SYNTHETIC STUDIES IN BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS

SUBMITTED TO THE

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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Dedicated to my Parents

C E R T I F I C A T E

Certified that the work incorporated in the thesis **"SYNTHETIC STUDIES IN BIOLOGICALLY ACTIVE COMPOUNDS"**, submitted by Shri Sunil Madhav Kher 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)
Research Guide
National Chemical Laboratory,
Poona 411 008

January 1990.

ACKNOWLEDGEMENTS

I take this opportunity to record my sinceremost appreciation to Dr.G.H. Kulkarni, my research guide and mentor. His guidance was instrumental in the successful completion of this thesis. His encouragement, timely advice and good knowledge of the work provided a fine driving force throughout the course of this work.

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Finally, I would like to thank the Director, NCL for permitting me to work and submit the work in the form of thesis.

(S.M. Kher)

C O N T E N T S

CHAPTER - 3

Synthesis of 3-isopropenyl-hept-6-en-l-al, key intermediate for the synthesis of California red scale pheromone

CHAPTER - 4

Some interesting rearrangements encountered during the attempts to synthesize spiro-fused cyclopropane carboxylates

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.

2. All temperatures are recorded on centigrade scale.

3. Numbers given to charts, figures and structures in each chapter of the thesis refer to that particular chapter only. The references and spectra are given at the end of each chapter.

4. A brief summary of each chapter is given at the beginning of that chapter.

5. All the solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range 60-80°.

6. TLC analyses were carried out on glass plates with a mixture of silicic acid and plaster of Paris (85:15, 200-300 mesh) and activated at 120° for 3 hr. Solvent systems used were pet.ether, benzene, ethyl acetate and chloroform or a suitable mixture of two or more of these solvents depending upon the nature of the compound. The plates were developed by keeping in an iodine chamber or by spraying with sulphuric acid.

7. Unless otherwise stated, all solutions were dried over anhydrous sodium sulfate.

8. Unless otherwise stated, all b.ps. refer to the bath temperature.

9. The infrared spectra of liquid were recorded as liquid films and that of solids as nujol mulls on a Perkin-Elmer infracord spectrophotometer model 137-B and on Perkin-Elmer infracord spectrophotometer model 599-B using sodium chloride optics. IR bands are express in $\nu\ cm^{-1}$.

10. The p.m.r. spectra were taken on Varian T-60 MHz spectrometer (in CCl_4 solution), on Varian FT-80 MHz spectrometer (in $CDCl_3$ solution) and

the chemical shifts are measured in δ units.

11. Mass spectra were recorded on CEC-21-110B and Finnigan Mat 1020 automated GC/MS.

12. In the list of IR bands given in the experimental section, the significant bands described in the present work are underlined.

13. In the description of PMR signals, the abbreviations d,t,q,m,br s, br d means doublet, triplet, quarter, multiplet, broad singlet and broad doublet respectively.

14. Column chromatography was carried using silica gel (60-120 mesh) which was activated at 125-130° for 3 hr.

CHAPTER - 1

SYNTHETIC STUDIES DIRECTED TOWARDS THE APLYSIN - A MARINE SESQUITERPENE WHICH IS ISOLATED FROM 'APLYSIA KURODAI'

SUMMARY

Synthetic studies towards aplysin- a tricyclic marine sesquiterpenoid (1) are described in this chapter. Results obtained during our attempts are divided into two parts.

Part (A) describes an attempted but unsuccessful intramolecular (2+2) cycloaddition approach between ketene and olefin. Our effort to bring about the said cycloaddition reaction resulted actually in intramolecular 'ene' reaction. This restricted the formation of required product (**34**) to a very minor extent (10% yield). The cyclic conjugated ketone (**35**) and unconjugated ketone (**36**) dominated since they resulted from the intramolecular 'ene' reaction. All our efforts to bring about a substantial increase in the yield of cyclobutanone (**34**) remained unfruitful.

The required acid intermediate (**33**) for the expected cycloaddition reaction was obtained starting from 2'-hydroxy-5'-methyl acetophenone (**29**). MeMgI Grignard gave the diol (**30**) which was alkylated with ethyl-2-bromopropionate to yield hydroxy ester (**31**). Dehydration with $POCl_3$-pyridine followed by saponification gave the required acid intermediate (**33**). This acid was converted to its chloride and ketene was generated in-situ by treatment of acid chloride with triethyl amine at benzene reflux. But as mentioned earlier, the reaction ended up going intramolecular 'ene' way. Hence this approach was shelved.

In part (B) the focus was shifted from intramolecular cycloaddition approach to intermolecular approach. For this approach, the ether intermediate (**39**) was taken as the key building block. The olefin function of (**39**) was attacked on methyl chloro ketene (which was generated in-situ) to get a mixture of cyclobutanones (**40A**) and (**40B**) which was separted on

silica gel; (40B) was regio selectively transformed to cyclopentanone (41). Bromination of (41) led to the formation of bromo cyclopentanone (42). This intermediate has already been synthesized by Yamada et al. [see chart II (B)] and converted into aplysin. Hence it completes a formal synthesis of aplysin.

INTRODUCTION

Quantitatively, the number of known naturally occurring compounds is vastly outdistanced by number of known synthetic organic compounds. Yet, natural products continue to hold an empire of their own, not only because of their relationship to the organisms from which they are derived or because of their potential usefulness to man, but chiefly because each new structural type reveals something new about nature's architecture and poses new questions as to how and why these compounds are being produced. Since comparatively few natural products have been isolated from marine sources, it's not possible yet- except in a few isolated areas which have been well studied to make intelligent predictions about the likely outcome of an investigation. This very feature makes the area of marine natural products research particularly attractive.

Marine natural products are generally divided into five groups: (1) Isoprenoids (terpenoids and carotenoids) (2) sterols, (3) benzenoids, (4) nitrogenous compounds (like amines, amino acids etc.) and (5) non-aromatic compounds with unbranched carbon skeletons.

The molecule of this chapter (i.e. aplysin) belongs to the isoprenoid class [sesquiterpenoid, to be precise] of marine natural products.

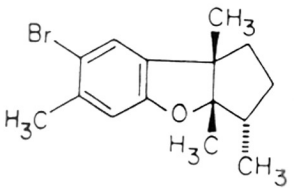
Wallach[1] first recorded the remarkable observation that a distinct group of naturally occurring substrates may be formally derived from branched five carbon units. The ensuing theory that these compounds, the terpenoids, are biosynthesized from branched five carbon modules was stated by Ruzicka and Stoll[2]. Ruzicka's theory has been one of the most fruitful in organic chemistry. In their own right, the terpenoids

have mirrored the development of organic chemistry. At the outset, as the extracts of terrestrial plants, the terpenoids were prized for their pleasant aroma. For many years, they were an interesting subject for academic research. More recently, with the advent of sophisticated methods of isolation, separation and structural determination, terpene research has expanded greatly and has established these compounds as one of the most diverse and intriguing groups of natural products. The terpenes are logically and conveniently divided according to its carbon contents into mono (C_{10}), sesqui (C_{15}), di (C_{20}) etc. The largest (still very modest) number of terpenoids from marine sources are sesquiterpenoids.

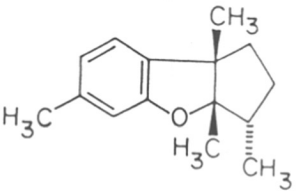
The marine sesquiterpenoids of novel structure fall into four well-defined categories. By far, the most numerous group, based on a rearranged farnesyl skeleton, has been isolated from sea hares and red algae of a single genus. Many of these compounds contain chlorine and bromine.

One of the first halogenated sesquiterpenes to be isolated from marine sources was (-) aplysin (1) (chart I), which occurs in sea hare **Aplysia Kurodai**, that inhabits the eastern pacific[3,4]. It is also found in **opistho-branchs** which inhabit the coasts of North America[4]. These mollusks tend to accumulate aplysin and related substances in the gut alongwith presumptive aplysin precursor debromoaplysin (2) (chart I). These compounds tend to function as antifeedants which make these slow-moving shellless creatures unpalatable to predators. They also function as anti-oxidants to scavange reactive halogen which would explain the frequent co-occurrence of the unhalogenated forms.

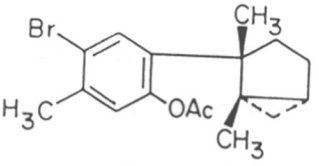
CHART - I



(1)



(2)



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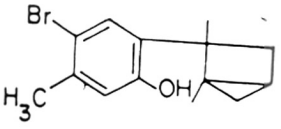
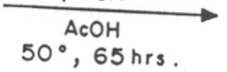
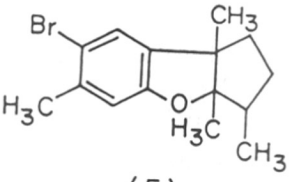


(4)





(5)

The sesquiterpenes in **aplysia** appear to be derived from the red-algae which constitute their principal dietary component. These algae, especially the genus **Laurencia** have been shown to be a rich source of unusual terpenoids containing both bromine and chlorine. Aplysin (1) appears to be a metabolite derived from the algal constituent laurinterol (3) (chart I); bio-conversion of (3) to (1)is supported by the facile acid-catalyzed cyclization of (1) observed in vitro[5]. The absolute configuration of (1) is determined[6] and is as shown in figure.

Yamamura and Hirata's work on the constituents of **aplysia kurodai** followed an earlier inconclusive study by Tanaka and Toyama[7]. As part of an extensive investigation into the lipids of marine organisms, these authors detected two crystalline bromine containing compounds in the unsaponifiable portion of **A. kurodai** but could not assign the structures. Yamamura and Hirata followed up on this work in an attempt to verify the occurrence of the bromo constituents of sea hares. They extracted whole dry animals with ether and saponified the ether extract with methanolic KOH. The unsaponifiable matter was again extracted with ether and then hexane. The hexane soluble residue was chromatographed. From the hexane fraction, the authors isolated debromoaplysin (2). With benzene, they elluted colorless, crystalline aplysin (1), m.p.85-86°C, $[\alpha]_D^{27^\circ}$ -85.4. Structures of these compounds were determined by a combination of chemical degradation and spectral data.

Both these aplysins were also isolated from red algae of the genus **Laurencia Okamurai Yamada** by Irie and co-workers[8]. In their continued quest for sesquiterpenoid constituents of the genus **Laurencia** intermediate, Irie and collaborators isolated from **Laurencia intermedia**, three phenols-

laurinterol, (3) debromolaurinterol and isolaurinterol. Isolation and purification of these three compounds were best achieved via their acetates. The stereochemical assignment of laurinterol (3) as shown in figure was determined by single crystal X-ray diffraction of laurinteryl acetate. Since laurinterol was earlier shown to transform to aplysin upon heating with TsOH in AcOH[3] (chart I), the absolute stereochemistry of aplysin as shown in figure (chart I) was arrived at[6].

Isolation of aplysin along with laurinterol from marine red algae **Marginisporum aberrans** was also reported by Ohta and Takagi[9]. Same authors also observed the presence of these compounds in **Amphiroa zonata** Yendo and **Corallina pilulifera postels et Ruprecht** collected at Cape Omaezaki, Japan.

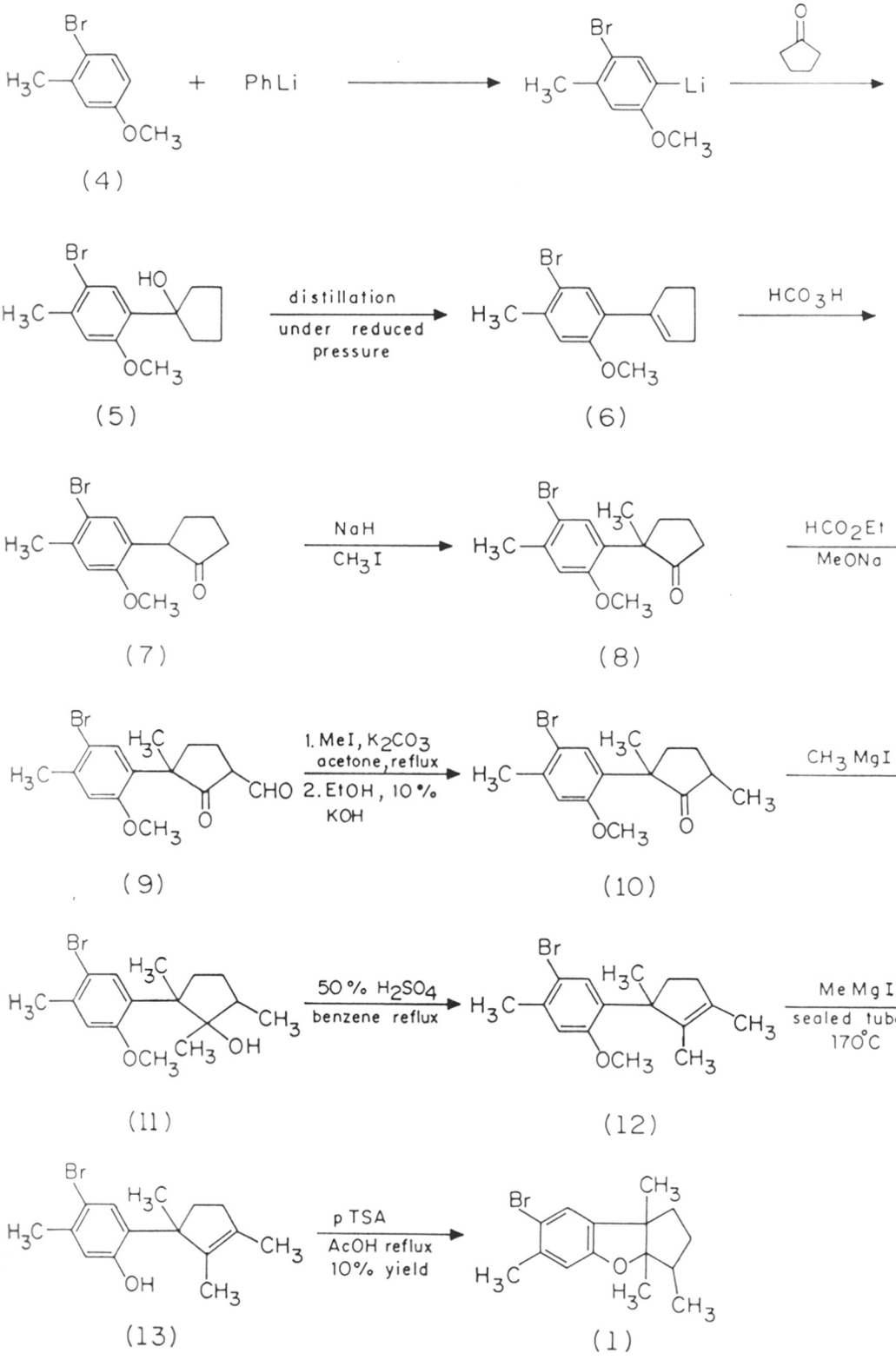
Sporadic reports on the synthesis of aplysin have appeared in the literature[10-15].

The first synthetic route was described by Yamada et al.[10] [see chart II (A)]. Lithium salt of 4-bromo-3-methyl anisole (**4**) was treated with cyclopentanone to afford cyclopentanol (**5**) which upon dehydration and subsequent oxidation gave cyclopentanone derivative (**7**). This on dialkylation gave α,α' dimethyl aryl cyclopentanone (**10**) which on Grignard reaction with MeMgI and dehydration gave the trimethyl cyclopentene (**12**). Cleavage of phenyl methyl ether and acid catalyzed cyclization gave the aplysin (**1**).

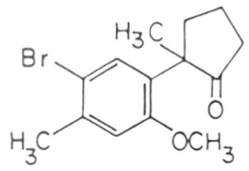
Same group of workers reported another shorter route [chart II (B)] starting with 2-methyl-2-(5'-bromo-4'-methyl-2'-methoxy phenyl) cyclopentanone (**8**) which was an intermediate in their earlier scheme. MeMgI Grignard and dehydration led to cyclopentene (**15**) which was oxidised to cyclopentanone (**16**) with performic acid.

CHART - II

(A) K. YAMADA , H. YAZAWA , M. TODA , Y. HIRATA

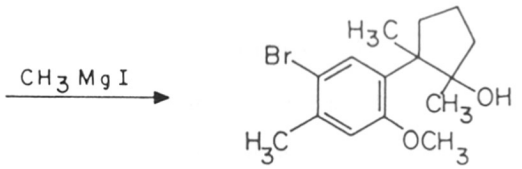


(4) (5) (6) (7) (8) (9) (10) (11) (12) (13) (1)



prepared as above

(8)



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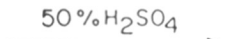
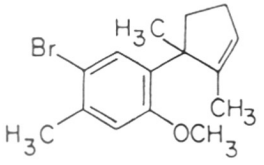
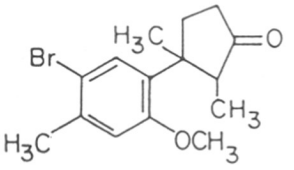




(15)



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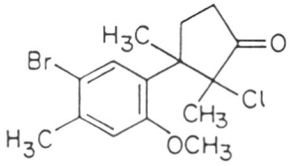
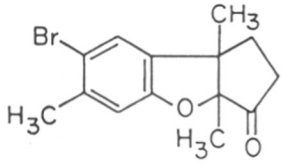


(17)



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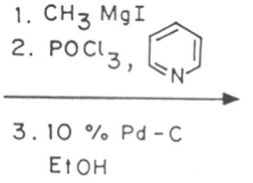
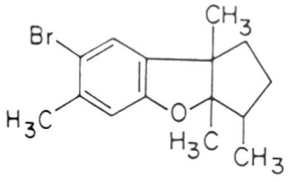




(1)

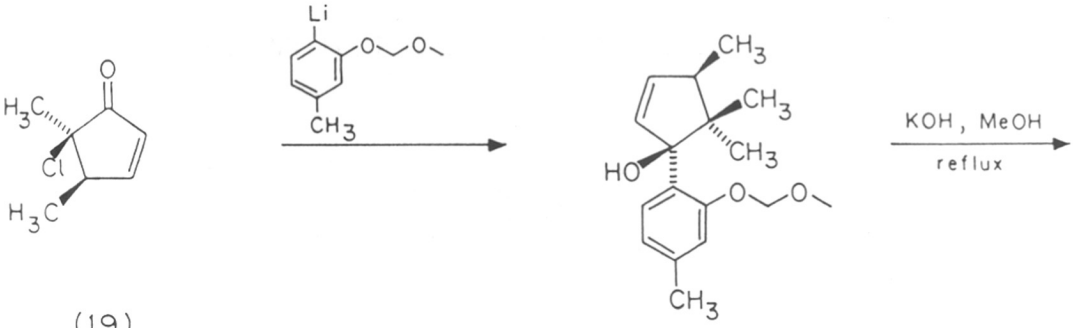
Chlorination ∝ to cyclopentanone (16), cleavage of aryl methyl ether in the resultant cyclopentanone (17) and subsequent cyclization led to tricyclic pentanone (18). The manipulation of carbonyl group of cyclopentanone (18) by Grignard reaction with MeMgI, dehydration and hydrogenation resulted in aplysin (1).

The third synthesis described by R.C. Ronald[12] is an opitcally active one. Chiral cyclopentenone (19) was treated with o-lithiated m-cresol in which phenolic -OH group was protected as MOM ether . The resultant cyclopentenol (20) was cyclised by treating it with KOH at methanol reflux to give chiral tricyclic pentenol (21). The -OH group of (21) was converted first into Br by treatment with PBr_3 and was then coupled with MeMgBr to obtain ring junction methyl group of (22), required for the aplysin skeleton. Double bond isomerization was brought about by heating (22) with PPh_3 Wilkinson's catalyst in 1:1 mixture of toluene and isobutanol to afford the penultimate intermediate (23).

Goldsmith et al.[13] made use of an intermediate (10) from the synthetic route of Yamada. The aryl methyl ether function was replacaed to give aryl acetate (24). Chlorination ∝ to cyclopentanone was effactuated by sulfuryl chloride to give a mixture of isomer (25, 26) in which anti isomer (26) dominated. Treatment with DBN resulted in a Filiformine derivative (27) bearing cyclic ketone. This was subjected to Wittig reaction to get (28). Tosic acid treatment of (28) resulted in the formation of aplysin skeleton (23). Double bond of (23) was hydrogenated to give aplysin (1).

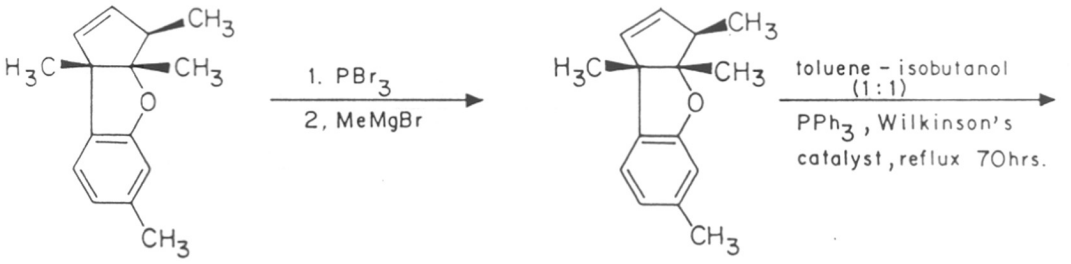
Our attempts to synthesize aplysin arose mainly from our keen desire to employ (2+2) cycloaddition reaction between ketene and olefin as a synthetic tool.

(C) R.C. RONALD



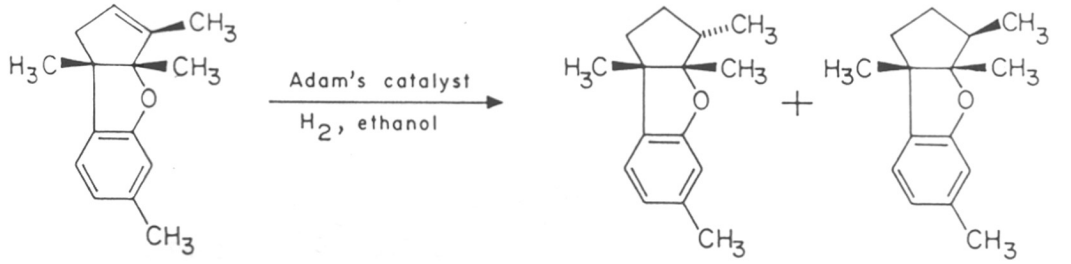
(19)

(20)



(21)

(22)



(23)

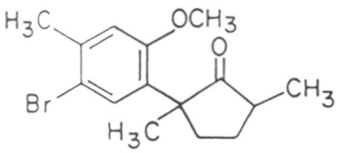
95 %

5 %

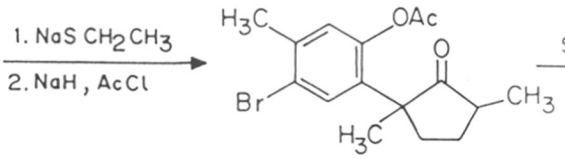
(1)

separated on silica gel

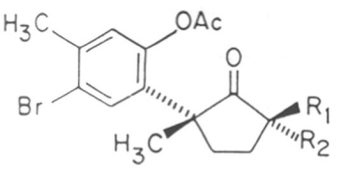
(D) D. J. GOLDSMITH , T. K. JOHN , C. D. KWONG , G. R. PAINTER III



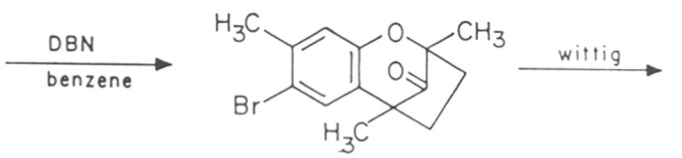
(10)



(24)



(25) $R_1 = CH_3$, $R_2 = Cl$
+
(26) $R_1 = Cl$, $R_2 = CH_3$ (major)



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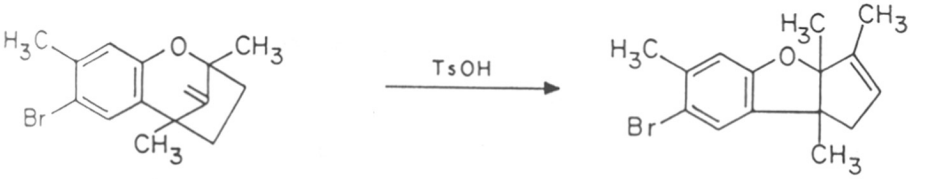

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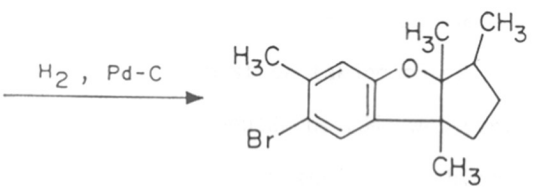
(23)



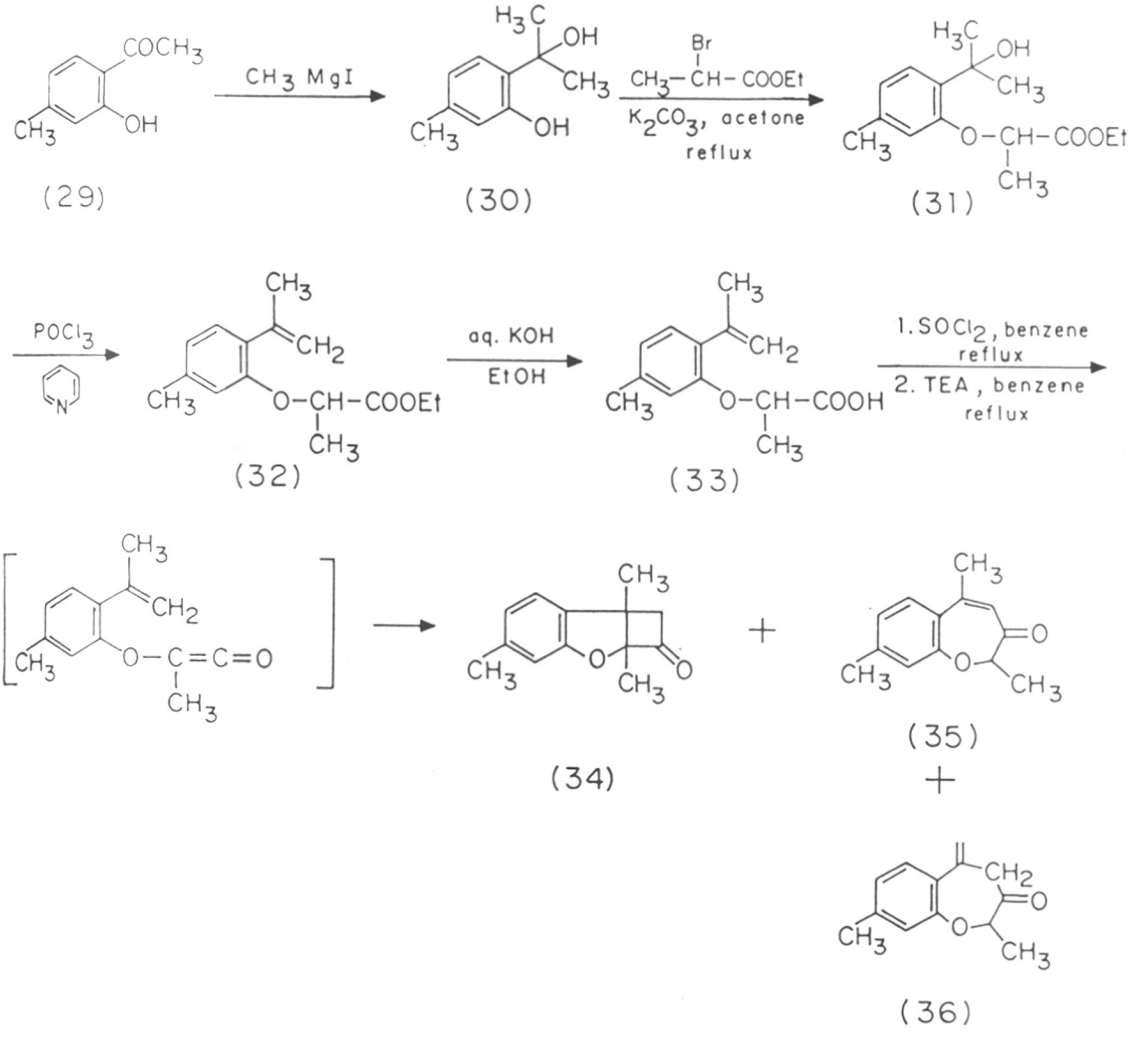
(1)

PRESENT WORK-PART 'A'

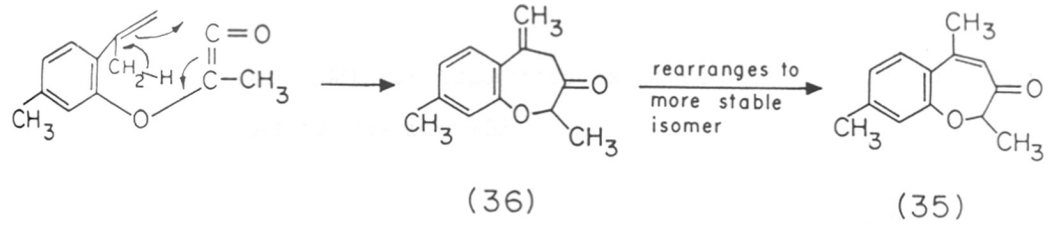
The intramolecular (2+2) cycloaddition reaction between ketene and olefin has been well-studied and documented[16]. However, it has not been exploited much, in terms of its application to synthesize natural products. We decided to make use of this versatile reaction, which in one shot, affords a bicyclic or tricyclic ring system, present in molecules like aplysin. The vital step in our approach was to generate the ketene intermediate in-situ from acid (**33**) via its acid chloride [see scheme (A)]. We expected this ketene intermediate to cyclize immediately through a (2+2) cycloaddition reaction leading exclusively to the formation of cyclobutanone (**34**). However, contrary to our expectation, the ketene and olefin functions reacted in an intramolecular 'ene' fashion through a favourable six membered transition state to afford (**35**) and (**36**) as the main products [see the proposed mechanism in scheme (A)]. The expected cyclobutanone (**34**) was obtained as a minor product. No change in reaction condition or concentration could increase the yield of cyclobutanone. Heating the cyclobutanone (**34**) with triethylamine at benzene reflux could not transform it to (**35**) or (**36**), which ruled out the possibility of cyclobutanone (**34**) forming initially and then getting transformed to (**35**) and (**36**). This further consolidated our view that a predominant intramolecular 'ene' reaction must be taking place during the reaction. Since the yield of expected cyclobutanone (**34**) was very less, this approach was discontinued.

The starting material, 2'-hydroxy'4'-methyl acetophenone (**29**), was prepared by the traditional Fries rearrangement of m-cresyl acetate. It was subjected to Grignard reaction using two equivalents of methyl

SCHEME (A)



POSSIBLE MECHANISM FOR INTRAMOLECULAR 'ENE' REACTION:



magnesium iodide to give diol (**30**) as a solid compound.

IR: 3500 (-OH), 1610, 1580 (aromatic).

PMR (CCl_4): 1.53 (6H, s, gem dimethyls), 2.2 (3H, s, aromatic methyl), 3.77 (1H, br s, D_2O exchangeable, -OH), 6.25 (2H, d overlapping s, aromatic protons), 6.83 (1H, d, 8 Hz, aromatic proton).

Diol (**30**) was alkylated with ethyl-2-bromo propionate using K_2CO_3 as base to give hydroxy ester (**31**).

IR: 3500 (-OH), 1740 (ester carbonyl), 1620, 1580 (aromatic).

PMR ($CDCl_3$): 1.19 (3H, t, 6.4 Hz, ester methyl), 1.56 (6H, s, gem dimethyls), 1.59 (3H, d, 6.4 Hz, O-CH-$\underline{CH_3}$), 2.25 (3H, s, aromatic methyl), 3.5 (1H, br s, D_2O exchangeable, -OH), 4.16 (2H, q, 6.4 Hz, ester methylene), 4.88 (1H, q, 6.4 Hz, Ph-O-$\underline{CH}$-CH_3), 6.5 (1H, s, aromatic proton), 6.69 (1H, d, 8 Hz, aromatic proton), 7.16 (1H, d, 8 Hz, aromatic proton).

Dehydration of hydroxy ester (**31**) was affected by $POCl_3$ and pyridine to give ester (**32**).

IR: 1740 (ester carbonyl), 1610, 1570 (aromatic).

PMR (CCl_4): 1.21 (3H, t, ester methyl), 1.6 (3H, d, 7 Hz, O-CH-$\underline{CH_3}$), 2.13 (3H, s, methyl on double bond), 2.33 (3H, s, aromatic methyl), 4.16 (2H, q, 7 Hz, ester methylene), 4.68 (1H, q, 7 Hz, -O-$\underline{CH}$-CH_3), 5.03 (2H, s, olefinic protons), 6.34 (1H, s, aromatic proton), 6.66 (1H, d, 8 Hz, aromatic proton), 7.06 (1H, d, 8 Hz, olefinic proton).

Ester (**32**) was saponified using ethanol and aqueous KOH at room temperature to give acid (**33**).

IR: 1720 (acid carbonyl), 1620, 1580 (aromatic).

PMR: 1.54 (3H, d, 7 Hz, -O-CH-$\underline{CH_3}$), 2.09 (3H, s, methyl on double bond), 2.26 (3H, s, aromatic methyl), 4.73 (1H, q, 7 Hz, O-$\underline{CH}$-CH_3), 5.05 (2H, s, olefinic protons), 6.5 (1H, s, aromatic proton), 6.66 (1H, d, 8 Hz, aromatic proton), 7.0 (1H, d, 8 Hz, aromatic proton), 11.2 (1H, br s, D_2O exchangeable, -COOH).

Acid (**33**) was converted to acid chloride with excess of thionyl chloride in benzene reflux and acid chloride as such, after removing excess $SOCl_2$ was treated with triethyl amine at benzene reflux as per Snider's[16] procedure. Three compounds were obtained in this reaction which were separated on silica gel and characterized as (**34**), (**35**) and (**36**).

Compound (34): IR - 1790 (carbonyl), 1620, 1600 (aromatic).

PMR ($CDCl_3$): 1.52 and 1.57 (3H each, s each, methyls on ring junction), 2.31 (3H, s, aromatic methyl), 3.1 and 3.33 (1H each, d each, 18 Hz each, methylene (to carbonyl), 6.66 (1H, s, aromatic proton), 6.77 (1H, d, 8 Hz, aromatic proton), 7.1 (1H, d, 8 Hz, aromatic proton).

Compound (35): IR - 1670 (carbonyl), 1610 (aromatic).

PMR ($CDCl_3$): 1.46 (3H, d, 7 Hz, -O-CH-$\underline{CH_3}$), 2.33 and 2.36 (3H each, s each, aromatic methyl and methyl on double bond), 4.28 (1H, q, 7 Hz, -O-$\underline{CH}$-CH_3), 6.34 (1H, s, olefinic proton), 6.93 (1H, s, aromatic proton), 7.0 (1H, d, 8 Hz, aromatic proton), 7.4 (1H, d, 8 Hz, aromatic proton).

Compound (36): IR - 1720 (carbonyl), 1620, 1570 (aromatic).

PMR ($CDCl_3$): 1.44 (3H, d, 7 Hz, -O-CH-$\underline{CH_3}$), 2.38 (3H, s, aromatic methyl), 3.44 and 4.0 (1H each, d each, 13 Hz each, allylic

$-CH_2-CO$), 4.46 (1H, q, 7 Hz, O-$\underline{CH}$-CH_3), 5.08 and 5.48 (1H each, s each, olefinic protons), 6.8 (1H, s, aromatic proton), 6.9 (1H, d, 8 Hz, aromatic proton), 7.42 (1H, d, 8 Hz, aromatic proton).

By the time we published this interesting deviation[17], around same time, Venkateswaran et al.[14] reported the same intramolecular (2+2) cycloaddition reaction to proceed in 86% yield giving only the expected cyclobutanone (**34**). With such high yield, they have obviously been able to complete aplysin synthesis. The entire synthetic route they followed, differed only in one aspect from that of ours, namely the preparation of acid chloride from the acid (**33**). While we used thionyl chloride, they used oxalyl chloride. It, of course, remains to be ascertained whether this change in reagent can alter the reaction pathway so drastically.

EXPERIMENTAL

2-(2'-Hydroxy-4'-methyl phenyl)-propan-2-ol (30)

The solution of methyl magnesium iodide, prepared from Mg (1.4 g, 0.058 mole) and methyl iodide (10.06 g, 0.07 mole) in dry ether (65 ml) was cooled to 0°C. Solution of (**29**) (4.25 g, 0.028 mole) in dry ether (50 ml) was added to it over half hour and stirred overnight at room temperature. Usual workup with aqueous saturated ammonium chloride furnished a solid 4.3 g, crystallized from hot pet.ether to give diol (**30**) as white needles, 4.2 g, m.p.65°C in 89% yield.

IR: 3500, 1610, 1580, 1370, 1250, 930.

Mass: M^+: 166.

Elemental analysis for $C_{10}H_{14}O_2$:

calculated: C, 72.26; H, 8.49;

observed: C, 72.12; H, 8.37;

Ethyl α-[2'(2-hydroxy isopropyl)5'-methyl phenoxy] propionate (31)

A mixture of diol (**30**) (4 g, 0.024 mole), ethyl-2-bromo propionate (4.36 g, 0.024 mole), anhydrous potassium carbonate (3.33 g, 0.024 mole) and a pinch of potassium iodide was refluxed in dry acetone (100 ml) for 8 hr. Acetone was removed under reduced pressure, reaction mixture diluted with water and extracted repeatedly with ether. Combined ether layer was washed with water, brine and dried. Removal of solvent gave 5.4 g of crude product, purified by column chromatography over silica gel (eluted with pet.ether + 10% ethyl acetate) to give 5.2 g of pure (**31**) as a colorless liquid in 81% yield.

IR: 3500, 1740, 1620, 1580, 1500, 1370, 1000, 950, 810.

Mass: M^+ - 266.

Elemental analysis for $C_{15}H_{22}O_4$

calculated: C, 67.64; H, 8.33;

observed: C, 67.49; H, 8.16;

Ethyl α-(2'-isopropenyl-5'-methyl phenoxy) propionate (32)

To an ice-cooled and stirred solution of hydroxy ester (**31**) (5 g, 0.019 mole) in dry pyridine (15 ml), phosphorous oxychloride (2.9 g, 0.019 mole) was added dropwise and the reaction mixture stirred overnight. Usual workup of the reaction mixture gave a liquid (4.5 g), chromatographed over silica gel (eluted with pet.ether + 5% ethyl acetate) to give 3.86 g of pure (**32**) in 82% yield as a liquid.

IR: 1740, 1610, 1570, 1500, 1450, 1280, 1180.

Mass: M^+ - 248.

Elemental analysis for $C_{15}H_{20}O_3$:

calculated: C, 72.55; H, 8.12;

observed: C, 72.41; H, 7.94;

α-(2'-Isopropenyl-5'-methyl phenoxy) propionic acid (33)

To a solution of ester (**32**) (3 g, 0.012 mole) in methanol (30 ml), a solution of KOH (1.35 g, 0.024 mole) in water (5 ml) was added and the homogenous mixture was stirred overnight at room temperature. Workup afforded the acid (**33**), 1.98 g as a liquid in 75% yield, which was used as such for the next reaction.

Formation of cyclobutanone (34) and benzoxepinenone (35), (36):

To a solution of acid (**33**) (0.5 g, 0.002 mole) in dry benzene (10 ml), was added thionyl chloride (0.54 g, 0.0045 mole). The reaction

mixture was refluxed for 3 hr. Benzene and excess of thionyl chloride were distilled off to give acid chloride. Fresh dry benzene (10 ml) was added to acid chloride and this solution was added dropwise to a gently refluxing solution of triethylamine (0.35 g, 0.034 mole) in dry benzene (10 ml) and the heating continued for additional 3 hr. Workup in usual manner gave 0.4 g crude liquid showing three spots on TLC. This was chromatographed over silica gel using different compositions of pet.ether and chloroform for elution.

The least polar fraction, eluted with pet.ether+(5%) chloroform gave 0.092 g (20%) of a liquid identified as 2,3,4,5-tetrahydro-2,8-dimethyl-5-methylene-1-benzoxepin-3-one (**36**).

IR: 1720, 1620, 1570, 1420, 1300, 1170, 900.

Mass: M^+ - 202.

Elemental analysis for $C_{13}H_{14}O_2$

calculated: C, 77.2; H, 6.98;

observed: C, 77.11; H, 6.88;

The middle fraction eluted with pet.ether +10% chloroform gave 0.045 g (10%) cyclobutanone (**34**) as a liquid.

IR: 1790, 1620, 1600, 1500, 1270, 1140.

Mass: M^+ - 202.

Elemental analysis for $C_{13}H_{14}O_2$

calculated: C, 77.2; H, 6.98;

observed: C, 77.07; H, 6.86;

The tail fraction eluted with pet.ether + 15% chloroform gave 0.2 g (45%) of a liquid identified as 2,3-dihydro-2,5,8-trimethyl-1-benzoxepin-

4-ene-3-one (**35**).

IR: 1670, 1610, 1450, 1250, 1150, 1100.

Mass: M^+ - 202.

Elemental analysis for $C_{13}H_{14}O_2$

calculated: C, 77.2; H, 6.98;

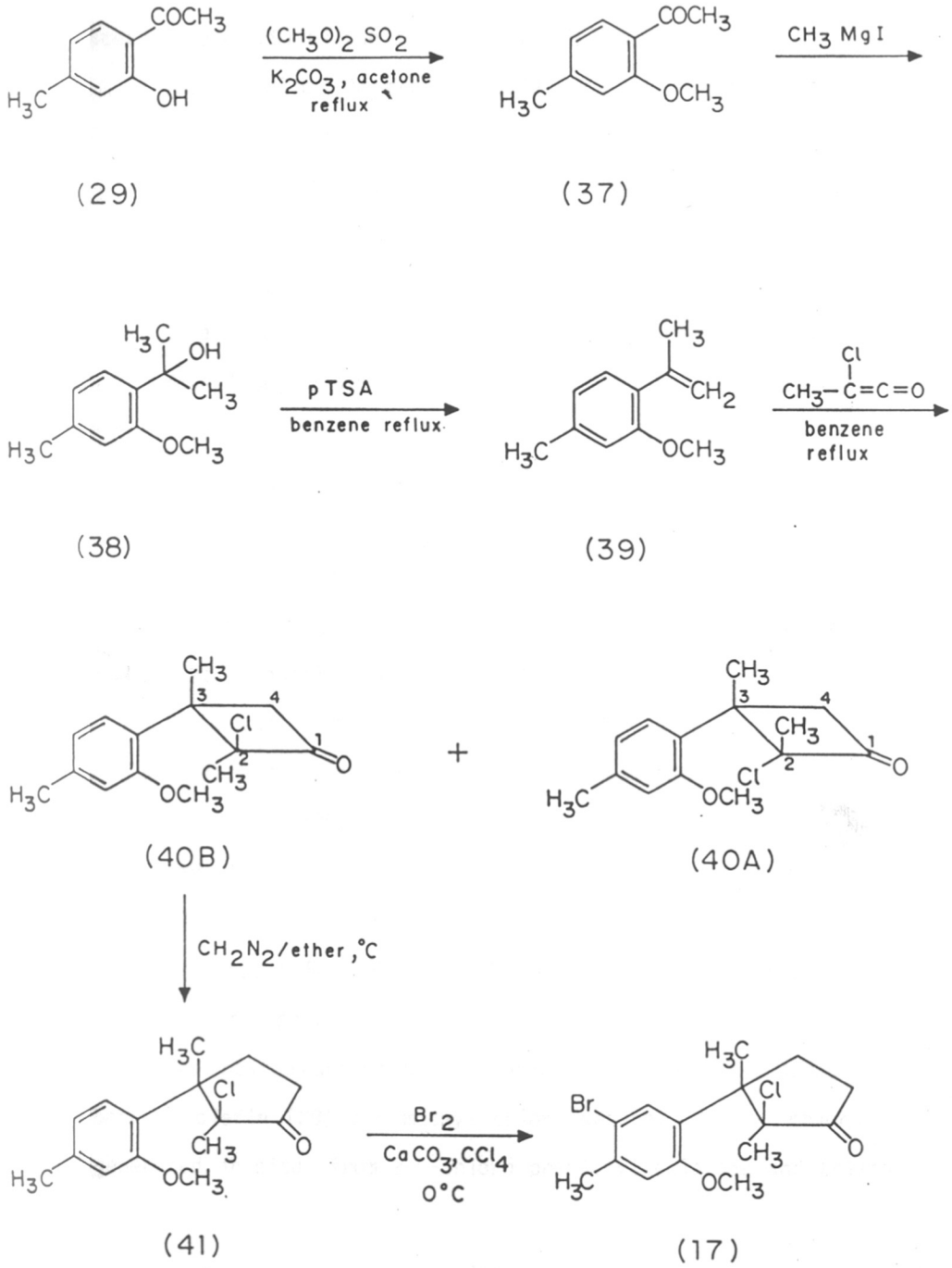
observed: C, 77.05; H, 6.81;

PRESENT WORK-PART 'B'

Since the earlier intramolecular approach did not give favourable results, we chalked out an intermolecular approach, again between ketene and olefin. Intermolecular (2+2) cycloaddition reaction between ketene and olefin to yield cyclobutanone and its subsequent regioselective ring expansion to cyclopentanone has been developed as a very efficient strategy called three carbon annelation[18]. It gives an easy access to cyclopentanone derivatives which are part of many natural products.

We decided to operate the above mentioned three carbon annelation on olefin (**39**). Thus olefin (**39**) was reacted with methyl chloro ketene (generated in-situ) to give cyclobutanones (**40A**) and (**40B**) which were separated on silica gel. On the basis of molecular modelling and observed chemical shifts in its p.m.r. spectrum, compound (**40B**) was assigned the anti stereochemistry. This was then regioselectively transformed to cyclopentanone (**41**) with diazomethane. Mono bromination on the aromatic ring gave the targeted molecule viz. cyclopentanone (**17**). Yamada et al. have already cyclized this intermediate to yield the cis fused ring junction of aplysin skeleton and further converted it to aplysin which is identical in all its spectral characteristics to the naturally occurring aplysin [see chart II(B)]. Thus our synthesis of cyclopentanone (**17**) constitutes a formal synthesis of aplysin.

SCHEME (B)


COCH3
H3C
OH
(CH3O)2 SO2
K2CO3, acetone
reflux
(29)
COCH3
H3C
OCH3
(37)
CH3 MgI
H3C C OH
CH3
H3C
OCH3
(38)
pTSA
benzene reflux
CH3
CH2
H3C
OCH3
(39)
Cl
CH3–C=C=O
benzene
reflux
CH3
3
4
Cl
1
2
CH3
H3C
OCH3
O
(40B)
+
CH3
3
4
CH3
1
2
Cl
H3C
OCH3
O
(40A)
CH2N2/ether, °C
H3C
Cl
CH3
H3C
OCH3
O
(41)
Br2
CaCO3, CCl4
0°C
H3C
Cl
Br
CH3
H3C
OCH3
O
(17)

The intermolecular approach also employed 2'-hydroxy-4'-methyl acetophenone (**29**) as the starting material.

The phenolic -OH group of (**29**) was protected as its methyl ether (**37**) by treatment with anhydrous potassium carbonate and dimethyl sulfate.

IR: 1680 (carbonyl), 1610, 1570 (aromatic).

PMR (CCl_4): 2.33 (3H, s, aromatic methyl), 2.5 (3H, s, $-COCH_3$), 3.87 (3H, s, $-OCH_3$), 6.71 (1H, d, 8 Hz, aromatic proton), 6.77 (1H, s, aromatic proton), 7.62 (1H, d, 8 Hz, aromatic proton).

Methyl magnesium iodide Grignard reaction of (**37**) gave the tertiary alcohol (**38**).

IR: 3500 (-OH), 1630, 1590 (aromatic).

PMR (CCl_4): 1.47 (6H, s, gem dimethyls), 2.3 (3H, s, aromatic methyl), 3.5 (1H, s, D_2O exchangeable, -OH proton), 3.77 (3H, s, $-OCH_3$), 6.43-6.8 (2H, s overlapping d, aromatic protons), 7.07 (1H, d, 8 Hz, aromatic proton).

Dehydration with p-toluene sulfonic acid (catalytic) in benzene reflux afforded the required olefin intermediate (**39**).

IR: 1620, 1580, 1510 (aromatic).

PMR (CCl_4): 2.05 (3H, s, CH_3-C=C), 2.26 (3H, s, aromatic CH_3), 3.67 (3H, s, $-OCH_3$), 5.0 (2H, s, olefinic proton), 6.5 (1H, s, aromatic proton), 6.58 (1H, d, 8 Hz, aromatic proton), 6.97 (1H, d, 8 Hz, aromatic proton).

The next reaction was intermolecular (2+2) cycloaddition reaction between olefin (**39**) and methyl chloro ketene. Methyl chloro ketene was generated in-situ. from 2- -chloro propionyl chloride and triethyl amine.

This reaction gave the two diastereomers of cyclobutanone, presumably syn (40A) and anti (40B), as suggestged by the p.m.r. spectrum of their mixture. They were separated on silica gel column which resulted in the isolation of one of the isomers as a solid. This solid isomer was further purified by crystallization from aqueous ethanol. It was assigned the anti structure (40B) on the basis of its p.m.r. signals which can be explained considering the molecular model. The p.m.r. spectrum of (40B) shows chemical shifts for the tertiary methyl groups at 1.44 and 1.73 . The significant downward shift of one of the methyl groups at 1.73 can be explained on the basis of molecular models of syn and anti-isomers (40A and 40B). The methyl group at C_2 in the anti isomer(40B) falls almost in the plane of aromatic ring and hence deshielded considerably while in the syn isomer (40A), since no such effect is operative, the chemical shifts of both the methyl groups are observed closer in the p.m.r. viz. at 1.44 and 1.48 .

40A: IR: 1800 (carbonyl), 1620, 1590 (aromatic).

PMR ($CDCl_3$): 1.44 (3H, s, C_3 methyl), 1.48 (3H, s, C_2 methyl), 2.35 (3H, s, aromatic methyl), 2.9 (1H, d, 16 Hz, C_4 proton), 3.61 (1H, d, 16 Hz, C_4 proton), 3.81 (3H, s, $-OCH_3$), 6.71 (1H, s, aromatic proto 6.75 (1H, d, 7 Hz, aromatic proton), 6.98 (1H, d, 7 Hz, aromatic proton.

40B: IR: 1800 (carbonyl), 1620, 1590 (aromatic).

PMR ($CDCl_3$): 1.44 (3H, s, C_3 methyl), 1.75 (3H, s, C_2 methyl), 2.36 (3H, s, aromatic methyl), 2.93 (1H, d, 16 Hz, C_4 proton), 3.82 3.82 (3H, s, $-OCH_3$), 4.0 (1H, d, 16 Hz, C_4 proton), 6.73 (1H, s,

aromatic proton), 6.77 (1H, d, 7 Hz, aromatic proton), 6.98 (1H, d, 7 Hz, aromatic proton).

Isomer (**40B**) was regioselectively ring expanded to give cyclopentanone (**41**) with ethereal solution of diazomethane.

IR: 1760 (carbonyl), 1620, 1580 (aromatic).

PMR ($CDCl_3$): 1.32 (3H, s, C_3 methyl), 1.75 (3H, s, C_2 methyl), 2.1-2.56 (4H, m, methylene protons at C_4 and C_5), 2.3 (3H, s, aromatic methyl), 3.78 (3H, s, $-OCH_3$), 6.68 (1H, s, aromatic proton), 6.71 (1H, d, 6.4 Hz, aromatic proton), 7.2 (1H, d, 6.4 Hz, aromatic proton).

Bromination of (**41**) with Br_2 in carbon tetrachloride containing anhydrous calcium carbonate gave the mono brominated, required intermediate (**17**), thereby completing a formal, total synthesis of aplysin.

IR: 1760 (carbonyl), 1610, 1510 (aromatic).

PMR ($CDCl_3$): 1.23 (3H, s, C_3 methyl), 1.70 (3H, s, C_2 methyl), 2.32 (3H, s, aromatic methyl), 2.15-2.6 (4H, m, methylene protons at C_4 and C_5), 3.67 (3H, s, $-O-CH_3$), 6.6 (1H, s, aromatic proton), 7.42 (1H, s, aromatic proton).

EXPERIMENTAL

2'-Methoxy-4'-methyl acetophenone (37)

A mixture of 2'-hydroxy-4'-methyl acetophenone (**29**) (7 g, 0.047 mole), dimethyl sulfate (7 g, 0.057 mole) and anhydrous potassium carbonate (9.67 g, 0.07 mole) in dry acetone (120 ml) was refluxed for 10 hr. Acetone was distilled out to give a residue which was diluted with water and extracted repeatedly with ether. The combined ether layer was washed with cold, dilute, aqueous sodium hydroxide solution to remove unreacted phenol, followed by water, brine and dried. Removal of ether yielded the pure product (6.2 g, 81%) which was used as such for the next reaction.

IR: 2960, 1680, 1610, 1570, 1410, 1290, 1170.

Mass: M^+ - 164.

Elemental analysis for $C_{10}H_{12}O_2$

calculated: C, 73.14; H, 7.37;

observed: C, 72.95; H, 7.2;

2(2'-Methoxy-4'-methyl phenyl) propan-2-ol (38)

Solution of methyl magnesium iodide in ether was prepared from methyl iodide (7.79 g, 0.055 mole) and magnesium (1.33 g, 0.055 mole) in dry ether (100 ml). This solution was cooled to 0°C and a solution of acetophenone (**37**) (6 g, 0.036 mole) in dry ether (70 ml) was added dropwise. After the addition was completed, the reaction mixture was allowed to come to room temperature and stirred overnight at room temperature. Decomposition with cold, saturated aqueous ammonium chloride and usual work up, gave 6 g crude alcohol which was purified on silica gel column by eluting with pet.ether + 7% ethyl acetate, to afford 5.83 g (88.5%) pure material as a thick liquid.

IR: 3500, 2980, 1630, 1590, 1520, 1270, 1180.

Mass: M^+ - 180.

Elemental analysis for $C_{11}H_{16}O_2$

calculated: C, 73.3; H, 8.95;

observed: C, 73.19; H, 8.83;

2(2'-Methoxy-4'-methyl phenyl) propene (39)

A solution of alcohol (**38**) (5.8 g, 0.032 mole) and p-toluene sulfonic acid (.56 g) was refluxed in dry benzene (60 ml) for 1.5 hr using a Dean Stark unit for azeotropic removal of water, formed during the reaction. The reaction mixture was cooled to room temperature and washed with water, bicarbonate and brine. After drying, benzene was removed under vacuum and crude oily product was filtered through a short column of silica gel, eluting with pet.ether. The pure product was thus obtained in 5.05 g (95%) yield as a mobile liquid.

IR: 2960, 1620, 1580, 1510, 1475, 1280, 1175.

Mass: M^+ - 162.

Elemental analysis for $C_{11}H_{14}O$

calculated: C, 81.44; H, 8.7;

observed: C, 81.26; H, 8.61;

Cyclobutanones (40A and 40B)

To a gently refluxing solution of olefin (**39**) (5 g, 0.03 mole) and triethyl amine (6.4 g, 0.063 mole) in dry benzene (100 ml), a solution of 2-chloro propionyl chloride (7.65 g, 0.06 mole) in dry benzene (100 ml) was added over 4 hr. The reaction mixture was refluxed for additional 2 hr. It was then filtered through a short column of silica gel to remove the tarry material. The filterate was washed with water, bicarbonate,

brine and dried. Removal of solvent under vacuum gave an oil which was chromatographed over silica gel. Initial elution with pet.ether removed the unreacted olefin. Further elution with pet.ether + 20% benzene and careful fractionation separated the cyclobutanones (**40A**) and (**40B**).

Isomer (**40A**) was obtained as colorless free flowing liquid, 1.34 g (17%)yield and was assigned the syn. structure.

IR: 2980, 1800, 1620, 1590, 1470, 1290, 1040, 815.

Mass: M^+ - 252 (^{35}Cl), 254 (^{37}Cl).

Elemental analysis for $C_{14}H_{17}ClO_2$

calculated: C, 66.53; H, 6.78; Cl, 14.03;

observed: C, 66.39; H, 6.62; Cl, 13.86;

Isomer (**40B**) was obtained as a solid. It was further purified by crystallization from aqueous ethanol to get 0.7 g (10%) pure material showing m.p. 105-107°C.

IR: 2980, 1800, 1620, 1590, 1470, 1290, 1040, 815.

Mass: M^+ - 252 (^{35}Cl), 254 (^{37}Cl).

Elemental analysis for $C_{14}H_{17}ClO_2$

calculated: C, 66.53; H, 6.78; Cl, 14.03;

observed: C, 66.36; H, 6.67; Cl, 13.9;

Cyclopentanone (41)

Cyclobutanone (**40B**) (0.3 g, 0.0012 mole) was taken up in dry ether (3 ml) and was treated with ethereal solution of diazomethane (generated freshly from nitroso monomethyl urea) and a drop of absolute alcohol. The solution was kept stoppered at 0°C for 4 days. (Early work-up led to partial reaction). Usual work-up and purification on silica gel

column (pet.ether + 30% benzene) led to the isolation of cyclopentanone (**41**) (0.27 g, 85%) as a colorless liquid.

IR: 2920, 1760, 1620, 1580, 1420, 1270.

Mass: M^+ - 266 (^{35}Cl), 268 (^{37}Cl)

Elemental analysis for $C_{15}H_{19}ClO_2$

calculated: C, 67.53; H, 7.18; Cl, 13.29;

observed: C, 67.36; H, 7.05; Cl, 13.21;

Brominated cyclopentanone (17)

To an ice-cooled suspension of cyclopentanone (**41**) (0.16 g, 0.0006 mole) and anhydrous calcium carbonate (0.06 g, 0.0006 mole) in dry carbon tetrachloride (2 ml), Br_2 (0.1 g, 0.00063 mole) was added and the contents were stirred at 0°C for 2 hr. Usual work-up gave 0.152 g crude product which was purified by chromatography over silica gel by eluting with pet. ether +30% benzene to get 0.141 (68%) pure, mono brominated product (**17**), which matched in its spectral characteristics with the one reported by Yamada[11].

IR: 2920, 1760, 1610, 1510, 1450, 1260.

Mass: M^+ - 348, 346 and 344 with intensities of 1:4:3.

Elemental analysis for $C_{15}H_{18}BrClO_2$

calculated: C, 52.11; H, 5.25; Br, 23.12; Cl, 10.26;

observed: C, 52%, H, 5.08; Br, 22.97; Cl, 10.13;

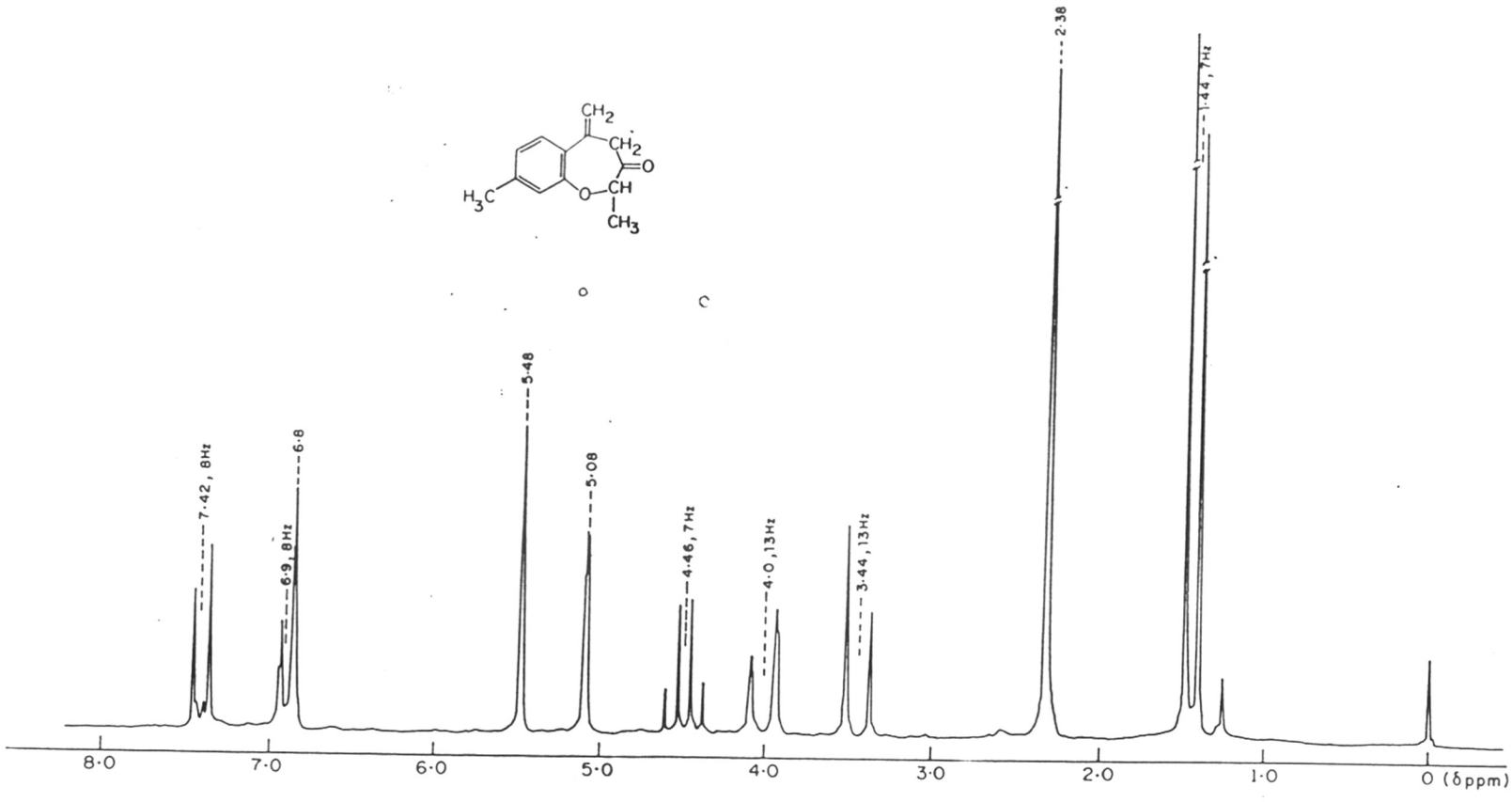


FIG. I : NMR OF COMPOUND No. 36

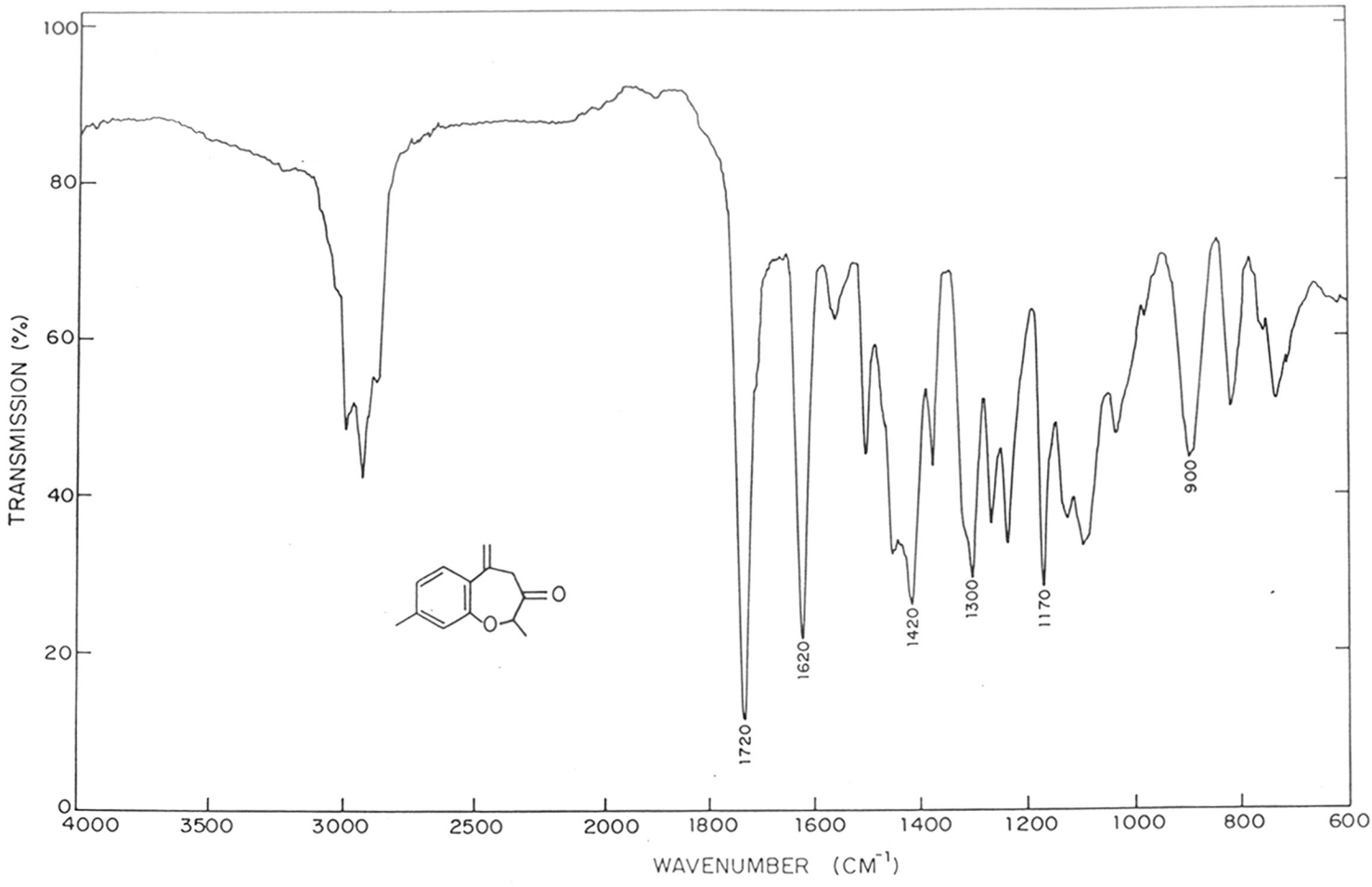


FIG. II IR OF COMPOUND No. 36

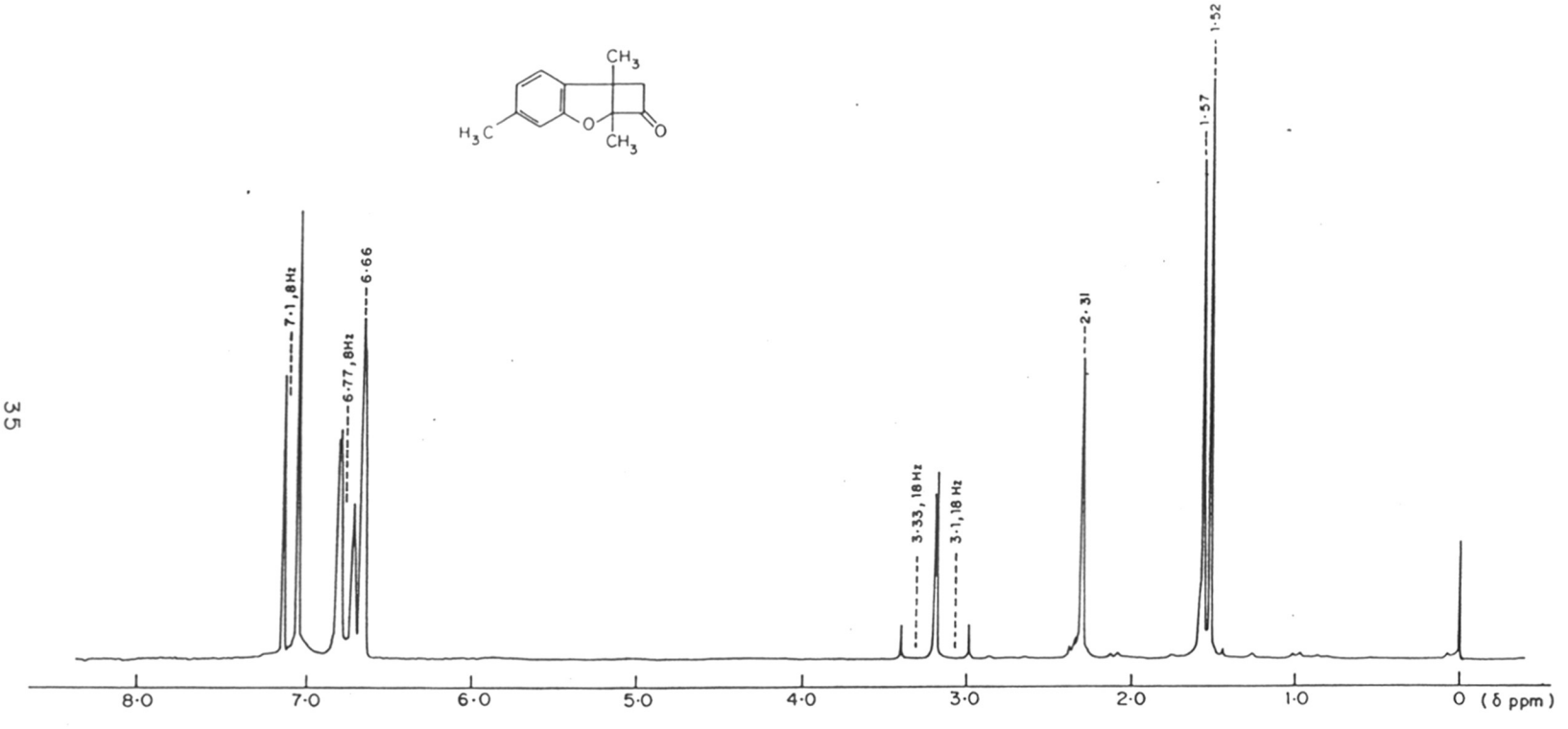


FIG. III : NMR OF COMPOUND No. 34

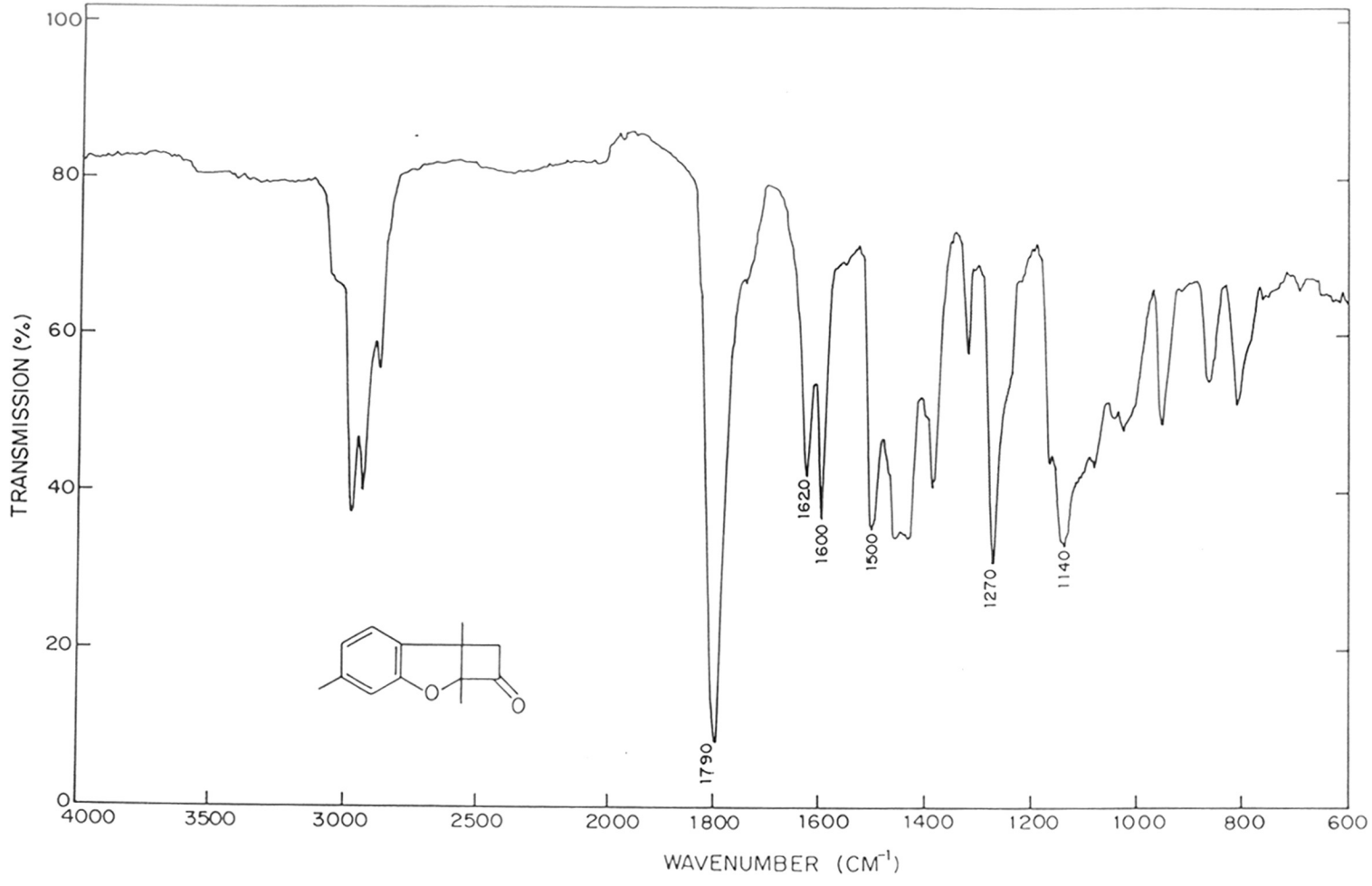


FIG. IV : IR OF COMPOUND No. 34

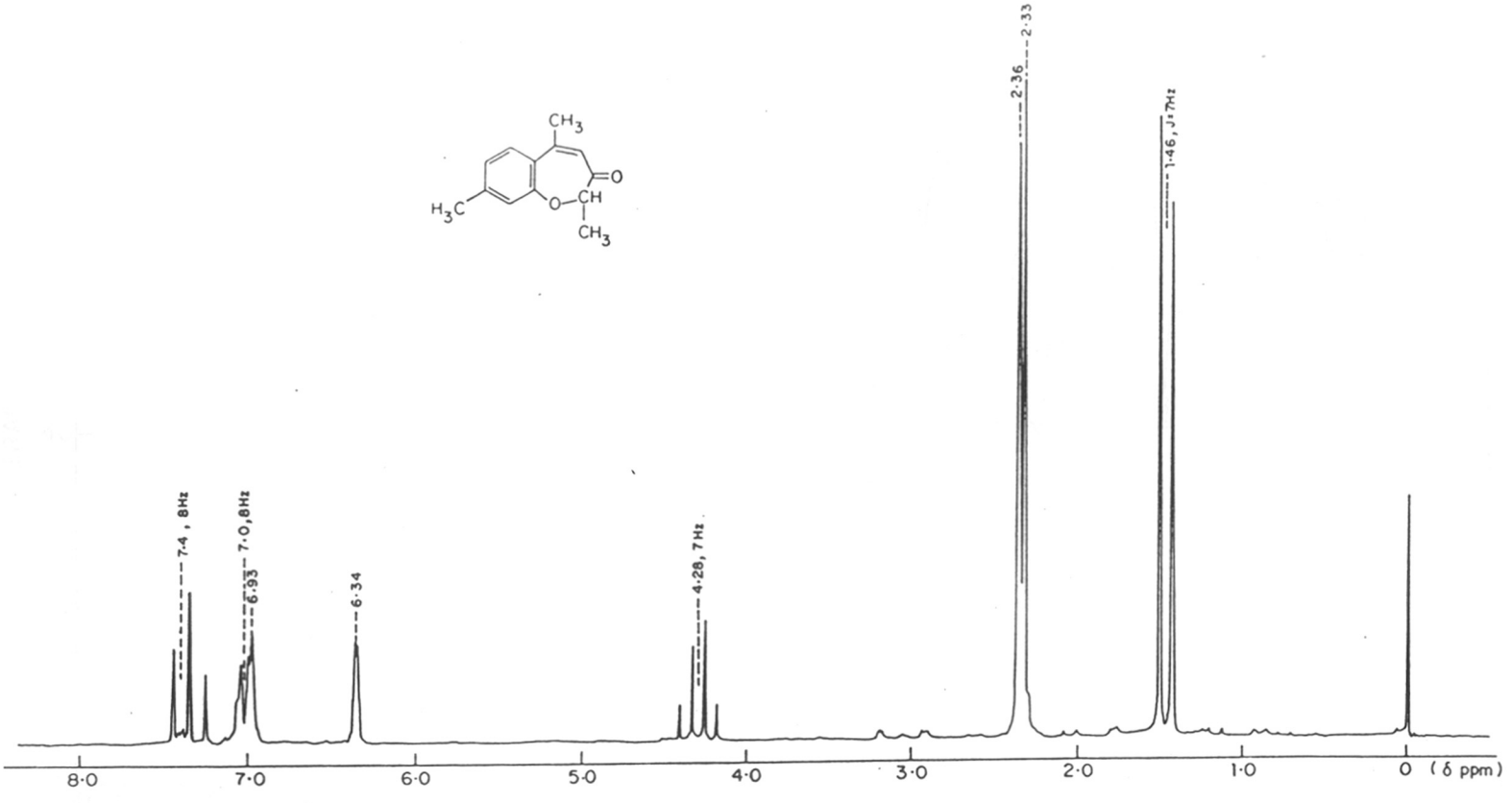


FIG. V : NMR OF COMPOUND No. 35

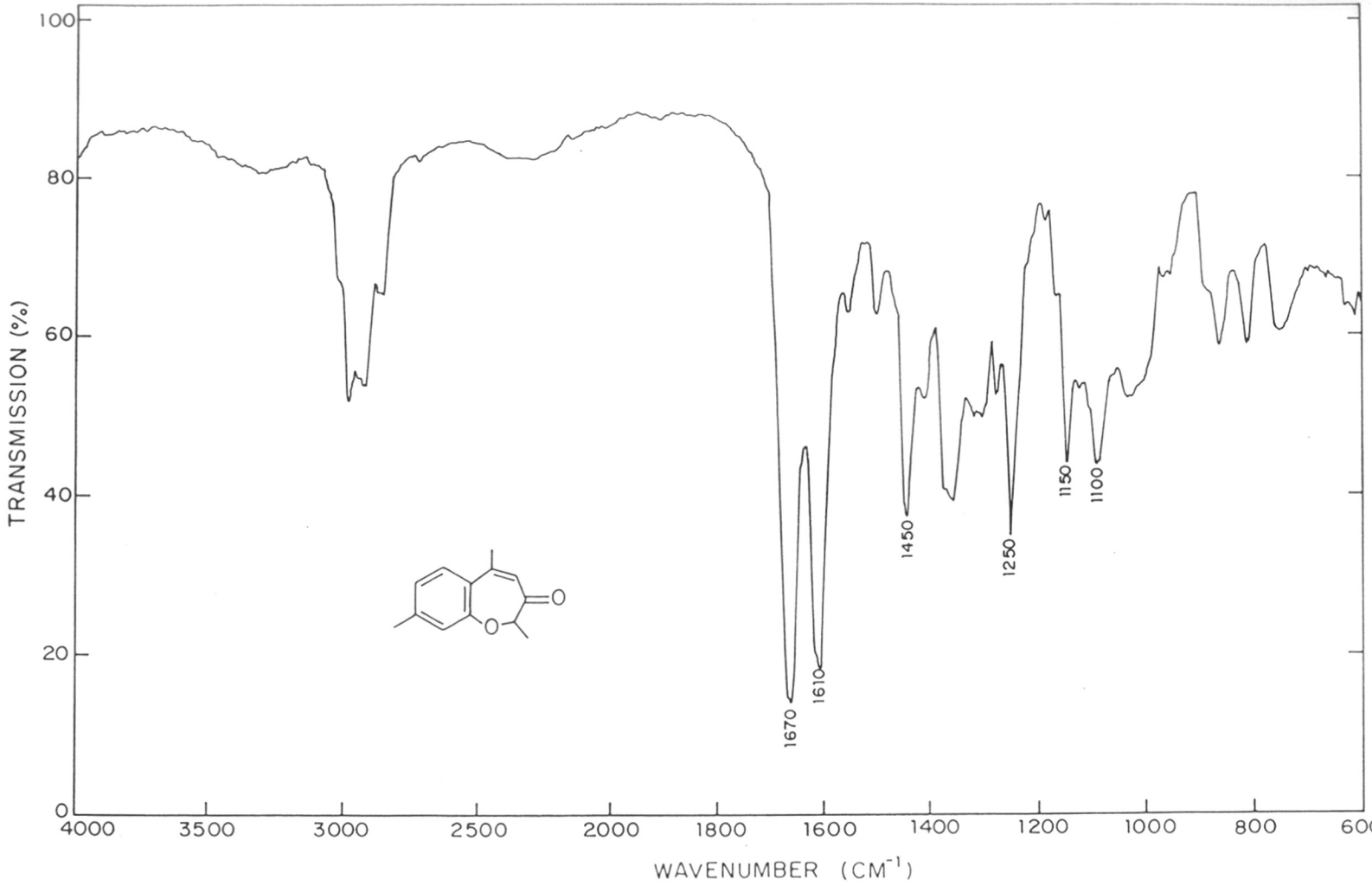


FIG. VI : IR OF COMPOUND No. 35

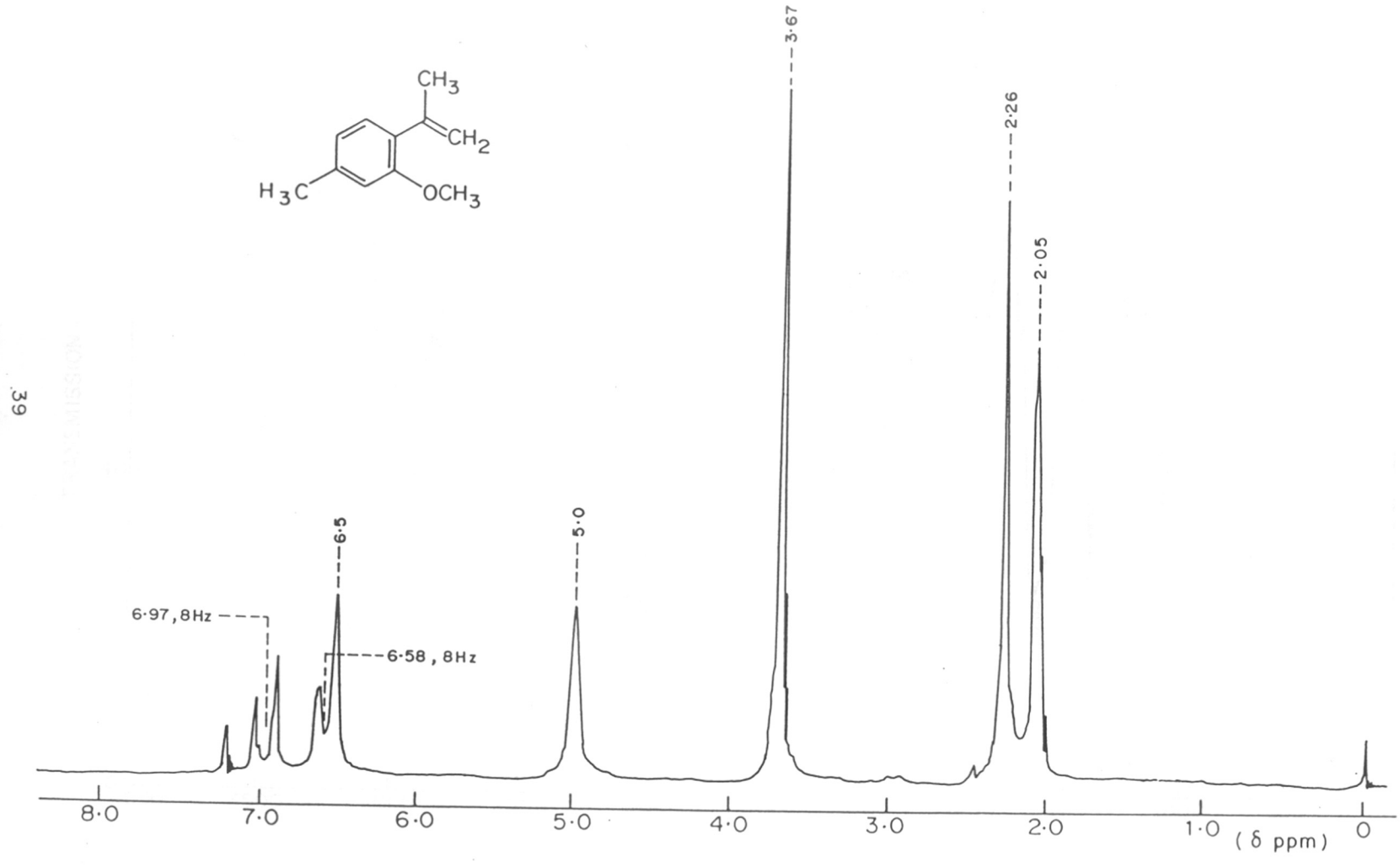


FIG. VII : NMR OF COMPOUND No. 39

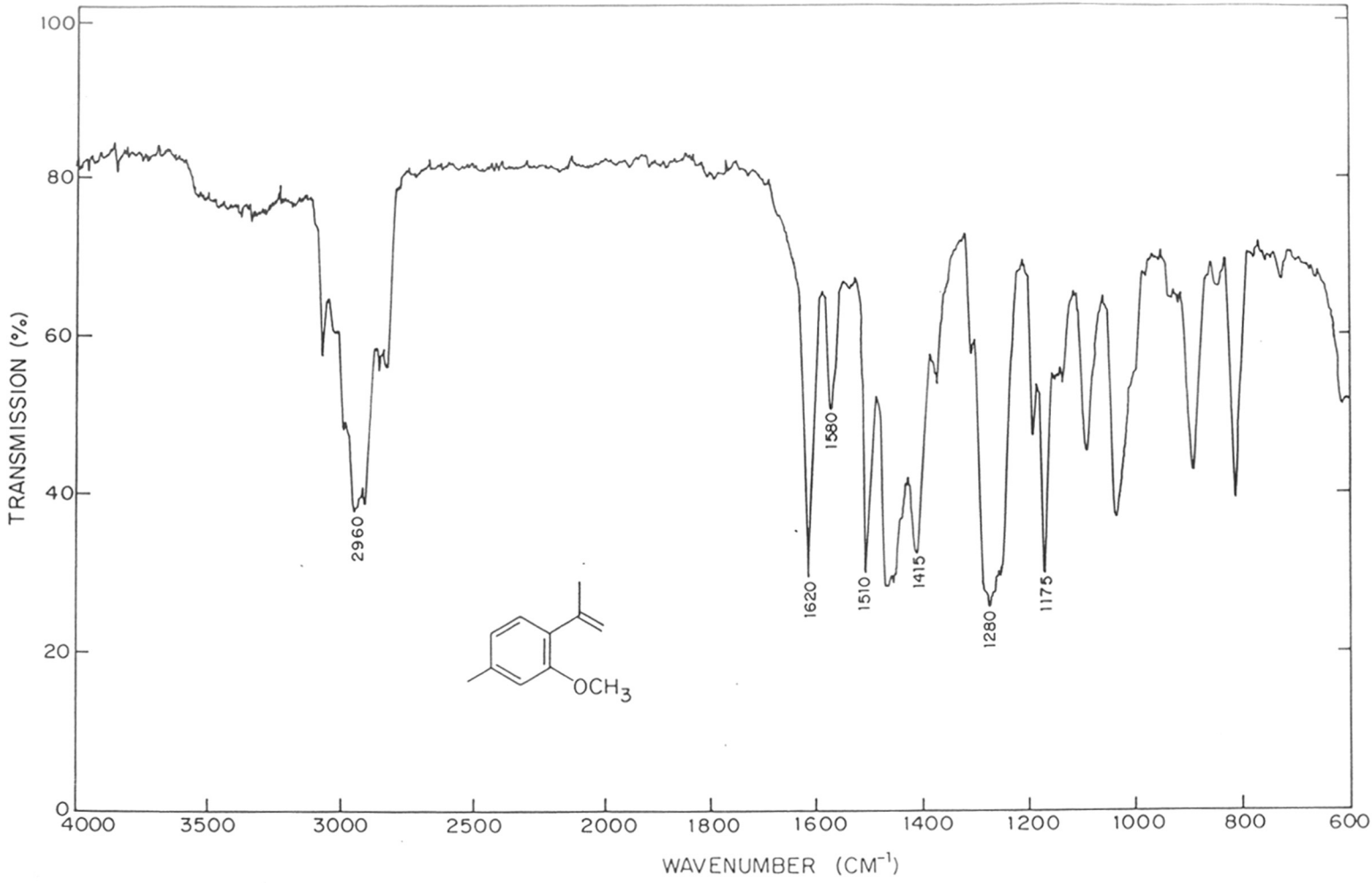


FIG. VIII : IR OF COMPOUND No. 39

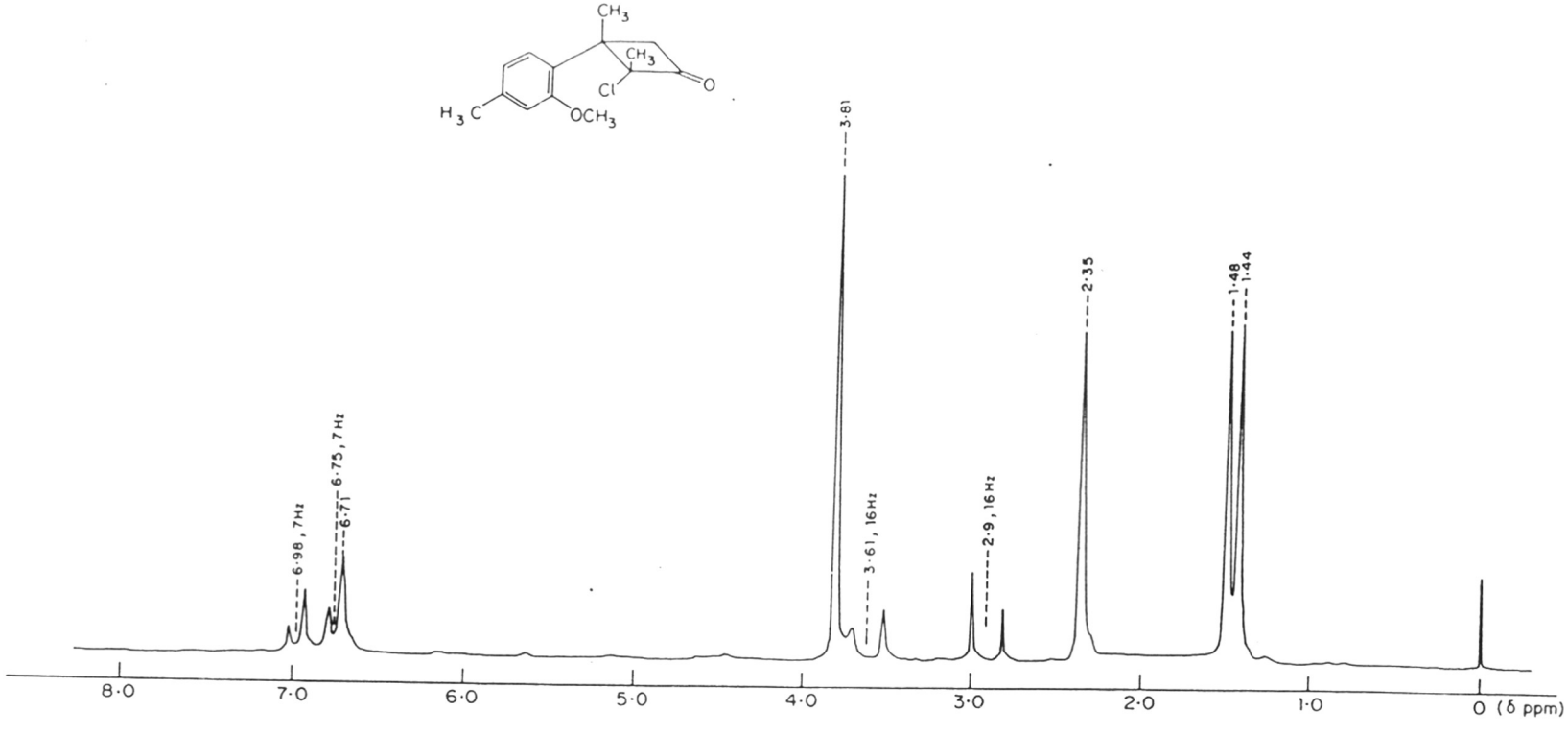


FIG. IX A : NMR OF COMPOUND No. 40 A

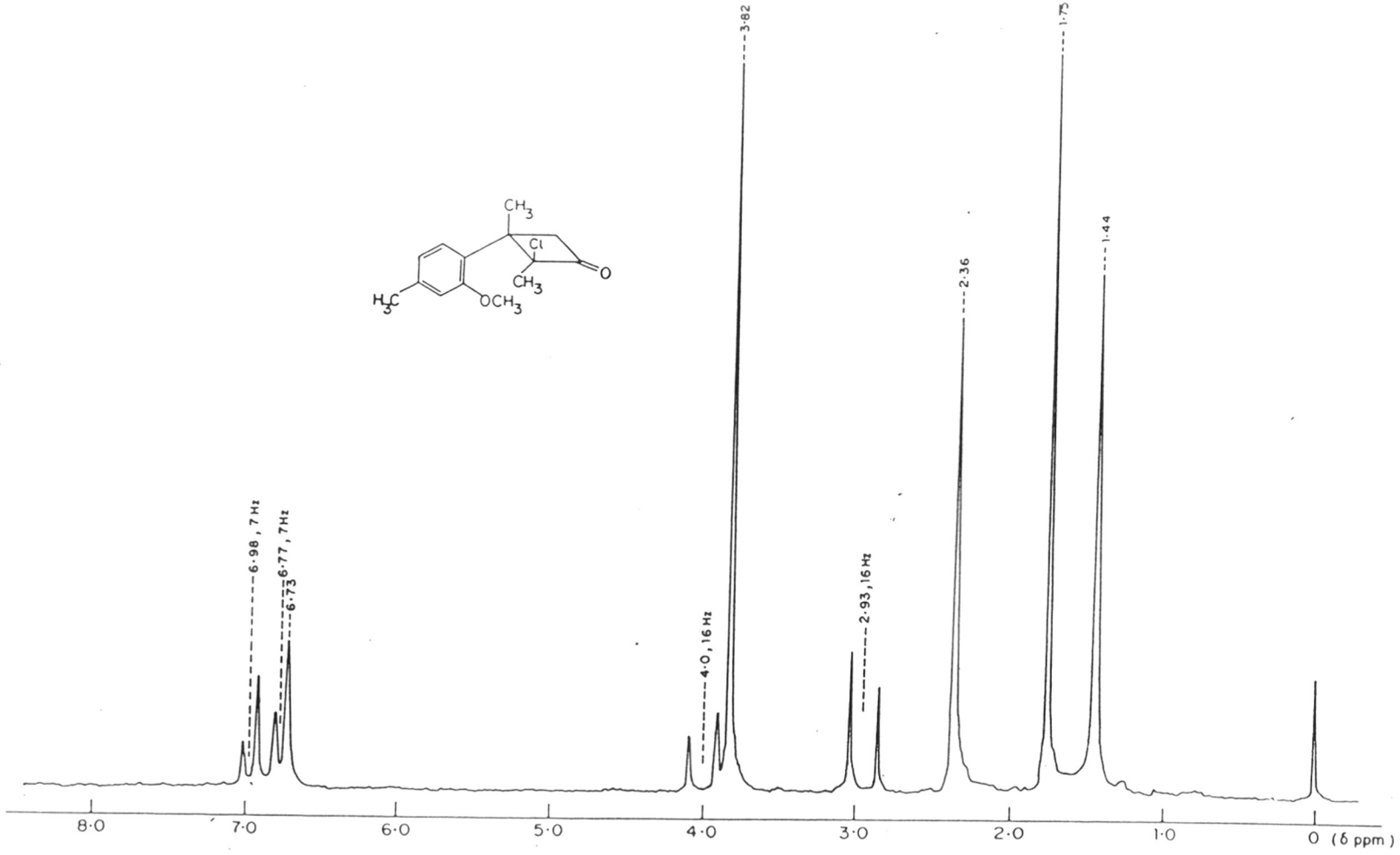


FIG IX B : NMR OF COMPOUND No. 40'B

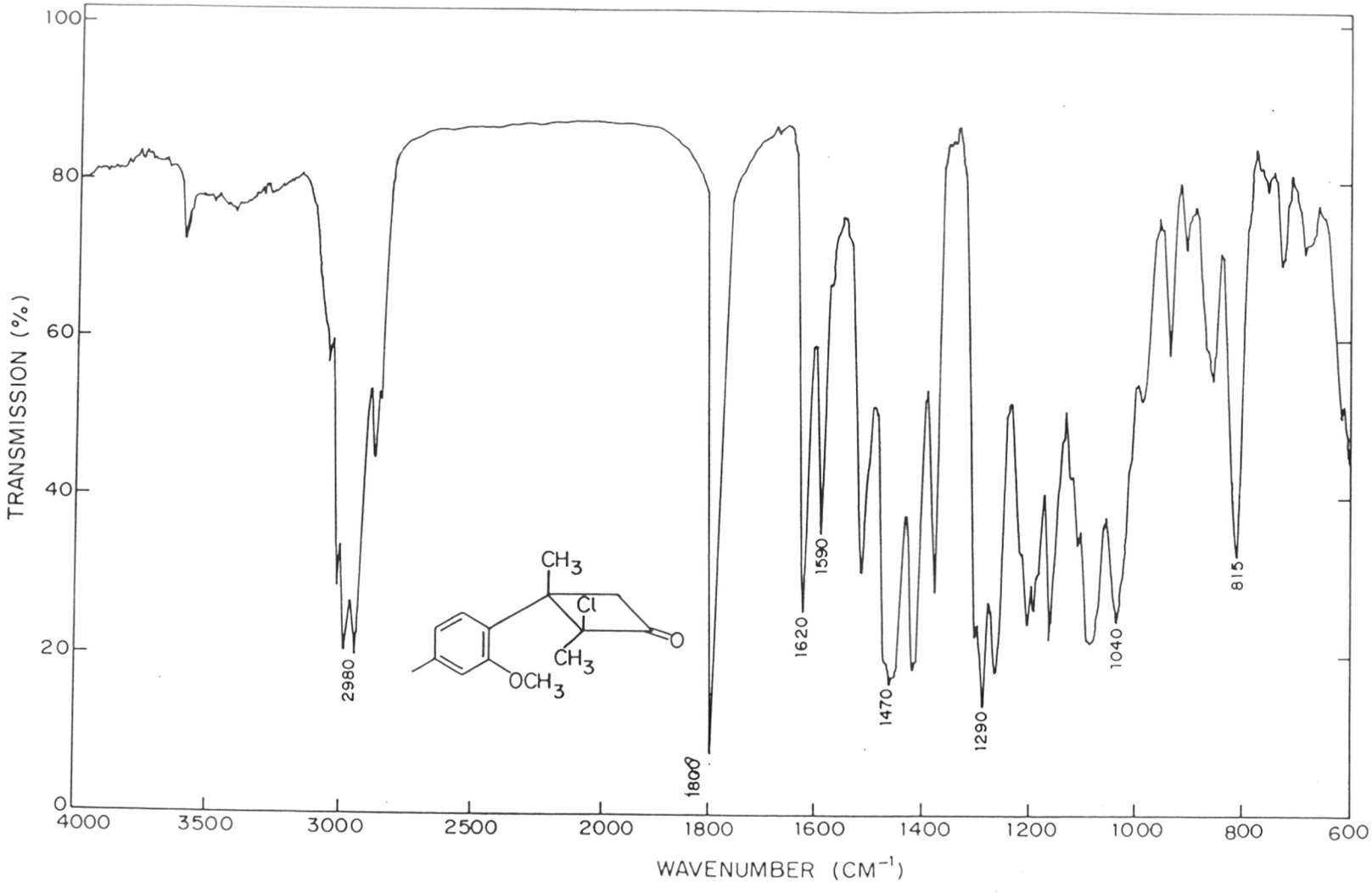


FIG. X : IR OF COMPOUND No. 40 B

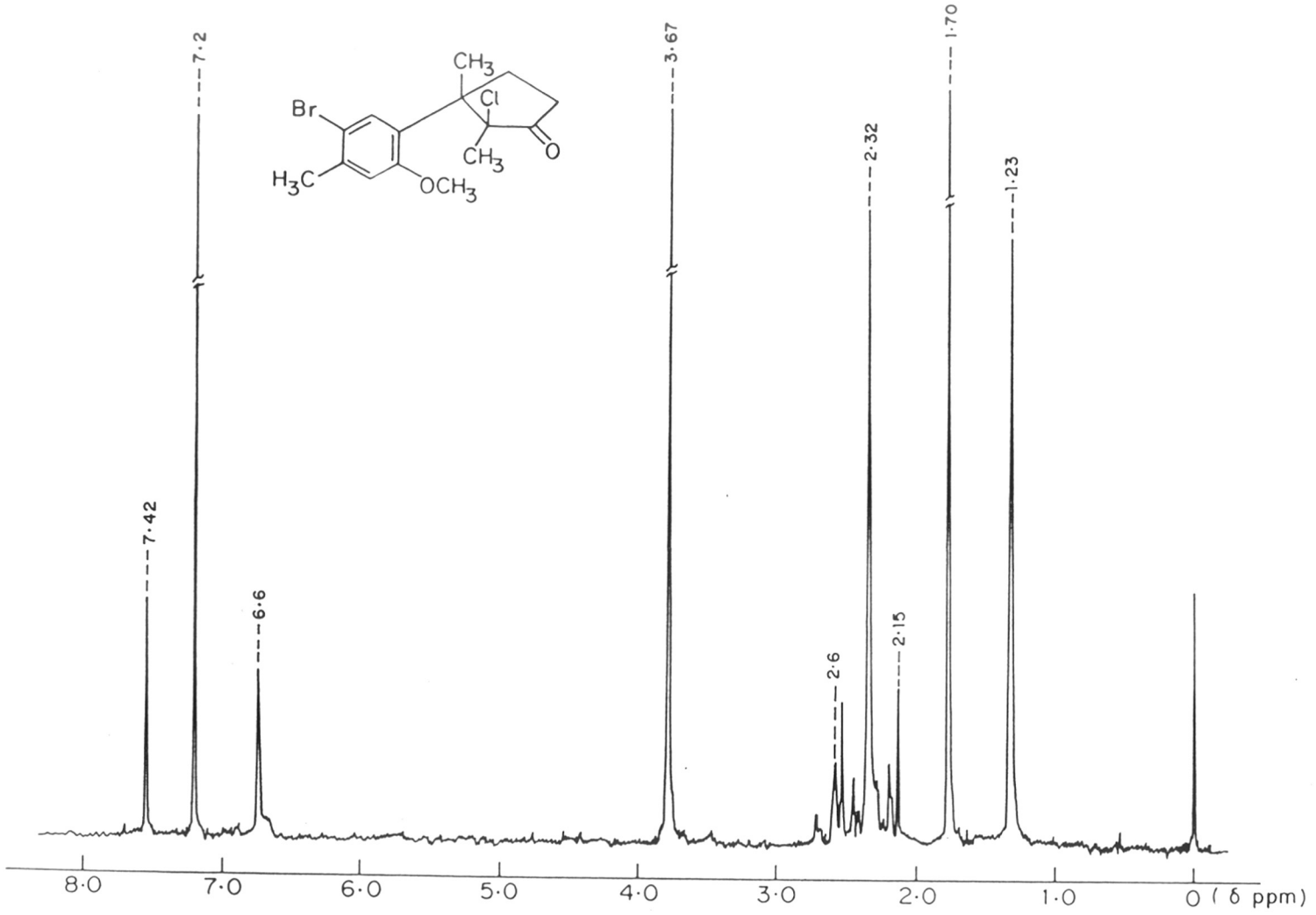


FIG. XI : NMR OF COMPOUND No. 17

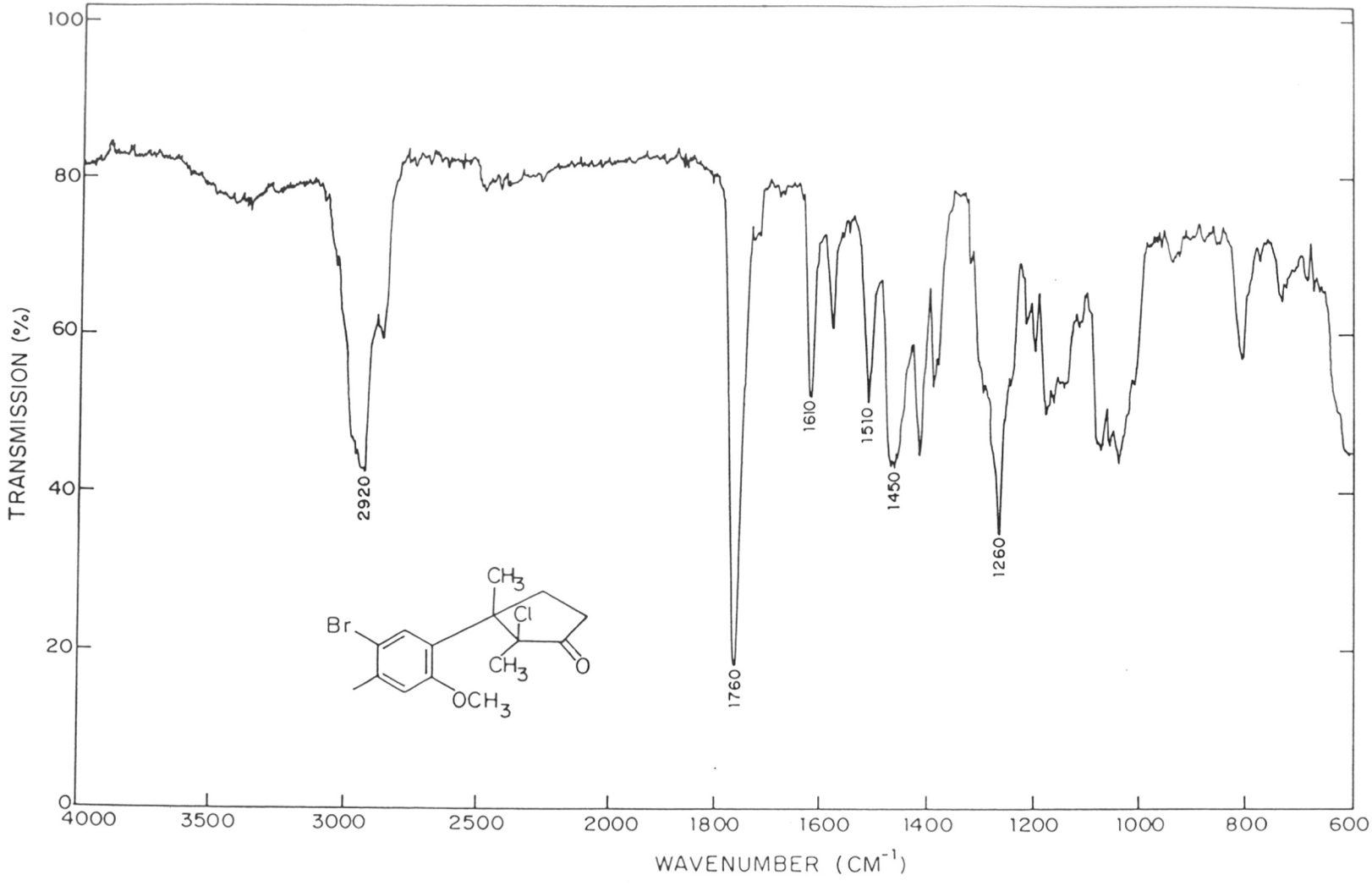


FIG. XII : IR OF COMPOUND No. 17

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CHAPTER-2

SYNTHESIS OF HIGHER HOMOLOGUES OF FENVALERATE- A HIGHLY ACTIVE AND WIDELY COMMERCIALIZED NON-CYCLOPROPANE CARBOXYLATE INSECTICIDE

SUMMARY

In this chapter, the syntheses of (±) α-(RS) cyano,3-phenoxybenzyl-4-methyl-3-phenyl/p-substituted phenyl pentanoates which resemble structurally to 1,2-secopyrethroids, has been described (Chart IV). These compounds feature a phenyl /p-substituted phenyl ring in place of conventional vinyl group. They can also be viewed as the higher homologues of fenvalerate (Chart II).

Grignard reaction of benzaldehyde/p-substituted benzaldehyde (1a-d) with isopropyl magnesium iodide furnished the corresponding alcohols (see the Scheme). These without purification and oxidation with Jones chromic acid reagent gave the isobutyrophenones (2a-d). Reformatsky's reaction on the ketones (2a-d) with ethyl bromo acetate and zinc furnished the expected β-hydroxy esters (3a-d). Dehydration of the esters (3a-c) afforded the mixture of unsaturated esters (4a-c and 5a-c). While dehydration of (3d) under similar conditions, gave the totally unexpected hydrocarbon, identified by its spectral data as (4d). Possible pathway for the formation of (4d) could not be ascertained.

Catalytic hydrogenation (10% Pd-C) of mixture of esters (4a-c, 5a-c) gave the corresponding saturated esters (6a-c). Saponification of (5a-c) (aqueous KOH, EtOH) furnished the corresponding acids (7a-c) which were converted to its acid chlorides ($SOCl_2$/benzene reflux). Acid chlorides as such were esterified with α-cyano-3-phenoxy benzyl alcohol, prepared in-situ using 3-phenoxy benzaldehyde, sodium cyanide and water under phase transfer conditions, using TEBA as PTC, to afford the α(RS) cyano-3-phenoxy benzyl esters (8a-c). These were purified by chromatography and characterized by spectral properties.

INTRODUCTION

New insecticides with a wide range of physical, chemical and biological properties will be needed as long as present methods of crop protection continue and until diseases transmitted by insects no longer affect man and his livestock. Millions of human beings owe their freedom from starvation and protection from diseases, to insecticides. Nevertheless, the present range of compounds is inadequate because resistant insect species have emerged to diminish their affectiveness or because they are also harmful to non-targeted subjects like mammals or because they are not selective between pests and beneficial insects.

Generally insecticides are classified in four major areas. (1) Carbamates (2) Organophosphates (3) Organochlorines and (4) Pyrethroids.

The deficiencies in the earlier three classes of compounds, such as high persistence, high mammalian toxicity and environmental pollution, have restricted their use as insecticides. Most of these deficiencies are overcome in naturally occurring and synthetic pyrethroids. The present introduction and the subsequent work described in this chapter centres around pyrethroids and structurally related analogues with special reference to 'seco-pyrethroids'- the cut-up analogs of pyrethroids.

What are Pyrethroids?

The term pyrethroid has emerged from the word "pyrethrum'[1]. The term 'pyrethrum' refers to the dried and powdered flower heads of chrysanthemum cinerariaefolium. The time and place of the discovery of the insecticidal activity of pyrethrum are unknown. It is likely that it was discovered

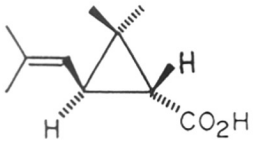
at least twice in the Caucasus-Iran region of Asia, the region between the Black and Caspian seas, and in Dalmatia, now part of the Adriatic coast of Yugoslavia, where C.cinerariaefolium is a native plant. Already in the middle ages it was commercialized by Caucasians as a potent insecticide. In Europe, it became popular in the early 19th century. The active ingredients of the pyrethrum powder are esters of chrysanthemic acids (I) and pyrethric acid (II): viz cinerins(IIIa,IVa), jasmolins(IIIb, IVb) and pyrethrins (IIIc, IVc) (Chart I).

By and large, most pyrethroids can be defined as the compounds whose structure can be reasonably derived from the natural pyrethrins and which exhibit a range of biological properties that overlap to a considerable degree with those of existing members of the group.

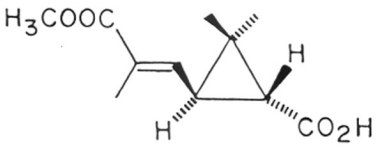
The pyrethrum constituents had the big advantage of being innocuous to mammals and birds. But at the same time, they suffered from serious skeletal drawbacks. Both the acid and the alcohol components [see compounds IIIa, IIIb, IIIc and IVa, IVb, IVc in Chart I) were extremely sensitive to photostimulated oxidative degradation. Thus no agricultural application could be envisaged until structural modifications provided sufficient chemical stability. So, efforts were directed towards the synthesis of pyrethroids, bearing close structural resemblance to natural pyrethrins but having photostable alcohol as well as acid moieties.

The first attempts were undertaken by Staudinger and Ruzicka, shortly after they had completed simultaneously with R. Yamamoto[2], the structure elucidation[3] of the chrysanthemic acid as well as a first synthesis They began by replacing cyclopentenone moiety of the cyclopropane carboxy-

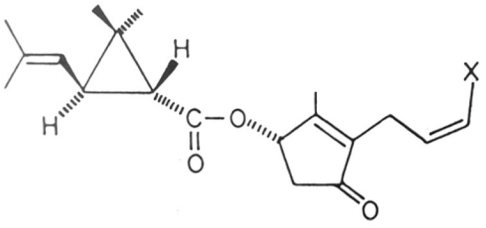
CHART I



I Chrysanthemic acid



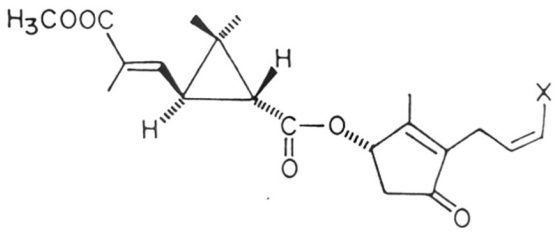
II Pyrethric acid



III a : X = CH_3 (Cinerin 1)

III b : X = C_2H_5 (Jasmolin 1)

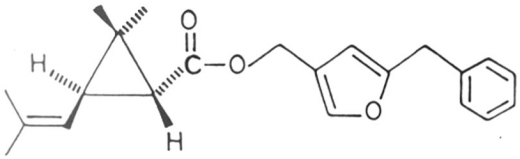
III c : X = CH = CH_2 (Pyrethrin 1)



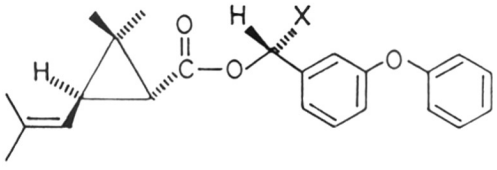
IV a : X = CH_3 (Cinerin 2)

IV b : X = C_2H_5 (Jasmolin 2)

IV c : X = CH = CH_2 (Pyrethrin 2)



V Resmethrin



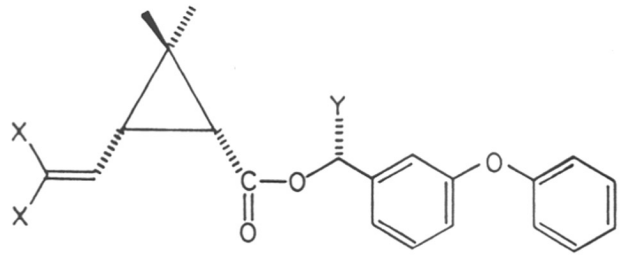
VI a : X = H, Phenothrin

VI b : X = CN, Cyphenothrin

lates with a benzyl or p-anisyl group. Unfortunately, all biological activity was lost. In contrast, esterification with modified five membered ring alcohol such as 5-benzylfurfurol[4] leading to resmethrin (V) (Chart I) was rewarded with considerable success. Thus the benzyl type substitution was considered as a dead-end until the m-phenoxy benzyl and α-cyano m-phenoxybenzyl chrysanthemates (VIa, VIb) [5,6,7] (Chart I) marked a breakthrough in the field of photostable synthetic pyrethroids.

In the meantime, another important and highly rewarding result was obtained by modifying the acid moiety. When the terminal methyl groups at the vinyl side-chain were replaced by electronegative substituent, the photochemical degradation was retarded substantially, if not eliminated totally. In this respect, permethrinic acid, first described by Sorm et al.[8] turned out to be an important milestone. When combined with m-phenoxy and α-cyano-m-phenoxy benzyl alcohols, the new esters (VIIa)[9,10] and (VIIb)[9,10] (Chart II) exhibited the most impressive properties. Although similar in toxicity, they outperformed their natural counterparts as insecticides by orders of magnitude. The dibromo analog (VIIc) (deltamethrin) showed still enhanced activity[9]. Amazingly, one stereocentre had to be inverted compared with the natural model. Thus, halogenated synthetic pyrethroids of type (VII) will not be highly potent unless their side-chain occupies cis position with respect to ester function, although naturally occurring active constituents have trans relationship between these two functional groups. It is also essential to have 1R configuration in cyclopropane carboxylic acids. Esters of cyclopropane carboxylic acids possessing 1S configuration are either inactive or much less active.

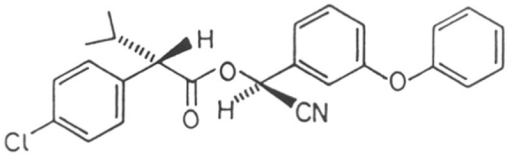
CHART II



VII , a : X = Cl , Y = H Permethrin

b : X = Cl , Y = CN Cypermethrin

c : X = Br , Y = CN Deltamethrin



VIII : Fenvalerate

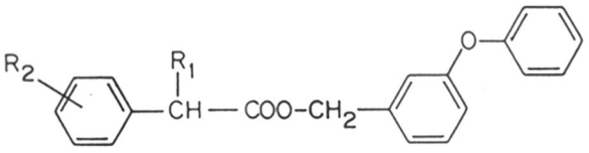
Staudinger and Ruzicka in 1920, prepared pyrethronyl esters of various acids such as aliphatic, olefinic, aromatic and terpenic, bearing some structural resemblance to chrysanthemic acid and examined their biological activity. These esters did not show any appreciable activity and hence it was commonly believed that cyclopropane ring is essential for insecticidal activity.

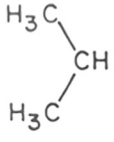
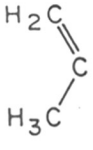
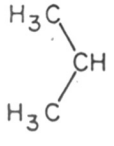
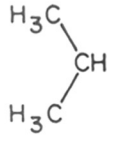
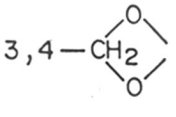
An important land-mark in pyrethroid history was the discovery of α-cyano-3-phenoxybenzyl alcohol ester with a carboxylic acid such as 2-isopropyl-4'-chlorophenyl acetic acid, commonly known as fenvalerate[11] (Chart II) which Ohno et al. demonstrated to be an important insecticide. In fenvalerate, the isopropyl group on the benzylic carbon atom can be considered as the steric equivalent of gem dimethyl group on the cyclopropane of chrysanthemates with the unsaturated centre placead on α-carbon atom of the acid. The insecticidal activity of alkyl-aryl acetates is very sensitive to structural changes and substitution pattern (Chart III). Thus, phenyl acetates whose substituents are isopropyl, isopropenyl or t-butyl group, are highly toxic to insects while corresponding methyl, n-propyl, n-butyl are non-toxic. Marked enhancement is observed when functional groups like methyl, methoxy, chloro or bromo are introduced in the meta or para position of the aromatic ring.

These comparative results indicate that the presence of a gem dimethyl or its steric equivalent to the carboxylate function is one of the important structural requirement, both in case of chrysanthemates and α-substituted phenyl acetates.

Subsequent studies on the acid moieties confirmed that the presence of intact cyclopropane ring is not necessary[12-19]. The study of seco pyreth-

CHART III



R_1	R_2	LC_{50} (mg / 100ml.)	Relative toxicities
	4—Cl	83	375
CH_3CH_2	4—Br	197	158
	3—Cl	108	288
	4—OCH_3	65	478
	3,4— 	49	635
	Pyrethrin	311	100

roids has, thus, attracted considerable attention in recent years. Seco-pyrethroids can be considered as open chain equivalent of cyclopropane carboxylic acids. Cyclopropane ring can be cleaved in three ways (Chart IV) leading to three types of "cut-up chrysanthemates" or "seco-pyrethroids". In the first two types, 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 type they are separated by a three carbon unit.

In our laboratory efforts have been directed towards syntheses of 1,3 and 2,3 secopyrethroids[20,21] [see G.H. Kulkarni et al. in Chart (V)]. Chart (V) also shows some of the selected approaches towards the synthesis of seco-pyrethroids.

CHART IV

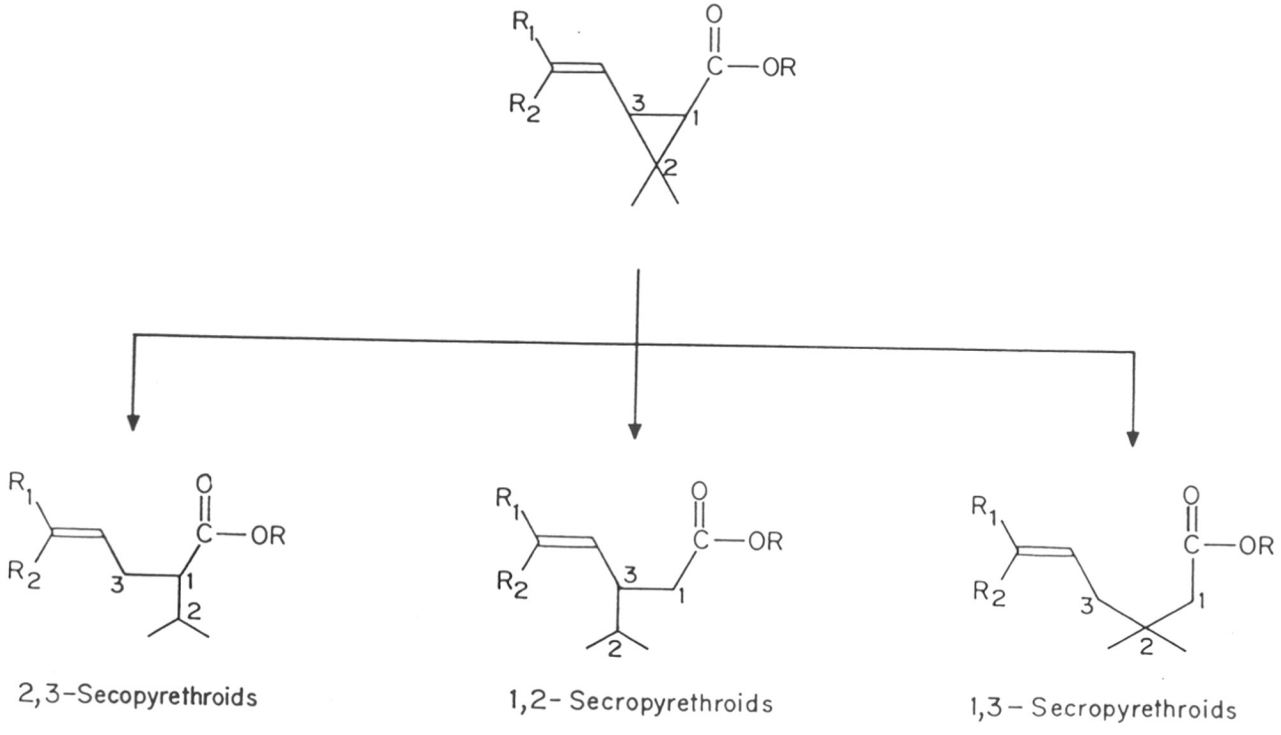
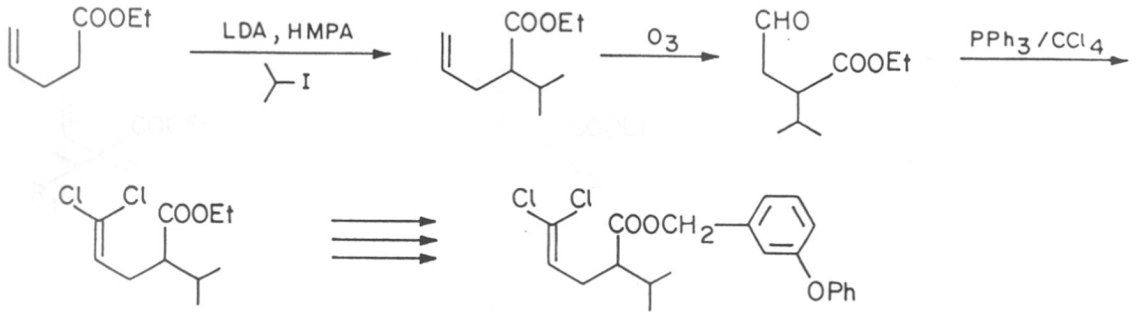
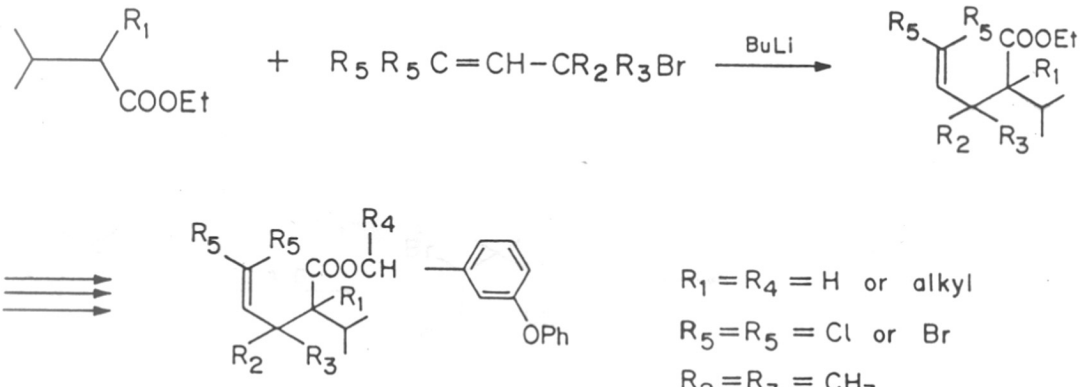

R1
R2
O
C—OR
3
1
2
2,3-Secopyrethroids
1,2- Secropyrethroids
1,3 – Secropyrethroids

CHART - V

(A) W. G. TAYLOR et al



(B) WINTERNITZ PAROL (Hoffman La Roche) et al

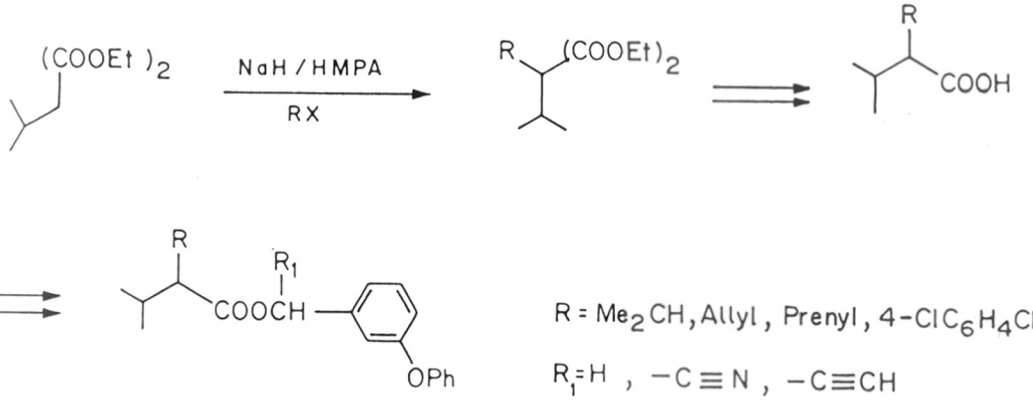


$R_1 = R_4 = H$ or alkyl

$R_5 = R_5 = Cl$ or Br

$R_2 = R_3 = CH_3$

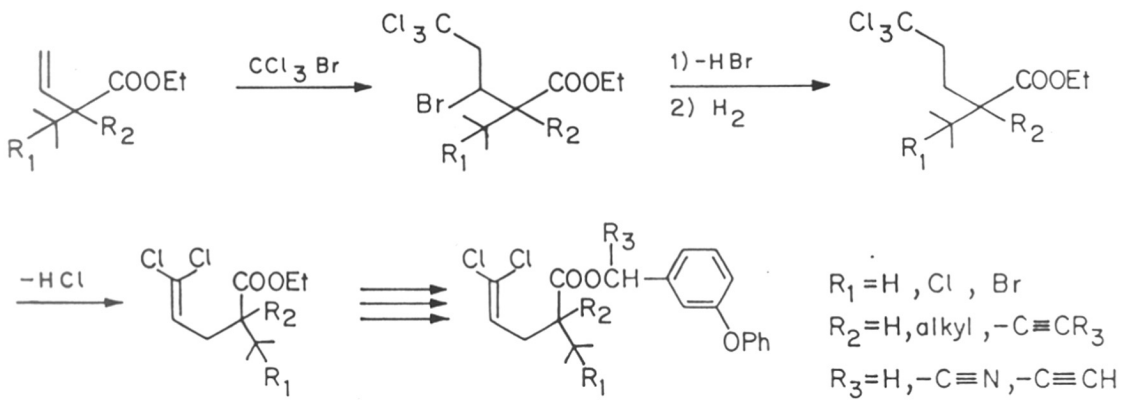
(C) MICHAEL BULL et al



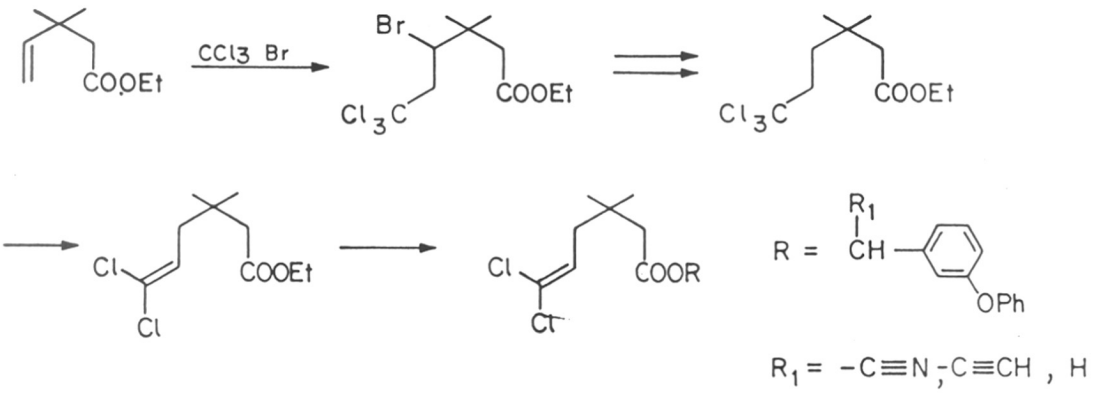
R = Me_2CH, Allyl, Prenyl, 4-$ClC_6H_4CH_2$

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

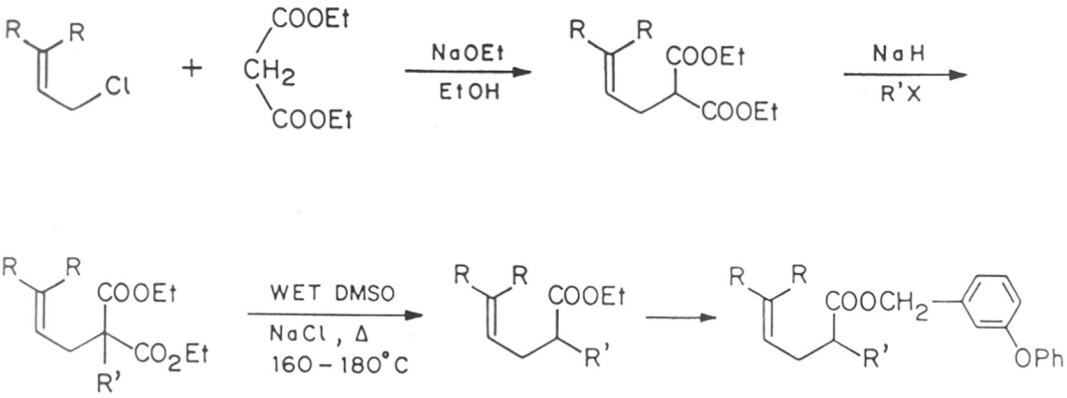
(D) OMURA et al



(E) OMURA et al

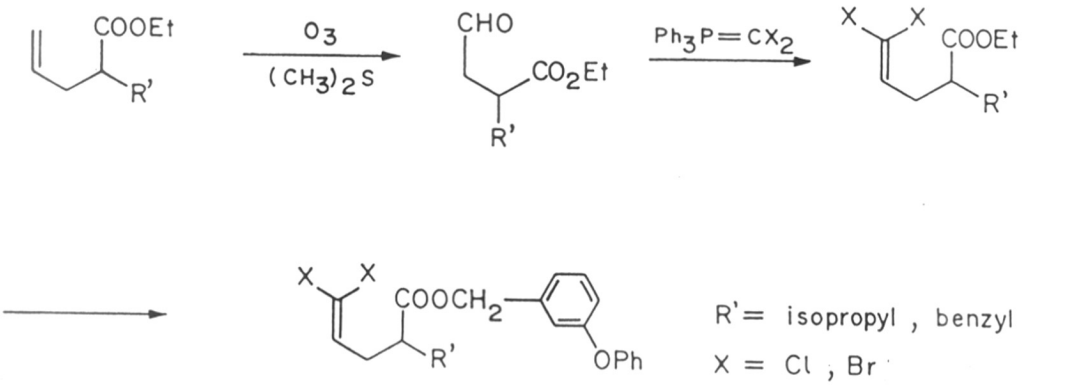


(F) G. H. KULKARNI et al



R = H R' = H , CH_3 , CH_2CH_3 , $CH(CH_3)_2$, CH_2Ph ,

R = CH_3 R' = ibid



R' = isopropyl , benzyl

X = Cl , Br

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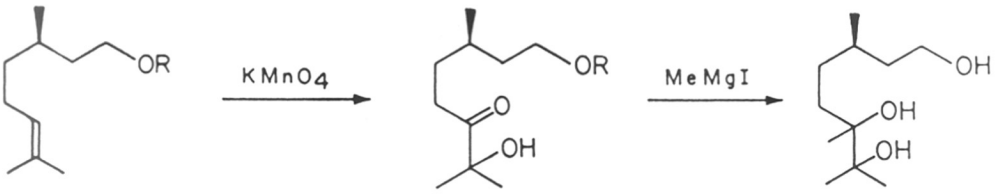
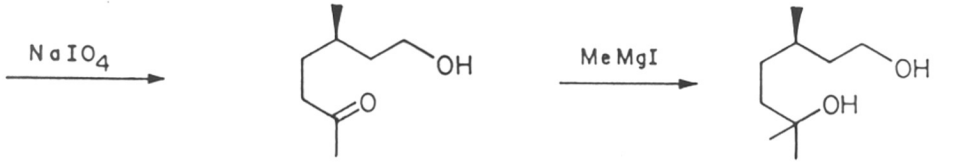
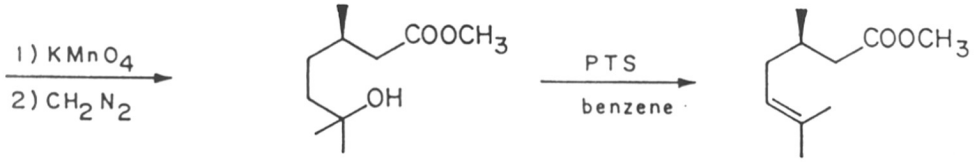
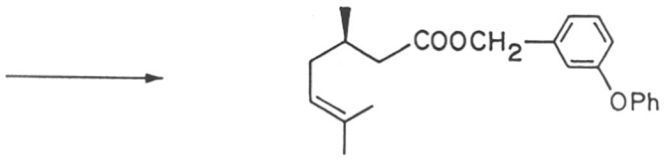


R = Ac

Citronellol acetate







PRESENT WORK

Synthesis of (±)α-(RS)-cyano-3-phenoxybenzyl-4-methyl-3-phenyl/p-substituted phenyl pentanoates (8a-c) (Scheme)

The title compounds in which conventional vinyl side-chain is replaced by a phenyl/p-substituted phenyl ring, resemble structurally to the 1,2-secopyrethroids (Chart IV).

Grignard reaction of benzaldehyde (1a) was carried out with isopropyl magnesium iodide to yield the alcohol. Jones chromic acid oxidation of the crude alcohol gave the isobutyrophenone (2a) which was purified by chromatography.

IR: 1685 (aromatic carbonyl), 1600, 1590 (aromatic).

PMR: 1.21 (6H, d, 6 Hz, isopropyl methyls), 3.06-3.72 (1H, m, isopropyl methine proton), 7.13-7.5 (3H, m, aromatic protons), 7.63-7.93 (2H, m, aromatic protons).

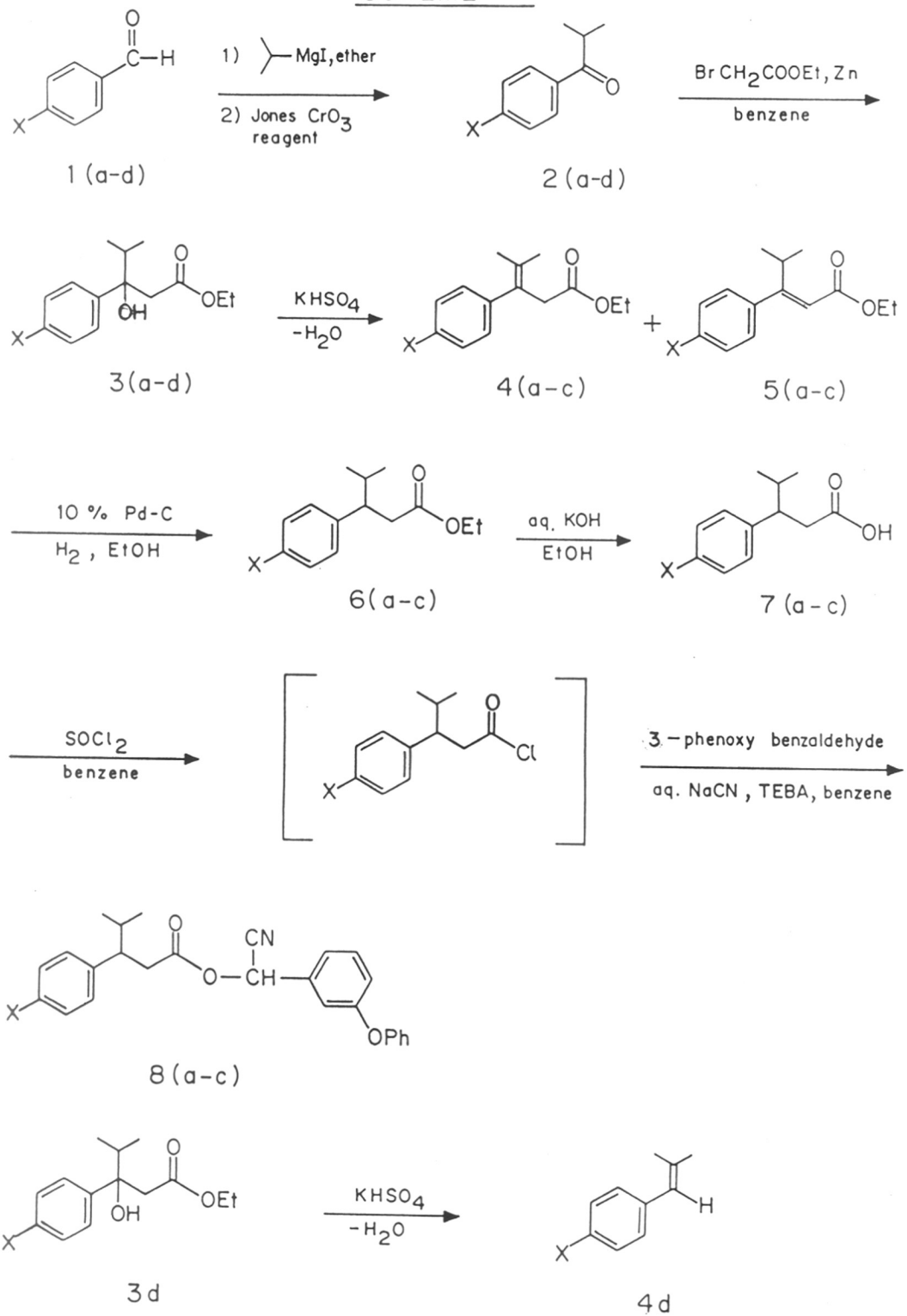
Reformatsky's reaction on (2a) with ethyl bromo acetate and zinc in dry benzene (reflux) afforded the β-hydroxy ester (3a).

IR: 3500 (-OH), 1720 (ester carbonyl), 1600 (aromatic).

PMR: 0.7 -1.13 (9H, t overlapping two d, isopropyl methyls and ester methyl), 1.64-2.16 (1H, m, isopropyl methine proton), 2.8 (2H, ABq, J_1=15 Hz, J_2=18 Hz, protons α to ester), 3.92 (2H, q, 7 Hz, ester methylene), 4.15 (1H, s, D_2O exchangeable, -OH proton), 7.0-7.5 (5H, m, aromatic protons).

Dehydration of β-hydroxy ester (3a) with anhydrous $KHSO_4$ (catalytic amount, first reflux for 15 minutes and then distill under vacuum) gave the mixture of esters (4a) and (5a).

SCHEME



a : X=H , b : X=Cl , c : X=CH_3 , d : X=OCH_3

IR: 1740, 1720 (ester carbonyls of 4a and 5a respectively), 1640 (double bond of 5a), 1600 (aromatic).

PMR: 1.0-1.25 (two t overlapping two d, isopropyl methyls of 5a and ester methyls of 4a and 5a), 1.63 and 1.81 (s each, methyls on double bond of 4a), 2.44-2.84 (m, isopropyl methine proton of 5a), 3.44 (s, methylene α to ester of 4a), 3.94 and 4.0 (overlapping q, ester methylenes of 4a and 5a), 5.81 (br s, olefinic proton of 5a), 7.0-7.41 (m, aromatic protons of 4a and 5a).

Catalytic hydrogenation of the mixture of (4a) and (5a) over 10% Pd-C in ethanol at room temperature gave the saturated isomer (6a).

IR: 1735 (ester carbonyl), 1600 (aromatic)

PMR: 0.75 and 0.94 (3H each, d each, 6.4 Hz each, isopropyl methyls), 1.06(3H, t, 6.4 Hz, ester methyl), 1.7-2.0(1H, m, isopropyl methine proton), 2.44-3.0 (3H, m, methylene α to ester carbonyl and benzylic proton), 4.0 (2H, q, 6.4 Hz, ester methylene), 7.12-7.5 (5H, m, aromatic protons).

Saponification of (6a) using aqueous KOH in ethanol at room temperature yielded the acid (7a).

IR: 1700 (acid carbonyl), 1600 (aromatic)

PMR: 0.75 and 0.93 (3H each, d each, 7 Hz each, isopropyl methyls), 1.64-2.07 (1H, m, isopropyl methine proton), 2.56-2.98 (3H, m, benzylic proton and methylene α to acid carbonyl), 7.11-7.51 (5H, m, aromatic protons), 9.24 (1H, br s, D_2O exchangeable, -COOH proton).

Acid (7a) was converted to acid chloride with thionyl chloride in benzene reflux which was then esterified as such with α(RS) cyano-3-phenoxybenzyl alcohol, prepared in situ from 3-phenoxy benzaldehyde, sodium cyanide and water in benzene medium, under phase transfer conditions using TEBA as PTC at room temeprature to get the title compound viz. (±) α (RS)-cyano-3-phenoxybenzyl-4-methyl-3-phenyl pentanoate (8a).

IR: 1750 (ester carbonyl), 1590 (aromatic).

PMR: 0.75, 0.93 and 0.97 (6H, d each, 7 Hz each, isopropyl methyls of both the diastereomers), 1.66-2.08 (1H, m, isopropyl methine proton), 2.58-3.07 (3H, m, benzylic proton and methylene α to ester), 6.17 and 6.31 (1H, s each, -CH-CN of both the diastereomers), 6.89-7.56 (14H, m, aromatic protons).

By following an analogous sequence of reactions, the other α(RS) cyano-3-phenoxybenzyl-3-p-substituted phenyl-4-methyl pentanoates were synthesised. The spectral characteristics of intermediates and final esters are described below.

2b; IR: 1690 (aromatic carbonyl), 1590 (aromatic).

PMR: 1.2 (6H, d, 7 Hz, isopropyl methyls), 3.37-3.88 (1H, m, isopropyl methine proton), 7.63 and 8.1 (2H each, d each, 9 Hz each, aromatic protons).

3b: IR: 3500 (-OH), 1720 (ester carbonyl).

PMR: 0.75 and 0.88 (3H each, d each, 6.4 Hz each, isopropyl methyls), 1.06 (3H, t, 6.4 Hz, ester methyl), 1.5 (1H, D_2O exchangeable s, -OH proton), 1.63-2.0 (1H, m, isopropyl methine proton), 2.84 (2H, ABq, J_1=16 Hz, J_2=19.2 Hz, methylene α to ester), 3.94,

(2H, q, 6.4 Hz, ester methylene), 7.0-7.5 (4H, m, aromatic protons).

4b and 5b IR: 1730, 1710 (ester carbonyls of 4b and 5b), 1640 (double bond of 5b), 1595 (aromatic).

PMR: 1.08-1.26 (m, isopropyl methyls of 5b and ester methyls of 4b and 5b), 1.62 (s, methyls on double bond of 4b), 2.44-2.84 (m, isopropyl methine proton of 5b), 3.35 (s, methylene α to ester of 4b), 3.87-4.22 (two overlapping q, ester methylene of 4b and 5b), 5.9 (s, olefinic proton of 5b), 7.0-7.18 and 7.22-7.4 (m, aromatic protons of 4b and 5b).

6b: IR: 1730 (ester carbonyl), 1590 (aromatic).

PMR: 0.72 and 0.92 (3H each, d each, 7 Hz each, isopropyl methyls), 1.06 (3H, t, 7 Hz, ester methyl), 1.71-1.93 (1H, m, isopropyl methine proton), 2.44-2.89 (3H, m, benzylic proton and methylene α to ester), 3.96 (2H, q, 7Hz, ester methylene), 7.0-7.33 (4H, m, aromatic protons).

7b: IR: 1710 (acid carbonyl), 1590 (aromatic).

PMR: 0.75 and 0.94 (3H each, d each, 6.4 Hz each, isopropyl methyls), 1.63-2.0 (1H, m, isopropyl methine proton), 2.38-3.0 (3H, m, benzylic proton and methylene α to acid carbonyl), 7.0-7.31 (4H, m, aromatic protons), 9.51 (1H, br s, D_2O exchangeable, -COOH).

8b: IR: 1760 (ester carbonyl), 1590 (aromatic).

PMR: 0.72, 0.90 and 0.94 (6H,d each,6.4 Hz, each isopropyl methyls of both the diastereomers), 1.63-2.0 (1H, m, isopropyl methine proton) 2.5-3.0 (3H, m, benzylic proton and methylene α to ester carbonyl), 6.12 and 6.25 (1H each, s each, -CH-CN of both the diastereomers), 6.75 -7.5 (13H, m, aromatic protons).

2c: IR: 1680 (aromatic carbonyl), 1600, 1570 (aromatic)

PMR: 1.16 (6H, d, 7 Hz, isopropyl methyls), 2.36 (3H, s, aromatic methyl), 3.13-3.67 (1H, m, isopropyl methine proton), 7.08 and 7.71 (2H each, d each, 8Hz each, aromatic protons).

3c: IR: 3490 (-OH), 1720 (ester carbonyl), 1600 (aromatic).

PMR: 0.71 and 0.83 (3H each, d each, 7Hz each, isopropyl methyls), 1.0 (3H, t, 7Hz, ester methyl), 1.6-2.13 (1H, m, isopropyl methine proton), 2.25 (3H, s, aromatic methyl), 2.76 (2H, ABq, J_1=15Hz, J_2=18 Hz, methylene α to ester), 3.91 (2H, q, 7 Hz, ester methylene), 4.1 (1H, D_2O exchangeable s, -OH), 6.94 and 7.17 (2H each, d each, 8Hz each, aromatic protons).

4c & 5c; IR: 1735, 1720 (ester carbonyls of 4c and 5c), 1640 (double bond of 5c), 1610 (aromatic).

PMR: 0.86 and 1.23 (m, isopropyl methyls of 5c & ester methyls of 4c & 5c), 1.6 & 1.8 (s each, methyls on double bond of 4c), 2.28 and 2.33 (two s, aromatic methyls of 4c and 5c), 3.22 (s, methylene α to ester of 4c), 3.67-4.15 (two overlapping q, ester methylenes of 4c and 5c), 5.67 (s, olefinic proton of 5c), 6.77-7.17 (m, aromatic protons of 4c and 5c).

6c: IR: 1740 (ester carbonyl).

PMR: 0.75 and 0.92 (3H each, d each, 6.4 Hz each, isopropyl methyls), 1.06 (3H, t, 6.4 Hz, ester methyl), 1.59-2.0 (1H, m, isopropyl methine proton), 2.28 (3H, s, aromatic methyl), 2.43-2.81 (3H, m, benzylic proton and methylene α to ester), 3.94 (2H, q, 6.4 Hz, ester methylene), 6.75-7.19 (4H, m, aromatic protons).

7c: IR: 1710 (acid carbonyl).

PMR: 0.75 and 0.91 (3H each, d each, 6.4 Hz each, isopropyl methyls), 1.59-2.0 (1H, m, isopropyl methine proton), 2.25 (3H, s, aromatic methyl), 2 44-3.0 (3H, m, benzylic proton and methylene α to ester), 7.0 (4H, s, aromatic protons), 9.31 (1H, br s, D_2O exchangable, -COOH).

8c: IR: 1760 (ester carbonyl), 1590 (aromatic).

PMR: 0.73, 0.91 and 0.95 (6H, d each, 6.4 Hz each, isopropyl methyls of both the diastereomers), 1.66-1.98 (1H, m, isopropyl methine proton), 2.27 (3H, s, aromatic methyl), 2.6-3.0 (3H, m, benzylic proton and methylene α to ester), 6.18 and 6.37 (1H,S, -CH-CN of both the diastereomers), 6.88-7.56 (13H, m, aromatic protons).

2d: IR: 1680 (aromatic carbonyl), 1600, 1580 (aromatic).

PMR: 1.15 (6H, d, 7 Hz, isopropyl methyls), 3.13-3.66 (1H, m, isopropyl methine proton), 3.83 (3H, s, $-OCH_3$), 6.76 and 7.76 (2H each, d each, 8 Hz each, aromatic protons).

3d: IR: 3500, 1720, 1610.

PMR: 0.78 and 1.0 (3H each, d each, 6.4 Hz each, isopropyl methyls), 1.16 (3H, t, 6.4 Hz, ester methyl), 1.5 (1H, D_2O exchangeable s, -OH), 1 66-2.0 (1H, m, isopropyl methine proton), 2.88 (2H, ABq, J_1=16 Hz, J_2=22.4 Hz, $-CH_2-\overset{O}{\overset{\|}{C}}-O$), 3.69 (3H, s, $-OCH_3$), 3.94 (2H, q, 6.4 Hz, ester methylene), 6.78 and 7.25 (2H each, d each, 9.6 Hz each, aromatic protons).

4d: IR: 1610, 1580 (aromatic).

PMR: 0.85 and 0.88 (3H each, d each, 2 Hz each, methyls on double bond), 3.88 (3H, s, $-OCH_3$), 6.22 (1H, br s, olefinic proton), 6.86 and 7.17 (2H each, d each, 8 Hz each, aromatic protons).

EXPERIMENTAL

Isobutyrophenone (2a):

To a stirred suspension of magnesium turnings (1.72 g; 0.07 mole) in dry ether (10 ml), was added dropwise, the solution of isopropyl iodide (12 g; 0.07 mole) in dry ether (20 ml) in such a way that ether refluxed gently. When all the magnesium reacted, the ether solution was cooled to 0°C. To this, was added, the solution of benzaldehyde (5g; 0.047 mole) in dry ether (60 ml). After the addition was completed, the reaction mixture was stirred at room temperature overnight. The reaction contents were then cooled to 0°C and decomposed with cold, saturated aqueous ammonium chloride solution. Ether layer was separated and aqueous layer extracted repeatedly with ether. Combined ether layer was washed with water, brine and dried. Ether was distilled off and crude alcohol (6.5 g) was used as such for the Jones chromic acid oxidation.

To the ice-cooled and stirred solution of alcohol (6.5 g) in acetone (30 ml), Jones chromic acid reagent was added slowly till the reaction mixture retained the brown colour of the reagent. Reaction was carried through out at 0°C and followed by TLC. Acetone was removed under reduced pressure. The contents were diluted with ether and washed thoroughly with water, bicarbonate and brine. Ether removal gave 5.9 g of crude isobutyrophenone which was purified on silica gel eluting with pet.ether -10% $CHCl_3$ to give pure isobutyrophenone (2a) (5.71 g; 89%).

IR: 2960, 1685, 1600, 1590, 1470, 1445, 1220, 975.

Ms: M^+ 148.

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

calculated: C, 81.04, H, 8.16;

observed: C, 80.9; H, 8.05;

Ethyl 3-hydroxy 4-methyl 3-phenyl pentanoate (3a):

A mixture of isobutyrophenone (2a) (5 g; 0.034 mole) and Zn (6.63 g; 0.102 mole) was heated to reflux in dry benzene (100 ml). To the refluxing solution, was then slowly added, the solution of ethyl bromo acetate (16.92 g; 0.102 mole) in dry benzene (100 ml). After the addition, reaction mixture was further refluxed for 3 hr. It was then cooled to 0°C and decomposed with 20% H_2SO_4 and stirred at 0°C for 1 hr. Benzene layer was separated and aqueous layer extracted with benzene. Combined benzene layer was washed with water, bicarbonate, brine and dried. Benzene was removed under vacuum to give crude β-hydroxy ester (3a) which was purified on silica gel eluting with pet.ether -15% $CHCl_3$ to give pure (3a) (6.1 g; 82%).

IR: 3500, 2980, 1720, 1600, 1440, 1370, 1170, 1010.

Mass M^+: 236.

Analysis for $C_{14}H_{20}O_3$:

calculated: C, 71.16; H, 8.58;

observed: C, 71.01; H, 8.4;

Ethyl 4-methyl-3-phenyl-pent-3-enoate (4a)

Ethyl 4-methyl-3-phenyl-pent-2-enoate (5a):

A mixture of β-hydroxy ester (3a) (6 g; 0.025 mole) and anhydrous $KHSO_4$ (0.6 g) was taken up in a distillation unit and initially heated

under reflux at 100°C/8 mm for 15 minutes and then distilled at 120°-125°C/8 mm to give mixture of (4a) and (5a) (3.9 g; 70%).

IR: 2990, 1740, 1720, 1640, 1600, 1575, 1460, 1370, 1160, 1030.

Mass: M^+ -218.

Analysis for $C_{14}H_{18}O_2$:

calculated: C, 77.03; H, 8.31;

observed: C, 76.85; H, 8.18;

Ethyl 4-methyl-3-phenyl pentanoate (6a):

The mixture of unsaturated esters (4a) and (5a) (3 g; 0.014 mole), in dry ethanol (20 ml) and activated 10% Pd-C (0.3 g) was taken in hydrogenation flask. After flushing the flask with hydrogen to displace air, the atmosphere of hydrogen gas was maintained at 25 psi pressure inside the reaction flask. The contents were then shaken for 2 hr. The reaction mixture was then filtered and residue washed with ethanol. Ethanol was removed under pressure and residue diluted with pet.ether and passed through a short column of silica gel to yield pure (6a) (2.75 g; 91%).

IR: 2940, 1735, 1600, 1250, 1150, 1100, 1030, 700.

Mass: M^+ 220.

Analysis for $C_{14}H_{20}O_2$

calculated: C, 76.32; H, 9.15;

observed: C, 76.16; H, 8.98;

4-Methyl-3-phenyl pentanoic acid (7a)

Ester (6a) (2 g; 0.009 mole) was dissolved in 15 ml ethanol. To it, was added, aqueous solution of NaOH (0.55 g; 0.014 mole) in minimum volume of water; the reaction contents were stirred overnight at

room temperature. Ethanol was removed under pressure and residue diluted with water and extracted with CH_2Cl_2. Aqueous layer was cooled to 0°C and dilute HCl was added slowly till the medium was acidic to pH paper. Aqueous layer was repeatedly extracted with ether. Combined ether layer was washed with water and brine and dried. Removal of ether gave acid (7a) (1.24 g; 71%) which was used as such for next reaction.

IR: 1700, 1600, 1500, 1410, 1300, 750, 700.

(±)α(RS) Cyano 3-phenoxy benzyl-4-methyl-3-phenyl pentanoate (8a):

Acid (7a) (0.9 g; 0.005 mole) was dissolved in dry benzene (10 ml). $SOCl_2$ (1.12 g; 0.0095 mole) was added to it and the solution was refluxed for 4 hr. Excess of $SOCl_2$ and benzene were removed under reduced pressure and residue taken up in dry benzene (10 ml). The benzene solution of acid chloride, was then added dropwise, to a gently stirred mixture of 3-phenoxy benzaldehyde (0.95 g; 0.0048 mole), sodium cyanide (0.4g; 0.0081 mole), dry benzene (5 ml), water (0.6 ml) and TEBA (0.070 g). After the addition, the mixture was stirred at room temperature for 5 hr. Organic layer was separated and aqueous layer extracted with benzene. Combined benzene layer was washed with water, bicarbonate, brine and dried. Removal of benzene under reduced pressure and purification of residue on silica gel column (pet.ether -50% benzene) gave pure (8a) (1.412 g; 82.5%).

IR: 2980, 1750, 1590, 1490, 1250, 750, 690.

Mass: M^+ 399.

Analysis for $C_{26}H_{25}NO_3$

calculated: C, 78.17; H, 6.3%

observed: C, 78.06; H, 6.23;

Similarly esters (8b) and (8c) were synthesised employing an identical set of reactions and characterising all the intermediates (1b-8b).

Isobutyrophenone (2b)

Yield: 83%

IR: 2920, 1690, 1600, 1470, 1220, 1100, 980, 840.

Mass: M^+ -182 (^{35}Cl)

-184 (^{37}Cl)

Analysis for $C_{10}H_{11}ClO$

calculated: C, 65.76; H, 6.07; Cl, 19.41;

observed: C, 65.62; H, 5.96; Cl, 19.22;

β -Hydroxy ester (3b)

Yield: 76%.

IR: 3500, 2980, 1720, 1490, 1370, 1210, 1090, 1000, 820.

Mass: M^+ -270 (^{35}Cl)

-272 (^{37}Cl)

Analysis for $C_{14}H_{19}ClO_3$

calculated: C,62.1; H, 7.07; Cl, 13.09;

observed: C,61.95; H, 6.94; Cl, 12.91;

Mixture of unsaturated esters (4b) and (5b)

Yield: 72%.

IR: 2980, 1730, 1710, 1640, 1590, 1490, 1160, 1090, 820.

Mass: M^+ -252 (^{35}Cl)

-254 (^{37}Cl)

Analysis for $C_{14}H_{17}ClO_2$

calculated: C, 66.53; H, 6.78; Cl, 14.03;

observed: C, 66.45; H, 6.67; Cl, 13.87;

Saturated ester (6b):

Yield: 88%.

IR: 2.970, 1730, 1590, 1480, 1240, 1150, 810.

Mass: M^+ -254 (^{35}Cl)

-256 (^{37}Cl)

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

calculated: C, 66; H, 7.52; Cl, 13.92;

observed: C, 65.83; H, 7.39; Cl, 13.78;

Acid (7b):

Yield: 73%.

IR: 2980, 1710, 1590, 1490, 1090, 1000, 810.

Cyano ester (8b):

Yield: 79%

IR: 2990, 1760, 1590, 1490, 1450, 1250, 1140, 815.

Mass: M^+ -433 (^{35}Cl)

-435 (^{37}Cl)

Analysis for $C_{26}H_{24}ClNO_3$

calculated: C, 71.96; H, 5.56; Cl, 8.17;

observed: C,71.8; H,5.44;Cl, 8.06;

Isobutyrophenone (2c):

Yield: 86%.

IR: 2980, 1680, 1600, 1570, 1460, 1380, 1230, 820.

Mass: M^+ -162.

Analysis for $C_{11}H_{14}O$:

calculated: C, 81.44; H, 8.7;

observed: C, 81.33; H, 8.55;

β -Hyddroxy ester (3c):

Yield: 80%.

IR: 3490, 2990, 1720, 1600, 1370, 1200, 1170, 810.

Mass: M^+ -250.

Analysis for $C_{15}H_{22}O_3$

calculated: C, 71.97; H, 8.86;

observed: C, 71.8; H, 8.73;

Mixture of unsaturated esters (4c) and (5c):

Yield: 89%.

IR: 2980, 1735, 1720, 1640, 1610, 1520, 1160, 1040, 820.

Mass: M^+ 232

Analysis for $C_{15}H_{20}O_2$

calculated: C, 77.55; H, 8.68;

observed: C, 77.45; H, 8.54;

Saturated ester (6c):

Yield: 91%.

IR: 2990, 1740, 1520, 1260, 1160, 1120, 810.

Mass: M^+ -234.

Analysis for $C_{15}H_{22}O_2$

calculated: C, 76.88; H, 9.46;

observed: C, 76.76; H, 9.29;

Acid (7c):

Yield: 87%

IR: 1710, 1520, 1420, 1300, 1120, 810.

Cyano ester (8c):

Yield: 82%.

IR: 2975, 1760, 1590, 1480, 1250, 1140, 690.

Mass: M^+ -413.

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

calculated: C,78.42; H, 6.58;

observed: C, 78.31; H, 6.42;

Isobutyrophenone (2d):

Yield: 89%.

IR: 2980, 1680, 1600, 1580, 1510, 1230, 1150, 970, 830.

Mass: M^+ -178.

Analysis for $C_{11}H_{14}O_2$

calculated: C, 74.13; H, 7.92;

observed: C, 74.05; H, 7.82;

β-Hydroxy ester (3d):

Yield: 89%.

IR: 3500, 2990, 1720, 1610, 1520, 1250, 1180, 1080, 820.

Mass: M^+ -266.

Analysis for $C_{15}H_{22}O_4$

calculated: C, 67.64; H, 8.33;

observed: C, 67.47; H, 8.21;

4'-Methoxy-2,2-dimethyl styrene (4d):

Yield: 79%.

IR: 2900, 1610, 1580, 1510, 1240, 1170, 1030, 840.

Mass: M^+ -162.

Analysis for $C_{11}H_{14}O$

calculated: C, 81.44; H, 8.7;

observed: C, 81.27; H, 8.57;

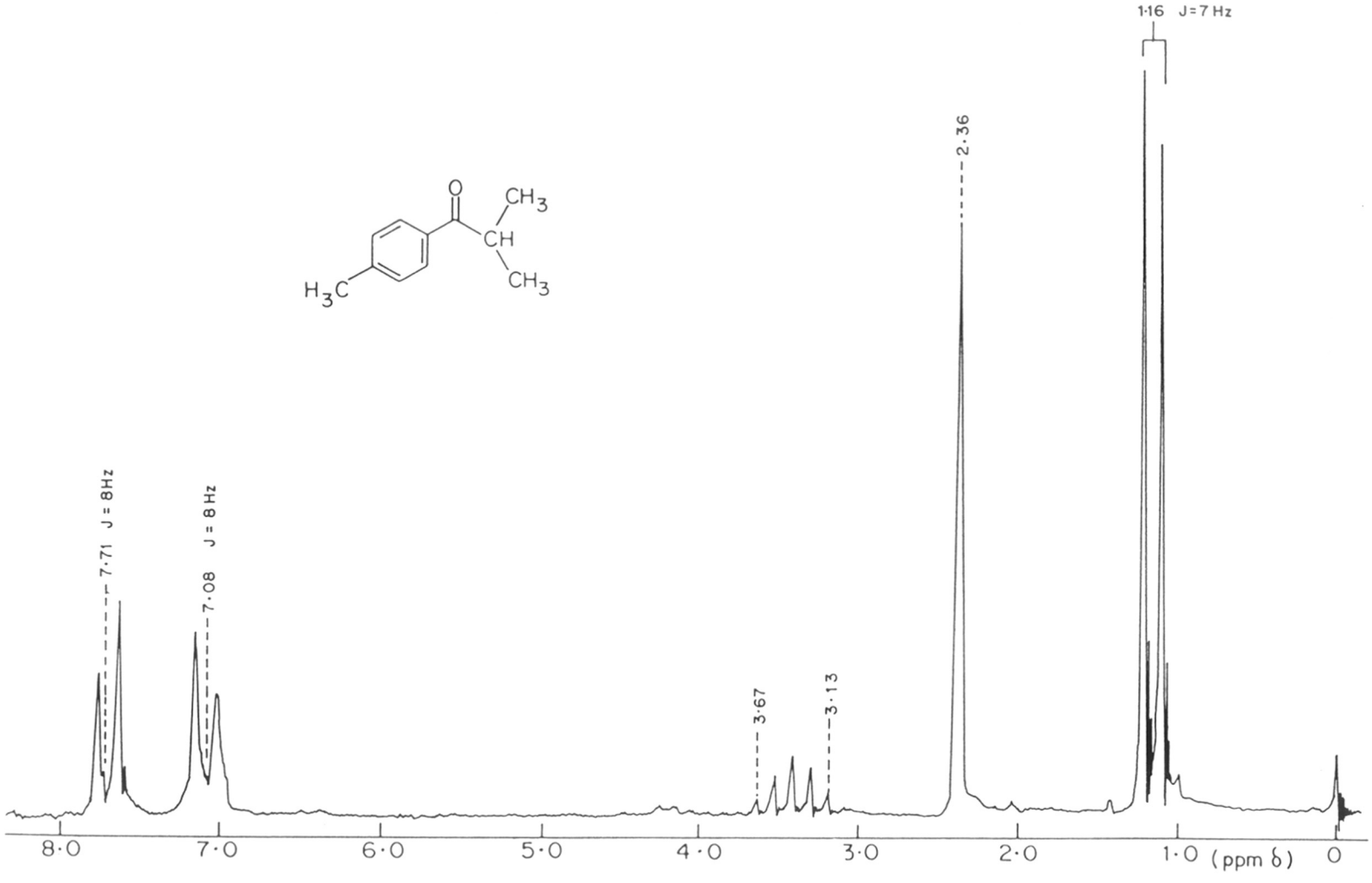


FIG. I : NMR OF COMPOUND No. 2c

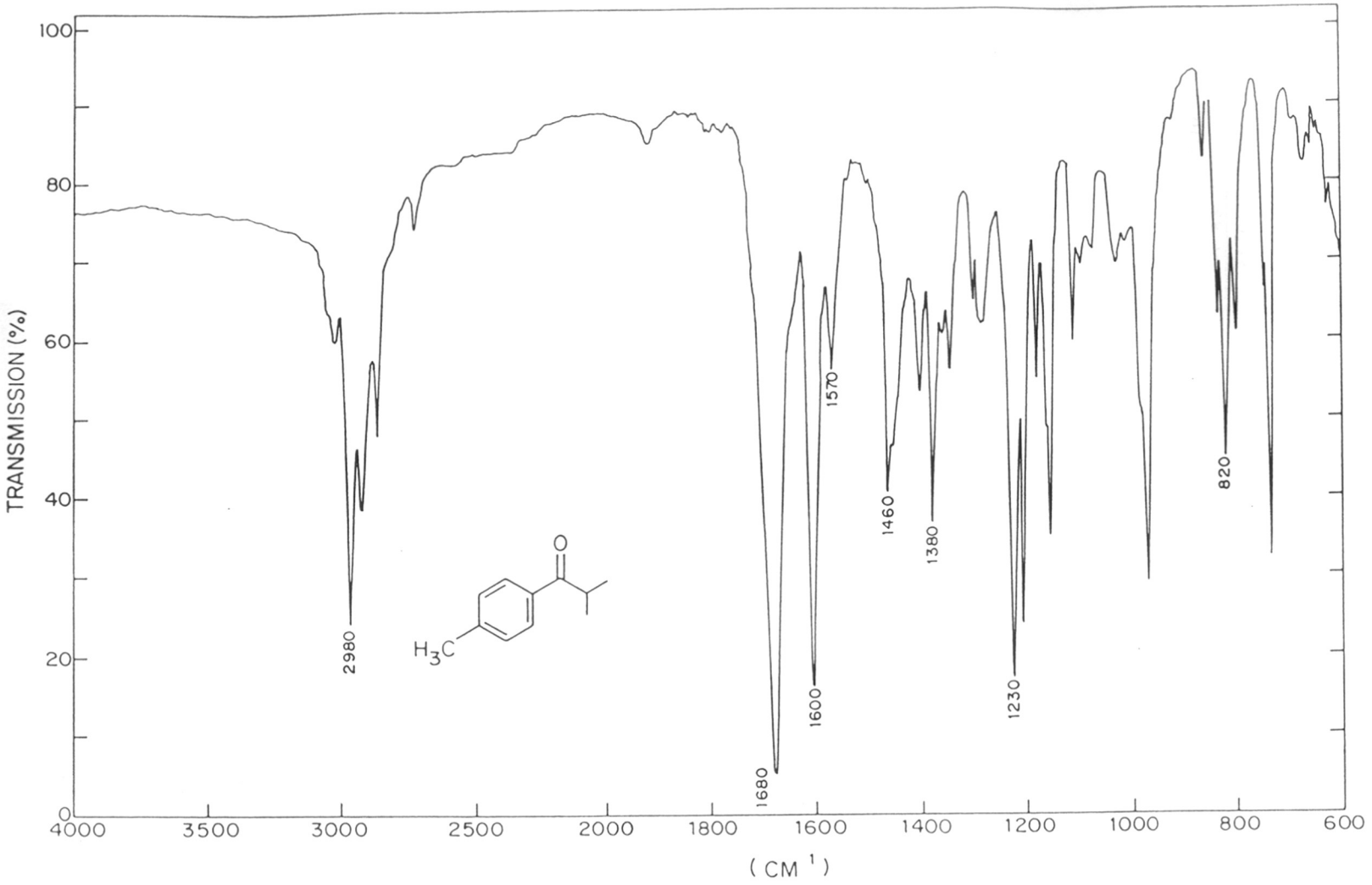
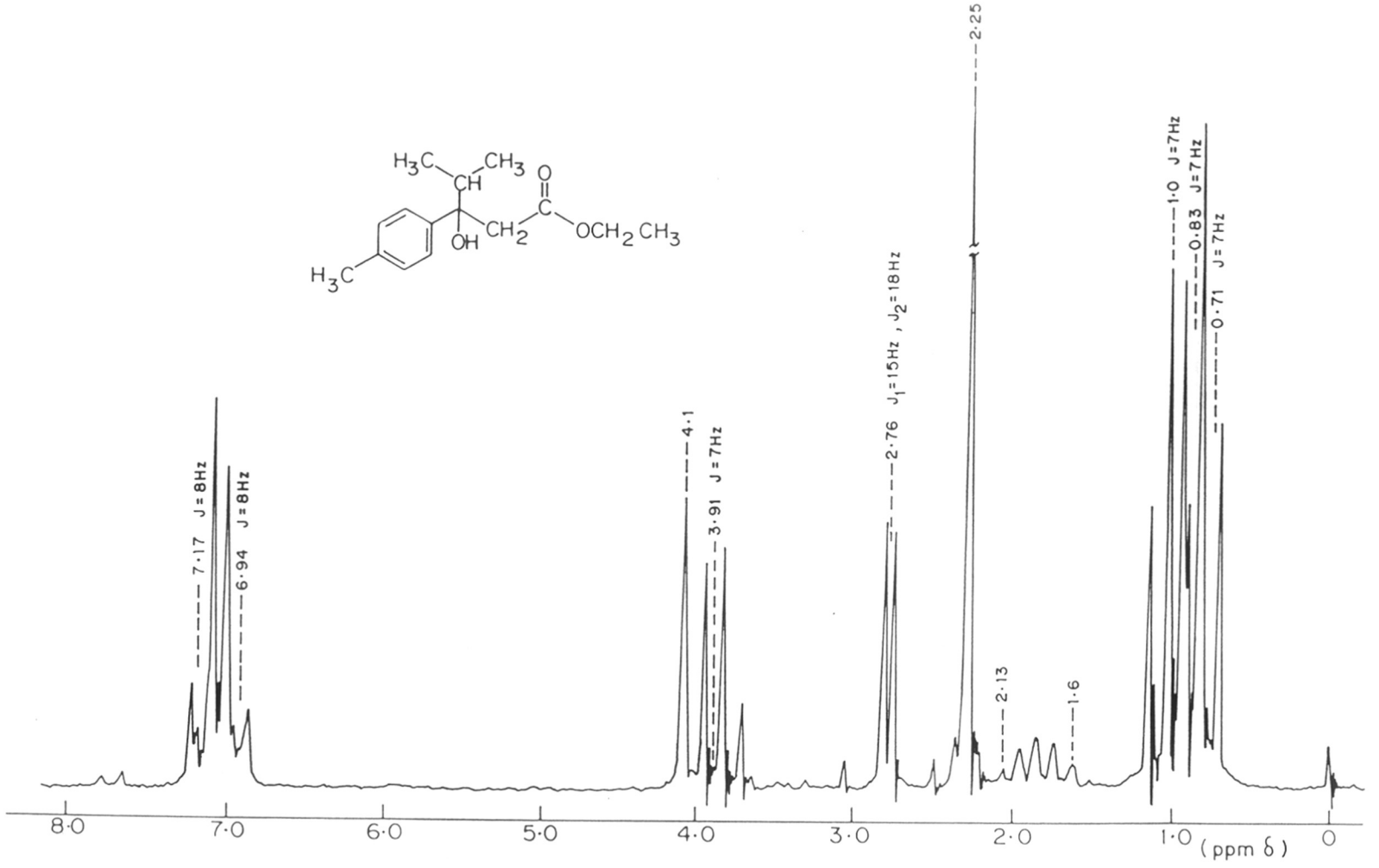


FIG. II : IR OF COMPOUND No. 2c



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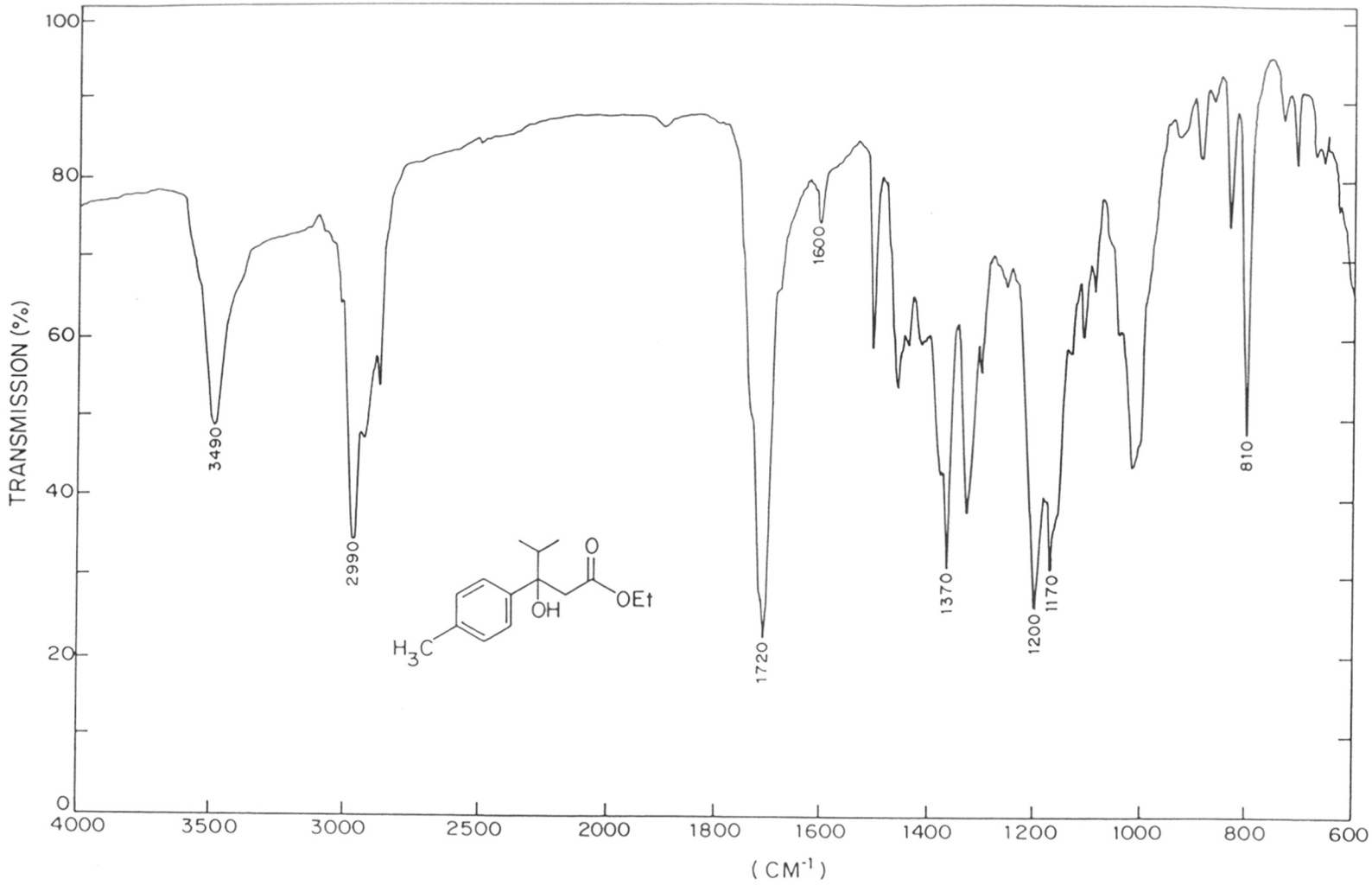

FIG. IV : IR OF COMPOUND No. 3c

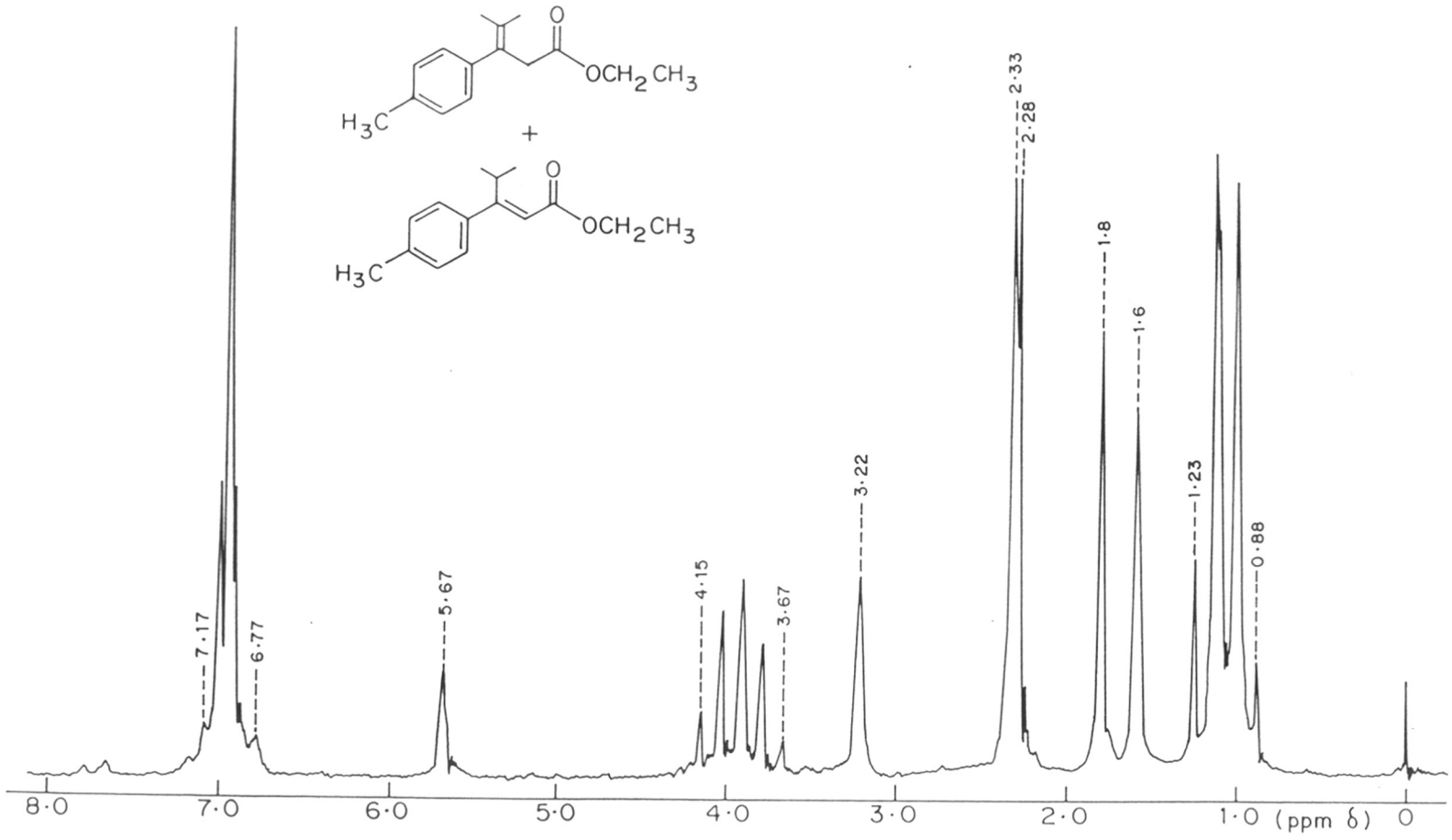

FIG. V : NMR OF COMPOUND Nos. 4c+5c

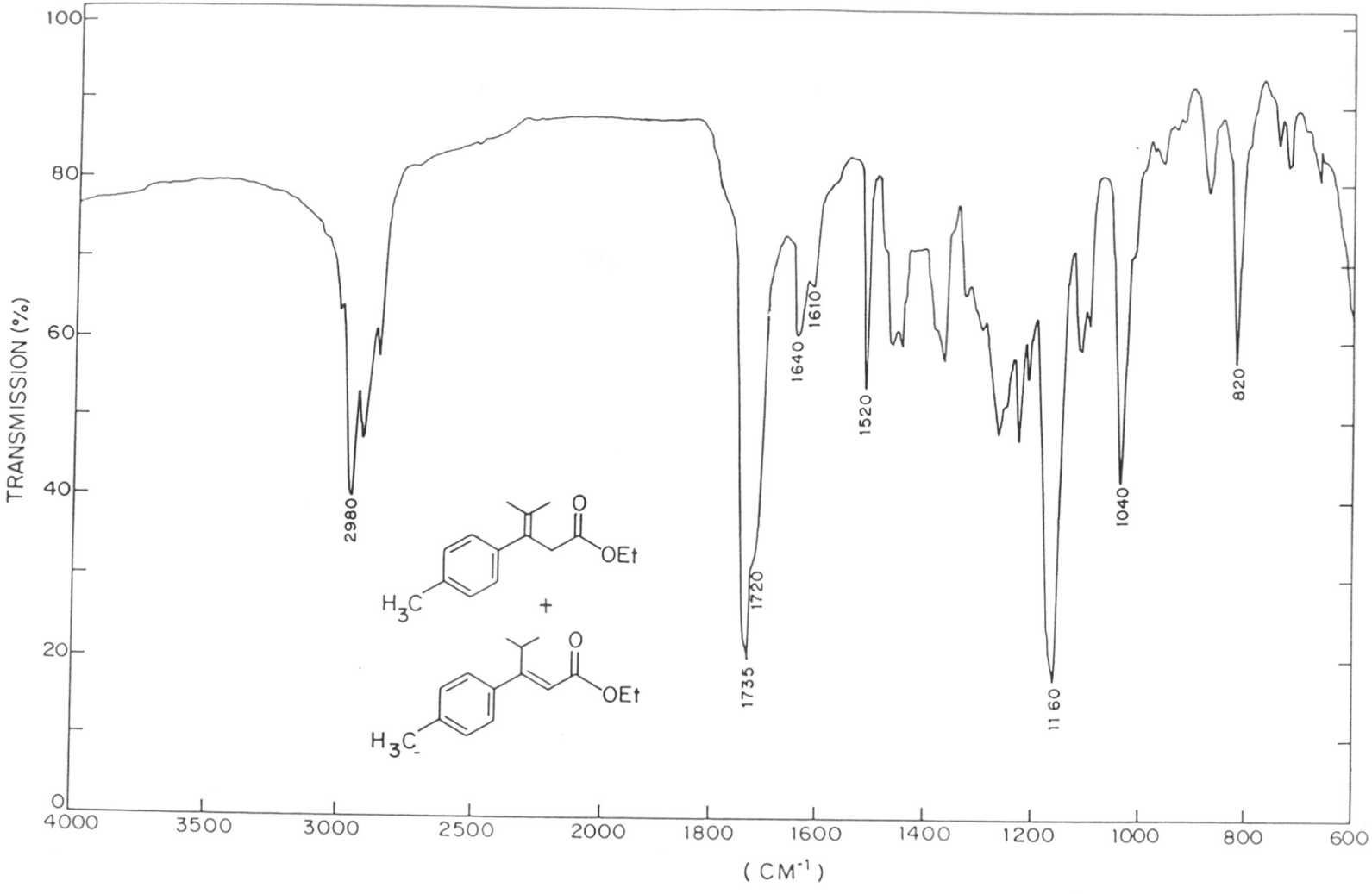

FIG. VI : IR OF COMPOUND Nos. 4_c+5_c

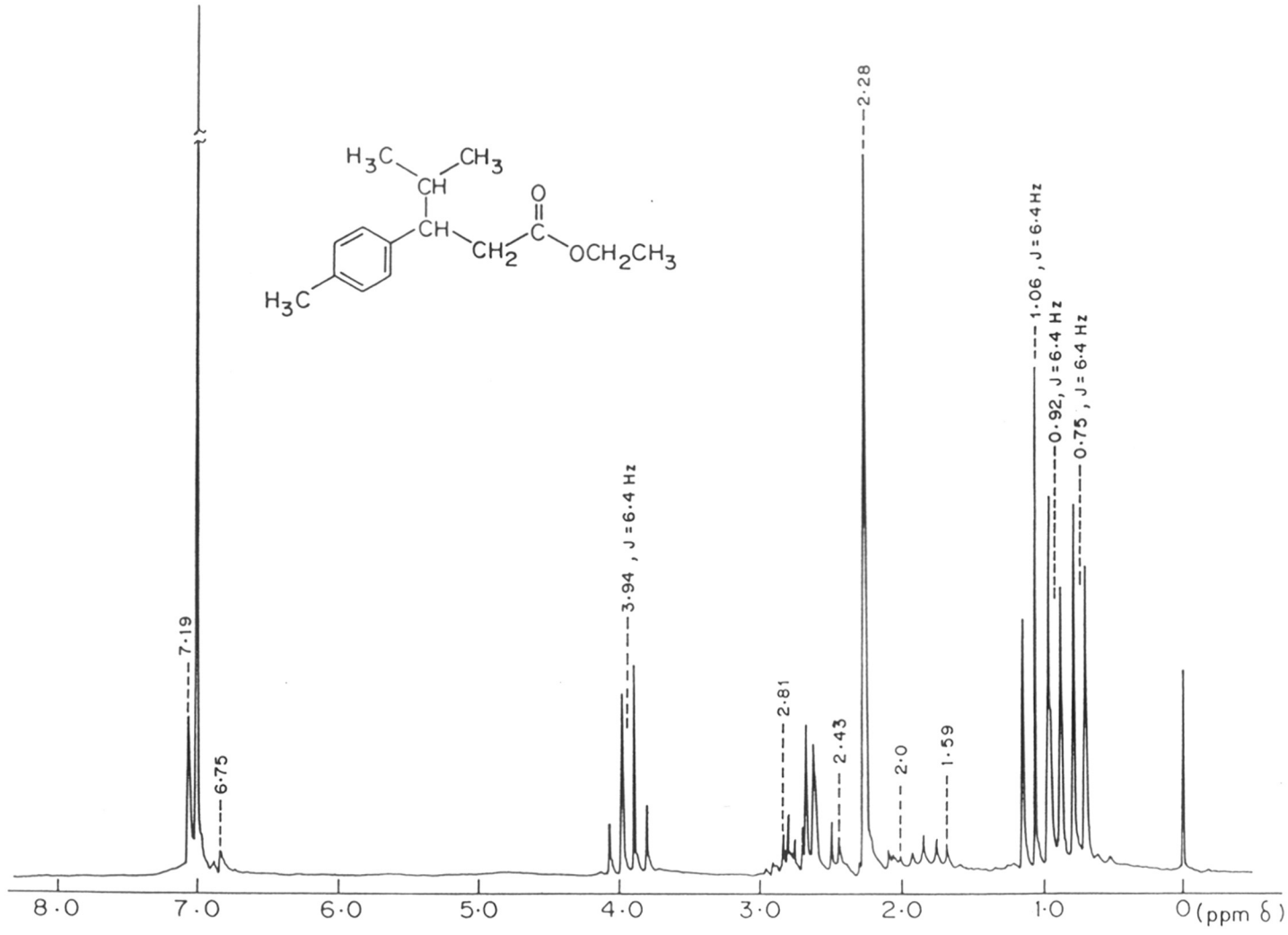

FIG. VII : NMR OF COMPOUND No. 6c

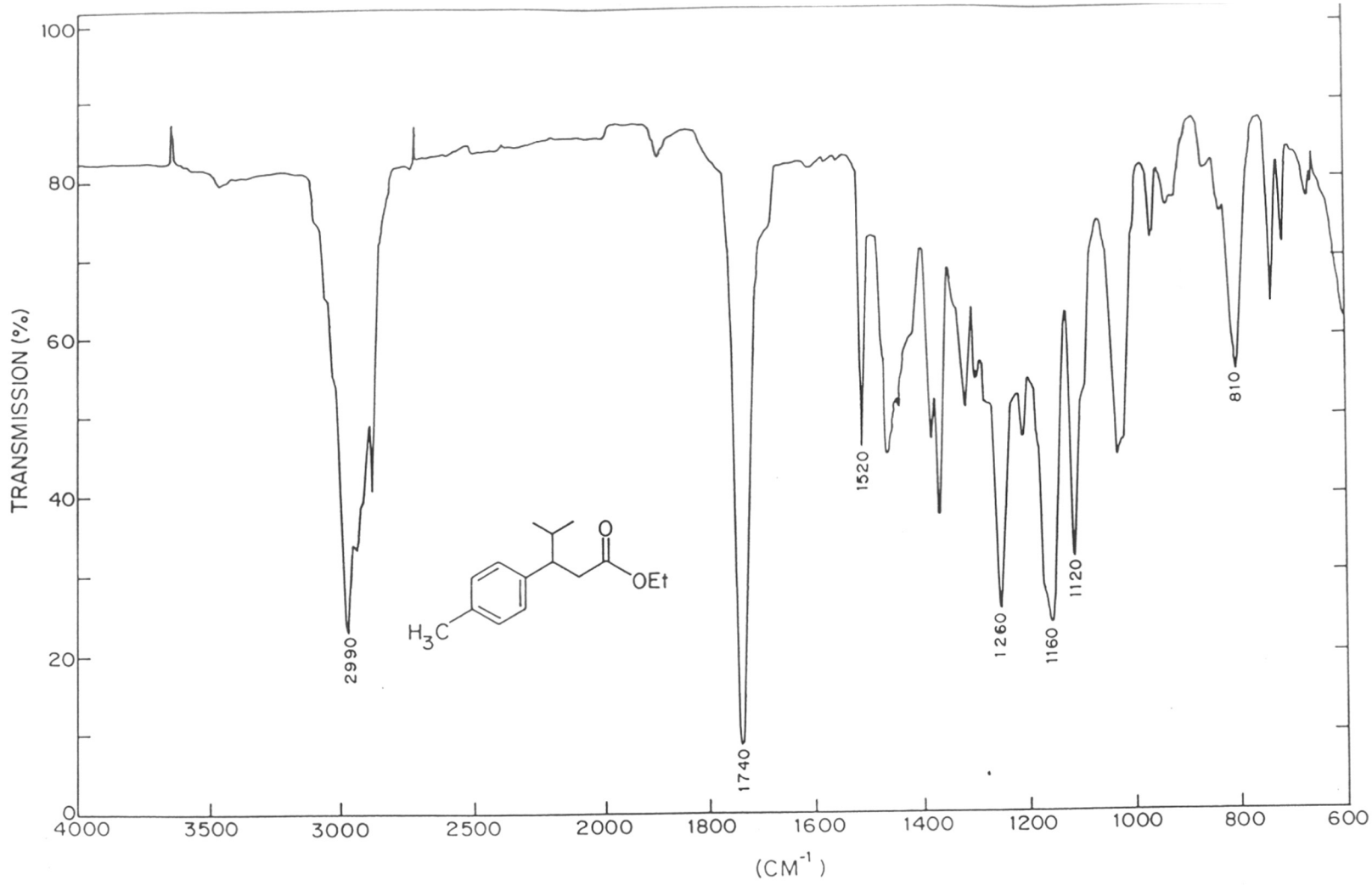

FIG. VIII : IR OF COMPOUND No. 6c

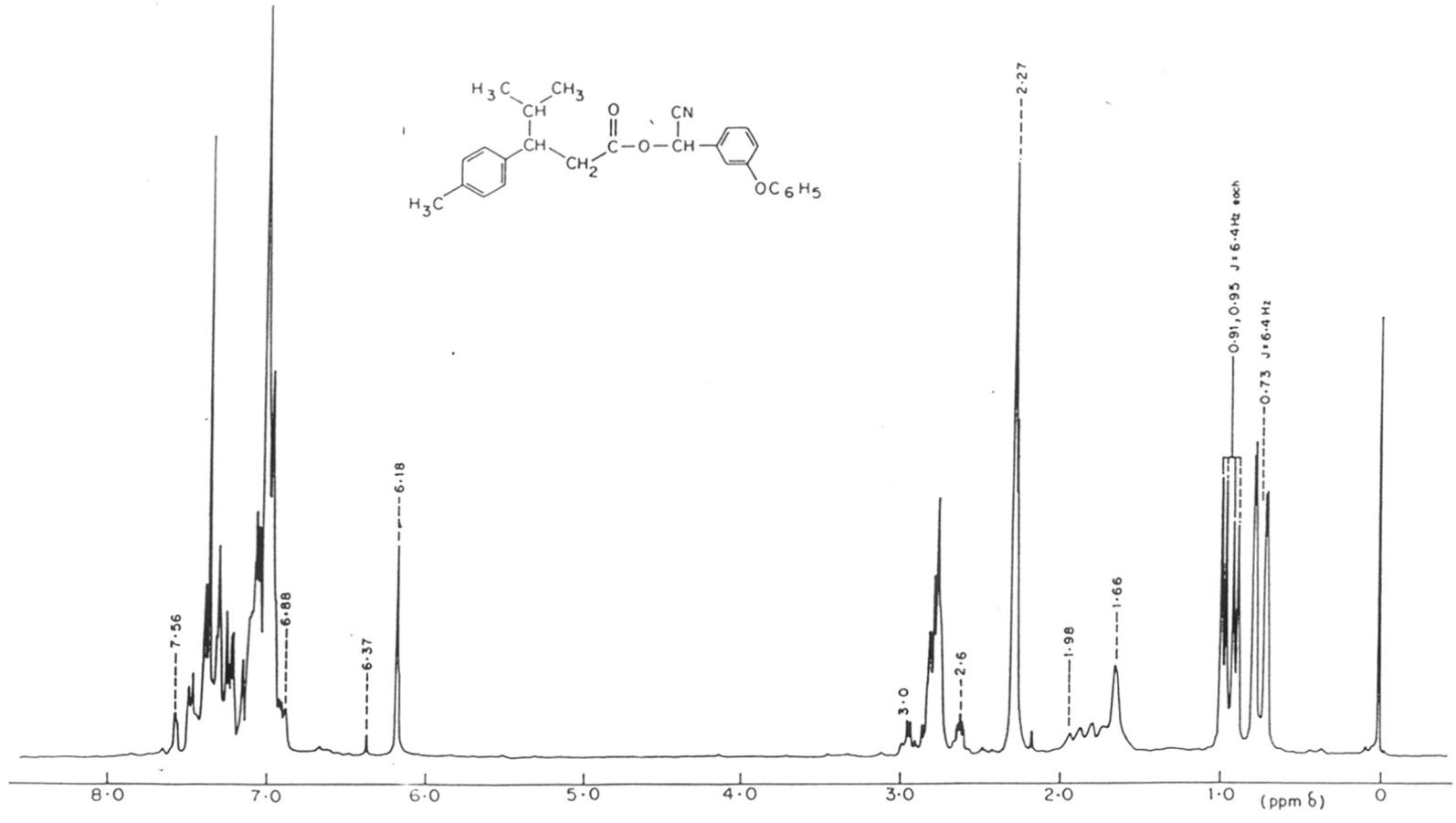

FIG. IX : NMR OF COMPOUND No. 8c

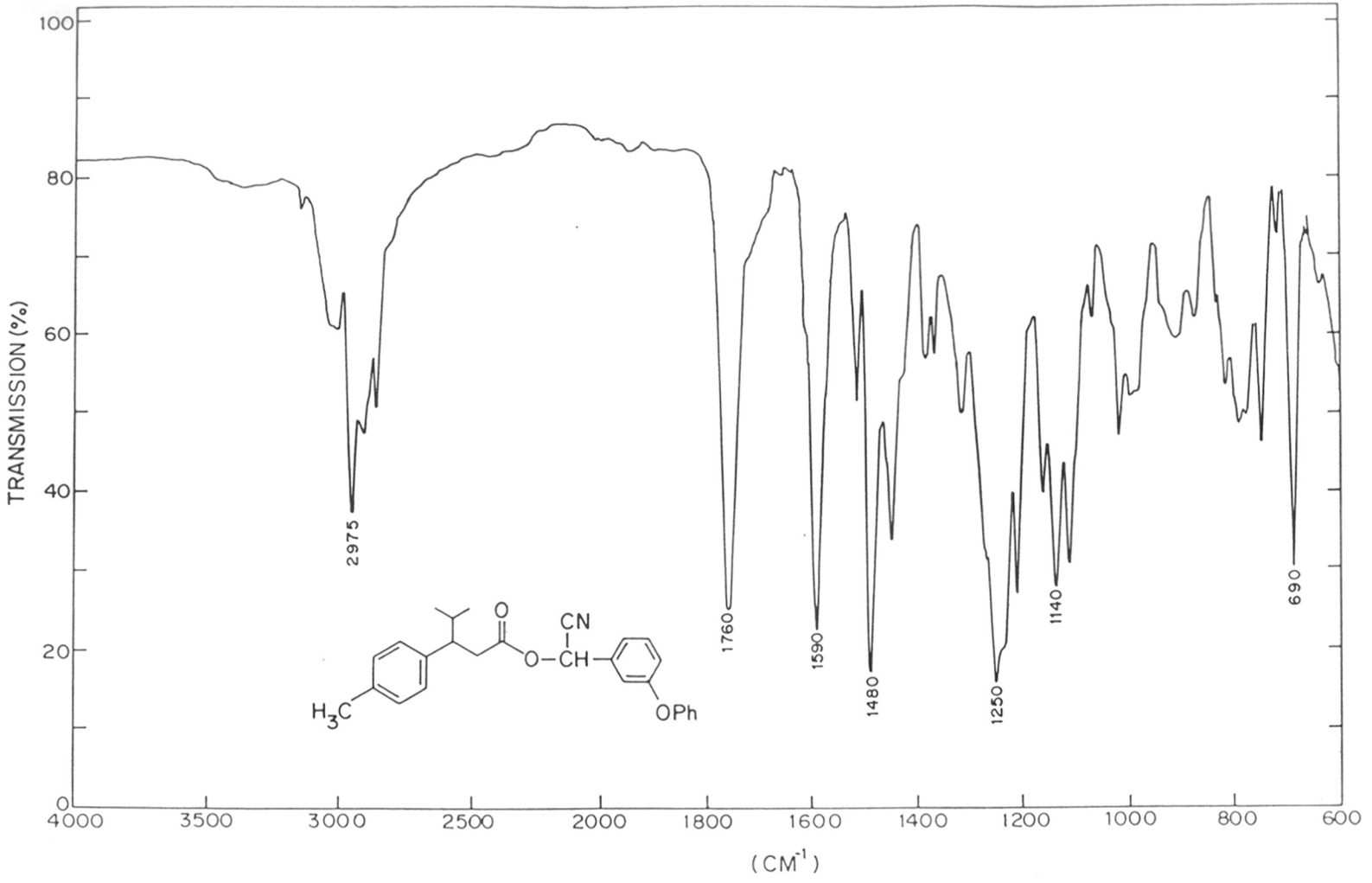

FIG. X : IR OF COMPOUND No. 8c

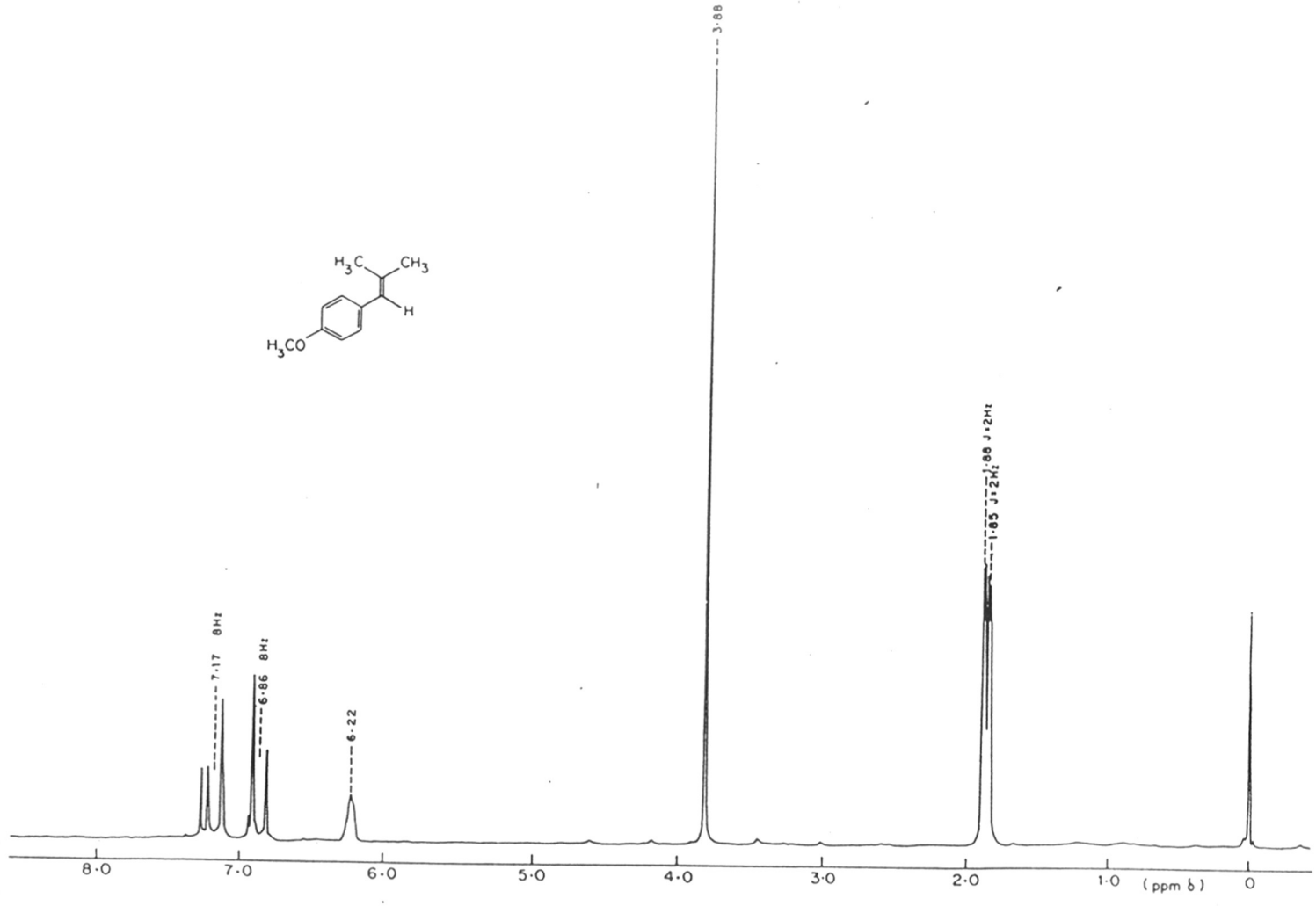

FIG. XI : NMR OF COMPOUND No. 4d

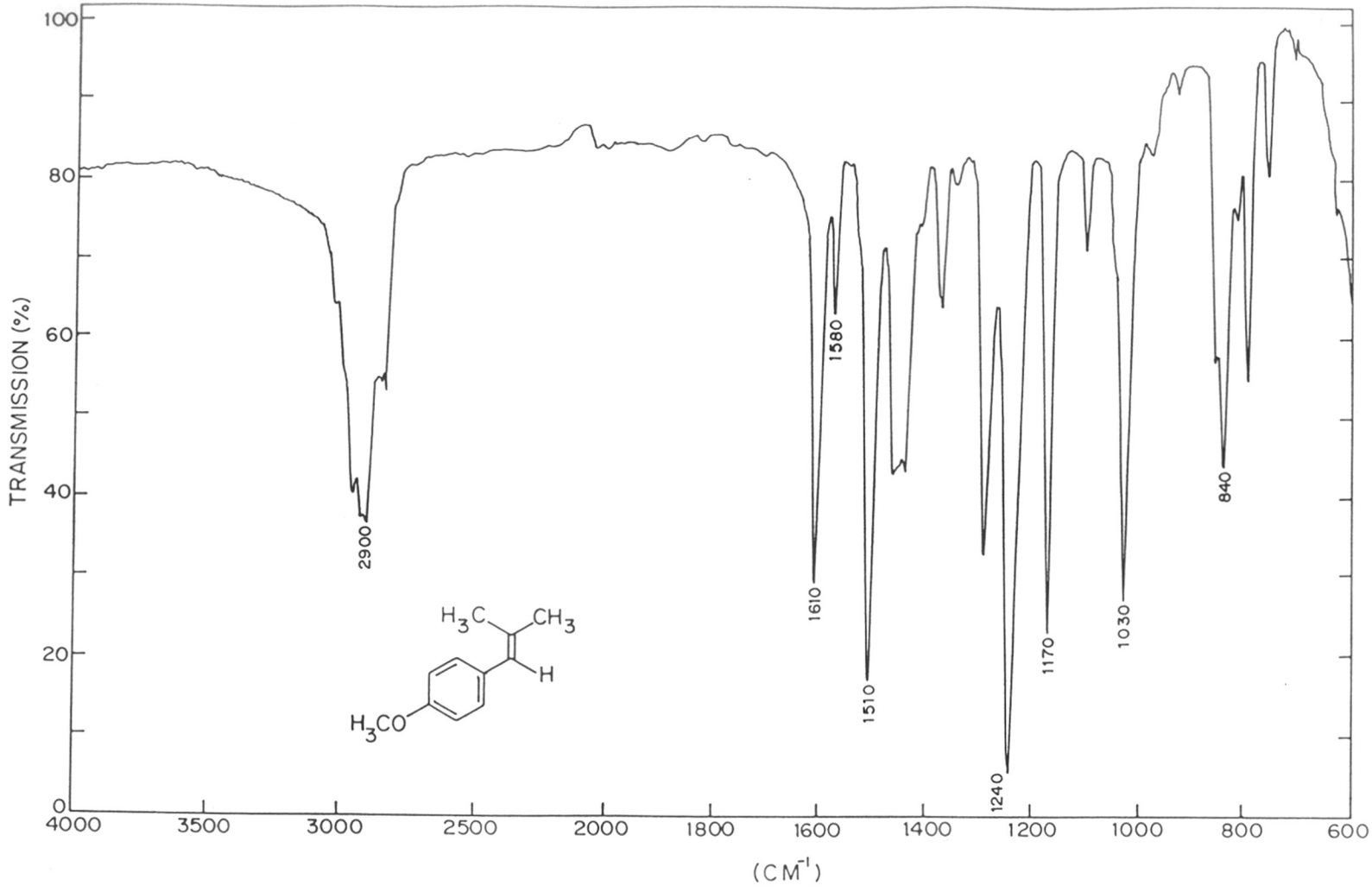

FIG. XII : IR OF COMPOUND No. 4d

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CHAPTER-3

SYNTHESIS OF 3-ISOPROPENYL-HEPT-6-EN-1-AL, KEY INTERMEDIATE FOR THE SYNTHESIS OF CALIFORNIA RED SCALE PHEROMONE

SUMMARY

Synthesis of 3-isopropenyl-hept-6-en-1-al (**25**), an intermediate characterized earlier for California red scale pheromone[20,21, 24,25], has been synthesized starting from tetrahydro furfuryl chloride (**35**). The chloride (**35**) was opened-up with sodium metal in ether to give 4-penten-1-ol (**19**). Alcohol (**19**) was oxidised with PCC to get aldehyde (**20**). This aldehyde on Wittig-Horner reaction with the ylide generated from triethylphosphono-2-propionate and sodium hydride yielded the conjugate ester (**36**). Selective reduction of the ester group gave the allylic alcohol (**37**). The latter was then subjected to Claisen orthoester rearrangement with triethyl orthoacetate to give diene ester (**38**). Aluminium hydride reduction of ester (**38**) gave the diene alcohol (**34**) which on subsequent oxidation with PCC furnished the target aldehyde (**25**), thereby completing the formal synthesis of California red scale pheromone.

INTRODUCTION

Man has wondered at the spectacular scenes of metamorphosis, aggregation and mating of insects for many years. During the last two decades, it has gradually become clear that these biological phenomena are regulated by chemical substances, known as insect hormones and pheromones. Insect chemistry, the study of natural products of insect origin, is now regarded as an established branch of natural products chemistry.

Man has, at the same time, been unable to develop a stable system of agriculture for the expanding world population. This is partly due to the fierce competition from insects for his food and fibre. Insects are constant sources of depredation to humans. They devour plants, spread diseases and are generally a great nuisance to man. Application of insecticides is still the most widely used approach to control insects and other invertibrate pests. These substances have often provided effective control. Unfortunately the solution has often been of short term and side effects have been sometimes worse than the original problem. These insecticides are not only harmful to the humans but are also pertinent in the environment. They show low selectivity to insects and kill harmless and useful insects like honey-bee and predators. Therefore, several other approaches, which are long term, more selective and environmentally acceptable, have been found necessary.

The roles of chemicals used for communication among insects and other animals is summarized in chart (II). This form of communication includes attraction between two sexes for mating, alerting members of a colony for the purpose of defence, the use of defensive secretions

to fight off predators, terretorial making and tailmarking to assist in gathering food for colony.

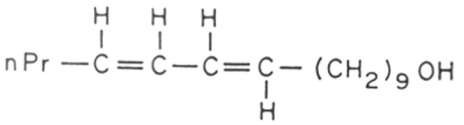
The substances which are used for communication among same species are called pheromones. The term pheromone is derived from Greek 'Pherin'- to transfer and hormon-to excite. After the discovery of Bombykol[1] (1) (see chart I), the first insect pheromone, the term pheromone was defined[2] as the substance that is secreted to the outside by an individual and received by a second individual of the same species, in which it releases a specific reaction like a definite behaviour or a developmental process.

Insects have managed to persist in the hostile surroundings because they have developed extraordinary adaptations, one of which is a highly specialized sense of smell. Because many insects depend for their survival on their sense of smell, they can be frequently attracted to a trap by a chemical for detection purposes, to a toxicant that destroys them or to a substance that makes them incapable of fertile mating.

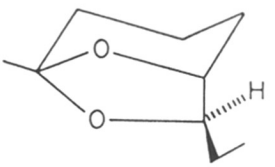
The attractants may be classified as sex, food or oviposition lures. A chemical is probably a sex attractant if it brings to it an insect, which then assumes a mating postion or attempts to mate with the chemical or with an object on which the chemical is placed. Sex attractants, usually released by a female to male, are important links in the process by which the sexes locate each other for mating. The odors released by a female is usually to attract males from a distance, while the odors released a male is to excite the female sexually, making her more receptive to the male's advance (Aphrodisiacs).

The pheromones thus tend to be used in three different ways for the crop protection.

CHART I



(10E, 12Z)-1



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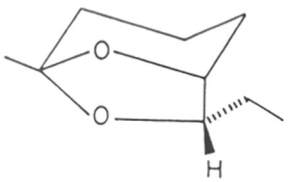

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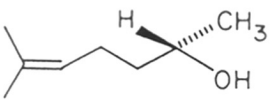

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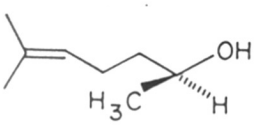

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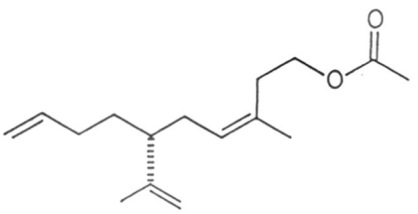

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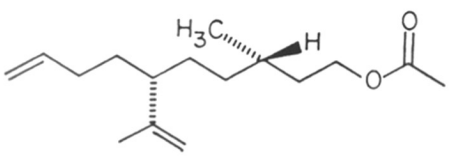
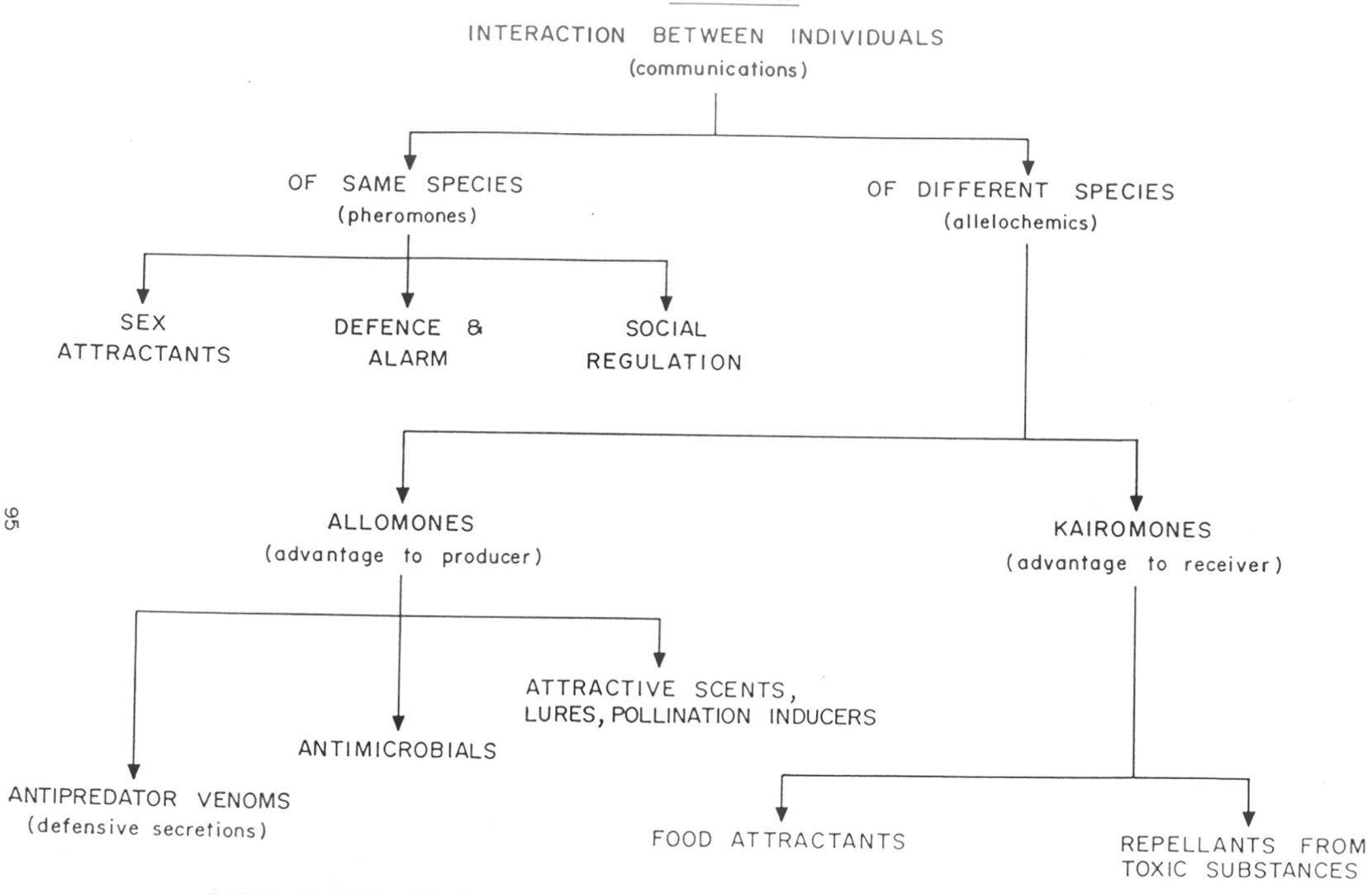


7

CHART II



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

1. For monitoring an insect population to see if it exceeds an economic threshold, when damage of crops becomes significant.
2. For mating disruption, where a male insect may be led to believe that a female is nearby when actually there is none. So no breeding takes place.
3. To attract lure and kill. Here a small amount of insecticide is placed in very close proximity to the lure.

Such methods of pest control have considerable advantages over the use of conventional insecticides because (1) relatively small amounts of attractant is required (2) minimizes the possibility of environmental pollution and (3) the species specificity of the natural attractants reduces the risk of destroying beneficial insects.

Considering these advantages of pheromones, the synthetic approach became very much inevitable. More so because of the limited availability of natural pheromones from insects. (usually less than several miligrams). Synthetic work in insect pheromones may be classified into three categories.

1. Synthesis as the final proof of the proposed structure.
2. Synthesis that provides enough material for biological study such as field test.
3. Synthesis of a number of analogs and isomers to clarify the structure - activity relationship.

Recent studies on structure-activity relationship reveals the importance of stereochemical aspect in the pheromone perception by insects. Three types of isomerism-structural, geometrical and optical are all shown to affect the biological activity. Following examples illustrate this point.

All the four possible isomers of Bombykol (1) were synthesized[3,4,5] and their activity was compared to the natural isomer. It was observed that only (10E, 12Z) was almost identical with the natural Bombykol. Similarly two stereoisomers of 7-ethyl-5-methyl-6,8-dioxabicyclo [3,2,1] octane (brevicomin) were isolated from the frass of western pine beetle (**Dendroctonus brevicomis**)[6]. Only one of them, exo brevicomin (2) (see chart I) was found to be biologically active. The endo isomer was inactive. Sulcatol is the aggregation pheromone produced by the males of **Gnathotrichus Sulcatus**[7]. Both the (+)-Sulcatol [(S)-9] (4) and (-)-Sulcatol [(R)-9] (5) (see chart I) were synthesized. But surprisingly, none of them individually was found to be active. However, when combined to give a racemic mixture of 65% of (S)-9 and 35% of (R)-9, it was more active than the natural pheromone. The comparison of above three cases establish that the aspect of stereochemistry is of paramount importance both, scientifically and economically.

Because of the importance of pheromones, number of organic chemists from the well-known groups throughout the world, have become involved in this area of research. A large number of papers have been published on pheromones[8-13]. A number of reviews are available on the chemical aspects of pheromones. Rossi reviewed the synthesis of both, achiral and chiral[14] pheromones. In 1981, Kenji Mori reviewed[15] comprehensively "On the synthesis of insect pheromones".

California Red Scale Pheromone

The **California Red scale, Aonidiella aurantii (Maskel),** is the most important citrus pest in California, Australia and the Mediterranean

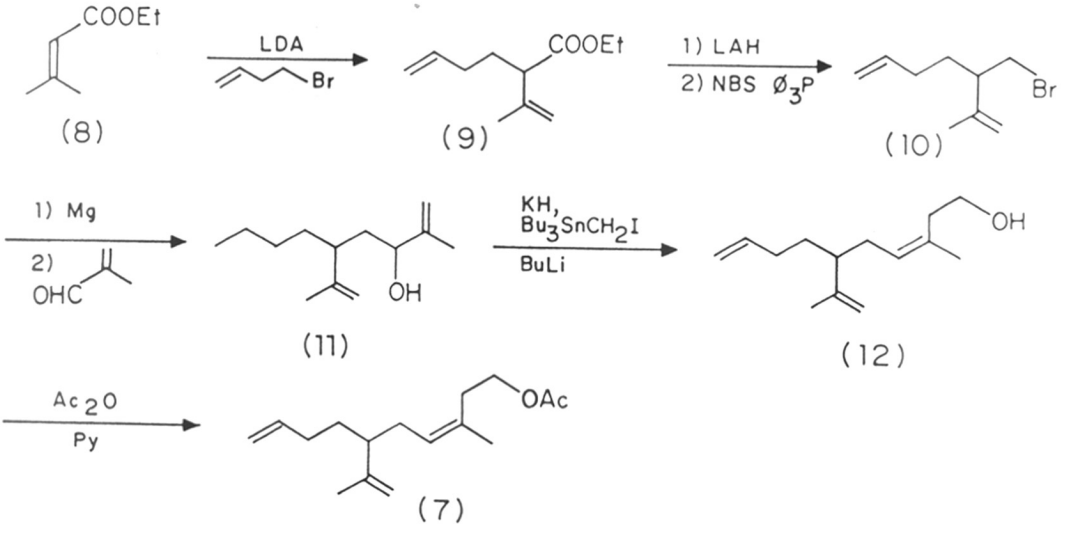
countries. It was found that red scale females attract males with a sex pheromone. The preliminary studies[16] had indicated that a branched acetate may be involved. Much interest was generated in the identification of this pheromone because the synthetic analog had immediate application in replacing the commercial virgin female traps used extensively in monitoring this pest. The sex pheromone of California red scale consists of two novel components, 3-methyl-6-isopropenyl-9-decen-1-yl acetate (6, chart I) and (Z)-3-methyl-6-isopropenyl-3,9-decadien-1-yl acetate (7, chart I). The norsesquiterpene structures represent an interesting biosynthetic pathway, since they do not merely involve head-to-tail coupling of the isoprenoid units. Preliminary field tests confirmed that the strong attractancy of (R)-Z isomer of (7) compared well with the standard virgin female traps (200 females per trap). Moreover, synthetic (R)-Z isomer had identical retention time with the natural pheromone. 25-130 ng of synthetic (R)-Z isomer of (7) is competitive with 25 virgin females, whereas the other isomers are inactive.

Several syntheses[17-22] of this pheromone have appeared in the literature since its isolation, some of which are described below (see chart III).

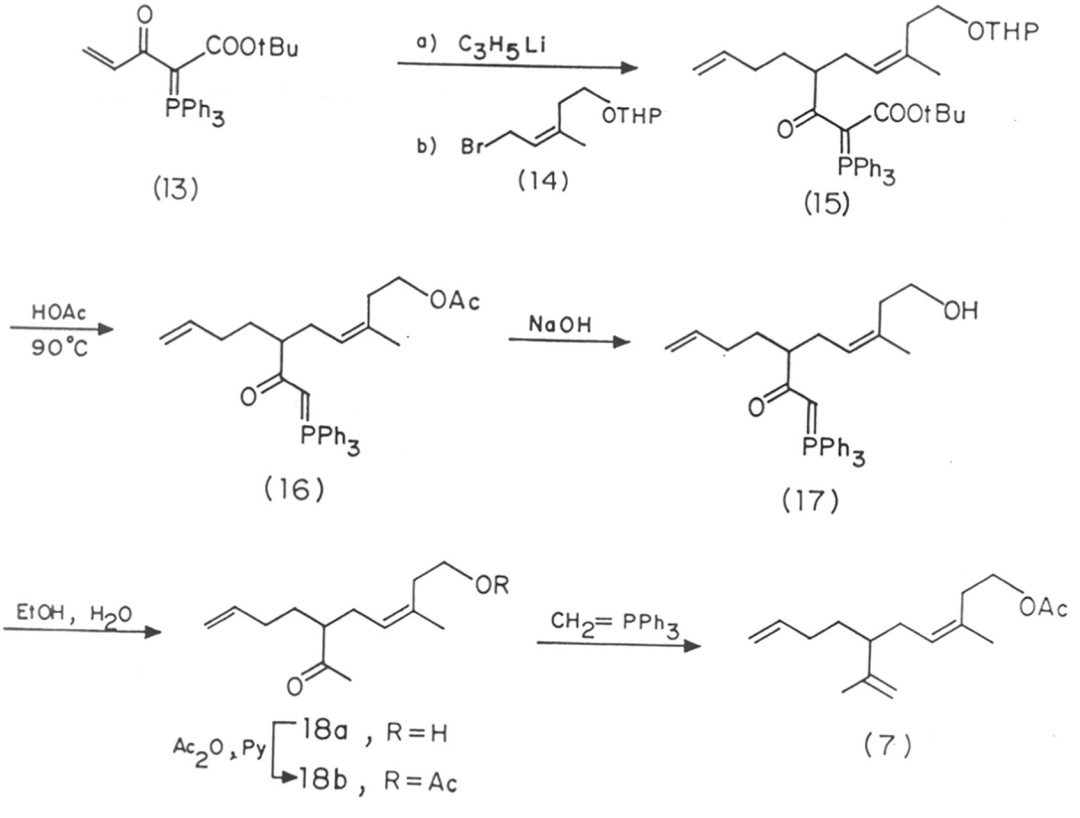
W.C. Still and A. Mitra[17] (see chart III-A) reported the racemic synthesis of California red scale pheromone, starting with ethyl ester of β,β-dimethyl acrylic acid (8). Alkylation with 4-bromo butene gave the β,γ-unsaturated ester (9) in 80% yield. LAH reduction and NBS-phosphine bromination gave the bromide (10). This was converted to its Grignard reagent and then reacted with methacrolein to yield a mixture of diastereo-

CHART III

(A) W. CLARK STILL , A. MITRA



(B) MANNING P. COOKE Jr., DIANA L. BURMAN



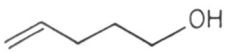
meric alcohol (11). Alkylation with iodomethyltributyltin and butyllithium induced [2,3] sigmatropic rearrangement (-78°C) proceeded smoothly to alcohol (12) which was acetylated to give racemic Z-isomer of 95% purity.

The synthetic route of M.P. Cooke and D.L. Burman[18] (chart III-B) involved charge directed 1,4 addition reaction as the key step. Thus, treatment of (13) with C_3H_5Li and alkylation of ylide anion with bromopyranyl ether (14) gave the functionalized ylide (15) in 87% yield. Decarboxylation was achieved with HOAc at 70°C to give acetate (16) which was hydrolyzed to ylide alcohol (17). Further heating with aqueous ethanol gave the keto alcohol (18A) which was acetylated to corresponding keto acetate (18B). Treatment of (18B) with slight excess of methylenetriphenylphosphorane gave the desired pheromone in 28% yield (for Wittig reaction).

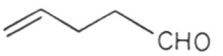
Leznoff et al.[19] (chart III-c) started their optically active approach with 4-penten-1-ol (19). It was oxidised with PCC to its aldehyde (20). Treatment of (20) with malonic acid in pyridine and pyrrolidine gave (E) 2,6-heptadienoic acid (21), contaminated by some of the (Z) isomer. The mixture of (E) and (Z) isomer was treated with thionyl chloride to give pure (E) 2,6-heptadienoyl chloride (22). Compound (22) was converted to (23) by treatment with l-ephedrine in the presence of proton sponge[23]. Treatment of (23) with isopropenyl magnesium bromide gave (24) in 86% ee. Compound (24) was cleaved with DIBAL at 0°C to give the optically active aldehyde (25). This intermediate was already involved in two different synthetic routes[24,25] leading to California red scale pheromone (7).

John Hutchinson[20] furnished the enantiospecific synthesis of dienealdehyde (25), starting with (+)-camphor (26). It was converted to its dibromo

(C) M. WHITTAKER , C.R. McARTHUR , C.C. LEZNOFF



(19)



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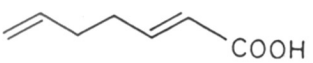

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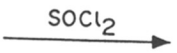

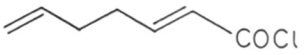

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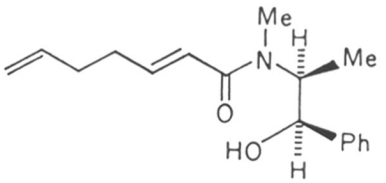

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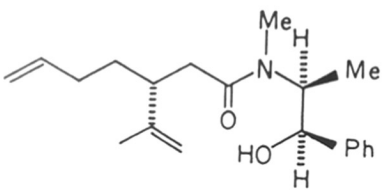

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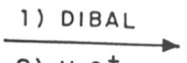

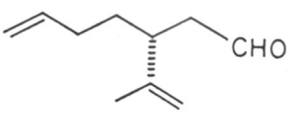

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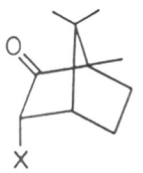
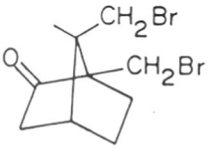


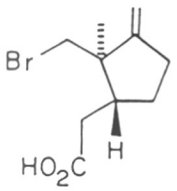
26 , X = H
27 , X = Br

1) $Br_2 / ClSO_3H$, 1 hr.
2) $Br_2 / ClSO_3H$, 5 days
3) $Zn / HOAc / Et_2O$, 0°C



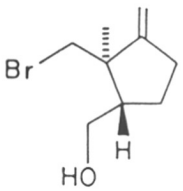
(28)

KOH / DMSO / H_2O



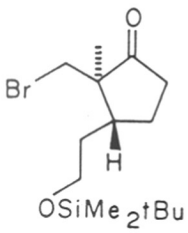
(29)

LAH



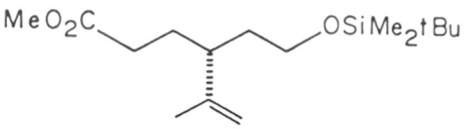
(30)

O_3 / MeOH ; Me_2S
$tBuMe_2SiCl$ / DMAP



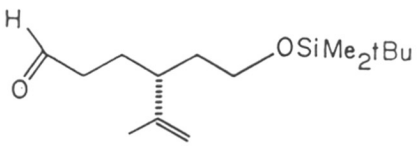
(31)

NaOMe / MeOH
60°C



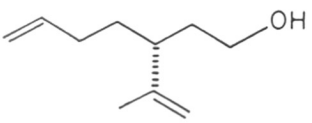
(32)

1) LAH
2) PDC



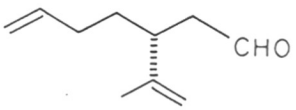
(33)

1) $CH_2 = PPh_3$
2) Bu_4NF



(34)

PDC



(25)

analog (27) which was then cleaved with sodium or potassium hydroxide to give bromo acid (28). Reduction of acid (28) followed by ozonolysis and protection of hydroxy group produced cyclopentanone derivative (30). Treatment of bromo ketone with sodium methoxide provided acyclic ester (31). Reduction of (31) with LAH followed by oxidation with PDC/CH_2Cl_2 provided aldehyde (32). Compound (32) on Wittig reaction with methylene-triphenylphosphorane gave the diene. The protecting group was removed (Bu_4NF/THF) to yield diene alcohol which upon PCC oxidation gave the diene aldehyde. (25)

PRESENT WORK

A formal, total synthesis of California Red Scale pheromone was achieved by synthesizing an established intermediate viz. diene aldehyde (25). This intermediate has been involved, earlier, in two different synthetic routes[24,25]. Later, two more groups also achieved the formal synthesis of California Red Scale pheromone by preparing the diene aldehyde (25)[19,20].

Tetrahydro furfuryl chloride (35) was used as the starting material. It was treated with sodium metal in dry ether at 0°C to furnish 4-penten-1-ol (19) as per the reported procedure . This alcohol was then oxidised with PCC as per Corey's procesdure, already reported[26], to give aldehyde (20).

IR: 1735

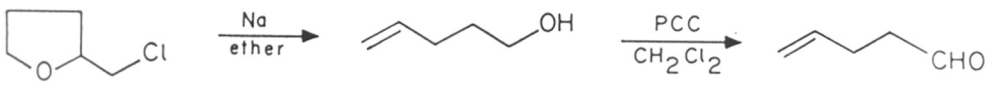
PMR (CCl_4): 2.08-2.76 (4H, m, allylic CH_2 and methylene α to CHO), 4.8-5.22 (2H, m, $\underline{CH_2}$=C), 5.56-6.3 (1H, m, -CH=), 9.72 (1H, t, J 2 Hz, CHO).

The aldehyde (20) on Wittig-Horner reaction with the ylide generated from triethyl-2-phosphono propionate and sodium hydride in ether at 0°C gave the conjugated ester (36).

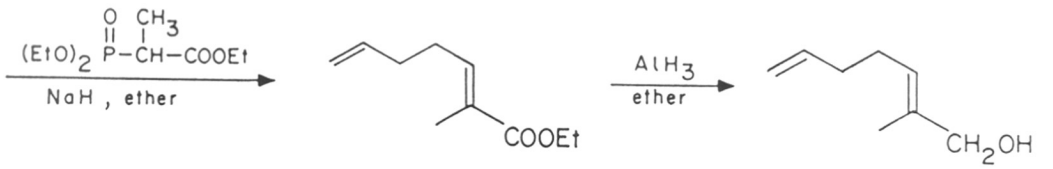
IR: 1710, 1645, 900.

PMR ($CDCl_3$): 1.29 (3H, t, 8 Hz, ester methyl), 1.84 (3H, br s, methyl on double bond), 2.11-2.37 (4H, m, allylic methylenes) 4.2 (2H, q, 8 Hz, ester methylene), 4.88-5.2 (2H, m, CH_2=C-), 5.57-6.13 (1H, m, =CH-), 6.64-6.88 (1H, m, CH=C-COOR).

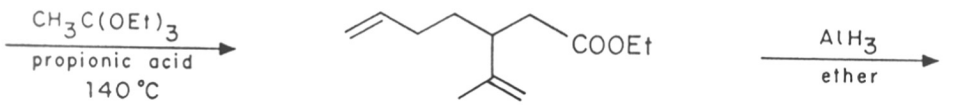
SCHEME



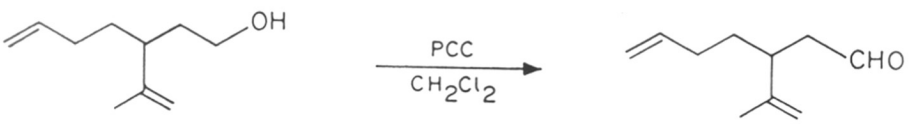
(35) (19) (20)



major (36) (37)



(38)



(34) (25)

Selective reduction of the ester group with aluminium hydride (generated in-situ from aluminium chloride and lithium aluminium hydride) in dry ether at 0°C gave the allylic alcohol (**37**).

IR: 3300, 1640, 900.

PMR ($CDCl_3$): 1.47 (1H, s, D_2O exchangeable, -OH), 1.67 (3H, br s, methyl on double bond), 2.12 (2H, d, 3 Hz, one of the allylic methylene), 2.23 (2H, d, 10 Hz, second allylic methylene), 4.02 (2H, s, $=CH_2-O$), 4.93-5.09 (2H, m, $CH_2=C$), 5.33-5.53 (1H, m, CH=C), 5.64-6.02 (1H, m, $H_2C=\underline{CH}-$)

Allylic alcohol (**37**) was then subjected to Claisen ortho ester rearrangement[27] with triethyl orthoacetate and propionic acid as a catalyst at 140°C for 1.5 hr to furnish diene ester (**38**).

IR: 1740, 1645, 900.

PMR ($CDCl_3$): 1.13 (3H, t, 6.4 Hz, ester methyl), 1.28-1.5 (m, 2H, methylene protons), 1.56 (3H, br s, methyl on double bond), 1.75-2.75 (5H, m, three allylic protons and methylene protons α to ester function), 4.0 (2H, q, 6.4 Hz, ester methylene), 4.88-5.06 (4H, m, terminal olefinic protons), 5.44-6.0 (1H, m, olefinic proton).

Reduction of diene-ester (**38**) with aluminium hydride in dry ether at 0°C gave the diene alcohol (**34**).

IR: 3340, 1640, 890.

PMR ($CDCl_3$): 1.26-1.53 (7H, s overlapping m, alphatic methylenes and methyl on double bond), 1.73-2.24 (3H, m, allylic protons), 3.48 (2H, t, 6 Hz, $-CH_2O$ protons), 4.57-5.0 (4H, m, terminal olefinic protons), 5.46-5.93 (1H, m, olefinic proton).

Oxidation of diene alcohol (**34**) with PCC in CH_2Cl_2, gave the target aldehyde (**25**), thus completing a formal synthesis of California red scale pheromone.

IR: 2720, 1730, 1645, 900.

PMR ($CDCl_3$): 1.34-1.62 (**5H**, s overlapping m, methyl on double bond and aliphatic methylene proton), 1.78-2.0 (2H, m, allylic methylene), 2.25-2.44 (m, 2H, methylene protons α to aldehyde function), 2.53-2.78 (1H, m, allylic methine proton), 4.69-5.13 (4H, m, terminal olefinic protons), 5.5-5.94 (1H, m, olefinic proton), 9.68 (1H, t, 2 Hz, CHO).

EXPERIMENTAL

4-Penten-1-al (20)

Following the method of Corey and Suggs, 4-penten-1-ol (**19**) (5.5 g, 0.064 mole) was oxidized by pyridinium chlorochromate (PCC) (24.8 g, 0.115 mole) in methylene chloride (120 ml). Distillation and careful fractionation gave the volatile aldehyde (**20**) (3.5 g, 60% yield); b.p. 103-105°C as a colorless liquid.

IR: 3780, 2720, 1735, 1640, 890.

Mass: M^+ - 84.

Elemental analysis for C_5H_8O

calculated: C, 71.39; H, 9.59

observed: C, 71.28; H, 9.46%.

Ethyl 2-methyl-hept-2,6-dienoate (36)

To an ice cooled and stirred suspension of sodium hydride (1.03 g, 0.043 mole) in dry ether (25 ml), was added, dropwise, the solution of triethyl-phosphono-2-propionate (10.21 g, 0.043 mole) in dry ether(100 ml). After the addition, the solution was stirred at 0°C for 30 minutes and aldehyde (**20**) (3 g, 0.036 mole) in dry ether (20 ml) was then added slowly. The reaction mixture was stirred at 0°C for 3 hr and then stirred overnight at room temperature. Usual work-up afforded 5.1 g crude conjugated ester (**36**). Chromatographic purification on silica gel and elution with pet.ether + 6% ethyl acetate gave pure ester (**36**) as a major product (95% by GC) in 4.46 g (74%) yield as a mobile liquid.

IR: 2980, 1710, 1645, 1260, 1090, 900.

Mass: M^+ - 168.

Elemental analysis for $C_{10}H_{16}O_2$

calculated: C, 71.39; H, 9.59

observed: C, 71.27; H, 9.44%.

2-Methyl-hept-2,6-dien-1-ol (37)

Lithium aluminium hydride (2.71 g, 0.072 mole) was taken up in dry ether (50 ml) and cooled to 0°C. To it was added, portionwise, aluminium chloride (3.17 g, 0.024 mole). After the addition, mixture was stirred at 0°C for 30 minutes and solution of ester (**36**) (4 g, 0.024 mole) in dry ether (35 ml) was added to it. Reaction mixture was allowed to come to room temperature and progress of the reaction was monitored by t.l.c. Usual work-up gave 2.86 g of crude alcohol (**37**). On purification upon silica gel and elution with (pet.ether + 10% ethyl acetate), it afforded 2.43 g (81% yield) of pure alcohol (**37**).

IR: 3300, 2920, 1640, 1440, 1000, 900.

Mass: M^+ - 126.

Elemental analysis for $C_8H_{14}O$

calculated: C, 76.14; H, 11.18

observed: C, 75.98; H, 11.09%.

Ethyl 3-isopropenyl-6-enoate (38)

Allylic alcohol (**37**) (2 g, 0.016 mole) was taken up in triethyl orthoacetate (18 g, 0.111 mole). 2-3 drops of propionic acid was added to it and mixture held at 140°C for 1.5 hr. Continuous removal of ethanol was maintained during this time. Excess of triethyl orthoacetate was removed by distillation and residue diluted with pet.ether and passed through a short column of silica gel to furnish 2.55 g (82%) of pure ester (**38**).

IR: 2980, 1740, 1645, 1180, 900. Mass: M^+ - 196

Elemental analysis for $C_{12}H_{20}O_2$

calculated: C, 73.43; H, 10.27

observed: C, 73.32; H, 10.12%.

3-Isopropenyl-hept-6-en-1-ol (34)

Aluminium hydride was generated from lithium aluminium hydride (1.16 g, 0.03 mole) and aluminium chloride (1.36 g, 0.01 mole) in dry ether (30 ml) as described earlier. Ester (**38**) (2 g, 0.01 mole) in dry ether (15 ml) was added to it slowly. Reaction mixture was stirred at 0°C for 2 hr and then, at room temperature overnight. Usual work-up gave 1.4 g crude alcohol (**34**). Purification on silica gel (pet.ether + 9% ethyl acetate) gave 1.13 g (72%) pure alcohol (**34**).

IR: 3340, 2930, 1640, 1445, 1380, 1050, 890.

Mass: M^+ - 154.

Elemental analysis for $C_{10}H_{18}O$

calculated: C, 77.86; H, 11.76.

observed: C, 77.74; H, 11.65%.

3-Isopropenyl-hept-6-en-1-al (25)

Alcohol (**34**) (0.8 g, 0.005 mole) in dry methylene chloride (5 ml) was added in one lot to a suspension of pyridinium chlorochromate (1.34 g, 0.006 mole) in dry methylene chloride (10 ml). The reaction mixture was stirred for 10 hr. At the end of reaction, mixture was diluted with dry ether. The contents were then passed through a column of florisil. Removal of solvent and purification on silica gel (pet.ether) gave pure aldehyde (**25**) in 0.44 g (55%) aldehyde.

IR: 2930, 2720, 1730, 1645, 1445, 1000, 900

Mass: M^+ - 152.

Elemental analysis for $C_{10}H_{16}O$

calculated: C, 78.89; H, 10.59

observed: C, 78.74; H, 10.45%.

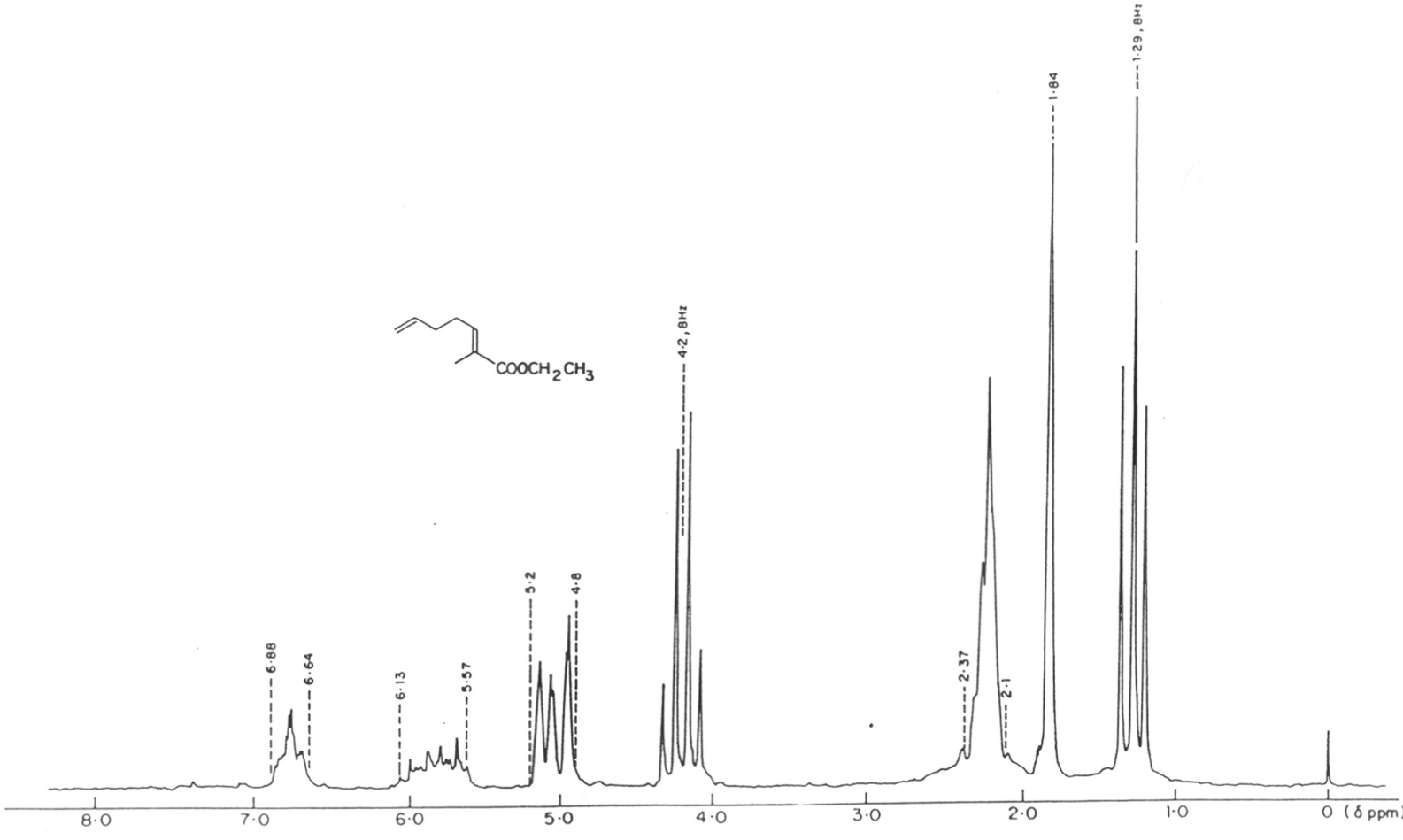


FIG. I : NMR OF COMPOUND No. (36)

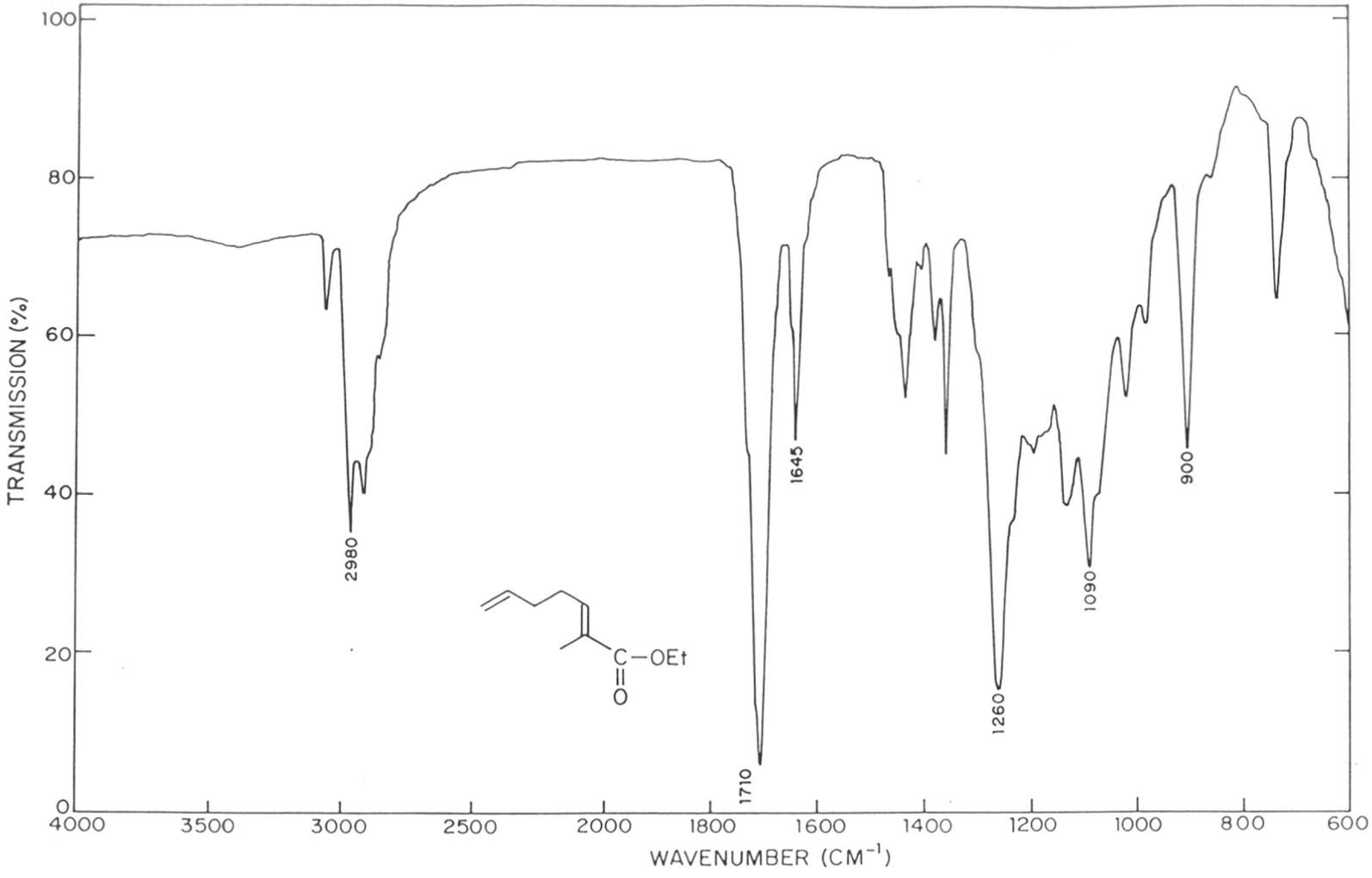


FIG. II : IR OF COMPOUND No. (36)

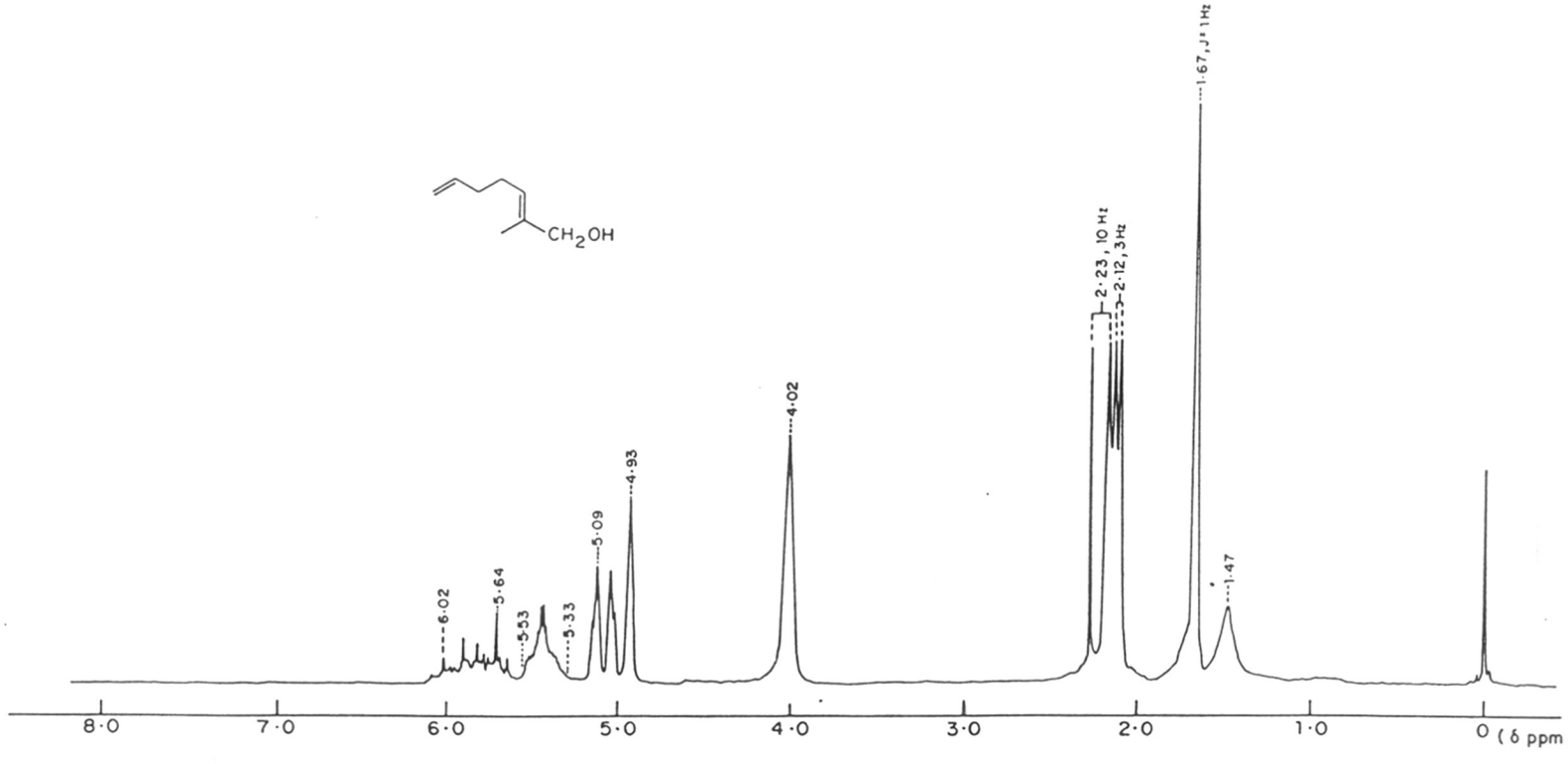


FIG. III : NMR OF COMPOUND No. (37)

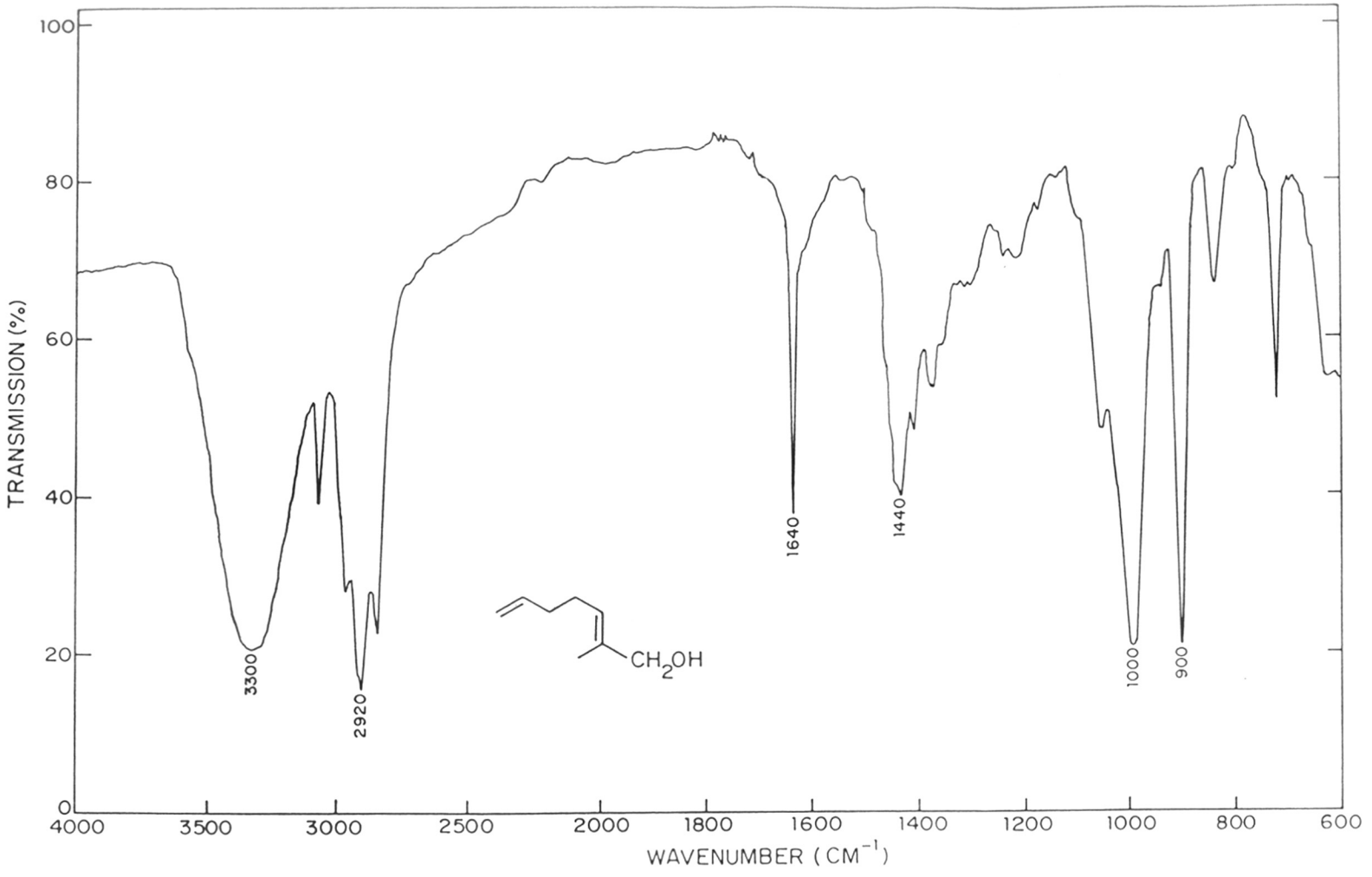


FIG. IV : IR OF COMPOUND No. (37)

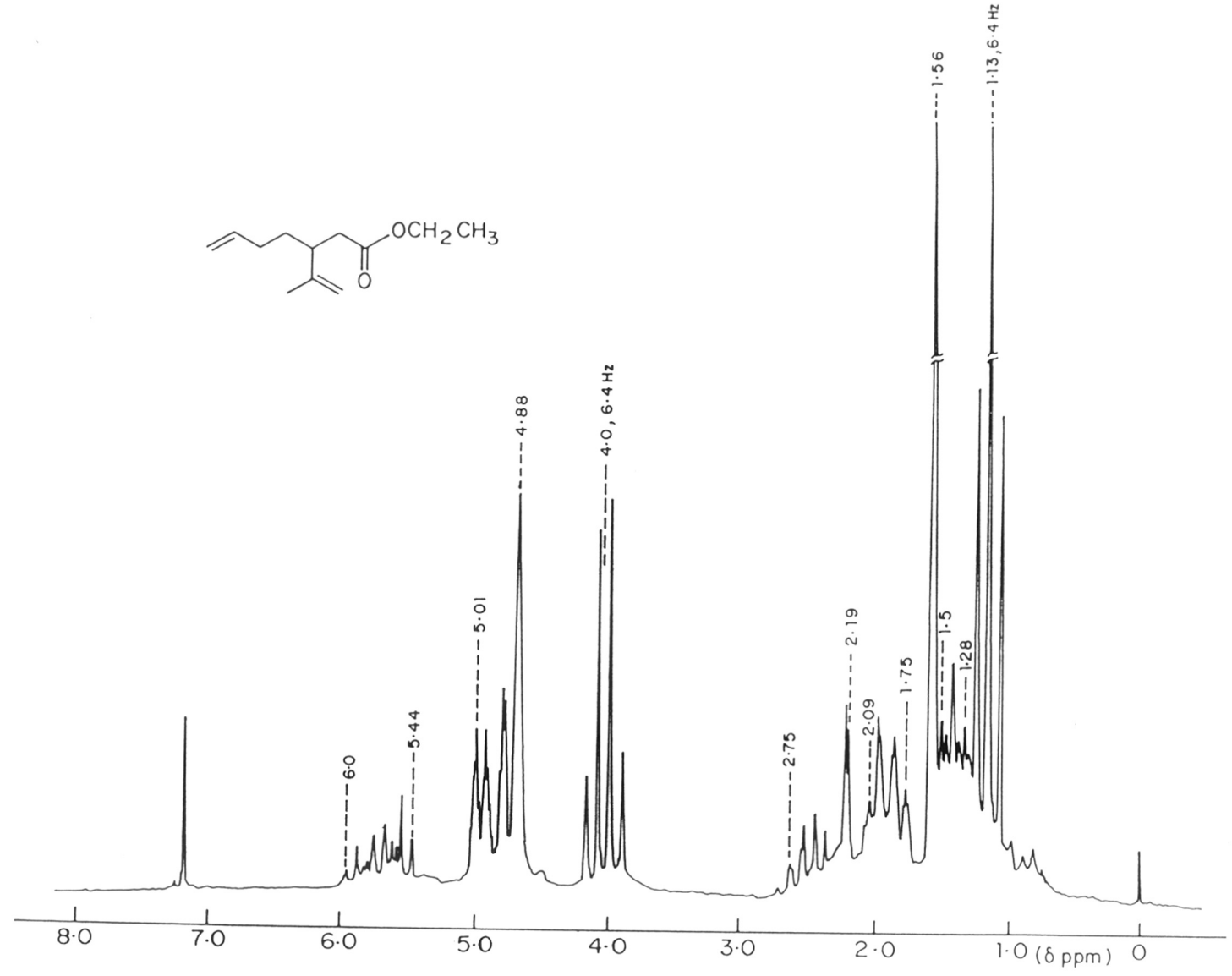
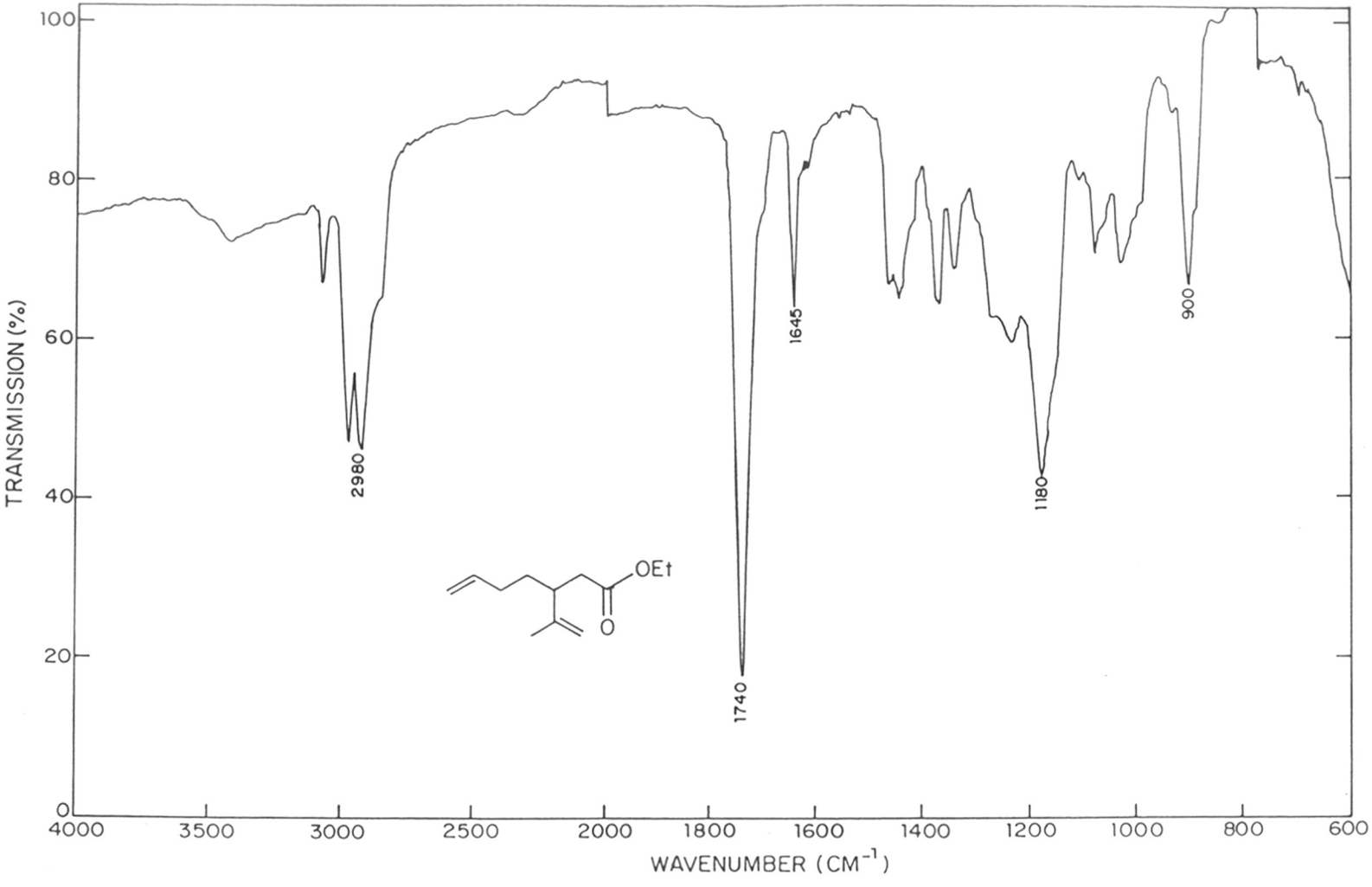


FIG. V : NMR OF COMPOUND No. (38)



FIG_VI : IR OF COMPOUND No. (38)

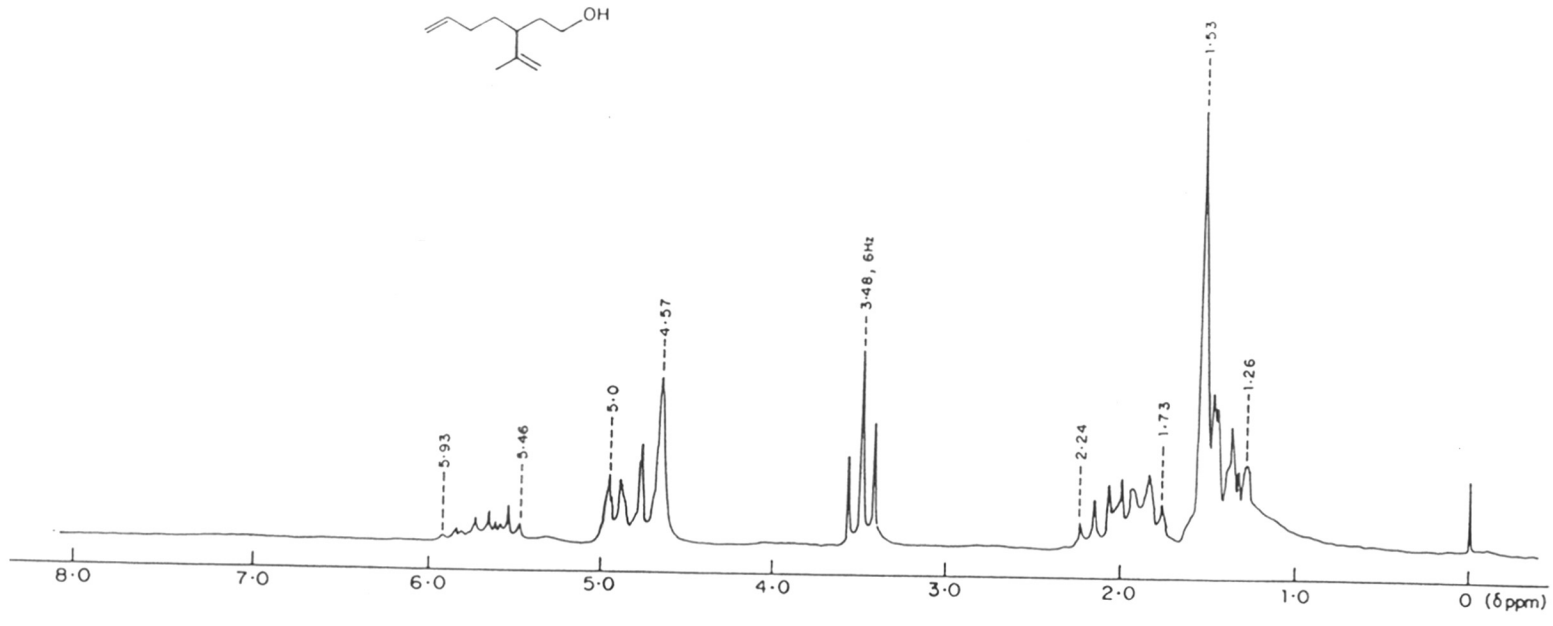


FIG VII NMR OF COMPOUND No. (34)

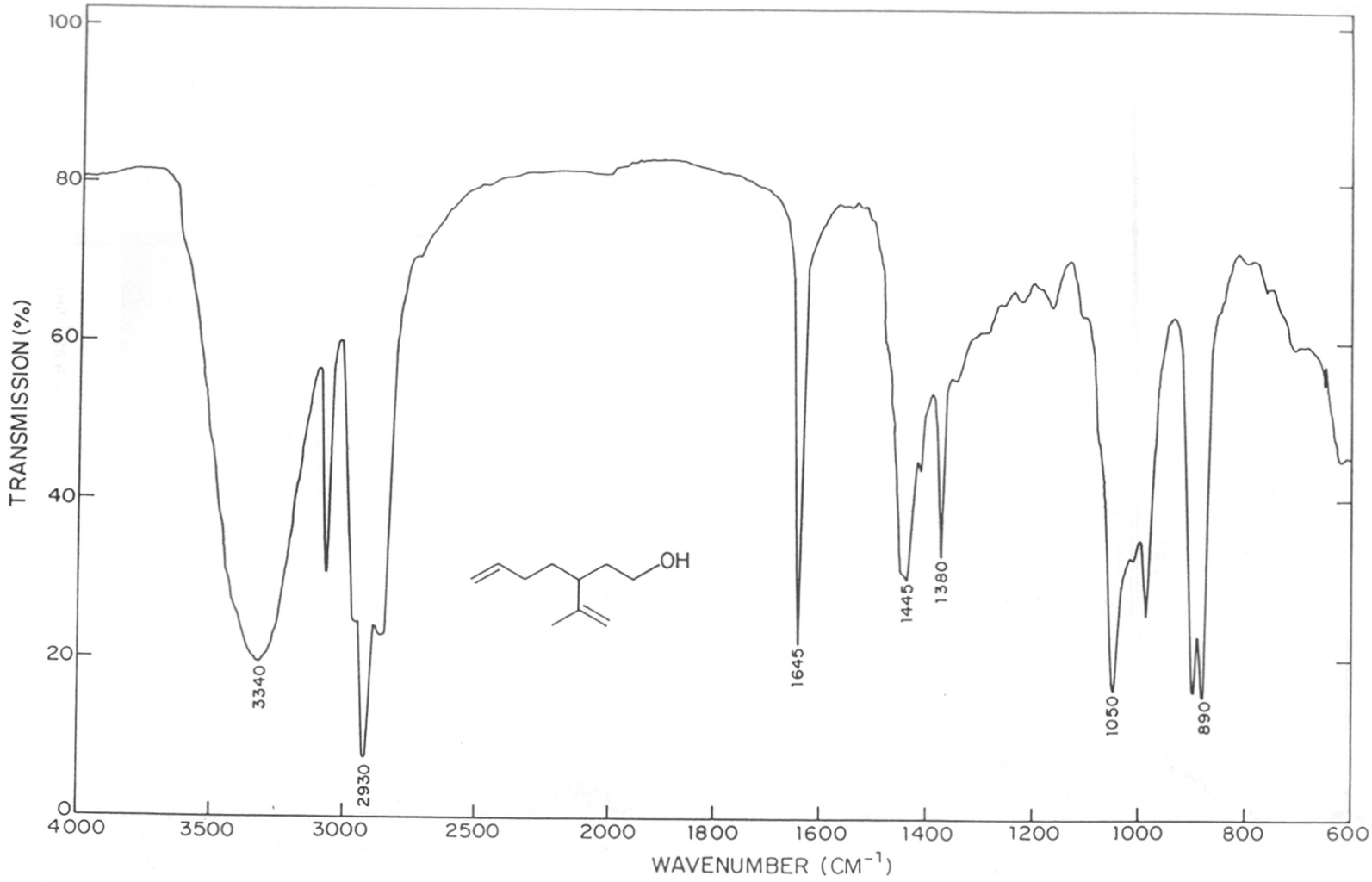


FIG. VIII : IR OF COMPOUND. No. (34)

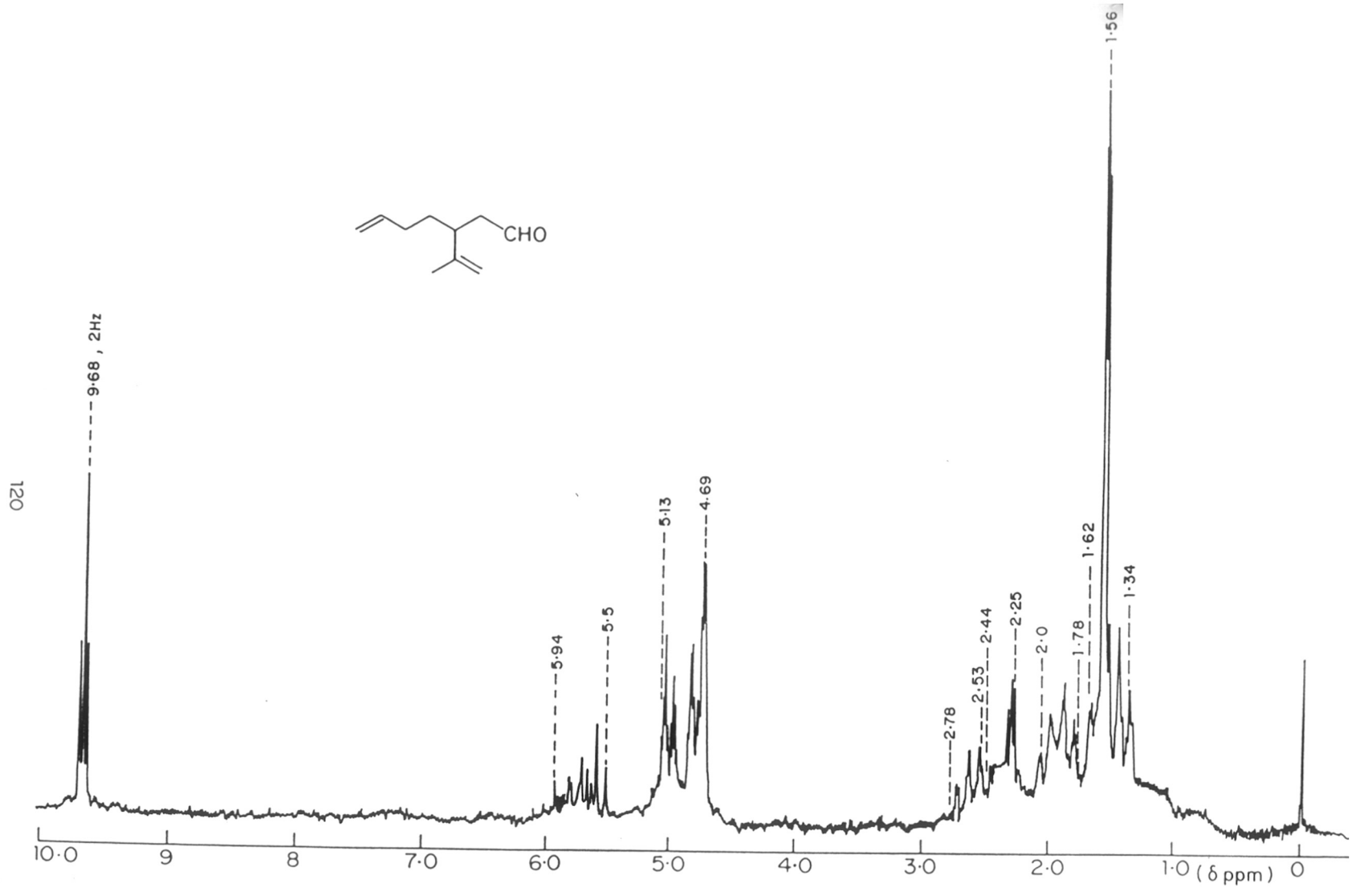


FIG. IX : NMR OF COMPOUND No. (25)

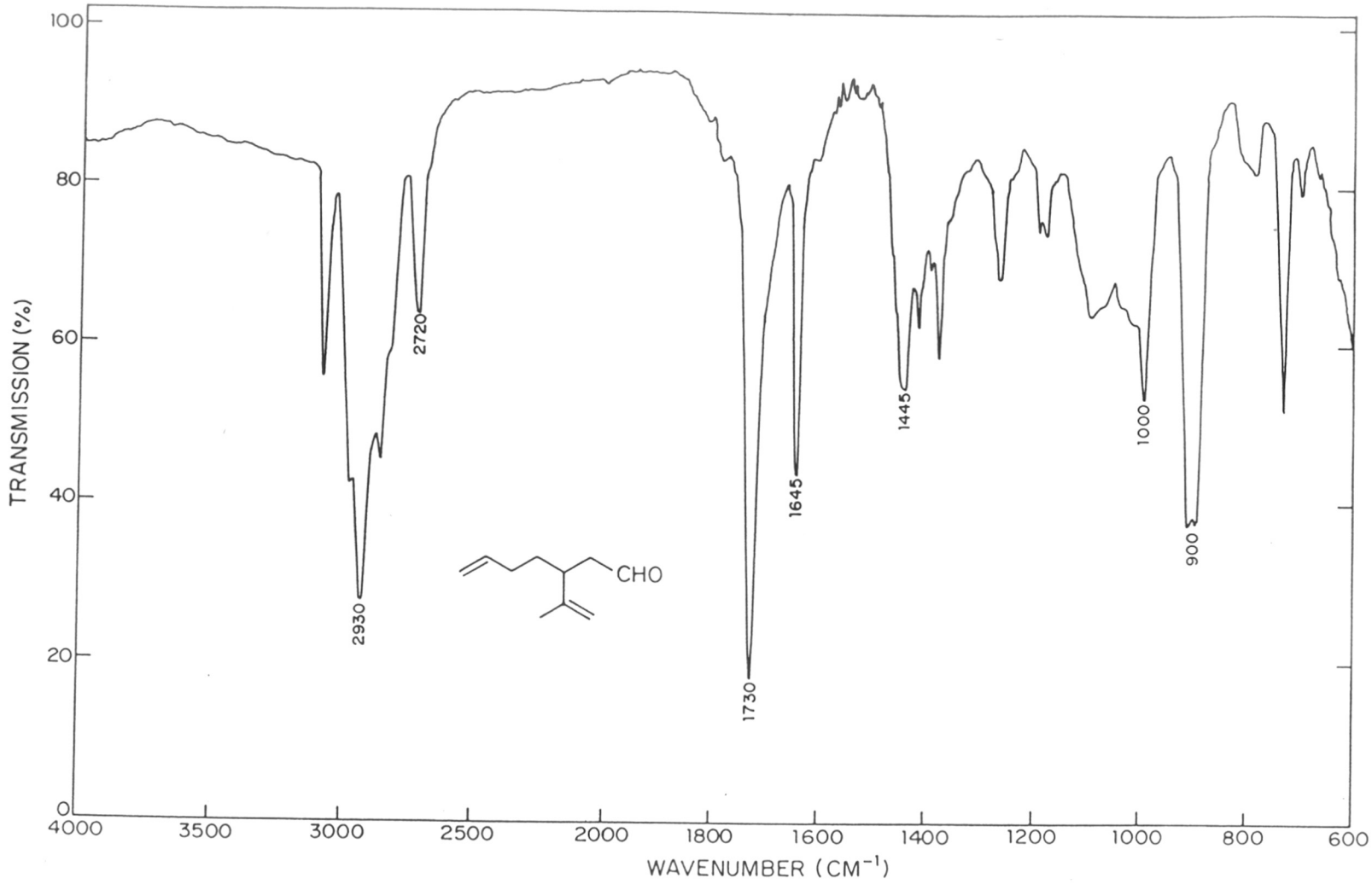


FIG. X : IR OF COMPOUND No. (25)

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CHAPTER-4

SOME INTERESTING REARRANGEMENTS ENCOUNTERED DURING THE ATTEMPTS TO SYNTHESIZE SPIRO-FUSED CYCLOPROPANE CARBOXYLATES

SUMMARY

2-Isobutylidene/benzylidine-1-indanol/tetralol (23, n=1,2) were required for the synthesis of benzospirofused cyclopropane carboxylates of the type (28) (chart V). However, 2-isobutylidene/benzylidine-1-indanone/tetralones (22, n=1,2), prepared by Aldol condensation of 1-indanone/tetralones with isobutyraldehyde/benzaldehyde respectively, when subjected to sodium borohydride reduction in methanol, gave the unexpected alcohols (29, n=1, 2), identified by spectral data. The structures (29, n=1,2) assigned to the alcohols were further confirmed by their oxidation using PCC to the corresponding conjugated ketones (30, n=1,2) which were different from the starting ketones. Claisen ortho ester rearrangement on the allylic alcohols (29, n=1,2), using triethyl orthoacetate and propionic acid resulted in the formation of hydrocarbons (32, n=1,2), in place of the expected esters. However, the structurally related 2-benzylidene cyclopentanol (33) gave the dehydrated product (34)under Claisen reaction condition.

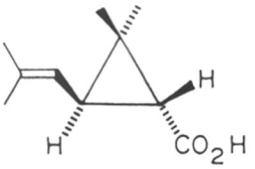
The conjugated ester (36), prepared by Wittig Horner reaction on 1-indanone, when subjected to AlH_3 reduction gave the rearranged homoallyl alcohol (37A) instead of the expected allylic alcohol (37).

INTRODUCTION

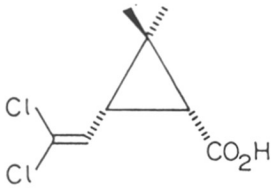
Esters of both 1R cis and 1R trans isomers of 2,2,3-trisubstituted cyclopropane carboxylic acids such as (+) trans chrysanthemic acid (1, chart I) and 3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane-1-carboxylic acid (2, chart I) (also known as DV acid) with alcohols like 3-phenoxybenmzyl and α(RS) cyano-3-phenoxy benzyl alcohol exhibit high insecticidal activity against a wide range of insect species. The other type of cyclopropane carboxylic acid is represented by 2,2,3,3-tetramethyl cyclopropane carboxylic acid (3, chart I) and this also gives highly active insecticidal esters. for example, terallethrin (4, chart I) and fenpropathrin (5, chart I).

In order to change the acid moiety and test the moidified compounds for insecticidal activity (in order to learn more about structure-activity relationship), an attempt was made by introducing an additional methyl group at C-3 position on the cyclopropane ring of the chrysanthemic acid. But this effort proved to be fruitless[1]. Another attempt was made by replacing the pair of geminal methyl groups of the tetramethyl cyclopropane carboxylate with spiro-fused ring[2,3], that afforded significant perspectives. Similarly, Japanese workers at the **Sumitomo Chemical Co.Ltd.** extended this work and synthesized benzo-spirofused cyclopropane carboxylates[4] (chart I, 6,7 and 8) which showed high insecticidal activity against **Musca domestica** (house-fly), 4th instar larvae of tobacco cutworm (**spodoptera litura**) and German cockroach (**Blatella germanica**). The α-cyano-3-phenoxybenzyl esters of these acids were prepared for the testing purpose. Insecticidal activity of these cyano esters is shown in chart II and compared with cypermethrin and fenpropathrin. As can be seen from the chart, the activity of benzo-

CHART – I



(1)



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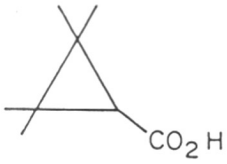

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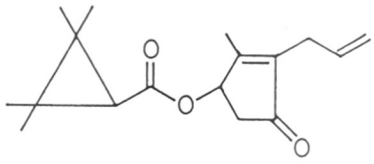

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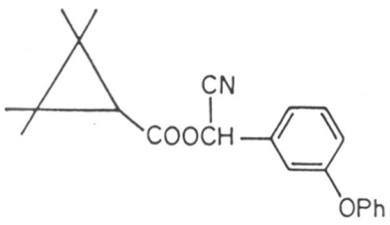
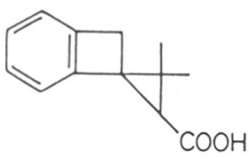
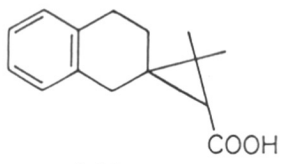


(5)

(6)



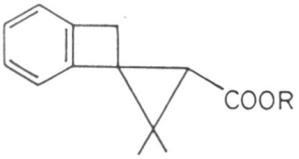
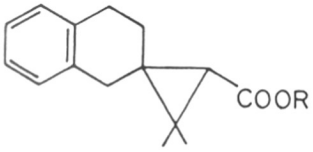
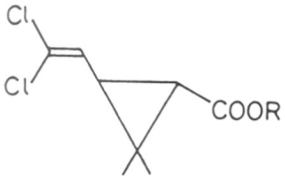
(7)



(8)

CHART - II

INSECTICIDAL ACTIVITY OF α-CYANO-3-PHENOXYBENZYL ESTERS:

	COMPD.	HOUSEFLY LD_{50} (μg)	TOBACCO CUTWORM LC_{50} (ppm)	GERMAN COCKROACH LD_{50} (mg/m^2)
	6	0·0045	2·0	0·60
	7	0·019	5·0	1·0
	8	0·22	50-150	>7·3
	REFERENCE	0·039	1·5	2·6
	REFERENCE	0·0075	0·73	0·17

spiro ester (6) against M.domestica is higher than even cypermethrin and fenpropathrin.

The acid components of (6), (7) and (8) were synthesized as shown in chart III and as described below.

1,2-Di(bromomethyl)benzene was reacted with ethylacetoacetate in presence of potassium carbonat and dimethyl formamide to give substituted β-keto ester (9). Wittig reaction with methylenetriphenylphosphorane furnished the olefin ester (10). The ester (10) was converted to nitrile (11) by treating it with a sequence of reagents like LAH, TsCl and NaCN. The nitrile (11) was then reacted with HCl to get halo-nitrile (12) which on reaction with LDA furnished the cyano-cyclopropane and this on hydrolysis afforded the benzo-spirofused cyclopropane carboxylic acid (6).

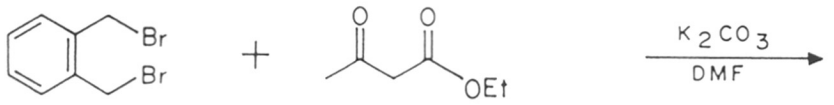
The benzo-spirofused cyclopropane carboxylic acid (7) was synthesised from benzofused cyclobutanoic acid (13). This on sequential treatment with diazomethane and CH_3MgI yielded the tertiary alcohol (14). Dehdyration ($POCl_3$/Py) gave the tetrasubstituted olefin (15). The olefin function was cyclopropanated with ethyl diazo acetate and then saponified to get the acid (7).

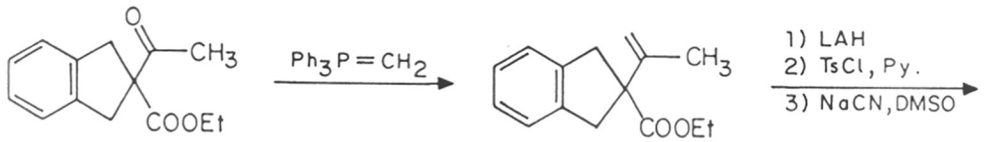
The last benzo-spirofused cyclopropane carboxylic acid (8) was prepared from 2-carbethoxy-tetrahydronaphthalene (16). The ester was converted to tertiary alcohol (17) with CH_3MgI. It was then dehydrated, cyclopropanated and saponified (in this order) to furnish the cyclopropane carboxylic acid (8).

Recently, the work on benzo-spirofused cyclopropane carboxylic acid was also carried out in our laboratory[5]. The compounds which were synthesized

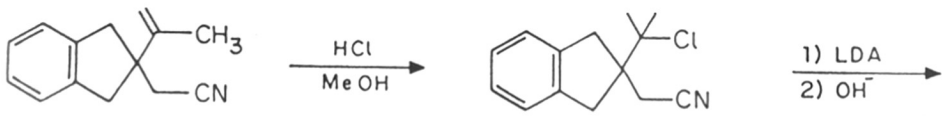
CHART - III

(A): SYNTHESIS OF BENZO - SPIROFUSED CYCLOPROPANE CARBOXYLIC ACID 6 :





(9) (10)

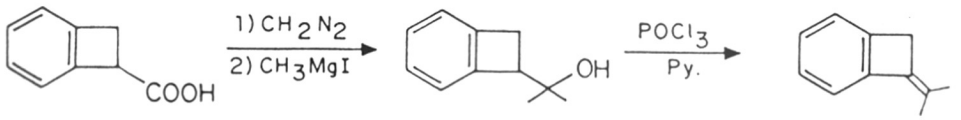


(11) (12)

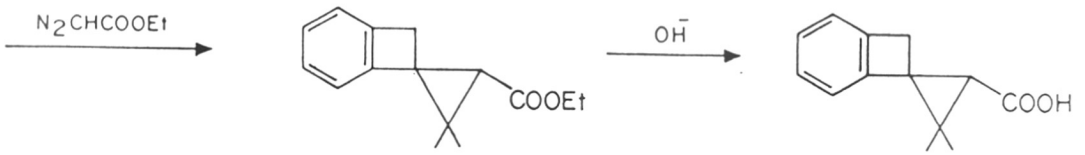
(6)

CHART- III (contd.)

B : SYNTHESIS OF BENZO-SPIROFUSED CYCLOPROPANE CARBOXYLIC ACID 7:

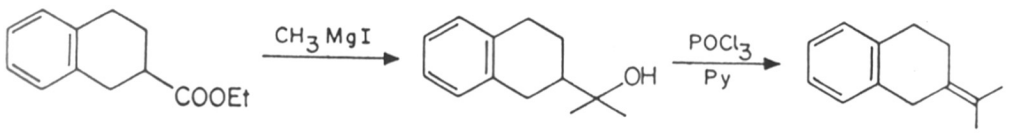


(13) (14) (15)

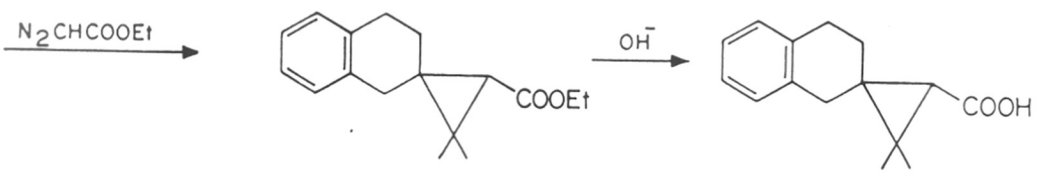


(7)

C SYNTHESIS OF BENZO-SPIROFUSED CYCLOPROPANE CARBOXYLIC ACID 8:



(16) (17)



(8)

in our laboratory, showed activity against M. domestica at micro-dosage level. The synthetic strategy (chart IV) adopted, used 2-isopropylidene-1-indanone/tetralone (18) as the starting materials. Reaction of (18) with the sulfur ylide (19) gave the cyclopropane carboxylates (20) which were then saponified to yield benzo-spirofused cyclopropane carboxylic acids (21).

The encouraging results described above, prompted us to explore further, this promising area of research with ample scope for the study of structure-activity relationship, which is an important aspect of pyrethroid research.

Our proposed scheme is outlined in chart V and discussed below.

We planned to start our scheme with 2-isobutylidene-1-indanone/tetralone (22, n=1,2). The borohydride reduction of (22) was expected to afford the allylic alcohols (23), which, in turn, were expected to furnish the ene-esters (24) on Claisen orthoester rearrangement with triethyl orthoacetate. We planned to convert these ene-esters (24) into dihalo esters (25), by addition of halogen to the double bond of (24). The dihalo esters (25) were then to be cyclized selectively at the homobenzylic position by treatment with a base like LDA to get esters (26). It was then planned to reduce the benzylic halogen to afford the cyclopropane esters (27) and convert these ethyl esters into cyano esters (28). Both the cyano esters were to be tested for their possible insecticidal activity against M. domestica.

However, the sequence of reactions proposed above, could not be carried out successfully and this chapter describes a series of unexpected reactions, encountered during the practical implementation of the scheme.

Sodium borohydride reduction of 2-isobutylidene-1-indanone/tetralone (22, n=1,2) in methanol under mild experimental condition (and without

CHART-IV

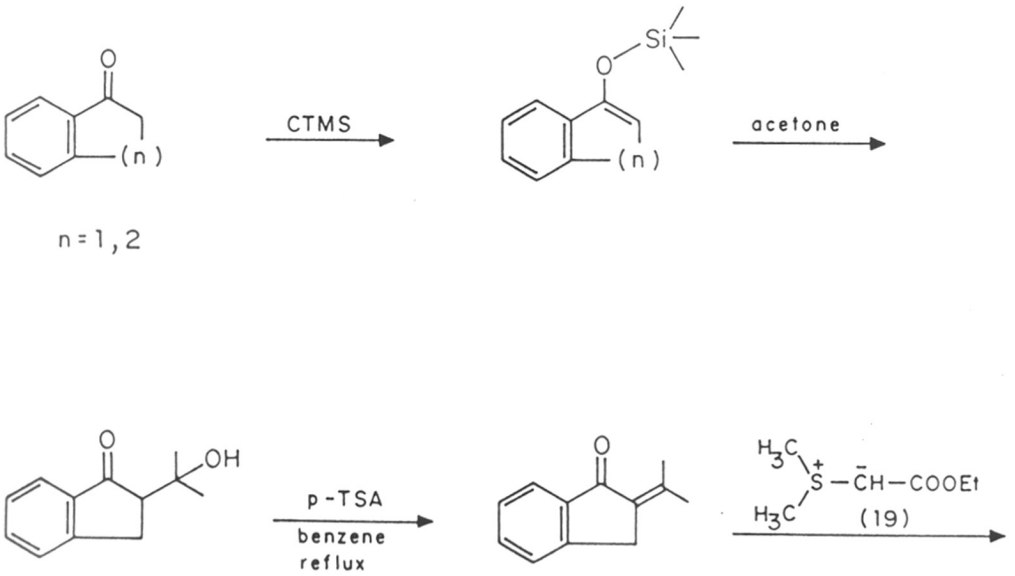
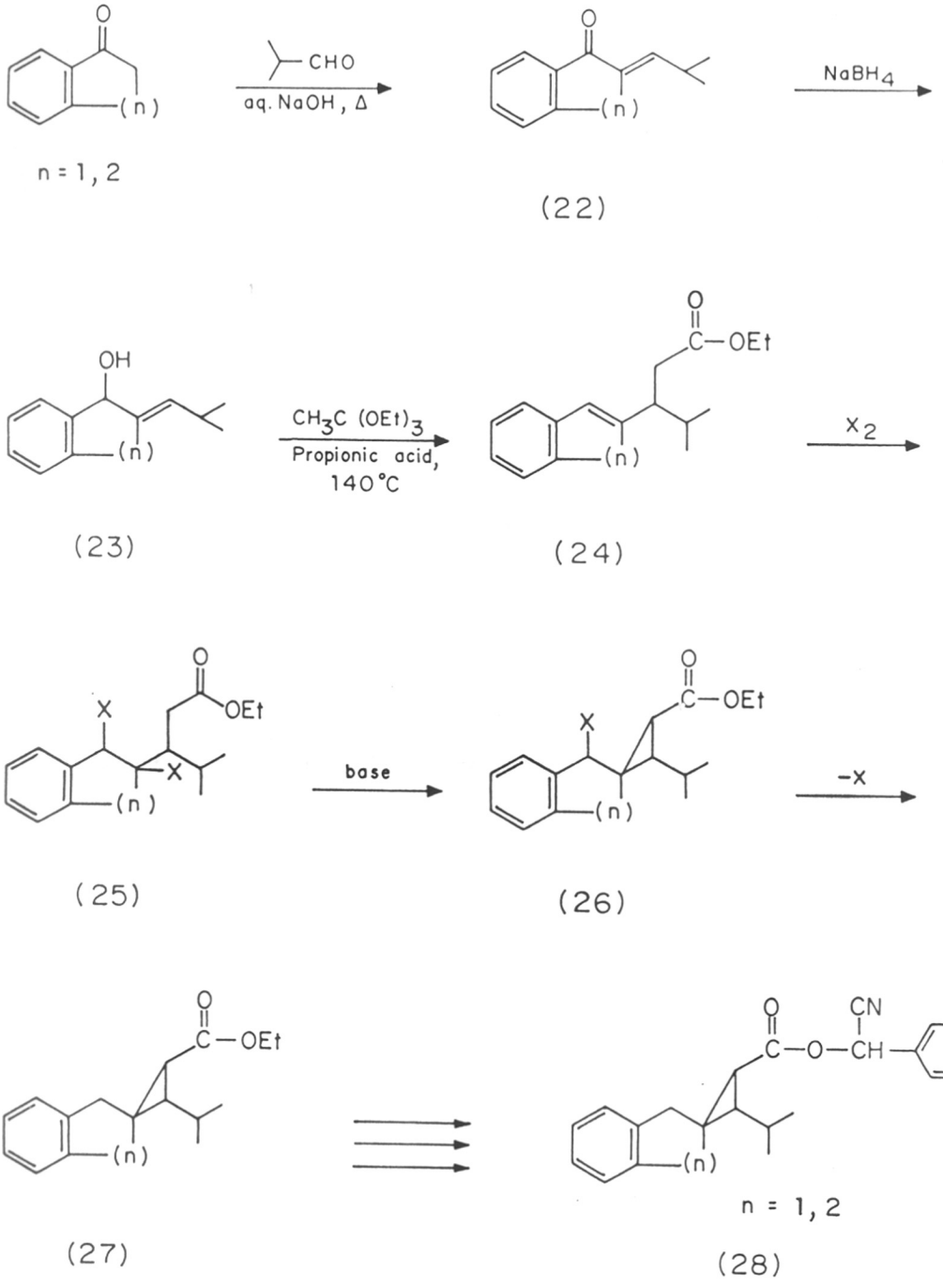

O
(n)
CTMS
Si
O
(n)
acetone
n = 1, 2
OH
p-TSA
benzene
reflux
H3C
S
CH—COOEt
H3C
(19)
(18)
OEt
OH
COOH
(20)
(21)

CHART - V


O
(n)
n = 1, 2
CHO
aq. NaOH, Δ
(22)
NaBH4
OH
(23)
CH3C (OEt)3
Propionic acid,
140 °C
C—OEt
(24)
X2
X
(25)
base
(26)
-X
CN
O—CH
OPh
(27)
(28)

employing any acid, either in reaction or in work-up) afforded, contrary to our expectations, the allylic alcohols (29, n=1,2) as indicated by ^1H ^1H n.m.r. spectra, instead of the normal reduction products (23, n=1,2) (chart VI,A). The structures assigned to these alcohols were further proved by oxidation studies, employing mild oxidising agent like pyridinium chlorochromate. Thus, oxidation of alcohols (29, n=1,2) by PCC in methylene chloride gave conjugated ketones (30, n=1,2) which were distinctly different from the starting ketones (22, n=1,2) in their p.m.r. signals (chart VI, A) since during work-up, no acid was employed, the possibility of an allylic rearrangement of the initially formed normal reduction products is ruled out. The charge separation (i.e. the formation of cation at some stage of the reaction) is also ruled out, because in that case, solvation by methanol (solvent) would have resulted, giving rise to the $-OCH_3$ signal in the p.m.r. of the product, which is not seen at all.

Repeated experiments by varing the reaction concentration, time and amount of borohydride used, gave the consistent results. Similar results were obtained when the borohydride reduction was carried out on 2-benzylidene-1-tetralone, although little difference was observed in the p.m.r. spectra of starting ketone and the rearranged ketone in the benzylidene series.

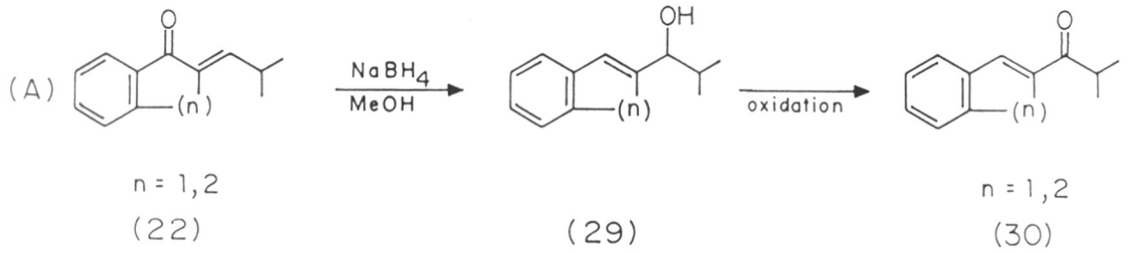
We then decided to go further with the next reaction viz. Claisen orthoester rearrangement, hoping to synthesize ultimately, the fused cyclopropane carboxylates of the type (31, n=1,2) (chart VI, B) by carrying out the sequential reactions mentioned in the chart V. But here again, totally unexpected products were obtained when the allylic alcohols (29,

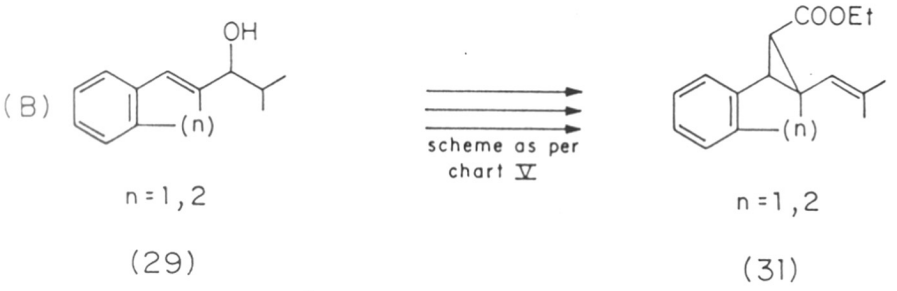
n=1,2) were subjected to Claisen orthoester rearrangement. These unexpected products were characterized from their i.r., p.m.r and mass as the hydrocarbons (32, n=1,2) (chart VI, C). Since the abnormality observed during the borohydride reduction and Claisen orthoester rearrangement were reproducible in indanone as well as tetralone series, we thought that the hydrogenolysis observed during Claisen orthoester rearrangement is taking place in molecules of the type,  . We decided to try this reaction on other compound containing this framework. Reaction, therefore, was carried out on compound (33) with a view to see whether we can generalize the above mentioned reaction. Compound (33) was easily obtained by aldol condensation between cyclopentanone and benzaldehyde, followed by borohydride reduction (chart VI, D). But during Claisen rearrangement, neither normal Claisen product, nor the hydrogenolysis product was obtained. What we observed during the Claisen conditions was the simple dehydration to give the diene (34) while the treatment of alcohol (33) at room temperature with $BF_3.Et_2O$ and triethyl orthoacetate gave the o-ethylated product (35).

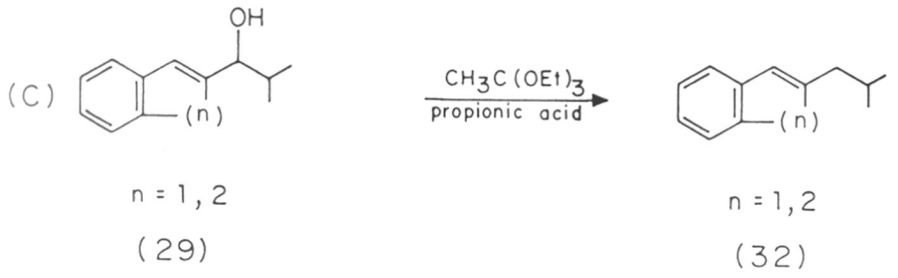
No other byproducts were obtained in all above reactions, which made the task of suggesting even a tentative mechanism, difficult.

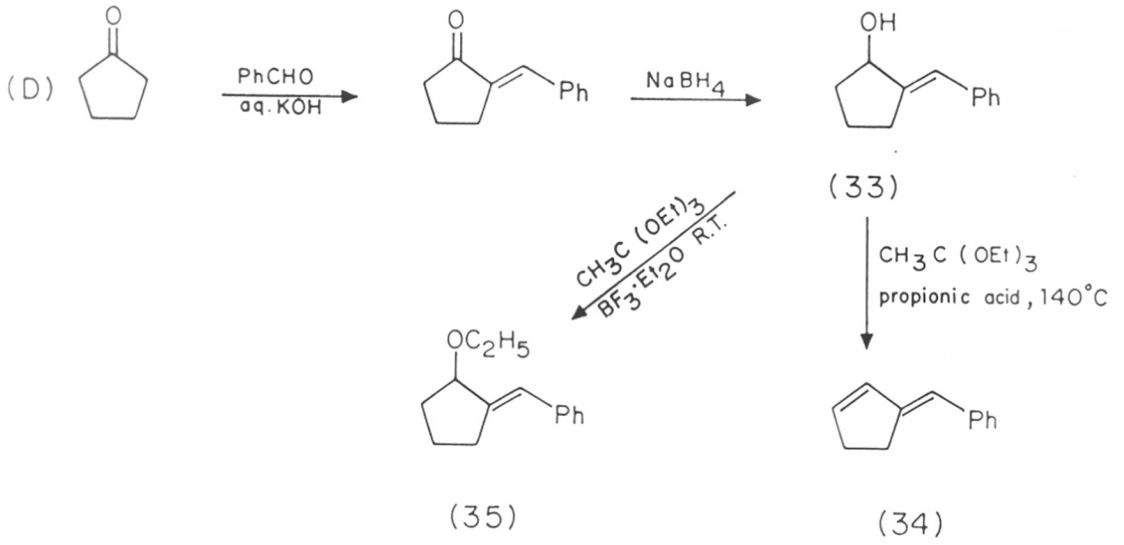
Despite the failures encountered above, we were still interested in spiro-fused cyclopropane carboxylates. Hence we thought of a new strategy to synthesize spiro-fused cyclopropane carboxylates of the type (41). The new strategy that we thought of, is as shown in chart VII A. Wittig-Horner reaction of 1-indanone with ylide generated from triethylphosphono-2-propionate and sodium hydride was expected to give conjugated ester (36) which on selective reduction with aluminium hydride should afford allylic alcohol

CHART - VI


(A)
NaBH4
MeOH
oxidation
n = 1,2
(22)
(29)
n = 1,2
(30)


(B)
scheme as per chart V
n = 1,2
(29)
n = 1,2
(31)

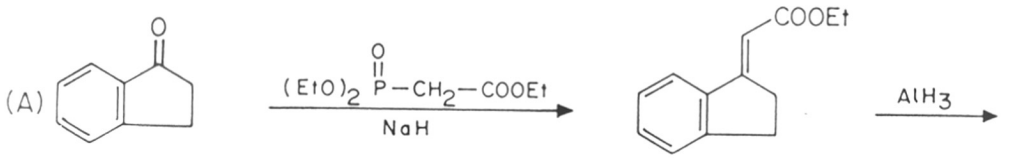

(C)
CH3C(OEt)3
propionic acid
n = 1,2
(29)
n = 1,2
(32)


(D)
PhCHO
aq. KOH
NaBH4
(33)
CH3C(OEt)3
BF3·Et2O R.T.
CH3C(OEt)3
propionic acid, 140°C
(35)
(34)

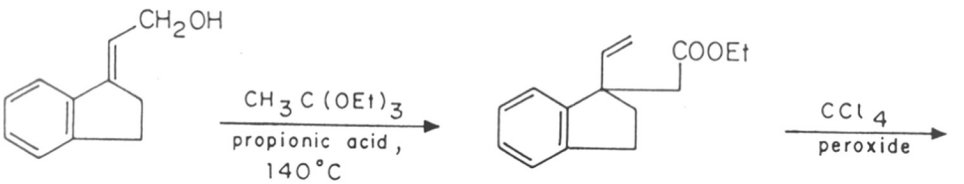
(37). This on Claisen orthoester rearrangement was expected to yeld ene-ester (38). Free radical addition of CCl_4 to the double bond should furnish tetrachloro ester (39) which on treatment with base should give benzo-spirofused cyclopropane carboxylate (40) which was to be converted to α-cyano ester (41). This cyano ester was then to be tested for its insecticidal acitivity. The indanone moiety was chosen with a view to get more activity (chart II).

The first reaction viz. Wittig Horner, gave the required conjugated ester (36) as per expectations, although in low yield. But the aluminium hydride reduction failed to provide the necessary allylic alcohol (37). Instead, we isolated the homoallylic alcohol (37A) (chart VIIB). It was also characterized as its acetate (42). Since the required allylic alcohol (37) (necessary for Claisen rearrangement) could not be obtained, we could not proceed with the proposed scheme of chart VIIA.

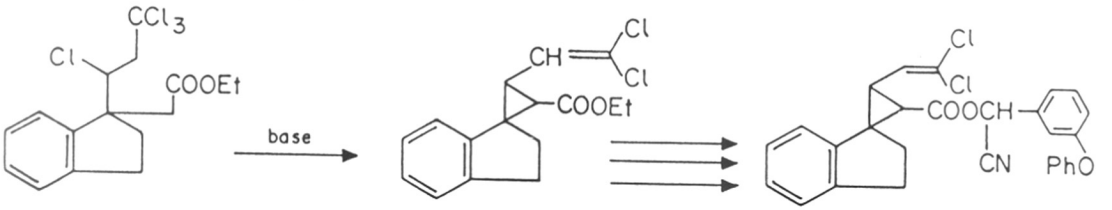
CHART - VII



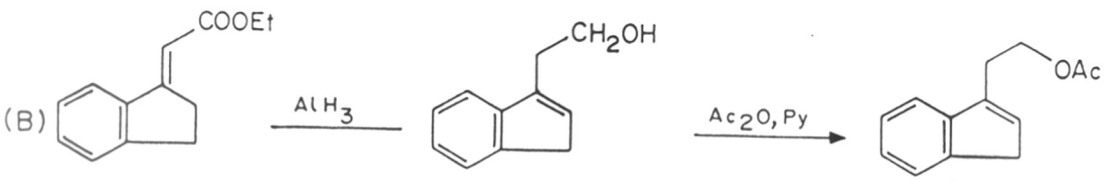
(36)



(37) (38)



(39) (40) (41)



(36) (37 A) (42)

PRESENT WORK

The following text describes the observations made regarding the spectral characteristics of the compounds isolated while carrying out our proposed scheme.

The aldol condensation of 1-indanone with isobutyraldehyde in presence of aqueous sodium hydroxide at 60-70°C afforded the conjugated ketone (22, n=1) in good yields.

IR: 1710, 1655, 1620.

PMR: 1.11 (6H, d, 7 Hz, isopropylmethyls), 2.46-2.87 (1H, m, isopropyl methine proton), 3.64 (2H, fine doublet, 2 Hz, benzylic methylenes split due to allylic coupling). 6.71 [1H, d split into two t, 2 Hz (allylic coupling), 10 Hz (main doublet)], 7.33-7.6 (3H, m, aromatic protons), 7.84 (1H, d, 8 Hz, aromatic proton).

Sodium borohydride reduction of (22, n=1) in methanol at room temperature gave the unexpected allylic alcohol (29, n=1).

IR: 3400, 1615,

PMR: 0.86 and 0.98 (3H each, d each, 7 Hz each, isopropylmethyls), 1.67-2.11 (1H, m, isopropyl methine proton), 2.0 (1H, s, D_2O exchangeable, -OH), 3.31 (2H, s, benzylic protons), 4.24 (1H, d, 8 Hz, CH-OH), 6.64 (1H, s, olefinic proton), 7.0-7.44 (4H, m, aromatic protons).

PCC oxidation of alcohol (29, n=1) in methylene chloride gave 2-isobutanoylindene (30, n=1)

IR: 1670, 1620.

PMR: 1.0 and 1.19 (3H each, d each, 6.4 Hz each, isopropyl methyls), 3.09-3.5 (1H, m, isopropyl methine proton), 3.69 (2H, br s, benzylic protons), 7.27-7.81 (5H, m, aromatic protons and olefinic proton).

Allylic alcohol (29, n=1) was heated with triethyl orthoacetate and propionic acid (as a catalyst) at 140°C for 4 hr to get the hydrocarbon (32, n=1).

IR: 1615.

PMR: 0.94 (6H, d, 6.4 Hz, isopropyl methyls), 1.69-2.09 (1H, m, isopropyl methine proton), 2.31 (2H, d, 6.4 Hz, allylic methylene protons on the side chain), 3.25 (2H, s, benzylic protons), 6.44 (1H, s, olefinic proton), 7.0-7.38 (4H, m, aromatic protons).

Similarly, 1-tetralone was also heated with isobutyraldehyde in presence of aqueous sodium hydroxide at 60-70°C to furnish 2-isobutylidene-1-tetralone (22, n=2)

IR: 1680, 1620.

PMR: 1.06 (6H, d, 6.4 Hz, isopropylmethyls), 2.5-3.06 (5H, m, two benzylic protons and three allylic protons), 6.75 (1H, d, 9.6 Hz, olefinic proton), 7.09-7.5 (3H, m, aromatic protons), 8.09 (1H, d, 6.4 Hz, aromatic proton).

Sodium borohydride reduction of conjugated ketone (22, n=2) at room temperature furnished the allylic alcohol (29, n=2).

IR: 3460.

PMR: 0.91 (6H, two d overlapping to give a t, $J_1=J_2=6.4$ Hz, isopropylmethyls), 1.65-2.0 (1H, m, isopropyl methine proton), 2.06-2.38 (2H, m, allylic protons), 2.63-2.94 (2H, m, benzylic protons), 3.88 (1H, d, 6.4 Hz, <u>CH</u>-OH), 6.34 (1H, s, olefinic proton), 7.06 (4H, m, aromatic protons).

PCC oxidation of the allylic alcohol (29, n=2) in methylene chloride at room temeprature afforded the conjugated ketone (30, n=2).

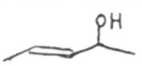
IR: 1670, 1630.

PMR: 1.13 (6H, d, 6.4 Hz, isopropyl methyls), 2.38-2.94 (4H, m, allyic and benzylic protons), 3.16-3.66 (1H, m, proton α to carbonyl), 7.19 (4H, s, aromatic protons), 7.38 (1H, s, olefinic proton).

The allylic alcohol (29, n=2) was heated with triethyl orthoacetate and propionic acid (as a catalyst) at 140°C for 4 hr to furnish the hydrocarbon (32, n=2).

IR: 1650.

PMR: 0.77 (6H, d, 6 Hz, isopropylmethyls), 1.57-2.2 (5H, m, four allylic protons and one isopropyl methine proton), 2.35-2.8 (2H, m, benzylic protons), 5.95 (1H, s, olefinic proton), 7.0 (4H, s, aromatic protons).

To see whether hydrogenolysis is taking place during Claisen orthoacetate conditions is also reproducible in other systems of the type 

, we prepared 2-benzylidene cyclopentanol by reducing 2-benzylidene cyclopentanone, which in turn, was prepared by aldol condensation of cyclopentanone, benzaldehyde and aqueous sodium hydroxide.

Thus, the aldol condensation between cyclopentanone and benzaldehyde in presence of aqueous sodium hydroxide at room temperature gave the 2-benzylidene cyclopentanone.

IR: 1710, 1630.

PMR: 1.91-2.22 (2H, m, methylene protons at C-4 of cyclopentanone), 2.42 (2H, t, 7 Hz, protons α to carbonyl group), 2.99 (2H, t, split

due to allylic coupling, J=2 Hz (allylic coupling), 7 Hz, allylic methylene protons), 7.31-7.64 (5H, m, aromatic protons).

Sodium borohydride reduction of 2-benzylidene cyclopentanone in methanol at room temeprature gave the allylic alcohol (33).

IR: 3350, 1600.

PMR: 1.27-1.83 (4H, m, methylene protons at C-4 and C-5 of cyclopentanol), 2.17-2.83 (2H, m, allylic protons at C-3 of cyclopentanol), 4.27 (1H, m, CH-OH), 6.28 (1H, s, olefinic proton), 7.03 (5H, s, aromatic protons).

By subjecting allylic alcohol (33) to reaction with triethyl ortho- - acetate amd propionic acid (as a catalyst) at 140°C for 4 hr, mainlydehydration took place giving 3-benzylidene cyclopentene (34).

IR: 1520.

PMR: 2.55-3.0 (4H, m, allylic protons), 6.08-6.44 (3H, m, olefinic protons), 7.29-7.42 (5H, m, aromatic protons).

Treating the alcohol (33) to triethyl orthoacetate and $BF_3.Et_2O$ (catalyst) at room temperature, gave the 2-benzylidene-1-ethoxy cyclopentane (35).

IR: 1600.

PMR: 1.2 (3H, t, 7 Hz, CH_3-CH_2), 1.61-2.0 (4H, m, methylene protons at C-4 and C-5 of cyclopentane), 2.42-2.71 (2H, m, allylic methylene protons), 3.5 (2H, q, 7Hz, O-CH_2-CH_3), 4.07-4.27 (1H, m, CH-OEt), 6.5 (1H, fine d, 2 Hz, olefinic proton), 7.26 (5H, m, aromatic protons).

Spectral characteristics for 2-benzylidene tetralone series

The aldol condensation between 1-tetralone and benzaldehyde in presence

of aqueous sodium hydroxide solution gave the 2-benzylidene tetralone as a solid.

IR: 1670, 1610, 1600.

PMR: 2.75-3.25 (4H, m, benzylic and allyic protons), 7.2-7.5 (8H, m, aromatic protons), 7.81 (1H, s, olefinic proton), 8.09 (1H, d, 6.4 Hz, aromatic proton).

Sodium borohydride reduction of 2-benzylidene-1-tetralone furnished the alcohol whose spectral properties are as shown below.

IR: 3400, 1610.

PMR: 2.06-2.28 (3H, m overlapping s, allylic protons and -OH proton), 2.72 (2H, t, 8 Hz, benzylic protons), 5.25 (1H, s, CH-OH), 6.59 (1H, fine d, 2 Hz, olefinic proton), 7.0-7.44 (9H, m, aromatic protons).

PCC oxidation of the alcohol as described above furnished 2-benzoyl 3,4-dihydro naphthalene.

IR: 1650, 1620.

PMR: 2.5-3.0 (4H, m, two allylic and two benzylic protons), 7.0-7.81 (10H, m, olefinic and aromatic protons).

α,β-Unsaturated ester (36)

Wittig-Horner reaction on 1-indanone with the ylide generated from triethyl phosphono acetate and sodium hydride in THF at room temperature furnished the above mentioned ester in low yield.

IR: 1710, 1640, 1600.

PMR: 1.27 (3H, t, 6.4 Hz, ester methyl), 2.81-3.37 (4H, m, allylic and benzylic protons), 4.2 (2H, q, 6.4 Hz, ester methylene), 6.22 (1H, s split into t due to allylic coupling, 2 Hz, (allylic coupling) olefinic proton), 7.2-7.61 (4H, m, aromatic protons).

Aluminium hydride reduction of the α,β-unsaturated esster (**36**) gave 'the double bond migrated' alcohol (**37A**).

IR: 3400, 1600.

PMR: 1.91 (1H, br s, D_2O exchangeable, -OH), 2.82 (2H, t split due to allylic coupling, 2 Hz (allylic coupling) 7 Hz, allylic methylene protons on the side chain), 3.33 (2H, br s, benzylic protons), 3.88 (2H, t, 7 Hz, $-\underline{CH_2}-OH$), 6.31 (1H, br s, olefinic proton), 7.0-7.55 (4H, m, aromatic protons).

Acetylation of alcohol (**37A**) acetic anhydride and pyridine at room temperature furnished the corresponding acetate (**42**).

IR: 1740, 1610.

PMR: 2.0 (3H, s, $-OCOCH_3$), 2.88 (2H, t, split due to allylic coupling, 2 Hz, (allylic coupling), 7 Hz, allylic protons on the side chain), 3.32 (2H, fine d, 2 Hz, benzylic protons), 4.35 (2H, t, 8 Hz, CH_2-OCO), 6.24 (1H, fine t, 2 Hz (allylic coupling), olefinic proton), 7.13-7.37 (4H, m, aromatic protons).

EXPERIMENTAL

2-Isobutylidene-1-tetralone (22, n = 2)

A mixture of 1-tetralone (5 g, 0.034 mole), isobutyraldehyde (4.94 g, 0.068 mole), sodium hydroxide (1.4 g, 0.034 mole) in 37 ml water was initially heated at 60°C and followed by TLC. It was then acidified and extracted repeatedly with ether. Combined ether layer was washed with water, brine and dried. Ether was removed and crude product was purified by chromatography on silica gel. Elution with pet.ether + 40% benzene gave the pure (22, n = 2) 5.2 g (76%) as a thick liquid.

IR: 2960, 1680, 1620, 1310, 1240, 910.

Mass: M^+ - 200.

Elemental analysis for $C_{14}H_{16}O$

calculated: C, 83.96; H, 8.05

observed: C, 83.85: H, 7.96%.

Allylic alcohol (29, n = 2)

Conjugated ketone (22, n=2) (5 g, 0.025 mole) was taken up in methanol (50 ml). To it was added, portionwise, sodium borohyride (1.13 g, 0.029 mole). The reaction contents were stirred at room temperature for 4 hr. Methanol was removed under vacuum. Residue was taken up in ether and washed with water, brine and dried. Removal of solvent gave a crude product which was purified on silica gel by eluting with pet.ether + 60% benzene to afford 3.76 g (74%) pure alcohol (29, n=2) as a colorless liquid.

IR: 3400, 2980, 1490, 1010, 890.

Mass: M^+ - 202.

Elemental analysis for $C_{14}H_{18}O$

calculated: C, 83.12· H, 8.97

observed : C, 82.99; H, 8.85%.

2-Isobutanoyl-3,4-dihydro napthalene (30, n=2)

PCC (0.64 g, 0.003 mole) was suspended in dry methylene chloride (6 ml). To this stirred suspension, was then added allylic alcohol (29, n=2) (0.5 g, 0.0024 mole) in dry methylene chloride (2 ml) in one lot. The reaction mixture was stirred at room temperature and followed by T.L.C. The reaction mixture was then filtered through celite. Removal of solvent gave 0.38 g (78%) pure ketone (30, n=2) as thick liquid.

IR: 2980, 1670, 1630, 1570, 1390, 1275, 1150.

Mass: M^+ - 200.

Elemental analysis for $C_{14}H_{16}O$

calculated: C, 83.96; H, 8.05

observed: C, 83.82; H, 7.91%.

2-Isobutyl-3,4-dihydro naphthalene (32, n=2)

Allylic alcohol (29, n=2) (3 g, 0.015 mole) was taken up in triethyl orthoacetate (7.23 g, 0.045 mole). 2-3 drops of propionic acid were added to it. The mixture was heated at 140°C for 4 hr. Continuous removal of ethanol was maintained during this time. Excess of triethyl orthoacetate was removed by distillation. The residue was diluted with pet.ether and passed through a short column of silica gel. Removal of pet.ether furnished pure (32, n=2), 1.83 g (66%) as mobile liquid.

IR: 2980, 1650, 1455, 1370, 1035.

Mass: M^+ - 186.

Elemental analysis for $C_{14}H_{18}$

calculated: C, 90.26; H, 9.74

observed: C, 90.11; H, 9.61%.

2-Isobutylidene-1-indanone (22, n=1)

A mixture of 1-indanone (5 g, 0.038 mole), isobutyraldehyde (5.46 g, 0.076 mole) and sodium hydroxide (1.6 g, 0.04 mole) in water (40 ml) was heated at 60°C and the progress of the reaction followed by T.L.C. The reaction mixture was then acidified and extracted repeatedly with ether. Combined ether layer was washed with water, brine and dried. Removal of solvent gave a crude product which was purified by chromatography over silica gel. Elution with pet.ether + 35% benzene gave 5.75 g (81%) pure (22, n=1) as a thick liquid.

IR: 2980, 1710, 1655, 1620, 1470, 1270, 910.

Mass: M^+ -186.

Elemental analysis for $C_{13}H_{14}O$

calculated: C, 83.83; H, 7.58

observed: C, 83.66; H, 7.49%.

Allylic alcohol (29, n=1)

Conjugated ketone (22, n=1) (5 g, 0.027 mole) was taken up in methanol (50 ml). Sodium borohydride (1.22 g, 0.032 mole), was added to it, portion-wise. After the addition, reaction mixture was stirred at room temperature for 4 hr. Methanol was removed under vacuum. Residue was diluted with ether and ether layer was washed with water, brine and dried. Removal of ether gave the crude product which was purified on silica gel. Elution with pet ether + 45% benzene gave 3.84 g(76%) pure(29,n=1),as a colorless liquid.

IR: 3400, 2980, 1615, 1465, 1400, 1020, 870.

Mass: M^+ - 188

Elemental analysis for $C_{13}H_{16}O$

calculated: C, 82.93; H, 8.57

observed: C, 82.77; H, 8.45%.

2-Isobutanoyl indene (30, n=1)

PCC (0.69 g, 0.003 mole) was suspended in dry methylene chloride (6 ml). To this stirred suspension was then added, allylic alcohol (29, n=1) (0.5 g, 0.0024 mole) in dry methylene chloride (2 ml) in one lot. The reaction mixture was then stirred at room temperature and followed by T.L.C. It was then filtered through celite and removal of solvent from filterate gave 0.36 g (72%) pure ketone (30, n=1) as thick liquid.

IR: 2980, 1670, 1620, 1470, 1390, 1140.

Mass: M^+ - 186.

Elemental analysis for $C_{13}H_{14}O$

calculated: C, 83.83; H, 7.58

observed: C, 83.69; H, 7.41%.

2-Isobutyl indene (32, n=1)

Allylic alcohol (29, n=1) (3 g, 0.016 mole) was dissolved in triethyl orthoacetate (7.76 g, 0.047 mole). To it, were added 2-3 drops of propionic acid. The solution was heated at 140°C for 4 hr. Excess of triethyl orthoacetate was then distilled off. Residue was diluted with pet.ether and passed through a short column of silica gel. Removal of solvent gave 1.88 g (69%) pure hydrocarbon (32, n=1).

IR: 2960, 1615, 1465, 1370, 1205, 1020.

Mass: M^+ - 172.

Elemental analysis for $C_{13}H_{16}$

calculated: C, 90.64; H, 9.36

observed: C, 90.47; H, 9.22%.

2-Benzylidene cyclopentanone

A mixture of cyclopentanone (3 g, 0.036 mole), benzaldehyde (1.89 g 0.018 mole) and sodium hydroxide (0.89 g, 0.022 mole) dissolved in water (35 ml) was stirred for 1 hr at room temperature. Alkali was neutralized with addition of dilute hydrochloric acid. It was then extracted repeatedly with ether. Ether layer was washed with water, brine and dried. Removal of ether, gave the oil which was distilled 165-168°/10 mm to get 2.14 g (69%) pure 2-benzylidene cyclopentanone which solidified upon cooling. It was crystallized from hexane-methanol to give yellow crystals, m.p.68-69°C.

IR: 2920, 1710, 1630, 1450, 1230, 1180, 930.

Mass: M^+ - 172.

Elemental analysis for $C_{12}H_{12}O$

calculated: C, 83.69; H, 7.02

observed: C, 83.57; H, 6.88%.

2-Benzylidene cyclopentanol (33)

2-Benzylidene cyclopentanone (2 g, 0.012 mole) was dissolved in methanol (25 ml). To it, was added, sodium borohydride (0.53 g, 0.014 mole) in small portions. The reaction contents were stirred at room temperature for 4 hr. Methanol was removed under vacuum, residue was diluted with water. Extracted with ether. Ether layer was washed with water, brine and dried. Removal of solvent gave crude product which was purified upon silica gel by eluting with pet.ether + 60% benzene. It yielded 1.83 g (90%) pure (33) as thick liquid.

IR: 3350, 2980, 1600, 1490, 1450, 1090, 915.

Mass: M^+ - 174.

Elemental analysis for $C_{12}H_{14}O$

calculated: C, 82.72; H, 8.10

observed: C, 82.56; H, 7.96%.

2-Benzylidene cyclopentene (34)

Allylic alcohol (33) (0.5 g, 0.0029 mole) was dissolved in triethyl orthoaceatate (0.93 g, 0.0057 mole) and a drop of propionic acid was added to it. The mixture was then heated at 140°C for 4 hr. Unreacted triethyl orthoacetate was removed and residue diluted with pet.ether. The pet.ether solution was passed through a short column of silica gel. Removal of pet. ether furnished 0.31 g (70%) pure (34) as a mobile liquid.

IR: 2920, 1520, 1380, 1020, 890.

Mass: M^+ - 156.

Elemental analysis for $C_{12}H_{12}$

calculated: C, 92.26; H, 7.74

observed: C, 92.15; H, 7.56%.

1-Ethoxy-2-benzylidene cyclopentane (35)

Allylic alcohol (**33**) (0.5 g, 0.0029 mole) was dissolved in triethyl orthoacetate (0.93 g, 0.0057 mole) and boron trifluoride etherate was added in catalytic quantity . The reaction mixture was stirred at room temperature overnight. Work-up afforded the crude product which was purified on a short column of silica gel using pet.ether as an eluant. The pure ether (**35**) was thus obtained in 0.39 g (68%) yield.

IR: 2980, 1600, 1450, 1110, 1080, 915.

Mass: M^+ - 202.

Elemental analysis for $C_{14}H_{18}O$

calculated: C, 83.12; H, 8.97

observed: C, 82.97; H, 8.8%.

Experimental for borohydride reduction of benzylidene derivatives :

2-Benzylidene-1-tetralone

When a mixture of benzaldehyde (1.45 g, 0.014 mole), 1-tetralone (2 g, 0.014 mole) was heated with 4% solution of sodium hydroxide (0.66 g, 0.016 mole), it became warm and crystals were deposited almost immediately. After 2 hr, the solution was neutralized with acetic acid. Water was added to it and the crystals were filtered off. Crystallized from ethanol to get 2.72 g (85%) pure 2-benzylidene-1-tetralone, m.p. 105°C.

IR: 1670, 1610, 1600, 1470, 1300, 960.

Mass: M^+ -234.

Elemental analysis for $C_{17}H_{14}O$

calculated: C, 87.15; H, 6.02

observed: C, 87.01; H, 5.84%.

Reduction of 2-benzylidene-1-tetralone

2-Benzylidene-1-tetralone (1 g, 0.0043 mole) was dissolved in a mixture of 20 ml methanol and 5 ml benzene. To it, was added, sodium borohydride (0.19 g, 0.005 mole) in small portions. After addition, the reaction contents were stirred at room temperature for 4 hr. Methanol was removed under vacuum. Residue was diluted with water, extracted with ether. Ether layer was washed with water, brine and dried. Removal of ether gave crude which was purified upon silica gel by eluting with pet.ether + 70% benzene. The pure reduced product was obtained in 0.76 g (76%) yield as colorless liquid.

IR: 3400, 2920, 1610, 1500, 1460, 1100, 1030.

Mass: M^+ -236.

Elemental analysis for $C_{17}H_{16}O$

calculated: C, 86.40; H, 6.83

observed: C, 86.29; H, 6.71%.

2-Benzoyl-3,4-dihydro naphthalene

To a stirred suspension of pyridinium chlorochromate (0.55 g, 0.002 mole) in dry methylene chloride (10 ml), alcohol prepared above (0.5 g, 0.002 mole) in dry methylene chloride (5 ml) was added in one lot and stirring continued and reaction followed by T.L.C. At the end of reaction, the mixture was filtered through celite. Removal of solvent gave pure 2-benzoyl-5,4-dihydronaphthalene in 0.40 g (80%) yield as a liquid.

IR: 1650, 1620, 1570, 1290, 1225.

Mass: M^+ -234.

Elemental analysis for $C_{17}H_{14}O$

calculated: C, 87.15; H, 6.02

observed: C, 87.03; H, 5.86%.

Conjugated ester (36)

To the ylide generated from triethyl phosphono-2-propionate (4 g, 0.018 mole) and sodium hydride (0.43 g, 0.018 mole) in dry tetrahydrofuran (50 ml) at 0°C, solution of 1-indanone (1.18 g, 0.009 mole) in dry tetrahydrofuran (25 ml) was added dropwise. After the addition, reaction contents were warmed to room temperature and stirred overnight at room temperature. Tetrahydrofuran was removed under vacuum and residue was diluted with water and extracted repeatedly with ether. The combined ether layer was washed with water, brine and dried. Removal of ether gave crude thick liquid which

upon purification on silica gel and elution with pet.ether + 4% ethyl acetate furnished 0.68 g (37%) pure conjugated ester (**36**).

IR: 2980, 1710, 1640, 1600, 1370, 1200, 1050.

Mass: M^+ - 202.

Elemental analysis for $C_{13}H_{14}O_2$

calculated: C, 77.20; H, 6.98

observed: C, 77.04; H, 6.81%.

Alcohol (37A):

To a stirred and ice-cooled solution of aluminium hydride, generated from aluminium chloride (0.33 g, 0.0024 mole) and lithium aluminium hydride 0.282 g, 0.0074 mole) in dry ether (5 ml), solution of ester (**36**) (0.5 g, 0.0024 mole) in dry ether (5 ml) was added dropwise. After the addition, reaction mixture stirred at room temperature for 48 hr. Even after such a prolonged stirring, much of the starting material remained unreacted. Hence reaction discontinued. Usual work-up afforded the crude product which was purified on silica gel by eluting with pet.ether + 20% ethyl acetate to give pure alcohol (**37A**) in 0.32 g (80%) yield. [depending on recovered alcohol(37A

IR: 3400, 2920, 1600, 1460, 1390, 910.

Mass: M^+ -160.

Elemental analysis for $C_{11}H_{12}O$

calculated: C, 82.46; H, 7.55

observed: C, 82.35; H, 7.4%.

Acetate (42)

To a mixture of alcohol (**37A**) (0.1 g, 0.0006 mole) in pyridine (2 ml), acetic anhydride (0.076 g, 0.00074 mole) was added and the reaction

mixture stirred at room temperature Reaction was monitored by T.L.C. Usual work-up afforded crude acetate which was purified on silica gel by elution with pet.ether + 3% ethyl aceatate to yield 0.115 g (91%) pure acetate (42).

IR: 2960, 1740, 1610, 1370, 1240, 1040.

Mass: M^+ -202.

Elemental analysis for $C_{13}H_{14}O_2$

calculated: C, 77.20; H, 6.98

observed: C, 77.03; H, 6.87%.

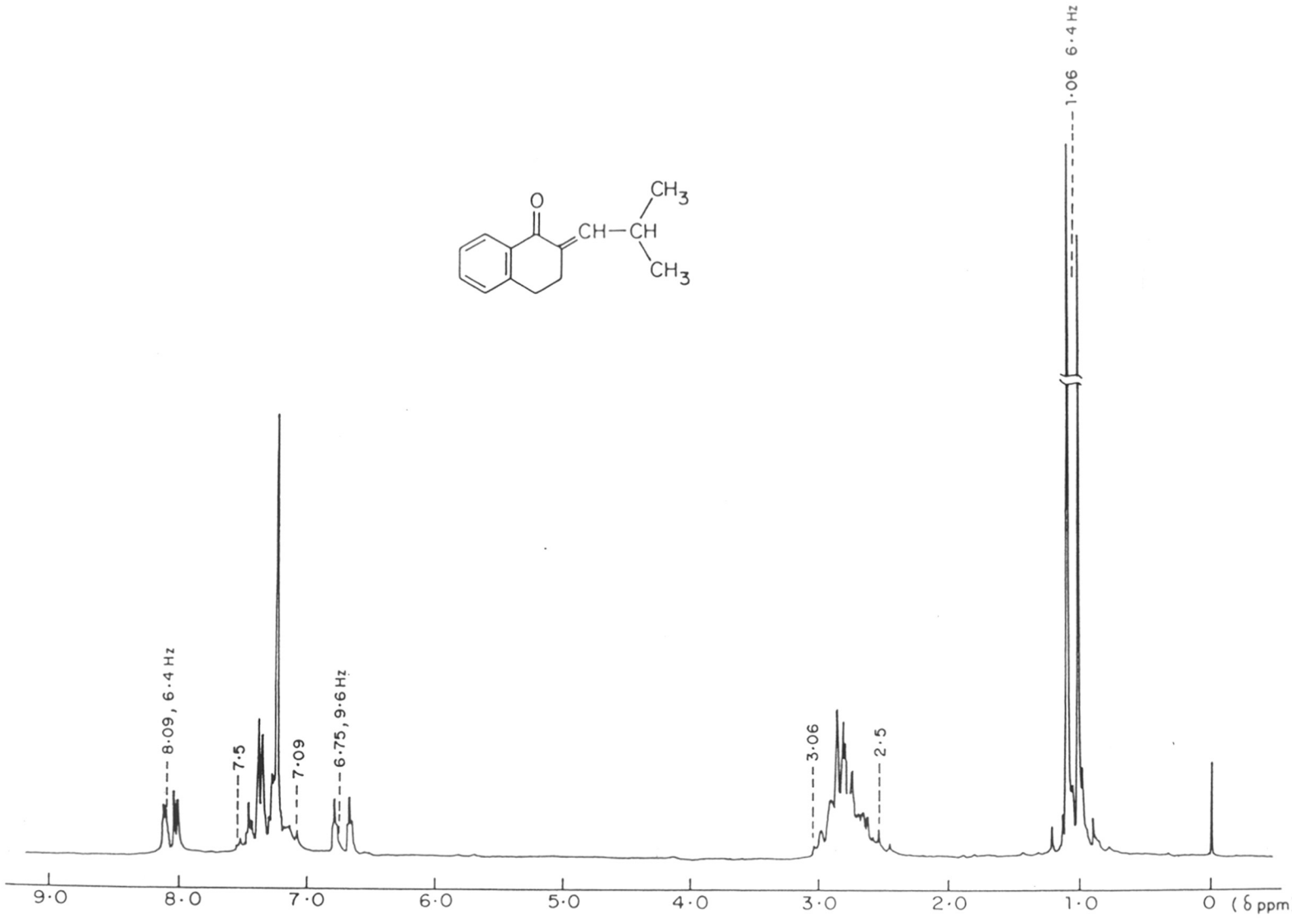


FIG. I: NMR OF COMPOUND No. (22, n=2)

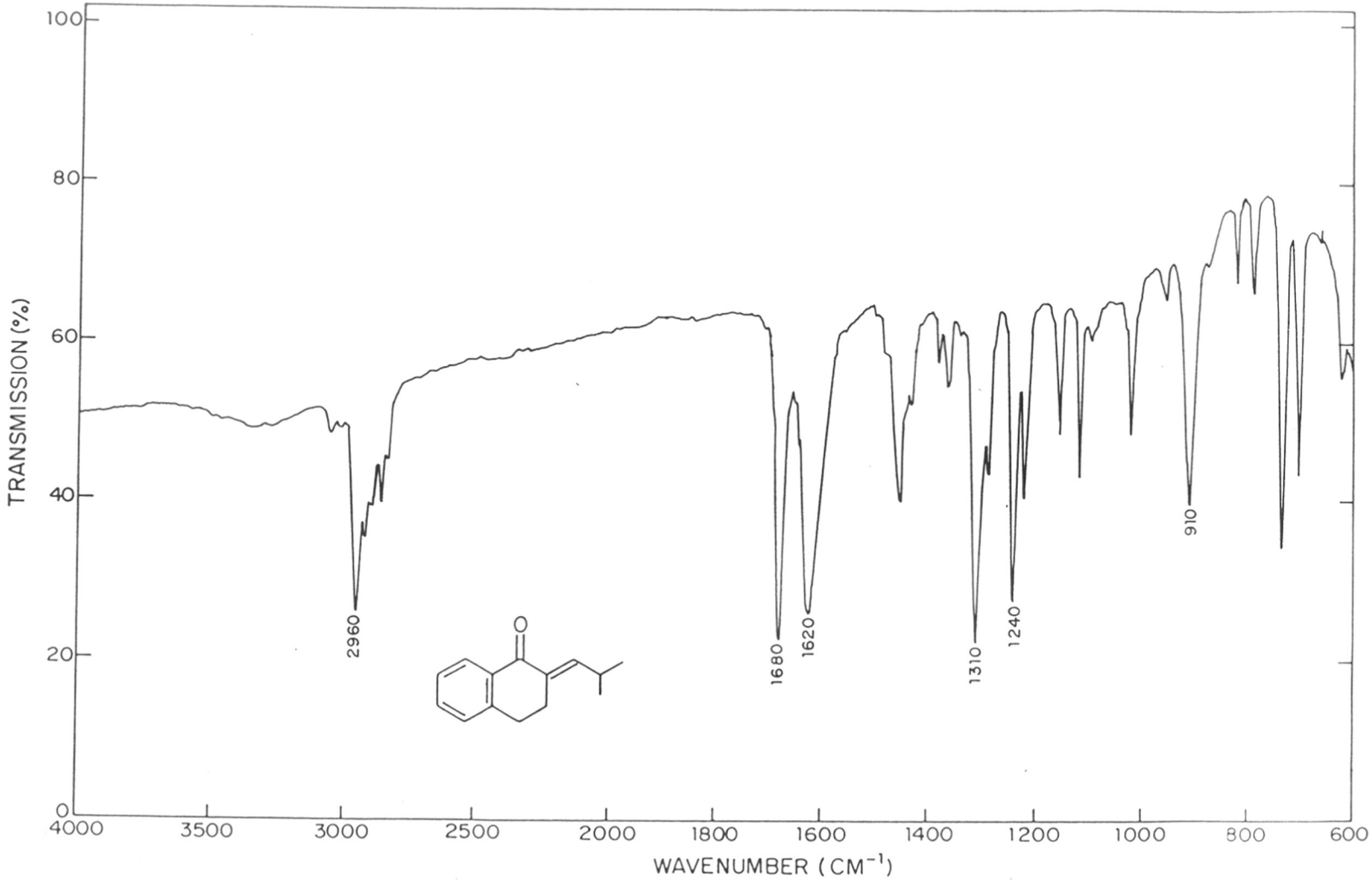


FIG. II : IR OF COMPOUND No. (22, n = 2)

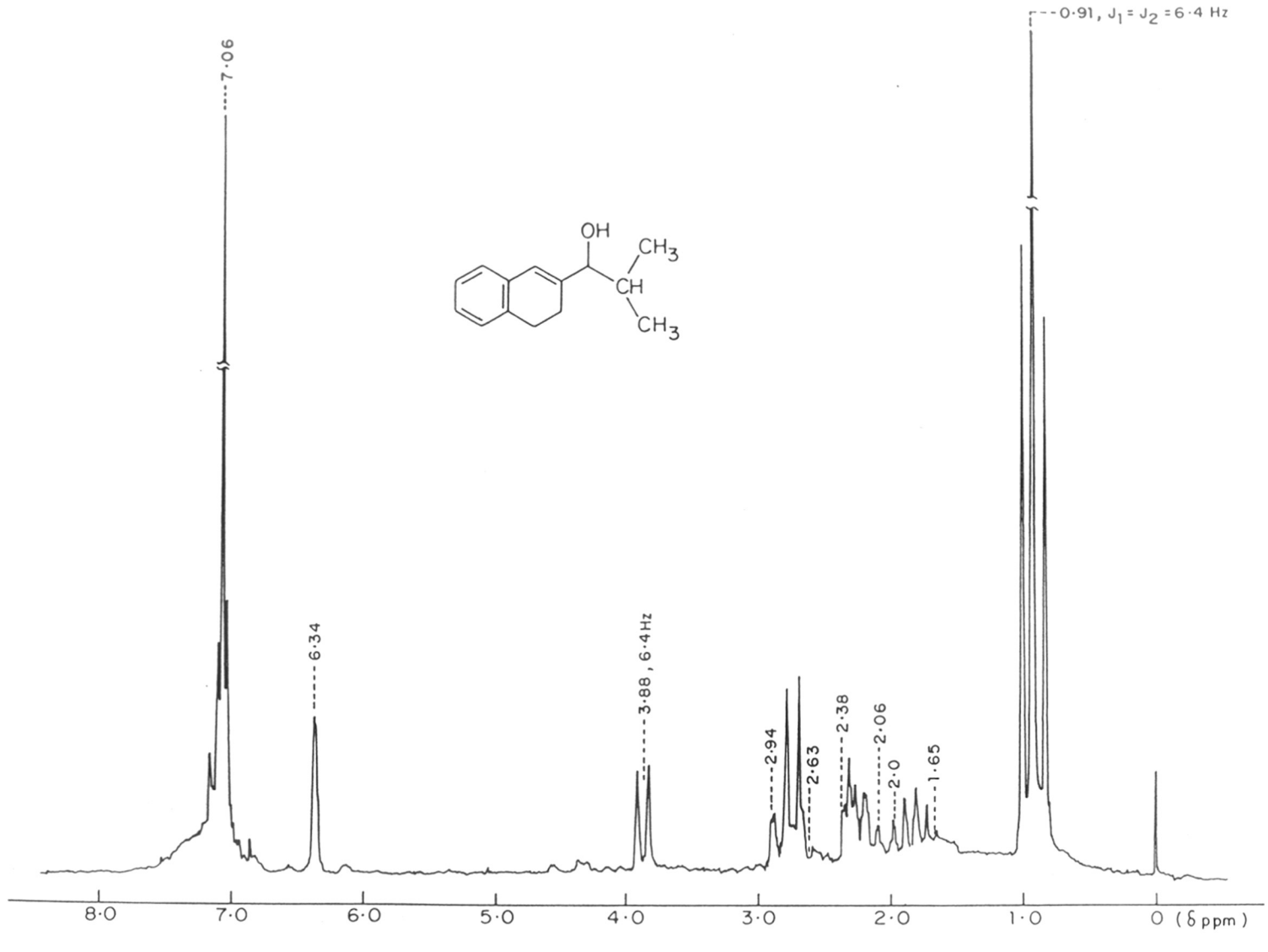


FIG. III : NMR OF COMPOUND No. (29, n=2)

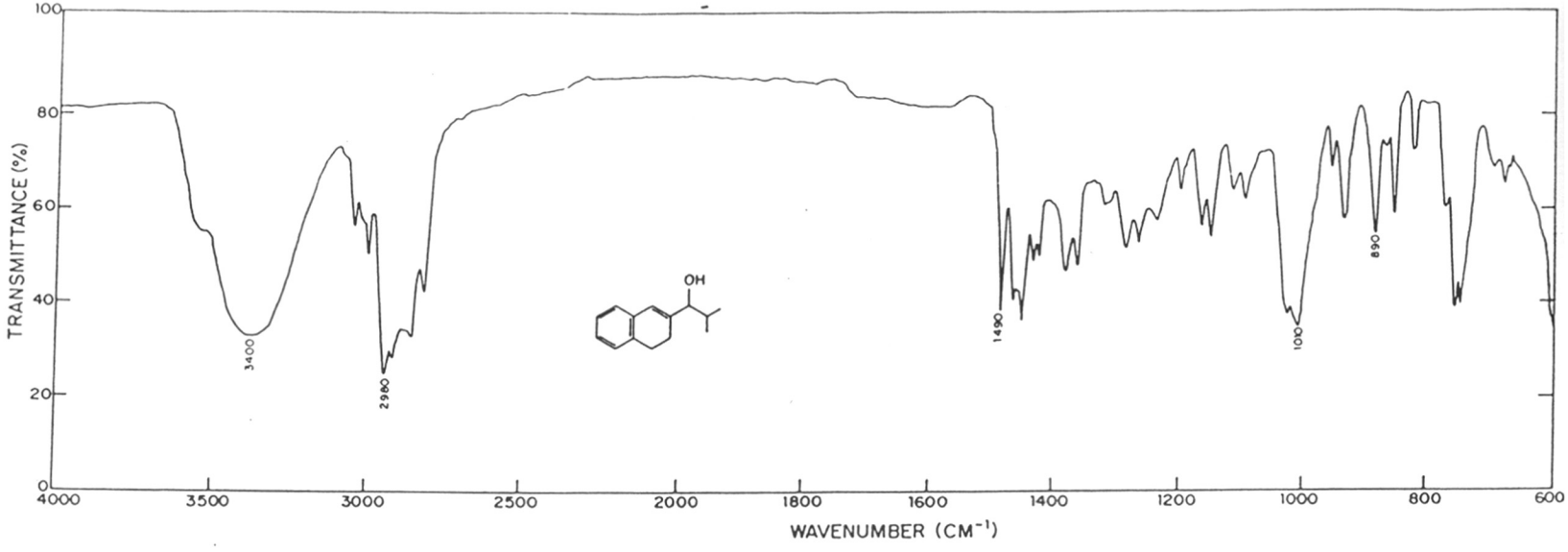


FIG. IX : IR OF COMPOUND No. (29, n = 2)

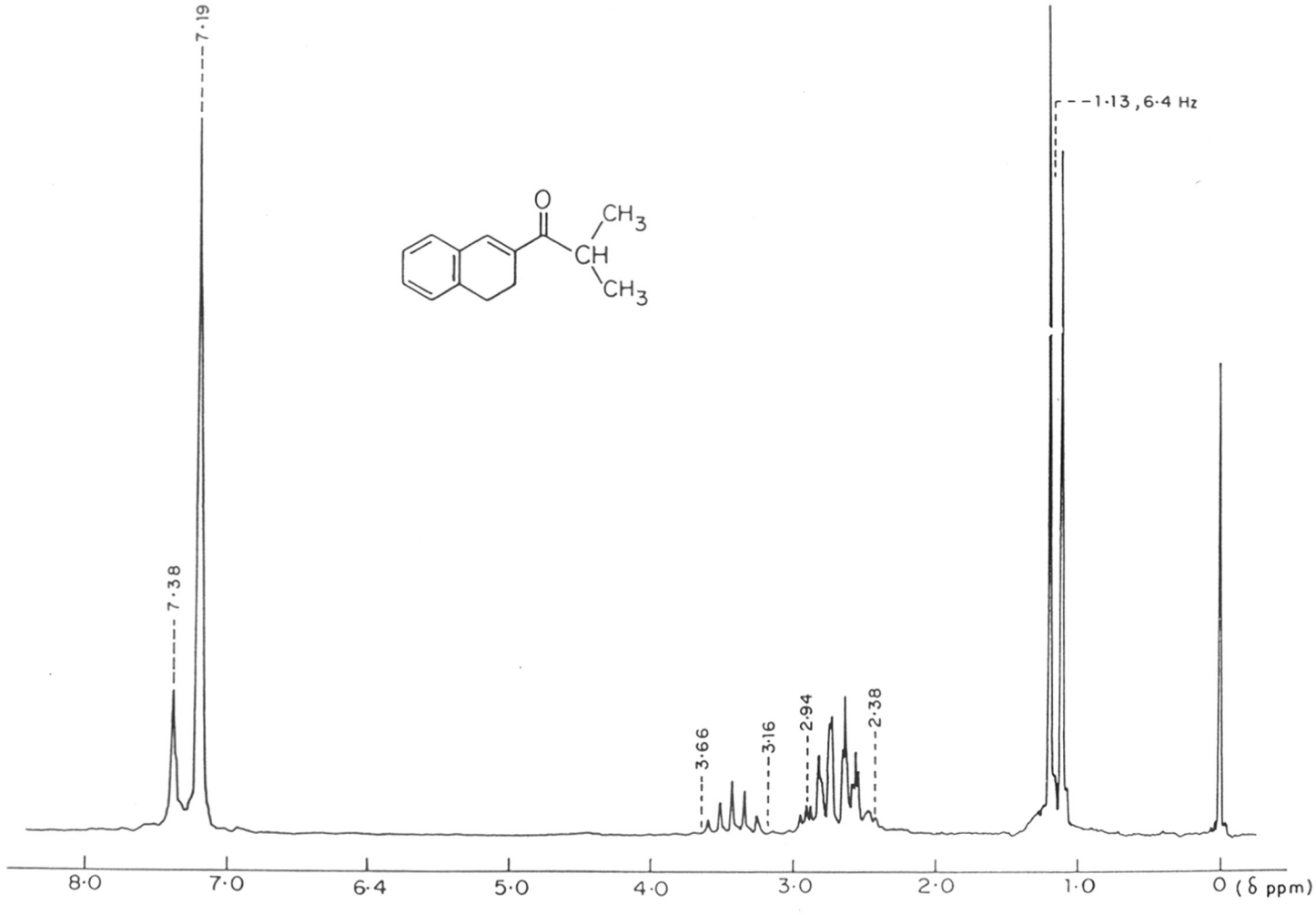


FIG. V : NMR OF COMPOUND No. (30, n=2)

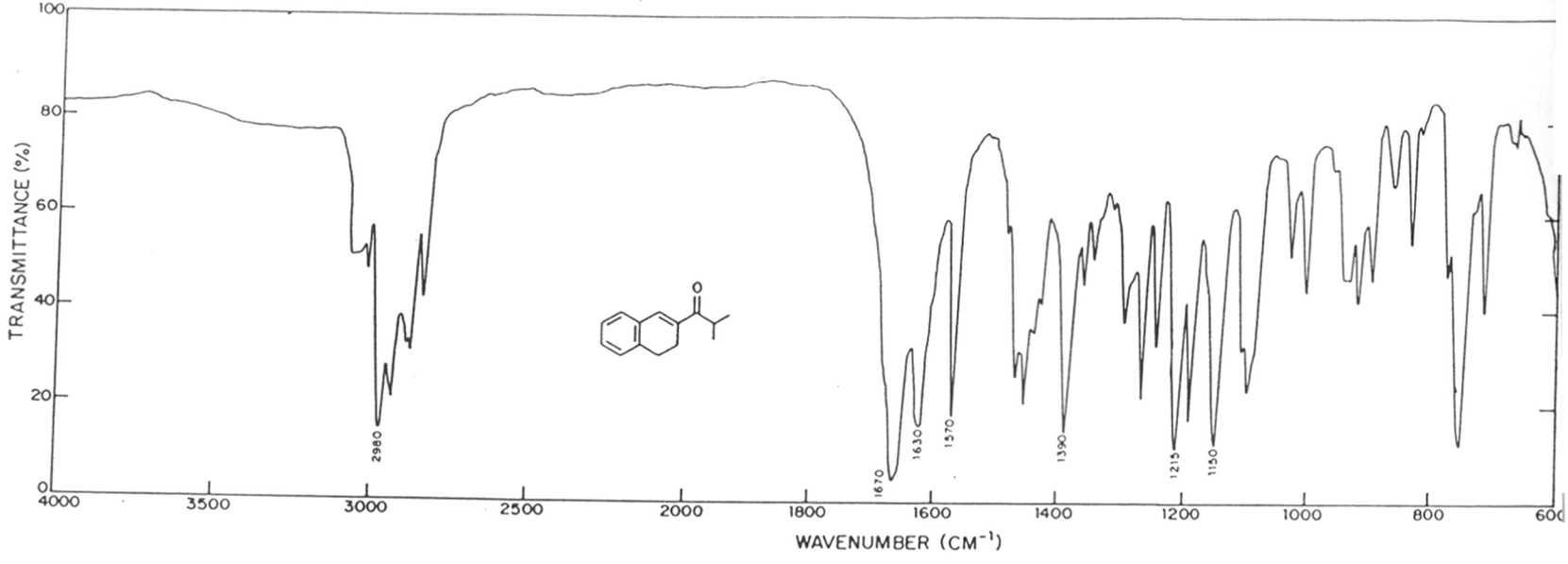


FIG. VI : IR OF COMPOUND No. (30, n = 2)

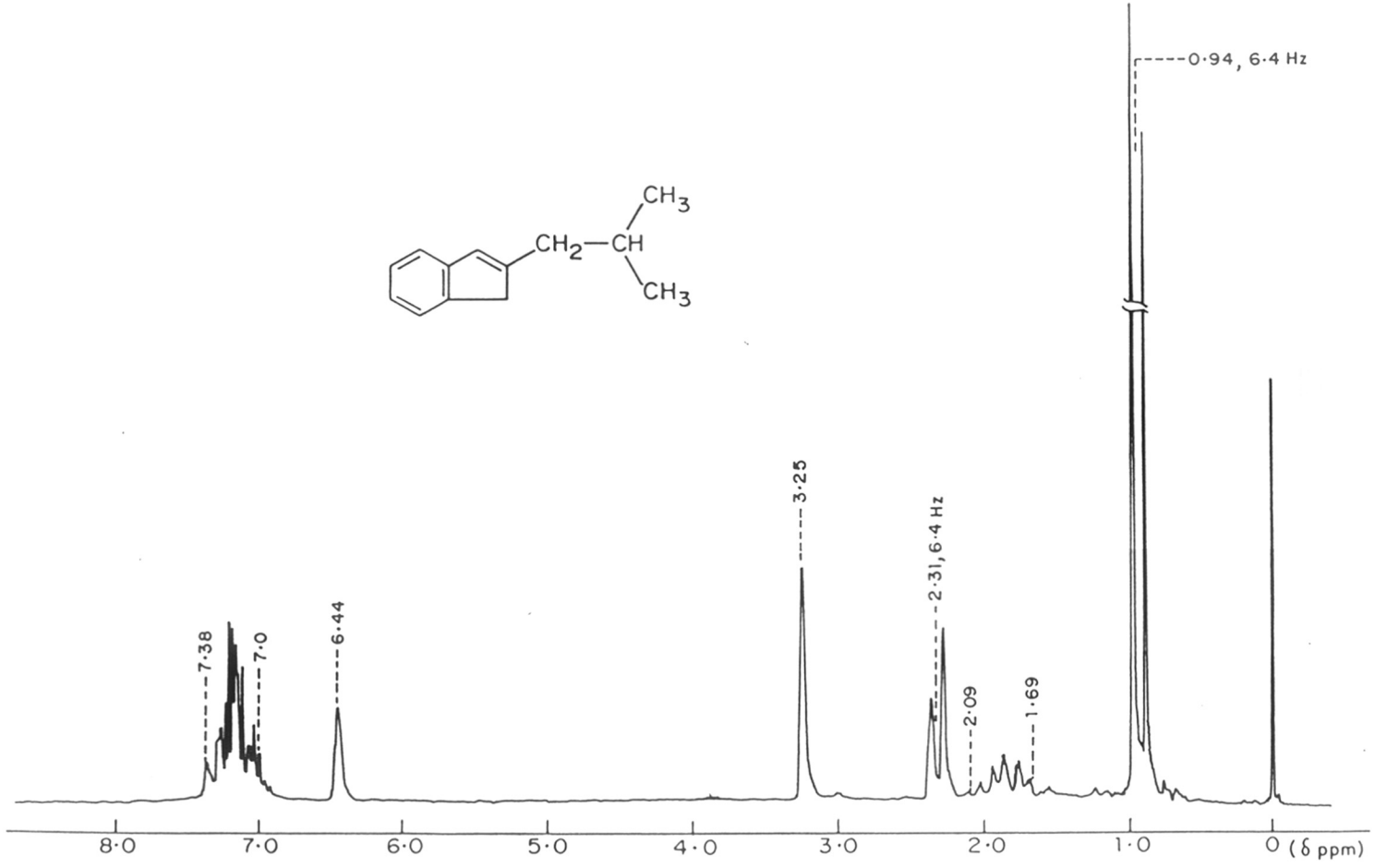


FIG. VII : NMR OF COMPOUND No.(32,n=1)

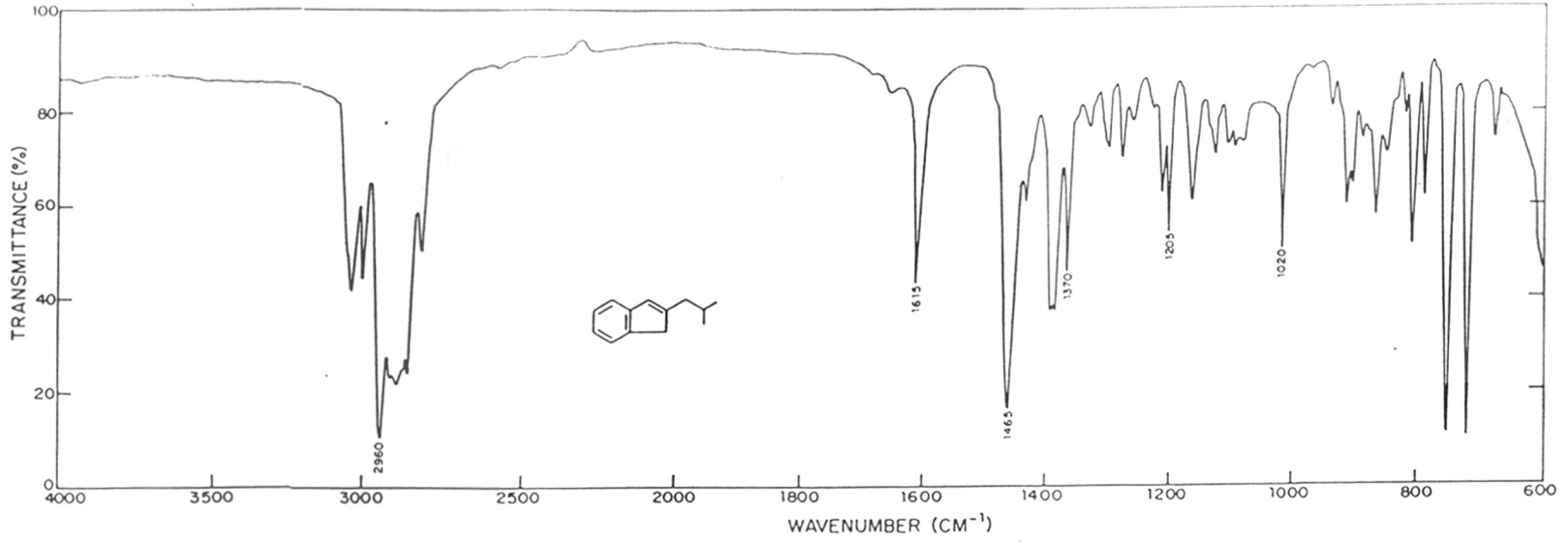


FIG. VIII : IR OF COMPOUND No. (32, n = 1)

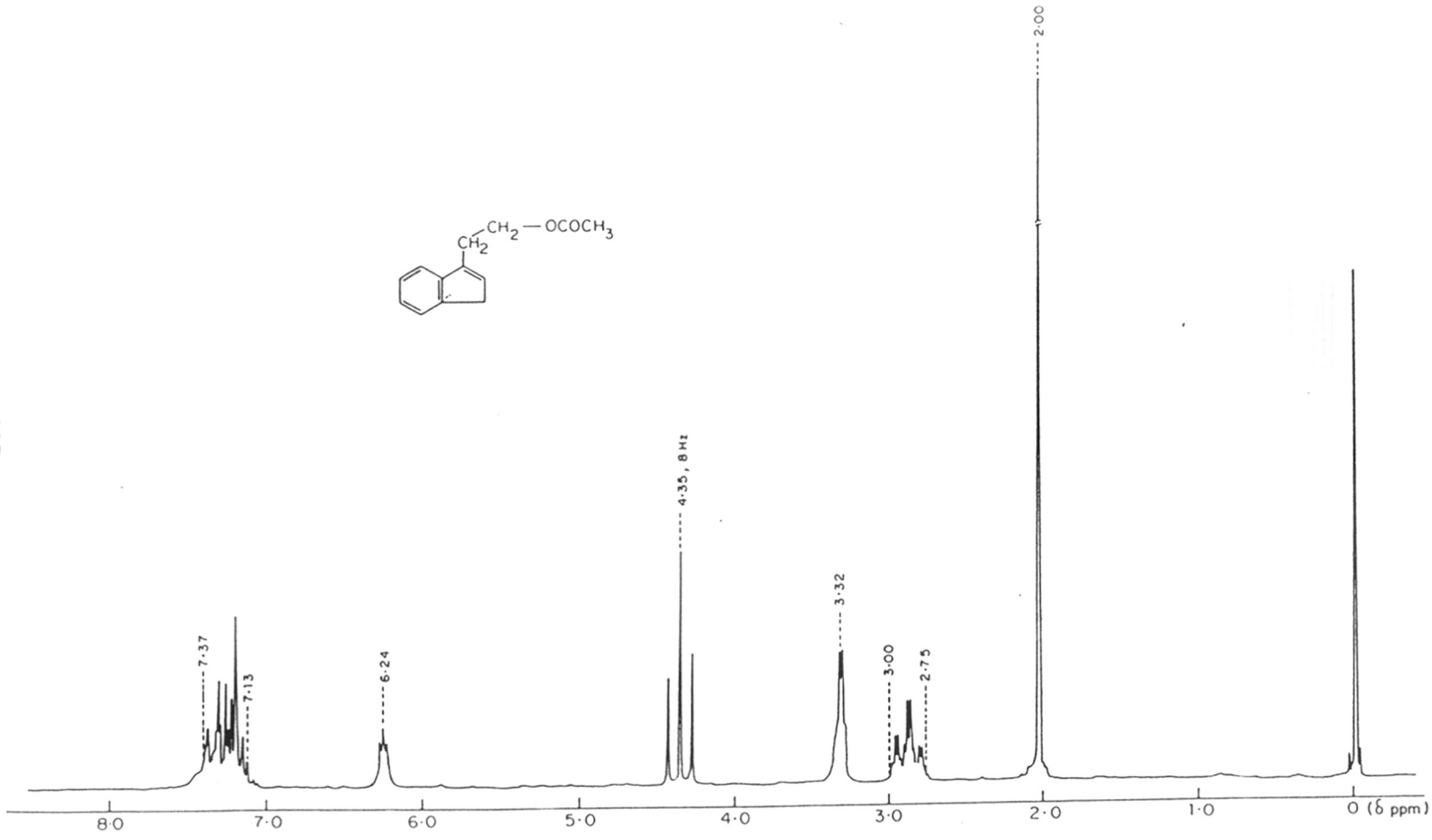


FIG IX NMR OF COMPOUND No (42)

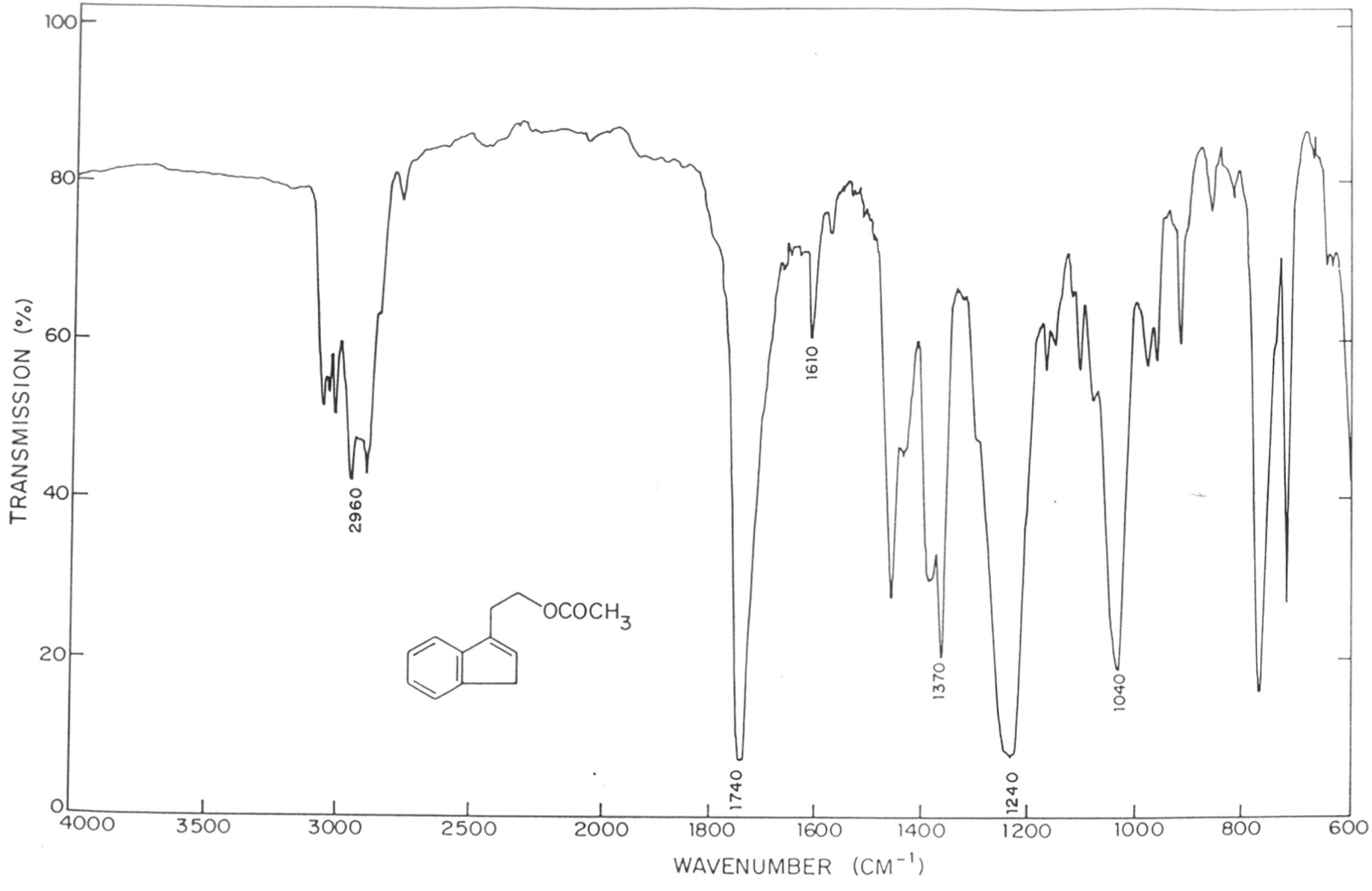


FIG. X : IR OF COMPOUND No. (42)

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