STUDIES IN THE SYNTHESIS OF BIOLOGICALLY ACTIVE TERPENOIDS

A THESIS

SUBMITTED TO

UNIVERSITY OF POONA

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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PUNE - (INDIA)

1986

DEDICATED TO MY
LOVING PARENTS
& WIFE

CERTIFICATE

Certified that the work incorporated in the thesis "Studies in the Synthesis of Biologically Active Terpenoids", submitted by Shri Dilip Digambar Shinde 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. R.B. Mitra)
Research Guide
National Chemical Laboratory, Pune-8

December 1986

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

I owe a deep debt of gratitude to Dr. R.B. Mitra, Acting Director, National Chemical Laboratory, Poona, under whose inspiring and encouraging guidance, this work was successfully carried out. I am also profoundly grateful to Dr. B.N. Joshi and Dr. (Miss) M.V. Natekar for the keen interest they evinced in the progress of the work and the valuable suggestions they made from time to time.

I express my sincere thanks to Mr. A.A. Arbale, Dr. P.L. Joshi and Dr. R.H. Naik for their cheerful and ungrudging co-operation.

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

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

(Dilip D. Shinde)

National Chemical Laboratory,
Poona-411008

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CHAPTER IV

Total synthesis of cyclopropane insecticides

Part A: Synthesis of miticidal esters

Part B: Synthesis of insecticidal ethers

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. All liquid samples whose b.p. are reported were checked for purity on GLC.
3. Pet.ether refer to the fraction boiling between 60-80°.
4. Alumina refers to neutral grade made in this laboratory.
5. IR spectra were recorded as liquid film or nujol mull on Perkin-Elmer Infrared Spectrometer model 137B or 599B; ν_{max} values are given in cm^{-1}.
6. PMR spectra were recorded on a Varian T-60 or WH-90 FT-Spectrometers, using TMS as internal standard (chemical shift in ppm)
7. Mass spectra were recorded on CEC-21-110B Spectrometer and MS-30 and Finnigan-Mat-1020B.
8. Optical rotations were taken on JASCO-DIP 181 polarimeter.
9. Microanalysis were carried out in the microanalytical section of this laboratory.
10. TLC was performed on silica gel made in this laboratory. Rf values refers to TLC using the solvent system mentioned in the respective brackets.
11. The numbers assigned to the charts and figures in each chapter of this thesis refer only to that particular chapter only.

CHAPTER - I

GENERAL INTRODUCTION TO MITICIDES

General Introduction to Miticides

This introductory chapter on synthetic miticides reviews the compounds now available, and stresses development of our understanding of relationship between chemical structure and miticidal activity, photostability and mammalian toxicity. The general implication of the discovery of more stable compounds synthesised in the recent past, which may be considered to contribute a new group of miticides, are important themes of this collection.

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

The framework of mite classification was developed between late 1800's and 1950's. Acarology really emerged

as a field of modern science with the remarkable work of Italian acarologist, Antonio Berlese. In his publications, he described the mites associated with cultivated plants. Berlese recognised the importance of this work and established the genus oligonychus. He developed a basic higher classification in Acarotheca Italica (1913) in which, the Tenuipalpidae was separated from the Tetranychidae and the spider mite tribes Bryobini and Tetranychidae were characterised.

Canestrini (1890) presented family classification of various mites.

In the United States, Banks (1900), published, 'The red spiders of the United States' (Tetranychus and Stigmaceous) and it was the finest review of the spider mite in the country. Tetranychus of Banks now consist of many types of spider mite species. Ewing began publishing on mites in 1907 and described several species.

Mc Gregor began to describe spider mite in 1914. In 1950, he published the summation of his life's work - Mites of the family Tetranychidae, which included 15 genera and 89 species in the world. Also included were species in the present family, Tuckerellidae, Linotetrnidae and Allochaetophoridae. Spider mites are plant feeders and cause serious damage to orchard trees, field crops, greenhouse plants

and many other vegetation. They feed on foliage of fruit plants and trees and attack a variety of plants and trees due to their wide distribution. The family Tetranychidae includes, Tetranychus urticae, T.atlanticus, T.bioculatus, T.canodensis, T.cinnabarrinus and T.pacificus.

Pritchand and Baker (1955) revised Tetranhychidae for the whole world, including 18 genera and 154 species. The family was divided into the sub-families, Bryobinae and Tetranychidae which respectively contained the tribes, Bryobini, Petrobini, Histrichonychini and the Tetranychini, Tenuipalpoidini, Eurytetranychini.

The modern phase of characterisation of mites began with the study of Gutierrez, Helle and Bolland (1970) which combined cytogenic information to external morphological characters and host information. They presented phytogenetic relationships among the tribes in the Tetranychidae[2].

Biochemical aspects

The factors that govern the selective activity of miticides, are doubtless the same as those for other xenobiotics. However, only little information is available with respect to the penetration, mode of action and metabolism in both target and non-target species. On the basis of available data on miticides

metabolism, mode of action and structure activity relationship, it has become possible to designate certain groupings in the molecule that could confer an opportunity for selectivity. Several materials are available commercially for controlling phytophagus mites active against eggs as well as other stages of evolution of mites. These are effective against targetted mites at dosage levels and are harmless to predators and pollinating insects.

Mites and ticks (acari) are sufficiently different from insects in their biochemistry[3], for certain compounds to be highly toxic to them (acaricidal) while they are relatively innocuous to true insects. Many acaricides are also fungicidal, providing a valuable combination of activity for the control of pests[4]. The low insecticidal activity of many acaricides is also an advantage because most of the natural predators of mites are insects.

Classification of Miticides (acaricides)

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

1) Organophosphates

2) Carbamates

3) Chlorinated hydrocarbons

4) Nitrophenol derivatives

5) Diphenyl aliphatic derivatives

6) Sulphonates, sulphites and sulphides

7)Formamidines and

8) Organofluorines

It is apparent from the above listed compounds that, miticidal activity occurs among different classes of chemicals of diverse molecular structures. Many of them are non-specific in their activity towards numerous mites, as they destroy both the beneficial and harmful organisms. These differ widely in their toxicity spectrum.

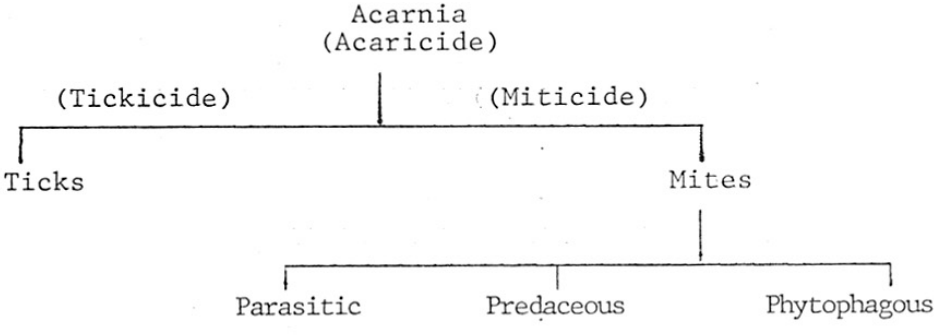
Selectivity classification

A more recent classification of the miticides is based on their selectivity towards different mites. This classification is represented below:

Table - I

Type	Selectivity level	toxic to	class
I	Non-specific	mites, insects mammals	Organophosphorous carbamates
II	Moderately selective	mites, insects	Nitrophenol derivatives, organofluorines and formamidines
III	Highly selective	mites	diphenyl aliphatic compounds

This chapter will focus on the mites, particularly those of agricultural importance. Parasitic and phytophagous mites are primary targets for acaricide chemicals, the latter being more significant from an agricultural standpoint. Phytophagous mites are of economic importance on numerous agronomic, horticultural and ornamental crops. Certain non-target organisms, including the predaceous mites, are effective in reducing populations of phytophagous mites. Predaceous mites are susceptible to many of the commonly used acaricides; therefore, they also should be included in a consideration of acaricide selectivity. There are other mites, in addition to predaceous, parasitic and phytophagous species, but they are generally not important in terms of chemical control. In this instance[5], these terms are relegated to designate the mites as given in figure.



The consequences of mite infestation are probably the least understood of all types of infestation[6]. Control of mites is desirable since they attack animals

and as well as causing annoyance, they carry certain diseases. They damage and cause loss of foodstuff. Probably the most widespread and therefore damaging mite is the Flour and Grain mite (Tyroglyphus ferinae), commonly found in cereals,flour, dried fruit, animal feeding stuffs etc. Some control of mites, particularly tick mites is achieved by use of Pyrethrin (I) or preferably synergized pyrethrin sprays, but preferably former to prevent an increase in local humidity. Lindane sprays have alsc been used, but it is not advised to apply directly to foods, food containers.

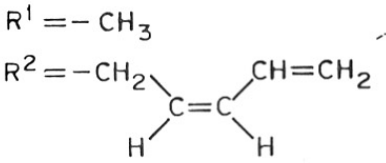
Endrin (2) has been found to give excellent control of certain important species of tarronemid mites. Rothane (3) which is 1,1-dichloro-2,2-di(p-chlorophenyl) ethane (often called as DDD) is applied as a dust, combined with sulphur, against caterpillar and mites. Fenson (4) is a common name for pentachlorophenyl benzene sulphonate[7], a material which has shown itself recently to be of value in the control of red- spider and other mites. It is particularly toxic to the eggs and has some capacity for moving through plant tissue. It is particularly more effective against mites on beans, cotton, melons and grapes and is completely harmless to mammals and the domestic animals. It is quite compatible with DDT, TEPP, lead arsenate, parathion and other common insecticides and fungicides.

Indeed, it has been discovered that several bridged diphenyl derivatives, some of which are closely related to DDT, are valuable acaricides against phytophagus mites and ticks, although, they are almost devoid of toxicity to insects[8]. One example is dicofol (5), which was introduced as an acaricide in 1952. Another related compound is chlorobenzilate (6) prepared from (Scheme I) p-chlorobenzaldehyde via benzoin condensation. A more recent acaricide of this type is bromopropylate or isopropyl 4,4'-dibromobenzilate.

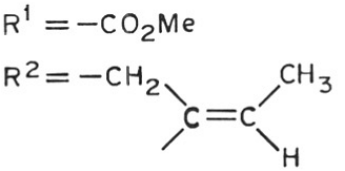
The earliest acaricide was azobenzene (1945) which was used for many years as an aerosol or smoke to control red-spider mites in green houses. Another early compound was benzyl benzoate, whose acaricidal properties were substantially enhanced by the introduction of two chlorine atoms in the para-position giving Neotran (7), obtained from methylene chloride and sodium-p-chlorophenate.

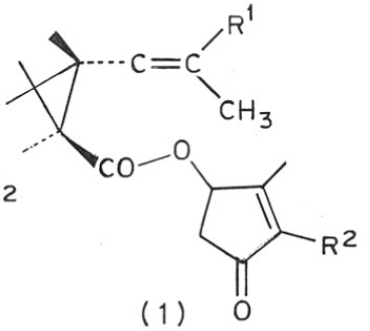
Diphenyl sulphone is also acaricidal and is especially toxic to eggs of the fruit tree spider mite. As has been observed with azobenzene, the introduction of one chlorine atom did not reduce the ovicidal activity of diphenyl sulphone, but 4,4'-dichlorophenylsulphone, both had reduced toxicity. On the other hand, further chlorination of 4,4'-dichlorodiphenylsulphone

I

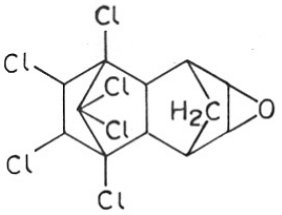


II

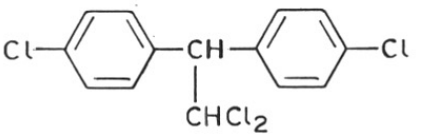




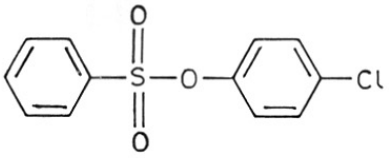
(1)
PYRETHRIN



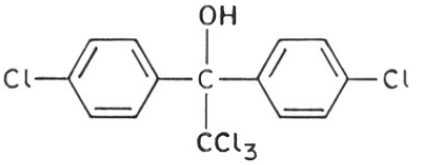
(2)
ENDRIN



(3)
ROTHANE (DDD)

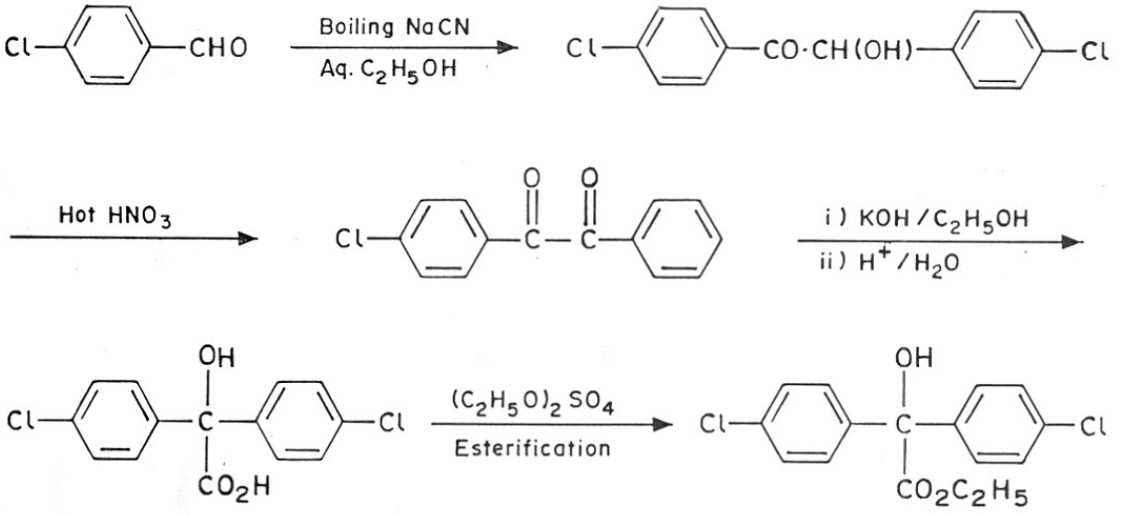


(4)
FENSON



(5)
DICOFOL

SCHEME –1



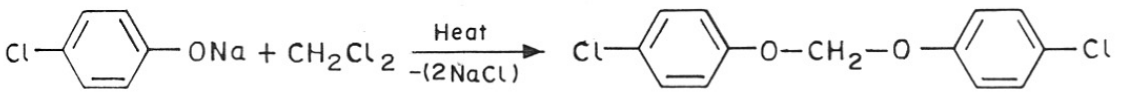
CHLOROBENZILATE (6)

restored the acaricidal properties[8]. Thus both 2,4,5-trichlorodiphenyl sulphone and 2,4,5,4-tetrachloroderivative are valuable agricultural acaricides. They are persistent in their action and are less phytotoxic than diphenyl sulphone[9,10] and is commonly called as Tetradifon (8)which is obtained from 1,3,4-trichlorobenzene. Tetradifon has, for many years, been the most important acaricide for the protection of fruit trees and is active against all stages and eggs of phytophagous mites, but many mites are developing resistance to this compound and so new acaricides were urgently needed.

Substituted phenyl benzene sulphonates show acaricidal properties; the most effective ovicide was the 4,4'-dichloroderivative known as chlorfenson (9) (or ovex). This is very useful since, with rapidly breeding mite control against the egg stage, is often more effective than killing the mites themselves. Ovex has found wide use in the control of various mites on fruits and ornamental trees and shrubs. One special feature of it is its relatively long residual activity. On adult mite, it does not effect a rapid kill. Chlorfenson is compatible with most of the commonly used insecticides and fungicides.

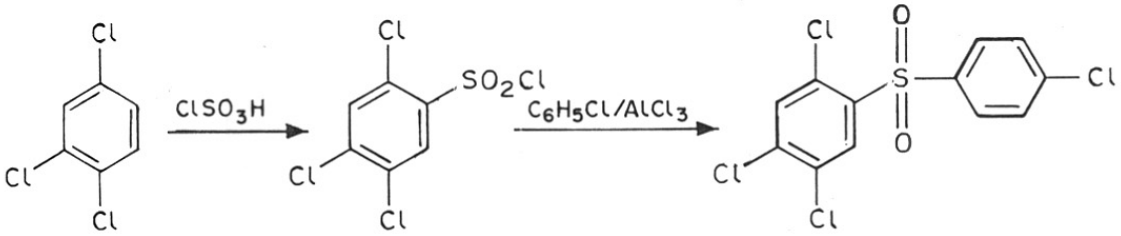
Benzyl phenyl sulphides are also acaricidal and again the best known example is the 4,4'-dichloro-

SCHEME–II

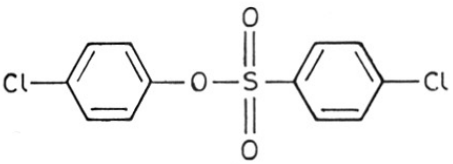


(7) NEUTRAN

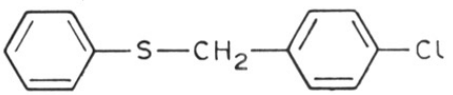
SCHEME–III



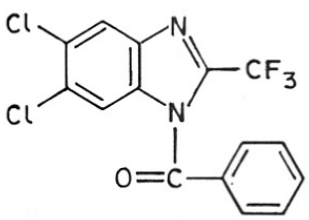
(8) TETRADIFON



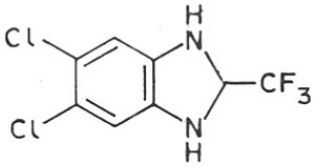
(9) CHLORFENSON (OVEX)



(10) CHLORBENSIDE

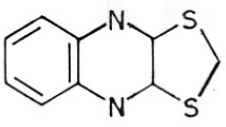


(11) FENAZAFLOR

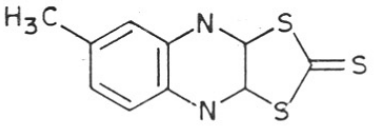


(12)

5,6–DICHLORO–2–TRIFUORO–METHYL BENZIMIDAZOLE



(13) THIOQUINOX



(14) CHINOMETHIONAT

derivative or chlorbenside (10) introduced in 1953. This showed good systemic acaricidal activity in treated plants and was quite persistent.

Nothing appears to be known about the biochemical mode of action of these miticides[11], although this is not surprising since the study of mite was much less developed than that of insects[12]. The wide variety of different possible bridging groups between the two phenyl rings made it difficult to formulate precise structure-activity relationships[9(c)].

The chemistry of the acaricides has been reviewed[13,14]. Most of the compounds have selective toxicity to mites, some of them, in addition, show selectivity towards specific species of mites. However, mites were rapidly becoming resistant to bridged diphenyl derivatives.

Other compounds of different structures which have been developed as acaricides, include the benzimidazole derivative, Fenzaflor (11) introduced in 1966[8,15] which shows promise for controlling mites, resistant to tetradifon.

On hydrolysis, Fenzaflor (11) gives 5,6-dichloro-2-trifluoromethylbenzimidazole (12) considered to be active toxicant in vivo, since this compound interferes in respiration by coupling oxidative phosphorylation[11(b)],

in mite mitochondria. This is supported by observation[11(b)] that fenzaflor increased oxygen uptake of mites.

Other aromatic nitrogen heterocyclic acaricides are thioquinox (13) and chinomethionat (14). These compounds also possess useful fungitoxicity against powdery mildews; both have low mammalian toxicity and are effective against spider mites[11].

Among the chlorinated hydrocarbons Kelthane (15) (1,1-bis-(chlorophenyl)-2,2,2-trichloroethanol) is chemically quite similar to DDT, differs markedly in its biological properties. It is specifically an acaricide, with harmful effects on bees or beneficial predators. It is claimed to be active against an unusually broad range of mites and possesses rapid killing action having long residual effect.

Aramite based on 2-chloroethyl-2-(p-tertbutyl-phenoxy)-isopropyl sulphite, was first used on commercial scale in 1950, for the control of european red mite, pacific mite and two spotted mite, clover mite, citrus red mite upon apple, peaches, cherries and figs.

German investigators have led to development of cheaper dinitrophenolic compound, 2,2-dimethyl-acrylyl ester, very phytotoxic and also known as HOE 2784. This pesticide may prove valuable where

mites have become resistant to organophosphorous compounds and the range of ovolarvicides.

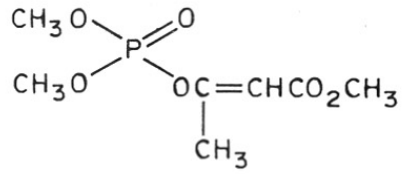
A number of organophosphorous insecticides show acaricidal properties, for example, Mevinphos (16), parathion (17), malathion (18), and diazinon (19) with fairly good residual properties[16].

Among the carbamate compounds carbofuran (20) has a broad spectrum acaricidal activity[17].

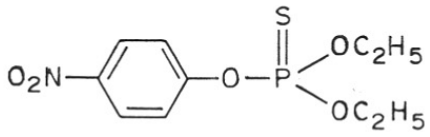
Dinitrophenols and their derivatives are very versatile pesticides among which, 2-methyl-4,6-dinitrophenol (21, R = CH_3) called as DNOC and the corresponding 2-cyclohexylphenol (21, R = cyclohexyl) are active against red spider mites. Various esters (22) and (23) are used against powdery mildews and mites.

Some important new types of acaricides include amidines, such as formamidines like chlordimeform (24) (1972) which acts as a broad spectrum acaricide effective against adult mite eggs and larvae[14].

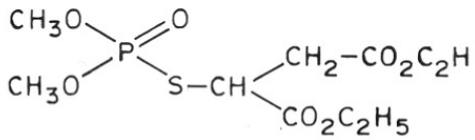
Several other amidines are useful acaricides. An important example is Mitac (25) developed by Boots Ltd., (1973) and prepared from 2,4-xylidene, ethyl orthoformate and methylamine[10] (Scheme IV). Mitac is active against all stages of wide range of mites and controls mites which are resistant to other



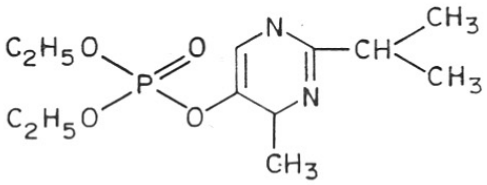
(16) MEVINPHOS



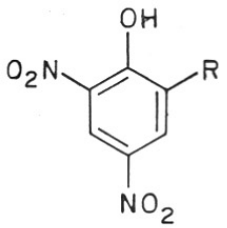
(17) PARATHION



(18) MALATHION



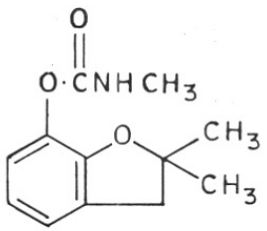
(19) DIAZINON



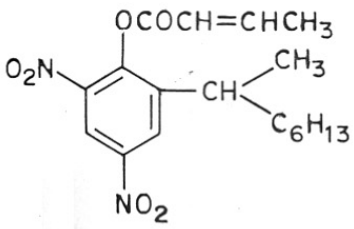
(21)

R = CH_3 – DNOC

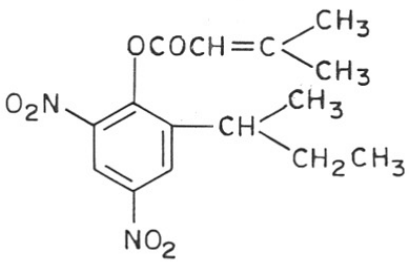
R = CYCLOHEXYL



(20) CARBOFURAN



(22)



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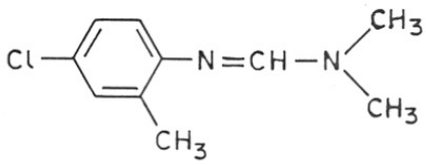
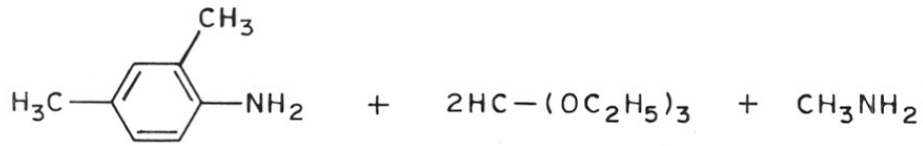
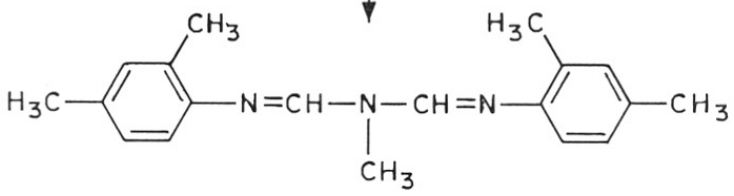


(24) CHLORDIMEFORM

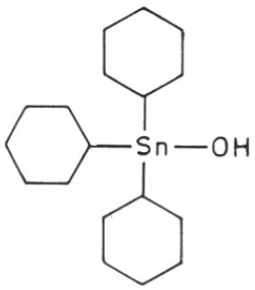
SCHEME – IV



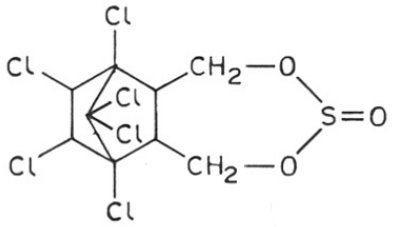
2,4–XYLIDENE ETHYL CHLOROFORMATE



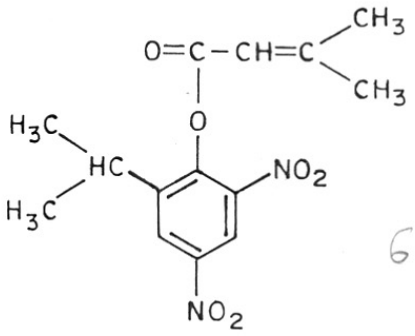
(25) MITAC



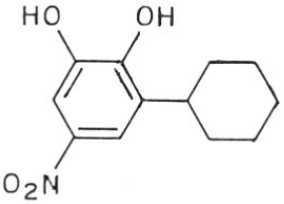
(26) PLICTRAN (CYHEXATIN)



(27) ENDOSULFAN



(28) BINAPACRYL



(29) DINITROCYCLOHEXYLPHENOL

miticides[14]. It provides no danger to the environment and has a low mammalian toxicity; LD_{50}(oral) to rats 800 mg per kg.

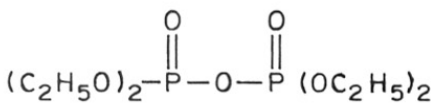
Some organotin compounds are useful miticides; the best known example is cyhexatin (26) which is now one of the leading miticides, in spite of rather slow acting, and sometimes phytotoxic. It has the important advantage of low toxicity to predatory mites[18]. Cyhexatin (26) has a low mammalian toxicity; LD_{50}(oral) to rats is 540 mg/kg.

Among all cyclodine group of compounds, endosulfan (27) (Thiodan) has a spectrum of insecticidal activity, except that it is also miticidal[18]. Endosulfan is sometimes used in combination with oil for eriophyid control. It is used against Acalitrus essigi and Epitrimerus pyri.

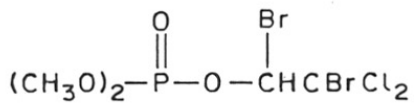
Majority of phenols, especially those containing chlorine as toxic to microorganisms, act as acaricides. Binapacryl (28) is closely related to dinacap and is used for control of red-spider mites and powdery mildew on apple[17,19]. Dinitrocyclohexyl phenol (29) is also an acaricide used against red-spider mites.

More examples of numerous synthetic organic compounds differing markedly in their chemical configurations possess acaricidal activity[20] which have not been explained so far, are listed on pages 19,20,23 according to their respective chemical groups.

ORGANOPHOSPHATES ACTIVE AS MITICIDES



TEPP



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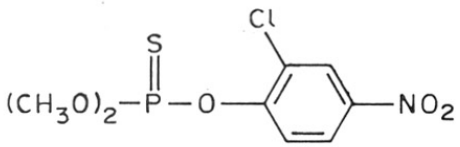

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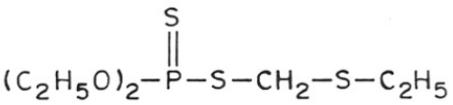

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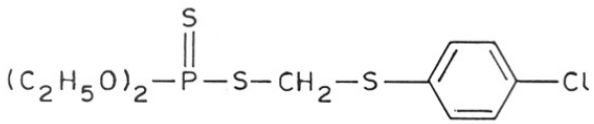

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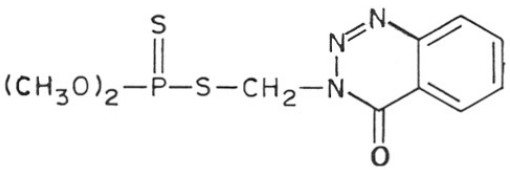
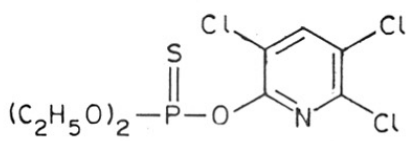
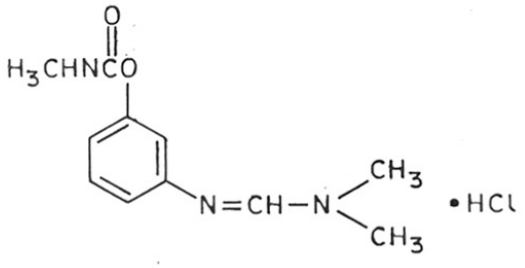


AZINPHOSMETHYL



CHLORPYRIFOS

CARBAMATES ACTIVE AS MITICIDES



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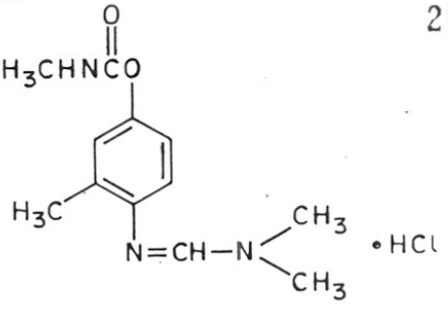

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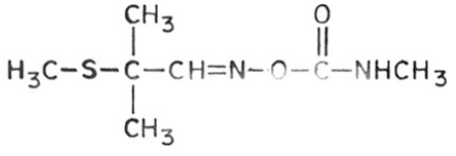
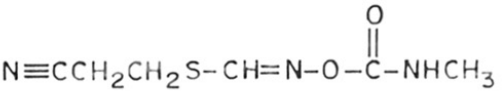
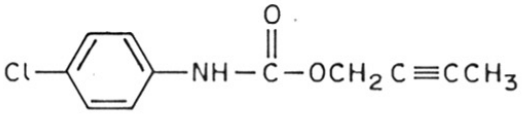


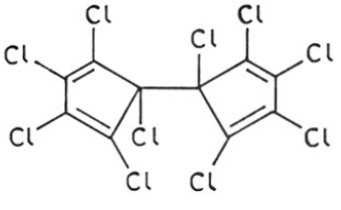
ALDICARB



SD-17250

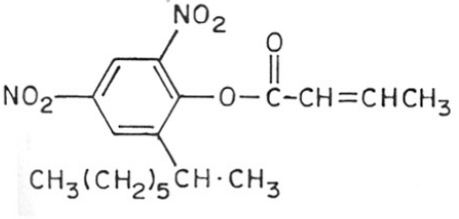


CHLORINATED HYDROCARBONS ACTIVE AS MITICIDES

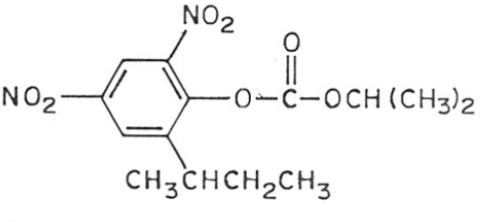


PENTAC

NITROPHENOL DERIVATIVES ACTIVE AS MITICIDES

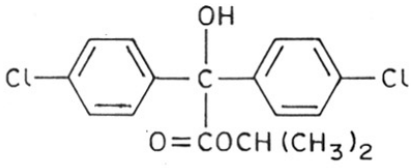


DINACAP

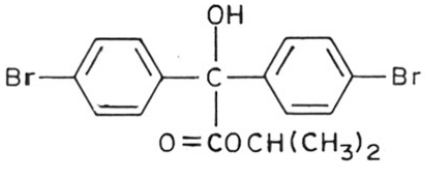


DINOBUTON

DIPHENYL ALIPHATICS ACTIVE AS MITICIDES

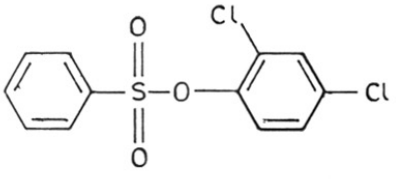


CHLOROPROPYLATE

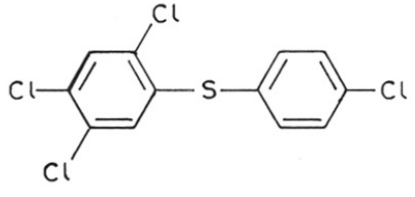


BROMOPROPYLATE (ACAROL)

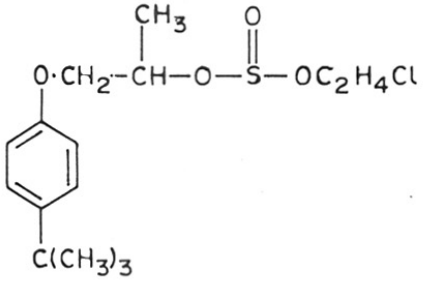
SULFONATES, SULFONES, SULFIDES, SULFITES AS ACARICIDES



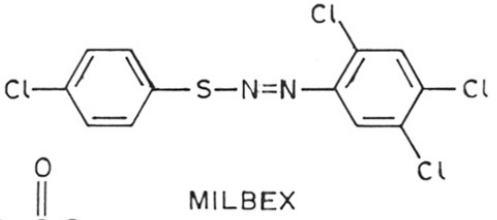
GENITE



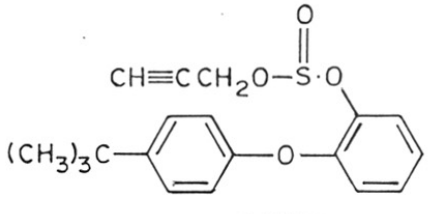
TETRASUL



ARAMITE

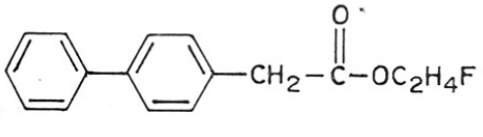


MILBEX

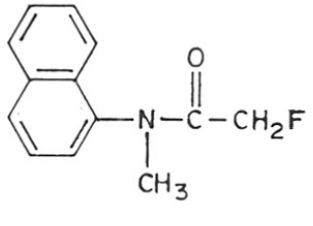


OMITE

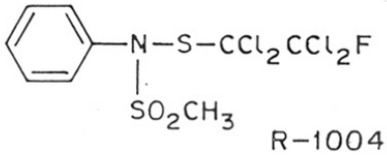
ORGANOFLUORINES ACTIVE AS MITICIDES



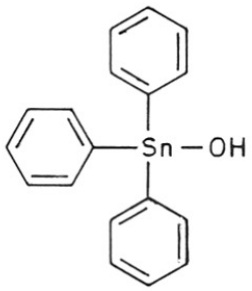
FLUENETHYL



NISSOL

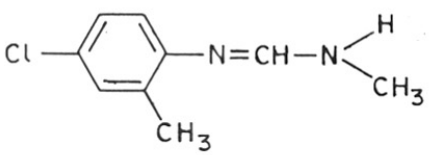


ORGANOTIN COMPOUND ACTIVE AS MITICIDES

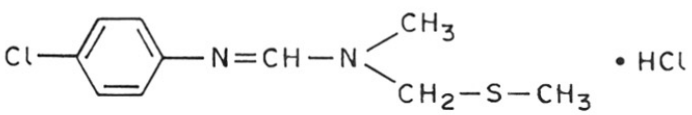


DU-TER

FORMAMIDINES ACTIVE AS MITICIDES

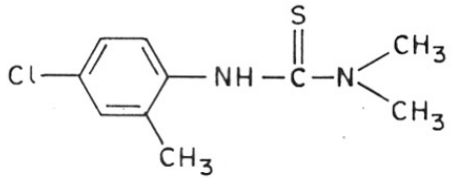


C-8520



H-20013

MISCELLANEOUS COMPOUNDS ACTIVE AS MITICIDES



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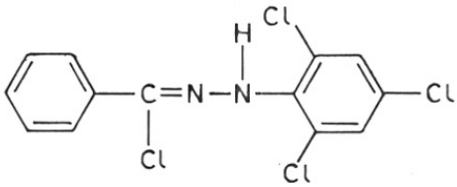
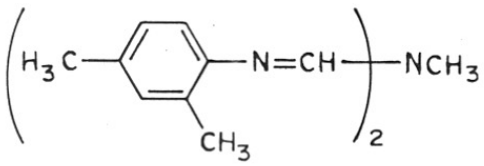
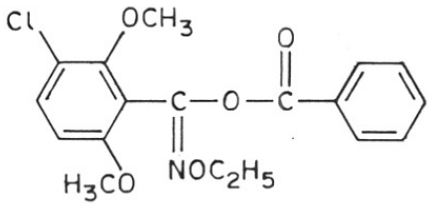


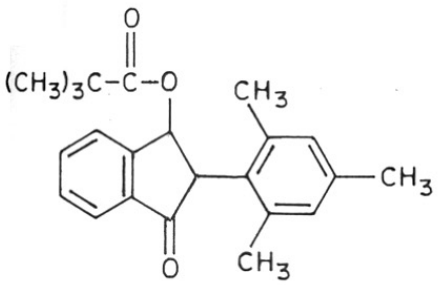
(BANAMITE)



U-36059



BENZAMATE



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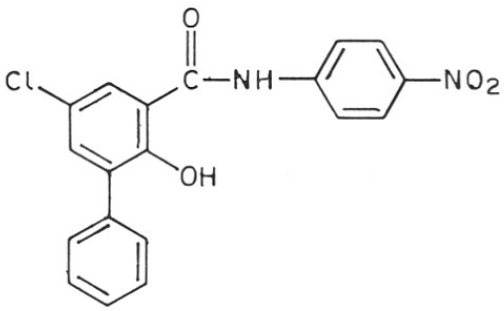

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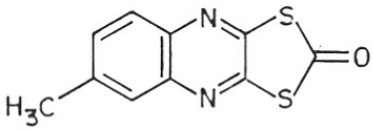


OXYTHIOQUINOX

Upto this point, acaricide selectivity has been considered with respect to groups of different organisms, for example mammals, insects and mites (see Table I, Page 6). However, even closely related mite species can differ in their susceptibility to acaricides[21]. It is desirable to have acaricides that can be used under conditions such that harmful mite populations can be reduced to desired levels without appreciably affecting levels of predaceous mites. Table II shows the toxicity of the specific acaricides (Type II and III in Table I) to phytophagus and predaceous mites. These conclusions, based largely on the results of field experiments, show that Plictran, chlorobenzilate, chloropropylate and Acarol generally possess this kind of selectivity[22-26].

Stage specificity, another kind of selectivity exhibited by certain acaricides, occurs when an acaricide shows differential toxicity to various stages of the same mite species. For instance, with the two-spotted spider mite, (Tetranychus urtiae koch), chlorobenzilate was equitoxic to an adult and larval stages but was less active against the eggs[27].

Mites have a high reproductive potential, and they may have several generations during a season.

Table II

Toxicity of specific acaricides (Type II and III in Table I) to Phytophagus and Predaceous Mites

Compound	Chemical group	Toxic to	
		Phytophagous mites	Predaceous mites
Plictron	Organotin	*T	**LT
Chlorobenzilate	Diphenyl aliphatic	T	LT
Chloropropylate	Diphenyl aliphatic	T	LT
Acarol	Diphenyl aliphatic	T	LT
UC-41305	Arylindone	T	-
Dinobuton	Nitrophenol derivative	T	T
Chlordimeform	Formamidine	T	T
U-36059	Diaryltriaza-pentadiene	T	T
Banamite	Phenylhydrazone	T	T
Oxythioquinox	Quinoxaline derivative	T	T

*T = Highly toxic

**LT= Less toxic

Thus, they can be subjected to continuous selection, and resistance can develop rapidly. This resistance phenomenon is the primary reason for so many different classes of acaricides.

In general, the advent of DDT-resistant insects resulted in the substitution first of lindane or γ-HCH, followed by organophosphates for their control. However, after about 6 years the pests, in many cases, developed strains showing multiple resistance. Carbamate insecticides like carbaryl were often useful, but unfortunately pests which have acquired tolerance to organophosphates often showed cross resistance. Many important pests and disease vectors have multiple resistance and are consequently difficult to control Red-spider mites in many parts of the world are an outstanding example of this problem. The addition of synergists was often helpful in overcoming resistance[28]. However, pests can become resistant to the synergists themselves, which can substantially reduce the effectiveness of synergist-pesticide mixture to another every 5-6 generations of pests[29].

The valuable insecticidal and acaricidal properties of synthetic pyrethroids were recognised in the 19th century and stimulated detailed examination of the chemical constitution of the active esters in

the first quarter of 20th century. Staudinger and Ruzicka[30] for the first time isolated two active compounds from pyrethrum (I) extract and identified them as esters with keto alcohols and named them as pyrethrin I and pyrethrin II respectively. Later 4 more active esters[31-34] were isolated from pyrethrum extract. The insecticidal activity of pyrethrum is attributed to the presence of these six esters. Pyrethroids, natural and synthetic ones, are becoming increasingly important as pest control agents because they possess a unique combination of desirable properties including low mammalian toxicity and rapid biodegradability.

Table III[35] demonstrates the relative advantage of pyrethroid over other classes of insecticides and acaricides.

Table III

Class	LD_{50} Rats mg/kg	LD_{50} Insects mg/kg	Selectivity Ratio
Carbamates	45	2.8	16
Organophosphates	67	2.0	33
Organochlorines	230	2.6	91
Pyrethroid	2000	0.45	4500

Relative safety is indicated by the ratio of toxicities to rats and insects.

Inspite of the high insecticidal activity and low mammalian toxicity of pyrethrum, a major disadvantage, especially for use against agricultural pests, lies in its lack of persistence due to its instability in the presence of air and light. For this reason it was necessary to modify the natural pyrethrin, keeping appropriate stereochemstry necessary for biological activity, intact and increasing photo-stability.

The activity shown by the first important synthetic pyrethroid, allethrin indicated that the side-chain in the alcohol component may be modified without loss of activity. Barthel[36] showed that variety of substituted benzyl esters of chrysanthemic acid are appreciably more active than allethrin.

Newallis and Walker[37] for the first time claimed that the vapour of certain alkylcyclopropane-carboxylic acid ester (Chart II, Compound 11) possessing C-1 to C-4 carbon chain, were active against both adult as well as egg of two-spotted spider mites. But they did not discuss in detail the contact activity of such type of compounds.

Janiak[38] prepared certain aryl esters of cyclopropanecarboxylic acids (Chart III, compounds 2) and calimed that they possess the biocidal activity, preferably, for the weed members of class, arachondria, bacteria and fungi.

Henrik[39] prepared methyl, ethyl, isopropyl esters of 2,4-dodecadienoic acid, which showed high insect activity, especially as high as potent insect growth regulators. However, they were found to be devoid of any activity against spider mites.

Staal et al.[40] have prepared a new class of compounds derived from cyclopropylmethyl alcohol and cyclopropanecarboxylic acid (listed in Chart II and III) which showed high and predominantly ovicidal activity against two-spotted spider mites, Tetranychus urticae Koch, commonly occurring on strawberry plant. Activity was obtained against eggs in all stages of embryonic development following, either direct application to eggs or deposition of eggs upon sprayed leaves. The acute contact ovicidal activity and the longevity of foliar residues exposed to normal outdoor conditions, were in the range of activity observed for current miticides in comparative tests. The diaryl esters showed 5 to 20 times greater contact activity against mite eggs and larvae than monoaryl esters.

Chemical preparations of all compounds (ChartII and III) were from commercially available acids or acid chlorides, with the exception of acid chlorides for 4,5,6 and 7 (which were prepared according to Henrik et al., 1973), and appropriate commercially available alcohols (the one exception was cyclopropanol which was prepared by oxygenation of cyclopropyl magnesiumbromide in THF; cf: Roberts and Chamber, 1951) in presence of pyridene to yield the desired esters.

The biological evolution is determined by various chemical composition methods to test in following stages:

i) Direct contact ovicidal activity
ii) Foliar residual ovicidal activity and
iii) Direct contact larvicidal activity

As against the present stated compounds, ovicidal and larvicidal activity of certain commercial miticides against Tetranychus urticae, have been shown in Chart I.

Chart I

Name	Ovicidal			Larvicidal
	Direct contact	Foliar residual 0 days	Foliar residual 7 days	Direct contact
Dicofol	390	49	310	5.4
Ovex	670	280	1000	120
Omite	1000	300	310	20
Tetradifon	27	334	3.5	2.9
Plictran	86	31	50	0.56

CHART–II

OVICIDAL AND LARVICIDAL ACTIVITY OF CERTAIN ESTERS OF CYCLOPROPYLMETHYL ALCOHOL AGAINST TETRANYCHUS URTICAE KOCH (LC_{50} IN ppm)

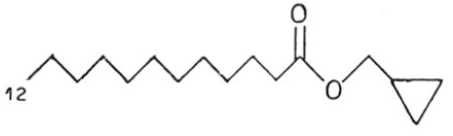
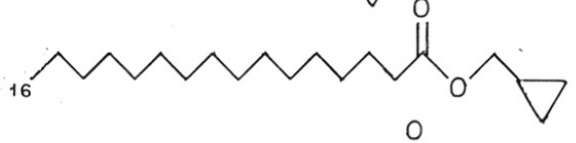
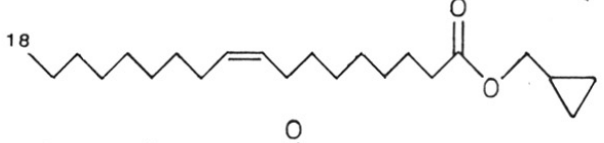
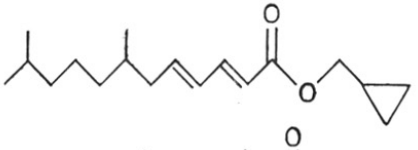
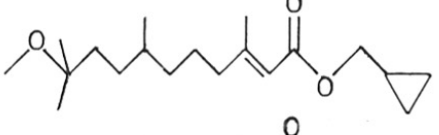
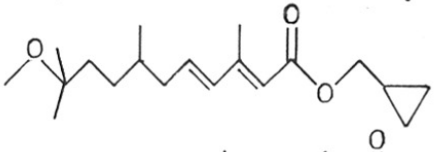
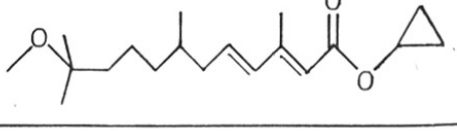
No.	STRUCTURE	OVICIDAL			LARVICIDAL
		DIRECT CONTACT	FOLIAR RESIDUAL		DIRECT CONTACT
			0 DAYS	7 DAYS	
1		60	>1000	—	230
2		68	>1000	—	400
3		250	>1000	—	350
4		> 1000	590	> 1000	240
5		410	320	> 1000	100
6		390	300	> 1000	200
7		> 1000	—	—	—

CHART – II (Contd.)

OVICIDAL AND LARVICIDAL ACTIVITY OF CERTAIN ESTERS OF CYCLOPROPYLMETHYL ALCOHOL AGAINST TETRANYCHUS URTICAE KOCH (LC_{50} IN ppm)

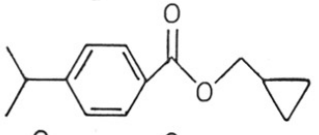
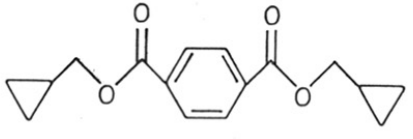
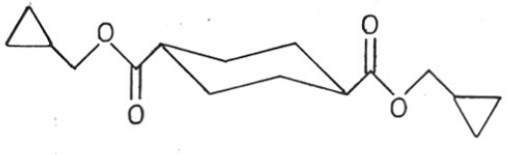
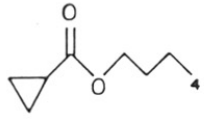
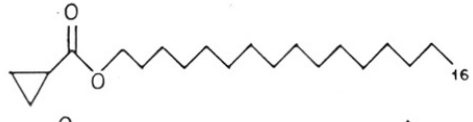
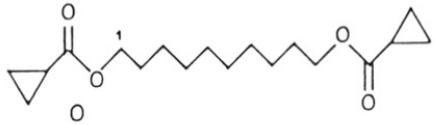
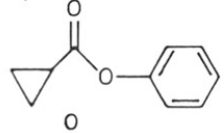
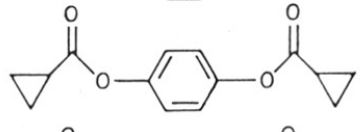
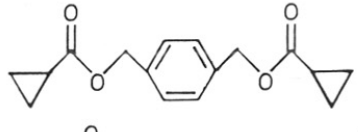
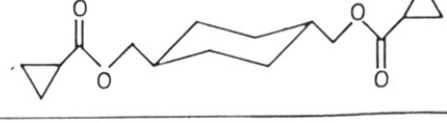
No.	STRUCTURE	OVICIDAL			LARVICIDAL
		DIRECT CONTACT	FOLIAR RESIDUAL		DIRECT CONTACT
			0 DAYS	7 DAYS	
8		300	1000	—	110
9		37	210	>1000	200
10		20	950	920	76

CHART-III

OVICIDAL AND LARVICIDAL ACTIVITY OF CERTAIN CYCLOPROPANECARBOXYLIC ACID ESTERS AGAINST TETRANYCHUS URTICAE KOCH (LC_{50} IN ppm)

No.	STRUCTURE	OVICIDAL			LARVICIDAL
		DIRECT CONTACT	FOLIAR RESIDUAL		DIRECT CONTACT
			0 DAYS	7 DAYS	
11		2400	>1000	—	> 1000
12		26	390	>1000	230
13		43	330	>1000	210
14		630	>1000	—	4400
15		120	180	280	370
16		29	290	1000	300
17		35	290	380	160

Although the requirement of high activity in the remainder of the molecule were not sharply defined, certain structure-activity relationships have been observed and the optimum chain length has been determined (Zoecon Corp., unpublished data).

On the basis of the comparative data, it appears that a major difference between esters derived from cyclopropylmethyl alcohol and cyclopropanecarboxylic acid lies in the activity of spray residues, especially the persistance of activity under external exposure. For example, compound 9 Vs 16 and 10 Vs 17 in which activity of the acid persists longer than that of alcohol derivatives.

The data from the simple direct dip test indicate that several of the compounds exhibit ovicidal activities which match or surpass those of several currently available mite ovicides and larvicides. Systemic activity has not been observed in these compounds when either the existed stem or the soil drench technique was used for the most active compounds.

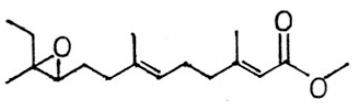
Although these ovicides generally appear to have little effect on insect eggs, an exception has been found in the case of compound No.16 (in Chart III), which had contact ovicidal activity in the greenhouse whitefly, Trialeurodes vaporariorum (Zoecon Corp., unpublished data).

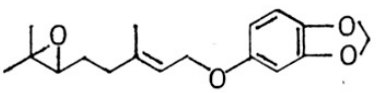
In general, these compounds prevent the hatch of eggs due to effects observable during the late stages of embryonic development even when treatment is applied during the 1st of 24 hours following oviposition.

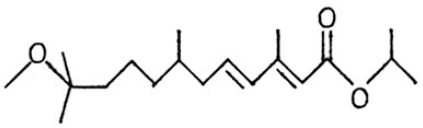
To date, no knowledge has been obtained as to the biochemical mechanism(s) of action of these compounds on embryonic development. However, one important difference is that, these new compounds can act throughout the course of embryonic development whereas some types typically act only on insect embryos in a very early stage of development.

Laboratory experiments and field studies in strawberries on the two-spotted spider mites by Nelson and Shaw[41] have revealed that compounds derived from cyclopropylmethyl alcohol and cyclopropanecarboxylic acid has satisfactory control of population of T. urticae Koch and have a good residual property, direct ovicidal effects, and temporary sterilization of adult female. They have also shown that, these compounds have no recognised hormonal activity and should not be referred to as JHA.

Structures showing hormonal activity are shown below:

1  (Roller et. al., 1977)

2  (Bowers 1969)

3  (Henrik et. al., 1973)

Staal (1972) reported that JHA active on many insect groups, show no significant effect on eggs or nymphs of spider mites or ticks. Bull et al. (1973) reported that, 2nd stage caramine spider mites, Tetranychus cinnabarinus (Boisduval) evinced no visible effects of hormonal action when dipped in 50% aqueous ethanol solution containing JHA at 0.01 and 0.1%.

Kramer and McGregor[42] have evaluated successfully hexadecyl cyclopropanecarboxylate (ZR-856, Zardex) by application to high moisture wheat and artificial rearing medium at the ratio of 10-500 ppm and reduced the population of Tyrophagus putrescentiae (Schrank).

Wolfenberger et al.[43] reported (3-phenoxyphenyl) methyl (±) cis-trans (2,2-dichloroethenyl) 2,2-dimethyl-cyclopropanecarboxylate against Trileurodes abutilonea,

Pesudatomoscelis seriatus and also against predator complex. They have revealed that cis-isomer was more active than trans one.

In addition, in our laboratory, some esters[44] of 2,2-dimethyl-3-n-propyl-cyclopropane-acetic acid have been prepared and examined for their miticidal activity against tuber mites (Rhizoglyphus echinopus) and found to be active more than tetradifon, which was applied for comparison. Similarly, some esters of 2,2-dimethyl-3 (2-oxopropyl)cyclopropane-1-acetic acid and 2,2-dimethyl-3(n-propyl) cyclopropyl ethanol have also been prepared and patented[45] for their miticidal activity (Chapter II).

During the last decade many synthetic approaches[46-50] for obtaining an isomeric mixture of cis- and trans-3-(2-chloro/cyano styryl and 2-E styryl) 2,2-dimethyl cyclopropanecarboxylic acid esters (±) trans-3-(2-chloro-2-phenylvinyl)2,2-dimethyl cyclopropane-carboxylic acid esters have been reported. Many pyrethroid esters with alcohols like 3-phenoxybenzyl, ∝-cyano-3-phenoxybenzyl and 6-phenoxy pyridine-2-methanol were reported to possess high and selective miticidal and ectoparaciticidal activity.

Recently[51-53] many esters of trans-2,2-dimethyl-3-(2E-phenylalkenyl and 2-chloro-2p-chlorophenylvinyl) cyclopropanecarboxylic acid with alcohols like

3-phenoxy benzyl,∝-cyano-4-fluoro-3-phenoxybenzyl alcohol and 6-phenoxypyridene-2-methanol have been reported to be prepared from acyclic substrates and patented them for their miticidal and ectoparaciticidal activities.

In our laboratory[54] the following three, E and Z isomers of 3-phenoxybenzyl esters, from (+)-3-carene have been prepared-

i) 3-phenoxybenzyl (+) 1R-trans-2,2-dimethyl-3-(2-chloro-2-p-chlorophenylvinyl)cyclopropane-carboxylate.

ii) 3-phenoxybenzyl (+) 1R-trans-2,2-dimethyl-3-(2E-p-chlorostyryl)cyclopropanecarboxylate.

iii) 3-phenoxybenzyl (+)1R-trans-2,2-dimethyl-3-(chlorophenylethynyl)cyclopropanecarboxylate.

These esters are prepared with a view to examine them for possible miticidal activity.

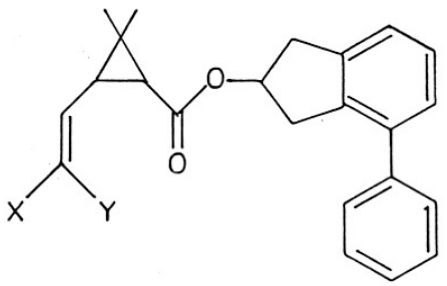
Recently, high acaricidal activity is shown by 4,4'-dichlorodiphenylethoxymethyl carbinol which is known as Ethoxynol and also by 4,4'-dichloro-diphenylethynyl carbinol.

The discovery of a new class of potent insecticides based on 4-phenyl-2-indanol[55], is the first example of foliar active pyrethroids known to be highly active against agriculturally important insects which do not contain either benzyl alcohol or an alpha-

cyanobenzyl alcohol moiety in their structure. The acaricidal activity for this series proved to be quite interesting and is tabulated in Table IV for various acids and indanol combinations, including esters with the resolved alcohols.

Table IV

Acaricidal Activity of Indanyl pyrethroids against two-spotted spider mites



Compound	X	Y	Acid	Alcohol	LC_{50} (ppm)
1	CF_3	Cl	cis	R,S	3.8
2	Cl	Cl	cis	R,S	7.8
3	Br	Br	cis	R,S	7.7
4	CF_2Cl	F	cis	R,S	5.0
5	CF_3	Cl	cis	S	2.5
6	CF_3	Cl	1R,cis	S	1.5

During the last 3-4 years, various cyclopropenoid and non-cyclopropenoid derivatives have been synthesised by groups of Japanese, Russian, European and American workers as well as various commercial manufacturers and have been patented for their miticidal activity. These are discussed ahead.

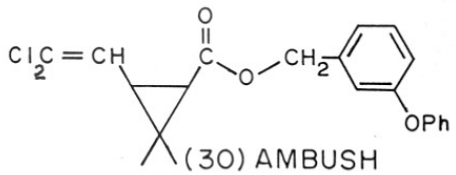
Ambush (30), Sumicidin, Decis, Ripcord (31) have been reported[56] to control codling moth 97-100% and increased apple yield. They killed acariphagus which increased damage by mites, Pananychus ulmi, Tetranychus viennensis and Schizotetranychus pruni.

Some carboxylic esters like (32) and (33), 3'-aniline ∝-cyanobenzyl-2,2-dimethyl-3-(2,2-dimethyl-3-(2,2-dichlorovinyl)cyclopropanecarboxylate is reported[57] to be effective against Tetranychus tetralius and flies.

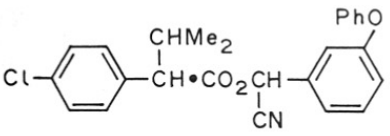
Nowakowshi et al.[58], reported that by 0.05% Danitol (fenpropathrin, 34), P. Ulmi infestation on apples were substantially decreased.

Some isovaleric esters[59], like (35) 3'-phenoxy-∝-cyanobenzyl,∝-(2,4-dichlorophenyl)isovalerate controlled Tetranychus urticae.

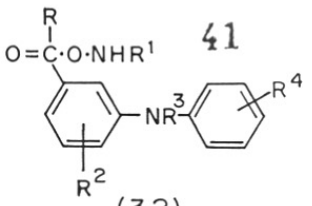
Total control on two-spotted spider mites (T.urticae) on pinto beans has been reported by Engel et al.[60], by application of biphenylmethyl-



(30) AMBUSH

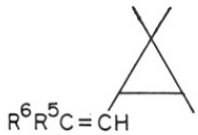


(31) RIPCORD



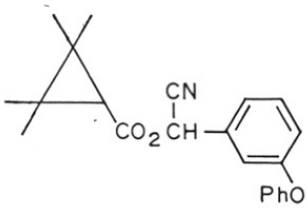
(32)

R^1 = H , CN
R^2 = R^4 = H , Halo, Me / OMe
R^3 = H , Me
R = (33)

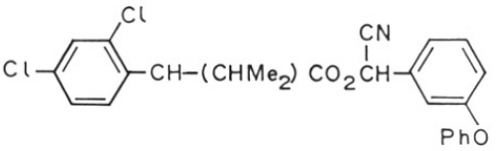


(33)

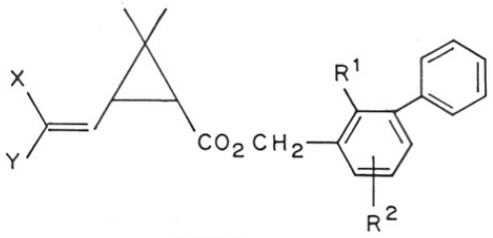
R^5 and R^6 = Me, Halo, Halomethyl



(34) FENPROPATHRIN

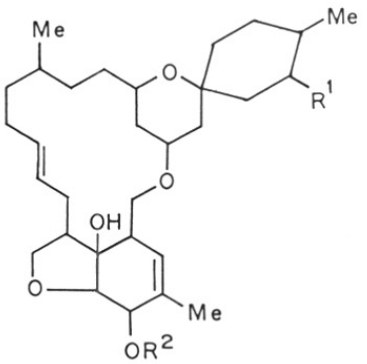


(35)



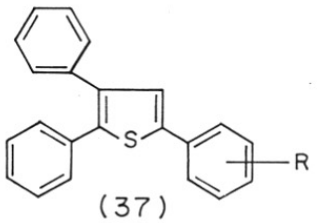
(36)

X and Y = Halo / CF_3
R^1 and R^2 = H, Halo/Lower alkyl



(38)

R^1 = Me, Et, $CHMe_2$
R^2 = H, CO_2R^3
R^3 = (un) protected sugar alc. or acid



(37)

R = Halo, H, Me, MeO, Me_3C

perhaloalkylvinyl cyclopropanecarboxylate (36). Similarly many other cyclopropane derivatives have been recently reported[61-63] to be active against various mites, one and multi-host ticks and are patented.

Some diphenyl thiophene derivatives control citrus rust mites are reported[64]. Thus, 2,4-diphenyl-thiophene and 2,3-di-p-anisyl-5-p-tolnylthiophene (37) were prepared and found to be useful for total control of citrus mites.

Some heterocyclic synthons[65-67] for acaricidal phosphate esters and some biologically active hetero-cyclic hydroxyimidates[57] and carbamate ester derivatives having acaricidal activity have been patented. Similarly some heterodiamido (di) thioates are also reported[68] to give 100% kill of two-spotted spider mites.

About 29 pesticidal cyano enol phosphates showing better two-spotted mite killing activity, than kelthane, have been reported by D'Silva et al., of Union Carbide Corporation[69] last year.

During early 1986, compounds containing substituted phenylacetic acid and isopropargyl esters were used as bioacids and were reported[70] to be acaricides. Similarly, N-benzoyl-n'-stilbenyl urea derivatives[71] have also been reported to give 100% mite control.

Very recently many workers from Japanese chemical industries have developed the acaricidal formulations with variety of other pesticides to get enhanced synergistic miticidal composition, effective against resistant mites. These are discussed below in brief.

Miticidal composition[72] containing benzomate, kelthane, chlorobenzilate, chloropropylate and dimethioate act as effective acaricide for resistant mites.

Some of the insecticidal mixtures show enhanced miticidal activity[73]. For example, activity of amitraz is enhanced by pyrethroids such as deltamethrin, alfoxylate, phenothrin, and cyphenothrin. The ratio of amitraz/pyrethroid vary over a wide range. This mixture are broad range miticides.

A compound containing DMAP and 0,0-di-iso-PrS-Etsulfinylmethylphosphorodithioate and its analogoues is a good acaricide[74] and control Myzus persiae on cabbage. Some carboxylic acid esters and acaricidal composition have also been reported[75]. Similarly, phospholipides enhance the activity of known miticides[76]. Thus, compound containing dicofol and phosphatidylcholine totally controlled red-spider mites on ornamental plants.

Compounds containing thiadiazines and synthetic pyrethroids or miticides are reported[77] to be good miticides.

Milbemycin-5-carbonate derivatives (38) and its composition have acaricidal activity[78]. It can be applied both internally and topically in an appropriate formulation.

Synergistic miticidal composition comprising 2,4-diamino-6-cyclopropylamino-6-triazine and cypermethrin in 9:1 weight ratio show good acaricidal activity.

Future scope

The original synthetic miticides were general poisons with non-specific activity such as hydrogen cyanide, lead arsenate with a wide spectrum of mammalian toxicity. Later work led to the discovery of less poisonous and more selective organic chemicals, illustrative examples were certain organophosphate, carbamates and other chlorine-containing compound.

There is now much greater awarness of the dangers of environmental pollution arising from the widespread application of these chemicals which have to pass increasingly stringent test regarding toxicity, selectivity and residue formation before they can be utilised. So, there is necessity and desirability to

develop new miticides with extremely high target specificity. There are numerous mite species of economic importance, and in some cases a single crop can contain simultaneously several different species of phytophagus mites. So it is desirable and practicable to develop new acaricides which are selective to individual mite species. In general these new acaricides should possess the properties desired of insect control agents with respect to environmental compatibility, including minimal side effects on non-target species. For example, they should be effective against target mites at dosage levels which will not harm predators and pollinating insects such as honeybees. It is noteworthy that chlorobenzilate, has been used successfully to control the acarine disease of bees without affecting the honeybees themselves[79]. In this respect, a favourable selective toxicity ratio between predaceous mites and phytophagus mites is required.

The increasing emphasis on systemic rather than contact miticides leads to more effective use of the chemicals and less danger of environmental pollution. During the last ten years, the most significant breakthrough in chemical pesticide research has certainly been the introduction of commercially viable

synthetic pyrethroids which are highly active and specific in their toxicity.

Finally, the availability of more selecstive acaricides permit them to be used in conjunction with biological control methods and that integrated biological-chemical measures of pest control will become more common in future.

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CHAPTER - II

SYNTHESIS OF NEW, POTENT MITICIDAL ESTERS OF 2,2-DIMETHYL-3(2-OXOPROPYL) CYCLOPROPANE ACETIC ACID AND 2,2-DIMETHYL-3-(n-PROPYL) CYCLOPROPANE ACETIC ACID FROM (+)-3-CARENE

SUMMARY

This chapter deals with the synthesis of new, potent miticidal esters of 2,2-dimethyl-3-(2-oxopropyl)-cis-cyclopropaneacetic acid, 2,2-dimethyl-3-(n-propyl) cis-cyclopropaneacetic acid and some reversed esters of 2,2-dimethyl-3-(n-propyl)-cis-cyclopropyl ethanol from naturally occurring (+)-3-carene.

(+)-3-Carene was canverted into 3β, 4α-carane-diol (II) which, on Jones chromic acid oxidation gave keto acid (III). Wolf-Kishner reduction of this keto acid (III), yielded reduced acid (IV).

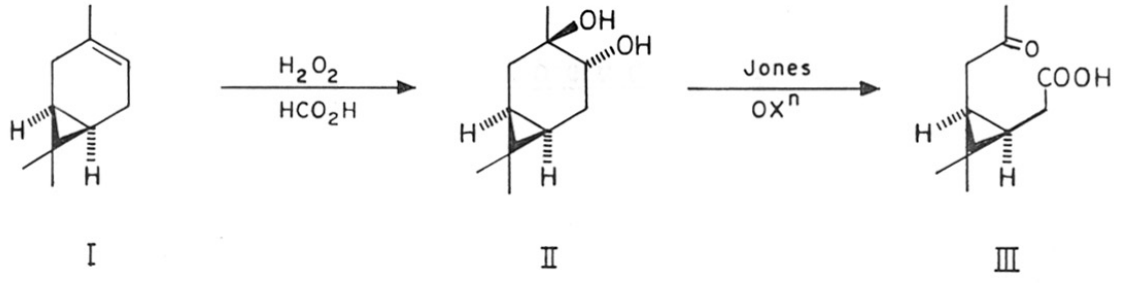
In the first method, substituted alkyl, cyclo-hexyl, cyclohexylalkyl, aryl and aralkyl esters were prepared from acid (III) and (IV) via their acid chlorides.

In the second method, acid (III) and acid (IV) were converted into their respective methyl esters (V and VI), which were transesterified with 2-phenoxy ethanol and m-phenoxybenzyl alcohol in presence of catalytic n-butyl titanate respectively.

In the third method, LAH reduction of methyl ester (VI), afforded primary alcohol (IX) from which, two reversed esters, viz. paratoluyl and p-anisoyl esters were prepared.

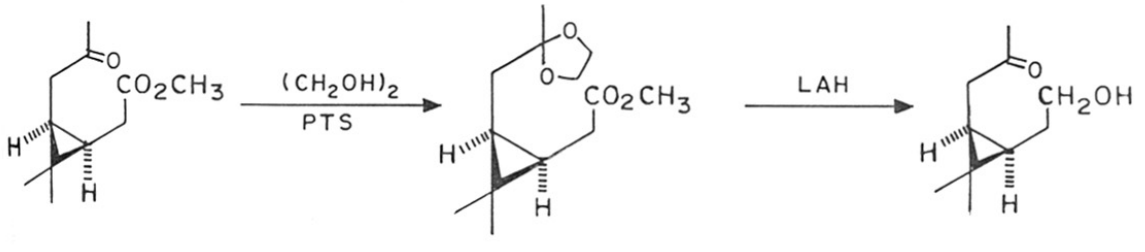
Ketalisation of keto ester (V), afforded ketal ester (VII). LAH reduction of (VII) and subsequent deketalisation furnished keto alcohol (VIII) which was esterified with paratoluic acid chloride.

The bio-efficacy of most of these esters were carried out by testing against different types of species of mites from different areas in the country.

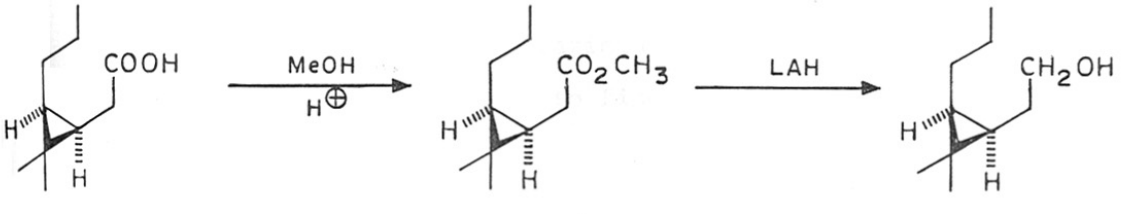


I II III

IV III



V VII VIII



IV VI IX

INTRODUCTION

Synthetic pyrethroids belong to an almost ideal group of modern insecticides due to their high insecticidal activity combined with low mammalian toxicity and rapid biodegradability. While several pyrethroids with potent insecticidal action have been synthesised[1], search for analogues with higher photochemical stability and other pesticidal activity continues. One major drawback of synthetic pyrethroids currently in use, is their low acaricidal activity. In this connection, some esters of 2,2-dimethyl-3 (2-aryl-2-chlorovinyl)cyclopropanecarboxylic acid have recently been reported[2-4]. The developing physiological and biochemical understanding of pesticide toxicology, soon provided an outline of the essential principles for selective pesticide action in relation to chemical properties of the compounds[5].

Numerous synthetic organic compounds differing markedly in their chemical configurations possess acaricidal activity[6,7]. It is noteworthy that currently more different classes of chemicals are used commercially as acaricides than as insecticides. Thus, one would expect to find acaricides to have a

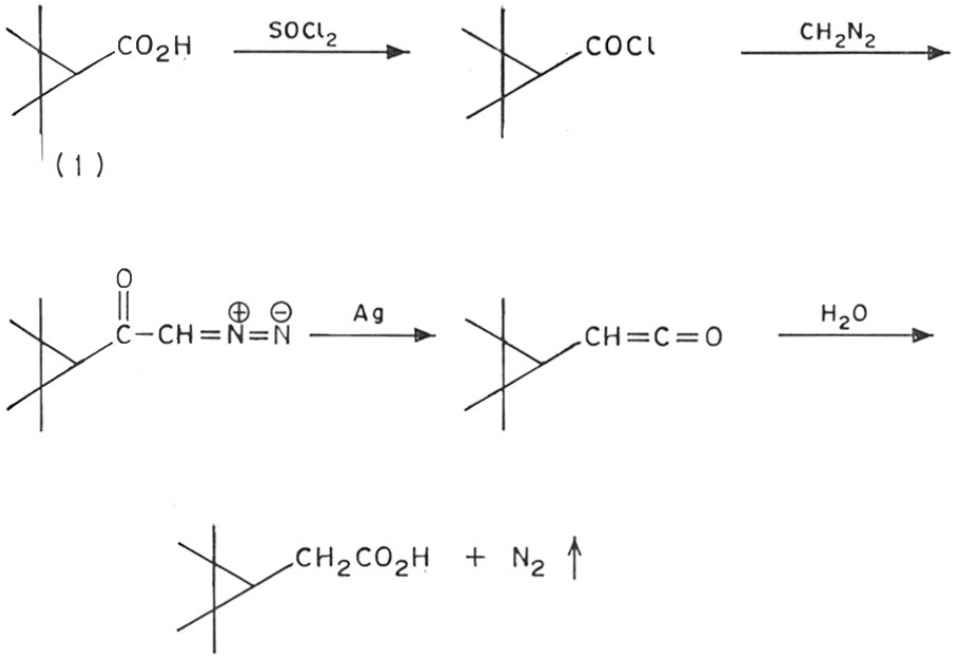
broad selectivity spectrum. Acariside selectivity has been considered with respect to groups of different organisms, for example mammals, insects, and mites. However, even closely related species can differ in their susceptibility to miticdes[8]. Some miticides show differential toxicity to various stages of the same mite species. For instance, with two-spotted spider mite, Tetranychus urticae koch, chlorobenzilate was equitoxic to the adult and larval stages but was less active against the eggs[9]. There are numerous examples of this particular type of miticide selectivily[7,10].

In case of miticides, only meager information is available with respect to penetration, mode of action and metabolism in target and non-target species. However, differential metabolism seems to be involved in many instances[11]. So, by taking into account the available data on miticide metabolism as well as mode of action and structure-activity relationships, it is possible to designate certain chemical groupings in the molecule for the better selection of miticide. In this regard, a number of compounds derived from cyclopropyl methyl alcohol and from cyclopropane-carboxylic acid are known[12-14].

Matsui et al.[15] have synthesised number of 2,2-dimethyl-3-alkylcyclopropanecarboxylic acid esters, possessing different alkyl groups at C-3 position of cyclopropane and studied their rethronyl esters for insecticidal activity and compared them with natural pyrethrins. Since the acid moiety of such esters were prepared starting from acyclic precursor, dl mixtures of cis- and transcyclopropanecarboxylic acids were produced. Among the compounds they prepared 2,2,3,3-tetramethylcyclopropaneacetic acid (2), a homo acid of (1) was synthesised by Arndt-Eistert reaction (Scheme I). The kill effect of rethronyl ester of this homoacid (2) on the housefly and mosquito shows LC_{50} mg/100 ml is more than 1080 and indicates activity.

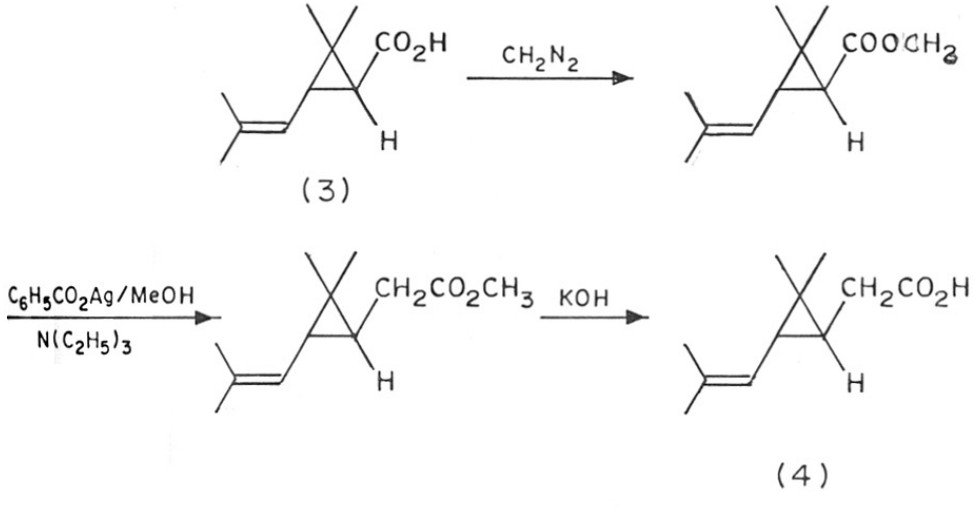
The higher homologue of (+) cis chrysanthemic acid viz. (+) cis-homochrysanthemic acid [methyl 2,2-dimethyl-3-(2-methyl-prop-1-enyl)cis-cyclopropane-1-acetate], has been prepared earlier by crombie et al.[16] by Arndt-Eistert homologation of (+) cis-chrysanthemic acid, followed by optical resolution of the resulting dl-homochrysanthemic acid with (+) -α methylbenzylamine. Crombie has converted authentic (+)-trans-chrysanthemic acid (3) into crystalline (±)-trans-homochrysanthemic acid (4) by the amide

SCHEME – I



SCHEME – II CROMBIE'S METHOD

SYNTHESIS OF (±) TRANS-HOMOCHRYSANTHEMIC ACID



(±) TRANS-HOMOCHRYSANTHEMIC ACID

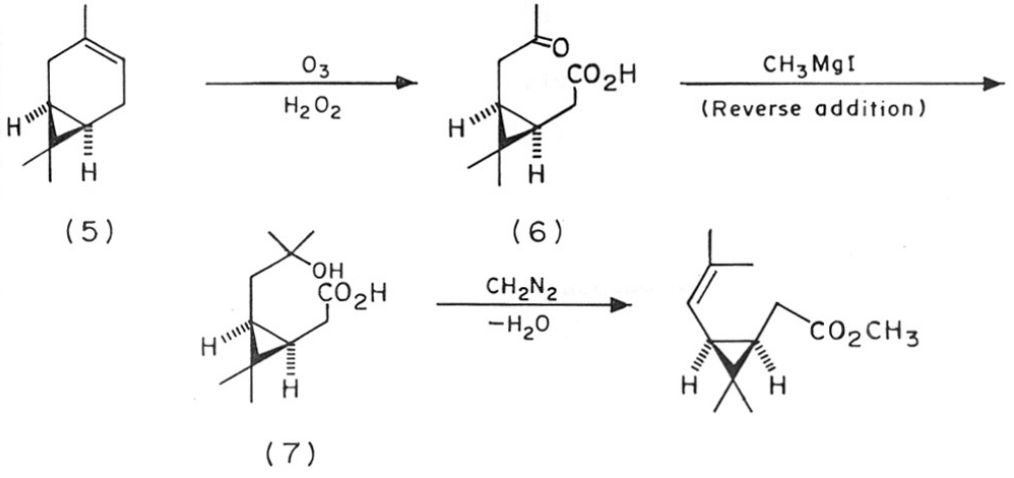
sequence (Scheme II); better yields were obtained by the silver benzoate-triethylamine route[17], through methyl ester. Subsequently, synthesis of homochrysanthemic acid was achieved from (+)-3-carene by Sasaki et al.[18] (Scheme III). Ozonolysis of (+)-3-carene, followed by oxidative workup of the resulting ozonoid, gave the 2,2-dimethyl-3-(2-oxopropyl) cyclopropane-1-acetic acid (6) which on Grignard reaction using MeMgI (reverse addition), afforded the hydroxy acid (7). The corresponding methyl ester on dehydration, gave methyl (+) cis-homochrysanthemate (8).

The acaricidal properties of esters of (+)-cis-homochrysanthemic acid appears not to have been investigated, though they are not likely to possess good insecticidal activity, since they lack a carboxylate function directly attached to the cyclopropane. In this case, our keto acid (III), conveniently prepared from (+)-3-carene, can act as a crucial intermediate for the preparation of (+)-cis-homochrysanthemic acid esters.

In view of this observation, it was felt desirable to prepare some esters at C-1 of cyclopropane, the difference being mainly in the nature of side chain at C-3.

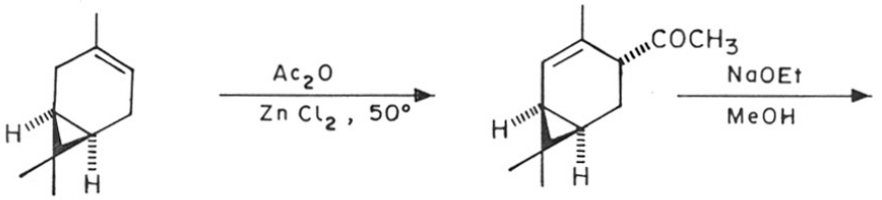
The keto carboxylic acid has been obtained by known method[19] (Scheme IV) from 4-acetyl car-2-ene(9).

SCHEME-III

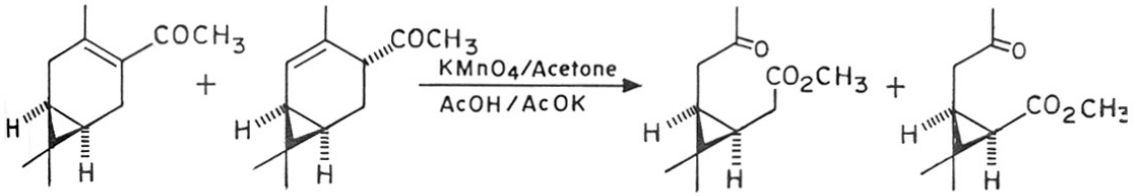


(5) (6) (7)

SCHEME-IV

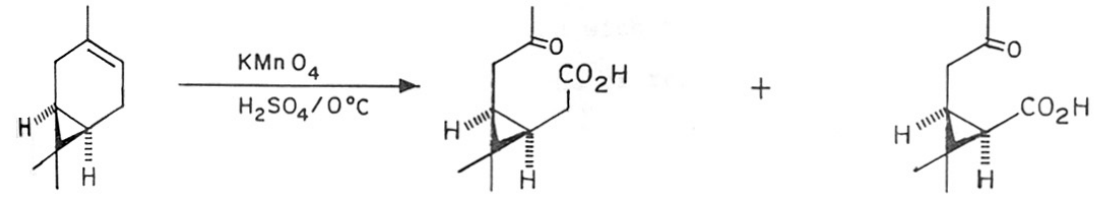


(5) (9)



(10) (9) (11) (12)

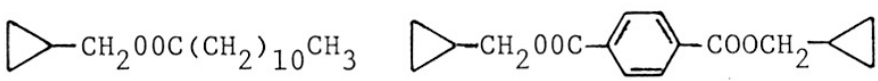
SCHEME-V



(5) (13) (14)

In this, the acetyl derivative was rearranged under basic condition, to afford a mixture of 4-acetyl car-3-ene (10) and the unreacted starting compound (9) When the mixture was oxidized with $KMnO_4$ in acetone under buffer condition (acetic acid + potassium acetate), it afforded a mixture of two acids which was subsequently converted into a mixture of two keto methyl esters (11) and (12) as shown in Scheme IV. The same mixture of keto acids has also been obtained[14] by direct oxidation of (+)-3-carene with $KMnO_4$ in presence of sulfuric acid at 0° (Scheme V).

Hurkova et al.[20] have studied the effects of two cyclopropane miticides on Tetranychus urticae (Acari Tetranychidae). These are cyclopropylmethyl dodecanoate (A) and cyclopropylmethyl terephthalate (B) and were found to be ovicidal against two-spotted spider mites, having Lc_{50} values of 0.003% and 0.012% respectively, compared with 0.00026% of tetradifon.

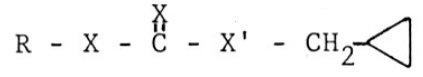


(A) (B)

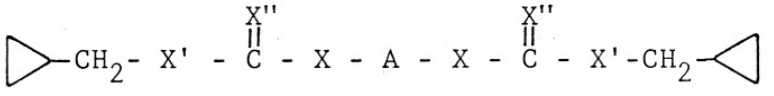
A multiple resistant strain of T.urticae showed a cross resistance to (A) and (B) of 5.0 to 1.6 times respectively, compared with the susceptible strain. After three generations of repeated selection of the

resistant strain with compound (A), treatment of eggs with compound (A) failed to kill any eggs laid on plant leaves. A study of embryonic development of eggs, treated with compound (A) showed that 62% of mature larvae died in the chorian, 17% died on hatching, 6% stopped to develop after pigmentation and 1% prior to pigmentation. Recently extensive work has been carried out to evaluate the miticidal activity of a number of esters of cyclopropane-carboxylic acid and cyclopropyl methyl alcohol by a group of workers from Zoecon Corporation, USA. They observed the association between mite ovicidal activity and cyclopropylmethyl moiety in these compounds.

Henrik et al.[21] invented many novel compounds, characterised by cyclopropylmethyl moiety, which are of the following types:



(C)

and  (D)

wherein

X, X' and X'' are independently oxygen or sulfur;

R is a monovalent organic radical and (C) is alkylene, alkenylene or alkynylene.

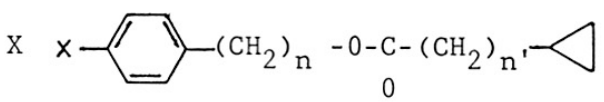
Typical compounds of formula (C) are those wherein R is alkyl, alkenyl, or alkynyl of 10 to 20 carbon atoms, alkylcyclopropane, wherein the alkyl portion contains one to four carbon atoms, or aralkyl.

Typical compounds of formula (D) are those, wherein, (A) is alkylene of one to 20 carbon atoms, or alkenylene or alkynylene of two to 20 carbon atoms. Here cyclopropylmethyl alcohols have been prepared by many reported methods[22-24].

The various compounds prepared by Henrik et al., had effective control over mites at any stage, namely, during the egg, larvae, nymphal or adult. It was applied in view of their effect in causing abnormal development leading to death, inability to pass from one stage to the next or inability to reproduce. Here no limitations had been placed on the chain length in the case of R when it represents an acyclic monovalent organic radical, which has a chain length of 5 to 30 carbon atoms that can be saturated or unsaturated and branched or straight one. The acyclic organic radical was substituted with one or more heteratoms, such as hydroxy, halogen atom, alkoxy, amino or alkylthio. The organic radical was also carbocyclic of from 3 to 10 carbon atoms such as

cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cycloxadienyl and the like. The organic radical was also aryl or alkaryl group of from six to 15 carbon atoms.

Henrik et al.[25] have further reported synthesis of many esters of the following general formula-



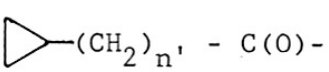
wherein,

n is a positive integer from 1 to 4

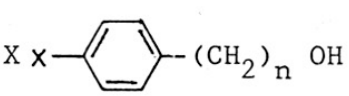
n' is zero or a positive integer from one to 4 and

X is hydrogen, aryl, aralkyl, alkoxy or aralkoxy.

The esters of this invention have been prepared using conventional esterification procedures that are well known. For example, by the reaction of an acid halide of the formula.



with an alcohol of the formula



or by direct esterification of an acid with the alcohol in presence of an acid catalyst. These esters are found to be effective for the control of spider mites.

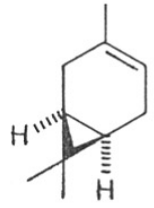
On the basis of these observations, in our laboratory, Mitra et al.[26] have synthesised a number of potential miticidal derivatives from naturally occurring (+)-3-carene. Some of these compounds exhibit more efficacy than tetradifon, when tested against tuber mites, Rhizoglyphus echinopus. In this keto acid (III), was obtained by direct oxidation of (+) trans-3,4-diol (II) with Jones reagent at room temperature during two hours, which was a more convenient route as against the earlier one where, keto acid (III) was obtained by cleavage of the diol (II) by metaperiodate[27] followed by $KMnO_4$ oxidation[28] or by ozonolysis of (+)-3-carene followed by chromic acid oxidation[29].

The miticidal activity data of these compounds have been summarised in Table I. Here, the esters (Va to Vd) were prepared from the reduction of the tosylhydrazone derivative of keto esters (IVa to IVd) with $NaBH_4$. The esters, summarised in the Table I along with some more (not mentioned here), were evaluated at Central Potato Research Station, Rajgurunagar, Maharashtra, against potato mites, the results of which is tabulised in Table II.

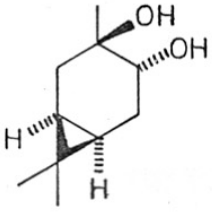
These above esters were also tested at Tokalai Experimental Station, (Tea research association)

against red-spider mites and observed the percentage mortality at various concentrations. The data is given in Table III.

The experimental data for evaluation of these long-chain esters of fatty alcohols and phenols from cyclopropaneacetic acids, shows that they have effective control over these variety of mites.



I



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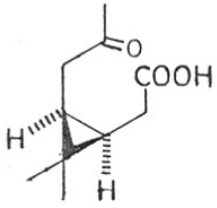

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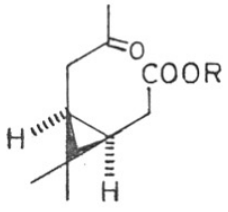


IV

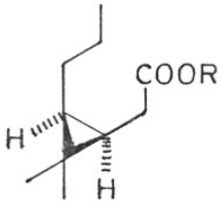
R =

a: C_4H_9

b: $C_{12}H_{25}$

c: $C_{16}H_{33}$

d: C_6H_5



V

Table I

No.	Name of the compound	Miticidal activity
IVa	Butyl keto ester	15/30
IVb	Lauryl keto ester	15/30
IVc	Cetyl keto ester	3/30
IVd	Phenyl keto ester	1/30
Va	Butyl ester	6/30
Vb	Lauryl ester	9/30
Vc	Cetyl ester	7/30
Vd	Phenyl ester	17/30
	Tetradifon	11/30
	Control water	1/30

Mortality 48 hrs. after treatment (total 3 replicates)

Table II

No.	Name of the compound	Average population reduction after 24 hrs (%)
1	Lauryl ester	41.71
2	Lauryl keto ester	30.71
3	Butyl keto ester	20.98
4	Cetyl ester	48.85
5	Cetyl keto ester	80.16
6	Tetradifon	43.24
7	C_{14} Keto ester	79.56
8	C_{14} ester	43.16
9	Phenyl ester	35.14
10	Phenyl keto ester	67.38

Table III

No.	Name of the compound	Concentration	%Mortality 24 hrs of treatment
1	Cetyl ester	1	100
2	Cetyl keto ester	1	100
3	Cetyl ester	0.5	100
4	Tetradifon	1	100
5	Phenyl keto ester	1	100
6	Phenyl keto ester	0.5	100
7	Control water	-	-

Present work and discussion

Indian terpentine oil is rich in (+)-3-carene as can be seen from Table IV[30]. So, in our programme, this abundant and naturally occurring monoterpene was utilised for the synthesis of substituted cyclopropaneacetic acid and corresponding alcohol moieties for the preparation of various potent miticidal esters. Our lead was from the recent work carried out at Zoecon Corporation, USA on the similar derivatives, of which, some such as, Zr-51R are already commercial. However, these are mainly mite ovicides with practically no adulticidal effect. Our compounds derived from (+)-3-carene (I), have been tested successfully at various agricultural research institute in the country and the bio-efficacy of many structurally related esters of cyclopropaneacetic acid and cyclopropylethanol reported. The names of these research stations are

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

ii) Tea Research Association, Tocklai (Assam)

iii) Potato Research Station, Simla

iv) Potato Research Station, Rajgurunagar

v) United Planters Association, Coonoor, Southern India.

The preliminary tests indicated highly promising adulticidal effect on the red spider mite, potato mites, Rhizoglyphus echinopus and Polyphagotarsonemus latus as well as pink and purple mites, Acaphyllus theae in comparison with Tedion, Tetradifon and dicofol (Kelthane). We thought that if we could functionalise C-5 of (+)-3-carene, then we could get these acids (III and IV) by oxidative degradation. With this strategy in mind, (+)-3-carene (I), was converted into carane diol (II) by usual method[31], using performic acid, in 52% yield and obtained as a white crystalline solid; m.p. 87-88° (5% of ethyl acetate in pet.ether).

Jones chromic acid oxidation of caranediol (II) afforded keto acid (III), a brown coloured liquid; $C_{10}H_{16}O_3$, M^+ 184 and shows IR (liquid film) bands at bands at 3300, 1738, 1724 and PMR (CCl_4, δ) signals at 0.9 (4H, brs, one gemdimethyl at C-2 overlapping cyclopropane proton at C-3), 1.15 (4H, s, other gemdimethyl or cyclopropane overlapping cyclopropane proton at C-1), 2.1 (3H, s, $-COCH_3$), 2.15 - 2.5 (4H, m, 2 x $COCH_3$), 7.5 (1H, brs, acid proton).

Wolf-Kishner reduction of keto acid (III) with 80% aqueous solution of hydrazine hydrate in diethylene glycol/KOH solution, yielded acid (IV) in 90% yield as a yellowish liquid; $C_{10}H_{18}O_2$, M^+ 170 and showed

Table IV

Typical analysis of Terpentine

	USA %	France %	India %	USSR %	Portugal %	Sweden %	Japan %
-Pinene	65-75	60	20-30	75	80	80	85
-Pinene	20-30	25-30	5-10	-	15-17	5	10
^{3}-Carene	-	-	55-65	15	-	15	5
Longifolene	-	-	2-5	-	-	-	-
Other terpenes	5	5-10	3-5	10	3-5	-	-

IR (liquid film) bands at 3300 (strong acid OH) and PMR (CCl_4, δ) signals at 0.7 (2H, m, cyclopropane protons), 0.9, 1.1 (6H, 2s, 2X-CH_3 at C-2) 1.15-1.47 (7H, m, n-propyl at C-3), 2.3 (2H, d, J = 7 Hz, -CH_2 at C-1 and 11.5 (1H, brs, acid proton).

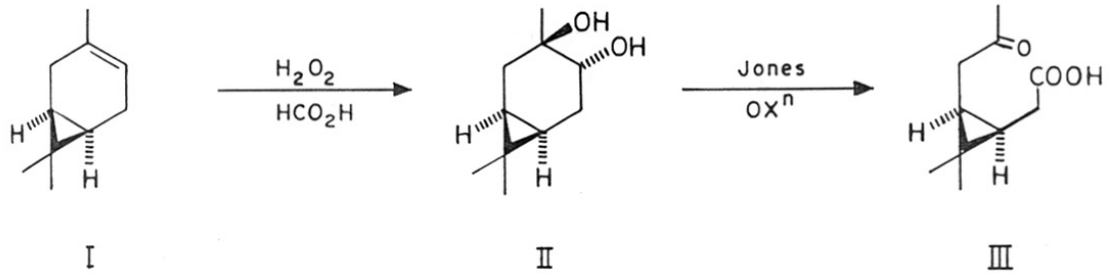
About thirtyfive alkyl, aralkyl, halo- and alkoxy-substituted aryl monoesters and five diesters were prepared from acid (III) and acid (IV) by mainly three different methods.

Method A

Acids (III) and (IV) were converted into their acid chlorides with thionyl chloride and catalytic DMF and pyridine in ice-cold condition. Thirty two esters and diesters (as shown on page 78) were prepared by condensing various substituted alcohols and phenols (listed in Chart II, column 2 on page 99) and diols with the above acid chlorides. The final esters were prurified by silica gel column chromatography.

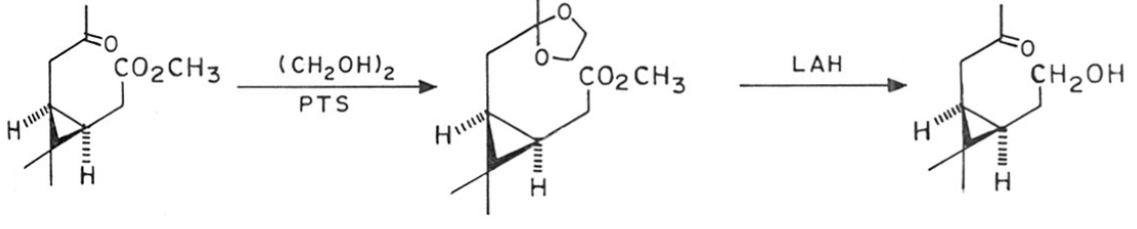
Method B

The acid (III) was converted into its methyl ester (V) with ethereal solution of diazomethane. Transesterification of ester (V) with 3-phenoxybenzyl alcohol and 2-phenoxyethanol catalysed by n-butyl titanate at 140-150°, afforded respectively, 3-phenoxy-benzyl ester (19) and 2-phenoxy ethyl ester (27) which

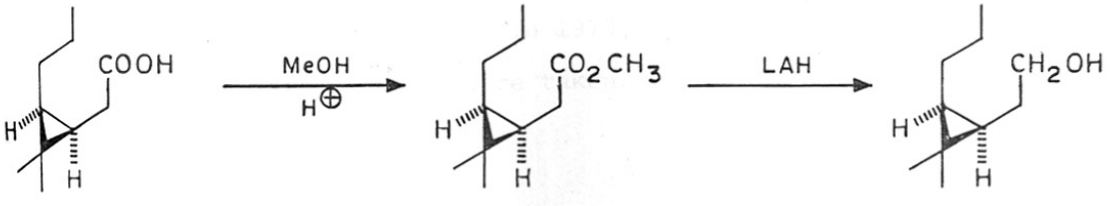


I II III

IV III



V VII VIII



IV VI IX

were purified by chromatography using silica gel.

Acid (IV) was converted into its methyl ester (VI) which on LAH reduction, afforded primary alcohol (IX) in 90% yield. Transesterification of this alcohol (IX) with methyl sebacate with Catalytic n-butyltitanate, gave diester (39).

Method C

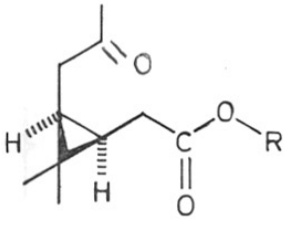
Ketalization of keto ester (V) with ethylene glycol and catalytic PTSA, afforded ketal ester (VII), which on LAH reduction and subsequent deketalisation, yielded keto alcohol (VIII). Esterification of this alcohol (VIII) with p-toluyl acid chloride furnished ester (35).

Similarly primary alcohol (IX) was also esterified with the acid chlorides of para-toluic acid, p-chlorobenzoic acid and p-anisic acid respectively to get esters (36), (37) and (38) respectively. Two diesters (39) and (40) were prepared by similar method by the reaction of primary alcohol (IX) with acid chlorides of sebasic acid and terephthalic acid.

The experimental data and spectral analysis is charted in Chart II and Chart III (on pages 99, 101)

In continuation of the work carried out by R.B. Mitra et al.[26], in 1978, some fatty alcohol esters and cresyl esters were taken for evaluation of their

CHART – I



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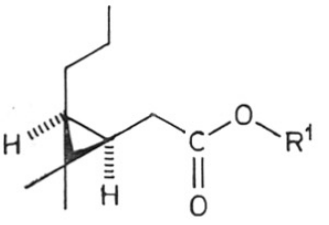
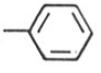
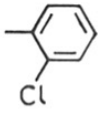


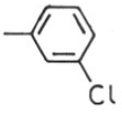
IV

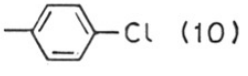
R = $-C_4H_9$ (1)

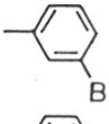
 (5a)

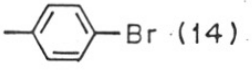
$-C_6H_{13}$ (3)

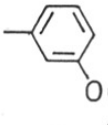
 (6)

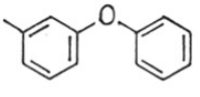
 (8)

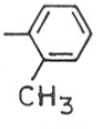
 (10)

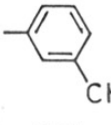
 (12)

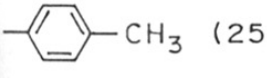
 (14)

 (16)

 (19)

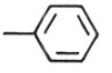
 (21)

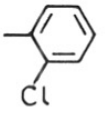
 (23)

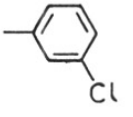
 (25)

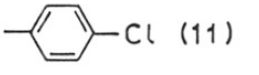
$R^1 = -C_4H_9$ (2)

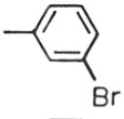
$-C_9H_{19}$ (4)

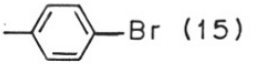
 (5)

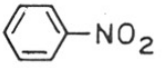
 (7)

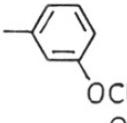
 (9)

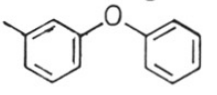
 (11)

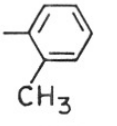
 (13)

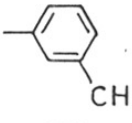
 (15)

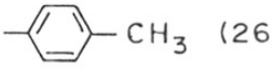
 (17),

 (18)

 (20)

 (22)

 (24)

 (26)

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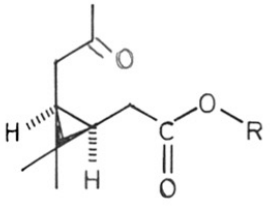

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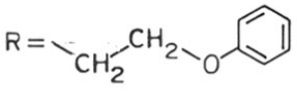

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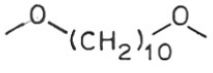

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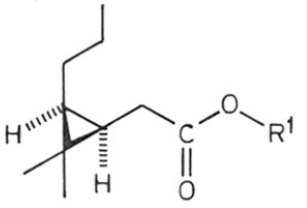

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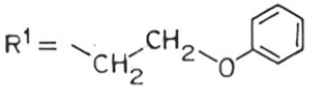

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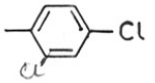

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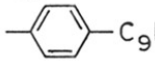

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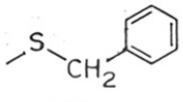

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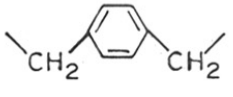

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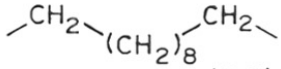

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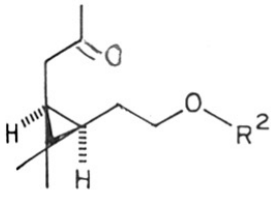

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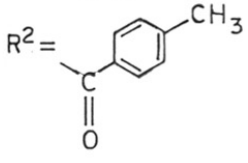

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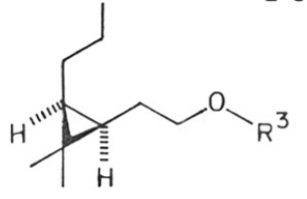

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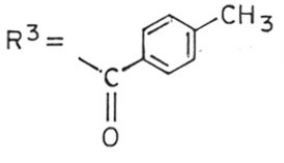

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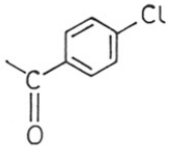

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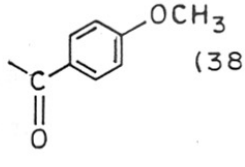

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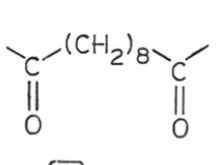

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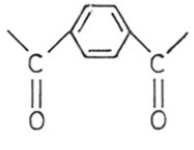

(40)

miticidal activity. The evaluation of some samples (data in Table V) on potato mites were carried out by spraying the solution of all the compounds in acetone solvent. The mite, Rhzoglyphus echinopus was used as test organism for determining the bio-efficacy of these compounds. The solution at 0.5% concentration was sprayed inside the test-tube by hand automiser. A piece of infected potato was placed inside each test-tube before spraying, for feeding the mites. After the spray film had dried, ten adult mites were liberated in each treatment. Inside of the tubes were later plugged with cotton. After the treatment, mortality data were recorded 48 hr. after liberation. The tests were repeated twice and the results are reported. The samples were tested upto 0.005% concentration on potao mites at Central Potato Research Centre at Rajgurunagar (Maharashtra). Among these compounds, meta cresyl keto ester (23) was found to give maximum activity (87.81%) with average population reduction after 24 hours.

Substituted phenyl esters were tested at concentration upto 0.01 and 0.005% for evaluation on pink and purple mites, at United Planters' Association in Southern India (UPASI), Coonoor. These mites commonly occur on tea plantation in the niligiris. The mortality data for these miticides is given in

Table VI.

The evaluation of nine other esters has been reported in Table VII. Here the compounds were dissolved in acetone and tested at the concentrations of 0.5%, 0.1% and 0.05% against the pink mite (Acaphyllus theae) and the purple mite (Calacarus carinatus). Each treatment had three replications. The percentage mortality of mites, after 24 and 48 hours after treatment is given in Table VII.

The most common acaricide recommended for controlling pink and purple mite is dicofol (Kelthane). It is normally used at the rate of 750-1200 ml of the formulation per hectare, or 140-180 g active ingrediant per hectare. Hence the recommended dilution rate is 1:200. Three reversed esters namely, p-toluylethyl ester (36), p-anisoyl ethyl ester (38) and terephthalyldiester (40) have been tested for their bio-efficacy in the laboratory, at the concentration of 0.03%, 0.02%, 0.01% and 0.005%. Among these p-anisoyl ester (38) has shown total control over pink and purple mites even at concentration of 0.005%. Since this compound (38) contain only C,H and O in its molecule, we felt that could be a very good and safe substitute for Kelthane.

Table V

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

Table VI

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

Table VII

Treatment against		Percentage mortality after					
		24 hours			48 hours		
		Concentration			Concentration		
a) Pink mites	No.	0.5%	0.1%	0.05%	0.5%	0.1%	0.05%
m-cresyl ester	(24)	100	100	96.5	100	100	96.6
phenyl keto ester	(5a)	96.6	92.5	31.2	100	92.5	59.4
phenyl ester	(5)	95.4	34.7	25	94.4	40	34.7
m-cresyl keto ester	(23)	100	80.7	70	100	96	85
Tedion	-	95.41	89	60.8	100	92.8	73.9
Control	-	nil	nil	nil	nil	nil	nil
b) Purple mites							
m-cresyl ester	(24)	100	100	100	100	100	100
phenyl keto ester	(5a)	90.4	69.5	69.5	90.4	73.9	73.9
phenyl ester	(5)	57.8	40.9	14.2	57.8	45.4	14.2
m-cresyl keto ester	(23)	100	73.6	47.6	100	84	61
Tedion	-	62.5	41.6	42	87.5	70.8	57.8
Control	-	nil	nil	nil	nil	nil	nil

As metacresyl ester (24) showed excellent results in laboratory trials in UPASI, field trials were undertaken (as described in Table VIII). The field experiment was conducted in randomised block design; each block consisting of 100 tea bushes. All the treatment had three replications. The performance of m-cresyl ester (24) (dissolved in acetone to make 18.5% solution, w/w) was compared with that of dicofol, ethion and cyhexatin. The dosage/ha of the different chemicals is given in Table IX. The spray volume used was 375 lit/ha and spraying was done by using motorised air blast sprayers. Sprays were given at weakly intervals. Pink mite (Acaphylla theae) population were monitored at weekly intervals for a period of four week to determine the field efficacy of the different chemicals.

Although in laboratory test, this compound (24) gave excellent control, it was found to be far below expectation in field trials. The reason for poor field performance might be due to lack of balanced formulation. In order to eliminate this draback, small quantity of formulated product (24, 20EC, in Table VI) has been sent for laboratory tests.

para-Anisyl ester (38) was also tested against two-spotted spider mites at FMC Corporation, USA on

carmine mites, which are predominant mites in United States. However, these mies have shown poor response and found to be quite resistant for these esters.

In conclusion, these cyclopropenoid esters have been observed to give excellent control over pink and purple mites occurring on tea leaves, while they have moderate control over potato mites and have poor control over red-spider especially carmine mites of USA.

Table VIII

Name of compound	%age mortality after 24 hrs			after 48 hrs.		
m-cresyl ester (24)	0.5	0.1	0.05	0.5	0.1	.05
Pink mites	100	100	96.5	100	100	96.5
Purple mites	100	100	100	100	100	100

Table IX

Field-efficacy of m-cresyl ester (24) against pink mite (Acaphyllus theae) of tea

Treatment	Dosage/ha	Pre-treatment	Post-treatment Incidence of Pink mite 1st day	7th day	14th day	21st day
cyhexatin	1000 g	235 (19.63)a	4 (4.41)a	5 (4.73)a	1 (3.41)a	2 (3.73)a
Ethion 50EC	1000 ml	243 (25.57)	47 (12.10)a	20 (8.26)a	4 (4.41)a	9 (5.41)a
Dicofol	1000 ml	235 (26.66)a	47 (12.10)a	20 (8.26)a	4 (4.41)a	9 (5.41)a
m-cresyl ester 18.5 EC(W/W)	1000 ml (in acetone)	165 (22.31)a	57 (13.32)ab	132 (19.55)b	39 (10.70)b	103 (17.41)b

Note: 1) Figures in parenthesis are sum of transformed values of three replications

2) Figures followed by the same letter of a column are non-significantly different at 1% level

EXPERIMENTAL

Preparation of 3β, 4α-carane diol (II)

In a 2-litre, 3-necked round bottom flask, equipped with a mechanical stirrer and a dropping funnel was placed formic acid (90%, 525 ml, 12.5 mol) and freshly distilled (+)-3-carene (I) (200 g, 1.47 mol) was added with stirring, through a dropping funnel. Hydrogen peroxide (30%, 300 ml) was then added, dropwise, maintaining the temperature of the reaction mixture between 35-45° (2 hr). Stirring was continued at that temperature for 6 hrs and reaction mixture was kept overnight. A solution of NaOH (160 g in 400 ml water) was added slowly to the reaction mixture under stirring, keeping the temperature around 25° (1 hr). The reaction mixture was transfered to a 2L separating funnel and the upper oily layer (approx. 280 g) was separated and transfered back to the reaction flask and remaining amount of NaOH (40 g in 1L water) was added, slowly, under vigorous stirring maintaining the temperature between 25-30°. After stirring for one hour and cooling to 5°, the solid diol separated out. It was filtered, residue washed with cold water and dried; 135 g, m.p. 68°. This crude diol was crystallised from pet.ether + 5% ethyl acetate mixture to give

127 g of diol (II), 52% m.p. 87-88°.

Analysis: Calculated for, $C_{10}H_{18}O_2$: C, 70.5; H, 10.7%
observed: C, 70.7; H, 10.6%.

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

2,2-Dimethyl-3-(2-oxopropyl) cis-cyclopropane-1-acetic acid (III)

To a vigorously stirred solution of carane diol (II) (51 g, 0.3 mol) in acetone (275 ml) was added, Jones chromic acid reagent (136 ml, 0.36 mol), dropwise maintaining temperature 5-10° (1.5 hr). It was further stirred for 2 hours at room temperature, diluted with water (400 ml) and extracted with chloroform (2 x 150 ml). Organic layer was washed with water (200 ml x 2) and then saturated aqueous Na_2CO_3 solution (2 x 150 ml). The chloroform layer containing portion was not investigated. The aqueous portion was acidified with 50% hydrochloric aacid at 5°-10° (2 pH) and extracted with chloroform (2 x 100 ml). Chloroform layer was washed with water (2 x 150 ml); finally with brine, dried over anhydrous sodium sulphate, to get brown oily liquid (III, 42 g, 76% yield).

IR (Liquid film) bands at 3540, 1720, 1738 cm^{-1}

PMR (in CCl_4 δ): 0.8 (2H, m, C-1 and C-3 protons), 0.95, 1.15 (6H, 2s, 2x-CH_3 gemdimethyl of cyclopropane at C-2), 2.1 (3H, s, -$COCH_3$), 2.2 - 2.6 (4H, 2d, overlapping, -$COCH_2$ at C-3 and C-1), 7.5 (1H, brs, exchangeable with D_2O, acid H).

m-Cresyl ester of 2,2-dimethyl-3-(2-oxopropyl) cis-cyclopropane-1-acetic acid (23)

(Method A)

To the ice-cooled solution of keto acid (III, 2.76 g, 15 mmol) in benzene (25 ml) was added thionyl chloride (2.67 g, 22 mmol) followed by DMF (0.5 ml) and pyridene (1 ml). The reaction mixture was stirred at 0-5° for 4 hours. Unreacted thionyl chloride was removed by distillation under vacuum and again the reaction mixture was cooled to 0°. Solution of m-cresol (1.62 g, 15 mmol) in benzene (10 ml) and pyridine (1 ml) was added and the reaction mixtue was kept stirring initially at 0° for 2 hours and then at room temperature for 26 hours, diluted by water (25 ml),washed the benzene by water (2 x 50 ml), 2N H_2SO_4, 10% NaOH solution and finally with brine dried over anhydrous sodium sulfate, evaporated to get crude ester which was purified by eluting over silica gel column. Fraction eluted with

16% chloroform in pet.ether afforded TLC (8% ethyl-acetate in pet.ether) pure m-cresyl ester (23) (3.06 g, 74.3% yield) whose spectral data and analysis has been described in Chart III.

2,2-Dimethyl-3-(n-propyl) cis-cyclopropane-1-acetic acid (IV)

Keto acid (III) (10 g, 0.06 mol) was added to a solution of potassium hydroxide (10 g, 0.18 mol) in diethylene glycol (55 ml). Added hydrazine hydrate (80% aq.soln, 16 ml) and the reaction mixture was heated to reflux at 125-30° for 4 hours. Excess hydrazine hydrate was removed by distillation and the residue was heated strongly utp 185-90° for 5 hours, cooled, dilute with water, extracted with ether (2 x 50 ml). Ethereal layer was discarded and the aqueous layer containing potassium salt of an acid was acidified with 50% HCl upto 2 pH. It was then extracted by ether (2 x 100 ml). The thereal extract was washed by water (2 x 150 ml) and finally with brine; dried over anhydrous sodium sulphate, distilled out solvent to get yellow oily liquid reduced acid (IV, 8.2 g, 90% yield).

IR (liquid film) : 3600, 1718(C = 0) cm^{-1}

PMR (in CCl_4, δ) 0.7 (2H, m, cyclopropyl protons), 0.9, 1.1 (6H, 3 each, s each, gemdimethyl protons) 1.25 (7H, m, n-propyl at C-3), 2.25 (2H, d, J = 8 Hz, CH_2 protons at C-1) and 11.7 (1H, bs, acid proton).

Analysis: Calculated for, $C_{10}H_{18}O_2$ C, 70.58; H, 10.59
observed C, 70.26; H, 9.97%.

m-Phenoxybenzyl ester of 2,2-dimethyl-3-(n-propyl) cis-cyclopropane-1-acetic acid (20)

(Method A)

To the ice-cooled and stirring solution of acid (IV, 1.7 g, 10 mmol) in benzene (25 ml) was added freshly distilled thionyl chloride (1.77 g, 15 mmol) followed by DMF (0.5 ml) and pyridine (1 ml) and the reaction mixture kept stirring for 3 hours, removed unreacted thionyl chloride by distillation under vacuum. Cooled the acid chloride, added benzene (20 ml) and a solution of m-phenoxybenzyl alcohol (2 g, 10 mmol) in benzene (5 ml) and pyridine (1 ml). The reaction mixture was kept stirring for two hours at 0° and then at room temperature for 12 hours, diluted by water, washed benzene solution by water (2 x 50 ml), saturated aqueous solution of

$CuSO_4$, 10% KOH solution, finally with brine, dried over anhydrous sodium sulfate, evaporated to get the crude ester, which was purified by silica gel column chromatography. Fractions eluted with 7% chloroform in pet.ether afforded TLC (5% ethylacetate in pet.ether) pure m-phenoxybenzyl ester (20, 2.81 g, 81%). The spectral data and analysis is explained in Chart III.

Methyl 1R-*cis*-2,2-dimethyl-3-(2-oxopropyl)cyclopropane acetate (V)

Keto acid (III) (3.68 g, 0.02 mol) was esterified by an ethereal solution of diazomethane. The methyl ester (V, 3.87 g) thus obtained, was further purified by distillation to afford colourless ester; b.p.110-12°/ 2 mm.

IR : 3000, 1724, 1739 cm^{-1}

PMR (in CCl_4, δ) - 0.8 (2H, m, cyclopropane protons), 0.9, 1.1 (6H, 3 each, s each, gemdimethyl of cyclopropane), 2.1 (3H, s, $-COCH_3$), 2.3 (4H, m, 2x-$COCH_2$ at C-1 and C-3 partly overlapped) and 3.6 (3H, s, ester methyl protons).

Analysis: Calculated for $C_{11}H_{18}O_3$ C, 66.6; H, 5.5%
observed C, 6.37; H, 5.2%.

3-Phenoxy benzyl (-) 1R-cis-2,2-dimethyl-3(2-oxopropyl) cyclopropane acetate (19) by transesterification (Method B)

A solution of keto ester (V, 0.95 g, 5 mmol) and 3-phenoxy benzyl alcohol (1.4 g, 7 mmol) in xylene containing butyl titanate (5 mg), was refluxed for 16 hours. Xylene was distilled off, residue dissolved in benzene (1 ml) and purified by silica gel column chromatography. The fraction eluted with chloroform + pet.ether (1:4) afforded a TLC (benzene) pure thick yellow liquid identified as 3-phenoxy benzyl ester (19, 1.38 g, 87%) the spectral data and analysis of which is described in Chart III.

Methyl 1R cis-2,2-dimethyl-3(2-ethylene ketal propyl) cyclopropane-1-acetate (VII)

A solution of keto ester (V, 3.96 g, 20 mmol) in dry benzene (150 ml) containing ethylene glycol (freshlyl distilled, 5 ml) and p-toluenesulphonic acid (200 mg) was refluxed in dean-stark apparatus azeotropically for 8 hours, cooled the reaction mixture, washed the benzene solution with water (2 x 200 ml), 10% $NaHCO_3$ solution and finally with brine, dried over

anhydrous sodium sulfate to get liquid ketal ester (VII, 4.2 g, 89%).

IR : 1740 (ester C-= 0), 1240 (C-O-C of ketal) cm^{-1}

PMR: 0.75 (2H, m, cyclopropane protons), 0.9, 1.1 (6H, 3 each, s each, gemdimethyl), 1.3 (3H, s, methyl protons adjacent to ketal function), 1.5 (2H, d, J = 7 Hz, $-CH_2$ at C-3), 2.2 (2H, d, J = 7 Hz, $-CH_2$ at C-1), 3.6 (3H, s, $-OCH_3$) and 3.8 (4H, s, 2x-CH_2 of ketal).

Analysis calculated for $C_{13}H_{22}O_4$ C, 6.44; 9.0%

observed C, 6.28; H, 8.89%.

2,2-Dimethyl-3-(2-oxopropyl) cis-cyclopropane-1-ethanol (VIII)

To an ice-cooled and stirred solution of lithium aluminium hydride (0.54 g, 15 mmol) in ether (50 ml) in anhydrous condition was added dropwise, solution of ketal ester (VII, 1.21 g, 5 mmol), in dry ether (15 ml). The reaction mixture was stirred initially at 0° for one hour and then for 24 hours at room temeprature (26°). The reaction mixture was deketalized by adding, 6% HCl (2N) in ice cold condition and kept stirring for 24 hours. Ether layer was separated and aqueous suspension was extracted with ether (2 x 50 ml). The combined ethereal layer was washed with water (2 x 100 ml), brine, dried over anhydrous sodium sulfate, evaporated to get a pale yellow liquid (0.74 g, 88%) keto alcohol (VIII).

IR (liquid film) : 3460 (strong OH), 3000, 1724 (C = O)
PMR: 0.6 (2H, m, cyclopropane protons) 0.9, 1.1 (6H, 2s, 2X-CH_3 gemdimethyl), 1.5 (2H, m, methylene protons at C-1), 2.1 (3H, s, -$COCH_3$), 2.3 (2H, d, J = 8 Hz,-$COCH_2$ at C-3), 3.2 (1H, brs, exchangeable with D_2O, -OH proton) and 3.5 (2H, t, methylene protons of primery alcohol).
Analysis calculated for $C_{10}H_{18}O_2$, C, 70.58; H, 9.14
observed C, 70.24; H, 8.9%.

p-Toluic ester of 2,2-dimethyl-3 (2-oxopropyl) cis-cyclopropane-1-ethanol (35) (Method C)

A mixture of p-toluic acid (3.4 g, 0.25 mol) and thionyl chloride (3.7 g, 0.33 mol) in benzene solvent (50 ml) was refluxed for 6 hour. Distilled out unreacted thionyl chloride and the crude acid chloride thus formed was purified by distillation at 80/6 mm. To the ice cooled solution of keto alcohol (VIII, 1.7 g, 10 mmol) in ether (50 ml) was added solution of p-toluic acid chloride (1.85 g, 12 mmol) in dry ether (10 ml) and little pyridine (1 ml). The reaction mixture was stirred at 0° for 2 hours and then at room temperature for 24 hours, Diluted with water, washed the ether solution with water, saturated aqueous solution of copper sulphate (2 x 50 ml), finally brine, dried over anhydrous

sodium sulphate. The crude ester was purified by silica gel column chromatography and the fraction eluted with 20% chloroform in pet.ether, afforded TLC (10% ethyl acetate in pet.ether) pure p-toluic ester (35). The spectral data is described in Chart III.

Methyl (-) 1R cis-2,2-dimethyl-3-(n-propyl)-cyclopropane-1-acetate (VI)

Acid (IV, 3.4 g, 20 mmol) was esterified by an ethereal solution of diazomethane. The methyl ester (VI, 3.6 g) thus obtained was further purified by distillation to furnish colourless ester (VI)
b.p. 95-100°/10 mm.
IR: 3000, 1730, 1450, 1370, 1160.
PMR (in CCl_4, δ) 0.7 (2H, m, cyclopropane protons), 0.97, 1.1 (6H, 2s, 2X $-CH_3$ gemdimethyl) 1.25 - 1.5 (7H, m, n-propyl at C-3), 2.15 (2H, d, J = 6 Hz, $-CH_2$ at C-1) and 3.65 (3H, s, $-OCH_3$).
Analysis calculated for $C_{11}H_{20}O_2$, C, 71.73; H, 22.22%
observed C, 71.37; H, 21.88%.

2,2-Dimethyl-3-(n-propyl) cis-cyclopropane-1-ethanol (IX)

To an ice-cooled and stirred solution of LAH (0.54 g, 15 mmol) in ether (40 ml) in anhydrous condition was added, dropwise, a solution of ester (VI, 1.84 g, 10 mmol), in dry ether (20 ml). The reaction mixture was stirred initially at 0° for one

hour and then kept stirring at room temperature for 24 hours; decomposed by adding, dropwise, ethylacetate, followed by water in ice cold condition. Ether layer was separated and aqueous suspension was extracted with ether (2 x 50 ml). The combined ethereal layer was washed with water (2 x 100 ml), brine, dried over anhydrous sodium sulfate, evaporated to get pale yellow liquid of primary alcohol (IX, 1.4 g, 90%).

IR: 3470(OH), 3000, 1450, 1370, 1050.

PMR: 0.5 (2H, m, cyclopropane protons), 0.9, 1.05 (6H, 2s, 2X $-CH_3$), 1.2 - 1.7 (9H, m, n-propyl protons at C-3 and $-CH_2$ at C-1), 3.3 (1H, s, exchangeable with D_2O, -OH proton) and 3.55 (2H, t, $-CH_2$ protons of primary alcohol).

p-Anisoyl ester of 2,2-dimethyl-3-n-propyl-cis-cyclopropane-1-ethanol (38) (Method C)

To the solution of freshly distilled p-anisoyl chloride (b.p. 100-105°/1.5 mm, 2.55 g, 15 mmol) in benzene (50 ml) was added the solution of primary alcohol (IX, 1.8 g, 12 mmol) in dry benzene in ice-cold condition and pyridene (1 ml) and the reaction mixture kept stirring initially for one hour at 0° and then at room temperature for 24 hours, diluted the reaction mixturewithwater, washed organic layer with water (2 x 50 ml) saturated solution of copper sulphate

(2 x 50 ml) and finally with brine, dried over anhydrous sodium sulfate, evaporated. The crude ester was purified with silica gel column chromatography and the fraction elutedwith5% $CHCl_3$ in pet.ether, afforded TLC (benzene) pure p-anisoyl ester (38, 2.62 g, 74%). The spectral data and analysis is described in Chart III.

Chart II

Substrate Acid/MeE/Alc	MeE/Alcohol/Phenol/acid	Product structure No.	Method of reaction	Total Reaction time/hr.	Yield %	TLC 10% ethylacetate in pet.ether solvent system Rf value
1	2	3	4	5	6	7
III	n-butanol	1	A	21	71	0.67
IV	n-butanol	2	A	18	76	0.81
III	n-hexenol	3	A	20	78	0.65
IV	Nonyl alcohol	4	A	23	72	0.79
IV	Phenol	5	A	19	73	0.84
III	Phenol	5a	A	20	75	0.62
III	-o-chlorophenol	6	A	24	69	0.59
IV	o-chlorophenol	7	A	22	76	0.79
III	m-chlorophenol	8	A	17	77	0.63
IV	m-chlorophenol	9	A	16	79	0.81
III	p-chlorophenol	10	A	18	76	0.64
IV	p-chlorophenol	11	A	15	78	0.85
III	m-bromophenol	12	A	21	72	0.59
IV	m-bromophenol	13	A	20	71	0.78
III	p-bromophenol	14	A	24	75.5	0.60
IV	p-bromophenol	15	A	21	79.5	0.82
III	m-methoxyphenol	16	A	18	71	0.58

Chart II (continued)

1	2	3	4	5	6	7
IV	p-nitrophenol	17	A	16	74	0.85
IV	m-methoxyphenol	18	A	16	79	0.78
V	m-Phenoxybenzyl alcohol	19	B	24	87	0.52
IV	m-phenoxybenzyl alcohl	20	A	18	80	0.72
III	o-Cresol	21	A	16	79	0.67
IV	o-Cresol	22	A	18	81	0.83
III	m-Cresol	23	A	21	76	0.62
IV	m-Cresol	24	A	20	79	0.78
III	p-cresol	25	A	17	75	0.59
IV	p-cresol	26	A	15	77.5	0.81
III/V	2-phenoxy ethanol	27	A/B	18/23	69/73	0.64
IV	2-phenoxy ethanol	28	A	18	71	0.77
III	Decanediol	29	A	26	78.7	0.53
IV	2,4-dichlorophenol	30	A	24	84	0.85
IV	nonylphenol	31	A	22	76	0.58
IV	Benzylthiol	32	A	18	69	0.66
IV	Terephthalyl alcohol	33	A	24	82	0.71
IV	decanediol	34	A	22	70	0.72
VIII	p-toluic acid	35	C	27	78	0.56
IX	p-toluic acid	36	C	25	81	0.76
IX	p-chlorobenzoic acid	37	C	23	79.5	0.68
IX	p-anisic acid	38	C	16	74	0.83
IX	methyl sebacate/S.acid	39	B/C	24/18	80/78.5	0.62
IX	Terephthalic acid	40	C	24	82	0.78

CHART III

Ester No.	Functional group	IR cm^{-1}	PMR	Molecular Formula	Analysis Calculated C	Calculated H %	Observed C	Observed H %
1	2	3	4	5	6	7	8	9
1	Ester C = 0	1740 1724	0.8(2H, m, C-1 and C-3 proton), 0.9, 1.15 (6H, 2s, 2X $-CH_3$ at C-2), 1.4-1.7 (7H, m, n-C_3H_7 at C-3), 2.27 (2H, d, J=7 Hz, $-COCH_2$), 4.0 (2H, t, J = 8 Hz, $-OCH_2$)	$C_{14}H_{24}O_3$	69.96	10.07	69.71	9.87
2	Ester C = 0	1745	0.5-0.8 (2H, m, C-1 and C-3 proton), 0.93, 1.1 (6H, 2s, 2X $-CH_3$ at C-2), 1.16-1.8(14H, m, n-C_3H_7 at C-3 and n-butyl protons), 2.17 (2H, d, J=7 Hz, $-COCH_2$), 4.07(2H, t, $-OCH_2$)	$C_{14}H_{26}O_2$	72.84	12.23	72.68	11.97
3	Ester C = 0 Free C = 0	1748 1724	0.8(2H, m, C-1, C-3 proton), 0.95, 1.15 (6H, 2s, 2X $-CH_3$ at C-2), 1.3 -2.0(11H, m, 4X $-CH_2$ of n-hexyl), 2.1 (3H, s, $-COCH_3$), 2.3 (4H, d, J = 8 Hz, 2X $-COCH_2$), 4.0 (2H, t, $-OCH_2$)	$C_{16}H_{28}O_3$	71.60	10.52	71.42	10.37
4	Ester C = 0	1742	0.9(2H, m, C-1, C-3 proton), 0.95, 1.05 (6H, 2s, 2X $-CH_3$ at C-2), 1.1-1.95 (24H, m, 7H of n-C_3H_7 at C-3, 17H of nonyl), 2.1 (2H, d, J=7 Hz $-COCH_2$), 3.97(2H, t $-OCH_2$)	$C_{19}H_{36}O_2$	76.97	12.24	76.69	11.98
5	Ester C = 0	1754	0.5-0.87 (2H, m, C-1 and C-3 proton), 0.97, 1.07 (6H, 2s, 2X $-CH_3$ at C-2), 1.17-1.6 (7H, m, n-C_3H_7 at C-3), 2.43 (2H, d, J=8 Hz, $-COCH_2$), 6.9-7.5 (5H, m, aromatic)	$C_{16}H_{22}O_2$	78.01	9.0	77.86	8.82

Chart III (continued)

1	2	3	4	5	6	7	8	9
5a	Ester C=0 Free C=0	1746 1709	0.72 (2H, m, C-1 and C-3 proton), 0.9,1.1 (6H, 2s, 2X $-CH_3$ at C-2), 2.13 (3H, s, $-COCH_3$), 2.27 - 2.33 (4H, 2d, overlapping 2X $-COCH_2$), 6.79 - 8.5 (5H, m, aromatic protons)	$C_{16}H_{20}O_3$	55.38	7.7	55.09	7.64
6	Ester C=0 Free C=0	1744 1724	0.67-0.8 (2H, m, C-1, C-3 proton), 0.9, 1.1 (6H, 2s, 2X $-CH_3$ at C-2), 2.08 (3H, s, $-COCH_3$), 2.15 - 2.56 (4H, 2d, overlapped, 2X $-COCH_2$ at C-1 and C-3), 6.7 - 6.36 (4H, m, aromatic)	$C_{16}H_{19}ClO_3$	70.58	6.8	70.31	6.62
7	Ester C=0	1761	0.6-0.9 (2H, m, C-1, C-3 proton), 1.0,1.1 (6H, 2s, 2X $-CH_3$ at C-2), 7.23 - 1.67 (7H, m, n-C_3H_7 at C-3), 2.57 (2H, d, J=8 Hz, $-COCH_2$), 7.05 - 7.67 (4H, m, aromatic)	$C_{16}H_{21}ClO_2$	68.57	7.5	68.29	7.28

Chart III (continued)

Ester No.	Functional group	IR cm^{-1}	PMR	Molecular formula	Analysis Calculated C	H	Cl/Br	observed C	H	Cl/Br
1	2	3	4	5	6	7	8	9	10	11
8	Ester C=0 Free C=0	1745 1704	0.7-0.87 (2H, m, C-1, C-3 proton), 0.95, 1.1(6H, 2s, 2X $-CH_3$ at C-2), 2.1 (3H, s, $-COCH_3$), 2.37 (2H, d, J=6Hz, $-COCH_2$ at C-3), 2.4(2H, d, J=6 Hz, $-COCH_2$ at C-1), 6.86 - 7.4 (4H, m, aromatic)	$C_{16}H_{19}ClO_3$	65.3	6.46	11.9	65.17	6.35	11.73
9	Ester C = 0	1750	0.66-0.9(2H, m, C-1, C-3 proton), 1.0, 1.13 (6H, 2s, 2X $-CH_3$ at C-2), 1.2-1.5 (7H, m, $n-C_3H_7$ at C-3), 2.46 (2H, d, J=7 Hz, $-COCH_2$), 6.9 - 7.43 (4H, m, aromatic)	$C_{16}H_{21}ClO_2$	68.57	7.5	17.5	68.28	7.36	17.43
10	Ester C=0 Free C=0	1742 1702	0.67-0.7 (2H, m, C-1, C-3 proton), 0.9 1.1 (6H, 2s, 2X $-CH_3$ at C-2), 2.15-2.47 (7H, s of $-COCH_3$ overlapped with 2d of 2X $-COCH_2$), 7.1 (2H, d, J = 10 Hz, aromatic ortho to Cl), 7.6 (2H, d, J=10 Hz, aromatic m- to Cl)	$C_{16}H_{19}ClO_3$	65.3	6.46	11.9	65.18	6.19	11.82
11	Ester C=0	1740	0.6-0.85 (2H, m, C-1, C-3 proton), 1.0, 1.1 (6H, 2s, 2X $-CH_3$ at C-2), 1.2-1.5 (7H, m, $n-C_3H_7$ at C-3), 2.43 (2H, d, J = 7 Hz, $-COCH_2$), 6.87 (2H, d, J=10 Hz, aromatic ortho to Cl), 7.3 (2H, d, J=10 Hz, H meta to Cl)	$C_{16}H_{21}ClO_2$	68.57	7.5	17.5	68.50	7.41	17.2

Chart III (continued)

1	2	3	4	5	6	7	8	9	10	11
12	Ester C=0 Free C=0	1747 1709	0.87 (2H, m, C-1, C-3 proton), 0.9, 1.15 (6H, 2s, 2X $-CH_3$ at C-2), 2.1 (3H, s, $-COCH_3$), 2.25-2.5 (4H, m, 2d overlapped, 2X $-COCH_2$), 6.9-7.3 (4H, m, aromatic)	$C_{16}H_{19}BrO_3$	56.3	5.6	23.59	56.35	5.51	23.37
13	Ester C=0	1754	0.6-0.9 (2H, m, C-1, C-3 protons), 1.0, 1.1 (6H, 2s, 2X $-CH_3$ at C-2), 1.15-1.5 (7H, m, n-C_3H_7 at C-3), 2.45, 2H, d, J=8 Hz $-COCH_2$), 6.9 - 7.4 (4H, m, aromatic)	$C_{16}H_{21}BrO_2$	59.0	6.46	24.61	58.77	6.21	24.44
14	Ester C=0 Free C=0	1748 1709	0.68 - 0.73 (2H, m, C-1, C-3 proton), 0.95, 1.13 (6H, 2s, 2X $-CH_3$ at C-2), 2.1-2.5 (7H, m, s of $-COCH_3$ overlapping 2d of 2X $-COCH_2$), 7.15 (2H, d, J=10 Hz, aromatic H ortho to Br), 7.65 (2H, d, J=10 Hz, aromatic meta to Br)	$C_{16}H_{19}BrO_3$	56.63	5.6	23.59	56.39	5.38	23.4
15	Ester C=0	1742	0.7-0.85(2H, m, C-1, C-3 proton), 1.0,1.15 (6H, 2s, 2X $-CH_3$ at C-2), 1.2-1.4 (7H, m n-C_3H_7 at C-3), 2.5 (2H, d, J=8 Hz, $-COCH_2$), 7.0 (2H, d, J=10 Hz, aromatic, ortho to Br), 7.5 (2H, d, J=10 Hz, aromatic meta to Br)	$C_{16}H_{21}BrO_2$	59.0	6.46	24.61	58.83	6.42	24.58

Chart III (continued)

Ester No.	Functional group	IR cm^{-1}	PMR	Molecular Formula	Analysis Calculated C	Calculated H	Calculated N	observed C	observed H	observed N
1	2	3	4	5	6	7	8	9	10	11
16	Ester C=0 Free C=0	1740 1718	0.87(2H, m, C-3 proton), 0.95, 1.15 (6H, 2s, 2X-CH_3 at C-2), 2.07 (3H, s, -$COCH_3$), 2.4 (4H, m, 2d overlapping 2X -$COCH_2$), 3.77(3H, s, -OCH_3), 6,3-7.4 (4H, aromatic)	$C_{17}H_{22}O_4$	70.32	7.64		70.19	7.38	
17	Ester C=0	1747	0.7 (2H, m, C-1, C-3 proton), 1.0, 1.14 ((6H, 2s, 2X-CH_3 at C-2), 1.17-1.5(7H, m, n-C_3H_7 at C-3), 2.5 (2H, d, J=8 Hz, -$COCH_2$), 7.26 (2H, d, J=10 Hz, aromatic meta to -NO_2), 8.2 (2H, d, J=10 Hz, aromatic ortho to NO_2)	$C_{16}H_{21}NO_4$	65.97	7.21	4.81	65.91	7.08	4.57
18	Ester C=0	1754	0.56-0.8 (2H, m, C-1, C-3 proton),1.0 1.13 (6H, 2s, 2X -CH_3 at C-2), 1.18-1.5(7H, m, n-C_3H_7 at C-3) 2.46 (2H, d, J=8 Hz, -$COCH_2$), 3.8 (3H, s, -OCH_3) 6.5-7.4 (4H, m, aromatic)	$C_{17}H_{24}O_3$	73.88	8.75		73.62	8.69	
19	Ester C=0 Free C=0	1737 1709	0.75 (2H, m, C-1, C-3 proton), 0.93, 1.1 (6H, 2s, 2X -CH_3 at C-2), 1.97 (3H, s, -$COCH_3$), 2.13 (2H, d, J=5 Hz, -$COCH_3$ of oxopropyl), 2.27 (2H, d, J=4 Hz, -$COCH_2$ adj. to C-1), 4.0(2H, s, -OCH_2), 6.7-7.36 (9H, m, aromatic protons)	$C_{22}H_{24}O_4$	74.97	6.86		74.73	6.79	

Chart III (continued)

1	2	3	4	5	6	7	8	9	10
20	Ester C=0	1724	0.6-0.8 (2H, m, C-1, C-3 proton), 0.9, 1.1 (6H, 2s, 2X $-CH_3$ at C-2), 1.16-1.5 (7H, m, n-C_3H_7 at C-3), 2.2 (2H, d, J=7 Hz, $-COCH_2$ at C-1), 5.0 (2H, s, $-OCH_2$) 6.6-7.3 (9H, m aromatic)	$C_{22}H_{26}O_3$	78.07	7.74		77.88	7.67
21	Ester C=0 Free C=0	1748 1706	0.87(2H, m, C-1, C-3 proton), 1.0, 1.1 (6H, 2s, 2x $-CH_3$ at C-2), 2.1 (3H, s, $-CH_3$), 2.2 (3H, s, $-COCH_3$), 2.35 (2H, d, J=7 Hz, $-COCH_2$ of oxopropyl gr.), 2.43 (2H, d, J=7 Hz, $-COCH_2$ at C-1), 6.8-7.4 (4H, m, aromatic)	$C_{17}H_{22}O_3$	74.42	8.08		74.19	7.88
22	Ester C=0	1742	0.67 (2H, m, C-1, C-3 proton), 1.0, 1.1(6H, 2s, 2X $-CH_3$ at C-2), 1.2-1.56 (7H, m, n-C_3H_7 at C-3), 2.3 - 2.63 (5H, m, s of $-CH_3$ overlapping d of $-COCH_2$), 6.8-7.4 (4H, m aromatic)	$C_{17}H_{24}O_2$	78.42	9.29		78.37	9.04
23	Ester C=0 Free C=0	1736 1709	0.85 - 0.9 (2H, m, C-1, C-3 proton), 1.0, 1.14 (6H, 2s, 2X $-CH_3$ at C-2), 2.08 (3H, s, $-CH_3$), 2.16 - 2.8 (7H, m, s of $-COCH_3$ overlapping 2d of 2X $-COCH_2$), 6.3 - 7.4 (4H, m, aromatic)	$C_{17}H_{22}O_3$	74.42	8.08		74.35	8.01

Chart III (continued)

1	2	3	4	5	6	7	8	9	10	11
24	Ester C=0	1741	0.7(2H, m, C-1, C-3 proton), 1.0,1.13 (6H, 2s, 2X $-CH_3$ at C-2), 1.2-1.6 (7H, m, n-C_3H_7 at C-3), 2.3 - 2.6 (5H, s of CH_3 overlapping d of $-COCH_2$), 6.7-7.5 (4H, m, aromatic)	$C_{17}H_{24}O_2$	78.42	9.29		78.29	8.96	
25	Ester C=0 Free C=0	1754 1724	0.93(2H, m, C-1,C-3 proton) 1.0,1.2 (6H, 2s, 2X $-CH_3$ at C-2), 2.1(3H, s, $-CH_3$), 2.2-2.5 (7H, s of $-COCH_3$ overlapping 2d of 2X $-COCH_2$), 6.87 (2H, d, J = 10 Hz, aromatic ortho to $-CH_3$), 7.1 (2H, d, J=10 Hz, aromatic meta to $-CH_3$)	$C_{17}H_{22}O_3$	74.42	8.08		74.19	8.12	
26	Ester C=0	1740	0.7-0.88 (2H, m, C-1,C-3 proton), 1.0, 1.1(6H, 2s, 2X $-CH_3$ at C-2), 1.15 - 1.5 (7H, m, n-C_3H_7 at C-3), 2.42 (5H, s of CH_3 overlapping d of $-COCH_2$), 6.9 (2H, d, J=10 Hz, aromatic ortho to CH_3), 7.13 (2H, d, J=10 Hz, aromatic meta to CH_3)	$C_{17}H_{24}O_2$	78.42	9.29		78.37	9.05	
27	Ester C=0 Free C=0	1744 1706	0.8 (2H, m, C-1,C-3 proton), 0.9, 1.13 (6H, 2s 2X-CH_3 at C-2), 2.03 (3H, s, $-COCH_3$), 2.1-2.4 4H, m, 2d overlapping, 2X $-COCH_2$), 3.8-4.55 (4H, m, 2t overlapping, 2X $-OCH_2$), 6.7-7.4 (5H, m, aromatic)	$C_{18}H_{24}O_4$	71.02	7.95		70.84	7.69	
28	Ester C=0	1736	0.5-0.8 (2H, m, C-1, C-3 proton), 0.95, 1.1(6H, 2s, 2X $-CH_3$ at C-2), 1.15-13 (7H, m, n-C_3H_7 at C-3), 2.3 (2H, d, J=8 Hz, $-COCH_2$), 4.0-4.6 (4H, m, 2 t overlapping, 2X $-OCH_2$), 6.8 - 7.5 (5H, m, aromatic)	$C_{18}H_{26}O_3$	74.44	9.03		74.38	8.97	
29	Ester C=0 Free C=0	1748 1718	0.8(2H, m, C-1,C-3 proton), 0.9,1.15 (6H, 2s, 2X $-CH_3$ at C-2), 1.3-1.95 (16H, m, 8X $-CH_2$ of decyl) 2.35 (4H, 2d, overlapping, 2X $-COCH_2$), 4.1 (4H, t, 2X $-OCH_2$ of decyl)	$C_{30}H_{50}O_6$	7.11	9.95		70.92	9.86	

Chart III (continued)

Ester No.	Functional group	IR cm	PMR	Molecular Formula	Analysis calculated C	H	Cl,S	observed C	H	Cl,§
1	2	3	4	5	6	7	8	9	10	11
30	Ester C=0	1742	0.5-0.77 (2H,m,C-1,C-3 proton),0.97,1.1 (6H,2s, 2X $-CH_3$ at C-2), 1.2-1.6 (7H, m, n-C_3H_7 at C-3), 2.5(2H, d, J=8 Hz,$-COCH_2$), 6.86-7.5 (3H, m, aromatic)	$C_{10}H_{21}ClO_2$	57.7	10.96	16.63	57.58	10.70	16.49
31	Ester C=0	1729	0.8(2H,m,C-1,C-3 proton),1.0,1.1 (6H, 2s, 2X-CH_3 at C-2), 1.25-2 [26H, brm, (7H of n-C_3H_7 at C-3, 19H of nonyl gr)], 2.4 (2H, d, J = 8 Hz, $-COCH_2$), 6.7-7.3 (4H, aromatic)	$C_{25}H_{40}O_2$	80.59	10.82		80.45	10.79	
32	Ester C=0	1736	0.5-0.87(2H, m, C-1,C-3 proton), 0.9,1.1 (6H, 2s, 2X-CH_3 at C-2), 1.16-1.5 (7H, m, n-C_3H_7 at C-3), 2.45 (2H, d, J=8 Hz $-COCH_2$), 4.0 (2H, s, $-SCH_2$), 7.35 (5H, s, aromatic)	$C_{17}H_{24}OS$	73.96	11.22	15.69	73.68	10.98	15.4
33	Ester C=0	1754	0.5-0.8(4H, m, C-1, C-3 proton), 0.9,1.05 (12H,2s, 4X $-CH_3$ at C-2), 1.1-1.4 (14H, m, 2X n-C_3H_7 at C-3), 2.1 (4H, d, J=6 Hz, 2X $-COCH_2$), 4.7 (4H, s, 2X $-OCH_2$), 6.7 (4H, s, aromatic)	$C_{28}H_{42}O_4$	75.97	9.56		75.88	9.37	
34	Ester C=0	1745	0.6-0.8 (2H,m, C-1,C-3 proton), 0.95,1.1 (6H, 2s, 2X $-CH_3$ at C-2), 1.2-1.9 (30H, brm, 2X n-C_3H_7 at C-3, 3X $-CH_2$ of decyl gr.), 2.2 (4H, d, J=8 Hz, 2X-$COCH_2$), 4.1 (4H, t, 2X $-OCH_2$ of decyl gr.)	$C_{30}H_{52}O_4$	75.58	11.0		75.41	10.87	

Chart III (continued)

1	2	3	4	5	6	7	8	9	10	11
35	Ester C=0 Free C=0	1747 1712	0.8(2H,m,C-1,C-3 proton),0.97,1.15 (6H, 2s, 2X $-CH_3$ at C-2), 1.43-1.87(2H, m, CH_2 at C-1), 2.1 (3H, s, $-CH_3$), 2.23 (2H, d, J=8 Hz, $-COCH_2$ of oxopropyl gr.), 2.36(3H,s, $-COCH_3$), 4.3 (2H, t, $-OCH_2$), 7.2 (2H, d, J=9 Hz, aromatic ortho to $-CH_3$), 7.9 (2H, d, J = 9 Hz, aromatic meta to $-CH_3$)	$C_{18}H_{24}O_3$	74.97	8.39		74.89	8.31	
36	Ester C=0	1724	0.5(2H, m, C-1,C-3 proton),1.0,1.1(6H,2s, 2X $-CH_3$ at C-2),1.2-1.9 (9H,m,n-C_3H_7 at C-3, $-CH_2$ at C-1), 2.5 (3H, s, $-CH_3$),4.4 (2H, t, $-OCH_2$), 7.3 (2H, d, J=8 Hz, aromatic ortho to $-CH_3$), 8.1 (2H, d, J=8 Hz, aromatic meta to $-CH_3$)	$C_{18}H_{26}O_2$	78.79	9.55		78.62	9.41	
37	Ester C=0	1724	0.5(2H, m,C-1, C-3 proton), 0.95,1.05(6H, 2s, 2X-CH_3 at C-2), 1.1-1.8 (9H, brm, n-C_3H_7 at C-3, $-CH_2$ at C-1), 4.15 (2H, t, $-OCH_2$), 7.1 (2H, d, J=10 Hz,aromatic meta to Cl), 7.7(2H, d, J=10 Hz aromatic ortho to Cl)	$C_{18}H_{23}ClO_2$	60.0	6.4	11.43	59.76	6.38	11.32
38	Ester C=0	1738	0.5(2H,m,C-1,C-3 protons),0.95,1.05(6H,2s, 2X $-CH_3$ at C-2),1.15-1.9(9H,m, n-C_3H_7 at C-3 and $-CH_2$ adj. to C-1),3.9(3H,s,$-OCH_3$), 4.35(2H, t,$-OCH_2$),6.95(2H, d,J=10 Hz, aromatic meta to $-OCH_3$) 8.1(2H,d, J=10 Hz, aromatic ortho to $-OCH_3$)	$C_{18}H_{26}O_3$	74.44	9.03		74.38	8.97	
39	Ester C=0	1745	0.5(2H,m,C-1, C-3 proton),0.95,1.05(6H,2s, 2X $-CH_3$ at C-2), 1.15-1.7(26H,brm, 2X n-C_3H_7 and 12 sebacyl protons),2.2(4H,t, 2X-$-COCH_2$ of sebacyl),4.0(4H,t, 2X $-OCH_2$)	$C_{30}H_{54}O_4$	75.26	11.37		75.15	11.31	
40	Ester C=0	1724	0.5(2H, m,C-1,C-3 proton),0.95,1.05(6H,2s, 2X $-CH_3$ at C-2), 1.2 - 1.9 (18H, brm, 2X n-C_3H_7, $-CH_2$ adj. to C-1), 4.25 (4H, 2X $-OCH_2$) 7.9 (4H, s, aromatic)	$C_{28}H_{42}O_4$	75.97	9.56		75.82	9.41	

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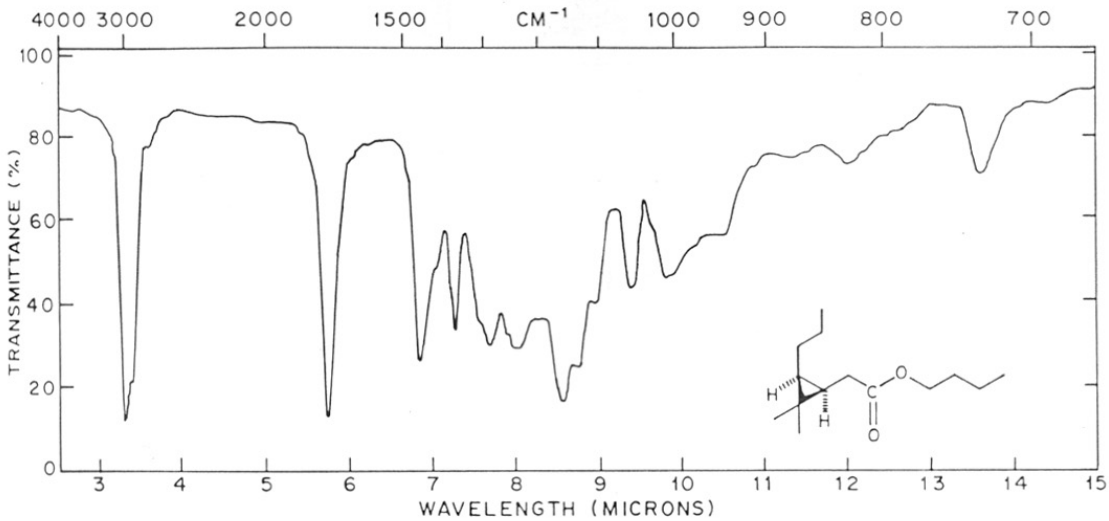
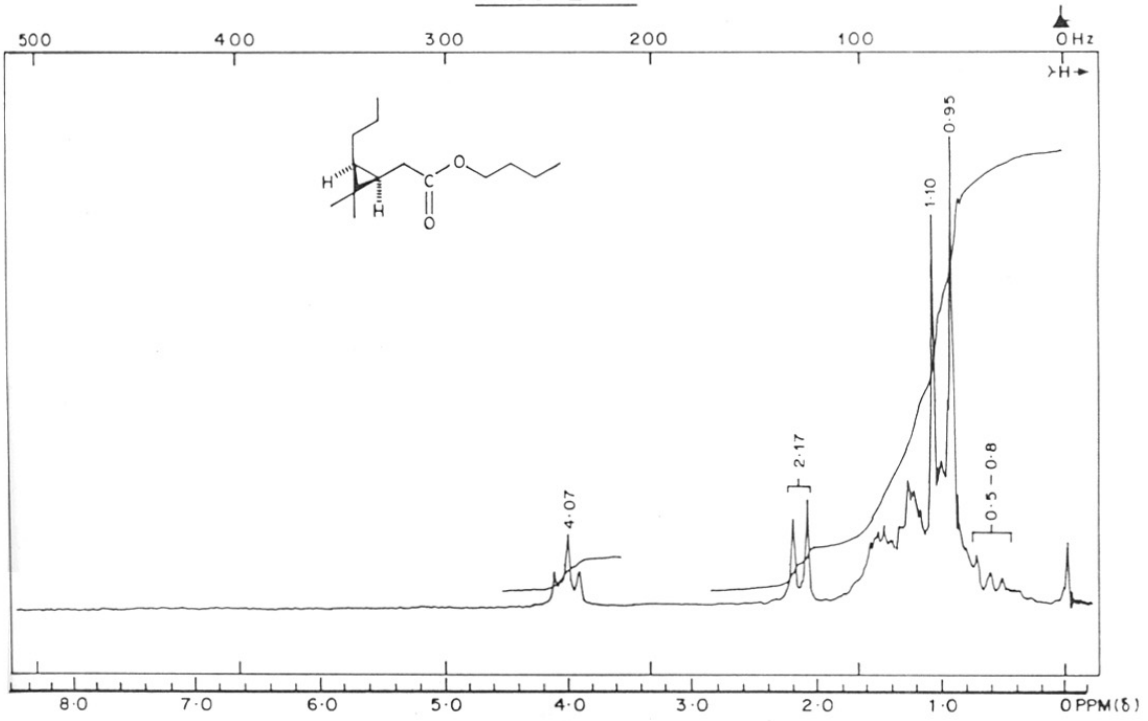


FIGURE 2



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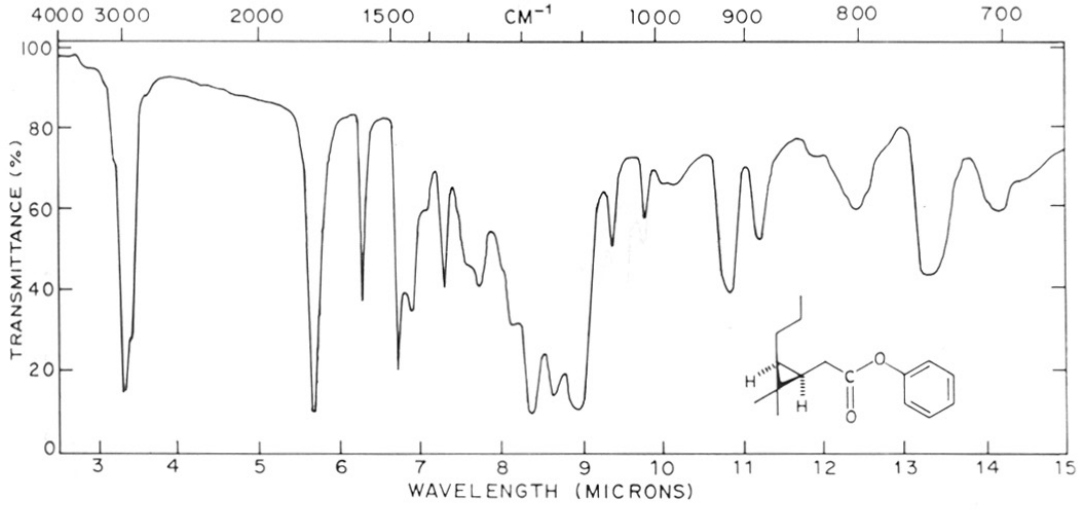


FIGURE 5a

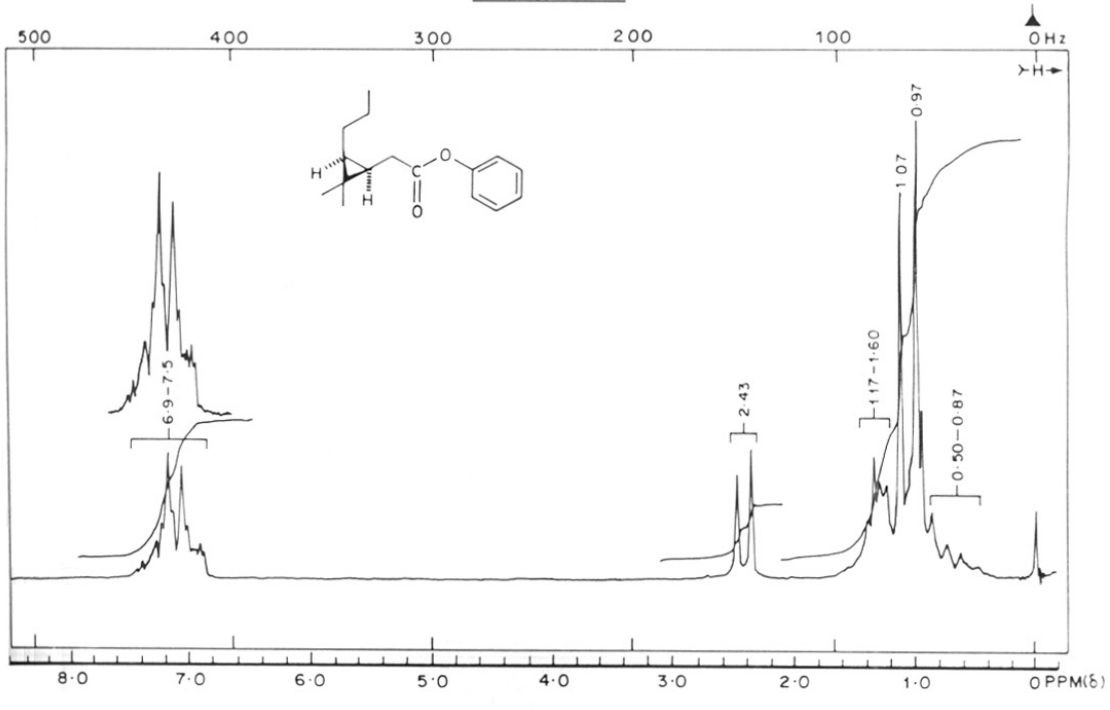
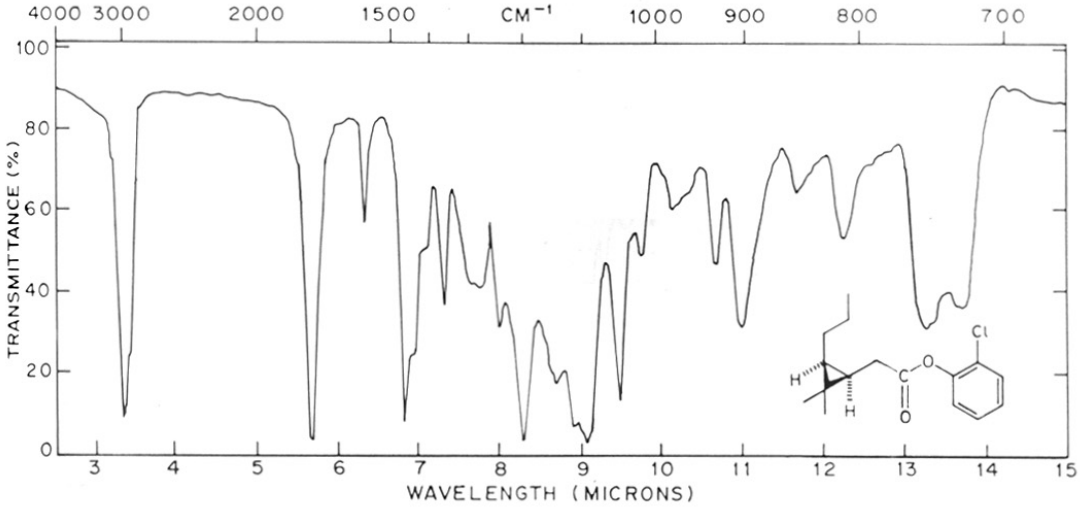


FIGURE 5a



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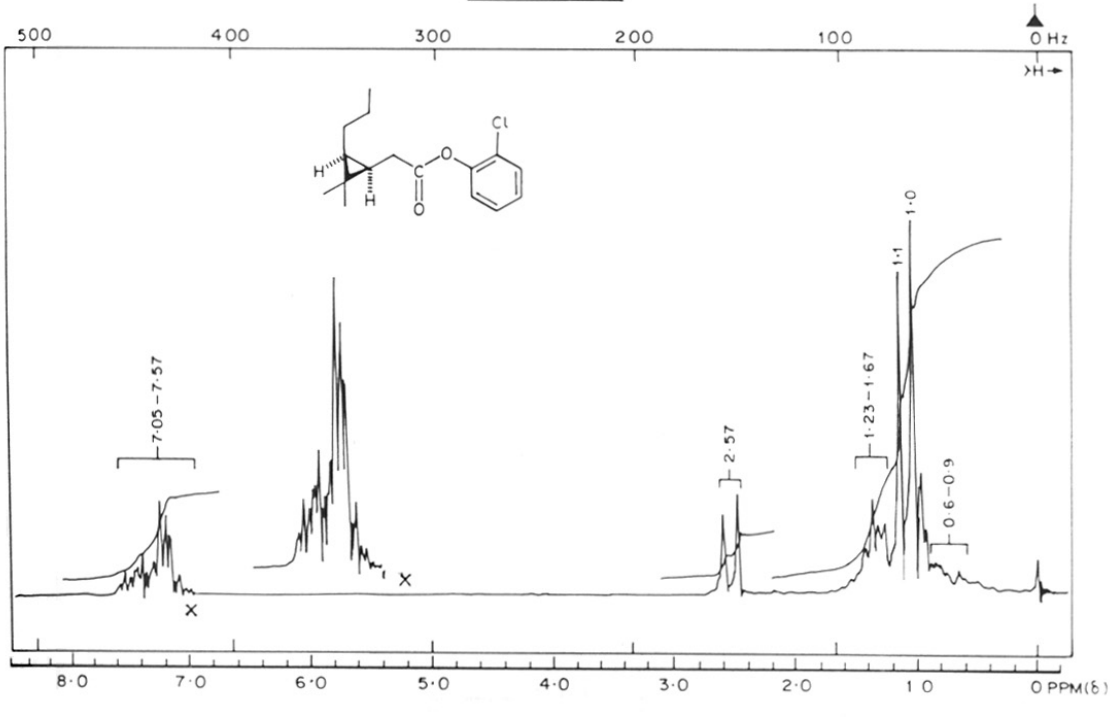

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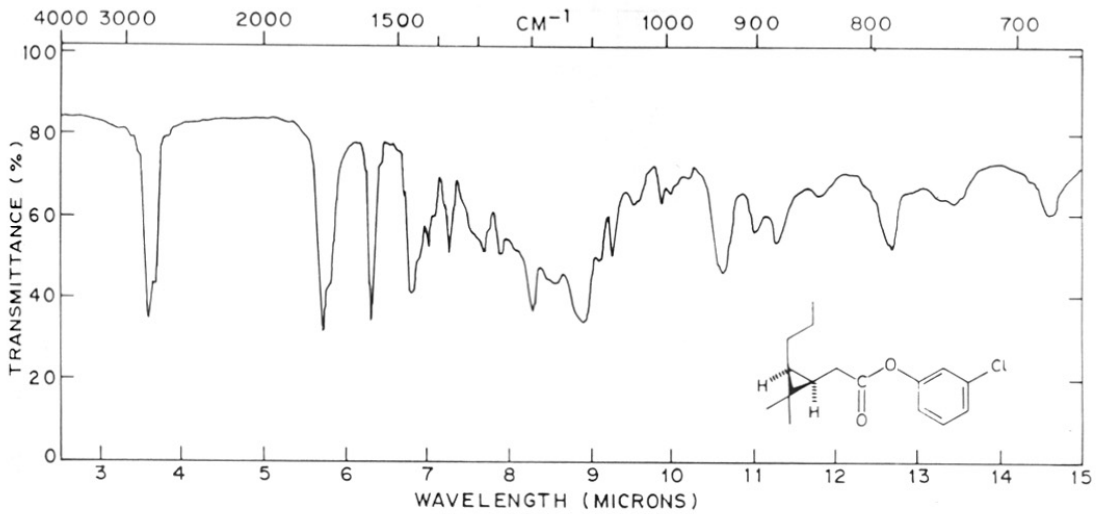

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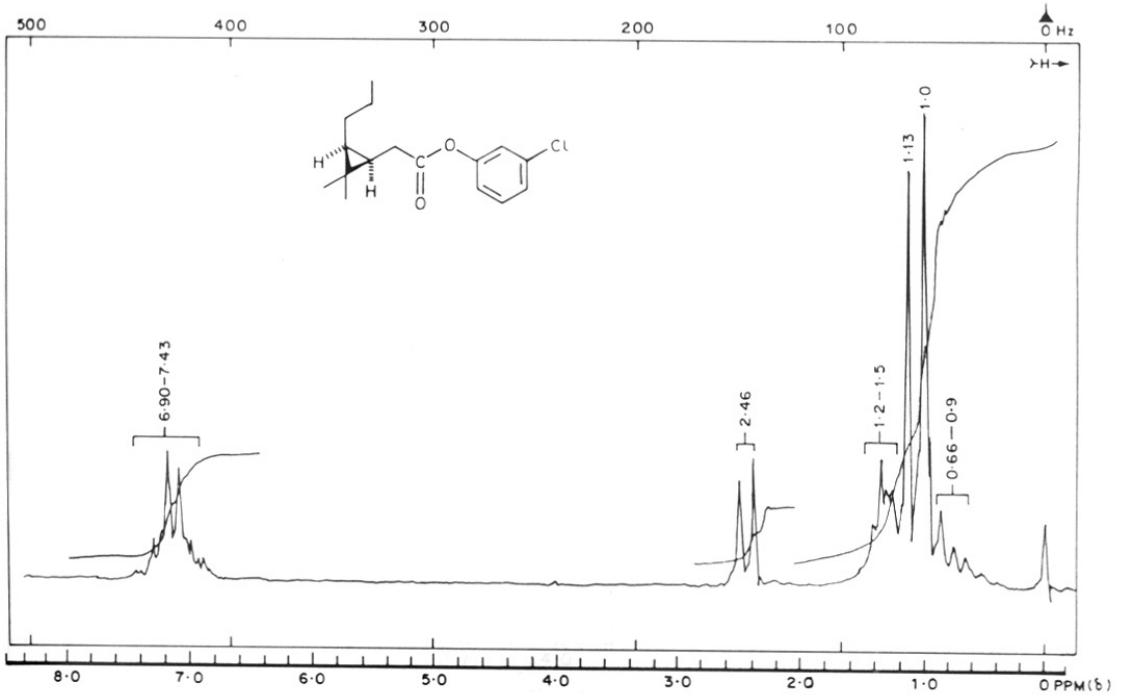

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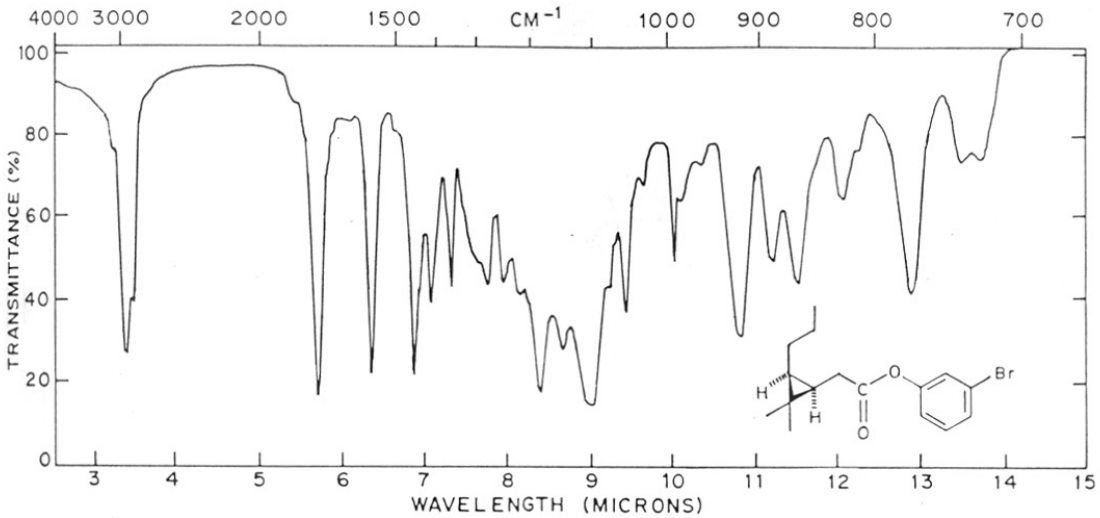

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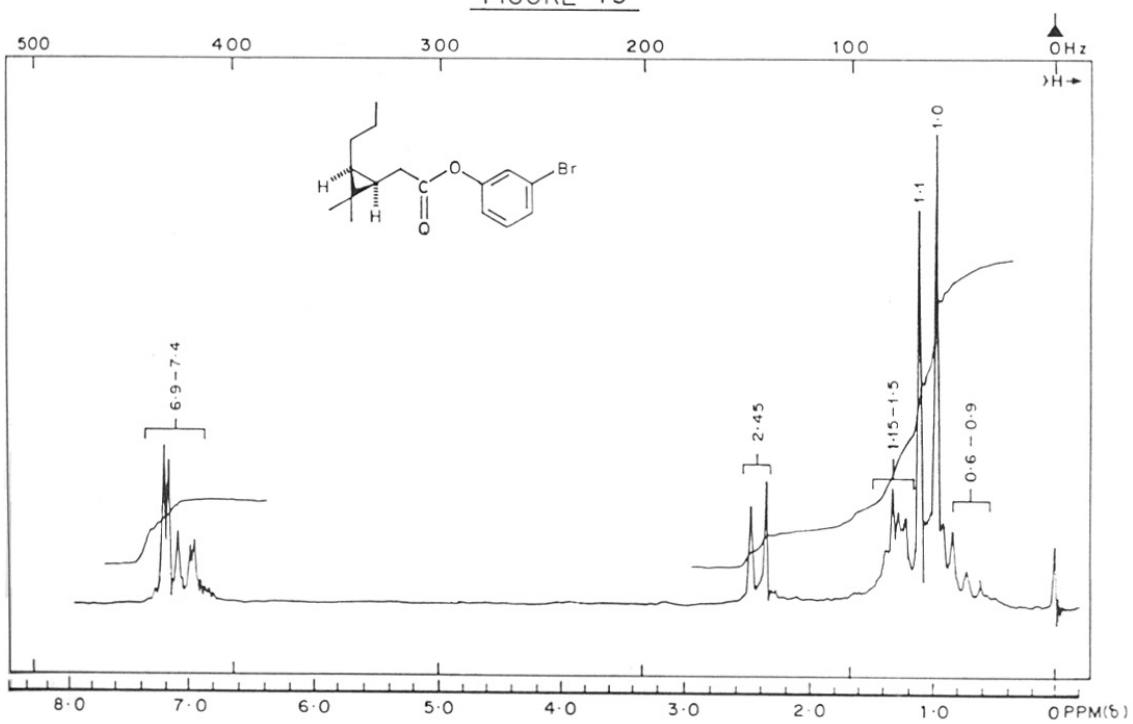

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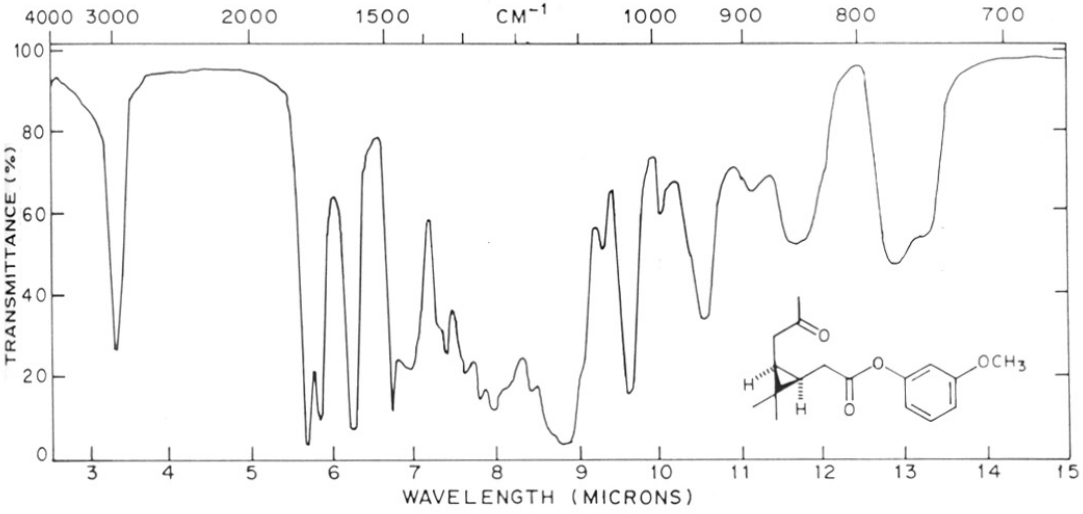

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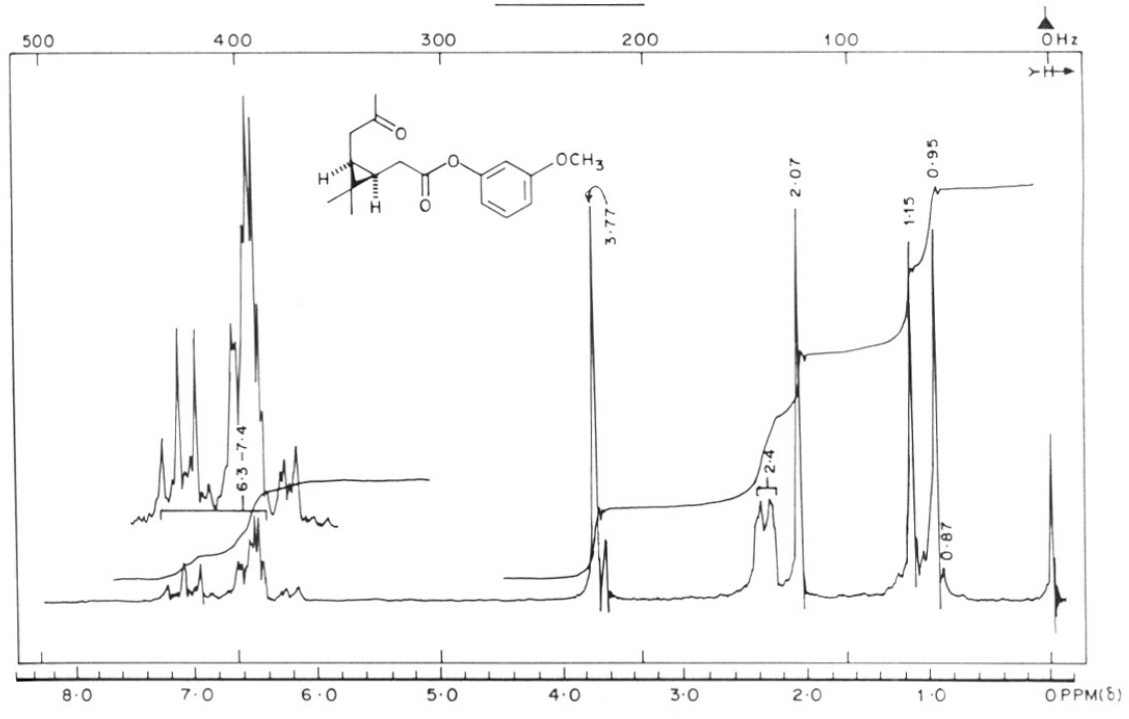

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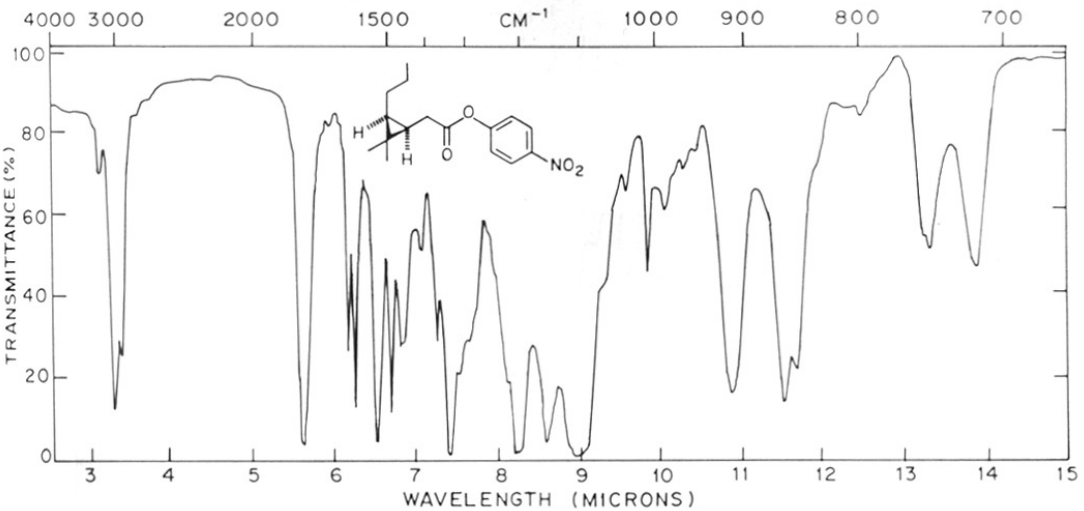

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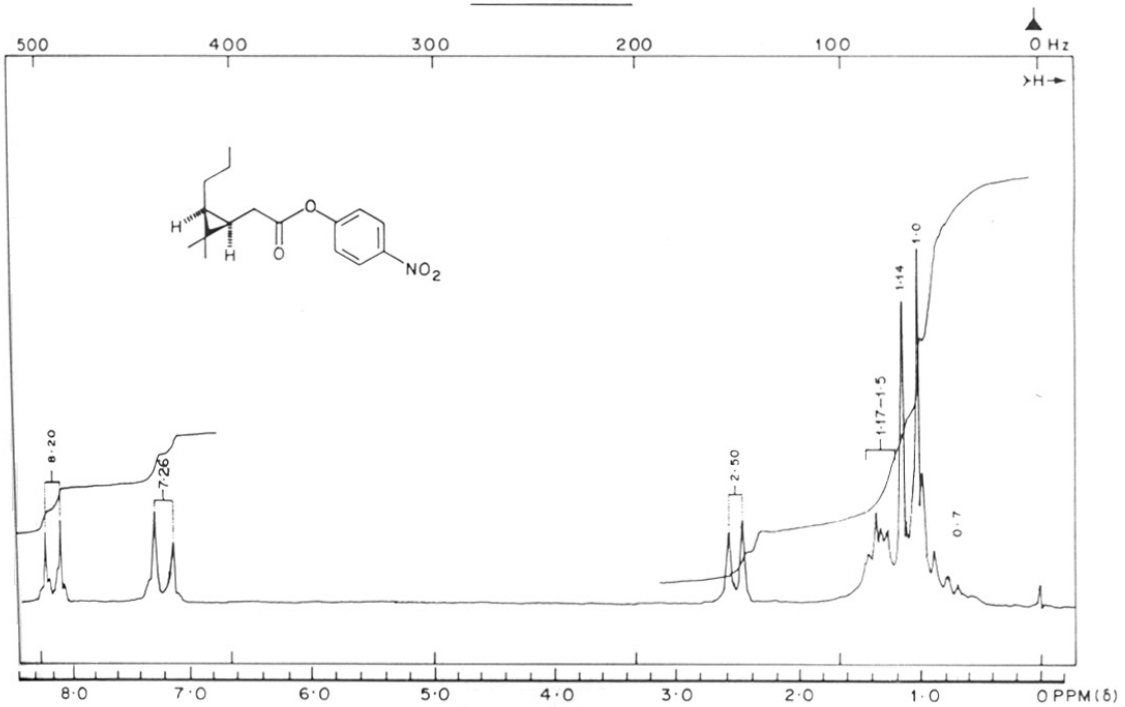

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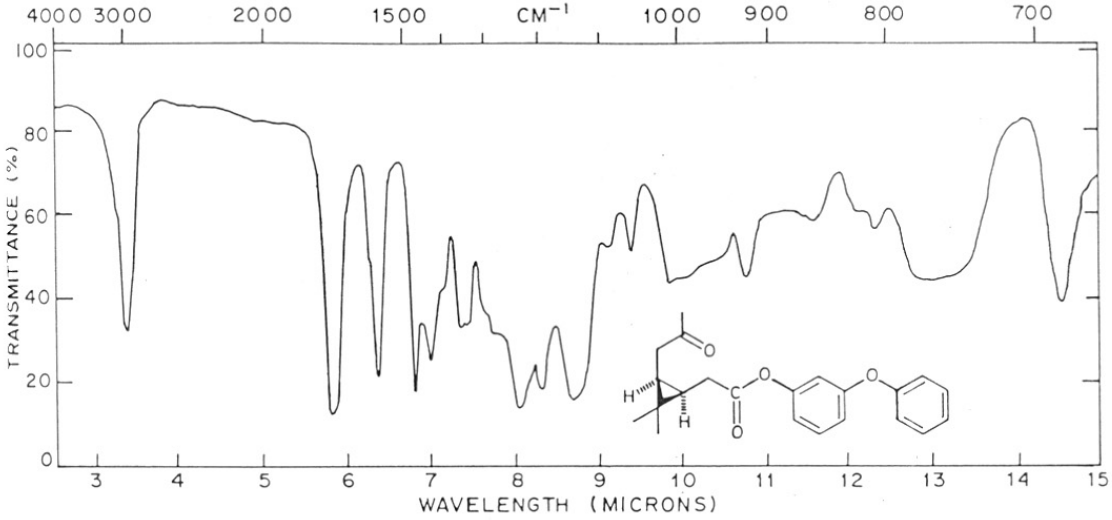

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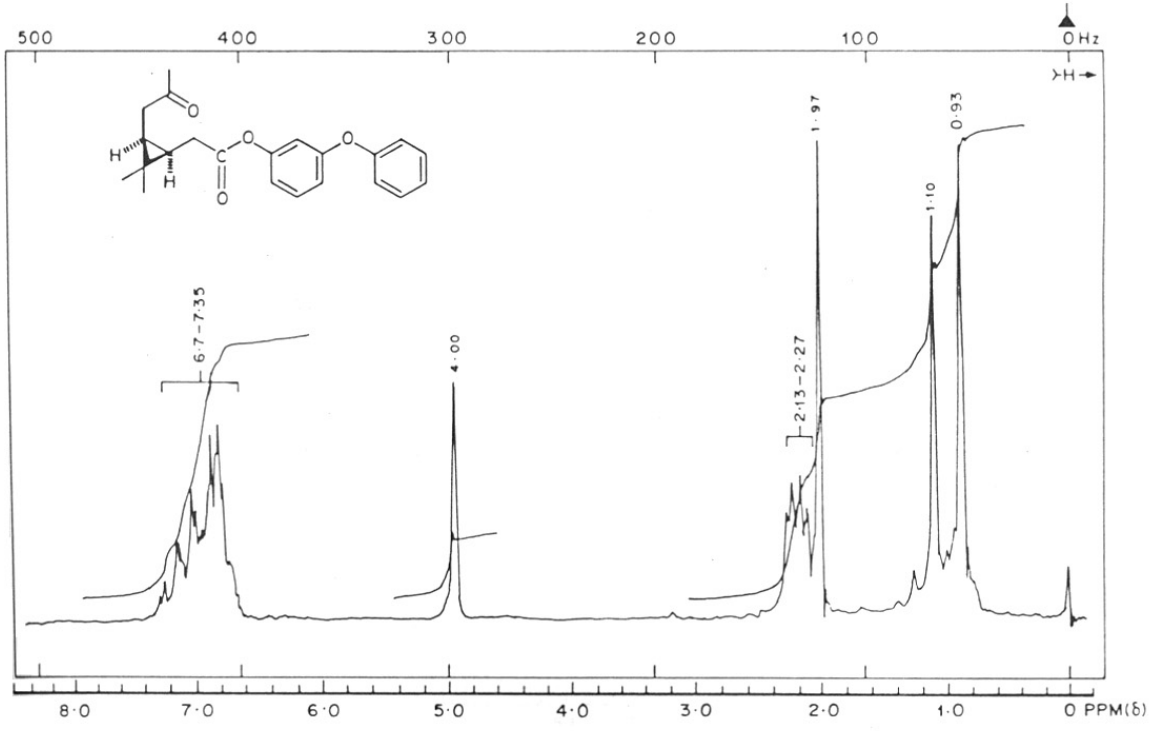

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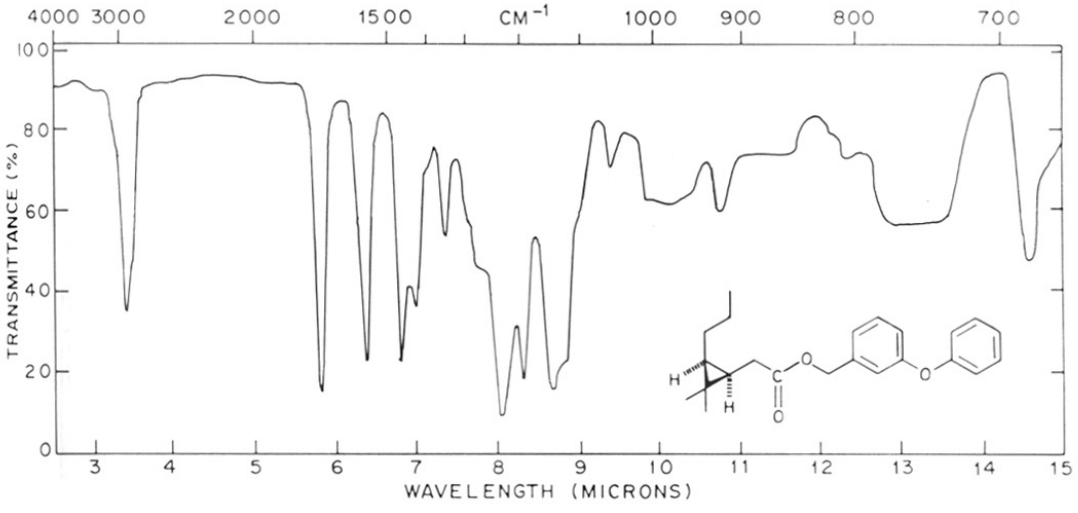

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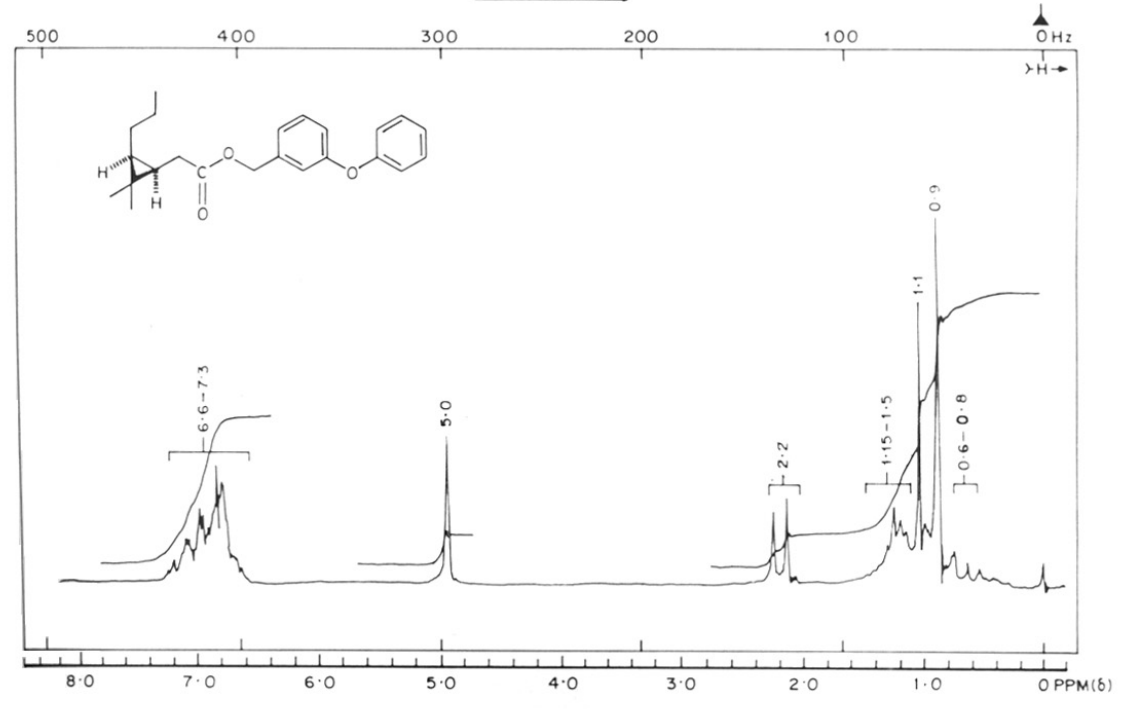

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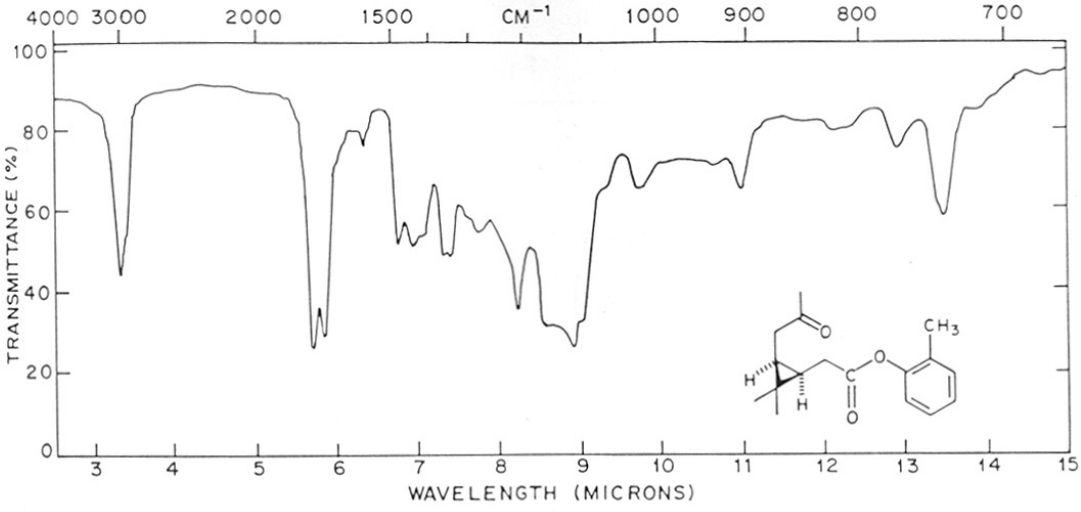

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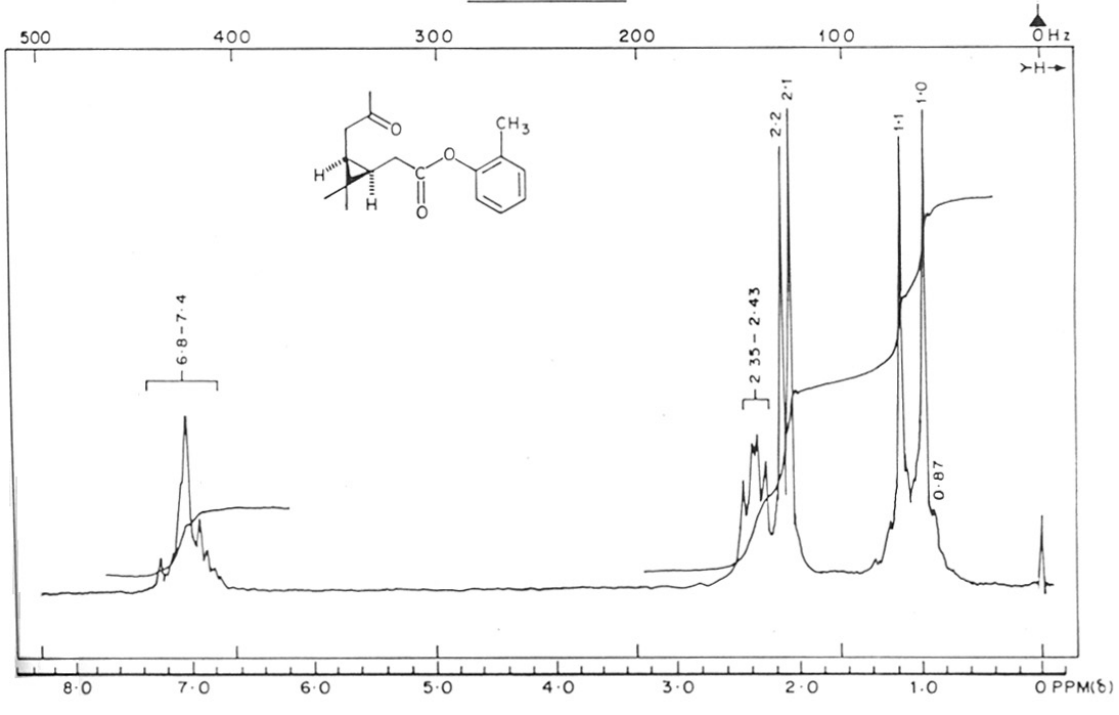

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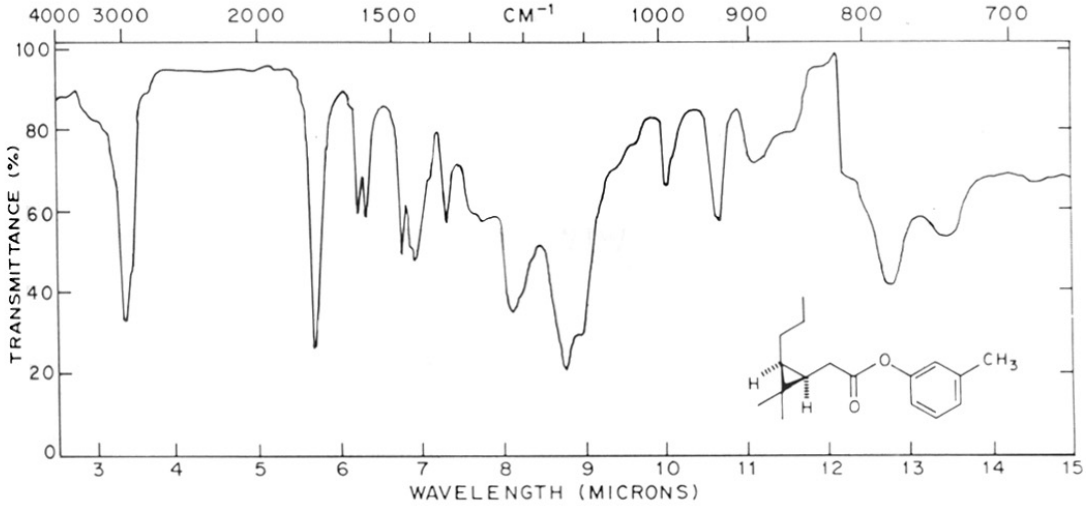

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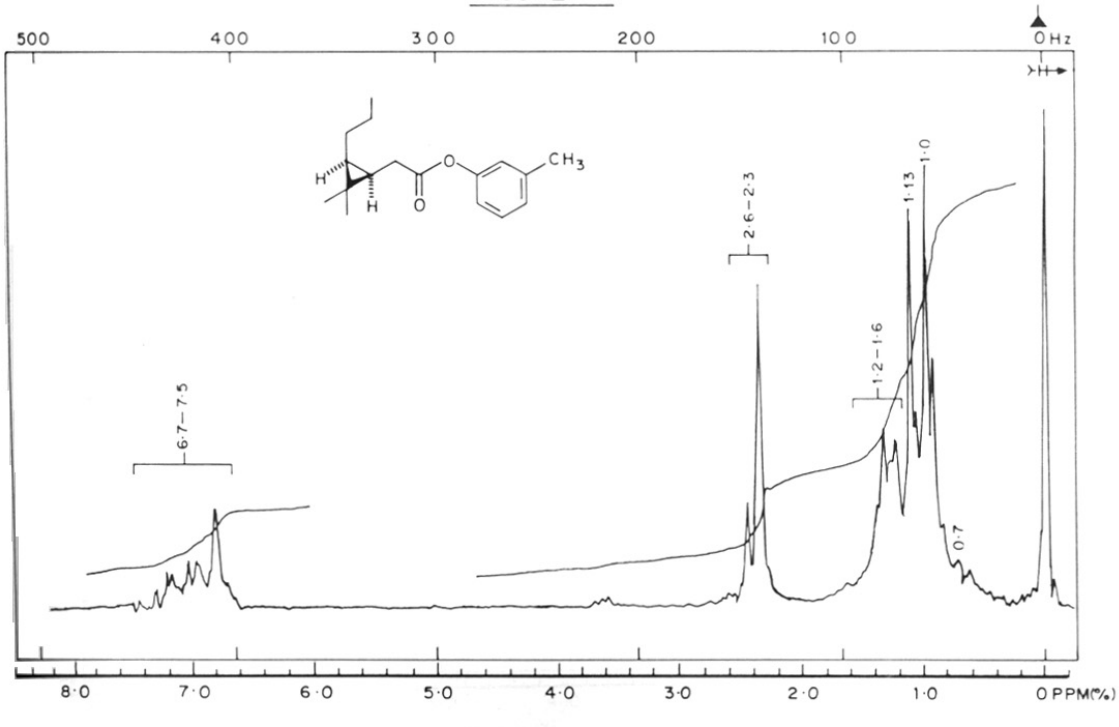

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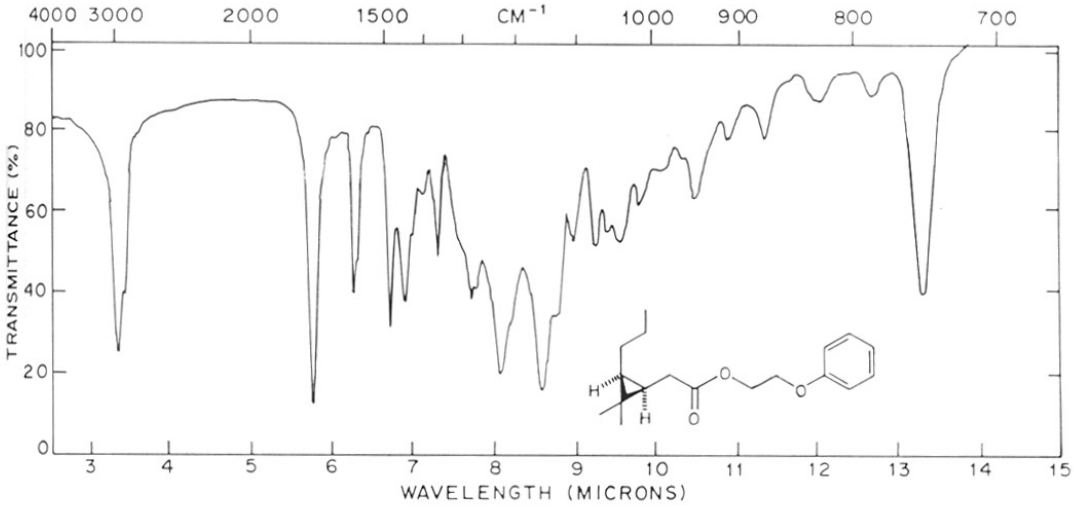

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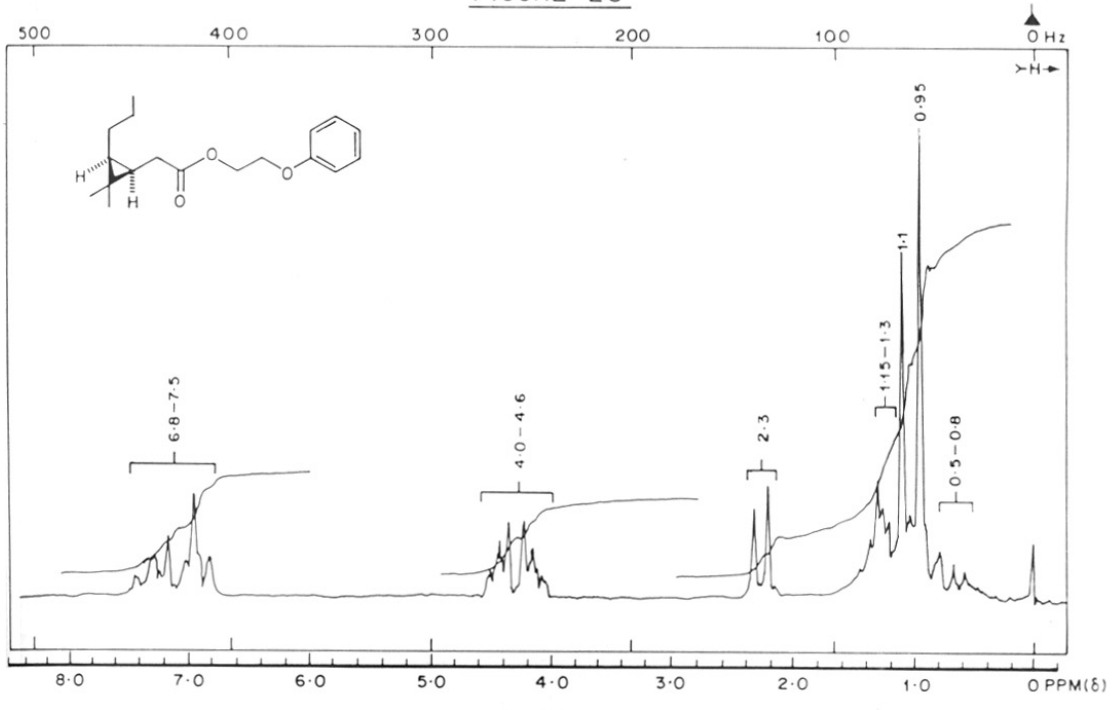

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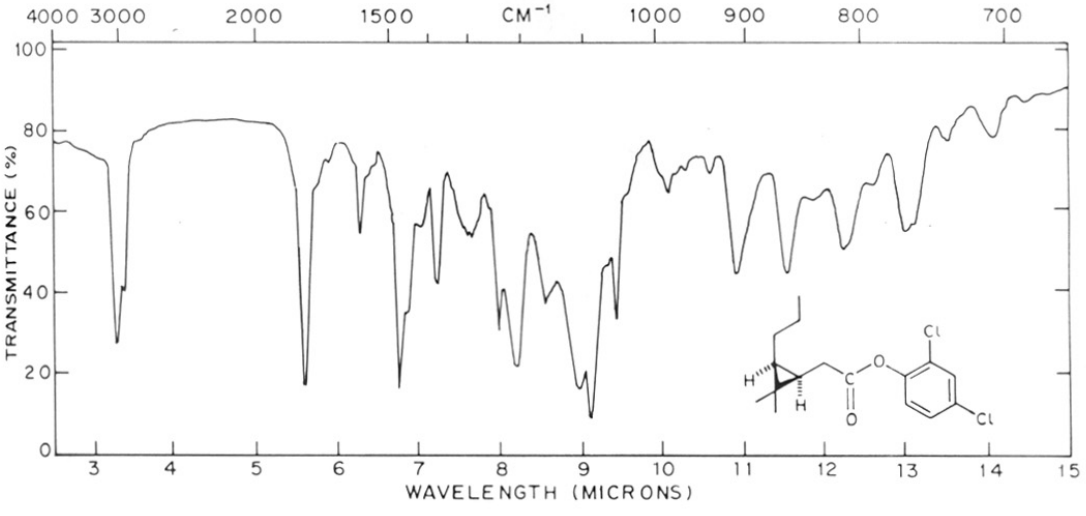

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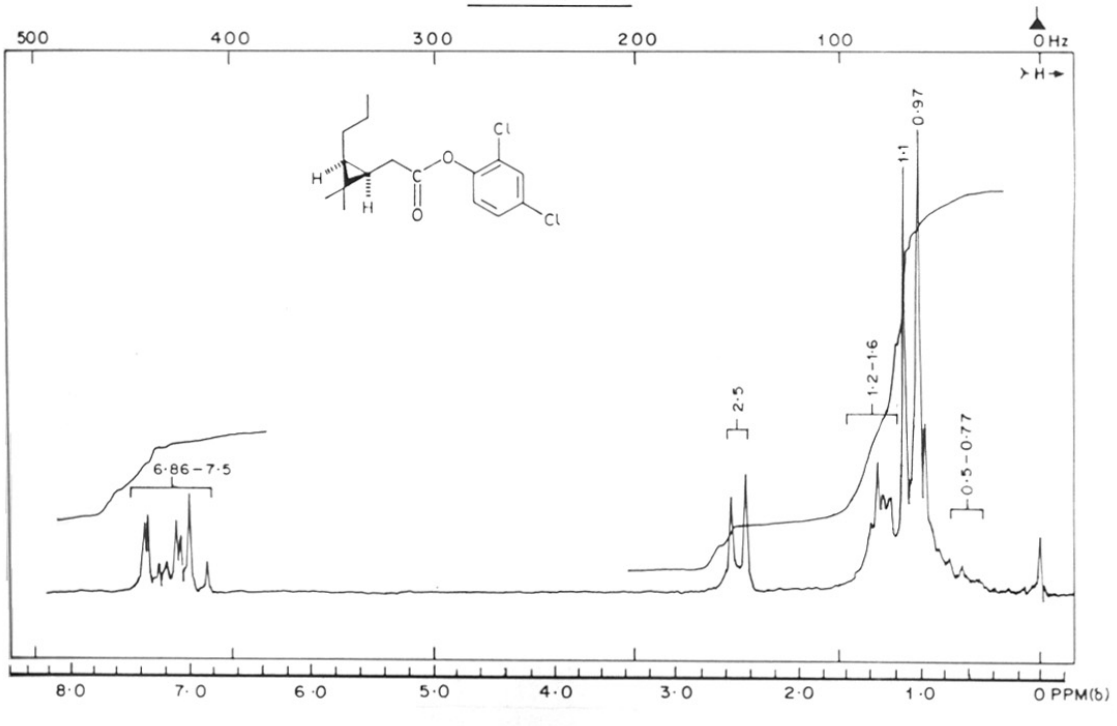

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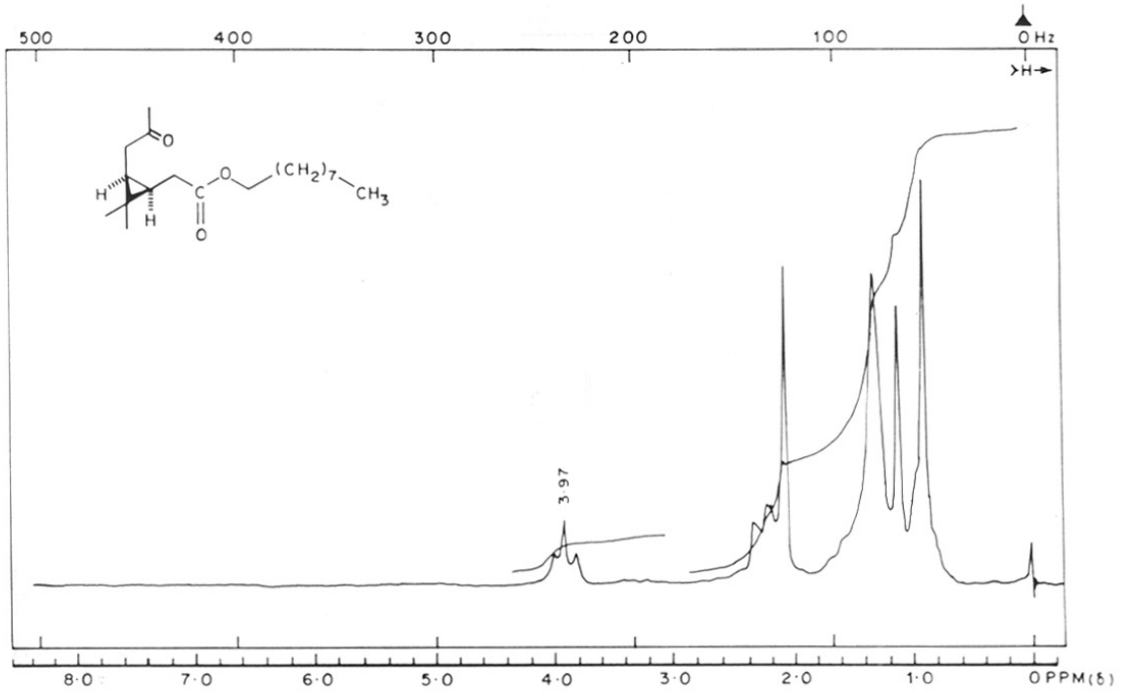

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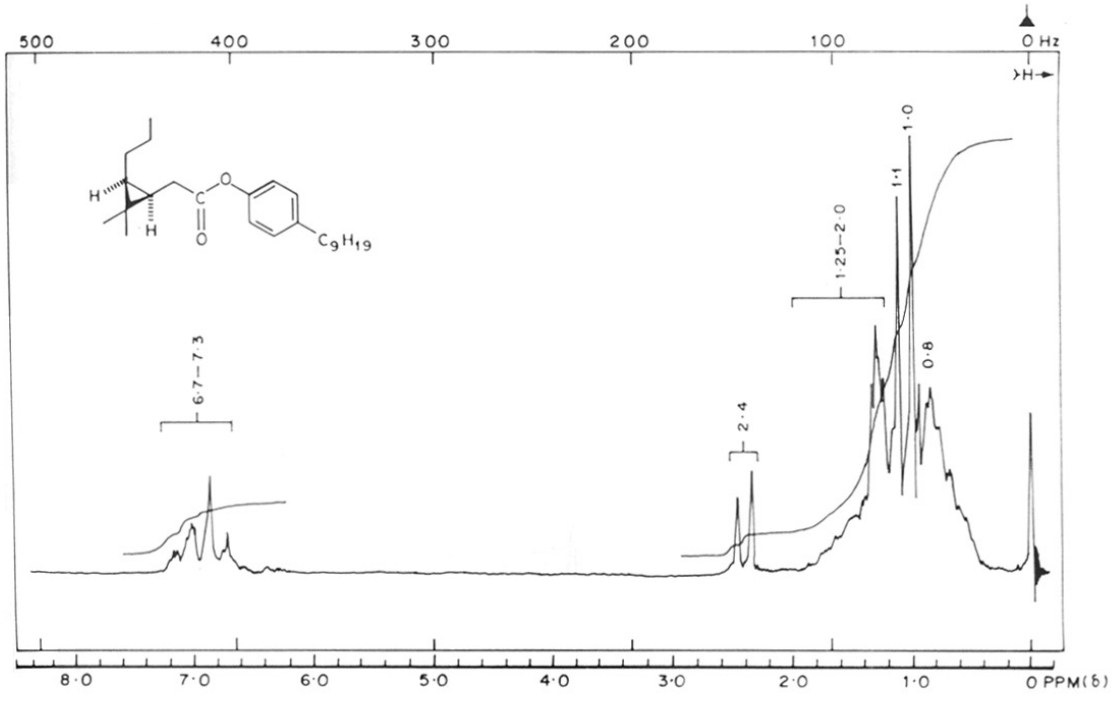

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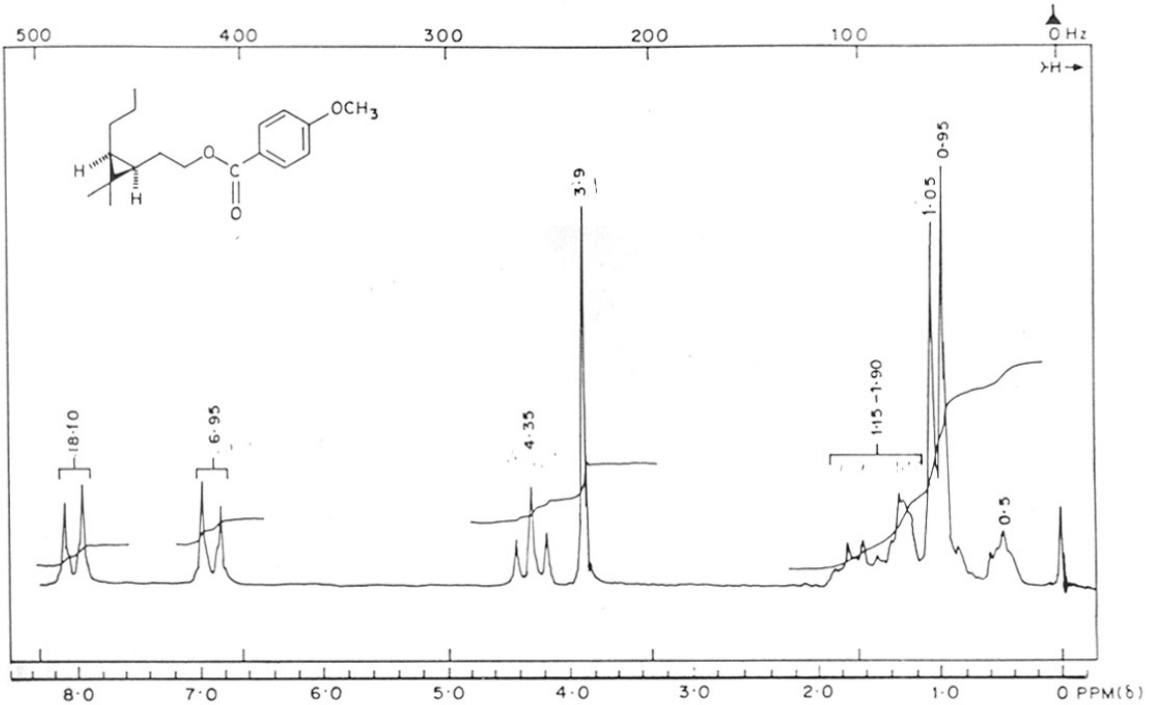

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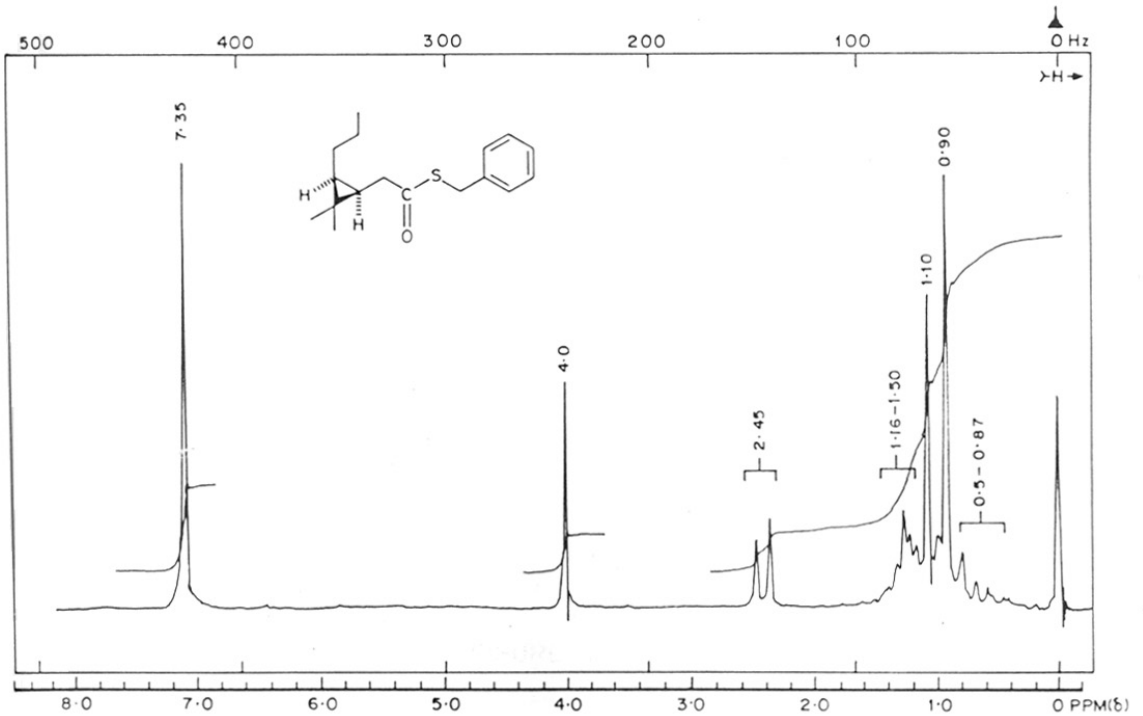

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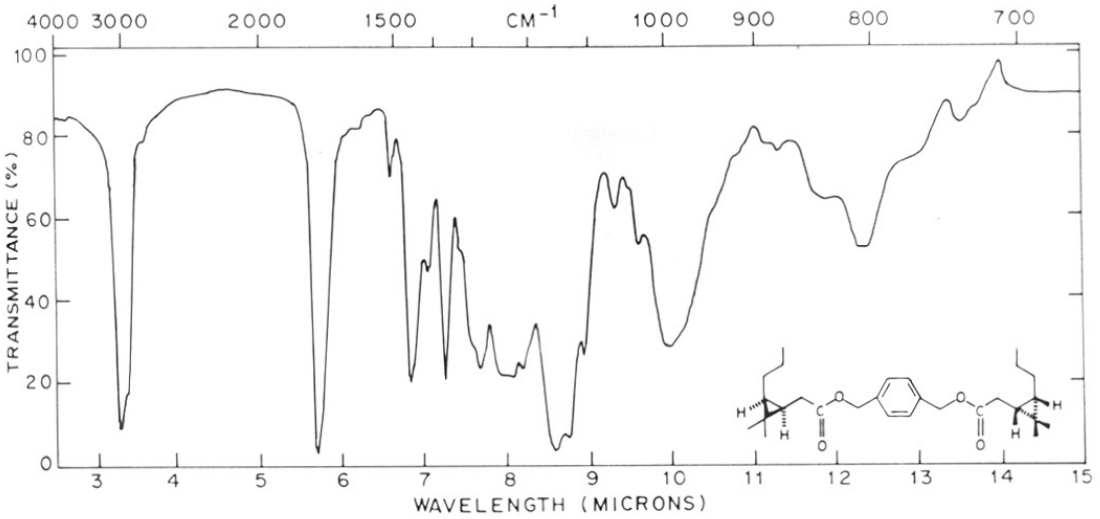

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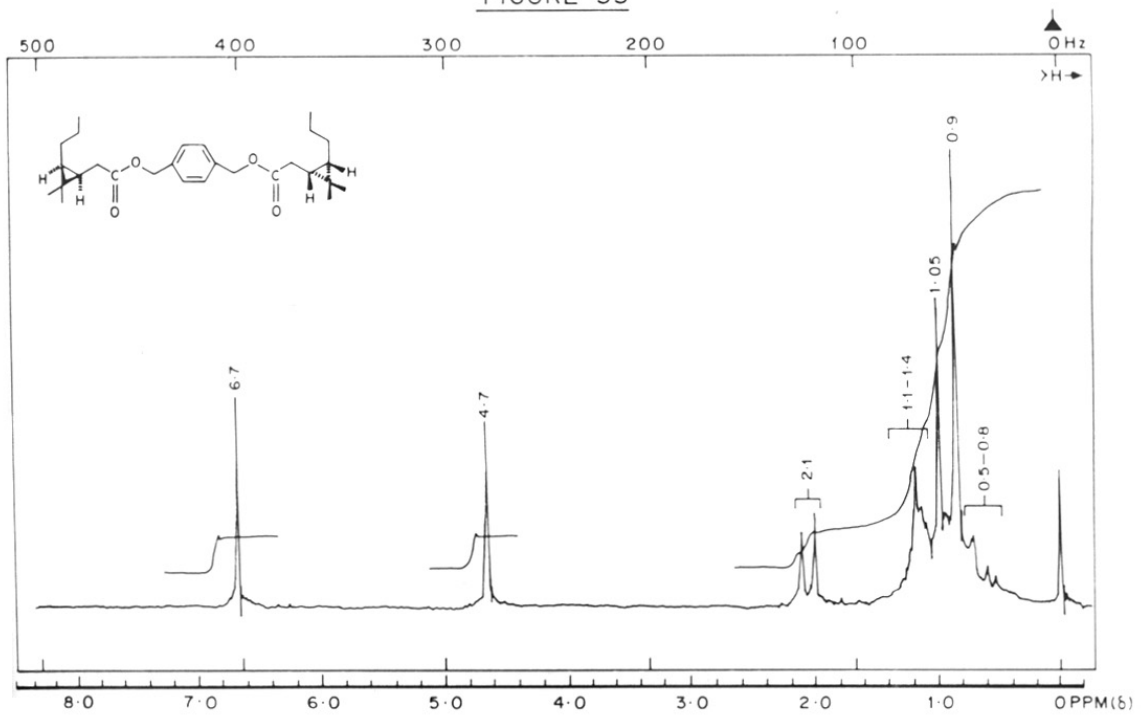

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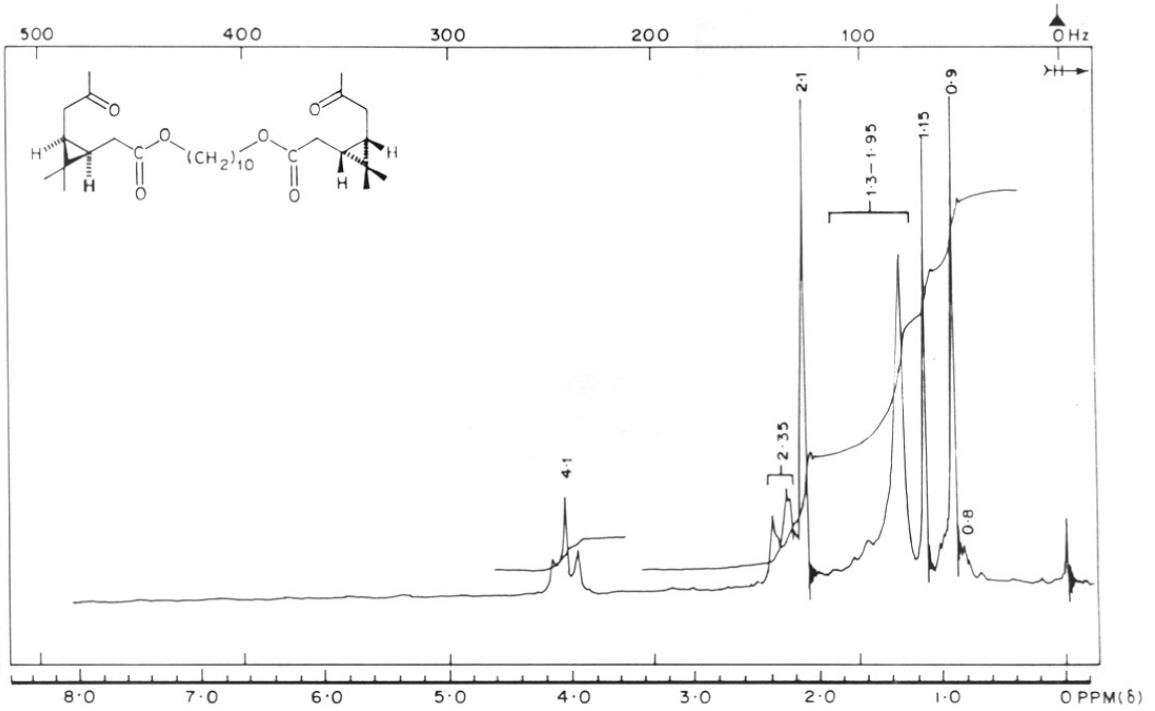

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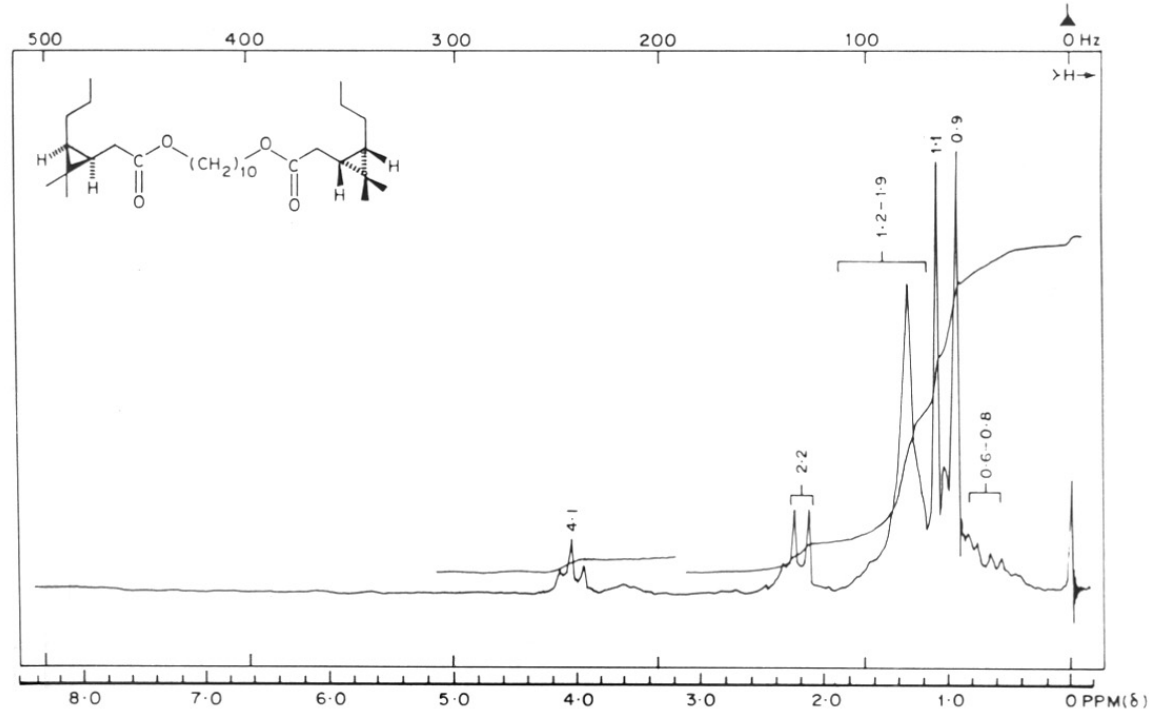

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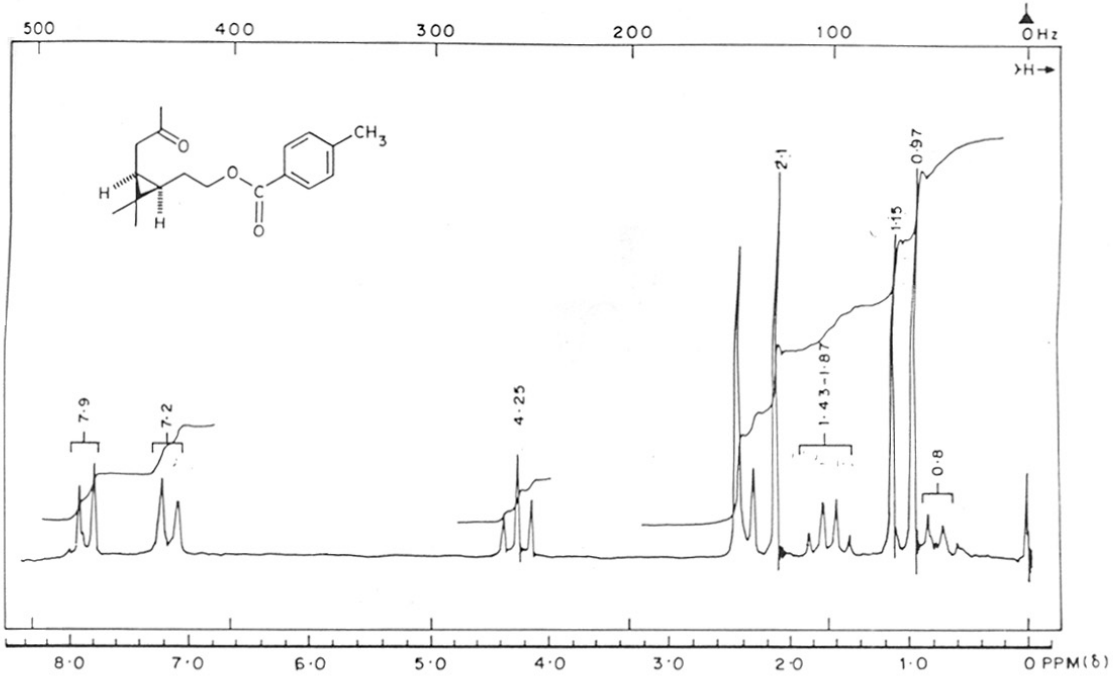

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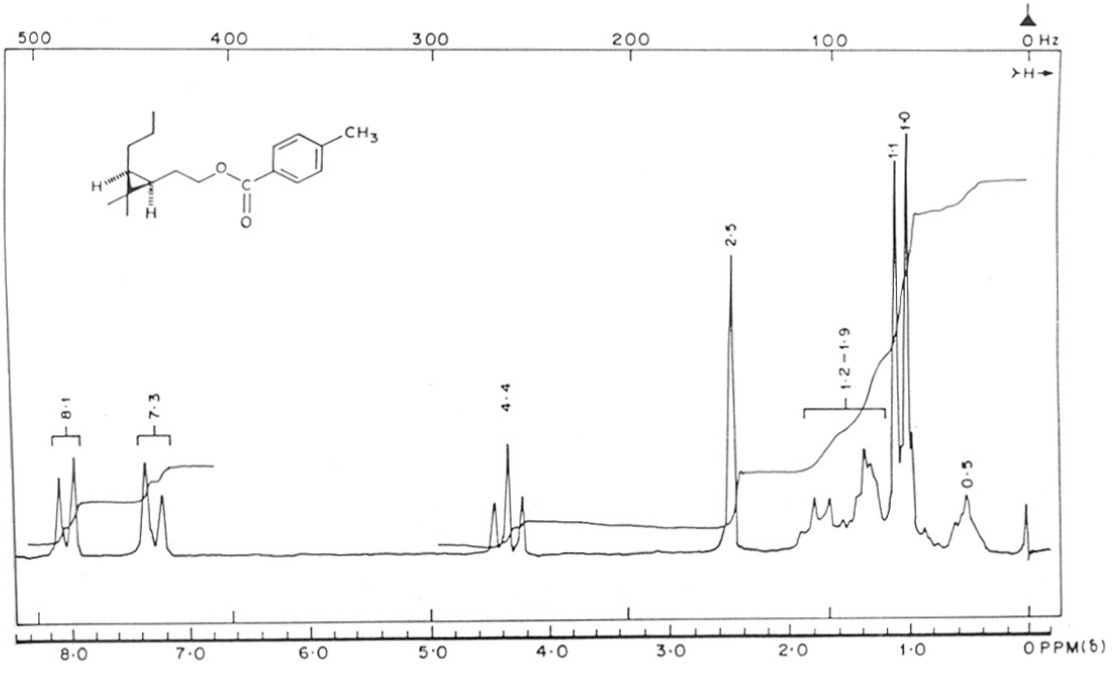

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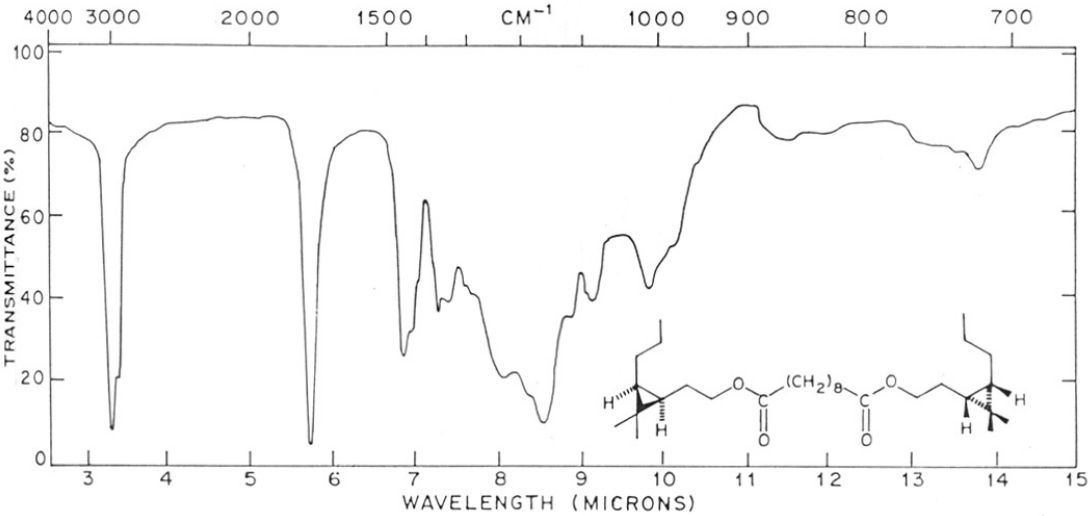

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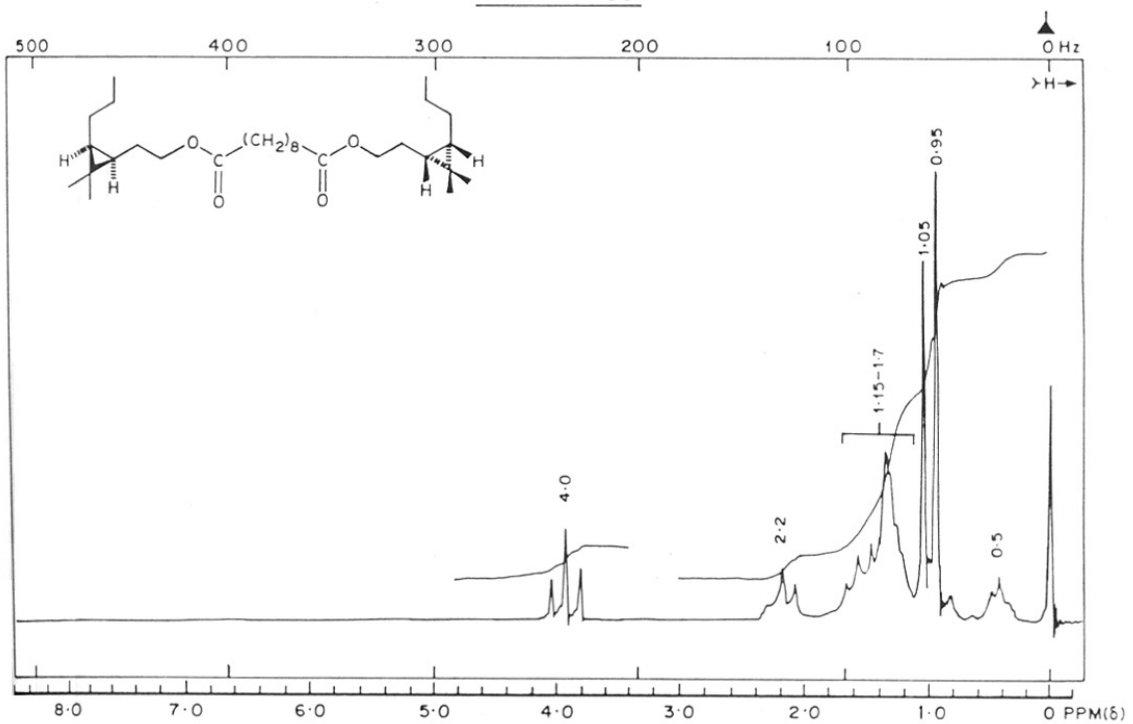

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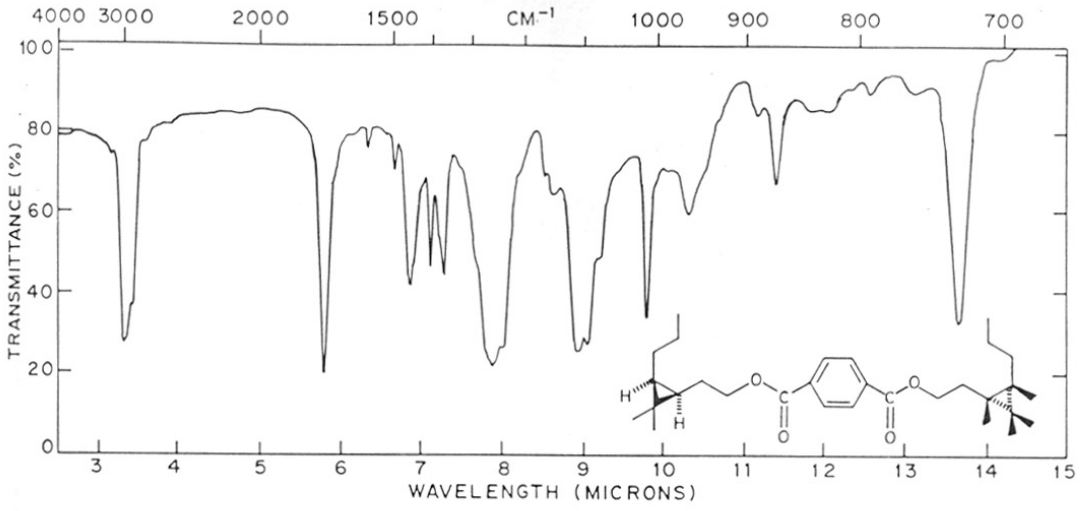

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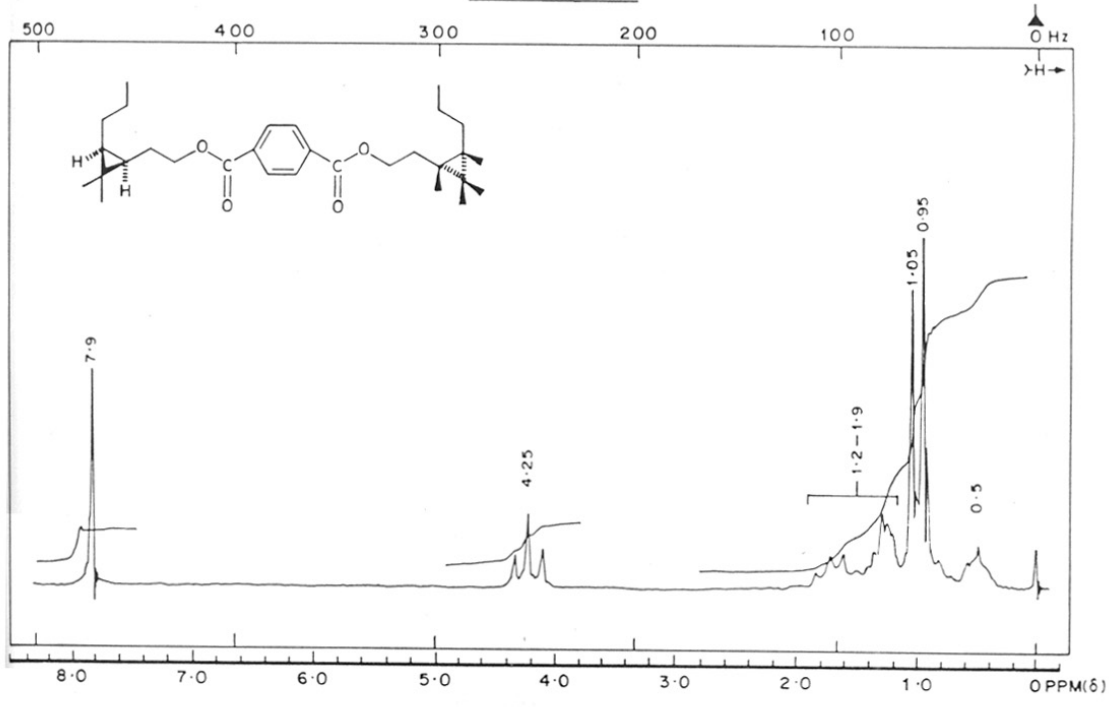


FIGURE 40

CHAPTER - III

PREPARATION OF SOME KEY INTERMEDIATES USEFUL FOR THE SYNTHESIS OF BIOLOGICALLY ACTIVE CYCLOPROPANE CARBOXYLATES

SUMMARY

This chapter deals with the synthesis of 3-phenoxybenzyl (±) 1R-*cis*-2,2-dimethyl-3-n-propyl-cyclopropanecarboxylate, 2,2-dimethyl-3-(n-propyl)-*cis*-cyclopropanecarboxylic acid and 2,2-dimethyl-3-(n-propyl) *cis*-cyclopropyl methanol. These three compounds have been synthesised by five different methods via two common intermediates, viz. 2,2-dimethyl-3-(n-propyl) *cis*-cyclopropane acetic acid methyl ester and 2,2-dimethyl-3-(n-propyl) *cis*-cyclopropaneacetaldehyde.

In the first approach, (+)-3-carene (I) was converted into carane diol (II) which, on Jones chromic acid oxidation, gave keto acid (III). Wolf-Kishner reduction of this keto acid (III) and subsequent esterification of acid (IV), furnished methyl ester (V). On Grignard reduction, using methyl magnesium iodide, of (V) afforded tertiary alcohol (VI), which on dehydration with PTSA, yielded isomeric mixture of unsaturated hydrocarbon (VII and VIII), which was, as such, oxidised by $KMnO_4$ in acetone to give acid (IX). This acid (IX), was esterified with diazomethane to give ester (X). The neutral oxidation product gave ketone (XI) and

hydroxy ketone (XIa). Transesterification of ester (X) with metaphenoxybenzyl alcohol, catalysed by n-butyl titanate, afforded the 3-phenoxybenzyl ester (XII) and LAH reduction of ester (X), yielded the primary alcohol (XIII).

In the second approach, the methyl ester (V) was condensed with benzaldehyde in presence of sodium methoxide in methanol in dry condition, to get aldol type condensation product (XIV), which, on dehyration with $POCl_3$/pyridine, gave a mixture of E and Z isomers (XVI). On ozonolysis, this α,β-unsaturated ester (XVI) yielded the required acid (IX) along with benzoic acid as a byproduct.

The β-hydroxy ester (XIV), on Jones chromic acid oxidation, afforded β-keto ester (XVIII), which on simultaneous hydrolysis and decarboxylation gave ketone (XIX). Bayer-Villiger oxidation of ketone (XIX) with m-chloroperbenzoic acid followed by hydrolysis of the perbenzoate with methanolic KOH, finally furnished the primary alcohol (XIII)

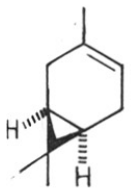
In the next approach, carane diol (II), was oxidised with sodium metaperiodate to get keto aldehyde (XX) which was converted into its dimethyl acetal (XXI) with excess methanol and catalytic HCl. Wolf-Kishner reduction of keto dimethyl acetal (XX),

afforded acetal (XXII). On treatment with 2% H_2SO_4, the aldehyde (XXIII) was regenerated from acetal (XXII).

Treatment of isopropenyl acetate with catalytic PTSA on aldehyde (XXIII) yielded the isomeric mixture of enol acetate (XXIV), which on ozonolysis and subsequent oxidative workup of the resulting ozonoid with Jones chromic acid, furnished the required acid (IX).

Self-condensation of aldehyde (XXIII) with potassium-tert-butoxide in tertiary butanol solvent, afforded aldol (XXV) along with its dehydrated product (XXVI). On $KMnO_4$ oxidation in acetone, this mixture (XXV amd XXVI), afforded mixture of acids (III and IX). Methyl esterification of this mixture of acids (III and IX) and the chromatographic separation of their methyl esters, furnished the desired ester (X).

The key intermediate aldehyde (XXIII), on treatment with PCl_5 without solvent, gave a geometric mixture of vinyl chloride (XXVII). Ozonolysis of this vinyl chloride (XXVII), afforded the required acid (IX) characterised by its methyl ester (X).



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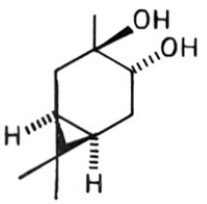

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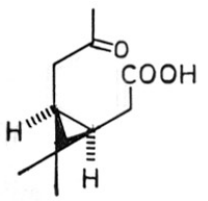

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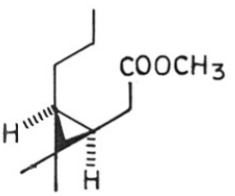

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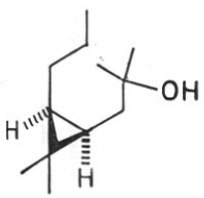

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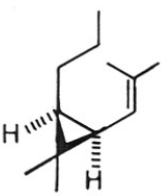

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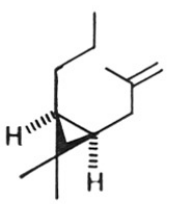

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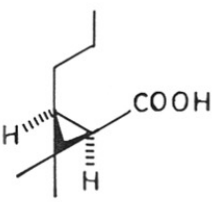

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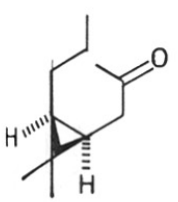

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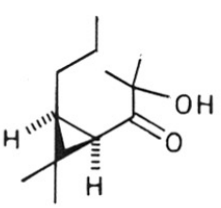

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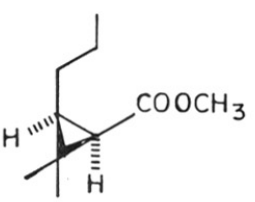

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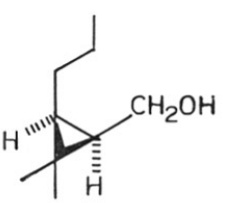

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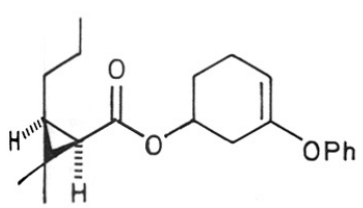

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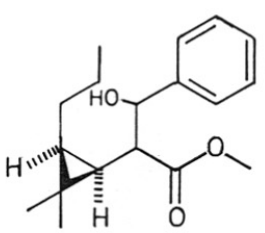

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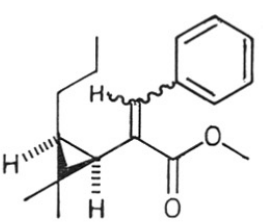

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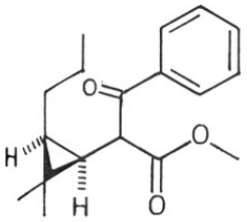

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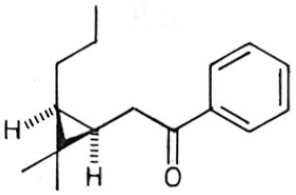

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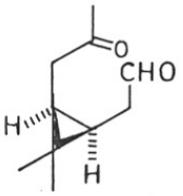

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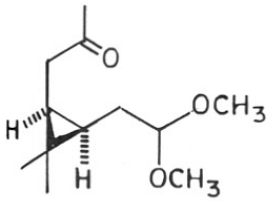

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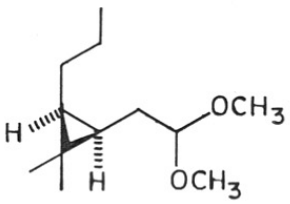

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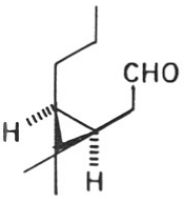

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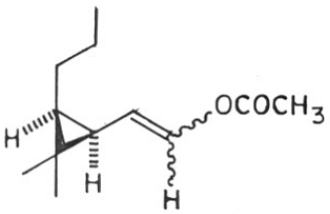

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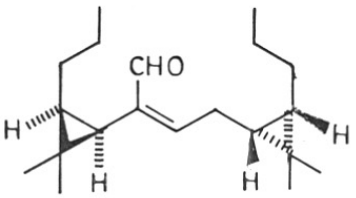

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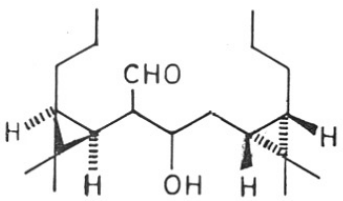

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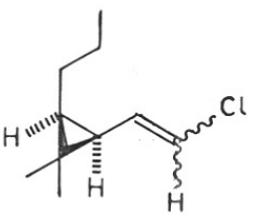

XXVII

INTRODUCTION

Many workers have investigated the correlation of chemical structures of compounds with their insecticidal activity. For example Staudinger and Ruzicka[1] prepared the pyrethronyl esters of various acids, such as aliphatic, olefinic, aromatic, terpene and cyclopropane-carboxylic acid, which resemble chrysanthemic acid, and examined their biological activities.

LaForge et al.[2] also tested activities of the rethronyl esters of many cyclopropane carboxylic acids. As a result, it was proposed that the necessary structural requirement for the acid component of pyrethrins to provide the activity is as follows: It should be cyclopropanecarboxylic acid substituted with an appropriate carbon chain, such as isobutenyl groups. The contribution of the geminal dimethyl substitutent to the activity is relatively small. The alcoholic component must contain an unsaturated side-chain, which may be alkenyl, cycloalkenyl benzyl or aromatic ring (e.g. furyl, benzyl or phenoxy). The whole cyclopentenolone ring can be replaced by structures that maintain the essential stereochemistry between the gem-dimethyl group on the cyclopropane ring and the unsaturated centre in the alcohol side-chain. For example (+) trans-chrysanthemates of

5-benzyl-3-furyl methyl and 3-phenoxybenzyl alcohol are active[3].

Due to the outstanding properties of the new pyrethroids, several research workers and industrial reserarchers were attracted towards this field. Several new synthetic routes for cyclopropanecarboxylates were developed[4] and the work is still going on for the development and preparation of new acid components of pyrethroids.

Newallis and Walker[5] for the first time claimed that vapours of certain alkylcyclopropanecarboxylic acid ester, possessing C-1 to C-4 carbon chain were active against both adult as well as eggs of two spotted spider mites. But they did not discuss in detail the contact activity of such compounds.

Jeniak[6] prepared certain aryl esters of cyclopropanecarboxylic acids and claimed that they possess the biocidal activity, preferably for the weed members of the class, Arachnoidae, bacteria and fungi.

Henrik et al.[7], prepared methyl, ethyl, isopropyl esters of 2,4-dodecanoic acids, which showed high insecticidal activity, especially as high as potent insect growth regulators. However, they are found to be devoid of any activity against mites.

Staal et al.,[8,9] have prepared various esters derived from cyclopropylmethyl alcohol and cyclo-

propanecarboxylic acid and tested its derivatives againt Tetranychus urticae koch.

Matsui et al.[10], synthesised number of 2,2-dimethyl-3-alkyl cyclopropanecarboxylic acid esters, possessing different alkyl groups at C-3 position of cyclopropane and studied their rethronyl esters for insecticidal activity against houseflies and compared with natural pyrethrins. Since the acid moiety of these esters were prepared starting from acyclic precursors, dl-mixtures of cis- and trans-cyclopropanecarboxylic acids were produced. 2,2,3,3-Tetramethylcyclopropanecarboxylic acid ester with rethronyl ester was found to show maximum insecticidal activity. The other three alkyl-cyclopropanecarboxylic acid esters, however, showed comparatively less activity.

Although the question of stereochemistry does not arise in the case of 2,2,3,3-tetramethylcyclopropane-carboxylate, since the molecule is symmetrical, the other three monoalkyl esters do show stereoisomerism. The insecticidal activity is greatly influenced by the absolute configuration at the chiral centre C-1, bearing the ester moiety and hence the individual pure stereoisomers are expected to differ in their insecticidal activity.

Preparations of some of the cyclopropane-carboxylic acids are described below:

a) 2-Methylcyclopropanecarboxylic acid (1), and 2,2-dimethylcyclopropanecarboxylic aic (2) were prepared by method of Julia et al.[11] (Scheme A).

b) Synthesis of 2,3-dimethylcyclopropanecarboxylic acid (3) and 2,2,3-trimethylcyclopropanecarboxylic acid (4) was done by the same route[11]. The Reformastsky reaction of methylethyl ketone, the starting material of the (3) and methyl isopropyl ketone, that of the (4), with ethyl bromoacetate, afforded β-hydroxy esters, which, without purification, were treated with 60% H_2SO_4 to β-methyl-γ-valero-lactone and βγ-dimethyl-γ-valerolactone respectively. The lactones were treated with thionyl chloride, the product obtained, treated with ethanol and then with a base to get ethyl esters of (3) and (4) acids (see Scheme B).

c) Synthesis of 2,2,3,3-tetramethylcyclopropane-carboxylic acid (5)[12].

The ethyl ester of acid (5) was prepared from tetramethyl ethylene by addition of ethyl diazo-acetate in the presence of cupric sulfate as a catalyst and successive alkaline hydrolysis (Scheme C). 2,2,3,3-Tetramethylcyclopropane acetic acid (6), the bromo acid of (5), was synthesised from (5) by means

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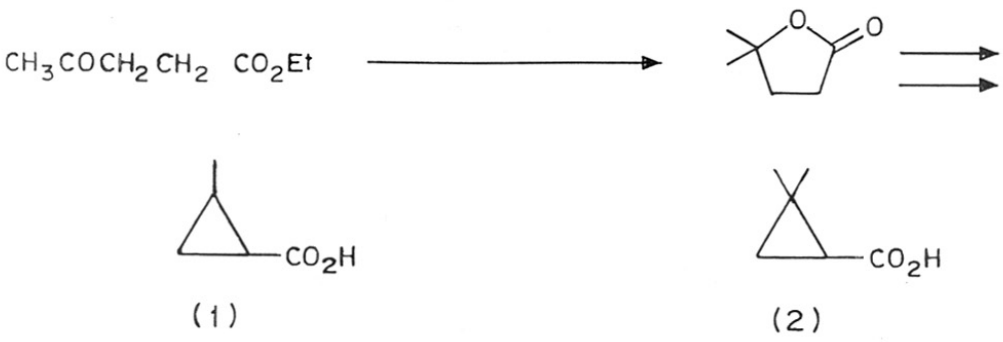

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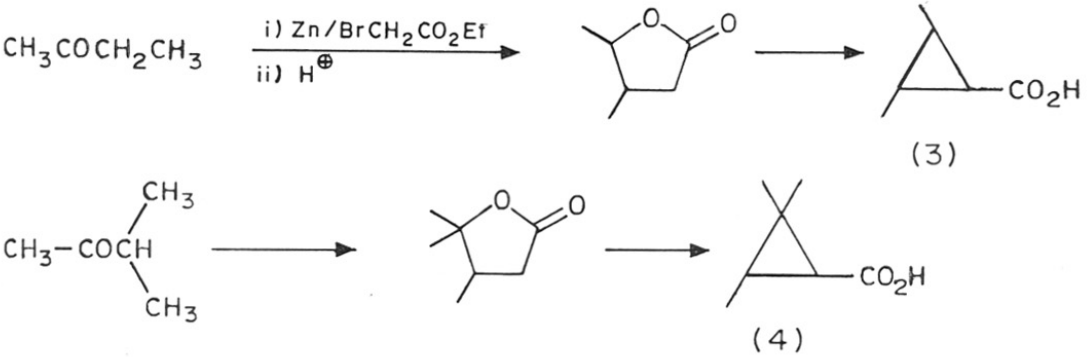
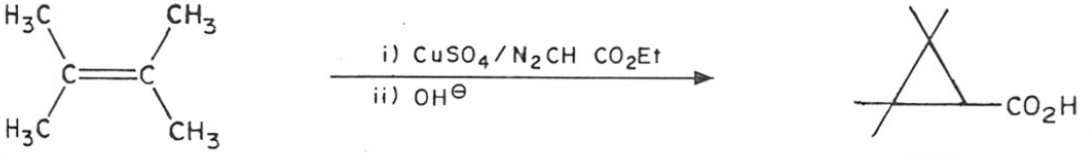
SCHEME – B



(3) (4)

SCHEME – C



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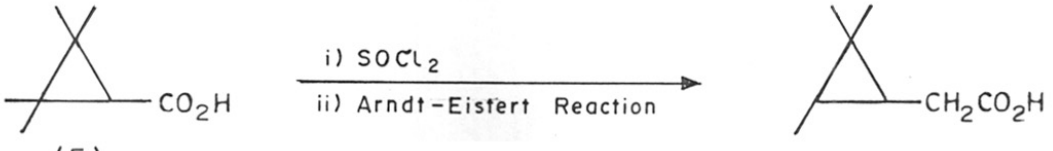
SCHEME – D



(5)

Arndt-Eistert reaction (Scheme D). Alkylation of ethyl senecioate with isopropyl bromide and sodium amide[13], subsequent treatment with alkoxide and then saponfiication, gave ∝-isopropyl-senecioic acid (7) (Scheme E).

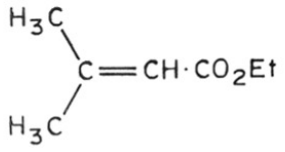
The following acids, from (8) to (13) were prepared from the corresponding olefins by the method of synthesis of (5) as described above. These are-

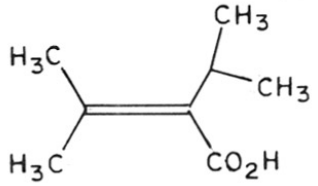
2,2-Dimethyl-3-ethylcyclopropanecarboxylic acid (8) 2,2-dimethyl-3-n-propylcyclopropanecarboxylic acid (9), 2,2-dimethyl-3-isopropylcyclopropane-carboxylic acid (10), 2,2-dimethyl-3-cyclopropyl-cyclopropanecarboxylic acid (11), 2,3,3-trimethyl-2-ethylcyclopropanecarboxylic acid (12) and finally 2,3,3-trimethyl-2-phenylcyclopropanecarboxylic acid (13), (compounds 8-13 under Scheme E).

Synthesis of 2,3,3-trimethyl-2-methoxycarbonyl-cyclopropanecarboxylic acid (or 1,2,2-trimethyl-3-methoxy-carbonylcyclopropanecarboxylic acid) (14).

Acid (14) was prepared by reduction of ethyl-∝ methyl-senecioate with lithium aluminium hydride and subsequent acetylation, gave trimethylallyl acetate. Upon addition of ethyldiazo acetate to this acetate, an acetoxy ester was obtained. It was hydrolysed with aqueous alkaline solution and without isolation,

SCHEME–E





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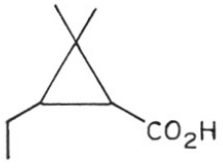

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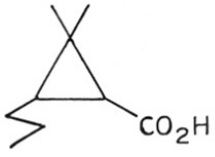

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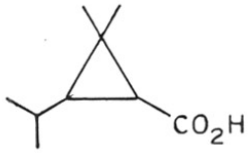

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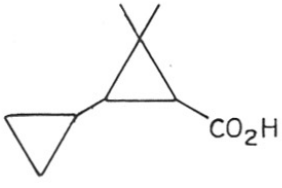

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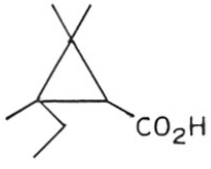

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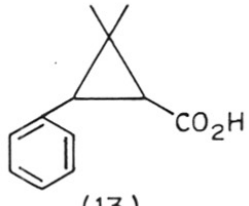

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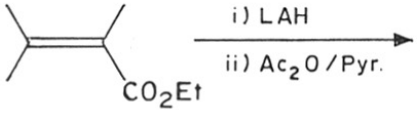
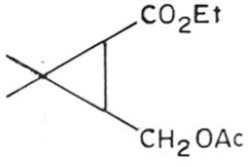
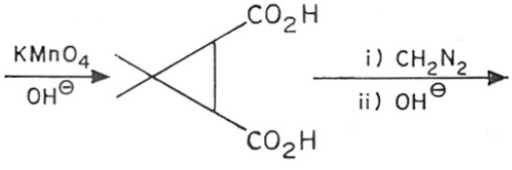
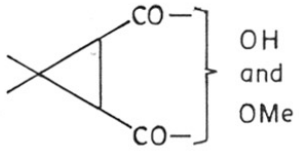
SCHEME–F









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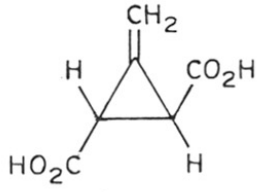

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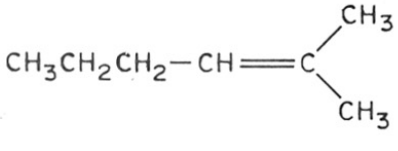
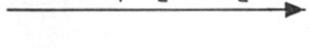
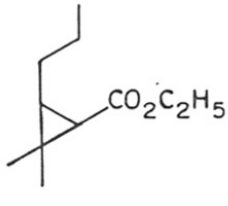
SCHEME–G







(16)

oxidized with potassium permanganate to a diacid. Esterification of the diacid with diazomethane and subsequent half-hydrolysis with alcohol-alkali, afforded (14) (Scheme F). Feist's acid (15) was obtained by the method of Goss and Ingold[14].

Allethrolone was mainly used as the alcoholic part, since allethrin, a synthetic insecticide, has as high an activity as pyrethrin. The acids, except (15),were converted into the corresponding acyl chlorides, then eserified with allethrolone in the presence of a base catalyst. (15) was treated with acetic anhydride to give the anhydride[15], then mixed with allethrolone in pyridine to get half-ester. This half-ester was esterified with diazomethane. Thus, fifteen allethronyl and rethronyl esters were given for biological tests. From the results, it was concluded that, firstly, increase on the methyl substitution on the cyclopropane ring contributes to the activity. Secondly, the existance of the cyclopropane ring is indispensible. As it is also known that, the rethronyl ester of homochrysanthemic acid is ineffective[16], the carboxylic group must apparently be attached directly to the cyclopropane ring.

Thirdly, until now, the presence of an unsaturated side chain has been widely believed to be necessary. However, ester of acid (5), despite its possessing no such substituent, has a strong effect, so the certainty of this rule is in doubt.

Ethyl-2,2-dimethyl-3-n-propylcyclopropanecarboxylate (Scheme G) (16).

Addition of ethyldiazo acetate to 2-methyl-hex-2-ene in presence of cupric sulfate as a catalyst afforded (16). Table I shows the activity of the rethronyl esters against housefly and mosquito.

As far as the insecticidal effect on the houseflies are concerned, as the number of methyl substituents on the cyclopropane ring increased, the activity indicated a higher value in the case of (1) and (5).

In particular, (5) showed an activity 70% high as that of allethrin. Ester of acid (3), which has vicinal dimethyl groups had no effect, while ester of acid (2) substituted with the geminal dimethyl groups had a little, though these substances possess the same molecular formula.

(6) is the homo-acid of (5), and (7) has a molecular formula identical with that of (5), but an open chain structure. Despite their structural resemblance to (5), (6) and (7) had no effect. Among

Table I

Kill effect of Rethronyl Esters on the housefly and Mosquito

Rethronyl esters of acid	kill effect on house fly LC_{50} mg/100 ml	Notes	Kill effect on mosquito LC_{50} ppm	Notes
1	>1000	(-)	> 3	(-)
2	920	(+)	3.5	(+)
3	>1000	(-)	> 3	(-)
4	500	(++)	0.29	(+++)
5	135	(+++)	0.34	(+++)
6	>1000	(-)	-	-
7	>1000	(-)	-	-
8	1015	(+)	1.15	(++)
9	>1000	(-)	0.84	(++)
10	>1000	(-)	1.0	(++)
11	>1000	(-)	3.4	(+)
12	>1000	(-)	-	-
13	>1000	(-)	-	-
14	>1000	(-)	-	-
15	>1000	(-)	-	-
Alletrin	100 ~ 130	-	0.105	-

(-) Indicates no activity
(+) indicates slight activity
(++) indicates medium activity and
(+++) indicates relatively high activity

other esters, ester of acid (8) showed slight effect, but the othrs were ineffective Although the activity on mosquito was random, esters of acids (4) and (5) showed fairly high activity.

In addition to above experiments, in our laboratory synthetic routes for methyl (-) 1R-cis-2,2-dimethyl-3-n-propycyclopropanecarboxylate and methyl-(+)-1S-cis-2,2-dimethyl-3-n-propyl-cyclopropanecarboxylate, starting from (+)-3-carene has been carried out[17]. The methyl esters mentioned above, were converted into corresponding alcohols viz., 1R- and 1S-cis-2,2-dimethyl-3-n-propylcyclopropyl methyl alcohol which may find to be key intermediates to prepare reversed esters with possible insecticidal activity.

This part of the thesis describes the different synthetic approaches for the preparation of 2,2-dimethyl-3-(n-propyl)-cis-cyclopropanecarboxylic acid and 2,2-dimethyl-3-(n-propyl) cis-cyclopropyl methanol from cheeply available (+)-3-carene, with a view to prepare esters with long chain fatty alcohols and various substituted phenols and acids respectively and to study these esters for possible insecticidal and acaricidal activity.

The above statement can be supported by the observation. Hurkova et al.[18] who have studied the effects of cyclopropylmethyl dodecanoate and cyclo-

propylmethyl terephthalate, on tetranychus urticae (Acari Tetranychidae) and found to be ovicidal against these two-spotted spider mites, having Lc_{50} value of 0.003% and 0.012% respectively, compared with 0.00026% of tetradiflow. Henrik et al.[19] invented many alkyl, alkenyl/alkynyl, alkenylene, alkynylene compounds from cyclopropylmethyl moiety.

In our laboratory, various alkyl, cyclohexyl, cyclohexylalkyl, aryl, aralkyl esters of 2,2-dimethyl-3-n-propyl-cis-cyclopropaneacetic acid and 2,2-dimethyl-3-n-propyl-cis-cyclopropyl ethanol with many structurally related alcohols and acids respectively, have been reported to possess high miticidal activity as already described in Chapter II of this thesis.

Present work and discussion

Stereochemistry plays a vital role for the insecticidal activity in synthetic pyrethroids[20]. In most of the synthetic as well as natural pyrethroids, 1R-configuration in the acid part is one of the essential requirements for high insecticidal activity[21-24]. Pyrethroids with 1S-configuration is almost inactive. Insecticidal potency differences are observed between distereoisomeric pyrethroids having the R-configuration at C-1 but differing in configuration at C-3. In most insect species, the 1R-cisisomer of a distereomer pair

is more toxic than the corresponding 1R-trans isomer. The toxicity difference can be as much as ten-fold, depending upon both the species and pyrethroid examined[25].

In view of this, we synthesised 1R-cis-2,2-dimethyl-3-n-propyl-cyclopropanecarboxylic acid (IX) and 1R-cis-2,2-dimethyl-3-n-propyl-cyclopropylmethanol (XIII) from the abundantly available (+)-3-carene which may prove to be crucial intermediate for the synthesis of new potent insecticidal and acaricidal esters.

(+)-3-Carene, on treatment with performic acid was converted into the formoxy hydroxy carene which on alkali hydrolysis, gave the known[26] 3β-4α-carane diol (II), $C_{10}H_{18}O_2$ in 55% yield; m.p.82-83° (pet.ether). It showed IR (Nujol) bands at 3448 (OH), 1058 and PMR (CCl_4,δ) signals at 0.7 (2H, m, cyclopropane protons at C-1 and C-3), 0.97 (6H, s, gemdimethyl on cyclopropane), 1.17 (3H, s -CH_3 at C-3), 1.74-2.23 (4H, m, 2 x CH_2 protons), 3.27 (1H, q, proton at C-4) and 3.63 (2H, m, exchangeable with D_2O, OH proton).

Jones chromic acid oxidation of diol (II) at 0° gave keto acid (III) in 76% yield. Wolf-Kishner reduction of keto acid (III), afforded acid (IV) in 90% yield[27] which was converted to its methyl ester in almost quantitative yield to give methyl ester (V), a pale yellow liquid, $C_{11}H_{20}O_2$, M^+ 184, dist. at

95-100°/10 mm. It showed IR (liquid film) bands at 1738 (ester C=0) and PMR (CCl_4, δ) signals at 0.7 (2H, m, cyclopropyl protons at C-1 and C-3), 0.97, 1.1 (6H, 3 each, s each, gemdimethyl of cyclopropane at C-2), 1.25 - 1.5 (7H, m, n-propyl protons at C-3), 2.15 (2H, d, J=8 Hz, $-CH_2$ at C-1), 3.65 (3H, s, $-OCH_3$).

The methyl ester (V) was a vital intermediate for the preparation of the required acid (IX) by following two different approaches.

In the first approach, Grignard reaction of methyl magnesium iodide on methyl ester (V) furnished tertiary alcohol (VI) as a yellow oily liquid; $C_{12}H_{24}O$, M^+ 184 $[\alpha]_D^{28}$ - 8° (c, 1.5). IR (liquid film) bands at 3358 (OH) and PMR (80 MHz, $CDCl_3$ signals at 0.48 (2H, m, cyclopropane protons at C-1 and C-3), 0.96 (6H, s, overlapping the triplet, one of the cyclopropane methyls and primary methyl of n-C_3H_7 gr. at C-3), 1.12 (3H, s, another cyclopropane methyl), 1.28 (8H, s, hydroxy isopropyl methyls and protons of one of the $-CH_2$ gr.), 1.3-1.55 (4H, m, other 2X $-CH_2$ gr.), 2.6 (1H, brs, OH).

Dehydration of tertiary alcohol (VI) with catalytic p-toluenesulphonic acid in dry benzene, gave dark yellow coloured oily E and Z isomeric mixture of unsaturated hydrocarbon (VII and VIII) in 78% yield,

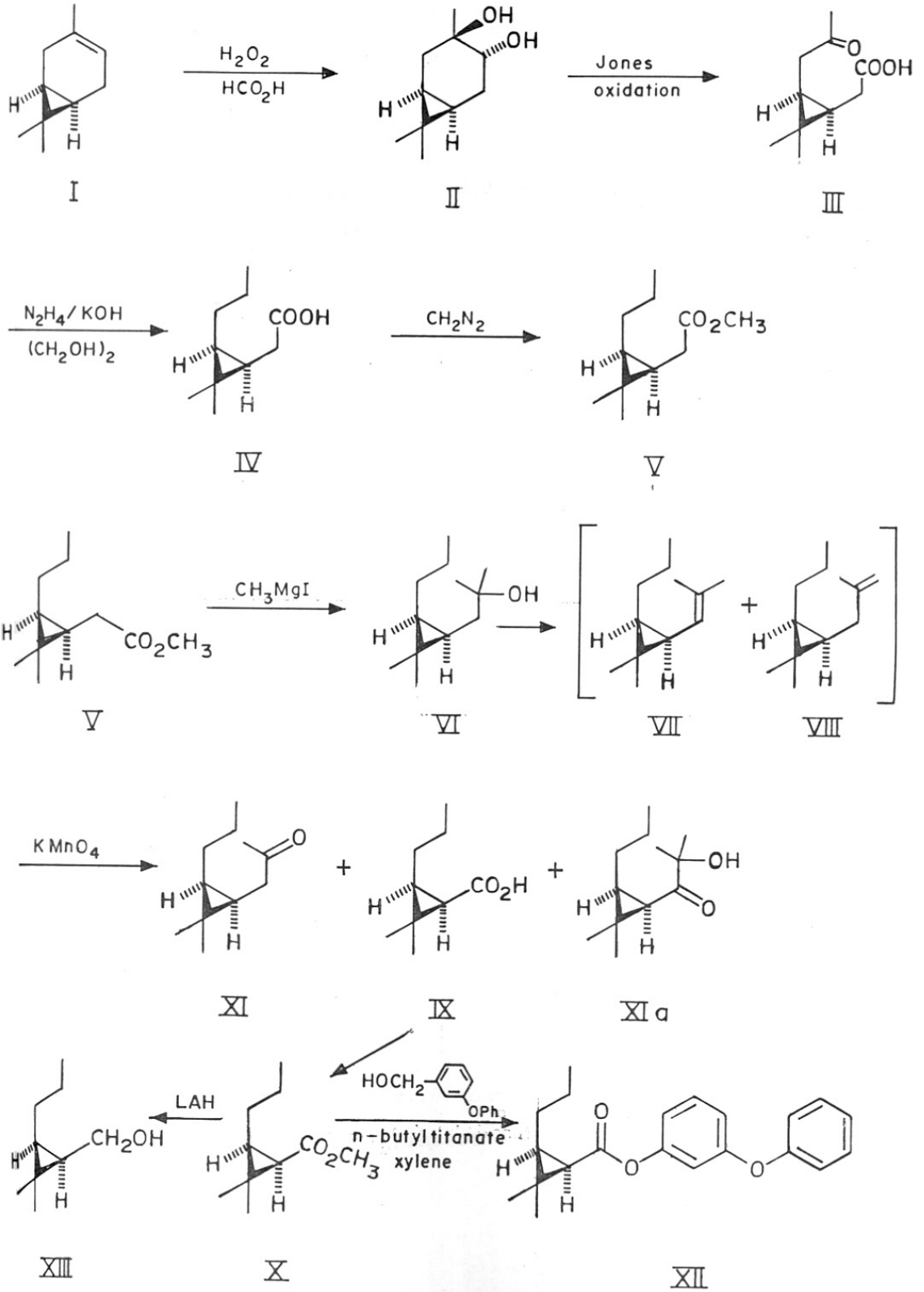
$C_{12}H_{22}$, M^+ 166. On chromatographic separation and purification over silica gel, the mixture (VII and VIII) showed spectral properties; IR (liquid film) bands at 1650 (C=C), PMR (CCl_4,δ) signals at 0.4-0.6 (2H, m, cyclopropane protons at C-1 and C-3 in VIII and C-3 in VII, 0.92 (6H, s, overlapping a triplet, one of the cyclopropane methyl of n-C_3H_7 gr. at C-3 in both isomers VII and VIII), 1.08 (3H, s, another cyclopropane methyl of both VII and VIII), 1.41 - 1.48 (m, -CH_2 protons at C-3 and C-1 in both VII and VIII and cyclopropane proton at C-1 in VII), 1.68, 1.74 (both s, vinyl methyls in both isomers), 4.72 (2H, brs, -C=CH_2 in VIII) and 4.92 (1H, d, J=8 Hz, olefinic proton in VII).

Oxidation of the mixture of unsaturated hydrocarbons (VII and VIII) as such, with potassium permanganate in acetone at 0-5°, afforded mixture of products. The acidic oxidation product was converted into its methyl ester, using an ethereal solution of diazomethane to yield liquid ester in 38% yield, $C_{10}H_{18}O_2$, M^+ 170, $[\alpha]_D^{28}$ -61° (c, 1.2). It was identified as ester (X) by IR (liquid film) bands at 1728 (ester C=O); PMR (90 MHz; $CDCl_3$) signals at 0.91 (4H, t, J=6 Hz, primary methyl of n-C_3H_7 gr. and proton at C-3), 1.14, 1.22 (6H, 3H each, s each, gemdimethyl of cyclopropane), 1.27 - 1.52 (4H, m, -CH_2 of n-C_3H_7 gr. at C-3), 1.62 (1H, d, J=7 Hz,

cyclopropane proton at C-1) and 3.61 (3H, s, $-OCH_3$).

The neutral liquid products of oxidation were purified by column chromatography over silica gel and eluted with mixture of chloroform and pet.ether. The earlier fractions eluted with 25% chloroform + pet. ether gave a liquid in 22% yield, identified as ketone (XI), $C_{11}H_{20}O$, M^+ 168, $[\alpha]_D^{28}$ -13 (c, 0.9); IR bands at 1721 (C=O); PMR (CCl_4, δ) signals at 0.5 - 0.7 (2H, m, cyclopropane protons at C-1 and C-3), 0.9 (6H, s, overlapping a t, one of the cyclopropane methyls and primary methyl of n-C_3H_7 gr. at C-3), 1.1 (3H, s, another cyclopropane methyl), 1.12-1.5 (4H, m, CH_2 protons of n-C_3H_7 at C-3), 2.1 (3H, s, $COCH_3$) and 2.2 (2H, d, J=6 Hz, $-CH_2$ at C-1). This ketone is obviously resulting by the oxidation of unsaturated hydrocarbon (VIII), also present in the mixture.

The latter fractions eluted with 50% chloroform in pet.ether (60-80° fra.) gave the liquid, hydroxy ketone (XIa) in 15% yield, $C_{12}H_{22}O_2$, M^+ 198, $[\alpha]_D^{28}$ - 88° (c, 1.2). It showed IR (liquid film) bands at 3445 (-OH), 1676 (C=O); PMR (90 MHz; $CDCl_3$) signals at 0.91 (4H, t, J=6 Hz primary methyl of n-propyl gr. at C-3 and cyclopropane proton at C-3), 1.16, 1.23 (6H, 3 each, s each, gemdimethyl of cyclopropane), 1.38, 1.42 (6H, 3 each, s each,


H2O2
HCO2H
OH
OH
Jones
oxidation
O
COOH
I
II
III
N2H4/KOH
(CH2OH)2
COOH
CH2N2
CO2CH3
IV
V
CH3MgI
CO2CH3
OH
+
V
VI
VII
VIII
KMnO4
O
+
CO2H
+
OH
O
XI
IX
XI a
HOCH2
OPh
n-butyltitanate
xylene
LAH
CH2OH
CO2CH3
O
O
O
XIII
X
XII

hydroxyisopropyl methyl), 1.46-1.71 (4H, brm, 2X -CH_2 of n-propyl gr. at C-3), 1.85 (1H, d, J=8 Hz, cyclopropane proton at C-1) and 3.44 (1H, brs, exchangeable with D_2O, -OH proton). Compound (XIa) was resulted from the hydrocarbon (VII) by oxidation.

Transesterification[27] of ester (X), with 3-phenoxybenzyl alcohol catalysed by n-butyl titanate, afforded 3-phenoxybenzyl ester (XII) as a thick liquid in 89% yield; $C_{22}H_{26}O_3$; M^+ 338, $[\alpha]_D^{27}$ - 20 (c, 1.5), identified by IR (liq. film) bands at 1726 (ester C=O), 1588, 690 (aromatic) and PMR (80 MHz:$CDCl_3$) signals at 0.9 (4H, t, J=6 Hz, primary methyl of n-propyl gr. at C-3 and cyclopropane proton at C-3), 1.14, 1.2 (6H, 3-each, s each, gem-dimethyl), 1.28 - 1.6 (5H, m, 2 x -CH_2 of n-propyl gr. at C-3 and cyclopropane proton at C-1), 5.08 (2H, s benzylic protons) and 6.92 - 7.44 (9H, m, aromatic protons).

The 3-phenoxybenzyl ester (XII) was tested for its insecticidal activity against musca domestica (houseflies). The ester (XII) was applied topically on the insects with the help of microsyringe. The food was provided to the insects and the mortality was observed after 24 hours. It showed 100% mortality at 5 μg/insect dosage level (minimum three

replicates were done and average mortality was observed).

Similarly the same ester (XII) was tested for larvicidal activity against 4th instar larvae of Acdes aegypti, (yellow fever mosquito). The ester was added in 50 ml water in desired concentration Minimum 10 No. of larvae were released in this water, normal food was supplied and mortality was observed after 24 hr. It showed 65% and 100% mortality at 5 ppm and 10 ppm dose respectively (minimum three replicates were done and average mortality was found).

Lithium aluminium hydride reduction of ester (X), afforded primary alcohol (XIII) in 85% yield; $C_9H_{18}O$; M^+ 142, $[\alpha]_D^{26}$ -10 (c, 1.2) and showed IR (liquid film) bands at 3410 (-OH) and PMR (80 MHz: $CDCl_3$) signals at 0.6 - 0.95 (5H, m, $-CH_3$ of n-propyl and cyclopropane proton at C-1 and C-3), 1.05, 1.1 (6H, 3-each, s each, 2 x $-CH_3$ at C-2), 1.3 (4H, m, 2 x $-CH_2$ of n-propyl at C-3) and 3.6 (2H, d J = 8 Hz, $-CH_2OH$ at C-1).

The methyl ester (V) has a reactive methylene group adjacent to the ester carbonyl group. So Claisen condensation of ester (V) with freshly distilled benzaldehyde with sodium methoxide in dry methanol was carried out at room temperature for three hours when β-hydroxy ester (XIV) was obtained

in 55% yield. Removal of unreacted benzaldehyde by distillation, gave thick dark yellow liquid; $C_{18}H_{26}O_3$, M^+ 290 and shows IR (liquid film)bands 3620 (-OH), 1590 (aromatic) and PMR (CCl_4,) signals at 0.65 (2H, m, cyclopropyl protons at C-1 and C-3), 0.95, 1.0 (6H, 3-each, s each, gemdimethyl of cyclopropane), 1.1 - 1.3 (7H, m, n-propyl at C-3), 2.3 (1H, d, J = 8 Hz, proton α to ester methyl of one isomer), 2.45 (1H, d, J=8 Hz, proton α-to ester methyl of other isomer), 2.8 (1H, brs, exchangeable with D_2O, -OH proton), 3.65 (3H, s, $-OCH_3$ of one isomer), 3.7 (3H, s, $-OCH_3$ of other isomer), 4.65 (1H, d, J = 6 Hz, benzylic proton of one isomer), 4.9 (1H, d, J=6 Hz, benzylic proton of other isomer), 7.2 (5H, s, aromatic protons).

On dehydration with phosphorous oxychloride in pyridine at 0°, the erythro- and threo-isomeric mixture of -hydroxy ester (XIV), afforded α,β-unsaturated ester as a mixture of E and Z isomers (XVI). It was purified by silica gel column chromatographyand eluted with pet.ether to get pale yellow oil in 78% yield; $C_{18}H_{24}O_2$, M^+ 272 and shows IR (liquid film) bands at 1610 (C=C), 1600 (aromatic), and PMR (CCl_4, δ) signals at 0.9 (1H, s, cyclopropane proton at C-1), 1.1 - 1.7 (14H, m, gemdimethyl, primary methyl and methylene proton of n-propyl gr.

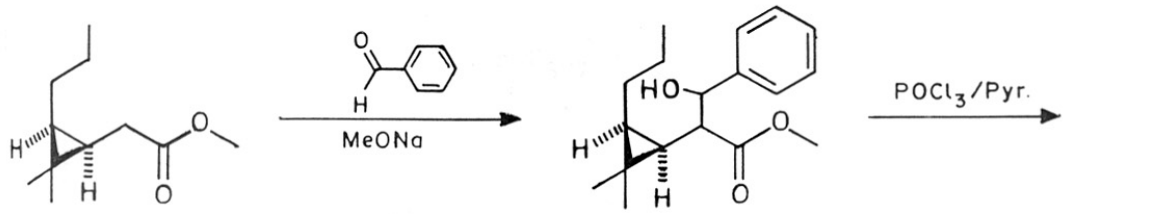
at C-3and cyclopropane protonat C-3), 3.7 (3H, s, $-OCH_3$ of one isomer), 3.76 (3H, s, $-OCH_3$ of other isomer), 4.65 (1H, s, benzylic proton of one isomer), 4.8 (1H, s, benzylic proton of other isomer) and 7.25 (5H, s, aromatic).

Similarly, furfurylidene derivative (XV) was prepared from ester (V) with furfuraldehyde and potassium-tert-butoxide in tert-butanol solvent. But since this reaction was sluggish and the yield obtained, after much efforts,was 5-6%, it was not carried out further.

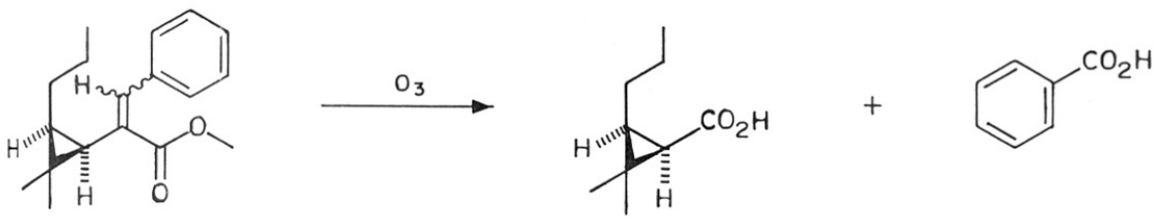
Ozonolysis of the isomeric mixture of α,β-unsaturated benzylidene derivative (XVI) yielded the desired acid (IX) along with benzoic acid as a byproduct.

The β-hydroxy ester (XIV) provided us a new approach for the peparation of 2,2-dimethyl-3-(n-propyl)-cis-cyclopropylmethanol (XIII) which is as follows-

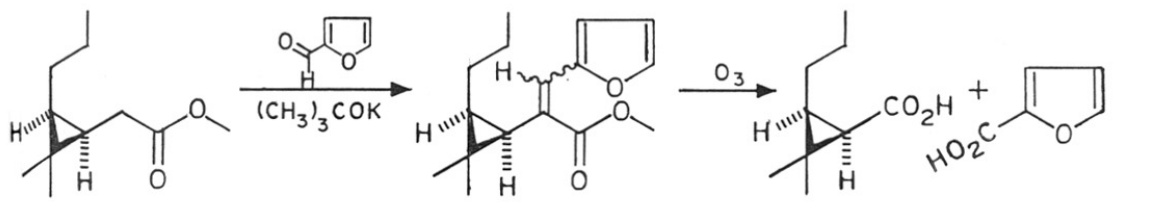
Jones chromic acid oxidation of the β-hydroxy ester (XIV) at 10-15°C in acetone, afforded β-keto ester (XVIII), a liquid; $C_{18}H_{24}O_3$, M^+ 188; and shows IR (liquid film) bands at 1739 (ester C=0), 1685 (benzoyl C=0), 1595 (aromatic); PMR (CCl_4, δ) signals at 0.73 (2H, m, cyclopropane protons at C-1 and C-3), 1.05, 1.1 (6H, 2s, 2 x $-CH_3$ at C-2),



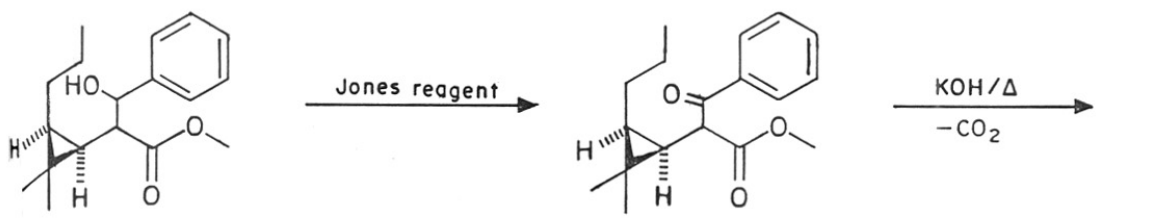
V XIV



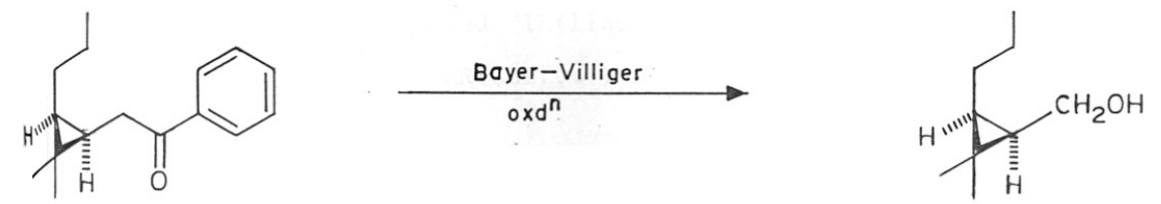
XVI IX



V XVII IX



XIV XVIII



XIX XIII

1.25 - 1.6 (7H, m, n-C_3H_7 at C-3), 4.0 (1H, d, J=12 Hz, proton adjacent to two C=0 gr.), 7.1 (3H, m, aromatic protons) and 7.8 (2H, m, aromatic ortho protons).

Simultaneous hydrolysis and decarboxylation of β-keto ester (XVIII) with aqueous alcoholic sodium hydroxide by heating on water bath for 2 hr., afforded a ketone (XIX) as a pale yellow oil; $C_{16}H_{22}O$, M^+ 230; shows IR (liquid film) bands at 1680 (benzoyl C=0), 1595 (aromatic); PMR (CCl_4, δ) signals at 0.7 (2H, m, cyclopropyl protons at C-1 and C-3), 0.95, 1.1 (6H, 2s, 2 x $-CH_3$ at C-2), 1.25 (7H, m, n-propyl gr. at C-3), 2.75 (2H, d, J = 12 Hz, $-CH_2$ at C-1), 7.15 (3H, m, aromatic) and 7.6 (2H, m, aromatic ortho protons).

Bayer-Villiger oxidation[28,29] of ketone (XIX) using m-chloroperbenzoic acid in chloroform and subsequent hydrolysis of the corresponding perbenzoate with aqueous methanolic potasium hydroxide, gave the required primary alcohol (XIII) identified by spectral analysis explained earlier.

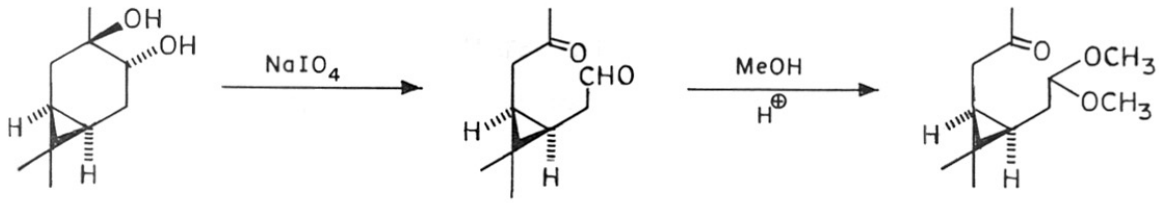
Sodium metaperiodate oxidation[30] of vicinal diol (II), furnished the ketoaldehyde (XX) in 85% yield as a yellowish oil; $C_{10}H_{16}O_2$, b.p.85-87°/1.5 mm M^+ 168. It showed IR(liquid film) bands at 2740(CHO), 1724(C=0) and PMR(CCl_4, δ) signals at 0.83 (2H, m,

cyclopropane protons at C-1 and C-3), 1.0, 1.13 (6H, 3 each, s each 2 x $-CH_3$ at C-2), 2.1 (3H, s, $-COCH_3$) and 2.43 (4H, m, 2 x $-COCH_2$).

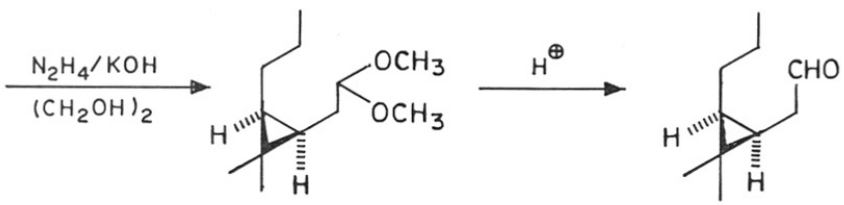
Freshly prepared keto aldehyde (XX) on treatment with methanol and catalytic quantity of HCl at 0°C, furnished ketodimethyl acetal (XXI) in 87% yield as liquid, $C_{12}H_{22}O_3$, b.p.106-109°/1 mm, M^+ 214. It showed IR (liquid film) bands at 1724 (C=O) and PMR (CCl_4, δ) signals at 0.66 (2H, m, cyclopropane protons at C-1 and C-3), 0.9, 1.08 (6H, 2s, 2 x $-CH_3$ at C-2), 1.45 (2H, d, J=6 Hz, $-CH_2$ at C-1), 2.06 (3H, s, $-COCH_3$), 2.33 (2H, d, J=6 Hz, $-COCH_2$), 3.23 (6H, s, 2 x $-OCH_3$ of acetal)and 4.15 (1H, t, J = 6 Hz, -CH of acetal).

Wolf-Kishner reduction of keto dimethyl acetal (XXI) with the help of hydrazine hydrate, diethylene glycol and KOH at 185°-95°, afforded reduced acetal (XXII); $C_{12}H_{24}O$, M^+ 200, b.p.90-100°/1.5 mm and showed IR (liquid film) bands at 1080, 1070 ($-OCH_3$ stretch) and PMR (CCl_4, δ) signals at 0.32 (2H, m, cyclopropane protons at C-1 andC-3), 0.95, 1.05 (6H, 2s, 2 x $-CH_3$ at C-2), 1.4 (7H, m, n-propyl gr. at C-3), 3.3 (6H, s, 2 x $-OCH_3$), 4.3 (1H, t, J = 6 Hz, -CH of acetal).

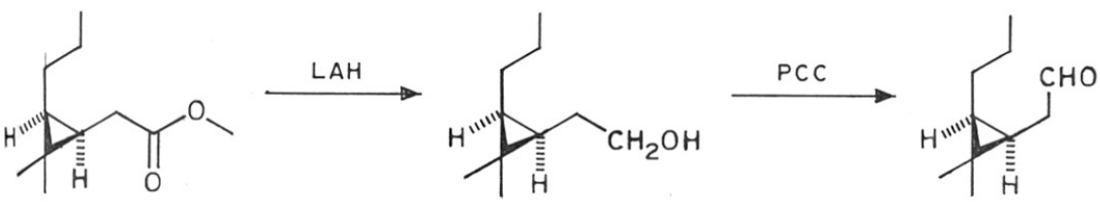
The corresponding aldehyde (XXIII) was regenerated from acetal (XXII) by warming the acetal (XXII) with



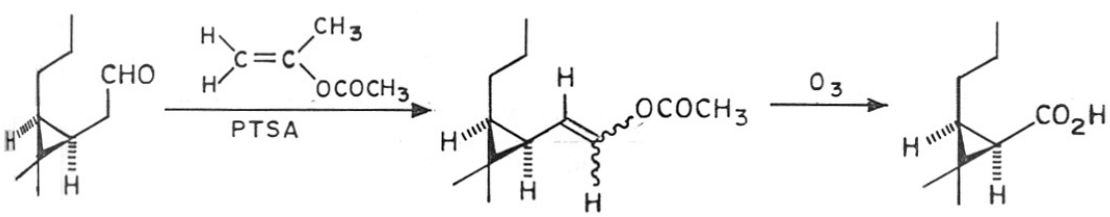
II XX XXI



XXII XXIII



V XV XXIII



XXIII XXIV IX

2% sulphuric acid[31] for 1 hr. at 80-90° in 72% yield; $C_{10}H_{18}O$, M^+ 154 and shows IR(liquid film) bands at 2778 (CHO), 1739 (C=O); PMR(CCl_4, δ) signals at 0.7 (2H, m, cyclopropane protons at C-1 and C-3), 0.95, 1.1 (6H, 2s, 2 x $-CH_3$ at C-2), 1.15 - 1.4 (7H, m, n-propyl gr. protons at C-3), 2.26 (2H, m, $-COCH_2$ adjacent to aldehyde), 9.7 (1H, t, J=4 Hz, aldehyde proton).

The above crucial intermediate, aldehyde (XXIII) was also prepared by another route, from methyl ester (V), as follows:

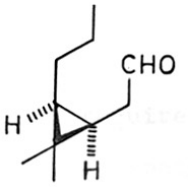
Lithium aluminium hydride reduction of ester (V), furnished primary alcohol (XV) in 90% yield as a colourless liquid; $C_{10}H_{20}O$, M^+ 156 whose spectral data has been described in Chapter II. Pyridinium-chlorochromate oxidation of this primary alcohol (XV), using anhydrous methylene chloride solvent, afforded aldehyde (XXIII), purified by column chromatography using alumina (neutral), to get pure aldehyde (XXIII).

Enol acetalization[32] of aldehyde (XXIII) with isopropenylacetate using catalytic p-toluene sulphonic acid, yielded cis- and trans-isomeric mixture of enol acetate (XXIV) in 70% yield; purified by silica gel chromatography and elued with pet.ether, as a pale yellow oily liquid; $C_{12}H_{20}O_2$, M^+ 196, and showed IR (liquid film) bands at 1786 (acetate C=O),

1667 (C=C) and PMR (CCl_4, δ) signals at 0.6 (1H, m, cyclopropane proton at C-3), 0.95 - 1.2 (9H, 4s, of gemdimethyl protons overlapping t of primary methyl of both the isomers), 1.33 (4H, brs, 2 x-CH_2 at C-3), 1.55 (1H, m, cyclopropane proton at C-1), 2.1 (3H, s, -$COCH_3$ of one isomer), 2.2 (3H, s, -$COCH_3$ of other isomer), 4.13 (1H, t, J=8 Hz, proton adjacent to C-1), 4.5 (1H, d, J=7 Hz, olefinic proton of one isomer) and 4.7 (1H, d, J=7 Hz, olefinic proton of other isomer).

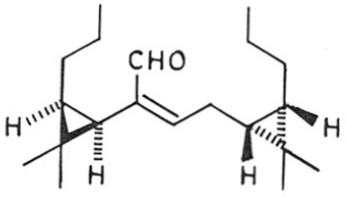
Ozonolysis of the isomeric mixture of enol acetate (XXIV) in ethyl acetate followed by oxidative workup of the resulting ozonoid with Jones chromic acid, gave the required acid (IX) chracterised and identified through its methyl ester whose spectral data has been explained earlier.

Self aldol condensation of aldehyde (XXIII) with potassium-tert-butoxide in dry tert-butanol led to a mixture of an aldol (XXV) and its corresponding dehydrated product (XXVI), obtained as liquid mixture, (M^+ 308 showed the presence of aldol); IR bands at: 3407 (OH), 2770, 1721 (CHO), 1681 (conjugated aldehyde), 1630 (conjugated C=C). The crude aldol mixture, as such, on oxidation with $KMnO_4$ in acetone gave, in the acid part, mixture of acids which were converted into their methyl esters by ethereal solution



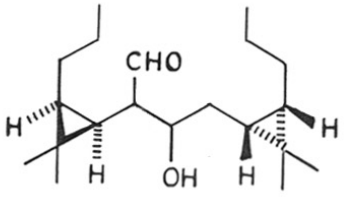
XXIII

$(CH_3)_3COK$



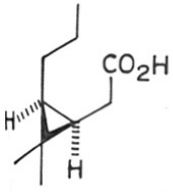
XXVI

+



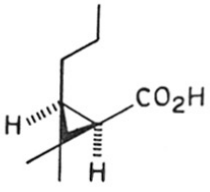
XXV

Acetone $KMnO_4$

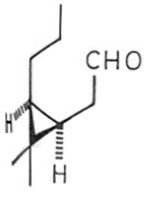


IV

+

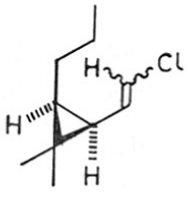


IX



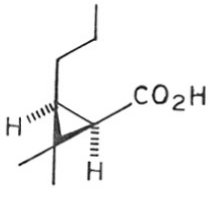
XXIII

PCl_5



XXVII

O_3



IX

of diazomethane. Silica gel chromatography of the mixture of esters, using (1:1) benzene + chloroform, afforded (TLC pure) required ester as a yellowish liquid, the IR and NMR spectrum of which resembled with that of ester (X).

The aldehyde (XXIII) was treated with phosphorous pentachloride with initial cooling at 0° and then left at room temperature overnight. The reaction mixture was poured over crushed ice and extracted with ether, the ether layer was washed with water, dried over anhydrous sodium sulfate and solvent was removed to get crude chlorovinyl compound as a mixture of geometric isomers (XXVII). The mixture was purified by silica gel column chromatography and eluted with (1:1). Pet.ether-benzene mixture showed a multiplet at 5.3 δ for vinyl proton and pair of doublets at 5.0 for HC-Cl proton. The purified isomeric mixture was isolated as colourless oil in 65% yield; $C_{10}H_{17}Cl$, M^+ 172; IR(liquid film) bands at 860 (HC-Cl stretch) and PMR (CCl_4, δ) signals at 0.95 (2H, m, cyclopropane protons at C-1 and C-3), 1.1, 1.25 (6H, 2s, 2 x $-CH_3$ at C-2), 1.3 (7H, m, n-propyl protons at C-3), 4.9 (1H, d, J=4 Hz, HC-Cl proton of one isomer), 5.0 (1H, d, J=4 Hz, HC-Cl proton of other isomer), 5.35 (2H, m, vinyl protons of both the isomers).

Ozonolysis of the purified isomeric mixture of vinyl chloride (XXVII), as such, was carried out to get the final required acid (IX).

EXPERIMENTAL

2,2-Dimethyl-3-n-propyl-cis-(2-methyl-2-hydroxy propyl) cyclopropane (VI)

Methyl magnesium iodide (7.14 g, 60 mmole), prepared in ether under anhydrous condition, was cooled in an ice-bath and the ester (V) (5.52 g, 30 mmol), dissolved in ether (100 ml), was added to it dropwise with stirring. After addition was complete (1 hr), the ice-bath was removed and the reaction left stirring overnight. After cooling in an ice-bath, the reaction mixture was decomposed with saturated aqueous solution of ammonium chloride. The ether layer was separated and the aqueous layer extracted with ether (2 x 100 ml). The combined ethereal layer was washed with water, brine, dried over anhydrous sodium sulphate and evaporated to give (VI) as a pale yellow oil (5.18 g, 93%).

IR (liquid film) 3358.

PMR (80 MHz, $CDCl_3$): 0.48 (2H, m, cyclopropane protons at C-1 and C-3), 0.96 (6H, s, overlapping the triplet, one of the cyclopropane methyls and primary methyl of n-C_3H_7 gr. at C-3), 1.12 (3H, s, another cyclopropane methyl), 1.28 (8H, s, hydroxy isopropyl methyls and protons of one of the -CH_2 gr.), 1.3 - 1.55 (4H, m, other 2 x -CH_2 gr.), 2.6 (brs, OH proton).

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

observed: C, 78.09; H, 13.05%.

2,2-Dimethyl-3-n-propyl-cis-1-(2-methyl-prop-1-enyl cyclopropane (VII) and its double bond isomer (VIII)

Tertiary alcohol (VI, 6.5 g, 35.3 mmol) was dissolved in pyridene (20 ml), cooled in an ice-bath and phosphorous oxychloride (8.1 g, 52.9 mmole) was added slowly under stirring. The reaction was stirred in cold for two hours and then at room temperature (25°) for 24 hrs, poured on to crushed ice (100 g) and extracted with ether (100 ml x 2). The combined ethereal extract was washed with dil HCl, to remove excess of pyridene, followed by water, brine, dried over anhydrous sodium sulfate and evaporated to give brown oily liquid (5.65 g) crude product was purified by silica gel column chromatography (60 g, 1:10) and eluted with pet.ether (60-80° Fra.). The fractions eluted with pet.ether gave TLC (pet.ether + benzene, 1:1) pure unsaturated hydrocarbon (4.95 g, 85%) as a liquid which however, was found to be a mixture of two isomeric hydrocarbons (VII and VIII)by PMR spectrum.
IR (liquid film) 1650.
PMR (CCl_4, δ) 0.4 - 0.6 (2H, m, cyclopropane protons at C-1 and C-3 in VIII and C-3 in VII), 0.92 (6H, s, overlapping a triplet, one of the cyclopropane methyl of n-C_3H_7 gr. at C-3 in both isomes (VII and VIII), 1.08 (3H, s, another cyclopropane methyl of both VII and VIII), 1.41 - 1.48 (m -CH_2 protons at C-3 and C-1

in both VII and VIII and cyclopropane proton at C-1 in VII), 1.68, 1.74 (both s, vinyl methyls in both isomers), 4.72 (2H, brs, $-C=CH_2$ in VIII), 4.92 (1H, d, J=8 Hz, olefinic proton in VII).

Analysis calculated for $C_{12}H_{22}$: C, 86.66; H, 13.34

observed: C, 86.37; H, 13.25%.

1R-cis-2,2-Diemthyl-3-n-propyl-cyclopropanecarboxylic acid (IX) and its methyl ester (X)

To an ice-cooled solution of a mixture of unsaturated hydrocarbons (VII and VIII) (4.15 g, 25 mmol) in acetone (40 ml), powdered potassium permanganate (10 g, 65 mmol) was added in portion, with stirring, during one hour and the stirring continued for 1.5 hr at 0° and then at room temperature for 2 hrs. The reaction mixture was filtered, precipitate was repeatedly washed with acetone (25 ml x 3) and extracted with hot water (25 ml x 3). The combined aqueous extract was concentrated to one-third of total volume, cooled at 0° and acidified with HCl (2 pH), extracted with ether (50 ml x 3). The combined ethereal extract was washed with water (100 ml x 2), brine, dried over anhydrous sodium sulfate, evaporated to give an acid (IX), a dark yellow liquid, which was esterified with an ethereal solution of diazomethane to give crude ester (2.1 g). The ester was purified by chromatography over

silica gel (25 g, 1:1.2) and eluted with pet.ether and chloroform-pet.ether mixture Fraction eluted with chloroform-pet. ether mixture (1:3), gave TLC (benzene) pure liquid, identified as ester (X, 2.0 g, 40%), b.p.115-118°/15 mm, $[\alpha]_D^{28}$ - 61° (c, 1.2).

IR (liquid film): 1728.

PMR (90 MHz; $CDCl_3$): 0.91 (4H, t, J=6 Hz, primary methyl of n-C_3H_7 gr. and proton at C-3), 1.14, 1.22 (6H, 2s, 2 x -CH_3 at C-2), 1.27-1.52 (4H, m, -CH_2 of n-C_3H_7 gr. at C-3), 1.62 (1H, d, J=7 Hz, cyclopropane proton at C-1) and 3.61 (3H, s, -OCH_3).

Analysis calculated for, $C_{10}H_{18}O_2$, C, 70.54; H, 10.66

observed: C, 70.41; H, 10.52%.

The neutral oxidation products (XI) and (XIa)

The combined acetone filtrate was concentrated, the residue diluted with water (100 ml) and extracted with ether (50 ml x 2). The combined ethereal extract was washed with water, brine, dried over sodium sulfate and concentrated to give a mixture of two products (as seen on TLC, 5% ethyl acetate in benzene). The crude product (1.9 g) was purified by chromatography over silica gel (35 g, 1:15) and eluted with pet.ether, pet.ether + chloroform mixture. Fractions eluted with chloroform-pet.ether (1:4) gave TLC (5% ethylacetate in benzene) pure liquid, identified as 2,2-dimethyl-3-n-propyl-cis-1-(2-oxopropyl) cyclopropane

(XI, 0.74 g), $[\alpha]_D^{26}$ - 11° (c, 0.9) b.p.105-108°/2.5 mm.
IR (liquid film): 1721 (C=0).
PMR (CCl_4, δ): 0.5 - 0.7 (2H, m, cyclopropane protons at C-1 and C-3), 0.9 (6H, s, overlapping t, one of the cyclopropane methyls and primary methyl of n-C_3H_7 gr. at C-3), 1.1 (3H, s, another cyclopropane methyl protons), 1.12 - 1.5 (4H, m, -CH_2 protons of n-C_3H_7 at C-3), 2.1 (3H, s, -$COCH_3$) and 2.2 (2H, d, J = 6 Hz, -CH_2 at C-1).
Analysis calculated for $C_{11}H_{20}O$: C, 78.51; H, 11.98%
observed C, 78.42; H, 11.85%.

The later fraction eluted with pet.ether-chloroform (1:1) gave another TLC (5% ethyl acetate in benzene) pure liquid, further purified by distillation and identified as 2,2-dimethyl-3-n-propyl-cis-1-(2-methyl-2-hydroxy-1-oxopropyl)cyclopropane (XIa, 0.80 g), b.p.118-123°/5 mm, $[\alpha]_D^{28}$ - 88° (c, 1.2).
IR (liquid film): 3445 (-OH), 1676 (C=0).
PMR (90 MHz, $CDCl_3$): 0.91 (4H, t, J=6 Hz, primary methyl of n-propyl gr. at C-3 and cyclopropane proton at C-3), 1.16, 1.23 (6H, 3 each, s each, gemdimethyl of cyclopropane), 1.38, 1.42 (6H, 3 each, s each, hydroxy isopropyl methyl), 1.46-1.71 (4H, brm, 2 x -CH_2 of n-propyl gr. at C-3), 1.85 (1H, d, J=8 Hz, cyclopropane proton at C-1) and 3.44 (1H, brs, exchangeable with D_2O, -oH proton).

Analysis required for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18%
observed C, 72.58; H, 11.05%.

3-Phenoxybenzyl-(-)-1R-cis-2,2-dimethyl-3-n-propyl-cyclopropane carboxylate (XII)

A solution of ester (X, 0.8 g, 4.7 mmol) and 3-phenoxy benzyl alcohol (1.4 g, 7 mmol)in xylene containing butyl titanate (5 mg) was refluxed for 16 hours. Xylene was distilled off, residue dissolved in benzene (1 ml) and purified by chromatography over silica gel (25 g). The fractions eluted with chloroform + pet.ether (1:5) afforded a TLC (benzene) pure thick yellowish liquid identified as 3-phenoxy benzyl ester, (XII, 1.34 g, 88%), $[\alpha]_D^{27}$ -20°(c, 1.5).
IR (liquid film): 1726 (ester C=0), 1588, 690.
PMR (80 MHz, $CDCl_3$): 0.9 (4H, t, J=6 Hz,primary methyl of n-C_3H_7 gr. at C-3 and cyclopropane proton at C-3), 1.14, 1.2 (6H, 2s, 2 x -CH_3 at C-2), 1.28, 1.6 (5H, m, 2 x -CH_2 of n-propyl at C-3 and cyclopropane proton at C-1), 5.08 (2H, s, benzylic proton) and 6.92-7.44 (9H, m, aromatic protons).
Analysis calculated for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74%
observed C, 78.12; H, 7.68%.

2,2-Dimethyl-3-n-propyl-cis-cyclopropyl-1-methanol (XIII)

To an ice cooled and stirred solution of lithium aluminium hydride (0.54 g, 13.9 mmol), in ether (30 ml), anhydrous condition, was added dropwise, solution of ester (X, 0.6 g, 3.53 mmol), in dry ether (10 ml). The reaction mixture was stirred initially at 0° for one hour and then for 24 hour at room temperature (25°). The reaction mixture was decomposed by adding, dropwise, ethyl acetate followed by water, in cold condition. Ether layer was separated and aqueous suspension was extracted with ether (25 ml x 2). The combined ethereal layer was washed with water (100 ml x 2), brine, dried over anhydrous sodium sulfate, evaporated to get a pale yellow liquid (0.56 g), purified by chromatography over silica gel (10 g, 1:20).

The fraction eluted with benzene + chloroform (1:2)mixture furnished TLC (15% ethyl acetate in benzene) pure primary alcohol (XII, 0.45 g, 85%), $[\alpha]_D^{26}$ - 10° (c, 1.2).

IR (liquid film): 3410 (-OH).

PMR (80 MHz, $CDCl_3$): 0.6 - 0.95 (5H, m, $-CH_3$ of n-propyl and cyclopropane protons at C-1 and C-3), 1.05, 1.1 (6H, 2s, 3-each, 2 x $-CH_3$ at C-2), 1.3 (4H, m, 2 x $-CH_2$ at n-C_3H_7 gr. at C-3) and 3.6

(2H, d, J=8 Hz, $-CH_2OH$ at C-1).

Analysis calculated for $C_9H_{18}O$: C, 76.05; H, 12.68%

observed C, 75.85; H, 12.42%.

Methyl ester of 1R-cis-2,2-dimethyl-3-n-propyl-1-(2-hydroxy benzyl) cyclopropane acetic acid XIV

To the ice cold and stirred solution of sodium methoxide (1.62 g, 60 mmol), in dry methanol, under N_2 atmosphere, was added, dropwise, methyl ester (V) (5.5 g, 30 mmol). The reaction mixture was kept stirring in cold condition for one hour. Freshly distilled benzaldehyde (3.18 g, 30 mmol) was dropwise added. The reaction mixture was kept stirring for 3 hours, diluted with water, acidified with dil. HCl, extracted with ether (50 ml x 2). The ether extract was washed with water, 10% aqueous solution of sodium carbonate, again with water and brine, dried evaporated. The unreacted benzaldehyde was distilled off under vacuum. The brown oily residue was purified by silica gel column chromatography and eluted with chloroform + pet.ether (1:3) mixture to get TLC (10% ethyl acetate in pet.ether) pure thick β-hydroxy ester (XIV, 4.5 g, 55%) which was a mixture of threo and erithro isomers as seen by PMR spectral analysis. IR (liquid film): 3620 (-OH), 1590.

PMR (CCl_4, δ): 0.65 (2H, m, cyclopropane protons at C-1 and C-3), 0.95, 1.0 (6H, 2s, 3 each, 2 x $-CH_3$ at C-2), 1.1 - 1.3 (7H, m, n-propyl at C-3), 2.3 (1H, d, J=8 Hz, proton to ester methyl of one isomer), 2.45 (1H, d, J=8 Hz, proton (α-to ester methyl of other isomer), 2.8 (1H, brs, exchangeable with D_2O, -OH proton), 3.65 (3H, s, $-O-CH_3$ of one isomer), 3.7 (3H, s, $-OCH_3$ of other isomer), 4.65 (1H, d, J=6 Hz, benzylic proton of one isomer), 4.9 (1H, d, J=6 Hz, benzylic proton of other isomer), 7.2 (5H, s, aromatic).

Analysis calculated for $C_{18}H_{25}O_2$: C, 79.12; H, 9.15;
observed: C, 79.08; H, 8.92%.

Benzylidene derivative of methyl 1R-cis-2,2-dimethyl-3-n propyl-1-cyclopropane acetate(IXIV)

β-Hydroxy ester, (XIV), (4.35 g, 15 mmol) was dissolved in pyridene (25 ml), cooled in an ice-bath and phosphorous oxychloride (3.04 g, 20 mmol) was added under stirring. The reaction was stirred in cold for 2 hours and then at room temperature for 24 hours, poured on to crushed ice (50 g) and extracted with ether (50 ml x 2). The combined ethereal extract was washed with dil. HCl, to remove excess of pyridene, followed by water, brine, dried

over anhydrous sodium sulfate and evaporated to give crude yellow oily liquid which was purified over silica gel chromatography and eluted with pet.ether to give

TLC pure (pet.ether + benzene 1:1) E & Z isomeric mixture of α,β-unsaturated ester (XVI, 3.66 g, 80%). IR (liquid film): 1610 (C=C), 1600 (aromatic). NMR (CCl_4, δ): 0.9 (1H, s, cyclopropane proton at C-1),1.1 - 1.7 (14 H, m, gemdimethyl, primary methyl and $-CH_2$ proton of n-C_3H_7 gr. at C-3 and cylopropane proton at C-3), 3.7 (3H, s, $-OCH_3$ of one isomer), 3.76 (3H, s, $-OCH_3$ of other isomer), 4.65 (1H, s, benzylic proton of one isomer), 4.8 (1H, s, benzylic proton of other isomer) and 7.25 (5H, s, aromatic protons).

Analysis calculated for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88
observed: C, 78.87; H, 8.52%.

1R-cis-2,2-dimethyl-3-n-propyl-cyclopropane carboxylic acid (IX) and its methyl ester (X)

A stream of ozonised oxygen was bubbled through an ice-cooled solution of the isomeric mixture of α,β-unsaturated ester (XVI) (2.74 g, 10 mmole) in ethyl acetate (150 ml), till the absorption of ozone was completed (indicated by starch iodide paper). Jones chromic acid reagent was then added to the cooled and stirred solution of the ozonide till

brown colour persisted; stirring was continued at 0° for one hour and then at room temeprature for two hours. It was then diluted with water (50 ml), ethyl acetate layer separated, washed with water (100 ml x 2), extracted with 10% aqueous sodium carbonate. The carbonate layer was acidified by dilute sulphuric acid (1:10), followed by extraction with ether (100 ml x 2). The ether layer was washed with water, dried over sodium sulphate and evaporated to furnish the mixture of acid (IX) and benzoic acid. This was converted to the methyl esters by an ethereal solution of diazomethane and separated by chromatography over silic gel. Fractions eluted with pet.ether chloroform (1:1) afforded TLC (5% ethyl acetate in benzne) pure required ester (X, 1.1 g, 65%), b.p.115-118°/15 mm. Spectral data and analysis has been explained earlier.

Methyl ester of 1R-cis-2,2-dimethyl-3-npropyl-1-(2-oxophenyl) cyclopropane acetic acid (XVIII)

To the vigerously stirred solution of β-hydroxy ester (XIV, 4.33 g, 15 mmol) in acetone (50 ml) was added Jones chromic acid reagent, dropwise, maintaining the temeprature between 0° to 5° during 10 min,, till the colour persisted, diluedwithwater (50 ml) and extracted with ether (50 ml x 2). The ether layer was washed with water (100 ml x 2) 20% aqueous

sodium bicarbonate solution, brine and dried over sodium sulfate, evaporated to get yellow oily liquid, β-keto ester (XVIII, 2.49 g, 92%).

IR (liquid film): 1739 (ester C=0), 1685 (benzoyl C=0), 1595 (aromatic).

PMR (CCl_4 δ): 0.73 (2H, m, cyclopropane protons at C-1 and C-3), 1.05, 1.1 (6H, 2s, 3-each, 2 x $-CH_3$ at C-2), 1.25 - 1.6 (7H, m, n-C_3H_7 at C-3), 4.0 (1H, d, J=12 Hz, proton adjacent to two C=0 gr.), 7.1 (3H, m, aromatic protons), 7.8 (2H, m, aromatic ortho protons).

Analysis calculated for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39%.
observed C, 74.68; H, 8.26%.

2,2-Dimethyl-cis-3-n-propyl-1-(2-oxo-2-phenylethyl) cyclopropane (XIX)

To a solution of sodium hydroxide (0.2 g, 5 mmol) in water (1 ml) and ethanol (2 ml) -keto ester (XVIII, 1.15 g, 4 mmol) was added and the mixture was heated at 80-90° for 2 hours and then kept stirring at room temperature overnight, added cold water (10 ml) extracted with ether (20 ml). Ether layer washed with water (25 ml x 2), dried over anhydrous sodium sulfate, evaporated to get crude yellow oil which is purified by silica gel chromatography and eluted with mixture of pet.ether + benzene (1:1) to get TLC (10% ethyl acetate in pet.ether) pure pale yellow oily liquid

of ketone (XIX, 0.69 g, 75%).

IR (liquid film): 1680 (benzoyl C=0), 1595 (aromatic).

PMR (CCl_4, δ): 0.7 (2H, m, cyclopropyl protons at C-1 and C-3), 0.95, 1.1 (6H, 2s, 3-each, 2 x $-CH_3$ at C-2), 1.25 (7H, m, n-propyl at C-3), 2.75 (2H, d, J=12 Hz, $-CH_2$ at C-1), 7.15 (3H, m, aromatic) and 7.6 (2H, m, aromatic ortho protons).

Analysis calculated for $C_{16}H_{22}O$: C, 83.43; H, 9.65%

observed C, 82.98; H, 9.39%.

2,2-Dimethyl-3-n-propyl-1-cyclopropyl methanol (XIII)

To an ice-cooled and stirred solution of benzoyl ketone (XIX, 0.92 g, 0.004 mol) in chloroform (10 ml), a solution of m-chloroperbenzoic acid (0.82 g,0.005 mol) in chloroform (5 ml) maintaining the temperature below 5°C. Stirring was continued at 0-5° for one hour and then at room temperature for 48 hours. The chloroform solution was washed with saturated aqueous solution of sodium carbonate (25 ml x 2), water (25 ml x 2) and dried over anhydrous sodium sulfate. Removal of chloroform by distillation afforded pale yellow oily perbenzoate which was dissolved in methanol (10 ml) and aqueous solution of potassium hydroxide (0.5 g,0.0082 mole) in water (2 ml). This mixture was stirred for 24 hr at room temeprature, diluted by water (20 ml) extracted by

ether (25 ml x 3). The ether extract was washed with water and then with saturated brine solution, dried over anhydrous sodium sulfate and solvent was distilled off to afford liquid primary alcohol (XIII, 0.442 g, 80%)whose spectral analysis is explained earlier.

2,2-Dimethyl-3-n-propyl-cis-cyclopropane-1-ethanol

To an ice-cooled and stirred suspension of LAH (1.08 g, 30 mmol) in dry ether (100 ml), a solution of methyl ester (V, 3.68 g,20 mmol) in dry ether (50 ml) was added dropwise during one hour. Stirring was continued at 0° for three hours, and further refluxed for three hours. The reaction mixture was cooled, excess LAH decomposed by addition of ethyl acetate, followed by water. The ether layer separated and the aqueous layer was extracted with ether (50 ml x 2). The combinedethereal extract was washed with water (100 ml x 2), saturated brine, dried over anhydrous sodium sulfate, to get liquid primary alcohol (2.71 g, 87%).

The spectral data of which has been described on page in Chapter II.

3,3-Dimethyl-2-(2'-oxopropyl)-1-acetaldehyde-cyclopropane (XX)

Carane diol (II) (30.0 g, 0.176 mol) was dissolved in acetone (500 ml) and water (150 ml).

Powdered sodium metaperiodate (60.0 g, 0.28 mol) was added portionwise,with stirring at room temp. in about one hour. The mixture was stirred at room temeprature for two hours. The sodium iodate separated out was removed by filteration and the filterate was concentrated to 200 ml at room temeprature. Cold water was added to the residue and extracted with ether (3 x 150 ml). The ether extract was washed with water and dried over anhydrous sodium sulphate. The solvent was removed at room temperature to get colourless oil (26.0 g, 87.7%), b.p.86-87°/9.5 mm.

IR (liquid film): 2740 (CHO), 1724 (C=O).

PMR (CCl_4, δ): 0.83 (2H, m, cyclopropane protons at C-1 and C-3), 1.0, 1.13 (6H, 2s, 3-each, 2 x $-CH_3$ at C-2), 2.1 (3H, s, $-COCH_3$) and 2.43 (4H, m, 2 x $-COCH_2$).

Analysis: calculated for $C_{16}H_{16}O_2$: C, 71.39; H, 9.59
observed C, 70.87; H, 9.48%.

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

The ketoaldehyde (XX, 26 g), dissolved in methanol (200 ml) was cooled to 0°C and dil. HCl (1.2 N, 5 ml) added to it and the mixture kept at 0°C for 24 hours. The solution was concentrated almost

at room temperature under reduced pressure, diluted with water (250 ml) and extracted with chloroform (3 x 150 ml). Organic layer was washed with aqueous Na_2CO_3 solution (15%), then again with water and brine and finally dried over anhydrous sodium sulphate. Removal of chloroform furnished the pale yellow liquid of keto-dimethyl acetal (XXI, 27.5 gms, 82%).

IR (liquid film): 1724 (C=0).

PMR (CCl_4, δ): 0.66 (2H, m, cyclopropane protons at C-1 and C-3), 0.9, 1.08 (6H, 2s, 2 x $-CH_3$ at C-2), 1.45 (2H, d, J=6 Hz, $-CH_2$ at C-1), 2.06 (3H, s, $-COCH_3$), 2.23 (2H, d, J=6 Hz, $-COCH_2$), 3.23 (6H, s, 2 x $-OCH_3$ of acetal) and 4.15 (1H, t, J=6 Hz, -CH of acetal).

Analysis calculated for $C_{12}H_{22}O_3$: C, 64.3; H, 10.4

observed C, 64.2; H, 10.2%.

2,2-Dimethyl-3-(n-propyl) cis-cyclopropane-1-acetaldehyde dimethyl acetal (XXII)

Keto acetal (XXI, 8.56 g, 0.004 mol) was added to a solution of potassium hydroxide (10 g, 0.18 mol)in diethylene glycol (60 ml). Added hydrazine hydrate (15 ml, 80% aqueous solution) and the reaction mixture was heated to reflux at 125-30° for 4 hr. Excess hydrazine hydrate was removed by distillation and the residue was heated strongly upto 185-190° for 5 hours, cooled, diluted with water (100 ml), extracted with

ether (75 ml x 2). Ether extract was washed with water (100 ml x 3) and finally with brine water, dried over anhydrous sodium sulfate and distilled out solvent to get brown yellow oily liquid reduced acetal (XXII, 6.46 g, 82%).

IR (liquid film): 1080, 1070 ($-OCH_3$ stretch).

PMR (CCl_4, δ): 0.32 (2H, m, cyclopropane protons at C-1 and C-3), 0.95, 1.05 (6H, 2s, 2 x $-CH_3$ at C-2), 1.4 (7H, m, n-propyl gr. at C-3), 3.3 (6H, s, 2 x $-OCH_3$), 4.3 (1H, t, J=6 Hz, -CH of acetal).

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

observed C, 77.87; H, 13.02%.

2,2-Dimethyl-3-n-propyl-cis-cyclopropane-1-acetaldehyde (XXIII)

Method (A)

The reduced acetal (XXII, 3.0 g, 15 mmol) was dissolved in 2% sulphuric acid (10 ml) and heated on a water bath for 1 hr at 80-90°. The solution was cooled, diluted with water (25 ml), extracted with ether (150 ml x 2). The ether layer was washed with aqueous 10% Na_2CO_3 solution, followed by water and dried over anhydrous sodium sulfate. Removal of ether, afforded the aldehyde as pale yellow liquid (XXIII, 1.84 g, 80%).

IR (liquid film): 2778 (CHO), 1739 (C=O).

PMR (CCl_4, δ):0.7 (2H, m, cyclopropane proton at C-1 and C-3), 0.95, 1.1 (6H, 2s, 2 x $-CH_3$ at C-2), 1.15-1.4 (7H, m, n-propyl gr. protons at C-3), 2.26 (2H, m, $-COCH_2$ adjacent to aldehyde function), 9.7 (1H, t, J=4 Hz aldehyde proton).

Analysis calculated for $C_{10}H_{18}O$: C, 77.86; H, 11.76%.

observed C, 77.19; H, 11.24%,

Method (B)

To the suspension of freshly pepared pyridinium chloro chromate (3.23 gm, 15 mmol) in dichloromethane (25 ml) was added primary alcohol (1.56 g, 10 mmol). The reaction mixture was stirred vigorously at room temeprature which was rapidly blackened within an hour. After two hours the supernatant liquid is decanted and filtered over cellucel bed in a buckner funnel. The remaining complex of the reaction mixture was washed by dry ether (50 ml x 2) and filtered. The combined filterate was concentrated at room temerature. The crude product was purified by column chromatography and eluted over neutral alumina (25 g). Fractions eluted with pet.ether gave TLC (benzene) pure aldehyde (XXIII, 1.13 g, 74%).

2,2-Dimethyl-3-n-propyl-cis-1-(2-vinyl acetate cyclopropane (XXIV)

A solution of aldehyde (XXIII) (2.31 g, 15 mmol) in isopropenyl acetate (50 ml) and PTSA (150 mg) was

heated to reflux for 24 hours, cooled, washed by water (100 ml x 3) to remove PTSA, dried over anhydrous sodium sulfate, evaporated to get crude isomeric mixture. It was purified by column chromatography, eluted over silica gel (55 g). Fractions eluted with pet.ether + benzene (1:1) afforded TLC (5% chloroform in pet.ether) pure isomeric mixture of enol acetate as a yellow oily liquid (XXIV, 2.1 g, 70%).

IR (liquid film): 1786 (acetate C=0), 1667 (C=C).

PMR (CCl_4, δ): 0.6 (1H, m, cyclopropane proton at C-3), 0.95-1.2 (9H, 4s, gemdimethyl protons overlapping t of primary methyl of both the isomers), 1.33 (4H, brs, 2 x $-CH_2$ at C-3), 1.55 (1H, m, cyclopropane proton at C-1), 2.1 (3H, s, $-COCH_3$ of one isomer), 2.2 (3H, s, $-COCH_3$ of other isomer), 4.13 (1H, t, J= Hz, proton adjacent to C-1), 4.5 (1H, d, J= Hz, olefinic proton of one isomer) and 4.7 (1H, d, J= Hz, olefinic proton of other isomer).

Analaysis calculated for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68
observed C, 74.08; H, 9.19%.

2,2-Dimethyl-3-n-propyl-cis-cyclopropane 1-carboxylic acid

Ozonolysis of the isomeric mixture of enol acetate (2.94 g, 15 mmol) was carried out by the procedure already mentioned earlier to get the acid

(IX, 1.3 g, 58%) which was characterised and identified by its methyl ester (X), whose spectral data has been explained earlier.

Self aldol condensation of (XXIII) and oxidation of aldol by potassium permanganate

A solution of aldehyde (XIII, 10 g) in tertiary butanol (35 ml) was added to an ice-cooled solution of potassium t-butoxide [prepared from potassium metal (1 g) in t-butanol (20 ml)] and the solution thus obtained was stirred at room temperature for 5 hr. Excess t-butanol was removed under reduced pressure, the residue poured into crushed ice with stirring, extracted with chloroform (100 ml x 2), the chloroform layer washed with water (150 ml x 2) and dried over anhydrous sodium sulfate. Removal of chloroform furnished a mixture of aldol (XXV) and its dehydrated product (8.78 g, 88%) identified by spectral data. IR (liquid films) bands at 3407, (OH), 2770, 1721 (CHO), 1681 (conjugated aldehyde), 1630 (conjugated HC=C<)

To an ice-cooled stirred solution of mixture of aldol and its dehdyrated product (10 g, XXV and XXVI), powdered potassium permanganate (15 g) was added in small lots during one hour. Stirring was continued at 0° for 3 hr and at room temperature for 1 hr. The reaction mixture was filtered and the precipitate

obtained was washed with acetone and extracted with hot water (75 ml x 3). The combined aqueous extract was concentrated to 50 ml, cooled, acidified with HCl, extracted with chloroform (50 ml x 3) chloroform layer was washed with water, dried, evaporated to give a mixture of acids (6 g), which was esterified with an ethereal diazomethane to give a mixture of methyl esters (5 g). It was chromatographed over silica gel (100 g) and the Fractions eluted with benzene + chloroform (1:1) gave a TLC pure ester (2.1 g) resembled in its PMR spectrum with that of ester (X).

2.2-Dimethyl-3-n-propyl-cis-1(2,chlorovinyl) cyclopropane (XXVII)

To the ice-cooled and stirred aldehyde (2.0 g, 13 mmol) was added all at once phosphorous pentachloride (3.09 g, 15 mmol). The reaction was gradually brought to room temeprature and left overnight. The reaction mixture was then poured over crushed ice (50 g), extracted with ether. Ether layer was washed with water, brine, dried over anhydrous sodium sulfate and evaporated to give an oil (1.65 g). The oil was purified by column chromatography using silica gel. The product was eluted with benzene + pet. ether

(1:1) to get an oily liquid (XXVII, 1.4 g, 65%) as a isomeric mixture.

M/e: 172, 137 (M^+ -Cl).

IR (liquid film): 860 (HC-Cl stretch).

PMR (CCl_4, δ): 0.95 (2H, m, cyclopropane protons at C-1 and C-3), 1.1, 1.25 (6H, 2s, 2 x $-CH_3$ at C-2), 1.3 (7H, m, n-propyl gr. protons at C-3), 4.9 (1H, d, J=4 Hz, HC-Cl proton of one isomer), 5.0 (1H, d, J=4 Hz, HC-Cl proton of other isomer), 5.35 (2H, m, vinyl protons of both the isomers).

Analysis calculated for $C_{10}H_{17}Cl$,

C, 68.76; H, 9.77; Cl, 20.4%

observed C, 68.08; H, 9.58; Cl, 19.97

Ozonolysis of the purified isomeric mixture of vinyl chloride (XXVII, 1.37 g, 8 mmol), as such was carried out by the procedure mentioned earlier to get acid (IX, 0.74 g, 60%) whose spectral data explained earlier.

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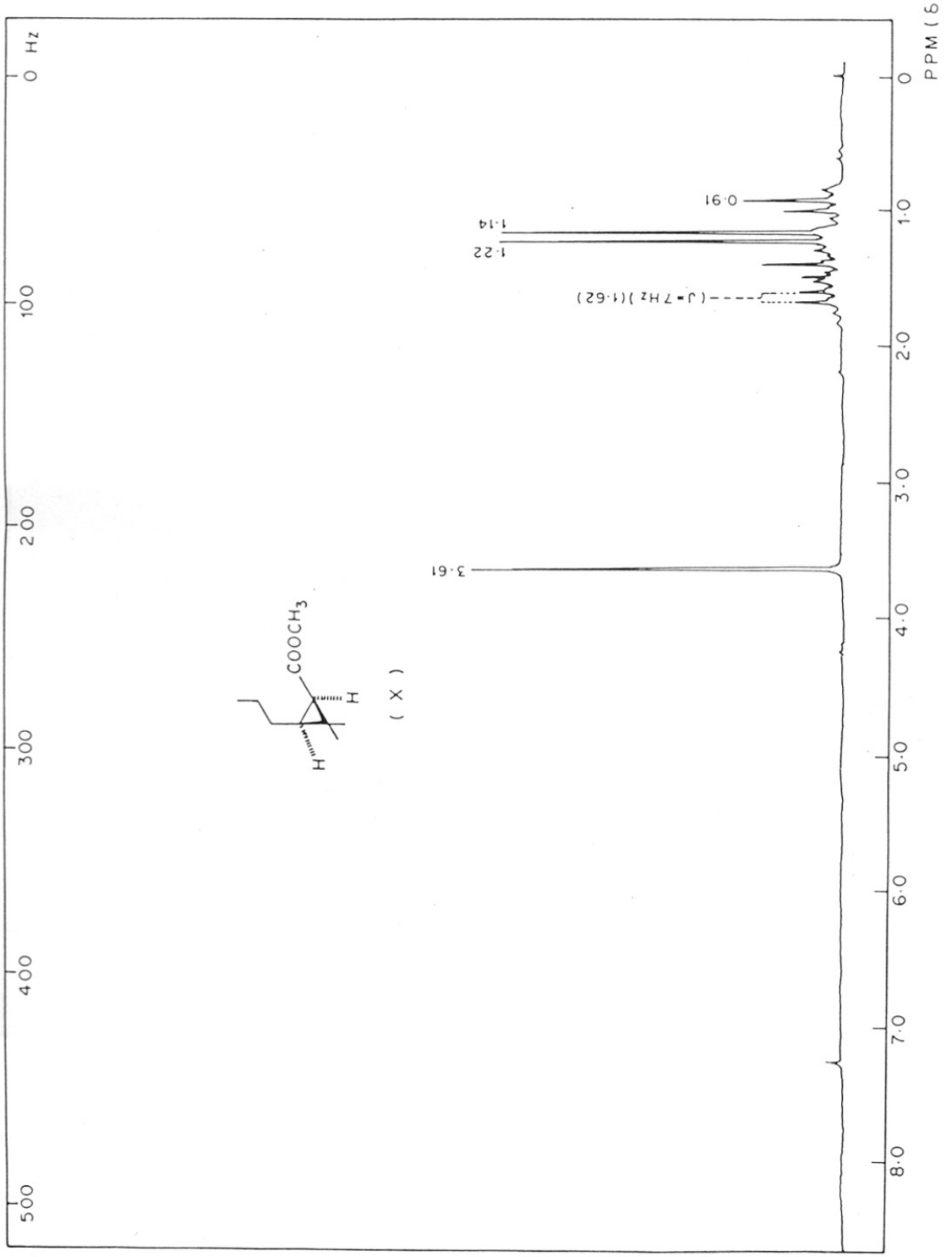
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200
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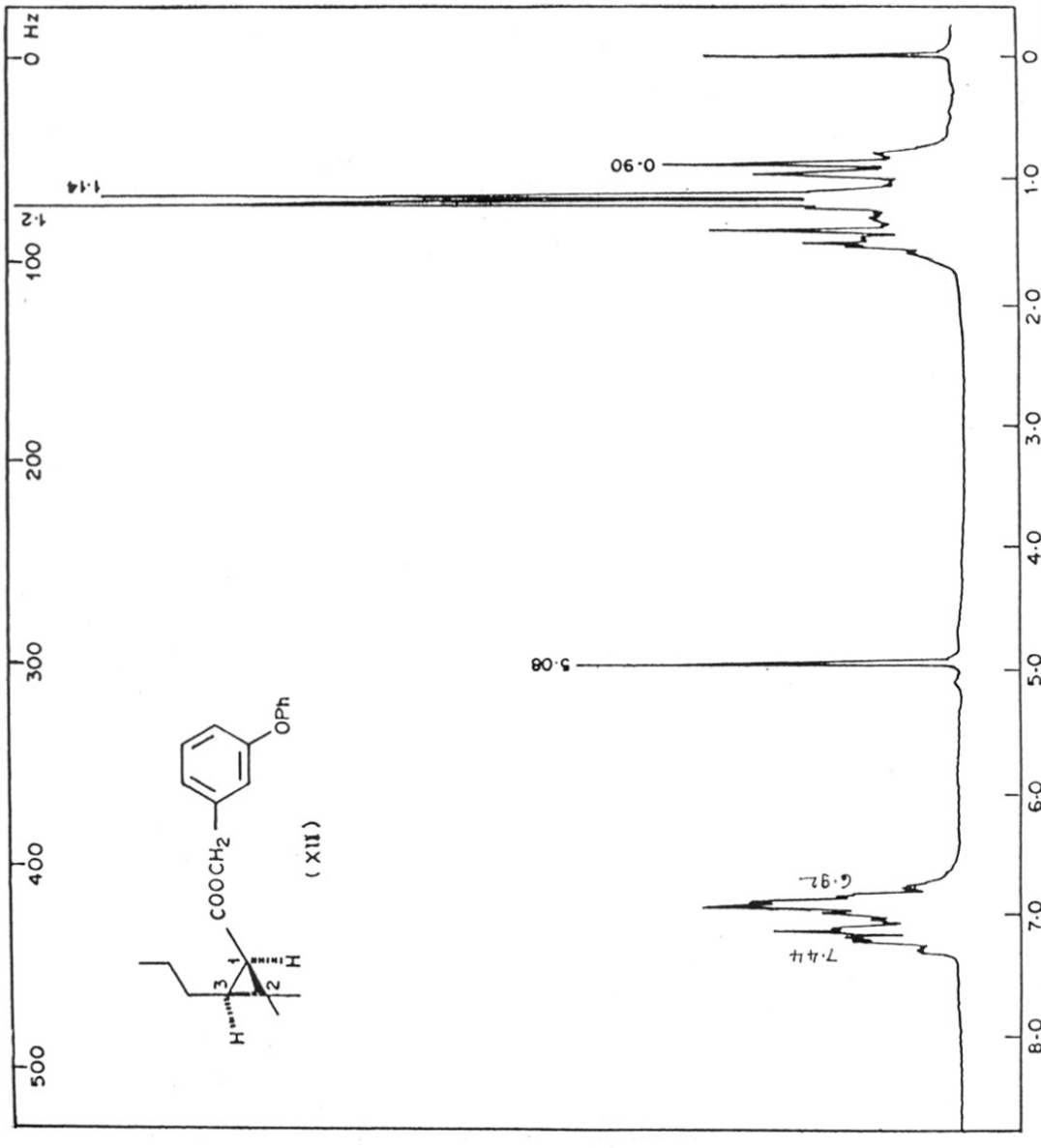
0
1·0
2·0
3·0
4·0
5·0
6·0
7·0
8·0
PPM (δ)
0·91
1·14
1·22
(J=7Hz)(1·62)
3·61
COOCH3
H
H
(X)

FIG. X


0 Hz
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200
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500
1·2
1·14
0·90
3·08
6·92
7·44
0
1·0
2·0
3·0
4·0
5·0
6·0
7·0
8·0
PPM (δ)
OPh
COOCH2
H
H
1
2
3
(XII)

FIG. XII

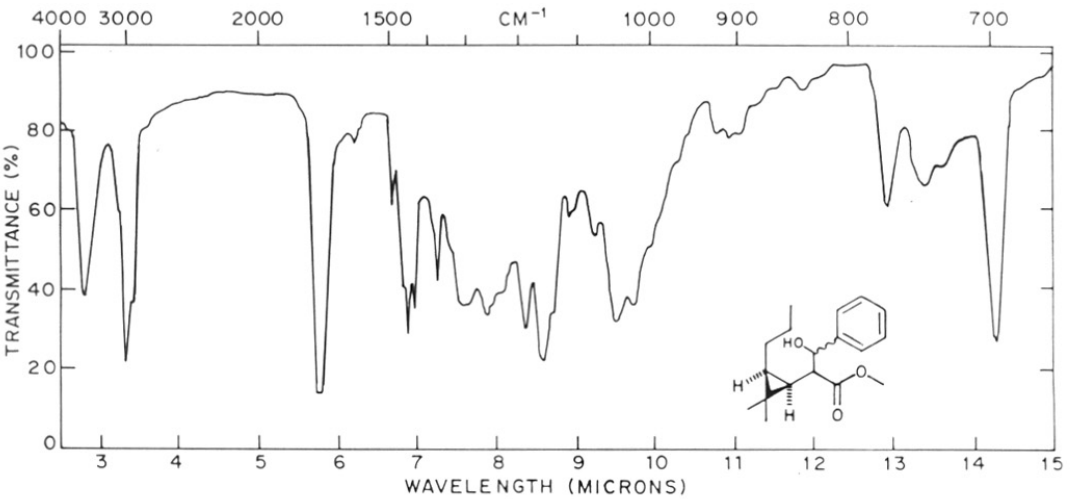
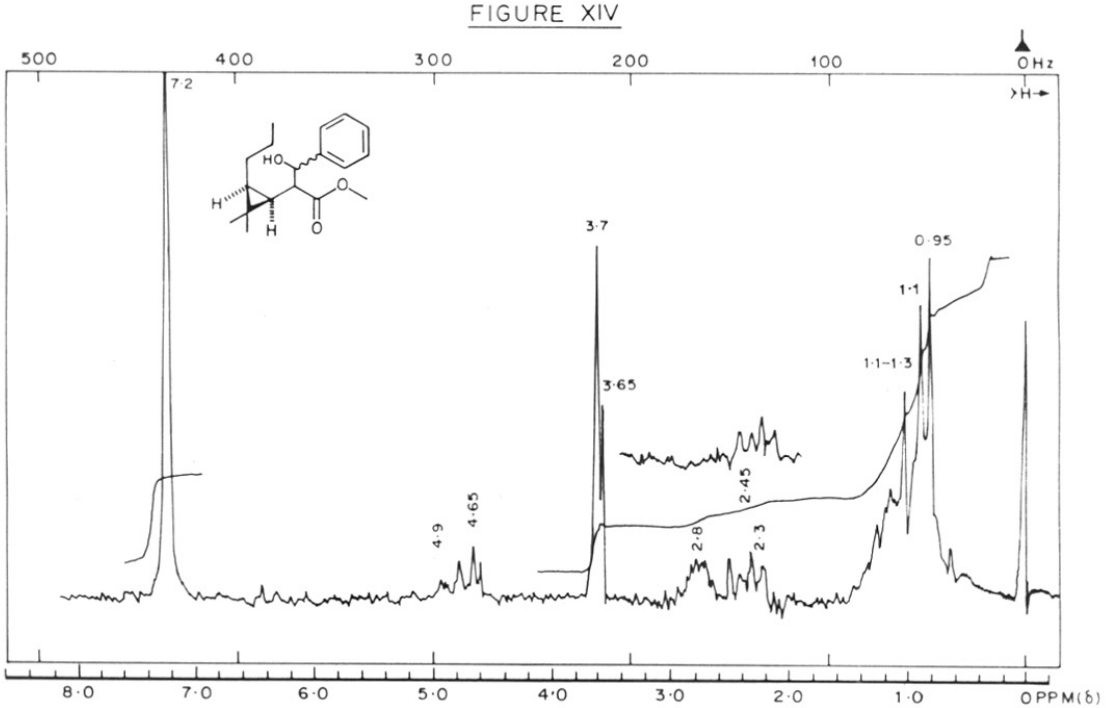


FIGURE XIV



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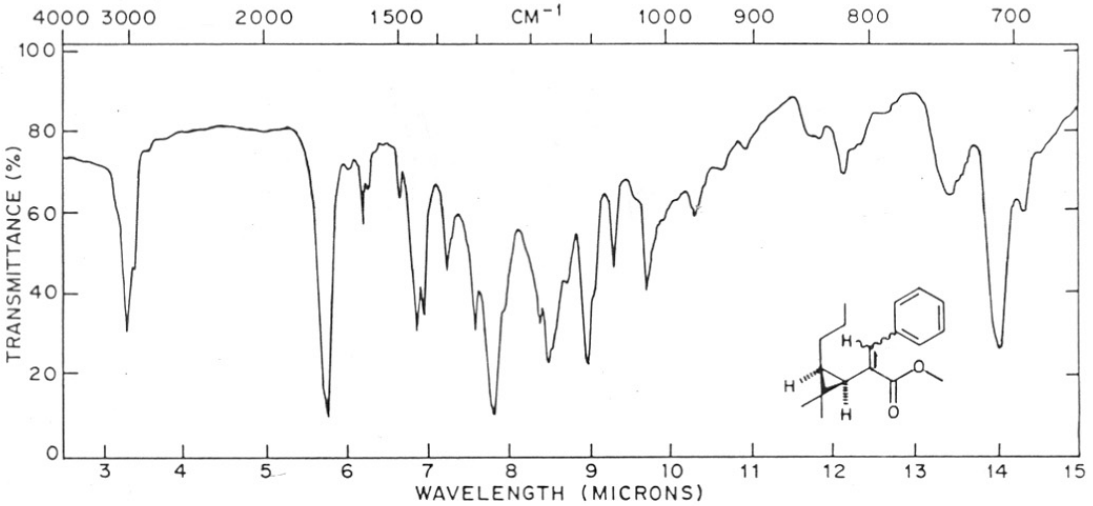


FIGURE XVI

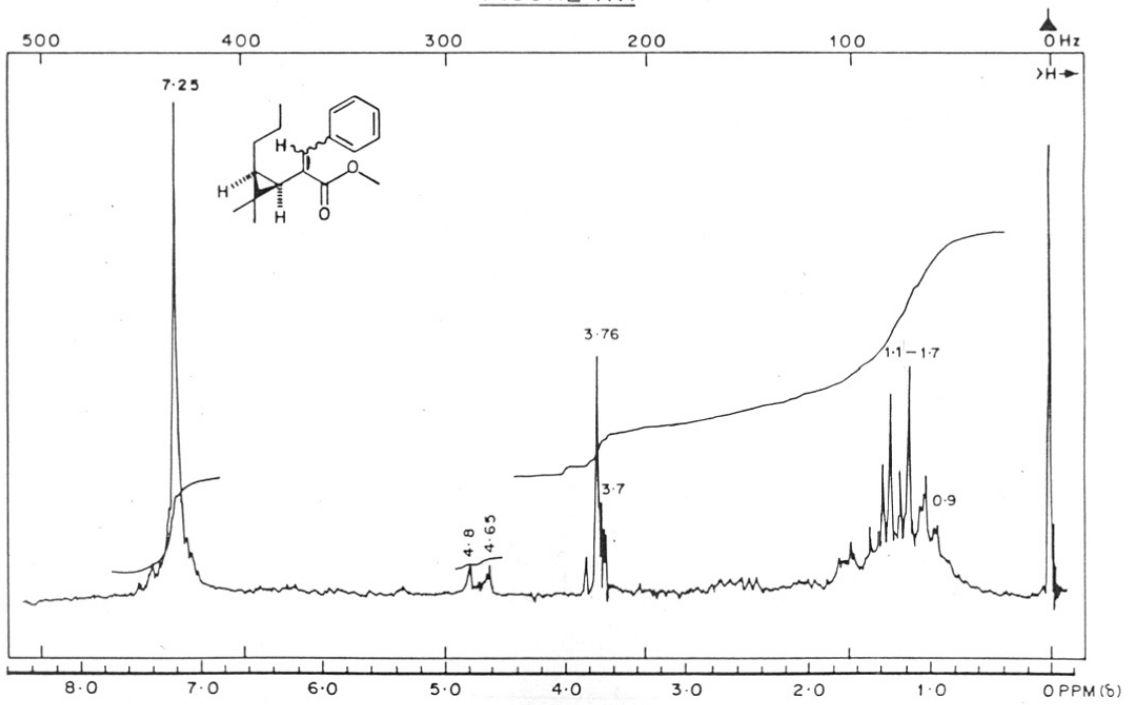


FIGURE XVI

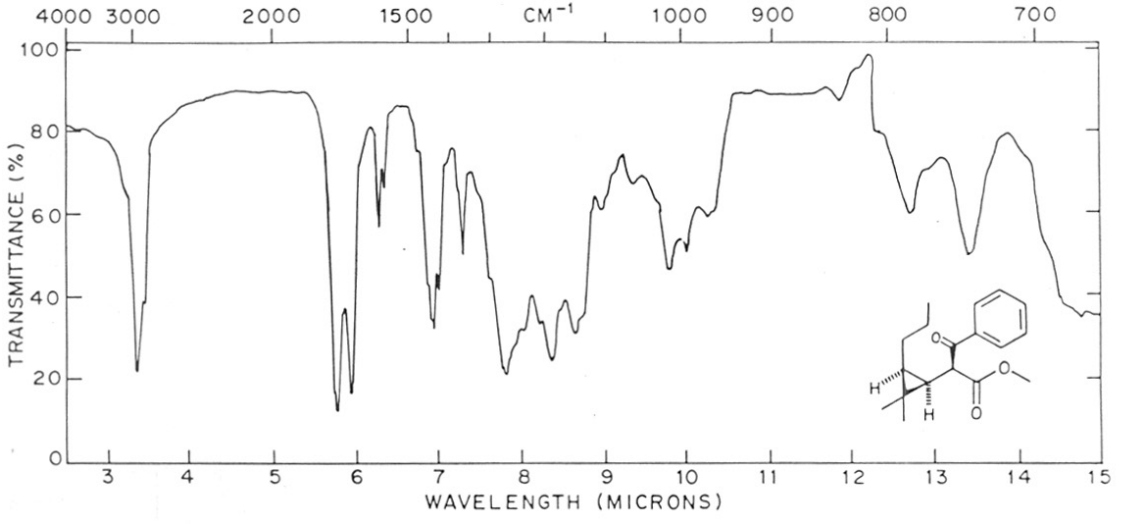


FIGURE XVIII

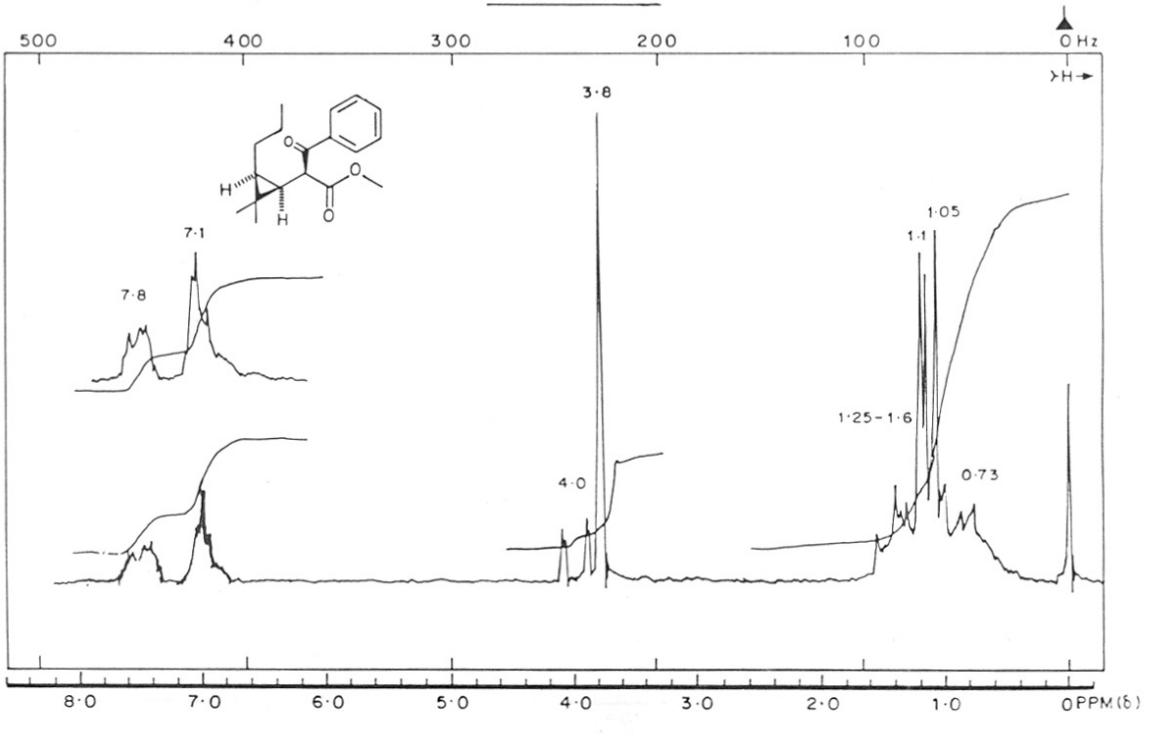


FIGURE XVIII

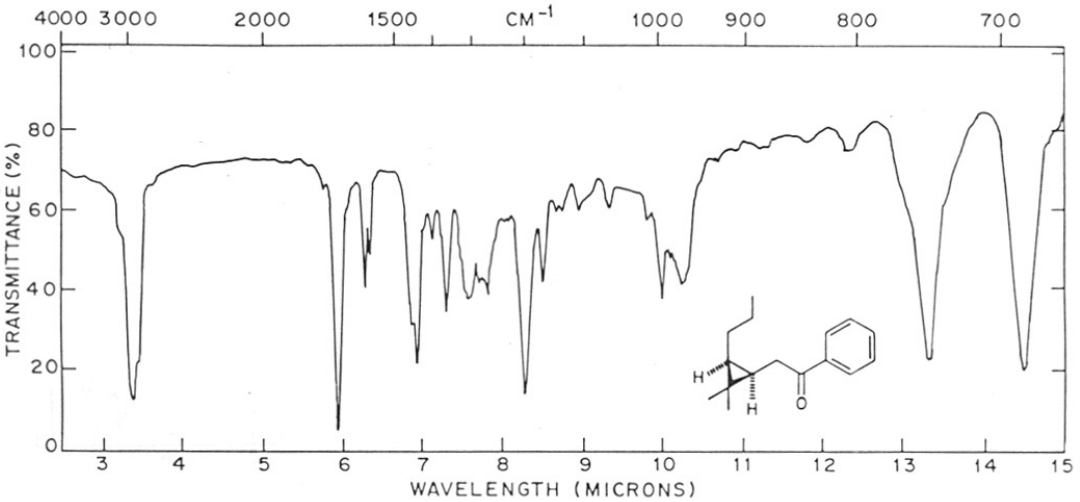


FIGURE XIX

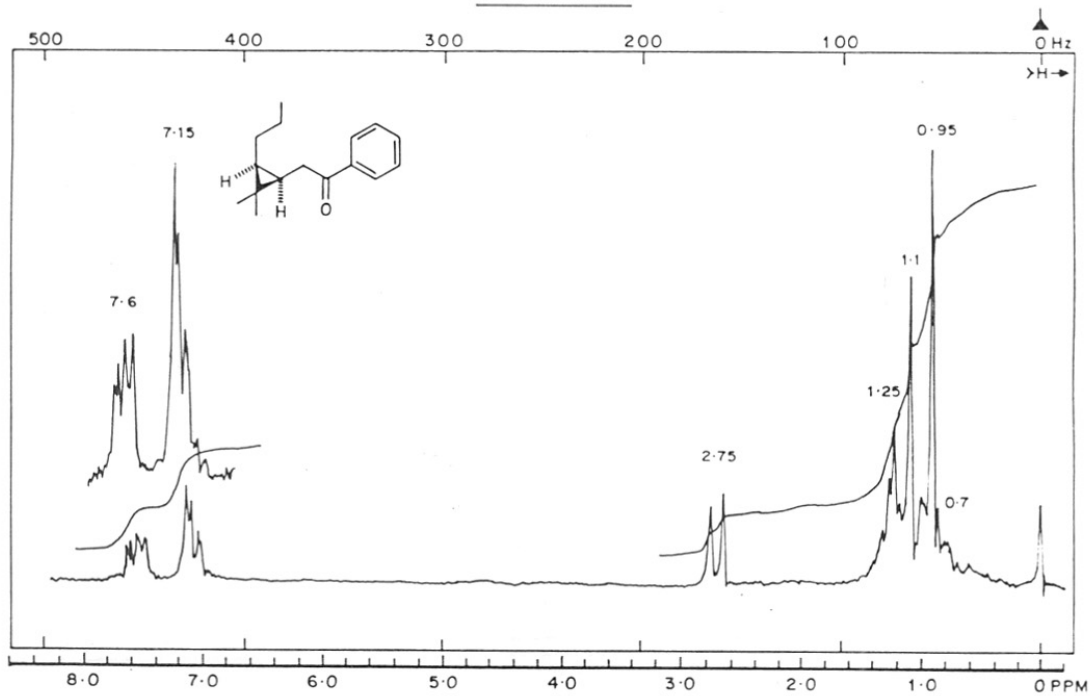


FIGURE XIX

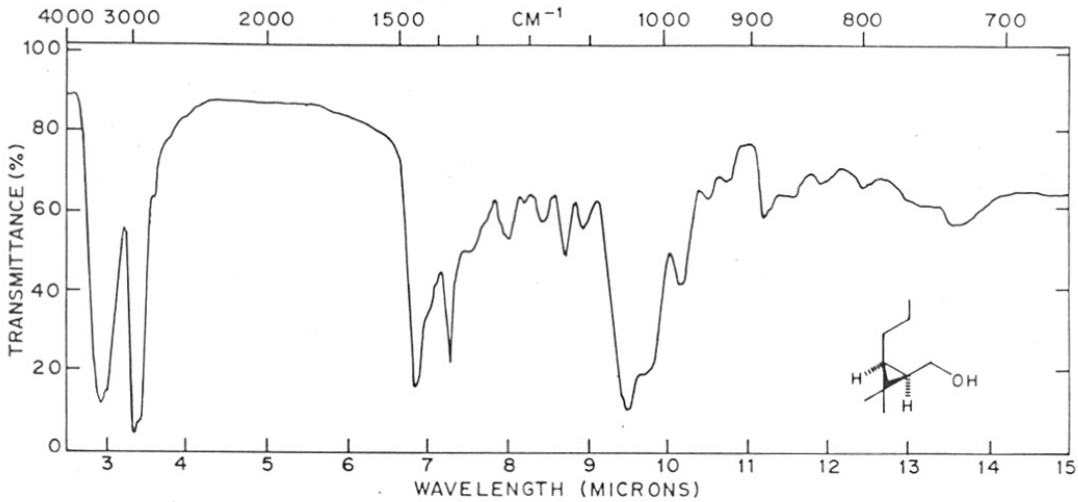


FIGURE XV

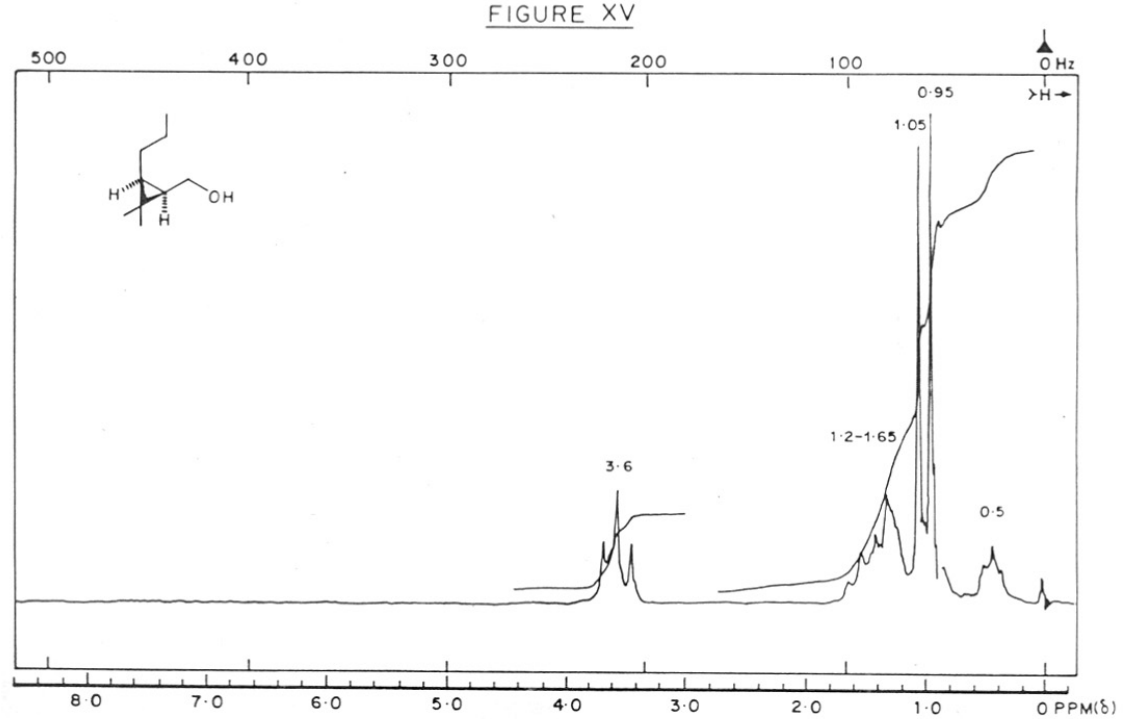
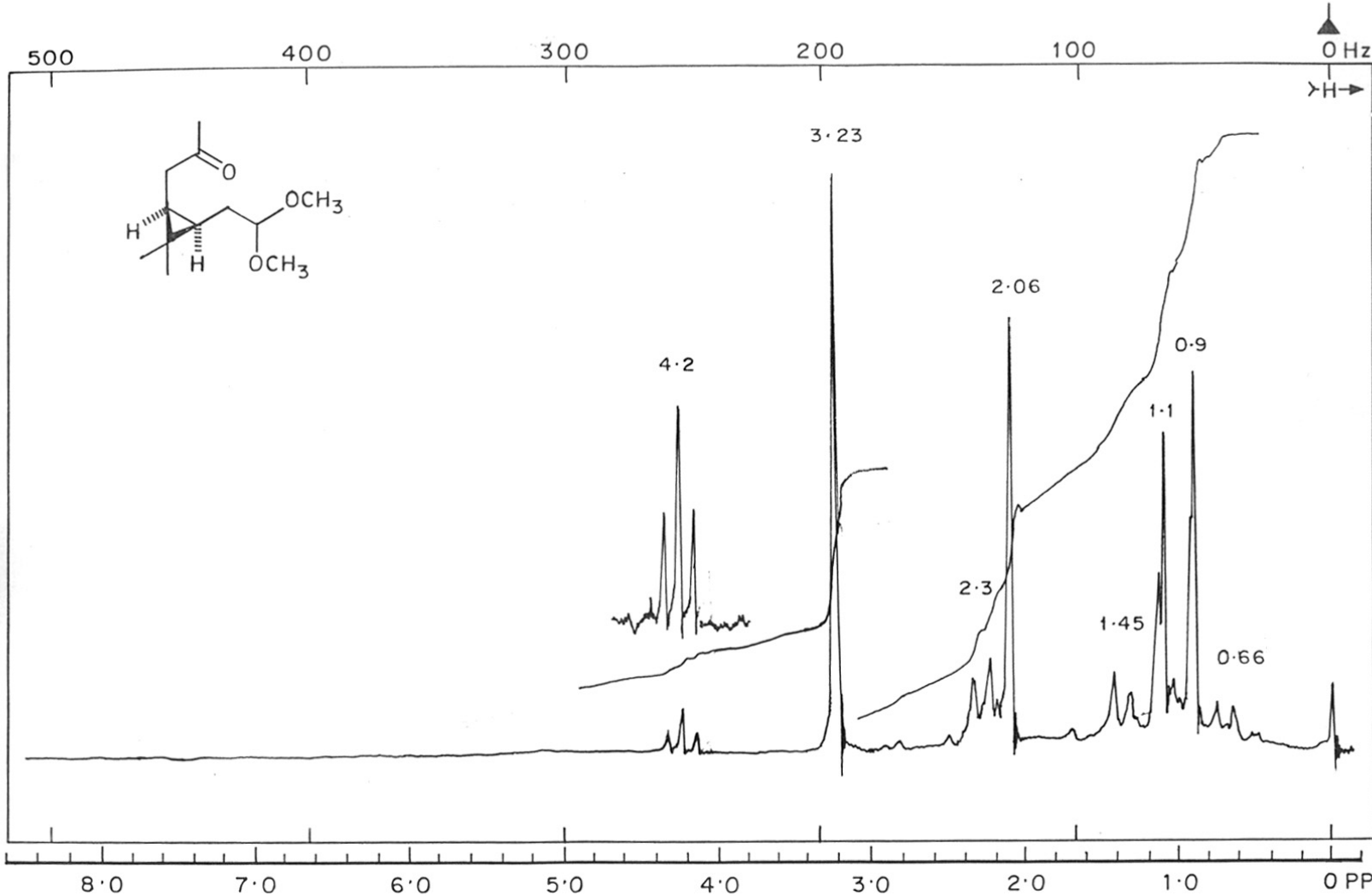


FIGURE XV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O
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2·3
1·45
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7·0
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5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE XXI

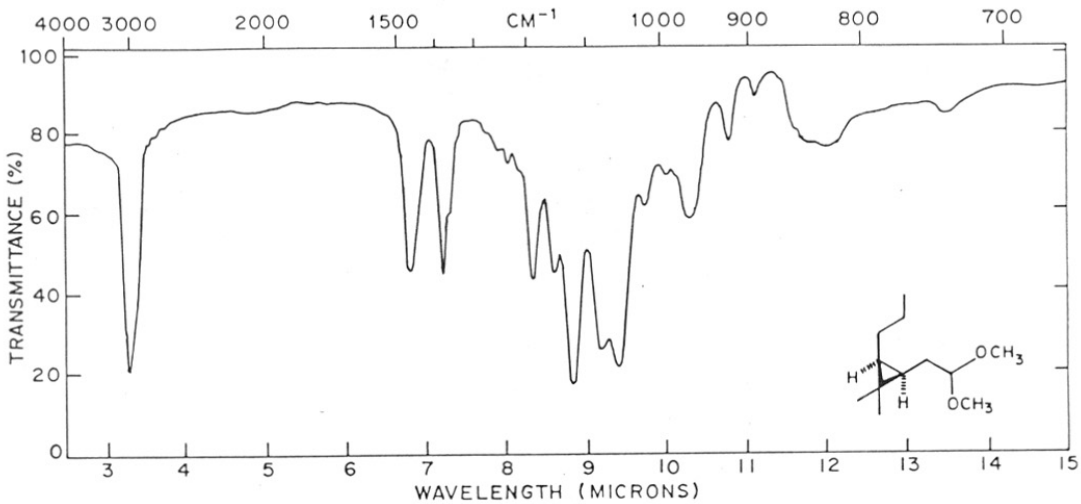


FIGURE XXII

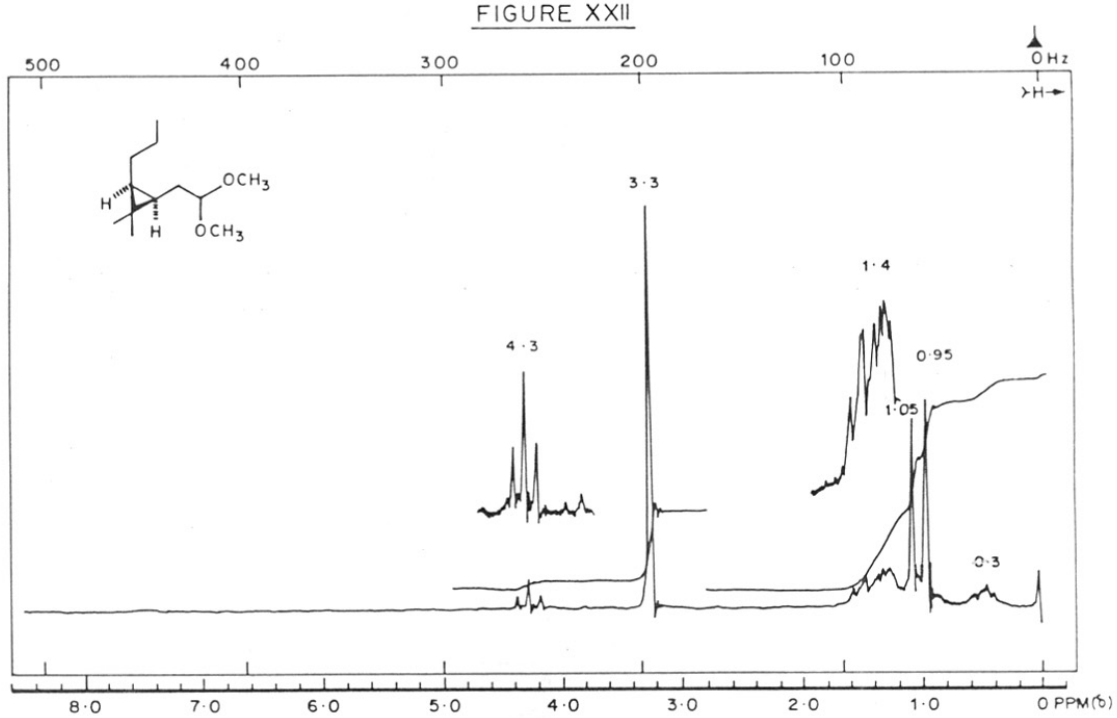


FIGURE XXII

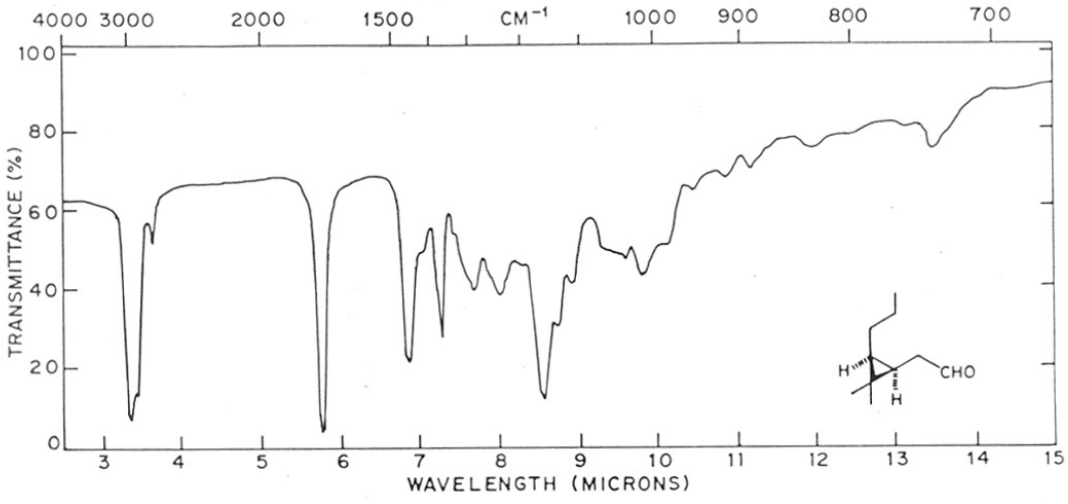


FIGURE XXIII

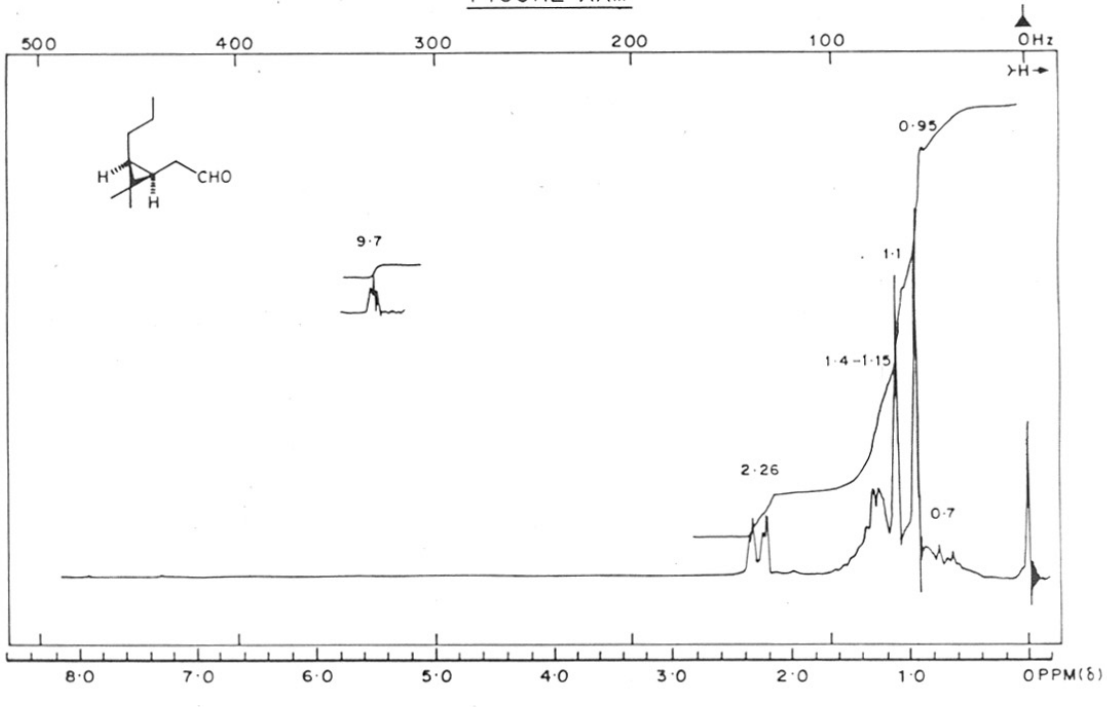


FIGURE XXIII

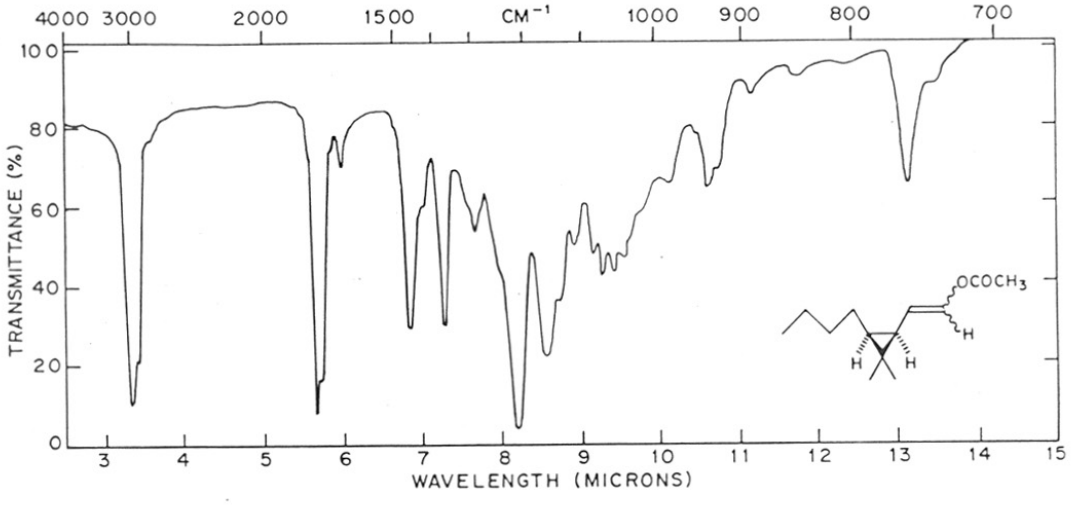


FIGURE XXIV

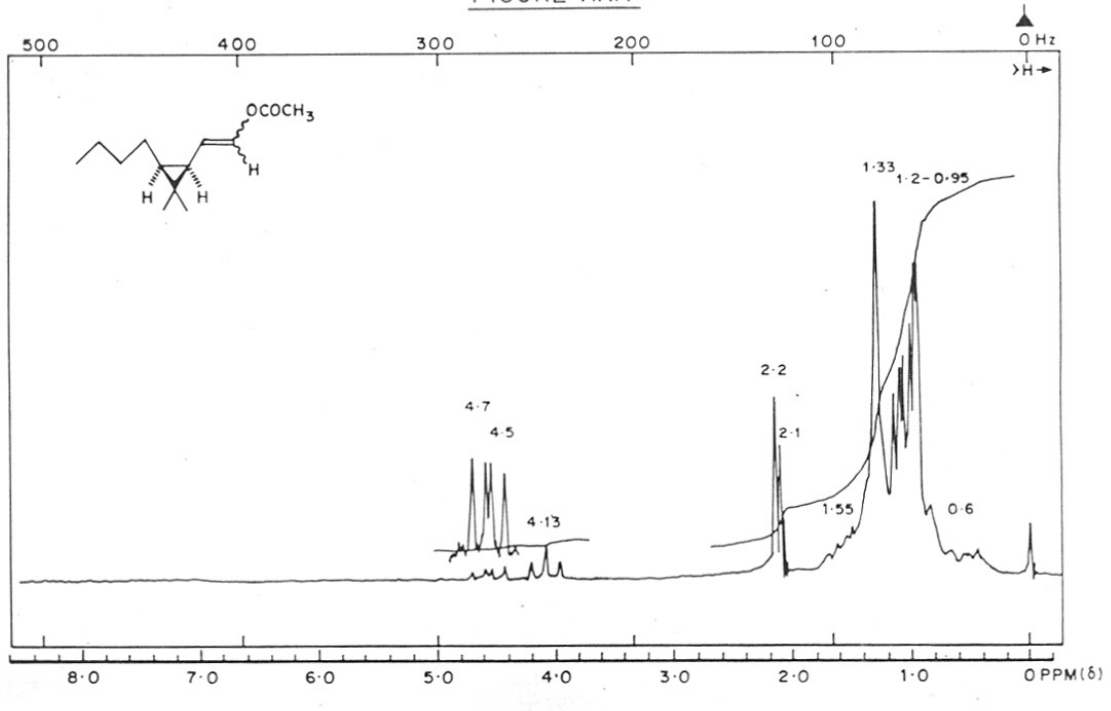


FIGURE XXIV

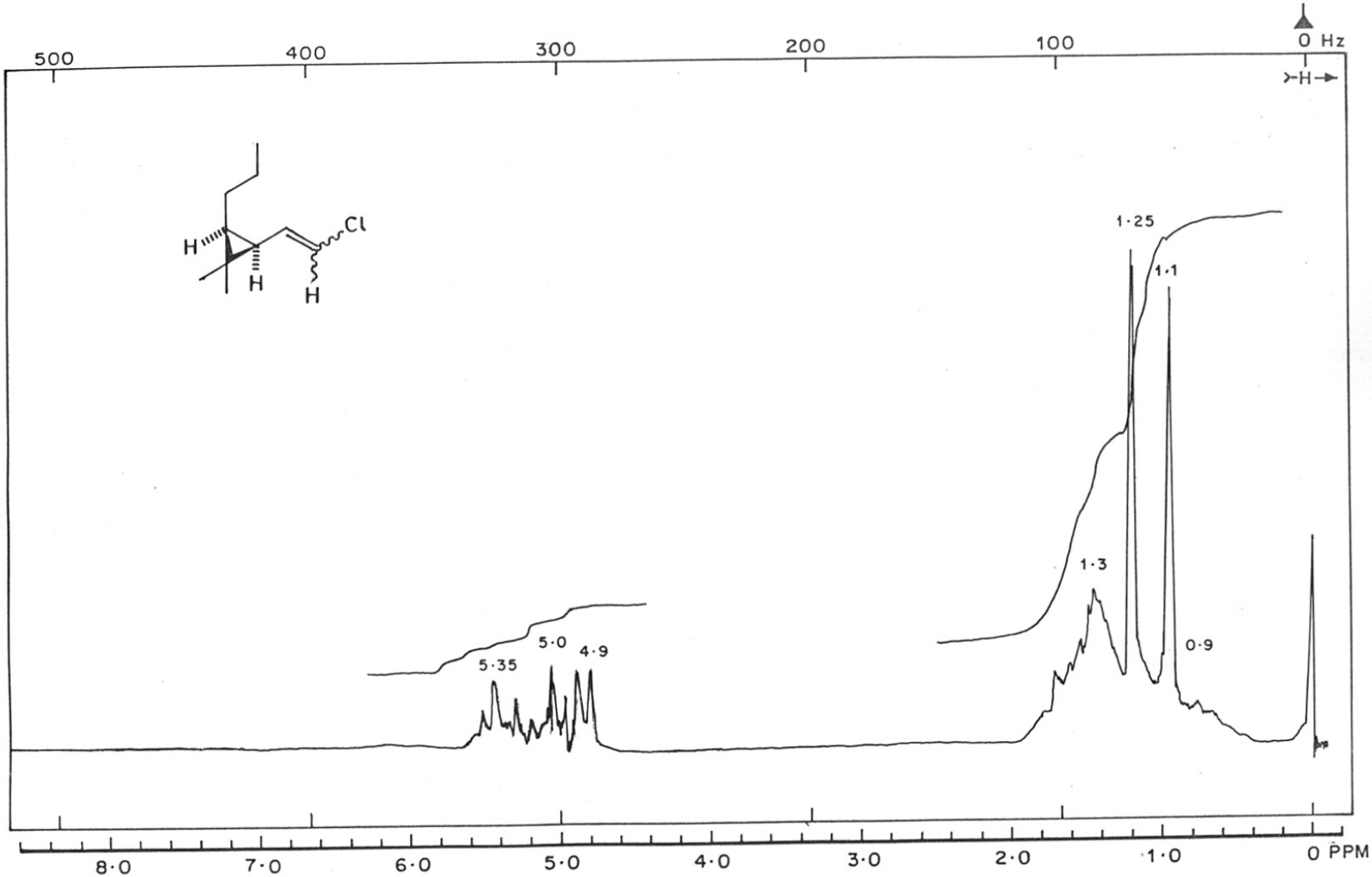


FIGURE XXVII

CHAPTER - IV

TOTAL SYNTHESIS OF CYCLOPROPANE INSECTICIDES

PART-A :- SYNTHESIS OF MITICIDAL ESTERS

PART-B :- SYNTHESIS OF INSECTICIDAL ETHERS

SUMMARY

Part A: Synthesis of Miticidal esters

3-benzoyl-n-propanol (4) obtained by a known procedure on Grignard reaction with CH_3MgI, afforded liquid diol (5) which, on dehydration with PTSA in benzene, gave dehydrated alcohol (6), characterised as acetate (7). Dichlorocyclopropanation of (7), yielded 2,2-dichloro-3-methyl-3'-phenylcyclopropane-1-ethanol (9) which on condensation with p-anisic acid, gave corresponding ester (10).

Similarly, Simmon's-Smith reaction on (7), furnished 3-methyl-3'-phenyl-cyclopropane-1-ethanol (11), which gave ester (13) on condensation with p-anisic acid.

Wittig reaction (PPh_3/EtI) on 2-benzoyl ethanol (16), which was obtained by a known procedure, yielded 3-phenyl-3-pentene-1-ol (17). Dichlorocyclopropanation of this alcohol (17) using phase transfer catalyst, gave 2,2-dichloro-3-methyl-1-phenyl-cyclopropane-1-ethanol (18) which on condensation with p-anisic acid, gave corresponding ester (19).

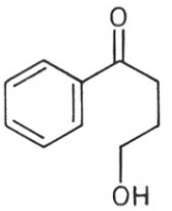
Similarly, Simmon's-Smith reaction on (17) gave 3-methyl-1-phenyl-cyclopropane-1-ethanol (20), which on condensation with p-anisic acid, yielded the corresponding ester (21).

Part B: Synthesis of insecticidal ethers -

Bromohydrin (23) obtained from ∝-methyl styrene (22) was subjected to dehydration by distilling under vacuum over PTSA when a mixture of unsaturated isomers was obtained. Chromatographic separation and purification furnished isomer (24) and (25). On condensation with m-phenoxybenzyl alcohol and subsequent dichlorocyclopropanation with phase transfer catalyst, both the isomers (24) and (25), gave final pyrethroid ethers (27) and (29) respectively.

Similarly, dibromostyrene (31) obtained from bromination of styrene (30), was dehydrobrominated with potassium acetate and DMF to get bromostyrene (32) which was converted into its dichlorocyclopropane ether (34) by usual procedure.

All the final compounds were tested for their insecticidal activity against Musca domestica (Houseflies) in our entomological department.



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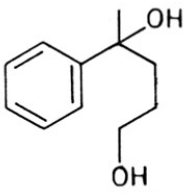

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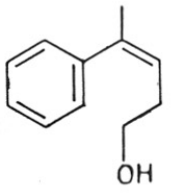

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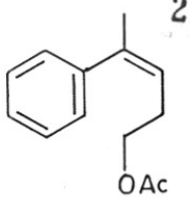

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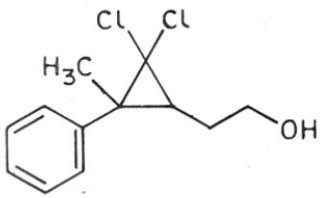

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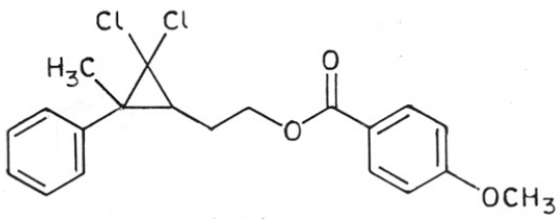

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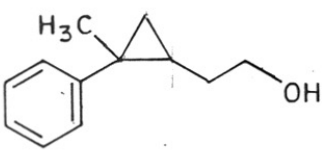

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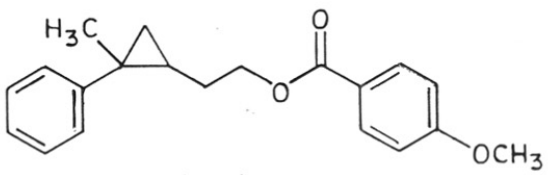

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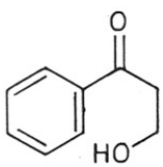

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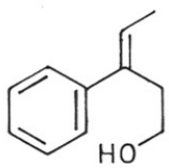

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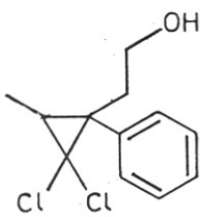

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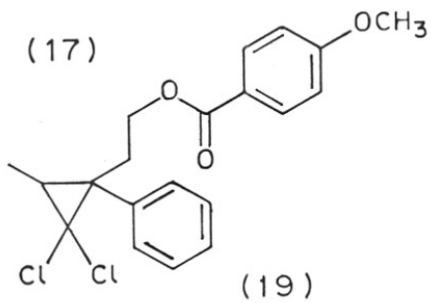

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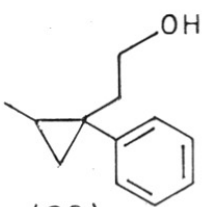

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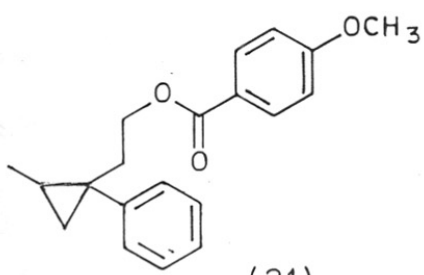

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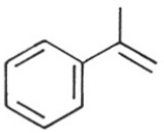

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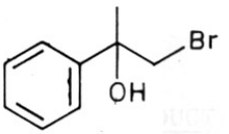

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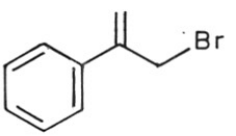

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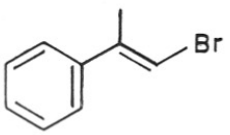

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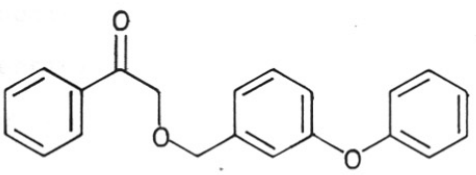

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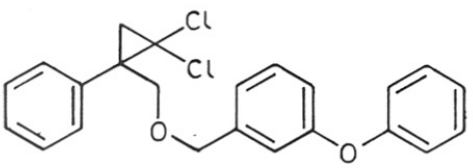

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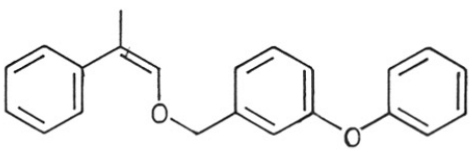

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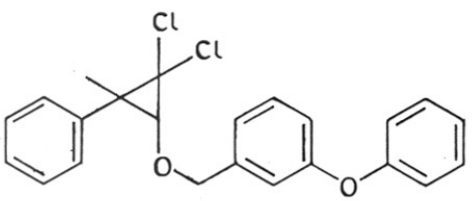

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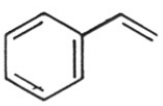

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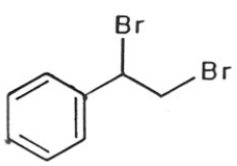

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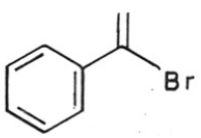

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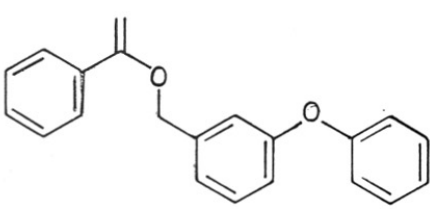

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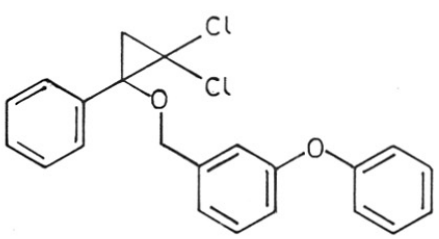

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INTRODUCTION

One of the most controversial subjects in recent years has been the use of chemical insecticides in pest control. An ideal insecticide must have a number of biological and chemical properties along with effective insecticidal activity. An essential requirement of insecticide is that, they should not be toxic to humans exposed to them, either on short or long term basis. They should also have a physiological specificity in that, all the beneficial microorganisms, insects and exposed plants must be spared of their effect. Moreover, the residues of the compound must dissipate by physical or chemical means so that, hazardous levels do not accumulate which should disrupt the natural balance maintained in the food chain.

Insecticide with a wide range of physical, chemical and biological properties will be required for, as long as present methods of crop protection continue and until diseases transmitted by insects no longer affect mankind and his livestock.

The commercial insecticides being used were carbamates, organophosphates and organochlorine compounds. The discovery of pyrethroids with enhanced insecticidal

activity and low mammalian toxicity led to an abundance of new synthetic results in the chemistry of pyrethroids.[1]

The evolution of pyrethroids and their identification on the basis of synthetic, spectroscopic and degradative properties have been reviewed comprehensively by Casida[2] and also by Elliott et.al[3,4]. An interesting fact that surfaced was that, few classes of biologically active compounds have such great potential for structure variation with retention of enhancement of insecticidal potency as natural pyrethrum[4].

For effective activity, pyrethroids depend on at least two centres having appropriate chirality[4] i.e. in chrysanthemates, the gem-dimethyl cyclopropane acids, the configuration at C-I carbon must be 'R' and the unsaturated side-chain at C-3 must be trans- to the C-1 carboxylic group. Mainly, the alcohol component, methyl cyclopentanolones should have 'S' configuration at the site of attachment of the alcoholic oxygen. It has been conclusively proved that C-1 'S' cyclopropane acids or 'R' alcohols give almost inactive esters.

As soon as the nature of active constituents were known, analogues were investigated in attempts to elucidate principles governing activity and to discover simple or more potent insecticides. Initial indication of the valuable influence of changing the C-3 substituent in the chrysanthemic acid, stimulated synthesis of other analogues.

Prompted chemists in many companies around the world, modified structure of pyrethroids, led to a rapid expansion of this field and the commercialisation of these compounds for agricultural applications. Elliott and Janes and their co-workers have continued to work in this area over the past decade and their work has contributed greatly to our knowledge of structure-activity relationship in pyrethroids[3,4]. One of the interesting developments in this field is that the structural requirements of pyrethroids for insecticidal and acaricidal activity are much broader than originally thought. Concurrently, Elliott and his co-workers[6,7] were developing highly active insecticides based on modification of the structure of naturally occurring pyrethrum.

Synergistic activity of a large number of chemicals derived from varied structures towards pyrethrum[8-10] and carbamate[11] insecticides, have

been reported earlier. Synergistic activity of some α,β-unsaturated compounds has been reported earlier[8]. When the same compounds are converted into dihalocyclopropane derivatives, the synergistic activity improves[12].

Elliott et.al[13] have examined a number of different C-3 substituents on the cyclopropane ring of the resmethrin type of pyrethroids. The insecticidal activity of these analogues, depends on the nature and the stereochemistry of the C-3 substituent. They have initially examined the modification of permethrin and cypermethrin but did not find a substituent that was superior overall to the dihalovinyl group. Their one report did include a number of alkoxy, arylkoxy and aryl substituents. The simple alkoxy and 4-chloro-phenoxy substituents at C-3 gave analogues, which showed reasonable activity. Other workers[14-16] have also studied analogues containing alkoxy and phenoxy groups at C-3. Analogues with a 4-chloro-phenyl group at C-3 position, showed most activity[17] as did the compounds with a styryl group at C-3. The 2-naphthyl analogue at C-3 showed poor activity.

Elliott et.al[18-20] also prepared number of analogues of fenvelarate in which chlorophenyl, alkyl, alkenyl and cycloalkyl analogues showed some activity. Elliott and his co-workers have also extensively investigated variations in the alcohol moiety of the pyrethroid structure[21,22].

Since the discovery of the insecticidal activity of DDT, many structural theories of its mode of action have been proposed and they have all tried to explain the uniqueness of this seemingly simple hydrocarbon. Among these, Mullins[23,24] has described moiety like 1,3 di (p-chlorophenyl)-2,2-dichlorocyclopropane of several molecules of DDT which are effective in a nerve-membranepore channel in insects. On the basis of this report, Holan[25] has reported new halocyclopropane insecticides and their mode of action of DDT. Initially, the 1,1-di(p-chlorophenyl)-2,2-dichlorocyclopropane and its conformer, trans-1,3-di-(p-chlorophenyl)-2,2-dichlorocyclopropane were designed and then synthesised. Later on, Holan et.al[26] have described structural and biological link between pyrethroids and DDT in new

insecticides, in which some of their most active DDT isoesters (Chart II) contained a similar structural feature with the pyrethroids, namely the relatively uncommon disubstituted cyclopropane ring.

In this respect, Van den Berken[27] found a close relationship between the action of these two classes of compounds, in experiments with DDT and pyrethroid, allethrin. This has prompted to examine the synthesis of compounds which would combine in one molecule, the structural features of both the DDT and the pyrethroid insecticides. Holan has reported[26] the structures and properties of compounds (see Chart II) which have been evaluated biologically on susceptible strain of the housefly (Musca domestica) and the Australian sheep blowfly (Lucilia cuprina W.). These new DDT-pyrethroid combination structures proved to be active insecticides.

Staal et.al[28,29] have prepared various esters derived from both cyclopropanecarboxylic acid cyclopropyl methyl alcohol (for more details, see charts in Chapter I). Some of these esters were

CHART – II

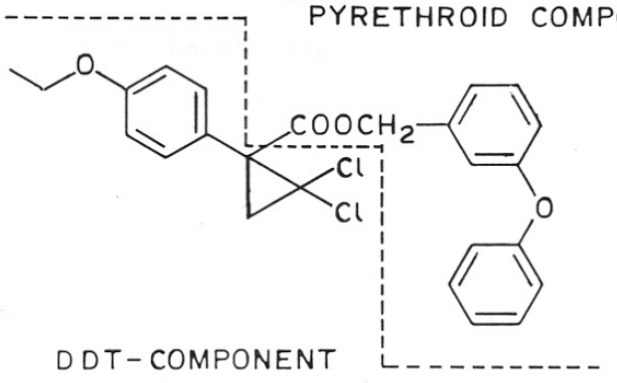
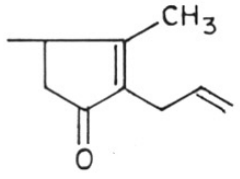


FIG. 1

R =



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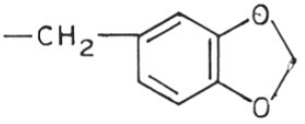

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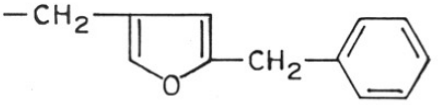

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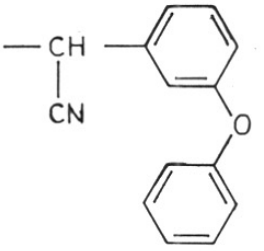

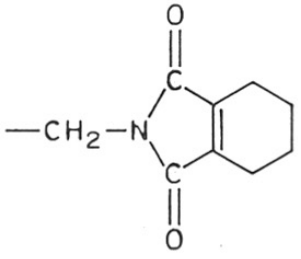

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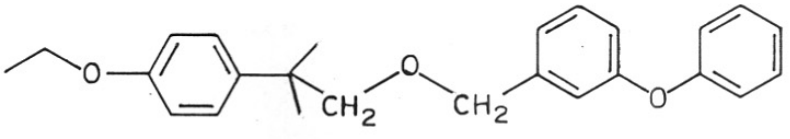


MTI – 500

FIG. 2

tested against two spotted spider mites (Tetranychus urticae Koch), commonly occurring on strawberry plant, for both ovicidal and larvicidal activity. They tested these derivatives by following either direct application to eggs or by deposition of eggs on previously sprayed leaves and found that these derivatives exhibit high and predominantly contact ovicidal and larvicidal activity. Here, the diaryl esters showed 5-20 times greater contact activity against mite eggs and larvae than monoaryl esters. These derivatives are especially active against all the stages of embryonic development. Because of the phytotoxic nature of organophosphorous or other similar commercially available compounds, these cyclopropane derivatives are generally more suitable for application.

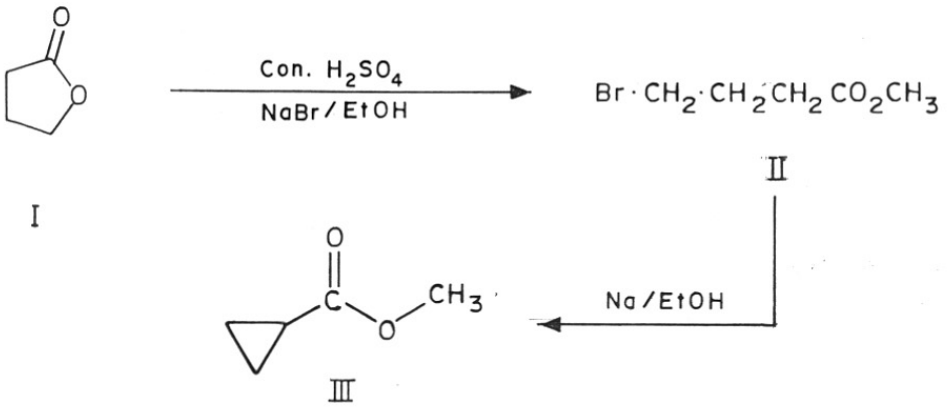
Hurkova et.al[30] have studied the effects of two cyclopropane miticides, namely, cyclopropyl methyl dodecanoate and cyclopropyl methyl terephthalate on Tetranychus urticae (acaritetranychidae) and were found to be ovicidal, having LC_{50} values of 0.003% and 0.012% respectively, compound with 0.00026% of tetradifon.

Henrik et.al.[31,32] invented many novel compounds, characterised by cyclopropyl methyl moiety and observed to have effective control over mites at all stages.

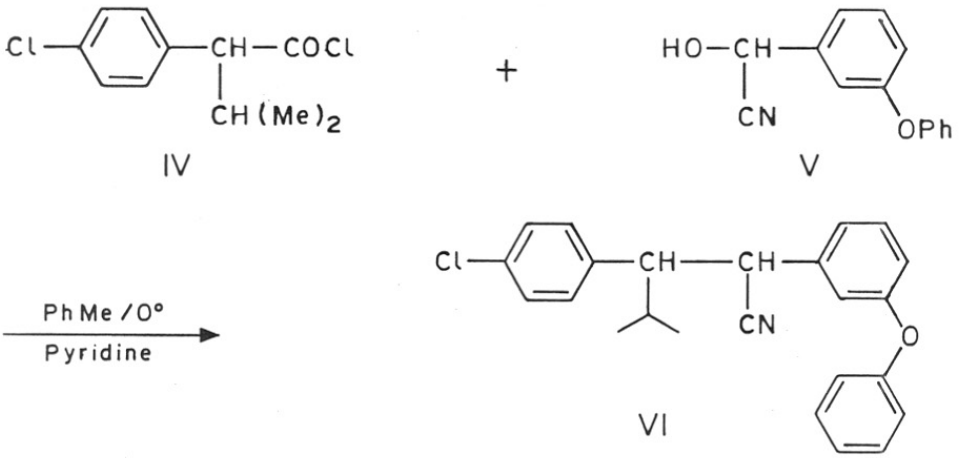
Yago et.al.[33] have reported cyclopropane-carboxylic esters and their precursor, haloalkonoate esters. One example of it is described in Scheme I in which the cyclic ester (III) was prepared by cyclisation of (II) which was prepared by the reaction of lactone (I) with HBr. Thus, conc. H_2SO_4 was added to a mixture of lactone (I), ethanol and NaBr at 0-5° and the mixture stirred for 6 hours at 25-30° to give 85% (II) which was refluxed with sodium in ethanol for 30 minutes to give 80% (III). Many such alkyl and aralkyl cyclopropanecarboxylic esters and haloalkonoate esters were prepared.

Ackermann et.al.[34] have reported α-isopropyl and α-cyclopropyl phenyl acetates and their use in pest control (Scheme II). Thus, heating (IV) in toluene successively with pyridine and (V) at 0°, then stirring for 12 hours at 20° gave VI. Similarly, reaction of (VII) with (V) in toluene with pyridine at 0° yielded (VIII) (Scheme III).

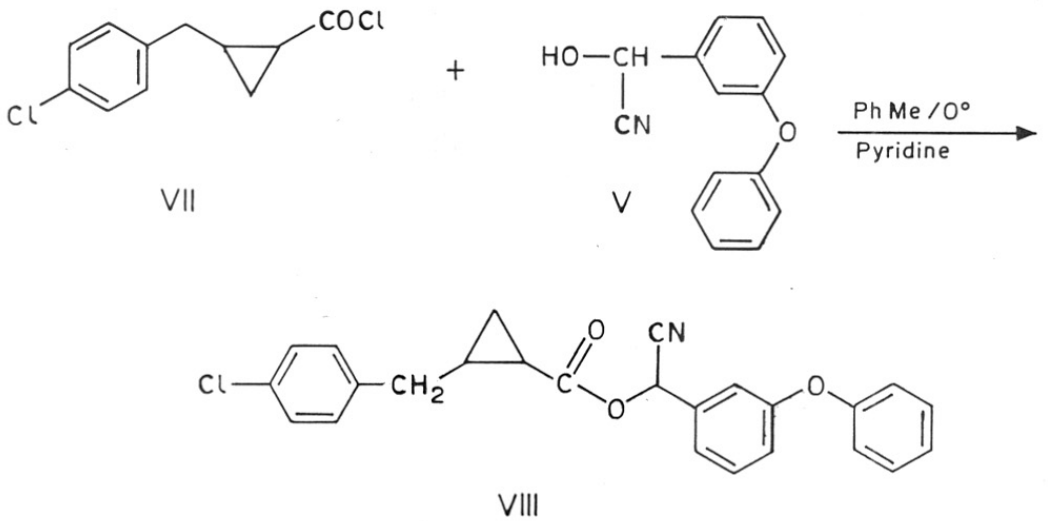
SCHEME – I



SCHEME – II



SCHEME III



This α-cyclopropyl phenyl ester killed 70-100% Laspeyresa pomonella larvae. In addition, in our laboratory, some of the esters of 2,2-dimethyl-3-n-propyl-cyclopropyl ethanol have been synthesised by us (see Chapter II of this thesis) and tested for their bio-efficacy in the laboratory at various concentrations. Among these, p-anisoyl ester (Fig. No.38 in Chapter II) has shown total control over pink mites (Acaphyllus theae) and purple mites (Calacarus carinatus) even at concentration of 0.005%.

MTI-500[35] (Chart II), which is [2-(4-ethoxy-phenyl)2-methoxypropyl-3-phenoxybenzyl ether] is a compound composed of C, H and O only, which exerts a pyrethroid like activity; but differs from natural and synthetic pyrethroids in lacking cyclopropane ring and ester bond. It has high insecticidal activity against various pests, including Lepidoptera, Hemiptera, Coleoptera, Diptera and Orthoptera but has remarkably weak toxicity to mammals. In addition, it is less toxic to fish than the conventional pyrethroids. MTI-500 is stable under acidic or alkaline condition and is characterised by the advantage that it can be mixed with alkaline agricultural chemicals[36].

Presently MTI-500 has been extensively used as a pesticide for rice, vegetables and fruits as well as for medical, veterinary, urban, industrial and forest uses. It has a TLM value of 5 ppm which shows the weak toxicity to fish. The LD_{50} value of MTI-500 was determined by diluting with 5% sugar solution and feeding to insects. Effect of MTI-500 and other compound against Tobacco entworm (4th instar larvae) by baiting method is given in Table I.

Table-I

	Mortality (%) mg/g bait		
Compound	1.0	0.1	0.001
MTI-500	100	100	80
Fenvalerate	100	100	30
Trichlorfon	100	70	0
Methomyl	100	90	40

In addition, MTI-500 kills insects resistant to phosphorous and carbamate preparations. Its activity was stable or rather enhanced after being mixed with Bordeaux as has been shown in Table II below

Table-II

Compound	LD_{50} ppm alone	LD_{50} ppm *Bordeaux mixture
MTI-500	2.0	0.6
Cypermethrin	0.39	1.1
Deltamethrin	0.05	0.8

* Bordeaux mixture; type 5-5(pH 12.5)-$CuSO_4$ + CaO 5g + 5g/lit of water

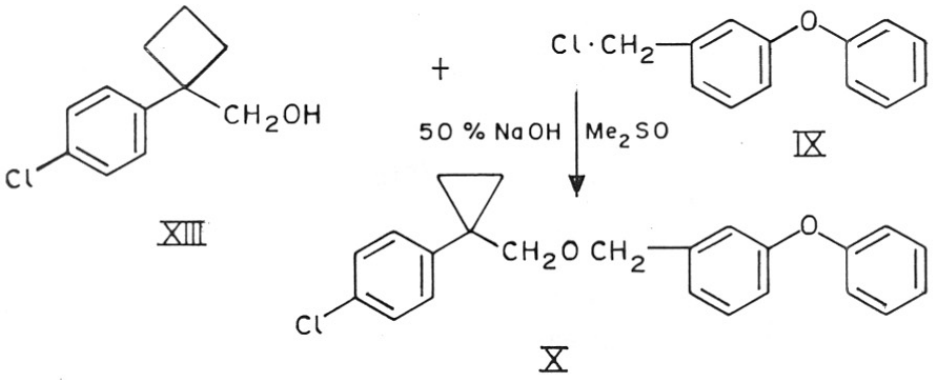
It is also found that some of the compounds with an alkynylene (-CH=CH-CH_2) or alkylene (-CH_2-CH_2-CH_2) bond in addition to ether bond, have strong insecticidal activity. However, substitution of ester bond with an ether or alkylenebond led to this low toxicity to fish of the resulting compound.

Mitsui Toatsu Chemical Inc., Japan, has reported[37] many compounds containing 2-aryl ethyl ethers and thioethers as potent acaricides and insecticides. These compounds containing ether alongwith Tetranychus urticae on beans.

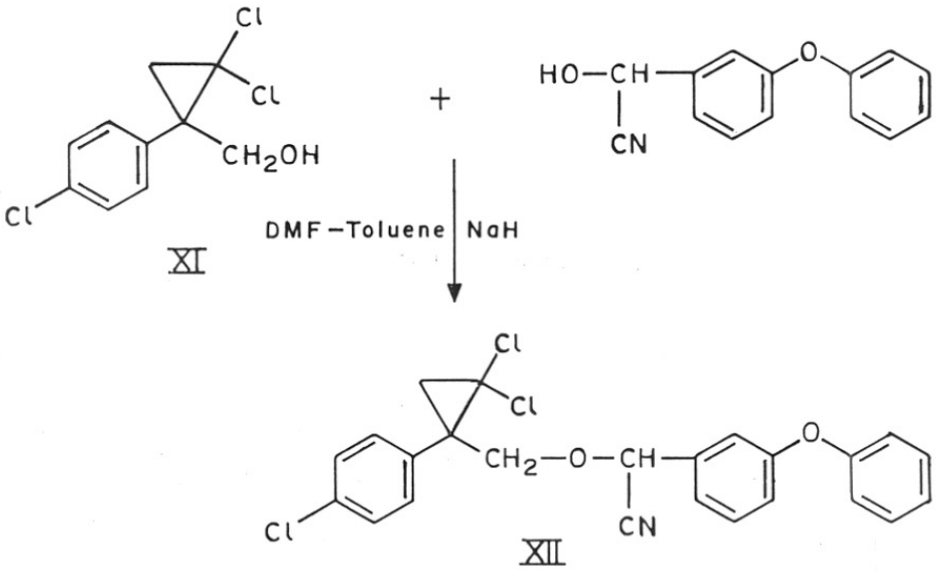
Fifty-three 2-arylethyl ethers and thio ethers were synthesised[38] and were observed to be insecticides and miticides. The evaluation data of these compounds was taken against Prodenia litura. One example among these compounds was prepared by treating a mixture of 1-(4-Chlorophenyl)1-cyclobutane methanol (VIII),, 50% NaOH solution, 3-phenoxybenzyl chloride (IX) and dimethyl sylphoxide for one hour at 130° to give ether (X) as shown in Scheme IV.

Ackermann et.al[39] have prepared number of similar insecticidal 3-phenoxybenzyl-2-phenyl-2, 2-alkylene ethyl ethersand thio ethers with various alkyl, haloalkyl, alkoxy, haloalkoxy substituents at C-1 as well as phenoxybenzyl and cyanophenoxybenzyl linkage at C-1 position and halo, C_{1-5} alkyl at C-2 and C-3 positions respectively. One example among these types of compounds was prepared as shown in Scheme V in which treatment of 2,2-dichloro-1(4-chlorpphenyl) cyclopropane methanol (XI) with sodium hydride and m-phenoxybenzyl cyanide in DMF- toluene to give ether (XII).

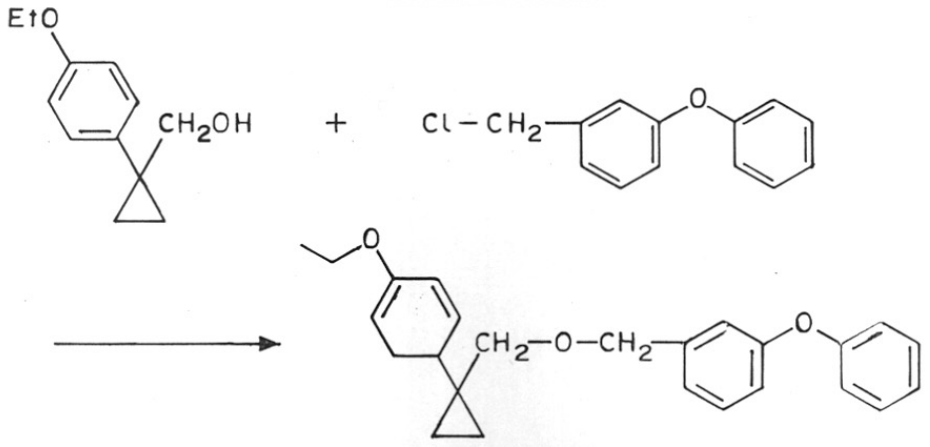
SCHEME – IV



SCHEME – V



SCHEME VI



Axel et.al[40] have reported many arylcycloalkyl ether derivatives and were found to be acaricidal, nematocidal and insecticidal. About fortyfour various substituted ethers were prepared and have been patented. Preparation of one illustrated compound (XIII) is shown in Scheme VI. At 0.050μg, (XIII) gave almost complete to complete kill of Musca domestica and was found to be more effective than permethrin.

Present work and Discussion

Part A -

Number of different C-3 substituents on the cyclopropane ring in pyrethroids have been studied in relation to their insecticidal activity[13-16]. The effect of varying the alcohol moiety largely depends on the active acid involved and the structure-activity relationship can differ considerably with different insect species. Such a delicate balance between structure and activity in pyrethroids has become obvious in looking at these variations.

Very recently, we synthesised many potent miticidal esters from (+)-3-carene as has already been explained in Chapter II of this thesis. Among these esters, particularly p-anisoyl ester of 2, 2-dimethyl-3-n-propyl-cyclopropyl ethanol has shown promising activity against potato mites (Rhizoglyphus echinopus), pink mites (Acaphyllus theae) and purple mites (Calacarus carinatus) which commonly occur on tea leaves. This ester (Fig. No.38 in Chapter II) has shown total control over these species of mites upto 0.005% concentration.

In our work, we have synthesised the esters of cyclopropane ethanol by replacing alkyl and aryl as C-3 substituents and replacing also the usual alcohol component of 3-phenoxybenzyl group by p-anisoyl group.

β-benzoyl propionic acid (1) was prepared by Friedel-Crafts acylation of benzene with succinnic anhydride, in presence of aluminium chloride according to the procedure reported by Deshpande and Nairgund[41]. This acid (1) was then converted into its methyl ester (2) using methanol and catalytic HCl and characterised by spectral data.

The methyl ester (2) was converted into 3-benzoyl-1-propanol (4) by the procedure reported by Harold et.al.[42] in an overall yield of 55%. The white solid keto alcohol (4); $C_{10}H_{12}O_2$; crystallised from carbon tetrachloride to mp. 31-32°C (lit.32-33°) and showed IR (nujol) bands at 3460 cm^{-1} (OH), 1690 cm^{-1} (c=o) and PMR (CCl_4, δ) signals at 1.6-2.1 (2H, m, $-\underline{CH_2}-CH_2-OH$), 2.9 (2H, t, J=6 Hz, $-COCH_2$ protons), 3.6 (2H, t, J=6 Hz, $-C\underline{H_2}OH$ protons), 4.0 (1H, s, exchangeable with D_2O, -OH proton), 6.0-7.67 (3H, aromatic protons) and 7.7-8.1 (2H, m, aromatic ortho

protons)¦ mass spectrum, m/e (relative intensity) 164(4), 146(45), 115(19), 105(100) and 77(48).

Grignard reaction using CH_3MgI on keto alcohol (4), furnished liquid diol (5) as a thick oil; $C_{11}H_{16}O_2$, M^+ 180 and showed IR(liquid film) bands at 3360 cm^{-1} (OH); PMR (CCl_4, δ) signals at 1.43 (3H, s, $-CH_3$), 1.6-2.1 (2H, m, $-CH_2-CH_2-OH$ proton), 2.95 (2H, t, $CH_2CH_2CH_2-OH$ protons), 3.5 (2H, t, $-CH_2OH$ protons), 4.1 (2H, brs, exchangeable with D_2O -OH proton) and 6.0-6.73 (5H, m, aromatic protons).

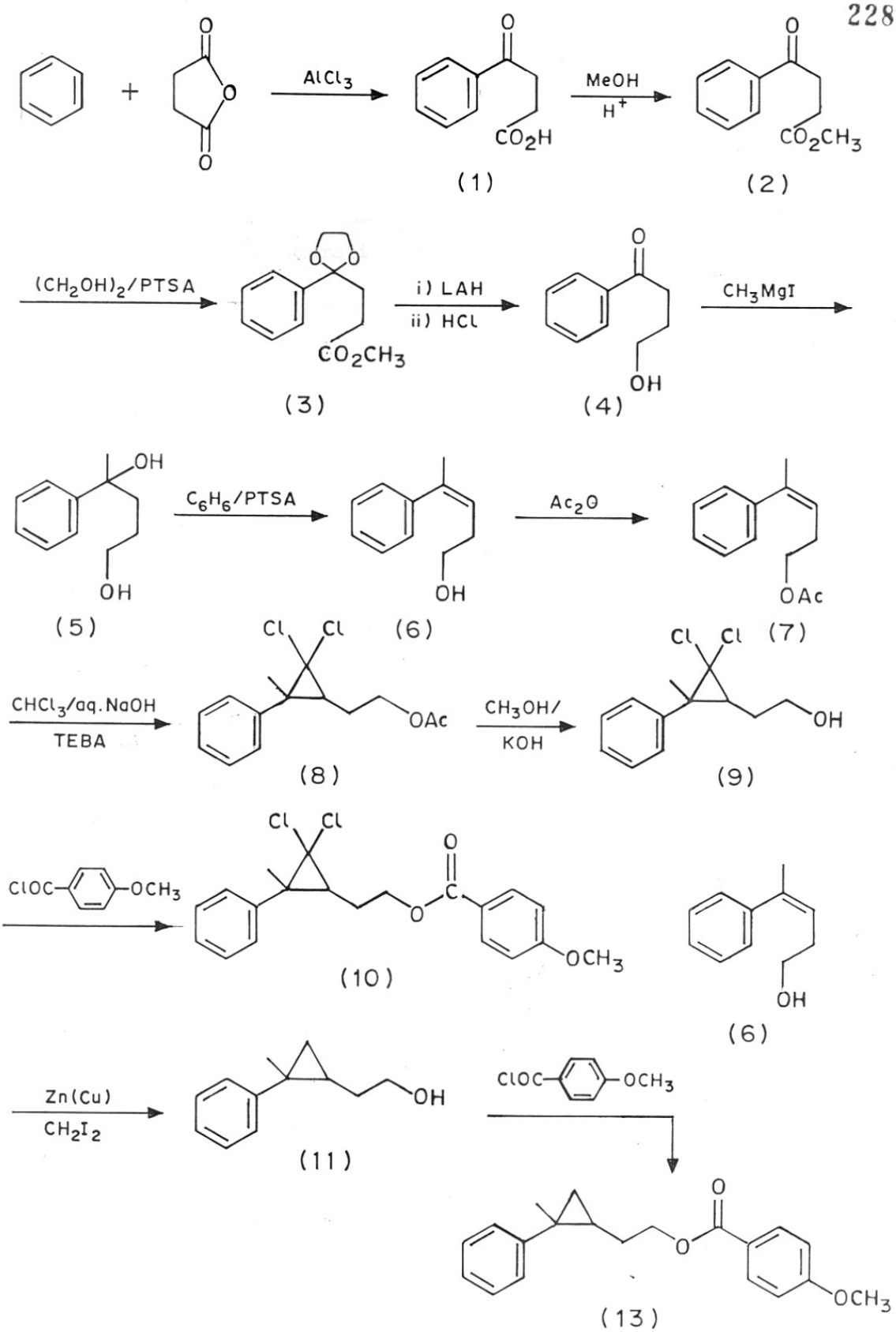
Dehydration of diol (5) in benzene with catalytic PTSA, afforded dehydrated alcohol (6) identified as acetate (7); $C_{13}H_{16}O_2$, M^+ 204; IR (liquid film) bands at 1690 cm^{-1} (acetate c=o), 1600 (c=c) and PMR (CCl_4, δ) signals at 1.97 (3H, s, $-COCH_3$ protons), 2.05 (3H, s, $-CH_3$ on double bond), 2.25-2.7 (2H, m, $=CH-CH_2-CH_2-OAc$ protons), 4.1 (2H, t, J=8 Hz, CH_2-OAc protons), 5.1 (1H, t, J=8Hz olefinic protons) and 7.0-7.6 (5H, m, aromatic protons).

Dichlorocyclopropanation of acetate (7) in $CHCl_3$/aq. NaOH using PTC (triethyl benzyl ammonium bromide), yielded the corresponding dichlorocyclo-propane acetate (8) as a liquid; $C_{14}H_{16}Cl_2O_2$ and

showed IR (liquid film) bands at 1690 (c=o) and PMR (90 MHz, $CDCl_3$), 1.47 (3H, s, $-CH_3$ at C-3), 1.6 (1H, t. J=3 Hz, cyclopropane proton at C-1), 1.82-1.98 (2H, m, $-CH_2-CH_2-OAc$ protons), 2.1 (3H, s, $-OCOCH_3$ protons), 4.3 (2H, t, J=8 Hz, $-CH_2-OAc$ protons) and 7.18 (5H, m, aromatic protons).

Regeneration of alcohol (9) from acetate (8) with methanolic KOH and subsequent condensation of this alcohol (9) with p-anisoyl chloride, furnished the final required ester (10) as a thick liquid; $C_{20}H_{20}Cl_3O_2$ and showed IR (liquid film) bands at 1720 cm^{-1} (ester c=o) and PMR (80 MHz, $CDCl_3$) signals at 1.55 (3H, s, $-CH_3$ protons at C-3), 2.0-2.25 (3H, m, C-1 cyclopropane proton and adjacent $-CH_2$ protons), 3.85 (3H, s, $-OCH_3$ protons), 4.5 (2H, t, J=5 Hz, $-OCH_2$ protons), 6.95 (2H, d, J=6 Hz, anisoyl aromatic proton ortho to $-OCH_3$), 7.3 (5H, brs, phenyl aromatic protons), 8.05 (2H, d, J=6 Hz, anisoyl aromatic protons ortho to c=o gr).

Cyclopropanation of alcohol (6) using freshly prepared zinc-copper couple and methylene iodide, afforded cyclopropane alcohol (11) as a liquid; $C_{14}H_{18}O_2$ which showed IR bands at 3340 cm^{-1} (OH), 1600 (aromatic) and PMR (90 MHz, $CDCl_3$), 0.85-1.68


AlCl3
MeOH
H+
CO2H
CO2CH3
(1)
(2)
(CH2OH)2/PTSA
i) LAH
ii) HCl
CH3MgI
OH
(3)
(4)
C6H6/PTSA
Ac2O
OAc
(5)
(6)
(7)
Cl
CHCl3/aq.NaOH
TEBA
CH3OH/
KOH
(8)
(9)
ClOC
OCH3
(10)
Zn(Cu)
CH2I2
(11)
(13)

(5H, m, cyclopropane protons at C-1 and C-2 and $C\underline{H}_2$ protons adjacent to C-1), 1.35 (3H, s, $-CH_3$ at C-3), 4.15 (3H, t of $-CH_2OH$ overlapping -OH proton), 7.25 (5H, m, aromatic protons).

Condensation of cyclopropane alcohol (11) with p-anisoyl chloride, gave the final ester (13) as a thick liquid, $C_{20}H_{22}O_3$, M^+ 310 and showed IR bands at 1740 (ester C=0) and PMR (90 MHz, $CDCl_3$) signals at 0.87 - 1.7 (5H, m, C-1 and C-2 cyclopropane protons and CH_2 adjacent to C-1), 1.35 (3H, s, $-CH_3$ protons at C-3 , 3.95 (3H, s, $-OCH_3$ of anisoyl gr.) 4.4 (2H, t, J=8 Hz, $-OCH_2$), 6.76 - 7.0 (2H, m, anisoyl aromatic proton ortho to $-OCH_3$), 7.3 (5H, brs, aromatic protons) and 7.75 - 8.05 (2H, m, anisoyl aromatic protons ortho to C=0 group).

The preparation of miticidal ester with methyl substituent at C-3 position and phenyl substituent as well as p-anisoyl ester component at C-1 position of the cyclopropane ring was achieved by the following method -

Ethyl benzoyl acetate (14) was prepared by the treatment of ethyl acetoacetate with benzoyl chloride using aqueous NaOH (33%) by the reported procedure[43].

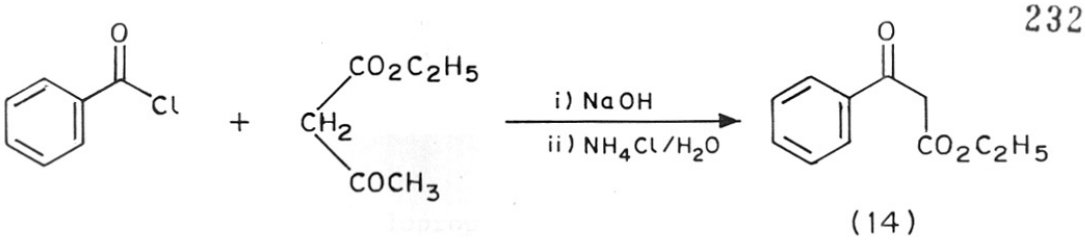
3-hydroxypropiophenone (16) was then prepared from (14) by the procedure reported by Harold R. Ward et.al[42] in 76% yield as a liquid; $C_9H_{10}O_2$, M^+ 150 and showed IR (liquid film) bands at 3460 cm^{-1} (OH), 1696 (c=o) and PMR (CCl_4, δ) signals at 3.1 (2H, t, J=7Hz, -CH_2CO protons), 3.6 (1H, brs, exchangeable with D_2O, OH proton), 3.85 (2H, t, J=7 Hz, -OCH_2), 7.0-7.35 (3H, m, aromatic protons meta to c=o) and 7.5-8.0 (2H, m, aromatic protons ortho to c=o gr.).

Wittig reaction on keto alcohol (16) using iodoethyltriphenyl phosphorane (prepared from C_2H_5I and PPh_3), afforded in moderate yields, the 3-phenyl-3-penten-1-ol (17) as a liquid, $C_{11}H_{14}O$ and showed IR (liquid film) bands at 3460 cm^{-1} (OH), 1595 (c=c) and PMR (CCl_4, δ) signals at 2.0-2.3 (5H, d, of -CH_3 overlapping t of CH_2 adjacent to c=c), 3.4 (1H, brs. exchangeable with D_2O, -OH proton), 4.0 (2H, t, J=6Hz, -CH_2OH) and 5.75-5.9 (1H, m, olefinic proton), 7.0-7.6 (5H, m, aromatic protons).

Dichlorocyclopropanation of alcohol (17) with chloroform/aq. NaOH solution using PTC (TEBA), afforded 2,2-dichloro-3-methyl-1-phenyl cyclopropane-1-ethanol (18); $C_{12}H_{14}Cl_2O$ which showed IR (liquid film) bands at 3460 cm^{-1} (OH), 1600 (aromatic) and PMR (CCl_4, δ) signals at 1.2-1.55 (4H, m, d of CH_3 at C-3 overlapping CH proton at C-3), 1.95 (2H, t, J=7 Hz, $-CH_2$ adj. to C-1), 3.5 (1H, brs, exchangeable with D_2O, -OH proton), 4.0 (2H, t, J=7 Hz, $-CH_2OH$) 7.2-7.8 (5H, m, aromatic protons).

Condensation of dichlorocyclopropane ethanol (18) with p-anisoyl chloride,yielded the final required ester (19) as a white solid purified by column chromatography over silica gel which showed IR (nujol) bands at 1739 cm^{-1} (c=o) and PMR (80 MHz, $CDCl_3$) signals at 1.3-1.45 (4H, m, $-CH_3$ proton signals overlapping cyclopropane proton at C-3), 2.0 (2H, t, J=8 Hz, $-CH_2$ protons adjacent to C-1), 3.65 (2H, t, J=8 Hz, $-OCH_2$), 6.8-7.1 (2H, d, J=9 Hz, anisoyl aromatic protons ortho to $-OCH_3$), 7.3 (5H, brs, aromatic adj. to C-1), 7.9-8.2 (2H, d, J=9Hz, anisoyl aromatic protons ortho to c=o gr.).

Simmon's-Smith reaction on alcohol (17) using zinc-copper couple and methylene iodide, followed by purification with silica gel column chromatography,



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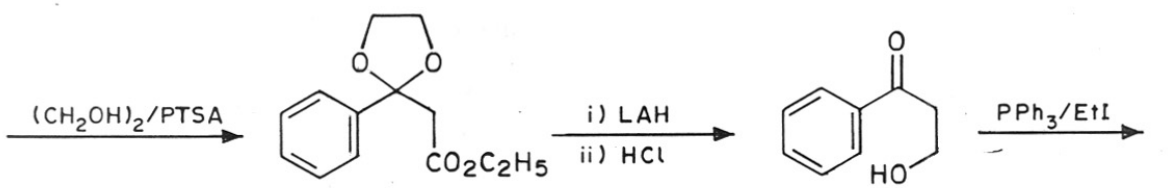

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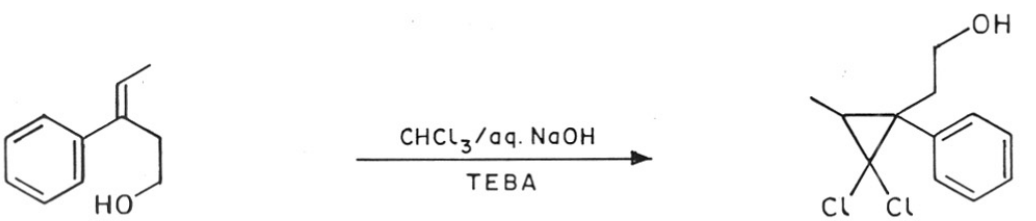

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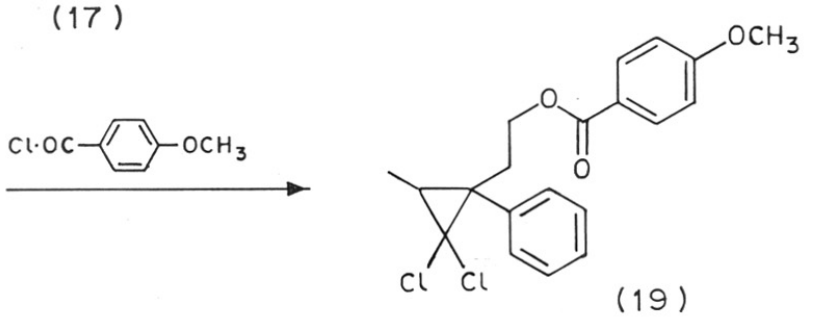

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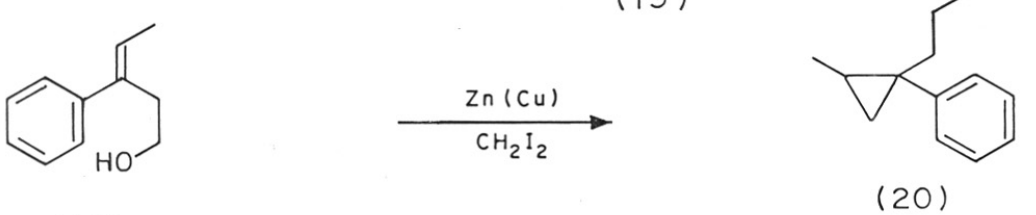

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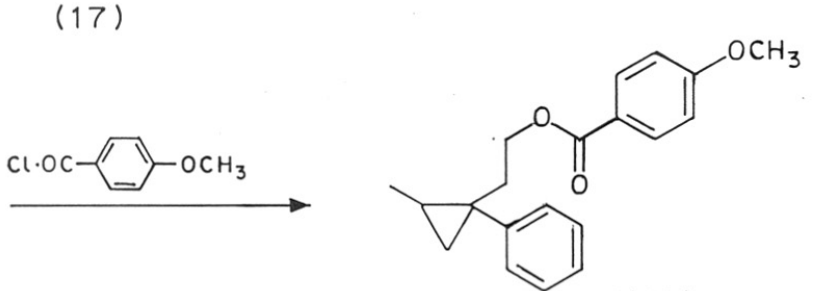


(21)

afforded cyclopropane ethanol (20) as a liquid; $C_{12}H_{16}O$, which showed IR (liquid film) bands at 3380 cm^{-1} (OH), 1600 (aromatic) and PMR (CCl_4, δ) signals at 0.87-1.8 (6H, m, $-CH_3$ and -CH protons at C-3 and cyclopropane protons at C-2), 2.0 (2H, t, J=6 Hz, CH_2-CH_2-OH protons), 3.9 (3H, t of CH_2 overlapping -OH proton signal) 7.15 (5H, brs, aromatic protons).

Similar condensation of cyclopropane alcohol (20) with p-anisoyl chloride, furnished the final ester purified by silica gel column chromatography. Fraction eluted with pet ether + ethyl acetate (5%) gave TLC (benzene) pure ester (21) as a solid; which showed IR (nujol) bands at 1738 cm^{-1} (c=o), 1595 (strong aromatic) and PMR (90 MHz, $CDCl_3$) signals at 0.9-1.85 (8H, m, cyclopropane proton at C-2, C-3 and CH_2 proton adjascent to C-1, CH_3 at C-3) 4.15 (2H, t, J=7 Hz, $-OCH_2$), 6.7-6.85 (2H, m, anisoyl aromatic protons ortho to $-OCH_3$ gr.), 7.25 (5H, brs, aromatic gr. adj. to C-1), 7.8-8.05 (2H, m, anisoyl aromatic protons ortho to c=o).

Present work and discussion

Part B -

This part of the chapter describes the synthesis of insecticidal ethers. Total synthesis of these dichlorocyclopropane ethers was achieved by simple and convenient methods from easily and cheaply available styrene and its methyl derivative.

In the first approach, bromination of ∝-methyl styrene (22) with NBS, afforded bromohydrin (23) as a liquid; $C_9H_{11}BrO$ and showed IR (liquid film) bands at 3448 cm^{-1} (OH) and PMR (CCl_4, δ) signals at 1.65 (3H, s, $-CH_3$ protons), 3.0 (1H, brs, exchangeable with D_2O, -OH proton), 3.7 (2H, s, $-CH_2Br$) and 7.15-7.65 (5H, m, aromatic protons).

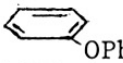
Dehydration of bromohydrin (23) with $POCl_3$/ pyridine at 0° followed by chromatographic purification, gave isomeric mixture of unsaturated bromides identified by its spectral data. This mixture was separated by chromatography over silica gel impregnated with 10% $AgNO_3$. Earlier fractions eluted with pet-ether gave TLC pure isomer (25), as a liquid; C_9H_9Br, which showed IR (liquid film) 1595 (aromatic), 835 ($\rangle C=CH$), and PMR (CCl_4, δ) signals at 2.2 (3H, s, $-CH_3$ protons),

6.45 (1H, s, olefinic proton) and 7.1-7.6 (5H, m, aromatic protons).

Later fractions eluted with pet-ether + benzene (1:1) mixture gave TLC pure other isomer (24) and showed IR (liquid film) bands at 1600 (aromatic), 890 (c=c); and PMR (CCl_4 δ) signals at 4.35 (2H, s, $-CH_2Br$ protons), 5.5 (2H, d, J=4 Hz, aromatic protons).

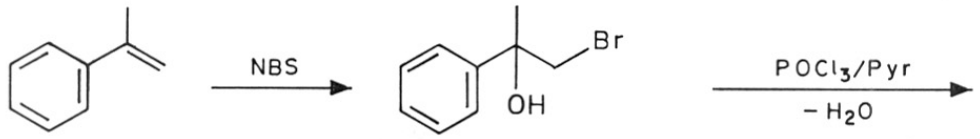
The exo-isomer (24) was condensed with m-phenoxybenzyl alcohol using sodium metal in dioxane solvent in anhydrous condition under N_2 atmosphere to give ether (26) as a liquid; $C_{21}H_{18}O_2$ and showed IR (liquid film) bands at 1600 (aromatic), 1080 (ether), 890 and PMR (CCl_4, δ) signals at 4.4 (2H, s, $-OCH_2$ protons), 4.55 (2H, s, $-OCH_2$ benzylic protons), 5.3 (1H, d, exo-proton), 5.5 (1H, brs, other exo-proton), 6.8-7.55 (14H, brm, aromatic protons).

Dichlorocyclopropanation of ether (26) using PTC (TEBA) with $CHCl_3$/aq. NaOH solution, at 65°C, afforded the final ether (27) which was purified by column chromatography using alumina. Fractions eluted with 25% benzene in pet-ether gave TLC pure dichlorocyclopropane ether (27) in 72% yield as a

pale yellow oily liquid, $C_{23}H_{20}Cl_2O_2$ which showed mass spectrum of which (27) showed significant molecular ion at m/z 398 (< 0.1%). The base peak m/z 183 (100%) was due to benzylic cleavage ($^{+}CH_2$- ) and IR (liquid film) bands at 1600, 1090 (c-o-c) and PMR (CCl_4, δ) signals at 1.55-1.9 (2H, 2d overlapping cyclopropane protons at C-3) 3.7 (2H, s, $-OCH_2$ protons), 4.27 (2H, s, $-OCH_2$ of benzylic protons) and 6.7-7.45 (14H, brm, aromatic protons).

The endo isomer (25) was similarly condensed with sodium salt of m-phenoxybenzyl alcohol under N_2 atmosphere to get ether (28); $C_{23}H_{20}Cl_2O_2$; which was purified by column chromatography using alumina. Fraction eluted with pet ether + benzene (4:1) gave TLC pure ether (28) which showed IR (liquid film) bands at 1600, 1065, 835 cm^{-1} and PMR (CCl_4, δ) signals at 4.55 (2H, s, $-OCH_2$), 6.3-6.5 (2H, m, olefinic protons), 6.7-7.4 (14H, brm, aromatic protons).

Dichlorocyclopropanation of this ether (28) with $CHCl_3$/aq. NaOH solution using PTC (TEBA), furnished dichlorocyclopropane ether which was



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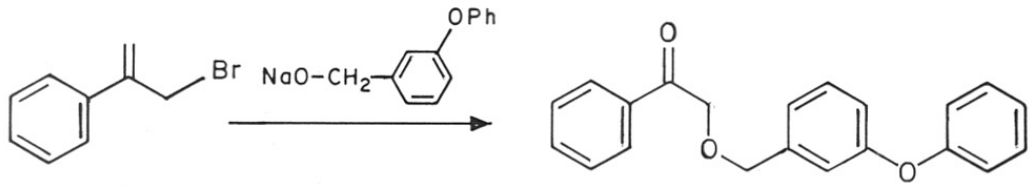
(24) (25)



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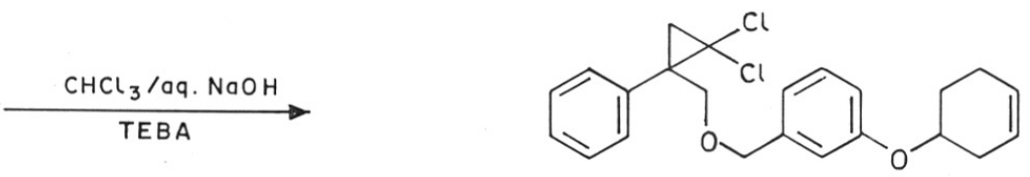

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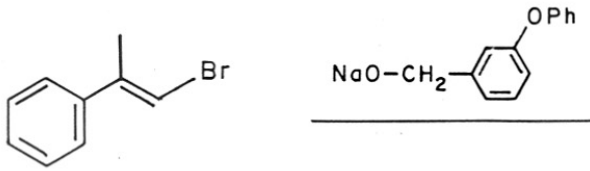

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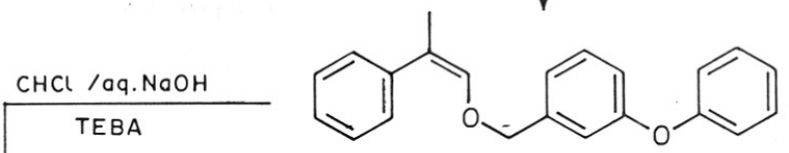

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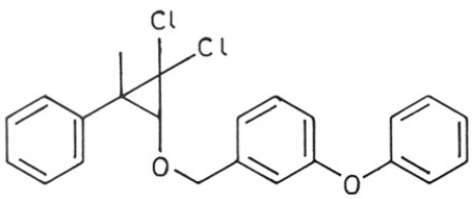

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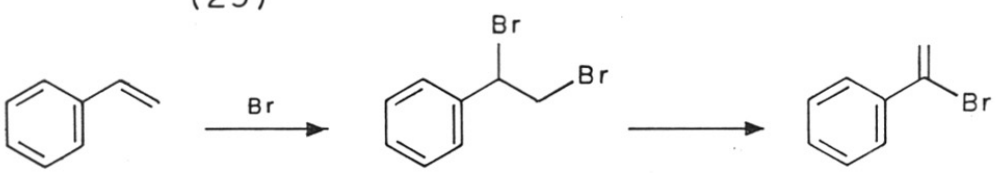
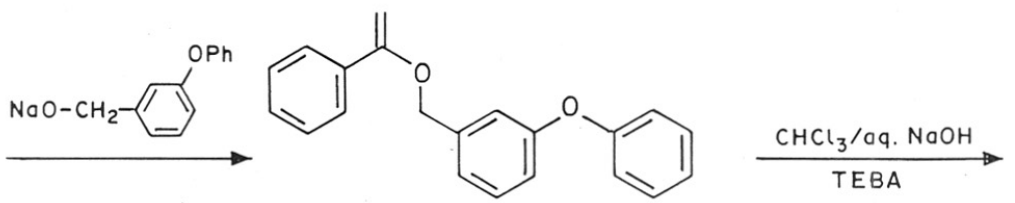


(30) (31) (32)



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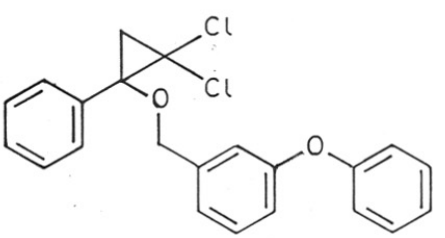


(34)

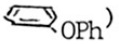
purified by column chromatography using alumina. Fraction eluted with pet ether benzene (1:1) mixture gave TLC pure ether (29) which showed mass spectrum peak at 199 m/z due to α-cleavage to the cyclopropane ring. By successive loss of HCl, m/z 163 and -Cl loss, m/z 128 producing strong peaks at these masses and IR (liquid film) bands at 1600, 1060 and PMR (CCl_4, δ) signals at 1.65 (3H, s, CH_3 at C-3), 2.15 (1H, brs, cyclopropane proton at C-1), 4.0 (2H, s, $-OCH_2$) and 6.7-7.35 (4H, m, aromatic protons).

Bromination of styrene (30) with liquid bromine in $CHCl_3$, yielded styrene dibromide (31) as a white crystalline solid m.p. 74°C, identified by its PMR (CCl_4, δ) signals at 4.0 (2H, m, $-CH_2Br$ protons), 5.07 (1H, m, CHBr proton) and 7.2 (5H, m, aromatic protons).

Dehydrobromination of styrene dibromide (31) with DMF and pot.acetate was carried out by distilling at 90-95° at 10 mm to get bromostyrene (32) as a yellowish liquid in 84% yield; C_8H_7Br which showed IR (liquid film) bands at 1640 cm^{-1} (c=c) and PMR (CCl_4, δ) signals at 5.7 (1H, m, olefinic proton),

6.05 (1H, m, other olefinic proton) and 7.1 - 7.7 (5H, m, aromatic protons).

Condensation of this styrene bromide (32) with sodium salt of m-phenoxybenzyl alcohol in dioxane under N_2 atmosphere, afforded ether (33) as a liquid purified by column chromatography using alumina. Fraction eluted with pet.ether + benzene (1:1) gave TLC pure ether (33) which showed IR (liquid film) bands at 1600 (aromatic), 1060, 890 and PMR (CCl_4,δ) signals at 4.5 (2H, s, $-OCH_2$), 5.7 (1H, m, olefinic proton), 6.05 (1H, m, other olefinic proton) and 6.5-7.65 (14H, m, aromatic protons).

Dichlorocyclopropanation of ether (33) using phase transfer catalyst (TEBA) with $CHCl_3$/aq. NaOH solution, furnished the final dichlorocyclopropane ether (34) as a yellowish oil; $C_{22}H_{18}Cl_2O_2$, M^+ 384 which showed insignificant molecular ion at m/z 384 (>0.1%). The spectrum showed base peak at (100%) m/z 183 was due to benzylic cleavage ($^+CH_2$-  $_{OPh}$) and showed strong peaks at 218, 264 m/z and IR (liquid film) bands at 1090 (C-O-C) and PMR (CCl_4, δ) signals at 2.3 (2H, s, cyclopropane proton at C-3), 4.5 (2H, s, $-OCH_2$ protons) and 6.6 - 7.5 (14H, brm, aromatic protons).

Four cyclopropane esters (10), (13), (19) and (21), and three insecticidal ethers (27), (29) and (34) were tested to study their insecticidal activity against Musca domestica (Houseflies). 2-3 days old adults of M.domestica were treated at the dose of 10μg/insect by topical application method. The mortality count was taken after 24 hrs. Minimum three replicates were taken for each compound. All these compounds were dissolved in AR grade acetone. For each test, the untreated flies were taken as control.

The results are summarised in the following table:

Sr.No.	Compound No.	% Mortality after 24 hrs. Musca domestica
1	(10)	20
2	(13)	45
3	(19)	40
4	(21)	35
5	(27)	45
6	(29)	40
7	(34)	20

These compounds may be tried for their possible miticidal activity as well as insecticidal activity against other insects of order diptera.

EXPERIMENTAL

Part A -

3-benzoyl-n-propanol (4)

Yield 56% (on the basis of 2), $C_{10}H_{12}O_2$, M^+ 164; IR (liquid film) : 3460 (OH), 1690 (c=o); PMR (CCl_4, δ): 1.6-2.1 (2H, m, $-CH_2-\underline{CH_2}-CH_2-OH$ protons), 2.9 (2H, t, J=6Hz, $-COCH_2$ protons), 3.6 (2H, t, J=6Hz, CH_2OH), 4.0 (1H, s, exchangeable with D_2O, OH proton), 6.0-7.67 (3H, m, aromatic protons), 7.7-8.1 (2H, m, aromatic ortho protons). Analysis calculated for $C_{10}H_{12}O_2$ C, 73.14, H, 7.37%. Observed C, 72.94; H, 7.15%.

2-hydroxy-2'-phenyl-5-pentanol (5)

A solution of keto alcohol (4) (2.7g 16.4 mmol) in dry ether (50ml) was introduced, dropwise, under stirring into ice-cold solution of CH_3MgI, prepared from magnesium turnings (0.6g 25mmol) and methyl iodide (1.8g, 25mmol) in dry ether (100ml). After the addition, it was stirred at room temperature for 2 hrs, then 2 hr under reflux and kept overnight. The reaction mixture was cooled to 0° and a cold saturated solution of NH_4Cl (100ml) was introduced dropwise with vigorous stirring. After stirring for 0.5 hr at room temperature, ethereal layer was

separated and the aqueous suspension extracted with ether (100ml x 2). The combined etheral layer was washed with water (100ml x 2), finally with brine, dried over anhydrous Na_2SO_4 and evaporated the solvent to furnish a diol (5, 2.6g, 89%) as a yellowish viscous oily liquid. IR (liquid film) bands at: 3448, PMR (CCl_4, δ) signals at: 1.43 (3H, s, $-CH_3$ protons). 1.6-2.1 (2H, m, $\underline{CH_2}-CH_2OH$), 2.95 (2H, t, J= 6 Hz, $\underline{CH_2}-CH_2-CH_2-OH$), 3.5 (2H, t, J= 6 Hz, $-CH_2OH$ protons), 4.1 (2H, brs, exchangeable with D_2O, 2x OH protons), 6.0-6.7 (5H, m, aromatic protons).

3-Phenyl-3-pentene-1-ol (6)

A solution of diol (5) (2.4g, 13 mmol) in dry benzene (50ml) was refluxed with catalytic PTSA (0.1g) for 12 hrs, using a Dean-Stark unit for removal of water. The reaction mixture was cooled, washed with water (100ml x 4), dried and evaporated to get (6) purified by chromatography over silica gel (45 g, 1:20) and eluted with pet-ether +5% benzene to give TLC pure (benzene) (6, 1.64g, 76%) which was converted into acetate (7). IR (liquid film) bands at: 1690,1600 PMR (CCl_4, δ) signals at: 1.97 (3H, s, acetate protons), 2.05 (3H, s, $-CH_3$ on double bond), 2.25-2.7 (2H, m, $=C-\underline{CH_2}-CH_2-OH$ protons), 4.1 (2H, t, J=8Hz,

adjascent to acetate function), 5.1 (1H, t, J=8Hz, olefinic proton) and 7.0-7.6 (5H, m, aromatic protons).

Analysis calculated for $C_{11}H_{14}O$, C, 81.44, H, 8.70%
Observed C, 81.32, H, 8.58%.

2,2-dichloro-3-methyl-3-phenyl-cyclopropane-1-acetate(8)

A mixture of acetate (7) (1.53g, 7.5mmol), 50% aqueous NaOH solution (25ml), chloroform (20ml) and catalytic amount of Triethyl benzyl ammonium bromide (TEBA, 0.1g) was stirred at 40° for 5 hr, diluted by water (50ml). Chloroform layer was separated, washed with water (50ml x 2), dil. HCl, again with water and finally with brine, dried, evaporated to get oily (8) liquid (1.75g, 82%). IR (liquid film) bands at 1690,1600 PMR (90 MHz, $CDCl_3$): 1.47 (3H, s , CH_3 at C-3), 1.6 (1H, t, cyclopropane proton at C-1), 1.82-1.98 (2H, m, $-CH_2-CH_2-OAc$), 2.1 (3H, s, acetate protons), 4.3 (2H, t, J Hz, $-CH_2$ adjascent to OAc gr.) and 7.8 (5H, m, aromatic protons).

Analysis calculated for $C_{14}H_{16}Cl_2O_2$; C, 58.74, H, 5.6. Cl, 24.5%. C, 58.59, 5.52, Cl, 24.39%.

P-anisoyl ester of 2,2-dichloro-3-phenyl-3-methyl-cyclopropane-1-ethanol (10)

The acetate (8, 2.4g) was dissolved in the solution of methanolic KOH (20 ml) and refluxed on

the water bath for 2 hr, cooled, diluted by water, extracted with ether. The ether layer was washed with water, dried evaporated to regenerate the alcohol(9)(2.1g, 8.6 mmol) which, in benzene, (25ml) was added at room temperature to the solution of freshly prepared p-anisoylchloride (1.70g, 10 mmol) in benzene (50ml). To this, added pyridene (1ml) and the mixture was stirred at room temperature overnight, washed with water (50ml x 2) 10% aq. sodium bicarbonate solution, brine, dried and evaporated the solvent. The crude ester was eluted over alumina column with pet-ether + benzene mixture (1:1) to **get TLC pure**(benzene) ester (10) (2.34 g, 72%) IR (liquid film) bands at: 1720. PMR (80 MHz, $CDCl_3$) signals at: 1.4 (3H, s, CH_3) 2.0-2.25 (3H, m, C-1 cyclopropane proton and adj. CH_2 protons), 3.85 (3H, s, OCH_3), 4.5 (2H, t, J= 4 Hz, OCH_2), 6.95 (2H, d, J= 7 Hz, anisoyl aromatic protons ortho to $-OCH_3$ gr) 7.3 (5H, brs, phenyl protons), 8.05 (2H, d, J= 7 Hz, anisoyl aromatic protons ortho to c=o gr). Analysis calculated for $C_{20}H_{20}Cl_2O_3$; C, 63.49, H, 5.29, Cl, 18.51. Observed C, 63.37, H, 5.23, Cl, 18.48%.

3-methyl-3-phenyl-cyclopropane-1-ethanol (11)

Zinc-copper couple was prepared by the method of Shank and Shechter[44]. Methylene iodide (5.36g, 20 mmol) and iodine (0.015g, 6 mmol) were added to a mixture of zinc-copper couple (1.63g of Zn, 25 mmole) and dry ether (25 ml) and stirred the mixture when iodine colour was disappeared immediately. The initial gray-coloured mixture was then refluxed for 30 minutes. During this period, the mixture turned darker accompanied by a gentle exothermic reaction. Alcohol (6 , 6.4g, 40 mmol) in dry ether (25ml) was added dropwise in 15 minutes and the mixture was refluxed for 30 hours. The mixture was then cooled and filtered through a super cell pad on a Buckner funnel. The residue was washed with ether (50ml x 2). The filterate was washed with 5% HCl (3 x 50ml) (to remove dissolved zinc iodide), aqueous sodium bicarbonate (3 x 50ml), brine, dried evaporated to get cyclopropane ethanol (11) (3.19 g, 46% yield). IR (liquid film) bands at: 3340 (OH), 1600 (aromatic) PMR (90 MHz, $CDCl_3$) 0.85-1.68 (5H, m, cyclopropane protons at C-1 and C-2 and CH_2 protons adj. to C-1), 1.35 (3H, s, $-CH_3$ at C-3), 3.9 (3H, s, $-OCH_3$ of anisoyl gr.), 4.15 (3H, t of $-CH_2OH$ overlapping -OH proton, 7.25 (5H, m, aromatic protons).

Analysis calculated for $C_{12}H_{16}O$; C, 81.77, H, 9.15%.
Observed C, 81.69, H, 9.06%.

p-Anisoyl ester of 3-methyl-3-phenyl-cyclopropane-1-ethanol (13)

Cyclopropane alcohol (11) (2.54g, 15 mmol) in benzene was added to the solution of freshly prepared p-anisoyl chloride (3.4g, 20mmol) in dry benzene. Pyridene was added (1ml) and the reaction mixture was stirred at room temperature overnight. It was washed with water (50ml x 2), 10% aqueous sodium biocarbonate solution, brine, dried and evaporated the solvent. The crude product was eluted over alumina column with pet-ether + benzene mixture (1:1) to get TLC (benzene) pure (13, 3.62g, 78% yield). IR (liquid film) bands at: 1740 (c=o) PMR (90 MHz, $CDCl_3$) : 0.87-1.7 (5H, m, cyclopropane proton at C-1 and C-2 and CH_2 adj. to C-1), 1.35 (3H, s, $-CH_3$ at C-3), 3.95 (3H, s, $-OCH_3$ of anisoyl gr.) 4.4 (2H, t, J=8 Hz, $-OCH_2$), 6.75-7.0 (2H, m, anisoyl aromatic proton ortho to $-OCH_3$), 7.3 (5H, brs, aromatic protons) and 7.75-8.05 (2H, m, anisoyl aromatic protons ortho to c=o group).
Analysis calculated for $C_{20}H_{22}O_3$, C, 77.39, H, 7.14%.
Observed C, 77.20, H, 7.08%.

2-benzoyl ethanol (16) : Viscous oily liquid

Yield 67%

IR (liquid film) bands at: 3460, 1696

PMR (CCl_4, δ) signals at: 3.0 (2H, t, J=7 Hz, $-COCH_2$), 3.6 (1H, brs, exchangeable with D_2O, -OH proton), 3.85 (2H, t, J= 7 Hz, $-OCH_2$), 7.0-7.3 (3H, m, aromatic protons), 7.5-8 (2H, m, aromatic ortho protons).

Analysis calculated for $C_9H_{10}O_2$; C, 71.98, H, 6.71%.

Observed C, 71.67, H, 6.61%.

3-phenyl-3-pentene-2-ol (17)

A mixture of sodium hydride (.36g, 15 mmole) and dry DMSO under N_2 atmosphere was heated at 75-80° with stirring for one hour or until evolution of H_2 gas ceases. The resulting solution of methyl sulfinyl carbanion was colled in ice-bath and ethyl triphenylphosphonium iodide salt (6.17g, 15 mmole) in DMSO (25ml) was added dropwise. A red coloured solution of ethylidene phosphorane was stirred at room temperature for 0.5 hr. Keto alcohol (16), (3.0g, 20 mmole) in DMSO (25 ml) was added to it and the reaction mixture was kept stirring at room temperature under N_2 atmosphere for 0.5 hr, then at 60° for 3 hr. and then kept stirring again at room temperature

overnight. Poured the reaction mixture onto crushed ice (100g). The dark coloured solid separated out was filtered. The filterate was extracted with ether. Ether layer was washed by water (100ml x 2), brine dried, evaporated to get (17) (1.36g, 42% yield), IR (liquid film) bands at 3460, 1595, PMR (CCl_4, δ) signals at: 2.0-2.3 (5H, m, d of CH_3 overlapping t of $-CH_2$ adj. to c=c), 3.4 (1H, brs, exchangeable with D_2O, OH proton), 4.0 (2H, t, $-CH_2OH$), 6.2 (1H, m, olefinic proton), 7.0-7.6 (5H, m, aromatic protons).
Analysis calculated for $C_{11}H_{14}O$; C, 81.44, H, 8.70%.
Observed C, 81.28, H, 8.59%.

2,2-Dichloro-3-methyl-1-phenyl-cyclopropane-1-ethanol (18)

A mixture of alcohol (17) (3.2g, 20 mmole) 50% aqueous NaOH solution (20ml) chloroform (25ml) and catalytic amount of TEBA (0.1g) was stirred at 60° for 5 hrs, cooled, diluted by water (50ml) chloroform layer was separated, washed with water (50ml x 2), dil. HCl, again with water, finally with brine, dried and evaporated to get oily iuqiid (3.8g 80% yield). IR (liquid film) bands at: 3460,1600 PMR (90 MHz, $CDCl_3$) signals at: 0.8 (3H, d, CH_3 at

C-3), 1.95 (2H, t, J=7 Hz, -CH_2 adj. to C-1), 3.5 (1H, brs, exchangeable with D_2O, OH proton), 4.0 (2H, t, J=6 Hz, CH_2OH protons), 7.2 - 7.8 (5H, m, aromatic protons).

Analysis calculated for $C_{12}H_{14}Cl_2O$, C, 59.01; H, 5.73; Cl, 28.68. Observed C, 58.88; H, 5.68; Cl, 28.49%.

p-Anisoyl ester of 2,2-dichloro-3-methyl-1-phenyl-cyclopropane-1-ethanol (19)

To the stirred solution of freshly prepared p-anisoyl chloride (18) (1.27 g, 7.5 mmole) in dry benzene (25 ml) was added alcohol (1.22 g, 5 mmole) in dry benzene (10 ml). Pyridene (1 ml) was then added and the reaction mixture was kept stirring at room temperature overnight. It was washed with water (50 ml x 2), 10%) aqueous sodium bicarbonate solution, brine, dried, evaporated. The crude ester was purified by eluting over alumina column with peth.ether + benzene mixture (1:1) to get pure solid ester (19), (1.37 g, 73% yield). IR(nujol) bands at: 1739, PMR (80 MHz, $CDCl_3$) signals at: 1.739, PMR (80 MHz, $CDCl_3$) signals at: 1.3 - 1.45 (4H, m -CH_3 protons overlapping cyclopropane proton at C-3), 2.0 (2H, t, J = 8 Hz, -CH_2 adj. to C-1), 3.65 (2H, t, J = 8 Hz, -OCH_2), 6.8 - 7.1 (2H, d, J=9Hz, anisoyl

aromatic protons ortho to -OCH_3 gr.). 7.3 (5H, brs, aromatic adjacent to C-1) 7.9 - 8.2 (2H, d, J = 9 Hz, anisoyl aromatic proton ortho to C=O group).
Analysis calculated for $C_{20}H_{20}Cl_2O_3$: C, 63.49, H, 5.29; Cl, 18.51. Observed C, 63.37; H, 5.21; Cl, 18.39%.

3-Methyl-1-phenyl-cyclopropane-1-ethanol (20)

Cyclopropanation of alcohol (17, 6.4 g, 40 mmol) was carried out using Zn-Cu couple (1.63 g, 25 mmol), iodine (.015 g mole), methylene iodide (5.36 g, 20 mmol) in dry ether (25 ml) by similar method described earlier to get cyclopropane ethanol (20) (3.0 g, 44% yield). IR (liquid film) bands at: 3380, 1600. PMR (90 MHz, $CDCl_3$) signals at: 0.87 - 1.8 (6H, m, -CH_3 and -CH at C-3 and cyclopropane protons at C-2), 2.0 (2H, t, J=6 Hz, -CH_2 adj. to C-1), 3.9 (3H, t, of -CH_2OH overlapping s of -OH proton), 7.15 (5H, brs, aromatic protons).
Analysis calculated for $C_{12}H_{16}O$: C, 81.77; H, 9.15%
Observed C, 81.63; H, 9.02%.

p-Anisoyl ester of 3-methyl-1-phenyl-cyclopropane-1-ethanol (21)

To the freshly prepared p-anisoyl chloride (1.27 g, 7.5 mmole) in dry benzene (25 ml) was added alcohol (20) (0.88 g, 5 mmol) in dry benzene and pyridene (1 ml) and the mixture was stirred at room temperature overnight.

It was washed with water (50 ml x 2), aqueous sodium bicarbonate, brine, dried, evaporated the solvent. The crude ester was purified by column chromatography using alumina and eluted with pet.ether + benzene mixture (1:1) to get TLC (benzene) pure ester (21, 0.9 g, 66% yield). IR (nujol)·bands at: 1738, 1595.

PMR (90 MHz, $CDCl_3$) signals at: 0.9 - 1.85 (8H, brm, cyclopropane protons at C-2, C-3 and CH_2 adj. to C-1 and CH_3 at C-3), 4.15 (2H, t, J=7 Hz, $-OCH_2$), 6.7 - 6.85 (2H, m, anisoyl aromatic ortho to $-OCH_3$), 7.25 (5H, brs, phenyl protons), 7.8 - 8.05 (2H, m, anisoyl aromatic proton ortho to C=O group).

Analysis calculated for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14%

Observed C, 77.18; H, 7.06%.

Part B -

1-Bromo-2-hydroxy-2-phenyl-propane (23)

To the cooled (5°-10°) solution of ∝-methyl styrene(22, 11.8g, 0.1 mole) in DMSO, was added pinchwise, freshly recrystallised N-bromosuccinimide (27g; 15 mole) during 0.5 hr. with vigorous stirring. After the addition, the reaction mixture was kept stirring overnight at room temperature, diluted by water (100ml) and kept stirring for another one hour (to decompose excess NBS). It was extracted with $CHCl_3$. Chloroform layer was washed by water (100ml x 3), brine, dried and evaporated to get yellowish oily liquid bromohydrin (23, 19.9g, 93% yield). IR (liquid film) bands at: 3448,3000, PMR (CCl_4, δ) signals at: 1.65 (3H, s, $-CH_3$), 3.0 (1H, brs, exchangeable with D_2O, OH proton), 3.7 (2H, s, $-CH_2Br$ protons) and 7.15-7.65 (5H, m, aromatic protons).
Analysis calculated for $C_9H_{11}BrO$; C, 50.23, Br,37.2
Observed C, 50.08, Br, 37.06%.

1-Bromo-2-phenyl-prop-1-ene (25)

To the ice-cold and stirred solution, Bromohydrin (23, 4.3g, 20 mmole) in pyridene (25ml) was

added phosphorous oxychloride (2.3g, 15 mmole). The reaction mixture was kept stirring at 0° for one hour and then at room temperature overnight. It was then poured onto the crushed ice (50g), extracted by ether (50ml). Ether layer was washed by water (50ml x 2), dil. HCl, again with water and finally with brine, dried and evaporated to get isomeric mixture of unsaturated compounds which was separated and purified by column chromatography using silica gel impregnated with 10% $AgNO_3$. Earlier fractions eluted with pet-ether gave pure (25, 1.42g) which showed spectral data as follows: IR Liquid film) bands at: 1600, 1595, 1500, 835, 700 PMR (CCl_4, δ) signals at: 2.2 (3H, s, CH_3 protons), 6.45 (1H, s, olefinic proton) and 7.1-7.6 (5H, m, aromatic protons).

Analysis calculated for C_9H_9Br, C, 54.82, H, 4.56, Br, 40.60. Observed C, 54.78, H, 4.39, Br, 40.53%.

1-Bromo-2-phenyl-prop-2-ene (24)

Later fractions from the above isomeric mixture eluted with pet-ether + benzene (1:1) gave TLC pure (24) (1.87g) and showed IR (liquid film) bands at:1600 1595, 890, PMR (CCl_4, δ) signals at: 4.35 (2H, s, $-CH_2Br$ protons), 5.5 (2H, d, J=4Hz, exo protons)

and 7.2-7.7 (5H, m, aromatic protons).
Analysis calculated for C_9H_9Br; C, 54.82, H, 4.56, Br, 40.53%.
Observed C, 54.79, H, 4.50, Br, 40.47%.

m-Phenoxybenzyl ether of 1-hydroxy-2-phenyl-prop-2-ene (26)

In a 3-necked 100ml round bottom flask fitted with refluxing condensor, N_2 inlet tube and a dropping funnel was added dry 1,4-dioxane (10ml), sodium metal (120mg, 5 mmole) and m-phenoxybenzyl alcohol (1.0g, 5 mmole) and the mixture was refluxed in N_2 atmosphere for 5 hr., till all Na-metal was dissolved. The reaction mixture was cooled at room temperature, added dioxane (10ml) solution of (24) (.985g, 5 mmole) and the mixture was again heated to reflux for 4 hrs, cooled, diluted with water, extracted with ether (50ml). Ether layer was washed with water (50ml x 3), dried, evaporated. The crude ether (26) was eluted over alumina with pet-ether + benzene mixture (1:1) to get TLC (benzene) pure ether (26, 0.94g, 62% yield).
IR (liquid film) bands at: 1600, 1456, 1080, 895.
PMR (CCl_4, δ) signals at: 4.4 (2H, s, $-OCH_2$ protons), 4.55 (2H, s, OCH_2 benzylic protons), 5.3 (1H, d, J= Hz,

exo proton), 5.5 (1H, d, J= Hz, other exo-proton), 6.8-7.55 (14H, brm, aromatic protons).
Analysis calculated for $C_{21}H_{20}O_2$, C, 82.86, H, 6.62%.
Observed C, 82.79, H, 6.49%.

m-Phenoxybenzyl ether of β-hydroxy-α-methyl styrene (28)

Etherification was carried out by refluxing the dioxane solution of isomer (25) (1.0g, 5.1 mmole) and sodium salt of m-phenoxybenzyl alcohol (1.1g, 5.1 mmole) under N_2 atmosphere by the similar method already described before, to get ether, which was purified by column chromatography using alumina. Fraction eluted with pet-ether + benzene mixture (1:1) afforded TLC (benzene) pure ether (28, 0.79g, 47% yield). IR (liquid film) bands at:1600,1065, 835 PMR (CCl_4, δ) signals at: 2.1 (3H, s, $-CH_3$ protons), 4.55 (2H, s, $-OCH_2$ protons), 6.3-6.5 (2H, m, olefinic proton), 6.7-7.4 (14H, m, aromatic protons).
Analysis calculated for $C_{21}H_{20}O$; C, 87.46, H, 6.99%.
Observed C, 87.29, H, 6.71%.

m-Phenoxybenzyl ether of 2,2-dichloro-1-phenyl-cyclopropane-1-methanol (27)

A mixture of ether (26), (0.608g, 2 mmole), chloroform (20ml), 50% NaOH solution (20ml) and catalytic amount of triethyl benzyl ammonium bromide (TEBA,

50 mg) was heated at 60° for 4 hr. It was cooled, washed by water (25ml x 2), brine, dried and evaporated to get crude product which was purified by column chromatography over alumina. Fractions eluted with 25% benzene in pet-ether gave TLC (benzene) pure dicyclopropane ether as a liquid (27, 0.676g, 85%). IR (liquid film) bands at: 1600, 1090 PMR (CCl_4, δ) signals at: 1.55-1.9 (2H, 2d, overlapping cyclopropane protons at C-3), 3.7 (2H, s, $-OCH_2$ protons); 4.27 (2H, s, OCH_2 benzylic protons) and 6.7-7.45 (14H, brm, aromatic protons). Analysis calculated for $C_{23}H_{20}Cl_2O_2$; C, 69.34; Cl, 17.58. Observed C, 69.28, Cl, 17.39%.

m-phenoxybenzyl ether of 2,2-dichloro-3-methyl-3'-phenyl-cyclopropane-1-ol (29)

A mixture of ether (28) (0.912g, 3.3 mmol), chloroform (20ml), 50% aq. NaOH solution (20ml) and TEBA (50mg) was heated between 60-65° for 4 hrs. It was cooled, washed with water (25ml x 2), brine, dried and evaporated. The crude ether was eluted with 50% benzene in pet-ether over alumina to get oily liquid (29) (0.91g, 77% yield).
IR (liquid film) bands at: 1600, 1450, 1218.
PMR (CCl_4, δ) signals at: 1.65 (3H, s, $-CH_3$ at C-3),

2.15 (1H, brs, cyclopropane proton at C-1), 4.0 (2H, s, $-OCH_2$), 6.7 - 7.35 (14H, m, aromatic proton).

Analysis calculated for $C_{23}H_{20}Cl_2O_2$: C, 69.34; Cl, 17.58.

Observed C, 69.25; Cl, 17.52%.

(1,2-Dibromoethyl) benzene (31)

To an ice-cooled and stirring solution of styrene (30) (20 g, 0.19 mmole) in chloroform (25 ml) was added dropwise bromine (32 g, 0.2 mmole) in chloroform (25 ml) maintaining temperature 5-10°C until bromine colour persisted (45 minutes). The reaction mixture was further stirred for 15 minutes and to it was added saturated aqueous solution of sodium bisulfite and stirred further for 15 minutes. Chloroform layer was separated and washed with water (100 ml x 2) brine, dried and evaporated to get white solid dibromide (31, 45.8 g, 90% yield) m.p. 73-74°C.

PMR (CCl_4, δ) signals at: 4.0 (2H, m $-CH_2$ Br protons) 5.07 (1H, m, CHBr proton) 7.2 (5H, m, aromatic proton).

Analysis calculated for $C_8H_8Br_2$: C, 36.36; Br, 60.60%.

Observed C, 36.18; Br, 60.48%.

1-Bromo-1-phenylethylene (32)

A mixture of dibromostyrene (31) (5.28 g, 0.2 mmole) and dimethyl formamide (1.77 g, 0.3 mole) in DMSO (20 ml) was heated in a 50 ml RB flask fitted with distillation condensor under vacuum (10 mm). Fraction distilled between 95-100° at 10 mm afforded (32) (3.18 g, 87% yield).

IR (liquid film) bands at: 1640.

PMR (CCl_4, δ) signals at: 5.7 (1H, m, olefinic proton), 6.05 (1H, m, other olefinic proton) and 7.1 - 7.7 (5H, m, aromatic protons).

Analysis calculated for C_8H_7Br: C, 52.45; Br,43.71%.

Observed C, 52.37; Br, 43.62%.

m-Phenoxybenzyl ether of α-hydroxy styrene (33)

Etherification was carried out by refluxing dioxane (20 ml) solution of α-bromostyrene (32, 0.915 g, 5 mmole) and sodium salt of m-phenoxy benzyl alcohol (1.1 g, 5 mmole) under N_2 atmosphere by the similar method described earlier to get crude ether which was purified by column chromatography using (neutral). Fractions eluted with pet.ether + benzene mixture (1:1) gave TLC (5% ethylacetate in pet.ether) pure ether (33, 0.785 g, 52% yield) as a liquid.

IR (liquid film) bands at: 1600, 890, PMR (CCl_4, δ) signals at:4.5 (2H, s, $-OCH_2$), 5.7 (1H, m, oxo-proton), 6.05 (1H, m, other oxo-proton) and 6.5 - 7.65 (14H, brm , aromatic protons).

Analysis calculated for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00%.

Observed C, 83.28; H, 5.86%.

m-Phenoxybenzyl ether of 2,2-dichloro-1-phenyl cyclopropane-1-ol (34)

A mixture of ether (33) (1.0 g, 3.2 mmole) chloroform (20 ml), 50% aqueous NaOH solution (20 ml) and catalytic TEBA (50 mg) was heated between 60-65°C for 4 hours. It was cooled, washed with water (25 ml x 2), brine, dried and evaporated. The crude ether (34) was eluted with 30% benzene in pet.ether over alumina to get pure ether as oily liquid (34, 1.02 g, 81% yield). IR (liquid film) bands at: 1600, 1090.

PMR (CCl_4, δ) signals at: 2.3 (2H, s, cyclopropane protons at C-3), 4.5 (2H, s, $-OCH_2$ protons) and 6.6 - 7.5 (14H, brm, aromatic protons).

Analysis calculated for $C_{22}H_{18}Cl_2O_2$: C, 68.75; Cl, 18.22%.

Observed C, 68.68; Cl, 18.08%.

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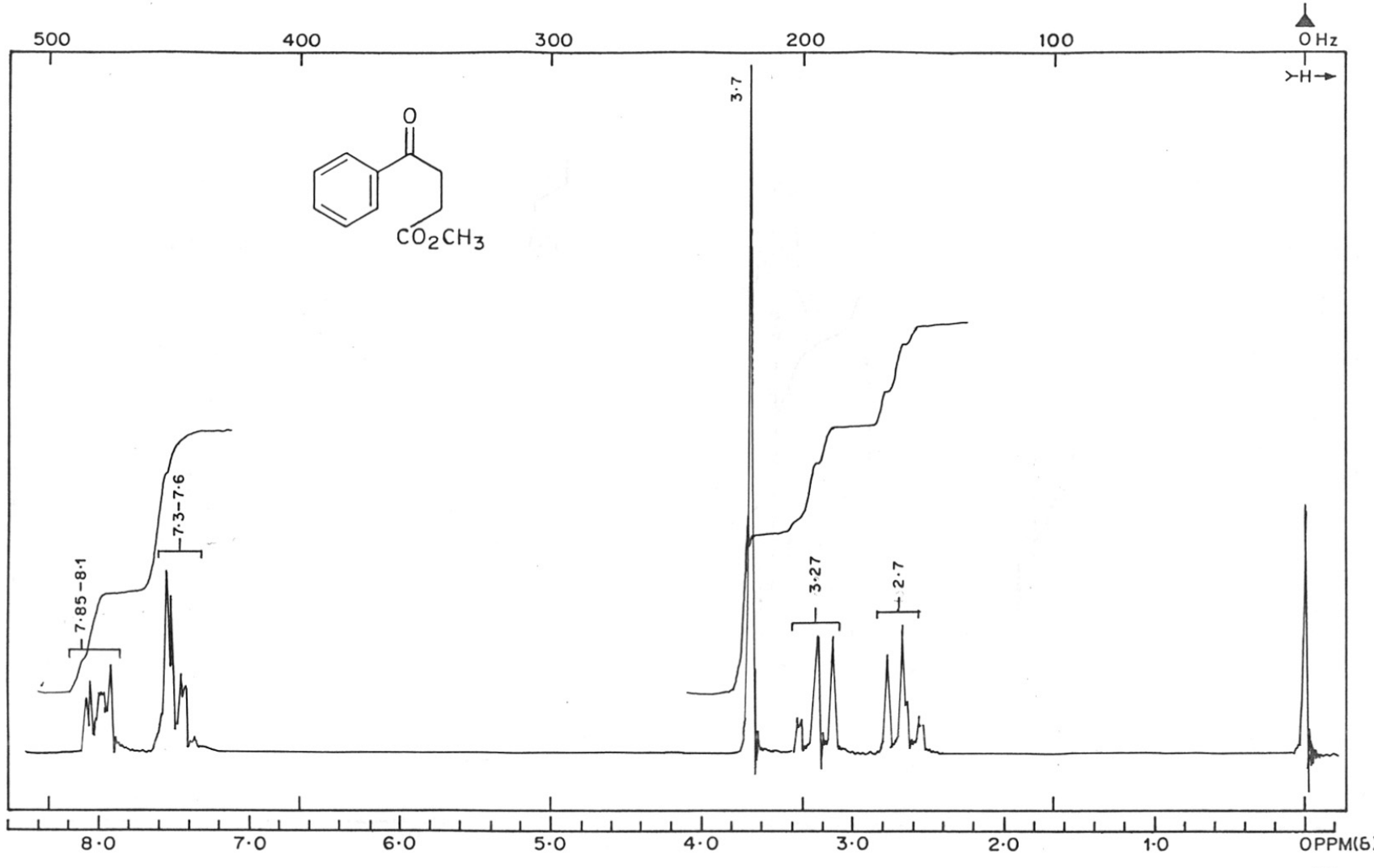
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100
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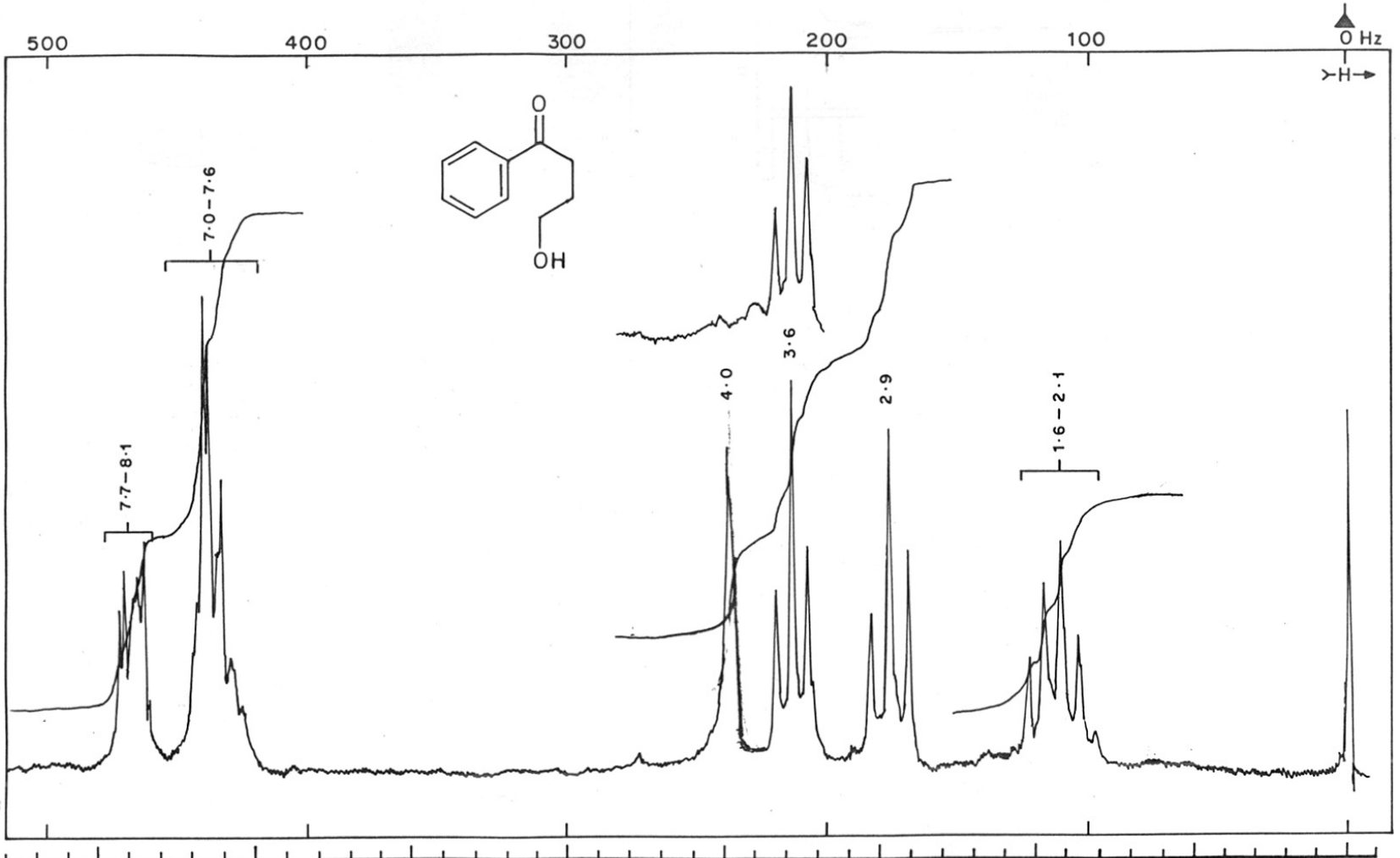
TMS
O
CO2CH3
3·7
7·85-8·1
7·3-7·6
3·27
2·7
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE 2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400
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100
0 Hz
δH
O
OH
7·0 – 7·6
7·7 – 8·1
4·0
3·6
2·9
1·6 – 2·1
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

FIGURE 4

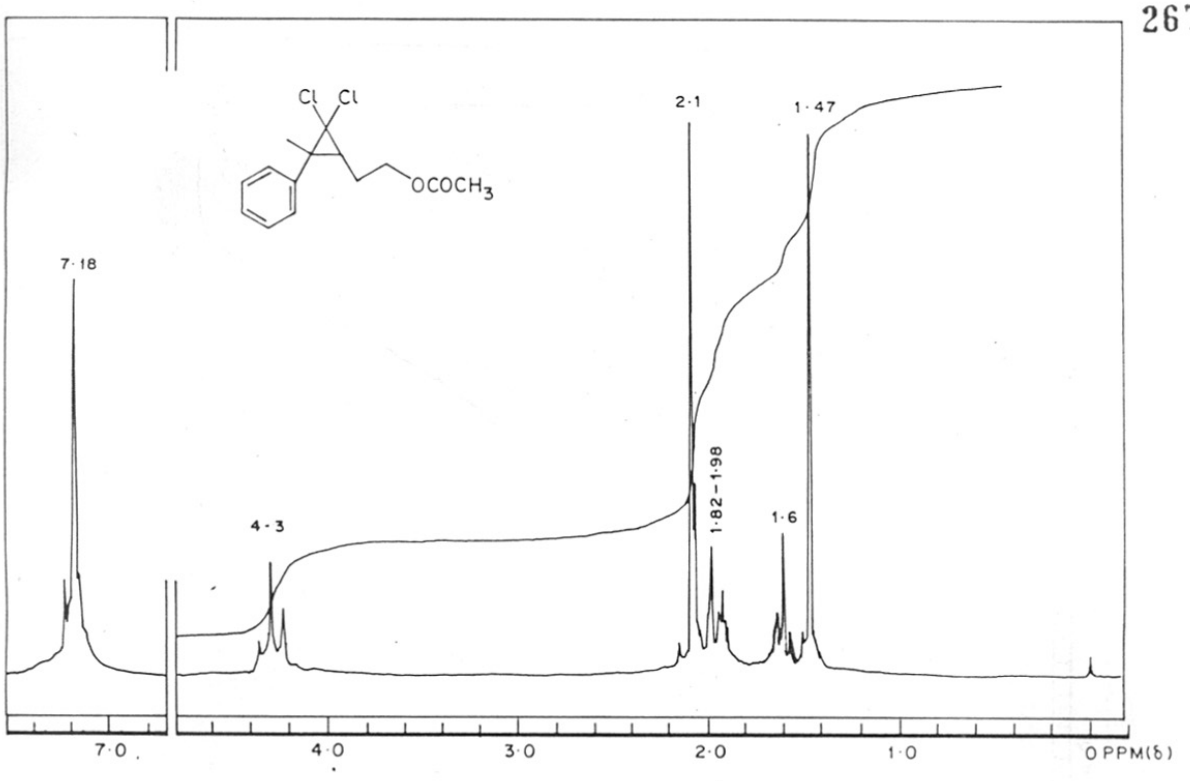


FIGURE 8

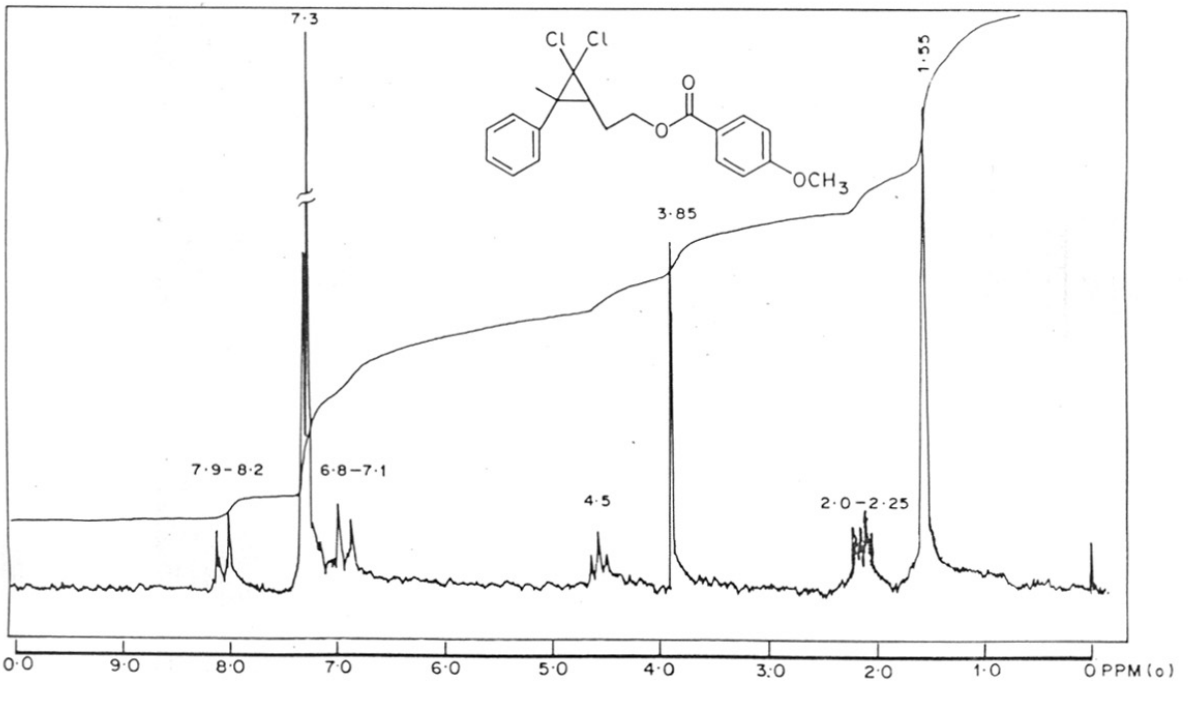


FIGURE 10

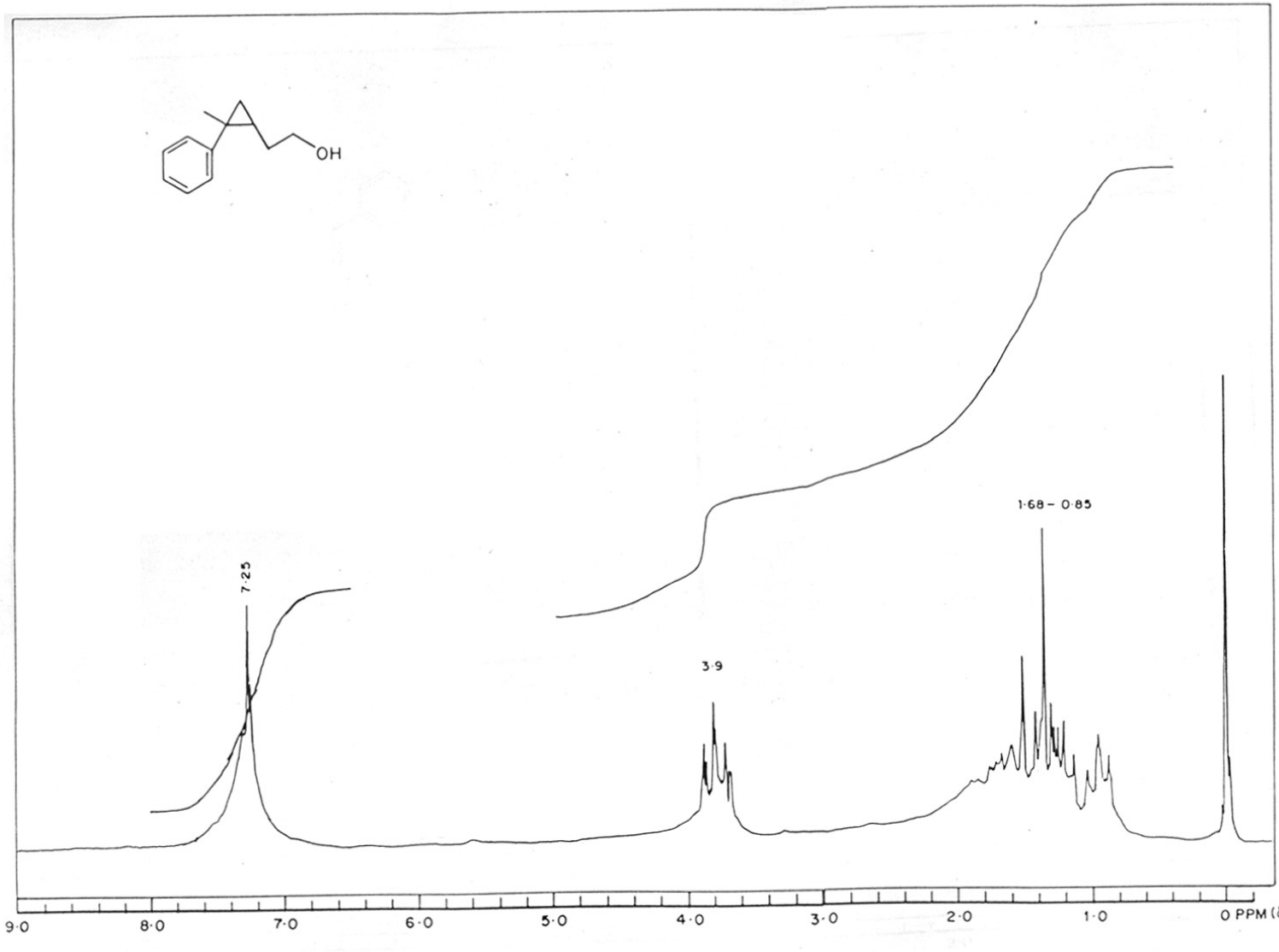
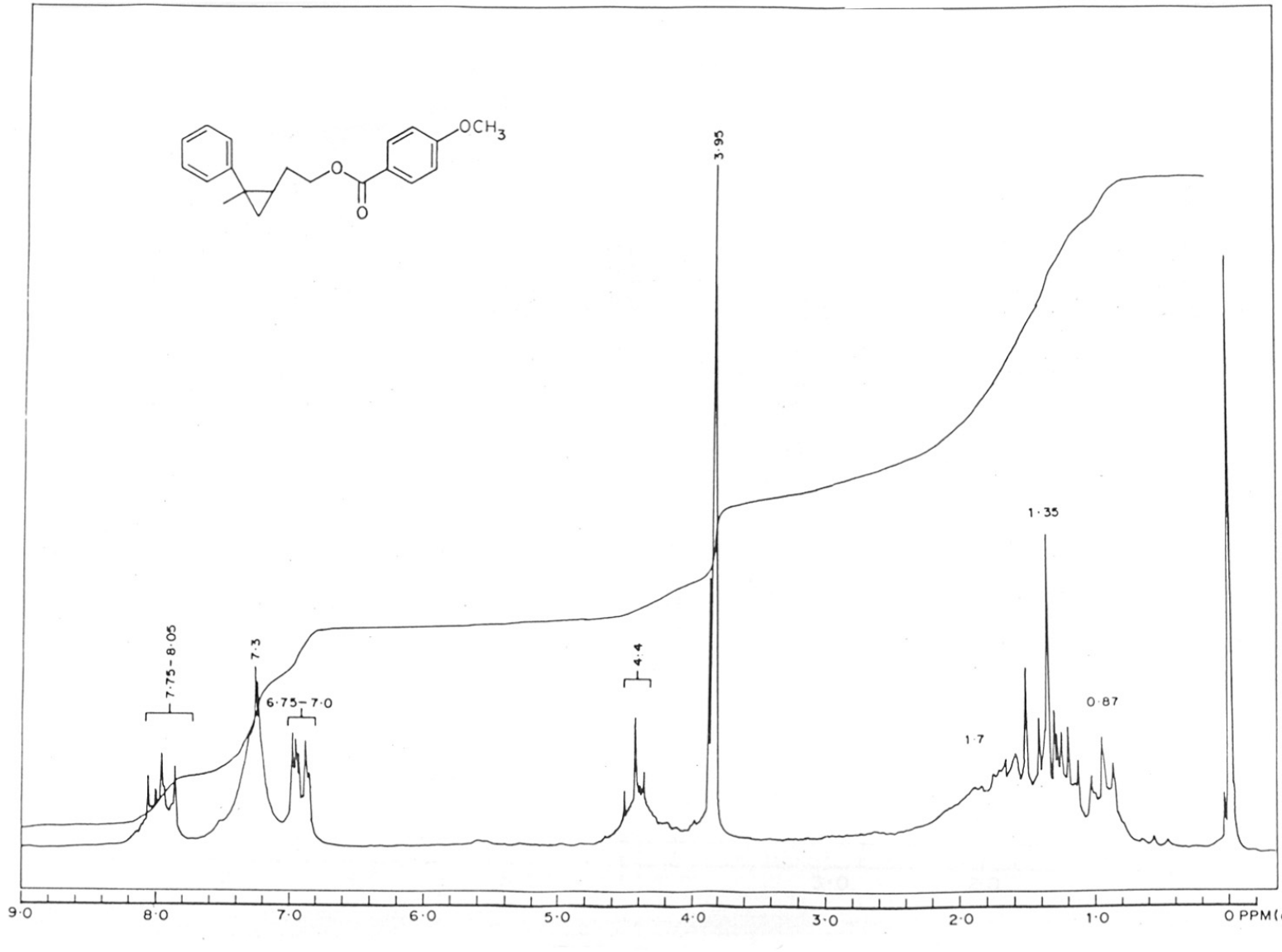


FIGURE 11


OCH3
O
O
3·95
1·35
0·87
1·7
4·4
7·3
7·75-8·05
6·75-7·0
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8·0
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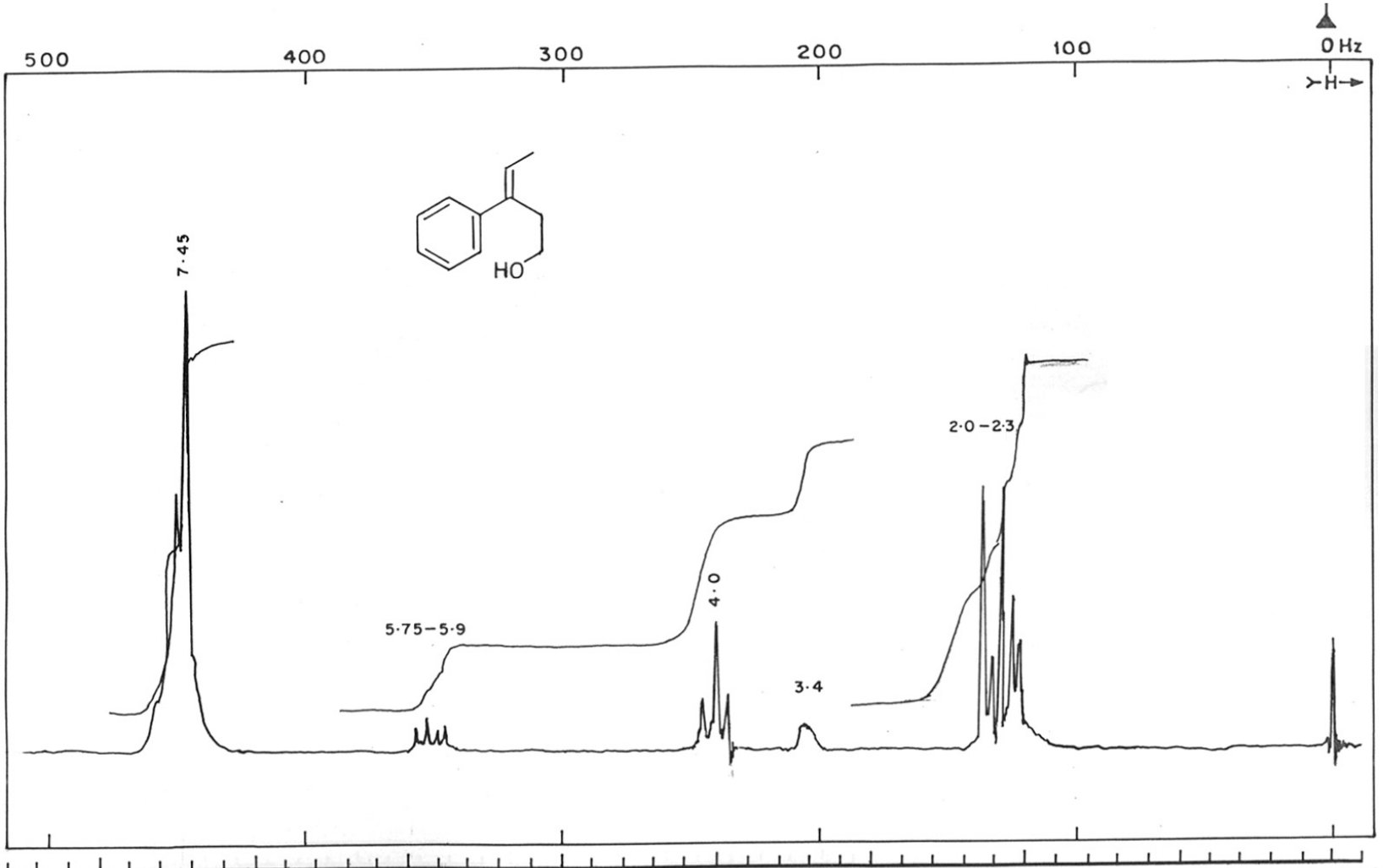
5·0
4·0
3·0
2·0
1·0
0 PPM(o)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HO
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3·4
2·0–2·3
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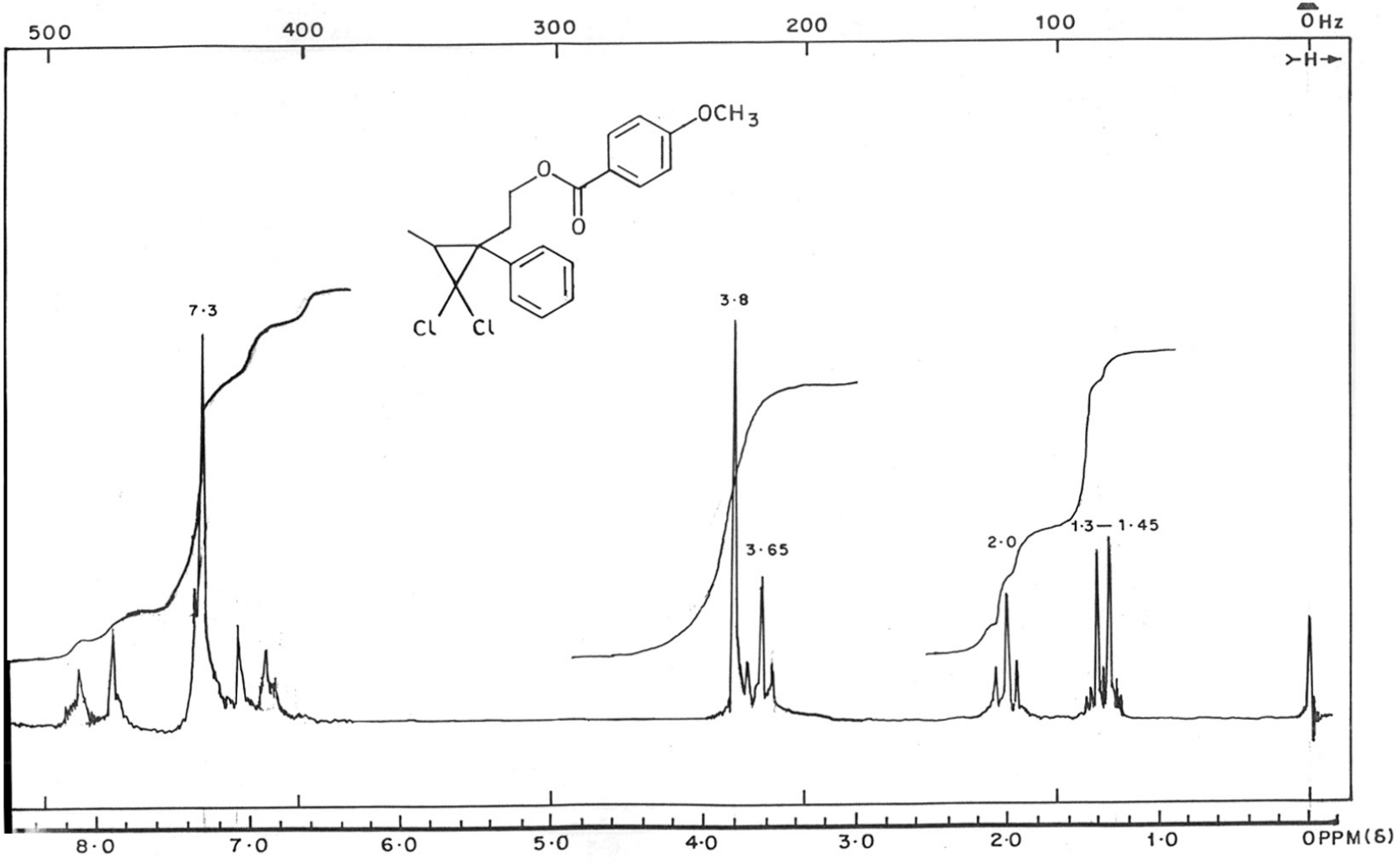
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

FIGURE 17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400
300
200
100
0 Hz
→H→
OCH3
O
O
Cl
Cl
7·3
3·8
3·65
2·0
1·3—1·45
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ)

FIGURE 19

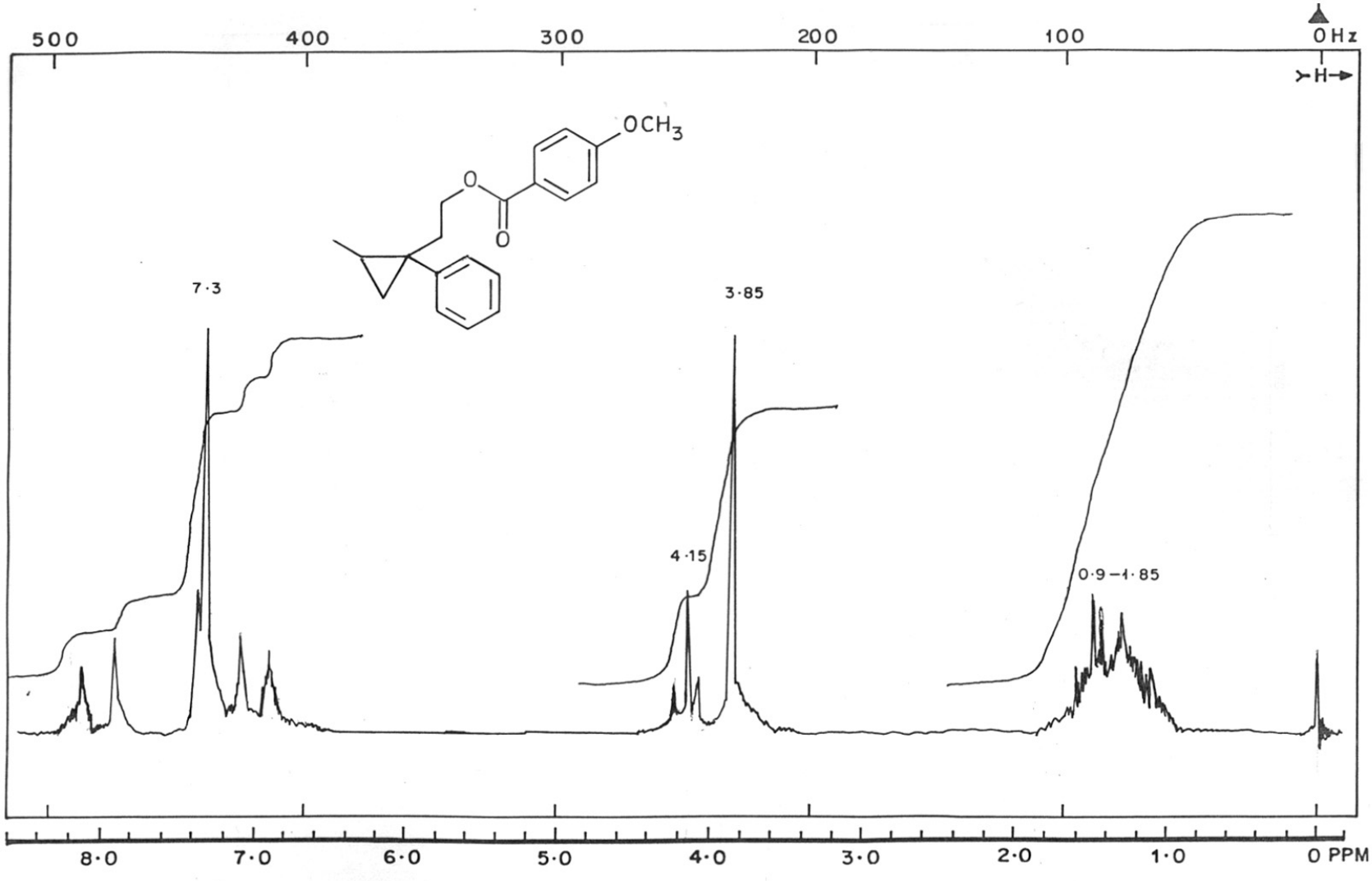

500
400
300
200
100
0 Hz
Y-H→
OCH3
O
O
7·3
3·85
4·15
0·9–1·85
8·0
7·0
6·0
5·0
4·0
3·0
2·0
1·0
0 PPM(δ

FIGURE 21

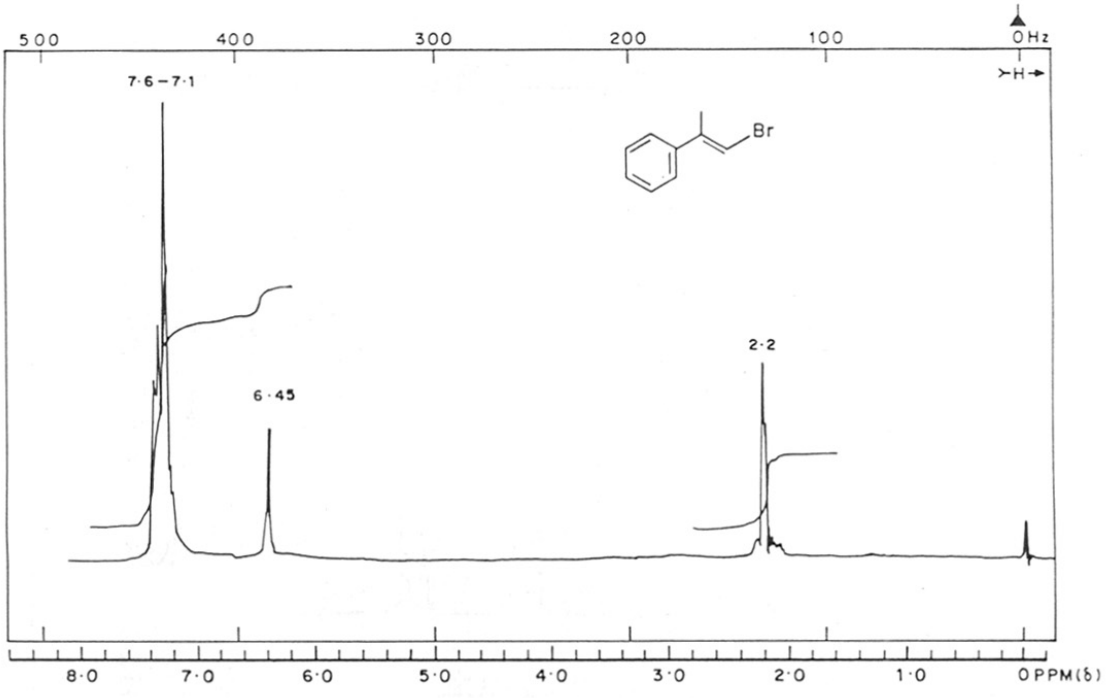
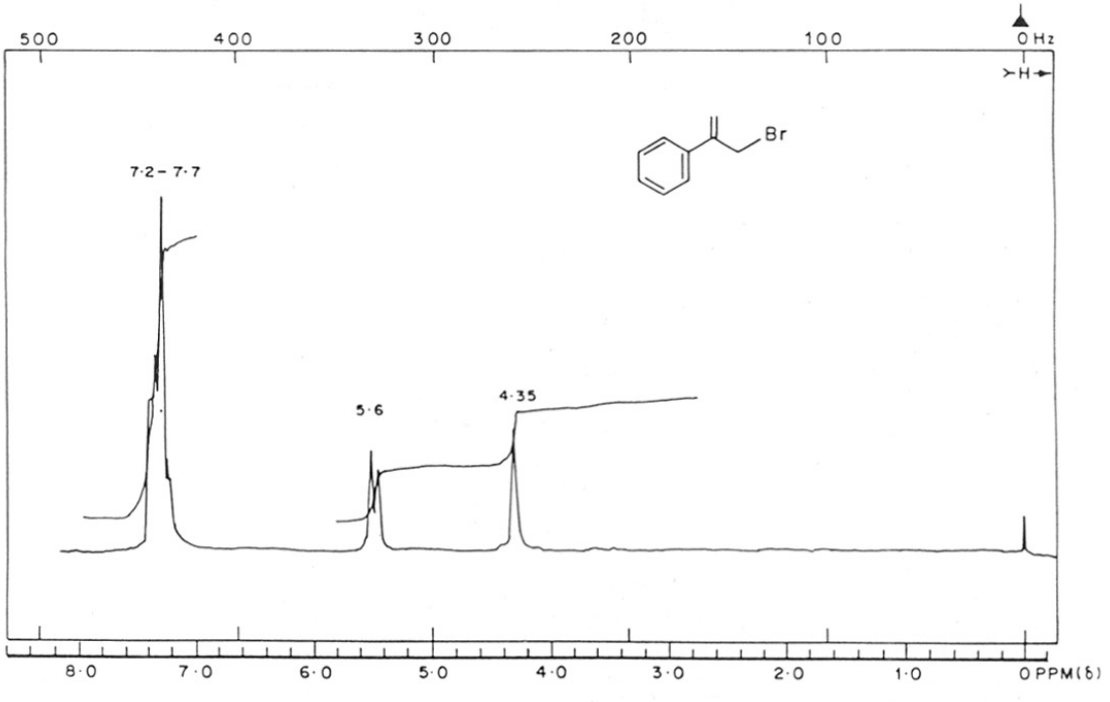


FIGURE 25



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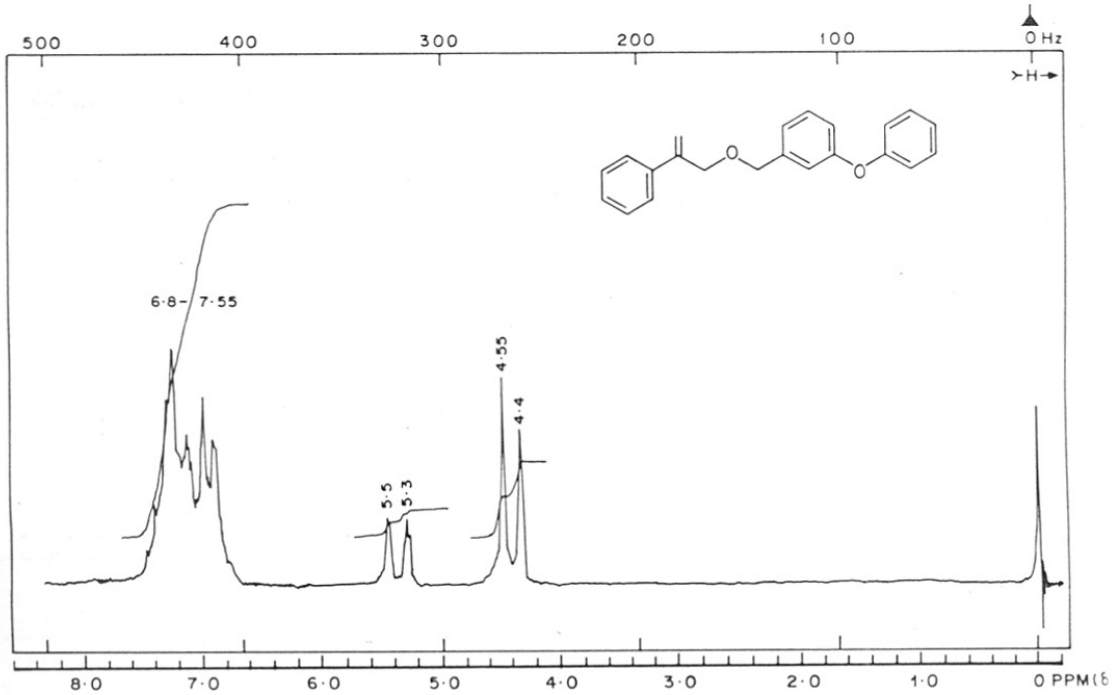

FIGURE 26

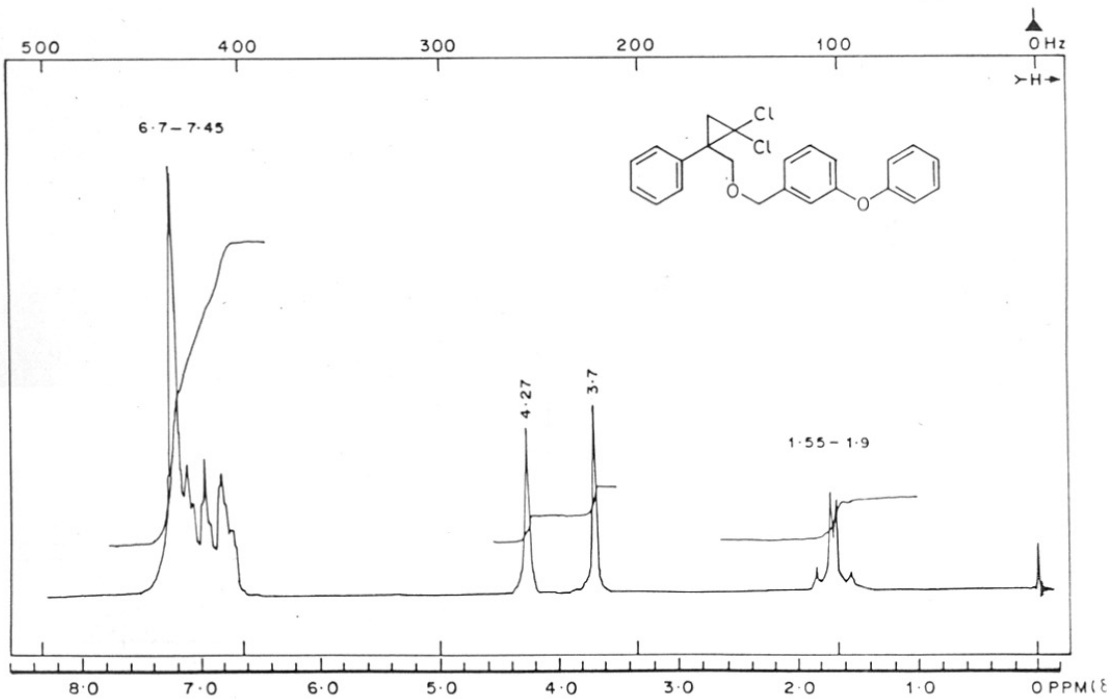

FIGURE 27

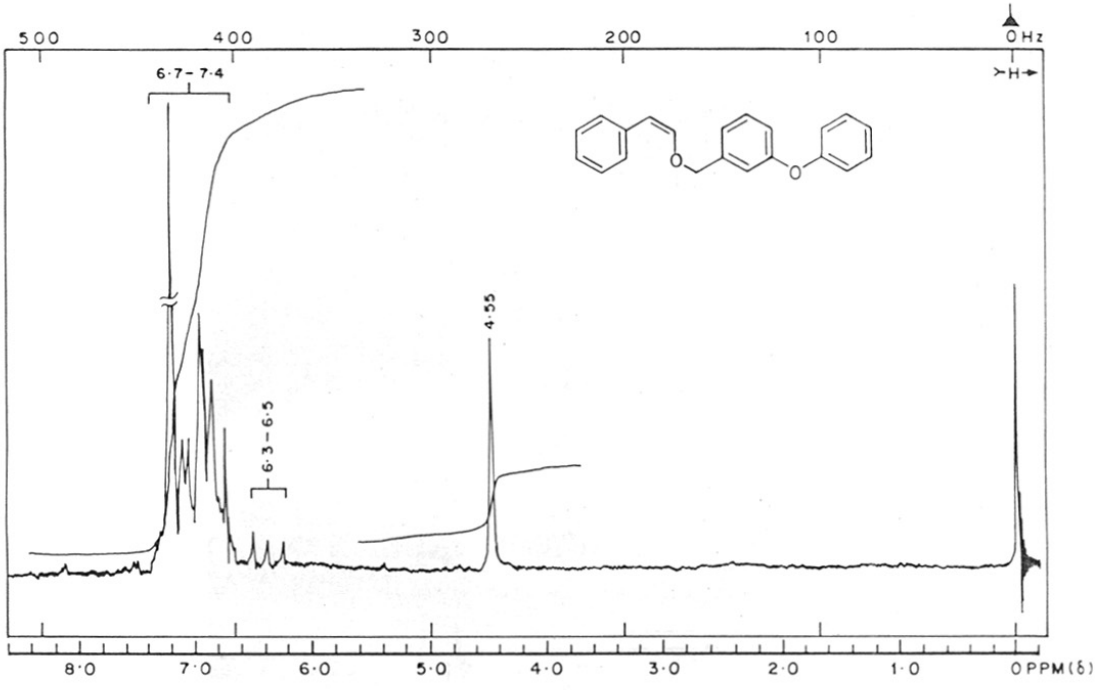

FIGURE 28

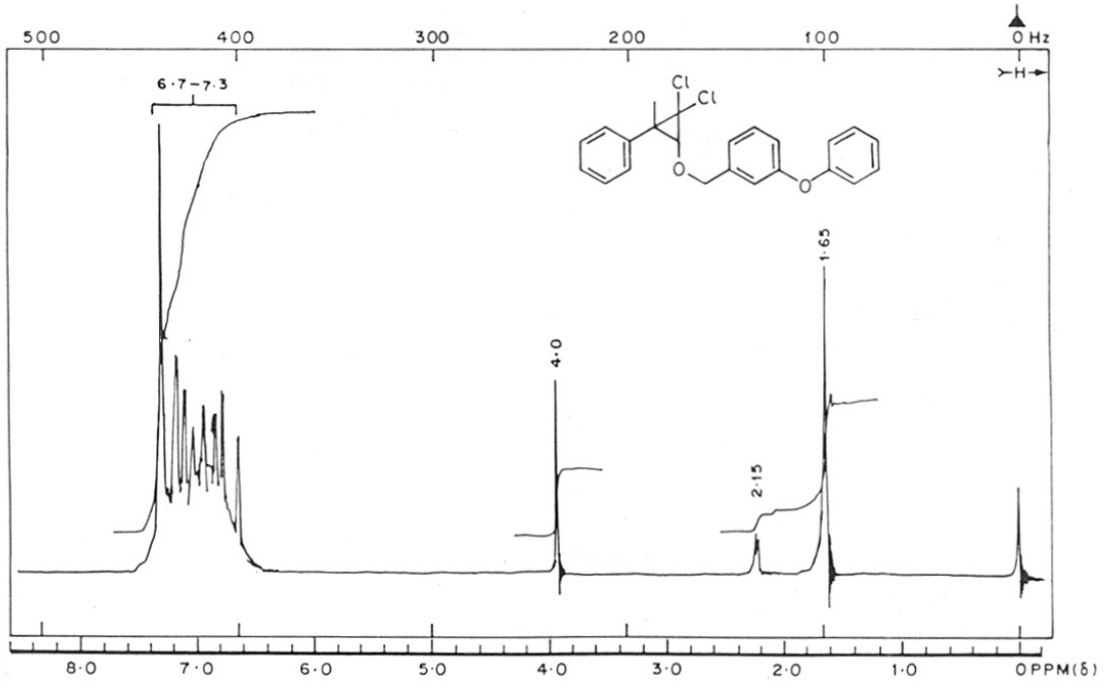

FIGURE 29

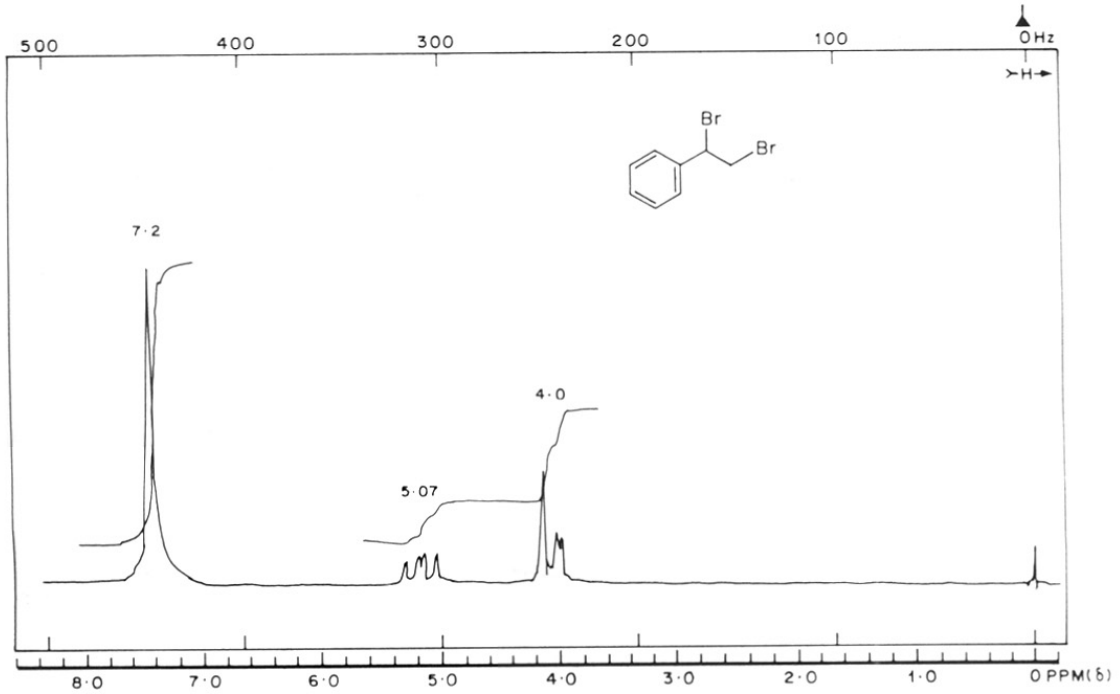

FIGURE 31

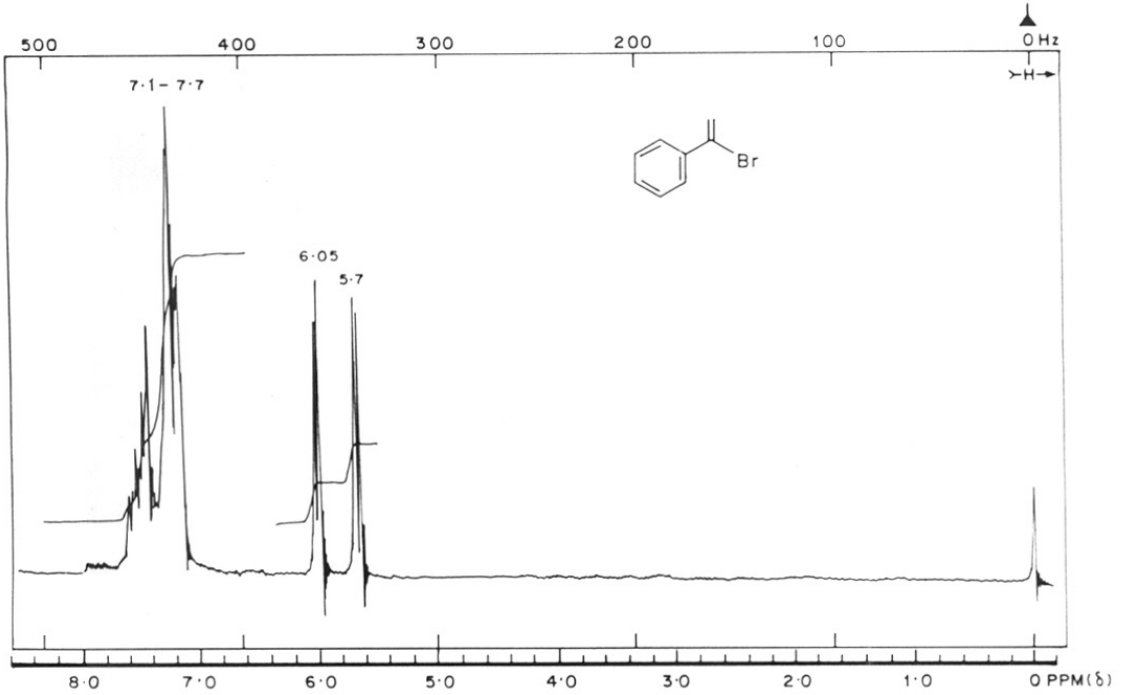

FIGURE 32

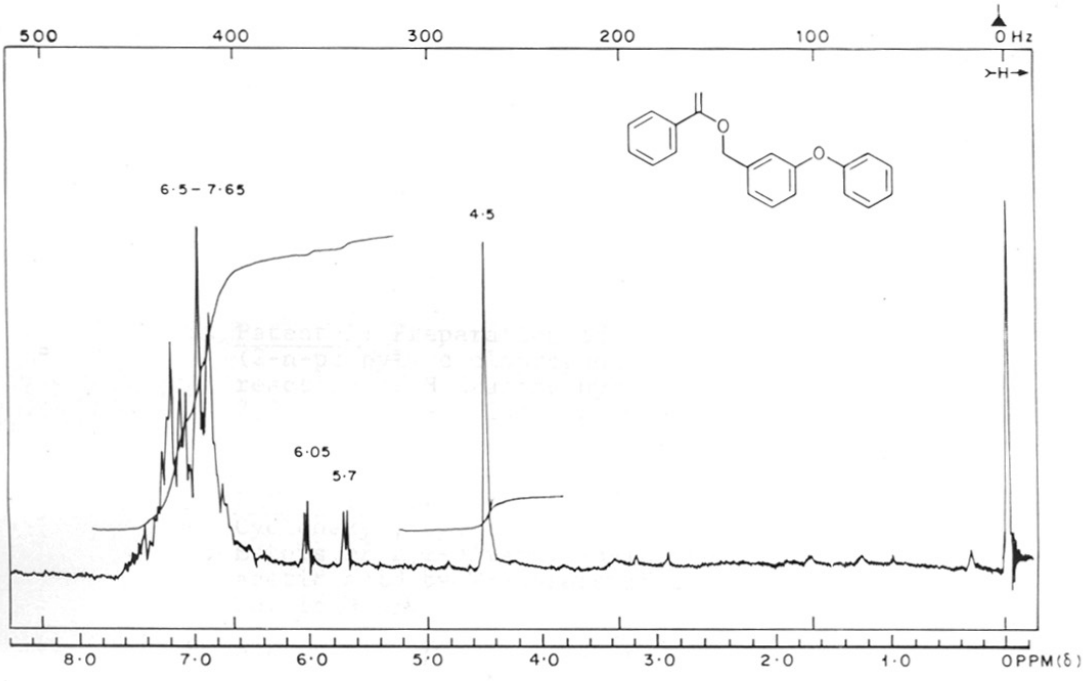

FIGURE 33

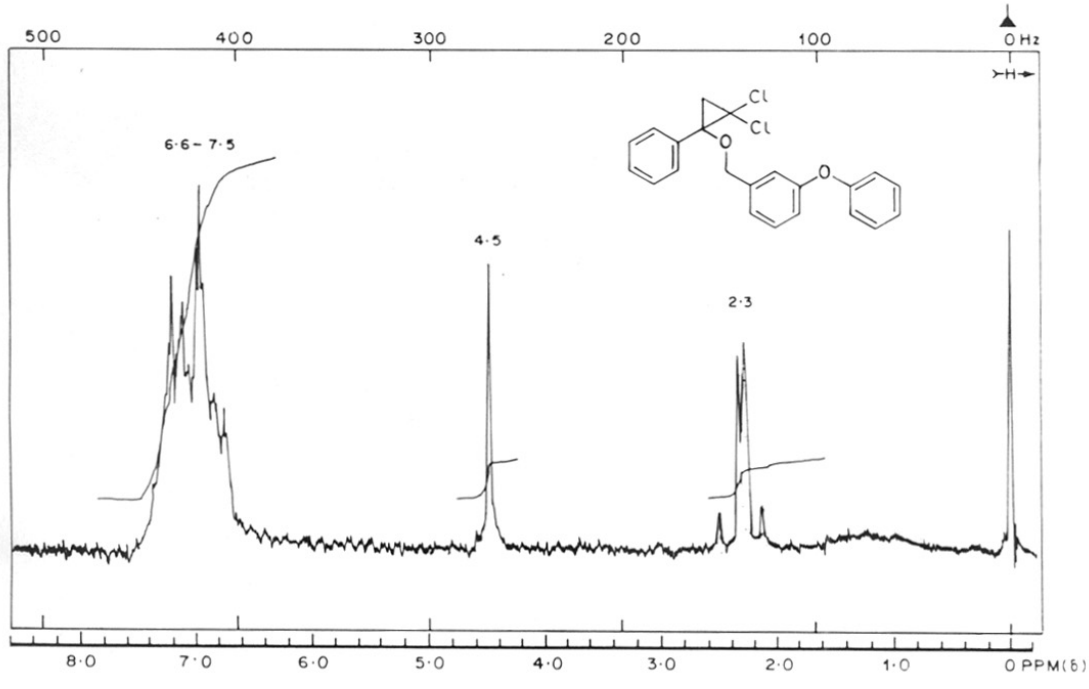

FIGURE 34

Number of Publications

1. Patent I: Preparation of 2,2-dimethyl-3-(2-n-propyl) cyclopropane acetic acid by reaction of Hydrazine hydrate with 2,2-dimethyl-3-(2-oxo-propyl) cyclopropane acetic acid. No.115/DEL/84.

2. Patent II: Preparation of substituted Alkyl, Cyclohexyl, cyclohexylalkyl, Aralky, Aryloxyalkyl. Esters of 2,2-dimethyl-3-(n.propyl) cyclopropane acetic acid by Transesterification. No.116/DEL/84.

3. Patent III: Preparation of substituted alkyl, cyclohexyl, cyclohexylalkyl, aryl, aralkyl esters of 2,2-dimethyl-3-(2-oxopropyl) cyclopropane acetic acid and 2,2-dimethyl-3-(2-propyl) cyclopropane acetic acid derived from (+)-3-carene as potential miticides by reaction with thionyl chloride. No.191/DEL/84.

4. Paper on: Synthesis of some key intermediates useful for the synthesis of biologically active cyclopropane carboxylates is being communicated.

5. Paper on: Total synthesis of cyclopropane insecticides to be communicated.