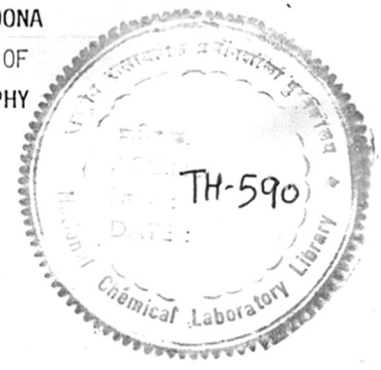
SYNTHETIC STUDIES IN PYRETHROIDS AND RELATED COMPOUNDS

A
THESIS
SUBMITTED TO
UNIVERSITY OF POONA
FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)



DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE - (INDIA)

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JAN. 1989

CERTIFICATE

Certified that the work incorporated in the thesis "Synthetic Studies in pyrethroids and related Compounds" submitted by Shri A.A. Arbale was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(Dr. G.H. Kulkarni)
Supervisor

dedicated to
hard work ...

ACKNOWLEDGEMENT

I owe a deep debt of gratitude to Dr.G.H.Kulkarni, Scientist, National Chemical Laboratory, Poona, under whose inspiring and encouraging guidance, this work was successfully carried out.

I have been very fortunate with the highly experienced and expert organic chemists, Dr. D.G. Panse and Dr. R.H. Naik who, took keen interest in the progress of the work. I wish to express my gratitude to my friends for their cheerful and ungrudging co-operation.

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Services of co-workers from microanalysis, spectroscopy, entomology are gratefully acknowledged.

Finally I am thankful to the Director, National Chemical Laboratory, Poona for permitting me to submit this work in the form of a thesis.

(A.A. ARBALE)

National Chemical Laboratory,
Poona-411008

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GENERAL REMARK

1. All melting points and boiling points are uncorrected.
2. All temperatures are recorded on the Centigrade scale.
3. Unless otherwise stated, all rotations were taken in chloroform solutions. Concentrations are expressed in g/100 ml of the solution.
4. The infrared spectra of liquids were recorded as liquid films and that of solids as nujol mulls on a Perkin-Elmer infracord spectrophotometer model 137-B, and Perkin-Elmer infracord spectrophotometer model 599-B using sodium chloride optics.
5. Unless otherwise stated, all NMR spectra were taken in carbontetrachloride solution, using tetramethylsilane as the internal reference on a T-60 MHz Varian instrument, and in $CDCl_3$ solution on FT-80A (Varian 80 MHz FT NMR spectrometer), WH-90 (Bruker 90 MHz FT NMR spectrometer) and the chemical shifts are measured in δ units.
6. The mass spectra were recorded on a Funnigan Mat 1020 automated GC/MS.
7. Acid washed activated alumina standardised as per Brockmann's procedure and silicic acid for chromatographic purposes, after activation, were employed for column chromatography
8. TLC analyses were carried out on glass plates coated with a mixture of silicic acid and plaster of Paris (85:15; 200 mesh), and activated at 120° for 3 hr.

Solvent systems used were pet.ether, benzene, ethyl-acetate and acetone or a suitable mixture of two or more of these solvents, depending upon the nature of the compounds. The plates were developed by keeping in an iodine chamber or by spraying with H_2SO_4.

9. Numbers given to charts, figures and structures in each chapter of the thesis refer to that particular chapter only.
10. References pertaining to each chapter are given at the end of that particular chapter.
11. Unless otherwise stated, all solutions were dried over anhydrous sodium sulphate.
12. Unless otherwise stated, all b.ps. refer to the bath temperature.
13. In the list of IR bands given in the experimental section, the significant bands described in the theory are underlined.
14. A brief summary of each chapter is given at the beginning of that chapter.
15. In the description of NMR signals, the abbreviations brs, br.d and br.m means broad singlet, broad doublet and broad multiplet respectively.
16. Infrared bands are expressed in frequency ν cm^{-1}.
17. The thick liquid compounds which were found to be unstable above 200°C(bath)/1 mm were not purified by distillation.

CHAPTER I

SYNTHESIS OF INSECTICIDALLY ACTIVE 3-PHENOXY BENZYL/∝ (RS) CYANO-3-PHENOXY BENZYL (±) TRANS 2-(2,2-DICHLOROVINYL) SPIRO(2,5)-OCTANE-1-CARBOXYLATES

SUMMARY

Wittig reaction of triphenyl carbethoxy methylene phosphorane on cyclohexanone gave in good yield cyclohexylidene acetate (1). Selective reduction of acetate group using AlH_3 afforded cyclohexylidene ethanol (2). Claisen ortho ester rearrangement on 2 using triethyl ortho acetate gave in 77% yield the pentenoate (4). Free radical initiated carbon tetrachloride addition to 4 afforded the tetrachlorohexanoate (5). The latter has been cyclized using base by two different methods to afford a mixture of (±) cis and (±) trans cyclopropane esters, from which the predominent (±) trans isomer was separated by column chromatography and ultimately converted into insecticidally active ∝-cyano 3-henoxybenzyl ester (12).

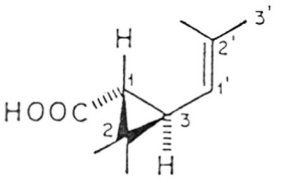
INTRODUCTION

Since the ancient times the dried flowers of the plant Chrysanthemum cinerarieaefolium (pyrethrum cinerariaefolium, Trev) known as pyrethrum was useful for controlling various types of insects[1].

Insecticidal principls in pyrethrum are called "Pyrethrins" and for long time have been considered harmless to mammals and plants, while very toxic to insects. Today the they are becoming increasingly important as insect control agents because they possess a unique combination of desirable properties including exceptionally good insecticidal activity, low mammalian toxicity and rapid biodegradation.

The valuable properties of pyrethrum stimulated detailed examination of the chemical constitution of active principles in the first quarter of 20th century. Staudinger[2] and Ruzicka for the first time isolated two active compounds from the pyrethrum extract and identified them as esters of (+) trans chrysanthemic acid and (+) trans pyrethric acid with the ketol pyrethrolone and named them as pyrethrin I and pyrethrin II respectively. Later, four more closely related active esters viz. cinerin I, cinerin II[3], jasmolin I and jasmolin II[4-6] were also isolated from pyrethrum extract (Chart 1 and 2). Thus, insecticidal activity of pyrethrum is attributed to the presence of these six constituents. Out of these six esters, pyrethrin I, cinerin I, and jasmolin I

CHART – 1



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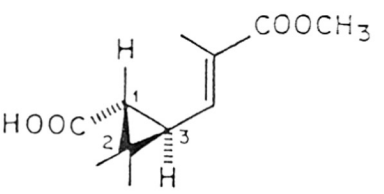

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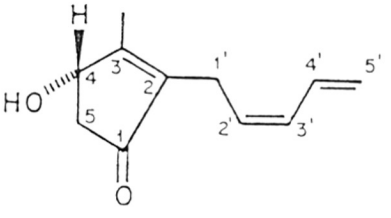
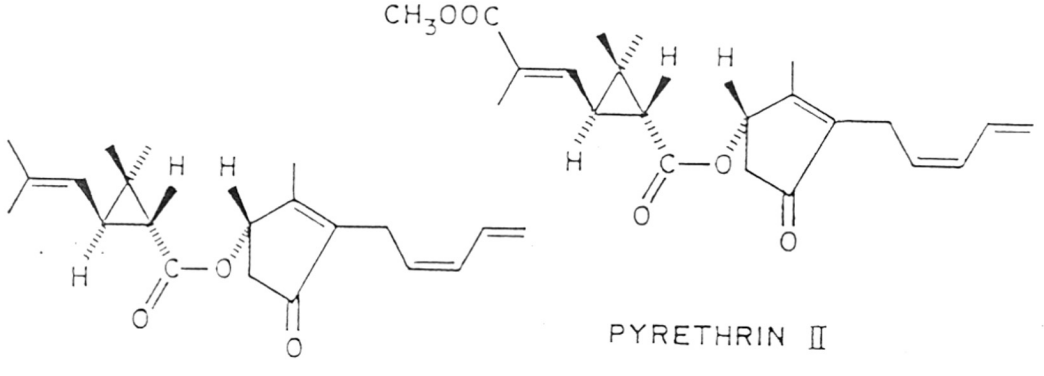
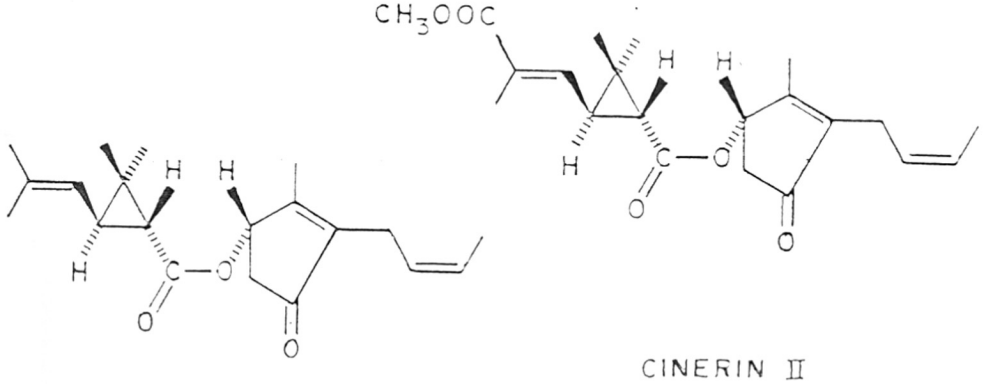


(+) PYRETHROLONE



PYRETHRIN I

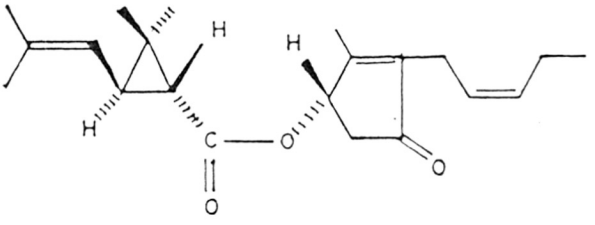
PYRETHRIN II



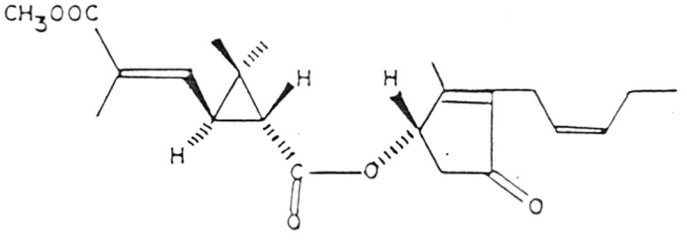
CINERIN I

CINERIN II

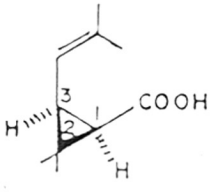
CHART 2



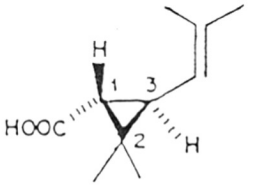
JASMOLIN I



JASMOLIN II



IR (+) CIS CHRYSANTHEMIC ACID



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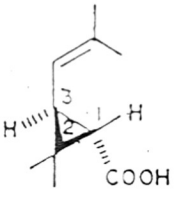
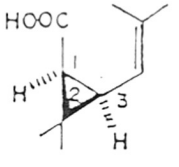


IS(−) TRANS CHRYSANTHEMIC ACID



IS(−) CIS CHRYSANTHEMIC ACID

contain (+) trans chrysanthemic acid as the common acid moiety while pyrethrin II, cinerin II and jasmolin II contain (+) trans pyrethric acid as the common acid moiety. The alcohol moieties of these naturally occurring esters are all hydroxy cyclopentenone derivatives viz. pyrethrolone, cinerolone and jasmolone. This class of active insecticidal esters, occurring in pyrethrum was named as "pyrethroids". Now the word "pyrethroid" is not limited to natural pyrethrins alone, but is applied also to biologically active chrysanthemates and modified cyclopropane carboxylic acid esters of various alcohols.

Although the natural pyrethrins and cinerins possessed many of the desirable properties of a good insecticide, they suffer from some drawbacks viz. their photo-instability and high cost of their production. For these reasons they are not suitable for use for controlling agricultural pests. Extensive research work on the structure-activity relationship led ultimately to the syntheses of more photostable analogues with enhanced insecticidal activity by eliminating the photolabile centres in both acid and alcohol moieties.

In the first phase of research work towards this goal, esters of (+) trans chrysanthemic acid with different photo-stable alcohols were prepared, which exhibited not only increased insecticidal activity, but also low mammalian toxicity and higher photo-stability. 3-Phenoxy-benzyl

alcohol, ∝-cyano-3-phenoxy-benzyl alcohol and 5-benzyl-3-furyl methyl alcohol are some of the important alcohol moieties, which give rise to esters more potent in insecticidal activity than the natural pyrethrins. Prominent examples of synthetic chrysanthemates are bioallethrin , biophenothrin and bioresmethrin.

Subsequently photolabile centers in acid moiety (allylic methyls) were also replaced by the more stable dihalo vinyl side chain to give more potent insecticides and tested for their insecticidal activity. In addition to conferring higher photostability, as compared to natural pyrethrins, increase in insecticidal activity was also observed with such esters.

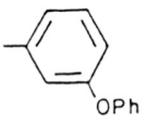
Potent synthetic pyrethrdids

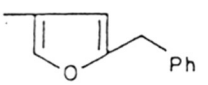
Chemically, potent synthetic pyrethroids are esters of 2,2-dimethyl-3-(2,2-dihalovinyl)cyclopropanecarboxylic acids with photostable alcohols like 3-phenoxybenzyl alcohol. ∝-cyano-3-phenoxybenzyl alcohol. Important members of synthetic[7,8] pyrethroid group, which were prepared and used with success during the last two decades in UK, USA, Japan and other advanced countries are (1) permethrin[9] (NRDC-143), (2) cypermethrin[10] (NRDC-149), (3) deltamethrin[11](NRDC-161). The acid moieties of above pyrethroids viz. DV acid or chloroxanthemic acid, is usually commercially prepared by synthesis from acyclic precursors and is invariably obtained as dl mixtires of both cis and trans cyclopropanecarboxylates

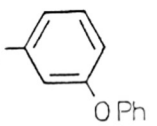
CHART - 3

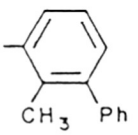
HIGHLY - POTENT PYRETHROIDS

ACTIVE - ALCOHOLES

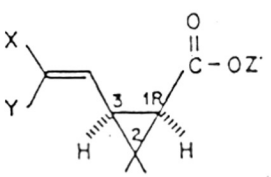
R_1 = 

R_3 = 

R_2 = 

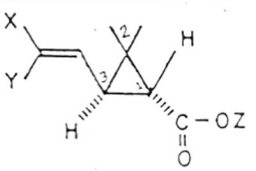
R_4 = 

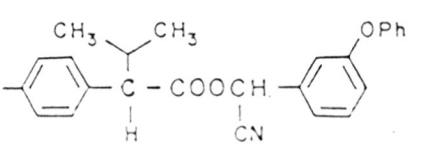
1R - CIS - PYRETHROIDS



1) PERMETHRIN (NRDC-143) : X = Y = Cl, Z = R_1
2) CYPERMETHRIN (NRDC-149) : X = Y = Cl, Z = R_2
3) DELTAMETHRIN (NRDC-161) : X = Y = Br, Z = R_2
4) CYHALOTHRIN : X = Cl, Y = CF_3, Z = R_2
5) FMC-54800 : X = Cl, Y = CF_3, Z = R_4

1R - TRANS PYRETHROIDS



1) BIOPERMETHRIN : X = Y = Cl , Z = R_1
2) BIORESMETHRIN : X = Y = CH_3 , Z = R_3
3) BIOPHENOTHRIN : X = Y = CH_3 , Z = R_1
4) NRDC - 173 : X = Y = F , Z = R_3
5) BIODELTAMETHRIN : X = Y = Br , Z = R_2
6) BIOCYPERMETHRIN : X = Y = Cl , Z = R_2
7) FENVALERATE : 

(chart 3). This mixture is as such, used for preparing the commercial permethrin, cypermethrin. However, the individual optically active pyrethroids viz. 1R-cis-permethrin[12] (NRDC-167), 1R-trans-permethrin[9] (biopermethrin), trans-deltamethrin (biodecamethrin), NRDC-134[13], NRDC-173[8] have been independently prepared and found to be much more active than the commercial samples (chart 3). Thus, in the highly potent pyrethroids 2,2-dihalovinyl side chain not only increases significantly insecticidal activity, but also confers higher photostability when compared to the natural pyrethrins and other chrysanthemates.

A second generation of more potent pyrethroids has come up during the last few years, some of which are mentioned in chart 3. These are (1) cyhalothrin[14] (2) Baythroid and (3) FMC-54800. In some of these esters, the acid moiety is 1R-cis-2,2-dimethyl-3-(2-chloro-2-trifluoromethyl-vinyl) cyclopropanecarboxylic acid, while the alcohol moieties are different like 2-methyl-3-phenylbenzyl alcohol and ∝-cyano-3-phenoxy-4-fluorobenzyl alcohol. In addition to good insecticidal activity some of these show good miticidal activity.

In addition to the cyclopropane containing pyrethroids mentioned above Ohno et.al.[15] have prepared an ester of ∝-(4-chloro-phenyl) isovaleric acid with ∝-cyano-3-phenoxy-benzyl alcohol viz. fenvalerate (chart 3); lacking a cyclopropane ring, but comparable to the commercial pyrethroids in

its insecticidal activity.

Synthesis of acid moieties of pyrethroids

A number of ingenious syntheses of racemic chrysanthemic acids[16-22] and also of (+) cis and (+) trans chrysanthemic acids[30-35] are on record, so also their optical resolution forms the subject matter of several patents[23-26] and papers[27]. Most of the methods for the synthesis of acid moiety of pyrethroids are well documented in literature[28,29]. In all the methods reported for the acid moiety, a substituted cyclopropane ring is built up, starting with a suitable acyclic substrate. As a result, the resulting acids are usually mixtures of both (±) cis and (±) trans cyclopropane carboxylic acids in varying proportions. However, recently some methods have been developed which give rise preferentially to either (±) cis or (±) trans isomers in higher proportion. Some of the methods are described briefly below.

From acyclic substrates

Diazoacetate addition Method

The building up of cyclopropanecarboxylic acid by addition of diazoacetic acid ester to 2,5-dimethyl-2,4-hexadiene system was initially investigated by Farakas. Many modifications of this method have been carried out for getting substituted chrysanthemic acids, including DV acid[30]

of commercially important (chart 4, scheme E). In a recent method reported by Aratani et al.[31], 2,5-dimethyl 2,4-hexadiene is condensed with (-) menthyl diazoacetate ($N_2CHCOOR$) in the presence of chiral catalyst (Cu-Ligand) to get a mixture of trans and cis chrysanthemates in 9:1 proportion (chart 4, scheme A).

Julia's method

Julia et al.[32a,b] synthesized trans chrysanthemic acid by a novel sequence of reactions, starting from 2-methyl-2-hydroxy butyne as depicted in chart 4, scheme B.

NRDC method

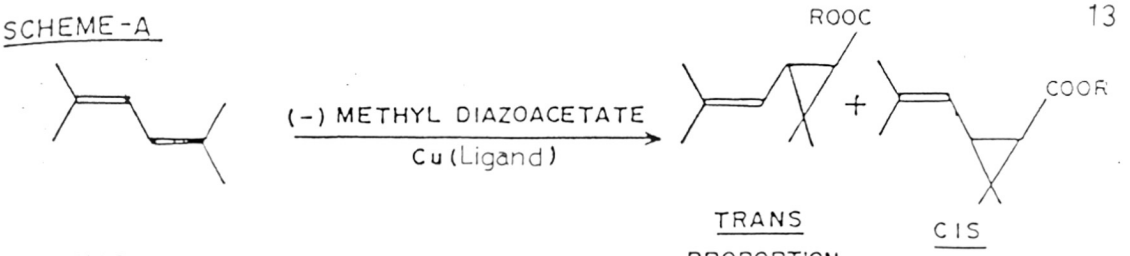
In NRDC method developed by M. Elliott et al.[13,33] the key intermediate viz. caronaldehyde esters were obtained by ozonolysis of the corresponding chrysanthemic acid. Wittig reaction on caronaldehyde esters using appropriate 1,1-dihalo methylene triphenyl phosphorane afforded the acid moieties of highly potent pyrethroids. The method is of special importance for the preparation of acid moieties of highly potent pyrethroids like deltamethrin, cyahlothrin etc. (chart 4, scheme C).

From isomerically pure precursors

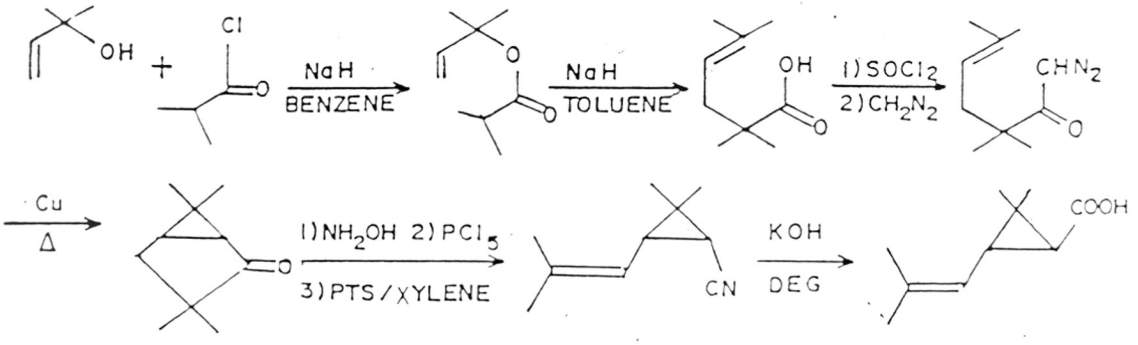
Krief et al.[34] have devised several synthetic methods for both trans and cis-3-formyl-2,2-dimethyl-1-cyclopropane-carboxylates. Reaction of 4,4-dimethoxy-trans-2-butenoate

CHART-4

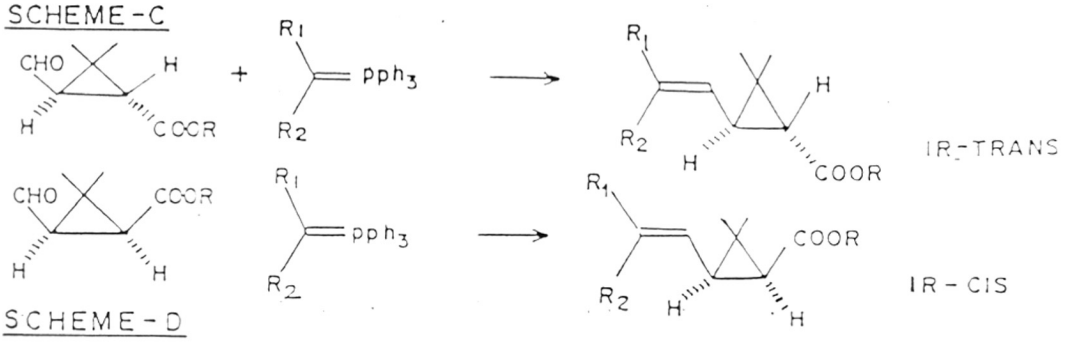
SCHEME-A



SCHEME-B



SCHEME-C



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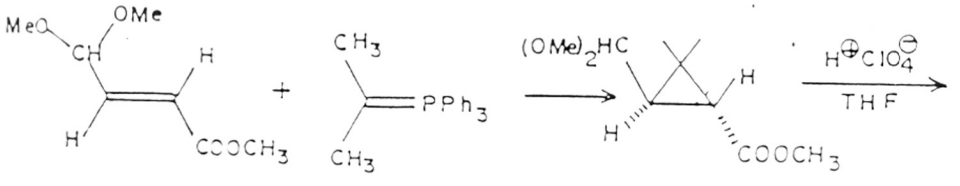
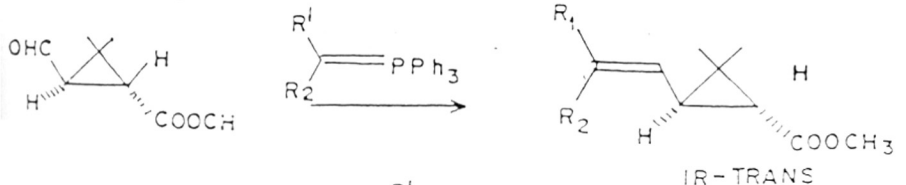
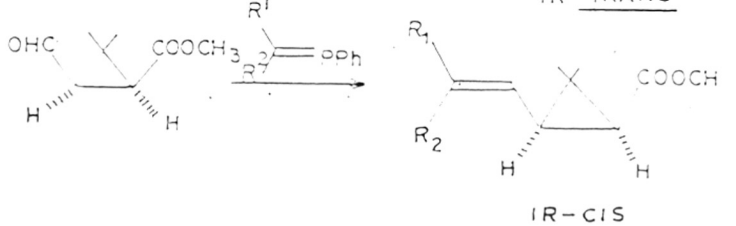




SIMILARLY



with 1,1-dimethylmethylene triphenylphosphorane leads stereo-selectively to the trans-caronaldehyde dimethyl acetal ester. The aldehyde can be regenerated and converted to trans-chrysanthemic acid by choosing proper Wittig reagent (chart 4, scheme D). In another approach[34] they synthesised cis-caronaldehydic ester by stereospecific conversion of butanolide and converted it into substituted cyclopropane acid derivatives by using the method mentioned above.

Two more commercially important processes for DV acid are as follows:

Ciba-Geigy method[35]

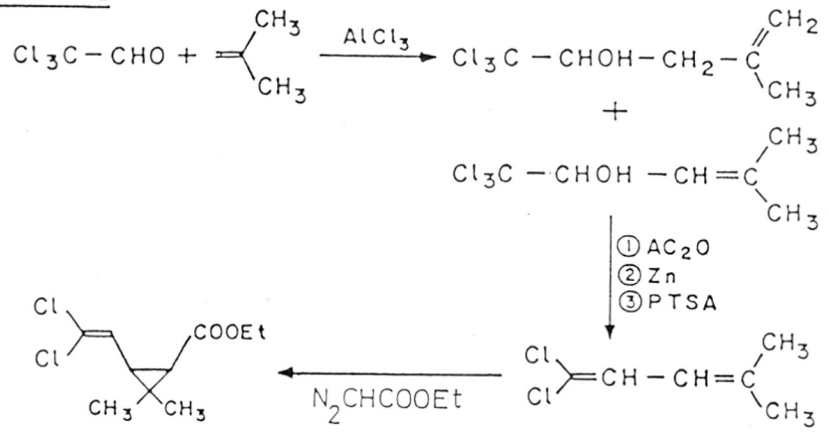
The key step in this method is the quasi Favorskii (semi benzylic acid) rearrangement of the α-halo cyclobutanone derivative prepared in high yields from acrylic acid or acrylonitrile. This method gives 80% (±) cis isomer (chart 4, scheme F).

Sagamis's method[36]

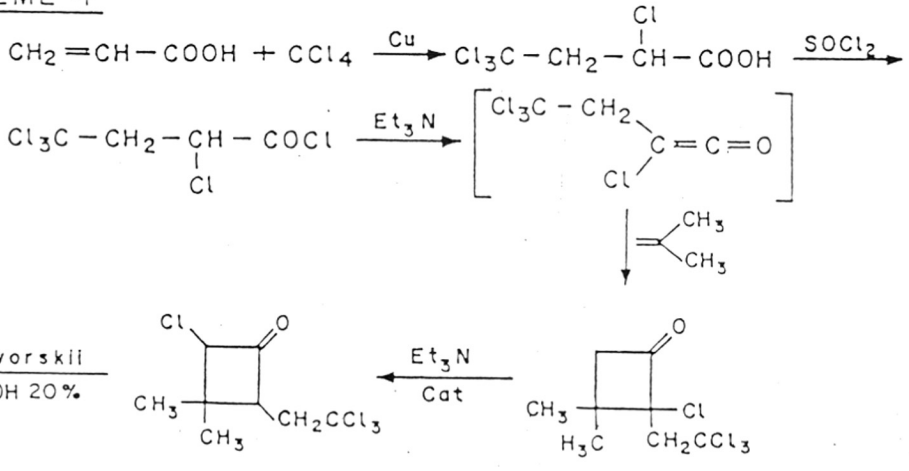
In the three step Sagamis's method the important intermediate viz. 3,3-dimethyl-4-pentenoate is obtained by a Claisen ortho ester condensation of prenol. The latter on free radical initiated CCl_4 addition afforded ethyl tetra chloro hexanoate. The base induced cyclization of latter can be modified by a suitable choice of base so as to get either the (±) cis or (±) trans isomer in higher proportion (chart 4, scheme G).

CHART – 4 (continued)

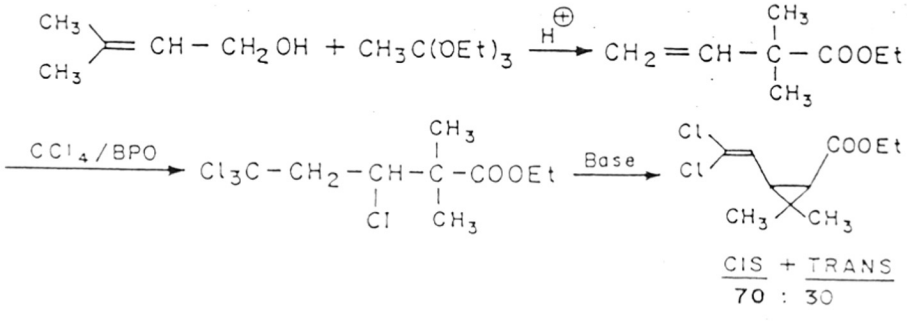
SCHEME – E



SCHEME – F



SCHEME – G



Structure activity relationship

The natural pyrethrins and synthetic pyrethroids are flexible molecules and their insecticidal action depends on their ability to adopt a conformation in which all the structural features, essential for potency are appropriately oriented with respect to each other and to a complementary receptor. A characteristic feature of the pyrethroids is the sensitivity of their insecticidal action to changes in the substituents at certain important centres, by which either the balance of conformers present, is disturbed or contact of molecule with a receptor is obstructed.

To possess high insecticidal activity, pyrethroids must have a precise steric relationship between an unsaturated centre in the alcohol moiety and gem-dimethyl group or an equivalent subtituent in the acid moiety. This generally requires a 1R-configuration in the cyclopropanecarboxylic acids[38,48]. It has been observed that for pyrethroids the absolute configuration R at the site bearing the ester function is responsible for higher insecticidal activity, irrespective of whether the cyclopropane ring is having a cis or trans geometry[8]. Inversion at this optical center drastically alters the potency without greatly changing the physical properties. Thus (+) 1R-trans and (+) 1R-cis chrysanthemic acid esters with suitable alcohols, possessing

1R-configuration, are found to be quite active insecticides, whereas esters of (-) trans and (-) cis-chrysanthemic acid which possess the 1S-configuration are found to be inactive or much less active (chart 2). However, in the case of pyrethroids possessing a dihalovinyl side chain at C-3 in the acid moiety viz. permethrin and deltamethrin, it has been found that the 1R-cis-esters are found to be about twice as active as the corresponding 1R-trans isomers[37].

The potency of 3-(2,2-dihalovinyl) substituted cyclopropanecarboxylic acid ester is also sensitive to the substitution at or on the side chain at C-3[38]. For example esters derived from 3-(2,2-dichlorovinyl) 2,2-dimethyl cyclopropane-1-carboxylic acid are more active than those derived from the corresponding 3-methyl analogue.

Thus in the acid moiety of pyrethroids, the side chain attached at C-3 position of cyclopropane ring system is a position where structural changes greatly influence insecticidal activity, which again depends on the nature of substituents. For example modification in the structure of side chain at C-3 in bioresmethrin[13] where isobutenyl group is replaced by but-1-enyl group produces still greater activity, but retains low mammalian toxicity. Similarly esters with simple vinyl substituents were found to be less active than the chrysanthemates but the monomethyl vinyl ester was more active. Maximum activity[13] was observed in case of the esters with but-1-enyl side-chain at C-3.

The high activity is attained in esters with E- and Z-butadienyl and pentadienyl substituents[38] at C-3, trans and cis to the 1R-carboxylic centre, provided no methyl groups are present at C-3 or C-1 at cyclopropane ring system. Subsequently M. Matsui et al.[39] prepared a number of 3-alkylsubstituted 2,2-dimethyl cyclopropanecarboxylic acids from acyclic substrates and compared their insecticidal activities with chrysanthemates. He observed that increase of methyl substitution at C-3 contributes to the maximum activity as observed in 2,2,3,3-tetramethyl cyclopropane-carboxylic acid ester (NRDC-108) which is found to be more active than the corresponding 3-monomethyl derivatives. This observation leads to the conclusion that presence of unsaturated side-chain at C-3 (as in chrysanthemic acid) is not essential structural feature for insecticidal activity as believed earlier.

Another important structural feature for insecticidal activity is the presence of a gem-dimethyl group[37,40] or its steric equivalent to carboxylate function. This is evident from the fact that the natural pyrethrins and potent pyrethroids[41,42] all possess in their structure the gem-dimethyl grouping at cyclopropane ring. However, substitution of one of the methyl groups by an ethyl group in C-2 position of cyclopropane is enough to cause a sharp reduction in the

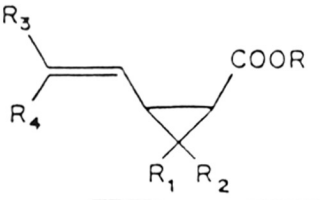
insecticidal activity. The all known[42] cyclopropyl esters lacking gemdimethyl group are inactive. From this it appears that the function of gem-dimethyl group in the pyrethroid esters is probably related more to their steric rather than chemical characteristics. The structural variations at different carbon atoms in cyclopropanecarboxylic acids are shown in chart 5. Cyclopropanecarboxylic esters in which the gem-dimethyl group at C-2 is replaced by a gem-dichloro[42,43] group (chart 5, structure II) are also found to be active insecticides. A number of interesting spiro compounds[44] were prepared (chart 5), bearing close structural resemblence to 2,2,3,3-tetramethyl cyclopropane in which one of the gem-dimethyls is replaced by a spiro cycloalkane ring. Also DV acid analogues in which the gem-dimethyl group at C-2 is replaced by a spiro fused cycloalkyl ring have been synthesized which showed moderately good insecticidal activity against caterpillars and rapid knockdown effect on houseflies[45].

Syntheses of the spiro fused cycloalkyl cyclopropanecarboxylic acids were achieved by following methods.

In the first method the cyclopropane ring was built-up by reaction with ethyl diazoacetate on suitably substituted olefin (chart 6, scheme A)[45]. In the second method the key step is the quasi Favorskii rearrangement of an ∝-chlorocyclobutanone obtained as one of the products during the (2 + 2) cycloaddition reaction of an olefin with chloro-

CHART – 5

Modfied cyclopropane carboxylic acid esters

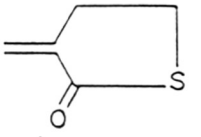


R = CH_3, C_2H_5 or pyrethroid alcohols

I $R_1 = R_2 = R_3 = R_4 = CH_3$

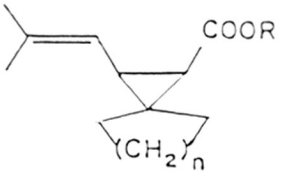
II $R_1 = R_2 = Cl$; $R_3 = R_4 = CH_3$

IV $R_1 = R_2 = CH_3$; R_3, R_4 = Cycloalkyl

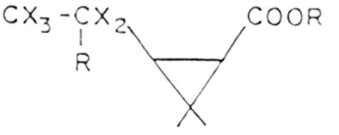
V $R_1 = R_2 = CH_3$; R_3, R_4 = 

VII $R_1 = R_2 = CH_3$; R_3, R_4 = =N–O Alkyl

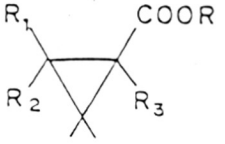
IX $R_1 = R_2 = CH_3$; $R_3 = R_4 = Cl$

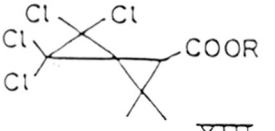


III



VI X = Cl, Br, R = H or Cl



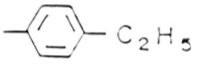


XIII

VIII $R_1 = CH_3$, $R_2 = CH = CCl_2$, $R_3 = H$

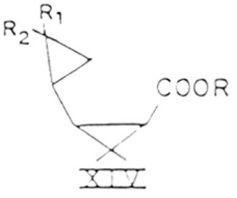
X $R_1 = R_2 = CH_3$, $R_3 = H$

XI $R_1 = R_2 = Cl$, $R_3 = H$

XII $R_1 = R_2 = Cl$, $R_3 =$ 

XV $R_1 = CH_3$, $R_2 = CH_2OR$, $R_3 = H$

XVI $R_1 = H$, $R_2 = CH_2OR$, $R_3 = H$



XIV

R_1, R_2 = H or Halogen

ketene (chart 6, scheme B)[46]. In addition to chloroketene, others like dimethyl ketnes were also employed for obtaining the cyclobutanone derivatives, which were subsequently converted to cyclopropanecarboxylic acids via the α-bromo derivatives by quasi Favorskii rearrangement (chart 6, scheme C)[45].

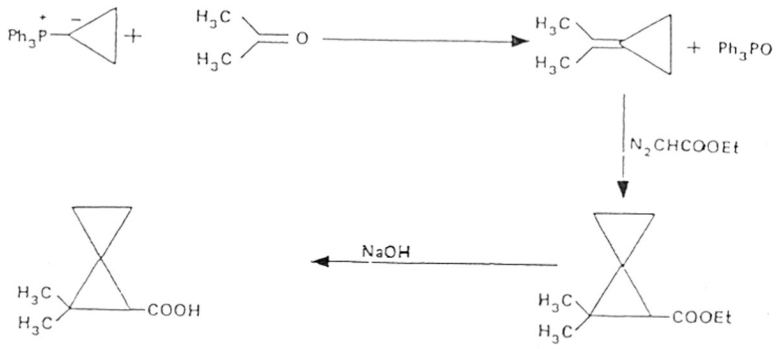
The DV acid analogues possessing the spiro cycloalkyl ring in place of gem-dimethyl group were synthesized by a different route as depicted in the chart 6, scheme D[37,47]. However, in the last-step of synthesis the reaction of ethyl diazoacetate on the more reactive double bond was employed.

In this chapter a simple, elegant alternate approach for the synthesis of (±) cis and (±) trans methyl/ethyl 2-(2,2-dichlorovinyl) spiro (2,5) octane-1-carboxylates in which the trans isomer predominated, has been described as a representative example.

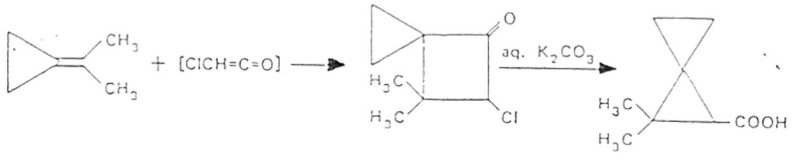
The strategy employed in this synthesis is the initial preparation of the ethyl 3,3-cyclohexyl 4-pentenoate which was subsequently converted to ethyl 4,6,6,6-tetra chloro hexanoate by free radical initiated CCl_4 addition and finally base induced cyclization to give the desired cyclopropane carboxylic acid. The later was ultimately converted into insecticidally active 3-phenoxy benzyl and α-cyano-3-phenoxy benzyl esters.

CHART 6

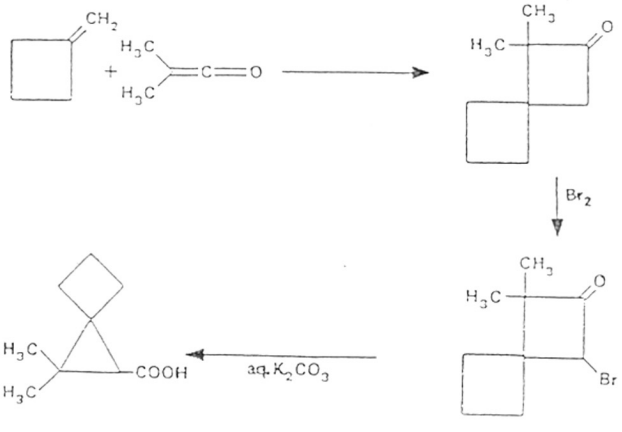
SCHEME A



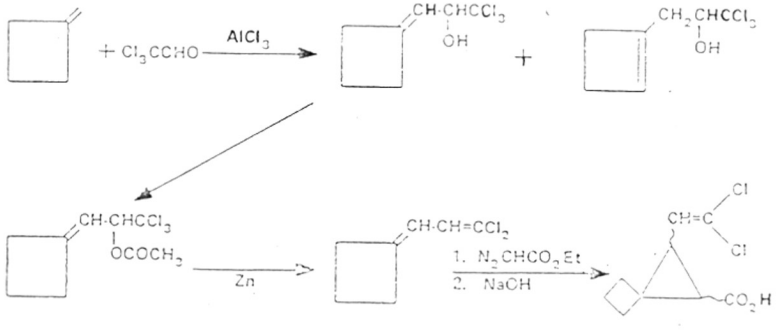
SCHEME B



SCHEME C



SCHEME D

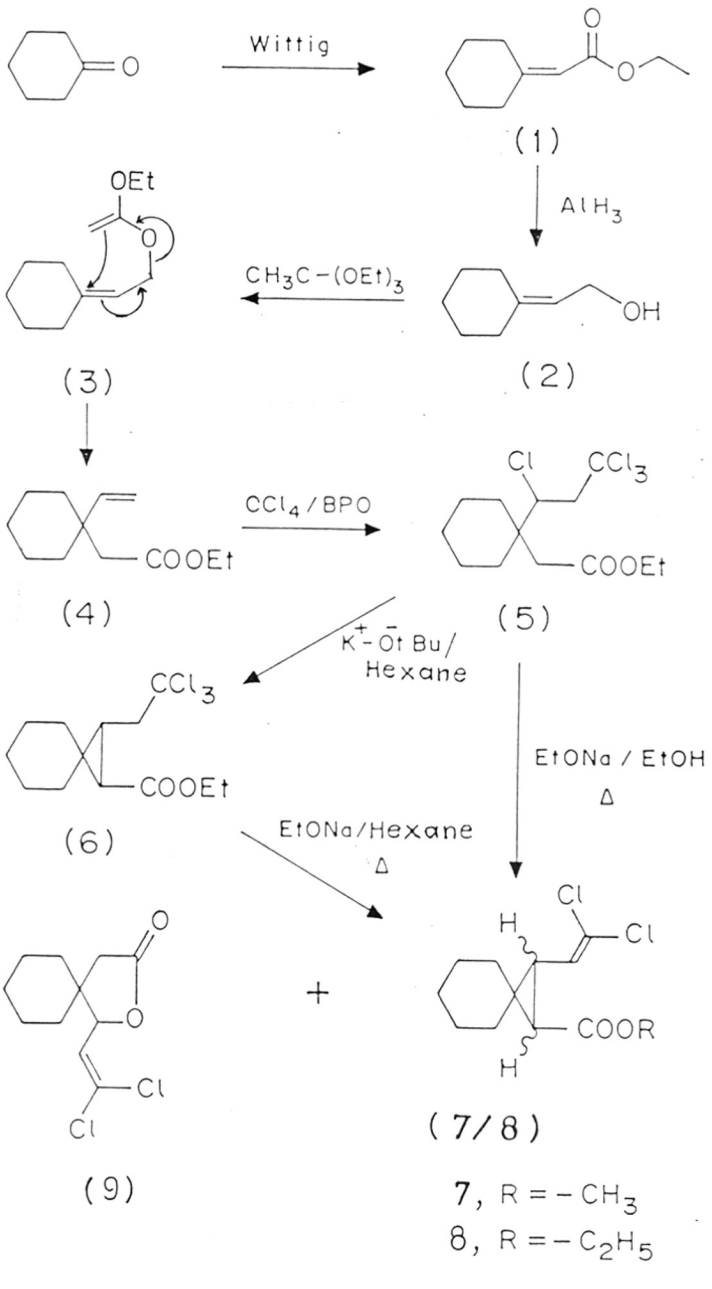


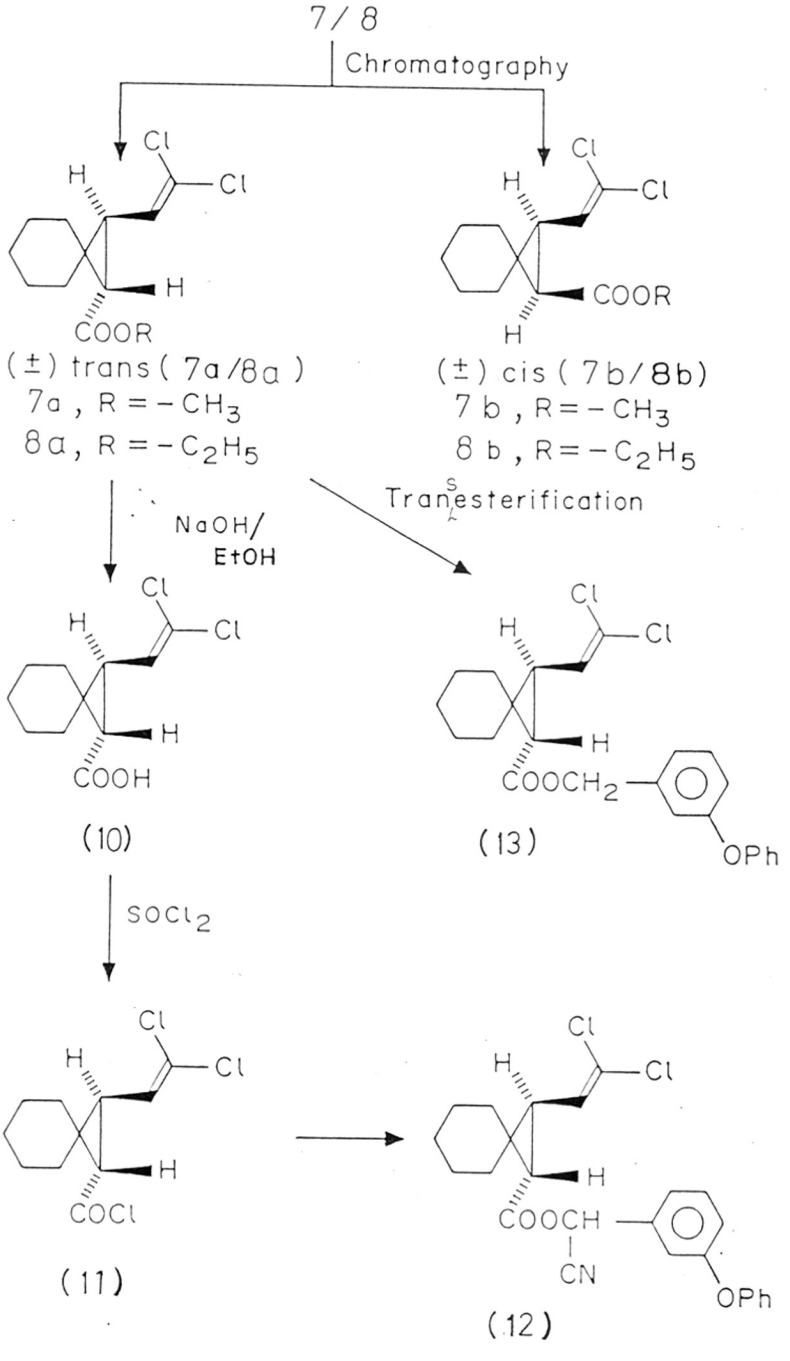
PRESENT WORK

Wittig reaction on cyclohexanone using triphenyl carbethoxy methylene phosphorane afforded cyclohexylidene acetate (1) in 87% yield (GLC: 96%); characterized by following spectral data as ethyl cyclohexylidene acetate (1); M.S.: m/e 168 (M^+); IR (liquid film) (Fig. 2): 1730 (ester>C=O), 1660 (-C=CH-) cm^{-1}; NMR ($CDCl_3$) (Fig. 1): 1.25 (3H, t, J=8 Hz, ester-CH_3), 1.54 (6H, br s, 3 x -CH_2- non-adjacent to double bond), 2.15, 2.78 (2H each, br s each, 2 x -CH_2- adjacent to double bond), 4.09 (2H, q, J=8 Hz, ester -CH_2-), 5.56 (1H, s, olefinic proton).

The conjugated ester (1) was then converted into the allylic alcohol (2) in 83% by preferential reduction of the ester functionality using AlH_3 (prepared in situ from LAH and $AlCl_3$ in 4:1 molar proportion in ether), under which conditions the conjugated double bond of 1 remains unaffected. The alcohol thus obtained was purified by distillation to obtain pure 2 (GLC: 99.8%); M.S.: m/e 126 (M^+); IR (liquid film) (Fig. 4): 3200 (-OH), 1670 (>C=CH-) cm^{-1}. NMR (CCl_4) (Fig. 3) 1.58 (6H, br s, 3 x -CH_2- nonadjacent to double bond), 2.17 (5H, br s, 2 x -CH_2- adjacent to double bond and -OH proton, partly exchangeable with D_2O), 4.05 (2H, d, J=7 Hz, -CH_2-OH), 5.32 (1H, t, J=7 Hz, olefinic proton).

Condensation of 2 with two equivalents of triethyl ortho acetate in presence of acidic catalysts like O-cresol and phosphoric acid according to the method developed by


Wittig
(1)
AlH3
OH
(2)
CH3C-(OEt)3
OEt
(3)
CCl4 / BPO
COOEt
(4)
Cl
CCl3
COOEt
(5)
K+ -Ot Bu/
Hexane
CCl3
COOEt
(6)
EtONa / EtOH
Δ
EtONa/Hexane
Δ
+
H
Cl
Cl
COOR
H
(7/8)
7, R = -CH3
8, R = -C2H5
O
O
Cl
Cl
(9)


7/8
Chromatography
(±) trans (7a/8a)
7a, R = -CH3
8a, R = -C2H5
(±) cis (7b/8b)
7b, R = -CH3
8b, R = -C2H5
NaOH/
EtOH
Transesterification
(10)
(13)
SOCl2
(11)
(12)

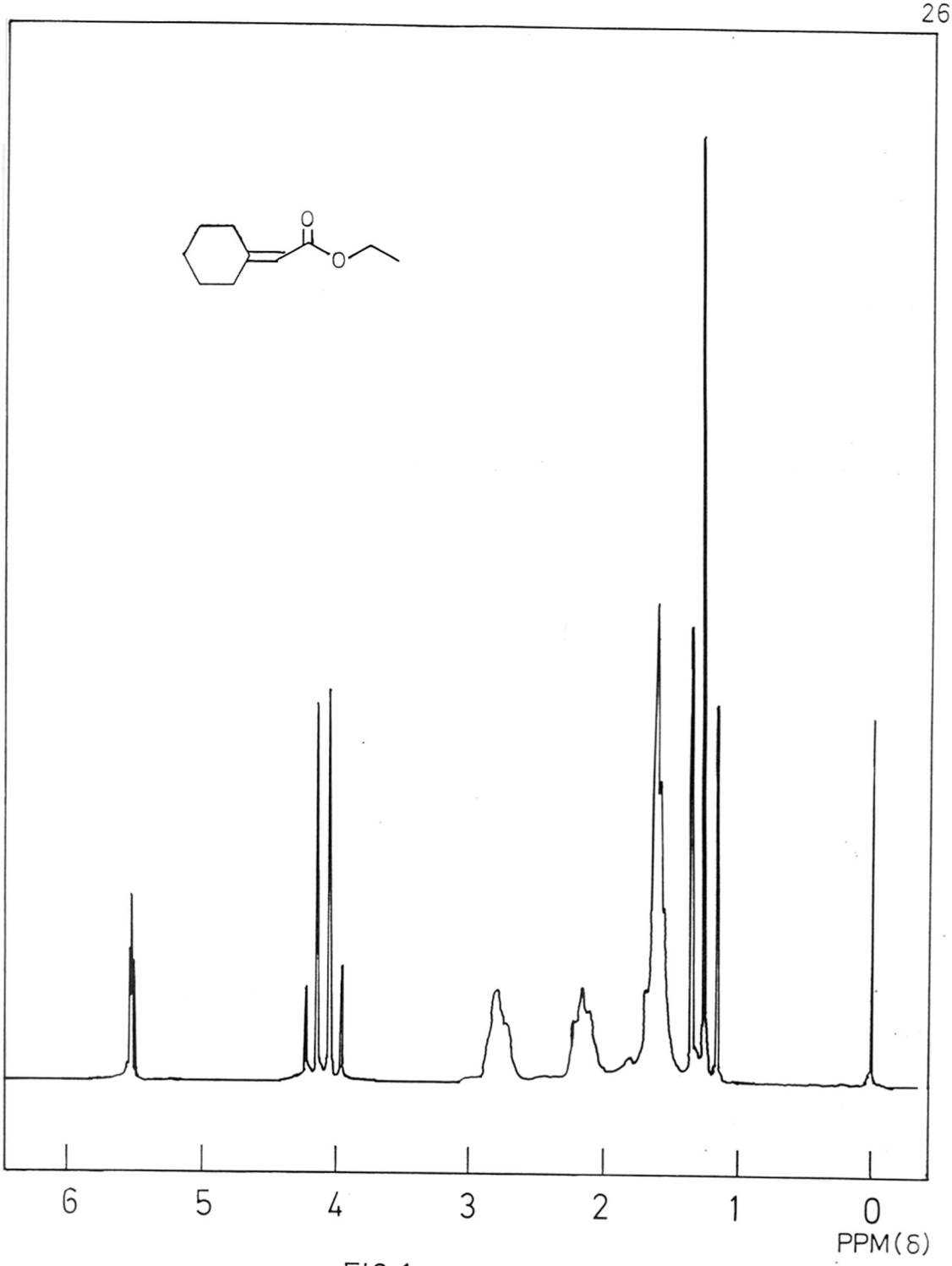


FIG 1

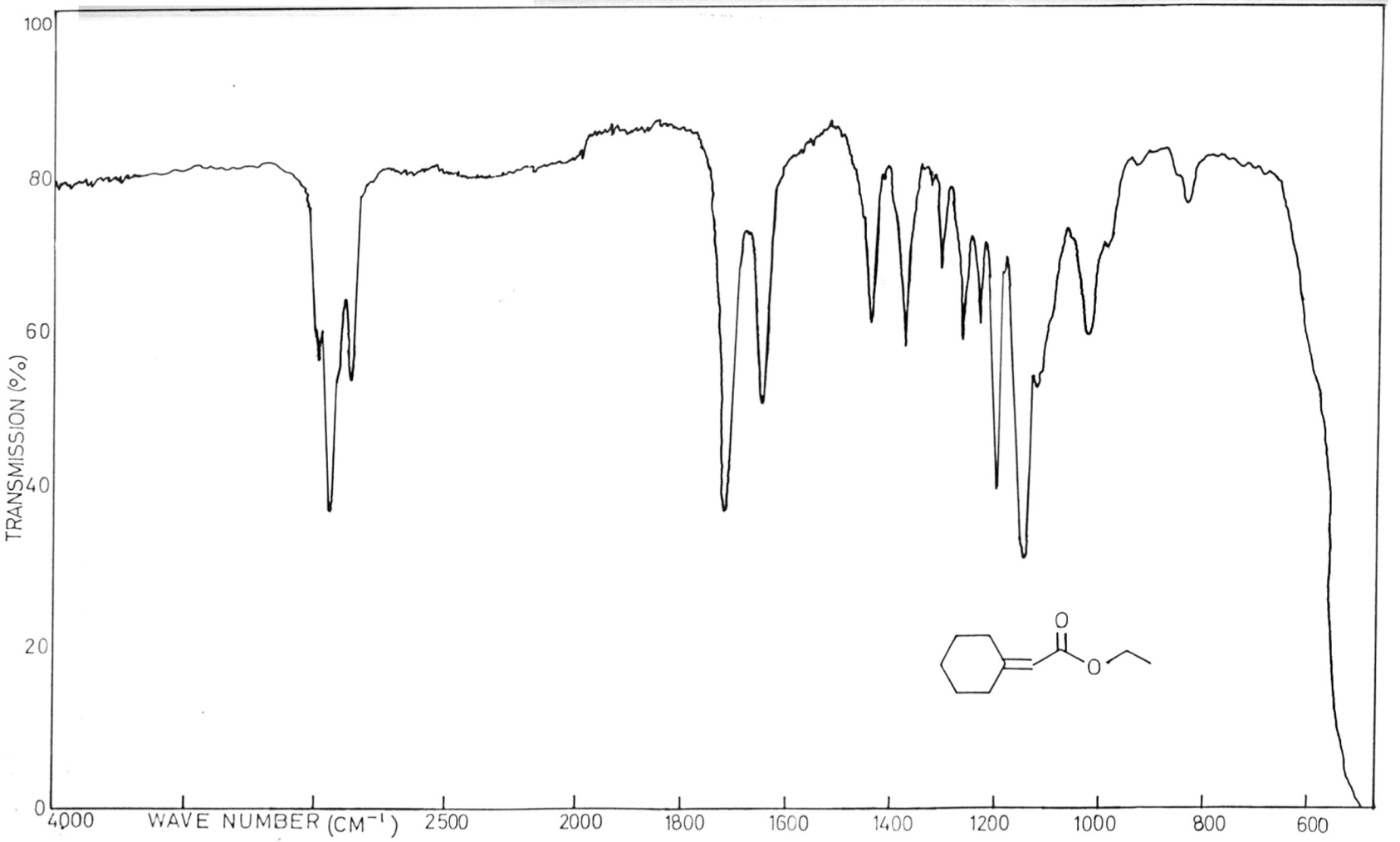

100
80
60
40
20
0
TRANSMISSION (%)
4000
WAVE NUMBER (CM⁻¹)
2500
2000
1800
1600
1400
1200
1000
800
600
O
O

FIG. 2

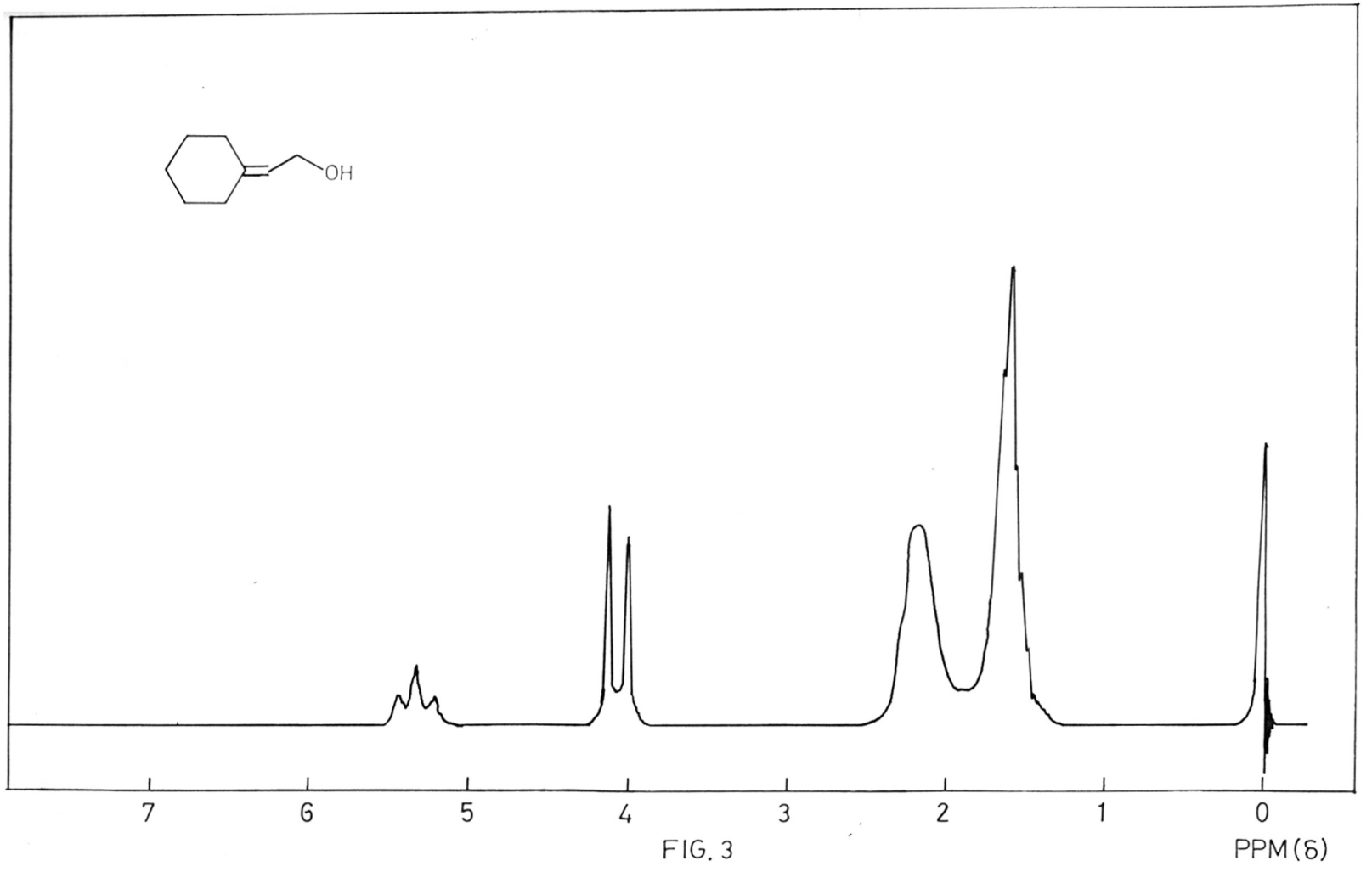


FIG. 3

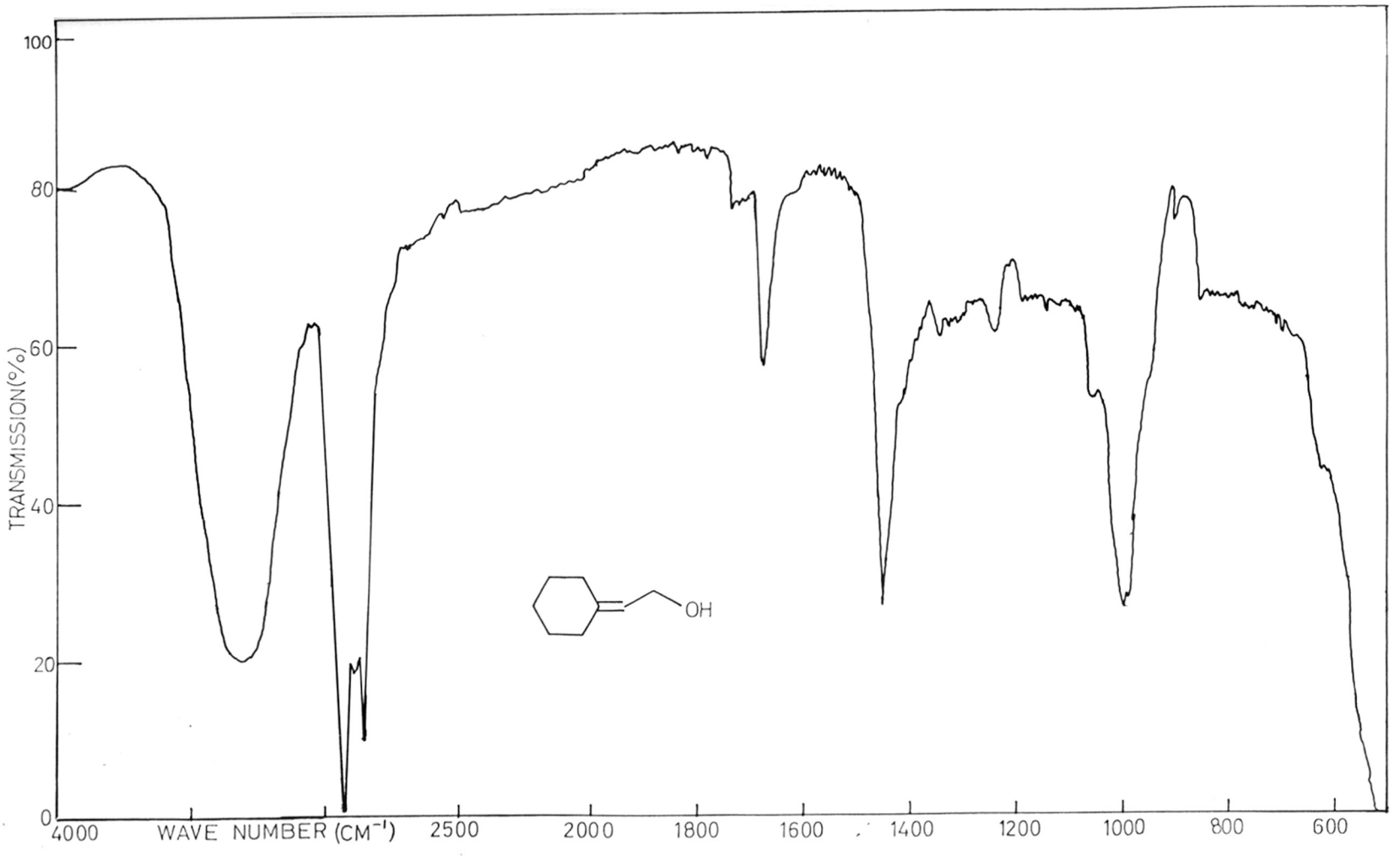

100
80
60
40
20
0
TRANSMISSION(%)
4000
WAVE NUMBER (CM⁻¹)
2500
2000
1800
1600
1400
1200
1000
800
600
OH

FIG. 4

K. Kondo et al.[51] afforded pentenoate (4) purified by distillation, in 77% yield (GLC: 97%) by Claisen ortho ester rearrangement. The formation of 4 proceeds via the rearrangement of the intermediate ether (3). M.S.: m/e 197(M^+); IR (liquid film) (Fig. 6): 1740 (ester>C=O), 1640, 910 (>C=CH_2); NMR ($CDCl_3$) (Fig. 5): 1.22 (3H, t, J=6 Hz, ester -CH_3), 1.43 (10H, br s, 5 x -CH_2- of cyclohexyl), 2.29 (2H, s, -CH_2- adjacent to carboxylate), 4.06 (2H, q, J=6 Hz, ester -CH_2-), 5.00 (2H, m, -CH=CH_2), 5.75 (1H, dd, J_1=11 Hz, J_2=17 Hz, -CH=CH_2).

4,6,6,6-Tetrahcloro 3-(1,1-cyclohexyl)-hexanoate (5) was prepared by free radical initiated CCl_4 addition to the double bond of 4 using catalytic benzoyl peroxide as a free radical initiator. The reaction was carried out by refluxing the CCl_4 solution of pentenoate (4) for 32 hr, adding small amounts of benzoyl peroxide in the form of CCl_4 solution at regular intervals of 6 hr. The crude product obtained was purified by distillation to afford 5 in 72% yield (GLC: 98%), identified by following spectral data; MS: m/e 350 (M^+); IR (liquid film): 1740 (ester>C=O) cm^{-1}; NMR ($CDCl_3$) (Fig. 7) 1.25 (3H, t, J=8 Hz, ester -CH_3), 1.56 (10H, m, 5 x -CH_2- of cyclohexyl), 2.51 (2H, s, -CH_2-adjacent to carboxylate), 2.85 (2H, m, -CH_2- adjacent to -CCl_3), 4.09 (2H, q, J=8 Hz, ester -CH_2-), 4.5 (1H, dd, J_1=3 Hz, J_2=8 Hz, -CHCl-).

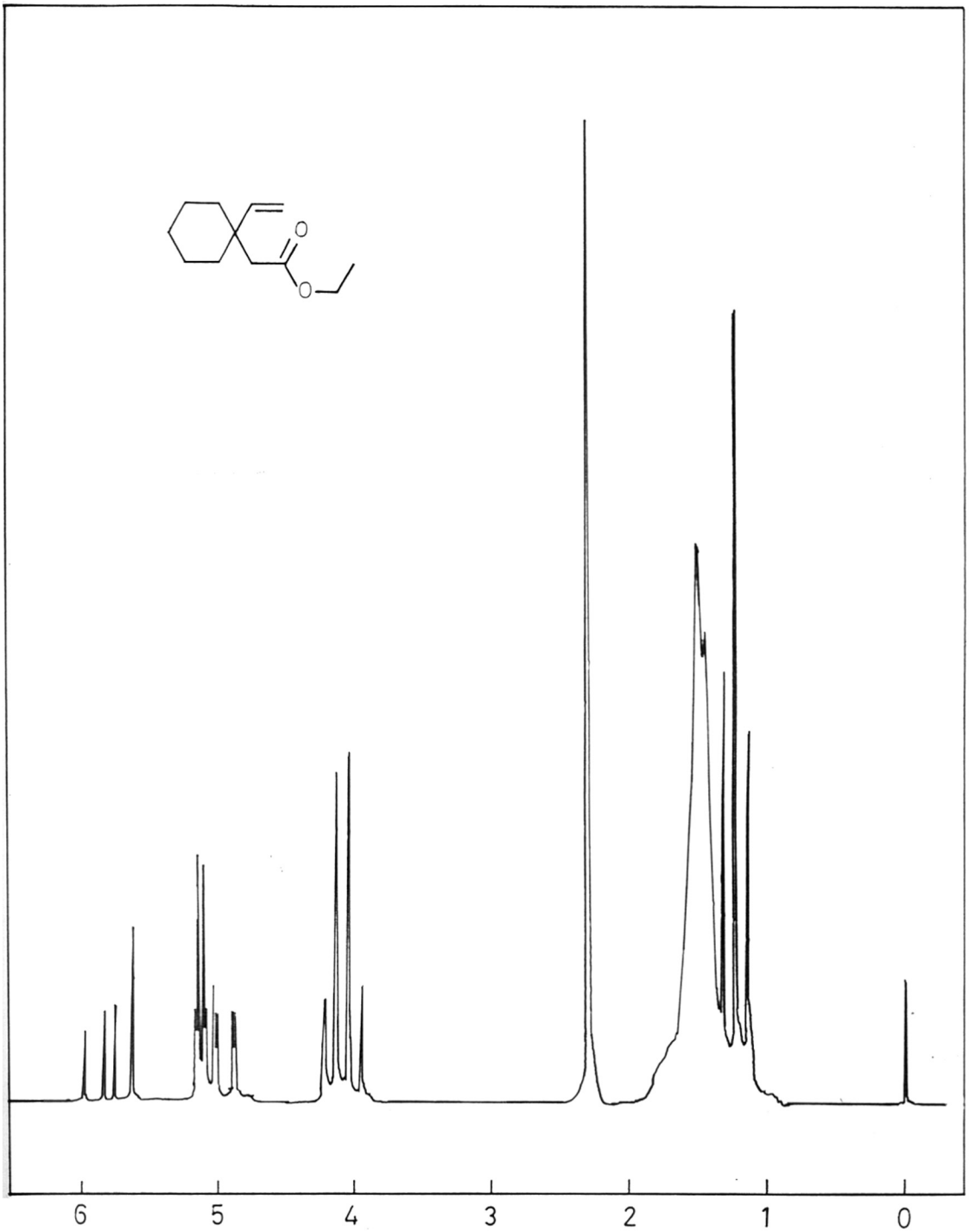


FIG. 5

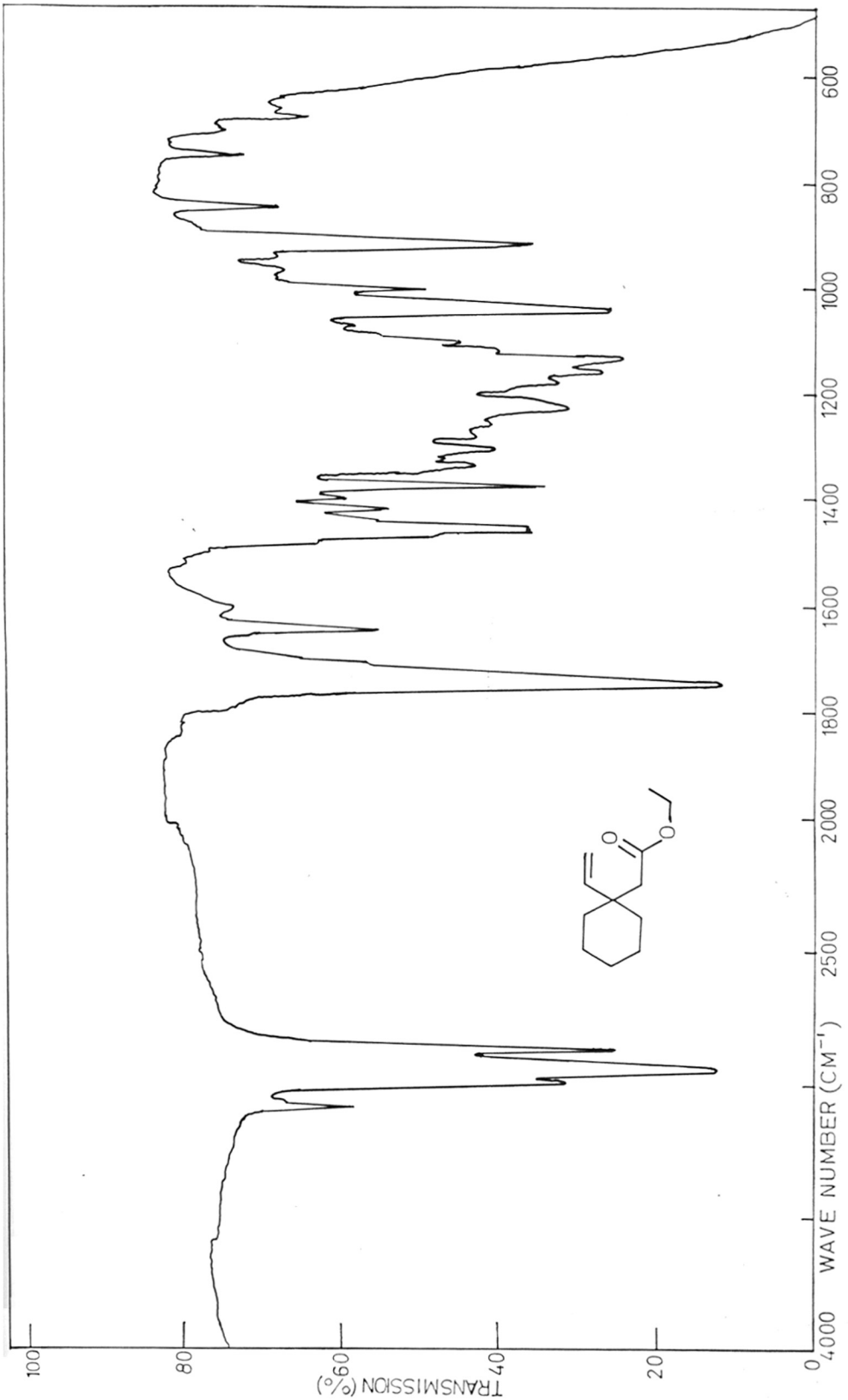

100
80
60
40
20
0
TRANSMISSION (%)
4000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVE NUMBER (CM⁻¹)
O
O
O

FIG. 6

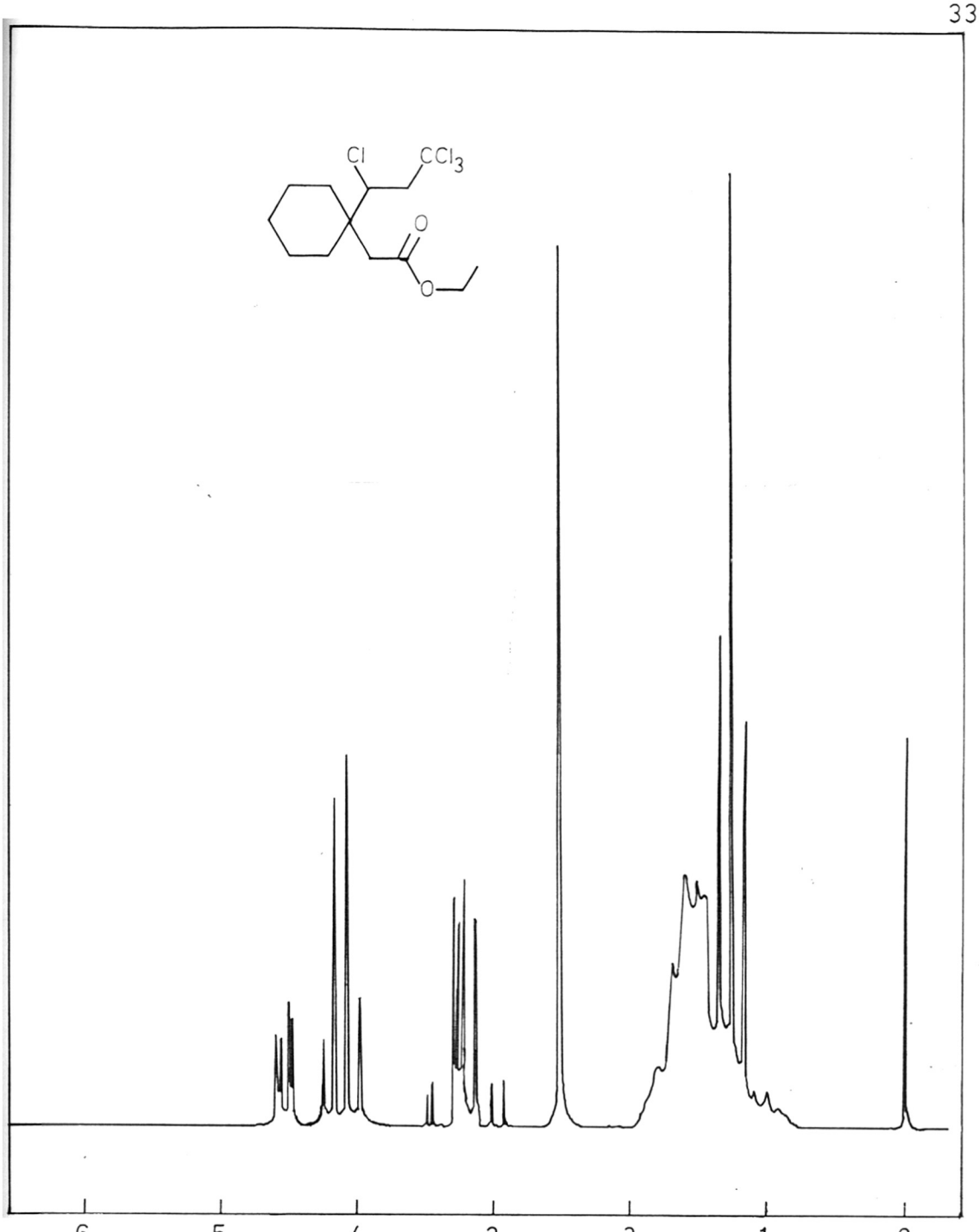


FIG. 7

With a view to obtaining ultimately the cis isomer (7b) as major product, ester (5) was cyclized initially by using K-OtBu, with N,N-dimethyl acetamide as co-base, in n-hexane at -40°C. The product obtained was, however, found to be a mixture of six compounds (GLC). GCMS analysis indicated the mixture to consist of ethyl (±) cis and (±) trans 2-(2,2,2 trichloro ethyl) spiro (2,5) octane-1-carboxylates (6) and corresponding dehydrohalogenated product viz. 2-(2,2-dichlorovinyl) analogues (7) along with minor impurities of corresponding acetylinic compounds, formed as the result of further dehydrohalogenation and unreacted tetrachlorohexanoate (5). Treatment of this mixture as such with NaOEt in dry n-hexane under reflux, followed by esterification of the resulting acids, afforded a mixture of methyl (±) cis and (±) trans 2-(2,2-dichlorovinyl)spiro (2,5) octane-1-carboxylate in 20:80 ratio along with small quantity of γ-lactone (9). The mixture as such was distilled and the distillate in hexane cooled at 0°C to give a solid (0.04 g), identified by spectral properties described below as lactone (9); M.S.: m/e 248 (M^+); IR (nujol): 1790 (lactone >C=O), 1620 (-HC=CCl_2) cm^{-1}; NMR (CCl_4): 1.4 (10H, br s 5 x -CH_2- of cyclohexyl), 2.33 (2H, s, -CH_2- adjacent to carboxylate), 4.7 (1H, d, J=9 Hz, -H adjacent to vinyl group) 5.8 (1H, d, J=9 Hz, olefinic proton).

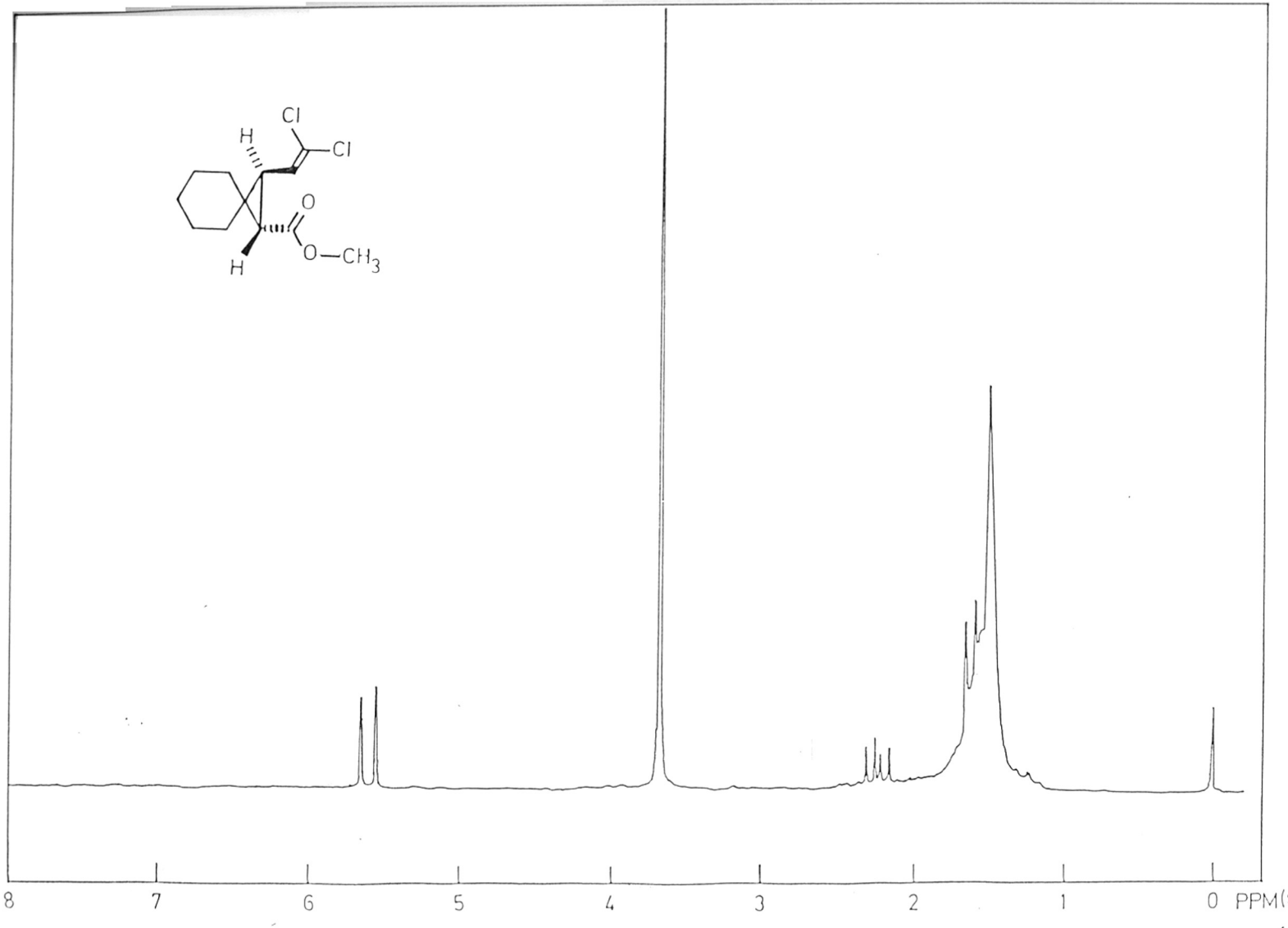


FIG. 8

In the column chromatography, middle fractions afforded the mixture of (±) cis and (±) trans esters in varying proportion, but the tail fractions eluted with 2% benzene + pet.ether gave the pure (±) trans ester (7a) identified by spectral data; M.S.: m/e 262 (M^+); IR (liquid film): 1735 (ester >C=0), 1615 (-HC=CCl_2) cm^{-1}; NMR ($CDCl_3$) (Fig. 8): 1.5 (10H, br s, 5 x -CH_2- of cyclohexyl), 1.6 (1H, d, J=5 Hz, C_1 -H), 2.2 (1H, dd, J_1 = 5 Hz, J_2 = 8 Hz, C_3 -H), 3.66 (3H, s, ester -CH_3), 5.6 (1H, d, J=9 Hz, olefinic proton).

Since the above procedure failed to give the expected (±) cis isomer (7b) in higher proportion and gave instead the (±) trans isomer (7a) as the major product, an alternate simpler method was employed for getting the latter. Cyclization and dehydrohalogenation of (5) with two equivalents of NaOEt in ethanol under reflux afforded in the neutral part of the reaction product, a mixture of the ethyl esters (8a) and (8b) in 74% yield. GLC analysis indicated that in this case also (±) trans isomer is the major product (cis:trans, 13:87 GLC). The acid portion (24%) was converted to methyl esters (7a) and (7b) possessing almost a similar composition of cis and trans isomer.

Ester (8a) was isolated in pure state by column chromatography of the neutral reaction product and characterized as follows: M.S.: m/e 276 (M^+); IR (liquid film): 1730 (ester >C=0), 1620 (-HC=CCl_2) cm^{-1}; NMR (CCl_4): 1.3 (3H, t, ester -CH_3), 1.55 (11H, br s, 5 x -CH_2- of cyclohexyl

and C_1 -H), 2.16 (1H, dd, J_1=5 Hz, J_2=8 Hz, C_3 -H), 4.13 (2H, q, ester -CH_2-), 5.57 (1H, d, J=9 Hz, olefinic proton).

Saponification of ester (8a) afforded the (±) trans 2-(2,2-dichlorovinyl)-spiro (2,5)- octane-1-carboxylic acid (10) in 95% yield as a solid, m.p.110°C (n-hexane); M.S.: m/e 248 (M^+); IR (nujol): 1620 (-HC=CCl_2), 1685 (>C=0 of -COOH) cm^{-1}; NMR ($CDCl_3$) (Fig. 9): 1.53 (10H, m, 5 x -CH_2- of cyclohexyl), 1.62 (1H, d, J=5 Hz, C_1-H), 2.3 (1H, dd, J_1=5 Hz, J_2=8 Hz, C_3-H), 5.65 (1H, d, J=9 Hz, olefinic proton), 7.45 (1H, hump, acid proton exchangeable with $D_2$0).

Acid (10) was converted into the acid chloride (11) by reacting it with $SOCl_2$ in dry benzene. The acid chloride was then reacted with the 3-phenoxy benzaldehyde cyanohydrin prepared insitu from 3-phenoxy benzaldehyde, NaCN and water in pet.ether using TEBA as phase transfer catalyst, according to a reported procedure[49]. The ester thus obtained,was purified by column chromatography and identified as ∝(RS) cyano-3-phenoxy benzyl ester (12) by spectral data; M.S.: m/e 455 (M^+); IR (liquid film) (Fig. 11): 1740 (ester >C=0), 1585 (aromatic) cm^{-1}; NMR ($CDCl_3$) (Fig. 10): 1.45 (10H, br s 5 x -CH_2- of cyclohexyl), 1.66 (1H, d, J=5 Hz, C_1-H), 2.25 (1H, m, C_3-H), 5.58 (1H, d, J=8 Hz, olefinic proton), 6.32, 6.38 (1H, two s, -CHCN- of both the diastereomers), 7.15 (9H, m, aromatic protons).

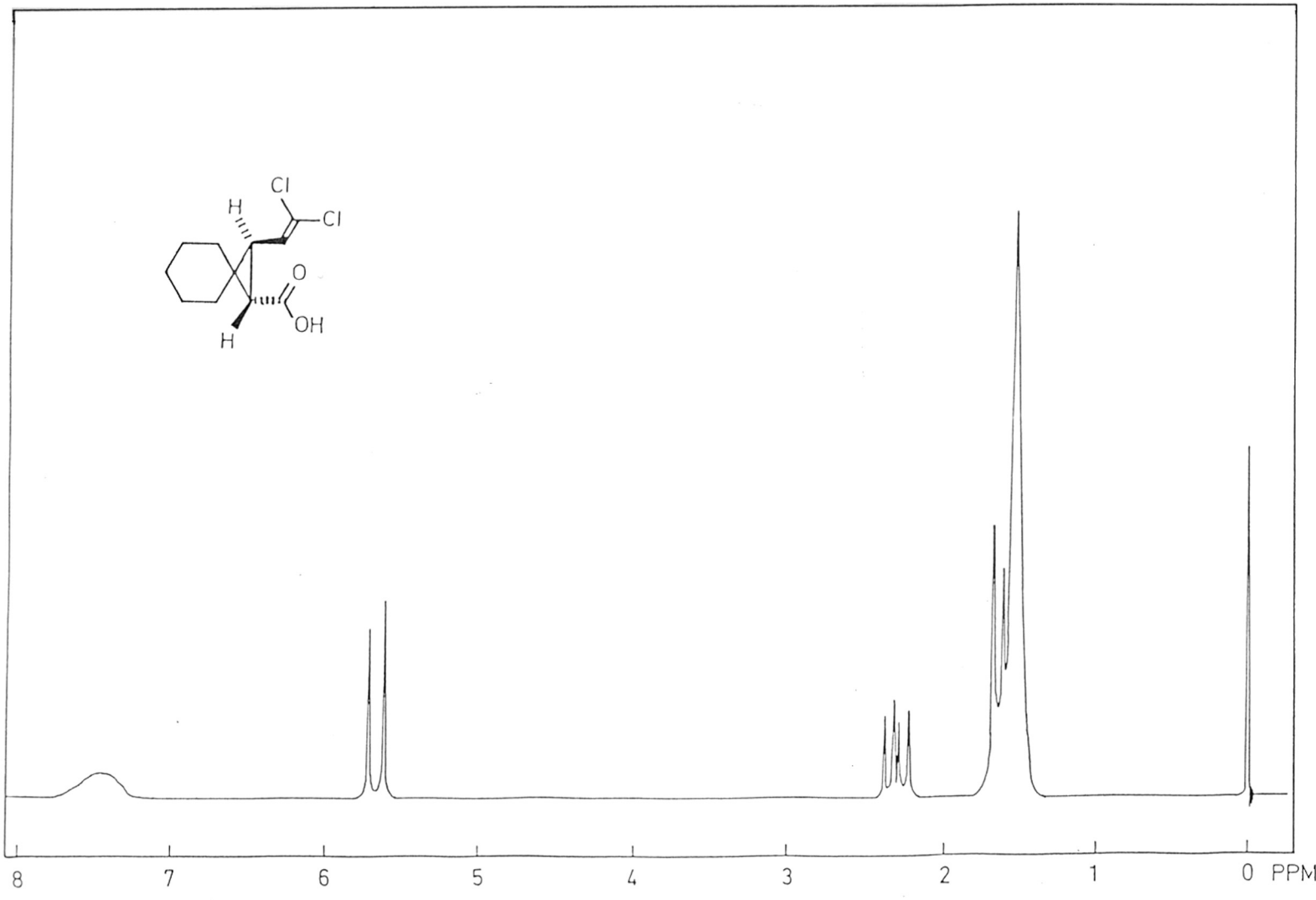


FIG. 9

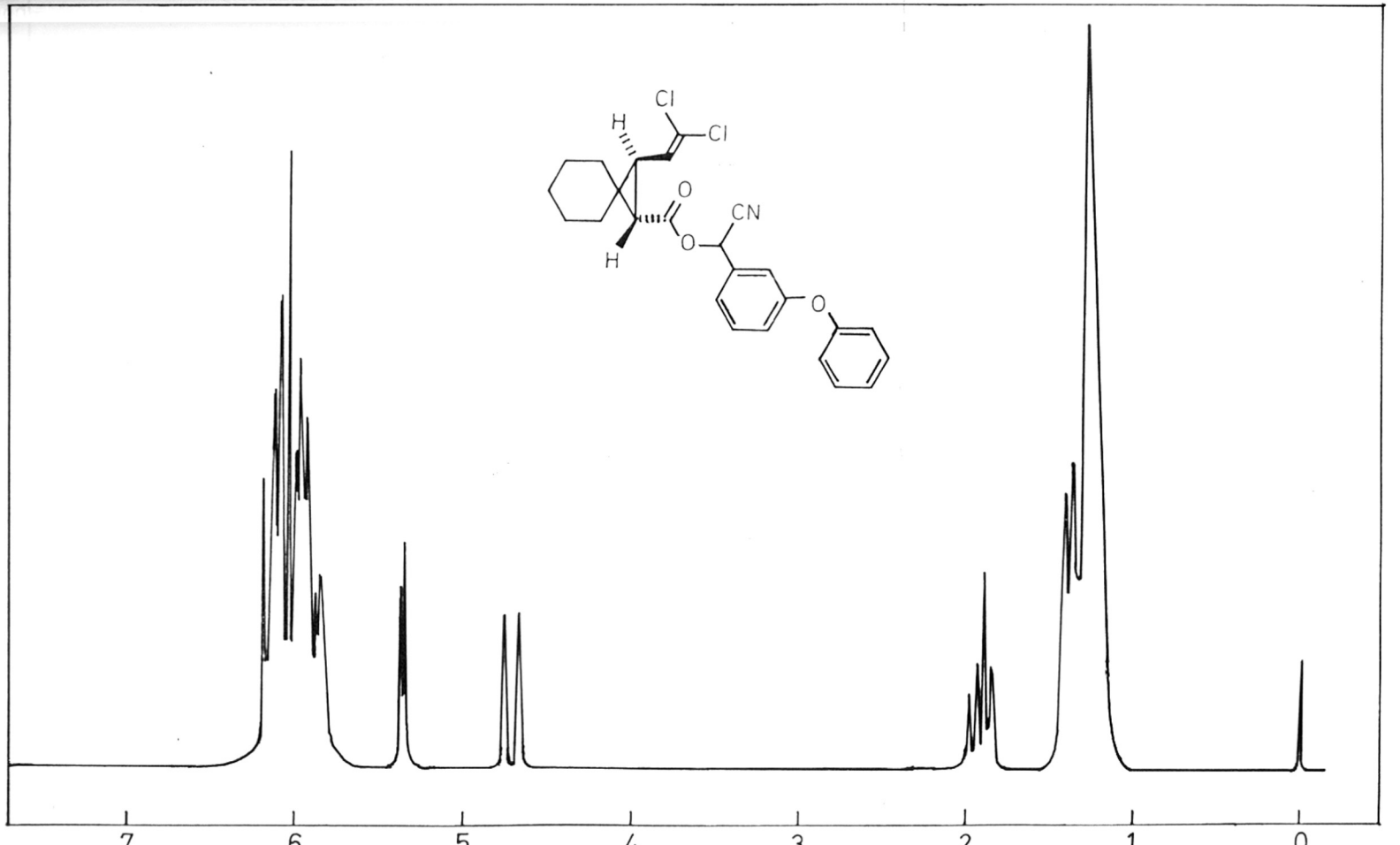
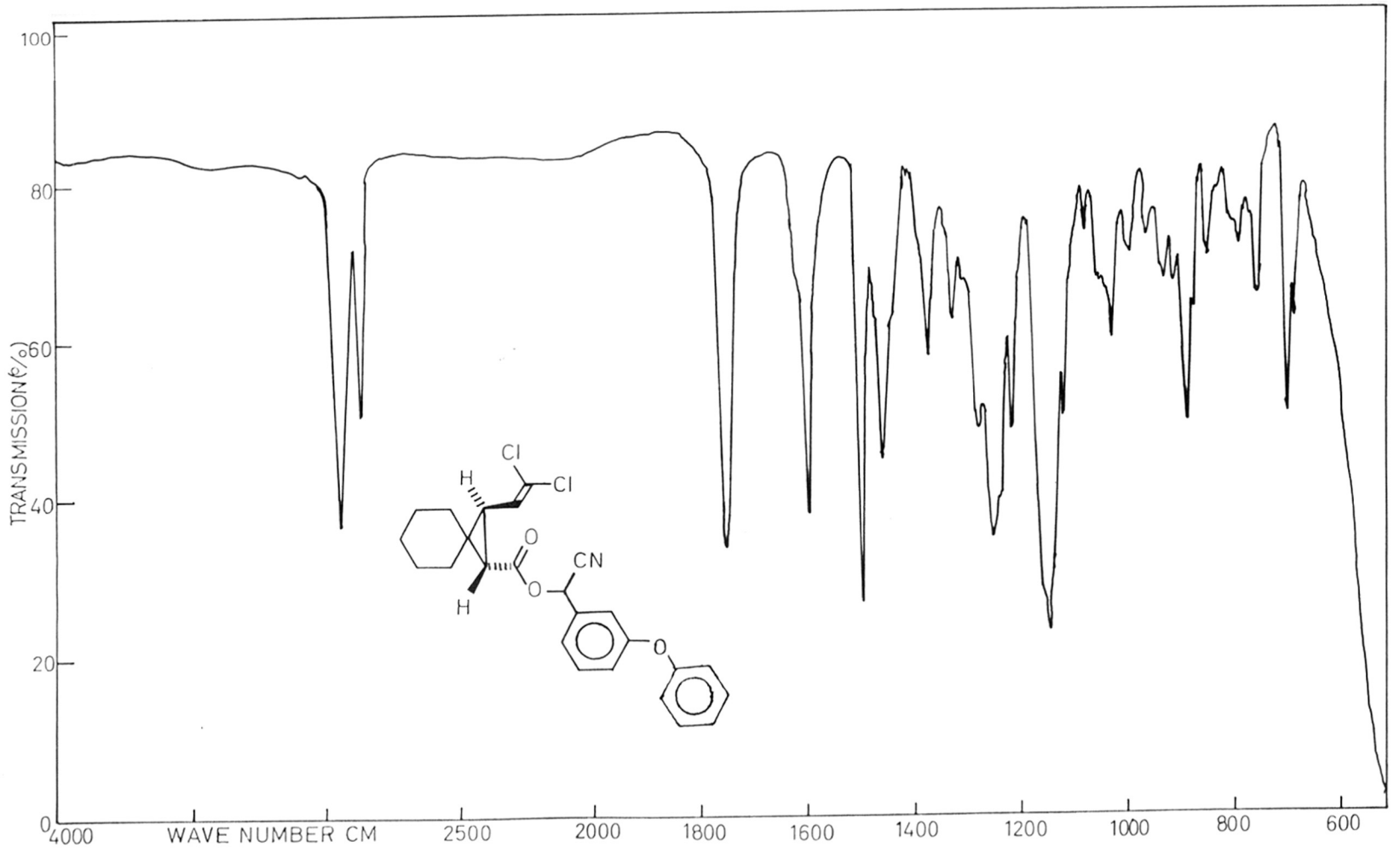


FIG. 10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TRANSMISSION(%)
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FIG. 11

3-Phenoxy benzyl (±) trans 2-(2,2-dichlorovinyl)-spiro (2,5)-octane-1-carboxylate (13) was prepared by transesterification of (8a) using 3-phenoxy benzyl alcohol catalysed by n-butyl titanate[50] and purified by chromatography; M.S.: m/e 430 (M^+); IR (liquid film) (Fig.13): 1725 (ester >C=O), 1585 (aromatic) cm^{-1}. NMR ($CDCl_3$)(Fig. 12): 1.5 (10H, m, 5 x $-CH_2-$ of cyclohexyl), 1.66 (1H, d, J=5 Hz, C_1-H), 2.22 (1H, dd, J_1=5 Hz, J_2=8 Hz, C_3-H), 5.07 (2H, s, benzylic $-CH_2-$), 5.55 (1H, d, J=8 Hz, olefinic proton), 7.1 (9H, m, aromatic protons).

Ester (12) exhibited insecticidal activity against Musca domestica (100% mortality at 10 µg/insect). It also showed larvicidal activity against fourth instar mosquito larvae (Aedes aegyptii) with 90% mortality at 100 ppm. However, ester (13) was found to be inactive at micro dosage level.

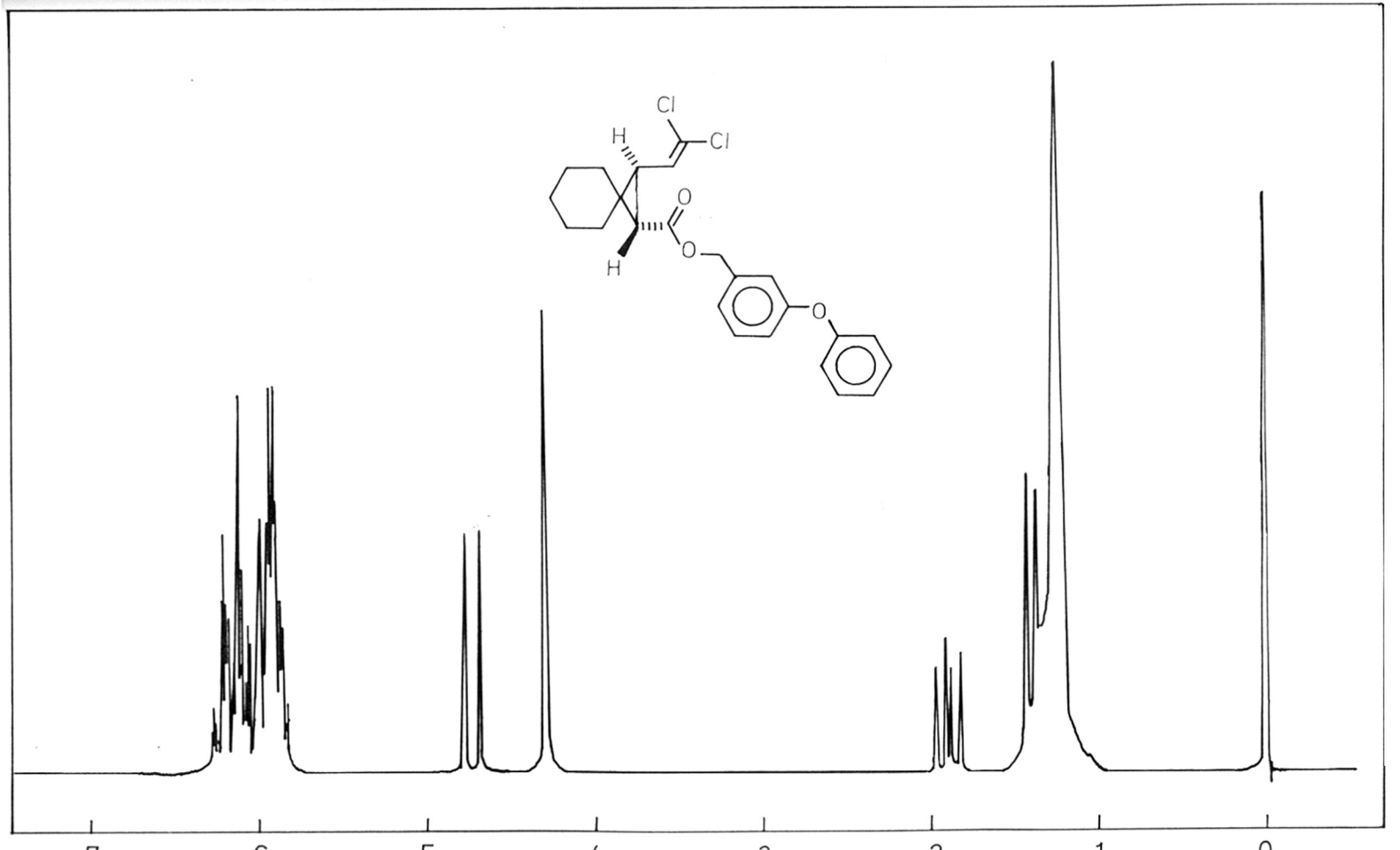
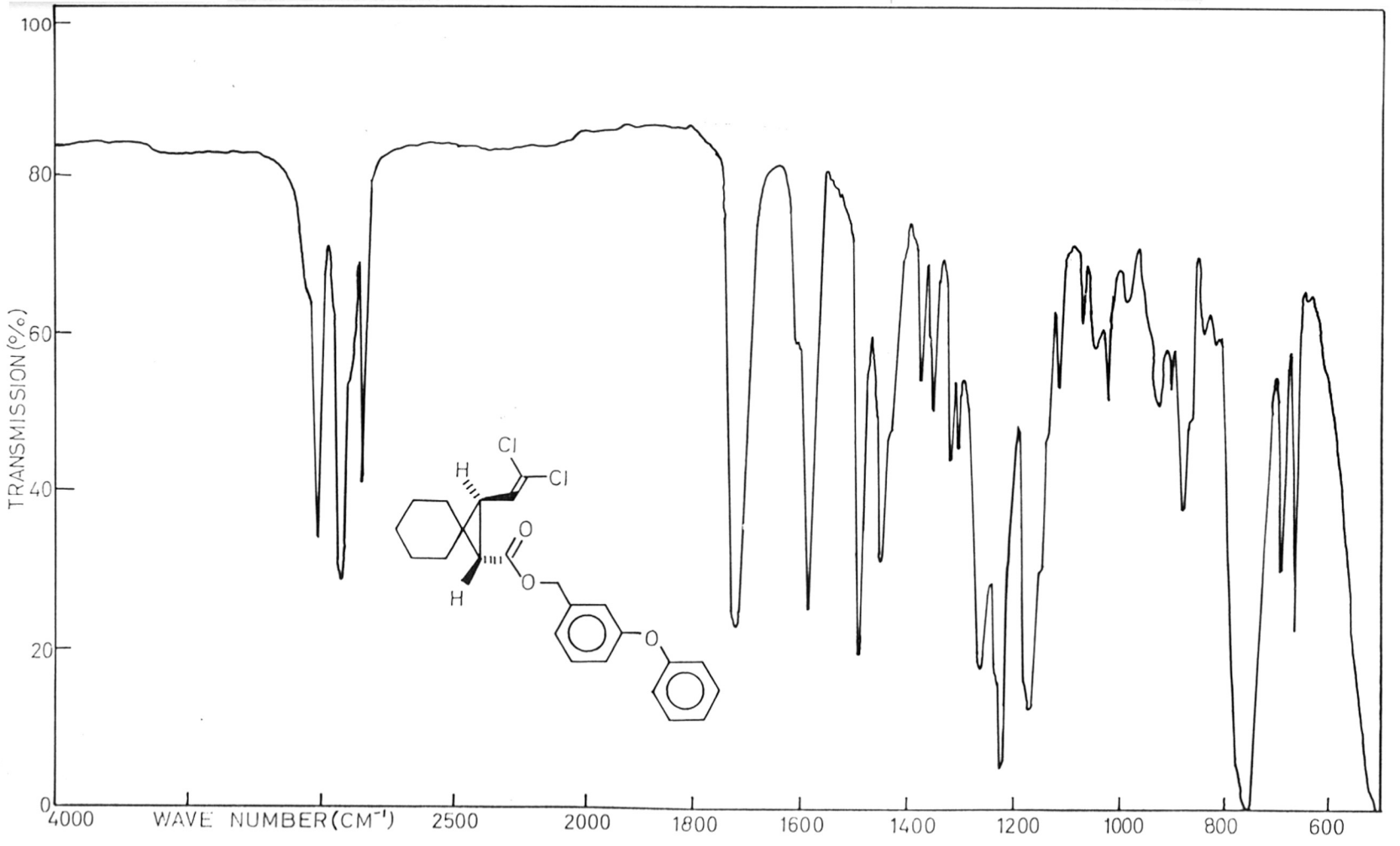


FIG. 12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600
Cl
Cl
H
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FIG. 13

EXPERIMENTAL

Ethyl cyclohexylidene acetate (1)

To a solution of triphenyl carbethoxymethylene phosphorane (44 g, 0.126 mol) in dry xylene (100 ml), freshly distilled cyclohexanone (12.5 g, 0.126 mol) was added and the mixture refluxed for 6 hr in an oil-bath. Reaction mixture was cooled and xylene removed under reduced pressure. Residue was hot extracted with n-hexane (100 ml x 4). Hexane extract was washed with water, dried and solvent removed to give a crude product, which was further purified by distillation (b.p.78°C/2 mm) to give a pure colourless liquid, identified as (1, 13.9 g, 87%). GLC: 98%.

Analysis

Found: C, 71.4; H, 9.3; $C_{10}H_{16}O_2$

requires: C, 71.39; H, 9.59%.

IR bands at: 2950, 2880, 1730, 1660, 1463, 1392, 1219, 1168, 1045 cm^{-1}.

Cyclohexylidene ethanol (2)

Aluminium hydride was prepared as follows:

To a cooled and stirred suspension of LAH (6.1 g, 0.16 mol) in ether (50 ml) a solution of $AlCl_3$ (5.38 g, 0.04 mol) was slowly added during 15 minutes and mixture stirred for 15 minutes more at 0°C.

A solution of ester (1, 9.0 g, 0.054 mol) in dry ether (50 ml) was then added to the AlH_3 solution dropwise under

stirring during 30 min. The stirring continued for 30 min more at same temperature. Excess AlH_3 was decomposed by dropwise addition of moist ether. The ether layer was separated and aqueous layer extracted with ether (50 ml x 3). Combined ether extract was washed with water, brine and dried. Removal of ether gave an oil, which was further purified by distillation (b.p.63°C/1 mm) to give pure alcohol (2, 5.6 g, 83%). GLC: 99.8%.

Analysis

Found: C, 76.0; H, 11.3; $C_8H_{14}O$

requires: C, 76.14; H, 11.18%.

IR bands at: 3200, 2910, 2850, 1670, 1455, 990 cm^{-1}.

Ethyl 3-(1,1-cyclohexyl)-pent-4-enoate (4)

A mixture of alcohol (2, 7.56 g, 0.06 mol), triethyl ortho acetate (19.44 g, 0.12 mol) and O-cresol (0.5 ml) was heated at 140-150°C for 7 hr removing continuously ethanol (1.1 ml) formed in the reaction. Excess triethyl ortho acetate was then distilled off (170-80°C) and the reaction mixture cooled to room temperature, phosphoric acid (0.5 ml) was added and heating continued at 170-80°C for further 7 hr. The reaction mixture was diluted with water, neutralized with dil. NaOH solution (5%) and extracted with ether (75 ml x 3). Ether extract was washed with water, dried and distilled to give a liquid, purified by distillation (b.p.70°C/1 mm) to afford 4 (9.1 g, 77%). GLC: 97%.

Analysis

Found: C, 73.2; H, 10.10; $C_{12}H_{20}O_2$

requires: C, 73.43; H, 10.27%.

IR bands at: 2935, 2840, 1740, 1640, 1455, 1370, 1035, 910 cm^{-1}.

Ethyl 4,6,6,6-tetrachloro 3-(1,1-cyclohexyl)-hexanoate (5)

To a solution of ester (4, 9.0 g, 46 mmol) in dry carbon tetrachloride (60 ml), a solution of benzoyl peroxide in CCl_4 (5 ml, 6%) was added and homogenous mixture refluxed for 32 hr, adding fresh benzoyl peroxide solution at regular intervalsof 6 hr. Reaction mixture was diluted with CCl_4 (50 ml) and successively washed with Na_2SO_3, 10% Na_2CO_3 followed by water and dried, removal of CCl_4 furnished a liquid, purified by distillation (b.p.76°C/1 mm) to afford pure carbon tetrachloride addition product(5, 11.4 g, 72%).

Analysis

Found: C, 44.7; H, 5.62; Cl, 40.4; $C_{13}H_{20}O_2Cl_4$

requires: C, 44.59; H, 5.75; Cl, 40.5%.

IR bands at: 2982, 2930, 2860, 1740, 1555, 1370, 1034, 900 cm^{-1}.

Methyl/ethyl (±) trans, 2-(2,2-dichlorovinyl)-spiro (2,5) octane-1-carboxylate (7)/(8)

The mixture of (±) cis and (±) trans esters have been prepared by two methods.

(A) Cyclization at -40°C and then dehydrohalogenation

To a cooled (-40°C) and stirred solution of hexanoate (5, 5.25 g, 15 mmol), N,N-dimethyl acetamide (4.8 ml, 40 mmol) in dry hexane (30 ml), KOtBu (3.364 g, 30 mmol) was then added in eight lots during 24 hr. First four lots were added at the intervals of 15 min each and remaining lots added at the interval of about six hr. The reaction product was diluted with ice-coled water and extracted with hexane, washed with water (50 ml x 3), dried and evaporated to give mixture of esters, which according to GCMS consisted of cis; trans (6) and cis; trans (7) along with small quantities of unreacted (5) and the corresponding acetylenic ester. The mixture as such was further treated with NaOEt as follows:

To a suspension of dry NaOEt (1.118 g, 16 mmol) in hexane (20 ml), was added mixture of esters obtained above and refluxed for 12 hr. It was diluted with water, extracted with ether to remove the neutral product. Evaporation of ehter gave only traces of liquid material,not investigated further. The aqueous portion was acidified with dil.HCl(10%) to 2 pH, extracted with ether to give a mixture of acids, esterified with diazomethane to afford a liquid,mainly consisting of mixture of 7a, 7b along with small quantity of 8 and other unidentified products according to GLC. The crude product was distilled to give a liquid (1.47 g),

which on cooling in hexane solution at 0°C, gave a solid (0.04 g), identified as the lactone (9), m.p.105°C.

Analysis

Found: C, 52.91; H, 5.51; Cl, 28.5; $C_{11}H_{14}O_2Cl_2$

requires: C, 53.02; H, 5.66; Cl, 28.45%.

IR bands at: 2910, 2820, 1790, 1450, 1165, 1005, 905 cm^{-1}.

The mother-~~liquid~~ liquor consisting of 7a and 7b (20:80 by GLC) was chromatographed over silica gel 28 g (~1:20). The earlier fractions eluted with 2% benzene + pet.ether afforded mixtures of 7a and 7b in varying composition while the tail fractions eluted with the same solvent afforded a liquid, identified as (±) trans-isomer 7a (0.32 g). GLC: 98%.

Analysis

Found: C, 54.79; H, 6.09; Cl, 26.8; $C_{12}H_{16}O_2Cl_2$

requires: C, 54.76; H, 6.12; Cl, 26.94%.

IR bands at: 2935, 2860, 1735, 1615, 1445, 1168, 878 cm^{-1}.

(B) Cyclization and dehydrohalogenation at 78°C.

To an ice-cooled solution of NaOEt (2.799 g, 0.411 mol) in dry ethanol (25 ml), was added a solution of tetrachloro ester (5, 6.0 g, 0.171 mol) in ethanol (25 ml) and the mixture refluxed for 12 hr. Ethanol was removed by distillation, the residue diluted with ice-cold water and extracted with ether. Removal of ether gave an oil consisting chiefly of 8a and 8b (3.5 g, 74%) in the proportion of 13.87. The oily product was chromatographed

over silica gel and the tail fractions eluted with 2% benzene + pet.ether afforded the pure trans isomer (8a, 1.2 g).

Analysis

Found: C, 56.4; H, 6.44; Cl, 25.6; $C_{13}H_{18}O_2Cl_2$

requires: C, 56.32; H, 6.54; Cl, 25.51%.

IR bands at: 2936, 2860, 1730, 1620, 1452, 1182, 865 cm^{-1}.

(±) trans, 2-(2,2-Dichlorovinyl)-spiro (2,5)-octane-1-carboxylic acid (10)

To a solution of NaOH (0.058 g, 0.145 mmol in 0.5 ml water) in ethanol (10 ml) was added the ester (8a, 0.4 g, 145 mmol). The mixture was stirred for 16 hr at 28°C. Ethanol was removed under reduced pressure, the residue diluted with water (10 ml), extracted with ether (25 ml x 3), washed with water, dried and evaporated to give a solid acid (10, 0.34 g, 95%) m.p.110°C (n-Hexane).

Analysis

Found: C, 53.1; H, 5.51; Cl, 28.5; $C_{11}H_{14}O_2Cl_2$

requires: C, 53.02; H, 5.66; Cl, 28.46%.

IR bands at: 2920, 1685, 1620, 1455, 1255, 1105, 870 cm^{-1}.

α(RS) Cyano-3-phenoxy benzyl (±) trans 2-(2,2-dichlorovinyl)-spiro (2,5)-octane-1-carboxylate (12)

The acid chloride (11) was prepared by reacting acid (10, 0.326 g, 1.3 mmol) with excess $SOCl_2$ (1 ml) and dry benzene (10 ml) under stirring for 2 hr at 50-60°C. Excess

$SOCl_2$ and benzene were removed by distillation under reduced pressure. A mixture of acid chloride (0.3 g, 1.1 mmol) and 3-phenoxy benzaldehyde (0.387 g, 2 mmol) in dry pet.ether (30 ml) was added dropwise during 2 hr at 35-40°C to a stirred mixture of NaCN (0.138 g, 2 mmol), water (0.2 ml), TEBA (50 mg) in dry pet.ether (10 ml), stirring continued for 2 hr at the same temperature. Extractive workup gave the crude ester purified by column chromatography on silica gel (10 g). Fraction eluted with 5% benzene + pet.ether gave the required ester (12) in pure state as a liquid (0.35 g, 72%).

Analysis

Found: C, 65.61; H, 5.2; Cl, 15.71; N, 3.1; $C_{25}H_{23}Cl_2NO_3$

requires: C, 65.79; H, 5.08; Cl, 15.53; N, 3.06%.

IR bands at: 2920, 2845, 1740, 1585, 1485, 1038, 870 cm^{-1}.

3-Phenoxy benzyl (±) trans 2-(2,2-dichlorovinyl)-spiro (2,5)-octane-1-carboxylate (13)

A mixture of (8a, 0.681 g, 2.5 mmol), 3-phenoxy benzyl alcohol (1.0 g, 5 mmol) and n-butyl titanate (catalytic amount) was refluxed in dry xylene for 8 hr. Xylene was distilled off and the residue chromatographed on silica gel, eluted with 5% benzene + pet.ether to afford ester (13) as a liquid in pure state (0.79 g, 75%).

Analysis

Found: C, 66.9; H, 5.5; Cl, 16.3; $C_{24}H_{24}Cl_2O_3$

requires: C, 66.82; H, 5.60; Cl, 16.44%.

IR bands at: 3018, 2930, 2850, 1725, 1585, 1490, 1220, 760 cm^{-1}.

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CHAPTER II

SYNTHESIS OF SPIRO-FUSED FUNCTIONALIZED CYCLOALKYLCYCLOPROPANE CARBOXYLATES.

SUMMARY

This chapter deails with the syntheses of esters of type 6, wherein initial preparation of the required conjugated ketones viz. benzylidene/furfurylidene/isobutylidene derivatives 2 from the corresponding cycloalkanones by an Aldol type condensation with the desired aldehydes, under basic conditions. Conjugated ketones (2) were then reacted with ethyl dimethyl sulfuranylidene acetate to obtain the cyclopropane carboxylates (3) in the form of ethyl esters. These esters (3) were then saponified to give the corresponding keto carboxylic acids (4). The latter were then converted into the corresponding acid chlorides (by thionyl chloride) (5) and reacted with 3-phenoxy benzyl or isopropyl alcohols or 3-phenoxy benzaldehydo cyanohydrin, in presence of pyridine, to give the corresponding esters (6). Sodium borohydride reduction of (6) furnished the corresponding hydroxy esters (8) which were subsequently converted into acetate esters (9)

INTRODUCTION

Ylides are an interesting class of carbanionoid compounds in which the negative charge on carbon is stabilized by an adjacent positively charged heteroatom from group V or VI of periodic table. The compounds are electrically netural, yet they possess a significant degree of charge separation. Because of $p\pi$ - $d\pi$ bonding, two canonical forms can be written for phosphorus and sulfur ylides, but only one form for nitrogen ylides (Chart 1). Phosphorus ylides are much more stable than the nitrogen ylides due to resonance. However, sulfur ylides inspite of of their resonance have a low stability.

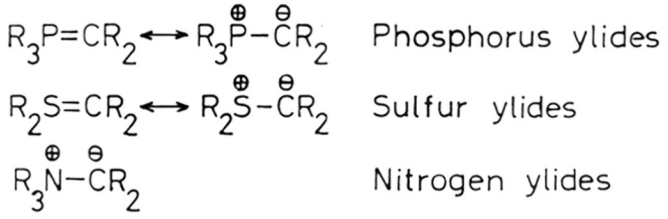
Ylides have become extremely important reagents in organic synthesis because one can achieve the conversion of a ketone to an olefin with regiospecificity, in contrast to the result in the Reformatsky reaction and in most of the base-catalyzed condensation or the Grignard reaction followed by dehydration.

The cis-trans ratio of the product can often be changed by a change in solvent or by the addition of salts or carrying out reactions at low temperature. It has been found possible to control the reaction so that either the cis or the trans olefin is the main product[1].

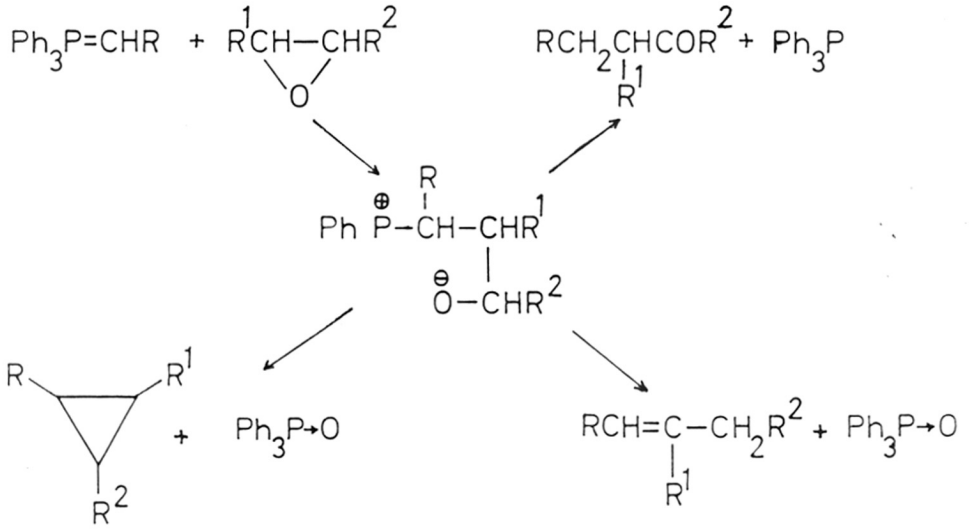
Phosphorus ylides

Another important use of ylides is the built up a cyclopropane ring. Treatment of epoxide with certain

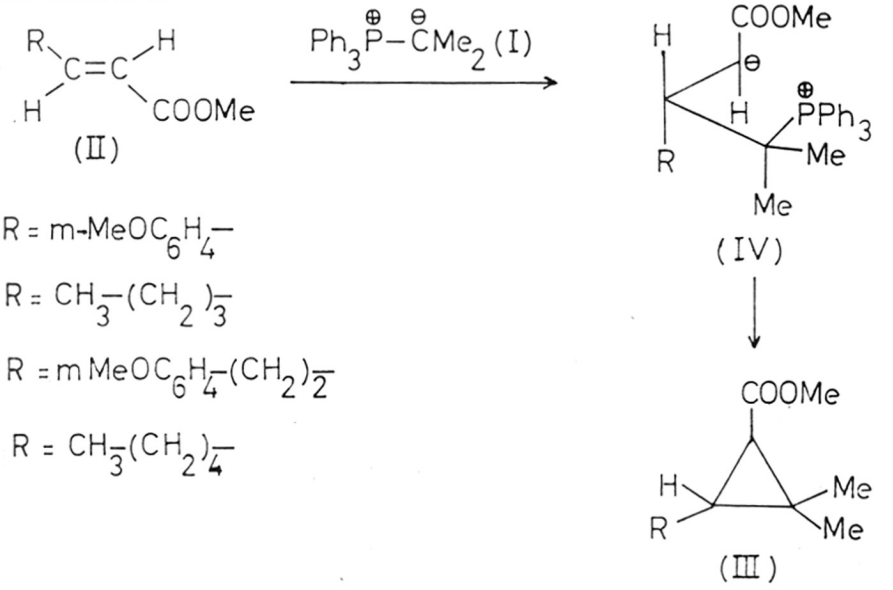
CHART 1



REACTION-1



REACTION-2



a R = m-MeOC$_6$H$_4$—

b R = CH$_3$—(CH$_2$)$_3$—

c R = m MeOC$_6$H$_4$—(CH$_2$)$_2$—

d R = CH$_3$—(CH$_2$)$_4$—

phosphorus ylides has been reported to give substituted cyclopropanes[2]; reaction of a phosphorane on an epoxide leads to a number of products depending upon the stability of the reacting ylides[3]. The different products of reaction can be explained on the basis of initial formation of "betain" intermediate, which can then rearrange to give different products depending upon the group R of the phosphorane (chart 1, reaction 1).

Triphenylphosphonium isopropylide was successfully employed to construct the gem-dimethyl cyclopropane unit[4]. 1,4 Addition of triphenylphosphonium isopropylide to α,β-unsaturated esters gave the gem-dimethyl cyclopropanation. In their capacity as nucleophiles, alkylidene phosphoranes can add to activated double bonds to form an intermediate IV which might be expected to undergo cyclopropane formation accompanied by the elimination of triphenyl phosphine (chart 1, reaction 2).

Sulfur ylides

In 1965 E.J. Corey et al. discovered an important reaction in which the sulfur ylide viz. dimethyl oxosulfonium methylide reacted in different ways with isolated and conjugated ketones, e.g. 3-carbomethoxy methyl cyclohexanone on treatment with the above ylide afforded the corresponding epoxide[5], (chart 2, reaction 3), while the same reagent when reacted with chalcone afforded

trans 1-benzoyl-2-phenyl cyclopropane[6] (chart 2, reaction 4). It is interesting to note that the corresponding dimethyl sulfonium methylide (ylide prepared from dimethyl sulfide) produced only the epoxide with the same chalcone .

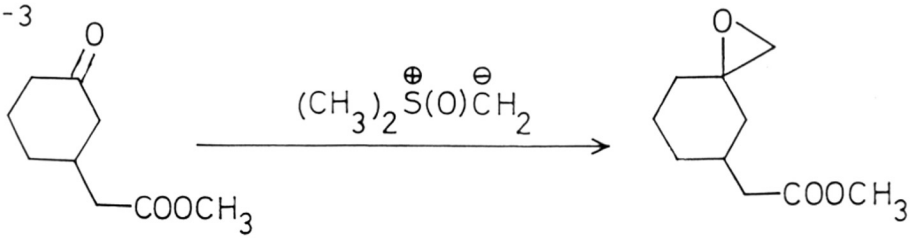
The reaction of one equivalent of ylide with α,β-unsaturated ketones (which are susceptible to Michael addition) results in selective methylene transfer to the α,β-carbon-carbon double bond to form cyclopropyl ketones rather than addition to the carbonyl group. In case of completely conjugated dienone system like eucarvone it is noteworthy that the reaction of ylide involves methylene transfer to the α,β rather than the γ,δ double bond. This selectivity may be due to partly, to a shielding effect of the gem-dimethyl group, which inhibits attack at C_δ. In case of reaction of dimethyl oxosulfonium methylide with α,β-unsaturated carboxylic acid derivatives e.g. esters and acid-chlorides, either Michael addition or carbonyl attack or both can occur[6]. Methylene transfer to the α,β-double bond is more favourable with amides.

For the first time William E. Truce[7] in 1964 prepared cyclopropyl sulfones by use of dimethyl sulfonium methylide on vinylic sulfones (chart 2, reaction 5).

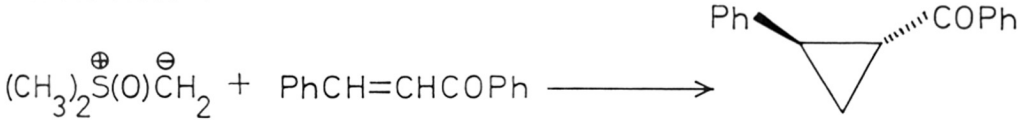
A novel and direct approach to the gem-dimethyl-cyclopropane system using the reaction of diphenylsulfonium isopropylide with conjugated carbonyl compounds was discovered by E.J. Corey[8]. The availability of the

CHART 2

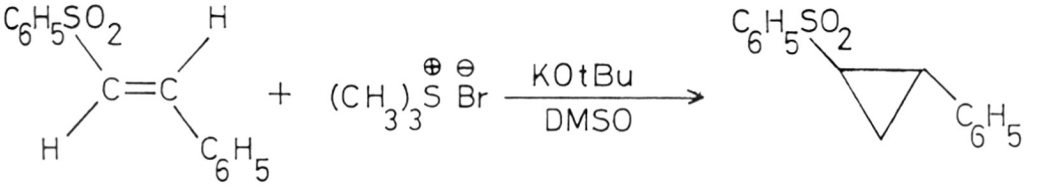
REACTION-3

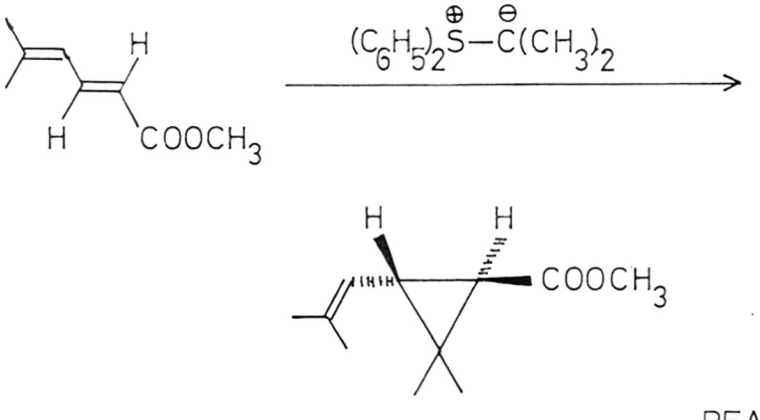


REACTION-4



REACTION-5





REACTION-6

isopropylidene transfer reagent has made possible a new synthesis of the important insecticidally active natural product chrysanthemic acid by a particularly simple, stereospecific route. Methyl 5-methyl-trans-2, 4-hexadienoate, which is readily available from the reaction of methallyl chloride, acetylene and methanol in the presence of nickel carbonyl followed by treatment with NaOMe, afforded cleanly methyl (±) trans-chrysanthemate by reaction with isopropylide (chart 2, reaction 6).

Numerous examples of cyclopropanation of α,β-unsaturated ketones with sulfur ylides offer the best opportunity to evaluate the effect of substituents on olefin. Alkyl substitution on the double bond diminishes reactivity as illustrated by the series of methyl substituted cyclopentenones[9]. Although substitution at either the α or β-carbon atoms causes such a retardation, substituents on the α carbon atom appear to have greater effect. The severe steric hinderance to conjugate addition completely inhibits cyclopropanation in some cases. Ring size of the α,β-unsaturated cyclic ketones also plays an important role in the reactivity. In case of five, six and seven membered enones the reaction takes place smoothly[10].

The presence of additional functional groups, such as hydroxyl, sulfhydryl, amino, imino, nitro, nitrile, isonitrile, carbonyl, sulfonyl and sulfoxide as well as

isolated double and triple bonds in the α,β-unsaturated ketones do not interfere with the cyclopropanation reaction. An outstanding example of the chemospecificity of the oxosulfonium ylides is the successful reaction of these reagents with cephalosporin derivatives without affecting the sensative β-lactam[11] group.

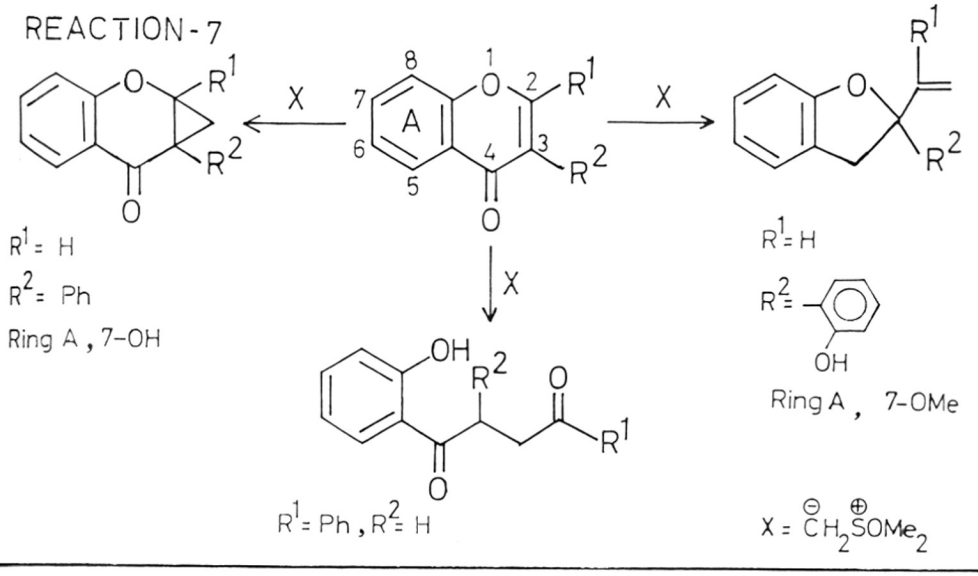
α,β-Unsaturated systems, substituted in the β-position with a good leaving group, may lead to anomalous products. For example, Ollis and his co-workers observed that the flavones may react in one or all of three possible modes depending on the substituents, when treated with dimethyl-oxosulfonium methylide[12] (chart 3, reaction 7).

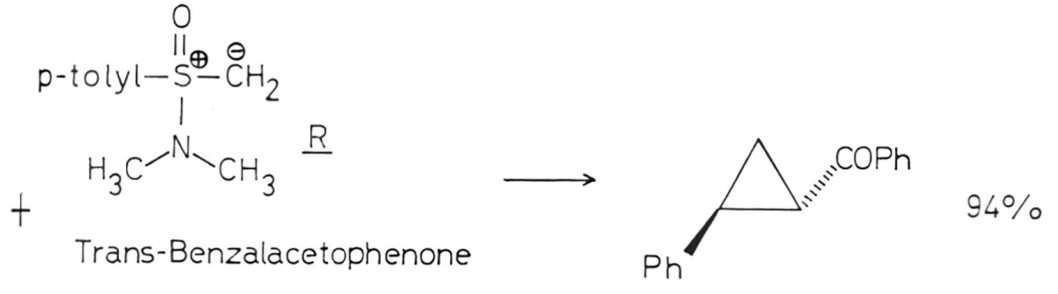
In addition to selectivity with respect to relative configurations, sulfur ylides offer an approach to generate specific absolute configurations. By the use of optically active ylides with asymmetry at sulfur, optically active cyclopropanes can be obtained directly in delightfully high optical purity with oxosulfonium ylides[13] but not with sulfonium ylides[14]. For example R-dimethyl amino-p-tolyloxosulfonium methylide transfers methylene to a variety of acceptors with optical purity of enantiomer ranging from 15-37% (chart 3, reaction 8 and 9).

The stabilized ylides generally undergo only cyclo-propanation with conjugated carbonyl compounds. The success of this reaction in contrast to its failure to form epoxides

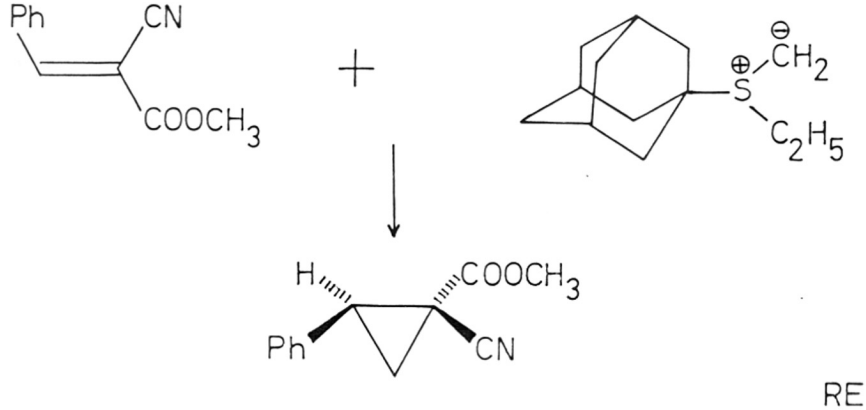
CHART 3

REACTION - 7





REACTION - 8

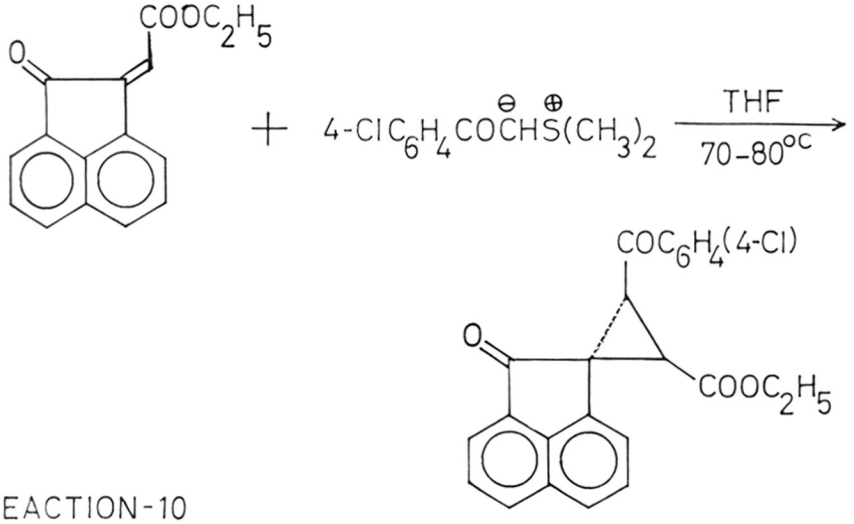


REACTION - 9

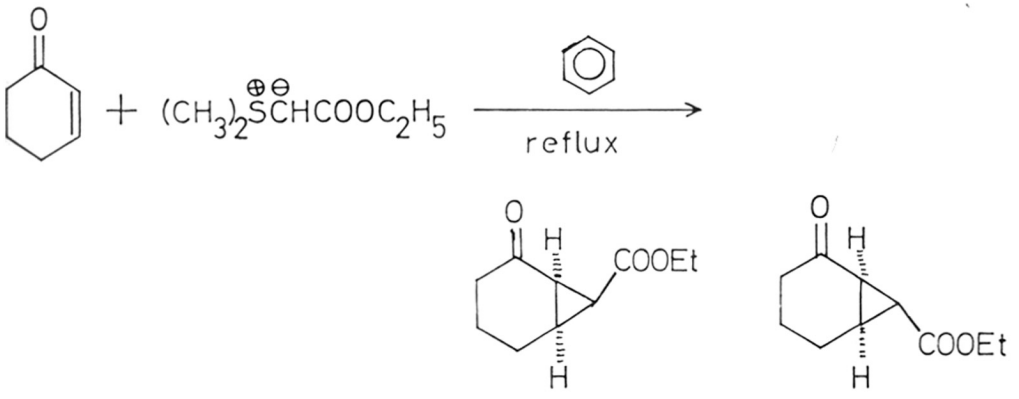
with saturated ketones, suggests that the addition of stabilized ylides to an enone, requires the additional delocalization of charge over the conjugated system in the transition state, for the reaction to occur. In fact, the major problem appears to be the lack of reactivity of the stabilized ylides. Ylides stabilized by only one group normally cyclopropanate the typical Michael acceptors, ketones[15], esters[16] and cyano[17] groupings have also served as the stabilizing functions (chart 4, reaction 10,11,12). On the other hand, ylides stabilized by two such functions such as dimethyl sulfonium dicyano-methylide[18,19] or dimethylsulfonium dibenzoylmethylide[20] fail to react with even the relatively reactive Michael acceptors like chalcone. The delocalization of the negative charge reduces its nucleophilicity, compared to the non-stabilized sulfonium ylides. Thus dimethylsulfonium phenacylide does not react with ketones to form epoxides but does form cyclopropanes with suitable Michael acceptors[21].

Conjugated aldehydes and ketones react with most stabilized ylides to give in good yields the cyclopropanes in which the stabilizing group is <u>trans</u> to the electron withdrawing substituent of the Michael acceptor. Thus 2-methyl propenal or 2-butenal reacts with ethyl (dimethyl-sulfuranylidene) acetate to produce the <u>trans</u> products

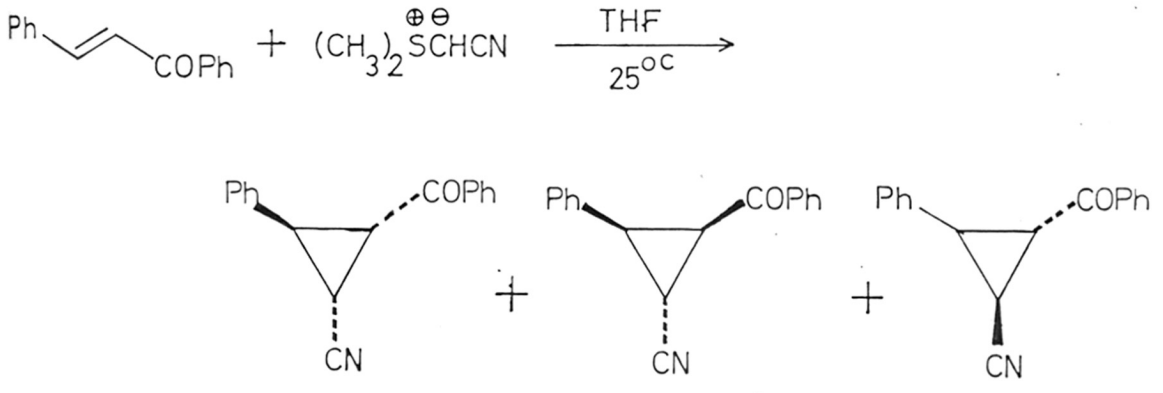
CHART 4



REACTION-10



REACTION-11 1 : 2



REACTION-12 4 : 1 : 25

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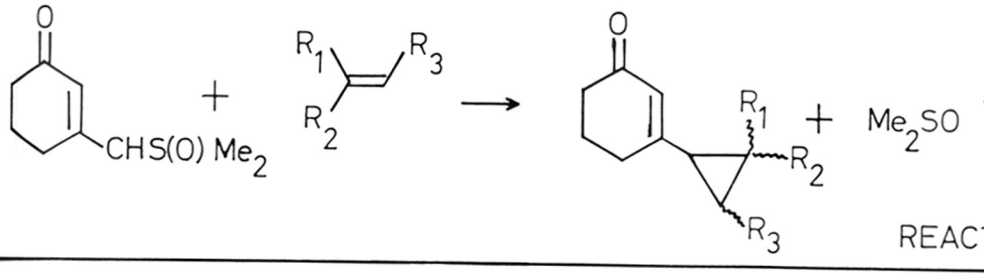
predominantly[16]. Analyses of conformational stabilities of the zwitterions, provide a rational for the observed stereochemistry. Alkyl substitution hinders cyclopropanation. Thus the above ylide (EDSA) cyclopropanates methyl vinyl ketones in 87% yield after only 2.5 hr in refluxing methylene chloride, but requires refluxing in benzene for 18 hr to cyclopropanate 2-methyl-2-penten-4-one in 75% yield[16].

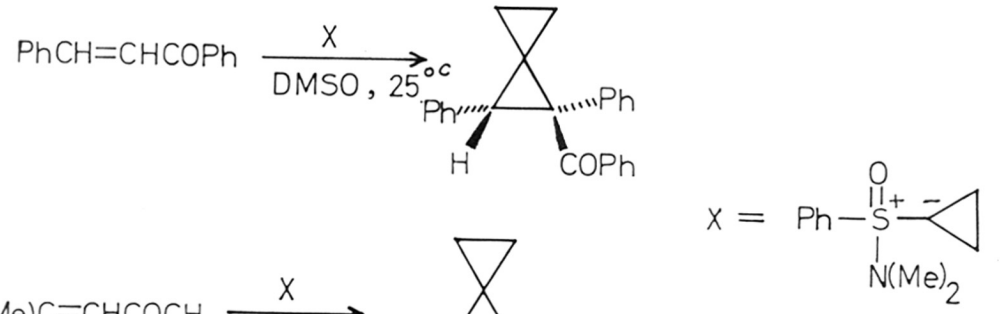
Another class of sulfur ylides where methylene group is replaced by a more stabilized conjugated enone system have also been employed for the synthesis of vinyl cyclopropanes[22] as shown in chart 5, reaction 13.

In addition to the oxosulfonium ylides described above, other modified ylides stabilized by sulfoximidoyl group have been utilized for the synthesis of a variety of spiro cyclopropane compounds. A number of symmetrical s,s-dialkyl and s-alkyl-s-aryl-N-(p-tolylsulfonyl) sulfoximines have been prepared by a general method employing the copper catalysed reaction of p-toluenesulfonyl azide with sulfoxides. Reaction of these sulfoximines with NaH or n-BuLi afforded sulfonimidoyl stabilized ylides, which act as nucleophilic alkylidene transfer reagents. Such type of ylides on reaction with substrates containing electrophilic double bond like (i) ketone (ii) imine (iii) α,β-unsaturated ketone afforded oxiranes, aziridene and spiro fused cycloalkyl cyclopropanes respectively with regio and stereoselectivity[23]. Thus benzalacetophenone on reaction with

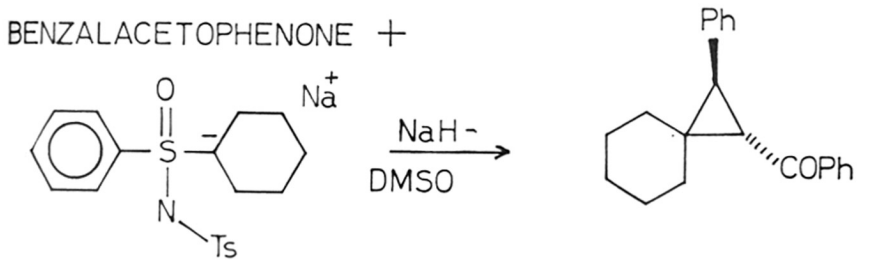
CHART 5



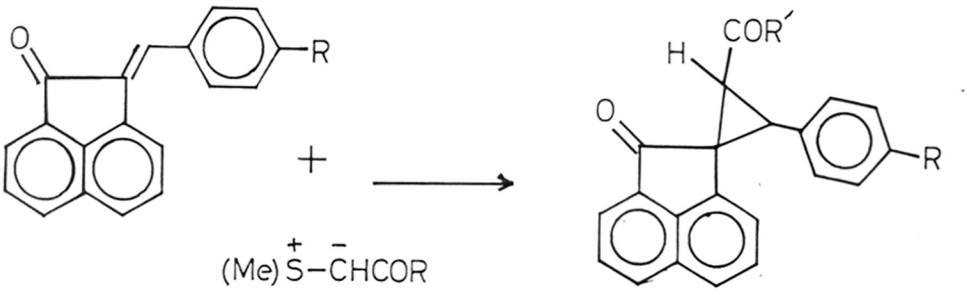
REACTION-13



REACTION-14



REACTION-15



REACTION-16

above ylide gave substituted spiro (2,5) octane (chart 5, reaction 15). In similar manner substituted spiro (2,2) pentanes have also been prepared[24] (chart 5, reaction 14).

The reaction of EDSA has been studied on benzylidene and p-substituted benzylidene derivatives prepared from acenaphthenones[28] to afford the corresponding spiro cyclopropyl keto ester in good yields (chart 5, reaction 16). The cyclopropane derivativs thus obtained, have been assigned the cis-geometry to the cyclopropane on the bases of coupling constants of the cyclopropane protons observed in NMR spectra.

In our laboratory EDSA reaction has been employed to synthesize[29] 2,2-dimethyl-4-oxo/hydroxy/acetoxy-5,6-benzo spiro (2,4) heptane and (2,5) octane-1-carboxylates. Some of which showed moderate insecticidal activity.

∝ (RS)-Cyano-3-phenoxybenzyl (±) cis and (±) trans-2-(2,2-dichlorovinyl) spiro (2,5)-octane-1-carboxylates are reported to exhibit moderatly good insecticidal activity against many species of insects, like cotton-leaf worms, house-fly etc. with a good knockdown effect on flying insects[25]. Esters of the above type are the spirocycloalkyl analogues of the conventional highly potent pyrethroids like cypermethrin, in which the gem-dimethyl grouping on cyclopropane is replaced by a cycloalkyl ring.

In the first chapter, the synthesis of spiro (2,5-octane-1-carboxylate was described . This chapter deals with the syntheses of ethyl/isopropyl/3-phenoxy benzyl/ α-cyano-3-phenoxybenzyl 2-alkyl/aryl-4-oxo/hydroxy/acetoxy-spiro (2,5) octane and spiro (2,4) heptane-1-carboxylates, using EDSA for building up of cyclopropane ring. These esters have been prepared with a view to evaluating them, for possible insecticidal/larvicidal properties. These esters possess a functionalized spiro-cycloalkyl ring in place of unsubstituted cycloalkyl ring and phenyl/2-furyl unit at C-2 position in place of dihalovinyl grouping at C-2. In addition, ester with an isopropyl group at C-2 position, analogues of 2,2,3-trialkyl cyclopropane carboxylates, have also been synthesized.

The strategy employed in the synthesis of the above esters involves initially the preparation of alkylidene/ benzylidene/fufurylidene derivatives of the cycloakanones by an aldol condensation of cycloalkanones with the appropriate aldehydes under basic conditions. The exo α,β-unsaturated ketones thus obtained, were then reacted with ethyl dimethyl sulfuranylidene acetate to furnish the cyclopropane keto esters. The corresponding acids obtained by saponification of ethyl esters, were converted into acid chlorides, which in turn were reacted with isopropanol/3-phenoxy benzyl alcohol/α-(RS) cyano-3-phenoxy

benzyl alcohol to furnish the keto esters (6). The latter were then reduced by $NaBH_4$ to the corresponding hydroxy esters (8), which were then converted to the acetate esters (Ac_2O/py).

PRESENT WORK

Cyclohexanone benzylidene (monomer) derivative (2a) was prepared from the cyclohexanone by an Aldol type condensation with benzaldehyde, under basic condition[26] in 70% yield as a solid; characterized by following spectral data; IR (Nujol): 1680 (>C=O), 1595 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.83 (m, 4H, 2 x $-CH_2-$ non-adjacent to carbonyl and double bond), 2.36, 2.80 (m each, 2H each, methylenes adjacent to carbonyl and double bond), 7.43 (brs, 6H, aromatic and olefinic protons).

Similarly 2b-e and 2f[27] (dimer) were prepared by condensing desired aldehydes with corresponding cyclo-alkanones and characterized as follows:

2b: yield 65%; IR (liquid film): 1690 (>C=O), 1630 (>C=CH-) cm^{-1}; NMR ($CDCl_3$): 0.96, 1.06 (s each, 3H each, 2 x $-CH_3$ of isopropyl), 1.8 (m, 4H, 2 x $-CH_2-$ non-adjacent to carbonyl and double bond), 2.38 (m, 5H, 2 x $-CH_2-$ adjacent to carbonyl and double bond and $-CH(CH_3)_2$], 6.2 (d, 1H, J=8 Hz, olefinic proton).

2c: yield 71%; IR (liquid film): 1710 (>C=O of cyclo-pentenone), 1622 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 2.06 (m, 4H, two methylenes adjacent and non-adjacent to double bond), 2.91 (m, 2H, $-CH_2-$ adjacent to carbonyl), 7.3 (m, 6H, aromatic and olefinic protons).

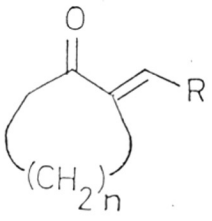
1

a n = 3

b n = 2

R-CHO

aq. NaOH



2

a n = 3 , R = Ph

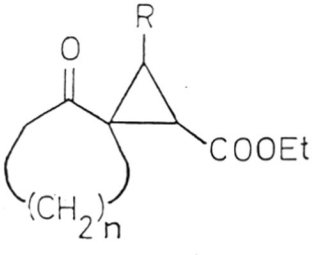
b n = 3 , R = 

c n = 2 , R = Ph

d n = 3 , R = 

e n = 2 , R = 

EDSA



3

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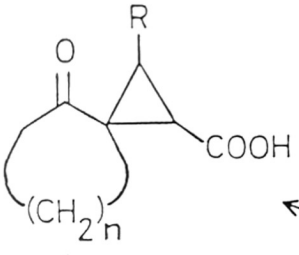
b n = 3 , R = 

c n = 2 , R = Ph

d n = 3 , R = 

e n = 2 , R = 

Saponification



4

a n = 3 , R = Ph

b n = 3 , R =

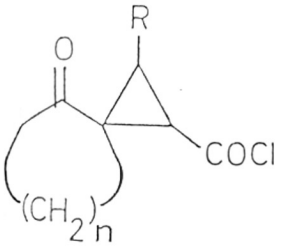
c n = 2 , R = Ph

d n = 3 , R = 

$SOCl_2$/PhH

Δ

5



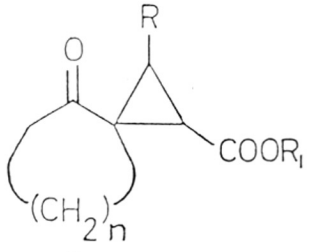
5

a n = 3 , R = Ph

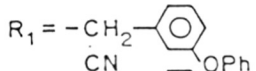
b n = 3 , R = 

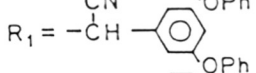
c n = 2 , R = Ph

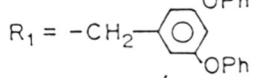
R_1-OH / PhH



6

a n = 3 , R = Ph , R_1 = 

b n = 3 , R = Ph , R_1 = 

c n = 3 , R =  , R_1 = 

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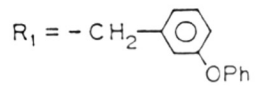
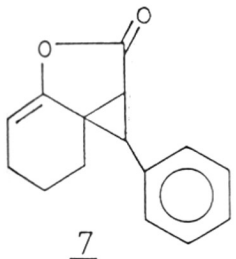
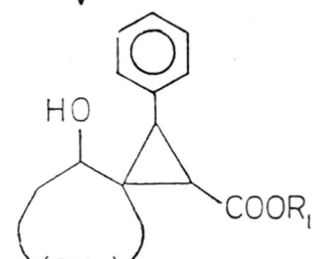
e n = 2 , R = Ph , R_1 = 

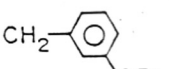


7

$NaBH_4$ / MeOH



8

a n = 3 , R_1 = 

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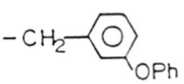
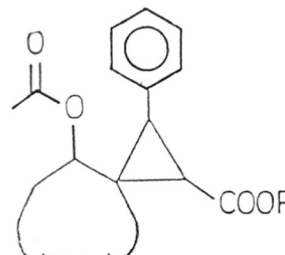
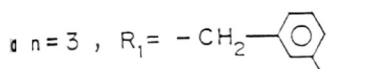
c n = 2 , R_1 = 

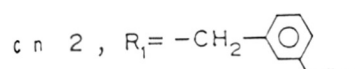
$(CH_3CO)_2O$/py.

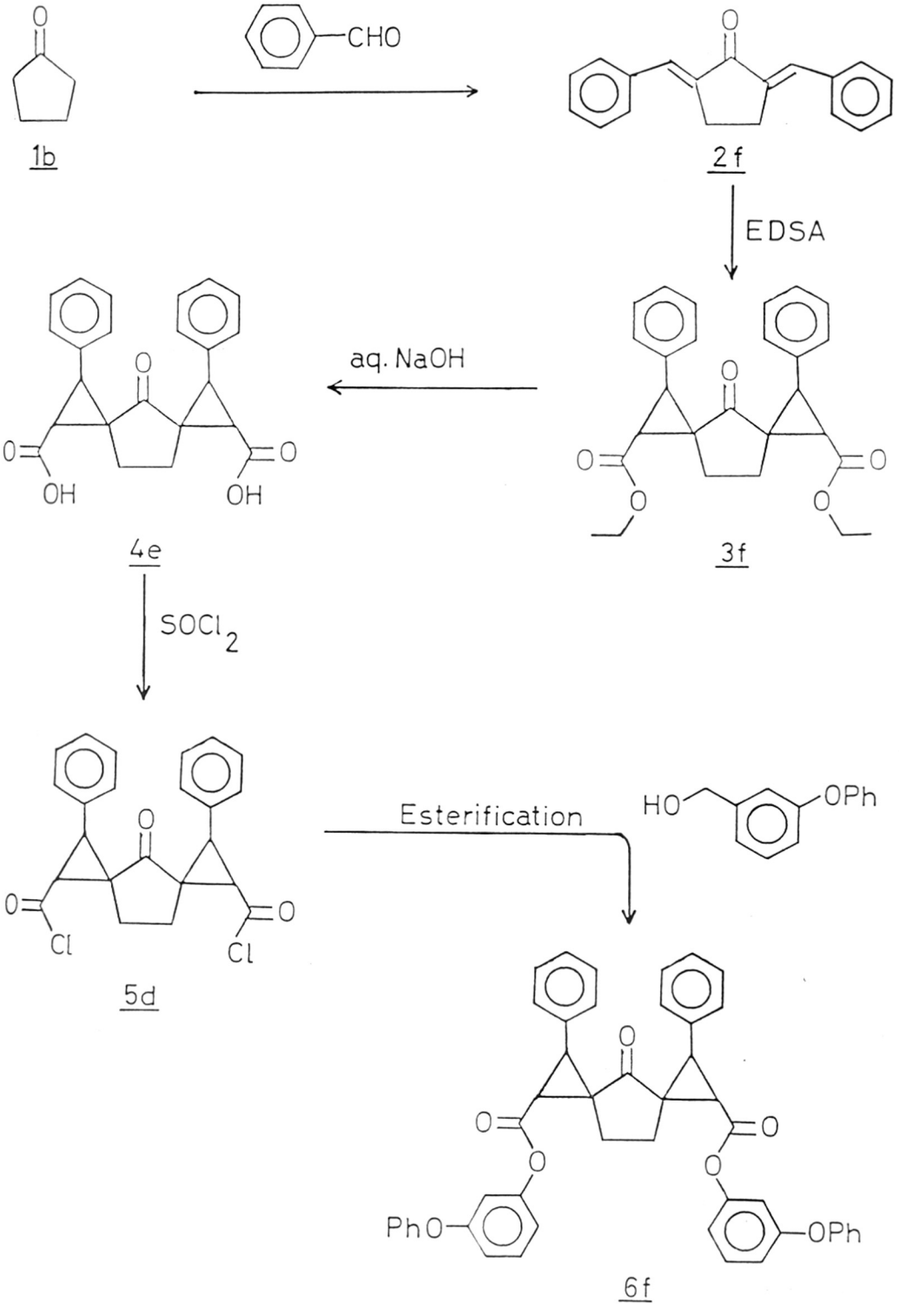


9

a n = 3 , R_1 = 

b n = 3 , R_1 = 

c n 2 , R_1 = 


CHO
1b
2f
EDSA
3f
aq. NaOH
4e
SOCl2
5d
Esterification
HO
OPh
6f
PhO
OPh

2d: 64% yield; IR (liquid film): 1670 (>C=O), 1600 (furan ring unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.85 (m, 4H, 2 x $-CH_2-$ non-adjacent to carbonyl and double bond), 2.38, 2.71 (m each, 4H, two methylenes, adjacent to carbonyl and double bond), 6.48 (m, 2H, two β-protons of furan ring), 7.2 (m, 1H, α-proton of furan ring), 7.45 (s, 1H, olefinic proton).

2e: yield 59%; IR (Nujol): 1715 (>C=O of cyclopentenone), 1630 (furan ring unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.95 (m, 4H, two methylenes adjacent and non-adjacent to double bond), 2.98 (m, 2H, $-CH_2-$adjacent to carbonyl), 6.55 (m, 2H, two β-protons of furan ring), 7.08 (m, 1H, α-proton of furan ring), 7.38 (s, 1H, olefinic proton).

2f: yield 78%; IR (Nujol): 1690 (>C=O of cyctopentenone), 1628 (olefinic unsaturation), 1600 (aromatic unsaturation) cm^{-1}; NMR (CCl_4): 3.12 (brs, 4H, two methylenes of cyclopentenone), 7.5 (m, 12H, 2 x 5H aromatic protons and 2 x 1H olefinic protons).

Cyclohexanone benzylidene derivative (2a) was reacted with ethyl dimethyl sulfuranylidene acetate to afford keto ethyl ester (3a) which contains spiro fused substituted cyclopropane, in 75% yield; characterized by spectral data: M.S.: m/e 272 (M^+); IR (liquid film): 1732 (ester >C=O), 1705 (ketone>C=O), 1610 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.3 (t, 3H, J=6 Hz, ester $-CH_3$), 1.81 (m, 6H, 3 x $-CH_2-$ non-adjacent to ketone), 2.31 (m, 2H, $-CH_2-$adjacent

to ketone), 2.93 (d, 1H, J=7 Hz, C_1-H), 3.41 (d, 1H, J=7 Hz, C_2-H), 4.2 (q, 2H, J=6 Hz, ester $-CH_2-$), 7.2 (m, 5H, aromatic protons).

Similarly other conjugated ketones were reacted with EDSA to obtain the spiro fused cycloalkyl cyclopropane carboxylates (3b-f) and characterized by following spectral data:

3b: 70% yield: M.S. m/e 238 (M^+); IR (liquid film): 1732 (ester >C=0), 1702 (ketone >C=0) cm^{-1}; NMR ($CDCl_3$); 0.84 (m, 6H, 2 x $-CH_3$ of isopropyl), 1.14 (t, 3H, J=8 Hz, ester $-CH_3$), 1.78 [m, 9H, 4 x $-CH_2-$ and $-CH(CH_3)_2$], 2.16 (m, 1H, C_2-H), 2.5 (d, 1H, J=5 Hz, C_1-H), 4.04 (q, 2H, J=8 Hz, ester $-CH_2-$).

3c: 76% yield; M.S.: m/e 258 (M^+): IR (liquid film): 1740 (cyclopentanone >C=0), 1720 (ester>C=0), 1600 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.3 (t, 3H, J=7 Hz, ester $-CH_2$), 2.16 (m, 6H, 3 x $-CH_2$ of cyclopentyl), 2.78 (d, 1H, J=7 Hz, C_1-H), 3.01 (d, 1H, J=7 Hz, C_2-H), 4.16 (q 2H, J=7 Hz, ester $-CH_2-$), 7.18 (s, 5H, aromatic protons).

3d: yield 64%; M.S.: m/e 262 (M^+); IR (liquid film): 1730 (ester >C=0), 1680 (ketone >C=0), 1595 (furan ring unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.13 (t, 3H, J=7 Hz, ester $-CH_3$), 1.78 (m, 6H, 3 x $-CH_2-$ non adjacent to ketone) 2.03 (m, 2H, $-CH_2-$adjacent to ketone), 2.56 (d, 1H, J=6 Hz, C_1-H), 2.9 (d, 1H, J=6 Hz, C_2-H), 3.96 (q, 2H,

J=7 Hz, ester $-CH_2-$), 5.7 (br d, β-proton of furan), 6.01 (m, 1H, another β-proton of furan), 7.11 (m, 1H, ∝-proton of furan).

3e: yield 67%; M.S.: m/e 248 (M^+); IR (liquid film): 1742 (cyclopentanone >C=0), 1725 (ester >C=0), 1605 (furan ring unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.27 (t, 3H, J=7 Hz, ester $-CH_3$), 2.23 (m, 6H, 3 x $-CH_2$-cyclopentyl protons), 2.75 (d, 1H, J=6 Hz, C_1-H), 3.2 (d, 1H, J=6 Hz, C_2-H), 4.18 (q, 2H, J=7 Hz, ester $-CH_2-$), 6.17 (d, 1H, J=4 Hz, β-proton of furan), 6.31 (m, 1H, another β-proton of furan), 7.32 (m, 1H, ∝-proton of furan).

3f: yield 81%; M.S.: m/e 359 (M^+); IR (nujol): 1735 (cyclopentanone >C=0), 1718 (ester >C=0), 1605 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.3 (t, 6H, J=7 Hz, 2 x ester $-CH_3$), 2.78 (d, 2H, J=8 Hz, 2 x C_1-H), 3.01 (d, 2H, J=8 Hz, 2 x C_2-H), 4.22 (q, 4H, J=7 Hz, 2 x ester $-CH_2-$), 6.93 (m, 10H, 2 x 5 aromatic protons).

Keto ethyl ester (3a) was then saponified to give the corresponding keto carboxylic acid (4a); characterized as follows: yield 86%; M.S.: m/e 244 (M^+), IR (Nujol): 1710 (ketone >C=0), 1695 (acid >C=0), 1605 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 1): 1.85 (m, 6H, 3 x $-CH_2-$ non-adjacent to ketone), 2.41 (m, 2H, $-CH_2-$ adjacent to ketone), 2.99(d, 1H, J=7 Hz, C_1-H), 3.43 (d, 1H, J=7 Hz, C_2-H), 7.2 (m, 5H, aromatic protons).

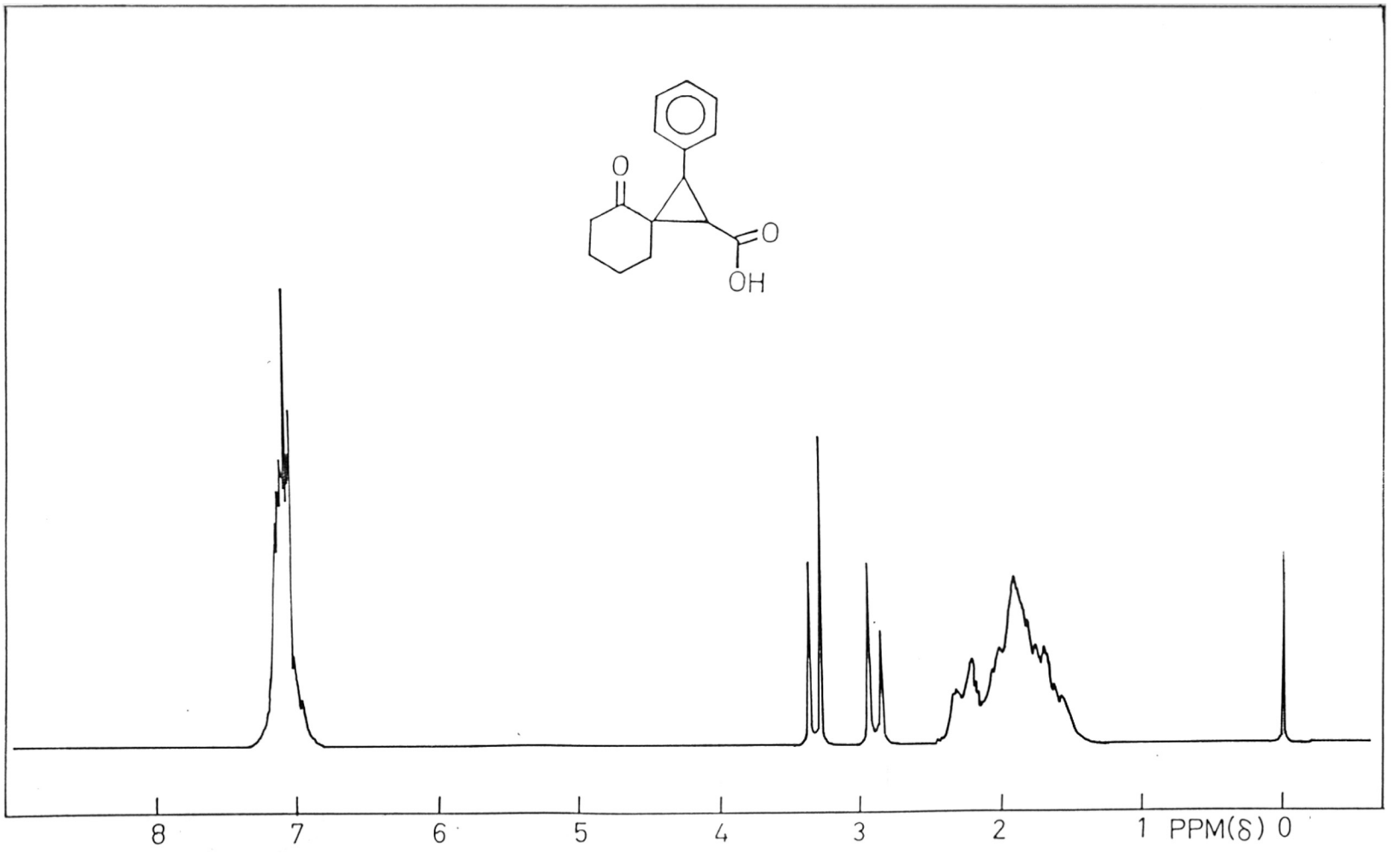


FIG 1

Similarly other ethyl esters were saponified to give the corresponding acids (4b-e) and showed the following spectral properties:

4b: yield 90%; M.S.: m/e 210 (M^+); IR (Nujol): broad band at 1730 (ketone and acid >C=0); NMR (CCl_4): 1.0 (d, 6H, J=5 Hz, 2 x $-CH_3$ of isopropyl), 2.05 [m, 11H, 4 x $-CH_2-$ of cyclohexyl, C_1-H, C_2-H and $-CH(CH_3)_2$].

4c: 92% yield: M.S. m/e 230 (M^+); IR (Nujol): 1730 (ketone >C=0), 1680 (acid >C=0), 1600 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 2.26 (m, 6H, 3 x $-CH_2-$ cyclopentyl protons), 2.93 (d, 1H, J=7 Hz, C_1-H), 3.18 (d, 1H, J=7 Hz, C_2-H), 7.26 (m, 5H, aromatic protons).

4d: 87% yield; M.S.: m/e 234 (M^+); IR (Nujol): 1720 (ketone >C=0), 1697 (acid>C=0), 1605 (furan ring unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 2): 2.0 (m, 8H, 4 x $-CH_2-$ cyclohexyl proton), 2.81 (d, 1H, J=7.4 Hz, C_1-H), 3.18 (d, 1H, J=7.4 Hz, C_2-H), 5.9 (d, 1H, J=4 Hz, β-proton of furan), 6.18 (m, 1H, another β-proton of furan), 7.22 (m, 1H, ∝-proton of furan).

4e: yield 85%; M.S.: m/e 376 (M^+); IR (Nujol): 1730 (cyclopentanone >C=0), 1695 (acid>C=0), 1610 (aromatic unsaturation) cm^{-1}; NMR was not taken because of insolubility of compound in any solvent.

The keto carboxylic acid (4a) was converted to acid chloride (5a) by refluxing with $SOCl_2$ in benzene. It showed IR (liquid film) bands at 1784 (acid chloride >C=0),

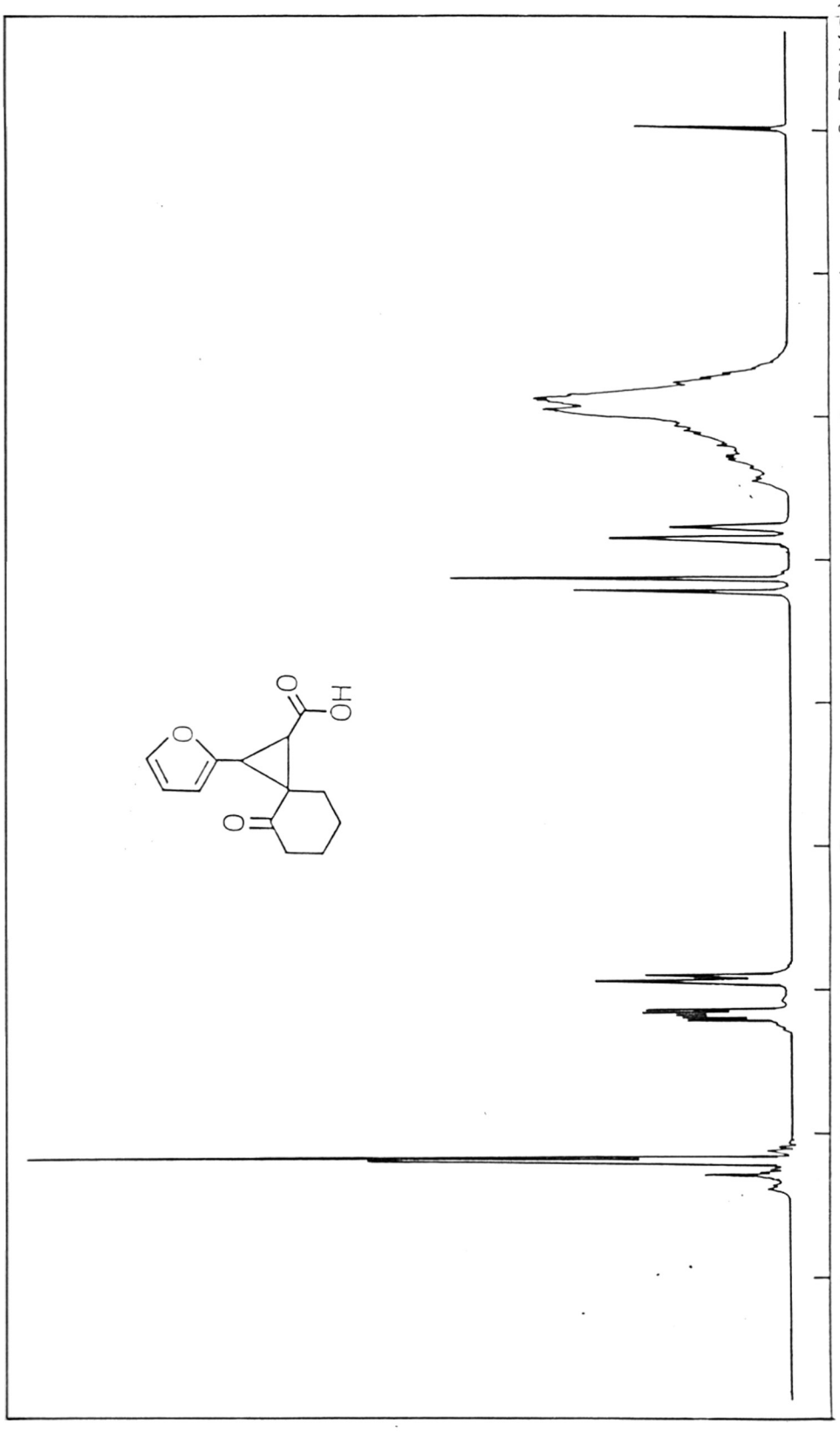


FIG.2

1700 (ketone >C=0), 1603 (aromatic unsaturation) cm^{-1}.

Similarly acid chlorides (5b and c) were prepared, which showed IR bands as follows:

5b: 1785 (acid chloride >C=0), 1705 (ketone >C=0) cm^{-1}.

5c: 1790 (acid chloride >C=0), 1740 (cyclopentanone >C=0), 1610 (aromatic unsaturation) cm^{-1}.

Without further characterization acid chlorides were used for esterification with different alcohol moieties.

3-Phenoxy benzyl ester (6a) was prepared in 75% yield by stirring benzene solution of acid chloride (5a) with benzene solution of 3-phenoxy benzyl alcohol and pyridine at room temperature; characterized by following spectral data; M.S.: m/e 426 (M^+): IR (Nujol) (Figure 4): 1725 (ester >C=0), 1700 (ketone>C=0), 1585 (aromatic unsaturation cm^{-1}; NMR ($CDCl_3$) (Figure 3): 1.86 (m, 6H, 3 x $-CH_2-$ non-adjacent to ketone), 2.33 (m, 2H, $-CH_2-$adjacent to ketone), 3.00 (d, 1H, J=8 Hz, C_1 -H), 3.48 (d, 1H, J=8 Hz, C_2 -H), 5.24 (s, 2H, benzylic $-CH_2-$), 7.34 (m, 14H, aromatic protons).

Similarly other esters (6b-f) were prepared and characterized by following spectral data:

6b: 59% yield; M.S.: m/e 451 (M^+), IR (liquid film): 1740 (ester >C=0), 1700 (ketone>C=0), 1585 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 5): 2.01 (m, 8H, 4 x $-CH_2-$ cyclohexyl protons), 3.01 (d, 1H, J=7 Hz, C_1 -H), 3.44 (d, 1H, J=7 Hz, C_2-H), 6.35, 6.41 (2s, 1H,

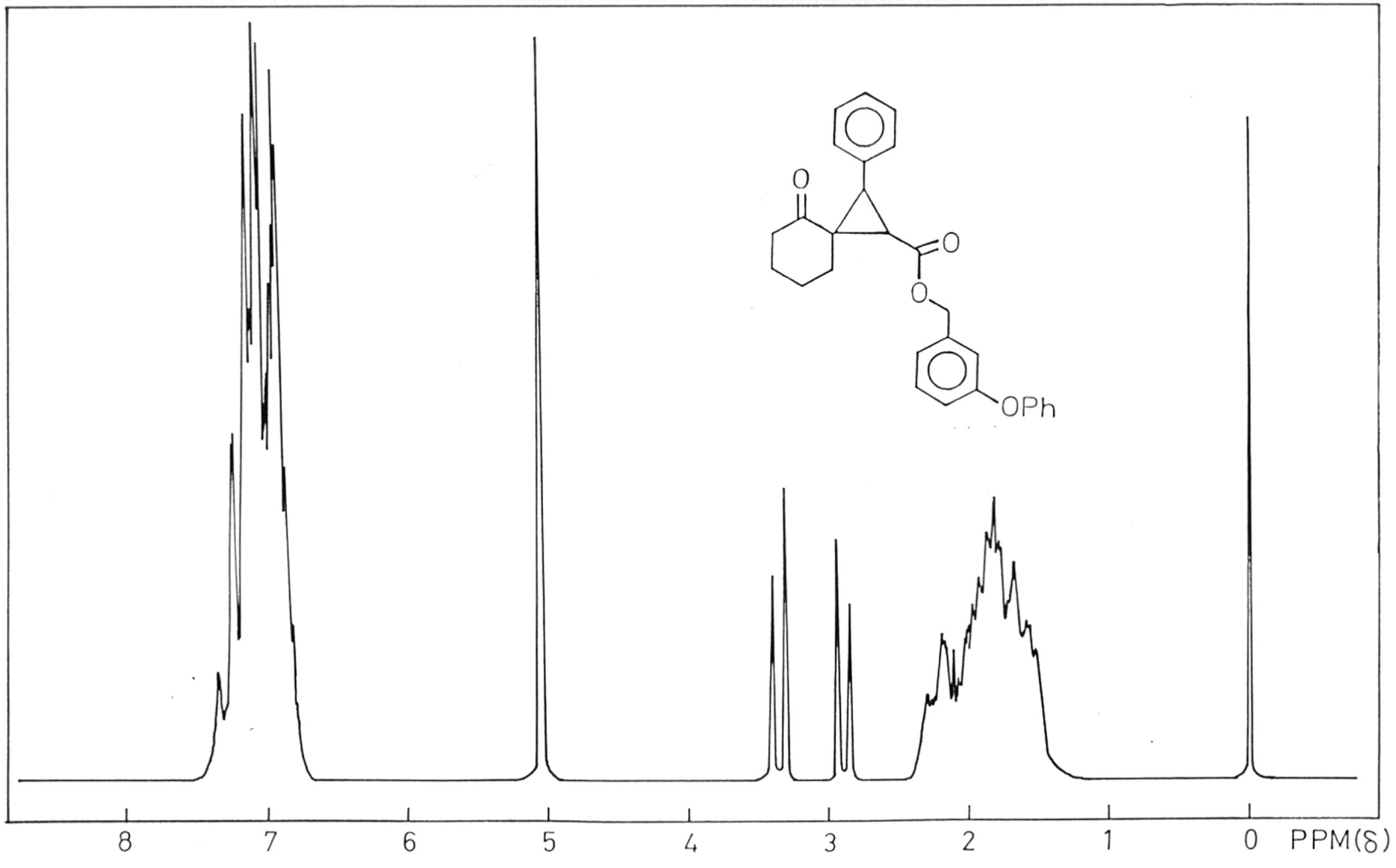
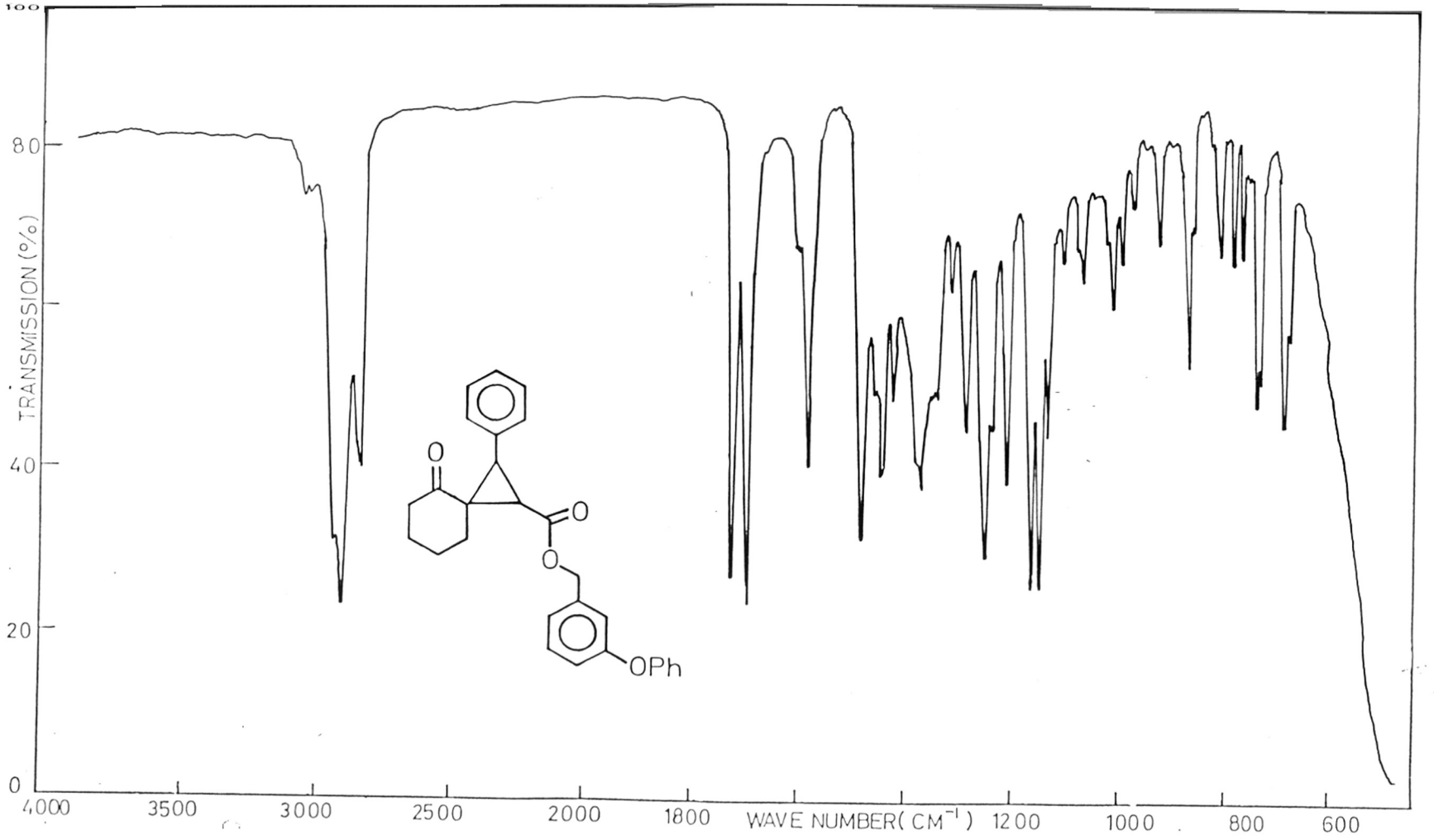


FIG. 3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TRANSMISSION (%)
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OPh

FIG. 4

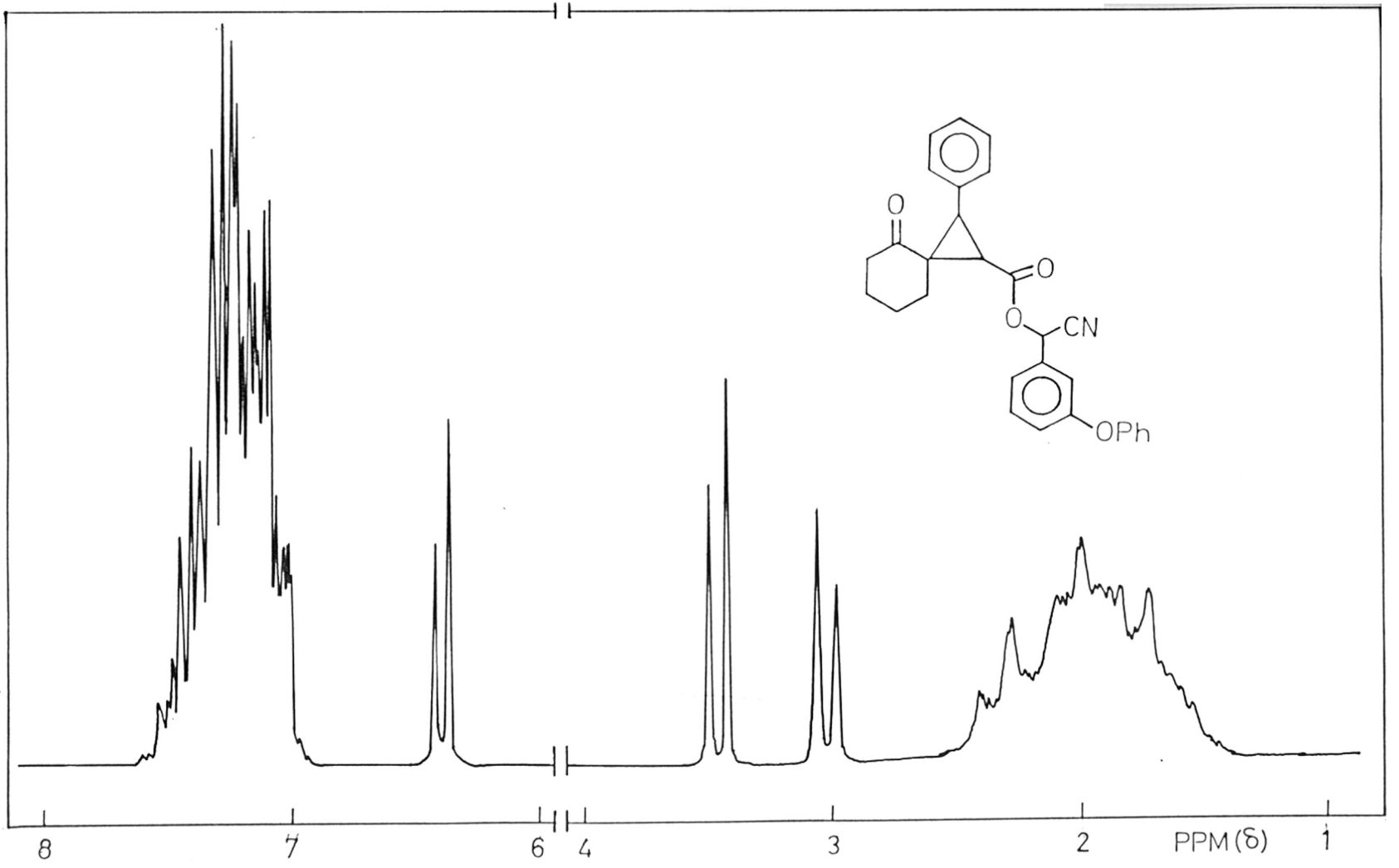


FIG. 5

-CH(CN)- of two diastereomers), 7.23 (m, 14H, aromatic protons).

6c: yield 64%; M.S.: m/e 392 (M^+), IR (liquid film): 1740 (ester >C=0), 1705 (ketone >C=0), 1595 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 0.9 (m, 6H, 2 x $-CH_3$ of isopropyl), 1.8 [m, 9H, 4 x $-CH_2$, cyclohexyl protons and $-CH(CH_3)_2$], 2.36 (m, 1H, C_2 -H), 2.66 (d, 1H, J=6 Hz, C_1-H), 5.08 (s, 2H, benzylic $-CH_2-$), 7.22 (m, 9H, aromatic protons).

6d: 56% yield; M.S.: m/e 286 (M^+); IR (Nujol) (Figure 7): 1725 (ester >C=0), 1705 (ketone>C=0), 1605 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 6): 1.27 (d, 6H, J=8 Hz, 2 x $-CH_3$ of isopropyl), 1.9 (m, 6H, 3 x $-CH_2-$ non-adjacent to ketone), 2.24 (m, 2H, $-CH_2-$ adjacent to ketone), 2.94 (d, 1H, J=8 Hz, C_1-H), 3.34 (d, 1H, J=8 Hz, C_2-H), 5.06 [m, 1H, $-CH(CH_3)_2$], 7.26 (m, 5H, aromatic protons).

6e: 70% yield; M.S.: m/e 412 (M^+); IR (liquid film): 1740 (cyclopentanone >C=0), 1725 (ester >C=0), 1585 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 2.18 (m, 6H, 3 x $-CH_2-$ cyclopentyl protons), 2.96 (d, 1H, J=6 Hz, C_1 -H), 3.14 (d, 1H, J=6 Hz, C_2-H), 5.18 (s, 2H benzylic $-CH_2-$), 7.22 (m, 14H, aromatic protons).

6f: yield 76%; M.S.: m/e 740 (M^+); IR (Nujol): 1735 (cyclopentanone >C=0), 1718 (ester >C=0), 1580 (aromatic

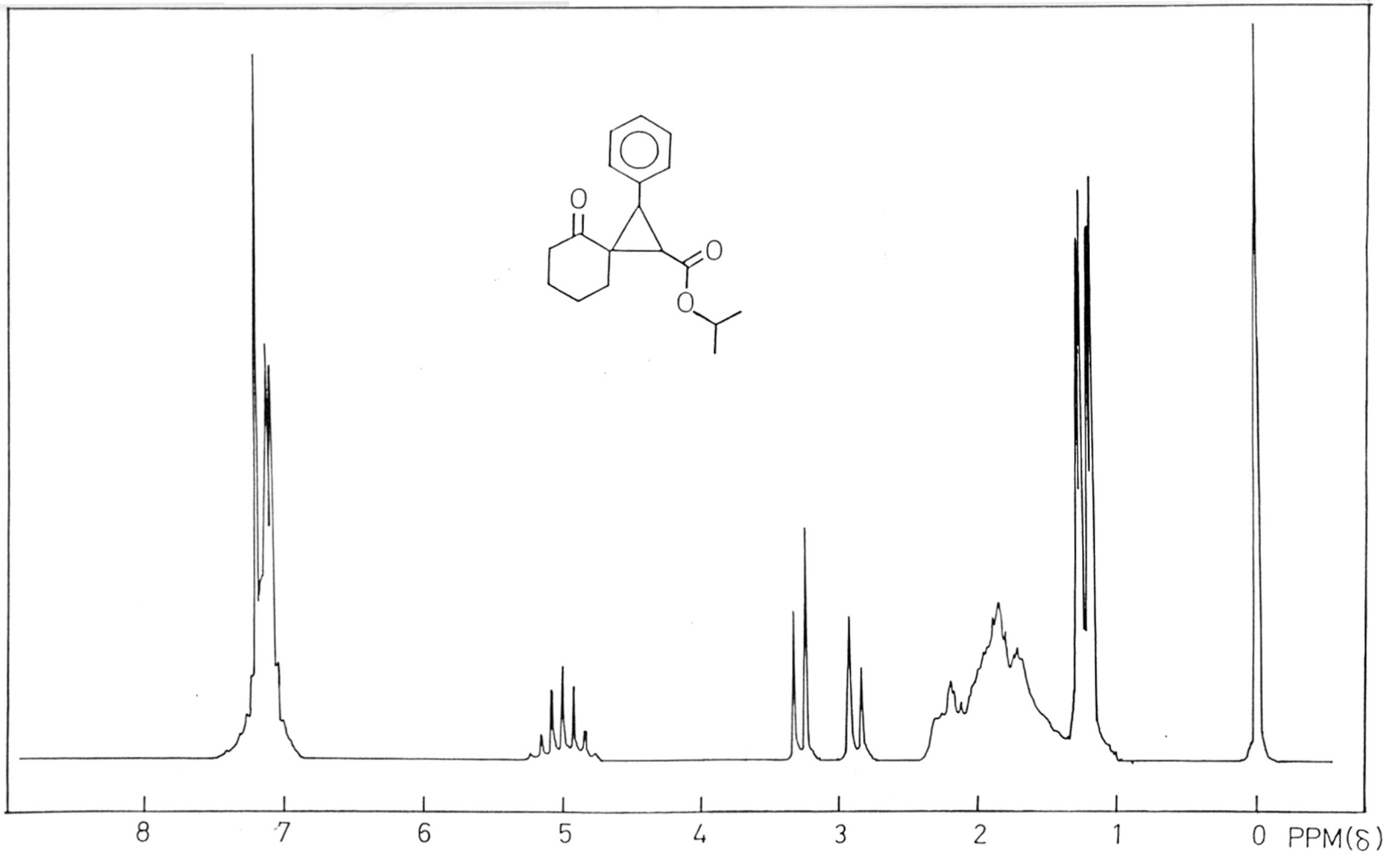
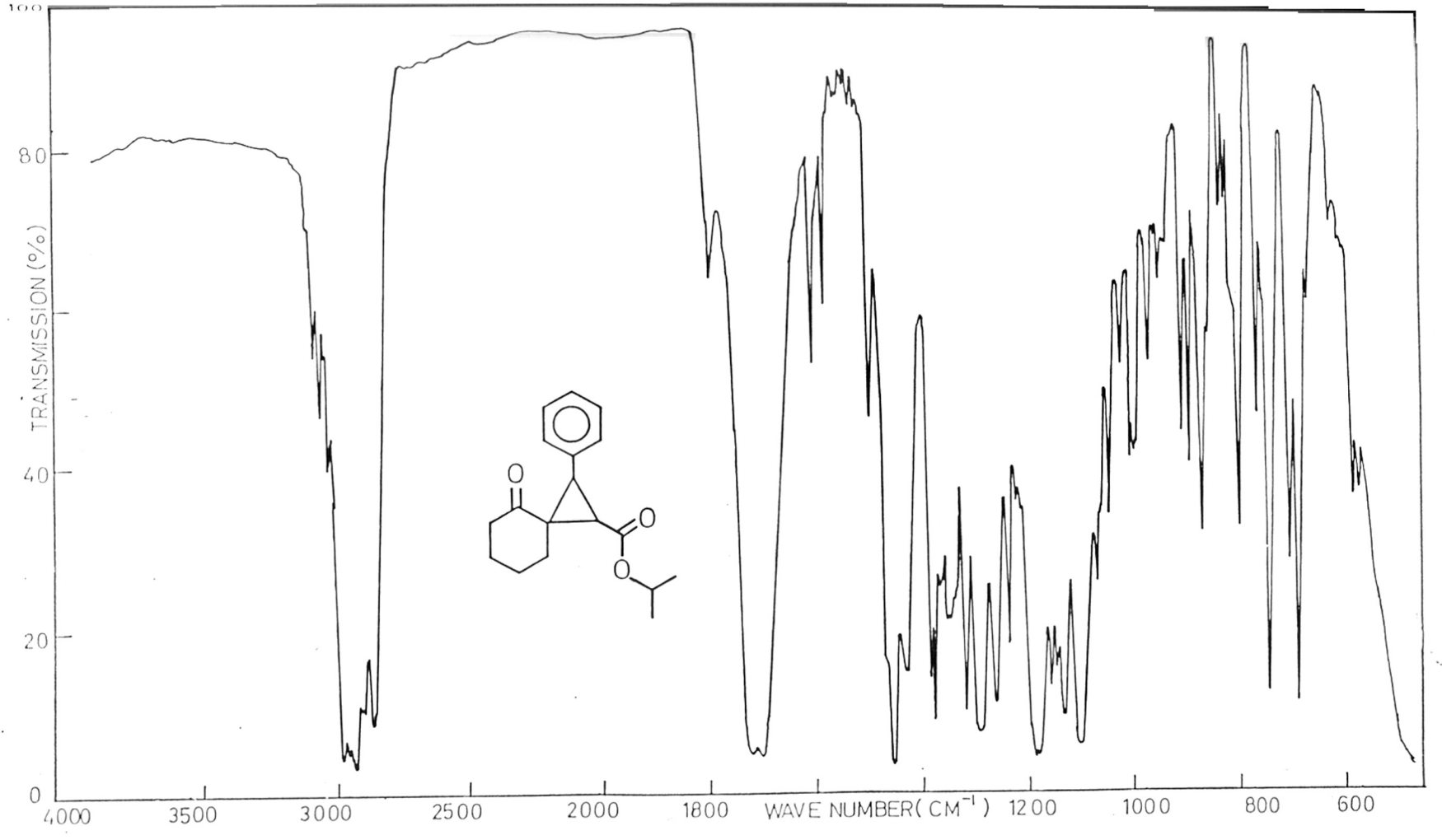


FIG. 6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3500
3000
2500
2000
1800
WAVE NUMBER(CM^{-1})
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1000
800
600
O
O
O

FIG.7

unsaturation) cm^{-1}; NMR ($CDCl_3$): 2.36 (m, 4H, 2 x $-CH_2-$ cyclopentyl protons), 2.82 (d, 2H, J=7 Hz, 2 x C_1 -H), 3.1 (d, 2H, J=7 Hz, 2 x C_2 -H), 5.14 (s, 4H, 2 x benzylic $-CH_2-$), 7.16 (m, 28H, aromatic protons).

During the preparation of isopropyl ester (6d) from the acid chloride (5a) another minor reaction product was obtained in 10% yield, which has been identified as the enol lactone (7) by following spectral data:
M.S.: m/e 226 (M^+); IR (Nujol) (Figure 9): 1785 (γ-lactone), 1695 (enolic double bond), 1600 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 8): 1.56 (m, 4H, 2 x $-CH_2-$ non-adjacent to double bond), 2.22 (m, 2H, $-CH_2-$ adjacent to double bond), 2.66 (d, 1H, J=3 Hz, C_1 -H), 2.8 (d, 1H, J=3 Hz, C_2-H), 5.34 (t, 1H, J=3 Hz, olefinic proton), 7.33 (m, 5H, aromatic protons). ^{13}C NMR spectrum ($CDCl_3$) showed chemical shifts of δ (ppm) with multiplicities (from TMS internal standard) as follows: C-9 (s) -172.34, C-4 (s)-158.62, C-1' (s) - 133.44, C-2' to C-6' (d) - 128.38, 127.49 and 126.94, C-5 (d) - 99.08, C-6 (t) - 35.48, C-1 (d) - 33.73, C-2 (d) - 27.37, C-3 (s) - 22.75, C-7 (t) - 21.45, C-8 (t) - 20.39.

Sodium borohydride reduction of 6a gave the hydroxy ester (8a) in 95% yield, identified by following spectral data:

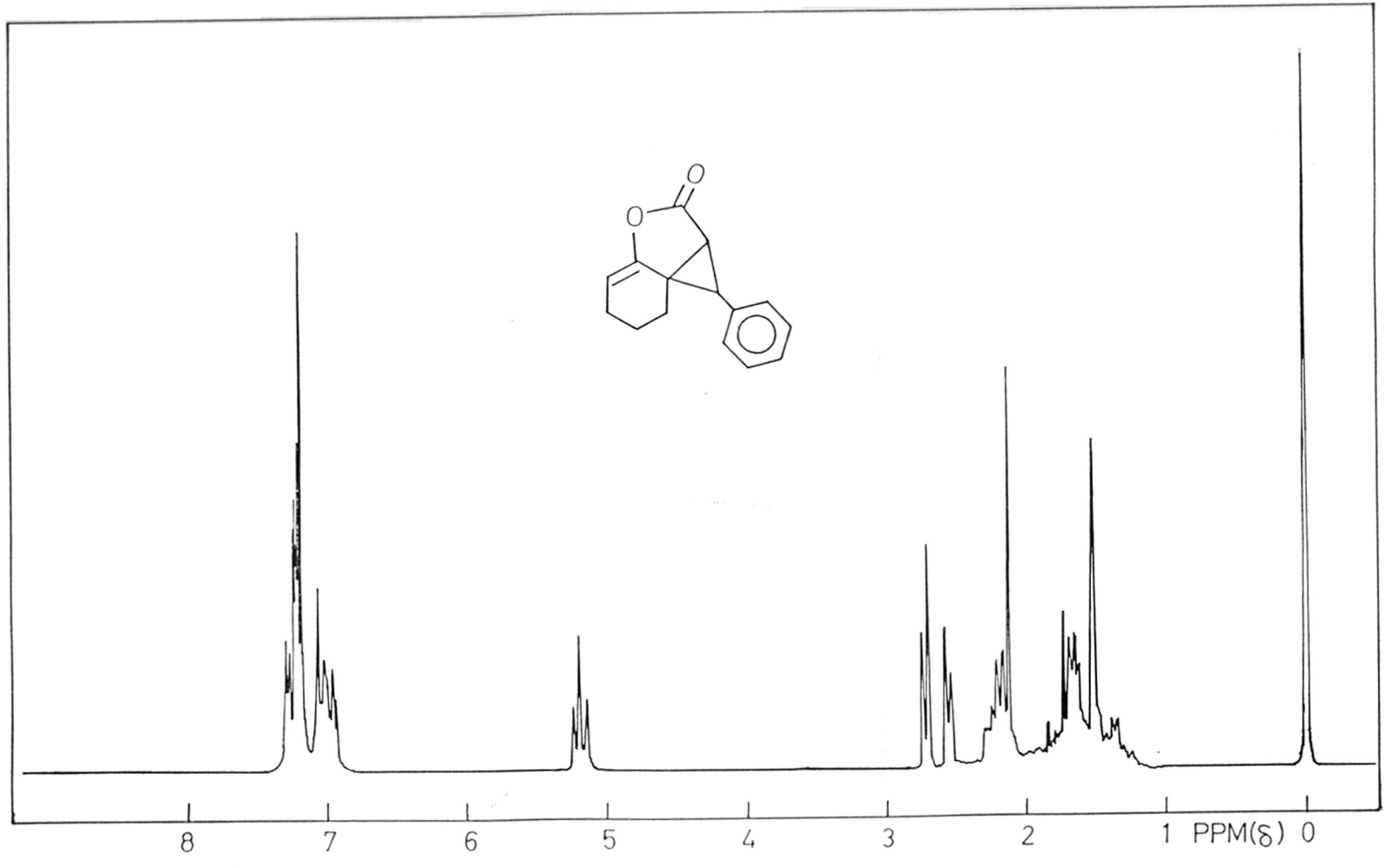
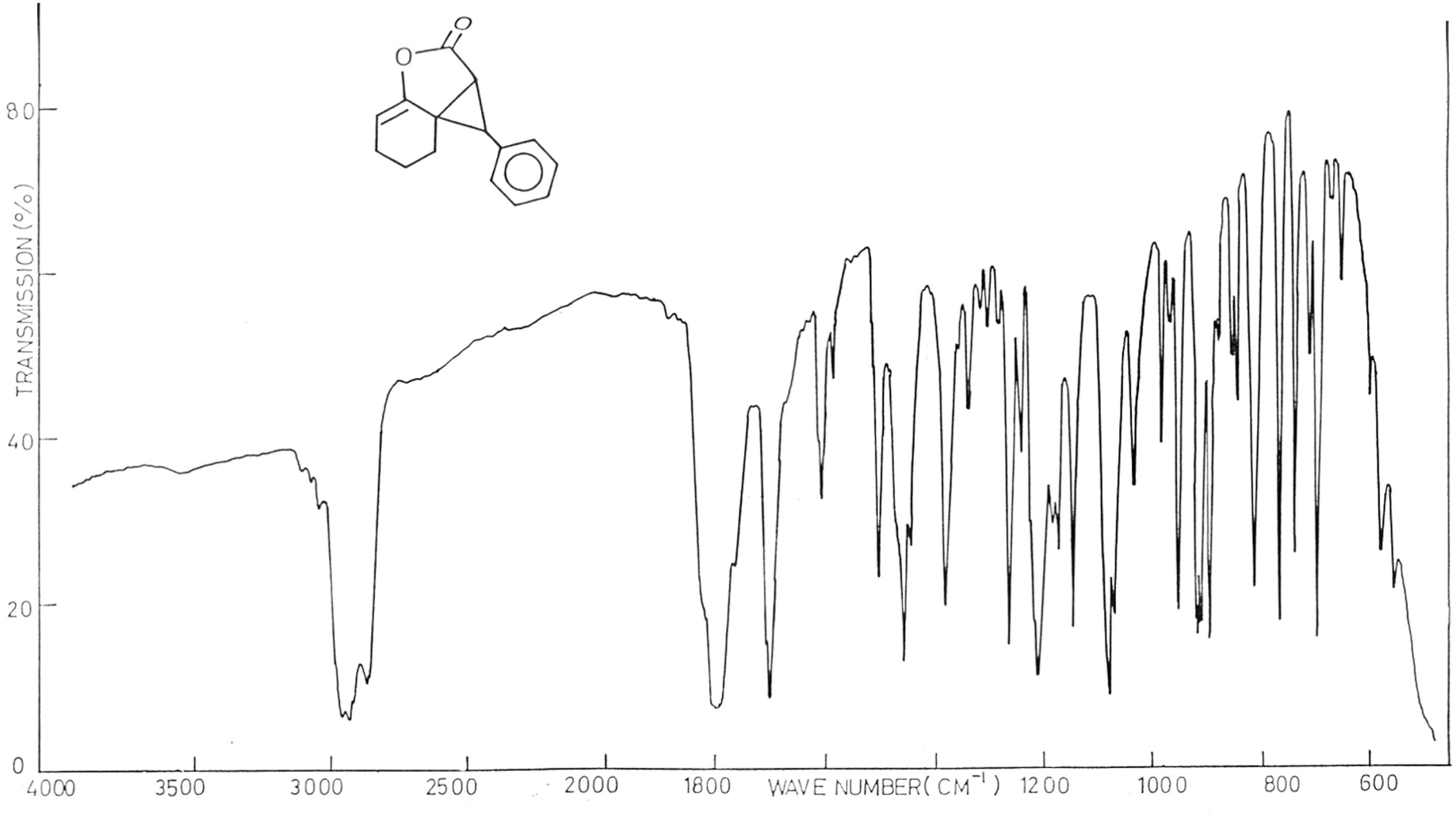


FIG. 8


TRANSMISSION (%)
80
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WAVE NUMBER(CM^{-1})
1200
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800
600
O
O

FIG. 9

M.S.: m/e 428 (M^+); IR (liquid film): 3440 (-OH), 1728 (ester >C=0), 1585 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 10): 1.55 (m, 8H, 4 x $-CH_2-$ cyclohexyl protons), 2.05 (m, 1H, C_1 -H of both diastereomers), 2.68 (d, 1H, J=6 Hz, C_2 -H), 3.05 (br s, 1H, -CH(OH)-), 4.51, 5.1 (2 s, 2H, benzylic $-CH_2-$ of two diastereomers), 7.1 (m, 14H, aromatic protons).

Similarly 8b and 8c were prepared and characterized.

8b: yield 96%; M.S.: m/e 288 (M^+); IR (Nujol): 3470 (-OH), 1715 (ester >C=0), 1605 (aromatic unsaturation) cm^{-1}; NMR (CCl_4): 1.27 (d, 6H, J=8 Hz, 2 x $-CH_3$ of isopropyl), 1.56 (m, 8H, 4 x $-CH_2-$ cyclohexyl protons), 1.95 (d, 1H, J=6 Hz, C_2 -H), 2.61 (d, 1H, J=6 Hz, C_1 -H), 3.01 (br s, 1H, -CH(OH)-), 4.93 (m, 1H, $-CH(CH_3)_2$), 7.13 (br s, 5H, aromatic protons).

8c: yield 90%; M.S.: m/e 414 (M^+); IR (liquid film): 3420 (-OH), 1730 (ester >C=0), 1590 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.78 (m, 6H, 3 x $-CH_2-$cyclopentyl protons), 2.41 (m, 1H, C_1 -H of two diastereomers), 2.92 (d, 1H, J=6 Hz, C_2-H), 3.83 (br t, 1H, -CH(OH)-), 4.64 and 5.11 (2 s, 2H, benzylic $-CH_2-$ of two diastereomers), 7.13 (m, 14H, aromatic protons).

Above hydroxy esters were acetylated using acetic anhydride/pyridine, purified by column chromatography/ crystallization and characterized as follows:

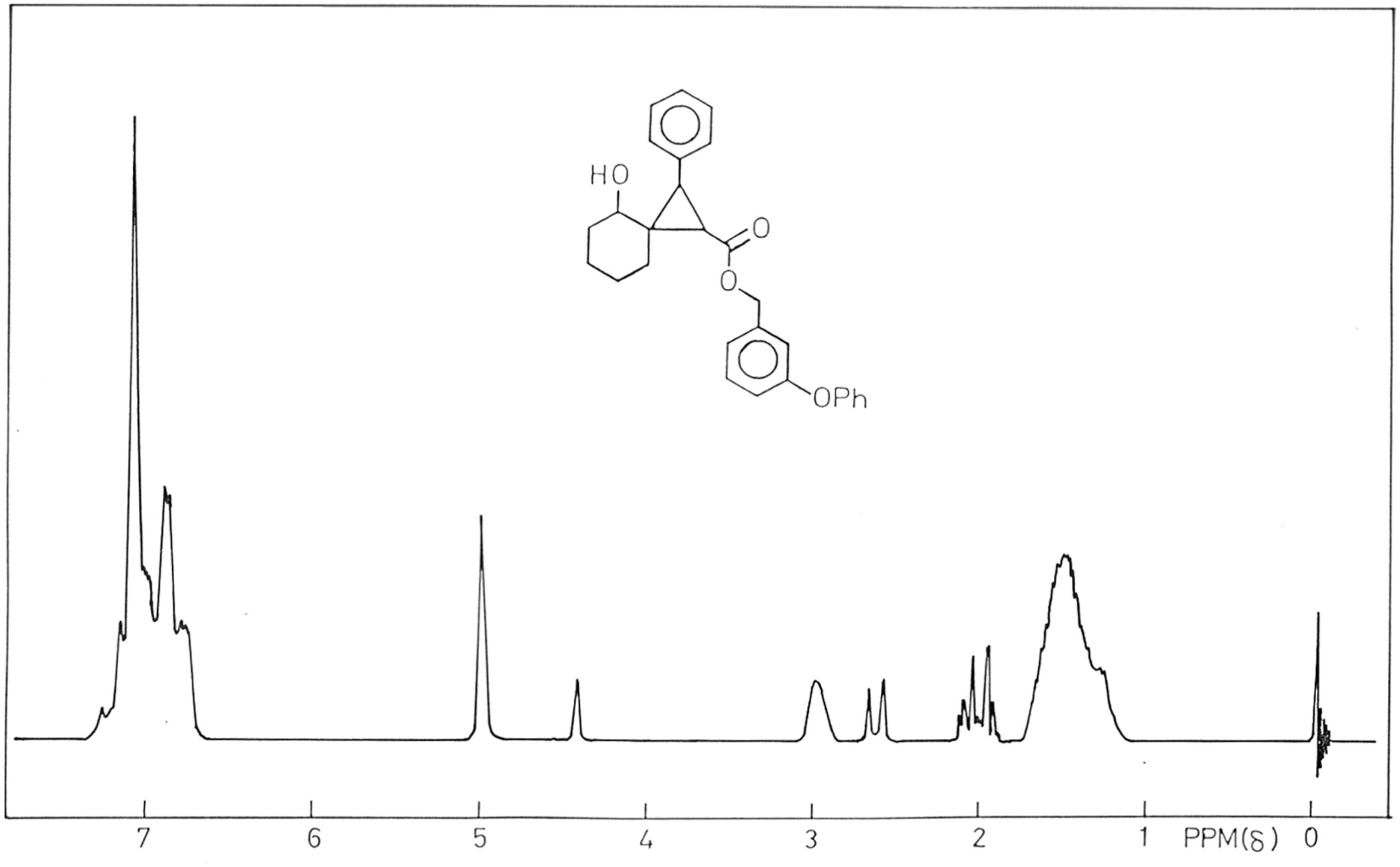


FIG.10

9a: yield 87%, obtained as solid, m.p.107°C; M.S.: m/e 470 (M^+); IR (Nujol): 1730 (acetate >C=0), 1720 (ester >C=0), 1580 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Figure 11): 1.54 (m, 8H, 4 x $-CH_2-$ cyclohexyl protons), 1.8 (s, 3H, acetate $-CH_3$), 2.2 (d, 1H, J=6 Hz, C_1 -H), 2.8 (d, 1H, J=6 Hz, C_2 -H), 4.1 (br s, 1H, $-CH(OCOCH_3)-$), 5.28 (s, benzylic $-CH_2-$), 7.36 (m, 14H, aromatic protons).

9b: yield 80% obtained as a liquid; M.S.: m/e 330 (M^+); IR(liquid film): 1740 (acetate >C=0), 1725 (ester >C=0), 1605 (aromatic unsaturation) cm^{-1}.; NMR ($CDCl_3$): 1.27 (d, 6H, J=8 Hz, 2 x $-CH_3$ of isopropyl), 1.56 (m, 8H, 4 x $-CH_2-$ cyclohexyl protons), 1.83 (s, 3H, acetate $-CH_3$), 2.08 (d, 1H, J=8 Hz, C_2-H), 2.74 (d, 1H, J=8 Hz, C_1 -H), 4.06 (br s, 1H, $-CH(OCOCH_3)-$), 5.08 [m, 1H, $-CH(CH_3)_2$], 7.3 (br s, 5H, aromatic protons).

9c: yield 75% obtained as a liquid; M.S.: m/e 456 (M^+); IR (liquid film): 1740 (acetate >C=0), 1725 (ester >C=0), 1583 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.6 (m, 6H, 3 x $-CH_2-$ cyclopentyl protons), 2.44 (d, J=6 Hz, C_1 -H), 2.93 (d, 1H, J=6 Hz, C_2-H), 4.8 (br s, 1H, $-CH(OCOCH_3)-$), 5.13 (s, 2H, benzylic $-CH_2-$), 7.2 (m, 14H, aromatic protons).

It is well know that cis cyclopropanes exhibit higher coupling constant of 8-10 Hz than those of corresponding trans-isomers which exhibit coupling constants of the order of 5.3 - 6.6 Hz[28,30]. A careful examination of coupling

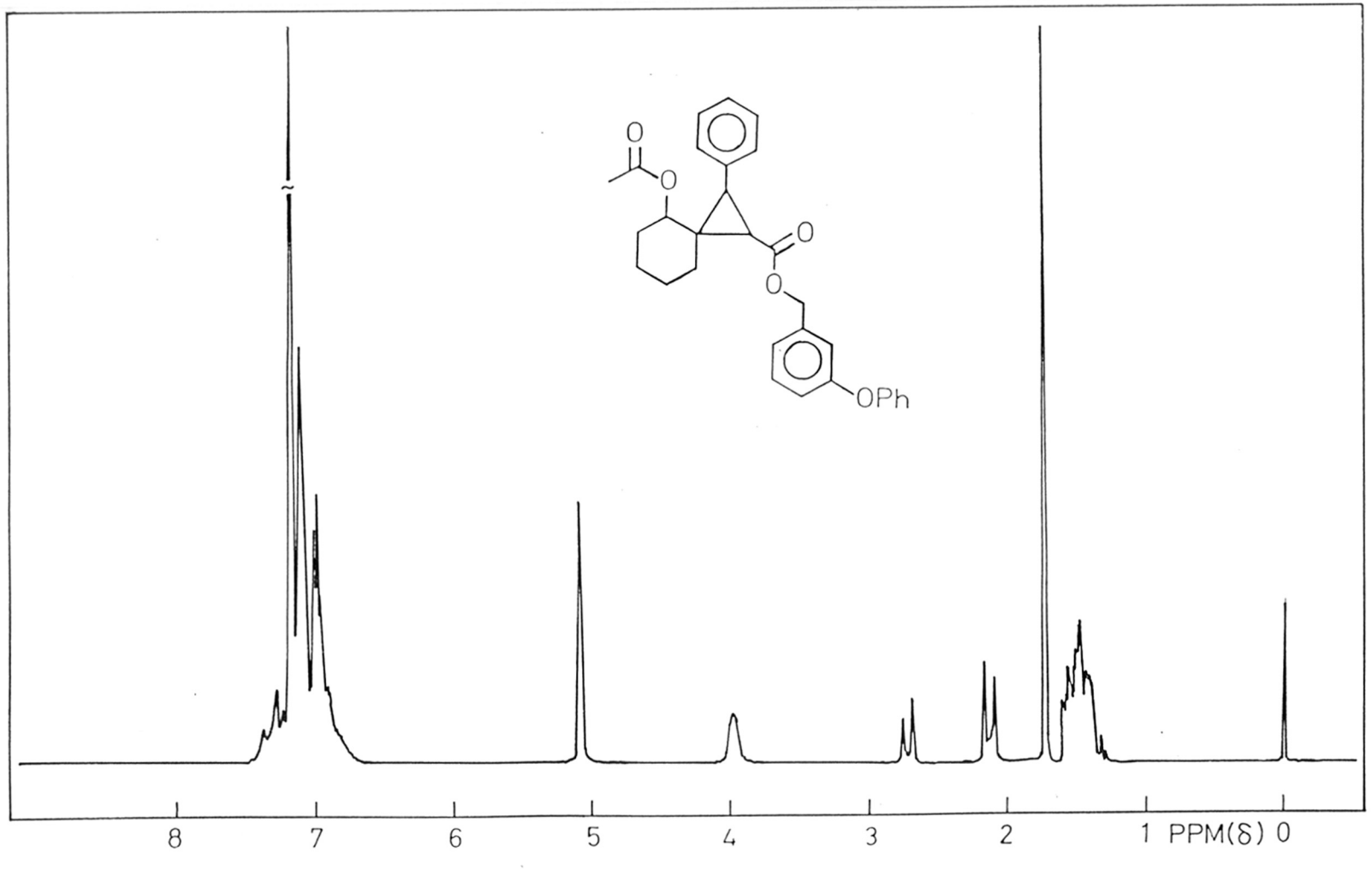
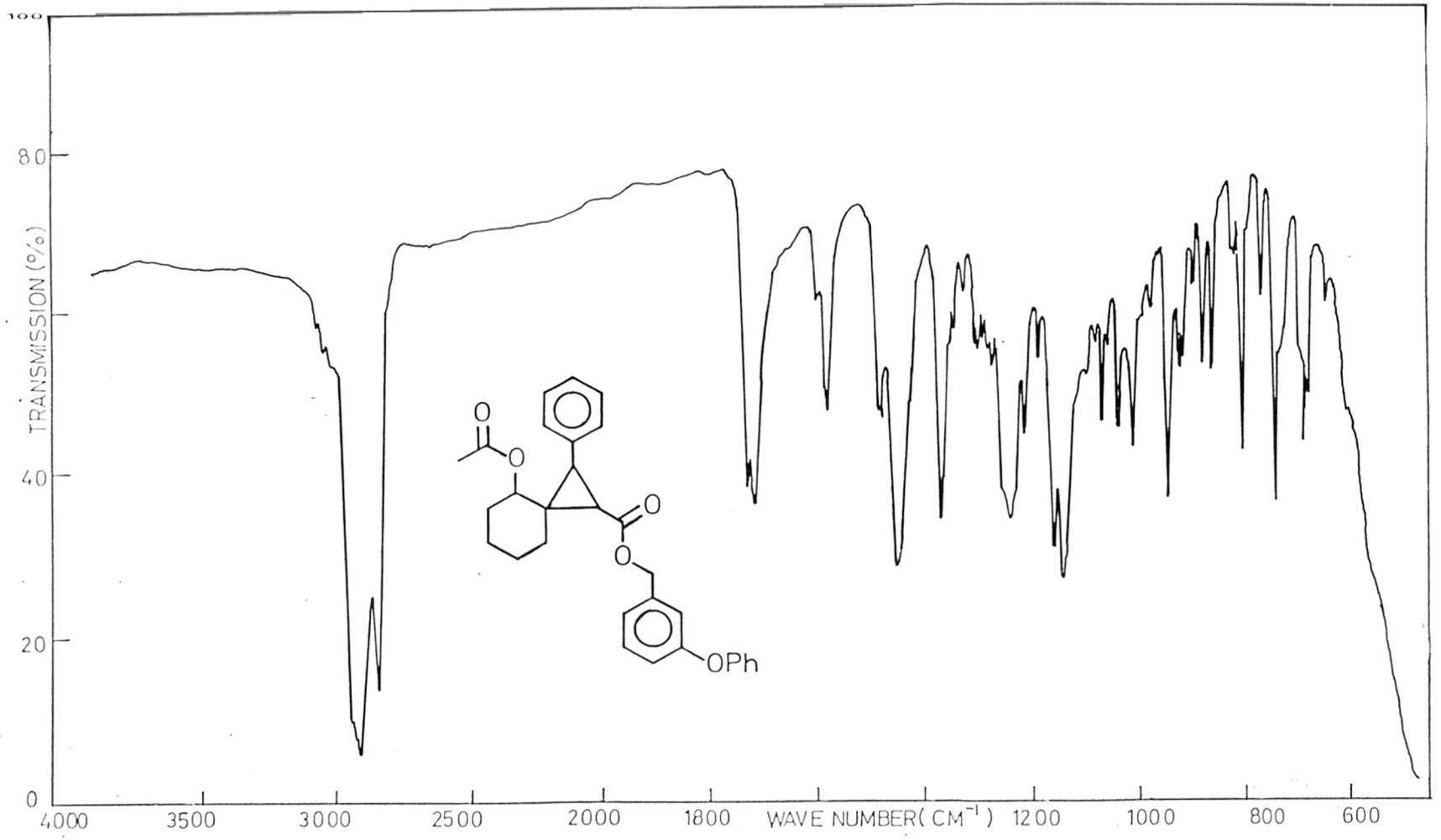


FIG. 11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TRANSMISSION (%)
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WAVE NUMBER(CM^{-1})
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O
O
OPh

FIG. 12

constants of C_1 cyclopropane protons of esters (3a and 4a, b, e) indicates that the cyclopropane may possess a cis-geometry (J=7-8 Hz). A tentative assignment of the cis geometry to the cyclopropane ring has been made on the basis of coupling constants.

In the case of similar cyclopropane keto esters formed from benzylideneacenaphthenones by EDSA, an explanation has been given by an inspection of Dreiding models of both the possible betain intermediates, for the preferential formation of cis-isomer. Normally in such cyclopropanation reactions the trans isomer is preferred one but in this particular case the free rotation of $C\alpha$- $C\beta$ bond in betain intermediate (for the formation of trans-isomer) is hindered by the steric interaction between the acenapthanone ring and phenyl group and also the steric repulsion between the ester group and acenaphthanone ring during intramolecular ring closure[28]. Both these factors make it very difficult for the trans-isomer to be formed.

It is significant to note that the cyclopropane compounds where the C_2-substituent is not a phenyl ring but either an alkyl or a furan ring (3b, d, e) lower coupling constants are observed for the C_1 cyclopropane protons, which indicates that they may possess a trans-cyclopropane geometry, where the steric repulsion between the cyclohexanone ring and the alkyl or furan substituent appears to be

not significant in the betain intermediate. However, all these assignments are purely tentative and the conformation of the stereochemical assignments are required by X-ray crystallographic study of some of the solid cyclopropane esters.

EXPERIMENTAL

Preparation of benzylidene/isopropylidene derivatives of cycloalkanones 2a/b and c

A mixture of benzaldehyde (106 g, 1.0 mol), cyclohexanone (109 g, 1.1 mol) and 1N NaOH (500 ml) solution was heated under reflux for 3 hr and kept at room temperature overnight. Methylene chloride was added to the mixture; the aqueous layer was separated and extracted with the same solvent. The combined methylene chloride layer was washed with dilute acetic acid, followed by water, dried and solvent removed to furnish the residue, which was distilled (b.p. 112°C/3 mm) to give pure 2-benzylidene cyclohexanone (2a, 130 g, 70%) as a solid, m.p.53°C.

Analysis

Found: C, 83.61; H, 7.44; $C_{13}H_{14}O$

requires: C, 83.83; H, 7.58%.

IR bands at: 2936, 1680, 1595, 1255, 1140 cm^{-1}.

In a similar manner the following derivatives have been prepared.

2-Isopropylidene cyclohexanone (2b) prepared in 65% yield, b.p.105°C/7 mm.

Analysis

Found: C, 78.51; H, 10.41; $C_{10}H_{16}O$

requires: C, 78.89; H, 10.59%.

IR bands at: 2955, 1690, 1630, 1600, 1460, 1300, 895 cm^{-1}.

2-Benzylidene cyclopentanone (2c) was obtained in 64% yield by stirring the mixture of reactants at room temperature for 48 hr, followed by work-up.

Analysis

Found: C, 83.61; H, 6.91; $C_{12}H_{12}O$

requires: C, 83.69; H, 7.02%.

IR bands at: 2918, 1710, 1622, 1455, 972 cm^{-1}.

Preparation of 2-fufurylidene cyclohexanone 2d

Furfural (24.5 g, 0.25 mol) was added in two equal portions to a stirred mixture of cyclohexanone (25 g, 0.256 mol) and 1N NaOH solution (250 ml). After addition of the 12 g furfural, the reaction mixture warmed up gradually to 34°C. Two hr later when the temperature had dropped to 30°C, the remainder of the furfural was added and stirring continued for a total of 21 hr. A yellow precipitate was obtained which was separated by filtration and washed repeatedly with water till neutral. The solid cake was washed by slurring with pet.ether to remove unreacted reactants and filtered, dried to give yellow crystals of 2c (31.2 g, 71%), m.p.46°C (b.p.120-125°C/8 mm).

Analysis

Found: C, 74.81; H, 6.72; $C_{11}H_{12}O_2$

requires: C, 74.97; H, 6.86%.

IR bands at: 2910, 1670, 1600, 1460, 1255, 1135 cm^{-1}.

Preparation of 2-furfurylidene cyclopentanone 2e

A mixture of furfural (32.0 g, 0.33 mol), cyclopentanone (28.0 g, 0.33 mol), ether (150 ml) and 0.1N NaOH solution (300 ml) was stirred with external cooling to moderate the exothermic reaction. After about 30 minutes, yellow crystalline material (dimer) began to separate in rapidly increasing amounts. The mixture was filtered under suction after stirring for a total of 45 minutes. The solid as well as the aqueous filtrate were extracted with ether. The combined ether layer was washed with water, dried and solvent removed to give a residue which was distilled under reduced pressure (b.p. 90°C/0.7 mm) to furnish 2e (54 g, 59%) as a yellow solid m.p.59°C.

Analysis

Found: C, 74.0; H, 6.15; $C_{10}H_{10}O_2$
requires: C, 74.05; H, 6.22%.

IR bands at: 2900, 1715, 1630, 1465, 1178, 735 cm^{-1}.

Preparation of 2,4-dibenzylidene cyclopentanone (2f)

A mixture of cyclopentanone (8.4 g, 0.1 mol), benzaldehyde (21.2 g, 0.2 mol), ethanol (100 ml) and 1.25 N NaOH solution (50 ml) was stirred for 16 hr. at room temperature when a solid separated, it was filtered, washed with water and the solid crystallized from benzene + pet.ether (3:1) to give yellow crystalline product 2f

(20.3 g, 78%), m.p.196°C.

Analysis

Found: C, 87.64; H, 6.09; $C_{19}H_{16}O$

requires: C, 87.66; H, 6.19%.

IR bands at: 2900, 1690, 1628, 1600, 1450, 1375, 1172 cm^{-1}.

Preparation of ethyl dimethyl sulfuranylidene acetate (EDSA)

A) Carbethoxymethyl dimethylsulfonium bromide

A mixture of ethyl bromoacetate (26.5 g, 0.159 mol) and dimethyl sulfide in acetone (50 ml) was allowed to stand at 0°C with occasional shaking for 3 days. The solid separated was filtered, washed with acetone and dried to give required bromide (32.6 g, 90%), m.p.78-80°C.

B) Ethyl dimethylsulfuranylidene acetate

A solution of sulfonium bromide (16.3 g, 0.071 mol) in chloroform (565 ml) was stirred vigorously at 5-10°C and a mixture of saturated aqueous K_2CO_3 solution (42.5 ml) and NaOH (12.5 N, 5.66 ml) was added in one lot. The reaction mixture warmed to 15-20°C and was held at that temperature for an additional 15 minutes. After removal of inorganic salt by filtration, the filtrate was separated and the upper chloroform layer was dried for 2 hr over K_2CO_3. Removal of solvent under reduced pressure at 25°C gave ylide (100 g, 95%) as light yellow liquid.

Analysis

Found: C, 48.6; H, 8.1; S, 21.8; $C_6H_{12}O_2S$

requires: C, 48.6; H, 8.2; S, 21.6%.

IR bands at: 1610, 1390, 1370, 1317, 1140, 1090, 1065, 1020, 890 cm^{-1}.

General method for preparation of ethyl 2-phenyl/isopropyl/2-furyl-4-oxo spiro (2,5) octane and ethyl 2-phenyl/2-furyl-4-oxo spiro (2,4) heptane-1-carboxylates (3a/b/d and 3c/e) respectively

To a solution of 2 (54 mmol) in dry benzene (20 ml), ethyl dimethylsulfuranylidene acetate (11.99 g, 81 mmol) was added and the mixture refluxed for 8 hr, cooled, washed with water (3 x 75 ml), dried and solvent distilled to give a liquid residue by distillation to afford 3

3a: yield 75%, b.p.120-30°C/0.5 mm.

Analysis

Found: C, 74.81; H, 7.20; $C_{17}H_{20}O_3$

requires: C, 74.97; H, 7.40%.

IR bands at: 2930, 1732, 1705, 1610, 1450, 1290, 1180 cm^{-1}.

3b: yield 70%, b.p.90-95°C/0.8 mm.

Analysis

Found: C, 70.25; H, 9.11; $C_{14}H_{22}O_3$

requires: C, 70.55; H, 9.31%.

IR bands at: 2960, 2865, 1732, 1702, 1450, 1370, 1195, 1160, 1035 cm^{-1}.

3c: yield 76%, b.p. 150-60°C/0.9 mm.

Analysis:

Found: C, 74.30; H, 6.91; $C_{16}H_{18}O_3$

requires: C, 74.39; H, 7.02%.

IR bands at: 2960, 1740, 1720, 1600, 1440, 1360, 1260, 1025, 830 cm^{-1}.

3d: yield 64%, 130-40°C/0.9 mm.

Analysis

Found: C, 68.51; H, 6.82; $C_{15}H_{18}O_4$

requires: C, 68.68; H, 6.92%.

IR bands at: 2940, 2860, 1730, 1680, 1595, 1545, 1210, 1020, 735 cm^{-1}.

3e: yield 67%, b.p.145-50°C/0.9 mm.

Analysis:

Found: C, 67.61; H, 6.49; $C_{14}H_{16}O_4$

requires: C, 67.73; H, 6.50%.

IR bands at: 2980, 1742, 1725, 1605, 1322, 1170, 730 cm^{-1}.

Similarly bis ethyl 2,8-diphenyl-4-oxo dispiro (2,4,2)-nonane 1,9 dicarboxylate (3f) prepared using 1:3 molar proportion of EDSA corresponding to 2f and purified by chromatography using silica gel and pet.ether + benzene (10:1 v/v) as eluent in 81% yield.

Analysis

Found: C, 74.75; H, 6.41; $C_{27}H_{28}O_5$

requires: C, 74.98; H, 6.53%.

IR bands at: 2920, 1735, 1718, 1605, 1450, 1325, 1265, 1175, 1010, 820 cm^{-1}.

General method for preparation of carboxylic acids (4a-e)

To a cooled aqueous solution (2 ml) of NaOH (0.4 g, 10 mmol) was added solution of keto ester (3, 5 mmol) in ethanol (6 ml) and the homogenous solution stirred for 16 hr at 28°C. Ethanol was removed under reduced pressure, residue diluted withwater (10 ml) and extracted with dichloromethane (25 ml) to remove neutral material. The aqùeous layer was acidified with dilute HCl (10%) to 2 pH and extracted with dichloromethane (3 x 25 ml). The organic layer was washed with water, dried and solvent evaporated to give an acid, crystallized from pet.ether + benzene (4: 1 v/v) to furnish the pure keto acid (4).

4a: yield 85%, m.p. 182°C

Analysis

Found: C, 73.80; H, 6.70; $C_{15}H_{16}O_3$

requires: C, 73.75; H, 6.60%.

IR bands at: 2920, 1710, 1695, 1605, 1460, 1310, 1140, 940, 880, 732 cm^{-1}.

4b: yield 90%, m.p.161°C.

Analysis:

Found: C, 68.21; H, 8.71; $C_{12}H_{18}O_3$

requires: C, 68.54; H, 8.63%.

IR bands at: 2950, 1730, 1693, 1450, 1225, 1140, 925 cm^{-1}.

4c: yield 92%, m.p.146°C.

Analysis

Found: C, 72.84; H, 6.01; $C_{14}H_{14}O_3$

requires: C, 73.02; H, 6.13%.

IR bands at: 2910, 1730, 1680, 1600, 1450, 1375, 1270, 1095, 952, 852 cm^{-1}.

4d: yield 86%, m.p.175°C.

Analysis:

Found: C, 66.34; H, 5.92; $C_{13}H_{14}O_4$

requires: C, 66.65, H, 6.02%.

IR bands at: 2930, 1720, 1697, 1605, 1458, 1305, 1137, 1022, 942, 735 cm^{-1}.

4e: yield 95%, m.p. 285°C.

Analysis

Found: C, 73.15; H, 5.42; $C_{23}H_{20}O_5$

requires: C, 73.39; H, 5.36%.

IR bands at: 2920, 1730, 1695, 1610, 1460, 1272, 1085, 910, 690 cm^{-1}.

General method for preparation of acid chlorides (5a-c)

To a solution of acid (4, 3.7 mmol) in dry benzene (10 ml), thionyl chloride (0.528 g, 4.4 mmol) was added and the mixture refluxed for 1 hr. Excess thionyl chloride and benzene were distilled under reduced pressure to give

acid chloride 5 as a liquid. Acid chlorides thus obtained, in almost quantitative yield were used as such without further purification for preparing 3-phenoxy benzyl and other esters.

5a:

IR bands at: 2940, 1784, 1700, 1603, 1450, 1255, 1018, 745, 690 cm^{-1}.

5b:

IR bands at: 2960, 1785, 1705, 1460, 1360, 1250, 1135, 1025, 825 cm^{-1}.

5c:

IR bands at: 2970, 1790, 1740, 1610, 1455, 1010,850, 755 cm^{-1}.

General method for preparation of 3-phenoxy benzyl/∝(RS)--cyano-3-phenoxy benzyl/isopropyl esters (6a-e)

To an ice-cooled and stirred solutions of acid chloride (3.6 mmol) and 3-phenoxy benzyl alcohol/∝-cyano-3-phenoxy benzyl alcohol/isopropyl alcohol (4.3 mmol) in dry benzene (15 ml) was added a solution of pyridine (1.0 ml) in dry benzene (5 ml) during 0.5 hr. Stirring was continued for 16 hr at 28°C. The reaction mixture was washed with dilute HCl (10%) followed by water (3 x 25 ml) dried and solvent evaporated to furnish a thick liquid residue. This was chromatographed and eluted with suitable mixture of (5 to 10%) benzene in pet.ether to afford the TLC pure ester.

6a: yield 75%, m.p.104°C.

Analysis

Found: C, 78.61; H, 6.03; $C_{23}H_{26}O_4$
requires: C, 78.85; H, 6.15%.

IR bands at: 2920, 2840, 1725, 1700, 1585, 1485, 1375, 1252, 1150, 870 cm^{-1}.

6b: yield 59% obtained as liquid.

Analysis:

Found: C, 76.92; H, 5.41; N, 2.85; $C_{29}H_{25}NO_4$

requires: C, 77.14; H, 5.58; N, 3.10%.

IR bands at: 2920, 2840, 1740, 1700, 1585, 1445, 1210, 1135, 870, 755 cm^{-1}.

6c: yield 64%, obtained as liquid.

Analysis

Found: C, 76.23; H, 7.03; $C_{25}H_{28}O_4$

requires: C, 76.50; H, 7.19%.

IR bands at: 2970, 2880, 1740, 1705, 1595, 1500, 1265, 1155, 790 cm^{-1}.

6d: yield 56%, m.p.69°C.

Analysis

Found: C, 75.24; H, 7.68; $C_{25}H_{28}O_4$

requires: C, 75.50; H, 7.74%.

IR bands at: 2920, 2865, 1725, 1705, 1605, 1452, 1295, 1185, 1100, 875 cm^{-1}.

During the chromatography of isopropyl ester 6d, the earlier fractions eluted with pet.ether + benzene (20:1 v/v) gave a solid in 10% yield, crystallized from pet.ether, m.p.106°C, identified as enol lactone (7).

Analysis

Found: C, 79.43; H, 6.38; $C_{15}H_{14}O_2$

requires: C, 79.62; H, 6.24%.

IR bands at: 2930, 1785, 1695, 1600, 1450, 1200, 1075, 890, 762 cm^{-1}.

6e: yield 70%, obtained as liquid.

Analysis

Found: C, 78.21; H, 5.68; $C_{27}H_{24}O_4$

requires: C, 78.62; H, 5.86%.

IR bands at: 2960, 2870, 1740, 1725, 1585, 1490, 1260, 1155, 760 cm^{-1}.

Similarly the ester (6f) was prepared in 76% yield by using 1:2.4 molar proportion of 3-phenoxy benzyl alcohol corresponding to the acid chloride (5d), m.p.115°C.

Analysis

Found: C, 79.22; H, 5.51; $C_{49}H_{40}O_7$

requires: C, 79.43; H, 5.44%.

IR bands at: 2910, 2840, 1735, 1718, 1580, 1485, 1255, 1165 cm^{-1}.

General method for preparation of hydroxy ester 8a-c

To a cooled and stirred solution of ester (6, 0.94 mmol) in methanol (30 ml) was added $NaBH_4$ (0.108 g, 2.82 mmol) during one hr in small lots and the stirring continued for 16 hr at 28°C. Methanol was removed under reduced pressure. Residue was diluted with water(5 ml) and extracted with dichloromethane (3 x 10 ml). Organic layer was washed with

water, dried and distilled to give residue, which was purified by chromatography over silica gel and eluted with pet.ether and benzene + pet.ether mixtures to give TLC pure hydroxy ester (8).

8a: yield 95%, obtained as liquid.

Analysis

Found: C, 78.31; H, 6.37; $C_{28}H_{28}O_4$

requires: C, 78.48; H, 6.59%.

IR bands at: 3440, 2930, 1728, 1585, 1490, 1255, 1360, 725 cm^{-1}.

8b: yield 96% obtained as solid, 89°C m.p.

Analysis

Found: C, 74.63; H, 8.13; $C_{18}H_{24}O_3$

requires: C, 74.97; H, 8.39%.

IR bands at: 3470, 2930, 1715, 1605, 1455, 1370, 1175, 955, 690 cm^{-1}.

8c: yield 90%, obtained as liquid.

Analysis

Found: C, 78.03; H, 6.18; $C_{27}H_{26}O_4$

requires: C, 78.24; H, 6.32%.

IR bands at: 3420, 2955, 1730, 1590, 1490, 1445, 1255, 1160, 755 cm^{-1}.

General method for preparation of acetate esters (9a-c)

To a cooled and stirred solution of hydroxy ester (8, 0.47 mmol) in pyridine (1.5 ml), acetic anhydride (1 ml) was added and the mixture kept at 30°C for 24 hr. The reaction mixture was poured on to crushed ice and extracted with dichloromethane (3 x 10 ml). The organic layer was washed with dilute HCl (10%) followed by water (3 x 25 ml), dried and solvent distilled to give a crude product, purified either by crystallization or chromatography.

9a: yield 87%, obtained as solid, m.p.107°C.

Analysis

Found: C, 76.26; H, 6.29; $C_{30}H_{30}O_5$

requires: C, 76.57; H, 6.43%

IR bands at: 2910, 1730, 1720, 1580, 1455, 1370, 1230, 1142, 1010, 945, 805 cm^{-1}.

9b: yield 80%, obtained as liquid.

Analysis

Found: C, 72.58; H, 7.80; $C_{20}H_{26}O_4$

requires: C, 72.70; H, 7.93%.

IR bands at: 2940, 1740, 1725, 1605, 1445, 1240, 1105, 950, 690 cm^{-1}.

9c: yield 75%, obtained as liquid.

Analysis

Found: C, 76.36; H, 6.05; $C_{29}H_{28}O_5$

requires: C, 76.29; H, 6.18%.

IR bands at: 2930, 1740, 1725, 1588, 1480, 1240, 1010, 740 cm^{-1}.

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CHAPTER III

SYNTHESIS OF METHYL 1S-CIS-2,2-DIMETHYL -3-n- ALKYLCYCLOPROPANE CARBOXYLATE AND 2,2-DIMETHYL-3-n-ALKYLCYCLOPROPANE METHANOLS FROM (+)-3-CARENE.

SUMMARY

The transformation of (+)-3-carene (1) into 1S-*cis*-2,2-dimethyl-3-*n*-alkylcyclopropanecarboxylates and 2,2-dimethyl-3-*n*-alkylcyclopropane methanols is described in this chapter.

The *trans*-carane diol (2), obtainable from 1, on oxidation with sodium metaperiodate gave the keto aldehyde (3), keto-dimethyl acetal (4) obtained from 3 on selective protection of aldehyde group. Baeyer-Villiger oxidation of keto-dimethyl acetal (4), followed by regeneration of the aldehyde group afforded the acetate-aldehyde (26). This on Huang-Minlon reduction gave primary alcohol (27). Oxidation of 27 either by Jones chromic acid reagent or $KMnO_4$ in acetone at 0°C, afforded corresponding acid which was esterified with diazomethane to give ester (28).

The higher homologues of (28) are prepared as follows:

Grignard reaction on 4 with MeMgI afforded the hydroxy acetal (5). The corresponding hydroxy aldehyde (6) was regenerated from 5 by treatment with 0.1% oxalic acid at 35°C. Hydroxy aldehyde (6) on Grignard reaction with $n\text{-}C_4H_9MgBr$/ $n\text{-}C_8H_{17}MgBr$ gave diols (7)/(16) respectively. Jones chromic acid oxidation of diols (7)/(16), afforded hydroxy ketones (8)/(17) respectively. Huang-Minlon reduction of hydroxy ketones (8)/(17) gave tertiary alcohols (9)/(18) respectively. Dehydration of 9 by $POCl_3$/pyridine afforded an isomeric mixture of hydrocarbons (10) and (11), in which unexpectedly the latter predominated. This as such on ozonolysis and

oxidative workup gave a mixture of products separated into acidic and neutral parts. The acidic part obviously resulting from 10, on esterification with diazomethane afforded the ester (12), the neutral product gave the expected ketone (13) resulting from other double bond isomer (11). Following the similar reaction sequence, mixture of hydrocarbons (19) and (20) gave acidic and neutral parts. However, esterification of acidic part followed by chromatographic purification failed to give pure ester (21). The neutral part chiefly consisted of ketone (22).

Baeyer-Villiger oxidation of ketones (13)/(22) afforded the corresponding acetates (14)/(23) respectively, which on saponification gave the corresponding primary alcohols (15)/(24). Potassium permanganate oxidation of alcohol (24) followed by esterification of the resulting acid afforded the methyl ester (21).

INTRODUCTION

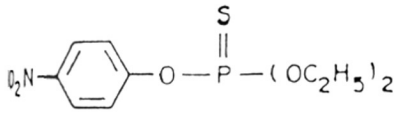
Miticides constitute an important group of pesticides, which are used for protecting the plants from harmful pests[1]. The order of Acarina consists of ticks and mites. The term acaricide is generally used to designate the chemicals active against such organisms. More specific term such as tickicide and miticide have also been commonly used. Mites are both ecto and endo-parasites of animals and those that feed on plant have been controlled by a variety of chemical compounds, differing widely in their structures. Chemicals useful for controlling plant feeding mites, such as red, scarlet and purple mites on different plantation are becoming increasingly important from agricultural point of view.

The synthetic acaricides are broadly classified into following categories depending upon the functional group present in the molecule, considered to be mainly responsible for acaricidal activity (Chart 1).

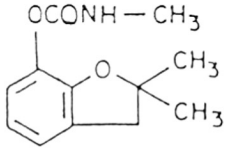
1. Organophosphorous compounds e.g. parathion
2. Carbamates e.g. Carbofuran
3. Chlorinated hydrocarbon e.g. Endosulfan
4. Nitrophenol derivatives - e.g. Dinitrocyclohexyl phenol.
5. Diphenyl aliphatic derivatives e.g. Dicofol,Acarol Chlorobenzilate
6. Sulphonates, suphites and sulphides e.g. Ovex, Tetradifon, Tetrasul.

CHART – 1.

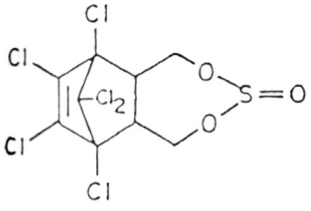
SYNTHETIC ACARICIDES



PARATHION



CARBOFURAN



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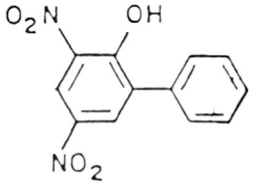
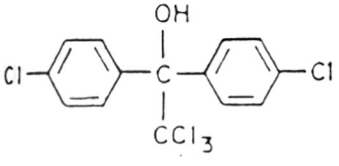
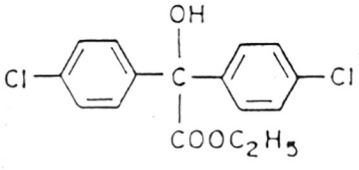


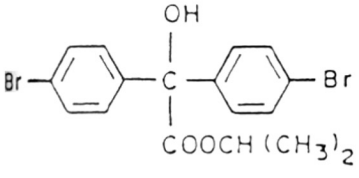
DINITROCYCLOHEXYL PHENOL



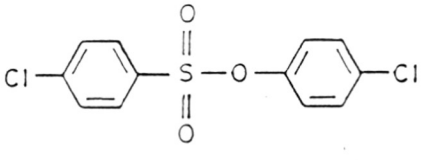
DICOFOL



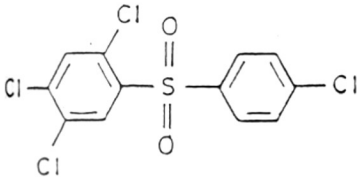
CHLOROBENZILATE



ACAROL



OVEX



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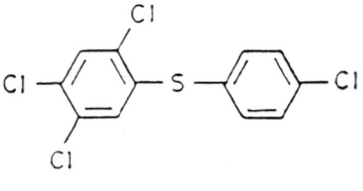
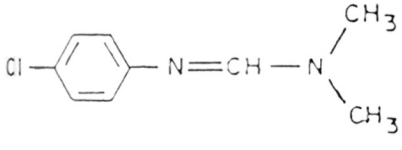
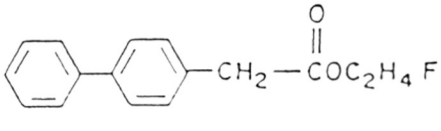


TETRASUL



CHLORODIMEFORM



FLUENETHYL

7. Formamidines e.g. chlorodimeform

8. Organofluarines e.g. Fluenthyl

A more recent classification of the miticides represented below is based on their selectivity towards insects, mites or mammals.

Type	Selectivity level	Toxic to	Class
I	Non-selective	mites, insects, mammals.	Organophosphates carbamtes
II	Moderately-selective	mites, insects.	Nitrophenol derivatives, organofluarines, formamidines
III	Highly-selective	mites.	diphenyl aliphatic compounds

From the above classification we can see that many of the compounds are non-specific in their activity towards mites and insects, as they destroy both beneficial and harmful organisms. Also they differ widely in their toxicity spectrum.

The original synthetic miticides were found to be generally toxic and non-specific in their activity pattern, with a wide spectrum of mammalian toxicity. Later work led to the discovery of less poisonous and more selective organic chemicals. There is now much greater awareness of the dangers of environmental pollution, arising out of the widespread application of these miticides. So it is necessary and desirable to develop new miticides with

extremely high target specificity. For this reason miticides which are structurally related to natural pyrethrins are increasingly becoming important as ideal miticides. They possess unique combination of desirable properties of an ideal miticide, such as high and selective miticidal activity, low mammalian toxicity[2] and greater biodegradability.

Newallis and Walker[3], for the first time claimed that the vapours of certain alkylcyclopropanecarboxylic acid esters (chart 2, compound 1) were active against both adult as well as eggs of two spotted spider mites .

Janiak[4] prepared certain aryl esters of cyclopropane-carboxylic acids (chart 2, compound 2) and claimed that they possess the biocidal activity for the Arachinoidea, bacteria and fungi.

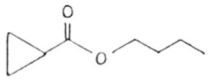
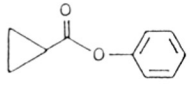
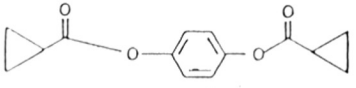
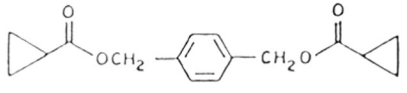
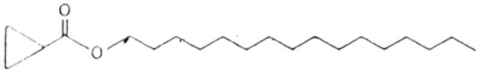
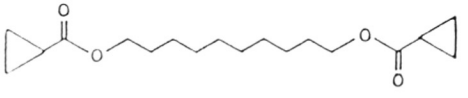
Staal et al.[5,6] have prepared various esters derived from both cyclopropanecarboxylic acid and cyclopropyl methyl alcohol, listed in (chart 2, compound 1-14). Some of these esters were tested against two spotted spider mites (Tetranychus urticae koch) and found to be active especially against all the stages of embryonic development.

Matsui et al.[7] synthesised a number of 2,2-dimethyl-3-alkyl cyclopropanecarboxylic acid esters, possessing different alkyl groups at C-3 position of cyclopropane.

In our laboratory some of the esters[8] of 2,2-dimethyl-3-n-propyl cyclopropane acetic acid have been prepared and

CHART - 2

ACTIVITY OF CYCLOPROPANECARBOXYLIC ACID ESTERS

NO	ESTER STRUCTURE	ACTIVITY	
		OVICIDAL	LARVICIDAL
1		2400	>1000
2		630	4400
3		120	370
4		29	300
5		26	230
6		43	210

ACTIVITY OF CYCLOPROPROPYLMETHYL ALCOHOL ESTERS

NO	ESTER STRUCTURE	ACTIVITY	
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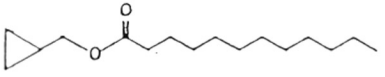
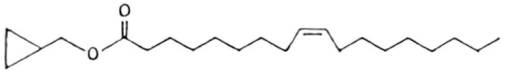
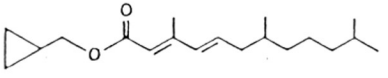
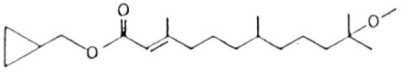
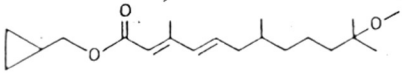
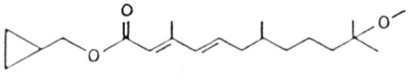
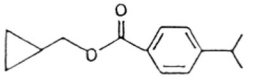
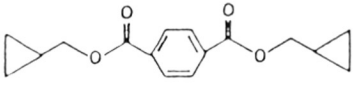
7		60	230
8		250	350
9		1000	240
10		410	100
11		390	200
12		>1000	—
13		300	110
14		37	160

examined for their miticidal activity against the potato tuber mite (Rhizoglyphus echinopus). Some of these esters exhibited enhanced miticidal activity than tetradifon, which was taken for comparison. The esters[9] of 2,2-dimethyl-3-n-propyl cyclopropyl ethanol have also been prepared and patented for their miticidal activity. In addition 1R-cis/1S-cis-2,2-dimethyl-3-n-propyl cyclopropanecarboxylic acids (in the form of methyl esters) have been synthesised from (+)-3-carene[10] for testing some of their esters for possible miticidal activity.

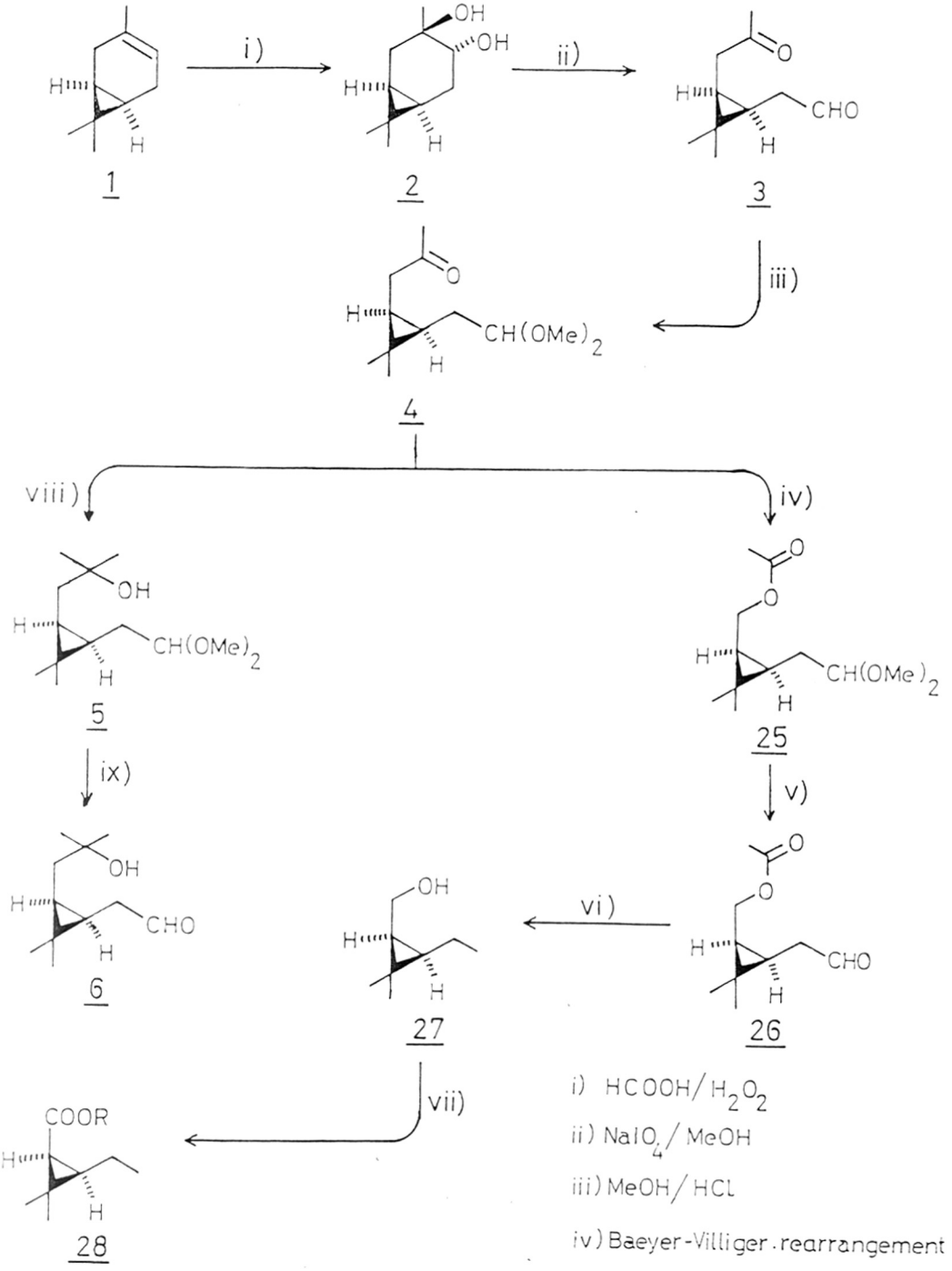
With the ultimate object of evaluating some more esters prepared from 2,2-dimethyl-3-n-alkyl cyclopropanecarboxylic acidsand corresponding cyclopropyl methyl alcohols, it was felt desirable to convert (+)-3-carene into acid and alcohol moieties possessing higher n-alkyl group in place of n-propyl group at C-3 position. The strategy employed in the synthetic transformation leading to target compound was the conversion of Carene into 2,2-dimethyl-3-(2-hydroxy 2-methyl propyl) cis-cyclopropane-1-acetaldehyde by a sequence of known reactionsand then to convert the latter into the cyclopropane carboxylic acids and alcohols.

PRESENT WORK

(+)-Car-3-ene (1), on treatment with performic acid was converted to the formoxy hydroxy carane, which on hydrolysis gave the known[11] 3β,4α-carane diol (2) in 45% yield; m.p.82-83° (pet.ether), $C_{10}H_{18}O_2$; it showed IR bands at:3448 (OH), 1058 (-C-O) and NMR signals at:0.7 (2H, m, cyclopropane protons at C-1 and C-3); 0.97 (6H, s, gemdimethyl on cyclopropane), 1.17 (3H, s, $-CH_3$ at C-3), 1.73 to 2.23 (4H, m, $-CH_2$ protons), 3.27 (1H, q, proton at C-4) and 3.63 (2H, m, OH protons).

Carane diol (2) was cleaved by sodium metaperiodate to afford the known[11] keto aldehyde (3) in 82% yield, $C_{10}H_{16}O_2$, b.p.85-87°/1.5 mm. It showed IR bands at:2740 (CHO), 1724 (C=O) and NMR signals at:0.83 (2H, m, cyclopropane protons), 1.0, 1.13 (3H each, s, each, gemdimethyl on cyclopropane), 2.1 (3H, s $-COCH_3$) and 2.43 (4H, m, methylene protons).

Keto aldehyde (3) on treatment with methanol and catalytic quantity of HCl at 0° furnished the keto dimethyl acetal (4), in 88% yield, $C_{12}H_{22}O_3$, b.p.105-8°/1 mm. It showed IR bands at 1719 (C=O) and NMR signals at 0.66 (2H, m, cyclopropane protons), 0.90, 1.08 (3H each, s each, gem-dimethyl of cylopropane), 1.4 (2H, t, J=6 Hz, CH_2 at C-3), 2.06 (3H, s, $COCH_3$), 2.23 (2H, d, J=6 Hz, CH_2 at C-1), 3.23 (6H, s, $2 \times OCH_3$ of acetal) and 4.15 (1H, t, J=6 Hz, CH of acetal).



i) $HCOOH/H_2O_2$

ii) $NaIO_4$ / MeOH

iii) MeOH / HCl

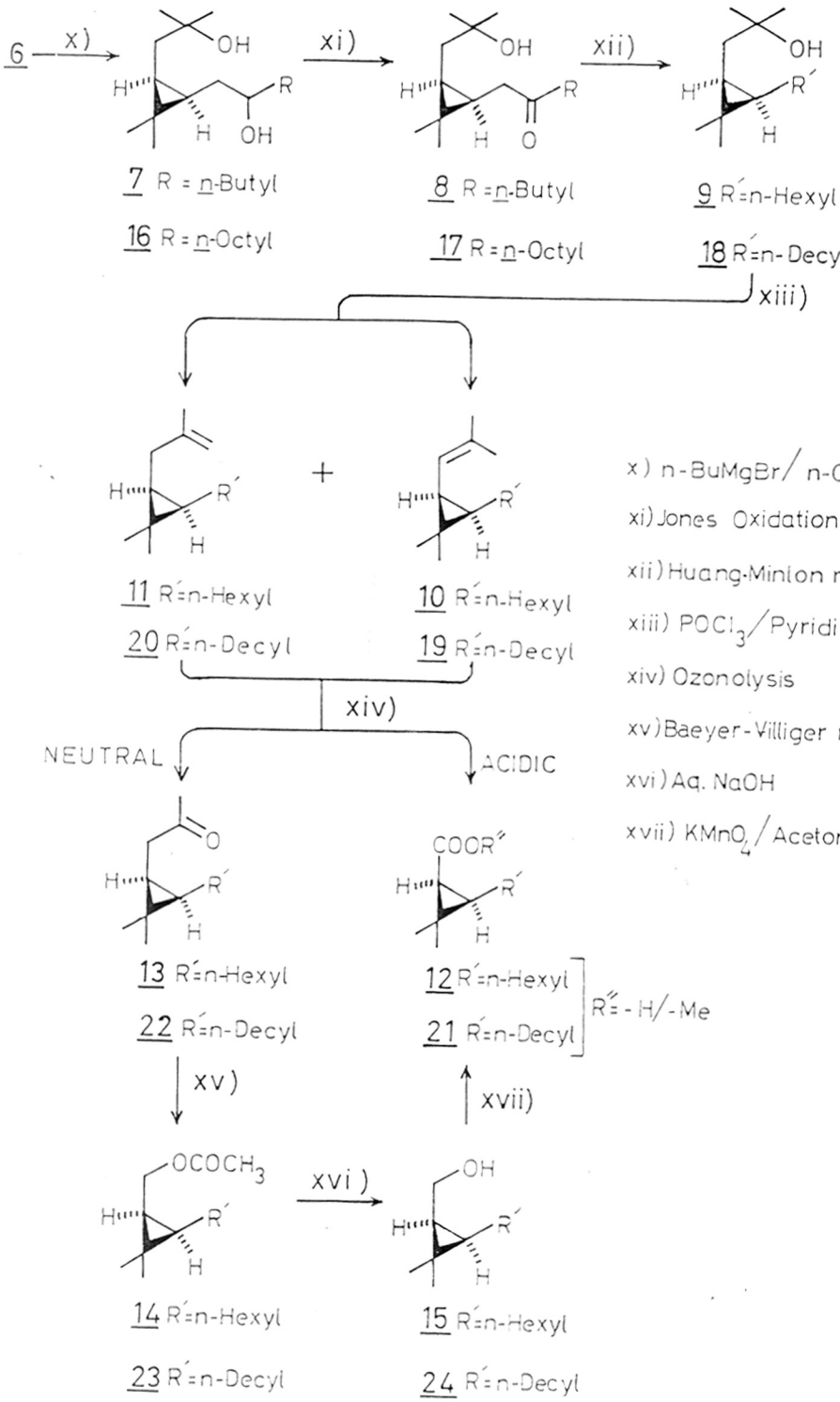
iv) Baeyer-Villiger rearrangement

v) & ix) 0·1% $(COOH)_2$

vi) Huang-Minlon reduction

vii) $KMnO_4$ / Acetone

viii) MeMgI


6
x)
xi)
xii)
7 R = n-Butyl
16 R = n-Octyl
8 R = n-Butyl
17 R = n-Octyl
9 R´=n-Hexyl
18 R´=n-Decyl
xiii)
11 R´=n-Hexyl
20 R´=n-Decyl
10 R´=n-Hexyl
19 R´=n-Decyl
xiv)
NEUTRAL
ACIDIC
13 R´=n-Hexyl
22 R´=n-Decyl
12 R´=n-Hexyl
21 R´=n-Decyl
R´´= -H/-Me
xv)
xvii)
14 R´=n-Hexyl
23 R´=n-Decyl
xvi)
15 R´=n-Hexyl
24 R´=n-Decyl
x) n-BuMgBr/ n-Oct MgBr
xi) Jones Oxidation
xii) Huang-Minlon reduction
xiii) POCl3/Pyridine
xiv) Ozonolysis
xv) Baeyer-Villiger rearrangment
xvi) Aq. NaOH
xvii) KMnO4/Acetone

Baeyer Villiger oxidation of (4), using perbenzoic acid (PBA) (2.5 N, 10-13°, 50 hr) afforded acetate dimethyl acetal (25) in 68% yield, b.p.115-25°/1 mm, $[\alpha]_D^{25°}$ + 11° (c 1.5, $CHCl_3$), $C_{12}H_{22}O_4$, MS: m/e 230 (M^+). IR bands at: 1732, 1240 (acetate) and NMR (Fig. 1) signals at:0.73 (2H, m, C-1 and C-3 protons), 1.03, 1.08 (3H each, s each, gemdimethyl on cyclopropane), 1.51 (2H, t, J=6 Hz, CH_2 at C-3), 1.93 (3H, s, acetate methyl), 3.20 (6H, s, 2 x OCH_3 of acetal), 3.96 (2H, d, J=8 Hz, CH_2 at C-1) and 4.23 (1H, t, J=6 Hz, CH-attached to OCH_3). The corresponding acetate aldehyde (26) was regenerated from acetate acetal (25) by warming it with 0·1% aq. oxalic acid, in 97% yield, $C_{10}H_{16}O_3$, b.p.100-115°/1.5 mm and showed the following spectral properties. IR bands: broad band at 1725 (acetate C=0, aldehyde C=0), 2720 (aldehyde); NMR signals at:0.93 (1H, m, C-1 proton), 1.06 (3H, s, one of cyclopropane methyl), 1.2 (4H, s, overlaping m, C-3 proton and another cyclopropane methyl), 1.96 (3H, s, acetate methyl), 2.43 (2H, m, CH_2 at C-1), 4.1 (2H, m, CH_2 at C-3) and 9.4 (1H, ~~bs~~ br s, aldehyde proton).

Huang-Minlon reduction of 26 gave the primary alcohol, purified by distillation to give 27 in 76% yield, identified by spectral data; $C_{18}H_{16}O$, M.S.:m/e 128 (M^+), $[\alpha]_D^{28}$ + 22° (c, 2.2). It showed IR band at: 3360 (-OH) and NMR (CCl_4) (Fig. 2): 0.45 to 0.83 (2H, m, C_1 and C_3 cyclopropane protons), 0.95

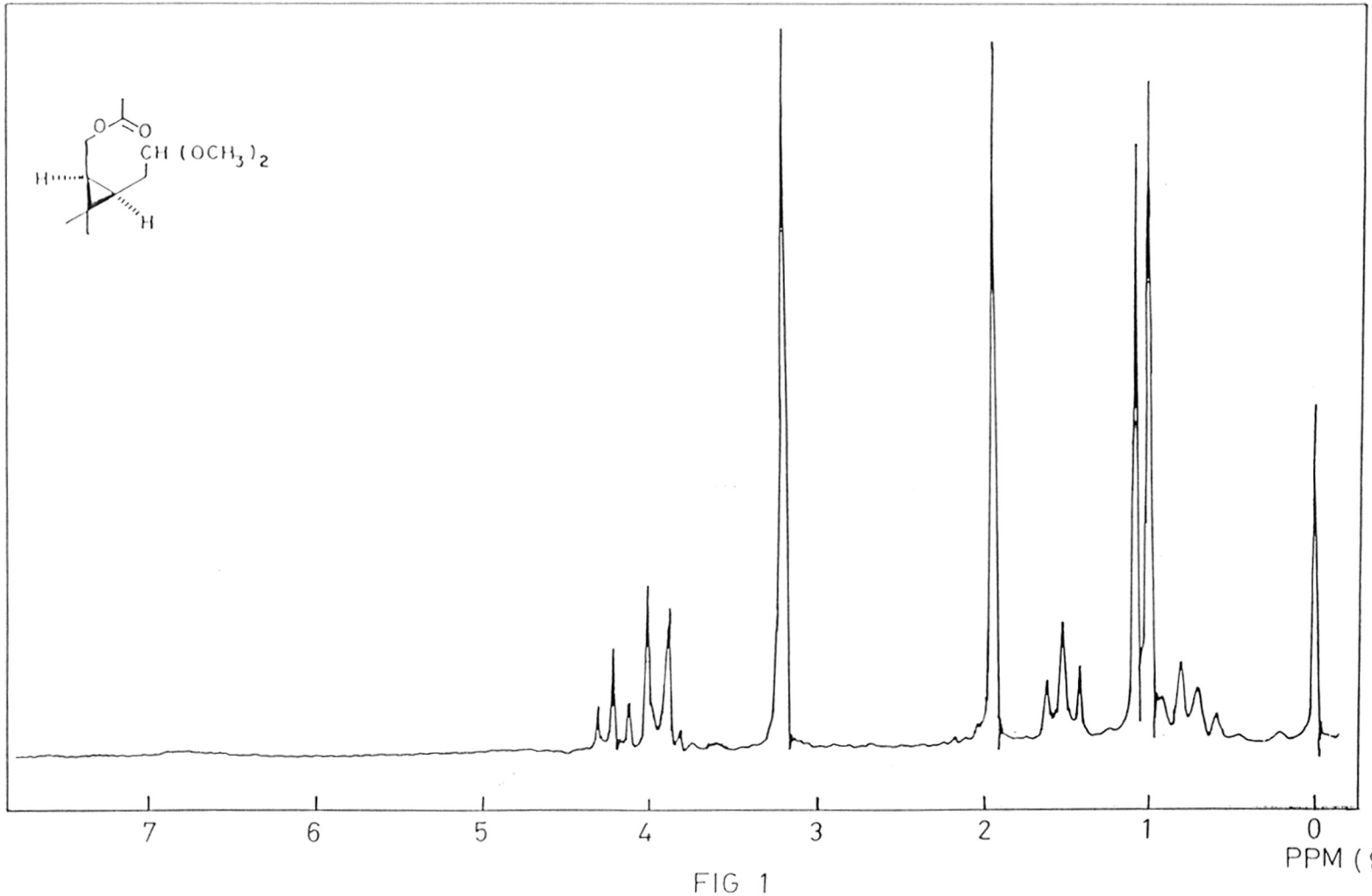


FIG 1

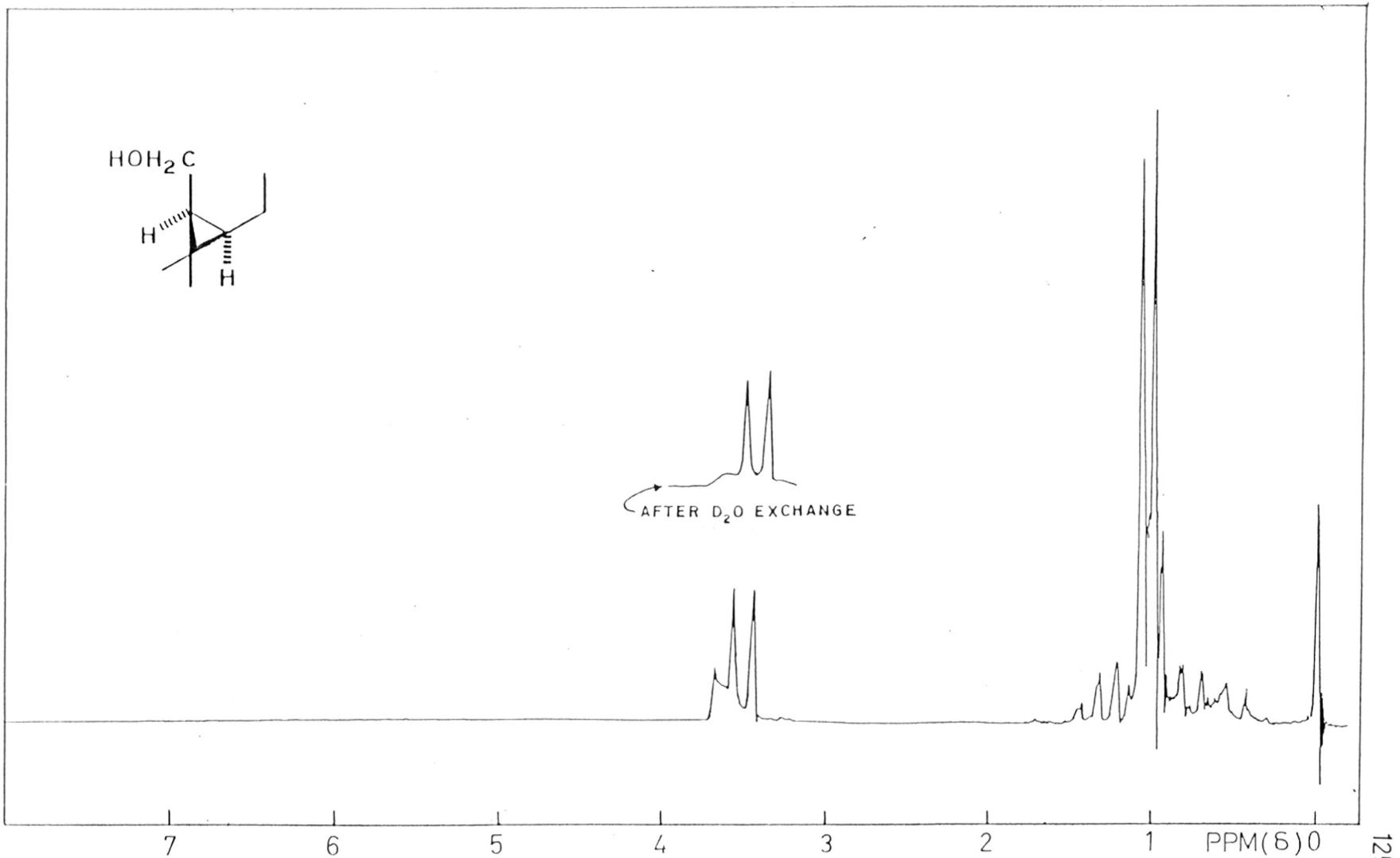


FIG 2

(3H, t, J=7 Hz, $-CH_2-CH_3$), 1.00,1.08 (3H each, s each, gem-dimethyl on cyclopropane),1.15 to 1.45 (2H, m, $-CH_2$ at C_3),3.51 (2H, d, J=6 Hz, $-CH_2-$ at C_1) and 3.66 (1H, hump, exchangeable with D_2O, -OH proton).

Oxidation of 27 either by Jones chromic acid or $KMnO_4$ in acetone at 0°C, afforded in fairly high yields the corresponding carboxylic acid, which was converted into its methyl ester (28) by an etheral solution of diazomethane. The crude ester was chromatographed over silica gel (1:10)and eluted with pet.ether, to give TLC pure liquid in 33% (via Jones chromic acid oxidation) and 41% (via $KMnO_4$ oxidation) yield, identified by spectral data as follows:$C_9H_{16}O_2$, MS: m/e 156 (M^+),$[\alpha]_D^{28}$ + 23.85°(c,1.2); IR bands at:1730,(ester $\geq C=O$), 1174;NMR(CCl_4)(Fig.3): 1.0(4H, t overlapping a m, primary $-CH_3$ and C_3 cyclopropane proton),1.25, 1.3 (3H each, s each, gem-dimethyl on cyclopropane),1.36 to 1.85 (3H, m, C_1 proton and $-CH_2-$ at C_3) and 3.65(3H, s, ester $-CH_3$).

Higher homologues of 28 viz. 12 and 21 were prepared from keto dimethyl acetal(4) as described below.

Grignard reaction on 4 using CH_3MgI gave the acetal alcohol (5, 81.4%)as a liquid, $C_{13}H_{26}O_3$, MS: m/e 230 (M^+),which showed IR bands at: 3546 (-OH) and NMR signals at: 0.5 (2H, m,cyclopropane protons),0.88, 1.08 (3H each, s each, gem dimethyl), 1.1 (6H, s, methyls of hydroxyisopropyl), 1.4 (4H, m, 2 x $-CH_2-$ of C_1 and C_3), 3.21 (6H, s, 2 x $-OCH_3$ of acetal), 4.85 (1H, t, J=6 Hz, -CH- at the acetal) and 2.21 (1H, s, exchangeable with D_2O, -OH proton).

The hydroxy aldehyde (6) was regenerated from 5 by warming at 35°C with 0.1% aqueous oxalic acid solution, in 96% yield

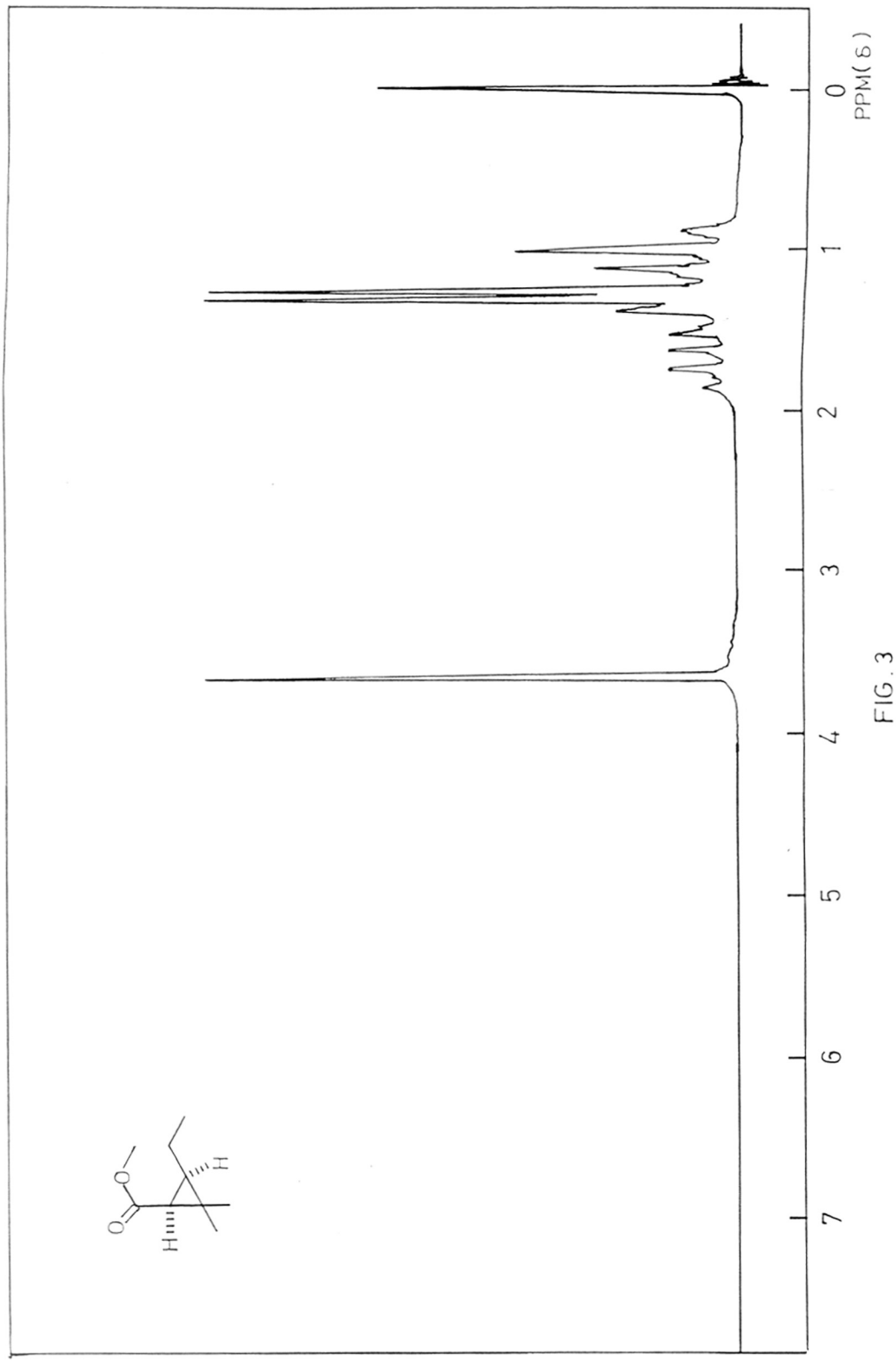


FIG. 3

as a liquid, $C_{11}H_{20}O_2$, MS: m/e 184 (M^+); IR bands at 3534(-OH), 2778, 1725 (aldehyde); NMR signals at:0.8 (2H, m, cyclopropane protons), 0.91, 1.15 (3H each, s each, gem dimethyl), 1.25 (6H, s, methyls of hydroxyisopropyl),1.4 (2H, d, J=6 Hz, -CH_2- at C_3), 2.2 (2H, br m, -CH_2- at C_1), 5.51 (1H, s, exchangeable with D_2O, -OH proton) and 9.83 (1H, s, aldehyde proton).

Grignard reaction on hydroxy aldehyde (6) using n-BuMgBr afforded a diastereomeric mixture of diols (7) as a liquid in 59% yield, $C_{15}H_{30}O_2$, MS: m/e 242 (M^+). It showed IR bands at (Fig. 4) 3356 (-OH), NMR (CCl_4): 0.55 (2H, m, cyclopropane protons), 0.88 (6H, s overlapping a t, one of the cyclopropane -CH_3 and primary -CH_3 of -C_4H_9), 1.06 (3H, s, another cyclopropane methyl), 1.21 (6H, s, methyls of hydroxyisopropyl), 1.35 (10H, br m, 5 x -CH_2-),3.42 (1H, m, proton on carbon bearing hydroxyl group), 3.75(2H, hump, exchangeable with D_2O, 2 x -OH protons).

Similarly the diol (16) was prepared in 65% yield by reaction of (6) with n-octyl magnesium bromide and characterized by spectral data; $C_{19}H_{38}O_2$, MS: m/e 298 (M^+), $[\alpha]_D^{26}$ + 0.27° (c, 2), IR bands at:3448 (-OH),NMR(CCl_4): 0.58 (2H, m, cyclopropane protons),0.88(6H, s overlapping a t, one of the cyclopropane methyl and -CH_3 of -C_8H_{17}), 1.08 (3H, s, another cyclopropane methyl),1.21(6H, s, methyls of hydroxyisopropyl),1.33 (18H, br s, 9 x -CH_2-),3.41 (3H, m, partly exchangeable with D_2O, proton on carbon bearing hydroxyl group at 2 x -OH protons).

The hydroxy ketone (8) was then obtained in 78% yield by Jones chromic acid oxidation of 7, $C_{15}H_{28}O_2$, MS: m/e 240 (M^+), IR bands at (Fig. 6): 3390 (-OH), 1709 (>C=O);

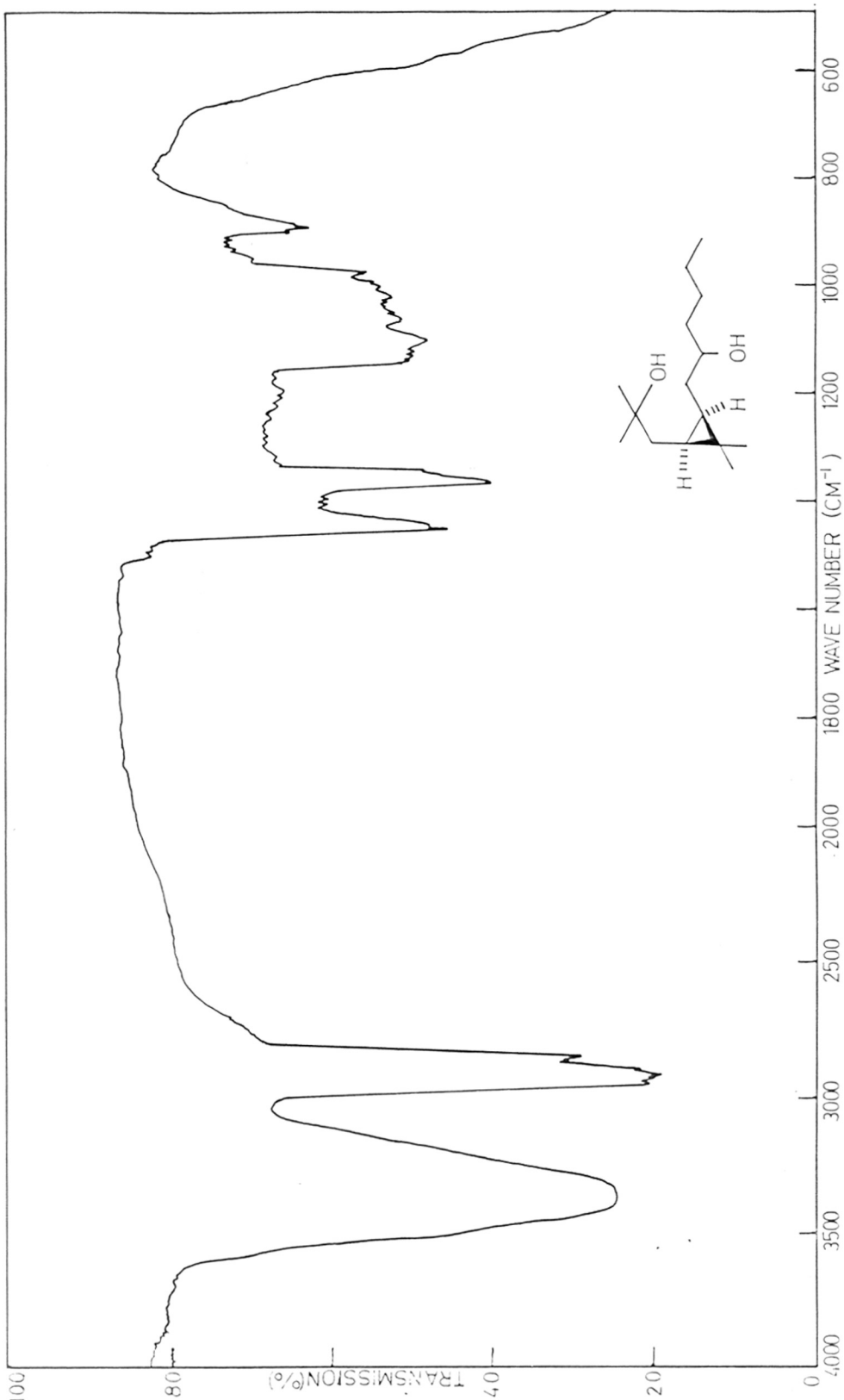

100
80
40
20
0
TRANSMISSION(%)
4000
3500
3000
2500
2000
1800
1200
1000
800
600
WAVE NUMBER (CM⁻¹)
OH
H
OH
H

FIG. 4

NMR ($CDCl_3$) (Fig. 5): 0.66 (2H, m, cyclopropane protons), 0.9 (6H, s overlapping a t, one of the cyclopropane methyls and -CH_3 of C_4H_9), 1.1 (3H, s, another cyclopropane methyl), 1.24 (10H, br s, 2 x -CH_3 of hydroxyisopropyl group and 2 x -CH_2- in the side chain, non-adjacent to keto group), 1.38 (2H, d, J=6 Hz, -CH_2- adjacent to hydroxyisopropyl), 1.7 (1H, s, exchangeable with D_2O, -OH proton), 2.34 (4H, m, 2 x -CH_2- adjacent to carbonyl group).

Similarly the hydroxy ketone (17)was prepared in 81% yield as a liquid from diol (16) and characterized; $C_{19}H_{36}O_2$, MS: m/e 296 (M^+), $[\alpha]_D^{26}$ + 12.2° (c, 2). It showed IR bands at: 3425 (-OH), 1718 (>C=O); NMR ($CDCl_3$): 0.88 (8H, s, overlapping a t, C_1 and C_3 cyclopropane protons, one of the cyclopropane methyls and -CH_3 of -C_8H_{17}), 1.1 (3H, s, another cyclopropane methyl), 1.24 (18H, br s, 2 x -CH_3 of hydroxyisopropyl and 6 x -CH_2- non-adjacent to keto group), 1.38 (2H, d, J=6 Hz, -CH_2- adjacent to hydroxyisopropyl), 1.7 (1H, s, exchangeable with D_2O, -OH proton), 2.36 (4H, m, 2 x CH_2- adjacent to keto group).

Huang-Minlon reduction of hydroxy ketone (8) afforded the tertiary alcohol (9) as a liquid in 74% yield, $C_{15}H_{30}O$, MS: m/e 226 (M^+), IR bands at (Fig. 8): 3356 (-OH); NMR (CCl_4) (Fig. 7): 0.45 (2H, m, cyclopropane protons), 0.9 (6H, s overlapping a t, one of the cyclopropane methyls

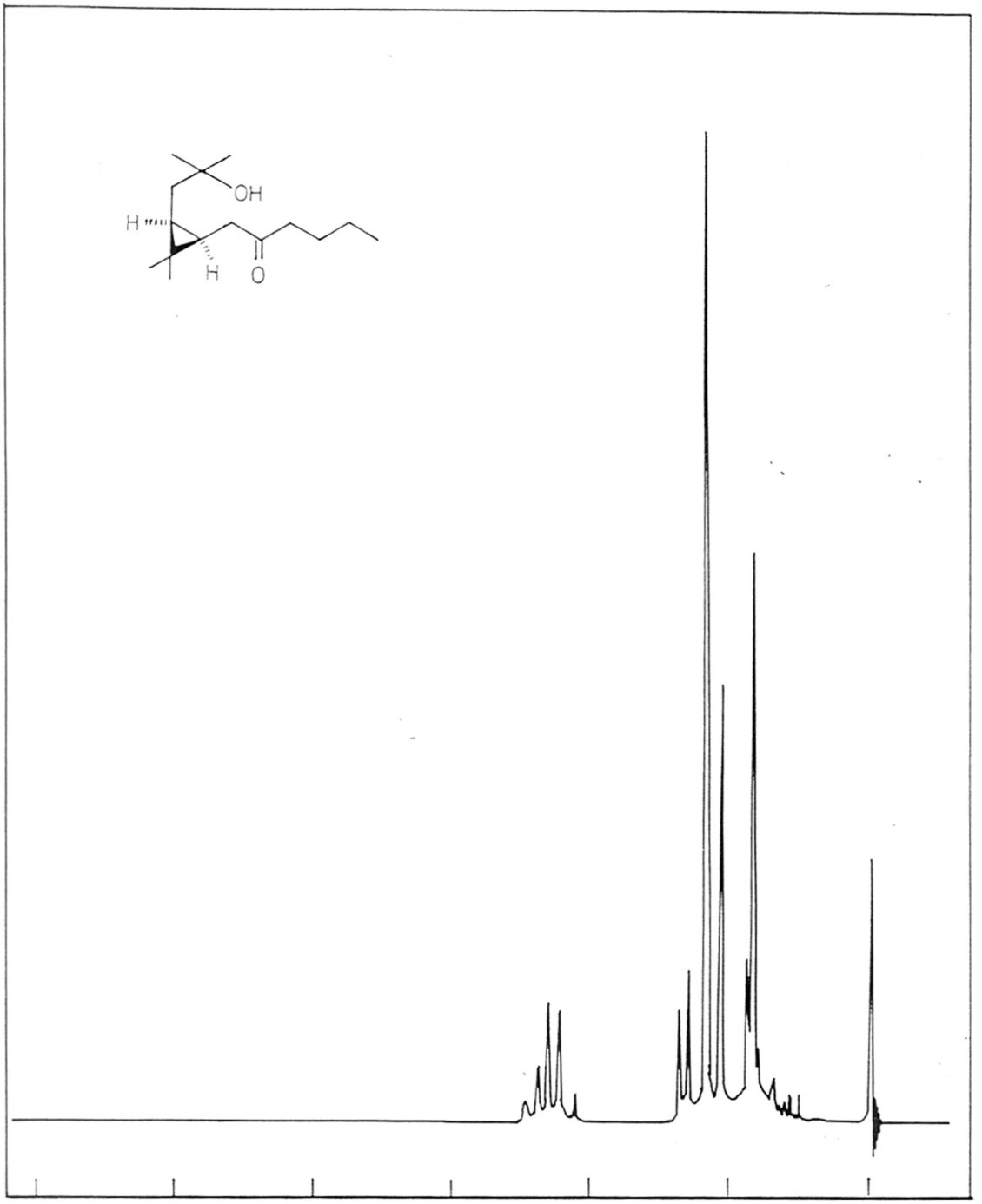


FIG. 5

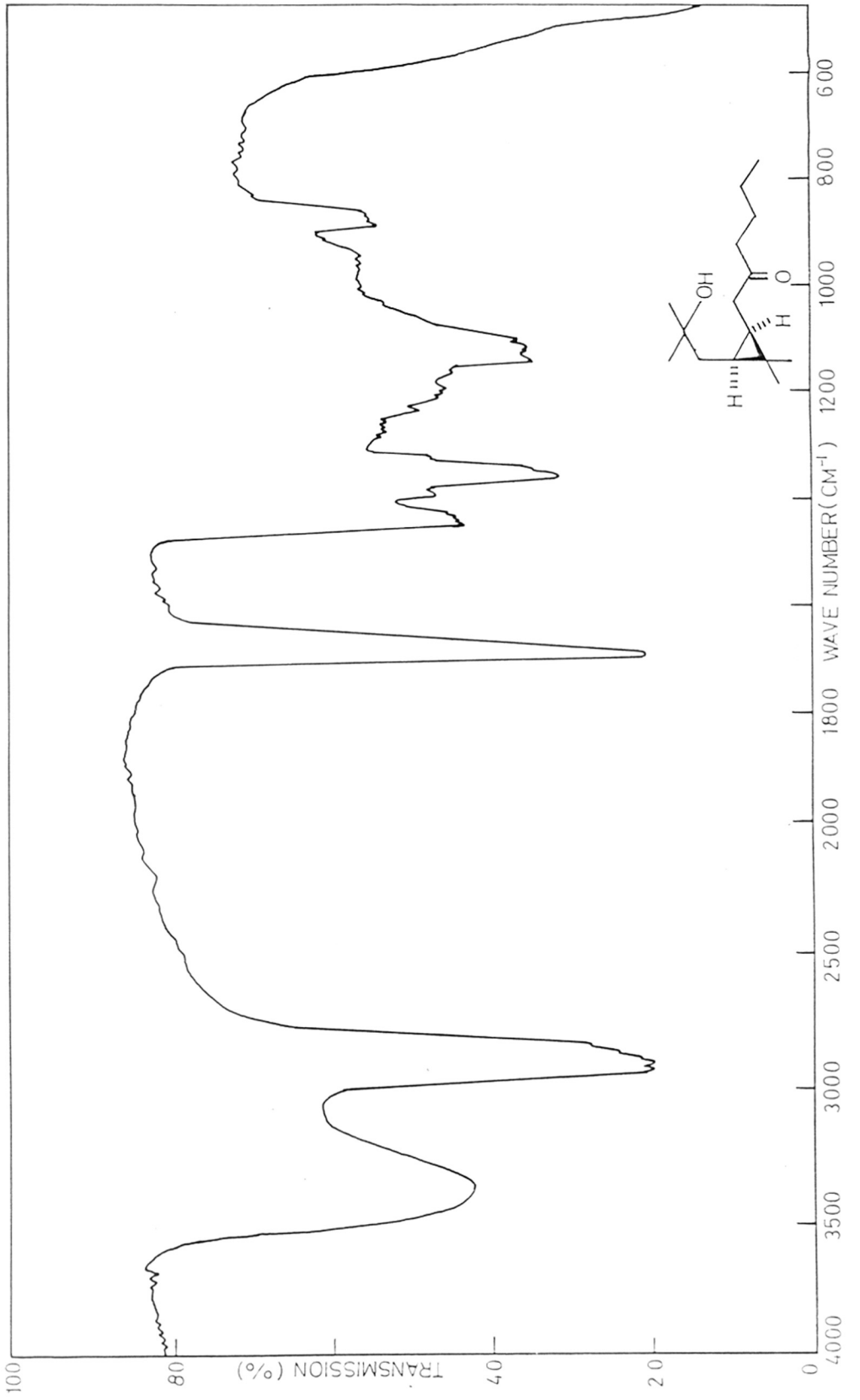

100
80
60
40
20
0
TRANSMISSION (%)
4000
3500
3000
2500
2000
1800
1200
1000
800
600
WAVE NUMBER(CM⁻¹)
OH
H
O
H

FIG. 6

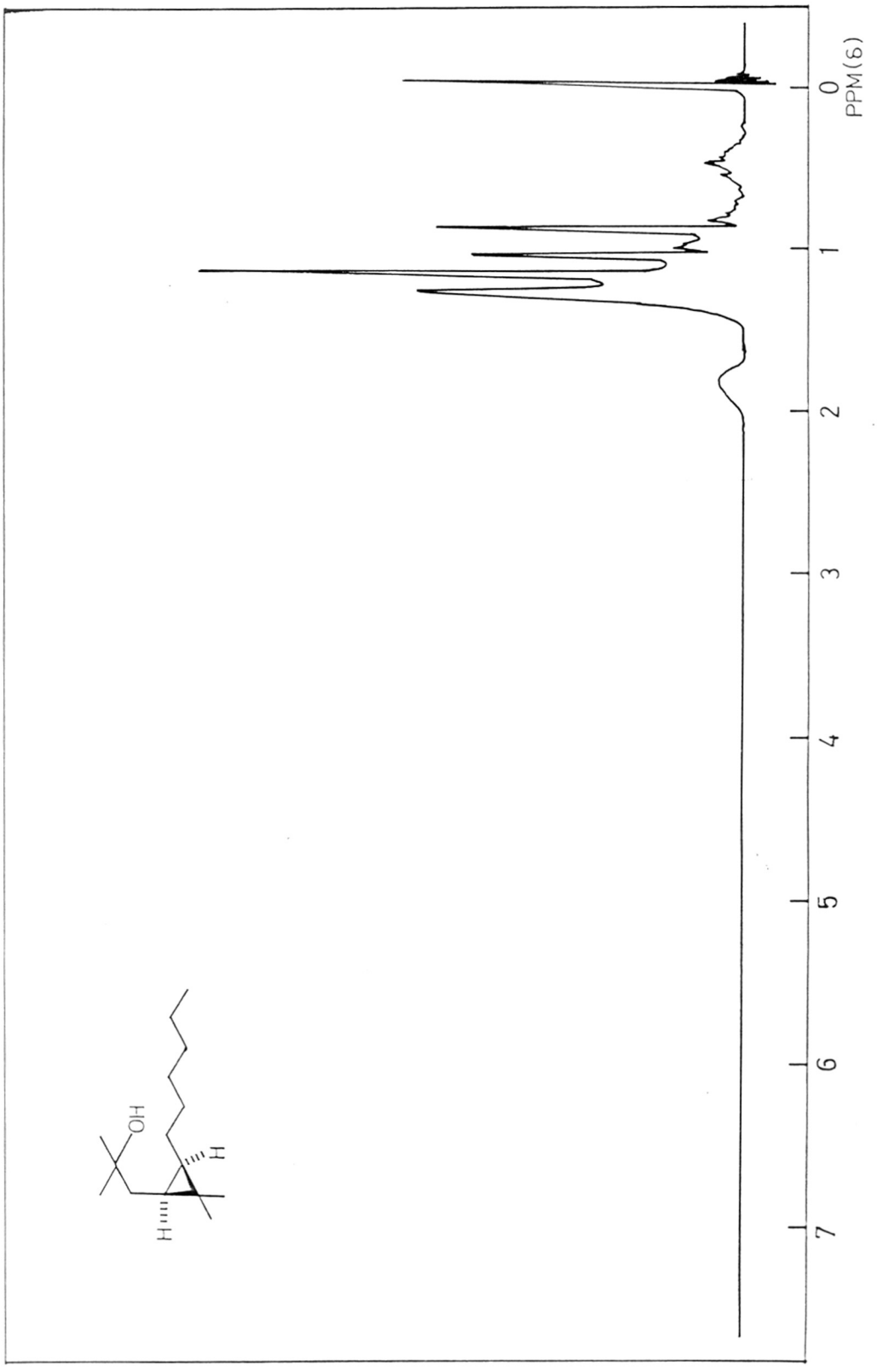


FIG. 7

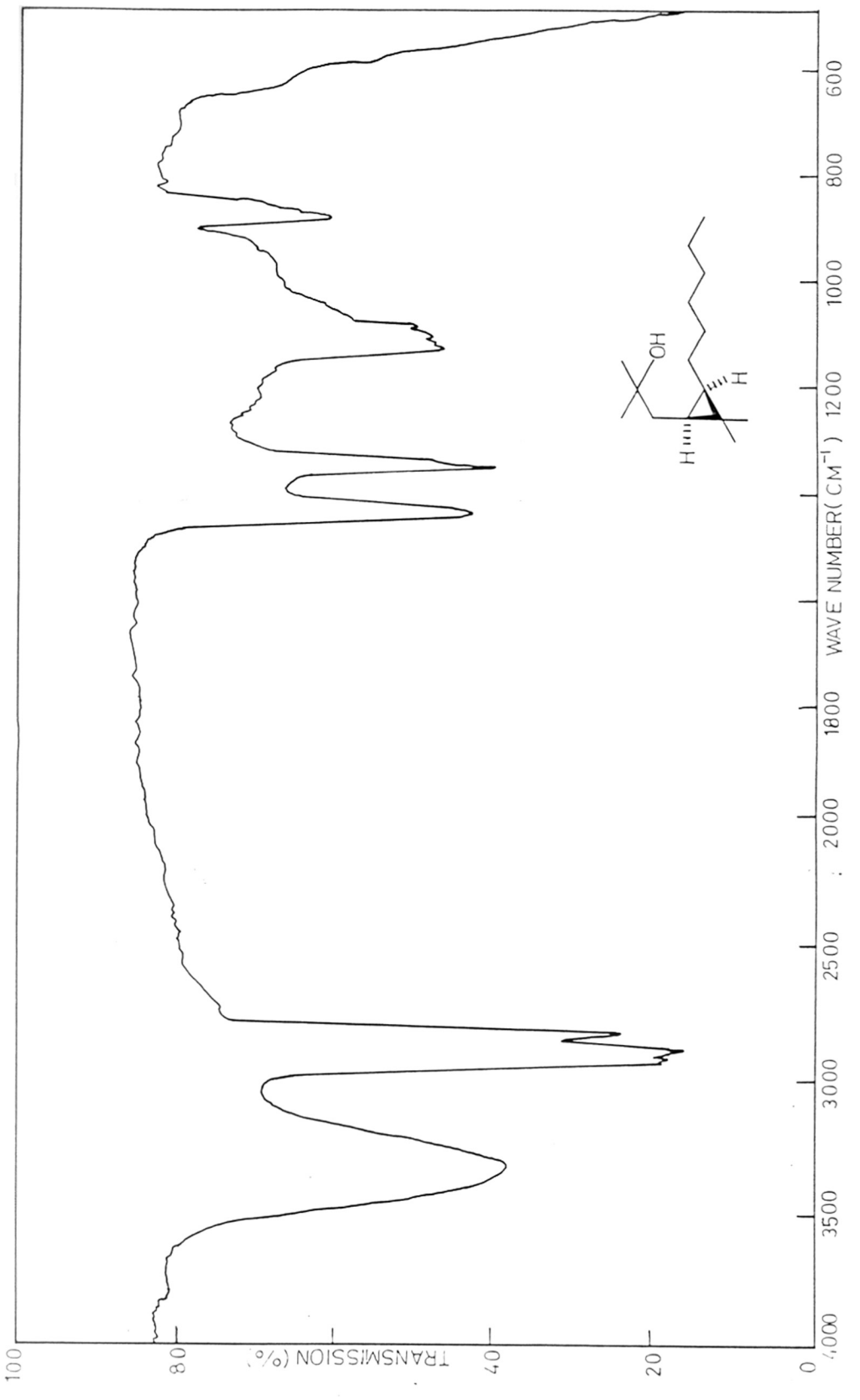

100
80
40
20
0
TRANSMISSION (%)
4000
3500
3000
2500
2000
1800
1200
1000
800
600
WAVE NUMBER(CM⁻¹)
OH
H
H

FIG. 8

and-C<u>H</u>$_3$ of -C_6H_{13}), 1.06 (3H, <u>s</u>, another cyclopropane methyl), 1.18 (6H, <u>s</u>, 2 x -C<u>H</u>$_3$ of hydroxyisopropyl), 1.3 (12H, <u>br s</u>, 6 x -C<u>H</u>$_2$-) and 1.83 (1H, <u>hump</u>, exchangeable with D_2O, -O<u>H</u> proton).

Similarly the tertiary alcohol (<u>18</u>) was prepared by Huang-Minlon reduction of (<u>17</u>) as a liquid in 70% yield, $C_{19}H_{38}O$, MS: m/e 282 (M^+), $[\alpha]_D^{26}$ + 5.6° (<u>c</u>, 2); IR bands at: 3378 (-OH); NMR (CCl_4): 0.43 (2H, <u>m</u>, cyclopropane protons), 0.88 (6H, <u>s</u> overlapping a <u>t</u>, one of the cyclopropane methyls and -C<u>H</u>$_3$ of -$C_{10}H_{21}$), 1.06 (3H, <u>s</u>, another cyclopropane methyl), 1.18 (6H, <u>s</u>, 2 x -C<u>H</u>$_3$ of hydroxyisopropyl group), 1.3 (20H, <u>br s</u>, 10 x -C<u>H</u>$_2$-), 1.85 (1H, <u>hump</u>, exchangeable with D_2O, -O<u>H</u> proton).

Dehydration of tertiary alcohol (<u>9</u>) using $POCl_3$/pyridine at 0°C followed by chromatography of the resulting product over silica gel afforded a mixture of two unsaturated hydrocarbons viz. <u>10</u> and its double bond isomer <u>11</u> in 75% yield; $C_{15}H_{22}$, MS: m/e 202 (M^+), identified by spectral properties; IR bands at: 890, 1660 (>C=C<u>H</u>$_2$); NMR (CCl_4) (Fig. 9): 0.48 (1H, <u>m</u>, C_3 cyclopropane proton), 0.91 (6H, <u>s</u> overlapping a <u>t</u>, one of the cyclopropane methyls and -C<u>H</u>$_3$ of -C_6H_{13}), 1.08 (3H, <u>s</u>, another cyclopropane methyl), 1.28 (10H, <u>br s</u>, 5 x -C<u>H</u>$_2$-), 1.66, 1.71 (< 7H, two <u>s</u>, overlapping a <u>m</u>, vinyl methyls of both the isomers and C_1 cyclopropane proton), 4.68 (>1H, <u>br s</u> overlapping a <u>d</u>, olefinic protons of

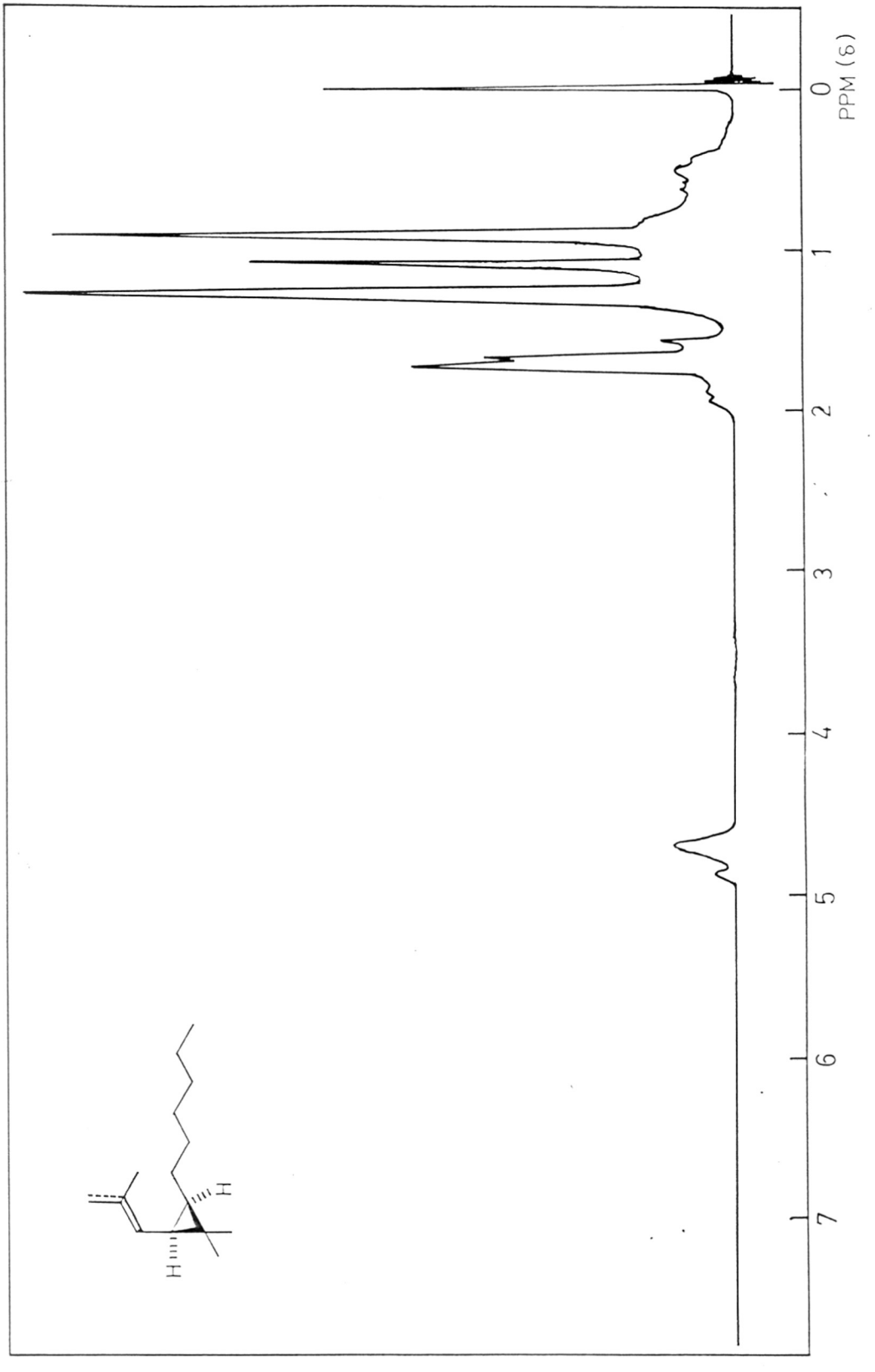


FIG. 9

both the double bond isomer).

Similarly the unsaturated hydrocarbon mixture (19) and (20) ($C_{19}H_{36}$) was obtained in 79% yield from alcohol (18) and characterized; MS: m/e 264 (M^+); it showed IR bands at: 890, 1600 (>C=CH_2); NMR (CCl_4): 0.58 (1H, m, C_3 cyclopropane proton), 0.91 (6H, s overlapping a t, one of the cyclopropane methyls and -CH_3 of -$C_{10}H_{21}$), 1.08 (3H, s, another cyclopropane methyl), 1.3 (18H, br s, 9 x -CH_2-), 1.71 (< 7H, two s overlapping a m; vinyl methyls of both the isomers and C_1 cyclopropane proton), 4.71 (>1H, s overlapping a d, olefinic protons of both the double bond isomers).

Ozonolysis of the mixture of unsaturated hydrocarbons (10 and 11) in ethyl acetate at 0°C followed by oxidative work up (Jones chromic acid), afforded a mixture of products, separated into acidic and neutral parts by carbonate extraction. The acidic product was converted to its methyl ester, using an etheral solution of diazomethane to give liquid ester in 8.6% yield, $C_{13}H_{24}O_2$, $[\alpha]_D^{27}$ + 30.1° (c, 1.5). It was identified as ester (12) by the following spectral data, MS: m/e 212 (M^+); IR bands at (Fig. 11) 1739 (ester >C=0); NMR ($CDCl_3$) (Fig. 10): 0.87 (4H, t overlapping a m, C_3 cyclopropane proton and -CH_3 of -C_6H_3), 1.16 , 1.22 (3H each, s each, gem dimethyl on cyclopropane), 1.27 to 1.46 (10H, br s overlapping a m, 5 x -CH_2- of -C_6H_{13}), 1.62 (1H, d, J=7 Hz, C_1 cyclopropane proton) and 3.63 (3H, s,

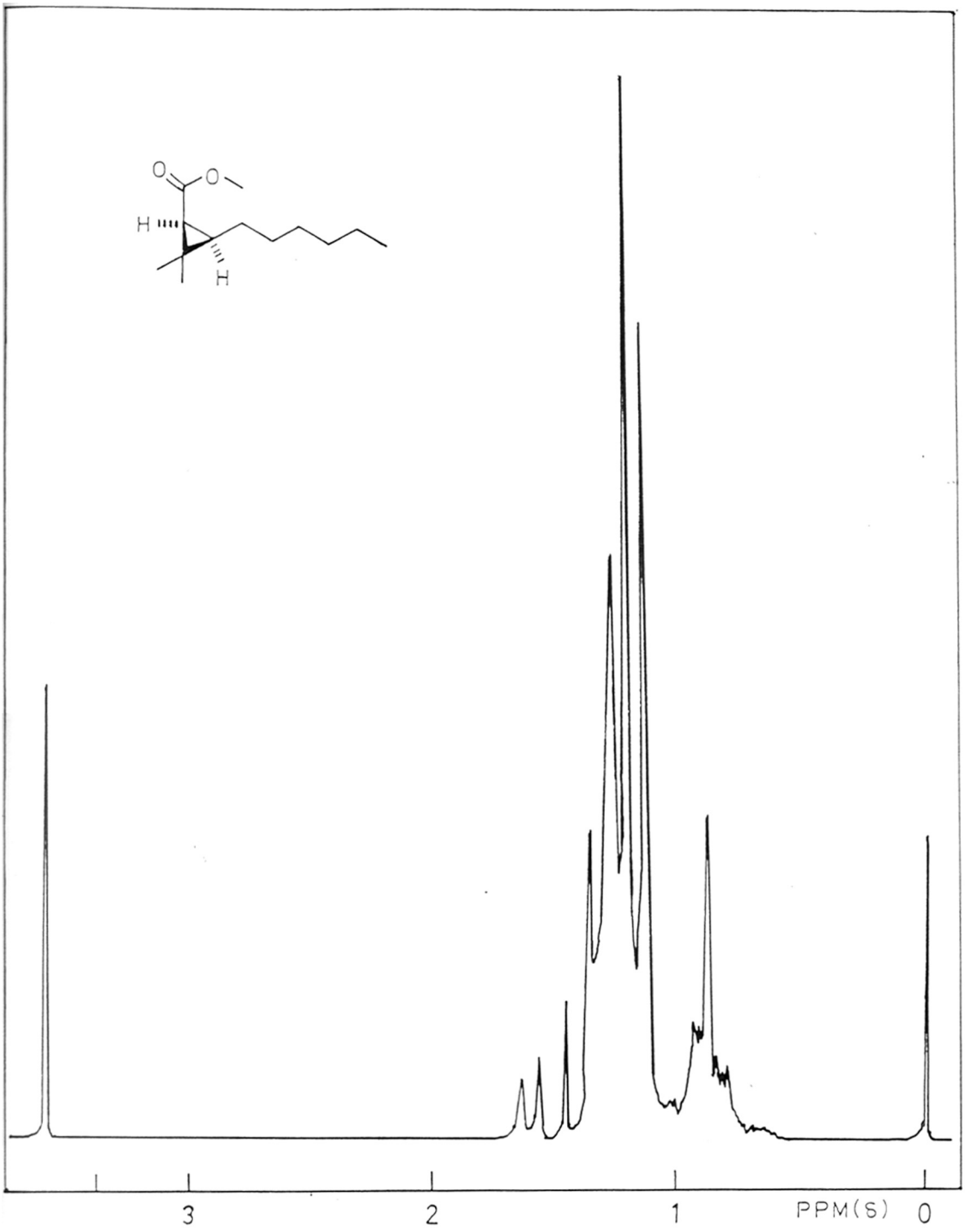


FIG. 10

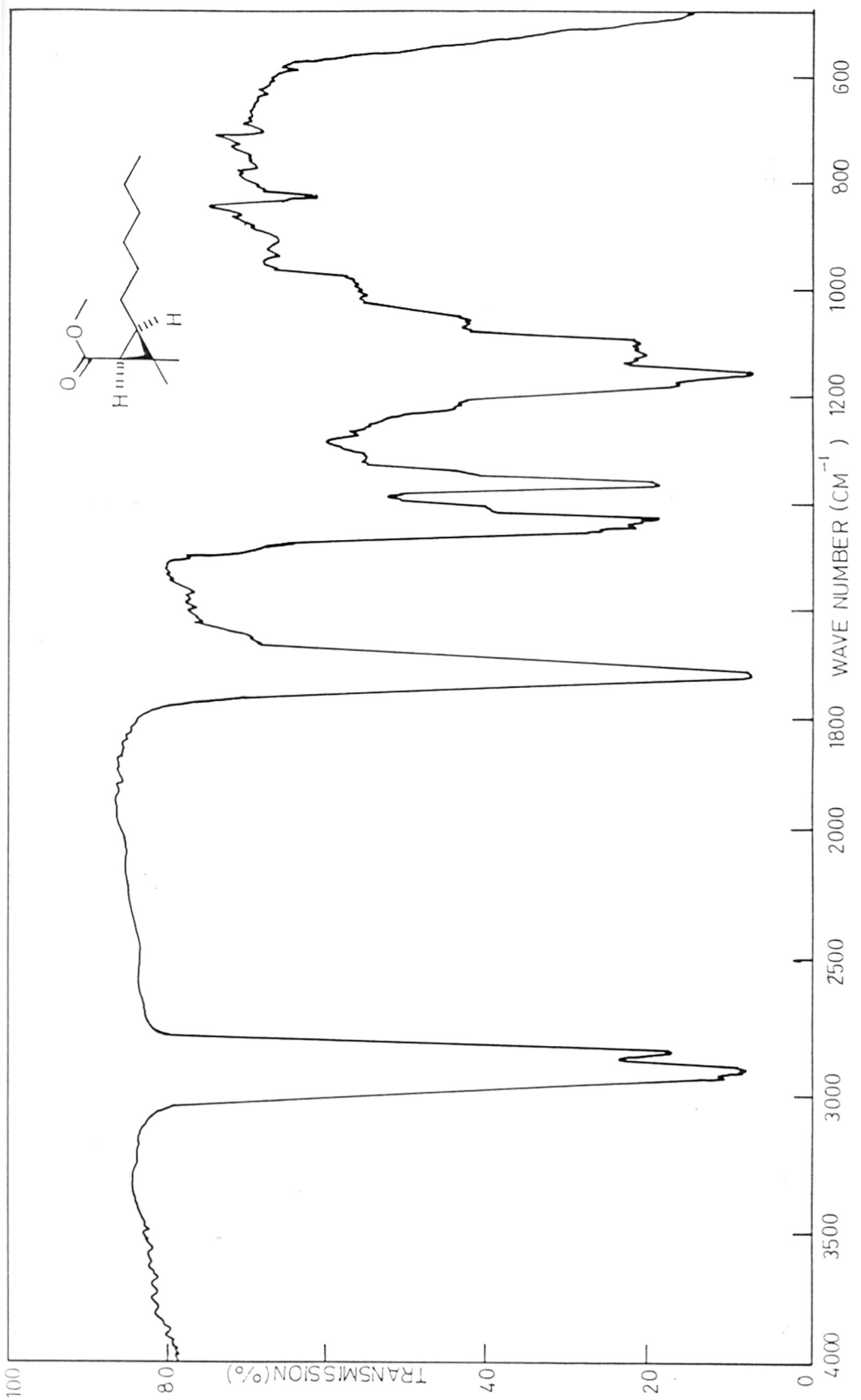

100
80
40
20
0
TRANSMISSION (%)
4000
3500
3000
2500
2000
1800
1200
1000
800
600
WAVE NUMBER (CM⁻¹)
O
O
H
H

FIG. 11

ester -C<u>H</u>$_3$).

The neutral product of ozonolysis was purified by distillation (b.p. 120°C/0.5 mm) to give a liquid as the major product in 37% yield, identified as ketone (<u>13</u>), $C_{14}H_{26}O$, $[\alpha]_D^{27}$ + 8.8° (<u>c</u>, 1.5); IR bands at: 1709 (>C=O); NMR ($CDCl_3$) (Fig. 12): 0.58 to 0.82 (2H, <u>m</u>, cyclopropane protons), 0.9 (6H, <u>s</u>, overlapping a <u>t</u>, one of the cyclopropane methyls and -C<u>H</u>$_3$ of -C_6H_{13}), 1.06 (3H, <u>s</u>, another cyclopropane methyl), 1.16 to 1.68 (10H, <u>br s</u> overlapping a <u>m</u>, 5 x -C<u>H</u>$_2$- of -C_6H_{13}), 2.18 (3H, <u>s</u>, -COC<u>H</u>$_3$) and 2.34 (2H, <u>d</u>, J=9 Hz, methylene adjacent to keto group).

In similar manner the unsaturated hydrocarbon mixture (<u>19</u> and <u>20</u>) on ozonolysis furnished in low yields a mixture of acids, the major reaction product being in the neutral portion. Esterification of the acid mixture followed by chromatographic purification failed to give the methyl ester (<u>21</u>) in pure state. The latter, however, was prepared by different route starting from ketone (<u>22</u>) isolated from neutral product of ozonolysis described subsequently.

Distillation of neutral product afforded the ketone (<u>22</u>) in 32% yield, $C_{18}H_{34}O$, MS: m/e 266 (M^+), $[\alpha]_D^{26}$ + 11.7° (<u>c</u>, 2) and identified by spectral data; IR bands at: 1701 (>C=O); NMR (CCl_4): 0.56 (2H, <u>m</u>, cyclopropane protons), 0.88 (6H, <u>s</u> overlapping a <u>t</u>, one of the cyclopropane methyls and -C<u>H</u>$_3$ of -$C_{10}H_{21}$), 1.08 (3H, <u>s</u>, another cyclopropane methyl), 1.2 to 1.58 (18H, <u>br s</u> overlapping a <u>m</u>,

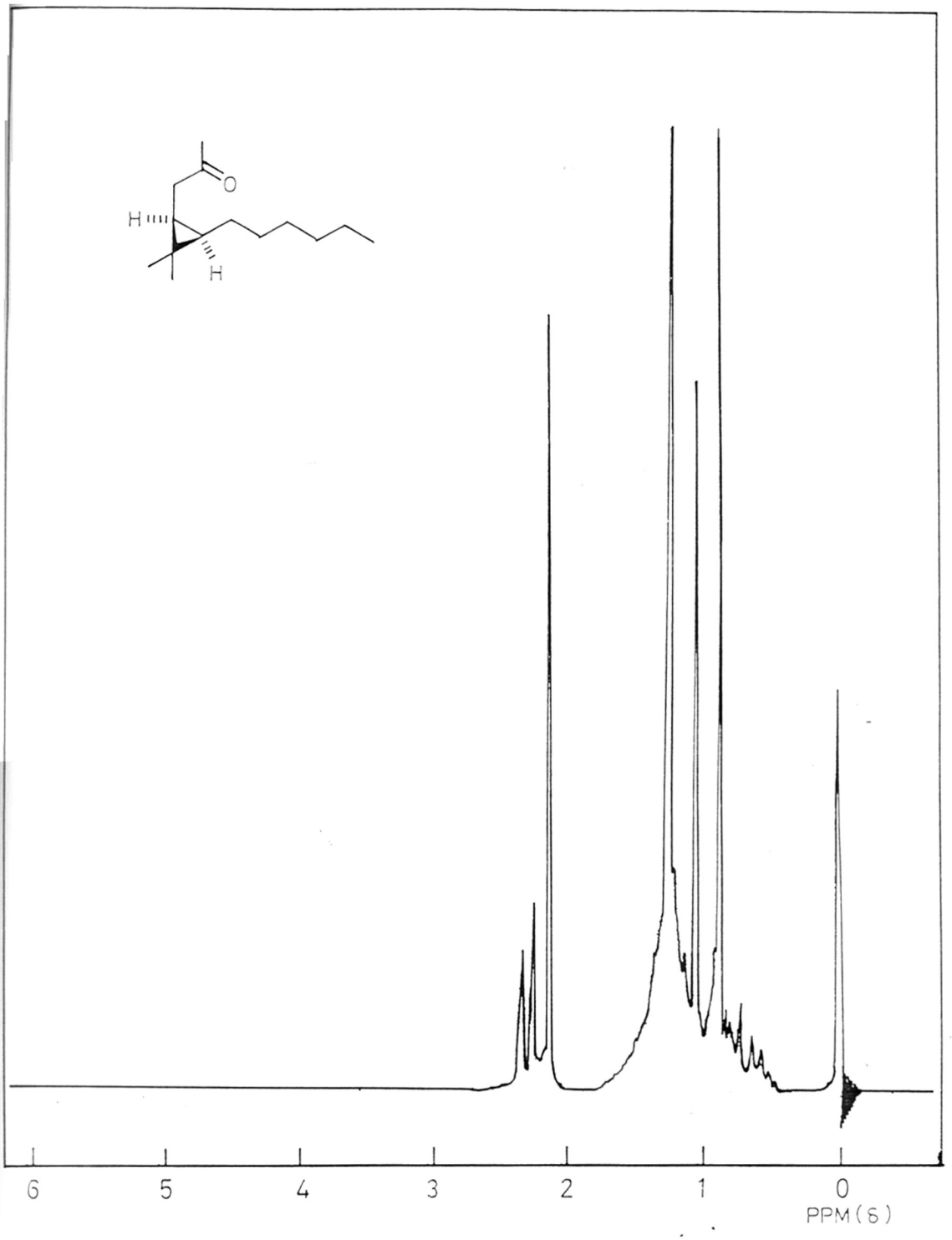


FIG. 12

9 x $-CH_2-$ of $-C_{10}H_{21}$), 2.08 (3H, s, $-COCH_3$), 2.43 (2H, d, J=6 Hz, methylene adjacent to keto group).

Baeyer-Villiger oxidation of 13 using perbenzoic acid gave the acetate, further purified by distillation (b.p.98°C/0.5 mm) to give pure acetate (14), $C_{14}H_{26}O_2$, MS: m/e 226 (M^+), in 92% yield characterized by following spectral data; IR bands at:1742, 1242 cm^{-1} (acetate); NMR (CCl_4) (Fig.13) 0.79 to 0.9 (5H , t overlapping a m, C_1, C_3 cyclopropane protons and $-CH_3$ of $-C_6H_{13}$), 1.01, 1.10 (3H each, s each, gem-dimethyl on cyclopropane), 1.3 (10H, br s, 5 x $-CH_2-$ of $-C_6H_{13}$), 2.0 (3H, s, $-COCH_3$) and 4.01 (2H, d, J=8 Hz, $-CH_2-$ adjacent to $-O-COCH_3$ group).

Similarly the acetate (23) $C_{18}H_{34}O_2$, MS: m/e 282 (M^+), was obtained in 80% yield by Baeyer-Villiger oxidation of ketone (22); IR bands at: 1745, 1235 (acetate); NMR (CCl_4): 0.63 to 0.9 (5H, m, C_1, C_3 cyclopropane protons and $-CH_3$ of $-C_{10}H_{21}$), 1.03, 1.10 (3H each, s each, gem dimethyl on cyclopropane), 1.3 (18H, br s, 9 x $-CH_2-$ of $-C_{10}H_{21}$), 1.97 (3H, s, $-COCH_3$) and 4.0 (2H, d, J=7 Hz, $-CH_2-$ adjacent to $-O-COCH_3$ group).

Saponification of acetate (14) by aqueous KOH/methanol gave crude alcohol, which was purified by distillation [b.p.120°C(bath)/0.5 mm] to give pure alcohol (15) in 95% yield, $C_{12}H_{24}O$, MS: m/e 184 (M^+), characterized by following spectral data. It showed IR bands at: 3356 (-OH); NMR(CCl_4)

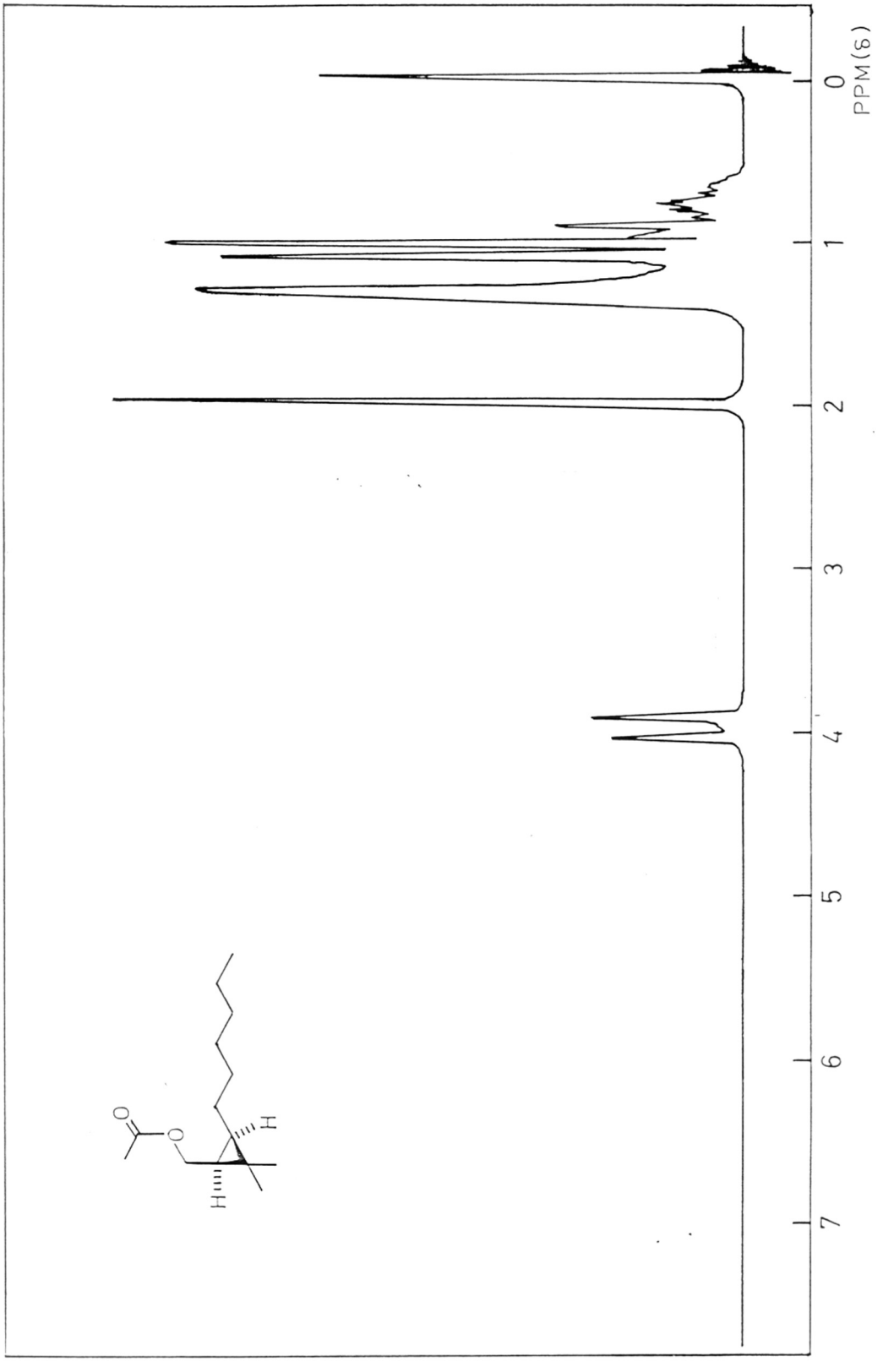


FIG. 13

(Fig. 14) 0.7 to 0.9 (5H, m, C_1, C_3 cyclopropane protons and $-C\underline{H}_3$ of $-C_6H_{13}$), 1.01, 1.08 (3H each, s each, gem dimethyl on cyclopropane), 1.3 (10H, br s, 5 x $-C\underline{H}_2-$ of $-C_6H_{13}$) and 3.61 (2H, d, J=7 Hz, $-C\underline{H}_2OH$).

Similarly the alcohol (24) was prepared from acetate (23) in 90% yield and characterized; $C_{16}H_{32}O$, MS: m/e 240 (M^+), IR bands at: 3322 (-OH); NMR (CCl_4): 0.56 to 0.88 (5H, m, C_1, C_3 cyclopropane protons and $-C\underline{H}_3$ of $-C_{10}H_{21}$), 1.00, 1.08 (3H each, s each, gem-dimethyl on cyclopropane), 1.26 (18H, br s, 9 x $-C\underline{H}_2-$ of $-C_{10}H_{21}$) and 3.5 (2H, d, J=7 Hz, $-C\underline{H}_2OH$).

As stated earlier ozonolysis of hydrocarbon mixture (19 and 20) failed to give the predicted acid (21) (in the form of its methyl ester) in pure state. Hence it was prepared from the alcohol (24) by $KMnO_4$ oxidation in acetone at 0°C. Acid thus obtained was esterified with an etheral solution of diazomethane to give crude product. It was purified by chromatography over silica gel and eluted with benzene + pet.ether (1:4) to give pure ester (21), $C_{17}H_{32}O_2$, MS: m/e 268 (M^+), $[\alpha]_D^{26}$ + 9.4 (c, 1) in 31% yield, characterized by spectral data. It showed IR bands at: 1745 (ester >C=O); NMR ($CDCl_3$): 0.87 (4H, t overlapping a m, C_3 cyclopropane proton and $-C\underline{H}_3$ of $-C_{10}H_{21}$), 1.12, 1.20 (3H each, s each, gem dimethyl on cyclopropane), 1.22 to 1.33 (18H, br s overlapping a m, 9 x $-CH_2-$ of $-C_{10}H_{21}$), 1.62 (1H, d, J=7 Hz, C_1 cyclopropane proton) and 3.6 (3H, s, ester $-C\underline{H}_3$).

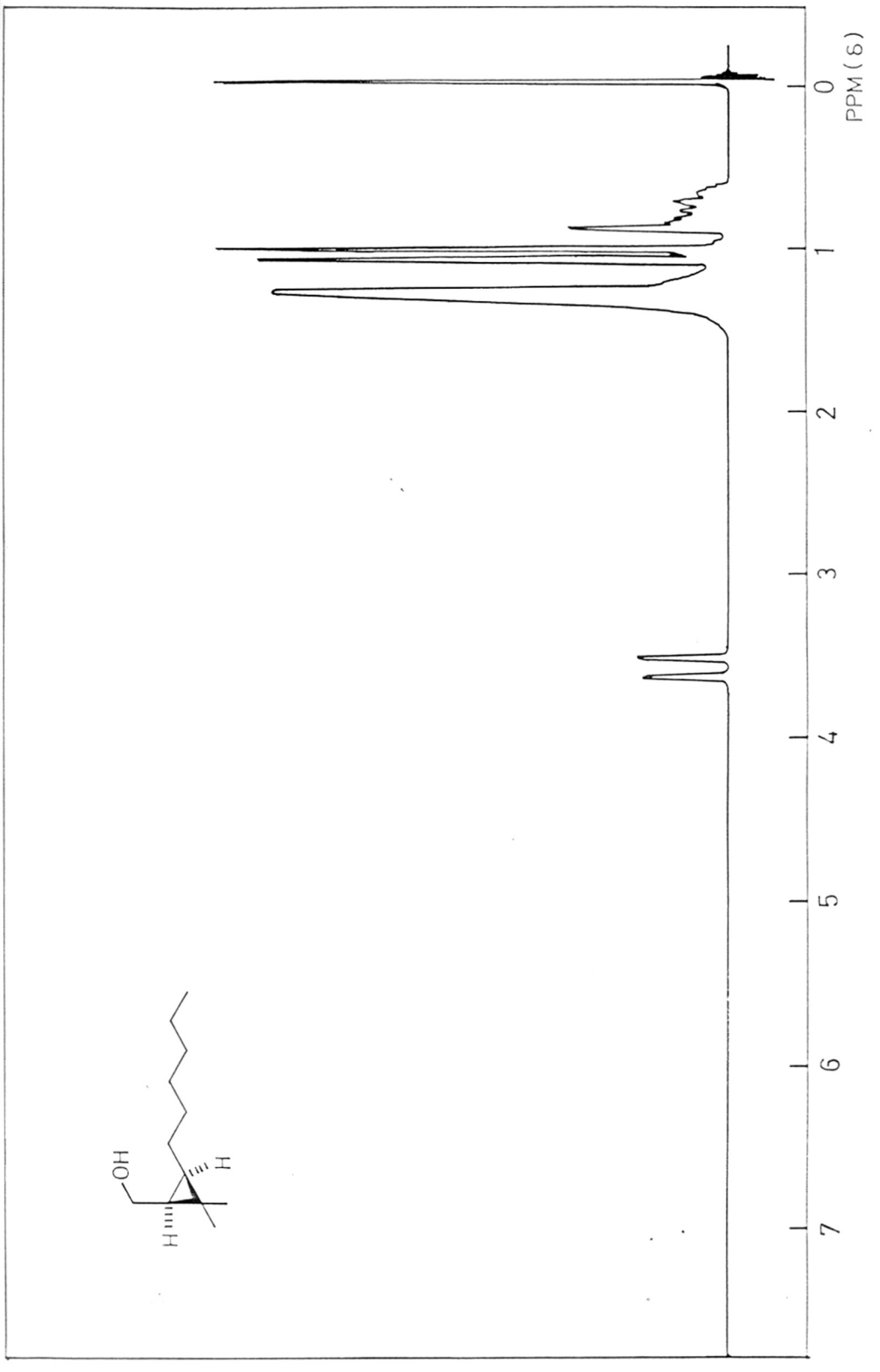


FIG. 14

EXPERIMENTAL

Preparation of 3-β ,4-∝ -carane diol (2).

In a 3 litre 3 necked round bottom flask, equipped with mechanical stirrer, was placed formic acid (90%, 525 ml) and freshly distilled 1 (195.5g) was added dropwise under stirring. Hydrogen peroxide (30%, 300 ml) was then added dropwise, maintaining the temperature of the reaction mixture between 20-30°C (2 hr). Stirring was continued at 20-30° for 6 hr and allowed to stand over-night. A solution of sodium hydroxide (160 g, in 400 ml H_2O), was added slowly to the reaction mixture under stirring, keeping the temperature around 25°C (1 hr). The reaction mixture was then transfered to a 3 lit. separating funnel and the layers were allowed to separate. The top oily layer (approx. 250 g) was transfered back to the reaction flask and further amount of solution of sodium hydroxide (40 g in 1000 ml H_2O), was added slowly under vigorous stirring, maintaining the temperature at 25-30°. After stirring for 5 hr and cooling to 5-10°C, the solid diol separated. It was filtered, residue washed with cold water and dried, yield 120 g, m.p.68°C. The crude diol was crystallised from pet.ether + 5% ethyl acetate to give pure diol (2 , 110 g, 45%), m.p.82-83°C.

Analysis

Found: C, 70.81; H, 10.52; $C_{10}H_{18}O_2$

requires: C, 70.54; H, 10.66%.

IR (Nujol): 3448, 2900, 1460, 1375, 1058, 945 and 815 cm^{-1}.

2,2-Dimethyl-3-(2-oxopropyl)cyclopropane-1-acetaldehyde (3).

In a one litre three necked flask equipped with an overhead mechanical stirrer, were taken carane diol (2, 102 g, 0.6 mol), methanol (400 ml) and water (150 ml). The contents were stirred for 10 minutes. Finely powdered sodium meta-periodate (140 g, 0.66 mol), was then added portionwise to the above solution with stirring. After addition the reaction mixture was stirred for 2 hr. It was then filtered and the residue washed with methanol (100 ml). The combined filtrate was diluted with water (600 ml) and extracted with chloroform (3 x 200 ml). The chloroform layer was washed with water (3 x 500 ml), dried and evaporated to give keto aldehyde (3, 83 g, 82%); b.p.85-87°C/1.5 mm.

Analysis

Found: C, 70.90; H, 9.48; $C_{10}H_{16}O_2$
requires: C, 71.39; H, 9.59%.

IR bands at: 2985, 2740, 1724, 1439, 1351, 1163, 1124, 1047 and 962 cm^{-1}.

2,2-Dimethyl-3-(2-oxopropyl)-cis-cyclopropane-1-acetaldehyde dimethyl acetal (4).

Freshly prepared keto aldehyde (3, 67.0g, 0.40 mol), dissolved in methanol (250 ml) was cooled to 0°C and dilute hydrochloric acid (1.2 N, 10 ml), was added to it and the

solution kept at 0°C for 48 hr. Excess of methanol was removed under reduced pressure. The residual reaction mixture was diluted with water (500 ml) and extracted with chloroform (300 ml x 3). The combined chloroform layer was washed with aqueous solution of sodium carbonate (10%), followed by water and dried. Removal of chloroform by distillation furnished keto dimethyl acetal 4 (75 g, 88%), b.p. 105-8°/1 mm.

Analysis

Found: C, 67.10; H, 10.3; $C_{12}H_{22}O_3$

requires : C, 67.3; H, 10.4%.

IR bands at: 2940, 1719, 1380, 1360, 1130, 1070, 970 and 860 cm^{-1}.

2,2-Dimethyl-3-(acetoxymethyl)-cis-cyclopropane-1-acetaldehyde dimethyl acetal (25)

To a stirred and ice cooled solution of keto dimethyl acetal (4, 71.30 g, 0.33 mol) in chloroform (50 ml) was added a chloroform solution of perbenzoic acid (PBA) (total 400 ml, 2.5 N at regular intervals of 10 hr) and the solution stirred for 50 hr, maintaining the temperature at 10-15°C. The reaction mixture was then diluted with chloroform (400 ml) and washed repeatedly with 10% aqueous solution of sodium sulphite to decompose excess of perbenzoic acid. Then it was repeatedly extracted with 10% aqueous solution of sodium carbonate to remove benzoic acid. Chloroform layer was then washed with water and dried. Removal of chloroform by

distillation gave the product which was further purified by distillation to give acetate dimethyl acetal (25, 52.0 g, 68%, b.p.115-25°/1 mm, $[\alpha]_D^{25}$ + 11° (c, 1.5).

Analysis

Found: C, 62.35; H, 9.52; $C_{12}H_{22}O_4$

requires: C, 62.58; H, 9.63%.

IR bands at: 2910, 2720, 1725, 1390, 1253, 1014 cm^{-1}.

2,2-Dimethyl-3-(acetoxy methyl)-cis-cyclopropane-1-acetaldehyde (26)

Acetate dimethyl acetal (25, 23.0 g, 0.10 mol) in aqueous oxalic acid (0.1%, 460 ml) was heated at 35°C for 2 hr, extracted with chloroform (150 ml x 3). The chloroform layer was washed with water, dried and evaporated to give acetate aldehyde (26, 12.86 g, 97%), b.p.100-115°/1.5 mm.

Analysis

Found: C, 65.3; H, 8.58; $C_{10}H_{16}O_3$

requires: C, 65.19; H, 8.75%.

IR bands at: 2940, 1725, 2720, 1370, 1240, 1125, 970 and 715 cm^{-1}.

3-Ethyl-2,2-dimethyl-cis-1-hydroxymethyl cyclopropane (27)

In a three-necked 100 ml round bottom flask, KOH (7 g, 0.125) was dissolved in ethylene glycol (20 ml), to which hydrazine hydrate (13 ml) and the acetate aldehyde (26, 7.5 g, 40 mmol) were added and refluxed under nitrogen atmosphere for 5 hr. Excess of hydrazine hydrate was

distilled off and the temperature raised upto 190°C when more distillate was collected. Combined distillates were diluted with water (50 ml) and extracted with ether (50 ml x 3). The ether layer was washed with water, dried. Removal of ether furnished a crude product purified by distillation (b.p.115-20°C/4 mm) to give a liquid, identified as the primary alcohol 27 (3.8 g, 75.8%). $[\alpha]_D^{28}$ + 22° (c, 2.2).

Analysis

Found: C, 74.6; H, 12.4; $C_8H_{16}O$

requires: C, 74.9; H, 12.6%.

IR bands at: 3360, 2899, 1452, 1374, 1048, 1017, 758 and 672 cm^{-1}.

Methyl 1S-cis 2,2-dimethyl-3-ethyl cyclopropanecarboxylate (28)

a) To an ice-cooled and stirred solution of primary alcohol (27) (1.0 g, 7.8 mmol), in acetone (10 ml), Jones chromic acid was added dropwise till the brown colour persisted. The mixture was stirred at 0°C for 3 hr, diluted with water (30 ml) and extracted with ether (25 ml x 3). The combined ether layer was washed with water (20 ml x 2) and dried. Removal of ether gave crude acid which was treated with an etheral solution of diazomethane to furnish the ester. This was then chromatographed over silica gel (5 g, 1:10) and eluted with pet.ether, to give the TLC pure liquid ester identified by spectral data as 28 (0.4 g, 32.8%); $[\alpha]_D^{28}$ + 23.85° (c, 1.2).

Analysis

Found: C, 69.5; H, 10.2; $C_9H_{16}O_2$

requires: C, 69.2; H, 10.2%.

IR bands at: 2951, 1730, 1456, 1438, 1379, 1372, 1228, 1190 1174, 1141, 1107, 1095, 923, 849 and 758 cm^{-1}.

b) The same cis ester (28) was obtained in better yields by carrying out oxidation of the alcohol (27) using $KMnO_4$ as described below:

To an ice cooled and stirred solution of primary alcohol (27, 1 g, 7.8 mmol), in acetone (15 ml), powdered $KMnO_4$ (2 g, 12.65 mmol) was added in small portions during 1 hr and stirring continued further for 1 hr at 0°C and 3 hr at room temperature. The reaction mixture was filtered and the precipitate was washed repeatedly with acetone, the precipitate extracted with hot water (25 ml x 3). The combined aqueous extracts were concentrated to small bulk (5 ml), cooled to 0°C and acidified with dilute HCl, extracted with ether (25 ml x 3). The ether layer after drying was treated with etheral solution of diazomethane to give crude ester (0.56 g). The ester was purified by chromatography over silica gel (6 g, 1:10). The fractions eluted with pet.ether gave a liquid (TLC pure), identified as cis-ester (28, 0.5 g, 41%) by spectral data and physical constants.

2,2-Dimethyl-3-(2-hydroxy-2-methyl propyl) cis-cyclopropane -1-acetaldehyde dimethyl acetal (5)

To an ice-cooled and stirred solution of CH_3MgI [prepared from Mg (9.6 g, 0.4 mol) and CH_3I (56.8 g, 0.4 mol)], in dry ether (250 ml), a solution of 4 (40 g, 0.18 mol), in dry ether (150 ml), was added dropwise during 0.5 hr. Stirring was continued for 2 hr at 0°C and thereafter the reaction mixture refluxed for 5 hr and kept overnight. The Grignard complex was cooled to 0°C, decomposed by addition of cold aqueous NH_4Cl, the ether layer separated and the aqueous layer extracted with ether (150 ml x 2). The combined ether layer was washed with water, dried and evaporated to give crude 5, which was further purified by chromatography (Alumina grade II, 1:10). The fractions eluted with chloroform gave the pure hydroxy dimethyl acetal (5, 35 g, 81.4%).

Analysis

Found: C, 67.5; H, 11.2; $C_{13}H_{26}O_3$

requires : C, 67.8; H, 11.4%.

IR bands at: 3546, 3012, 1462, 1372, 1124, 909, 858 and 758 cm^{-1}.

2,2-Dimethyl-3-(2-hydroxy-2-methyl propyl) cis-cyclopropane-1-acetaldehyde (6)

The hydroxy acetal (5, 35 g) was stirred with 700 ml of aqueous oxalic acid (0.1%) solution at 35°C for 2 hr and

extracted with ether (150 ml x 3). The ether layer was washed with water, dried and removal of ether furnished the hydroxy aldehyde as a liquid (6, 26.88 g, 96%).

Analysis

Found: C, 71.3; H, 10.8; $C_{11}H_{20}O_2$
requires: C, 71.7; H, 10.9%.

IR bands at: 3534, 3012, 2778, 1725, 1462, 1374, 1153, 910 and 760 cm^{-1}.

2,2-Dimethyl-3-(2-hydroxyhexyl/decyl) cis-1-(2-methyl-2-hydroxypropyl) cyclopropane (7)/(16)

In a 500 ml two necked round bottom flask fitted with a reflux condenser and a dropping funnel were taken magnesium turnings (2.58 g, 0.1 mol), in dry ether (50 ml) and a crystal of iodine. A solution of n-butyl bromide (14.7 g, 0.1 mol) in dry ether (50 ml) was taken in the dropping funnel. Initially a few ml. of bromide solution was added and reaction started by gentle warming, the remaining solution was then added by dropwise addition within 0.5 hr and stirring continued till all the magnesium dissolved. The Grignard reagent thus obtained was then cooled to 0°C and a solution of hydroxy aldehyde (6, 6.6 g, 36 mmol), in ether (50 ml) was then added dropwise under vigorous stirring. After the addition was completed, it was stirred for additional 2 hr at 0°C and thereafter heated under reflux for 6 hr and left overnight. The reaction mixture was cooled to 0°C, excess

reagent and magnesium complex were decomposed by adding dropwise, a saturated solution of ammonium chloride (75 ml) at 0-5°C. The ether layer was separated and aqueous portion extracted with ether (150 ml x 2). The combined ether layer was washed with water, dried and evaporated to furnish the crude diol, which was further purified by distillation to give a pure colourless liquid, identified as diol (7, 5.1 g, 59%), b.p.120°C/0.2 mm.

Analysis

Found: C, 74.3; H, 12.4; $C_{15}H_{30}O_2$

requires: C, 74.3; H, 12.5%.

IR bands at: 3356, 2920, 1460, 1375, 1120, 900 cm^{-1}.

Similarly alcohol (16) was prepared by Grignard reaction on (6, 5.52 g, 0.01 mol), using octyl magnesium bromide to give TLC pure diol (16, 5.811 g, 65%). $[\alpha]_D^{26}$ + 0.27° (c, 2).

Analysis

Found: C, 76.4; H, 12.8; $C_{19}H_{38}O_2$

requires: C, 76.5; H, 12.8%.

IR banda at: 3448, 2910, 1465, 1380, 1160, 910 cm^{-1}.

2,2-Dimethyl-3-(2-oxohexyl/decyl) cis-1-(2-methyl-2-hydroxy propyl) cyclopropane (8)/(17)

To an ice cooled and stirred solution of diol (7, 13 g, 54 mmol) in acetone (100 ml) was added dropwise Jones chromic acid reagent (20 ml) till the brown colour persisted.

The reaction mixture was stirred at 0°C for 10 minutes, diluted with water (200 ml) and extracted with ether (100 ml x 2). The combined ether layer was washed with water (100 ml x 2) brine and dried. Removal of ether by distillation gave crude product which was chromatographed over silica gel (240 g, 1:20) and eluted with pet.ether + benzene (1:1) to give TLC pure hydroxy ketone (8, 10 g, 78%).

Analysis

Found: C, 74.9; H, 11.5; $C_{15}H_{28}O_2$

requires: C, 75.0; H, 11.7%.

IR bands at: 3390, 2910, 1709, 1560, 1378, 965, 908 cm^{-1}.

Similarly hydroxy ketone (17)was prepared by Jones chromic acid oxidation of the diol (16). After work up crude product was purified by chromatography to give pure hydroxy-ketone (17, 6.2 g, 70%).

Analysis

Found: C, 76.9; H, 12.1; $C_{19}H_{36}O_2$

requires: C, 77.0; H, 12.2%.

IR bands at: 3425, 2915, 2847, 1718, 1367, 1380, 1105, 912 cm^{-1}.

2,2-Dimethyl-3-n hexyl/decyl cis-1-(2-methyl-2-hydroxy-propyl) cyclopropane (9)/(18)

In a 250 ml round bottom flask NaOH (10 g, 0.25 mol) was dissolved in ethylene glycol (100 ml) by warming. Hydrazine hydrate (10 ml, 80%) and hydroxy ketone (8, 10 g, 42 mmol)

were then added to it, mixture refluxed under nitrogen atmosphere for 5 hr in a sand bath. Excess of hydrazine hydrate was distilled off, the temperature raised to 190°C and heating continued further for 4 hr. Reaction mixture was cooled to room temperature and diluted with water (200 ml). Extracted with ether (50 ml x 3). The combined ether layer was washed with water (50 ml x 2), brine and dried. Removal of ether gave a TLC pure liquid, identified as the alcohol (9, 6.9 g, 74%).

Analysis

Found: C, 79.5; H, 13.3; $C_{15}H_{30}O$

requires: C, 79.5; H, 13.4%.

IR bands at: 3356, 2905, 2840, 1453, 1372, 1150, 903 cm^{-1}.

Similarly Huang-Minlon reduction of hydroxy ketone (17, 5.92 g, 20 mmol) using ethylene glycol and NaOH gave the alcohol (18, 3.94 g, 70%). $[\alpha]_D^{26}$ + 5.6° (c, 2).

Analysis

Found: C, 80.8; H, 13.5; $C_{19}H_{38}O$

requires: C, 80.8; H, 13.6%.

IR bands at: 3378, 2946, 2860, 1467, 1380, 1150, 908 cm^{-1}.

2,2-Dimethyl-3-n-hexyl/decyl cis-1-(2-methyl prop-1-enyl) cyclopropane (10)/(19) and their double bond isomers (11)/(20) respectively

To an ice-cooled and stirred solution of alcohol (9, 6.5 g, 28 mmol) in pyridine (30 ml), $POCl_3$ (7 g, 46 mmol)

was added dropwise at 0°C. The mixture was allowed to stand for 24 hr at 25°C, poured on to crushed ice (50 g) and extracted with ether (100 ml x 2). The combined ether layer was washed with dil. HCl, to remove excess of pyridine, followed by water, dried and evaporated to give a liquid product, which on coloumn chromatography over silica gel and elution with pet.ether gave a TLC pure liquid, which was however found to be a mixture of unsaturated hydrocarbons (10) and (11) (3.95 g, 75%) identified by NMR spectrum.

Analysis

Found: C, 86.2; H, 13.6; $C_{15}H_{28}$

requires: C, 86.46; H, 13.54%.

IR bands at: 2941, 2860, 1660, 1462, 1387, 1120, 890 cm^{-1}.

In a similar manner dehydration of alcohol (18) using $POCl_3$/pyridine afforded a mixture of unsturated hydrocarbons (19) and (20) as a liquid in 79% yield.

Analysis

Found: C, 86.1; H, 13.8; $C_{19}H_{36}$

requires: C, 86.28; H, 13.72%.

IR bands at: 2930, 2860, 1650, 1465, 1385, 890 cm^{-1}.

Methyl 1S cis 2,2-dimethyl-3-n-hexyl cyclopropanecarboxylate (12) and 2,2-dimethyl-3-n-hexyl/decyl cis-1-(2-oxopropyl) cyclopropane (13)/(22)

A stream of ozonized oxygen (approximately 1 g/hr), was bubbled through an ice-cold (-5°C) solution of the unsaturated

hydrocarbon mixture (10 and 11, 3.149 g, 15 mmol) in ethyl acetate (100 ml), till the absorption of ozone was completed (tested by starch iodide paper). The solution of ozonide was transfered to a 250 ml round bottom flask and cooled to to 0°C. To a stirring solution of ozonide, Jones chromic acid reagent was then added dropwise, till the brown colour persisted. Stirring was continued at 0°C for 1 hr and at room temperature for 2 hr. The reaction mixture was then diluted with water (100 ml), the ethyl acetate layer separated, washed with water (50 ml x 2), extracted with 10% aq. Na_2CO_3. The carbonate layer was acidified by dil. H_2SO_4 (1:10) followed by extraction with ether (50 ml x 2). The ether layer was washed with water, dried and distilled off to furnish the acid (12, 0.29 g, 8.6%) as a minor product. This was converted to the methyl ester (12, R" = CH_3, 0.31 g) by an etheral solution of diazomethane.

Analysis

Found: C, 73.4; H, 11.4; $C_{13}H_{24}O_2$
requires: C, 73.5; H, 11.4%.

IR bands at: 2919, 2842, 1739, 1435, 1378, 1165, 842 cm^{-1}.

The ethyl acetate layer was dried and distilled off to give crude product, further purified by distillation (b.p.120°C/0.5 mm) to give pure ketone (13, 1.32 g, 37%) as the major product.

Analysis

Found: C, 79.9; H, 12.4; $C_{14}H_{26}O$
requires: C, 80.0; H, 12.5%.

IR bands at: 2910, 2860, 1709, 1455, 1350, 1222, 1160, 672 cm^{-1}.

Similarly the hydrocarbon mixture (19 and 20) on ozonolysis furnished in low yields the acid mixture, the major reaction product being in the neutral portion. Esterification of the acid mixture followed by chromatographic purification failed to give the methyl ester (21) in pure state. The latter, however, was prepared by $KMnO_4$ oxidation of the alcohol (24).

The corresponding ketone (22) was obtained similarly from neutral product in 32% yield.

Analysis

Found: C, 80.0; H, 12.8; $C_{18}H_{34}O$

requires: C, 81.1; H, 12.9%.

IR bands at: 2920, 2845, 1701, 1445, 1360, 1222 cm^{-1}.

2,2-Dimethyl-3-n-hexyl/decyl cis-1-acetoxymethyl-cyclopropane (14)/(23)

To an ice-cooled and stirred solution of (13, 0.4 g, 1.9 mmol) in chloroform (10 ml), a chloroform solution of perbenzoic acid (2 ml, 2N) was added and the contents stirred for 6 hr at 0°C. Another portion of perbenzoic acid solution (2 ml, 2N) was then added and the stirring continued at 10-15°C for 72 hr. Reaction mixture was diluted with chloroform (10 ml), excess perbenzoic acid was decomposed by aq. sodium sulfite followed by extraction with aqueous Na_2CO_3. The chloroform layer was washed with water, dried

and distilled to furnish crude product, further purified by distillation (b.p.98°C/0.5 mm) to give pure acetate (14, 0.394 g, 92%).

Analysis

Found: C, 74.3; H, 11.6; $C_{14}H_{26}O_2$

requires: C, 74.3; H, 11.6%.

IR bands at: 2942, 2876, 1742, 1455, 1380, 1290, 1242 cm^{-1}.

Similarly the acetate (23) was prepared in 80% yield.

Analysis

Found: C, 76.4; H, 12.1; $C_{18}H_{34}O_2$

requires: C, 76.5; H, 12.1%

IR bands at: 2930, 2860, 1745, 1370, 1235, 790 cm^{-1}.

2,2-Dimethyl-3-n-hexyl/decyl cis-1-hydroxymethyl cyclopropane (15)/(24)

Acetate (14, 0.39 g, 1.7 mmol) was added to a mixture of aqueous KOH (0.6 g in 1.5 ml water) and methanol (20 ml). Homogeneous solution was refluxed on water-bath for 6 hr. Most of the methanol was removed under reduced pressure and the residue diluted with water (50 ml) and extracted with ether (25 ml x 3). The combined ether layer was washed with water, dried and distilled off to give crude product, purified by distillation (b.p.120°C(bath)/0.5 mm), to give pure alcohol (15, 0.3 g, 95%).

Analysis

Found: C, 78.1; H, 13.0; $C_{12}H_{24}O$

requires: C, 78.2; H, 13.1%.

IR bands at: 3356, 2920, 2850, 1460, 1010 cm^{-1}.

Similarly saponification of the acetate (23) furnished the alcohol (24) in 90% yield.

Analysis

Found: C, 79.9; H, 13.3; $C_{16}H_{32}O$

requires: C, 80.0; H, 13.4%.

IR bands at: 3322, 2930, 2860, 1465, 1380, 1015 cm^{-1}.

Methyl 1S cis, 2,2-dimethyl-3-n-decyl cyclopropanecarboxylate(21)

To an ice cooled and stirred solution of alcohol (24, 0.3 g, 1.25 mmol) in acetone (5 ml) powdered $KMnO_4$ (0.3 g, 3.8 mmol) was added in small portions during 1 hr. Stirring was continued further for 1 hr at 0°C and 3 hr at 25°C. Reaction mixture was then filtered and the precipitate washed repeatedly with acetone (10 ml x 3). The precipitate was then extracted with hot water (10 ml x 3) and the aqueous extract treated as described earlier to give acid which was esterified with an etheral solution of diazomethane to give crude ester. It was purified by chromatography over silica gel (3 g, 1:20) and eluted with benzene + pet.ether (1:4) to give pure ester (21, 0.12 g, 31%).

Analysis

Found: C, 76.0; H, 11.9; $C_{17}H_{32}O_2$

requires: C, 76.1; H, 12.0%.

IR bands at: 2931, 2860, 1745, 1440, 1380, 1175 cm^{-1}.

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CHAPTER IV

SYNTHESIS OF SUBSTITUTED PHENOLIC ESTERS OF (±) CIS 2,2-DIMETHYL-3-(2,2 -DICHLOROVINYL) CYCLOPROPANE -1-CARBOXYLIC ACID.

SUMMARY

A number of esters of (±) cis 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropane-1-carboxylic acid with ortho, meta, para substituted phenols have been prepared with a view to evaluating them for their miticidal properties.

The general method adopted for the synthesis of such esters consist of reacting (±) cis 2,2-dimethyl-3-(2,2-dichlorovinyl) cyclopropane-1-carboxylic acid chloride with the phenol in an inert solvent like benzene and in presence of pyridine as a catalyst. Esters thus obtained have been purified by crystallization and characterized by spectral data.

INTRODUCTION

In the chapter 1 of this thesis various processes have been described for the synthesis of (±) cis and (±) trans 2,2-dimethyl 3-(2,2-dichlorovinyl) cyclopropane carboxylic acid, commonly known as DV acid. The latter is the acid component of the commercially important pyrethroids like permethrin and cypermethrin, useful for controlling coleoptrons and other pests infesting the cash crops. It is known in the case of pyrethroid possessing a dihalo vinyl side chain at C_3 of the cyclopropane that the 1R cis esters are about twice as active as the corresponding 1R trans isomers. Taking into consideration the higher insecticidal activity of the esters derived from cis isomers, efforts have been made to obtain the DV acid in which the (±) cis isomer predominates. The method developed by Ciba-Geigy[1], described in chapter 1 (chart 4, scheme F) is one such method, which gives rise to DV acid cis:trans ratio 80:20. The Sagami method, developed by Japanese workers, initially for commercial DV acid has been suitably modified[2,3] so as to get the (±) cis DV acid in high proportion. Only recently it has been observed that the cyahalothrin is about 50 to 100 times more active[4] against mites than permethrin.

During the course of our research efforts aimed at synthesizing cyclopropane containing miticides, from (+)-3-carene, an indigenously abundantly available raw material we observed that certain phenolic esters[5,6] of

2,2 dimethyl 3-(2-oxo-propyl) cyclopropane acetic acid and 2,2 dimethyl 3-n propyl cyclopropane acetic acid were found to be much more active against red spider mite, potato mite, Rhizoglyphus echinopus and polyphagotarsonemus latus as well as pink and purple mites, when compared with standard miticides like tedion, tetradifon and dicofol. Amongst phenolic moieties it was found that the esters of meta-cresol were active at micro dosage level against pink and purple mites. In addition many other phenolic esters of these two acids (chart I, compound III and IV) were found to be active against pink and purple mites.

Our compounds derived from (+)-3-carene (I), have been tested successfully at the following research institutes in the country.

i) Department of Entomology, National Chemical Chemical Laboratory, Pune.

ii) Tea Research Association, Tocklai (Assam)

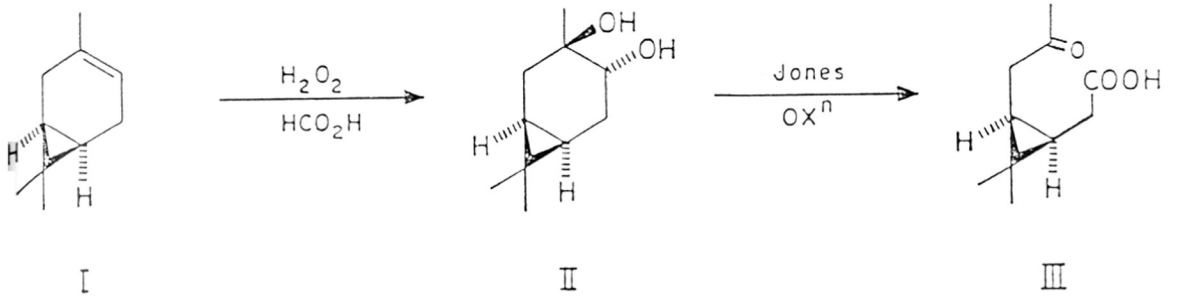
iii) Potato Research Station, Rajgurunagar

iv) Potato Research Station, Simla

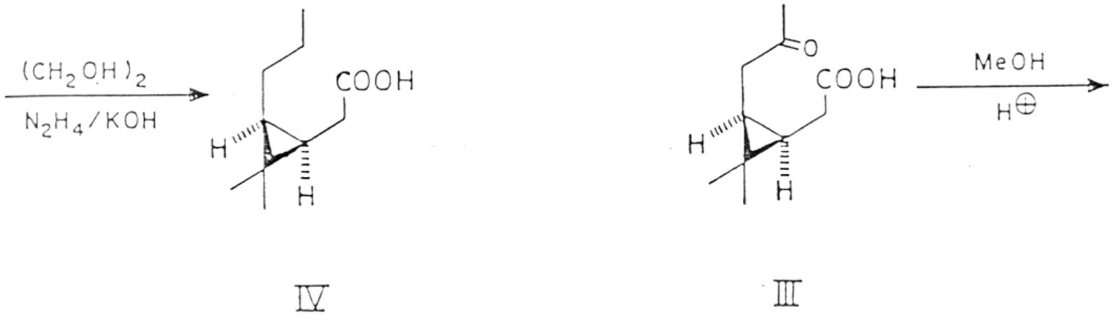
v) United Planters Association in Southern India, Coonoor

The bio-efficacy data of many structurally related esters of cyclopropane acetic acids III and IV with different alcohols and substituted phenols given in chart II are described in Tables 1,2,3. The samples were tested upto 0.005% concentration on potato mite as well as pink and purple mites. Also some of these esters were tested against

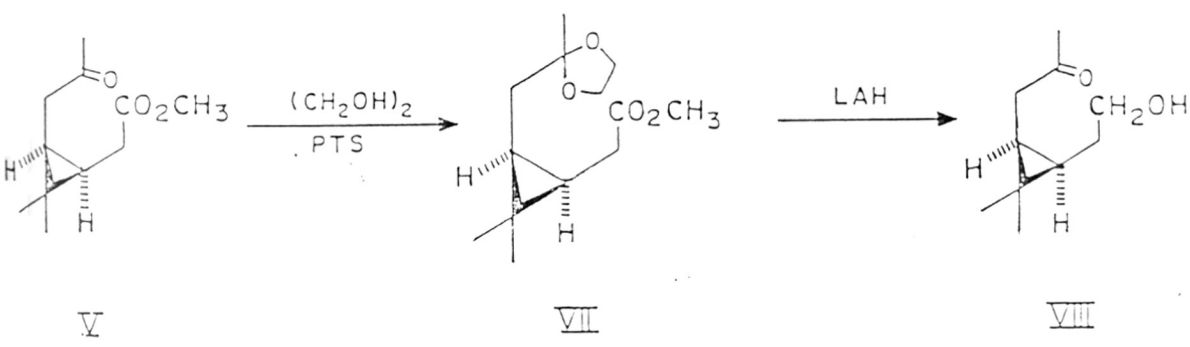
CHART I



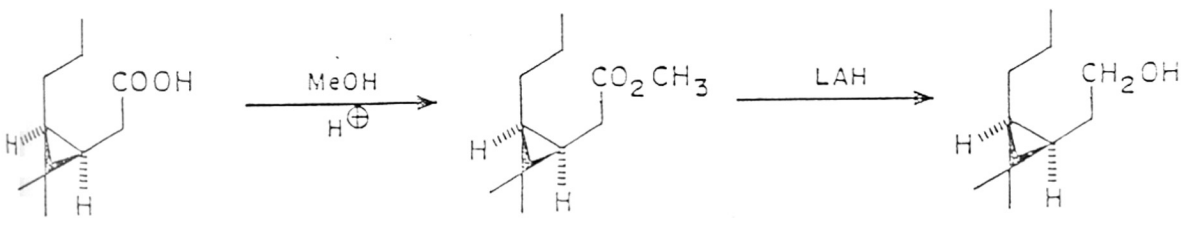
I II III



IV III

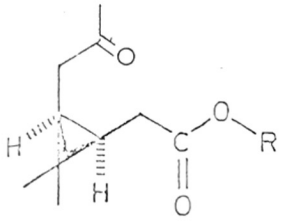


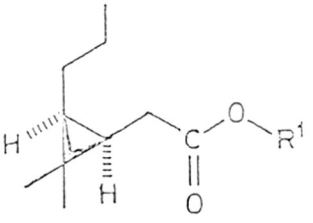
V VII VIII



IV VI IX

CHART – II

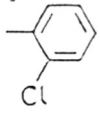


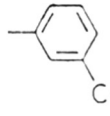


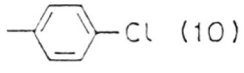
R = $-C_4H_9$ (1)

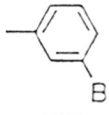
 (5a)

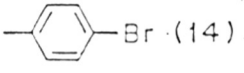
$-C_6H_{13}$ (3)

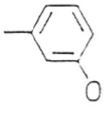
 (6)

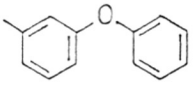
 (8)

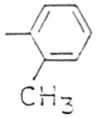
 (10)

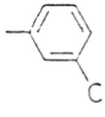
 (12)

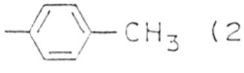
 (14)

 (16)

 (19)

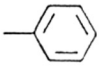
 (21)

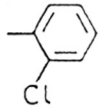
 (23)

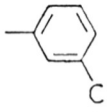
 (25)

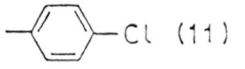
$R^1 = -C_4H_9$ (2)

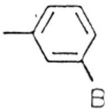
$-C_9H_{19}$ (4)

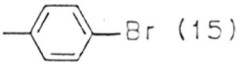
 (5)

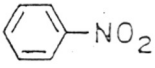
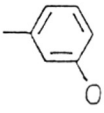
 (7)

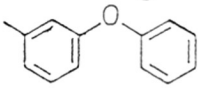
 (9)

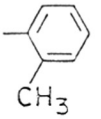
 (11)

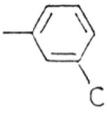
 (13)

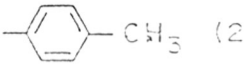
 (15)

 (17),  (18)

 (20)

 (22)

 (24)

 (26)

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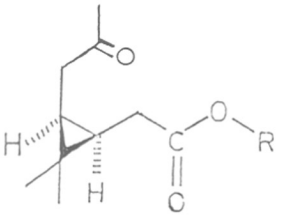

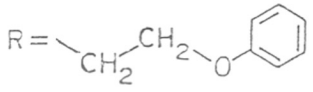
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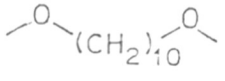
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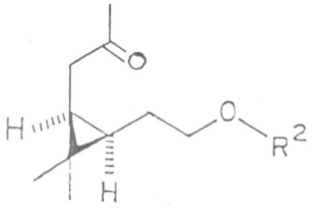

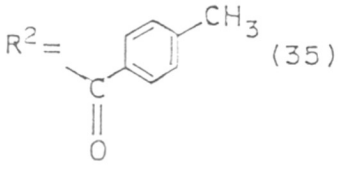
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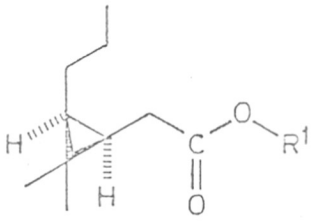

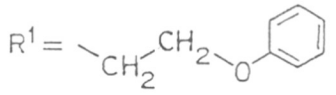
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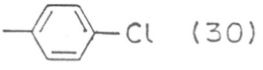
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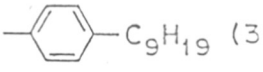
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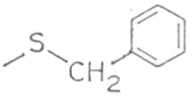
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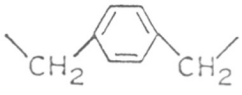
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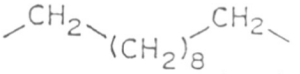
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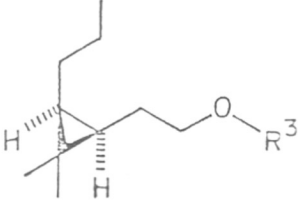

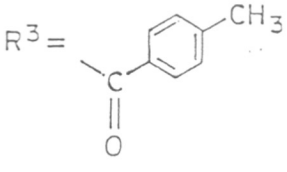
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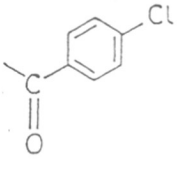
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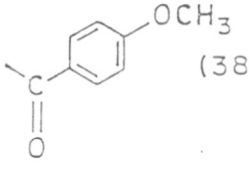
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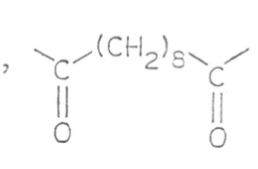
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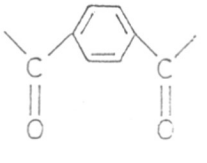

(40)

Table 1

Treatment against		Percentage mortality after					
		24 hours			48 hours		
		Concentration			Concentration		
a) Pink mites	No.	0.5%	0.1%	0.05%	0.5%	0.1%	0.05%
m-cresyl ester	(24)	100	100	96.5	100	100	96.6
phenyl keto ester	(5a)	96.6	92.5	31.2	100	92.5	59.4
phenyl ester	(5)	95.4	34.7	25	94.4	440	34.7
m-cresyl keto ester	(23)	100	80.7	70	100	96	85
Tedion	-	95.41	89	60.8	100	92.8	73.9
Control	-	nil	nil	nil	nil	nil	nil
b) Purple mites							
m-cresyl ester	(24)	100	100	100	100	100	100
phenyl keto ester	(5a)	90.4	69.5	69.5	90.4	73.9	73.9
phenyl ester	(5)	57.8	40.9	14.2	57.8	45.4	14.2
m-cresyl keto ester	(23)	100	73.6	47.6	100	84	61
Tedion	-	62.5	41.6	42	87.5	70.8	57.8
Control	-	nil	nil	nil	nil	nil	nil

Table 2

No.	Name of compound	Percentage population reduction after 24 hrs.
-	C_{14} ester	43.16
-	Cetyl keto ester	74.45
-	Cetyl ester	57.88
24	m-cresyl ester	61.21
26	p-cresyl ester	35.14
25	p-cresyl keto ester	67.38
23	m-cresyl keto ester	87.81
-	Tetradifon	79.10

Table 3

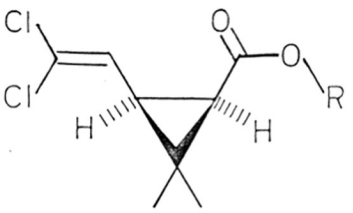
Name of the compound	Compd. No.	Percentage mortality after 24 hrs. Pink mites	Purple mites
m-bromophenyl ester	(13)	100	100
p-cresyl keto ester	(25)	100	100
p-cresyl ester	(26)	100	100
o-chlorophenyl ester	(7)	100	86.6
o-chlorophenyl keto ester	(6)	100	100
m-chlorophenyl ester	(9)	100	100
2,4-dichlorophenyl ester	(30)	100	100
Terephthalyl diester	(40)	100	100
m-bromophenyl keto ester	(12)	100	100
p-nitrophenyl ester	(17)	100	100
m-methoxyphenyl ester	(18)	88.8	100
m-methoxyphenyl keto ester	(16)	100	100
p-toluyl ester	(36)	100	100
p-anisoyl ester	(38)	100	100
m-cresyl ester	(24)	100	100
m-cresyl ester(20% EC soln.)	(24)	100	100

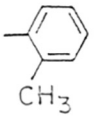
two-spotted spider mites at FMC, USA. However, these esters were found to be not quite active against the above mite.

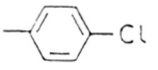
Based on these observations it appeared promising to prepare some phenolic esters of (±) cis DV acid with a view to evaluate their miticidal activity. In the preparation of such esters it was desired to bring about a combination of the acid moiety of highly potent pyrethroids and the phenolic moiety of active miticides. In this connection the following mentioned substituted phenols have been condensed with (±) cis DV acid to give corresponding esters (chart III) and characterized by spectral data.

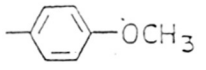
i) ortho-Cresol
ii) para-Chloro phenol
iii) para-methoxy phenol
iv) para-nitro phenol
v) para-benzyloxy-phenol
vi) phenol
vii) 2,4-dichloro phenol
viii) ortho-ethoxy phenol
ix) meta-cresol
x) ortho-chloro phenol
xi) ortho-methoxy phenol

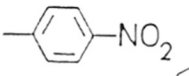
CHART III

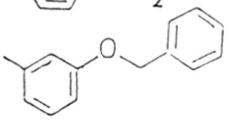


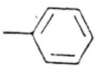
A , R = 

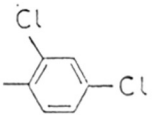
B , 

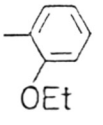
C , 

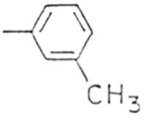
D , 

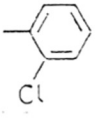
E , 

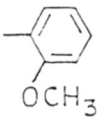
F , 

G , 

H , 

I , 

J , 

K , 

EXPERIMENTAL

General method for preparation of phenolic esters of (±) cis DV acid

DV acid (2.19 g; 0.01 mol) and thionyl chloride (4.8 g, 0.04 mol) were stirred for 3 hr at 50-60°C. Excess thionyl chloride was distilled off to get acid chloride (2.5 g, 98%).

To a cooled (5°C) and stirred solution of acid chloride (2.5 g, 9.8 mmol) and phenol (9.8 mmol) in dry benzene (20 ml), pyridine (1 ml) was added dropwise during 15 minutes and the reaction mixture stirred at room temperature for 16 hr.

The reaction mixture after dilution with benzene was washed successively with cold 10% aqueous NaOH, 10% dilute HCl followed by water and dried. Removal of solvent by distillation gave the crude ester, further purified by crystallization to give pure ester (yield 61-80%) characterized by physical constants (Table 4) and spectral data (Table 5).

Table 4

Structure No,	Yield %	m.p. °C	Molecular formula	Analysis							
				Found %				requires %			
				C	H	Cl	N	C	H	Cl	N
A	72	78	$C_{15}H_{16}Cl_2O_2$	60.05	5.42	23.77	-	60.21	5.39	23.70	-
B	69	77	$C_{14}H_{13}Cl_3O_2$	52.70	4.15	33.30	-	52.60	4.09	33.28	-
C	78	102	$C_{15}H_{16}Cl_2O_3$	57.10	5.20	22.50	-	57.15	5.11	22.49	-
D	61	107	$C_{14}H_{13}Cl_2NO_4$	50.75	3.80	21.40	4.20	50.77	3.95	21.41	4.23
E	75	109	$C_{21}H_{20}Cl_2O_3$	64.30	5.20	18.10	-	64.29	5.14	18.07	-
F	80	80	$C_{14}H_{14}Cl_2O_2$	58.75	4.90	24.80	-	58.75	4.93	24.78	-
G	77	65	$C_{14}H_{12}Cl_4O_2$	47.40	3.41	40.00	-	47.48	3.41	40.05	-
H	72	65	$C_{16}H_{18}Cl_2O_3$	58.33	5.49	21.60	-	58.36	5.51	21.54	-
I	74	45	$C_{15}H_{16}Cl_2O_2$	60.10	5.35	23.72	-	60.21	5.39	23.70	-
J	71	71	$C_{14}H_{13}Cl_3O_2$	52.69	4.20	33.10	-	52.60	4.09	33.28	-
K	78	82	$C_{15}H_{16}Cl_2O_3$	57.05	5.16	22.30	-	57.15	5.11	22.49	-

Table 5

Structure No.	IR cm^{-1}	NMR* ppm(δ)	Mass (M^+)
A	1740 1620 1592	1.31, 1.33 (3H each, s each, gem-dimethyl), 2.15 (5H, s overlapping two m, aromatic $-CH_3$ and C_1, C_3 protons), 6.24 (1H, m, olefinic proton), 7.08 (4H, m, aromatic protons).	298
B	1742 1612 1590	1.29, 1.33 (3H each, s each, gem-dimethyl), 1.93 (1H, d, J=8 Hz, C_3-H), 2.20 (1H, d, J=8 Hz, C_1-H), 6.10 (1H, m olefinic proton), 7.00, 7.26 (2H each, d each, J=8 Hz, aromatic protons).	318
C	1735 1615 1600	1.29, 1.30 (3H each, s each, gem-dimethyl), 2.04 (1H, d, J=8 Hz, C_3-H), 2.22 (1H, d, J=8 Hz, C_1-H), 3.76 (3H, s, $-OCH_3$), 6.25 (1H, m, olefinic proton), 7.09 (4H, m, aromatic protons).	314
D	1745 1615 1593	1.31, 1.37 (3H each, s each, gem-dimethyl), 2.09 (2H, m, C_1 and C_3 -H), 6.15 (1H, d, J=8 Hz, olefinic proton), 7.25, 8.19 (2H each, m each, aromatic protons).	329

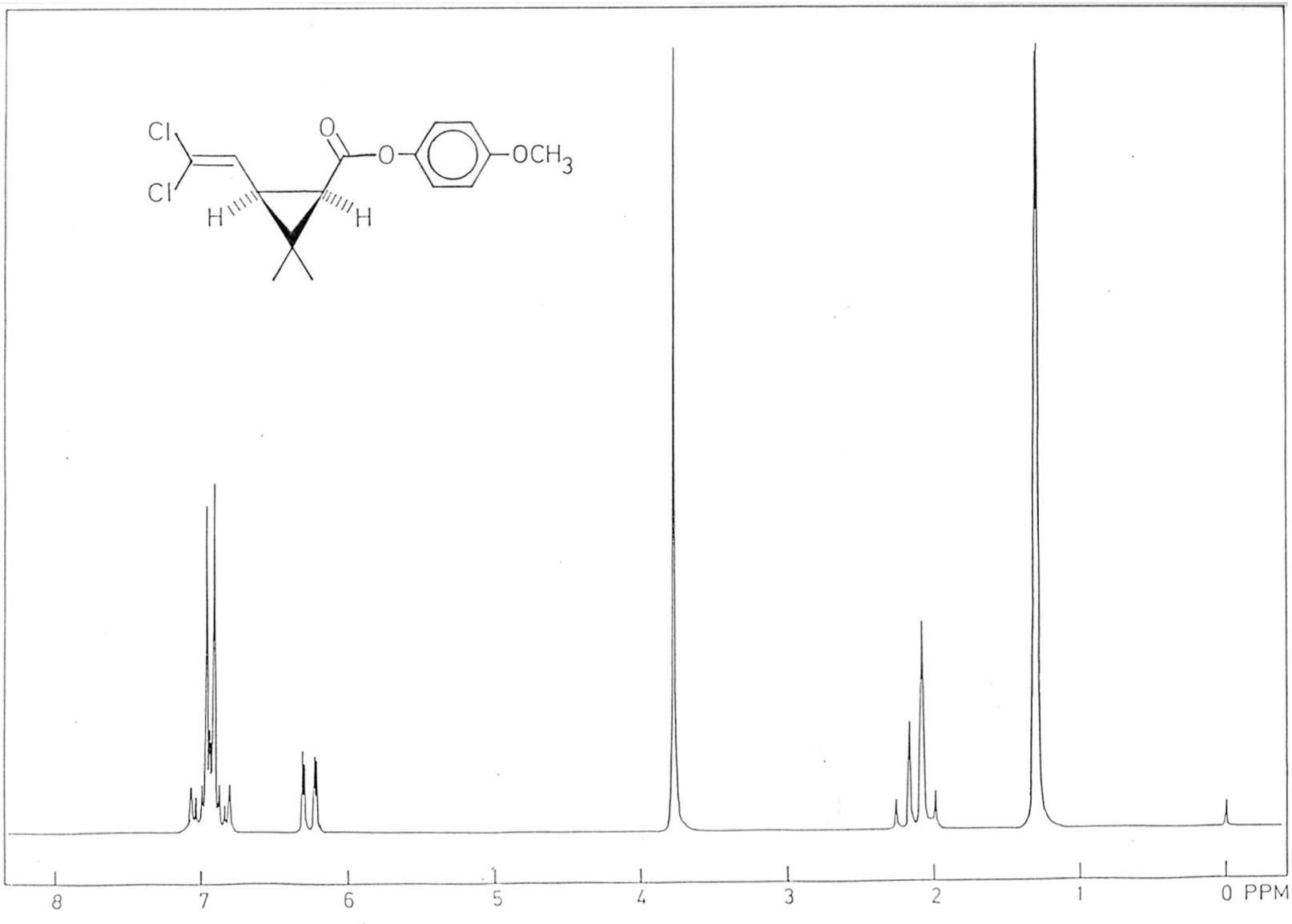


FIG.1

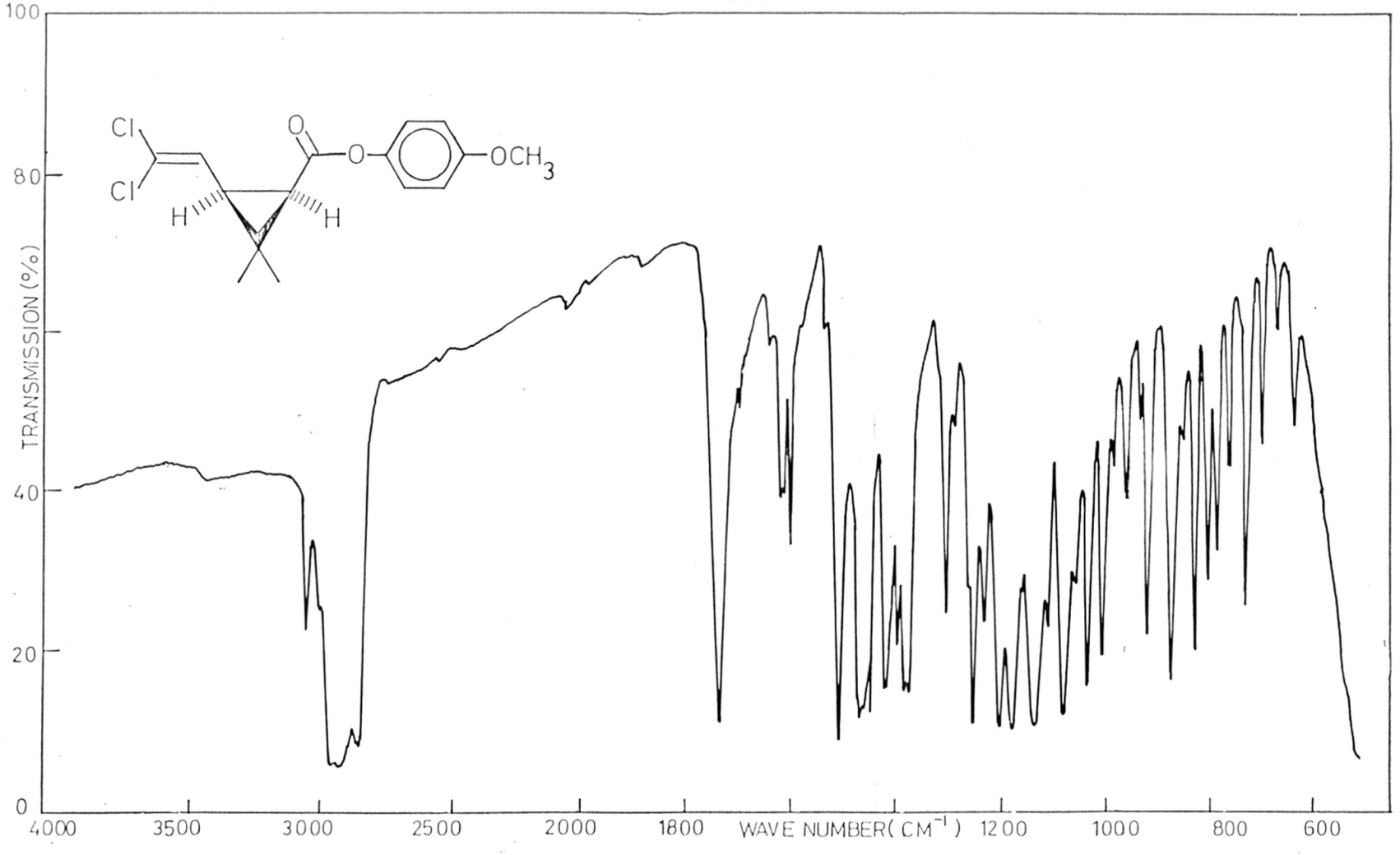

100
80
40
20
0
TRANSMISSION (%)
Cl
Cl
H
H
O
O
OCH3
4000
3500
3000
2500
2000
1800
WAVE NUMBER(CM-1)
1200
1000
800
600

FIG. 2

Table 5 (continued)

Structure No.	IR cm^{-1}	NMR* ppm(δ)	Mass
E	1745, 1612, 1600	1.28, 1.39 (3H each, s each, gem-dimethyl), 1.84 (1H, d, J=6 Hz, C_1 -H), 2.38 (1H, dd, J_1=5 Hz, J_2=8 Hz, C_3-H), 5.06 (2H, s, $-CH_2-C_6H_5$), 5.69 (1H, d, J=8 Hz, olefinic proton), 7.00 (4H, s, $-O-C_6H_4-O-$), 7.40 (5H, m, $-CH_2-C_6H_5$).	390
F	1745 1620 1600	1.33,1.35 (3H each, s each, gem -dimethyl), 2.09 (1H, d, J=8 Hz, C_1-H), 2.24 (1H, d, J=8 Hz, C_3-H), 6.28 (1H, m, olefinic proton), 7.27 (5H, m, aromatic protons).	284
G	1743 1620 1588	1.31, 1.34 (3H each, s each, gem-dimethyl), 2.12 (1H, d, J=8 Hz, C_1-H), 2.29 (1H, d, J=8 Hz, C_3-H), 6.19 (1H, m, olefinic proton), 7.24 (3H, m, aromatic protons).	352
H	1750 1610 1590	1.39 (9H, s overlapping a t, gem-dimethyl and $-OCH_2-CH_3$), 1.5 (1H, d, J=7 Hz, C_1-H), 2.12 (1H, m, C_3-H), 4.00 (2H, q, J=8 Hz, $-O-CH_2-CH_3$), 6.22 (1H, m, olefinic proton), 7.00 (4H, m, aromatic protons).	328

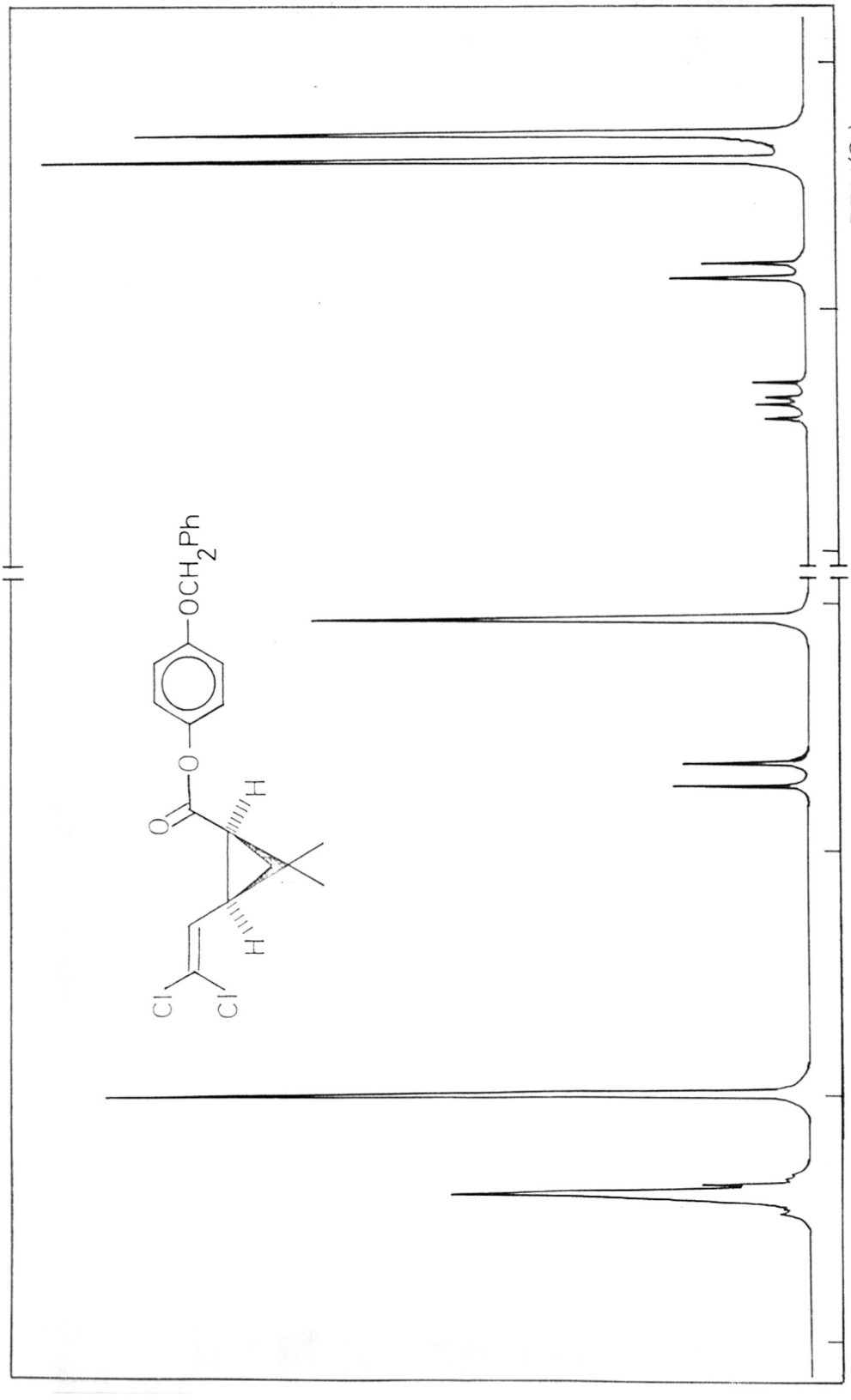


FIG. 3

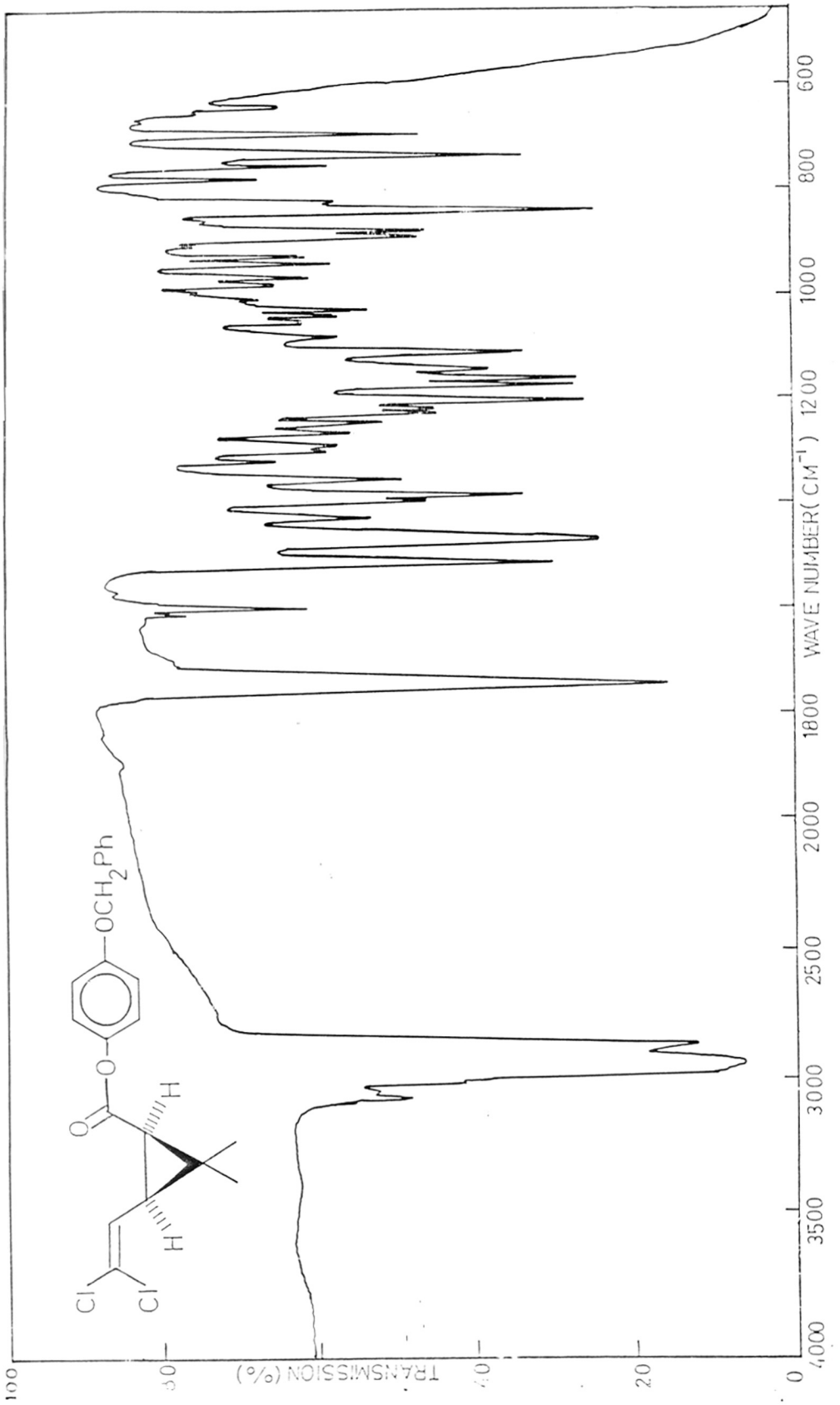

TRANSMISSION (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
WAVE NUMBER(CM^{-1})
OCH$_2$Ph
O
O
H
H
Cl
Cl

FIG. 4

Table 5 (continued)

Structure No.	IR cm^{-1}	NMR* ppm(δ)	Mass
I	1747 1615 1587	1.30, 1.33 (3H each, s each, gem-dimethyl), 2.04 (1H, d, J=8 Hz, C_3-H), 2.22 (1H, d, J=8 Hz, C_1-H), 2.35 (3H, s, $-C_6H_5-CH_3$), 6.23 (1H, m, olefinic proton), 7.04 (4H, m, aromatic proton).	298
J	1745 1610 1580	1.31, 1.34 (3H each, s each, gem-dimethyl), 2.13 (1H, d, J=8 Hz, C_3-H), 2.17 (1H, d, J=8 Hz, C_1-H), 6.22 (1H, m, olefinic proton), 7.25 (4H, m, aromatic protons).	318
K	1745 1607 1585	1.31 (6H, s, gem-dimethyl), 2.12 (2H, two d overlapping, C_1 and C_3 -H), 3.84 (3H, s, $-OCH_3$), 6.22 (1H, m, olefinic proton), 7.00 (4H, m, aromatic protons).	314

*The olefinic proton in most of the phenolic esters studied showed multiplet instead of doublet in NMR spectrum, because it forms the X part of the ABX system.

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CHAPTER V

SYNTHESIS OF SOME NOVEL 1,2 SECOPYRETHROIDS VIA CLAISEN ORTHO ESTER REARRANGEMENT.

SUMMARY

This chapter describes the synthesis of 1,2-seco-pyrethroids viz. ∝(RS) cyano-3-phenoxy benzyl-3-(1-cyclohexyl/cyclopenlynyl)-4-methyl pentenoates for evaluation of their insecticidal properties. Aldol type condensation of cyclohexanone/cyclopentanone (1a/b) with isobutaraldehyde gave the 2-isobutylidene cyclohexanone/cyclopentanone (2a/b). $NaBH_4$ reduction of 2 gave the corresponding allylic alcohols (3a/b). Claisen ortho ester rearrangement on the later using triethyl ortho acetate afforded ethyl esters (4a/b), which were saponified to give the corresponding acids (5a/b). The ∝(RS)-cyano-3-phenoxy benzyl esters (7a/b) were prepared by reaction of ∝(RS)-cyano-3-phenoxy benzyl alcohol (prepared in-situ)with the acid chlorides (6a/b) prepared from acids (5a/b) using $SOCl_2$.

INTRODUCTION

It has been widely recognized 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 replacing the existing compounds which have ceased to give reliable control because of development of immunity by insects or on account of deficiencies, such as (i) excessive persistance (ii) harmful effect on non-targeted organisms and (iii) lack of appropriate mobility in soil or plant. The work described in this chapter is aimed at contributing towards the synthesis and development of new insecticides, concentrating on "Secopyrethroids" or "Cut up chrysanthemates" which can be considered as acyclic analogues of pyrethroids.

It was suggested that the presence of a gem-dimethyl or its steric equivalent β to the carboxylate function is one of the important structural features contributing towards insecticidal activity, in the case of chrysanthemates.

Subsequent studies on the acid moiety of these insecticides have shown that the presence of intact cyclopropane ring is unnecessary for high insecticidal activity[1a-h]. 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. Seco-pyrethroids can be considered as open chain equivalents of active cyclopropane carboxylates and derived from the latter by cleavage of cyclopropane ring of pyrethroids can be cleaved in three different ways leading to three possible types of "Cut up chrysanthemates" or "Seco-pyrethroids" (chart 1). 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.

A good deal of work already been carried out on the synthesis on 1,2 and 2,3 secopyrethroids and many of these compounds have been found to be active insecticides. Some of the synthetic routes leading to 1,2 and 2,3 secopyrethroids have been described in chart 2 and 3.

In our laboratory 3-phenoxy benzyl-2-alkyl-5-methyl hex-4-enoates and 2-alkyl pent-4-enoates have been synthesized[2] (Scheme I) starting from diethyl malonate employing a simple sequence of reactions like alkylation, decarbethoxylation and transesterification. Many of these esters exhibited insecticidal activity against Musca domestica and adult Aedes aegyptii, at moderately lower concentrations.

By following a slightly modified procedure, 3-phenoxy-benzyl-2-isopropyl 5,5-dichloro/dibromo pent-4-enoates were

CHART 1

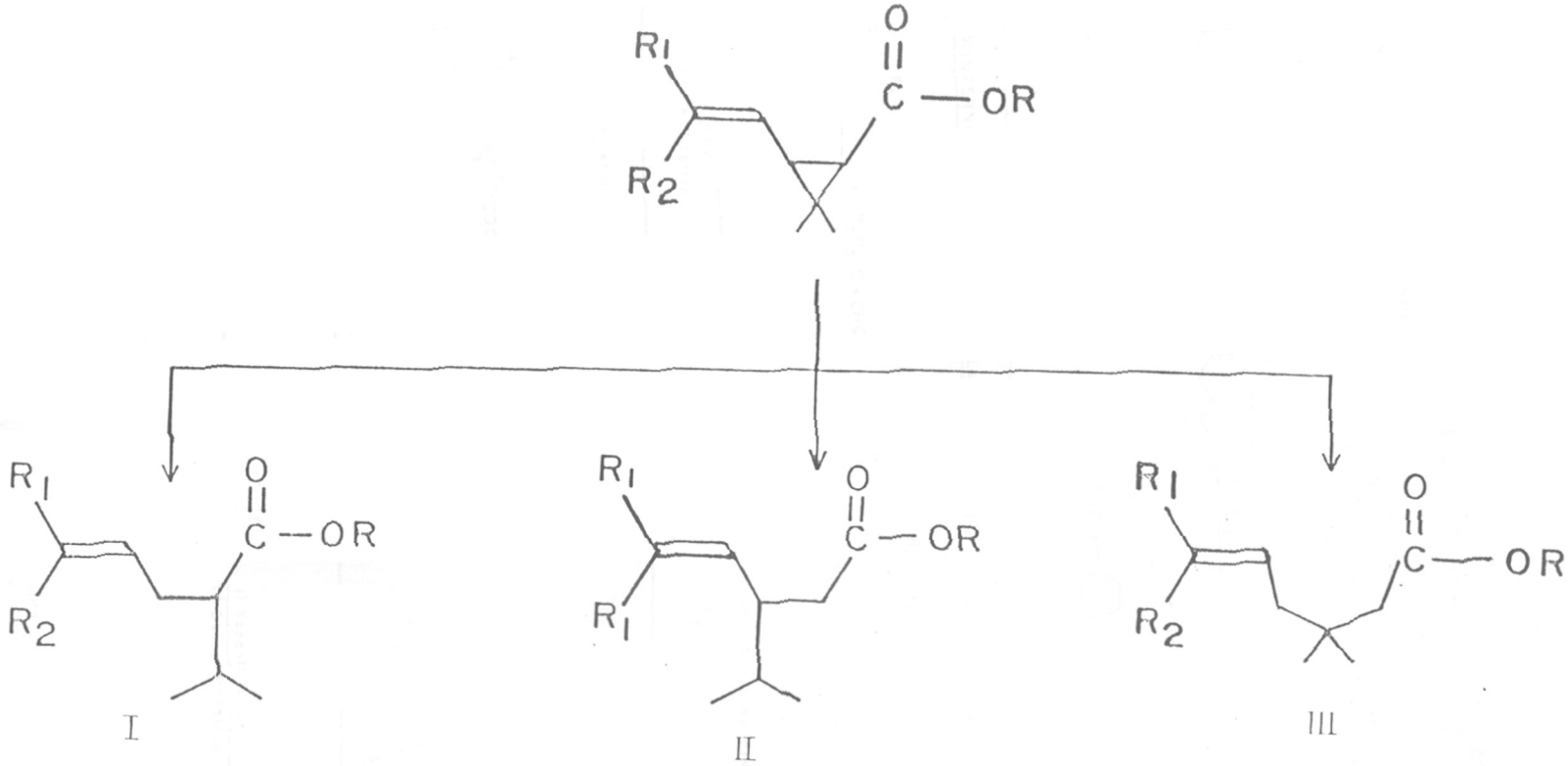
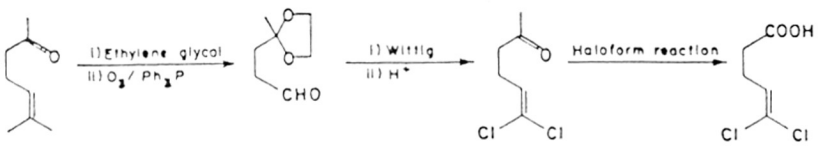
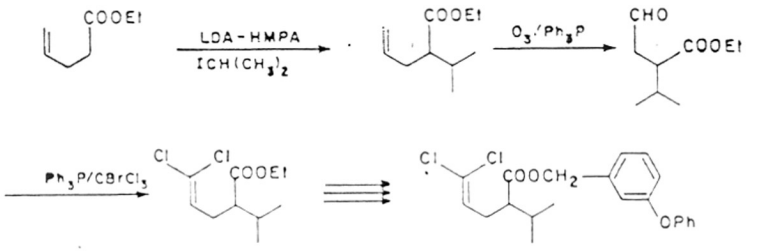

R1
R2
O
C — OR
I
II
III
2,3 - Secopyrethroids
1,2 - Secopyrethroids
1,3 - Secopyrethroids

CHART 2

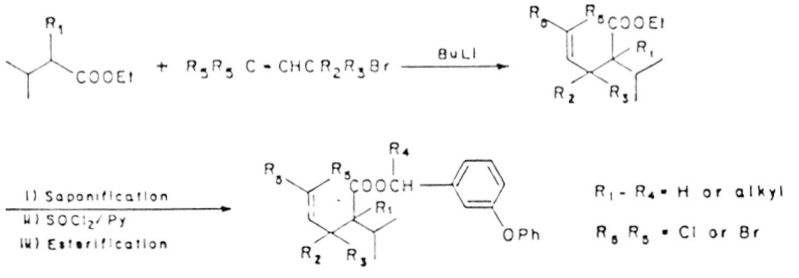
A) W. G. TAYLOR (1980)



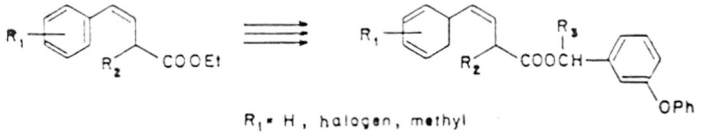
B) W. G. TAYLOR (1984)



C) WINTERNITZ PAROL (Hoffmann La Roche und Co)



D) MEYER W et al

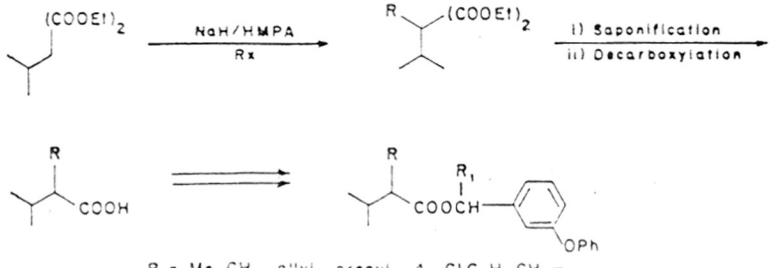


R_1 = H, halogen, methyl

R_2 = H, alkyl

R_3 = H, $-C\equiv N$, $-C\equiv CH$

E) BULL MICHAEL et al

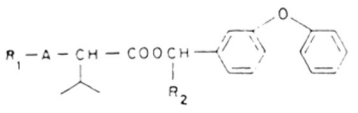


R = Me_2CH, allyl, propyl, 4 - $ClC_6H_4CH_2-$

R_1 = H, $-C\equiv N$, $-C\equiv CH$

CHART 3

F) KUTSUDA et al (1980)



I

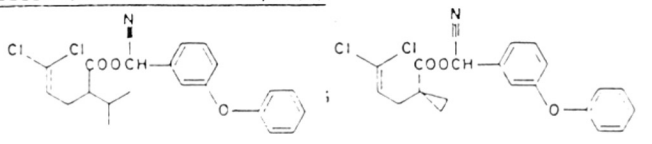
A = O , NH , CH_2

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

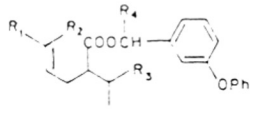
A = CH_2, R_1 = Haloalkyl or haloalkenyl radical with 1-5 carbon atoms

R_2 = H or C≡N

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



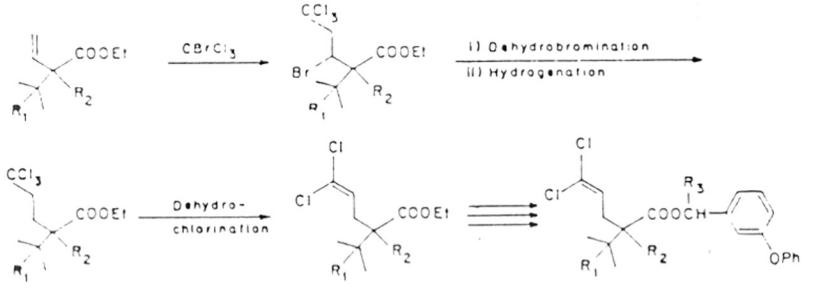
H) DRABEK J et al (Ciba-Geigy A-G)



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

R_2 = H, Cl ; R_4 = H, $-C\equiv N$, $-C\equiv CH$

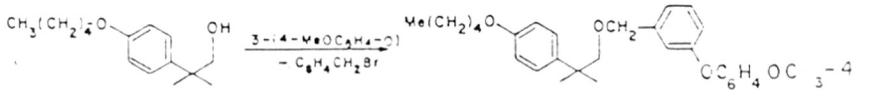
I) OMURA Y (Kuraray Co Ltd)



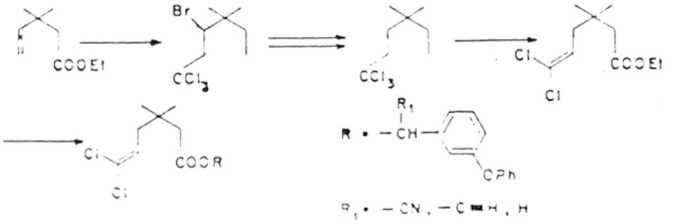
R_1 = Cl, Br, H ; R_2 = H, alkyl, $-C\equiv CR_3$, $-CH_2CH=CR_1R_1$

R_3 = H, $-C\equiv N$, $-C\equiv CH$

J) N. UMEMOTO

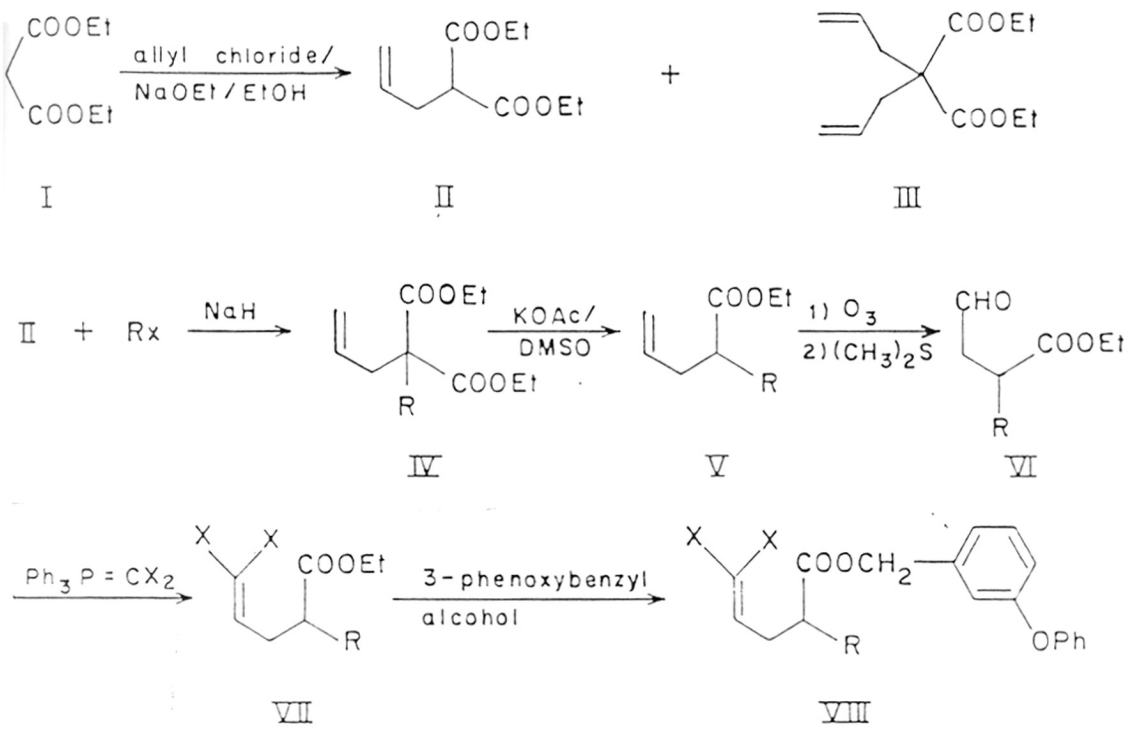


K) OMURO et al



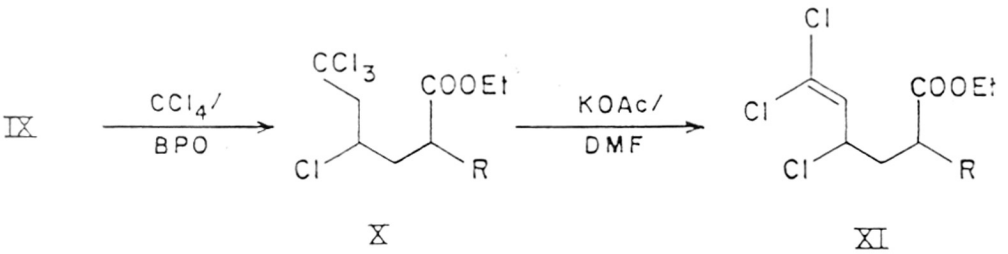
R_1 = $-CN$, $-C\equiv H$, H

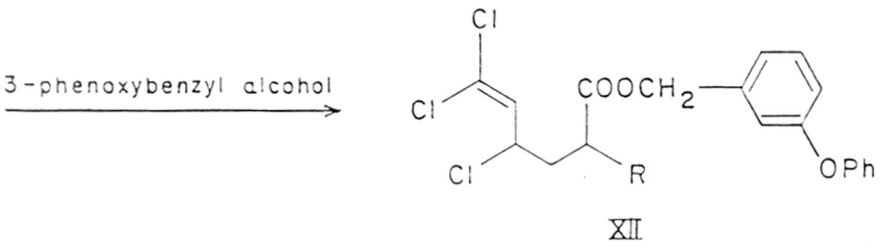
SCHEME 1



X = Cl or Br

R = a, isopropyl; b, benzyl





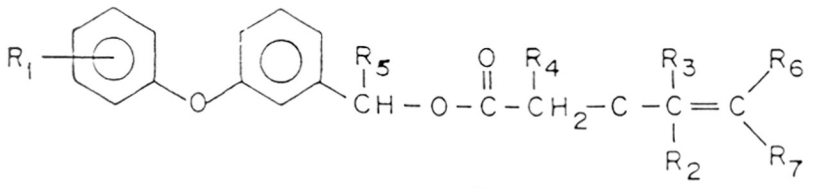
R = a, isopropyl; b, benzyl

synthesized[2] (Scheme II) showing better insecticidal and larvicidal activity against Musca domestica (1 μg/insect) and 100% mortality against 4th instar 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.

In another sequence of reaction, 3-phenoxy benzyl 2-isopropyl-5-chloro/cyano hex-4-enoates have been synthesized starting from 6-methyl-hept-5-ene-2-one (Scheme III), which exhibited good larvicidal activity at 10 ppm dose against 4th instar mosquito larvae.

Although a good deal of work has been carried out on the synthesis and evaluation of 1,3 and 2,3 secopyrethroids for their insecticidal and larvicidal properties, little work appears to have been carried out on 1,2 secopyrethroids. This chapter describes the synthesis of some 1,2-secopyrethroids. In the structures of these compounds the isopropyl group is present in γ position to the carboxylate function and the δ double bond forms a part of cycloalkyl ring.

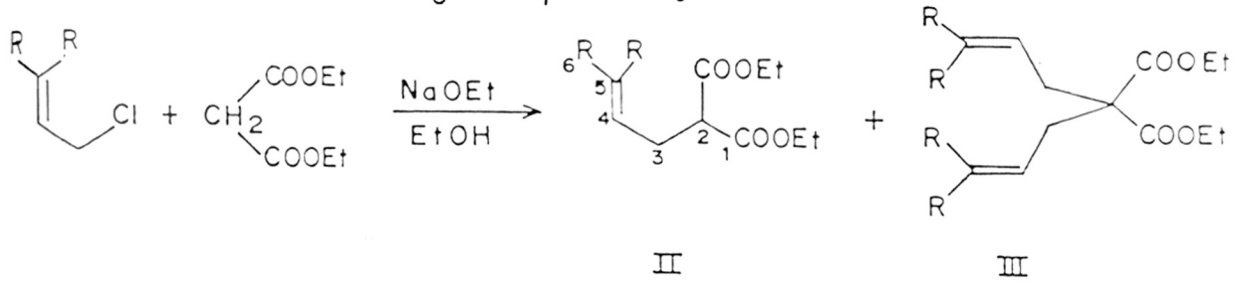
SCHEME 2



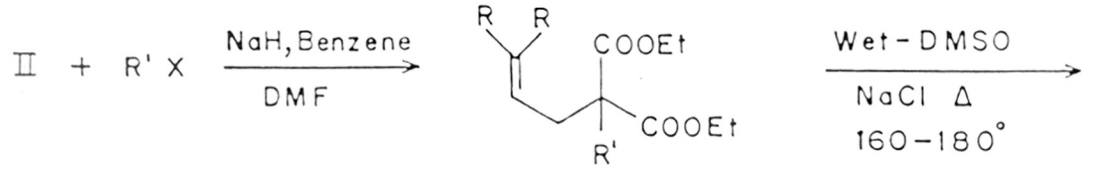
I

R_1 to R_5 = Alkyl or H

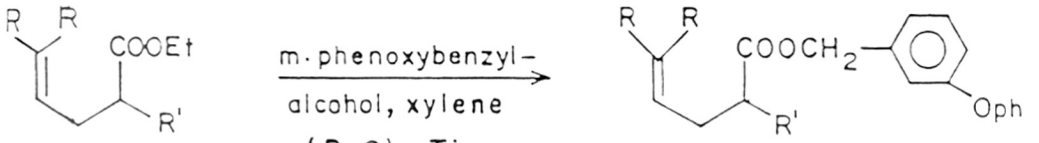
R_6 & R_7 = Halogen.



II III



IV



V VI

VI

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-Ph

f. R = H , R' = allyl

g. R = CH_3 , R' = H

h. R = CH_3 , R' = CH_3

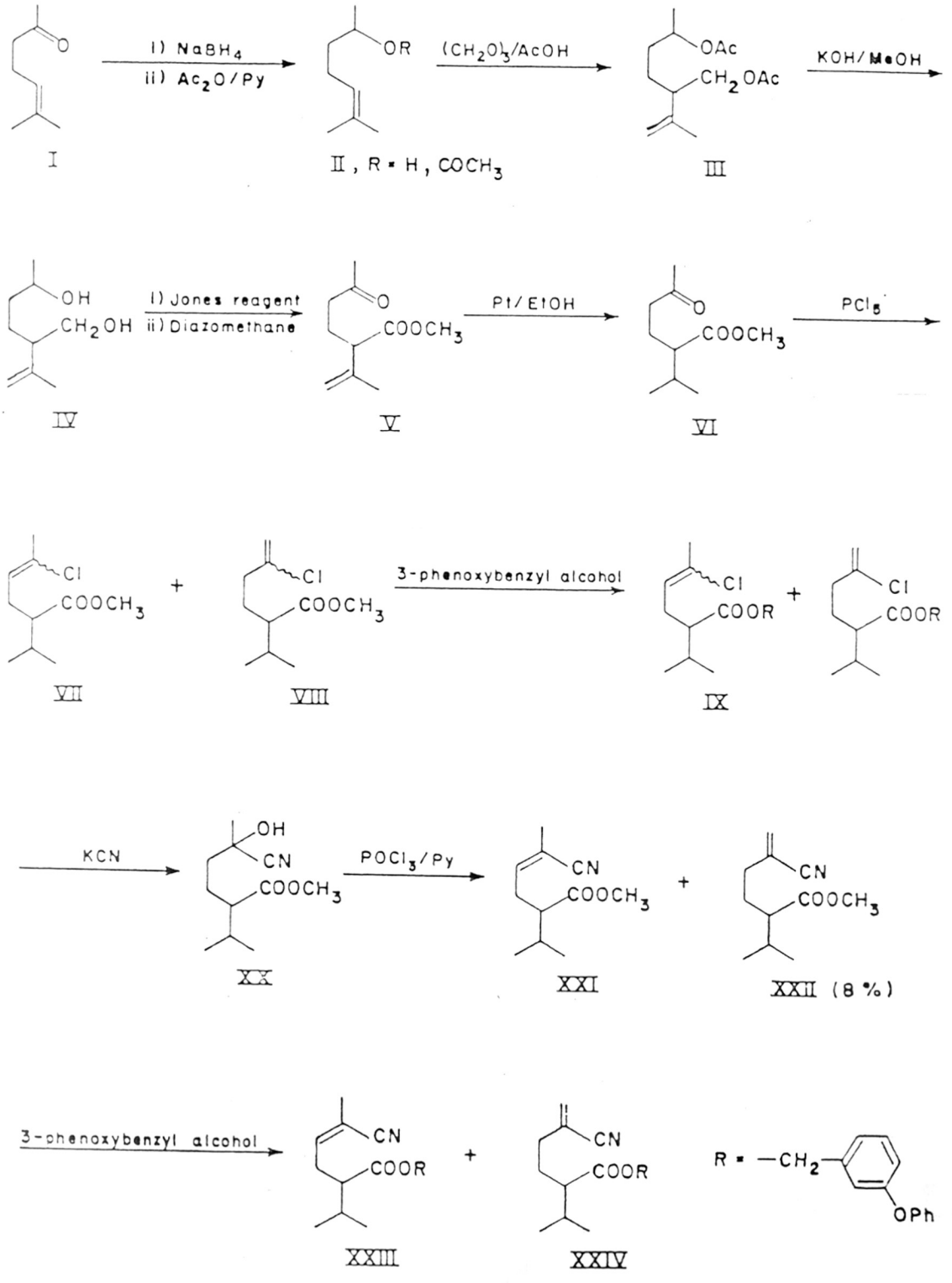
i. R = CH_3 , R' = CH_2CH_3

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

k. R = CH_3 , R' = CH_2-Ph

l. R = CH_3 , R' = allyl

SCHEME 3


I
1) NaBH4
ii) Ac2O/Py
OR
II, R = H, COCH3
(CH2O)3/AcOH
OAc
CH2OAc
III
KOH/MeOH
OH
CH2OH
1) Jones reagent
ii) Diazomethane
IV
O
COOCH3
V
Pt/EtOH
VI
PCl5
Cl
COOCH3
VII
VIII
3-phenoxybenzyl alcohol
COOR
IX
KCN
CN
XX
POCl3/Py
XXI
XXII (8 %)
XXIII
XXIV
R = —CH2
OPh

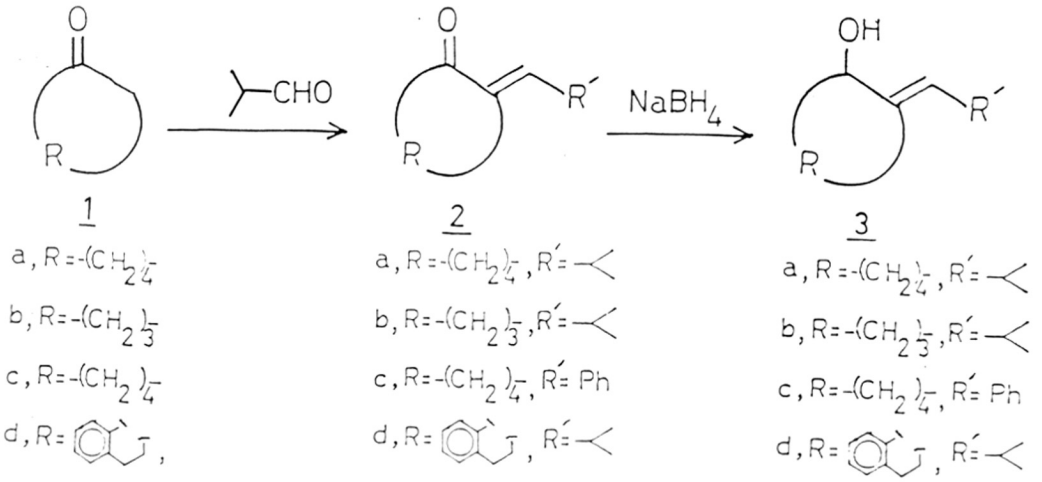
PRESENT WORK

Cyclohexanone isobutylidene (monomer) derivative (2a) was prepared from the cyclohexanone by an Aldol type condensation with isobutaraldehyde, under basic conditions[3], as described in Chapter 2 in 65% yield and obtained as a liquid; with the following spectral data; IR (liquid film): 1693 (keto >C=O), 1631 (-CH=C<) cm^{-1}; NMR (CCl_4): 1.03 (6H, d, J=7 Hz, 2 x $-CH_3$, isopropyl methyls), 1.75 (4H, m, 2 x $-CH_2-$ non-adjacent to ketone and double bond), 2.36(5H, m, 2 x $-CH_2-$ adjacent to ketone and double bond and $-CH(CH_3)_2$), 6.21 (1H, m (due to homoallylic coupling), olefinic proton).

Similarly conjugated ketones 2b - d were prepared by condensing appropriate aldehydes with corresponding cycloalkanones and characterized by spectral data; 2b: yield 71%. IR (liquid film): 1725 (cyclopentanone), 1651 (-CH=C<); NMR (CCl_4): 1.08 (6H, d, J=7 Hz, 2 x $-CH_3$, isopropyl methyls), 2.00 (4H, m, 2 x $-CH_2-$, allylic and non-adjacent to carbonyl), 2.59 (3H, m, $-CH_2-$ adjacent to carbonyl and $-CH(CH_3)_2$), 6.2 (1H, m, olefinic proton).

2c: yield 70%.

IR (nujol): 1680 (>C=O), 1595 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$): 1.83 (4H, m, 2 x $-CH_2-$ non-adjacent to carbonyl and double bond), 2.36, 2.80 (2H each, m each, methylenes adjacent to carbonyl and double bond), 7.43 (6H, br s, aromatic and olefinic protons).



1

a, R = -(CH2)4-

b, R = -(CH2)3-

c, R = -(CH2)4-

d, R = ,

2

a, R = -(CH2)4-, R' =

b, R = -(CH2)3-, R' =

c, R = -(CH2)4-, R' = Ph

d, R = , R' =

3

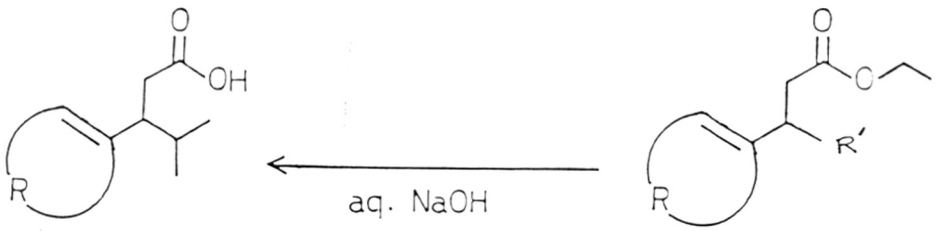
a, R = -(CH2)4-, R' =

b, R = -(CH2)3-, R' =

c, R = -(CH2)4-, R' = Ph

d, R = , R' =

Claisen ortho ester rearrangement



5

a, R = -(CH2)4-

b, R = -(CH2)3-

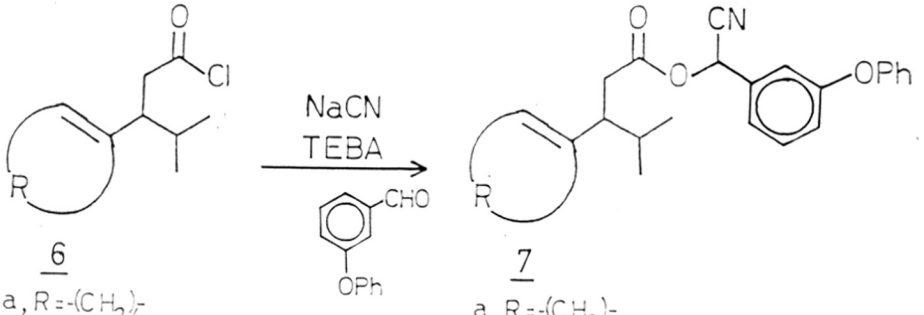
4

a, R = -(CH2)4-, R' = 

b, R = -(CH2)3-, R' = 

c, R = -(CH2)4-, R' = Ph

SOCl2



6

a, R = -(CH2)4-

b, R = -(CH2)3-

7

a, R = -(CH2)4-

b, R = -(CH2)3-

2d: yield 75%,

IR (liquid film): 1680 (>C=O), 1622 (-CH=C<), 1600 (aromatic unsaturation) cm^{-1}; NMR (CCl_4): 1.13 (6H, d, J=7 Hz, 2x $-CH_3$, isopropyl methyls), 2.85 (5H, m, 2 x $-CH_2-$ and $-CH(CH_3)_2$), 6.6 (1H, d, J=9 Hz, olefinic proton), 7.23 (4H, m, aromatic protons).

Sodium borohyride reduction of 2a gave the allylic alcohol (3a) in 89% yield, identified by following spectral data: M.S.: m/e 154 (M^+);

IR (liquid film): 3340 (-OH) cm^{-1}; NMR (CCl_4): 0.95 (6H, d, J=7 Hz, 2 x $-CH_3$, isopropyl methyls), 1.50 (6H, m, 3 x $-CH_2-$, non-adjacent to double bond), 2.36 (3H, m, allylic methylene and $-CH(CH_3)_2$), 3.92 (1H, br m, >CHOH), 5.10 (1H, d, J=9 Hz, olefinic proton).

Similarly 3b and c were prepared and characterized;

3b: yield 85%; M.S.: m/e 140 (M^+);

IR (liquid film): 3340 (-OH), 1665 (-CH=C<) cm^{-1};

NMR (CCl_4): 0.98 (6H, d, J=7 Hz, 2 x $-CH_3$, isopropyl methyls), 1.63 (4H, m, 2 x $-CH_2-$ non-adjacent to double bond), 2.34 (3H, m, allylic $-CH_2-$ and $-CH(CH_3)_2$), 4.22 (1H, br m, >CHOH), 5.27 (1H, br d, olefinic proton).

3c: yield 88%; M.S.: m/e 188 (M^+);

IR (liquid film): 3340 (-OH), 1651 (-CH=C<), 1595 (aromatic unsaturation);

NMR ($CDCl_3$): 1.6 (6H, m, 3 x $-CH_2-$ non-adjacent to double bond),

2.57 (2H, m, allylic $-CH_2-$), 4.12 (1H, br m, $>CHOH$), 6.46 (1H, s, olefinic proton), 7.18 (5H, s, aromatic protons).

Sodium borohyride reduction of 2d gave a mixture of four compounds from which it was not possible to isolate the desired hydroxy compound 3d in pure state. Hence further reactions could not be carried out.

Condensation of 3a with two equivalents of triethyl ortho acetate in presence of acidic catalyst like o-cresol and phosphoric acid according to the method developed by K. Kondo et al.[4] afforded ethyl ester (4a) purified by distillation in 61% yield by Claisen ortho ester rearrangement.

M.S.: m/e 224 (M^+);

IR (liquid film): 1737 (ester $>C=O$) cm^{-1};

NMR ($CDCl_3$): 0.88, 0.90 (3H each, d each, J=7 Hz each, isopropyl methyls), 1.2 (3H, t, J=8 Hz, ester $-CH_3$), 1.53 (5H, m, 2 x $-CH_2-$ non-adjacent to double bond and $-CH(CH_3)_2$), 1.87 (4H, m, 2 x $-CH_2-$, adjacent to double bond), 2.28 (3H, m, $-CH_2COOEt$ and allylic methine proton), 4.04 (2H, q, J=7 Hz, ester $-CH_2-$), 5.38 (1H, br t, olefinic proton).

Similarly 4b was prepared in 65% yield and characterized;

M.S.: m/e 210 (M^+);

IR (liquid film): 1739 (ester $>C=O$), 1660 ($-CH=C<$) cm^{-1};

NMR ($CDCl_3$): 0.88, 0.90 (3H each, d each, J=7 Hz each, isopropyl methyls), 1.14 (3H, t, J=7 Hz, ester $-CH_3$), 1.72 (3H, m, $-CH_2-$ non-adjacent to double bond and $-CH(CH_3)_2$), 2.12 (4H, m, 2 x $-CH_2-$, adjacent to double bond), 2.5 (3H, m,

-CH_2COOEt and allylic methine proton), 4.00 (2H, q, J=7 Hz, ester -CH_2-), 5.27 (1H, br t, olefinic proton).

Claisen ortho ester rearrangement on 3c failed to give the expected ester (4c) but instead gave other compounds which were not investigated further.

Ethyl ester (4a) was then saponified to give the corresponding carboxylic acid (5a) in 89% yield:
M.S.: m/e 196 (M^+);
IR (liquid film): 1715 (acid >C=0) cm^{-1}; NMR (CCl_4): 0.87, 0.93 (3H each, d each, J=7 Hz each, isopropyl methyls), 1.58 (5H, m, 2 x -CH_2- non-adjacent to double bond and -$CH(CH_3)_2$), 1.97 (4H, m, 2 x -CH_2-, adjacent to double bond), 2.38 (3H, m, -CH_2COOEt and allylic methine proton), 5.40 (1H, br t, olefinic proton).

Similarly 4b was saponified to give 5b in 92% yield, characterized as follows; M.S.: m/e 182 (M^+); IR (liquid film): 1715 (acid >C=0) cm^{-1}; NMR ($CDCl_3$): 0.87 (6H, d, J=7 Hz, 2 x -CH_3, isopropyl methyls), 1.8 (3H, m, -CH_2- non-adjacent to double bond and -$CH(CH_3)_2$), 2.22 (4H, m, 2 x -CH_2-, adjacent to double bond), 2.52 (3H, m, -CH_2COOEt and allylic methine proton), 5.52 (1H, br t, olefinic proton).

The carboxylic acid (5a) was converted to acid chloride (6a) by refluxing with $SOCl_2$ in dry benzene. It showed IR (liquid film) band at 1790 (acid chloride >C=0) cm^{-1}.

Similarly 6b was prepared which showed IR (liquid film) band at 1795 (acid chloride) cm^{-1}.

The acid chloride (6a) without further purification was then reacted with the 3-phenoxy benzaldehydo cyanohdyrin prepared in-situ from 3-phenoxy benzaldehyde, NaCN and water in pet.ether using TEBA as phase transfer catalyst, according to a reported procedure[5]. The crude ester thus obtained was purified by column chromatography over silica gel, eluted with 2% benzene + pet.ether to give a liquid ester identified as ∝(RS)-cyano-3-phenoxy benzyl ester (7a) by spectral data;

M.S.: m/e 403 (M^+);

IR (liquid film): 1758 (ester >C=O), 1620 (-CH=C<), 1591 (aromatic unsaturation) cm^{-1};

NMR ($CDCl_3$): 0.80, 0.85 (3H each, d each, J=7 Hz each, isopropyl methyls), 1.5 (5H, m, 2 x $-CH_2-$ non-adjacent to double bond and $-CH(CH_3)_2$), 1.8 (4H, m, 2 x $-CH_2-$ adjacent to double bond), 2.25 (3H, m, $-CH_2COOEt$ and allylic methine proton), 5.24 (1H, br t, olefinic proton), 6.26 (1H, s, -CHCN-), 7.16 (9H, m, aromatic protons).

Similarly 7b was prepared in 64% yield and characterized. M.S.: m/e 389 (M^+), IR (liquid film) (Fig.2): 1751 (ester >C=O), 1615 (-CH=C<), 1590 (aromatic unsaturation) cm^{-1}; NMR ($CDCl_3$) (Fig. 1): 0.84 (6H, d, J=7 Hz, isopropyl methyls), 1.74 (3H, m, $-CH_2-$ non-adjacent to double bond and $-CH(CH_3)_2$), 2.19 (4H, m, 2 x $-CH_2-$ adjacent to double bond), 2.51 (3H, m, $-CH_2COOEt$ and allylic methine proton), 5.38 (1H, br t, olefinic proton), 6.40 (1H, s, -CHCN-), 7.16 (9H, m, aromatic protons).

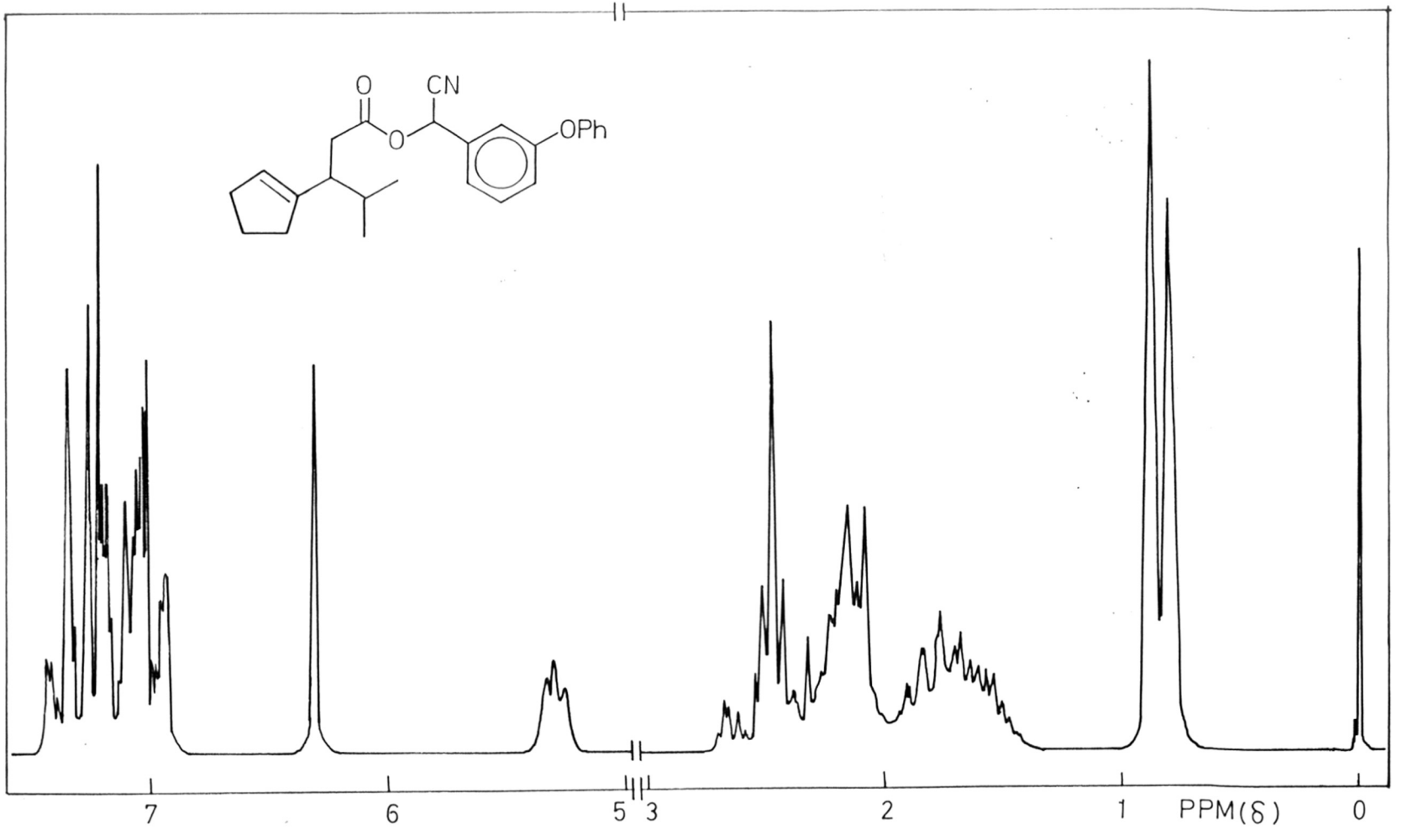


FIG. 1

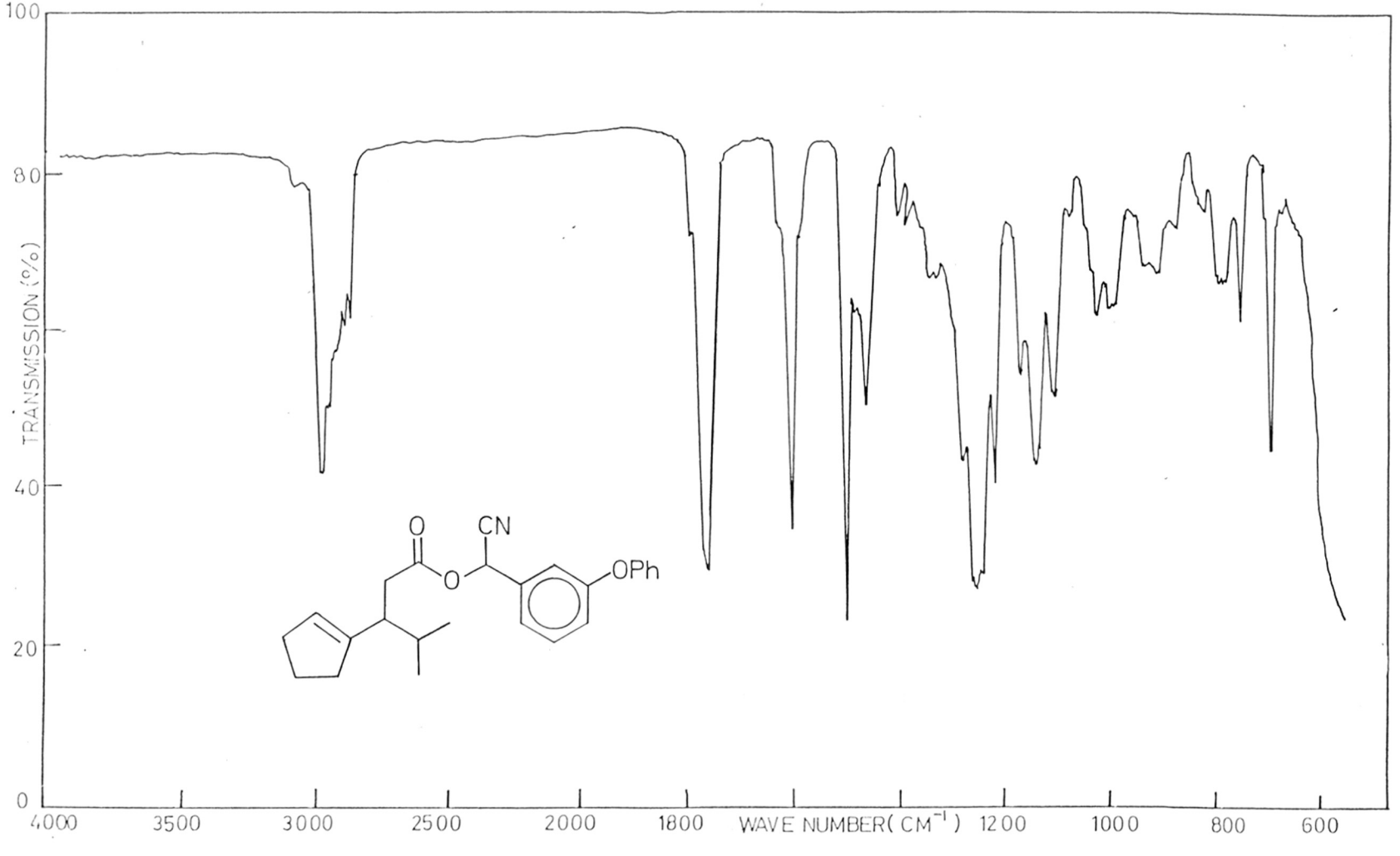

100
80
40
20
0
TRANSMISSION (%)
4000
3500
3000
2500
2000
1800
WAVE NUMBER(CM^{-1})
1200
1000
800
600
O
CN
O
OPh

FIG. 2

200

EXPERIMENTAL

Preparation of isopropylidene/benzylidene derivatives of cycloalkanones 2a-d

A mixture of isobutaraldehyde (72 g, 1.0 mol), cyclohexanone (109 g, 1.1 mol) and 1N NaOH (500 ml) solution was heated under reflux for 3 hr and kept stirring at room temeprature over-night. Methylene chloride was added to the mixture, the aqueous layer was separated and extracted with the same solvent. The combined methylene chloride layer was washed with dilute acetic acid, followed by water, dried and solvent removed to furnish a residue, which was distilled (b.p.107°C/7 mm) to give pure 2-isobutylidene cyclohexanone (2a, 98.8 g, 65%) as a liquid.

Analysis

Found: C, 78.91; H, 10.55; $C_{10}H_{16}O$

requires: C, 78.89; H, 10.59%.

IR bands at: 2970, 2878, 1693, 1631, 1467, 1260, 900 cm^{-1}.

In a similar manner the following derivatives have been prepared.

2b: yield 71%.

Analysis

Found: C, 78.30; H, 10.10; $C_9H_{14}O$

requires: C, 78.21; H, 10.21%.

IR bands at: 2960, 2866, 1725, 1651, 1467, 1205, 820 cm^{-1}.

2c yield 70%.

Analysis:

Found: C, 83.61; H, 7.44; $C_{13}H_{14}O$

requires: C, 83.83; H, 7.58%.

IR bands at: 2936, 1680, 1595, 1255, 1140 cm^{-1}.

2d: yield 75%.

Analysis

Found: C, 83.80; H, 8.15; $C_{14}H_{16}O$

requires: C, 83.96; H, 8.05%.

IR bands at: 2970, 1680, 1622, 1600, 1455, 1310, 1241, 735 cm^{-1}.

General method for preparation of hydroxy compounds(3a-d)

To a cooled and stirred solution of ketone (2, 0.1 mol) in methanol (150 ml) was added $NaBH_4$ (7.6 g, 0.2 mol) during 30 minutes in small lots and the stirring continued for 16 hr at 28°C. Methanol was removed under reduced pressure. Residue was diluted with water (100 ml) and extracted with dichloro methane (3 x 100 ml). Organic layer was washed with water, dried and distilled to give residue, which was purified by column chromatography over silica gel and eluted with benzene + pet.ether mixture to give TLC pure allylic alcohol (3).

3a: yield 89%, obtained as a liquid.

Analysis

Found: C, 77.75; H, 11.60; $C_{10}H_{18}O$

requires: C, 77.86; H, 11.76%.

IR bands at: 3340, 2929, 1471, 1453, 1090, 997 cm^{-1}.

3b: yield 85% obtained as a liquid.

Analysis

Found: C, 77.20; H, 11.60; $C_9H_{16}O$

requires: C, 77.09; H, 11.50%.

IR bands at: 3340, 2958, 1665, 1461, 1085, 972 cm^{-1}.

3c: yield 88%, obtained as a solid, m.p.58°C (pet.ether).

Analysis

Found: C, 82.71; H, 8.61; $C_{13}H_{16}O$

requires: C, 82.93; H, 8.57%.

IR bands at: 3340, 2924, 1651, 1595, 1440, 1070, 690 cm^{-1}.

General method of preparation of esters (4a-b)

A mixture of alcohol (3, 15 mmol), triethyl ortho acetate (7.29 g, 45 mmol) and o-cresol (4 drops) was heated at 140-50°C for 7 hr removing continuously ethanol (0.2 ml) formed in the reaction. Excess triethyl ortho acetate was then distilled off (170-80°C) and the reaction mixture cooled to room temperature, phosphoric acid (2 drops) was added and heating continued at 170-80°C for further 7 hr. The reaction mixture was diluted with water, neutralized with dil. NaOH solution (5%) and extracted with dichloro methane (3 x 50 ml). Dichloro methane extract was washed with water, dried and distilled to give a liquid, purified by distillation to afford 4.

4a: 61% yield, b.p.109°C/3 mm.

Analysis

Found: C, 74.75; H, 10.87; $C_{14}H_{24}O$

requires: C, 74.95; H, 10.78%.

IR bands at: 2915, 2854, 1737, 1445, 1255, 1110, 915 cm^{-1}.

4b: yield 65%, b.p.101°C/3 mm.

Analysis

Found: C, 74.12; H, 10.61; $C_{13}H_{22}O_2$

requires: C, 74.24; H, 10.54%.

IR bands at: 3000, 1739, 1660, 1466, 1370, 1242, 1149, 1035 cm^{-1}.

General method for preparation of carboxylic acids (5a-b)

To a cooled aqueous solution (0.6 ml) of NaOH (240 mg, 6 mmol) was added a solution of ester (4, 3 mmol) in ethanol (10 ml) and the homogenous solution stirred for 16 hr at 28°C. Ethanol was removed under reduced pressure, residue diluted with water (10 ml) and extracted with dichloromethane (50 ml) to remove any neutral material. The aqueous layer was acidified with dilute HCl (10%) to 2 pH and extracted with dichloro methane (3 x 50 ml). The organic layer was washed with water, dried and solvent evaporated to give the liquid acid (5).

5a: yield 89%.

Analysis

Found: C, 73.50; H, 10.31; $C_{12}H_{20}O_2$

requires: C, 73.43; H, 10.27%.

IR bands at: 2940, 1715, 1420, 1285, 924 cm^{-1}.

5b: obtained as a liquid in 92% yield.

Analysis

Found: C, 72.52; H, 9.87; $C_{11}H_{18}O_2$

requires: C, 72.49; 9.96%.

IR bands at: 2960, 1715, 1280, 930 cm^{-1}.

General method for preparation of acid chlorides (6a and b)

To a solution of acid (5, 0.96 mmol) in dry benzene (20 ml), thionyl chloride (1.37 g, 1.15 mmol) was added and the mixture refluxed for 1.5 hr. Excess thionyl chloride and benzene were distilled under reduced pressure to give acid chloride (6) as a liquid. Acid chlorides thus obtained, in almost quantitative yield, were used as such without further purification for preparing ∝(RS)-cyano-3-phenoxy benzyl esters.

6a:

IR bands at: 2930, 1790, 1470, 1223, 1000, 700 cm^{-1}.

6b:

IR bands at: 2950, 1795, 1460, 970 cm^{-1}.

General method of preparation of ∝(RS)-cyano-3-phenoxy benzyl esters (7a-b)

A mixture of acid chloride (0.96 mmol) and 3-phenoxy benzaldehyde (1.78 g, 0.9 mmol) in dry pet.ether (10 ml) was added dropwise during 2 hr at 35-40°C to a stirred mixture of NaCN (0.94 g, 1.92 mmol), water (0.2 ml), TEBA (50 mg) in

dry pet.ether (10 ml). Stirring was continued for 16 hr at the same temperature. Extractive work up gave the crude ester, purified by column chromatography on silica gel, fractions eluted with 5% benzene + pet.ether gave the required ester (7) in TLC pure state as a liquid.

7a: yield 68%.

Analysis

Found: C, 77.45; H, 7.21; N, 3.37; $C_{26}H_{29}NO_3$

requires: C, 77.39; H, 7.24; N, 3.47%.

IR bands at: 2930, 1758, 1620, 1591, 1450, 1250, 1100, 918, 690 cm^{-1}.

7b: 62% yield.

Analysis

Found: C, 77.04; H, 6.81; N, 3.52; $C_{25}H_{27}NO_3$

requires: C, 77.09; H, 6.99; N, 3.6%.

IR bands at: 2978, 1751, 1615, 1590, 1490, 1130, 685 cm^{-1}.

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