SYNTHETIC TRANSFORMATIONS LEADING TO BIOLOGICALLY ACTIVE COMPOUNDS

A THESIS
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IN CHEMISTRY

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Dedicated to my parents and teachers

C E R T I F I C A T E

Certified that the work incorporated in the thesis "Synthetic Transformation Leading to Biologically Active Compounds" submitted by Shri Ramnarayan Satyanarayan Randad was carried out by the candidate under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

(Dr.G.H. Kulkarni)
Supervisor

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

It is a matter of great pride for me to thank Dr. Gurunath Hanmanthrao Kulkarni, Scientist, National Chemical Laboratory, Poona, for suggesting problems, his invaluable guidance and constant encouragement throughout the course of this investigation.

My thanks are also due to Drs. K.G. Gore, B.M. Bhawal, senior staff members of the Division of Organic Chemistry (I), and to my colleagues for their cheerful and ungruding co-operation.

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I am thankful to the CSIR, New Delhi, for the award of research fellowship.

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(R.S. Randad)

National Chemical Laboratory,
Poona-411008

C O N T E N T S

CHAPTER-I

SYNTHESIS OF POTENT 2,3-SECO-PYRETHROIDS

GENERAL REMARKS

1. All melting points and boiling points are uncorrected.
2. All temperatures are recorded on the Centigrade scale..
3. Unless otherwise stated, all rotations were taken in chloroform solutions. Concentrations are expressed in g/100 ml of the solution.
4. The infrared spectra of liquids were recorded as liquid films and that of solids as nujol mulls on a Perkin-Elmer infracord spectrophotometer model 137-B, and Perkin-Elmer infracord spectrophotometer model 599-B using sodium chloride optics.
5. Unless otherwise stated, all PMR spectra were taken in carbontetrachloride solution, using tetramethylsilane as the internal reference on a T-60 MHz Varian instrument, and in $CDCl_3$ solution on FT-80A (Varian 80 MHz FT PMR spectrometer), WH-90 (Bruker 90 MHz FT PMR spectrometer) and the chemical shifts are measured in units.
6. The mass spectra were recorded on a CEC-21-110B mass spectrometer.
7. Acid washed activated alumina standardised as per Brockmann's procedure and silicic acid for chromatographic purposes, after activation, were employed for column chromatography.
8. TLC analyses were carried out on glass plates coated with a mixture of silicic acid and plaster of Paris (85:15; 200 mesh), and activated at 120° for 3 hr.

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

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

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

11. Unless otherwise stated, all solutions were dried over anhydrous sodium sulphate.

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

13. In the list of IR bands given in the experimental section, the significant bands described in the theory are underlined.

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

15. In the description of NMR signals, the abbreviations brs, br.d. and br.m means broad singlet, broad doublet and broad multiplet respectively.

16. Infrared bands are expressed in frequency ν cm^{-1}.

17. The thick liquid compounds which were found to be unstable above 200°(bath)/1 mm were not purified by distillation.

SUMMARY

This chapter describes the synthesis and insecticidal activity of 3-phenoxybenzyl 2-isopropyl/benzyl-5,5-dichloro/dibromo -4-pentenoates; 3-phenoxybenzyl 2-isopropyl/benzyl-4,6,6-trichloro-5--hexenoates and transformations of methyl heptenone,to 3-phenoxybenzyl 2-(isopropyl)-5-chloro/cyano-4-hexenoates.

The alkylation of diethyl malonate with allyl chloride afforded a mixture of mono and dialkylated products XI, XII separated by fractionation. Compound XI was realkylated with isopropyl iodide or benzyl chloride by using sodium hydride and dimethylformamide,in benzene to yield XIIIa,b respectively. Decarboethoxylation of XIIIa,b by wet-DMSO-KOAc method, afforded quantitatively the esters XIVa,b. Ozonolysis of XIVa,b in ethyl acetate-acetic acid (3:1), solvent mixture gave aldehydo ester XVa, b in 85% yield. The latter on Wittig reaction,with 1,1-dihalomethylene triphenyl phosphoranes afforded dihalovinyl esters (XVIa,b; X=Cl or Br), which were subsequently converted to insecticidally active 3-phenoxybenzyl esters (XVIIa,b; X=Cl/Br), by transesterification.

In another series of reaction, free radical initiated addition of carbon tetrachloride to the unsaturated esters (XIVa,b), gave tetrachloro esters (XVIIIa,b), in high yields. The latter, on controlled and selective dehydrochlorination (DMF/KOAc), gave the unsaturated trichloro ester (XIXa,b)

which were similarly converted into 3-phenoxybenzyl esters (XXa,b), by transesterification with 3-phenoxybenzyl alcohol.

A synthetic route has been developed for the synthesis of 2,3-secopyrethroids, possessing methyl as one of the substituent on the vinyl function, starting from methyl heptenone. Methyl heptenyl acetate (XXII, R=Ac), was subjected to Prins reaction with paraformaldehyde in glacial acetic acid to give diacetate (XXIII), converted to diol (XXIV), by saponification. Jones chromic acid oxidation of diol XXIV, gave in the acid part, the keto acid, characterised as its methyl ester XXV, Catalytic hydrogenation of XXV, gave the dihydroderivative (XXVI). PCl_5 reaction on XXVI, followed by chromatographic purification, gave XXVII as a mixture of E and Z isomers. The keto ester (XXVI), was converted to cyanohydrine ester (XXX), which on dehydration ($POCl_3$/ pyridine), gave the Z isomer of XXXI, identified by spectral data. Both the compounds XXVII and XXXI, were transesterified with 3-phenoxybenzyl alcohol, to afford XXIX and XXXIII respectively in good yields as liquids. These compounds showed good insecticidal activity.

INTRODUCTION

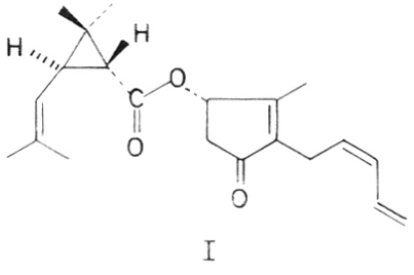
Pesticide is defined as any substance or a mixture of substances, intended for preventing, destroying, repelling or mitigating any pest or as any substance intended for use as a plant regulator, defoliant or desiccant.

The sequence of compounds synthesised to control pests can be graded in four major classes,(1) organochlorines (2) carbamates (3) organophosphorous compounds and (4) pyrethroids. The deficiencies in the earlier three classes of compounds, such as, high persistance, harmful effect on non-targeted organisms, high mammalian toxicity and environmental pollution have restricted their use as insecticides. Most of these deficiencies are absent in the naturally occurring insecticides like pyrethrins and cinerins.

The flowers of chrysanthemum cinerariaefolium were used since ancient times[1] for controlling pests. Insecticidal principles in pyrethrum (dried flowers of C. cinerariaefolium Trev) are called as "pyrethrins". In the first quarter of 20th century, Staudinger and Ruzicka[2], for the first time, isolated and identified two active principles from pyrethrum extract and named them as Pyrethrin I and Pyrethrin II. Later, four more related active esters[3,4] viz. cinerin I, cinerin II, jasmolin I and jasmolin II (Chart I) were also isolated from pyrethrum extract. These are esters[5] of

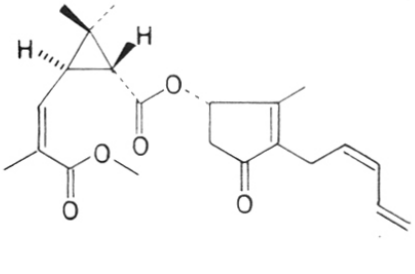
(+) trans chrysanthemic acid (Pyrethrin I, Cinerin I and Jasmolin I) and (+) trans Pyrethric acid (Pyrethrin II, Cinerin II and Jasmolin II). They possess unique combination of desired properties such as, good insecticidal activity, low mammalian toxicity and higher biodegradability. However, their use is limited mainly because of their high cost and photoinstability. So, efforts were directed towards the synthesis of pyrethroids, bearing close structural resemblance to natural pyrethrins, by making suitable changes in the alcohol as well as in cyclopropanecarboxylic acid moiety. The pyrethroids thus obtained, combine high and selective insecticidal activity, low mammalian toxicity and greater biodegradability with photostability. During the first phase of research in this direction, some synthetic chrysanthemates were synthesised in which the acid moiety was the same as in natural pyrethrins, viz. (+) trans chrysanthemic acid but the alcohol moiety is either 3-phenoxybenzyl alcohol[6] or 5-benzyl-3-furylmethyl alcohol, both of which are photostable alcohol moieties. These esters are not only more photostable as compared to natural pyrethrins but also show increased insecticidal activity while maintaining low mammalian toxicity. Subsequently, modifications were also made in the acid moiety by eliminating photolabile centres as a result of which, acid moieties of potent pyrethroids like DV acid and its dibromo-analogues were synthesised. The esters of these acids with

CHART I

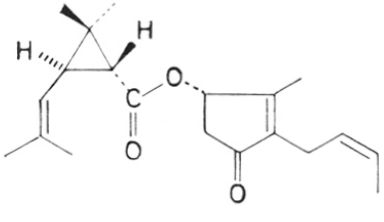


I

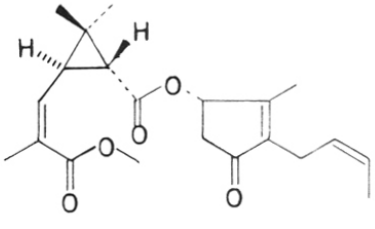
PYRETHRIN I



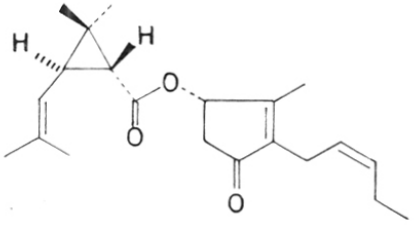
PYRETHRIN II



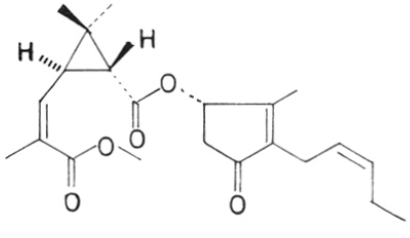
CINERIN I



CINERIN II

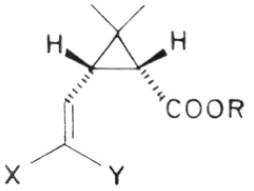


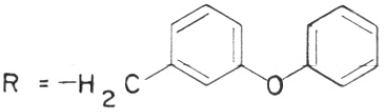
JASMOLIN I

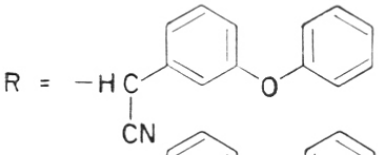


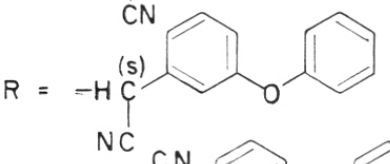
JASMOLIN II

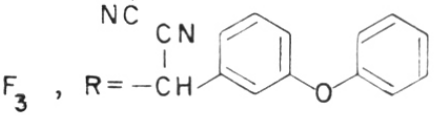
CHART I (contd.)

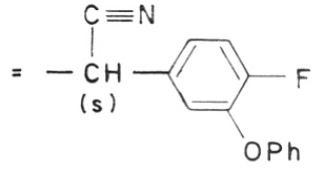


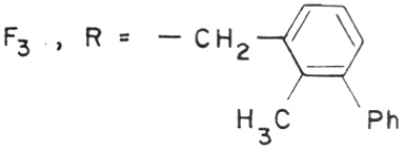
PERMETHRIN X , X = Cl , R = 

CYPERMETHRIN X , X = Cl , R = 

DELTAMETHRIN X , X = Br , R = 

CYHALOTHRIN X = Cl , Y = CF_3 , R = 

BAYTHROID X , Y = Cl , R = 

FMC — 54800 X = Cl , Y = CF_3 , R = 

the photostable alcohols mentioned above, give rise to highly potent pyrethroids[7,8] like permethrin, cypermethrin and deltamethrin. These pyrethroids are at present in commercial use. In recent years, a second generation of pyrethroids[9] like cyhalothrin, baythroid, FMC-54800, has also come up (Chart I).

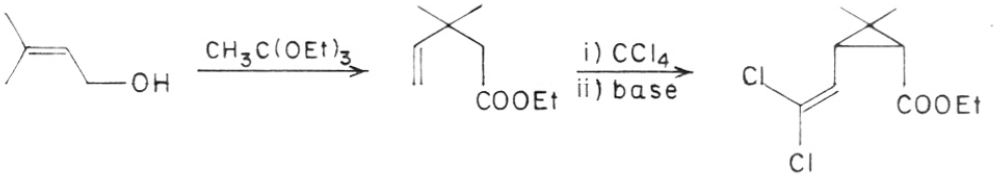
To possess high insecticidal activity pyrethroids must have a precise steric relationship between the unsaturated center in the alcohol moiety and the gem-dimethyl group or its equivalent substituent in the acid moiety. This requires 1R configuration[5,10] in the cyclopropanecarboxylic acids. Inversion at this chiral centre, drastically alters potency without greatly changing the physical properties. Thus, (+) trans and (+) cis chrysanthemic acid esters possessing 1R configuration with suitable alcohol moieties are found to be active insecticides, while esters of (-) trans and (-) cis chrysanthemic acids possessing 1S configuration are inactive or much less active. In NRDC-143 and NRDC-149, cis isomer is twice[11] more toxic to insects than the corresponding 1R trans isomer. Therefore 1R cis pyrethroids are generally preferred than the corresponding 1R trans pyrethroids from the point of potency criteria.

A number of ingenious syntheses of chrysanthemic acids are on record[12-22]. In Farakas method[23], 1,1-dichloro-4-methyl-1,3-pentadiene is condensed with ethyl diazoacetate to give the DV acid ester (Chart II, Scheme A). However, a safe and steady handling of ethyl diazoacetate and the preparation of 1,1-dichloro-4-methyl-1,3-pentadiene, appear

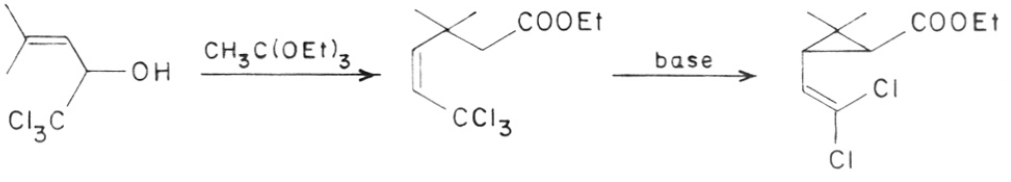
CHART II

A) FARAKAS METHOD

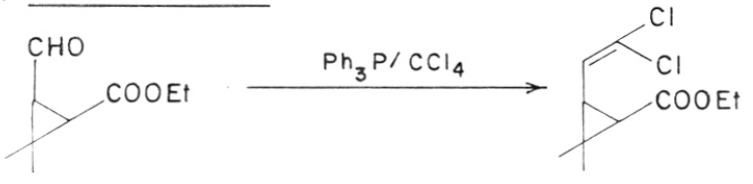
B) SAGAMI METHOD



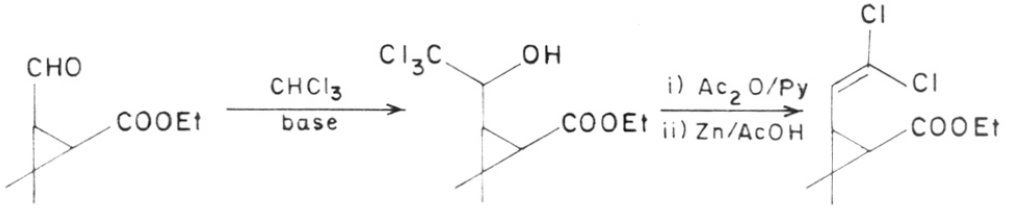
C) KURARAY METHOD



D) NRDC METHOD



E) N. ITAYA



to be a major problem . In Sagami method (Chart II, Scheme B) 3-methylbut-2-ene-1-ol is condensed with ethyl orthoacetate by a Claisen's allylic rearrangement to afford ethyl 3,3-dimethyl-4-pentenoate . Redox or peroxide catalysed addition of carbon tetrachloride to the pentenoate[28] gives tetrachlorohexanoate which on treatment with base, undergoes both cyclopropane ring closure and dehydrohalogenation to afford DV-acid (cis:trans - 3:7). In Sagami[24] and Kuraray's[25] (Chart II, Scheme C) methods, ethyl orthoacetate is a common requisite, which does not seem to be available yet, at an economic price. Moreovere, Claisen rearrangement affords the respective olefinic ester only in moderate yields. In the NRDC method[26] (Chart II, Scheme D) the caronaldehyde ester is subjected to Wittig reaction using 1,1-dihalomethylene-triphenyl phosphorane. It is however doubtful whether Wittig reaction can be employed for large scale preparation. In a new approach which avoids the Wittig reaction, the caronaldehyde acid is subjected to the aldol condensation using trihalo-methyl carbanion[27], followed by acetylation of the resulting hydroxy acid and subsequent treatment with zinc and acetic acid. The corresponding trihalolactone has also been employed for getting the DV-acid moiety (Chart II, Scheme E).

In most of these methods for the synthesis of acid moiety, the substituted cyclopropane ring is built up, starting from a suitable acyclic substrate. These methods lack in

selectivity and invariably dl mixtures of cis and trans isomers (active and inactive) are obtained in varying proportions. A few stereospecific syntheses of chrysanthemic acid, starting from cheap and abundantly occurring terpenes viz. carene[29,30] and ∝-pinene[31] have been reported. These methods are not likely to be used commercially, as they either involve several steps or give lower yields. Furthermore, cyclopropane ring is sensitive to photochemical reactions[32], leading to isomerization or ring cleaved products. These photodegraded products are much less active. Though, Pyrethrin I and synthetic pyrethroids are known to have a quick knock-down effect on the flying insects, fast recovery has also been observed. Therefore repeated applications are necessary for bringing about complete mortality. The synthesis of sterically hindered gem-dimethylcyclopropane-carboxylic acid with the required absolute configuration also poses problems.

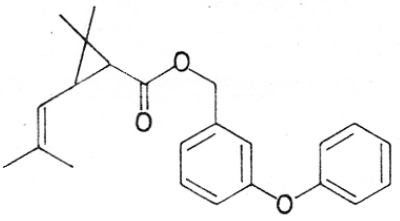
It has been widely recognised that technical changes and innovations are of major importance in economic growth. New insecticides will continue to be needed in the foreseeable future, for controlling pests more effectively and economically, by replacing the existing compounds which have ceased to give reliable control because of development of immunity by insects or on account of deficiencies, such as (1) excessive persistance (2) harmful effect on non-targeted organisms and

(3) lack of appropriate mobility in soil or plant. The work described in the thesis is aimed at contributing towards the synthesis and development of new insecticides, concentrating on 'Secopyrethroids' or 'Cut up chrysanthemates' which can be considered as acyclic analogues of pyrethroids and also to understand the fundamental principles determining the relationship between chemical structure and biological activity.

Staudinger and Ruzicka[33] in 1920 prepared pyrethronyl esters of various acids such as aliphatic, olefinic, aromatic, terpenic and cyclopropanecarboxylic acids, bearing some structural resemblence to chrysanthemic acid and examined their biological activity. The insecticidal esters thus synthesised, did not show any appreciable insecticidal activity and hence it was commonly believed that the cyclopropanecarboxylic acid moiety is essential for insecticidal activity.

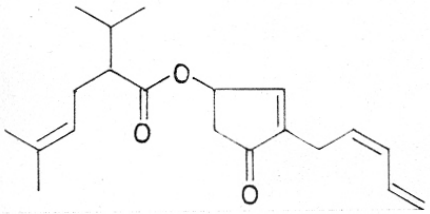
An important land-mark in the evolution of pyrethroids for use in agriculture, was the discovery of α-cyano-3-phenoxybenzyl alcohol ester with a non-cyclopropane acid such as α-isopropyl-4-chlorophenylacetic acid, commonly known as fenvalerate[34], which Ohono et al. in 1974 demonstrated it to be an important insecticide. In fenvalerate, the isopropyl group on the benzylic carbon atom can be considered as the steric equivalent of gem-dimethyl group on the cyclopropane of chrysanthemates with the unsaturated centre placed on α-carbon atom of the acid. The insecticidal activity of isopropylaryl acetates is very sensitive to structural changes and substitution pattern (Chart III). These phenylacetates whose

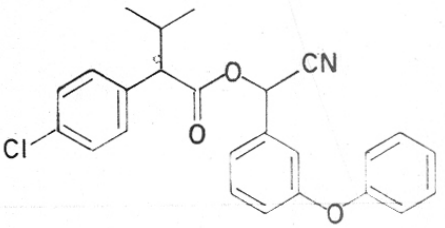
CHART III



PERMETHRIN

ELLIOTT, FUJIMOTTO, 1971

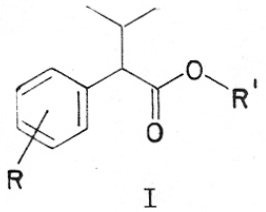




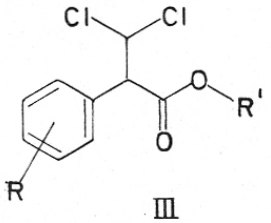
FENVELERATE

OHONO et al, 1974

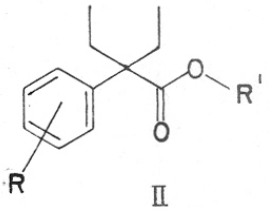
STAUDINGER AND RUZICKA, 1924



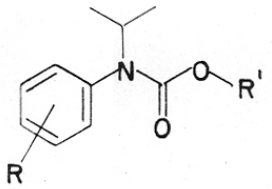
I



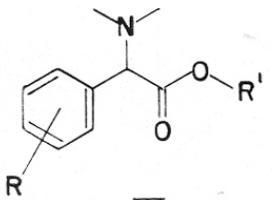
III



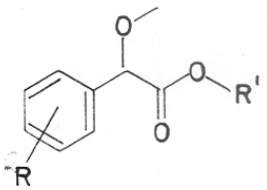
II



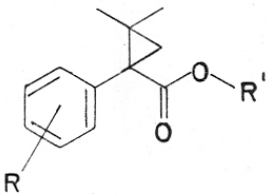
V



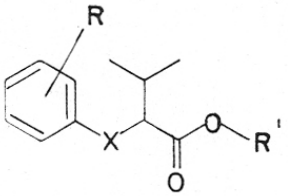
IV



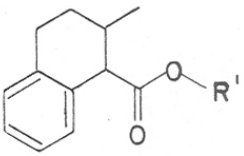
IX



VII



VI, X= CH_2, O



VIII

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

substituents[35] are isopropyl, isopropenyl or t-butyl group are highly toxic to insects, while the corresponding esters with the α-methyl, α-n-propyl, α-n-butyl or higher analogues are non-toxic as well as the unsubstituted ones. The α-diethyl compound[34] (II) is slightly less toxic than the α-isopropyl derivative. Marked enhancement is observed when appropriate functions such as methyl, methoxy, chloro, bromo groups are introduced in the para or meta position of phenyl group. Substitution in ortho position causes decrease in toxicity. In general, esters of 3-phenoxybenzyl alcohol are several times more toxic than those with 5-benzyl-3-furyl methyl, 5-propargyl-2-furylmethyl and allethronyl alcohols.

The dichloroisostere (III) of isopropyl compounds, is inactive, possibly because HCl is eliminated extremely rapidly to give monochloro olefin, lacking structural characteristic of insecticidal action. The isosteric amines (IV) and carbamates (V)[35] are also inactive. In another series of esters (VI), synthesised, the aromatic centre is displaced by an oxygen[35] or methylene bridge to a position remote from the chiral centre; such compounds are also found to be inactive. The other analogues viz. VII, VIII and IX are also inactive.

These comparative results suggest that the presence of a gem-dimethyl or its steric equivalent β-to the carboxylate function is one of the important structural features contributing towards insectiicidal activity, both in the case of chrysanthemates

and α - substituted phenylacetates.

Subsequent studies on the acid moiety of these insecticides have shown that the presence of intact cyclopropane ring is unnecessary for high insecticidal activity[36-43]. This suggests that an insecticidally active analogue of cyclopropyl pyrethroid may be a ring cleaved or secoproduct. The study of secopyrethroids has attracted much attention in recent years because of their promising biological activity and simplicity of structure. Secopyrethroids can be considered as open chain equivalents of active cyclopropanecarboxylates and derived from the latter by cleavage of cyclopropane ring. Cyclopropane ring of pyrethroids can be cleaved in three different ways leading to three possible types of "Cut up chrysanthemates" or"Secopyrethroids"(Chart IV). In the first two classes,the vinyl group and the carboxylate functions are separated by a two carbon unit with substituents on αor β carbon atom, whereas in the third case they are separated by a three carbon chain.

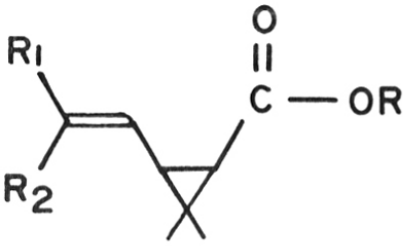
Synthesis of Secopyrethroids

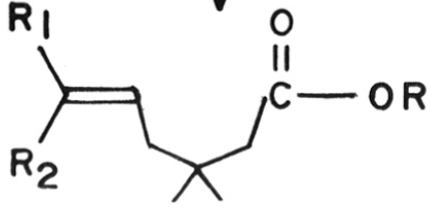
Some methods of synthesis of "Cut up chrysanthemates" are on record[36-43], most of these compounds are patented[38-43] for insecticidal activity. Some novel synthetic approaches for both 2,3- and 1,3-secopyrethroids are described below.

Compounds with two carbon chain between vinyl function and ester group

1. W.G. Taylor[36] (1980, Chart V, Scheme A) has prepared from methyl heptenone, 5,5-dichloropent-4-enoic acid,considered as an

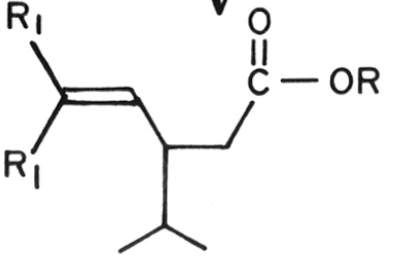
CHART IV





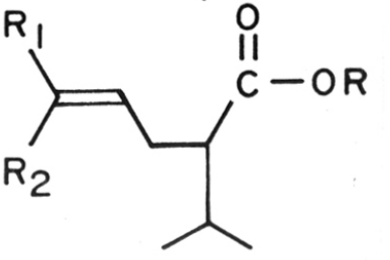
III

1, 3 – Secopyrethroids



II

1, 2 – Secopyrethroids



I

2, 3 – Secopyrethroids

important intermediate for the synthesis of insecticidal esters. The reaction sequence for the acid moiety involves ozonolysis on the ketal of methyl heptenone followed by reductive workup of the resulting ozonide to afford the ketal aldehyde. Wittig reaction on the ketalaldehyde with 1,1-dichloromethylenetriphenyl phosphorane, regeneration of ketone and subsequent Hoffmann haloform reaction on the resulting 6,6-dichloro-2-oxohept-5-ene gave 5,5-dichloro-4-pentenoic acid.

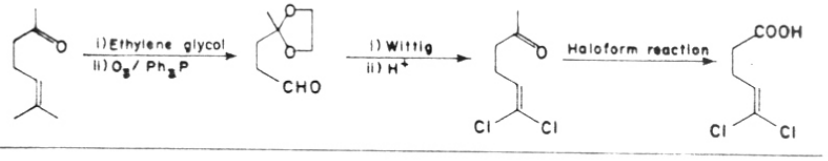
2. W.G. Taylor[37] (1984, Chart V, Scheme B) has synthesised 2,3-secopermethrin from methyl-4-pentenoate by its α-alkylation with isopropyl iodide in presence of LDA in HMPA. Ozonolysis of the resulting α-isopropyl-pent-4-enoate and reductive workup of the ozonide gave the aldehydo ester, Wittig reaction on the aldehydo-ester and subsequent transesterification gave 2,3-secopermethrin.

3. Witernitz Parol[38] (Chart V, Scheme C) has patented a large number of compounds of general formula I, prepared by alkylation of α-substituted ethylacetate with 3,3-dichloro-1-bromo-2-propene by using butyl lithium in tetrahydrofuran at -70°. Esterification of the resulting compounds with 3-phenoxybenzyl alcohol via the acid chloride, furnished the esters showing good insecticidal and acaricidal activity.

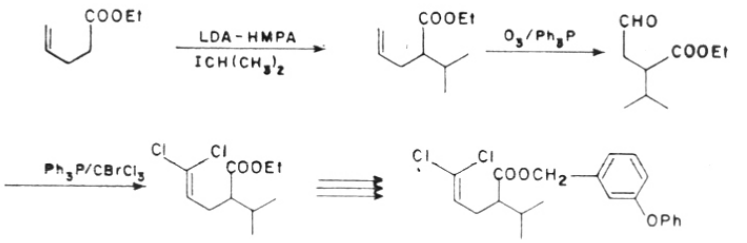
4. W. Meyer et al.[41] (Chart V, Scheme D) have synthesised α-cyano 3-phenoxybenzyl esters of 2-isopropyl-4-phenyl/substituted phenyl-3-butenoic acids. The acid moiety was synthesised by α-alkylation of 4-phenyl/substituted phenyl-3-butenoates by isopropyl iodide followed by hydrolysis of resulting ester and

CHART V

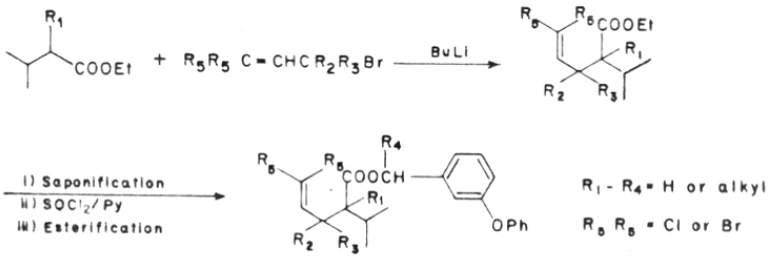
A) W. G. TAYLOR (1980)



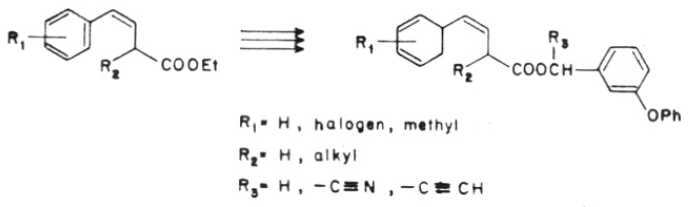
B) W. G. TAYLOR (1984)



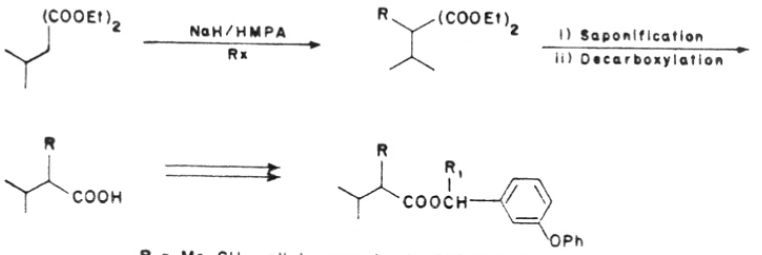
C) WINTERNITZ PAROL (Hoffmann La Roche und Co)



D) MEYER W et al



E) BULL MICHAEL et al



esterification of the acid via its acid chloride. These esters showed 100% mortality against Spodoptera littoralis, Heliothis virenscens at 0.05% and against Aphis fabae at 100 ppm. They also prepared the corresponding aliphatic analogues of general formula (I) and found them active against different species of agricultural pests.

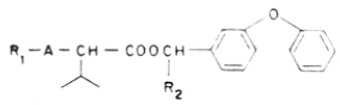
5. Michael Bull and co-workers[40] (Chart V, Scheme E) have prepared thirty five insecticidal esters from α-alkyl/alkenyl/aralkyl/phenyl substituted aralkyl, isovaleric acids with α-cyano-3-phenoxybenzyl and other related alcohols and patented them for their insecticidal activity. The synthesis involves α-alkylation of isopropyl diethylmalonate followed by saponification, decarboxylation and esterification of the resulting monocarboxylic acid with different alcohols via its acid chloride; 1% dose of these compounds gave 100% kill of house flies.

6. Y. Katsuda[44] (Chart VI, F): A large number of isovaleric acid esters of general formula I have been patented by Katsuda Y. for their broad spectrum of insecticidal activity.

7. T.N. Wheeler[45] (Chart VI, G) of Union Carbide Co.(1981) has synthesised α-cyano-3-phenoxybenzyl esters of α-isopropyl/cyclopropyl-5,5-dichloropentenoic acids, which were effective against adult and nymphal stage of bean Aphids, larvae of Spodoptera cridania, cram, larvae of mexican bean beetle, adult and nymphal stage of spotted mites, Tetranychus urticae Koch.

CHART VI

F) KUTSUDA et al (1980)



I

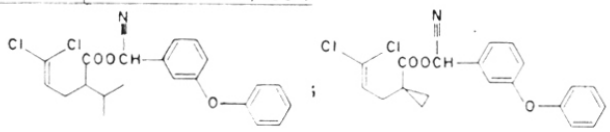
A = O, NH, CH_2

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

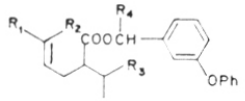
A = CH_2, R_1 = Haloalkyl or haloalkenyl radical with 1-5 carbon atoms

R_2 = H or C≡N

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



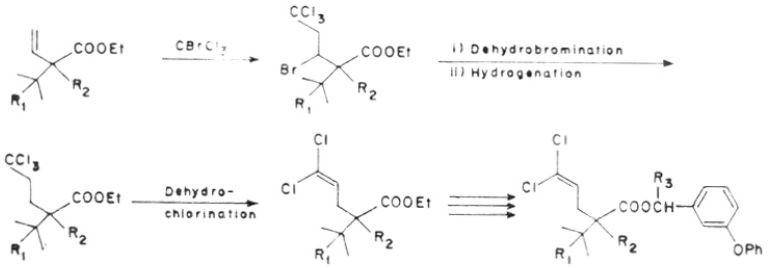
H) DRABEK J et al (Ciba-Geigy A-G)



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

R_2 = H, Cl; R_4 = H, −C≡N, −C≡CH

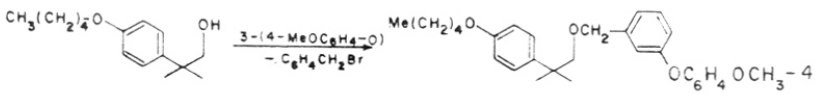
I) OMURA Y (Kuraray Co. Ltd.)



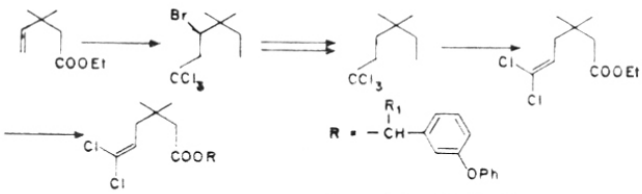
R_1 = Cl, Br, H; R_2 = H, alkyl, $-C\equiv CR_3$, $-CH_2CH=CR_1R_1$

R_3 = H, −C≡N, −C≡CH

J) N. UMEMOTO



K) OMURO et al



R =

R_1 = −CN, −C≡H, H

8. Josef Drabek and coworkers[39] (Chart VI, H) have similarly prepared a large number of esters of α-substituted isovaleric acids and patented them for their insecticidal and larvicidal property. Synthetic details were however, not available. These are effective against Spodoptera littoralis and Heliothis virenscens at 0.05% and Aphis fabae at 1000 ppm.

Synthesis of 1,3-Secopyrethroids

Omura Y.[42] (1978, Chart VI, Scheme I) of Kuraray Co.Ltd. has synthesised a large number of esters of general formula I, wherein ester group and the vinyl function are separated by a two or three carbon chain. These compounds gave 100% kill of mosquitoes and house-flies at 1% dose. The key step in the reaction involves, addition of $CBrCl_3$ to a suitable olefin, selective dehydrobromination, hydrogenation of resulting olefin and dehydrochlorination of the hydrogenated product, to give dihalovinyl ester. These ester were then saponified and the acids thus obtained, were esterified with pyrethroidal alcohols via their acid chloride.

Using a similar sequence of reactions, 1,3-secopyrethroids containing β-gemdimethyl grouping is prepared from ethyl 3,3-dimethyl-4-pentenoate as shown in Chart VI, Scheme K.

In addition to the insecticidal esters described above, Umemoto Nagata et al.[46] (1984, Chart VI, Scheme J) have prepared some ethers derived from alkoxyphenyl-2-methylpropyl alcohol and 3-phenoxybenzyl or substituted 3-phenoxybenzyl alcohols. Friedel Crafts alkylation of ortho chlorophenatole with methallyl chloride

in presence of Conc. H_2SO_4 afforded 3-chloro-4-(1,1-dimethyl-2-chloroethyl)phenatol. This was then reacted with 3-phenoxybenzyl alcohol in presence of KOH and 1,3-dimethyl-2-imidazolidinone to give phenolic compound which was alkylated with diethyl sulphate and alkali at 50-70°, to afford insecticidally active ethers. These compounds show insecticidal, acaricidal and insect repellent activity.

Although a large number of Secopyrethroids are synthesised by different workers, it appears that the relationship between chemical structure and biological activity is not adequately defined. The extent to which α-substituent and the vinyl function influence insecticidal activity is not fully understood.

Keeping the above points in view, work was undertaken on the synthesis of 1,3-and 2,3-Secopyrethroids to understand more about the structural requirements for insecticidal activity. This allows a wide range of structural variation both in the vinyl function and in the α-substitution which may be of help in finding useful combination, for high insecticidal activity.

Synthetic methods described for the acid moieties of Secopyrethroids deal with both total synthetic approaches as well as from naturally occurring substrates. In all the Secopyrethroids prepared by us, the alcohol moiety viz. 3-phenoxybenzyl alcohol was kept constant. 3-Phenoxybenzyl alcohol is particularly favourable alcohol component for it is not photolabile, gives esters of low mammalian toxicity and high insecticidal activity.

This chapter deals with synthesis of the acid moieties of secopyrethroids from both naturally occurring substrates as well as by total synthetic approach.

PRESENT WORK

For the synthesis of secopyrethroids, possessing a dihalovinyl function, showing maximum activity amongst the compounds chosen for structure activity studies, diethyl malonate was thought to be an ideal substrate because of its two acidic hydrogens which can be substituted selectively with different alkyl groups.

The method described by W. Parol[38] for this type of esters (Chart V, C) involves the use of expensive chemicals like BuLi, 3,3-dichloro-1-bromoprop-2-ene and also very low temperature conditions (-70°). In the W.G. Taylor's[36,37] method the alkylation of 4-pentenoate, for introducing α-isopropyl group is carried out using expensive base like LDA and also ozonolysis of 4-pentenoate in methanol at -70°, gave only moderate yields of aldehyde (Chart V, Scheme A & B).

A more general and straight forward route for the synthesis of 2,3-secopyrethroids, in high yields from readily available substrate, like diethyl malonate, has now been developed (as shown in Scheme I) and described below.

Alkylation of diethyl malonate with allyl chloride using stoichiometric amount of NaOEt in ethanol[47], gave a 70:30 mixture of mono(XI) and dialkylated (XII) products, separated by fractionation on a spinning band column and isolated in a pure state. Compound XI,

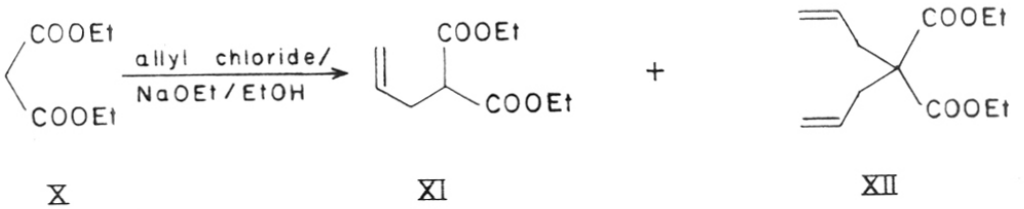
$C_{10}H_{16}O_4$; GLC: 2.41 min, 98%, column OV-101, column temperature 145°; showed IR bands at: 1735 (ester C=0), 1640, 910 ($CH=CH_2$); PMR signals at: 1.28 (6H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.53 (2H, t, J=7 Hz, allylic CH_2), 3.31 (1H, dd, J_1=7 Hz, J_2=15 Hz, $\underline{CH}$ adjacent to ester groups), 4.11 (4H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.86 - 5.08 (2H, m, $CH=\underline{CH}_2$) and 5.73 (1H, m, $\underline{CH}=CH_2$).

Compound XII, $C_{13}H_{20}O_4$; GLC: 5.73 min, 96%, column temperature, 145°, column, OV-101; Nitrogen flow rate, 30 ml/min. It showed IR bands at: 1725 (ester C=0), 1645, 915 ($CH=CH_2$); PMR signals at : 1.23 (6H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.51 (4H, d, J=7 Hz, allylic CH_2), 4.08 (4H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.9 - 5.06 (4H, m, $CH=\underline{CH}_2$) and 5.6 (2H, m, $\underline{CH}=CH_2$). It showed absence of signal at 3.3 for $\underline{CH}$,adjacent to ester groups.

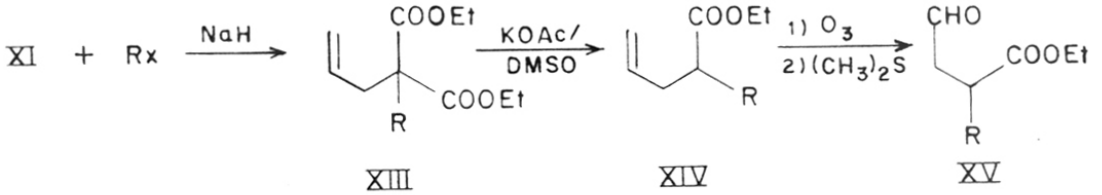
The second alkylation of XI with isopropyl iodide, using sodium hydride as base in benzene, lead to recovery of starting material. However, in presence of dimethyl formamide, the reaction went smoothly at room temperature to give the dialkylated product (XIIIa), $C_{13}H_{22}O_4$. It showed IR bands at: 1732 (ester C=0), 1645, 915 ($CH=CH_2$); PMR (80 MHz, $CDCl_3$) signals at: 0.95 (6H, d, J=6 Hz, methyls of isopropyl), 1.3 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 2.52 (1H, m, $\underline{CH}(CH_3)_2$), 2.7 (2H, d, J=6 Hz, allylic CH_2), 4.22 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.76 - 5.11 (2H, m, $CH=\underline{CH}_2$) and 5.78 (1H, m, $\underline{CH}=CH_2$).

The corresponding benzyl compound (XIIIb), $C_{17}H_{22}O_4$, was prepared in the similar manner. It showed IR bands at: 1730 (ester C=0), 1600, 700 (aromatic), 1645, 910 ($CH=CH_2$); PMR(80 MHz,

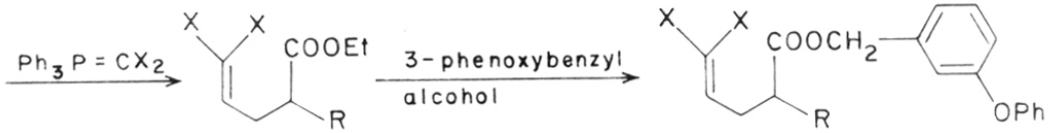
SCHEME I



X XI XII



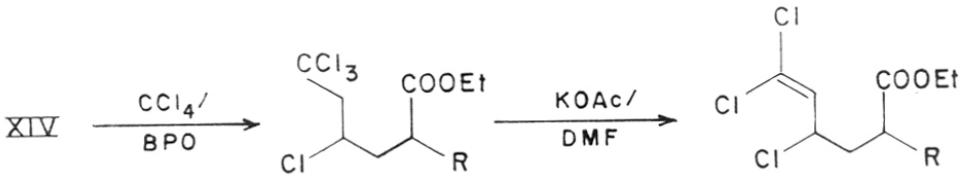
XIII XIV XV



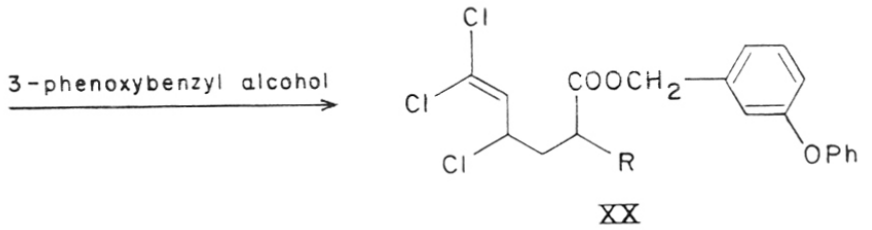
XVI XVII

X = Cl or Br

R = a, isopropyl; b, benzyl



XVIII XIX



XX

R = a, isopropyl; b, benzyl

$CDCl_3$) signals at: 1.11 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 2.23 (2H, d, J=6 Hz, allylic CH_2), 2.95 (2H, s, benzylic CH_2), 3.86 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.66-4.83 (2H, m, $CH=\underline{CH}_2$), 5.31 (1H, m, $\underline{CH}=CH_2$) and 6.63 (5H, s, aromatic H).

The dialkylated diethyl malonate (XIII), thus obtained was subjected to decarbethoxylation by wet DMSO-NaCl[48], resulting in only 25% conversion of starting material to the desired product. After trying different methods like wet DMSO-NaCN[49] and wet DMSO-NaCl, wet DMSO-KOAc[50] method, appeared to be the method of choice. Only moderate yields of the desired product were obtained when decarboethoxylation was carried out using wet DMSO-KOAc at 160° for 6 hr. However, excellent yields of the product were obtained when reaction was carried out under reflux conditions for 4 hr. Using the same reagents following decarboethoxylated products have been prepared; compound XIVa, $C_{10}H_{18}O_2$ showed IR bands at: 1733 (ester C=0), 1645, 920 ($CH=CH_2$); PMR (Fig. 1) signals at: 0.88, 0.91 (each 3H, d, J=6 Hz, methyls of isopropyl), 1.21 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.9 (1H, m, $\underline{CH}(CH_3)_2$), 2.2 (3H, m, allylic CH_2 and C_2-protons), 4.06 (2N, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.76-4.98 (2H, m, $CH=\underline{CH}_2$) and 5.56 (1H, m, $\underline{CH}=CH_2$).

Compound XIVb, $C_{14}H_{18}O_2$ showed IR bands at: 1738 (ester C=0), 1645, 900 ($CH=CH_2$) and 1590, 700 (aromatic); PMR (Fig. 2, 80 MHz, $CDCl_3$) signals at: 1.18 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 2.25 (2H, m, allylic CH_2), 2.5 (1H, m, C_2-proton), 2.75 (2H, d, J=3 Hz, benzylic CH_2), 4.06 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.8, 5.08

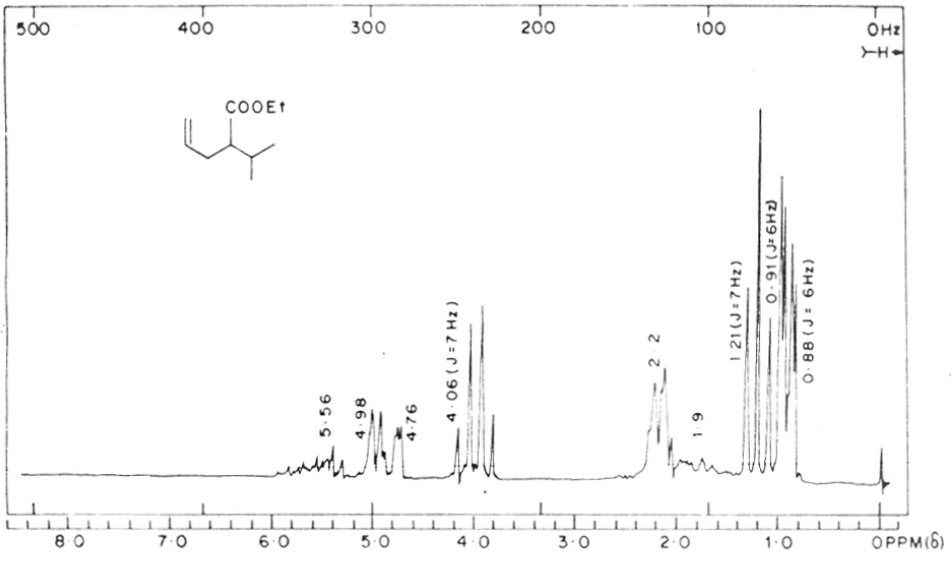


FIG. 1. ETHYL 2-ISOPROPYLPENT-4-ENOATE, XIV a

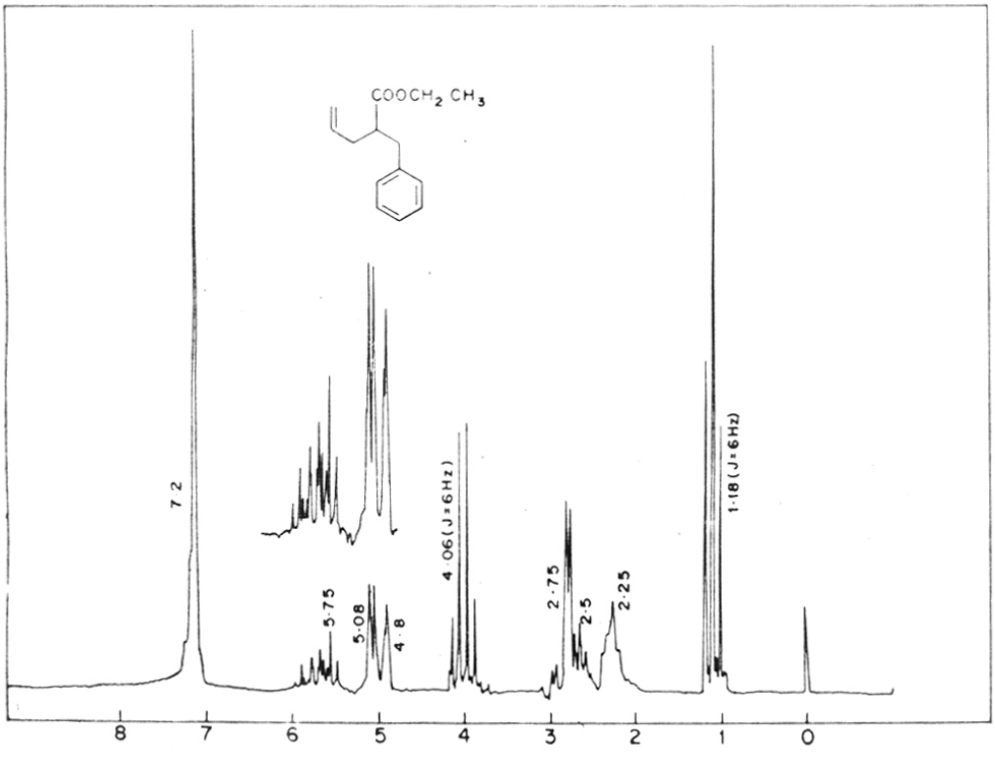


FIG. 2. ETHYL 2-BENZYLPENT-4-ENOATE, XIV b

(2H, m, $CH=C\underline{H}_2$), 5.75 (1H, m, $C\underline{H}=CH_2$) and 7.2 (5H, s, aromatic H).

W.G. Taylor has reported[37] the ozonolysis of unsaturated ester (XIVa), in methanol at -78°, to give the aldehydoester (XV), in 60% yield. It has now been possible to get the aldehydoester in 85% yield by carrying out the ozonolysis under slightly different conditions. After trying different solvents viz.methanol, methylene chloride, ethyl acetate, acetic acid and various combinations of ethyl acetate, acetic acid the ratio 3:1 of ethyl acetate and acetic acid, was found to be better suited for higher yields of aldehyde (85%). Ozonolysis of unsaturated ester (XIV), in ethyl acetate and acetic acid (3:1) followed by reductive workup of the resulting ozonide with dimethyl sulfide gave aldehydoester (XV).

Compound XVa, $C_9H_{13}O_3$; showed IR bands at: 2710, 1715 (aldehyde), 1735 (ester C=O); PMR (Fig. 3) signals at: 0.95, 0.97 (each 3H, d, J=6 Hz, methyls of isopropyl), 1.25 (3H, t, J=6 Hz, $COOCH_2C\underline{H}_3$), 2.06 (1H, m, $-C\underline{H}(CH_3)_2$), 2.73 (4H, m, C_2 and C_3-protons), 4.14 (2H, q, J=6 Hz, $COOC\underline{H}_2CH_3$) and 9.8 (1H, br s, $C\underline{H}O$).

The corresponding α-benzyl analogue XVb, $C_{13}H_{16}O_3$, was prepared similarly; IR bands at: 2710 (aldehyde), 1730 (aldehyde and ester C=O); PMR (80 MHz, $CDCl_3$) signals at: 1.28 (3H, t, J=6 Hz, $COOCH_2C\underline{H}_3$), 2.41-3.13 (5H, m, C_2, C_3- protons and benzylic CH_2), 4.05 (2H, q, J=6 Hz, $COOC\underline{H}_2CH_3$), 7.16 (5H, s, aromatic H) and 9.9 (1H, br s, $C\underline{H}O$).

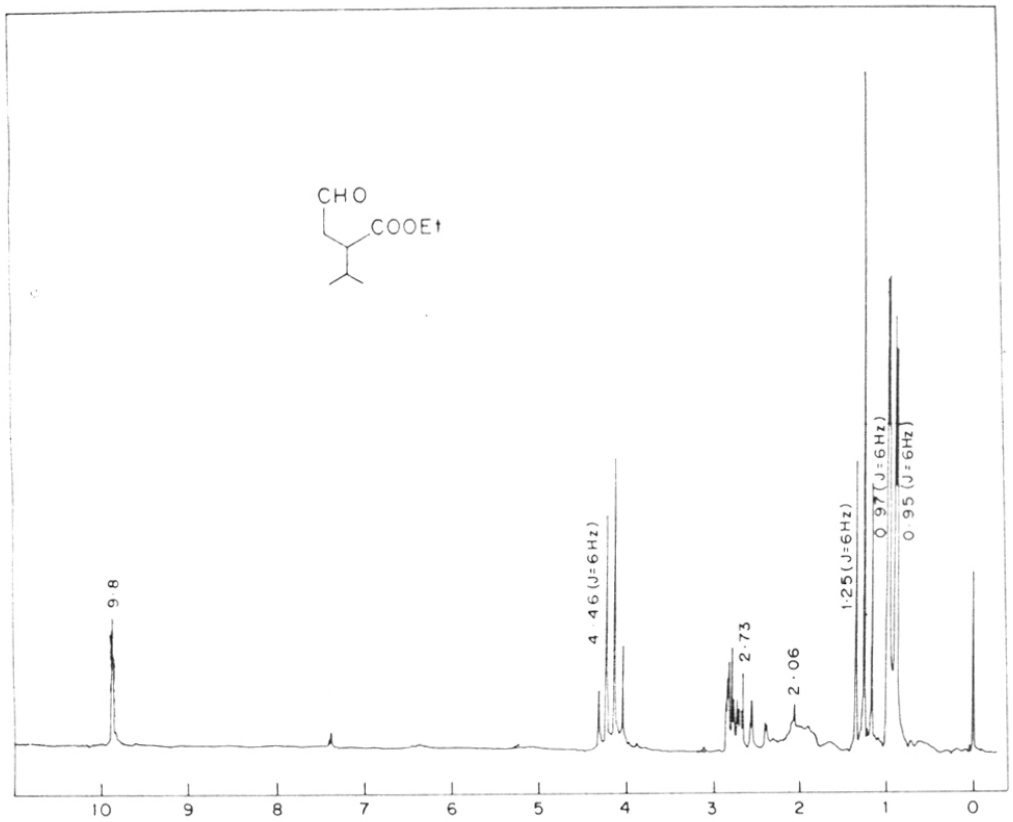


FIG. 3. ETHYL 2-ISOPROPYL-3-FORMYLPROPIONATE, XV a

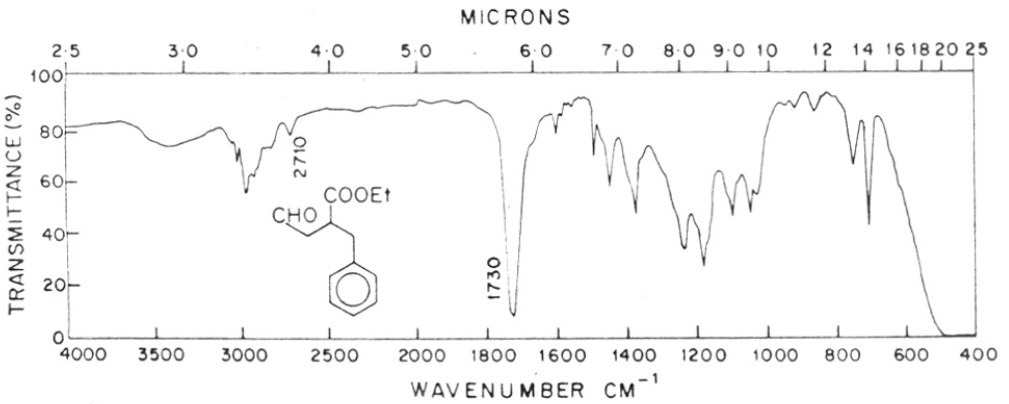


FIG. 4. ETHYL 2-BENZYL-3-FORMYLPROPIONATE, XV b

Aldehydes (XVa,b) were subjected to Wittig reaction using 1,1-dihalomethylenetriphenyl phosphoranes[51,52] under nitrogen atmosphere, to give ethyl 5,5-dihalovinyl-4-pentenoates (XVIa,b; X=Cl or Br).

Ethyl 2-isopropyl-5,5-dichloropent-4-enoate (XVIa, X=Cl), $C_{10}H_{16}O_2Cl_2$; showed IR bands at: 1735 (ester C=O), 1620, 900 ($C=CCl_2$); PMR (Fig. 5) signals at: 0.95 (6H, d, J=6 Hz, methyls of isopropyl), 1.28 (3H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 1.63 (1H, m, $\underline{CH}(CH_3)_2$), 2.33 (3H, m, C_2 and C_3 protons), 4.13 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$) and 5.83 (1H, t, J=7 Hz, vinylic proton).

Ethyl 2-isopropyl-5,5-dibromopent-4-enoate (XVIa, X=Br), $C_{10}H_{16}O_2Br_2$; showed IR bands at: 1730 (ester C=O); PMR (80 MHz, $CDCl_3$) signals at: 0.97 (6H, d, J=6 Hz, isopropyl methyls), 1.26 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.8 (1H, m, $\underline{CH}(CH_3)_2$), 2.23 (3H, m, C_2 and C_3 protons), 4.18 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$) and 6.3 (1H, t, J=7 Hz, vinylic H).

Ethyl 2-benzyl-5,5-dichloropent-4-enoate (XVIb, X=Cl), $C_{14}H_{16}O_2Cl_2$, showed IR bands at: 1730 (ester C=O), 1620, 900 ($CH=CCl_2$), 1605, 700 (aromatic); PMR (80 MHz, $CDCl_3$) signals at: 0.96 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 2.23-2.86 (5H, m, C_2, C_3 and benzylic protons), 4.06 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 5.7 (1H, t, J=7 Hz, vinylic H) and 7.16 (5H, s, aromatic H).

Ethyl 2-benzyl-5,5-dibromopent-4enoate (XVIb, X=Br), $C_{14}H_{16}O_2Br_2$, showed IR bands at: 1735 (ester C=O); PMR (80 MHz, $CDCl_3$) signals at: 1.26 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 2.3 (2H, brt,

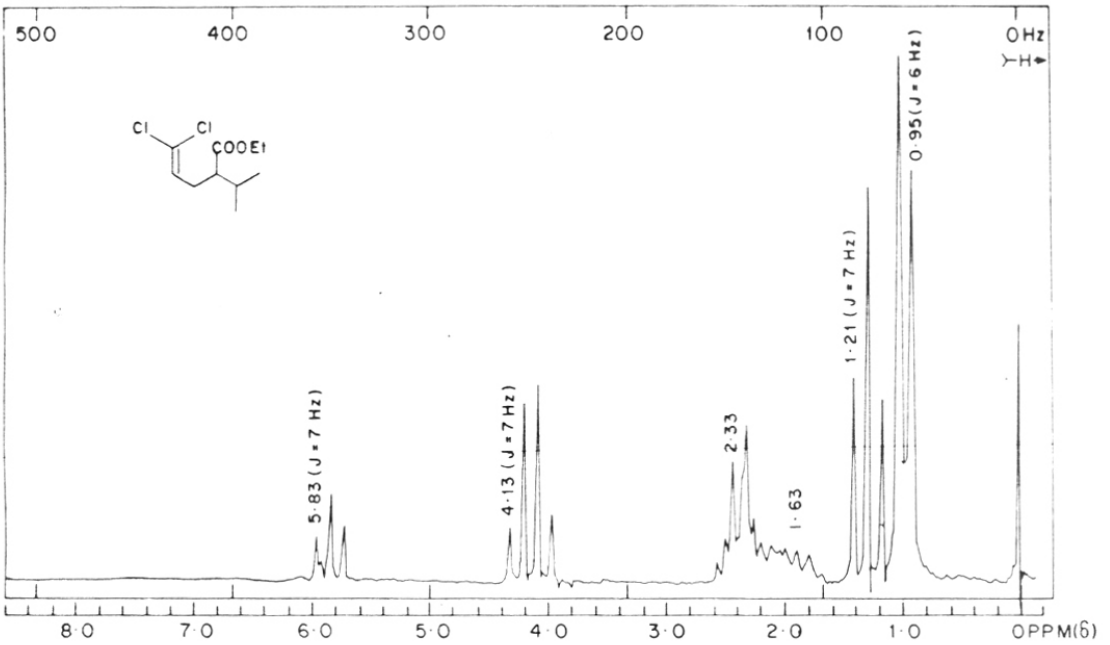


FIG. 5. ETHYL 2-ISOPROPYL-5,5-DICHLOROPENT-4-ENOATE, XVI (X = Cl)

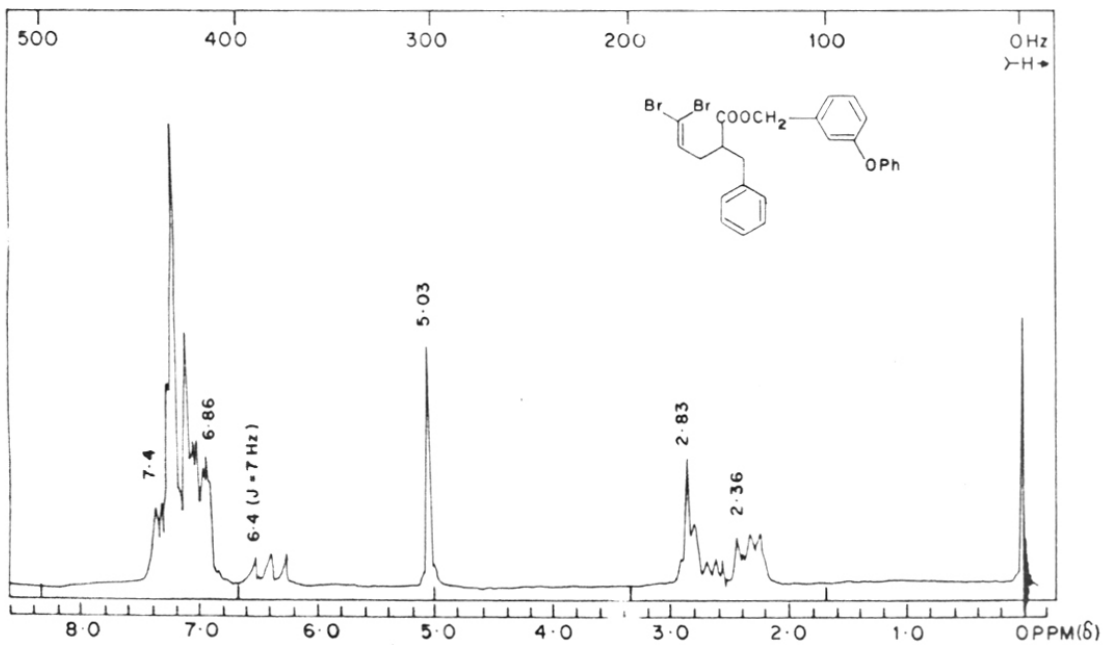


FIG. 6. 3-PHENOXYBENZYL 2-BENZYL-5,5-DIBROMOPENT-4-ENOATE, XVII b (X = Br

C_3 protons), 2.61-3.08 (3H, m, C_2 and benzylic protons), 4.06 (2H, q, J=6 Hz, $COOC\underline{H}_2CH_3$), 6.3 (1H, t, J=7 Hz, vinylic H) and 7.16 (5H, m, aromatic H).

Transesterification of compounds XVIa,b (X=Cl or Br), with 3-phenoxybenzyl alcohol using butyl titanate as a catalyst[53], gave the corresponding 3-phenoxybenzyl esters (XVIIa,b; X=Cl or Br), in excellent yields.

Ester (XVIIa, X=Cl), $C_{21}H_{22}O_3Cl_2$ showed IR bands at: 1733 (ester C=O), 1620, 880 ($CH=CCl_2$), 1587, 693 (aromatic); PMR (Fig. 7, 90 MHz, $CDCl_3$) signals at : 0.9 (6H, d, J=6 Hz, methyls of isopropyl), 1.93 (1H, m, $C\underline{H}(CH_3)_2$), 2.3 (3H, m, C_2 and C_3 protons), 5.0 (2H, s, benzylic CH_2), 5.7 (1H, t, J=7 Hz, vinylic H) and 6.7-7.3 (9H, m, aromatic H).

Ester (XVIIa, X=Br), $C_{21}H_{22}O_3Br_2$ prepared similarly, showed IR bands at: 1735 (ester C=O); PMR signals at: 0.91 (6H, d, J=6 Hz, isopropyl methyls), 2.31 (3H, m, C_2 and C_3 protons), 5.06 (2H, s, benzylic CH_2), 6.28 (1H, t, J=7 Hz, vinylic H) and 6.81-7.4 (9H, m, aromatic H).

Ester (XVIIb, X=Cl), $C_{25}H_{22}O_3Cl_2$ showed IR bands at: 1735 (ester C=O), 1585, 700 (aromatic); PMR signals at: 2.4 (3H, m, C_2 and C_3 protons), 2.8 (2H, m, benzylic CH_2 at C_2), 4.96 (2H, s, benzylic CH_2 of ester), 5.76 (1H, t, J=7 Hz, vinylic H) and 6.75-7.3 (14H, m, aromatic H).

3-Phenoxybenzyl ester (XVIIb, X=Br), $C_{25}H_{22}O_3Br_2$, showed IR bands at: 1735 (ester C=O), 1590, 695 (aromatic); PMR (80 MHz, $CDCl_3$, Fig. 6) signals at: 2.36 (3H, m, C_2 and C_3 protons), 2.83

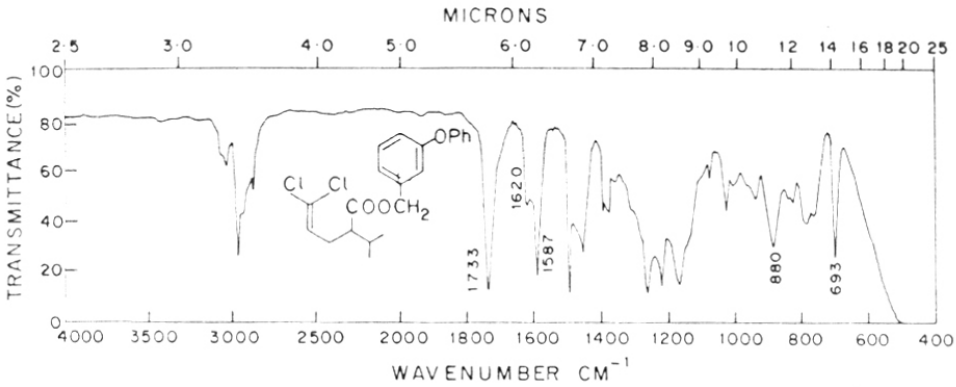


FIG.7. 3-PHENOXYBENZYL 2-ISOPROPYL-5,5-DICHLOROPENT-4-ENOATE, XVII a (X = Cl).

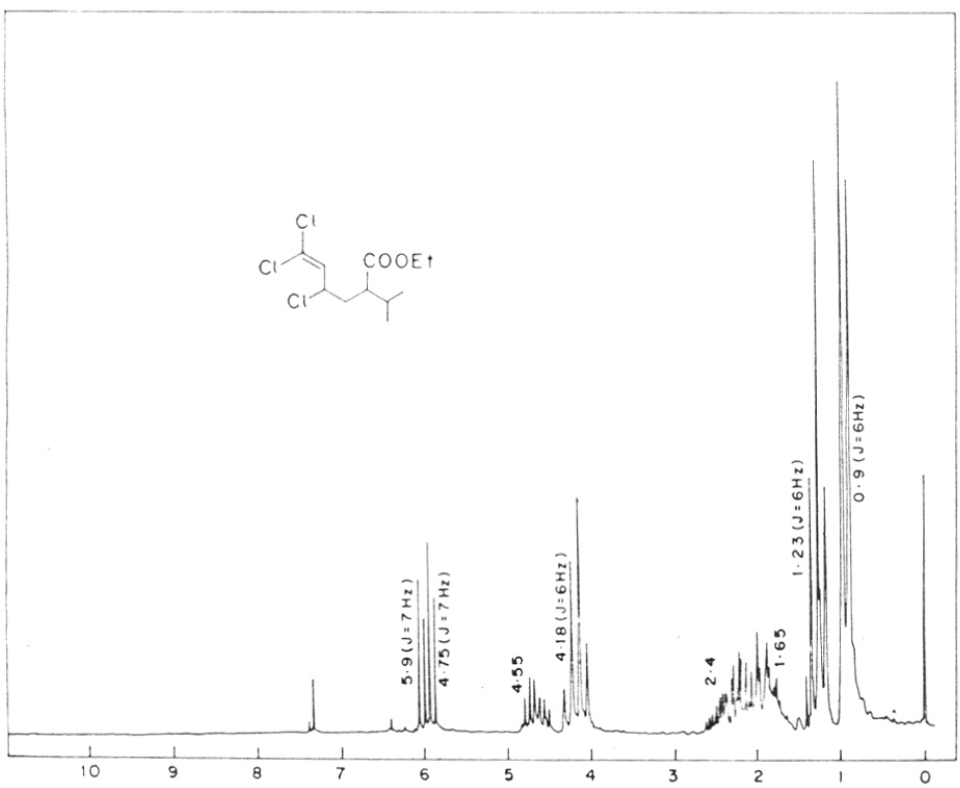


FIG.8. ETHYL 2-ISOPROPYL-4,6,6-TRICHLOROHEX-5-ENOATE, XIX a

(2H, m, benzylic CH_2 at C_2), 5.03 (2H, s, benzylic CH_2 of ester), 6.4 (1H, t, J=7 Hz, vinylic H) and 6.86-7.4 (14H, m, aromatic H).

The notable advantages of the synthetic scheme described above are (1) ready availability and inexpensive nature of starting materials (2) overall compatability if desired (3) a wider choice for both α-and vinyl substitution. The aldehydoester obtained in high yields, is an important intermediate, as a large number of related secopyrethroids can be prepared by varying Wittig reagent or its equivalent.

In another sequence of reactions, esters XIVa,b were converted to ethyl 4,6,6-trichloro-5-haxenoates which could be converted into 3-phenoxybenzyl or related esters. Analogous esters have been shown to possess good insecticidal activity by Y. Omura et al.[42]. In their synthetic approach (Chart VI, Scheme I and K) bromochloroform was added to 3,3-dimethyl-4-pentenoate and the resulting compound was selectively dehydrobrominated to give a trichloro-4-haxenoate, which was subsequently hydrogenated catalytically, to afford the dihydroester. Controlled dehydrochlorination of dihydroester gave 6,6-dichloro-3,3-dimethyl-5-haxenoate, which could be alternately converted to insecticidal esters. One of the drawbacks of this method is the use of ethyl orthoacetate, which is still not available in bulk quantities at economic price. The starting material used in our synthetic scheme can be made readily from the diethyl malonate by a stage-wise dialkylation followed by

decarboethoxylation. The compounds synthesised by us possess an additional chlorine atom, which is expected to contribute towards enhancement of insecticidal activity.

Free radical initiated[54] (benzoyl peroxide) addition of carbon tetrachloride, to the pentenoate (XIV), afforded tetrachloro ester (XVIII), purified by distillation. The compound XVIIIa, $C_{11}H_{18}O_2Cl_4$, showed IR bands at: 1733 (ester C=O); PMR signals at: 0.95 (6H, d, J=6 Hz, isopropyl methyls), 1.23 (3H, t, J=6 Hz, $COOGH_2\underline{C}H_3$), 1.96-2.5 (3H, br m, C_2 and C_3 protons); 3.23 (2H, m, C_5-CH_2) and 4.16 (3H, q, J=6 Hz, $COO\underline{C}H_2CH_3$).

Compound XVIIIb, $C_{15}H_{18}O_2Cl_4$ was similarly prepared. It showed IR bands at: 1730 (ester C=O), 1585, 700 (aromatic); PMR (80 MHz, $CDCl_3$) signals at: 1.21 (3H, t, J=6 Hz, $COOCH_2\underline{C}H_3$), 2.1 (2H, m, C_3 protons), 2.63-3.31 (3H, m, C_2-H and benzylic -CH_2), 4.16 (2H, q, J=6 Hz, $COO\underline{C}H_2CH_3$), 4.64 (1H, m, $C\underline{H}Cl$) and 7.2 (5H, m, aromatic H).

Selective dehydrohalogenation of tetrachloroester (XVIII), using DMF-KOAc[55] gave the unsaturated trichloroester(XIX). The reaction conditions were optimized for selective dehydrohalogenation, better yields being obtained when the reaction was done at 100° for 3 hr. However, prolonged heating (more than 8 hr) lead to polymeric material, probably due to the formation of conjugated dieneic esters. The trichloroesters were obtained as diastereomeric mixtures.

Compound XIXa, $C_{11}H_{17}O_2Cl_3$ showed IR bands at: 1730 (ester C=0),1620, 900 ($CH=CCl_2$); PMR (80 MHz, $CDCl_3$, Fig.8) signals at: 0.9 (6H, d, J=6 Hz, methyls of isopropyl), 1.23 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.65-2.4 (4H, m, C_2 and C_3 protons and $\underline{CH}(CH_3)_2$), 4.18 (2H, q, J=6 Hz, $COO\underline{CH_2}CH_3$), 4.55 (1H, m, $\underline{CH}Cl$), 5.75 and 5.9 (1H, each d, J=7 Hz each, vinylic H of diastereomers).

Compound XIXb, $C_{15}H_{17}O_2Cl_3$, showed IR (Fig. 9) bands at: 1735 (ester C=0), 1620, 860 ($CH=CCl_2$), 1605, 700 (aromatic); PMR (80 MHz, $CDCl_3$) signals at: 1.21, 1.26 (3H, t each, J=6 Hz, $COOCH_2\underline{CH_3}$ of diastereomers), 2.1 (2H, m, C_3 protons), 2.63-3.31 (3H, m, C_2-H and benzylic CH_2), 4.21, 4.29 (2H, q each, J=6 Hz each, $COO\underline{CH_2}CH_3$ of diastreomers), 4.68 (1H, m, $\underline{CH}Cl$), 5.73, 5.82 (1H, each d, J=7 Hz each, vinylic H of diastereomers) and 7.3 (5H, m, aromatic H).

The ethyl esters (XIX a,b) were transesterified with 3-phenoxybenzyl alcohol using butyl titanate as a catalyst, to give 3-phenoxybenzyl esters (XXa,b), as liquids.

Ester (XXa), $C_{22}H_{23}O_3Cl_3$, showed IR bands at: 1730 (ester C=0), 1620, 900 ($CH=CCl_2$), 1587, 691 (aromatic); PMR (Fig. 10) signals at: 0.91 (6H, d, J=6 Hz, methyls of isopropyl), 1.82 (1H, m, $\underline{CH}(CH_3)_2$), 2.25 (3H, m, C_2 and C_3 protons), 4.6 (1H, m, $\underline{CH}Cl$), 5.06 (2H, s, benzylic CH_2), 5.8, 5.9 (1H, each d, J=7 Hz, vinylic proton of diastereomers) and 6.76 - 7.5 (9H, m, aromatic H).

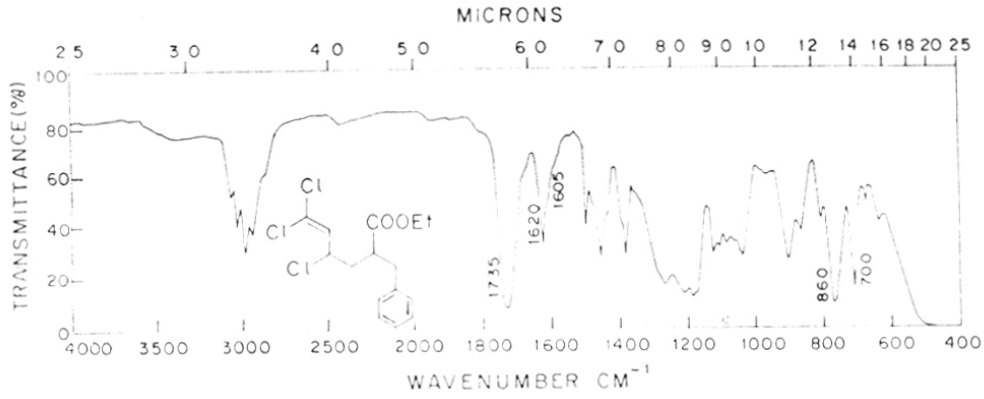


FIG. 9. ETHYL 2-BENZYL-4,6,6-TRICHLOROHEX-5-ENOATE, XIX b

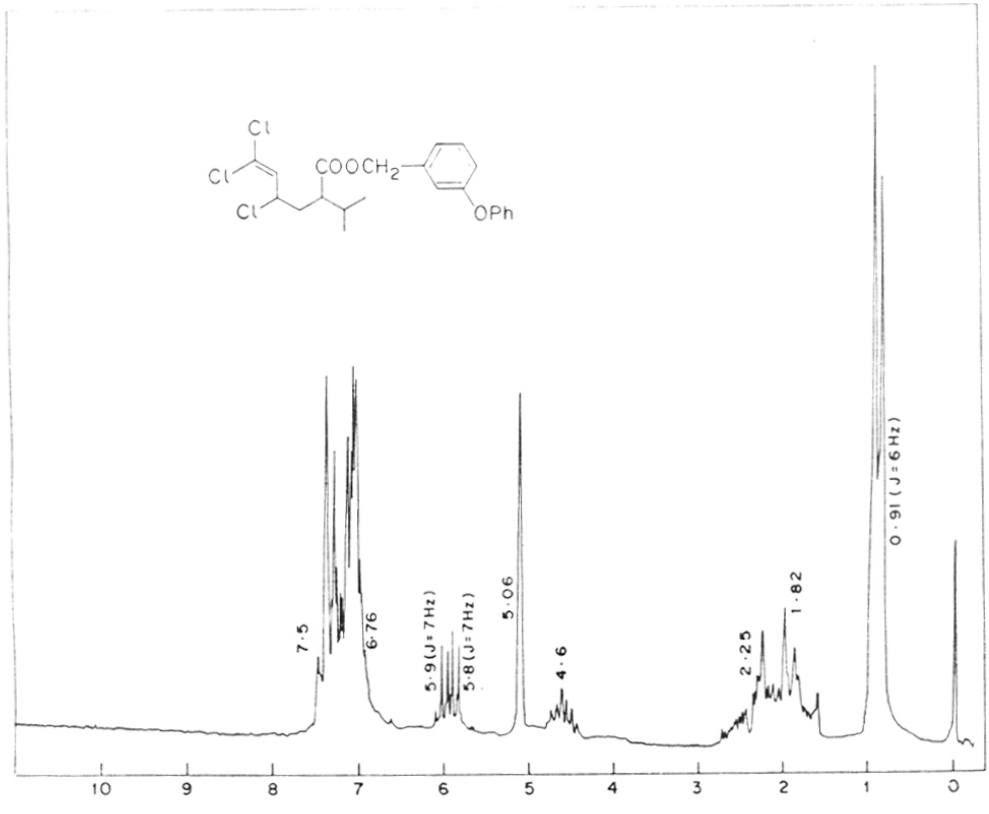


FIG. 10. 3-PHENOXYBENZYL 2-ISOPROPYL-4,6,6-TRICHLOROHEX-5-ENOATE, XX a

Compound XXb, $C_{26}H_{23}O_3Cl_3$, showed IR bands at: 1735 (ester C=O), 1620, 895 ($CH=CCl_2$), 1590, 695 (aromatic); PMR signals at: 2.17 (2H, m, C_3-CH_2), 2.73-3.24 (3H, m, C_2 proton and benzylic CH_2 at C_2), 4.59 (1H, m, C<u>H</u>Cl), 5.68 - 5.79 (1H, d each, J=7 Hz each, vinylic proton of diastereomers) and 6.94-7.4 (14H, m, aromatic H).

J. Drabek and co-workers[39] of Ciba-Geigy have synthesised a number of aliphatic carboxylic acid esters with 3-phenoxybenzyl, α-cyano-3-phenoxybenzyl and other related alcohols (for e.g. α-cyano-3-phenoxybenzyl-2-isopropyl-5-chloro-4-haxenoate). Details regarding their synthesis were however, not mentioned (Chart VI, H); these esters show insecticidal activity against insect species like, spodoptera littoralis, Heliothis virenscens and Aphis fabae. The 3-phenoxybenzyl ester can be considered as 2,3-seco-analogue of an important pyrethroid- Indothrin- synthesised in our laboratory from (+) 3-carene[30]. The acid moiety of the above ester along with its cyano analogue have been synthesised by a sequence of well-known reactions starting from methyl heptenone (Scheme II), which can be prepared in high yields from the naturally occurring, abundantly available, monoterpene, citral, by a known method[56]. With the object of introducing acetoxymethyl grouping at C-5 position, Prins reaction was carried out on methyl heptenone using paraformaldehyde and glacial acetic acid. However, complex mixture of products resulted, probably due to additional sites available viz.

α-to carbonyl function, for other competing reaction, It was therefore, thought desirable to try the Prins reaction on methyl heptenyl acetate.

Sodium borohydride reduction of methyl heptenone (XXI), in aqueous methanol gave methyl heptenol (XXII, R=H), $C_8H_{16}O$, purified by distillation, b.p.84-85°(vapour)/20 mm (lit.[57] b.p. 78-81°/16 mm); It showed IR bands at: 3460 (-OH); PMR signals at:1.15 (3H, d, J=6 Hz, C_1-CH_3), 1.64, 1.73 (each 3H, s, vinyl methyls), 2.17 (1H, br s, -CHO$\underline{H}$, exchangable with D_2O), 3.77 (1H, m, C$\underline{H}$OH) and 4.94 (1H, br t, vinylic H); MS: m/z, 128 (M^+).

Acetylation of methyl heptenol by using acetic anhydride pyridine afforded methyl heptenyl acetate (XXII, R=Ac) showing the following spectral properties. IR bands at: 1733 (acetate C=O), 1240 (acetate); PMR signals at: 1.2 (3H, d, J=7 Hz, CH_3 at C_2), 1.58, 1.66 (each 3H, s, vinyl methyls), 1.96 (3H, s, OCOC$\underline{H}_3$) and 4.9 (1H, t, J=6 Hz, olefinic proton).

Prins reaction (HCHO/AcOH) on XXII, R=Ac gave as the main product the diacetate (XXIII), showed IR (Fig. 11) bands at: 1718, 1242 (acetate), 1645, 885 ($C=CH_2$). This was saponified (MeOH/KOH) followed by fractional distillation gave a thick liquid diol (XXIV), $C_9H_{18}O_2$, in 66% yield. Diol (XXIV) showed IR bands at: 3344 (-OH), 1645, 889 ($C=CH_2$); PMR signals at: 1.18 (3H, d, J=6 Hz, methyl at C-5), 1.73 (3H, s, vinyl methyl), 3.51 (2H, d, J=7 Hz, C$\underline{H}_2$OH), 3.71 (1H, m, C_5-H), 3.86 (2H,

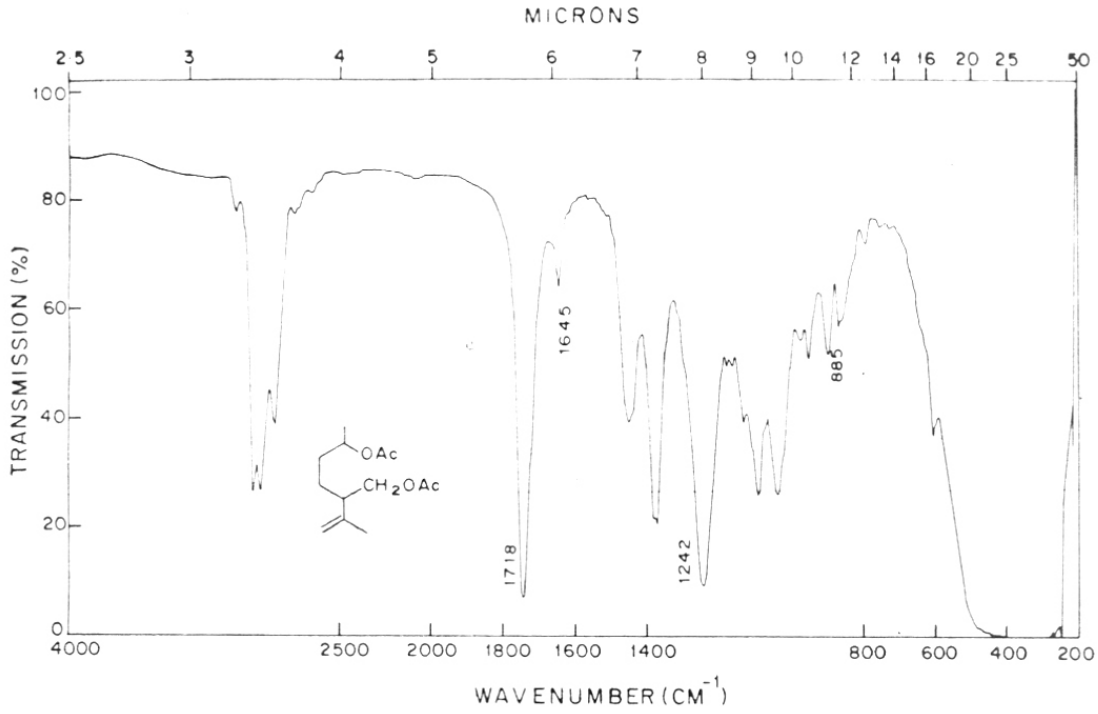


FIG. 11. 1,5-DIACETOXY-2-ISOPROPENYLHEXANE, XXIII

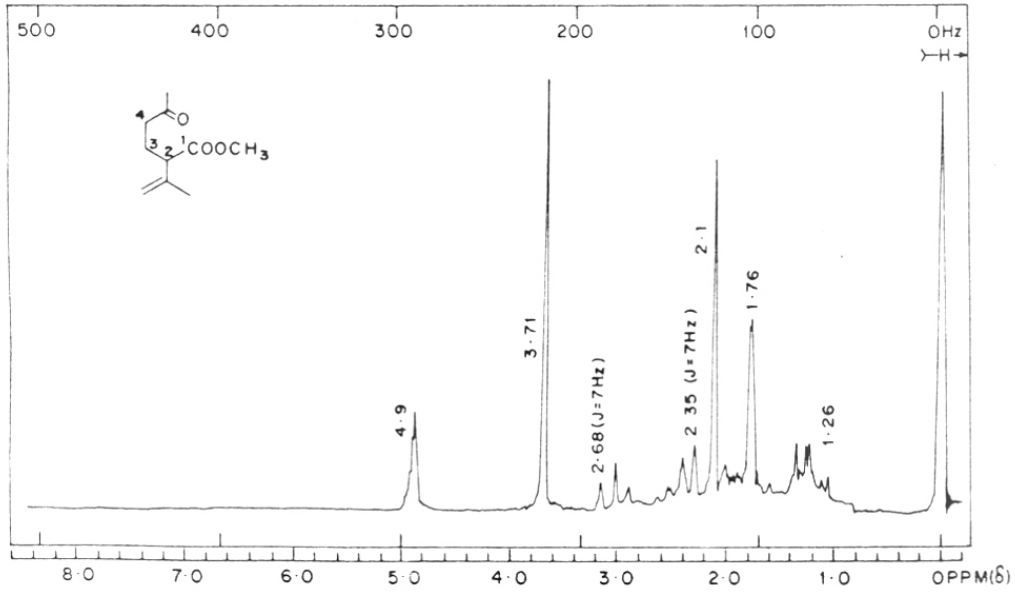


FIG. 12. METHYL 2-ISOPROPENYL-5-OXOHEXANOATE, XXV

br s, -OH, exchangable with D_2O) and 4.83 (2H, br s, $C=C\underline{H}_2$).

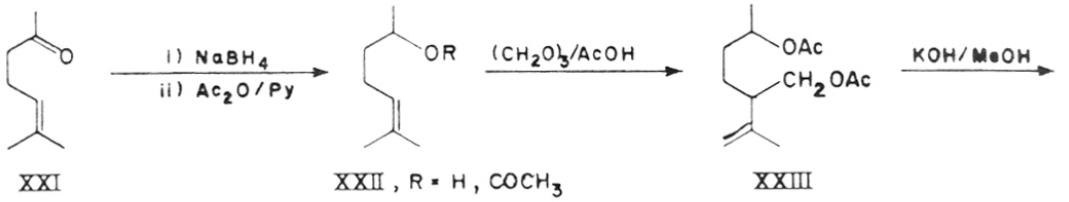
Catalytic hydrogenation of the diol (XXIV), using Pd/C (5%) as catalyst at atmospheric pressure and room temperature (25^{o}) or hydrogenation under pressure, did not proceed satisfactorily, as major portion of the starting compound recovered unreacted and also due to the formation of hydrogenolysis product. This difficulty was overcome by carrying out the hydrogenation on the keto-ester (XXV) prepared from diol (XXIV), as follows.

Jones chromic acid oxidation of XXIV followed by esterification (diazomethane) of the resulting acid, afforded methyl 2-isopropyl-5-oxohexenoate (XXV), $C_{10}H_{16}O_3$ as a liquid; IR bands at: 1736 (ester C=O), 1720 (keto C=O), 1647, 900 ($C=CH_2$); PMR (Fig. 12) signals at: 1.76 (3H, s, vinyl methyl), 2.1 (3H, s, $-COC\underline{H}_3$), 2.35 (2H, t, J=7 Hz, C_4-CH_2), 2.68 (1H, t, J=7 Hz, C_2 proton), 3.71 (3H, s, ester methyl) and 4.9 (2H, s, $C=CH_2$); MS : m/z 184 (M^+).

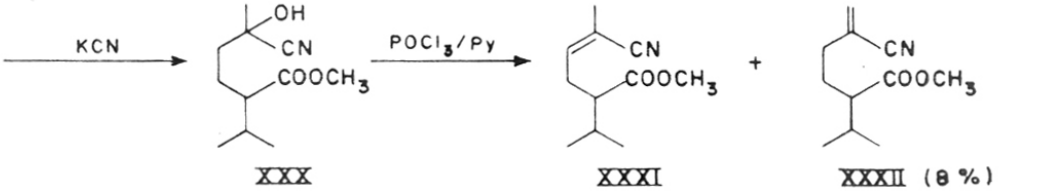
Catalytic hydrogenation of XXV with platinum as a catalyst (710 mm, 25^{o}), in ethanol gave in almost quantitative yield, the dihydroester (XXVI), $C_{10}H_{18}O_3$; IR bands at: 1730 (ester C=O), 1716 (keto C=O); PMR signals at: 0.88, 0.96 (each 3H, d, J=6 Hz, methyls of isopropyl), 2.06 (3H, s, $COC\underline{H}_3$), 2.28 (3H, m, C_2 and C_4 protons) and 3.65 (3H, s, ester methyl); MS: m/z, 186 (M^+).

Reaction of phosphorous pentachloride[58] on XXVI in methylene chloride, followed by chromatographic purification, gave

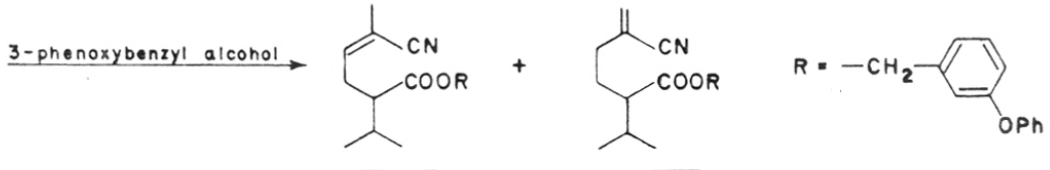
SCHEME II



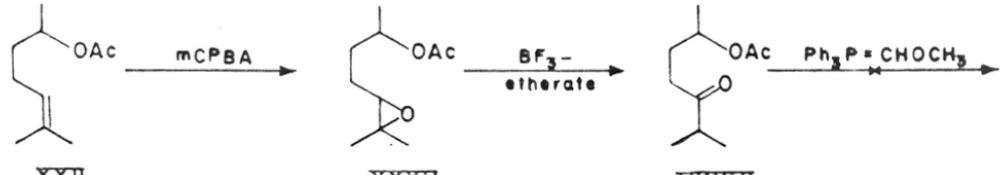
XXI XXII, R = H, $COCH_3$ XXIII XXIV XXV XXVI XXVII XXVIII XXIX



XXX XXXI XXXII (8 %)



XXXIII XXXIV



XXII XXXV XXXVI

TLC pure vinyl chloroester $C_{10}H_{17}O_2Cl$, in 42% yield. IR bands at: 1742 (ester C=O). However, GLC analysis indicated it to be a mixture of E and Z isomers in 3:2 proportion along with minor impurity (8%) of double bond isomer XXVIII; (GLC: 5.87 min, 54%, 6.2 min, 38%, 7.30 min, 8%, column-OV-101-5%, column temperature - 120°, flow rate, nitrogen 30 lbs/cm^2). The latter however, could not be eliminated even after elaborate column chromatography or by attempted double bond isomerisation, by using paratoluene sulphonic acid in benzene under reflux conditions. PMR (Fig. 13) signals at: 0.87, 0.95 (3H each, d, J=6 Hz, methyls of isopropyl), 2.04, 2.06 (3H, s each, methyls on double bond of E and Z isomers), 3.6 (3H, s, ester methyl), 5.27 (1H, two overlapping t each, olefinic protons of E and Z isomers) and low intensity signal at 5.1 (s, C=CH_2 of double bond isomer impurity). MS: m/z, 204(M^+), 206 (^{37}Cl).

The esters (XXVII, as such 8%) was converted by trans-esterification into 3-phenoxybenzyl ester (XXIX), $C_{22}H_{25}O_3Cl$, IR bands at: 1739 (ester C=O), 1587, 690 (aromatic); PMR signals at: 0.89, 0.91 (each 3H, d each, J=6 Hz, methyls of isopropyl), 2.02, 2.04 (3H, s each, vinyl methyls of E and Z isomers), 5.01 (2H, s, benzylic CH_2), 5.49 (1H, m, olefinic protons of E and Z isomers), 6.8-7.48 (9H, m, aromatic H) and low intensity singlet at 5.17 (C=CH_2 of double bond isomer); MS: m/z, 372 (M^+), 374, (^{37}Cl).

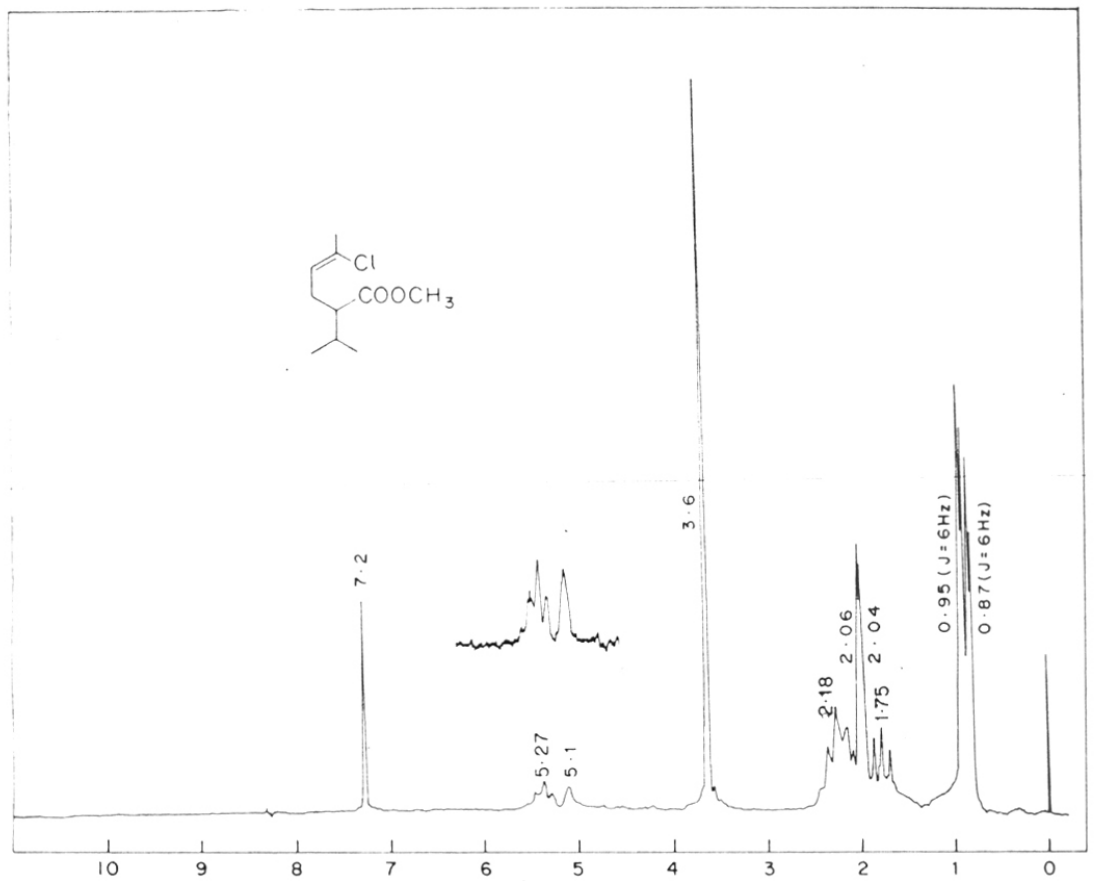


FIG. 13. METHYL 2-ISOPROPYL-5-CHLOROHEX-4-ENOATE, XXVII (XXVIII - 8%)

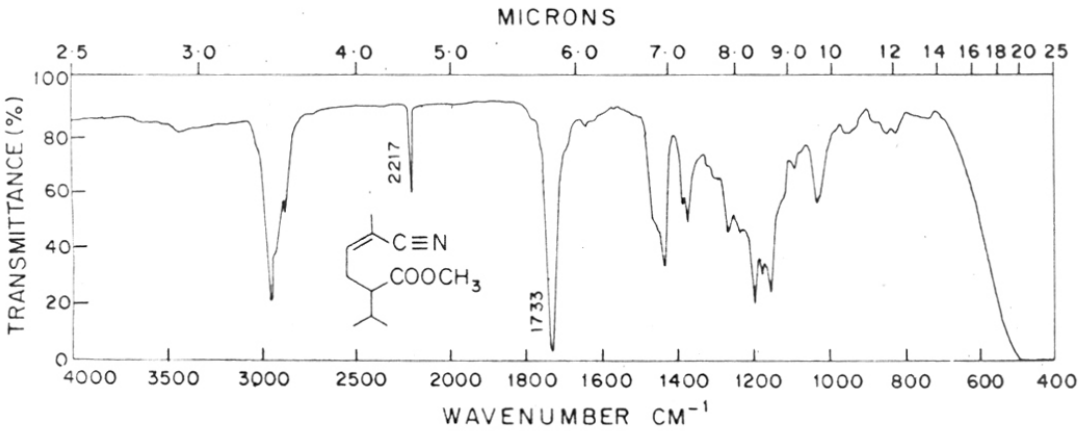


FIG. 14. METHYL 2-ISOPROPYL-5-CYANOHEX-4-ENOATE, XXXI, XXXII, 8%

The keto ester (XXVI) was converted to the cyanohydrin ester (XXX), by reacting with potassium cyanide[60] in acetic acid and ethanol; IR bands at: 2210 (C≡N), 1736 (C=0). The latter on dehydration ($POCl_3$/Py) gave unsaturated ester purified by column chromatography over silicic acid, impregnated with $AgNO_3$ (15%). The fraction eluted with pet.ether + benzene (1:1), gave XXXI in 50% yield. It showed IR (Fig. 14) band at: 2217 (C≡N), 1733 (ester C=0). However, according to GLC and PMR it consisted mainly of Z isomer of XXXI, along with a small impurity of double bond isomer XXXII; GLC: Z isomer, 8.48 min, 92% ; double bond isomer, 9.86 min, 8%; column, OV-101 5%; temperature - 120°C: H_2 flow rate, 30 lbs/cm^2. Compound XXXII, however, could not be eliminated even by elaborate column chromatography; PMR (90 MHz, $CDCl_3$) signals at: 0.92, 0.94 (3H each, d each, J=6 Hz each, methyls of isopropyl), 1.9 (3H, s, methyl on double bond), 3.54 (3H, s, ester methyl), 6.06 (1H, t of quartets, J=7 Hz, $J_{\text{homoallylic cisoid}}$ = 1.5 Hz, olefinic proton of Z isomer) and two low intensity singlets at 5.6 and 5.73 (C=CH_2 protons of XXXII). The signal at 5.73 is assigned to the proton cis to cyano group (anisotropic deshielding). The assignment of Z configuration to XXXI is based on the observed chemical shift value for olefinic proton (6.06 δ), which is in close agreement with the calculated value (6.04 δ)[59] and its homoallylic coupling constant (J_{cisoid} = 1.5 Hz), with C_6 protons[61]. It was

converted similarly into 3-phenoxybenzyl ester (XXXIII), $C_{23}H_{25}O_3N$, by transesterification; IR bands at: 2219 (C≡N), 1730 (ester C=O), 1587, 709 (aromatic); PMR (90 MHz, $CDCl_3$, Fig.-15) signals at: 0.89, 0.91 (each 3H, d, J=6 Hz, methyls of isopropyl), 1.9 (3H, s, methyl on double bond), 5.1 (2H, s, benzylic $C\underline{H}_2$), 6.08 (1H, t of quartets, J=8 Hz, $J_{homoallylic\ cisoid}$ = 1.5 Hz, olefinic proton of Z isomer) and 6.9-7.4 (9H, m, aromatic H). In addition two low intensity singlets at 5.6 and 5.8 were also observed due to $C=C\underline{H}_2$ protons of double bond isomer impurity XXXIV; MS: m/z, 363(M^+).

The acetate (XXII), on treatment with metachloroperbenzoic acid gave the corresponding epoxide (XXXV), $C_{10}H_{18}O_3$, as a liquid in almost quantitative yield. It showed IR bands at: 1740, 1240 (acetate); PMR signals at: 1.25 (9H, m, methyls), 1.58 (4H, m, methylenes), 1.96 (3H, s, $OCOC\underline{H}_3$), 2.56 (1H, t, J=5 Hz, C_5-C<u>H</u>) and 4.83 (1H, m, C_2-H). The latter, on treatment with BF_3-Et_2O gave the corresponding ketone (XXXVI), $C_{10}H_{18}O_3$, as a liquid; IR bands at: 1742 (acetate C=O), 1721 (keto C=O), 1240 (acetate); PMR signals at: 1.08, 1.1 (each 3H, d, J=6 Hz, methyls of isopropyl), 1.98 (3H, s, $OCOC\underline{H}_3$), 2.43 (3H, m, protons adjacent to C=O) and 4.76 (1H, m, C<u>H</u>OAc).

With the ultimate object of introducing an aldehyde function at C-5, the ketone (XXXVI), was subjected to the Wittig reaction, using methoxymethylenetriphenyl phosphorane, hoping to get the methoxyenol ether, which on acid hydrolysis would lead to the aldehydoacetate. However, Wittig reaction on ketone under different experimental conditions was unsuccessful.

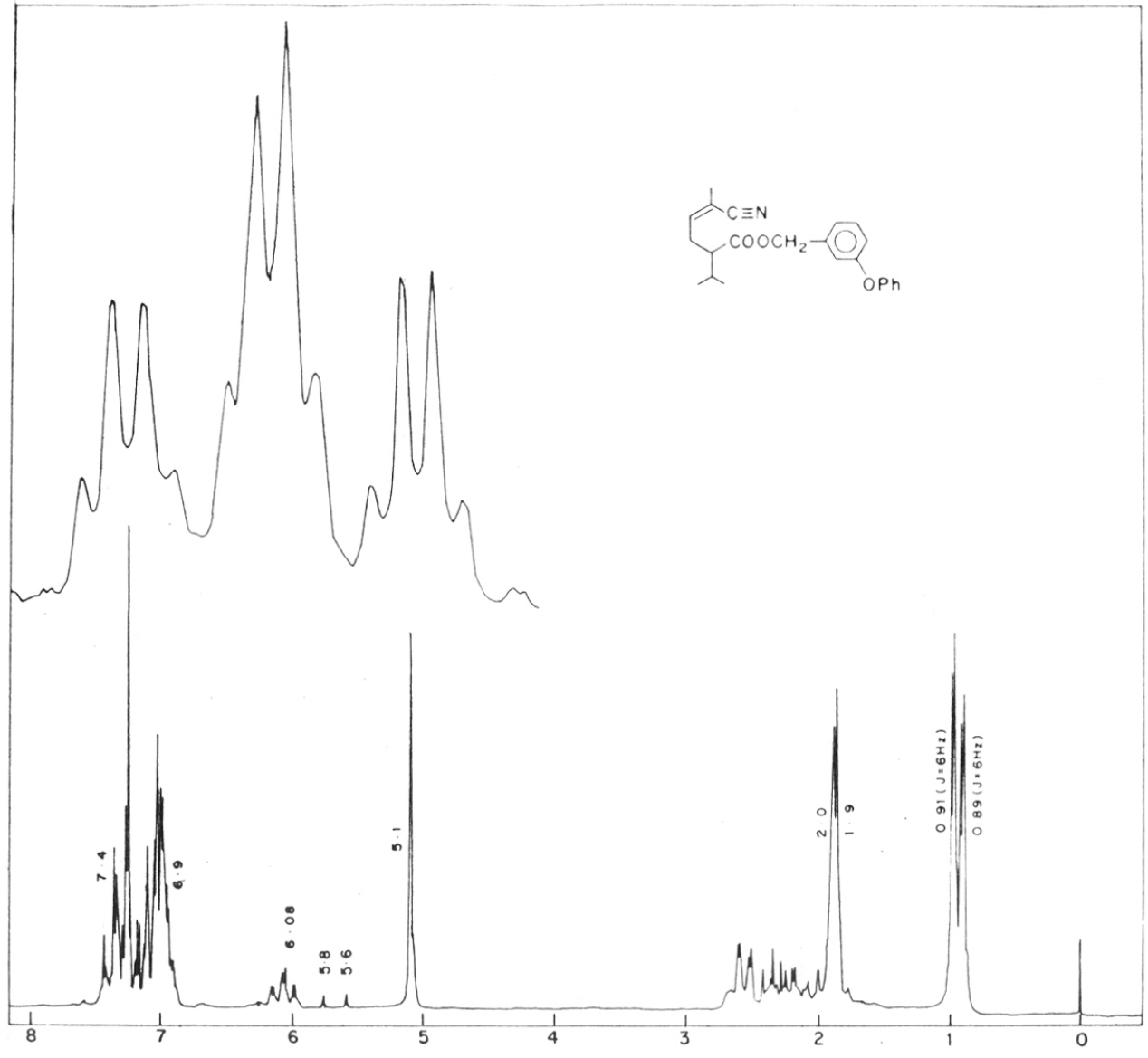


FIG. 15 3-PHENOXYBENZYL 2-ISOPROPYL-5-CYANOHEX-4-ENOATE, XXXIII

All these compounds viz. XVIIa, XVIIb(X=Cl), XVIIa, XVIIb, (X=Br), XXa, XXb, XXIX, XXXIII were tested for their insecticidal and larvicidal activity against mosquitoes (Aedes aegypti), house-flies (Musca domestica) and larvicidal activity against 4th instar mosquito larvae (Aedes aegypti, yellow fever larvae).

3-Phenoxybenzyl esters were tested for their insecticidal activity against house-flies (Musca domestica) by topical application. Testing against mosquitoes (Aedes aegypti) was carried out by exposure for 24 hr to the residual deposites, obtained on filter paper dipped in 10 or 5% solution of compound in acetone. In larvicidal test, esters were added to 50 ml water in desired concentration. Minimum 10 number of larvae were released in this water; normal food was supplied and mortality counts were taken after 24 hr.

In all these tests carried out, the results are based on the basis of minimum three replicates in each case and mortality was observed after 24 hr. Average mortality figures are shown in the table.

Test Compound No.	Insecticidal activity (% mortality)				Larvicidal activity (% mortality)	
	Musca domestica		Aedes aegypti		4th Instar mosquito larvae	
	Dose		Dose		Dose	
	1 μg/ insect	10 μg/ insect	1% soln.	5% soln.	10 ppm	100 ppm
XVIIa, X=Cl	100	100	100	100	100	
XVIIa, X=Br	100	100	100	100	100	
XVIIb, X=Cl	0	0	0	0	0	0
XVIIb, X=Cl	0	0	0	0	0	0
XXa	100	100	100	100	100	
XXb	0	0	0	0	0	0
XXIX	90	100	80	100	-	-
XXXIII	60-70	80	40	70	-	-

EXPERIMENTAL

Ethyl 2-carboethoxy pent-4-enoate (XI):

Dry ethanol (500 ml), was placed in a 1 litre round bottom flask fitted with reflux condenser and overhead mechanical stirrer. Sodium (22 g, 0.95 mol), was added to it in small portions with stirring over a period of 3 hr. Stirring was continued for additional 3 hr, cooled and diethyl-malonate (150 g, 0.94 mol), was added slowly through a dropping funnel during 4 hr. The reaction mixture was stirred for additional 4 hr, at room temperature to ensure the complete anion formation. The contents were then cooled to 0^{o} and allyl chloride (70 g, 0.92 mol), was added to it during 30 min under stirring. Stirring continued for 10 hr, heated on water-bath for 1 hr, cooled, diluted with water (2 litres) and transfered to a separating funnel. The organic layer separated and the aqueous layer extracted with ether (200 ml x 2). Combined organic layer was washed with water, brine, dried and evaporated to give a liquid (200 g), which was fractionated on a spining band column (height 1 meter, reflux ratio 1:20) and fractions were collected. The fraction boiling at 110^{o} (vapour)/6 mm, gave the ester (XI), of 98% purity (80 g); GLC: 2.41 min., 98%; column, OV-101; column temperature, 145^{o}; carrier gas nitrogen, flow rate, 30 ml/min.

Analysis:

Found: C, 59.8; H, 8.0; $C_{10}H_{16}O_4$

requires: C, 60.0; H, 8.0%.

IR bands at: 3030, 2980, 1735, 1640, 1440, 1365, 1270, 1150, 1035, 910 and 850 cm^{-1}.

The fraction boiling at 145°(vapour)/6 mm, gave the dialkylated compound (XII, 25 g) of 96% purity, GLC: 5.73 min, 96%, column temperature 145°, column, OV-101, carrier gas, nitrogen flow rate 30 ml/min.

Analysis :

Found: C, 64.8; H, 8.4; $C_{13}H_{20}O_4$

requires: C, 65.0; H, 8.3%.

IR bands at: 3028, 2970, 1733, 1645, 1435, 1360, 1270, 1150, 1030 and 905 cm^{-1}.

Ethyl 2-carboethoxyl-2-isopropylpent-4-enoate (XIIIa):

To a stirred suspension of sodium hydride (1.8 g, 0.075 mol) in dry benzene (50 ml) and DMF (10 ml), pentenoate (XI, 10 g, 0.06 mol), was added slowly with stirring under nitrogen atmosphere and stirring continued for 2 hr to ensure complete anion formation. Isopropyl iodide (9 ml, 15.3 g, 0.09 mol), was added to it during 15 min under stirring and reaction mixture stirred overnight, then heated on waterbath for 2 hr, cooled, diluted with water and extracted with ether (100 ml, 50 ml x 2). The combined organic layer was washed with water, brine, dried and evaporated to give a TLC pure

liquid XIIIa (9 g, 74%), b.p.105°(vapour)/10 mm.

Analysis:

Found: C, 64.1; H, 9.0; $C_{13}H_{22}O_4$

requires: C, 64.5; H, 9.1%.

IR bands at: 3030, 2980, 1732, 1645, 1435, 1360, 1280, 1200, 1150, 1030, 915 and 850 cm^{-1}.

Ethyl 2-carboethoxy-2-benzylpent-4-enoate (XIIIb):

To a stirred suspension of sodium hydride(1.5 g, 62 mmol), in dry benzene (85 ml), containing DMF (15 ml), pentenoate (XI, 10 g, 41 mmol), was added slowly with stirring under nitrogen and stirring continued for 2 hr. Benzyl chloride (10 g, 0.78 mol), was added to the above suspension during 15 min. and the mixture stirred overnight. The reaction mixture was then heated on a water-bath for 2 hr, cooled, diluted with water and worked up as described earlier to give XIIIb (14 g, 96%), b.p.: 110°(vapour)/2 mm;

MS: m/z, 290 (M^+).

Analysis:

Found: C, 70.1; H, 7.5; $C_{17}H_{22}O_4$

requires: C, 70.3; H, 7.6%.

IR bands at: 2890, 1730, 1645, 1600, 1440, 1270, 1205, 1040, 920, 860, 745 and 700 cm^{-1}.

General procedure for decarboethoxylation:

Ethyl 2-isopropylpent-4-enoate (XIVa):

To a solution of ester (XIIIa, 23 g, 0.95 mol), in DMSO (200 ml), solid potassium acetate (19 g, 0.19 mol) and water

(3.6 ml, 0.2 mol), was added and the mixture heated under reflux for 6 hr, until no further evolution of carbon dioxide can be detected (tested by bubbling in lime solution). It was then cooled, diluted with water and extracted with ether (100 mlx 3). The combined organic layer was washed with water, brine, dried and evaporated to give an oil, purified by distillation to give XIVa (16 g, 99%); b.p.: 150°(vapour)/ 60 mm.

Analysis:

Found: C, 70.2; H, 10.5; $C_{10}H_{18}O_2$

requires: C, 70.5; H, 10.6%.

IR bands at: 3040, 2980, 2940, 1733, 1645, 1470, 1445, 1390, 1375, 1182, 1040 and 920 cm^{-1}.

Ethyl 2-benzyl pent-4-enoate (XIVb):

To a solution of ester (XIIIb, 11 g, 37 mmol), in wet DMSO (100 ml, containing 1.2 ml water), solid potassium acetate (6.5 g, 0.66 mol) was added. The reaction mixture was heated under reflux for 4 hr, cooled and workedup as described earlier to give a TLC pure ester (XIVb), further purified by distillation (8.1 g, 98%), b.p. 120°(vapour)/40 mm.

Analysis:

Found: C, 76.8; H, 8.3; $C_{14}H_{18}O_2$

requires: C, 77.1; H, 8.2%.

IR bands at: 3030, 2990, 1735, 1645, 1590, 1445, 1280, 1245, 1205, 1180, 900, 865, 749 and 700 cm^{-1}.

Ethyl 2-isopropyl-3-formyl propionate (XVa):

A stream of ozonised oxygen (approx. 1 g/hr), was bubbled through an ice cooled (-5^{o}) solution of XIVa (3 g, 17 mmol), in ethyl acetate (75 ml) and acetic acid (25 ml), till the absorption of ozone was completed (tested by starch iodide paper). The solution of ozonide in ethyl-acetate and acetic acid was transfered to a 250 ml round bottom flask and cooled to 0^{o}. Dimethyl sulfide (2.4 ml, 0.2 mol), was then added dropwise to it with stirring, maintaining temperature at 0 to 5^{o} under nitrogen atmosphere. The mixture was then stirred at the same temperature for one hour and 1 hr at room temperature. The reaction mixture was then washed thoroughly with water, brine and dried. Concentration of organic layer gave TLC pure aldehyde (XVa, 2.6 g, 85%) as a liquid.

Analysis:

Found: C, 62.4; H, 9.3; $C_9H_{16}O_3$

requires: C, 62.8; H, 9.3%.

IR bands at: 2980, 2710, 1715, 1735, 1470, 1392, 1373, 1230, 1180, 1140, 1040, 927 and 865 cm^{-1}.

Ethyl 2-benzyl-3-formyl propionate (XVb) :

A stream of ozonised oxygen (approx 1 g/hr), was bubbled through an ice cooled solution of XIVb (2 g, 9 mmol), in ethyl acetate (35 ml) and acetic acid (12 ml), till no more ozone is

absorbed. Usual reductive workup of ozonide, as described earlier gave TLC pure aldehyde (XVb, 1.6 g, 81%), as a liquid. Analysis:

Found: C, 70.6; H, 7.3; $C_{13}H_{16}O_3$

requires: C, 70.9; H, 7.3%.

IR bands at: 3010, 2990, 2710, 1730, 1453, 1385, 1240, 1184, 1100, 1050, 750 and 700 cm^{-1}.

General procedure for Wittig reaction:

Ethyl 2-isopropyl-5,5-dichloropent-4-enoate (XVIa, X=Cl):

Aldehyde (XVa, 1.7 g, 9 mmol), was added by a syringe to a well stirred mixture of bromochloroform (3.5 g, 15 mmol) and triphenyl phosphine (6 g, 20 mmol), in dry benzene (15 ml), at 0° under nitrogen. The reaction mixture was stirred in an ice bath for 4 hr, then allowed to attain room temperature and stirred overnight. The reaction mixture was transfered to a separating funnel washed with water, organic layer separated, dried and concentrated. Residue was repeatedly extracted with hot pet.ether ($60-80^{\circ}$, 20 ml x 5), to remove most of the insoluble triphenylphosphine oxide. The crude product, obtained after evaporation of pet.ether (2 g), was purified by column chromatography over silicic acid (25 g) and eluted successively with pet.ether, pet.ether-chloroform mixtures and chloroform. The fraction eluted with pet.ether + 10% chloroform was composed entirely of dihalovinyl ester (XVIa, X=Cl, 1.3 g, 56%), b.p. 110°/10 mm; MS: m/z, 237 (M^+), 239, 241 (^{37}Cl).

Analysis:

Found: C, 50.4; H, 6.6; Cl, 29.2; $C_{10}H_{16}O_2Cl_2$

requires: C, 50.6; H, 6.7; Cl, 29.5%.

IR bands at: 2980, 1735, 1620, 1470, 1375, 1170, 1030, 900, 870, 850, 790 and 760 cm^{-1}.

Ethyl 2-benzyl-5,5-dichloropent-4-enoate (XVIb, X=Cl):

Aldehyde (XV^b, 1.1 g, 5 mmol), was added to a stirred and cooled solution of bromochloroform (3 g, 15 mmol) and triphenyl phosphine (2.7 g, 10 mmol), in dry benzene (20 ml), stirring continued at 0° for 4 hr, then at room temperature for 16 hr. Extractive workup of the reaction mixture as described earlier, gave a product, purified by column chromatography over silicic acid (20 g) and eluted with pet.ether containing 15% chloroform to give XVIb, X=Cl (1.0 g, 60%); b.p.150°/10 mm; MS: m/z, 286(M^+), 288, 290 (^{37}Cl).

Analysis:

Found: C, 58.6; H, 5.5; Cl, 24.1; $C_{14}H_{15}O_2Cl_2$

requires: C, 58.8; H, 5.6; Cl, 24.5%.

IR bands at: 3010, 2990, 1730, 1620, 1605, 1495, 1450, 1365, 1170, 1035, 900, 750 and 700 cm^{-1}.

Ethyl 2-isopropyl-5,5-dibromopent-4-enoate (XVIa, X=Br):

To an ice cooled and stirred solution of triphenyl phosphine (5.2 g, 19 mmol) and carbon tetrabromide (3.3 g, 9.9 mmol), in dry methylene chloride (20 ml), under nitrogen, a

solution of aldehyde (XVa, 1.7 g, 9.8 mmol), in methylene chloride (5 ml), was added by syringe. Stirring was continued at 0° for 30 min, allowed to attain room temperature, stirred for additional 4 hr, and washed with water. Excess of methylene chloride was skipped off and the residue was repeatedly extracted with hot pet.ether (60-80°, 20 ml x 5). Oil obtained, after evaporation of pet.ether, was purified by column chromatography over silicic acid (30 g) and eluted with pet.ether containing 25% chloroform to give TLC pure dibromovinyl ester, as a liquid (XVIa, X=Br, 1.9 g, 61%); b.p.150°/6 mm; MS: m/z, 320 (M^+), 322, 324 (^{81}Br).

Analysis:

Found: C, 37.0; H, 4.6; Br, 49.5; $C_{10}H_{16}O_2Br_2$

requires: C, 37.2; H, 4.6; Br, 49.7%.

IR bands at: 3040, 2980, 1730, 1470, 1375, 1185, 1040 and 1000 cm^{-1}.

Ethyl 2-benzyl-5,5-dibromopent-4-enoate (XVIb, X=Br):

To an ice cooled and stirred solution of triphenyl phosphine (1.7 g, 6 mmol) and carbon tetrabromide (1.1 g, 3 mmol), in dry methylene chloride (20 ml), under nitrogen, a solution of aldehyde (XVb, 0.6 g, 2.7 mmol), was added and stirring continued for another period of 4 hr. Usual workup of the product as described earlier and chromatographic purification, gave dibromovinyl ester (XVIb, X=Br, 0.565 g, 54%), as a liquid; MS: m/z, 372 (M^+), 374, 376 (^{81}Br).

Analysis :

Found: C, 45.4; H, 4.3; Br, 42.6; $C_{14}H_{16}O_2Br_2$

requires: C, 45.2; H, 4.3; Br, 43.0%.

IR bands at: 3030, 3010, 2985, 1735, 1620, 1450, 1380, 1225, 1180, 1165, 1035, 910, 880, 850, 750 and 700 cm^{-1}.

3-Phenoxybenzyl 2-isopropyl-5,5-dichloropent-4-enoate (XVIIa. X=Cl):

A solution of ester (XVIa, X=Cl, 0.47 g, 2 mmol), 3-phenoxybenzyl alcohol (0.6 g, 3 mmole), in xylene (10 ml), containing butyl titanate (0.005 g), was heated under reflux for 10 hr, excess of xylene distilled off, residue taken up in pet.ether and purified by chromatography over silicic acid (10 g). The column was successively eluted with pet.ether, pet.ether-benzene mixtures and chloroform. The fraction eluted with pet.ether-benzene (1:1), gave TLC pure XVIIa, X=Cl (0.65 g, 84%) as a thick liquid; MS: m/z, 392 (M^+), 394, 396 (^{37}Cl).

Analysis:

Found: C, 64.1; H, 5.6; Cl, 17.5; $C_{21}H_{22}O_3Cl_2$

requires: C, 64.3; H, 5.6; Cl, 17.8%.

IR bands at: 3020, 2980, 1733, 1620, 1587, 1450, 1260, 1215, 1165, 880 and 699 cm^{-1}.

3-Phenoxybenzyl 2-isopropyl-5,5-dibromopent-4-enoate (XVIIa, X=Br):

A solution of XVIa, X=Br (0.467 g, 1.4 mmol) and 3-phenoxybenzyl alcohol (0.4 g, 2 mmol), in xylene (10 ml), containing butyl titanate (0.001 g), was refluxed for 10 hr. The reaction mixture on usual workup and chromatographic purification as described above gave XVIIa, X=Br (0.63 g, 90%) as a thick liquid; MS: m/z, 480(M^+), 482, 484 (^{81}Br).

Analysis:

Found: C, 52.1; H, 4.6; Br, 33.0; $C_{21}H_{22}O_3Br_2$

requires: C, 52.3; H, 4.6; Br, 33.2%.

IR bands at: 3020, 2980, 1735, 1588, 1480, 1450, 1260, 1215, 1160, 790 and 692 cm^{-1}.

3-Phenoxybenzyl 2-benzyl-5,5-dichloropent-4-enoate (XVIIb, X=Cl):

A solution of ester (XVIb, X=Cl , 0.43 g, 1.5 mmol) and 3-phenoxybenzyl alcohol (0.4 g, 2 mmol), in xylene (10 ml), containing butyl titanate (0.005 g), was heated under reflux for 12 hr. Excess of xylene was distilled, residue taken up in pet.ether and purified by column chromatography over silicic acid (10 g). The fraction eluted with pet.ether containing 25% benzene gave TLC pure 3-phenoxybenzyl ester (XVIIb, X=Cl, 0.612 g, 92%), as a thick liquid; MS: m/z 440 (M^+), 442, 444 (^{37}Cl).

Analysis:

Found: C, 68.4; H, 5.1; Cl, 15.8; $C_{25}H_{22}O_3Cl_2$

requires: C, 68.2; H, 5.0; Cl, 15.9%.

IR bands at: 3025, 3010, 2970, 1735, 1585, 1490, 1450, 1255, 1215, 1160, 750 and 700 cm^{-1}.

3-Phenoxybenzyl 2-benzyl-5,5-dibromopent-4-enoate (XVIIb, X=Br):

A solution of XVIb, X=Br (0.341 g, 0.9 mmol), 3-phenoxybenzyl alcohol(0.3 g, 1.5 mmol), in xylene (10 ml), containing butyl titanate (0.005 g) was refluxed for 12 hr, workedup and purified as described earlier to give XVIIb, X=Br (0.43 g, 88%); MS: m/z, 528 (M^+), 530, 532 (^{81}Br).

Analysis :

Found: C, 56.2; H, 4.1; Br, 29.9; $C_{25}H_{22}O_3Br_2$

requires: C, 56.6; H, 4.1; Br, 30.2%.

IR bands at: 3030, 2980, 1735, 1590, 1490, 1450, 1260, 1215, 1165, and 695 cm^{-1}.

Ethyl 2-isopropyl-4,6,6,6-tetrachlorohexanoate (XVIIIa):

To a refluxing solution of ester (XIVa, 3 g, 17 mmol), in carbon tetrachloride (50 ml), benzoyl peroxide (0.3 g in 5 ml CCl_4 and dried over anhydrous sodium sulphate), was added in small portions at regular intervals of 6 hr. Refluxing was continued for another period of 48 hr. The reaction mixture was then cooled, transfered to separating funnel and washed with water, aq. sodium bisulfite solution, aq. sodium carbonate, brine and dried. Evaporation of carbon tetrachloride gave crude tetrachloroester (XVIIIa, 5.2 g, 95%), purified by distillation under reduced pressure; b.p.160°/5 mm; MS: m/z 322 (M^+), 324, 326, 328, 330 (^{37}Cl).

Analysis:

Found: C, 41.2; H, 5.6; Cl, 39.8; $C_{11}H_{18}O_2Cl_4$

requires: C, 41.4; H, 5.6; Cl. 40.1%.

IR bands at: 2980, 2885, 1733, 1467, 1375, 1175, 1045, 800 and 700 cm^{-1}.

Ethyl 2-benzyl-4,6,6,6-tetrachlorohexanoate (XVIIIb):

To a refluxing solution of ester (XIVb, 3 g, 14 mmol), in carbon tetrachloride (30 ml), a solution of benzoyl peroxide (0.3 g in 5 ml CCl_4), was added in small portions at regular intervals of 6 hr. Refluxing was continued for another period of 40 hr, and worked up as described earlier to give crude product XVIIIb (4.8, 95%), purified by distillation, b.p. 180°/1 mm; MS: m/z, 370 (M^+), 372, 374, 376, 378 (^{37}Cl).

Analysis:

Found: C, 48.2; H, 4.8; Cl, 37.4; $C_{15}H_{18}O_2Cl_4$

requires: C, 48.6; H, 4.9; Cl, 37.8%.

IR bands at: 2980, 2885, 1730, 1585, 1467, 1375, 1175, 1045, 800 and 700 cm^{-1}.

Ethyl 2-isopropyl-4,6,6-trichloro-5-hexenoate (XIXa):

A mixture of carbon tetrachloride adduct XVIIIa (0.5 g, 1.6 mmol), potassium acetate (0.17 g, 1.6 mmol), in dry DMF (5 ml), was heated under stirring at 100° for 3 hr. The reaction mixture was cooled, diluted with water and extracted with ether (25 ml x 3). The combined ether layer was washed with water, brine, dried and concentrated to give an oil

(0.41 g), purified by chromatography over silicic acid (1:10). The column was successively eluted with pet.ether, pet.ether-chloroform mixtures and chloroform. The fraction eluted with pet.ether + 15% chloroform gave a TLC pure colourless liquid identified as XIXa (0.280 g, 63%).

Analysis:

Found: C, 46.0; H, 5.8; Cl, 36.4; $C_{11}H_{17}O_2Cl_3$

requires: C, 46.1; H, 5.9; Cl, 36.7%.

IR bands at: 2980, 1730, 1620, 1470, 1375, 1205, 1175,1140, 1040 and 900 cm^{-1}.

Ethyl 2-benzyl-4,6,6-trichloro-5-hexenoate(XIXb):

A mixture of tetrachloroester (XVIIIb, 0.370 g, 1 mmol) and KOAc (0.098 g, 0.97 mmol), in dry DMF (5 ml), was heated in an oil bath with stirring at 100° for 3 hr. The reaction mixture was workedup as described earlier and purified by chromatography over silicic acid, to give TLC pure XIXb, as a liquid (0.285 g,77%); MS: m/z, 334 (M^+), 336, 338, 340 (^{37}Cl).

Analysis:

Found: C, 53.7; H, 5.1; Cl, 31.1; $C_{15}H_{17}O_2Cl_3$

requires: C, 53.9; H, 5.1; Cl, 31.4%.

IR bands at: 3030, 3010, 2990, 1735, 1620, 1585, 1450, 1380, 1210, 1180, 1030, 895 and 700 cm^{-1}.

3-Phenoxybenzyl 2-isopropyl-4,6,6-trichlorohex-5-enoate(XXa):

A solution of ethyl ester (XIXa, 0.4 g, 1.4 mmol), 3-phenoxybenzyl alcohol (0.5 g, 2.5 mmol) and butyl titanate

(0.015 g), in xylene (10 ml), was refluxed for 12 hr. Usual workup of the product followed by chromatographic purification gave XXa (0.56 g, 91%), as a thick liquid; MS: m/z, 440 (M^+), 442, 444, 446 (^{37}Cl).

Analysis:

Found: C, 59.8; H, 5.1; Cl, 23.8; $C_{22}H_{23}O_3Cl_3$

requires: C, 60.0; H, 5.2; Cl, 23.9%.

IR bands at: 3020, 2980, 1730, 1620, 1587, 1490, 1450, 1260, 1218, 1160, 900 and 691 cm^{-1}.

3-Phenoxybenzyl 2-benzyl-4,6,6-trichlorohex-5-enoate (XXb):

To a solution of XIXb (0.46 g, 1.42 mmol), 3-phenoxybenzyl alcohol (0.5 g, 2.5 mmol) and butyl titanate (0.025 g) in xylene (10 ml), was refluxed for 12 hr, workedup and purified by column chromatography to give XXb (0.6 g, 89%), as a thick liquid.

Analysis:

Found: C, 63.7; H, 4.6; Cl, 21.2; $C_{26}H_{23}O_3Cl_3$

requires: C, 63.9; H, 4.7; Cl, 21.5%

IR bands at: 3010, 2980, 1735, 1620, 1590, 1490, 1445, 1258, 1215, 1160, 895, 860 and 695 cm^{-1}.

6-Methyl-hept-5-ene-2-ol (XXII):

To a solution of methyl heptenone (XXI, 32.0 g, 0.25 mol), in methanol (150 ml), at 0°, containing 2 ml water, sodium borohydride (8 g) was added over a period of 30 min.

The mixture was stirred at room temperature for 12 hr. Excess of methanol was distilled under reduced pressure, the residue diluted with water and extracted with ether (100 ml x 3), washed with water, brine, dried and evaporated to give a liquid, purified by distillation to furnish pure XXII, R=H (28 g, 86%), b.p.84-85° (vapour)/20 mm, (reported[57] b.p.78-81°(vapour)/16 mm).

Analysis:

Found: C, 73.9; H, 13.8; $C_8H_{16}O$

requires: C, 73.8; H, 13.8%.

IR bands at: 3460, 2980, 2930, 1450, 1375, 1125 and 1050 cm^{-1}.

2-Acetoxy 6-methylhept-5-ene (XXII, R=Ac):

To an ice cooled and stirred solution of XXII, R=H (100 g, 0.78 mol), in pyridine (150 ml), acetic anhydride (102 g, 1 mol), was added in small lots with shaking during 30 min. The mixture was kept at room temperature for 12 hr, poured onto crushed ice under stirring, allowed to stand for 30 min. and extracted with chloroform. The chloroform extract was washed with water, dil. HCl, water, brine, dried and evaporated to furnish acetate (XXII, R=Ac, 112 g, 90%).

Analysis:

Found: C, 70.4; H, 10.5; $C_{10}H_{18}O_2$

requires: C, 70.6; H, 10.6%.

IR bands at: 2960, 2920, 1733, 1438, 1370, 1240, 1130, 1063, 1018, 950 and 840 cm^{-1}.

1,5-Diacetoxy-2-isopropenylhexane (XXIII):

A mixture of methylheptenyl acetate (XXII, R=Ac, 25 g, 0.147 mol), paraformaldehyde (4.5 g, 0.05 mol) and glacial acetic acid (250 ml), was refluxed for 48 hr. Excess of acetic acid was distilled. The reaction mixture was cooled, diluted with water and extracted with ether (100 ml x 3). The combined organic layer was washed with water, brine, dried and concentrated to give a dark coloured oil (27 g, 81.6%), containing diacetate XXIII as a major product.

IR bands at: 2985, 2965, 1718, 1645, 1450, 1375, 1242, 1045, 1025, 950 and 885 cm^{-1}.

1,5-Dihydroxy-2-isopropenylhexane (XXIV):

To a stirred solution of an oil XXIII (27 g, 0.119 mol), in methanol (250 ml), 50% solution of potassium hydroxide (30 g, 0.5 mol), was added slowly and refluxed for 6 hr. Excess of methanol was distilled off, the residue cooled, diluted with water and extracted with ether (100 ml x 3). Combined organic layer was washed with water, brine and dried. Distillation of ether gave a crude product, purified by fractionation using 1 ft high vigroux column. The fraction boiling at 105°(vapour)/6 mm, gave diol (XXIV, 17 g, 66% on XXII), as a thick sweet smelling liquid.

Analysis:

Found: C, 68.2; H, 11.3; $C_9H_{18}O_2$

requires: C, 68.3; H, 11.4%.

IR bands at: 3344, 2980, 2960, 1645, 1450, 1375, 1040 and 889 cm^{-1}.

Methyl 2-isopropenyl-5-oxohexanoate (XXV):

To an ice cooled and stirred solution of XXIV (5 g, 32 mmol), in acetone (30 ml), placed in a 500 ml three necked round bottom flask fitted with an overhead mechanical stirrer, reflux condensor and a droping funnel, Jones chromic acid reagent was added dropwise, till brown colour persisted (35 ml). Stirring was continued for 2 hr at 0^{o} and 1 hr at room temperature, excess of acetone was distilled off under reduced pressure. The reaction mixture was diluted with water and extracted with ether (50 ml x 3). The combined organic layer was washed with water and separated into acidic and neutral components, by extracting with aqueous sodium carbonate (10% solution, 100 ml). The alkaline layer was washed with ether (25 ml x 1), acidified with dilute HCl (10%, till acidic to litmus) and extracted with ether (25 ml x 3). The organic layer was washed with water, brine, dried and treated with an ethereal solution of diazomethane and kept for 1 hr at 0^{o}. It was then washed with aqueous sodium carbonate, water, brine, dried and evaporated to give ketoester (XXV, 3.2 g, 51%), b.p.110^{o}/5 mm; MS: m/z, 184 (M^{+}).

Analysis:

Found: C, 64.9; H, 8.6; $C_{10}H_{16}O_3$

requires: C, 65.2; H, 8.7%.

IR bands at: 2970, 1736, 1720, 1647, 1435, 1370, 1155 and 900 cm^{-1}

Methyl 2-isopropyl-5-oxohexanoate (XXVI):

A solution of ketoester ((XV, 4.6 g, 24.7 mmol), in ethanol (40 ml), containing platinum oxide (0.36 g), was hydrogenated at atmospheric pressure (710 mm) and room temperature ($27^{o}C$), till the absorption is completed. The volume of hydrogen absorbed (518 ml at NTP), corresponded to 0.93 mol. The product was then carefully filtered and alcohol was distilled off under reduced pressure, residue obtained was diluted with water and extracted with ether (50 ml x 3). The combined ether layer was washed with water, brine, dried, evaporated and purified by distillation to give XXVI (4.5 g, 92%); b.p.90-95^{o}/3 mm; MS: m/z, 186 (M^{+}).

Analysis:

Found: C, 64.6; H, 9.8; $C_{10}H_{18}O_3$

requires: C, 64.5; H, 9.8%.

IR bands at: 2975, 1730, 1716, 1435, 1370, 1200 and 1150 cm^{-1}.

Methyl 2-isopropyl-5-chlorohex-4-enoate (XXVII)

Phosphorous pentachloride (3.1 g, 14 mmol), was added in small lots to an ice cooled solution of XXVI (1.2 g, 6.4 mmol), in dry methylene chloride (10 ml) and then stirred at room temperature for 10 hr. The reaction mixture was poured onto crushed ice, and extracted with methylene chloride, combined organic layer was washed with water, brine, dried and

evaporated to give an oil (1.2 g), which was chromatographed over silicic acid, impregnated with 15% $AgNO_3$ (30 g) and eluted with pet.ether, pet.ether- benzene mixtures and benzene. The fraction eluted with pet.ether containing 10% benzene gave a TLC pure (benzene) liquid, identified as XXVII (0.51 g, 42%); MS: m/z, 204 (M^+), 206 (^{37}Cl).

Analysis:

Found: C, 58.4; H, 8.2; Cl, 17.1; $C_{10}H_{17}O_2Cl$

requires: C, 58.8; H, 8.3; Cl, 17.4%.

IR bands at: 2980, 1742, 1435, 1370, 1195, 1170 and 1030 cm^{-1}.

3-Phenoxybenzyl 2-isopropyl-5-chlorohex-4-enoate (XXIX):

A mixture of chloroesters (XXVII, XXVIII-8%, 0.24 g, 1.17 mmol), 3-phenoxybenzyl alcohol (0.4 g, 2 mmol) and butyl titanate (0.05 g), in xylene was refluxed for 12 hr, workedup and purified by chromatography over silicic acid (6 g). The fraction eluted with pet.ether containing 10% benzene gave TLC pure XXIX, as a thick liquid (0.43 g, 86%), MS: m/z, 372 (M^+), 374 (^{37}Cl).

Analysis:

Found: C, 70.6; H, 6.6; Cl, 9.6; $C_{22}H_{25}O_3Cl$

requires: C, 70.8; H, 6.7; Cl, 9.8%.

IR bands at: 2975, 1739, 1587, 1490, 1450, 1260, 1213, 1160 and 690. cm^{-1}.

Methyl 2-isopropyl-5-cyano-hex-4-enoate (XXXI):

To an ice cooled and stirred solution of ketoester (XXVI, 1.8 g, 9.6 mmol), in ethanol (20 ml), acetic acid (10 ml) and

water (7 ml), potasium cyanide (4 g, 61 mmol), was added in small lots during 30 min. The reaction mixture was stirred at 0^{o} for 2 hr and 1 hr at 25^{o}. It was then diluted with water and extracted with ether (50 ml x 3). The combined ether layer was washed with water, brine, dried and distilled to give cyanohydrin ester (XXX), as a liquid. This was dissolved in pyridine (10 ml), cooled to 0^{o} and $POCl_3$ (3 ml), was added dropwise with stirring and left overnight. The reaction mixture was then poured onto crushed ice (50 g), extracted with ether (50 ml x 3), washed with water, brine, dried and evaporated to give crude ester (1.4 g) as a liquid, purified by chromatography over silicic acid (30 g). The fraction eluted with pet.ether-benzene (1:1) mainly consisted of cyanoester (XXXI, 0.53 g, 50%); b.p.120^{o}/5 mm; MS: m/z, 195 (M^{+}).

Analysis:

Found: C, 67.6; H, 8.8; N, 7.2; $C_{11}H_{17}O_2N$

requires: C, 67.4; H, 8.7; N, 7.0%.

IR bands at: 2978, 2217, 1733, 1438, 1200, 1150 and 1030 cm^{-1}.

3-Phenoxybenzyl 2-isopropyl-5-cyanohex-4-enoate (XXXIII):

A solution of XXXI, XXXII- 8% (0.26 g, 1.3 mmol) and 3-phenoxybenzyl alcohol (0.4 g, 2 mmol), in xylene (10 ml), containing butyl titanate(0.01 g), was refluxed for 10 hr, workedup and purified as described earlier to give XXXIII (0.45 g, 93%), as a liquid; MS:m/z, 363 (M^{+}).

Analysis:

Found: C, 75.8; H, 6.9; N, 3.7; $C_{23}H_{25}O_3N$

requires: C, 76.0; H, 6.9; N, 3.8%.

IR bands at: 2975, 2219, 1730, 1587, 1490, 1450, 1255, 1213, 1150, 1020, 778 and 709 cm^{-1}.

2-Acetoxy-6-methyl-5,6-epoxyheptane (XXXV):

To a solution of methylheptenyl acetate (XXII, 11 g, 59 mmol), in chloroform (100 ml), perbenzoic acid (60 ml, 2.8N, $CHCl_3$), was added slowly with stirring during 30 min. and left overnight at 0°. Reaction mixture was filtered, washed with water, aqueous sodium carbonate, water, brine and dried. Evaporation of organic layer gave TLC (benzene + 1 % ethyl acetate) pure XXXV, as a liquid (11.4 g, 95%).

Analysis:

Found: C, 63.5; H, 9.6; $C_{10}H_{18}O_3$

requires: C, 63.8; H, 9.5%.

IR bands at: 2970, 1740, 1572, 1484, 1240, 1150, 1060 and 875 cm^{-1}.

2-Acetoxy-5-oxo-6-methylheptanoate (XXXVI):

To a cooled and stirred solution of XXXV (11 g, 54 mmol), in anhydrous ether (60 ml), freshly distilled BF_3-etherate (2 ml), was added slowly during 10 min, stirring continued for 1 hr. Reaction mixture was washed with water, brine, dried and evaporated to give acetoxyketone (XXXVI, 9 g, 75%) purified by distillation, b.p.100°/5mm; MS: m/z, 222 (M^+).

Analysis:

Found: C, 70.0; H, 8.1; $C_{13}H_{18}O_3$

requires: C, 70.2; H, 8.1%.

IR bands at: 2980, 1742, 1721, 1580, 1280, 1240, 1040 and 870 cm^{-1}.

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CHAPTER-II

SYNTHESIS OF 2,3-SECO-PYRETHROIDS

S U M M A R Y

The method described in chapter I, for the synthesis ot potent 2,3-secopyrethroids, is of general applicability and has been extended for the preparation of a large number of analogues by varying alkylating halides, for structure-activity study.

Alkylation of diethyl malonate with allyl or prenyl chloride gave 70:30 mixture of mono and dialkylated compounds II and III, R=H or CH_3 respectively, which were separated by fractionation. The monoalkylated diethyl malonate II, R=H/CH_3 was subjected to a second alkylation, with alkyl halides like methyl, ethyl, isopropyl and benzyl to give dialkyl malonates IVb-e, h-l in good yields. These were decarboethyoxylated (DMSO-KOAc), to afford corresponding monocarboxylic acid esters (Va-l), which were then transesterified with 3-phenoxy-benzyl alcohol to give 3-phenoxybenzyl esters (VIa-l) as liquids. These were tested for their insecticidal and larvicidal activity.

In another series of esters prepared, variations were made in the vinyl function and Friedel Craft's acylation was employed in one of the steps.

γ-Benzoyl butyric acids VIIIa-d obtained by Friedel-Craft's acylation of benzene or substituted benzenes with glutaric anhydride, were converted into corresponding methyl

esters ($MeOH/H^+$) IXa-d. These were then treated with phosphorous pentachloride in methylene chloride to afford Z isomers of methyl 5-chloro-5-phenyl/p-substituted phenyl-4-pentenoates (Xa-d). These were subsequently converted to 3-phenoxybenzyl esters (XIa-d) by transesterification. All these compounds exhibited moderate larvicidal activity.

Similarly Friedel Craft's acylation of benzene or monosubstituted benzene with succinic anhydride afforded β-benzoyl propionic acids XIIIa—d. Methyl esters of these acids were subjected to Wittig reaction, using 1,1-dichloro-methylene triphenyl phosphorane, to afford methyl 5,5-dichloro-4-phenyl/p-substituted phenyl-4-pentenoates (XVa-d). The corresponding 4-methyl analogue XVIII, was prepared from methyl levulinate (XVII). The methyl esters thus obtained, were converted to 3-phenoxybenzyl esters (XVIa-d, XIX), by trans-esterification with 3-phenoxybenzyl alcohol.

INTRODUCTION

As already described in Chapter I of this thesis, it has been observed that the presence of cyclopropane ring system is not an essential structural requirement for insecticidal activity. As a result of extensive research, insecticides like fenvalerate and other related compounds have been developed, which have proved to be as potent as pyrethroids (see Introduction of Chapter I). A new group of compounds of general formula (I), have been synthesised by W. Parol[1] and have been patented for their insecticidal activity.

In the first detailed approach towards the synthesis of noncyclopropane insecticidal esters, Michael Elliott[2] synthesised analogues of fenvalerate viz. 3-methyl butyric acid esters and other related esters. The acid moieties of such esters were prepared by using either alkylation of diethyl malonate or by Reformatski's reaction. The acid moities thus obtained were converted into ester with pyrethroidal alcohols like,3-phenoxybenzyl,α-cyano-3-phenoxybenzyl alcohols. Such esters have been prepared to study the effect of substituents,on the insecticidal activity.

Michael Bull and co-workers[3] have synthesised thirty-five insecticidal esters. The acid moieties of these esters have been prepared fromα-isopropyl diethyl malonate by reacting with different alkyl halides in presence of sodium hydride and HMPA.

The resulting diesters on hydrolysis and decarboxylation gave the acid moieties which were then esterified with 3-phenoxybenzyl alcohol and ∝-cyano 3-phenoxybenzyl alcohol. 1% solution of these compounds in acetone gave 100% kill of mosquitoes.

The encouraging results obtained by the above workers prompted us to investigate some more non-cyclopropane esters for their insecticidal activity.

∝-Isopropyl pent-4-enoic acid and ∝-isopropyl 5-methyl hex-4-enoic acid esters have been patented for their insecticidal activity. It was therefore felt desirable to study the effect of other substituents at C_2, on insecticidal activity. With this object in view, acid moieties were synthesised from ∝-allyl diethyl malonate and ∝-prenyl diethyl malonate, by introducing different alkyl and aralkyl substituents at the C_2 position by a second alkylation. The acids were subsequently converted into insecticidal esters.

Meyer Willy[4] has synthesised ∝-isopropylstyryl acetic acid esters and found them to be good insecticides.

In the latter part of this Chapter the synthesis of 5-chloro-5-phenyl or p-substituted phenyl-4-pentenoic acid esters has been described. These esters are the higher homologues of styryl acetic acids, described by Meyer Willy but lacking the ∝-isopropyl substitution. These compounds, however, did not show any insecticidal activity but exhibited moderate larvicidal activity against fourth instar mosquitoe larvae. In addition,

esters of 5,5-dichloro-4-methyl/phenyl/p-substituted phenyl-4-pentenoic acids with 3-phenoxybenzyl alcohol, were also prepared which, however, were inactive in insecticidal or larvicidal tests.

In a recent German patent, described by Parol W.[1], several insecticidally active acyclic esters of general formula I , have been described. In such esters the vinyl function and the carboxylic group are separated by a two carbon chain, with substituents on α or β or both carbon atoms. The work described in this chapter of the thesis deals with the total synthetic approaches for the acid moieties of such acyclic esters, possessing different substituents on the α-carbon atom and the vinyl function. Some of such acyclic esters without α or β substituents have also been synthesised.

PRESENT WORK

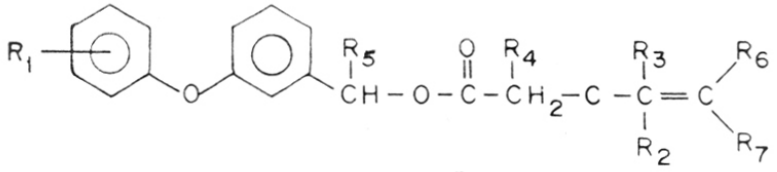
Synthesis of 4-pentenoates:

Alkylation of diethyl malonate with allyl chloride as per the procedure already described in Chapter I of this thesis, gave a mixture of mono II, R=H and dialkylated III, R=H, products, which were separated by fractionation on a spinning bond column. Monoallyl compound showed following properties, IR bands at: 1735 (ester C=0), 1640, 910 ($CH=CH_2$); PMR signals at: 1.28 (6H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.53 (2H, t, J=7 Hz, allylic CH_2), 3.31 (1H, dd, J_1=7 Hz, J_2=15 Hz, $C\underline{H}$ adjacent to ester groups), 4.11 (4H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.88-5.08 (2H, m, $CH=C\underline{H}_2$) and 5.73 (1H, m, $C\underline{H}=CH_2$).

The monoallyl compound II, R=H, so obtained was alkylated with various halides like methyl, ethyl, isopropyl and benzyl, using sodium hydride as base, in benzene and dimethyl formamide, as a solvent in 8:2 ratio, to give dialkylated compounds, purified by distillation and identified by spectral data. In PMR spectrum of these esters the absence of signal around 3.3 δ chracteristic of proton α- to ester function was observed.

Decarboethoxylation of dialkyl malonates by wet-DMSO-KOAc[5], under reflux conditions for 4 to 6 hr gave the corresponding decarboethoxylated product, in almost quantitative yield. All these compounds exhibited signals around 2.3 δ arising from C_2 and C_3 protons.

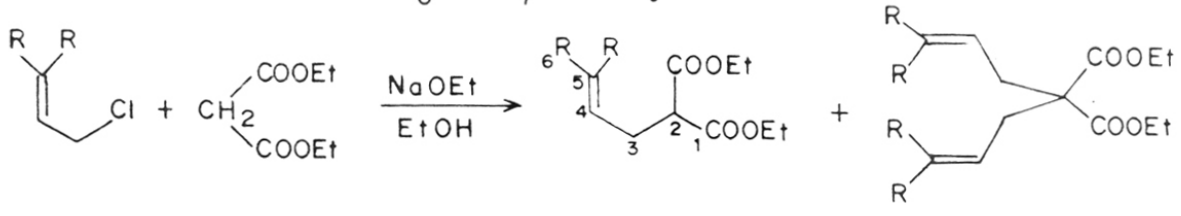
SCHEME I



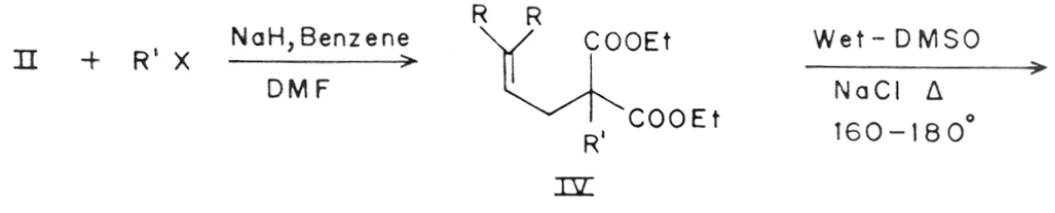
I

R_1 to R_5 = Alkyl or H

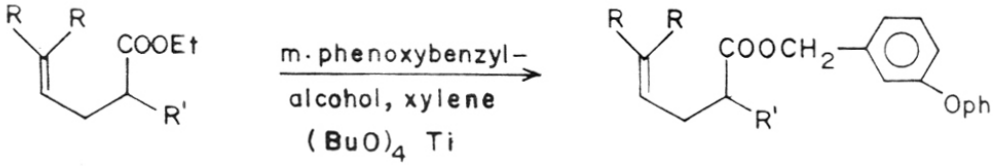
R_6 & R_7 = Halogen.



II III



IV



V VI

VI

a. R = H , R' = H

b. R = H , R' = CH_3

c. R = H , R' = CH_2CH_3

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

e. R = H , R' = CH_2-Ph

f. R = H , R' = 

VI

g. R = CH_3 , R' = H

h. R = CH_3 , R' = CH_3

i. R = CH_3 , R' = CH_2CH_3

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

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

l. R = CH_3 , R' = 

These compounds were then transesterified with 3-phenoxybenzyl alcohol using butyl titanate as a catalyst[6] in refluxing xylene, esters thus obtained were purified by column chromatograhy and characterised by spectral data. 3-Phenoxybenzyl esters exhibited signal around 5δ characteristic of ester benzylic CH_2 in PMR.

Synthesis of -4-hexenoates:

Similar alkylation of diethyl malonate, with prenyl chloride afforded a mixture of mono II, R=CH_3 and dialkylated III, R=CH_3 products, purified by fractionation over spinning band column, to get pure monoalkylated product II, R=CH_3. It was then further dialkylated with different alkyl halides, to give dialkylated products IV, 1-k. Subsequent decarboethyoxylation and transesterification with 3-phenoxybenzyl alcohol gave 3-phenoxybenzyl esters, purified by column chromatography and identified by spectral data.

Our aim was then to synthesise, 3-phenoxybenzyl5-chloro-5-p-substituted phenyl pent-4-enoates and 4-methyl/phenyl/p-substituted phenyl-5,5-dichloropent-4-enoates for evaluating their insecticidal activity. The synthesis of the acid moieties of these esters was achieved from γ-aroyl and β-aroyl butyric and propionic acids respectively, by employing PCl_5 and Wittig reactions on the corresponding methyl esters.

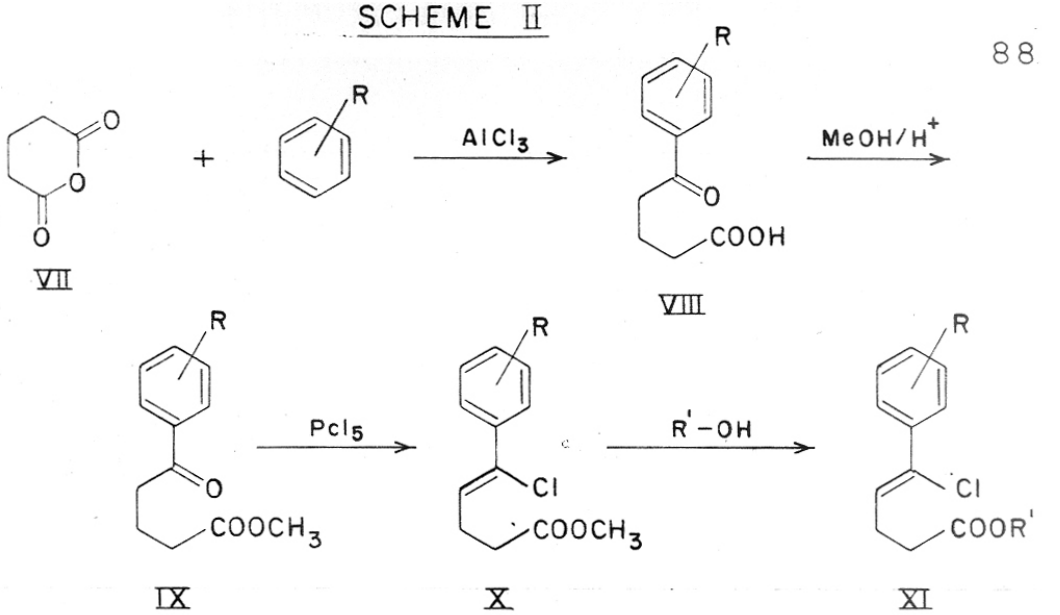
Synthesis of 5-chloro-5-phenyl/p-substituted phenyl-4-pentenoates:

Friedel-Craft's acylation reactionsof aromatic compounds using anhydrides of dicarboxylic acids are of great importance

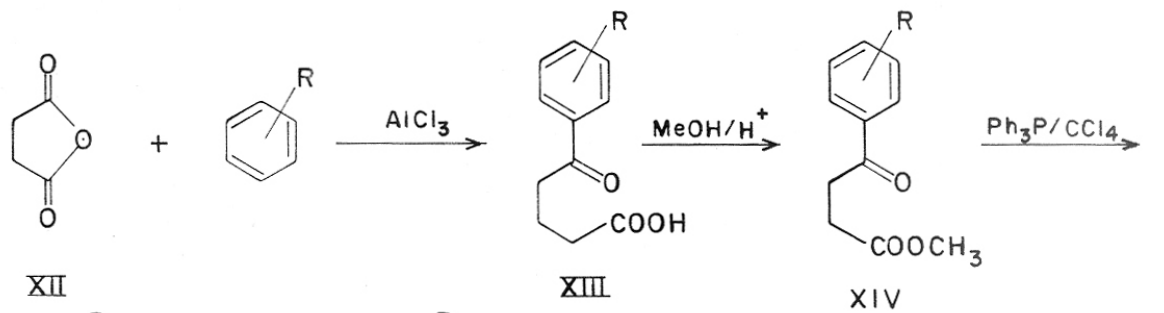
in organic synthesis, especially for the synthesis of higher condensed aromatic systems, via the keto acids. While the acid anhydrides of monocarboxylic acids yield aromatic ketones, the dicarboxylic acid anhydrides afforded the benzoyl aliphatic acids for example, reaction of phthalic anhydride with benzene afford o-benzoyl benzoic acid, which can ultimately be converted to anthraquinone. Deshpande and Nargund[7] have standardised the reactions for Friedel-Craft's acylation of benzene and substituted benzene with succinic acid to afford β-benzoyl propionic acid in good yield. By following analogous procedure, Friedel-Craft's acylation of benzene and substituted benzenes with glutaric anhydride, afforded γ-benzoyl butyric acids. The γ-aroyl butyric acids (VIII, a-d), thus obtained were converted into corresponding methyl esters (IX, a-d, $MeOH/H^+$) and characteised by the spectral data.

Phosphorous pentachloride reaction[8], on γ-benzoyl butyric esters in methylene chloride under reflux conditions, afforded 5-chloro-5-phenyl or substituted phenyl pent-4-enoates (X, a-d) which were characterised by spectral data. They showed IR absorption band around 1740 cm^{-1} due to ester carbonyl, while the absorption band around 1690 cm^{-1} observed in the spectra of keto esters, was totally absent in the spectra of these esters. In the PMR spectra of these esters, chemical shifts for the methylene protons ∝to carboxyl function and allylic methylene, were observed as multipletes in the region of 2.4 δ. The olefinic protons of

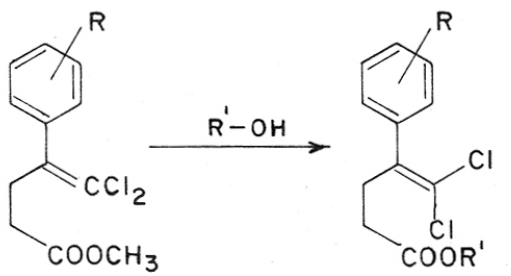
SCHEME II



VII VIII IX X XI



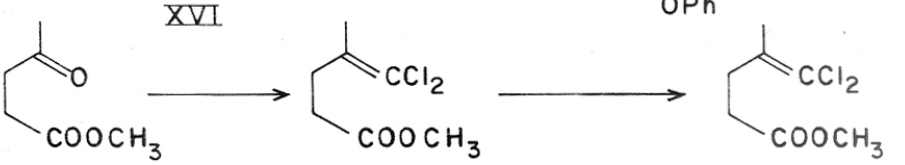
XII XIII XIV



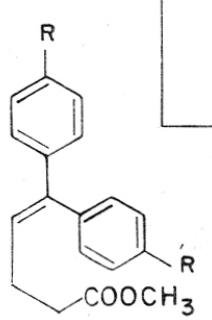
XV XVI

R, a = H, b = CH_3, c = Cl, d = Br

R' = — CH_2 — OPh



XVII XVIII XIX



XX

R, a = Cl, b = Br

of these esters were observed in the region of 6.1 δ,as broad triplet. The Z configuration is tentatively assigned for the double bond on the basis of the observed chemical shift for the olefinic proton,which is in close agreemwnt with the calculated value (6.12)[9]. However, in the case of compound Xd, the chemical shift for the C_4-proton appeared as a broad triplet at 5.25 δ;no satisfactory explanation could be given for this anomaly .

The methyl esters were then transesterified with 3-phenoxybenzyl alcohol using butyl titanate as a catalyst, to afford the 3-phenoxybenzyl esters (XI, a-d) and characterised by spectral data.

Synthesis of 5,5-dichloro-4-methyl/phenyl/p-substituted phenyl -4-pentenoates:

β-Benzoyl propionic acids (XIII, a-d) were prepared by Friedel-Craft's acylation of benzene and monosubstituted benzene , with succinic anhydride,in presence of aluminium chloride,according to the procedure reported by Deshpande and Nargund[7]. These acids were then converted into their methyl esters ($MeOH/H^+$) and characterised by spectral data.

Wittig reaction on methyl β-benzoyl propionates (XIV,a-d) using 1,1-dichloromethylenetriphenyl phosphorane[9] (prepared from CCl_4 and PPh_3), afforded in moderate yields the 5,5-dichloro-4-phenyl/p-substituted phenyl-4-pentenoates (XV, a-d),identified

by spectral data. They showed an absorption band around 1750 cm^{-1} in the IR spectra, due to ester carbonyl group. In the PMR spectra multipletes were observed around 2.4δ and 2.8δ, due to methylene protons adjacent to ester carbonyl and allylic to the double bond and around 3.6δ, 7.2δ, due to ester methyl and aromatic protons respectively. Following an analogous procedure, 5,5-dichloro-4-methyl-4-pentenoate (XVIII), was also prepared starting from methyl levilunate (XVII).

The methyl esters thus obtained, were converted into 3-phenoxybenzyl esters by transesterification and identified by spectral data.

All these compounds were tested for their insecticidal and larvicidal activity. The compounds XIa-d showed 80-90% mortality against 4th instar mosquitoe larvae at 100 ppm. They did not show any adulticidal activity. The compounds XVII, a-d. amd XIX were totally inactive in insecticidal and larvicidal tests.

The insecticidal activity data of 3-phenoxybenzyl 4-pentenoates and 4-hexenoates (VIa-l), is described in Table.

Compound	Mortality (%)	
	Adese aegptii (adult) (*)	Musca domestica (10 g/insect by topical application
VIa	0	0
VIb	90	0
VIc	90	0
VId	100	40
VIe	100	10
VIf	100	20
VIg	0	0
VIh	40	0
VIi	40	0
VIj		Ref. 4
VIk	40	0
VIl	60	100

None of the compounds showed larvicidal activity against 4th instar mosquito larvae at 50 ppm dose.

*Adult mosquitoes were exposed to the residual deposits of the compounds by spraying 1 ml of 5% solution in acetone on a 12.5 cm diameter Whatmann filter paper for 24 hr, after which mortality counts were taken.

EXPERIMENTAL

Preparation of prenyl chloride (I):

Isoprene (102 g, 1.5 mol), was placed in a 500 ml, two necked round bottom flask, fitted with a reflux condensor carrying a guard tube and an inlet for dry hydrochloric acid gas and cooled in an ice-salt bath (-10°C). Dry hydrochloric acid gas (generated by dropwise addition of conc. sulphuric acid to sodium chloride and passed through a concentrated sulphuric acid trap), was bubbled through cooled isoprene, till one mole of hydrochloric acid is absorbed (10 hr), indicated by increase in the weight to 156 g. The reaction mixture was then washed with water, brine, dried and distilled. The fraction distilling at 57-59°/100 mm, gave almost pure prenyl chloride I.

PMR signals at: 1.8 (6H, s, vinyl methyls), 4.21 (2H, d, J=8 Hz, CH_2Cl) and 5.63 (1H, t, J=6 Hz, olefinic proton).

General Experimental Procedure:

Ethyl 2-carboethoxy-5-methylhex-4-enoate (II, R=CH_3):

Diethyl malonate (111 g, 0.69 mol), was added slowly over a period of 2 hr, to a stirred solution of sodium ethoxide in ethanol, prepared by addition of sodium (19 g, 0.82 mol), to dry ethanol (300 ml). Stirring was continued for 2 hr, to ensure complete anion formation. Prenyl chloride (94 g, 0.895 mol), in ethanol (100 ml), was added to the above mixture during 15 min.

The reaction mixture was stirred overnight, most of the ethanol was distilled under reduced pressure and the residue diluted with water, organic layer separated and aqueous layer was extracted with ether (500 ml x 2). The combined organic layer was washed with water, brine, dried and concentrated to give crude product (130 g). It showed two spots on TLC (benzene) analysis. These were separated by fractional distillation, using 1 meter long spinning band column and 1:20 reflux ration. The lower boiling fractions consisting of diethyl malonate and unreacted prenyl chloride were discarded. The fraction distilling at 112^{o}(vapour)/6 mm, gave II, R=CH_3 (75 g) and the one at 135^{o}(vapour)/6 mm, gave III, R=CH_3 (20 g). Compound II, R=CH_3 showed IR band at: 1735 (ester C=0) and PMR signals at: 1.28 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.66, 1.75 (6H, each s, vinyl methyls), 2.6 (2H, br t, C_3-CH_2), 3.31 (1H, dd, J_1=3.5 Hz, J_2=7 Hz, C_2-H), 4.18 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$) and 5.15 (1H, br t, olefinic H). Analysis:

Found: C, 62.9; H, 8.5; $C_{12}H_{20}O_4$

requires: C, 63.1; H, 8.7%.

Compound III, R=CH_3; b.p.135^{o}(vapour)/6 mm, showed IR band at: 1740 (ester C=0) and PMR signals at: 1.18 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.56, 1.64 (each 6H, s, vinyl methyls), 2.23 (4H, d, J=7 Hz, C_3 and C_3'-CH_2), 3.95 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$) and 4.93 (2H, m, olefinic protons).

Analysis:

Found: C, 68.6; H, 9.3; $C_{17}H_{28}O_4$

requires: C, 68.9; H, 9.4%.

Mono(II, R=H)and diallyl diethyl malonates(III, R=H), were prepared as per the procedure,already described in Chapter I of the thesis.

Ethyl 2-carboethoxy-2-isopropyl-5-methylhex-4-enoate (IVj):

Diester (II, 12 g, 52 mmol),was stirred with sodium hydride (1.8 g, 75 mmol), in dry benzene (120 ml) and DMF (30 ml), at room temperature under nitrogen. Isopropyl iodide (12 g, 64 mmol), was added to it in one lot. After stirring at room temperature for 6 hr, the reaction mixture was heated for 1 hr on water-bath, cooled, diluted with water, benzene layer separated, washed with water, brine, dried and evaporated to give IVj (11 g, 79%); b.p.130°(vapour)/6 mm; IR band at: 1738 (ester C=0); PMR signals at: 0.96 (6H, d, J=7 Hz, isopropyl methyls), 1.21 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.56, 1.63 (3H each, s, vinyl methyls), 2.26 (3H, m, C_2 and C_3 protons), 4.06 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$) and 5.03 (1H, t, J=6 Hz, olefinic proton).

Analysis:

Found: C, 66.3; H, 9.4; $C_{15}H_{26}O_4$

requires: C, 66.6; H, 9.6%.

By following the analogous procedure, the following diethyl dialkyl malonates were prepared.

a) Ethyl 2-carboethoxy-2,5-dimethylhex-4-enoate (IV, h):
Yield, 85%; b.p.110°(vapour)/6 mm; showed IR band at: 1735 (ester C=0); PMR signals at: 1.16 (6H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 1.24 (3H, s, C_2-CH_3), 1.55, 1.61 (each 3H, s, vinyl methyls), 2.35 (2H, d, J=8 Hz, allylic methylene protons), 3.91 (4H, q, J=7 Hz, $COO\underline{CH_2}CH_3$) and 4.71 (1H, t, J=6 Hz, vinylic proton).
Analysis:

Found: C, 64.1; H, 9.0; $C_{13}H_{22}O_4$
requires: C, 64.4; H, 9.1%.

b) Ethyl 2-carboethoxy-2-ethyl-5-methylhex-4-enoate (IV, i):
Yield, 82%; b.p.115° (vapour)/7 mm; showed IR band at: 1732 (ester C=0); PMR signals at: 0.76 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$ at C_2), 1.18 (6H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 1.58, 1.63 (each 3H, s, vinyl methyls), 1.76 (2H, q, J=7 Hz, $-\underline{CH_2}CH_3$ at C_2), 2.41 (2H, d, J=7 Hz, allylic methylene protons), 4.0 (4H, q, J=7 Hz, $COO\underline{CH_2}CH_3$) and 4.75 (1H, t, J=6 Hz, vinylic proton).
Analysis:

Found: C, 65.0; H, 9.3; $C_{14}H_{24}O_4$
requires: C, 65.2; H, 9.3%.

c) Ethyl 2-carboethoxy-2- benzyl-5-methylhex-4-enoate (IV, k):
Yield, 80%; b.p.160°/6 mm; showed IR bands at: 1730 (ester C=0), 1587, 700 (aromatic); PMR signals at: 1.15 (6H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.56, 1.76 (each 3H, s, vinyl methyls), 2.43 (2H, d, J=8 Hz, allylic $\underline{CH_2}$), 3.15 (2H, s, $-CH_2$ at C_2), 4.06 (4H, q, J=6 Hz, $COO\underline{CH_2}CH_3$), 5.05 (1H, t, J=6 Hz, vinyl proton) and 7.0 (5H, s, aromatic H).

Analysis:

Found: C, 71.5; H, 8.0; $C_{19}H_{26}O_4$

requires: C, 71.7; H, 8.1%.

Similarly, following analogous procedure, the dialkyl diethyl malonate from mono allyl diethyl malonate, were prepared.

d) Ethyl 2-carboethoxy-4-pentenoate (II, a): Yield, 67%, b.p.110°(vapour)/10 mm; showed IR bands at: 1735 (ester C=0), 1640, 910 ($CH=CH_2$) and PMR signals at: 1.28 (6H, t, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.53 (2H, t, J=7 Hz, allylic CH_2), 3.31 (1H, dd, J_1=7 Hz, J_2=15 Hz, $C\underline{H}$ adjacent to ester groups), 4.11 (4H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.86-5.08 (2H, m, $CH=C\underline{H}_2$) and 5.73 (1H, m, $C\underline{H}=CH_2$).

Analysis:

Found: C, 59.6; H, 7.6; $C_{10}H_{16}O_4$

requires: C, 60.0; H, 8.0%.

e) Ethyl 2-carboethoxy-2-allyl-4-pentenoate (III, R=H): Yield, 22%; b.p.145°(vapour)/10 mm; showed IR bands at: 1725 (ester C=0), 1645, 915 ($CH=CH_2$); PMR signals at: 1.23 (6H, J=7 Hz, $COOCH_2\underline{CH}_3$), 2.51 (4H, d, J=7 Hz, allylic CH_2's), 4.08 (4H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.9-5.06 (4H, m, $CH=C\underline{H}_2$) and 5.6 (2H, m, $C\underline{H}=CH_2$)

Analysis:

Found: C, 67.6; H, 8.5; $C_{13}H_{20}O_4$

requires: C, 67.8; H, 8.7%.

f) Ethyl 2-carboethoxy-2-methyl-4-pentenoate (IV, b): Yield, 88%; b.p.130°/11 mm; showed IR bands at: 1733 (ester C=0), 1637,

889 ($CH=CH_2$); PMR signals at: 1.25 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.3 (3H, s, methyl at C_2), 2.51 (2H, d, J=7 Hz, allylic CH_2), 4.1 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.9-5.1 (2H, m, $CH=\underline{CH}_2$) and 5.6 (1H, m, $\underline{CH}=CH_2$).

Analysis:

Found: C, 61.4; H, 8.1; $C_{11}H_{18}O_4$

requires: C, 61.7; H, 8.4%.

g) Ethyl 2-carboethoxy-2-ethyl-4-pentenoate (IV, c): Yield, 82%; b.p.120°/8 mm; showed IR bands at: 1732 (ester C=0), 1642, 900 ($CH=CH_2$) and PMR signals at: 0.81 (3H, t, J=7 Hz, $-CH_2\underline{CH}_3$ at C_2), 1.21 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.81 (2H, q, J= 7 Hz, $-\underline{CH}_2CH_3$ at C_2), 2.53 (2H, d, J=7 Hz, allylic CH_2), 4.1 (2H, q, J=7 Hz, $COO\underline{CH}_2CH_3$), 4.86-5.06 (2H, m, $CH=\underline{CH}_2$) and 5.46 (1H, m, $\underline{CH}=CH_2$).

Analysis:

Found: C, 63.0; H, 8.7; $C_{12}H_{20}O_4$

requires: C, 63.1; H, 8.7%.

h) Ethyl 2-carboethoxy-2-isopropyl-4-pentenoate (IV, d): yield, 76%; b.p.125°/8 mm; showed IR bands at: 1732 (ester C=0), 1645, 915 ($CH=CH_2$); PMR signals at: 0.95 (6H, d, J=6 Hz, methyls of isopropyl), 1.3 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 2.51 (1H, m, $\underline{CH}(CH_3)_2$), 2.7 (2H, d, J=6 Hz, allylic CH_2), 4.22 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.76-5.11 (2H, m, $CH=\underline{CH}_2$) and 5.78 (1H, m, $\underline{CH}=CH_2$).

Analysis:

Found: C, 64.1; H, 9.0; $C_{13}H_{22}O_4$

requires: C, 64.4; H, 9.1%.

i) Ethyl 2-carboethoxy-2-benzyl-4-pentenoate (IV, e): yield, 80%; b.p.160°/7 mm; showed IR bands at: 1730 (ester C=0), 1600, 700 (aromatic); PMR signals at: 1.11 (6H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 2.23 (2H, d, J=6 Hz, allylic CH_2), 2.91 (2H, s, benzylic CH_2), 3.86 (4H, q, J=6 Hz, $COO\underline{CH_2}CH_3$), 4.66-4.83 (2H, m, $CH=\underline{CH_2}$), 5.31 (1H, m, $\underline{CH}=CH_2$) and 6.63 (5H, s, aromatic H).

Analysis:

Found: C, 70.1; H, 7.5; $C_{17}H_{22}O_4$

requires: C, 70.3; H, 7.6%.

Ethyl 2-isopropyl-5-methylhex-4-enoate (V, j):

A mixture of diethyl ester (IV, j, 10 g, 37 mmol), DMSO (60 ml), water (1.3 ml, 72 mmol) containing solid potassium acetate (7 g, 71 mmol) was heated under reflux with stirring in an oil bath for 6 hr, until no further evolution of carbon dioxide can be detected. It was then poured onto crushed ice and extracted with ether (100 ml x 3). The combined organic layer was washed with water, brine, dried and concentratd to give V, j (7.4 g, 96%), further purified by distillation, b.p. 110° (vapour)/60 mm; IR band at: 1733 (ester C=0); PMR signals at: 0.88, 0.91 (each 3H, d, J=6 Hz, isopropyl methyls), 1.21 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.56, 1.63 (each 3H, s, vinyl methyls), 2.26 (3H, m, C_2 and C_3 protons), 4.06 (2H, q, J=6 Hz, $COO\underline{CH_2}CH_3$) and 5.03 (1H, t, J=6 Hz, olefinic proton).

Analysis:

Found: C, 72.5; H, 11.0; $C_{12}H_{22}O_2$

requires: C, 72.7; H, 11.1%.

By following similar procedure for decarboethoxylation the following mono esters have been prepared.

a) Ethyl 5-methyl 4-hexenoate (V, g): yield, 98%; b.p.100°(vapour)/ 80 mm; showed IR band at: 1735 (ester C=0); PMR signals at: 1.15 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.55, 1.61 (each 3H, s, vinyl methyls), 2.13 (4H, d, J=2 Hz, C_2 and C_3 protons), 3.86 (2H, q, J=6 Hz, $COO\underline{CH_2}CH_3$) and 4.81 (1H, m, olefinic proton).

Analysis:

Found: C, 69.3; H, 10.2; $C_9H_{16}O_2$

requires: C, 69.2; H, 10.2%.

b) Ethyl 2,5-dimethyl-4-hexenoate (V, h):yield, 94%; b.p.110°/ 80 mm; showed IR band at: 1740 (ester C=0); PMR signals at: 1.06 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.15 (3H, d, J=7 Hz, CH_3 at C_2), 1.55, 1.63 (each 3H, s, vinyl methyls), 2.13 (3H, m, C_2 and C_3 protons), 3.86 (2H, q, J=6 Hz, $COO\underline{CH_2}CH_3$) and 4.78 (1H, t, J=6 Hz, olefinic proton).

Analysis:

Found: C, 70.4; H, 10.4; $C_{10}H_{18}O_2$

requires: C, 70.6; H, 10.6%.

c) Ethyl 2-ethyl-5-methyl-4-hexenoate (V, i): yield, 96%, b.p.110°/75 mm; showed IR band at: 1733 (ester C=0); PMR (Fig.1) signals at: 0.83 (3H, t, J=7 Hz, $CH_2\underline{CH_3}$ at C_2), 1.21 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.65, 1.74 (each 3H, s, vinyl methyls), 2.25 (3H, br d, C_2 and C_3 protons), 4.2 (2H, q, J=6 Hz, $COO\underline{CH_2}CH_3$) and 5.0 (1H, br t, olefinic proton).

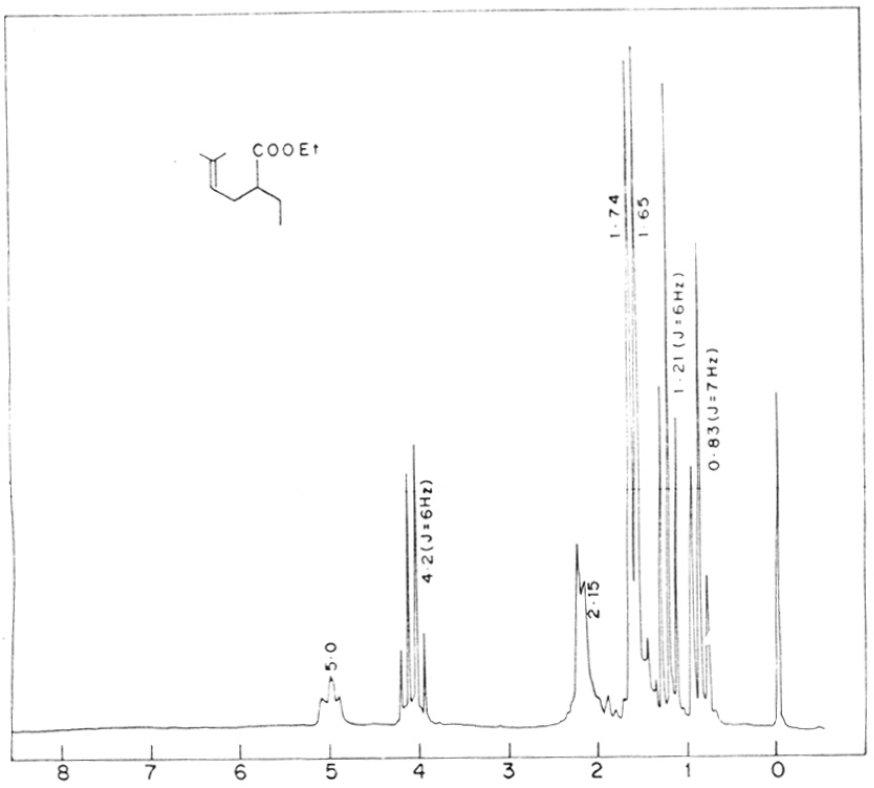


FIG. 1 ETHYL 2-ETHYL-5-METHYL-4-HEXENOATE, V i

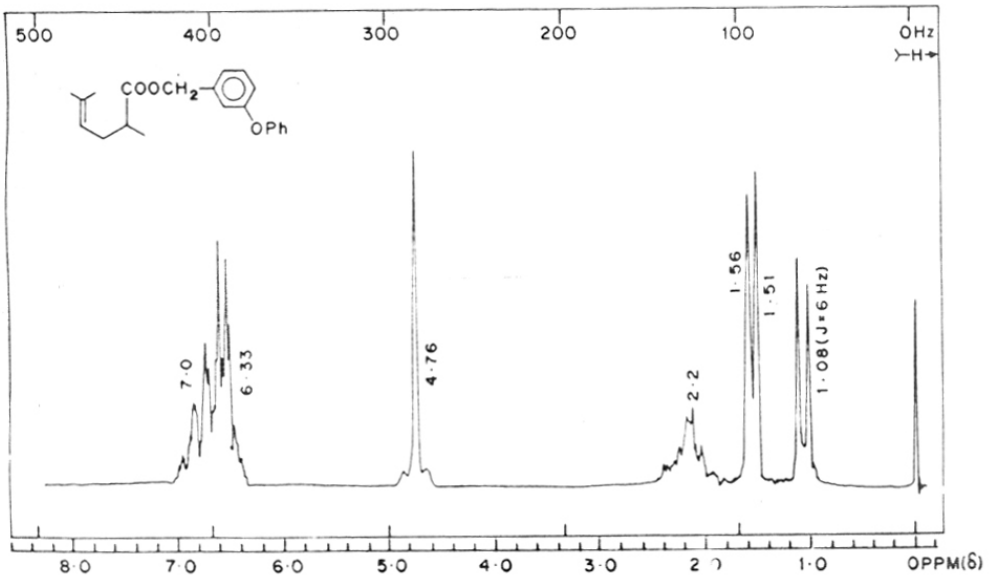


FIG. 2 3-PHENOXYBENZYL 2,5-DIMETHYL-4-HEXENOATE, VI h

Analysis:

Found: C, 71.9; H, 10.6; $C_{11}H_{20}O_2$

requires: C, 71.7; H, 10.8%.

d) Ethyl 2-benzyl-5-methyl-4-pentenoate (V, k): Yield, 98%, b.p.120°(vapour)/40 mm; showed IR bands at: 1738 (ester C=0), 1587, 699 (aromatic) and PMR signals at: 1.11 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.61, 1.73 (each 3H, s, vinyl methyls), 2.3 (3H, m, C_2 and C_3 protons), 2.83 (2H, m, benzylic CH_2 at C_2), 4.1 (2H, q, J=6 Hz, $COOCH_2CH_3$), 5.23 (1H, m, olefinic proton) and 7.26 (5H, s, aromatic H).

Analysis:

Found: C, 80.6; H, 8.7; $C_{16}H_{22}O_2$

requires: C, 80.9; H, 8.9%.

e) Ethyl 2-(3-methyl but-2-ene)-5-methyl-4-hexenoate (V, l): yield, 93%, b.p.140°/50 mm; IR bands at: 1740 (ester C=0); PMR signals at: 1.15 (3H, t, J=6 Hz, $COOCH_2\underline{CH_3}$), 1.53, 1.61 (each, 3H, s, vinyl methyls), 2.11 (5H, m, C_2, C_3 and C_3' protons), 3.86(2H, q, J=6 Hz, $COO\underline{CH_2}CH_3$) and 4.8 (2H, m, olefinic proton).

Analysis:

Found: C, 74.7; H, 10.5; $C_{14}H_{24}O_2$

requires: C, 75.0; H, 10.7%.

f) Ethyl 4-pentenoate (V, a): yield, 96%, b.p.90°/70 mm; showed IR bands at: 1735 (ester C=0), 1642, 912 ($CH=CH_2$) and PMR signals at: 1.15 (3H, t, J=7 Hz, $COOCH_2\underline{CH_3}$), 2.16 (4H, d, J= 2Hz, C_2 and C_3 protons), 3.85 (2H, q, J=7 Hz, $COO\underline{CH_2}CH_3$), 4.57-4.78 (2H, m, $CH=C\underline{H_2}$) and 5.43 (1H, m, $C\underline{H}=CH_2$).

Analysis:

Found: C, 65.3; H, 9.3; $C_7H_{12}O_2$

requires: C, 65.6; H, 9.4%,

g) Ethyl 2-methyl-4-pentenoate (V, b): yield, 94%, 110°/80 mm; showed IR bands at: 1733 (ester C=O), 1640, 905 ($CH=CH_2$); PMR signals at: 1.13 (3H, t, J=6 Hz, $COOCH_2\underline{CH}_3$), 1.23 (3H, d, J=6 Hz, C_2-CH_3), 2.36 (3H, m, C_2 and C_3 protons), 4.13 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.8-5.03 (2H, m, $CH=\underline{CH}_2$) and 5.66 (1H, m, $\underline{CH}=CH_2$).

Analysis:

Found: C, 67.3; H, 9.6; $C_8H_{14}O_2$

requires: C, 67.6; H, 9.8%.

h) Ethyl 2-ethyl-4-pentenoate (V, c): yield, 92%; b.p.120°/80 mm; showed IR bands at: 1733 (ester C=O), 1645, 915 ($CH=CH_2$); PMR signals at: 0.88 (3H, t, J=6 Hz, $CH_2\underline{CH}_3$ at C_2), 1.21 (3H, t, J=6 Hz, $COOCH_2CH_3$), 2.25 (3H, m, C_2 and C_3 protons), 4.06 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.81-5.05 (2H, m, $CH=\underline{CH}_2$) and 5.6 (1H, m, $\underline{CH}=CH_2$).

Analysis:

Found: C, 68.9; H, 10.2; $C_9H_{16}O_2$

requires: C, 69.2; H, 10.2%.

i) Ethyl 2-isopropyl-4-pentenoate (V, d): yield, 94%, b.p.110°/50 mm; IR bands at: 1738 (ester C=O), 1645, 895 ($CH=CH_2$); PMR signals at: 0.88, 0.91 (each 3H, d, J=6 Hz, methyls of isopropyl), 1.21 (3H, t, J=6 Hz, $COO\underline{CH}_2CH_3$), 2.2 (3H, br d, C_2 and C_3 protons), 4.06 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$), 4.76-4.98

(2H, m, $CH=C\underline{H}_2$) and 5.56 (1H, m, $C\underline{H}=CH_2$).

Analysis:

Found: C, 70.3; H, 10.5; $C_{10}H_{18}O_2$

requires: C, 70.6; H, 10.6%.

j) Ethyl 2-benzyl-4-pentenoate (V, e): Yield, 98%; b.p.120° (vapour)/40 mm; IR bands at: 1735 (ester C=0), 1645, 900 ($CH=CH_2$), 1590, 700 (aromatic); PMR signals at: 1.18 (3H, t, J=6 Hz, $COOCH_2C\underline{H}_3$), 2.25 (2H, m, allylic CH_2), 2.5 (1H, m, C_2-proton), 2.75 (2H, d, J=3 Hz, benzylic CH_2 at C_2), 4.06 (2H, q, J=6 Hz, $COOC\underline{H}_2CH_3$), 4.8-5.08 (2H, m, $CH=C\underline{H}_2$), 5.75 (1H, m, $C\underline{H}=CH_2$) and 7.2 (5H, s, aromatic H).

Analysis:

Found: C, 76.7; H, 8.1; $C_{14}H_{18}O_2$

requires: C, 77.0; H, 8.2%.

k) Ethyl 2-allyl-4-pentenoate (V, f): yield, 97%; b.p.120° (vapour)/50 mm; showed IR bands at: 1735 (ester C=0), 1645, 910 ($CH=CH_2$); PMR signals at: 1.15 (3H, t, J=6 Hz, $COOCH_2C\underline{H}_3$), 2.16 (4H, m, C_2 and C_3 protons), 3.83 (2H, q, J=6 Hz, $COOC\underline{H}_2CH_3$), 4.58-4.78 (4H, m, $CH=C\underline{H}_2$) and 5.4 (2H, m, $C\underline{H}=CH_2$).

Analysis:

Found: C, 71.1; H, 9.4; $C_{10}H_{16}O_2$

requires: C, 71.4; H, 9.5%.

3-Phenoxybenzyl 2-isopropyl-5-methylhex-4-enoate (VI, j):

A solution of ester (V, j, 0.4 g, 2 mmol), 3-phenoxybenzyl alcohol (0.5 g, 2.5 mmol), in xylene (10 ml), containing butyl

titanate (0.005 g),was refluxed for 12 hr. Xylene was removed under suction, residue was taken up in pet.ether, and chromatographed on silicic acid (10 g). Elution with 25% benzene in pet.ether gave TLC pure liquid ester (VI, j, 0.6 g, 89%); IR bands at: 1735 (ester C=0), 1590, 695 (aromatic);PMR signals at: 0.8, 0.87 (each 3H, d, J=7 Hz, methyls of isopropyl), 1.54, 1.61 (each 3H, s, vinyl methyls), 2.26 (3H, m, C_2 and C_3 protons), 5.06 (3H, br s, benzylic and olefinic protons) and 6.8-7.5 (9H, m, aromatic H); MS:m/z, 352 (M^+).

Analysis:

Found: C, 78.1; H, 7.7; $C_{23}H_{28}O_3$

requires: C, 78.4; H, 7.9%.

a) 3-Phenoxybenzyl 5-methyl-4-hexenoate (VI, g):yield. 88%; MS: m/z 310 (M^+); IR bands at: 1735 (ester C=0), 1585, 699 (aromatic); PMR signals at: 1.56, 1.62 (each 3H, s, vinyl methyls), 2.23 (4H, d, J=2 Hz, C_2 and C_3-CH_2), 4.88 (3H, br s, benzylic CH_2 and olefinic proton) and 6.58-7.2 (9H, m, aromatic H).

Analysis:

Found: C, 77.5; H, 7.1; $C_{20}H_{22}O_3$

requires: C, 77.4; H, 7.1%.

b) 3-Phenoxybenzyl 2,5-dimethyl-4-hexenoate (VI, h): yield, 89%; MS: m/z 324 (M^+): IR bands at: 1735 (ester C=0), 1585, 699 (aromatic); PMR (Fig. 2) signals at: 1.08 (3H, d, J=6 Hz, C_2-CH_3), 1.51, 1.56 (each 3H, d, J=6 Hz, vinyl methyls), 2.2

(3H, m, C_2 and C_3 protons), 4.76 (3H, br s, benzylic and olefinic protons) and 6.33-7.0 (9H, m, aromatic H).

Analysis:

Found: C, 77.4; H, 7.1; $C_{21}H_{24}O_3$

requires: C, 77.7; H, 7.4%.

c) 3-Phenoxybenzyl 2-ethyl-5-methyl-4-hexenoate (VI, i): yield, 83%; MS: m/z 338 (M^+); IR bands at: 1738 (ester C=O), 1583, 698 (aromatic); PMR signals at: 0.81 (3H, t, J=7 Hz, CH_3 of ethyl at C_2), 1.37 (2H, m, CH_2 of ethyl at C_2), 1.5, 1.57 (each 3H, s, vinyl methyls), 2.13 (3H, br s, C_2 and C_3 protons), 4.76 (3H, br s, benzylic and olefinic protons) and 6.5-7.05 (9H, m, aromatic H).

Analysis:

Found: C, 78.2; H, 7.7; $C_{22}H_{26}O_3$

requires: C, 78.1; H, 7.7%.

d) 3-Phenoxybenzyl 2-benzyl-5-methyl-4-hexenoate (VI, k): yield, 88%; MS: m/z, 400 (M^+); IR bands at: 1738 (ester C=O), 1587, 693 (aromatic) and PMR signsls at: 1.55, 1.67 (each 3H, s, vinyl methyls), 2.8 (2H, m, benzylic protons at C_2), 4.91 (2H, s, ester benzylic $C\underline{H}_2$), 5.05 (1H, m, olefinic proton)and 6.76-7.38 (14H, m, aromatic H).

Analysis:

Found: C, 80.6; H, 7.1; $C_{27}H_{28}O_3$

requires: C, 81.0; H, 7.0%.

e) 3-Phenoxybenzyl 2-(3-methylbut-2-enyl)-5-methyl-4-hexenoate(VI,i): yield, 88%; MS: m/z 378 (M^+): IR bands at: 1735 (ester C=0), 1585, 910 (aromatic); PMR signals at: 1.48, 1.57 (each 6H, s, vinyl methyls), 2.16 (5H, m, C_2, C_3 and C_3 protons), 4.81 (4H, br s, benzylic and olefinic protons) and 6.5-7.15 (9H, m, aromatic H).
Analysis:

Found: C, 79.1; H, 7.7; $C_{25}H_{30}O_3$
requires: C, 79.3; H, 7.9%.

f) 3-Phenoxybenzyl 4-pentenoate (VI, a): yield: 82%; MS: m/z, 282 (M^+); IR bands at: 1740 (ester C=0), 1642, 915 ($CH=CH_2$), 1602, 690 (aromatic); PMR signals at: 2.33 (4H, d, J=2 Hz, C_2 and C_3 protons), 4.9 (2H, s, benzylic CH_2), 5.01 - 5.16 (2H, m, $CH=C\underline{H}_2$), 5.56 (1H, m, $C\underline{H}=CH_2$) and 6.63-7.26 (9H, m, aromatic H).
Analysis:

Found: C, 76.4; H, 6.3; $C_{18}H_{18}O_3$
requires: C, 76.6; H, 6.4%.

g) 3-Phenoxybenzyl 2-methyl-4-pentenoate (VI, b): yield, 87%, MS: m/z, 296 (M^+); IR bands at: 1735 (ester C=0), 1640, 885 ($CH=CH_2$), 1585, 690 (aromatic); PMR signals at: 1.13 (3H, d, J=6 Hz, C_2-CH_3), 2.33 (3H, m, C_2 and C_3 protons), 4.73, 5.0 (2H, m, $CH=C\underline{H}_2$), 4.91 (2H, s, benzylic CH_2), 5.50 (1H, m, $C\underline{H}=CH_2$) and 6.56-7.31 (9H, m, aromatic H).
Analysis:

Found: C, 76.7; H, 6.9; $C_{19}H_{20}O_3$
requires: C, 77.0; H, 7.0%.

h) 3-Phenoxybenzyl 2-ethyl-4-pentenoate (VI, c): yield, 86%; MS: m/z 316 (M^+); IR bands at: 1742 (ester C=0), 1640, 920 ($CH=CH_2$), 1585, 690 (aromatic H); PMR signals at: 0.86 (3H, t, J=6 Hz, C_2-CH_2CH_3), 2.26 (3H, m, C_2 and C_3 protons), 4.76-5.05 (2H, m, $CH=CH_2$), 5.0 (2H, s, benzylic CH_2), 5.66 (1H, m, $CH=CH_2$) and 6.75-7.36 (9H, m, aromatic H).

Analysis:

Found: C, 75.7; H, 6.7; $C_{20}H_{22}O_3$

requires: C, 75.9; H, 6.9%.

i) 3-Phenoxybenzyl 2-isopropyl-4-pentenoate (VI, d): yield, 89%; MS: m/z, 324 (M^+); IR bands at: 1740 (ester C=0), 1640, 890 ($CH=CH_2$), 1587, 698 (aromatic); PMR signals at: 0.86, 0.9 (each 3H, d, J=6 Hz, isopropyl methyls), 2.33 (3H, m, C_2 and C_3 protons), 4.76-5.0 (2H, m, $CH=CH_2$), 4.96 (2H, s, benzylic CH_2), 5.46 (1H, m, $CH=CH_2$) and 6.76-7.2 (9H, m, aromatic H).

Analysis:

Found: C, 77.4; H, 7.2; $C_{21}H_{24}O_3$

requires: C, 77.7; H, 7.4%.

j) 3-Phenoxybenzyl 2-benzyl-4-pentenoate (VI, e): yield, 91% MS: m/z 372 (M^+); IR bands at: 1735 (ester C=0), 1645, 885 ($CH=CH_2$), 1590, 700 (aromatic); PMR signals at: 2.33 (3H, m, C_2 and C_3 protons), 2.86 (2H, br s, benzylic CH_2 at C_2), 5.07 (2H, s, ester benzylic CH_2), 5.09-5.3 (2H, m, $CH=CH_2$), 5.9 (1H, m, $CH=CH_2$) and 7.23-7.6 (14H, m, aromatic H).

Analysis:

Found: C, 80.2; H, 6.2; $C_{25}H_{24}O_3$

requires: C, 80.6; H, 6.4%

k) 3-Phenoxybenzyl 2-allyl-4-pentenoate (VI, f): yield, 92%; MS: m/z, 322 (M^+); IR bands at: 1730 (ester C=O), 1640, 915 ($CH=CH_2$), 1585, 690 (aromatic); PMR signals at: 2.18 (5H, m, C_2, C_3 and C_3' protons), 4.58–4.75 (4H, m, $CH=C\underline{H}_2$), 4.97 (2H, s, benzylic CH_2), 5.86 (2H, m, $C\underline{H}=CH_2$) and 6.33-6.9 (9H, m, aromatic H).

Analysis:

Found: C, 77.9; H, 6.6; $C_{21}H_{22}O_3$

requires: C, 78.2; H, 6.8%.

General procedure for the preparation of p-substituted benzoyl butyric acids:

Preparation of p-chlorobenzoyl butyric acid (VIII,c):

Anhydrous aluminium chloride (20 g, 156 mmol), was gradually added to a mechanically stirred solution of glutaric anhydride (6 g, 52 mmol), in dry chlorobenzene (100 ml), placed in a 250 ml three-necked round bottom flask, fitted with a reflux condensor carrying a gas outlet tube. The mixture was heated on a steam bath until the evolution of hydrochloric acid gas ceased. It was cooled, decomposed by ice and concentrated HCl. Excess of chlorobenzene was distilled and the residue digested with 10% solution of sodium carbonate (150 ml). The cold aqueous filtrate

was washed with ether. Acid was precipitated by acidifing the aqueous layer to pH-2, solid acid was crystalised from boiling water, to get white needles, m.p. 121°C.

Esterification: A solution of 4-chlorobenzoyl butyric acid (2.27, g) in methanol (100 ml), containing concentrated sulphuric acid (0.5 g), was refluxed for 3 hr. Excess of methanol was skipped off, residue was cooled, diluted with water and extracted with ether (50 ml x 3). The combined organic layer was washed with water, 10% sodium bicarbonate, followed by water, dried and concentrated to give ester (IX, 2.2 g), purified by distillation, b.p.160°/5 mm. IR (Fig.3) bands at: 1739, 1689 (ester and benzoyl C=0); PMR signals at:2.0 (2H, m, C_3-CH_2), 2.3 (2H, t, J=6 Hz, C_2-CH_2), 2.96 (2H, t, J=7 Hz, C_4-CH_2), 3.63 (3H, s, ester methyl), 7.36 and 7.93 (each 2H, d, J=8 Hz, aromatic H). Analysis:

Found: C, 59.7; H, 5.2; Cl, 14.6; $C_{12}H_{13}O_3Cl$
requires: C, 60.0; H, 5.4; Cl, 14.8%.

Other γ-benzoyl butyric acids were prepared and esterified by employing the same procedure described above.

The methyl esters of 4-bromo and 4-chloro-γ-benzoyl butyric acids thus prepared, were found to be non-homogeneous according to TLC (benzene + 2% ethyl acetate) and contained a minor impurity of less polar compound. These were therefore chromatographed over silicic acid (1:10) for obtaining the methyl esters in pure state. The less polar impurity in each case was eluted from

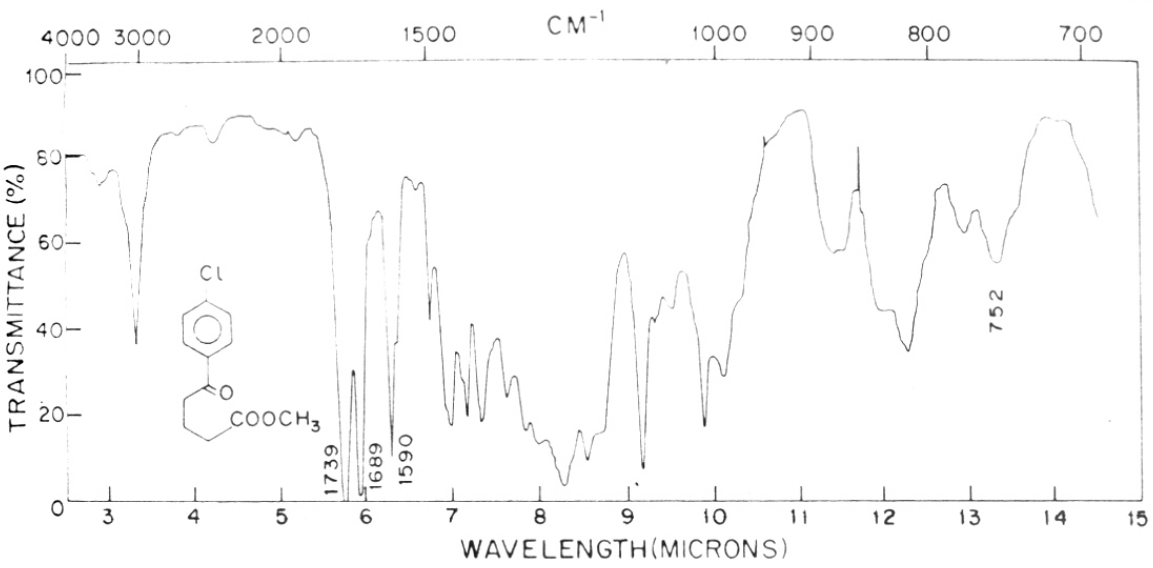


FIG. 3. METHYL γ-p-CHLOROBENZOYL BUTYR ATE, VIII C

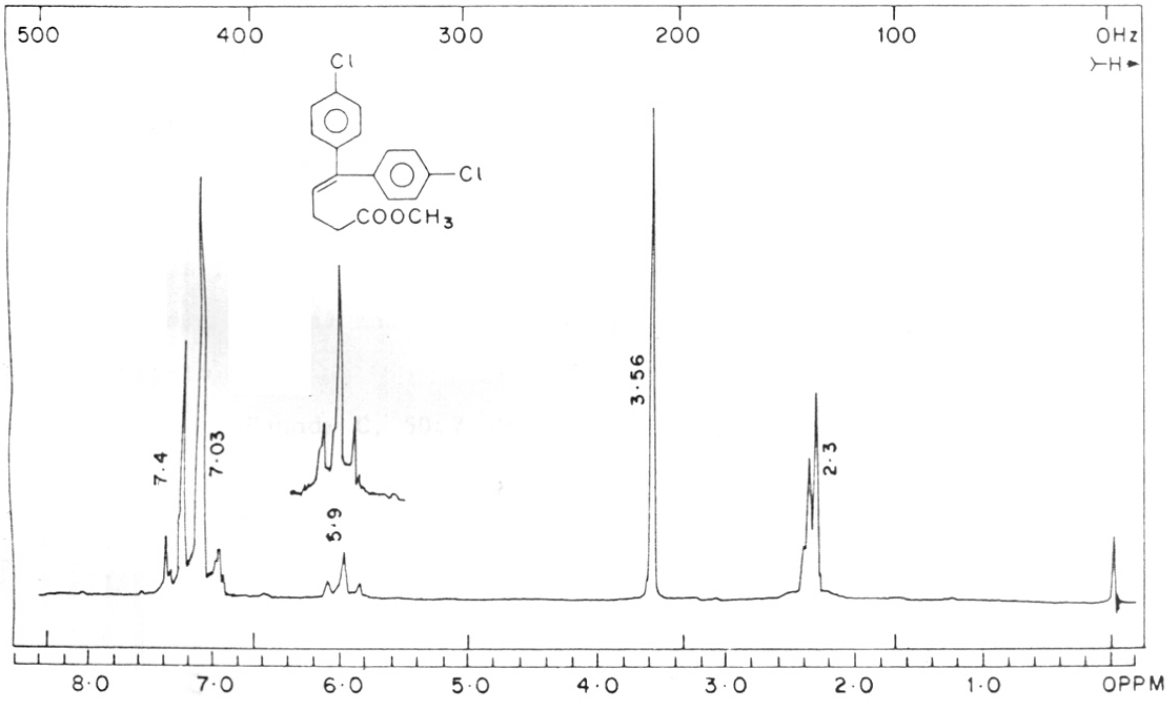


FIG. 4. METHYL 5,5-DI-P-CHLOROPHENYL-4-PENTENOATE, XX

the column with pet.ether + 25% benzene and obtained as a crystaline solid, and identified from M^+ ion, micro analysis and spectral data as XXa,b.

Methyl 5,5-di-p-chlorophenyl-4-pentenoate (XX, a): yield, 5%; MS: m/z, 336 (M^+), 338, 340 (^{37}Cl); IR band at: 1724 (ester C=0); PMR (Fig. 4) signals at: 2.3 (4H, d, J=2 Hz, C_2 and C_3 methylene protons), 3.56 (3H, s, ester methyl), 5.9 (1H, t, J=6 Hz, olefinic proton) and 7.03, 7.4 (each 4H, d, J=8 Hz, aromatic H); m.p.30°C.

Analysis:

Found: C, 63.9; H, 5.2; Cl, 20.8; $C_{18}H_{18}O_2Cl_2$

requires: C, 64.1; H, 5.3; Cl, 21.0%.

Methyl 5,5-di-p-bromophenyl-4-pentenoate (XX, b): yield, 4%; MS: m/z, 424 (M^+), 426, 428 (^{81}Br); IR band at: 1730 (ester C=0); PMR signals at: 2.1 (4H, d, J=2 Hz, C_2 and C_3 methylene protons), 3.56 (3H, s, ester methyl), 5.8 (1H, t, J=6 Hz, olefinic proton) and 6.63-7.4 (8H, m, aromatic H), m.p.35°C.

Analysis:

Found: C, 50.7; H, 4.1; Br, 37.7; $C_{18}H_{18}O_2Br_2$

requires: C, 50.7; H, 4.2; Br, 38.0%.

The fraction eluted with pet.ether + benzene (1:1) gave TLC pure methyl esters (IXa-d), identified by spectral data.

γ-Benzoyl propionic acids were similarly prepared as per the procedure described above, by Friedel Craft acylation of

benzene and substituted benzenes with succinic anhydride and were then esterified with $MeOH/H^+$, to afford the methyl esters. All the compound have been identified, by comparison of the spectral data with those reported, in literature for authentic samples.

Methyl 5-chloro-5-p-chlorophenylpent-4-enoate (X, c):

To a stirred solution of ester (IX, c, 1 g, 4.1 mmol), in methylene chloride (10 ml), phosphorous pentachloride (2 g) was added in small lots. The reaction mixture was refluxed for 6 hr, poured onto crushed ice with stirring and extracted with methylene chloride (50 ml x 3). The organic layer was washed with water, 10% aqueous sodium carbonate, followed by water and dried. Removal of methylene chloride furnished a crude mixture of chloroesters (0.98 g), which was purified by chromatography over silicic acid (1:15) and eluted with pet.ether + 20% benzene, to give X, c (0.7 g, 65%); MS: m/z, 258 (M^+), 260, 262 (^{37}Cl); IR band at: 1735 (ester C=0); PMR signals at: 2.65 (4H, m, C_2 and C_3-CH_2), 3.65 (3H, s, ester methyl), 6.04 (1H, m, olefinic proton), 7.36 and 7.93 (each 2H, d, J=6 Hz, aromatic H).

Analysis:

Found: C, 55.2; H, 4.3; Cl, 26.9; $C_{12}H_{12}O_2Cl_2$ requires: C, 55.6; H, 4.6; Cl, 27.4%.

By following analogous procedure the following chloroesters have been prepared.

a) Methyl 5-chloro-5-phenyl-4-pentenoate (X, a): yield, 70%; MS: m/z, 224 (M^+), 226 (^{37}Cl); IR bands at: 1745 (ester C=0), 1600, 755 (aromatic); PMR signals at: 2.46 (4H, m, C_2 and C_3-CH_2), 3.6 (3H, s, ester methyl), 5.85 (1H, m, olefinic proton), 7.26 (5H, m, aromatic H).

Analysis:

Found: C, 63.9; H, 5.6; Cl, 15.2; $C_{12}H_{13}O_2Cl$

requires: C, 64.1; H, 5.8; Cl, 15.8%.

b) Methyl-5-chloro-5- tolyl-4-pentenoate (X, b): yield, 70%; b.p.180°/2 mm; MS: m/z , 238 (M^+), 240 (^{37}Cl); IR bands at: 1735 (ester C=0), 1600, 775 (aromatic); PMR (Fig. 5) signals at: 2.4 (3H, s,aromatic CH_3), 2.46 (4H, m, C_2 and C_3 methylenes), 3.6 (3H, s, ester methyl), 5.95 (1H, m, olefinic proton) and 7.06,7.5 (2H each, d, J=8 Hz, aromatic H).

Analysis:

Found: C, 65.7; H, 6.1; Cl, 14.5; $C_{13}H_{15}O_2Cl$

requires: C, 65.4; H, 6.3; Cl, 14.7%.

c) Methyl-5-chloro-5(p-bromo)phenyl-4-pentenoate (X, d): yield, 65%; MS: m/z, 302 (M^+), 304, 306 (^{37}Cl, ^{81}Br); IR bands at: 1748 (ester C=0), 1600, 1490, 833 (aromatic); PMR signals at: 2.4 (4H, m, C_2 and C_3 protons), 3.65 (3H, s, ester methyl), 6.1 (1H, m, olefinic H) and 7.5, 7.9 (2H each, d, each, J=7 Hz, aromatic H).

Analysis:

Found: C, 47.4; H, 3.9; $C_{12}H_{12}O_2ClBr$

requires: C, 47.7; H, 3.9%.

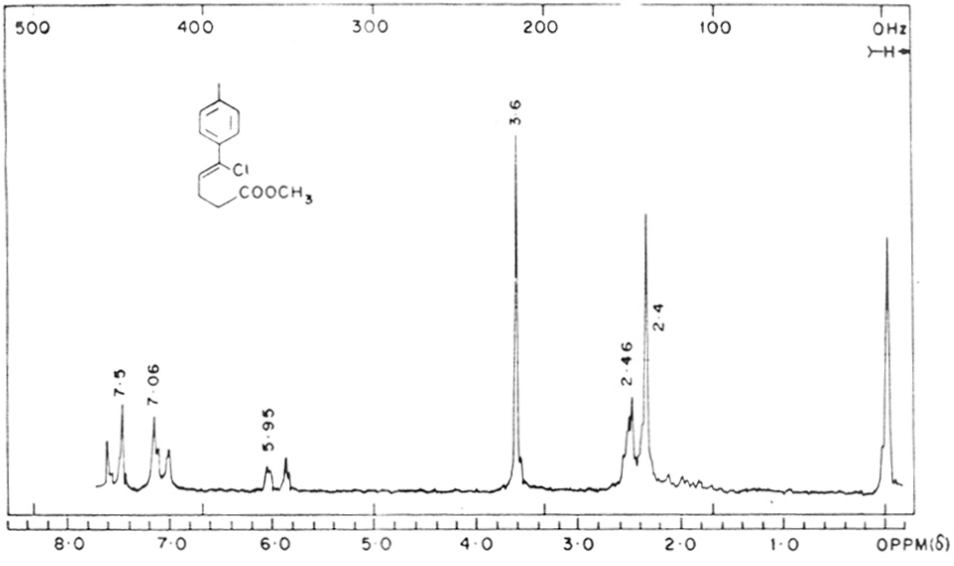


FIG. 5. METHYL 5-CHLORO-5-TOLYL-4-PENTENOATE, X b

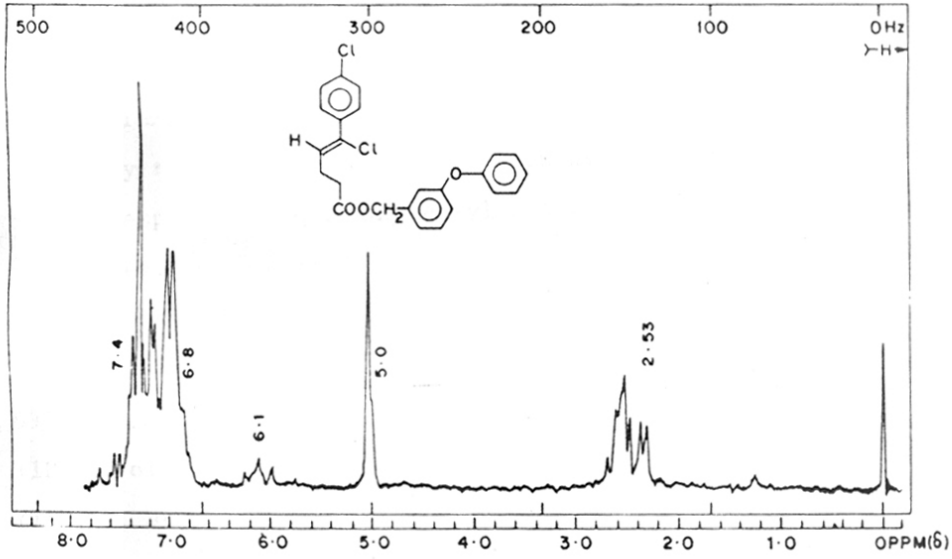


FIG. 6. 3-PHENOXYBENZYL 5-CHLORO-5-P-CHLOROPHENYL-4-PENTENOATE, XI C

3-Phenoxybenzyl-5-chloro-5-p-chlorphenylpent-4-enoate (XI,c):

A solution of chloroester (X, c, 0.4 g, 1.5 mmol), 3-phenoxybenzyl alcohol (0.4 g, 2 mmol), in xylene (10 ml), containing butyl titanate (0.005 g), was erfluxed for 8 hr. Xylene was removed under suction, the residue taken up in pet.ether (2 ml) and chromatographed on silicic acid (8 g) and eluted with pet.ether + 20% benzene to furnish XI, c (0.55 g, 83%), TLC one spot (benzene + 1% ethyl acetate), identified by spectral data. IR band at: 1742 (ester C=0); PMR (Fig. 6) signals at:2.53 (4H, m, C_2 and C_3-CH_2), 5.0 (2H, s, benzylic CH_2), 6.1 (1H, m, olefinic proton) and 6.8-7.4 (13H, m, aromatic H); MS:m/z, 426(M^+), 428, 430 (^{37}Cl).

Analysis:

Found: C, 66.9; H, 4.4; Cl, 16.7; $C_{24}H_{20}O_3Cl$

requires: C, 67.4; H, 4.6; Cl, 16.4%

All the methyl 5-chloro-4-pentenoates (Xa-d) and 5,5-dichloro-4 alkyl/aryl-4-pentenoates (XVa-d, XVIII) were similarly transesterified with 3-phenoxybenzyl alcohol to afford the corresponding 3-phenoxybenzyl esters, identified by spectral properties.

a) 3-Phenoxybenzyl 5-chloro-5-phenyl-4-pentenoate (XIa):yield, 85%; MS: m/z, 393 (M^+) 394 (^{37}Cl); IR bands at: 1745 (esterC=0); 1587, 692 (aromatic); PMR signals at: 2.5 (4H, m, C_2 and C_3-CH_2), 5.93 (1H, m, olefinic proton), 4.93 (2H, s, benzylic CH_2) and 7.1 (14H, m, aromatic H).

Analysis:

Found: C, 72.8; H, 5.1; Cl, 8.7; $C_{24}H_{21}O_3Cl$

requires: C, 73.3; H, 5.3; Cl, 9.0%.

b) 3-Phenoxybenzyl 5-chloro-5-tolyl-4-pentenoate (XI, b): yield, 84%; MS: m/z, 406 (M^+), 408 (^{37}Cl); IR bands at: 1735 (ester C=O), 1575, 775, 690 (aromatic); PMR signals at: 2.36 (3H, s, aromatic CH_3), 2.55 (4H, m, C_2 and C_3 protons), 5.68 (1H, m, olefinic proton), 5.05 (2H, s, benzylic CH_2) and 7.13 (13H, m, aromatic H).

Analysis:

Found: C, 73.4; H, 5.4; Cl, 8.4; $C_{25}H_{23}O_3Cl$

requires: C, 73.3; H, 5.6; Cl, 8.7%.

c) 3-Phenoxybenzyl-5-chloro-5-(p-bromo)phenyl-4-pentenoate (XI,d): yield, 88%; MS: m/z, 472 (M^+), 474, 476 (^{37}Cl, ^{81}Br); IR bands at: 1740 (ester C=O), 1593, 1494, 830 (aromatic); PMR signals at: 2.5 (4H, m, C_2 and C_3 protons), 5.05 (2H, s, benzylic CH_2), 6.13 (1H, m, olefinic proton) and 7.3 (13H, m, aromatic H).

Analysis:

Found: C, 60.3; H, 4.1; $C_{24}H_{20}O_3ClBr$

requires: C, 60.8; H, 4.3%.

Methyl 4-p-chlorophenyl-5,5-dichloropent-4-enoate (XV, c):

Ester (XIV, c, 2 g, 8.7 mmol), was added to a solution of triphenyl phosphine (6.5 g, 24 mmol), in carbon tetrachloride (25 ml), placed in a 50 ml round bottom flask. Reaction

mixture was then heated under stirring in nitrogen atmosphere at 60° for 4 hrs. Excess of carbon tetrachloride was distilled off, the residue extracted repeatedly with hot pet.ether, when triphenyl phosphine oxide separated as a solid. Evaporation of organic layer gave a crude ester (2 g), purified by column chromatography over grade II alumina (60 g, 1:30). The fraction eluted with pet.ether gave XV, c (1.1 g, 48%) as a liquid. It showed IR bands at: 1748 (ester C=0); PMR signals at: 2.31 (2H, m, C_2-CH_2), 2.87 (2H, m, C_3-CH_2), 3.56 (3H, s, ester methyl), 7.23 and 7.48 (each 2H, d, J=8 Hz, aromatic H); MS: m/z, 292(M^+), 294, 296, 298 (^{37}Cl).

Analysis:

Found: C, 48.6; H, 3.6; Cl, 35.9; $C_{12}H_{11}O_2Cl_3$

requires: C, 49.0 H, 3.7; Cl, 36.2%.

Dihalovinyl function was similarly introduced in other β-benzoyl propionate (XIVa-d) and methyl levulinate (XVII).

a) Methyl 4-tolyl -5,5-dichloro-4-pentenoate (XVb): yield, 52%; MS: m/z, 272 (M^+) 274, 276 (^{37}Cl); IR bands at: 1742 (ester C=0), 1626, 1527, 820 (aromatic); PMR (Fig. 7) signals at: 2.26 (2H, t, J=6 Hz, C_2-CH_2), 2.33 (3H, s, C_6H_4-CH_3), 2.86 (2H, br t, C_3-CH_2), 3.55 (3H, s, ester methyl) and 7.21 (4H, s, aromatic H).

Analysis:

Found: C,56.9; H, 5.2; Cl, 25.6; $C_{13}H_{14}O_2Cl$

requires: C,57.1; H, 5.1; Cl, 26.0%.

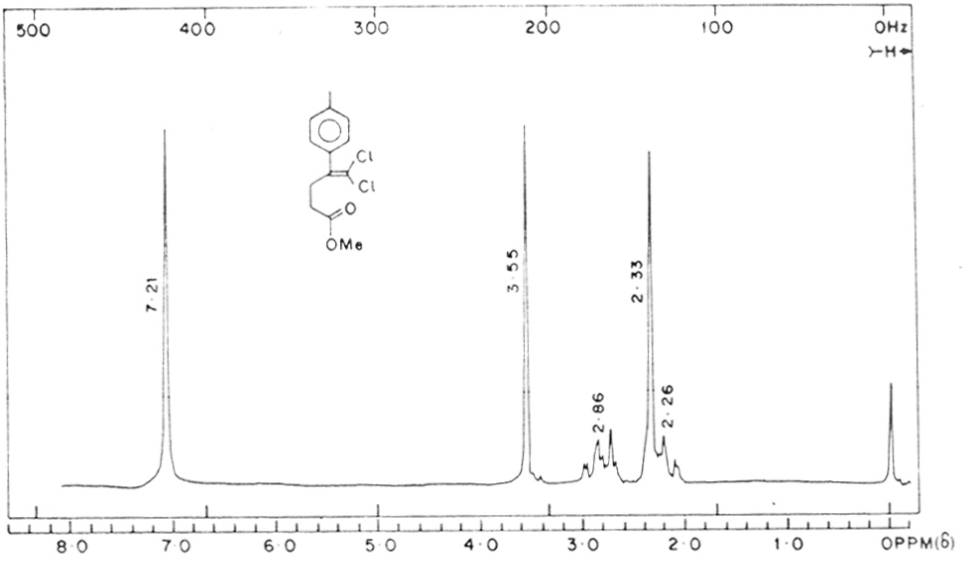


FIG. 7. METHYL 4-TOLYL —5,5-DICHLORO-4-PENTENOATE, XV b

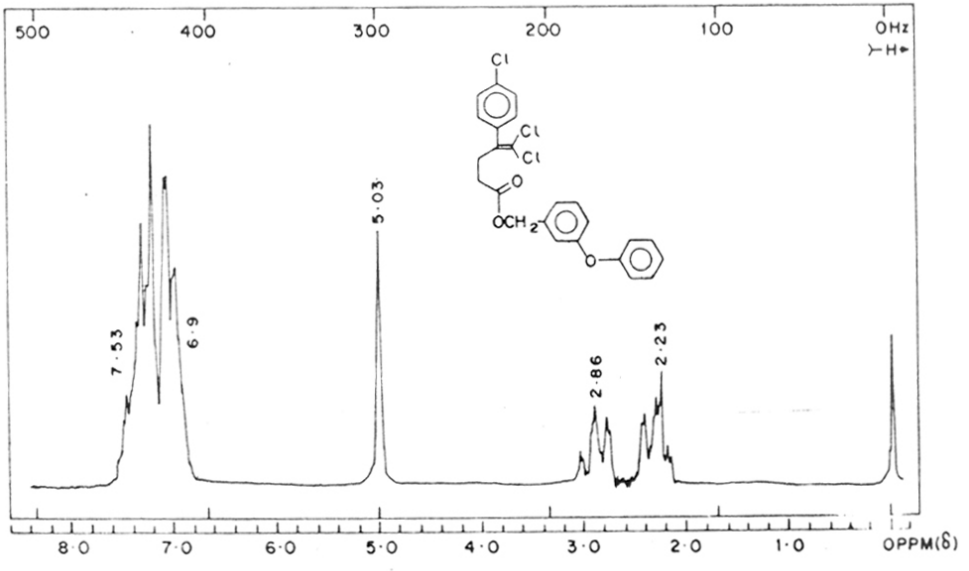


FIG. 8. 3-PHENOXYBENZYL-4-P-CHLOROPHENYL-5,5-DICHLORO-4-PENTENOATE, XVI C

b) Methyl 4-phenyl-5,5-dichloro-4-pentenoate (XVa): yield, 58%; MS: m/z, 258 (M^+), 260, 262 (^{37}Cl); IR bands at: 1729 (ester C=0), 1590, 885, 700 (aromatic); PMR signals at: 2.33 (2H, m, C_2-CH_2), 2.85 (2H, m, C_3-CH_2), 3.53 (3H, s, ester methyl) and 7.16 (5H, s, aromatic H).

Analysis:

Found: C, 55.4; H, 4.5;Cl, 27.2; $C_{12}H_{12}O_2Cl_2$

requires: C, 55.6; H, 4.6; Cl, 27.4%.

c) Methyl 4-(p-bromo) phenyl-5,5-dichloro-4-pentenoate (XVd): yield, 53%; MS: m/z, 338 (M^+), 340, 342, 344 (^{37}Cl, ^{81}Br); IR bands at: 1739 (ester C=0), 1587, 693 (aromatic) and PMR signals at: 2.46 (2H, m, C_2-CH_2), 2.86 (2H, br t, C_3-CH_2), 3.6 (3H, s, ester methyl) 7.23 and 7.5 (each 2H, d, J=8 Hz, aromatic H).

Analysis:

Found: C, 42.4; H, 3.1; $C_{12}H_{11}O_2Cl_2Br$

requires: C, 42.3; H, 3.2%.

d) Methyl 4-methyl-5,5-dichloro-4-pentenoate (XVIII): yield, 48%; MS: m/z 196 (M^+), 198, 200 (^{37}Cl); b.p.140°/6 mm; IR bands at: 1742 (ester C=0), 1645, 887 ($C=CCl_2$); PMR signals at: 1.8 (3H, s, vinyl methyl), 2.13 (2H, m, C_3-CH_2), 2.48 (2H, m, C_2-CH_2) and 3.61 (3H, s, ester methyl).

Analysis:

Found: C, 42.6; H, 5.0; Cl, 36.1; $C_7H_{10}O_2Cl_2$

requires: C, 42.6; H, 5.1; Cl, 36.0%.

a) 3-Phenoxybenzyl 4-phenyl-5,5-dichloropent-4-enoate (XVIa): yield, 88%; MS: m/z, 426 (M^+), 428, 430 (^{37}Cl); IR bands at: 1748 (ester C=0), 1600, 694 (aromatic); PMR signals at: 2.36 (2H, m, C_2-CH_2), 2.93 (2H, m, C_3-CH_2), 4.96 (2H, s, benzylic CH_2) and 6.86-7.36 (14H, m, aromatic H).

Analysis:

Found: C, 67.4; H, 4.5; Cl, 16.4; $C_{24}H_{20}O_3Cl_2$

requires: C, 67.4; H, 4.7; Cl, 16.6%.

b) 3-Phenoxybenzyl 4-tolyl -5,5-dichloro-4-pentenoate (XVI,b): yield, 90%; MS: m/z, 440 (M^+), 442, 444 (^{37}Cl); IR bands at: 1733 (ester C=0), 1600, 825 (aromatic); PMR signals at: 2.27 (2H, m, C_2-CH_2), 2.28 (3H, s, benzylic CH_3), 2.78 (2H, m, C_3-CH_2), 5.01 (2H, s, ester benzylic CH_2) and 6.84-7.43 (13H, m, aromatic H).

Analysis:

Found: C, 68.1; H, 5.1; Cl, 15.6; $C_{25}H_{22}O_3Cl_2$

requires: C, 68.0; H, 5.0; Cl, 15.9%.

c) 3-Phenoxybenzyl 4-(4-chloro)phenyl-5,5-dichloro-4-pentenoate (XVI, c): yield, 88%, MS: m/z, 460 (M^+), 462, 464, 468 (^{37}Cl); IR bands at: 1739 (ester C=0), 1587, 884, 775 (aromatic); PMR signals at: 2.23 (2H, m, C_2-CH_2), 2.86 (2H, m, C_3-CH_2), 5.03 (2H, s, benzylic CH_2) and 6.9-7.53 (13H, m, aromatic H).

Analysis:

Found: C, 62.3; H, 4.0; Cl, 22.9; $C_{24}H_{19}O_3Cl_3$

requires: C, 62.4; H, 4.1; Cl, 23.1%.

d) 3-Phenoxybenzyl 4-(4-bromo)phenyl-4-pentenoate (XVI, d): yield, 86%; MS: m/z 504 (M^+), 506, 508, 510 (^{37}Cl, ^{81}Br); IR bands at: 1738 (ester C=0), 1585, 692 (aromatic); PMR (Fig. 8) signals at: 2.26 (2H, m, C_2-CH_2), 2.83 (2H, m, C_3-CH_2), 5.0 (2H, s, benzylic CH_2) and 6.6-7.3 (13H, m, aromatic H). Analysis:

Found: C, 56.8; H, 3.5; $C_{24}H_{19}O_3ClBr$

requires: C, 56.9; H, 3.7%.

e) 3-Phenoxybenzyl 4-methyl-5,5-dichloro-4-pentenoate (XIX): yield, 87%; MS: m/z 364 (M^+), 366, 368 (^{37}Cl); IR bands at: 1738 (ester C=0), 1595, 1493, 694 (aromatic); PMR signals at: 1.86 (3H, s, vinyl methyl), 2.5 (4H, m, C_2 and C_3-CH_2), 5.03 (2H, s, benzylic CH_2) and 6.83-7.36 (9H, m, aromatic H). Analysis:

Found: C, 62.1; H, 4.5; Cl, 19.1; $C_{19}H_{18}O_3Cl_2$

requires: C, 62.4; H, 4.9; Cl, 19.4%.

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CHAPTER–III

SYNTHESIS OF 1, 3-SECO-PYRETHROIDS

SUMMARY

Transformations of (+) citronellol and (+) citronellal into 1,3-secopyrethroids has been described in this part of the thesis.

Potassium permanganate oxidation of citronellol acetate (III) under buffer conditions according to the method of Srinivasan and Lee, gave ketol acetate (IV), as the major product which on Grignard reaction with methyl magnesium iodide, gave the triol viz 1,6,7-trihydroxy-3,6,7-trimethyl octane (VI). The latter, posssessing vicinal diol grouping, was oxidatively cleaved by sodium metaperiodate to give keto alcohol (VII). Further oxidation of VII with Jones chromic acid reagent, followed by esterification of the resulting acid (diazomethane) gave methyl 3-methyl-6-oxoheptenoate (VIII). The keto ester (VIII), when reacted with PCl_5 in methylene chloride, gave E and Z mixture of (IX). The keto ester (VIII), was converted to cyanohydrin ester (XIV) and the latter dehydrated ($POCl_3$/ pyridine), to give Z isomers of XV. Grignard reaction on keto alcohol (VII) or acetate ester (V), using methyl magnesium iodide afforded the diol (XIX), which was oxidised by potassium permanganate to give hydroxy acid (XX). Methyl ester of the latter, on dehydration (PTS/benzene), afforded XXI, as the major product. The compound IX, XV and XXI were transesterified with 3-phenoxybenzyl alcohol to yield insecticidal esters XII, XVII and XXII respectively. By employing similar sequence

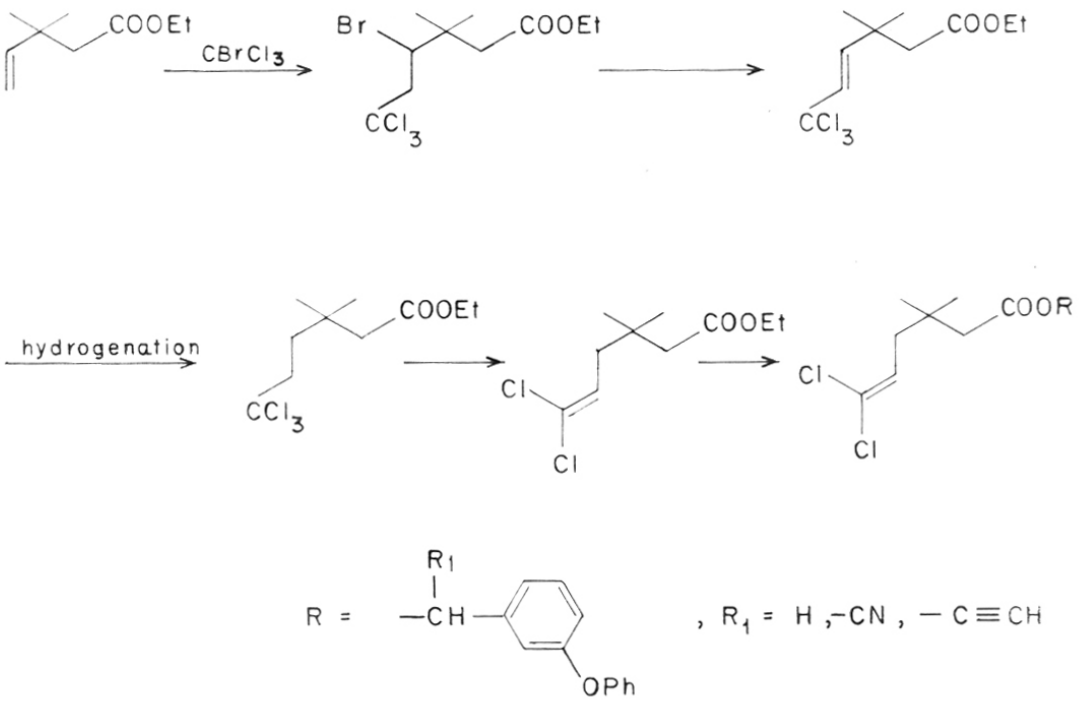
By employing similar sequence of well-known reactions like Grignard, oxidation with $KMnO_4$ or CrO_3 and PCl_5 reaction on carbonyl compounds, (+) citronellal (XXIII) has been converted into 3-phenoxybenzyl esters XXIX, XXXIV, XL, XLV which show larvicidal,insecticidal activity.

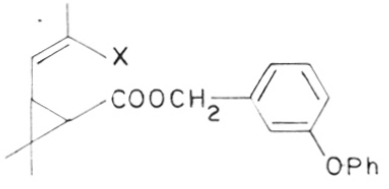
INTRODUCTION

In the previous two chapters, the synthesis of acid moieties of 2,3-secopyrethroids and chrysanthemates has been described. As already mentioned secopyrethroids can be considered to have been derived from their corresponding cyclopropane derivatives, by cleavage of one of the three bonds of cyclopropane. In this chapter, the synthesis of some acid moieties of 1,3-secopyrethroids has been described from naturally occurring substrates like citronellol and citronellal. The acid moieties thus synthesised, were converted into their 3-phenoxybenzyl esters for examining them for their insecticidal activity. In this type of esters the disubstituted vinyl function and the ester function are separated by a three carbon chain, bearing a methyl substituent either on β or γ carbon atom.

Omura et al.[1] (Chart-I) have synthesised 6,6-dichloro-3,3-dimethylhex-5-enoic acid esters with alcohols, like 3-phenoxybenzyl, α-cyano-3-phenoxybenzyl and other related alcohols and claimed to possess high insecticidal activity. These compounds can be considered as 1,3-secopyrethroids, derived from highly potent pyrethroids like permethrin and cypermethrin. Ethyl 3,3-dimethyl-4-pentenoate can be obtained[2], by condensation of 3-methylbut-2-ene-1-ol with triethyl orthoacetate, involving a Claisen's allylic rearrangement. Free radical initiated bromochloroform addition to the pentenoate afforded ethyl 3,3-dimethyl-

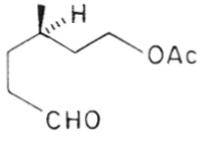
CHART I





X = Cl or CN

I



A

4-bromo-6,6,6-trichlorohexanoate. Selective dehydrobromination of the latter followed by catalytic hydrogenation of the resulting unsaturated trichloroester, gave ethyl 3,3-dimethyl-6,6,6-trichlorohexanoate. This was then dehydrochlorinated under controlled conditions to give ethyl 3,3-dimethyl-6,6-dichloro-hex-5-enoate, which was subsequently converted into the insecticidally active 1,3-secopyrethroids.

In our laboratory, some new 1R-cis pyrethroids have been synthesised from (+) 3-carene[3], for example, 3-phenoxybenzyl 1R-cis 2,2-dimethyl-3-(2-chloro/cyano prop-1-enyl)cyclopropane-carboxylates (Chart I, Structure I) as E and Z mixtures, which show comparable insecticidal activity to permethrin. So we were interested in synthesis of 1,3-secoanalogues of these compounds, with a view to test them for insecticidal activity. However, compounds synthesised by us, though resemble closely in structure, differ from them in that they contain only one methyl group on the β or γ carbon atom instead of gemdimethyl.

For our work, cheap and abundantly available naturally occurring monoterpenes, like (+) citronellal and (+) citronellol were selected. The citronellol contains an alcohol function and vinyl group situated idealy for its transformation into acid moieties of 1,3-secopyrethroids. The absolute configuration at the chiral center C_3 has been well established as R, which is not disturbed during the sequence of reactions used, in our synthetic scheme.

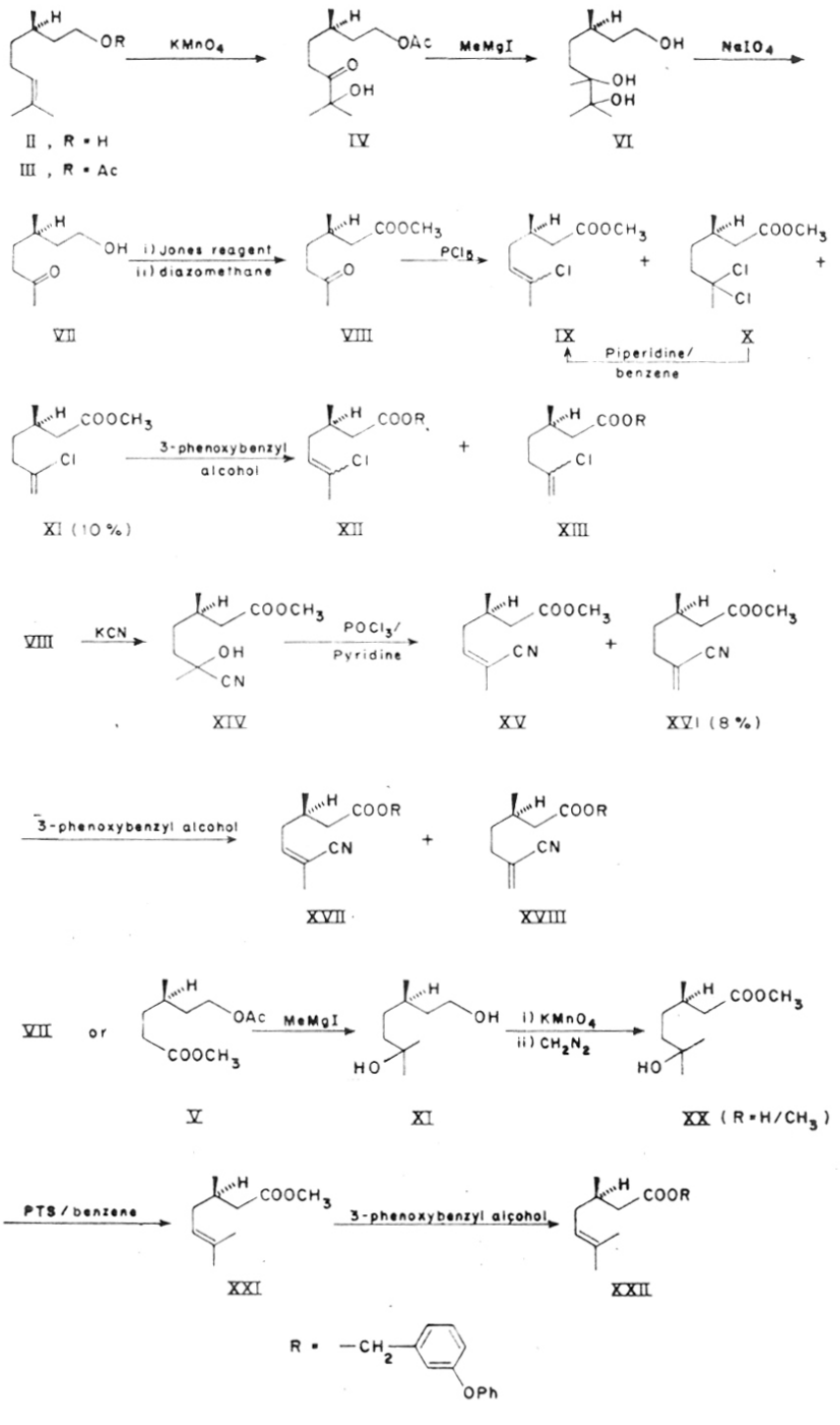
PRESENT WORK

The desired key intermediate for our synthetic route is 3-methyl-6-oxoheptane-1-ol (VII), from which acid moieties of 1,3-secopyrethroids could be synthesised. Compound VII can be obtained from the aldehyde (Chart I, A), by Grignard reaction followed by oxidation. In our initial attempts, citronellol acetate was subjected to ozonolysis followed by reductive cleavage of the ozonide to get the aldehyde viz. 6-acetoxy-4-methylhexanal. However, due to the unstable nature of the aldehyde and moderate yields in ozonolysis, the method was given up.

Performic acid oxidation of citronellol, followed by hydrolysis, gave the triol 3,7-dimethyl-1,6,7-trihydroxy octane. It showed IR bands at: 3450 (-OH) and PMR signals at: 0.9 (3H, d, J=6 Hz, C_3-CH_3), 1.13, 1.16 (each 3H, s, methyls of hydroxy-isopropyl), 1.43 (7H, m, methylene and methine protons), 3.1 (s, exchangable with D_2O, -OH protons), 3.6 (2H, t, J=6 Hz, $C\underline{H}_2OH$) and 3.78 (1H, m, $C\underline{H}OH$). Metaperiodate oxidation of this triol, however, failed to give the desired aldehyde in good yields. A different strategy therefore was followed for the desired intermediate, as described below (Scheme I).

Citronellol acetate (III,R=Ac), was obtained by acetylation of citronellol (II,R=H), with acetic anhydride in pyridine in almost quantitative yield. It showed IR bands at: 1739, 1242, (acetate) and PMR signals at: 0.9 (3H, d, J=6 Hz, C_3-CH_3), 1.55, 1.6 (each 3H, s, methyls on double bond), 1.9 (3H, s,

SCHEME I


KMnO4
MeMgI
NaIO4
II , R = H
III , R = Ac
IV
VI
i) Jones reagent
ii) diazomethane
PCl5
VII
VIII
IX
X
Piperidine/
benzene
3-phenoxybenzyl
alcohol
XI (10 %)
XII
XIII
KCN
POCl3/
Pyridine
XIV
XV
XVI (8 %)
3-phenoxybenzyl alcohol
XVII
XVIII
VII or
MeMgI
V
XI
i) KMnO4
ii) CH2N2
XX (R = H/CH3)
PTS / benzene
3-phenoxybenzyl alcohol
XXI
XXII
R =
OPh

$COC\underline{H}_3$), 3.93 (2H, t, J=7 Hz, $C\underline{H}_2OAc$) and 4.93 (1H, t, J=6 Hz, olefinic H).

Oxidation of citronellol acetate (III, R=Ac), by $KMnO_4$ under buffer conditions according to the method of Srinivasan and Lee's[4], afforded a mixture of two products, separated into, acidic and neutral components by carbonate extraction. The acidic part, minor product of reaction, was esterified with an ethereal solution of diazomethane and identified as methyl 6-acetoxy-4-methylhexanoate (V). IR bands at: 1745 (C=0 of ester and acetate), 1240 (acetate); PMR signals at: 0.93 (3H, br d, C_4-CH_3), 1.53 (4H, m, methylene protons), 1.9 (3H, s, $COC\underline{H}_3$), 2.3 (2H, t, J=6 Hz, C_2-CH_2), 3.53 (3H, s, $COOC\underline{H}_3$) and 3.94 (2H, t, J=6 Hz, $C\underline{H}_2OAc$). The neutral portion containing the major product, gave the expected 7-hydroxy-3,7-dimethyl-6-oxo-1-octanol acetate (IV), as a liquid; IR (Fig. 1) bands at: 3571 (-OH), 1742 (ester C=0), 1724 (acetate C=0), 1240 (acetate) and PMR (Fig. 2) signals at: 0.9 (3H, br d, C_3-CH_3), 1.25 (6H, s, methyls of hydroxyisopropyl), 1.95 (3H, s, $OCOC\underline{H}_3$), 2.53 (2H, t, J=7 Hz, $COC\underline{H}_2$), 3.7 (1H, s, exchangable with D_2O, $O\underline{H}$ proton) and 4.0 (2H, t, J=6 Hz, -$C\underline{H}_2OAc$).

Grignard reaction on IV using methyl magnesium iodide, gave 1,6,7-trihydroxy-3,6,7-trimethyloctane (VI), in 80% yield as a thick glassy liquid. It showd IR band at: 3425 (-OH); PMR signals at: 0.9 (3H, d, J=6 Hz, C_3-CH_3), 1.21 (9H, s, hydroxy-isopropyl methyls and C_6-CH_3) and 3.53 (2H, t, J=6 Hz, $C\underline{H}_2OH$).

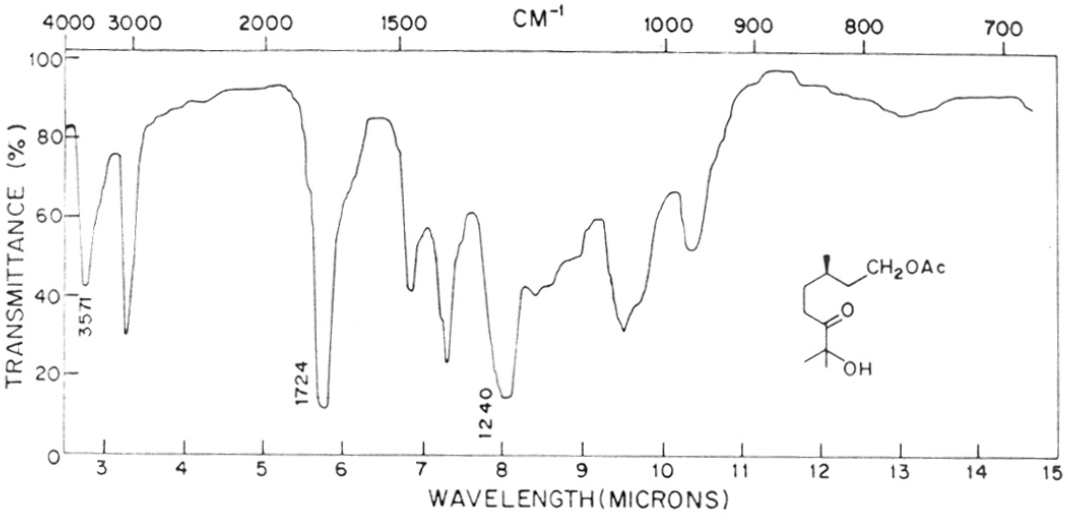


FIG. 1. 7-HYDROXY-3,7-DIMETHYL-6-OXO-1-OCTANOL ACETATE, IV

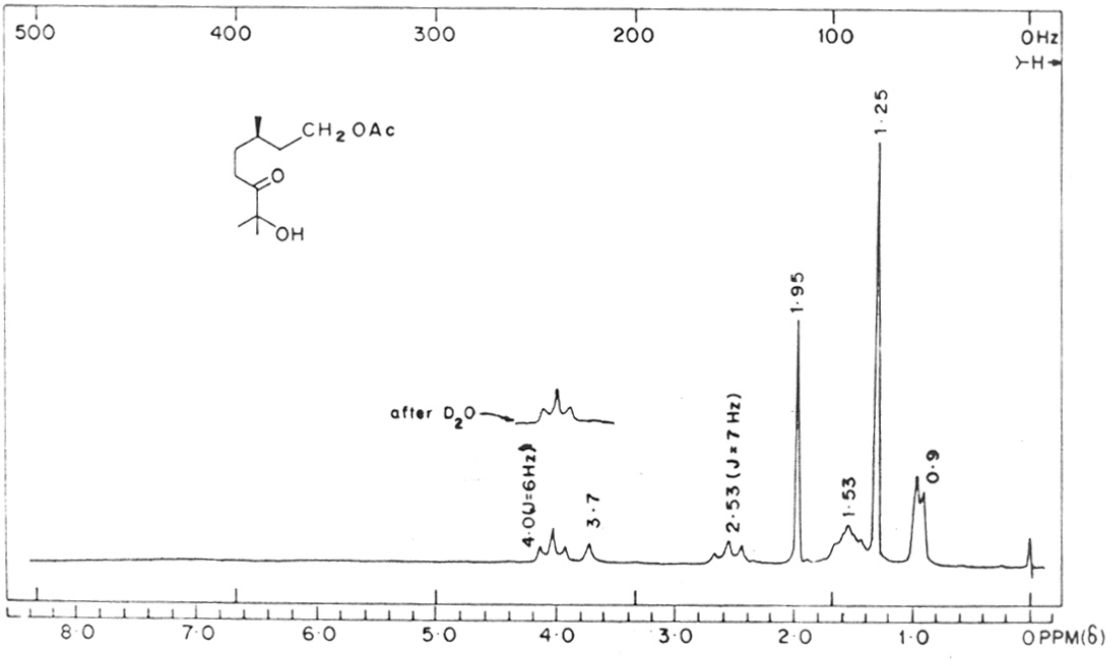
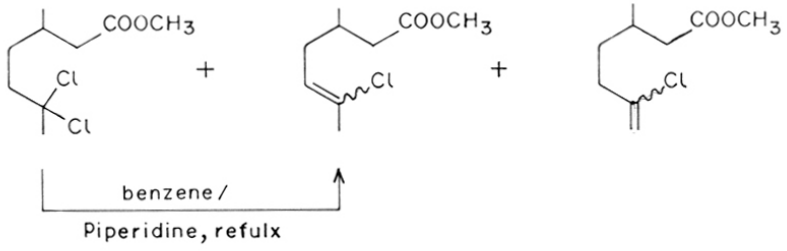


FIG. 2. 7-HYDROXY-3,7-DIMETHYL-6-OXO-1-OCTANOL ACETATE, IV

Sodium metaperiodate oxidation of triol (VI), in acetone-water mixture afforded keto-alcohol (VII), $C_8H_{16}O_2$, as a liquid in 89% yield, Purified by distillation, b.p.125°/8 mm, $[\alpha]_D^{27}$ + 1.5° (c, 7.38). It showed IR bands at: 3570 (-OH), 1720 (C=O) and PMR signals at: 0.9 (3H, d, J=5 Hz, C_3-CH_3), 2.06 (3H, s, $COC\underline{H}_3$), 2.38 (2H, t, J=7 Hz, $C\underline{H}_2CO$) and 3.51 (2H, t, J=6 Hz, $C\underline{H}_2OH$).

The keto alcohol (VII) was oxidised by Jones chromic acid reagent at 0°, to afford an acid (70%), which was converted into its methyl ester by an ethereal solution of diazomethane and purified by distillation to afford ester (VIII), $C_9H_{16}O_3$; b.p.135°/6 mm; $[\alpha]_D^{27}$ + 2.5° (c, 1.7). It showed IR bands at: 1748, 1724 (ester and ketone C=O respectively); PMR (Fig. 3) signals at: 0.9 (3H, d, J=6 Hz, C_3-CH_3), 2.05 (3H, s, $COC\underline{H}_3$), 2.26 (4H, m, CH_2 adjacent to $COOCH_3$ and $COCH_3$) and 3.56 (3H, s, $COOC\underline{H}_3$).

Action of phosphorous pentachloride[5] on ketoester (VIII), afforded a mixture of three isomeric products IX, X, XI,



X IX XI

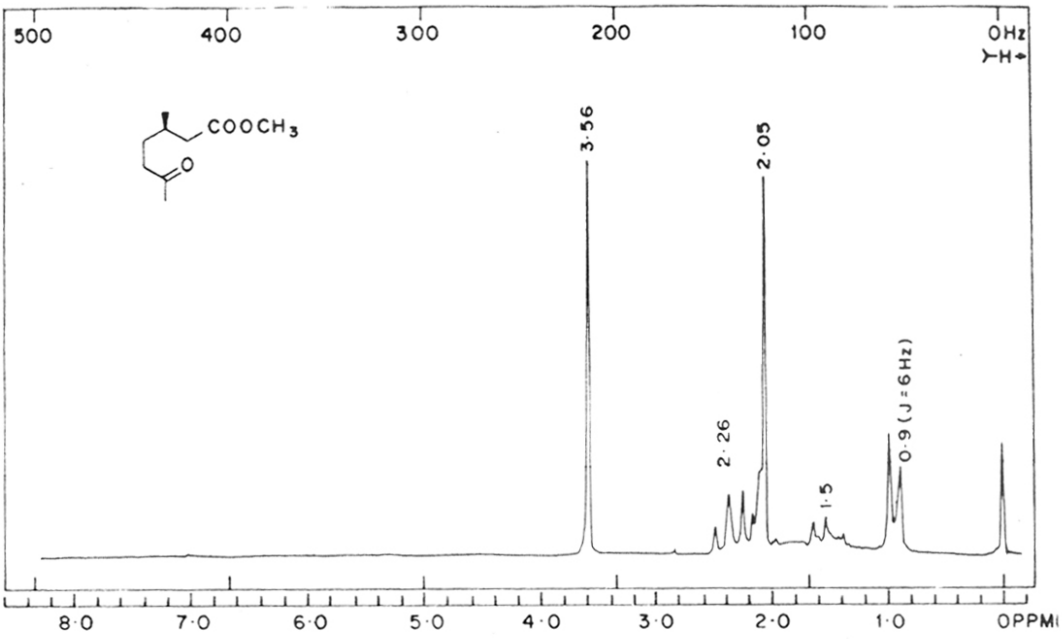


FIG. 3. METHYL 3-METHYL-6-OXOHEPTANOATE, VIII

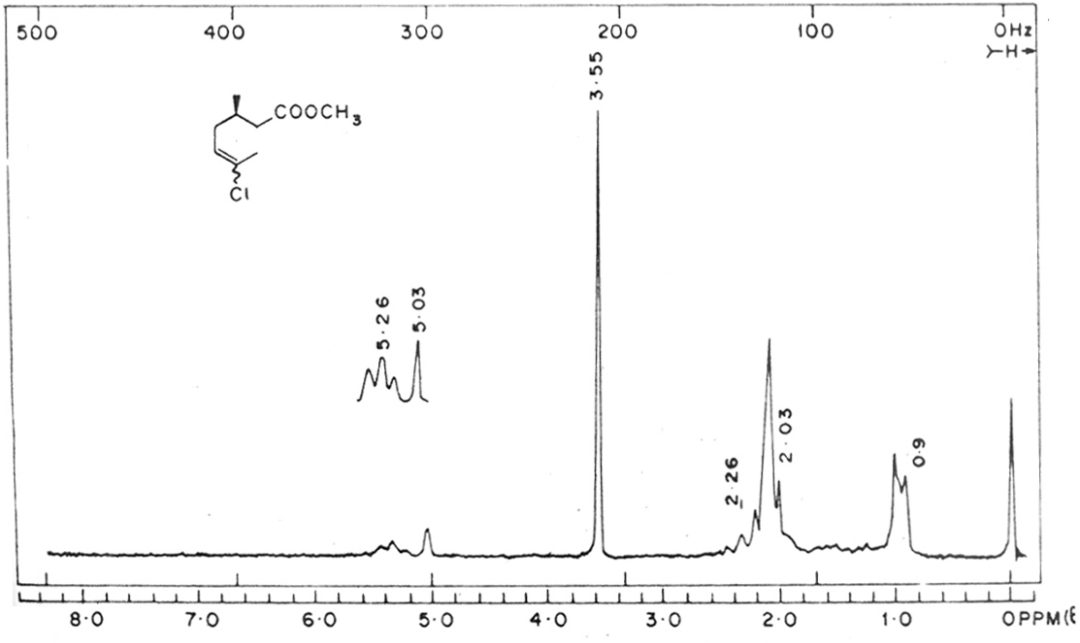


FIG. 4. METHYL 6-CHLORO-3-METHYLHEPT-5-ENOATE, IX, XI (10%)

analysed by GLC: column temperature 110° on a mixed column OV-210 (1.5%) and OV-17 (1.5%), using hydrogen as carrier gas, flow rate 30 ml/min., retention time, 5.51 min., 48%, 6.54 min. 11%, 13.59 min. 39%. The impurity of gem-dichloro compound (X) showing retention time of 13.59 min. was successfully converted into vinylchloro compound (IX) by refluxing the above mixture with piperidine in benzene, followed by chromatographic purification and distillation of the resulting product. The GLC analysis of the distilled product showed the presence of only two compounds showing the retention times at: 5.39 min., 89.9%; 6.32 min. , 9.8%; column, OV-210 (1.5%) + OV-17 (1.5%); column temperature, 120°; hydrogen flow rate, 30 ml/min. The impurity of XI (9.8%) could not, however, be eliminated even by elaborate column chromatography over silicic acid, impregnated with silver nitrate (15%) or by attempted isomerisation with para-toluene-sulphonic acid in refluxing benzene. It showed IR band at: 1736 (ester C=0) and PMR (Fig. 4) signals at: 0.9 (3H, d, J=6 Hz, C_3-CH_3), 2.03 (3H, s, C_6-CH_3), 2.26 (4H, m, C_2 and C_4 methylene protons), 3.55 (3H, s, ester methyl), 5.03 (s, C $=CH_2$ arising from impurity of XI) and 5.26 (1H, br t, olefinic proton). The ester mixture IX, XI (90:10) was transesterified[6] with 3-phenoxybenzyl alcohol using butyl titanate as a catalyst in refluxing xylene to give the ester (XII, XIII-10%), $C_{21}H_{23}O_3Cl$. It showd IR bands at: 1735 (ester C=0), 1585, 690 (aromatic) and PMR (Fig. 5) signals at: 0.91 (3H, d, J=6 Hz, C_3-methyl), 1.9 to 2.3 (4H, m, C_2 and C_4

methylene protons), 4.91 (2H, s, benzylic CH_2), 5.0 (s, C $=C\underline{H}_2$, arising from minor impurity of XIII), 5.23 (1H, br t, J=6 Hz, olefinic proton) and 6.6-7.16 (9H, m, aromatic H); MS: m/z, 358 (M^+), 360 (^{37}Cl).

The ketoester (VIII) was converted to cyanohydrin ester(XIV) by reacting it with potasium cyanide in acetic acid and ethanol as per the known procedure[7]. Cyanohydrin ester was obtained as an equilibrium mixture with starting ketoester. The mixture as such, on dehydration ($POCl_3$/pyridine)followed by chromatographic purification, afforded in the earlier fractions (pet.ether-benzene, 7:3), methyl 6-cyano-3-methylhept-5-enoate (XV), as the major compound along with a minor (8%) impurity of double bond isomer XVI. The latter, however, could not be eliminated even by elaborate column chromatography over silicic acid, impregnated with 15% $AgNO_3$. The unsaturated cyanoester was assigned $\underline{Z}$ configuration tentatively. The assignment of $\underline{Z}$ configuration to the compound XV is based on the observed value of chemical shift (6.03 δ) which is in close agreement with the value, calculated for $\underline{Z}$ isomer (6.04 δ)[8]. It showed IR bands at: 2203 (-CN), 1735 (ester C=O); PMR (90 MHz, $CDCl_3$) signals at: 0.96 (3H, d, J=6 Hz, C_3-CH_3), 1.93 (3H, br s, C_6-CH_3), 2.16 (4H, m, CH_2 adjacent to ester group and allylic CH_2), 3.6 (3H, s, ester methyl) and 6.03 (1H, t, J=8 Hz, olefinic proton); in addition two low intensity singlets at 5.63 δ and 5.7 δ were also observed due to impurity of double bond isomer XVI. MS: m/z, 181 (M^+). The high

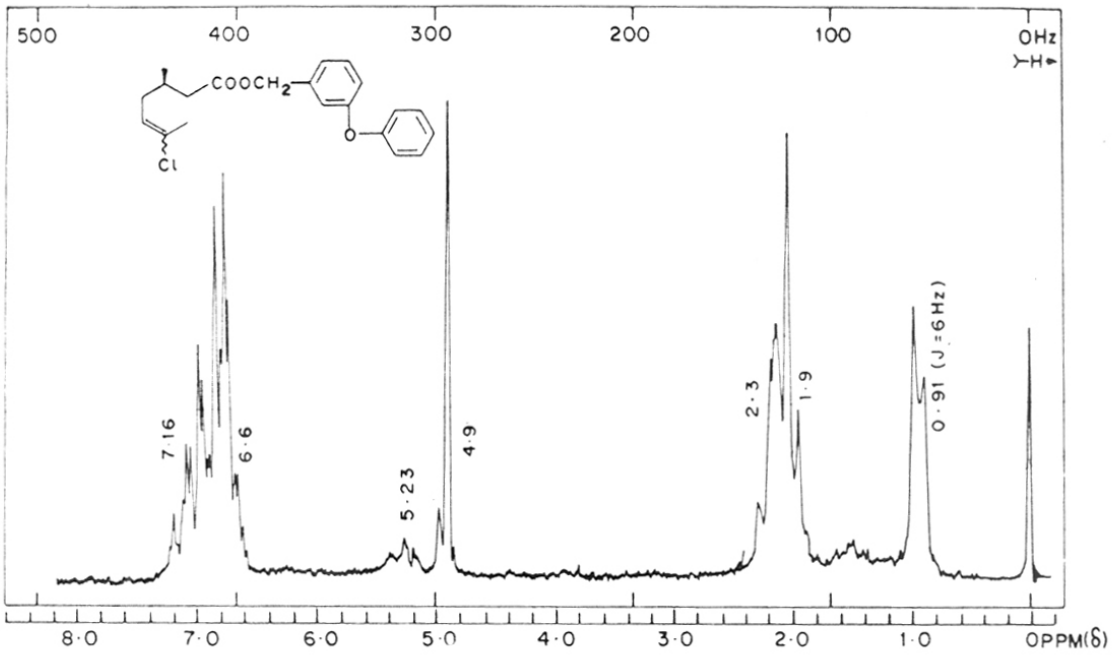


FIG. 5. 3-PHENOXYBENZYL 6-CHLORO-3-METHYLHEPT-5-ENOATE, XII, XIII (10%)

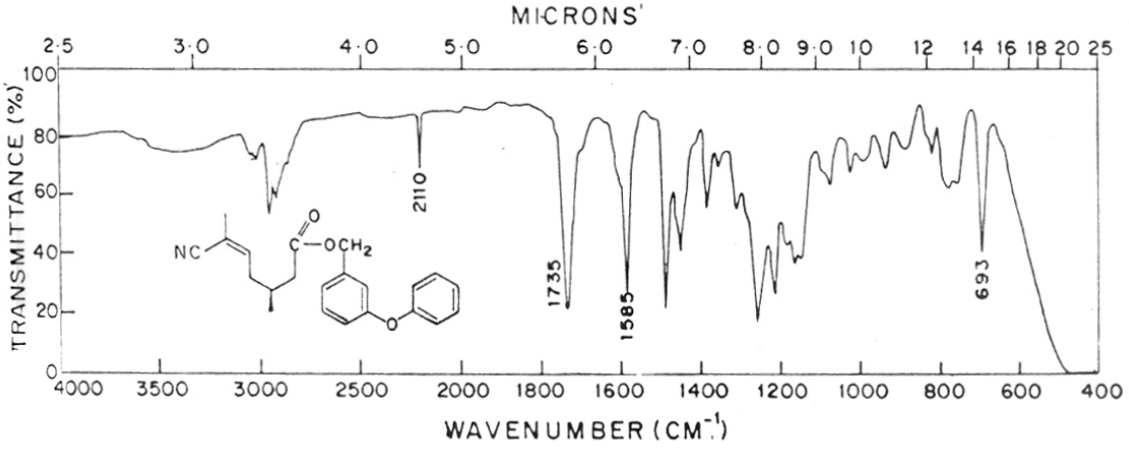


FIG. 6. 3-PHENOXYBENZYL 6-CYANO-3-METHYLHEPT-5-ENOATE, XVII, XVIII-(8%)

value (5.7 δ) is assigned to the proton cis to cyano group (anisotropic deshielding). GLC: Z isomer, 8.81 min., 92%, 9.44 min. 8%; column, OV-101 (5%), column temperature, 150°; hydrogen flow fate, 30 ml/min; $[\alpha]_D^{27}$ + 4.2° (c, 1.9).

Transesterification of XV with 3-phenoxybenzyl alcohol gave the 3-phenoxybenzyl 6-cyano-3-methylhept-5-enoate (XVII), along with minor impurity of double bond isomer XVIII, as a liquid; $C_{22}H_{23}O_3N$; IR (Fig. 6) bands at: 2110 (-C≡N), 1735(ester C=O), 1585, 693 (aromatic) and PMR (Fig. 7) signals at: 0.97 (3H, d, J=6 Hz, C_3-CH_3), 1.93 (3H, s, methyl on double bond), 2.23 (4H, br s, allylic CH_2 and CH_2 adjacent to ester C=O), 5.93 (2H, s, benzylic $C\underline{H}_2$), 6.08 (1H, t, J=8 Hz, olefinic proton) and 6.88-7.52 (9H, m, aromatic H); in addition two low intensity singlets at 5.68 δ and 5.77 δ were also observed due to double bond isomer impurity of XVIII.

Grignard reaction on ketoalcohol(VII), using methyl magnesium iodide gave diol, 1,6-dihydroxy-3,6-dimethylheptane (XIX). Alternatively the diol (XIX), $C_9H_{20}O_2$, can also be obtained by Grignard reaction on acetate ester (V), with excess of methyl magnesium iodide. It showed IR band at: 3465 (-OH) and PMR signals at: 0.9 (3H, d, J=6 Hz, C_3-CH_3), 1.16 (6H, s, methyls of hydroxy isopropyl group), 3.5 (2H, t, J=6 Hz, $C\underline{H}_2OH$) and 3.83 (1H, br s, exchangable with D_2O, -O$\underline{H}$).

Attempts to prepare hydroxy acid (XX, R=H), by oxidation of alcohol (XIX), with Jones chromic acid reagent, gave undesired

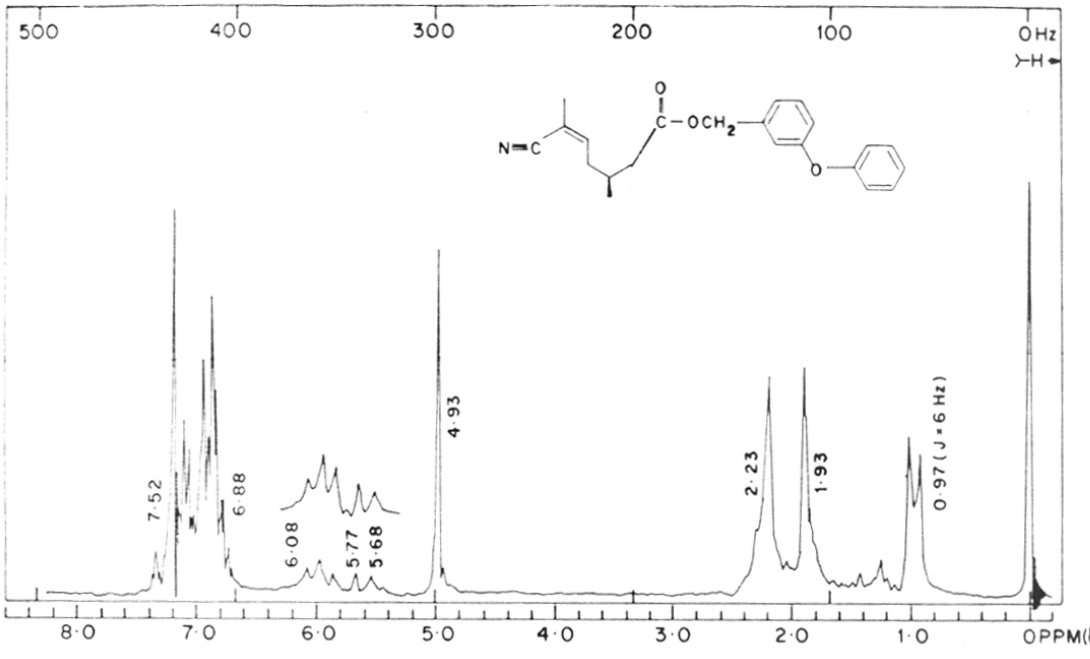


FIG. 7. 3-PHENOXYBENZYL 6-CYANO-3-METHYLHEPT-5-ENOATE, XVII, XVIII (8%)

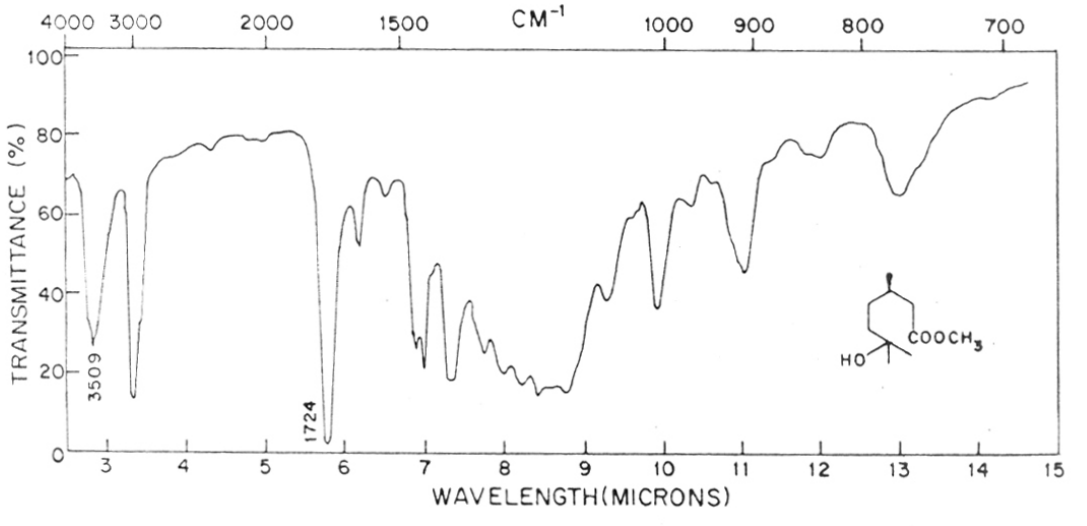


FIG. 8. METHYL 6-HYDROXY-3,6-DIMETHYLHEPTANOATE, XX

products, which however, were not characterised. The difficulty was overcome by oxidising diol (XIX), by $KMnO_4$ under buffer conditions to give in the acid part hydroxy acid, which was converted into methyl ester (XX), by an ethereal solution of diazomethane. It showed IR (Fig. 8) bands at: 3509 (-OH), 1735 (ester C=O) and PMR signals at:0.9 (3H, d, J=6 Hz, C_3-CH_3), 1.1 (6H, s, methyls of hydroxyisopropyl), 2.1 (2H, m, $C\underline{H}_2$ adjacent to ester) and 3.53 (3H, s, ester methyl).

Dehydration of XX by PTS in refluxing benzene (12 hr), followed by chromatographic purification and distillation of the resulting product, afforded methyl 3,6-dimethylhept-5-enoate (XXI), $C_{10}H_{18}O_2$, as the sole product; b.p.120°/4 mm; $[\alpha]_D^{27}$ + 2.2°(c, 3.4). It showed IR bands at: 1736 (ester C=O) and PMR (Fig. 9) signals at: 0.9 (3H, br d, C_3-CH_3), 1.56, 1.67 (each 3H, s, vinyl methyls), 2.03 (4H, m, CH_2 adjacent to ester group and allylic $C\underline{H}_2$), 3.56 (3H, s, ester methyl) and 5.06 (1H, t, J=6 Hz, olefinic proton); MS: m/z, 170 (M^+).

Ester (XXI) was transesterified with 3-phenoxybenzyl alcohol using butyl titanate as a catalyst, to give 3-phenoxybenzyl ester (XXII), as a thick liquid. It showed IR bands at: 1740 (C=O), 1590, 690 (aromatic) and PMR (Fig. 10) signals at: 0.9 (3H, br d, C_3-CH_3), 1.53, 1.63 (each 3H, s, vinyl methyls), 2.1 (2H, d, J=4 Hz, CH_2 adjacent to ester), 4.93 (2H, s, benzylic $C\underline{H}_2$), 5.06 (1H, t, J=6 Hz, olefinic proton) and 6.63-7.3 (9H, m, aromatic H).

The synthetic approach outlined above for the preparation of XII, XVII, XXII, from the ketones IV, VII can be extended to the

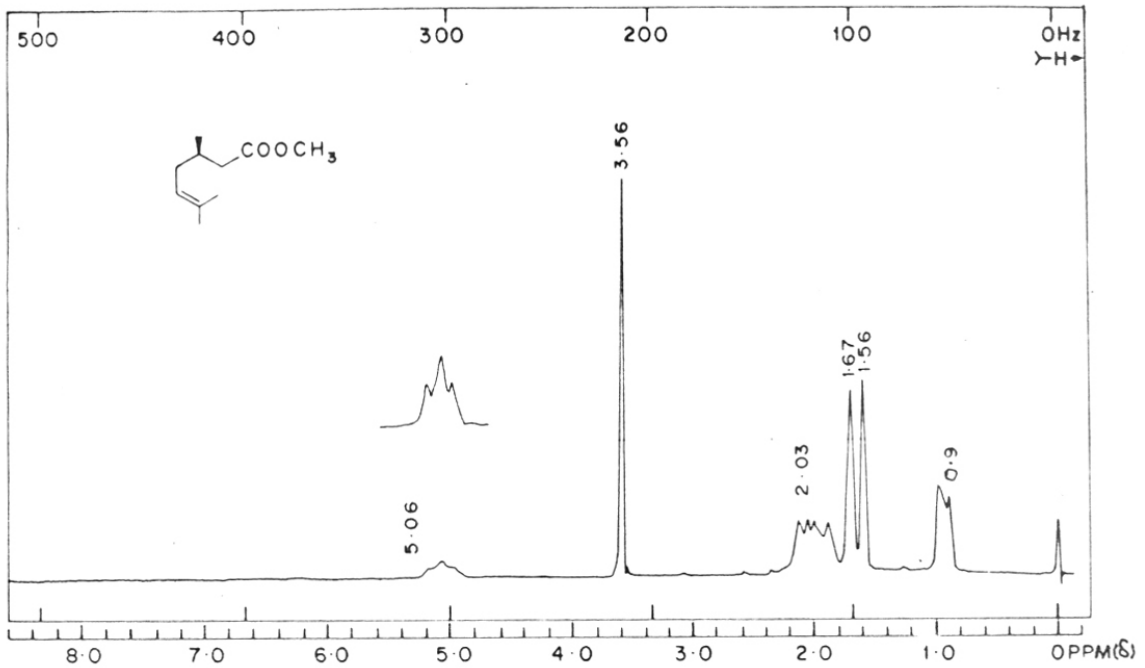


FIG. 9. METHYL 3,6-DIMETHYLHEPT-5-ENOATE, XXI

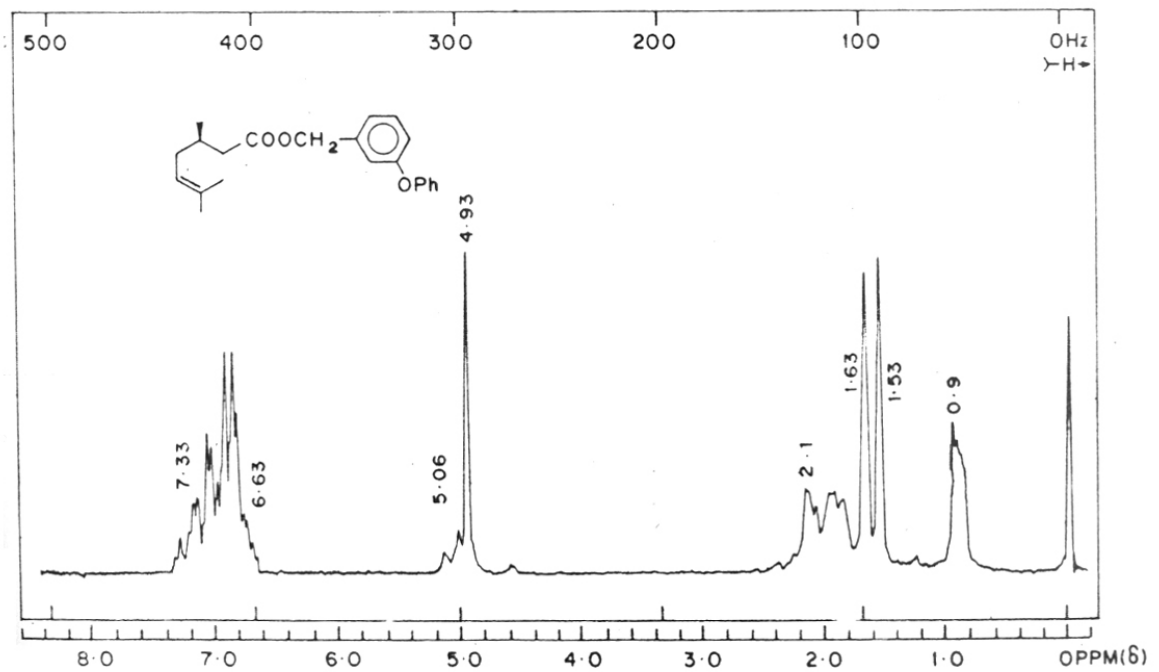


FIG. 10. 3-PHENOXYBENZYL 3,6-DIMETHYLHEPT-5-ENOATE, XXII

preparation of a large number of anlogues, by varying Grignard reagent or its equivalents on ketones. Thus, instead of methyl, different analogues with aryl and alkyl can be prepared.

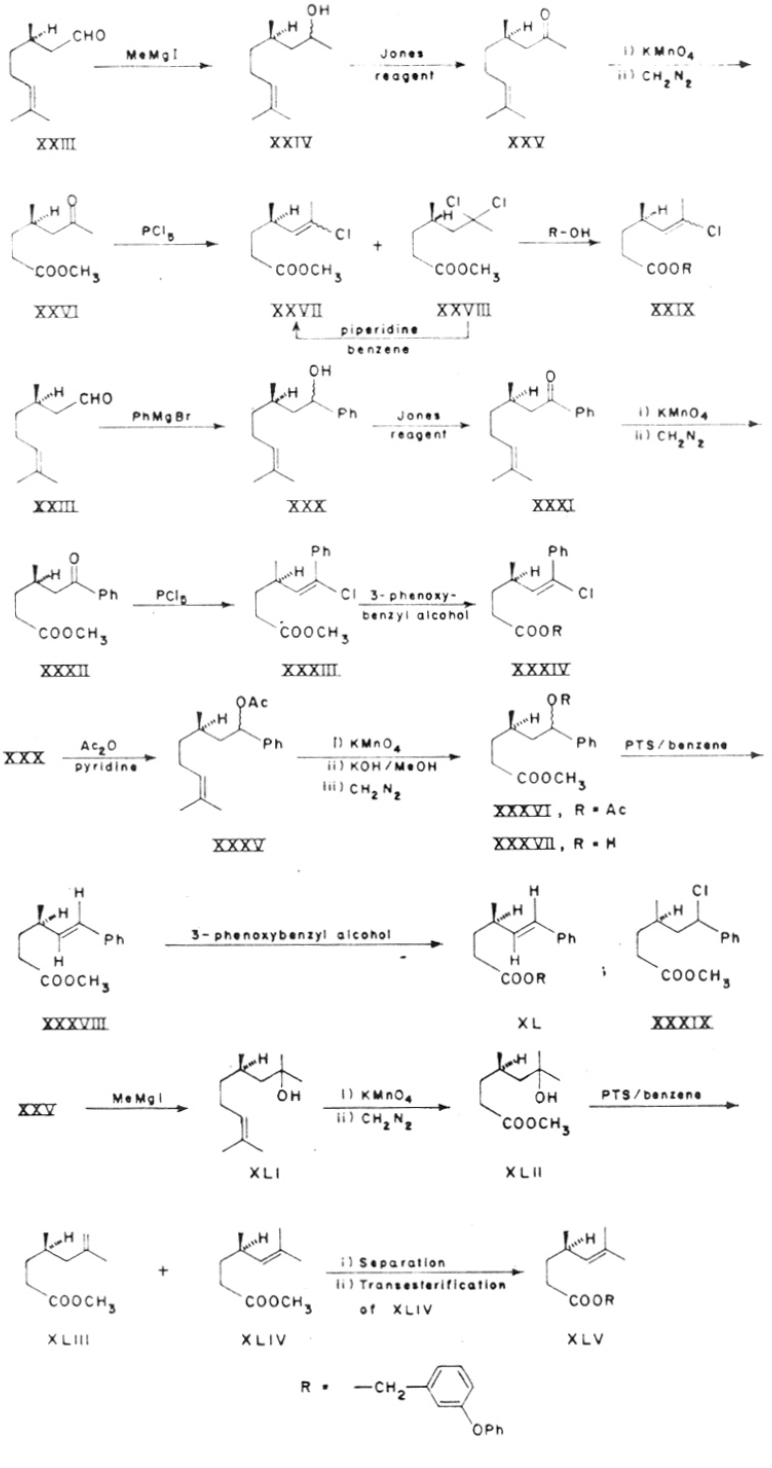
The 3-phenoxybenzyl esters (XII, XVII and XXII) showed larvicidal activity against 4th instar mosquitoe larvae (Aedes aegypti). Compounds showed: XII, 90%; XVII, 70-80%; XXII, 50-60% mortality at 100 ppm. However, these compounds were inactive in insecticidal tests against adult mosquitos (Aedes aegypti) and house-flies (musca domestica).

In an another sesquence of reactions, 1,3-secopyrethroids were prepared from (+) citronellal. The compounds thus synthesised possess a methyl group on γ carbon atom, instead of the gem-dimethyl function on β-carbon atom with respect to the ester group. (Scheme II).

Grignard reaction on citronellal (XXIII), using methyl magnesium iodide, afforded a liquid diastereomeric mixture of alcohols (XXIV), in 80% yield. It showed IR band at: 3448 (-OH) and PMR signals at: 0.96 (3H, d, J=6 Hz, C_4 methyl), 1.18 (3H, d, J=6 Hz, -CHOHC$\underline{H}_3$), 1.65, 1.8 (each 3H, s, vinyl methyls), 3.16 (1H, br s, exchangable with D_2O, -OH proton), 3.85 (1H, m, C_2 proton), and 5.16 (1H, t, J=7 Hz, olefinic H).

Jones chromic acid oxidation of XXIV, gave the liquid ketone (XXV), $C_{11}H_{20}O$, b.p.85^{o}(vapour)/2 mm. It showed IR (Fig. 11) band at 1715 (C=O) and PMR signals at: 0.93 (3H, d, J=6 Hz, C_4-CH_3), 1.63, 1.76 (each 3H, s, vinyl methyls), 2.06 (3H, s,

SCHEME II


CHO
MeMgI
OH
Jones reagent
O
i) KMnO4
ii) CH2N2
XXIII
XXIV
XXV
COOCH3
PCl5
Cl
+
R-OH
COOR
XXVI
XXVII
XXVIII
XXIX
piperidine
benzene
PhMgBr
Ph
XXX
XXXI
XXXII
XXXIII
XXXIV
3-phenoxy-benzyl alcohol
Ac2O
pyridine
OAc
i) KMnO4
ii) KOH/MeOH
iii) CH2N2
OR
PTS/benzene
XXXV
XXXVI, R = Ac
XXXVII, R = H
3-phenoxybenzyl alcohol
XXXVIII
XL
XXXIX
XXV
MeMgI
XLI
XLII
i) Separation
ii) Transesterification of XLIV
XLIII
XLIV
XLV
R = —CH2
OPh

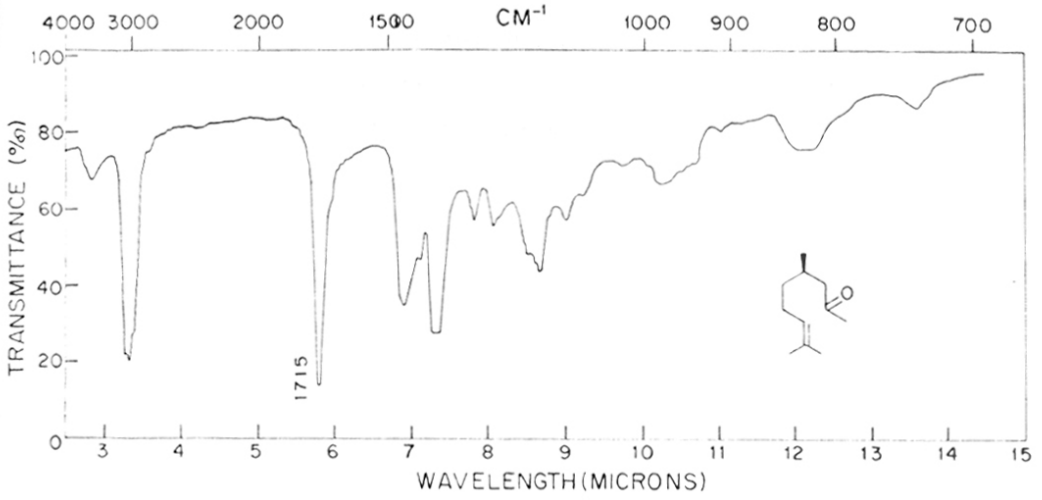


FIG. 11 4,8-DIMETHYL-7-NONENE-2-ONE, XXV

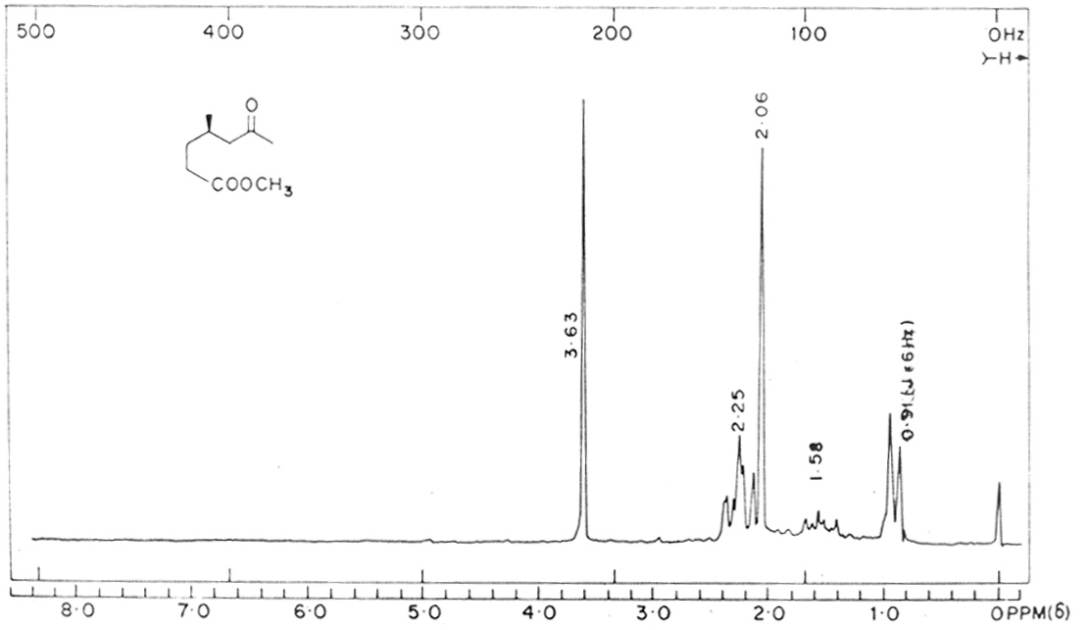


FIG. 12 METHYL 4-METHYL-6-OXOHEPTANOATE, XXVI

$COC\underline{H}_3$), 2.23 (2H, m, CH_2 adjacent to C=0) and 5.05 (1H, t, J=7 Hz, vinylic proton).

$KMnO_4$ oxidation of XXV, gave in acid fraction, a keto acid, which was converted into its methyl ester by diazomethane and purified by distillation to give the liquid ester (XXVI, R=CH_3). Alternatively keto acid (XXVI, R=H), could also be obtained directly from alcohol (XXIV), by Jones chromic acid oxidation for prolonged period (12-16 hr) and converted to its methyl ester (diazomethane). in 64% yield; b.p. 95°(vapour)/2 mm; $[\alpha]_D^{27}$ + 6.4° (c, 2.8). It showed IR bands at: 1740, 1718 (C=0 of ester and ketone respectively) and PMR (Fig.12) signals at: 0.9 (3H, d, J=6 Hz, C_4 methyl), 2.06 (3H, s, $COC\underline{H}_3$), 2.25 (4H, m, methylenes at C_2 and C_5) and 3.63 (3H, s, ester methyl).

Phosphorous pentachloride reaction on keto ester (XXVI) in methylene chloride, afforded a mixture of two compounds XXVII and XXVIII. The gemdichloro (XXVIII) analogue was converted into the vinylchloro compound (XXVII), by refluxing with piperidine (1 equivalent) in benzene, followed by chromatographic purification over silicic acid and distillation, to give vinylchloro ester (XXVII) as a mixture of $\underline{E}$ and $\underline{Z}$ isomers; b.p.115°/2 mm. It showed IR band at: 1739 (ester C=0) and PMR signals at: 0.97, 1.1 (3H, d each, J=6 Hz each, C_4 methyls of $\underline{E}$ and $\underline{Z}$ isomers), 2.11, 2.2 (3H, s each, vinyl methyls of geometric isomers), 2.34 (3H, m, CH_2 at C_2 and methine proton), 3.7 (3H, s, ester methyl), 5.2 and 5.41 (1H, d each, J=8 Hz, vinylic H of $\underline{E}$ and $\underline{Z}$ isomers).

Transesterification of XXVII with 3-phenoxybenzyl alcohol, catalysed by butyl titanate, gave 3-phenoxybenzyl 4(R)-methyl-6-chlorohept-5-enoate (XXIX), as a thick liquid, $C_{21}H_{23}O_3Cl$, $[\alpha]_D^{26}$ + 1.5° (c, 1.2); MS:m/z, 358(M^+),360 (^{37}Cl). It showed IR bands at: 1739 (ester C=0), 1587, 718 (aromatic) and PMR (Fig.13) signals at: 0.93, 1.06 (3H, each d, J=5 Hz, C_4 methyl), 2.0, 2.08 (3H, s, vinylmethyl of E and Z isomers), 5.03 (2H, s, benzylic CH_2), 5.12, 5.2 (1H, each d, J=8 Hz, vinylic proton) and 6.81-7.28 (9H, m, aromatic H).

When citronellal (XXIII), was reacted with phenylmagnesium bromide, a liquid diastereomeric mixture of alcohols, $C_{16}H_{24}O$, (XXX), was obtained. It showed IR bands at: 3509 (-OH), 1585, 701 (aromatic) and PMR signals at: 0.9 (3H, d, J=6 Hz, C_3-methyl), 1.63, 1.73 (each 3H, s each, vinyl methyls), 4.61 (1H, dd, J_1=6 Hz, J_2=10 Hz, benzylic CH_2), 5.06 (1H, t, J=7 Hz, olefinic proton) and 7.2 (5H, s, aromatic H).

Alcohol (XXX) was oxidised with Jones chromic acid reagent, to afford after work up the liquid ketone (XXXI). It showed IR bands at: 1695 (C=0), 1600, 1590, 698 (aromatic) and PMR (Fig. 14) signals at: 1.0 (3H, d, J=6 Hz, C_2 methyl), 1.6, 1.73 (each 3H, s each, vinyl methyl), 2.73, 2.83 (2H, d each, J=4 Hz, CH_2 adjacent to C=0), 5.08 (1H, t, J=6 Hz, olefinic proton) and 7.41-7.9 (5H, m, aromatic H).

Oxidation of (XXXI), either by $KMnO_4$ or by Jones chromic acid reagent for prolonged period, afforded the keto acid in the

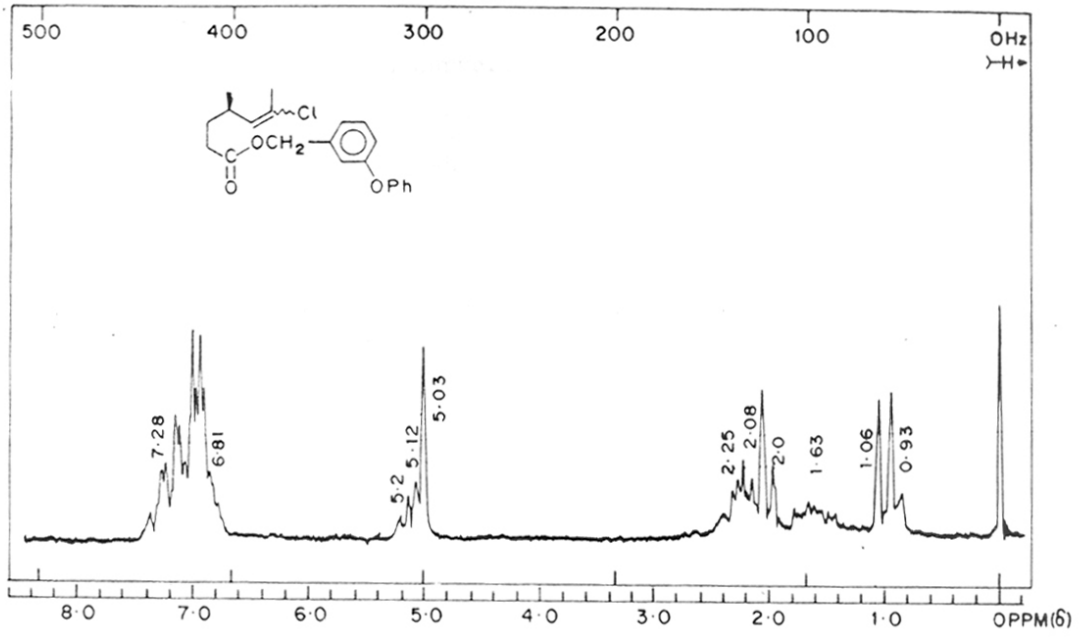


FIG. 13. 3-PHENOXYBENZYL 4-METHYL-6-CHLOROHEPT-5-ENOATE, XXIX

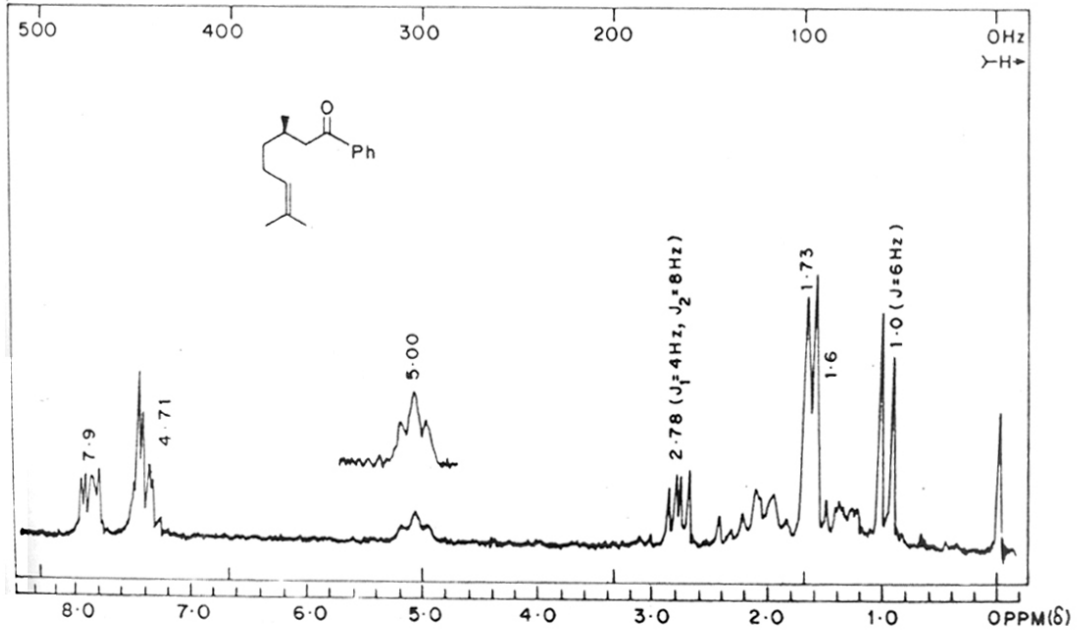


FIG. 14. 1-BENZOYL-2,6-DIMETHYLHEPT-5-ENE, XXXI

acid portion, which was converted into its methyl ester by diazomethane, to give keto ester (XXXII), $C_{14}H_{18}O_3$, b.p.180°/2 mm, $[\alpha]_D^{27}$ -15° (c, 1.7). It showed IR (Fig. 15) bands at: 1738 (ester C=O), 1695 (keto C=O), 1587, 714 (aromatic) and PMR signals at: 0.96 (3H, d, J=6 Hz, C_4 methyl), 2.28 (2H, t, J=7 Hz, CH_2 adjacent to ester group), 2.76 (1H, dd, J_1=3.5 Hz, J_2=7 Hz, $C\underline{H}_2$ adjacent to -COPh), 3.56 (3H, s, ester methyl) and 7.3-7.76 (5H, m, aromatic H).

Phosphorous pentachloride reaction on XXXII, gave E isomer of XXXIII. The assignment of E configuration to compound XXXIII, is based on the observed value of chemical shift of the olefinic proton (5.86 δ) which is in close agreement with that of calculated value (5.81 δ)[8]. It showed IR bands at: 1739 (ester C=O), 1600, 696 (aromatic) and PMR (Fig. 16) signals at: 1.13 (3H, d, J=6 Hz, C_4 methyl), 2.26 (2H, m, CH_2 adjacent to $COOCH_3$), 3.63 (3H, s, ester methyl), 5.86 (1H, d, J=9 Hz, olefinic proton of E isomer) and 7.16-7.63 (5H, m, aromatic H).

The ester (XXXIII) was converted into the corresponding 3-phenoxybenzyl ester (XXXIV); $C_{26}H_{25}O_3Cl$, by transesterification with 3-phenoxybenzyl alcohol. It showed IR bands at: 1739 (ester C=O), 1587, 689 (aromatic) and PMR signals at: 0.96 (3H, d, J=6 Hz, C_4-methyl), 2.35 (2H, m, CH_2 adjacent to ester group), 4.95 (2H, s, benzylic $C\underline{H}_2$), 5.85 (1H, d, J=9 Hz, olefinic proton of E isomer) and 7.0-7.25 (14H, m, aromatic H).

The alcohol (XXXI), was acetylated (Ac_2O/pyridine), to give quantitatively a diastereomeric mixture of acetates (XXXV); it

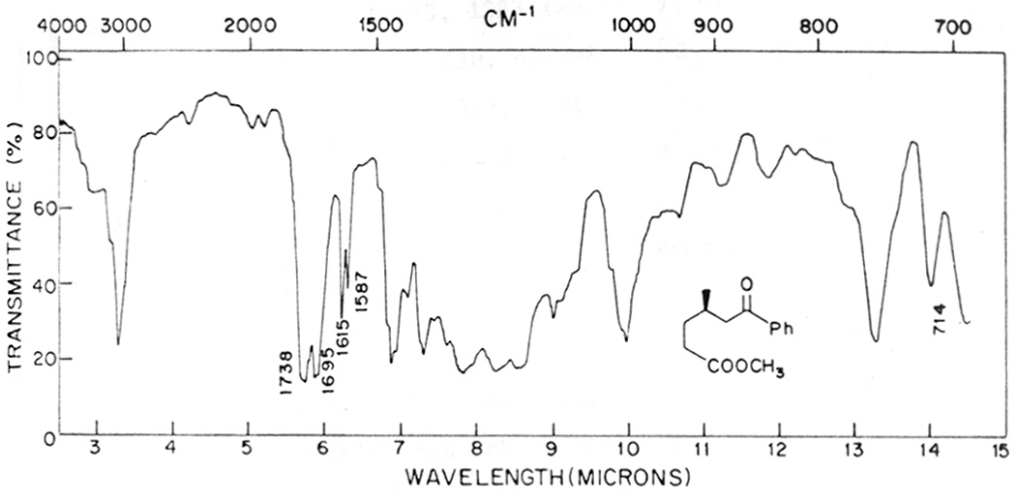


FIG. 15. METHYL 4-METHYL-5-BENZOYLVALERATE, XXXII

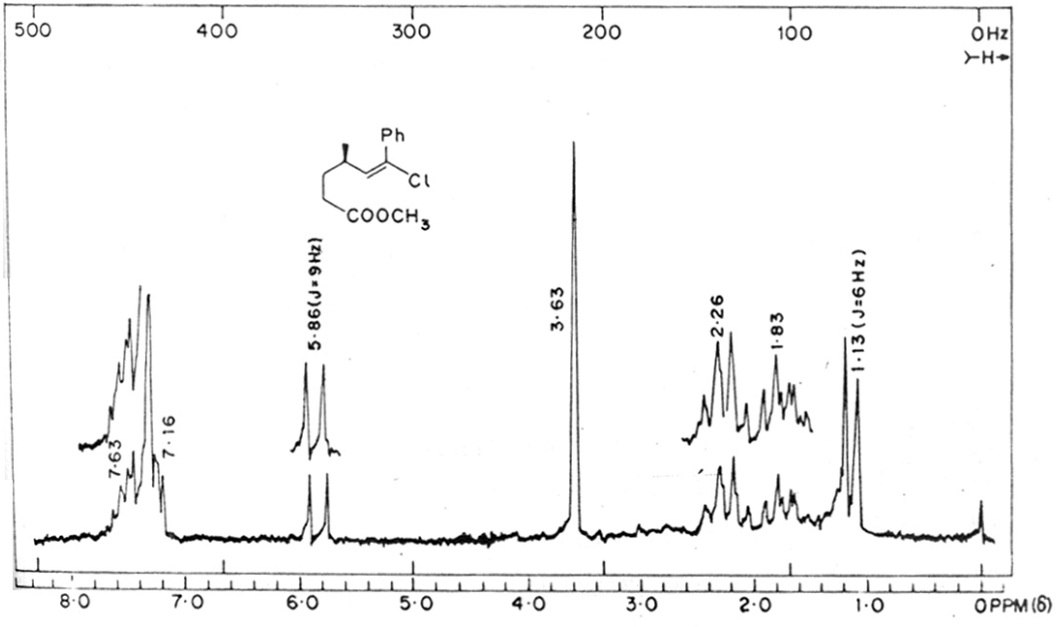


FIG. 16. METHYL 4-METHYL-6-CHLORO-6-PHENYLHEX-5-ENOATE, XXXIII

showed IR bands at: 1733, 1233 (acetate), 1600, 700 (aromatic) and PMR signals at: 0.9 (3H, d, J=6 Hz, C_3-methyl), 1.63, 1.73 (3H each, s, vinyl methyls), 1.96 (3H, s, $OCOC\underline{H}_3$), 4.93 (1H, dd, J_1=6 Hz, J_2=10 Hz, benzylic H), 5.06 (1H, t, J=7 Hz, olefinic H) and 7.2 (5H, s, aromatic H).

The acetate (XXXV), on oxidation with potasium permanganate in acetone, afforded in the acidic part acetoxyacid as the major product, characterised through its methyl ester (XXXVI). It showed IR bands at: 1730 (CO of ester and acetate), 1232 (acetate), 1600, 700 (aromatic) and PMR signals at: 1.03 (3H, d, J=6 Hz, C_4-methyl), 2.06 (3H, s, $COC\underline{H}_3$), 3.63 (3H, s, ester methyl), 5.8 (1H, dd, J_1=5 Hz, J_2=10 Hz, C_6 proton) and 7.3 (5H, s, aromatic H).

Hydrolysis of acetate acid (XXXVI) by methanolic potassium hydroxide (10%) afforded the corresponding hydroxy acid, as a liquid in 95% yield, converted into its methyl ester (XXXVII) by diazomethane, $C_{14}H_{20}O_3$; IR (Fig. 17) bands at: 3571(-OH)-1739 (ester C=O), 1595, 699 (aromatic) and PMR signals at: 0.9 (3H, d, J=6 Hz, C_4 methyl), 2.2 (2H, m, CH_2 adjacent to ester), 3.56 (3H, s, ester methyl), 4.61 (1H, br t, benzylic H) and 7.23 (5H, s, aromatic H).

Dehydration of XXXVII, using $POCl_3$/pyridine, gave after work up a TLC pure compound, which however, according to PMR was composed of unsaturated ester (XXXVIII), along with chloro-ester (XXXIX) in equal proportions. Attempts to separate the mixture of esters (XXXVIII and XXXIX), were unsuccessful as they

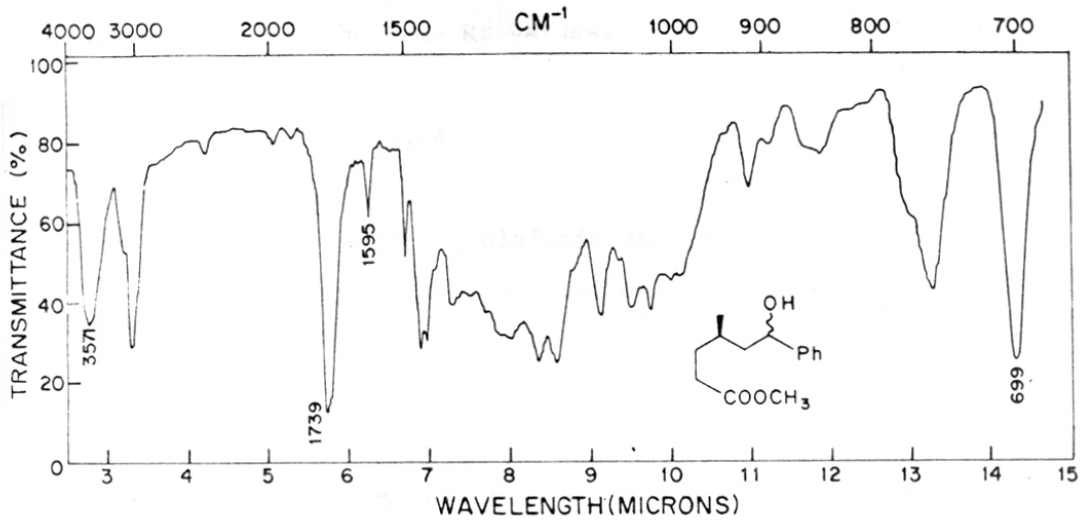


FIG. 17. METHYL 4-METHYL-6-HYDROXY-6-PHENYLHEXANOATE, XXXVII

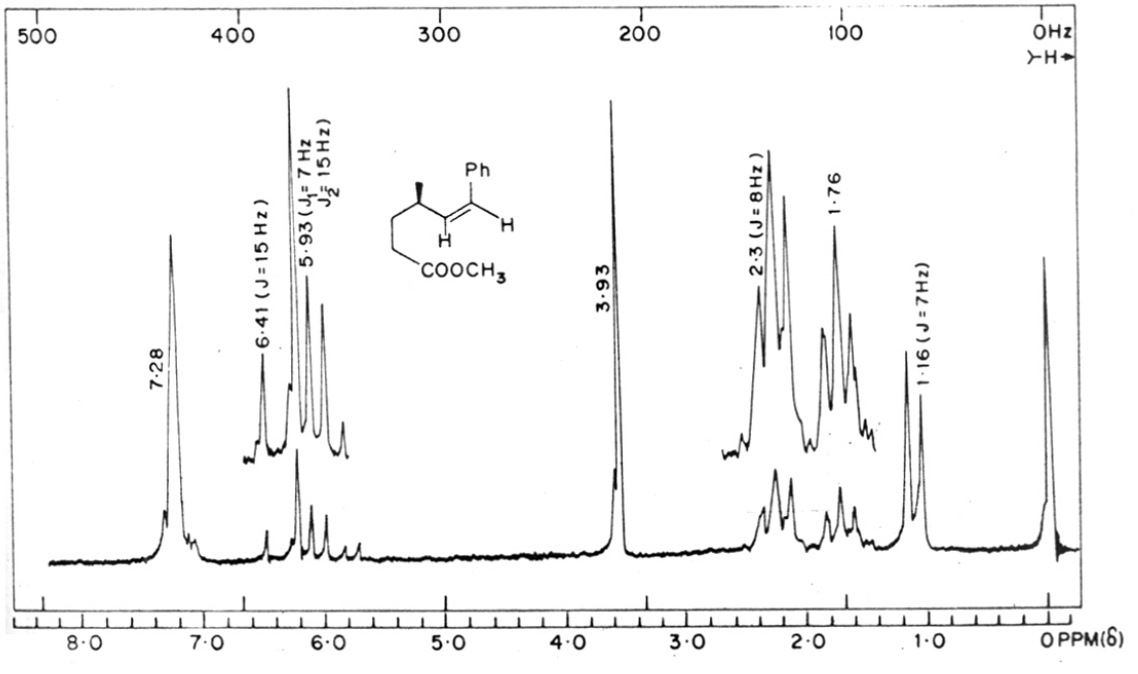


FIG. 18. METHYL 4-METHYL-6-PHENYLHEX-5-ENOATE, XXXVIII

possess nearly the same Rf values. PMR of mixture: 0.97 (3H, m, C_4-methyl), 2.23 (2H, m, $\underline{CH}_2$ adjacent to ester), 3.56, 3.63 (3H, s each, $COO\underline{CH}_3$), 4.9 (1H, dd, J_1=4 Hz, J_2=8 Hz, $\underline{CH}Cl$), 5.83, 6.08 (1H, dd, J_1=7 Hz, J_2=17 Hz, C_5 olefinic proton), 6.41 (1H, d, J=16 Hz, C_6 olefinic proton) and 7.23 (5H, s, aromatic H). This suggested that only one of the diastereomers is getting dehydrated whereas -OH of another isomer is undergoing neucleophilic substitution.

Dehydration of ester (XXXVII), by paratoluene sulphonic acid in refluxing benzene, resulted in the dehydration of only one of the diastereomersof XXXVII, to give the unsaturated ester (XXXVIII) along with another diastereomer of XXXVII (resistant to dehydration), separated by column chromatography over silicic acid. Earlier fractions eluted with pet.ether + benzene (1:1) gave the unsaturated ester (XXXVIII). It showed the following spectral properties; IR bands at: 1749 (ester C=0), 1608, 698 (aromatic), 965 (trans disubstituted double bond) and PMR (Fig. 18) signals at: 1.16 (3H, d, J=6 Hz, C_4-methyl), 2.3 (2H, t, J=8 Hz, CH_2 adjacent to $-COOCH_3$), 3.63 (3H, s, ester methyl), 5.93 (1H, dd, J_1=7 Hz, J_2=16 Hz, C_5 olefinic proton), 6.41 (1H, d, J=16 Hz, C_6-olefinic proton) and 7.28 (5H, s, aromatic H). In both the reactions, same dehydrated isomer is formed, as is evident from the coupling constant and the chemical shifts of the olefinic protons. The compound has been tentatively assigned the E configuration. The assignment is based on the value of chemical

shifts of C_6 proton (6.41 δ) and C_5-proton (5.93 δ) which are in close agreement with the calculated values for E isomer[8] (C_6-H, 6.37 ; C_5-H, 5.93) and also large coupling constant of 16 Hz (observed in case of trans olefines, in case of cis olefins J=8 to 12 Hz)[9]. In addition the IR spectrum of the ester showed a strong band at 960 cm^{-1}, characteristic of trans disubstituted double bond. The tail fraction eluted with chloroform gave the unreacted diastereomer, identified by spectral data.

Tranesterification of XXXVIII, with 3-phenoxybenzyl alcohol afforded 3-phenoxybenzyl 4(R) methyl-6-phenylhex-5-enoate (XL), as a liquid. It showed IR (Fig. 19) bands at: 1745 (ester C=0), 1595, 698 (aromatic), 965 (trans disubstituted double bond) and PMR signals at: 1.16 (3H, d, J=7 Hz, C_4-CH_3), 2.3 (2H, t, J=7 Hz, CH_2 adjacent to ester), 5.03 (2H, s, benzylic CH_2), 5.97, 5.93 (1H, dd each, J_1=7 Hz, J_2=16 Hz, olefinic proton at C_5), 6.34 (1H, d, J=16 Hz, C_6 olefinic H) and 7.05-7.23 (14H, m, aromatic H).

Grignard reaction on ketone (XXV), using methyl magnesium iodide furnished the unsaturated alcohol (XLI). It showed IR band at: 3504 (-OH) and PMR signals at: 1.0 (3H, d, J=6 Hz, C_4-CH_3), 1.08, 1.2 (3H each, s, methyls of hydroxyisopropyl), 1.56, 1.63 (3H each, s, vinyl methyls) and 5.03 (1H, m, olefinic H).

Oxidation of alcohol (XLI), with $KMnO_4$ in acetone gave hydroxy acid, converted into its methyl ester (XLII), by diazomethane, $C_{10}H_{20}O_3$. It showed IR bands at: 3636 (-OH),

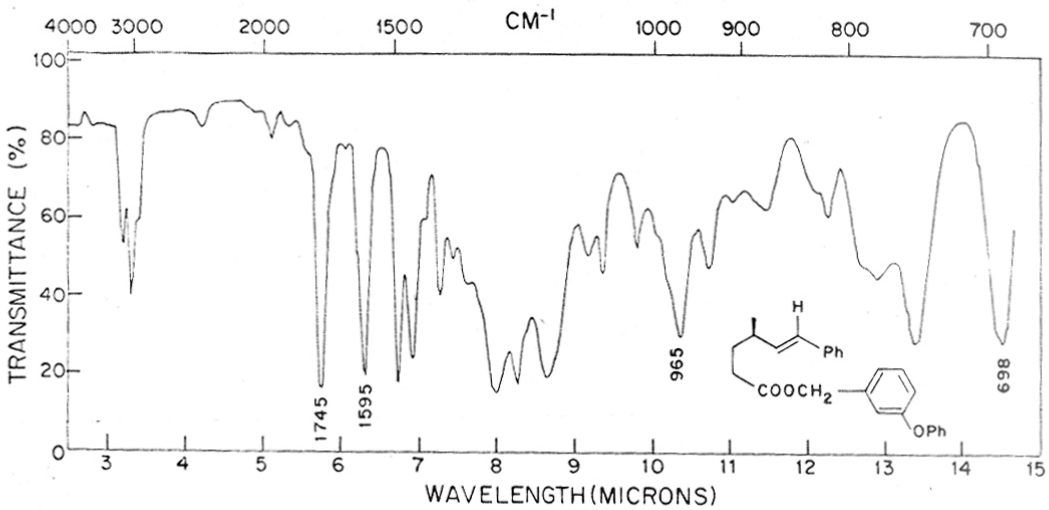


FIG. 19. 3-PHENOXYBENZYL 4-METHYL-6-PHENYLHEX-5-ENOATE, XL

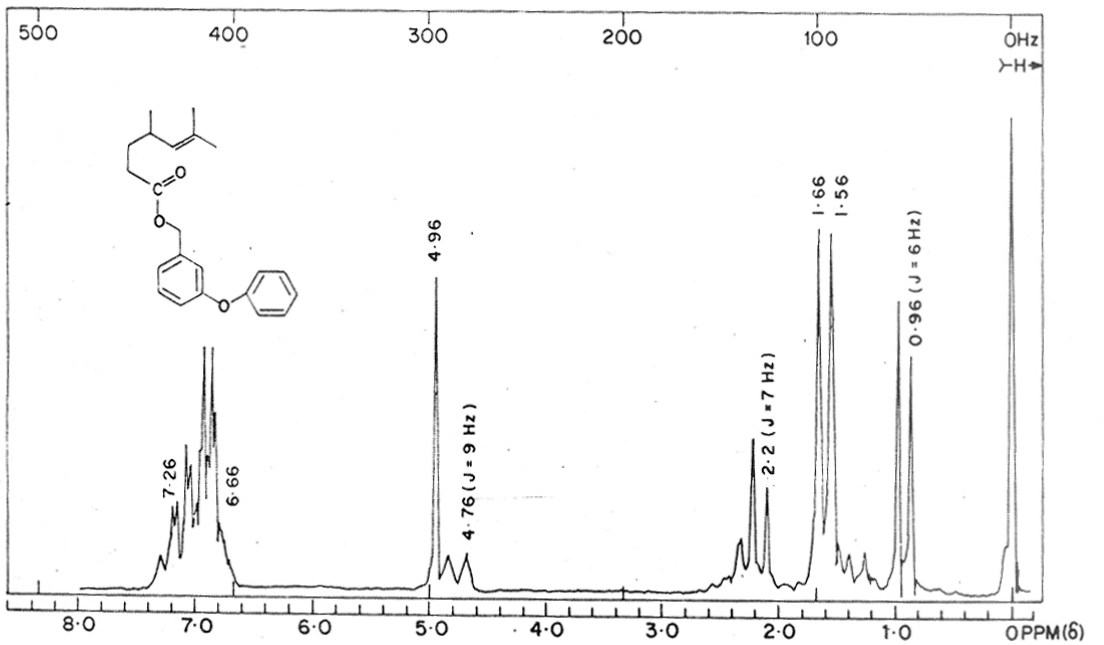


FIG. 20. 3-PHENOXYBENZYL 4,6-DIMETHYLHEPT-5-ENOATE, XLV

1735 (ester C=O) and PMR signals at: 1.0 (3H, d, J=6 Hz, C_4-CH_3), 1.23 (6H, s, methyls of hydroxyisopropyl), 2.26 (2H, m, CH_2 adjacent to $COOCH_3$) and 3.63 (3H, s, ester methyl).

Dehydration of XLII, by $POCl_3$/pyridine afforded a mixture of two unsaturated esters (XLIII and XLIV), separated by column chromatography over silicic acid, impregnated with 10% silver nitrate; compound XLIV showed IR band at: 1739 (ester C=O) and PMR signals at: 0.96 (3H, d, J=6 Hz, C_4-CH_3), 1.63, 1.76 (each 3H, s each, vinyl methyls), 2.15 (2H, t, J=7 Hz, CH_2 adjacent to ester), 3.63 (3H, s, ester methyl) and 4.83 (1H, d, J=9 Hz, olefinic H). The compound eluted in the latter fractions (benzene) was identified by spectral data as XLIII. It showed IR bands at: 1740 (ester C=O), 1640, 890 ($C=CH_2$) and PMR signals at: 0.88 (3H, d, J=6 Hz, C_4-methyl), 1.66 (3H, s, vinyl methyl), 2.23 (2H, t, J=6 Hz, CH_2 adjacent to $COOCH_3$), 3.63 (3H, s, ester methyl) and 4.63 (2H, s, $C=C\underline{H}_2$).

The ester (XLIV), was converted into 3-phenoxybenzyl ester (XLV), by transesterification with 3-phenoxybenzyl alcohol using butyl titanate as catalyst. It showed IR bands at: 1745 (ester C=O), 1595, 704 (aromatic) and PMR (Fig. 20) signals at: 0.96 (3H, d, J=6 Hz, C_4-methyl), 1.53, 1.66 (3H each, s each, vinyl methyls), 2.2 (2H, t, J=7 Hz, $C\underline{H}_2$ adjacent to ester), 4.76 (1H, d, J=9 Hz, olefinic H), 4.96 (2H, s, benzylic $C\underline{H}_2$) and 6.66-7.26 (9H, m, aromatic H).

Ester (XXIX) showed larvicidal activity against 4th instar mosquito (Aedes aegypti) larvae (80% mortality at 100 ppm) and ester (XLV) showed insecticidal activity against musca domestica (40% mortality at 100 ppm).

EXPERIMENTAL

7-Hydroxy-3,7-dimethyl-6-oxo-1-octanol acetate (IV):

To an ice-cooled and stirred solution of (+) citronellol acetate (III, R=Ac, 30 g, 0.144 mol), in acetone (200 ml), acetic acid (40 ml) and water (40 ml), was added powdered $KMnO_4$ (40 g, 0.25 mol) in small portions during 1 hr at 30°. Stirring was continued at 30° for 2 hr. The reaction mixture was treated simultaneously with sodium nitrite (18 g) and dilute sulphuric acid (1:8, 500 ml), to dissolve the manganese oxide, formed in the reaction. The clear yellow solution thus obtained was diluted with water (200 ml) and extracted with chloroform (300 ml x 2). The chloroform layer was washed with water and extracted with aqueous sodium carbonate (10%), to remove the acid formed in the reaction, washed with water, brine and dried. Removal of chloroform furnished a TLC pure liquid, identified as IV (24 g, 69%); $[\alpha]_D^{27}$ + 2.5° (c, 2.1).

Analysis:

Found: C, 62.4; H, 9.5; $C_{12}H_{22}O_4$

requires: C, 62.6; H, 9.6%.

IR bands at: 3571, 3030, 1742, 1724, 1471, 1370, 1242, 1053 and 966 cm^{-1}.

The carbonate layer was acidified with dilute hydrochloric acid and extracted with chloroform (100 ml x 3). The combined

organic layer was washed with water, brine, dried and evaporated to give the acid (V, 6 g, 21%), which was esterified with ethereal solution of diazomethane; MS: m/z, 202 (M^+).

Analysis:

Found: C, 59.3; H, 8.8; $C_{10}H_{18}O_4$

requires: C, 59.4; H, 8.9%.

IR bands at: 2985, 1736, 1449, 1240, 1047 and 905 cm^{-1}.

1,6,7-Trihydroxy-3,6,7-trimethyloctane (VI):

To an ice-cooled and stirred solution of MeMgI [prepared from magnesium (17 g, 0.71 mol) and methyl iodide (110 g, 0.77 mol), in dry ether (250 ml)], in dry ether, a solution of IV (30 g, 0.19 mol), in dry ether (100 ml), was added dropwise during 2 hr. Stirring was continued for 2 hr at 0°, then refluxed for 6 hr and left overnight. Excess of reagent and magnesium complex were decomposed by careful addition of saturated solution of ammonium chloride (300 ml), at 0°. The mixture was stirred for 1 hr at room temperature. The ether layer was separated and the aqueous portion was extracted with ether (100 ml x 2). The combined ether layer was washed with water, brine, dried and concentrated to furnish VI (20 g, 79%), as a liquid; $[\alpha]_D^{27}$ + 4° (c, 2.7).

Analysis:

Found: C, 64.4; H, 11.8; $C_{11}H_{24}O_3$

requires: C, 64.7; H, 11.8%.

IR bands at: 3425, 2905, 1460, 1380, 1150, 1050, 1000, 950 and 890 cm^{-1}.

3-Methyl-6-oxoheptane-1-ol (VII):

To a stirred solution of VI (18 g, 88 mmol), in acetone (200 ml) and water (50 ml), powdered sodium metaperiodate (17.5 g, 0.175 mol), was added in small lots during 1 hr and stirring continued for 4 hr. The reaction mixture was filtered under suction, the residue washed with acetone (100 ml). Most of the acetone, from the filtrate was distilled off and the residue diluted with water and extracted with chloroform (100 ml x 3). The combined organic layer was washed with water, brine, dried and solvent stipped off to give VII as a liquid (12 g, 89%), b.p. 125°/8 mm; $[\alpha]_D^{27}$ + 1.5° (c, 7.38); MS: m/z, 144 (M^+). Analysis:

Found: C, 66.4; H, 11.1; $C_8H_{16}O_2$

requires: C, 66.6; H, 11.2%.

IR bands at: 3570, 2940, 1720, 1325, 1250 and 1070 cm^{-1}.

Methyl 3-methyl-6-oxoheptanoate (VIII)

To an ice cooled and stirred solution of VII (3 g, 21 mmol) in acetone (30 ml), Jones chromic acid reagent (12 ml), was added dropwise during 30 min and stirring continued for 3 hr. The reaction mixture was diluted with water (50 ml) and extracted with chloroform (50 ml x 3). The combined organic layer was washed with water and separated into acidic and neutral portions by sodium carbonate (aqueous, 10%) extraction. The chloroform layer containing the neutral product was not investigated further. The carbonate layer was acidified with dilute hydrochloric acid and

extracted with chloroform (50 ml x 3). The combined chloroform layer was washed with water dried and solvent removed to give acid, which was esterified with an ethereal solution of diazomethane to furnish VIII (2.5 g, 70%), as a liquid, purified by distillation, b.p. 135°/6 mm, $[\alpha]_D^{27}$ + 2.5° (c, 1.7); MS: m/z, 172(M^+).

Analysis:

Found: C, 62.6; H, 9.3; $C_9H_{16}O_3$

requires: C, 62.8; H, 9.3%.

IR bands at: 3030, 1748, 1724, 1592, 1429, 1361, 1250 and 1005 cm^{-1}.

Methyl 6-chloro-3-methylhept-5-enoate (IX):

Phosphorous pentachloride (2 g), was added in small lots to ice cooled keto ester (VIII, 1 g, 6 mmol) and kept overnight at room temperature (25°). It was then poured on to crushed ice and extracted with methylene chloride (50 ml x 3). The organic layer was washed with water, aqueous sodium carbonate, water, dried and solvent removed to give an oil (1 g), which was refluxed in benzene (25 ml) containing piperidine (0.5 g). Benzene layer was washed with water and dried. The oil obtained after evaporation of benzene, was chromatographed over silicic acid, impregnated with 15% silver nitrate (20 g). The fraction eluted with pet.ether-benzene (1:1), gave a TLC pure liquid (0.5 g, 45%). The PMR spectrum and GLC analysis however, indicated it to be a mixture of E and Z isomers IX (90%) and (XI (10%); MS: m/z, 190 (M^+), 192 (^{37}Cl).

Analysis:

Found: C, 56.4; H, 8.0; Cl, 18.2; $C_9H_{15}O_2Cl$

requires: C, 56.8; H, 7.9; Cl, 18.4%.

IR bands at: 2975, 1736, 1435, 1381, 1260, 1165, 1009, 880 and 785 cm^{-1}.

3-Phenoxybenzyl 6-chloro-3-methylhept-5-enoate (XII):

A solution of chloroesters (IX- 90% and XI- 10%, 0.285 g, 1.48 mmol), 3-phenoxybenzyl alcohol (0.4 g, 2 mmol) and butyl titanate (0.015 g), in xylene (20 ml), was refluxed for 12 hr. Xylene was removed under reduced pressure, residue taken up in pet.ether and chromatographed over silicic acid (5 g). The fraction eluted with pet.ether-benzene (1:1) gave esters XII-90% + XIII- 10%, as a liquid, (0.3 g, 80%); MS: m/z, 358 (M^+) and 360 (^{37}Cl).

Analysis:

Found: C, 70.4; H, 5.8; Cl, 10.0; $C_{21}H_{23}O_3Cl$

requires: C, 70.7; H, 5.9; Cl, 10.4%.

IR bands at: 3015, 2980, 1735, 1585, 1488, 1450, 1380, 1265, 1215, 1162, 775 and 670 cm^{-1}.

Methyl 6-cyano-3-methylhept-5-enoate (XV):

a) To an ice cooled and stirred solution of the keto ester (VIII, 1.2 g, 7 mmol), in ethanol (20 ml), acetic acid (10 ml) and water (7 ml), potassium cyanide (5 g), was added in small lots during 30 min, stirred at 0^o for 2 hr, at room temperature for 1 hr, diluted with water (50 ml) and extracted with methylene

chloride (50 ml x 3). The combined organic layer was washed with water, aqueous sodium carbonate (10%), water, dried and solvent stripped off to give cyanohydrin ester (XIV, 1.2 g, 87%), as a liquid.

IR bands at: 3450, 2950, 2220, 1735, 1460, 1438, 1005, 960 and 890 cm^{-1}.

b) Dehydration of cyanohydrin ester (XIV): To a stirred solution of XIV (1 g), in pyridine (10 ml), $POCl_3$ (1.2 ml), was added dropwise and the reaction mixture left overnight at room temperature. It was then poured onto crushed ice, extracted with chloroform (25 ml x 3). The combined organic layer was washed with dil. hydrochloric acid, water and dried. Removal of solvent furnished a liquid (0.8 g), purified by chromatography over silicic acid (10 g). The fraction eluted with pet.ether-benzene (7:3), gave TLC pure XV, as a liquid (0.65 g, 72%). However, PMR and GLC analysis showed it to be a mixture of Z isomer XV and double bond isomer XVI; MS: m/z, 181 (M^+).

Analysis:

Found: C, 66.4; H, 8.3; N, 7.6; $C_{10}H_{15}O_2N$

requires: C, 66.6; H, 8.3; N, 7.7%.

IR bands at: 2945, 2203, 1735, 1435, 1310, 1200, 1008 and 880 cm^{-1}.

3-Phenoxybenzyl 6-cyano-3methylhept-5-enoate (XVII):

A solution of the ester (XV, XVI- 8%, 0.134 g, 0.74 mmol) and 3-phenoxybenzyl alcohol (0.2 g, 1 mmol), in xylene (10 ml),

containing butyl titanate (0.01 g), was refluxed for 8 hr and the reaction mixture was worked up and purified by chromatography as described earlier to give XVII, XVIII- 8%, as a liquid (0.214 g, 83%); $[\alpha]_D^{27}$ + 2° (c, 2.2); MS:m/z, 349 (M^+).

Analysis:

Found: C, 75.4; H, 6.5; N, 3.9; $C_{22}H_{23}O_3N$

requires: C, 75.6; H, 6.6; N, 4.1%.

IR bands at: 3010, 2975, 2960, 2110, 1735, 1585, 1490, 1450, 1260, 1215, 1060, 777 and 693 cm^{-1}.

3,6-Dimethyl-1,6-dihydroxyheptane (XIX):

a) To an ice cooled and stirred solution of methyl magnesium iodide [prepared from magnesium (1.3 g, 54 mmol) and methyl iodide (9 g, 66 mmol), in dry ether (50 ml)], a solution of the keto alcohol (VII , 3.5 g, 24 mmol), in dry ether (20 ml) was added dropwise during 30 min. Stirring was continued for 2 hr at 0°, refluxed for 6 hr, left overnight and worked up as described earlier to give the diol (XIX, 1.8 g, 74%), as a thick liquid; $[\alpha]_D^{27}$ + 2.5° (c, 0.9).

b) To an ice cooled and stirred solution of methyl magnesium iodide [prepared from magnesium (5 g, 208 mmol), methyl iodide (30 g, 211 mmol), in dry ether (100 ml)], a solution of ester (V, 10 g, 62 mmol), in ether (60 ml), was added dropwise during 30 min, stirred for 2 hr at 0°, refluxed for 6 hr, kept overnight and worked up as described earlier to give XIX (7.4, 89%), as a thick liquid, identical in all respects with the one, obtained by method (a); MS: m/z, 160 (M^+).

Analysis:

Found: C, 67.2; H, 12.4; $C_9H_{20}O_2$

requires: C, 67.5; H, 12.5%.

IR bands at: 3465, 2976, 1475, 1390, 1115, 1065 and 1035 cm^{-1}.

Methyl 6-hydroxy-3,6-dimethylheptanoate (XX):

To a stirred solution of XIX (5 g, 31.2 mmol), in acetone (30 ml), acetic acid (10 ml), water (6 ml), powdered potassium permanganate (8 g, 51 mmol), was added in small lots during 30 min. The reaction mixture was stirred for 2 hr and worked up as described earlier to give the acid (XX, R=H, 3.8 g, 65%). Esterification of XX with an ethereal solution of diazomethane gave the methyl ester (XX), purified by distillation; b.p.135°/ 6 mm; $[\alpha]_D^{27}$ + 2.2° (c, 3.4); MS: m/z 188 (M^+).

Analysis:

Found: C, 69.6; H, 11.6; $C_{10}H_{20}O_3$

requires: C, 69.7; H, 11.7%.

IR bands at: 3509, 2985, 1735, 1449, 1429, 1370, 1010, and 908 cm^{-1}.

Methyl 3,6-dimethylhept-5-enoate (XXI):

A solution of hydroxy ester (XX, 3 g, 16 mmol), in dry benzene (100 ml), was refluxed with para toluene sulphonic acid (0.1 g), using a Dean-Stark separator for azeotropic removal of water, till no more water was collected (12 hr). The organic layer was washed with water, aqueous sodium carbonate (10%), followed by water

and benzene removed to furnish a liquid (2.8 g), which was chromatographed over silicic acid (30 g) impregnated with 15% silver nitrate. The silica gel column was exhaustively eluted with pet.ether and pet.ether-benzene mixtures. The fraction eluted with pet.ether containing 30% benzene, gave a TLC pure colourless liquid ester (XXI, 1.9 g, 69%); b.p.135°/4 mm; $[\alpha]_D^{27}$ + 2.2° (c, 3.4); MS: m/z, 170 (M^+).

Analysis:

Found: C, 70.4; H, 10.6; $C_{10}H_{18}O_2$

requires: C, 70.5; H, 10.6%.

IR bands at: 2985, 1736, 1429, 1372, 1302, 1250, 1198, 1149, 1075, 1010 and 860 cm^{-1}.

3-Phenoxybenzyl-3,6-dimethylhept-5-enoate (XXII):

A solution of XXI(0.3 g, 1.76 mmol), and 3-phenoxybenzyl alcohol (0.4 g, 2 mmol), in xylene (15 ml), containing butyl titanate (0.021 g) was refluxed for 12 hr. The reaction mixture was worked up and purified by chromatography as described earlier to give XXII (0.484 g, 81%), as a thick liqud; $[\alpha]_D^{27}$ + 1.5° (c, 4.3); MS: m/z, 338 (M^+).

Analysis:

Found: C, 77.9; H, 7.7; $C_{22}H_{26}O_3$.

requires: C, 78.1; H, 7.7%.

IR bands at: 3010, 2980, 2960, 1740, 1590, 1492, 1450, 1380, 1310, 1260, 1220, 1150, 1078, 770 and 699 cm^{-1}.

4,8-Dimethyl-7-nonene-2-ol (XXIV):

To an ice cooled and stirred solution of methyl magnesium iodide [prepared from magnesium (7 g, 0.29 mol) and methyl iodide (43 g, 0.30 mol), in dry ether (150 ml)], a solution of citronellal (XXIII, 31 g, 0.20 mol, $[\alpha]_D^{27}$ + 11° (c, 2.2)] in dry ether (100 ml) was added dropwise during 30 min. Stirring was continued for further 2 hr at 0°. The reaction mixture was refluxed for 4 hr, left overnight and worked up as described earlier to give the alcohol (XXIV, 35.5 g, 98%), as a liquid; b.p.80°(vapour)/2 mm; MS:m/z, 170 (M^+).

Analysis:

Found: C, 77.1; H, 12.9; $C_{11}H_{22}O$

requires: C, 77.5; H, 13.0%.

IR bands at: 3448, 2976, 1448, 1370, 1124, 1053, 935 and 883 cm^{-1}.

4,8-Dimethylnon-7-ene-2-one (XXV) and XXVI:

To an ice cooled and stirred solution of XXIV (20 g, 0.117 mol), in acetone (200 ml), Jones chromic acid reagent was added dropwise during 1 hr till brown colour persisted (120 ml). Stirring was continued for 2 hr. The reaction mixture was diluted with water (500 ml) and extracted with chloroform (100 ml x 3). The combined chloroform layer was washed with water, and extracted with aqueous sodium carbonate (10%) to remove acid formed. The organic layer was washed with water (75 ml x 2), dried and distilled to give ketone XXV (16 g, 80%), purified by distillation, b.p.85°(vapour)/

2 mm, $[\alpha]_D^{26}$ - 0.4° (c, 4.9). MS: m/z, 168 (M^+).

Analysis:

Found: C, 77.5; H, 12.4; $C_{11}H_{20}O$

requires: C, 77.2; H, 12.6%.

IR bands at: 3003, 1715, 1449, 1361 and 1156 cm^{-1}.

a) The aqueous sodium carbonate layer was acidified with dilute hydrochloric acid and extracted with chloroform (50 ml x2). The chloroform layer was washed with water, brine, dried and concentrated to give keto acid (XXVI, R=H, 3 g), which was treated with ethereal solution of diazomethane to give methyl ester (XXVI, $R=CH_3$), purified by distillation, b.p.95°(vapour)/2 mm, $[\alpha]_D^{26}$ + 6.4° (c, 2.8).

b) To a solution of alcohol (XXIV, 25 g, 0.147 mol), dissolved in acetone (250 ml), Jones chromic acid reagent (190 ml) was added slowly over a period of 2 hr and left overnight. Work up of the reaction mixture as described above, gave in the acid part, the keto acid (XXVI, R=H, 18 g, 72%), which was converted to methyl ester (XXVI, $R=CH_3$) and distilled to give pure ester (16 g, 64%), identical in all respects with the one, obtained above.

Analysis:

Found: C, 62.4; H, 9.4; $C_9H_{16}O_3$

requires: C, 62.8; H, 9.3%.

IR bands at: 3030, 1740, 1718, 1429, 1368, 1258, 1176, 1099 and 1010 cm^{-1}.

Methyl 4(R)-methyl-6-oxoheptanoate (XXVI):

To an ice cooled and stirred solution of XXV (20 g, 0.119 mol), in acetone (200 ml), powdered potassium permanganate (30 g, 0.192 mol), was added during 1.5 hr. Stirring was continued for 3 hr. at 0^{o} and for 1 hr. at room temperature. The reaction mixture was filtered under suction and the residue washed with acetone. The residue was extracted with hot water (75 ml x 3) and the combined aqueous extract was concentrated to 50 ml, cooled, acidified with dilute hydrochloric acid to pH 2. The acid liberated, was extracted with ether (100 ml x 3). The ether layer was washed with water, brine, dried and evaporated to give acid (XXVI, R=H, 9.5 g, 48%). It was esterified with ethereal solution of diazomethane to give methyl ester (XXVI, $R=CH_3$), b.p. 95^{o}(vapour)/2 mm, identical (IR and PMR) with the ester, obtained by the procedure described above. MS: m/z, 172 (M^{+}).

Methyl 4(R)-methyl-6-chlorohept-5-enoate (XXVII):

To an ice cooled and stirred solution of XXVI (4 g, 23.2 mmol), in methylene chloride (25 ml), was added phosphorous pentachloride (6 g), during 30 min., reaction mixture stirred for 16 hr, refluxed for 2 hr., cooled and poured onto crushed ice. It was then extracted with methylene chloride (75 ml x 3), the combined organic layer washed with 10% sodium carbonate solution, followed by water and dried. Removal of methylene chloride furnished a mixture of chloroesters. It was then

refluxed with benzene (50 ml), containing piperidine (0.5 g) for 6 hr, worked up and purified by chromatography. The fraction eluted with benzene gave a TLC pure chloroester (XXVII, 2 g), b.p.110°/2 mm, $[\alpha]_D^{26}$ + 1.4° (c, 2.6); MS: m/z, 190(M^+), 192(^{37}Cl).

Analysis:

Found: C, 55.9; H, 8.1; Cl, 18 .3; $C_9H_{15}O_2Cl$

requires: C, 56.3; H, 8.3; Cl, 18.4%.

IR bands at: 3013, 1739, 1460, 1379, 1250, 1176, 1111, 1020 and 952 cm^{-1}.

3-Phenoxybenzyl 4(R)-methyl-6-chlorohept-5-enoate (XXIX):

A solution of chloroester (XXVII, 0.78 g 4.1 mmol), 3-phenoxybenzyl alcohol (1 g, 5 mmol), in xylene (15 ml), containing butyl titanate (0.015 g), was refluxed for 12 hr, worked up and purified by chromatography as described earlier to give XXIX (1.2 g, 82%), as a liquid, $[\alpha]_D^{26}$ + 1.5° (c, 1.2), MS: m/z, 358(M^+), 360 (^{37}Cl).

Analysis:

Found: C, 70.1; H, 6.2; Cl, 9.7; $C_{21}H_{23}O_3Cl$

requires: C, 70.2; H, 6.4; Cl, 10.0%.

IR bands at: 3021, 1739, 1587, 1481, 1445, 1374, 1250, 1211, 1163, 1111, 939, 775 and 718 cm^{-1}.

3,7-Dimethyl-1-phenyloct-6-ene-1-ol (XXX):

To an ice cooled solution of phenyl magnesium bromide [prepared from magnesium (4.4 g, 0.183 mol) and bromobenzene (37.5 g, 0.258 mol), in dry ether (100 ml)], a solution of

citronellal (XXIII, 21.5 g, 0.136 mol), in ether (50 ml), was added dropwise during 2 hr at 0°, refluxed for 4 hr and kept overnight. It was then decomposed by ammonium chloride(aqueous) and worked up as described earlier to give an alcohol, as a liquid. This product showed on TLC (6% ethyl acetate in benzene) one major spot with less polar impurity. The less polar impurity was separated from the major product by chromatography over alumina (grade II, 200 g) and not investigated further. The fraction eluted with chloroform gave the TLC pure alcohol (XXX, 25 g, 81%); $[\alpha]_D^{26}$ + 3.9° (c, 1.6); MS:m/z, 232 (M^+).

Analysis:

Found: C, 82.3; H, 10.3; $C_{16}H_{24}O$

requires: C, 82.7; H, 10.3%.

IR bands at: 3509, 2985, 1585, 1449, 1379, 1053, 1026, 860 and 701 cm^{-1}.

1-Benzoyl-2,6-dimethylhept-5-ene (XXXI):

To an ice cooled and stirred solution of XXX (20 g, 86 mmol), in acetone (200 ml), Jones chromic acid reagent (110 ml), was added dropwise during 1 hr and stirring continued for 2 hr. The reaction mixture was diluted with water, worked up as usual to give XXXI (15 g, 70%), purified by distillation, b.p.165°/2 mm; $[\alpha]_D^{27}$ -12° (c, 1.6); MS: m/z,230 (M^+).

Analysis:

Found: C, 83.8; H, 9.5; $C_{16}H_{22}O$

requires: C, 83.5; H, 9.6%.

IR bands at: 3012, 1695, 1600, 1449, 1379, 1282, 1212, 1000, 751 and 698 cm^{-1}.

Methyl 4(R)-methyl-5-benzoylvalerate (XXXII):

To an ice cooled and stirred solution of XXXI (8 g, 34.7 mmol), in acetone (100 ml), powdered potassium permanganate (12 g, 77 mmol), was added during 2 hr. Stirring was continued for 3 hr. at 0^{o} and for 1 hr at room temperature. The reaction mixture was filtered, residue washed with acetone, extracted with hot water (75 ml x 3) and worked up as usual to give an acid, which was esterified with ethereal solution of diazomethane to give methyl ester (XXXII, 3.4 g, 42%), b.p.180^{o}/2 mm; $[\alpha]_{D}^{27}$ -15^{o} (c, 1.7); MS: m/z, 234 (M^{+}).

Analysis:

Found: C, 71.7; H, 7.6; $C_{14}H_{18}O_{3}$

requires: C, 71.8; H, 7.7%.

IR bands at: 3030, 1738, 1695, 1610, 1587, 1449, 1370, 1000, 760 and 714 cm^{-1}.

Alternatively, oxidation of XXX (5 g, 21.5 mmol), dissolved in acetone (50 ml), by Jones chromic acid reagent (30 ml), for 10 hr gave after similar work up and esterification of the resulting acid, the ester XXXII (3.2 g, 65%), identified by comparative TLC and spectral data.

Methyl 4(R)-methyl-6-chloro-6-phenylhex-5-enoate (XXXIII):

To an ice cooled and stirred solution of XXXII (2 g, 8.5 mmol), in methylene chloride (20 ml), phosphorous pentachloride

(3 g), was added in small portions during 30 min, and the mixture stirred for 16 hr, refluxed for 8 hr, cooled and poured onto crushed ice under stirring and extracted with methylene chloride (50 ml x 3). The organic layer was washed with water, 10% aqueous sodium carbonate, followed by water, dried and concentrated to give an oil. Purification of crude product by chromatography over silicic acid, followed by distillation, gave the TLC pure chloro ester (XXXIII, 1.2 g, 56%), identified as E isomer, b.p.150-160°/2 mm, $[\alpha]_D^{27}$ -6.7°(c, 2.5); MS: m/z, 252 (M^+), 254 (^{37}Cl).

Analysis:

Found: C, 66.9; H, 6.6; Cl, 13.9; $C_{14}H_{17}O_2Cl$

requires: C, 67.2; H, 6.8; Cl, 14.0%.

IR bands at: 3003, 1739, 1639, 1600, 1440, 1439, 1163, 757 and 696 cm^{-1}.

3-Phenoxybenzyl 4(R)-methyl-6-chloro-6-phenylhex-5-enoate(XXXIV):

A solution of XXXIII (0.68 g, 2.7 mmol), 3-phenoxybenzyl alcohol (0.7 g, 3.7 mmol), in xylene (15 ml), containing butyl titanate (0.012 g), was refluxed for 12 hr. Xylene was removed under reduced pressure and residue taken up in pet.ether and purified by column chromatography. The silica gel column (20 g), was eluted with benzene to give pure XXXIV (0.95 g, 84%), as a liquid; MS: m/z, 420 (M^+), 422 (^{37}Cl).

Analysis:

Found: C, 74.0; H, 5.7; Cl, 9.6; $C_{26}H_{25}O_3Cl$

requires: C, 74.1; H, 5.9; Cl, 9.7%.

IR bands at: 3030, 1739, 1587, 1481, 1439, 1250, 1208, 1160, 751 and 689 cm^{-1}.

1-Acetoxy-1-phenyl-3,7-dimethyloct-6-ene (XXXV):

To a cooled solution of alcohol (XXX, 43 g, 0.185 mol), in pyridine (150 ml), acetic anhydride (26 g, 0.282 mol), was added dropwise during 30 min. The reaction mixture was left overnight at room temperature, heated on water bath for 3 hr, poured onto crushed ice under stirring, allowed to stand for 30 min and extracted with chloroform (200 ml x 3). The combined chloroform layer was washed with dilute hydrochloric acid to remove pyridine, followed by water and dried. Removal of chloroform furnished the TLC pure (2% ethyl acetate in benzene), acetate (XXXV, 48.7 g, 96%), b.p.190°/2 mm; MS: m/z, 274(M^+). Analysis:

Found: C, 78.6; H, 9.7; $C_{18}H_{26}O_2$

requires: C, 78.8; H, 9.5%.

IR bands at: 3030, 1739, 1600, 1493, 1233, 1026, 800 and 700 cm^{-1}.

Methyl 4(R)-methyl-6-acetoxy-6-phenylhexanoate (XXXVI):

To an ice cooled and stirred solution of XXXV (44 g, 0.16 mol), in acetone (500 ml), powdered potassium permanganate (40 g, 0.25 mol), was added in small lots during 2 hr. Stirring was continued for 3 hr at 0° and 1 hr at room temperature. The reaction mixture was worked up as described earlier to give an acid (35 g, 42%), which was esterified with ethereal solution

of diazomethane to give the ester (XXXVI), b.p.200°/2 mm; MS: m/z 262 (M^+).

Analysis:

Found: C, 69.4; H, 7.9; $C_{16}H_{22}O_4$

requires: C, 69.1; H, 8.0%.

IR bands at: 3021, 1730, 1600, 1493, 1429, 1232, 1015, 757 and 700 cm^{-1}.

Methyl 4(R)-methyl-6-hydroxy-6-phenylhexanoate (XXXVII):

The acetate acid (XXXVI, 31 g, 0.118 mole), was dissolved in a solution of methanolic potassium hydroxide (8 g, 0.142 mol, methanol- 100 ml, water- 20 ml) and refluxed for 6 hr on water bath. Most of the methanol was removed under reduced pressure, the residue diluted with water and extacted with ether(100 ml x 3). The aqueous layer was acidified with dilute hydrochloric acid to pH-2 and extracted with chloroform (100 ml x 3). The chloroform layer was washed with water, dried and evaporated to give hydroxy acid (25 g, 93%), which was esterified with diazomethane to give methyl ester (XXXVII), MS: m/z, 236 (M^+).

Analysis:

Found: C, 70.9; H, 8.4; $C_{14}H_{20}O_3$

requires: C, 71.1; H, 8.4%..

IR bands at: 3571, 2985, 1739, 1595, 1481, 1429, 760 and 699 cm^{-1}.

Methyl 4(R)-methyl-6-phenylhex-5-enoate (XXXVIII):

A solution of ester (XXXVII, 3 g, 12.7 mmol), in dry benzene (100 ml), was refluxed with paratoluene sulphonic acid (0.05 g),

using a Dean-Stark water separator, till no more water collected (12 hr). It was then cooled, washed with water and dried. Removal of benzene furnished a mixture of two products (2.3 g), which was chromatographed on alumina (grade II, 60 g, 1:25) and eluted with pet.ether, pet.ether-benzene mixtures and chloroform. The fraction eluted with pet.ether + 10% benzene gave the TLC pure ester (XXXVIII, 1.7 g, 63%), b.p.150-160°/2 mm; $[\alpha]_D^{27}$ + 0.7° (c, 0.29). It was identified as E isomer, by spectral data (IR and PMR); MS: m/z, 218 (M^+).

Analysis:

Found: C, 76.7; H, 8.0; $C_{14}H_{18}O_2$

requires: C, 77.1; H, 8.2%.

IR bands at: 3030, 1749, 1608, 1493, 1449, 1429, 1170, 965, 754 and 698 cm^{-1}.

3-Phenoxybenzyl 4(R)-methyl-6-phenylhex-5-enoate (XL):

A solution of XXXVIII (0.4 g, 1.8 mmol), 3-phenoxybenzyl alcohol (0.5 g, 2.5 mmol) and butyl titanate (0.026 g), in xylene (15 ml), was refluxed for 12 hr. Usual work up and purification by chromatography over silica gel (10 g) and elution with pet.ether-benzene (1:1), gave XL, as a thick liquid (0.6 g, 85%); MS: m/z, 387 (M^+).

Analysis:

Found: C, 80.1; H, 6.6; $C_{26}H_{27}O_3$

requires: C, 80.6; H, 6.9%.

IR bands at: 3028, 1745, 1595, 1488, 1444, 1250, 1212, 1163, 1070, 965, 754 and 698 cm^{-1}.

2,4,8-Trimethyl-non-7-ene-2-ol (XLI):

To an ice-cooled and stirred solution of methyl magnesium iodide in ether [prepared from magnesium (2.5 g, 0.104 mol), methyl iodide (16 g, 0.112 mol), in ether (50 ml)], an ethereal solution of ketone (XXV, 10 g, 59 mmol), in ether (50 ml), was added dropwise during 1 hr, the reaction mixture stirred for 2 hr at 0^{o}, refluxed for 6 hr and left overnight. Usual work up of the reaction product gave XLI (10 g, 91%), as a liquid, b.p.80-90^{o}/2 mm, $[\alpha]_{D}^{27}$ -0.4^{o} (c, 4.8); MS: m/z, 184 (M^{+}).

Analysis:

Found: C, 77.9; H, 12.9; $C_{12}H_{24}O$

requires: C, 78.3; H, 13.0%.

IR bands at: 3504, 3021, 1449, 1374, 1170, 1136, 901 and 826 cm^{-1}.

Methyl 6-hydroxy-4,6-dimethylheptanoate (XLII):

To an ice-cooled and stirred solution of XLI (5.5 g, 29 mmol), dissolved in acetone (60 ml), powdered potassium permanganate (10 g, 64 mmol), was added during 30 min, the reaction mixture stirred at 0^{o} for 3 hr, and for 1 hr. at room temperature. Usual work up gave the acid (3.9 g, 54%), in the acidic part, which was converted into methyl ester (XLII), with ethereal solution of diazomethane, b.p.120-130^{o}/2 mm; MS: m/z, 188 (M^{+}). Neutral oxidation products formed in the reaction, were not investigated further.

Analysis:

Found: C, 63.3; H, 10.6; $C_{10}H_{20}O_{3}$

requires: C, 63.8; H, 10.7%.

IR bands at: 3636, 3022, 1735, 1451, 1379, 1176, 995 and 781 cm^{-1}.

Methyl 4,6-dimethylhept-5-enoate (XLIV) and its double bond isomer (XLIII):

To an ice cooled and stirred solution of hydroxy ester (XLII, 2.5 g, 13.2 mmol), in pyridine (10 ml), $POCl_3$ (3 ml) was added dropwise and the reaction mixture left at room temperature for 12 hr. It was then poured onto crushed ice, extracted with chloroform (50 ml x 3). The combined chloroform extract was washed with dil. hydrochloric acid, followed by water and dried. Removal of solvent by distillation, furnished a TLC pure liquid, which, however, showed two spots on TLC (SiO_2 + 10% $AgNO_3$, benzene). This was chromatographed on silicic acid, impregnated with 10% $AgNO_3$ (40 g) and eluted with pet.ether, pet.ether-benzene mixtures. The fraction eluted with pet.ether + 30% benzene, gave XLIV as a liquid; b.p.110°/1 mm; MS: m/z, 170 (M^+).

Analysis:

Found: C, 76.7; H, 11.5; $C_{10}H_{18}O_2$

requires: C, 77.0; H, 11.6%.

IR bands at: 2984, 1739, 1437, 1368, 1111 and 990 cm^{-1}.

The column was later eluted with benzene to give XLIII as a liquid (0.7 g).

IR bands at: 3030, 1740, 1640, 1438, 1356 and 885 cm^{-1}.

3-Phenoxybenzyl 4,6-dimethylhept-5-enoate (XLV):

A solution of ester (XLIV, 0.5 g, 3 mmol), 3-phenoxybenzyl alcohol (0.7 g, 3.5 mmol), in xylene (20 ml), containing butyl titanate (0.01 g), was refluxed for 12 hr. Usual work up and purification by chromatography gave the ester (XLV, 0.7 g, 87%), as a liquid, $[\alpha]_D^{27}$ - 18° (c, 2.2); MS: m/z, 338 (M^+).

Analysis:

Found: C, 78.6; H, 7.5; $C_{22}H_{26}O_3$

requires: C, 78.1; H, 7.8%.

IR bands at: 3030, 1745, 1595, 1493, 1449, 1379, 1258, 1220, 1163, 1073, 935, 775 and 704 cm^{-1}.

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CHAPTER-IV

STRUCTURE ACTIVITY STUDIES OF SECO-PYRETHROIDS SYNTHESISED

S U M M A R Y

This chapter describes the structure activity studies of various secopyrethroids synthesised. The influence of (1) -substitution and its nature, (ii) nature of substitution on vinyl function and (iii) the effect of chain length between ester group and vinyl function, on the insecticidal activity, are some of the important points discussed in this chapter.

STRUCTURE-ACTIVITY STUDIES OF SECOPYRETHROIDS SYNTHESISED

It was established by many workers that nature and position of substituents has a definate influence on the insecticidal activity, in the case of pyrethroids as well as their open chain equivalents like fenvalerate. It is not necessary to stress the interest of study, of structure activity relationship in the discovery of new pesticides, since, chemists and biologists are quite conscious of the advantages that may be obtained therefrom. Thus, the discovery of new pesticides is certainly not only due to chance.

To investigate the effect of substitution and the carbon chain length on the insecticidal activity, various compounds were tested; 4th Instar mosquitoes larvae, Adult mosquitoes (Aedes aegypti) and house-flies (Musca domestica) were chosen as test insects, to demonstrate the effect of such compounds on insecticidal activity.

This work showed feasibility of carrying out a direct correlation between chemical structure and acute toxicity.

Method

The 3-phenoxybenzyl esters were tested for their insecticidal activity against

1. Musca domestica (house flies): by topical application. The esters 1 µg/insect were applied topically on the insect with the help of microsyringe. The normal food was provided

to the test insects and mortality counts were taken after 24 hr. Minimum three replicates were carried out and average mortality was found.

2. Adult mosquitoes (Aedes aegypti): were exposed to the residual deposite of the compound by spraying 1 ml of 5% soluion in acetone, on a 12.5 cm diameter whatmann filter paper, for 24 hr., after which mortality counts were taken.

3. 4th Instar mosquitoe larvae (yellow fewer mosquitoes): In a larvicidal test esters were added to 50 ml water in desired concentration. Minimum 10 number of larvae were released in this water, normal food was supplied and mortality was observed after 24 hr.

Minimum three replicates were taken in each case and average mortality was found.

Effect of chain length on the insecticidal activity:

In the acyclic 3-phenoxybenzyl esters studied by us, it has been observed that the esters in which vinyl function and carboxylate group are separated by two carbon chain (type A), showed enhanced activity than those in which these functions are separated by three carbon unit (Type B).

Substituents on the vinyl function are Cl, CN, CH_3, H, Ph and substituted aryl.

Effect of substitution:

No activity was observed in case of esters of type B, when phenyl group is present as one of the substituents in the

vinyl function, irrespective of the nature of other substituent like Cl (XXXIII) or H (XXXIV).

While in the esters of type B, replacement of phenyl by methyl (XXVIII-XXXII), showed favourable increase in the activity. Further improvement in the insecticidal activity was observed when one of the methyl group was replaced by chloro (XXIX, XXXII) or cyano (XXX),

Chloro derivative XXIX, XXXII, on the whole showed better activity than its cyano counterpart XXX.

Contrary to esters of type B, the esters of type A, with phenyl or para substituted phenyl as one of the substituents, in the vinyl function showed moderate larvicidal activity (XIX-XXII), However, para substitution in the phenyl group viz. methyl (XX), chloro (XXI), bromo (XXII), seems to have non-additive effect on the activity.

It thus appears that phenyl substituents are of minor significance towards their contribution to insecticidal activity.

In another series of variations in the type A esters, possessing substituent α-to the carboxylate function, considerable change in the activity was observed by replacing phenyl group of the vinyl function, with substituents like H, methyl or halogens. However, it was observed that esters lacking an α-substituent (I, VII) were found to be totally inactive. The introduction of α-substituent also brings about a change in the insecticidal activity pattern, as such compounds show good insecticidal activity and are no more active as larvicides.

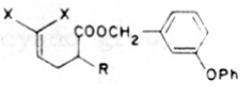
The ∝-substituent plays an important role, in its contribution towards the insecticidal activity of the molecules viz. the compounds with ∝-methyl and ∝-ethyl (II, III, VIII, XIX) show enhanced insecticidal activity as compared to their unsubstituted analogues. Insecticidal activity increases with increased steric hindrance on C_2 carbon atom, the most favourable substituent being isopropyl (IV, X).

This suggests that ∝-substituent is an essential factor for insecticidal action in this class of compounds. This behaviour is analogous to the one observed, in the case of active chrysanthemates, potent pyrethroids and fenvalerate. One of the essential structural features, for insecticidal activity in such compounds is the presence of gem dimethyl or its steric equivalent, β-to the carboxylate function. This condition is also satisfied in some of the open chain analogues by the presence of a isopropyl group on the ∝-carbon atom.

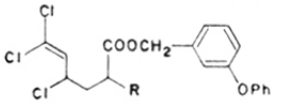
It is interesting to note that corresponding ester with ∝-benzyl substituent, are found to be inactive (V, XI).

Regarding the effect of substituents in the vinyl function of such esters, a gradual increase in the insecticidal activity was observed when both the substituents were changed from H to methyl to halogen. Thus esters with an ∝-isopropyl substituent and a dihalovinyl group (XIII, XV) are found to be most potent in the series. The activity of such compounds is comparable to that of dichlorovos.

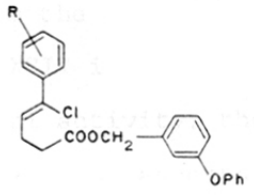
CHART I



Compound No	X	R	Compound No	X	R
I	H	H	IX	CH_3	C_2H_5
II	H	CH_3	X	CH_3	C_3H_7
III	H	C_2H_5	XI	CH_3	$-CH_2C_6H_5$
IV	H	C_3H_7	XII	CH_3	
V	H	$-CH_2C_6H_5$	XIII	Cl	isopropyl
VI	H		XIV	Cl	benzyl
VII	CH_3	H	XV	Br	isopropyl
VIII	CH_3	CH_3	XVI	Br	benzyl

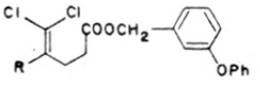


XVII R = isopropyl ; XVIII R = benzyl



XIX R = H ; XX R = CH_3 ; XXI R = Cl

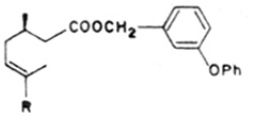
XXII X = Br



XXIII R = CH_3 ; XXIV R = $-C_6H_5$

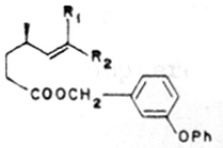
XXV R = $-C_6H_4CH_3$; XXVI R = $-C_6H_4Cl$

XXVII R = C_6H_4Br



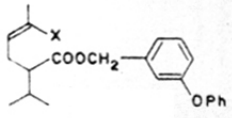
XXVIII R = CH_3 ; XXIX R = Cl

XXX R = $-CN$



XXXI R_1 R_2 = CH_3 ; XXXII R_1 = CH_3, R_2 = Cl

XXXIII R_1 = Ph, R_2 = Cl ; XXXIV R_1 = Ph, R_2 = H



XXXV X = Cl ; XXXVI X = CN

The insecticidal activity of compounds XXXV and XXXVI possessing chlorine or cyano group respectively in the vinyl function as one of the substituents, the other being methyl group were found to be less active than the corresponding dichloro-analogues. However, as compared to the dimethyl analogues they exhibited greater activity.

From this it appears that the general trend of insecticidal activity with respect to vinyl substitution is as shown below dibromo $\geqslant$ dichloro > monochloro > monocyano > dimethyl $\geqslant$ unsubstituted.

Comparable insecticidal activity associated with trichloro-compound XVII (the ester of type B), may be attributed to the presence of additional halogen substituent. However, the ester with α-benzyl substituent XVIII, was found to be inactive.

From the insecticidal data collected in the compounds XIII, XV, XVII it is observed that they possess fairly good insecticidal activity, though extensive entomological studies are necessary for ascertaining their broad spectrum of insecticidal activity.

5,5-Dichloro-4-phenyl or substituted aryl pentenoates (XXIII-XXVII), though possessing a dichlorovinyl function, were found to be totally inactive from which it appears that the presence of α-substituent in the vinyl function, is unfavourable for insecticidal activity. This is supported further by the fact that the corresponding esters in which phenyl group is replaced by methyl group are also found to be inactive.

CONCLUSIONS:

It may therefore be safely deduced from the foregoing facts that the presence of ∝-isopropyl substituent and a 5,5-dihalovinyl pattern, confers greater overall biological activity and comparatively broader spectrum of insecticidal activity.

While the insecticidal activity depends on many factors, it is interesting to note, from the activity data of compounds examines, the following is the general descending order of activity.

a) dihalovinyl > halovinyl > methyl > H > phenyl.

b) ∝-isopropyl > ∝-ethyl ≥ ∝-methyl > H or ∝-benzyl

c) 4- pentenoates > 5-hexenoates

CHAPTER-V

SYNTHESIS OF 4,8-DIMETHYL-DECANAL; AN AGGREGATION PHEROMONE OF RED FLOUR BEETLES

S U M M A R Y

In this chapter transformation of rhodinal (XIX) to 4,8-dimethyl decanal (XVII), an aggregation pheromone of red flour beetles, T. casteneum and T. confusum has been described.

Huang-Minlon reduction of rhodinal under slightly modified conditions gave octene (XX), in 94% yield. In situ hydroboration of octene (XX), gave 2,6-dimethyl octane-1-ol (XXI), which on treatment with triphenyl phosphine dibromide, gave the corresponding bromide (XXII). Alkylation of diethyl malonate with bromide (XXII), under the optimized conditions afforded monoalkylated product (XXIII), in 88% yield. the latter on refluxing with KOAc in DMSO, underwent decarboethoxylation to furnish XXIV, in almost quantitative yield. LAH reduction of XXIV and subsequent oxidation of the resulting alcohol (XXV), by pyridinium chlorochromate gave 4(RS), 8(S)-dimethyl decanal (XVII), converted to its dimethyl acetal (XXVI) and identified by spectral comparison.

INTRODUCTION

The interdisciplinary investigationsof insect kingdom by biologists and chemists have established the importance and complexity of chemosensory communication amongst insects. Many facets of insect behaviour have been shown to be regulated by chemical stimuli[1-10]. The current outcry over indiscriminate use of insecticides has provided much motivation for this work, since the species-specificity and high potency of chemosensory substances hold great promise for manipulation and control of insect population.

Natural insect attractants fall broadly into two categories (i) secretions of insect origin, which produce responses for mating, aggregation, particularly amongst beetles (Coleoptera) and foraging with a single species. The term pheromone applies to this type of intra-specific attractants. Some insects use alarm pheromone to alert the members of their species, for example, the alarm pheromone of the texas leaf cutting ant (Atta texana), shown to be S(+) 4-methyl-3-heptanone, (ii) volatile constituents of plant and animal hosts, utilized by insects, in searching for food and egg-laying sites.

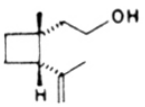
The response may be due to an individual chemical or as is often the case, a mixture of chemicals, for example, male boll weevils (Anthonomus Grandis) produce a mixture of alicyclic

pheromones I, II, III and IV. Here is an instance wherein total mixture acts as the pheromone. In such cases the total effect is greater than the sum of the effects of individual components. This phenomenon is termed as synergism.

The term "pheromone", coined by Karlson and Liisher is derived from the Greek word; phrein - to transfer and harmon- to excite. Pheromones are defined as substances, that are secreted outside by an insect and received by the other insect of the same species, as a means of intra-specific communication.

A variety of chemicals have been identified as pheromones by screening. Lately, it has been realized that the activity of these pheromones very largely depends upon the geometrical and optical isomers of the components. Since the quantity of pheromone isolated from natural resources, are in extremely small quantities, it has been frequently impossible to establish their structure and optical purity. Thus, structure determination rests heavily on information derived from spectroscopic studies, like mass spectrum, nuclear magnetic resonance, infra-red and ultraviolet. The outcome of such study on pheromones, has resulted in the structure elucidation of many compounds,[11] such as, (+) exobrevicomin VII, (-) frantalin VIII and α-(-)-multistriantin IX. Enantiomeric compositions of alcohols like, (+) sucatol X, (-) trans verbenol XI, (-) ipsdienol XII, were found out by forming,

CHART I



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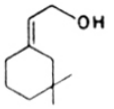

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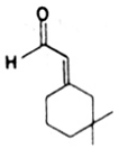

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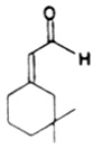

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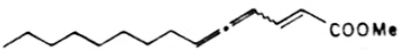

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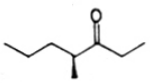
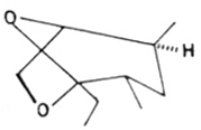


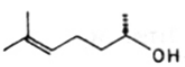
VI

VII

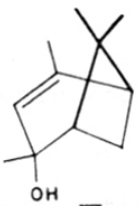
VIII



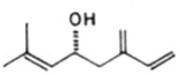
IX



X

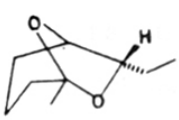


XI



Ipsdienol

XII

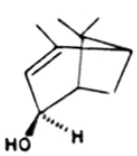


XIII

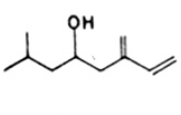
XIV

XV

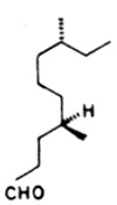
XVI



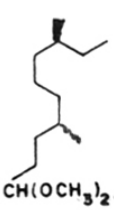
cis Verbinol



Ipsenol



XVII



XXVI

α-methoxy-α-trifluoromethylphenyl acetyl derivatives[12-14]. At present, ^{13}C-NMR technique has become a powerful tool for structure identification. It was very helpful in identifying the structure and stereochemistry[14] of endo-brevicomin XIII, γ(-) multistriantin XIV and γ(+) multistriantin XV.

The ultimate proof for the structure of pheromones, rests on an unambiguous synthesis, followed by demonstration of equivalent biological activity of synthetic material, in the field trials. These syntheses may not prove all that dfficult, since pheromones have comparatively simpler structures. The striking simplicity observed, in the structures of most of the pheromones, may be partly due to the fulfilment of requirement of high volatility and rapid diffusion in the air.

The potential economic and environmental importance of biological pest control is currently undergoing experimental evaluation. Natural insect attractants have been successfully employed for control of pests. One of the most important insect pests in USA, in terms of crop loss economics, is boll weevil (Anthonomus Grandis). More than 3/4 of the losses to cotton crop, in this country (USA), have been due to these pests[15]. With the availability of resources, it has now become easy to control them. There are some reports about the commercial operation against the pink boll worm in cotton field, in 1977. In addition to crop protection, premeeting

with gossyplure XVI, with concomitant reduction of 50-80% in pesticides used, resulted in yield improvements of as much as 20-50%. This is the first instance of successful commissioning of a sex pheromone for protection of crops. In years to come, many more spectacular results are expected. These have also been used in the confusion technique, whereby normal mating behaviour is disrupted by premeeting in the atmosphere with synthetic attractants, The relatively small requirement of synthetic attractants minimises the possibility of environmental pollution and their species-specificity reduces risk of destroying beneficial insects, such as predators, parasites and pollinators. Furthermore, evolution of strains of pest population, resistant to natural attractants is very unlikely.

The main use of pheromones in insect control are (a) for study of population movements and distribution (b) as crop monitor or warning system by relating catches in traps to subsequent larval infestation and (c) for controlling insects either by mass trapping or by direct application techniques, using an attractant or inhibitor.

Synthetic approach is very important in pheromone research, because of limited availability of natural pheromones. Synthesis thus ensures ample and frequent supplies, to facilitate the use in agriculture and forestry.

PRESENT WORK

T. Suzuki[16] in 1980, isolated 760 μg of the aggregation pheromone of the red flour beetles, Tribolium casteneum from 2,40,000 male equivalents (600 males x 40 days), by an air extraction method using porapak Q columns and identified it as 4,8-dimethyl decanal. The same compound was also found to be the pheromone of confused flour beetles, T.confusum[16,17]. T. casteneum and T.confusum are major pests, infesting nearly all kinds of cereals. The pheromone have two chiral centres and hence four isomers are possible. T. Suzuki reported[16,17] the synthesis of racemate, which showsless attractancy than the natural pheromone.

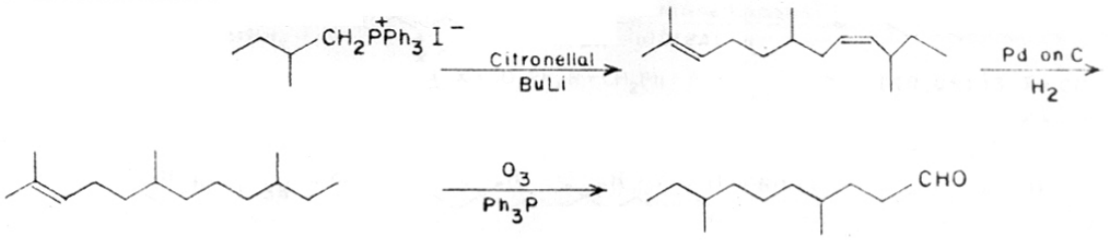
The pheromone, 4,8-dimethyl decanal, is secreted by male species and attracts both the sexes. Thus it is termed as aggregation pheromone of red flour beetles. In order to establish the absolute configuration of natural pheromone, Kenji Mori[18], synthesis all the possible four isomers. The highest activity associated with the 4(R), 8(R) isomer lead to the assumption that the natural pheromone may have 4(R), 8(R) configuration at the chiral centres. Furthermore, 1:1 mixture of 4(R), 8(R) and 4(S), 8(S) dimethyl decanal evokes both the sexes of T. casteneum and t. confusum[19] with little lower potency than the 4(R), 8(R) isomer, one may conclude that the activity of the 4(R), 8(R) stereoisomer is not inhibited by the presence of its optical antipode.

The synthesis of the racemic 4,8-dimethyl decanal was first reported by T. Suzuki,[16] from citronellal. The C-10 compound (citronellal) was converted to a C-15 unit, by a Wittig reaction with 2-methyl-1-butylenetriphenyl phosphorane, followed by hydrogenation of disubstituted double bond to yield a dihydroproduct. The latter on ozonolysis and reductive cleavage of the resulting ozonide, afforded 4,8-dimethyl decanal as the racemate (Chart II, Scheme A). However, the route had certain disadvantages viz. the catalytic hydrogenation is not quite selective and a mixture of hydrogenated products are obtained. For the separation of individual isomers in the pure state, preparative GLC has to be carried out. In another route developed by T. Suzuki[17], the Wittig reaction was replaced by Grignard reaction (Chart II, Scheme B).

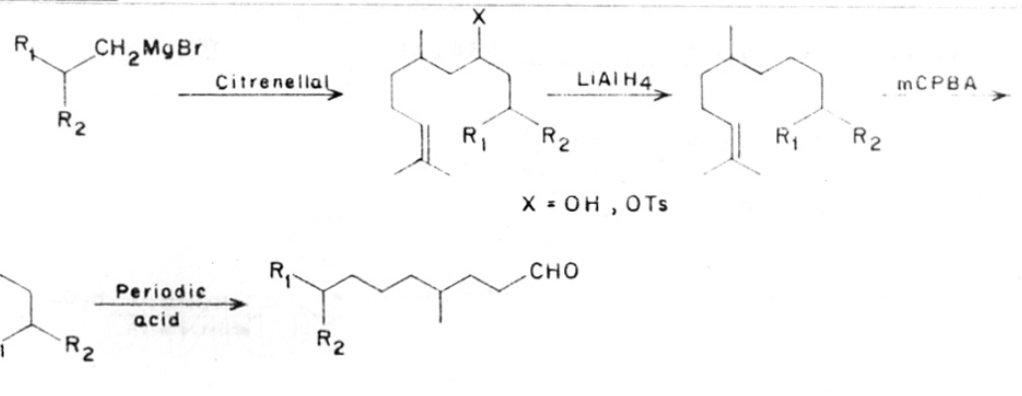
While our work towards the synthesis of pheromone was in progress, a paper by K. Mori et al.[18] appeared, describing the synthesis of all four possible stereoisomers of 4,8-dimethyl decanal, for ascertaining the absolute configuration of the natural pheromone at the two chiral centres, as 4(R), 8(R). The synthesis was achieved from (+) citronellic acid with the known absolute configuration at chiral centre C_3 as R. The synthetic strategy followed by them was to convert citronellal or citronellic acid into suitable smaller fragments, without disturbing the chiral centre and then to join them appropriately to achieve the stereospecific synthesis of the isomers of 4,8-dimethyl decanal. The 4(R),8(R)-isomer was found to possess the maximum activity (Chart II , Scheme C).

CHART I

a) T. Suzuki (1980)

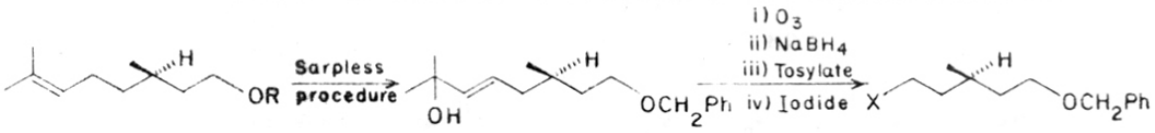


b) T. Suzuki (1981)



c) Kenji Mori et al (1982)

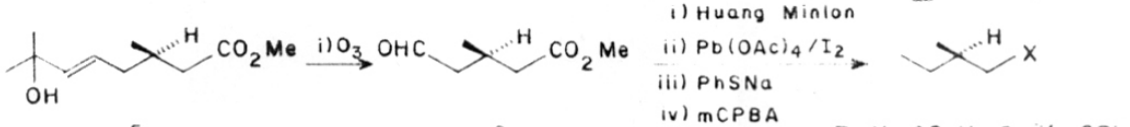
SYNTHESIS OF (4R,8R) AND (4R,8S) 4,8-DIMETHYLDECANAL



1a R = H
b R = CH_2Ph

2

3a X = OH
b X = OTs
4 X = I

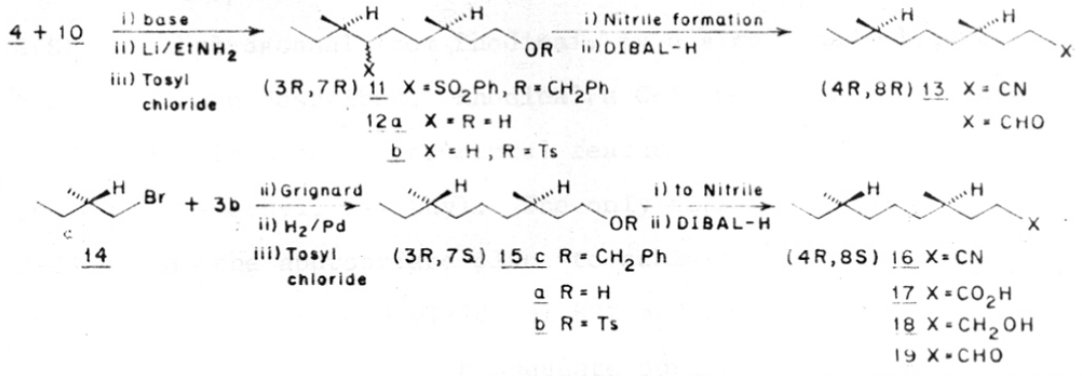


5

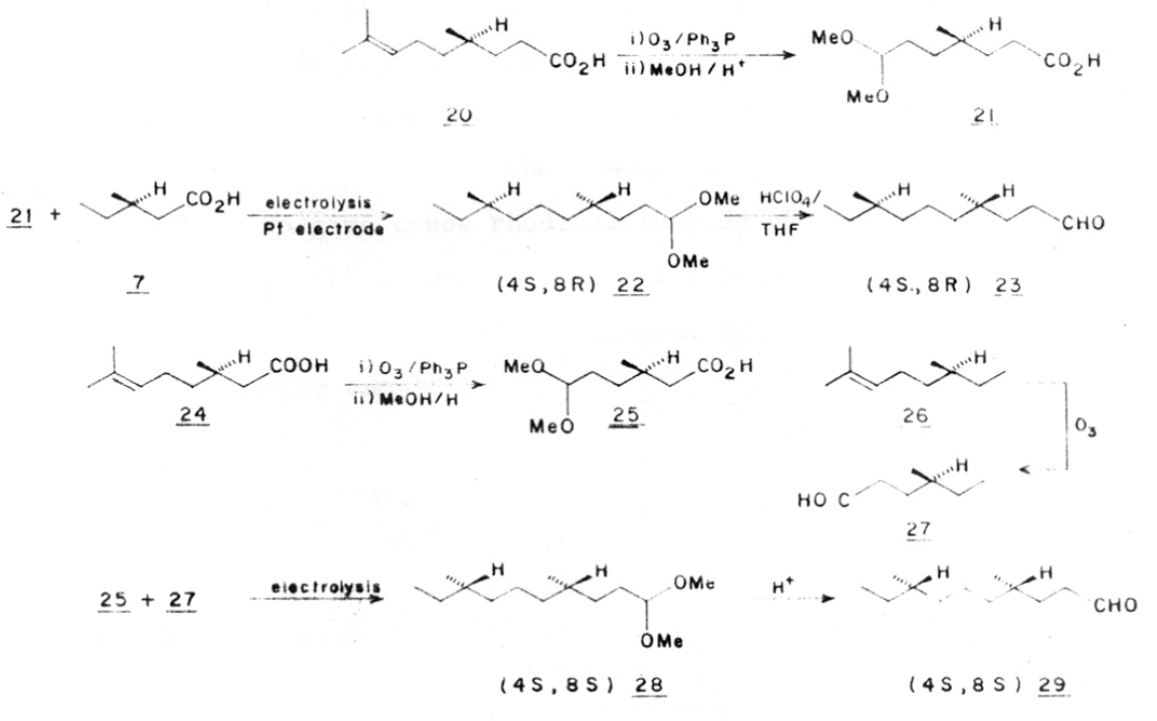
6

7 X = CO_2H, 8 X = SPh
9 X = I , 10 X = SO_2Ph

CHART I (Contd.)

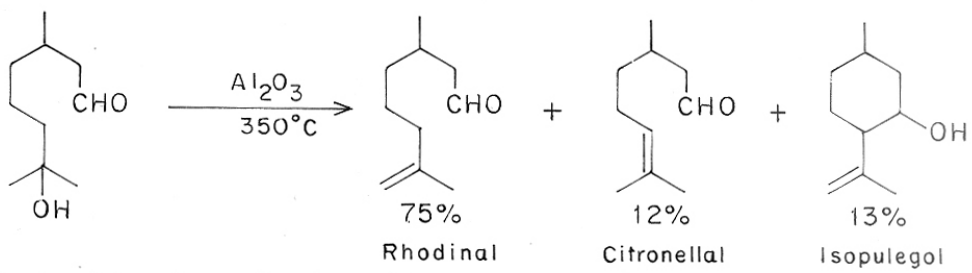


SYNTHESIS OF (4S,8R) AND (4S,8S) 4,8-DIMETHYLDECANAL



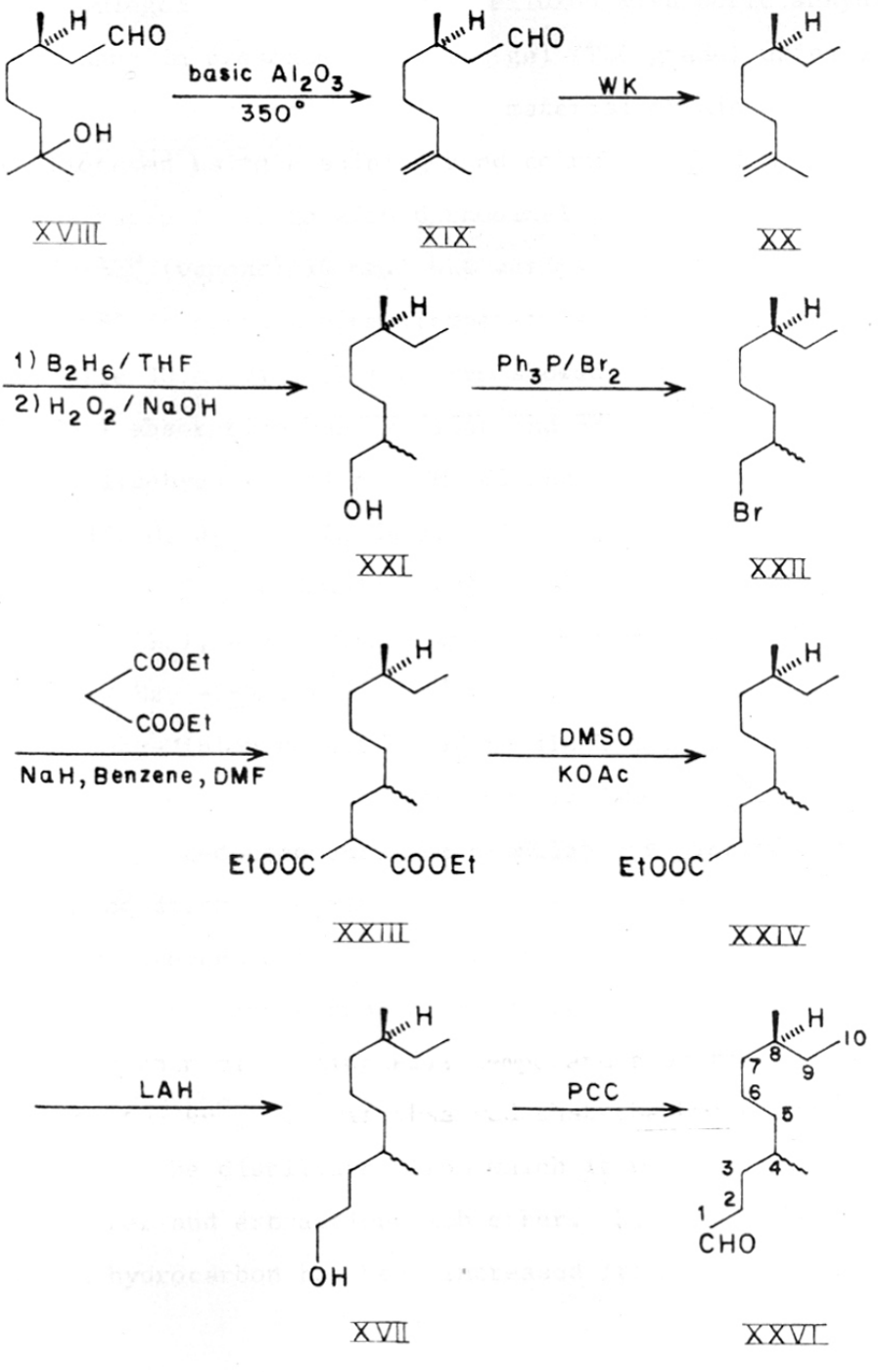
In this part of the thesis, the synthesis of 4(RS), 8(S) dimethyl decanal from rhodinal, by a simple and elegant route has been described. Rhodinal, a C-10 monoterpene possess most of the favourable structural features, such as, 8-carbon chain, 3(R)-methyl, 7-methyl. The only task was to add a C-2 unit at the appropriate place to achieve the synthesis. In our scheme very good yields of 80% and above were obtained in each and every step, with adequate purity of the intermediate compounds (Scheme I).

The rhodinal required for our synthesis, was prepared by thermal dehydration of commercial 7-hydroxy citronellal (XVIII), over alumina (basic, Grade I), at 350° by a reported procedure[20]. Water was separated from the thermally dehydrated product and distilled to give crude rhodinal (b.p.55-60°/10 mm), which according to GLC showed the following composition, rhodinal, 75%; citronellal, 12% and isopulegol, 13% (by comparison with authentic samples)



The residue from the distillation consisting mainly of hydroxy citronellal, was recyclced for the dehydration purpose. In order to convert the citronellal, present in the crude rhodinal

SCHEME I


H
CHO
OH
basic Al_2O_3
350°
H
CHO
WK
H
XVIII
XIX
XX
1) B_2H_6 / THF
2) H_2O_2 / NaOH
H
OH
Ph_3P/Br_2
H
Br
XXI
XXII
COOEt
COOEt
NaH, Benzene, DMF
H
EtOOC
COOEt
DMSO
KOAc
H
EtOOC
XXIII
XXIV
LAH
H
OH
PCC
H
10
8
7
9
6
5
3
4
2
1
CHO
XVII
XXVI

to isopulegol, the mixture was refluxed with boric anhydride in toluene in presence of silica gel (TLC grade), using a Dean Stark water separator. The material obtained was fractionated using a spining band column (1 feet high, reflux ratio 18:1) to afford rhodinal (XIX), in pure state, b.p.55-61° (vapour)/10 mm. GLC analysis showed its purity to be 98% on carbwaxcolumn; temperature, 150°; carrier gas, N_2; flow rate 30 ml/min; IR spectrum showed strong methylenic ($C=CH_2$) absorption band at 1640 and 885 cm^{-1} and 1730 and 2760 due to aldehyde function; PMR (80 MHz, $CDCl_3$) signals at: 0.91 (3H, d, J=5 Hz, C_3-CH_3), 1.34 (5H, m, C_3, C_4 and C_5 protons), 1.7 (3H, s, CH_3 on double bond), 1.94 (4H, m, C_2-CH_2 and allylic -CH_2), 4.7 (2H, m, vinylic protons) and 9.7 (1H, t, J=1.7 Hz, -C<u>H</u>O).

Huang-Minlon reduction of rhodinal has been reported[20] to give in 60% yield the expected 2,6-dimethyl oct-1-ene (XX). In the reported procedure the reaction was carried out in refluxing diethylene glycol for 6 hr. By slight modification of above procedure i.e. by heating rhodinal with hydrazine hydrate, potassium hydroxide in diethylene glycol at 130° for 2 hr and then distilling, till temperature of the contents reaches to 200°, it was observed that the hydrocarbon was mostly in the distillate, from which it was isolated by dilution with water and extraction with ether. By this method the yield of the hydrocarbon has been increased from 60% to 94%. The

hydrocarbon was further purifiedby distillation,b.p.156° (vapour)/740 mm. It showed IR bands at: 1645, 885 ($C=CH_2$) and PMR signals at: 0.89 (6H, m, methyls at C_6 and C_7), 1.25 (7H, m, methylene and methine protons), 1.66 (3H, s, vinyl methyl), 1.91 (2H, m, allylic CH_2) and 4.6 (2H, s, $C=C\underline{H}_2$).

In situ hydroboration of 2,6-dimethyl-1-octene (XX), in dry tetrahydrofuran,as per the known procedure[21], gave 2,6-dimethyl-1-octanol (XX) in 92% yield. It showed IR band at: 3340 (-OH) and PMR (Fig. 1) signals at: 0.8-0.93 (9H, m, CH_3 protons), 1.1-1.4 (10H, m, methylene and methine protons), 2.91 (1H, s, exchangable with D_2O, -OH proton) and 3.36 (2H, d, J=5 Hz, $C\underline{H}_2OH$).

Octanol XXI,on treatment with triphenylphosphine dibromide under nitrogen in dry methylene chloride gave corresponding bromide (XXII). IR spectrum showed the absence of band due to -OH; PMR signals at: 0.88-1 (9H, m, methyls), 1-1.72 (10H, br m, methylene and methine protons) and 3.31 (2H, d, J=5 Hz, $C\underline{H}_2Br$); MS: m/z, 220 (M^+), 222 (^{81}Br).

Alkylation of diethyl malonate with bromide (XXII), was attempted under different conditions. No alkylation was evident (TLC), by using sodium hydride in benzene alone, even after 24 hr of stirring at room temperature and/or 20 hr of refluxing. So, the condition of alkylation of diethyl malonate with XXII, has been optimised, so as to ensure (a) high yield of monoalkylated product (b) to reduce or avoid

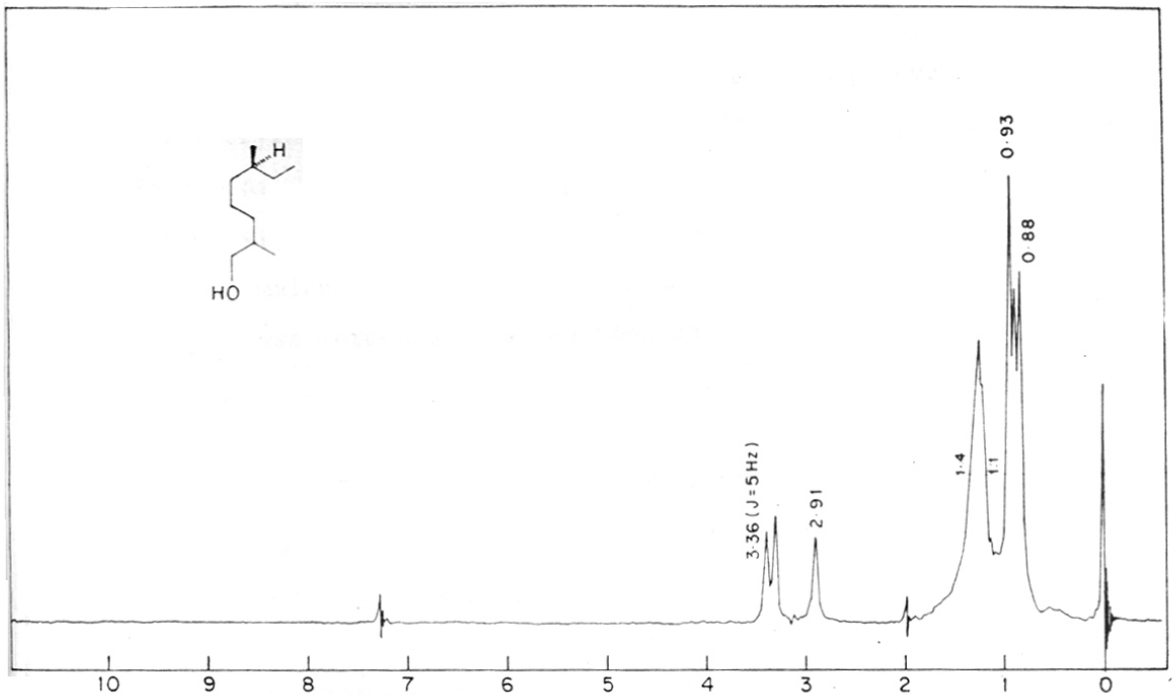


FIG. 1. 2,6-DIMETHYL-1-OCTANOL, XXI

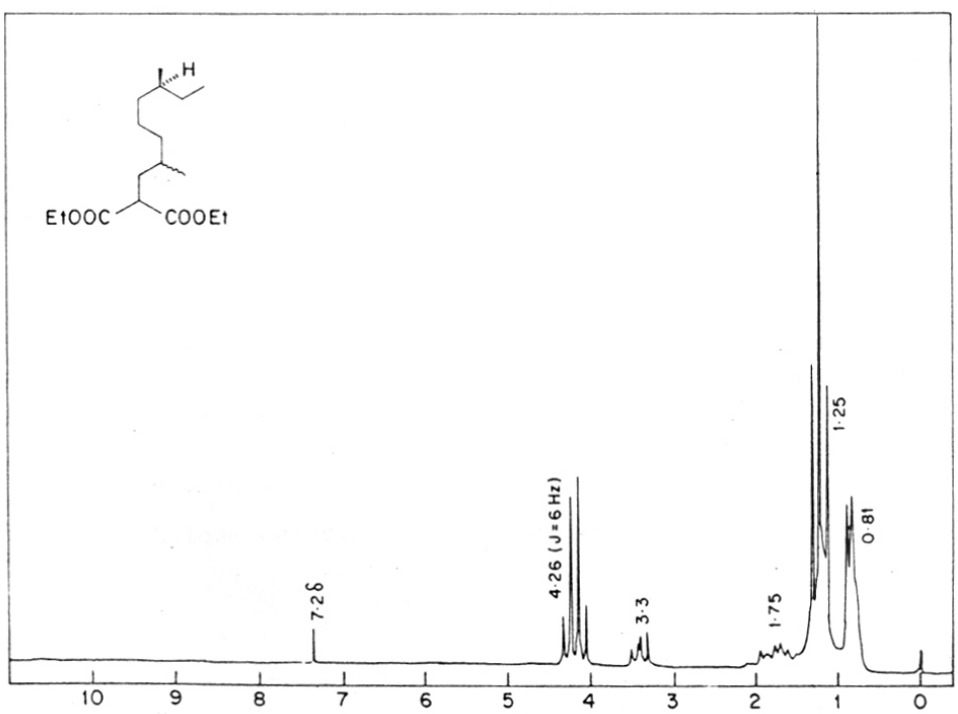


FIG. 2. ETHYL 2-CARBOETHOXY-4,8-DIMETHYL DECANOATE, XXIII

the formation of unwanted possible dialkylated product. After trying various combinations of benzene and dimethyl formamide, the ratio 1:1 was found to be best suited for higher yield (88%) and smooth reaction, for the alkylation of diethyl malonate with sodium hydride as the base. No dialkylated product was formed in the reaction under the conditions employed. Monoalkylated product (XXIII), showed IR bands at: 1750, 1738 (ester C=0) and PMR (Fig. 2) signals at: 0.81 (9H, br d, methyls), 1.25 (6H, t, J=6 Hz, $COOCH_2\underline{CH}_3$ and methylenes), 1.75 (2H, m, C_4- and C_8 protons), 3.3 (1H, t, J=5.5 Hz, C_2-H) and 4.16 (4H, q, J=6 Hz, $COO\underline{CH}_2CH_3$).

Refluxing of ethyl 2-carboethoxy-4,8-dimethyldecanoate (XXIII), in DMSO containing potassium acetate, afforded the decarboethoxylated[22] product (XXIV), in almost quantitative yield, purified by distillation, b.p.150°/10 mm. IR bands at: 1733 (ester C=0); PMR (Fig. 3) signals at: 0.86 (9H, br s, methyls), 1.1-1.74 (15H, m, $COOCH_2\underline{CH}_3$, methylene and methine protons), 2.25 (2H, t, J=5 Hz, C_2-CH_2) and 4.08 (2H, q, J=6 Hz, $COO\underline{CH}_2CH_3$).

Lithium aluminium hydride reduction of XXIV, gave XXV in 90% yield, as a TLC pure liquid; IR band at: 3330 (-OH); PMR (Fig. 4) signals at: 0.87 (9H, m, methyls), 1-1.65 (14H, m, methylene and methine protons), 1.75 (1H, s, exchangable with D_2O, -O<u>H</u>) and 3.64 (2H, t, J=5 Hz, $-\underline{CH}_2OH$).

Pyridinium chlorochromate oxidation of alcohol (XXV), in dry methylene chloride under nitrogen atmosphere gave 4,8-

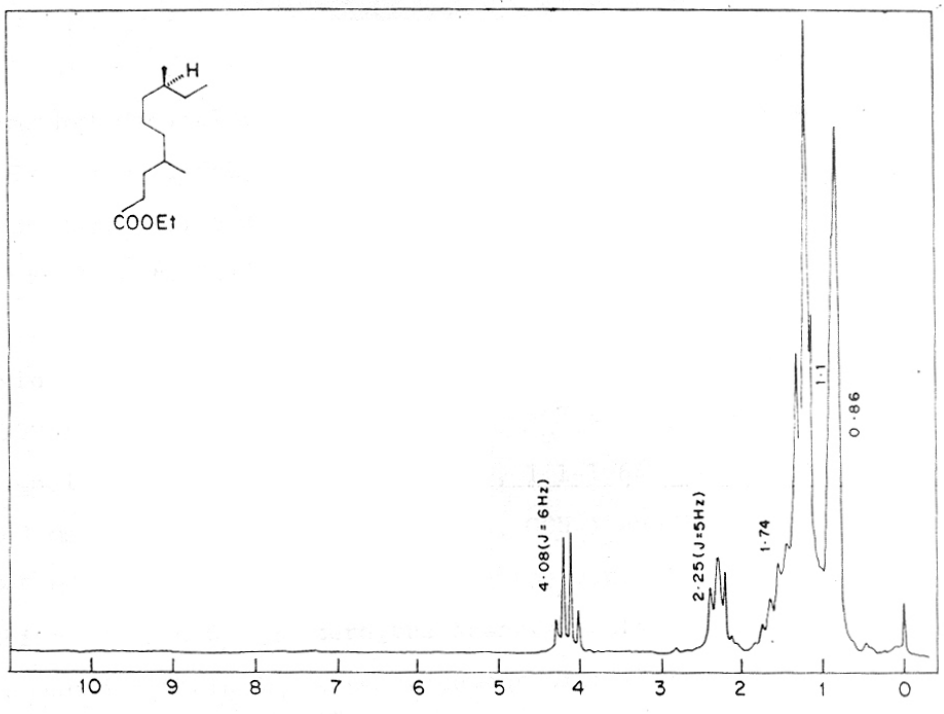


FIG.3. ETHYL 4,8-DIMETHYL DECANOATE, XIV

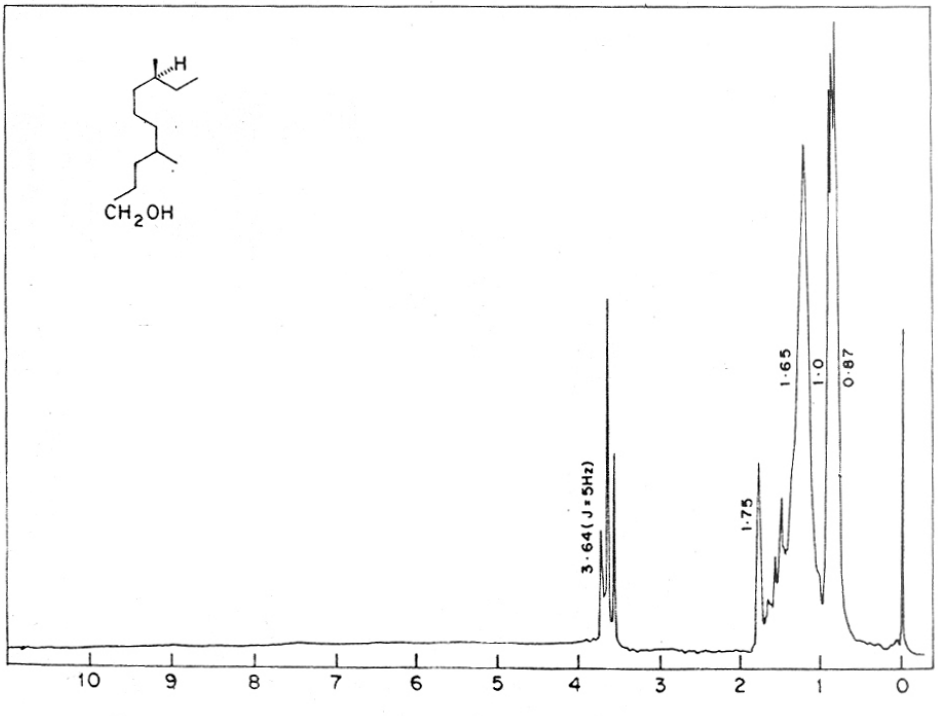
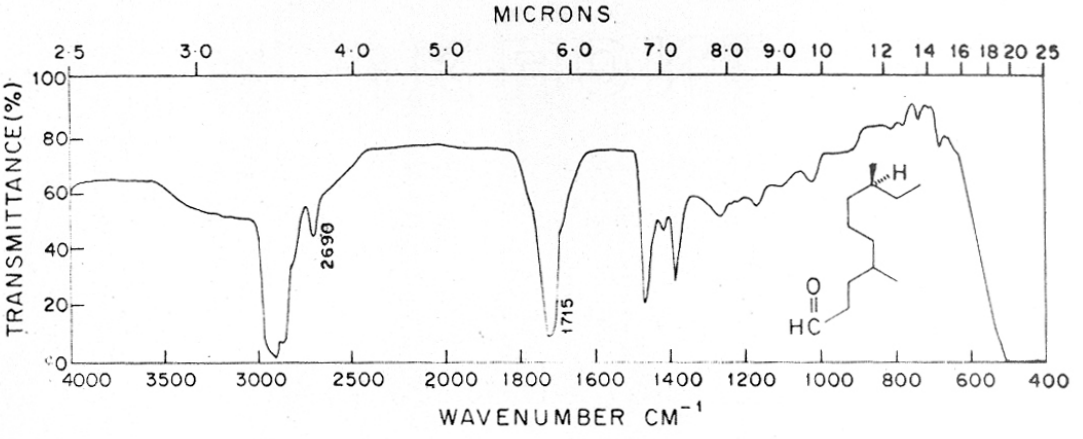
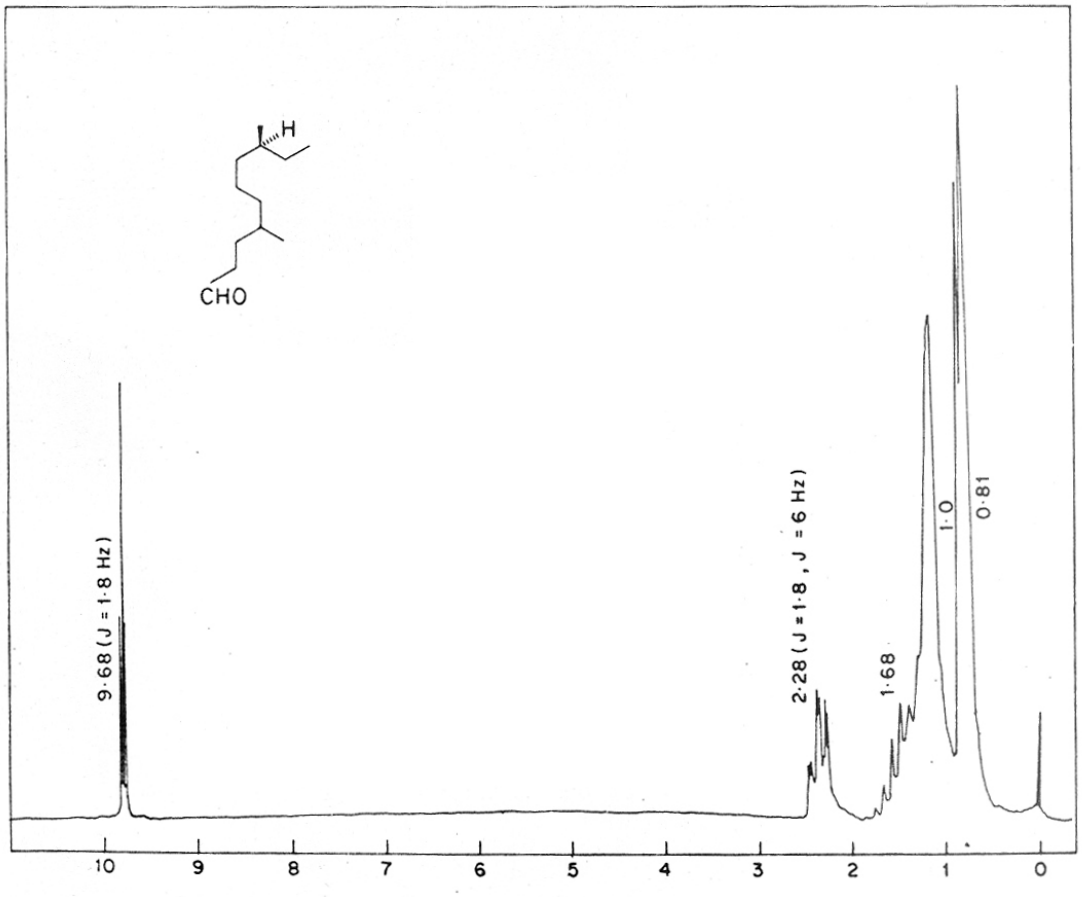


FIG. 4. 4,8-DIMETHYL DECAN-1-OL, XXV

dimethyl decanal (XVII), in 90% yield: IR (Fig. 5) bands at: 2690, 1715 (aldehyde); PMR (Fig. 6) signals at: 0.81 (9H, m, methyls), 1-1.68 (12H, m, methylene and methine protons), 2.28 (2H, dt, J_1=1.8 Hz, J_2=6 Hz, C_2-CH_2) and 9.68 (1H, t, J=1.8 Hz, C<u>H</u>O). As the aldehyde was susceptible to auto-oxidation, it was converted into its dimethyl acetal (XXVI, MeOH/H^+, 0^o, 24 hr), obtained as a liquid; $[\alpha]_D^{28}$ + 1^o (c, 2.3); PMR signals at: 0.76 (9H, m, methyls), 1.1-1.64 (14H, m, methylene and methine protons), 3.23 (6H, s, OC<u>H</u>$_3$) and 4.25 (1H, t, J=5 Hz, -C<u>H</u>$(OMe)_2$). Considering the contribution due to chiral centre C_4 as zero, the observed optical rotation for compound XXVI, is in close agreement with that reported for, S(+) 8-methyl decanal[23]



FIG·5· 4,8-DIMETHYL DECANAL, XVII



FIG·6· 4,8-DIMETHYL DECANAL, XVII

EXPERIMENTAL

Preparation of rhodinal (XIX):

7-Hydroxy citronellal (XVIII, 140 g, 0.81 mol), $[\alpha]_D^{25}$ + 9.7° was introduced at a rate of 100 g/hr at 350°, into a borosilicate glass column 70 cm long, 15 cm diameter, packed with 40 g of basic alumina. The reaction product was collected in a cooled reservoir under vacuum (100 mm), separated from water, dried and distilled. The fraction boiling at 65°(vapour)/1.5 mm, was composed mainly of rhodinal along with minor products viz. citronellal and isopulego. The above fraction was mixed with boric anhydride (1g), silica gel (TLC grade 1 g), toluene (300 ml) and refluxed for 1 hr at 130-135° using Dean-Stark unit for azeotropic removal of water. Removal of toluene followed by fractionation on a spinning band column of the residue, gave in the earlier fractions rhodinal (XIX, 85 g, 70%); b.p.69°(vapour)/2 mm; $[\alpha]_D^{25}$ + 9.6° (c, 1.6).

IR bands at: 2920, 2760, 1720, 1640, 1450, 1375 and 885 cm^{-1}.

2,6-Dimethyl-1-octene (XX):

Hydrazine hydrate (30 g of 85%) was added to a solution of rhodinal (XIX, 46 g, 0.3 mol), in diethylene glycol (300 ml). The temperature of the contents rose to 50°C, potassium hydroxide

pellets (32 g, 57 mmol), were then added and the reaction mixture refluxed for 2 hr on a heating mantle. It was then distilled, till the reaction temperature reaches 200°C. The aqueous layer was separated, organic layer washed with water, brine dried and purified by distillation, (39 g, 94%); b.p.165°/714 mm, $[\alpha]_D^{25}$ + 6.5° (c, 2.3) and identified as 2,6-dimethyl-1-octene (XX): MS: m/z, 140 (M^+).

Analysis:

Found: C, 85.3; H, 14.2; $C_{10}H_{20}$

requires: C, 85.7; H, 14.3%.

IR bands at: 3030, 2975, 1645, 1450, 1375 and 885 cm^{-1}.

2,6-Dimethyloctane-1-ol (XXI):

In a one litre four necked round bottom flask, fitted with a reflux condensor carrying a calcium chloride guard tube, half moon stirrer, a dropping funnel and an inlet for nitrogen, a mixture of sodium borohydride (5 g, 0.131 mol), dry and peroxide free tetrahydrofuran (200 ml) and octene (XX, 32 g, 0.228 mol), was taken. The contents were stirred and BF_3-etherate (20 ml), was added slowly during 4 hr, under dry nitrogen atmosphere. Stirring continued for another period of 12 hr and excess sodium borohydride was destoryed by careful addition of water. To the alkylborane thus formed was added 3N aqueous sodium hydroxide (100 ml), followed by dropwise addition of hydrogen peroxide (30%, 100 ml), during 5 hr,

maintaining the temperature at 25° through out. Stirring was continued for another 8 hr, after which organic layer was separated and the aqueous layer extracted with ether (100 ml x 3). Combined organic layer was washed with water, brine, dried and evaporated to give TLC pure alcohol (XXI, 34 g, 92%); MS: m/z, 158 (M^+).

Analysis:

Found: C, 75.4; H, 14.1; $C_{10}H_{22}O$

requires: C, 75.9; H, 14.0%.

IR bands at: 3340, 2940, 1455, 1375 and 1030 cm^{-1}

1-Bromo-2,6-dimethyl octane (XXII):

To a stirred and cooled solution of triphenyl phosphine (1.3 g, 5 mmol), in dry methylene chloride (10 ml), under nitrogen, a solution of bromine (0.3 ml), in carbon tetrachloride (3 ml), was added slowly during 15 min. Stirring was continued for 30 min. after which, octanol (XXI, 0.84 g, 5.3 mmol), in methylene chloride (2 ml), was added slowly. Reaction mixture was allowed to attain room temperature and left overnight. Excess of solvent was stripped off and the residue was repeatedly extracted with hot pet.ether. Evaporation of pet.ether gave TLC pure bromide (XXII, 0.98 g, 84%), purified by distillation, b.p.135°(vapour)/95 mm; MS: m/z, 221 (M^+), 223 (^{81}Br).

Analysis:

Found: C, 53.6; H, 9.7; Br, 36.1; $C_{10}H_{22}Br$

requires: C, 53.8; H, 9.8; Br, 36.3%.

IR bands at: 2940, 1450 and 1370 cm^{-1}.

Ethyl 2-carboethoxy-4,8-dimethyl decanoate (XXIII):

To a well stirred suspension of sodium hydride (1.44 g, 65 mmol), in benzene (50 ml), and DMF (50 ml), diethyl malonate (9.6 g, 60 mmol), was added slowly under nitrogen atmosphere and stirring continued for additional 2 hr. The bromide (XXII, 13 g, 58 mmol), was then added to the above suspension and the reaction mixture was heated in an oil bath at 100° for 4 hr with stirring. Reaction mixtue was cooled, diluted with water and extracted with benzene (50 ml x 3). Evaporation of benzene layer gave XXIII (15.5 g, 88%), b.p.135°/2 mm; MS: m/z, 300 (M^+).

Analysis:

Found: C, 67.6; H, 10.6; $C_{17}H_{32}O_4$

requires: C, 68.0; H, 10.7%.

IR bands at: 2960, 2940, 1750, 1738, 1460, 1370, 1350, 1240 and 930 cm^{-1}.

Ethyl 4,8-dimethyl decanoate (XXIV):

A solution of XXIII (1.5 g, 5 mmol), in DMSO (20 ml), containing potassium acetate (1.14 g, 11 mmol) and water (0.18 g, 10 mmol), was refluxed for 6 hr, cooled, diluted with water and extracted with ether (50 ml x 3). The combined organic layer was washed with water, brine, dried and concentrated to give XXIV (1.09 g, 98%), b.p. 150°/10 mm; MS: m/z, 228 (M^+).

Analysis:

Found: C, 77.2; H, 8.4; $C_{14}H_{28}O_2$

requires: C, 77.0; H, 8.3%.

IR bands at: 2960, 2900, 1733, 1455, 1370, 1250, 1170 and 1030 cm^{-1}.

4,8-Dimethyl decane-1-ol (XXV):

To a stirred and cooled suspension of lithium aluminium hydride (0.38 g, 10 mmol), in dry ether (75 ml), XXIV (2.2 g, 9.6 mmol), in dry ether (10 ml), was added slowly during 30 min and stirred overnight. Reaction mixture was cooled, excess of lithium aluminium hydride destoryed by careful addition of 1 ml water, 1 ml 10% sodium hydroxide, followed by addition of 3 ml of water, when a solid residue separated. Ether was decanted and the residue extracted with ether (40 ml x 3). Combined ether layer was washed with water, brine, dried and evaporated to give TLC pure XXV (1.6 g, 90%), as a liquid; $[\alpha]_D^{25}$ + 1.9° (c, 1.4); MS: m/z, 186 (M^+).

Analysis:

Found: C, 70.9; H, 12.6; $C_{12}H_{26}O$

requires: C, 71.2; H, 12.9%.

IR bands at: 3330, 2940, 2910, 1455, 1372 and 1050 cm^{-1}.

4,8-Dimethyl decanal (XVII):

To a stirred suspension of pyridinium chlorochromate (1.8 g, 5.3 mmol), in dry methylene chloride under nitrogen, a solution of XXV (0.5 g, 2.6 mmol), in dry methylene chloride

(2 ml), was added and stirring continued for 1 hr. After which dry ether (50 ml) was added, supernatant liquid decanted, from the black gummy mass. The residue was washed 3 times with 25 ml portion of dry ether. Combined organic layer was passed over florosil and solvent removed by distillation. The crude oil was purified by chromatography over silica gel (5 g) and the fraction eluted with 1:1 mixture of pet.ether-benzene, gave TLC pure aldehyde (XVII, 0.435 g, 88%); $[\alpha]_D^{25}$ + 0.93° (c, 1.8).

IR bands at: 2900, 2690, 1715, 1460 and 1375 cm^{-1}.

Since the aldehyde (XVII) was suspectible to autooxidation, it was converted into dimethyl acetal as follows. The aldehyde (XVII), was dissolved in methanol (10 ml, containing 0.2 ml of concentrated hydrochloric acid) at 0° and kept for 24 hr. It was then diluted with water and extracted with ether (40 ml x 3). The ether layer was washed with water, brine, dried and evaporated to give dimethyl acetal (XXVI), as a liquid; $[\alpha]_D^{25}$ + 1°(c, 2.3).

Analysis:

Found: C, 72.7; H, 13.0; $C_{14}H_{30}O_2$

requires: C, 73.0; H, 13.1%.

IR bands at: 2960-2840, 1450, 1365, 1190, 1120 and 1050 cm^{-1}.

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