CHAPTER-II

BIOMIMETIC CYCLISATION OF ACYCLIC ALLYLIC TERPENE DIETHYL PHOSPHATE ESTERS IN SOLID MATRICES

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ABSTRACT

Experimental parameters governing π- electrons participation during cyclisation of acyclic terpene allylic diethyl phosphate esters, on active alumina, have been investigated. Cyclisations of geranyl-, neryl-, (E,E)-farnesyl-, (Z,E)-farnesyl- and (E,E,E)-geranylgeranyl diethyl phosphate esters on active alumina are reported and the reaction products are characterised in each case.

In all these series of experiments (mono-, sesqui- and diterpene), it is observed that (Z)-isomer gives a relatively higher proportion of cyclisation products (from π -electron participation) than the (E)-isomer. The mechanistic pathways of these reactions are discussed.

INTRODUCTION

For more than 30 years, the Biogenetic Isoprene Rule has served as a central and unifying hypothesis for the rationalization of terpenoid biogenesis and the design and interpretation of biosynthetic experiments[1]. As initially formulated by Ruzicka and elaborated subsequently by several groups of authors[2], intramolecular electrophilic cyclization of simple acyclic substrates geranyl pyrophosphate, farnesyl pyrophosphate and geranylgeranyl pyrophosphate followed by appropriate carbocation transformations, including rearrangements, deprotonations, and further cyclizations, can account for the formation of enormous variety of cyclic monoterpenes, sesquiterpenes, and diterpenes respectively.

In order to explore such intramolecular cyclization and in view of the cardinal importance of geranyl, farnesyl and geranylgeranyl cations in mono-, sesqui- and diterpene biogenesis, it was of interest to study the cyclization reactions of geranyl, neryl, 2(Z), 6(E)- and 2(E), 6(E)-farnesyl and (E,E,E)-geranylgeranyl diethyl phosphate esters (these diethyl phosphate esters were used as models for pyrophosphate esters in biological processes), wherein one could visualize the generation of the corresponding

"carbocations", and to ascertain the fate of these ions under the non-enzymatic biomimetic reaction conditions. The present chapter presents the results of these investigations.

The individual steps in biogenetic scheme may be designated as initiating, propagating and terminating[3]. From the figure in the 1st Chapter, we observe two types of initiating reactions.

(i) Protonation of C=C or epoxides and

(ii) Pyrophosphate ionization

The biogenesis of the more abundant group of monocyclic and bicyclic monoterpene proceeds through 3 main stages.

I. Cyclization of an acyclic precursor to the menthane skeleton (see Fig. 1)

II. Cyclization to the pinanes and rearrangements

III. Cyclization to the thujanes

Cyclization of acyclic to monocyclic monoterpene is long known. Since both neryl and linaloyl pyrophosphates[4] (or some equivalent species) have been seriously considered as likely acyclic precursors to this family of monoterpenes, it is appropriate to examine first the cationic reactions of these two compounds. A great many investigations have shown that, while geranyl derivatives undergo substitution

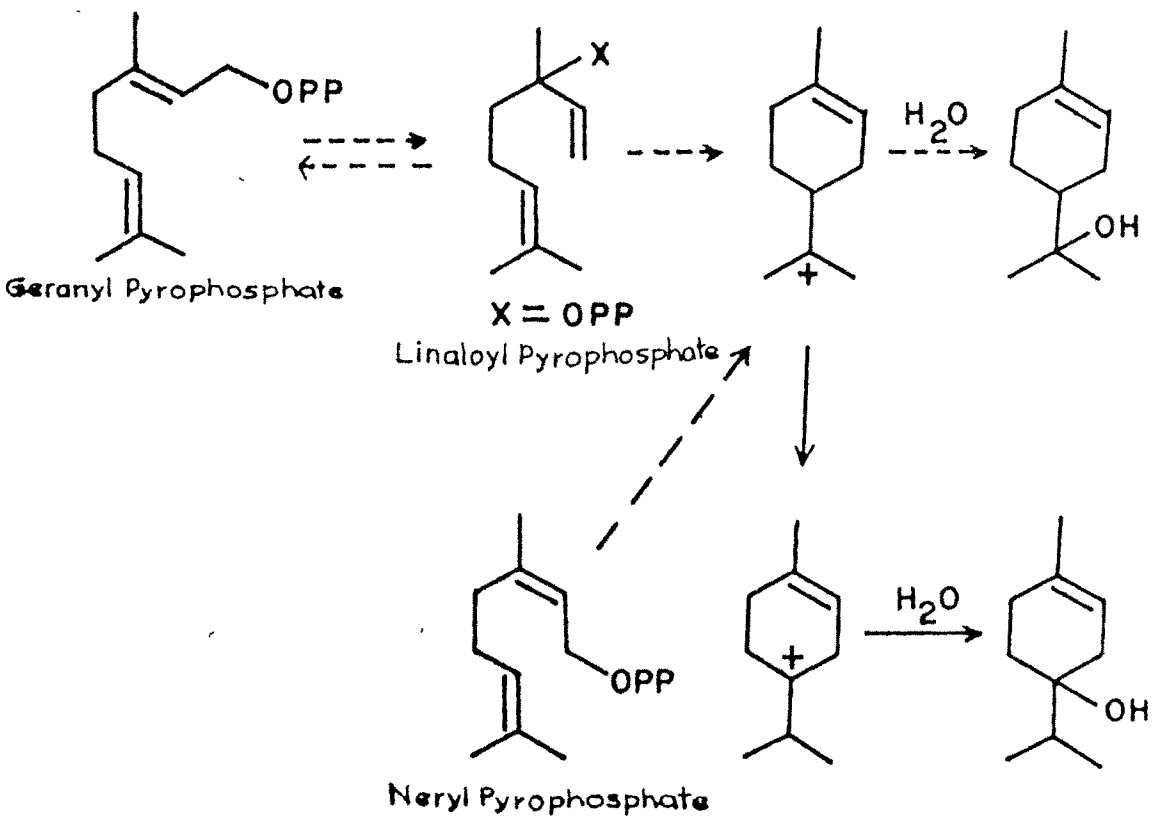

OPP
Geranyl Pyrophosphate
X
X = OPP
Linaloyl Pyrophosphate
H_2O
OH
OPP
Neryl Pyrophosphate
H_2O
OH

FIG.-1

reactions in a fashion typical of an allylic substrate, both neryl and, less efficiently, linaloyl derivatives lead to cyclic products such as α-terpineol, and its dehydrated relatives limonene, and terpinolene[5-12]. A thorough examination of both rates and products in the hydrolysis of pyrophosphates established that linaloyl and neryl pyrophosphates react predominantly by distinct pathways[5-7]. The higher yield of cyclic products from neryl pyrophosphate (NPP) is attributed to anchimeric assistance (an estimated rate enhancement of 2.5 times in the case of NPP) by the 6,7-double bond in the ionization step. Linaloyl pyrophosphate evidently reacts in part from a transoid conformer to give geraniol and from a cisoid conformation to give nerol and cyclic products.

Zeitschel[10] inferred the cis-configuration of nerol from the fact that it cyclises 9 times faster to terpin hydrate via α-terpineol in dil.H_2SO_4 than geraniol which is of trans-configuration. There is considerable evidence for the configurational stability of allylic carbocation[13], and hence interconversion seems improbable. However, in 1967 Osvaldo Cori et al.[14] reported the acidcatalyzed hydrolysis of neryl and geranyl pyrophosphates. They showed that the rate of isomerisation of nerol to the cyclic α-terpineol is more than 18 times greater than the corresponding isomerisation of geraniol. They further observed that the rate of transformation of geraniol into the open chain linalool is

greater than the analogous isomerisation of nerol. These results are in good agreement with that of Zeitschel[10]. They further shown that the acid catalyzed hydrolysis of neryl pyrophosphate to form α-terpineol is 50 times faster than the (trans)-isomer (geranyl pyrophosphate). These observations lend some support to the working hypothesis that the neryl pyrophosphate may be the more probable precursor of cyclic monoterpenes in biological systems.

In 1967. W. Rittersdorf et al.[5,6] reported the cyclization of neryl and linaloyl phosphate esters during their solvolysis reaction and the same authors[7] in 1968, reported the probable mechanism of such cyclization reactions. They showed that cyclization of phosphate esters of nerol and linalool occurs via an anchimerically assisted nucleophilic attack of the 6,7-double bond on C_1 of the acyclic moiety and excluded the possibility of internal return in neryl carbonium ions, after conducting the experiments by O^{18} labelling.

Halley, Miller and Wood[15] have studied the decomposition of geranyl, neryl diphenyl phosphates in anhydrous ether as model reaction for the biosynthesis of monoterpenes. They have observed that in both these cases cyclic products are formed (apart from the usual elimination products), although the amount of cyclized products was more in the case of cis-isomer (nerol). The authors[15] suggest that geranyl

diphenyl phosphate by internal return gives linaloyl diphenyl phosphate which cyclises with ease although they are unable to detect any linaloyl diphenyl phosphate in the reaction mixture. These authors[29] have further shown that geranyl chloride on alkaline hydrolysis did not give any cyclised products since the internal return mechanism is not possible in the case of geranyl chloride.

In 1972, C.A. Bunton et al.[16] reported the deuterium isotope effects in cyclization of monoterpenoids. These authors explained that the ionization of both geranyl and neryl derivatives can be assisted by allylic participation, but from the geometry of neryl this participation is at the expense of π-participation from the isopropylidene double bond. These authors[16] further showed that the major solvolysis products of neryl and geranyl chlorides in acetone:water (70:30 v/v) at 25°, are similar to those found for phosphate ester solvolysis. They observed that the products change markedly when 3.5 M $LiClO_4$ is added (values in parenthesis) Table-1). Elimination increases and geranyl chloride gives a large amount of cyclic products. These authors suggested that perchlorate ion probably forms an ion pair with geranyl cation and increases its life time so that it can be converted to neryl cation. The same authors[17] in 1979 reported the hydrolysis and methanolysis of chlorides, phosphates and pyrophosphates of monoterpenoids (ex. geranyl and neryl).

TABLE-1 : MAJOR PRODUCTS FROM SOLVOLYSIS OF CHLORIDES(a)

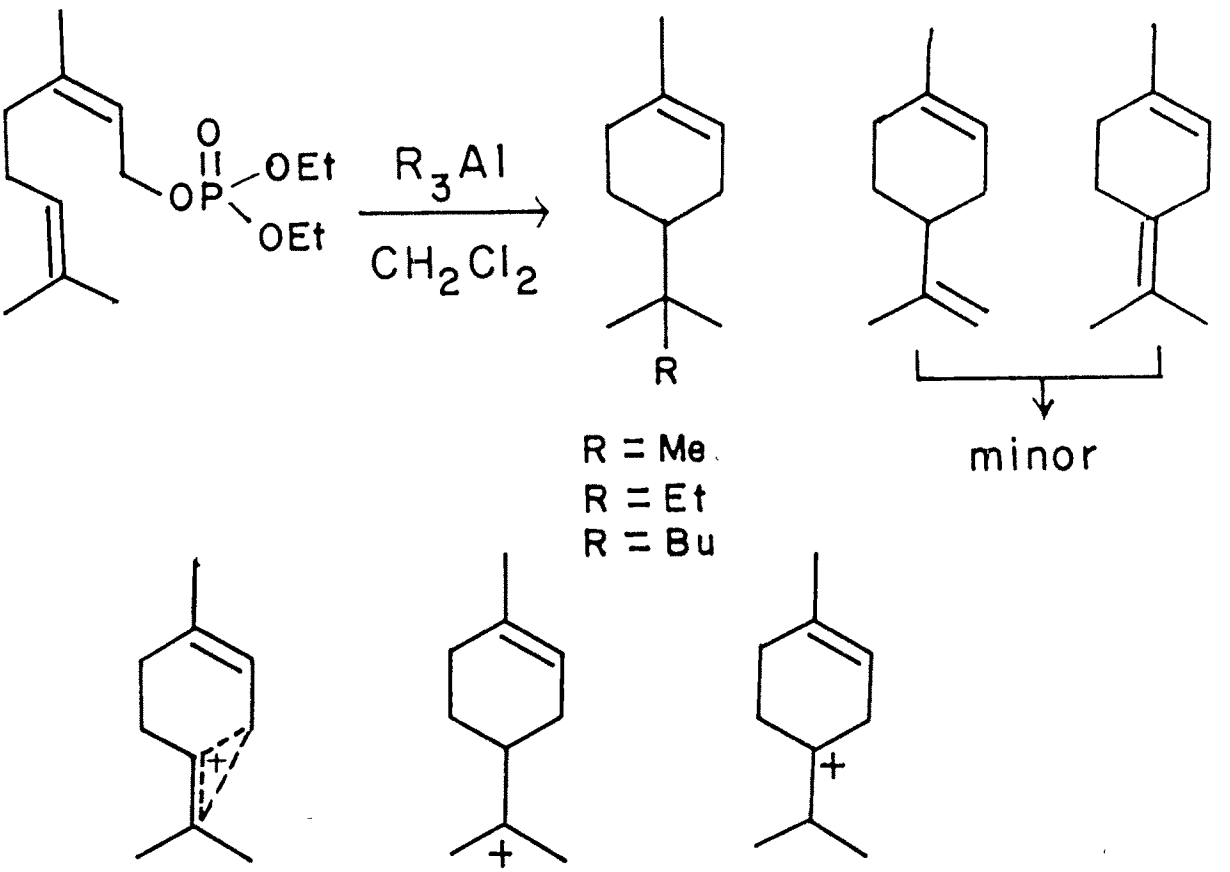
	Neryl	Geranyl
Open chain olefins	1 (10)	3 (50)
Cyclic olefins	1 (29)	4 (29)
linalool	17 (1)	70
nerol	3	-
geraniol	-	16
α-terpineol	78 (58)	6 (19)

(a) Mole % products at 25° in acetone:water 70:30 v/v. The cyclic olefins were limonene and terpinolene and the major open chain olefins was myrcene.

In 1972 K.L. Stevans et al.[18] reported the decomposition of geraniol in aq. oxalic acid. These authors found the formation of 23 identified products, most of which retain the oxidation level of geraniol and result from simple hydration and proton transfer reactions. They also found the formation of a large quantity of the reduced alcohol, citronellol along with cymenol, the oxidation product of α-terpineol, indicating that hydride ion transfer reactions play a major role in these terpene alcohol interconversions. These authors further showed that under similar conditions linalool decomposed to give essentially the same products as geraniol.

Kobayashi et al.[19] in 1976 reported the reaction of 2-fluoro pyridinium salt with geraniol and nerol as non-enzymatic biogenetic like cyclization to limonene. Robert L. Baxter et al.[20] in 1978 reported the formation of the various cyclic and acyclic products from the reaction of linalool, geraniol and nerol, and their acetates in aqueous citric and hydrochloric acids at 24°C. Mark C. Whiting et al.[21] in 1976 studied the acetolysis of 2,4-dinitrophenolates of nerol, geraniol, linalool, and α-terpineol. In 1976, Y. Kitagawa et al.[22] have reported the alkylative cyclization of neryl diethyl phosphate with organo aluminium reagents. When neryl diethyl phosphate reacted with trimethyl aluminium, these authors observed

the predominant formation of 4-tert-butyl-1-methyl cyclohexene, in addition to limonene and terpinolene, resulting from the direct alkylation of non-classical carbonium ions or an alkylation of classical terpinyl ion (Fig. 2). These authors further shown that when the same procedure applied to geranyl diethyl phosphate led to (cross coupling in a stereospecific manner) nucleophilic substitution with methyl groups by replacing $-O\ P(O)(OEt)_2$. (Fig. 2).


OEt
OP
OEt
R3Al
CH2Cl2
R
R = Me
R = Et
R = Bu
minor

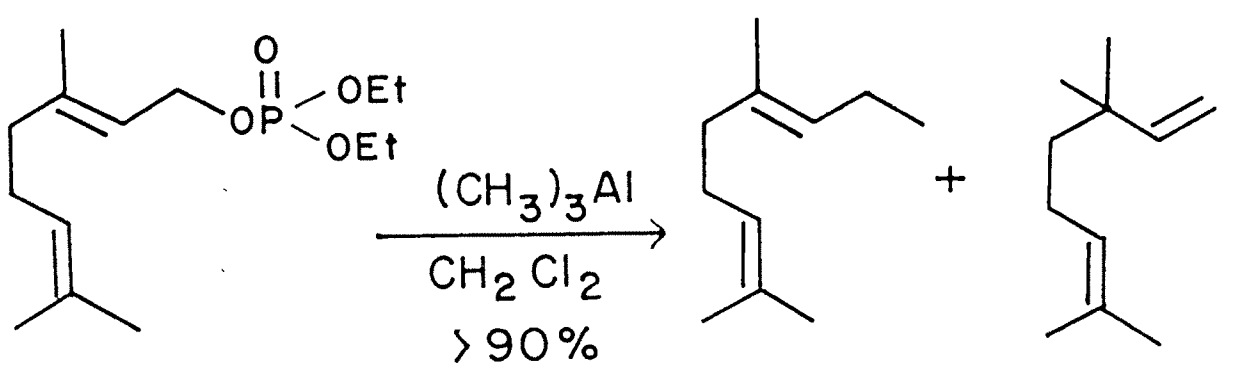
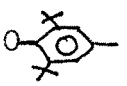

OEt
OP
OEt
(CH3)3Al
CH2Cl2
> 90%
+
9 : 1

FIG.

These authors[22] further shown that certain organo aluminium reagents such as R_2AlX, when treated with geranyl and neryl diethyl phosphate esters in hexane solution, where the O $PO(OEt)_2$ group is replaced by X group without affecting both olefinic bonds in any sense of the words. A dramatic change in the reaction course was observed by these authors, when the same reaction was carried out in CH_2Cl_2 or in THF, instead of hexane, yielded a mixture of limonene and terpinolene (Table-2). The substitution products account for a negligible fraction. The limonene/terpinolene ratios are dependent on the reagents, solvents, and reaction conditions.

These authors explained the formation of cyclised products in the reactions of geranyl diethyl phosphate with excess of TIBAO/THF, in terms of intermediacy of the "free" allylic carbonium ion in this reagent, solvent system.

TABLE-2 : RELATIVE YIELDS OF LIMONENE AND TERPINOLENE IN THE REACTION OF NERYL DIETHYL PHOSPHATE WITH VARIOUS ORGANO ALUMINIUM COMPOUNDS

Reagent	Solvent	Yield[a] %	Limonene: Terpinolene
TIBAO[b]	CH_2Cl_2	75	88:12
Me_2AlOPh	CH_2Cl_2	69	86:14
$(Me_2Al)_2NPh$	CH_2Cl_2	71	80:20
Me_2Al NHPh	CH_2Cl_2	62	79:21
TIBAO[b]	THF	80	63:37
TIBAO[b]	THF[c]	75	63:37
i-BuAl-O- 	hexane	50	99:1

(a) Limonene-terpinolene mixture (b) Tetra isobutyl dialuminoxane (i-Bu_2Al-O-Al i-Bu_2) (c) Geranyl diethyl phosphate was used instead of neryl diethyl phosphate.

Very recently Hisashi Yamamoto et al.[23] in 1983, reported the first asymmetric synthesis of limonene in a biogenetic manner, from the reaction of biphenol mononeryl ether and bimaphthol mononeryl ether with organo aluminium reagents (eg. AlR_3, DIBAH, etc.).

It is demonstrated by these authors that organo aluminium reagents, which in addition to their high oxyphilicity, are endowed with ambiphilic character, have a pivotal role in biomimetric terpene syntheses.

H. Nozaki et al.[24] im 1978 reported the cyclization of nerol to terpinyl chloride or bromide in the presence of TiX_4-PhNHMe (1:1) complex (X=Cl, Br) which would belong to the same category of combined Lewis acid-base reagents as organo aluminium reagents mentioned earlier. Here, in contrast to the organo aluminium reactions, terpinyl cation is stabilized by halide ion-uptake rather than by proton loss. These authors further shown that, anologous treatment of geraniol with each of the above complexes produced the respective geranyl halides quantitatively. Recently from our laboratories, Sukh Dev et al.[25] reported the photo chemical transformations of geranyl and neryl iodides, leading to the formation of acyclic and cyclic monoterpene hydrocarbons.

In sesquiterpene series, the biogenesis of monocyclic sesquiterpenes begins in a manner analogous to the menthanes in monoterpenes. In these series, the various important modes of ring closure in the case of typical substrate, farnesyl pyrophosphate are depicted in Fig. 3. Closure to six membered ring requires a cis-configuration of the terminal double bond (about C_1-C_4) in the acyclic precursor (ie) either (cis), (trans)-farnesyl pyrophosphate, or alternatively (trans),(trans)-farnesyl pyrophosphate could serve as a predecessor provided it subsequently undergoes allylic isomerisation to nerolidol derivative. C.D. Gutsche et al.[26] in 1968, reported the acid catalyzed cyclization of farnesol and nerolidol in formic acid and they observed that nerolidol reacts somewhat more rapidly than farnesol and cis,trans- and trans,trans-farnesols react at the same rate and give the same ratio of products. They further found that reaction rate falls off rapidly with increased water content of the formic acid. Other chemically induced cyclization of farnesols, nerolidols and their derivatives were reported by Ruzicka et al.[27] in 1925 and Y. Ohta et al.[28] in 1972.

H.C. Wood et al.[29] have studied the decomposition of cis,trans- and trans,trans-farnesyl diphenyl phosphates in anhydrous ether as model reactions for the biosynthesis of sesquiterpenes. They have observed that in both these cases

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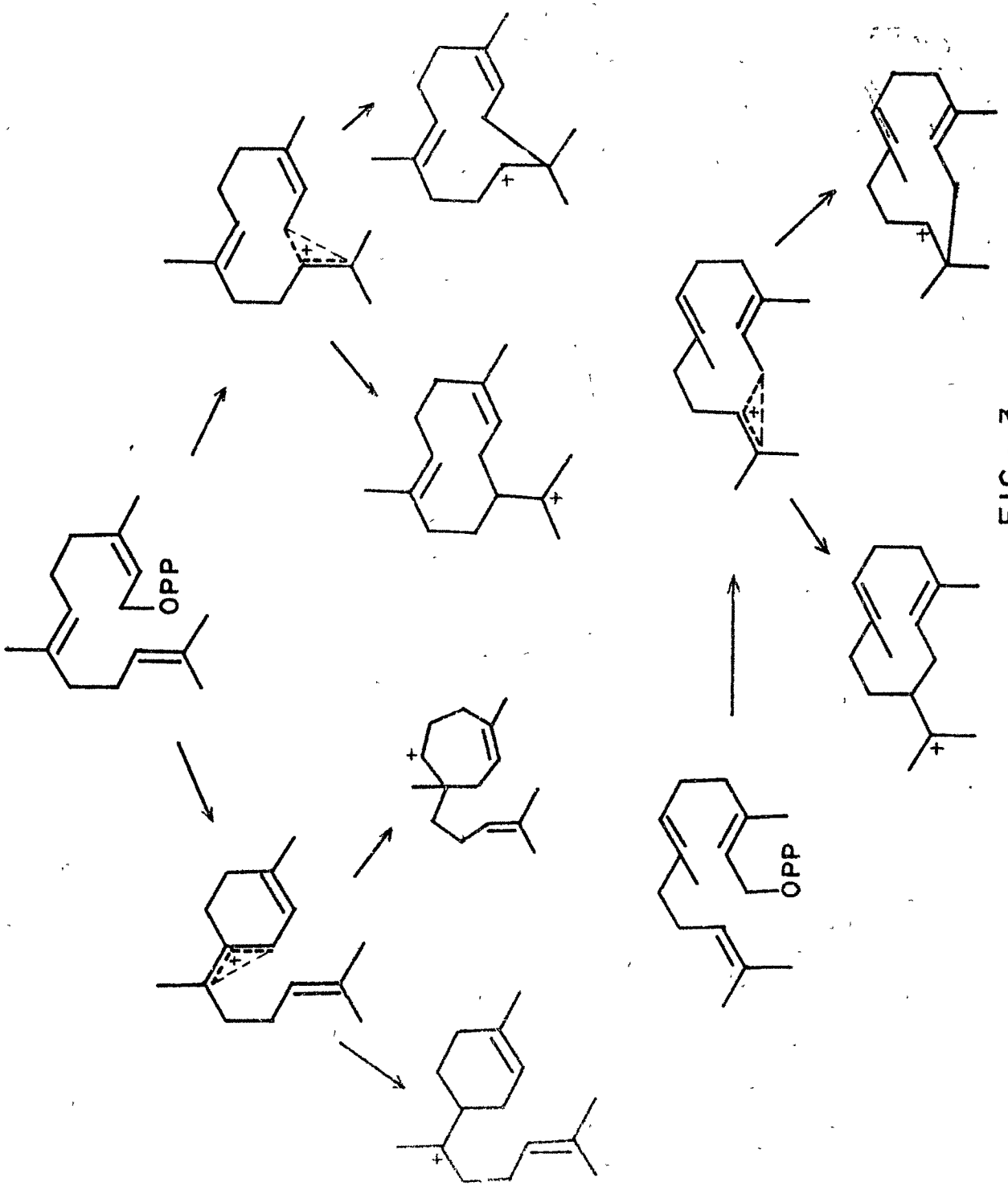

FIG.—3

cyclic products are formed (apart from the usual elimination products), although the amount of cyclized products was more in the case of cis-isomer. Since, there is considerable evidence for the configurational stability of allylic carbocations, and hence interconversion seems improbable, these authors suggest that (trans),(trans)-diphenyl phosphate by internal return gives nerolydyl diphenyl phosphate which cyclises with ease, although they are unable to detect any nerolydyl diphenyl phosphate in the reaction mixture Fig. 4.

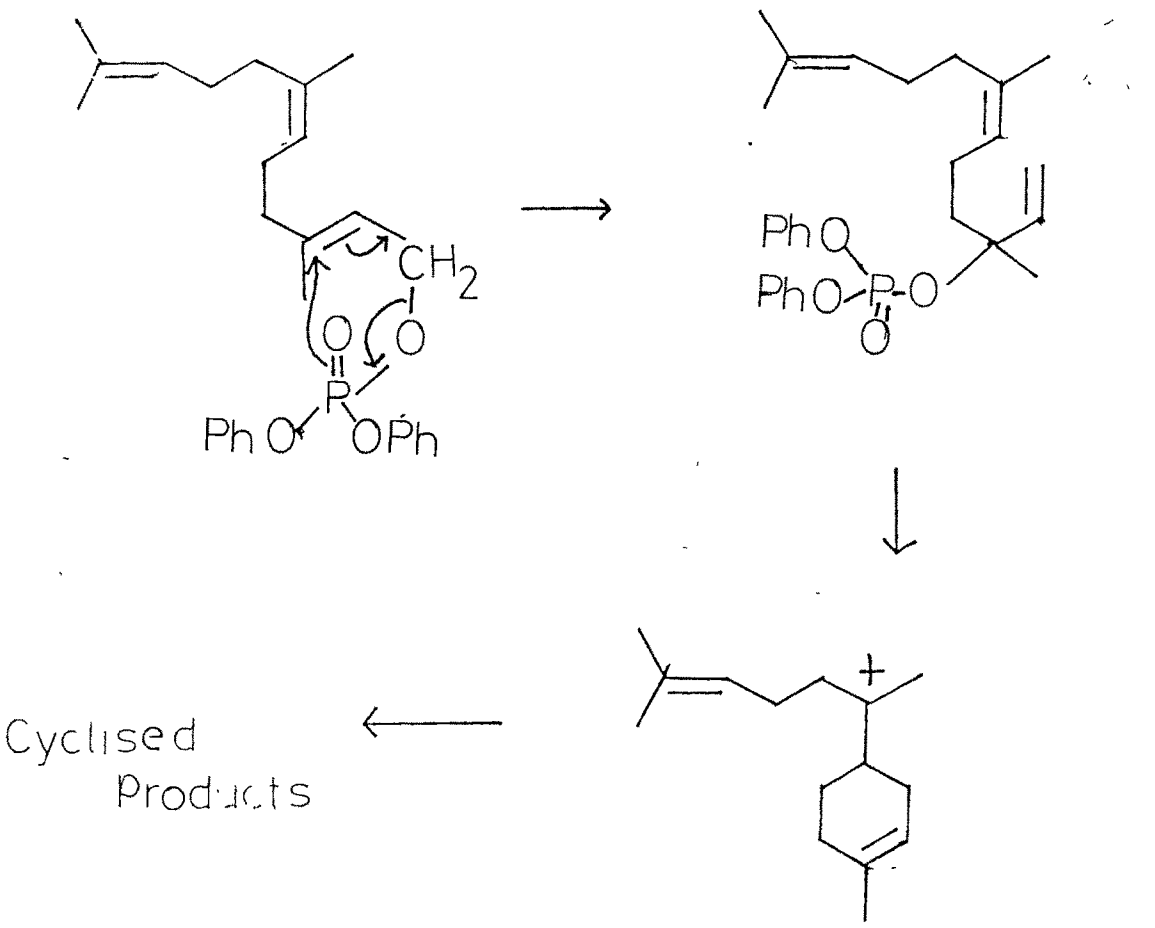

Fig - 4

Also Kobayashi et al.[30] have observed biogenetic like cyclization of farnesol and nerolidol to bisabolene by the use of 2-fluoro benzothiazolium salt.

In 1977, C.D. Gutsche et al.[31] have studied the mechanism of the acid catalyzed decomposition of the farnesyl phosphates. The rates and products of the acid catalyzed decomposition of (Z,E)- and (E,E)-farnesyl phosphates; (Z,E)- and (E,E)-1,1-diduetero farnesyl phosphates; (Z)- and (E)-6,7-10,11-tetrahydro farnesyl phosphate, were studied by these authors in order to determine whether (Z,E)-farnesyl phosphate ionizes with intramolecular assistance from the C-6/C-7 double bond or via an unassisted process leading to a simple allylic cation. Recently from our laboratories, Sukh Dev et al.[25] reported the photo chemical transformations of (Z,E)- and (E,E)-farnesyl iodides leading to the formation of acyclic and cyclic sesquiterpene hydrocarbons. Very recently, Hisashi Yamamoto et al.[23] reported the first asymmetric synthesis of bisabolenes in a biogenetic manner, from the reaction of biphenol (Z,Z)-monofarnesyl ether and R-(+) binaphthol (Z,Z)-monofarnesyl ether with organo aluminium reagents such as DIBAH and aluminium trifluoro methane sulphonate.

In diterpene series, (E,E,E)-geranylgeranyl pyrophosphate is immediate precursor for all diterpene hydrocarbons. The various important modes of ring closure in the case of

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typical substrate (E,E,E)-geranylgeranyl pyrophosphate, from the ionization of the pyrophosphate group (at the tail end of the acyclic precursor), are dipicted in Fig. 5. Skeletal types arising from this mode were rather limited till a decade ago, but have rapidly proliferated since then. It is interesting to note that this pathway is apparently, preferred in marine organisms.

Clearly, there are three distinct possibilities (A, B, C Fig. 5) available to the ion resulting from ionization of the acyclic precursor (eg. GGPP) for the initial intramolecular electrophilic attack, depending on the proximity (in suitable orientation) of a particular olefinic linkage, which in turn will be dictated by folding of the substrate on the cyclase. This, then generates several options for the initial cyclization mode (Fig. 5), and these in turn would determine the course of any further cyclization. All these possibilities are known to occur in nature. But so far, no such chemical induced cyclizations have been reported.

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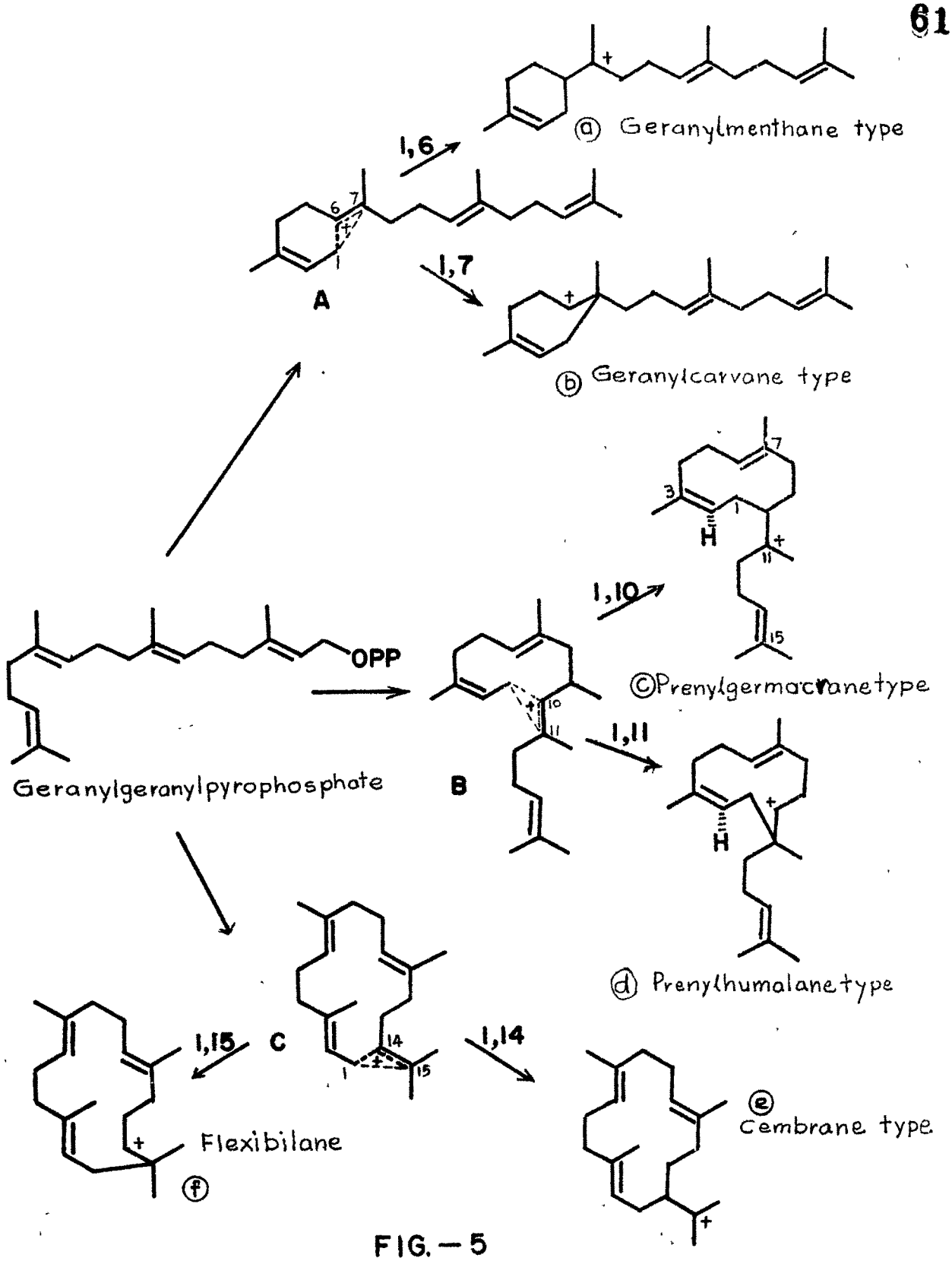

ⓐ Geranylmenthane type
1,6
1,7
A
ⓑ Geranylcarvane type
1,10
©Prenylgermacranetype
OPP
Geranylgeranylpyrophosphate
B
1,11
ⓓ Prenylhumalanetype
1,15
C
1,14
Flexibilane
ⓕ
ⓔ
Cembrane type

FIG. — 5

PRESENT WORK

(A) SYNTHESIS OF SUBSTRATES

The substrates chosen for our present study were the diethyl phosphate esters of the monoterpene primary allylic alcohols, geraniol and nerol; the corresponding diethyl phosphate esters of their sesquiterpene analogues, (E,E)- and (Z,E)-farnesols and the corresponding diethyl phosphate esters of diterpene analogue (E,E,E)-geranylgeraniol, since these are the fundamental units for mono-, sesqui- and diterpene biogenesis. It was, therefore, necessary to obtain these allylic alcohols with highest purity possible of required stereochemistry. Monoterpene allylic alcohols, geraniol and nerol, which are available in our laboratory, were purified by distillation under reduced pressure. These were characterised by their spectral assignments (the doublet due to CH_2-OH at 4.0 ppm). IR and PMR of geraniol (1) are shown in Figs.6 and 7. IR and PMR of nerol (2) are shown in Figs.8 and 9.

For the synthesis of (Z,E)- and (E,E)-farnesols, the method had to be so chosen that the starting material was readily available to us. Thus, the choice fell on (trans)-geranyl acetone, as it would fix the geometry of the 6,7-double bond in the final product as (E)- and thereby reduce complexity of farnesols into a mixture of

two, instead of four isomers. PMR of trans-geranyl acetone is shown in Fig. 10.

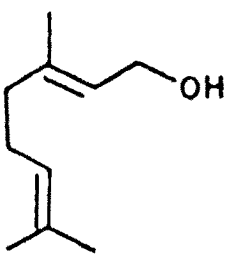
After examining the various synthetic methods for the preparation of farnesols, finally we chose to follow the O.P. Vig et al's [32] method, by slightly modifying the reaction conditions.

The first step involves the Wittig-Horner reaction between (trans)-geranyl acetone and the ylide generated from $(EtO)_2P(O)\ CH_2CO_2Et$, using sodium hydride as base. 1,2-dimethoxy ethane was reported as solvent and refluxing temperatures were used. In our hands, however, the reaction did not proceed smoothly. We found that the reaction proceeds very smoothly at (30^oC) in benzene solvent, giving almost quantitative yields of the esters. Furthermore the product ratio obtained was 73 percent of (trans)-ester (3b), 23 percent of (cis)-ester (3a) and only 3 percent of unwanted isomers. Studies also showed that the product ratio obtained is sensitive to the amount of reagents used and to the reaction conditions employed. The required (Z)- and (E)-esters (3a and 3b) were separated by precise fractionation on an annular teflon spinning band column of 80 theoritical plates and characterised by their PMR spectra.

The LAH reduction of the α,β-unsaturated esters (3a and 3b) was reported at room temperature and supposedly gave 67 percent yield of alcohol after three hours reaction

period. Our observation was that this reduction was not so facile, longer reaction times and lower reaction temperatures were necessary. There were also signs of the formation of a side-product which probably is the α,β-saturated alcohol (a broad peak at 3.61 ppm in the PMR spectrum, possibly for the α- to hydroxyl protons). This impediment was overcome by first stirring at -5°C for 2 hours, then gradually allowing the reaction temperature to attain 0° and further stirred at this temperature for 6 hrs. These alcohols were characterised by their PMR spectrum (the doublet due to $\underline{CH_2}$-OH at 4.0 ppm). IR and PMR of 2(Z), 6(E)-farnesol (4a) are given in Figs.11 and 12 and of 2(E), 6(E)-farnesol (4b) are given in Figs.13 and 14.

(E,E,E)-Geranylgeraniol, which was isolated from our laboratories by our earlier workers from the wood of cedrela toona[33], was purified by precise column chromatography (Silica-gel G, grade IIB) and distilled the pure alcohol fractions under reduced pressure. It was characterised by its spectral assignments (the doublet due to $\underline{CH_2}$-OH at 4.0 ppm). IR and PMR of (E,E,E)-geranylgeraniol are shown in Figs.15 and 16.



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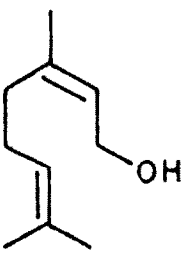

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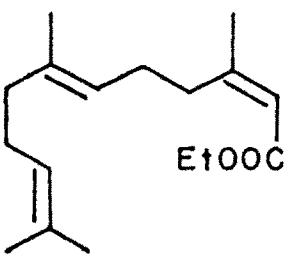
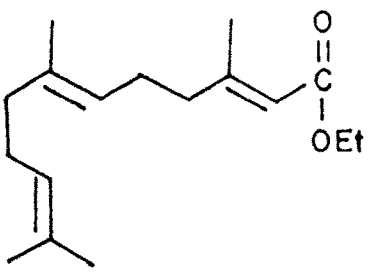
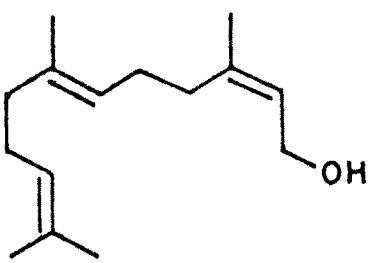


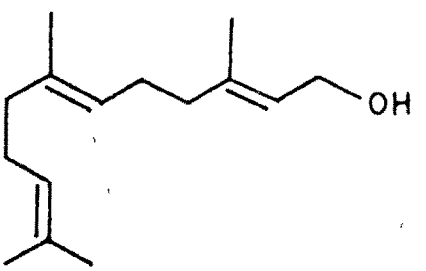
3a



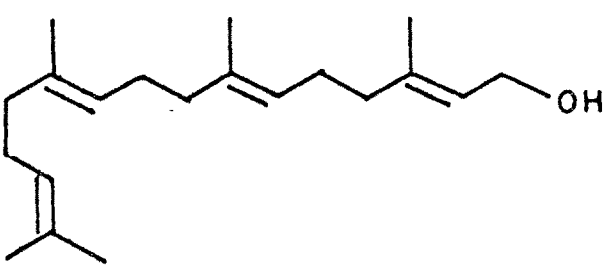
3b



4a



4b



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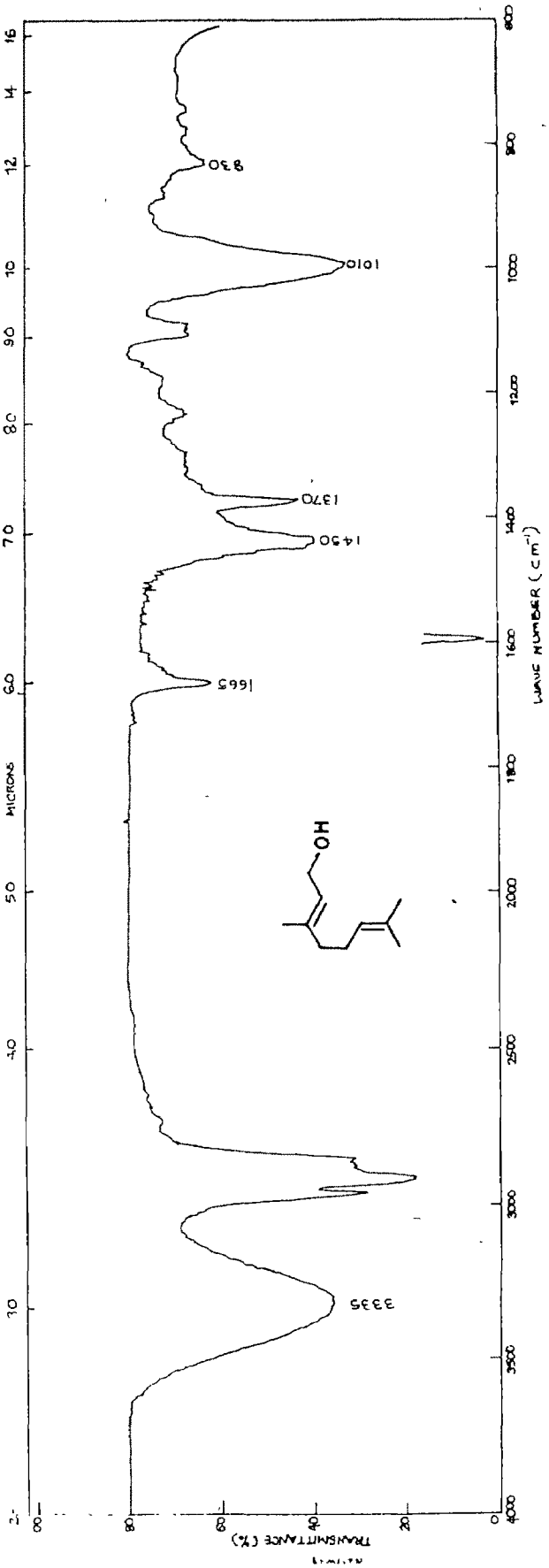

Fig.6 : IR spectrum of geraniol (1)

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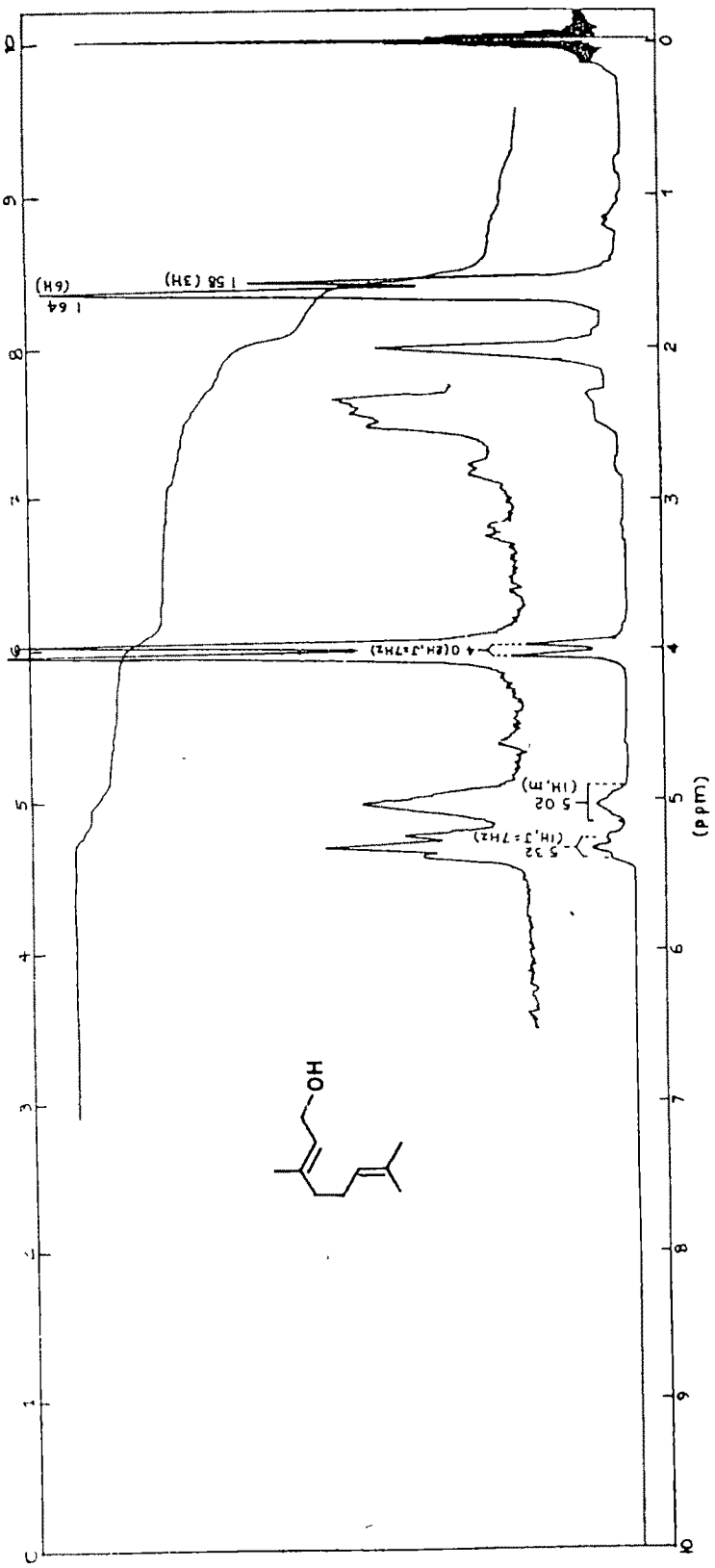


Fig.7 : PMR spectrum of geraniol (1)

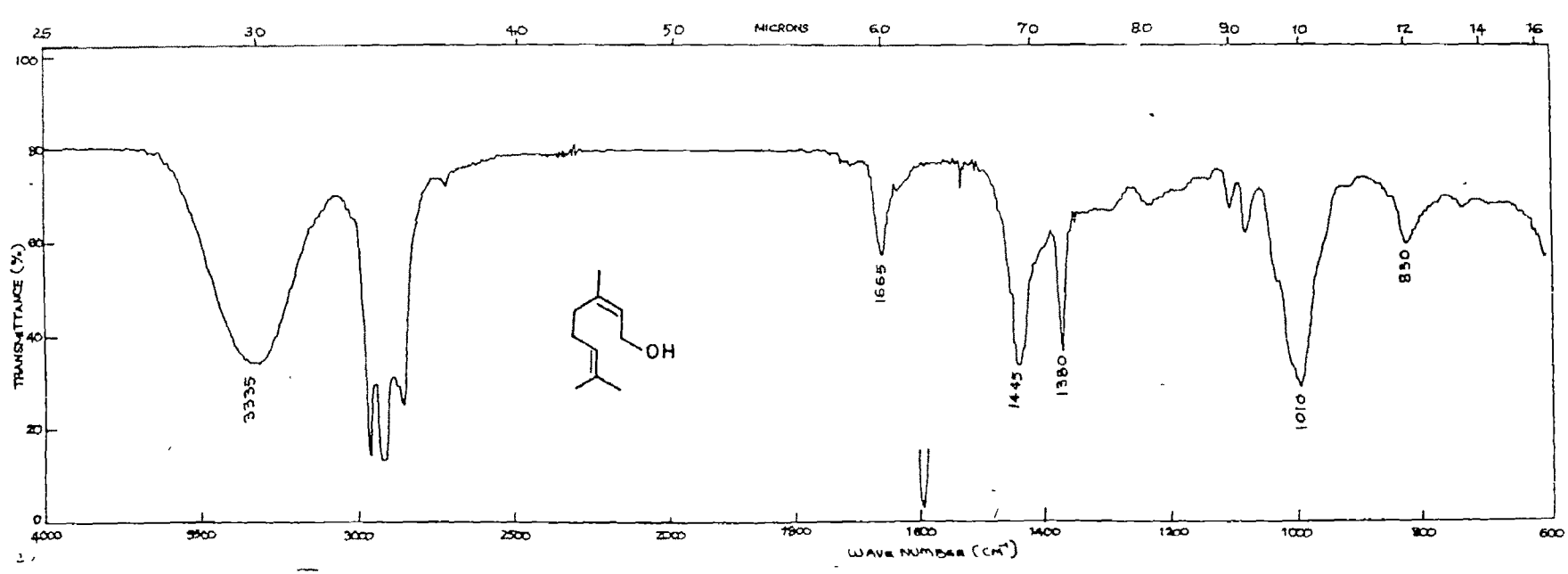


Fig.8 : IR spectrum of nerol (2)

69

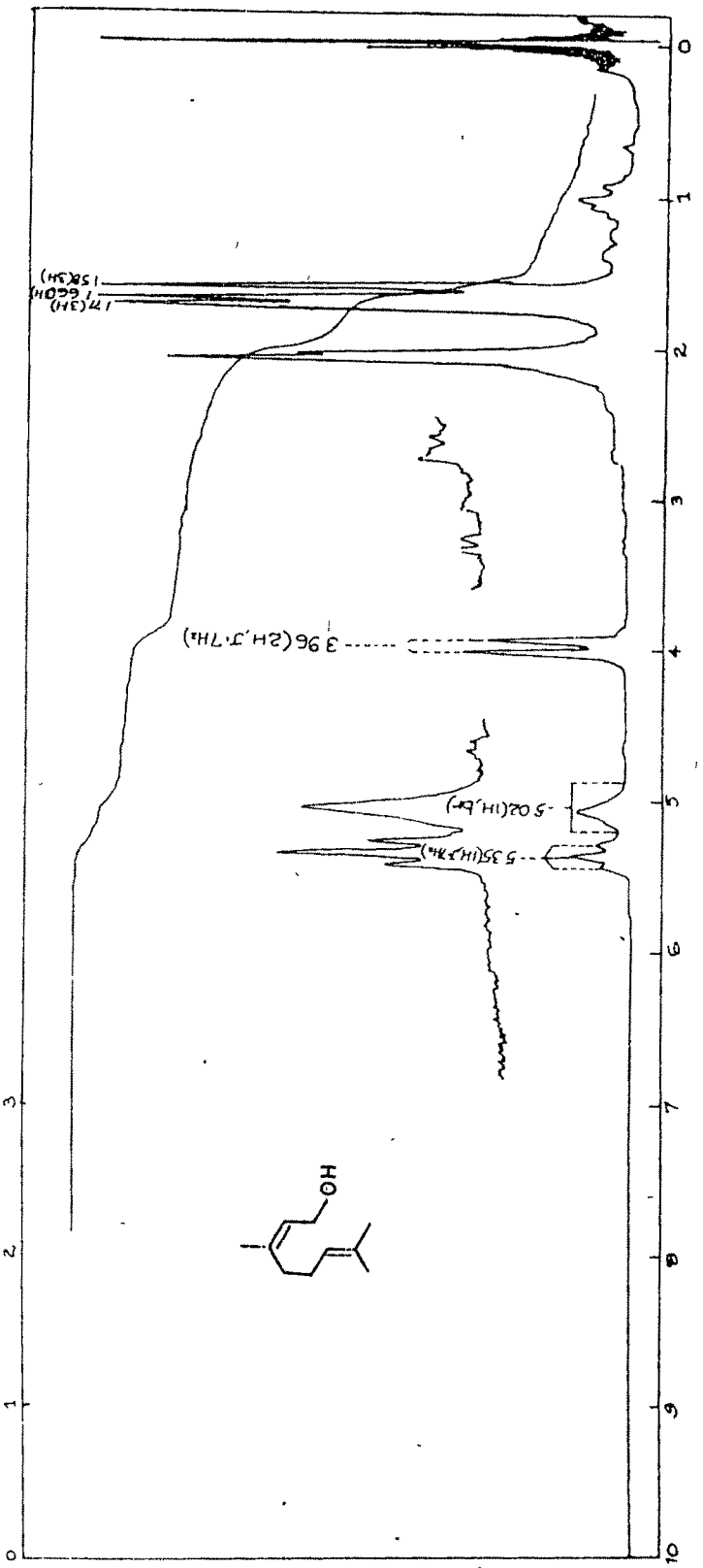


Fig.9 : PMR spectrum of nerol (2)

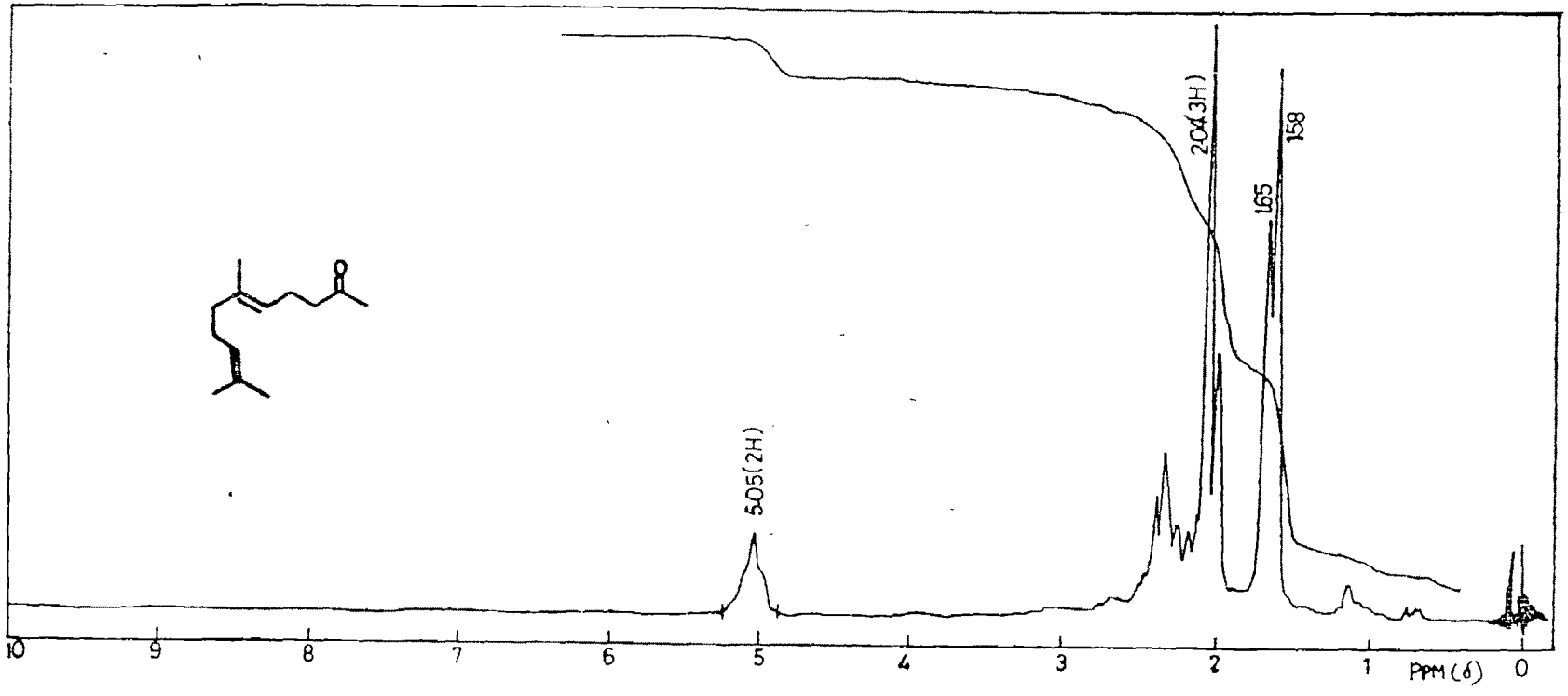


Fig.10 : PMR spectrum of (E)-geranyl acetone

71

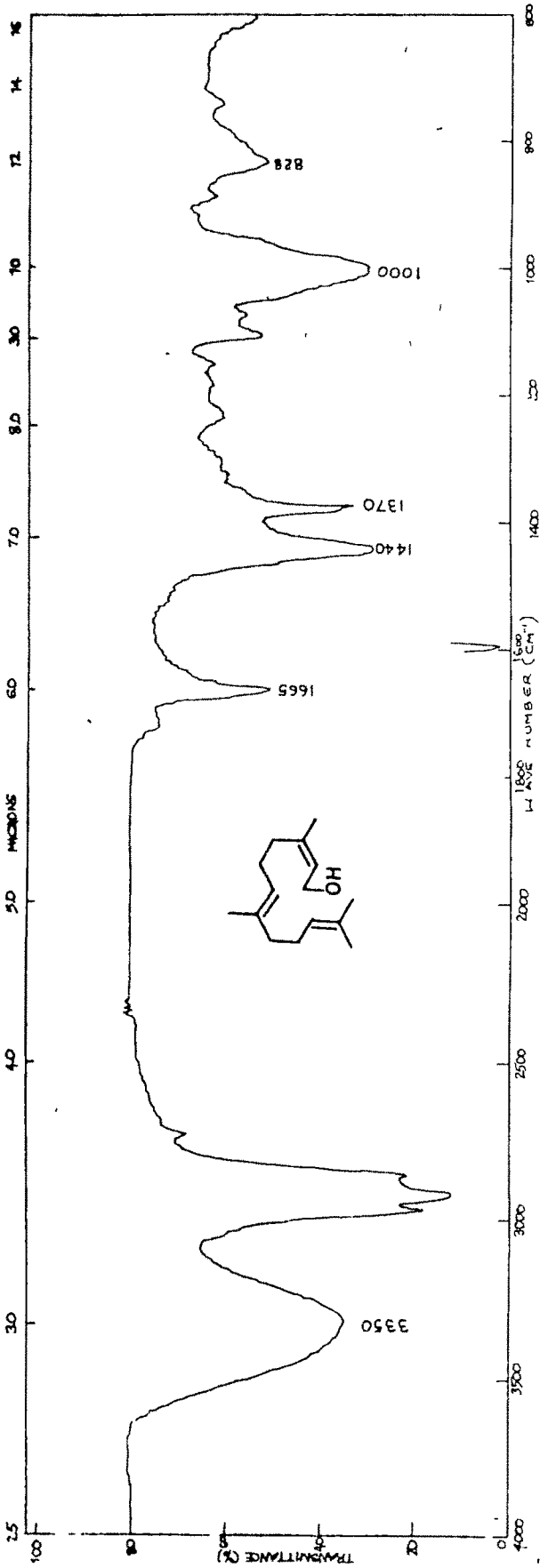


Fig.11 : IR spectrum of 2(Z), 6(E)-farnesol (4a)

72

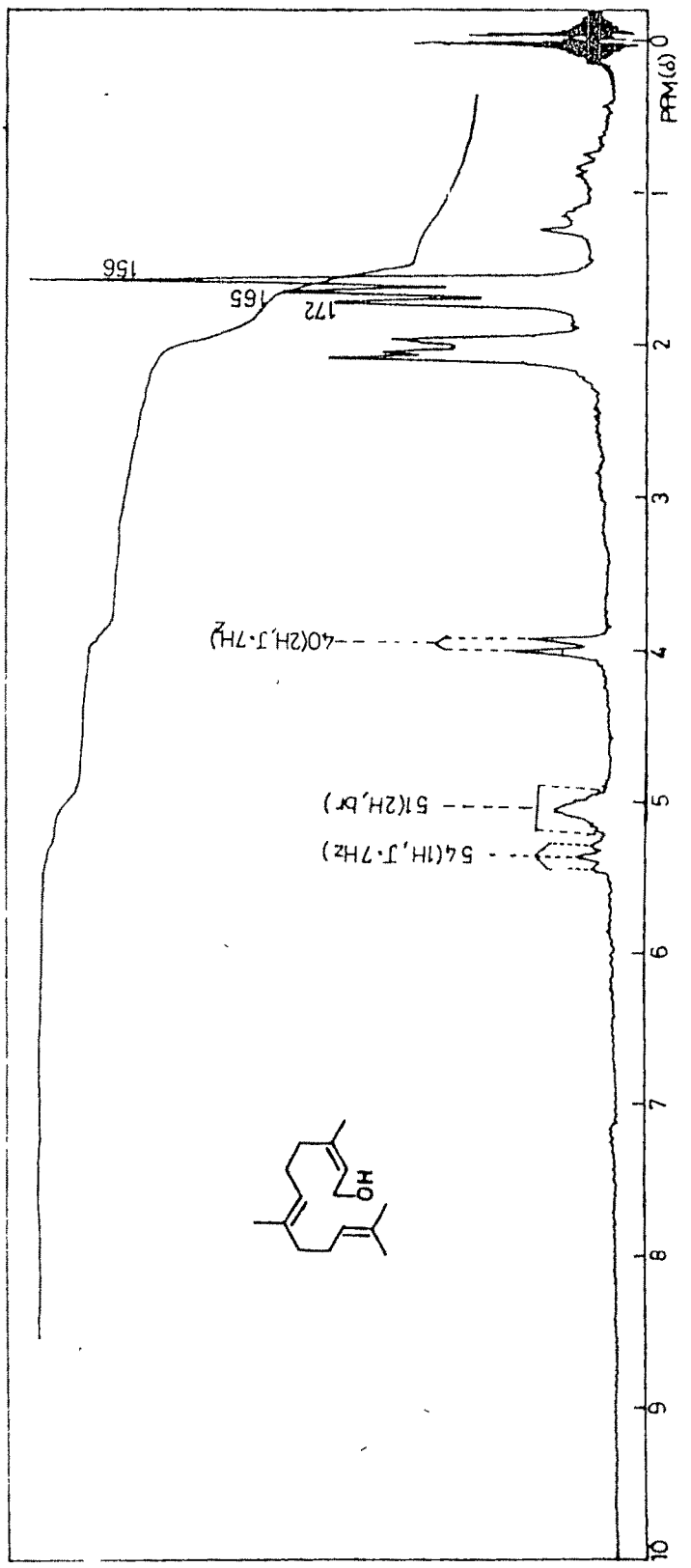


Fig.12 : PMR spectrum of 2(Z), 6(E)-farnesol (4a)

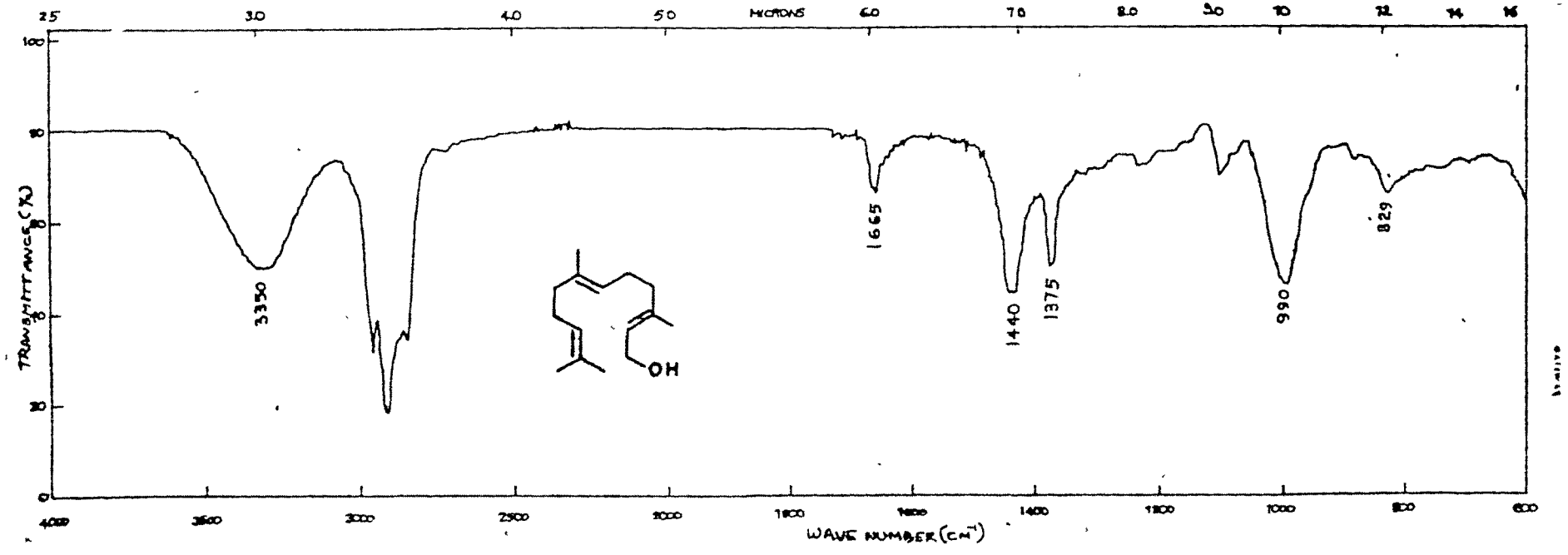


Fig.13 : IR spectrum of 2(E), 6(E)-farnesol (4b)

74

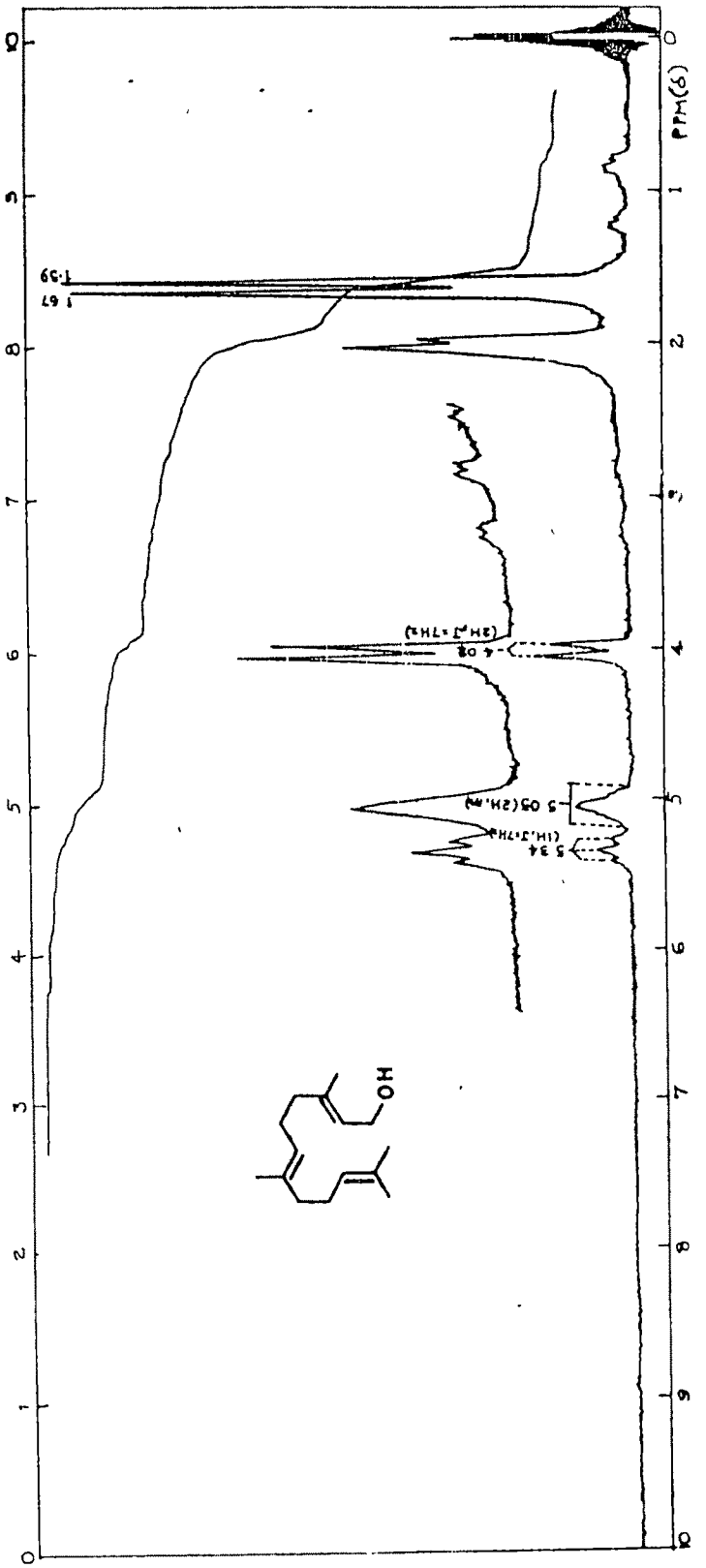


Fig.14 : PMR spectrum of 2(E), 6(E)-farnesol (4b)

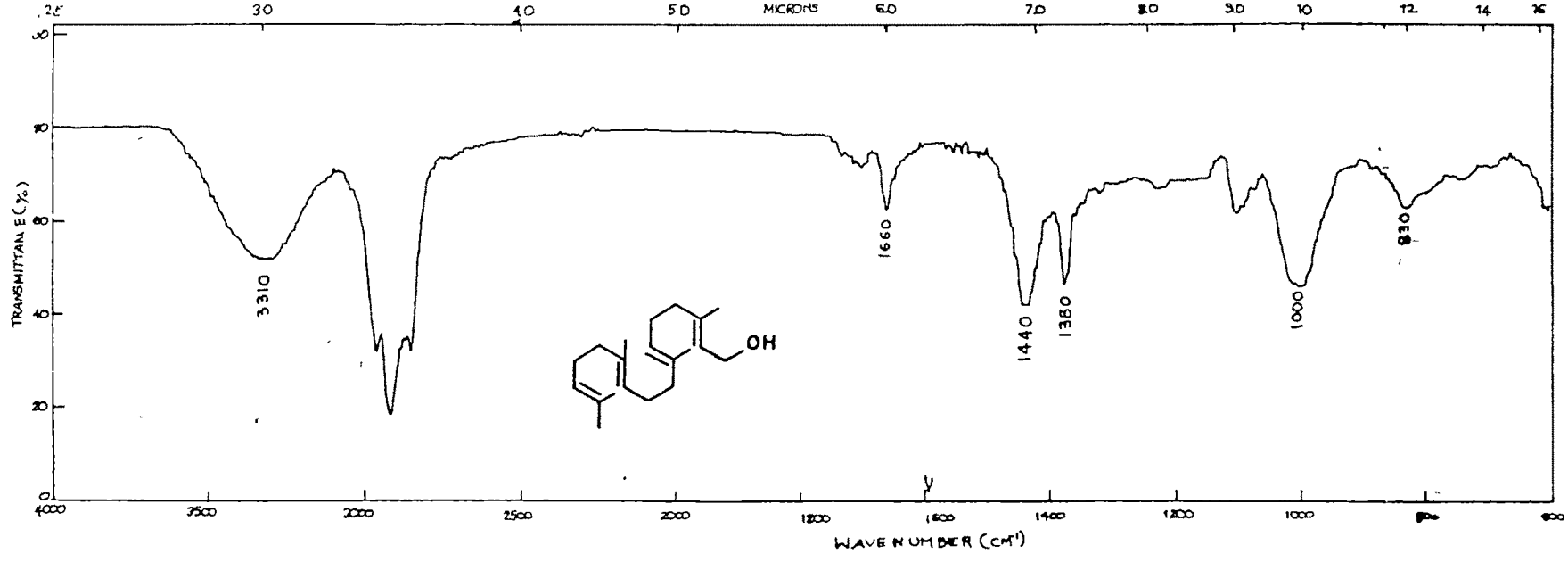


Fig.15 : IR spectrum of (E,E,E)-geranylgeraniol (5)

76

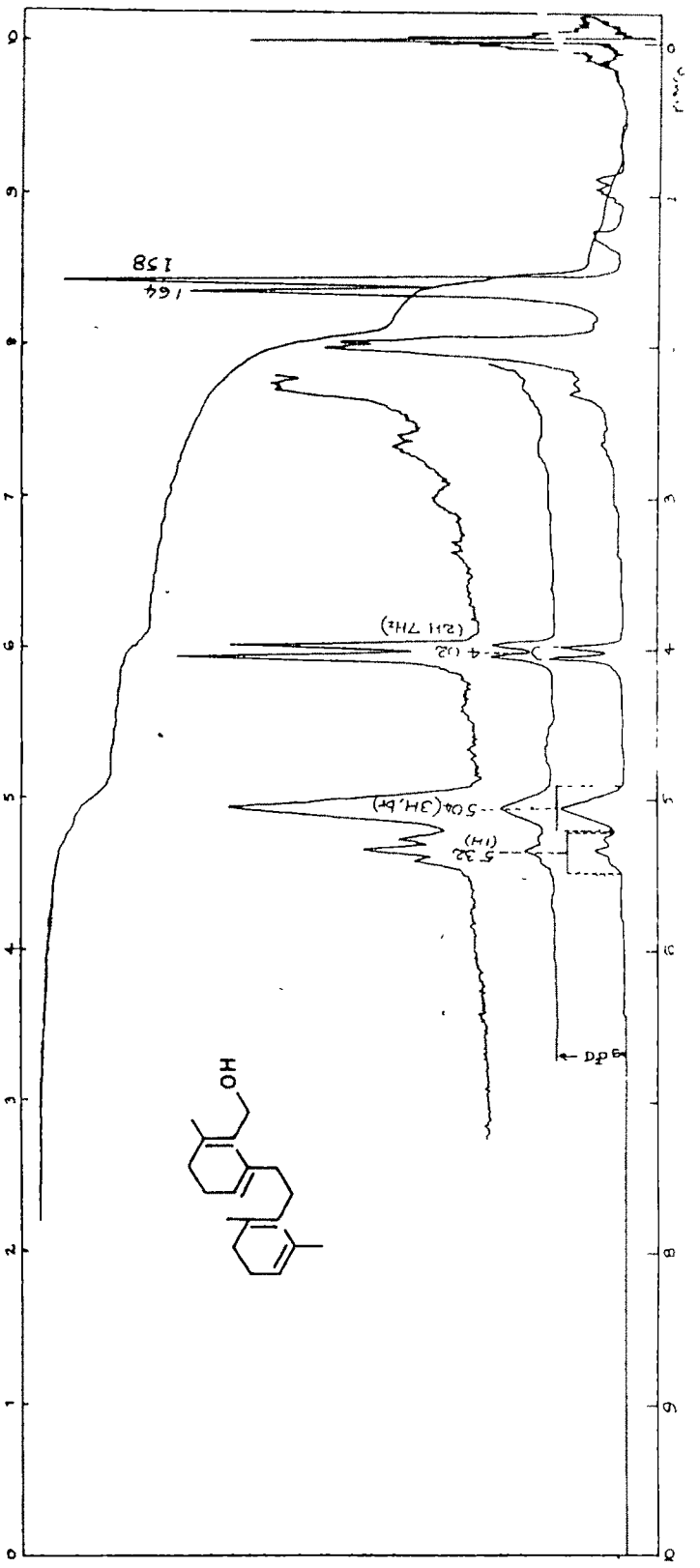


Fig.16 : PMR spectrum of (E,E,E)-geranylgeraniol (5)

77

SYNTHESIS OF ALLYLIC DIETHYL PHOSPHATE ESTERS

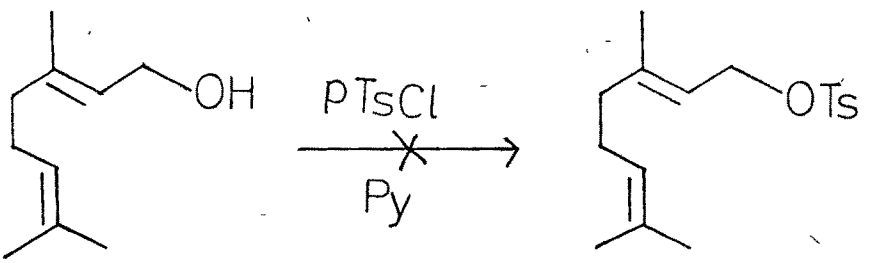
Allylic diethyl phosphate esters, which can simulate the role played by pyrophosphate esters in biological systems, were chosen as models for our present studies.

After trying several unsuccessful methods to synthesise allylic derivatives (eg. tosylates and mesylates), it was finally possible to obtain pure allylic diethyl phosphate esters by the reaction of the respective allylic alcohols with diethyl-chloro-phosphate and pyridine.

The alternative methods tried, for the preparation of allylic derivatives, are briefly enumerated below with appropriate comments.

1. Attempted preparation of geranyl tosylate:

In our initial experiments involving conventional methods, geraniol was treated with p-toluene sulfonyl chloride in presence of base like pyridine or collidine (in solvent like CH_2Cl_2 or THF) at low temperatures (varying from $-5^{\circ}C$ to $25^{\circ}C$). In all these cases geranyl tosylate could not be isolated, instead a mixture of decomposed products were obtained, which were not analysed further.



2. Attempted preparation of geranyl mesylate:

Literature survey of allylic alcohol mesylation revealed the preparation of farnesyl mesylate from farnesol using methanesulfonyl chloride and triethyl amine in dichloromethane at -5°C, during their targeted synthesis of geranylfarnesol, by O.P. Vig et al.[34]. But in our case geraniol, under similar reaction conditions afforded geranyl chloride (6), indicating S_N2 displacement of the initially formed mesylate by the chloride ions, present in the reaction mixture. PMR spectrum of geranyl chloride is shown in Fig. 17. A precedent in literature[35], of similar S_N2 displacement, is provided by the abnormal chlorination of 3-hydroxy-4,5-epoxy 6,11 β H-eudesm-1-en-6,12-olid , with methanesulfonyl chloride.

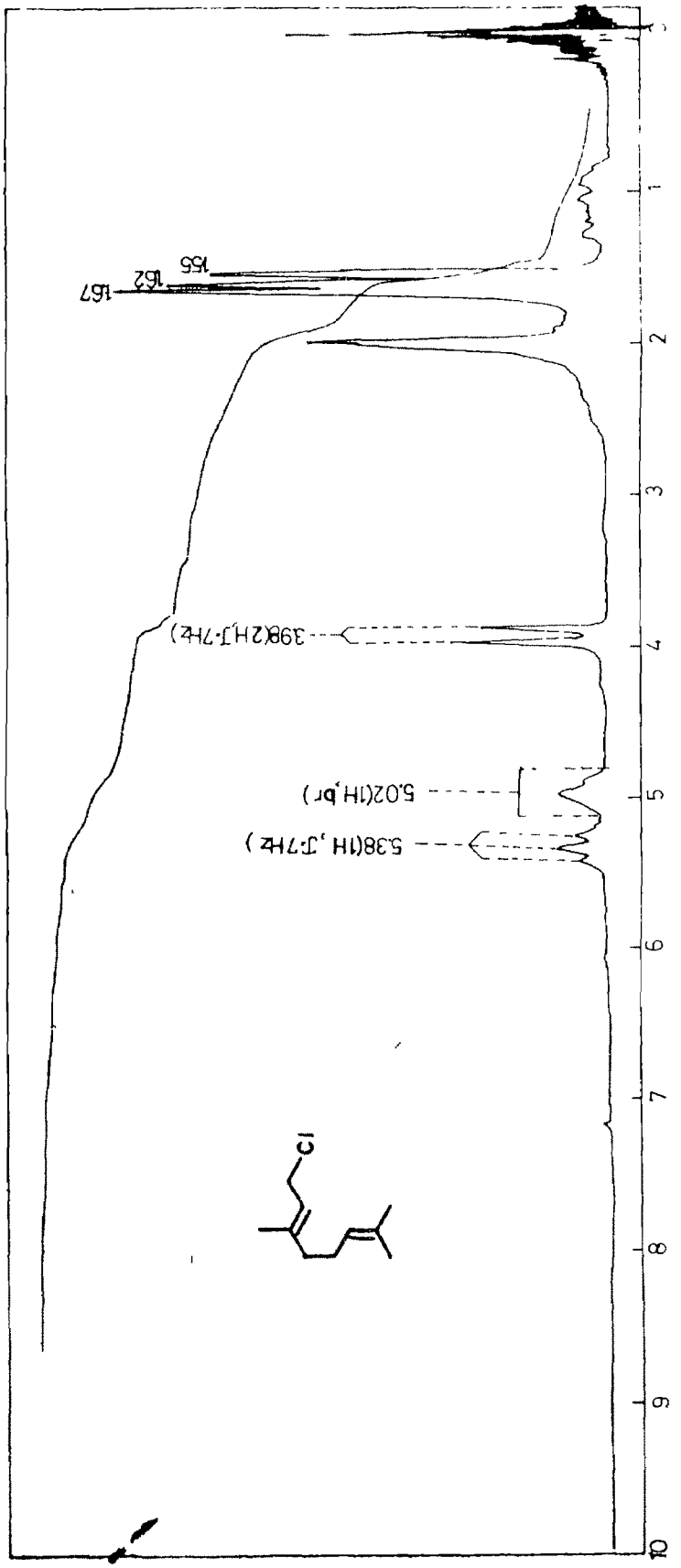
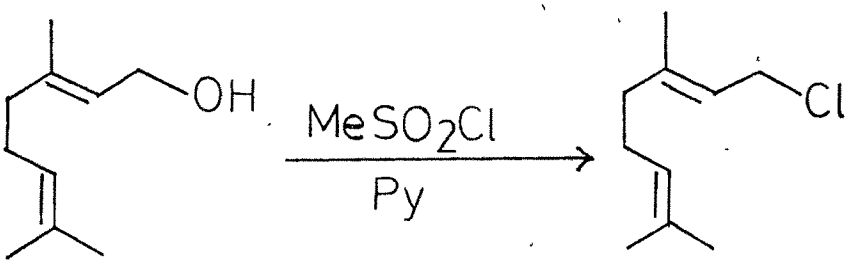


Fig.17 : PMR spectrum of geranyl chloride (6)

A number of other methods were also tried to prepare geranyl mesylate, using methane sulfonyl-chloride, under different reaction conditions. In all these cases geranyl chloride was isolated.



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3. Attempted preparation of geranyl mesylate using methane sulfonic anhydride:

Since the method above described, consists essentially of SN^2 displacement of initially formed geranyl mesylate by chloride ions, present in the reaction mixture, it was thought to use methane sulfonic anhydride for mesylation, which serves to exclude the formation of geranyl chloride. The reagent, methane sulfonic anhydride, was prepared from refluxing methane sulfonic acid with thionyl chloride and distilling off excess thionyl chloride, which gave very hygroscopic white crystals. (m.p.: 71-72°C; reported 70-71°C).

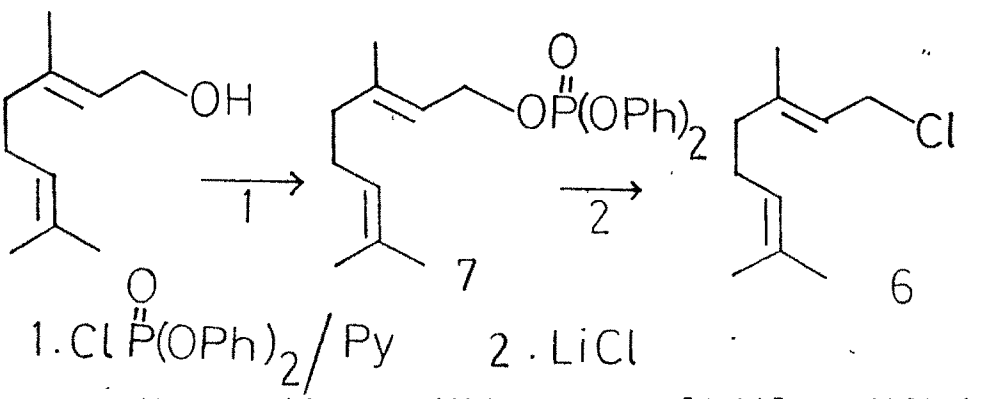
A reaction of geraniol with methane sulfonic anhydride using triethyl amine in dry dichloromethane at -5°C, gave a mixture of decomposed products, instead of geranyl mesylate, which were not analysed further. A series of attempts were made to prepare geranyl mesylate using methane sulfonic anhydride in different bases, different solvents under varying reaction conditions. But none of these reactions gave desired geranyl mesylate, probably after formation of the geranyl mesylate (allylic), due to its high instability, it is undergoing decomposition, leading to the formation of several compounds.

4. Preparation of geranyl diphenyl phosphate (7):

After various unsuccessful efforts to prepare geranyl tosylate and geranyl mesylate, it was decided to prepare allylic phosphate esters, which simulate the role played by pyrophosphates in nature. Literature survey showed[36] that allylic diphenyl phosphates have been prepared by the reaction of diphenyl chlorophosphoridate with a mixture of pyridine and allylic alcohol at low temperatures (0°C), under exclusion of moisture.

In our hands, however, under the similar reaction conditions geraniol afforded geranyl chloride (6), via

SN^2 displacement of diphenyl phosphate by chloride ions, present in the reaction mixture. Recently such a reaction was reported by S. Araki et al.[37] in stereoselective conversion of allylic alcohols to halides via allylic diphenyl phosphates.



So, the reaction comditions were slightly modified in order to get geranyl diphenyl phosphate in good yields. To a stirred solution of geraniol and pyridine in dry dichloromethane at -10°C, diphenyl chlorophosphoridate in dry dichloromethane was added dropwise maintaining the temperature at -10°C (temperature rise was observed during the addition) and the reaction mixture was stirred further for 3 hrs at -10°C. After usual work-up, it gave geranyl diphenyl phosphate (7) in excellent yield. The PMR of this product showed the presence of d,d (merged to form triplet) at 4.5 ppm (due to $\underline{CH_2}$-O-P(O)(OPh)$_2$ which reveals the formation of diphenyl phosphate ester. PMR of geranyl diphenyl phosphate is shown in Fig. 18. Even though pure geranyl

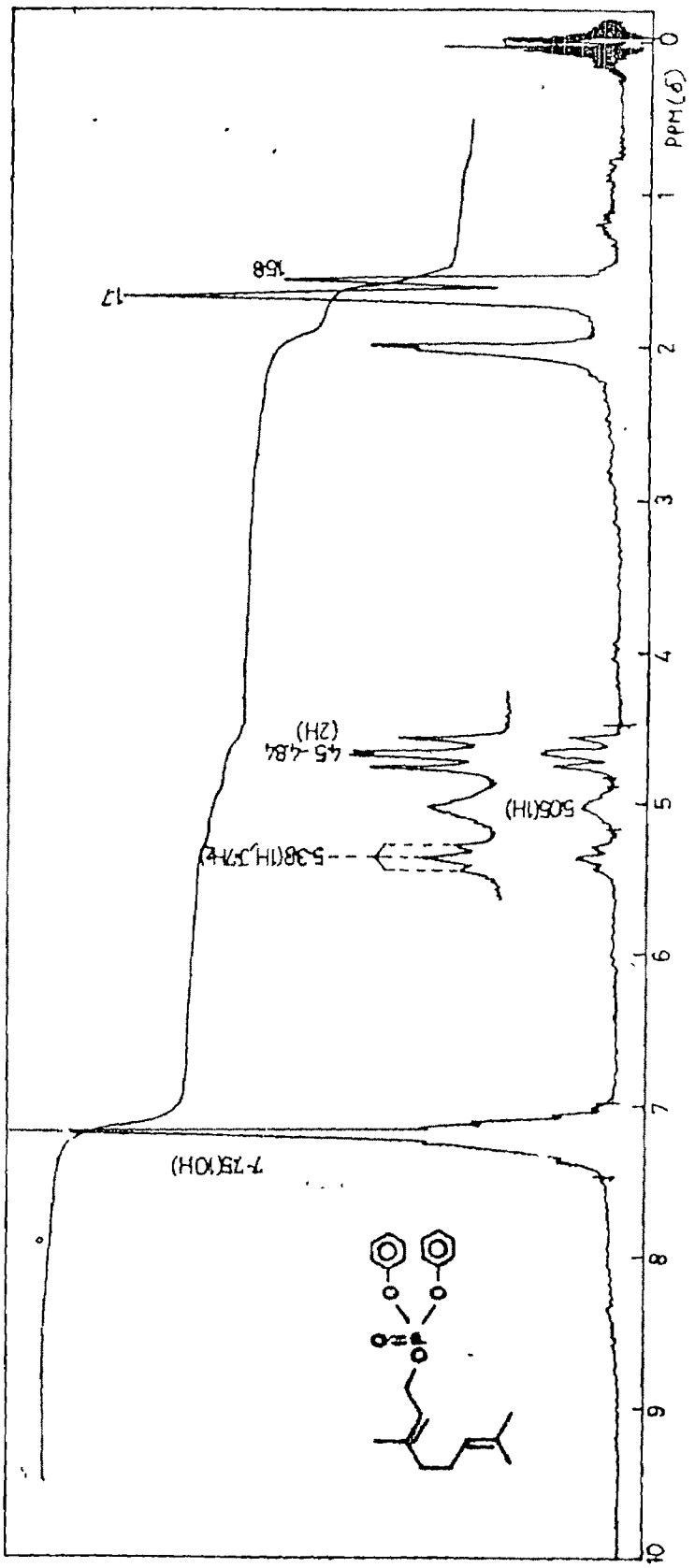


Fig.18 : PMR spectrum of geranyl diphenyl phosphate (7)

diphenyl phosphate could be isolated, it was found that its deterioration in few hours after isolation owing to its instability. In an endeavour to make comparatively more stable allylic phosphate esters, our choice fell on allylic diethyl phosphate esters.

Literature survey shows[22] that allylic diethyl phosphate esters were prepared in 80 percent yield by the reaction of allylic alcohol and diethyl chloro-phosphate, using n-butyl lithium and triethyl amine under very low reaction temperatures (-78°C). We found these reaction conditions can be modified in order to get allylic diethyl phosphate esters with maximum purity, in excellent yields.

Taking the clue from the experiment (described in the synthesis of diphenyl phosphate esters), it was decided to develop a general method of preparing allylic diethyl phosphate esters from the corresponding allylic alcohols. For this purpose, nerol was chosen as model substrate. To a stirred solution of allylic alcohol (nerol, 1 mol) and pyridine (2.5 mol) in dry dichloromethane at (-5° to 0°C), diethyl chloro phosphate (1.25 mol) in dry dichloromethane was added dropwise maintaining the temperature at 0°C (it is observed, the temperature rises during addition) and

stirred the reaction mixture further for 3 hrs at 0°C. After usual work up, it gave pure allylic (neryl) diethyl phosphate ester (8) in 90 % yield, homogeneous by TLC analysis (15 % EtOAc/pet. ether 60-80°C), and spectroscopically consistent. The PMR of the product (Fig.19) showed the presence of d,d (merged to form triplet) at 4.3-4.6 ppm (due to $\underline{CH_2}$-OP(O)$(OEt)_2$) and a multiplet at 3.85-4.3 ppm [due to CH_2-OPO$(O\underline{CH_2}CH_3)_2$]. The disappearance of doublet due to $\underline{CH_2}$-OH (at 4.0 ppm) and appearance of d,d (merged as triplet) at 4.46 ppm reveals the formation of allylic diethyl phosphate ester. It was not further purified due to its lability towards heat and adsorbents.

B. CYCLISATION STUDIES

The various types of cyclization reactions of terpene precursors, were briefly surveyed in the preceding chapter. The facile cyclization of properly designed terpene allylic derivatives had been utilized in synthetic work by various investigators earlier. The cyclisation of terpene allylic diethyl phosphate esters, containing a suitably situated ethylenic linkage, in solid matrices is reported here for the first time.

In view of the synthetic and mechanistic interest of these cyclisation reactions in terpenes, it was felt worthwhile, to study, systematically various solid matrices

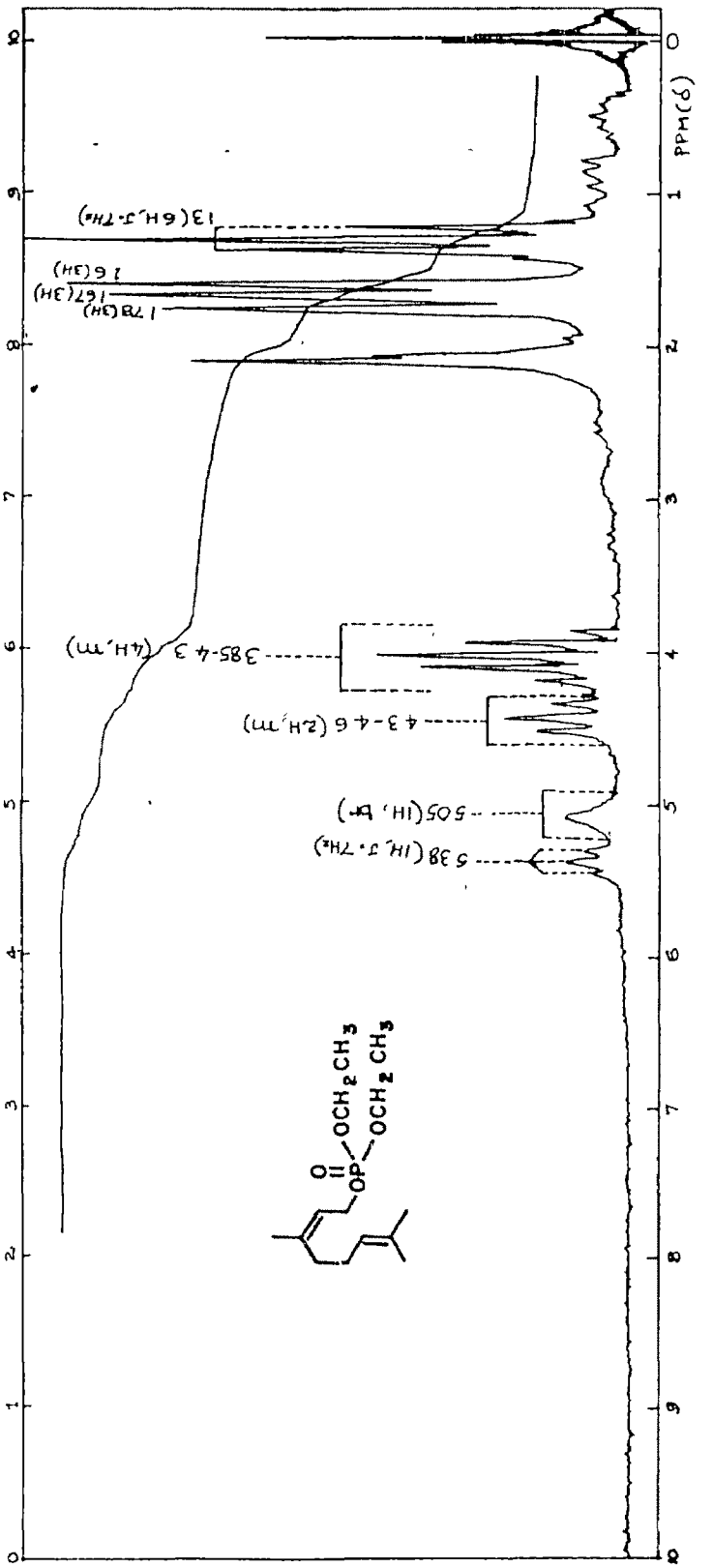


Fig.19 : PMR spectrum of neryl diethyl phospahte (8)

as reagents to induce biomimetic cyclisations of allylic phosphate esters and to study the effect of temperature and solvent on these reactions, so as to arrive at optimal conditions favouring cyclisation, using neryl diethyl phosphate as the substrate. Once these parameters were established, these could be employed for the cyclisation of other suitable allylic diethyl phosphate esters. It was also of interest to seek evidence supporting mechanistic pathways in these cyclisation reactions. The present section describes the work carried out with these objectives. It further presents the results of cyclisation reactions of geranyl-, 2(Z),6(E)- and 2(E),6(E)-farnesyl- and (E,E,E)-geranylgeranyl diethyl phosphate esters, under the optimal conditions established for neryl diethyl phosphate. It also presents the effect of ultrasonic waves in these cyclisation reactions of allylic diethyl phosphate esters.

As it was already established by earlier investigations that organo aluminium reagents, due to their high oxyphilicity and ambiphilic character, could cause cyclisation of suitably constituted acyclic allylic terpene precursors, we have undertaken a systematic study of these cyclisation reactions, using solid inorganic ambiphlic reagents and allylic diethyl phosphate esters.

Attempted reaction of neryl diethyl phosphate on Aluminium phosphate:

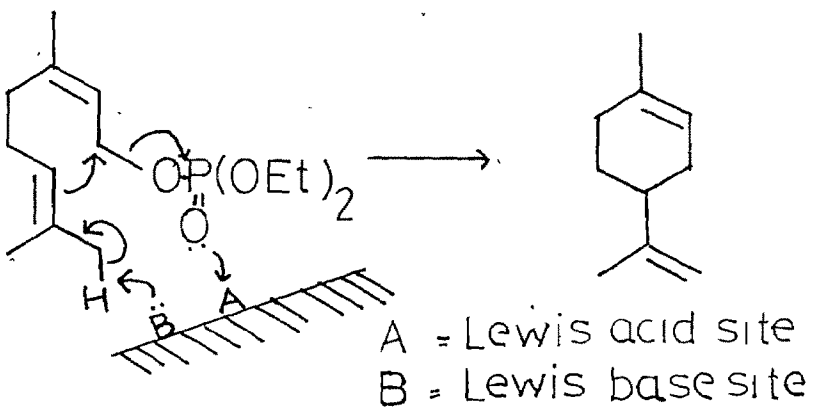
It is known[38] that, aluminium phosphate is having both acidic and basic sites on its surface. Because of its bifunctional catalytic activity, it was thought to use this reagent for cyclisation of neryl diethyl phosphate. The stirred suspension of aluminium phosphate (commercial, activated at 250°/24 hrs) in dry pet. ether (60-80°) was treated with neryl diethyl phosphate, at room temperature (30°C). It was further stirred for 20 hrs at 30°C and found no reaction has taken place. Starting material was recovered.

Reaction of neryl diethyl phosphate on aluminium sulphate:

Since, the above reaction did not yield any reaction products, it was thought to use aluminium sulphate[39], a solid acid catalyst, which also exhibits bifunctional catalytic activity.

Reaction of neryl diethyl phosphate was carried out, by stirring with aluminium sulphate (commercial, activated at 300°/3 hr, sieved through 100 mesh) in anhydrous pet. ether (60-80) for 3 hrs at room temperature (30°C) under exclusion of moisture. After usual filtration work up, it afforded a crude product, which on distillation gave a

hydrocarbon mixture. GLC of the distillate showed the formation of atleast six compounds. The major products were identified as myrcene (1.68 %), α-terpinine (30%), limonene (9.24 %), cis-ocimene (3.36 %), trans-ocimene (22 %), and terpinolene (33 %) by mixed GLC with authentic samples. Since the yields of these reactions are low, a search for alternative reagent, to get more yields of the reaction product, is called for. It is known[39] that on aluminium sulphate surface, both Bronsted and Lewis acid sites are known to exist. The oxygen of aluminium sulphate exhibits basic character. Based on these active sites, the probable mechanism, is suggested for the cyclization of neryl diethyl phosphate on aluminium sulphate as follows.



It is found by these observations that a bifunctional catalyst is needed for the effective cyclization of terpene allylic phosphate esters. The alternative choice fell on alumina which is known to exhibit both acid and basic sites on its surface.

Cyclisation studies on alumina:

Initial experiments were carried out using various aluminas (eg. chromatographic alumina, water washed alumina) with neryl diethyl phosphate ester, under a variety of reaction conditions but none of them gave good yields of reaction products. And also, it was found that the formation of elimination products was more than cyclised products, in these reactions. Finally, active alumina , prepared from the hydrolysis of aluminium isopropoxide, was found effective in the cyclization of neryl diethyl phosphate..

Cyclization reaction of neryl diethyl phosphate was carried out using active alumina (activated at 250°/24 hrs, pH=7, activity: grade I) in dry dichloromethane by shaking the reaction flask, using mechanical shaker, under the exclusion of moisture, for 4 hrs at room temperature (30°C) and kept at room temperature (25°) for 12 hrs. After usual filtration work up, solvent was carefully distilled to give a crude hydrocarbon mixture in good yields. It was distilled to get pure hydrocarbon mixture. GLC of this showed atleast 4 compounds. These were identified by mixed GLC on two different columns with authentic samples. These were identified as myrcene (10), limonene (12), cis-ocimene (13) and terpinolene (15) (Fig.20). Limonene and terpinolene were identified from the PMR of total cyclised product as well as mixed GLC with authentic samples by the peak-accentuation

technique. It is reported[40] in the literature that linalool on dehydration gives myrcene, α-terpinene, limonene, cis-ocimene, trans-ocimene and terpinolene (in order of their retention times on GLC column : 10 ft long, 10 % carbowax 20 M on 60-80 mesh, silane treated celite at column temperature of 100°C). These compounds are further confirmed by comparing the RRTs (relative retention times) of components of our mixture with that of reported[25]. The percentage of various cyclic and acyclic compounds formed and identified are summarised in Table-3. GLC of the total reaction product (obtained for optimal conditions) is depicted in Fig.21.

Cyclisation reaction of neryl diethyl phosphate in dry pet-ether (60-80°):

The cyclisation reaction of neryl diethyl phosphate on active alumina in dry pet-ether (60-80°) was carried out by refluxing the heterogeneous reaction mixture, under stirring in anhydrous conditions, for 4 hrs and kept at room temperature (25°C) for 12 hours. After usual work up, the crude was distilled to get pure hydrocarbon mixture. The various compounds formed were identified by GLC and mixed PMR studies as described in the above experiment. The percentage of various cyclic and acyclic compounds formed and identified are summarised in Table-4.

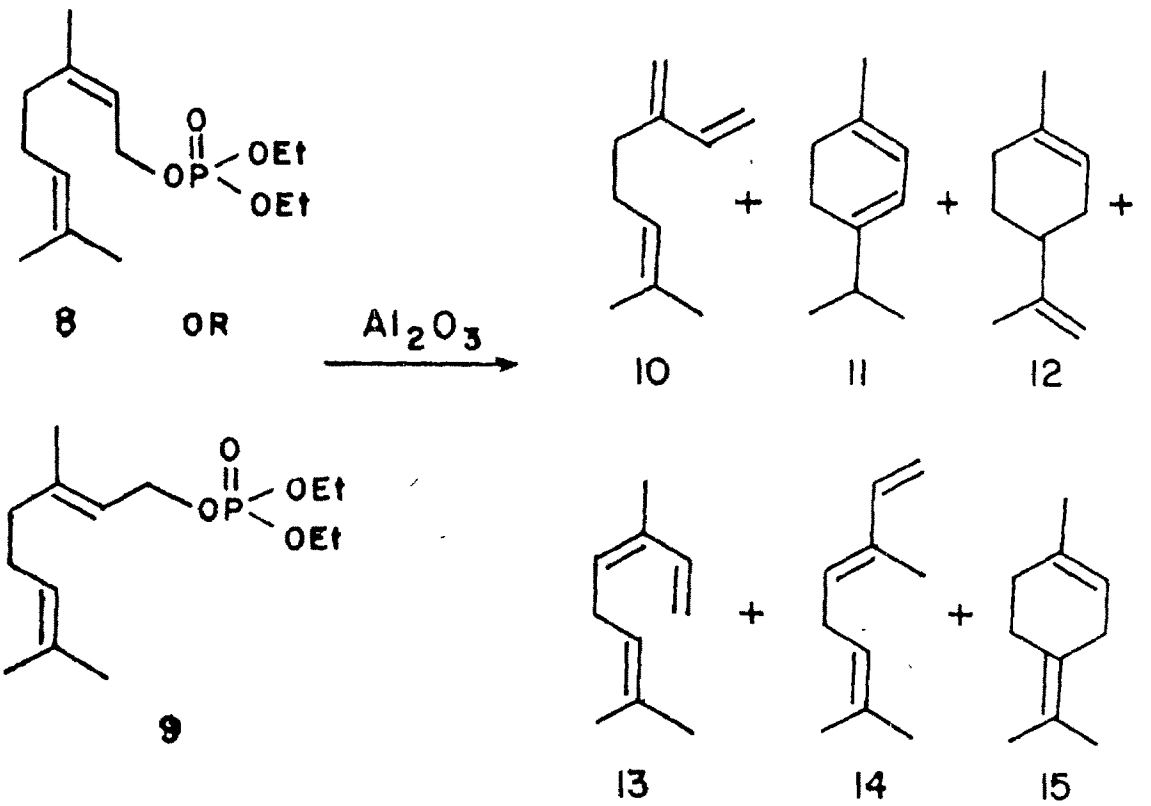


FIG. — 20

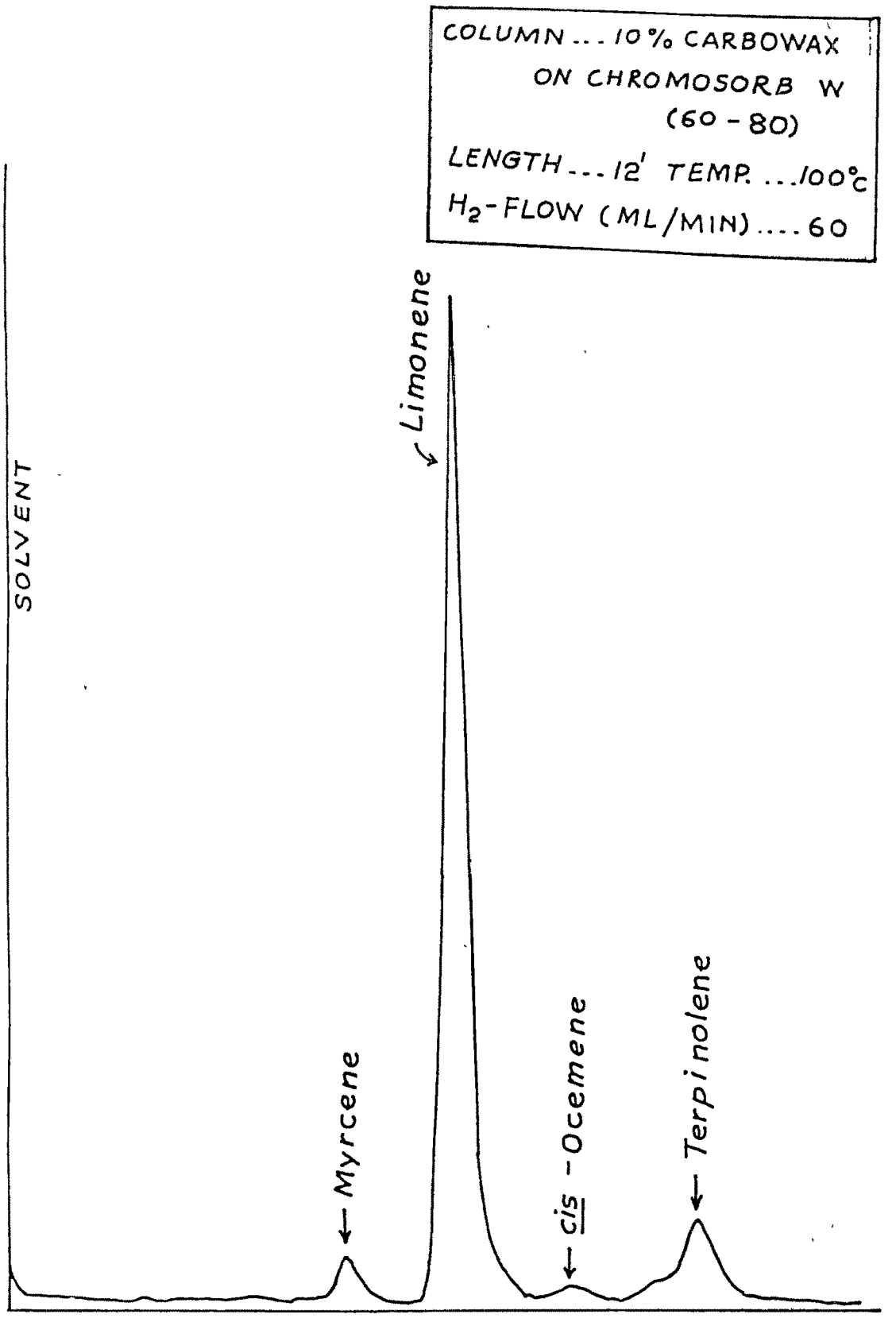


Fig.21 : GLC of reaction products from the reaction of neryl diethyl phosphate with active alumina

TABLE-3 : PRODUCTS FROM THE REACTION OF GERANYL AND/NERYL DIETHYL PHOSPHATES ON ACTIVE ALUMINA [a]

GLC[b] component product from (isomer) 2(E)	2(Z)	Relative retention time (RRT)	Product	Product composition (% GLC)[b] from isomer 2(E)	2(Z)
1	-	0.2;0.48	Unidentified	6.5	-
2	1	1	myrcene (10)	17	2.4
3	-	1.2	α-terpinene (11)	1.7	-
4	2	1.33	limonene (12)	34.5	86
5	3	1.57	cis-ocimene (13)	10.7	1.45
6	-	1.71	trans-ocimene	15.2	-
7	4	2.0	terpinolene[c] (15)	14.2	8.7

(a) Substrate: reagent ratio (gm) 1:30, solvent dry CH_2Cl_2, shaking at room. temp. (~30°).

(b) Column: 360 cm X 0.32 cm Stainless steel column packed with 10 % Carbowax on 60-80 mesh Chromosrob W; temp. 100°C; carrier gas: 60 ml H_2/min.

(c) It has been observed that under the above conditions used for GLC, p-cymene and terpinolene do not separate clearly. Hence, presence of small % of p-cymene under the terpinolene will not be [illegible]

TABLE-4: PRODUCTS FROM THE REACTION OF GERANYL AND NERYL DIETHYL PHOSPHATES ON ACTIVE ALUMINA [a]

GLC[b] component product from (isomer) 2(E)	2(Z)	Relative retention time (RRT)	Product	Product composition (% GLC)[b] from isomer 2(E)	2(Z)
1	1	1	myrcene (10)	3.31	6.0
2	2	1.2	α-terpinene (11)	9.54	9.93
3	3	1.33	limonene (12)	11.82	24.01
4	-	1.57	cis-ocimene (13)	7.88	-
5	4	1.71	trans-ocimene (14)	16.59	11.18
6	5	1.92	Unidentified	13.07	6
7	6	2.0	terpinolene[c] (15)	37.75	42.85

(a) Substrate: reagent ratio (gm) 1:10; solvent: pet.ether (60-80°). Refluxing for 4 hrs.

(b) Column: 360 cm X 0.32 cm Stainless steel column packed with 10 % Carbowax on 60-80 mesh Chromosorb W; temp. 100°C; Carrier gas: 60 ml H_2/min.

(c) It has been observed that under the above conditions used for GLC, p-cymene and terpinolene do not separate [illegible]. Hence, the presence of small % of p-cymene [illegible] terpinolene peak is not excluded.

Several investigations were carried out, on the effect of activation temperature of alumina and polarity of the solvent, on the product distribution and the overall yields in these biomimetic cyclisation reactions of allylic diethyl phosphate esters. In the light of above experiments, it was observed the formation of more elimination products and in less overall yields in the reactions with active alumina, activated at higher temperatures (>400^{o}C). Since the catalytic activity of alumina depends on the surface active acidic and basic sites, the nature of these active sites may vary with activation temperatures of alumina. At low activation temperatures basic character is exhibited more, due to the surface hydroxy ions. High activation temperatures would favour the desorption of hydroxyl ions, which leave exposed Al^{+3} ions on the surface, as a result the alumina shows pronounced acidic character. Probably this varying nature of the surface active sites would alter the course of the reaction and hence the unusual product variation.

Under the present study in the effect of solvent polarity, it is observed, in more polar solvents (diethyl ether, acetonitrile), the total reaction yields are low and elimination products are more when compared in the less polar solvents (dichloromethane and pet ether 60-80), in these cyclisation reactions. This is probably due to more adsorptive power of allylic diethyl phosphate ester on alumina in non-polar

solvents when compared to polar solvents.

From the above considerations and from practical point of view, the following parameters were selected as optimal conditions for facile cyclization of allylic diethyl phosphate esters. Solvent: dry dichloromethane, temperature 30°C, reaction conditions: shaking with active alumina (derived from the hydrolysis of aluminium isopropoxide, activated at 250°/24 hrs, pH=7; activity: grade I). Under these conditions neryl diethyl phosphate gave maximum amount of cyclised products (~95%).

Geranyl diethyl phosphate (9):

Geranyl diethyl phosphate (9) was prepared from geraniol by the same method, as was used for neryl diethyl phosphate ($Cl\ PO(OEt)_2$, pyridine, dry dichloromethane). After usual aq. work up, it afforded pure geranyl diethyl phosphate ester, homogeneous by TLC analysis (15% EtOAc/pet.ether 60-80°) and spectroscopically consistent. The PMR of the product showed the presence of d,d (merged as triplet) at 4.3-4.6 ppm (due to $\underline{CH_2}$-OP(O)$(OEt)_2$) and multiplet at (3.85-4.2 ppm) due to CH_2-OPO$(O\underline{CH_2}$-$CH_3)_2$. The disappearance of doublet due to $\underline{CH_2}OH$ (at 4.0 ppm) and appearance of d, d (merged as triplet) at 4.3 ppm reveals the formation of geranyl diethyl phosphate. PMR of geranyl diethyl phosphate ester is shown in Fig.22.

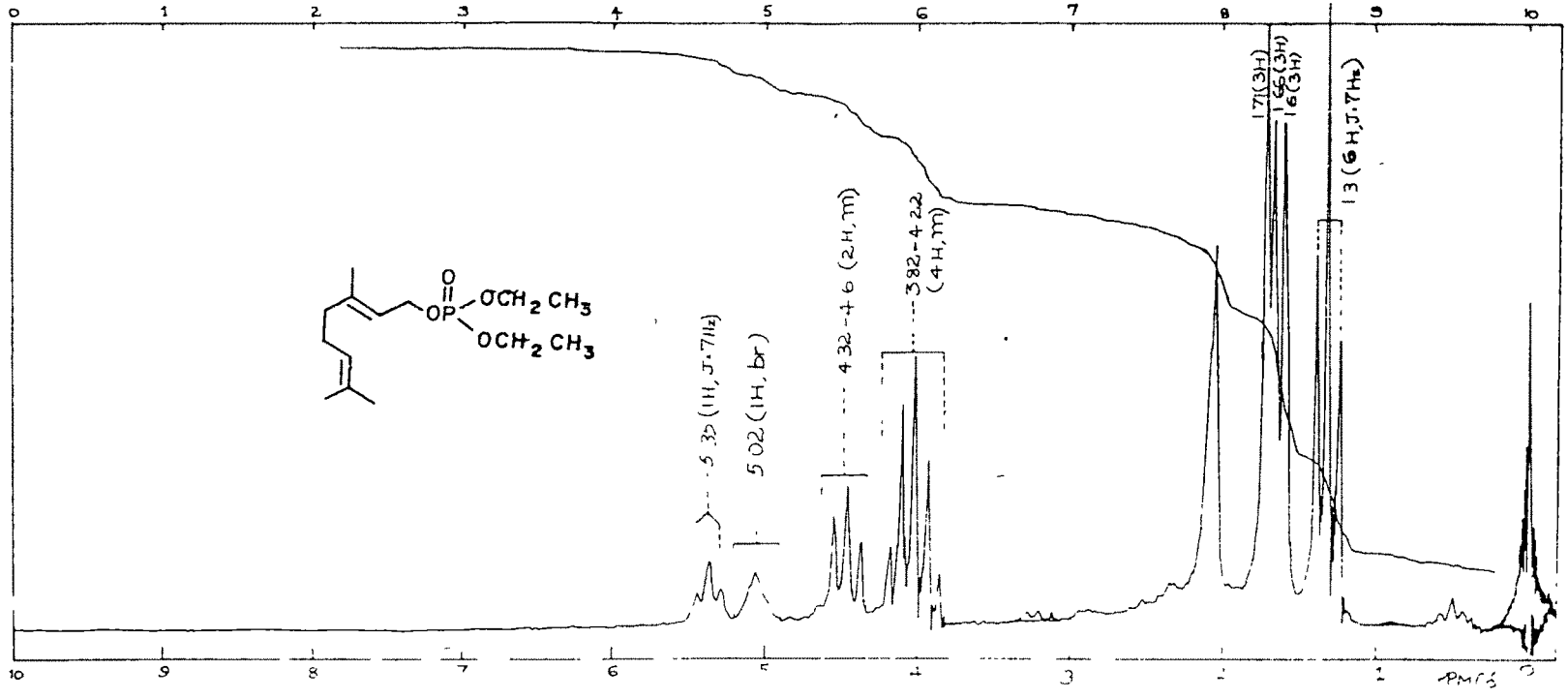


Fig.22 : PMR spectrum of geranyl diethyl phosphate (9)

Having attained the optimal experimental conditions largely favouring cyclisations in the case of neryl diethyl phosphate, a systematic study of cyclisation of geranyl diethyl phosphate was carried out under these conditions as follows.

Cyclization reaction of geranyl diethyl phosphate (9) was carried out, on active alumina (activated at 250°/24 hrs, pH=7; activity: grade I) in dry dichloromethane by shaking the reaction flask using mechanical shaker, following the same experimental procedure as was used for neryl diethyl phosphate. After usual filtration work up, the crude was distilled to give a hydrocarbon mixture mostly boiling at 120-130°C (oil bath) at 40-50 mm. The GLC of this product showed six major compounds. These were identified by mixed PMR as well as mixed GLC. These compounds were identified as myrcene (10), α-terpinene (11), limonene (12), cis-ocimene (13), trans-ocimene (14) and terpinolene (15) (Fig.20). The compounds of the reaction product, is further confirmed by comparing the RRTs of components of our mixture with that of reported[25]. GLC of the reaction product is shown in Fig.23. The percentage of various cyclic and acyclic compounds formed and identified are summarised in Table-3. It is interesting to note here that geranyl diethyl phosphate ester, with its unfavourable geometry (trans-), yielded around 50 percent of cyclised products of the total reaction product.

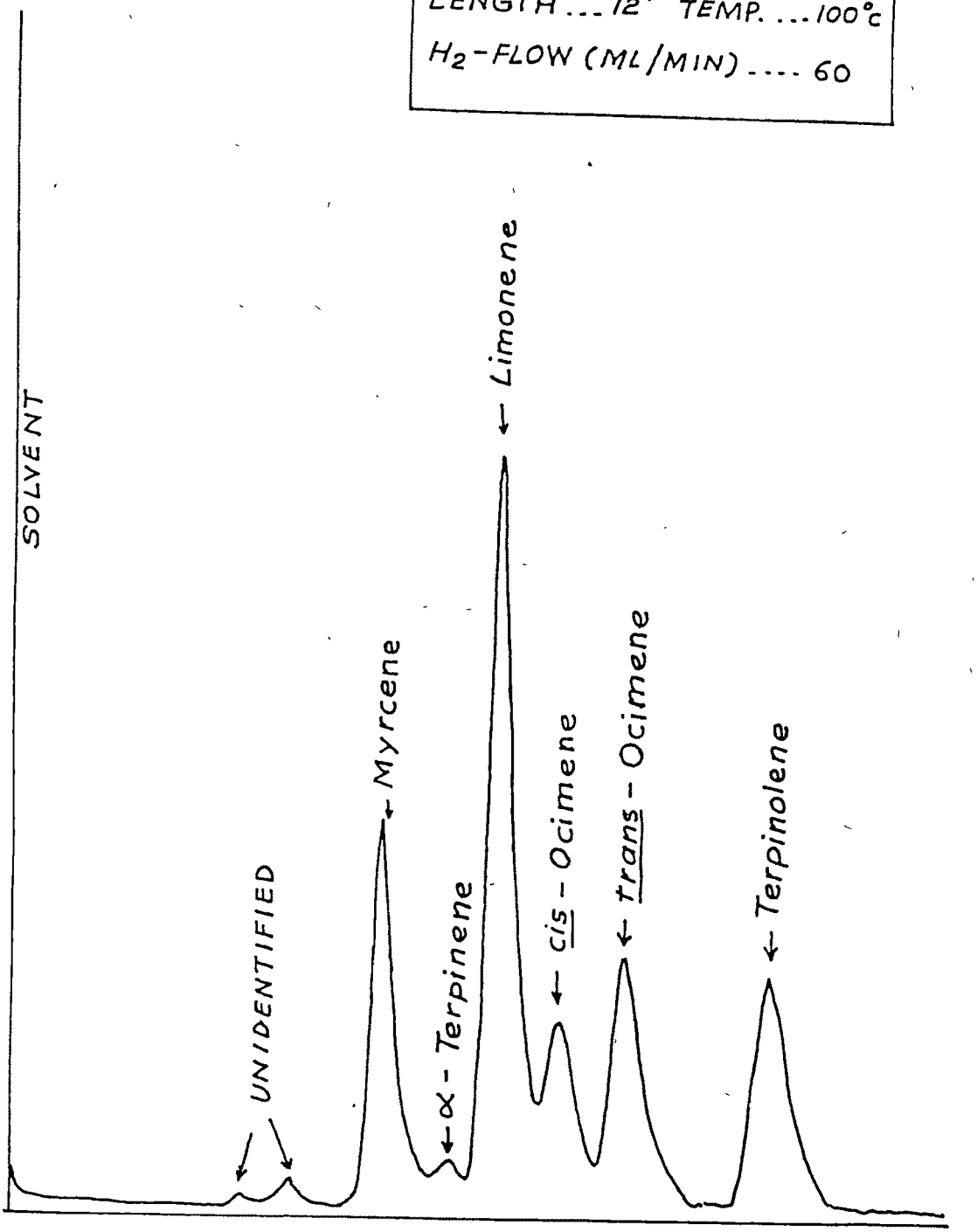


Fig.23 : GLC of reaction products from the reaction of geranyl diethyl phosphate with active alumina

Cyclisation reaction of geranyl diethyl phosphate on active alumina in dry pet.ether (60-80°):

The cyclization reaction of geranyl diethyl phosphate on active alumina in dry pet.ether (60-80°), was carried out by refluxing the heterogeneous mixture under stirring using anhydrous conditions for 4 hrs and kept 12 hrs at room temperature (~25°C). After usual filtration work up, the crude was distilled and identified the compounds by mixed PMR and mixed GLC studies, as was done in the above experiment. The percentage of various cyclic and acyclic compounds formed and identified are summarised in Table-4. It was found that the relative ratio of cyclised products to the elimination products was enhanced. Table-5.

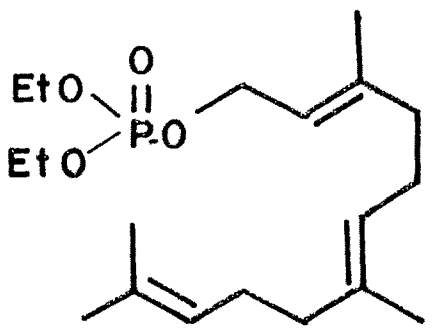
TABLE-5

Substrate used for reaction	Experimental conditions	Relative ratio of cyclized products to elimination products
Geranyl diethyl phosphate	Shaking with active alumina : 4 hrs (~30°) and kept overnight for 12 hrs (~25°C), Solvent: dry dichloromethane	1.17
Geranyl diethyl phosphate	Refluxing with pet. ether (60-80°) on active alumina for 4 hrs and kept overnight for 12 hrs (~25°C)	2.12
Neryl diethyl phosphate	Shaking with active alumina 4 hrs (~30°C) and kept overnight for 12 hrs (~25°C), Solvent: dry dichloromethane	24.59
Neryl diethyl phosphate	Refluxing with pet. ether (60-80°) and active alumina for 4 hrs and kept overnight for 12 (~25°C)	4.46

CYCLIZATION OF FARNESYL DIETHYL PHOSPHATES

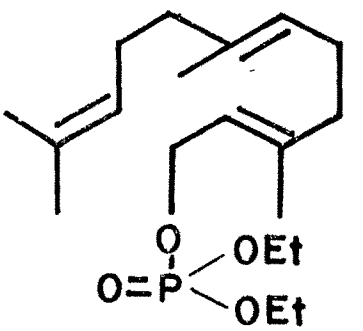
The foregoing study on the cyclisation of monoterpene primary allylic diethyl phosphate esters on active alumina reveals the formation of cyclisation products under π-bond participation of the species formed under the conditions described. The cyclisation, as expected, is more facile with neryl diethyl phosphate (cis) than with the geranyl diethyl phosphate (trans). It was of interest to extend the study to the sesquiterpene analogues, (Z,E)-farnesyl diethyl phosphate (16) and (E,E)-farnesyl diethyl phosphate (17) (Fig. 24), as these offer the interesting possibility of cyclisation into 6- and/or 10-membered ring compounds, besides the elimination products.

The required substrates were prepared by first synthesising the sterically pure (Z,E)- and (E,E)-farnesols (described in detail in experimental section).

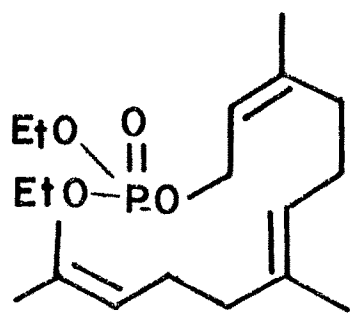


a

17

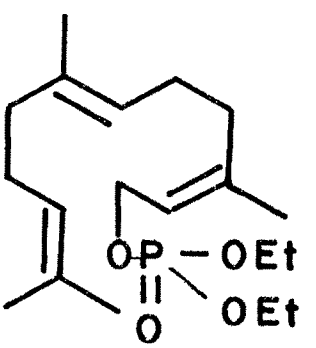


b



a

16



b

FIG. — 24

(Z,E)-Farnesyl diethyl phosphate (16):

(Z,E)-Farnesol was converted into its corresponding diethyl phosphate ester by the same method as that used for neryl diethyl phosphate ester. [Cl P(O)$(OEt)_2$, pyridine, CH_2Cl_2]. (Z,E)-farnesyl diethyl phosphate, so obtained, was pure by TLC analysis (15 % EtOAc/pet-ether 60-80°) and spectroscopically consistent. The PMR of this compound showed the presence of d, d (merged as triplet) at 4.3-4.6 ppm due to $\underline{CH_2}OPO(OEt)_2$, which reveals the formation of diethyl phosphate ester. It was not further purified due to its lability towards heat and adsorbents. PMR of (Z,E)-farnesyl diethyl phosphate ester is shown in Fig.25.

Cyclisation reaction of (Z,E)-farnesyl diethyl phosphate was carried out on active alumina (activated at 250°/24 hrs, pH=7; activity: grade I), using dichloromethane as solvent, under the optimal experimental conditions, used for neryl diethyl phosphate. After the usual work up (see experimental) the crude was distilled using micro bulb distillation unit. The distillate consists of atleast six compounds, of which four major compounds, accounting for 97 % of the total, were identified as trans-β-farnesene (18), β-bisabolene (19) and trans-α-bisabolene (20) + a r curcumene (21) (Fig.26), by mixed PMR, GLC (by comparing the

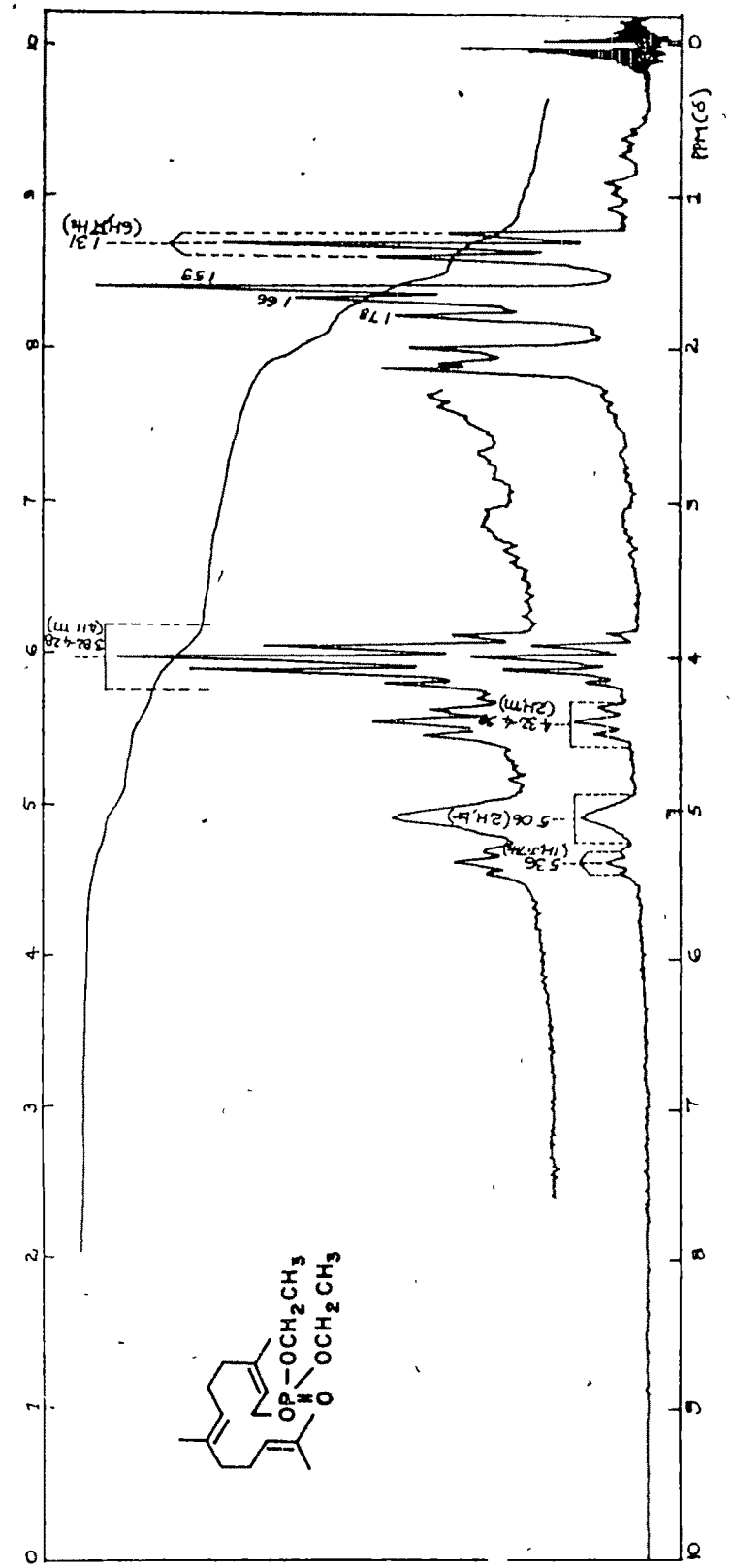


Fig.25 : PMR spectrum of 2(Z), 6(E)-farnesol diethyl phosphate (16)

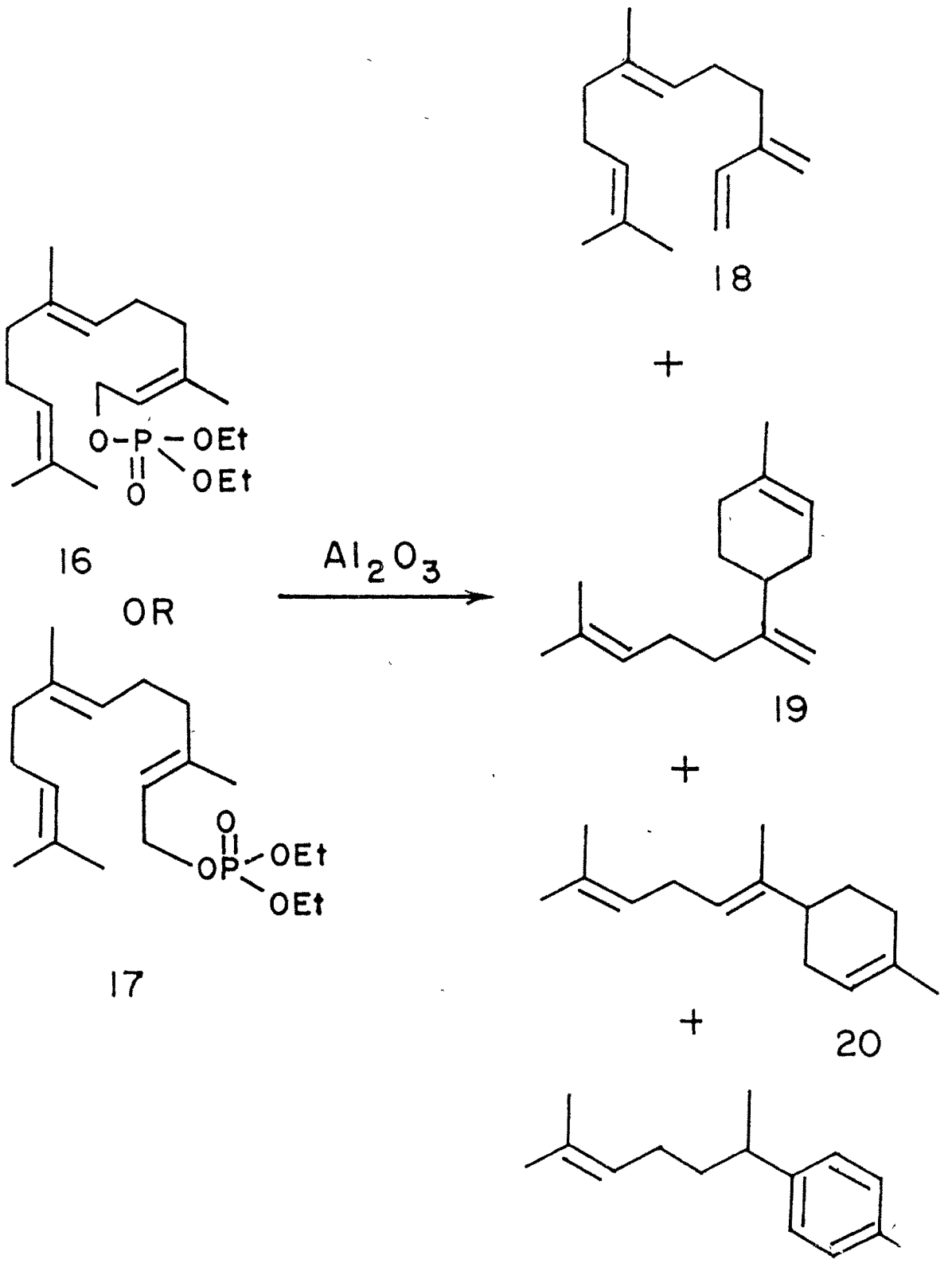


FIG. — 26

relative retention times with the reported values)[25]. The percentage of various products formed and identified are summarised in Table-6. GLC of the total reaction product is shown in Fig.27.

Cyclisation reaction of (Z,E)-farnesyl diethyl phosphate ester on active alumina in dry pet. ether (60-80°C):

Cyclisation reaction of (Z,E)-farnesyl diethyl phosphate was carried out on active alumina, using dry pet. ether (60-80°), by refluxing the stirring heterogeneous mixture, as described in the case of neryl derivative. After usual filtration work up, the solvent was stripped off carefully to get a crude reaction product, which was distilled by using micro bulb distillation unit. The product analysis of the distillate showed the formation of trans-β-farnesene (4.3 %), β-bisabolene (41.73 %) and trans-α-bisabolene + a r-curcumene (43.47 %). The relative ratio of cyclised products to elimination products was enhanced and given in Table-7.

(E,E)-Farnesyl diethyl phosphate (17):

(E,E)-Farnesol was converted into its corresponding diethyl phosphate ester by the same method as that was used for neryl diethyl phosphate ester [Cl $P(O)(OEt)_2$, pyridine, CH_2Cl_2]. (E,E)-farnesyl diethyl phosphate, so obtained, was pure by TLC analysis (15 % EtOAc/pet. ether 60-80°) and

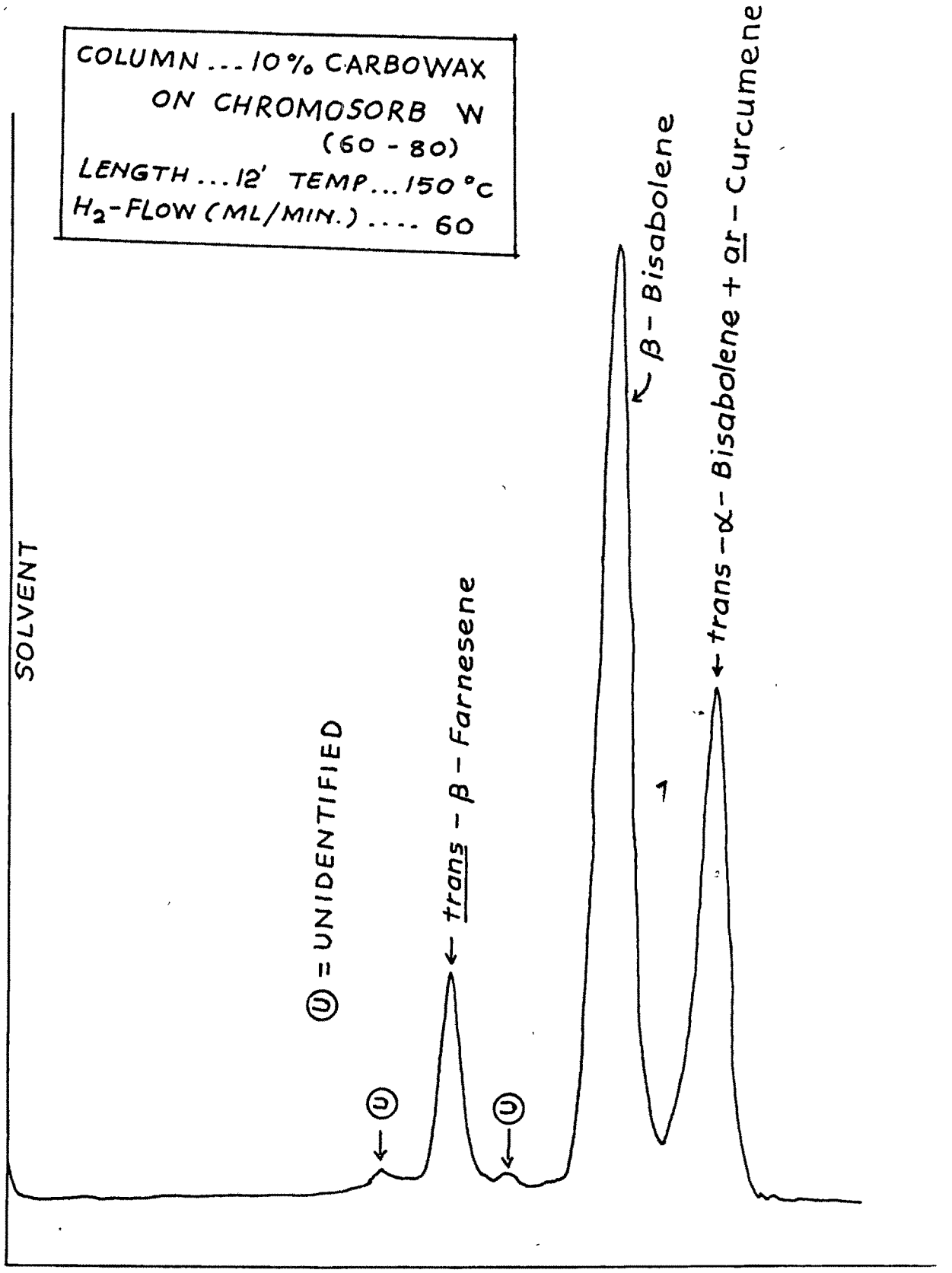


Fig.27 : GLC of reaction products from the reaction of 2(Z), 6(E)-farnesyl diethyl phosphate with active alumina

TABLE-6 : PRODUCTS FROM THE REACTIONS OF 2(E), 6(E)- AND 2(Z), 6(E)-FARNESYL DIETHYL PHOSPHATES ON ACTIVE ALUMINA [a]

GLC[b] Component product from (isomer) (E,E)	(Z,E)	Relative retention time (RRT)	Product	Product composition (% GLC)[b] from isomer (E,E)	(Z,E)
1,2	1,2	0.86; 0.94	Unidentified	2.97	0.88
3	3	1	trans-β-farnesene (18)	20.6	11.03
4	4	1.15	Unidentified	1.14	1.32
5	5	1.25	Unidentified	4.8	0.66
6	6	1.3	β-bisabolene (19)	43.47	56.3
7	7	1.6	trans-α-bisabolene[c] (20)	24.02	29.8
8	8	1.6	ar-curcumene (21)		

(a) Substrate: reagent ratio (gm) 1:30; Solvent: dry CH_2Cl_2, Shaking at R.T. (~30°C).

(b) Column: 360 cm X 0.3 cm. Stainless steel column packed with 10 % Carbowax on 60-80 mesh Chromosorb W; temp. 150°C. Carrier gas: 60 ml H_2/min.

(c) Both 20 and 21 have the same RRT on Carbowax under the above conditions used for GLC. So, presence of 21 under the peak of 20 can not be excluded.

spectroscopically consistent. The PMR of this compound showed the presence of d, d (merged as triplet) at 4.32-4.6 ppm due to $\underline{CH_2}OP(O)(OEt)_2$, which reveals the formation of diethyl phosphate ester. It was also not further purified due to its lability towards heat and adsorbents. PMR of (E,E)-farnesyl diethyl phosphate ester is shown in Fig.28.

Cyclisation reaction of (E,E)-farnesyl diethyl phosphate was carried out on active alumina (activated at 250°/24 hrs, pH=7; activity: grade I) using dichloromethane as solvent under the optimal experimental conditions, established for neryl diethyl phosphate. After usual filtration work up, the crude was distilled. The distillate consists of atleast 7 compounds, of which four major compounds accounting for 88% of the total, were identified, as trans-β-farnesene (20.6 %), β-bisabolene (43.47 %) and trans-α-bisabolene + a r curcumene (24 %) (Fig.26), by mixed PMR and GLC studies (and by comparing the relative retention times with the reported values[25]). The percentage of various products formed and identified are summarised in Table-6. GLC of the total reaction product is shown in Fig.29.

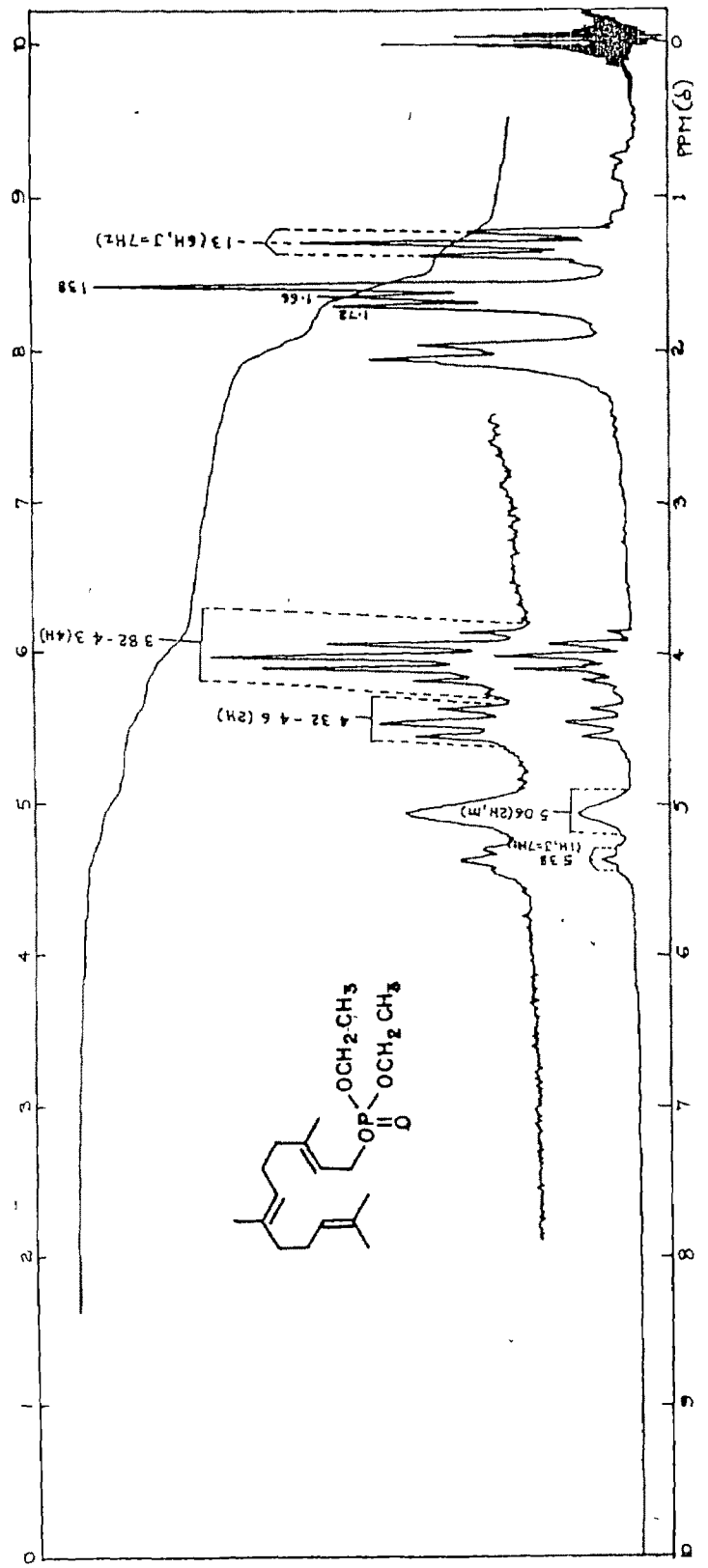


Fig.28 : PMR spectrum of 2(E), 6(E)-farnesyl diethyl phosphate (17)

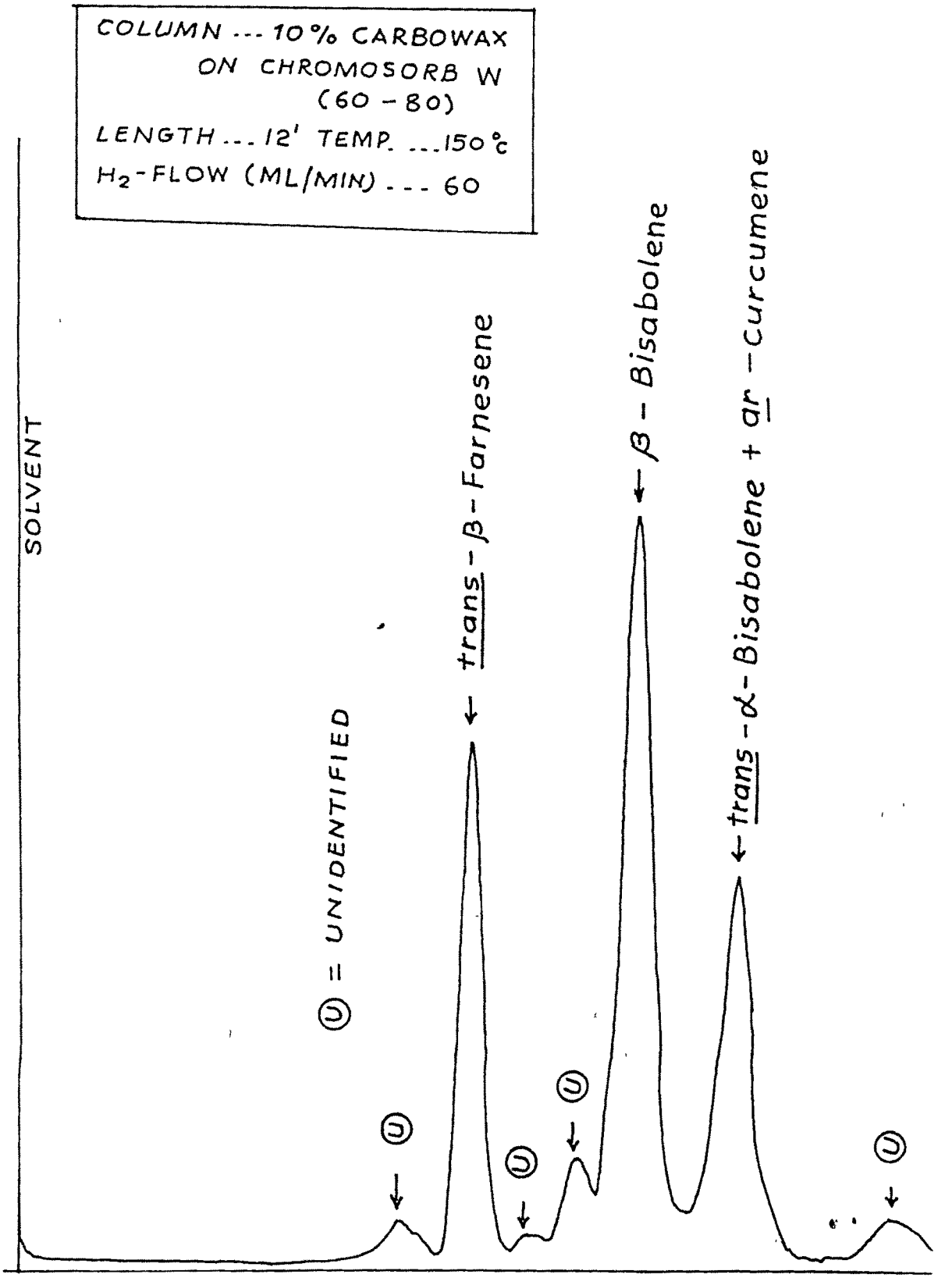


Fig.29 : GLC of reaction products from the reaction of 2(E), 6(E)-farnesyl diethyl phosphate with active alumina

Cyclisation reaction of (E,E)-farnesyl diethyl phosphate in dry pet. ether (60-80°):

Cyclisation reaction of (E,E)-farnesyl diethyl phosphate was carried out on active alumina, using dry petroleum ether (60-80°), by refluxing the stirring heterogeneous mixture, as described in the case of neryl derivative. After usual filtration work up, the crude was distilled using micro bulb distillation unit. The product analysis of the distillate showed the formation of trans-β-farnesene (7.7 %), β-bisabolene (29.6 %) and trans-α-bisabolene + a r currumene (34.72 %). The relative ratio of cyclised products to elimination products was enhanced and given in Table-7.

TABLE-7

Substrate used for reaction	Experimental conditions	Relative ratio of cyclized products to elimination products
2(E),6(E)-Farnesyl diethyl phosphate	Shaking with active alumina 4 hrs (30°C) and kept overnight for 12 hrs (30°C). Solvent: dry dichloromethane	3.27
2(E),6(E)-Farnesyl diethyl phosphate	Refluxing with pet. ether (60-80°) on active alumina for 4 hrs and kept overnight 12 hrs (~25°C).	8.83
2(Z),6(E)-Farnesyl diethyl phosphate	Shaking with active alumina 4 hrs (~30°C) and kept overnight 12 hrs (~25°C); Solvent: dry dichloromethane	7.80
2(Z),6(E)-Farnesyl diethyl phosphate	Refluxing with pet. ether (60-80°C) on active alumina for 4 hrs and kept overnight for 12 hrs at 25°C.	19.63

(E,E,E)-Geranylgeranyl diethyl phosphate (22):

The foregoing study on the cyclisation reactions of mono- and sesquiterpene allylic diethyl phosphate esters reveals the formation of various cyclisation products under π -bond participation of the species formed under the conditions described. It was of interest to extend the study to the diterpene analogue, (eg. (E,E,E)-geranylgeranyl diethyl phosphate) as it offers the interesting possibility of cyclisation into six, ten, and fifteen-membered-ring compounds, besides the elimination products.

(E,E,E)-Geranylgeraniol, which was isolated from wood of cedrela toona and purified by precise and systematic chromatography, was converted into its diethyl phosphate ester using diethyl chlorophosphate,, pyridine and dichloromethane under exactly similar experimental conditions, described in the case of neryl diethyl phosphate. After usual aqueous work up, an excellent yield (90 %) of pure (E,E,E)-geranylgeranyl diethyl phosphate (22), which is homogeneous by TLC analysis (20 % EtOAc/pet. ether (60-80°)) and spectroscopically consistent, was obtained. The PMR of this compound showed the presence of d,d (merged as triplet) at 4.3-4.6 ppm due to $\underline{CH_2}$-OP(O)(OEt)$_2$, which reveals the formation of (E,E,E)-geranylgeranyl diethyl

phosphate ester. IR and PMR of (E,E,E)-geranylgeranyl diethyl phosphate are given in Fig.29 and Fig.29-a. In view of its lability towards heat and adsorbents, purification was not attempted and used as such for cyclisation studies.

Cyclisation reaction of (E,E,E)-geranylgeranyl diethyl phosphate ester was carried out on active alumina (activated at 250°/24 hrs, pH=7; activity: grade I) using dichloromethane as solvent, under the optimal experimental conditions, established for neryl diethyl phosphate. After usual filtration work up, the crude was distilled using micro bulb distillation unit. GLC of the distillate showed the formation of four major compounds, and is given in Fig.30. The mass spectra of all these four compounds were recorded by using computerised GC/mass spectrometer. The mass spectrum of peak No. 1 of GLC corresponds to the reported mass spectrum of β-springene (23)[41].

In order to isolate these isomeric hydrocarbons, various methods were tried. Finally, it was decided to separate these isomers by passing through a column, packed with 15 % $AgNO_3$-SiO_2-gel. Two compounds could be isolated in pure form and these were characterised by their spectral characteristics (IR, PMR and Mass) as 8-geranylmenth-2,7(19)-diene (24) and 8-geranylmenth-2,7(8)(trans)-diene (25) (Fig.32). PMR and mass spectra of the compound (24) are given Figs.33 and 34. The PMR and mass spectra of the compounds(25) are given in Fig.35 and 36. The percentage of various products formed and identified are summarised in Table-8.

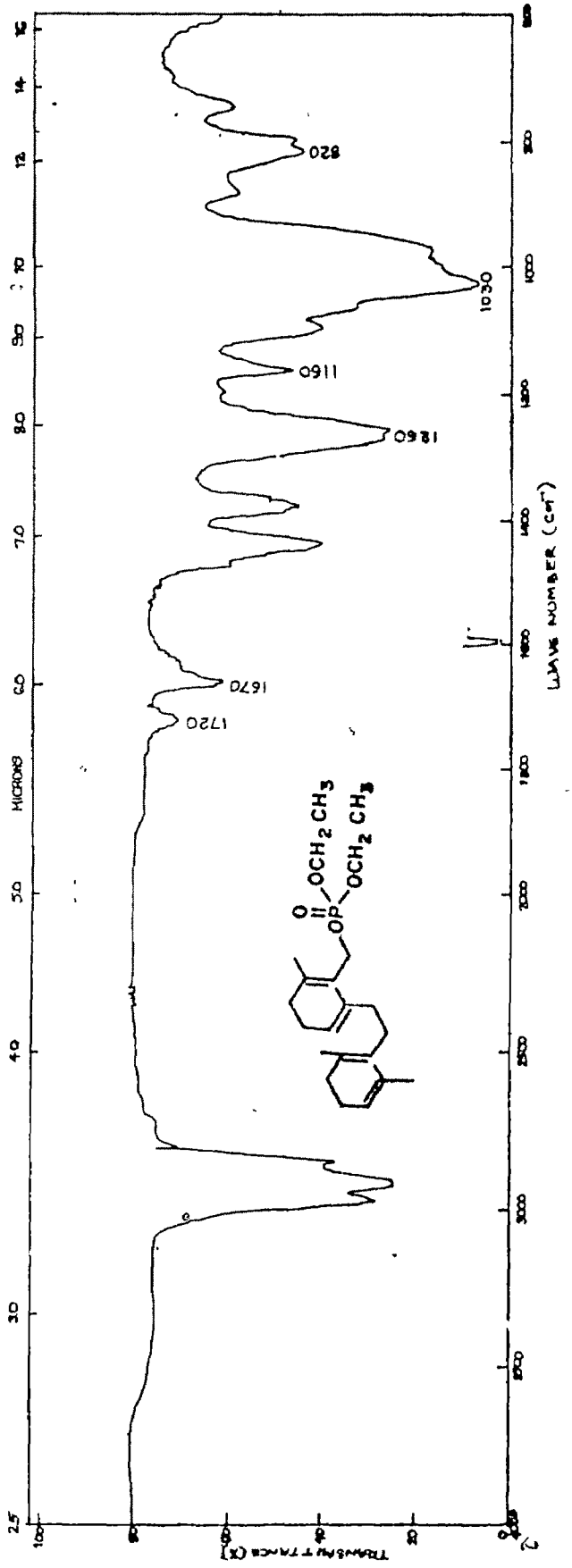


Fig.29 : IR spectrum of (E,E,E)-geranylgeranyl diethyl phosphate (22)

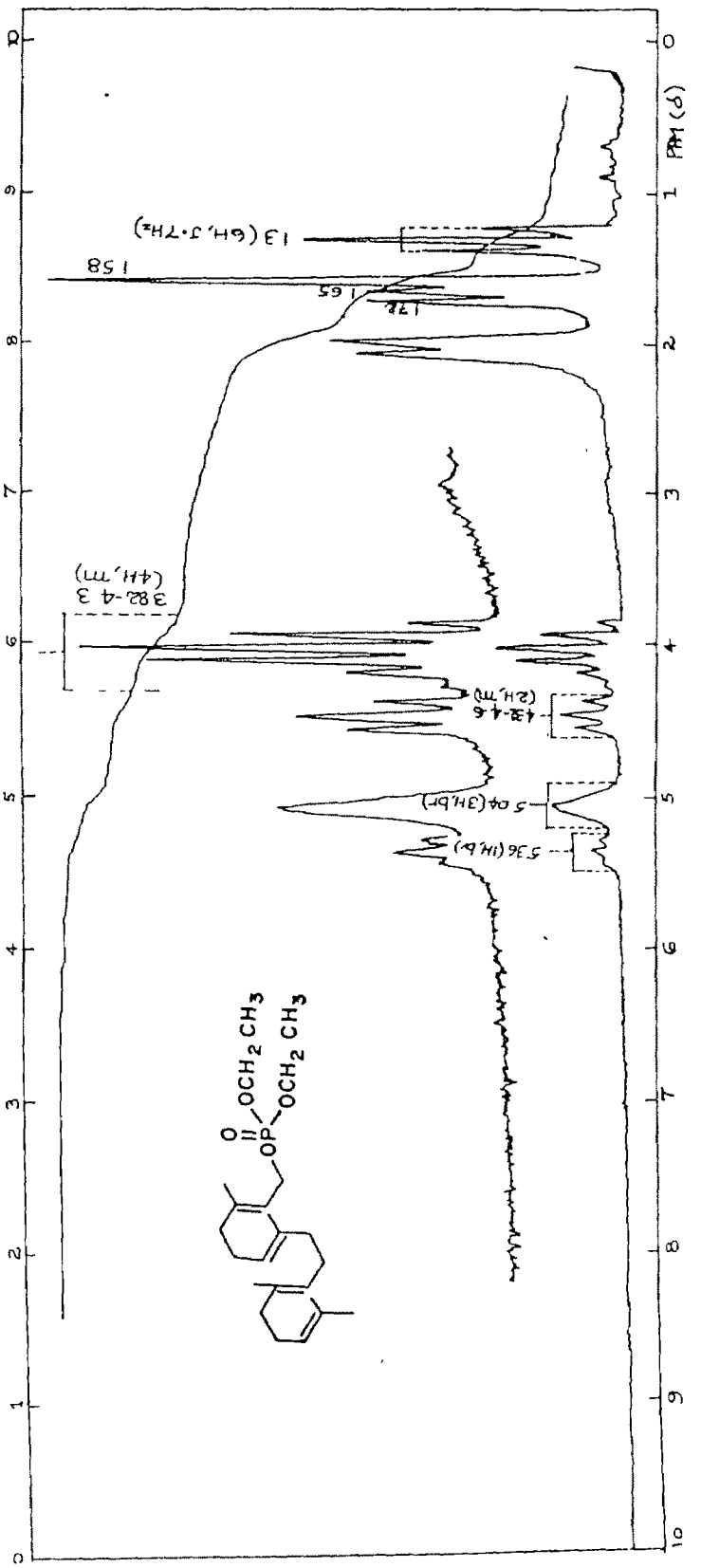


Fig.29a : PMR spectrum of (E,E,E)-geranylgeranyl diethyl phosphate (22)

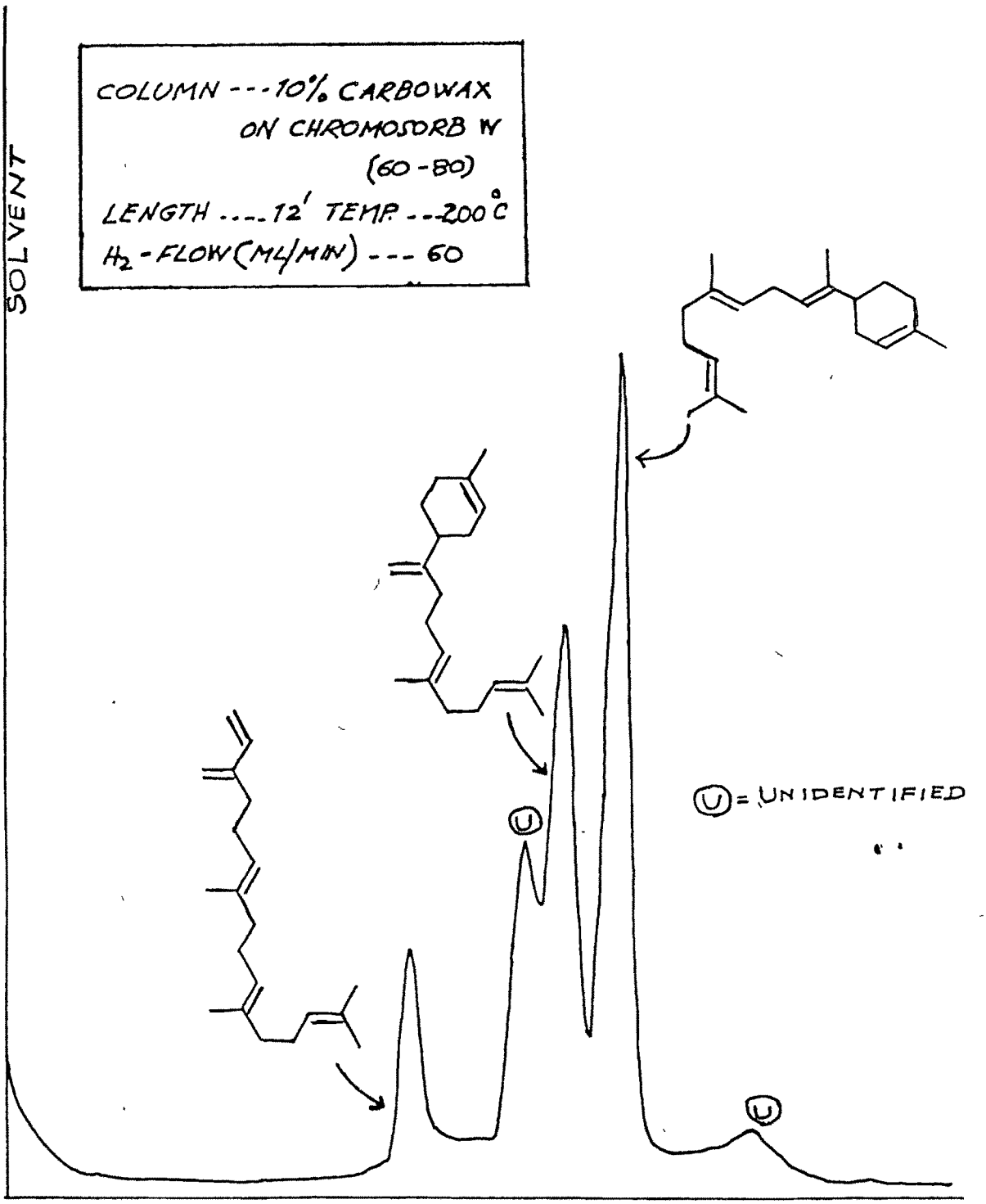
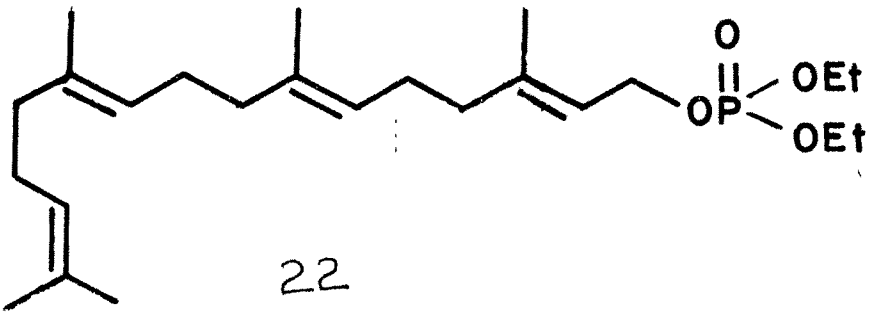


Fig.30 : GLC of reaction products from the reaction of (E,E,E)-geranylgeranyl diethyl phosphate with active alumina

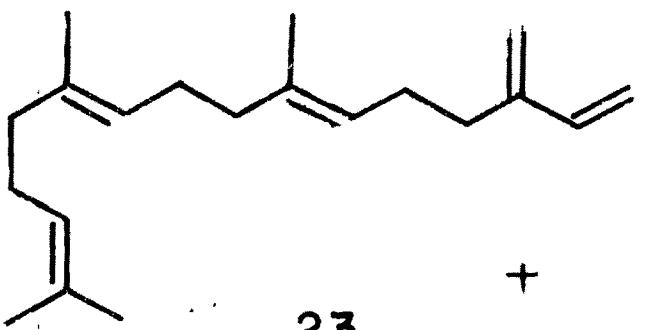
Cyclisation of (E,E,E)-geranylgeranyl diethyl phosphate ester on active alumina in dry pet. ether (60-80°)

Cyclisation reaction of (E,E,E)-geranylgeranyl diethyl phosphate was carried out on active alumina, using dry pet. ether (60-80°) by refluxing the stirring heterogeneous mixture, as described in the case of neryl diethyl phosphate. After usual filtration work up, the crude was distilled by using micro bulb distillation unit. The percentage of various products formed and identified are summarised in Table-8.

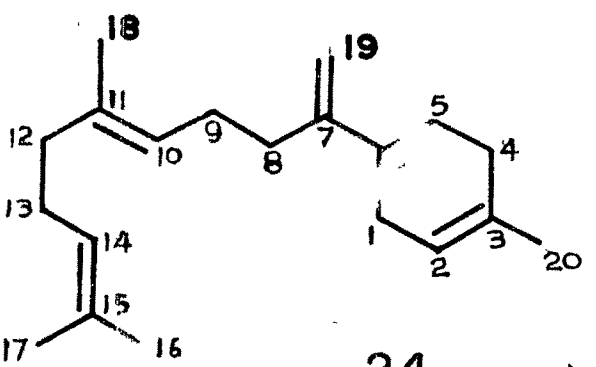


22

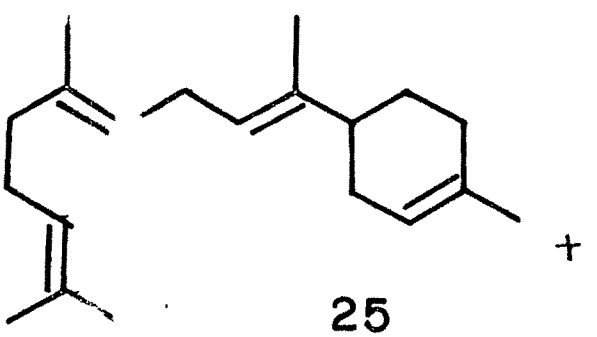
Al_2O_3



23 +



24 +



25 +

UNIDENTIFIED COMPOUND

FIG. – 32

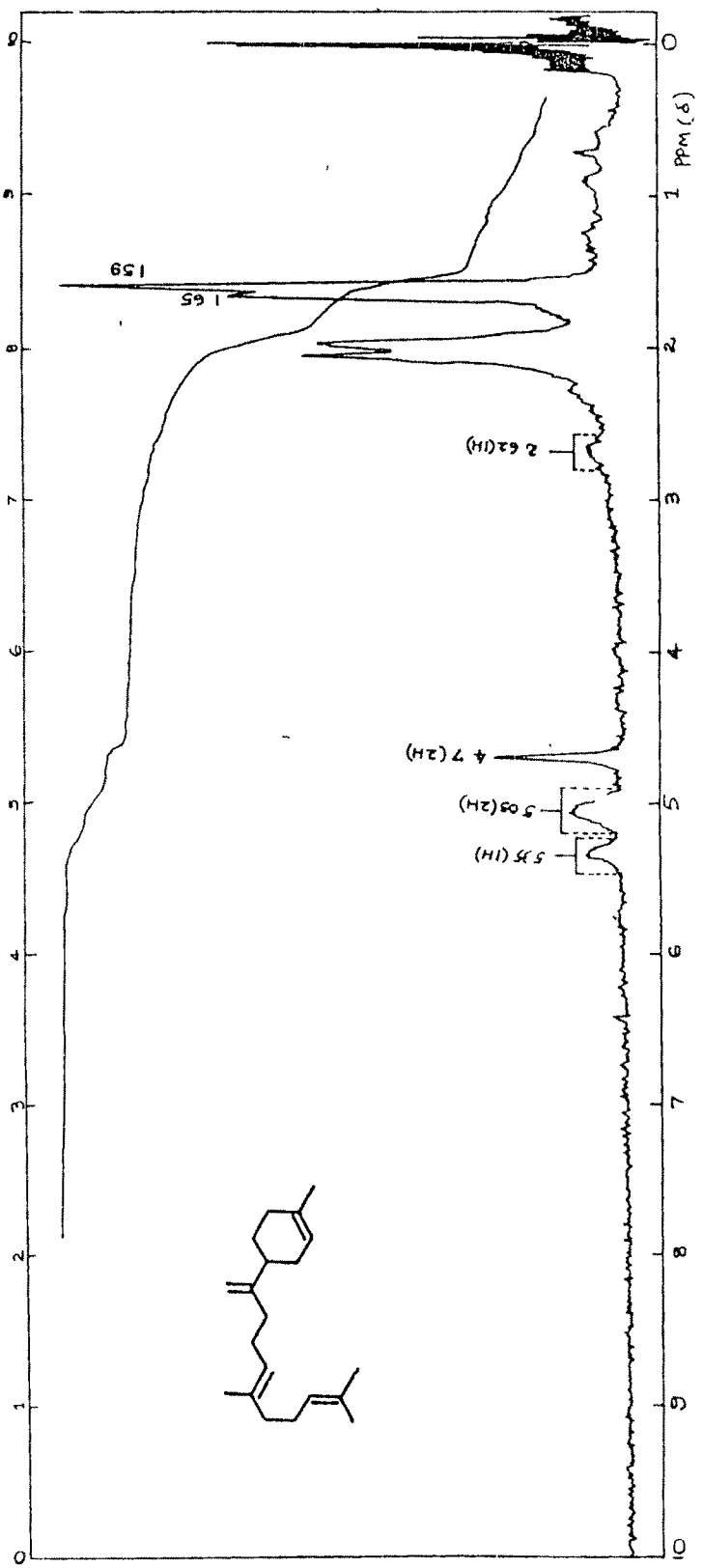


Fig.33 : PMR spectrum of 8-geranylmenth-2,7(19)-diene (24)

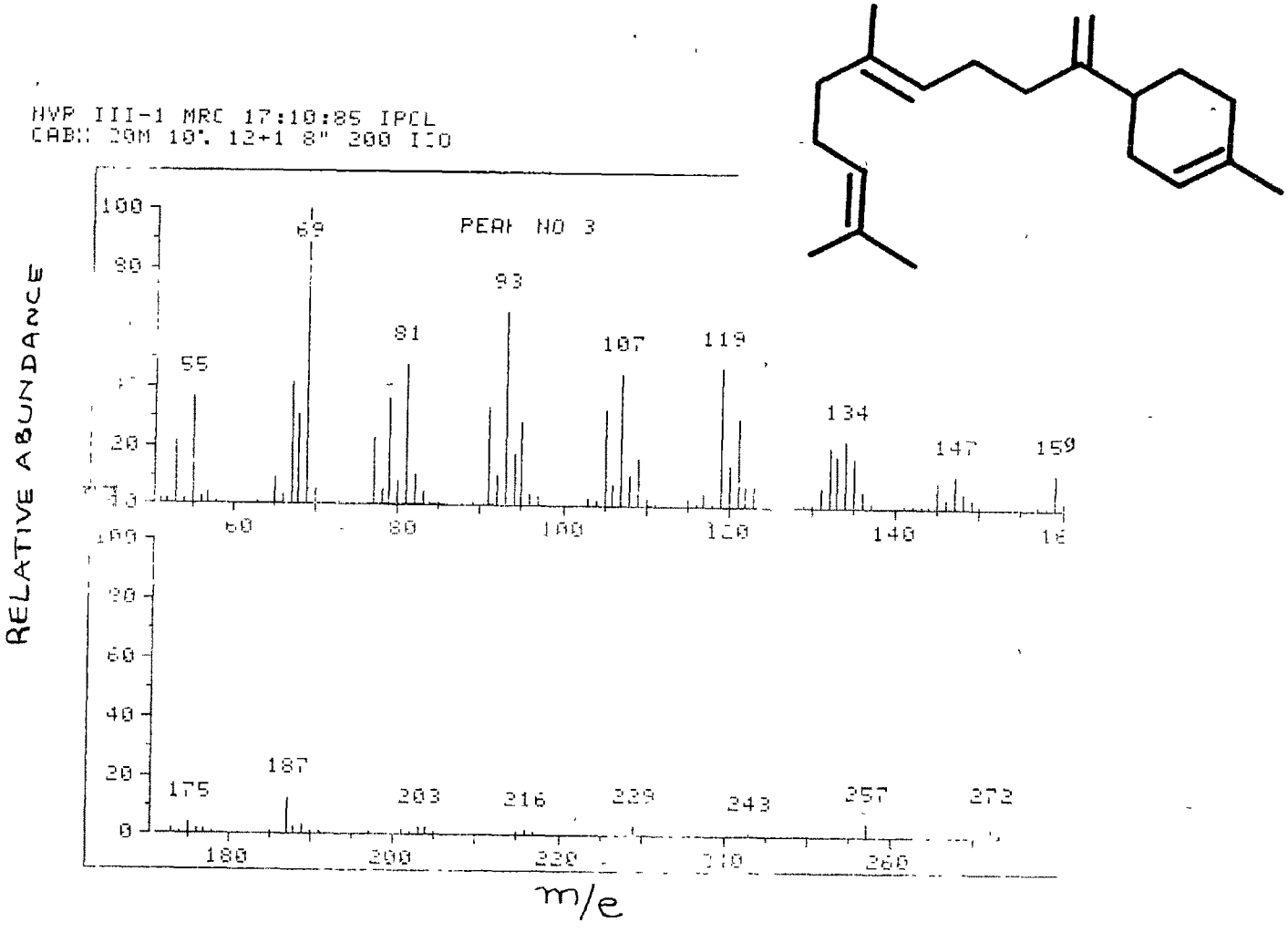


Fig.34 : Mass spectrum of 8-geranylmenth-2,7(19)-diene (24)

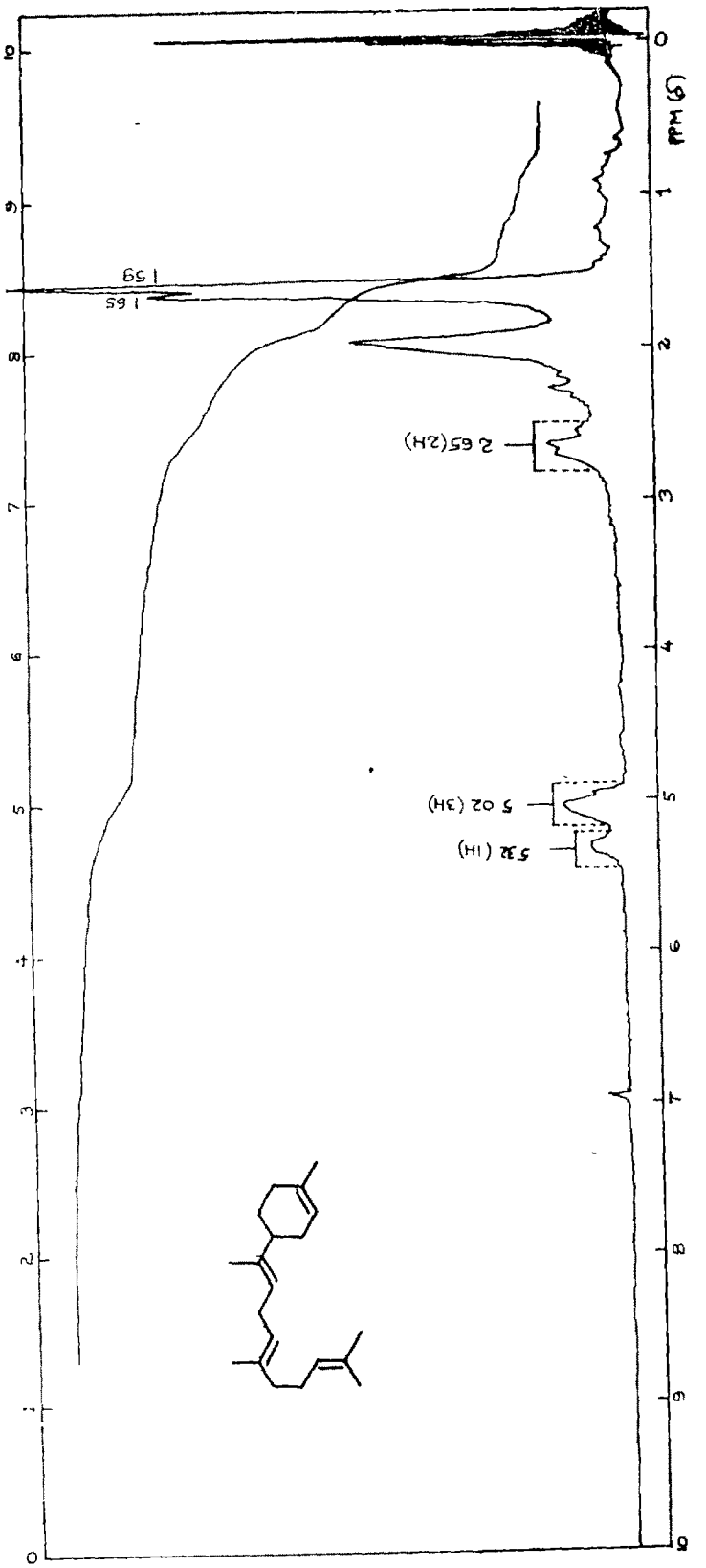


Fig. 35 : PMR spectrum of 3-geranylmenth-2,7(8)(trans)-diene (25)

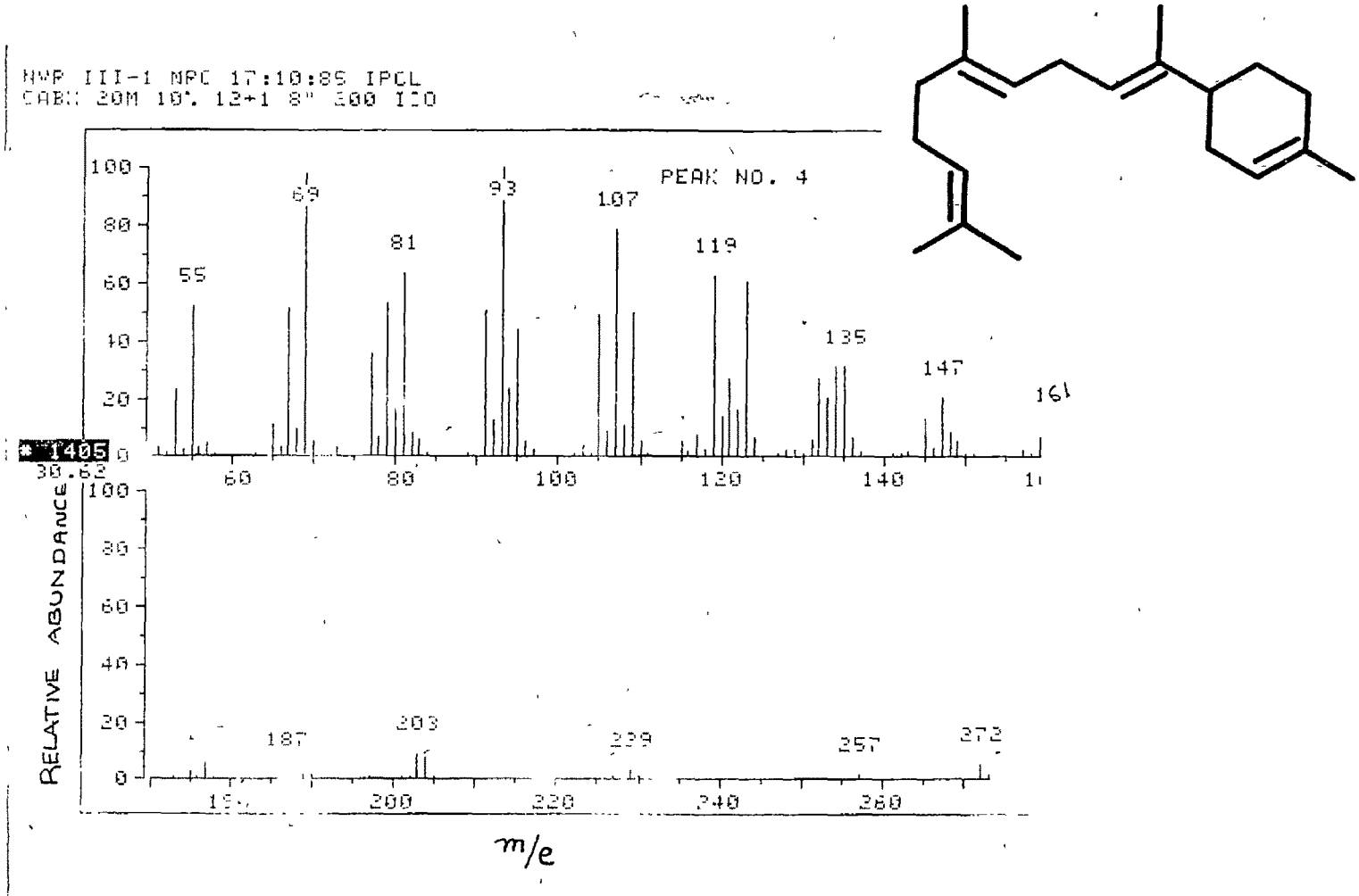
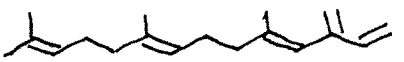
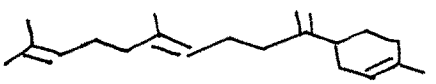
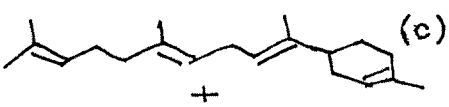
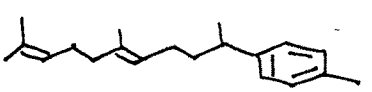


Fig.36 : Mass spectrum of 8-geranylmenth-2,7(8)(trans)-diene (25)

TABLE-8 : PRODUCTS FROM REACTIONS OF (E,E,E)-GERANYLGERANYL DIETHYL PHOSPHATE ON ACTIVE ALUMINA [a]

GLC[b] Component product from isomer (E,E,E)-	Relative retention time (RRT)	Product	Product composition (% GLC)[b] A	B
1	0.68, 0.9	Unidentified	-	3.26
2	1	 (23)	9	12.0
3	1.25	Unidentified	19.8	18.73
4	1.38	 (24)	29.35	30.90
5	1.50	 [c] (25) +  (25a)	36.86	33.72

(a) A. Substrate: reagent ratio (gm) 1:30; solvent: dry CH_2Cl_2; shaking at room temperature (~30°C).

B. Substrate: reagent ratio (gm) 1:10; solvent: dry pet. ether (60-80). Refluxing 4hrs.

(b) Column: 360 cm X 0.32 cm, Stainless steel column packed with 10 % Carbowax on 60-80 mesh Chromosorb W; temperature 200°C; Carrier gas: 60 ml H_2/min.

(c) Both 25 and 25(a) have the same RRT on carbowax, under the above conditions used for GLC. So the presence of 25(a) under the peak of 25 can not be excluded.

C. EFFECT OF SONICATION

Application to biomimetic cyclisation of terpene allylic phosphate esters

Ultrasounds have rarely been employed by Organic Chemists. Recently, they have been reported to accelerate the hydrolysis of carboxylic esters[42], to induce the cleavage of C-X bonds of various halides[43] and to assist in the mercury reduction of α-α-dibromo ketones[44]. Several other processes, most of them destructive[45], have also been discussed. But to our knowledge, the application of ultrasonic vibrations, no finding to date, in the domain of biomimetic terpene cyclisations, was observed.

Any reaction heterogeneous in nature, usually requires a large reagent and prolonged reaction times. We have found that ultrasonic irradiation affords a significant amelioration in reducing the reaction times of the biomimetic cyclisations of allylic diethyl phosphate esters (eg. neryl diethyl phosphate) on active alumina.

The substrate chosen for the present study is neryl diethyl phosphate. It was prepared from nerol and diethyl chlorophosphate, under similar reaction conditions, described earlier. Cyclisation reaction of neryl diethyl phosphate ester on active alumina in dichloromethane was

carried out in ultrasonic vibrations bath, by keeping the reaction flask in an area, where the effective ultrasonic vibrations are high and sonicated for 30 minutes by maintaining the reaction temperature at 25°C. After usual filtration work up, the product analysis showed the formation of five major compounds and these are identified as myrcene (10), limonene (12), cis-ocimene (13), trans-ocimene (14) and terpinolene (15).

A parallel reaction, using neryl diethyl phosphate and active alumina in dichloromethane, was carried out under shaking conditions to compare the yields and product distribution. The percentage of various compounds formed and identified in these above experiments is summarised in Table-9. Eventhough, it is not yet possible to interpret the exact effects of ultrasounds in biomimetic cyclisations in reducing the reaction times, the following explanations are discussed.

TABLE-9 : EFFECT OF SONICATION: APPLICATION TO BIOMIMETIC CYCLISATION OF TERPENE ALLYLIC PHOSPHATE ESTERS ON ALUMINA

Sr. No.	Substrate	Mode of reaction 25°C/time CH_2Cl_2	Product composition[a] (% GLC)						% yield
			10	12	13	14	15	UI	
1.	Neryl diethyl phosphate	Sonication/ 30 min.	5	63.5	3	3	19.1	5.7	78
2.	-do-	Shaking/ 30 min.	6	74.8	3	2	8.1	6.	58
3.	-do-	Sonication/ 15 min.	5.2	64.5	3	3	21.	2.6	74

(a) Column: 360 cm X 0.3 cm. Stainless steel column packed with 10 / Carbowax on 60-80 mesh Cromosorb W; temp. 100°C; Carrier gas: 60 ml H_2/min.

UI - Unidentified products

This may be due to the strong agitation of the reaction mixture, results from the cavitation phenomenon. Cavitation, is a phenomenon in ultrasounds, which produces microscopic gas bubbles in the solution as a result of pressure changes. Their formation and implosion liberates considerable energy. It has been calculated that in cavitation phenomenon, the temperature at the centre of collapsing bubbles to rise to 10^4 to 10^6 degrees kelvin and its pressure to increase upto several thousand atmospheres.

In addition to these primary effects of cavitation, the secondary effects includes macroscopic heating due to sound absorption and resonance characteristics of the medium and vessel are responsible in the reactions of sonication.

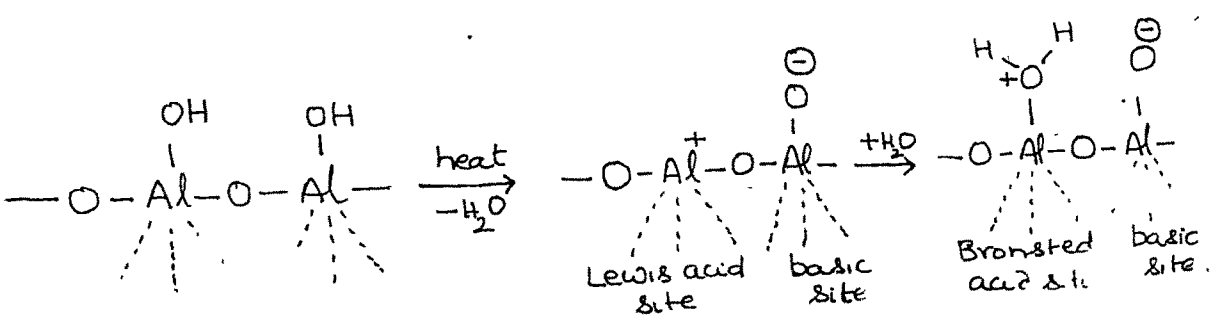
It can also be supposed that mechanical effects caused by ultrasound energy, which produces some alterations at the metal surface and keep the metal surface free from derived species in such a way that it remains highly activated.

Conclusions Ultrasonic irradiation of heterogeneous reaction mixtures can offer some important advantages, such as improved yields, reduced reaction times and the possibility of using reduced amounts of reagents. It is believed that application of ultrasounds may serve to catalyze other heterogeneous reactions in a simple and facile manner.

Discussion :

There has been considerable interest in mechanisms of cyclisation reactions of open chain monoterpenoics, neryl, geranyl; sesquiterpenoids, 2(Z), 6(E)- and 2(E), 6(E)-farnesyl and diterpenoid, (E,E,E)-geranylgeranyl derivatives. Now, we discuss here the mechanistic implications of non-enzymic biomimetic cyclisations of terpene allylic diethyl phosphate esters on active alumina.

Before rationalising the mechanistic pathways in these cyclisation reactions, it is essential first to state, in a brief manner, our present understanding of the nature of alumina surface. It is generally agreed that alumina has dipolar character[46] and there are both electron-donar and electron-acceptor sites on its surface and acts as an acid-base bifunctional catalyst. Some valuable information is also available[47] about the surface groups of alumina. Water removal from alumina surface, on heat treatment, is shown below.



The Lewis acid site is visualized as an incompletely coordinated aluminium atom formed by dehydration, and the weak Bronsted acid site as a Lewis site which has adsorbed moisture, while the basic site is considered to be a negatively charged oxygen atom. And it has been stated that random removal of all hydroxyl pairs leaves the surface as illustrated in Fig.37. The remaining $OH^{(-)}$ ions cover

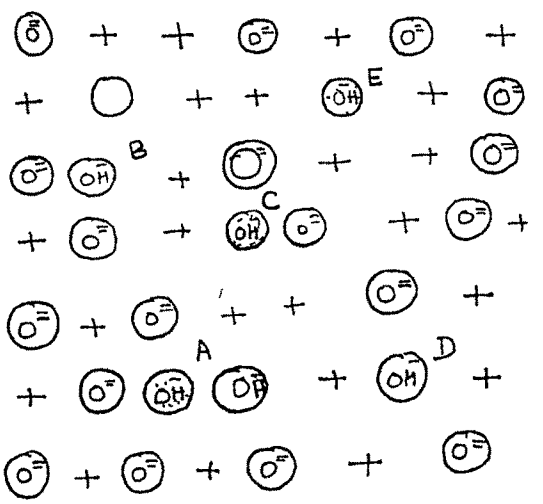
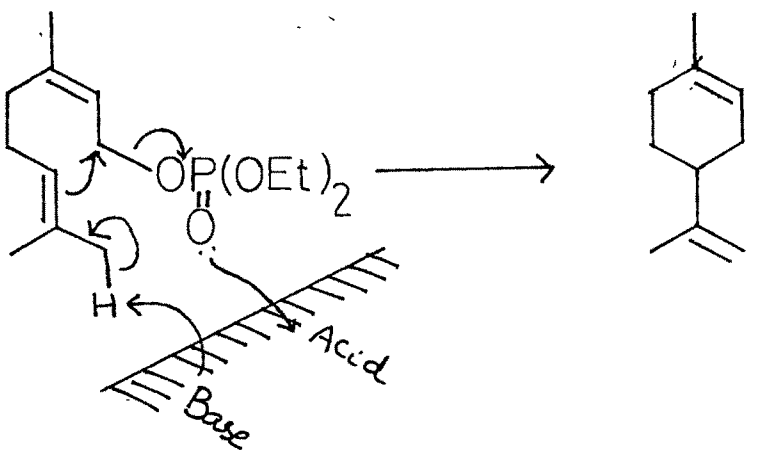


Fig.37 : Alumina surface after dehydration
[(+) denotes Al ion in lower layer]

about 10 % of the alumina surface and have been grouped into 5 types. (A,B,C,D and E in Fig.37) having from four to zero nearest oxide neighbours. These five types of -OH ion sites should vary in chemical properties, site A being the most basic acid site [47(b)].

The transformations of allylic diethyl phosphate esters, discussed, can now be rationalized in terms of this character of alumina. Thus, one can picture the coordination of phosphate oxygen with an electron-acceptor site on alumina surface, during the formation of limonene from neryl diethyl phosphate, which brings about C-O bond cleavage, with simultaneous proton elimination and its capture by an electron-donar site. This is graphically depicted here.



The formation of cyclohexanoid ring from an acyclic precursor requires a syn- or Z- conformation either in the ground state or in the activated complex. In the E- or anti-geometry, the distance between C_1 and C_6 is too large to form a bond. So, in non-enzymic reactions, neryl derivatives form cyclic products at higher rates and in high proportions than geranyl derivatives which yield predominantly elimination products. This chemically ·tional picture was complicated by the fact that enzymes

in the biological sources form cyclic monoterpenes from GPP. In the present study of active alumina induced cyclisation of allylic diethyl phosphate esters, the formation of more than 50 percent cyclic products, from the precursor having $\Delta^{2,3}$ trans-geometry, calls for an explanation.

One way to explain the transformation of (trans)-allylic diethyl phosphates into cyclic terpenes, in spite of the steric limitations, would be to assume allylic E-Z cation isomerisation, followed by cyclisation. This mechanism, interconversion of allylic E-and Z-cations has been discounted in view of considerable evidence for the configurational stability of allylic carbocation. In biological processes, this mechanism has been ruled out completely, because no such enzyme isomerisation of GPP or NPP has been obtained in a number of different enzyme preparations. Chemical evidence has stressed, in the past, the retention of the geometry of the substrate in solvolysis or elimination reactions of geranyl or neryl derivatives. Equilibrium and rates favour the formation of cyclic compounds from neryl derivatives and of open chain compounds from geranyl derivatives. (This was the rationale to look for NPP as the direct precursor of cyclic monoterpenes in nature). So, it is thus pertinent to investigate models

for the less predominant processes, (ie) the cyclic products from geranyl, 2(E), 6(E)-farnesyl and (E,E,E)-geranylgeranyl diethyl phosphate esters by active alumina.

The facile cyclisation of substrates with (E)-geometry is explained by invoking the intermediacy of a linaloyl, nerolidyl and geranyllinaloyl derivatives of geranyl, 2(E), 6(E)-farnesyl and (E,E,E)-geranylgeranyl diethyl phosphates respectively, via an internal return mechanism (in view of the configurational stability of allylic cation). The formation of acyclic products (elimination) from these phosphate esters is believed to be via the respctive allylic cations or by a concerted process, while the formation of cyclised products from 2(cis)-substrates is ascribed to an anchimeric assistance by the 6,7-double bond, in the ionization step. It is interesting here to note that deamination of geranyl amine, where internal return is not possible, also gives some cyclisation to p-menthene system[16].

Cyclic products (like γ-bisabolene) are formed to the extent of 41 % in the reaction of 2(E), 6(E)-isomer of farnesyl biphenyl phosphate in non aq. solvents. Rearrangement of sesquiterpene alcohols in 100 % formic acid occurs with the formation of 45 % cyclic product (γ-bisabolol), independent of the E or Z-conformation of the substrates. The elimination products of geranyl diphenyl phosphate were 33 % Cyclic hydrocarbons as

compared with 76% from the neryl isomer. The difference between E-and Z-derivatives is much less marked than those observed in the solvolysis of the pyrophosphates in 0.1N acid, where the amount of cyclic hydrocarbons formed from NPP exceeds by a factor of 9 to those formed from GPP. In the solvolysis of geranyl chloride, the addition of $ClO_4^{(-)}$ as a counter ion increases the proportion of cyclic products by a factor 5 to 7 and in concentrated acids geranyl derivatives rearrange to 72% of cyclised products. In our present investigations of alumina reactions, cyclic products are formed to an extent of 50% in the case of geranyl diethyl phosphate and 94% in case of neryl derivatives. Similarly, ~67% and 86% cyclic products are formed from 2(E), 6(E)- and 2(Z), 6(E)-farnesyl diethyl phosphates respectively.

The percentage composition of hydrocarbons, formed from other chemically induced methods, from the suitable derivatives of mono-and sesquiterpene alcohols are summarised in Tables 10 and 11 respectively.

It may also be noted that cyclisation of 2(Z), 6(E)- and 2(E), 6(E)-farnesyl diethyl phosphates and (E,E,E)-geranylgeranyl diethyl phosphate, like any solvolytic reaction did not lead to any detectable amount of cyclisation to 10-membered ring compounds, though this mode is quite frequent for enzymatic cyclisation occuring in nature[48].

Thus, the role of alumina as a template and as an activator of reactant resembles current chemical models of the function of some enzymes in nature.

TABLE-10

Starting substrate	Reaction conditions	% of hydrocarbon formed								
		Myrcene	cis-ocimene	trans-ocimene	Limonene	Terpinolene	α-Terpinene	γ-Terpinene	p-Cymene	References
1	2	3	4	5	6	7	8	9	10	11
Geranyl-P	Acid hydrolysis	37	21	32	6	2	-	-	-	5
Geranyl-PP	,,	18	29	44	4	5	-	-	-	5
Neryl-P	,,	9	2	5	45	35	-	4 (α, - terpinene		
Neryl-PP	,,	3	1	3	44	46	-	3 (α, - terpinene)		5
Geraniol[a]	85 % H_3PO_4 + pentane	-	-	-	11	-	19	10	11	
Nerol[a]	,,	-	-	-	11	-	37	11	8	

contd.2/.

TABLE-10

1	2	3	4	5	6	7	8	9	10	11
Geranyl chloride	Alkaline solvolysis	No cyclic products formed								29
Geranyl diethyl phosphate	Tetra isobutyl di aluminoxane (TIBAO)	-	-	-	46.8(b)	28.1(b)	-	-	-	22
Neryl diethyl phosphate	,,	-	-	-	50	30	-	-	-	22
Geranyl diphenyl phosphate	Decomposition in inert solvent	23	14	30	23.5	9.5	-	-	-	15
Neryl diphenyl phosphate	,,	8.5	25	13	57	19	-	-	-	15
Geranyl iodide	Photolysis in n-hexane, $N(C_2H_5)_3$	71	3.8	3.8	4.2	-	-	-	-	25
Neryl iodide	,,	51.35	4	7	27.3	7.4	-	-	-	25
Bipher mono-neryl	DIBAH (disobutyl aluminium hydride) - Hexane solution	-	-	-	88.8	11.1	-	-	-	23

contd.3/-

TABLE-10

- 3 -

1	2	3	4	5	6	7	8	9	10	11
Geranyl diethyl phosphate	Active alumina (dichloromethane)	17	10.7	15.2	34.5	14.2	1.7	-	-	Present study
Neryl diethyl phosphate	Active alumina	2.4	-	1.45	86	8.7	-	-	-	"

(a) Other hydrocarbons like isoterpinolene, 3-p-menthene and an unidentified compound were also formed from this experiment.

(b) The authors suggest the high efficiency (75 % yield) of cylised products by exposure to excess of TIBAO in THF is probably due to the intermediacy of free allylic carbonium ion in this reagent-solvent system.

TABLE-11

Starting substrate	Reaction conditions	% of hydrocarbon formed									References
		trans-β-Farnesene	cis-α-Farnesene	trans-α-Farnesene	cis-α-Bisabolene	β-Bisabolene	γ-Bisabolene	trans-α-Bisabolene	ar-curcumene	Unidentified and other	
2		3	4	5	6	7	8	9	10	11	12
(E,E)-farnesyl diphosphate	Decomposition in diethyl ether	20	55	34	5	20.5	2.5	12.5	-	-	29
(E,E)-farnesyl diphenyl phosphate	,,	10	3	14.5	9.0	39	4.0	22.5	-	-	29
(E,E)-farnesyl iodide	Photolysis in n-heptane, $(C_2H_5)_3N$	79.5	-	-	-	12.0	-	1.2	0.4	4.1	25
(Z,E)-farnesyl iodide	,,	18.7	-	-	-	38.2	-	10.56	3.5	28.5	25
Biphenol (Z,Z)-monofarnesyl ether	DIBAH	-	-	-	4.32	60	9	11.67	-	-	23

contd.2/-

TABLE-11

- 2 -

	2	3	4	5	6	7	8	9	10	11	12
Bip[illegible] (Z,E)-monofarnesyl ether	DIBAH	-	-	-	8.3	34	7	21.66	-	-	23
(E,E)-farnesyl diethyl phosphate	Active alumina dichloromethane	20.6	-	-	-	43.47	-	24.02	-	8.91	Present study
(Z,E)-farnesyl diethyl phosphate	,,	11.03	-	-	-	56.3	-	29.8	-	2.86	Present study

EXPERIMENTAL

All m.p.'s and b.p.'s are uncorrected. All solvent extracts were finally washed with brine solution before drying (Na_2SO_4).

The following instruments were used for spectral/analytical data. Perkin-Elmer, infrared spectrophotometer, model 781; Perkin-Elmer, model R 32 (90 MHz) PMR spectrometer; Varian Mat CH 7 mass spectrometer (70 ev, direct inlet system); Hewlett-Packard 5712 A (analytical) gas chromatograph (stainless steel column: 360 cm X 0.23 cm); support, 60-80 mesh Chromosorb W; stationary phases used - Carbowax, Diethylene glycol succinate and SE 30; Carrier gas: H_2.. IR spectra were recorded on smears. All PMR spectra were recorded with 15-20 percent solution in CCl_4 with TMS as internal standard; signals are reported in ppm (δ); while citing PMR data, following abbreviations have been used - s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. While summarising mass spectral data, besides the molecular ion, ten most abundant ions (m/e) are reported with their relative intensities. Computerised GC/Mass: Hewlett-Packard 5985 B with quadrapole mass filter, EMU-2000, ion source temp. 270°C with 1000 E series.

Solvents: Solvents used for cyclisation reactions were purified as under.

Dichloromethane : by keeping 24 hrs over anhy. $CaCl_2$ and distilled. It was then refluxed over anhy. P_2O_5 and distilled. It was stored over molecular sieves 4 A°.

Pet.ether (60-80) : by keeping 24 hrs over anhy. $CaCl_2$ and distilled and stored over sodium wire.

Synthesis of substrates

i) Geraniol

Geraniol (20 gm, commercial) was distilled under vacuum to get 98 % pure alcohol; b.p. 121-122°C/17 mm, n_D^{25} 1.4748 (Lit. b.p. 120.5-122.5°/17 mm, n_D^{20} 1.4766).

IR (Neat) : 3335, 2910, 1665, 1450, 1370, 1015 cm^{-1}

PMR : Three $\underline{H_3}C-C=C$ (9H; 3H, s, 1.6 ppm; 6H, s, 1.66 ppm); $\underline{CH_2}-OH$ (2H, d, J=7Hz, 4.05 ppm); $\underline{HC}=C$ (1H, ill resolved m, 5.09 ppm); $=\underline{CH}-CH_2OH$ (1H, t, J-7Hz, 5.38 ppm).

ii) Nerol

Nerol (20 gm, available in our laboratory) was purified by distillation under vacuum to get 96 % pure alcohol; b.p. 85-86.5°/3 mm, n_D^{25} 1.473 (Lit. n_D^{25} 1.4670).

IR (Neat) : 3335, 3940, 1665, 1445, 1380, 1010 cm^{-1}

PMR : Three H_3C-C= (9H; 3H, s, 1.58 ppm; 3H, s, 1.66 ppm; 3H, s, 1.71 ppm); CH_2-OH (2H, d, J=7Hz, 4.0 ppm); HC=C (1H, ill resolved t, 5.09 ppm); =CH-CH_2OH (1H, t, 5.35 ppm, J=7Hz).

iii) Synthesis of farnesols

(trans)-Geranyl acetone was distilled under vacuum to get pure ketone (99 %).

IR (Neat) : 1715, 1370, 1350, 830 cm^{-1}

PMR : Three H_3C-C= (9H, singlets at 1.61 and 1.67 ppm); CH_3-C=O (3H, s, 2.04 ppm); two HC=C (2H, ill resolved t, 5.04 ppm).

Wittig-Horner reaction on (trans)-geranyl acetone

Sodium hydride (6 gm, 50 percent, 0.125 mol) was placed in dry benzene (125 ml) and the slurry cooled to 15-20°C. Triethyl phosphonoacetate (freshly distilled, 21 gm, 0.0937 mol) was added dropwise under stirring in dry nitrogen atmosphere. After completion of the addition stirring was continued at room temperature for 1 hr. At the end of this period, (trans)-geranyl acetone (freshly distilled, 15 gm, 0.076 mol) was added dropwise, during which some evolution of heat was observed. It was

stirred at room temperature (~30°) for 8 hrs. It was heated under stirring at 50°C for 4 hrs during which time a red slurry is formed. The reaction mixture was then cooled and taken up in large excess of water (100 ml) and extracted with ether (50 ml X 4). The combined ethereal extract was washed successively with water, brine and dried (Na_2SO_4). The solvent was evaporated to give the crude mixture of cis- and trans-ethyl farnesates (20 gm, ~100 % yield).

Separation of Z- and E-esters

Ethyl farnesate (a mixture of 23% (Z)- and 73 % (E)-isomer) was fractionated on an annular teflon spinning band column of 80 theoritical plates, and the pure (Z)- and (E)-ethyl farnesates were isolated in good yields.

Amount of ethyl farnesate [(Z)- and (E)- mixture]

loaded = 28 gm

Reflux ratio : 20:1 ; Variac : 52-53.

Fr. No.	Head Temp B.P./mm	Wt. (g)	Remarks
1	80-84/03	0.36	Impurities
2	90-94/0.3	0.48	Impurities + 2(Z),6(E)-Ethyl farnesate (56 %)
3	92-94/0.3	0.27	Impurities + 2(Z),6(E)-Ethyl farnesate (72 %)
4	93-94/0.3	0.24	Impurities + 2(Z),6(E)-Ethyl farnesate (72 %)
5	94-96/0.4	1.407	2Z, 6E and 2E, 6E-Ethyl farnesate (90 % and 10 %).
6	93/0.25	1.19	2(Z),6(E)-Ethyl farnesate (100 %)
7	93/0.25	2.20	2(Z),6(E)-Ethyl farnesate (100 %)
8	93/0.25	1.25	2(Z),6(E)-Ethyl farnesate (100 %)
9	92-93/0.2	0.58	2(Z) and 2(E)-Ethyl farnesates (78 % and 22 %)
10	92-94/0.2	0.73	2(Z) and 2(E)-Ethyl farnesates (70 % and 30 %)
11	92-94/0.2	0.54	2(Z) and 2(E)-Ethyl farnesates (56 % and 44 %)
12	92-94/0.2	0.68	2(Z) and 2(E)-Ethyl farnesates (26 % and 73 %)
13	92-94/0.2	1.46	2(Z) and 2(E)-Ethyl farnesates (11 % and 89 %)
14	93-94/0.2	0.42	2(Z) and 2(E)-Ethyl farnesates (9 % and 91 %)
15	93-94/0.2	0.81	2(Z) and 2(E)-Ethyl farnesates (7 % and 93 %)
16	93-94/0.2	0.58	Pure 2(E),6(E)-Ethyl farnesate
17	93-94/0.2	0.46	Pure 2(E),6(E)-Ethyl farnesate
18	93-94/0.2	1.14	Pure 2(E),6(E)-Ethyl farnesate
19	93-94/0.2	2	Pure 2(E),6(E)-Ethyl farnesate
20	93-94/0.2	1.03	Pure 2(E),6(E)-Ethyl farnesate
21	93-94/0.2	1.15	Pure 2(E),6(E)-Ethyl farnesate
22	94-95/0.2	[illegible]	High boiling impurities

2(Z), 6(E)-Ethylfarnesate

IR (Neat) : 1720, 1650, 1160, 860 cm^{-1}

PMR : $\underline{H_3C}-CH_2$ (3H, t, J=7Hz, 1.22 ppm); 3 $\underline{H_3C}-C=C$ (9H; 3H, s, 1.58 ppm; 6H, s, 1.63 ppm); $\underline{H_3C}-C=C$ (cis)- (3H, s, 1.88 ppm); $\underline{CH_2}-C=C-\overset{O}{\overset{\|}{C}}$ (2H, t, J=7Hz, 2.6 ppm); $O-\underline{CH_2}-CH_3$ (2H, qr, J=7Hz, 4.08 ppm); $\underline{HC}=C$ (2H, m, 5.08 ppm); $C=\underline{CH}-\overset{O}{\overset{\|}{C}}$ (1H, s, 5.56 ppm).

2(E), 6(E)-Ethylfarnesate

IR (Neat) : 1720, 1650, 1225, 870 cm^{-1}

PMR : $\underline{H_3C}-CH_2$ (3H, t, J=7Hz, 1.22 ppm); three $\underline{H_3C}-C=C$ (9H; 3H, s, 1.59 ppm; 6H, s, 1.65 ppm). $\underline{H_3C}-C=C$ (trans)- (3H, s, 2.2 ppm); $O-\underline{CH_2}-CH_3$ (2H, qr, J=7Hz, 4.08 ppm); $\underline{HC}=C$ (2H, ill resolved t, 5.04 ppm); $C=\underline{CH}-\overset{O}{\overset{\|}{C}}-$ (1H, s, 5.58 ppm).

Reduction of the esters to the alcohols

A suspension of 200 mg lithium aluminium hydride in dry ether was cooled to $-5^{\circ}C$ and to it was added a solution of the ester (2(Z), 6(E)-isomer; 1 gm, 0.0038 mol) in dry ether (1 ml) in a dropwise manner, under stirring over a period of 15 minutes. After completion of addition the stirring was continued for 6 hrs at $-5^{\circ}C$. There the reaction mixture was allowed gradually to attain room

temperature and the stirring continued for a further period of 2 hrs. The reaction mixture was then decomposed with saturated solution of sodium sulphate and extracted with ether (10 ml X 3). The combined extract was washed with water, brine and dried (Na_2SO_4). The solvent was evaporated to yield crude 0.8 gm of the alcohol. It was distilled, 149-151° (bath temp.)/1.3 mm, to get 0.72 gm (85 % yield) of pure (Z,E)-farnesol.

2(Z), 6(E)-Farnesol

IR (Neat) : 3350, 1665, 1000, 828 cm^{-1}

PMR : four H_3C-C= (12H; 6H, s, 1.6 ppm; 3H, s, 1.68 ppm; 3H, s, 1.74 ppm); CH_2OH (2H, d, 3.98 ppm, J=7Hz). two H-C= (2H, ill resolved t, 5.07 ppm); =CH-CH_2 (1H, t, 5.38 ppm, J=7Hz).

2(E), 6(E)-Farnesol

IR (Neat) : 3350, 1665, 990, 829 cm^{-1}

PMR : four H_3C-C= (12H; 6H, s, 1.59 and 6H, s, 1.66 ppm); CH_2-OH (2H, d, J=7Hz, 4.02 ppm); two HC= (2H, ill resolved t, 5.05 ppm); =CH-CH_2 (1H, t, 5.35 ppm, J=7Hz).

(E,E,E)-Geranylgeraniol

It was obtained by the column chromatography (silica gel G, grade: II B) of the toluene extract of wood of cedrela toona.

CHROMATOGRAM-I

Column dimensions

SiO_2-gel-G: grade II B : 150 gm

Wt.of compd loaded : 5.6315 gm

Frn No.	Solvent	Vol. of eluate	Wt. (gm)	Remarks
1-2	Pet.ether	50 ml x 2	0.51	Unidentified compound
3-6	5 % EtOAc/PE	50 ml x 4	0.32	,,
7-12	,,	50 ml x 6	0.1077	,,
13-16	,,	50 ml x 4	0.5090	,,
17-20	,,	50 ml x 4	0.5002	,,
21-28	,,	50 ml x 8	0.6437	,,
29-32	,,	50 ml x 4	0.1405	(E,E,E)-Geranylgeraniol
33-36	,,	50 ml x 4	0.0559	,,
37-44	7 % EtOAc/PE	50 ml x 8	0.230	,,
45-54	25 % EtOAc/PE	50 ml x 10	0.4043	Unidentified compound
55-62	50 % EtOAc/PE	50 ml x 8	0.1834	,,
63-70	Ethyl acetate	50 ml x 8	0.2034	,,

(E,E,E)-Geranylgeraniol, so obtained, was pure by TLC analysis and spectroscopically consistent. It was distilled under vacuum

BP : 145°C/0.35 mm

IR (Neat) : 3310, 1660, 1000, 830 cm^{-1}

PMR : Five $\underline{H_3C}$-C=C (15H, s, 1.58 and 1.64 ppm); $\underline{CH_2}$-OH (2H, d, J=7Hz, 4.02 ppm); $\underline{HC}$=C (3H, br, 5.04 ppm). C=$\underline{CH}$-CH_2OH (1H, t, J=7Hz, 5.32 ppm).

Attempted preparation of geranyl tosylate

p-Toluene sulfonylchloride (0.382 gm, 0.002 mol) was added to a stirred solution of geraniol (0.154 gm, 0.001 mol) in a mixture of pyridine (0.24 gm, 0.003 mol) and dichloromethane at 0°C, the mixture stirred for 8 hrs at 0°C. and poured into water (ice-cold) and taken up in solvent ether (10 ml x 3). The total organic extract was washed with saturated solution of copper sulphate (10 ml x 3), water, brine and dried over anhy. Na_2SO_4 (3 gm) and evaporation of solvent at room temp. under vacuum (to avoid the possible decomposition of geranyl tosylate), furnished light yellow oil 0.12 gm. PMR of this revealed as a complex mixture of many compounds and it didn't show any traces of geranyl tosylate.

Attempted preparation of geranyl mesylate

Methane sulfonylchloride (0.327 gm, 0.0028 mol) in dry dichloromethane (2 ml) was added dropwise over a period of 30 minutes to a stirred solution of geraniol (0.308 gm, 0.002 mol) in a mixture of triethyl amine (0.325 gm, 0.0032 mol) and dichloromethane at ($-8^{\circ}C$). The mixture stirred for 6 hrs at $-5^{\circ}C$ and poured into water (ice-cold), and taken up in solvent ether (10 ml x 3). The total organic extract was washed with cold water (7 ml x 3) till the washings are neutral to pH, and then with brine solution. It was dried over Na_2SO_4(anhy.). Solvent was evaporated at room temperature under vacuum (to avoid the possible decomposition of geranyl mesylate), which afforded 0.293 gm of colourless oil, with raw mango smell. PMR of this revealed it as geranyl chloride. It didn't show any traces of geranyl mesylate.

PMR : three $\underline{H_3C}$-C= (9H; 3H, s, 1.6 ppm; 3H, s, 1.68 and 3H, s, 1.73 ppm); -$\underline{CH_2}$Cl (2H, d, 4.0 ppm: J=7Hz); $\underline{HC}$= (ill resolved m, 5.04 ppm); =$\underline{CH}$-CH_2Cl (1H, t, J=7Hz, 5.41 ppm).

Attempted mesylation of geraniol with methane sulfonic-anhydride

A stirred mixture of geraniol (0.308 gm, 0.002 mol), triethyl amine (0.324 gm, 0.0032 mol) and dry dichloromethane (2 ml) was treated with methane sulfonic anhydride

(freshly recrystallised, 0.487 gm, 0.0028 mol) dissolved in dry dichloromethane, at -5°C. The reaction mixture was further stirred for 5 hrs at 0°C. It was poured in 5 % aq. ammonium sulphate solution (5 ml) and the organic layers were washed with water, dried over anhy. sodium sulphate. Solvent was evaporated at room temperature under reduced pressure, which afforded the crude product as colourless oil (0.214 gm). PMR of this oil did not show any traces geranyl mesylate. It was not identified further.

Attempted preparation of geranyl diphenyl phosphate

Diphenyl phosphorochloridate (freshly distilled, 0.564 gm, 0.00209 mol) was added dropwise during one hour to a mixture of geraniol (freshly distilled, 0.308 gm, 0.002 mol) and pyridine (0.316 gm, 0.004 mol) at 0° in a 3-necked round bottom flask protected from atmospheric moisture. Stirring was continued for a period of 10 hrs at 0°C. The reaction mixture poured in water (ice-cold) and extracted with ether (8 ml x 3). The combined extracts were washed successively with dil. H_2SO_4 (5 % aq. 5 ml x 2), dil. $NaHCO_3$ (5 % aq. 5 ml x 2) and with water till the washings are neutral. After drying over anhy. sodium sulphate, the solution was filtered and evacuated in vacuo to give a crude colourless oil (0.22 gm). PMR of this compound revealed the geranyl chloride.

Present approach to the preparation of geranyl diphenyl phosphate

Diphenyl phosphorochloridate (freshly distilled, 1.128 gm, 0.00418 mol) in dry dichloromethane (2 ml) was added dropwise during 1 hr to a mixture of geraniol (0.308 gm, 0.002 mol), pyridine (0.632 gm, 0.008 mol) at $-5^{\circ}C$, under the exclusion of atmospheric moisture. Stirring was continued for a period of 6 hrs at $-5^{\circ}C$. The reaction mixture was poured over ice-water and extracted with solvent ether (10 ml x 3). The combined extract was washed successively with dil. H_2SO_4 (5% aq. 3 ml x 3), dil. $NaHCO_3$ (5 % aq. 3 ml x 3) and with water, till the washings are neutral to pH, and dried over anhy. sodium sulphate. The solvent was filtered and evacuated in vacuo to give a colourless oil, 0.64 gm (83 % yield). It was pure by TLC analysis [15 % EtOAc/pet.ether($60-80^{\circ}C$)] and spectroscopically consistent. It was not purified further due to its lability towards heat and adsorbents.

PMR : Three $\underline{H_3C}$= (9H; 3H, s, 1.58 ppm; 6H, s, 1.7 ppm); $\underline{CH_2}$-O-P (2H, d,d, 4.5-4.84 ppm); $\underline{HC}$= (1H, ill resolved multiplet, 5.05 ppm); =$\underline{CH}$-CH_2-O- (1H, t, 5.38 ppm; J=7Hz); aromatic $\underline{CH}$ (10H, br, 7-7.5 ppm).

Preparation of neryl diethyl phosphate

Diethyl chlorophosphoridate (5.3685 gm, 0.0312 mol) in dry dichloromethane (4 ml) was added dropwise during 1 hr to a stirred mixture of nerol (freshly distilled, 4 gm, 0.025 mol), pyridine (4.9 gm, 0.062 mol), and dichloromethane (4 ml) under the exclusion of moisture, at 0°C. Stirring was continued for a period of 3 hrs at 0°C. The reaction mixture was poured over ice-water and extracted with solvent ether (10 ml x 3). The combined extract was washed successively with dil. H_2SO_4 (5 % aq. 5 ml x 2), dil. $NaHCO_3$ (5 % aq., 5 ml x 2) and with water till the water washings are neutral to pH and dried over anhy. sodium sulphate. The solvent was filtered and evacuated in vacuo to give a colourless oil, 7.2 gm (96 % yield). Neryl diethyl phosphate was pure by TLC analysis (15% EtOAc/ pet.ether 60-80°C) and spectroscopically consistent.

IR (Neat) : 1670, 1265, 1035, 820 cm^{-1}

PMR : 2 $\underline{H_3C}-CH_2-O-\overset{O}{\overset{\|}{P}}-$ (6H, t, 1.3 ppm, J=7Hz); 3 $\underline{H_3C}-C=C-$ (9H; s, 1.6 ppm; s, 1.67 ppm; s, 1.78 ppm); 2 $H_3C-\underline{CH_2}-O-\overset{O}{\overset{\|}{P}}$ (4H, m, 3.85-4.3 ppm); $-\underline{CH_2}-O\overset{O}{\overset{\|}{P}}$ (2H, m, 4.3-4.68 ppm); $\underline{HC}=C<$ (1H, br, 5.05 ppm); $\underline{CH}=C=$ (1H, t, 5.38 ppm, J=7Hz).

Cyclization reaction of neryl diethyl phosphate on aluminium sulphate

To a stirred suspension of aluminium sulphate (commercial, activated at 300°/3 hrs, 5 gm) in dry pet. ether (60-80°, 10 ml), neryl diethyl phosphate (0.6 gm, 0·002 mol) was added dropwise in five minutes at room temp. (~30°) under exclusion of moisture ($CaCl_2$ guard tube). It was further stirred at this room temp. for 3 hrs. The reaction mixture was transferred into a chromatographic column and eluted with pet.ether (10 ml x 10). The solvent was removed by careful distillation. It afforded the crude, 0.27 gm as colourless oil, Which was distilled (140-50°C (bath)/~110 mm) to afford 0.17 gm (60 % yield) of distilled product. PMR of this product shows apart from usual signals of ocimene, a singlet at 4.68 ppm due to $=\underline{CH_2}$ of limonene.

Preparation of active alumina

Active alumina was prepared from the hydrolysis of aluminium isopropoxide in the following way.

$$Al(OPr^i)_3 \xrightarrow[\Delta]{H_2O} Al(OH)_3 \xrightarrow[-H_2O]{\Delta} Al_2O_3 \xrightarrow[\text{at } 250^\circ/ \\ 24 \text{ hr}]{\text{Activation}} \text{active alumina}$$

Aluminium isopropoxide, prepared by conventional method, was distilled under vacuum, which on cooling, solidified

after 4 hrs. Aluminium isopropoxide (412 gm) was finely powdered and digested with D.M. water (4 ltrs) on water bath (90°C) for 4 hrs, under occasional stirring with glass rod. The precipitated aluminium hydroxide was filtered on buchner funnel under suction, and washed it with 500 ml hot water. The resultant aluminium hydroxide was dried in heating oven (50°C/8 hrs). Aluminium oxide lumps were formed during that time. These were powdered in iron mortor and sieved through 100 mesh sieve and activated this powdered alumina at 250°C for 24 hrs in the muffle furnace. It was transfered into a bottle while it was hot and stoppered it and cooled to room temperature in a dessicator. Activity of this alumina was found to be grade-I.

Cyclisation reaction of neryl diethyl phosphate on active alumina

Active alumina (grade-I, 15 gm) was made a slurry with dry dichloromethane (15 ml) in a single necked r.b.f. and to this slurry, neryl diethyl phosphate (0.5 gm, 0·0017 mol) in dichloromethane (5 ml) was added, while shaking the reaction flask manually. The reaction flask was flushed with dry N_2 gas and stoppered it. It was shaken for 4 hrs by mechanical shaker at room temperature (~30°C) and kept overnight for 12 hrs at room temp. (~25°C). The reaction

contents were transfered to a vertical chromatographic column and eluated with dichloromethane (15 ml X 10). The combined solvent eluants were distilled off very carefully using perkin triangle, which afforded a crude colourless oil. It was distilled (120-130°C(bath)/~50 mm) to furnish 0.169 gm (73 % yield) of distilled product and 0.030 gm of residue. PMR of the distilled product shows, apart from other signals, a singlet at 4.68 ppm due to $=\underline{CH_2}$ of limonene.

Cyclisation reaction of neryl diethyl phosphate on active alumina in dry pet.ether (60-80°)

Neryl diethyl phosphate (0.5 gm, 0.0017 mol) was added slowly to a stirred suspension of active alumina (activated at 250°/24 hrs, grade-I, 5 gm) in dry pet.ether [(60-80), 10 ml] at room temp. (30°C) under the exclusion of moisture. The stirred reaction mixture was refluxed for 4 hrs (bath temp. 80°C) and kept at room temp. (~25°C) for 12 hrs. The reaction contents were transfered to a vertical chromatographic column and eluated with dichloromethane (15 ml x 10). The combined solvent eluants were distilled off carefully to afford a colourless crude oil. It was distilled (120-130°C(bath)/~50 mm) to furnish 0.185 gm (80 % yield) of distilled product and 0.010 gm of residue.

Preparation of geranyl diethyl phosphate

The experimental procedure is same as that used for neryl diethyl phoshpate with only modification is that in this case the reaction temperature was kept at -5°C. Geraniol (6.2 gm, 0.04 mol); pyridine (7.84 gm, 0.099 mol), diethyl chlorophosphoridate (8.47 gm, 0.049 mol), dichloromethane (8 ml). After usual aqueous work up, it afforded 11.0 gm (92 % yield) of geranyl diethyl phosphate which was pure to TLC analysis [15 % EtOAc/pet.ether (60-80°)] and spectroscopically consistent.

IR (Neat) : 1670, 1265, 1035, 820 cm^{-1}

PMR : two $\underline{H_3C}-CH_2-O\overset{O}{\overset{\|}{P}}$ (6H, t, J=7Hz, 1.30 ppm); three $\underline{H_3C}-C=C-$ (9H, s, 1.60 ppm; s, 1.66 ppm; s, 1.71 ppm); two $-O\overset{O}{\overset{\|}{P}}-O\underline{CH_2}CH_3$ (4H, m, 3.82-4.22 ppm); $--\underline{CH_2}-O\overset{O}{\overset{\|}{P}}$ (2H, m, 4.32-4.6 ppm); $\underline{HC}=C<$ (1H, br, 5.02 ppm); $\underline{HC}=C$ (1H, t, J=7Hz, 5.35 ppm).

Cyclisation reaction of geranyl diethyl phosphate on active alumina

The experimental procedure is same as that used for cyclisation of neryl diethyl phosphate. Geranyl diethyl phosphate (0.5 gm, 0.0017 mol), active alumina (15 gm, grade-I), dry dichloromethane (20 ml). After work up, it afforded a colourless crude oil which was distilled

(120-130°/~50 mm) to furnish 0.152 gm of distilled product and 0.020 gm of the residue.

PMR of this distilled product shows apart from usual signals of myrcene, a singlet at 4.68 ppm due to $=\underline{CH_2}$ of limonene.

Cyclisation reaction of geranyl diethyl phosphate on active alumina in dry pet.ether (60-80)

Geranyl diethyl phosphate (0.5 gm, 0.0017 mol) was added to a stirred suspension of active alumina (5 gm, grade-I) in pet.ether [(60-80), 10 ml] and the resulting reaction mixture was refluxed for 4 hrs under exclusion of moisture, and kept at room temperature (30°C) for 12 hrs. After usual work up, it afforded a crude colourless oil, which was distilled (120-130°(bath)/~50 mm) to afford 0.156 gm of distillate and 0.020 gm of residue.

Preparation of (Z,E)-farnesyl diethyl phosphate

(Z,E)-Farnesol was converted into its diethyl phosphate ester by the same procedure as that used for preparation of neryl diethyl phosphate. (Z,E)-Farnesol (0.53 gm, 0.0023 mol), pyridine (0.45 gm, 0.0058 mol), diethyl chlorophosphoridate (freshly distilled, 0.524 gm, 0.003 mol) and dichloromethane (2 ml). After usual aqueous work up, it afforded pure (E,E)-farnesyl diethyl phosphate

(0.7 gm, 81% yield).

IR (Neat) : 1670, 1270, 1035, 828 cm^{-1}

PMR : two $\underline{H_3C}-CH_2-O-\overset{O}{\overset{\|}{P}}$ (6H, t, J=7Hz, 1.31 ppm);

four $\underline{H_3C}-C=C$ (12H, s, 1.59 ppm; s, 1.66 ppm; s, 1.78 ppm); $-O-\underline{CH_2}-CH_3$ (4H, m, 3.82-4.28 ppm); $-\underline{CH_2}-O-\overset{O}{\overset{\|}{P}}$ (2H, m, 4.32-4.58 ppm); $\underline{HC}=C$ (2H, br, 5.06 ppm); $\underline{HC}=C<$ (1H, t, J=7Hz, 5.36 ppm).

Cyclisation reaction of (Z,E)-farnesyl diethyl phosphate in active alumina

The experimental procedure is same as that used for the cyclisation of neryl diethyl phosphate. (Z,E)-Farnesyl diethyl phosphate (0.358 gm, 0.001 mol), active alumina (activated at 250°/24 hrs, activity: grade-I, 11 gm), dry dichloromethane (10 ml). After usual filtration work up (same as described in neryl diethyl phosphate's reaction), it afforded a crude colourless oil. It was distilled (140-160°/1.5 mm) to furnish 0.139 gm of distilled product and 0.016 gm of the residue.

Cyclisation reaction of (Z,E)-farnesyl diethyl phosphate on active alumina in dry pet.ether (60-80°)

(Z,E)-Farnesyl diethyl phosphate (0.5 gm, 0.0014 mol) was added to a stirred suspension of active alumina (5 gm,

activity: grade-I) in dry pet.ether [(60-80°), 12 ml] and the resulting reaction mixture was refluxed for 4 hrs under exclusion of moisture, and kept at room temp. for 12 hrs (30°C). After usual filtration work up, it afforded a crude colourless oil. It was distilled (140-160°(bath)/ 1.5 mm) to furnish 0.185 gm of distilled product and 0.015 gm of the residue.

Preparation of (E,E)-farnesyl diethyl phosphate

(E,E)-Farnesol was converted into its diethyl phosphate ester by the same procedure as that used for the preparation of neryl diethyl phosphate. (E,E)-Farnesol (0.53 gm, 0.0023 mol), pyridine (0.459 gm, 0.0058 mol), diethyl chlorophosphoridate (freshly distilled, 0.524 gm, 0.003 mol) and dichloromethane (2 ml). After usual aqueous work up, it afforded pure (E,E)-farnesyl diethyl phosphate (0.70 gm, 81 % yield).

IR (Neat) : 1670, 1270, 1035, 830 cm^{-1}

PMR : two $\underline{H_3C}-CH_2-O\overset{O}{\overset{\|}{P}}$ (6H, t, J=7Hz, 1.3 ppm); four $\underline{H_3C}-C=C-$ (12 H, s, 1.58 ppm; s, 1.66 ppm; s, 1.72 ppm); $P-O-\underline{CH_2}-CH_3$ (4H, m, 3.82-4.3 ppm); $-\underline{CH_2}-O\overset{O}{\overset{\|}{P}}$ (2H, m, 4.32-4.6 ppm); $\underline{HC}=C$ (2H, br, 5.06 ppm); $\underline{HC}=C<$ (1H, t, J=7Hz, 5.38 ppm).

Cyclisation reaction of (E,E)-farnesyl diethyl phosphate on active alumina

The experimental procedure is same as that used for the cyclisation of neryl diethyl phosphate under shaking conditions, (E,E)-farnesyl diethyl phosphate (0.358 gm, 0.001 mol), active alumina (activity: grade-I, 11 gm) and dry dichloromethane (10 ml). After usual filtration work up (same as described in the case of neryl diethyl phosphate), it afforded a crude colourless oil. It was distilled (140-160°(bath)/1.5 mm) to furnish 0.086 gm of distilled product and 0.046 gm of the residue.

Cyclisation reaction of (E,E)-farnesyl diethyl phosphate on active alumina in dry pet.ether (60-80°)

(E,E)-Farnesyl diethyl phosphate (0.5 gm, 0.0014 mol) was added to a stirred suspension of active alumina (activity: grade-I, 5 gm) in dry pet.ether [(60-80°), 12 ml] and the resulting reaction mixture was refluxed for 4 hrs under exclusion of moisture, and kept at room temp. for 12 hrs (30°C). After usual filtration work up, it afforded a crude colourless oil. It was distilled (140-160°(bath)/1.5 mm) to furnish 0.2 gm (~72 % yield) of distilled product and 0.010 gm of the residue.

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Preparation of (E,E,E)-geranylgeranyl diethyl phosphate

The experimental procedure is same as that used for neryl diethyl phosphate, with only modification that in this case the reaction temperature was kept at -10°C. (E,E,E)-Geranylgeraniol (freshly distilled, 0.29 gm, 0.001 mol), diethyl chlorophosphoridate (freshly distilled, 0.215 gm, 0.00125 mol), dry pyridine (0.188 gm, 0.0025 mol) and dichloromethane (2 ml). After usual aqueous work up, it afforded 0.33 gm (~78% yield) of pure (E,E,E)-geranylgeranyl diethyl phosphate.

IR (Neat) : 1670, 1260, 1030, 820 cm^{-1}

PMR : two $\underline{H_3}C-CH_2O\overset{O}{\overset{\|}{P}}$ (6H, t, J=7Hz, 1.3 ppm); five $\underline{H_3}C-C=C-$ (15H, s, 1.58 ppm; s, 1.65 ppm; s, 1.72 ppm); $P-O-\underline{CH_2}-CH_3$ (4H, m, 3.82-4.3 ppm); $-\underline{CH_2}-O\overset{O}{\overset{\|}{P}}-$ (2H, m, 4.32-4.6 ppm); $\underline{HC}=C<$ (3H, br, 5.04 ppm); $\underline{HC}=C<$ (1H, t, J=7Hz, 5.36 ppm).

Cyclisation reaction of (E,E,E)-geranylgeranyl diethyl phosphate in active alumina

The experimental procedure is same as that used for the cyclisation of neryl diethyl phosphate (E,E,E)-Geranylgeranyl diethyl phosphate (0.2 gm, 0.00047 mol), active alumina (activated at 250°C/24 hrs, activity: grade-I, 6 gm) and dry dichloromethane (10 ml). After

usual filtration work up, it afforded a crude colourless oil. It was distilled (160-170°(bath)/1 mm) to furnish 0.075 gm of distilled product and 0.015 gm of the residue.

Separation of cyclisation reaction products of (E,E,E)-geranylgeranyl diethyl phosphate

In order to separate the pure isomeric hydrocarbons some SiO_2-gel TLC's were run using different solvents, but it did not give any encouraging results. Furthermore, several TLC's were run on SiO_2-gel impregnated with $AgNO_3$ using 5 % , 10 % and 15 % $AgNO_3$ using different solvent systems; best conditions for the separation being achieved by using 15 % $AgNO_3$ impregnated SiO_2-gel and running the plate in solvent (10 % EtOAc/pet.ether 60-80). Hence, it was decided to separate these isomers by passing through a column packed with 15 $AgNO_3$-Silica gel. The various fractions were monitored by TLC on $AgNO_3$-SiO_2 gel.

CHROMATOGRAM-II

The pure compounds (24) and (25) were isolated by column chromatography of the reaction product mixture on 15 % $AgNO_3$-SiO_2-gel (~II B).

Compound loaded : 0.2 gm

Column dimensions : 0.6 x 56 cm

Amt.of 15 % $AgNO_3$-SiO_2-gel : 5 gm (grade IIB)

Frn No.	Solvent	Vol. of eluate	Wt. (mg)	Remarks
1-5	Pet.ether	8 ml x 5	-	-
6-15	-do-	8 ml x 10	70	pure compd (25)
16-18	-do-	8 ml x 3	-	-
19-28	0.5 % EtOAc/PE	8 ml x 10	15	pure compd (24)
29-35	-do-	8 ml x 7	10	mixture of compounds
36-45	-do-	8 ml d 10	10	mixture of compounds
46-50	1 % EtOAc/PE	8 ml x 5	20	decomposed products

8-Geranylmenth-2,17(19)-diene (24)

IR (Neat) : 1640, 890, 830, 800 cm^{-1}

PMR : four H_3C-C=C- (12H, s, 1.59 ppm; s, 1.65 ppm); HC-C= (1H, br, 2.62 ppm); H_2C=C< (2H, s, 4.7 ppm); HC=C< (2H, br, 5.05 ppm); HC=C- (1H, br, 5.35 ppm).

Mass : m/e 272 (M^+, 4.9 %), 257 (4.4 %), 229 (3.5 %), 187 (12.8 %), 159 (12.1 %), 119 (51 %), 107 (44.3 %), 93 (69.9 %), 81 (50 %), 69 (100 %). (Found: C, 88.30; H, 11.25, $C_{20}H_{32}$ requires C, 88.23; H, 11.76 %).

8-Geranylmenth-2,7(8)(trans)-diene (25)

IR (Neat) : 1650, 1620, 1240, 840, 790 cm^{-1}

PMR : five H_3C-C=C- (15H, s, 1.59 ppm; s, 1.65 ppm); C=C-CH_2-C= [2H, br, 2.65 ppm; integration corresponds to 2 protons, which shows the geometry of double bond is (trans)]. HC=C- (3H, br, 5.02 ppm); HC=C- (1H, br, 5.32 ppm).

Mass : m/e 272 (M^+, 5.9 %), 257 (1.9 %), 203 (9.9 %), 177 (5.2 %), 161 (11.2 %), 135 (30.4 %), 119 (64.1 %), 107 (73.4 %), 93 (100 %), 69 (98.9 %). (Found: C, 88.30; H, 11.25, $C_{20}H_{32}$ requires C, 88.23; H, 11.76 %).

REFERENCES

1. L. Luzicka, A. Eschenmoser, H. Heusser, Experientia 9, 357 (1953); L. Ruzicka, Pure Appl. Chem., 6, 493 (1963); L. Ruzicka, Proc.Chem.Soc., 341 (1959).

2. (a) J. Hendrickson, Tetrahedron, 7, 82 (1959),
   (b) J.H. Richards, J. Hendrickson "Biosynthesis of Steroids, Terpenes and Acetogenins", W.A. Benzamin. New York, 225 (1964),
   (c) W. Parker, J.S. Roberts, R. Remage, Q.Rev.Chem. Soc., 21, 331 (1967),
   (d) T.K. Devon, A.I. Scott "Hand book of naturally occuring compounds", Academic Press: New York, 2, 56 (1972).

3. Robert M. Coates, Progress in the Chemistry of Organic Natural Products (Edited by W. Herz, H. Grisebach and G.W. Kirby). Vol.33, pp.73-230. Springer-Verlag, Wein New York (1976).

4. J.W. Cornforth, Angew.Chem.Intern. Ed.7, 903 (1968).

5. F. Cramer and W. Rittersdorf, Tetrahedron, 23, 3015 (1967).

6. W. Rittersdorf and F Cramer, Tetrahedron, 23, 3023 (1967).

7. ibid., Tetrahedron, 24, 43 (1968).

8. S. Winstein, A. Valkanas and C.F. Wilcox, J.Am.Chem. Soc., 94, 2286 (1972).

9. K. Stephan, J.Prakt.Chem., 58, 109 (1898).

10. O. Zeitschel, Ber.Dtsch.Chem.Ger., 39, 1780 (1906).

11. C.A. Bunton, D.L. Hachey and J.P. Leresche, J.Org.Chem. (USA), 37, 4036 (1972).

12. D. Whittaker, The monoterpenes. In A.A. Newman (ed.), Chemistry of Terpenes and Terpenoids, Chapter 2. London : Academic Press (1972).

13. S. Winstein, Bull.Soc.Chim.Fr., C 43 (1951).

14. O.Cori and P. Velenzuela, Tetrahedron Letters, 3089 (1967).

15. R.C. Haley, J.A. Miller and H.C.S. Wood, J.Chem.Soc. (C)., 264 (1969).

16. C.A. Bunton, J.P. Leresche and D. Hachey, Tetrahedron Letters, 2431 (1972).

17. C.A. Bunton, O. Cori, D. Hachey, J.P. Leresche, J.Org.Chem., 44, 3238 (1979).

18 K.L. [illegible], L. J[illegible] Manner, Tetrahedro[illegible], 28, [illegible].

19. S. Kobayashi, M. Tsutsui and T. Mukaiyama, Chem.Lett., (10), 1137-8 (1976).

20. Robert L. Baxter, W.A. Laurie and David Mchale, Tetrahedron, 34, 2195 (1978).

21. Mark C. Whiting and K. Brian Astin, J.Chem.Soc., perkin II, 1160 (1976).

22. Y. Kitagawa, S. Hashimoto, S. Iemura, H. Yamamoto, H. Nozaki, J.Am.Chem.Soc., 98, 5030 (1976).

23. Soichi Sakane, J. Fujiwara, Keiji Mamoka and Hisashi Yamamoto, J.Am.Chem.Soc., 105, 6154 (1983).

24. H. Nozaki, K. Oshima, A. Itah and T. Saito, Tetrahedron Letters, 3519 (1979).

25. K.M. Saplay, N.P. Damodaran and Sukh Dev, Tetrahedron, 39, 2999 (1983).

26. C.D. Gutsche, J.R. Maycock and C.T. Chang, Tetrahedron, 24, 859 (1968).

27. L. Ruzicka and E. Capato, Helv.Chim.Acta., 8, 259 (1925).

28. Y. Ohta and Y. Hirose, Chemistry Letters, 263 (1972).

29. J[illegible] Larkin, Dere[illegible] C. Nonhebel and Hamish C.S. Wood, J.Ch[illegible] [illegible]n I, [illegible] (19[illegible]

30. Kobayashi, Susumu, Tsutsui, Mikio, Mukaiyama, Temaki, Chemistry Letters, (10), 1169-72 (1977).

31. Ernest P. Brody and C. David Gutsche, Tetrahedron, 33, 723 (1977).

32. O.P. Vig, J.C. Kapur, C.K. Khurana and B. Vig, J.Ind.Chem.Soc., 46, 505 (1969).

33. B.A.N. Pagi, L. Yankov and Sukh Dev, Tetrahedron Letters, 189 (1967).

34. O.P. Vig, S.D. Sharma, S.S. Bari and S.S. Rana, Ind.J.of Chem., 17B, 31 (1979).

35. Y. Fujimoto, T. Shimizu and T. Tatsuno, Chem. and Pharm.Bull., 24, 365 (1976).

36. J.A. Miller and H.C.S. Wood, J.Chem.Soc.(C)., 1837 (1967).

37. Shuki Araki, Koichi Ohmori, Yasuo Butsugan, Synthesis, 841 (1984).

38. J.B. Peri, Disc. Faraday Soc., 52, 55 (1971); Hidenobee Itoh, Akiojada and Hideshi Hattori, J.Cataly., 76, 235 (1982).

39. T. Takeshita, R. Ohnishi and K. Tanabe, Catalysis Reviews, Vol.8 (Marcel Dekker, New York) 29, 1974; Kozo Tanabe and Tsuneichi Takeshita, Advances in catalysis, Vol.17 (Academic Press, New York) 1967, 35.

40. B.M. Mitzner, S. Lemberg, E.T. Theimer, Can.J.Chem., 44, 1090 (1966).

41. B.V. Burger, M. Le Roux, H.S.C. Spies, V. Truter and R.C. Bigalke, Tetrahedron Letters, 5221 (1978).

42. Sung Moon, L. Duchin, J.V. Cooney, Tetrahedron Letters, 3917 (1979).

43. S. Prakash, J.D. Pandey, Tetrahedron, 21, 903 (1965).

44. A.J. Fry, G.S. Ginsburg, R.A. Parente, J.Chem.Soc., Chem.Commun., 1040 (1978).

45. W.H. Staas, L.A. Spurlock, J.Chem.Soc., Perkin Trans.I, 1675 (1975); S.B. Reifsneider, L.A. Spurlock, J.Am. Chem.Soc., 95, 299 (1973).

46. S.E. Tung and E. Mc Ininch, J.Catalysis, 3, 229 (1964).

47. (a) H.P. Boehm, Adv.Catalysis, 16, 254 (1966);
(b) B.C. Lippens and J.J. Steggerda cited in Physical and Chemical aspects of adsorbents and catalysts, ed. ed by B.G. Linsen (Academic Press Inc., Ne. York) 203, (1970).

48. D.V. Banthrope and B.V. Charlwood, Secondary plant products (Edited by E.A. Bell and B.V. Charlwood), p. 190. Springer-Verlag, Berlin (1980).