SYNTHETIC STUDIES IN PHEROMONES, SECO-PYRETHROIDS AND RELATED COMPOUNDS

A THESIS

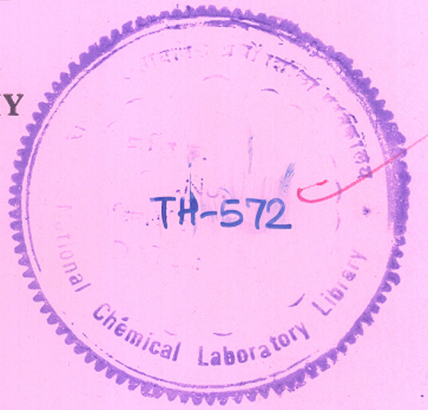
SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

[IN CHEMISTRY]



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Dedicated To

My Loving Brother

A C K N O W L E D G E M E N T

It is a matter of great pleasure and pride for me to thank Dr.G.H.Kulkarni, Scientist, National Chemical Laboratory, Pune, for suggesting my research programme, his valuable guidance and constant encouragement throughout the course of this investigation.

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(S.V. Kelkar)

C O N T E N T S

GENERAL REMARKS

1. All melting points and boiling points are uncorrected. In case of boiling points these refer to bath temperatures.

2. The infrared spectra of liquids were recorded as liquid films and that of solids as nujol mull on a Perkin-Elmer infrared spectrophotometer model 137-B, and Perkin-Elmer infrared spectrophotometer model 599-B using sodium chloride optics. Infrared bands are expressed in cm^{-1}.

3. The PMR spectra were taken on Varian T-60 MHz spectrometer (in CCl_4 solution), on Varian FT-80 MHz spectrometer (in $CDCl_3$ solution) and/or Brucker WH-90 MHz spectrometer (in $CDCl_3$ solution) and the chemical shifts are measured in units.

4. In the description of PMR signals the abbreviations dist. br s, br m, s, d, t, q, m, dd mean distorted, broad singlet, broad multiplet, singlet, doublet, triplet, quartet, multiplet, double doublet respectively.

5. Mass spectra were recorded on a CEC-21-110B mass spectrometer.

6. TLC analysis was carried out on glass plates coated with a mixture of silica gel (200 mesh) and plaster of paris (85:15). The plates were developed by keeping in an iodine chamber or by spraying with H_2SO_4.

7. Numbers given to charts, figures and structures in each chapter of the thesis refer to that particular chapter only.

8. References pertaining to each chapter are given at the end of that particular chapter.

CHAPTER-I

A NEW APPROACH TO THE SYNTHESIS OF (Z)-5-DODECENYL AND (Z)-5-TETRADECENYL ACETATES: PHEROMONE COMPONENTS OF LEPIDOPTERA NOCTUIDAE SPECIES

GENERAL INTRODUCTION

Man has been unable to develop a stable system of agriculture for the expanding world population. This is partly due to the fierce competition of insects for his food and fibre. Insects are constant source of depredation to humans. They devour plants, spread diseases and are generally a great nuisance to man.

Application of insecticides is still the most generally used approach for controlling insects and other invertibrate pests. These substances have often provided very effective control. Unfortunately the solution has often been only short term and side effects have sometimes been worse than the original problem. These insecticides are not only harmful to humans but many are very persistent in environment[1]. They show low selectivity to insects and kill harmless and useful insects like honey-bees and predators. Therefore, several other longterm approaches, which are more selective and environmentally acceptable to combat the insect pest have been suggested by many research groups all over the world[2-12]. One of the important approaches depends on an understanding of how insects use chemicals to communicate.

The interdisciplinary invesigation of insect kingdom by biologists and chemists has established the importance and complexity of chemosensory communication among insects. Many facets of insect behaviour have been shown to be regulated by chemical stimuli[13-22]. There is potential to utilize this information to combat insects in ways that are highly selective and environmentally acceptable. The role of chemicals used for communication

of insects and other animals is summarised in flow* sheet[23]. This form of communication includes attraction between two sexes for mating, alerting members of a colony for the purpose of defence, the use of defensive secretions to flight off predators, territorial marking and trail-marking to assist in gathering food for colony. Natural insect attractants fall broadly into two categories (i) secretions of insect origin, which produce responses for mating, aggregation, particularly amongst beetles (coleoptera) and foraging with a single species (ii) volatile constituents of plant and animal hosts, utilized by insects, in searching for food and egg laying sites.

The substances which are used for communication between different species are called allelochemics. These include defensive secretions and repellents formed from the toxic substances. Pheromones are the chemicals used for communication between the same species.

The term pheromone[24] is derived from the Greek word pherein - 'to transfer' and harmon- 'to excite'. Pheromones are defined as substances that are secreted outside by an insect and received by the other insect of the same species, as a means of intra-specific communication.

Pheromones are classified into two distinct types by Wilson[25] according to the response they elicit. First category are called 'releaser' pheromones. They trigger a behavioural response almost immediately. Second category are called 'primer' pheromones. They cause no simple behavioural effects but cause an enduring physiological response, usually by influencing harmonal activity.

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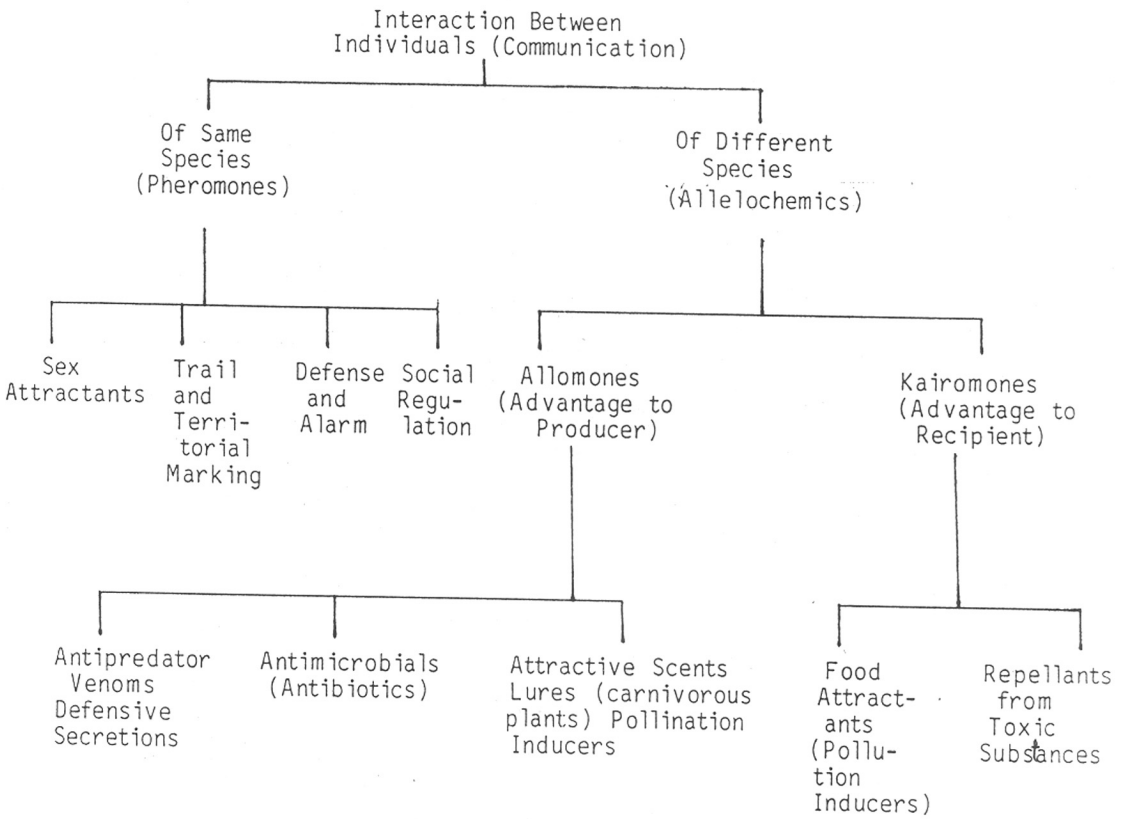
FLOW SHEET OF THE ROLE OF CHEMICALS USED FOR COMMUNICATION IN INSECTS AND OTHER ANIMALS



A variety of chemicals have been identified as pheromones by screening as attractive to one sex, but until these compounds are isolated and identified from the opposite sex, they are termed as 'para-pheromones'. The response may be due to an individual chemical or as often the case, a mixture of chemicals, where total mixture acts as the pheromone. In such cases the total effect is greater than the sum of the effects of individual components. This phenomenon is termed as synergism.

Pheromones as insect controlling agents

Importance of biological pest control is currently undergoing experimental evaluation. During the past two decades, intense research has been going on in using insect attractants (pheromones) for pest control. Several research groups have reported the successful use of insect pheromones[7-12]. The pheromones tend to be used in three ways in crop protection,

1. for monitoring an insect population to see if it exceeds an economic threshold, when damage of crops becomes significant.
2. for mating disruption, where a male insect may be led to believe that a female is nearby, when actually there is none. This avoids breeding.
3. to attract lure and kill, where a small amount of insecticide is placed in very close proximity to the lure.

These methods of pest control have considerable advantages over the use of conventional insecticides. Relatively small amount of synthetic attractant required, minimizes the possibility of environmental pollution and the species specificity of the natural attractants reduces the risk

of destroying beneficial insects such as predators, parasites and pollinators. The most general application of pheromones probably lies, in integrated pest control measures as population survey tools, to probe the degree of infestation. Limited application of chemical pesticides could then suffice in areas of intolerable infestation.

Synthetic studies in pheromones

Synthetic approach is very important in pheromone research because of the limited availability of natural pheromones from insects. Synthetic work in pheromones may be classified into three categories.

1. Synthesis as the final proof of the proposed structure including olefin geometry and relative as well as absolute stereochemistry.
2. Syntheses that provide sufficient material for biological study, such as field tests.
3. Syntheses of a number of isomers and analogues to clarify the structure -activity relationship.

Synthesis thus ensures ample supplies and facilitates the practical use in agriculture and forestry.

Because of the importance of synthetic pheromones, a number of organic chemists from well known groups throughout the world have become involved in this area of research. A large number of papers have been published on pheromones, some of which include synthesis and their applications in agriculture and forestry. A number of reviews are available on chemical aspects of pheromones. Rossi[22] has reviewed the synthesis of both achiral and chiral pheromones. Henrick[26] has discussed lepidoptera, coleoptera and diptera pheromones in depth. In 1981 Mori[27] reviewed comprehensively

on 'the synthesis of insect pheromones' in which he has described the syntheses of as many as ninety six pheromones. Katzenellenbogen's[28] review has focussed on the methodological point of view.

Besides references 29-33 mentioned, some reviews[34-36] are also available on pheromone biology and their applications.

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SUMMARY

The synthesis of (Z)-5-dodecenyl and (Z)-5-tetradecenyl acetates has been described in this chapter.

C-Alkylation of the dianion of 4-pentyn-1-ol using n-hexyl bromide and n-octyl bromide yielded respectively the corresponding acetylenic alcohols **(18)** and **(19)**. Scheme (IV).

Controlled and selective hydrogenation of **(18)** and **(19)** using Lindlar catalyst afforded the Z isomers of the olefinic alcohols.

The olefinic alcohols were converted to the corresponding bromides via the corresponding mesylates by treating the latter with LiBr in acetone.

The bromides were then converted to the corresponding cyanides by treating them with sodium cyanide in DMSO. The nitriles were then hydrolysed to the corresponding carboxylic acids, identified and characterised through their methyl esters.

LAH reduction of the methyl esters afforded the primary alcohols which were then acetylated to furnish the title pheromones.

INTRODUCTION

The compound (Z)-5-dodecenyl acetate **(1)** is the active sex pheromone component of Euxoa Ochrogaster[1] (Lepidoptera Noctuidae) males, Euxoa drewsani[2], cossus cossus[3] and Loxagrotis Albicosta[4]. (Z)-5-Tetradecenyl acetate **(2)** has been identified as one of the main components of sex pheromone of Agrotis exclamationis[5] (Lepidoptera Noctuidae) and oak leaf roller month[6].

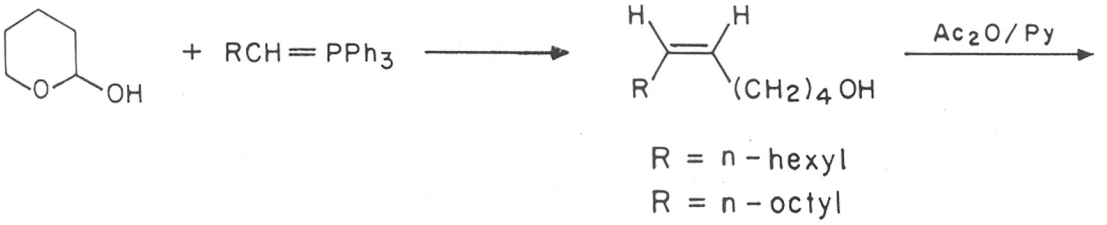
The acetates **(1)** and **(2)** have also been isolated from the absolute oil of Hibiscus abelmoschus[7].

Some of the reported syntheses for compounds **(1)** and **(2)** are briefed here.

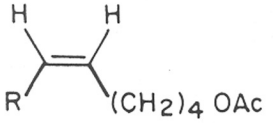
B. Maurer and A. Grieder[7] have synthesised the acetates **(1)** and **(2)** stereoselectively (Scheme I), involving the Wittig reaction between tetrahydropyran-2-ol and an alkylidenetriphenylphosphorane in the key step.

In the method developed by Testsu et al.[8] one of the synthons used is prepared from 1,4-dihydroxy butane **(3)**. Partial bromination of **(3)** gave 1-bromo 4-hydroxy butane which was converted to the tetrahydropyrenyl ether **(4)**. This was then reacted with lithium acetylide in the form of ethylene diamine complex in DMSO to yield the tetrahydropyrenyl ether **(5)**. The alkyne **(5)** was then coupled with n-hexyl and n-octyl halides respectively in THF-HMPT to give the key intermediate **(6)**. Reduction of **(6)** by lithium-ethylamine affords the E isomer of the monoene, while catalytic hydrogenation using Lindlar catalyst ($Pd\text{-}BaCO_3$, poisoned with

SCHEME (I)

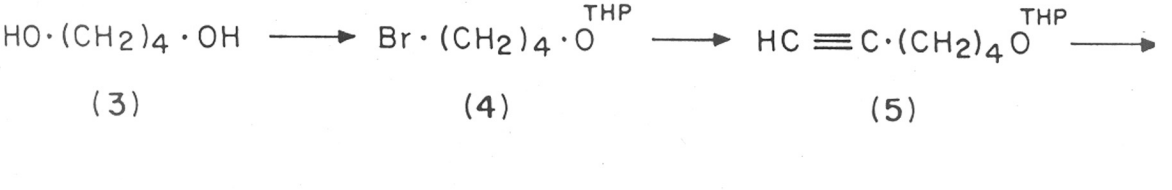


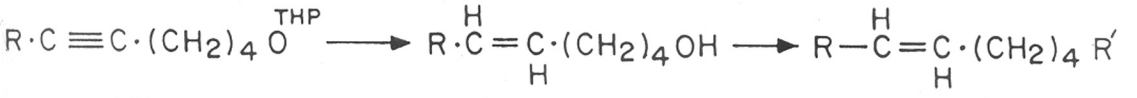
R = n-hexyl
R = n-octyl



(1) R = n-hexyl
(2) R = n-octyl

SCHEME (II)





R = n-hexyl
R = n-octyl

(1) R = n-hexyl, R′ = OAc
(2) R = n-octyl, R′ = OAc

quinoline) gave stereoselectively the corresponding Z isomer. The desired alcohols were then obtained from **(6)** by hydrolytic cleavage of the pyrenyl group with PTSA. Acetylation of the alcohols using Ac_2O/pyridine gave the acetates **(1)** and **(2)** respectively. (Scheme II).

H.J. Bestman et al.[9] have reported the synthesis of (Z)-5-tetradecenyl acetate **(2)** (Scheme III).

Reaction of triphenylphosphine with 4-pentenyl bromide **(7)** afforded 4-pentenyl phophonium bromide which on treatment with base **(8)** afforded the Wittig reagent **(9)**. Stereoselective reaction of **(9)** with nonanal **(10)** at -78° afforded 1(Z), 5(Z) tetradecadiene **(11)**. The latter on hydroboration using 9 BBN followed by oxidation afforded (Z)-5-tetradecen-1-ol, which on acetylation gave in 76% yield, the acetate **(2)**.

In a recent synthesis by A.A. Botar et al.[10] bisdecynyl mercury **(12)** was reacted with lithium in diglyme at 90-110° and after transmetalation was treated with tetrahydropyran or 4-bromo-butane-1-ol tert. Bu-ether **(13)** to give after heating for 2 hr. at 110°, 5-dodecyn-1-ol tert. Bu-ether **(14)**. The latter was then acetylated by a mixture of AcOH, AcCl (10:1) for 48 hr. to afford 5-dodecyn-1-yl acetate **(15)**. Catalytic stereoselective hydrogenation using NiP2 catalyst [prepared from $Ni(OAc)_2$], $NaBH_4$ in EtOH gave (Z)-5-dodecenyl acetate **(1)**. (Scheme IV).

(Z)-5-Tetradecenyl acetate **(2)** was prepared[11] by an analogous sequence of reactions.

SCHEME (III)

$$Br(CH_2)_3CH=CH_2 \xrightarrow[(b)\ NaN[Si(CH_3)_3]_2\ (8)]{(a)\ Ph_3P} Ph_3\overset{+}{P}-\overset{-}{C}H(CH_2)_2CH=CH_2$$

(7) (9)

$$(9) + CH_3(CH_2)_7CH=O \xrightarrow{-78^\circ} CH_3(CH_2)_7\overset{H}{C}=\overset{H}{C}(CH_2)_2CH=CH_2$$

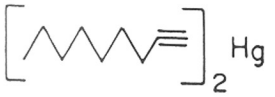
(10) (11)

$$\xrightarrow[(b)\ H_2O_2/\bar{O}H]{(a)\ 9\text{-BBN}} CH_3(CH_2)_7\overset{H}{C}=\overset{H}{C}(CH_2)_4OH \xrightarrow{Ac_2O/Py}$$

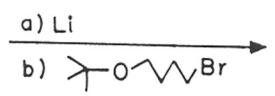
$$CH_3(CH_2)_7\overset{H}{C}=\overset{H}{C}(CH_2)_4OCOCH_3$$

(2)

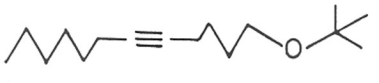
SCHEME (IV)



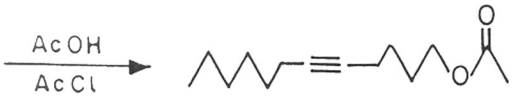
(12)



(13)



(14)



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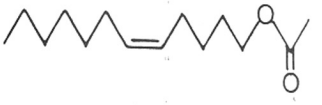


(1)

PRESENT WORK

The present work deals with an alternate simple high yield route for the synthesis of (Z)-5-dodecenyl acetate **(1)** and (Z)-5-tetradecenyl acetate **(2)**. The salient features of the molecules **(1)** and **(2)** are the presence of acetate and cis double bond functionalities.

The attractancy of the majority of the pheromones, particularly belonging to the order Lepidoptera (moths and butterflies species) is associated with the functional moieties (acetate, alcohol or aldehyde), the double bonds (position, number and the configuration E or Z) or the length of the carbon chain.

A simple, facile, high yield synthetic route for the pheromone components **(1)** and **(2)** via the dianion **(17)** of 4-pentyn-1-ol is described here (Scheme V).

Alkylation of dianion of 4-pentyn-1-ol **(17)** prepared in situ from tetrahydrofurfuryl chloride **(16)** and lithium amide in liquid ammonia, with n-hexyl bromide as per the reported procedure[12], afforded the expected 4-undecyn-1-ol **(18)**.

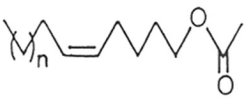
IR: 3320(-OH) cm^{-1}.

PMR: 0.88 (3H, dist. t, C_{11} methyl), 1.1-1.8 (10H, m, C_2,C_7,C_8, C_9 and C_{10} methylenes), 1.65 (1H, s, D_2O exchangeable, -OH proton), 2.0-2.3 (4H, m, C_3 and C_6 methylenes),3.7(2H,t, J=6 Hz, C_1 methylene).

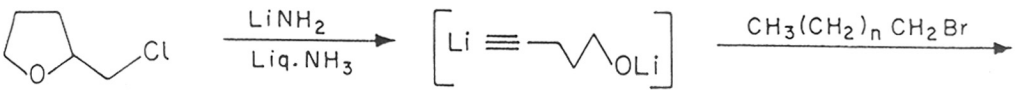
Catalytic controlled hydrogenation of **(18)** using Lindlar catalyst[13] gave the (Z)-4-undecene-1-ol **(20)**.

IR: 3340 (-OH) cm^{-1}.

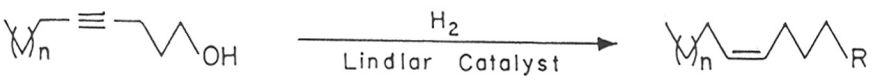
SCHEME (V)



(1) n = 4 (2) n = 6



(16) (17)



(18) n = 4
(19) n = 6

(20) to (31)

(20) n = 4 , R = OH

(21) n = 6 , R = OH

(22) n = 4 , R = O–S(=O)(=O)–CH3

(23) n = 6 , R = O–S(=O)(=O)–CH3

(24) n = 4 , R = Br

(25) n = 6 , R = Br

(26) n = 4 , R = CN

(27) n = 6 , R = CN

(28) n = 4 , R = $COOCH_3$

(29) n = 6 , R = $COOCH_3$

(30) n = 4 , R = CH_2OH

(31) n = 6 , R = CH_2OH

PMR: 0.88 (3H, dist t, C_{11} methyl), 1.1-1.8 (10H, m, C_2,C_7,C_8,C_9 and C_{10} methylenes), 1.45 (1H, s, D_2O exchangeable, -OH proton), 1.8-2.25 (4H, m, C_4 and C_7 allylic methylenes), 3.6 (2H, t, J=6 Hz, C_1 methylene), 5.2-5.45 (2H, m, C_4 and C_5 olefinic protons).

The olefinic alcohol **(20)** was converted to its mesylate **(22)** by reacting it with mesyl chloride in presence of triethylamine.

IR: 1360, 1180($-OSO_2CH_3$) cm^{-1}.

PMR: 0.89 (3H, dist t, C_{11} methyl), 1.3 (8H, br s, C_7, C_8, C_9, C_{10} methylenes), 1.56-2.4 (6H, m, C_2, C_3, C_6 methylenes), 2.9 (3H, s, mesyl methyl), 4.1 (2H, t, J=6 Hz, C_1 methylene), 5.1-5.5 (2H, m, C_4 and C_5 olefinic protons).

The mestylate **(22)** upon treatment with LiBr in acetone afforded the bromide **(24)**.

PMR: 0.88 (3H, dist. t, C_{11} methyl), 1.1-1.53 (10H, br m, C_2,C_7,C_8, C_9, C_{10} methylenes), 1.73-2.43 (4H, m, C_3, C_6 allylic methylenes), 3.36 (2H, t, J=6 Hz, C_2 methylene), 5.1-5.67 (2H, m, C_4, C_5 olefinic protons).

Conversion of the bromide **(24)** to cyano **(26)** was done by reacting the former with sodium cyanide in DMSO.

IR: 2240 ($-C\equiv N$) cm^{-1}.

PMR: 0.88 (3H, dist t, C_{12} methyl), 1.0-1.45 (8H, br s, C_8,C_9,C_{10}, C_{11} methylenes), 1.55-2.4 (8H, m, C_2,C_3,C_4,C_7 methylenes), 5.0-5.6 (2H, m, C_5, C_6 olefinic protons).

The cyano compound **(26)** was hydrolysed using KOH in ethylene glycol at reflux temperature to obtain the corresponding acid. Methyl ester (28) of the acid was obtained by reaction with diazomethane.

IR: 1745 (ester carbonyl) cm^{-1}.

PMR: 0.88 (3H, dist. t, C_{12} methyl), 1.15-1.45 (8H, br s, C_8,C_9,C_{10}, C_{11} methylenes), 1.45-2.4 (8H, m, C_2, C_3, C_4, C_7 methylenes), 3.6 (3H, s, ester methyl), 5.18-5.4 (2H, m, C_5 and C_6 olefinic protons).

The methyl ester **(28)** was reduced by LAH to alcohol **(30)**.

IR: 3340 (-OH) cm^{-1}.

PMR: 0.88 (3H, dist. t, C_{12} methyl), 1.11-1.80 (12H, br m, C_2, C_3, C_8, C_9, C_{10}, C_{11} methylenes), 1.44 (1H, s, D_2O exchangeable, OH proton), 1.84-2.42 (4H, m, C_4, C_7 allylic methylenes), 3.66 (2H, t, J=6 Hz, C_1 methylene), 5.20-5.60 (2H, m, C_5, C_6 olefinic protons).

Acetylation of the alcohol **(30)** using acetic anhydride and dry pyridine gave the pheromone (Z)-5-dodecenyl acetate **(1)**.

IR: 1740 (acetate carbonyl) cm^{-1}.

PMR: 0.88 (3H, dist t, C_{12} methyl), 1.13-1.86 (12H, br m, C_2, C_3, C_8, C_9, C_{10}, C_{11} methylenes), 2.04 (7H, singlet overlapping multiplet, acetate methyl, C_4 and C_7 allylic methylenes), 4.06 (2H, t, J=6Hz, C_1 methylene), 5.17-5.58 (2H, m, C_5, C_6 olefinic protons).

4-Tridecyn-1-ol **(19)** was similarly obtained by alkylation of **(17)** with n-octyl bromide as per the reported procedure[12].

IR: 3340 (-OH) cm^{-1}.

PMR: 0.88 (3H, dist t, C_{13} methyl), 1.3 (12H, br s, C_7 to C_{12} methylenes), 1.6-1.85 (2H, m, C_2 methylene), 1.65 (1H, s, D_2O exchangeable, OH proton), 1.95-2.3 (4H, m, C_3, C_6 methylenes), 3.7 (2H, t, J=6 Hz, C_1 methylene).

Acetylenic alcohol **(19)** was hydrogenated partially using Lindlar catalyst[13] to obtain the Z isomer of the olefinic alcohol **(21)**.

IR: 3320 (-OH) cm^{-1}.

PMR: 0.88 (3H dist t, C_{13} methyl), 1.13-1.80 (14H, br m, C_2, C_7 to C_{12} methylenes), 1.53 (1H, s, D_2O exchangeable, OH proton), 1.86-2.42 (4H, m, C_3, C_6 allylic methylenes), 3.67 (2H, t, J=6 Hz, C_1 methylene), 5.20-5.62 (2H, m, C_4, C_5 olefinic protons).

The olefinic alcohol **(21)** was converted to its mesylate **(23)** by reacting it with mesyl chloride in presence of triethylamine in methylene chloride solvent.

IR: 1360, 1180 ($-OSO_2CH_3$) cm^{-1}.

PMR: 0.88 (3H, dist t, C_{13} methyl), 1.28 (12H, br s, C_7-C_{12} methylenes), 1.53-2.3 (6H, m, C_2,C_3,C_6 methylenes), 3.02 (3H, s, mesyl methyl), 4.24 (2H, t, J=6Hz, C_1 methylene), 5.17-5.64 (2H, m, C_4, C_5 olefinic protons).

The mesylate **(23)** was treated with LiBr in acetone to get the bromide **(25)**.

PMR: 0.88 (3H, dist t, C_{13} methyl), 1.2 (12H, br s, C_7-C_{12} methylenes), 1.65-2.35 (6H, m, C_2, C_3, C_6 methylenes), 3.35 (2H, t, J=6 Hz, C_1 methylene), 5.05-5.55 (2H, m, C_4, C_5 olefinic protons).

The bromide **(25)** was reacted with sodium cyanide in DMSO to get the cyano compound **(27)**.

IR: 2235 ($-C\equiv N$) cm^{-1}.

PMR: 0.88 (3H, dist t, C_{14} methyl), 1.24 (12H, br s, C_8-C_{13} methylenes), 1.5-2.55 (8H, m, C_2,C_3,C_4,C_7 methylenes), 5.0-5.6 (2H, m, C_5, C_6 olefinic protons).

The cyano compound **(27)** was refluxed in ethylene glycol with KOH, to hydrolyse it to an acid. The acid was esterified by diazomethane to get the methyl ester **(29)**.

IR: 1740 (ester carbonyl) cm^{-1}.

PMR: 0.88 (3H, dist. t, C_{14} methyl), 1.25 (12H, br. s, C_8-C_{13} methylenes), 1.5-2.4 (8H, m, C_2, C_3, C_4 and C_7 methylenes), 3.6 (3H, s, ester methyl), 5.05-5.5 (2H, m, C_5, C_6 olefinic protons).

Methyl ester **(29)** was reduced to alcohol **(31)** using LAH.

IR: 3340 (-OH) cm^{-1}.

PMR: 0.88 (3H, dist. t, C_{14} methyl), 1.1 - 1.7 (16H, m, C_2, C_3, C_8-C_{13} methylenes), 1.4 (1H, s, D_2O exchangeable, -OH proton), 1.8-2.2 (4H, m, C_4 and C_7 methylenes), 3.6 (2H, t, J=6 Hz, C_1 methylene), 5.05-5.55 (2H, m, C_5, C_6 olefinic protons).

Acetylation of **(31)** using acetic anhydride and dry pyridine gave (Z)-5-tetradecenyl acetate **(2)**.

IR: 1740 (acetate carbonyl) cm^{-1}.

PMR: 0.88 (3H, dist t, C_{14} methyl), 1.05-1.75 (16H, br m, C_2, C_3, C_8-C_{13} methylenes), 2.0 (7H, singlet overlapping a multiplet, acetate methyl and C_4, C_7 methylenes), 4.0 (2H, t, J=6 Hz, C_1 methylene), 5.16-5.4 (2H, m, C_5, C_6 olefinic protons).

EXPERIMENTAL

4-Undecyn-1-ol (18) and 4-tridecyn-1-ol (19)

Lithium (1.05 g; 0.15 g atom) in presence of ferric nitrate (50 mg) was dissolved in freshly distilled ammonia (250 ml) which is indicated by disappearance of blue colour. To this freshly prepared lithium amide solution was added tetrahydrofurfuryl chloride (6 g; 0.05 mole) during 10 min and was stirred for 2 hr. at -33°C. After all the tetrahydrofurfuryl chloride had reacted (by tlc), n-hexyl bromide (8.25 g; 0.05 mole) dissolved in tetrahydrofuran (10 ml) was added dropwise to the stirred and cooled (-33°) reaction mixture. It was stirred for additional 0.5hr and ammonia was allowed to evaporate by bringing it to room temperature The residue was treated with saturated NH_4Cl solution (100 ml) and extracted with ether (4 x 50 ml). The ether layer was dried and distilled. The alcohol **(18)** was purified by column chromatography over silica gel (eluent-pet.ether + 5% ethyl acetate),(6.72 g; 80%).

IR: 3320 (-OH), 2920, 2840, 1460, 1050, 920, 720 cm^{-1}.

Ms: m/e 168.

Analysis calculated for $C_{11}H_{20}O$ C, 78.51; H, 11.19

Found C, 78.20; H, 11.22%.

4-Tridecyn-1-ol **(19)** was similarly obtained in 82% yield.

IR 3340, 2930, 2860, 1470, 1060, 930, 720 cm^{-1}.

Ms: m/e 196.

Analaysis calculated for $C_{13}H_{24}O$ C, 79.53; H, 12.32

Found C, 79.57; H, 12.28%.

(Z)-4-Undecen-1-ol (20) and (Z)-4-tridecen-1-ol (21)

The compound **(18)** (6.4 g; 0.038 mole) was partially hydrogenated

using Lindlar catalyst (300 mg) in n-hexane (100 ml) containing one drop of quinoline, at atmospheric pressure. After absorption of calculated volume of hydrogen, the reaction mixture was filtered. The residue was washed with n-hexane (100 ml). Filtrate and washings together, were distilled to remove n-hexane. The residue was pure (Z)-4-undecen-1-ol **(20)** (6.37g; 98%).

IR 3340, 2920, 2840, 1460, 1060, 720 cm^{-1}.

Ms: m/e 170.

Analysis calculated for $C_{11}H_{22}O$ C, 77.58; H, 13.02

Found C, 77.50; H, 13.10%.

Similarly (Z)-4-tridecen-1-ol **(21)** was obtained in 97% yield.

IR 3320, 3000, 2910, 2840, 1465, 1050, 715 cm^{-1}. Ms: m/e 198.

Analysis calculated for $C_{13}H_{26}O$ C, 78.72; H, 13.21

Found C, 78.60; H, 13.30%.

1-Mesyl(Z)-4-undecene (22) and 1-mesyl(Z)-4-tridecene (23)

A solution of **(20)** (6.35 g; 0.037 mole) and triethylamine (11.31g; 0.11 mole) in dichloromethane (50 ml) was stirred with methane sulfonyl chloride (5.13 g; 0.044 mole) at 0° for 0.5 hr and then at room temperature for 6 hr. Dichloromethane was distilled and the residue diluted with water, extracted with ether (3 x 50 ml). The ether layer was washed with water, dried and distilled to give the mesylate **(22)**, which was purified by column chromatography over silica gel (eluent-pet.ether) (9.26g; 90%).

IR 2940, 2860, 1470, 1360, 1180, 970, 925, 830, 720 cm^{-1}.

Ms: m/e 248.

Analysis calculated for $C_{12}H_{24}O_3S$ C, 58.04; H, 9.74; S, 12.90

Found C, 58.20; H, 9.80; S, 12.83%.

Similarly compound **(23)** was obtained in 92% yield.

IR 2920, 2840, 1470, 1360, 1180, 970, 930, 830, 720 cm^{-1}.

Ms: m/e 276.

Analysis calculated for $C_{14}H_{28}O_3S$ C, 60.84; H, 10.21; S, 11.60

Found C, 60.60; H, 10.30; S, 11.75%.

1-Bromo(Z)-4-undecene (24) and 1-bromo-(Z)-4-tridecene (25)

Mesylate **(22)** (4.0 g; 0.016 mole) was stirred with lithium bromide (5.6 g; 0.064 mole) in dry acetone (100 ml) for 5 hr. at room temperature. Acetone was distilled, and residue was extracted with ether (4 x 50 ml). The ether layer was washed with water, brine, dried and distilled to afford the bromide **(24)**, which was purified by column chromatography over silica gel (eluent pet.ether) (7.2 g; 96%).

Ms: m/e (^{79}Br)232, (^{81}Br)234.

Analysis calculated for $C_{11}H_{21}Br$ C, 56.65; H, 9.08; Br, 34.26

Found C, 56.30; H, 9.31; Br, 33.92%.

Similarly 1-bromo-4-tridecene **(25)** was obtained in 86% yield.

Ms: m/e (^{79}Br)260, (^{81}Br)262.

Analysis calculated for $C_{13}H_{25}Br$ C, 59.76; H, 9.64; Br, 30.58

Found C, 59.38; H, 9.41; Br, 30.28%.

1-Cyano (Z)-4-undecene (26) and 1-cyano (Z)-4-tridecene (27)

A mixture of compound **(24)** (2.5 g; 0.01 mole) and sodium cyanide (0.735 g; 0.015 mole) in DMSO (15 ml) was stirred overnight at room temperature. The reaction mixture was then diluted with water and extracted with ether (3 x 40 ml). Ether layer was washed with water, brine, dried and distilled. The cyano compound was purified by column chromatography over silica gel (eluent1% ethyl acetate in pet.ether (1.4 g; 73%).

IR 3000, 2930, 2860, 2240, 1450, 710 cm^{-1}.

Ms: m/e 179.

Analysis calculated for $C_{12}H_{21}N$ C, 80.38; H, 11.81; N, 7.81

Found C, 80.00; H, 11.98; N, 8.12%.

Similarly compound **(27)** was obtained in 86% yield.

IR 3000, 2920, 2840, 2235, 1450, 710 cm^{-1}.

Ms: m/e 207.

Analysis calculated for $C_{14}H_{25}N$ C, 81.09; H, 12.15; N, 6.76

Found C, 81.40; H, 12.37; N, 7.10%.

Methyl (Z)-5-dodecenoate (28) and methyl (Z)-5-tetradecenoate (29)

The cyano compound **(26)** (1.4 g; 0.0078 mole) and KOH (1.31 g; 0.023 mole) were refluxed in ethylene glycol for 6 hr. The reaction mixture was diluted with water and extracted with ether (2 x 25 ml) to remove the neutral portion. The aqueous layer was acidified using cold dil. HCl and then extracted with ether (4 x 25 ml). The ether layer was washed with water, brine, dried and distilled to give the acid, which was esterified with an ethereal solution of diazomethane. The pure methyl ester (1.3 g; 93%) was obtained by column chromatography using silica gel (eluent 2% ethyl acetate in pet.ether).

IR 3000, 2920, 2840, 1745, 1440, 1210, 1160, 720 cm^{-1}.

Ms: m/e 212.

Analysis calculated for $C_{13}H_{24}O_2$ C, 73.53; H, 11.39

Found C, 73.19; H, 11.18%.

Similarly, methyl (Z)-5-tetradecenoate **(29)** was obtained in 92% yield.

IR: 2990, 2920, 2840, 1740, 1450, 1430, 1160, 1010, 710 cm^{-1}.

Ms: m/e 240.

Analysis calculated for $C_{15}H_{28}O_2$ C, 74.95; H, 11.94

Found C, 75.10; H, 11.55%.

(Z)-5-Dodecene-1-ol (30) and (Z)-5-tetradecen-1-ol (31)

The solution of methyl ester **(28)** (0.532 g; 0.0025 mole) in dry ether (20 ml) was added dropwise to the suspension of LAH (0.19 g; 0.005 mole) in ether (20 ml) at 0° under stirring. After the addition was completed stirring continued for 3 hr at room temeprature. Excess of LAH was carefully decomposed at 0° by adding cold water. The ether layer was separated and aqueous layer extracted with ether (3 x 20 ml). The combined ether layer was washed with water, brine, dried and distilled. The pure alcohol (0.466 g; 96.6%) was obtained by column chromatography using silica gel (eluent 5% ethyl acetate in pet.ether).

IR 3340, 3320, 2940, 2860, 1460, 1070, 720 cm^{-1}.

Ms: m/e 184.

Analysis calculated for $C_{12}H_{24}O$ C, 78.19; H, 13.13

Found C, 78.54; H, 13.34%.

Similarly (Z)-5-tetradecen-1-ol **(31)** was obtained in 90% yield.

IR 3340, 3000, 2920, 2860, 1470, 1160, 1060, 725 cm^{-1}.

Ms: m/e 212.

Analysis calculated for $C_{14}H_{28}O$ C, 79.18; H, 13.29

Found C, 78.82; H, 13.47%.

(Z)-5-Dodecenyl acetate (1) and (Z)-5-tetradecenyl acetate (2)

The alcohol **(30)** (0.466 g; 0.0025 mole) in pyridine (1 ml) was treated with acetic anhydride (0.516 g; 0.005 mole) at room temperature for 24hr. The reaction mixture was diluted with ice cold water, extracted with ether

(3 x 20 ml). Combined ether layer was washed with a solution of copper sulphate (0.5 M), water, brine, dried and distilled to remove the solvent. Column chromatography over silica gel (eluent 2% ethyl acetate in pet.ether) gave the pure acetate **(1)** (0.529 g; 96%).

IR: 2990, 2920, 2840, 1740, 1460, 1360, 1235, 1030 cm^{-1}.

Ms: m/e 226.

Analysis calculat ed for $C_{14}H_{26}O_2$ C, 74.28; H, 11.58

Found C, 74.05; H, 11.35%.

Similarly (Z)-5-tetradecenyl acetate **(2)** was obtained in 74% yield.

IR; 3000, 2910, 2840, 1740, 1460, 1360, 1230, 1030, 710 cm^{-1}.

Ms: m/e 254.

Analysis calculated for $C_{16}H_{30}O_2$ C, 77.53; H, 11.89

Found C, 77.63; H, 11.65%.

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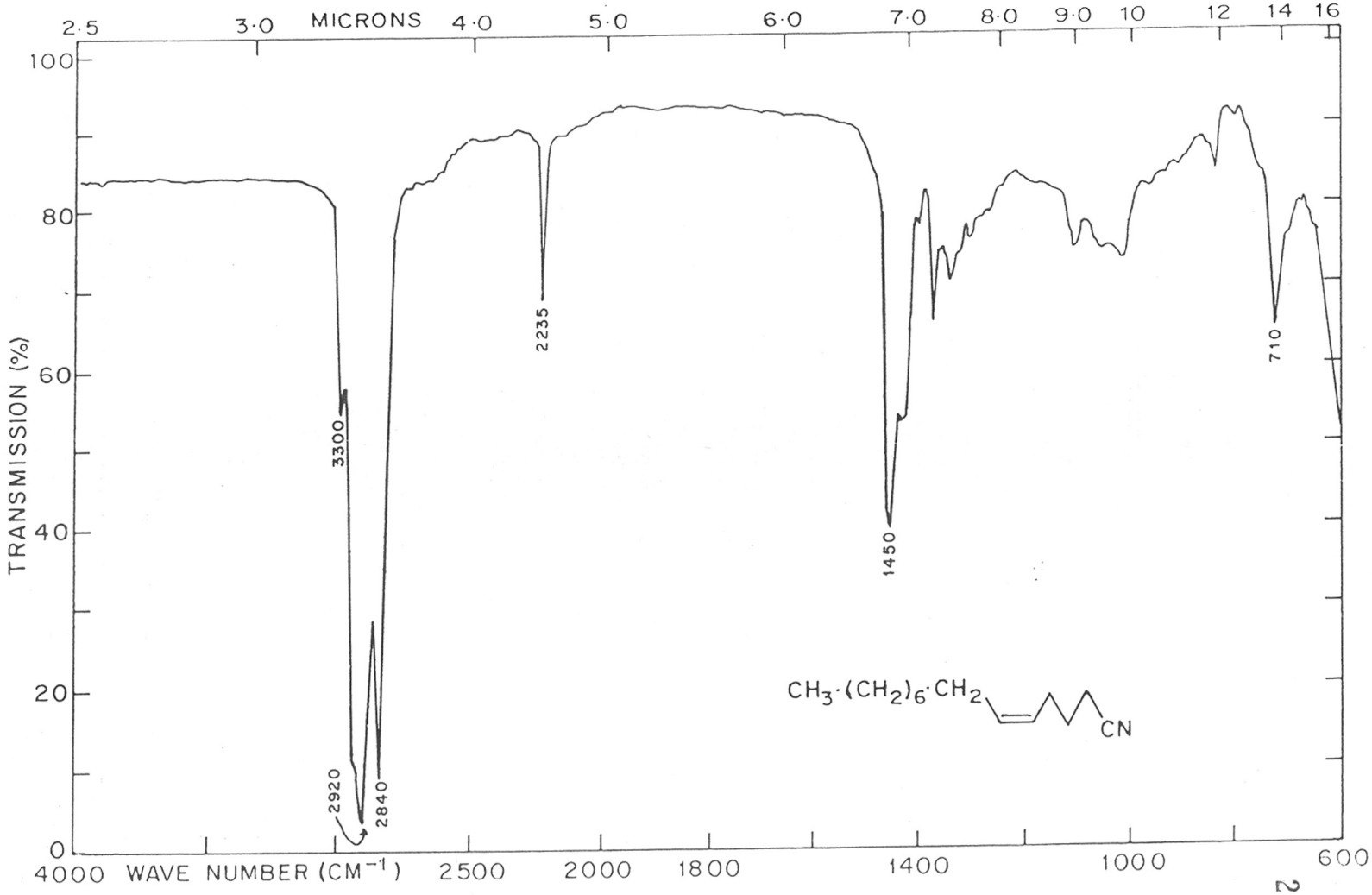


FIG. 1. IR SPECTRUM OF 1-CYANO-(Z)-4-TRIDECENE (27)

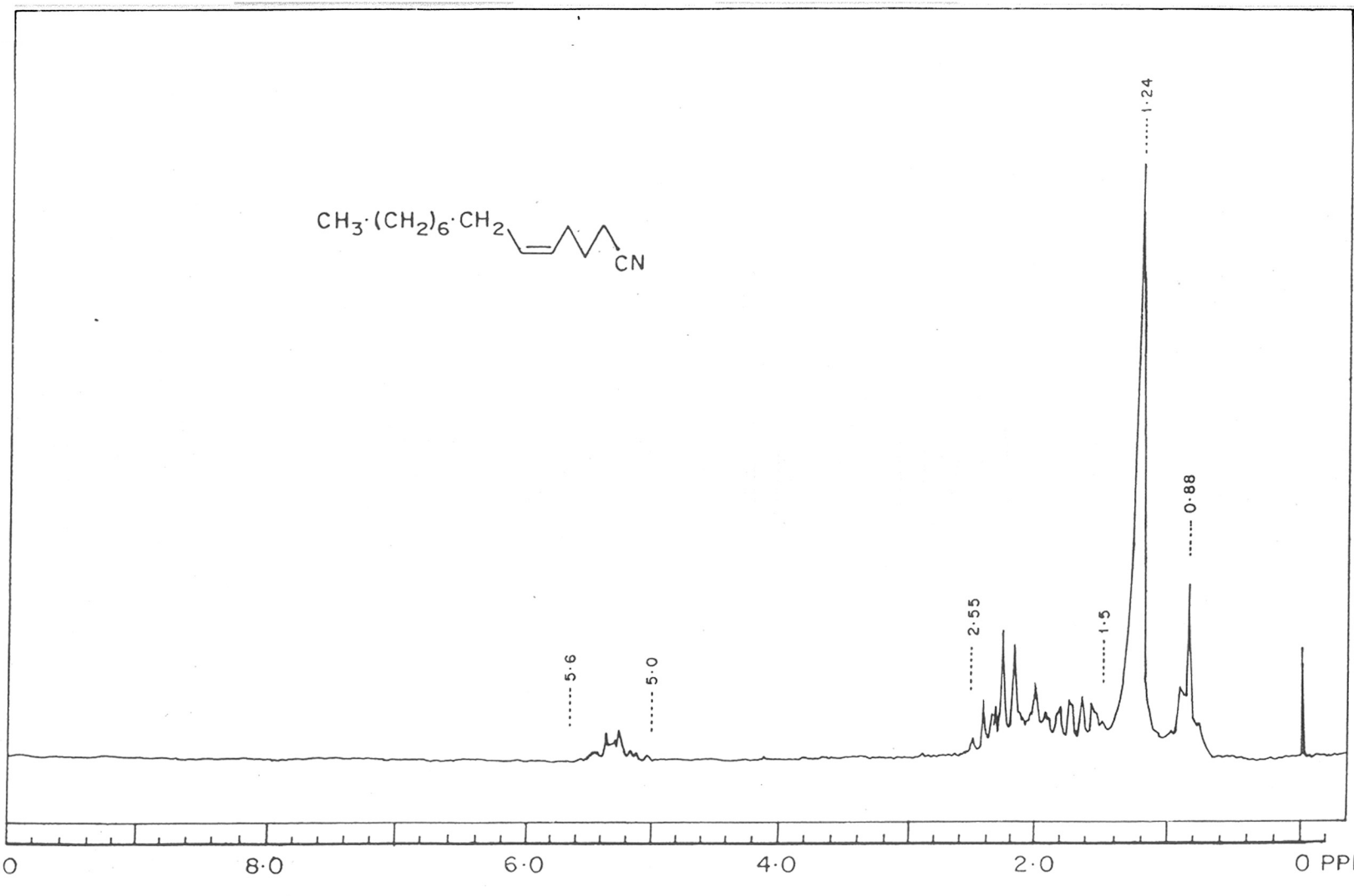


FIG. 2. PMR SPECTRUM OF 1-CYANO-(Z)-4-TRIDECENE (27)

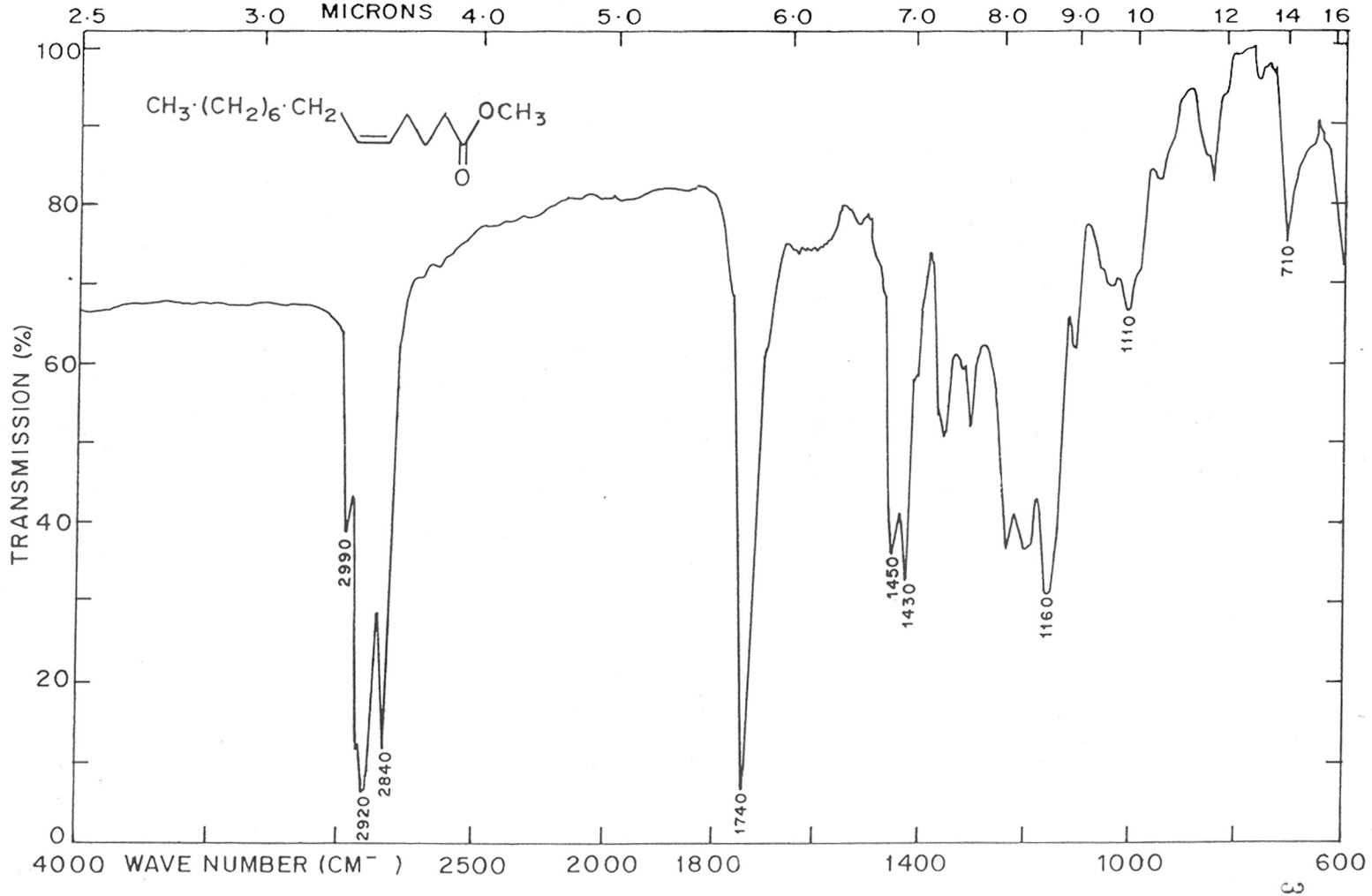


FIG. 3. IR SPECTRUM OF METHYL-(Z)-5-TETRADECENOATE (29)

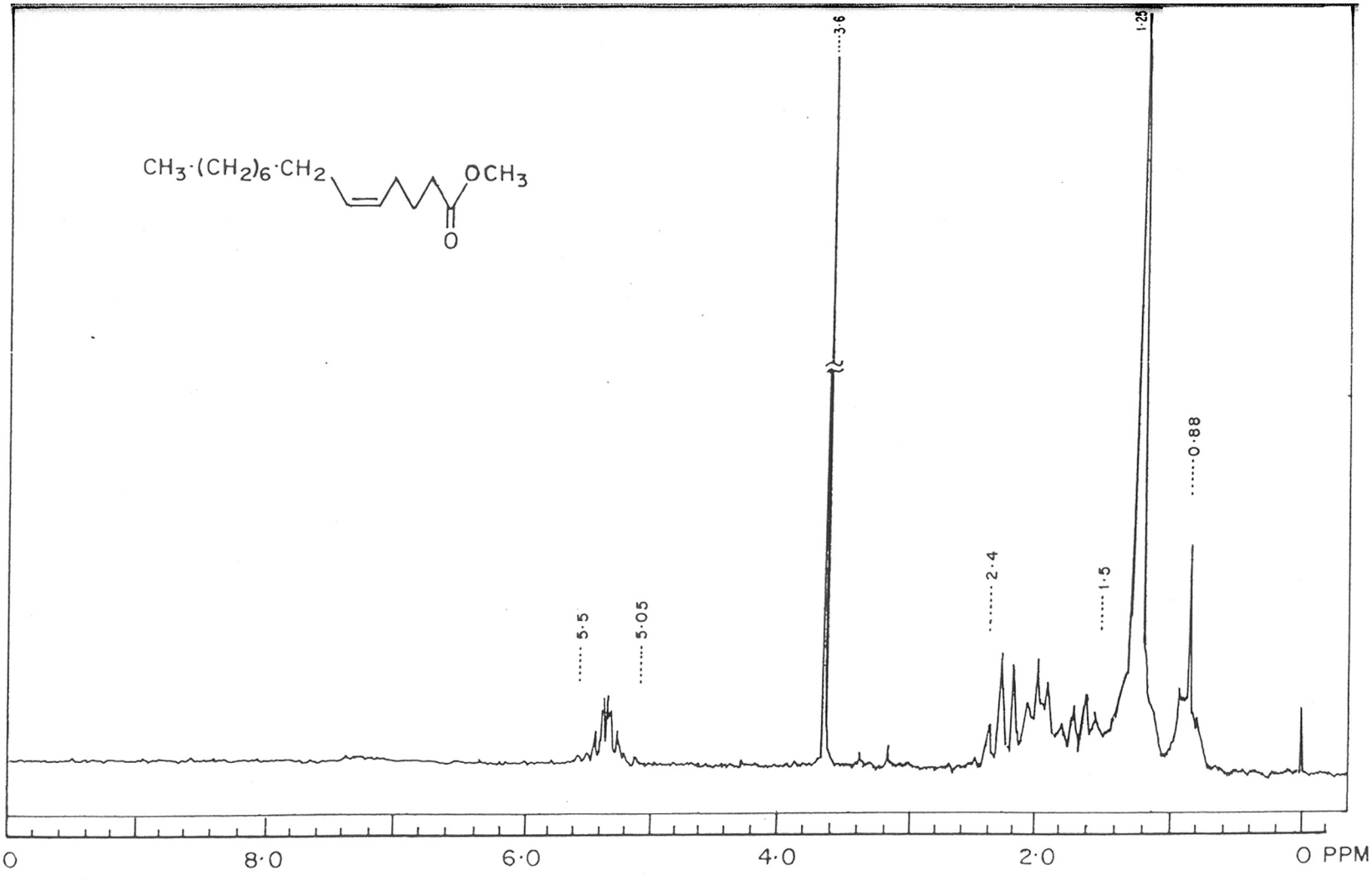


FIG. 4. PMR SPECTRUM OF METHYL-(Z)-5-TETRADECENOATE (29)

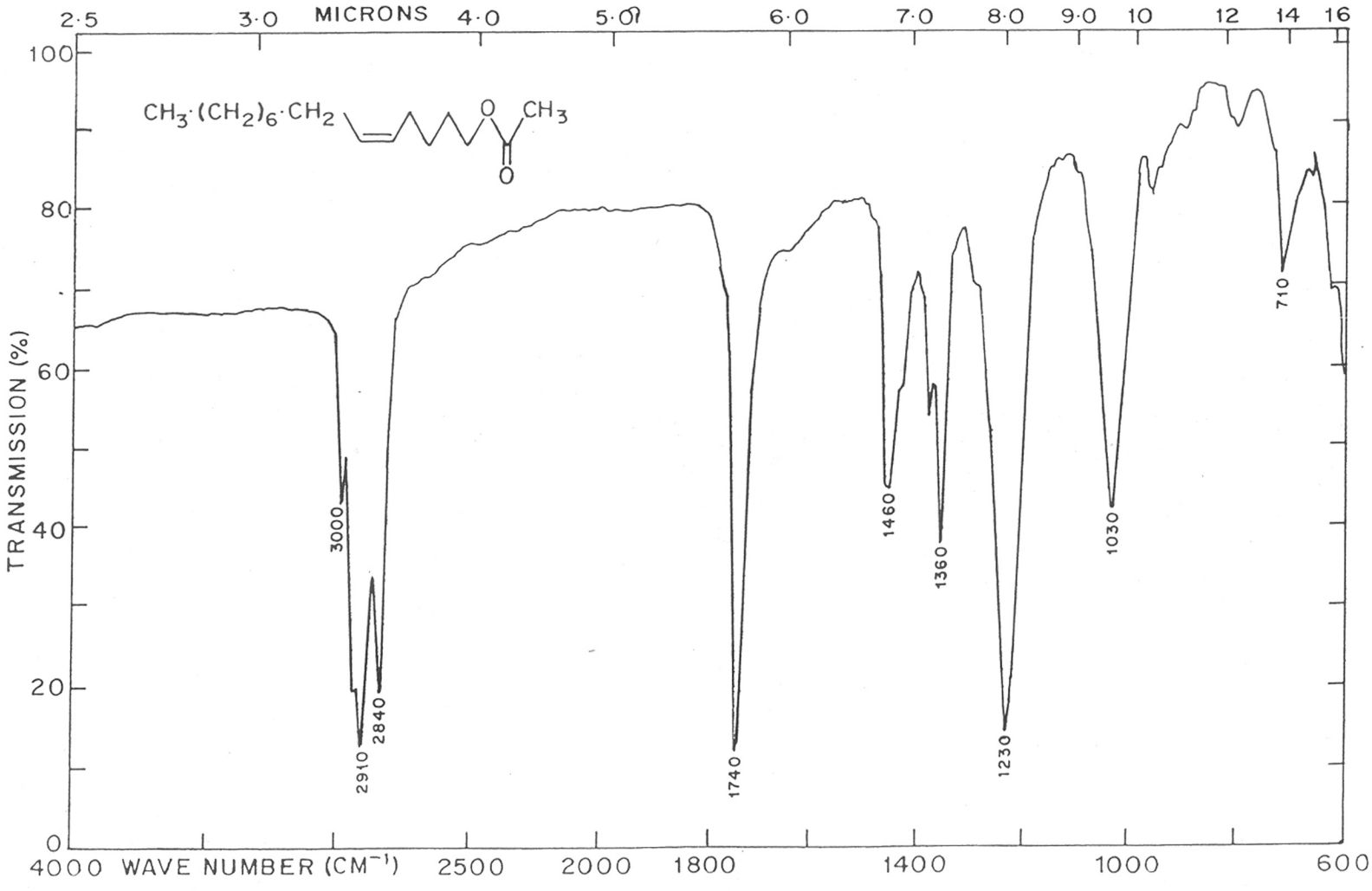


FIG. 5. IR SPECTRUM OF (Z)-5-TETRADECENYL ACETATE (2).

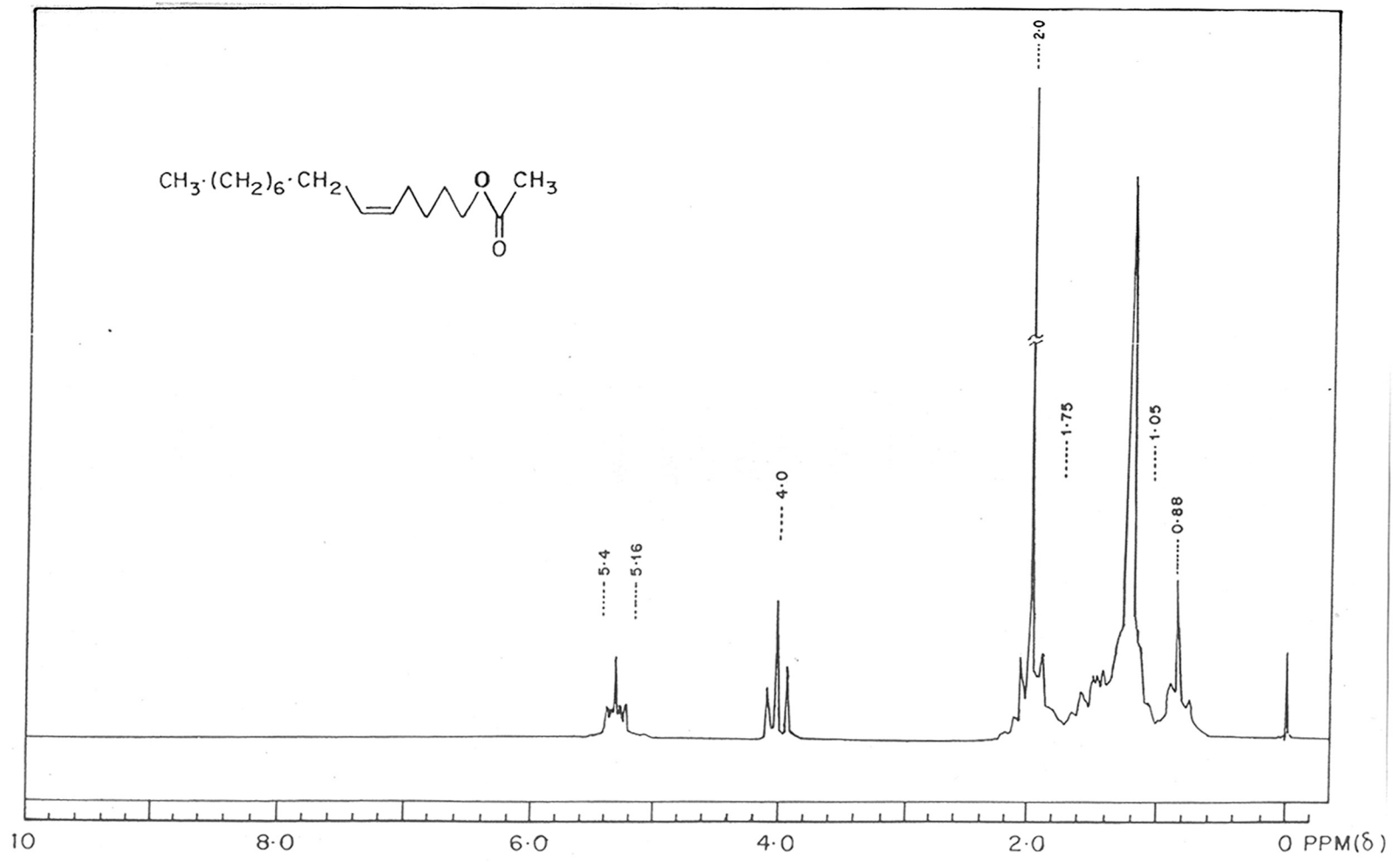


FIG. 6. PMR SPECTRUM OF (Z)-5-TETRADECENYL ACETATE (2).

CHAPTER-II

A NOVEL APPROACH TO THE SYNTHESIS OF 9-(Z)-TRICOSENE AND 7(Z),11(Z)-NONACOSADIENE: PHEROMONE COMPONENTS OF MUSCA DOMESTICA AND DROSOPHILA MELANOGASTER RESPECTIVELY

SUMMARY

This chapter deals with the synthesis of the hydrocarbon pheromones, 9(Z)-tricosene **(1)** and 7(Z), 11(Z)-nonacosadiene **(2)**.

The key step in both the syntheses is bis alkylation of N,N-dimethylacetone hydrazone **(3)** using one equivalent of n-butyl lithium at each step (Scheme VI).

The stepwise bis alkylation of N,N-dimethylacetone hydrazone **(3)** with 1-bromo-4-(Z)-tridecene and 1-bromo heptane afforded the 1,3-dialkylated N,N-dimethyl acetone hydrazone. The latter on deprotection gave 9(Z)-tricosen-15-one which was reduced by sodium borohydride. The alcohol obtained was converted to mesylate and then reacted with LAH to get the title pheromone **(1)**.

Similarly alkylation of **(3)** using 1-bromo 5 (Z), 9 (Z) hexadecadiene, followed by second alkylation with 1-bromo decane afforded the 1,3-dialkylated product, which on deprotection gave the corresponding carbonyl compound. The carbonyl compound was reduced by sodium borohydride. The alcohol obtained was converted to the mesylate and then treated with LAH to get the title pheromone **(2)**.

INTRODUCTION

9-(Z)-Tricosene also known as muscalure and muscamone is the biologically most active hydrocarbon isolated from the extracts of cuticular and fecal lipids of sexually mature female house flies Musca domestica. Several other homologous hydrocarbons are also present, but showing less activity. This sex attractant was found by Carlson and Beroza to be active in field tests[1].

This compound has been synthesised by different routes[2,3] and is used commercially to enhance the effectiveness of a sugar-base fly bait containing insecticides. [The Starbar Division of Zoecon Industries Inc., Markets "Super Golden Malrin^{R} Fly Bait" containing Muscamone^{R} fly attractant for the control of flies in cattle and poultry operations. This is the first commercial EPA (Environmental Protection Agency, U.S.) registered product utilizing a pheromone for insect control purposes].

Chemical analysis of cuticular extracts of female D.melanogaster (Caton-S)[4,5,6] using mass spectrometry coupled with GC showed it to be a mixture of mainly linear long chain hydrocarbons with 23 to 29 carbons. These hydrocarbons were further separated according to their unsaturation level. Amongst them only unsaturated hydrocarbons- both monoenes and dienes- and not alkanes, were found behaviorally active for an amount close to the total amount of hydrocarbons borne by a single female ($\sim$1.5μg). Finally these hydrocarbons were separated according to their chain length which leads to 12 fractions; each fraction corresponds to a mixture of isomers of hydrocarbons with a given chain length and nil, one or two double bonds.

Subsequent investigation indicated that many of the monoenes possessed

a double bond at 7 position along with small amounts of 9-tricosene and 9 pentacosene. In the case of dienes the double bonds were found in positions 7 and 11 for most of the hydrocarbons of different chain length, along with smaller amounts of dienes possessing double bonds at 5-9 and 9-13 positions and monoenes with a double bond at 5 position.

Bioassays of such fractions have indicated that, heptacosadiene is very abundant in female cuticle.

It has also been shown that other female cuticular compounds structurally related to 7,11 heptacosadiene are also present predominantly. These are hydrocarbons with 27 ± 2 carbons and at least one double bond in position 7. Among them only 7,11 nonacosadiene and 7 pentacosene are present in quantities higher than or equal to 100 ng and thus play a prominent role.

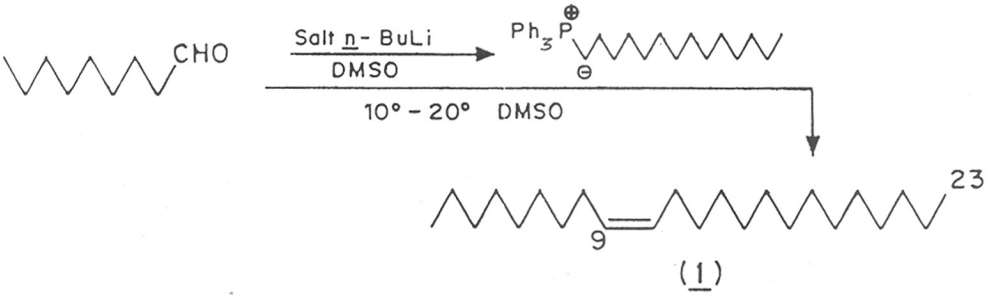
9(Z)-Tricosene **(1)** was prepared[7] initially by the Wittig condensation of triphenyl phosphonium tetradecylide with 1-nonanal in DMSO which gave a mixture of Z and E isomers in the ratio 85:15 respectively, in 73% yield from the phosphonium salt (Scheme I). The isomers were separated by column chromatography in hexane on silver nitrate-silica gel.

Muscalure has also been prepared[8a] via acetylenic intermediates. Conversion of 1-pentadecyne to its lithium salt with n-butyllithium and alkylation of this salt with n-octyl bromide in diglyme at 120° gave high yields of 9-tricosyne. Partial hydrogenation of the triple bond over Lindlar catalyst[8b] gave **(1)** in quantitative yield (Scheme II).

Muscalure has been synthesised[9] in 85% yield from erucic acid by conversion of the latter into the methyl ketone with methyllithium followed by Haung-Minlon reduction (Scheme III).

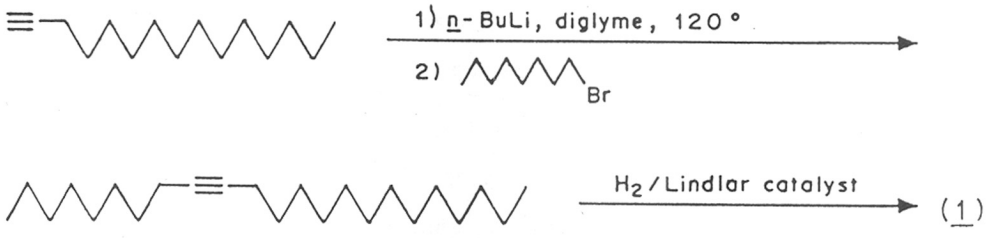
A similar route[10] for the pheromone involved the reaction of oleic acid with n-pentyllithium to give (Z)-14-tricosen-6-one which was reduced

SCHEME - (I)



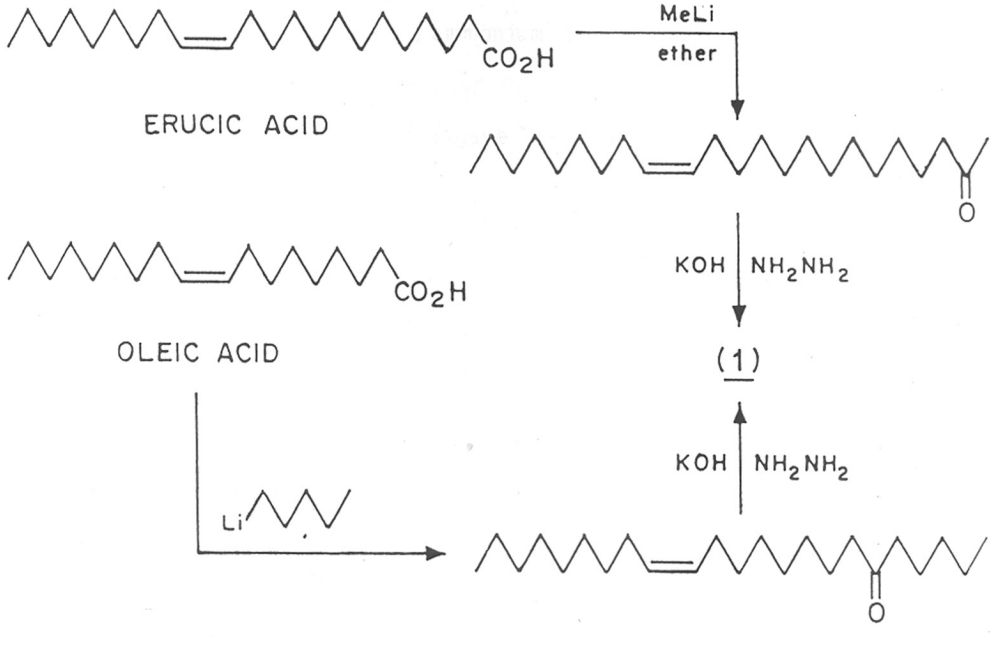
(1)

SCHEME - (II)



(1)

SCHEME - (III)

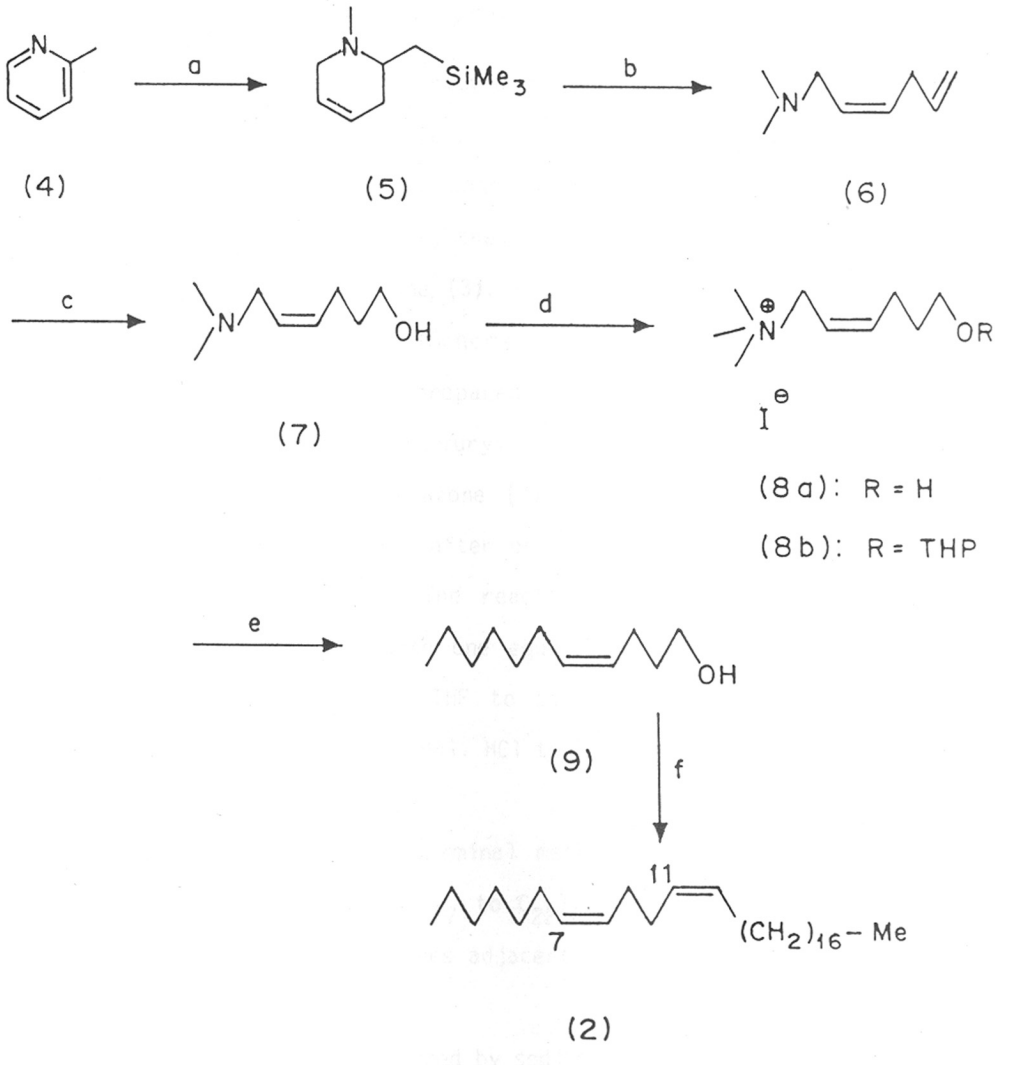


under Haung-Minlon conditions to give **(1)** in 77% overall yield (Scheme III).

The synthesis of 7(Z), 11(Z)-nonacosadiene **(2)**, has been reported[11] recently from a tetrahydropyridine derivative involving a silicon induced fragmentation reaction in the crucial step of the synthesis (Scheme IV).

2-Methyl pyridine **(4)** after alkylation with trichloromethyl silane was treated with methyl iodide. The pyridinium salt thus obtained was subjected to regioselective reduction by $NaBH_4$ to obtain 1,2,3,6 tetrahydro pyridine **(5)**. The tetrahydropyridinium salt was subjected to fragmentation reaction in presence of cesium fluoride to afford the dimethylamino hexadiene **(6)**. Regioselective hydroboration of this compound by 9 BBN gave 6-dimethylamino hex-4-ene 1-ol **(7)**. The compound **(7)** was transformed to **(8)** by treating the former with methyl iodide in methanol. A systematic study of the substitution of these allylic substrates with 7(Z)-configuration, by diverse organometallics showed good stereoselectivity and was obtained in case of the alkylation of quaternary ammonium salt **(8b)** by Grignard reaction. The employment of diorganocuprate or cuprate of superior order gave partial isomerisation of the double bond Z in case of ammonium salt **(8a)**, containing unprotected alcohol function. Compound **(9)** after PCC oxidation gave the corresponding aldehyde which on Wittig reaction gave the pheromone **(2)**.

SCHEME-(IV)



a: 1) LDA, Me_3SiCl, THF; 2) IMe, MeOH; 3) $NaBH_4$, MeOH

b: 1) IMe, MeOH; 2) CsF, THF

c: 1) 9BBN, THF; 2) H_2O_2, NaOH

d: 1) IMe, MeOH

e: 1) $C_5H_{11}MgCl$, Li_2CuCl_4, THF; 2) H_3O^+

f: 1) PCC, CH_2Cl_2; 2) $Ph_3P^{\oplus}C_{18}H_{37}Br^{\ominus}$, $NaN(SiMe_3)_2$, THF

PRESENT WORK

The present work deals with a novel, high yield, synthetic approach for 9(Z)-tricosene **(1)** and 7(Z), 11(Z) nonacosadiene **(2)**. The molecules **(1)** and **(2)** contain cis double bond functionalities.

The key step of the synthesis is the stepwise bis alkylation of N,N-dimethylacetone hydrazone **(3)**.

The alkyl halide **(14)** (Scheme V) was synthesised from the alcohol **(13)**, which in turn was prepared from the dianion of 4-pentyn-1-ol, obtainable from tetrahydrofurfuryl chloride, as described in Chapter I.

N,N-Dimethylacetone hydrazone **(3)** in dry THF at 0° was treated with one equivalent of n-BuLi and after one hr; with a solution of **(14)** in THF, to cause mono-alkylation. The reaction mixture was again cooled to 0° and treated successively with one equivalent of n-BuLi and after one hr; with a solution of **(22)** in THF to cause dialkylation. The dialkylated product was deprotected with dil. HCl to get the ketone **(24)** (Scheme VI).

IR: 1720 (carbonyl) cm^{-1}.

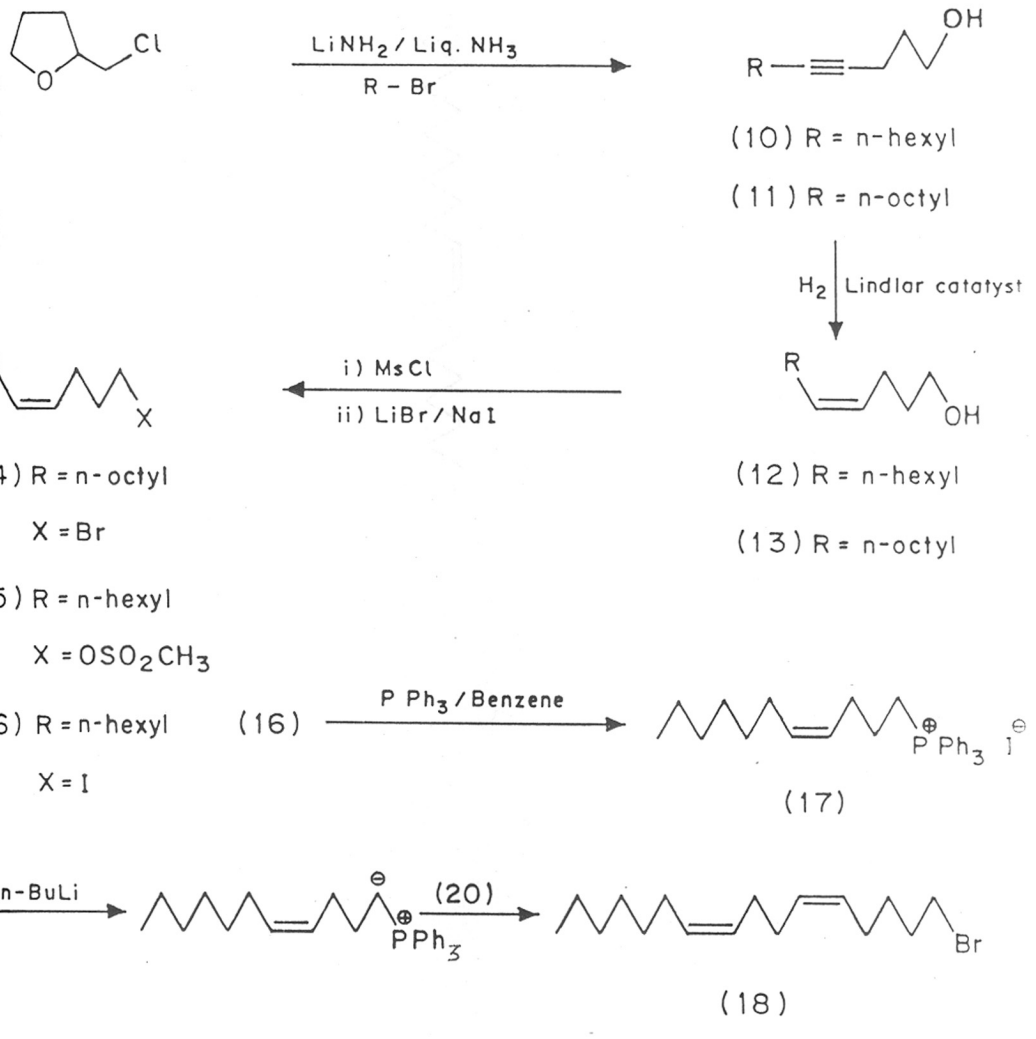
PMR: 0.88 (6H, dist t, terminal methyls), 1.3 (28H, br s, methylenes at C_2 to C_7, C_{12}, C_{13} and C_{17} to C_{22}), 2.0 (4H, m, allylic methylenes), 2.35 (4H, t, J=8 Hz, methylenes adjacent to carbonyl), 5.3 (2H, m, olefinic protons).

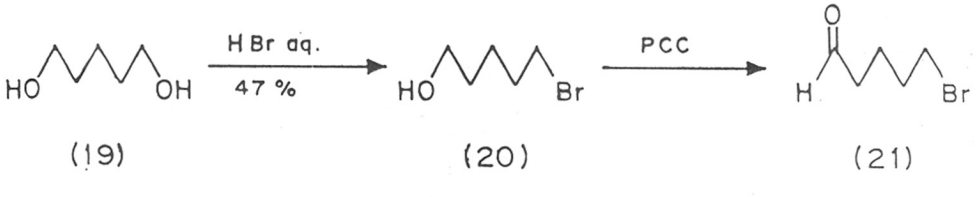
The ketone **(24)** was reduced by sodium borohydride to the alcohol **(25)**.

IR: 3340 (-OH) cm^{-1}.

PMR: 0.88 (6H, dist t, terminal methyls), 1.3 (32H, br s, methylenes at C_2 to C_7, C_{12} to C_{14} and C_{16} to C_{22}), 1.4 (1H, s, D_2O exchangeable, -OH proton), 2.0 (4H, m, allylic methylenes), 3.45 (1H, m, CHOH proton), 5.25 (2H, m, olefinic protons).

SCHEME - (V)



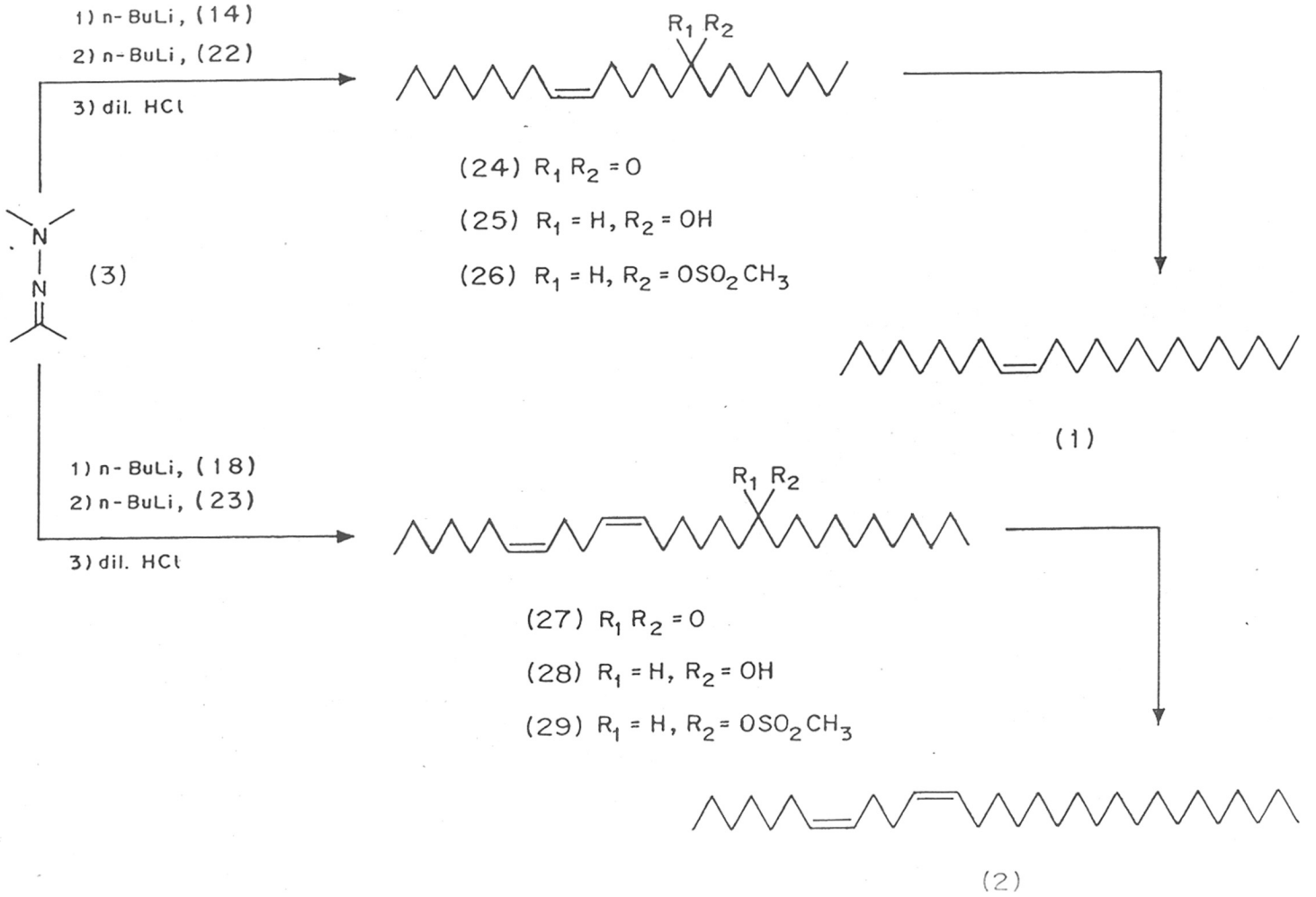


$CH_3 \cdot (CH_2)_n \cdot CH_2 \cdot Br$

(22) n = 5

(23) n = 8

SCHEME– (VI)


1) n-BuLi, (14)
2) n-BuLi, (22)
3) dil. HCl
R_1 R_2
(24) $R_1R_2 = O$
(25) $R_1 = H$, $R_2 = OH$
(26) $R_1 = H$, $R_2 = OSO_2CH_3$
(3)
(1)
1) n-BuLi, (18)
2) n-BuLi, (23)
3) dil. HCl
R_1 R_2
(27) $R_1R_2 = O$
(28) $R_1 = H$, $R_2 = OH$
(29) $R_1 = H$, $R_2 = OSO_2CH_3$
(2)

The alcohol **(25)** was converted to mesylate **(26)** which was reduced by LAH to get the title pheromone **(1)**.

PMR: 0.88 (6H, dist t, terminal methyls), 1.26 (34H, br s, methylenes at C_2 to C_7, C_{12} to C_{22}), 2.0 (4H, m, allylic methylenes), 5.35 (2H, m, olefinic protons).

4-Undecen-1-ol **(12)** (Scheme V) was prepared as described in Chapter I The alcohol **(12)** was converted to its mesylate **(15)** and the latter refluxed with sodium iodidein acetone to furnish **(16)**.

PMR: 0.9 (3H, dist t, terminal methyl), 1.3 (10H, br s, methylenes at C_2, C_7 to C_{10}), 2.0 (4H, m, allylic methylenes), 3.1 (2H, t, J=6 Hz, methylene at C_1), 5.23 (2H, m, olefinic protons).

The iodide **(16)** and triphenyl phosphine in benzene were refluxed to get the phosphonium salt **(17)**.

In another sequence of reactions (Scheme V) the bromoaldehyde **(21)** required for the Wittig reaction was prepared as described below.

1,5-Pentane diol **(19)** was partially brominated by HBr aq. to get 5-bromo-1-pentanol **(20)**.

IR: 3350 (-OH) cm^{-1}.

PMR: 1.79 (6H, m, methylenes at C_2, C_3, C_4), 3.41 (2H, t, J=6 Hz, methylene at C_5), 3.60 (2H, t, J=6 Hz, methylene at C_1), 3.73 (1H, s, D_2O exchangeable -OH proton).

The bromoalcohol **(20)** was then oxidised using PCC, to the aldehyde **(21)**.

IR: 2720, 1725 (-CHO) cm^{-1}.

PMR: 1.76 (4H, m, methylenes at C_3, C_4), 2.3 (2H, t, J=6 Hz, CH_2CO), 3.3 (2H, t, J=6 Hz, CH_2Br), 9.96 (1H, dist t, aldehydic proton).

The Wittig salt **(17)** was treated with n-BuLi and then reacted with the bromoaldehyde **(21)** at -78° to get the bromide **(18)**.

(It is known that when Wittig reactions are carried out at very low temeprature (-78°), preferentially give the Z isomer. Whereas the reaction when carried out at high temperature the E isomer is obtained. In order to ensure the preferential formation of Z isomer, the reaction was carried out at -78°).

PMR: 0.88 (3H, dist t, terminal methyl), 1.4 (12H, br s, methylenes at C_2, C_3, C_{12} to C_{15}), 2.0 (8H, m, allylic methylenes), 3.2 (2H, t, J=6Hz, methylene at C_1), 5.3 (4H, m, olefinic protons).

Stepwise dialkylation of N,N-dimethylacetone hydrazone **(3)** was carried out as described earlier, using the bromides **(18)** and **(23)** (Scheme VI). The dialkylated product was deprotected by treatment with dil.HCl to get the ketone **(27)**.

IR: 1720 (carbonyl) cm^{-1}.

PMR: 0.88 (6H, dist t, terminal methyls), 1.24 (32H, br s, methylenes at C_2 to C_5, C_{14} to C_{16}, C_{20} to C_{28}), 2.04 (8H, m, allylic methylenes), 2.37 (4H, t, J=7 Hz, methylenes adjacent to carbonyl), 5.35 (4H, m, olefinic protons).

The ketone **(27)** was reduced by sodium borohydride to the alcohol **(28)**.

IR: 3600 (-OH) cm^{-1}.

PMR: 0.88 (6H, dist t, terminal methyls), 1.3 (36H, br s, methylenes at C_2 to C_5, C_{14} to C_{17} and C_{19} to C_{28}), 1.65 (1H, br s, D_2O exchangeable -OH proton), 2.0 (8H, m, allylic methylenes), 3.5 (1H, m, C<u>H</u>OH proton), 5.3 (4H, m, olefinic protons).

The alcohol **(28)** was converted to its mesylate **(29)** which was reduced by LAH to get the pheromone **(2)**.

IR: 1650, 720 (cis disubstituted double bond) cm^{-1}.

PMR: 0.88 (6H, dist t, terminal methyls), 1.25 (38H, br s, methylenes at C_2 to C_5 and C_{14} to C_{28}), 2.04 (8H, m, allylic methylenes), 5.35 (4H, m, olefinic protons).

EXPERIMENTAL

1-Bromo-4-(Z)-tridecene (14)

This was prepared as described in chapter I.

9-(Z)-Tricosen-15-one (24)

To an ice cooled solution of **(3)** (0.25 g; 0.0025 mole) in THF (15ml) under N_2 atmosphere was added n-BuLi (1.2 ml, 2.3 N, n-hexane solution, 0.0025 mole) and stirred for 0.5 hr. To this, a solution of **(14)** (0.653g; 0.0025 mole) in THF (5 ml) was added and stirring continued for 2 hr. at room temperature. The reaction mixture was cooled to 0° and n-BuLi (0.0025 mole) was again added and stirred for 0.5 hr. To it, a solution of 1-bromo-heptane **(22)** (0.447 g; 0.0025 mole) in THF (5 ml) was added and stiring continued for additional 2 hr. at room temperature. Removal of THF afforded the residue, which was dissolved in ether and stirred with 0.5 N HCl (2 ml) for 10 minutes to effect deprotection. The ether layer was then washed with water, brine, dried and distilled. The crude ketone was purified by column chromatography over silica gel and eluted with 5% ethyl acetate in pet.ether to furnish **(24)** (0.666 g; 80%) as a pale yellow liquid.

IR: 3000, 2920, 2840, 1720 (carbonyl) 1460, 1380, 710 cm^{-1}.

Ms: m/e 336.

Analysis Calculated for $C_{23}H_{44}O$ C, 82.07; H, 13.18

Found C, 82.15; H, 13.00%.

9-(Z)-Tricosen-15-ol (25)

A solution of **(24)** (0.666 g; 0.002 mole) in methanol (10 ml) was reduced by $NaBH_4$ (0.076 g; 0.002 mole) and stirred for 2 hr. at room temperature. Methanol was removed, residue diluted with water and extracted with ether (3 x 40 ml). The ether layer was washed with water, brine,

dried and distilled to furnish the alcohol **(25)** (0.636 g; 95%) as a colourless liquid.

IR: 3340 (-OH), 3000, 2920, 2840, 1460, 1370, 1080, 710 cm^{-1}.

Ms: m/e 338.

Analysis Calculated for $C_{23}H_{46}O$ C, 81.58; H, 13.69

Found C, 81.34; H, 13.80%.

9-(Z)-Tricosene (1)

To an ice cooled and stirred solution of **(25)** (0.636 g; 0.0019 mole) and triethyl amine (0.57 g; 0.0056 mole) in methylere chloride (10 ml) was added methane sulfonyl chloride (0.258 g; 0.0022 mole) and the reaction mixture was stirred for 0.5 hr. at 0° and further 4 hr. at room temperature. The residue left, after removal of the solvent was diluted with water and extracted with ether (3 x 20 ml). Ether layer was washed with water, brine, dried and distilled to get the mesylate **(26)**. This after column chromatography over silica gel and elution with pet.ether gave pale yellow colored liquid (0.76 g; 97%).

To an ice cooled and stirred suspension of LAH (0.068 g; 0.0018 mole) in ether (10 ml) was added a solution of mesylate **(26)** (0.76 g; 0.0018mole) in ether (5 ml) during 10 minutes. The reaction mixture was stirred for 0.5 hr at 0° and then at room temperature for an additional hr. Excess of LAH was decomposed by ethyl acetate followed by cold water. Ether layer was separated and the aqueous portion extracted with ether (3 x 25 ml). Combined ether layer was washed with water, brine, dried and evaporated to get the crude product, further purified by column chromatography over silica gel and elution with pet.ether to afford the hydrocarbon **(1)** as a liquid (0.56 g; 96%).

IR: 2980, 2900, 2820, 1450, 1320, 950, 710 cm^{-1}.

Ms: m/e 322.

Analysis Calculated for $C_{23}H_{46}$ C, 85.63; H, 14.37

Found C, 85.45; H, 14.14%.

1-Iodo-4-(Z)-undecene (16)

4-(Z)-Undecen-1-ol **(12)** and its mesylate **(15)** were prepared as per the procedures given in Chapter I.

Mesylate **(15)** (2.56 g; 0.009 mole) and sodium iodide (3.27 g;0.02 mole) in dry acetone (50 ml) were refluxed for 3 hr. Acetone was removed by distillation and the residue diluted with water and extracted with ether (3 x 25 ml). The combined ether layer was washed with water, brine, dried and distilled to afford the iodide **(16)** (3.0 g; 93%) as a liquid after column chromatography over silica gel and elution with pet.ether.

Ms: m/e 280.

Analysis Calculated for $C_{11}H_{21}I$ C, 47.14; H, 7.50; I, 45.35

Found C, 47.25; H, 7.33; I, 45.22%.

4-(Z)-Undecenyl triphenyl phosphonium iodide (17)

The iodide **(16)** (2.8 g; 0.01 mole) and triphenyl phosphine (2.62 g; 0.01 mole) in dry benzene (12 ml) were refluxed for 48 hr. The separated oily layer on treatment with pet.ether at 0°, solidified. It was filtered and washed with dry ether. The pale yellow colored crystalline solid (4.8 g; 90%) was dried under vacuum, m.p.110°.

5-Bromo-1-pentanol (20)

1,5-Pentane diol **(19)** (5.2 g; 0.05 mole) and aq. HBr (47%). (4.05 g; 8.4 ml, 0.05 mole) were refluxed in benzene for 6 hr. The organic layer was separated and washed with saturated solution of NaCl and solvent removed

to get the crude bromo alcohol. Column chromatography over silica gel and elution with 40% ethyl acetate in pet.ether afforded the pure bromo alcohol **(20)** as a liquid (6.6 g; 80%).

IR: 3350 (-OH), 2940, 2860, 1450, 1430, 1055 cm^{-1}.

Ms: m/e (^{79}Br) 166, (^{81}Br) 168.

Analysis Calculated for $C_5H_{11}BrO$ C, 35.92; H, 6.58; Br, 47.90

Found C, 36.00; H, 6.50; Br, 47.68%.

5-Bromo-1-pentanal (21)

To a stirred solution of PCC (2.58 g; 0.012 mole) in dry methylene chloride (50 ml) at room temperature was added 5-bromo-1-pentanol (1.67g; 0.01 mole) and the mixture stirred for 2 hr. After completion of reaction (tlc), the dichloromethane solution was filtered through silica gel column and further eluted with 100 ml methylene chloride. The solvent was removed by distillation and the crude product obtained was purified by column chromatography over silica gel and eluted with 2% ethyl acetate in pet.ether, to afford a liquid **(21)** (1.48 g;90%).

IR: 2940, 2820, 2720, 1725 (-CHO), 1390, 1255 cm^{-1}.

Ms: m/e (^{79}Br)164, (^{81}Br) 166.

Analysis Calculated for C_5H_9BrO C, 36.36; H, 5.45; Br, 48.48

Found C, 36.11; H, 5.22; Br, 48.25%.

1-Bromo 5(Z), 9(Z)-hexadecadiene (18)

To an ice cooled solution of 1-[4(Z)-undecenyl] triphenylphosphonium iodide **(17)** (2.7 g; 0.005 mole) in THF (25 ml) was added n-BuLi (2.1 ml, 2.3 N, n-hexane solution, 0.005 mole) under N_2 atmospehre and stirred for 0.5 hr. The contents were then cooled to -78°and a solution of 5-bromo-1-pentanal **(21)** (0.825 g; 0.005 mole) in THF (5 ml) was added to it in

one lot. The reaction mixture was stirred further for 2 hr. at -78°. The reaction mixture was allowed to come to room temperature, THF distilled under reduced pressure and the residue extracted with pet.ether(3 x 40ml). The organic layer was washed with water, brine, dried and distilled to furnish the crude product, purified by column chromatography over silica gel and elution with pet.ether to afford the pure bromide **(18)** (0.978 g; 65%).

IR:3000, 2940, 2860, 1460, 1210, 1170, 970, 720 cm^{-1}.

Ms: m/e (^{79}Br)300, (^{81}Br)302.

Analysis Calculated for $C_{16}H_{29}Br$ C, 63.78; H, 9.60; Br, 26.57

Found C, 63.50; H, 9.39; Br, 26.30%.

7(Z), 11(Z)-Nonacosadien -18-one (27)

To an ice cooled solution of **(3)** (0.15 g; 0.0015 mole) in THF (15ml) n-BuLi (0.7 ml, 2.3 N, n-hexane solution, 0.0015 mole) was added under N_2 atmosphere, stirred for 0.5 hr and a solution of **(18)**(0.46g;0.0015 mole) was then added to it and stirred for 2 hr. at room temperature.

It was then cooled to 0°, n-BuLi (0.7 ml, 0.0015 mole) was added to it and stirred for 0.5 hr. To this a solution of 1-bromodecane **(23)** (0.331g; 0.0015 mole) in THF (5 ml) was added and the stirring was continued for additional 2 hr. at room temeprature. Removal of THF afforded a residue, an ethereal solution of which was stirred with 0.5 N HCl (2 ml) for 10 minutes to effect the deprotection. The ether layer was then washed with water, brine, dried and distilled. The crude ketone was purified by column chromatography over silica gel and elution with 2.5% ethyl acetate in pet. ether, to furnish pure ketone **(27)** (0.512 g; 80%) as a liquid.

IR: 3000, 2920, 2860, 1720 (carbonyl), 1460, 1380, 960, 720 cm^{-1}.

Ms: m/e 418.

Analysis Calculated for $C_{29}H_{54}O$ C, 83.18; H, 13.00

Found C, 83.10; H, 13.20%.

7(Z)-11(Z)-Nonacosadien-18-ol (28)

Ketone **(27)** (0.512 g; 0.0012 mole) in methanol (5 ml) was treated with $NaBH_4$ (0.046 g; 0.0012 mole) and stirred for 2 hr. Methanol was removed, residue diluted with water and extracted with ether (3 x 40 ml). The organic layer was washed with water, brine, dried and distilled to furnish the alcohol **(28)** as a low melting solid (0.514 g; 95%).

IR: 3600 (-OH), 3000, 2920, 2850 cm^{-1}.

Ms: m/e 420.

Analysis Calculated for $C_{29}H_{56}O$ C, 82.78; H, 13.42

Found C, 82.59; H, 13.19%.

7(Z),11(Z)-Nonacosadiene (2)

To an ice cooled and stirred solution of alcohol **(28)** (0.514 g; 0.0012 mole) and triethylamine (0.370 g; 0.0037 mole) in methylene chloride (10 ml) was added methane sulfonyl chloride (0.168 g; 0.00147 mole) and stirring continued for 0.5 hr. at 0° and then at room temperature for 4 hr. The residue left after removal of solvent was diluted with water and extracted with ether (3 x 20 ml). Ether layer was washed with water, brine, dried and distilled to get the mesylate **(29)** as a liquid after column chromatography over silica gel and elution with pet.ether (0.597 g; 98%).

To an ice cooled and stirred suspension of LAH (0.069 g; 0.0018 mole) in dry ether (10 ml) was added a solution of mesylate **(29)** (0.597 g; 0.002 mole) in ether (5 ml) during 10 minutes. The reaction mixture was stirred for 0.5 hr. at 0° and then at room temperature for an additional hr. Excess of LAH was decomposed by ethyl acetate followed by ice cold

water. Ether layer was separated and the aq. portion extracted with ether (3 x 25 ml). Combined ether layer was washed with water, brine, dried and evaporated to get the crude product, further purified by column chromatography on silica gel and eluted with pet.ether to afford the hydrocarbon **(2)** (0.460 g; 95%).

IR: 3000, 2900, 2860, 1470, 970, 720 cm^{-1}.

Ms: m/e 404.

Analysis Calculated for $C_{29}H_{56}$ C, 86.05; H, 13.95%

Found C, 85.88; H, 13.79%.

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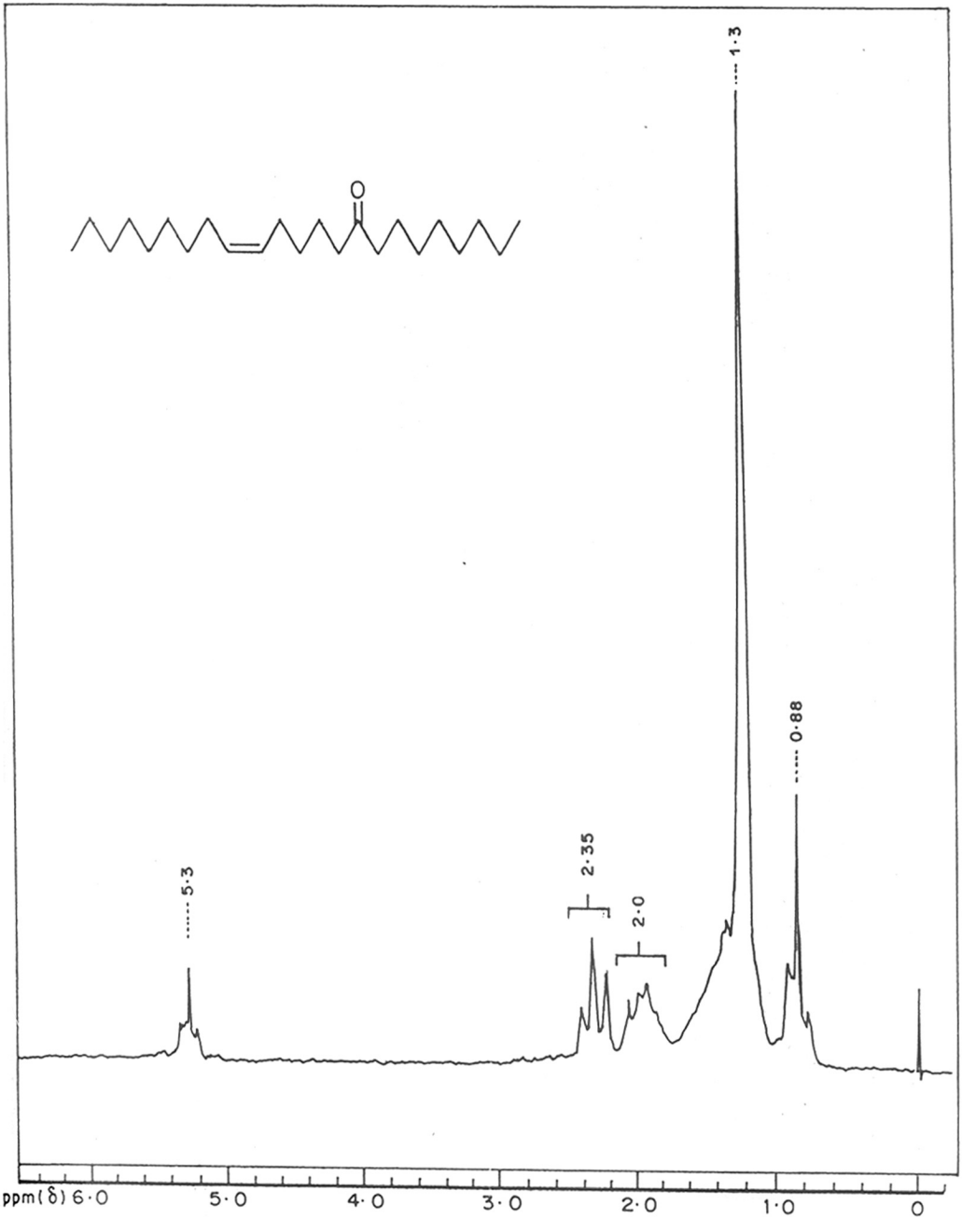


FIG. 1. PMR SPECTRUM OF 9-(Z)-TRICOSEN-15-ONE (24).

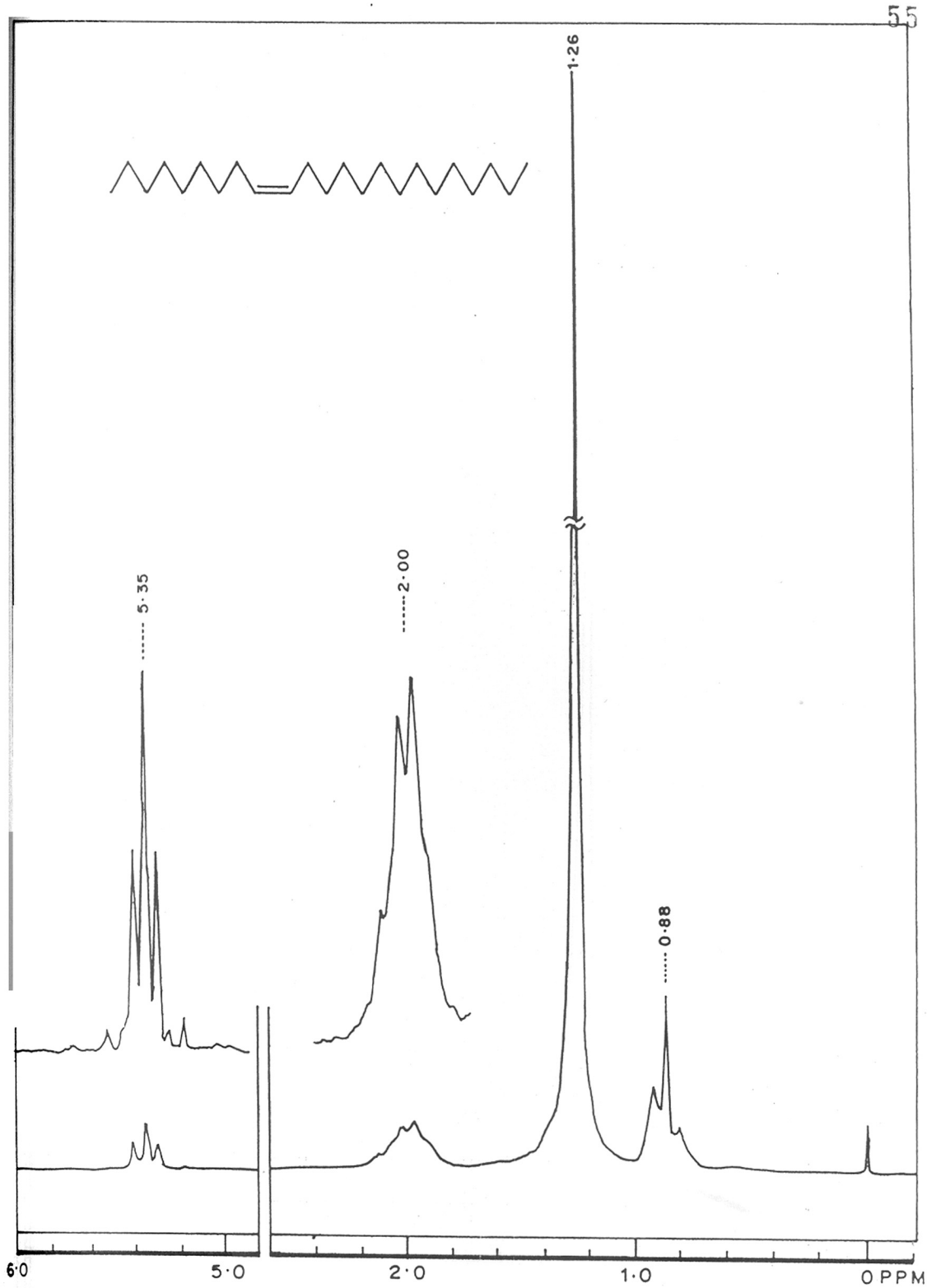


FIG. 2. PMR SPECTRUM OF 9-(Z)-TRICOSENE (1)

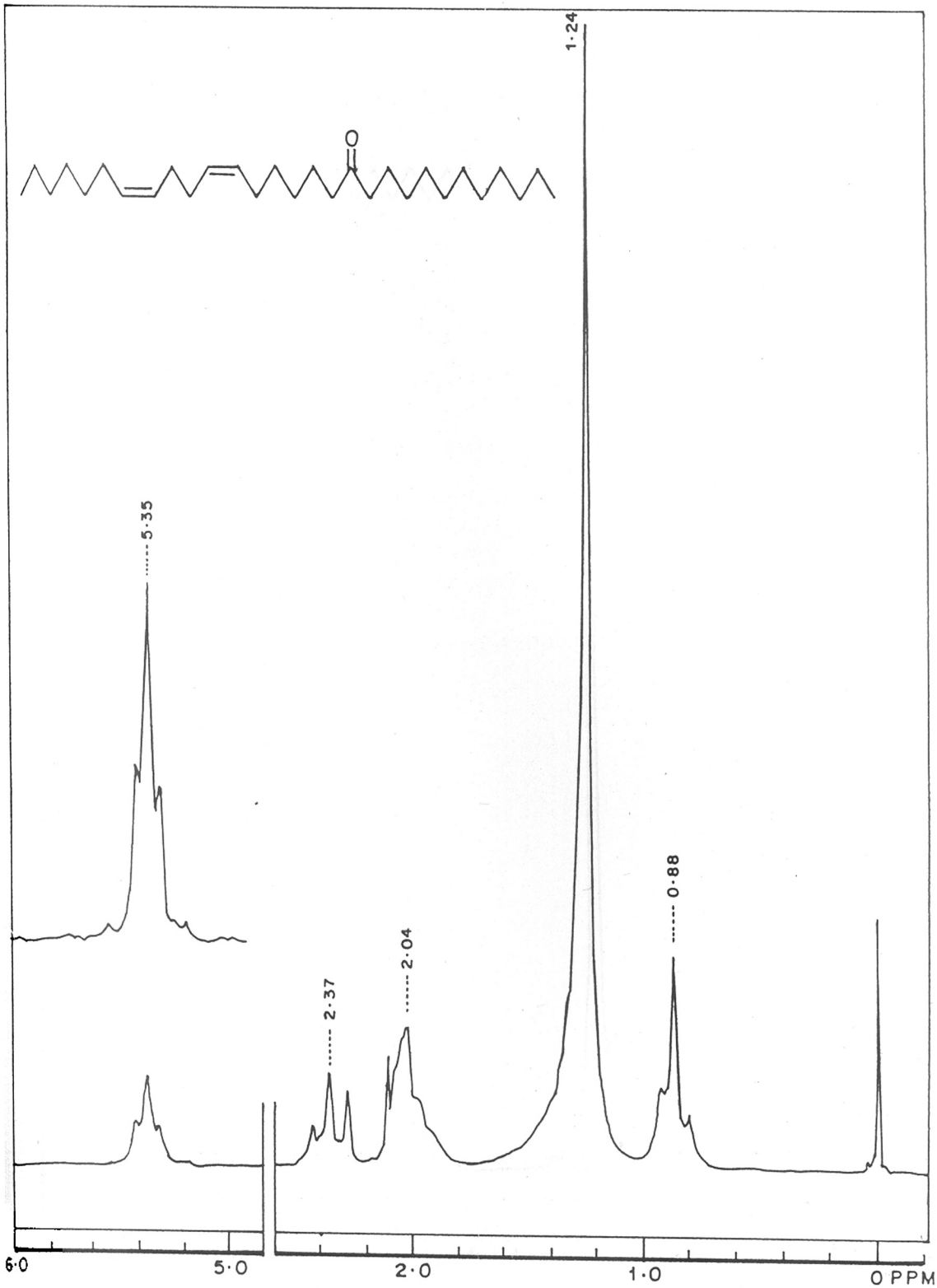


FIG. 3. PMR SPECTRUM OF 7(Z),11(Z), NONACOSADIEN-18-ONE (27)

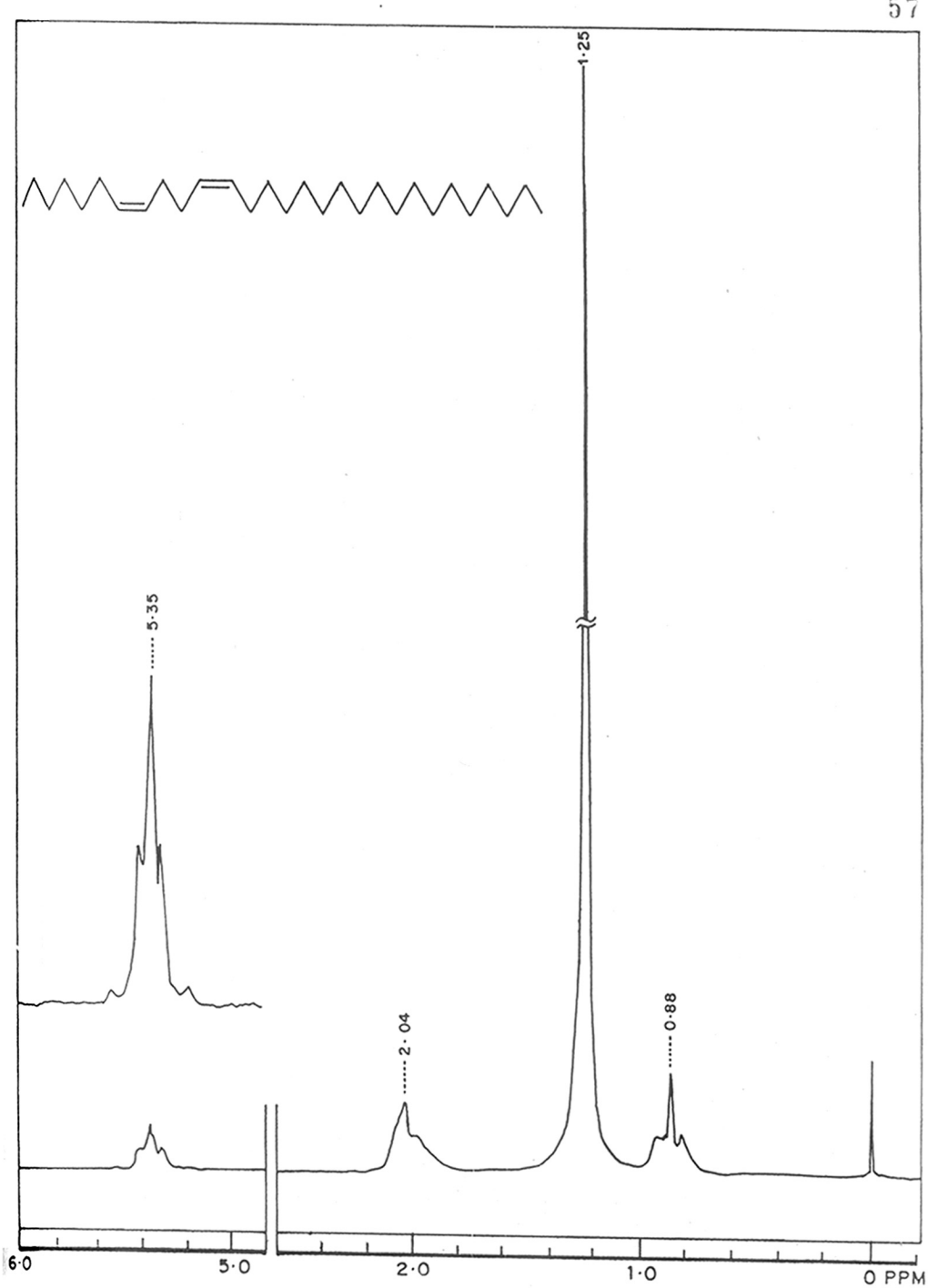


FIG. 4. PMR SPECTRUM OF 7 (Z),11 (Z), NONACOSADIENE (2)

CHAPTER-III

SYNTHETIC STUDIES IN 1,2 AND 2,3 SECO-PYRETHROIDS

SUMMARY

In this chapter synthesis of 3-phenoxybenzyl 3-alkyl-3-phenyl-/p-substituted phenyl and 3-phenoxybenzyl 2-alkyl-3-phenyl-/p-substituted phenyl propionates which resemble structurally with the 1,2 and 2,3-secopyrethroids respectively (Chart III) has been described. In these compounds the conventional vinyl function is replaced by an aromatic ring. These esters are also structurally related to the higher homologue of the potent insecticide fenvalerate (Chart II).

∝ (RS)-Cyano-3-phenoxybenzyl 3-isopropyl 5-methyl hex-4-enoate, the cyano 3-phenoxy benzyl ester of 1,2-secochrysanthemic acid has been synthesised in five steps, starting from isobutyraldehyde with a view to evaluate it for insecticidal and larvicidal properties.

In addition, several other acid moieties of 1,2-secopyrethroids possessing different substituents on the vinyl function as well as the unsubstituted analogue have been synthesised by similar methods. The preparation of cyano 3-phenoxybenzyl esters from these acid moieties is in progress.

Alkylation of diethyl malonate with aralkyl bromides (1) to (6) [Scheme I] using one equivalent of NaH in benzene-DMF afforded predominantly the monoalkylated diethyl malonates (7) to (12) which were decarbethoxylated by refluxing with KOAc in wet DMSO. The monoesters (13) to (18) thus obtained, were transesterified with 3-phenoxybenzyl alcohol to get the corresponding 3-phenoxybenzyl esters (19) to (24).

In another sequence of reactions (Scheme II), ethyl acetoacetate was alkylated with benzyl chloride in presence of one equivalent of sodium

ethoxide to afford ethyl ∝-benzyl acetoacetate (25) as the major product. Dialkylation of the latter with alkyl halides afforded the acetoacetates (26) to (28), which on treatment with C_2H_5ONa/C_2H_5OH or CH_3ONa/CH_3OH underwent deacetylation to furnish the monoesters (29) to (31), subsequently converted to the corresponding 3-phenoxybenzyl esters by transesterification.

Diethyl malonate was monoalkylated with p-chlorobenzyl bromide (Scheme III) to get the diester (9) which on second alkylation with isopropyl iodide afforded the dialkylated diester (35). The latter was decarbethoxylated with KOAc/wet DMSO to furnish the monoester (36), converted to the corresponding 3-phenoxybenzyl ester by transesterification.

Reaction of isobutyraldehyde (38) with the Wittig reagent, generated from triethylphosphonoacetate by treatment with sodium hydride, afforded the conjugated ester (39) which on reaction with excess MeLi gave the tertiary alcohol (40). The latter on Claisen orthoester rearrangement afforded the ester (41) which was saponified to the corresponding acid and then to the acid chloride (42). Esterification of the acid chloride with ∝-cyano-3-phenoxybenzyl alcohol (prepared from 3-phenoxybenzaldehyde, NaCN and water) under phase transfer conditions afforded the ∝-cyano-3-phenoxybenzyl ester (43). Scheme (IV).

The allylic alcohols (45) and (47) were both prepared from mesityl oxide by reduction with $NaBH_4$ and reaction with MeLi respectively (Scheme V).

The allylic alcohol (50) was prepared from citral (49) by reaction with MeLi.

The alcohols (45), (47) and (50) were subjected to Claisen orthoester rearrangement using triethylorthoacetate to furnish the ethyl esters (46), (48) and (51) respectively.

INTRODUCTION

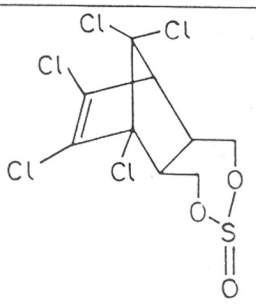
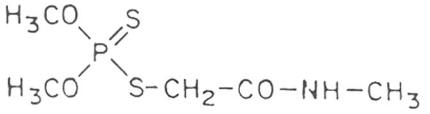
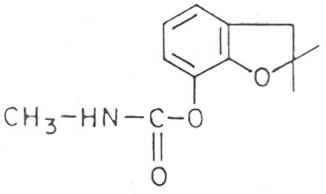
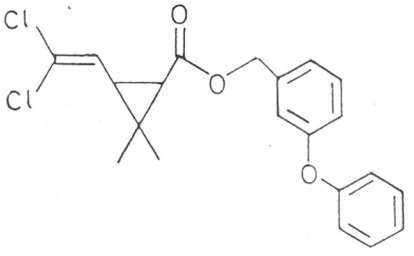
Pesticide is defined as any substance or a mixture of substances, intended for preventing, destroying, replling or mitigating any pest or as any substance intended for use as a plant regulator, defoliant or desiccant.

The sequence of compounds synthesised to control pests can be graded in four major classes (1) organochlorines (2) carbamates (3) organophosphorus compounds and (4) pyrethroids. Table (I) gives examples of each class.

The deficiencies in the earlier three classes of compounds, such as high persistance, harmful effect on non-targeted organisms, high mammalian toxicity and environmental pollution have restricted their use as insecticides. Most of these deficiencies are absent in the naturally occurring insecticides like pyrethrins and cinerins.

The flowers of chrysanthemum cinerariaefolium were used since ancient times[1] for controlling pests. Insecticidal principles in pyrethrum (dried flowers of C.cinerariaefolium Trev) are called as "pyrethrins". In the first quarter of 20th century, Staudinger and Ruzicka[2] for the first time, isolated and identified two active principles from pyrethrum extract and named them as Pyrethrin I and Pyrethrin II. Later, four more related active esters[3,4] viz. Cinerin I, Cinerin II, Jasmolin I and Jasmolin II (Chart I) were also isolated from pyrethrum extract. These (Pyrethrin I, Cinerin I and Jasmolin I) are esters[5] of (+) trans chrysanthemic acid, which is chemically (+) 1R trans 2,2 diemthyl 3-(2-methyl prop-1-enyl)cyclopropane carboxylic acid. Pyrethrin II, Cinerin II and Jasmolin II are esters of (+) trans pyrethric acid which is chemically (+) 1R trans 2,2-dimethyl 3-(2-carboxymethyl prop-1-enyl) cyclopropane carboxylic acid. They possess unique combination

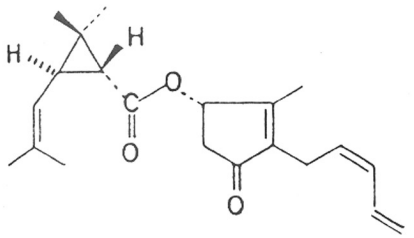
TABLE -1

S.No.	CLASS OF INSECTICIDE	EXAMPLE	STRUCTURE
1	ORGANOCHLORINE	ENDOSULFAN	
2	ORGANO PHOSPHOROUS	ROGOR	
3	CARBAMATES	CARBOFURAN	
4	PYRETHROIDS (Natural and Synthetic)	PERMETHRIN	

of desired properties such as good insecticidal activity, low mammalian toxicity and higher biodegradability. However, their use is limited mainly because of their high cost and photoinstability. So efforts were directed towards the synthesis of pyrethroids, bearing close structural resemblance to natural pyrethrins by making suitable changes in the alcohol as well as in cyclopropanecarboxylic acid moiety. The pyrethroids thus obtained, combine high and selective insecticidal activity, low mammalian toxicity and greater biodegradability with photostability. During the first phase of research in this direction, some insecticidal esters were prepared in which the acid moiety was the same as in natural pyrethrins, viz. (+) trans chrysanthemic acid, but the alcohol moiety is either 3-phenoxy benzyl alcohol[6] or 5-benzyl-3-furylmethyl alcohol, both of which are photostable alcohol moieties. These esters are not only more photostable as compared to natural pyrethrins but also show increased insecticidal activity while maintaining low mammalian toxicity. Subsequently, modifications were also made in the acid moiety by eliminating photolabile centres as a result of which, acid moieties of potent pyrethroids like DV acid and its dibromo analogues were synthesised. The esters of these acids with the photostable alcohols mentioned above, give rise to highly potent pyrethroids[7,8] like permethrin, cypermethrin and deltamethrin which are in commercial use at present. In recent years, a second generation of pyrethroids[9] like cyhalothrin, baythroid, FMC-54800 has also come up (Chart I).

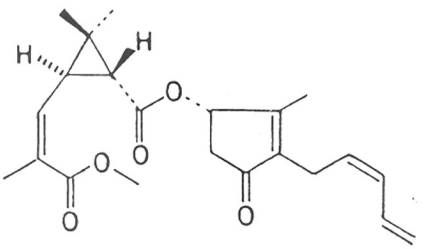
To possess high insecticidal activity pyrethroids must have a precise steric relationship between the unsaturated centre in the alcohol moiety and the gem-dimethyl group or its equivalent substituent in the acid moiety.

CHART I

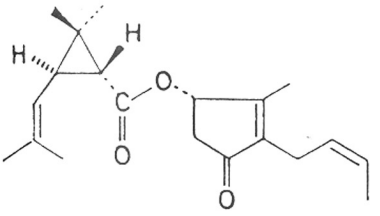


I

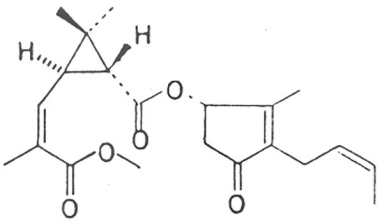
PYRETHRIN I



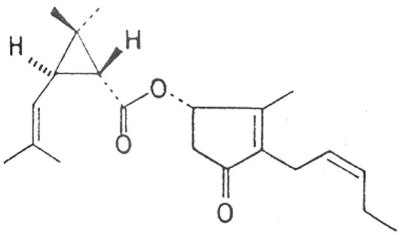
PYRETHRIN II



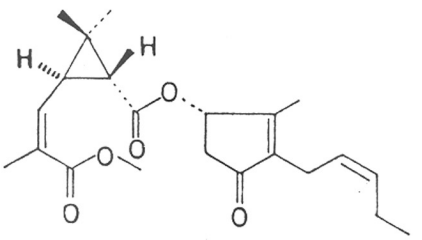
CINERIN I



CINERIN II

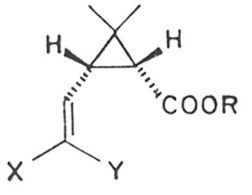


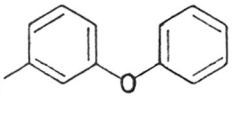
JASMOLIN I

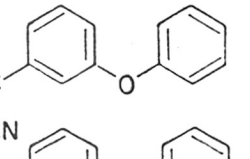


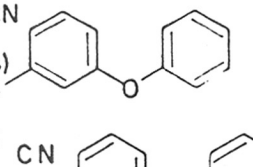
JASMOLIN II

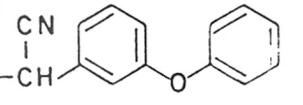
CHART I (contd.)

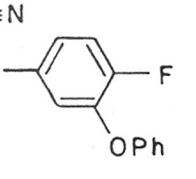


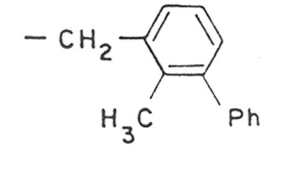
PERMETHRIN X , X = Cl , R = 

CYPERMETHRIN X,X = Cl , R = 

DELTAMETHRIN X,X = Br , R = 

CYHALOTHRIN X = Cl , Y = CF_3 , R = 

BAYTHROID X , Y = Cl , R = 

FMC — 54800 X = Cl , Y = CF_3 , R = 

This requires 1R configuration[5,10] in the cyclopropanecarboxylic acids. Inversion at this chiral centre, drastically alters potency without greatly changing the physical properties. Thus (+) trans and (+) cis chrysanthemic acid esters possessing 1R configuration with suitable alcohol moieties are found to be active insecticides while esters of (-) trans and (-) cis chrysanthemic acids posessing 1S configuration are inactive or much less active. In NRDC-143 and NRDC-149 1R cis isomer is twice[11] more toxic to insects than the corresponding 1R trans isomer. Therefore 1R cis pyrethroids are generally preferred to the corresponding 1R trans pyrethroids from the point of potency criterion.

It has been widely recognised that technical changes and innovations are of major importance in economic growth. New insecticides will continue to be needed in the foreseeable future, for controlling pests more effectively and economically, by replaing the existing compounds which have ceased to give reliable control because of development of immunity by insects or on account of deficiencies such as those mentioned earlier and lack of appropriate mobility in soil or plant.

The work described in this chapter is aimed at contributing towards synthesis and development of new insecticides, concentrating on "secoypyrthroids" or "cut-up-chrysanthemates", which can be considered as acyclic analogues of pyrethroids and also to understand the fundamental principles determining the relationship between chemical structure and biological activity.

Staudinger and Ruzicka[12] in 1920 prepared pyrethronyl esters of various acids such as aliphatic, olefinic, aromatic, terpenic, bearing some structural resemblance to chrysanthemic acid and examined their biological activity.

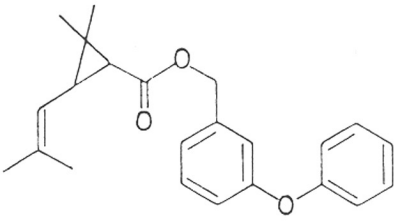
The esters thus synthesised, did not show any appreciable insecticidal activity and hence it was commonly believed that the cyclopropanecarboxylic acid moiety is essential for insecticidal activity.

An important landmark in the evolution of pyrethroids for use in agriculture was the discovery of an insecticide viz. fenvalerate[13] which is ∝-cyano-3-phenoxybenzyl 2-(4-chlorophenyl)-3-methyl butyrate by Ohono et al. In the structure of fenvalerate the isopropyl group on the benzylic carbon atom can be considered as the steric equivalent of gem-dimethyl group of chrysanthemates and aromatic ring as the equivalent of vinyl side chain. The insecticidal activity of 2-aryl 3-methyl butyrates (I) is very sensitive to structural changes and substitution pattern (Chart II). Thus, esters containing the substituents[14] like isopropyl, isopropenyl or t-butyl are highly toxic to insects, while the corresponding unsubstituted as well as the ∝-methyl, propyl, n-butyl and higher alkyl analogues are non-toxic. The ∝-diethyl compound (II) is less toxic than the∝-isopropyl derivative. Marked enhancement is observed when appropriate functions such as methyl, methoxy, chloro, bromo groups are introduced in the para or meta position of phenyl group (Chart II). Substitution in ortho position causes decrease in insecticidal activity. In general esters of 3-phenoxybenzyl and ∝-cyano 3-phenoxy benzyl alcohol are several times more toxic than those with 5-benzyl-3-furylmethyl, 5-propargyl-2-furylmethyl and allethronyl alcohols.

The dichlorostere (III) of isopropyl compound is inactive, possibly because HCl is eliminated extremely rapidly to give monochloro olefin, lacking structural characteristic of insecticidal action. The isosteric amines (IV) and carbamates (V)[14] are also inactive. Esters VI, VII, VIII, IX were found to be inactive.

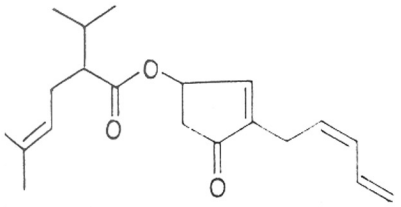
These comparative results suggest that the presence of a gem-dimethyl

CHART II

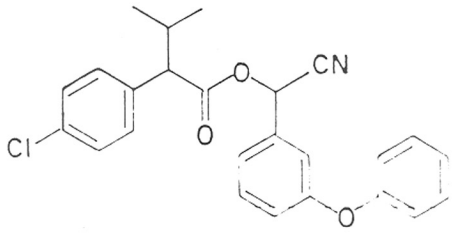


PERMETHRIN

ELLIOTT, FUJIMOTTO, 1971

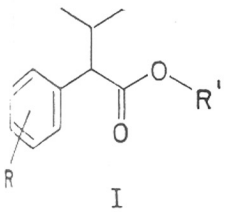


STAUDINGER AND RUZICKA, 1924

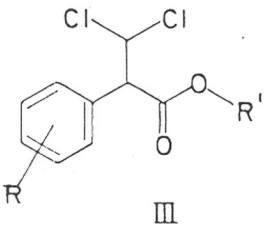


FENVELERATE

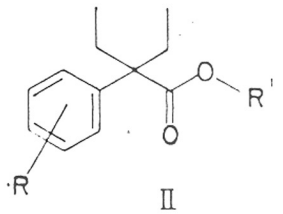
OHONO et al, 1974



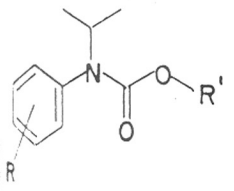
I



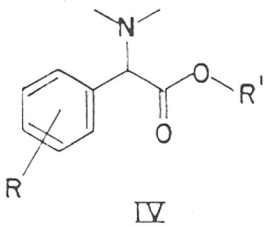
III



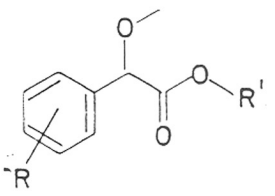
II



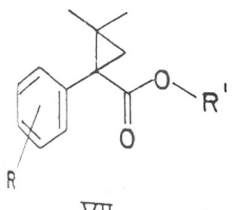
V



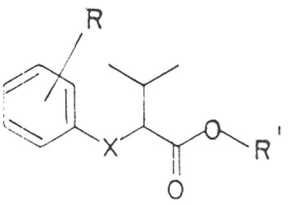
IV



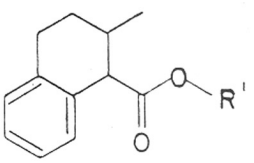
IX



VII



VI, X = CH_2, O



VIII

R = Cl, Br, Me, OMe ; R' = 3-$CH_2C_6H_4OPh$ or 3-$CH(CN)C_6H_4OPh$

or its steric equivalent β to the carboxylate function is one of the important structural features contributing towards insecticidal activity, both in the case of chrsaynthemates and α-substituted phenyl acetates.

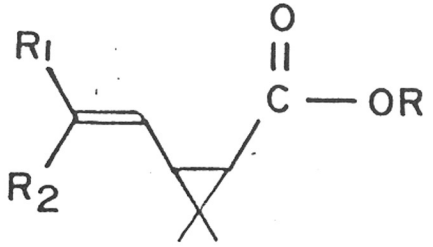
Subsequent studies on the acid moiety of these insecticides have shown that the presence of intact cyclopropane ring is unnecessary for high insecticidal activity[15-22]. This suggests that an insecticidally active analogue of cyclopropyl pyrethroid may be a ring cleaved or seco product. The study of secopyrethroids has attracted much attention in recent years because of their promising biological activity and simplicity of structure. Secopyrethroids can be considered as open chain equivalents of active cyclopropanecarboxylates and derived from the latter by cleavage of cyclopropane ring. Cyclopropane ring of pyrethroids can be cleaved in three different ways leading to three possible types of "cut up chrysanthemates" or "secopyrethroids" (Chart III). In the first two classes, the vinyl group and the carboxylate functions are separated by a two carbon unit, with substituents on α or β carbon atom, whereas in the third case they are separated by a three carbon chain.

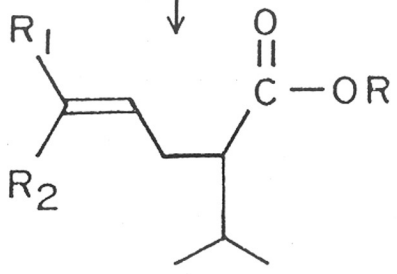
Synthesis of seco -pyrethroids

Some syntheses of "secopyrethroids" are on record [15-22] most of these compounds are patented[19-22] for insecticidal activity. Some novel synthetic approaches for both 2,3- and 1,3-secopyrethroids are given in charts IV and V.

In our laboratory 3-phenoxybenzyl 2-alkyl 5-methyl hex-4-enoates and 2-alkyl-pent-4-enoates have been synthesised[23] (Scheme A) starting from diethyl malonate employing a simple sequence of reactions like alkylation, decarbethoxylation and transesterification. Many of these esters exhibited

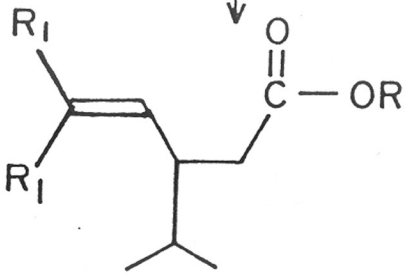
CHART III





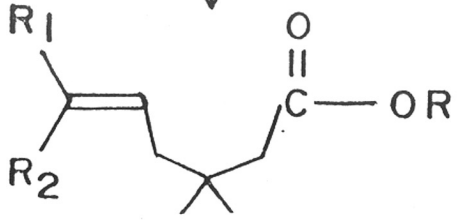
I

2,3-Secopyrethroids



II

1,2-Secopyrethroids

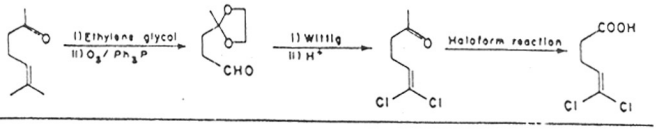


III

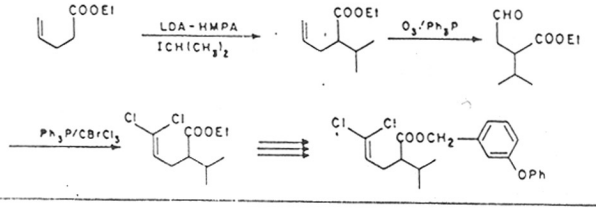
1,3-Secopyrethroids

CHART IV

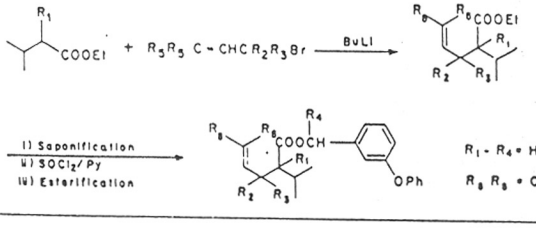
A) W. G. TAYLOR (1980)



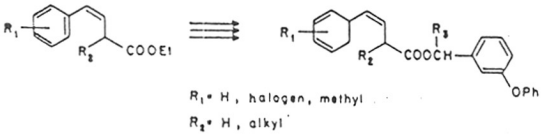
B) W. G. TAYLOR (1984)



C) WINTERNITZ PAROL (Hoffmann La Roche und Co)

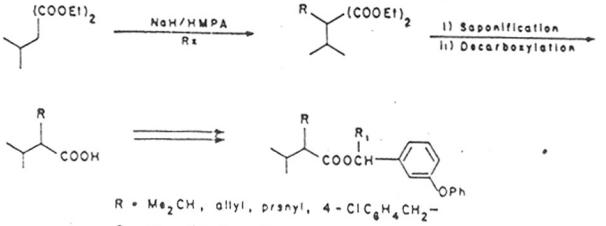


D) MEYER W et al



R_1 = H, halogen, methyl
R_2 = H, alkyl
R_3 = H, $-C\equiv N$, $-C\equiv CH$

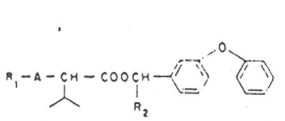
E) BULL MICHAEL et al



R = Me_2CH, allyl, propyl, 4 - $ClC_6H_4CH_2$-
R_1 = H, $-C\equiv N$, $-C\equiv CH$

CHART V

F) KUTSUDA et al (1980)



I

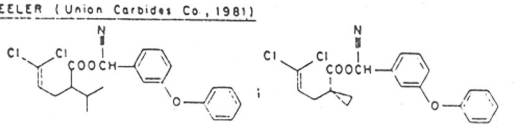
A = O, NH, CH_2

A = O or NH, R = alkyl or alkenyl, haloalkyl, haloalkenyl radical with 2 to 6 carbon atoms

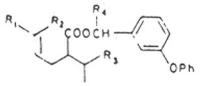
A = CH_2, R_1 = Haloalkyl or haloalkenyl radical with 1-5 carbon atoms

R_2 = H or C≡N

G) T N WHEELER (Union Carbides Co., 1981)



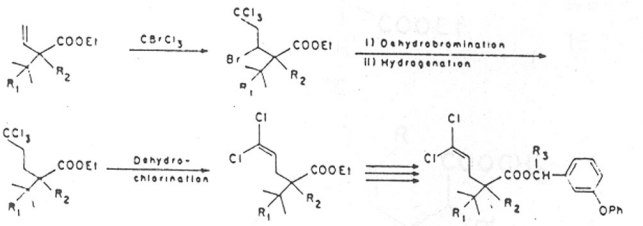
H) DRABEK J et al (Ciba-Geigy A-G)



R, R_2 = Cl, Br; R_3, R_1 = H, Me

R_2 = H, Cl; R_4 = H, −C≡N, −C≡CH

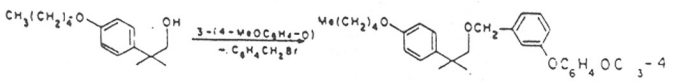
I) OMURA Y (Kuraray Co Ltd)



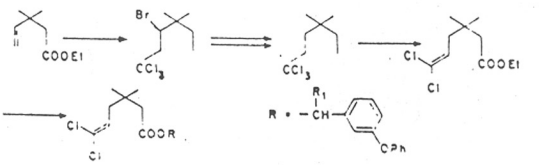
R_1 = Cl, Br, H; R_2 = H, alkyl, $-C{\equiv}CR_3$, $-CH_2CH=CR_1R_1$

R_3 = H, −C≡N, −C≡CH

J) N. UMEMOTO

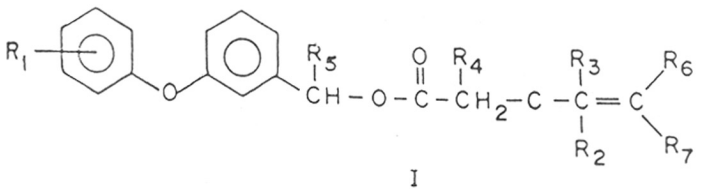


K) OMURO et al



R_1 = −CN, −C≡H, H

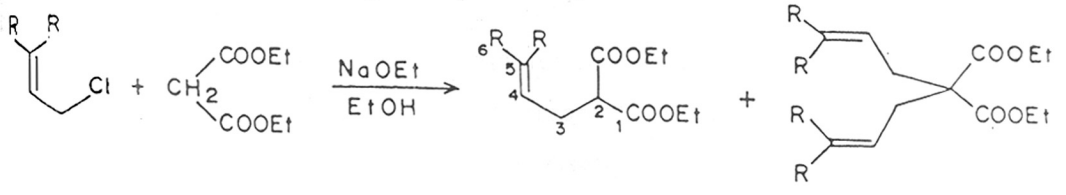
SCHEME A



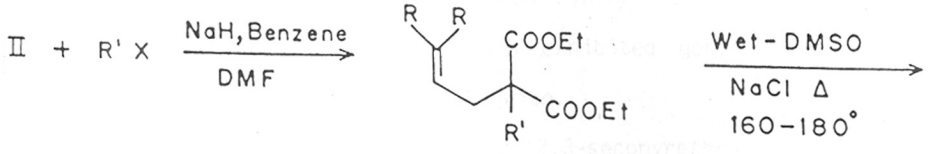
I

R_1 to R_5 = Alkyl or H

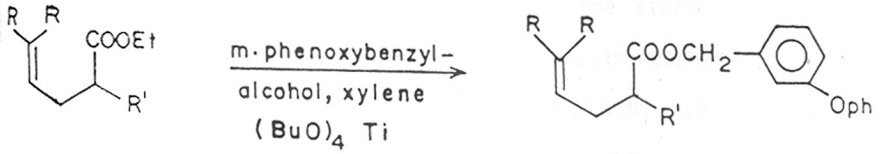
R_6 & R_7 = Halogen.



II III



IV



V VI

VII

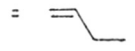
a. R = H , R' = H

b. R = H , R' = CH_3

c. R = H , R' = CH_2CH_3

d. R = H , R' = $CH(CH_3)_2$

e. R = H , R' = CH_2- 

f. R = H , R' = 

g. R = CH_3 , R' = H

h. R = CH_3 , R' = CH_3

i. R = CH_3 , R' = CH_2CH_3

j. R = CH_3 , R' = $CH(CH_3)_2$

k. R = CH_3 , R' = CH_2- 

l. R = CH_3 , R' = 

insecticidal activity against musca domestica and adult Aedes aegyptii at moderately lower concentrations.

By following a slightly modified procedure 3-phenoxybenzyl 2-isopropyl 5,5- dichloro/dibromo pent-4-enoates were synthesised[24] (Scheme B) showing better insecticidal and larvicidal activity against musca domestica (1 µg/ insect) and 100% mortality against 4th Instar mosquito larvae (aedes aegyptii) at 10 ppm dose. They also showed comparable activity against adult aedes aegyptii.

The same intermediate viz. α -isopropyl allyl diethylmalonate has also been converted into 1,3-secopyrethroids (Scheme B).

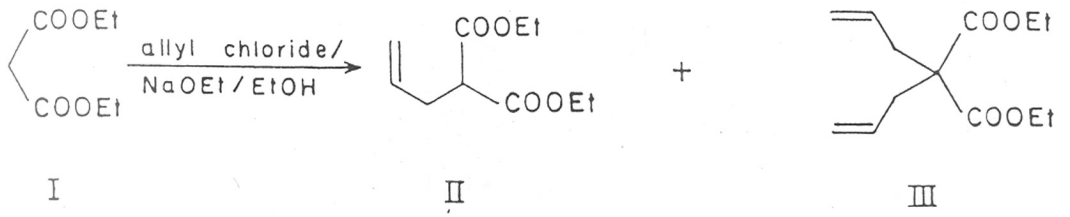
In another sequence of reactions, 3-phenoxybenzyl 2-isopropyl-5-chloro/cyano hex-4-enoates have been synthesised[25] starting from 6-methyl-hept-5-ene-2-one (Scheme C), which exhibited good larvicidal activity at 10 ppm dose against 4th Instar mosquito.

It appears from the study of 2,3-secopyrethroids that the presence of an isopropyl group which acts as the steric equivalent of gem-dimethyl function of cyclopropane of pyrethroids, is responsible for the higher insecticidal activity as the secopyrethroids with other lower alkyl and benzyl substituents were found to be either much less active or inactive.

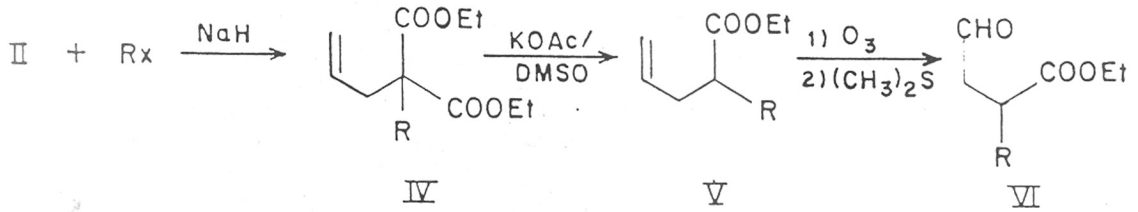
In order to find out whether an isopropyl group on the carbon atom γ to carbooxylic function acts as a steric equivalent of gem-dimethyl function of pyrethroids, it was felt desirable to synthesise some 1,2-secopyrethroids possessing an isopropyl group γ to carboxylate function and a double bond in δ position or an aromatic equivalent in its place.

With this objective in view, work was undertaken on the total synthesis of esters, structurally related to 1,2-secochrysanthemates to understand more about the structural requirement for insecticidal activity.

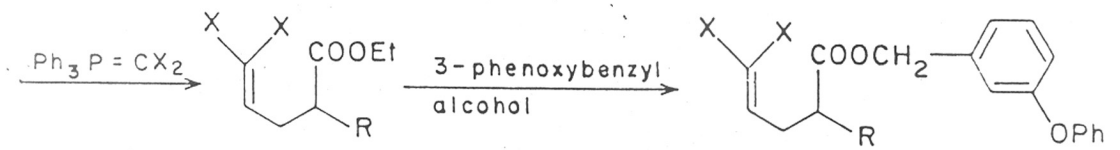
SCHEME B



I II III



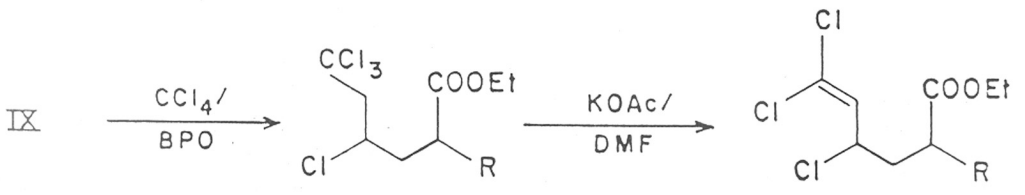
IV V VI



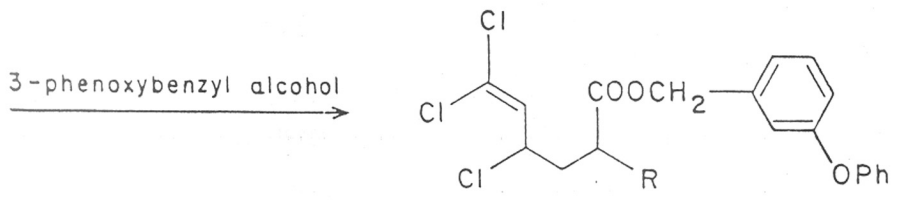
VII VIII

X = Cl or Br

R = a, isopropyl; b, benzyl



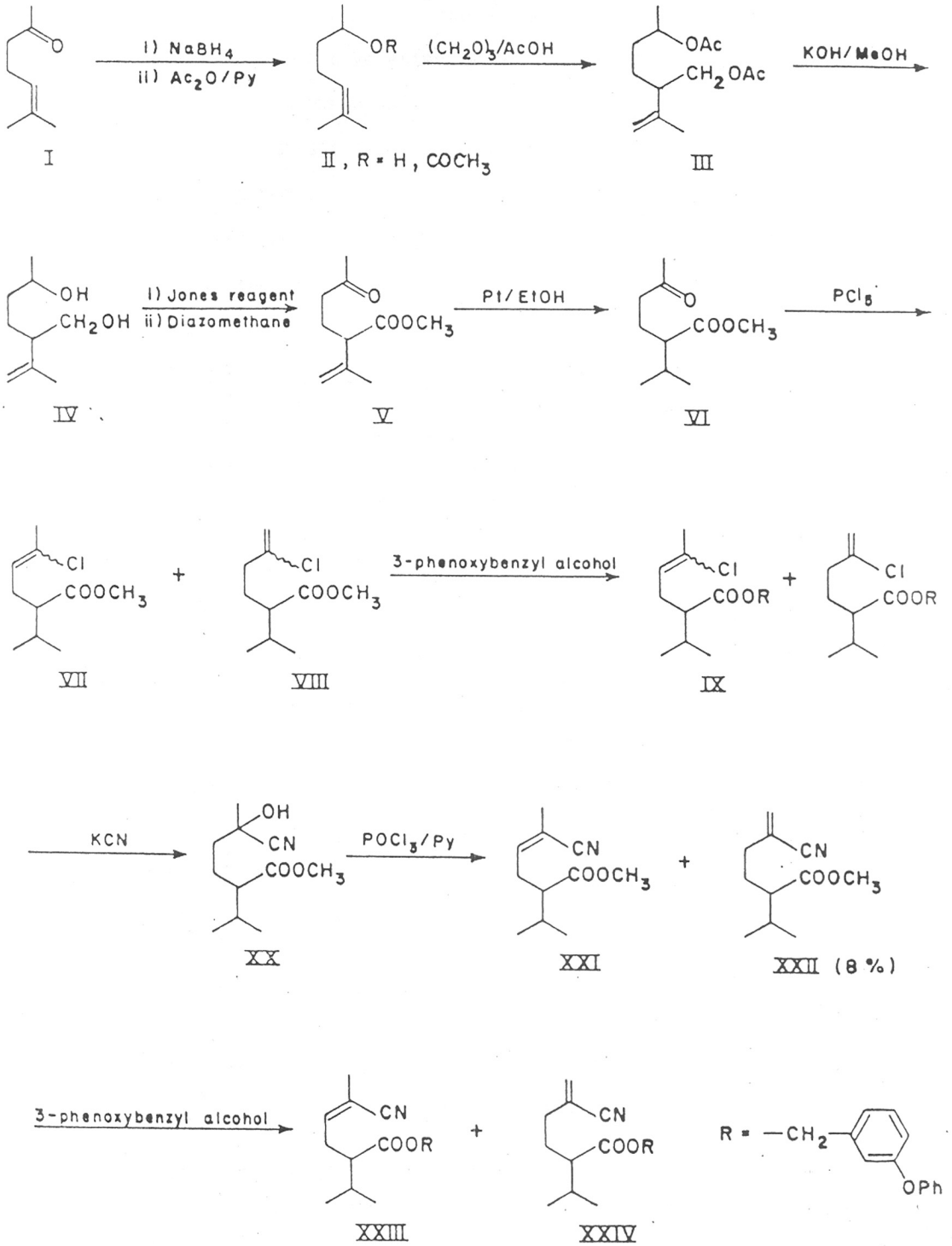
X XI



XII

R = a, isopropyl; b, benzyl

SCHEME C


I
i) NaBH4
ii) Ac2O/Py
II, R = H, COCH3
(CH2O)3/AcOH
III
KOH/MeOH
IV
i) Jones reagent
ii) Diazomethane
V
Pt/EtOH
VI
PCl5
VII
VIII
3-phenoxybenzyl alcohol
IX
KCN
XX
POCl3/Py
XXI
XXII (8 %)
3-phenoxybenzyl alcohol
XXIII
XXIV
R = —CH2
OPh

In most of the esters prepared, the alcohol moiety was 3-phenoxy benzyl alcohol, as it is known to give esters with low mammalian toxicity and high insecticidal activity in case of pyrethroids.

Initially the synthesis of 1,2-secopyrethroid analogues possessing a phenyl or a p-substituted phenyl group in place of a double bond at δ, ϵ position and an alkyl substituent in γ position was undertaken.

Subsequently, the synthesis of 1,2-secochrysanthemate analogues was also carried out.

PRESENT WORK

Synthesis of 3-phenoxybenzyl 3-alkyl-3-phenyl-/p-substituted phenyl propionates (19) to (24) (Scheme I)

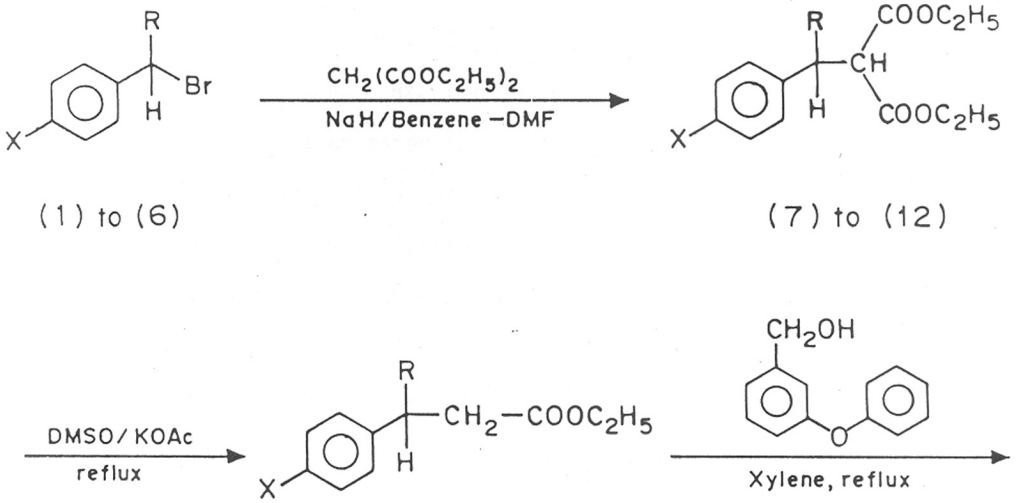
The title compounds in which the conventional vinyl function is replaced by an aromatic ring, resemble structurally with the 1,2-secopyrethroids of the type I (Chart III).

In addition, these esters are structurally related to higher homologues of the potent insecticide fenvalerate (Chart II).

The aralkyl bromides (1) to (6) (Scheme I) required for the monoalkylation of diethyl malonate were obtained by bromination of the corresponding alcohols, using PBr_3. The respective alcohols were either prepared from the corresponding aldehydes, using appropriate Grignard reagents or by $NaBH_4$ reduction of the acylophenones.

Monoalkylation of diethyl malonate with bromide (1) was carried out by using one equivalent of sodium hydride in benzene-DMF to afford the diester (7).

SCHEME - (I)



(1) to (6)

(7) to (12)

(13) to (18)

(19) to (24)

(1),(7), (13),(19) R = CH_3, X = Cl

(2),(8), (14),(20) R = C_2H_5, X = Cl

(3),(9), (15),(21) R = H, X = Cl

(4),(10),(16),(22) R = CH_3, X = NO_2

(5),(11),(17),(23) R = CH_3, X = H

(6),(12),(18),(24) R = C_2H_5, X = H

IR: 1760, 1740 (ester carbonyls) cm^{-1}.

PMR: 1.08 (3H, t, J=6.4 Hz, one of the ester methyls), 1.32, 1.36 (6H, t overlapping a d, another ester methyl and secondary methyl), 3.52 (2H, m overlapping a doublet, benzylic and methine proton), 3.96, 4.24 (2H each, q each, J=6.4 Hz each, methylenes of ester), 7.32 (4H, m, aromatic protons).

Decarbethoxylation of the diester (7) using KOAc in refluxing (wet) DMSO afforded the monoester (13).

IR: 1730 (ester carbonyl) cm^{-1}.

PMR: 1.13 (3H, t, J=7 Hz ester methyl), 1.23 (3H, d, J=7 Hz, secondary methyl), 2.43 (2H, d, J=7 Hz, $COCH_2$), 3.2 (1H, m, benzylic proton), 3.9 (2H, q, J=7 Hz, methylene of ester), 7.1 (4H, m, aromatic protons).

Transesterification of (13) with 3-phenoxybenzyl alcohol catalysed by butyl titanate afforded the ester (19).

IR: 1735 (ester carbonyl), 1590, 1490 (aromatic) cm^{-1}.

PMR: 1.21 (3H, d, J=7 Hz, secondary methyl), 2.46 (2H, d, J=7 Hz, $COCH_2$), 3.1 (1H, m, benzylic tertiary proton), 4.8 (2H, s, benzylic protons), 6.6 to 7.3 (13H, br m, aromatic protons).

By following an analogous sequence of reactions the other 3-phenoxybenzyl esters (20) to (24) have been synthesised. The spectral characteristics of the intermediates and the final esters are described below.

Diester (8)

IR: 1750, 1725 (ester carbonyls) cm^{-1}.

PMR: 0.72 (3H, t, J=8 Hz, primary methyl), 1.0, 1.32 (3H each, t each, J=8 Hz each, primary methyls of ester), 1.66 (2H, m, methylene), 3.32 (2H, m, methine and benzylic protons), 3.92, 4.26 (2H each, q each, J=6.4 Hz each

methylenes of ester), 7.1 to 7.4 (4H, m, aromatic protons)

Monoester (**14**)

IR: 1740 (ester carbonyl) cm^{-1}.

PMR: 0.8 (3H, t, J=8 Hz, primary methyl), 1.12 (3H, t, J=8 Hz, methyl of ester), 1.64 (2H, m, methylene), 2.56 (2H, d, J=6.4 Hz, $COCH_2$), 2.96 (1H, m, benzylic proton), 4.08 (2H, q, J=6.4 Hz, methylene of ester), 6.96 to 7.36 (4H, m, aromatic protons).

3-Phenoxybenzyl ester (**20**)

IR: 1740 (ester carbonyl), 1595, 1490 (aromatic) cm^{-1}.

PMR: 0.93 (3H, t, J=7 Hz, methyl), 1.3 (2H, m, methylene), 2.53 (2H, d, J=6 Hz, $COCH_2$), 2.97 (1H, m, benzylic proton), 4.9 (2H, s, benzylic CH_2), 6.66 to 7.4 (13H, br m, aromatic protons).

Diester (**9**)

IR: 1745, 1730 (ester carbonyls) cm^{-1}.

PMR: 1.23 (6H, t, J=7 Hz, methyl), 3.1 (2H, d, J=7 Hz, benzylic protons), 3.43 (1H, dd, J_1=6 Hz, J_2=9 Hz, proton α to ester), 4.13 (4H, q, J=7 Hz, ester methylene), 7.2 (4H, s, aromatic protons).

Monoester (**15**)

IR: 1740 (ester carbonyl) cm^{-1}.

PMR: 1.23 (3H, t, J=7 Hz methyl), 2.56 (2H, m, methylene adjacent to carbonyl), 2.83 (2H, m, benzylic protons), 4.1 (2H, q, J=7 Hz, methylene of ester), 7.13 (4H, br m, aromatic protons).

3-Phenoxybenzyl ester (**21**)

IR: 1740 (ester carbonyl), 1595, 1495 (aromatic) cm^{-1}.

PMR: 2.58 (2H, m, methylene adjacent to carbonyl), 2.8 (2H, m, benzylic protons), 5.0 (2H, s, $-OCH_2$), 6.76 to 7.4 (13H, br m, aromatic protons).

Diester (10)

IR: 1750, 1735 (ester carbonyl) cm^{-1}.

PMR: 1.06 (3H, t, J=7 Hz, one of the ester methyls), 1.36 (6H, d, overlapping at t, ester methyl and secondary methyl), 3.56 (2H, m, overlapping a d, both methine protons), 3.93, 4.2 (2H each, q each, J=7Hz each, ester methylenes), 7.43 (2H, d, J=9 Hz aromatic protons meta to nitro), 8.13 (2H, d, J=9 Hz, aromatic protons ortho to nitro).

Monoester (16)

IR: 1730 (ester carbonyl) cm^{-1}.

PMR: 1.16 (3H, t, J=7 Hz, ester methyl), 1.33 (3H, d, J=6 Hz, secondary methyl), 2.50 (2H, d, J=7 Hz, $COCH_2$), 3.33 (1H, m, benzylic proton), 4.0 (2H, q, J=7 Hz, ester methylene), 7.33 (2H, d, J=9 Hz, aromatic protons meta to nitro), 8.06 (2H, d, J=9 Hz, aromatic protons ortho to nitro group).

3-Phenoxybenzyl ester (22)

IR: 1730 (ester carbonyl), 1580, 1485 (aromatic) cm^{-1}.

PMR: 1.3 (3H, d, J=7 Hz, secondary methyl)2.56 (2H, d, J=7 Hz, $COCH_2$), 3.3 (1H, m, benzylic proton), 4.93 (2H, s, $COOCH_2$), 6.73 to 7.6 (11H, brm aromatic protons of 3-phenoxybenzyl group and protons meta to nitro group), 8.0 (2H, d, J=9 Hz, aromatic protons ortho to nitro group).

Diester (11)

IR: 1750,1730 (ester carbonyl) cm^{-1}.

PMR: 0.93 (3H, t, J=7 Hz, one of the ester methyls), 1.3 (6H, t, overlapping a d, another ester methyl and secondary methyl), 3.6 (2H, m, both the methine protons), 3.94, 4.13 (2H each q each, J=6.4 Hz each, ester methylenes),

7.13 (5H, br s, aromatic protons).

Monoester (17)

IR: 1735 (ester carbonyl) cm^{-1}.

PMR: 1.13 (3H, t, J=6 Hz, ester methyl), 1.3 (3H, d, J=7 Hz secondary methyl), 2.36 (2H, d, J=7 Hz, methylene α to ester carbonyl), 3.16 (1H, m, benzylic proton), 3.93 (2H, q, J=7 Hz, ester methylene), 7.0 (5H, br s, aromatic protons).

3-Phenoxybenzyl ester (23)

IR: 1735 (ester carbonyl), 1585, 1485 (aromatic) cm^{-1}.

PMR: 1.23 (3H, d, J=7 Hz, methyl), 2.4 (2H, d, J=7 Hz, $COCH_2$), 3.16 (1H, m, benzylic proton), 4.85 (2H, s, benzylic CH_2), 6.7 to 7.18 (14H, m, aromatic protons).

Diester (12)

IR: 1750, 1730 (ester carbonyl) cm^{-1}.

PMR: 0.73 (3H, t, J=7 Hz, primary methyl), 0.91, 1.1 (3H each, t each, J=7 Hz each, ester methyls), 1.66 (2H, m, methylene), 3.3 (2H, m, both the methine protons), 3.8, 4.1 (2H each, q each, J=8 Hz each, methylenes of ester), 6.9 to 7.16 (5H, br s, aromatic protons).

Monoester (18)

IR: 1735 (ester carbonyl) cm^{-1}.

PMR: 0.8 (3H, t, J=7 Hz, primary methyl), 1.13 (3H, t, J=7 Hz, ester methyl), 1.66 (2H, m, methylene), 2.53 (2H, d, J=7 Hz, methylene α to ester carbonyl), 2.93 (1H, m, benzylic proton), 4.0 (2H, q, J=7 Hz, ester methylene), 7.0 to 7.4 (5H, s, aromatic protons).

3-Phenoxybenzyl ester (24)

IR: 1735 (ester carbonyl), 1585, 1490 (aromatic) cm^{-1}.

PMR: 0.76 (3H, t, J=7 Hz, methyl), 1.56 (2H, m, methylene), 2.56 (2H, d, J=7 Hz, $COCH_2$), 2.9 (1H, m, benzylic proton), 4.86 (2H, s, CH_2OCO), 6.6 to 7.4 (14H, br m, aromatic protons).

However, alkylation of diethyl malonate with 1-bromo, 1-phenyl, 2-methyl propane was unsuccessful probably due to steric reasons. Under strong basic conditions elimination reaction predominated giving rise to styrene derivative.

Ethyl acetoacetate was alkylated with benzyl bromide in the presence of one equivalent of sodium ethoxide to afford ethyl α-benzylacetoacetate (25) as the major product (Scheme II).

IR: 1740, 1720 (carbonyls) cm^{-1}.

PMR: 1.16 (3H, t, J=7 Hz, ester methyl), 2.06 (3H, s, $COCH_3$), 3.06 (2H, d, J=7 Hz, benzylic protons), 3.56 (1H, t, J=7 Hz, methine proton), 4.03 (2H, q, J=7 Hz, ester methylene), 7.0 (5H, s, aromatic protons).

Ester (25) was further alkylated with methyl iodide in the presence of NaH/DMF in benzene to get the dialkyl ethylacetoacetate (26).

IR: 1740, 1720 (carbonyls) cm^{-1}.

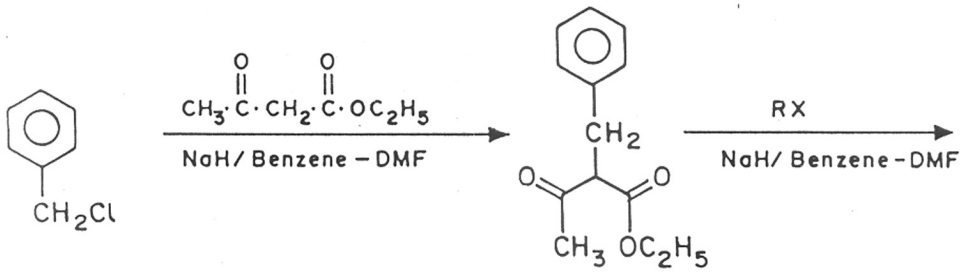
PMR: 1.16 (6H, s overlapping a t, tertiary methyl and ester methyl), 1.93 (3H, s, $COCH_3$), 2.93 (2H, dd, J_1=12 Hz, J_2=19 Hz, benzylic CH_2), 3.91 (2H, q, J=6 Hz, ester methylene), 6.7 (5H, br s, aromatic protons).

Deacetylation of (26) was achieved by refluxing it with sodium ethoxide in ethanol to furnish (29).

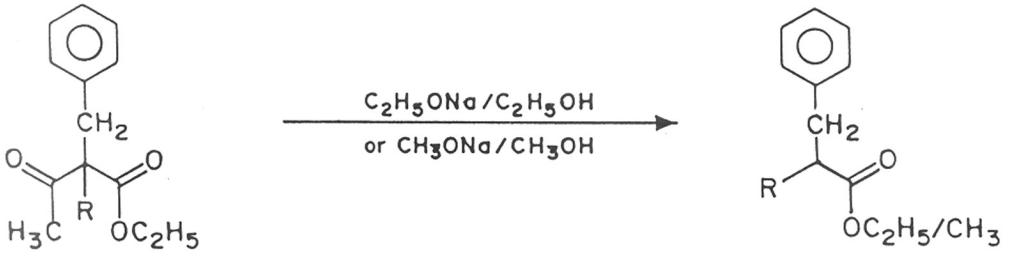
IR: 1730 (ester carbonyl) cm^{-1}.

PMR: 1.16 (6H, d overlapping a t, ester and secondary methyl), 2.56 (3H, m, benzylic CH_2 and tertiary proton), 3.96 (2H, q, J=7 Hz, ester methylene), 7.2 (5H, s, aromatic protons).

SCHEME-(II)



(25)



(26) R = CH_3

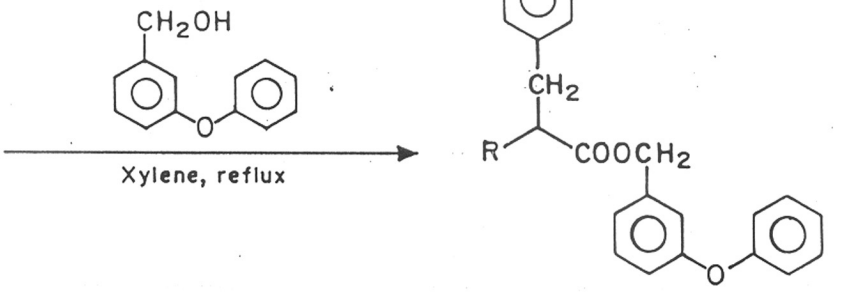
(27) R = C_2H_5

(28) R = $CH(CH_3)_2$

(29) R = CH_3

(30) R = C_2H_5

(31) R = $CH(CH_3)_2$



(32) R = CH_3

(33) R = C_2H_5

(34) R = $CH(CH_3)_2$

Transesterification as described earlier of (29) gave the ester (32).

IR: 1730 (ester carbonyl), 1585, 1490 (aromatic) cm^{-1}.

PMR: 1.13 (3H, d, J=7 Hz, secondary methyl), 2.7 (3H, m, benzylic CH_2 and CH α to ester carbonyl), 4.9 (2H, s, $COOCH_2$), 6.76 to 7.3 (14H, br m, aromatic protons).

Alkylation of (25) with ethyl iodide afforded the dialkylated keto ester (27).

IR: 1750, 1730 (carbonyls) cm^{-1}.

PMR: 0.83 (3H, t, J=7 Hz, primary methyl), 1.2 (3H, t, J=7 Hz ester methyl), 1.83 (2H, q, J=7 Hz, alkyl methylene), 2.01 (3H, s, $COCH_3$), 3.1 (2H, s, benzylic CH_2), 4.1 (2H, q, J=7 Hz, ester methylene), 7.1 (5H, br s, aromatic protons).

Deacetylation of (27) by refluxing it with sodium methoxide in dry methanol afforded the methyl ester (30).

IR: 1710 (carbonyl) cm^{-1}.

PMR: 0.9 (3H, t, J=7 Hz, primary methyl), 1.5 (2H, q, J=7 Hz, alkyl methylene), 2.46 (1H, m, tertiary proton), 2.7 (2H, m, benzylic CH_2), 3.53 (3H, s, ester methyl), 7.08 (5H, br s, aromatic protons).

Transesterification of (30) gave the ester (33).

IR: 1730 (carbonyl) 1580, 1485 (aromatic) cm^{-1}.

PMR: 0.86 (3H, t, J=7 Hz, primary methyl), 1.5 (2H, m, alkyl methylene), 2.5(1H, m, tertiary proton), 2.68 (2H, m, benzylic CH_2), 4.83 (2H, s, $COOCH_2$), 6.63 to 7.16 (14H, m, aromatic protons).

Alkylation of (25) with isopropyl iodide gave the compound (28).

IR: 1735, 1705 (carbonyls) cm^{-1}.

PMR: 0.91, 0.99 (3H each, d each, J=6.9 Hz each, secondary methyls of isopropyl), 1.2 (3H, t, J=6.4 Hz, primary methyl of ester), 1.96 (3H, s, $COCH_3$), 2.4 (1H, m, methine proton), 3.18 (2H, dd, J_1=8 Hz, J_2=10 Hz, benzylic CH_2), 4.14 (2H, q, J=6.4 Hz, ester methylene), 7.2 (5H, s, aromatic protons).

Deacetylation of (28) afforded the ester (31).

IR: 1735 (ester carbonyl) cm^{-1}.

PMR: 0.96, 1.09 (3H each, d each, J=6.4 Hz each, isopropyl methyls), 1.96 (1H, m, methine proton of isopropyl), 2.56 (1H, m, methine proton adjacent to carbonyl), 2.92 (2H, d, J=5 Hz, benzylic CH_2), 3.48 (3H, s, ester methyl), 7.2 (5H, m, aromatic protons).

Compound (31) on transesterification gave the ester (34).

IR: 1730 (ester carbonyl), 1590, 1490 (aromatic) cm^{-1}.

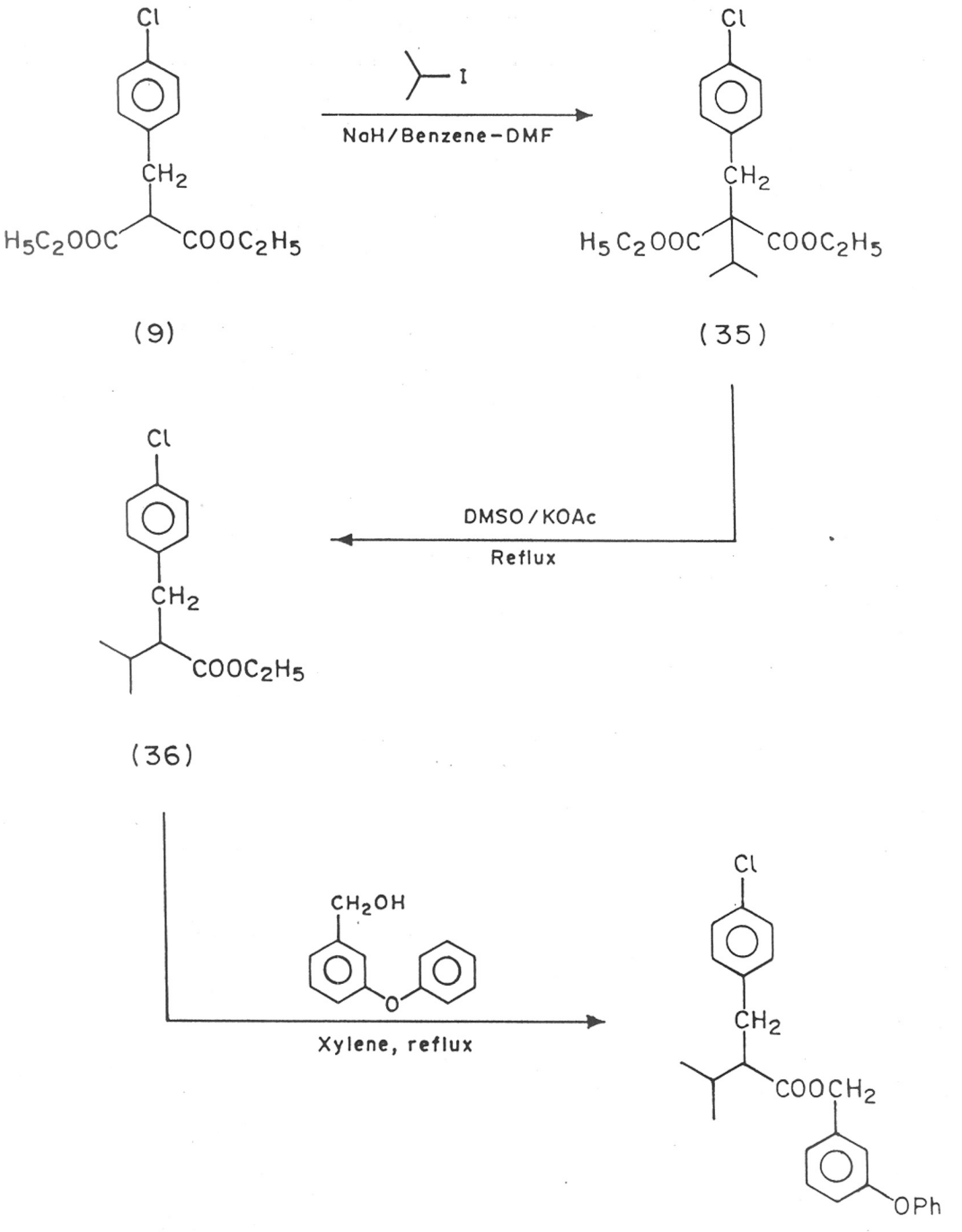
PMR: 0.93, 0.99 (3H each, d each, J=6 Hz each, secondary methyl of isopropyl), 1.8 (1H, m, methine proton of isopropyl), 2.36 (1H, m, methine proton adjacent to carbonyl), 2.83 (2H, d, J=8 Hz, benzylic CH_2), 4.8 (2H, s, benzylic CH_2 of ester), 6.7 to 7.36 (14H, m, aromatic protons).

Monoalkylation of diethyl malonate with p-chloro benzyl bromide, afforded the diester (9), which was further alkylated with isopropyl iodide to get the dialkylated diester (35) (Scheme III).

IR: 1755, 1735 (carbonyls) cm^{-1}.

PMR: 1.0, 1.1 (3H each, d each, J=7 Hz each, isopropyl methyls), 1.2 (6H, two overlapping t, primary ester methyls), 2.23 (1H, m, methine proton), 3.1 (2H, s, benzylic CH_2), 4.01 (4H, two overlapping q, methylenes of ester 7.1 (4H, br s, aromatic protons).

SCHEME-(III)


Cl
CH2
H5C2OOC
COOC2H5
I
NaH/Benzene-DMF
(9)
(35)
DMSO/KOAc
Reflux
(36)
CH2OH
O
Xylene, reflux
COOCH2
OPh
(37)

Decarbethoxylation of (35) gave the monoester (36).

IR: 1735 (ester carbonyl) cm^{-1}.

PMR: 0.98, 1.14 (3H each, d each, J=6.4 Hz each, isopropyl methyls), 1.06 (3H, t, J=8 Hz, ester methyl), 1.92 (1H, m, methine proton of isopropyl), 2.4 (1H, m, methine proton adjacent to carbonyl), 2.83 (2H, d, J=8 Hz, benzylic protons), 4.0 (2H, q, J=7 Hz, ester methylene), 7.15 (4H, m, aromatic protons).

Compound (36) was transesterified with 3-phenoxybenzyl alcohol to get the ester (37).

IR: 1735 (ester carbonyl), 1590, 1495 (aromatic) cm^{-1}.

PMR: 0.99, 1.04 (3H each, d each, J=6.4 Hz each, methyls of isopropyl), 1.96 (1H, m, methine proton of isopropyl), 2.52(1H,m, methine proton adjacent to carbonyl), 2.8 (2H, d, J=8 Hz, benzylic CH_2), 5.0 (2H, s, benzylic CH_2 of ester), 6.84 to 7.48 (13H, m, aromatic protons).

Reaction of isobutyraldehyde (38) with the Wittig reagent generated from triethyl phosphonacetate by treatment of latter with NaH afforded the unsaturated ester (39) (Scheme IV).

IR: 1730 (ester carbonyl) cm^{-1}.

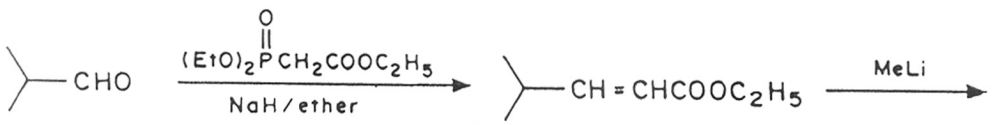
PMR: 1.12 (6H, t, J=7 Hz, isopropyl methyls), 1.3 (3H, t, J=7 Hz, ester methyl), 2.46 (1H, m, methine proton of isopropyl), 4.15 (2H, q, J=7 Hz, ester methylene), 5.6 (1H, d, J=15 Hz, α olefinic proton), 6.73, 7.0 (1H, dd, J_1=7 Hz, J_2=15 Hz, β olefinic proton).

Reaction of (39) with methyl lithium gave the tertiary alcohol (40).

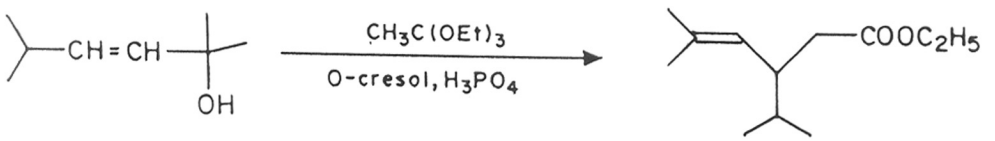
IR: 3380 (-OH) cm^{-1}.

PMR: 1.0 (6H, d, J=6.4 Hz isopropyl methyls), 1.3 (7H, s overlapping a m, methyls attached to carbon bearing -OH and methine proton), 2.22

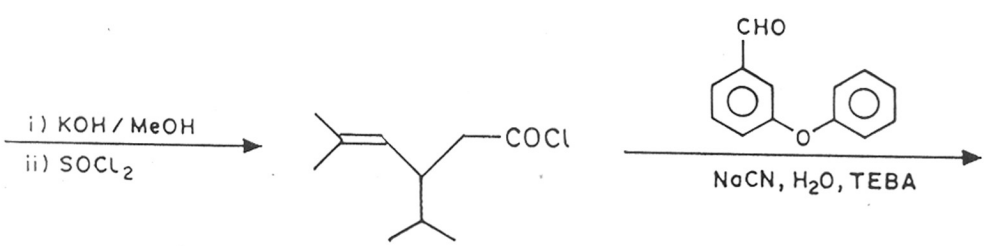
SCHEME - (IV)



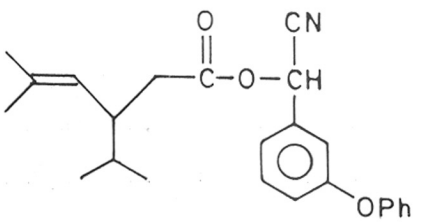
(38) (39)



(40) (41)



(42)



(43)

(1H, s, D_2O exchangeable -OH proton), 6.02 (2H, m, olefinic protons).

Claisen orthoester rearrangement of the tertiary alcohol (**40**) gave the ester (**41**).

IR: 1740 (ester carbonyl) cm^{-1}.

PMR: 0.81, 0.88 (3H each, d each, J=6 Hz each, isopropyl methyls), 1.21 (3H, t, J=7 Hz, ester methyl), 1.62, 1.72 (3H each, d each, J=2 Hz each, methyls on double bond), 1.8 to 2.37 (3H, m, ∝ methylene and isopropyl methine proton), 2.43 to 2.77 (1H, m, allylic methine proton), 4.08 (2H, q, J=7 Hz, ester methylene), 4.92 (1H, d, J=10 Hz, olefinic proton).

Ester (**41**) was saponified by KOH in methanol at room temperature to the acid, which was converted to the acid chloride (**42**), using $SOCl_2$ in dry benzene. The acid chloride was then reacted with ∝-cyano 3-phenoxy-benzyl alcohol, prepared in situ from 3-phenoxy benzaldehyde, sodium cyanide and water under phase transfer conditions to get the cyano ester (**43**).

IR: 1760 (carbonyl), 1595, 1495 (aromatic) cm^{-1}.

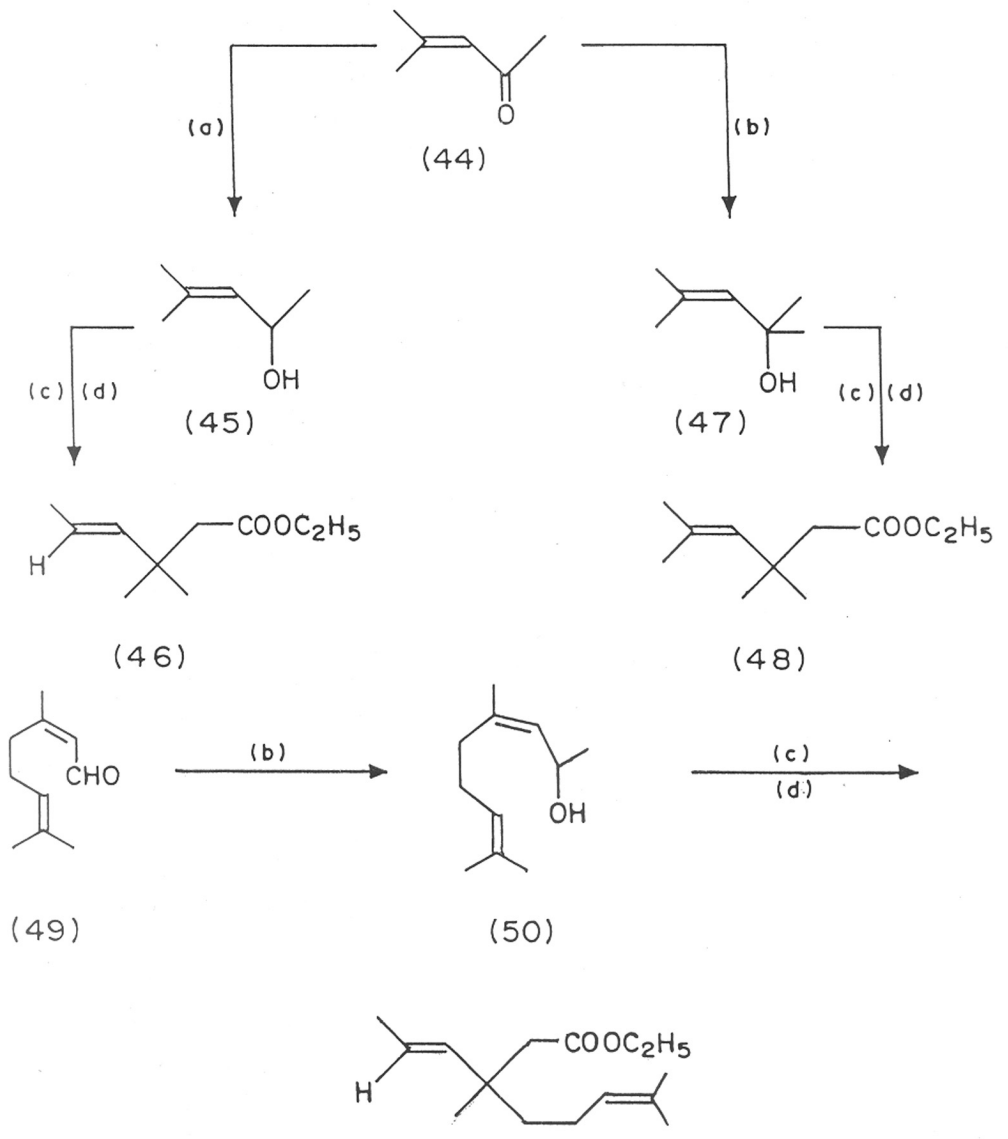
PMR: 0.84, 0.95 (3H each, t each, J=6.4 Hz each, isopropyl methyls), 1.54, 1.6, 1.65, 1.7 (7H, four s overlapping a m, vinyl methyls of both the diastereomers and isopropyl methine protons), 2.47 (3H, m, CH_2 to CO and allylic methine proton), 4.82 (1H, d, olefinic proton), 6.28, 6.5 (1H, singlets CHCN of both the diastereomers), 6.78 to 7.72 (9H, m, aromatic protons).

Reaction of (**44**) with $NaBH_4$ afforded the alcohol (**45**) (Scheme V).

IR: 3360 (hydroxy) cm^{-1}.

PMR: 1.1 (3H, d, J=7 Hz, secondary methyl), 1.66 (6H, s, vinyl methyls), 3.33 (1H, s, D_2O exchangeable OH proton), 4.46 (1H, m, CHOH proton) 5.2 (1H, d, J=9 Hz, olefinic proton).

SCHEME-(V)



(a) = $NaBH_4$

(b) = MeLi

(c) = $CH_3C(OEt)_3$

(d) = O-cresol, H_3PO_4

Claisen orthoester rearrangement of (45) gave the ester (46).

IR: 1740 (carbonyl) cm^{-1}.

PMR: 1.11 (6H, s, gem dimethyls), 1.22 (3H, t, J=7 Hz, ester methyl), 1.66 (3H, d, J=6 Hz, vinyl methyl), 2.24 (2H, s, C_2 methylene), 4.11 (2H, q, J=7 Hz, ester methylene), 5.4 (2H, m, olefinic porotons).

Reaction of (44) with MeLi gave the alcohol (47).

IR: 3360 (hydroxy) cm^{-1}.

PMR: 1.3 (6H, s, tert methyls), 1.63, 1.83 (3H each, s each, vinyl methyls), 3.46 (1H, s, D_2O exchangeable OH proton), 5.23 (1H, br s, olefinic proton).

Claisen orthoester rearrnagement of (47) afforded the ester (48).

IR: 1730 (carbonyl) cm^{-1}.

PMR: 1.15 (9H, s overlapping a t, gem dimethyls and ester methyl), 1.6, 1.7 (3H each, s each, vinyl methyls), 2.3 (2H, s, C_2 methylene), 4.0 (2H, q, J=8 Hz, ester methylene), 5.05 (1H, br s, olefinic proton).

Reaction of citral (49) with MeLi afforded the alcohol (50).

IR: 3340 (hydroxy) cm^{-1}.

PMR: 1.22 (3H, d, J=6 Hz, secondary methyl), 1.61 (3H, s, methyl on double bond), 1.68 (6H, two closely spaced singlets, vinyl methyls), 2.06 (4H, m, methylene protons), 4.15 (1H, s, D_2O exchangeable -OH proton), 4.57 (1H, m, CHOH proton), 5.15 (2H, m, olefinic protons).

Claisen orthoester rearrangement of (50) afforded the ester (51).

IR: 1740 (carbonyl) cm^{-1}.

PMR: 1.08 (3H, s, tertiary methyl), 1.2 (3H, t, J=7 Hz, ester methyl), 1.38 (2H, methylene protons), 1.58 (3H, d, J=6 Hz, vinyl secondary methyl), 1.62, 1.66 (3H each, s each, vinyl methyls at C_7), 1.88 (2H, m, allylic methylene protons), 2.48 (2H, s, CH_2 α to carbonyl), 4.1 (2H, q, J=7 Hz, ester methylene), 5.06 (1H, br t, C_6 olefinic proton), 5.37 (2H m, olefinic protons of the propenyl side chain).

EXPERIMENTAL

Ethyl 2-carbethoxy 3-p-chloro phenyl 3-methyl propionate (7)

Sodium hydride (50% emulsion, 1.268 g; 0.052 mole) was washed with (2 x 10 ml) dry benzene and then stirred with another 25 ml dry benzene and 8 ml dry DMF. To this, diethyl malonate (4.2 g; 0.026 mole) was added dropwise keeping the temperature between 5-10°. After the addition was completed, the contents were stirred for 0.5 hr at room temperature. The bromide (1) (5.8 g; 0.026 mole) in 10 ml dry benzene was added in one lot, followed by addition of 100 mg of TEBA and stirring continued for 1 hr at room temperature and for 3 hr. at the reflux temperature. The reaction mixture was allowed to attain the room temperature, diluted with water and organic layer separated. The aqueous layer was extracted with (2 x 30 ml) benzene. Combined organic layer was washed with water, brine, dried and distilled to remove the solvent and afford the diester (7), purified by distillation b.p.170°/2 mm (5.12 g; 65%).

IR: 2990, 1760, 1735, 1495, 1370, 1180, 1100, 1015, 830 cm^{-1}.

Ms: m/e (^{35}Cl) 298 (^{37}Cl) 300.

Analysis: Calculated for $C_{15}H_{19}ClO_4$

C, 60.30; H, 6.36; Cl, 11.90

Found: C, 60.47; H, 6.08; Cl, 11.73%.

Ethyl 3-methyl 3-p-chlorophenyl-propionate (13)

Diester (7) (4.5 g;0.015 mole), KOAc (3.0 g; 0.03 mole) and water (0.6 g; 0.03 mole) in DMSO (20 ml) were refluxed for 6 hr. The reaction mixture was cooled to room temperature, diluted with water and extracted with ether (2 x 30 ml). Combined ether layer was washed with water,brine,

dried and distilled to remove the solvent. The monoester (**13**) thus obtained was purified by distillation, b.p.135°/1 mm (2.49 g; 73%).

IR: 2980, 1730, 1495, 1370, 1170, 1090, 1015, 830 cm^{-1}.

Ms: m/e (^{35}Cl) 226 (^{37}Cl) 228

Analysis: Calculated for $C_{12}H_{15}ClO_2$

C, 63.57; H, 6.62; Cl, 15.67

Found: C, 63.70; H, 6.53; Cl, 15.30%.

3-Phenoxybenzyl 3-methyl 3-p-chlorophenyl propionate (19)

The monoester (**13**) (0.566 g; 0.0025 mole), 3-phenoxybenzyl alcohol (0.6 g; 0.003 mole) and butyl titanate (1 drop) were dissolved in dry xylene (20 ml) and the mixture refluxed for 12 hr. Xylene was removed by distillation under reduced pressure to obtain the 3-phenoxy benzyl ester (**19**), purified by column chromatography over alumina (grade II) and elution with pet.ether (0.637 g; 67%).

IR: 2965, 1735, 1590, 1490, 1440, 1380, 1260, 1220, 1170, 830, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 380 (^{37}Cl) 382

Analysis: Calculated for $C_{23}H_{21}ClO_3$

C, 72.53; H, 5.51; Cl, 9.32

Found: C, 72.41; H, 5.62; Cl, 9.45%.

Diesters **8** to **12**, monoesters **14** to **18** and 3-phenoxybenyl esters **20** to **24** were prepared and characterised in the same manner.

Diester (**8**)

Yield: 67%.

IR: 2960, 1735, 1485, 1360, 1300, 1170, 1020, 810 cm^{-1}.

Ms: m/e (^{35}Cl) 312 (^{37}Cl) 314

Analysis: Calculated for $C_{16}H_{21}ClO_4$

C, 61.49; H, 6.77; Cl, 11.34%.

Found: C, 61.33; H, 6.45; Cl, 11.22%.

Monoester (14)

Yield: 72%.

IR: 2980, 1740, 1500, 1370, 1240, 1170, 1095, 1020, 830 cm^{-1}.

Ms: m/e (^{35}Cl) 240 (^{37}Cl) 242

Analysis: Calculated for $C_{13}H_{17}ClO_2$

C, 64.91; H, 7.12; Cl, 14.74%.

Found: C, 64.79; H, 7.37; Cl, 14.85%.

3-Phenoxybenzyl ester (20)

Yield: 65%.

IR: 2950, 1740, 1585, 1490, 1440, 1260, 1210, 1160, 820, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 394 (^{37}Cl) 396.

Analysis: Calculated for $C_{24}H_{23}ClO_3$

C, 73.06; H, 5.87; Cl, 8.98

Found: C, 73.25; H, 5.52; Cl, 8.85%.

Diester (9)

Yield: 67%.

IR: 2900, 1740, 1460, 1380, 1265, 1175, 800 cm^{-1}.

Ms: m/e (^{35}Cl) 284 (^{37}Cl) 286.

Analysis: Calculated for $C_{14}H_{17}ClO_4$

C, 59.05; H, 5.97; Cl, 12.47

Found: C, 59.23; H, 6.08; Cl, 12.53%.

Monoester (15)

Yield: 70%.

IR: 3000, 1740, 1500, 1375, 1180, 1095, 1020, 820 cm^{-1}.

Ms: m/e (^{35}Cl) 212 (^{37}Cl) 214.

Analysis: Calculated for $C_{11}H_{13}ClO_2$

C, 62.11; H, 6.11; Cl, 16.7

Found: C, 62.25; H, 6.23; Cl, 16.47%.

3-Phenoxybenzyl ester (21)

Yield: 64%.

IR: 3050, 1740, 1595, 1495, 1450, 1260, 1160, 1100, 700 cm^{-1}.

Ms: m/e (^{35}Cl) 366 (^{37}Cl) 368.

Analysis: Calculated for $C_{22}H_{19}ClO_3$

C, 72.03; H, 5.18; Cl, 9.68

Found: C, 72.25; H, 5.23; Cl, 9.85%.

Diester (10)

Yield: 62%.

IR: 2980, 1750, 1735, 1600, 1520, 1350, 1020, 850 cm^{-1}.

Ms: m/e 309.

Analysis: Calculated for $C_{15}H_{19}NO_6$

C, 58.25; H, 6.14; N, 4.53

Found: C, 58.37; H, 6.17; N, 4.67%.

Monoester (16)

Yield: 67%.

IR: 2980, 1730, 1605, 1520, 1350, 1180, 1030, 855 cm^{-1}.

Ms: m/e 237.

Analysis: Calculated for $C_{12}H_{15}NO_4$

C, 60.75; H, 6.37; N, 5.90

Found: C, 60.67; H, 6.45; N, 6.08%.

3-Phenoxybenzyl ester (22)

Yield: 65%.

IR: 2960, 1730, 1580, 1520, 1485, 1440, 1340, 1250, 1210, 1160, 850, 750, 690 cm^{-1}.

Ms: m/e 391.

Analysis: Calculated for $C_{23}H_{21}NO_5$

C, 70.58; H, 5.37; N, 3.58

Found: C, 70.65; H, 5.23; N, 3.48%

Diester (**11**)

Yield: 66%.

IR: 2980, 1750, 1730, 1440, 1370, 1020, 750, 700 cm^{-1}.

Ms: m/e 264.

Analysis: Calculated for $C_{15}H_{20}O_4$

C, 68.16; H, 7.63

Found: C, 68.25; H, 7.75%.

Monoester (**17**)

Yield: 68%.

IR: 2970, 1735, 1610, 1495, 1440, 1370, 1280, 1170, 1020, 760, 700 cm^{-1}.

Ms: m/e 192.

Analysis: Calculated for $C_{12}H_{16}O_2$

C, 74.97; H, 8.39%.

Found: C, 74.85; H, 8.47%.

3-Phenoxybenzyl ester (23)

Yield: 62%.

IR: 3020, 2950, 1735, 1585, 1485, 1440, 1255, 1215, 1170, 750, 690 cm^{-1}.

Ms: m/e 346.

Analysis: Calculated for $C_{23}H_{22}O_3$

C, 79.74; H, 6.40

Found: C, 79.67; H, 6.53%.

Diester (12)

Yield: 67%.

IR: 2960, 1740, 1450, 1370, 1250, 1180, 1030, 750, 700 cm^{-1}.

M/s: m/e 278.

Analysis: Calculated for $C_{16}H_{22}O_4$

C, 69.04; H, 7.97

Found: C, 69.25; H, 8.15%.

Monoester (18)

Yield: 72%.

IR: 2960, 1735, 1495, 1445, 1375, 1240, 1160, 1025, 750, 700 cm^{-1}.

Ms: m/e 206.

Analysis: Calculated for $C_{13}H_{18}O_2$

C, 75.69; H, 8.80%.

Found: C, 75.56; H, 9.11%.

3-Phenoxybenzyl ester (24)

Yield: 63%.

IR: 2960, 1735, 1585, 1490, 1440, 1380, 1245, 1210, 1160, 750, 690 cm^{-1}.

Ms: m/e 360.

Analysis: Calculated for $C_{24}H_{24}O_3$

C, 79.97; H, 6.71

Found: C, 79.82; H, 6.85%.

Ethyl α-benzylacetoacetate (25)

To a stirred solution of sodium ethoxide in ethanol [prepared by dissolving sodium (2.3 g; 0.1 mole) in dry ethanol (100 ml)] was added ethyl acetoacetate (13.0 g; 0.1 mole) dropwise and stirring continued for 2 hr. A solution of benzyl chloride (12.6 g; 0.1 mole) in dry ethanol (15 ml) was then added dropwise and the mixture stirred for 24 hr., after which it was refluxed for 2 hr. Ethanol was removed by distillation under reduced pressure, residue diluted with water and extracted with ether (4 x 50 ml). Removal of ether furnished the keto ester (25), purified by distillation, b.p.110-20°/2 mm, (15.3 g; 70%).

IR: 2980, 1740, 1720, 1550, 1500, 1360, 1030, 855, 750, 700 cm^{-1}.

Ms: m/e 220.

Analysis: Calculated for $C_{13}H_{16}O_3$

C, 70.89; H, 7.32

Found: C, 70.82; H, 7.15%.

2-Carbethoxy 2-methyl 3-phenyl propinoate (26)

Sodium hydride (50% emulsion, 1.5 g; 0.0625 mole) was washed with (2 x 10 ml) dry benzene and then stirred with another 50 ml dry benzene and 5 ml dry DMF. A solution of ester (25) (6.6 g; 0.03 mole) in dry benzene (15 ml) was added dropwise under stirring during 10 minutes, stirring continued for 0.5 hr. at room temperature. A solution of methyl iodide (5.0 g; 0.035 mole) in dry benzene (10 ml) was then added during 10 minutes and the reaction mixture stirred for 1 hr at room temperature and for 3 hr at the reflux temperature. After cooling to room temperature the reaction mixture was diluted with water and organic layer separated.

The aqueous layer was extracted with benzene (3 x 50 ml). Combined benzene layer was washed with water, brine, dried. Removal of benzene by distillation afforded the dialkylated keto ester (**26**), purified by column chromatography over silica gel and elution with pet.ether (4.77g; 68%).

IR: 2975, 1740, 1700, 1600, 1500, 1450, 1365, 1355, 1220, 1170, 1080, 1025, 910, 860, 720 cm^{-1}.

Ms: m/e 234.

Analysis: Calculated for $C_{14}H_{18}O_3$

C, 71.77; H, 7.74

Found: C, 71.59; H, 7.55%.

Ethyl 2-methyl 3-phenyl propionate (29)

To a solution of sodium ethoxide in ethanol [prepared by dissolving sodium (0.25 g; 0.01 mole) in dry ethanol (20 ml)] was added at room temperature, the keto ester (**26**) (1.75 g; 0.0075 mole) and the reaction mixture refluxed for 4 hr. Ethanol was removed by distillation under reduced pressure, residue diluted with water, extracted with ether (3 x 30 ml). Combined ether layer was washed with water, brine, dried and solvent removed to get the deacetylated ester (**29**) purified by distillation b.p.120°/5 mm (0.90 g; 63%).

IR: 2980, 1730, 1495, 1450, 1375, 1170, 740, 700 cm^{-1}.

Ms: m/e 192.

Analysis: Calculated for $C_{12}H_{16}O_2$

C, 74.97; H, 8.39

Found: C, 74.89; H, 8.22%.

3-Phenoxybenzyl 2-methyl 3-phenyl propionate (32)

A mixture of ester (29) (0.5 g; 0.0026 mole), 3-phenoxybenzyl alcohol (0.624 g; 0.003 mole), butyl titanate (1 drop) in dry xylene (20 ml) was refluxed for 12 hr. Xylene was removed by distillation under reduced pressure. Purification by column chromatography over silica gel and elution with pet.ether afforded the ester (32) (0.522 g; 58%).

IR: 3020, 2970, 2930, 1730, 1585, 1490, 1450, 1370, 1350, 1260, 1160, 875, 820, 750, 700 cm^{-1}.

Ms; m/e 346.

Analysis: Calculated for $C_{23}H_{22}O_3$

C, 79.74; H, 6.40

Found: C, 79.52; H, 6.15%.

By following analogous procedures, keto esters (27), (28), methyl esters (30), (31) and 3-phenoxybenzyl esters (33), (34) were prepared from (25).

However, for alkylation of (25) with isopropyl iodide the reaction mixture was refluxed for 8 hr.

Use of CH_3ONa in CH_3OH for deacetylation of the keto esters (27) and (28), caused transesterification to afford the methyl esters (30) and (31). Spectral and analytical data of these compounds are given below:

Keto ester (27)

Yield: 70%.

IR: 2980, 1735, 1705, 1595, 1500, 1450, 1360, 1345, 1220, 1180, 1070, 1030, 915, 865, 710 cm^{-1}.

Ms: m/e 248.

Analysis: Calculated for $C_{15}H_{20}O_3$

C, 72.55; H, 8.12

Found: C, 72.36; H, 7.88%.

Methyl ester (30)

Yield: 64%.

IR: 2910, 1710, 1660, 1600, 1545, 1445, 1165 cm^{-1}.

Ms: m/e 192.

Analysis: Calculated for $C_{12}H_{16}O_2$

C, 74.97; H, 8.39

Found: C, 74.85; H, 8.47%.

3-Phenoxy benzyl ester (33)

Yield: 60%.

IR: 2950, 1730, 1580, 1485, 1450, 1380, 1250, 1150, 780, 750, 695 cm^{-1}.

Ms: m/e 360.

Analysis: Calculated for $C_{24}H_{24}O_3$

C, 79.97; H, 6.71

Found: C, 79.7; H, 6.43%.

Keto ester (28)

Yield: 65%.

IR: 2980, 1730, 1700, 1600, 1500, 1450, 1370, 1355, 1225, 1175, 1080, 1030, 915, 860, 730, 700 cm^{-1}.

Ms: m/e 262.

Analysis: Calculated for $C_{16}H_{22}O_3$

C, 73.25; H, 8.45

Found: C, 73.14; H, 8.32%.

Methyl ester (31)

Yield: 65%.

IR: 2975, 1740, 1490, 1460, 1380, 1175, 750, 710 cm^{-1}.

Ms: m/e 206.

Analysis: Calculated for $C_{13}H_{18}O_2$

C, 75.72; H, 8.80

Found: C, 75.55; H, 8.67%.

3-Phenoxybenzyl ester (34)

Yield : 60%.

IR: 2960, 1730, 1590, 1490, 1450, 1380, 1250, 1240, 1150, 1075, 1020, 750, 690 cm^{-1}.

Ms: m/e 374.

Analysis: Calculated for $C_{25}H_{26}O_3$

C, 80.18; H, 7.0

Found: C, 79.88; H, 7.11%.

Ethyl 2-carbethoxy 2-isopropyl 3-p-chlorophenyl propionate (35)

Sodium hydride (0.3 g; 0.0125 mole) was washed with dry benzene (2 x 10 ml), stirred with another 20 ml dry benzene and 8 ml dry DMF for 0.5 hr. The diester (9) (1.3 g; 0.0045 mole) in dry benzene (5 ml) was added dropwise during 10 minutes and stirring continued for 15 minutes at room temperature. A solution of isopropyl iodide (0.855 g; 0.005 mole) in dry benzene (5 ml) was then added dropwise and stirring continued for 2 hr. after which it was refluxed for 3 hr. The reaction mixture was cooled to room temperature, diluted with water and organic layer separated. Aqueous layer was extracted with (3 x 20 ml) benzene. Combined organic layer was washed with water, brine, dried and solvent removed

to afford the dialkylated ester (35), purified by column chromatography over silica gel and elution with pet.ether (1.05 g; 71%).

IR: 2980, 1750, 1730, 1500, 1370, 1100, 1030, 815 cm^{-1}.

Ms: m/e (^{35}Cl) 326, (^{37}Cl) 328.

Analysis: Calculated for $C_{17}H_{33}ClO_4$

C, 62.48; H, 7.0; Cl, 10.87

Found: C, 62.35; H, 7.15; Cl, 10.91%.

Decarbethoxylation of (35) afforded the monoester (36) which on transesterification gave the ester (37). Spectral and analytical properties of these compounds are given below.

Monoester (36)

Yield: 70%.

IR: 2980, 1740, 1500, 1380, 1170, 1020, 810 cm^{-1}.

Ms: m/e (^{35}Cl) 254 (^{37}Cl) 256.

Analysis: Calculated for $C_{14}H_{19}ClO_2$

C, 66.0; H, 7.46; Cl, 13.94

Found: C, 65.78; H, 7.58; Cl, 14.17%.

3-Phenoxybenzyl ester (37)

Yield: 65%.

IR: 2960, 1740, 1595, 1495, 1380, 1250, 1220, 1150, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 408 (^{37}Cl) 410

Analysis: Calculated for $C_{25}H_{25}ClO_3$

C, 73.43; H, 6.11; Cl, 8.69

Found: C, 73.25; H, 6.21; Cl, 8.47%.

Ethyl 4-methyl 2-pentenoate (39)

Sodium hydride (50% emulsion, 4.8 g; 0.1 mole) was washed with dry pet.ether (2 x 15 ml) and then stirred with dry ether (80 ml). To this was added triethylphosphonoacetate (22.4 g; 0.1 mole) in dry ether (50 ml) during 30 minutes keeping the temperature below 20° and stirring continued for 0.5 hr at room temperature. Isobutyraldehyde (**38**) (7.2g; 0.1 mole) in dry ether (20 ml) was added dropwise and stirring continued overnight at room temperature. Reaction mixture was diluted with water, ether layer separated and aqueous layer extracted with (3 x 50 ml) ether. Combined ether layer was washed with water, brine, dried and solvent removed to afford the unsaturated ester (**39**), purified by column chromatography over silica gel and elution with 4% chloroform in pet.ether (8.23g; 58%).

IR: 2970, 2880, 1730, 1660, 1475, 1380, 1310, 1230, 1195, 1135, 1040, 985, 860, 750 cm^{-1}.

Ms: m/e 142.

Analysis: Calculated for $C_8H_{14}O_2$

C, 67.57; H, 9.93

Found: C, 67.42; H, 9.82%.

2,5-Dimethyl hex-3-ene 2-ol (40)

To an ice cooled and stirred suspension of lithium (1.8 g; 0.25 mole; in the form of small pieces) in ether (50 ml) was added a solution of methyl iodide (15.62 g; 0.11 mole) in ether (10 ml) during one hr. maintaing the temperature at 0° and stirred for 1 hr. A solution of ester (**39**) (7.1 g; 0.05 mole) in dry ether (25 ml) was then added dropwise and stirring continued for 24 hr. at room temperature. The ice cooled

reaction mixture was treated with methanol to dissolve excess of lithium followed by water. Ether layer was separated and aqueous layer extracted with ether (4 x 50 ml). Combined ether layer was washed with water, brine, dried and solvent removed to afford the tertiary alcohol (**40**) purified by column chromatography over alumina and elution with chloroform (4.16 g; 65%).

IR: 3380, 2960, 2860, 1460, 1360, 1140, 970, 910 cm^{-1}.

M/s: m/e 128

Analysis: Calculated for $C_8H_{16}O$

C, 74.94; H, 12.58

Found: C, 74.81; H, 12.41%.

Ethyl 3-isopropyl 5-methyl hex-4-enoate (41)

A mixture of tertiary alcohol (**40**) (3.4 g; 0.026 mole), triethyl orthoacetate (8.6 g; 0.052 mole) and o-cresol (0.5 ml) was heated in an oil bath at 150° (bath temperature) for 7hr and further at 180° (bath temperature) for 3 hr. After cooling to room temperature, phosphoric acid (1 ml) was added and the reaction mixture refluxed at 180° (bath temeprature) for 7 hr. Purification by column chromatography over silica gel and elution with 40% benzene in pet.ether gave the pure ester (**41**) (2.8 g; 55%).

IR: 2950, 2920, 2880, 1740, 1470, 1370, 1260, 1200, 1150, 1090, 1030 cm^{-1}.

Ms: m/e 198.

Analysis: Calculated for $C_{12}H_{22}O_2$

C, 72.68; H, 11.18

Found: C, 72.75; H, 11.07%.

3-Isopropyl-5-methyl-4-hexenoic acid chloride (42)

To a stirred solution of KOH (1.12 g; 0.02 mole) in water (2 ml) and methanol (15 ml), ester (41) (2.0 g; 0.01 mole) was added at room temperature and mixture stirred for 24 hr. Methanol was removed by distillation under reduced pressure, residue diluted with water, extracted with ether (2 x 25 ml) to remove the neutral organic portion. Aqueous layer was cooled and acidified with dil. HCl and extracted with ether (3 x 30 ml) to afford the acid (1.63 g; 95%).

Acid (1.54 g; 0.009 mole) and thionyl chloride (2.15 g; 0.018 mole) in dry benzene were refluxed for 3 hr. Benzene and excess of thionyl chloride were removed by distillation under reduced pressure to get the acid chloride (42) (1.36 g; 80%).

∝(RS) Cyano-3-phenoxybenzyl 3-isopropyl 5-methyl hex-4-enoate (43)

A mixture of sodium cyanide (0.35 g; 0.007 mole), water (just to dissolve sodium cyanide), 3-phenoxybenzaldehyde (1.38 g; 0.007 mole) and TEBA (50 mg) in pet.ether (10 ml) was stirred for 15 minutes at room temperature, then heated and maintained at 60°. To this was added a solution of the acid chloride (42) (1.36 g; 0.007 mole) in pet.ether (4 ml), dropwise during 0.5 hr. The reaction mixture was stirred for further 4 hr. at room temperature, then diluted with water and pet.ether layer separated. Aqueous layer was extracted with pet.ether (3 x 25 ml). Combined pet.ether layer was washed with water, brine, dried and solvent removed to get the cyano ester (43), purified by column chromatography over silica gel and elution with 50% benzene in pet.ether (1.82g;67%).

IR: 2970, 2880, 1760, 1595, 1495, 1450, 1390, 1250, 1210, 1125, 1020, 920, 750, 690 cm^{-1}.

Ms: m/e 377.

Analysis: Calculated for $C_{24}H_{27}NO_3$

C, 76.36; H, 7.21; N, 3.71

Found: C, 76.11; H, 7.25; N, 3.69%.

4-Methyl-pent-3-ene-2-ol (45)

A stirred and ice cooled solution of mesityl oxide (**44**) (4.9 g; 0.05 mole) in methanol (20 ml) was treated in small lots with $NaBH_4$ (1.9 g; 0.05 mole). Stirring was then continued for 8 hr. at room temperature. Methanol was distilled under reduced pressure, the reaction mixture diluted with water and extracted with ether (3 x 25 ml). Combined ether layer was washed with water, brine, dried over Na_2SO_4 and ether removed by distillation to afford the alcohol (**45**) as a liquid purified by column chromatography over silica gel and elution with chloroform (4.85 g; 97%).

IR: 3360, 2980, 2940, 1680, 1450, 1380, 1280, 1200, 1140, 1060, 940, 865, 840, 750 cm^{-1}.

Ms: m/e 100.

Analysis: Calculated for $C_6H_{12}O$

C, 71.95; H, 12.08

Found: C, 71.87; H, 12.0%.

Ethyl 3,3-dimethyl-4-hexenoate (46)

Claisen orthoester rearrangement as described earlier of the alcohol (**45**) using triethylorthoacetate afforded the ester (**46**) as a liquid

purified by column chromatography over silica gel and elution with 3% ethyl acetate in pet.ether.

Yield: 63%.

IR: 3020, 2970, 2860, 1740, 1460, 1450, 1360, 1320, 1230, 1120, 1030, 965 cm^{-1}.

Ms: m/e 170.

Analysis: Calculated for $C_{10}H_{18}O_2$

C, 70.54; H, 10.66

Found: C, 70.43; H, 10.57%.

2,4-Dimethyl-3-penten-2-ol (47)

Reaction of mesityl oxide (**44**) with MeLi as described earlier afforded the alcohol (**47**) as a liquid purified by column chromatography over silica gel and elution with chloroform.

Yield: 68%.

IR: 3360, 2960, 2900, 1660, 1440, 1370, 1220, 1140, 1060, 950, 920, 810, 780 cm^{-1}.

Ms: m/e 114

Analysis: Calculated for $C_7H_{14}O$

C, 73.63; H, 12.36

Found: C, 73.54; H, 12.28%.

Ethyl-3,3,5-trimethyl-hex-4-enoate (48)

Claisen orthoester rearrangement of the alcohol (**47**) afforded the ester (**48**) as a liquid purified by column chromatography over silica gel and elution with 3% ethyl acetate in pet.ether.

Yield: 60%.

IR: 2945, 2900, 1730, 1440, 1360, 1310, 1210, 1150, 1100, 1025 cm^{-1}.

Ms: m/e 184

Analysis: Calculated for $C_{11}H_{20}O_2$

C, 71.69; H, 10.94

Found: C, 71.53; H, 10.81%.

4,8-Dimethyl-3,7-nonadien-2-ol (50)

Citral was reacted with MeLi as described earlier to afford the alcohol (**50**) as a liquid, purified by column chromatography over silica gel and elution with chloroform.

Yield: 80%

IR: 3340, 2960, 2920, 1670, 1450, 1380, 1285, 1130, 1110, 1060, 950, 870 cm^{-1}.

Ms: m/e 168.

Analysis: Calculated for $C_{11}H_{20}O$

C, 78.51; H, 11.98%

Found: C, 78.38; H, 11.81%.

Ethyl-3,7-diemthyl-3-(prop-1-enyl)-oct-6-enoate (51)

Claisen orthoester rearrangement of the alcohol (**50**) afforded the ester (**51**) as a liquid, purified by column chromatography over silica gel and elution with 3% ethyl acetate in pet.ether.

Yield : 61%.

IR: 2960, 2920, 1740, 1450, 1380, 1370, 1300, 1200, 1110, 1040, 970, 880, 830, 740 cm^{-1}.

Ms: m/e 238.

Analysis: Calculated for $C_{15}H_{26}O_2$

C, 75.58; H, 11.00

Found: C, 75.43; H, 10.87%.

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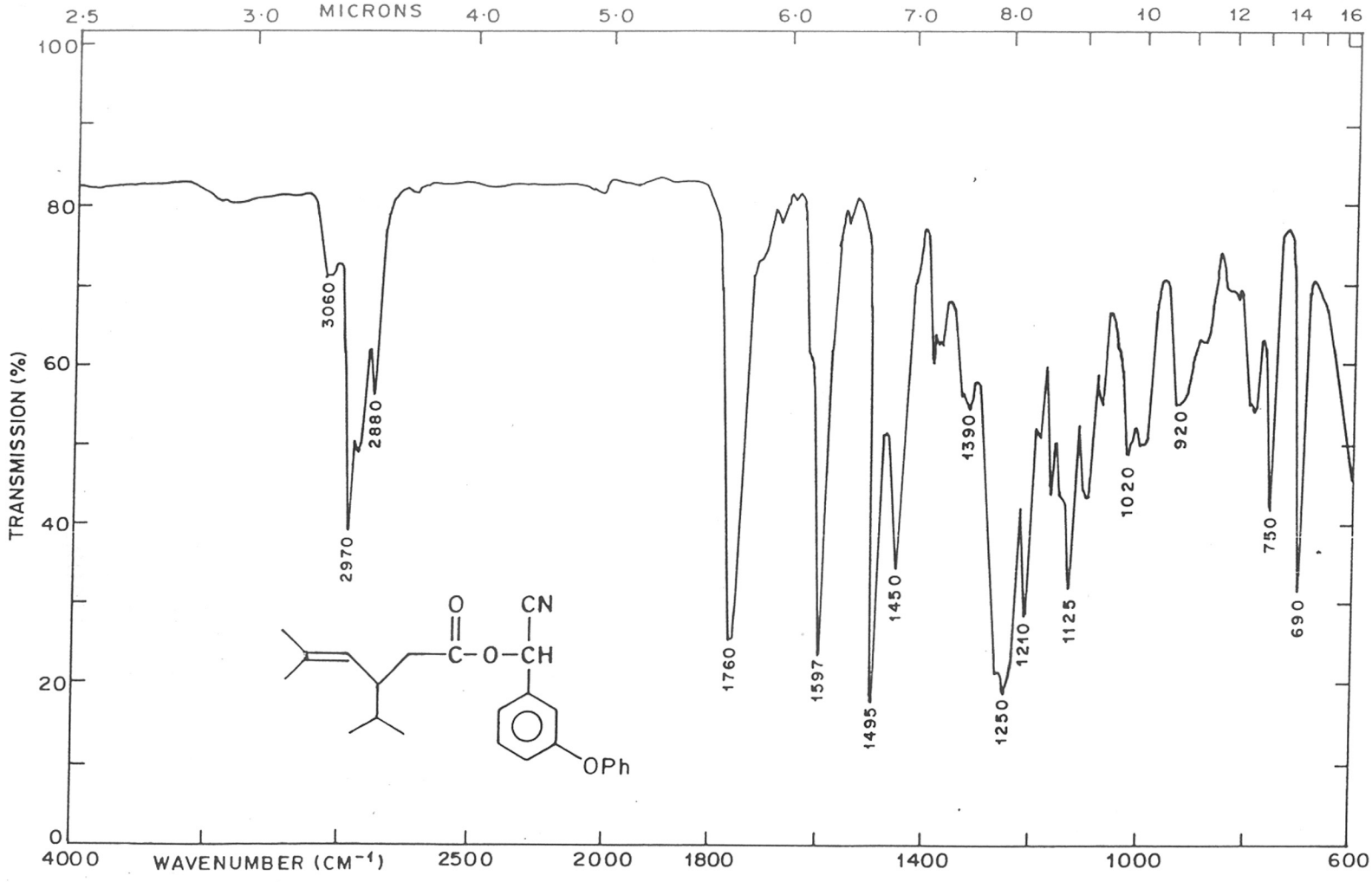


FIG. 1. IR SPECTRUM OF α-(RS)-CYANO-3-PHENOXYBENZYL-3-ISOPROPYL-5-METHYL-HEX-4-ENOATE (43)

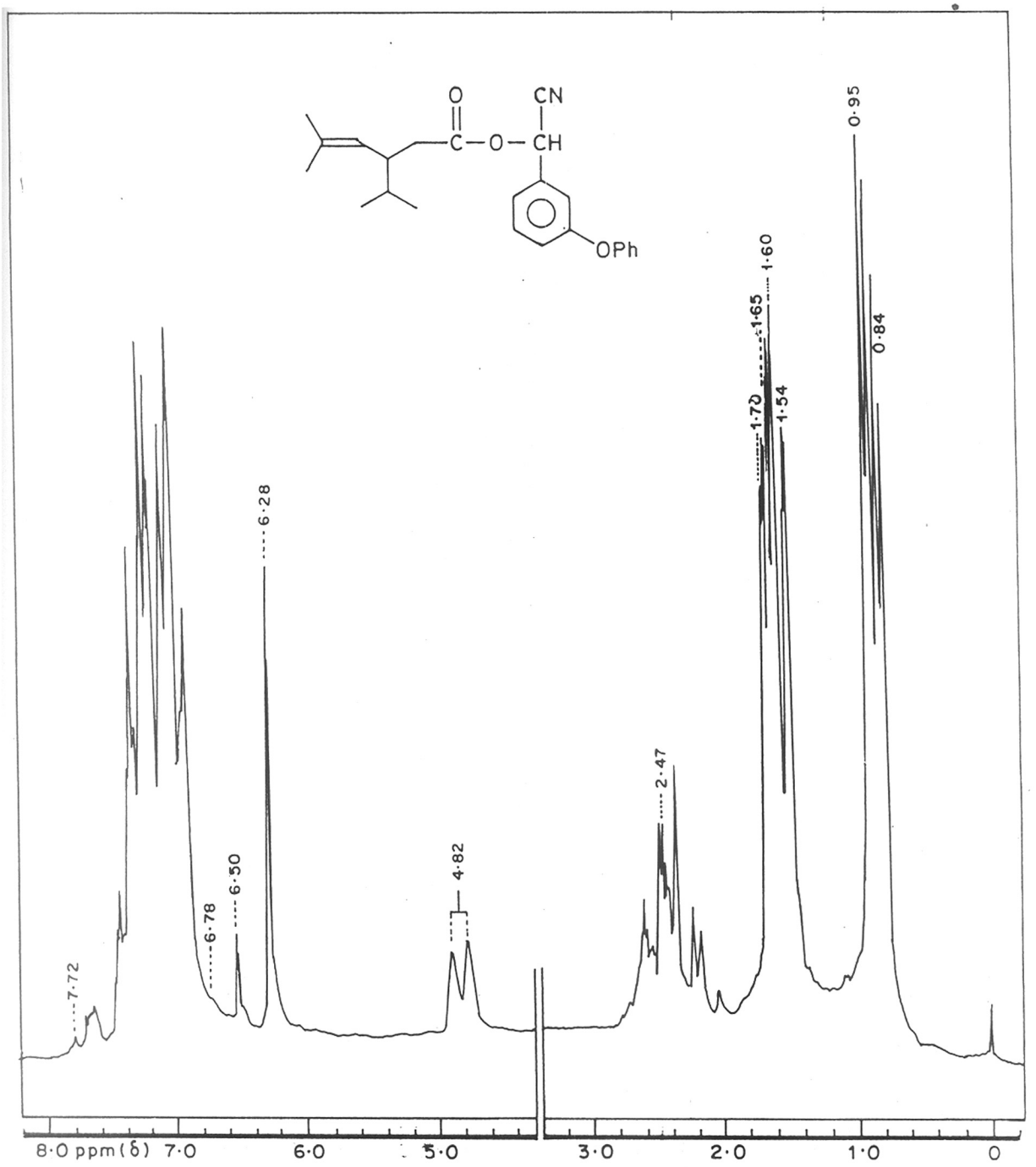


FIG. 2. PMR SPECTRUM OF α (RS)-CYANO-3-PHENOXYBENZYL-3-ISOPROPYL-5-METHYL-HEX-4-ENOATE (43)

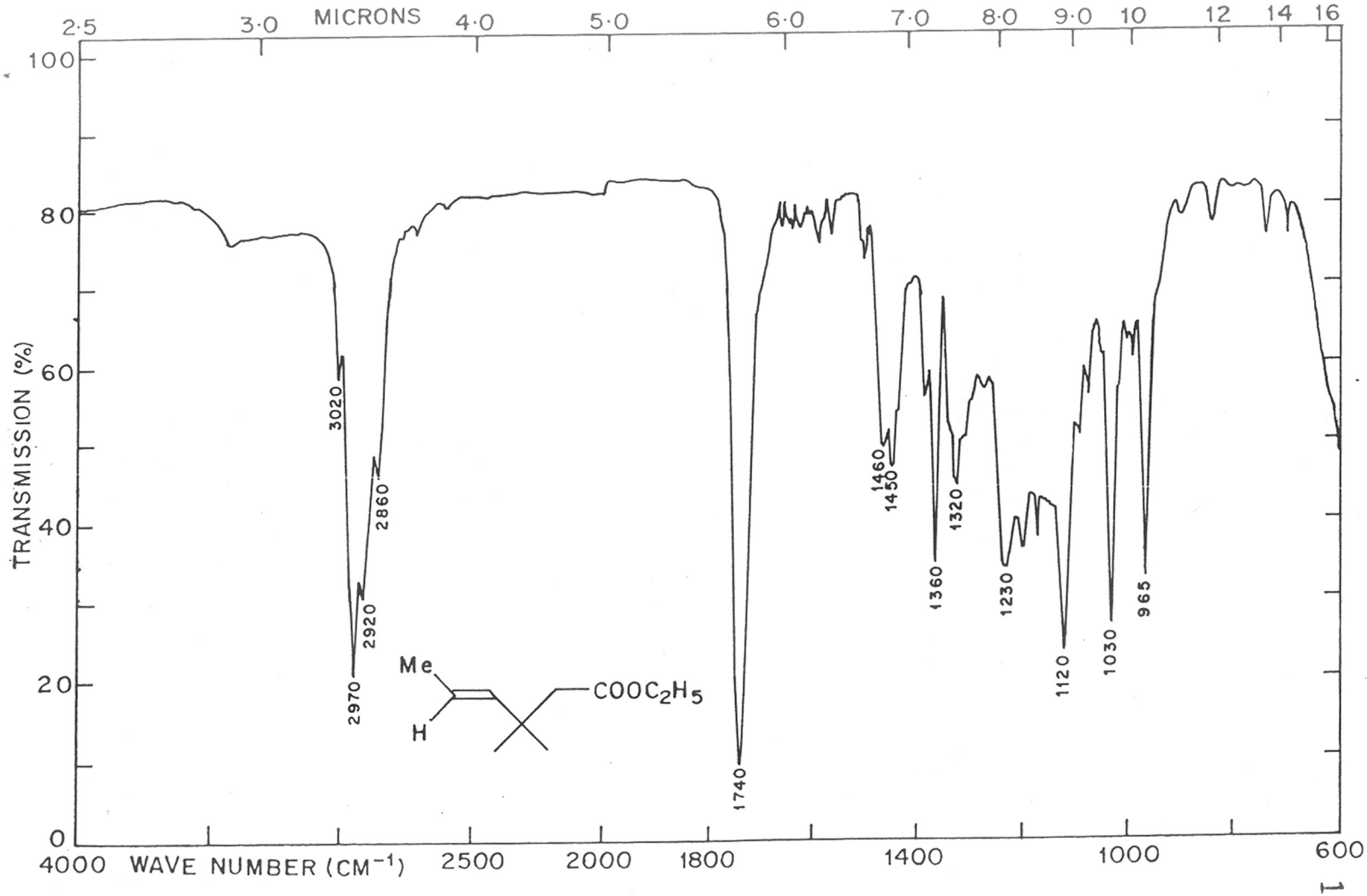


FIG. 3. IR SPECTRUM OF ETHYL-3,3-DIMETHYL-4-HEXENOATE (46)

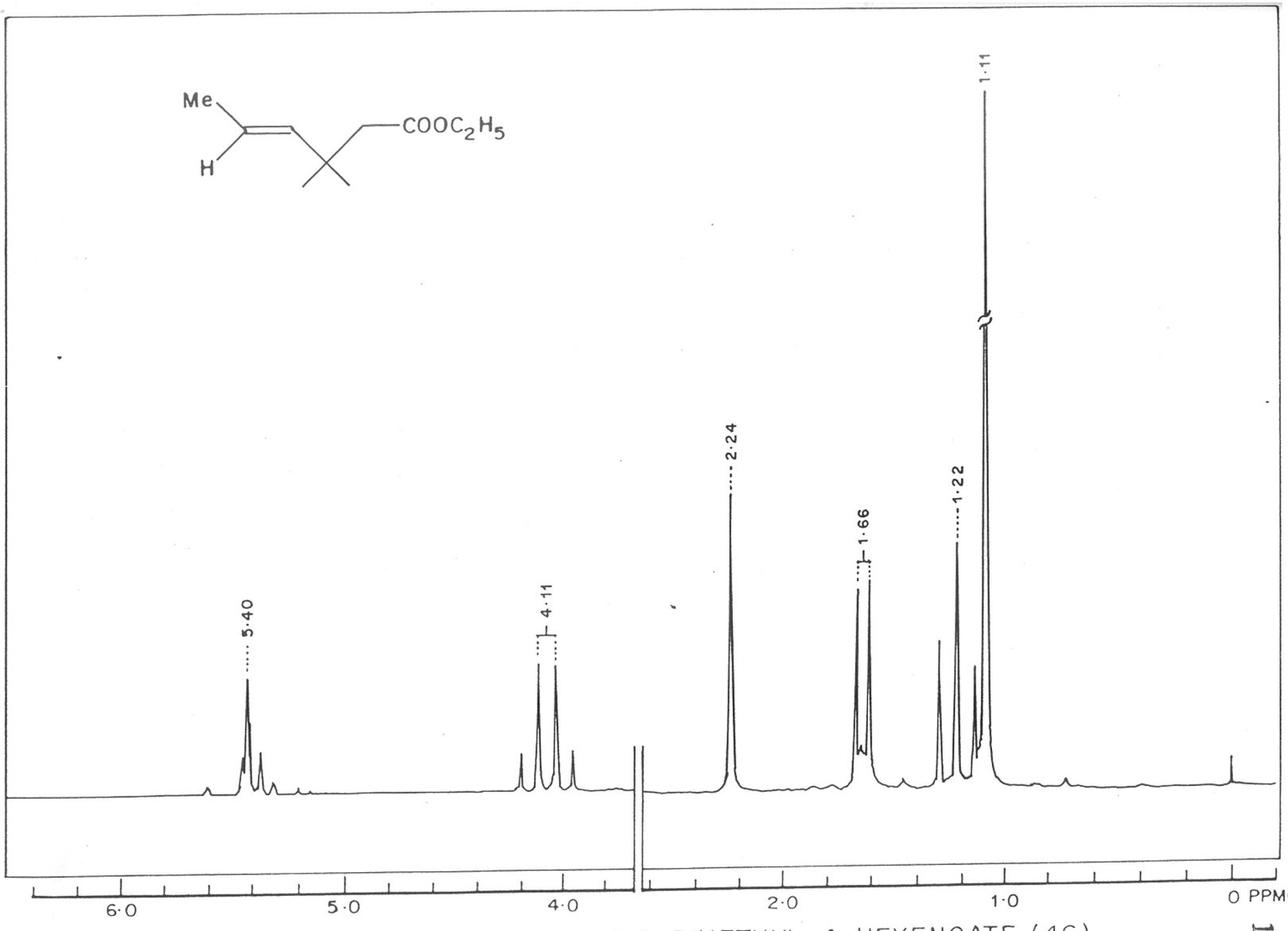


FIG. 4. PMR SPECTRUM OF ETHYL-3, 3-DIMETHYL-4-HEXENOATE (46)

CHAPTER-IV-A

SYNTHESIS OF SOME 3-PHENOXYBENZYL ETHERS DERIVED FROM 2,2-DICHLORO, 3,3-DIALKYL AND 3-ALKYL, 3-ARYL CYCLOPROPANE-1-ALKANOLS

SUMMARY

Total synthesis of some 3-phenoxybenzyl ethers derived from 2,2-dichloro 3,3-dialkyl/3-alkyl/aryl cyclopropane-1-alkanols has been described in this chapter.

The strategy followed in the synthesis of these ethers, is to prepare initially 3-phenoxybenzyl allyl ethers from suitably substituted allyl alcohols by Williamson's procedure (NaH/benzene/3-phenoxybenzyl bromide) and then convert the unsaturated ethers to the dichlorocyclopropane ethers by addition of dichlorocarbene under phase-transfer conditions using chloroform and aqueous 50% NaOH.

Thus, 3-methyl-pent-2-ene-1-ol, 3,5-dimethyl-hex-2-ene-1-ol, 3-phenyl-but-2-ene-1-ol and geraniol (3,7-dimethyl-2,6-octadien-1-ol) were respectively converted to the following ethers.

1. 3-Phenoxybenzyl-2,2-dichloro-3-methyl-3-ethyl-cyclopropyl methyl ether.
2. 3-Phenoxybenzyl-2,2-dichloro-3-methyl-3-isobutyl-cyclopropyl methyl ether.
3. 3-Phenoxybenzyl-2,2-dichloro-3-methyl-3-phenyl-cyclopropyl methyl ether.
4. 3-Phenoxybenzyl-2,2-dichloro-3-[2',2'dichloro, 3',3'-dimethyl cyclopropyl -1'-ethyl]-3-methyl cyclopropyl methyl ether.

While 2-cyclopentylidene ethan-1-ol and 2-cyclohexylidene ethan-1-ol were converted into 3-phenoxybenzyl 2-cyclopentylidene ethyl ether and 3-phenoxybenzyl 2-cyclohexylidene ethyl ether respectively.

Similarly (±) cis 2,2-dimethyl-3-(2,2-dichlorovinyl)-1-hydroxymethyl cyclopropane was converted to the 3-phenoxybenzyl (±) cis 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropane-1-methyl ether.

INTRODUCTION

Natural pyrethroids, synthetic pyrethroids and synthetic seco-pyrethroids as described in Chapter III have advantages and drawbacks of their own.

Synthetic chemists in this field have always been directing their efforts towards the synthesis much better insecticides having advantages over the existing ones and meeting the challenges of the date.

Insecticides like MTI-500[1] (Ethophenoprox) and MTI-800[2] (Chart I) prepared by Japanese worekrs are an outcome of such efforts. Unlike the conventional potent pyrethroids and chrysanthemates, these compounds do not possess a cyclopropane ring and the ester function . Chemically, these are ethers of (un)substituted 3-phenoxybenzyl alcohols with another aralkyl alcohol.

MTI-500[3] [2-(4-ethoxyphenyl)-2-methylpropyl-3-phenoxybenzyl ether] is highly active[4] against various insect species such as Lepidoptera, Hemiptera, Coleoptera, Diptera and Orthoptera with remarkably weak toxicity to mammals. In addition, MTI-500 is less toxic to fish than the conventional highly potent synthetic pyrethroids[5]. It is stable under acidic and alkaline conditions and therefore can be used in combination with other alkaline agricultural chemicals[6].

At present in Japan, efforts are being made to develop a market for MTI-500 and MTI-800 as pesticides.

Another far more interesting compound MTI-800 [Chart I] which is chemically [1-(3-phenoxy-4-fluorophenyl)-4-(4-ethoxyphenyl)-4-methylpentane], structurally closely related to MTI-500, but differing from the latter, in which the ether linking CH_2-O-CH_2 is replaced by CH_2-CH_2-CH_2 grouping[7] has also been synthesised.

The insecticidal activity of MTI-800 is several times stronger than MTI-500 and markedly less toxic to fish.

Large number of compounds with various substituents at X_1 and X_2 of the general formula (I) (Chart I) with an alkylene bond at position A have been synthesised and investigated for their structure activity relationship. It has also been found that the insecticidal activity is high when X_1 in the general formula (II) (Chart I) is substituted with chlorine, ethoxy or difluoromethyl groups and it is still higher when X_2 is substituted with fluorine than with hydrogen.

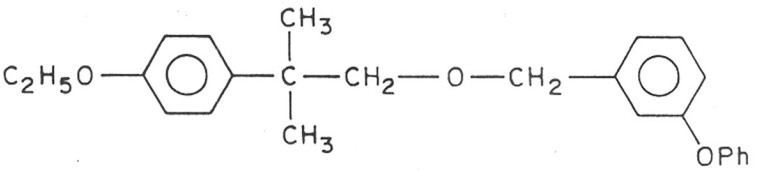
Mitsui Toatsu Chemical Incorporation[8], Japan, has patented a number of compounds containing 3-phenoxybenzyl ethers for their insecticidal and acaricidal activity at different concentrations. They have prepared and patented fifty three 2-arylethyl thio ethers useful as insecticides and miticides.

Sumitomo Chemical Co.Ltd.[9], Japan have prepared and patented fifty five phenoxy-alkyl-arylmethyl ethers of the general formula $R_1R_2C_6H_3XCH_2CR_3R_4\ CH_2\ OCH_2R$ useful as insecticides and miticides.

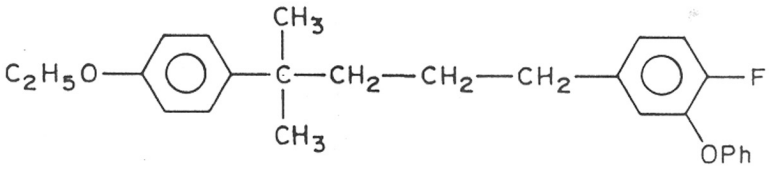
Holan et al.[10] have synthesised number of 1-(4-ethoxyphenyl),-2,2-fluoro-1-cyclopropylmethyl-3-phenoxybenzyl ethers (Chart II-I) and claimed as insecticides and anthropodicidal compounds. Frank et al.[11] have synthesised similar compounds and found them to be highly active against susceptible and resistant strains of the Musca Domestica.

Similar insecticidal 3-phenoxybenzyl-2-phenyl-2,2-alkylene ethyl ethers and thio ethers of the general formula (II) (Chart II) have been synthesised and reported[12] to possess insecticidal activity.

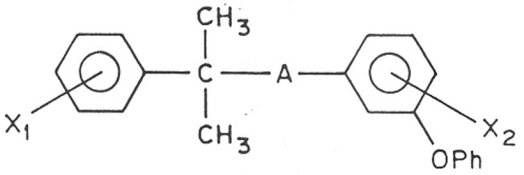
CHART (I)



MTI—500

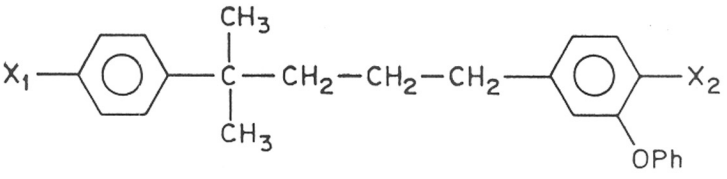


MTI—800



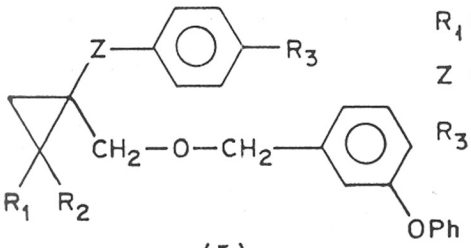
GENERAL FORMULA (I)

$$A = -CH_2-CH_2-CH_2 \geqslant -CH_2-O-CH_2- > -CH=CH-CH_2$$



GENERAL FORMULA (II)

CHART (II)

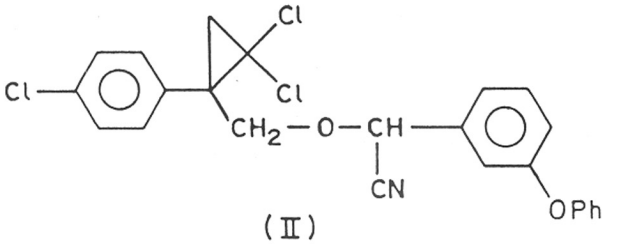


(I)

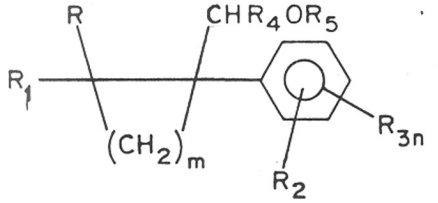
$R_1 = R_2 = Cl, F, Me$

$Z = O, S, SO$

$R_3 = H, OMe, OEt, Me, Et$



(II)



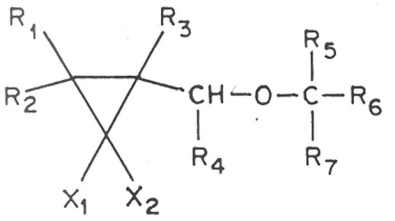
(III)

$R, R_1 =$ halo, H

$R_2, R_3 =$ H, halo, alkyl, alkoxy, haloalkyl

$R_4, R_5 =$ H, halo alkyl

$m = 1-5, n = 0-3$



(IV)

$X_1, X_2 = Cl, Br, F$

$R_6 =$ Trihalo, alkenyl, alkynyl, iodoalkynyl

$R_5, R_7 =$ H, alkyl, aryl, aralkyl

$R_1, R_4 =$ H, alkyl

$R_2, R_3 =$ H, alkyl, aryl, haloalkyl, heteroalkyl

Axel et al.[13] have prepared and patented arylcycloalkyl ethers which possess enhanced activity compared to permethrin (Chart II - III).

Many α,β -unsaturated carbonyl compounds of various structural types, when mixed with pyrethrum insecticides have been reported to exhibit synergistic activity[14,15]. It has been observed that the compounds in which the conjugated double bond is replaced by dichlorocyclopropane ring act as better synergists[16] than the original compounds and piperonyl butoxide.

Recently some 2,2-dihalo-3,3-dimethyl cyclopropylmethyl(ene) ethers have been synthesised and patented by Wolfgang et al.[17] and claimed to be better synergists for a series of insecticides than the conventional piperonyl butoxide (Chart II - IV).

In our laboratory some 3-phenoxybenzyl ethers derived from 2,2-dihalo-3,3-alkyl/aryl/dialkyl or aralkyl cyclopropane-1-alkanols were synthesised[18] and some of them were found to be active as insecticides and larvicides.

PRESENT WORK

Encouraged by the insecticidal activity shown by the compounds mentioned earlier, synthesis of some 3-phenoxybenzyl ethers derived from 3-alkyl/-aryl or 3,3-dialkyl-2,2-dichlorocyclopropane-1-alkanols has been undertaken with a view to evaluating them for possible insecticidal and larvicidal properties.

In addition, 3-phenoxybenzyl ethers derived from 2,2-dichlorospiro (2,4) heptane/spiro (2,5) octane-1-methyl ethers have also been synthesised for examining their insecticidal acitivity.

Since ethers prepared from (±) cis DV acid with suitable alcohols are potent pyrethroids, it was felt desirable to evaluate the insecticidal properties of the 3-phenoxybenzyl ether derived from 2,2-dimethyl-3-(2,2-dichloro vinyl) cis-1-hydroxymethyl cyclopropane.

(A) **3-Phenoxybenzyl-2,2-dichloro-3,3-dialkyl/3-alkyl 3-aryl-cyclopropyl methyl ethers (Schemes I and II)**

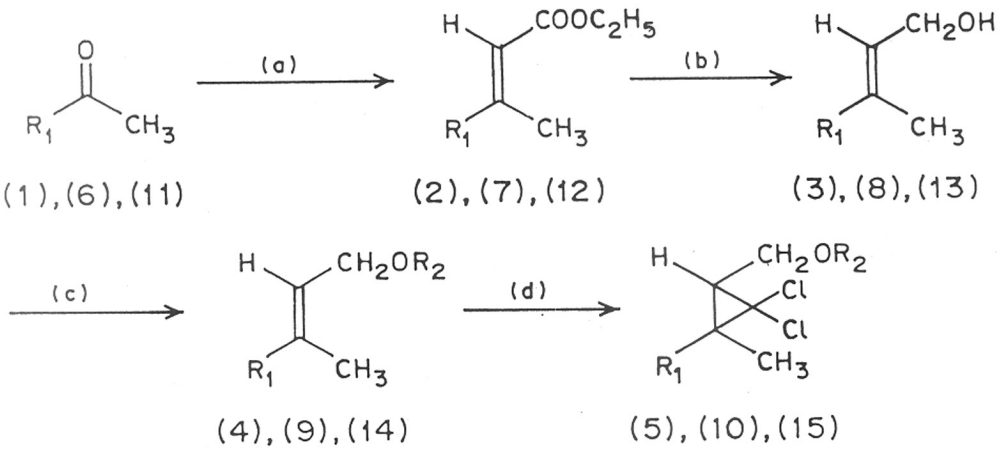
The strategy followed in the synthesis of such compounds, is to prepare the corresponding unsaturated 3-phenoxybenzyl ethers from suitably substituted allylic alcohols by reacting sodio derivative of the latter with 3-phenoxybenzyl bromide. The unsaturated ethers thus obtained, were then subjected to dichlorocyclopropanation, by reacting with dichlorocarbene generated in situ from chloroform and 50% aqueous NaOH, under phase transfer conditions using TEBA (triethyl benzyl ammonium bromide) as phase transfer catalyst.

The allylic alcohols required for preparation of ethers were in turn synthesised by the Wittig reaction on the suitable carbonyl compounds, using the phosphorane generated from diethyl ethoxycarbonylmethyl phosphate using NaH as a base, to afford the 3,3-disubstituted acrylates. The latter were subsequently converted to the allylic alcohols by AlH_3 reduction.

For the syntehsis of (**17**), Geraniol was employed for the preparation of 3-phenoxybenzyl ether (Scheme II).

Methyl ethyl ketone (**1**), methyl isobutyl ketone (**6**) and acetophenone (**11**) were subjected to Wittig reaction as desscribed earlier to get the 3,3-disubstituted ethyl acrylates. The latter were then selectively reduced by AlH_3 to afford the allylic alcohols, subsequently converted to 3-phenoxybenzyl ethers by Williamson's procedure. 3-phenoxybenzyl ethers were then reacted with dichlorocarbene generated in situ from chloroform and 50% aqueous NaOH under phase transfer conditions using TEBA to afford the 3,3-disubstituted 2,2-dichloro-cyclopropyl-3-phenoxybenzyl ethers (Scheme I)identified and characterised by spectral data as described below.

SCHEME (I)

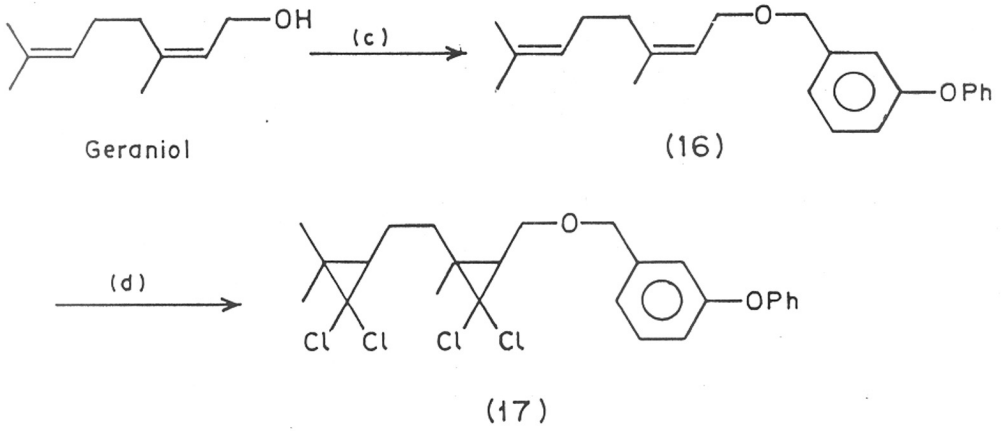


(1) to (5) $R_1 = C_2H_5$, R_2 = m-phenoxybenzyl

(6) to (10) $R_1 = CH_2CH(CH_3)_2$, R_2 = m-phenoxybenzyl

(11) to (15) $R_1 = C_6H_5$, R_2 = m-phenoxybenzyl

SCHEME (II)



(a) = $(EtO)_2-P(=O)-CH_2COOEt$ / NaH / ether

(b) = AlH_3 / ether

(c) = 3-phenoxybenzyl bromide / NaH / benzene

(d) = $CHCl_3$ / 50% aq. NaOH / TEBA

Ester (2)

IR: 1720 (ester carbonyl), 1650 (conjugated C=C) cm^{-1}.

PMR: 1.06 (3H, t, J=7 Hz, alkyl methyl), 1.26 (3H, t, J=7 Hz, ester methyl), 2.15 (5H, s, overlapping a m, methyl and methylene on double bond), 4.1 (2H, q, J=7 Hz, ester methylene), 5.58 1H, m due to homoallylic coupling, olefinic proton).

Alcohol (3)

IR: 3350 (-OH), 1660 (HC=C) cm^{-1}.

PMR: 1.03 (3H, two overlapping triplets, primary alkyl methyl of cis and trans isoemrs), 1.66, 1.7 (3H, two singlets, vinyl methyl of cis and trans isomers), 1.75-2.28 (2H, m, alkyl vinyl methylene of cis and trans isomers), 3.58 (1H, m, D_2O exchangeable OH proton), 4.0 (2H, d, J=7 Hz, CH_2OH), 5.31 (1H, two overlapping triplets, olefinic proton of cis and trans isomers).

Ether (4)

IR: 1580, 1485 (aromatic), 1250 (ether) cm^{-1}.

PMR: 1.03 (3H, two overlapping triplets, alkyl primary methyls), 1.6, 1.73 (3H, two singlets, vinyl methyl of cis and trans isomers), 2.06 (2H, m, alkyl vinyl methylene of cis and trans isomers), 3.93 2H, d, J=7 Hz, vinyl CH_2O), 4.43, 4.5 (2H, two singlets, benzylic CH_2 of cis and trans isomers), 5.23 (1H, m, olefinic proton of cis and trans isomers), 6.6-7.4 (9H, m, aromatic protons).

Dichlorocyclopropanated ether (5)

IR: 1590, 1490 (aromatic), 1255 (ether) cm^{-1}.

PMR: 0.96 (3H, two overlapping triplets, primary alkyl methyl of cis and trans isomers), 1.14 (3H, s, quaternary methyl at C_3), 1.42 (3H, m, C_1 cyclopropane proton and alkyl methylene), 3.52 (2H, m, 8 line pattern due to ABX

system CH_2O at C_1), 4.5 (2H, s, benzylic CH_2), 6.8-7.48 (9H, m, aromatic protons).

Ester (7)

IR: 1725 (ester carbonyl), 1655 (conjugated C=C) cm^{-1}.

PMR: 0.93 (6H, d, J=7 Hz, isopropyl methyls), 1.26 (3H, t, J=7 Hz, ester methyl), 2.1 (6H, s overlapping a m, methyl and methylene on double bond and isopropyl proton), 4.1 (2H, q, J=7 Hz, ester methylene), 5.6 (1H, m, due to homoallylic coupling, olefinic proton).

Alcohol (8)

IR: 3340 (-OH), 1660 (HC=C) cm^{-1}.

PMR: 0.9 (6H, d, J=7 Hz, isopropyl methyls), 1.6 (3H, s, methyl on double bond), 1.86 (3H, br m, methylene on double bond and methine proton), 3.1 (1H, s, D_2O exchangeable -OH proton), 4.0 (2H, d, J=7 Hz, CH_2O), 5.3 (1H, *m, olefinic proton).*

Ether (9)

IR: 1580, 1480 (aromatic), 1245 (ether) cm^{-1}..

PMR: 0.86 (6H, d, J=6 Hz, isopropyl methyls), 1.56 (3H, s, methyl on double bond), 1.83 (3H, br s, allylic CH_2 and methine proton), 3.88 (2H, d, J=7 Hz, allylic CH_2O), 4.33 (2H, s, benzylic CH_2), 5.21 (1H, m, olefinic proton), 6.65-7.31 (9H, br m, aromatic protons).

Dichlorocyclopropanated ether (10)

IR: 1520, 1480 (aromatic), 1245 (ether) cm^{-1}.

PMR: 0.88, 0.94 (3H each, d each, J=6 Hz,each, isopropyl methyls),1.14(3H,s, C_3 methyl), 1.15-1.92 (4H, m, $\underline{CH_2}\underline{CH}(CH_3)_2$ and cyclopropane proton); 3.62 (2H, m, 8 line pattern due to ABX system, CH_2O), 4.53 (2H, s, benzylic

CH_2), 6.95-7.42 (9H, m, aromatic protons).

Ester (12)

IR: 1725 (ester carbonyl), 1640 (conjugated C=C) cm^{-1}.

PMR: 1.31 (3H, t, J=7 Hz, ester methyl), 2.58 (3H, d, J=2 Hz, methyl on double bond), 4.24 (2H, q, J=7 Hz, ester methylene), 6.15 (1H, m, olefinic proton), 7.24-7.67 (5H, br m, aromatic protons).

Alcohol (13)

IR: 3360 (-OH) cm^{-1}.

PMR: 2.0 (3H, s, methyl on double bond), 3.93 (1H, s, D_2O exchangeable -OH proton), 4.26 (2H, d, J=7 Hz, CH_2O), 5.91 (1H, m, olefinic proton), 7.06-7.46 (5H, br m, aromatic protons).

Ether (14)

IR: 1585, 1490 (aromatic), 1250 (ether) cm^{-1}.

PMR: 2.0 (3H, s, methyl on double bond), 4.06 (2H, d, J=7 Hz, allylic CH_2), 4.4 (2H, s, benzylic CH_2), 5.83 (1H, t, J=7 Hz, olefinic proton), 6.83-7.33 (14H, br m, aromatic protons).

Dichlorocyclopropanated ether (15)

IR: 1590, 1490 (aromatic), 1260 (ether) cm^{-1}.

PMR: 1.4 (3H, s, C_3 methyl), 2.06 (1H, m, C_1 cyclopropane proton), 3.63 (2H, m, 8 line pattern due to ABX system, CH_2 attached to cyclopropane), 4.45 (2H, s, benzylic CH_2), 6.71-7.23 (14H, br m, aromatic protons).

Thus it is clear from the spectral data that in the case of methyl ethyl ketone, the ester, alcohol and 3-phenoxybenzyl ether were obtained as a mixture of cis-trans isomers, while in the other two cases (methyl isobutyl ketone and acetophenone) the trans isomer appears to be the sole product of the reaction.

Geraniol was converted by treatment with NaH in benzene to the corresponding alkoxide and the latter then reacted with 3-phenoxybenzyl bromide to give ether (**16**).

IR: 1600, 1500 (aromatic), 1250 (ether) cm^{-1}.

PMR: 1.63 (9H, br s, methyls on double bond), 2.05 (4H, br s, allylic methylenes), 3.98 (2H, d, J=7 Hz, allylic CH_2O), 4.41 (2H, s, benzylic CH_2), 5.1, 5.3 (1H each, m each, olefinic protons), 6.7-7.41 (9H, br m, aromatic protons).

Ether (17)

IR: 1595, 1495 (aromatic), 1250 (ether) cm^{-1}.

PMR: 1.14 (6H, s, gem dimethyl on cyclopropane at C_3), 1.28 (3H, s, cyclopropane methyl at C_3), 1.48, 1.73 (6H, m, methylenes and cyclopropane protons), 3.57 (2H, m, $-OCH_2$ attached to cyclopropane), 4.48 (2H, s, benzylic CH_2), 6.88-7.42 (9H, br m, aromatic protons).

(B) 3-Phenoxybenzyl-2,2-dichloro-spiro (2,4) heptane/spiro (2,5) octane-1-methyl ethers (Scheme III)

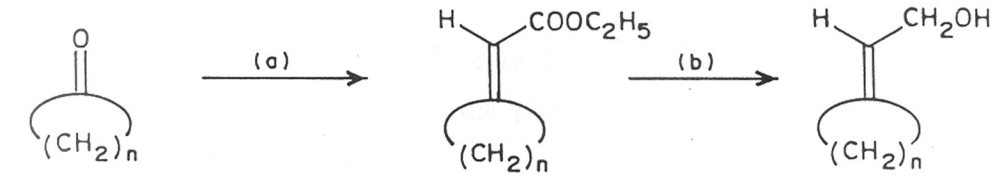
Wittig reaction on cyclopentanone using the phosphorane metnioned above afforded the ethyl cyclopentylidene acetate which on selective reduction afforded cyclopentylidene ethanol. The 3-phenoxybenzyl ether was preparred from the latter and subsequently converted to the dichlorocyclopropanated ether.

Ester (19)

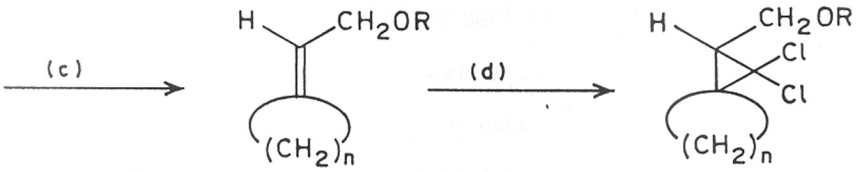
IR: 1720 (ester carbonyl), 1660 (conjugated C=C) cm^{-1}.

PMR: 1.25 (3H, t, J=7 Hz ester methyl), 1.76 (4H, br m, C_3, C_4 methylenes), 2.43, 2.76 (2H each, br m each, C_2, C_5 methylenes), 4.06 (2H, q, J=7 Hz, ester methylene, 5.68 (1H, s, olefinic proton).

SCHEME (III)



(18), (23) (19), (24) (20), (25)

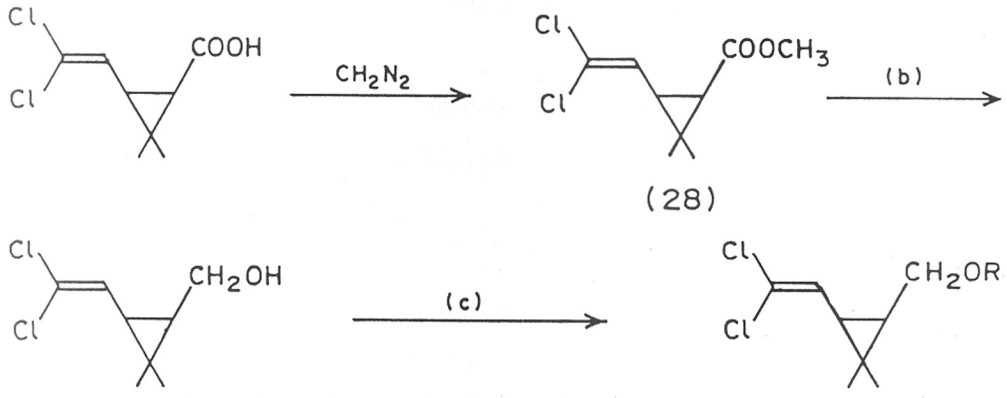


(21), (26) (22), (27)

(18) to (22) n=4
(23) to (27) n=6

R = m-phenoxybenzyl

SCHEME (IV)



(29) (30)

R= m-phenoxybenzyl

(a), (b), (c), (d) See schemes (I) and (II)

Ester (19) was reduced by AlH_3 to the alcohol (20).

IR: 3350 (-OH), 1680 (H-C=C) cm^{-1}.

PMR: 1.66 (4H, m, C_3, C_4 methylenes), 2.3 (4H, br m, C_2, C_5 methylenes), 3.61 (1H, br s, D_2O exchangeable -OH proton), 4.03 (2H, d, J=6 Hz, $\underline{CH_2}OH$), 5.4 (1H, m, olefinic proton).

Alcohol (20) was converted to the corresponding alkoxide by treatment with NaH in dry benzene and then reacted with 3-phenoxybenzyl bromide to get the ether (21).

IR: 1600, 1500 (aromatic), 1260 (ether) cm^{-1}.

PMR: 1.65 (4H, br m, C_3, C_4 methylenes), 2.23 (4H, br m, C_2, C_5 methylenes), 3.91 (2H, d, J=7 Hz, methylene on double bond), 4.4 (2H, s, benzylic CH_2), 5.41 (1H, m, olefinic proton), 6.76-7.43 (9H, br m, aromatic protons).

Ether (21) was reacted with aqueous NaOH (50%) and chloroform to get the dichlorocyclopropanated ether (22).

IR: 1595, 1495 (aromatic), 1260 (ether) cm^{-1}.

PMR: 1.76 (8H, br m, methylenes of cyclopentane), 2.14 (1H, dd, J_1=4 Hz, J_2 = 5 Hz), 3.56 (2H, total 8 lines due to ABX system, methylene attached to cyclopropane), 4.72 (2H, s, benzylic CH_2), 6.76-7.54 (9H, br m, aromatic protons).

Cyclohexanone (23) was subjected to analogous sequence of reactions to get the compounds (24), (25), (26) and (27), the spectral properties of which are as follows:

Ester (24)

IR: 1720 (ester carbonyl), 1650 (conjugated C=C) cm^{-1}.

PMR: 1.26(3H, t, J=7 Hz,ester methyl),1.63(6H,br m, C_3,C_4,C_5 methylenes), 2.2, 2.83 (2H each, br s each, C_2, C_6 methylenes),4.1(2H, q,J=7 Hz,ester

methylene), 5.51 (1H, s, olefinic proton).

Alcohol (25)

IR: 3320 (-OH), 1675 (HC=C) cm^{-1}.

PMR: 1.58 (6H, br s, C_3, C_4, C_5 methylenes), 2.11 (4H, br s, C_2, C_6 methylenes), 2.86 (1H, br s, D_2O exchangeable -OH proton), 4.01 (2H, d, J=7 Hz, $\underline{CH_2}OH$), 5.28 (1H, t, J=7 Hz, olefinic proton).

Ether (26)

IR: 1585, 1490 (aromatic), 1245 (ether) cm^{-1}.

PMR: 1.56 (6H,br s,C_3,C_4, C_5 methylenes), 2.08 (4H, br s, C_2, C_6 methylenes), 3.9 (2H, d, J=7 Hz, methylene on double bond), 4.36 benzylic CH_2), 5.21 (1H, m, olefinic proton), 6.7-7.36 (9H, br m, aromatic protons).

Dichlorocyclopropanated ether (27)

IR: 1595, 1495 (aromatic), 1265 (ether) cm^{-1}.

PMR: 1.55 (11H, br s, methylenes of cyclohexane and cyclopropane proton), 3.53(2H, m, 8 line pattern due to ABX system, CH_2 attached to cyclopropane), 4.45 (2H, s, benzylic CH_2), 6.75-7.38 (9H, br m, aromatic protons).

(C) **3-Phenoxybenzyl-2,2-dimethyl-3[2,2-dichlorovinyl]-cyclopropyl methyl ether (Scheme IV)**

(±) Cis DV acid was converted to its methyl ester by reaction with diazomethane.

Methyl ester (28)

IR: 1720 (ester carbonyl) cm^{-1}.

PMR: 1.28 (6H, s, gem diemthyl), 1.73 (1H, d, J=8 Hz, methine proton at C_1), 1.98 (1H, d, J=8 Hz, methine proton at C_3), 3.61 (3H, s, ester methyl), 6.15 (1H, d, J=8 Hz, olefinic proton).

Methyl ester **(28)** was reduced by AlH_3 to the alcohol (**29**).

IR: 3350 (-OH) cm^{-1}.

PMR: 1.08, 1.18 (3H each, s each, gem dimethyl), 1.33, 1.6 (1H each, d each, J=8 Hz each, cyclopropane protons at C_1 and C_3 respectively), 1.95 (1H, s, D_2O exchangeable -OH proton), 3.6 (2H, d, J=7 Hz, CH_2O), 5.58 (1H, d, J=8Hz, olefinic proton).

Alcohol (**29**) was converted by treatment with NaH in benzene to the corresponding alkoxide and the latter reacted with 3-phenoxybenzyl alcohol to furnish the ether (**30**).

IR: 1580, 1480 (aromatic), 1250 (ether) cm^{-1}.

PMR: 1.01, 1.14 (3H each, s each, gem dimethyl), 1.33 (1H, m, cyclopropane proton at C_1), 1.54 (1H, dd, J_1=8 Hz, J_2=16 Hz, cyclopropane proton at C_3), 3.47 (2H, d, J=7 Hz, CH_2O), 4.48 (2H, s, benzylic CH_2), 5.57 (1H, d, J=8Hz. olefinic proton), 6.84-7.44 (9H, br m, aromatic protons).

EXPERIMENTAL

Ethyl 3-methyl-3-ethyl-acrylate (2)

Sodium hydride (50% emulsion, 2.4 g; 0.1 mole) was washed repeatedly with dry pet.ether. To the residue, dry ether (25 ml) was added and the suspension was cooled to 10° and stirred. A solution of triethylphosphonoacetate (11.2 g; 0.05 mole) in ether 20 ml was then added dropwise under stirring, maintaining the temperature between 5-10°. After the addition was completed, stirring was continued for 1 hr at room temperature and a solution of methyl ethyl ketone (3.6 g; 0.05 mole) in ether (10 ml) was then added dropwise. The reaction mixture was stirred overnight.

Ether layer was decanted and residue diluted with water, extracted with ether (3 x 25 ml). Combined ether layer was washed with water, brine, dried and solvent removed by distillation to afford the ester (2), purified by column chromatography over silica gel and elution with pet.ether (4.5 g; 63%).

IR: 2970, 2940, 1720, 1650, 1440, 1380, 1310, 1220, 1140, 1095, 1035, 860 cm^{-1}.

Ms: m/e 142.

Analysis: Calculated for $C_8H_{14}O_2$

C, 67.6; H, 9.85

Found: C, 67.53; H, 9.78%.

3-Methyl-2-penten-1-ol (3)

To a stirred and cooled (10°) suspension of LAH (2.85 g; 0.075 mole) in dry ether (25 ml) was added in small lots anhydrous $AlCl_3$ (3.34 g; 0.025 mole) during 1 hr and stirring continued for 0.5 hr at room temperature.

A solution of ester (2) (3.55 g; 0.025 mole) in ether (10 ml) was added dropwise over a period of 0.5 hr and stirring continued for 2 hr. The reaction mixture was cooled to 0° and ethyl acetate (5 ml) added dropwise to decompose excess of AlH_3. Ether layer was separated and residue diluted with water, extracted with ether (3 x 20 ml). Combined organic layer was washed with water, brine, dried and distilled to remove the solvent to give the liquid residue, purified by column chromatography over silica gel and elution with 2.5% ethyl acetate in pet.ether (1.5 g; 58%).

IR: 3350, 2970, 2930, 2880, 1660, 1460, 1380, 1240, 1115, 1050, 1015 cm^{-1}.

Ms; M/e 100.

Analysis: Calculated for $C_6H_{12}O$

C, 72.0; H, 12.0

Found: C, 71.78; H, 11.88%.

3-Phenoxybenzyl-3-methyl-2-penten-1-yl ether (4)

Sodium hydride (50% emuslion, 0.6 g; 0.0125 mole) was washed with dry benzene (2 x 10 ml) and residue suspended in another 15 ml benzene. To this was added a solution of alcohol (3) (1.25 g; 0.0125 mole) in benzene (5 ml) and the mixture refluxed for 1.5 hr, cooled to room temeprature. A solution of 3-phenoxybenzyl bromide (3.28 g; 0.0125 mole) in benzene (5 ml) was then added to it and the reaction mixture refluxed for 6 hr. Cooled to room temeprature and decanted to separate the benzene layer. The residue was diluted with water, extracted with benzene (2 x 20 ml). Combined benzene layer was washed with water, brine, dried and distilled to remove benzene to give a liquid residue. The latter was purified by column chromatography

over silica gel and elution with 40% chloroform in pet.ether to give ether (4) (2.11 g; 60%).

IR: 2950, 2900, 2840, 1660, 1580, 1485, 1440, 1250, 1210, 1105, 1060, 1015, 945, 920, 860, 745, 680 cm^{-1}.

Ms: m/e 282.

Analysis: Calculated for $C_{19}H_{22}O_2$

C, 80.85; H, 7.80

Found: C, 80.77; H, 7.68%.

3-Phenoxybenzyl 2,2-dichloro-3-methyl-3-ethyl cyclopropyl methyl ether (5)

A solution of ether (4) (1.41 g; 0.005 mole) in chloroform (5 ml) along with TEBA (0.1 g) was stirred and cooled to 0°. An aqueous solution of NaOH (50%) (7 ml) was then added dropwise during 10 minutes and stirred for 0.5 hr at 0°. It was then stirred at room temeprature for 24 hr. Chloroform layer was separated and aqueous layer diluted with water, extracted with chloroform (4 x 10 ml). Combined chloroform layer was washed with water, brine, dried and distilled to get liquid residue which was purified by column chromatography over silica gel and elution with 1% ethyl acetate in pet.ether to furnish the ether (5) (1.0 g; 55%).

IR: 2960, 2920, 2860, 1590, 1490, 1445, 1255, 1210, 1095, 1020, 770, 680 cm^{-1}.

Ms: m/e (^{35}Cl) 364 (^{37}Cl) 368.

Analysis: Calculated for $C_{20}H_{22}Cl_2O_2$

C, 65.75; H, 6.03; Cl, 19.45

Found: C, 65.6; H, 6.1; Cl, 19.23%.

By following same procedures, the ethers (10), (15), (17), (22) and (27) were obtained. Ether (16) was prepared from geraniol. The spectral and analytical properties of the final compounds and intermediates are given below.

Ester (7)

Yield: 67%.

IR: 2970, 2880, 1725, 1655, 1470, 1375, 1280, 1230, 1160, 1120, 1040, 970, 865, 810 cm^{-1}.

Ms: m/e 170.

Analysis: Calculated for $C_{10}H_{18}O_2$

C, 70.58; H, 10.58

Found: C, 70.38; H, 10.35%.

Alcohol (8)

Yield: 61%

IR: 3340, 2940, 2850, 1660, 1460,1390, 1360, 1145, 1105, 1000, 910, 820 cm^{-1}.

Ms: m/e 128.

Analysis: Calculated for $C_8H_{16}O$

C, 75.0; H, 12.50

Found: C, 74.87; H, 12.41%.

Ether (9)

Yield: 60%

IR: 2940, 2900, 2860, 1685, 1580, 1480, 1440, 1380, 1350, 1245, 1155, 1075, 740, 680 cm^{-1}.

Ms: m/e 310.

Analysis: Calculated for $C_{21}H_{26}O_2$

C, 81.3; H, 8.38

Found: C, 81.15; H, 8.13%.

Dichlorocyclopropanated ether (10)

Yield: 55%.

IR: 2940, 2850, 1520, 1480, 1440, 1380, 1245, 1210, 1100, 740, 685 cm^{-1}.

Ms: m/e (^{35}Cl), 392 (^{37}Cl) 396.

Analysis: Calculated for $C_{22}H_{26}Cl_2O_2$

C, 67.17; H, 6.61; C, 18.06

Found: C, 67.07; H, 6.43; C, 18.10%.

Ester (12)

Yield: 66%.

IR: 3000, 1725, 1640, 1590, 1510, 1460, 1380, 1360, 1290, 1180, 1050, 880, 780, 710 cm^{-1}.

Ms: m/e 190.

Analysis: Calculated for $C_{12}H_{14}O_2$

C, 75.78; H, 7.36

Found: C, 75.83; H, 7.28%.

Alcohol (13)

Yield: 57%.

IR: 3360, 3060, 3020, 2920, 2880, 1620, 1550, 1500, 1490, 1450, 1380, 1270, 1150, 1100, 1060, 1015, 750, 690 cm^{-1}.

Ms: m/e 148.

Analysis: Calculated for $C_{10}H_{12}O$

C, 81.08; H, 8.10

Found: C, 80.98; H, 8.14%.

Ether (14)

Yield: 62%.

IR: 2980, 2920, 2860, 1580, 1490, 1440, 1370, 1250, 1160, 1050, 1020, 930, 810, 750, 680 cm^{-1}.

Ms: m/e 330.

Analysis: Calculated for $C_{23}H_{22}O_2$

C, 83.63; H, 6.66

Found: C, 83.40; H, 6.42%.

Dichlorocyclopropanated ether (15)

Yield: 55%.

IR: 3060, 3030, 2920, 2880, 1590, 1490, 1450, 1260, 1220, 1080, 760, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 412 (^{37}Cl) 416.

Analysis: Calculated for $C_{24}H_{22}Cl_2O_2$

C, 69.73; H, 5.32; Cl, 17.19

Found: C, 69.61; H, 5.24; Cl, 17.22%.

Ether (16)

Yield: 60%.

IR: 3060, 2980, 2940, 2870, 1685, 1600, 1500, 1455, 1390, 1250, 1220, 1170, 1075, 950, 760, 700 cm^{-1}.

Ms: m/e 336.

Analysis: Calculated for $C_{23}H_{28}O_2$

C, 82.14; H, 8.33

Found: C, 82.20; H, 8.21%.

Ether (17)

Yield: 52%

IR: 3050, 2970, 2940, 2860, 1595, 1495, 1450, 1380, 1250, 1220, 1170, 1080, 820, 780, 695 cm^{-1}.

Ms: m/e (^{35}Cl) 500 (^{37}Cl) 508.

Analysis: Calculated for $C_{25}H_{28}Cl_4O_2$

C, 59.76; H, 5.57; C, 28.28

Found: C, 59.63; H, 5.44; Cl, 28.20%.

Ester (18)

Yield: 61%.

IR: 2980, 2880, 1720, 1660, 1455, 1425, 1380, 1360, 1310, 1270, 1200, 1125, 1040, 860 cm^{-1}.

Ms: m/e 154.

Analysis: Calculated for $C_9H_{14}O_2$.

C, 70.12; H, 9.09

Found: C, 70.20; H, 8.91%.

Alcohol (19)

Yield: 58%.

IR: 3350, 2950, 2880, 2840, 1680, 1440, 1240, 1165, 1080, 1000 cm^{-1}.

Ms: m/e 112.

Analysis: Calculated for $C_7H_{12}O$

C, 75.0; H, 10.71

Found: C, 74.87; H, 10.82%.

Ether (21)

Yield: 67%.

IR: 3050, 2960, 2880, 1600, 1498, 1460, 1370, 1260, 1220, 1175, 1100, 1070, 950, 765, 695 cm^{-1}.

Ms: m/e 294.

Analysis: Calculated for $C_{20}H_{22}O_2$

C, 81.63; H, 7.48

Found: C, 81.55; H, 7.45%.

Dichlorocyclopropanated ether (22)

Yield: 55%.

IR: 3050, 2970, 2875, 1595, 1495, 1450, 1360, 1260, 1220, 1170, 1080, 950, 780, 695 cm^{-1}.

Ms: m/e (^{35}Cl) 376 (^{37}Cl) 380.

Analysis: Calculated for $C_{21}H_{22}Cl_2O_2$

C, 66.84; H, 5.83; Cl, 18.83

Found: C, 66.78; H, 5.79; Cl, 18.85%.

Ester (24)

Yield: 64%.

IR: 2980, 2930, 2850, 1720, 1650, 1450, 1385, 1315, 1280, 1240, 1210, 1160, 1040, 850 cm^{-1}.

Ms: m/e 168.

Analysis: Calculated for $C_{10}H_{16}O_2$

C, 71.42; H, 9.52

Found: C, 71.45; H, 9.58%.

Alcohol (25)

Yield: 59%.

IR: 3320, 2940, 2860, 1675, 1450, 1235, 1050, 980, 750 cm^{-1}.

Ms: m/e 126.

Analysis: Calculated for $C_8H_{14}O$

C, 76.20; H, 11.11

Found: C, 75.87; H, 11.17%.

Ether (26)

Yield: 65%.

IR: 3020, 2920, 2840, 1660, 1585, 1490, 1440, 1245, 1215, 1160, 1140, 1070, 940, 750, 690 cm^{-1}.

M/e: m/e 308.

Analysis: Calculated for $C_{21}H_{24}O_2$

C, 81.81; H, 7.79

Found: C, 81.78; H, 7.87%.

Dichlorocyclopropanated ether (27)

Yield: 53%.

IR: 2940, 2870, 1595, 1495, 1455, 1370, 1265, 1220, 1095, 880, 760, 695 cm^{-1}.

Ms: m/e(^{35}Cl) 390 (^{37}Cl) 394.

Analysis: Calculated for $C_{22}H_{24}Cl_2O_2$

C, 65.47; H, 6.13; Cl, 18.15

Found: C, 65.52; H, 6.03; Cl, 18.0%.

Methyl(±) cis 2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropane carboxylate(28)

(±) Cis DV acid (2.1 g; 0.01 mole) was dissolved in dry ether and treated with excess of ethereal solution of diazomethane to get the ester (28) (2.0 g; 90%) .

IR: 3040, 2920, 2840, 1720, 1610, 1435, 1400, 1360, 1220, 1190, 1140, 1080, 995, 925, 840, 805, 780, 640 cm^{-1}.

Ms: m/e (^{35}Cl) 222 (^{37}Cl) 226.

Analysis: Calculated for $C_9H_{12}Cl_2O_2$

C, 48.43; H, 5.38

Found: C, 48.22; H, 5.23%.

(±) Cis 2,2-dimethyl-3-(2,2-dichlorovinyl) 1-hydroxymethyl cyclopropane(29)

To a stirred and cooled (10°) suspension of LAH (0.92 g; 0.024 mole) in dry ether (20 ml) was added in small lots anhydrous $AlCl_3$ (1.07 g; 0.008 mole) during 1 hr and stirring continued for 0.5 hr. at room temperature. A solution of ester (28) (1.8 g; 0.008 mole) in ether (10 ml) was added dropwise over a period of 0.5 hr and stiring continued for 2 hr.

The reaction mixture was cooled to 0° and ethyl acetate (5 ml) added dropwise to decompose excess of AlH_3. Organic layer was decanted and residue diluted with water, extracted with ether (3 x 20 ml). Combined ether layer was washed with water, brine, dried and distilled to remove the solvent. The alcohol thus obtained was purified by column chromatography over silica gel and elution with 2.5% ethyl acetate in pet.ether (1.02 g; 65%).

IR: 3350, 2940, 2860, 1610, 1450, 1375, 1250, 1130, 1010, 915, 830, 640 cm^{-1}.

Ms: m/e (^{35}Cl) 194 (^{37}Cl) 198.

Analysis: Calculated for $C_8H_{12}Cl_2O$

C, 49.23; H, 6.15

Found: C, 48.97; H, 6.23%.

3-Phenoxybenzyl (±) cis-2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropane-1-methyl ether (30)

Sodium hydride (50% emulsion, 0.25 g; 0.005 mole) was washed with dry benzene and suspended in another 15 ml benzene. To this was added a solution of alcohol (**29**) (1.0 g; 0.005 mole) in benzene (5 ml) and the mixture refluxed for 1.5 hr, cooled to room temperature, and then to it was added a solution of 3-phenoxybenzyl bromide (1.35 g; 0.005 mole) in benzene (5 ml). The reaction mixture was refluxed for 6 hr, cooled to room temperature, decanted to separate the benzene layer. The residue was diluted with water, extracted with benzene (2 x 15 ml). Combined benzene layer was washed with water, brine, dried and distilled to remove benzene. The ether thus obtained was purified by column chromatography over silica gel and elution with 40% chloroform in pet.ether (0.98 g; 53%).

IR: 3010, 2920, 2860, 1580, 1480, 1245, 1210,1090, 1010, 910, 730, 675 cm^{-1}.

Ms: m/e (^{35}Cl) 360 (^{37}Cl) 364.

Analysis: Calculated for $C_{21}H_{22}Cl_2O_2$

C, 69.8; H, 6.09; Cl, 19.66

Found: C, 69.73; H, 6.12; Cl, 19.43%.

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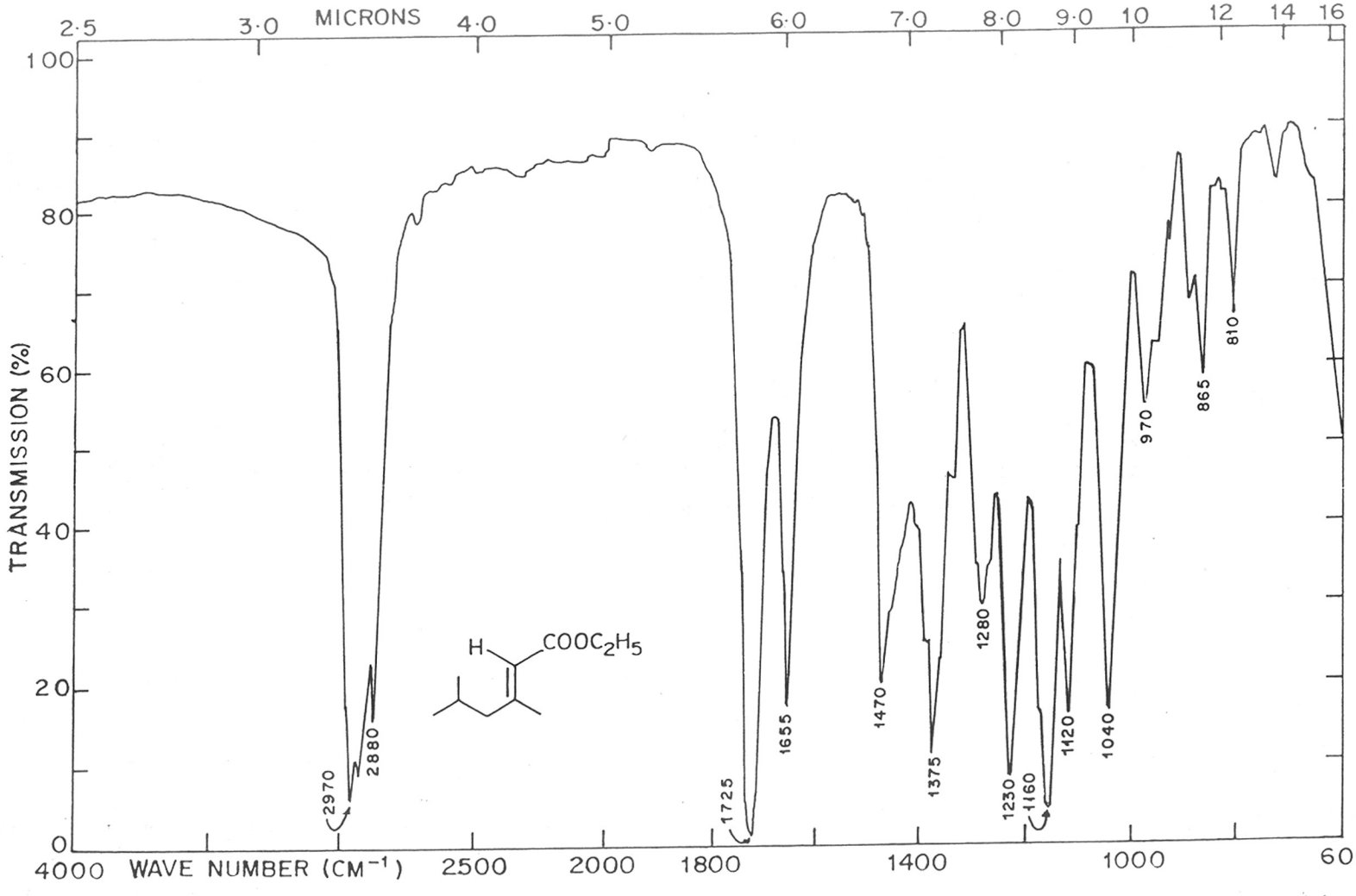


FIG. 1. IR SPECTRUM OF ETHYL 3-METHYL 3-ISOBUTYL ACRYLATE (7)

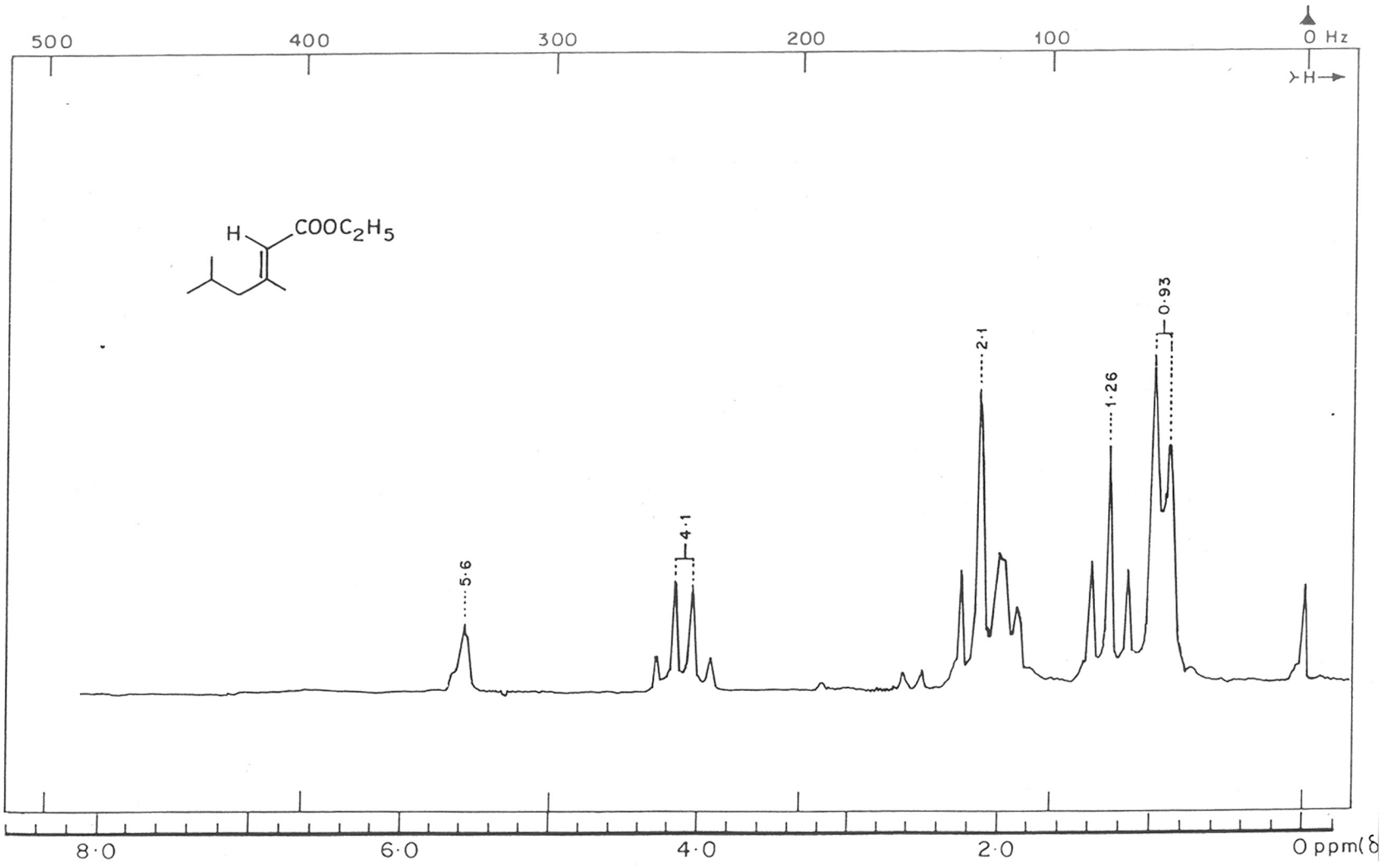


FIG. 2. PMR SPECTRUM OF ETHYL 3-METHYL 3-ISOBUTYL ACRYLATE (7)

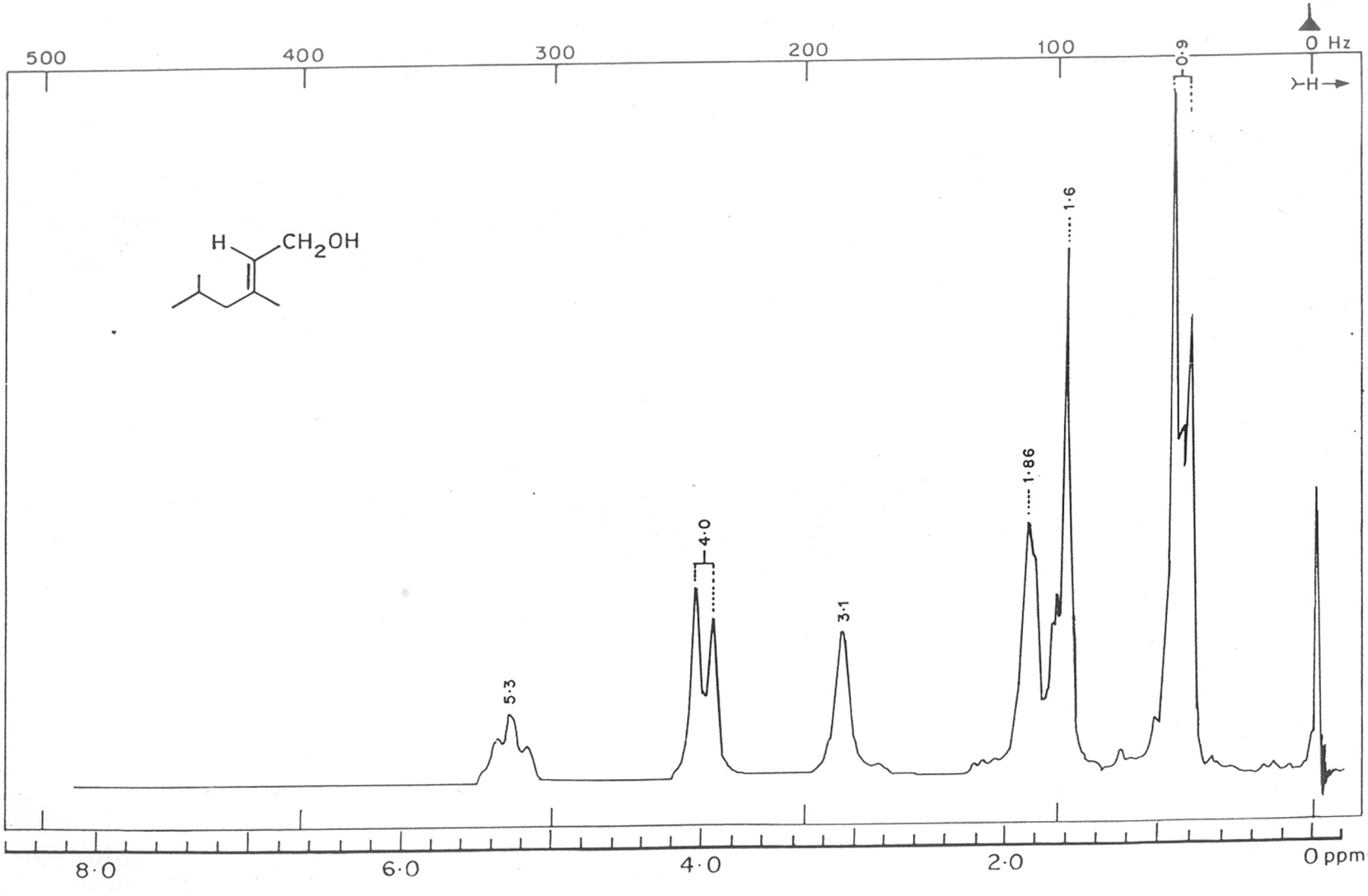


FIG. 3. PMR SPECTRUM OF 3,5-DIMETHYL HEX-2-ENE-1-OL (8)

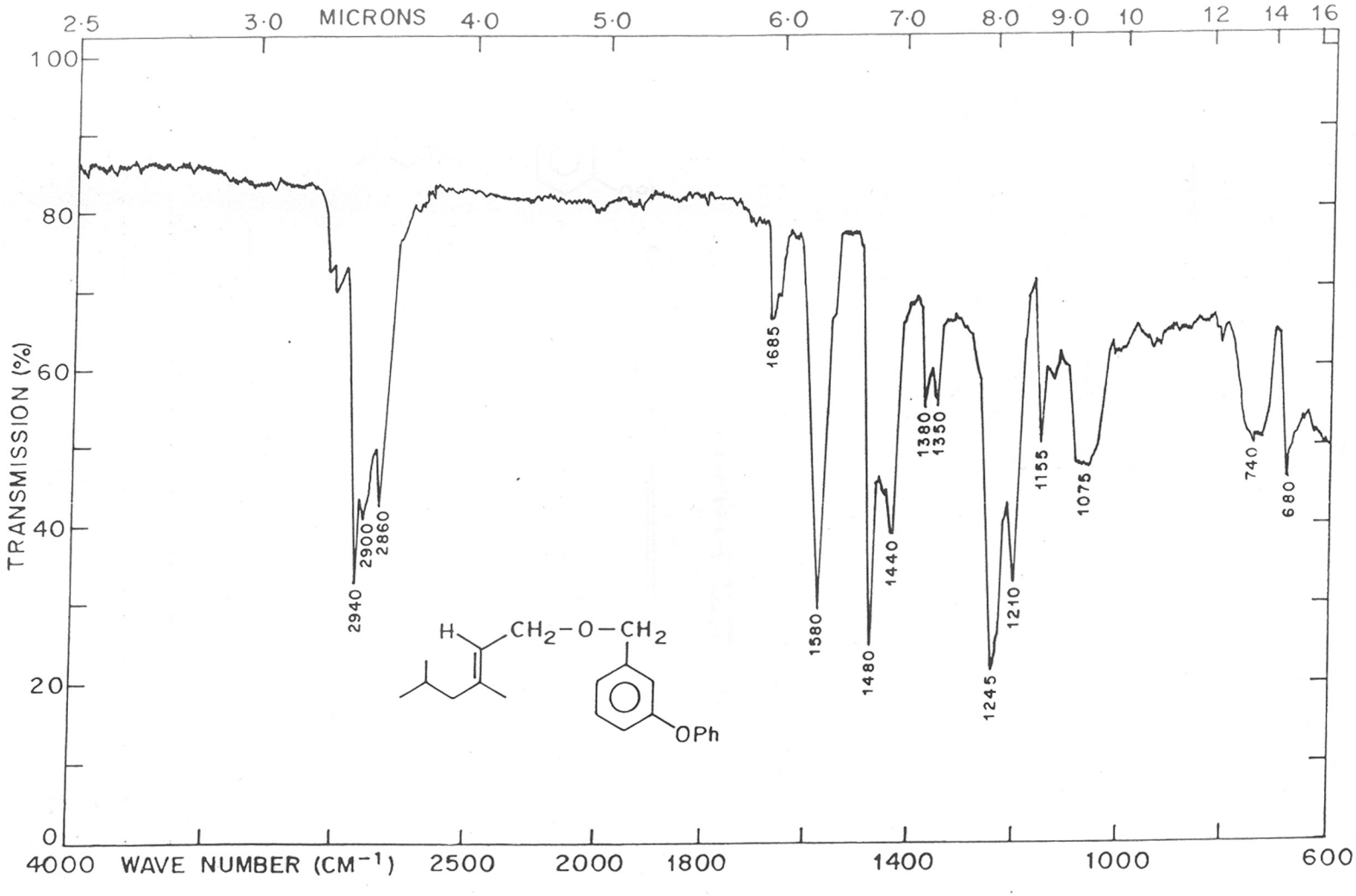


FIG. 4. IR SPECTRUM OF 3,5-DIMETHYL HEX-2-ENE-1-YL 3-PHENOXYBENZYL ETHER (9)

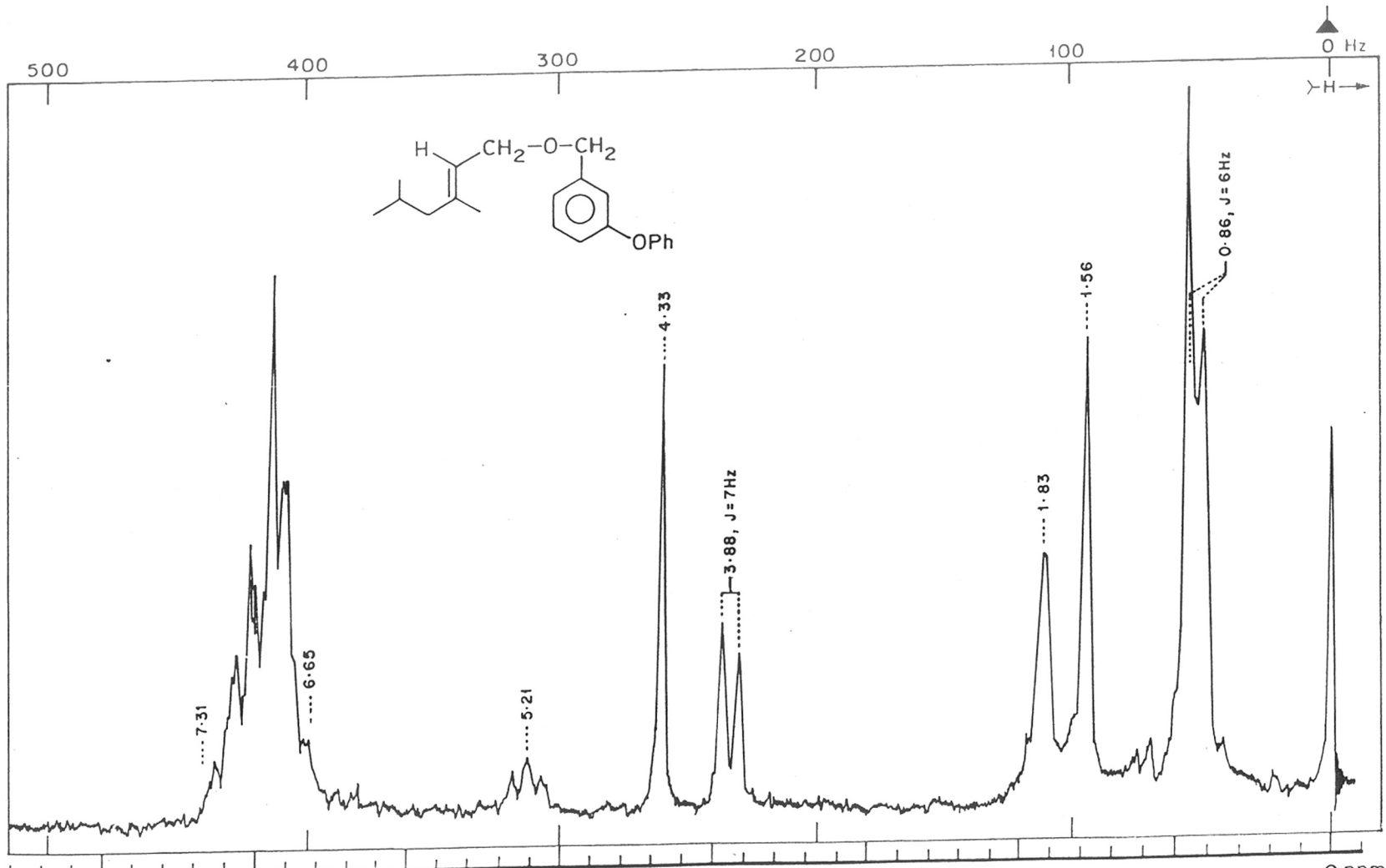


FIG. 5. PMR SPECTRUM OF 3,5-DIMETHYL HEX-2-ENE-1-YL 3-PHENOXYBENZYL ETHER (9)

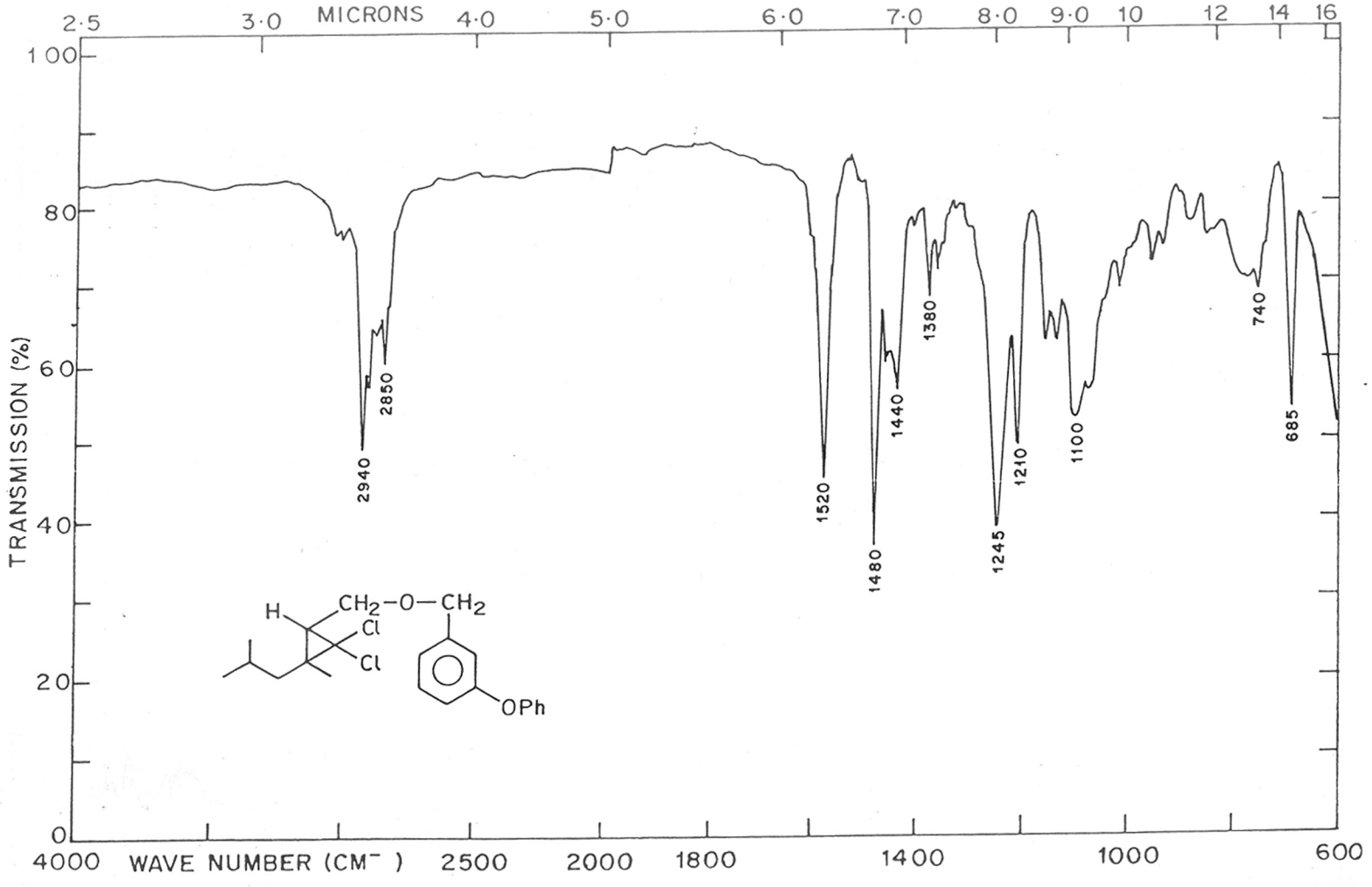


FIG. 6. IR SPECTRUM OF 2,2-DICHLORO 3-METHYL 3-ISOBUTYL CYCLOPROPYL METHYL ETHER (10)

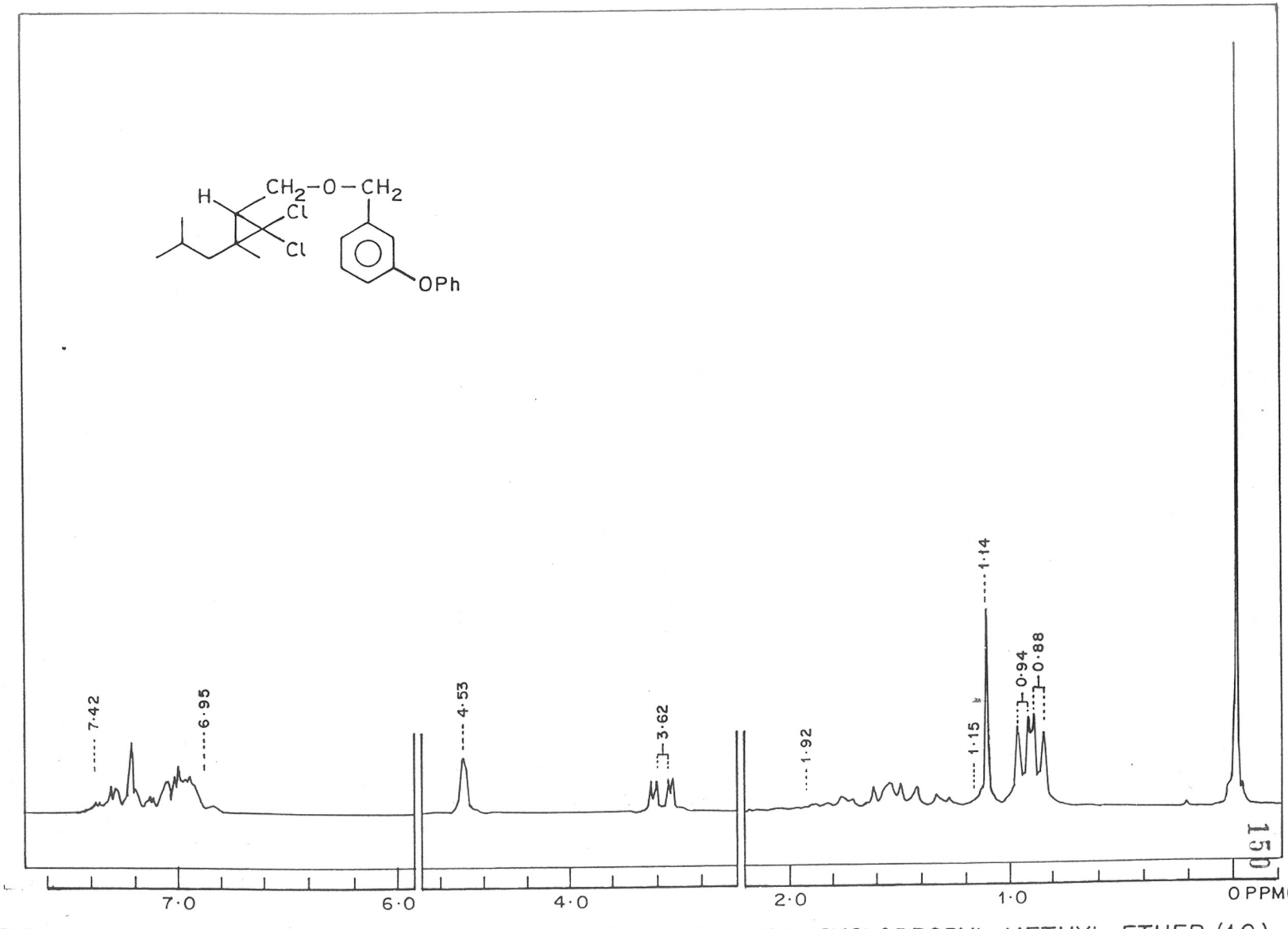


FIG. 7. PMR SPECTRUM OF 2,2-DICHLORO 3-METHYL 3-ISOBUTYL CYCLOPROPYL METHYL ETHER (10)

CHAPTER-IV-B

SYNTHESIS OF SOME NEW PYRETHROIDS: 3-PHENOXYBEZYL (±) CIS AND (±) TRANS 2-ISOPROPYL / 2-METHYL, 2-ISOBUTYL, 3-(2,2-DICHLOROVINYL) CYCLOPROPANE CARBOXYLATES

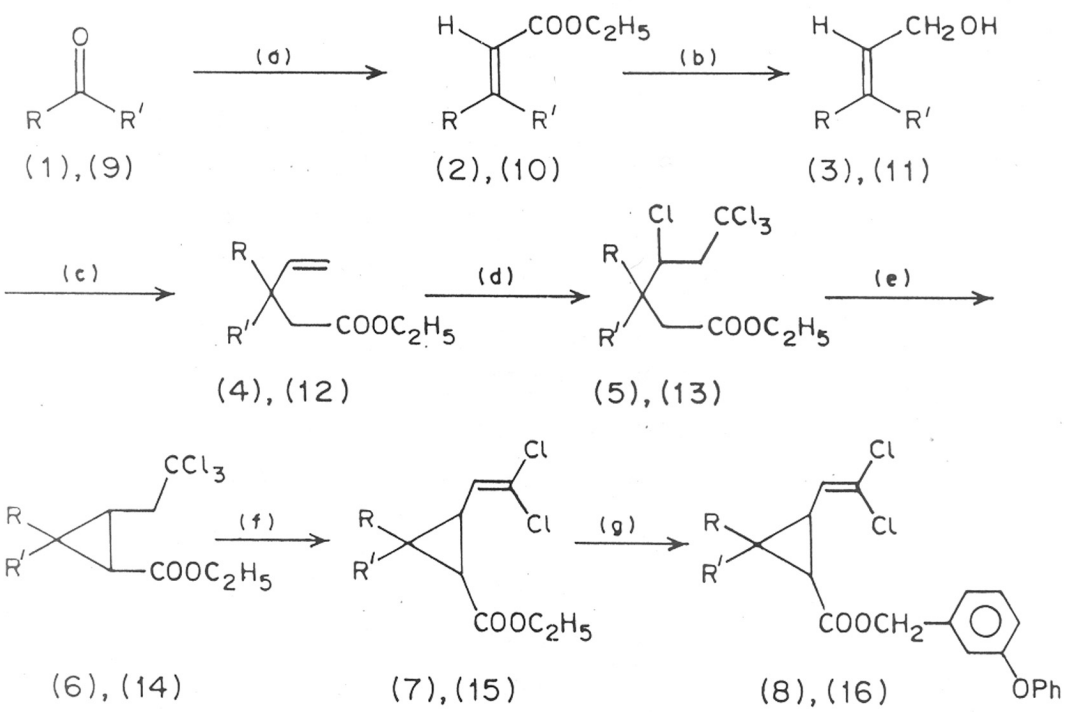
SUMMARY

Synthesis of 3-phenoxybenzyl (±) cis and (±) trans 2-isopropyl/2-methyl, 2-isobutyl, 3-(2,2-dichlorovinyl) cyclopropane carboxylates has been described in this chapter. Scheme (I).

Isobutyraldehyde (1) was subjected to Wittig reaction, using the phosphorne generated from triethylphosphonoacetate by treatment of the latter with NaH, to afford ethyl-4-methyl-2-pentenoate (2). The unsaturated ester (2) was selectively reduced by AlH_3 to furnish the corresponding allyl alcohol (3). The latter on Claisen orthoester rearrangement with triethylorthoacetate afforded ethyl-3-isopropyl-4-pentenoate (4). Free radical initiated CCl_4 addition to ethyl 3-isopropyl 4-petenoate gave ethyl 4,6,6,6-tetrachloro 3-isopropyl hexenoate (5). The latter was then cyclised using lithium diisopropylamine (LDA) to afford ethyl 2-isopropyl-3-(2,2,2-trichloroethyl)cyclopropane carboxylate (6). Treatment of latter with DBU in benzene followed by transesterification of the resulting dehydrohalogenated ester using 3-phenoxybenzyl alcohol furnished the title ester (8).

By following analogous sequence of reactions, using methyl isobutyl ketone as the substrate, the ester (16) was synthesised. Scheme (I).

SCHEME (1)



(1) to (8) $R=CH(CH_3)_2$, $R'=H$

(9) to (16) $R=CH_3$, $R'=CH_2CH(CH_3)_2$

(a) $=(EtO)_2\overset{O}{\overset{\|}{P}}CH_2COOEt/NaH$

(b) $=AlH_3$

(c) $=CH_3C(OEt)_3$, o-cresol, H_3PO_4

(d) $=CCl_4/Bz_2O_2$

(e) = LDA / THF

(f) = DBU / Benzene

(g) = 3-phenoxybenzyl alcohol, butyl titanate, xylene

INTRODUCTION

As described earlier in the Chapter III of the thesis, the insecticidal activity of the natural pyrethrins, synthetic chrysanthemates and potent pyrethroids depends on certain important structural features. One such important structural feature responsible for insecticidal activity is the presence of a gem dimethyl group or its steric equivalent β to carboxylate function.

Because it is observed that esters possessing one methyl group and without any alkyl substitution at C_2 position of cyclopropane were found to be much less active than the esters possessing a gem dimethyl group at C_2 position.

With a view to study the effect of esters possessing more bulkier groups like isopropyl at C_2 position of cyclopropane on the insecticidal activity it was felt desirable to synthesise such esters for evaluation of their insecticidal properties. Among the potent pyrethroids, possessing a gem dimethyl grouping at C_2 position, the esters with a 2,2 dihalo vinyl side-chain at C_3 position of the cyclopropane like permethrin, cypermethrin, deltamethrin etc. exhibit much enhanced insecticidal activity. Therefore, retaining the 2,2-dichlorovinyl side chain at C_3 position of cyclopropane, two new pyrethroids, as 3-phenoxybenzyl esters have been synthesised possessing an isopropyl group and a methyl and isobutyl group at C_2 position of cyclopropane by total synthetic approach for evaluating their insecticidal properties.

PRESENT WORK

The present work deals with the synthesis of 3-phenoxybenzyl (±) cis and (±) trans 2-isopropyl/2-methyl, 2-isobutyl, 3-(2,2-dichlorovinyl) cyclopropane carboxylates (**8**) and (**16**) respectively. Scheme (I).

Wittig reaction[1] on isobutyraldehyde (**1**), using the phosphorane generated from triethylphosphonoacetate by treatment of the latter with NaH in ether gave ethyl-4-methyl-2-pentenoate (**2**).

IR: 1730 (ester carbonyl), 1660 (conjugated C=C) cm^{-1}.

PMR: 1.06 (6H, d, J=7 Hz, isopropyl methyls), 1.23 (3H, t, J=7 Hz, ester methyl), 2.3 (1H, m, methine proton), 4.1 (2H, q, J=7 Hz, ester methylene), 5.53 (1H, d, J=14 Hz, olefinic proton adjacent to carbonyl), 6.76 (1H, dd, J_1=7 Hz, J_2=14 Hz, olefinic proton at C_3).

Reduction of the ester (**2**), by AlH_3[2] afforded 4-methyl-2-penten-1-ol (**3**).

IR: 3340, (-OH) cm^{-1}.

PMR: 1.0 (6H, d, J=7 Hz, isopropyl methyls), 2.16 (1H, m, methine proton), 3.33 (1H, br s, D_2O exchangeable OH proton), 3.9 (2H, m, methylene protons), 5.46 (2H, m, olefinic protons).

The alcohol (**3**) on Claisen orthoester rearrangement[3] with triethylorthoacetate afforded ethyl-3-isopropyl-4-pentenoate (**4**).

IR: 1740 (ester carbonyl), 1645, 910 ($CH=CH_2$) cm^{-1}.

PMR: 0.82, 0.88 (6H, two doublets, J=4 Hz, isopropyl methyls), 1.2 (3H, t, J=7 Hz, ester methyl), 1.55 (1H, m, methine proton of isopropyl), 2.0-2.53 (3H, dd, overlapping a m, CH_2CO and allylic methine proton), 4.06 (2H, q, J=7 Hz, ester methylene), 4.93 (1H, dd, J_1=2 Hz, J_2=4Hz, one of the olefinic

protons at C_5), 5.06, (1H, dd, $J_1 \approx J_2 = 16$ Hz, other olefinic proton at C_5), 5.64 (1H, m, olefinic proton at C_4).

Free radical initiated CCl_4 addition[4] to ethyl 3-isopropyl-4-pentenoate gave ethyl 4,6,6,6-tetrachloro-3-isopropyl hexenoate (**5**).

IR: 1735 (ester carbonyl) cm^{-1}.

PMR: 0.93, 1.06 (6H, two doublets, J=8 Hz each, isopropyl methyls), 1.26 (3H, t, J=6 Hz, ester methyl), 1.66 (1H, m, methine proton of isopropyl), 2.15 (1H, m, methine proton at C_3), 2.42 (2H, two overlapping double doublets, CH_2CO of isomers), 3.17 (2H, m, CH_2CCl_3 of isomers), 4.13 (2H, q, J=8 Hz, ester methylene), 4.51 (1H, m, C_4 proton of isomers).

Cyclization of the CCl_4 adduct (**5**) using lithium diisopropylamine gave the trichloro ester (**6**).

IR: 1740 (ester carbonyl) cm^{-1}.

PMR: 1.0 (7H, d overlapping a m, isopropyl methyls and cyclopropane proton at C_3), 1.25 (3H, t, J=6.4 Hz, ester methyl), 1.55 (3H, m, methine and cyclopropane protons at C_1 and C_2), 3.0 (2H, d, J=6.4 Hz, CH_2CCl_3), 4.1 (2H, q, J=6.4 Hz ester methylene).

The trichloro ester (**6**) was refluxed with DBU in benzene-DMF, to cause dehydrohalogenation and yield the dichloro ester (**7**).

IR: 1730 (ester carbonyl), 1620 ($C=CCl_2$) cm^{-1}.

PMR: Centred at 1.0 (6H, two overlapping doublets, isopropyl methyls), 1.26 (3H, t, J=6 Hz, ester methyl), 1.53 (2H, m, C_1 and C_2 cyclopropane protons of isomers), 1.88 (1H, m, methine proton of isopropyl of isomers), 2.28 (1H, m, C_3 cyclopropane proton of isoemrs), 4.08 (2H, q, J=7 Hz, ester methylene), 5.51, 5.93 (1H, two doublets, J=9 Hz each, olefinic proton of isomers).

Ester (7) was transesterified using m-phenoxybenzyl alcohol to afford the ester (8).

IR: 1730 (ester carbonyl), 1620 ($C=CCl_2$), 1585, 1490, 690 (aromatic) cm^{-1}.

PMR: 1.0 (6H, two overlapping doublets, isopropyl methyls), 1.53 (2H, m, C_1 and C_2 cyclopropane protons of isomers), 1.95 (1H, m, methine proton of isopropyl), 2.37 (1H, m, C_3 cyclopropane proton of isomers), 5.06 (2H, s, benzylic CH_2), 5.55, 5.95 (1H, two doublets, J=9 Hz each, olefinic proton of isomers), 6.84-7.44 (9H, m, aromatic protons).

By following an analogous sequence of reactions, 3-phenoxybenzyl ester (16) was obtained from methyl isobutyl ketone (9). Spectral properties of the final compound and intermediates are as follows.

Ester (10)

IR: 1725 (ester carbonyl), 1655 (conjugated C=C) cm^{-1}.

PMR: 0.93 (6H, d, J=7 Hz, isopropyl methyls), 1.26 (3H, t, J=7 Hz, ester methyl), 2.1 (6H, s overlapping a m, methyl and methylene on double bond and isopropyl methine proton), 4.1 (2H, q, J=7 Hz, ester methylene), 5.6 (1H, m, due to homoallylic coupling, olefinic proton).

Alcohol (11)

IR: 3340 (-OH), 1660 ($H\,C=\overset{|}{C}-$) cm^{-1}.

PMR: 0.9 (6H, d, J=7 Hz, isopropyl methyls), 1.6 (3H, s, methyl on double bond), 1.86 (3H, br m, methylene on double bond and methine proton), 3.1 (1H, s, D_2O exchangeable -OH proton), 4.0 (2H, d, J=7 Hz, CH_2O), 5.3 (1H, m, olefinic proton).

Ester (12)

IR: 1740 (ester carbonyl), 1640, 910 ($CH=CH_2$) cm^{-1}.

PMR: 0.91 (6H, d, J=7 Hz, methyls of isopropyl), 0.98 (3H, s, tertiary methyl), 1.23 (5H, t overlapping a m, ester methyl and methine of isobutyl), 1.76 (1H, m, centred at, methine proton), 2.23 (2H, s, CH_2CO), 4.0 (2H, q, J=7 Hz, ester methylene), 4.75, 5.0 (2H, m each, olefinic methylene protons), 5.8 (1H, dd, J_1=9.5 Hz, Jz=19 Hz other olefinic proton).

Ester (13)

IR: 1740 (ester carbonyl) cm^{-1}.

PMR: 0.91, 0.95 (6H, two doublets of isopropyls of diastereomers), 1.11 (3H, s, tertiary methyl), 1.22 (3H, two triplets of tert.methyls of diastereomers), 1.37-1.77 (3H, m, methylene of isobutyl and methine proton), 2.53 (2H, two closely overlapping doublets of $COCH_2$ due to two diastereomers), 3.2 (2H, m, CH_2CCl_3), 4.14 (2H, two overlapping quartets of two diastereomers, ester methylene), 4.64 (1H, m, CHCl).

Cyclised ester (14)

IR: 1730 (ester carbonyl) cm^{-1}.

PMR: 0.85-1.05 (6H, four pairs of closely overlapping doublets, methyls of isopropyl of diastereomers), 0.9, 1.1 (3H, s each, tertiary methyls) of diastereomers), 1.22 (3H, two closely overlapping triplets, J=8 Hz, ester methyl), 1.5-2.0 (5H, m, cyclopropane protons, methylene and methine protons of isobutyl), 2.4-2.7 (2H, m, CH_2CCl_3), 4.1 (2H, two closely overlapping quartets J=8 Hz, ester methylene of diastereomers).

Dehydrohalogenated ester (15)

IR: 1730 (ester carbonyl), 1630, ($C=CCl_2$) cm^{-1}.

PMR: 0.77-1.08 (6H, four pairs of closely overlapping doublets, methyls of isopropyl of diastereomers), 0.95, 1.13 (3H, two singlets of tertiary methyl), 1.26 (3H, two closely overlapping tripelts, J=7 Hz, ester methyls of diastereomers), 1.86-2.65 (5H, m, cyclopropane protons, methylene and

methine protons of isobutyl), 4.11 (2H, two closely overlapping quartets, J=Hz, ester methylene.), 5.82, 6.0, 6.26, 6.37 (1H, d each, J=7 Hz each, olefinic protons of diastereomers).

3-Phenoxybenzyl ester (16)

IR: 1735 (ester carbonyl), 1640 ($C=CCl_2$), 1590, 1490, 690 (aromatic)cm^{-1}.

PMR: 0.84-1.17 (6H, four pairs of closely overlapping doublets, methyls of isopropyl of diastereomers), 0.88, 1.11 (3H, s each, tertiary methyl of diastereomers), 1.86-2.66 (5H, m, cyclopropane protons, methylene and methine protons of isopropyl), 5.06 (2H, s, benzylic CH_2), 5.73, 5.95, 6.28, 6.4 (1H, d each, J=9 Hz each, olefinic protons of diastereomers), 6.84-7.55 (9H, m, aromatic protons).

EXPERIMENTAL

Ethyl 4-methyl-2-pentenoate (2)

Wittig reaction on isobutyraldehyde using the phosphorane, generated from triethylphosphonoacetate by treatment of the latter with NaH in ether as described in Chapter III, gave ethyl 4-methyl-2- pentenoate (2).

4-Methyl-2-penten-1-ol (3)

To a stirred and cooled (10°) suspension of LAH (2.4 g, 0.063 mole) in dry ether (40 ml) was added in small lots anhydrous $AlCl_3$ (2.8 g; 0.021 mole) during 1 hr and stirring continued for 0.5 hr at room temperature. A solution of ester (2) (9.0 g; 0.063 mole) in ether (30 ml) was added dropwise over a period of 0.5 hr and stirring continued for 2 hr.

The reaction mixture was cooled to 0° and ethyl acetate (5 ml) added dropwise to decompose excess of AlH_3. Organic layer was decanted and residue diluted with water, extracted with ether (3 x 20 ml). Combined ether layer was washed with water, brine, dried and distilled to remove the solvent. The alcohol thus obtained was purified by column chromatography over silica gel and eluted with 2.5% ethyl acetate in pet.ether to give pure alcohol (3) (4.56 g; 72%).

IR: 3340, 2960, 2870, 1670, 1465, 1365, 1010, 970 cm^{-1}.

Ms: m/e 100.

Analysis: Calculated for $C_6H_{12}O$

C, 71.95; H, 12.08

Found: C, 71.87; H, 12.20%.

Ethyl 3-isopropyl-4-pentenoate (4)

The alcohol (3) on Claisen orthoester rearrangement with triethyl-

orthoacetate as per the procedure described in Chapter III, afforded ethyl 3-isopropyl-4-pentenoate (**4**), as a liquid.

Yield: 69%.

IR: 3080, 2960, 2860, 1740, 1645, 1470, 1370, 1265, 1185, 1120, 1035, 1000, 920 cm^{-1}.

Ms: m/e 170.

Analysis: Calculated for $C_{10}H_{18}O_2$

C, 70.54; H, 10.66

Found: C, 70.37; H, 10.50

Ethyl 4,6,6,6-tetrachloro-3-isopropyl hexenoate (5)

To a solution of the ester (**4**) (4.0 g; 0.0235 mole) in dry CCl_4 (25 ml) was added dry solution (20 ml, 2%) of Bz_2O_2 and the mixture refluxed for 30 hr and then allowed to cool to room temperature. It was then washed with aqueous 5% Na_2SO_3 (3 x 50 ml), water, brine, dried and solvent removed by distillation under reduced pressure. The crude tertrachloro ester after column chroamtography over silica gel and elution with 1.5% ethyl acetate in pet.ether afforded the pure ester (**5**) as a liquid (5.94 g; 78%).

IR: 2950, 1735, 1385, 1365, 1175, 1110, 1020, 990, 965, 780, 695 cm^{-1}.

Ms: m/e (^{35}Cl) 322(^{37}Cl) 330.

Analysis: Calculated for $C_{11}H_{18}O_2Cl_4$

C, 40.74; H, 55.55; Cl, 43.82

Found: C, 40.80; H, 55.50; Cl, 43.90%.

Ethyl 2-isopropyl-3-(2,2,2-trichloroethyl)cyclopropane carboxylate (6)

To a solution of diisopropylamine (1.01 g; 0.01 mole) in dry THF (5 ml) at -78° was added by syringe n-BuLi (4.34 ml, 2.3N, n-hexane solution,

0.1 mole) under N_2 atmosphere, stirred for 0.5 hr. A solution of the ester (**5**) (3.24 g; 0.01 mole) in dry THF (7 ml) was then added and stirring continued for additional 0.5 hr at -78°. The reaction mixture was allowed to attain room temperature and stirring continued for 24 hr.

THF was removed under reduced pressure residue diluted with water, extracted with ether (3 x 30 ml). The combined ether layer was washed with water, brine, dried and solvent removed by distillation. The pure cyclised product was obtained after column chromatography over silica gel and elution with 1% ethyl acetate in pet.ether.

Yield: (2.0 g; 70%).

IR: 2980, 2940, 2880, 1740, 1480, 1460, 1380, 1350, 1190, 1050, 900, 825, 780, 710, 630 cm^{-1}.

Ms: m/e (^{35}Cl) 286 (^{37}Cl) 292.

Analysis: Calculated for $C_{11}H_{17}O_2Cl_3$

C, 45.91; H, 5.91; Cl, 37.0

Found: C, 45.80; H, 6.10; Cl, 37.3%.

Ethyl 2-isopropyl-3-(2,2-dichlorovinyl) cyclopropane carboxylate (7)

A mixture of ester (**6**) (1.9 g; 0.0066 mole), DBU (1.2 g; 0.0080 mole) in dry benzene (10 ml) was refluxed for 8 hr. The reaction mixture was diluted with water, washed with dil.HCl, water, brine, dried and solvent removed by distillation under reduced pressure to afford the dehydrohalogenated product. The latter after column chromatography over silica gel and elution with 1% ethyl acetate in pet.ether afforded pure ester (**7**) as a mixture of diastereomers in the form of a pale yellow liquid (1.11g; 67%).

IR: 3030, 2950, 2880, 1730, 1620, 1470, 1370, 1235, 1170, 1035, 930, 850, 755, 695 cm^{-1}.

Ms: m/e (^{35}Cl) 250 (^{37}Cl) 254.

Analysis: Calculated for $C_{11}H_{16}O_2Cl_2$

C, 52.58; H, 6.37; Cl, 28.28

Found: C, 52.40; H, 6.50; Cl, 28.40%.

3-Phenoxybenzyl (±) cis and (±) trans 2-isopropyl 3(2,2-dichlorovinyl) cyclopropane carboxylate (8)

The ester (7), (0.5 g; 0.002 mole), 3-phenoxybenzyl alcohol (0.44g; 0.0022 mole) and butyl titanate (1 drop) were dissolved in dry xylene (20 ml) and the mixture refluxed for 12 hr. Xylene was removed by distillation under reduced pressure to obtain the title ester (8), as a liquid, purified by column chromatography over silica gel and eluted with pet.ether (0.484 g; 60%).

IR: 3030, 2950, 2880, 1730, 1620, 1585, 1490,1445, 1380, 1330, 1255, 1210, 1165, 930, 865, 770, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 404(^{37}Cl) 408.

Analysis: Calculated for $C_{22}H_{22}O_3Cl_2$

C, 65.18; H, 5.43; Cl, 17.53

Found: C, 65.30; H, 5.32; Cl, 17.70%.

By following an analogous sequence of reactions, 3-phenoxybenzyl ester (16) was obtained from methyl isobutyl ketone (9). Spectral and analytical data for the final compound and intermediates are as follows:

Ester (10)

Yield: 67%.

IR: 2970, 2880, 1725, 1655, 1470, 1375, 1280, 1230, 1160, 1120, 1040, 970, 865, 810 cm^{-1}.

Ms: m/e 170.

Analysis: Calculated for $C_{10}H_{18}O_2$

C, 70.54; H, 10.66

Found: C, 70.60; H, 10.70%.

Alcohol (11)

Yield: 70%.

IR: 3340, 2940, 2850, 1660, 1460, 1390, 1360, 1145, 1105, 1000, 910, 820 cm^{-1}.

Ms: m/e 128.

Analysis: Calculated for $C_8H_{16}O$

C, 74.94; H, 12.58

Found: C, 74.70; H, 12.67%.

Ester (12)

Yield: 72%.

IR: 3090, 2960, 2880, 1740, 1640, 1470, 1370, 1210, 1130, 1035, 910 cm^{-1}.

Ms: m/e 198.

Analysis: Calculated for $C_{12}H_{22}O_2$

C, 72.68; H, 11.18

Found: C, 72.77; H, 10.93%.

Tetrachloro ester (13)

Yield: 81%

IR: 2960, 2880, 1740, 1460, 1370, 1225, 1030, 990, 780 cm^{-1}.

Ms: m/e (^{35}Cl) 350, (^{37}Cl) 358.

Analysis: Calculated for $C_{13}H_{22}O_2Cl_4$

C, 44.31; H, 6.25; C, 40.34

Found: C, 44.40; H, 6.40; C, 40.60%.

Trichloroester (14)

Yield: 68%.

IR: 2970, 2880, 1730, 1460, 1375, 1175, 1030, 765, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 314 (^{37}Cl) 320.

Analysis: Calculated for $C_{13}H_{21}O_2Cl_3$

C, 49.44; H, 6.65; Cl, 33.75

Found: C, 49.70; H, 6.80; Cl, 33.60%.

Dichloroester (15)

Yield: 66%.

IR: 2960, 2880, 1740, 1630, 1470, 1380, 1360, 1265, 1185, 1045, 920, 860 cm^{-1}.

Ms: m/e (^{35}Cl) 278 (^{37}Cl) 282.

Analysis: Calculated for $C_{13}H_{20}O_2Cl_2$

C, 55.91; H, 7.16; Cl, 25.44

Found: C, 56.10; H, 7.40; Cl, 25.70%.

3-Phenoxybenzyl ester (16)

Yield: 63%.

IR: 3060, 3040, 2960, 2865, 1735, 1640, 1590, 1490, 1450, 1380, 11350, 1260, 1215, 1160, 1070, 1020, 935, 870, 775, 750, 690 cm^{-1}.

Ms: m/e (^{35}Cl) 432 (^{37}Cl) 436.

Analysis: Calculated for $C_{24}H_{26}O_3Cl_2$

C, 66.51; H, 6.00; Cl, 16.40

Found: C, 66.43; H, 6.20; Cl, 16.55%.

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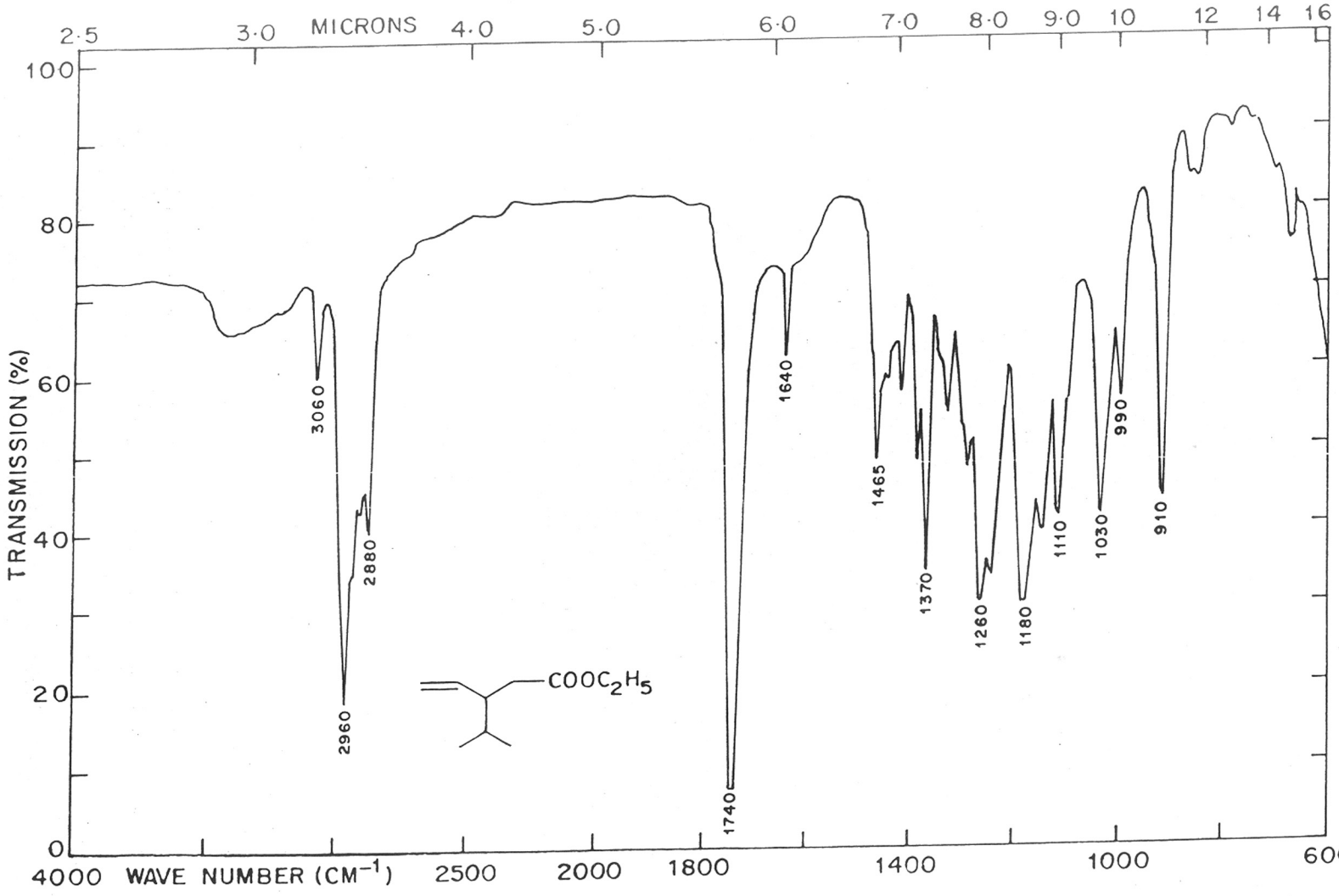

FIG. 1. IR SPECTRUM OF ETHYL 3-ISOPROPYL-4-PENTENOATE (4)

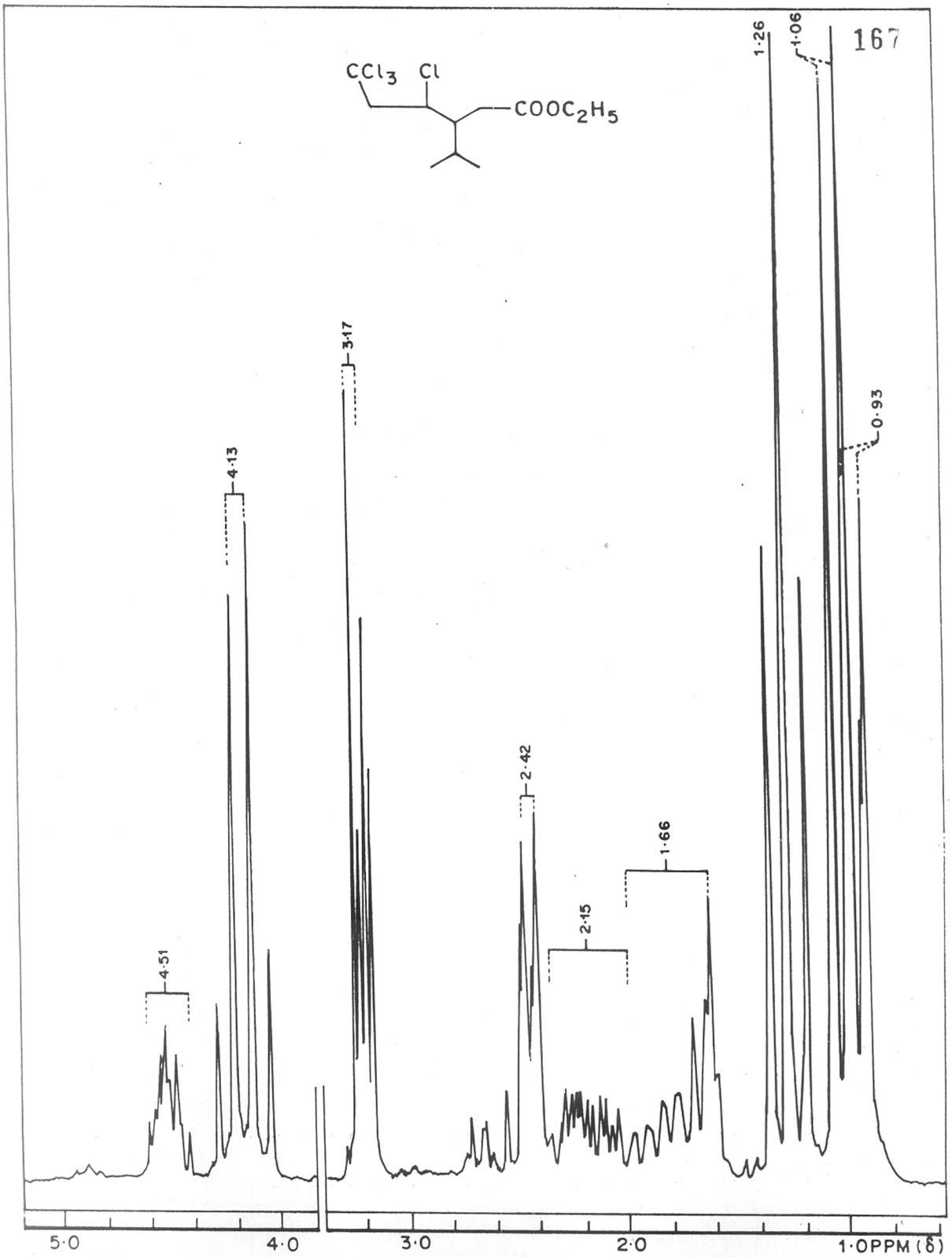

FIG. 2. PMR SPECTRUM OF ETHYL 4,6,6,6-TETRACHLORO 3-ISOPROPYL HEXENOATE (5)

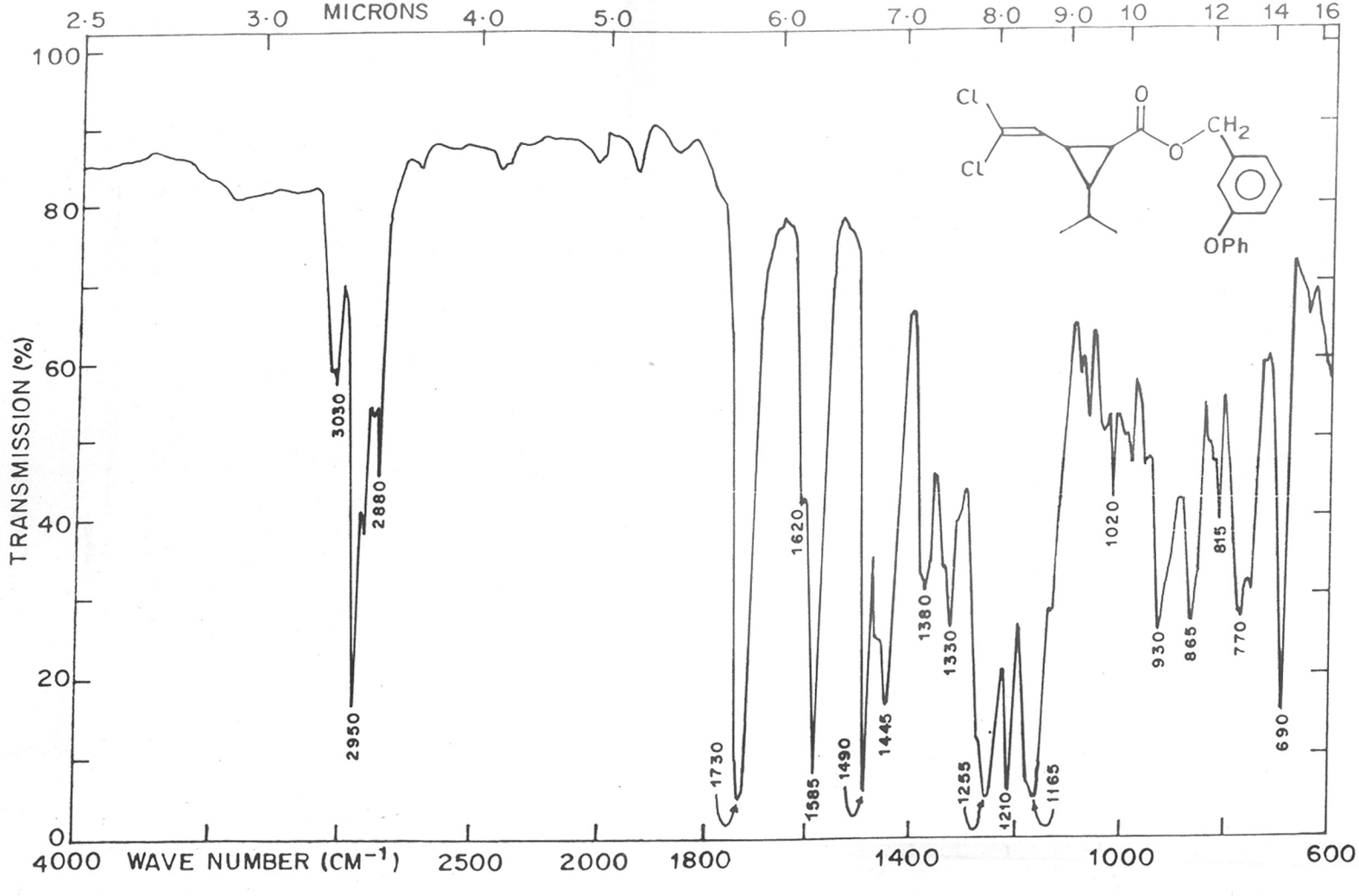

FIG. 3. IR SPECTRUM OF 3-PHENOXYBENZYL (±) CIS AND (±) TRANS 2-ISOPROPYL 3-(2,2-DICHLOROVINYL) CYCLOPROPANE CARBOXYLATE (8)

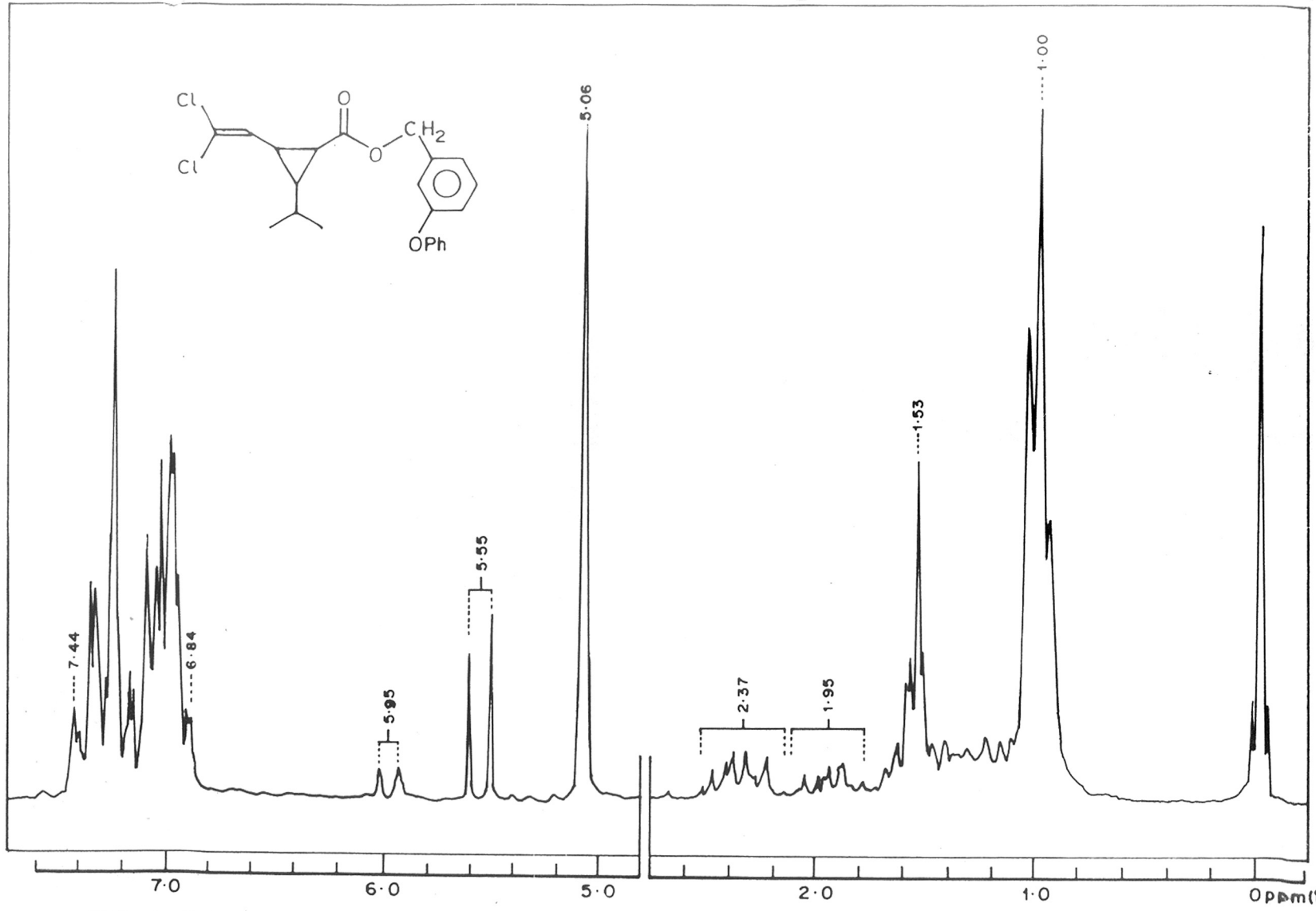

FIG. 4. PMR SPECTRUM OF 3-PHENOXYBENZYL (±) CIS AND (±) TRANS 2-ISOPROPYL 3-(2,2-DICHLOROVINYL) CHLOROPROPANE CARBOXYLATE (8)