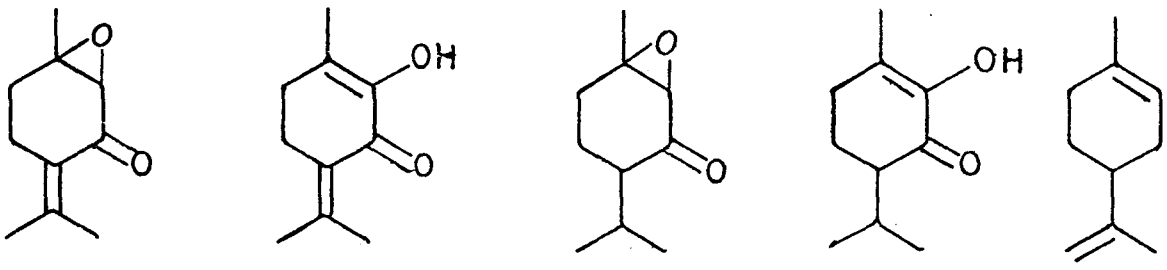


(57) (58)

SCHEME 3



(59) (58)



(60) (61) (62) (63) (64)

(4) Condensation of phenol and primary alcohol

This method is exemplified by the synthesis of 2-(2-hydroxyphenyl)-prop-2-ene (58).

Here 400 g. of phosphoric acid per gm mole of substance to be alkylated was used with a slight excess of alcohol. The reaction of phenol with either CH_2=CH CH_2OH or CH_2-$(CHOH)_2$ in presence of phosphoric acid as condensing agent furnished a polymerized product which when heated, depolymerized to give o-isopropenyl phenol[5]. (See scheme 3, chart 2).

Naturally occurring epoxides having p-menthane skeleton.

R. Reitsema[6] isolated a new ketone from oil of Mentha rotundifolia. The structure of 1,2-(epoxypulegone), (piperitenone oxide) (60) was proposed on the basis of spectra and degradation work. This ketone was the same as has been isolated from Indian 'spearmint' and from species of 'Lippia oils'.

Later on R. Reitsema[7] prepared piperitenone oxide by the action of alkaline hydrogen peroxide on piperitenone by the general method of Treibs[8]. The semicarbazone of piperitenone oxide was identical with the semicarbazone of naturally occurring M. rotundifolia ketone in respect to elementary analysis, UV spectra and in behavior in acid and base. Diosphenolene (61) was synthesized readily from (60) by treatment with dilute acid.

It was reported by S. Shimizu[9] that the presence of a new terpenic ketone in essential oil of M. rotundifolia was confirmed for oil produced in 1954 and 1955 in several places. The Japanese oil differed from that of the same species grown in Europe. Vacuum fractional distillation permitted isolation of new ketone rotundifolone (60). Rotundifolone was identified by its reactions[10] to be 1-methyl-4-isopropylidene-1,2-epoxy cyclohexan-3-one. This ketone seemed to be one of the intermediates between carvone and menthone series.

From the species of mint, Mentha sylvestris, a ketone was obtained[11] corresponding to the formula $C_{10}H_{16}O_2$. Through conversion to diosphenol (63) and progressive degradation studies, the structure of this material was shown to be ℓ-piperitone oxide (62).

It was reported by E. Klein et.al.[12] that the base catalyzed epoxidation of endocyclic double bond in piperitone was highly stereoselective resulting in a single epimer.

The limonene 1,2-oxides occur naturally in the essential oils of Cymbopogon densiflorus[13].

Oxidation of limonene (64) with organic peracids furnished a 1:1 mixture of cis and trans epoxides[14].

However, Royals et.al.[15] prepared (+) cis and (+) trans limonene 1,2-oxides. (+) trans-limonene 1,2-oxide (67) was first prepared from the (+) -1-hydroxy-neodihydrocarveol (65),

by the action of base on the easily formed tosylate (66). The (+) cis-limonene 1,2-oxide (69) was prepared by the action of base on (-)-1-mesylneodihydrocarvenyl acetate (68). (See chart 3.) The cis- and trans-pulegone oxide and piperitenone were found to be present in the volatile oil of the North American wild mint; (Mentha arvensis L. var. glabrata).[16]

Naturally occurring isobutyrates related to thymol

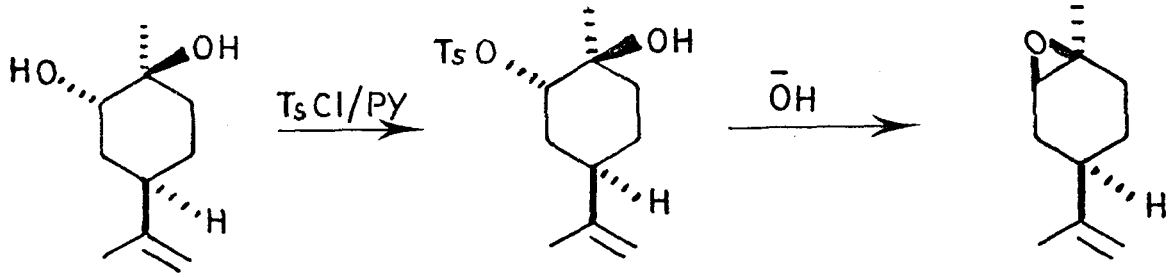
The root extracts of Arnica amplexicaulis were found to contain three thymol derivatives namely (70), (71), and (72)[17].

The root extracts of Helenium-Arten were found to contain number of esters which include a thymol derivative (73)[1].

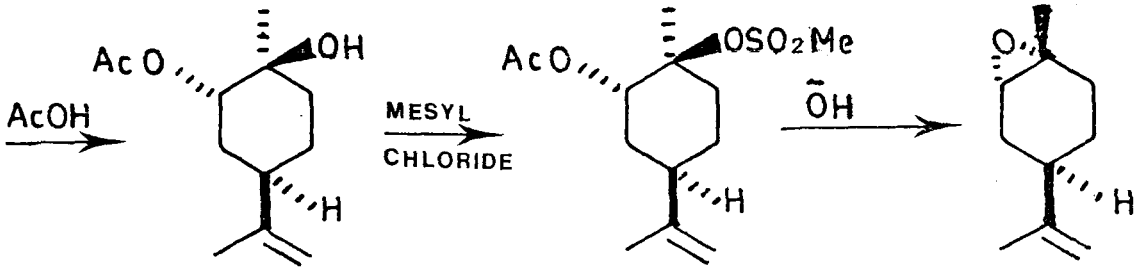
The presence of esters, which were found to be thymol derivatives, in the root extracts of Gaillardia and Helenium Arten was reported in the literature[18]. These compounds were identified from their spectral data and degradation reactions. The thymol derivatives which were found to be present were (74), (75), (76), (77), and (72).

Recently, it was reported by Bohlmann[19] that the investigation of six Mexican species of the old genus Eupatorium yielded large number of compounds. The two isobutyrates (72) and (73), which are thymol derivatives, were found to be present. (See chart 4.)

CHART 3



(65) (66) (67)



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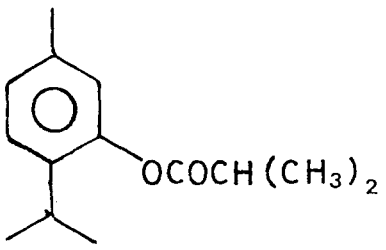

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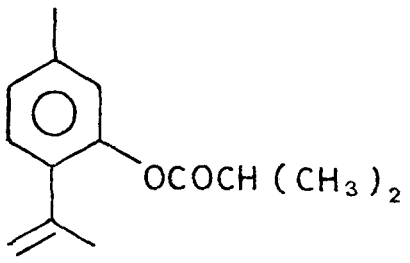

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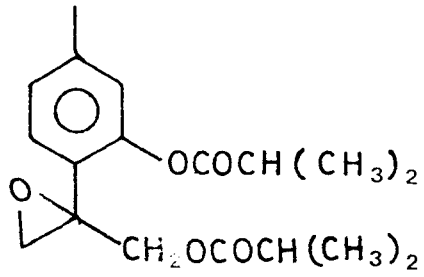

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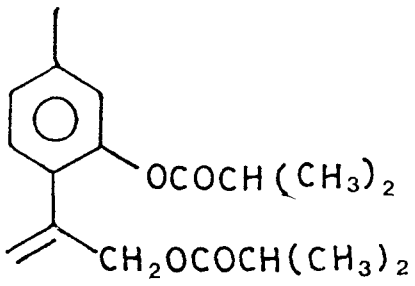

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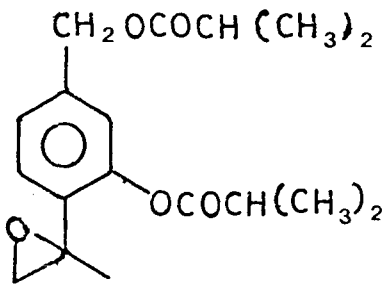

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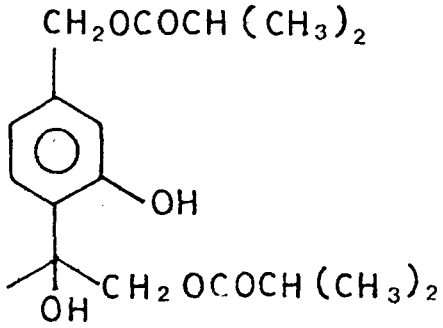

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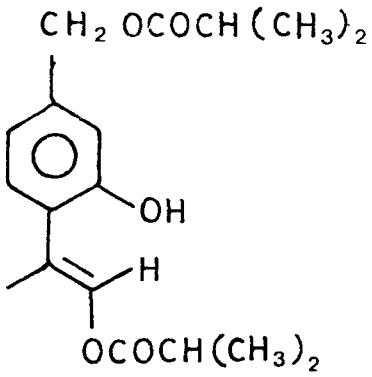

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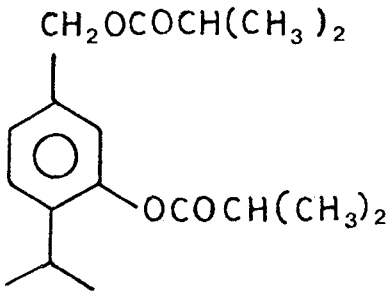


(77)

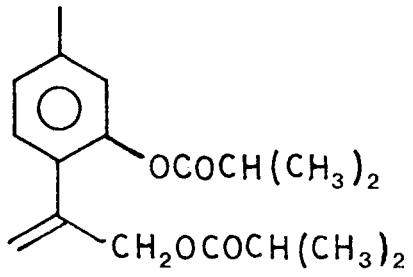
2.3 PRESENT WORK

The synthesis of naturally occurring thymol derivatives, diisobutyrate (25)[1], oxirane (27)[17] and the benzofuran derivatives (4) and (32), structurally related to the naturally occurring nematicide (35)[1] are presented in this chapter. A convenient route for the preparation of ortho isopropenyl phenols, developed in connection with the above synthetic investigations is also presented in this chapter.

o-isopropenyl phenol (28) is usually prepared by (i) dehydration of the diol[20] (55) (ii) action of heat on 3-(2-hydroxyphenyl)-but-2-(E)-enoic acid[21,22], or by other methods[20]. Since o-isopropenyl phenols are unstable in acidic medium[20] and attempted dehydration of (36) is reported[21] to furnish polymers it was considered of interest to prepare phenol (1) through a route in which prolonged contact of the product with acid is avoided. This led us to investigate the action of alkali on 4-methyl coumarins. Literature survey revealed that there are a number of papers[21-25] dealing with the action of alkali on coumarins; this reaction has proved useful in:

1. distinguishing coumarins from chromones[24],
2. preparation of 2-acetyl and other 2-substituted resorcinols[25] and
3. preparation of 3-aryl but-2-(E)-enoic acids[22,23].

CHART 5



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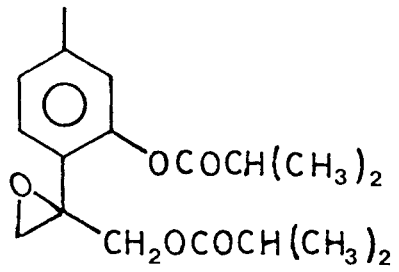

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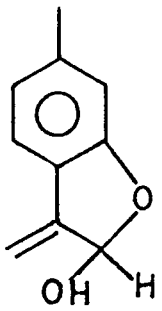

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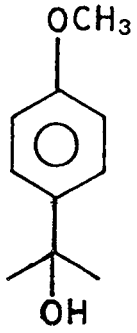

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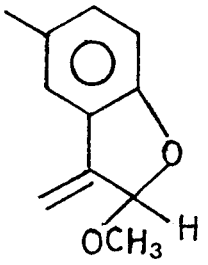

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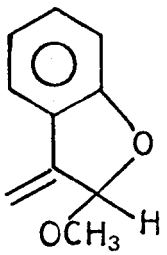

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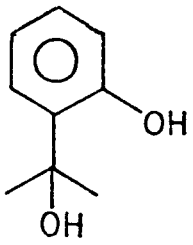


(55)

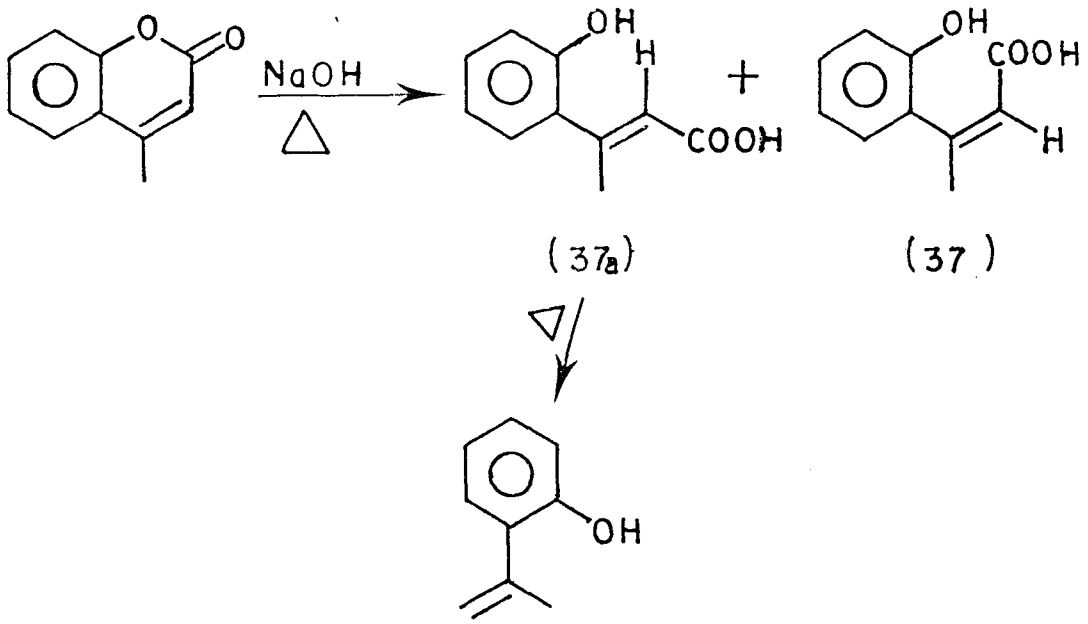
Fries et.al.[22] prepared o-isopropenyl phenol (28) starting from 4-methyl coumarin. 4-methyl coumarin was heated with aqueous alkali and the mixture of coumaric acids (37) and (37a) was isolated after acidification. Pyrolysis of the coumaric acid (37a) furnished o-isopropenyl phenol (28). It has been observed by us that the overall yield in the conversion of 4-methyl coumarin to (28) according to the method of Fries is only 30%. Moreover the decarboxylation step in the method of Fries et.al. is not convenient to carry out on large scale.

The route developed by us is more convenient from the manipulation point of view since the intermediate hydroxy acid is not isolated.

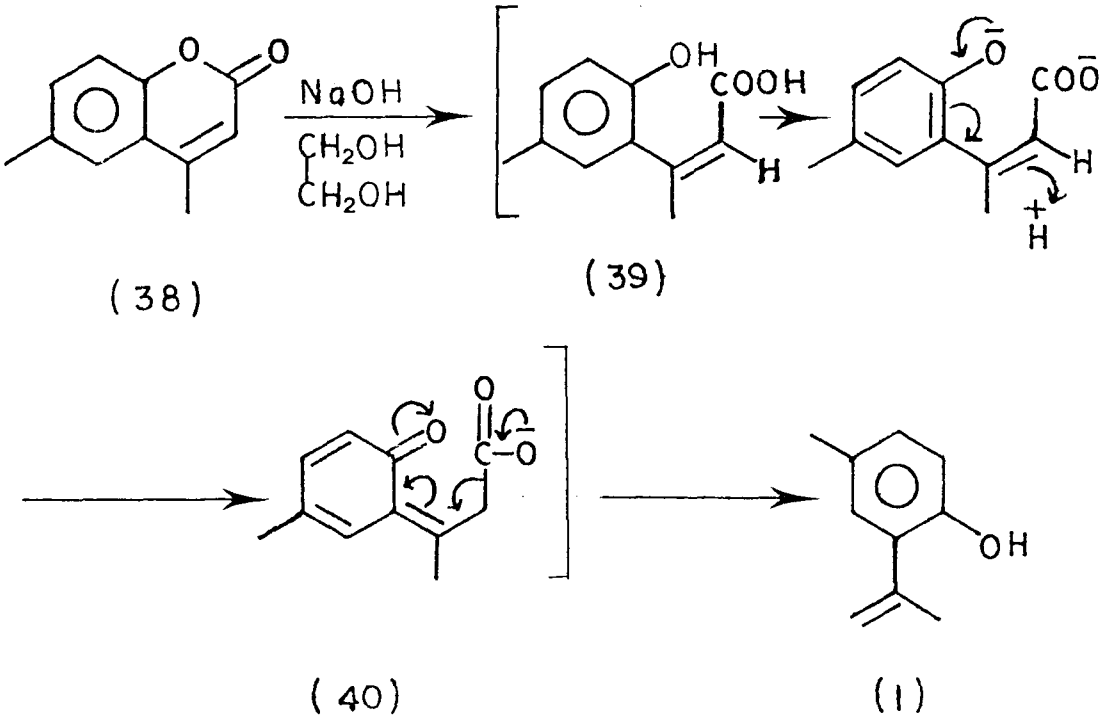
It was anticipated that if 4,6-dimethyl coumarin (38), is heated with alkali in a high boiling solvent-like ethane diol, it would initially produce the hydroxy acid (39), by the opening of the lactone ring. The dianion on protonation would furnish the quinone-methide (40) which, under the experimental conditions employed, would readily decarboxylate to give phenol (1). (See chart 6.)

The presence of OH group ortho to the butenoic acid side chain was essential for undergoing decarboxylation. This was supported by the fact that cinnamic acid and methoxy acid (53) failed to undergo decarboxylation under same experimental conditions, due to absence of hydroxy group ortho to acid side chain.

CHART 6



(37a) (37) (28)



(38) (39) (40) (1)

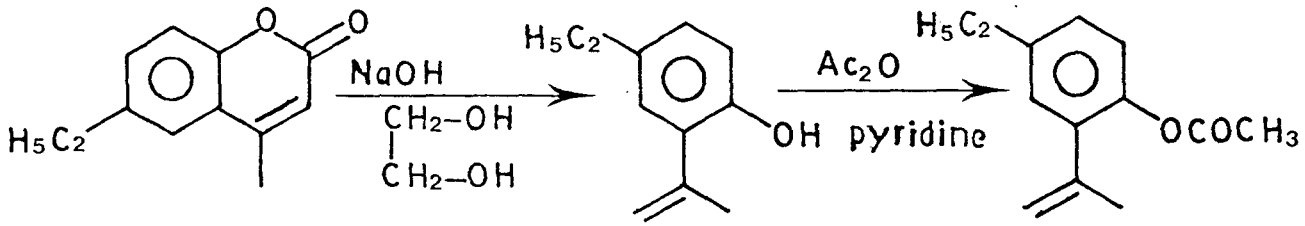
Thus, 4,6-dimethyl coumarin (38) was heated under reflux with sodium hydroxide in ethane diol; subsequent acidification of the reaction mixture was carried out in presence of an organic solvent. This facilitated the liberated phenol to be kept out of direct contact with the acidic medium. The o-isopropenyl phenol (1) was thus obtained in very good yield.

The structure of (1) was confirmed by its IR (fig. 7) and PMR spectra. While the IR spectrum exhibited band at 3.0μ due to -OH stretching. The PRM spectrum exhibited signals at 5.35δ and 5.15δ (multiplets due to vinyl protons) and doublet at 2.12 (due to CH_3-C=C-). Absence of carbonyl band in the IR spectrum showed (1) to be completely free from the starting coumarin.

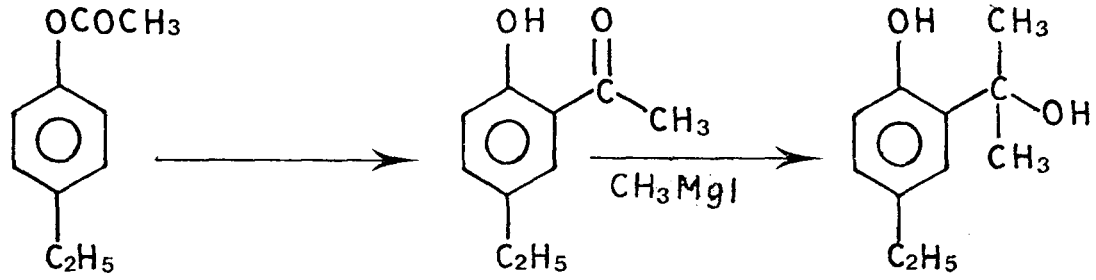
Similarly, the action of NaOH-ethane diol on 4-methyl-6-ethyl coumarin (41) gave the anticipated o-isopropenyl phenol (15). (See chart 7.) The IR spectrum of (15) showed a band at 2.99μ (C-OH stretching). The PMR spectrum of (15) (fig. 8) showed signals at 5.3δ and 5.1δ (due to vinyl protons).

When (15) was treated with acetic anhydride and pyridine at room temperature, it furnished the acetate (16) which showed in its IR spectrum (fig. 9) bands at 5.69μ and 8.9μ (due to acetate group). Its PRM spectrum showed signals at 2.2δ (doublet due to CH_3-C=C-) and 5.67δ , 4.93δ (multiplets due to vinyl protons).

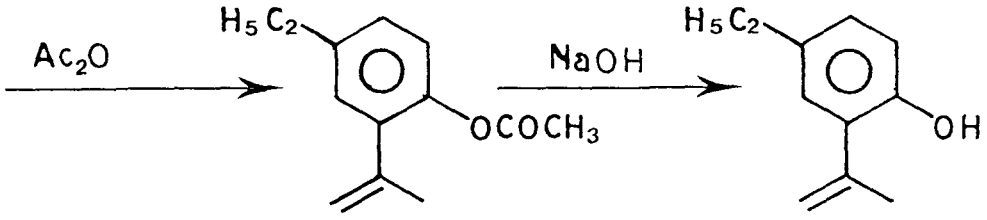
CHART 7



(41) (15) (16)



(42) (17) (18)



(19) (20)

The identity of the phenol (15) was rigorously established by comparison (through IR, PMR, and GLC) with an authentic sample prepared as follows:

Fries rearrangement of p-ethyl phenyl acetate (42) with aluminum chloride furnished the methyl ketone (17). (For PMR spectrum see fig. 10.) This on treatment with methyl magnesium iodide furnished the diol (18). Simultaneous dehydration and acylation of (18) was brought about by refluxing with acetic anhydride to obtain (19). Saponification of (19) furnished (20) which was identical with an authentic sample of (15). (See chart 7.)

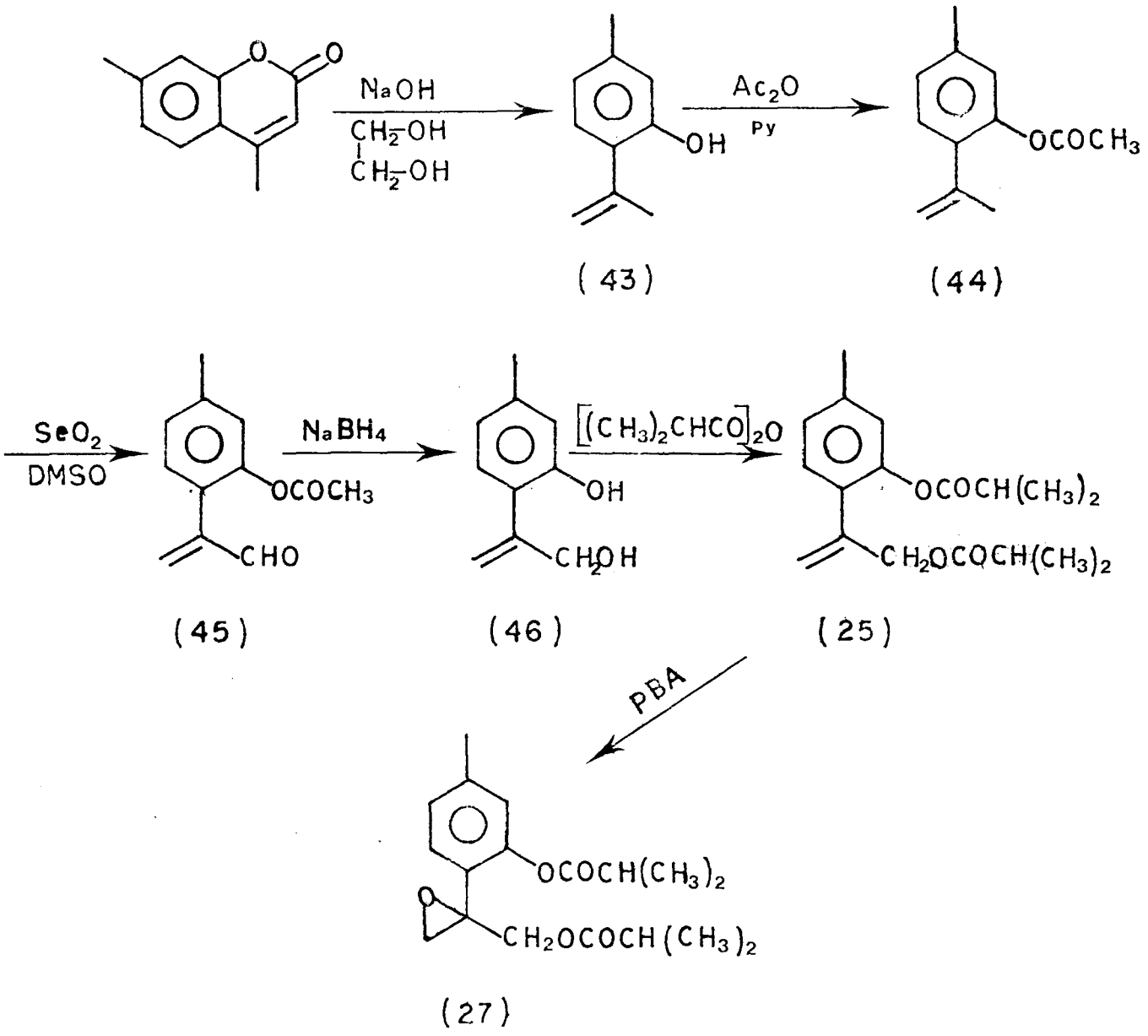
Synthesis of 2-(2-hydroxy-4-methyl phenyl)-2-propenol-diisobutyrate (25) and oxirane (27)

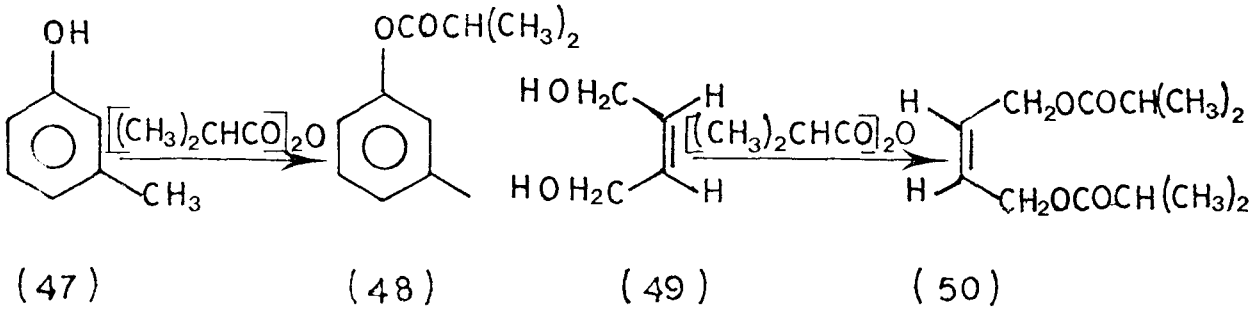
Divakar and Rao working in this laboratory have prepared the phenol (43) by the action of NaOH ethanediol on 4,7 dimethyl coumarin. Phenol (43) required for the investigation described below was prepared by this method.

Acetate (44) prepared from (43) was oxidized with SeO_2 in DMSO to furnish the aldehyde[26] (45), $NaBH_4$ reduction of the aldehyde (45) furnished the diol (46).

As diol (46) was prepared through a number of steps, isobutaroylation was initially carried out with some model compounds; thus optimum conditions for the acylation of m-cresol, cis-butene diol and methyl ether (23) were established. m-Cresol, cis-butene diol and (23) on heating with

CHART 8


NaOH
CH2-OH
CH2-OH
Ac2O
Py
OCOCH3
OH
(43)
(44)
SeO2
DMSO
NaBH4
[(CH3)2CHCO]2O
CHO
CH2OH
OCOCH(CH3)2
CH2OCOCH(CH3)2
(45)
(46)
(25)
PBA
(27)

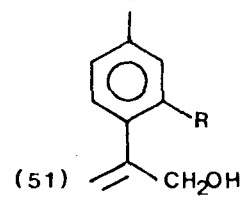

OH
[(CH3)2CHCO]2O
CH3
OCOCH(CH3)2
HOH2C
HOH2C
CH2OCOCH(CH3)2
(47)
(48)
(49)
(50)

isobutyric anhydride in presence of sodium isobutyrate furnished the anticipated isobutyrates (48), (50), and (24) respectively, in good yield.

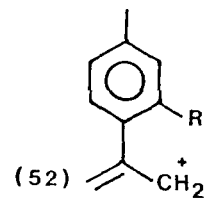
The alcohol (23) is structurally related to the diol (46). This was prepared from the readily available 4,6 dimethyl coumarin adopting a method devised earlier in this laboratory[26]. Thus, 4,6-dimethyl coumarin on hydrolytic methylation furnished the methoxy acid (53), which was pyrolyzed to furnish (21). (21) on selenium dioxide oxidation furnished (22) (for IR and PMR spectra, see figs. 11 and 12, respectively). Esterification of (23) with isobutyric anhydride in presence of sodium isobutyrate gave (24) which was identified by examining its IR (fig. 15) and PMR (fig. 16) spectra. Under the experimental conditions employed, acylation was practically complete and polymer formation was negligible*.

Employing similar conditions for acylation, (46) was transformed into the naturally occurring diester (25). IR of (25) (fig. 17), thus synthesized showed band at 5.7μ due to ester $-\overset{O}{\overset{\|}{C}}-$ stretching and PMR showed signals at 5.2 and 5.03 δ due to two vinyl protons (which show upfield shift as compared to the vinyl signals at 5.43δ and 5.22δ in the diol) and three multiplets at 4.66 ($-O-\underline{CH_2}$), 3.00-2.4δ

*Polymer formation is possible in case of allylic alcohol (51) since carbonium ion (52), being allylic can be formed readily.

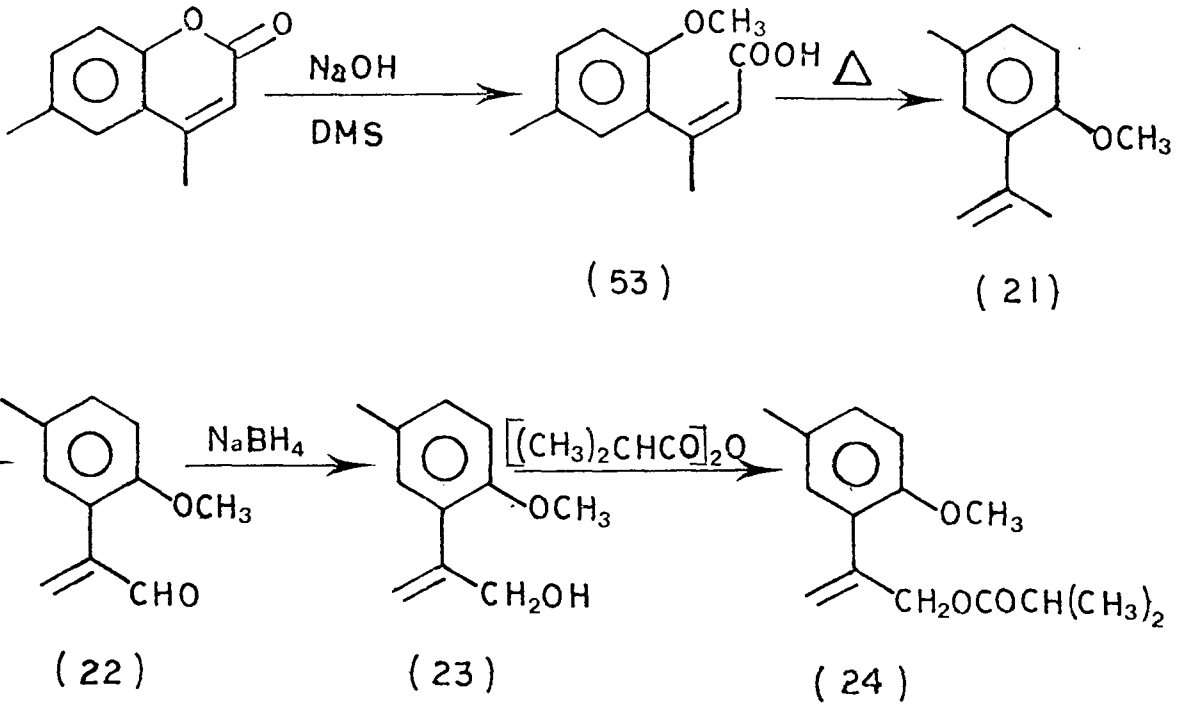


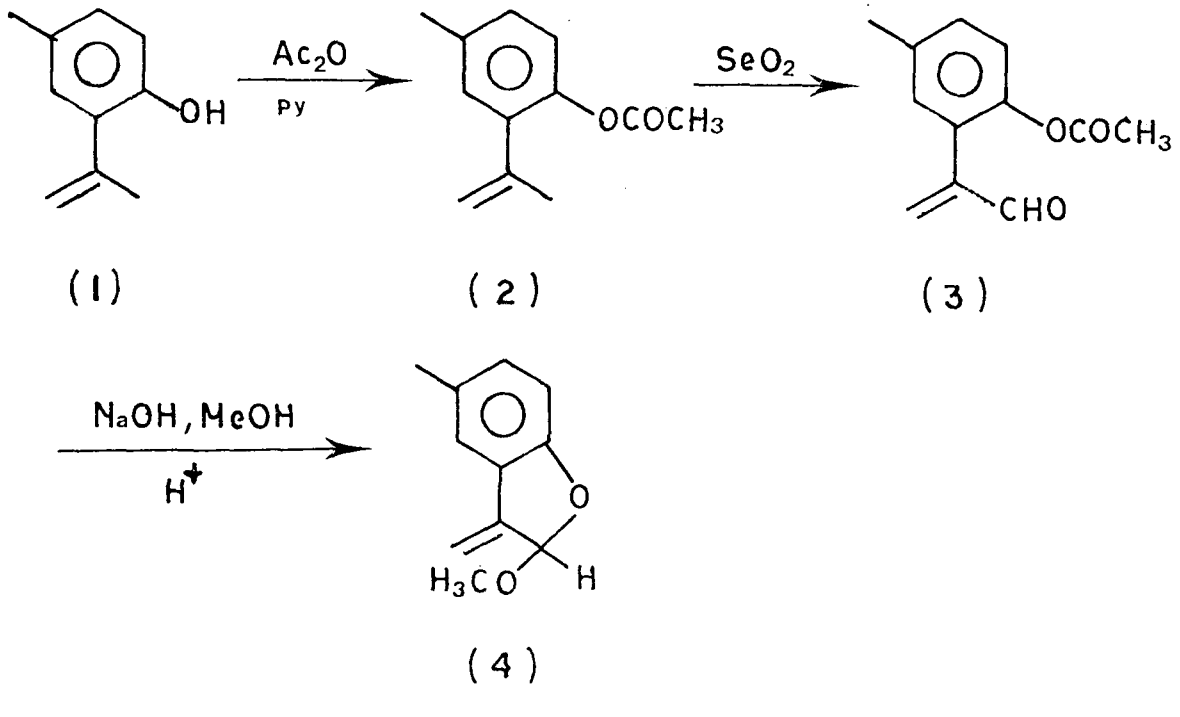
(51)



(52)

CHART 9


NaOH
DMS
OCH3
COOH
Δ
OCH3
(53)
(21)
SeO2
NaBH4
[(CH3)2CHCO]2O
OCH3
CHO
CH2OH
CH2OCOCH(CH3)2
(22)
(23)
(24)


OH
Ac2O
Py
OCOCH3
SeO2
OCOCH3
CHO
(1)
(2)
(3)
NaOH, MeOH
H+
O
H3CO
H
(4)

(-CO-CH-) and 1.30-1.03δ (-CH-$(CH_3)_2$). TLC of (25) showed a single spot which was having higher RF value than the spot due to diol (46), thus showing complete conversion of (46) to (25).

The diester (25) was epoxidized with chloroform solution of perbenzoic acid at 5°C for 48 hours to furnish the oxirane (27). The identity of (27) was established by its PMR and IR (fig. 18) spectra. PMR spectrum showed good agreement with that reported for the naturally occurring oxirane[18]. The signals due to -CO-CH- protons and oxirane protons overlapped. Absence of vinyl proton signals in the region 5.0 to 5.2δ showed complete conversion of diester (25) to oxirane (27).

Synthesis of 2,3 dihydro, 2-methoxy-3-methylene-5-methyl benzofuran (4), 2,3 dihydro, 2-ethoxy-3-methylene-5-methyl benzofuran (5) and 3,5 dimethyl-2-(3H)-benzofuranone (6).

The synthesis of phenol (1) starting from 4-6 dimethyl coumarin has been described earlier in this chapter.

Action of acetic anhydride and pyridine at room temperature on (1) furnished the acetate (2) which showed in its IR spectrum (fig. 19) band at 5.7μ and 8.4μ (due to acetate group). Its PMR spectrum (fig. 20) displayed signals at 2.1δ (multiplet due to CH_3-C=C-), 5.1-4.95 multiplets due to vinyl

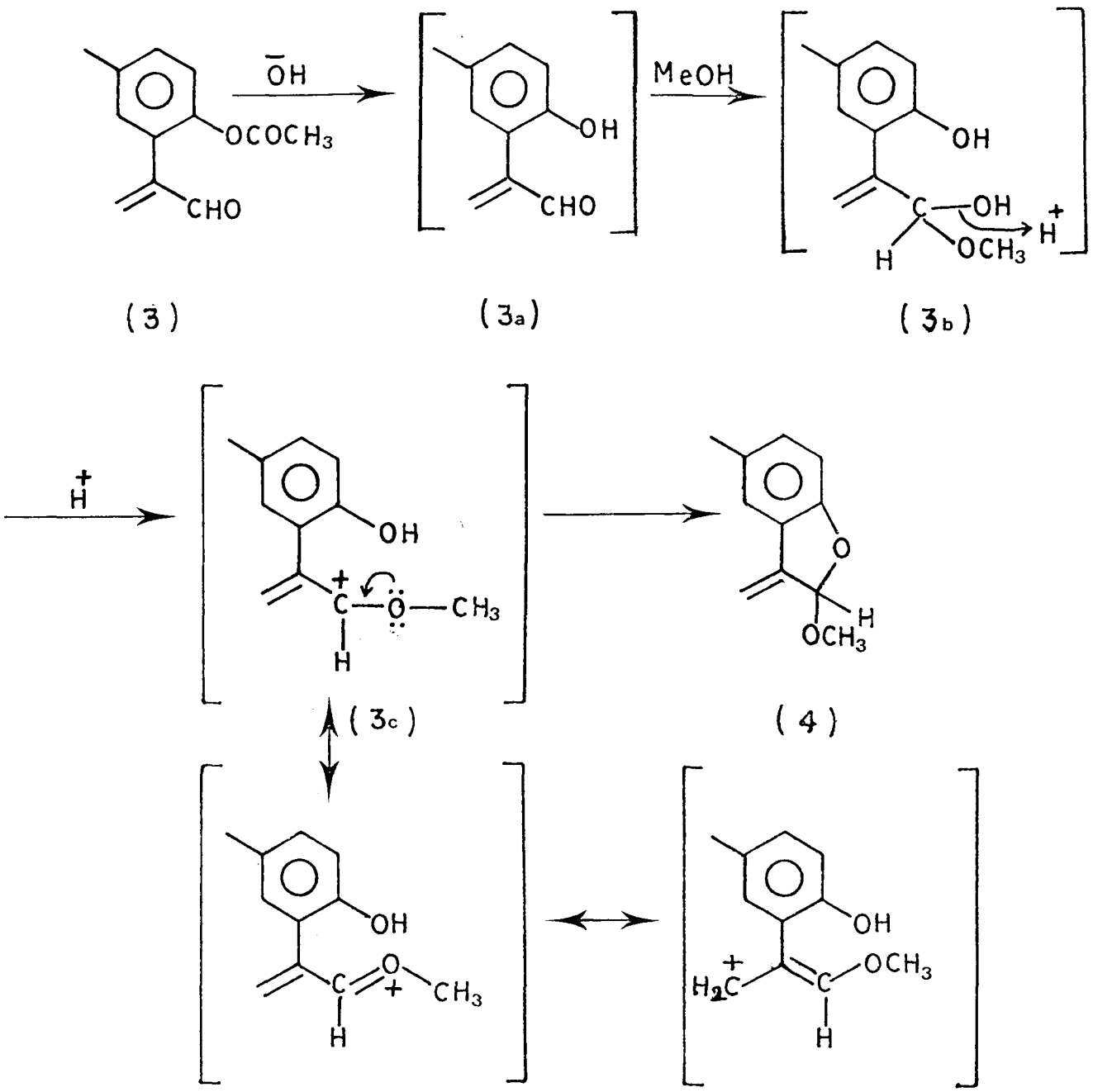
protons) and 2.2 (singlet due to CH_3-C(=O)-O).

The acetate (2) was subjected to the action of freshly sublimed SeO_2 in DMSO at 90° for 3 hrs. The aldehyde (3) was isolated by fractional distillation; (3) being obtained as the higher boiling cut (b.p.$^{\text{bath}}_{2\text{mm}}$ 140-150°). The IR spectrum of (3) (fig. 21) displayed band at 5.9δ which is characteristic of the conjugated -C=O group of aldehyde. The PMR spectrum (fig. 22) exhibited a singlet at 9.6δ (due to aldehyde proton) and multiplet at 6.3-6.15δ due to vinyl protons, (see chart 9).

It was anticipated that aldehyde (3) would give benzofuranol (54) by alkaline saponification. However, when (3) was stirred with molar equivalent of sodium hydroxide in methanol at 60° for 6 hours and subsequently acidified, the product isolated was not (54) but the methyl ether (4) as seen from its spectral data. The PMR spectrum of (4) (fig. 23) showed signals at 3.42δ (singlet due to $-OCH_3$), 5.9δ (triplet due to proton on 'C' bearing $-OCH_3$ group), and 5.6 and 5.25δ (multiplets due to vinyl protons). These data corroborated with the structure (4) of methyl ether.

A possible mechanism is presented in the chart 10. Saponification of the aldehyde (3) furnished the phenol (3a). In methanol, the solvent medium used for the reaction, the (3a) would exist as (3b). (3b) on acidification could form the cation (3c) which might cyclize to (4).

CHART 10


⁻OH
OCOCH3
CHO
MeOH
OH
OCH3
H+
CH3
(3)
(3a)
(3b)
(3c)
(4)
(5)
(54)
C2H5OH
H5C2O
HO
H2C

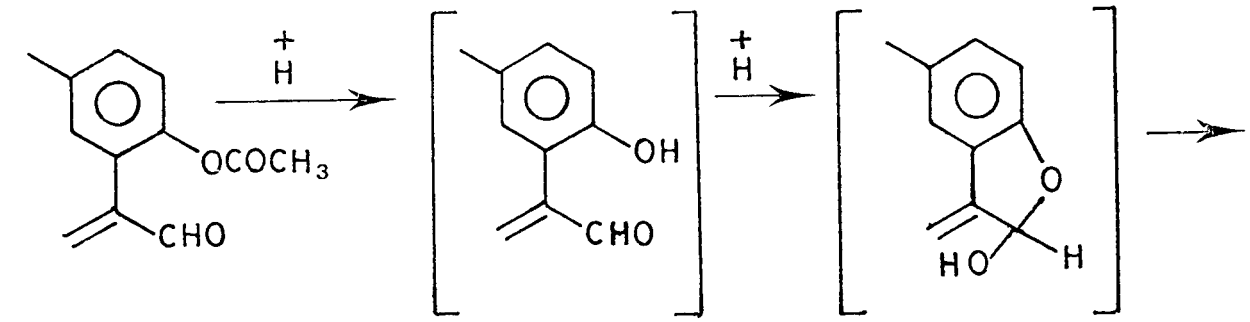
The mechanism suggested above was supported by the observation that when in the above reaction methanol was substituted by ethanol as the solvent, the ethyl ether (5) was obtained. The structure of (5) was confirmed by its PMR spectrum which displayed a quartet at 3.7δ, J=7Hz (due to $O-\underline{CH_2}-CH_3$), and a triplet at 1.28δ, J-7H_2 (due to $-CH_2-\underline{CH_3}$); rest of the signals being same as those in case of (4).

Since alkaline saponification failed to yield the desired benzofuranol (54), the aldehyde (3) was subjected to the acid catalyzed alcoholysis using a sulfonic acid exchange resin in refluxing ethanol. It was expected that the acetoxy aldehyde (3) would first be transformed to the hydroxy aldehyde (3a) which would cyclize to give the benzofuranol (54). However, the product isolated was the benzofuranone (6); IR of which showed band at 5.55δ due to lactone C=O stretching; PMR (fig. 24) showed signals at 1.53δ (doublet due to methyl on lactone ring at the benzylic position) and multiplet at 3.8-3.43δ (due to benzylic proton).

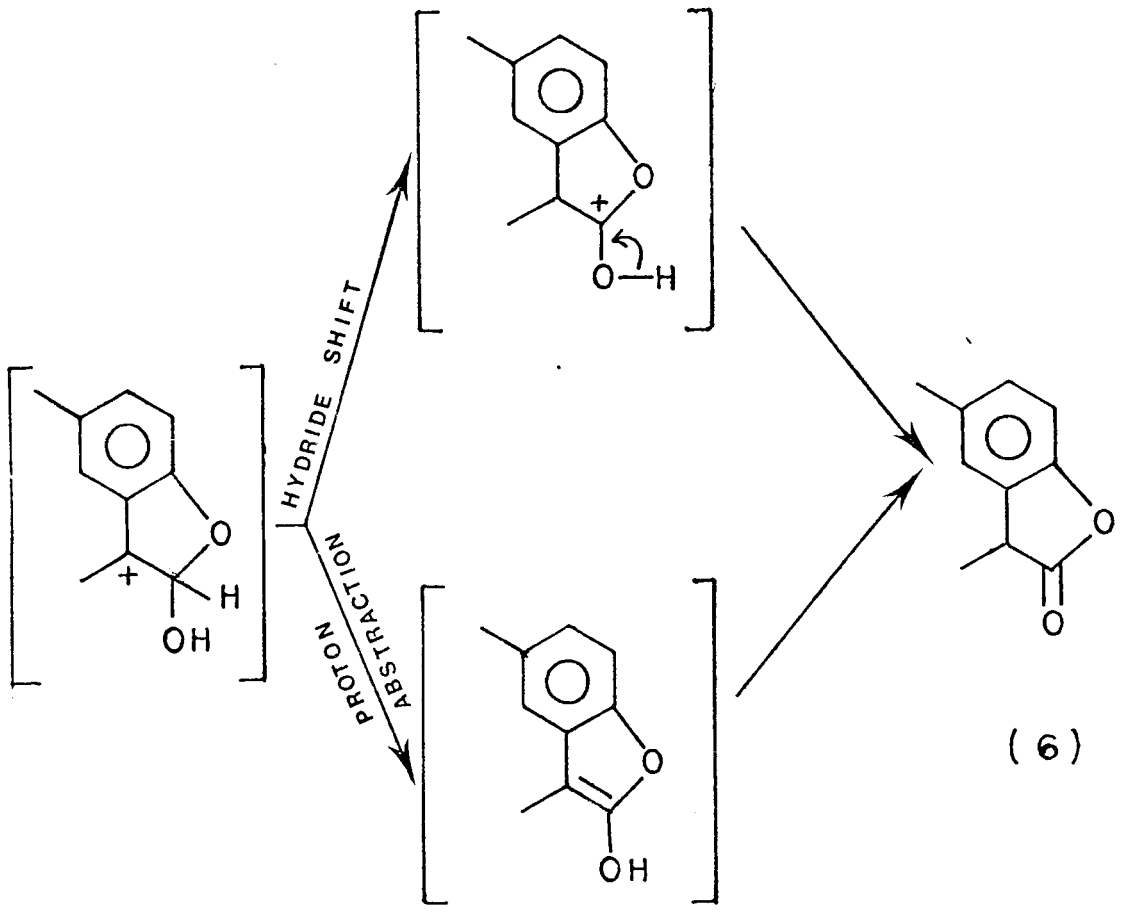
The probable mechanism for the above transformation is presented in chart 11. The hydroxyaldehyde (3a) might give rise to a carbonium ion, which on hydride shift and proton loss may furnish the lactone (6).

It may be pointed out that rearrangements are known,[27] where substituted allylic alcohols are transformed to their isomeric ketones.

CHART II



(3) (3a)



(6)

The structure of lactone (6) was further established by comparison of its spectral data with that of an authentic sample obtained as follows (chart 12).

Saponification of 4.6 dimethyl coumarin with aqueous sodium hydroxide and methylation of the resulting hydroxy acid in situ with dimethyl sulphate furnished the methoxy acid (53). Pyrolysis of (53) at atmospheric pressure provided the aryl propene (21) [PMR signals at: 5.0δ (multiplet due to vinyl proton and 2.13δ (multiplet due to $\underline{CH_3}$-C=C-)].

Selenium dioxide oxidation of (21) in refluxing ethanol furnished the aldehyde (22) IR spectrum of (22) (fig. 11) exhibited a band at 5.9μ (aldehyde -C=O stretching). PMR spectrum (fig. 12) of (22) exhibited signals at 9.63δ (singlet due to aldehyde H), and 6.16δ (multiplet due to the vinyl protons).

The methoxy aldehyde was hydrogenated to the saturated alcohol (9) (for IR and PMR spectra see fig. 25 and 26, respectively), at atmospheric pressure over Raney Nickel. Jones oxidation of the alcohol (9) followed by silver oxide oxidation of the resulting aldehyde (10) gave the acid (11) which was obtained as a solid (m.p. 104°) after sublimation.

The methoxy acid (11) was demethylated and cyclised by refluxing it with pyridine hydrochloride for 6 hrs. to get an authentic sample of (6).

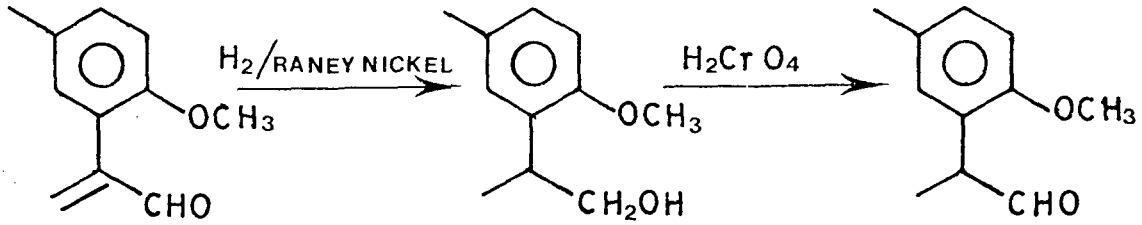
Synthesis of 2,3 Dihydro-2-methoxy-3-methylene-benzofuran (32), 2,3 Dihydro -2- ethoxy-3-methylene-benzofuran (33), and 3-methyl-2-(3H)-benzofuranone (34).

2-(2-hydroxyphenyl)-2-propene (28) was prepared by following the literature method.

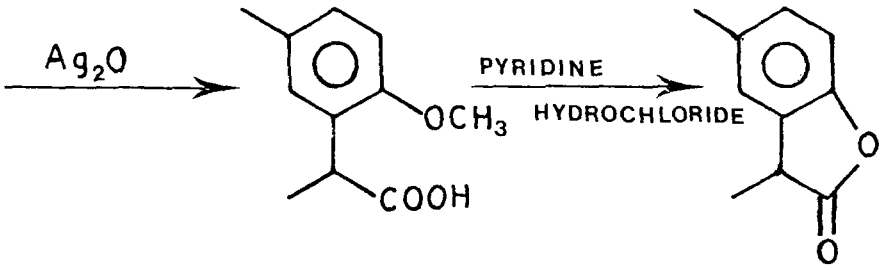
Acetylation of (28) with acetic anhydride and pyridine furnished the acetate (29). Its IR spectrum (fig. 27) showed bands at 5.69μ and 8.4μ (acetate group) and its PMR spectrum showed signals (fig. 28) at 2.25δ [(singlet, $-O-\overset{O}{\overset{\|}{C}}-\underline{C}H_3$) and 2.05δ (multiplet, $\underline{C}H_3-C=C-$)].

Following similar sequence of reactions as detailed for transformation of (3) to (4), (5), and (6), compound (29) was transformed [via aldehyde (31)] to the methyl ether (32) (for PMR see fig. 29), ethyl ether (33) (for PMR see fig. 30), and the lactone (34) respectively (see chart 12).

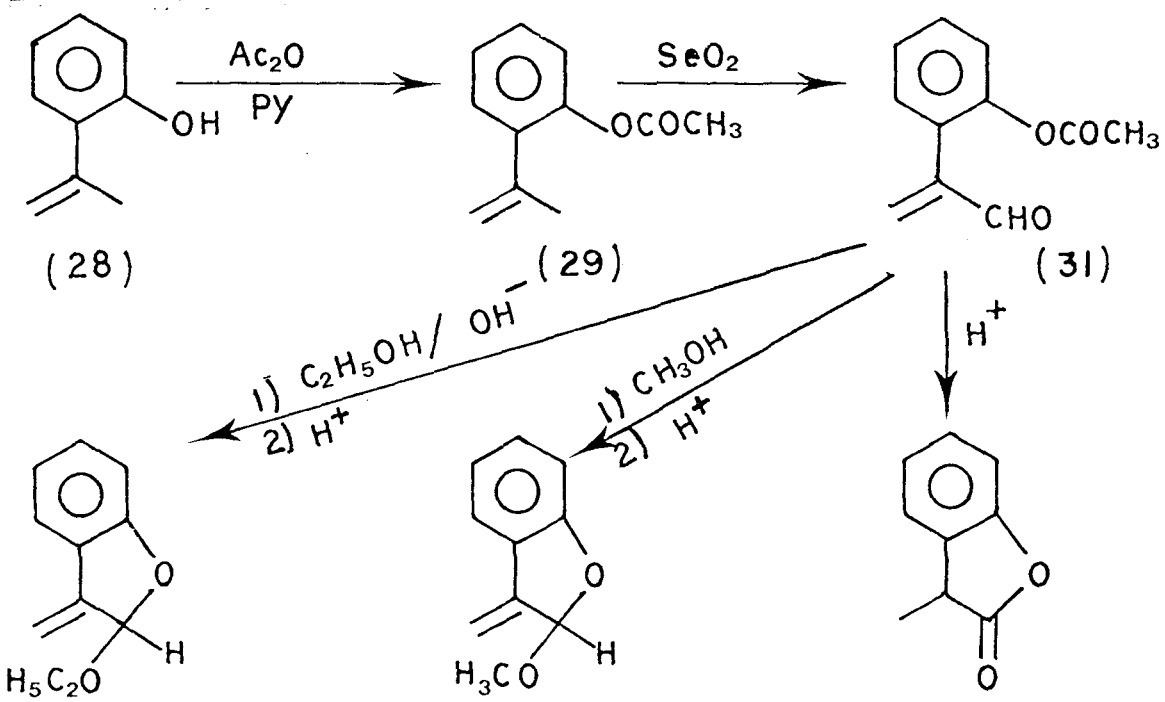
CHART 12



(8) (9) (10)



(11) (6)



(33) (32) (34)

2.4 EXPERIMENTAL

1) 2-(2-Hydroxy-5-methylphenyl)-1-propene (1)

A mixture of 4,6 dimethyl coumarin (30 g, 0.190 moles), sodium hydroxide (32.5 g, 0.82 moles) and ethane diol (210 ml) was refluxed under nitrogen atmosphere for 2 hours. The reaction mixture was cooled and poured over ice water, covered with petroleum ether and acidified with cooling by 2 N hydrochloric acid. The petroleum ether layer was separated and washed with water (3 x 200 ml) and dried over anhydrous sodium sulphate. Solvent was removed and the residue was vacuum distilled to furnish (1). (Yield: 18 g, 70.5%) b.p. $_{10mm}$ 125°

IR Spectrum (liquid film) showed bands at 3.0μ (-OH stretching), 6.15μ (-C=C- stretching), and 11μ (-C=C- bending). PMR Spectrum (CCl_4) showed signals at δ=7-6.7 (m, 3H, aromatic H), 5.5 (S, 1H, -OH), 5.35 (m, 1H, vinyl H), 5.15 (m, 1H, vinyl H), 2.3 (S, 3H, methyl on benzene ring), 2.12 (d, 3H, $\underline{CH_3}$-C=C-.

Analysis

	Found:	C, 80.78; H, 8.5
$C_{10}H_{12}O$	requires:	C, 81.04; H, 8.16%.

2) 2-(2-Acetoxy-4-methylphenyl)-1-propene (2)

A mixture of (1) (5.0 g, 0.033 moles), pyridine (50 ml) and acetic anhydride (8.5 ml, 0.08 moles) was allowed to stand at room temperature for 24 hrs. Then it was diluted with ice water and extracted with petroleum ether. The petroleum ether extracts were washed with 5% ice cold dilute HCl, aqueous sodium hydroxide solution and finally with water and dried over anhydrous sodium sulphate. Removal of solvent furnished a residue which was vacuum distilled to furnish (2)

(Yield: 4.8 g, 72%) b.p. $\overset{\text{(bath)}}{2\text{ mm}}$ 130-140°.

IR Spectrum (liquid film) showed bands at 5.7μ and 8.4μ (acetate group), 6.15μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.1-6.7 (m, 3H, aromatic H), 5.1 (m, 1H, vinyl H), 4.95 (m, 1H, vinyl H), 2.4 (S, 3H, methyl on benzene ring), 2.2 (3H, S, $\underline{CH_3}$-CO-O), 2.1 (m, 3H, $\underline{CH_3}$-C=C).

Analysis

Found: C, 75.58; H, 7.42

$C_{12}H_{14}O_2$ requires: C, 75.76; H, 7.36%

3) 2-(2-Acetoxy-5-methylphenyl)-2-propene-1-al (3)

A mixture of 2-(2-acetoxy-5-methylphenyl)-2-propene (4 g, 0.02 moles), freshly sublimed selenium dioxide (2.8 g, 0.024 moles) and dimethyl sulphoxide (25 ml) was heated on

steam bath for 3 hrs. It was left at room temperature for 24 hrs. The solution turned red in color, while black selenium particles settled at the bottom. Then it was filtered to remove selenium and residue washed with petroleum ether. The filtrate was diluted with plenty of water and extracted with petroleum ether (4 x 100 ml). All petroleum ether extracts were combined and washed successively with water and sodium carbonate (5% aq. solution) and again with water. After drying over anhydrous sodium sulphate and removal of solvent, dark colored residue was obtained which was fractionated.

Fraction	B.P. $_{2mm}$	Weight	Remarks
I	130-140° (bath)	2.05 g.	Starting acetate(2)
II	140-160° (bath)	0.65 g	aldehyde(3)

(Yield: 31.06%) based on (2) actually consumed.

IR Spectrum (liquid film) showed bands at 5.7 and 8.4μ (acetate group), 5.9μ (aldehyde -CO- stretching), 6.2μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=9.6 (S, 1H, -C-H), 7.1-6.8 (m, 3H, aromatic H), 6.3-6.15 (m, 2H, vinyl H), 2.4 (S, 3H, methyl on benzene ring), 2.1 (S, 3H, -O-CO-CH_3).

Analysis:

Found: C, 70.60; H, 6.3

$C_{12}H_{12}O_3$ requires: C, 70.58; H, 5.92%

4) 2,3 Dihydro-2-methoxy-3-methylene-5-methyl-benzofuran(4)

A mixture of (3) (0.61 g, 0.003 moles), sodium hydroxide (0.18 g, 0.0045 moles) and methanol (3.6 ml) was stirred at 60° for 6 hours. It was cooled to room temperature and was acidified with cold dilute hydrochloric acid until PH=2.0. Then the reaction mixture was diluted with water and extracted with ether. The ether layer was washed with water and dried over anhydrous sodium sulphate. The solvent was removed to get oily residue which was further purified by chromatography.

The residue was chromatographed on alumina (Gr. II, 1:40 ratio). Elution was done successively with petroleum ether, pet. ether + benzene mixture (1:1), benzene and alcohol. All pet.-ether fractions were combined and removal of solvent and vacuum distillation of the residue furnished (4).

(Yield: 55.0%) b.p. $\overset{\text{(bath)}}{_{10\ \text{mm}}}$ 180-200°C.

IR Spectrum (liquid film) showed band at 6.1μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.2-6.6 (m, 3H, aromatic H), 5.9 (t, 1H, proton on 'C' bearing $-OCH_3$ group), 5.6 (d, 1H, J=2Hz, vinyl H), 5.25 (d, 1H, J=2Hz vinyl H), 3.42 (S, 3H, $C\underline{H}_3$-O-), 2.3 (S, 3H, methyl on benzene ring).

Analysis:

Found: C, 75.27; H, 6.9

$C_{11}H_{12}O_2$ requires: C, 74.98; H, 6.86%

5) 2-3-Dihydro-2-ethoxy-3-methylene-5-methyl-benzofuran(5)

A mixture of (3) (0.61 g, 0.003 moles), sodium hydroxide (0.18 g, 0.0045 moles), and ethanol (4 ml) was stirred at 60°C for 6 hrs. Work-up was done as in the preparation of compound (4).

(Yield: 0.28 g, 50%) b.p. $\overset{(bath)}{3.5\ mm}$ 150-160°.

IR Spectrum (liquid film) showed band at 6.2μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.15-6.4 (m, 3H, aromatic H), 5.93 (t, 1H, proton on 'C' bearing OC_2H_5 group), 5.53 (d, 1H, J=2Hz, vinyl H); 5.18 (d, 1H, J=2Hz, vinyl H), 3.7 (q, 2H, J=7Hz, -O-$\underline{CH_2}$-CH_3), 2.3 (S, 3H, methyl on benzene ring), 1.28 (t, 3H, J=7Hz, -CH_2-$\underline{CH_3}$).

Analysis:

Found: C, 75.27; H, 7.6

$C_{12}H_{14}O_2$ requires: C, 75.01; H, 7.42%

6) 3,5 Dimethyl-2-(3H)-benzofuranone(6)

A mixture of (3) (0.7 g, 0.0042 moles), acid ion exchange resin (0.9 g) and ethyl alcohol (80 ml) was refluxed for 8 hours. The reaction mixture was cooled and filtered to remove resin and residue was washed with alcohol. Filtrate was evaporated to furnish residue which was filtered through alumina column. The benzofuranone was further purified by vacuum distillation.

(Yield: 0.35 g, 63.6%) b.p. $\overset{(bath)}{15\ mm}$ 200-210°.

IR Spectrum (liquid film) showed band at 5.55μ (lactone -CO- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.18 (m, 3H, aromatic H), 3.8-3.48 (m, 1H, benzylic H), 2.3 (S, 3H, methyl on benzene ring), 1.58 (d, 3H, J=7Hz, methyl on lactone ring).

7) 2-(2-Methoxy-5-methyl phenyl)-2-propene(7)

4,6 Dimethyl coumarin (20 g, 0.114 moles), was dissolved in a solution of sodium hydroxide (120 g, 3.0 moles) in water (300 ml). The mixture was heated on steam bath to dissolve coumarin. To the cooled reaction mixture was now added dropwise and with stirring dimethyl sulphate (150 ml, 1.52 moles) at such a rate that temperature was 50°. After the addition was over the contents were heated for one hour with stirring on steam bath. Finally reaction mixture was cooled, diluted with water (300 ml) and acidified with cooling in ice with aqueous dilute hydrochloric acid. The separated solid was filtered, washed with water and dried to get the acid. (m.p. 85°.) The acid on heating in sand bath at 250-260° furnished required compound (7). It was purified by vacuum distillation.

(Yield: 13.9 g, 75%) b.p. $_{2\ mm}$ 70°.

IR Spectrum (liquid film) showed band at 6.2μ (-C=C-) stretching.

PMR Spectrum (CCl_4) showed signals at δ=7.0-6.5 (m, 3H, aromatic H), 5.0 (m, 2H, vinyl H), 3.8 (S, 3H, $-OCH_3$), 2.33 (S, 3H, methyl on benzene ring), 2.16 (d, 3H, $CH_3-C=C-$).

8) 2-(2-methoxy-5-methyl phenyl)-2-propene-1-al (8)

A mixture of (7) (12.5 g, 0.077 mol), freshly sublimed selenium dioxide (10.6 g, 0.095 moles), and ethanol (500 ml) were refluxed on steam bath for 24 hours. After addition of water (200 ml), ethanol was removed on steam bath and the reaction mixture was filtered to remove black selenium residue. The residue was washed with petroleum ether and filtrate extracted with pet.-ether (400 ml). Organic layer was washed with water. After drying over anhydrous sodium sulphate and removal of solvent, dark colored residue was obtained which was further purified by fractionation.

Fraction	b.p. $_{2mm}$	Weight	Remarks
I	110°	2.5 g	starting compound
II	110-120°(bath)	1.1 g	aldehyde(8)
III	120-130°(bath)	2.0 g	aldehyde(8)

(Yield: 3.1 g, 27.1%) based on (7) actually consumed.

IR Spectrum (liquid film) showed bands at 5.9μ (aldehyde -CO- stretching), 6.1μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=9.63 (S, 1H, $-\overset{O}{\overset{\|}{C}}-H$), 7.1-6.5 (m, 3H, aromatic H), 6.16 (m, 2H, vinyl H), 3.83 (S, 3H, $-OCH_3$), 2.4 (S, 3H, methyl on benzene ring).

Analysis

Found: C, 74.77, H, 7.64

$C_{11}H_{12}O_2$ requires: C, 74.98; H, 6.8%

9) 2-(2-Methoxy-5-methyl phenyl)-propanoic acid(11)

Hydrogenation of aldehyde (8) was carried out with Raney Nickel at 2 atmospheric pressure. After hydrogenation was complete, the reaction mixture was filtered to remove the catalyst and the filtrate was evaporated to give a residue which was purified by vacuum distillation to furnish alcohol (9). b.p. $\overset{(bath)}{_{6\ mm}}$ 150-170°.

IR Spectrum (liquid film) showed band at 2.95μ (-OH-stretching).

PMR Spectrum (CCl_4) showed signals at δ=7-6.53 (m, 3H, aromatic H), 3.82 (S, 3H, $-OCH_3$), 2.33 (S, 3H, methyl on benzene ring), 3.6-3.13 (overlapping multiplet of benzylic H and $-CH_2-OH$).

To a well stirred and cooled solution of (9) (0.5 g, 0.0028 moles) in acetone (10 ml) Jone's reagent (prepared Jone's reagent as given in literature)[28] was added dropwise until the

reagent color persisted for few minutes. The reaction mixture was stirred for 20 minutes more after the addition was complete and finally methanol (3 ml) was added. The mixture turned dark green in color to which ether was added and ether layer was washed with water (2 x 20 ml), dried and solvent was removed to furnish aldehyde (10). Observation of IR and PMR spectra of (10) showed that it was a mixture of (10) and (11). It was used as such for the next reaction without purification. (Yield: 0.4 g, 80.9%).

A solution of silver nitrate (0.38 g, 0.0023 moles) in water (2.5 ml) was treated with stirring with a solution of sodium hydroxide (0.1 g, 0.0023 moles) in water (1 ml). The mixture was stirred for five minutes and silver oxide precipitate was collected by filtration and washed with water until the washings were free from nitrate. The wet freshly prepared precipitate was covered with water (5 ml) and treated with sodium hydroxide (0.5 g) with stirring. Temperature was maintained at 55-60° aldehyde (10) (0.4 g, 0.0023 moles) was added. Now, silver oxide was transformed to metallic silver. Stirring was continued for 10 minutes and precipitate of silver was removed by filtration, washed with hot water. Finally, filtrate was poured over 1:1 hydrochloric acid covered with ether. Ether layer was separated and washed with water, dried on anhydrous sodium

sulphate. Removal of solvent furnished a solid residue which was further purified by sublimation. (Yield: 0.258 g, 60.54%). m.p. 104°.

IR Spectrum (nujol mull) showed bands at 3.45μ (broad, -COOH group), 5.8 (acid -CO stretching).

Analysis

Found: C, 67.87; H, 7.28

$C_{11}H_{14}O_3$ requires: C, 68.05; H, 7.21%

10) 3,5-Dimethyl-2-(3H)-benzofuranone(6)

A mixture of acid (11) (0.7 g, 0.0036 moles) and pyridine hydrochloride (8.3 g, 0.072 moles) was refluxed for 6 hours. After cooling and diluting it with water it was extracted with ether. Ether layer was washed with water and aq. 5% sodium bicarbonate solution and again with water. Evaporation of organic solvent after drying with anhydrous sodium sulphate furnished a lactone (6) which was identified by its spectral data.

(Yield: 0.422 g, 72.19%) b.p. $\overset{\text{(bath)}}{1.5\text{ mm}}$ 150-165°.

11) (4-Methoxy phenyl) ethane(12)

A mixture of zinc granules (10.0 g, 0.153 g atom), mercuric chloride (1.0 g, 0.0036 moles), concentrated hydrochloric acid (0.5 ml) and water (15 ml) was shaken for five minutes and then aqueous layer was decanted. To the

now formed zinc mercury amalgam was added p-acetyl anisol (5.0 g, 0.033 moles); water (20 ml) and conc. hydrochloric acid (2.5 ml) and the mixture was refluxed for 2 hours. After the addition of more conc. hydrochloric acid (2.5 ml), the reaction mixture was again refluxed for 15 hrs. The cooled reaction mixture was decanted and extracted with chloroform. All chloroform extracts were combined, washed with water, chloroform layer was dried over anhydrous sodium sulphate. Evaporation of the solvent furnished a residue which was purified by vacuum distillation. (Yield: 6.6 g, 73.4%).

PMR Spectrum (CCl_4) showed signals at δ=7.1-6.55 (m, 4H, aromatic H), 3.7 (S, 3H, $-O\underline{CH_3}$) 2.57 (g, 2H, J-7Hz, $-\underline{CH_2}-CH_3$); 1.2 (t, 3H, J=7Hz, $-CH_2-\underline{CH_3}$).

12) (4-hydroxyphenyl) ethane (13)

A mixture of (12) (3.0 g), and hydroiodic acid (30 g, ten times by weight) was refluxed for 4 hrs. The cooled reaction mixture was diluted with water, and covered with ether. After acidification with dilute hydrochloric acid, the reaction mixture was extracted with ether, washed with sodium thiosulphate solution and then with water and dried over anhydrous sodium sulphate. Evaporation of solvent furnished a residue which was identified as (13).

(Yield: 1.5 g, 55.7%) b.p. $\overset{(bath)}{70\ mm}$ 170-180°

IR Spectrum (liquid film) showed band at 3.05μ (-C-OH stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.15-6.55 (m, 4H, aromatic H), 3.24 (S, broad, 1H, -OH), 2.54 (q, 2H, J-7Hz, $-CH_2-CH_3$), 1.13 (t, 3H, J=7Hz, $-CH_2-CH_3$).

13) 4-methyl-6-ethyl coumarin(14)

To a well stirred solution of (13) (4.0 g, 0.029 moles), and ethyl aceto acetate (3.7 g, 0.029 moles), was added cautiously concentrated sulphuric acid (10.0 ml) dropwise and with cooling. The reaction mixture was kept at room temperature for 72 hrs. and then poured on ice. Extraction was done with chloroform and chloroform layer was washed with water, dried over anhydrous sodium sulphate and solvent was evaporated to give coumarin (14).

b.p. $\overset{\text{(bath)}}{0.1\ \text{mm}}$ 200-210°

m.p. =68°

reported m.p. =69-70°[29]

IR Spectrum (Nujol mull) showed band at 5.8μ (-CO-stretching).

14) 2-(2-Hydroxy-5-ethyl phenyl)-2-propene(15)

A mixture of 4-methyl-6-ethyl coumarin (0.80 g, 0.0094 moles), sodium hydroxide (2.0 g, 0.05 moles) and ethane diol (10 ml) was refluxed under nitrogen atmosphere for two hours. The reaction mixture was cooled and poured over ice water,

covered with petroleum ether and acidified with cooling by 2 N hydrochloric acid. The petroleum ether layer was separated and washed with water (3 x 100 ml) and dried with soidum sulphate. Solvent was removed and the residue was vacuum distilled.

(Yield: 0.51 g, 69.6%). b.p. $\overset{\text{(bath)}}{0.1\text{ mm}}$ 170-180°

IR Spectrum (liquid film) showed bands at 2.99μ(-OH-stretching), 6.1μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7-6.5 (m, 3H, aromatic H), 5.45 (S, 1H, -OH), 5.3 (m, 1H, vinyl H), 5.1 (m, 1H, vinyl H), 2.56 (q, 2H, J=7Hz, $C\underline{H}_2$-CH_3), 2.13 (d, 3H, $C\underline{H}_3$-C=C-), 1.23 (t, 3H, J=7Hz, -CH_2-$C\underline{H}_3$).

15) 2-(2-Acetoxy-5-ethyl phenyl)-1-propene(16)

A mixture of (15) (0.40 g, 0.0064 moles), acetic anhydride (0.7 g, 0.0068 moles), and pyridine (10 ml) was allowed to stand at room temperature for 24 hrs. Then it was diluted with ice water and extracted with petroleum ether. The petroleum ether extracts were washed with 5% ice cold dil. HCl and aqueous sodium hydroxide solution. Finally, they were washed with water and then dried over anhydrous sodium sulphate. Removal of solvent furnished a residue which was vacuum distilled.

(Yield: 4.13 g, 82%) b.p. $\overset{\text{(bath)}}{0.1\text{ mm}}$ 190-200°

IR Spectrum (liquid film) showed bands at 5.69μ and 8.4μ (acetate group), 6.1μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.1-6.7 (m, 3H, aromatic H), 5.07 (m, 1H, vinyl H), 4.93 (m, 1H, vinyl H), 2.66 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 2.23 (S, 3H, $-O-CO-C\underline{H}_3$), 2.2 (S, 3H, $C\underline{H}_3-C=C-$), 1.26 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

Analysis

Found: C, 75.93; H, 8.0

$C_{13}H_{16}O_2$ requires: C, 76.44; H, 7.9

16) (3-Acetyl-4-hydroxyphenyl)-ethane(17)

Finely powdered aluminum chloride (4.07 g, 0.03 moles), was added to 2-(4-acetoxy phenyl) ethane (5.0 g, 0.030 moles). Immediately after addition, evolution of HCl gas started. The mixture was heated in oil bath at 125° until no more HCl gas was evolved. Finally, temperature was raised up to 165°. After cooling it at room temperature a red mass formed was decomposed by addition of 2N aqueous hydrochloric acid with cooling. Extraction with ether, washing ether layers with water, drying with anhydrous sodium sulphate and evaporation of solvent furnished a residue which was further purified by vacuum distillation.

(Yield: 3.25 g, 65%) b.p. $\overset{\text{(bath)}}{_{5\text{ mm}}}$ 130-140°

PMR Spectrum (CCl_4) showed signals at δ=7.53-6.73 (m, 3H aromatic H), 2.6 (q, 2H, $-C\underline{H}_2-CH_3$), 2.59 (S, 3H, $-CO-C\underline{H}_3$), 1.26 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

Analysis

Found: C, 73.07; H, 7.77

$C_{10}H_{12}O_2$ requires: C, 73.15; H, 7.37

17) 2-hydroxy-2-(2-hydroxy-5-ethyl phenyl)-propane(18)

Methyl magnesium iodide was prepared by treating magnesium pieces (0.9 g, 0.037 moles), in dry ether (10 ml), with methyl iodide (5.2 g, 0.037 moles). To this solution in dry ether ketone (16) (2.5 g, 0.015 moles) in ether (10 ml) was added dropwise and with cooling and stirring. The reaction mixture was stirred at 0° for 30 minutes and then at room temperature for one hour. Finally, this was decomposed by pouring over saturated ammonium chloride solution. The decomposed reaction mixture was covered with ether and acidified with dilute aqueous hydrochloric acid until acidic to congo red. Extraction was done with ether, ether layer washed with water three times and dried. Solvent evaporation furnished a residue which was identified as diol (18). (Yield 2.4 g, 87.4%).

18) 2-(2-Acetoxy-5-ethyl phenyl)-1-propene(19)

Acetate (19) was saponified by refluxing a mixture of (19) (0.50 g) and 10% alcoholic solution of sodium hydroxide (25 ml), for 3 hours on steam bath. The cooled reaction mixture was covered with ether and acidified with 2 N aqueous hydrochloric acid until acidic to congo red. Ether

layer was separated and washed with water, dried and evaporated to furnish a residue. IR, PMR and VPC comparison showed this product to be identical with the phenol (15).

20) 2-(2-Methoxy-5-methyl phenyl) prop-1-ene(21)

3-(2-Methoxy-5-methyl phenyl)-2-butenoic acid was prepared as given in the literature.

The acid (4.12 g) was taken in a distillation flask which was heated in a sand bath. When the temperature of molten acid in the distillation flask reached 210° there was vigorous evolution of carbondioxide and the pyrolysis product started distilling over. The contents of the flask were maintained at 210-240° until distillation was complete. The pyrolysis product was redistilled to furnish (21).

Yield: (2.2 g) b.p. $\overset{(bath)}{30\ mm}$ 130°.

PMR Spectrum (CCl_4) showed signals at δ=7.0-6.5 (m, 3H, aromatic H), 5.0 (m, 2H, vinyl H), 3.8 (S, 3H, -O-CH_3), 2.33 (S, 3H, methyl on benzene ring), 2.13 (m, 3H, methyl on double bond).

21) 2-(2-Methoxy-5-methyl phenyl) prop-2-en-1-al(22)

(22) was prepared following same procedure as given for compound (3).

22) 2-(2-Methoxy-5-methyl phenyl) prop-2-ēn-1-Ol(23)

A mixture of methoxy aldehyde (22), (0.3 g, 0.0017 moles), ethanol (10 ml), and sodium borohydride (0.065 g, 0.0017 moles) was stirred at room temperature for 12 hours. The reaction mixture was diluted with water and extracted with chloroform. The chloroform extract was washed with water and dried. Removal of solvent furnished the alcohol (23).

(Yield: 0.22 g, 72.5%)

IR Spectrum (liquid film) showed band at 3.4μ (C-OH-stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.1-6.6 (m, 3H, aromatic H), 5.446-4.96 (m, 2H, vinyl H), 3.8 (S, 3H, -O-CH_3), 2.3 (S, 3H, methyl on benzene ring).

23) 2-(2-Methoxy-5-methyl phenyl)-prop-2-en-1-ol isobutyrate(24)

A mixture of alcohol (23) (0.4 g, 0.002 moles), isobutyric anhydride (1.42 g, 0.09 moles), sodium isobutyrate (0.24 g, 0.002 moles), was heated at 150° for 3 hours, cooled to room temperature and diluted with water. The reaction mixture was kept at room temperature for 24 hours, diluted with water (10 ml) and extracted with ether. The ether extract was washed with aqueous Na_2CO_3, water and dried. Evaporation of solvent furnished the isobutyrate (24).

(Yield: 0.3 g, 53.8%).

For obtaining correct analysis on the product it was chromatographed on a column of alumina (Gr. II, 30 g). The column was eluted with pet.-ether. Removal of solvent and distillation of residue yielded (24). b.p. $\overset{\text{(bath)}}{0.5\text{ mm}}$ 160-170°.

IR Spectrum (liquid film) showed band at 5.79μ (-CO- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.13-6.53 (m, 3H, aromatic H), 5.4-4.83 (m, 2H, vinyl H), 3.83 (S, 3H, $-OCH_3$), 2.3 (S, 3H, methyl on benzene ring), 1.1 (d, 6H, J=7Hz, $-CH-(CH_3)_2$).

Analysis

Found: C, 72.27; H, 8.3

$C_{15}H_{20}O_3$ requires: C, 72.5; H, 8.12.

24) 2-(2-Hydroxy-4-methyl phenyl)-prop-2-en-1-ol diisobutyrate (25)

A mixture of 2-(2-Hydroxy-4-methyl phenyl)-prop-2-en-1-ol* (0.60 g, 0.0036 moles), isobutyric anhydride (3.50 g, 0.022 moles), and sodium isobutyrate (0.4 g), was heated at 150° for 3 hours; cooled to room temperature and diluted with water (50 ml) and extracted with ether. The ether extract was washed with aqueous sodium carbonate, water and dried. Evaporation of solvent furnished the diisobutyrate (25).

(Yield: 0.80 g, 71.9%).

*For preparation details see Ref. 26.

To get correct analysis of the compound, it was chromatographed on a column of alumina (Gr. II. 30 g). The column was eluted with pet.-ether. Removal of solvent and distillation of residue yielded (25). b.p. $\overset{(bath)}{0.5\ mm}$ 170-175°.

IR Spectrum (liquid film) showed band at 5.7μ (-CO- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.07 (d, 1H, J=8Hz, aromatic H), 6.90 (d, 1H, J=8Hz, aromatic H), 6.73 (S, 1H, aromatic H), 5.20 (m, 1H, vinyl H), 5.03 (m, 1H, vinyl H), 4.66 (m, 2H, -O- $C\underline{H}_2$-), 3.00-2.4 (m, 2H, -CO-$C\underline{H}$-), 2.35 (S, 3H, methyl on benzene ring), 1.30-1.03 (m, 12H, -CH-$(C\underline{H}_3)_2$).

Analysis

	Found:	C, 71.27, H, 8.08
$C_{18}H_{24}O_4$	requires:	C, 71.03, H, 7.95

25) m-Cresol isobutyrate (26)

Isobutyrate of m-cresol was prepared from m-cresol following the conditions described earlier, for acylation of (24).

IR Spectrum (liquid film) showed band at 5.73μ (-CO- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.4-6.67 (m, 4H, aromatic H), 3-2.4 (m, 1H, -CH-$(C\underline{H}_3)_2$), 2.4 (S, 3H, methyl on benzene ring), 1.37 (d, 6H, J=7Hz, -CH-$(C\underline{H}_3)_2$.

Analysis

Found: C, 74.26; H, 8.17

$C_{11}H_{14}O_2$ requires: C, 74.13; H, 7.92.

26) 2-Hydroxymethyl-2-(2-Hydroxy-4-methyl phenyl)-oxirane diisobutyrate(27)

Diisobutyrate (25) (0.2 g) was epoxidized with chloroform solution of perbenzoic acid (2N, 2 ml) at 5° for 48 hrs. The chloroform solution was diluted with 10 ml of $CHCl_3$, washed with aqueous sodium carbonate, water and dried. Removal of solvent and vacuum distillation furnished the oxirane (27).

IR Spectrum (liquid film) showed band at 5.7μ (-CO- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.20 (d, 1H, J=8Hz, aromatic H), 6.95 (d, 1H, J=8Hz, aromatic H), 6.80 (S, 1H, aromatic H), 4.28 (q, 2H with J_{AB}=12Hz, AB=0.35, -O-$\underline{CH}_2$-), 3.00-2.35 (m, 4H-CO-CH- and oxirane H), 2.35 (S, 3H, methyl on benzene ring), 1.3 (d, 6H, J=7Hz - CH-($\underline{CH}_3$)$_2$), 1.09 (d, 6H, J=7Hz, -CH-($\underline{CH}_3$)$_2$).

27) 2-(2-Acetoxy phenyl)-1- propene (29)

Method (a)

A mixture of 4-methyl coumarin (12.0 g, 0.075 moles), sodium hydroxide (12.83 g, 0.32 moles), ethane diol (100 ml) was refluxed under nitrogen atmosphere for two hours. Work

up was done as given for compound (1) to furnish phenol (28).

(Yield: 7.4 g, 75%) b.p. $\overset{\text{(bath)}}{0.1\text{ mm}}$ 140-150°.

IR Spectrum (liquid film) showed bands at 2.95μ (-OH- stretching), 6.1μ (-C=C- stretching), 10.95μ (-C=C- bending).
PMR Spectrum (CCl_4) showed signals at δ=7.67-6.63 (m, 4H, aromatic H), 5.26 (m, 1H, vinyl H), 5.13 (m, 1H, vinyl H), 2.33 (d, 3H, $C\underline{H}_3$-C=C-).

A mixture of (28) (7.4 g, 0.042 moles), pyridine (100 ml) and acetic anhydride (13.0 ml, 0.12 moles), was allowed to stand at room temperature. Work up was done as given earlier for acetate (2).

Removal of solvent furnished a residue which was vacuum distilled.

(Yield: 6.6 g, 67.9%) b.p. $\overset{\text{(bath)}}{0.1\text{ mm}}$ 140-150°.

IR Spectrum (liquid film) showed bands at 5.69μ and 8.4μ (acetate group), 6.1μ (-C=C- stretching).
PMR Spectrum (CCl_4) showed signals at δ=7.3-6.8 (m, 4H, aromatic H), 5.15 (m, 1H, vinyl H), 5.0 (m, 1H, vinyl H), 2.25 (S, 3H, -OCO-$C\underline{H}_3$), 2.05 (m, 3H, $C\underline{H}_3$-C=C-).

Analysis

Found: C, 74.90; H, 7.2

$C_{11}H_{12}O_2$ requires: C, 74.98; H, 6.86

Method (b)

To the magnesium (10.18 g, 0.41 gm. atom), in dry ether (20 ml) was added methyl iodide (28 ml, 0.45 moles)

with stirring. Stirring was continued until all magnesium was dissolved. Orthohydroxy acetophenone (20 g, 0.14 moles) was added dropwise to the above mixture with cooling and stirring. After the addition was over the reaction mixture was stirred at room temperature for one hour and then decomposed by pouring it over saturated ammonium chloride solution, acidified with aqueous HCl solution. Then extracted with ether, washed with water and dried over anhydrous sodium sulphate. Evaporation of solvent furnished the diol 2-(2-Hydroxyphenyl)-2-propanol (30)

(Yield: 18.0 g, 81.7%) b.p. $\overset{\text{(bath)}}{_{3\text{ mm}}}$ 140-150°.

IR Spectrum (liquid film) showed band at 3.05μ (-OH stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.1-6.5 (m, 4H, aromatic H), 3.5 (S, 2H, -OH), 1.64 (S, 6H, $(CH_3)_2\overset{OH}{\overset{|}{C}}-$).

A mixture of diol (30) (0.5 g, 0.0032 moles), acetic anhydride (3.0 ml, 0.032 moles), fused sodium acetate (0.2 g, 0.0097 moles) was refluxed for 5 hours. After cooling, the reaction mixture was poured over ice and left in contact with ice for one hour. Extraction of this with ether and evaporation of ether layer after drying over anhydrous sodium sulphate furnished compound (29).

IR and PMR spectra of (29) were found to be identical with those of the product obtained by earlier method.

28) 2-(2-Acetoxy phenyl)-2-propene-1-al(31)

A mixture of (29) (8.5 g, 0.0089 moles), freshly sublimed selenium dioxide (6.0 g, 0.04 moles), and dimethyl sulfoxide (50 ml) was heated on steam bath for 24 hrs. Work up was done as given for (3).

Removal of organic solvent furnished dark red colored residue which was purified by fractionation.

Fraction	b.p.	Weight	Remarks
I	62°	3.5 g	starting acetate(29)
II	105°	1.5 g	product aldehyde(31)

(Yield: 39.6% based on (29) actually consumed).

IR Spectrum (liquid film) showed bands at 5.7μ , 8.4μ(acetate group), 5.9μ (aldehyde -CO- stretching).
PRM Spectrum (CCl_4) showed signals at δ=9.7 (S, 1H, -CO-H), 7.68-6.6 (m, 4H, aromatic H), 6.4-6.28 (m, 2H, vinyl H), 2.13 (S, 3H, -O-CO-CH_3).

29) 2,3 Dihydro-2-methoxy-3-methylene-benzofuran(32)

A mixture of (31) (0.5 g, 0.002 moles), sodium hydroxide (0.15 g, 0.0037 moles), and methanol (3 ml), was stirred

at 60° for 6 hrs. Work up was done as given earlier for preparation of compound (4).

The residue after passing through the column of alumina furnished (32).

(Yield: 0.127 g, 30%) b.p. $\overset{\text{(bath)}}{35\text{ mm}}$ 180-200°.

IR Spectrum (liquid film) showed band at 6.09μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.48-7.67 (m, 4H, aromatic H), 5.93 (t, 1H, proton on 'C' bearing $-OCH_3$ group), 5.67 (d, 1H, vinyl H), 5.3 (d, 1H, vinyl H), 3.5 (S, 3H, $-OCH_3$).

Analysis

	Found:	C, 74.37, H, 7.00
$C_{10}H_{10}O_2$	requires:	C, 74.06, H, 6.31

30) 2,3 Dihydro-2-ethoxy-3-methylene-benzofuran(33)

A mixture of (31) (0.61 g, 0.003 moles), sodium hydroxide (0.18 g, 0.0045 moles) and ethanol (4 ml) was stirred at 60° for 6 hrs. Work up was done as given earlier for preparation of (32).

(Yield: 0.28 g, 50%) b.p. $\overset{\text{(bath)}}{20\text{ mm}}$ 160-170°.

IR Spectrum (liquid film) showed band at 6.2μ (-C=C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.35-6.6 (m, 4H, aromatic H), 6.0 (t, 1H, proton on 'C' bearing $-OC_2H_5$ group), 5.53 (d, 1H, J=2Hz, vinyl H), 5.2 (d, 1H, J=2Hz, vinyl H), 3.6 (q, 2H, J=7Hz, $-O-\underline{CH_2}-CH_3$), 1.27 (t, 3H, J=7Hz, $-CH_2-\underline{CH_3}$).

31) 3-methyl-2-(3H)-benzofuranone (34)

A mixture of (31) (0.7 g, 0.0036 moles), acid ion exchange resin (0.9 gm) and ethanol (80 ml) was refluxed for 8 hrs. The cooled reaction mixture was filtered to remove the resin and the residue washed with alcohol. Filtrate was evaporated to furnish residue which was filtered through alumina column.

The benzofuranone was further purified by vacuum distillation.

(Yield: 0.35 g, 65.2%) b.p. $\overset{\text{(bath)}}{_{20\text{ mm}}}$ 180-190°.

IR Spectrum (liquid film) showed band at 5.58μ (γlactone -CO- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.5-6.63 (m, 4H, aromatic H), 3.6 (m, 1H, benzylic H), 1.58 (d, 3H, methyl on lactone ring, J=7Hz).

Analysis

	Found:	C, 73.23; H, 5.75
$C_9H_8O_2$	requires:	C, 72.96; H, 5.44

2.5. REFERENCES

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2.6 FIGURES

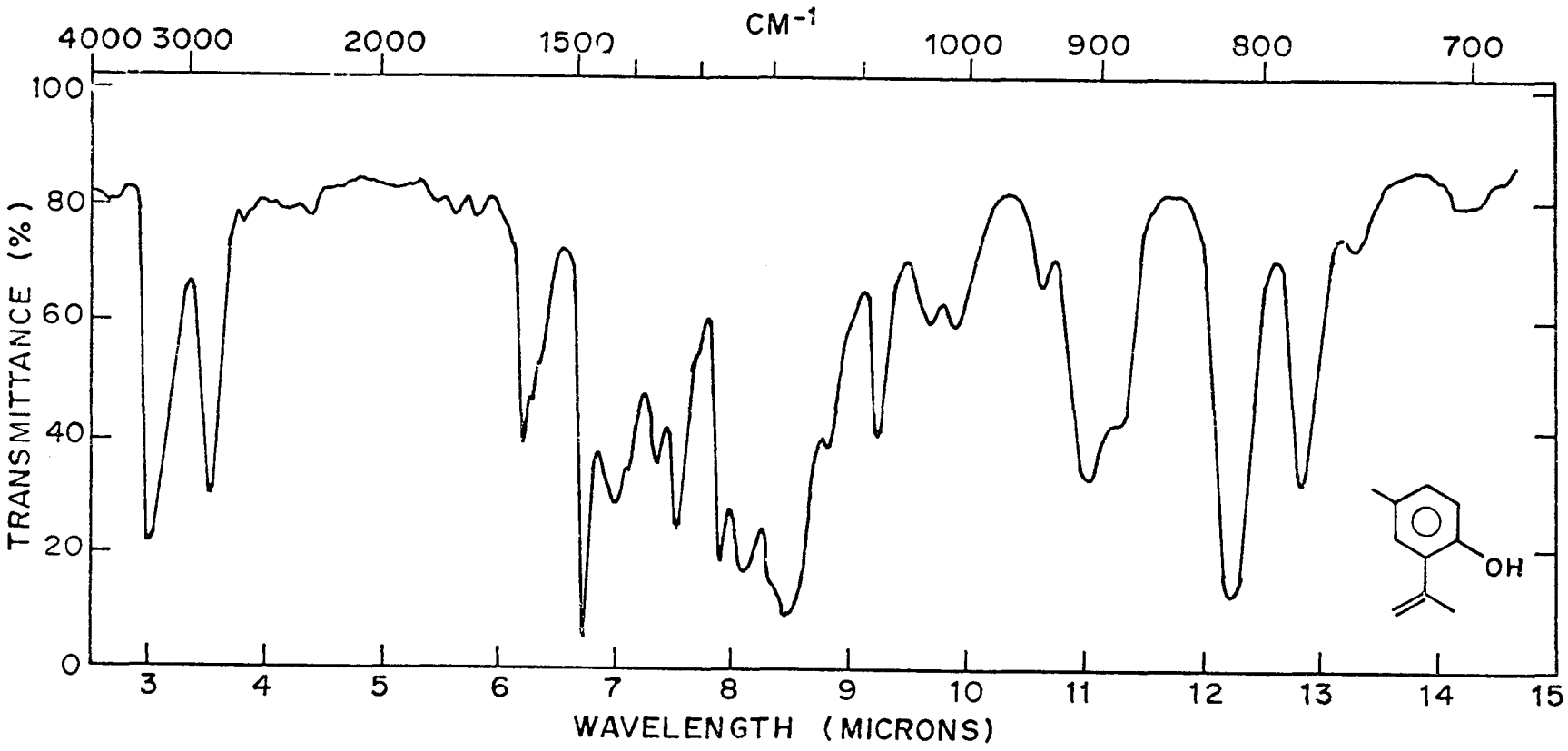
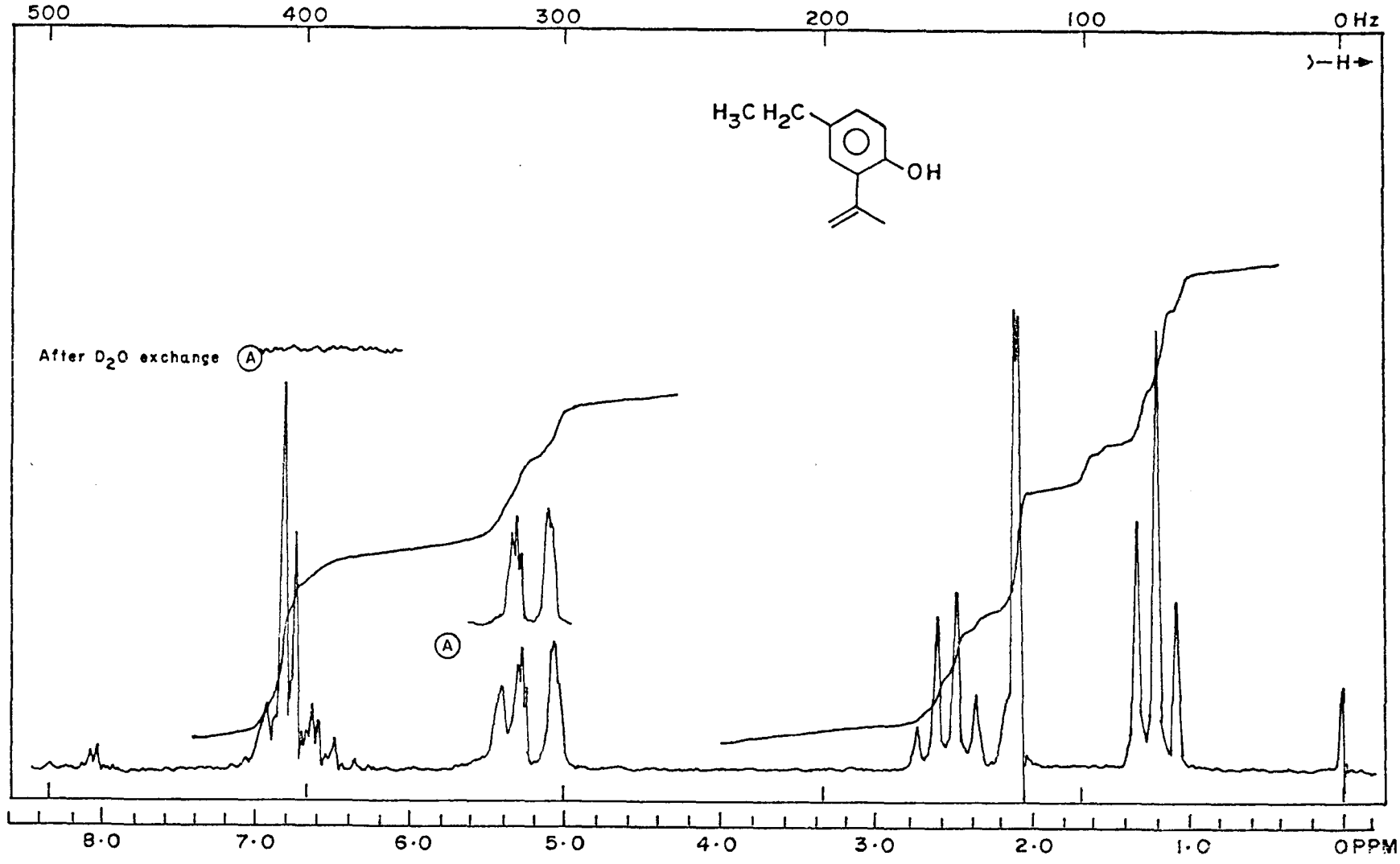


FIG. 7 IR SPECTRUM OF 2-(2-HYDROXY-5-METHYLPHENYL)-PROP-1-ENE(I)



FIG·8 PMR SPECTRUM OF 2-(2-HYDROXY-5-ETHYLPHENYL)-PROP-1-ENE(15)

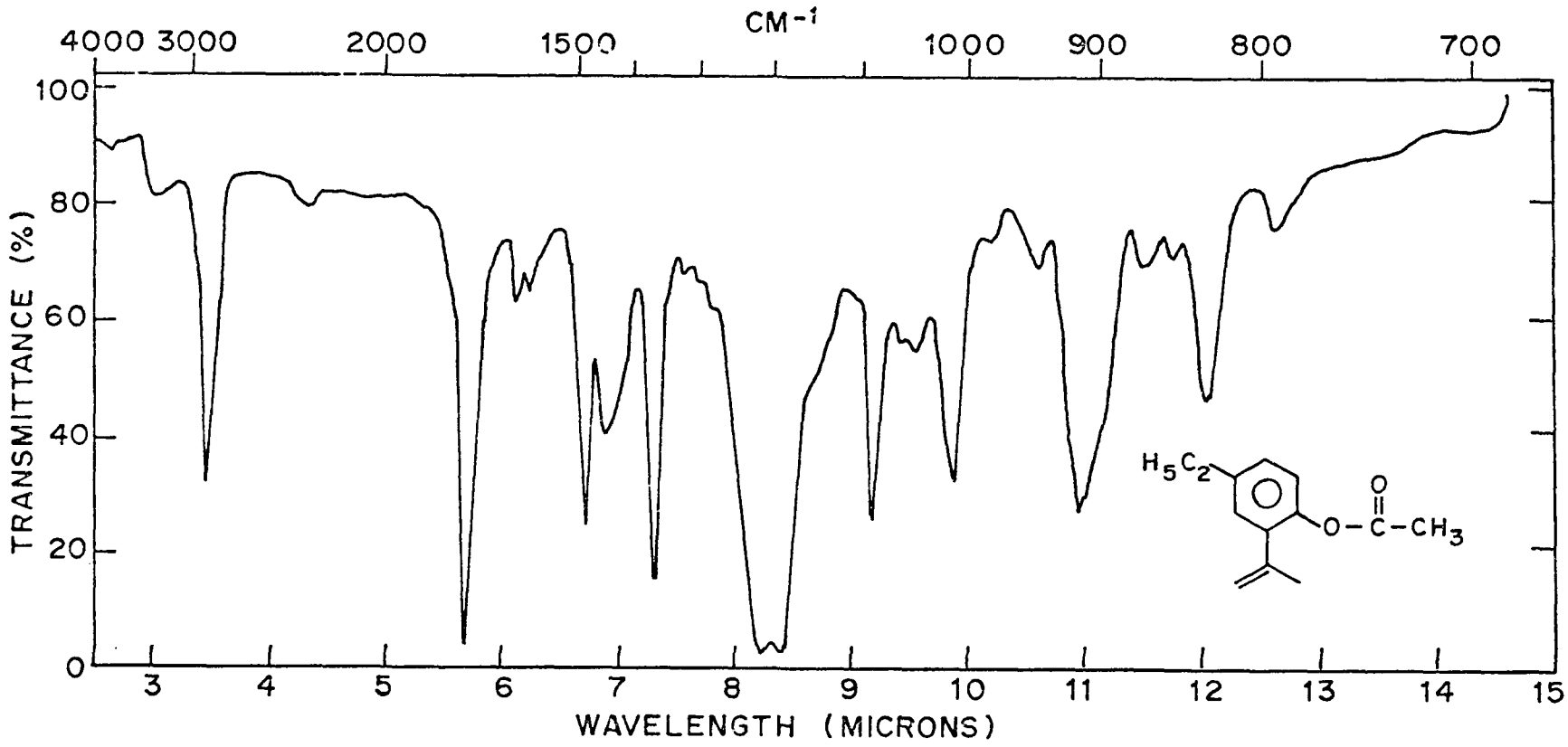


FIG. 9 IR SPECTRUM OF 2-(2-ACETOXY-5-ETHYLPHENYL)-PROP-1-ENE (16)

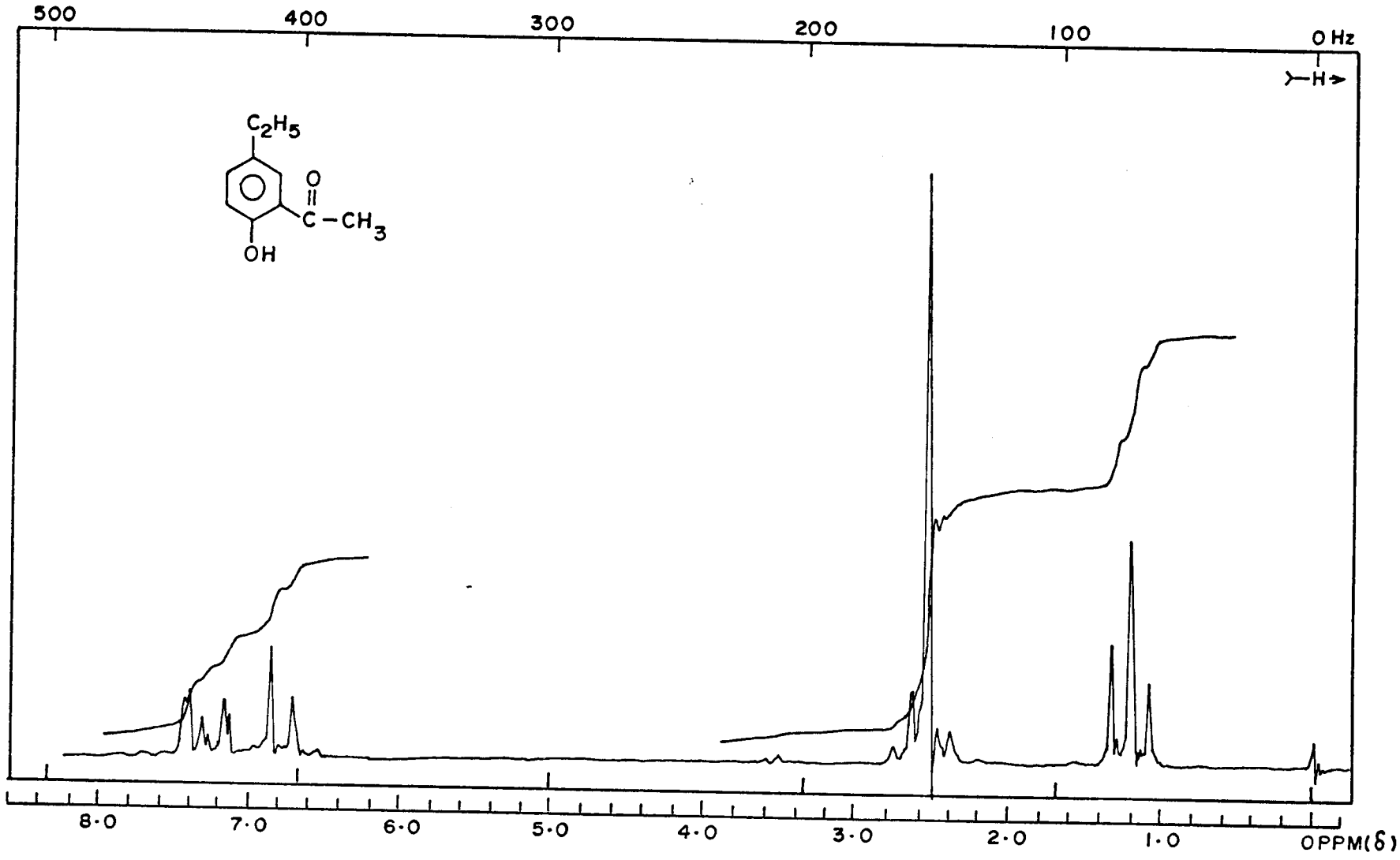


FIG. 10 PMR SPECTRUM OF (3- ACETYL -4-HYDROXYPHENYL)-ETHANE (17)

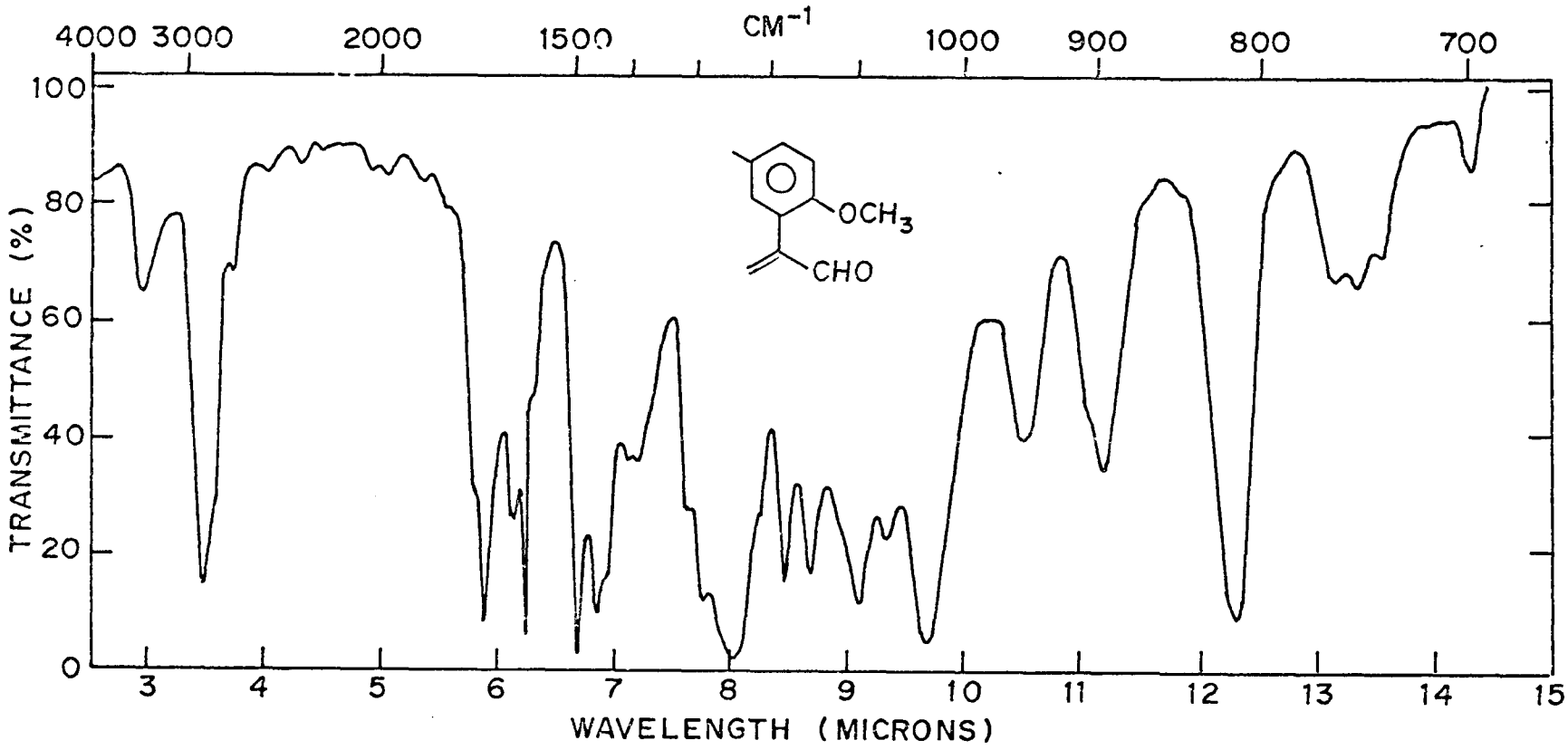


FIG. 11 IR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROP-2-EN-1-AL (22)

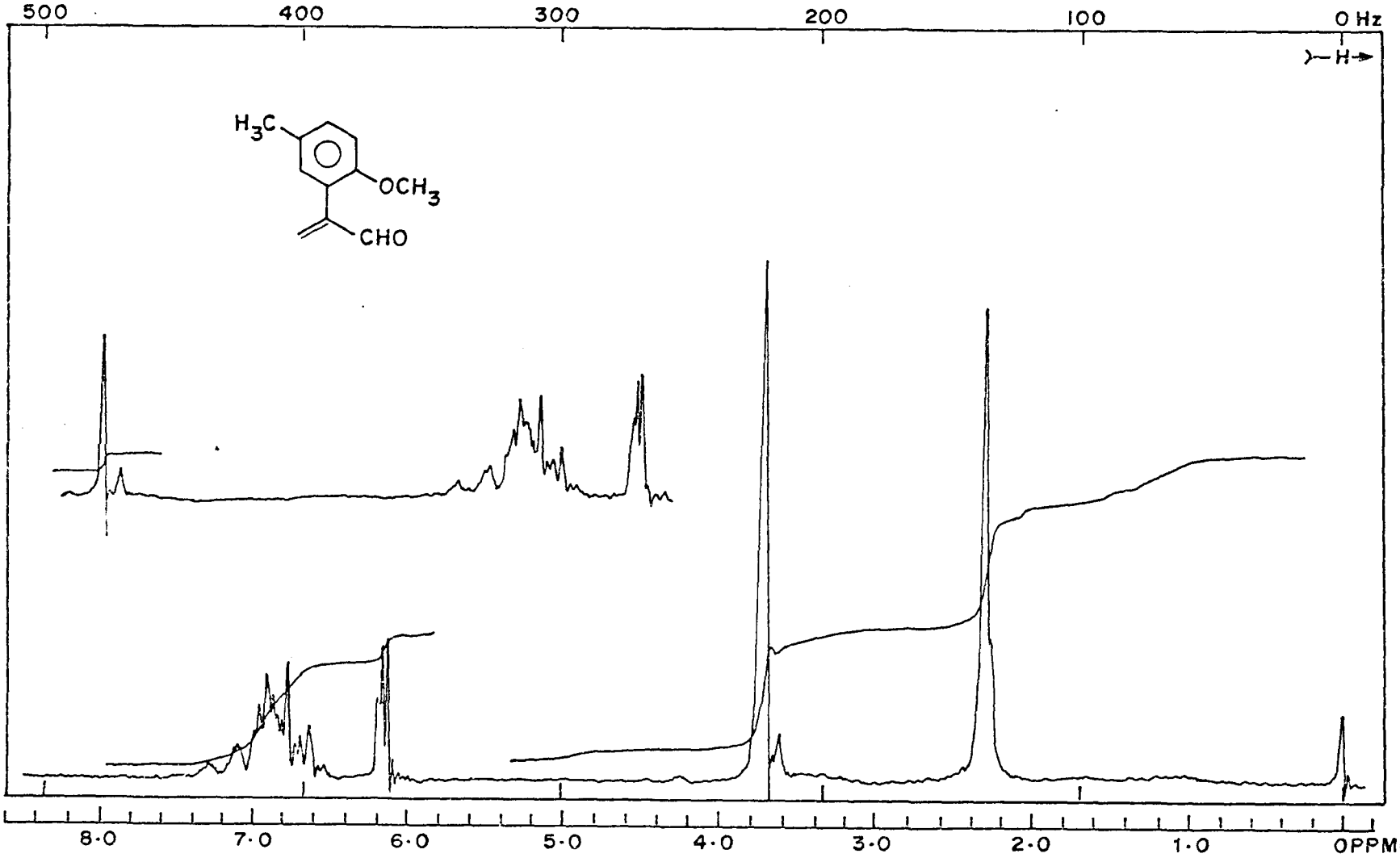
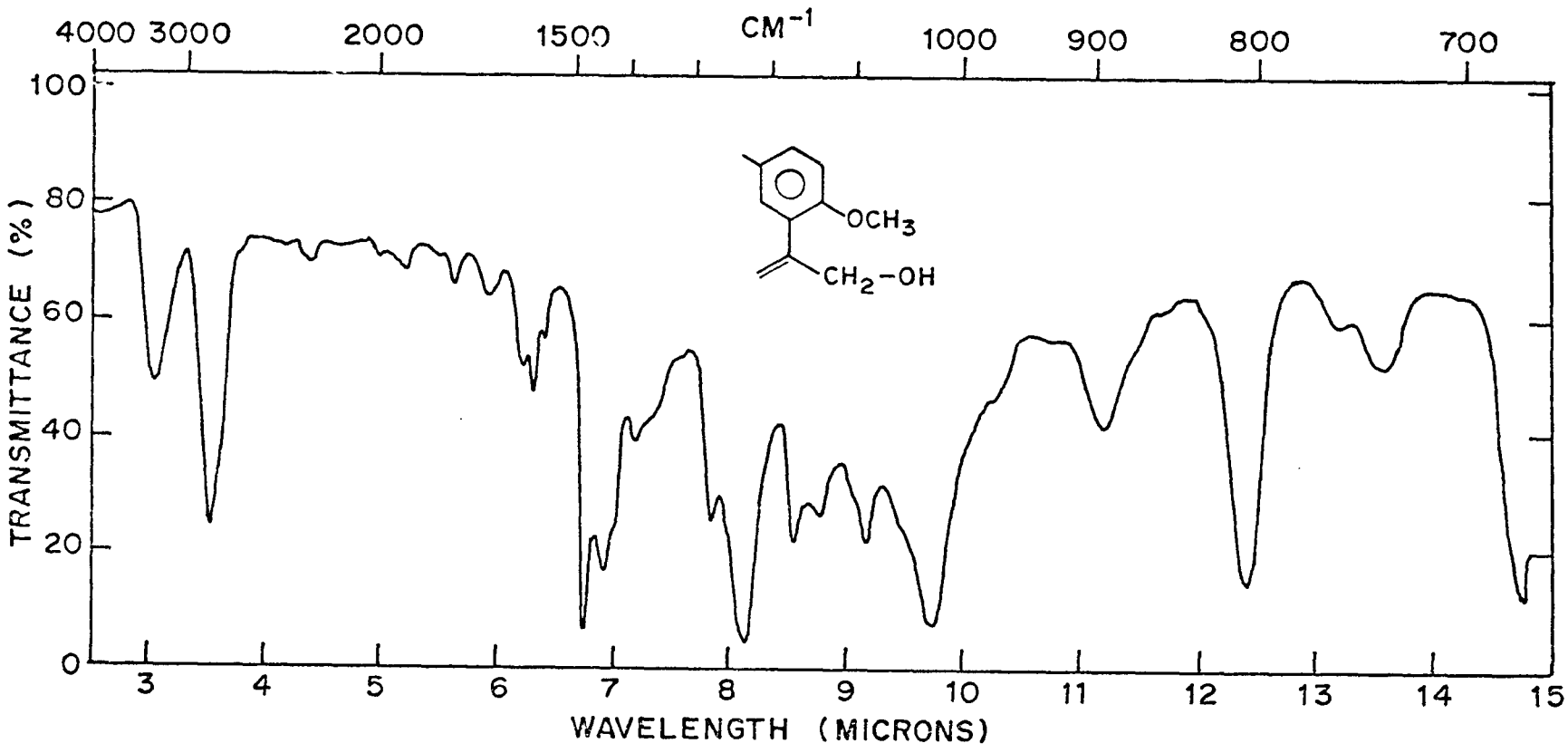
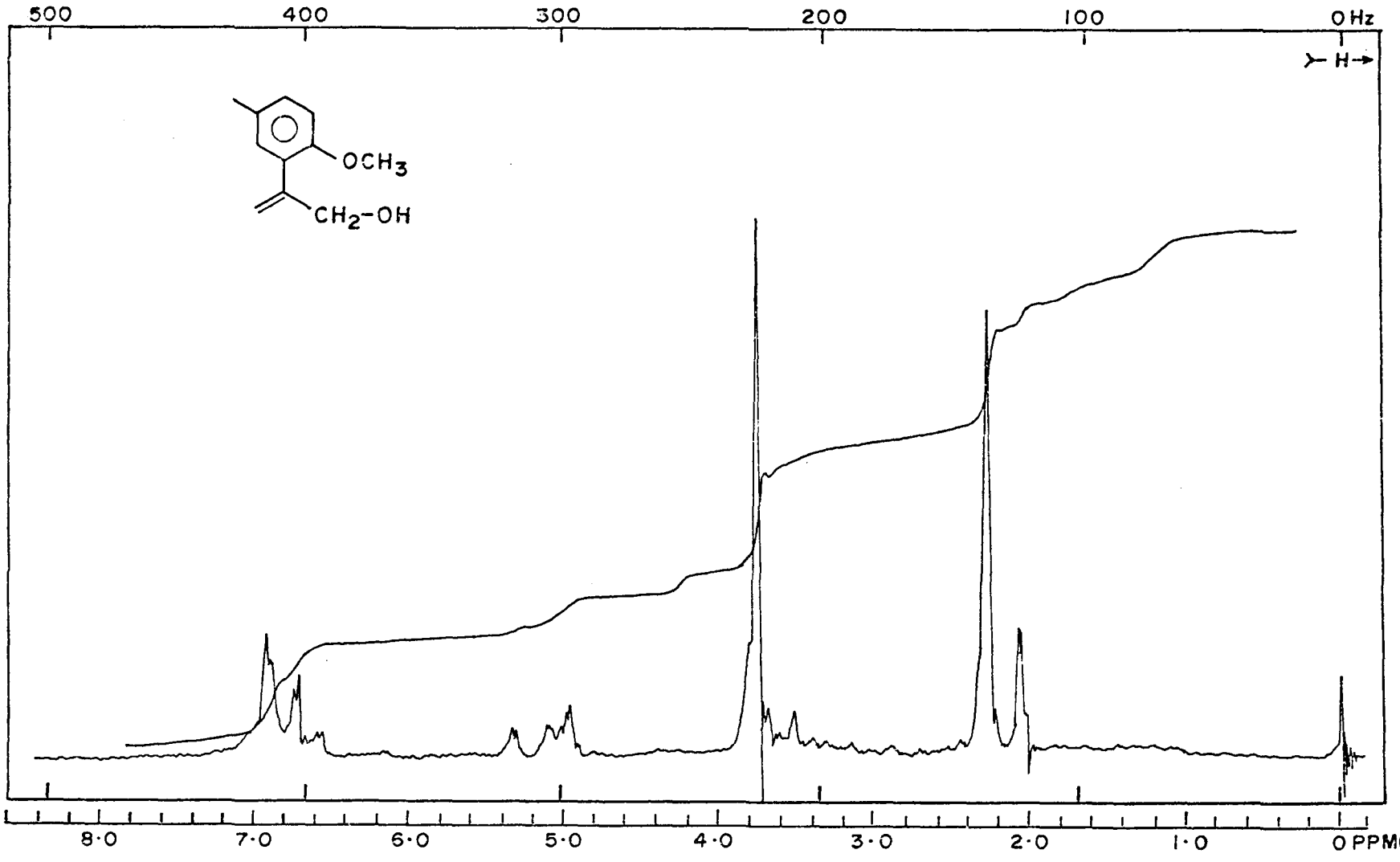


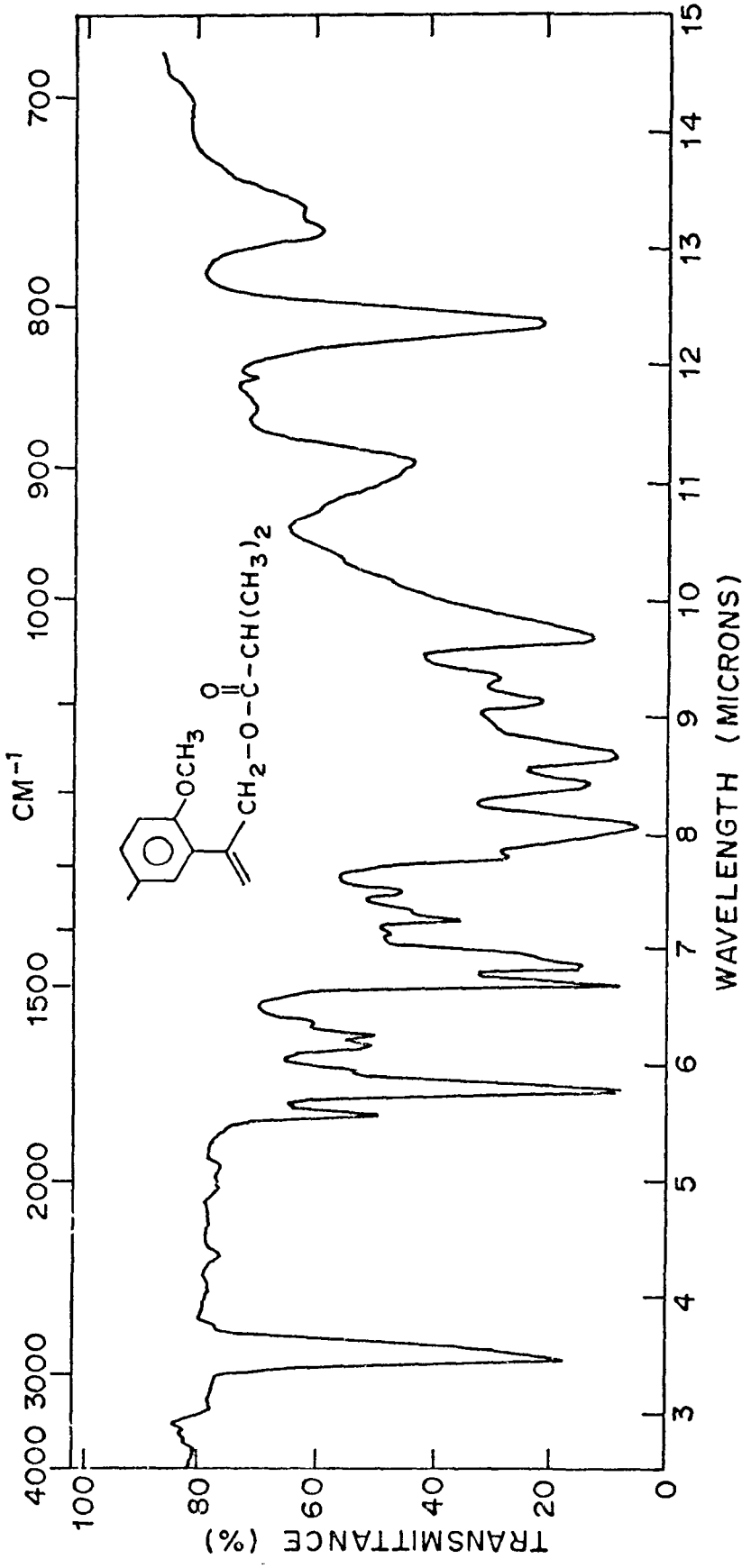
FIG. 12 PMR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROP-2-EN-1-AL (22)



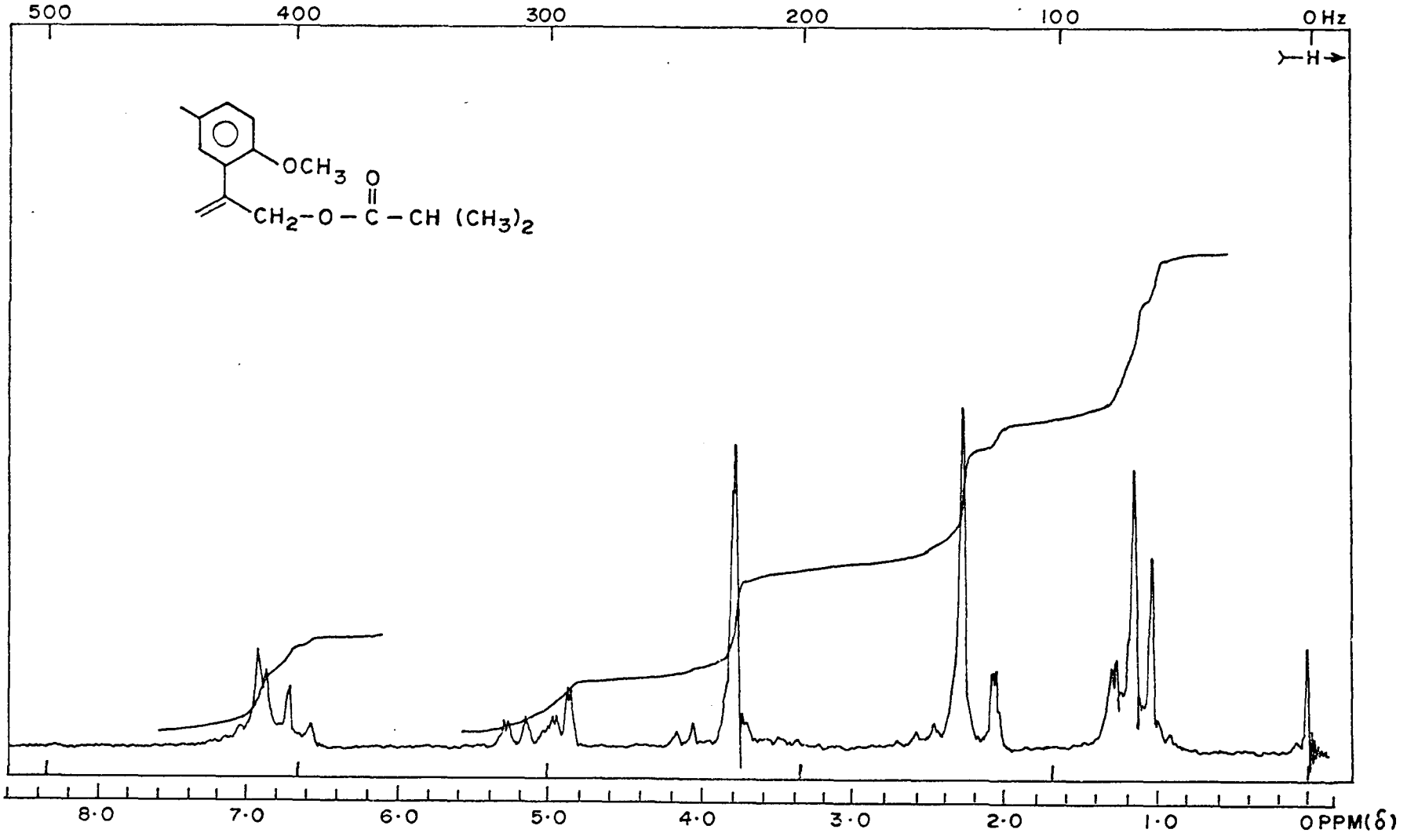
FIG·13 IR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROP-2-EN-1-OL(23)



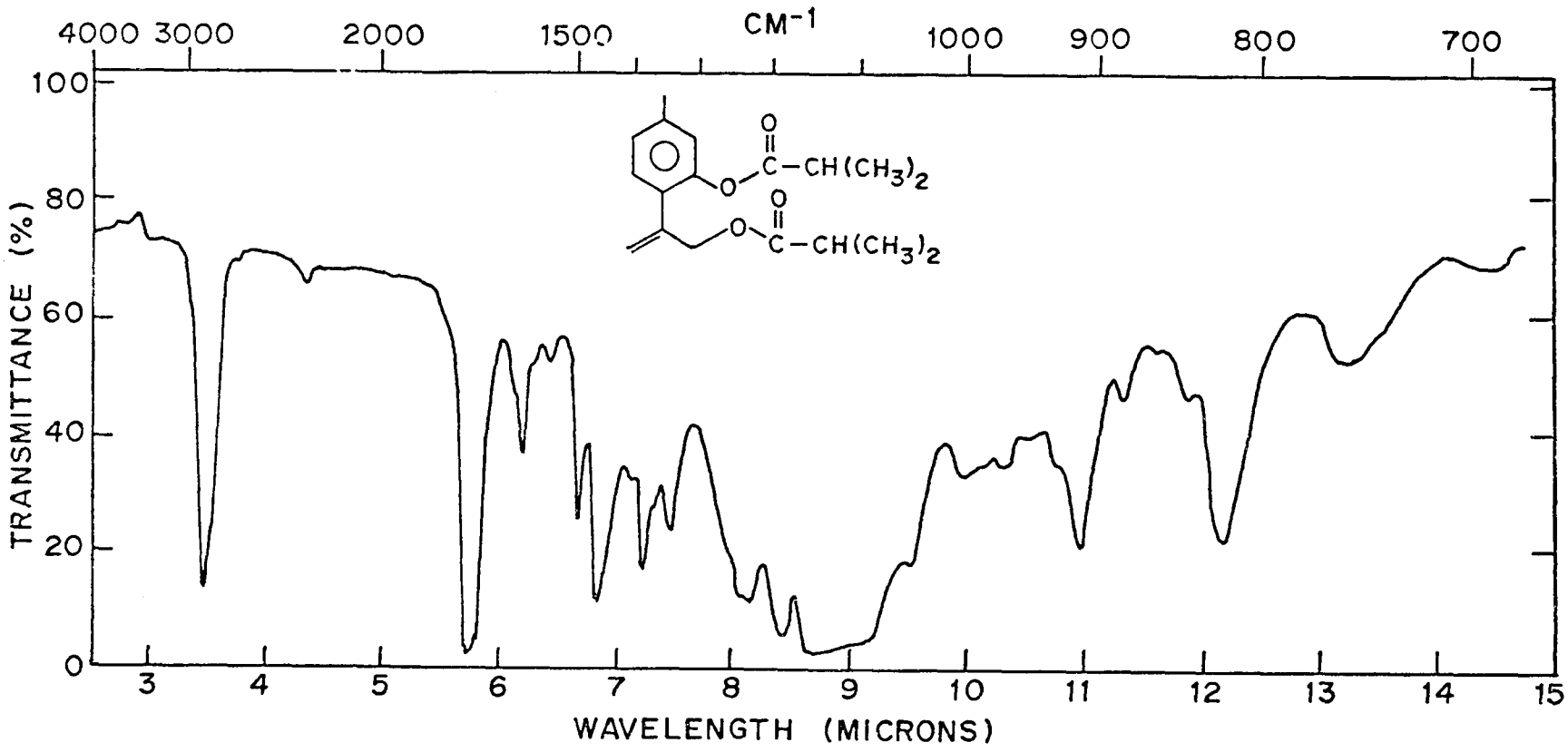
FIG·14 PMR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROP-2-EN-1-OL(23)



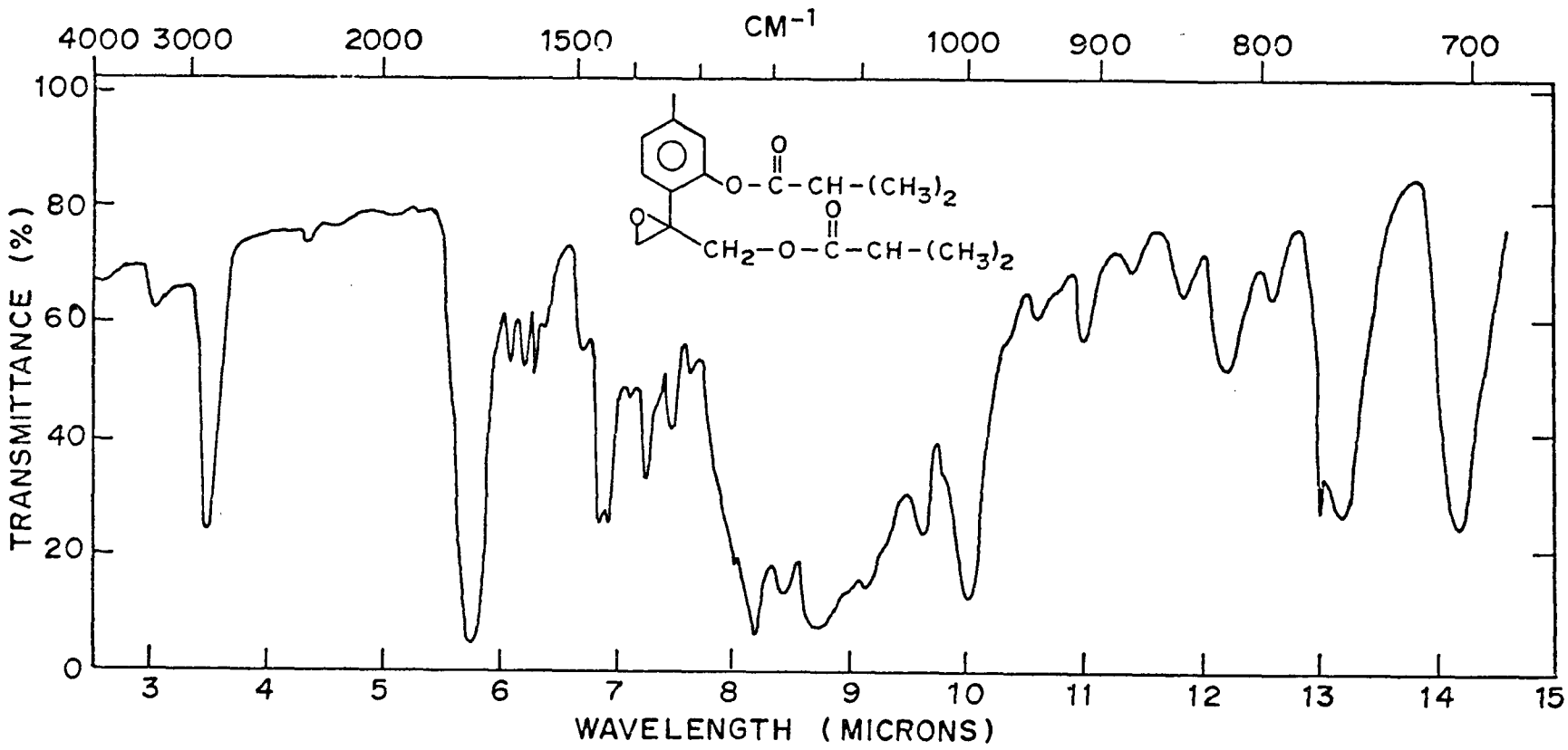
FIG·15 IR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROP-2-EN-1-OL ISOBUTYRATE (24)



FIG·16 PMR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROP-2-EN-1-OL ISOBUTYRATE(24)



FIG·17 IR SPECTRUM OF 2-(2-HYDROXY-4-METHYL PHENYL)-PROP-2-EN-1-OL DIISOBUTYRATE (25)



FIG·18 IR SPECTRUM OF 2-HYDROXYMETHYL-2-(2-HYDROXY-4-METHYLPHENYL) -OXIRANE DIISOBUTYRATE (27)

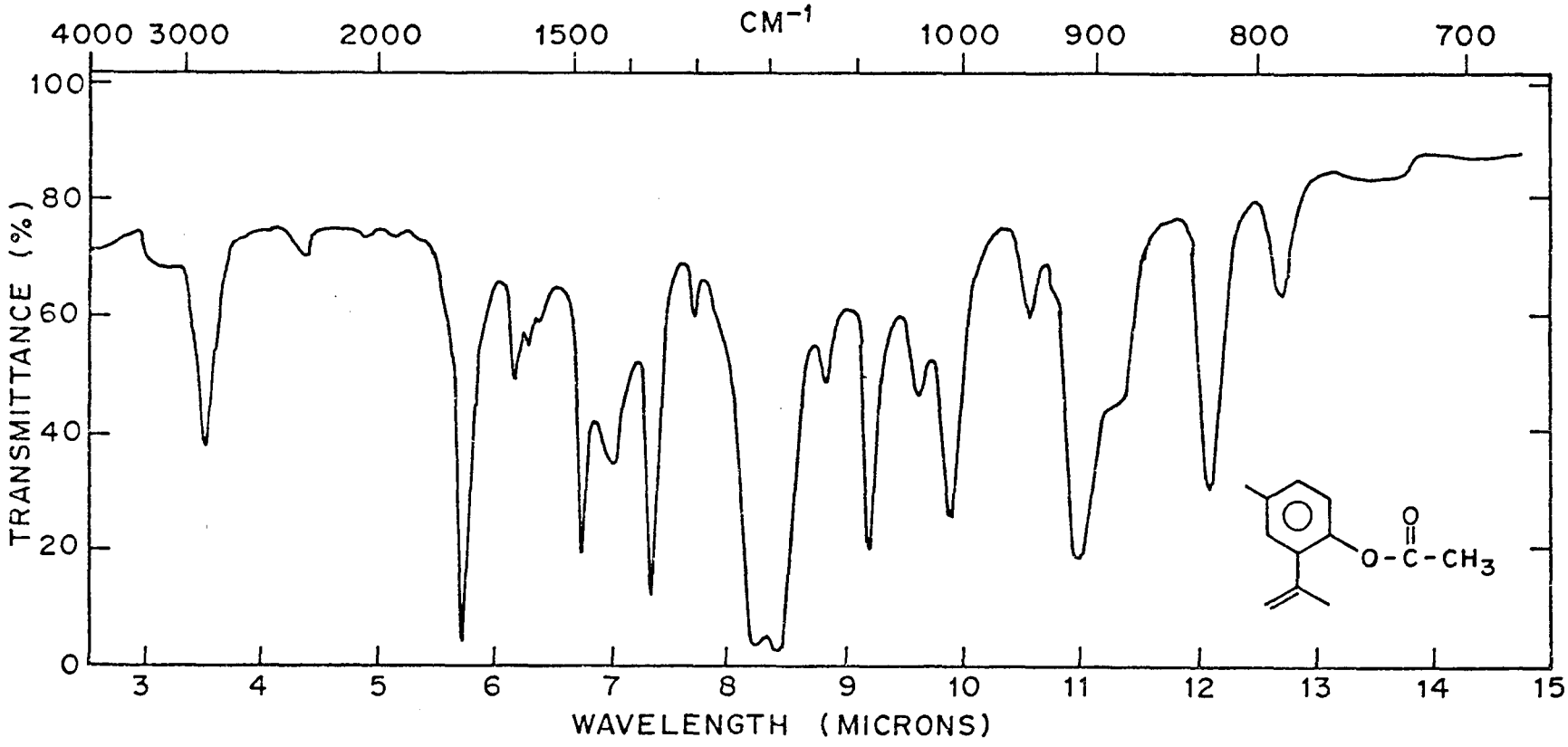
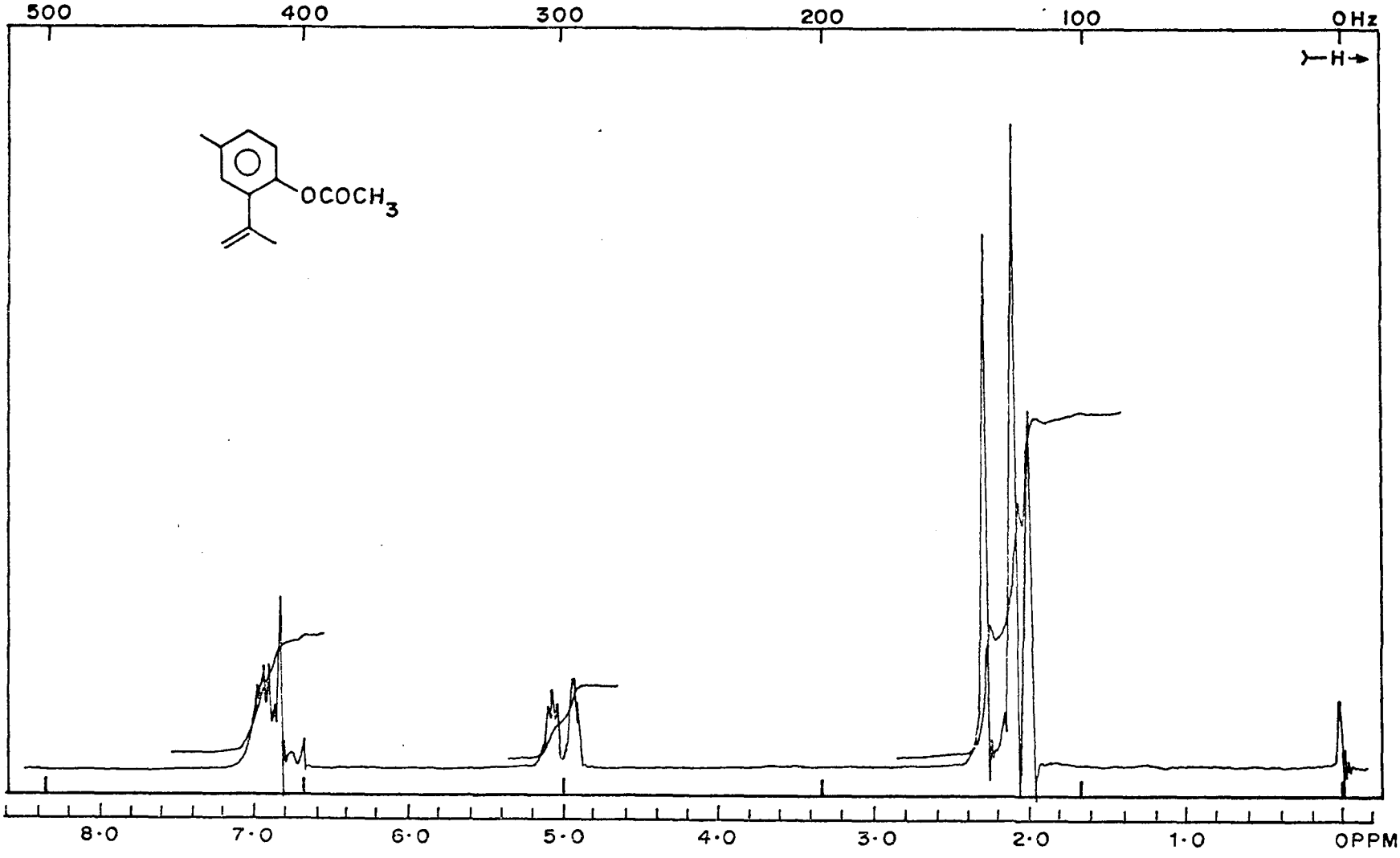
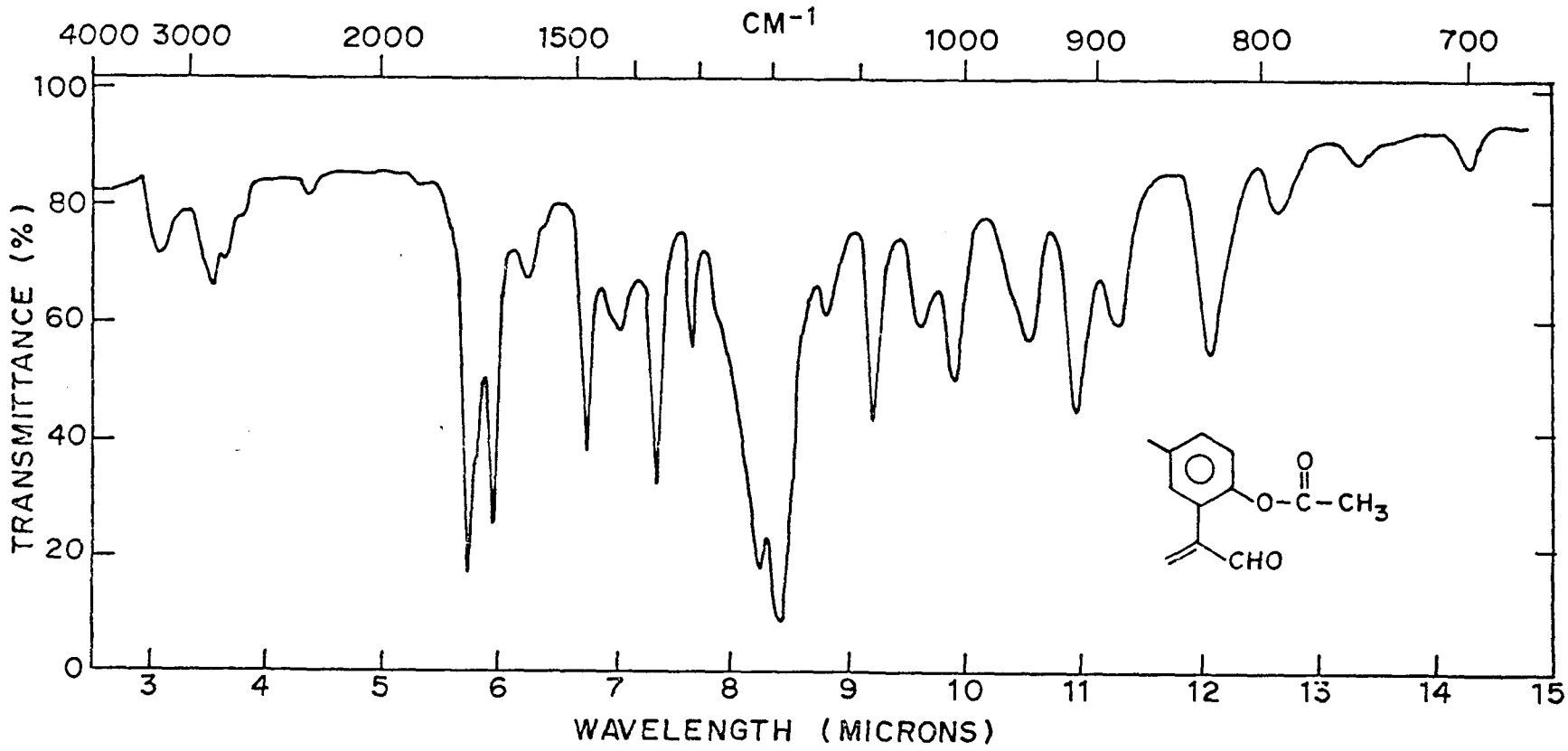


FIG. 19 IR SPECTRUM OF 2-(2-ACETOXY-5-METHYLPHENYL)-PROP-1-ENE(2)



FIG·20 PMR SPECTRUM OF 2-(2-ACETOXY-5-METHYLPHENYL)-PROP-1-ENE(2)



FIG·21 IR SPECTRUM OF 2-(2-ACETOXY-5-METHYLPHENYL)-PROP-2-EN-1-AL(3)

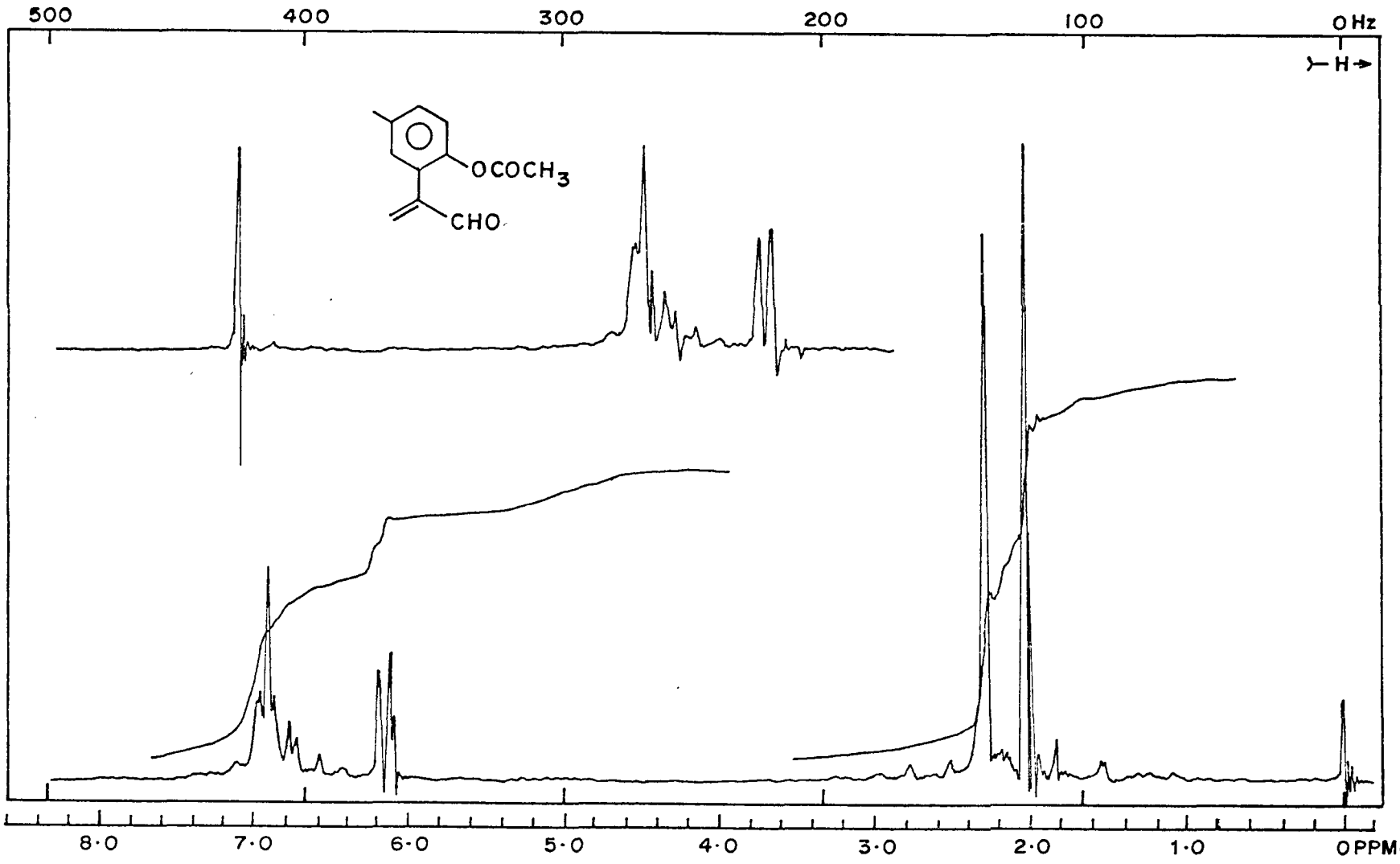
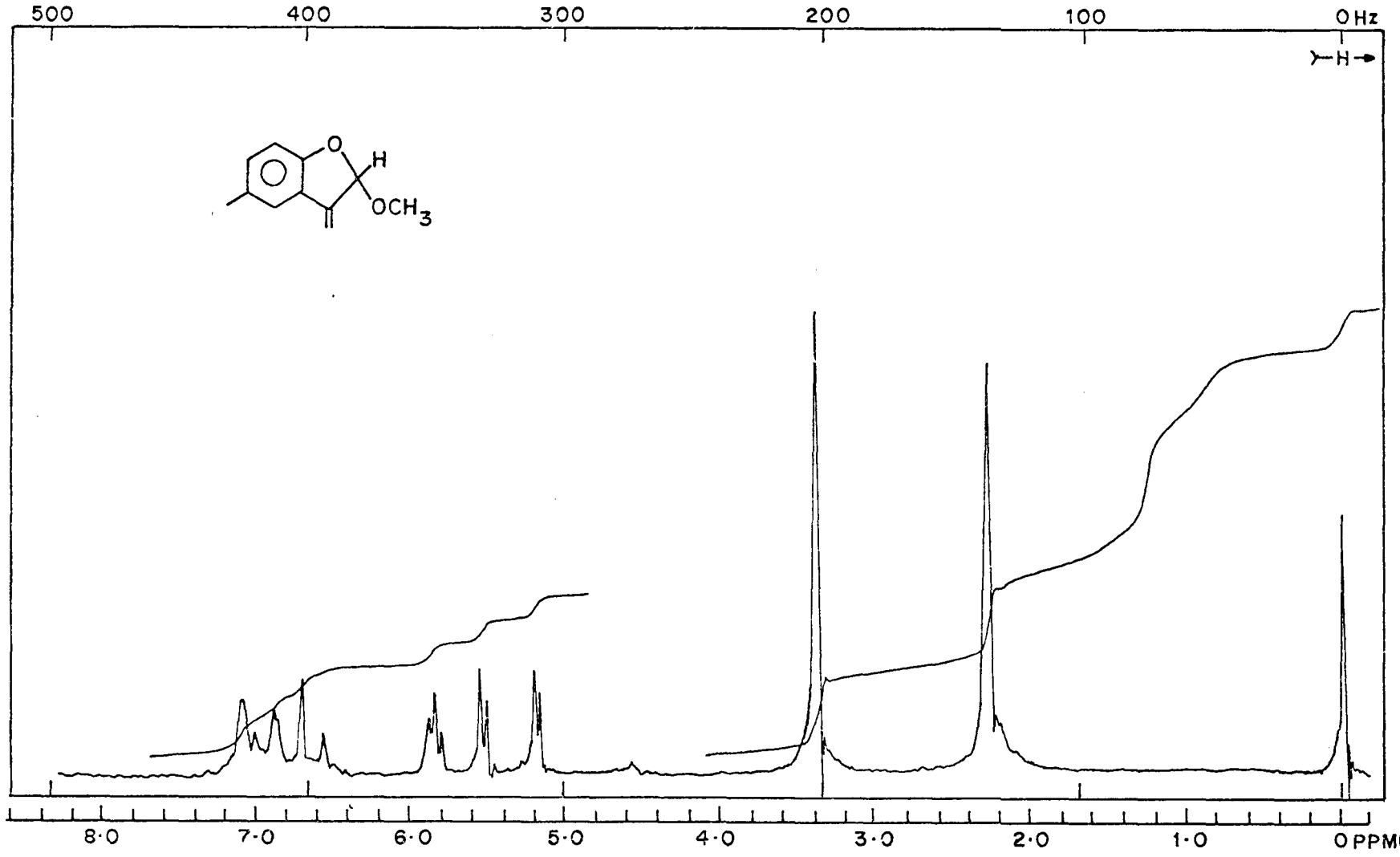


FIG. 22 PMR SPECTRUM OF 2-(2-ACETOXY-5-METHYLPHENYL)-PROP-2-EN-1-AL (3)



FIG·23 PMR SPECTRUM OF 2,3 DIHYDRO-2-METHOXY-3-METHYLENE-5-METHYL-BENZOFURAN(4)

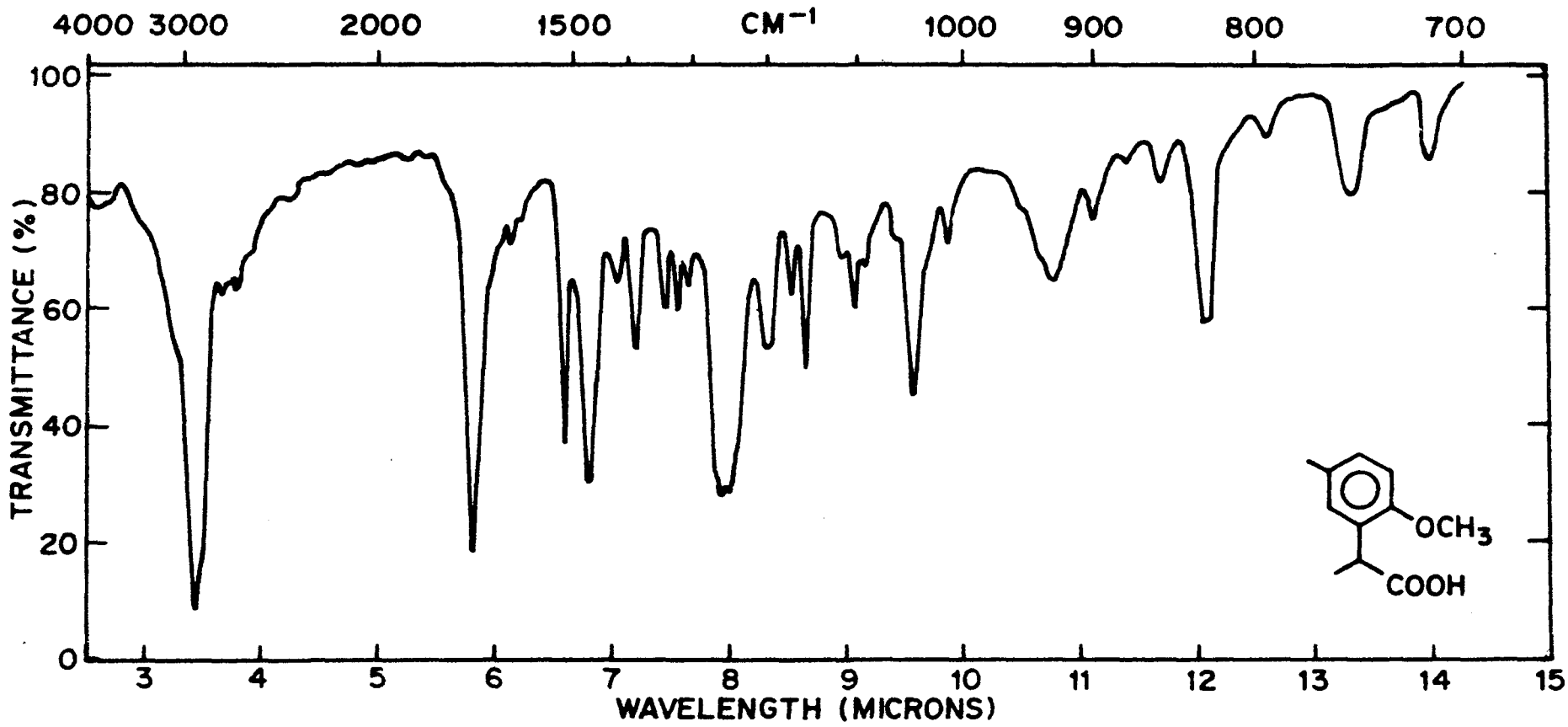


FIG. 24. IR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROPANOIC ACID (11)

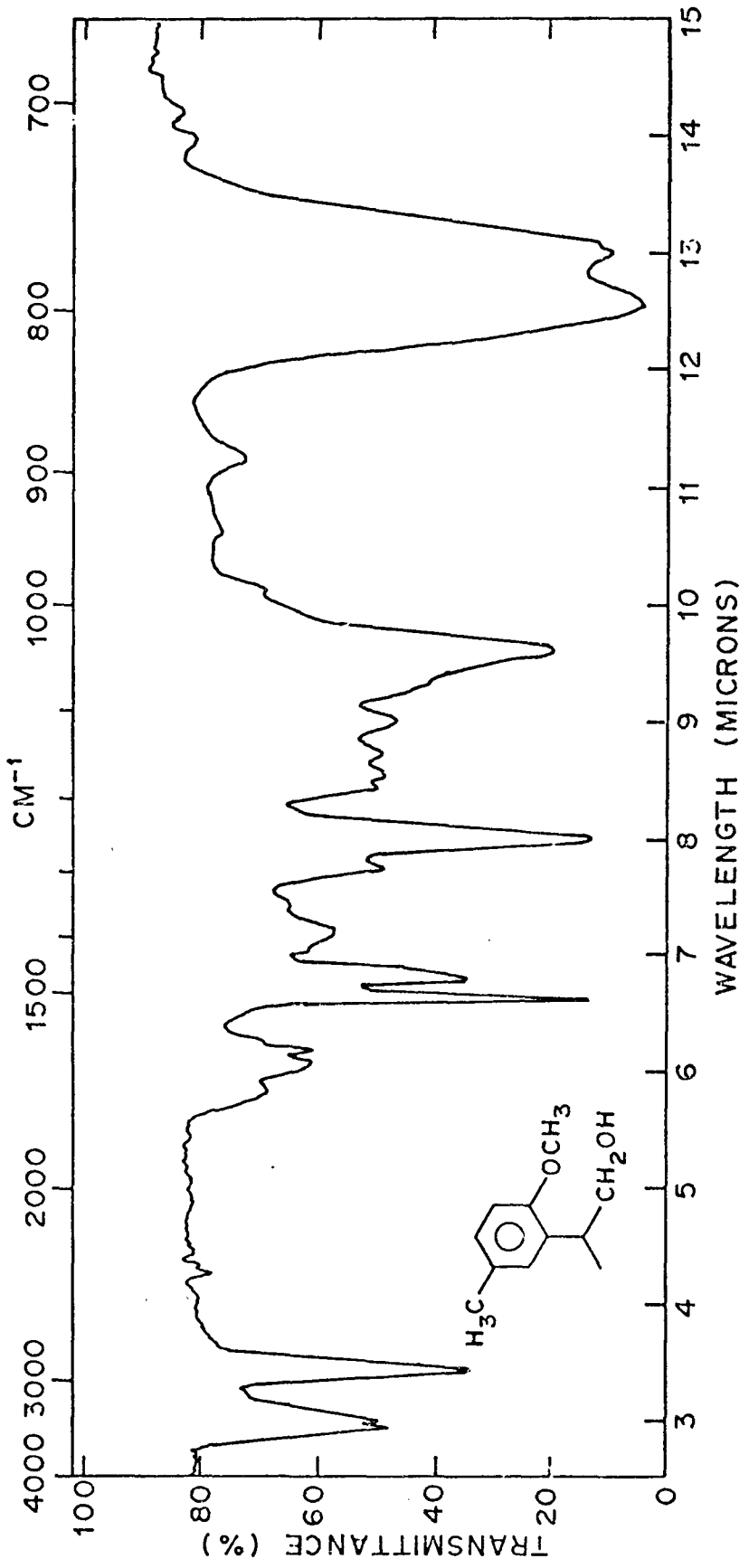
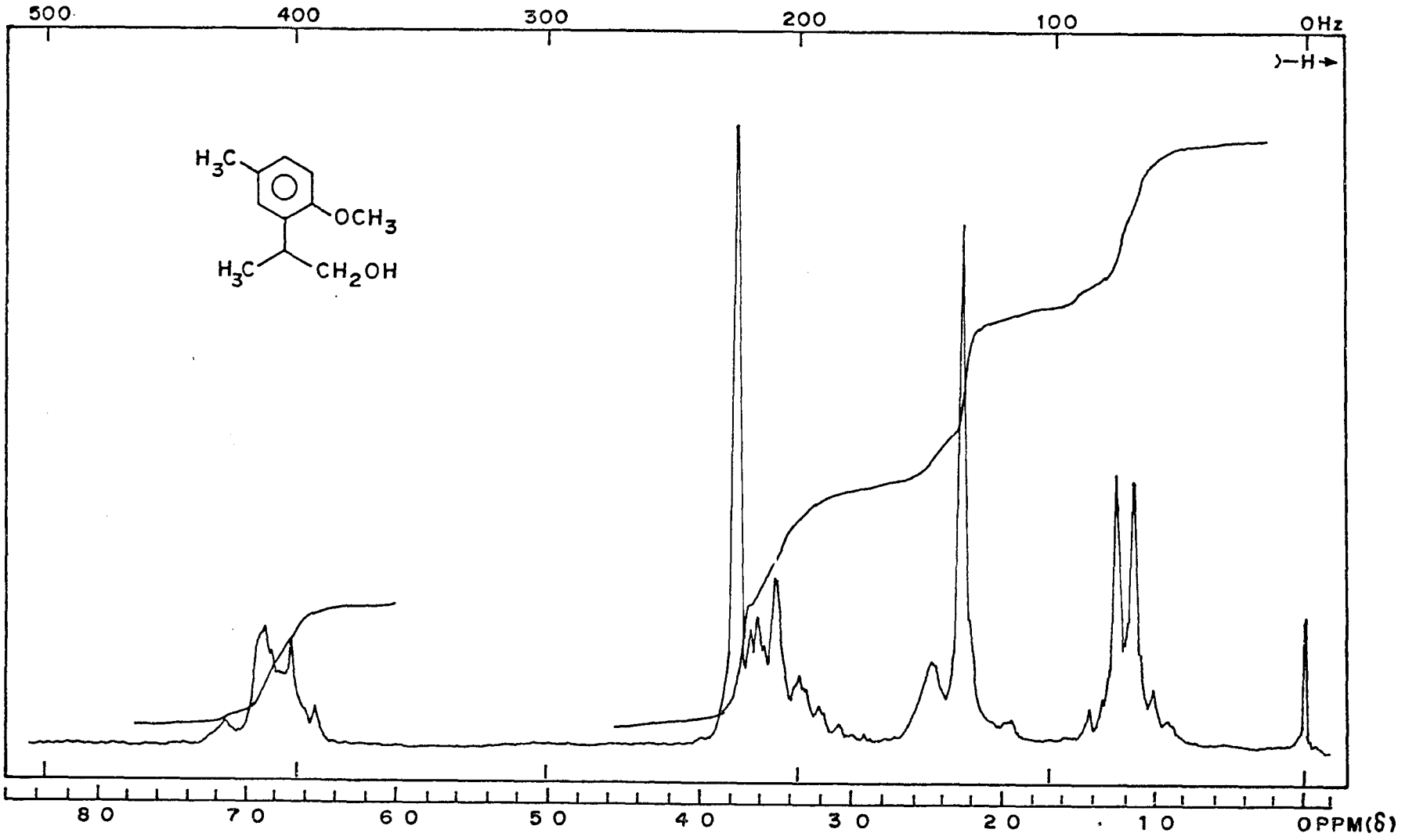
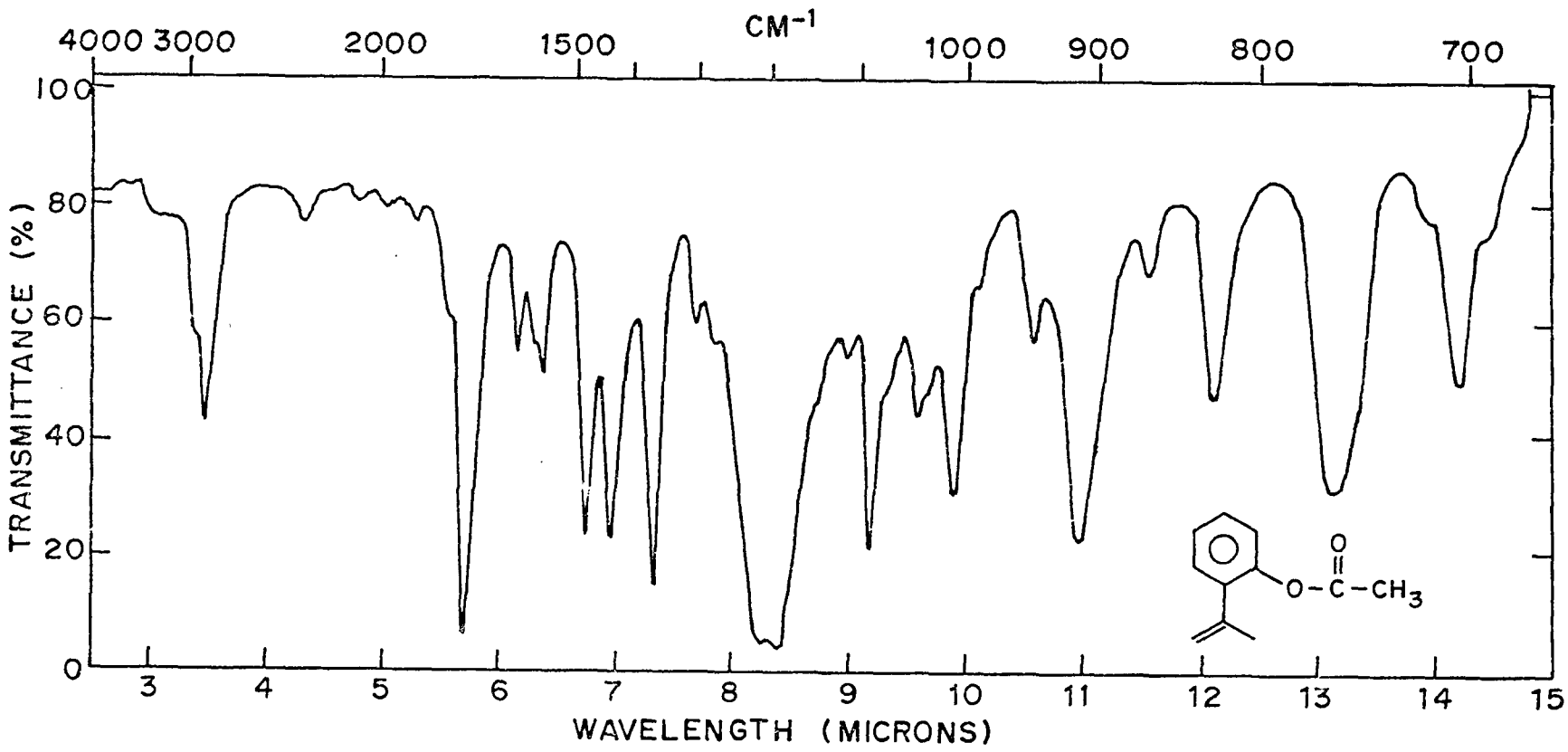


FIG.25 IR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROPAN-1-OL(9))



FIG·26 PMR SPECTRUM OF 2-(2-METHOXY-5-METHYLPHENYL)-PROPAN-1-OL (9)



FIG·27 IR SPECTRUM OF 2-(2-ACETOXYPHENYL)-PROP-1-ENE (29)

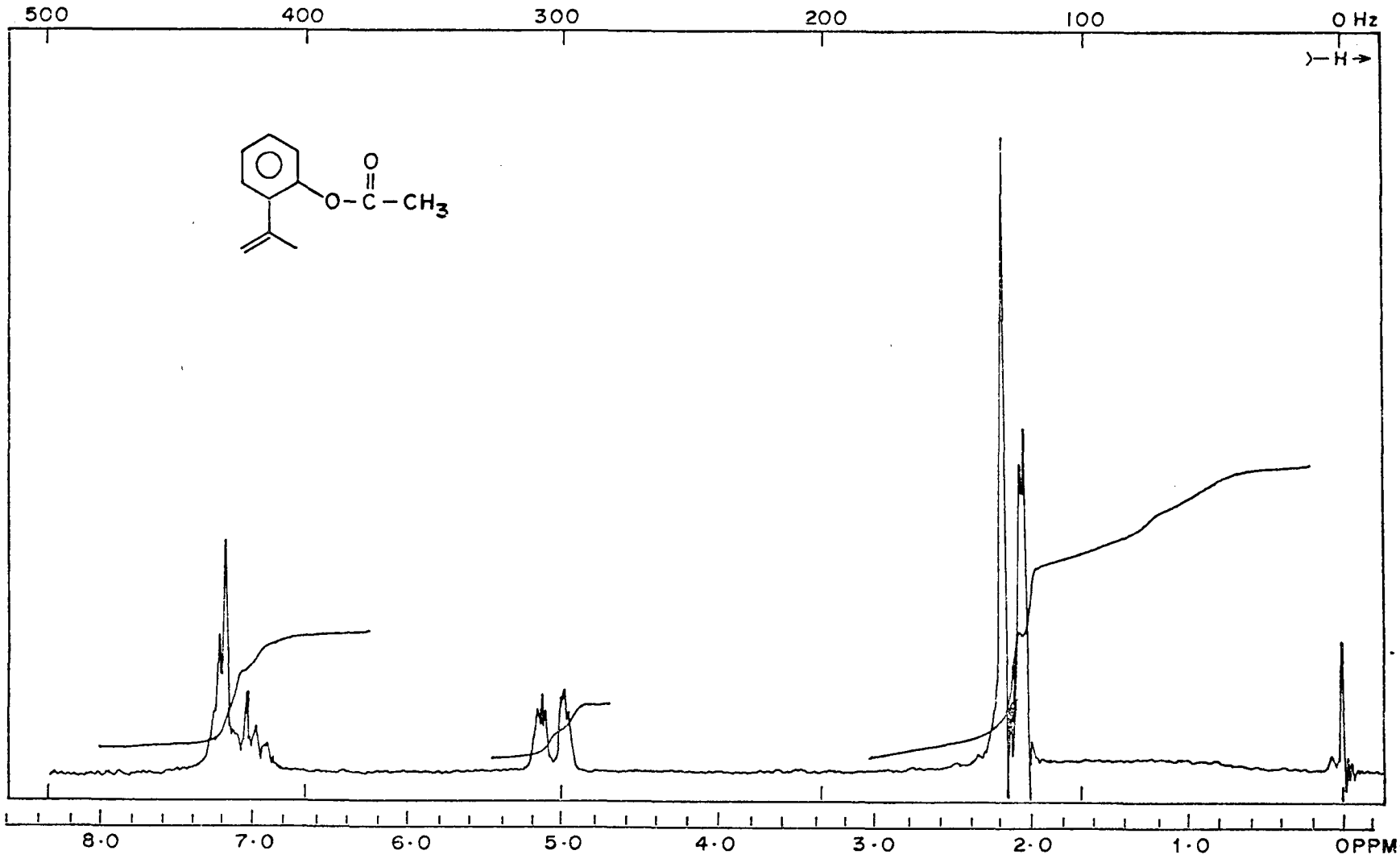
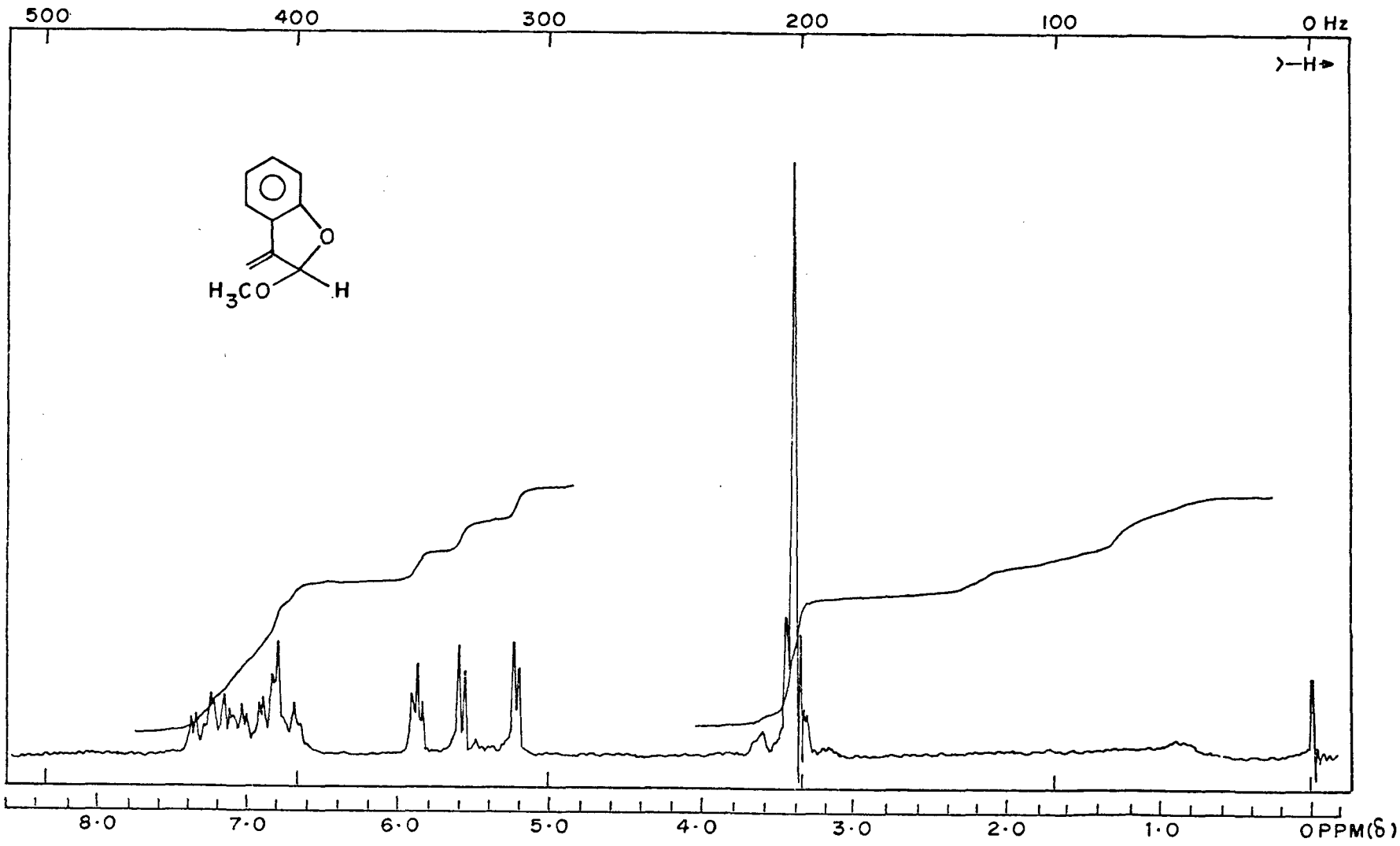
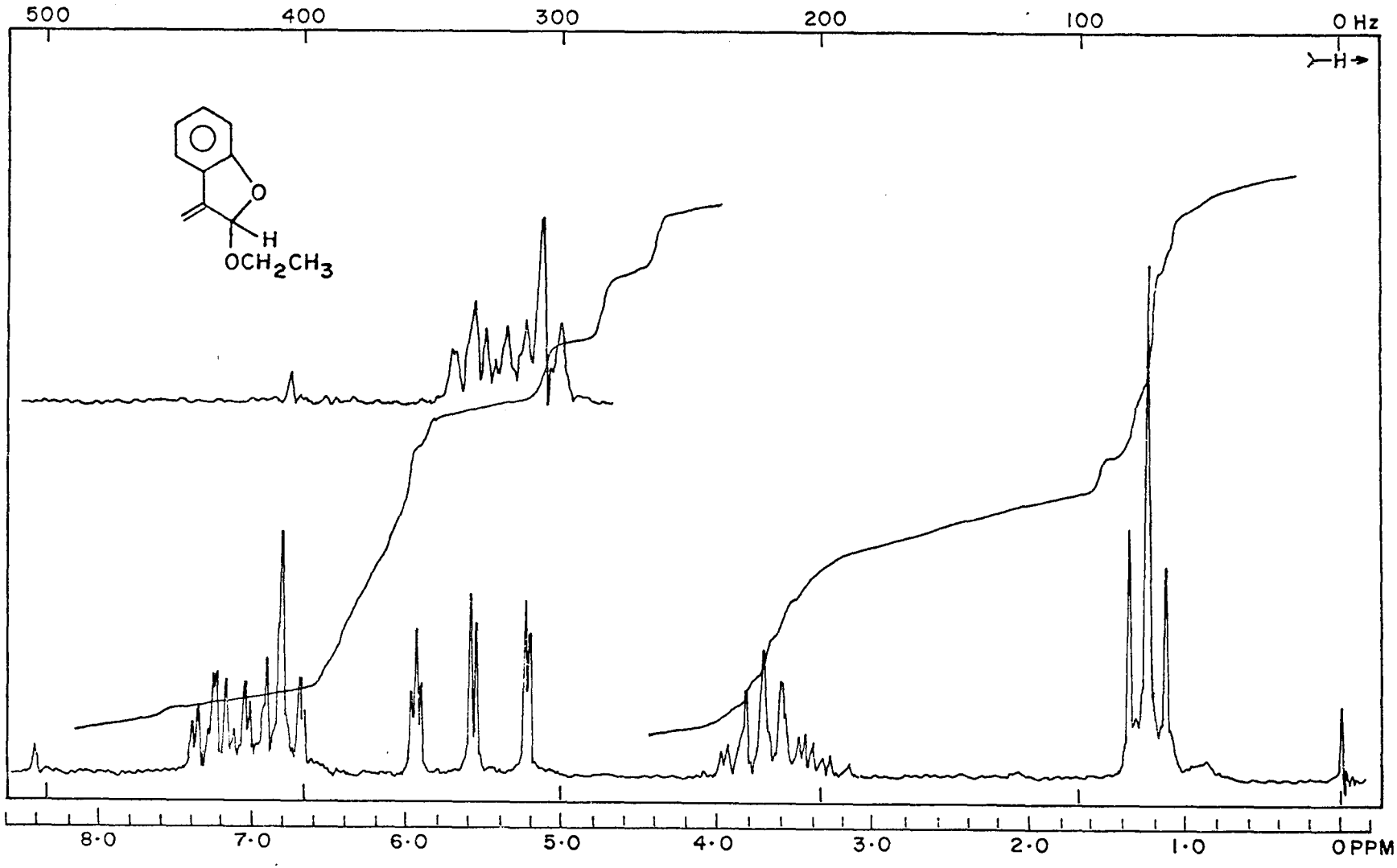


FIG. 28 PMR SPECTRUM OF 2-(2-ACETOXYPHENYL)-PROP-1-ENE(29)



FIG·29 PMR SPECTRUM OF 2,3 DIHYDRO-2-METHOXY-3-METHYLENE-BENZOFURAN (32)



FIG·30 PMR SPECTRUM OF 2,3 DIHYDRO-2-ETHOXY-3-METHYLENE-BENZOFURAN (33)

CHAPTER 3

SYNTHESIS OF

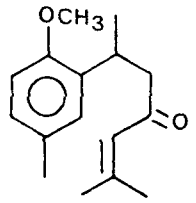
1) 2-HYDROXY-2-METHYL-6-(2-METHOXY-5-METHYLPHENYI)-HEPTANE

2) 2-METHYL-6-(2-METHOXY-5-METHYLPHENYL)-HPET-2-EN-4-ONE,

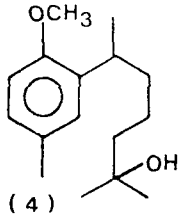
THE INTERMEDIATES FOR SYNTHESIS OF ELVIROL

3.1 SUMMARY

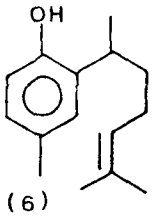
α,β-Unsaturated ketone (12) and tertiary alcohol (4) having the elvirol (6) carbon skeleton have been synthesized.



(12)



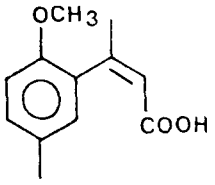
(4)



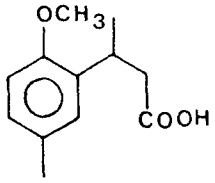
(6)

Acid (7), obtained through hydrolytic methylation of 4,6-dimethyl coumarin was reduced with Ni-Al alloy-alkali to the acid (8). Lithium salt of (8) reacted with isobutenyl lithium to furnish the ketone (12).

Alcohol (4) has been prepared in four steps starting from p-methoxytoluene and glutaric anhydride.



(7)



(8)

3.2 INTRODUCTION

The isolation of the phenolic sesquiterpene Elvirol (6), was reported[1] in 1969, from Elvira biflora. Literature reports three methods for synthesis of elvirol by different routes. The three syntheses are shown in the charts (1), (2), and (3), which are reported by Dennison et.al.[2], Bohlmann[3] and Vig et.al.[4] respectively.

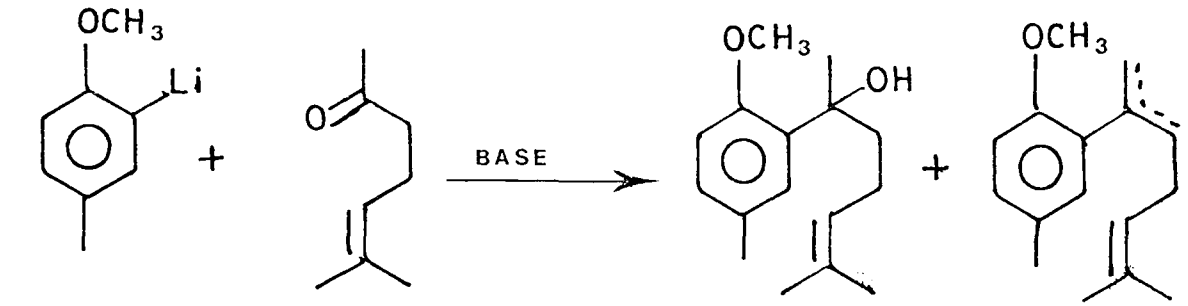
Use of organolithium reagents in the synthesis of ketones from carboxylic acids

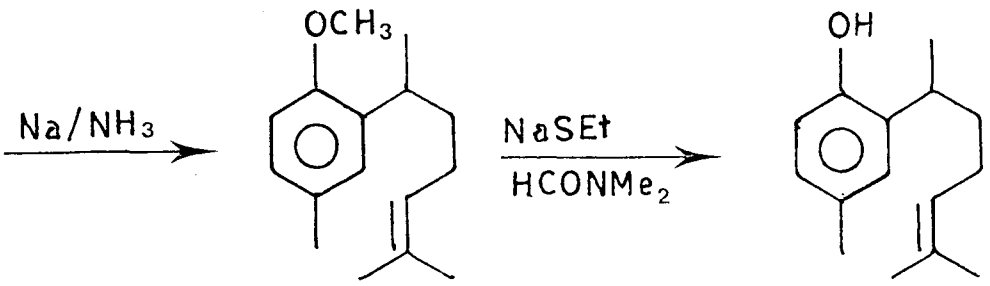
The reaction of organolithium reagents and carboxylic acids constitutes a simple general method for synthesis of ketones and has been reviewed by Jorgenson[5]. This reaction is known since 1933[6]. Utilization of this reaction has received impetus in recent years, since numerous organolithium reagents are available commercially. This method is found to be of great interest as it provides a route for direct conversion of carboxylic acids to ketones.

The synthetic potential of the reaction of carboxylic acids with organolithium reagents was first recognized by Gilman and Ess[6], who discovered this transformation as a side reaction during studies of the carbonation of organolithium reagents. When phenyl lithium was treated with carbondioxide, benzophenone was formed in 70% yield. Here

CHART I

DENNISON'S SYNTHESIS OF ELVIROL

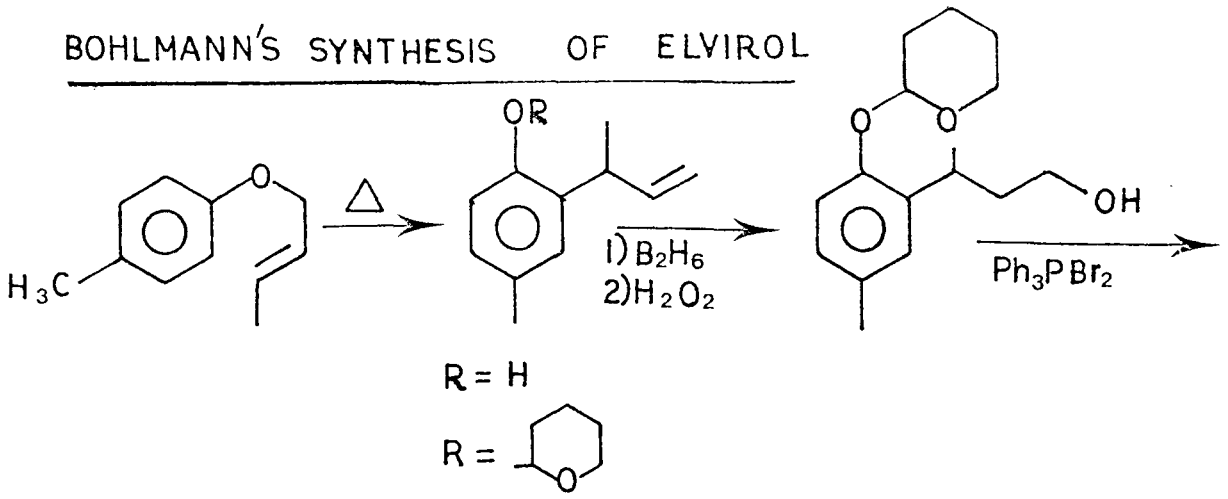


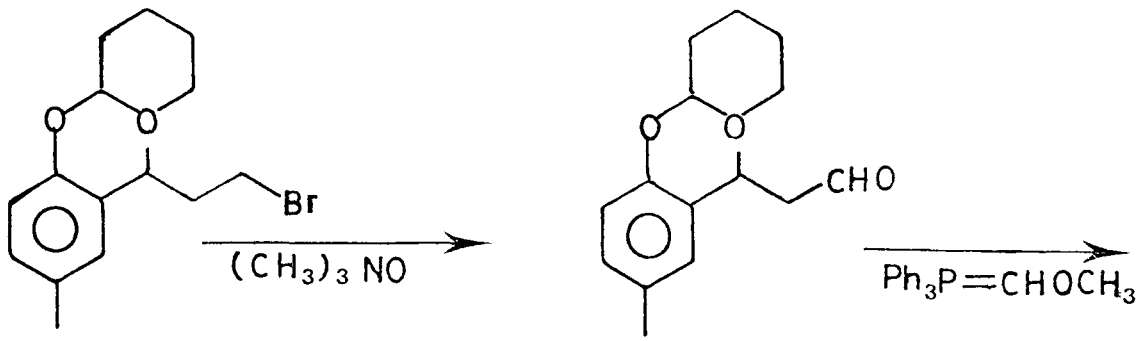


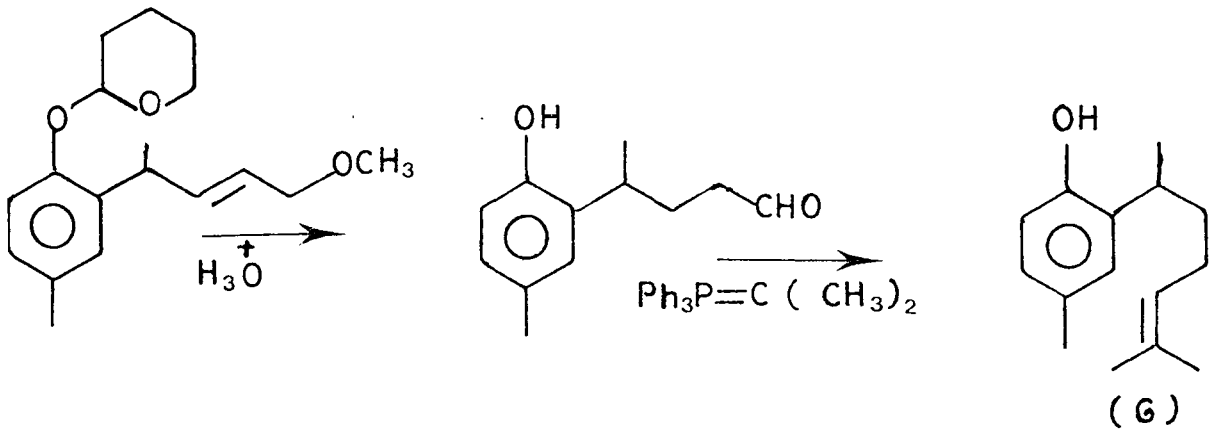
(G)

CHART 2

BOHLMANN'S SYNTHESIS OF ELVIROL



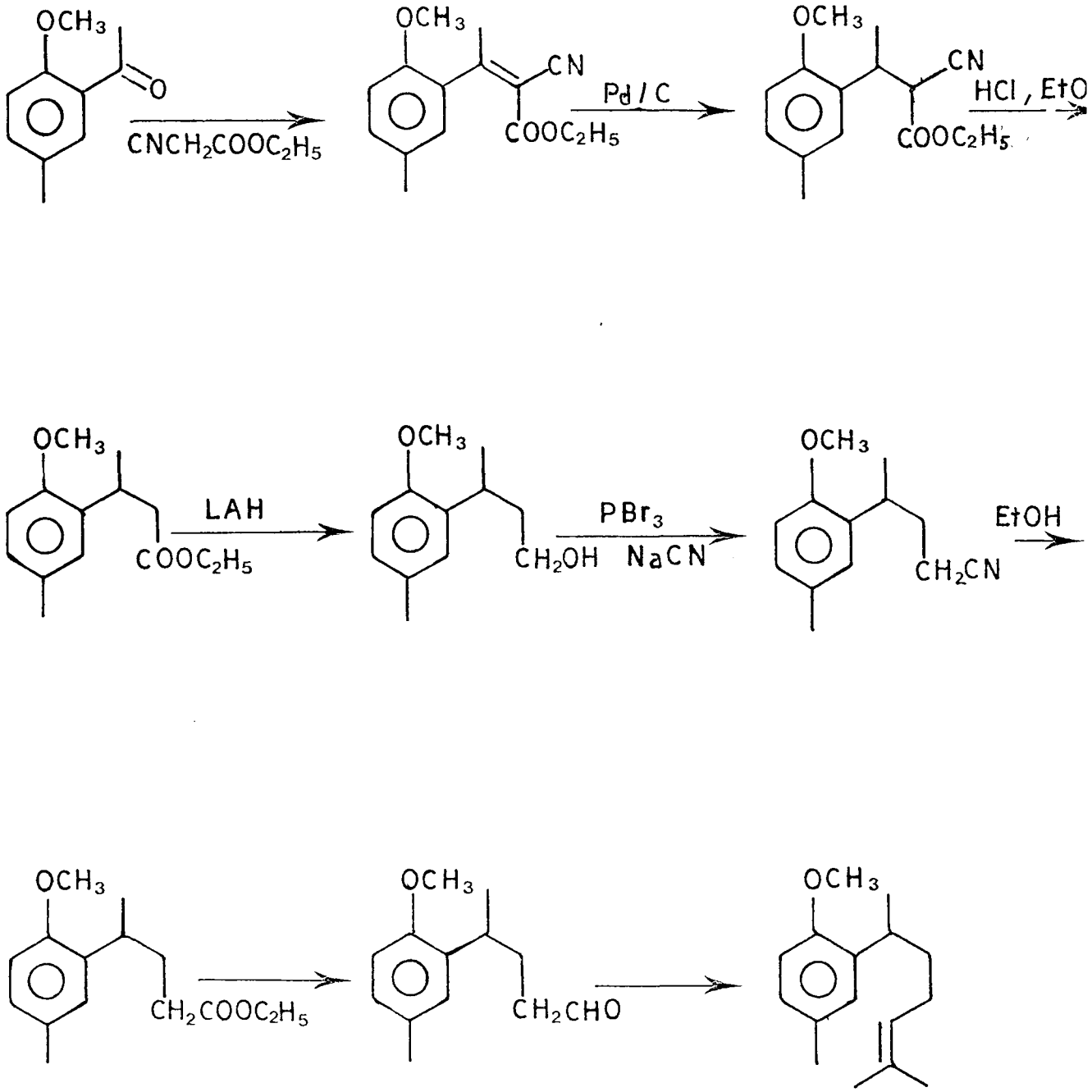




(G)

CHART 3

SYNTHESIS OF ELVIROL BY VIG



the process involved a two step reaction sequence which proceeds via lithium benzoate.

$$C_6H_5Li + CO_2 \longrightarrow C_6H_5COOLi$$

$$C_6H_5COOLi + C_6H_5Li \longrightarrow (\text{intermediate})$$

$$(\text{intermediate}) \xrightarrow{H_2O} C_6H_5\text{-}\overset{O}{\overset{\|}{C}}\text{-}C_6H_5$$

Thus the reaction requires two moles of organolithium reagent to react with one mole of carboxylic acid. This can be viewed as taking place in two direct steps; first step (Eq. 1) leads to the formation of lithium salt of carboxylic acid. The second step is the reaction of lithium carboxylate with another mole of organolithium reagent, to furnish an intermediate dilithium compound which on hydrolysis gives a ketone (Eq. 2)

$$R\text{-}COOH + R'\text{-}Li \longrightarrow RCO_2Li + R'H \qquad \text{Eq. 1}$$

$$RCO_2Li + R'Li \rightarrow \underset{\underset{R'}{|}}{R\text{-}\overset{OLi}{\overset{|}{C}}\text{-}OLi} \xrightarrow{H_2O} R\text{-}\overset{O}{\overset{\|}{C}}\text{-}R' + 2LiOH \qquad \text{Eq. 2}$$

(15)

Hence the acid itself or the lithium salt of the acid can serve as the starting material in this preparation. This method is applicable to synthesize symmetrical as well unsymmetrical ketones.

The singular feature believed to make the formation of ketones from carboxylic acids and organolithium reagents possible is the stability of the intermediate dilithium

compounds. In the reaction of organolithium compounds with carboxylic esters and acid chlorides or anhydrides, the organometallic intermediate formed undergoes facile decomposition to furnish tertiary alcohols rather than usual expected ketones.

The intermediate in the reaction of organolithium reagent and carboxylic acid can be formulated as (15) based on the chemical and analytical studies.

The reaction between RCO_2Li and R'Li can be considered to be a relatively slow nucleophilic attack by organolithium reagent on the carbonyl carbon atom of the lithium carboxylate. Whether the stability of the dilithio intermediate is the sole factor responsible for the high yields of ketones is not known. It can be concluded that four factors are responsible for the higher yields of ketones, with organolithium reagents as compared to those from the reaction with other organometallic reagents.

1) Organolithium reagents are better nucleophile than organomagnesium reagents.

2) Appreciable solubility of the less ionic lithium car boxylate

3) The carbonyl carbon atom of lithium carboxylate is more susceptible to nucleophilic attack.

4) The dilithium intermediate has greater solubility as compared to other metal dialkoxides.

The electronic factors inherent in the structure of organolithium reagent as well as external factors determine the reactivity of organo lithium reagents.

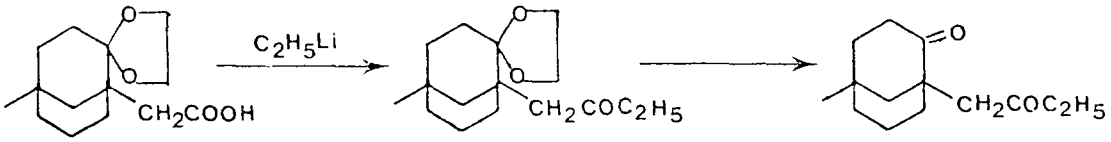
Steric effects in the organolithium reagent are not important. This can be explained from the fact that t-butyl lithium was found to react readily with lithium carboxylates.

The nucleophilic reactivity of the organolithium reagent depends on solvent, by affecting the degree of association and the degree of polarization of C-Li bond. In tetrahydrofuran metalations were found to occur more readily than in diethyl ether probably because of a more highly developed ionic character of organolithium reagent in the former. Reactive organolithium reagents such as t-butyl lithium and isopropyl lithium cannot be prepared or stored in common ethereal solvents at room temperatures because they react with these solvents. However, the same can be prepared below -40°.

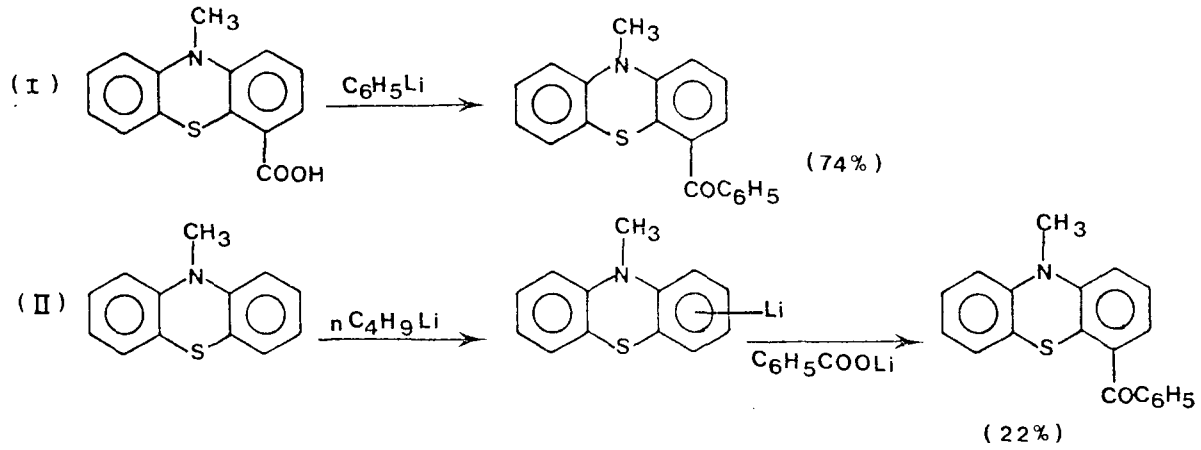
Methoxyl groups are not attacked by methyl[7,8], phenyl[9] or isopropyl lithium[10] reagents in the synthesis of ketones from carboxylic acids possessing methoxy substituent.

The acids having keto group can be easily converted to the anticipated ketones as keto group of acid can be protected by ketal or acetal formation, since acetals and ketals do not react with methyl lithium.[11]

For example:

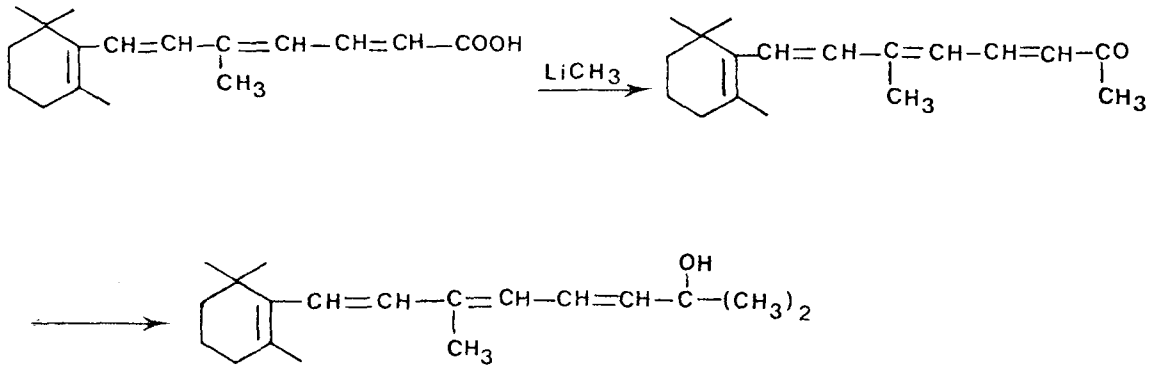


The pathway of choice for preparation of an unsymmetrical ketone is dictated by the availability of the carboxylic acid and lithium reagent. The preparation of more complex carboxylic acids being easier than the preparation of more complex organolithium reagent; frequently the pathway using simple organolithium reagent is preferred. This can be shown by direct comparison between the two approaches[12].

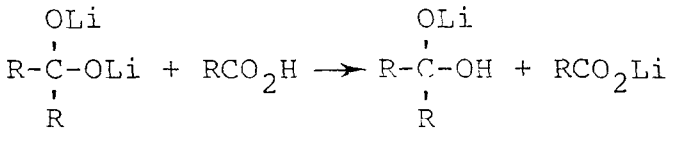


The most general side reaction during the conversion of acid to a ketone with lithium reagent, is the formation of tertiary alcohol. An excess of organolithium reagent

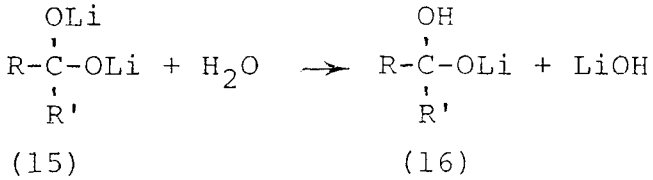
is harmful. For example, with a theoretical amount of methyllithium, no alcohol was formed in the conversion of 8-ionylidene crotonic acid, but with a 300% excess of lithium reagent the product consisted of 74% of alcohol[13].



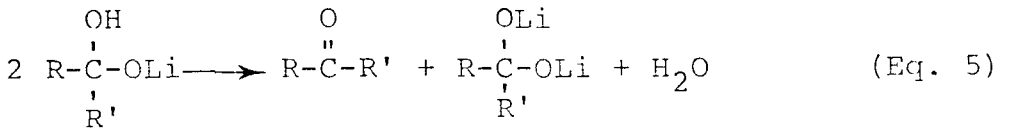
Tertiary alcohol is formed by way of the free ketone whose generation in the presence of organolithium reagent accounts for its formation. Two different reactions produce the monolithium salt (16), whose decomposition or disproportionation gives rise to free ketone and (15).



(15) (16) (Eq. 3)



(15) (16) (Eq. 4)



(Eq. 5)

The reaction represented in Eq. 3 could be arrested by assuring that free carboxylic acid and (15) are not present in the same medium, i.e. by the addition, with very efficient stirring of the carboxylic acid to organolithium reagent. However, since the rate of mixing is crucial in this operation, suppressing reaction in Eq. 3 is impossible. Therefore, the addition of organolithium reagent to carboxylic acid should be slow with very efficient stirring, so that all carboxylic acid is converted to its lithium salt before any appreciable amount of the dilithium intermediate has been produced.

To avoid formations of tertiary alcohol, precautions should be observed during work up. The organic reaction mixture should be added slowly, dropwise, to a large volume of hydrolyzing medium in order to cause hydrolysis of organolithium reagent before it can react with the freed ketone which is in organic layer. The rate of mixing of the organic and aqueous layer should be extremely rapid so that the organolithium reagent can be transported quickly out of organic layer into the aqueous medium for hydrolysis. When all these precautions were followed, it was shown that no alcohol was formed[14].

3.3 PRESENT WORK

The investigations on the synthesis of naturally occurring elvirol were initiated in this laboratory before the syntheses reported in the introductory chapter appeared. Two approaches were considered. In the first approach the initial objective was the synthesis of the α,β unsaturated ketone (12) having elvirol carbon skeleton; in the second approach the initial objective was the synthesis of a tertiary alcohol (4) having elvirol carbon skeleton. While we have been successful in achieving the initial objectives of synthesizing (12) and (4) which form the subject matter of the present chapter, we have not carried out further work with these compounds to realize the ultimate objective which was to transform them to elvirol in view of the recent appearance of three publications[2,3,4] dealing with the synthesis of elvirol.

The synthesis of (12) and (4) was chosen as initial objectives for the following reasons:

1) It should be possible to convert (12) as well as (4) to elvirol methyl ether (5); tosylhydrazone route on (12) should furnish diene (13); reduction of diene as in the case of conversion of (+) ar-turmerone to (+) ar-curcumene[16], should give (5). Dehydration of (4) should furnish (5) though there is the possibility of formation of (14) during dehydration, model experiments have indicated that under suitable conditions of dehydration, isopropenyl form (14) can be less

than 10% in the dehydration product.

2) The second reason for choosing (12) and (4) as intermediates for elvirol synthesis was the possibility that both (12) and (4) are likely to occur in nature. Allylic oxidations appear to be facile in nature and (12) can be regarded as the methyl ether of the allylic oxidation product of naturally occurring elvirol. It may be of interest to note that the oxygenation region of side chain in (12) corresponds to that of naturally occurring arturmerone.

3) The presence of-C=O group in (12) offers the possibility of purification (e.g. regeneration from semicarbazone) of this intermediate.

4) In the routes planned for the synthesis of (12) and (4) the steps are very few.

5) p-cresol, the starting material for the synthesis of (4) is readily available and 4,6 dimethyl coumarin, the starting material for the synthesis of (12) can be conveniently prepared from p-cresol.

(6) We were interested in finding out whether coumarins such as 4,6-dimethyl coumarin* and 4,7-dimethyl coumarin can be used as intermediates for the synthesis of mono and sesquiterpenes.

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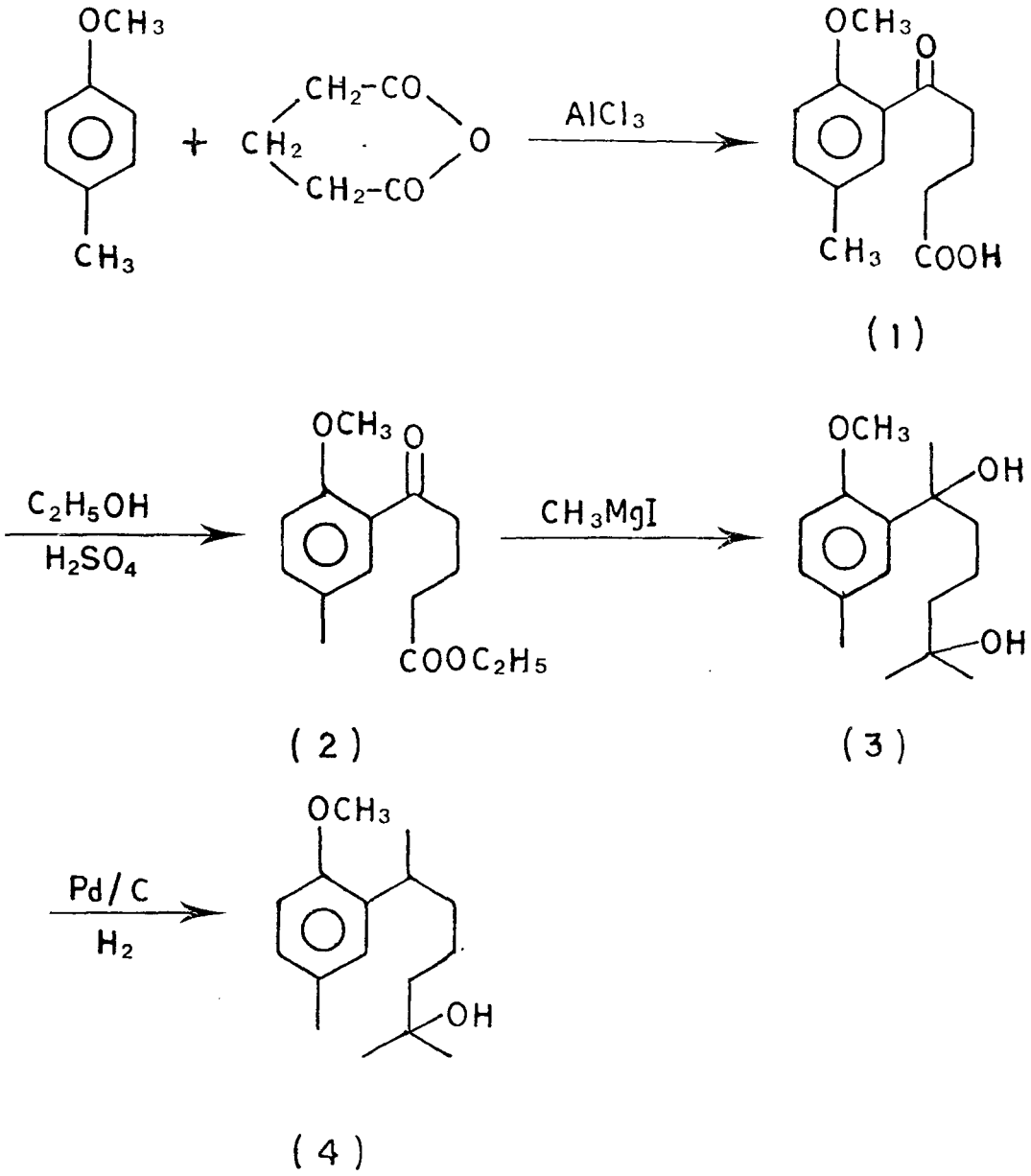
*Work on the synthesis of some monoterpenes from 4,7-dimethyl coumarin is presented in Chapter 2 of this thesis.

Synthesis of 2-Hydroxy-2-methyl-6-(2-methoxy-5-methyl phenyl)-heptane (4)

Freidel-Craft's acylations using glutaric anhydride in presence of aluminum chloride are well known[17]. Acylation of benzene[18], toluene[19], and anisole[20] with glutaric anhydride is reported to furnish corresponding γ-aroyl butyric acids. p-Cresol methyl ether when subjected to acylation with glutaric anhydride furnished the anticipated keto acid (1) (see chart 4). In IR spectrum (see fig. 31) it showed a broad band at 3.3μ which is characteristic of COOH group, and two carbonyl signals, one at 5.8μ (due to acid -C=O stretching). Its PMR (see fig. 32) showed multiplet at 10.66δ (due to acid proton) singlet at 3.86δ (due to $-OCH_3$) and triplet at 3.66δ (due to $\underline{CH}_2$-COOH).

Esterification of (1) furnsihed ester (2). (For IR and PMR spectra of 2, see figs. 33 and 34, respectively.) Grignard reaction on (2) with methyl magnesium iodide in dry ether was carried out using five moles of Grignard reagent. The benzylic carbonyl as well as ester carbonyl group were attacked to give the diol (3) (see chart 4). The IR spectrum of the diol showed a strong band at 2.75μ (due to -OH stretching while in its PMR (see fig. 35) singlet at 3.83δ (due to $-OC\underline{H}_3$), singlet at 1.56δ (due to benzylic $-C\underline{H}_3$), singlet at 1.13 (due to $-\underset{\underset{OH}{|}}{C}(C\underline{H}_3)_2$) were

CHART 4


OCH3
CH3
CH2-CO
CH2
CH2-CO
O
AlCl3
OCH3
O
CH3
COOH
(1)
C2H5OH
H2SO4
OCH3
O
COOC2H5
(2)
CH3MgI
OCH3
OH
OH
(3)
Pd/C
H2
OCH3
OH
(4)


OCH3
(5)
OH
(6)

present. For converting (3) to the required alcohol (4), it was only left to remove selectively benzylic hydroxyl group. This was achieved by the following way:

A mixture of (3), absolute ethanol, catalytic amount of palladium charcoal, and a few drops of glacial acetic acid was stirred at room temperature under hydrogen atmosphere for ten hours. After working up the product in the usual manner alcohol (4) was obtained in good yield (figs. 36, 37 for IR and PMR spectra). This route for the preparation of alcohol (4) is attractive as the intermediate compounds (1) and (3) are solids.

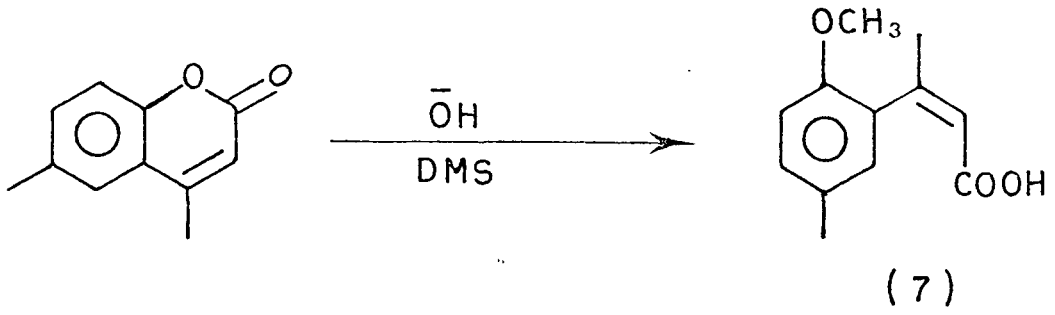
Synthesis of 2-methyl-6-(2-methoxy-5-methylphenyl)-hept-2-en-4-one.

It is well known that the reaction of an organolithium reagent with a carboxylic acid constitutes a simple general method for synthesis of a ketone[21]. We thought of using this reaction for the synthesis of ketone (12).

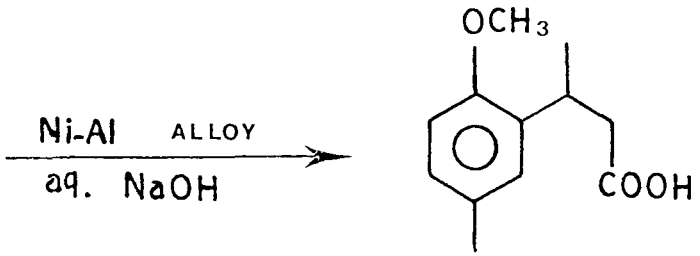
The starting compounds were prepared as follows:

Acid (9) was synthesized from the readily available solid 4,6-dimethyl coumarin. Opening of 4,6 dimethyl coumarin with aqueous sodium hydroxide and methylation of the resulting hydroxy acid with dimethyl sulphate furnished the methoxy acid (7). Reduction of acid (7) with Ni-Al-alloy-alkali furnished the acid (8) (see chart 5) as a solid m.p. 49°. PMR of (8) (fig. 38) showed a multiplet at 3.8-3.5δ (due to benzylic hydrogen); doublet at 1.35 (due to H-C-CH_3)

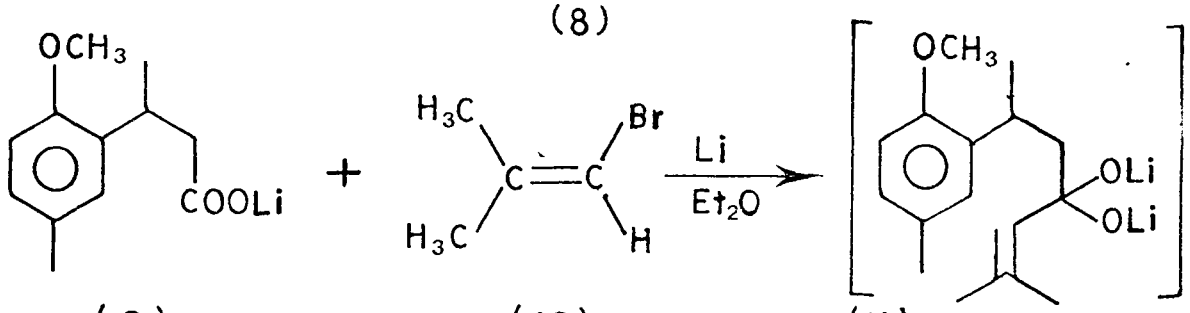
CHART 5



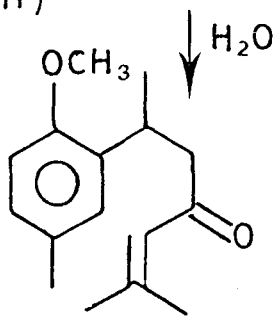
(7)



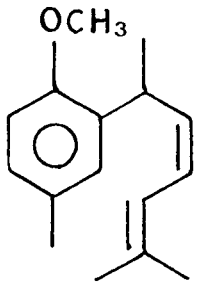
(8)



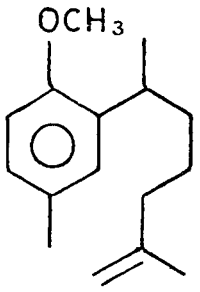
(9) (10) (11)



(12)



(13)



(14)

and two multiplets at 3.8-3.5δ and 2.8-2.5δ (due to two methylene protons). Absence of vinyl proton in the region 5.95-5.8 proved that (8) was completely free from starting unsaturated acid. It was converted to its lithium salt by reacting with lithium methoxide.

Condensation between (9) and (10) was carried out by adding dropwise a solution of isobutylene bromide to a mixture of (9) and lithium pieces, in dry ether at room temperature. The reaction of isobutylene bromide and lithium was a slow process and lithium disappeared slowly as reaction proceeded. The product obtained was subjected to vacuum distillation. The distilled product was chromatographed on alumina to furnish a pure sample of (12). In its IR spectrum (fig. 39) it showed a band at 5.98μ which is characteristic of conjugated ketone. Its PMR spectrum (fig. 40) showed multiplet at 6.0δ (due to vinyl proton), two doublets at 2.13δ and 1.9δ (due to methyl groups on double bond) and a doublet at 1.23 (due to benzylic $-CH_3$).

3.4 EXPERIMENTAL

(1) 5-Oxo-5-(2-methoxy-5-methyl phenyl) pentanoic acid (1)

P-Cresol methyl ether (40 g, 0.32 mol), and glutaric anhydride (37.38 g, 0.32 mol) were added to finely powdered aluminum chloride (87.54 g, 0.65 mol), in nitrobenzene (250 ml) at 0°. The reaction mixture was left at room temperature for 16 hrs. and nitrobenzene was removed by steam distillation. Steam nonvolatile portion was treated with 10% sodium bicarbonate solution and taken in benzene. Aqueous layer was acidified with dilute hydrochloric acid until acidic to congo red paper and then extracted with chloroform. Chloroform layer after washing with water (3 x 100 ml) and drying over anhydrous sodium sulphate furnished a solid which was further purified by crystallization from pet.-ether-benzene mixture.

(Yield: 17 g) m.p. 45°.

IR Spectrum (Nujol mull) showed bands at 3.3μ (broad, $-\overset{O}{\overset{\|}{C}}-OH$), 5.8 (benzylic $-\overset{O}{\overset{\|}{C}}-$ stretching), 6.0μ (acid $-\overset{O}{\overset{\|}{C}}-$ stretching).

PMR Spectrum (CCl_4) showed signals at δ=10.66 (m, 1H, acid proton), 7.6-6.7 (m, 3H, aromatic H), 3.86 (S, 3H, $-OCH_3$), 3.66 (t, 2H, $-CH_2-COOH$), 2.36 (S, 3H, methyl on aromatic).

Analysis

Found: C, 66.23; H, 6.99

$C_{13}H_{16}O_4$ requires: C, 66.09; H, 6.83%.

(2) Ethyl-5-oxo-5-(2-methoxy-5-methyl phenyl)-pentanoate (2)

A mixture of acid (1) (15 g, 0.068 mol), ethyl alcohol (50 ml), sulphuric acid (0.5 ml), benzene (200 ml) was refluxed azeotropically for five hours on steam bath. After removal of alcohol at reduced pressure the reaction mixture was diluted with water and extracted with benzene. Benzene layer was washed with water, 10% aqueous sodium bicarbonate, again with water. Drying and evaporation of the solvent furnished a residue which weighed 12 g.

(Yield: 12 g. 66.24%) b.p. $\overset{\text{(bath)}}{\underset{1.5\text{ mm}}{}}$ 180-200°

IR Spectrum (liquid film) showed bands at 5.7μ (ester-C=O stretching), 5.9μ (benzylic -C=O stretching), 8.0μ (ester group).

PMR Spectrum (CCl_4) showed signals at δ=7.5-6.67 (m, 3H, aromatic H), 4.1 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 3.87 (S, 3H, $-OC\underline{H}_3$), 2.3 (S, 3H, CH_3 on aromatic ring), 1.23 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

(3) 2,6 Dihydroxy-2-methyl-6-(2-methoxy-5-methyl phenyl heptane (3)

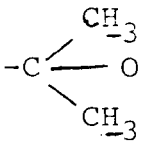
To a well stirred solution of methyl magnesium iodide [prepared from Mg (2.18 g, 0.089 gm atom, methyl iodide (2.1 g, 0.014 mol)] in dry ether (50 ml) a solution of ester (2) (4.0 g, 0.015 mol) in dry ether was added dropwise at 0°. The reaction mixture was stirred at room temperature for one half hour and refluxed for three hours.

The complex thus formed was decomposed with saturated ammonium chloride solution. The reaction mixture was extracted with ether, ether layer was washed with water (3 x 100 ml) and dried over anhydrous sodium sulphate. Evaporation of ether furnished a residue which solidified on keeping.

Yield: 3.6 g (89.3%) m.p. 72°C.

IR Spectrum (liquid film) showed band at 2.75μ (-C-OH stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.13-6.53 (m, 3H, aromatic H), 3.83 (S, 3H, $-OCH_3$), 2.26 (S, 3H, methyl on benzene ring), 1.56 (S, 3H, benzylic CH_3), 1.13 (S, 6H,



).

Analysis

Found: C, 72.07; H, 9.84

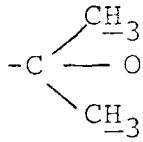
$C_{16}H_{26}O_3$ requires: C, 72.14; H, 9.84%

(4) 2-Hydroxy-2-methyl-6-(2-methoxy-5-methyl phenyl) heptane(4)

A mixture of diol (3) (0.8 g), absolute ethanol (100 ml), palladium charcoal (0.1 g) and glacial acetic acid (1 ml) was stirred under hydrogen atmosphere for ten hours. The reaction mixture was filtered and filtrate was diluted with ether. Ether layer was washed with water, aqueous sodium bicarbonate, and again with water. Evaporation of solvent after drying yielded a colorless liquid.

Yield: 0.6 g (79.8%) b.p. $\overset{(bath)}{0.5\ mm}$ 140-160°

IR Spectrum (liquid film) showed band at 2.8μ (-OH group). PMR Spectrum (CCl_4) showed signals at δ=6.93-6.5 (m, 3H, aromatic H), 3.76 (S, 3H, $-OCH_3$), 3.4-3.0 (m, 1H, benzylic H), 2.3 (S, 3H, benzylic CH_3), 1.13 (S, 6H



).

Analysis

Found: C, 76.77; H, 10.53

$C_{16}H_{26}O_2$ requires: C, 76.75; H, 10.47%

(5) 2-(2-Methoxy-5-methyl phenyl)-2-butenoic acid (7)

A mixture of 4,6-dimethyl coumarin (10.44 g, 0.06 mol) and aqueous solution of sodium hydroxide prepared from NaOH 60.0 g, 1.5 mol) and water (150 ml) was warmed on steam bath until all the coumarin dissolved (2 hrs.). Dimethyl sulphate (100.8 g, 0.8 mol) was added to it maintaining the reactants at 50°. After stirring for further 1 hr. at 50°, the reaction mixture was cooled to 5° and acidified with 2N HCl until acidic to congo red paper. The precipitated acid was filtered and washed with water until washings were neutral and air dried at 25-30°.

Yield: 11.2 g (97%).

Recrystallization of a sample from pet. ether-benzene mixture furnished a crystalline solid with m.p. 106-108°.

IR Spectrum (Nujol mull) showed band at 3.45μ (broad, carboxyl -OH stretching).

PMR Spectrum ($CHCl_3$) showed signals at δ=5.95, -5.8 (m, 1H, vinyl H), 3.69 (S, 3H, $-OCH_3$), 2.25 (S, 3H, methyl on benzene ring), 2.11 (d, 3H, $CH_3-C=C-$).

Analysis

Found: C, 70.24; H, 6.63

$C_{12}H_{14}O_3$ requires: C, 69.89; H, 6.84%

6) 3-(2-Methoxy-5-methyl phenyl)- butanoic acid (8)

A mixture of 3-(2-methoxy-5-methyl phenyl)-2-butenoic acid (7) (5 g, 0.027 mol) and 10% aqueous solution of sodium hydroxide (20 gms) was heated (90°). Nickel-Aluminum alloy (Raney Nickel grade) (15 g) was added in portions with vigorous stirring. Then the reaction mixture was stirred for one more hour. The hot solution was filtered. The residue on the filter paper was washed with 10% aqueous solution of NaOH and then with water. The filtrate was acidified with ice cold concentrated HCl. The acid was extracted with chloroform, the layer of which was washed with water and dried. The residue after solvent removal was vacuum distilled.

Yield: 3.9 g. b.p. $\overset{\text{(bath)}}{0.5\text{ mm}}$ 200-210°

m.p. 49°.

PMR Spectrum (CCl_4) showed bands at δ=7.3-6.8 (m, 3H, aromatic H), 3.90 (S, 3H, $-OCH_3$), 3.8-3.5 (m, 1H, benzylic H), 2.8-2.5 (m, 2H, methylene group), 2.35 (S, 3H, methyl on benzene ring), 1.35 (d, 3H, methyl on side chain, J=7Hz).

7) 2-Methyl-6-(2-methoxy-5-methyl phenyl)-hept-2-en-4-one (12)

Lithium salt of acid (8) was prepared by adding a solution of acid (8) in methanol. The precipitated lithium salt was filtered and dried at vacuum pump at room temperature.

To a well stirred solution of lithium salt of acid (1.0 g) dry ether (10 ml) and lithium pieces (0.07 g) isobutylene bromide was added dropwise (0.7 g) under nitrogen atmosphere. The reaction mixture was further stirred for 24 hrs. at room temperature. After stirring for 24 hrs. the reaction mixture became clear. It was poured slowly into a saturated solution of ammonium chloride containing 5% acetone. The ketone was extracted with ether, washed with water and dried over anhydrous sodium sulphate. The residue was vacuum distilled after removal of the solvent.

Yield: 0.86 g. b.p. $\overset{\text{(bath)}}{_{1.5\text{ mm}}}$ 170-180°.

However, TLC of the product showed that it was a mixture of compounds. So the ketone obtained was further purified by column chromatography. Ketone (0.7 g) was loaded on the (Gr. II) alumina column. It was subsequently

eluted with pet. ether, pet. ether-benzene (50% mixture), benzene and finally with alcohol. Second fraction of pet. ether was found to be pure ketone (found out by IR spectrum); and was distilled at 170-180° bath temperature at 1.5 mm to get the ketone as a colorless liquid.

IR Spectrum (liquid film) showed band at 5.98μ (-C=O stretching).

PMR Spectrum (CCl_4) showed signals at δ=7-6.53 (m, 3H, aromatic H), 6.0 (m, 1H, vinyl H), 3.83 (S, 3H, $-OCH_3$), 2.3 (S, 3H, methyl on benzene ring), 2.13 (d, 3H, $C=C(CH_3)(CH_3)$), 1.9 (d, 3H, $C=C(CH_3)(CH_3)$), 1.23 (d, 3H, benzylic CH_3 group, J=7Hz).

Analysis

Found: C, 78.16, H, 9.31

$C_{16}H_{22}O_2$ requires: C, 78.01; H, 9.00%

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21. M.J. Jorgenson, Organic Reactions, 18, 1 (1970).

3.6 FIGURES

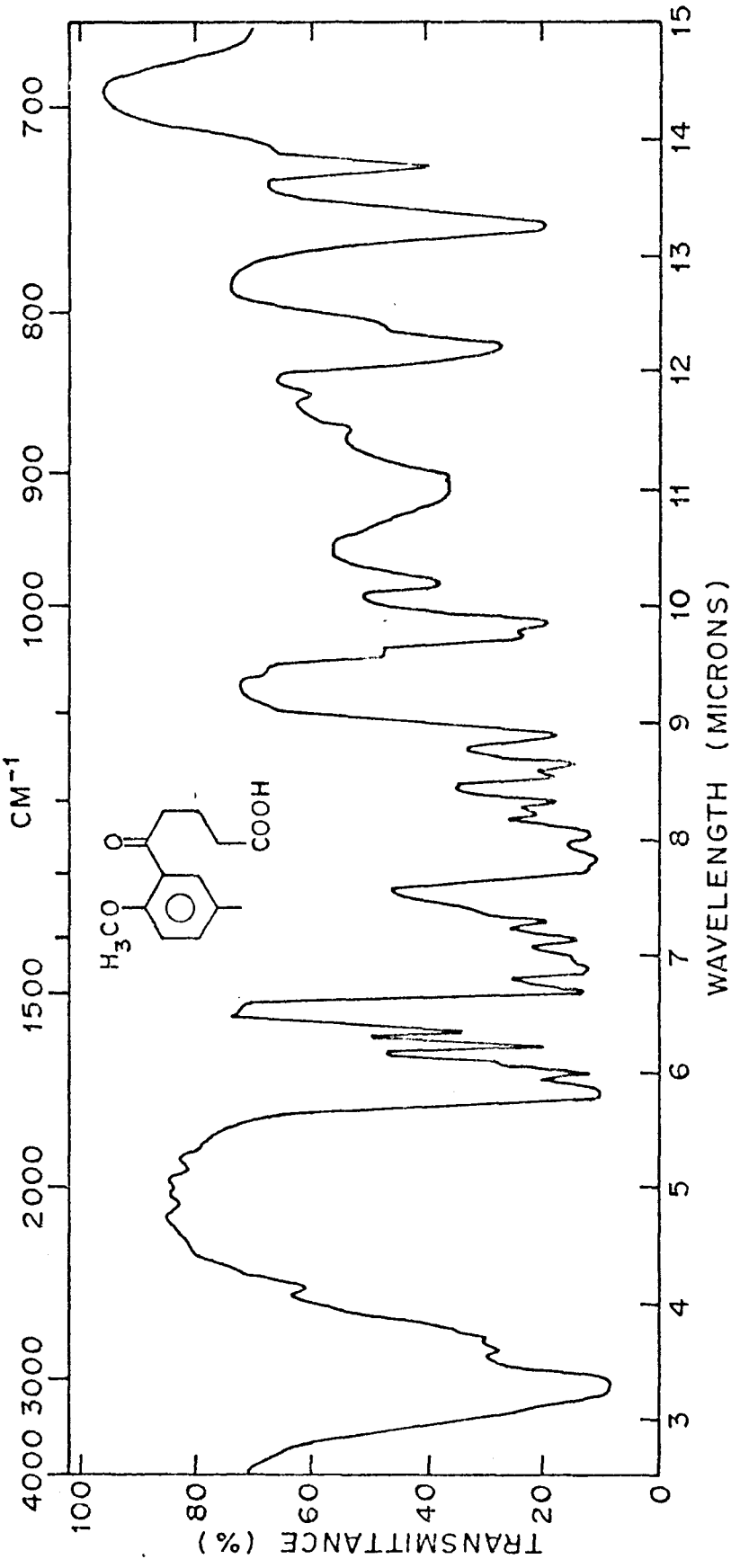


FIG. 31 IR SPECTRUM OF 5-OXO-5-(2-METHOXY-5-METHYLPHENYL)-PENTANOIC ACID(I)

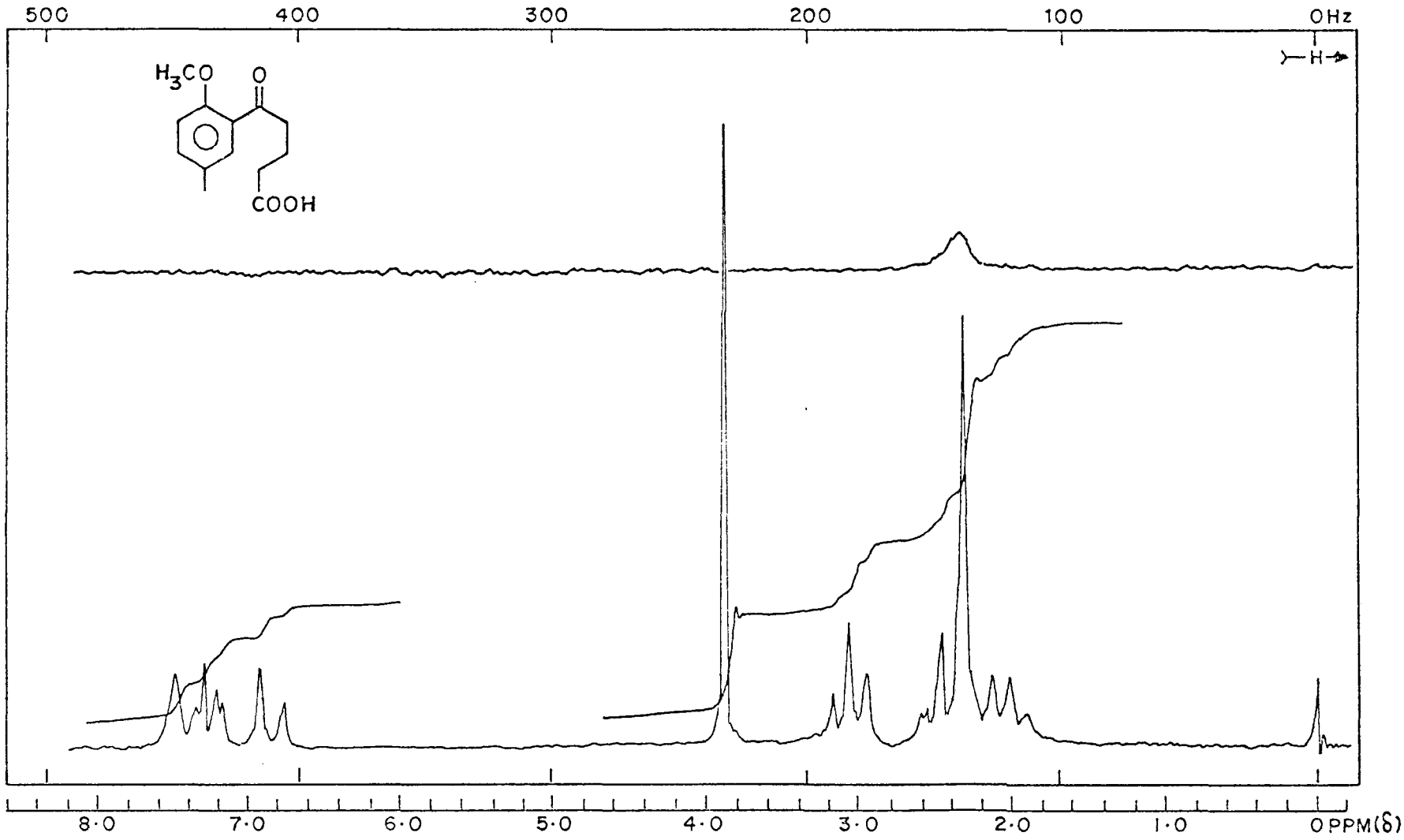


FIG. 32 PMR SPECTRUM OF 5-OXO-5-(2-METHOXY-5-METHYLPHENYL)-PENTANOIC ACID (I)

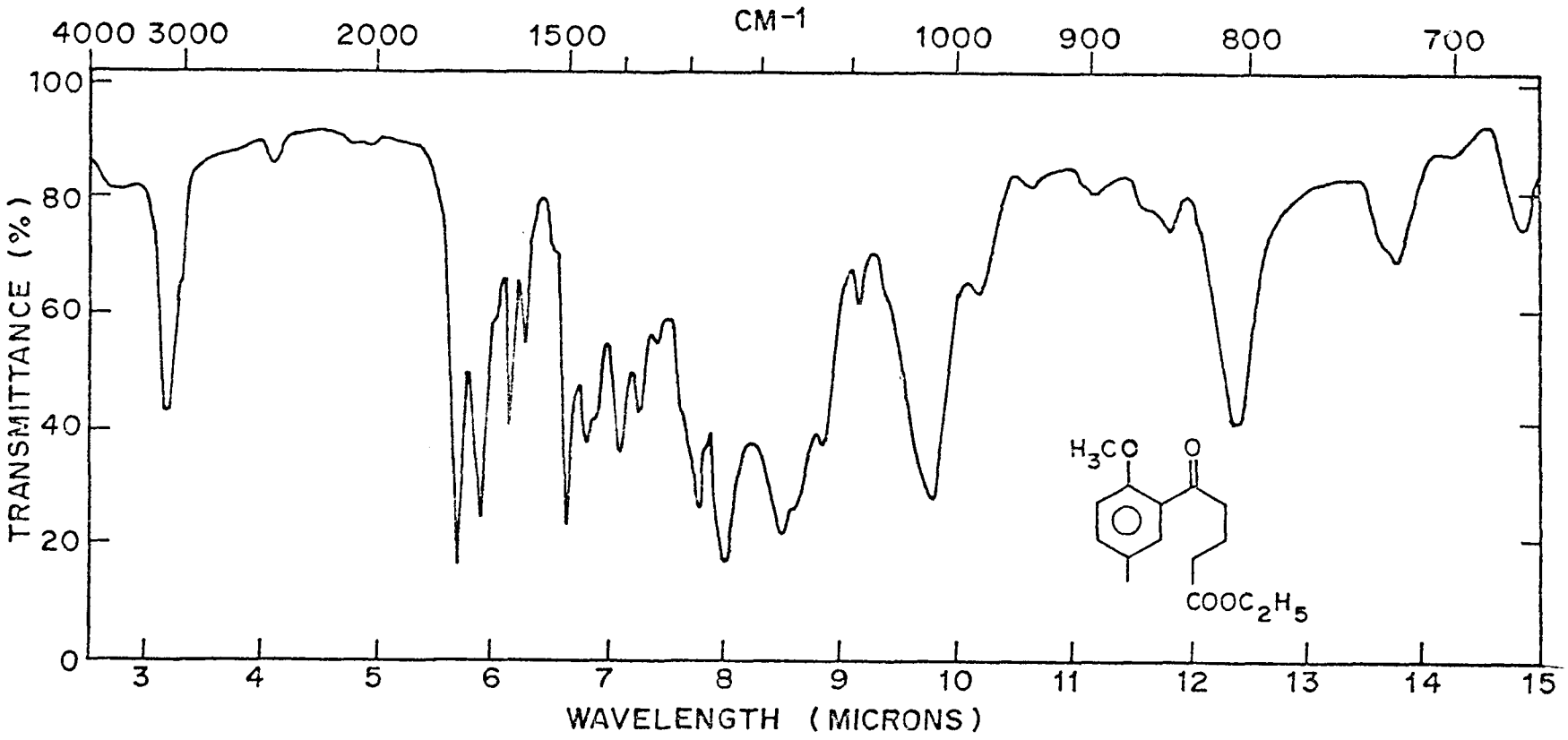
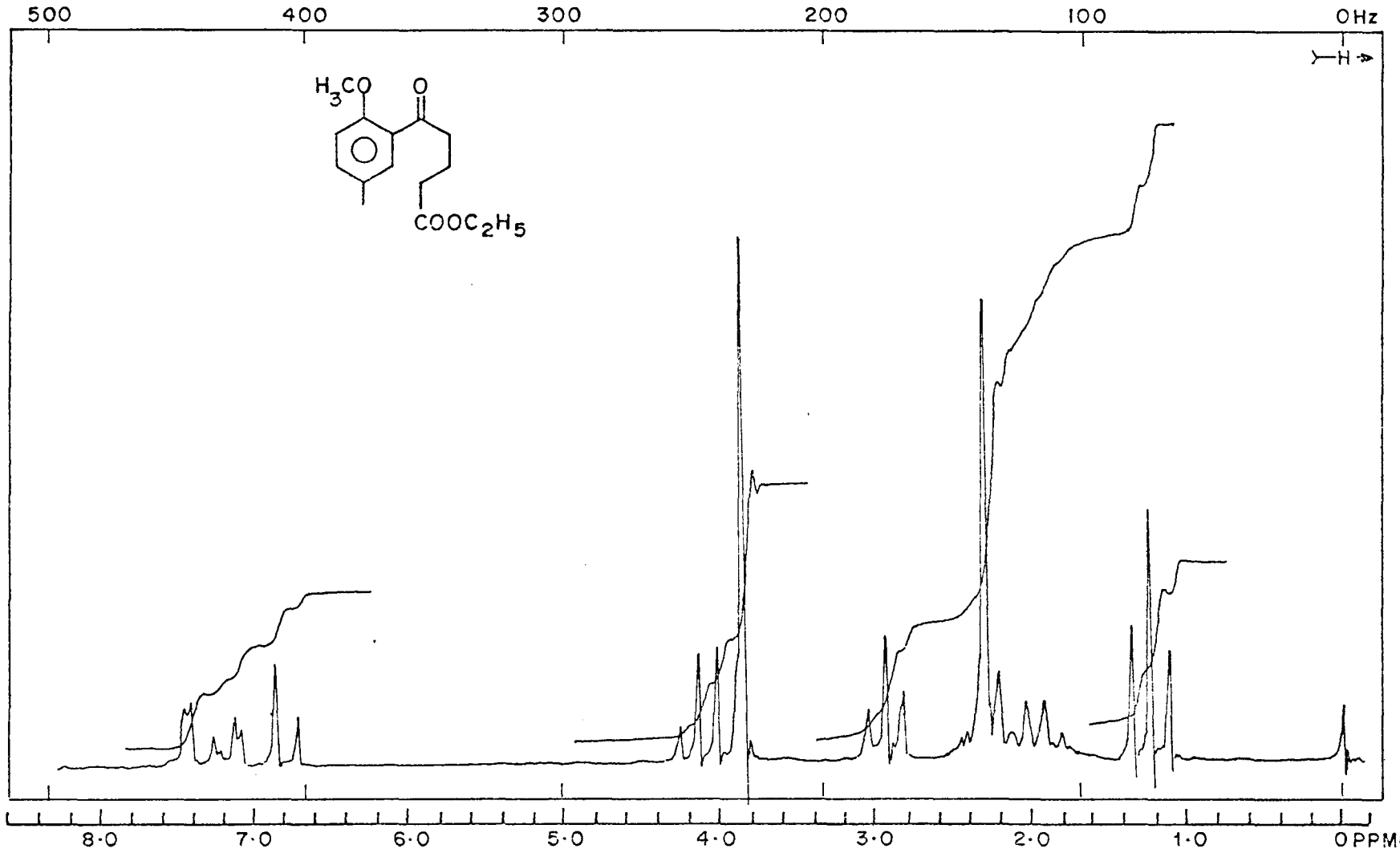


FIG. 33 IR SPECTRUM OF ETHYL-5-OXO-5-(2-METHOXY-5-METHYLPHENYL)-PENTANOATE (2)



FIG·34 PMR SPECTRUM OF ETHYL-5-OXO-5-(2-METHOXY-5-METHYL PHENYL)-PENTANOATE(2)

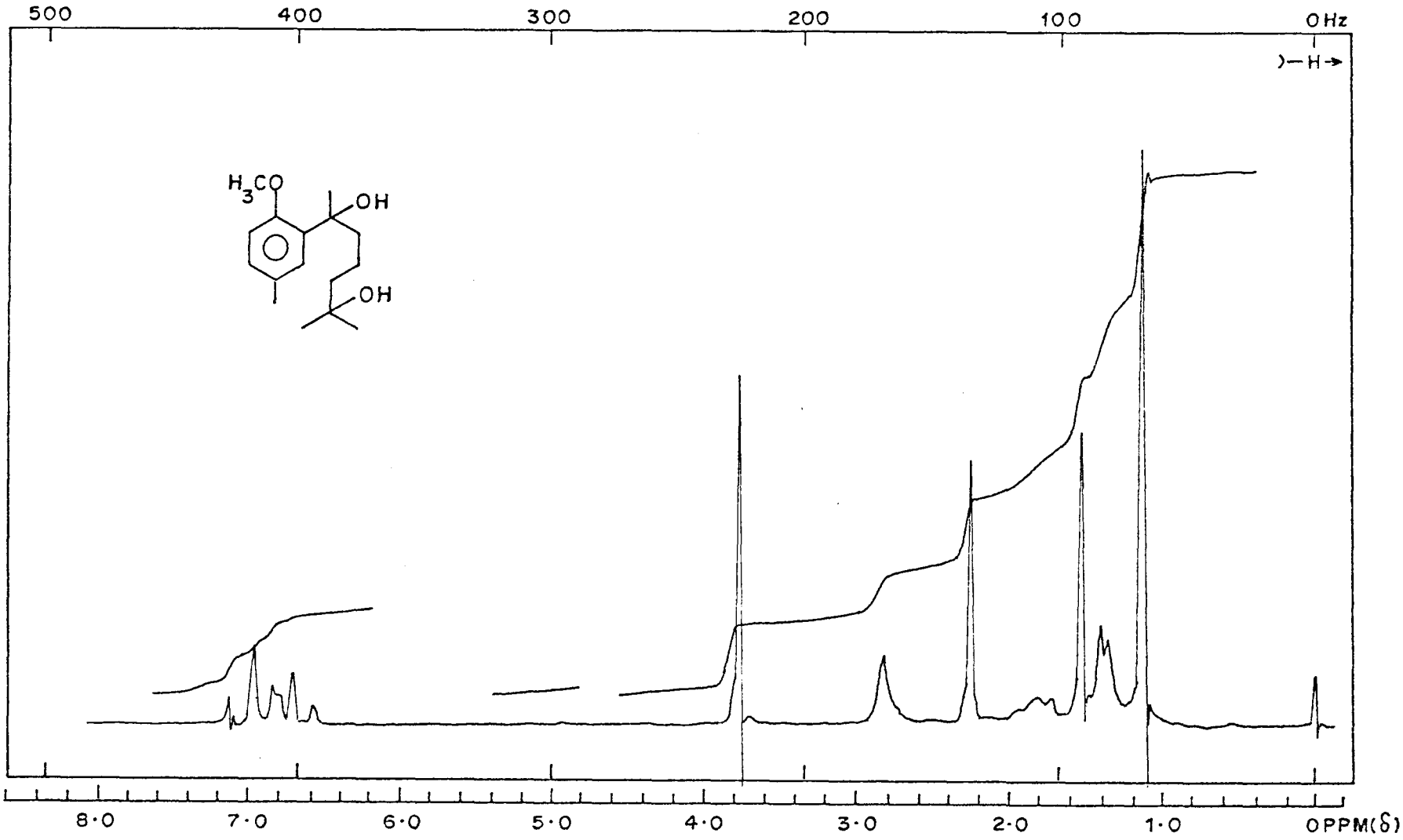
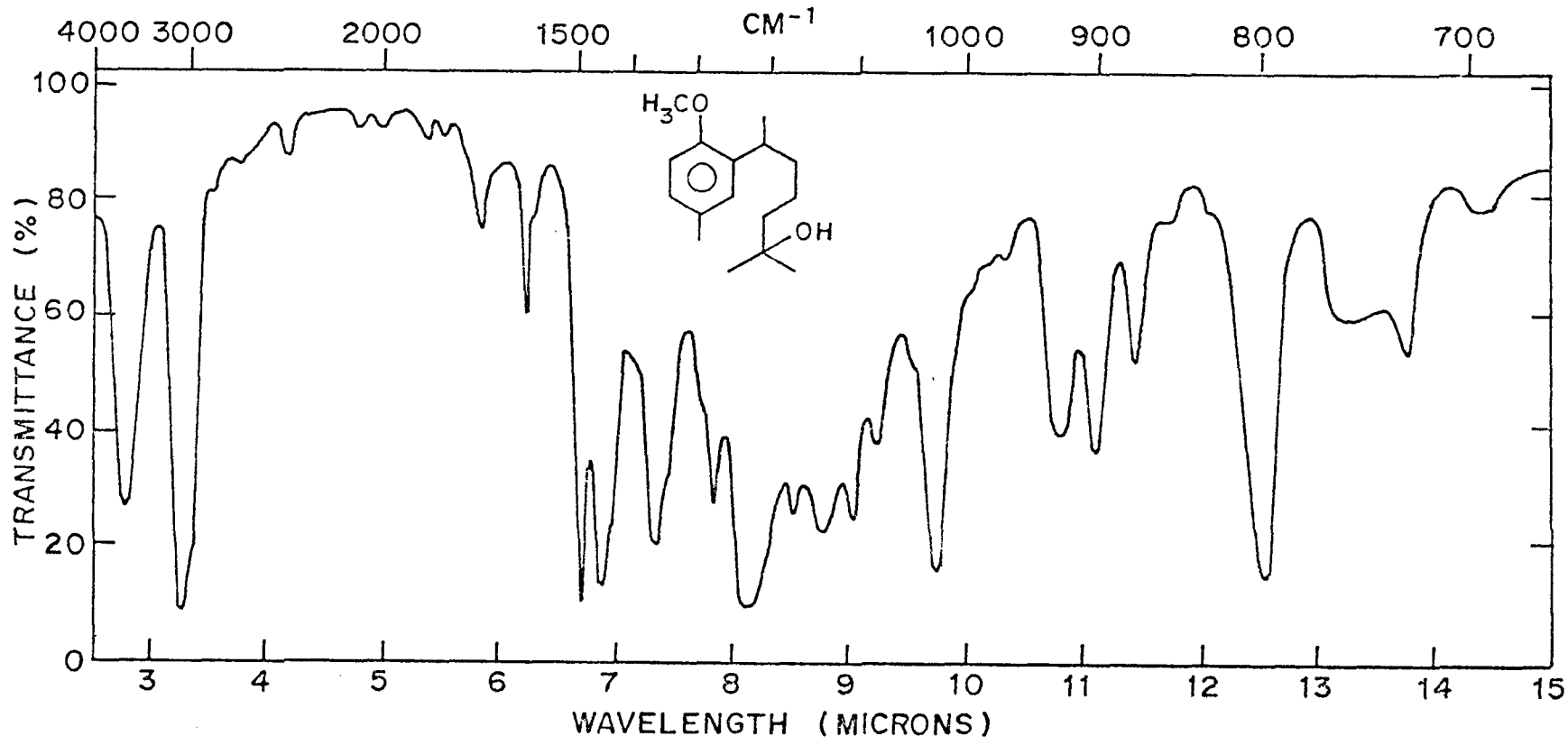
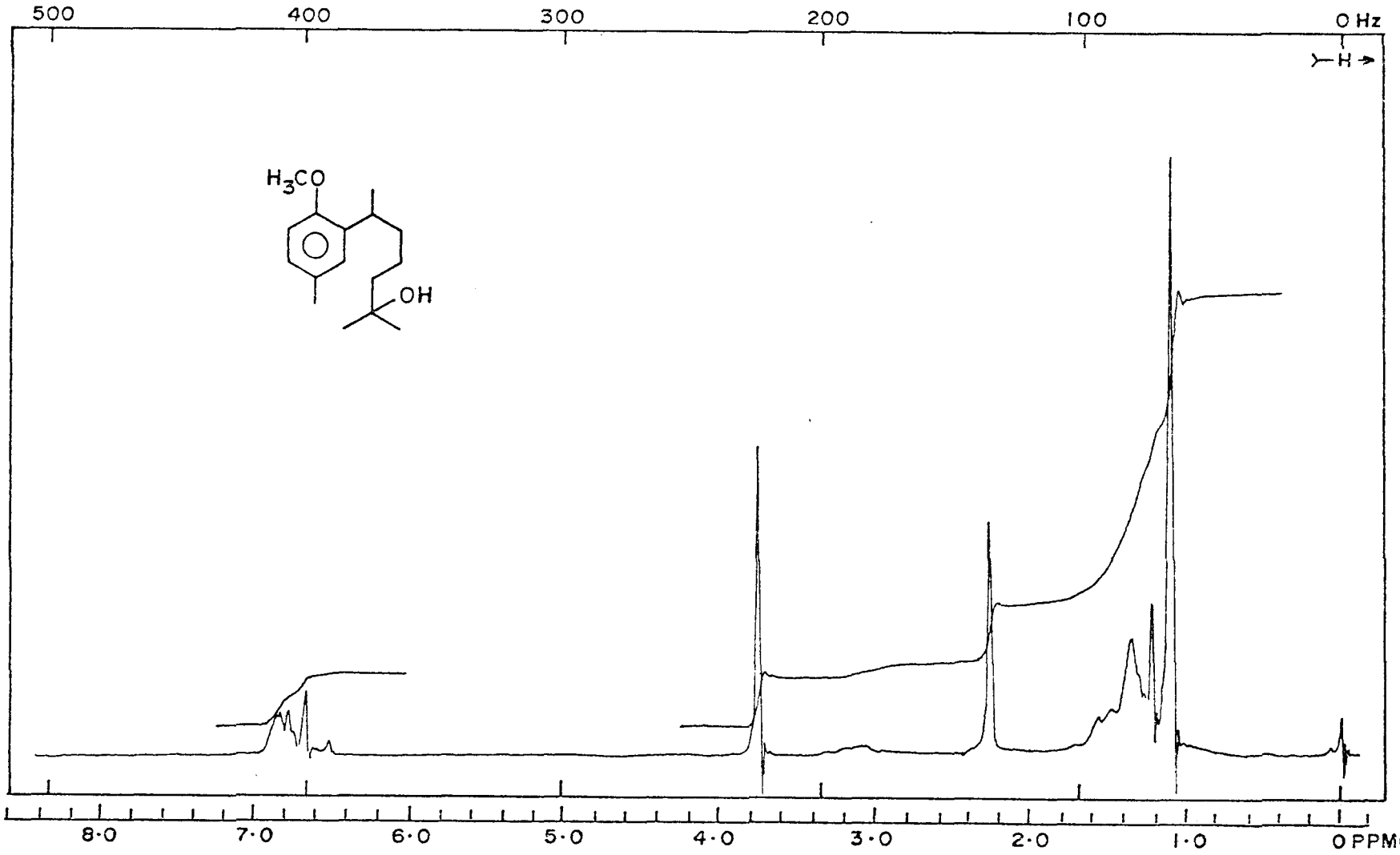


FIG. 35 PMR SPECTRUM OF 2,6-DIHYDROXY-2-METHYL-6-(2-METHOXY-5-METHYL PHENYL) -HEPTANE(3)



FIG·36 IR SPECTRUM OF 2-HYDROXY-2-METHYL-6-(2-METHOXY-5-METHYLPHENYL)-HEPTANE(4)



FIG·37 PMR SPECTRUM OF 2-HYDROXY-2-METHYL-6-(2-METHOXY-5-METHYL PHENYL)-HEPTANE (4)

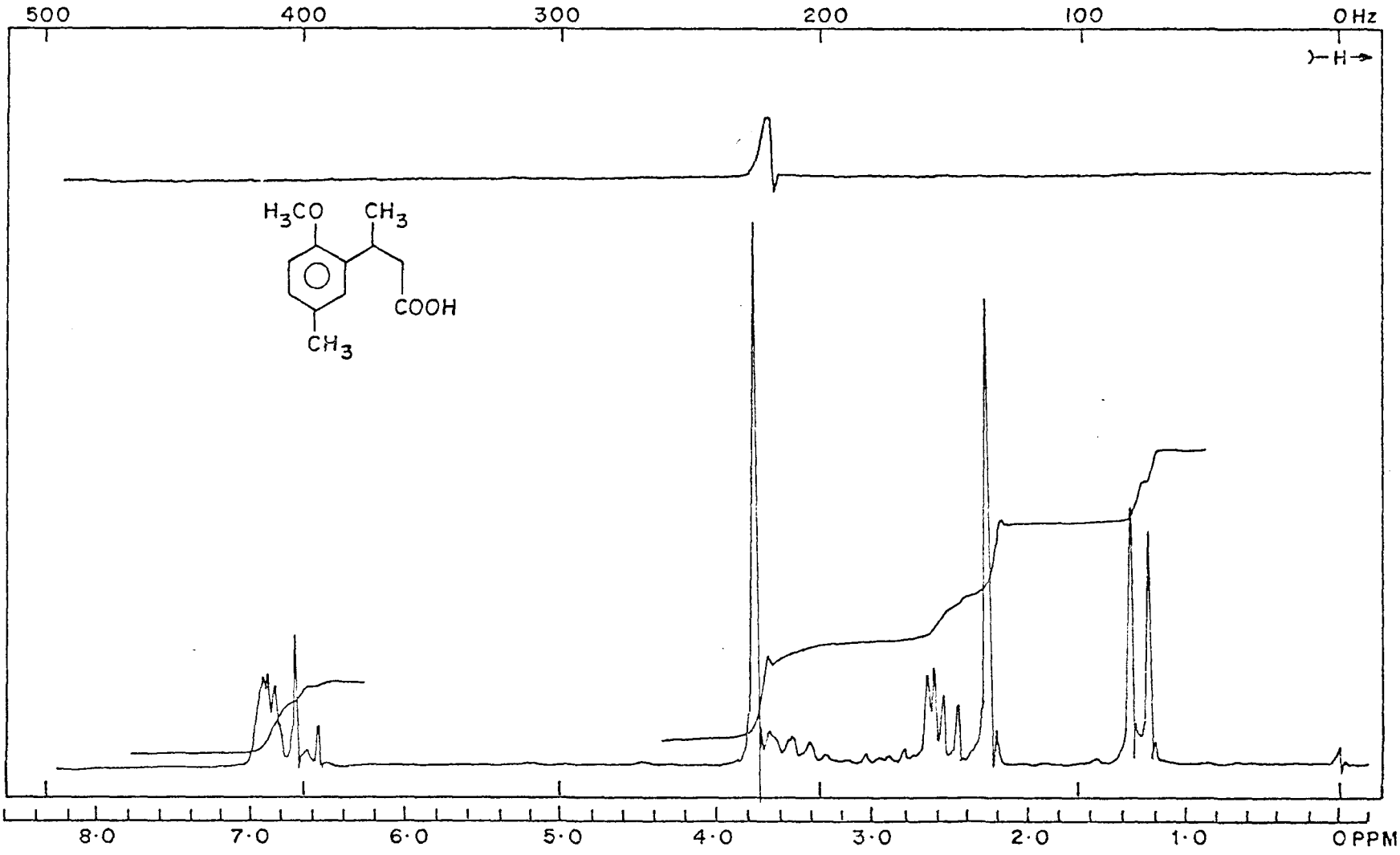


FIG.38 PMR SPECTRUM OF 3-(2-METHOXY-5-METHYL PHENYL)-BUTANOIC ACID (8)

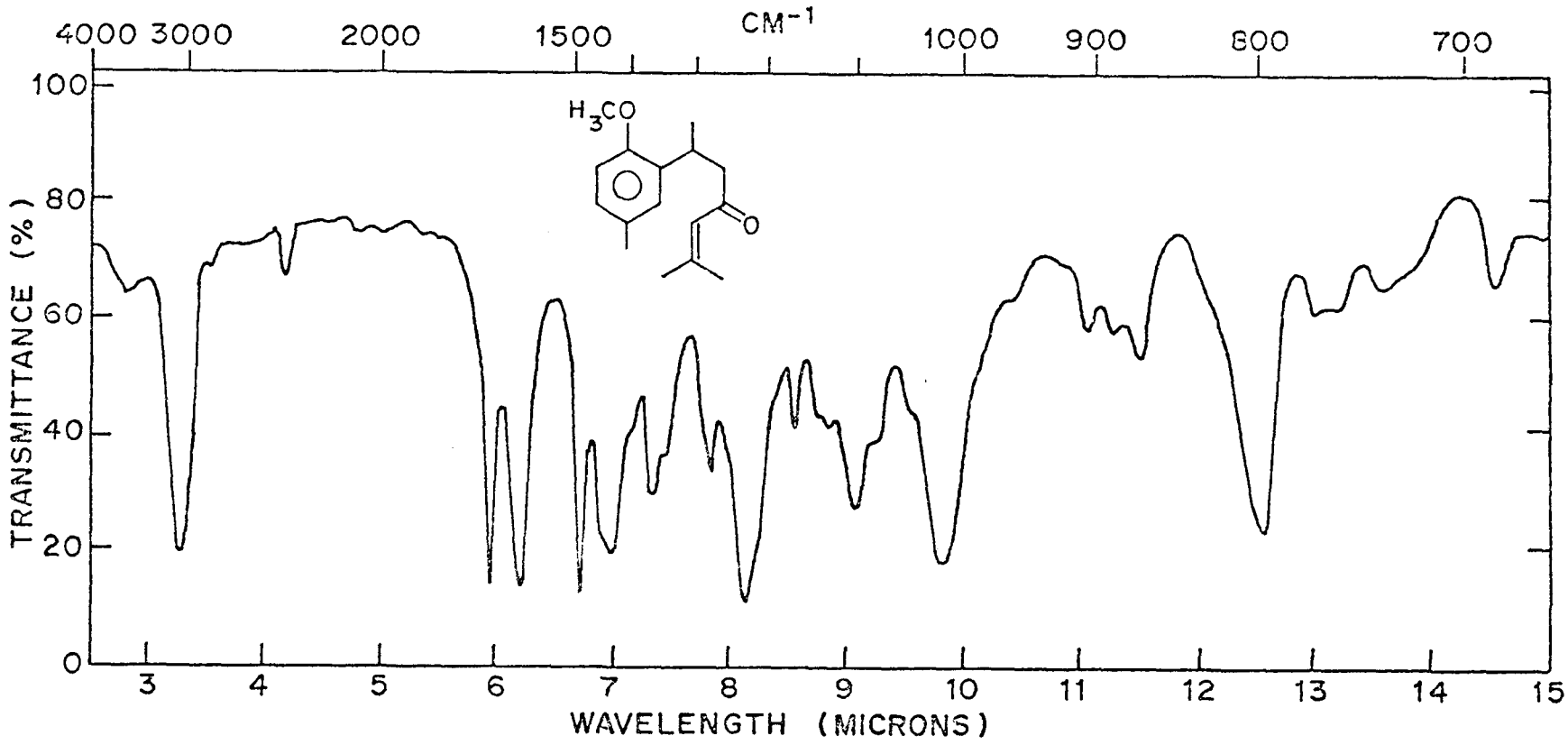


FIG. 39 IR SPECTRUM OF 4-OXO-2-METHYL-6-(2-METHOXY-5-METHYL PHENYL)-HEPT-2-ENE(12)

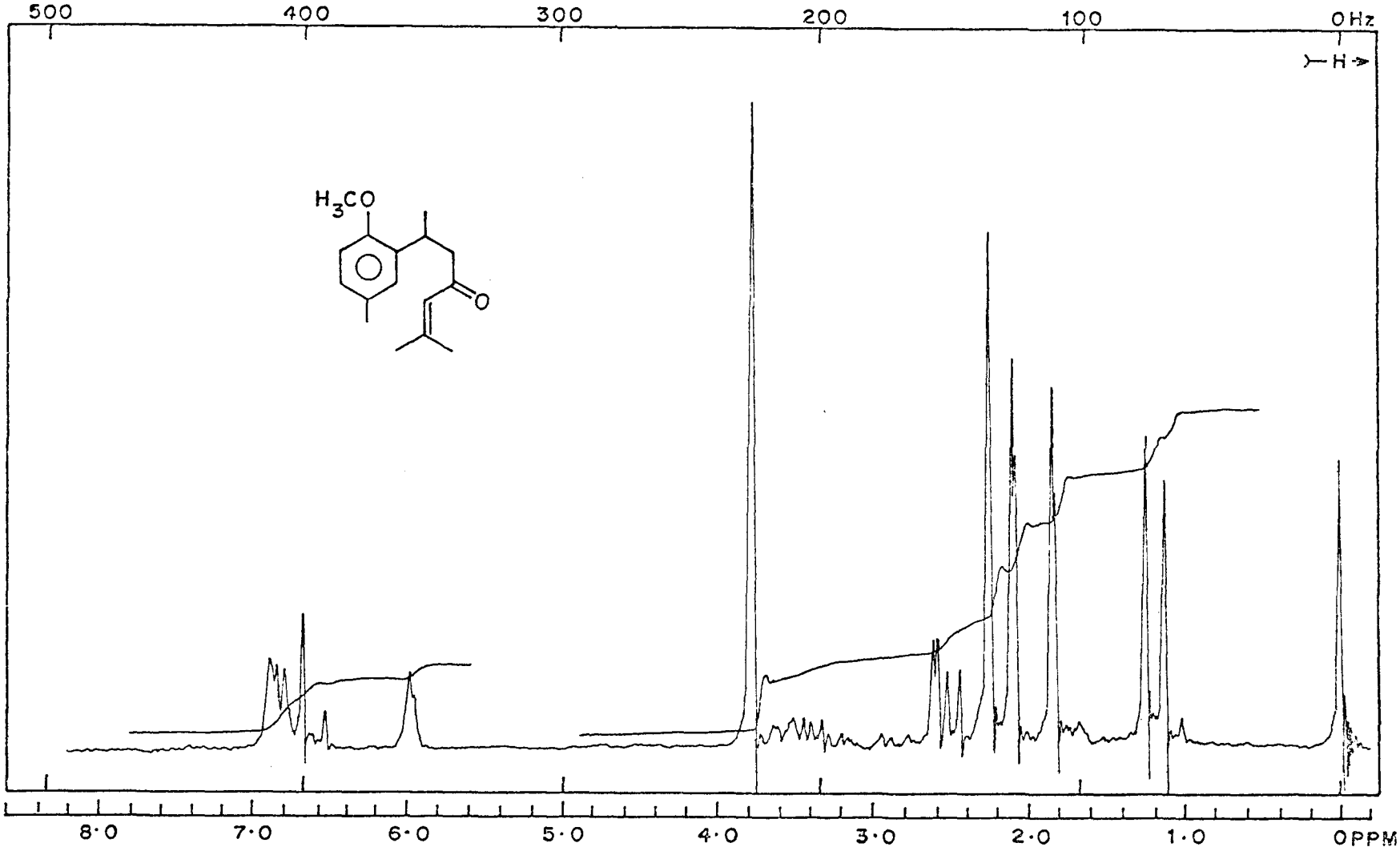


FIG. 40 PMR SPECTRUM OF 4-OXO-2-METHYL-6-(2-METHOXY-5-METHYL PHENYL)-HEPT-2-ENE(12)

CHAPTER 4

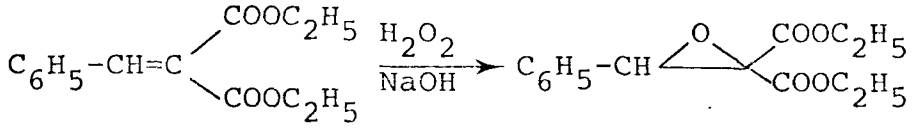
1) EPOXIDATION OF DIETHYL ARYLIDENE AND ALKYLIDENE MALONATES: A CONVENIENT ROUTE FOR THE PREPARATION OF α-KETO ACIDS

2) A NEW ROUTE FOR THE SYNTHESIS OF 2-METHYL-5-ISOPROPYL CYCLOPENTANONE

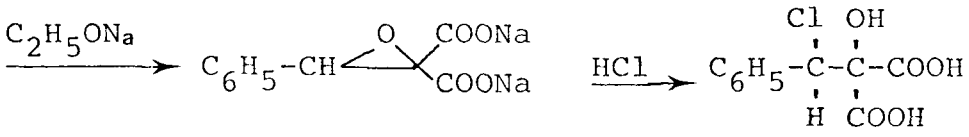
Please read the underlined as 2-ISOPROPYL-5-METHYL in this chapter.

4.1 SUMMARY

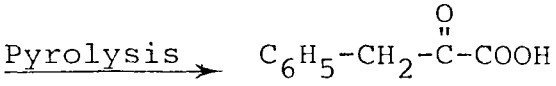
Epoxidation of diethyl arylidene and alkylidene malonates (1a, 5a, 9a, 13a, and 17a) using 30% H_2O_2 at PH=8 and room temperature afforded the corresponding epoxides (1, 5, 9, 13, 17) respectively which were transformed into the α keto acids (4, 8, 12, 16, and 20), respectively via the formation of disodium salts (2, 6, 10, 14, and 18) followed by opening of the epoxide ring by passing HCl gas to get chlorohydroxy acids (3, 7, 11, 15, and 19). When chlorohydroxy acids were heated in vacuo, HCl and CO_2 were readily eliminated resulting in the formation of α-keto acids which distilled out.



(1a) (1)

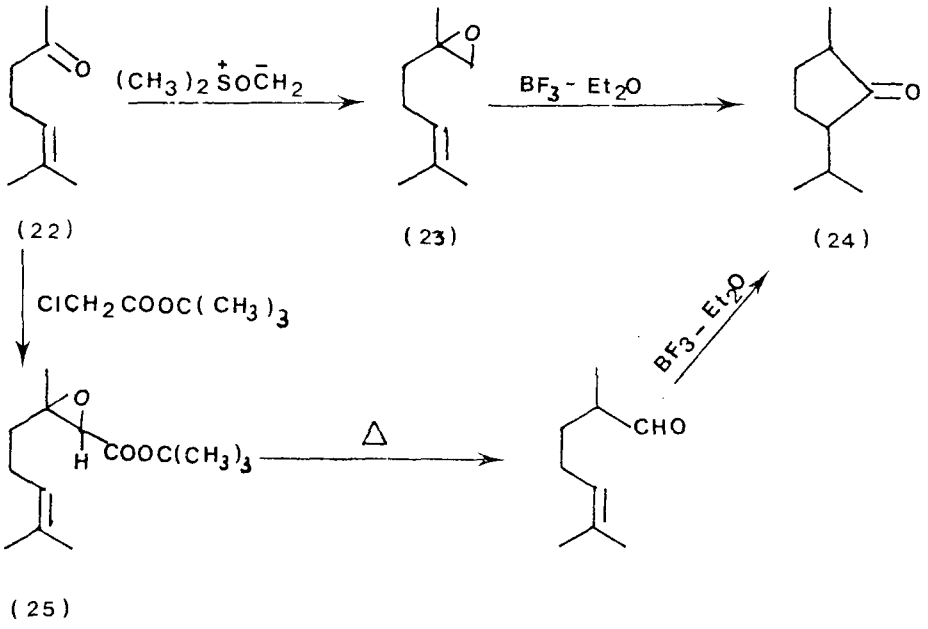


(2) (3)



(4)

Action of dimethyloxosulfonium methylide on methylheptenone furnished the oxirane (23) which underwent a novel rearrangement on treatment with BF_3-ether to furnish 2-methyl-5-isopropyl cyclopentanone (24). An alternate route to (24) was also developed. Methylheptenone was transformed to the glycidic ester (25) which furnished aldehyde (26) on pyrolysis. Treatment of (26) with BF_3-ether resulted in the formation of (24).



4.2 INTRODUCTION

α-keto acids find extensive use in the preparation of amino acids. The α-ketoacid, analogs of amino acids are of considerable biochemical interest as intermediates in the biosynthesis and degradation of amino acids. Several α-keto acids are also intermediates in the citric acid cycle.

Many synthetic methods have been devised for the synthesis of α-keto acids and esters. Some of the methods are presented below.

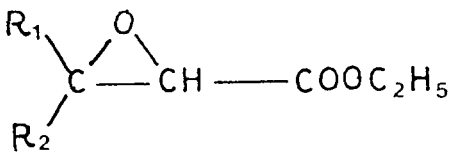
Examples of acid catalyzed isomerization of substituted glycidic esters (48) to substituted pyruvic esters (49) have been reported by a number of workers[1-5] (chart 1).

The rearrangement of glycidic ester in presence of acid was observed by Blicke and Faust[5]. They observed that when glycidic ester was heated in presence of hydrogen chloride or acetic acid, it rearranged to pyruvic ester. Thus ethyl ββ diphenyl glycidate (61) rearranged to ethyl diphenyl pyruvate (62) (chart 2).

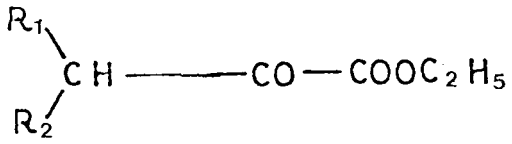
During the investigation of the conversion of ethyl α-phenyl glycidate (50) to ethyl α-formyl phenyl acetate (52), House et.al.[6] found that the actual product obtained was the keto ester (51) and not (52) as supposed earlier.

The conversion of glycidic ester (50) to the corresponding α-keto ester (51) was effected by passing the

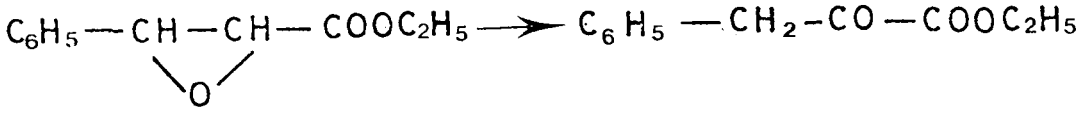
CHART I



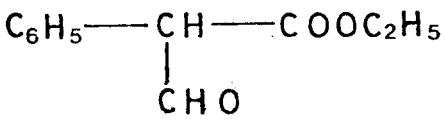
(48)



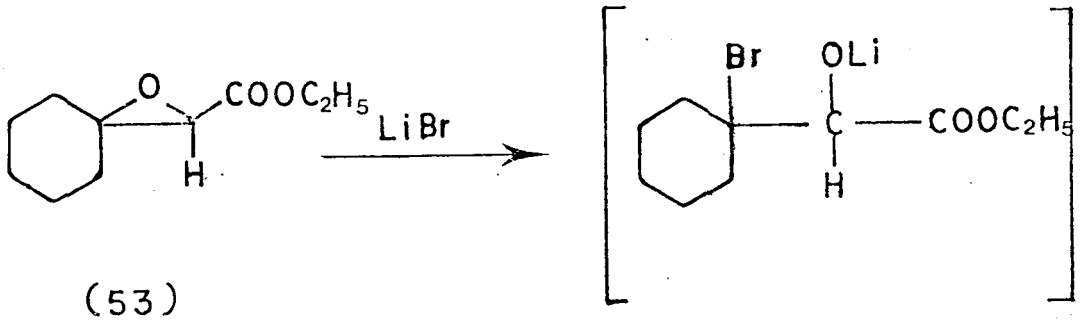
(49)



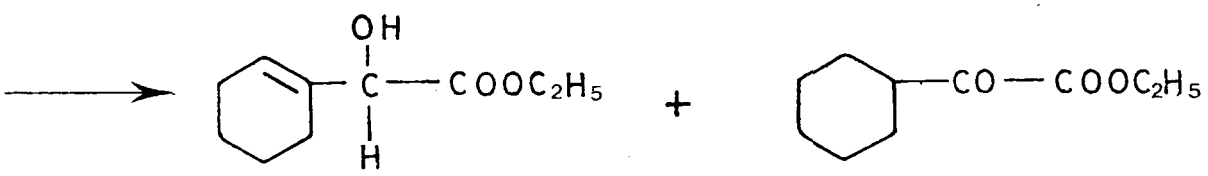
(50) (51)



(52)

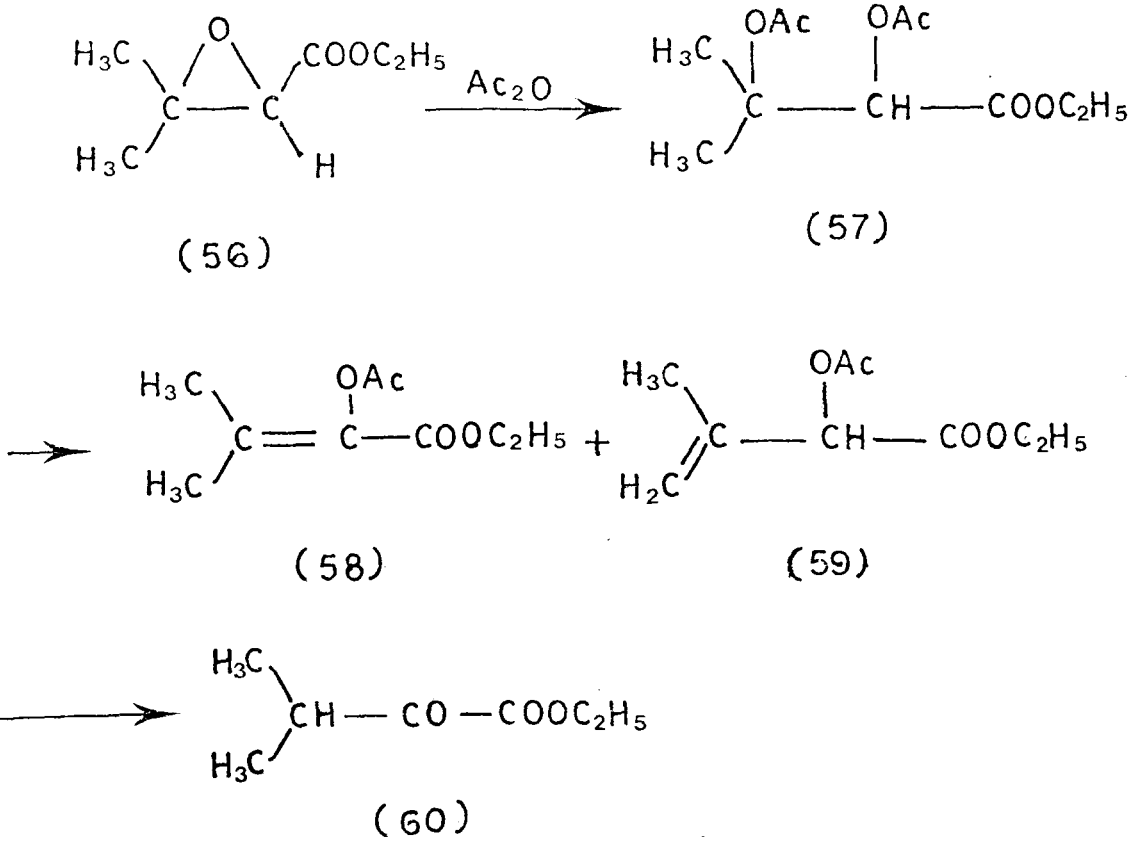


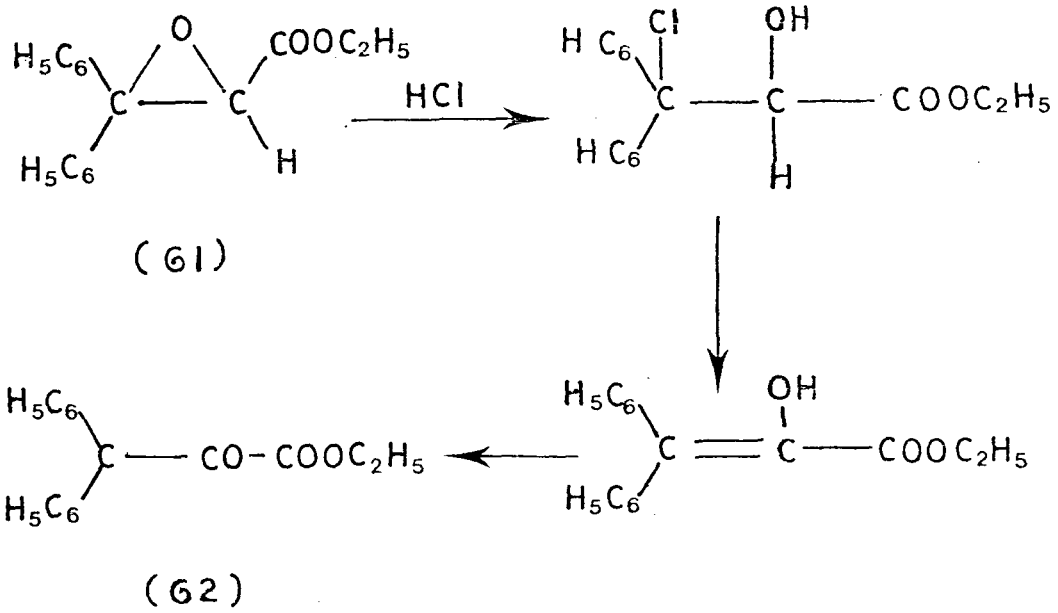
(53)



(54) (55)

CHART 2


H3C
O
COOC2H5
C
C
H3C
H
Ac2O
OAc
OAc
H3C
C
CH
COOC2H5
H3C
(56)
(57)
H3C
OAc
C
C
COOC2H5
H3C
+
H3C
OAc
C
CH
COOC2H5
H2C
(58)
(59)
H3C
CH
CO
COOC2H5
H3C
(60)


H5C6
O
COOC2H5
C
C
H5C6
H
HCl
H C6
Cl
OH
C
C
COOC2H5
H C6
H
(61)
H5C6
OH
C
C
COOC2H5
H5C6
H5C6
C
CO-COOC2H5
H5C6
(62)

glycidic ester vapor over either an aluminum containing clay or infusional earth at temperatures of 250-300°. Thus β-phenyl glycidic acid was isomerized to phenyl pyruvic acid in the presence of hydrochloric acid.[6] House et.al.[7] also investigated the rearrangement of the glycidic ester (50) in presence of benzene solution of boron-trifluoride gas. The isomerization product was the α keto ester (51) (see chart 1).

Recently Hartman and Rickborn[8] have reported the lithium salt catalyzed rearrangements of some β dialkyl glycidic esters in which α-keto ester is obtained as one of the products.

Lithium bromide, in solution with one mole of hexamethylphosphoramide gave at best moderate yields of rearranged material. The rearrangement of glycidic ester (53) with lithium bromide gave two products (54) and (55) which arise from the cleavage of the oxirane ring at the β carbon atom followed by elimination or hydrogen migration. Both the products may arise from carbonium ion process or might involve an intermediate halohydrin salt. The use of very hygroscopic lithium iodide led to increase in the glyoxylate product (55) (see chart 1).

Lithium perchlorate can also be used as a catalyst in the above reaction. A high yield synthesis of (55) using glycidic ester as starting material was accomplished by subjecting the $LiClO_4$ rearrangement product mixture to

catalytic hydrogenation followed by chromic acid oxidation.

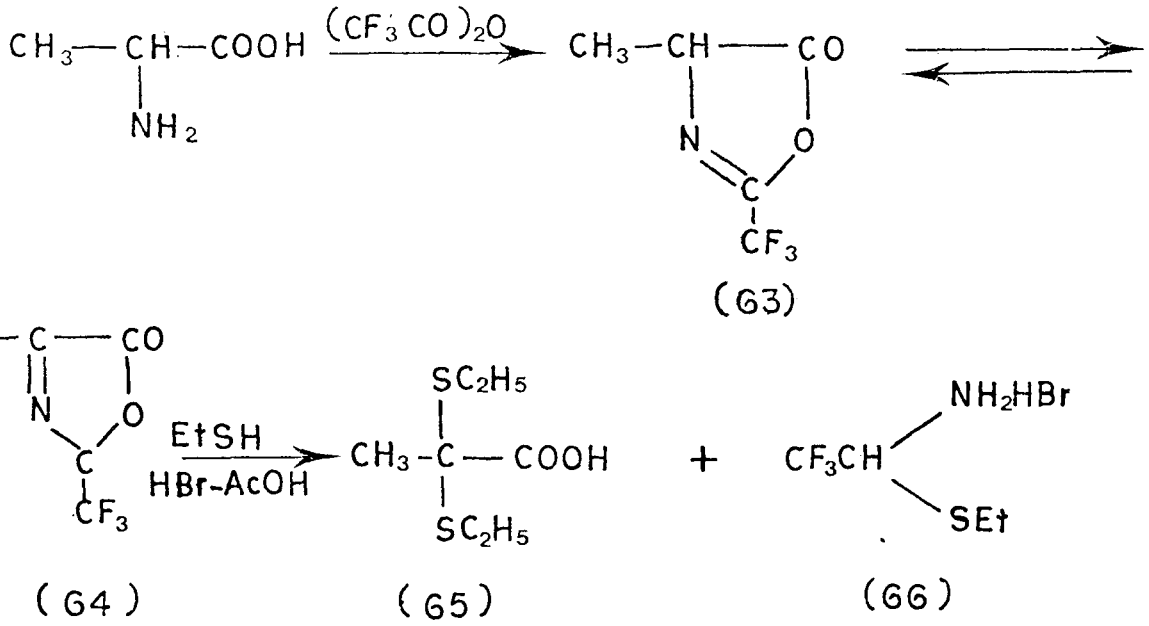
E. Vogel and H. Schinz[4] found that the oxirane ring of the glycidic ester was opened by the action of acetic anhydride in presence of small amount of sulphuric acid. Glycidic ester (56) furnished diacetate (57) by the action of acetic anhydride. Compound (57) on heating lost acetic acid to give a mixture of (58) and (59). Conversion of acetate group to the hydroxyl group furnished the desired α-keto ester (60) (see chart 2).

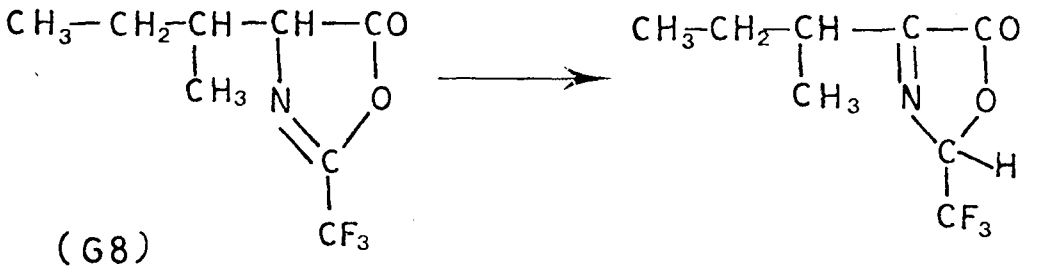
F. Weygand[9] developed an efficient process for the chemical transformation of α-amino acid into the corresponding α-keto acid.

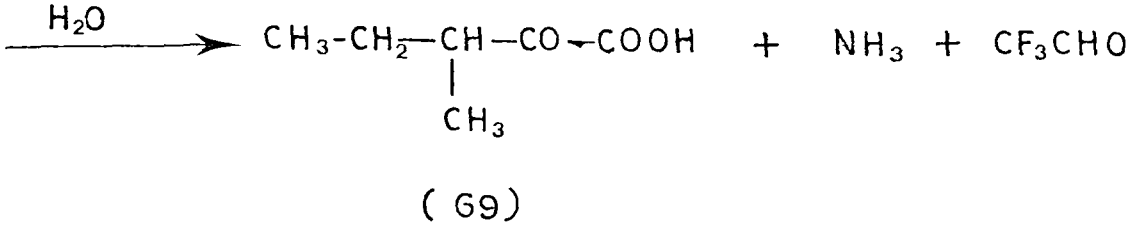
Reaction of alanine with trifluoroacetic anhydride at 140° gave the azlactone, 2-trifluoromethyl-5-oxazolonene which, according to PMR spectrum has the structure (63). The acid catalyzed reaction of (63) with ethyl mercaptan probably involved the less stable form (64) and affected cleavage to products (65) and (66). Hydrolysis of the diethylthioketal (65) with aqueous acetic acid afforded the α-keto acid (67) in 40-60% yield (see chart 3).

Later on, in 1962 Weygand et.al.[10] developed another method for opening of azlactone. The azlactone (68), synthesized by heating L-Isoleucin with trifluoroacetic anhydride at 140°, was hydrolyzed by heating with sodium hydroxide solution. It furnished α-keto acid (69), along with the

CHART 3


CH3—CH—COOH
NH2
(CF3CO)2O
CH3—CH—CO
N
O
C
CF3
(G3)
CH3—C—CO
N
O
C
CF3
EtSH
HBr-AcOH
CH3—C—COOH
SC2H5
SC2H5
+
CF3CH
NH2HBr
SEt
(G4)
(G5)
(G6)
AcOH
CH3COCOOH
(G7)


CH3—CH2—CH—CH—CO
CH3
N
O
C
CF3
(G8)
CH3—CH2—CH—C—CO
CH3
N
O
C
H
CF3


H2O
CH3-CH2—CH—CO-COOH
CH3
+
NH3
+
CF3CHO
(G9)

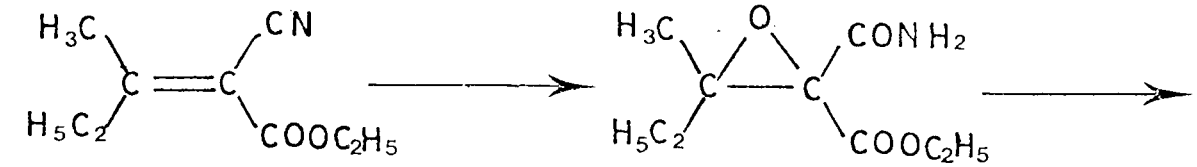
formation of trifluoroacetaldehyde and liberation of ammonia (see chart 3).

A novel preparation of α-keto amides and acids from ethylalkylidenecyanoacetate as starting material, was carried out by Igarashi et.al.[11]. Ethyl alkylidene cyanoacetate (70) was epoxidized at 70-80° in ethanol containing 30% hydrogen peroxide and sodium tungstate dihydrate. The resulting epoxyamide (71) reacted with alcoholic alkali at room temperature to give the compound (72). Decarboxylation and rearrangement of (72) to α-keto amide (73) was readily accomplished by heating with a small amount of water. Further treatment of (72) and (73) with dilute hydrochloric acid afforded α-keto acid (74) in good yield. α-Keto acids (75-80) (see chart 4) were prepared by following the above route.

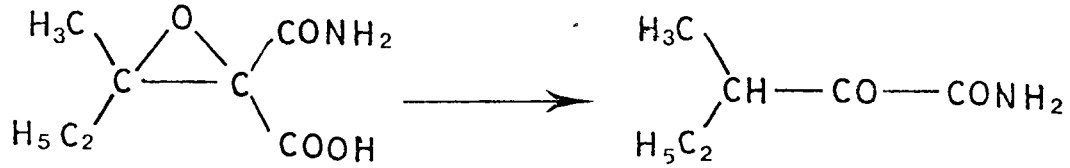
Later on the above procedure to obtain α-keto acids from ethyl alkylidene cyanoacetates, was extended to the synthesis of α-keto acids by the use of diethyl alkylidenemalonates, by Igarashi et.al.[12].

Epoxidation of diethyl alkylidene malonate (81) with hydrogen peroxide in the presence of sodium tungstate gave the epoxy ester (82). Alkaline hydrolysis of epoxy ester afforded the corresponding acid (83) which was readily decarboxylated to α-keto acid (83). The α-keto acids (85-89) were prepared by following the same route (see chart 5).

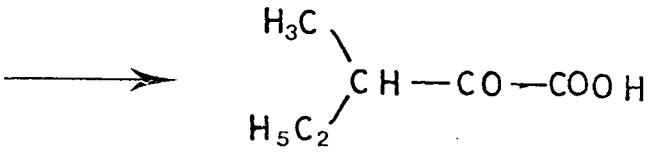
CHART 4



(70) (71)



(72) (73)

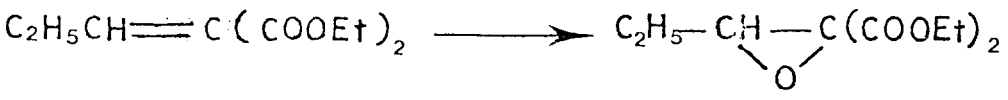


(74)

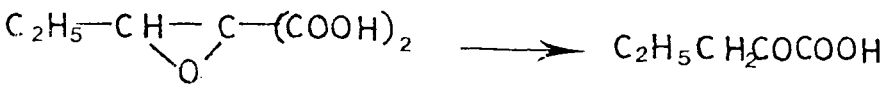
$RR'CHCOCOOH$

R	R′	
METHYL	ISOBUTYL	(75)
METHYL	HEXYL	(76)
METHYL	PROPYL	(77)
METHYL	PHENYL	(78)
	CYCLOHEXYL	(79)
	CYCLOPENTYL	(80)

CHART 5



(81) (82)



(83) (84)

$R CH_2COCOOH$

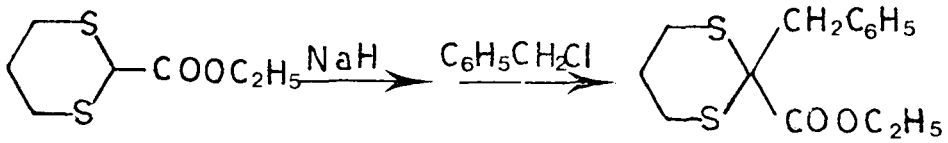
R = n-C_3H_7 (85)

R = i-C_3H_7 (86)

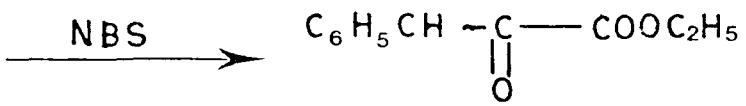
R = i-C_4H_9 (87)

R = n-C_5H_{11} (88)

R = n-C_6H_{13} (89)



(90) (91)



(92)

Recently a useful general method for the synthesis of α-keto esters was developed by Eliel et.al.[13]. This can be exemplified as given in chart 5. The ester (90) on treatment with sodium hydride in dimethylformamide, furnished its sodium salt which was then alkylated with benzyl chloride to give (91). Compound (91) was converted to the corresponding α-keto ester (92) by the treatment of N-bromosuccinimide.

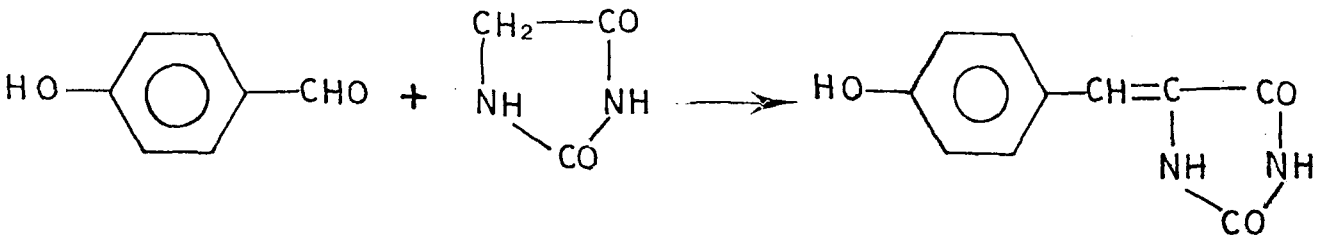
The syntheses of many substituted phenylpyruvic acids, were achieved by a method given by Billek[14].

This can be exemplified by the conversion of p-hydroxy benzaldehyde (93) to p-hydroxyphenyl pyruvic acid (97).

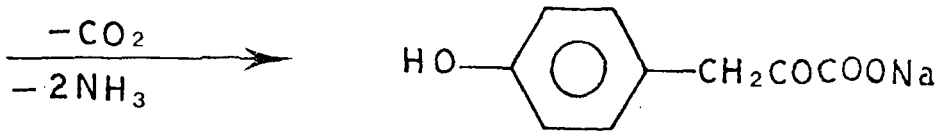
Compound (93) was treated with hydantoin (94) in presence of piperidine to furnish 5-(p-hydroxybenzal) hydantoin (95). Action of sodium hydroxide on (95) gave (96) which on treatment with hydrochloric acid furnished p-hydroxyphenylpyruvic acid (see chart 6).

There are a number of references (15-28) in the literature which give procedures for the formation of glyoxylic acids and esters.

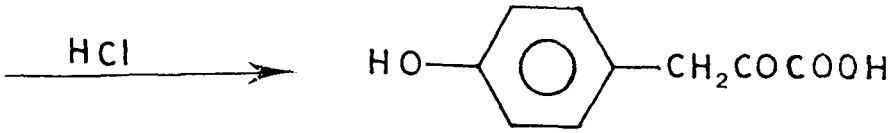
CHART 6



(93) (94) (95)



(96)



(97)

4.3 PRESENT WORK

Epoxidation of diethyl arylidene and alkylidene malonates

The epoxidation of some diethyl arylidene and alkylidene malonates has been investigated. This has led to a convenient route for the preparation of α-keto acids.

Diethyl arylidene and alkylidene malonates were obtained by well known Knoevenagel condensation[29]. Knoevenagel condensation is the reaction between an aldehyde or ketone and any compound having an active methylene group, brought about by an organic base or ammonia or their salts. The primary product is usually an unsaturated compound.

Thus, conversion of aldehydes to the corresponding diethyl arylidene and alkylidene malonates was achieved by condensation of the aldehyde and diethyl malonate in presence of piperidine. PMR spectra were used to characterize the compounds. Diethyl benzylidene malonate (1a) was prepared according to method given in literature[30], by condensing benzaldehyde and diethylmalonate. It showed a signal at 7.63δ due to vinyl proton in its PMR spectrum (see fig. 41). The arylidene and alkylidene malonates prepared by us are known compounds. The ready availability of arylidene and alkylidene malonates makes the approach presented here very attractive.

Payne[31] had observed that the epoxidation of diester (98) with H_2O_2 furnished the epoxide (99). Hence, we studied the action of H_2O_2 on some diethyl arylidene malonates. It was observed that epoxidation of ester (1a) could be carried out conveniently in ethanol solution with 30% H_2O_2 at PH=8, and at room temperature. H_2O_2 was added in portions to the well stirred reaction mixture, each addition was followed by addition of NaOH to maintain the PH at 8. The structure of the epoxide (1) was supported by its PMR spectrum (fig. 42), which showed triplets at 0.92 and 1.33δ (due to $C\underline{H}_3-CH_2-$), quartets at 3.97 and 4.3δ (due to $CH_3-C\underline{H}_2-$), and singlet at 4.47δ due to oxirane proton.

Epoxides (5) (for PMR spectrum see fig. 43), (9), (13), and (17) were prepared through H_2O_2 epoxidation of (5a), (9a), (13a), and (17a) respectively.

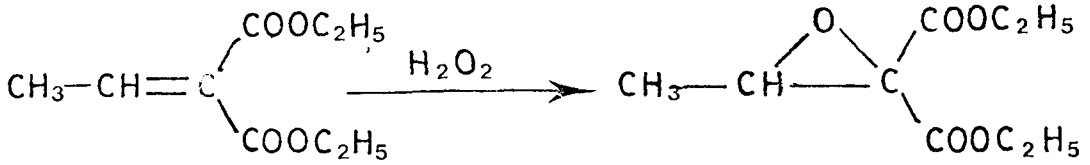
The structures of these epoxides were further supported by their transformations to appropriate α-keto acids*.

Epoxydiester (1) was first converted to the disodium salt (2). Ethanolic solution of epoxy diester (1) containing two molar equivalents of water furnished the disodium salt (2). The PMR spectrum of (2) in D_2O exhibited a signal at 4.27δ due to oxirane proton showing that oxirane

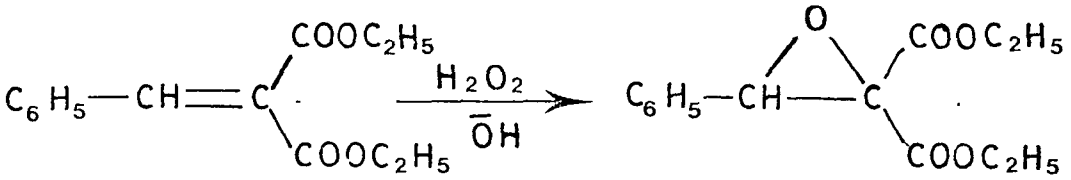
*Darzens[32] had observed that the addition of hydrogen chloride to glycidic acids produces α-hydroxy-β-chloro carboxylic acids.

We have made use of this observation in cleavage of epoxydiesters.

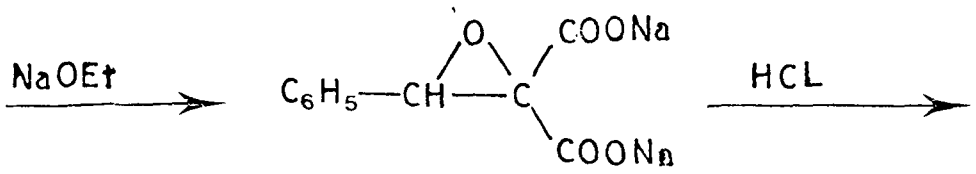
CHART 7



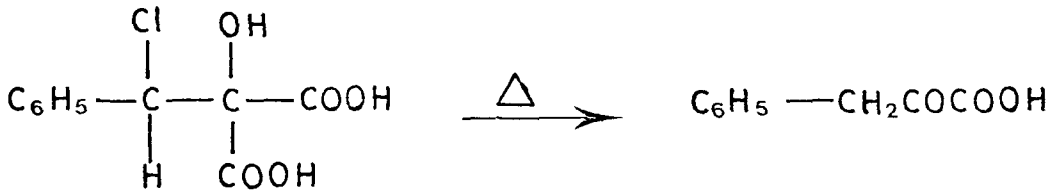
(98) (99)



(1a) (1)

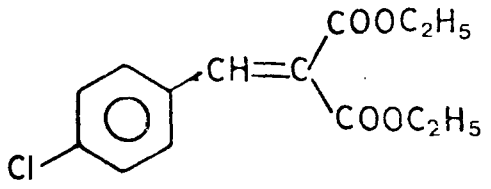


(2)

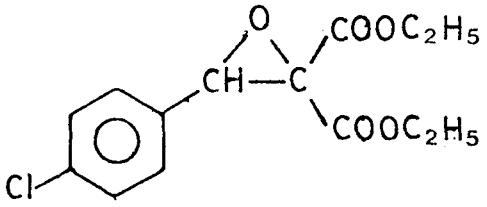


(3) (4)

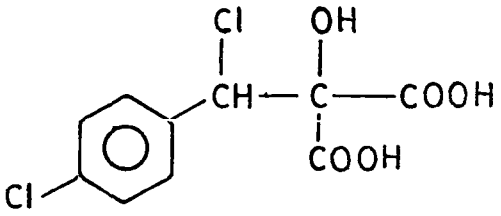
CHART 8



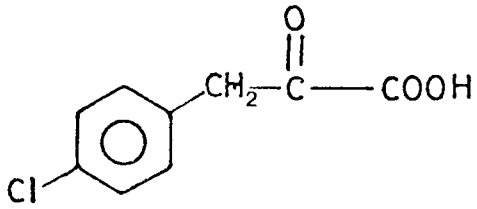
(5a)



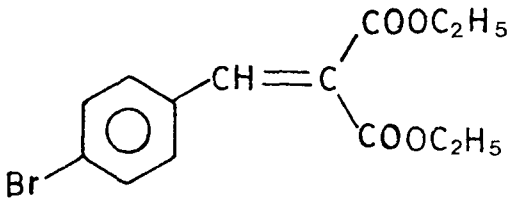
(5)



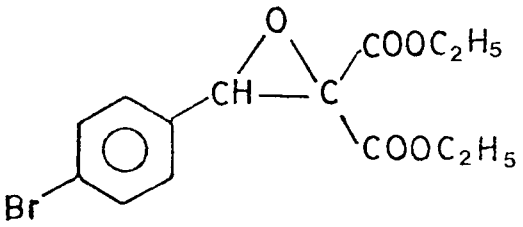
(7)



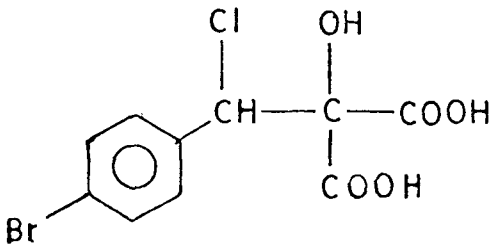
(8)



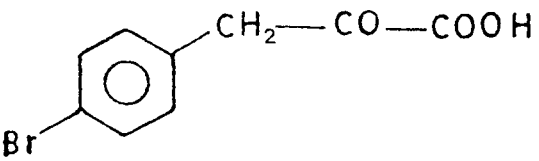
(9a)



(9)

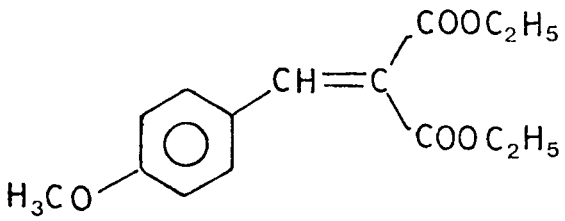


(11)

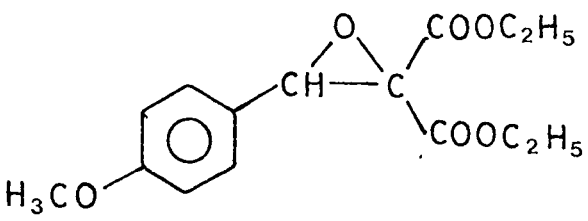


(12)

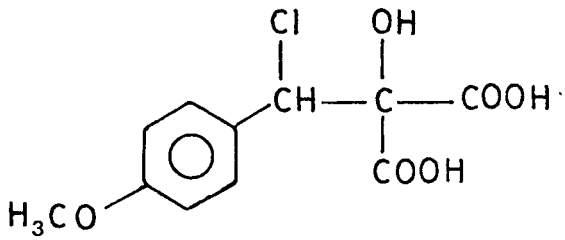
CHART 9



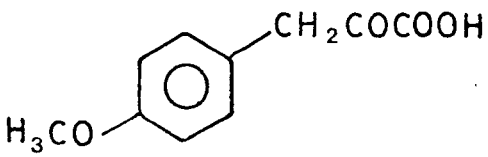
(13a)



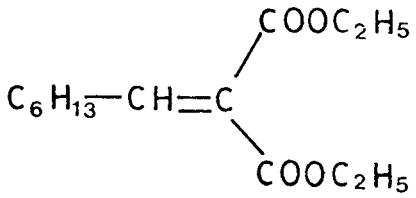
(13)



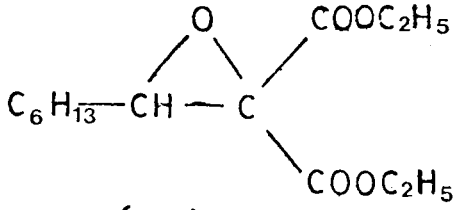
(15)



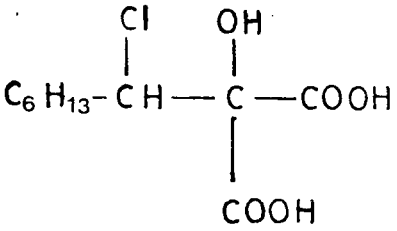
(16)



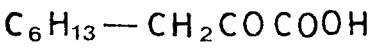
(17a)



(17)



(19)



(20)

ring was intact in the sodium salt. There were no signals in the higher field region indicating that both the ester groups of (1) were saponified.

Compound (2) was suspended in dry ether and dry hydrogen chloride gas was bubbled for 30 minutes. Ether and HCl were then removed from the reaction mixture carefully with suction. The residue was treated with ether and filtered to remove sodium chloride. Removal of ether from filtrate furnished acid (3). Equivalent weight determination was in agreement with the structure (3) for acid.

When chlorohydroxy acid (3) was heated in vacuum, it readily eliminated HCl and CO_2 and resulting keto acid (4) distilled out (see chart 7). Compound (4) was identified by comparison (mp, mixed mp, IR, PMR) with an authentic sample prepared according to the procedure given in the literature[33].

Following similar sequence of reactions diesters (5), (9), (13), and (17) have been transformed to α-keto acids (8), (12), (16), and (20) respectively (see charts 8 and 9).

4.4 INTRODUCTION

Use of tert.-butyl glycidic esters in the synthesis of aldehydes and ketones

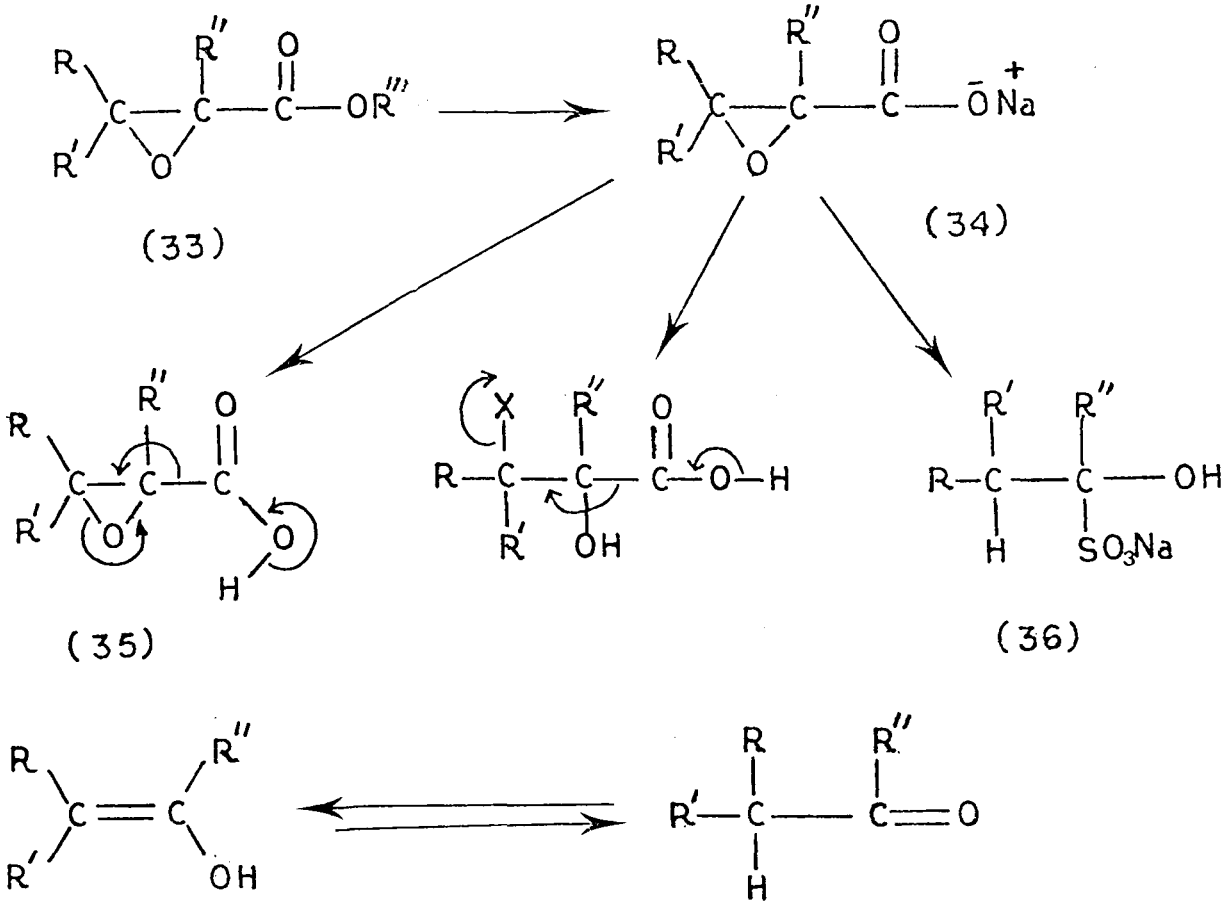
Blanchard and Buchi[34] developed a new method for the conversion of glycidic esters to aldehydes and ketones.

One of the more useful transformation of glycidic esters concerns their conversion to aldehydes and ketones. Three methods for effecting this change have been in general use. In all the three methods first step is the saponification of glycidic ester (33) to the corresponding alkali glycidate (34). The most commonly used sequence for effecting decarboxylation is represented by path A. The alkali glycidate (34) is transformed into the glycidic acid (35) which is pyrolyzed. Path B is based on the observation of Darzens[32] that addition of hydrogenchloride or hydrogen bromide to glycidic acids produces α hydroxy β halo carboxylic acids. Decarboxylation with simultaneous loss of hydrogen halide furnishes the desired aldehyde or ketone. Path C consists of heating the alkali glycidate (34) with a saturated aqueous solution of sodium bisulphite. This acid catalyzed decarboxylation is followed by formation of sodium bisulphite adduct (36) of aldehyde and ketone (see chart 10, scheme 1).

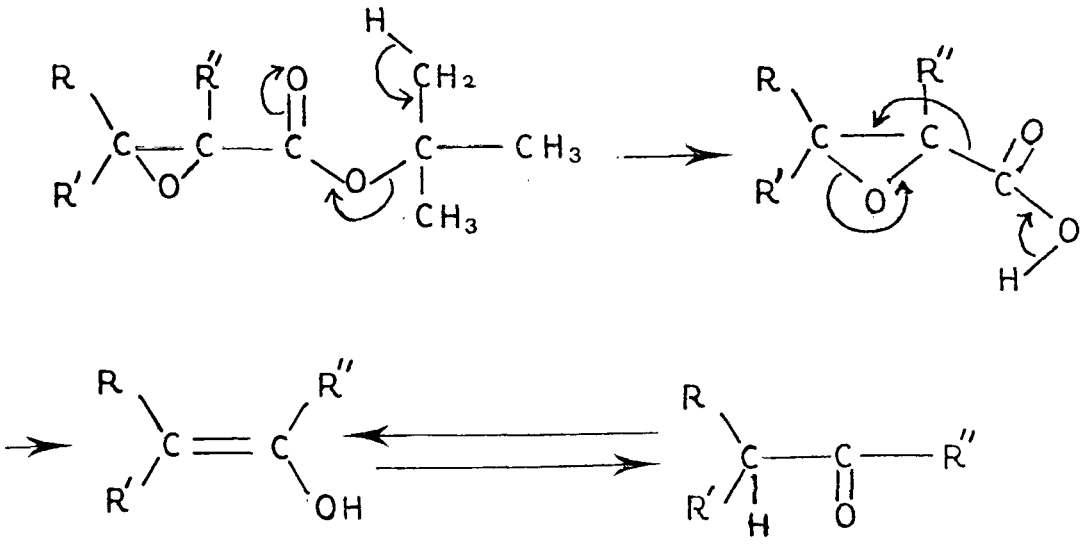
In each of these methods an intermediate is exposed to an acidic medium at one stage. For certain syntheses it is

CHART 10

SCHEME 1



SCHEME 2



advantageous to effect the conversion without recourse to acidic reagents. This is done by the direct pyrolysis of t-butyl glycidic esters to isobutylene, carbondioxide and the desired ketone. The actual mechanism is presented in chart 10, scheme 2.

Seven t-butyl glycidic esters were prepared by Büchi et.al.[34]. Pyrolysis of these by passage through a nitrogen swept tube packed with glass helices, at 350-360° furnished required aldehydes or ketones.

This method is extremely useful when the aldehydes and ketones to be synthesized are acid sensitive.

Synthesis of 2-methyl-5-isopropyl cyclopentanone

The synthesis of 2-methyl-5-isopropyl cyclopentanone has been achieved by means of several methods. A brief review on these methods is given here.

Cookson et.al.[35] during their study on cyclization of citral (37) by light, found out that one of the irradiation products of citral can be transformed into 2-methyl-5-isopropyl cyclopentanone.

Irradiation of citral with medium pressure mercury vapor arc gave a mixture of two isomers. The more abundant was the unconjugated, unsaturated aldehyde (38). The dihydroderivative of (38) was treated with methyl magnesium iodide to give an alochol, which was oxidized to a ketone. Baeyer-Villiger oxidation, hydrolysis, and then further oxidation

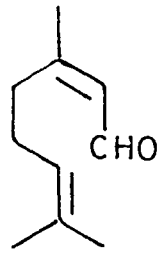
with chromic acid in acetic acid produced a ketone which was identified as 2-methyl-5-isopropyl cyclopentanone, by comparison of its semicarbazone and 2,4-dinitrophenyl hydrazone with authentic samples.

For investigating the structure of Nepetalactone (39), it was degraded to 2-methyl-5-isopropyl cyclopentanone by Meinwald[36]. Catalytic reduction of nepetalactone resulted in the hydrogenation and hydrogenolysis products. The acidic fraction which would correspond to (40) was reduced to alcohol (41) with lithium aluminium hydride. Subsequent acetylation gave the ester (42) which on pyrolysis at 530° liberated acetic acid with concomitant olefin (43) formation. Ozonolysis of this olefin gave formaldehyde and a ketone (24) which was identified as 2-methyl-5-isopropyl cyclopentanone by comparison of derivatives with authentic samples (see chart 11).

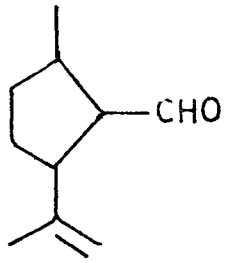
Raymond Calas[37] has reported that hydrogenation of 2-methyl-5-isopropylidene cyclopentanone (45) and 2-methyl-5-isopropyl Δ^4 cyclopentenone (46), furnished 2-methyl-5-isopropyl cyclopentanone in good yield. Hydrogenation of (45) and (46) in presence of Pt black or Ni furnished two isomers of 2-methyl-5-isopropyl cyclopentanone.

Kötz and P. Schüler[38] synthesized 2-methyl-5-isopropyl cyclopentanone starting from 1-carboxylic ester of 2-cyclopentanone (47) (see chart 12).

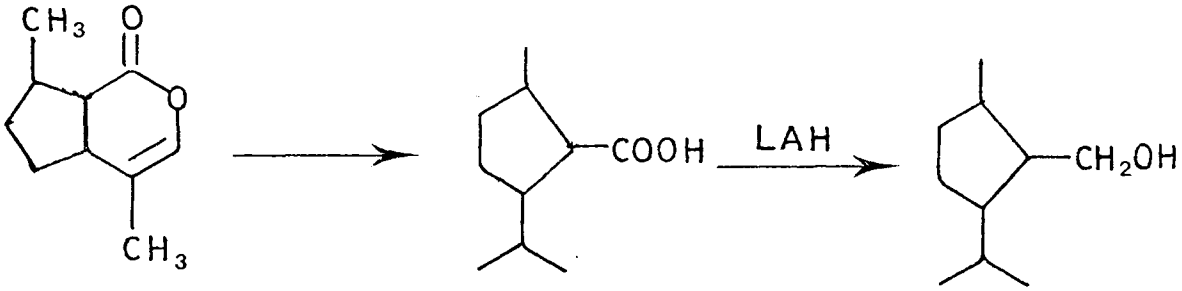
CHART II



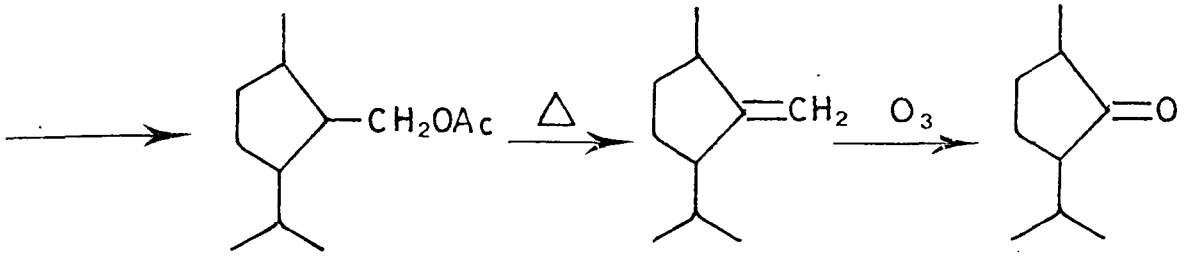
(37)



(38)



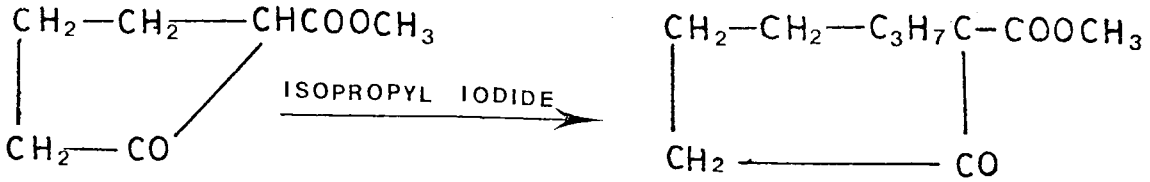
(39) (40) (41)



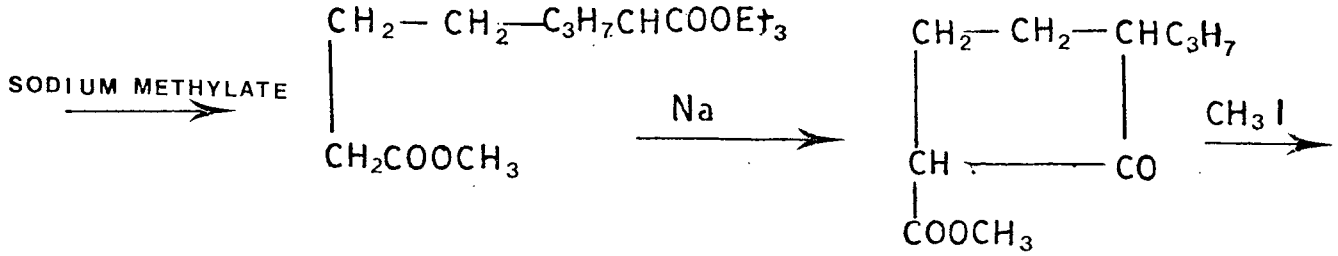
(42) (43) (24)

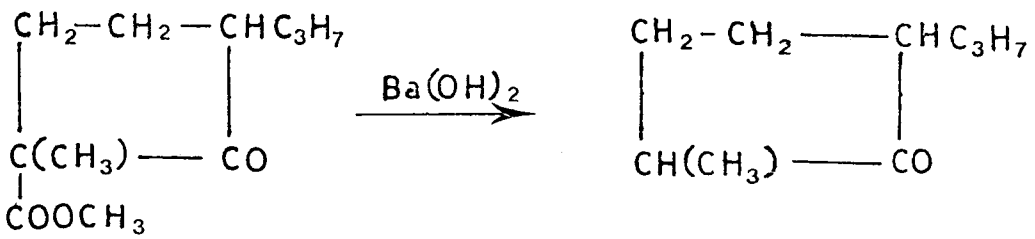
(45) (46)

CHART 12


CH2—CH2—CHCOOCH3
CH2—CO
ISOPROPYL IODIDE
CH2—CH2—C3H7C—COOCH3
CH2
CO

(47)


SODIUM METHYLATE
CH2— CH2—C3H7CHCOOEt3
CH2COOCH3
Na
CH2— CH2—CHC3H7
CH
CO
COOCH3
CH3 I

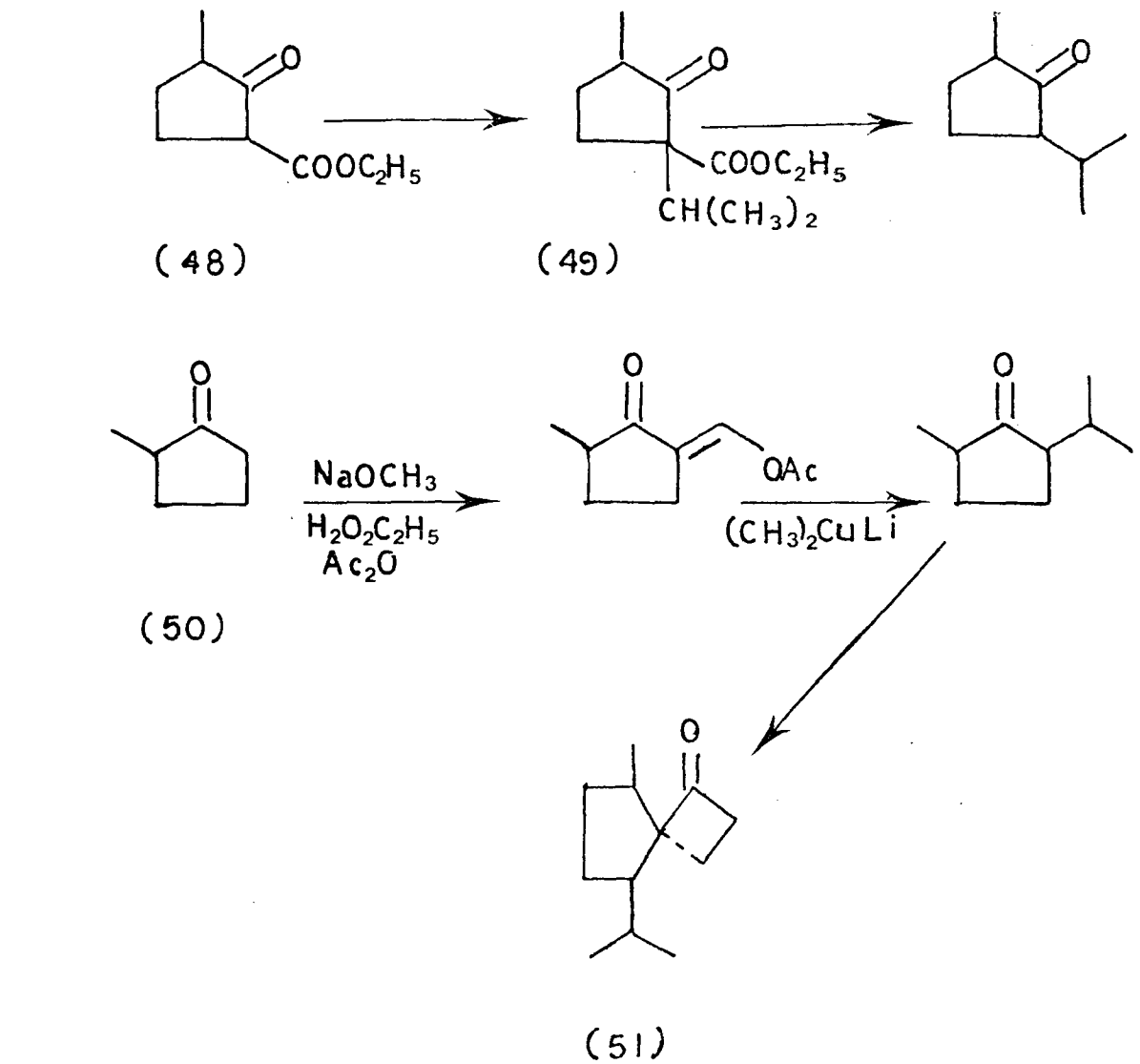

CH2—CH2—CHC3H7
C(CH3)—CO
COOCH3
Ba(OH)2
CH2-CH2—CHC3H7
CH(CH3)—CO

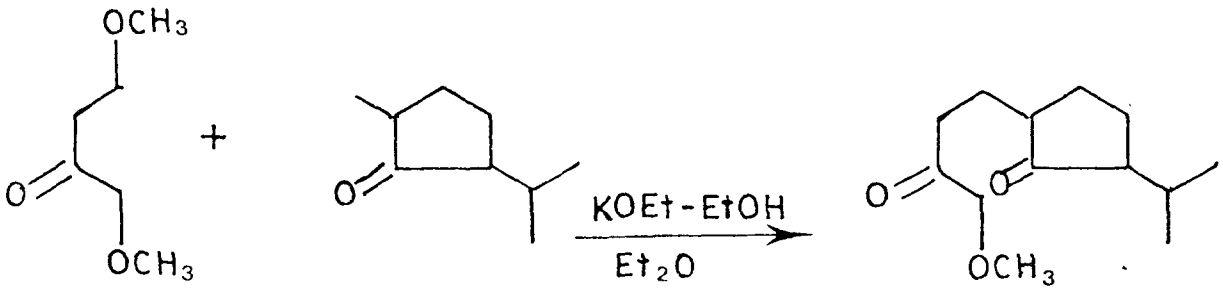
Sisido[39] et.al. have reported the synthesis of racemic 1,2-dimethyl-3-isopropyl cyclopentane, which involved 2-methyl-5-isopropyl cyclopentanone as an intermediate. The reaction of isopropyl iodide with 2-carbethoxy-5-methyl cyclopentanone (48) furnished 2-methyl-5-isopropyl cyclopentanone via the intermediate (49). The product was found to be a mixture of cis and trans isomers with trans compound predominating (see chart 13).

One of the interesting reactions of 2-methyl-5-isopropyl cyclopentanone was reported by Trost et.al.[40] 2-Methyl-5-isopropyl cyclopentanone was used as the starting material for the synthesis of acorenone B and was synthesized by the route given in chart (13), starting from 2-methyl cyclopentanone (50). The spiroannelation 2-methyl-5-isopropyl cyclopentanone with glide derived from cyclopropyldiphenylsulfoniumfluoroborate furnished (51), an intermediate in the synthesis of acorenone B.

2-Methyl-5-isopropyl cyclopentanone was also used in the preparation of one of the intermediates in the synthesis of dl-Oplopanone[41].

CHART 13


COOC2H5
COOC2H5
CH(CH3)2
(48)
(49)
NaOCH3
H2O2C2H5
Ac2O
OAc
(CH3)2CuLi
(50)
(51)


OCH3
OCH3
KOEt-EtOH
Et2O
OCH3

4.5 PRESENT WORK

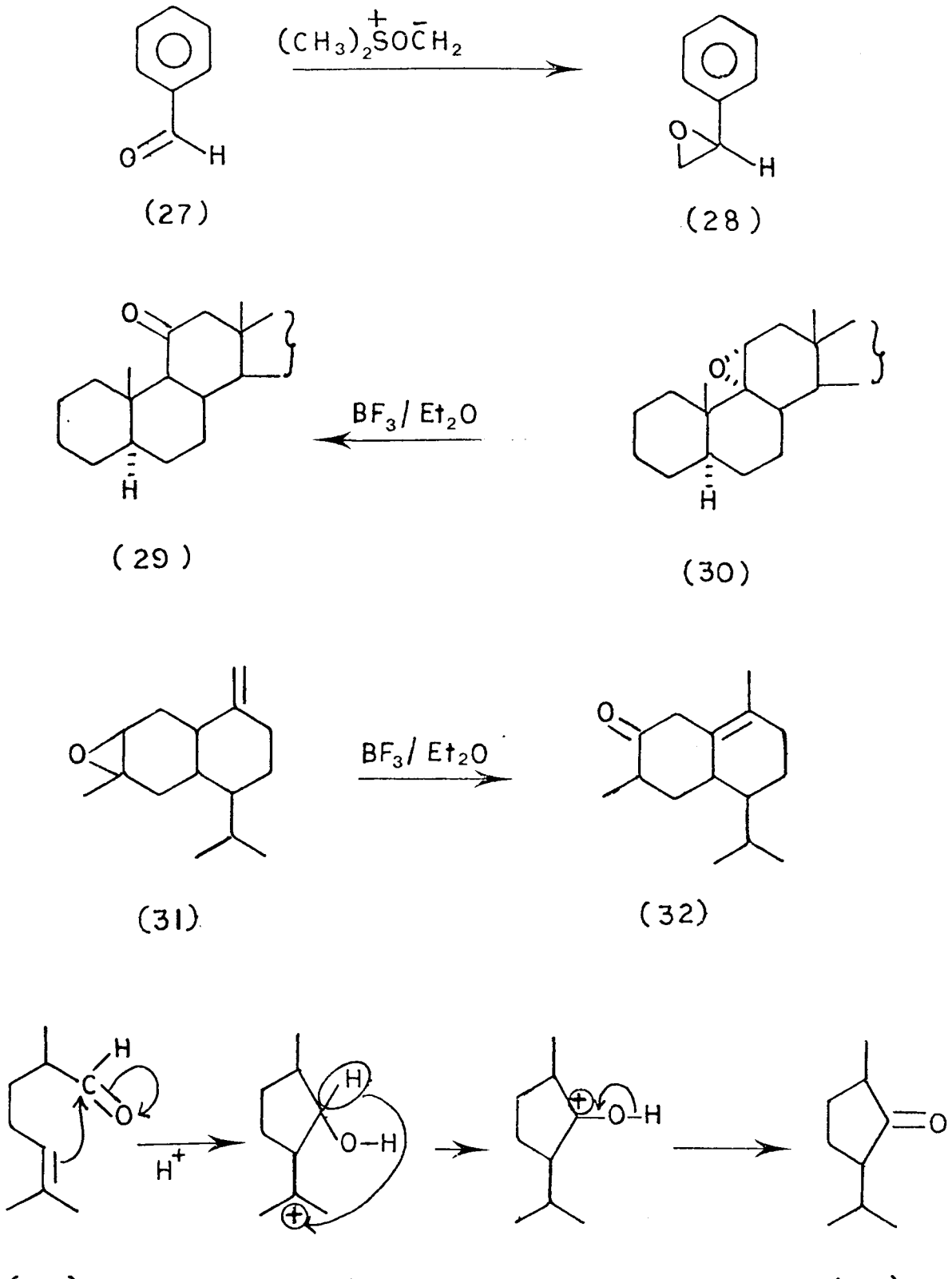
Here we present a new method for the synthesis of 2-methyl-5-isopropyl cyclopentanone (24) which is an intermediate for the synthesis of some terpenes*[42]. There are a number of methods available for synthesis of (24). The advantage of our method being, that it involves only two steps, starting from the readily available methyl heptenone (22).

Corey and Chaykovsky[43] observed that trimethylsulfoxonium halides undergo proton transfer to strong base with formation of dimethylsulfoxonium methylide, which transfers methylene group to the aldehydes or ketones to form oxiranes. For example, benzaldehyde (27) furnished styrene oxide (28) in 56% yield on reacting with the ylide[44]. (see chart 14).

Methylheptenone (22) was reacted with dimethyloxosulphonium methylide when the anticipated oxirane (23) resulted. Oxirane (23) showed absence of carbonyl band in its IR spectrum indicating that it was totally free from the starting ketone (22). Its PMR spectrum (fig. 44) showed signal at 2.5δ (singlet due to oxirane protons) and a singlet at 1.3δ (due to $-CH_3$ protons on the oxirane ring). A solution of (23) in dry benzene was treated with freshly distilled BF_3 etherate solution. The product obtained had the molecular formula $C_9H_{16}O$ on the basis of its analytical

*2-Methyl-5-isopropyl cyclopentanone was used as a starting compound for the synthesis of rac. 4-Epiacorenone-B.

CHART 14


(CH3)2SOCH2
BF3/ Et2O
BF3/ Et2O
H+
O-H
O-H
(27)
(28)
(29)
(30)
(31)
(32)
(26)
(26a)
(26b)
(24)

data; IR spectrum of the product showed a band at 5.75μ suggesting that it is a cyclopentanone derivative. From the molecular formula of the compound and the presence of cyclopentanone ring, it is evident that the product cannot contain any ethylenic linkage. In the PMR spectrum of the BF_3-treated product there are no olefinic proton signals and also there are no signals due to CH_3 attached to double bond in agreement with the above conclusion. The PMR spectrum suggested the presence of three CH_3 groups attached to hydrogen bearing carbons. Since the starting oxirane had an isopropylidene group, it appeared likely that the product may contain an isopropyl group; the IR and PMR data thus suggested that the product may be a methyl isopropylcyclopentanone. The melting points of semicarbazone and 2,4-dinitrophenylhydrazone derivatives of the product were in good agreement with the values reported for the corresponding derivatives of 2-methyl-5-isopropyl cyclopentanone. The identity thus deduced was established by comparison of IR spectra of the above derivatives with authentic samples. The PMR spectrum of our product (a mixture of cis and trans isomers of 2-methyl-5-isopropyl cyclopentanone) was identical with the published PMR spectrum of a mixture of cis and trans isomers of 2-methyl-5-isopropyl cyclopentanone (24).

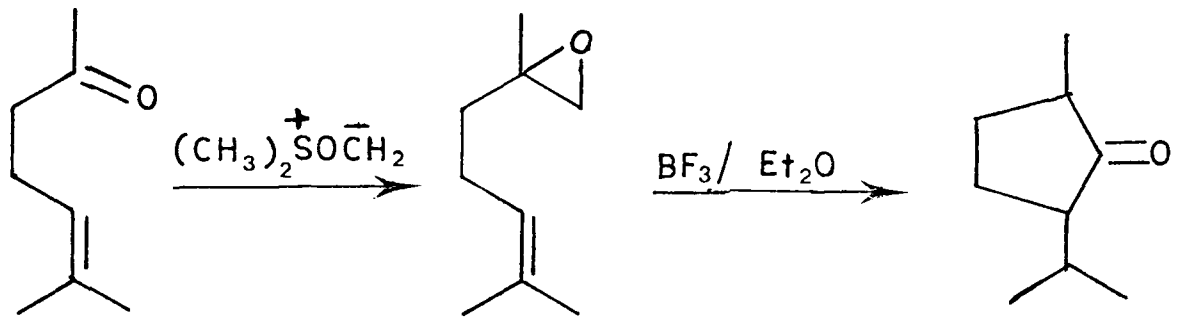
It is suggested that the oxirane (23) initially rearranges to the aldehyde (26). Similar type of convertion of oxiranes to aldehydes and ketones are known in the literature. This can be exemplified by the conversion of oxirane (29) to ketone[45] (30) and oxirane (31) to ketone[46] (32) by BF_3 etherate reaction (see chart 14).

Aldehyde (26) can rearrange in the presence of the acid catalyst, BF_3-ether to the cyclopentanone (24) as suggested in the (chart 14). The transformation of (26a) to (24) is comparable with the conversion of 2-methylene cyclopentanol to 2-methyl cyclopentanone in the presence of an acid[47]. To support the mechanism suggested above, the aldehyde (26) was synthesized (see below) and treated with BF_3-ether in benzene when the cyclopentanone (24) was obtained.

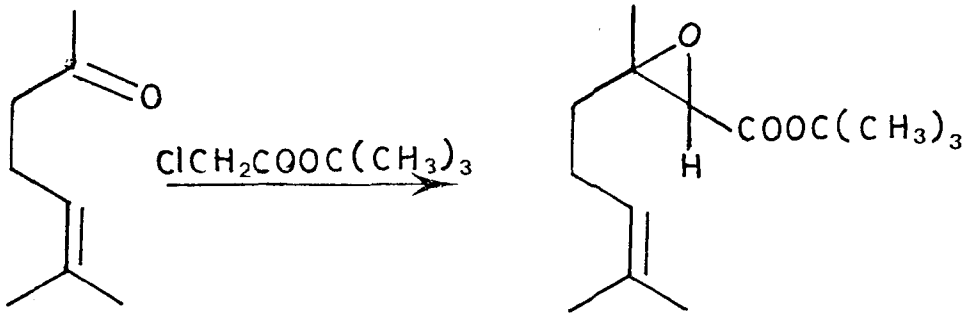
It was reported by Buchi and Blanchard[34], that pyrolysis of t-butyl glycidic esters is a suitable method for the preparation of aldehydes and ketones. The method is useful, particularly when products are acid sensitive.

This route was thought to be suitable for the synthesis of (26). The ketone (22) was first transformed into t-butyl glycidic ester (25). This was achieved by condensing ketone (22) with t-butyl chloroacetate in presence of potassium t-butoxide. Compound (25) showed in its IR spectrum band at 5.7μ (due to ester -C=O stretching). Its PMR spectrum (fig. 45) showed signals at 1.5δ (singlet corresponding to 9 protons $-C(C\underline{H}_3)_3$, 3.06δ (two singlets due to

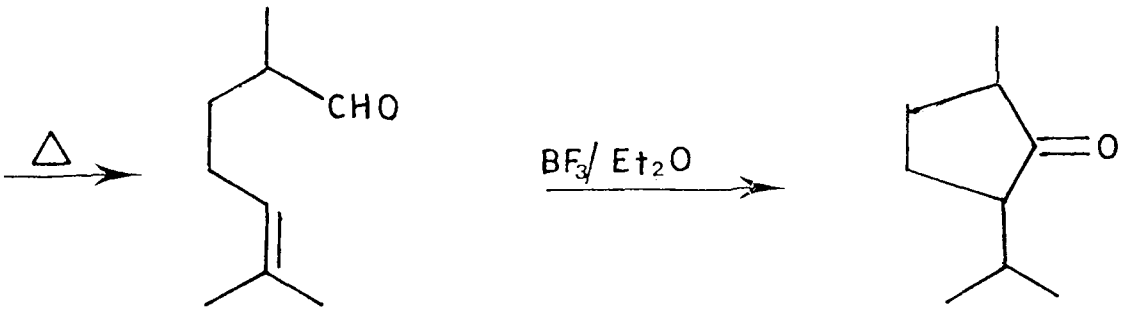
CHART 15



(22) (23) (24)

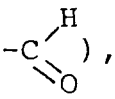
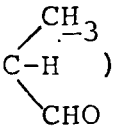


(22) (25)



(26) (24)

oxirane protons of two diastereomers and 1.33δ (singlet due to methyl protons on oxirane ring). These data corroborated with the one required for (25).

Compound (25) was pyrolyzed by heating at 360° in nitrogen atmosphere. The pyrolysate was washed with aqueous sodium carbonate solution and was distilled. The GLC and TLC of the product showed it to be a single pure compound. The structure (26) assigned for the pyrolysis product was supported by its IR (fig. 46) and PMR (fig. 47) spectra. It showed a band at 5.78μ in its IR spectrum due to aldehyde -C=O stretching. Its PMR showed signals at 9.6δ (doublet due to ), 1.13δ (doublet due to ), and showed absence of oxirane proton in the region 3.06δ.

Compound (26)* is a naturally occurring compound and was reported by Karlsson[48] et.al. in 1972.

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*The volatile fractions obtained from the leaves of Carphephorus corymbosus and Carphephorus arphephorus were found to contain more than 130 compounds. The low pressure distillation of acetone extracts of the leaves afforded small amounts of volatile compounds. One of them was found to be 2,6-dimethyl-hept-5-en-1-al (26), which was identified by its mass spectrum.

C.A. Henrick[49] et.al. have developed the synthesis of 4-thia-unsaturated esters and acids which are used as insect control agents. Aldehyde (26) is used for the synthesis of mercapto ester which is one of the starting compounds for synthesis of 4-thia unsaturated esters and acids.

Now it was only left to observe the action of BF_3-etherate on aldehyde (26). Aldehyde (26) on treatment with BF_3-etherate under similar conditions as employed for the preparation of (24) from (23), furnished a ketone which was found to be same as (24) as seen from its IR and PMR spectra. GLC comparison of (26) and (24) showed complete conversion of (26) to (24).

To isolate the aldehyde (26), oxirane (23) was exposed to the action of BF_3 for a short reaction period. However, all our attempts to isolate (26), failed. Even after reaction period of one minute, no aldehyde was traced as seen from GLC and TLC but the product was (24). Thus, the conversion of (26) to (24) must be a fast process.

The ketones obtained by ylide route and by t-butyl glycidate route were found to be the same thus suggesting that aldehyde (26) is the intermediate in the conversion of (23) to (24).

4.6 EXPERIMENTAL

1) Ethyl-2-carbethoxy-3-phenyl glycidate(1)

Diethyl benzylidene malonate (1a) was prepared according to the method given in the literature[30]. PMR spectrum of (1a) showed signals at δ=7.63 (S, 1H, vinyl H), 4.25 (q, 4H, J=7Hz, $CH_3-\underline{CH}_2-O$), 1.3 (t, 3H, J=7Hz, $\underline{CH}_3-CH_2-$), 1.23 (t, 3H, J=7Hz, $\underline{CH}_3-CH_2-$).

To the stirred solution of (1a) (9.9 g, 0.052 mol) in ethanol (30 ml) was added 30% H_2O_2 (14 ml) in five portions at one hour intervals. After each addition of H_2O_2, aqueous 1N NaOH solution was added to maintain the mixture at pH 8. After the final portion of H_2O_2 was added, the reaction mixture was stirred at room temperature (25-30°C) for 15 hrs. and then diluted with water and extracted with chloroform. The chloroform extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed and the residual liquid distilled to give epoxy diester (1).

(Yield: 7.4 g, 70%) b.p. $_{2\ mm}$ 170°C.

IR Spectrum (liquid film) showed band at 5.8μ (-C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.3 (S, 5H, aromatic H), 4.47 (S, 1H, oxirane H), 4.3 (q, 2H, J=7Hz, $\underline{CH}_3-CH_2-$), 0.93 (t, 3H, J=7Hz, $\underline{CH}_3-CH_2-$).

Analysis

Found: C, 63.80; H, 6.05

$C_{14}H_{16}O_5$ requires: C, 63.63; H, 6.10%

2) Disodium salt of ethyl-2-carbethoxy-3-phenyl glycidate (2)

Sodium (1.33 g, 0.057 gm. atom) was dissolved in absolute alcohol (25 ml) and the resulting solution cooled in ice. Epoxydiester (1) (7.0 g, 0.026 mol) was added gradually and the reaction mixture shaken frequently. Subsequently, water (1.3 ml) was slowly added. The reaction mixture was kept in refrigerator overnight and separated solid was filtered, washed with dry ether and dried in vacuum to furnish (2).

(Yield: 6.48 g, 97%)

PMR Spectrum (D_2O) showed signals at δ=4.27 (S, 1H, oxirane H).

3) 2-Carboxy-2-hydroxy-3-chloro-3-phenyl propanoic acid (3)

Dry HCl gas was bubbled for 30 minutes through a suspension of (2) (5.0 g) in dry ether (100 ml). Ether and HCl were then removed from the reaction mixture carefully with suction. The residual mass was treated with ether (50 ml) and filtered to remove NaCl. Evaporation of ether from the filtrate furnished acid (3) which was washed with a few drops of cold ether.

(Yield: 3.45 g, 70%). m.p. 95°C.

Equivalent weight 122.0 [$C_{10}H_9ClO_5$ requires equivalent weight 122.3].

4) 2-Oxo-3-phenyl propanoic acid (4)

The chloroacid (3) (2.45 g) was taken in a distillation flask which was kept evacuated (10 mm) and heated in an oil bath. When the bath temperature reached 180°, HCl and CO_2 were evolved and the product started distilling out. The distillate after solidification was washed with a few drops of chloroform and purified by sublimation in vacuum (2 mm) to furnish phenyl pyruvic acid (4).

(Yield: 1.07 g, 65%) m.p. 150°C. (Literature reports m.p. 150-154°)

5) Ethyl-2-carbethoxy-3-(4-chlorophenyl)-glycidate (5)

Diethyl-p-chlorobenzylidene malonate (5a) was prepared according to the method given in the literature.

PMR Spectrum (CCl_4) showed signals at δ=7.6 (S, 1H, vinyl H), 7.4 (4H, S, aromatic H), 4.3 (q, 4H, J=7Hz, $-C\underline{H}_2-CH_3$), 1.35 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 1.3 (t, 3H, J=7Hz, $CH_2-C\underline{H}_3$).

To the stirred solution of (5a) (5.0 g, 0.017 mol) in ethanol (15 ml), was added H_2O_2 (30%, 6.8 ml) in five portions. After each H_2O_2 addition, 1N NaOH was added to maintain pH=8. Work up was done as described earlier for compound (1).

The residual liquid was distilled under vacuum to furnish (5).

(Yield: 4.22 g, 80%) b.p. $\overset{(bath)}{2\ mm}$ 220°.

IR Spectrum (liquid film) showed band at 5.8μ (due to $-\overset{O}{\overset{\|}{C}}-$ stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.4 (S, 4H, aromatic H), 4.5 (S, 1H, oxirane H), 4.35 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 4.05 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 1.35 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 1.0 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

Analysis

	Found:	C, 56.70; H, 5.31
$C_{14}H_{15}O_5Cl$	requires:	C, 57.28; H, 5.03%

6) Disodium salt of ethyl-2-carbethoxy-3-(4-chlorophenyl)-glycidate (6)

The disodium salt of (5) was prepared by following the same procedure as given for the preparation of (2).

(Yield: 97%).

PMR Spectrum (D_2O) showed signals at δ=7.25 (S, 4H, aromatic H), 4.19 (S, 1H, oxirane H).

7) 2-Carboxy-2-hydroxy-3-chloro-3-(4-chlorophenyl)-propanoic acid (7)

Dry HCl gas was bubbled for 30 minutes through a suspension of (6) (2.0 g) in dry ether (30 ml). Residual mass

after removal of ether and HCl was treated with ether and filtered to remove NaCl. Solvent evaporation furnished acid (7).

(Yield: 1.9 g, 71.48%) m.p. 100°C.

8) 2-Oxo-3-(4-chlorophenyl)-propanoic acid (8)

The chloroacid (7) (1.5 g) was taken in a distillation flask which was evacuated and heated in an oil bath. Following the same procedure as for Compound (3), p-chlorophenyl pyruvic acid (8) was obtained.

(Yield: 0.64 g, 60%) m.p. 188°C.

9) Ethyl-2-carbethoxy-2-(4-bromophenyl) glycidate (9)

Diethyl-p-bromo-benzylidene malonate (9a) was prepared according to the method given in the literature.

PMR Spectrum (CCl_4) showed signals at δ=7.65 (S, 1H, vinyl H), 7.5-7.2 (m, 4H, aromatic H), 4.35 (q, 4H, J=7Hz, $-C\underline{H}_2-CH_3$), 1.3 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 1.25 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

To the stirred solution of (9a) (10.0 g, 0.03 mol), in ethanol (30 ml) was added 30% H_2O_2, 10.4 ml) in five portions at one hour intervals work up was done as described earlier.

The residual liquid was vacuum distilled to furnish epoxydiester (9).

(Yield: 7.1 g, 70%.) b.p. $_{1\ mm}$ 185°C.

IR Spectrum (liquid film) showed band at 5.8μ (-C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.7-7.2 (q, 4H, aromatic H), 4.55 (S, 1H, oxirane H), 4.4 (q, 2H, J=7Hz, $C\underline{H}_2-CH_3$), 4.15 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 1.4 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 1.05 (t, 3H, J-7Hz, $-CH_2-C\underline{H}_3$).

Analysis

	Found:	C, 49.40; H, 4.24
$C_{14}H_{15}O_5Br$	requires:	C, 49.00; H, 4.38%

10) Disodium salt of ethyl-2-carbethoxy-3-(4-bromophenyl)-glycidate (10)

The disodium salt of (9) was prepared by following similar procedure given earlier for the preparation of compound (2)

(Yield: 98%)

PMR Spectrum (D_2O) showed signals at δ=7.4 (q, 4H, aromatic H), 4.3 (S, 1H, oxirane H).

11) 2-Carboxy-2-hydroxy-3-chloro-3-(4-bromophenyl)propanoic acid (11)

Dry HCl gas was bubbled for 30 minutes through a suspension of (10) (3.7 g) in dry ether (60 ml). Residual mass after removal of ether and HCl was treated with ether and filtered to remove NaCl. Solvent evaporation furnished acid (11).

(Yield: 3.16 g, 85.0%)

12) 2-Oxo-3-(4-bromophenyl)propanoic acid (12)

The chloroacid (11) (1.63 g) was taken in a distillation flask which was evacuated and heated in an oil bath. Following the same procedure for Compound (3), p-bromophenyl pyruvic acid (12) was obtained.

(Yield: 0.64 g, 53.4%) m.p. 184°C.

13) Ethyl-2-carbethoxy-3-(4-methoxyphenyl)-glycidate (13)

Diethyl-p-methoxy benzylidene malonate (13a) was prepared according to the method given in literature.

PMR Spectrum (CCl_4) showed signals at δ=7.55 (S, 1H, oxirane H), 7.45-6.7 (q, 4H, aromatic H), 4.3 (q, 2H, J=7Hz, $-C\underline{H}_2-CH_3$), 3.85 (S, 3H, $-OC\underline{H}_3$), 1.3 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 1.25 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

To the stirred solution of (13a) (9.4 g, 0.031 mol) in ethanol (30 ml), was added 30% H_2O_2 (11.4 ml) in five portions at one hour intervals. Work up was done in similar way as described earlier.

The residual liquid was distilled under vacuum to furnish (13).

(Yield: 7.43 g, 75%) b.p. $_{1\ mm}$ 188°C.

IR Spectrum (liquid film) showed band at 5.75μ (-C(=O)- stretching).

PMR Spectrum (CCl_4) showed signals at δ=7.4-6.7 (m, 4H, aromatic H), 4.5 (S, 1H, oxirane H), 4.2 (q, 4H, J=7Hz,

$-C\underline{H}_2-CH_3$), 1.3 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$), 1.0 (t, 3H, J=7Hz, $-CH_2-C\underline{H}_3$).

Analysis

	Found:	C, 62.19; H, 6.03
$C_{15}H_{18}O_6$	requires:	C, 61.89; H, 6.17%

14) Disodium salt of ethyl-2-carbethoxy-3-(4-methoxy-phenyl)-glycidate (14)

The disodium salt (14) was prepared by following the same procedure as given for the preparation of disodium salt (2).

(Yield: 96.8%).

15) 2-Carboxy-2-hydroxy-3-chloro-3-(4-methoxy phenyl)-propanoic acid (15)

Dry HCl gas was bubbled for 30 minutes through a suspension of (14) (3.0 g) in dry ether (50 ml). Residual mass after removal of ether and HCl was treated with ether and filtered to remove NaCl. Solvent evaporation furnished acid (15).

(Yield: 2.04 g, 70.0%) m.p. 156°C.

16) 2-Oxo-3-(4-methoxyphenyl)-propanoic acid (16)

The chloroacid (15) (4.0 g) was taken in a distillation flask which was evacuated and heated in an oil bath. Following the same procedure as for obtaining Compound (4), p-methoxy phenyl pyruvic acid (16) was obtained.

(Yield: 1.4 g, 50.5%) m.p. 180°C.

17) Ethyl-2-carbethoxy-3-n-hexyl-glycidate (17)

Diethyl hexylidene malonate (17a) was prepared by the method reported in the literature.

PMR Spectrum (CCl_4) showed signals at δ=6.9 (t, 1H, vinyl H), 4.2 (two quartets, 4H, ester $-C\underline{H}_2-CH_3$), 1.33 (two triplets, 6H, ester $-CH_2-C\underline{H}_3$), 0.095 (t, 3H, $-CH_2-C\underline{H}_3$).

To the stirred solution of (17a) (9.8 g, 0.038 mol), in ethanol (30 ml) was added H_2O_2 (30%, 13 ml) in five portions at one hour intervals. Each H_2O_2 addition was followed by addition of 1N NaOH solution to maintain pH=8. Work up was done in the similar way as described earlier.

The residual liquid was distilled under vacuum to furnish (17).

(Yield: 8.5 g, 80.0%) b.p. $_{1\ mm}$ 140°C.

IR Spectrum (liquid film) showed band at 5.75μ ($-\overset{O}{\overset{\|}{C}}-$ stretching).

PMR Spectrum (CCl_4) showed signals at δ=4.46-3.95 (two quartets, 4H, ester $-C\underline{H}_2-CH_3$), 3.23 (S, 1H, oxirane H), 1.4 (t, 3H, ester $-CH_2-C\underline{H}_3$), 1.36 (t, 3H, ester $-CH_2-C\underline{H}_3$), 0.95 (t, 3H, $-CH_2-C\underline{H}_3$).

18) Disodium salt of ethyl-2-carbethoxy-3-(n-hexyl)-glycidate (18)

The disodium salt (18), was prepared by the same way as preparation of Compound (2).

(Yield: 99%)

19) 2-Carboxy-2-hydroxy-3-chloro-3-(n-hexyl)-propanoic acid (19)

Dry HCl gas was bubbled for 30 minutes through a suspension of (18) (4.0 g) in dry ether (60 ml). Residual mass after removal of ether and HCl was treated with ether and filtered to remove NaCl. Solvent evaporation furnished acid (19).

(Yield: 2.21 g, 56.5%).

20) 2-Oxo-3-(n-hexyl)-propanoic acid (20)

The chloro acid (19) (2.0 g) was taken in a distillation flask which was evacuated and heated in an oil bath. Following the same procedure for preparation of (4), acid (20) was obtained.

(Yield: 0.74 g, 55%).

21) Ethyl-2-oxo-3-(n-hexyl)propanoate (21)

A mixture of acid (20) (4.0 g) ethanol (20 ml) and concentrated hydrochloric acid (0.5 ml) was refluxed on water bath for 4 hrs. The cooled reaction mixture was extracted with chloroform. Chloroform layer was washed with water, aqueous 5% sodium bicarbonate and again with water. It was dried over anhydrous sodium sulphate. Evaporation of solvent furnished a residue of ester (21).

22) 2,4 Dinitrophenyl hydrazone of ester (21)

A mixture of ester (21) (0.06 g, 0.0003 mol), 2,4 dinitrophenyl hydrazine (0.058 g, 0.0003 mol), concentrated hydrochloric acid (one drop) was heated on steam bath for 10 minutes. After cooling the reaction mixture, 2,4 dinetrophenyl hydrazone separated which was collected by filtration and crystallized from ethanol. m.p. 74°C.

Analysis

Found: C, 53.65; H, 6.55; N, 14.81

$C_{17}H_{24}N_4O_6$ requires: C, 53.68; H, 6.31; N, 14.73%

23) 2-Methyl-2-(4-methyl-3 pentene)-oxirane (23)

To a stirred mixture of sodium hydride (2.0 g, 0.08 moles) and finely powdered and dry trimethyl oxosulfonium iodide (9.4 g, 0.04 mol), dry dimethylsulfoxide (53 ml) was added dropwise, in N_2 atmosphere. A rapid effusion of H_2 occurred after addition and the reaction mixture was further stirred for 20 min. To the now formed white slurry of the ylide, 2,6 dimethyl-hept-5-en-2-one (22) (4.2 g, 0.033 mol), in dimethyl sulfoxide (10 ml) was added slowly with stirring. Stirring was continued for 2 hrs at room temperature after addition was complete and for one hour at 50°. Finally, ice cold water was added and extracted with ether. All ether extracts were combined and washed with water, dried over anhydrous sodium sulphate and solvent evaporated to get a residue which was identified as (23).

(Yield: 3.13 g. 67.08%) b.p. $\overset{(bath)}{60\ mm}$ 140-150°C.

PMR Spectrum (CCl_4) showed signals at δ=5.1 (t, 1H, vinyl H), 2.43 (S, 2H, oxirane protons), 1.7 (S, 3H, methyl on double bond) 1.66 (S, 3H, methyl on double bond), 1.26 (S, 3H, methyl on oxirane).

Analysis

Found: C, 77.11; H, 11.39

$C_9H_{16}O$ requires: C, 77.14; H, 11.43%

24) 2-isopropyl-5-methyl-cyclopentanone (24)

To the solution of oxirane (23) (0.5 g, 0.0035 mol) in dry benzene (15 ml) was added freshly distilled BF_3-etherate (1.3 ml) and the solution was left at room temperature for three hours. After diluting this with water the reaction mixture was extracted with ether, washed with water thoroughly and dried over anhydrous sodium sulphate. Evaporation of solvent furnished a residue which was identified as (24).

(Yield: 0.4 g, 74.1%).

IR Spectrum (liquid film) showed band at 5.75μ (-$\overset{O}{\overset{\|}{C}}$- stretching)

25) 2:4 Dinitrophenyl hydrazone of ketone (24)

To the solution of ketone (24) (0.1 g, 0.6 mol) in ethanol (5 ml), was added 2:4 dinitrophenyl hydrazone (0.14 g, 0.7 mm) and two drops of hydrochloric acid. The

reaction mixture was heated on water bath to get clear solution. After refluxing for 30 minutes, cooled to room temperature. Separated 2:4 dinitrophenyl hydrazone was filtered.

m.p. 168°C (literature[36] reports m.p. 170-171.5°)

26) Semicarbazone of ketone (24)

To a solution of semicarbazide hydrochloride (0.1 g, 0.9 m mol) and sodium acetate (0.15 g, 1.8 m mol) in water (1 ml) was added ketone (24) (0.1 g, 0.6 m mol). Slight turbidity appeared which was discharged by adding alcohol (1 ml). Solution was warmed on waterbath for few minutes and was cooled at room temperature. Separated solid was collected by filtration and washed with water and cold alcohol. After crystallization from alcohol and drying, melting point was recorded.

m.p. - 196°C (literature[38] reports m.p. 193-194°C)

27) 2-Methyl-2-(4-methyl-3-pentenyl)-3-(t-butyloxy carbonyl)oxirane (25)

To a well stirred solution of ketone (22) (8.82 g, 0.07 mol) and t-butylchloro acetate (12 g, 0.079 mol) in nitrogen atmosphere was added, a solution of potassium tert. butoxide [prepared by dissolving potassium (2.73 g), in t-butanol (75 ml) at 10-15° over a period of one hour]. The reaction mixture was stirred at 10° for one hour after addition was complete. The t-butanol was removed from the reaction mixture by using vacuum at water bath temperature. Cooled reaction mixture was diluted with plenty of

water, extracted with ether and combined ether layers were washed with water. Drying of solvent over anhydrous sodium sulphate and evaporation of solvent furnished a residue which was further purified by fractionation.

	b.p.		
Fraction I	100°/65mm	4 gm	Starting ketone(22)
Fraction II	190-200° bath/30mm	3 gm	ester (25)

(Yield: 3.0 g), (based on the ketone (22) actually consumed)

IR Spectrum (liquid film) showed band at 5.73μ (-C(=O)- stretching).

PMR Spectrum (CCl_4) showed signals at δ=5.06 (t, 1H, vinyl H), 3.07 (d, 1H, oxirane H), 1.66 (d, 6H, methyl groups on double bond), 1.47 (S, 9H, t-butyl group protons).

28) 2,6 Dimethyl-hept-5-en-1-al (26)

The ester (25) (0.5 g) was taken in a distillation flask which was heated in a sand bath. When the temperature of molten ester in the distillation flask reached 280° there was vigorous evolution of gas and pyrolysis product started distilling over. The contents of the flask were maintained at 280-290° until distillation was complete. The pyrolysis product was redistilled to furnish (26) (0.23 g).

(Yield: 76.6%) b.p. 220° at atm. pressure.

IR Spectrum (liquid film) showed band at 3.74μ (C-H stretching), 5.78μ (-C- stretching).

PMR Spectrum (CCl_4) showed signals at δ=9.6 (d, 1H, -C-H), 5.06 (t, 1H, vinyl H), 1.66 (d, 6H, methyl groups on double bond), 1.13 (d, 3H, J=7Hz, $-CH_3$ - C(H)=O).

29) 2-Isopropyl-5-methyl cyclopentanone (27)

To the solution of aldehyde (26) (0.2 g, 0.0014 mol), in dry benzene (10 ml) was added freshly distilled BF_3-etherate (0.5 ml) and the solution was left at room temperature for three hours. After diluting with water, the reaction mixture was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Evaporation of solvent furnished a residue which was identified as (27) from its IR, PMR spectra. GLC comparison of IR and PMR comparison of (24) and (27) showed that they were identical compounds.

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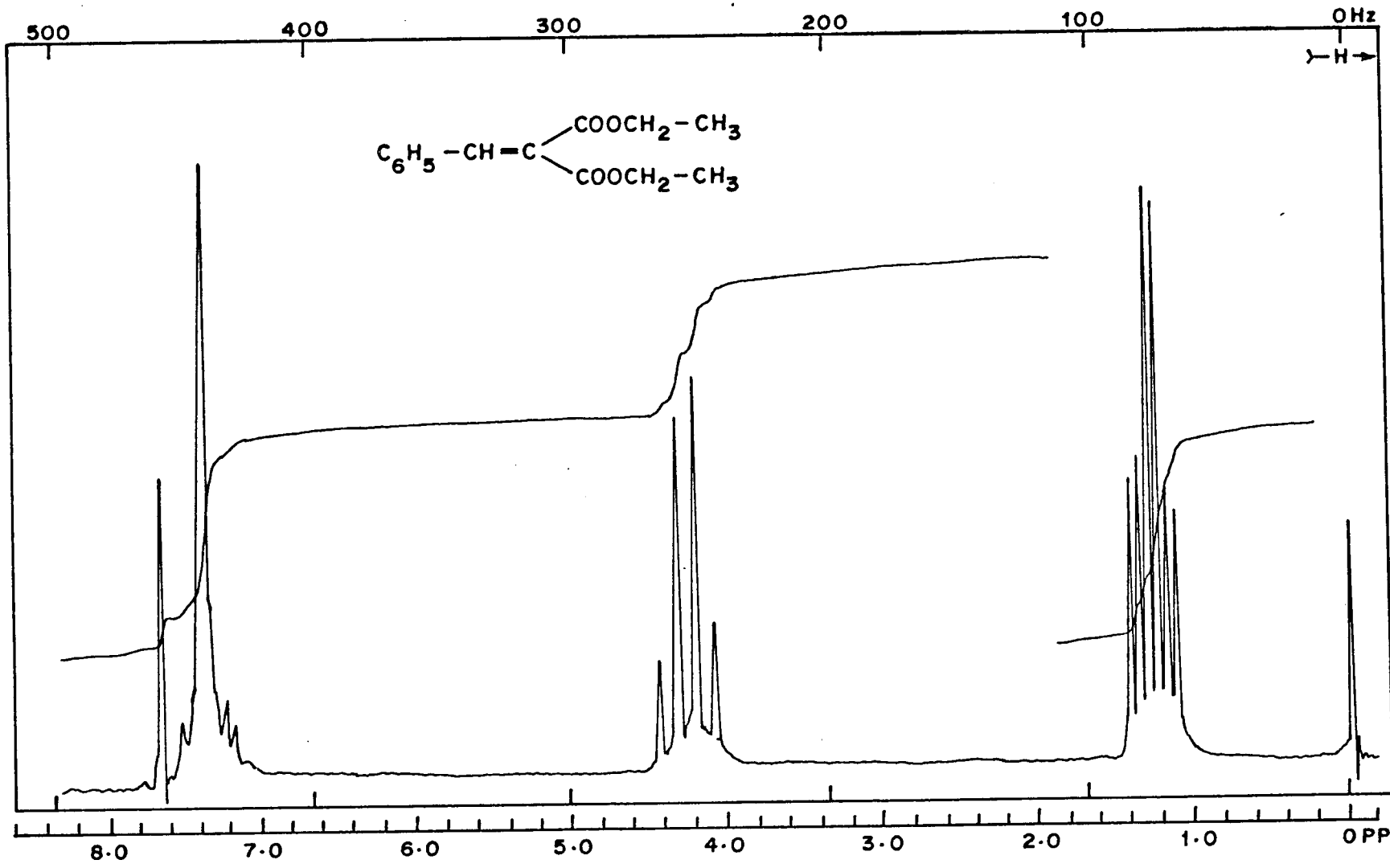
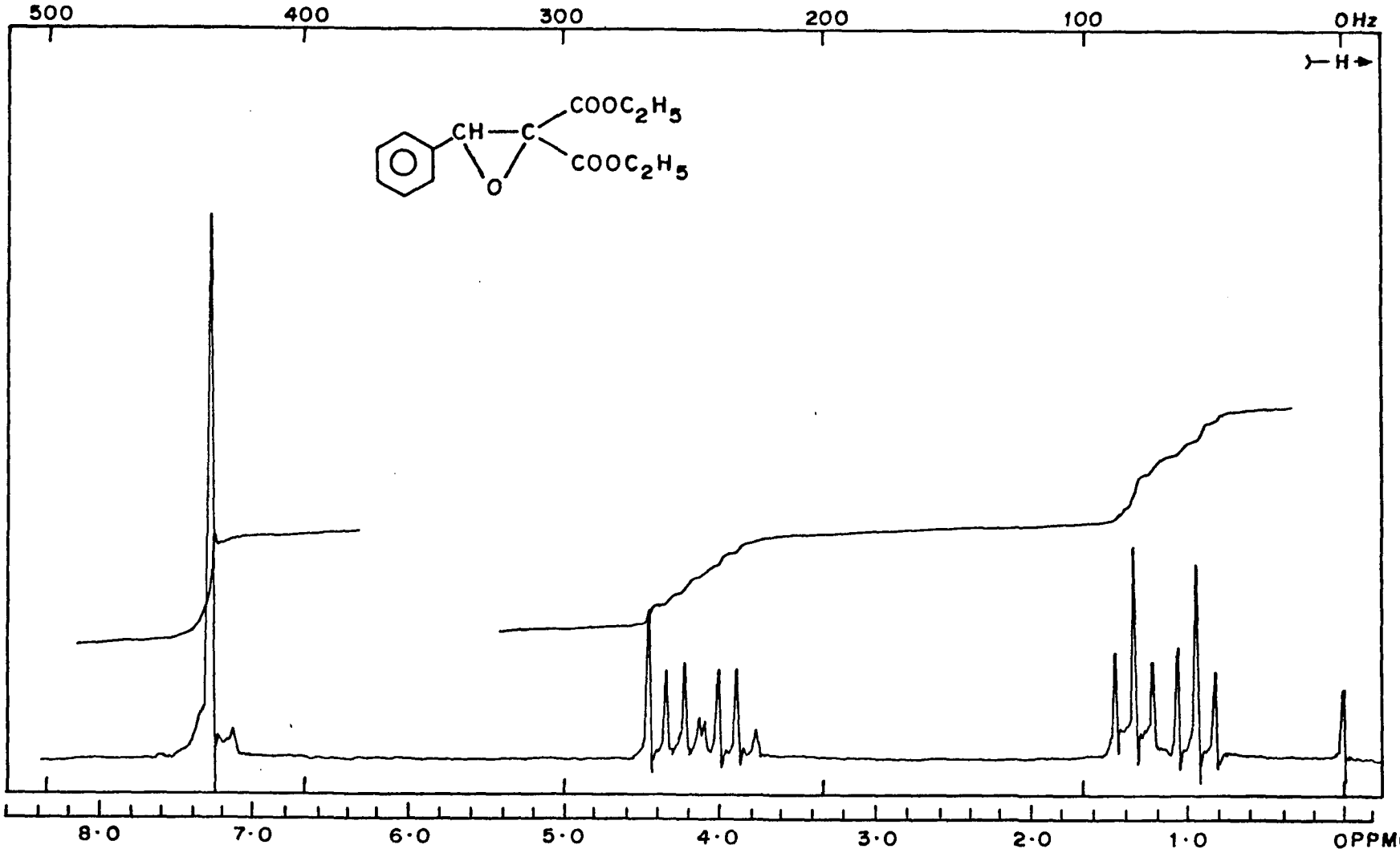
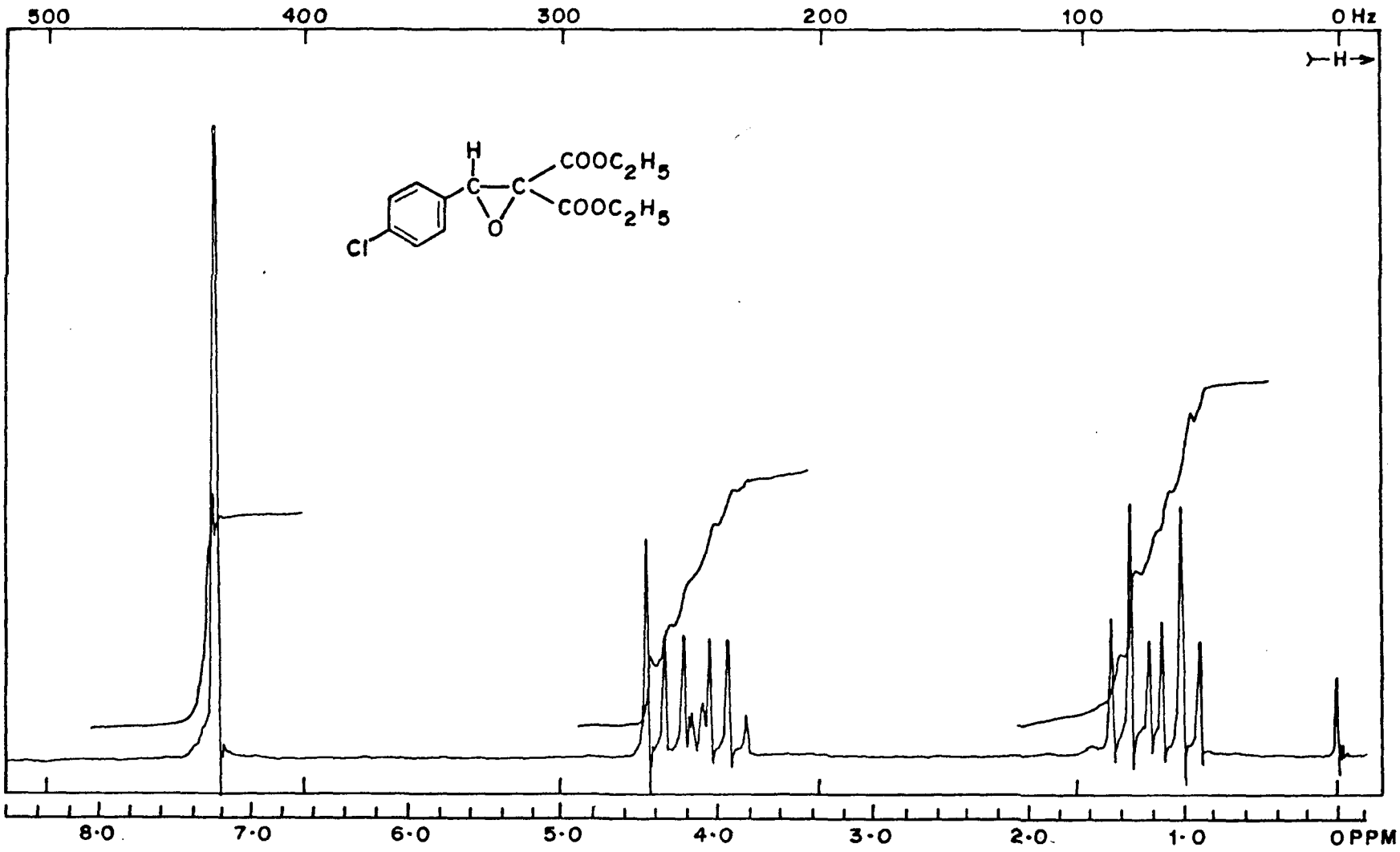
4.8 FIGURES



FIG· 41 PMR SPECTRUM OF ETHYL-2-CARBETHOXY-3-PHENYL-2-PROPENOATE(1a)



FIG· 42 PMR SPECTRUM OF ETHYL-1-CARBETHOXY-2-PHENYL-OXIRANE CARBOXYLATE (I)



FIG· 43 PMR SPECTRUM OF ETHYL-1-CARBETHOXY-2-(4-CHLOROPHENYL)-OXIRANE CARBOXYLATE (5)

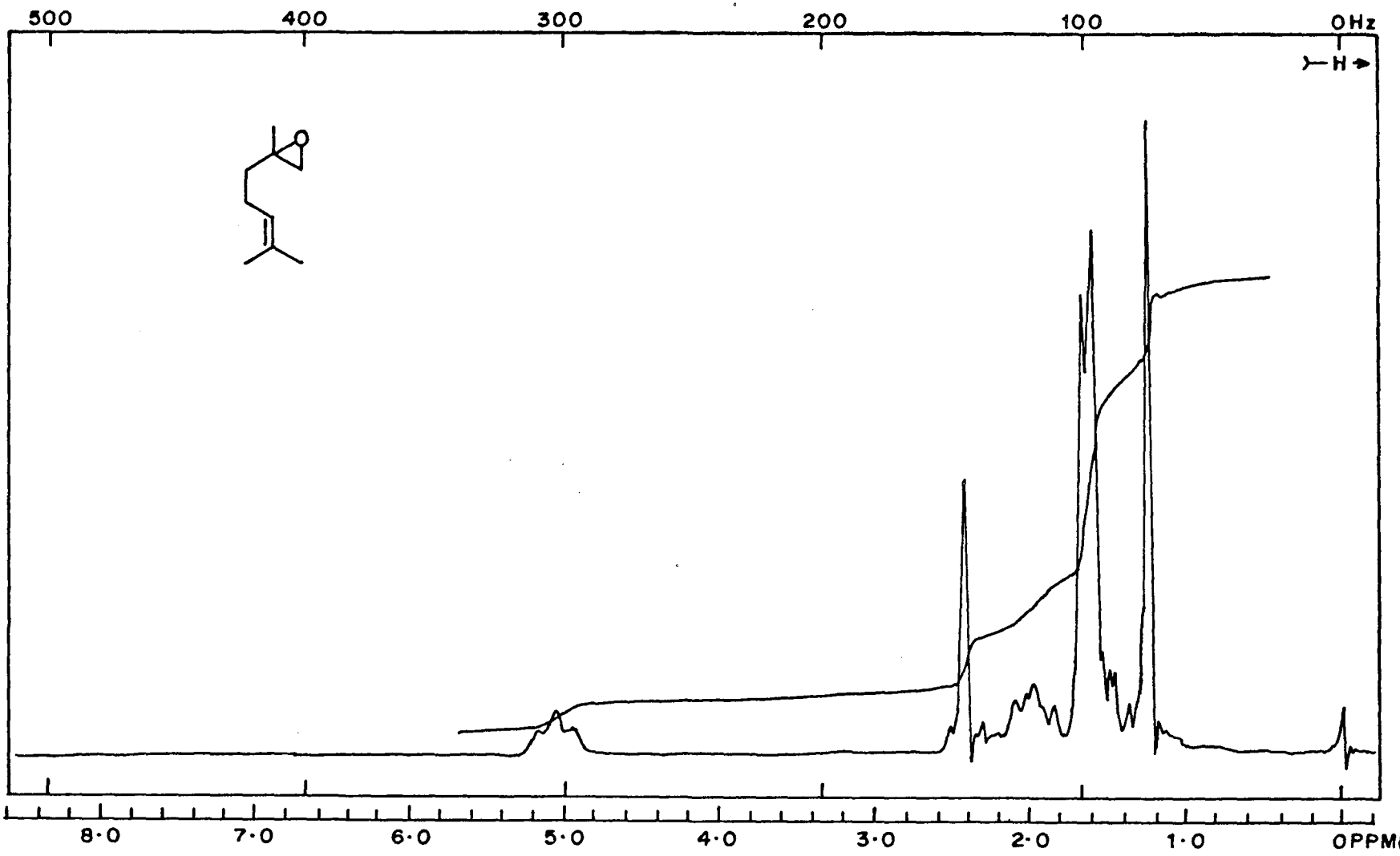


FIG. 44 PMR SPECTRUM OF 2-METHYL-2-(3-PENTENYL-4-METHYL)-OXIRANE(23)

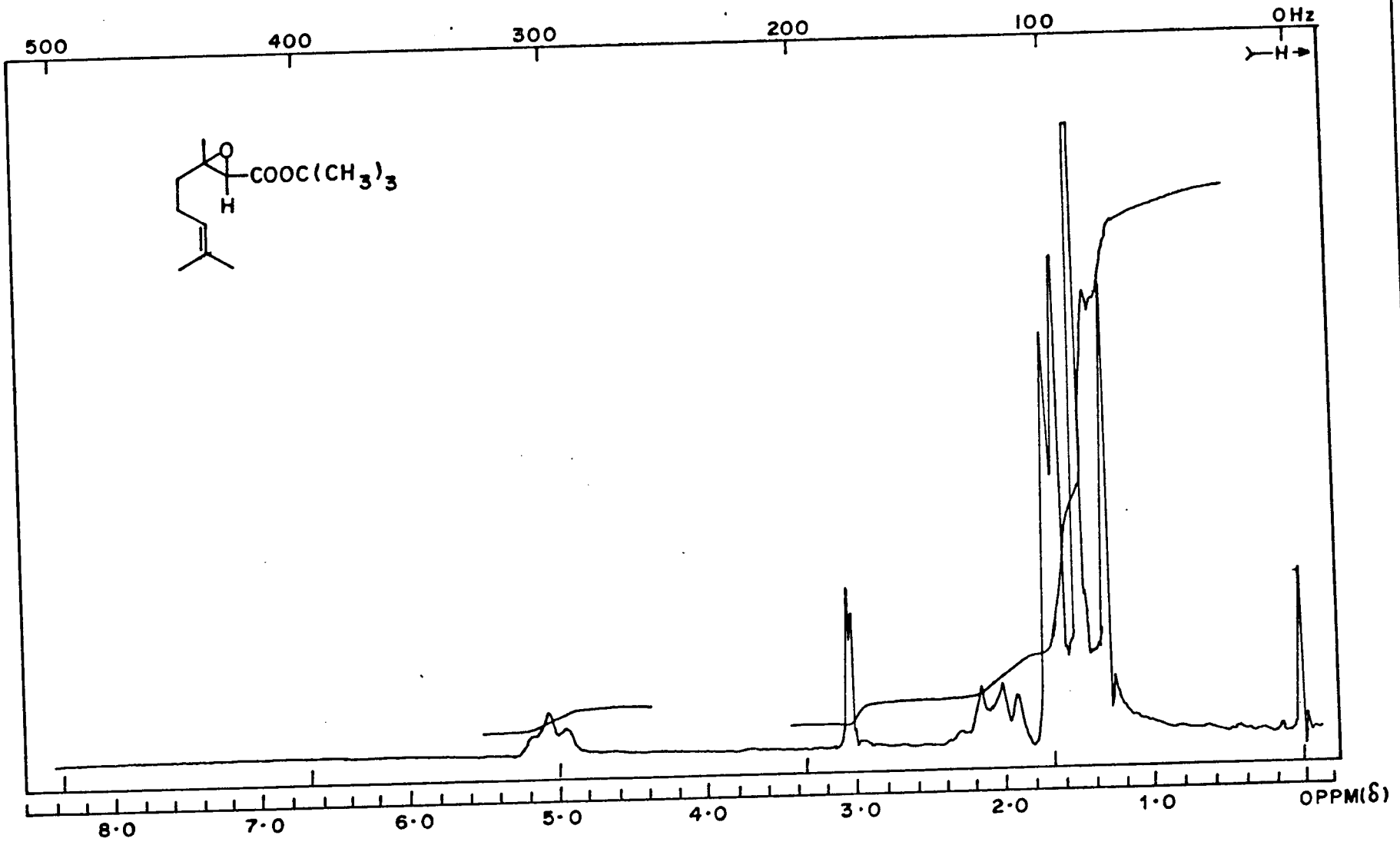


FIG. 45 PMR SPECTRUM OF 2-METHYL-2-(4 METHYL-3-PENTENYL)-3-(t-BUTYLOXY CARBONYL)-OXIRANE(25)

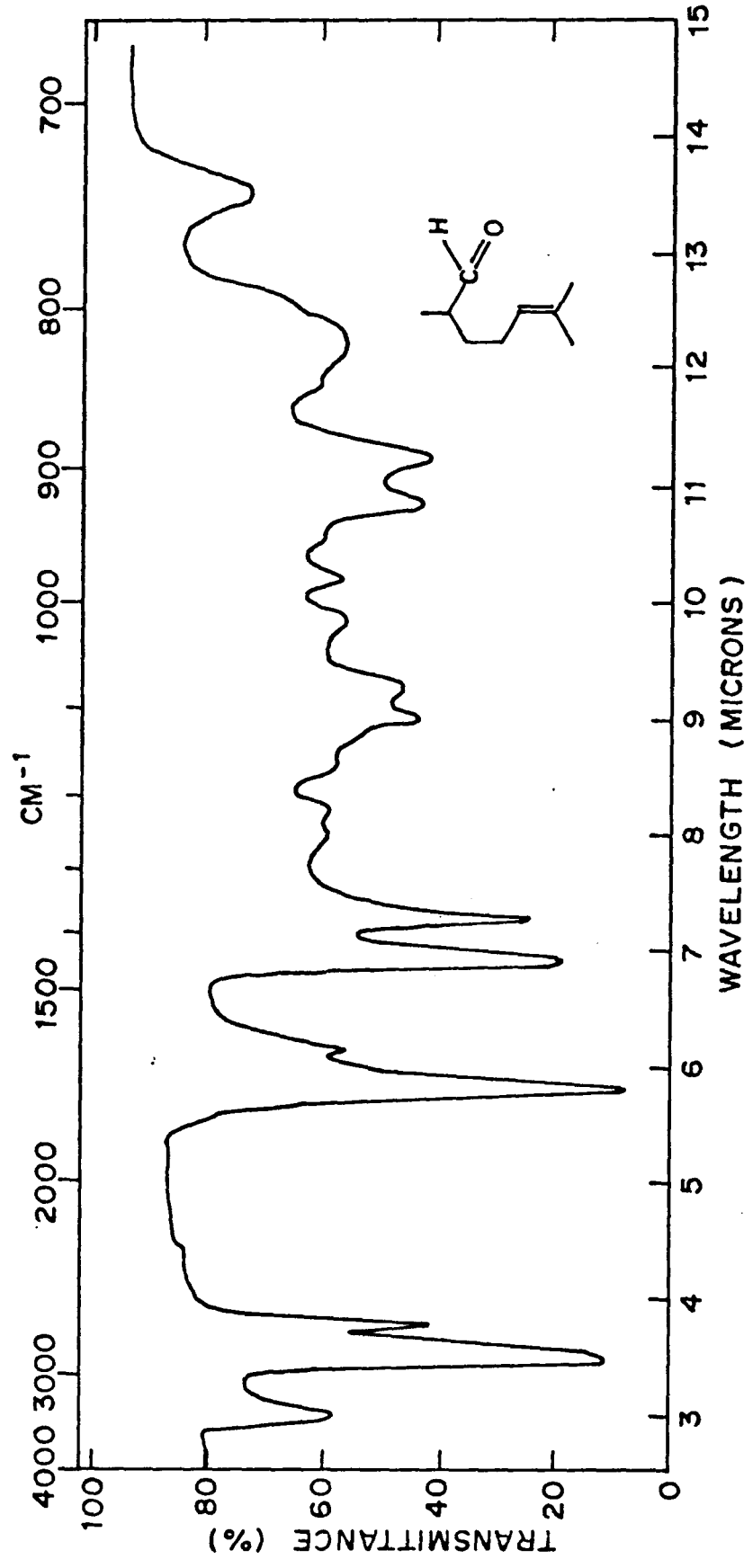
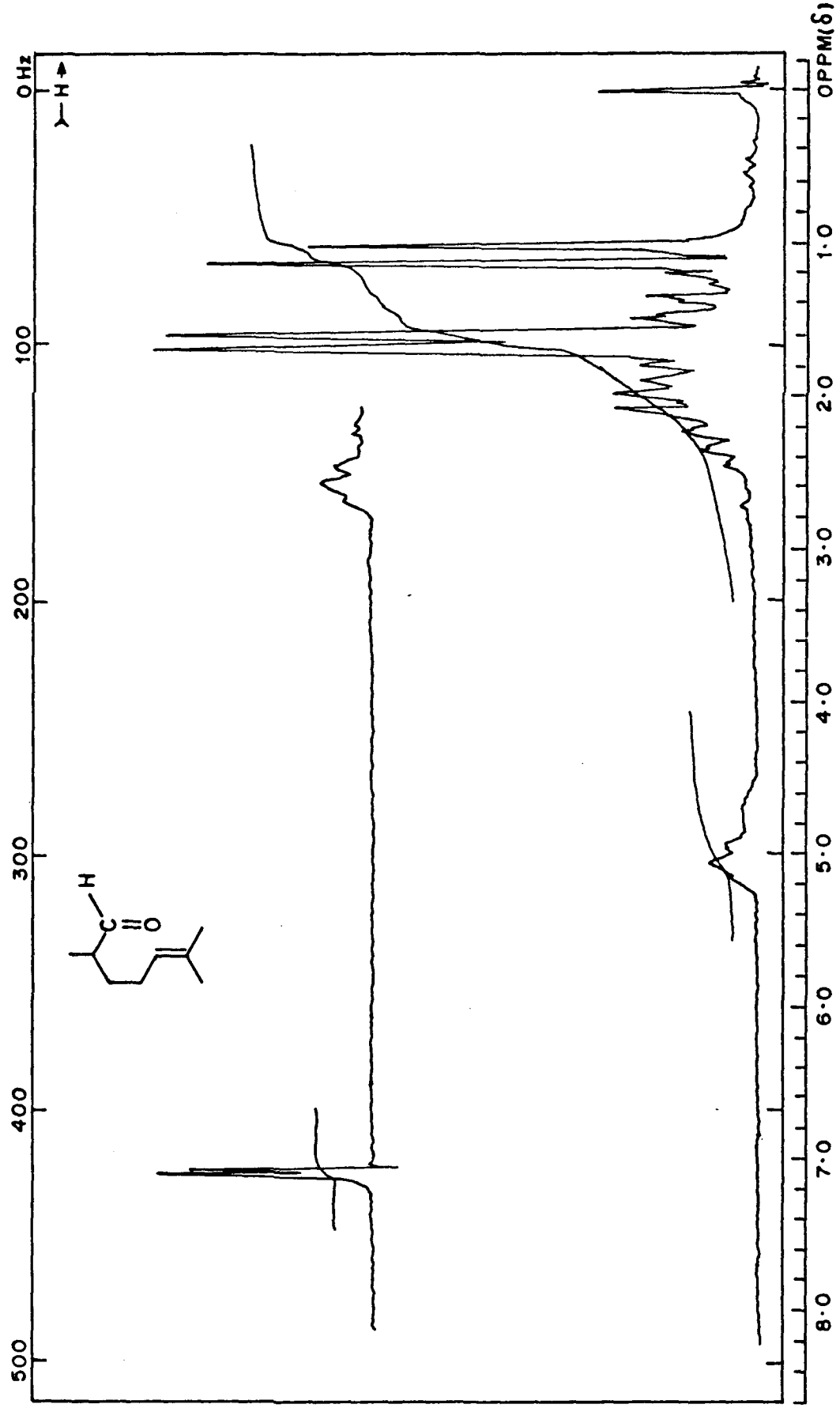


FIG.46 IR SPECTRUM OF 2,6 DIMETHYL-HEPT-5-EN-1-AL(26)



FIG·47 PMR SPECTRUM OF 2,6 DIMETHYL-HEPT-5-EN-1-AL(26)

APPENDIX

List of Publications

1. Epoxidation of diethyl arylidene and alkylidene malonates: A convenient route for the preparation of α-keto acids, B.D. Kulkarni and A.S. RaO, Indian Journal of Chemistry, 13, No. 10, 1097 (1975).

2. Action of Lead (IV) Acetate on sodium glycidates; a convenient route for the preparation of α-acetoxy-aldehydes, B.D. Kulkarni and A.S. RaO, Synthesis, No. 7, 454 (1976).

3. Synthesis of 2-(2'methoxy-4'-methylphenyl) prop-1-ene, 2-(2'-hydroxy-4'-methylphenyl)prop-2-en-1-ol diisobutyrate and 2-hydroxymethyl-2-(2'-hydroxy-4'-methylphenyl)-oxirane diisobutyrate, K.J. Divakar, B.D. Kulkarni and A.S. RaO, Indian Journal of Chemistry, 15B, 322 (1977).

4. Synthesis of 2,3-dihydro-2-hydroxy-3-methylene-6-methyl benzofuran, K.J. Divakar, B.D. Kulkarni, and A.S. RaO (Accepted for publication in Indian Journal of Chemistry)

5. Action of alkali on 4-methylcoumarins; A convenient route for preparation of some o-isopropenyl-phenols, V.V. Dhekne, B.D. Kulkarni, and A.S. RaO (sent for publication in Indian Journal of Chemistry).