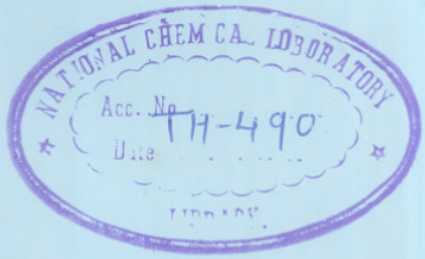
STUDIES IN TERPENE SYNTHESIS

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



BY

AVINASH SADASHIV PHADKE
M. Sc.

DIVISION OF ORGANIC CHEMISTRY
NATIONAL CHEMICAL LABORATORY
PUNE 411 008 (INDIA)

MARCH—1986

Dedicated to my Parents

CERTIFICATE

This is to certify that the work included in the thesis "STUDIES IN TERPENE SYNTHESIS" submitted by Shri A.S. Phadke was carried out by the candidate under my supervision in the National Chemical Laboratory, Poona. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

S. N. Kulkarni

(S. N. KULKARNI)
Supervisor

ACKNOWLEDGEMENTS

I take this opportunity to express my deep sense of gratitude to Dr.S. N. Kulkarni, Assistant Director, Division of Organic Chemistry, NCL for his inspiring guidance and generous help throughout the course of this investigation.

I am also grateful to Dr.T. Ravindranathan and Dr. S.V. Hiremath for helpful suggestions and constant encouragement.

I thank my colleagues Drs. M.V.Rangaishenvi, S.V.Kamath, Mrs. H.V. Kamath, Shri N.K.Bhamre, Shri A.M.Salunke and all other friends for their cheerful co-operation.

I wish to acknowledge the services rendered by the microanalytical group, the spectral (IR, NMR, Mass) and glass blowing sections.

Thanks are also due to Mr. S.Venkataraman for his technical assistance.

I shall remiss in my duty if I do not thank the Director, National Chemical Laboratory for kindly permitting me to submit this work in the form of a thesis.

I am grateful to Council of Scientific and Industrial Research (CSIR), New Delhi, for financial support.

A S Phadke

NCL, Poona 411 008 (A. S. PHADKE)

Dated February 1986

C O N T E N T S

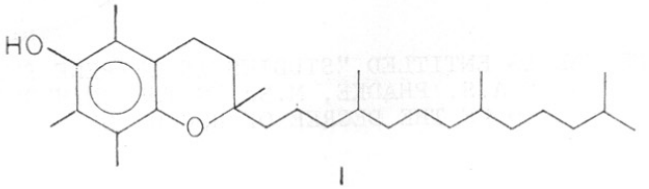
ABSTRACT

OF THE THESIS ENTITLED "STUDIES IN TERPENE SYNTHESIS" SUBMITTED BY A.S. PHADKE, M.Sc TO THE UNIVERSITY OF POONA FOR THE AWARD OF THE DEGREE OF DOCTOR OF PHILOSOPHY.

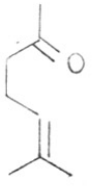
The thesis comprises of an introduction and three chapters. Introduction gives a survey on Vitamin E(1), its biological importance (antioxidant and antisterility properties), and different methods used for its synthesis. As this thesis is restricted to the synthesis of only aliphatic part of Vitamin E, literature methods for this are given in some detail. The strategy used in the present investigation is discussed at the end.

Chapter I Synthesis of 2,6,10,14-tetramethylpentadec-2-ene (7) using aliphatic nitro compounds. This chapter is divided into two parts.

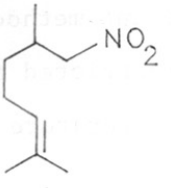
PART A. This part describes the synthesis of 2,6,10,14-tetramethylpentadec-2-ene-7-one (6), which is a precursor to the hydrocarbon (7). The C_9 nitro compound, 2,6-dimethyl-1-nitro hept-5-ene (3), was prepared from methylheptenone (2) and nitromethane followed by $NaBH_4$ reduction. It was then condensed with dihydrocitronellal bisulfite adduct (4) to the nitroalcohol which on acetylation and $NaBH_4$ reduction gave the C_{19} nitro compound, 2,6,10,14-tetramethylpentadec-2-ene-7-one (6). The ketone has already been converted to the titled hydrocarbon in our laboratory.The other nitro compounds used were the C_{10} nitro compound, 3,7-dimethyl-1-



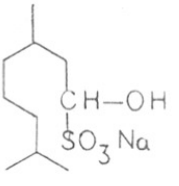
1



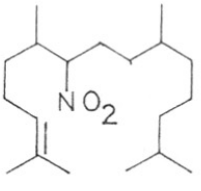
2



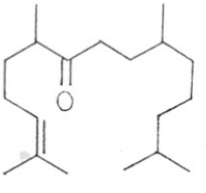
3



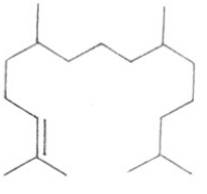
4



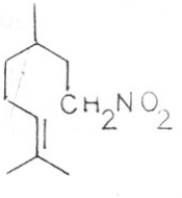
5



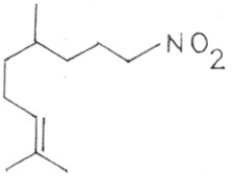
6



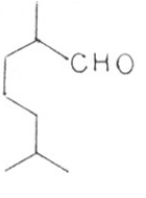
7



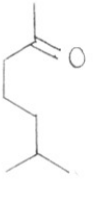
8



9



10



11

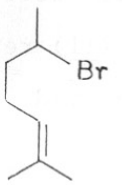
nitro-oct-6-ene (8) and a C_{11} nitrocompound, 4,8-dimethyl-1-nitro non-7-ene (9) and their reaction partners were 2,6-dimethyl heptanal (10) and methylheptanone (11) respectively but the condensation could not be achieved.

PART B. Synthesis of 2,6,10,14-tetramethylpentadec-2-ene (7) via Michael addition to nitro olefin (13). Organolithium reagent has been added to nitro olefin at room temperature using ultrasound technique. Methyl heptenylbromide (12), the nitro olefin 4,8-dimethyl-1-nitro nonane (13), and lithium metal in THF was irradiated in an ultrasound laboratory cleaner till all lithium dissolved. The reaction on work up gave 2,6,10,14-tetramethyl-8-nitropenta-dec-2-ene (14). This was then converted to the ketone 2,6,10,14-tetramethyl-8-oxo-pentadec-2-ene (15). The ketone (15) has been converted to the above hydrocarbon in our laboratory.

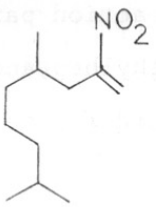
Chapter II. Synthesis of Phytone (19)

This chapter is divided into two parts.

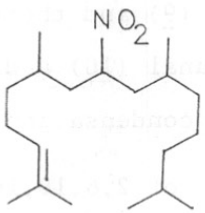
PART A. Synthesis of phytone using 1,3-dioxolane [2-methyl-2(3-chloropropyl)]. The chloroketal 1,3-dioxolane [2-methyl-2(3-chloropropyl)] (16) was converted to its magnesium salt and reacted with methylheptenone (2) to get the hydroxyketal which was dehydrated and deketalized in one pot to give the unsaturated ketone (17). One more Grignard reaction involving the chloroketal (16) and (17) followed by dehydration, deketalization and hydrogenation gave phytone (19). The ketone (17) was hydrogenated to hexahydropseudoionone (18). This was also reacted with the chloroketal, which on dehydration, deketalization and hydrogenation gave phytone.



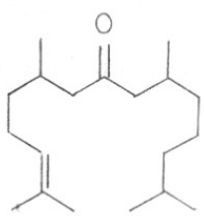
12



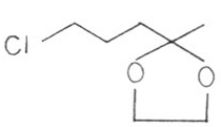
13



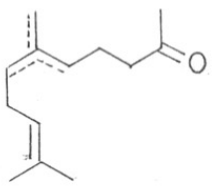
14



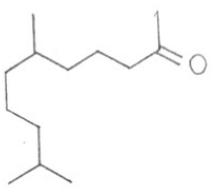
15



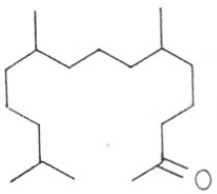
16



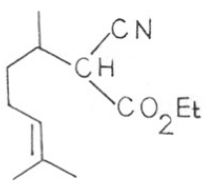
17



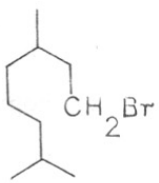
18



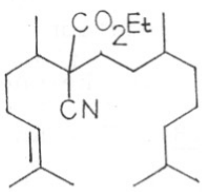
19



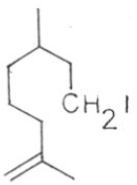
20



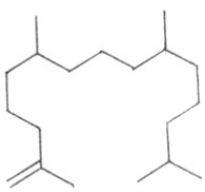
21



22



23



24

PART B. Synthesis of 2,6,10,14-tetramethylpentadec-2-ene (7) an intermediate to phytone using ethylcyanoacetate. Ethylcyanoacetate is used as a bridge to hook the two chains of eight and ten carbons to give the titled hydrocarbon (7). The cyanoacetate 3,7-dimethyl-2-cyanooct-6-enoic acid ethyl-ester (20) was prepared from methylheptenone and ethylcyano-acetate followed by $NaBH_4$ reduction. The cyano ester (20) was alkylated by dihydrocitronellylbromide (21) gave 2,6,10,14-tetramethyl-7-cyano-7-carbethoxypentadec-2-ene (22). Decarbo-ethoxylation and decyanation gave the required hydrocarbon (7). Conversion of this hydrocarbon to phytone is reported in literature.

Chapter III. Synthesis of Vitamin E(1).

This chapter is divided into two parts.

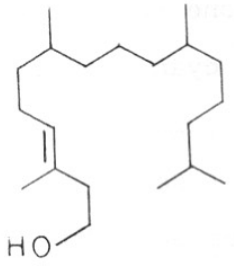
PART A. Synthesis of Norphytene (24)

Synthesis of norphytene has been described following the methodology used in Chapter II, Part B. The starting materials used were methylheptanone (11) and rhodinyl iodide (23).

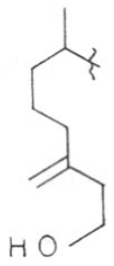
PART B. Synthesis of phytol isomers (25) (26) and their condensation with trimethylhydroquinone (27).

Prins reaction on norphytene followed by alkaline hydro-lysis gave phytol isomers (25) (26) (Prins alcohols). These were separated by $AgNO_3$ impregnated silica gel chromatography. The structure assignments were made by IR, PMR and mass studies

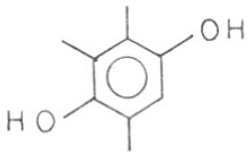
and synthesis from authentic phytol. This is preceded with a brief note on Prins reaction. The mixture of Prins alcohols were treated with trimethyl hydroquinone (27) in presence of $ZnCl_2$ to give vitamin E.



25



26



27

GENERAL REMARKS

1. The figure numbers, scheme numbers and reference numbers etc given in each Chapter refer to that particular chapter only. The references are given at the end of each chapter.

2. All melting and boiling points are uncorrected. Temperatures are recorded on centigrade scale.

3. Pet. ether refers to the fraction boiling in the range 60-80°C.

4. Column chromatography was carried out using silica gel (60-120 mesh) which was activated at 120° for 5 hrs. Unless otherwise mentioned alumina refers to neutral alumina.

5. The spots on TLC plate were visualized by exposing them to iodine vapours or by spraying with conc. H_2SO_4 followed by charring in an oven.

6. All extracts were finally dried over anhydrous Na_2SO_4.

7. The IR spectra of liquids were recorded as smears and of solids as nujol mulls on Perkin Elmer 'Infracord-137B', 599B and/or 683 model spectrometer using NaCl optics.

8. PMR spectra were recorded on Varian T-60, Bruker WH-90 or Varian FT-80 Spectrometers using TMS as internal standard.

9. Mass spectra were recorded on a CEC-2-110B double focussing spectrometer using direct inlet system at 70 eV.

10. Microanalyses were carried out in the microanalytical section of this laboratory.

11. GLC was run on Hewlett-Packard 5730A instrument using nitrogen as carrier gas and flame ionization detector.

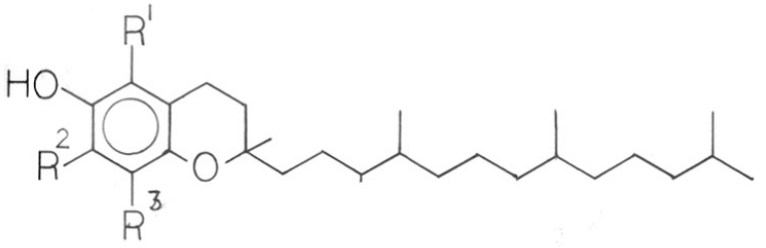
INTRODUCTION

A BRIEF REVIEW ON THE CHEMISTRY OF VITAMIN-E

INTRODUCTION

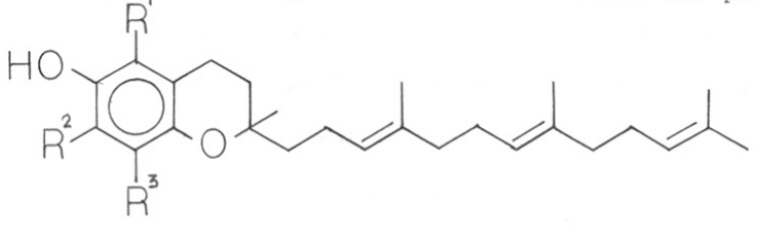
In the early twenties the existence of vitamins A, B and C had been established and that of vitamin D was essentially assured. It was observed by early workers that a diet providing an adequacy of these vitamins often failed to support reproduction. Evans[1] recognized the existence of a 'factor X' whose deficiency led to fatal death and resorption in the laboratory rat. Evans named this 'factor X' as vitamin E. Evans in 1936 isolated a compound having properties of vitamin E from wheat germ oil and named it α-tocopherol. Later β and γ-tocopherols were isolated but they had lesser activity. The richest source of α-tocopherol was found in wheat germ oil[2]. However, other sources of vegetable oils like cottonseed, lettuce, rice germ, and other seed germ oils, contained considerable amounts of substances exhibiting the activity of α-tocopherol. δ-Tocopherol was isolated from soyabean oil. Further investigation of these vegetable oils resulted in discovery of four more active compounds with a high degree of unsaturation. These were named as α, β, γ and δ-tocotrienols. The above group of chemicals is known as vitamin E.

The correct structure was established by Fernholz[3] by degradation studies of α-tocopherol using pyrolysis and chromic acid oxidation. The structure of different tocopherols can be represented as follows:

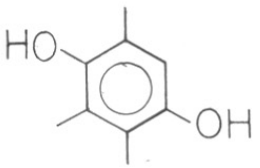


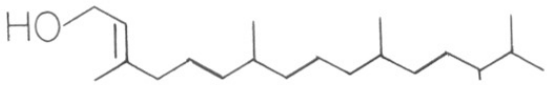
Compound	R^1	R^2	R^3
α-Tocopherol	CH_3	CH_3	CH_3
β-Tocopherol	CH_3	H	CH_3
γ-Tocopherol	H	CH_3	CH_3
δ-Tocopherol	H	H	CH_3

It was observed that α, β, γ & δ-tocotrienols on hydrogenation gave respective tocopherols. The structure was proved to be



As the tocopherols differ from each other in the number of methyls on the aromatic part they are regarded as derivatives of 2-methyl-6-chromanol. Tocopherols bear a saturated 16-carbon isoprenoid side chain attached to C-2 carbon and the methyls at C-5, C-7 and C-8. They can be considered as consisting of an aromatic part and an aliphatic part as shown below.





(Aromatic part) 3 (Aliphatic part) 4

Trimethyl hydroquinone Phytol and its derivatives

Biological importance

In recent years vitamin E has been receiving increasing attention due to its antioxidant and radical scavenging properties. Vitamin E is well known for its antisterility activity. There are lot of controversies regarding its biological activity but its role as a free radical scavenger is widely accepted.

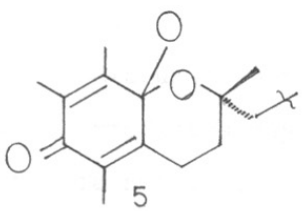
The World Health Organization has estimated 75% of the incidence of human cancer is caused by environmental factors[4], and Boyland[5] has suggested that 90% of human cancer may result from endogenous and environmental chemical carcinogens. Certain environmental agents are themselves free radicals or serve to generate low, but continual levels of free radicals in vivo Free radical and peroxides are also generated within our internal environment. The stomach and small intestines are most likely to be exposed to lipid hydroperoxides originating from oxidative rancidity of food[6]. The lungs, blood, heart are exposed to high concentration of O_2 which generates free radicals in vivo. These tissues are likewise exposed to NO_2, O_3, atmospheric pollutants that also cause damage through free radical mechanisms. Ionizing radiations produces many of its biological effects through the induced dissociation of

water and formation of H_2O_2.

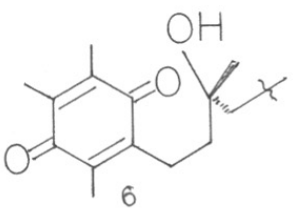
$$H_2O \longrightarrow H^{\cdot} + HO^{\cdot} \qquad 2\ HO^{\cdot} \longrightarrow H_2O_2$$

$HO^{\cdot}$ is also a product of lipid oxidation and it is among the most reactive of free radicals exposed to humanbeings. These radical species are highly reactive and may damage adjacent proteins and lipids. Reduction of free radicals by α-tocopherol will break the chain of events preventing lipid decomposition. In stopping radical propagation vitamin E itself becomes a free radical. Because the unpaired electrons are delocalized over its chromanol ring, it thereby stops the spread of free radical reaction.

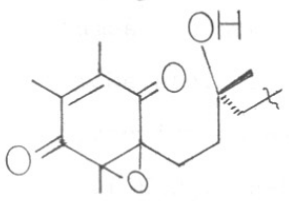
Recently, oxidation by singlet oxygen of tocopherols have been studied in detail, because of a plausible analogous mechanism by which tocopherols function as antioxidants. Grams *et al.*[7,8] irradiated [dl]-α-tocopherol in methanol in a pyrex vessel with a GE-300 W tungsten lamp in presence of proflavin and oxygen and established the structures of the oxidized products



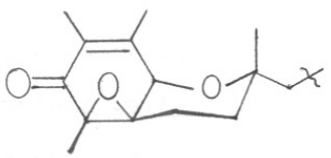
5



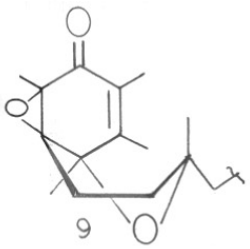
6



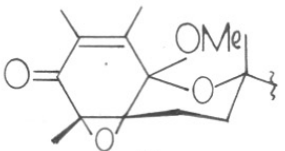
7



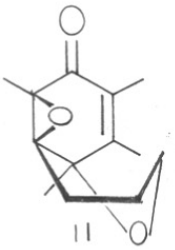
8



9



10



11

as 5 and 6 (quinones) and the epoxides 7 – 11. It has been suggested that quenching of singlet oxygen by tocopherols is the mechanism by which tocopherols inhibit lipid peroxidation[9].

Vitamin E deficiency has been related to aging in mammals because such animals have short life span[10], increased susceptibility to disease and accumulations of age pigment like lipopigment in long lived postmitotic cells[11]. The extent of the antioxidant action of vitamin E in these changes is not known. Studies have already shown that dietary supplementation of vitamin E or other anti-oxidants can significantly increase lifespan and retard changes that are known to occur in cultured cells.

As discussed earlier many chemical carcenogens and/or their intermediates may either be free radicals themselves or else may be activated by free radicals. These also include exhaust fumes, tobacco tars, cigarette smoke, charred foods, chimney smoke etc. Benzo[∝]pyrene is metabolized via a free radical mechanism to 6-OH-benzopyrene with concomitant formation of H_2O_2. 6-OH-Benzopyrene reacts covalently with

nucleic acids of in vitro cells free systems and induces strand breakage.

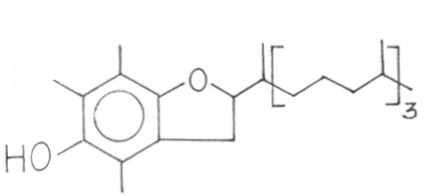
It has been reported[12] that chemical transformation of hamster cells can be inhibited by antioxidants like vitamin E, Se etc. Also, after feeding mice a diet including a mixture of antioxidants, it is possible to prevent formation, in irradiated skin, of cholesterol-α-oxide, a carcinogenic photoproduct of ultraviolet light induced skin cancer. Dietary Vitamin E also decreases the number of malignant growths resulting from feeding with carcinogens like 3-methyl-4'-dimethylaminobenzene and methyl chloranthracene.

The molecular mechanisms of antioxidant protection against cancer are not well understood. Antioxidants may prevent activation of various carcinogens to epoxides which are more effective than the parent compound in producing malgnant transformations. Antioxidant agents would be expected to inhibit peroxidation reactions which affect DNA molecules in many deleterious ways. These include covalent reaction of carcinogens with DNA and destruction of pyrimidine moieties. Shamberger[13] has shown that cells cultured with carcinogen dimethylbenzanthracene (DMBA) had 62.3% more chromosome breakage than those cultures which contained both DMBA and vitamin E in the incubation medium.

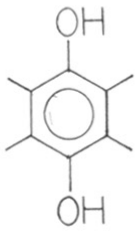
Nomenclature: The nomenclature of tocopherols and tocotrienols in the one recommended by IUPAC-IUB commission on biochemical nomenclature[14].

Structure and Stereochemistry

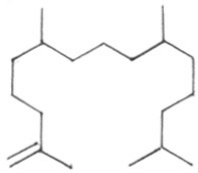
Karrer[15,16] and coworkers earlier proposed a coumaran structure 12 for α-tocopherol. However, the correct structure was established by Fernholz[3] by degradation studies of α-tocopherol using pyrolysis and chromic oxidation. The pyrolysis



12



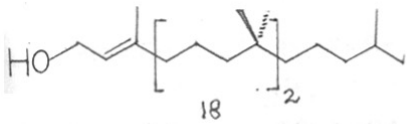
13



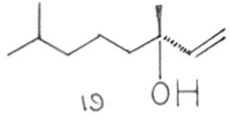
14

products of α-tocopherol, 13 and 14 are best explained by the chroman structure. The structure was further confirmed by its synthesis.

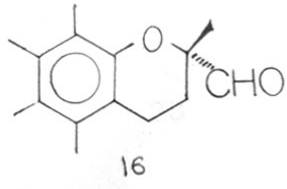
α-Tocopherol has three assymmetric centers, at C-2, C-4' and C-8' so eight stereoisomers are possible and all have been synthesized recently[17]. Absolute configuration of tocopherol was established by correlating natural α-tocopherol to phytol (18) of established R configuration at C-7 and C-11[18] and with (-)linalool (19) of established R configuration[19]. The stereochemistry



18



19



16

of natural tocopherol was established as 2R,4'R,8'R configuration.

It was further proved by its synthesis using the aldehyde (16). Similarly all tocopherols have been assigned 2R,4'R,8'R configuration.

Synthesis

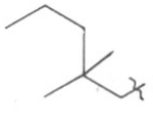
The synthetic methods for tocopherols that have been described in the literature can be classified as total and partial synthesis. The total syntheses have been divided in two parts:

i) Syntheses involving construction of the heterocyclic ring of tocopherols along with the isoprenoid side chain at C-2 using methylated hydroquinones and aliphatic reactants as the starting materials as shown in Scheme I.

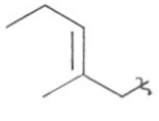
ii) The isoprenoid side chain is introduced into preformed, methylated-1-benzopyran system by formation of carbon-carbon bonds as shown in Scheme 2.

a) Synthesis of tocopherols by construction of the heterocyclic ring

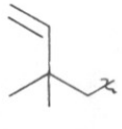
One of the main approach involves the construction of the heterocyclic ring of tocopherols along with the isoprenoid



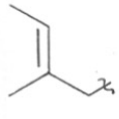
17, X=Br, Y=Br
23, X = Y=OH
25, X=Cl, Y=OH



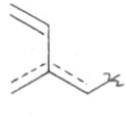
18, X=Br
19, X=OH
22, X=OAc



21

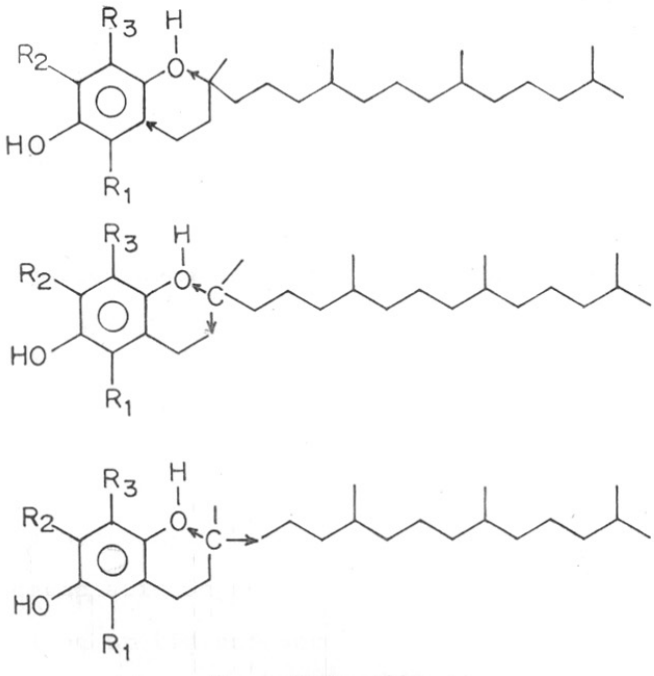


24



20

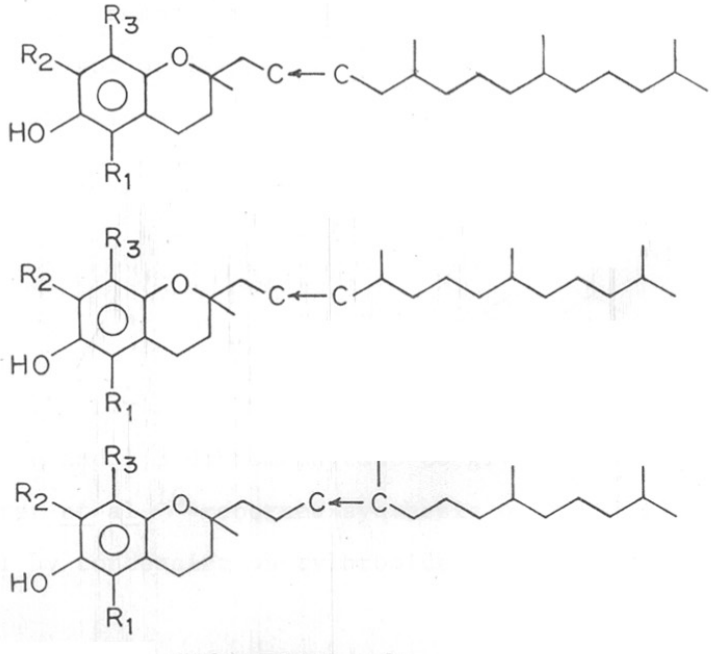
Total synthesis of tocopherols by construction of substituted hetrocyclic ring



$R_1 \longrightarrow R_3 = Me, H$

SCHEME-1

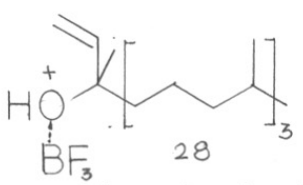
Total synthesis of tocopherols by construction of isoprenoid side chain



SCHEME-2

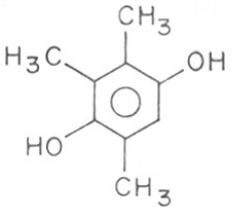
side chain at C_2 using methylated hydroquinone and an aliphatic reactant as starting material.

This principle has been used in many syntheses using trimethyl hydroquinone and different aliphatic reactants such as 1,3-dibromophytane (17), phytylbromide (18), phytol (4), phytadiene (20), isophytol (21), phytyl acetate (22), phytane-1,3-diol (23), phytenic acid (24), and halohydrin (25). Many catalysts and solvents have been used to achieve condensation in high yields. Zinc chloride and trichloroacetic acid in a carboxylic acid ester, powdered aluminium, iron or tin and borotrifluoride, zinc with sulfuric acid or p-toluene sulfonic acid and sodium hydrogen sulfate, zinc chloride in acetic acid and others. It has been shown that the addition of BF_3 to trimethylhydroquinone resulted in the formation of the complex (27) and of protonated phytol or isophytol (28), whose interaction gave tocopherol in high purity and yields.

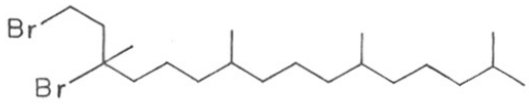


28

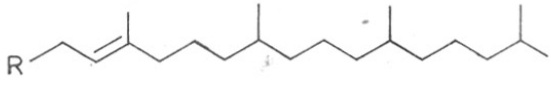
Isler et al.[20] for the first time condensed trimethyl-hydroquinone and 1,3-dibromophytane to give ∝-tocopherol. Later Karrer et al.[16] reported synthesis of 2(RS),4'R_1 8'R- -tocopherol by condensing phytylbromide obtained from natural



26

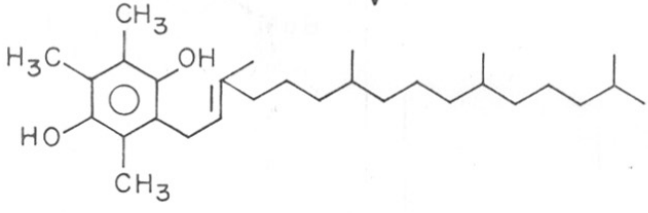


17

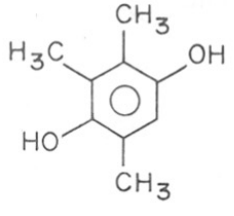


R = Br, OH

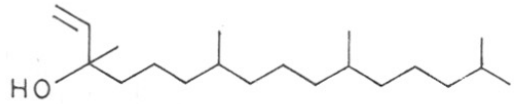
18 4



29



26



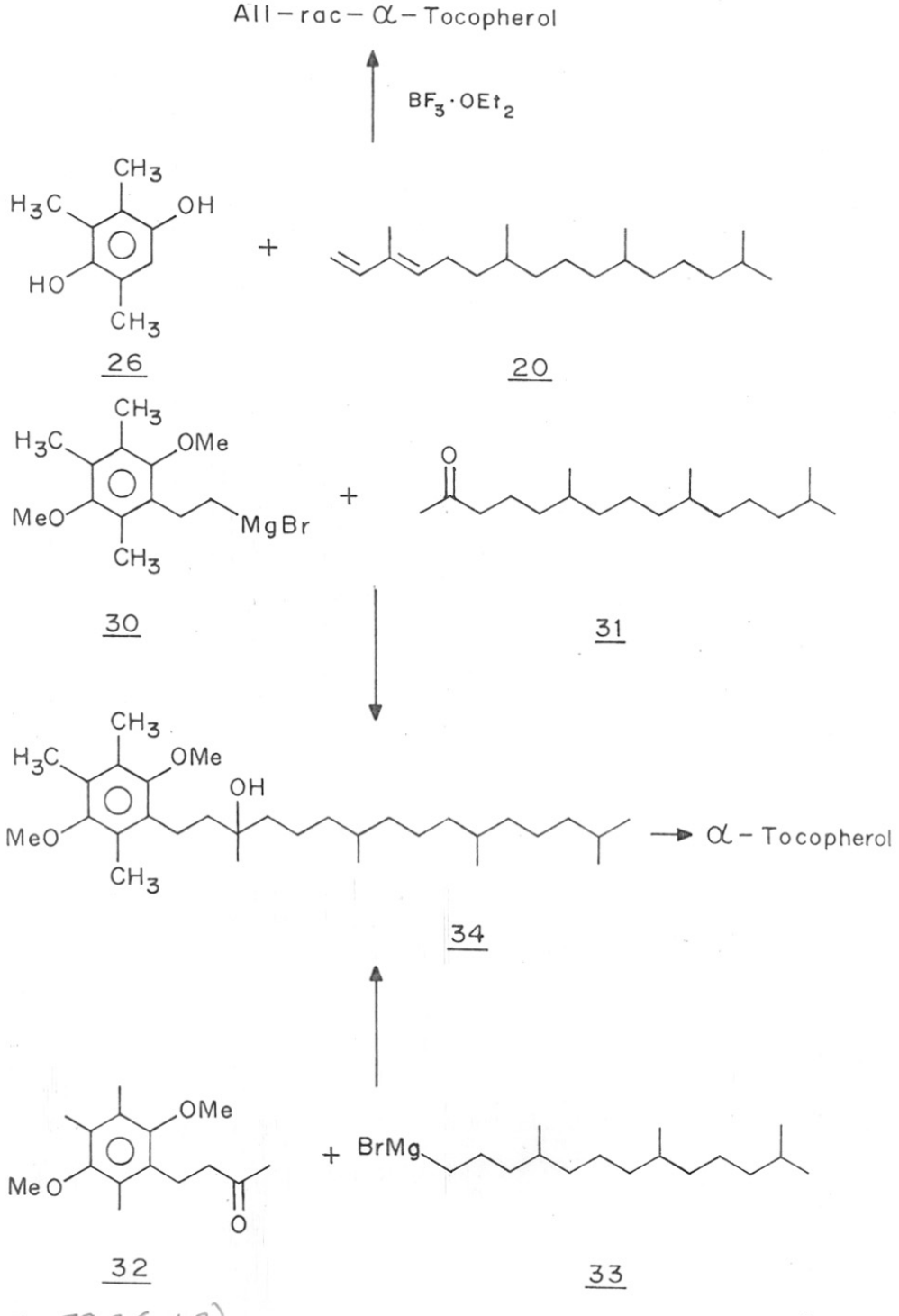
21

$BF_3 \cdot OEt_2$

All-rac-α-Tocopherol

SCHEME-3

SCHEME – 3 (Contd.)



547.596(043)
PHA

TH-490

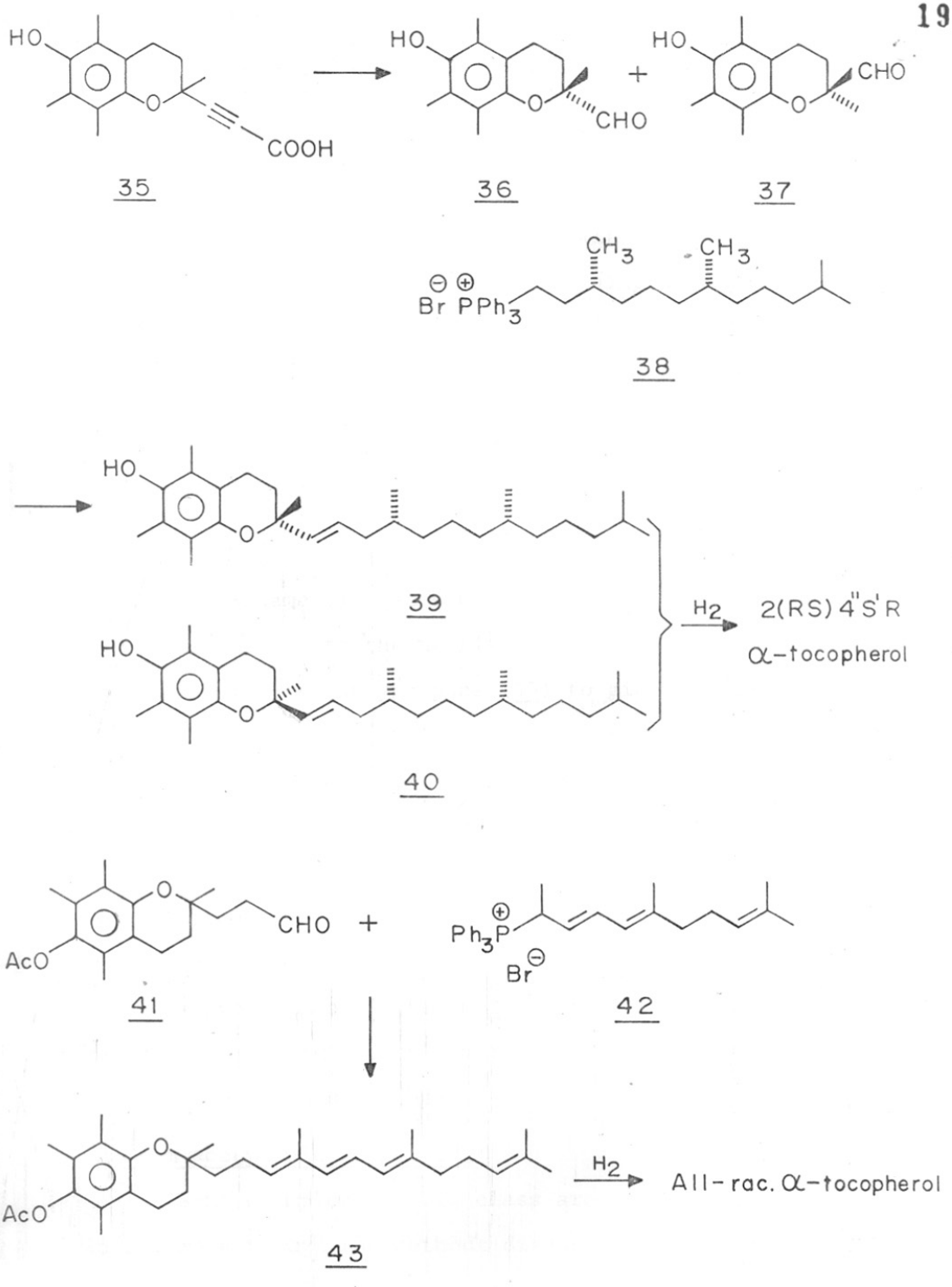
phytol and trimethyl hydroquinone (Scheme 3). The use of phytyl bromide gives a mixture of diastereomers of ∝-tocopherol which can be separated by piperazine complex. Synthesis of tocopherol from isophytol, phytadiene are reported. The reaction of the Grignard reagent (30) on phytone (31) or the reaction of (33) on (32) gives a tertiary alcohol (34) which can be cyclized to ∝-tocopherol.

Synthesis of tocopherol by construction of isoprenoid side chain

The preformed methylated benzopyran is reacted with an isoprenoid side chain. This principle has been used by Isler et al.[21] for the synthesis of epimeric tocopherols (Scheme 4) starting from propiolic acid (35). The propiolic acid was converted to the corresponding epimeric aldehydes (36) and (37). The aldehydes were treated with the phosphonium salt (38) to obtain (39) and (40) which on hydrogenation gave 2(R)4'R 8'R and 2(S)4'R 8'R-∝-tocopherols. Similarly Wittig reaction on the aldehyde (41) with the phosphonium salt (42) followed by hydrogenation gave ∝-tocopherol.

Partial synthesis

In partial synthesis, methyl groups are introduced in the aromatic ring of 5,8-dimethyl, 7,8-dimethyl or 8-methyltocol. This was achieved by chloromethylation with formaldehyde and hydrochloric acid followed by Clemensens


HO
COOH
35
HO
CHO
36
HO
CHO
37
CH3
CH3
Br PPh3
38
HO
39
HO
40
H2
2(RS) 4''S' R
α-tocopherol
AcO
CHO
41
Ph3P
Br
42
AcO
43
H2
All-rac. α-tocopherol

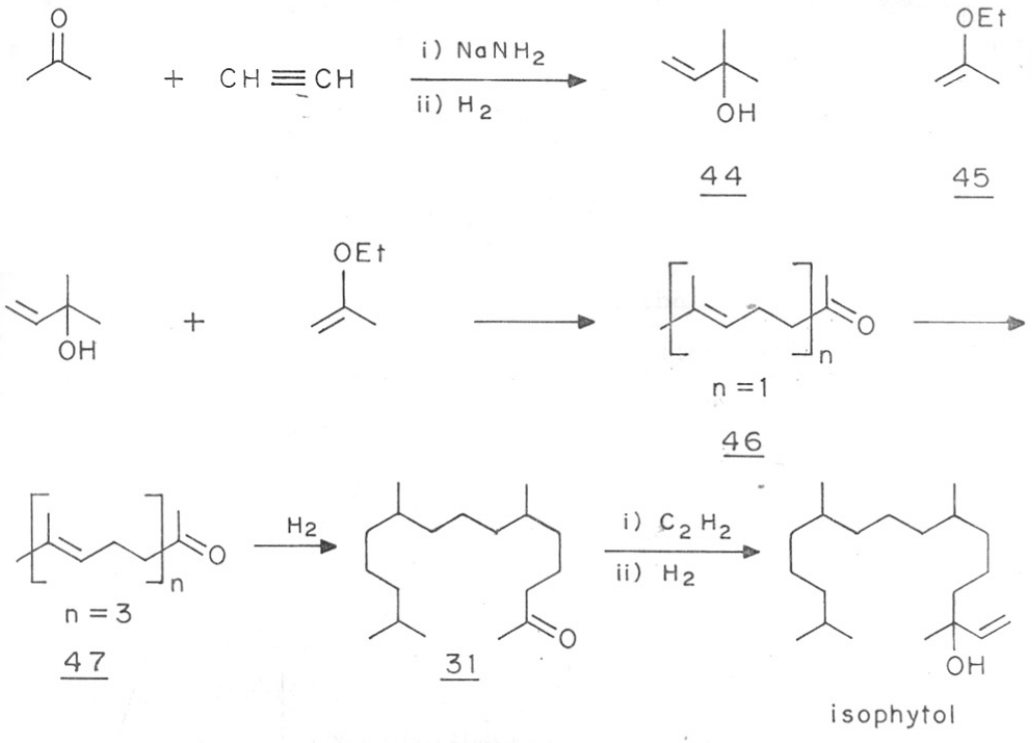
SCHEME—4

or catalytic reduction to give α-tocopherol, and many other methods.

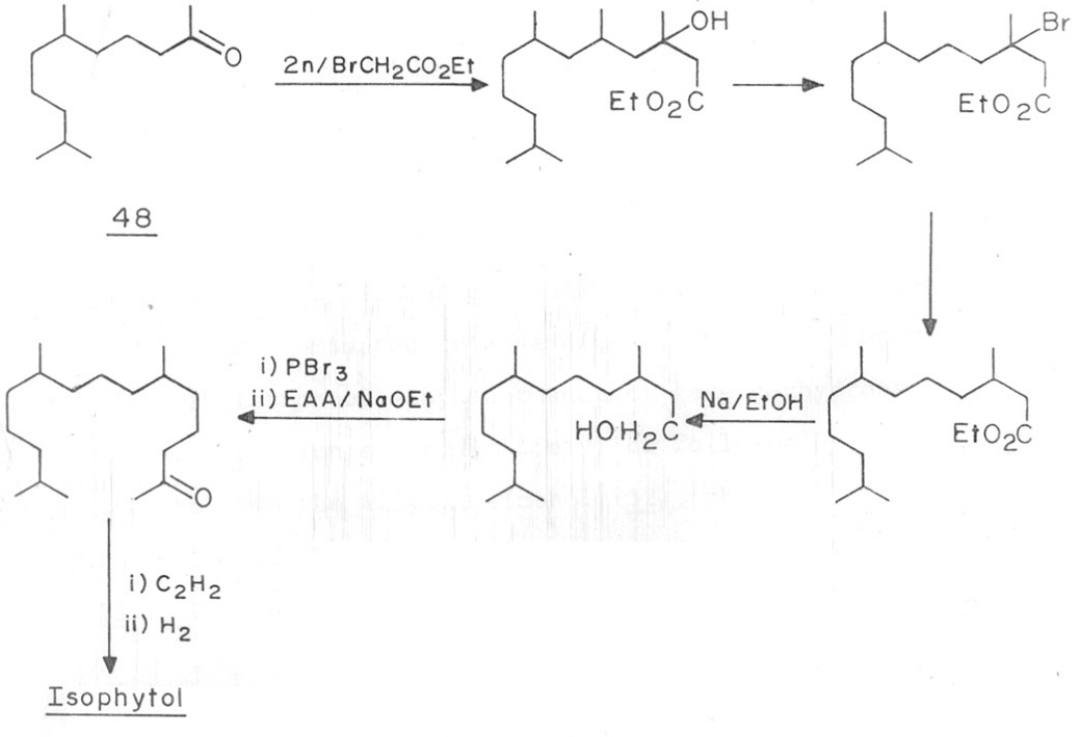
The present work mainly deals with the studies directed towards the synthesis of the aliphatic part of Vitamin E viz. isophytol and phytol. In the next few pages some main literature methods for the synthesis of isophytol and phytol has been described. Multistep synthesis of isophytol from pseudoionone citral, linalool was reported. However method using acetone and acetylene as starting materials is presently used to produce isophytol or phytol (Scheme 5). Acetone is converted by ethynylation and hydrogenation to the tertiary alcohol (44) which was condensed with 2-ethoxypropane (45) to give the ketone (46, n=1). Repeating this sequence many carbinols can be obtained. The ketone (31, n=3) was ethynylated and hydrogenated to give isophytol. Analogous chain extension of acetone can be achieved using ethylacetoacetate or a reaction with diketene. The methods can be broadly classified in the following ways: (i) using acetylenic compounds, (ii) using terpene analogs (iii) using cyano compounds, (iv) using isoprene (v) using mesityl oxide (vi) anoding coupling and (vii) miscellaneous syntheses.

i) From acetylinic compounds

Some examples of this class are described earlier in Scheme 4 though the methods discussed under terpene



SCHEME-5



SCHEME-6

analogs does involve reaction of acetylene.

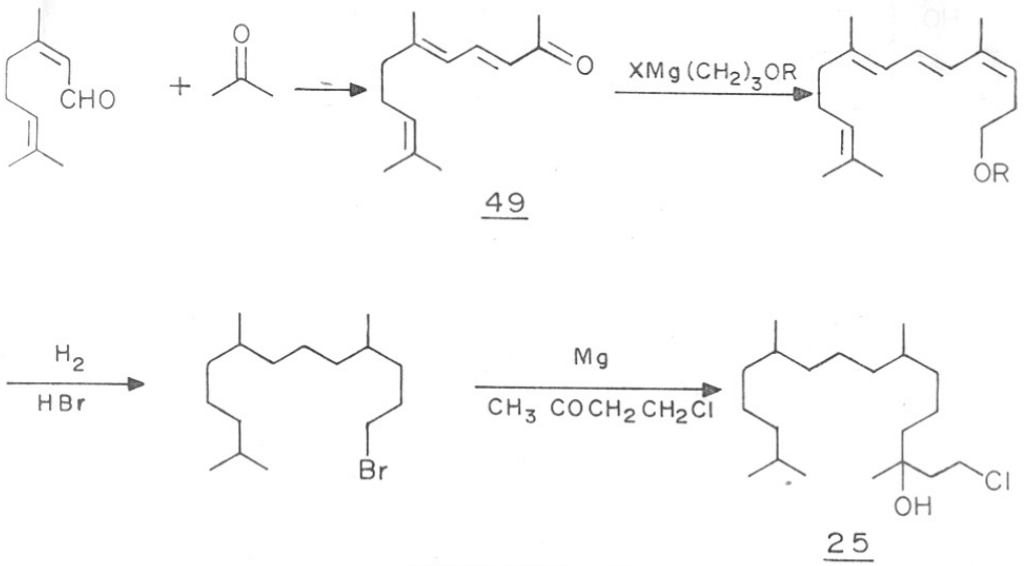
ii) From terpene analogs

Most of these synthesis involve the use of monoterpenes like citronellol, pulegone, linalool and others like pseudoionone or hexahydropseudo ionone.

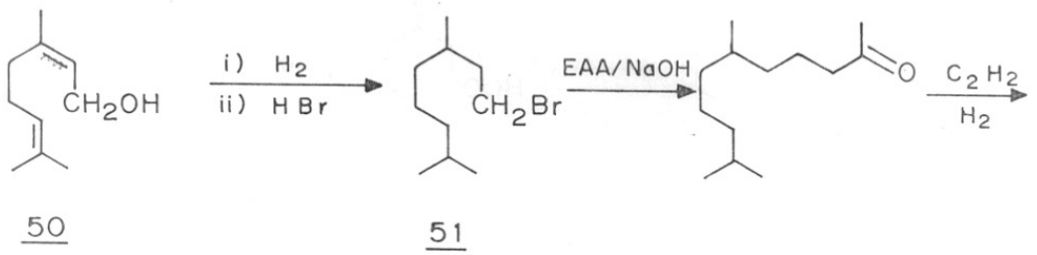
Hexahydropseudoionone (48) was used by Karrer et al.[22] in the synthesis of isophytol. Here (48) was subjected to Reformatsky reaction using zinc and ethylbromoacetate. The hydroxy ester so obtained was dehydroxylated via its corresponding bromoester. The ester on reduction, bromination and condensation with ethylacetoacetate gave phytone whose reaction with sodium acetylide and hydrogenation gave isophytol (Scheme 6).

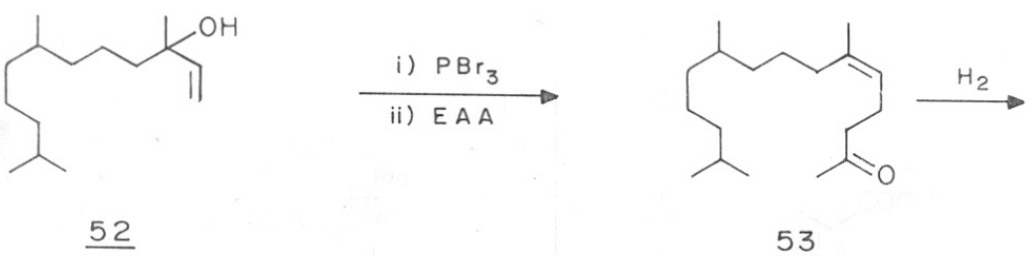
Smith et al.[23] has used pseudoionone (49) obtained from citral for the synthesis of halohydrin (25). The reaction sequence is outlined in Scheme 7.

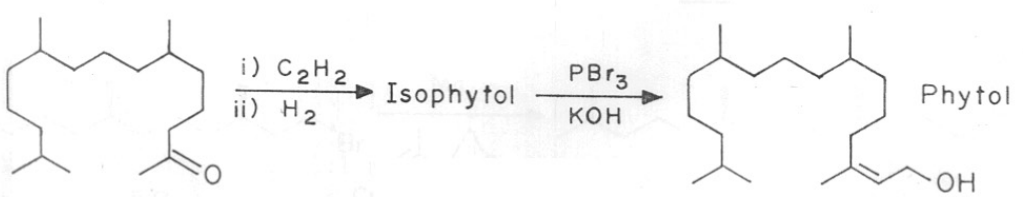
Karrer[24] again has reported the synthesis of phytol from citronellol (Scheme 8). Citronellol (50) was hydrogenated and brominated to give dihydrocitronellyl bromide (51). Alkylation of ethylacetoacetate gave hexhydropseudoionone. Reaction of sodium acetylide followed by hydrogenation gave the allylic alcohol (52), which on treatment with PBr_3 and then ethyl acetoacetate furnished the ketone (53). Hydrogenation of (53) gave phytone whose reaction



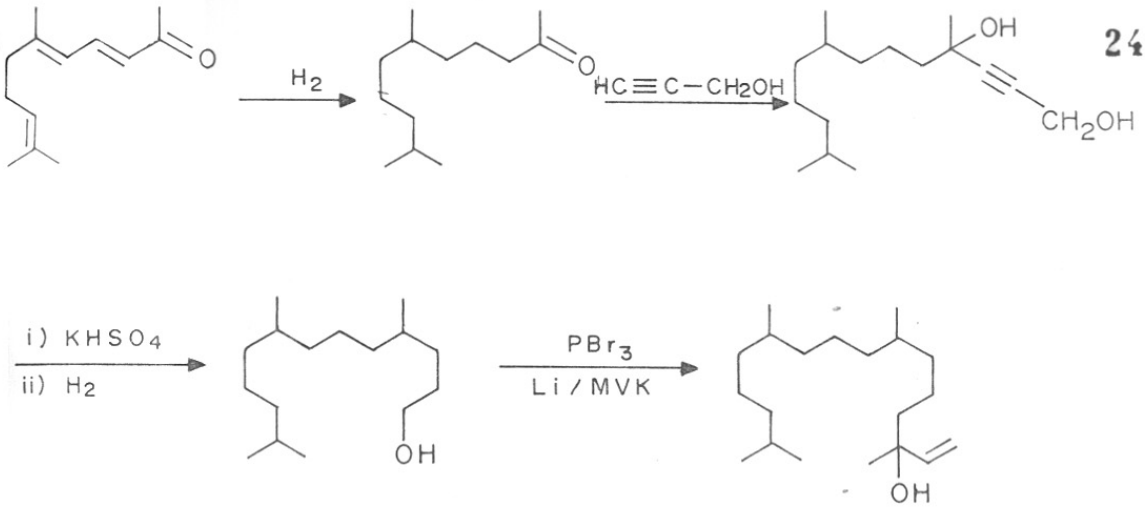
SCHEME – 7



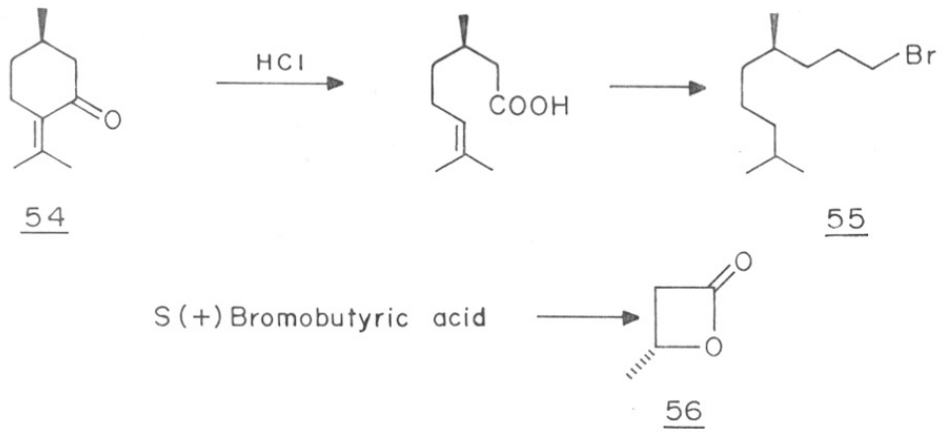


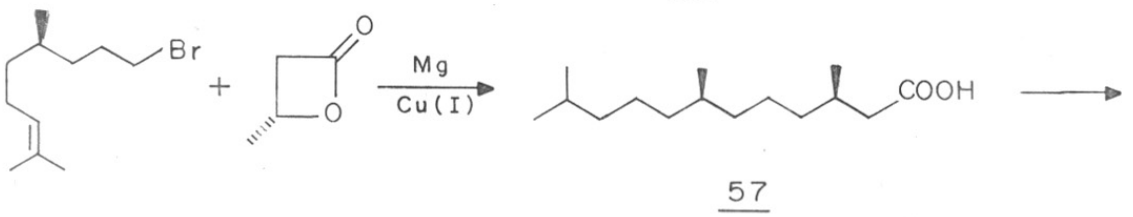


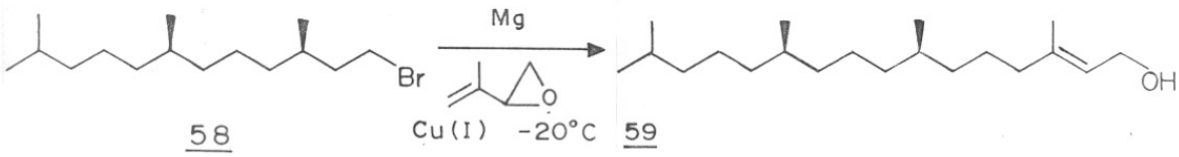
SCHEME – 8



SCHEME – 9







SCHEME – 10

with acetylene in sodium liquid ammonia followed by hydrogenation gave isophytol which is isomerised to phytol.

The synthesis of isophytol described by Sato et al.[25] uses pseudoionone and propargyl alcohol, and is outlined in (Scheme 9).

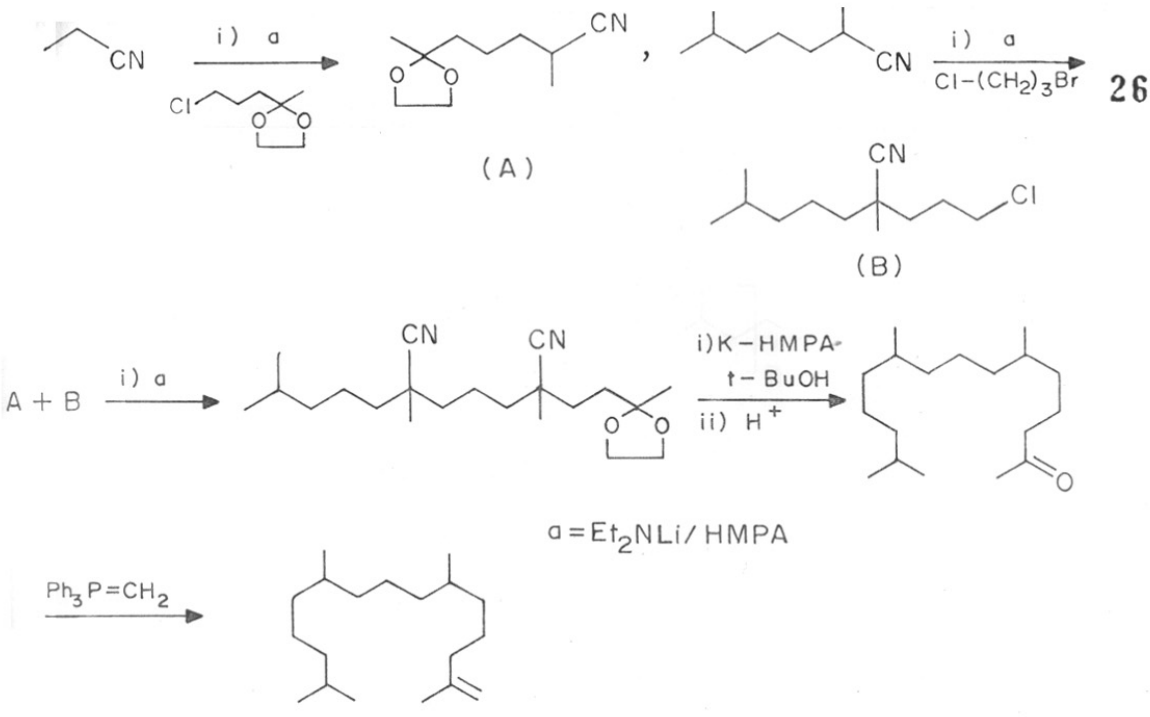
Recently T. Fujisawa[26] et al. have synthesised optically active (RR)phytol (Scheme 10). This synthesis involves the ring opening of (R)-3-methyl-β-propiolactone (56) and isopropenyl oxirane (59) and preparation of optically active C_{11} bromo compound (55) from (R)-pulegone (54). The reaction of the Grignard reagent prepared from (55) with (56) in presence of Cu(I) salt in THF-Me_2S at -20° gave the acid (57). The acid was converted to the bromide (58) by standard routes and its Grignard reaction on isopropenyl-oxirane (59) furnished phytol with 95% optical purity.

iii) From Cyano compounds

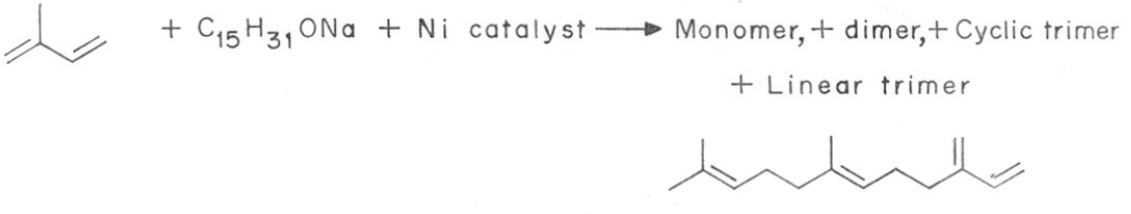
Larchereque and Cuvigny[27] have reported the synthesis of phytone and norphytene using nitrile (Scheme 11). The key step is the removal of the cyano group using potassium metal in HMPA and t-BuOH as co-solvent. The mechanism suggested is via the free radical mode. The phytone thus obtained on Wittig reaction gave norphytene.

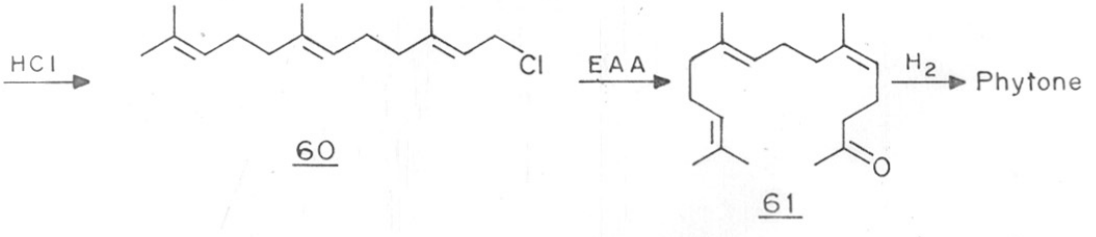
iv) Via isoprene

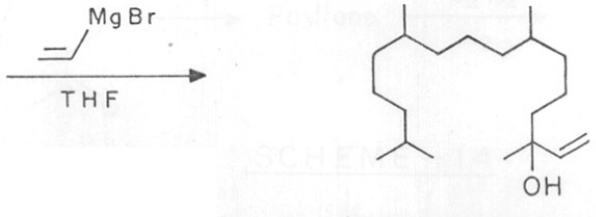
S. Akutagawa et al.[28] obtained 87% of the linear trimer



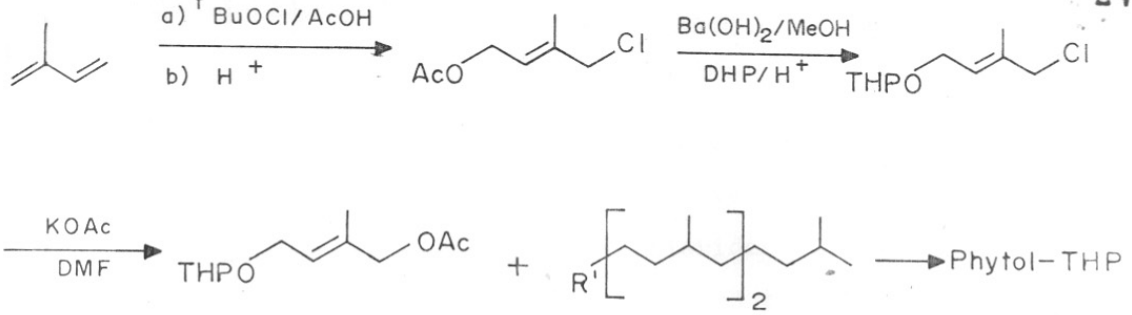
SCHEME – 11



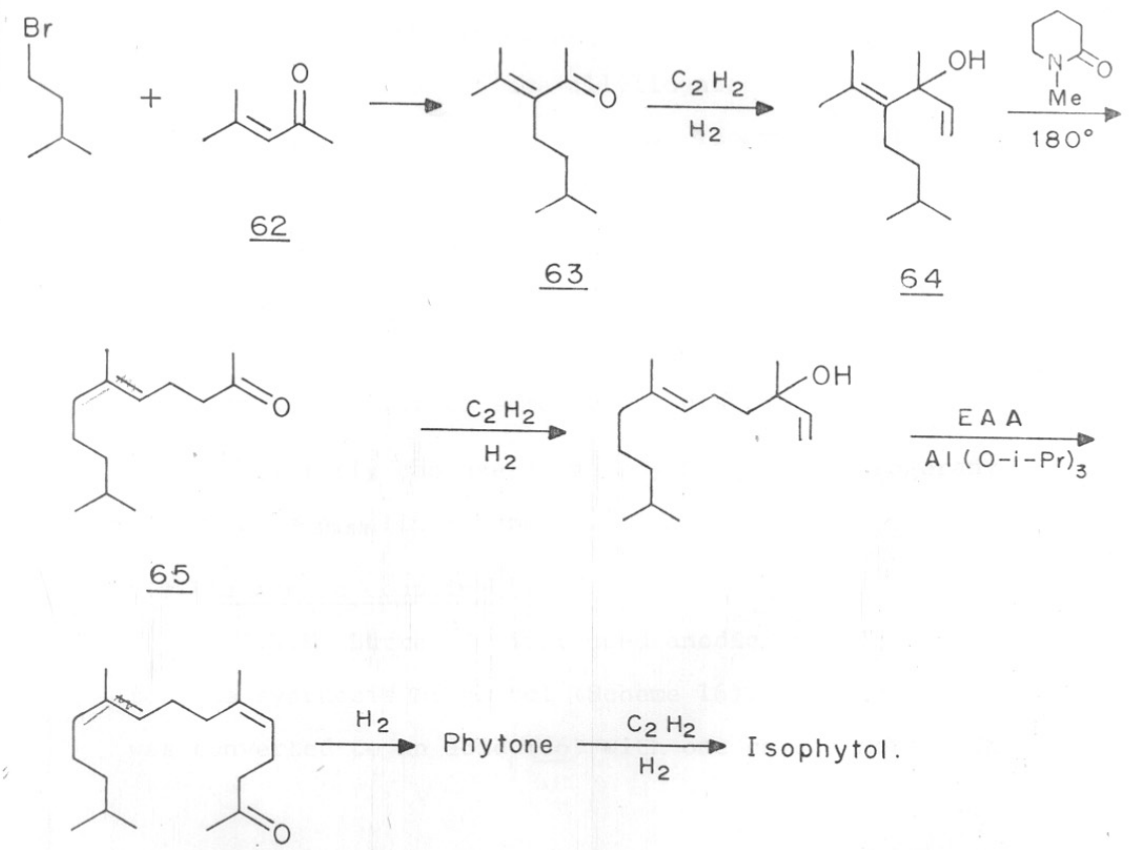




SCHEME – 12



SCHEME–13



SCHEME–14

of isoprene by treating isoprene with sodium salt of fatty alcohols in presence of Ni catalyst. The linear trimer was converted to farnesyl chloride (60) and condensed with ethyl acetoacetate to afford the ketone (61). Hydrogenation gave phytone. Phytone was converted to isophytol using vinyl magnesium bromide in THF (Scheme 12).

Schimdt et al. synthesised phytol from isoprene as outlined in Scheme 13.

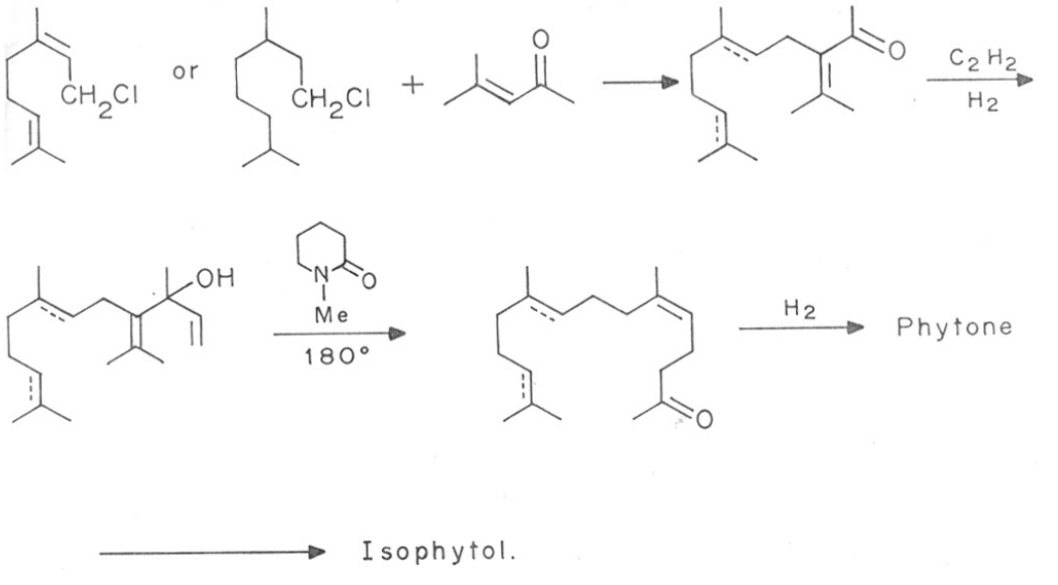
v) Using mesityl oxide

Recently many Japanese[29] workers have used mesityl oxide for the synthesis of phytone, here the main step is the rearrangement of the allylic alcohols to the ketones. Mesityl oxide (62) was alkylated by isoamylbromide to get the conjugated ketone (63). Ethynelation followed by partial hydrogenation gave the allylic alcohol (64). The allylic alcohol (64) was rearranged to the ketone (65) by heating it with N-methyl-2-pyridone at 180°. Further sequence of reaction is similar to some routes discussed earlier (Scheme 14).

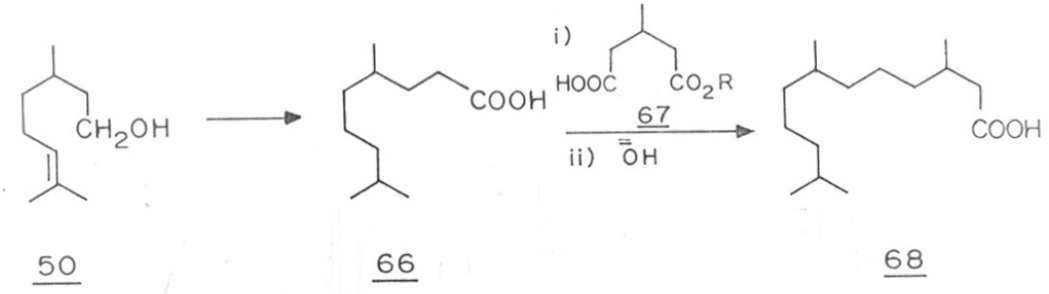
Similarly the use of geranyl or tetrahydrogeranyl chloride is shown in Scheme 15.

vi) Via anodic coupling

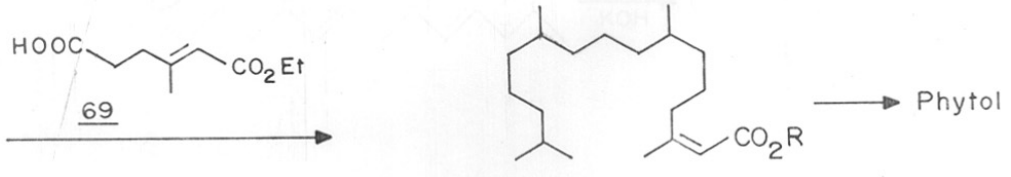
J.W.K. Burrel[31] first used anodic coupling of acids for the synthesis of phytol (Scheme 16). Citronellol (50) was converted to an acid (66) with one carbon more. The



SCHEME–15

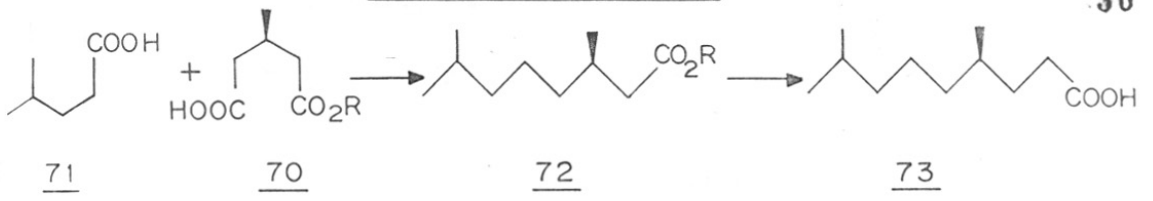


50 66 68

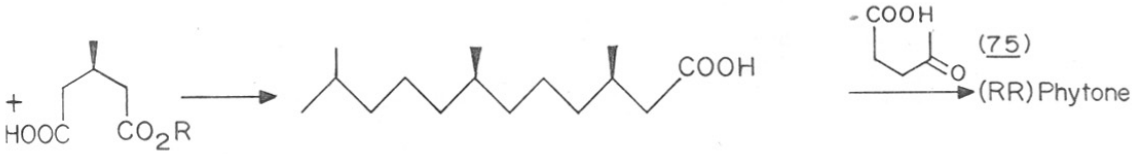


SCHEME–16

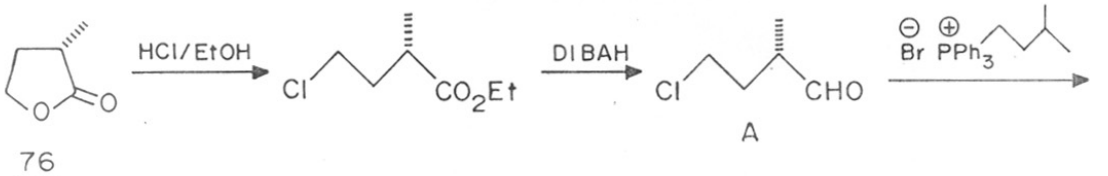
SCHEME – 16 (Contd.)



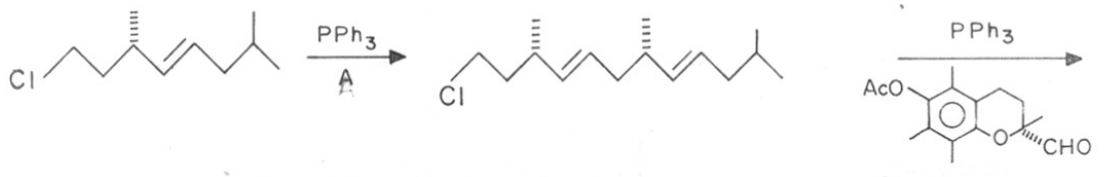
71 70 72 73

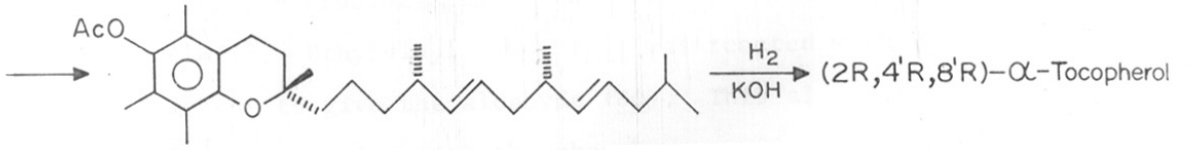


74



76





SCHEME – 17

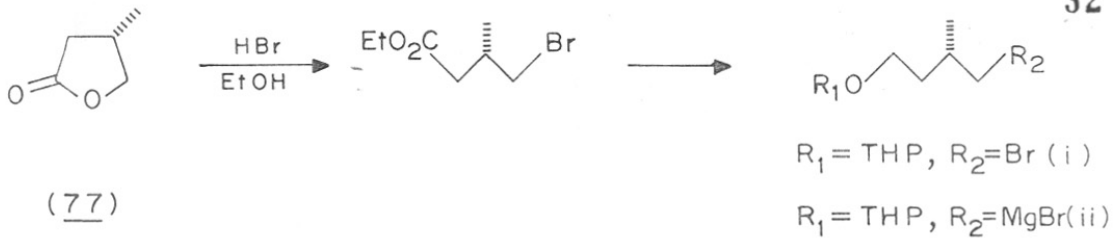
acid (66) was coupled with racemic half-ester of methyl-glutaric acid (67) furnishing the C-15 acid (68) after hydrolysis. This acid (68) was again coupled with 4-ethoxy-carbonyl-3-methylbut-3-ene-1-carboxylic acid (69) giving the ester which on reduction gave phytol.

Similarly opticayly active phytol has been synthesised by Weedon et al.[32]. Optically active half-ester of methyl-glutaric acid (70) was coupled with 4-methylpentanoic acid (71) to get optically active dihydrocitronellic acid (72) and then homologated to the next acid (73). (73) was again coupled with (70) to get the C-15 acid (74). This was coupled with levulenic acid (75) to give phytone which was converted to phytol.

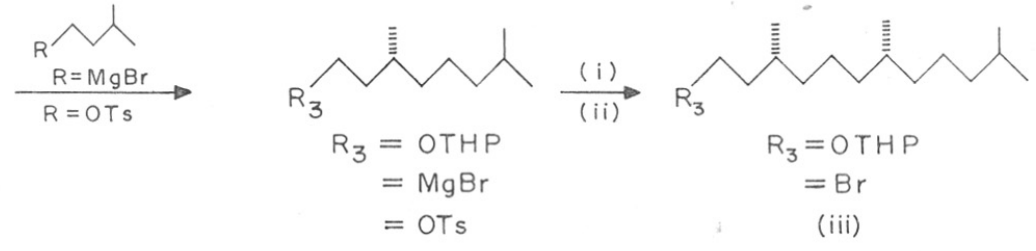
vii) Miscellaneous syntheses

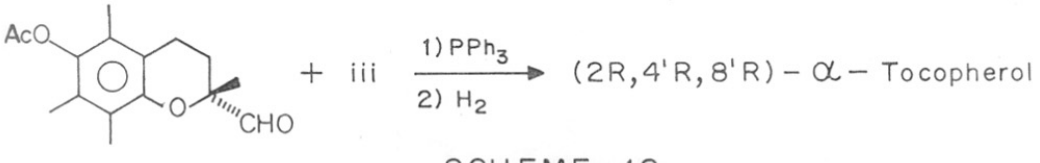
Total synthesis of natural tocopherol was reported by Fell[33] and Schmidt[34] in 1979 using optically active 2-methylbutyrolactone (76) and 3-methylbutyroacetone (77) respectively in Schemes17 & 18.

T. Mandai et al.[35] (Scheme 19) have used 2-hydroxy-methyl-4-phenylthio-1-butene (78) for the synthesis of phytol. Here the crucial step is the selective oxidation of terminal olefin. Ethylvinyl ether (79) was reacted with (78) in xylene to give the aldehyde (80). This aldehyde (80) on Wittig reaction with the phosphorane (81) furnished (82). Alkylation and oxidation with allylbromide of (82), desul-fonation and hydrogenation gave phytone which was converted

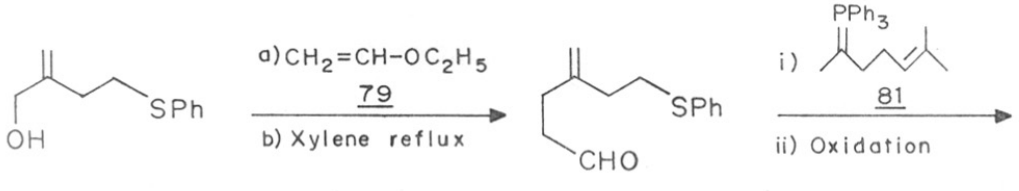


(77)

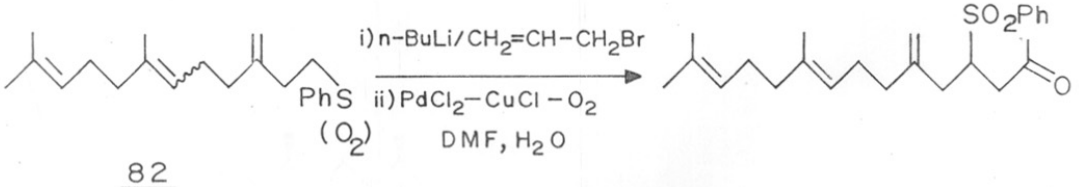




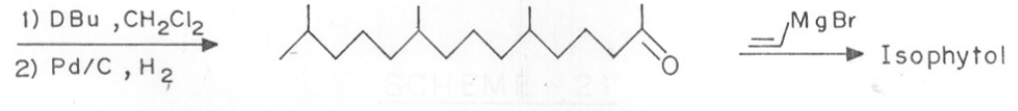
SCHEME-18



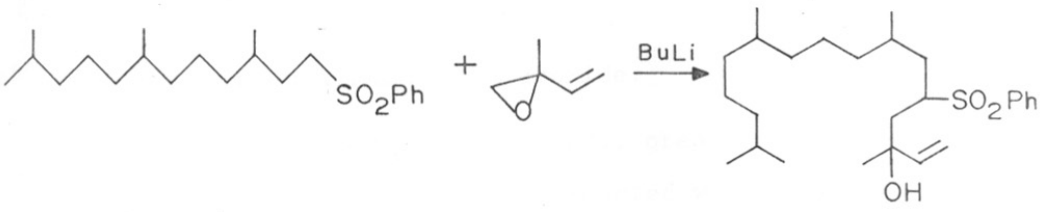
78 80



82



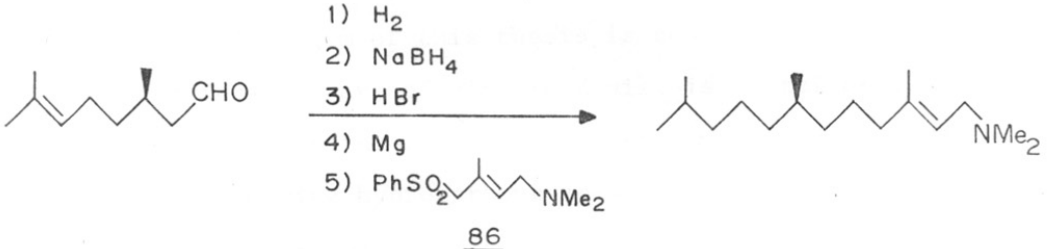
SCHEME-19



83 84 85

Na / Hg / EtOH → Isophytol.

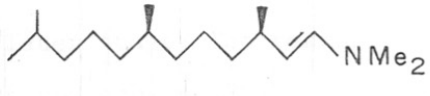
SCHEME-20



86

asymm. isomerization

$Rh[(-)-BINAP]_2ClO_4$, THF, 100°, 15 hrs. → H_2O



87

SCHEME-21

to phytol using vinylmagnesium bromide.

M. Julia[36] uses a sulfone (83), prepared from geranyl bromide and sodium sulfinate, was reacted with isoprene epoxide (84) using butyllithium to get (85) and then the sulfone was removed by sodiumamalgam in ethanol (Scheme 20).

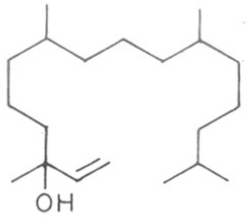
K. Takabe et al.[37] used citronellal and (86) for the synthesis of the aldehyde (87) which is condensed with chromanol to get vitamin E (Scheme 21).

In our laboratory a project was undertaken for the synthesis of vitamins. The object of the project was to initiate new routes for their synthesis, and explore them for commercial feasibility. The aim of this thesis is to explore new methods for the aliphatic part of vitamin E viz. isophytol or its intermediates. Earlier in our laboratory, conversion of the naturally occurring hydrocarbons norphytene and its isomer 2,6,10,14-tetramethylpentadec-2-ene to phytol and phytone was achieved, for the first time with indigenously available starting materials containing the isolated double bond and not forming it at a later stage. The retrosynthetic scheme envisaged is given in the scheme (22).

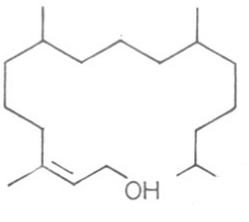
Based on the above retrosynthetic scheme, these C_{19} hydrocarbons have been synthesised using enamine route[38] meldrums acid[39] route and TosMIC[38].

This thesis is divided into three chapters:

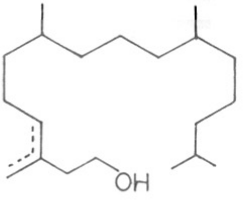
RETEROSYNTHETIC SCHEME



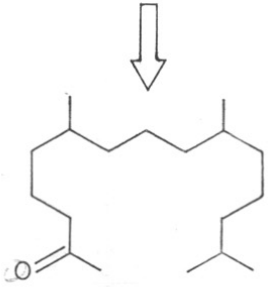
ISOPHYTOL



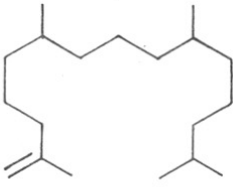
PHYTOL



PHYTOL ISOMERS

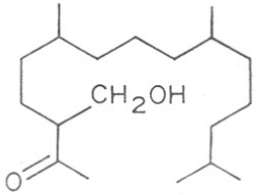


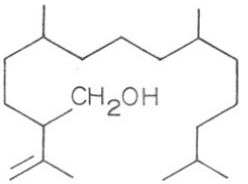
PHYTONE

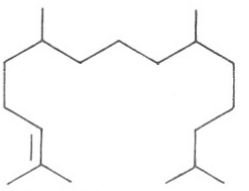


NORPHYENE

C_{19}– Hydrocarbon







2,6,10,14–TETRAMETHYL
PENTA DEC-2-ENE
C_{19}– Hydrocarbon

SCHEME-22

Chapter I

Part A: In this part synthesis of 2,6,10,14-tetramethylpentadec-2-ene using nitro compounds is discussed. Also an introduction to aliphatic nitrocompounds and their utility in organic synthesis is described in brief.

Part B: Describes synthesis of 2,6,10,14-tetramethylpentadec-2-ene via Michael addition to nitro-olefin.

Chapter II is titled "Synthesis of Phytone".

This chapter is divided in two parts:

Part A: describes synthesis of phytone using 1,3-dioxolane [2-methyl-2(3'chloropropyl)].

Part B: deals with the synthesis of 2,6,10,14-tetramethylpentadec-2-ene/ an intermediate of phytone using ethylcyanoacetate.

Chapter III Synthesis of Vitamin E

Part A: Synthesis of Norphytene (2,6,10,14-tetramethylpentadec-1-ene) and vit.E is described. Norphytene is synthesised using ethylcyanoacetate as described in Chapter II, Part B.

Part B Subjecting norphytene to Prins reaction gave phytol isomers from which two homoallylic alcohols viz. 7,11,15 trimethyl-3-methylene hexadecanol a naturally occurring alcohol and its isomer 3,7,11,15-tetramethyl hexadec-3-enol were isolated with trace quantity of phytol. Their structure was also proved by an unambiguous route. The phytol isomers (mixture) was then condensed with trimethyl hydroquinone to give vit.E. A brief introduction to Prins reaction is also given.

REFERENCES

1 Evans - H.M. Evans and K.C. Bishop
Science 56, 650 (1922).

2 Wheat Germ oil - M. Evans and G.O.Burr
J. Biol. Chem., 76, 273 (1928).

3 E. Fernholz
J. Am. Chem. Soc., 60, 700 (1938).

4 World Health Organization, Prevention of Cancer
(Ser. 276). Geneva, Technical Report Service, 1964.

5 E. Boyland
Prog. Exp. Tumor Res., 11, 222 (1969).

6 A. Tappel
Amer. J. Clin. Nutr., 27, 960 (1974).

7 G.W. Grams, K. Eskins and G.E.Inglet
J. Am. Chem. Soc., 94, 866 (1972).

8 G.W.Grams
Tetrahedron Lett., 4823 (1971).

9 G.W. Grams and K. Eskins
Biochemistry 11, 606 (1972).

10 K.E.Mason and I.R. Telford
Arch. Pathol. 43, 363 (1957).

11 L. Einarson and A. Ringsted
in Effect of Chronic Vitamin E Deficiency on the
Nervous System and Skeletal Musculature in Adult Rats.
Copenhagen, Levin and Munksgaard, 1938, p.163.

12 L. Piekarski and M. Koniewicz
Neoplasma (Bratisl), 22, 251 (1975).

13 R.J. Shamberger, F.F. Baughman, S.L.Kalchert,
C.E.Willis and G.C. Hoffman
Proc. Natl. Acad. Sci. USA 70, 1461 (1973).

14 IUPAC-IUB Commission on Biochemical nomenclature.
Nomenclature of tocopherols and related compounds
recommendations (1973)
Eur. J. Biochem., 46, 217 (1974).

15 P. Karrer, H. Fritzsche, B.H.Ringer and H.Salomon
Helv. Chim. Acta 21, 820 (1938).

16 P. Karrer, R.Escher, H. Fritzsche, H. Keller, B.H. Ringier and H. Salomon
Helv. Chim. Acta, 21, 939 (1938).

17 N. Cohen, C.G.Scott, C. Neukom, R.J.Lopresti, G. Weber and G. Saucy
Helv. Chim. Acta 64, 1158 (1981).

18 J.W.K.Burrell, L.M.Jackman and B.C.L.Weedon
Proc. Chem.Soc., 263 (1959).

19 R.H.Conforth, J.W.Cornforth and V. Prelog
Ann. Chem. 634, 197 (1960).

20 O. Isler, P. Schudel, H. Mayer, J. Wursch and R.Ruegg in Vitamins & Hormones, Vol.20, Ed.R.S.Harris & I.G.Wool N.Y. Academic (1962).

21 H. Mayer, P. Schudel, R. Ruegg and O.Isler
Helv. Chim. Acta, 46, 650 (1963).

22 P. Karrer and B.H. Ringier
Helv. Chim. Acta 22, 610 (1939).

23 L.I.Smith and J.A.Sprung
J. Am. Chem.Soc., 65, 1276 (1943).

24 P. Karrer, G.Geiger, H. Rentsohter, E. Zbindes and A. Kugler
Helv. Chim. Acta, 26, 1741 (1943).

25 A. Sato, Y. Kurihara and S. Abe
J. Org.Chem., 28, 45 (1967).

26 T. Fujisawa, T.Sato, T. Kawara and K. Okashi
Tetrahedron Lett., 22, 4823 (1981).

27 M.Larcheveque and T. Cuvigny
Tetrahedron Lett., 44, 3851 (1975).

28 S. Akutagawa, T. Taketami, H. Kumobayashi, K. Takayama, T. Someya and S. Otsuka
Bull. Soc. Chim. Japan, 1158 (1978).

29 CA 90: P 23332 g. Jpn. Kokai Tokkyo koho, 78, 105, 407.

30 CA 90: 55141 k. Jpn. Kokai Tokkyo koho, 78, 105, 409.

31 J.W.K.Burrell, R.F.Garwood, L.M.Jackman, E. Oskay and B.O.L.Weedon
J. Chem. Soc. (C), 2144 (1966).

32

33 R. Zell
Helv. Chim. Acta, 62, 474 (1979).

34 M. Schmid and R. Barner
Helv. Chim.Acta, 62, 464 (1979).

35 T. Mandai, H. Yamaguchi, K. Nishikawa, M. Kawada and J. Otera
Tetrahedron Lett., 22, 763 (1981).

36 M. Julia and D. Ugnen
Bull. Soc. Chim. Fr. 513 (1976).

37 K. Takabe, Y. Uchiyama, K. Okisaka, T. Yamada, T. Katogiri, T. Okazaki, Y. Oketa, H. Kumobayashi and A.S. Akutagawa
Tetrahedron Lett., 26, 5153 (1985).

38 S.V. Kamath, M.V.Rangaishenvi, and S.N. Kulkarni
Ind. J. Chem., 22B,1264 (1983).

39 M.V.Rangaishenvi, S.V.Kamath, A.S.Phadke and S.N.Kulkarni
Ind. J.Chem., 22B, 684 (1983).

CHAPTER - I

SYNTHESIS OF 2, 6, 10, 14 - TETRAMETHYL PENTADEC - 2 - ENE USING ALIPHATIC NITRO COMPOUNDS

This chapter describes the synthesis of 2,6,10,14-tetramethylpentadec-2-ene using aliphatic nitro-compounds.

The chapter is divided into two parts.

PART A.

This part describes the synthesis of 2,6,10,14-tetra-methylpentadec-2-ene-7-one via hydroxyalkylation of aliphatic nitro compounds. The basic strategy used is shown in the reterosynthetic scheme. A brief note on aliphatic nitro compounds is also given.

PART B.

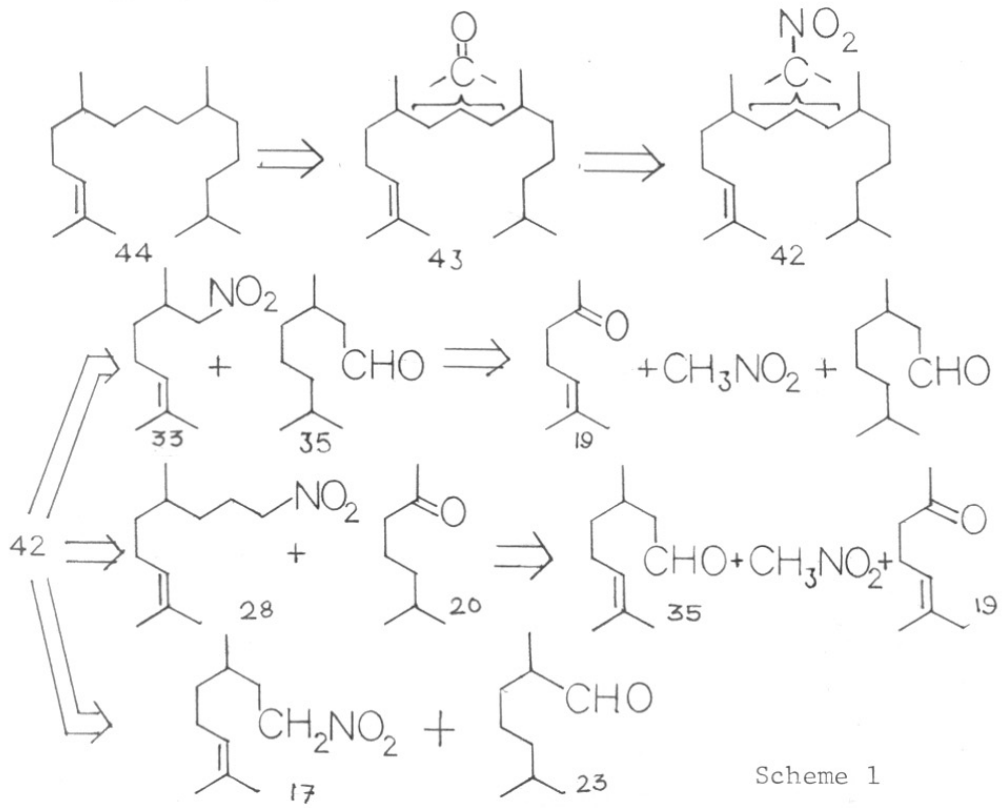
2,6,10,14-Tetramethylpentadec-2-ene-8-one is synthesised via Michael addition to nitro olefin using ultrasound technique.

CHAPTER - I

PART A

SYNTHESIS OF 2,6,10,14-TETRAMETHYL PENTADEC-2-ENE-7-ONE VIA HYDROXALKYLATION OF ALIPHATIC NITRO COMPOUNDS

As evident from the introduction, the main strategy employed for the synthesis of aliphatic part of Vitamin E is the preparation of C_{19} hydrocarbons as these can be converted into phytone or phytol isomers. In this chapter one of the approaches for the synthesis of 2,6,10,14-tetramethylpentadec-2-ene, is described. Similar approach can be utilized for the synthesis of norphytene a positional isomer of the above hydrocarbon. A reterosynthetic scheme using the aliphatic nitro group is given below (Scheme 1).



Scheme 1

The main purpose of this route was the utilisation of

abundantly available starting materials and using nitro group as a carbonyl equivalent. Since this chapter is concerned with the use of aliphatic nitro compounds, a brief general survey of their preparation, general reactions and usefulness as organic intermediates is given.

INTRODUCTION

The survey can be divided into three parts:

i) preparation of aliphatic nitro compounds without carbon-carbon bond formation,

ii) their conversion to other functional groups and

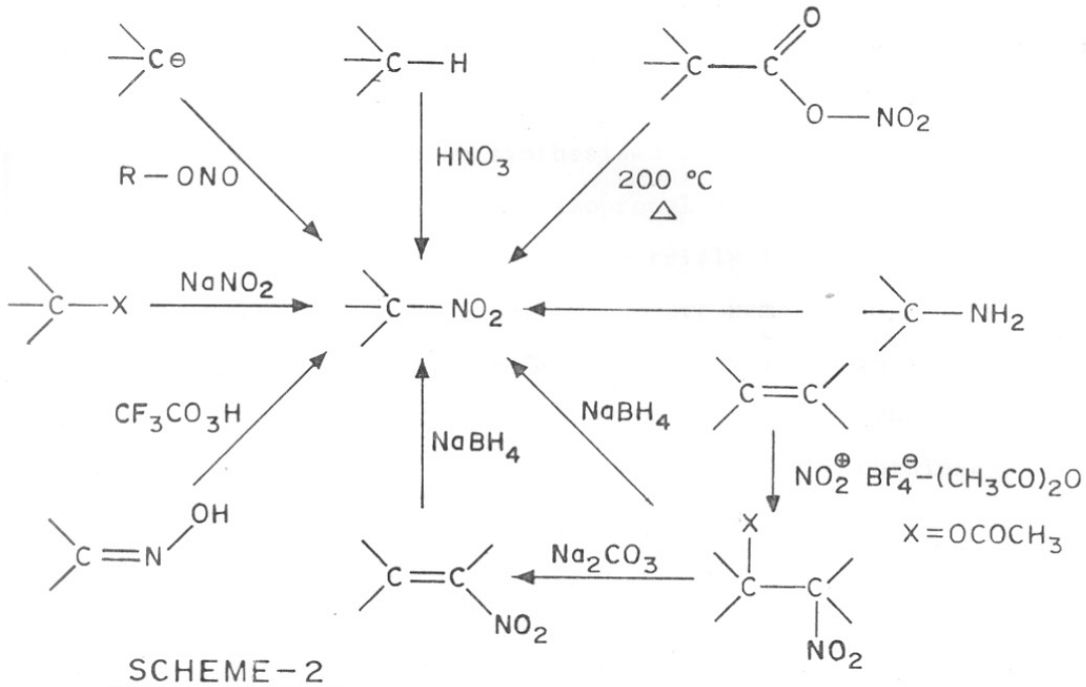
iii) use in C-C bond formation.

i) Preparation of nitrocompounds

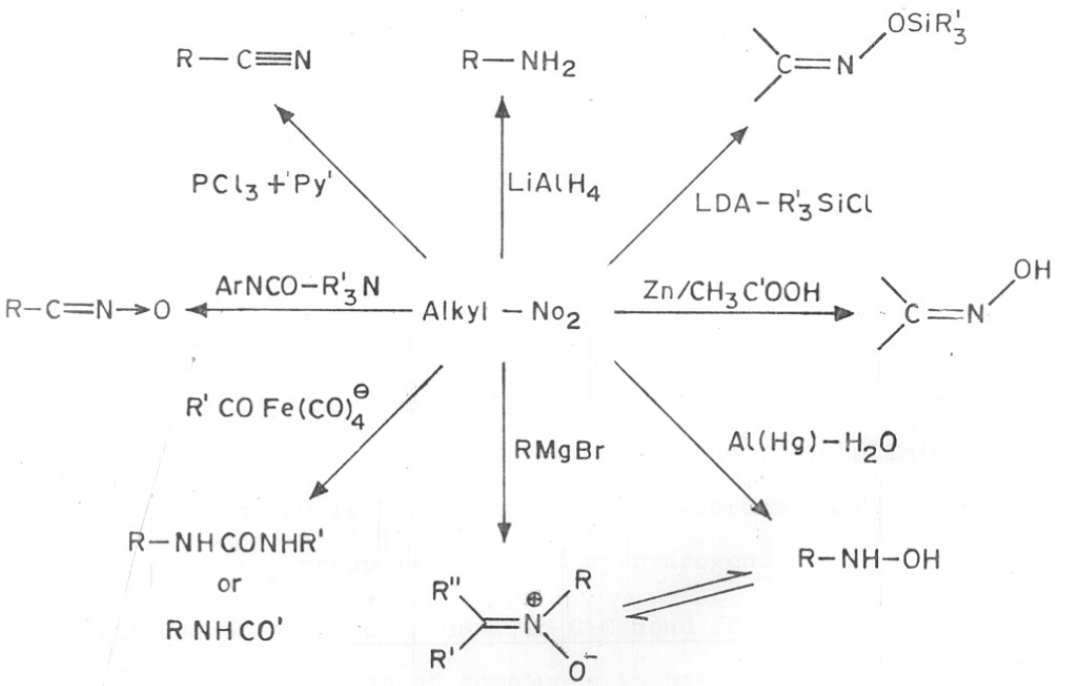
Scheme 2 surveys general methods used to prepare nitrocompounds, which do not involve C-C bond formation. Nitrocompounds are accessible from substrates such as alkylhalides, carbanionids, hydrocarbons, carboxylic acids, amines, oximes and alkenes.

ii) Conversion to other functional groups

The importance of nitrocompounds lie in their conversion into other functional groups like (i) amines (ii) amides (iii) hydroxyl amines (iv) nitrones, (v) oximes, (vi) nitriles, (vii) nitrile oxide and (viii) silylnitronates. The condition for these conversions are described in Scheme 3. Of these the



SCHEME – 2



SCHEME – 3

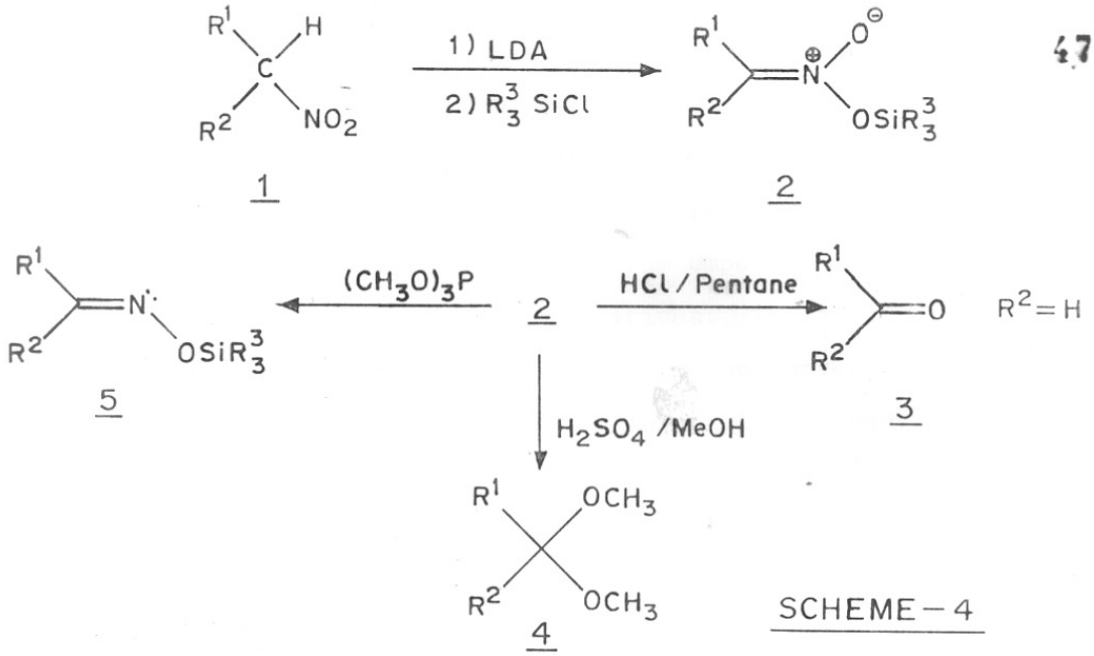
silyl nitronates have been synthesised only recently, and are best prepared[1] using lithium diisopropyl amide and quenching the resultant nitronate anion with a trialkylsilyl chloride followed by nonaqueous workup. These are remarkably stable in anhydrous condition (temp. > 100°) which is in marked contrast with alkylnitronate esters which readily fragment into carbonyl compounds and oximes. The silylnitronates obtained from primary nitroalkanes can be converted to aldehydes (3), acetals (4), and oxime silyl ethers (5), as given in Scheme 4.

The Nef reaction[2] is one of the most important transformation of nitroalkanes. As its success often depends on the nature of the substrate, many other variations are developed of the original procedure of solvolysis of alkali nitronates with aqueous or alcoholic sulfuric acid. Such variations include reductive [Ti(iii)[3], V(ii)[4]] and oxidative (O_3[5], RONO[6]) conditions, as well as the use of sodium methoxide impregnated silica gel. With concentrated mineral acids or $NaNO_2$/RONO/DMSO primary nitroalkanes were converted to carboxylic acids.

In addition to being a precursor to a variety of organic functional groups (Scheme 3) the nitrogroup can be removed under eliminative[7] or reductive conditions[8]. In eliminative condition a double bond is introduced whereas in reductive process nitro group is replaced by hydrogen.

iii) Use of nitro compounds in C-C bond formation

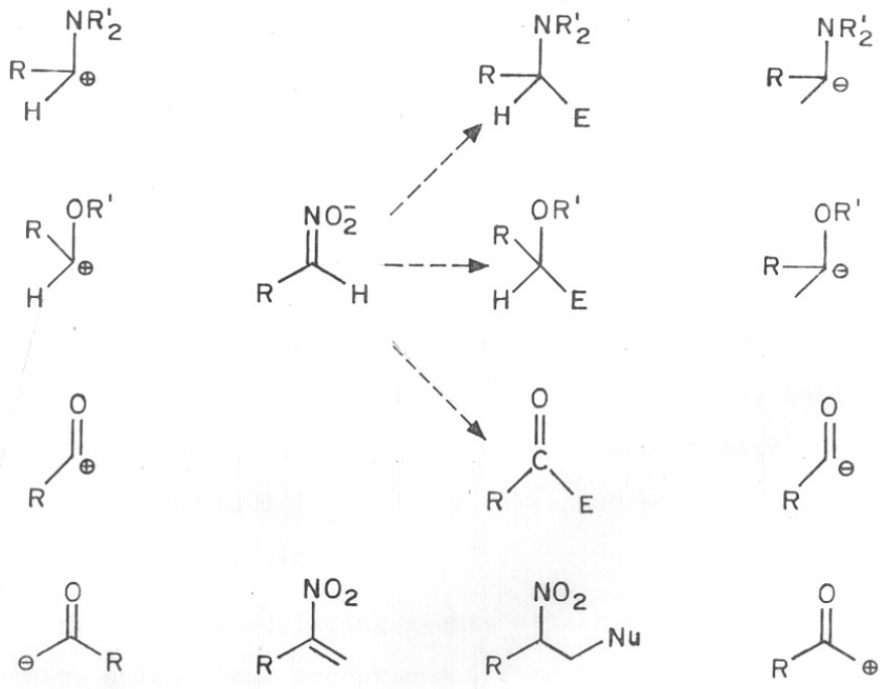
For any class of compounds to have a broad synthetic



SCHEME – 4

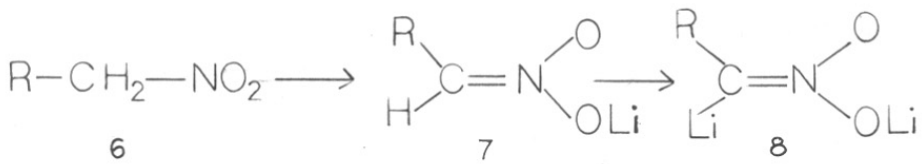
SYNTHONS WITH NORMAL ACTIVITY

SYNTHONS WITH REACTIVITY UMPOLUNG



SCHEME – 5

utility it must be amenable to carbon-carbon bond formation processes. For this purpose, nitroaliphatics appear to be especially attractive, since they provide umpolung of reactivity of amines, alcohols and carbonyl derivatives. The electrophilic attack on a nitronate anion at the carbon, and conversion of the product into an amine, alcohol or carbonyl compound demonstrates this reversed reactivity of amine, alcohol and carbonyl compound. Similar is the case with nitro olefins as shown in Scheme 5. The usefulness of an organic intermediate depends upon its ability to undergo the four most important reactions viz. alkylation, acylation, hydroxyalkylation and conjugate addition. Though alkylation and acylation lead to mostly O-acylated product, this difficulty was overcome by preparation of the dianion of the nitrocompound[9] using two moles of butyllithium in THF at -78°C.



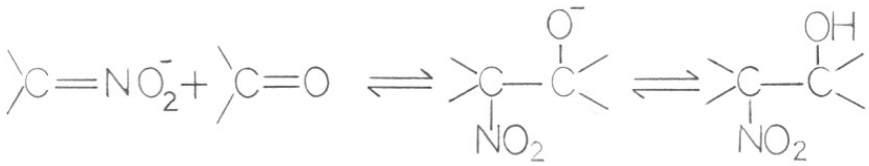
6 7 8

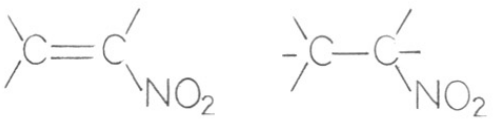
The acidity of the remaining proton in 7 is in the same range as that of diisopropylamine and can be abstracted by BuLi at -78°C. The dilithio salts (8) can be alkylated smoothly to higher nitroalkanes using primary alkyl and benzyl bromides and iodides in 50-70% yields.

Most of the acylating agents attack at oxygen of the nitronate anion. Some exceptions are methoxymethyl magnesium

carbonate, aroyl cyanides, and acyl imidazoles. Here also the dilithio derivatives acylate cleanly to give c-acylated products in good yields. These can be then converted to α-diketones by Nef reaction.

The addition of nitronate anions to aldehydes and ketones, the Henny reaction[10], or nitroaldol, is a classical carbon-carbon bond forming method. Due to the ease of reversibility, the reaction is generally carried out using



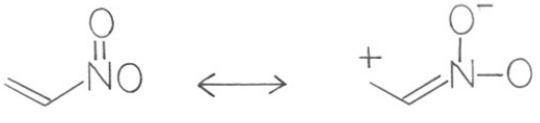


catalytic amount of base, although equimolar quantities of base have been used. A corollary of this reversibility is that yields of isolated nitroalcohols are only high in intramolecularly favoured cases, or with nitromethane and/or aldehydes as reaction partners. The product nitroalcohol can be dehydrated to get the olefine and further hydrogenated to get nitroalkanes. This constitutes an alternate method for alkylation. The dianion is useful in this reaction also.

The Michael reaction of nitroalkanes to α,β-unsaturated aldehydes, ketones, esters, nitriles as well as vinylsulfone and nitroolefins, in one of the most efficient C-C bond forming reactions. The same is true of the complimentary addition of active

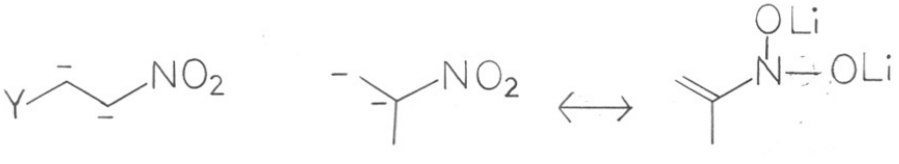
methylene compounds to nitroolefins. This reaction is most successful with well stabilized anions, yields decreasing with increasing reactivity of nucleophile, though alkyl groups can be added as dialkylcuparates[11] or cadmium alkyls[12]. Low temperature addition of lithium alkyls[13] to nitroalkenes and trapping the resulting nitronate with tetranitromethane gives 1,1-dinitro compounds. Nitroalkanes on addition to conjugated ketones, after Nef reaction give 1,4-diketones which can be cyclized to cyclopentenone ring[14].

Nitroolefins are electrophilic at β-carbon. This reactivity was changed when double deprotonation was tried on



9 10

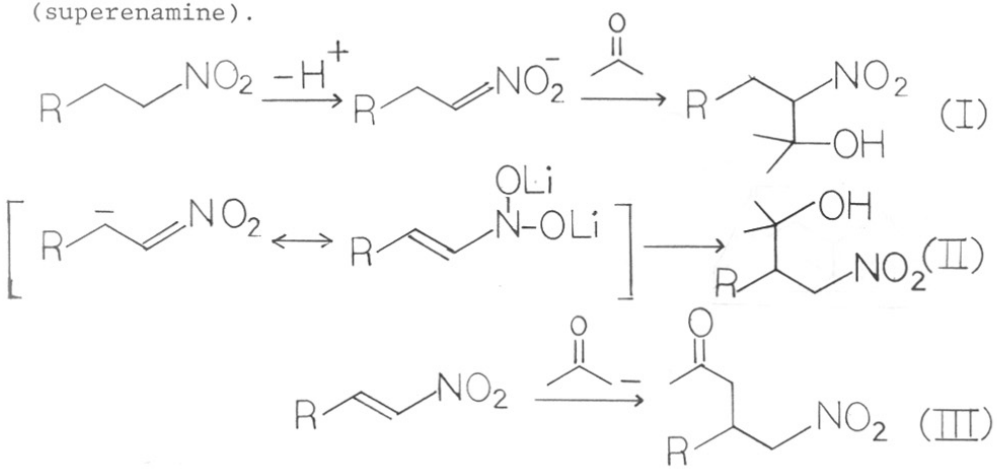
2-aryl nitroethane. The strong base sequentially removed the α and β protons to give (11). The Y group in (11) may be vinyl, aryl



11, Y=Ar, ═, CO_2Et. 12 13

or ester group. But when there is only one proton at α-carbon the proton at the β-carbon is abstracted viz. 2-nitropropane was sequentially treated with n-BuLi and t-BuLi to give (12). The species is actually believed to be is a N,N-dihydroxy enamine (13)

(superenamine).

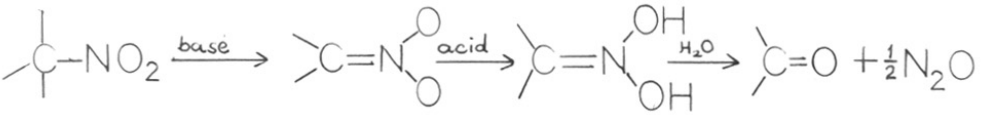


Studying equations (I), (II) and (III) shows that three entirely different structural types are available from precursors with the same carbon skeletons and functionality patterns. Acetone combines as an electrophile with nitronate anion to give 1,2-nitroalcohol, and with the dianion derivative to give an isomeric 1,3-nitroalcohol, while as its nucleophilic enolate, it adds to a nitro-olefin to give 1,4-nitro ketone. The above survey shows that aliphatic nitro compounds are amenable to both nucleophilic and electrophilic attack at α and β carbon atoms of their skeleton.

Conversion of Nitro group to Carbonyl

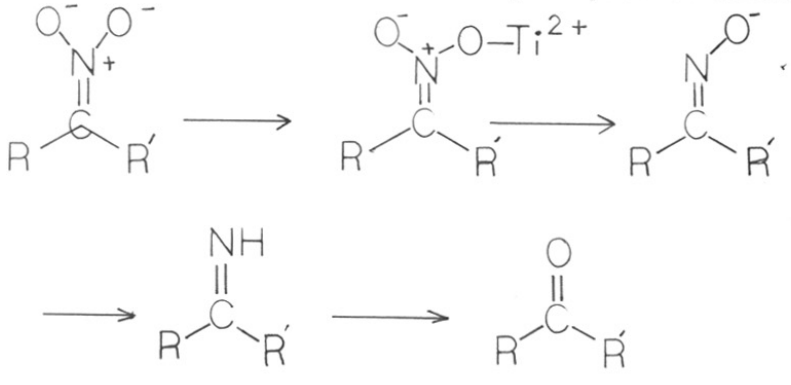
The Nef reaction in the traditional method for conversion of nitrocompounds to carbonyl compounds, but due to the drastic conditions used in this reaction, it was not used to large extent. The Nef reaction involves conversion of the nitroalkane to its nitronate anion and then treatment with a strong acid to yield the protonated nitronic acid which leads to carbonyl compound and

nitrous oxide.



Many types of functionalities are incompatible with these conditions and so many alternative methods have been examined. These include oxidation of nitronate anions with $KMnO_4$[15] or persulfate ion[16], reductive procedures with titanium (III) salts[2], ozonolysis of nitronated anions[4], the use of alkyl nitrite esters in combination with sodium nitrite.

McMurry[3] and his group have extensively studied the reductive method. The modification which seems most compatible with other functional groups, is the treatment of the nitronate salt in methanol with buffered aqueous titanium (III) chloride. The mechanism given is via deoxygenation of nitro to oxime and then oxime to imine which is hydrolysed to ketone at low pH.



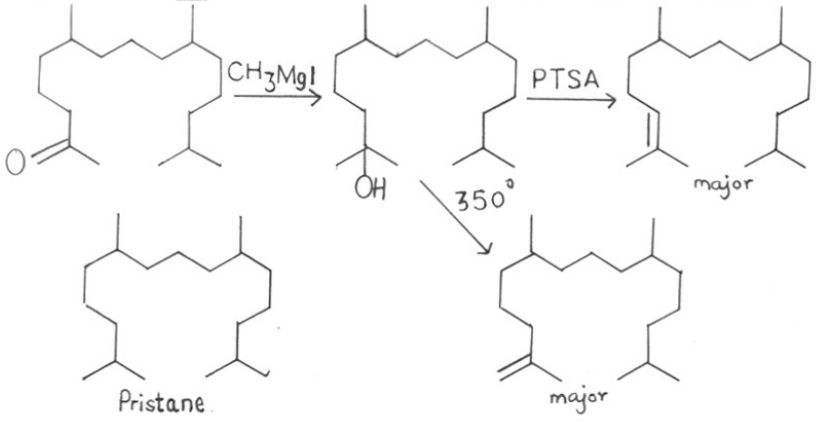
The details of the N-O bond cleavage step are not clear (although radicals are probably involved since Ti^{3+} is a one electron reducing agent).

PRESENT INVESTIGATION

This chapter deals with the synthesis of 2,6,10,14-tetramethylpentadec-2-ene-7-one (43) which can be converted to the corresponding hydrocarbon 2,6,10,14-tetramethylpentadec-2-ene. This hydrocarbon and its positional isomer norphytene are important intermediates for the synthesis of phytol isomers (reterosynthetic scheme 22 , in Introduction to Vit.E).

2,6,10,14-Tetramethylpentadec-2-ene is a naturally occurring C_{19} monoolefin obtained from mixed zooplankton in the Gulf of Main. Its structure was established by ozonolysis and hydrogenation studies. Ozonolysis gave C_{16} aldehyde whereas hydrogenation gave pristane which was confirmed by comparison with authentic samples[17].

The method so far reported for the synthesis of 2,6,10,14-tetramethylpentadec-2-ene involves Grignard reaction on phytone (14)[18]. The scheme is outlined below.



In the above synthesis the double bond is introduced at

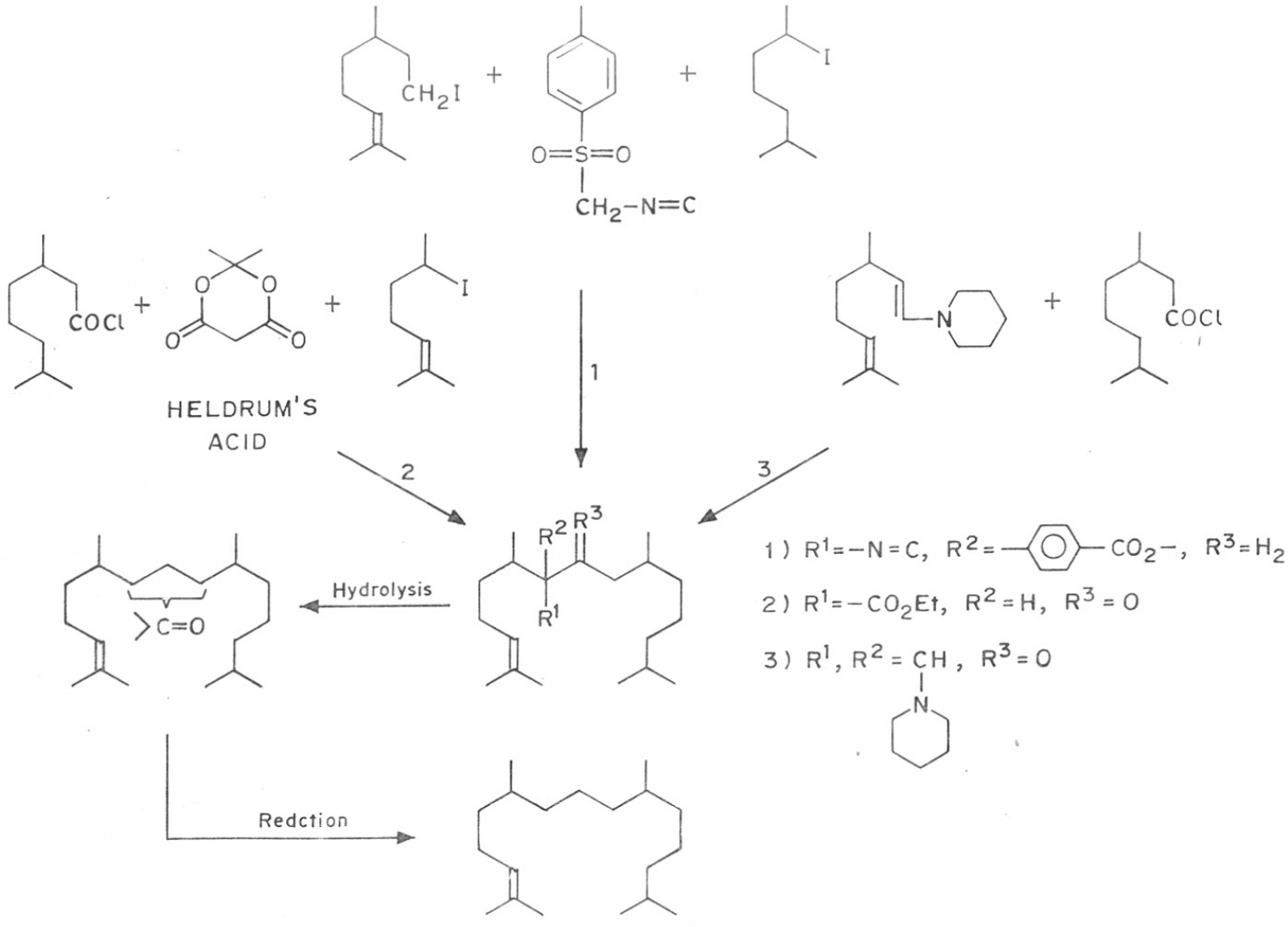
a later stage,but in the syntheses developed in our laboratory the starting materials like citronellal or methylheptenone were used which already possessed this functionality. The methods developed in our laboratory using (i) TosMIC[19] (ii) Enamines[19] and (iii) meldrums acid[20] are outlined in the scheme 6.

In continuation of this work the present chapter describes the synthesis of 2,6,10,14-tetramethylpentadec-2-ene (44) using aliphatic nitro compounds as intermediates. The three methods tried are outlined in the reterosynthetic scheme (Scheme 1).

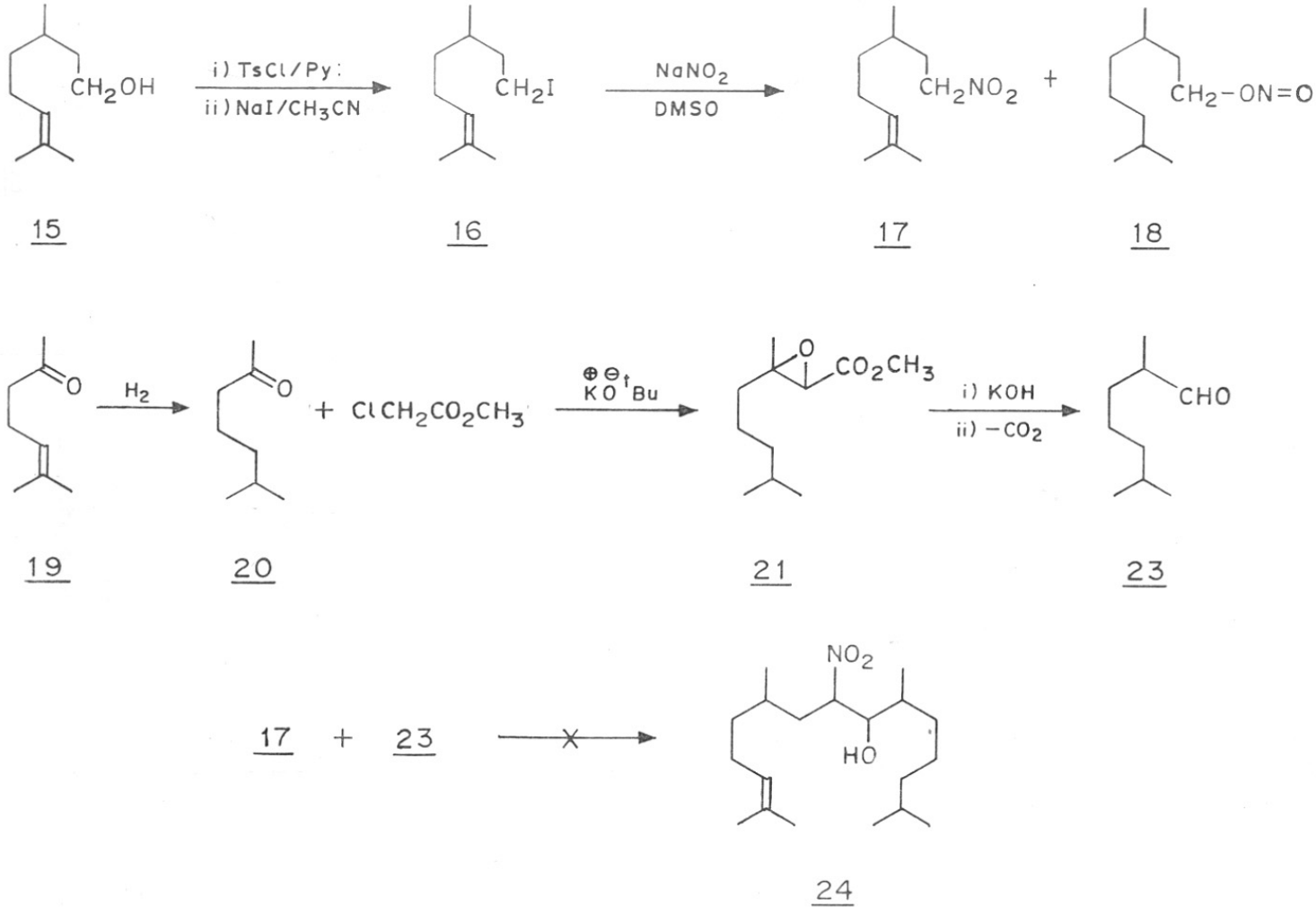
The first method attempted was the condensation of 1-nitro-3,7-dimethyloct-6-ene, a C_{10} nitrocompound, and 2,6-dimethylheptanal, a C_9 aldehyde (Scheme 7).

1-Nitro-3,7-dimethyloct-6-ene (17) was prepared from citronellol, a naturally occurring monoterpene. Citronellol (15) was tosylated using p-toluenesulfonylchloride in pyridine at 0° to 5°C. The tosylate was refluxed with sodium iodide in acetonitrile to get 1-iodo-3,7-dimethyloct-6-ene (16). It was purified by column chromatography on silica gel and eluting with pet.ether and characterized by its PMR (CCl_4) δ: 0.90 (d, 3H, $C\underline{H}_3$-CH-J=6 Hz) 1.6, 1.66 (2s, 6H, methyls on double bond),3.2 (t, 2H, -$C\underline{H}_2$-I, J=7 Hz), 5.00 (bt, olefinic proton). Yield: 90%; b.p. 100-102°/5 mm (lit.116-118°/10 mm[21]).

The iodooctene (16) was converted to the corresponding


HELDRUM'S ACID
1
2
3
Hydrolysis
Redction
1) R^1=–N=C, R^2= –CO_2–, R^3=H_2
2) R^1=–CO_2Et, R^2=H, R^3=O
3) R^1, R^2=CH, R^3=O

SCHEME–6


CH2OH
i) TsCl/Py:
ii) NaI/CH3CN
CH2I
NaNO2
DMSO
CH2NO2
+
CH2-ON=O
15
16
17
18
O
H2
O
+ ClCH2CO2CH3
⊕ ⊖ tBu
KO
O
CO2CH3
i) KOH
ii) -CO2
CHO
19
20
21
23
17 + 23
NO2
HO
24

SCHEME—7

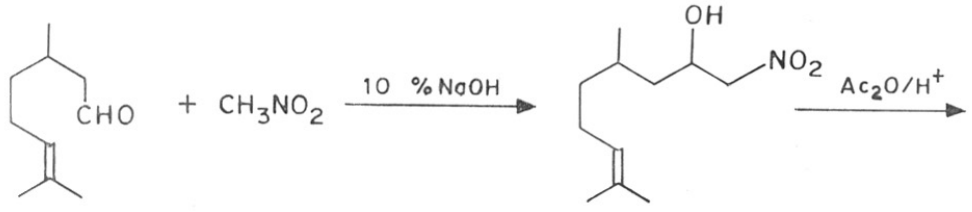
nitrocompound, 1-nitro-3,7-dimethyloct-6-ene (17) using sodiumnitrite in DMSO[22]. It was found to be a mixture of two compounds by TLC and was separated by column chromatography on silica gel. The less polar compound was obtained in PE + 25% benzene eluate and the more polar compound in benzene + 10% ethyl acetate eluate. The more polar spot was alkylnitrite (18) as seen from its IR and PMR. The PMR in CCl_4 showed a triplet at 3.6 for $\underline{CH}_2$-ONO and the IR showed band at 1660, 1610 cm^{-1} for (O-N=O). The less polar compound was identified as 1-nitro-3,7-dimethyloct-6-ene and was characterized by its IR, PMR and Mass spectrum M^+ 185, IR (liquid film) showed characteristic band for ($-NO_2$) at 1555 cm^{-1} and PMR showed methylene adjacent to nitrogroup at 4.4 . PMR(CCl_4) δ: 0.96 (d, 3H, $\underline{CH}_3$-CH-, J=5 Hz), 1.6, 1.66 (2s, 6H, methyls on double bond), 4.4 (t, 2H, -$\underline{CH}_2$-NO_2, J=7 Hz), 5.00 (bt, olefinic proton). Fig 1.1 Yield 52% b.p. 70-72°/2 mm.

The C_9 aldehyde (23) was prepared by Darzen's reaction using methylchloroacetate and methylheptanone (20). Methyl heptanone was prepared by hydrogenation of methylheptenone (19) on 10% Pd/C in ethanol under 3 atm. of hydrogen in quantitative yields. Methylheptanone (20) and methylchloroacetate were condensed in presence of potassium tertiary butoxide in t-butanol to furnish the epoxy ester (21). Alkaline hydrolysis of the epoxyester gave the epoxy acid (22) which on pyrolysis (heating at 200°) gave the aldehyde, 2,6-dimethylheptanal (23) in overall 20% yield. The structure of the

aldehyde was proved by its IR, PMR and Mass. IR (liquid film): 1772, 2700 cm^{-1} (-CHO). PMR(CCl_4) δ: 0.90 (d, 6H, 2 $\underline{CH}_3$-CH-, J=6 Hz), 1.05 (d, 3H, $\underline{CH}_3$-CH-, J=6 Hz), 2.1 (m, -$\underline{CH}$-CHO, 1H), 9.53 (s, 1H, -CHO), b.p. 80-90°/30 mm, m.p. of 2,4-DNP 95°C. Mass obtained was that of the corresponding acid implying that the aldehyde was susceptible to air oxidation.

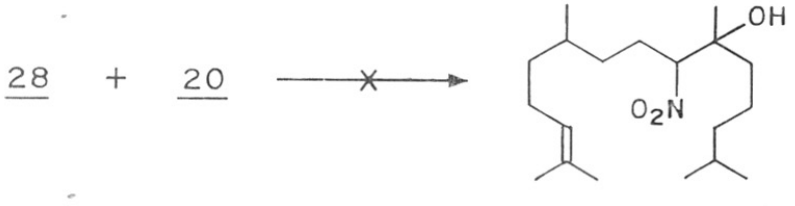
The condensation of the C-10 nitrocompound (17) with the C-9 aldehyde (23) was tried under various conditions, viz. (i) using aqueous alcoholic NaOH/KOH[23], (ii) sodium methoxide in methanol (iii) adding bisulfite adduct of the aldehyde to the sodium salt of (17) in DMSO[24]. Unfortunately all the above reactions failed to give the required nitroalcohol (24). Catalytic piperidine was also used. The reaction was unsuccessful. In most of the cases the starting materials or the acid of the starting aldehyde was obtained.

Another method tried was the condensation of a C-11 nitrocompound 1-nitro-4,8-dimethylnon-7-ene (28) and methylheptanone (20) (Scheme 8). The C-11 nitrocompound was prepared from citronellal and nitromethane. To an equimolar mixture of citronellal and nitromethane in alcohol 10% aqueous NaOH was added and stirred for 4 hrs, alcohol was evaporated poured in water, acidified and extracted to obtain the nitroalcohol (26) in 93% yields. This nitroalcohol was



26

27 28



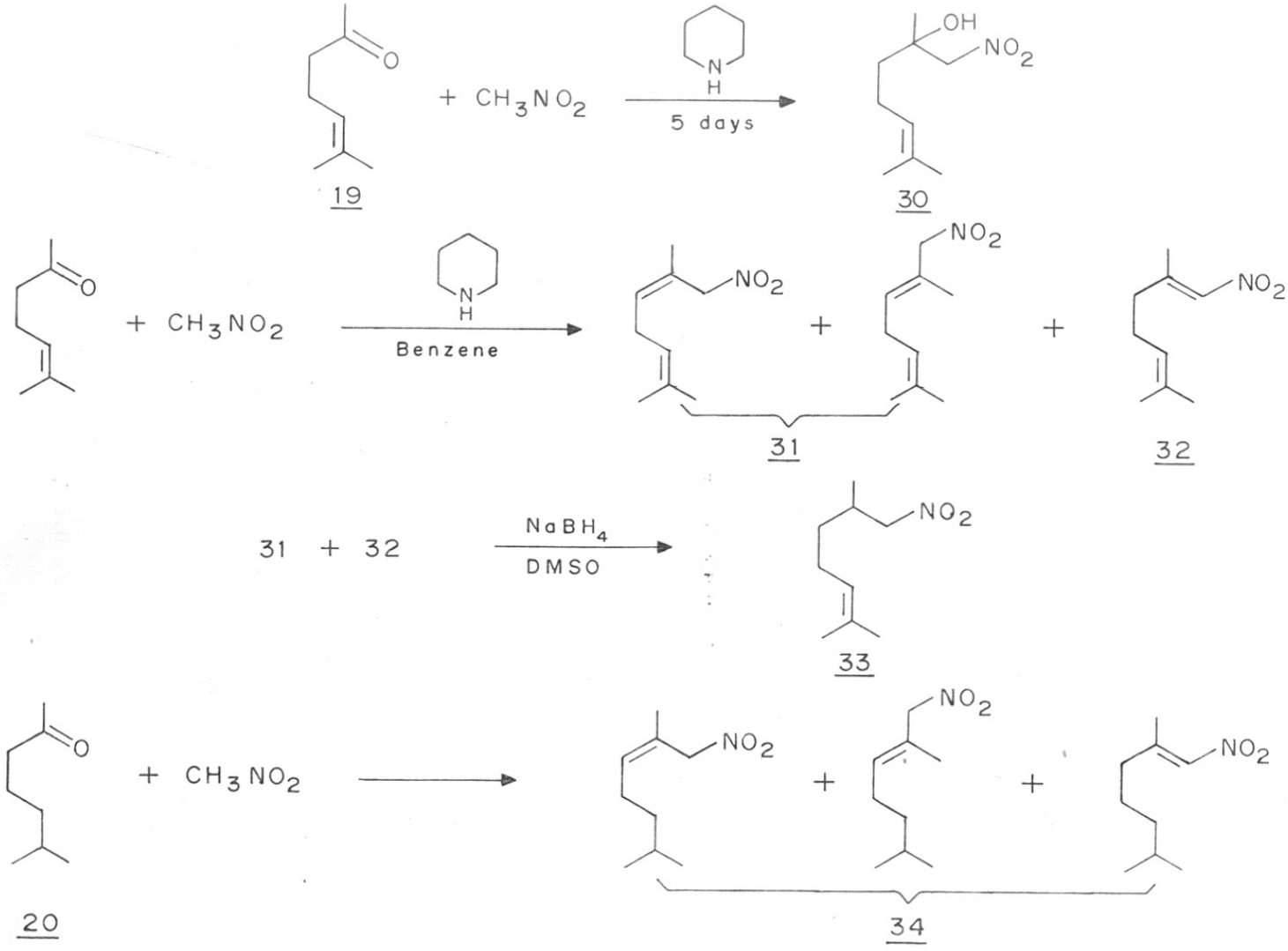
29

SCHEME-8

acetylated by aceticanhydride using concentrated sulfuric acid as catalyst. The nitroacetate (27) on treatment with sodiumborohydride in DMSO[25] gave the nitrocompound (28) in 76% yield. IR (liquid film): 1548 (NO_2) cm^{-1}. PMR (CCl_4)δ: 0.91 (d, 3H, $C\underline{H}_3$-$\dot{C}$H-, J=5 Hz), 1.6,1.66 (2s, 6H, methyls on double bond), 4.3 (t, 2H, -$\dot{C}\underline{H}_2$-NO_2, J=7 Hz), 5.03 (bt, 1H, olefinic proton). M^+ 199.

The different methods tried for the condensation of (28) and (20) were (i) using piperidine in benzene (ii) addition of bisulfite adduct of (20) to the sodium salt of (28) in DMSO and (iii) 2 moles BuLi in THF and HMPA mixture (5:1). Unfortunately all the above methods did not give the required nitroalcohol (29). Two moles of BuLi were used to create the dianion of (28), but on work up of the reaction only the starting materials were obtained. The α-proton of the ketone (20) must have been abstracted by the dianion and which was recovered after work up.

In the third method the strategy used was the condensation of the C-9 nitrocompound, 1-nitro-2,6-dimethyl hept-5-ene (33) and 3,7-dimethyloctanal (35) (Scheme 10). The ketone (43) finally obtained will have the carbonyl at the C-7 position. The C-9 nitrocompound was prepared from methylheptenone (19) and nitromethane (Scheme 9). Attempts to condense methylheptenone and nitromethane using bases


+ CH_3NO_2
5 days
19
30
+ CH_3NO_2
Benzene
31
32
31 + 32
$NaBH_4$
DMSO
33
+ CH_3NO_2
20
34

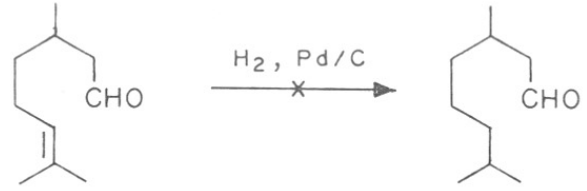
SCHEME-9

like NaOH, sodiummethoxide, ammonium acetate/acetic acid, had failed. Finally a mixture of (19) and nitromethane and a drop of piperidine were kept neat for five days and after usual work up about 30% nitroalcohol (30) was obtained and on refluxing the above mixture in benzene gave the nitroalkene (31, 32) in 45% yield. So in a modified procedure methylheptenone, nitromethane and catalytic piperidine was refluxed for 8 hrs in benzene using Dean-Stark apparatus to separate water. The reaction mixture was washed with water to remove piperidine, the unreacted starting materials were removed by distillation and the residue chromatographed to give 1-nitro-2,6-dimethylhepta-2,5-diene (31). The conjugated nitrocompound 1-nitro-2,6-dimethylhepta-1,5-diene (32) was also present in about 8% as detected by PMR. The reaction did not reach completion in 8 hrs but further heating led to polymerization and reduction in yields. To overcome this problem (19) was used in excess, even then the yield based on recovery of (19) was 55%. Use of excess nitromethane was also not of much help. The IR, PMR and mass spectra confirmed the structure of (31) and (32). IR (liquid film): 1560 cm^{-1} ($-NO_2$). PMR (CCl_4) δ: 1.6, 1.7, 1.76 (3s, methyls on double bonds), 2.73 (t, 2H, methylene allylic to two double bonds), 4.66, 4.83 (2s in the ratio 65:25 due to geometric isomers), 5.0 (t, 1H, olefinic proton at C_5),

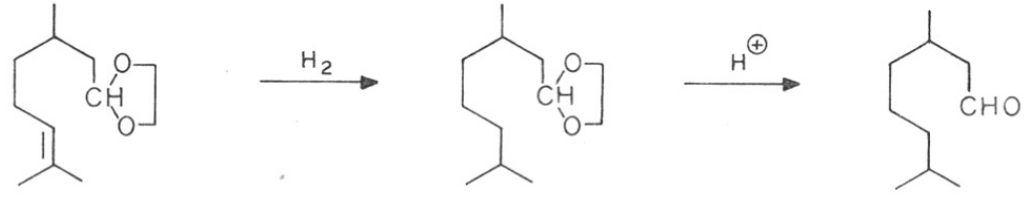
Fig 1-2

5.5 (t, 1H, olefinic proton on γ carbon to NO_2). The other isomer (32) was detected due to the presence of peaks at 2.2 for CH_3 on β-carbon to NO_2 and at 6.76 olefinic α-proton. The GLC (ov 101 temp. 150°) showed two major peaks in the ratio of 65:25 due to the E & Z isomers of (31). To substantiate the above results methyl-heptanone (20) was also condensed with nitromethane under identical conditions. This also showed small quantities of conjugated nitrocompound . GLC (ov 101 temp. 150°) showed E & Z isomers in the ratio of 64:27. PMR: δ 0.9 (d, 6H, $C\underline{H}_3$-$\underset{'}{C}$H-, J=6 Hz) remaining pattern same as above with the absence of a triplet at 5.0 which was due to the olefinic proton at C_5.

Sodiumborohydride has been used frequently in literature[25] for saturation of conjugated nitroolefins. Also β,γ-unsaturated nitroolefins can be equilibrated to α,β-unsaturated nitro-olefins in presence of a base[26]. The mixture of 31 and 32 was treated with sodiumborohydride in DMSO with a view that $NaBH_4$ will equilibriate 31 to 32 and then hydrogenate 32 to 33 the required C_9 nitrocompound. The yields of hydrogenation were about 85%. The C_9-nitrocompound 33 was characterized by its IR, PMR and mass spectra. IR (liquid film): 1560 cm^{-1} (NO_2). PMR: δ 0.98 (d, 3H, $C\underline{H}_3$-$\underset{'}{C}$H-, J=7 Hz), 1.6, 1.66 (2s, 6H, $\underset{\underline{C}\underline{H}_3}{\underline{C}\underline{H}_3}\!\!>\!=$), 4.09 (AB part of the ABX pattern, J_{AB}= 12 Hz, $J_{AX} = J_{BX}$= 6 Hz), 5.02 (bt, 1H, olefinic proton). Fig 1.3



25 35



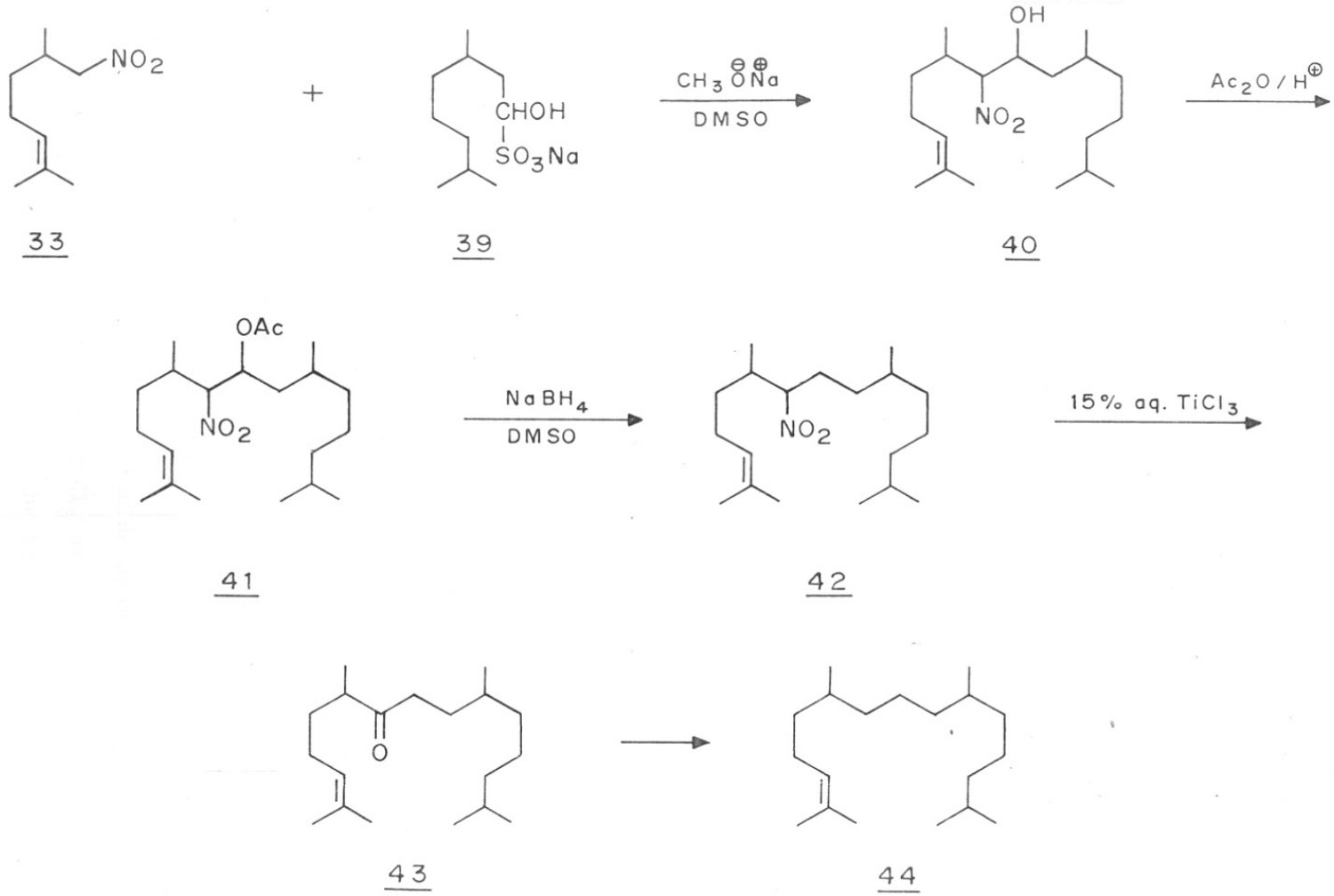
36 37 35

15 38 35 39

SCHEME -10

Dihydrocitronellal (35) was the C_{10} carbon unit used for the condensation with (33) (Scheme 10). Hydrogenation of citronellal is reported in literature[27] but it repeatedly failed in our hands, even when hydrogenation was carried out at 3 atm pressure of hydrogen. So citronellal was converted to its ketal 2,6-dimethyl-8,8-ethylenedioxyoct-2-ene (36), by literature procedure[28,30] b.p. 125-26°/4.5 mm. Yield 85%. The ketal hydrogenated smoothly in ethanol using 10% Pd/C at atmospheric pressure to furnish 2,6-dimethyl-8,8-ethylenedioxyoctane (37), which on treatment with aqueous acid furnished dihydrocitronellal (35), i.e. 3,7-dimethyl-octanal b.p. 83-84°/12 mm (lit. 81-82°/10 mm[29]). Alternatively citronellol (15), 3,9-dimethyloct-6-enol was hydrogenated using 10% palladized charcoal in ethanol and 3 atmospheric pressure. The saturated alcohol was then oxidized to the corresponding aldehyde using pyridinium chlorochromate in about 75% yield. This aldehyde (35) was shaken with saturated solutions of sodiumbisulfite to get a white solid. This was filtered and dried in a vacuum desiccator, m.p. decomposes at 360°.

The reaction sequence for the condensation of the C_9-nitrocompound (33) and dihydrocitronellal (35) to the required tetramethyloxopentadecene (43) is given in Scheme 11. The sodium salt of (33) was dissolved in dry DMSO and reacted with the bisulfite adduct of dihydrocitronellal (39)[26].



33 39 40

41 42

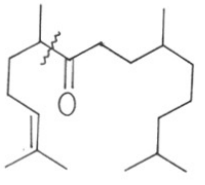
43 44

SCHEME –11

The reaction mixture was stirred overnight and after usual workup the nitroalcohol (40) was obtained in 36% yield. Other methods like refluxing in benzene using catalytic piperidine, stirring and refluxing with aqueous alcoholic (1:1) KOH failed to give the corresponding nitroalcohol 40. The nitroalcohol was purified by column chromatography on silica gel. IR spectra show -OH frequency at 3450 cm^{-1}, 1550 cm^{-1} (NO_2). Nitroalcohol 40 was acetylated using acetic anhydride and catalytic conc. sulphuric acid. The reaction was monitored by TLC. It was completed in 4 hrs. The acetate (41) after work up was used in the next step without further purification. The acetate (41) was treated with sodium borohydride according to literature procedure[25] to get the C_{19} nitrocompound, 2,6,10,14-tetramethyl -7-nitropentadec-2-ene (42). The reduction by borohydride is said to go via the nitroolefin and then hydrogenation by $NaBH_4$.

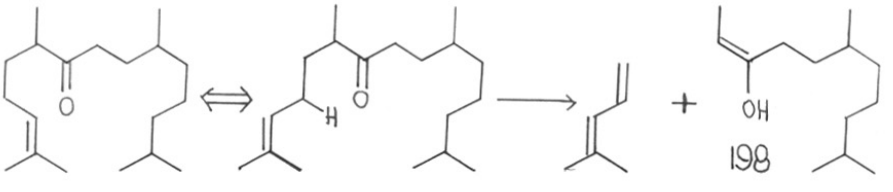
The Nef reaction[2] involves a sequential treatment of alkali and a strong mineral acid in that order to convert aliphatic nitrocompounds to the corresponding carbonyl compounds. Use of 15% aqueous titaniumtrichloride involves only one step i.e. stirring the aliphatic nitrocompound with $TiCl_3$[3]. But unfortunately just stirring failed to give the required ketone in our hands. So the nitrocompound (42) was converted to its sodiumsalt by sodium methoxide and then stirred with four equivalents of 15% aqueous $TiCl_3$ at room temperature for 5 hrs. After usual work up the ketone, 2,6,10,14-tetramethyl-

pentadec-2-ene-7-one (43) was obtained in 80% yield. It was purified by column chromatography followed by vacuum distillation, b.p. 150-152° (bath)/1 mm. The IR spectrum showed absence of $-NO_2$ peak and the $>C=O$ was seen at 1720 cm^{-1} Fig 1.6. The PMR showed the methyl on the carbon α to carbonyl separately from other methyl at 1.05. PMR (CCl_4) δ: 0.89 (d, 9H, 3 CH_3-CH-, J= 6 Hz). 1.05 (d, 3H, CH_3-CH-, J= 6 Hz), 1.56, 1.65 two singlets for methyls on double bond, and the olefinic proton showed at 5.00 as a broad triplet. Fig 1.7 The mass spectrum showed the molecular ion peak correctly at 280. The other main peaks were 198, 169 and 126. These can be explained as follows. Cleavage of the more substituted bond adjacent to the carbonyl explained the peak at 169.



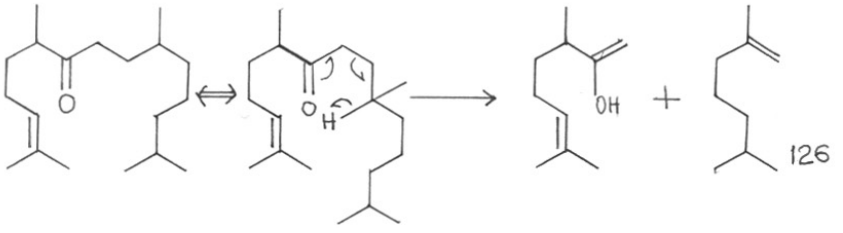
169

McLafferty rearrangement of γ-hydrogen on both sides of the carbonyl explained the other main peaks i.e. 198 and 126. These are shown below.



198

and



The mass spectral fragmentation data is in good agreement with the structure of the ketone.

The ketone (43) was identical in all respects with the ketone obtained earlier in our laboratory using TosMIC[18].

EXPERIMENTAL

Tosylate of citronellol (3,7-dimethyloct-6-en-1-ol).

General procedure:

To a ice-cold mixture of citronellol (15) (15.6 g) and pyridine, freshly crystallized p-toluenesulfonylchloride (30.0 g) was added with stirring and allowed to stand overnight. The reaction mixture was poured in water and extracted with ether (3 x 100 ml). The ether layer was washed thoroughly with water, 10% HCl and then aqueous copper sulfate to remove last traces for pyridine, dried and solvent evaporated to give a colourless liquid which was pure according to its TLC. Yield: 21.8 g (74%). IR (liquid film): 1350 and 1175 cm^{-1} (SO_2), PMR (CCl_4)δ: 0.89 (d, 3H, $\underline{CH}_3$-$\underline{C}$H, J=6 Hz), 1.63, 1.73 (2s, 6H, $\underline{CH}_3$—C(=)—$\underline{CH}_3$), 2.4 (s, 3H, Ar-$\underline{CH}_3$), 4.16 (t, 2H, -$\underline{CH}_2$-OTos, J=7 Hz), 5.2 (t, 1H, >=$\underline{CH}$-R), 7.6 and 8.3 (2d, 4H, Ar-H, J=8 Hz).

Citronellyl iodide (16)

A mixture of citronellyltosylate (10 g), sodium iodide (12 g) and acetonitrile 60 ml was refluxed for 3 hrs. The solvent was removed as much as possible and then poured in water and extracted with ether (3 x 50 ml). The ether layer was washed with 10% aqueous sodium thiosulfate, water and dried. Evaporation of solvent gave the iodide (8.1 g) in 90% yield. b.p.100-102°/5 mm (lit.[18] b.p. 116-118°/10 mm). PMR (CCl_4) δ: 0.90 (d, 3H, $\underline{CH}_3$-$\underline{C}$H-, J=6 Hz), 1.6, 1.6 (2s,

6H, $C\underline{H}_3-\!\!<\!\!^{C\underline{H}_3}$), 3.2 (t, 2H, -$C\underline{H}_2$-I, J=7 Hz), 5.00 (bt, 1H, olefinic proton).

3,7-dimethyl-1-nitrooct-6-ene (17)

General procedure[19]:

Citronellyliodide (16, 10.8 g) was added to a stirred solution of 50 ml of DMSO and 5.0 g of sodiumnitrite at room temperature. The reaction mixture was stirred for 4 hrs. It was then poured in 300 ml ice water and extracted with ether (3 x 50 ml). The ether layer was washed with water and dried. The solvet was removed and the residue was chromatographed on silica gel to get pure (17) in (3.9 g) 52% yield, b.p. 70-72°/2 mm. IR (liquid film): 1555 cm^{-1} (-NO_2). Mass: M^+ 185. m/e 168, 137, 123 and 109. PMR (CCl_4) δ: 0.96 (d, 3H, $C\underline{H}_3$-$\underset{'}{C}$H-, J=5 Hz), 1.6, 1.66 (2s, 6H, $C\underline{H}_3\!>\!C\!<\!C\underline{H}_3$), 4.3 (t, 2H, -$C\underline{H}_2$-$NO_2$, J=7 Hz), 5.00 (bt, 1H, olefinic proton). Fig 1.1

Analysis: Calculated: C, 64.8; H, 10.27; N, 7.56;

Found: C, 64.59; H, 10.03; N, 7.21%.

6-Methylheptan-2-one (20)

6-Methylhept-5-en-2-one (19, 21 g) was hydrogenated in ethanol using Pd/C 10% under 3 atmospheric pressure in a Parr hydrogenation apparatus. The reaction was continued for 2 hrs after hydrogen absorption ceased. The catalyst was filtered and ethanol distilled off and the residue distilled b.p. 78-80°/20 mm (lit. 34-35°/2 mm), yield 18.5 g (90%). IR (liquid film): 1720 cm^{-1} (>C=O). PMR (CCl_4) δ: 0.88 (d, 6H, $C\underline{H}_3$-$\underset{'}{C}$H-, J=6 Hz), 2.03, (s, 3H, -$\overset{O}{\overset{\|}{C}}$-$C\underline{H}_3$), 2.3 (m, 2H,

$-CH_2-CO-$), M^+ 128.

2,6-Dimethylheptanal (23)

To a stirred ice cold mixture of methylheptanone (25 g) and methylchloroacetate (21.0 g), $^tBuO^-K^+$ in ^tBuOH (7.8 g in 100 ml) was added dropwise and then stirred for 15 hrs. ^{t}Butanol was removed by distillation and poured in water and extracted with ether (3 x 100 ml), washed with water, dried, and removal of solvent gave epoxyester (21), 35 g . The epoxyester was hydrolysed by aqueous alcoholic potassium hydroxide, this gave the epoxy acid (22). The epoxy acid was pyrolysed to get the C_9 aldehyde in overall yields of 20%. 5.54 g,b.p. 80°-90°/30 mm, m.p. of 2,4-DNP derivative 95°C, m.p. semicarbazone derivative 166°C. IR (liquid film): 1723, 2700 (w), cm^{-1} (aldehyde). PMR (CCl_4) δ: 0.90 (d, 6H, 2 CH_3-CH-, J=6 Hz), 1.05 (d, 3H, CH_3-CH-, J=6 Hz), 2.1 (m, -CH-CHO, 1H), 9.53 (s, 1H, -CHO).

1-Nitro-4,8-dimethyl-2-hydroxy non-7-ene (26)

To a stirred mixture of citronellal (25, 15.4 g) and nitromethane (6.1 g) in 50 ml ethanol, 20 ml of 10% aqueous NaOH was added dropwise at 0°C. The reaction mixture was stirred for 4 hrs, when citronellal spot vanished from TLC (solvent,benzene). Ethanol was removed, poured in water, acidified by acetic acid and extracted with ether (3 x 50 ml). The organic layer was washed with water and dried. 20 g of nitroalcohol (26) was obtained. Yield 93%,

IR (liquid film): 3400 (-OH), 1545 ($-NO_2$) cm^{-1} PMR (CCl_4) δ: 0.95 (d, 3H, $\underline{CH_3}$-CH-, J=5 Hz), 1.6, 1.66 (2s, 6H, methyls on double bond), 3.7 (m, 1H, -O$\underline{H}$, exchangeable with D_2O), 4.3 (bs, 2H, -$\underline{CH_2}$-NO_2), 5.0 (bt, olefinic proton).

1-nitro-4,8-dimethyl-2-acetoxynon-7-ene

The nitroalcohol (26, 20 g) was stirred with acetic anhydride (15 ml) and conc. H_2SO_4 (4 drops) for 3 hrs at 5°C. The reaction was monitored by TLC. The reaction mixture was poured in water and extracted with ether (3 x 75 ml). The ether layer was washed with water and saturated $NaHCO_3$ solution and water again. Dried and solvent evaporated to get the nitroacetate (27) in 87.6% yield, 20.95 g. The nitroacetate obtained was used in the next reaction without further purification.

1-nitro-4,8-dimethyl non-7-ene

The nitroacetate (27, 20.0 g) was taken in 150 ml DMSO and to it 2 g of $NaBH_4$ was added in portions over a period of half hour. It was stirred till the nitroacetate vanished (TLC) (4 hrs). The reaction mixture was poured in water (600 ml) and extracted with pet.ether (3 x 100 ml), washed with water and dried. Evaporation gave crude nitroalkane (28) which was distilled under reduced pressure b.p. 100°-02°/1 mm, 11.79 g, 76% yield, M^+ 199. IR (liquid film): 1550 cm^{-1} ($-NO_2$). PMR (CCl_4) δ: 0.91 (d, 3H, $\underline{CH_3}$-CH-, J=5 Hz), 1.6, 1.66 (2s, 6H, methyls on double bond), 4.3 (t, 2H, -$\underline{CH_2}$-NO_2, J=7 Hz),

5.03 (bt, 1H, olefinic proton).

Analysis: Calculated: C, 66.3; H, 10.55; N, 7.03.

Found: C, 66.1; H, 10.55; N, 6.99 %.

1-Nitro-2,6-dimethylhepta-2,5-diene (31)

Methyl heptenone 19 (80.0 g), nitromethane (20.0 g) and catalytic amount of piperidene (1 ml) was taken in dry benzene in a 250 ml R.B. flask equipped with a Dean Stark water separator. The reaction mixture was refluxed for 8 hrs when 3 ml water separated. The benzene layer was washed with water (3 x 50 ml), dried on anhydrous Na_2SO_4 and then benzene was evaporated. The crude product was distilled under vacuum to remove unreacted methylheptenone (50 g) and the residue was chromatographed on silica gel to get pure (31), 18.0 g, 55% yield. The product also contained some conjugated nitrocompound (32) (~8%), b.p. 108°C/10 mm. GC (ov 101, temp. 150°) showed two major peaks for E&Z isomers of II in 65:25 ratio. M^+ 169. IR (liquid film): 1560 cm^{-1} ($-NO_2$). NMR (CCl_4) δ: 1.6, 1.7, 1.76 (3s, 9H, $\rangle C\underline{H}_3$), 2.73 (bt, 2H, $^4\underline{CH}_2$, J=7 Hz), 4.66, 4.83 (2s, 2H, $^1\underline{CH}_2$ due to E & Z), 5.0 (t, 1H, $\rangle{=}{}^{5}\underline{H}$, J=6 Hz), 5.5 (t, 1H, $\rangle{=}{}^{3}\underline{H}$ J=7 Hz), 2.2 (m, 6.8 olefinic proton) for compound III. Fig 1.2

1-Nitro-2,6-dimethyl hept-5-ene (33). Compound (31 & 32) 15.0 g in DMSO 50 ml and stirred with 0.75 mole ratio of $NaBH_4$ 1.3 g for 8 hrs. It was then poured in water acidified by dil. HCl and extracted with ether (3 x 100 ml).

Ether layer was washed with saturated $NaHCO_3$ and water dried and concentrated to give (33) in 85% yield, 13.0 g. (33) was further purified by column chromatography. GC (ov 101 temp. 150°) homogeneous. M^+ 171. b.p. 82°/5 mm. IR (liquid film): 1560 cm^{-1} NO_2. PMR (CCl_4) δ: 0.98 (d, 3H, $C\underline{H}_3$-$\underline{C}H$-, J=7 Hz) 1.6, 1.66 (2s, 6H, $\underline{C}H_3>=$), 4.09 (AB part of ABX pattern, J_{AB} = 12 Hz, $J_{AX}=J_{BX}=6$ Hz) $\underline{C}H_3$ 5.0 (bt, 1H, olefinic proton). Fig 1-3

Dihydrocitronellol (3,7-dimethyloctanol) (38)

Citronellol (15, 50 g)was dissolved in absolute alcohol (100 ml) and to this 0.500 g 10% Pd/C was added. This was hydrogenated using Parr hydrogenating apparatus at 3 atm.pressure. After absorption ceased it was filtered and solvent removed on rotary evaporator. The crude product was distilled, b.p. 87-90°/12 mm (lit. b.p. 83°/10 mm), yield, 85%. IR (liquid film): 3510 and 1013 cm^{-1} (primary -OH). NMR (CCl_4) δ: 0.96 (d, 9H, 3-$\underline{C}H$-$C\underline{H}_3$, J=6 Hz), 3.4 (bs, 1H, -CH_2-$O\underline{H}$, exchangeable with D_2O). 3.63 (t, 2H, -$C\underline{H}_2$-OH, J= 7 Hz).

Dihydrocitronellal (3,7-dimethyloctanal) (35)

3,7-Dimethyl octanol (38) 15.8 g was taken in 100 dry CH_2Cl_2 and to this 1.2 equivalents (25.8 g)of pyridinium-chlorochromate was added in small portions at 0°C stirring continued for 4 hrs after addition was complete. To this dry ether 100 ml was added and the reaction mixture filtered through celite. The filtrate was concentrated and distilled in vacuuo. b.p. 80-82°/10 mm (lit. 84-86°/12 mm). Yield, 75%, 12.1 g. IR (liquid film): 1724 (aldehyde $\rangle C=O$), 2820 (aldehyde $\overset{O}{\overset{\|}{C}}$-H).

NMR (CCl_4) δ: 0.94 (d, 9H, 3-CH-CH_3, J=6 Hz), 2.23 (m, 2H, -CH_2-CHO) and 9.76 (t, 1H, -CHO).

Bisulfite adduct of 3,7-dimethyloctanal (39)

The aldehyde 10.0 g was shaken vigorously with saturated aqueous solution of $NaHSO_3$ till a white solid separated. This was filtered and dried in vacuum desicator. m.p. decomposes at 350°C. Weight of adduct 7.23 g.

2,6,10,14-Tetramethyl-8-hydroxy-7-nitropentadec-2-ene (40)

Nitrocompound (33, 1.71 g) was added to a solution of sodium methoxide (0.230 g Na & 5 ml CH_3OH) and stirred for half hour. Methanol was evaporated and 10 ml DMSO added. The bisulfite adduct (39 2.44 g) was added and the reaction mixture stirred for 15 hrs under nitrogen. The reaction mixture was then poured in water, acidified and extracted with ether (3 x 50 ml). Ether layer dried and concentrated to give crude product with some starting materials. This was purified by column chromatography on silica gel. The nitro-alcohol (40) was obtained in 36% yield, 1.01 g. IR (liquid film): 3450 cm^{-1} (OH) and 1550 cm^{-1} ($-NO_2$). NMR (CCl_4) δ: 0.87 (d, 12H, 4CH_3-CH-, J=6 Hz), 1.6, 1.67 (2s, 6H, CH_3>=<CH_3) 4.13 (m, 2H, -CH-OH, -CH-NO_2), 5.06 (bt, 1H, olefinic proton).

Acetylation of 40 by Ac_2O/H^+

The nitroalcohol (40) 1.00 g was stirred with 3 ml of acetic anhydride and to it a conc. H_2SO_4 (1 drop) was added

and stirring continued for 4 hrs. The reaction mixture was poured in water and extracted with ether (3 x 50 ml). The organic layer was washed with saturated $NaHCO_3$ and water, dried and solvent removed to give the nitroacetate (41). This was used as such for the next step without purifying. Yield 1.053 g, 94%.

2,6,10,14-Tetramethyl-7-nitropentadec-2-ene (42)

The nitroacetate (41) obtained in earlier step 1.0 g was taken in DMSO 5 ml and to it $NaBH_4$ 0.1 g was added and stirred for 6 hrs. The reaction mixture was poured in ice-cold water and acidified by dilute HCl and extracted by ether (3 x 50 ml), washed with saturated $NaHCO_3$, water, dried and solvent evaporated to give the nitrocompound (42). The compound was purified by column chromatography on silica gel (1:10 ratio). The column was eluted by pet.ether exhaustively gave 0.547 g of (42), 65% yield. M^+ 311. IR (liquid film): 1556 cm^{-1} $-NO_2$. Fig 1.4 PMR(CCl_4) δ: 0.80 (d, 12H, 4 CH_3-CH-, J=7 Hz), 1.52, 1.58 (2s, 6H, CH_3 CH_3), 4.18 (m, 1H, $-CH-NO_2$), 5.00 (bt, 1H, olefinic proton). Fig 1.5

Analysis: Calculated: C, 73.3; H, 11.9; N, 4.57.

Found: C, 73.0; H, 11.5; N, 4.4%.

2,6,10,14-Tetramethylpentadec-2-ene-7-one (43)

The nitrocompound (42, 0.150 g) was dissolved in $NaOCH_3$ solution in CH_3OH. MeOH was evaporated, to it DME 5 ml was

added and then 4 equivalents (2 ml) of 15% aq. $TiCl_3$ was added and stirred for 5 hrs and then poured in ether. The aqueous layer was separated and again extracted with ether, the ether layers were mixed, washed with aq. $NaHCO_3$ and NaCl solution, dried and ether evaporated to give the ketone (43) with a trace of starting material. The ketone was purified by column chromatography on silica gel, and then distilled in vacuuo, b.p. 150°/1 mm. Yield, 0.100 g, 80%. m/z 280, 198, 169, 126. IR (liquid film): 1720 cm^{-1} (>C=O). Fig 1.6 PMR (CCl_4) δ: 0.89 (d, 9H, 3 $C\underline{H}_3$-CH-, J=7 Hz), 1.05 (d, 3H, $C\underline{H}_3$-CH-, J=7 Hz) 1.56, 1.65 (2s, 6H, $\underline{CH}_3$>C=, $\underline{CH}_3$), 5.00 (bt, 1H, olefinic proton). Fig 1.7

Analysis: Calculated: C, 81.4; H, 12.8;

Found: C, 81.3; H, 12.5%

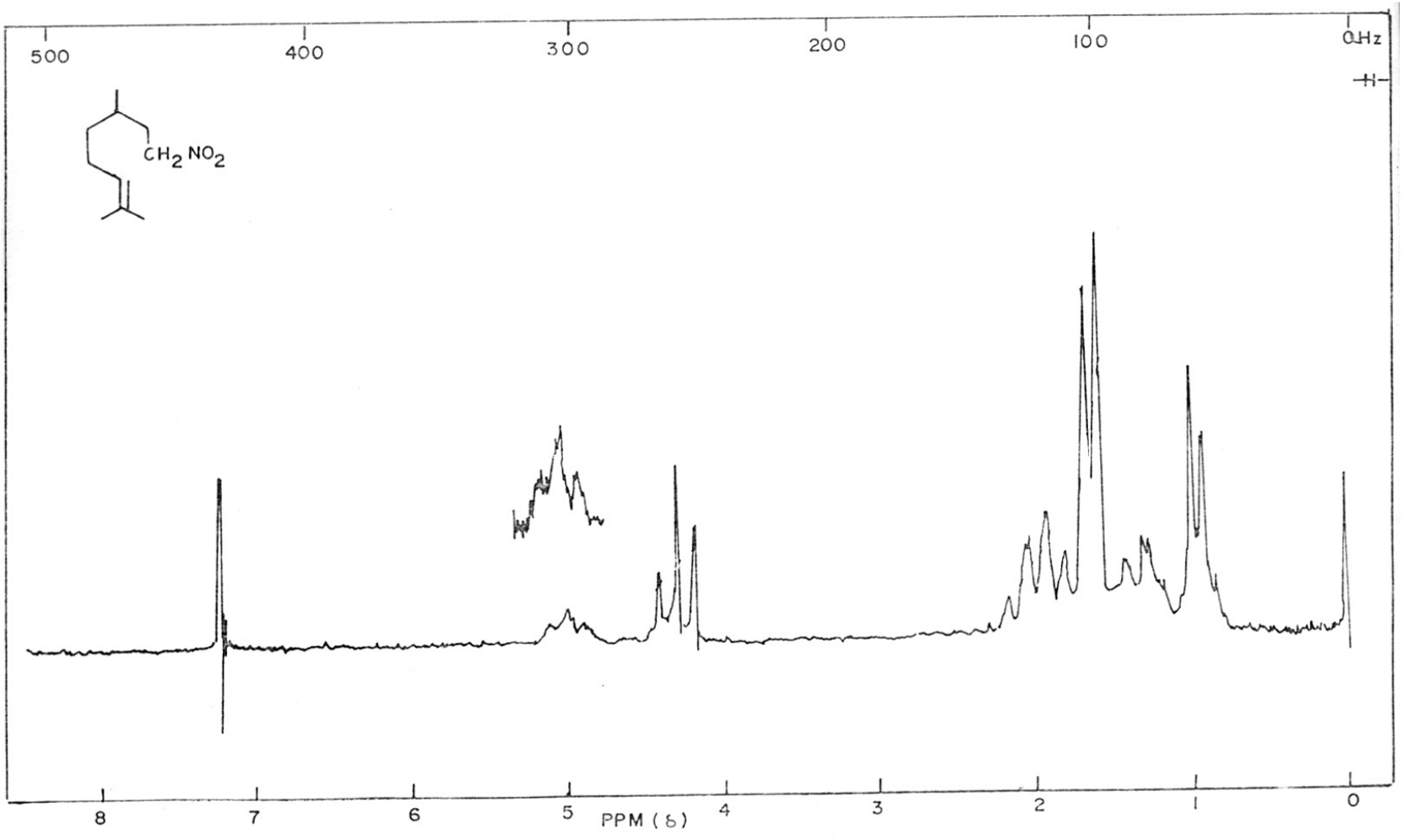


FIG 1.1 NMR SPECTRUM OF 1-NITRO-3,7-DIMETHYLOCT-6-ENE(17)

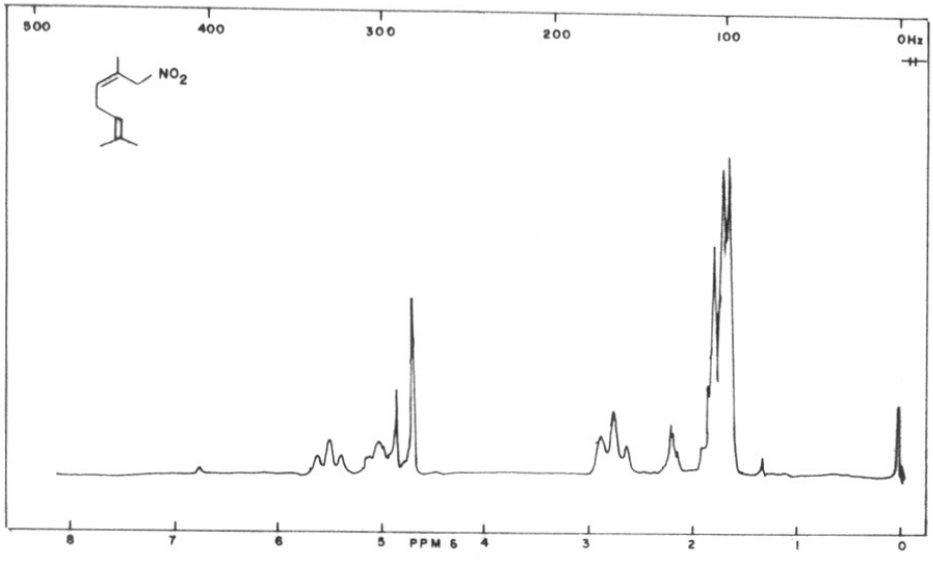


FIG 1·2 NMR SPECTRUM OF 1-NITRO-2,6-DIMETHYL HEPTA-2,5-DIENE (31)

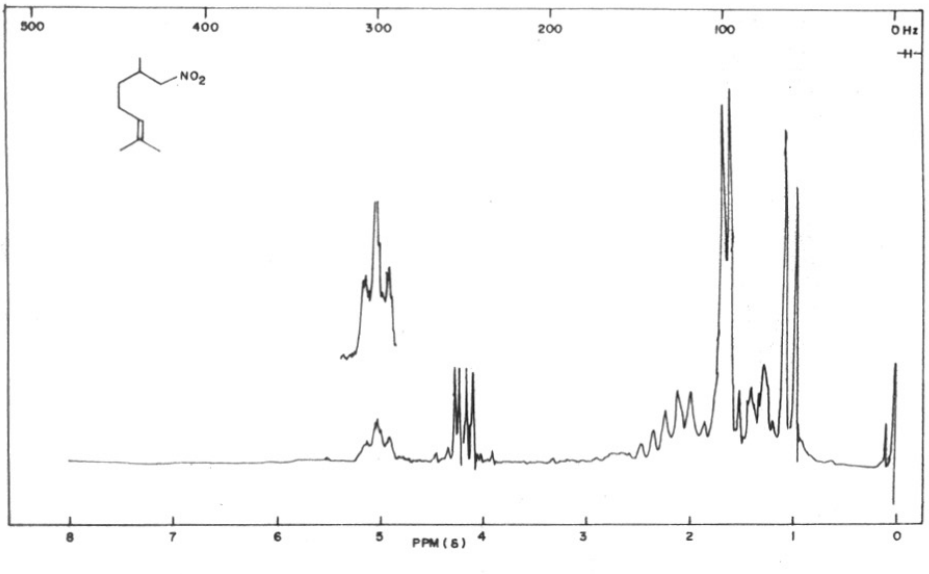


FIG. 1.3 NMR SPECTRUM OF 1-NITRO-2,6-DIMETHYL HEPT-5-ENE (33)

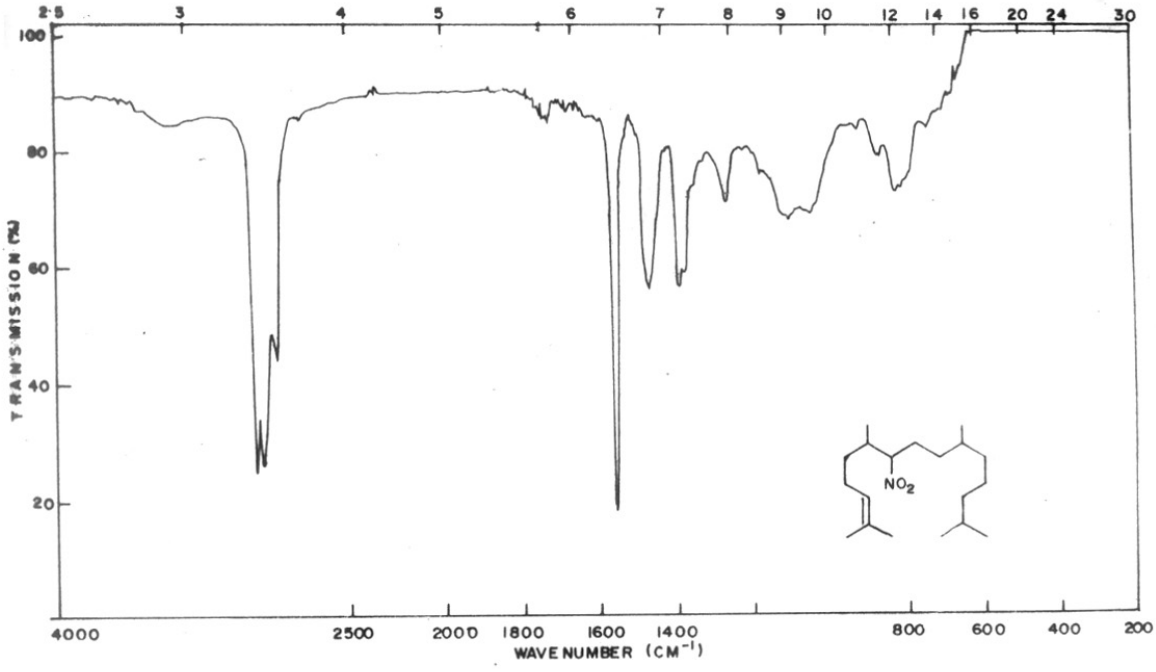


FIG 1.4 IR SPECTRUM OF 7-NITRO-2,6,10,14-TETRA METHYL PENTADEC-2-ENE(42)

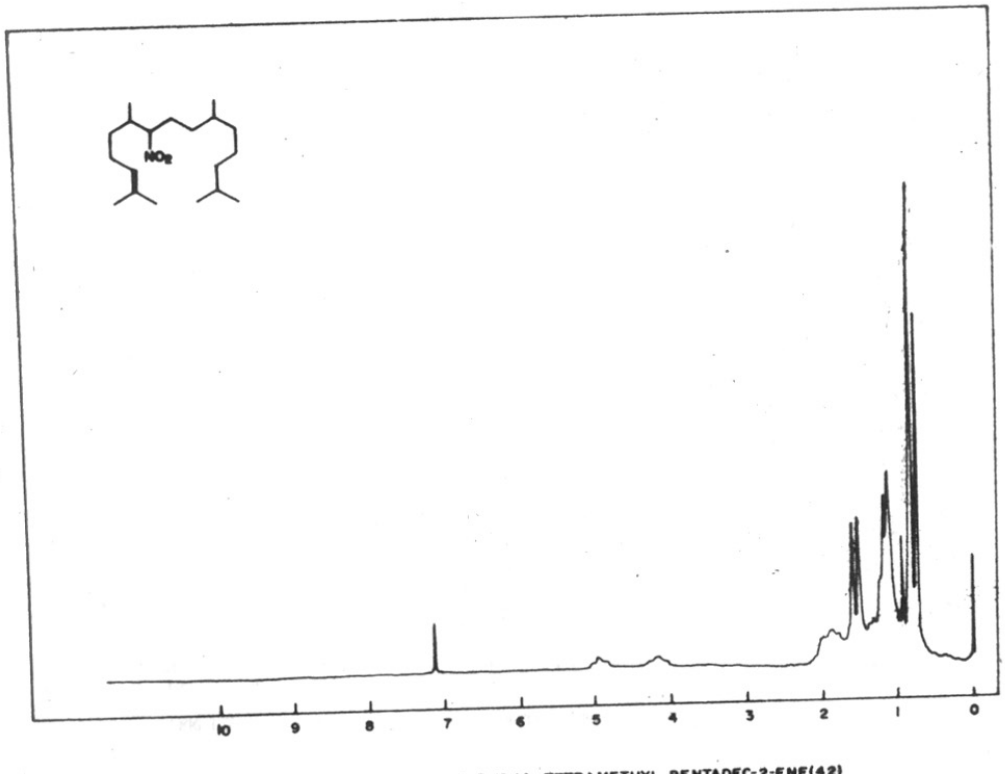


FIG 1.5 NMR SPECTRUM OF 7-NITRO-2,6,10,14-TETRAMETHYL PENTADEC-2-ENE(42)

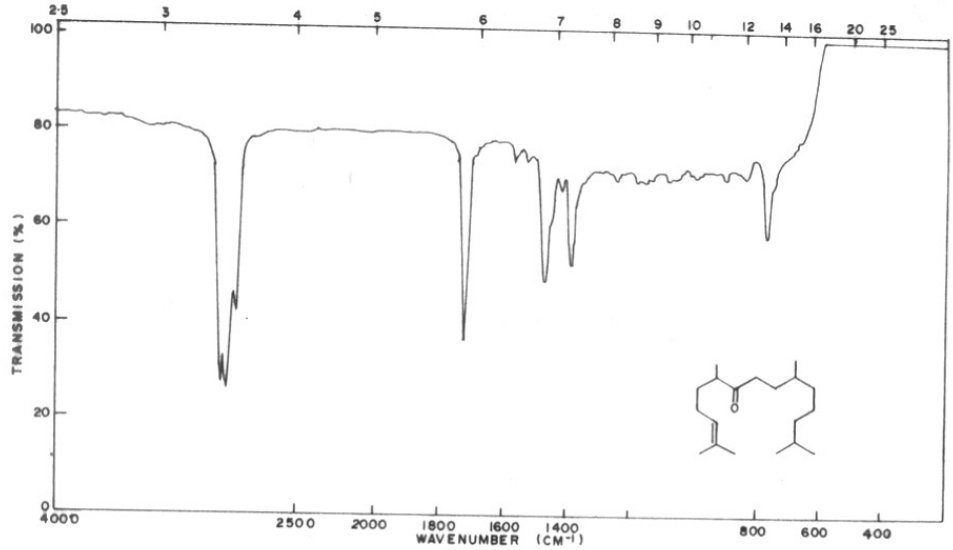


FIG 1·6 IR SPECTRUM OF 2,6,10,14 -TETRAMETHYL-7-OXO PENTADEC-2-ENE(43)

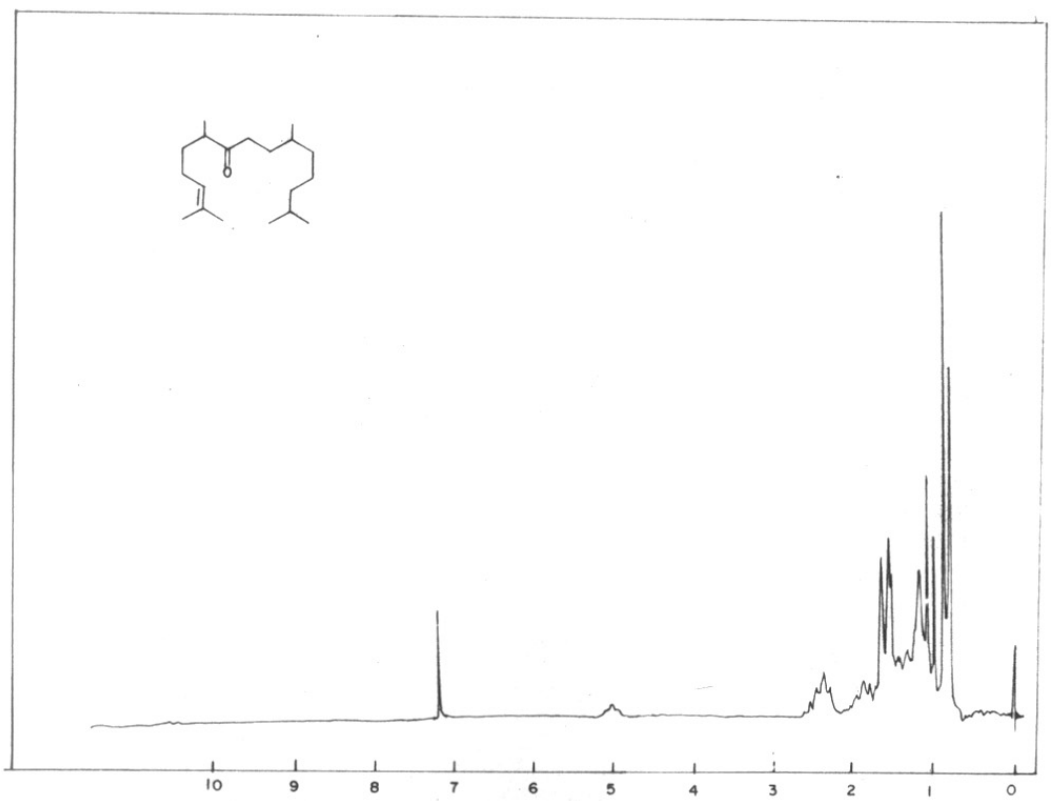


FIG 1·7 NMR SPECTRUM OF 2,6,10, 14-TETRAMETHYL -7-OXO PENTADEC-2-ENE(43)

CHAPTER - I

PART B

SYNTHESIS OF 2,6,10,14-TERTRAMETHYL PENTADEC 2-ENE-8-ONE BY MICHAEL ADDITION TO NITROOLEFINS

SUMMARY

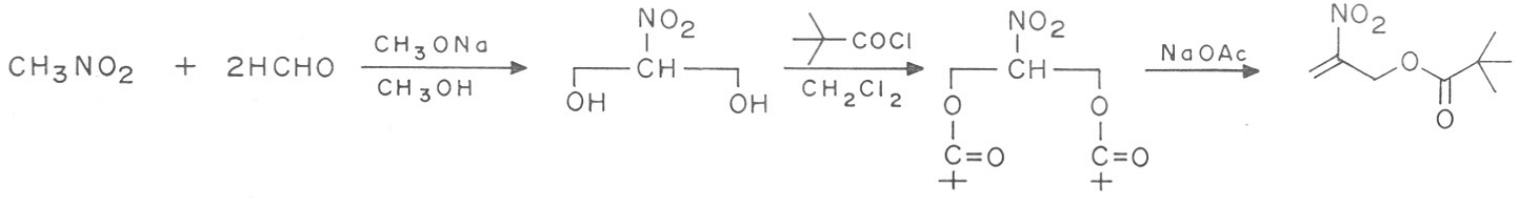
The synthesis of 2,6,10,14-tetramethyl-8-oxopentadec-2-ene from the corresponding nitro compound, 2,6,10,14-tetramethyl-8-nitropentadec-2-ene, which was obtained by conjugate addition of methylheptenylbromide to 4,8-dimethyl-1-nitro-non-1-ene using ultrasound technique.

PRESENT INVESTIGATION

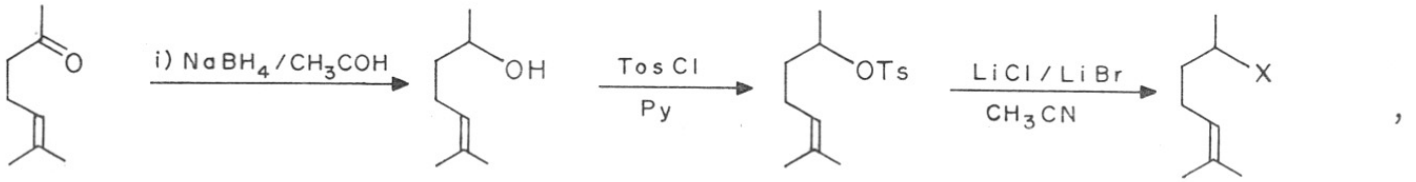
This part describes the synthesis of 2,6,10,14-tetramethylpentadec-2-ene (44) which is obtained from 2,6,10,14-tetramethyl-8-oxopentadec-2-ene (59). In Part A synthesis of 2,6,10,14-tetramethyl-7-oxopentadec-2-ene was described via the hydroxylalkylation of the nitrocompound, 2,6-dimethyl-1-nitrohept-5-ene. In this part (53) is synthesised via conjugate addition of alkyl lithiums to the nitroolefin.

First an attempt was made to synthesize (53) using methylheptanyl and methylheptenyl chlorides (preparation discussed ahead) (C_8-units), lithium metal and a multiple coupling reagent 2'-nitro-2'-propen-1'-yl 2,2-dimethylpropanoate (45)[31] [$C_8 + C_3 + C_8$ strategy] (Scheme 1). However, the addition of the chlorides (49) (51) to the multiple coupling reagent (45) could not be achieved according to literature procedure[31]. As the coupling of methylheptanyl chloride (51) with (45), which would have led to 4,8-dimethyl-1-nitronon-1-ene (52), could not be achieved, the same was prepared by another route involving a C_{10} nitrocompound (56) and formaldehyde (Scheme 2).

The C_{10} nitrocompound was prepared from dihydrocitronellol (54) as follows. Dihydrocitronellol (54) was refluxed with 48% HBr and conc. H_2SO_4 to give dihydrocitronellylbromide (55) in 85% yield. PMR (CCl_4) δ: 0.88 (d, 9H, $C\underline{H}_3$-$\dot{C}$H-, J=6 Hz), 3.36



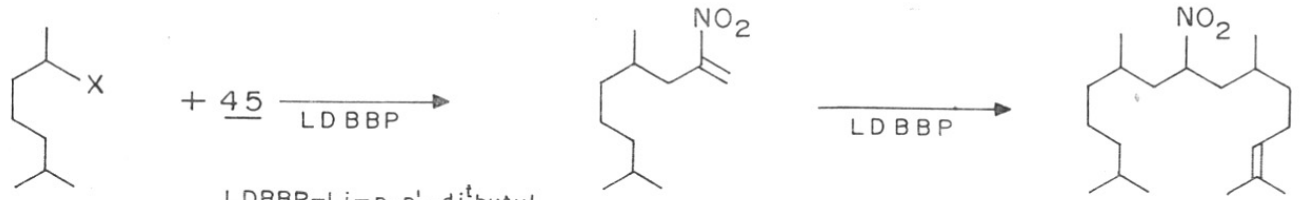
45



46 47 48

49 ; X = Cl

50 ; X = Br



LDBBP–Li–p-p'- di^{t}butyl biphenylide

51 ; X = Cl 52 53

SCHEME – 1

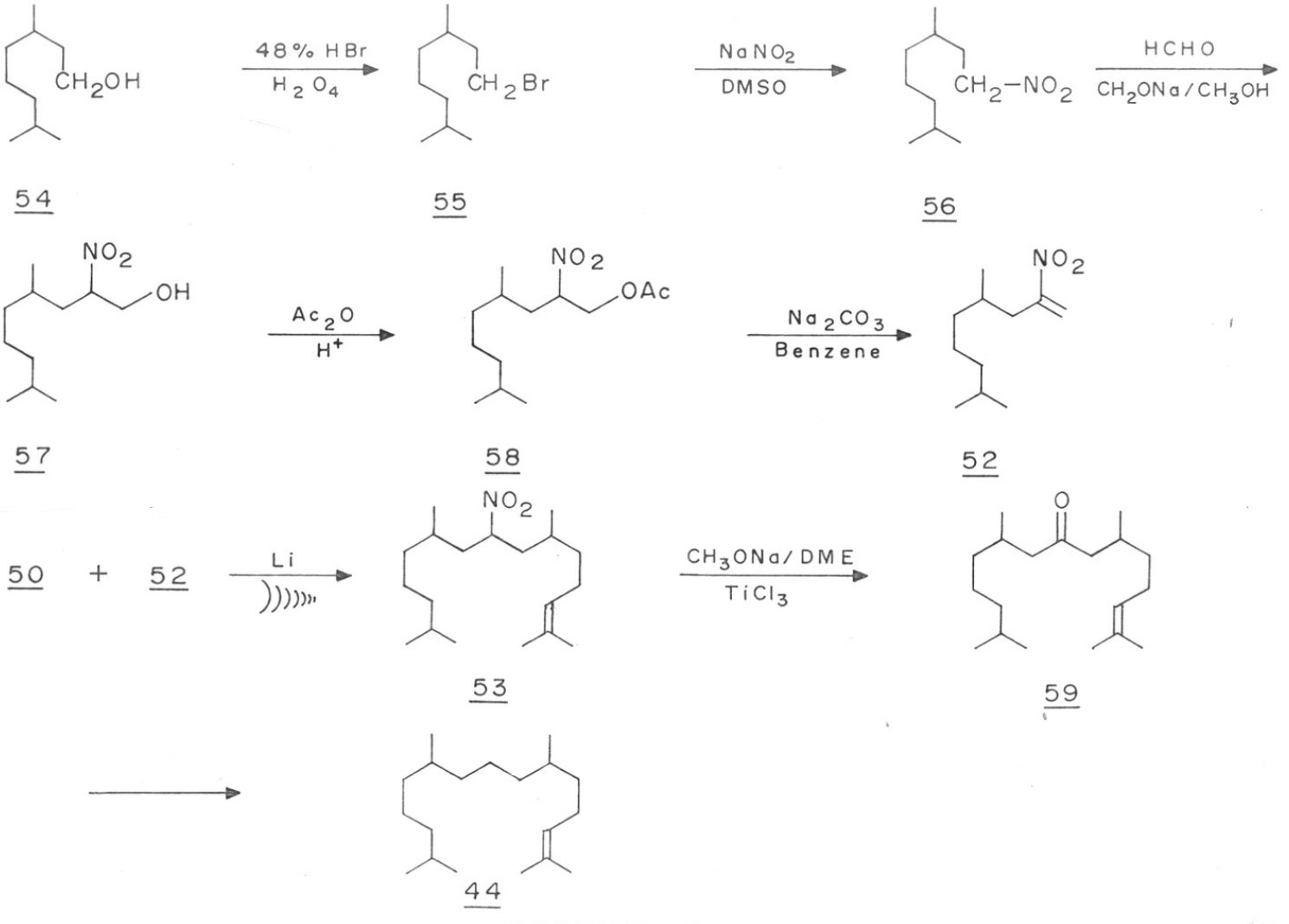
(t, 2H, -$C\underline{H}_2$Br, J=7 Hz). The bromide (55) was converted to the nitrocompound 3,7-dimethyl-1-nitrooctane (56) as described earlier (Part A) in 66% yield, b.p. 100-102°/15 mm. M^+- 187. IR (liquid film) showed band at 1550 (-NO_2) cm^{-1}. PMR(CCl_4) δ: 0.88 (d, 9H, 3 $C\underline{H}_3$-$\dot{C}$H-, J=6 Hz), 4.33 (t, 2H, -$\dot{C}\underline{H}_2$-NO_2, J=7 Hz). Analysed for $C_{10}H_{21}NO_2$.

The nitrocompound (56) was treated with equimolar quantities of paraformaldehyde in methanol using sodium methoxide as base. After work up the reaction mixture showed two spots (TLC solvent: Benzene). These were separated by column chromatography on silica gel. Elution by PE + 10% benzene gave the less polar spot and benzene elution gave the more polar spot which was the nitroalcohol (57) according to the IR and PMR spectrum. IR (liquid film): 3420 (-OH), 1560 (-NO_2) cm^{-1}. PMR (CCl_4) δ: 0.9 (d, 9H, $C\underline{H}_3$-$\dot{C}$H-, J=6 Hz), 3.83 (m, 3H, -$C\underline{H}_2$-$O\underline{H}$, partially exchanges with D_2O), 4.76 (m, 1H, -$\dot{C}\underline{H}$-NO_2). The nitroalcohol was acetylated using acetic-anhydride and catalytic H_2SO_4 (conc.) to give the corresponding nitroacetate (58) which was refluxed with sodiumcarbonate in benzene[31] to furnish 4,8-dimethyl-2-nitro non-1-ene (52) in 71.4% yield. The less polar spot obtained in pet.ether + 10% benzene eluate was identical with this nitroolefin (52) according to its IR and PMR. The total yield of (52) obtained was 51.6% b.p. 93-96°/1 mm. IR (liquid film) showed band at 1540 (-NO_2) cm^{-1}. Fig 1.8 PMR (CCl_4)δ: 0.86 (d, 6H, 2 $C\underline{H}_3$-$\dot{C}$H-, J=6 Hz), 0.89 (d, 3H, $C\underline{H}_3$-$\dot{C}$H, J=6 Hz), 2.48 (2H, -$C\underline{H}_2$-$\dot{C}$=NO_2, AB part of ABX

system J_{AB} = 15 Hz, $J_{AX}=J_{BX}$ = 7 Hz), 5.4 (bs, 1H, olefinic proton trans to $-NO_2$), 6.3 (sharp d, 1H,olefinic proton cis to $-NO_2$). Fig 1.3 The olefin analysed for $C_{11}H_{21}NO_2$.

The C_8 unit used for addition to the nitroolefin was prepared from methylheptenone. Methylheptenone (46) was reduced by sodiumborohydride in methanol to get the alcohol (47) in about 90% yield. The tosylate (48) of this alcohol, which was prepared by p-toluenesulfonyl chloride and pyridine, was refluxed with lithium chloride in acetonitrile to get 2-chloro-6-methylhept-5-ene (49). Refluxing the tosylate with lithiumbromide in acetonitrile gave 2-bromo-6-methylhept-5-ene (50). Similarly 2-chloro-6-methylhept-2-ene (51) were prepared from methylheptanone. Experimental details for the 2-bromo-6-methylhept-2-ene is given in the experimental part.

Addition of reactive nucleophiles to nitroolefins have been performed at low temperature (-78°C) as reported in literature. So the Grignard reagent of methylheptenylbromide (50) was prepared in THF using dibromoethane as initiator and cooled to -78°C. The nitroolefin (52) in THF was added to the Grignared reagent at -78°C and stirred for 4 hrs at -78° and then allowed to come to room temperature[30]. After usual work up the nitroolefin was recovered and 2-methylhept-2-ene was obtained. Formation of 2-methyl-2-heptene indicated that the Grignard reagent of (50) was formed but it did not add to the nitroolefin.


CH2OH
48% HBr
H2O4
CH2Br
NaNO2
DMSO
CH2–NO2
HCHO
CH2ONa/CH3OH
54
55
56
NO2
OH
Ac2O
H+
NO2
OAc
Na2CO3
Benzene
NO2
57
58
52
50 + 52
Li
NO2
CH3ONa/DME
TiCl3
O
53
59
44

SCHEME – 2

Similarly alkyl lithium reagent was prepared from methyl heptenyl chloride according to literature procedure (p,p'-diter.butylbiphenyl and Li)[32] cooled to -78°C and the nitro olefin in THF was added dropwise at -78°C. The reaction mixture was warmed to -30°C and worked up by adding acetic acid in THF. Again the nitroolefin was recovered unchanged.

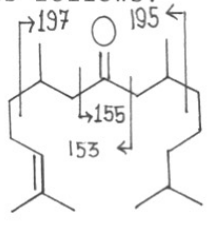
As the alkyl lithium did not add to the olefin at low temperature, it was decided to do the reaction at room temperature using sonication to accelerate the rate of reaction. Ultrasound is receiving increasing attention as it reduces the reaction time and also accelerates the reation. It is usually used in reactions involving metals like Zn, Mg, Li etc. Ultrasound has been used efficiently in Reformatsky[33], Grignard or reactions involving alkyl lithiums[34]. It is supposed that ultrasound energy keeps the metal surface free from the derived species (RLi, LiX or hydroxide) in such a way that it remains highly activated.

Equimolar quantities of nitroolefin (52, 0.160 g), alkyl halide (50, 0.170 g) and Li silvers (0.008 g) in THF were irradiated in a ultrasound laboratory cleaner(220 V,50 Hz). at room temperature till all the Li dissolved, about 45 minutes, under nitrogen atmosphere. The reaction mixture was poured in 10% NH_4Cl and extracted with ether. The product was purified by column chromatography on silica gel. The nitrocompound

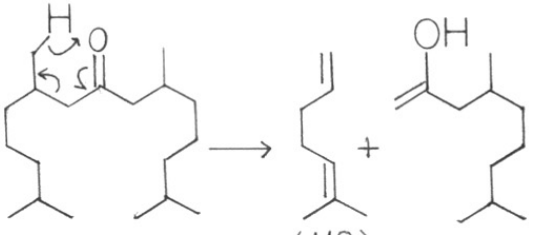
2,6,10,14-tetramethyl-8-nitropentadec-2-ene (53) was obtained in 40% yield. It was characterised by its IR, PMR and Mass. IR (liquid film) showed bands at 1555 ($-NO_2$) cm^{-1}. Fig 1.10 PMR ($CDCl_3$) δ: 0.86 (d, 12H, 4 CH_3-CH-, J=6 Hz), 1.6, 1.67 (2s, 6H, $=C(CH_3)_2$), 4.68 (m, 1H, $-CH-NO_2$), 5.04 (bt, 1H, olefinic proton). Fig 1.11 M^+ 311. b.p. 160-62°(bath)/2 mm analysed for $C_{19}H_{37}NO_2$. But repetition of reaction on a gram scale gave only 20% yield. Due to lack of time the reaction conditions were not standardized but reduction in temperature may increase the yield of the reaction.

The nitrocompound (53) was then converted to the ketone using $TiCl_3$[5] as described in Part A of this Chapter. The ketone, 2,6,10,14-tetramethyl-8-oxopentadec-2-ene (59) showed bands in IR (liquid film) at 1718 (>CO) cm^{-1}. Fig 1.12 PMR($CDCl_3$)δ: 0.84 (d, 12H, 4 CH_3-CH-, J=6 Hz), 1.56, 1.64 (2s, 6H, $=C(CH_3)_2$) 5.00 (bt, 1H, olefinic proton). Fig 1.13 b.p. 150-52° (bath)/2 mm (lit.148-50°/1 mm[20]). Yield 76%

M^+ 280 and fragments at 195,197, 155, 153 and 110. These can be explained as follows:



McLafferty rearrangement involving hydrogen gives a peak at 110.



(110)

The ketone (59) which can be elaborated to isophytol via 2,6,10,14-tetramethylpentadec-2-ene (44) is identical to the one obtained earlier in this laboratory through enamine[19] and meldrums acid[20] route.

EXPERIMENTAL

2'-Nitro-2'-propen-1'-yl-2,2-dimethylpropanoate (NPP) (45)

Sodium methoxide in methanol (8 g sodium in 150 ml methanol) was added to a mixture of nitromethane (21.0 g) and paraformaldehyde (20.0 g) in 100 ml methanol at 0°C with stirring. The temperature never exceeded above 6°C. The reaction mixture was allowed to come to room temperature and stirred for 12 hrs, the sodium salt was filtered and washed with methanol and dried in vacuuo. The weight of salt obtained was 64 g. Yield 94%.

50.0 g of sodium salt was stirred with salicylic acid 34 g in dry ether (250 ml) and refluxed for 1 hr, cooled and filtered to remove the sodiumsalicylate formed. Evaporation of ether gave 20.1 g of diol. Yield 68.8% m.p. 49-51°C (lit. 53°C). PMR (acetone-d_6) δ: 3.9 (d, 4H, $-O-\underline{CH_2}-\overset{NO_2}{\overset{|}{C}}H-\underline{CH_2}-O$, J= 6 Hz), 4.18 (s, 2H, 2-O$\underline{H}$), 4.7 (m, 1H, $-\underline{CH}-NO_2$).

The diol (15.0 g) was suspended in refluxing CH_2Cl_2 and to it 40 ml of pivaloyl chloride was added dropwise. The HCl evolution was monitored by a bubbler. Evolution of HCl stopped after 4.5 hrs, then the homogeneous mixture was cooled to room temperature. The solvent was removed on a rotary evaporator and excess pivaloyl chloride removed in vaccuo. The residue was taken in 75 ml CH_2Cl_2 and washed with 10% aq. KOH (3 x 25 ml). The organic layer was dried on Na_2SO_4 and solvent evaporated

and the residue distilled under vacuum to give 9.231 g of NPP. Yield 57%, b.p. 70-73°/1 mm (lit. 40-45°/0.01 mm). IR (liquid film): 1740 (-CO-O), 1530 ($-NO_2$) cm^{-1}. PMR (CCl_4) δ: 1.16 (s, 9H, $(C\underline{H}_3)_3C$-), 5.00 (s, 2H, $-C\underline{H}_2-C(NO_2)=$), 5.9 (bs, 1H, olefinic proton trans to NO_2, ), 6.6 (sharp d, 1H, olefinic proton cis to NO_2, ).

3,7-Dimethyloctylbromide (56)

Dihydrocitronellol (55, 15.6 g) was refluxed with 48% HBr 25 ml and 4 ml conc. H_2SO_4 till a layer of bromide separated, 3 hrs. The reaction mixture was poured in water, extracted with ether (3 x 100 ml), ether layer washed with 10% aq.$NaHCO_3$ and water. Evaporation of ether gave crude 3,7-dimethyloctylbromide (2). Chromatography on silica gel and elution with pet.ether gave pure bromide in 85% yield. 18.530 g. PMR (CCl_4) δ: 0.88 (d, 9H, 3 $C\underline{H}_3$-CH-, J=6 Hz), 3.36 (t, 2H, $-C\underline{H}_2$-Br, J=7 Hz).

1-Nitro-3,7-dimethyloctane (57)

Procedure same as used for 1-nitro-3,7-dimethyloct-6-ene (Part A).

Quantities:

bromide (56)	14.2 g
$NaNO_2$	6.0 g
DMSO	100 ml

Weight of nitrocompound .. 8.013 g. Yield 66%.

b.p. 100-103°/15 mm. M^+ 187.

IR (liquid film): 1550 ($-NO_2$) cm^{-1}.

PMR (CCl_4) δ: 0.88 (d, 9H, 3 $C\underline{H}_3$-CH-, J=6 Hz), 4.33 (t, 2H, $-CH_2-NO_2$, J=7 Hz).

Analysis: Calculated: C, 64.1; H, 11.23; N, 7.4.

Found: C, 63.8; H, 11.2; N, 7.2%.

2-Nitro-4,8-dimethylnon-1-ene (60)

1-Nitro-3,7-dimethyloctane (57, 9.00 g) and paraformaldehyde (1.6 g) were taken in 25 ml methanol and sodium methoxide (prepared for 1.15 g Na and 15 ml methanol) added dropwise with stirring at 0-5°C. The reaction mixture was stirred for 15 hrs poured in water, acidified with dil.HCl and extracted with ether (3 x 50 ml). The organic layer was washed with 10% aq. $NaHCO_3$ and water and dried on Na_2SO_4. Evaporation of solvent gave product containing a mixture of the nitroolefin (5, 0.938 g) and nitroalcohol (7.150 g). The nitroalcohol was separated by chromatography and acetylated by acetic anhydride and catalytic conc.H_2SO_4. The nitroacetate (7.281 g) was refluxed in benzene (25 ml) in presence of 4.0 g Na_2CO_3 for 24 hrs. The reaction mixture was poured in water and benzene layer separated, washed with water and dried on Na_2SO_4. Evaporation of benzene gave crude nitroolefin which was purified by column chromatography. Total nitroolefin (60) obtained was 4.938 g, 51.6% yield. IR (liquid film) 1540 cm^{-1} ($-NO_2$), b.p. 93-96°/1 mm. PMR (CCl_4) δ: 0.86 (d, 6H, 2 $(C\underline{H}_3)_2$-CH-, J=6 Hz), 0.89 (d, 3H, $C\underline{H}_3$-CH, J=6 Hz), 2.48 (2H, $-C\underline{H}_2-C(=NO_2)$, AB part of ABX system, J_{AB} = 15 Hz,

$J_{AX}=J_{BX}$ = 7 Hz), 5.4 (bs, 1H, olefinic proton trans to NO_2), 6.3 (sharp d, 1H, olefinic proton (cis to NO_2), M^+ 199.

Analysis: Calculated: C, 64.2; H, 11.2; N, 2.5.

Found: C, 63.9; H, 11.0; N, 7.46%.

6-Methyl-5-hepten-2-ol (47)

To a solution of (46, 16 g) in methanol (250 ml) at 0°C, sodiumborohydride (2.4 g) was added over a period of 30 minutes. The mixture was then stirred for 5 hrs at room temperature. The reaction mixture was poured in water and extracted with ether (3 x 50 ml). The organic layer was thoroughly washed with water and dried. The solvent removed and residue distilled. Yield 13.0 g (80%), b.p. 82-83°/10 mm (lit. b.p. 76-77°/8 mm). M^+ 128. IR (liquid film): 3350, 1110 (-CH-OH) cm^{-1}. PMR (CCl_4) δ: 1.2 (d, 3H, $C\underline{H}_3$-C(OH)H, J=6 Hz), 1.6, 1.73 (2s, 6H, $=C(CH_3)(C\underline{H}_3)$), 3.13 (m, 1H, -CH-O<u>H</u> exchangeable with D_2O), 3.73 (m, 1H, -C<u>H</u>-OH), 5.13 (bt, 1H, olefinic proton).

Tosylate (48)

Procedure as given in Part A.

Quantities:

Alcohol (7)	12.8 g
p-toluene sulfonyl chloride	30.0 g
Pyridine	100 ml

IR (liquid film): 1350, 1175 (SO_2) cm^{-1}. PMR (CCl_4) δ: 1.2 (d, 3H, $C\underline{H}_3$-CH-OTs, J=6 Hz), 1.56, 1.66 (2s, 6H, $=C(C\underline{H}_3)_2$), 2.45 (s, 3H, Ar-$C\underline{H}_3$), 4.57 (m, 1H, -C<u>H</u>-OTs), 5.03 (bt, 1H, olefinic

proton), 7.33, 7.8 (2d, 4H, J=8 Hz, aromatic protons).

2-Bromo-6-methylhept-5-ene (50)

A mixture of (8, 14.0 g), acetonitrile (80 ml) and lithiumbromide (5.5 g) was refluxed for 3 hrs. The bulk of the solvent was distilled off and the residue poured in water (100 ml), extracted with ether. The ether layer was washed with 10% aq.$Na_2S_2O_3$ solution (2 x 25 ml) and water and dried. The solvent removed and residue distilled. Yield 9.0 g (75%) b.p. 96-98°/10 mm. PMR (CCl_4) δ: 1.49 (d, 3H, $\underline{CH}_3$-$\underline{C}$H-Cl, J=7 Hz), 1.66, 1.7 (2s, 6H, $\begin{matrix}\underline{CH}_3\\ \underline{CH}_3\end{matrix}$), 3.95 (m, 1H, -$\underline{C}$H-Br), 5.00 (bt, 1H, olefinic proton).

2,6,10,14-tetramethyl-8-nitropentadec-2-ene (54)

Methylheptenylbromide (9, 0.170 g), nitroolefin (5, 0.160 g) in 2 ml THF. To this silvers of (0.008 g) lithium added. The reaction mixture under nitrogen atmosphere was irradiated in a ultrasound laboratory cleaner at room temperature till all lithium dissolved (45 minutes). The reaction mixture was poured in 20% NH_4Cl solution and extracted with ether (3 x 25 ml). Ether layer was washed with water and dried. Removal of solvent gave crude product which showed excess bromide and C_{19} (10) nitrocompound along with some more polar compound. (Solvent system: Pet.ether). C_{19} nitrocompound was isolated by chromatography on silica gel. Pet.ether eluate removed the excess bromide and C_{19} nitrocompound eluted in pet.ether + 15% benzene. Weight of C_{19} nitrocompound obtained

was 0.100 g 40%. Mass: M^+ 311, b.p. 160-62° (bath)/2 mm. IR (liquid film): 1555 ($-NO_2$) cm^{-1}. PMR (CCl_4) δ : 0.86 (d, 12H, 4 $\underline{CH_3}$-$\underline{C}$H-, J=6 Hz), 1.6, 1.67 (2s, 6H, $=C<^{\underline{CH_3}}_{\underline{CH_3}}$), 4.68 (m, 1H, -$\underline{C}$H-NO_2), 5.04 (bt, 1H, olefinic proton).

Analysis: Calculated: C, 73.3; H, 11.9; N, 4.5%

Found: C, 72.9; H, 11.8; N, 4.5%

2,6,10,14-Tetramethyl-8-oxopentadec-2-ene (61)

Sodium methoxide (from 0.010 g Na) in 1 ml methanol was added to the C_{19} nitrocompound - (10, 0.100 g) in 1 ml methanol. Methanol was removed after stirring for 0.5 hr. Dimethoxyethane 2 ml was added and then 15% aq. $TiCl_3$ (2 ml) was added and stirred for 4 hrs. The reaction mixture was extracted with ether (3 x 10 ml) washed with water and dried. Removal of solvent gave crude C_{19} ketone (11) which was purified by chromatography followed by distillation. Wt. of nitrocompound recovered 0.020 g. Yield: 0.055 g, 76%, b.p. 150-152° (bath)/2 mm. Homogeneous by VPC (column ov-101 temp. 180°). M^+ - 280. IR (liquid film): 1718 ($>C=O$) cm^{-1}. PMR ($CDCl_3$) δ: 0.84 (d, 12H, 4 $\underline{CH_3}$-$\underline{C}$H-, J=6 Hz), 1.56, 1.64 (2s, 6H, $=<^{\underline{CH_3}}_{\underline{CH_3}}$), 5.00 (bt, 1H, olefinic proton).

Analysis: Calculated: C, 81.36; H, 12.94.

Found: C, 81.53; H, 12.93%.

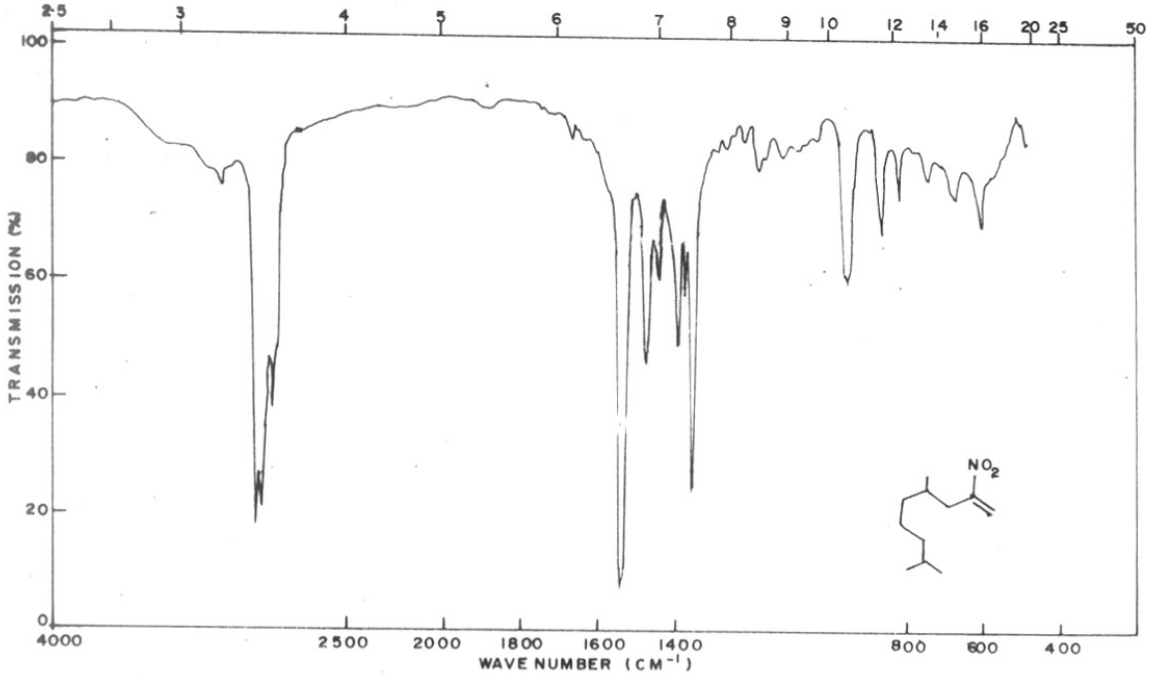


FIG 1.8, 2- NITRO - 4, 8 - DIMETHYLNON - 1 - ENE (52)

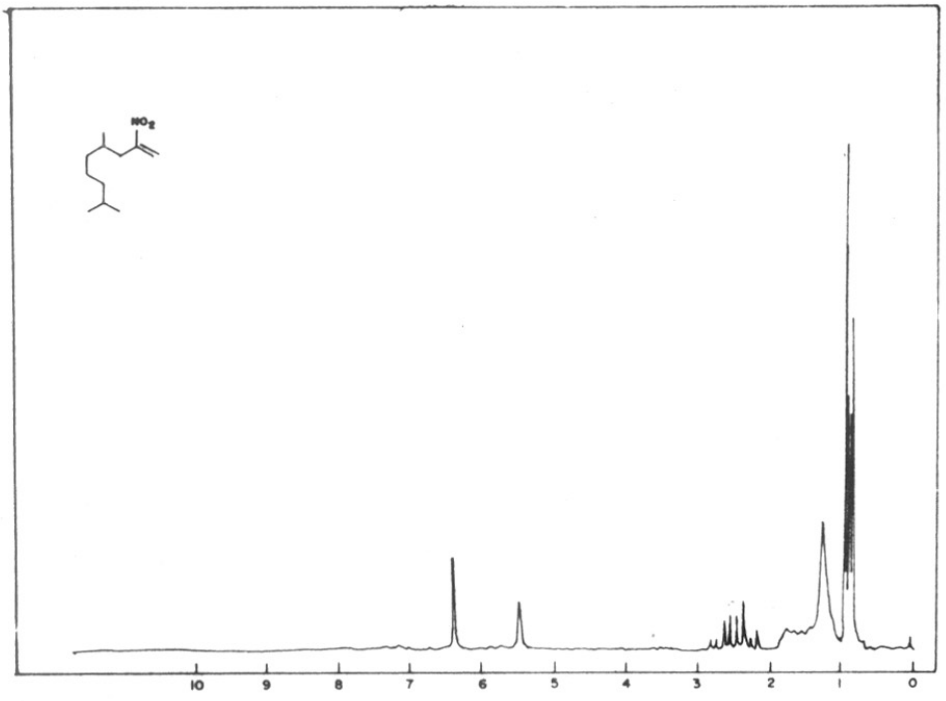


FIG 1·9, 2-NITRO - 4, 8 - DIMETHYLNON - 1 - ENE (52)

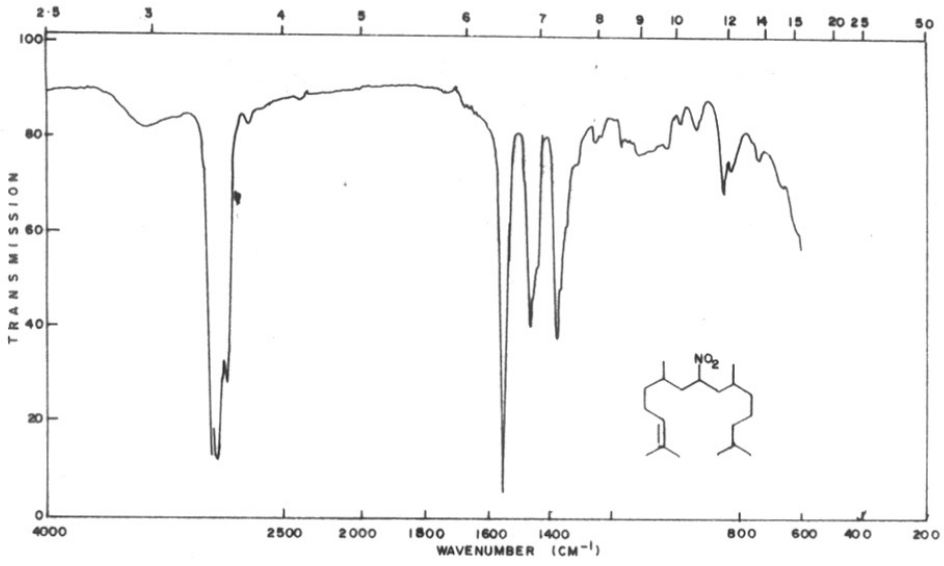


FIG I·10, 2, 6. 10, 14 – TETRAMETHYL-8—NITROPENTADEC-2-ENE (53)

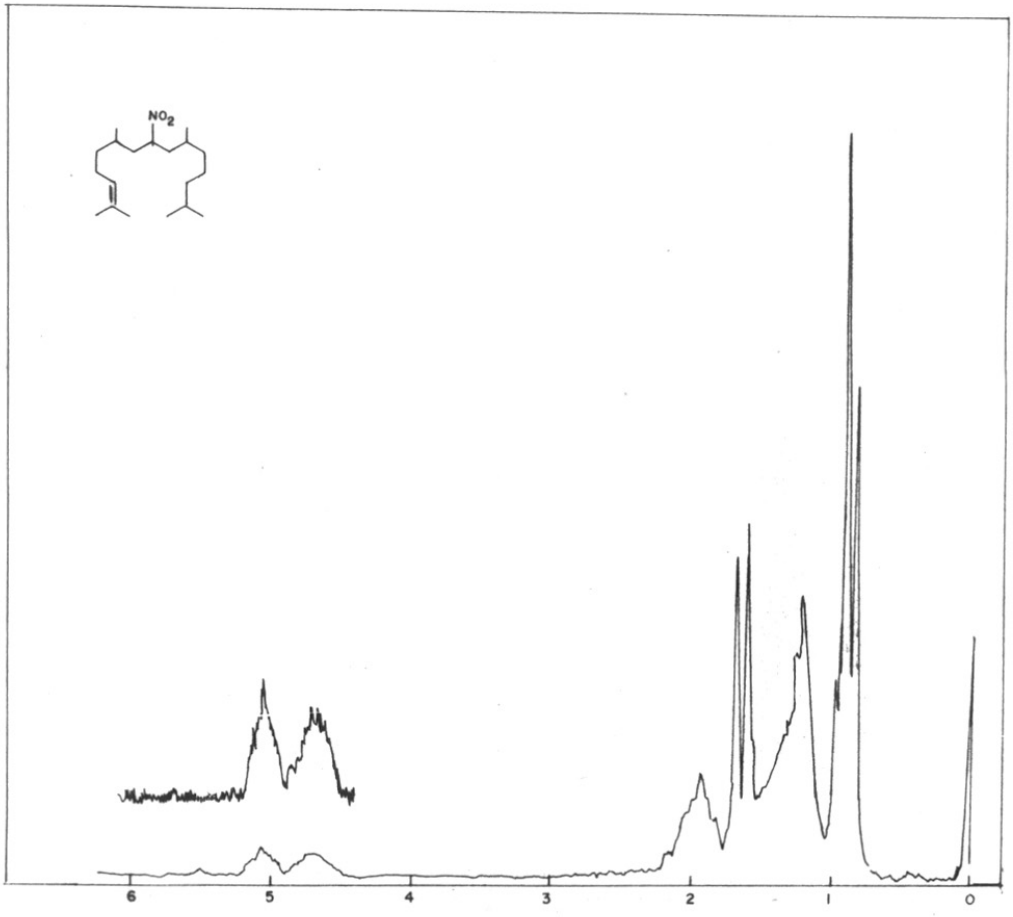


FIG I·11, 2,6,10,14 – TETRAMETHYL-8-NITROPENTADEC-2-ENE (53)

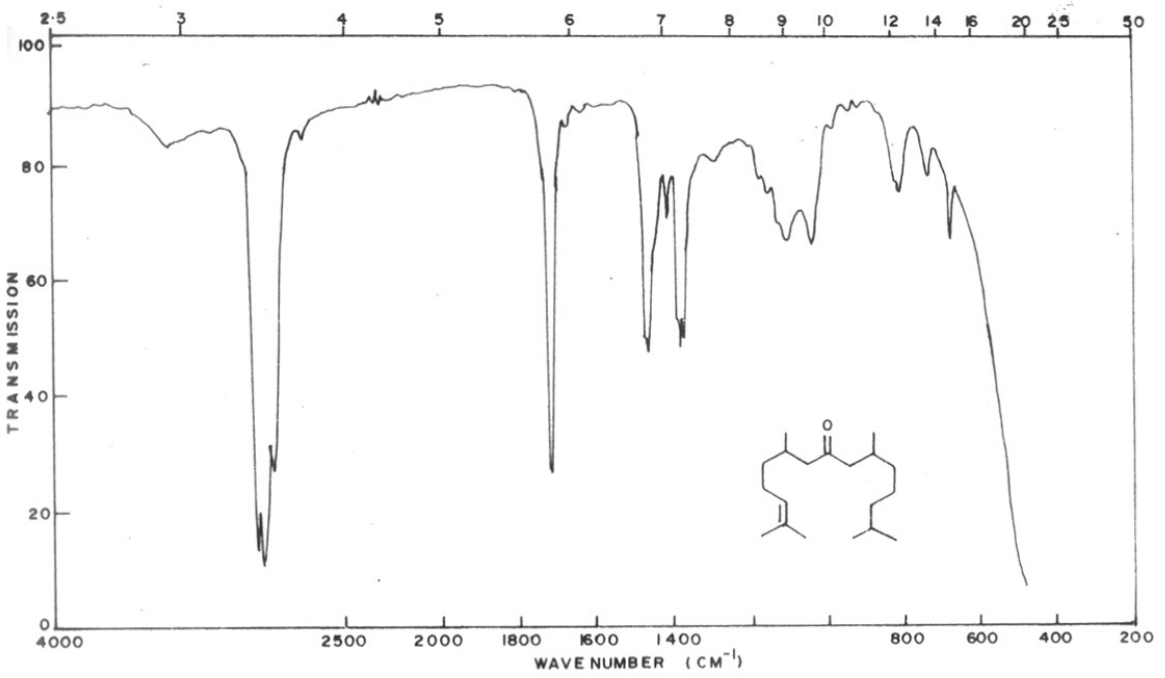


FIG 1·12 2,6,10,14-TETRAMETHYL-8-OXOPENTADEC-2-ENE (59)

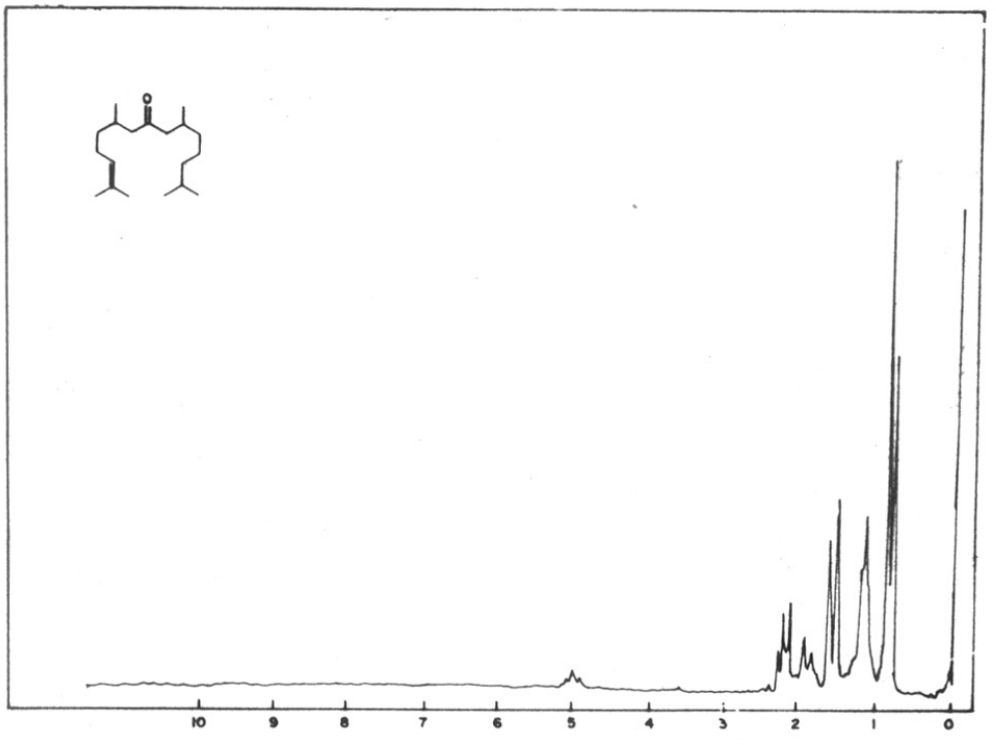


FIG 1·13, 2,6,10,14-TETRAMETHYL-8-OXOPENTADEC-2-ENE (59)

REFERENCES

1 E.W. Colvin and D. Seeboch
J.C.S.Chem. Commun. 689 (1978).

2 W.E. Noland
Chem. Rev., 55, 137 (1955).

3 J.E.McMurry and J. Melton
J. Am. Chem. Soc., 38, 4367 (1973).

4 R. Kirchhoff
Tetrahedron Lett., 2533 (1976).

5 J.E.McMurry, J. Melton and H. Padgett
J. Org. Chem., 39, 259 (1974).

6 N. Kornblum and P.A. Wade
J. Org. Chem., 38, 1418 (1973).

7 P.Bakuzis, M.L.F. Bakuzis and T.F. Weingartner
Tetrahedron Lett., 2371 (1978).

8 N. Kornblum, S.C.Carlson and R.G. Smith
J. Am. Chem. Soc., 100, 289 (1978).

9 D. Seebach
Angew Chem. Int. Ed., 18, 239 (1979).

10 I. Henry
Compt. Rend., 120, 1265 (1895).

11 S.B. Bowlers
Tetrahedron Lett., 3591 (1975).

12 J. Michel and E. Henry-Basch
C.R.Acad.Sc. Paris, 262, 1274 (1966).

13 C.D. Bedford and A.T. Nielsen
J. Org. Chem., 43, 2460 (1978).

14 M. Miyashita, T. Yanami and A. Yoshikoshi
J. Am. Chem. Soc., 98, 4679 (1976).

15 H. Shechter and F.T.Williams
J. Org. Chem., 27, 3699 (1962).

16 A.H. Pagano and H. Shechter
J. Org. Chem., 35, 295 (1970).

17 M. Blumer and D.W. Thomas
Science, 148, 370 (1965).

18 H. Mayer, P. Schudel, R. Ruegg and O. Isler
Helv. Chim. Acta, 46, 963 (1953).

19 S.V. Kamath, M.V. Rangaishenvi and S.N.Kulkarni
Ind. J. Chem., 22B, 684 (1983).

20 M.V. Rangaishenvi, S.V. Kamath, A.S. Phadke and
S.N. Kulkarni
Ind. J. Chem.,22B, 684 (1983).

21 P.D.Gokhale, A.P. Joshi, V.G. Naik, N.P.Damodaran,
U.R.Nayak and Sukh Dev
Tetrahedron, 32, 1391 (1970).

22 N. Kornblum and J.W. Powers
J. Org. Chem.,22, 455 (1957).

23 B. vanderbilt and H.Hass
Ind. Eng. Chem.,32, 34 (1940).

24 A. Sprang and E. Degering
J. Am. Chem. Soc., 64, 1063 (1942).

25 G.B. Bachman and R.J. Maleski
J. Org. Chem., 37, 2810 (1972).

26 Yu.V.Baskov and V.V.Perekalin
Dokl. Akad. Nauk SSSR 136, 1076 (1961).

27 K.J. Clork, G.I. Fray, R.H. Jaeger and Sir R.Robinson
Tetrahedron, 6, 217 (1959).

28 G.W.K.Carvil and F.B. Whitfield
Aust. J. Chem., 17, 1245 (1964).

29 S. Sebatey and J. Bleger
Bull. Soc. Chim. Fr., 43, 839 (1928).

30 D. Seebach and P.Krochel
Helv. Chim. Acta, 67, 261 (1984).

31 H.B. Hass, A.G. Susie and R.L. Heider
J. Org. Chem., 15, 8 (1950).

32 P.K. Freeman and L.L.Hutchinson
Tetrahedron Lett., 1849 (1976).

33 Byung-Hee Han and P. Boudjouk
J. Org. Chem., 5030 (1982).

34 C. Petrier, A.L. Gemal and J.L. Luche
Tetrahedron Lett., 3361 (1982).

CHAPTER-II

SYNTHESIS OF PHYTONE

This chapter entitled 'Synthesis of Phytone' is divided into two parts:

PART A.

Synthesis of phytone is described using Grignard reaction involving 1,3-dioxolane [2-methyl-2(3-chloropropyl)] and methylheptenone.

PART B.

This part describes the synthesis of 2,6,10,14-tetramethylpentadec-2-ene and intermediate to phytone using ethylcyanoacetate.

CHAPTER - II

PART A

SYNTHESIS OF 6, 10, 14-TRIMETHYL PENTADEC-2-ONE(PHYTONE) USING 1, 3-DIOXOLANE 2-METHYL[2-(3 CHLOROPROPYL)]

INTRODUCTION

Grignard reagent of 1,3-dioxolane-[2-methyl-2(3-chloropropyl)] (3) is reacted with methylheptenone (4) and the product after hydrolysis is again reacted with the Grignard reagent of (3) to give phytone (10), an important intermediate for the synthesis of Vitamin E.

PRESENT INVESTIGATION

The strategy involved as given in the introduction is the reaction of chloroketal (3) a C-5 carbon unit twice with methylheptenone (4) a C-8 unit [$C_8 + C_5 + C_5$].

2-Acetylbutyrolactone (1) is treated with 1:1 hydrochloric acid and the resulting 5-chloropentan-2-one (2) was continuously distilled[1]. The chloroketone (2) was then refluxed with ethylene glycol in benzene in presence of catalytic p-toluenesulfonic acid to give 1,3-dioxolane-[2-methyl-2(3-chloropropyl)] (3) in 79% yield, b.p. 70°/1 mm. The PMR (CCl_4) δ: showed a singlet at 1.23 for methyl adjacent to ketal oxygens, 1.7 and 1.78 (2s, $-CH_2-CH_2-$, 4H), 3.48 (t, 2H, $-CH_2-Cl$, J=7 Hz), 3.83 (s, 4H, $-O-CH_2-CH_2-O-$).

The Grignard reagent of the chloroketal (3) was prepared in THF using dibromoethane as initiator. Methylheptenone (4) in THF was added dropwise to the reagent at 0°C. After usual work up the hydroxyketal (5) was obtained in 45% yield[2]. IR (liquid film) showed bands at 3450 (-OH) cm^{-1} and PMR (CCl_4) δ: showed peaks at 1.1 (s, 3H, $CH_3-\overset{|}{C}-OH$), 1.23 (s, 3H, $CH_3-\overset{|}{C}\langle^{O}_{O}$]), 3.83 (s, 4H, $\begin{matrix}CH_2-O\\CH_2-O\end{matrix}$), 5.06 (bt, 1H, olefinic proton).

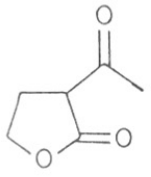
Though the yield reported in literature is 80% the hydroxy ketal was obtained in 45% along with a less polar product about 20% which was characterized as the self-condensed product of

methylheptenone. IR (liquid film) showed bands at 1680 (conjugated carbonyl) cm^{-1}. PMR (CCl_4) δ: 1.6, 1.67 (2s, 12H, $2=\!<^{CH_3}_{CH_3}$), 2.38 (s, 3H, $\underline{CH_3}$-C=C-C=O), 5.06 (bt, 2H, olefinic proton).

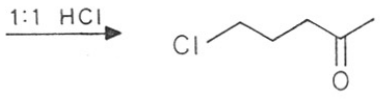
The Grignard reagent acts as a base in the self-condensation of methylheptenone.

The hydroxyketal (5) was dehydrated and deketalized in one pot using p-toluenesulfonic acid in dry benzene to furnish mixture of dienones (6) in 96% yield. The product (6) was a mixture of double bond isomers as seen from its PMR. IR (liquid film) showed band at 1710 ($>$C=O) cm^{-1}. PMR(CCl_4) δ: 1.6, 1.66 (methyls on double bond), 2.03 (s, 3H, -CO$\underline{CH_3}$), 4.66, 5.06 (olefinic protons). M^+ 194, b.p. 100-04°/5 mm. The dehydrated compound (6) was hydrogenated using 10% Pd/C in ethanol to give hexahydropseudoionone (7) in almost quantitative yield, b.p. 89-91°/2 mm (lit. 118-20/14 mm)[3]. The hexahydropseudoionone (7) obtained was identical with the authentic sample, obtained from citral and acetone[4] followed by hydrogenation, as shown by GLC analysis (ov-101, temp. 150°, homogeneous).

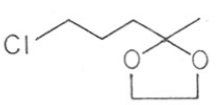
Grignard reagent of (3) was again reacted with hexahydropseudoionone (7) and the hydroxy compound (8) was obtained in 90% yield. IR (liquid film) showed band at 3450 cm^{-1}(-OH) and PMR (CCl_4) δ : 0.9 (d, 3H, 3$\underline{CH_3}$-CH-, J=6 Hz), 1.1 (s, 3H, CH_3-C-OH), 1.2 (s, 3H, CH_3-C$<^{O}_{O}$]), 3.82 (s, 4H, $^{\underline{CH_2}\text{-}O}_{\underline{CH_2}\text{-}O}$).



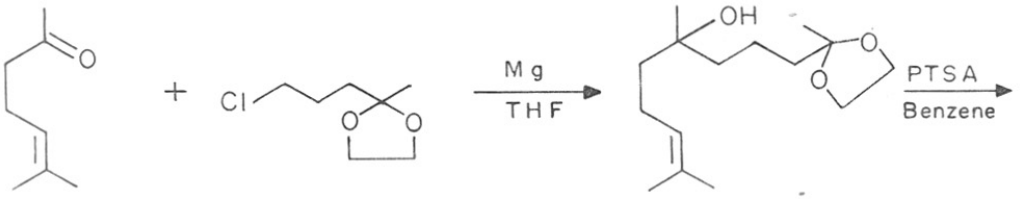
1



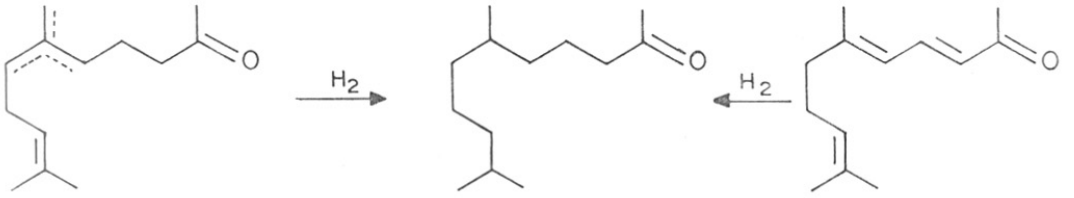
2



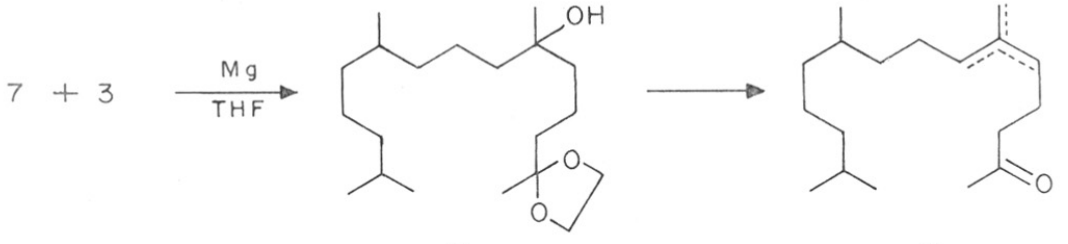
3



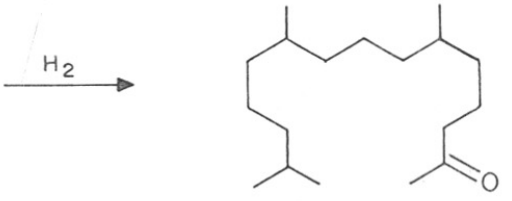
4 3 5



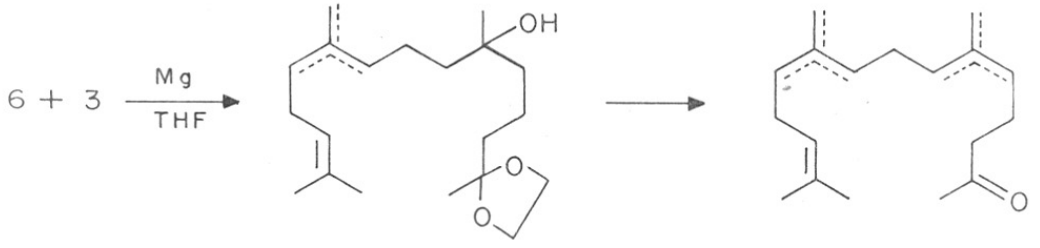
6 7 Pseudoionone



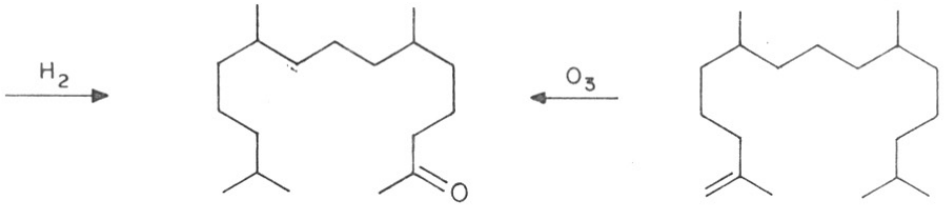
8 9



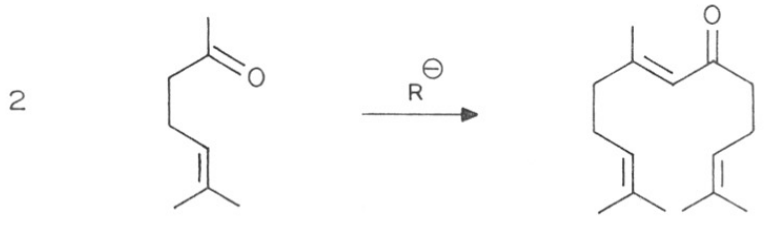
Phytone(10)



11 12



10 13



14

Dehydration and deketalization of (8) gave unsaturated phytone (9) in 78% yield. Hydrogenation of (9) gave phytone (10) in nearly quantitative yields, b.p. 135-37°/1 mm (lit. 118-122°/0.4 mm). IR (liquid film) showed bands at 1710 (>C=O) cm^{-1}. PMR (CCl_4) δ: 0.88 (d, 12H, 4 CH_3-CH-, J=6 Hz), 2.06 (s, 3H, CH_3-CO). GLC homogeneous (ov-101 temp. 200°C). The phytone (10) obtained had identical spectral properties with that of the authentic one obtained from oxidation of norphytene[5] which was obtained from pyrolysis of Vitamin E.

Grignard reaction was also carried out on (6) using (3). The hydroxyketal 11 thus obtained was dehydrated and deketalized as before to give unsaturated phytone (12) in overall 80% yield, b.p. 146-47°(bath)/2 mm (lit. 118-22°/4 mm). IR (liquid film) showed bands at 1718 (>C=O) cm^{-1}. PMR(CCl_4) δ: 1.6, 1.66 (2s, methyls on double bonds), 2.01 (s, 3H, CH_3-CO-), 4.7 (bs, >C=CH_2), 5.06 (bt, 1H, olefinic proton). Hydrogenation of (12) gave phytone in good yields. IR and PMR were superimposable on the one obtained earlier.

Phytone (10) can be further elaborated to isophytol by a reaction with vinyl magnesiumhalide[6] or a reaction of sodiumacetylide followed by hydrogenation[6a] which is an important intermediate for the synthesis of Vitamin E.

EXPERIMENTAL

Preparation of 1,3-Dioxolane [2-methyl-2(3'chloropropyl)] (3)

100 ml concentrated HCl and 100 ml of water was taken in a 500 ml three necked flask equipped with a dropping funnel and a distillation condenser. The 1:1 HCl was heated upto boiling and to it 44 g of 2-acetylbutyrolactone (1) was added dropwise, a vigorous reaction took place with evolution of carbondioxide. The chloroketone (2) formed was distilled off with water. 100 ml of water was added to remove most of the chloroketone formed. The distillate was extracted with chloroform (3 x 50 ml). The chloroform layer was washed with water, dried and concentrated to yield 30.4 g of (2), 72%. The chloroketone (2) was taken in benzene without further purification. To it ethyleneglycol 30 ml was added with catalytic p-toluenesulfonic acid 200 mg and refluxed under Dean-Stark water separation. After no more water separated the benzene layer was washed with water, dried and concentrated to give crude (3). The residue was distilled under reduced pressure to give pure (3) in 79% yield. 34.6 g b.p. 70°/1 mm. PMR (CCl_4) δ: 1.23 (s, 3H, CH_3-C<O,O>) 1.7, 1.76 (2s, 4H, -CH_2-CH_2-), 3.48 (t, 2H, -CH_2-Cl, J=7 Hz), 3.83 (s, 4H, -O-CH_2-CH_2-O-).

General procedure for Grignard reaction

A solution of (3, 2.00 g) in dry tetrahydrofuran (2 ml)

was added dropwise, with stirring and under a nitrogen atmosphere, to 0.300 g of magnesium turnings, previously activated with 1,2-dibromoethane. The reaction mixture was refluxed for 2 hrs and then cooled to 0°C. The reagent was diluted by adding 5 ml of tetrahydrofuran. Methyl-heptenone (4, 1.45 g) in 2 ml tetrahydrofuran was added dropwise, the reaction mixture stirred for 4 hrs at room temperature and then refluxed for 2 hrs, then poured into a saturated solution of NH_4Cl and extracted with ether (3 x 50 ml). The combined organic extracts were dried and solvent removed to afford crude (5). The hydroxy ketal (5) was purified by column chromatography on Alumina(neutral Grade III) to get pure (5) in 45% yield, 1.325 g. IR (liquid film): 3450 cm^{-1} (-OH). PMR(CCl_4) δ: 1.1 (s, 3H, $\underline{CH}_3$-C-OH), 1.23 (s, 3H, CH_3-C-O-), 1.6, 1.66 (2s, 6H, CH_3>=, 3.83 (s, 4H, -O-$\underline{CH}_2$-$\underline{CH}_2$-O-), 5.06 (bt, 1H, olefinic CH_3 proton).

General procedure for dehydration and deketalization of (5)

The hydroxyketal (5,1.325 g) was taken in dry benzene and refluxed in presence of catalytic p-toluenesulfonic acid 0.020 g for 3 hrs (monitored by TLC). The benzene layer was washed with water and dried. Removal of solvent gave crude (6). It was purified by column chromatography on alumina neutral (Grade II) to give pure (6) in 97% yield, 0.912 g, b.p. 100-104°/5 mm, M^+ 194. IR (liquid film):

1710 cm^{-1} (>C=O). PMR (CCl_4) δ: 1.6, 1.66 (2s, 9H, methyls on double bond), 2.03 (s, 3H, $C\underline{H}_3\dot{C}O$), 4.66 (bs, exomethylene obtained in dehydration), 5.06 (bt, olefinic proton).

General procedure for hydrogenation

Hydrogenation of (6) to hexahydropseudoionone (7)

0.912 g (6) was taken in 10 ml ethanol and 0.100 g of palladised charcoal 10% was added and hydrogenated at 3 atmosphereic pressure in Parr hydrogenation unit for 8 hrs. The catalyst filtered of and ethanol evaporated to give (7) in quantitative yield, b.p. 89-90°/2 mm (lit. 118-20°/14 mm). M^+ 198. GLC (ov 101, temp. 170°) homogeneous. IR (liquid film): 1715 (>C=O) cm^{-1}. PMR (CCl_4) δ: 0.81 (d, 9H, 3 $C\underline{H}_3$-$\dot{C}H$, J=6 Hz), 2.0 (s, 3H, $C\underline{H}_3\dot{C}O$).

Grignard of (3) on (7) to give (8)

Quantities taken:

Hexahydropseudoionone (7)	..	0.990 g
(3)	..	0.810 g
Mg	..	0.140 g
THF	..	5 ml
Initiator	..	dibromoethane

Yield of (8) .. 0.928 g, 55% wt. of ketone recovered. IR (liquid film): 3450 cm^{-1} (-OH). PMR (CCl_4) δ: 0.9 (d, 3H, $C\underline{H}_3$-$\dot{C}H$-, J=6 Hz), 1.1 (s, 3H, $C\underline{H}_3$-$\dot{C}$-O), 1.2 (s, 3H, $C\underline{H}_3$-$\dot{C}$(O)>), 3.82 (s, 4H, -O-$C\underline{H}_2$-$C\underline{H}_2$-O-).

Dehydration and deketalization of (8)

Quantities:

(7)	0.500 g
PTSA	0.050 g
Benzene	25 ml

Yield of (9) 0.290 g, 78%. IR (liquid film) 1715 cm^{-1} (>C=O). PMR (CCl_4) δ: 0.88 (d, 9H, CH_3-CH-, J=6 Hz), 1.63 (s, 3H, methyl on double bond), 2.08 (s, 3H, CH_3CO), 5.06 (m, 1H, olefinic proton).

Hydrogenation of (9) to give phytone (10)

Quantities:

(9)	0.200 g
Pd/C 10%	0.020 g
EtOH	10 ml

Yield of 10 quantitative, M^+ 268, b.p. 135-37°/1 mm (lit. 118-22°/14 mm). IR (liquid film): 1710 cm^{-1} (>CO). PMR (CCl_4) δ: 0.88 (d, 12H, 4 CH_3-CH-, J=6 Hz), 1.2 (bs, $-(CH_2)_n-$), 2.06 (s, 3H, CH_3CO), GC: homogeneous (ov 101, temp. 200°C).

Grignard of 3 on 6 to obtain 11

Quantities:

Chloroketal (3)	0.840 g
(6)	0.920 g
Mg	0.135 g
Initiator:	Dibromoethane

Ketone (6) recovered: 0.320 g

Yield of (11) 0.908 g, 88.1%. IR (liquid film): 3440 cm^{-1} (-OH). PMR (CCl_4) δ: 1.1 (s, 3H, CH_3-C(=O)-O-), 1.23 (s, 3H, CH_3-C(=O)-O), 1.61, 1.67 (2s, 9H, methyls on double bond), 3.84 (s, 4H, -O-CH_2-CH_2-O), 5.06 (m, 2H, olefinic proton).

Dehydration and deketalization of 11 to give 12

Quantities:

(11)	0.900 g
PTSA	0.100 g
Benzene	50 ml

Yield of (12) 0.722 g, 96.7%. GC (ov 101 temp. 200°) Homogeneous. b.p. 140-42°/1 mm.

IR (liquid film): 1718 cm^{-1} (>C=O). PMR (CCl_4) δ: 1.6, 1.66 (2s, 12H, methyls on double bonds), 2.01 (s, 3H, CH_3-CO), 4.7 (bs, >C=CH_2), 5.06 (bt, olefinic protons on all trisubstituted double bonds).

Hydrogenation of 12 to Phytone 10

Quantities:

(12)	0.500 g
10% Pd/C	0.050 g
Ethanol	20 ml

Yield of phytone (10) 0.451 g 88.2% GC (ov 101 temp. 200) Homogeneous. Identical to (10) obtained earlier,

IR (liquid film): 1720 cm^{-1} (>C=O), M^+ 268

b.p. 146-47°(bath)/2 mm (lit.118-20°/.4 mm). PMR(CCl_4) δ: 0.88 (d, 12H, 4 CH_3-CH-, J=6 Hz), 2.06 (s, 3H, CH_3-C(=O)-).

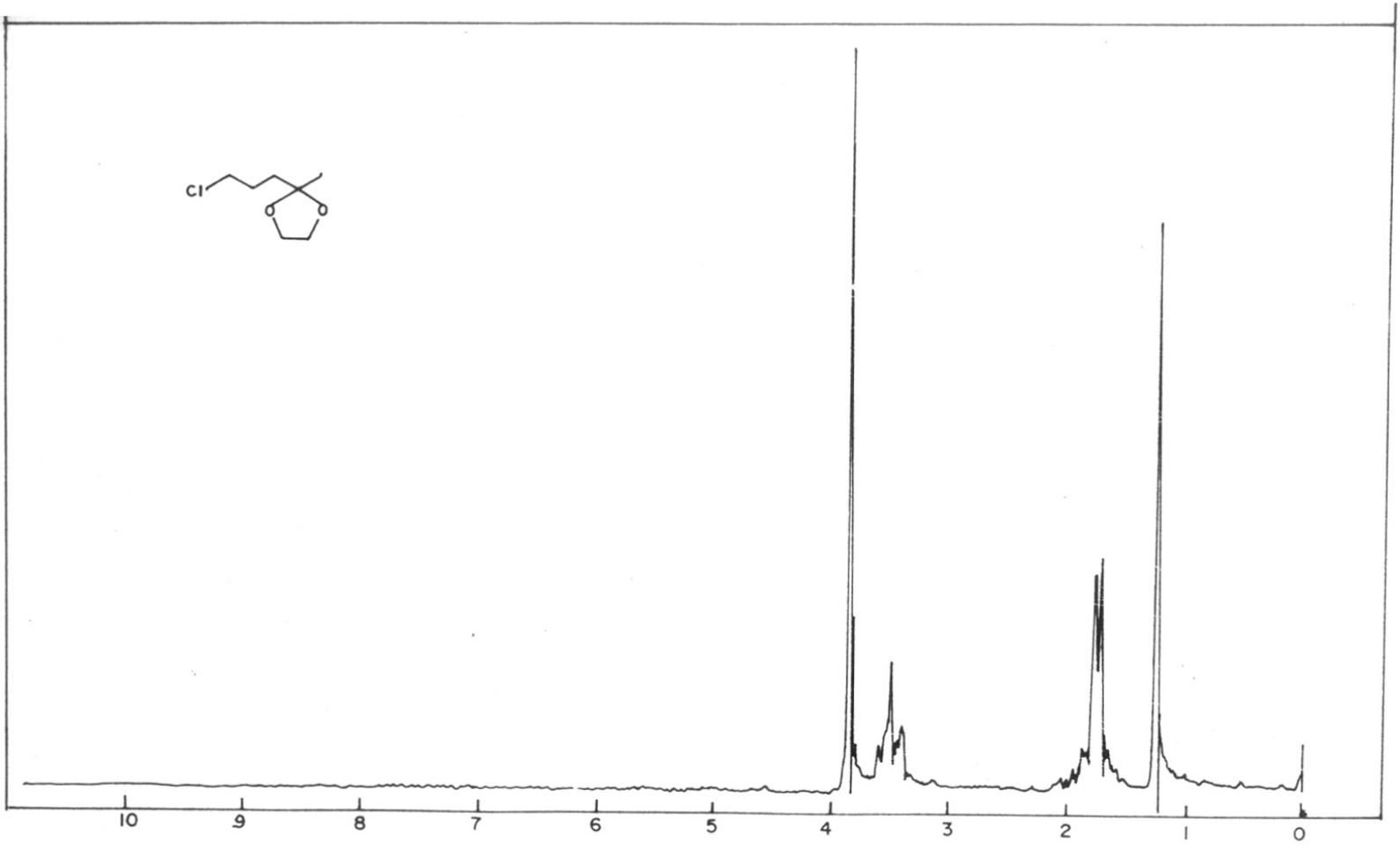


FIG 2.1 , NMR SPECTRUM OF 1,3-DIOXOLANE-[2-METHYL-2(3-CHLOROPROPYL)]

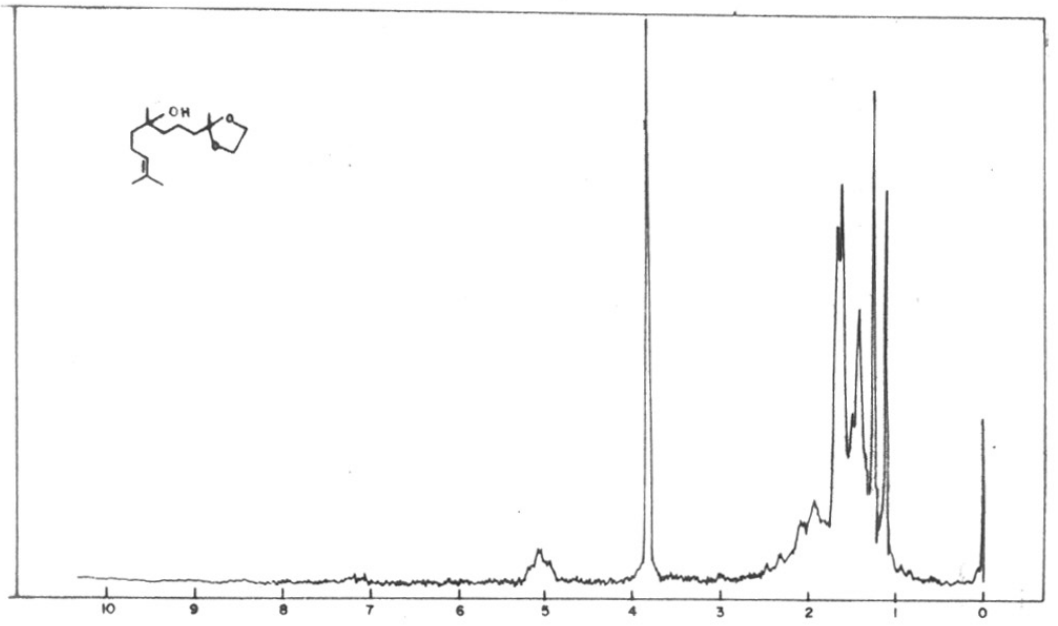


FIG 2.2 NMR SPECTRUM OF (5)

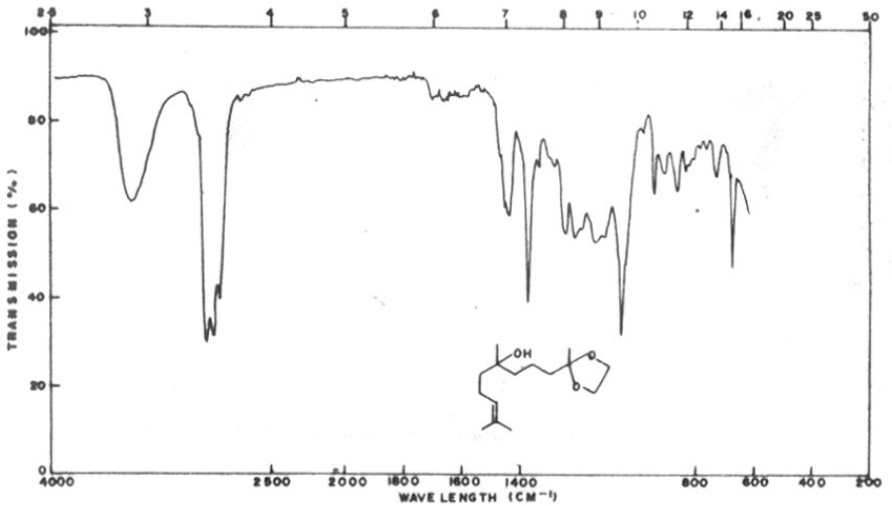


FIG 2·3, I R SPECTRUM OF (5)

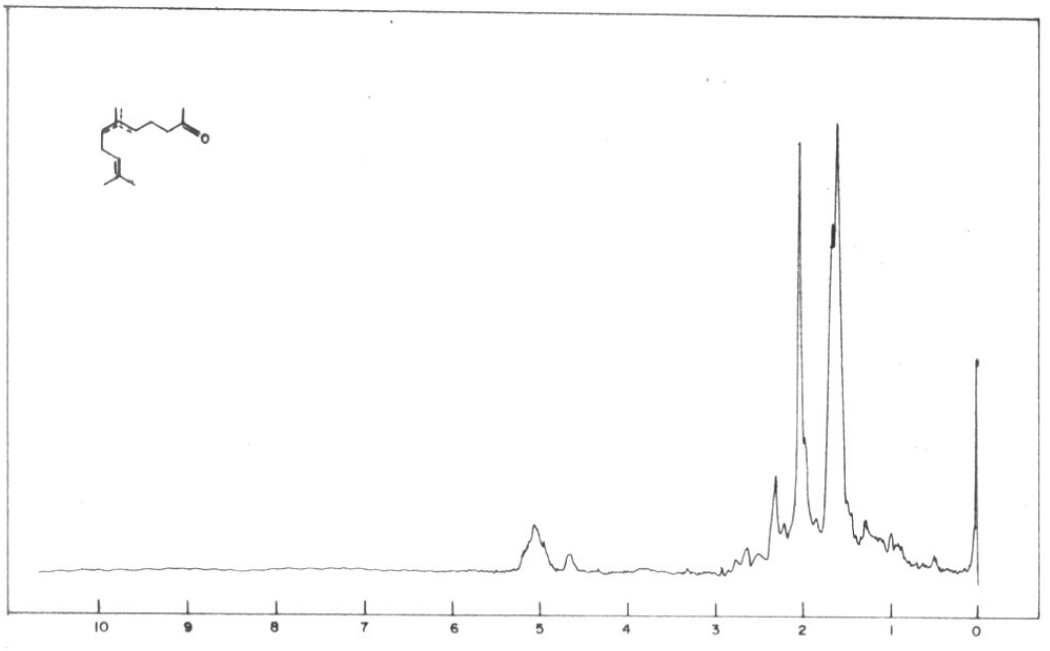


FIG 2.4, NMR SPECTRUM OF (6)

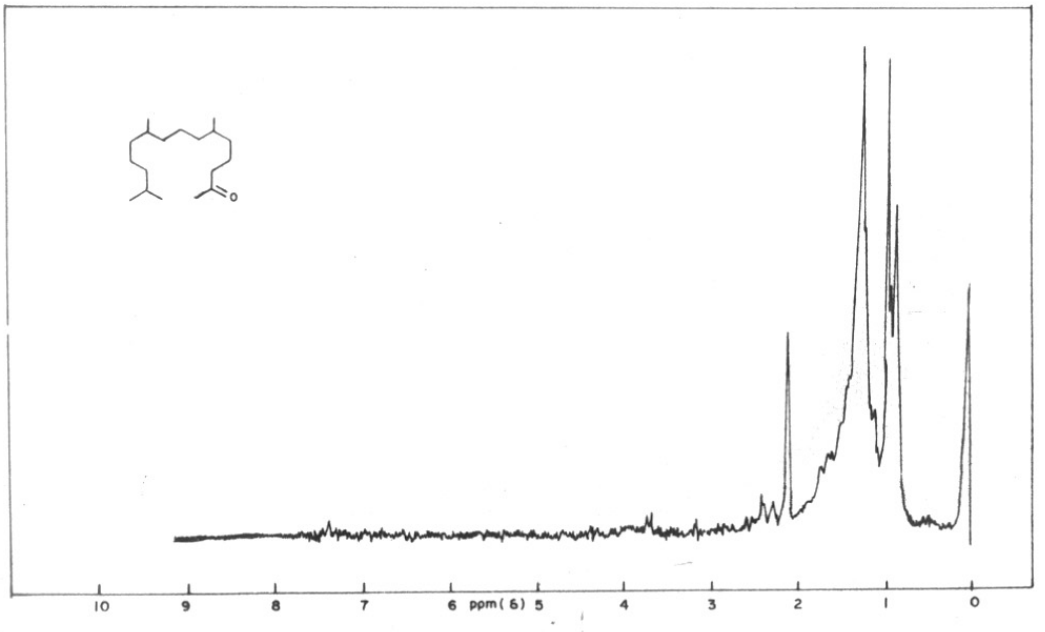


FIG 2.5, NMR SPECTRUM OF 6, 10, 14 - TRIMETHYL - 2-PENTADECANONE (10) PHYTONE

123

CHAPTER-II

PART B

SYNTHESIS OF 2,6,10,14-TETRAMETHYL PENTADEC-2-ENE AN INTERMEDIATE TO PHYTONE VIA ETHYLCYANOACETATE

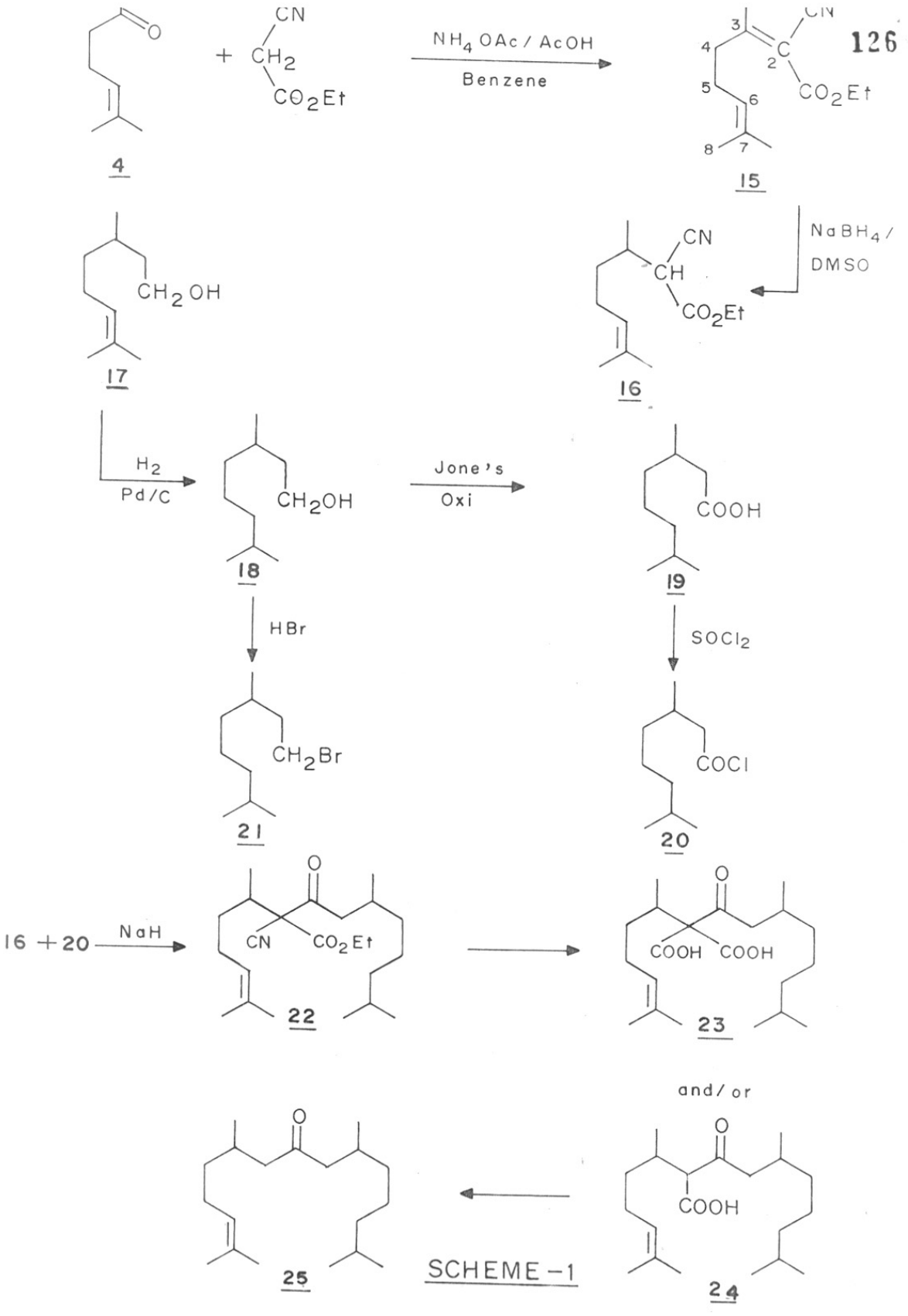
INTRODUCTION

Ethylcyanoacetate, an active methylene compound, is used as a bridge to hook two chains of eight and ten carbons. 3,7-Dimethyl-2-cyanooct-6-enoic acid ethyl ester (16) was alkylated by dihydrocitronellylbromide (21) to get 2,6,10,14-tetramethyl-7-cyano-7-carbethoxypentadec-2-ene (29). The alkylated product was decarbethoxylated and decyanated to give the titled hydrocarbon (31).

PRESENT INVESTIGATION

Methylheptenone (4) was condensed with ethylcyanoacetate in presence of ammonium acetate/acetic acid in refluxing benzene to give the alkylidene derivative, 3,7-dimethyl-2-cyanoocta-2,6-dienoic acid ethyl ester (15) in 75% yield, b.p. 145°/5 mm (lit.b.p.114-16/2 mm)[7]. The IR (liquid film) showed bands at 2240 (-CN) 1740 (-COOEt) cm^{-1} and PMR (CCl_4) δ: 1.33 (t, 3H, $C\underline{H}_3$-$\overset{|}{C}$= geometric isomers), 4.16 (q, 2H, -$\overset{||}{C}$-O$C\underline{H}_2$-CH_3, J=7 Hz), 5.0 (bt, 1H, olefinic proton on C_6). The alkylidene derivative (15) was reduced selectively using sodiumborohydride in DMSO[8]. Since catalytic hydrogenation did not give satisfactory results alkylidene cyanoacetate (15) was stirred with sodiumborohydride in DMSO for 3 hrs, which gave the reduced product 3,7-dimethyl-2-cyanooct-6-enoic acid ethylester (16), which was purified by chromatography and characterized by its IR and PMR. b.p. 100°/1 mm. IR (liquid film) showed bands at 2243 (-CN), 1760 (-COOEt) cm^{-1}. PMR(CCl_4)δ: 1.05, 1.11 (2d, 3H, $C\underline{H}_3$-$\overset{|}{C}$H-, diastereoisomers, J=6 Hz). 1.3 (t, 3H, $C\underline{H}_3$-CH_2-O-CO, J=7 Hz), 1.6, 1.66 (2s, 6H, $=\!\!<^{C\underline{H}_3}_{C\underline{H}_3}$), 3.41 (dd, 1H, -$C\underline{H}<^{CN}_{CO_2Et}$, J=5 Hz), 4.21 (q, 2H, -COO$C\underline{H}_2$-CH_3, J=7 Hz), 5.0 (bt, 1H, olefinic proton). The cyanoacetate (16) analysed for $C_{13}H_{21}NO_2$.

3,7-Dimethyl-6-octen-1-ol (17) was hydrogenated and then oxidized by Jones reagent to afford 3,7-dimethyl octanoic acid (19) in good yields. The acid (19) was converted to its acid


CN
CH2
CO2Et
NH4 OAc / AcOH
Benzene
CO2Et
4
15
CH2 OH
17
NaBH4 /
DMSO
CN
CH
CO2Et
16
H2
Pd/C
CH2OH
18
Jone's
Oxi
COOH
19
HBr
CH2Br
21
SOCl2
COCl
20
16 + 20
NaH
CN
CO2Et
22
COOH
COOH
23
and/or
COOH
24
25

SCHEME – 1

chloride (20) by using thionylchloride.

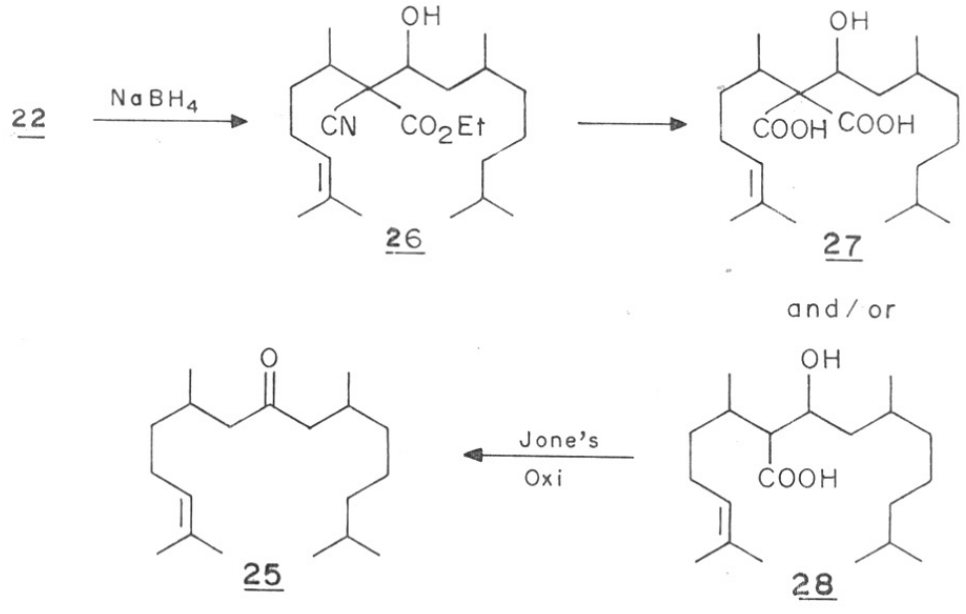
The cyanoacetate (16), was acylated with the above acid chloride (20) using sodiumhydride as a base. The acylated product 2,6,10,14-tetramethyl-7-cyano-7-carbethoxy-8-oxopentadec-2-ene (22) was obtained in 63% yield. M^+ 377, IR (liquid film): 2210 (-CN), 1766 ($-CO_2Et$), 1740 (>CO) cm^{-1}. PMR (CCl_4) δ : 0.86 (d, 12H, 4 CH_3-CH-, J=6 Hz), 1.58, 1.66 (2s, 6H, $=C<^{CH_3}_{CH_3}$), 4.18 (q, 2H, -CO-O-CH_2-CH_3, J=7 Hz), 5.00 (bt, 1H, olefinic proton).

The strategy used in the preparation of the ketone (25) was to hydrolyse (21) and decarboxylate the resulting keto acid (23/24) as shown in Scheme 1, however the usual methods like alkaline/acidic hydrolysis failed to give the ketone (25) in our hands.

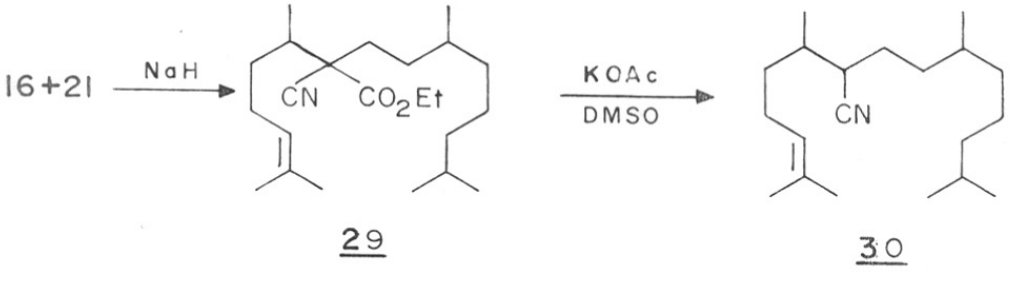
An alternative scheme to get the ketone (25) via the hydroxy compound (26) was tried unsuccessfully (Scheme 2).

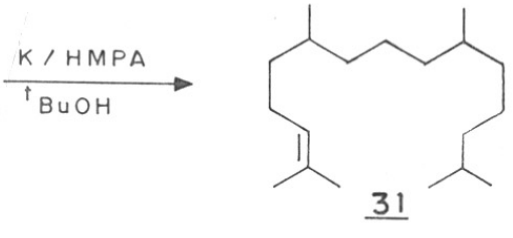
As the above reaction sequences to get the hydrocarbon (31) via the ketone (25) failed, an alternative method was planned as shown in Scheme 3.

Dihydrocitronellyl bromide (21) was prepared by refluxing dihydrocitronellol (18) with 48% HBr in presence of H_2SO_4. The cyanoacetate (16) was alkylated by (21) using sodiumhydride in benzene/HMPA (10:1) to get the product 2,6,10,14-tetramethyl-7-cyano-7-carbethoxypentadec-2-ene (29)



SCHEME 2





SCHEME-3

in 50% yield. IR (liquid film): 2220 (-CN), 1738 (-COOEt) cm^{-1} and PMR (CCl_4) δ : 0.85 (d, 9H, $3C\underline{H}_3$-$\underline{C}$H-, J=6 Hz), 1.33 (t, 3H, $C\underline{H}_3$-CH_2-O , J=7 Hz), 1.6, 1.66 (2s, 6H, $=C\begin{smallmatrix}\diagup\ C\underline{H}_3\\ \diagdown\ C\underline{H}_3\end{smallmatrix}$), 4.23 (q, 2H, -O-$C\underline{H}_2$-$CH_3$, J=7 Hz), 5.03 (m, 1H, olefinic proton at C_3). M^+ 363.

The alkylated product (29) was heated in wet DMSO in presence of potassium acetate at 150° for 4 hrs to furnish the decarbethoxylated product, 2,6,10,14-tetramethyl-7-cyano-pentadec-2-ene (30) in 96% yields. IR showed band due to -CN at 2225 cm^{-1}. PMR (CCl_4) δ : 0.8 (d, 9H, 3 $C\underline{H}_3$-$\underline{C}$H-, J=6 Hz), 1.0 (d, 3H, $C\underline{H}_3$-$\underset{6}{\underline{C}}$H- J=6 Hz), 1.56, 1.63 (2s, 6H, $=\underset{2}{C}\begin{smallmatrix}\diagup\ C\underline{H}_3\\ \diagdown\ C\underline{H}_3\end{smallmatrix}$). 5.00 (m, 1H, olefinic proton at C_3).

Decyanation was performed using literature conditions[10] to furnish the hydrocarbon 2,6,10,14-tetramethylpentadec-2-ene (31) in 76% yield. b.p. 125-27°(bath)/1 mm (lit.110°/0.3 mm[11]). It was characterized by its PMR and Mass. M^+ 266, analysed for $C_{19}H_{36}$. PMR(CCl_4)δ: 0.85 (d, 12H, 4 $C\underline{H}_3$-$\underline{C}$H-, J=6 Hz), 1.6,1.66 (2s, 6H, $=C\begin{smallmatrix}\diagup\ C\underline{H}_3\\ \diagdown\ C\underline{H}_3\end{smallmatrix}$), 5.06 (m,1H, olefinic proton).

The mechanism suggested[12] for decyanation is given below:

$$\text{HMPA} + M \longrightarrow (\text{HMPA } e^-)\ M^+$$

$$(\text{HMPA } e^-) + RCN \longrightarrow (R\text{-}\dot{C}\text{=}N)^-\ M^+ + \text{HMPA}$$

$$(R\text{-}\dot{C}\text{=}N)^- \longrightarrow R^\circ + CN^-$$

$$R^- \xleftarrow{e^-} R^\circ \qquad R^\circ \xrightarrow{H^\circ} RH \quad (\text{HMPA})$$

The spectral properties of hydrocarbon (31)
agreed in all respects with those reported in literature[10].

EXPERIMENTAL

Ethyl-3,7-dimethyl-2-cyanoocta-2,6-dienoate (15)

Methylheptenone (4, 12.6 g), ethylcyanoacetate (11.3 g) ammoniumacetate (1.0 g), acetic acid (3 ml) were taken in a 250 ml round bottom flask and refluxed, in benzene under a Dean Stark water separator, for 8 hrs. 1·3 ml of water separated. The reaction mixture was cooled and then washed with water thoroughly to remove ammonium acetate and acetic acid, dried on benzene, evaporated and the residue distilled under reduced pressure. The first fraction contained some starting materials and the next fraction gave pure alkylidene derivative of ethylcyanoacetate in 70% yield, b.p. 145°/5 mm. IR (liquid film): 2240 (-CN), 1740 (-COOEt) cm^{-1} and 1613, 1235, 1080 cm^{-1}. NMR (CCl_4) δ: 1.33 (t, 3H, CH_3-CH_2, J=7 Hz), 1.6, 1.66 (2s, 6H, 2 CH_3=), 2.23, 2.3 (2s, 3H, CH_3 geometric isomers), 4.16 (q, 2H, CH_3-CH_2, J=7 Hz), 5.0 (bt, 1H, olefinic proton).

Analysis: Calculated: C, 70.58; H, 8.6; N, 6.3.

Found : C, 71.21; H, 8.63; N, 6.39%.

Reduction of (15) to ethyl-3,7-dimethyl-2-cyano oct-6-enoate (16)

The alkylidene derivative (15, 6.6 g) was taken in 20 ml DMSO and to sodiumborohydride 0.600 g was added in small portions and stirred for 3 hrs. The reaction was then poured in water, acidified with dilute HCl and extracted with ether. The ether extract washed with aq. $NaHCO_3$ and water, dried and

solvent evaporated to give ethyl-3,7-dimethyl-2-cyanooct-6-enoate (16) in 75% yield. The product obtained was purified by column chromatography on silica gel, followed by distillation, b.p. 100°/1 mm. IR (liquid film) showed peak for CN at 2243 cm^{-1}, 1760 cm^{-1} (-COOEt) 1427, 1400, 1380, 990 cm^{-1}. NMR (CCl_4) δ: 1.05, 1.11 (2d, 3H, $C\underline{H}_3$-$C\underline{H}$-, diastereomers, J=7 Hz), 1.3 (t, 3H, $C\underline{H}_3$-CH_2, J=7 Hz), 1.6, 1.66 (2s, 6H, methyls on double bond), 3.41 (dd, 1H, -$C\underline{H}\langle^{CN}_{CO_2Et}$, J=4 Hz), 4.21 (q, 2H, CH_3-$C\underline{H}_2$, J=7 Hz).

Analysis: Calculated: C,69.85; H, 9.42; N, 6.28.
Found: C, 69.80; H, 9.31; N, 6.00%.

3,7-Dimethyloctanoic acid (19)

Dihydrocitronellol (17) was obtained as described in Chapter II. Dihydrocitronellol (18, 18.0 g) was taken in 50 ml acetone, cooled to 0° in an ice bath, and Jones reagent was added dropwise till red colour i.e. colour of the reagent persisted. The reaction mixture was further stirred for 2 hrs. Acetone was removed and water added and extracted with ether (3 x 100 ml). The organic layer was washed with 5% aqueous NaOH (2 x 100 ml) and then the alkaline layer was acidified and again extracted with ether (3 x 100 ml). The ether layer was washed with water thoroughly, dried and solvent evaporated to give the acid 8 , 16.03 g in 81% yield. b.p. 131-32°/1 mm. IR (liquid film): 1720 (>C=O) cm^{-1} and broad acid peak. NMR (CCl_4) δ: 0.93 (d, 9H, 3. $C\underline{H}_3$-$C\underline{H}$-, J=6 Hz), 2.20 (m, 2H, $C\underline{H}_2$-COOH)

and 10.03 (bs, 1H, -COOH, exchanges with D_2O).

3,7-dimethyloctanoylchloride (20)

Dihydrocitronellic acid (19, 17.2 g) was taken in 19.0 ml $SOCl_2$ and refluxed for 4 hrs till evolution of HCl stopped. Excess $SOCl_2$ was distilled off, dry benzene 20 ml was added and again distilled to remove last traces of $SOCl_2$. The residue was distilled to give pure acid chloride (20). Weight of acid chloride obtained 18.6 g. IR (liq. film): 1818 cm^{-1} (carbonyl of acid chloride). PMR (CCl_4) δ: 0.93 (d, 6H, 2 CH_3-CH-, J=6 Hz), 1.03 (d, 3H, CH_3-CH-, J=6 Hz), 2.73 (dd, 2H, CH_2-COCl).

2,6,10,14-tetramethyl-7-cyano-7-carbethoxy-8-oxo pentadec-2-ene (22)

Sodium hydride 50% dispersion in oil was taken in a 100 ml two necked flask and was washed with dry petroleum ether under the atmosphere of nitrogen. Pet. ether was removed and benzene 25 ml added and cooled in an icebath. To it cyano-acetate (16, 6.0 g) was added dropwise with stirring. Evolution of hydrogen was observed. The mixture was stirred for 0.5 hr and to it the acid chloride (20, 5.5 g was added dropwise with stirring at 0°C. The reaction mixture was then stirred for 8 hrs and then poured in water acidified and extracted with ether (3 x 50 ml) washed in water, dried and solvent evaporated to give the crude acylated product. It was purified by column chromatography on silica gel. Elution with PE + 10% benzene

gave the starting cyano compoound, 1.614 g. Weight of acylated product (22) was 6.446 g, yield 63.6%. Mass spectra showed M^+ 377. IR (liquid film): peak for -CN at 2210, ; 1766 (-COOEt), 1740 (>C=O), 1467, 1235 cm^{-1}. NMR (CCl_4) δ: 0.86 (d, 12H, 4 $\underline{CH_3}$-CH-, J=6 Hz), 1.58, 1.66 (2s, 6H, $(CH_3)_2C=$), 2.53, 2.63 (2m, 3H, -$\underline{CH}$-C(CN)(CO$_2$Et)-$\underline{CH_2}$), 4.18 (q, 2H, O-$\underline{CH_2}$-CH_3, J=6 Hz), 5.00 (bt, 1H, olefinic proton).

3,7-Dimethyloctylbromide (21) or dihydrocitronellylbromide

Citronellol was hydrogenated as described earlier. Dihydrocitronellol (18, 15.8 g) was taken in 50 ml 47% HBr and 5 ml of concentrated sulphuric acid was added and reaction mixture was refluxed for 6 hrs, when layer of bromide separated. The reaction mixture was poured in water and extracted with ether (3 x 100 ml). The ether layer washed with water and 10% aq. $NaHCO_3$ and water again, dried and solvent evaporated to give crude bromide (21), it was purified by column chromatography on silica gel and eluted with petroleum ether. 16.43 g of bromide was obtained, yields, 76%. PMR: δ 0.88 (d, 9H, $\underline{CH_3}$-CH- J=6 Hz), 3.36 (t, 2H, -$\underline{CH_2}$-Br, J=7 Hz).

2,6,10,14-Tetramethyl-7-cyano-7-carbethoxypentadec-2-ene (20)

Sodium hydride (50% dispersion in oil) 0.470 g was taken in a two-necked flask and washed with pet. ether to remove the oil and then benzene 10 ml added. To this (16, 2.1 g) in benzene 5 ml and HMPA 2 ml were added dropwise with vigorous stirring. It was then stirred for 0.5 hr till evolution

of H_2 stopped. Dihydrocitronellyl bromide (21, 2.08 g) was added and the reaction mixture refluxed under nitrogen for 8 hrs. The reaction was monitored by TLC. The reaction mixture was then poured in water and extracted with ether (3 x 50 ml) washed with water, dried and then purified by column chromatography on silica gel. PE elution gave the unreacted halide and PE + 20% benzene gave the alkylated product 2,6,10,14-tetramethyl-7-cyano-7-carbethoxypentadec-2-ene (29). Weight of the alkylated product was 1.670 g. Yield 50%. M^+ 363. IR (liquid film): 2220 (-CN), 1738 ($-CO_2Et$), 1210, 1035, 675 cm^{-1}. NMR (CCl_4) δ : 0.85 (d, 9H, 3.$C\underline{H}_3$-CH-, J=6 Hz), 1.33 (t, 3H, $C\underline{H}_3$-CH_2, J=7 Hz), 1.6, 1.66 (2s, 6H, $\underline{CH}_3\!>\!C=$), 4.23 (q, 2H, $\underline{CH}_3$ $C\underline{H}_2$-CH_3, J=7 Hz), 5.03 (bt, 1H, olefinic proton).

Analysis: Calculated: C, 76.00; H, 9.9; N, 3.8.

Found: C, 75.87; H, 9.9; N, 4.01%.

2,6,10,14-Tetramethyl-7-cyanopentadec-2-ene (30)

2,6,10,14-tetramethyl-7-cyano-7-carbethoxypentadec-2-ene 0.500 g of (29) was taken in 2 ml DMSO, 0.075 g potassium acetate added with a drop of water. This was heated at 150-60° for 4 hrs. The reaction was monitored by TLC by running the silica gel plate in PE twice before developing. The reaction mixture was poured in water and extracted with petroleum ether. Washed thoroughly with water to remove DMSO completely, dried on anhydrous Na_2SO_4 and solvent evaporated to get the crude product which was purified by column chromatography, eluted with

PE + 10% benzene. Weight of cyano compound (30) was 0.412 g i.e. 96% yield. M^+ 291. b.p.170°-72° (bath)/4 mm. IR (liquid film): 2225 (-CN), 1460, 1383 cm^{-1}. NMR:δ 0.8 (d, 9H, 3 $\underline{CH_3}$-CH-, J=6 Hz), 1.0 (d, 3H, $\underline{CH_3}$-CH, J=6 Hz), 1.56, 1.63 (2s, 6H, $\underline{CH_3}>$=,), 5.00 (bt, 1H,olefinic proton).

Analysis: Calculated: C, 82.5; H, 12.7; N, 4.81.

Found: C, 82.25; H, 12.43; N, 4.71%.

Decyanation of (30), preparation of 2,6,10,14-tetramethyl-pentadec-2-ene (31)

0.040 g of potassium metal was added to dry HMPA under nitrogen and stirred till potassium dispersed completely rendering the solution deep blue in colour. To this the cyano compound (30, 0.300 g) in equimolar t-butanol added and reaction mixtured stirred for 2 hrs. The reaction was monitored by TLC (solvent system: petroleum ether). The reaction mixture was poured in water (10 ml) and extracted thoroughly with P.E. The organic layer was washed with water thoroughly to remove all traces of HMPA, dried and solvent evaporated to get the crude hydrocarbon 2,6,10,14-tetramethylpentadec-2-ene. The TLC showed presence of starting material, so it was chromatographed on silica gel and eluted with P.E. to get pure hydrocarbon in 76% yield, 0.142 g. Recovered cyano compound 0.098 g; b.p. 125°-27° (bath)/1 mm. IR (liquid film): 2900, 1460, 1375 cm^{-1}. PMR (CCl_4) δ : 0.85 (d, 12H, 4.$\underline{CH_3}$-CH-, J=6 Hz), 1.6, 1.66 (2s, 6H, $\underline{CH_3}>$=), 5.06 (bt, 1H, olefinic proton).

Analysis: Calculated: C, 87.7; H, 14.30;

Found: C, 87.25; H, 14.2%.

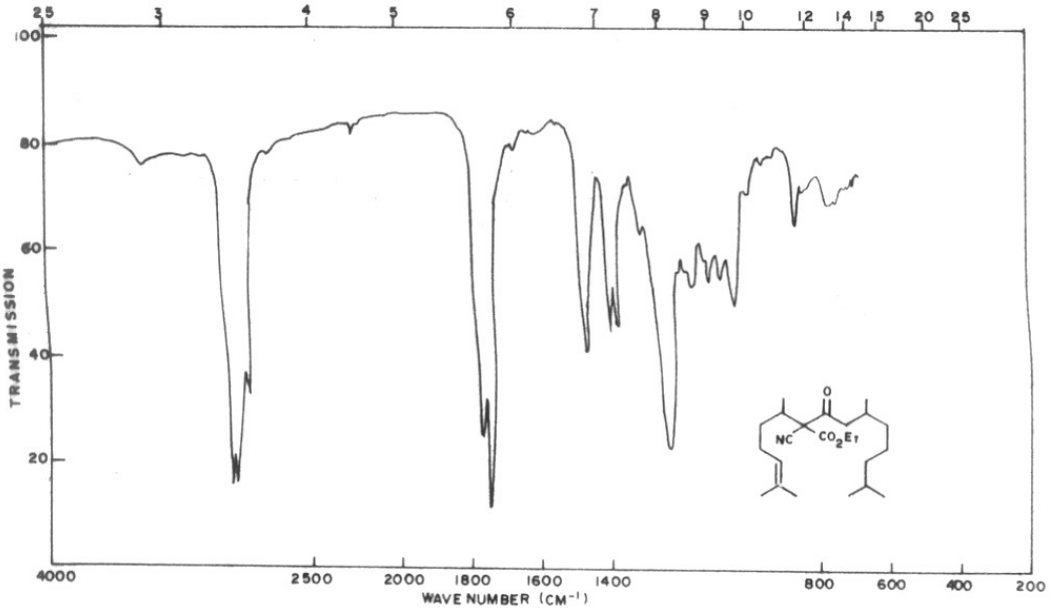


FIG 2.7, 2,6,10,14-TETRAMETHYL-7-CYANO-7-CARBETHOXY-8-OXO-PENTADEC-2-ENE (22)

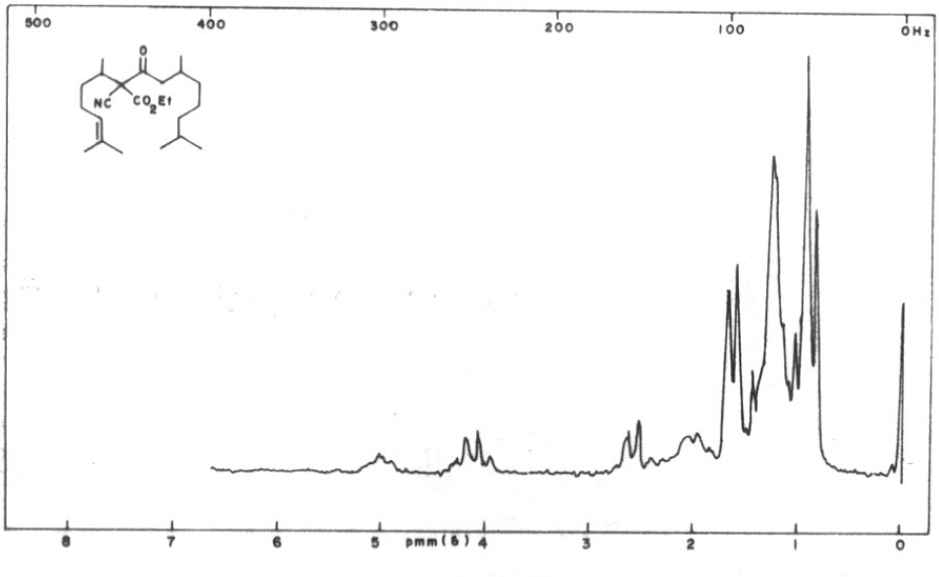


FIG 2.8, 2,6,10,14-TETRAMETHYL-7-CYANO-7-CARBETHOXY-8-OXO PENTADEC-2-ENE (22)

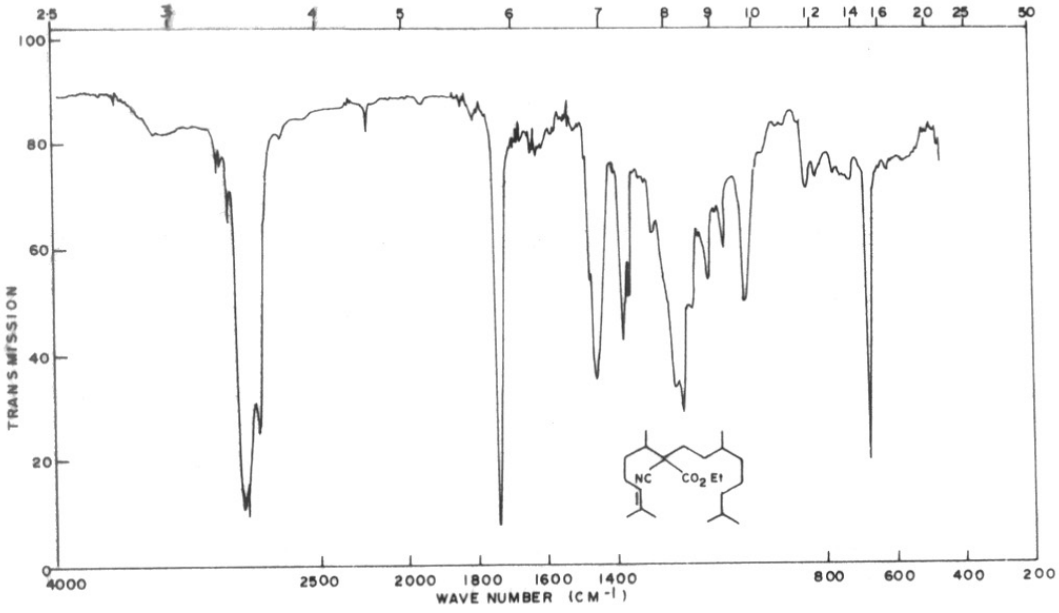


FIG 29, 2,6,10,14 - TETRAMETHYL -7-CYANO-7 - CARBETHOXY PENTADEC -2 -ENE (29)

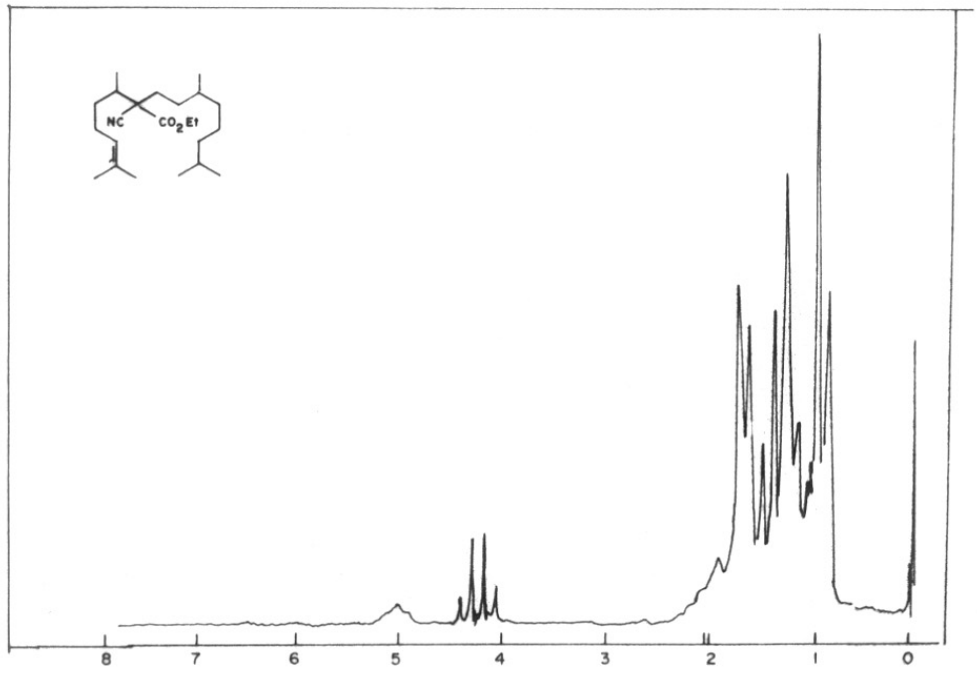


FIG 2·10, 2,6,10,14-TETRAMETHYL-7-CYANO-7-CARBETHOXY PENTADEC-2-ENE (29)

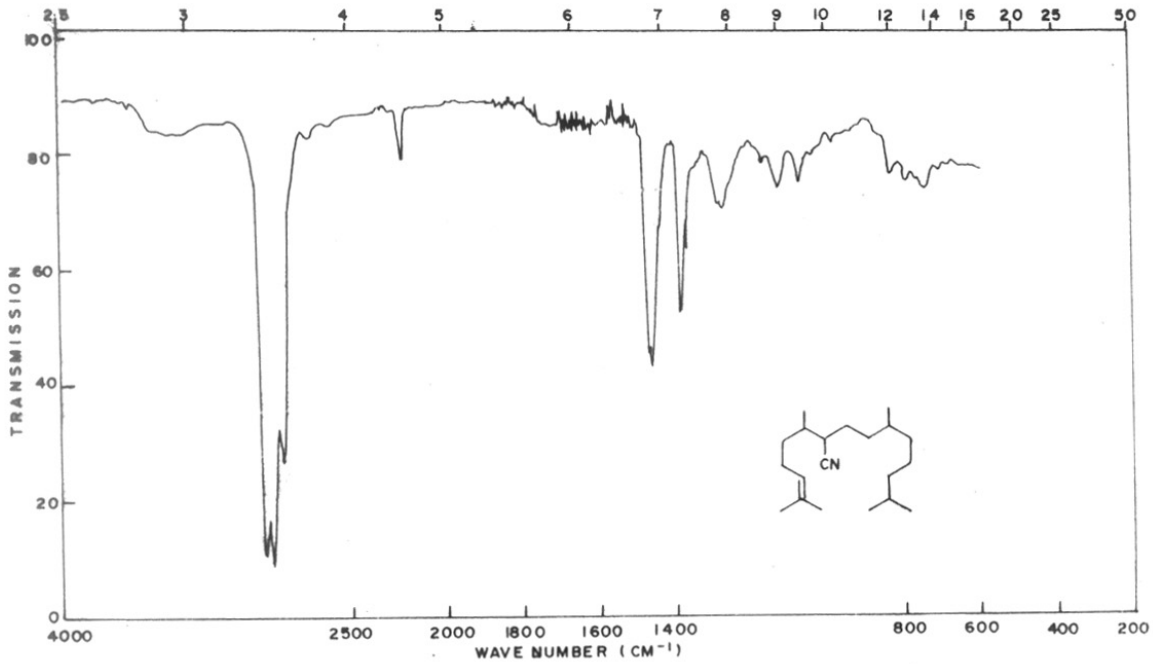


FIG 2.11, 2,6,10,14-TETRAMETHYL-7-CYANO PENTADEC-2-ENE (30)

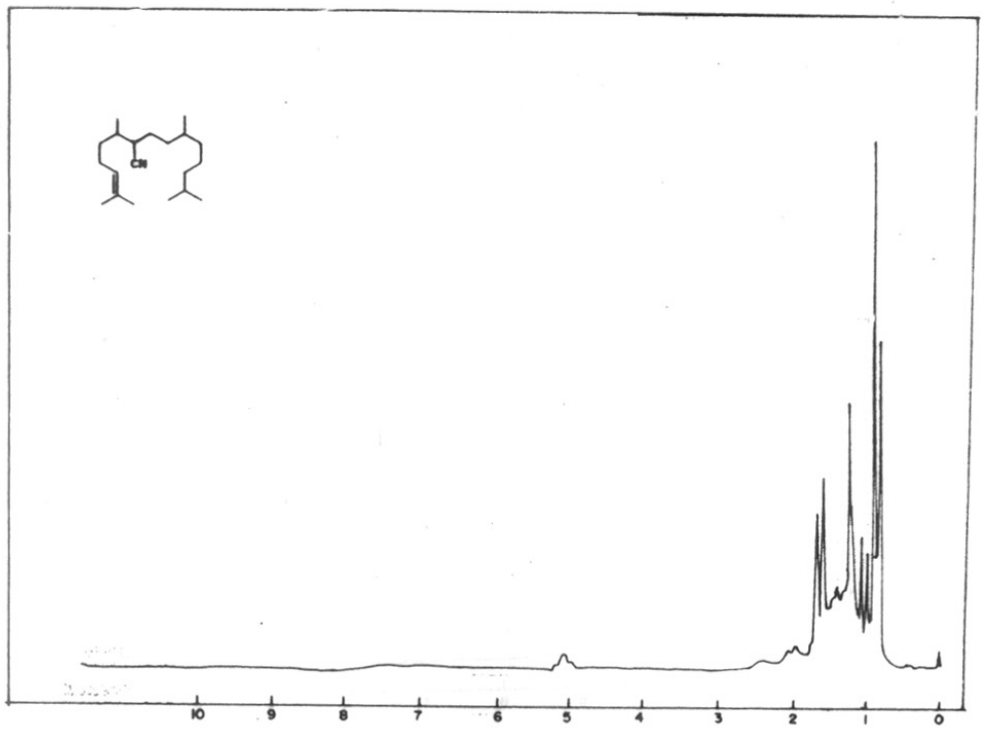


FIG 2.12, 2,6,10,14-TETRAMETHYL-7-CYNOPENTADEC-2-ENE (30)

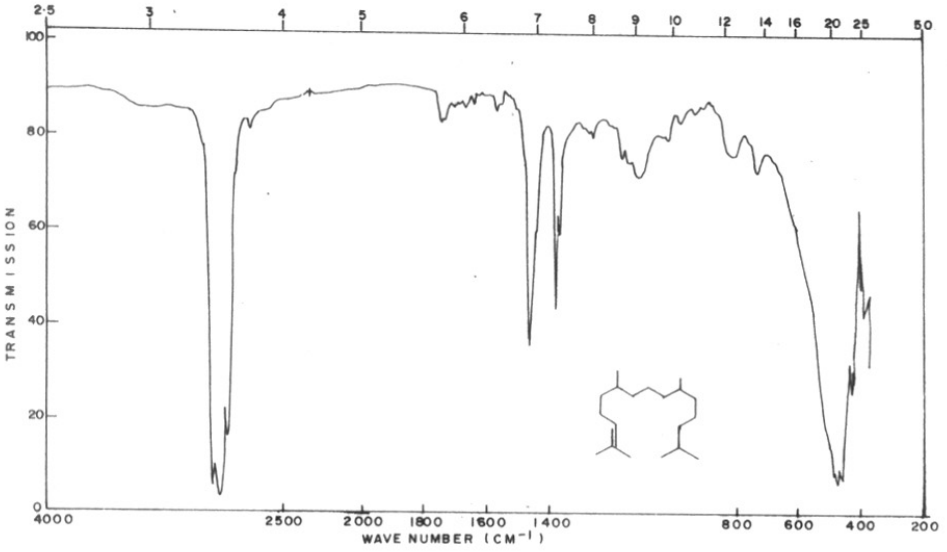


FIG 2·13, 2,6,10,14-TETRAMETHYL PENTADEC-2-ENE (31)

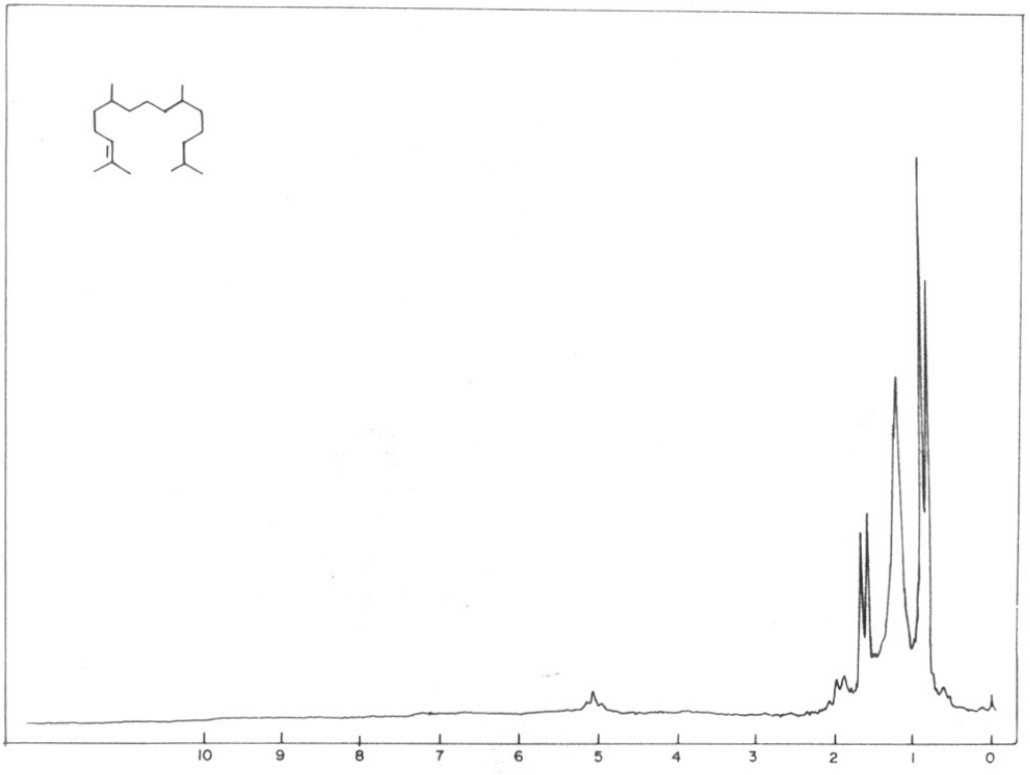


FIG 2·14, 2,6,10,14-TETRAMETHYL PENTADEC-2-ENE (31)

REFERENCES

1 Vogel's text book of practical organic chemistry
ELBS edition of the fourth edition 1978, 862.

2 P. Weyersthal and W. Zummack
Chem. Ber., 108, 377 (1975).

3 K. Sato, S. Mizuno and M. Hisayama
J. Org. Chem., 32, 177 (1967).

4 A. Russel and R.L.Kenyon
Org. Syn. 23, 78 (1943).

5 R. Pappo, D.S. Allen, R.U. Lemieux, W.S.Johnson
J. Org. Chem., 21, 478 (1956).

6 S. Akutagawa, T. Taketomi, H. Kunobayashi, K. Takayama,
T. Someya and O. Otsuka
Bull. Chem. Soc. Japan, 1158 (1978).

6a P.Karrer, G. Geigev, H. Rentsohter, E. Zbindes and A. Kugler
Helv. Chim. Acta, 26, 1741 (1943).

7 S. Watanabe, T. Fujita, K. Suga, H. Abe, H. Tsuruta
Yukagaker 27, 863 (1978).

8 J.A. Marshall and R.D. Carrol
J. Org. Chem., 30, 2748 (1965).

9 B.M. Trost and J. Cossy
J. Am. Chem. Soc., 104, 6881 (1982).

10 M. Larcheveque and T. Cuvigny
Tetrahedron Lett., 44, 3851 (1975).

11 H. Mayer, P. Schudell, R. Ruegg and O. Isler
Helv. Chim. Acta, 46, 963 (1963).

12 T. Cuvigny, M. Larcheveque and H. Normant
Bull. Soc. Chim. Fr. 1174 (1973).

CHAPTER – III

SYNTHESIS OF VITAMIN-E

Synthesis of norphytene (15) and its Prins reaction are described in this chapter. The chapter is divided into two parts.

Part A

This part describes the synthesis of norphytene (15) based on the methodology developed for its isomer 2,6,10,14-tetramethylpentadec-2-ene (Chapter II, part II).

Part B

This part describes the Prins reaction on norphytene (15), separation of the isomeric alcohols (Prins alcohols) obtained by silvernitrate impregnated silica gel chromatography, and their structure elucidation, and confirmation by alternative route. These Prins alcohols were condensed with trimethylhydroquinone (37) to get vitamin E. This is preceded by a brief note on Prins reaction.

CHAPTER-III

PART A

SYNTHESIS OF 2,6,10,14-TETRAMETHYLPENTADEC-1-ENE (NORTHYTENE)

Norphytene (2,6,10,14-tetramethylpentadec-1-ene, 15) along with its double isomers 2,6,10,14-tetramethylpentadec-2-ene and 2,6,10,14-tetramethylpentadec-8-ene, occurs in mixed zooplankton of Gulf of Maine, liver oils of basking shark, sperm whales and others[1]. It has also been isolated from cigarette smoke condensate[2]. It has a pristane skeleton proved by hydrogenation studies[1]. Ozonolysis of norphytene gave phytone a C_{18} ketone[1].

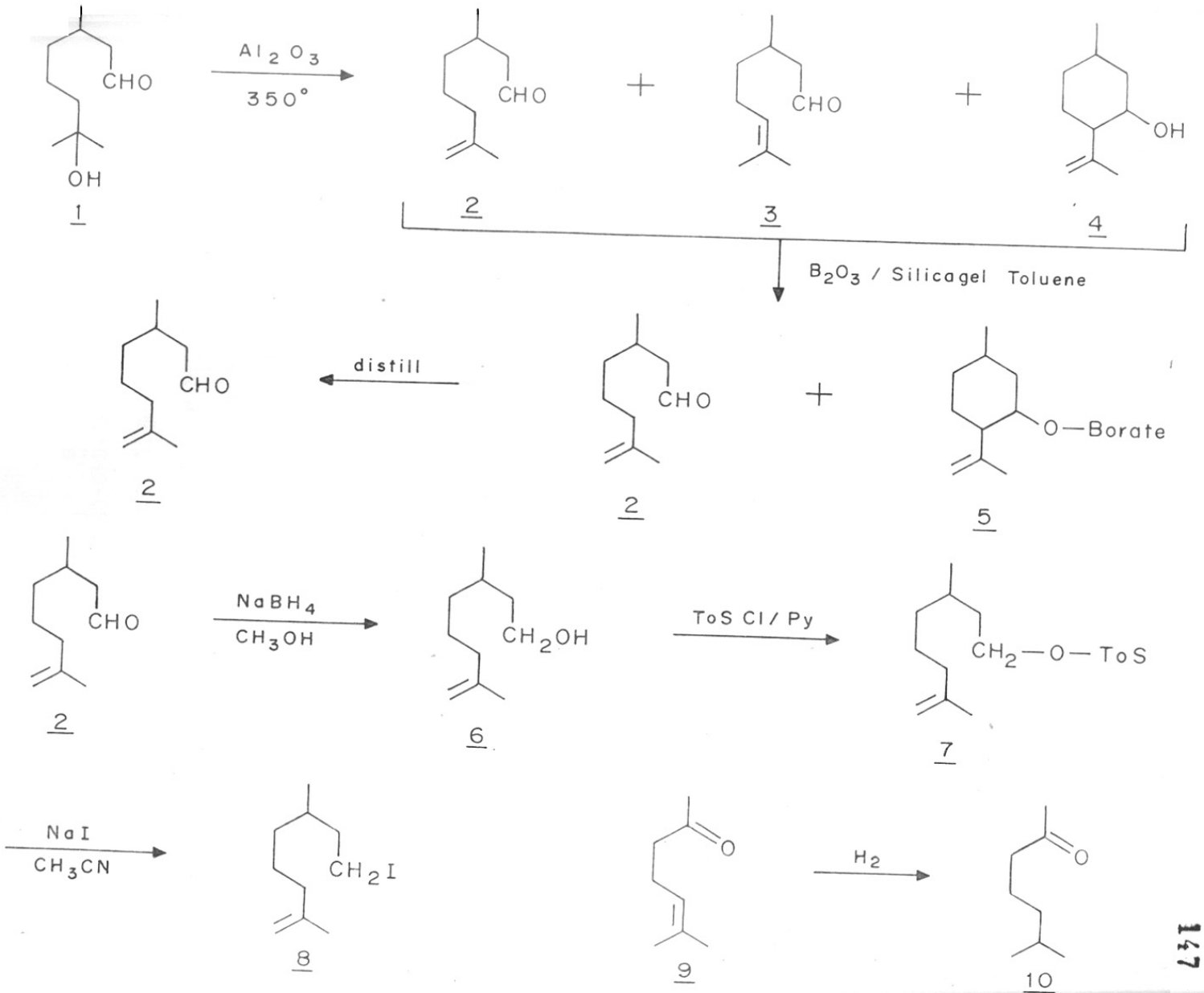
Methods reported in literature for the synthesis of norphytene include either a Grignard reaction[3] or a Wittig reaction[4] on phytone.

Rhodinal (2) was chosen as the starting material as it possesses the exomethylene moiety present in norphytene. Earlier norphytene was prepared in this laboratory using enamine[5], meldrums acid[6] and TosMIC[7].

PRESENT INVESTIGATION

Norphytene (15) used in the synthesis of phytol isomers was prepared using ethylcyanoacetate, methylheptanone (10) and rhodinyl iodide (8) (Scheme 2). Rhodinal (2) was prepared by pyrolysis of 7-hydroxycitronellal (1) over neutral alumina according to the literature procedure[8]. The pyrolysed product which contained about 75% rhodinal and 25% mixture of citronellal (3) and isopulegol (4) was mixed with freshly activated boricanhydride and silica gel and was refluxed in toluene, using Dean-Stark apparatus to remove water. In such acidic media, citronellal gets cyclized to isopulegol which in turn reacts with boric anhydride to furnish isopulegol borate (5). Rhodinal was then easily distilled off from the mixture by fractional distillation (Scheme 1). The rhodinal thus obtained had b.p. 60°/2 mm, purity 99% VPC (column FFAP 70°). Semicarbazone m.p. 72-73°C (lit. m.p. 72-73°). Rhodinal analysed for $C_{10}H_{18}O$: m/z 154 (M^+). Its IR spectrum exhibited bands at 1724 (s) and 2820 (w) cm^{-1} assignable to aldehyde group: 1639(w) and 890(s) cm^{-1} assignable to exomethylene group. Its PMR (CCl_4) spectrum displayed signals at δ 1.0 (d, 3H, $-\dot{C}H\underline{C}H_3$, J=6 Hz) 1.76 (s, 3H, $\rangle\!-\underline{C}H_3$), 4.76 (s, 2H, $\rangle\!=\underline{C}H_2$), and 9.86 (t, 1H aldehydic proton). This spectral data is in agreement with the structure of rhodinal.

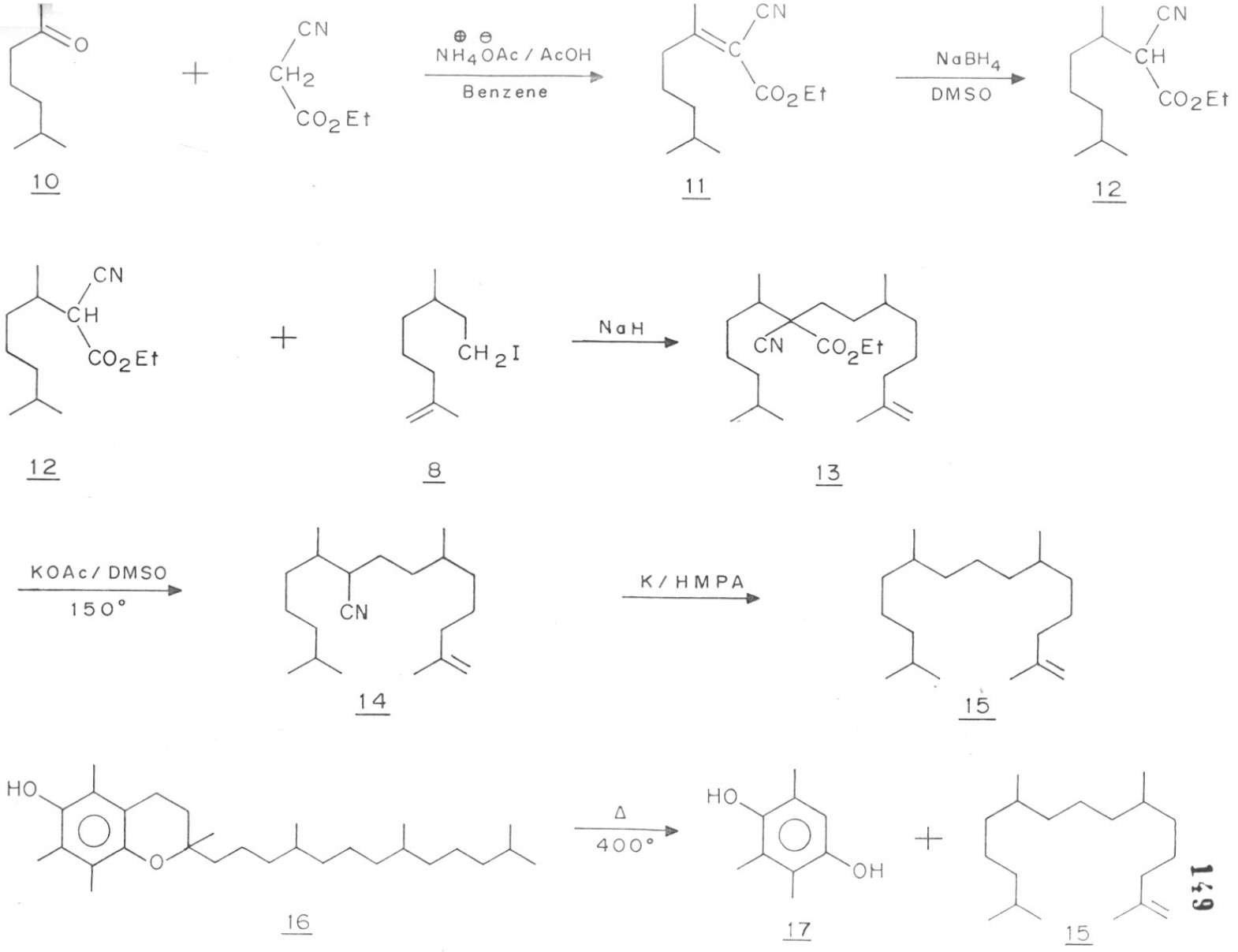
The residue after distillation (isopulegol borate) was decomposed with water to ispulegol, from which citronellic


CHO
OH
1
Al_2O_3
350°
CHO
CHO
OH
2
3
4
B_2O_3 / Silicagel Toluene
distill
CHO
2
CHO
2
O—Borate
5
CHO
2
$NaBH_4$
CH_3OH
CH_2OH
6
ToS Cl / Py
CH_2—O—ToS
7
NaI
CH_3CN
CH_2I
8
O
9
H_2
O
10

acid and other monoterpene units can be obtained after suitable transformations.

Rhodinal (2) was reduced to rhodinol (6) by sodium-borohydride in methanol in quantitative yields b.p. 70-73°/2 mm (lit. 79°/1 mm[9]). The alcohol was tosylated using p-toluene sulphonyl chloride in pyridine. The tosylate (7) was characterized by its PMR (experimental part). It was then converted to 3,7-dimethyl-7-octenyliodide (8) by refluxing it with sodium iodide in acetone in about 85% yield. The purification was achieved by column chromatography on neutral alumina followed by distillation b.p. 112-14°/10 mm. Its PMR spectrum showed signals at δ 0.86 (d, 3H, $-\underline{C}H-C\underline{H}_3$, J=6 Hz) 1.69 (s, 3H, $\rangle\!\!-C\underline{H}_3$), 3.1 (t, 2H, $-C\underline{H}_2-I$, J=7 Hz), 4.6 (s, 2H $\rangle\!=\!C\underline{H}_2$).

Methylheptenone (9) was hydrogenated to give methyl heptanone (10) in quantitative yields. Methylheptanone (10) was condensed with ethylcyanoacetate as described in Chapter II, Part B. The alkylidine derivative (11) was reduced by sodium borohydride in DMSO to furnish the alkyl derivative (12) in 86% yields. It was characterized by its IR, PMR and Mass spectral data. IR in liquid film showed peaks at 2230 (-CN), 1742 (-COOEt) and its PMR (CCl_4) showed signals at δ 0.85 (d, 6H, 2 $-CH-C\underline{H}_3$, J=6 Hz), 1.07 (dd, 3H, $-CH-C\underline{H}_3$, J=6 Hz), 1.3 (t, 3H, $C\underline{H}_3CH_2$, J=7 Hz), 3.45 (dd, 1H, $-C\underline{H}\langle^{CN}_{CO_2Et}$, J=5 Hz diastereomers) 4.2 (q, 2H, $-\underset{O}{\overset{}{C}}-O-C\underline{H}_2CH_3$, J=7 Hz).



10 11 12

12 8 13

14 15

16 17 15

The alkylethylcyanoacetate (17) was alkylated with rhodinyliodide (8) using sodium hydride in benzene and HMPA. The product 2,6,10,14-tetramethyl-9-cyano-9-carbethoxypentadec-1-ene (13) was purified by column chromatography on neutral alumina in 77% yield. The unreacted starting materials were recovered during chromatography. The IR spectrum of (13) showed (-CN) at 2230, (-COOEt) at 1742, and exomethylene at 885 and 1648 cm^{-1}. PMR (CCl_4) showed signals at δ 0.84 (d, 9H, 3 $C\underline{H}_3$-CH-, J=6 Hz), 1.04 (d, 3H, $C\underline{H}_3$-CH-, J=6 Hz) 1.3 (t, 3H, $C\underline{H}_3$-$C\underline{H}_2$, J=7 Hz), 4.25 (q, 2H, $C\underline{H}_2$-$C\underline{H}_3$, J=7 Hz) 4.6 (s, 2H, CH_2=<).

The dialkylated ethylcyanoacetate (13) was decarboethoxylated using potassium acetate in DMSO[10] and the cyano group was removed by potassium in HMPA and t-BuOH[4] following the procedure described in the earlier chapter. The norphytene (15) obtained was characterized by its IR, PMR and Mass spectra. IR (liquid film) showed exomethylene at 890 and 1640 cm^{-1} and PMR (CCl_4) δ : 0.80 (d, 4 -CH-$C\underline{H}_3$, 12H, J=6 Hz), 1.66 (s, 3H, >—$C\underline{H}_3$), 4.6 (s, >=$C\underline{H}_2$ 2H) b.p. 128-130°(bath)/1 mm. Mass showed M^+ (m/e) 266. For an authentic sample[3] of norphytene, dl-α-tocopherol (16) was pyrolysed by passing over a column of alumina at 400°C. The crude product contained a mixture of norphytene (15) and duroquinone (17). This was purified by column chromatography on alumina (Gr.I). The spectral properties of this authentic norphytene were in good agreement with the hydrocarbon obtained from the cyano compound (27).

EXPERIMENTAL

Rhodinal (2)

Freshly distilled 7-hydroxycitronellal (1, 42.0 g) was introduced at a rate of 100 ml per hour at 350° into a borosilicate glass column (100 cm long and 25 mm in diameter) containing 200 g of alumina (Gr.I) under the influence of vacuum (60 mm). The reaction product (37 g) was separated from water (3.5 ml) and distilled in vacuo and the fraction boiling at 55-60°/0.55 mm was collected (22.3 g). The distillate had a mixture of rhodinal (2), citronellal (3) and isopulegol (4). The residue contained mainly unreacted hydroxycitronellal (17).

The distillate (22.3 g) was mixed with 1.6 g of boric anhydride, 0.5 g of silica gel, 300 ml of anhydrous toluene and refluxed with Dean-Stark trap. After about an hour, when no more water separated, the solvent was removed in vacuo. Pure rhodinal was then distilled from the residual isopulegol borate (5) in 95% yield (16.80 g), b.p. 60°/2 mm Semicarbazone m.p. 72-73° (EtOH). Purity 99% by VPC (FFAP, 80°); IR (liquid film): bands at 1724, 2820 (aldehyde $-\overset{O}{\overset{\|}{C}}-H$), 1639 and 890 cm^{-1} (exomethylene). PMR (CCl_4) δ : 1.0 (d, 3H, $\underline{CH}_3-\overset{|}{C}H-$, J=6 Hz) 1.76 (s, 3H, $\diagup\!\!=\!\!\underline{CH}_3$), 4.76 (bs, 2H, $\diagup\!\!=\!\!\underline{CH}_2$) and 9.86 (t, 1H, $-\underset{H}{\underline{C}}=O$). Mass: m/z 154 ($M^+$).

Rhodinol (6)

To a stirred solution of rhodinal (2, 10.0 g) in methanol

sodium borohydride (1.00 g) was added in small portions (0.5 hr). The reaction mixture was stirred for 4 hrs, poured in water, acidified by CH_3COOH and extracted by ether (3 x 100 ml). Ether layer was washed with water and dried. Evaporation of the solvent, followed by distillation furnished pure rhodinol. Yield 9.730 g, 95.7%. b.p. 110°/10 mm (lit. b.p. 79°/1.7 mm). GLC analysis: 98.5% purity (ov 101, 120°). IR (liquid film): 3340 (-OH), 1640, 885 cm^{-1} exomethylene. PMR (CCl_4) δ : 0.9 (d, 3H, $C\underline{H}_3$-CH-, J=6 Hz), 1.7 (s, 3H, $>C(CH_3)-C\underline{H}_3$), 2.65 (bs, 1H, CH_2OH, exchangeable with D_2O), 3.56 (t, 2H, $-C\underline{H}_2$-OH) and 4.62 (s, 2H, $>C=C\underline{H}_2$).

Rhodinyl tosylate (7)

To an ice-cold mixture of rhodinol (6, 9.7 g) and pyridine (100 ml), freshly crystallised p-toluenesulfonylchloride (30 g) was added with stirring, and allowed to stand overnight at 5°C. The reaction mixture was poured on ice and extracted with ether (3 x 50 ml). Organic layer was washed thoroughly with water, dried and solvent evaporated to furnish the pure tosylate. Yield 14.39 g (75%). The IR spectrum showed bands at 1640, 885 (exomethylene) and 1350, 1175 cm^{-1} ($-SO_2$). PMR (CCl_4) δ : 0.85 (d, 3H, $C\underline{H}_3$-CH- J=6 Hz), 1.7 (s, 3H, $>C(CH_3)-C\underline{H}_3$), 4.05 (t, 2H, $-C\underline{H}_2$-O Tos), 4.66 (s, 2H, $>C=C\underline{H}_2$) and 7.4, 7.7 (2d, 4H, aromatic protons, J=8 Hz). 2.5 (s, 3H, Ar-$C\underline{H}_3$).

Rhodinyl Iodide (8)

A mixture of rhodinyl tosylate (7, 14.4 g), dry acetone

(100 ml) and dry sodium iodide (12 g) was refluxed for 4 hrs. Most of the acetone was distilled off and the residue poured in water (100 ml). Extracted with ether (4 x 50 ml), the extract was washed with 10% aqueous $Na_2S_2O_3$ (2 x 25 ml), brine and dried. The solvent was distilled and the residue passed on alumina (Gr.I) and eluted with pet. ether. It was then distilled b.p. 112-114°/10 mm. Yield 10.5 g, 85%. IR (liquid film): 1640, 855 cm^{-1} (exomethylene). PMR (CCl_4) δ: 0.86 (d, 3H, $\underline{CH_3}$-CH-, J=6 Hz), 1.69 (s, 3H, ), 3.1 (t, 2H, -$\underline{CH_2}$-I, J=7 Hz), 4.6 (s, 2H, ).

Analysis: Found: C, 45.32; H, 7.23.

$C_{10}H_{19}I$ requires: C, 45.11; H, 7.14%.

Methylheptanone (10)

Methylheptenone (9, 21 g) 10% palladised charcoal (0.200 g) and ethanol 50 ml was hydrogenated at 3 atmosphere using Parr hydrogenation apparatus. When absorption of hydrogen ceased, the reaction was stopped, catalyst filtered out. Evaporation of the solvent followed by distillation gave pure methylheptanone (10). Yield, 18.5 g (90%) b.p. 78-80°/20 mm (lit. 34-35°/2 mm) M^+ 128. IR (liquid film): 1720 cm^{-1} (>C=O). PMR (CCl_4) δ: 0.88 (d, 6H, $\underline{CH_3}$-CH-, J=6 Hz), 2.03 (s, 3H, -C(=O)-$\underline{CH_3}$), 2.3 (m, 2H, -$\underline{CH_2}$-$COCH_3$).

3,7-Dimethyl-2-cyanooct-2-enoic acid ethyl ester (11)

Procedure followed was same as used for 3,7-dimethyl-2-cyanooct-2,6-dienoic acid ethyl ester (2, Chapter II, Part B).

Quantities taken:

Methylheptanone (10)	..	6.4 g
Ethylcyanoacetate	..	5.5 g
Ammonium acetate	..	0.500 g
Acetic acid	..	1.5 ml
Benzene	..	150 ml

Weight of alkylidine derivative obtained .. 8.230 g

Yield, 74%, b.p. 113-115°/1.5 mm.

IR (liquid film): 2230 (CN), 1742 cm^{-1} (-COOEt).

PMR (CCl_4) δ : 0.91 (d, 6H, 2 $\underline{CH_3}$-$\dot{C}$H-, J=6 Hz), 1.36 (t, 3H, $\underline{CH_3}$-$\dot{C}H_2$, J=7 Hz), 2.26, 2.36 (2s, 3H, $\underline{CH_3}$-$\dot{C}$-, E & Z isomer), 4.25 (t, 2H, -$\underline{CH_2}$-$\dot{C}H_3$, J=7 Hz).

3,7-Dimethyl-2-cyanooctanoic acid ethyl ester (12)

Procedure followed was same as used for 3,7-dimethyl-2-cyanooct-6-enoic acid ethyl ester (3, Chapter II,Part B).

Quantities:

Alkylidine ethylcyanoacetate (11)	..	6.0 g
$NaBH_4$	..	0.600 g
DMSO	..	25 ml

Weight of (12) obtained .. 5.205 g. Yield .. 86%.

IR (liquid film): 2230 (-CN), 1760 (-COOEt) cm^{-1}.

PMR (CCl_4) δ: 0.85 (d, 6H, 2 $\underline{CH_3}$-$\dot{C}$H-, J=6 Hz), 1.05, 1.1 (d, 3H, $\underline{CH_3}$-$\dot{C}$H-, J=6 Hz diastereomers), 1.3 (t, 3H, $\underline{CH_3}$-CH_2, J=7 Hz), 3.4 (dd, 1H, -$\underline{CH}$<$^{CN}_{CO_2Et}$, J=5 Hz), 4.2 (q, 2H, -$\underline{CH_2}$-CH_3, J=7 Hz).

2,6,10,14-Tetramethyl-9-cyano-9-carbethoxypentadec-1-ene (13)

Procedure followed was same as used for alkylation of (3, Chapter II, Part B).

Quantities taken:

Alkylethylcyanoacetate (12)	..	0.900 g
Rhodinyl iodide (8)	..	1.064 g
NaH	..	0.100 g
Bz/HMPA	..	20 ml/2 ml

Weight of dialkylated product (13) .. 1.129 g, yield 77%.

IR (liquid film): 2230 (-CN), 1742 ($-CO_2Et$), 885, 1648 (exomethylene) cm^{-1}.

PMR (CCl_4) δ: 0.83 (d, 9H, 3 $\underline{CH_3}$-CH-, J=6 Hz), 1.05 (d, 3H, $\underline{CH_3}$-CH-, J=6 Hz), 1.3 (t, 3H, $\underline{CH_3}$-CH_2, J=7 Hz), 1.68 (s, 3H, $\underline{CH_3}$), 4.25 (q, 2H, -$\underline{CH_2}$-CH_3, J=7 Hz), 4.6 (bs, 2H, $=\underline{CH_2}$).

Mass spectrum: M^+ 363.

2,6,10,14-Tetramethyl-9-cyanopentadec-1-ene (14)
Decarboethoxylation of 13

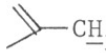
Procedure followed was same as used for (19, Chapter II, Part B).

Quantities:

Dialkylated product (13)	..	0.500 g
$K^+\bar{O}Ac$	..	0.150 g
DMSO	..	5 ml
Water	..	4 drops

Weight of cyano compound (14) obtained .. 0.383 g, yield 95%.

IR (liquid film): 2223 (-CN), 885 and 1645 cm^{-1} (exomethylene).

PMR (CCl_4) δ: 0.83 (d, 9H, 3 $\underline{CH_3}$-CH-, J=6 Hz), 1.0 (d, 3H, $\underline{CH_3}$-CH-, J=6 Hz), 1.68 (s, 3H, ), 2.43 (m, 1H, -$\underline{CH}$-CN), 4.6 (bs, 2H, ).

2,6,10,14-Tetramethylpentadec-1-ene (Norphytene) (15)

Procedure same as used for (20, Chapter II, Part B).

Quantities:

Cyanocompound (14)	..	0.100 g
K 2 g equivalents	..	0.023 g
HMPA	..	1 ml
^{t}BuOH	..	2 drops

Weight of the hydrocarbon (Norphytene 15) obtained 0.058 g and 0.025 g cyanocompound recovered. Yield, 64%. Yield based on recovery of cyanocompound 85%. M^+ - 266, b.p.128-130° (bath)/1 mm.

IR(liquid film) : 1640, 890 () cm^{-1}.

PMR (CCl_4) δ: 0.80 (d, 12H, 4 $\underline{CH_3}$-CH-, J=6 Hz), 1.66 (s, 3H, $\underline{CH_3}$), 4.6 (bs, 2H, ).

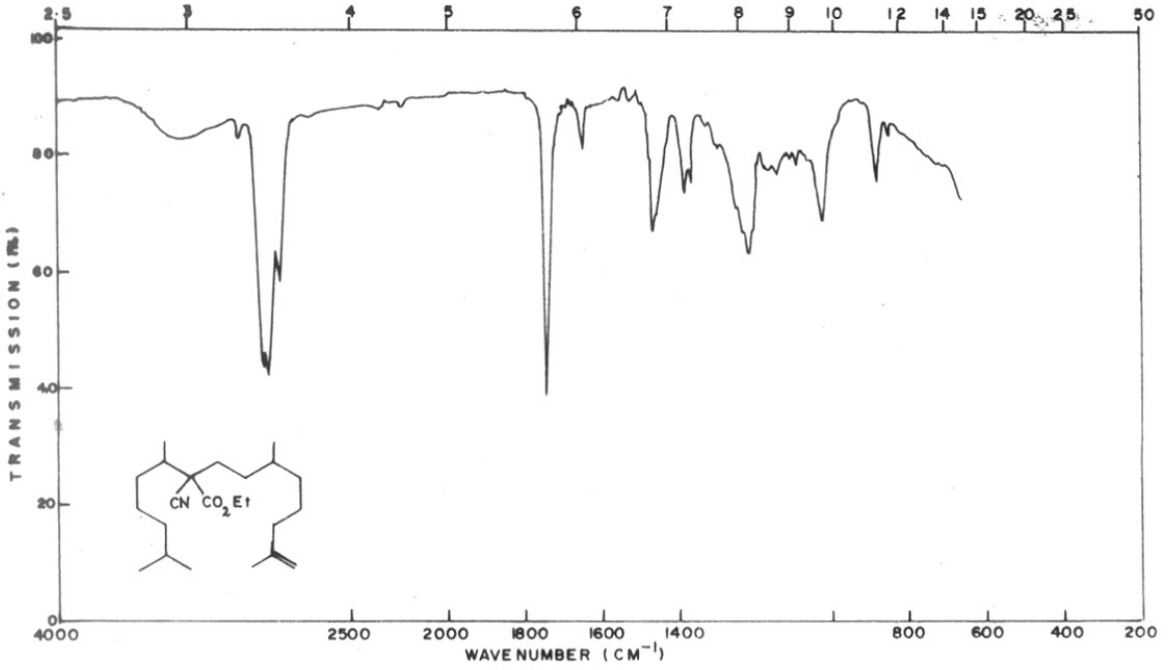


FIG 3.1, 2,6,10,14 -TETRAMETHYL-9-CYANO-9-CARBETHOXY PENTADEC-1-ENE (13)

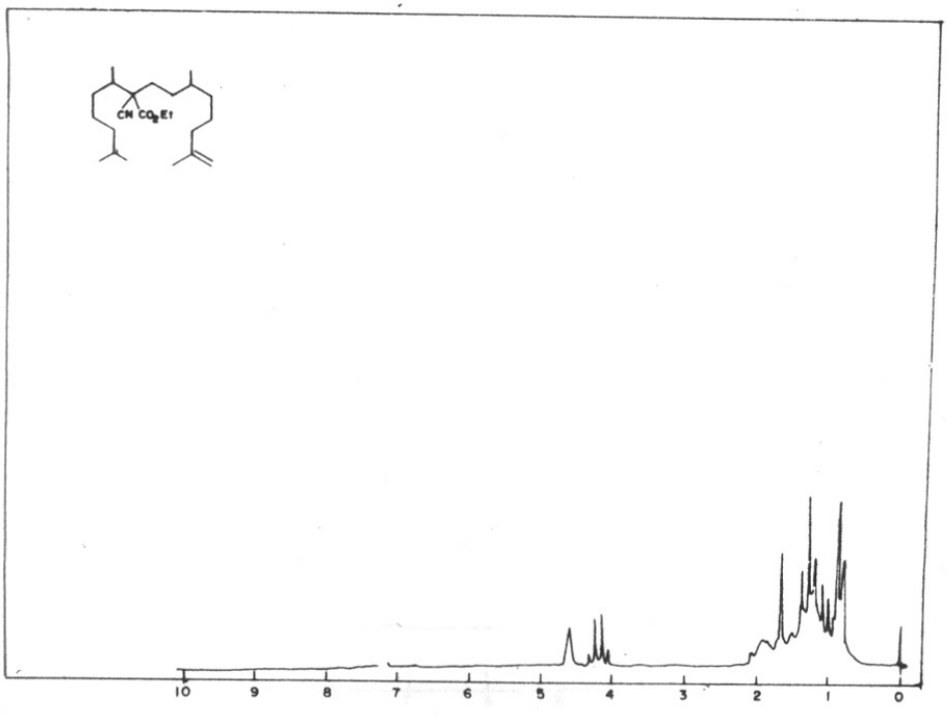


FIG 3.2, 2,6,10,14-TETRAMETHYL-9-CYANO-9-CARBETHOXYPENTADEC-1-ENE (13)

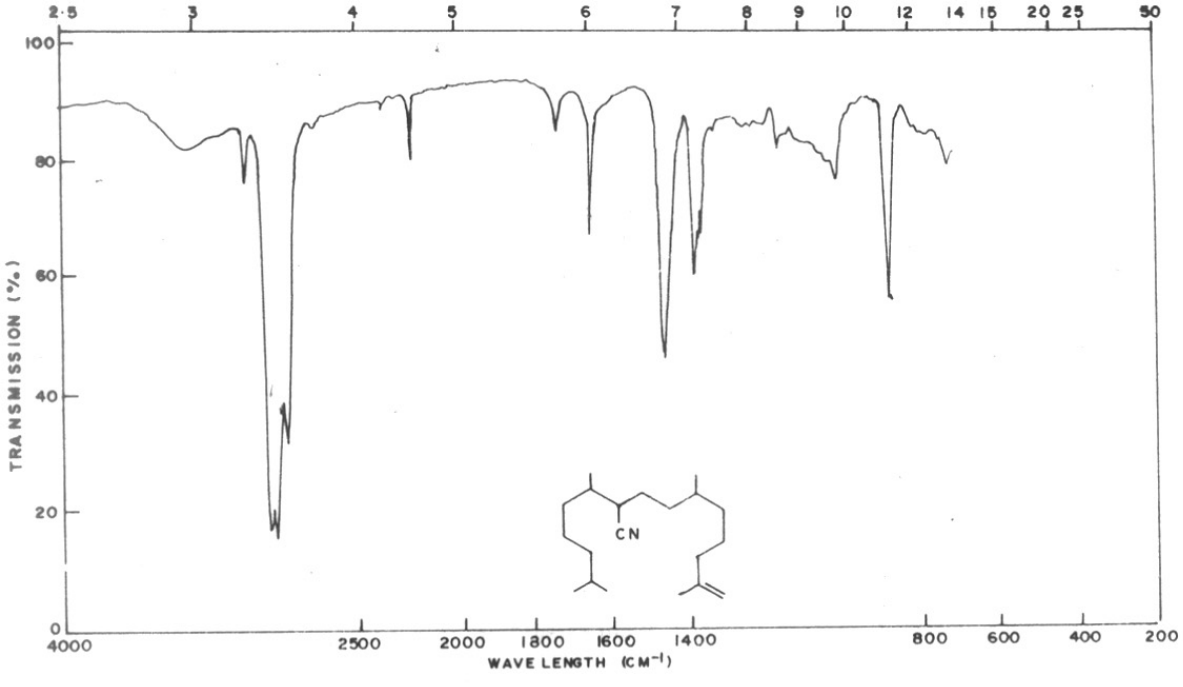


FIG 3·3, 2,6,10,14-TETRAMETHYL-9-CYANOPENTADEC-1-ENE (14)

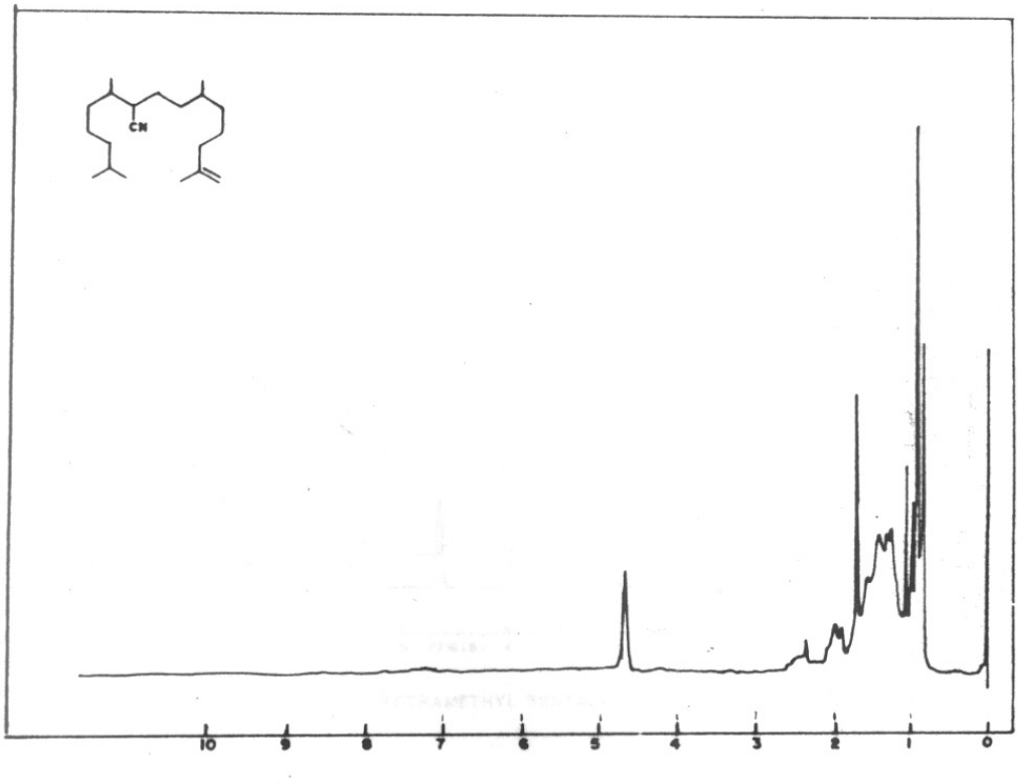


FIG 3·4, 2,6,10,14-TETRAMETHYL-9-CYANOPENTADEC-1-ENE (14)

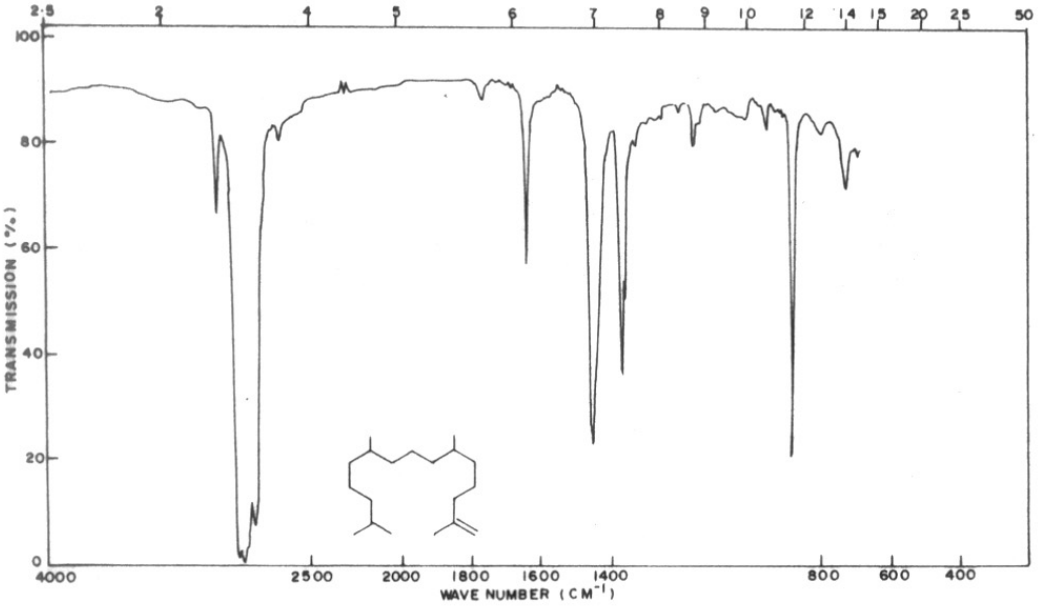


FIG3.5, 2,6,10,14-TETRAMETHYL PENTADEC-1-ENE (15)

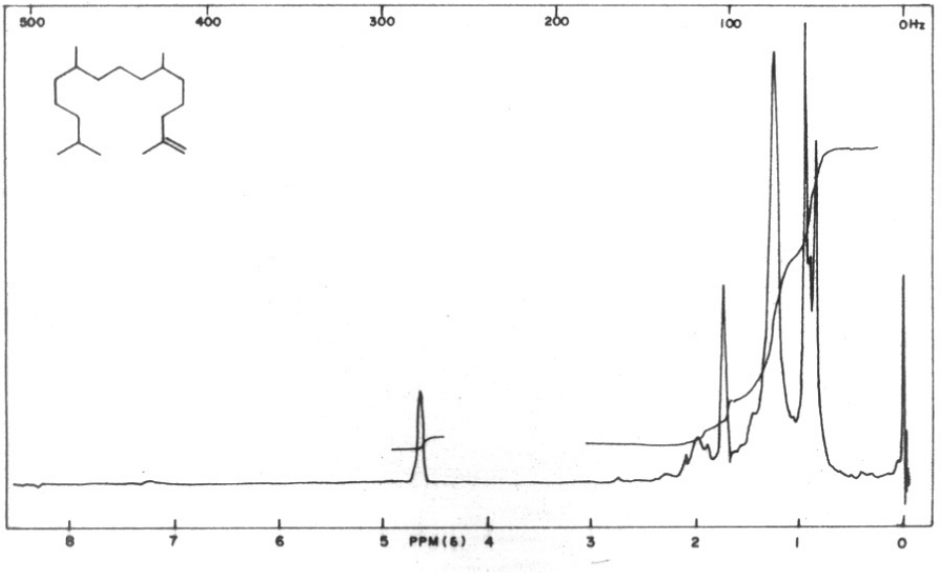
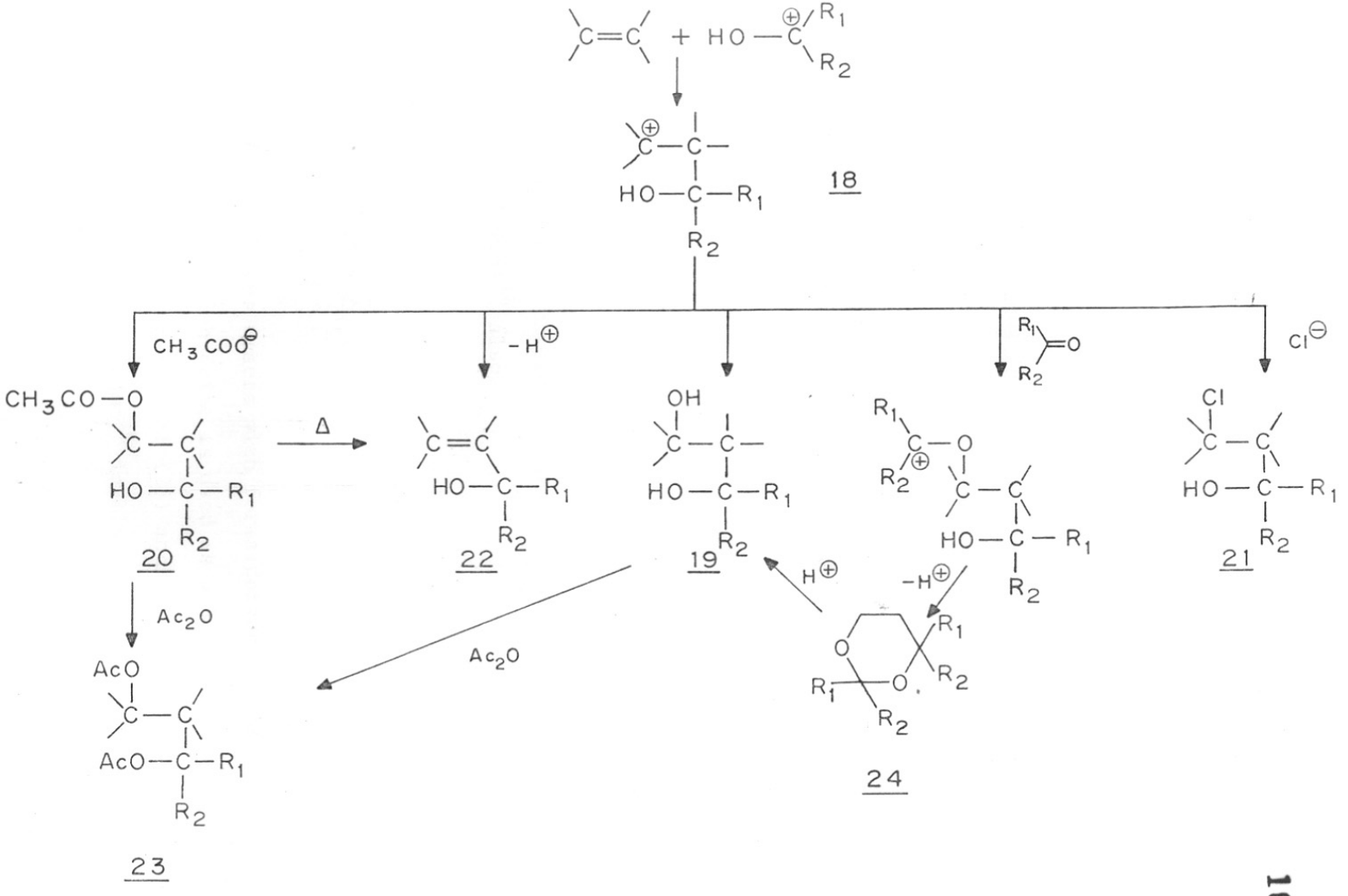


FIG3.6, 2,6,10,14-TETRAMETHYL PENTADEC-1-ENE (15)

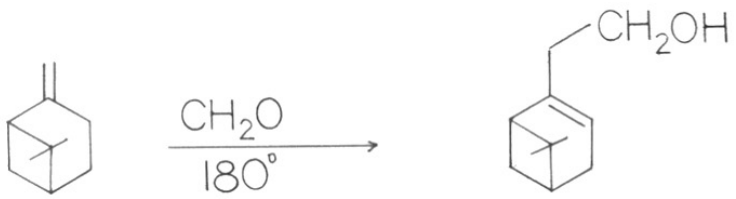
CHAPTER-III

PART B

NTHESIS OF PHYTOL ISOMERS AND THEIR CONDENSATION WITH TRIMETHYL HYDROQUINONE

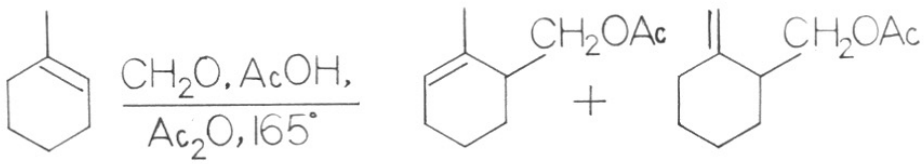

+
18
$CH_3COO^{\ominus}$
$-H^{\oplus}$
$Cl^{\ominus}$
Δ
20
22
19
21
Ac_2O
Ac_2O
$H^{\oplus}$
$-H^{\oplus}$
23
24

acetate to give monoacetate monoalcohol (20) with chloride to give chloroalcohol (21) with one more molecule of aldehyde to give dioxane (24) or lose a proton to give an allylic alcohol(22). The 'ene' reaction is usually considered to be a concerted process and is the indirect substituting addition of a compound with a double bond (enophile) to an olefin possessing an allylic hydrogen (ene). It involves the allylic shift of one double bond, transfer of the allylic hydrogen to the enophile, and bonding of the two terminii. For example,



25 26

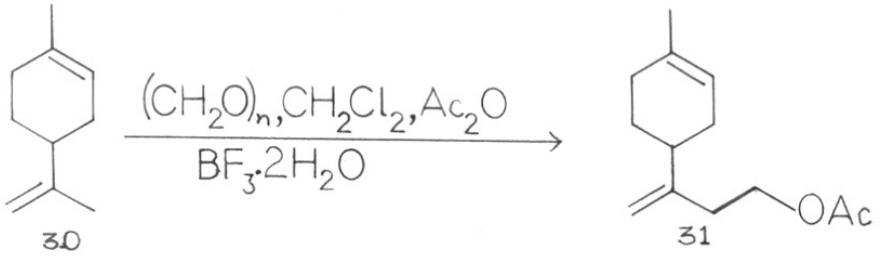
β-pinene (25) with paraformaldehyde in the absence of catalyst to give nopol (26)[14] also



27 28 29

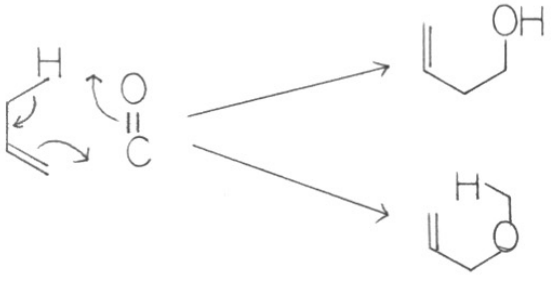
1-methyl cyclohexene reacts with formaldehyde at 165°C when acetic acid-acetic anhydride is used as a solvent, to give an approximately equal mixture of (28) and (29)[15]. Another improved method by Blomquist[16] involves treatment of formaldehyde

with limonene (30) in solvent CH_2Cl_2/Ac_2O in the presence of $BF_3.2\ H_2O$ gave (31) in 69% yield.



30 31

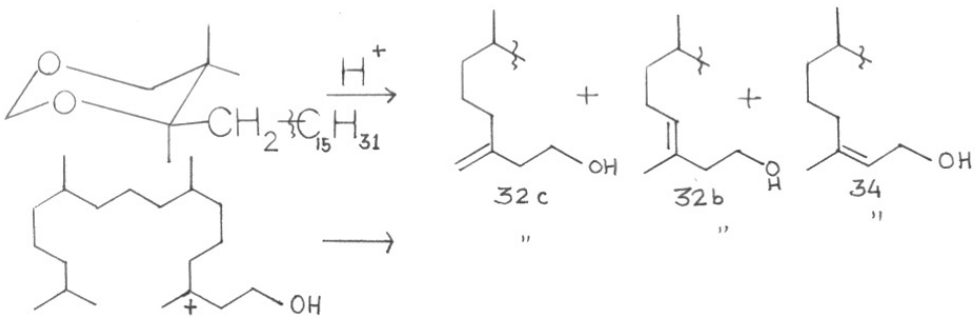
The mechanism for the ene reaction is given below.



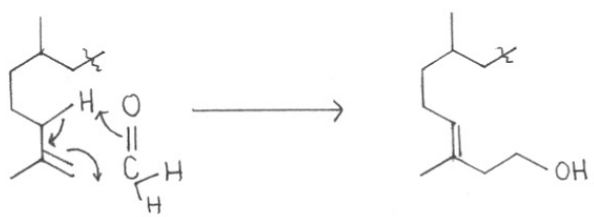
Formation of alcohols rather than the ether when carbonyl compounds are used as eneophiles can be rationalized by the greater gain in bond energy for the observed reaction[17].

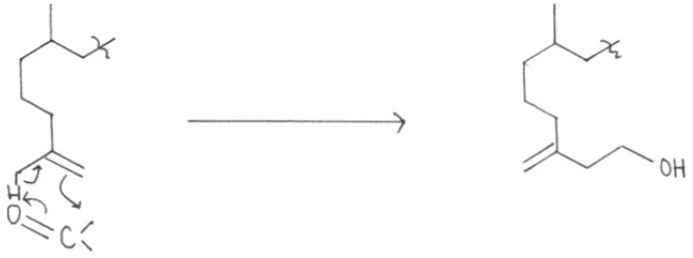
PRESENT INVESTIGATION

Norphytene (28) was prepared with the aim of using it as an intermediate in the synthesis of phytol through the Prins reaction under the influence of acid catalyst. As discussed earlier the reaction may either proceed via the dioxane intermediate, carbonium ion or via the 'ene' reaction. In the dioxane intermediate via the trans elimination all the three isomers should have been isolated. Similar is the case with the carbonium ion intermediate.



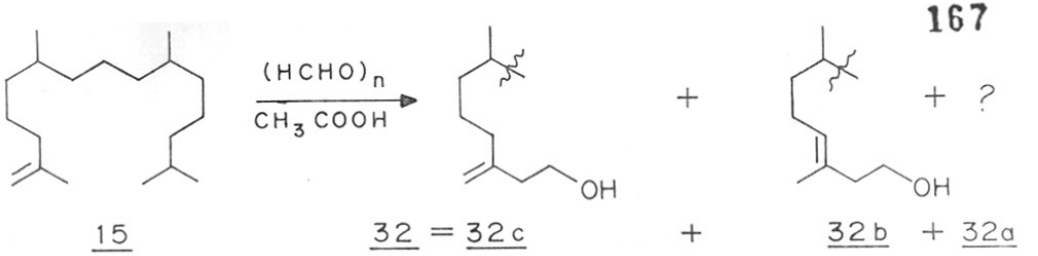
Synthesis of phytol from norphytene has been reported but when the reaction was repeated following the same reaction conditions only the isomers having the exo and endo double bond (homo-allylic alcohol) were obtained with a small quantity of phytol which was detected by NMR in one of the fractions of chromato-graphy. This implies the reaction in following mainly the 'ene' pathway. The mechanism is given below.



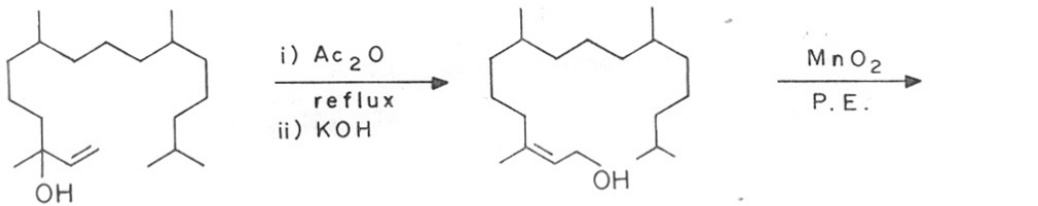


The reaction was carried out as follows, equimolar quantities of norphytene, paraformaldehyde was refluxed in glacial acetic acid for 30 hrs. On work up the acetates of the alcohols (32c), (32b) were obtained with some unreacted norphytene, which was removed by chromatography. The acetates were hydrolysed and the alcohols were obtained in an overall yield of 54%. The PMR of the isomeric alcohols indicate the presence of only homoallylic alcohol. IR (liquid film): 3350 (-OH), 1040, 885 and 1640 (exomethylene). PMR (CCl_4) δ: 0.81 (d, 12H, $C\underline{H}_3$-CH-, J=6 Hz), 1.6, 1.66 (2 bs, methyl on double bond), 3.5 (m, 2H, -$C\underline{H}_2$-OH), 4.7 (bs, $>C=C\underline{H}_2$), 5.18 (m, olefinic proton).

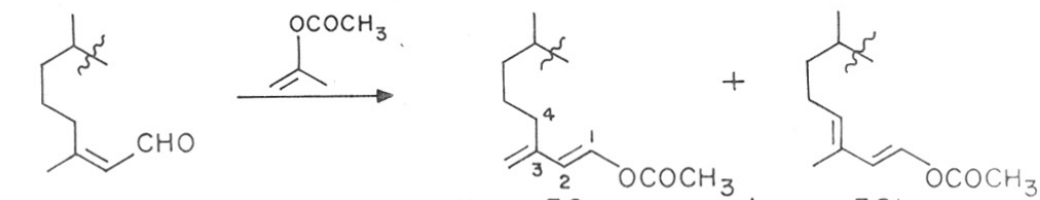
The alcohol mixture was subjected to silvernitrate impregnated silica gel chromatography. The two pure fractions obtained after exhaustive elution with benzene were the two homoallylic alcohols, 3-hexadecen-1-ol, 3,7,11,15-tetramethyl (32b) and naturally occurring hexadecanol-3-methylene-7,11,15-



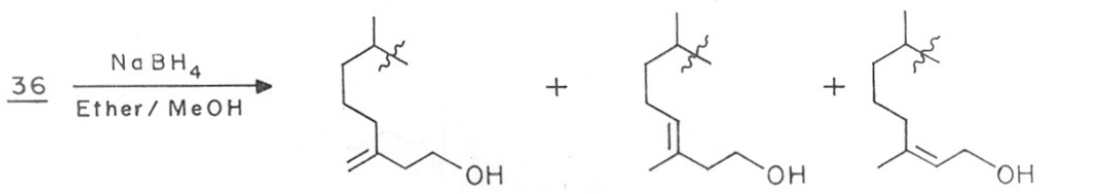
15 32 = 32c + 32b + 32a



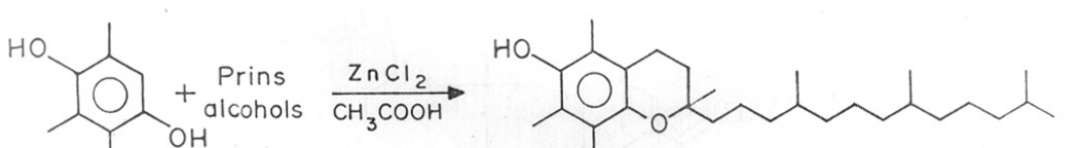
33 34



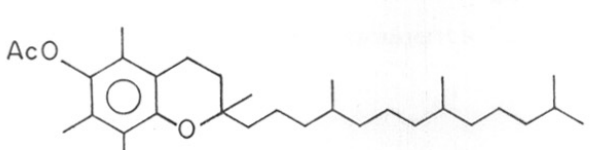
35 36 = 36a + 36b



32c 32b 34

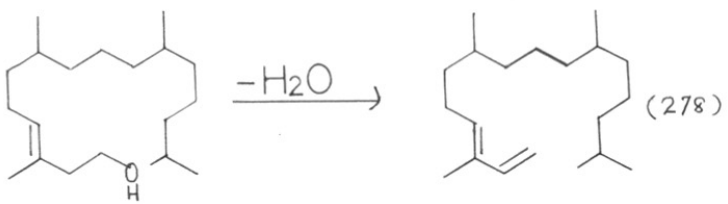


37 32a,b,c 16

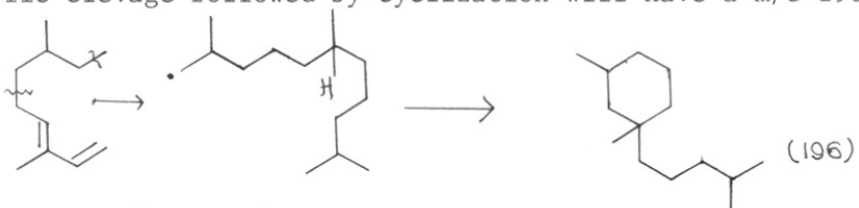


38

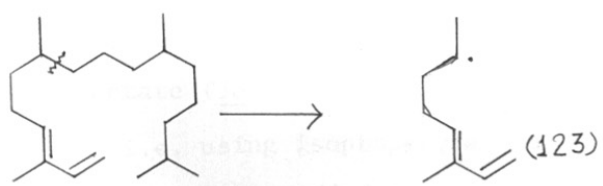
trimethyl (32c)[18]. These alcohols were identified and characterized by their IR, PMR and mass spectra. IR of (32b) showed bands at 3320 (-OH) and 1040 cm^{-1} were the only peaks other than the C-H stretching and bending. PMR (CCl_4) δ: 0.85 (d, 12H, 4 CH_3-CH-, J=6 Hz), 2.18 (t, 2H, allylic CH_2 and β to -OH), 3.6 (t, 2H, -CH_2-OH, J=7 Hz), 5.2 (bt, 1H, olefinic proton). The mass spectrum shows M^+ at 296 and fragments at 278, 196 and 123 (base peak). Dehydration will give rise to a peak at 278 (M-18 (20)).



Allylic clevage followed by cyclization will have a m/e 196.



and

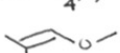


The other isomer (32c) 1-hexadecanol-3-methylene-7,11,15-trimethyl which is a naturally occurring C_{20} alcohol obtained from flue cured tobacco as one of its components. IR (liquid film):

3330 (-OH), 1040, 890 and 1640 (exomethylene). PMR (CCl_4) δ: 0.85 (d, 12H, 4 $\underline{CH_3}$-CH-, J=6 Hz), 2.23 (t, 2H, allylic CH_2 and β- to -OH), 3.63 (t, 2H, $\underline{CH_2}$-OH, J=7 Hz), 4.78 (bs, 2H, $\rangle$=$\underline{CH_2}$). The mass spectrum was exactly identical with the spectrum discussed earlier for (32b) in all respects. Hence it can be said that (32c) is isomerised to (32b) during electron impact and then giving the same fragmentation pattern.

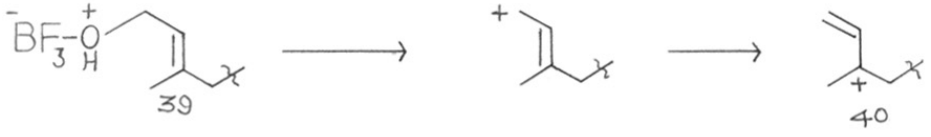
1-Hexadecanol-3-methylene-7,11,15-trimethyl (32c) is a naturally occurring diterpenic alcohol obtained from flue cured tobacco. Its structure was proved unambiguously by its synthesis from authentic phytol (34) obtained from isomerizing isophytol (33) by acetic anhydride[19]. Phytol was oxidized to phytenal (35) using active manganese dioxide[20] in petroleum ether, which gave a cis-trans mixture of phytenal (35) as seen from NMR spectra. A doublet at 0.85 for secondary methyls, 1.96 and 2.13 two singlets for the methyl on double bond (cis & trans), two broad singlets at 5.73 for the α-proton (cis and trans) and two doublets at 9.81 and 9.85 for the aldehydic proton. IR shows conjugated carbonyl at 1673 cm^{-1}.

The enol acetate (36) of phytenal was prepared by using standard method[21] i.e. using isopropenylacetate and p-toluene sulfonic acid. Phytenal was added to a hot mixture of isopropenylacetate, p-toluenesulfonic acid and cupric acetate and the acetone formed was simultaneously distilled off. The reaction product was then chromatographed on grade III alumina

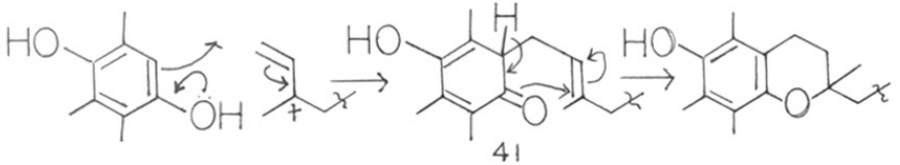
and exhaustively eluted with pet. ether to get enol acetate (33) which was a mixture of (36a) and (36b). It was characterized by its NMR (CCl_4) δ: 0.84 (d, 12H, 4 CH_3-CH-, J=6 Hz), 2.1 (s, 3H, CH_3-C(=O)-), 4.87 (bs, >C=CH_2), 5.3 (m, olefinic proton C4), 5.96 (d, 1H,  , J=12.5 Hz), 6.34 (d, 1H,  , J=12.5 Hz).

The enol acetate of phytenal (36) was then treated with $NaBH_4$, according to the literature procedure[21] used to prepare isocitral from citral. This gave a mixture of 1-hexadecanol-3-methylene-7,10,14-trimethyl (32c), 3-hexadecen-1-ol-3,7,10,14-tetramethyl (32b) and starting phytol (34) which were separated on silvernitrate impregnated silica gel to get the three isomers in pure form. These were compared with the homoallylic alcohols obtained from Prins reaction and they were found to be identical.

Phytol, isophytol has been condensed with trimethylhydroquinone (37) using many Lewis acids like zinc chloride in acetic acid, borontrifluoride etherate and others. The mechanism proposed is described below:

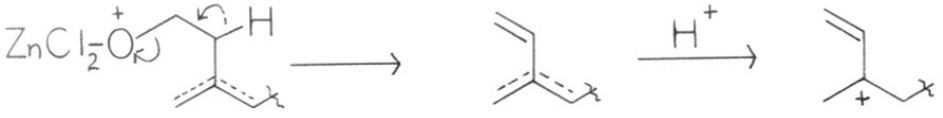


39 40



41

In order to establish whether the mixture of alcohols obtained from Prins reaction can be used for vitamin E preparation, the alcohol mixture (32) was treated with trimethyl hydroquinone (37) using standard reaction condition i.e. $ZnCl_2$ in acetic acid[22]. The reaction mixture was refluxed with stirring for 20 hrs and on work up a red oil was obtained whose R_f value was same as that of authentic vitamin E (16). The IR and NMR were superimposable. The mechanism suggested is similar to the one given above.



The NMR showed a doublet at 0.85 for all the secondary methyls and a broad singlet observed at 2.0 was due to all the aromatic methyls. IR showed -OH at 3455 cm^{-1} and other peaks at 1460 cm^{-1}.

The acetate of Vitamin E (38) was prepared using usual methods and then purified by column chromatography. The PMR of acetate showed all the aromatic methyl and -CO-CH_3 separately at 1.93, 2.0, 2.1, 2.2 and secondary methyls at 0.85 as a doublet J=6 Hz and IR (liquid film): 1718 (-OC-CH_3) and 1210 cm^{-1}. Vit.E acetate was identical in all respects with Vit.E acetate obtained commercially.

EXPERIMENTAL

Prins reaction on norphytene (28)

Norphytene (28, 1.9 g), paraformaldehyde (0.300 g) and acetic acid (25 ml) was refluxed for 30 hrs. The reaction mixture was then poured in water and extracted with ether (3 x 50 ml). Ether layer was washed with water and 10% $NaHCO_3$, water, dried. After evaporation of solvent the residue showed presence of starting norphytene which separated by column chromatography on alumina (Gr.II). The second spot corresponding to the product was then refluxed with aqueous alcoholic 10% KOH. After usual work up the alcohols were obtained in 1.3 g 54.6% yield. Silvernitrate impregnated silica gel TLC showed three spots which were separated by elaborate column chromatography using 15% silvernitrate impregnated silica gel. The column was eluted exhaustively with benzene. 15 ml fraction were collected and their TLC was compared with the TLC of the alcohol mixture.

Fraction No.	Eluant	
3,4,5	Benzene	mixture
8 - 20	Benzene	29b
22 - 26	Benzene + 5% EtOAc	29c

The first spot obtained could not be characterized by its IR, PMR and mass though it contained very small amounts of phytol as seen from the PMR of the first fraction. Phytol was identified by a broad doublet for CH_2 which is allylic and also adjacent

to the hydroxy group, which appears at 4.03 . The second spot corresponds to 3,7,11,15-tetramethylhexadec-3-en-1-ol (29b). IR (liquid film): 3320 (-OH), 1040 cm^{-1}, M^+ 296. PMR (CCl_4) δ: 0.85 (d, 12H, 4 $\underline{CH_3}$-CH-, J=6 Hz), 2.18 (t, 2H, allylic CH_2 and β to -OH), 3.6 (t, 2H, -$\underline{CH_2}$-OH, J=7 Hz), 5.2 (bt, 1H, olefinic proton), 1.6 (s, 3H, CH_3).

The third spot which was the most polar corresponds to the naturally occurring homoallylic alcohol 7,11,15-trimethyl-3-methylenehexadecanol (29c). IR (liquid film): 3320 (-OH), 1635, 883 (exomethylene), 1040 cm^{-1}. PMR (CCl_4) δ: 0.85 (d, 12H, 4 $\underline{CH_3}$-CH-, J=6 Hz), 2.23 (t, 2H, allylic CH_2 and β to -OH), 3.63 (t, 2H, -$\underline{CH_2}$OH, J=7 Hz), 4.78 (s, 2H, $\rangle=\underline{CH_2}$). Mass spectra showed both homoallylic alcohols were identical. M^+ 296 M-18 = 278 ($-H_2O$) m/z 196, 123.

Isomerization of isophytol to phytol (Authentic phytol) (34).

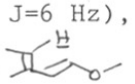
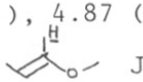
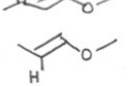
A mixture of acetic anhydride (2.0 g) and isophytol (5.0 g) was refluxed for 17 hrs. It was then cooled and poured in water. Extracted with ether (3 x 50 ml), drying and evaporation of solvent furnished a mixture of phytoacetate and phytadienes. They were separated by column chromatography on silica gel. Phytolacetate was hydrolysed by aqueous alcoholic potash. After usual work up 2.2 g of phytol was obtained. Yield 44% , b.p. 180-85°(bath)/1 mm. IR (liquid film): 3340 (-OH) cm^{-1}. PMR(CCl_4):δ 0.85 (d, 12H, 4 $\underline{CH_3}$-CH-, J=6 Hz), 1.66 (s, 3H, $\rangle-\underline{CH_3}$), 4.03

(bd, 2H, $C\underline{H}_2$-OH), 5.3 (bt, 1H, olefinic proton).

Phytenal (35)

Phytol (34), 8.5 g was taken in dry petroleum ether (250 ml) and activated manganesedioxide (60 g) was added in portion (0.5 hr) with vigorous stirring. The reaction was monitored by TLC, the reaction was complete in 4 hrs. MnO_2 was filtered and the filterate concentrated to furnish phytenal 8.3 g. Yield 98%, b.p. 158-61°/1 mm. IR (liquid film): 1673 (-$\overset{O}{\overset{\|}{C}}$H) cm^{-1}. PMR(CCl_4) δ: 0.85 (d, 12H, 4, $C\underline{H}_3$-$\overset{'}{C}$H-, J=6 Hz), 1.96, 2.13 (2s, methyl on double bond, E & Z isomers), 5.66, 5.8 (2bs, olefinic proton), 9.81, 9.85 (2d, 1H, =CH-$\overset{O}{\overset{\|}{C}}$-$\underline{H}$, J=7 Hz, E & Z isomers).

Enolacetate of phytenal

Phytenal (35, 6.0 g) was added to a hot mixture of isopropenylacetate (20 ml), p-toluene sulfonic acid (0.100 g) and cupricacetate (0.100 g). The acetone formed was distilled out simultaneously. Excess isopropenyl acetate was removed and the residue chromatographed on alumina (Gr.II) and exhaustively eluted with pet.ether. Weight of pure enolacetate obtained was 2.73 g, yield 40%. PMR (CCl_4) δ: 0.84 (d, 12H, 4 $C\underline{H}_3$-$\overset{'}{C}$H-, J=6 Hz), 2.1 (s, 3H, $C\underline{H}_3$-$\overset{O}{\overset{\|}{C}}$-), 4.87 (bs, 1H, $\rangle{=}C\underline{H}_2$), 5.3 (m, 1H ), 5.96 (d, 1H,  J=12.5 Hz), 6.43 (d,1H,  J=12.5 Hz).

Reduction of enol acetate

0.050 g of sodiumborohydride was added to the enolacetate

of phytenal (0.200 g) in a 1:1 mixture of ether and methanol. The reaction mixture was stirred for 45 minutes when the enolacetate disappeared. It was then poured in water and extracted with ether (3 x 20 ml), washed with water, dried. Evaporation of solvent gave the mixture of 29b, 29c and 31 as seen from the PMR of the mixture. The mixture was then chromatographed on 15% silvernitrate impregnated silica gel. The column was eluted with benzene exhaustively and fractions of 5 ml were collected.

Fractions	Compound
4 - 7	31
9 - 11	29b
14 - 18	29c

The PMR of the fraction (9 - 11) and 29b and of the fraction (14 - 18) and 29c were identical.

Vitamin E

An equimolar mixture of Prins alcohols (32, 0.503 g) and trimethylhydroquinone (37, 0.250 g) was refluxed for 20 hrs in acetic acid in presence of $ZnCl_2$ (fused) 0.125 g. The reaction mixture was poured in water and extracted with ether. The ether layer was washed with water and 5% aq. methanolic NaOH, water and dried. Evaporation of solvent and chromatography on neutral alumina (Grade II) gave vitamin E in 72% yield, 0.513 g.

PMR (CCl_4) : 0.85 (d, 15H, CH_3-$\dot{C}$-, J=6 Hz), 2.0 (bs, 9H, Ar-$C\underline{H}_3$).

The vitamin E so obtained was acetylated to give vitamin E acetate.

IR (liquid film): 1718 (-$OCOCH_3$), 1210 cm^{-1}.

PMR (CCl_4) : 0.85 (d, 15H, 5 CH_3-$\dot{C}$-, J=6 Hz), 1.93, 2.0, 2.1, 2.2 (4s, 12H, $C\underline{H}_3$-COO, Ar-$C\underline{H}_3$).

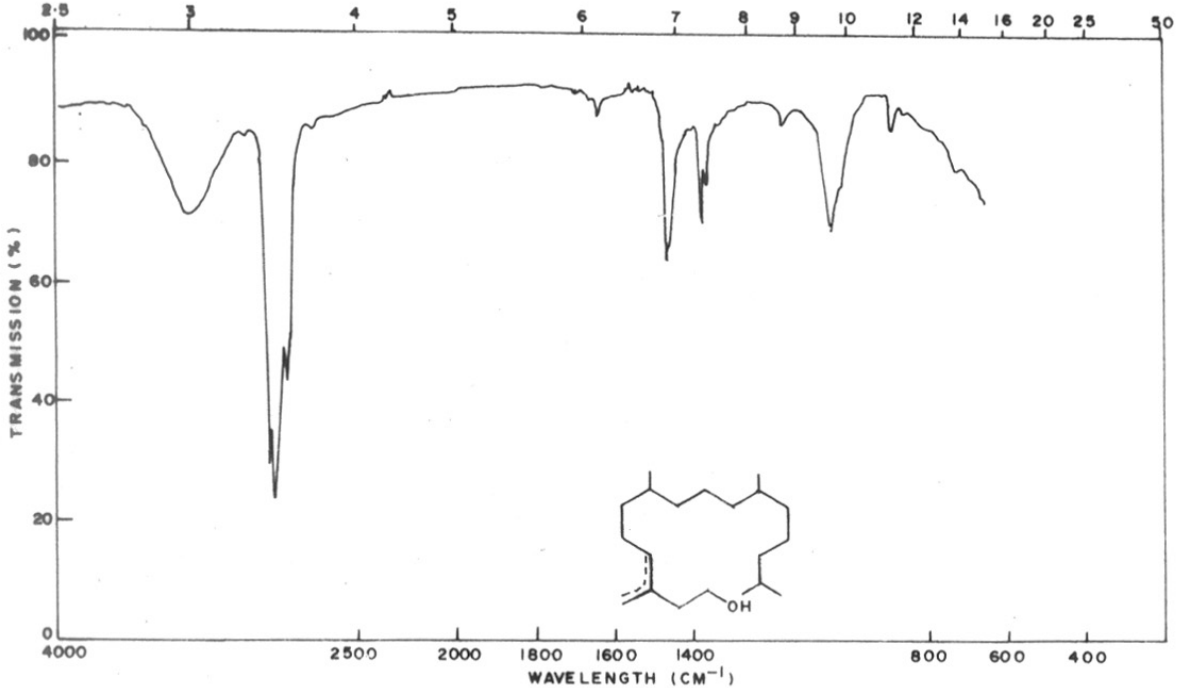


FIG 3·7, MIXTURE OF PRINS ALCOHOL (32)

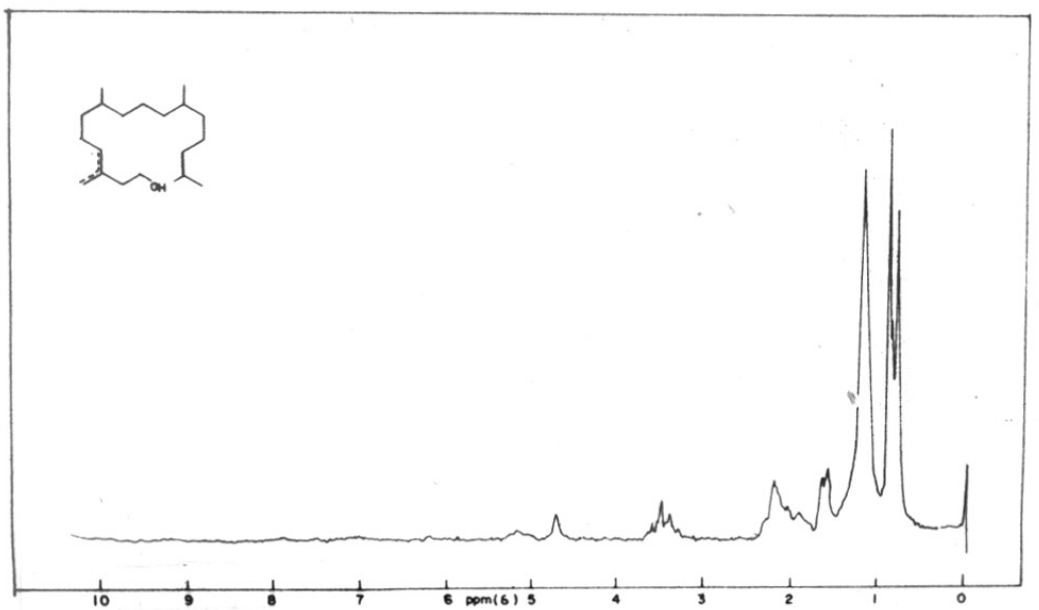


FIG 3·8, MIXTURE OF PRINS ALCOHOLS (32)

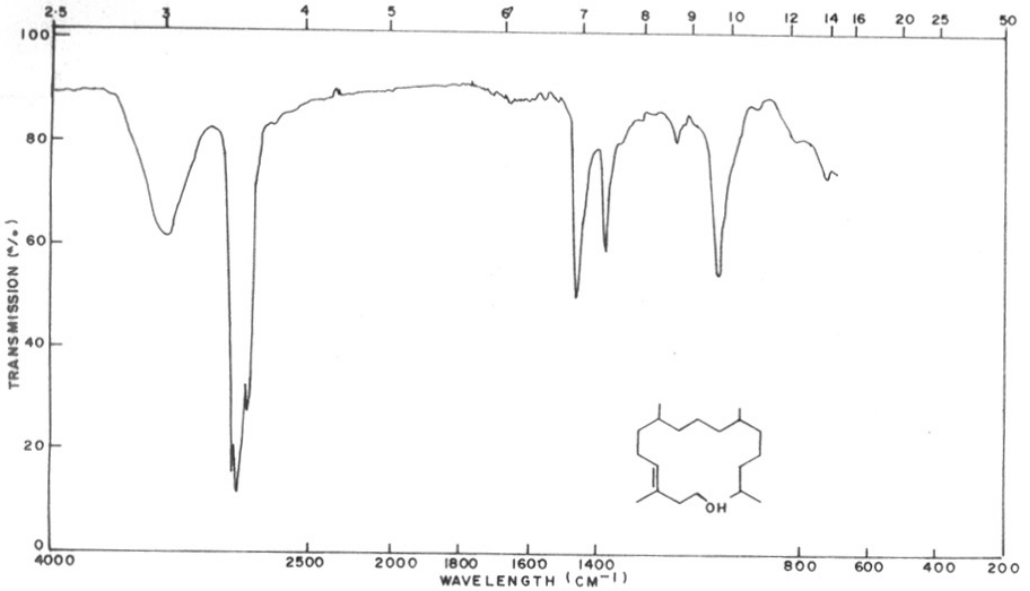


FIG 3·9, 3,7,11,15 - TETRAMETHYL HEXADEC-3-ENOL (32 b)

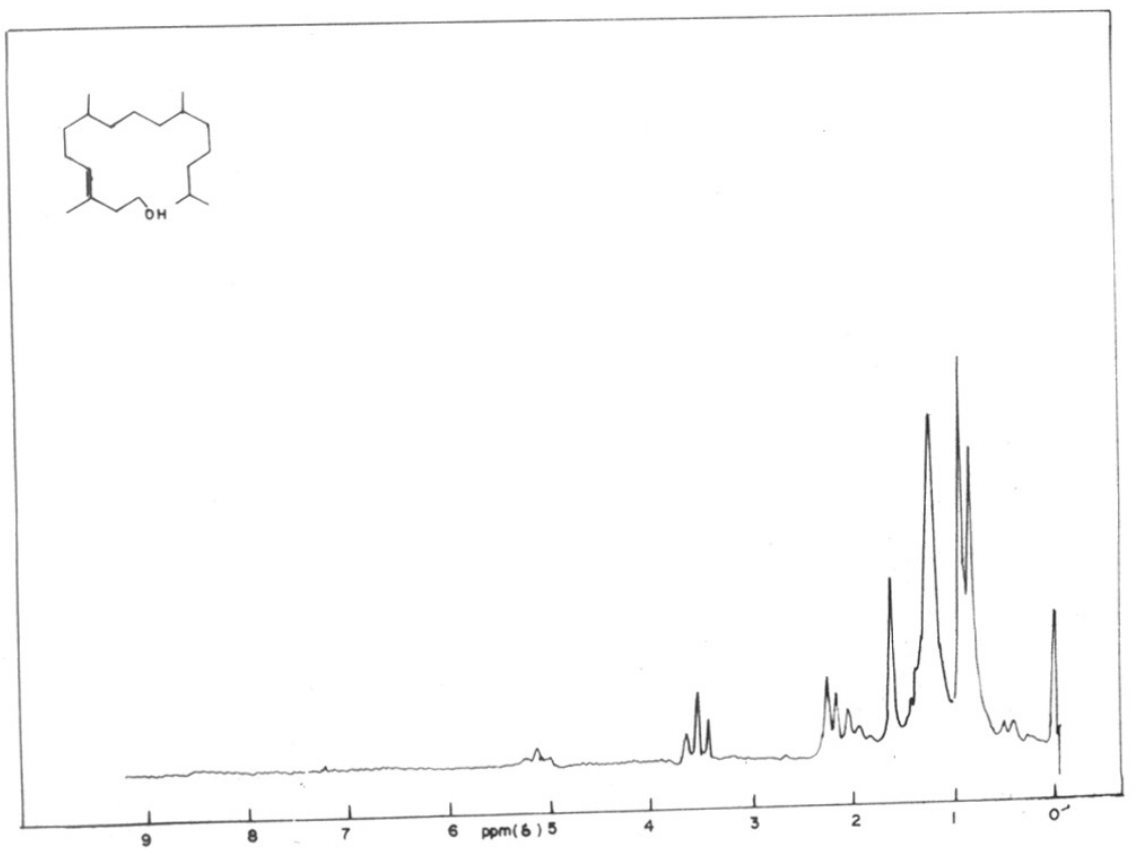


FIG 3·10, 3,7,11,15 - TETRAMETHYL HEXADEC-3 - ENOL (32 b)

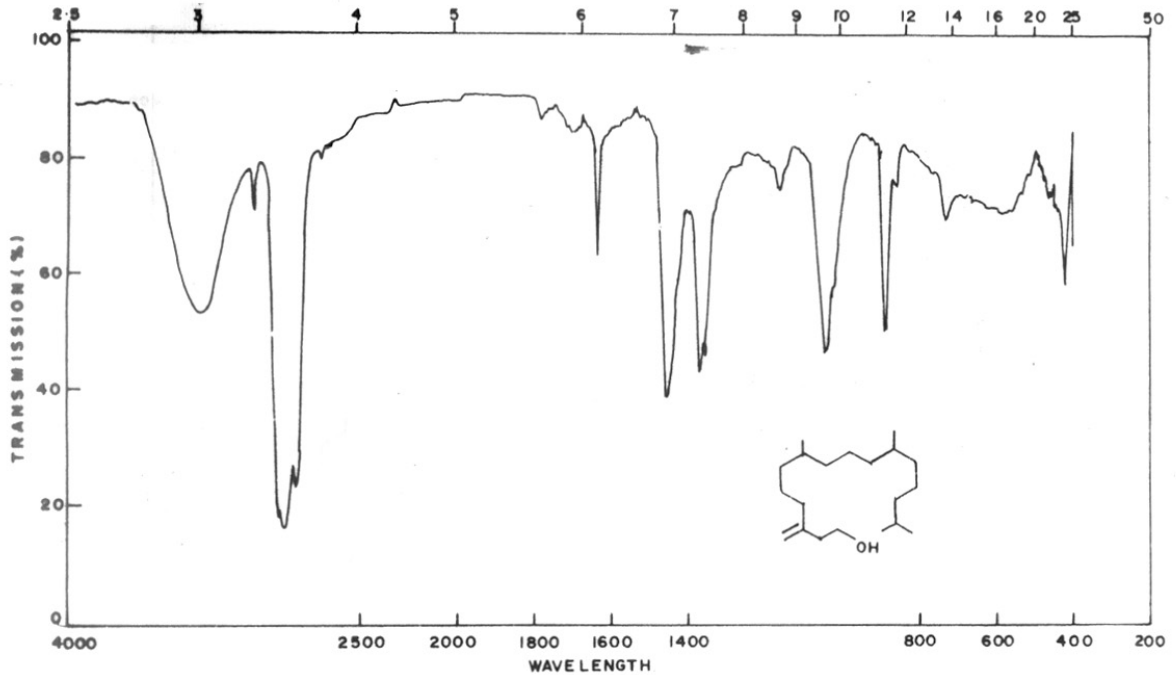


FIG 3-11, 7, 11, 15 - TRIMETHYL-3-METHYLENE HEXADECANOL (32 c)

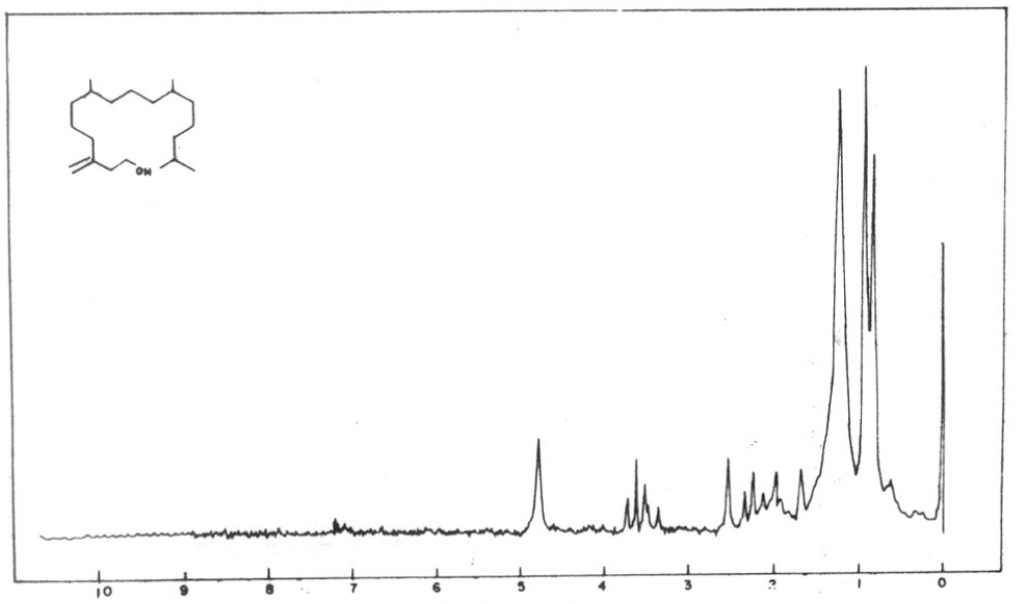


FIG 3-12, 7, 11, 15 TRIMETHYL-3-METHYLENEHEXADECANOL (32 c)

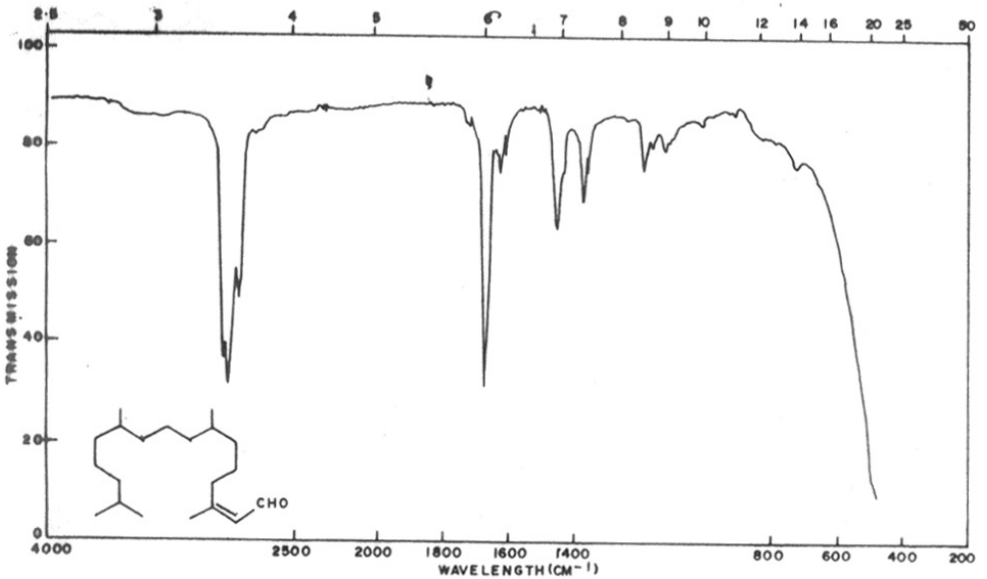


FIG 3·13, 3,7,11,15 -TETRAMETHYL-2-HEXADEC ENAL, PHYTENAL (35)

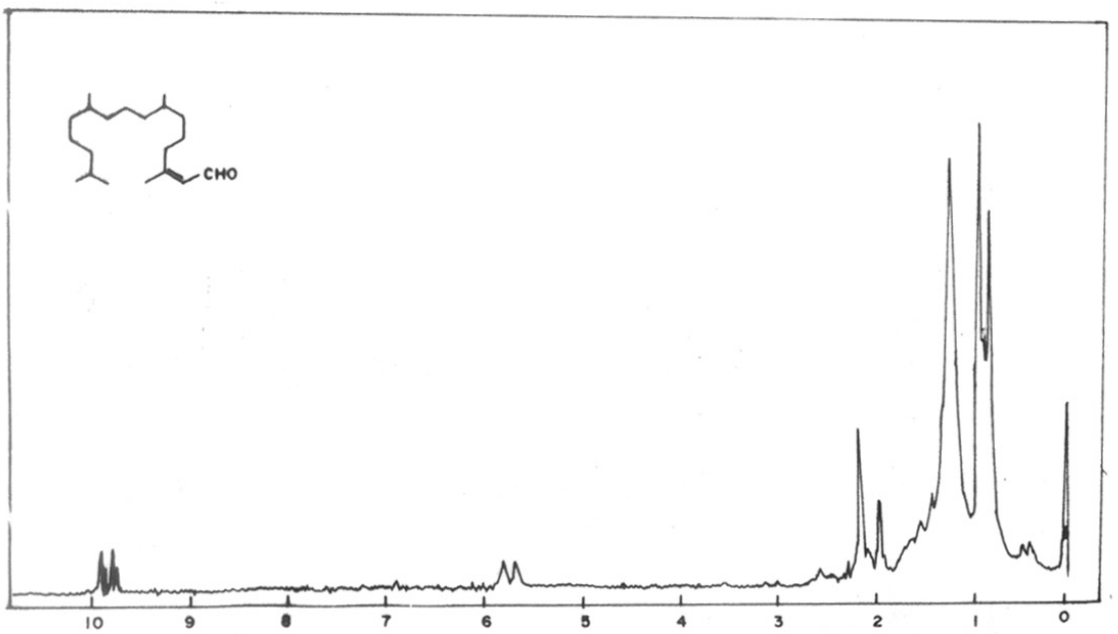


FIG 3·14, 3,7,11,15 -TETRAMETHYL-2-HEXADEC ENAL, PHYTENAL (35)

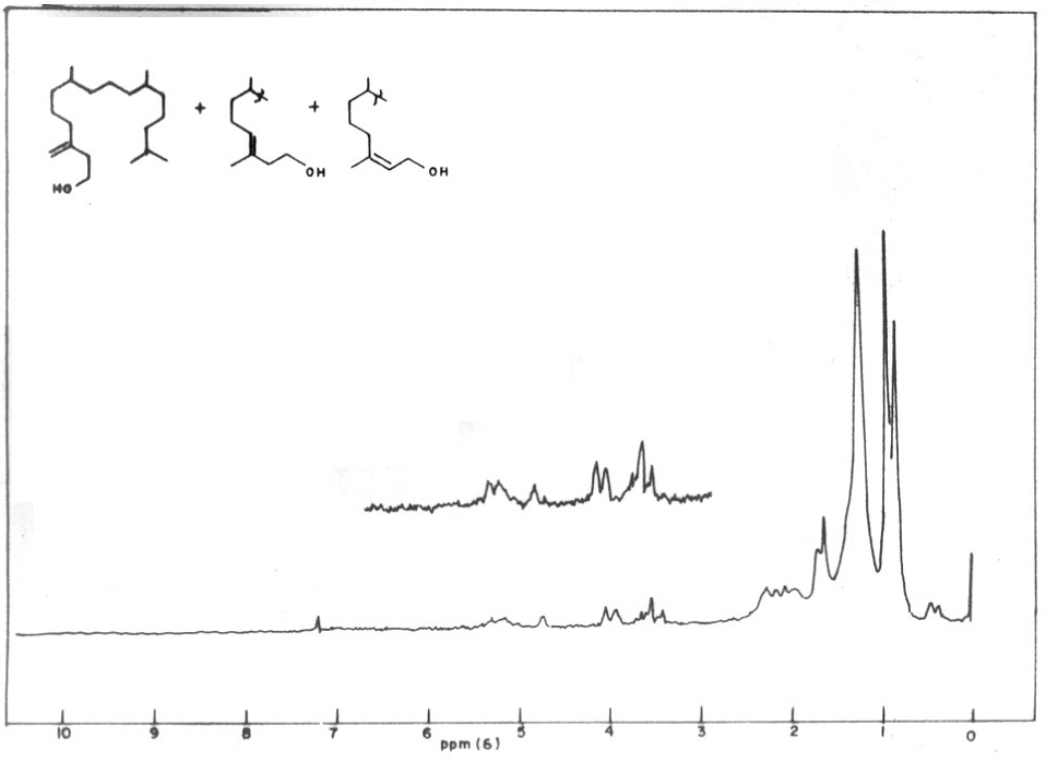


FIG 3·15 ALCOHOL MIXTURE FROM REDUCTION OF (36)

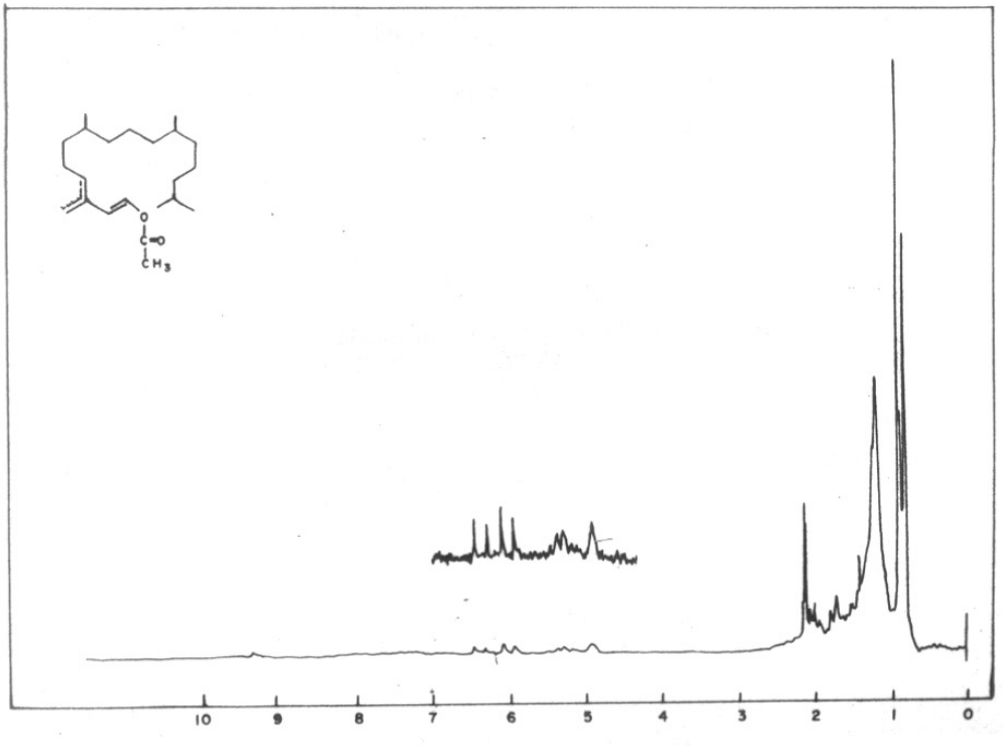


FIG 3·16 ENOLACETATE OF PHYTENAL (36)

REFERENCES

1 M. Blumer and D.W.Thomas
Science 148, 370 (1965).

2 A.W. Johnstone and P.M. Quan
J. Chem. Soc., 5706 (1963).

3 H. Mayer, P. Schudel, R. Ruegg and O. Isler
Helv. Chim. Acta, 46, 963 (1953).

4 M. Larcheveque and T. Cuvigny
Tetrahedron Lett., 44, 3851 (1975).

5 M.V. Rangaishenvi, S.V. Kamath, B.V. Bapat, S.V.Hiremath and S.N. Kulkarni
Ind. J. Chem., 22B, 398 (1983).

6 M.V. Rangaishenvi, S.V. Kamath, A.S. Phadke and S.N.Kulkarni
Ind. J. Chem., 22B, 684 (1983).

7 S.V. Kamath, M.V. Rangaishenvi, B.V. Bapat, S.V.Hiremath and S.N. Kulkarni
Ind. J. Chem., 22B, 921 (1983).

8 H.E. Eschinazi
J.Org. Chem., 26, 3072 (1961).

9 D.A. Peak and R.Robinson
J. Chem. Soc., 1590 (1937).

10 B.M. Trost and J. Cossy
J. Am. Chem. Soc., 104, 6881 (1982).

11 H.J. Prins
Chem.Week 16, 1072 (1919).

12 O. Meresz, K. PoLeung and A.S. Denes
Tetrahedron Lett., 2797 (1972).

13 G. Fodor, I. Tomuskozi
CA: 61: 10547 (1964) and
H. Griengl, W. Sieber
CA: 80: 47069 (1974).

14 J.P. Bain
J.Am. Chem. Soc., 68, 638 (1946).

15 A.T. Blomquist, J. Verdol, C.L.Adami, J. Wolinsky and D.D. Philips
J. Am. Chem. Soc., 79, 4976 (1957).

16 A.T.Blomquist, R.J. Himies
J. Org. Chem., 33, 1156 (1968).

17 W.J. Middleton
J. Org.Chem., 30, 1395 (1965).
W.J. Middleton, E.G. Howard and W.H. Sharkey
J. Am.Chem.Soc., 83, 2589 (1961).

18 R.A. Lloyd, C.W. Miller,D.L. Roberts, J.A. Giles,
J.P. Dikerson, N.H. Nelson, C.E. Rix and P.H. Ayers To b.
Sci. 20, 125 (1976).

19 P. Karrer and E. Bretscher
Helv. Chim. Acta, 26, 1758 (1943).

20 A. Bhati and K. Lloyd
Perfum. Essent. Oil Rec., 57, 699 (1966).

21 B.V. Burger, C.F. Garbers and F. Scott
J.S. Afr. Chem. Inst. 29, 143 (1976).

22 L.I. Smith and J.A. Sprung
J. Am. Chem. Soc., 65, 1276 (1943).