SYNTHESIS OF TERPENOIDS AND SOME APPLICATIONS OF DIELS-ALDER AND FRAGMENTATION REACTION

A Thesis

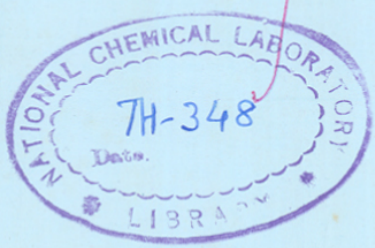
Submitted to the

University of Poona

for the degree of

DOCTOR OF PHILOSOPHY

in chemistry



BY

K. SHANKARAN

DIVISION OF ORGANIC SYNTHESIS
NATIONAL CHEMICAL LABORATORY
POONA – 411 008 (India)

1982

TO MY PARENTS

AND

TO MY BROTHER

ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to Dr. A. Somasekar Rao, Scientist, National Chemical Laboratory, Poona, India, for suggesting the problem, for his guidance, constant encouragement throughout the course of this investigation.

My thanks are due to my colleagues Dr. V. Dabral, Mr. Y.S. Sanghvi, Mr. J. Sohoni, Mr. K.S. Bhat and Mr. D.G. Talekar for their generous help and cheerful co-operation. The services of the co-workers from the microanalysis, spectroscopy and gas-chromatographic sections are gratefully acknowledged.

I am indebted to the Council of Scientific and Industrial Research, New Delhi, for the award of a research fellowship and to the Director, National Chemical Laboratory, Poona, India for providing all the facilities and permitting me to submit this work in the form of a thesis.

Poona [K. Shankaran]

CONTENTS

Pages

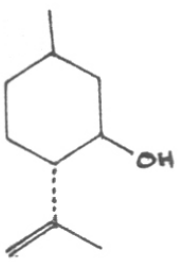
General Remarks

1. All melting and boiling points are uncorrected.
2. IR spectra were recorded as liquid film or nujol mull on a Perkin-Elmer infracord spectrophotometer Model 137B.
3. NMR spectra were recorded on a Varian T-60 spectrometer using TMS as internal standard.
4. Petroleum ether refers to the fraction boiling between 60-80°.
5. All extracts were finally dried over anhydrous sodium sulfate.
6. TLC were carried out on a silica gel made in this laboratory, plates being prepared by spreading the aqueous slurry, drying at room temperature and finally activating at 120° for 15 minutes.
7. "Alumina" refers to neutral alumina made in this laboratory.
8. Microanalyses were carried out in a microanalytical section of the laboratory.
9. All rotation were taken in chloroform solution at 27.5°. Concentrations are expressed in g/100 ml of the solution.

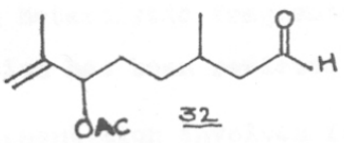
Chapter Ia: SYNTHESIS OF 3,7-DIMETHYL-6-OXO-OCTANOIC ACID

Summary

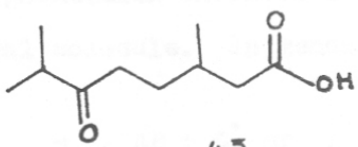
Isopulegol 25 on heating with lead tetraacetate underwent smooth fragmentation to give 6-acetoxy-3,7-dimethyl-oct-7-en-1-al 32. 32 was transformed to 3,7-dimethyl-6-oxo-octanoic acid 43. 3,7-Dimethyl-6-oxo-octanoic acid 43 is a constituent of geranium oil. Other transformations of 32 confirming its structure will be presented.



25



32



43

INTRODUCTION

Fragmentation reaction can be defined as the one which involves bond breaking process. In general this bond breaking process can be either heterolytic or homolytic. Heterolytic fragmentation involves the regulated cleavage of molecules containing certain combination of atoms such as carbon, oxygen, nitrogen, sulfur, phosphorus, silicon, boron and halogens. Heterolytic fragmentation can be acid or base catalyzed reaction. Carbocation and carbanion are the reactive species in heterolytic fragmentation. This fragmentation reaction has been reviewed by Grob et al.[1,2]

Homolytic fragmentation involves formation of a new radical and a neutral molecule. In general,

$$[ABC]^{\bullet} \rightarrow AB + C^{\bullet} \text{ or } A^{\bullet} + BC.$$

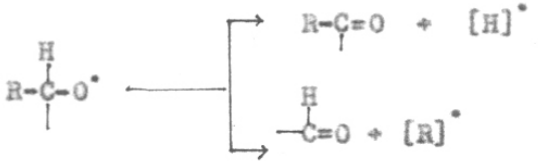
Homolytic fragmentation can be initiated thermally or photochemically. This fragmentation involves homolysis of a covalent bond β to the radical centre and is hence referred to as β-scission.

Lewis et.al.[3] observed that in the reaction of butanol with 1,1-dimethyl prop-2-en-1-yl phenyl sulphide 1, the radical 2 formed by addition of butyroyl radical to the olefinic double bond undergoes β-scission to afford 3

rather than abstract hydrogen from butanal to give the 1:1 adduct 4 (Chart I, Scheme I).

The loss of an atom β to a radical sometimes also involves the intermediacy of another radical. For e.g. the addition of trichloromethyl radicals to 2,3-dimethylbut-2-ene 5 affords radical 6[4]. Loss of the methyl hydrogen to the trichloromethyl radical results in the formation of chloroform and the product of the apparent β-scission 4,4,4-trichloro-2,3,3-trimethylbut-1-ene 7 (Chart I, Scheme II).

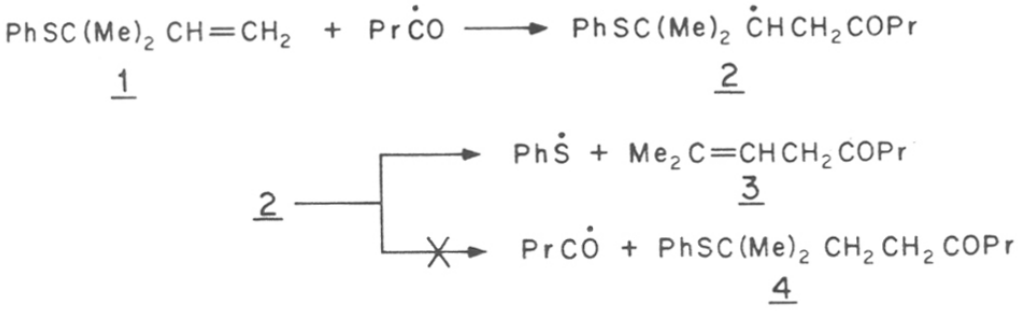
Sometimes, these fragmentation reactions are also termed as elimination reactions and the above two reactions are illustrative of this process[5]. β-Scission reaction can also involve the formation of carbon-carbon double bond as well as carbonyl function. An alkoxy radical can afford a carbonyl function by fission of a bond β to the radical centre.



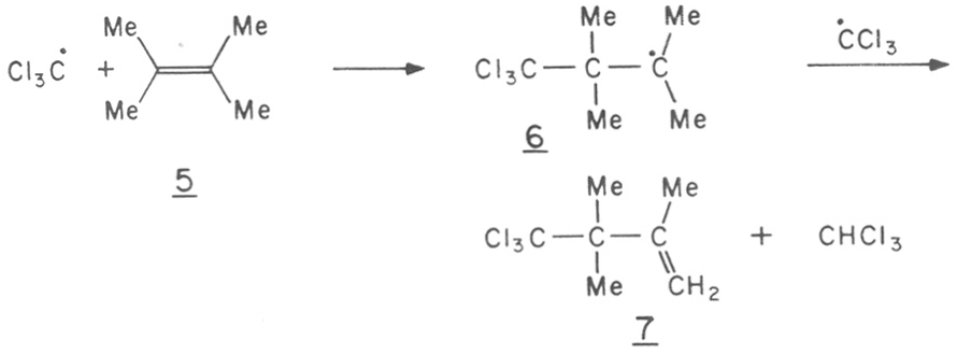
This is illustrated by the thermolytic decomposition of t-amyl hypochlorite 8 to afford acetone and ethyl chloride in a chain reaction[6] via 9 (Chart I, Scheme III).

CHART I

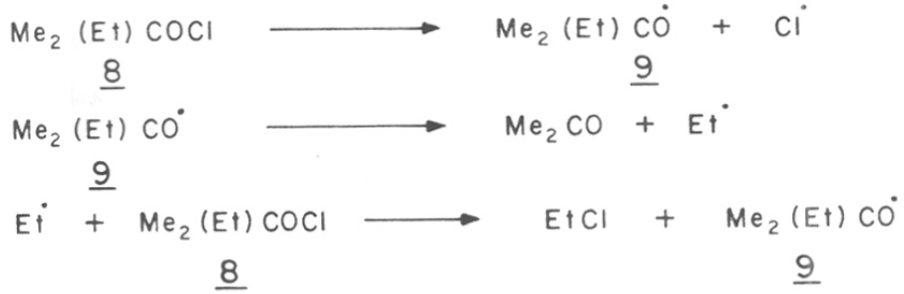
SCHEME I



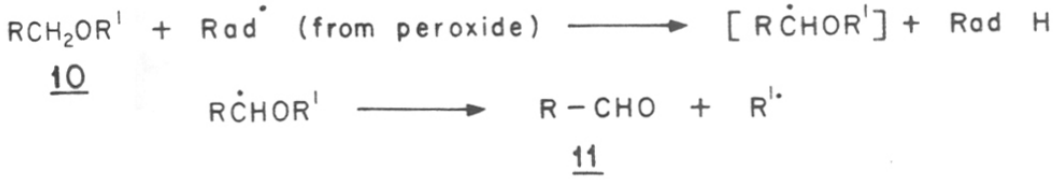
SCHEME II



SCHEME III



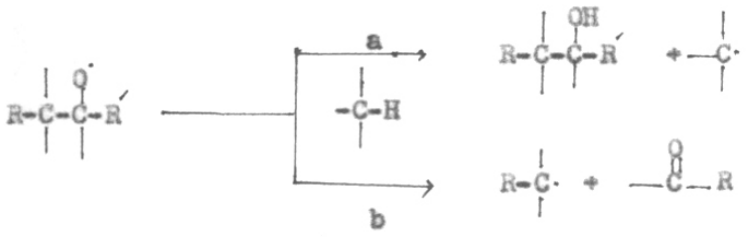
SCHEME IV



When the ether 10 is heated with a peroxide the intermediate β-alkoxy radical undergoes β-scission[7] to give 11 (Chart I, Scheme IV).

Requirement for fragmentation

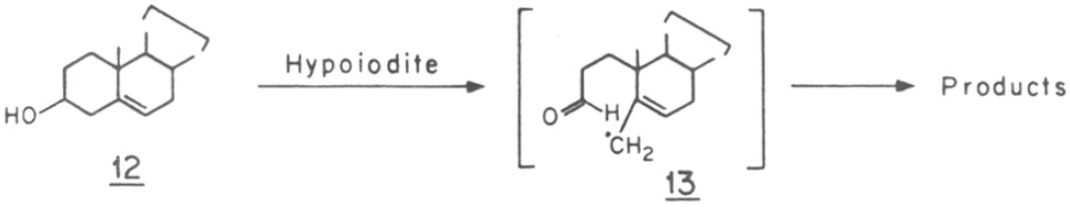
Alkoxy radical formed in general can undergo two different types of reactions, namely (a) abstraction of hydrogen in intramolecular fashion from ε-carbon atom (path a) and (b) fragmentation reactions which are energetically favoured[8] in some cases (path b).



The rate K_b of the cleavage reaction increases with the stability of the product of cleavage, R-C.[9,10]. Besides this other factors must play a part: the stability of the ketone or aldehyde formed, the decrease in strain by ejection of bulky groups[10], polar structures in the transition state stabilized by polarizing group R, entropy factors in the resonance stabilization of the radical formed by cleavage and in cyclic compounds (particularly with small rings), the decrease in strain as a result of ring opening. All these factors have been exemplified in the following cases.

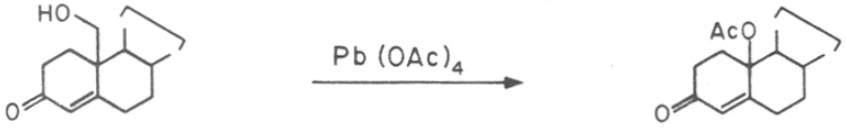
CHART II

SCHEME I



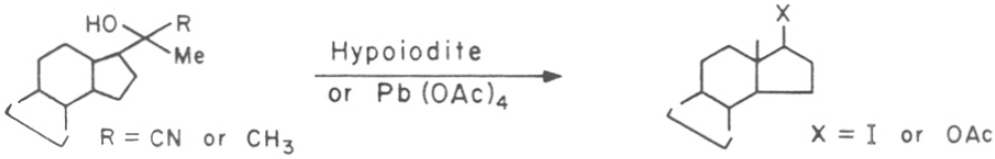
12 13

SCHEME II



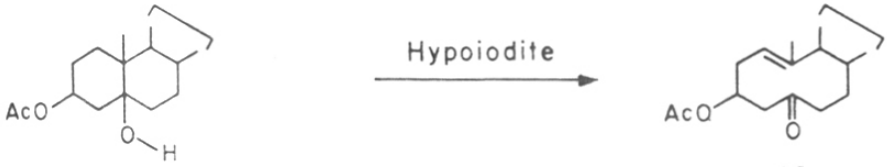
14 15

SCHEME III



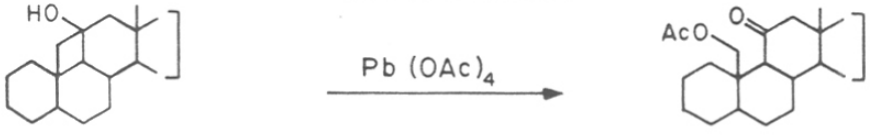
16 17

SCHEME IV



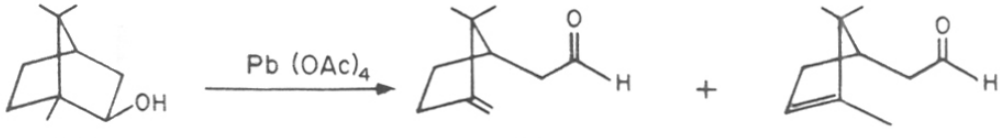
18 19

SCHEME V



20 21

SCHEME VI



22 23 24

Fragmentation as a result of resonance stabilization

The steroid alcohol 12 on hypoiodite reaction gave the products derived from the intermediate radical 13 [11] (Chart II, Scheme I). Similarly alcohol 14 gave the product 15 on reaction with lead tetraacetate[12] (Chart II, Scheme II). Formation of stable allylic radicals seems to be the driving force for the above reactions.

Fragmentation as a result of loss of bulky substituents

Tertiary 20-hydroxy steroids 16 in contrast to the reaction of secondary 20-hydroxy steroids, the hydrogen abstraction from C-18 is distinctly suppressed in favour of the fragmentation to give 17, although the carbon radical formed is not appreciably stabilized[13] (Chart II, Scheme III). A series of seco steroids were prepared by the fragmentation of alcohol 18 to the product 19[13a] (Chart II, Scheme IV).

Fragmentation as a result of decrease in strain

The ease of fragmentation as a result of relief of ring strain is shown by the conversion of 20 to 21[12] (Chart II, Scheme V).

Isoborneol 22 on treatment with lead tetraacetate afforded the products 23 and 24. The driving force for the above two reactions is relief in the strain as a result of ring opening[14] (Chart II, Scheme VI).

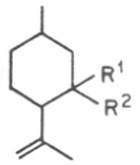
13a. M.Lj. Mihailovic, M. Stefanovic, Lj.Lorenc and M. Gasic, Tet.Lett., 28, 1867(1974).

PRESENT WORK

In the light of above mentioned observations it was decided to study the reaction of lead tetraacetate on (±)-Isopulegol 25. Isopulegol is a naturally occuring monoterpene secondary homo allylic alcohol. (±)-Isopulegol 25 can also be prepared by acid catalyzed cyclization[15] of (±)-citronellal 51. Menthol 29 is known to give tetrahydro menthofuran 30 on treatment with lead tetraacetate[16]. The mechanism for this reaction involves the formation of alkoxy radical 29a, which abstracts hydrogen atom from ε-carbon atom to give 29b. The intermediate 29b is then oxidised to 29c, which undergoes ring closure to give 30 (Chart III, Scheme I).

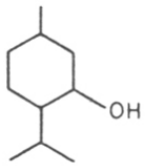
Hence it was anticipated that isopulegol 25 can also react in a similar manner to give ether 27 from alkoxy radical 26. It may be pointed out that this process should be facile, since the alkoxy radical 26, after abstraction of hydrogen atom from ε-carbon can lead to intermediate 26a. 26a - a stable allylic radical can then be oxidised to 26b, which then can undergo ring closure to give 27 (Chart III, Scheme II). It could also be possible to transform 27 to the α-methylene-γ-butyrolactone 28 by standard reactions. It is well established that α-methylene-γ-lactone moiety is responsible for biological activity associated with some antitumor compounds[17].

CHART III

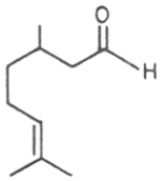


25 $R^1 = H$, $R^2 = OH$

31 $R^1 = CH_3$, $R^2 = OH$

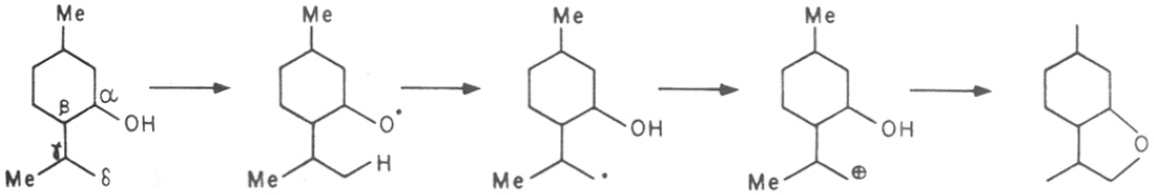


29



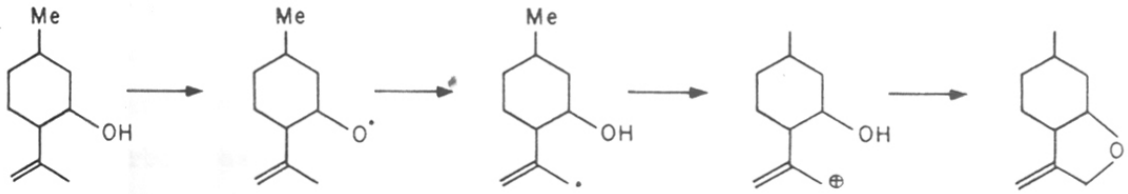
51

SCHEME I



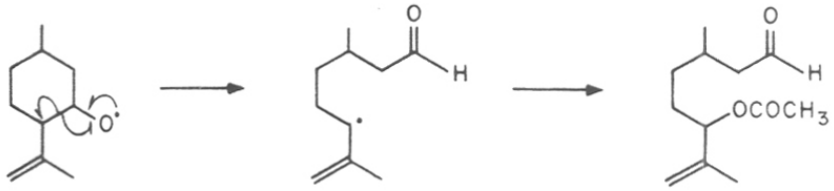
29 29a 29b 29c 30

SCHEME II



25 26 26a 26b 27

SCHEME III



26 26c 32

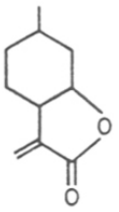
However when 25 was heated with lead tetraacetate (1:2) in refluxing benzene, the product obtained was not 27. The spectral data obtained for this product was consistant with the structure 32. Compound 32 in IR displayed bands at 2850 cm^{-1} (aldehyde) and 1230 cm^{-1} (acetate). NMR spectrum of 32 indicated signals at 9.75 (1H, m, -CHO), 5.04 (1H, t, J = 6Hz, -CHOAc).

A probable mechanism for the formation of 32 is shown (Chart III, Scheme III). The alkoxy radical 26 cleaves at β-position to give a new radical species 26c, which is then transformed to 32. Hence our results shows that the fragmentation reaction to give 32 is favoured other hydrogen abstraction to give 27. No isomerized product 49 could be detected. Saponification of 32 gave alcohol 33, which in its IR showed bands at 3650 cm^{-1} for OH stretching and 1710 cm^{-1} for aldehyde carbonyl. Its NMR spectrum displayed an upfield proton shift for proton attached to carbon bearing hydroxyl group i.e. 3.87 (1H, t, J= 6Hz, CHOH). Silver oxide[18] oxidation on 32 in the presence of alkali gave 38. 38 was esterified to methyl ester 39 with diazomethane. Ester 39 being an allylic alcohol, underwent active manganese dioxide[19] oxidation to give 44. The NMR spectrum of 44 showed downfield shift for the olefinic protons i.e. 5.68 and 5.90 δ. These experiments show that 32 is an allylic acetate.

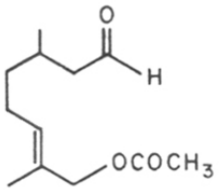
It is of interest to note that the aldehyde 32, has the oxygen functions at C_1 and C_6 in the dimethyl-octane carbon skeleton and hence is a potential intermediate for the synthesis of naturally occuring ketoacid 43. Keto acid 43 is a constituent of geranium oil[20]. The ketoacid 43 has the oxygen functions located on the same carbon atoms in the dimethyl-octane skeleton 32. Catalytic hydrogenation of 32 furnishes a mixture of the aldehyde 34 and the hydrogenolysis product 41. This mixture could be fractionally distilled to give 34. Saponification of the aldehyde 34 gave the hydroxy aldehyde 35. Oxidation of 35 with silver oxide[18] in the presence of alkali gave the hydroxy acid 36. The acid 36 was characterised as its methyl ester 37. The ester 37 is oxidised with Jones reagent[21] and the resulting keto ester 42 on saponification with alkali gave ketoacid 43. The IR and NMR spectra of 43 are identical with those of an authentic sample. Alternatively 43 could also be obtained by the direct oxidation of 36 with Jones reagent[22].

Incidentally we have prepared the diol 45 by carrying out sodium borohydride reduction of 32. This route to diol is superior to the reported method[23] of preparing it through photosensitized oxidation of citronellol. In the later route the diol 45 is a minor component. The

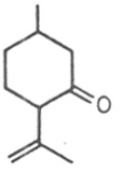
CHART IV



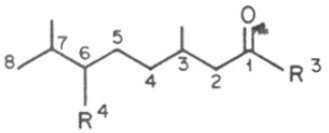
28



49



50



32 $R^3=H$, $R^4=OCOCH_3$
double bond at C_7-C_8

33 $R^3=H$, $R^4=OH$
double bond at C_7-C_8

34 $R^3=H$, $R^4=OCOCH_3$

35 $R^3=H$, $R^4=OH$

36 $R^3=R^4=OH$

37 $R^3=OCH_3$, $R^4=OH$

38 $R^3=R^4=OH$
double bond at C_7-C_8

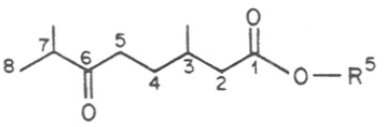
39 $R^3=OCH_3$, $R^4=OH$
double bond at C_7-C_8

40 $R^3=R^4=H$, OH at C_7

41 $R^3=R^4=H$

47 $R^3=CH_3$, $R^4=OCOCH_3$
double bond at C_7-C_8

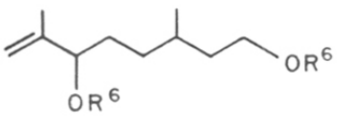
48 $R^3=CH_3$, $R^4=OH$
double bond at C_7-C_8



42 $R^5=CH_3$

43 $R^5=H$

44 $R^5=CH_3$
double bond at C_7-C_8



45 $R^6=H$

46 $R^6=COCH_3$

diol 45 was characterised as diacetate 46.

The reaction of lead tetraacetate on tertiary homoallylic alcohol 31 was also investigated. The alcohol 31 was obtained in two steps by carrying out pyridinium chlorochromate oxidation of isopulegol 25 to isopulegone 50[24]. Reaction of 50 with methyl magnesium iodide gave 31. When 31 was heated with lead tetraacetate and true to our expectation gave the fragmented product 47. NMR spectrum showed signals at 2.03 (3H, s, $-CO-CH_3$), 4.8 (2H, m, vinyl H), 5.03 (1H, t, J = 6Hz, -CHOAc). 47 on saponification gave 48.

Our work on alcohol 25 and 31 confirms the observation that homoallylic alcohol undergoes fragmentation reaction with lead tetraacetate. Since the yields are good, this reaction could be some preparative values. Another important feature of this reaction was that hydrolysis of 32 gave the hydroxy aldehyde 33, isomeric with widely used perfumeric material 7-hydroxy citronellal 40[25].

EXPERIMENTAL PROCEDURE

6-Acetoxy-3,7-dimethyl-oct-7-en-1-al (32)

To a boiling mixture of benzene (250 ml), anhydrous calcium carbonate (9 g) and lead tetraacetate (20 g, 0.045 M) was added a solution of isopulegol* 25 (4.31 g, 0.028 M) in benzene (20 ml). The reaction mixture was heated under reflux for 2 hours, cooled and filtered. The filtrate was washed with 10% potassium iodide solution, 10% sodium thiosulfate solution, water and dried. The residue obtained after the evaporation of benzene was fractionally distilled using a vigreux column (3 inches). The fraction with b.p. 94-95°/1 mm. (Yield 3.55 g; 60%) was composed of entirely acetoxyaldehyde (32).

IR spectrum (liquid film) showed bands at 2850 cm^{-1} (CHO), 1740 cm^{-1} (carbonyl of acetate and aldehyde), 1660 and 895 cm^{-1} (C = CH_2).

NMR spectrum (CCl_4 showed signals at τ 0.98 (3H, d, J = 6Hz, CH_3-CH) 1.72 (3H, m, CH_3-C=C), 2.03 (3H, s, CH_3-CO-O-), 4.81 (1H, m, vinyl H), 4.88 (1H, m, vinyl H), 5.04 (1H, m, -CHOAc).

Analysis: Found C, 67.67; H, 9.49.

$C_{12}H_{20}O_3$ requires C, 67.89; H, 9.50.

---

* Since isopulegol is obtained by cyclization of (±)-citronellal, all the compounds prepared in this series were racemic.

6-Hydroxy-3,7-dimethyl-oct-7-en-1-al (33)

A mixture of 32 (1 g, 0.0047 M), methanol (30 ml) and sodium hydroxide (0.92 g, 0.023 M) was heated under reflux for 1 hour, cooled, diluted with water and extracted with ether (2x50 ml). The ether extract was washed with water, dried and the solvent evaporated. Distillation of the residue under reduced pressure furnished 33 (0.58 g, 73%), b.p. 120°(bath)/1 mm.

IR spectrum (liquid film) showed bands at 3200 (OH), 2600 (-CHO), 1710 (carbonyl of aldehyde), cm^{-1}.

NMR spectrum (CCl_4) showed signals at δ 0.95 (3H, d, J = 6Hz, $C\underline{H}_3$-CH), 1.66 (3H, m, $C\underline{H}_3$-C=C), 3.35 (1H, m, OH exchanges with D_2O), 3.87 (1H, m, -C<u>H</u>OH), 4.65 (1H, m, vinyl H), 4.77 (1H, m, vinyl H), 9.77 (1H, m, -C<u>H</u>O).

Analysis: Found C, 70.17, H, 10.66.

$C_{10}H_{18}O_2$ requires C, 70.54, H, 10.66.

6-Acetoxy-3,7-dimethyl octanal (34)

A mixture of 32 (3.44 g; 0.016 M), acetone (35 ml) and palladium-charcoal (5%; 0.72 g) was stirred at room temperature in hydrogen atmosphere at atmospheric pressure. After the absorption of 0.02 M of hydrogen the rate of hydrogenation was virtually zero and the hydrogenation was stopped. The reaction mixture was filtered, solvent evaporated from the filtrate and the residue fractionally

distilled. Fraction (i), b.p. 85°(bath)/1 mm was characterised as 3,7-dimethyloctanal 41, since on oxidation furnished 3,7-dimethyloctanoic acid identified by comparison (NMR) with an authentic sample. Fraction (ii), b.p. 110° (bath)/1 mm (yield 2.25 g, 65%) was characterised as 6-acetoxy-3,7-dimethyl octanal 34.

IR spectrum (liquid film) showed bands at 2800 cm^{-1} (-CHO), 1730 cm^{-1} (carbonyl of acetate and aldehyde).

NMR spectrum (CCl_4) showed signals at τ 0.88 (6H, d, J = 6Hz, $\underline{CH}_3$ CH), 0.98 (3H, d, J = 6Hz, $C\underline{H}_3$-CH), 2.02 (3H, s, $C\underline{H}_3$-CO-O-), $C\underline{H}_2$ 4.82 (1H, m, -C$\underline{H}$OAc), 9.07 (1H, m, -C$\underline{H}$O).

Analysis: Found C, 66.71, H, 10.26.

$C_{12}H_{22}O_3$ requires C, 67.25; H, 10.35.

6-Hydroxy-3,7-dimethyl octanal (35)

A mixture of 34 (1 g, 0.0047 M), methanol (25 ml) and sodium hydroxide (0.92 g, 0.023 M) was heated under reflux for 2 hours, cooled, diluted with water and extracted with ether (2x30 ml). The ether extract was washed with water, dried, evaporated and distilled to give 35 (0.63 g, 78%), b.p. 122° (bath)/1 mm.

IR spectrum (liquid film) showed bands at 3580 cm^{-1} (OH), 2800 and 1720 cm^{-1} (-CHO).

NMR spectrum (CCl_4) showed signals at τ 0.88 [9H, d, J = 6 Hz, $(C\underline{H}_3)_2CH$ and $C\underline{H}_3$-CH], 3.22 [1H, m, -C<u>H</u>OH], 3.62 (1H, m, OH disappears on D_2O exchange), 9.67 (1H, m, -C<u>H</u>O).

Analysis: Found C, 69.47; H, 11.43.

$C_{10}H_{20}O_2$ requires C, 69.72; H, 11.70.

6-Hydroxy-3,7-dimethyl octanoic acid (36)

A mixture of 34 (0.785 g, 0.0037 M), ethanol (20 ml), water (10 ml), silver oxide (freshly prepared from 2.26 g of silver nitrate) and sodium hydroxide (0.7 g, 0.017 M) was stirred at room temp. for 48 hours. The filtrate was heated under reflux for 20 minutes, cooled, diluted with water and extracted with ether (1x100 ml). The ether layer was discarded. The aqueous layer was acidified with 10% hydrochloric acid (pH 2) and extracted with ether (2x50 ml). The ether extract washed with water, brine, dried the solvent, distilled off to furnish 36 (0.45 g, 70%).

IR spectrum (liquid film) showed band at 1706 cm^{-1} (carbonyl of acid).

NMR spectrum (CCl_4) showed signals at τ 0.88 [6H, d, J = 6Hz, $(C\underline{H}_3)_2CH$], 0.97 (3H, d, J = 6Hz, $C\underline{H}_3$-CH-), 3.30 (1H, m, -C<u>H</u>OH), 6.73 (2H, bm, OH exchanges with D_2O].

36 was further characterised as methyl 6-hydroxy-

3,7-dimethyloctanoate 37 by esterification with diazomethane in 90% yield, b.p. 153°(bath)/4 mm.

IR spectrum (liquid film) showed bands at 3620 cm^{-1} (OH), 1730 cm^{-1} (carbonyl of ester).

NMR spectrum (CCl_4) showed signals at τ 0.88 [6H, d, J = 6Hz, $(C\underline{H}_3)_2CH$], 0.95 [3H, d, J = 6Hz, CH_3-CH), 3.23 (1H, m, -C<u>H</u>OH), 3.58 (3H, s, -OC<u>H</u>$_3$).

Analysis: Found C, 65.60; H, 10.98.

$C_{11}H_{22}O_3$ requires C, 65.31; H, 10.96.

Methyl 3,7-dimethyl-6-oxo-octanoate (42)

To a mixture of 37 (0.195 g, 0.001 M) in acetone (15 ml) was added a Jones reagent at 0° till the orange colour of reagent was persistent. The reaction mixture stirred for 0.5 hour at the same temperature, poured into water, extracted with ether (2x25 ml). The etheral solution washed with water, brine, dried and evaporated to give the residue, which on distillation furnished 42 (0.173 g, 92%); b.p. 145°(bath)/6 mm.

IR spectrum (liquid film) showed bands at 1740 cm^{-1} (ester carbonyl), 1720 cm^{-1} (keto carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.97 (3H, d, J=6Hz, $C\underline{H}_3$-CH), 1.07 (6H, d, J = 6Hz,$(C\underline{H}_3)_2CH$), 3.62 (3H, s, OC<u>H</u>$_3$).

Analysis: Found C, 65.94; H, 10.22.

$C_{11}H_{20}O_2$ requires C, 65.97; H, 10.07.

3,7-Dimethyl-6-oxo-octanoic acid (43)+

Method (a): A mixture of 42 (0.12 g, 0.00061 M), sodium hydroxide (0.240g,0.006 M), methanol (25 ml) and water (1 ml) was heated under reflux for 2 hours, cooled, diluted with water and extracted with ether (2x20 ml). The etheral layer was washed with water, dried and solvent evaporated to give 43 (0.09 g, 82%), identified by comparison (IR, NMR) with an authentic sample.

IR spectrum (liquid film) showed band at 1709 cm^{-1} (acid and keto carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.88 (3H, d, J=6Hz, $C\underline{H}_3$-CH), 1.05 (6H, d, J=6Hz, $(C\underline{H}_3)_2CH$),10.0 (1H, m, $CO_2\underline{H}$, exchanges with D_2O).

Method (b): Oxidation of 36 with Jones reagent furnished 42 in 80% yield, identified through its IR, NMR spectrum.

6-Hydroxy-3,7-dimethyl-oct-7-enoic acid (38)

A mixture of 32 (2.14 g, 0.01 M), ethanol (50 ml), water (20 ml), silver oxide (freshly prepared from 7.2 g of silver nitrate) and sodium hydroxide (2.1 g, 0.05 M) was stirred at room temperature for 48 hours. The filtrate was heated under reflux for 20 minutes, cooled, diluted with water and extracted with ether (2x100 ml). The ether

---

+ For the synthesis of 43 by Bayer-Villigeer oxidation of pulegone see reference 26.

extract was rejected. The aqueous layer was acidified with 10% hydrochloric acid (pH 2) and extracted with ether (2x100 ml). The ether layer was washed with water, dried and the solvent evaporated to furnish 38 (1.40 g, 76%).

IR spectra (liquid film) showed band at 1709 cm^{-1} (carbonyl of carboxyl group).

NMR spectra (CCl_4) showed signals at τ 0.98 (3H, d, J = 6Hz, $C\underline{H}_3$-CH-), 1.68 (3H, m, $C\underline{H}_3$-C=C), 3.98 (1H, m, -C$\underline{H}$OH), 4.75 (1H, m, vinyl H), 4.87 (1H, m, vinyl H), 7.97 (2H, bm, OH, exchangeable with D_2O).

38 was further characterized as methyl ester 39 with diazomethane in 92% yield b.p. 130°(bath)/1 mm.

IR spectrum (liquid film) showed bands at 3650 cm^{-1} (OH), 1740 cm^{-1} (carbonyl of ester), 1645 and 840 cm^{-1} ($=CH_2$).

NMR spectra (CCl_4) showed signals at τ 0.99 (3H, d, J=6Hz, $C\underline{H}_3$-CH), 1.73 (3H, s, CH_3-C=C), 2.6 (1H, s, OH exchanges with D_2O), 3.6 (3H, s, -O$C\underline{H}_3$), 3.96 (1H, t, J = 6Hz, -C$\underline{H}$OH), 4.83 (2H, m, $=C\underline{H}_2$),

Analysis: Found C, 66.32; H, 9.90.

$C_{11}H_{20}O_3$ requires C, 65.97; H, 10.07%.

Methyl-3,7-dimethyl-6-oxo-oct-7-enoate (44)

A mixture of 39 (0.12 g, 0.00061 M), petroleum ether (20 ml) and active manganese dioxide (1 g) was stirred at room temperature for 2 hours. Evaporation of

petroleum ether gave the residue which when distilled in vacuum gave 44 (0.10 g, 70%), b.p. 150° (bath)/15 mm.
IR spectrum (liquid film) showed bands at 1740 cm^{-1} (ester carbonyl), 1675 cm^{-1} (conjugated carbonyl), 1625 cm^{-1} (carbon-carbon double bond).
NMR spectrum (CCl_4) showed signals at τ 0.97 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.85 (3H, m, $C\underline{H}_3$-C=C), 3.62 (3H, s, $OC\underline{H}_3$), 5.68 (1H, m, vinyl H), 5.90 (1H, m, vinyl H).
Analysis: Found C, 67.01; H, 9.28.
$C_{11}H_{18}O_3$ requires C, 66.68; H, 9.15.

3,7-Dimethyl-oct-7-en-1,6-diol (45)

A mixture of 32 (1.5 g, 0.0071 M), ethanol (30 ml), sodium borohydride (0.234 g, 0.0071 M) and water (5 ml) was stirred at room temperature for 24 hours and subsequently 10 ml of 5% sodium hydroxide solution was added and the stirring continued for 20 hours. The mixture poured into water and extracted with ether (2x50 ml). The ether layer was washed with water, brine, dried and evaporated to give the residue which after distillation gave 45 (0.90 g, 75%), b.p. 153°(bath)/2 mm.
IR spectrum (liquid film) showed bands at 3620 cm^{-1} (OH), 1645 and 890 cm^{-1} ($C=CH_2$).
NMR spectrum (CCl_4) showed signals at τ 0.90 (3H, d, J=6 Hz, $C\underline{H}_3$-CH-), 1.70 (3H, m, $C\underline{H}_3$-C=C), 3.55 (2H, m, $-C\underline{H}_2OH$), 3.90 (1H, m, -CHOH), 4.75 (1H, m, vinyl H), 4.85 (1H, m, vinyl H).

3,7-Dimethyl-oct-7-en-1,6-diacetate (46)

A mixture of 45 (1 g, 0.0058 M), pyridine (0.948 g, 0.012 M) and acetic anhydride (1.2 g, 0.012 M) kept at room temperature for 24 hours. The mixture diluted with water and extracted with ether (2x50 ml). The ether extract washed with 5% hydrochloric acid, water, brine, dried and solvent evaporated. The residue was distilled under vacuum to give 46 (1.3 g, 90%), b.p. 150° (bath)/5 mm.

IR spectrum (liquid film) showed bands at 1745 cm^{-1} (carbonyl of ester), 1645, 890 cm^{-1} ($=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 0.92 (3H, d, J=6 Hz, $\underline{CH}_3$-CH), 1.70 (3H, m, $\underline{CH}_3$-C=C), 1.93 (3H, s, $\underline{CH}_3$-C(=O)-O-), 1.97 (3H, s, $\underline{CH}_3$-C(=O)-O-), 3.95 (2H, m, -$\underline{CH}_2$-OAc), 4.77 (2H, m, vinyl H), 4.97 (1H, m, -$\underline{CH}$OAc).

Analysis: Found C, 65.16; H, 9.42.

$C_{14}H_{24}O_4$ requires C 65.59; H, 9.44.

(+)-Isopulegone (50)

A mixture of isopulegol 25 (4 g, 0.026 M), pyridinium chloro chromate[27] (16.0 g, 0.073 M) and methylene chloride (100 ml) was magnetically stirred at room temperature for 36 hours. The mixture was filtered through celite and the solids were washed thoroughly with methylene chloride. The filtrate was washed with 10% hydrochloric acid (2x50 ml), 10% sodium bicarbonate (2x50 ml), water, dried and evaporated to give residue, which upon distillation under vacuum

furnished 50 (3.8 g, 96%), b.p. 75° (bath)/1.5 mm.

IR spectrum (liquid film) showed bands at 1716 cm^{-1} (for carbonyl), 1645, 890 cm^{-1} ($=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 0.92 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.66 (3H, s, $C\underline{H}_3$-C=C-), 2.9 (1H, q, J = 6 Hz, H-$\underline{C}$H-$\overset{O}{\overset{\|}{C}}$-), 4.63 (1H, m, vinyl H), 4.8 (1H, m, vinyl H).

Preparation of (31)

To a solution of methyl magnesium iodide (5.01 g, 0.03 M, prepared from 4.3 g of methyl iodide and 0.7 g of magnesium) at 0° was added isopulegone 50 (2.5 g, 0.016 M) in 10 ml ether. The mixture stirred at 0° for 1 hour, and then at room temperature for 24 hours. The reaction was quenched with saturated solution of ammonium chloride. The etheral layer was washed with water, brine, dried and evaporated to give liquid which upon distillation under reduced pressure gave 31 (2.16 g, 82%), b.p. 93° (bath)/1.5 mm.

IR spectrum (liquid film) showed bands at 3550 cm^{-1} (OH), 1660, 890 cm^{-1} ($C=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 0.95 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.53 (3H, s, $C\underline{H}_3$-C-OH), 1.72 (3H, m, $C\underline{H}_3$-C=C), 4.88 (2H, m, vinyl H).

Analysis: Found C, 78.76; H, 11.87.

$C_{11}H_{20}O$ requires C, 78.51; H, 11.98.

7-Acetoxy-4,8-dimethyl-non-8-en-2-one (47)

To a boiling mixture of benzene (75 ml) anhydrous calcium carbonate (2.0 g, 0.02 M) and lead tetraacetate (5.1 g, 0.012 M) was added a solution of 31 (1.0 g, 0.006 M) in benzene (5 ml). The reaction mixture was heated under reflux for 2 hours, cooled and filtered. The filtrate was washed with 10% potassium iodide solution, 10% sodium thiosulphate solution, water, dried. The residue obtained after the evaporation of benzene was fractionally distilled. The fraction b.p. 128° (bath)/1.5 mm (0.929 g, 68%) was 47.

IR spectrum (liquid film) showed bands at 1742 cm^{-1} (acetate carbonyl), 1710 cm^{-1} (keto carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.83 (3H, d, J=6 Hz, $\underline{CH}_3$-CH-), 1.7 (3H, s, $\underline{CH}_3$-C=C), 2.0 (3H, s, -C(=O)-$\underline{CH}_3$), 2.03 (3H, s, -C(=O)-$\underline{CH}_3$), 4.8 (2H, m, vinyl H), 5.03 (1H, t, J=6 Hz, $\underline{CH}$OAc).

Analysis: Found C, 68.99; H, 9.80.

$C_{13}H_{22}O_3$ requires C, 68.81; H, 10.11.

7-Hydroxy-4,8-dimethyl-non-8-en-2-one (48)

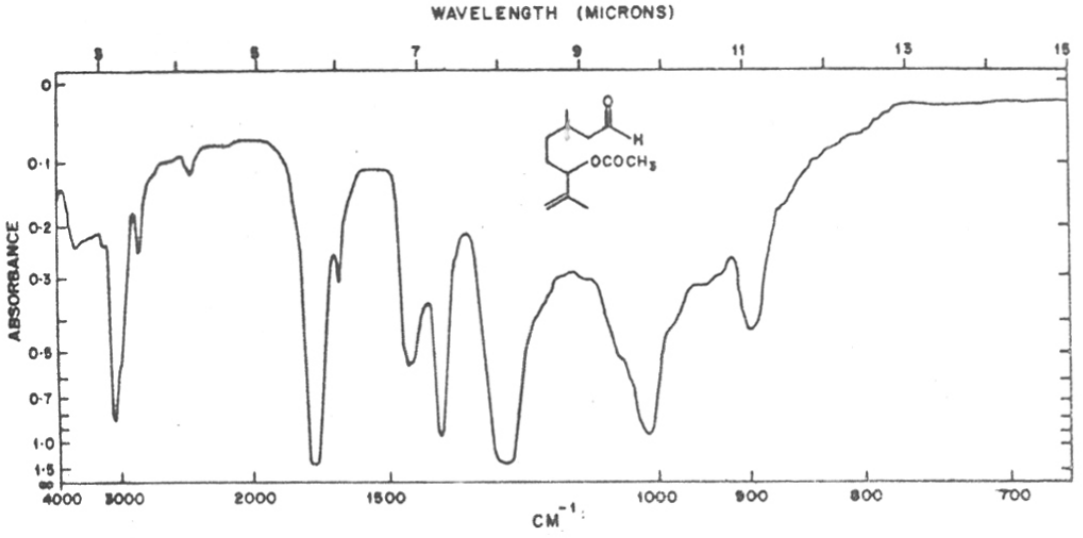
To a mixture of 47 (0.226 g, 0.001 M), ethanol (12 ml), sodium hydroxide (0.200 g, 0.005 M) and water (1 ml) heated to reflux for 3 hours. The mixture was cooled, diluted with water and extracted with ether (2x25 ml). The ether was washed with water, brine, dried and evaporated to give residue, which on distillation under vacuum gave 48 (0.156 g, 85%), b.p. 122° (bath)/1 mm.

IR spectrum ~~of~~ (liquid film) showed bands at 3600 cm^{-1} (OH) 1720 cm^{-1} (acetate carbonyl), 895 cm^{-1} ($C=CH_2$).

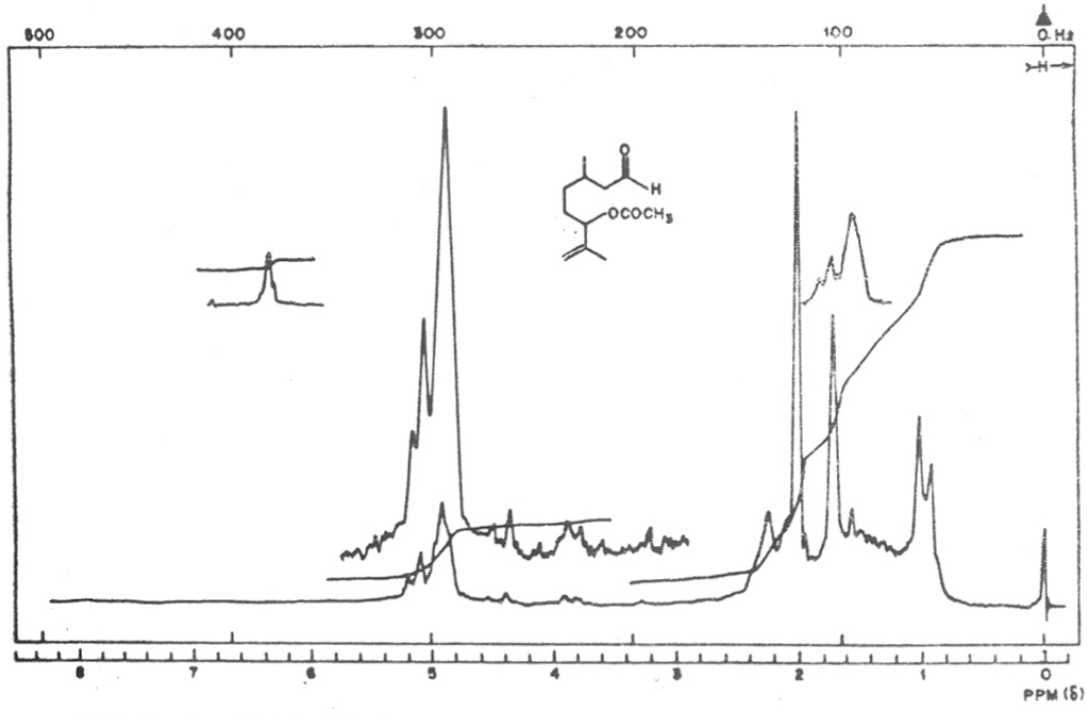
NMR spectrum (CCl_4) showed signals at τ 0.83 (3H, d, J= 6 Hz, $C\underline{H}_3$-CH-), 1.63 (3H, m, $C\underline{H}_3$-CH=CH-), 2.03 (3H, s, $-\overset{O}{\overset{\|}{C}}-C\underline{H}_3$), 3.06 (1H, m, OH exchangeable with D_2O), 3.8 (1H, t, J = 6 Hz, -C<u>H</u>OH), 4.7 (1H, m, vinyl H), 4.8 (1H, m, vinyl H).

Analysis: Found C, 71.69; H, 10.94.

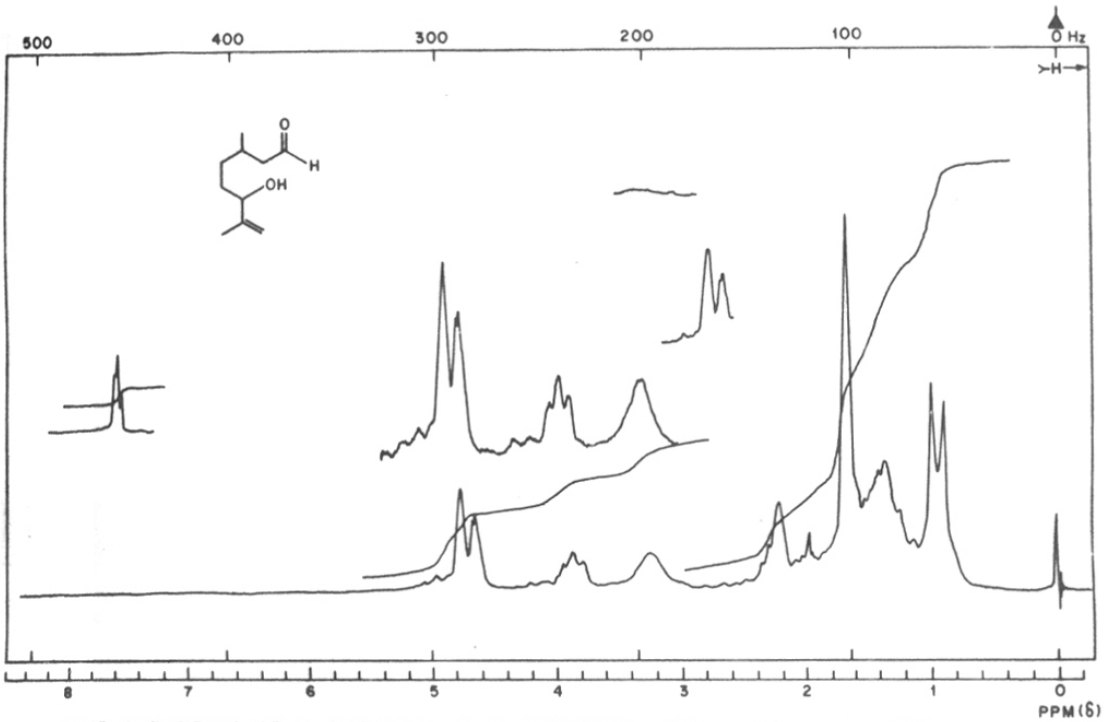
$C_{11}H_{20}O_2$ requires C, 71.80; H, 10.98.



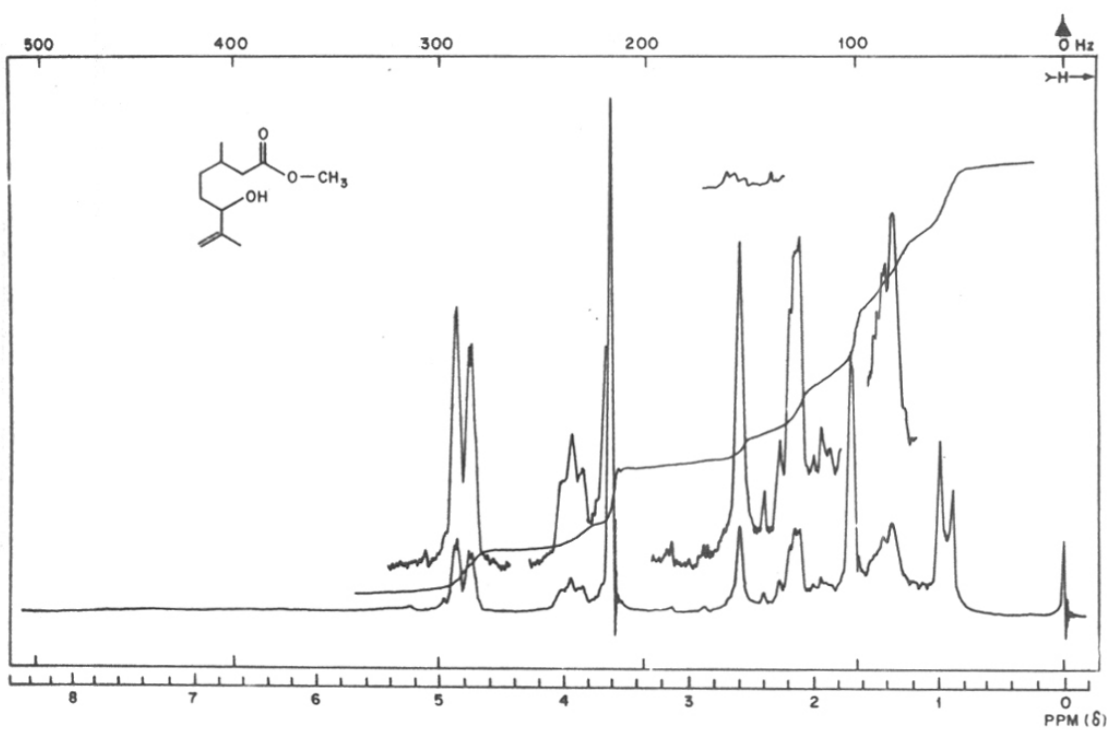
IR SPECTRUM OF 6-ACETOXY-3,7-DIMETHYL-OCT-7-EN-1-AL.(32)



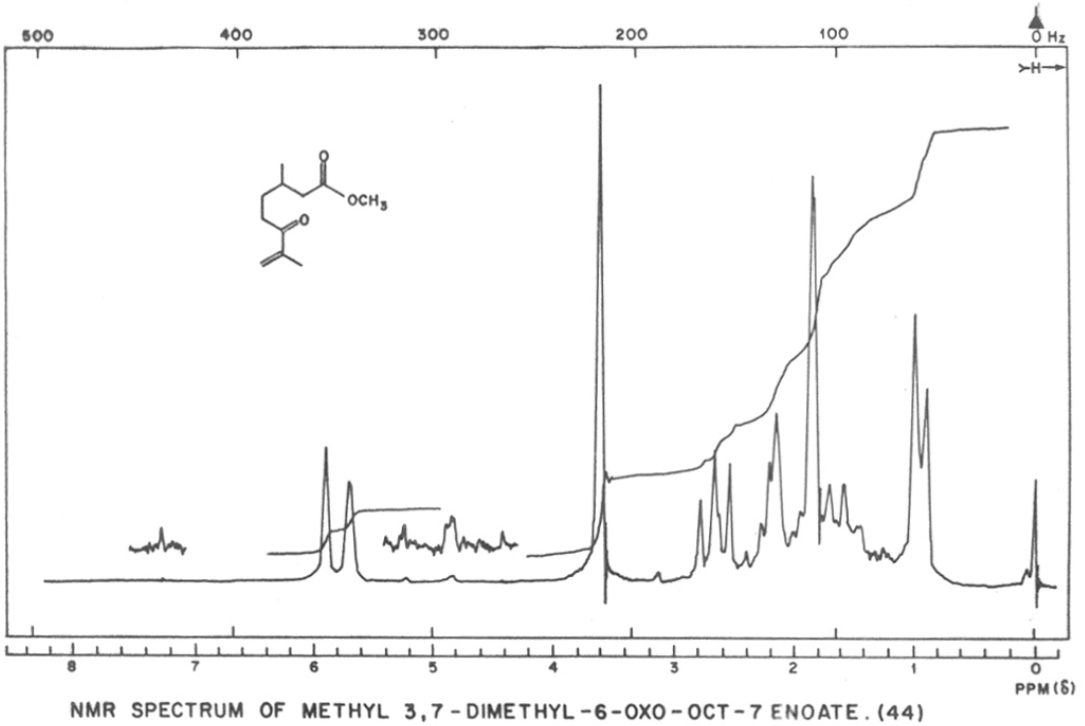
NMR SPECTRUM OF 6-ACETOXY-3,7-DIMETHYL-OCT-7-EN-1-AL.(32)



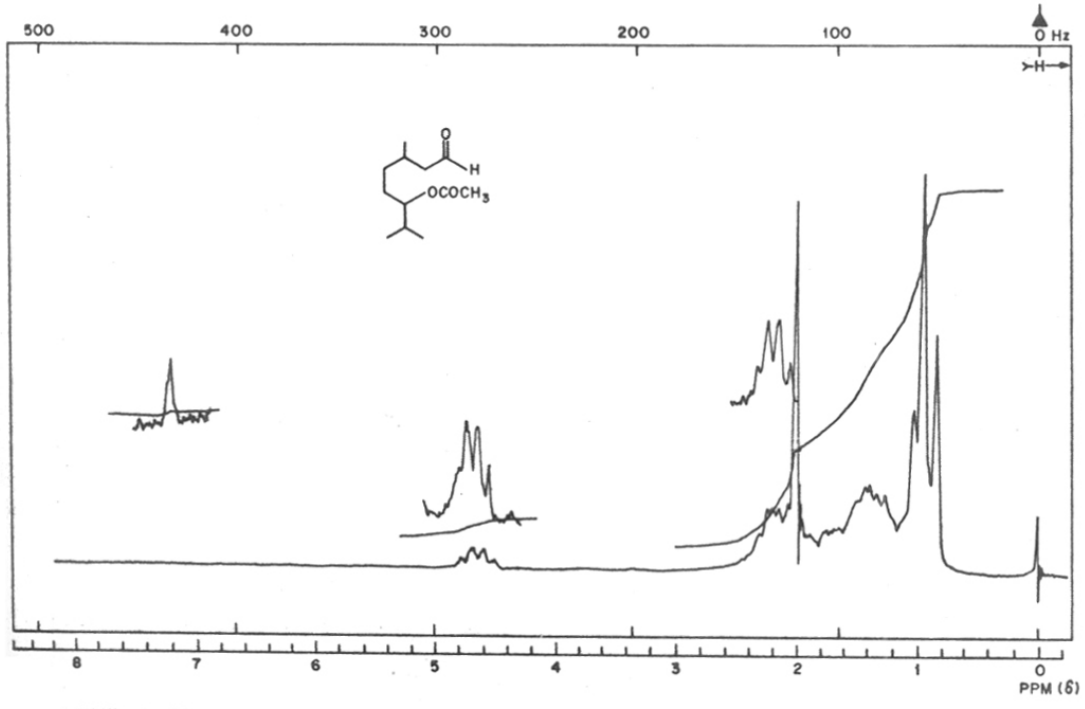
NMR SPECTRUM OF 6-HYDROXY-3,7-DIMETHYL-OCT-7-EN-1-AL. (33)



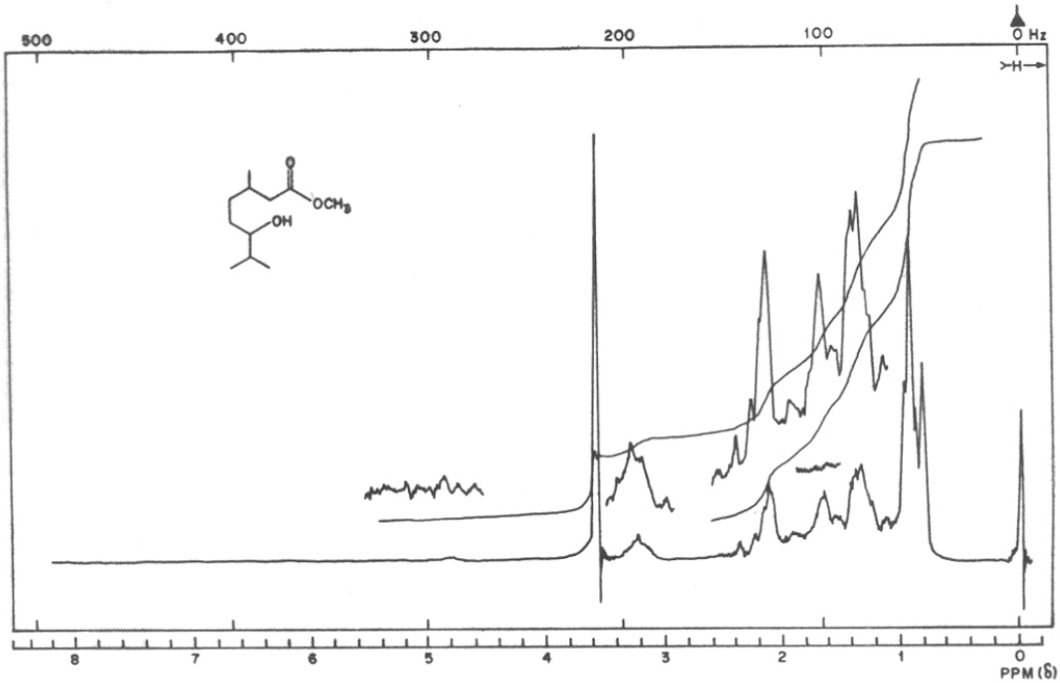
NMR SPECTRUM OF METHYL 6-HYDROXY-3,7-DIMETHYL-OCT-7 ENOATE. (39)



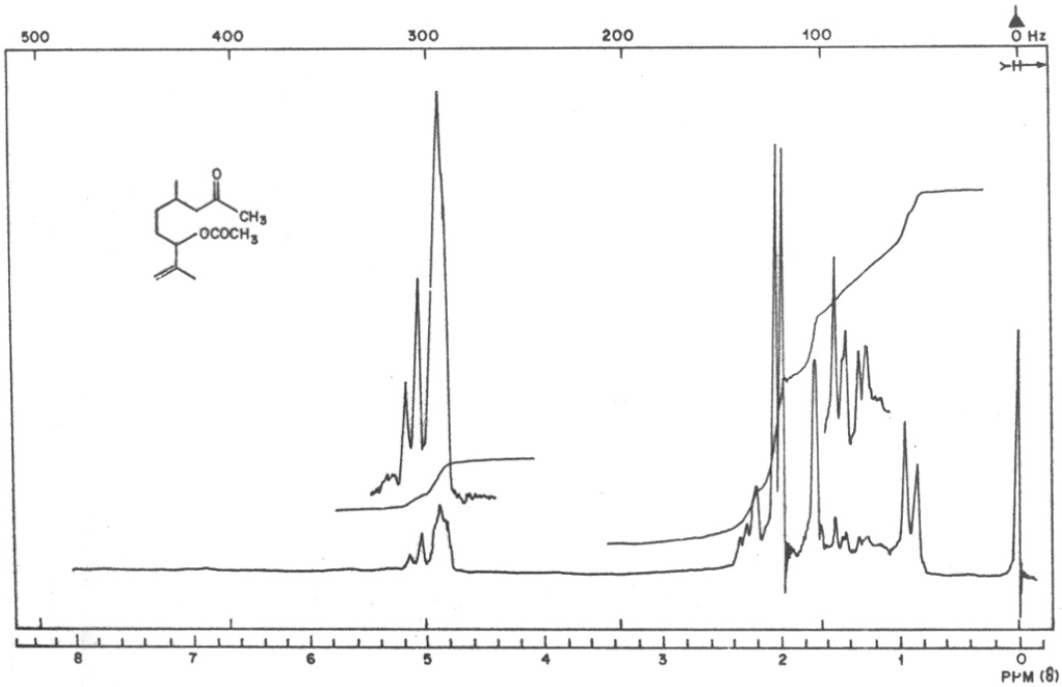
NMR SPECTRUM OF METHYL 3,7-DIMETHYL-6-OXO-OCT-7 ENOATE. (44)



NMR SPECTRUM OF 6-ACETOXY-3,7 DIMETHYLOCTANAL. (34)



NMR SPECTRUM OF METHYL 6-HYDROXY-3,7-DIMETHYL OCTANOATE. (37)



NMR SPECTRUM OF 7-ACETOXY-4,8-DIMETHYL-NON-8-EN-2-ONE. (47)

REFERENCES

1. C.A. Grob and P.W. Schiess, Ang.Chem.Int.Edn., 6, 1 (1967).

2. C.A. Grob, Ang.Chem.Int.Edn., 8, 535 (1969).

3. S.N. Lewis, J.J. Miller and S. Winstein, J.Org.Chem., 37, 1478 (1972).

4. H.Y. Loken, R.G. Lawler and H.S. Ward, J.Org.Chem., 38, 106 (1973).

5. J.W. Wilt, "Free Radical Rearrangements", Vol.I, Chapter 2, p.37.

6. F.D. Chattaway and O.G. Backeberg, J.Chem.Soc., 123, 2999 (1923).

7. P.I. Abell in "Free Radicals", Vol.II, Edited by J.K. Kochi, John Wiley & Sons, p.96, 1973.

8. P. Gray and A. Williams, Chem.Reviews, 59, 239 (1959).

9. J.K. Kochi, J.Amer.Chem.Soc., 84, 1193 (1962).

10. C.H. Walling and A. Padwa, J.Amer.Chem.Soc., 85, 1593 (1963).

11. E.A. Brande and O.H. Wheeler, J.Chem.Soc., 326 (1955).

12. M. Anorosa, L. Caglioti, G. Cainelli, H. Immer, J.Keller, H. Wehrli, M.Lj.Mihailovic, K. Schaffner, D. Arigoni and O. Jeger, Helv.Chim.Acta., 45, 2674 (1962).

13. H.-C. Mez, G. Rist, O. Emer, Lj.Loreng, J. Kalvoda and M.Lj.Mihailovic, Helv.Chim.Acta, 59, 1273 (1976).

14. R.E. Partch, J.Org.Chem., 28, 276 (1963).

15. B.D. Sully and P.L. Williams, Perf. & Ess.Oil Rec., 59, 365 (1968).

16. G. Ohlott, K.H. Schulte-Elte and B. Willhalm, Helv.Chim.Acta, 49, 2135 (1966).

17. S.M. Kupchan, Pure Appl.Chem., 21, 227 (1970).

18. K.J. Clark, G.I. Fray, R.H. Jaeger and R. Robinson, Tetrahedron, 6, 217 (1959).

19. E.J. Corey, N.N. Gilman and B.E. Ganem, J.Am.Chem.Soc., 90, 5616 (1968).

20. E. Klein and W. Rajahn, Chem.Abs., 87, 23525k (1977).

21. C. Djerassi, R.R. Engle and A. Bowers, J.Org.Chem., 21, 1547 (1956).

22. K. Shankaran and A.S. Rao, Ind.J.Chem., 18B, 507 (1979).

23. S.C. Datta, M.C. Nigam and T. Sen, Indian Perfum., 18, 47 (1974).

24. E.J. Corey, H.E. Ensley and J.W. Suggs, J.Org.Chem., 41, 380 (1976).

25. G. Ohloff and B. Leinhard, Helv.Chim.Acta, 48, 182 (1965).

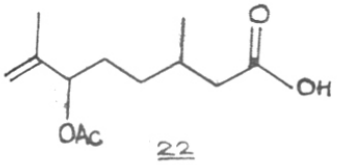
26. R.M. Silverstain, J.R. Handley and A.A. Swigar, J.Org.Chem., 44, 2954 (1979).

27. E.J. Corey and J.W. Suggs, Tet.Lett., 2647 (1975).

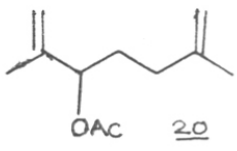
CHAPTER IB : SYNTHESIS OF 2,6-DIMETHYL-1,6-HEPTADIENE-3-OL-ACETATE. A POSSIBLE BIOGENESIS OF PHEROMONE-2,6-DIMETHYL-1,5-HEPTADIEN-3-OL-ACETATE INVOLVING 2,6-DIMETHYL-1,6-HEPTADIEN-3-OL-ACETATE AS A PRECURSOR

Summary

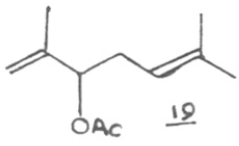
6-Acetoxy-3,7-dimethyl-7-en-octanoic acid 22 obtainable easily from isopulegol 25 was transformed to 2,6-dimethyl-1,6-heptadien-3-ol acetate 20 by oxidative decarboxylation. 20 is an analogue of 19. 19 is pheromone isolated from comstock mealybug. The analogue 20 is half as active as 19. Preparation of several other analogues of 20 will be presented. (-)-Menthone 26 was transformed to hydroxy acid 28, which on oxidation gave keto acid 42. The enantiomer of keto acid 42 i.e. 43 is naturally occurring and has been isolated from geranium oil.



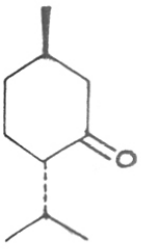
22



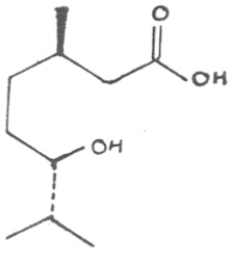
20



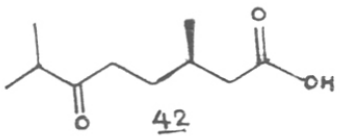
19



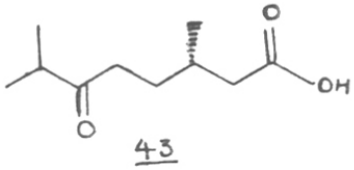
26



28



42



43

INTRODUCTION

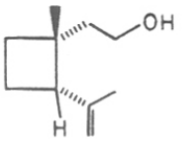
The pheromone structural spectrum is perhaps one of the richest in natural product chemistry. It embraces a wide variety of molecules whose number and structural type has grown enormously during the last few years and the trend is certain to continue in view of the continuous development in isolation, structure elucidation technique and synthesis.

That pheromones constitute a growing class of compounds is shown by number of books[1-6] and reviews[7-10] that have appeared in last decade. Pheromones are compounds released by the insects used for intraspecific communication and they can be classified according to the response they elicit. These responses may be due to an individual chemical or as is often the case, a mixture of chemicals. For example, male boll weevils (Anthonomus Grandis) produce a mixture of alicyclic pheromones 1, 2, 3 and 4 respectively. Here is an instance wherein the total mixture is the pheromone.and the individual chemicals that make up the pheromone are termed as pheromone components. In such cases the total effect is greater than the sum of the effects of individual components. This phenomenon is termed as synergism.

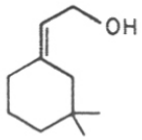
Sex pheromones are secreted by one sex to attract the other as an initial part of the mating process. A variety of chemicals have been identified by screening as attractive to one sex. For example, the pheromone of the dried bean beetle (Acanthoscelides Obtectus) is shown to have the structure 5. However, there are some instances known particularly among beetles (Coleoptera) where the pheromones may attract both the sexes and therefore serve more than one function. Such compounds are called as aggregation. Some insects use alarm pheromones to alert the members of their species. For example, the alarm pheromone of the Texas leaf cutting ant (Atta Texana) is shown to be (S)-(+)-4-methyl-3-heptanone 6.

Lately it has been realized that the activity of these pheromones vary largely depends upon the geometrical and optical isomers of the component. Since the quantity of pheromones isolated from natural resources are less than a milligram, it has been frequently been impossible to establish their structure, optical purity etc. Structure determination rests heavily on information derived from mass spectrum (MS), nuclear magnetic resonance (NMR), infra-red (IR) and ultraviolet (UV). A great deal of information has been recorded with these instruments. Latest method to arrive at the structure conclusion is

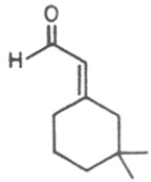
CHART I



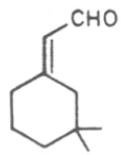
1



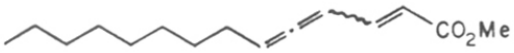
2



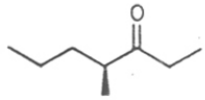
3



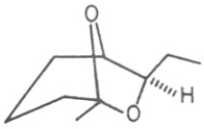
4



5

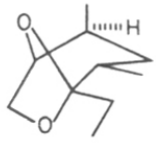


6

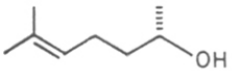


7

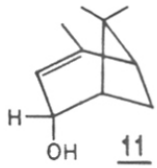
8



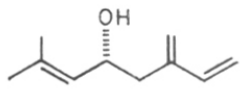
9



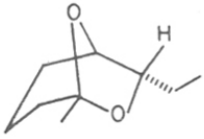
10



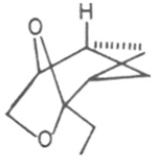
11



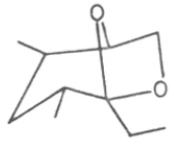
12



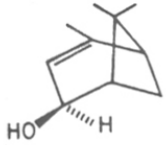
13



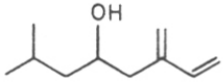
14



15

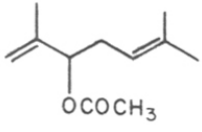


16

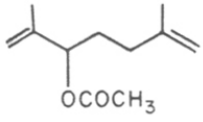


17

18



19



20

based on NMR studies in the presence of optically active lanthanide shift reagents[11]. The outcome of such a study was structure elucidiation of (+)-exo brevicomin 7, (-)-frontalin 8 and α-(-)-multistriatin 9 respectively[12]. Whereas enantiomeric composition of alcohol (+)-sucatol 10, (-)-trans-verbenol 11, (-)-ipsdienol 12 were found out by forming the derivatives of α-methoxy-α-trifluoromethyl-phenylacetyl derivatives[13-15]. At present C-13-NMR has become a powerful tool for structure identification. C-13-NMR has proved beneficial in identifying the structure and stereochemistry[15] of endo-brevicomin 13, γ-(-)-multistriatin 14 and γ-(+)-multistriatin 15. Few instances are known wherein optical rotatory disposition (ORD) measurements have been made to arrive at the structure and enantiomeric forms of related pheromones[16].

The ultimate proof for structure is unambiguous synthesis followed by demonstration of equivalent biological activity of synthetic material in the field. These synthesis may not prove all that difficult, since pheromones have comparatively simpler structure as compared to other natural products (This is due to part to the requirement for high volatility and rapid diffusion in the air). However despite all precautions, errors still may occur. For example, it becomes difficult to prove which of the

isomer is active. The principle component of the attractant pheromone produced by the bark beetle (Ips Paraconfusus) are three optically active component, namely, (+)cis-verbenol 16, (±) Ipsenol 17 and Ipsdienol 12. None of these compounds are attractive by itself, however in the field the flying beetles respond to the mixture of these three[17,18,19]. In 16 or 17 one does not know whether its R or S configuration alcohol shows activity. In such cases both R and S configuration alcohols are synthesised individually assessed for their activity. Thus 17 with S-configuration at alcohol bearing carbon is active, while R-configuration, has been proved to be nearly inactive[20].

Pheromones have many practical applications. The study of pheromones enhances understanding of insects and their behaviour. The bark beetle in the family of scolytidae has been the subject of several pheromone studies because of their economic importance. An annual loss of about $5x10^9$ bored feet of timber in the USA alone is attributed to them. One of the most important insects pests in the USA, in terms of crop loss economics, is the boll weevil (Anthonomus Grandis). More than three fourths of all insects losses to cotton in this country (USA) have been in fact due to these pests[21]. With the availability of resources, it has now become easy to control them. There are few reports like successful commercial operation against the pink bollworm in cotton fields in 1977 and the full

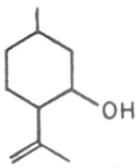
report on these studies are available. In addition to crop protection permeation with gossyplure 18 with concomitant reduction by 50-80% in pesticides use resulted in yield improvements of as much as 20-50%. This is the first instance of successful commissioning of a sex pheromone for protection of a crop. In years to come it is hoped that many more results will be expected.

PRESENT WORK

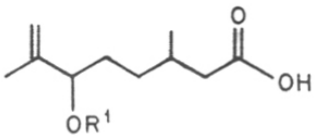
Recently, Mori et. al.[22] have shown that 2,6-dimethyl-1,5-heptadien-3-ol acetate 19 is the sex pheromone of Comstock mealybug Pseudococcus comstocki kuwana. Comstock mealybug is one of the most serious pests of apple, peas and other crops. Since the sex pheromone is highly attractive to native males, field trials could be carried out with as little as 0.1 mg of the synthetic (±)-19[23]. Some analogues of 19 were synthesised and analogue 20 was found to be half as active as 19. Considering the dramatic results stated above we have examined convenient routes for the preparation of 20 and many other derivatives of same skeleton. A possible biogenetic route for the formation of 19 involving 20 as an intermediate is suggested.

The two step synthesis of hydroxy acid 21 starting from isopulegol 20a.has been reported by us[24]. Acetylation of 21 with acetic anhydride in pyridine furnished the acetoxy acid 22. There are several reports in the literature[25] dealing with the transformation of primary carboxylic acids to alkenes. This process which is known as oxidative decarboxylation can be carried out by using lead tetraacetate in the presence of cupric acetate and pyridine. For example, acid 31 gave an oxidative decarboxylation 32 in good yield (Chart III, Scheme I).

CHART II

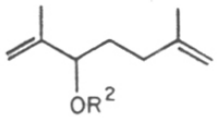


20a



21 $R^1 = H$

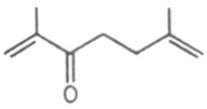
22 $R^1 = COCH_3$



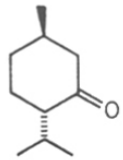
20 $R^2 = COCH_3$

23 $R^2 = H$

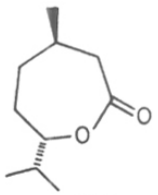
25 $R^2 = COCH_2CH_3$



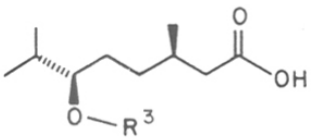
24



26

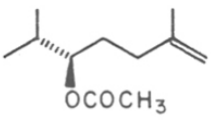


27

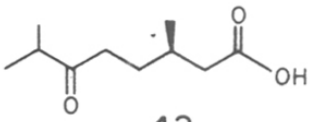


28 $R^3 = H$

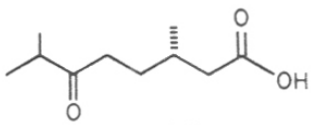
29 $R^3 = COCH_3$



30



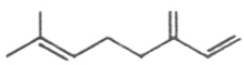
42



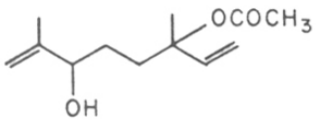
43

34

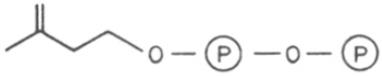
35



36

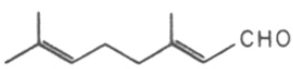


37



38

39

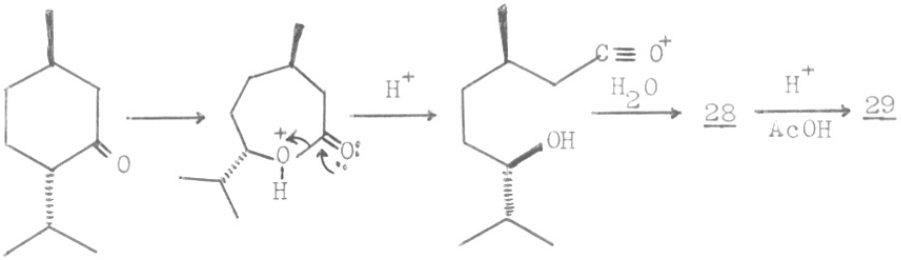


44

Hence acetoxy acid 22 was subjected to oxidative decarboxylation[26] and as expected the acetoxy alkene 20 was formed. The IR spectrum of 20 showed the absence of carboxyl group and showed bands at 1658 and 897 cm^{-1} attributable to the presence of exo methylene group ($C=CH_2$). The NMR spectrum[22] of 20 showed signals at τ 1.70 (6H, s, CH_3 on double bond), 1.95 (3H, s, $O-CO-CH_3$), 4.5-4.7 (4H, broad singlet, vinylic proton) and 5.1 (1H, t, J=6 Hz, -CHOAc).

Saponification of 20 furnished the hydroxy-alkene 23. IR spectrum of 23 showed absence of band at 1740 cm^{-1} (carbonyl from acetate) and a new band at 3546 cm^{-1} (OH stretching). NMR spectrum showed a signal at 4.03 τ (1H, t, J=6 Hz, -CHOH). 23 was transformed to the propionate 25 through acylation with propionic anhydride in pyridine. The NMR spectrum of 25 showed signals at 1.33 (3H, t, J=6 Hz, CH_3-CH_2), 2.33 (2H, q, J=6 Hz, $-CH_2-CH_3$) and 5.2 (1H, t, J=6 Hz $-CHOCOCH_2CH_3$). The IR spectrum of 25 showed reappearance of carbonyl group at 1739 cm^{-1}. Active MnO_2 oxidation of 23 gave 24. The IR spectrum showed band at 1667 cm^{-1} (conjugated carbonyl) and the NMR spectrum showed downfield shift for vinylic proton i.e. at 5.73 (H, m, vinylic proton) and 5.93 (1H, m, vinyl H).

We next turned our attention to the synthesis of analogue 30, which differs from 20, with respect to the double bond. Baeyer-Villiger oxidation of (-)-menthone 26 with 40% aqueous peracetic acid in the presence of sulfuric acid catalyst and subsequent work-up furnished a mixture of hydroxy acid 28 and acetoxy acid 29 instead of ϵ-lactone 27. It was evident that the acids 28 and 29 were formed by acid catalysed ring opening of the initially formed ϵ-lactone 27. A probable mechanism involving acylium ion (acyl-oxygen cleavage) is given below.



26 27 Acylium ion

There are several reports in the literature regarding Baeyer-Villiger oxidation on ketone next to an asymmetric carbon, migrating with the retention of configuration[28]. Hence we assume that the oxidation of (-)-menthone also proceeds with retention of configuration. Saponification of the total Baeyer-Villiger oxidation product gave hydroxy acid 28, which upon subsequent acetylation with acetic anhydride-pyridine gave 29. The

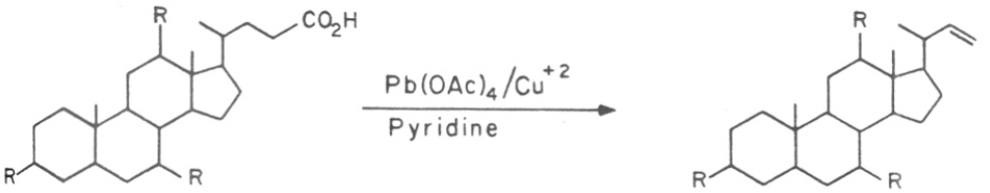
IR spectrum of 29 showed bands at 17.45 cm^{-1} (carbonyl of acetate) and 1718 cm^{-1} (acid carbonyl). 29 also showed $(\alpha)_D$= +12 ($CHCl_3$). NMR spectrum of 29 indicated signals at 2.06 (3H, s, -O-CO-CH_3) and 4.73 (1H, m, -CHOAc). Oxidative decarboxylation of 29 furnished the acetoxy alkene 30. The IR spectrum of 30 showed bands at 1739 cm^{-1} (acetate carbonyl), 1664 and 885 cm^{-1} ($C=CH_2$). The NMR spectrum showed signals at 2.0 (3H, s, -O-CO-CH_3), 4.66 (2H, m, vinyl hydrogen) and 4.83 (1H, t, J=6 Hz, -CHOAc).

A possible biogenesis of 19 involving 20 is reported here-in as outlined in Scheme II, Chart III. In view of the similarity of the carbon skeleton with monoterpenes such as citral 44 (Chart II), the two differ by only one carbon atom, it is tempting to assume that the pheromone 19 is of terpenic origin. Many pheromones like Verbenol 11 and 16, Ipsenol 17 and Ipsdienol 12 are derived from monoterpene precursor α-pinene 34 or β-pinene 35[29] and myrcene[30,36] The first step may be the formation of allylic alcohol 32a from acid 31a. In this connection it is of interest to note that compounds having allylic alcohol functionality of the type present in 32a are known to occur in nature. For example, a number of compounds have been isolated[31] from lavandin oil, one of them was 37.

The allylic alcohol 32a can undergo a very facile intramolecular michael addition to give 33, which may

CHART III

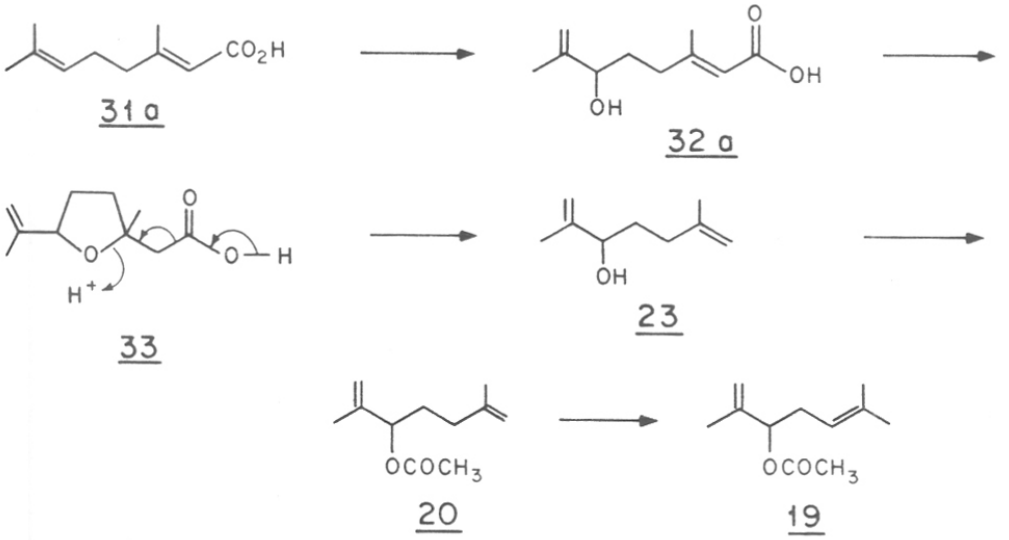
SCHEME I



31 R = OAc

32 R = OAc

SCHEME II



31a

32a

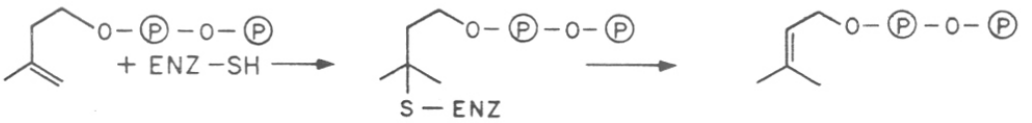
33

23

20

19

SCHEME III

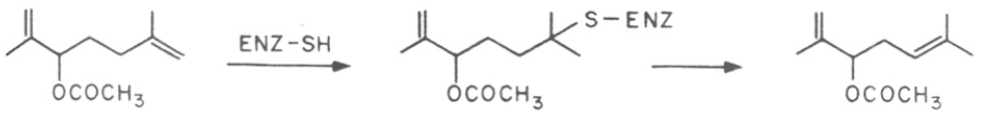


38

40

39

SCHEME IV



20

41

19

undergo β-elimination to give hydroxy alkene 23. 23 on acetylation gives 20. Conversion of 20 to 19 involves double bond migration and requires the presence of an enzyme.

During the course of biogenesis of terpenoids, Bloch[32] et al. isolated a metabolic product to which the structure Δ^3-isopentenol pyrophosphate (IPP) 38 (Chart I) was assigned. This phosphate ester 38 was shown to be a bio-genetic precursor of many of the terpenes. During the course of these investigations a preparation derived from Baker's yeast has been found to catalyze the migration of the unsaturated bond of IPP 38 to yield γ,γ-dimethylallyl pyrophosphate (DMPP) 39. Subsequently it was also realized that 39 also was incorporated in terpene biogenesis[33]. It was found that this enzyme had sulfhydryl groups[34], which led Lynen et.al. to conclude that a simple addition of enzyme and IPP to give enzyme substrate complex 40, which then undergoes elimination to give 39 and enzyme. This transformation can be written in the manner given in Scheme III, Chart III.

Precedent for the sulfide catalyzed migration of an olefinic double bond is found in the Willgerodt reaction, in which a saturated intermediate state also has been postulated[35,36].

On the basis of above mentioned arguments, we

assume that similar type of enzyme might be involved in the transformation of 20 to 19 via 41. A simple addition - elimination mechanism is given in Chart III, Scheme IV.

Incidentally we have also effected the synthesis of keto acid 42 from 28. The enantiomer of 42 i.e. 43 is naturally occuring[37]. 28 on oxidation with Jones reagent gave 42 in good yield. Compounds 21, 22, 23 and 25 were prepared from racemic isopulegol and hence are racemates. Compounds 28, 29 and 30 are prepared from (-)-menthone have the s-configuration at the acetoxy (or hydroxy) bearing carbon, since Baeyer-Villiger oxidation is known to proceed with retention of configuration[28].

EXPERIMENTAL PROCEDURE

3,7-Dimethyl-6-acetoxy-oct-7-enoic acid (22)

A mixture of hydroxy acid[24] 21 (3.0 g, 0.016 M), pyridine (2.5 g, 0.032 M) and acetic anhyride (3.2 g, 0.032 M) kept at room temperature for 24 hours. The mixture was diluted with water (100 ml), warmed upto 55-60° for 0.5 hour, cooled and extracted with ether (2x100 ml). The ether layer was washed with water, 10% solution of hydrochloric acid, 10% solution of sodium bicarbonate, water, brine, dried and evaporated to give residue, which on distillation under vacuum furnished 22 (2.9 g, 81%); b.p. 175° (bath)/0.3 mm.

IR spectrum (liquid film) showed bands at 1748 cm^{-1} (ester carbonyl), 1724 cm^{-1} (acid carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.93 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH-), 1.7 (3H, s, -$C\underline{H}_3$-C=C), 2.0 (3H, s, -$\overset{O}{\overset{\|}{C}}$-$C\underline{H}_3$), 4.86 (1H, m, vinyl H), 4.9 (1H, m, vinyl H), 5.03 (1H, t, J = 6 Hz, -C$\underline{H}$OAc), 9.7 (1H, broad singlet, OH exchangeable with D_2O).

Analysis: Found: C, 63.06; H, 8.88.

$C_{12}H_{20}O_4$ requires C, 63.13; H, 8.83.

2,6-Dimethyl-1,6-heptadien-3-ol-acetate (20)

A mixture of 22 (2.9 g, 0.01 M), cupric acetate (0.468 g, 0.0025 M), pyridine (0.300 g, 0.038 M), lead tetraacetate (12 g, 0.027 M) and benzene (75 ml) was stirred under nitrogen for 0.5 hour at room temperature

and under reflux for 2 hours. Excess of lead tetraacetate was destroyed with ethylene glycol. The product was separated into acidic and neutral positions with 10% aqueous sodium carbonate solution. Acidic part on work-up yielded compound 22 (1.1 g). Neutral part after work-up and on vacuum distillation furnishes 20 (0.825 g, 58% on the basis of 22 actually consumed), b.p. 135°(bath)/16 mm, (Lit.[22] b.p. 105-110°/13 mm).

IR spectrum (liquid film) showed bands at 1745 cm^{-1} (ester carbonyl), 1658, 897 cm^{-1} ($C=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 1.7 (6H, s, CH_3-C=C), 2.0 (3H, s, -O-CO-CH_3), 4.73 (2H, bm, $C=CH_2$), 5.0 (2H, m, $C=CH_2$), 5.2 (1H, t, J=6 Hz, -CHOAc).

2,6-Dimethyl-1,6-heptadien-3-ol (23)

A mixture of 20 (0.430 g, 0.0026 M), ethanol (10 ml) and sodium hydroxide (0.100 g, 0.025 M) was heated under reflux for 3 hours, cooled, diluted with water and extracted with ether (2x50 ml). The ether extract was washed with water, brine, dried and the solvent evaporated. Distillation of the residue in vacuum furnished 23 (0.257 g, 70%), b.p. 132° (bath)/15 mm (Lit.[22] reports b.p. 120-5°/13 mm).

IR spectrum (liquid film) showed bands at 3546 cm^{-1} (OH stretching).

NMR spectrum (CCl_4) showed signals at τ 1.7 (6H, s, CH_3-C=C-), 4.0 (1H, t, J=6 Hz, -CHOH), 4.6 (2H, bm, $C=CH_2$), 4.9 (2H, m, $C=CH_2$).

2,6-Dimethyl-1,6-heptadien-3-ol-propionate (25)

A mixture of 23 (0.250 g, 0.0178 M), pyridine (1.58 g, 0.02 M), propionic anhydride[38] (0.520 g, 0.04 M) was kept at room temperature for 48 hours. The mixture was poured into water and extracted with ether (2x50 ml). The etheral solution was washed with water, 10% hydrochloric acid solution, 10% sodium carbonate solution, brine, dried and evaporated to give the residue. The residue was vacuum distilled to give 25 (0.302 g, 84%), b.p. 121° (bath)/18 mm. IR spectrum (liquid film) showed bands at 1739 cm^{-1} (ester carbonyl), 1653 and 880 cm^{-1} (exo methylene).
NMR spectrum (CCl_4) showed signals at δ 1.33 (3H, t, J=6 Hz, $\underline{CH}_3-CH_2$), 1.73 (6H, s, $\underline{CH}_3-C=C$), 2.33 (2H, q, J=6 Hz, $-C-\underline{CH}_2-CH_3$), 4.76 (2H, m, $-C=\underline{CH}_2$), 4.96 (2H, m, $-C=CH_2$), 5.2 (1H, t, J=6 Hz, $-\underline{CH}OPr$).

Analysis: Found C, 73.55; H, 10.35.

$C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27.

2,6-Dimethyl-1,6-heptadien-3-one (24)

A mixture of 23 (0.175 g, 0.0013 M), petroleum ether (25 ml) and active manganese oxide was stirred at room temperature for 3 hours. The petroleum ether filtrate obtained after filtration was concentrated to give the residue, which on distillation under vacuum gave 24 (0.167 g, 93%), b.p. 105°(bath)/20mm.

IR spectrum (liquid film) showed bands at 1667 cm^{-1} (conjugated carbonyl), 1639 cm^{-1} ($C=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 1.76 (3H, s, CH_3-C=C), 1.86 (3H, s, CH_3 on double bond conjugated to carbonyl), 4.66 (2H, m, $C=CH_2$), 5.73 (1H, m, vinyl H), 5.93 (1H, m, vinyl H).

Analysis: Found C, 78.81; H, 10.30

$C_9H_{14}O$ requires C, 78.21; H, 10.20.

3R-7-Dimethyl-6S-hydroxy-octanoic acid (28)

A mixture of (-)-menthone[27] 26 (6.0 g, 0.038 M), glacial acetic acid (12 ml), peroxy acetic acid (10 ml, 40%) and concentrated sulfuric acid (0.250 g) was kept at room temperature for 18 hours and then heated at 50°C for 0.5 hour. The mixture was cooled, diluted with water and extracted with ether (2x75 ml). The etheral layer was washed with water and 10% sodium bicarbonate solution. Removal of ether led to the recovery of unreacted menthone. Aqueous portion after acidification with 10% hydrochloric acid solution and extracted with ether (1x100 ml). The ether was washed with water, brine, dried and evaporated to give a mixture of 28 and 29 (5.9 g). The above mixture was saponified with ethanolic sodium hydroxide and refluxed for 2 hours. The mixture was acidified with 10% hydrochloric acid solution and extracted with ether (2x100 ml). The ether layer was washed with water, brine, dried and evaporated to give 28 (5.1 g) identified by comparison of IR and NMR with authentic sample[24] reported by us.

3R-7-Dimethyl-6S-acetoxy-octanoic acid (29)

A mixture of 28 (2.5 g, 0.013 M), pyridine (1.97 g, 0.025 M) and acetic anhydride (2.55 g, 0.025 M) was kept at room temperature for 24 hours. The mixture was diluted with water and extracted with ether (2x50 ml). The etheral layer was washed with water, 10% hydrochloric acid solution, brine and evaporated to give residue, which after distillation gave 29 (1.8 g, 62%), b.p. 168°(bath)/0.3 mm. $(\alpha)_D$ = +12 (c, 40).

IR spectrum (liquid film) showed bands at 1745 cm^{-1} (ester carbonyl), 1718 cm^{-1} (acid carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.83 (6H, d, J = 6 Hz, $(CH_3)_2CH$, 1.03 (3H, d, J=6 Hz, CH_3-CH), 2.06 (3H, s, O-C-CH_3), 4.73 (1H, m, CHOAc).

Analysis: Found C, 62.88; H, 9.40.

$C_{12}H_{22}O_4$ requires C, 62.58; H, 9.63.

2,6-Dimethyl-hept-6-en-3S-ol acetate (30)

A mixture of 29 (1.0 g, 0.0043 M), cupric acetate (0.158 g, 0.00087 M), pyridine (0.100 g, 0.0012 M), lead tetraacetate (3.9 g, 0.0087 M) and benzene (25 ml) was stirred under nitrogen atmosphere for 0.5 hours at room temperature and under reflux for 2 hours. Excess of lead tetraacetate destroyed with ethylene glycol. The benzene layer was washed with water, 10% sodium carbonate solution, brine, dried and evaporated to give residue, which after distillation under vacuum gave 30 (0.265 g, 33%), b.p. 130-5° (bath)/16 mm. $(\alpha)_D$ = +3.3 (c, 12).

IR spectrum (liquid film) showed bands at 1739 cm^{-1} (carbonyl of ester), 1664 and 885 cm^{-1} ($C=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 0.88 (6H, d, J=6 Hz, $(C\underline{H}_3)_2CH$, 1.7 (3H, s, $-C\underline{H}_3-C=C$), 2.0 (3H, s, $\underset{O}{C}-C\underline{H}_3$), 4.66 (2H, m, $C=C\underline{H}_2$), 4.83 (1H, t, J=6 Hz, $-C\underline{H}OAc$).

Analysis: Found C, 71.69; H, 10.94.

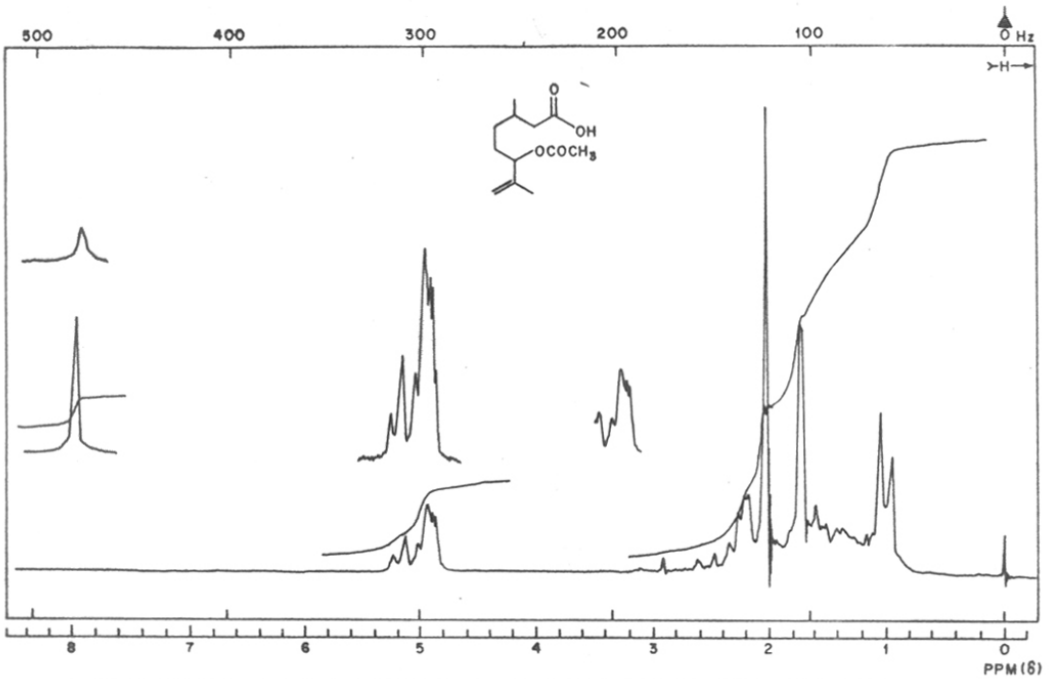
$C_{11}H_{20}O_2$ requires C, 72.08; H, 10.84.

3R,7-Dimethyl-6-oxo-octanoic acid (42)

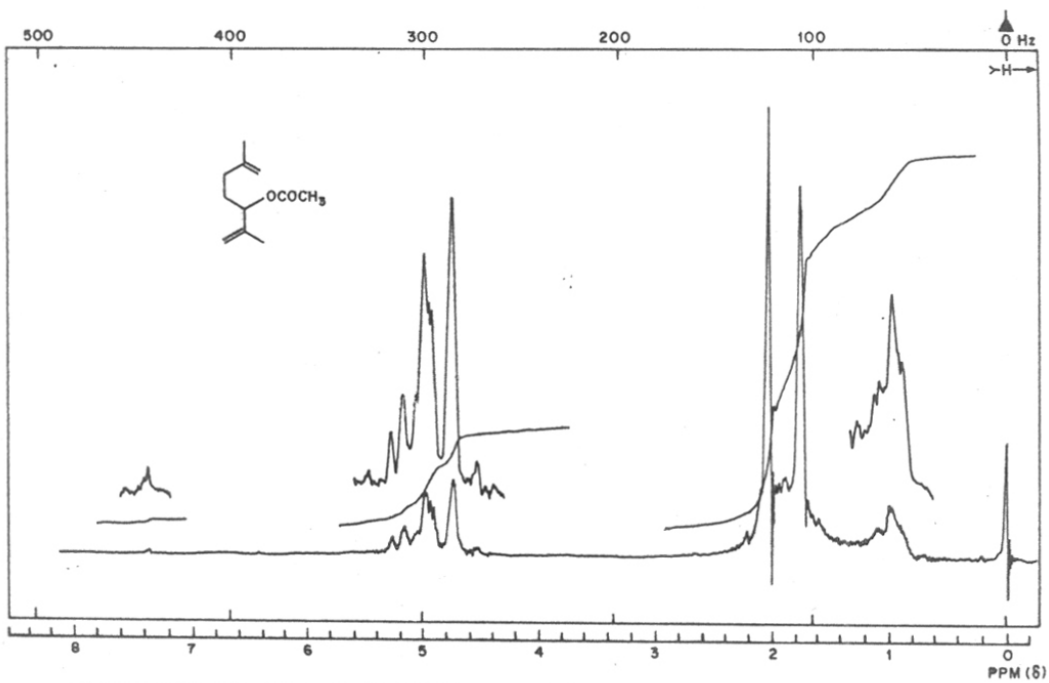
To a mixture of hydroxy acid 28 (2.0 g, 0.011 M) in acetone (30 ml) at 0° was added Jones reagent till the orange colour of reagent was persistent. The mixture stirred for 1 hour at room temperature, diluted with water and extracted with ether (2x50 ml). The etheral layer was washed with water, brine, dried and evaporated to give a liquid, which on distillation under vacuum gave 42 (1.9 g, 93%), b.p. 148° (bath)/0.6 mm. $(\alpha)_D$ = +7.8 (c, 40).

IR spectrum (liquid film) showed band at 1712 cm^{-1} (for keto and acid carbonyl).

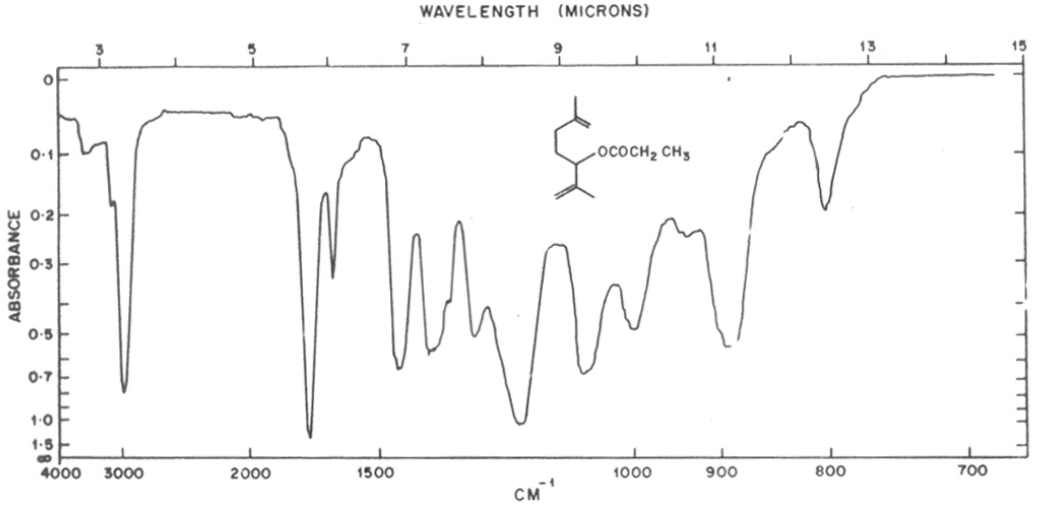
NMR spectrum (CCl_4) showed signals at τ 0.87 (3H, d, J=6 Hz, $C\underline{H}_3-CH$), 1.1 (6H, d, J= 6 Hz, $(CH_3)_2CH$), 2.2-2.7 (5H, m, $-CH_2$ and -CH- adjacent to carbonyl), 10.8 (1H, bs, $-COO\underline{H}$ exchanges on addition of D_2O).



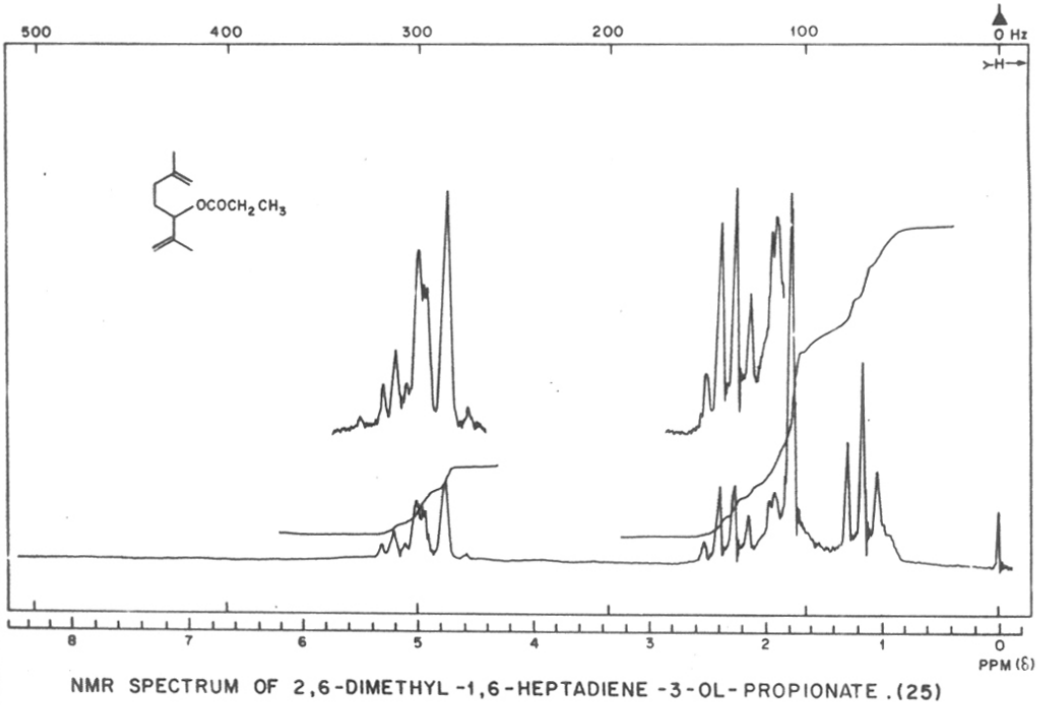
NMR SPECTRUM OF 3,7-DIMETHYL-6-ACETOXY-OCT-7 ENOIC ACID. (22)



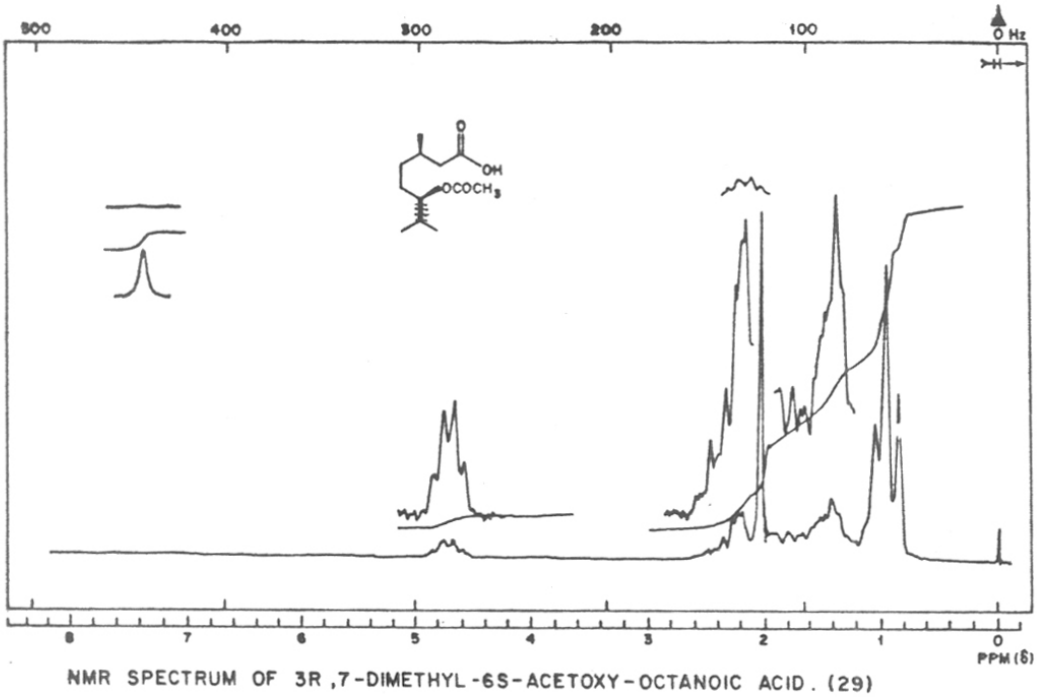
NMR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIEN-3-OL-ACETATE. (20)



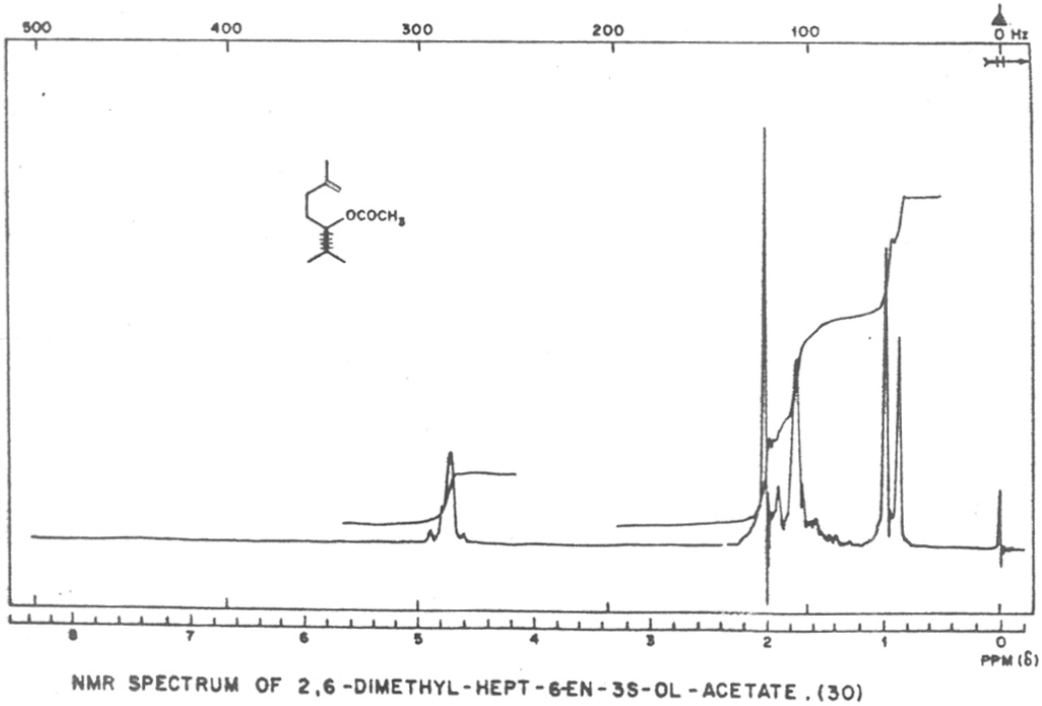
IR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIENE-3-OL-PROPIONATE.(25)



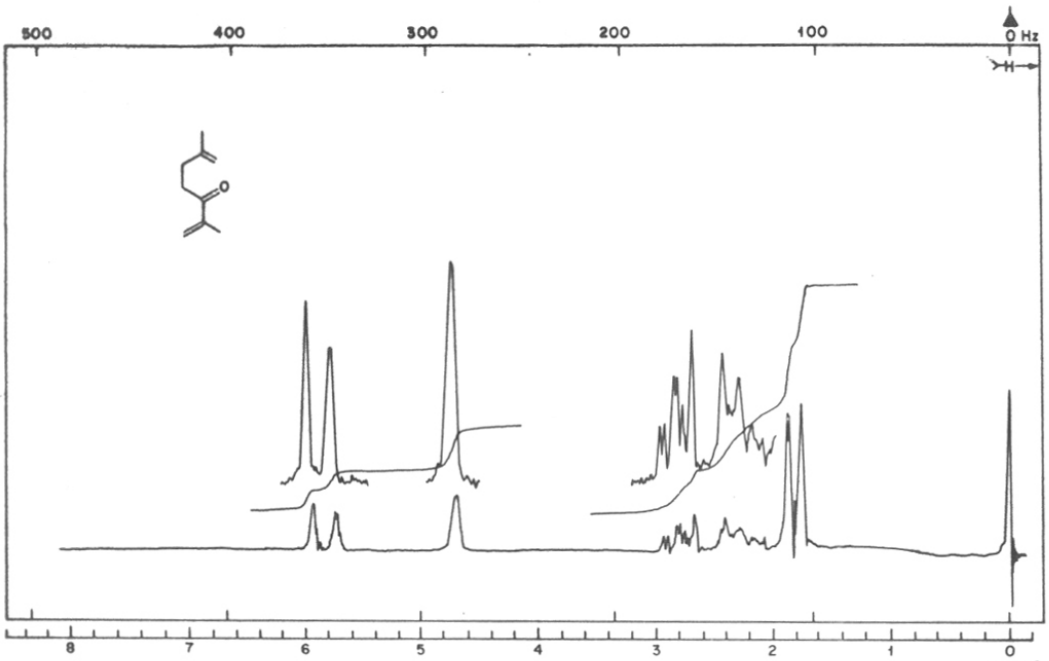
NMR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIENE-3-OL-PROPIONATE.(25)



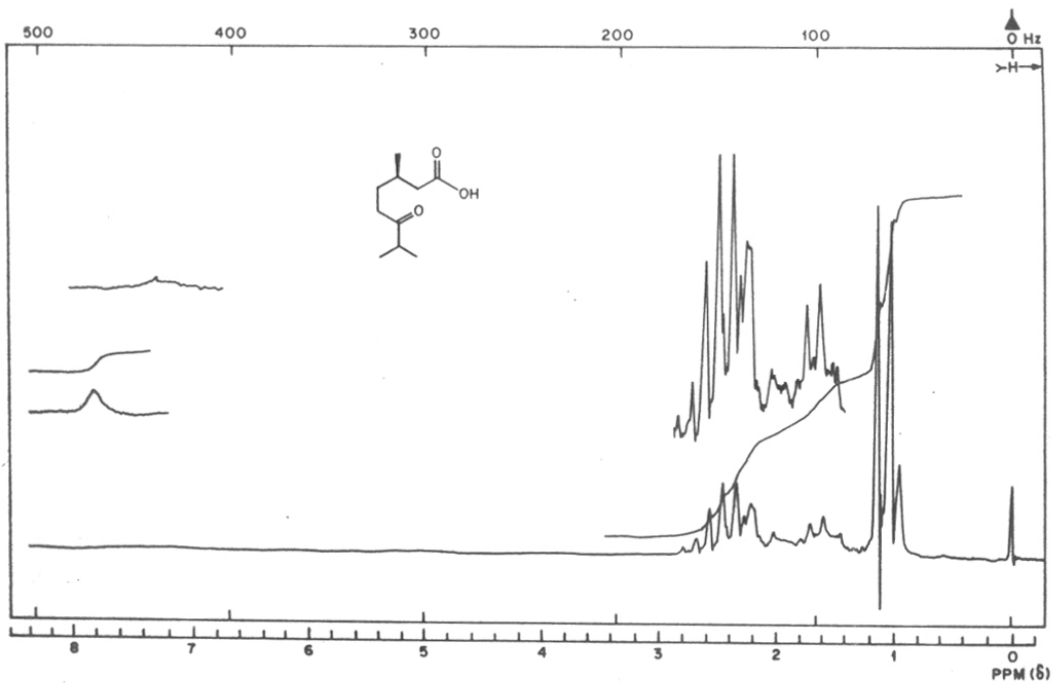
NMR SPECTRUM OF 3R,7-DIMETHYL-6S-ACETOXY-OCTANOIC ACID. (29)



NMR SPECTRUM OF 2,6-DIMETHYL-HEPT-6-EN-3S-OL-ACETATE. (30)



NMR SPECTRUM OF 2,6-DIMETHYL-1,6-HEPTADIEN-3-ONE.(24)



NMR SPECTRUM OF 3R,7-DIMETHYL-6-OXO-OCTANOIC ACID. (42)

REFERENCES

1. K. Eiter; Fortschr.Chem.Org.Natu., 28, 204 (1970).
2. D.L. Wood, R.M. Silverstein and M. Nakajima, Eds., Control of Insect Behaviour by Natural Products, New York, Academic Press, 1970.
3. M. Beroza, Ed., Chemicals Controlling Insect Behaviour, New York, Academic Press, 1970.
4. M. Jacobson, Insex Sex Pheromones, New York, Academic Press, 1972.
5. M.C. Birch, Pheromones, New York, American Elsevier, 1974.
6. J.M. Brand, J.C. Young and R.M. Silverstein, Fortschr.Chem.Org.Natu., 37, 1 (1979).
7. J.G. MacConnel and R.M. Silverstein, Angew.Chem.Int.Ed.Eng., 12, 644 (1973).
8. D.A. Evans and C.L. Green, Chem.Soc.Rev., 2, 75 (1973).
9. H.H. Shorey, Annu.Rev.Entomol., 18, 349 (1973).
10. R. Rossi, Synthesis, 413 (1978).
11. B.C. Mayo, Chem.Soc.Rev., 2, 49 (1973).
12. E.L. Plummer, T.E. Stewart, L.L. McCandless, J.R. West and R.M. Silverstein, J.Chem.Ecol., 3, 27 (1977).
13. K. Mori, Agri.Bio.Chem., 40, 415 (1976).
14. E.L. Plummer, T.E. Stewart, K. Byine, G.T. Pearce and R.M. Silverstein, J.Chem.Ecol., 2, 307 (1976).
15. G.T. Pearce, W.E. Gore and R.M. Silverstein, J.Mag.Res., 27, 497 (1977).
16. G.T. Pearce, W.E. Gore and R.M. Silverstein, J.Org.Chem., 40, 2797 (1976).
17. C.A. Reece et.al. Tetrahedron, 24, 4249 (1968).
18. D.L. Wood, R.W. Stark and R.M. Silverstein, Nature, 215, 206 (1967).
19. D.L. Wood et.al., Science, 159, 1373 (1968).

20. K. Mork, J.P. Vite, R. Hedden, Naturwissenschaften, 63, 43 (1976).

21. P.A. Hedin, Chem.Abs., 85, 138345 (1976).

22. M. Uchida, K. Nakagawa, T. Negishi, S. Asano and K. Mori, Agri.Bio.Chem., 45, 369 (1981).

23. T. Negishi, M. Uchida, T. Ishiwatari, S. Asano, K. Nakagawa, Y. Tamaki and K. Mori, Appl.Entomol.Zool., 15, 328 (1980).

24. K. Shankaran and A.S. Rao, Ind.J.Chem., 18B, 507 (1979).

25. R.A. Sheldon and J.K. Kochi, Org.Reactions, 19, 279 (1972).

26. A.S. Vaidya, S.M. Dixit and A.S. Rao, Tet.Lett., 5173 (1968).

27. L.T. Sandborn, Org.Synth., Coll. Vol.I, 340.

28. D. Rosenthal, A.O. Niederneyer and J. Fried, J.Org.Chem., 30, 510 (1965) and references cited therein.

29. J.A.A. Renwick, P.R. Hughes and I.S. Krull, Science, 191, 199 (1976).

30. P.R. Hughes, J.Insectphysiol., 20, 1271 (1974).

31. B.D. Mookherjee and R.W. Trenkle, J.Agri.Food.Chem., 21, 298 (1973).

32. K. Bloch, S. Chaykin, J.Law, A.H. Phillips and T.T. Tehen, Proc.Nat.Acad.Sci.U.S., 44, 998 (1958).

33. F. Lynen, V. Henning, H. Eggerer and B.H.Agranoff, J.Am.Chem.Soc., 81, 1254 (1959).

34. F. Lynen, B.W. Agranoff, H. Eggerer, V. Henning, and E.M. Moslen, Angew.Chem., 71, 657 (1959).

35. M. Carmack and D.L.F. Detar, J.Am.Chem.Soc., 68, 2029 (1946).

36. J.A. King and F.H. McMillan, J.Am.Chem.Soc., 68, 632 (1946).

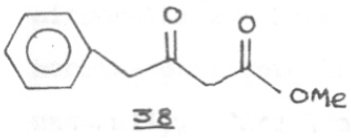
37. E. Klein and W. Rojohn, Dragoco Rep., 24, 55 (1977).

38. W. Gerrard and A.M. Thrush, J.Chem.Soc., 741 (1952).

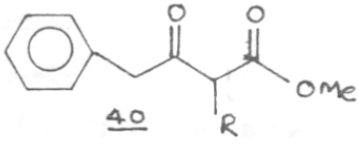
CHAPTER II : TRANSFORMATION OF ALKYL HALIDES TO ALDEHYDES CONTAINING TWO MORE CARBON ATOMS

Summary

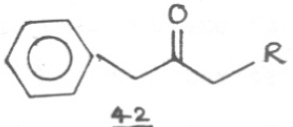
A four step process for the conversion of alkyl halides to aldehydes containing two extra carbon atoms forms the subject matter of this Chapter. Enolate derived from methyl-3-oxo-4-phenyl butyrate 38 by the action of sodium hydride/benzene on treatment with various alkyl halides gave alkylated esters 40. 40 on hydrolysis gave benzyl ketones 42. Sodium borohydride reduction of 42 formed alcohols 4. Reaction of 4 with lead tetraacetate gave aldehydes 5.



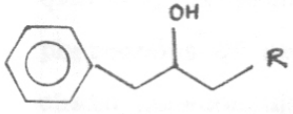
38



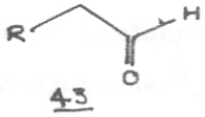
40



42



42

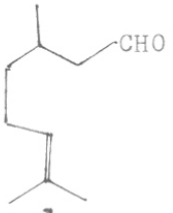


43

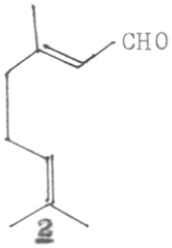
Introduction

As a consequence of their ready accessibility coupled with their versatile chemical properties aldehydes and ketones rank as the most important classes of compounds in organic chemistry. These compounds owe their importance as synthetic intermediates to the presence of the polarizable carbon-oxygen double bond which governs their chemical reactivity. The modern concept of umpulong or charge affinity inversion[1,2] has resulted in the extensive development methodology and has greatly diversified the nature of the chemical reactions available to the synthetic chemist for the construction of new carbon bonds.

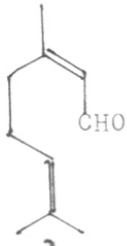
Several aldehydes are important in perfumery industry. In recent years, these have come from technical synthesis as well as from the traditional essential oils, such as citronella and lemongrass oils. Citronellal 1 is a monoterpene; both the (R)-(+)- and (S)-(-)-forms occur naturally. Citral exists as (E) and (Z) forms known as citral(a) 2 and citral(b) 3. The mixture is used in perfumery and is also important intermediate for the manufacture of α- and β-ionone. The characteristic flavours of many common fruits are due to the presence of small quantity of saturated aldehydes[3]. The sex attractant pheromones of several species of lepidoptera are straight chain non-conjugated olefinic aldehydes[4].



1



2



3

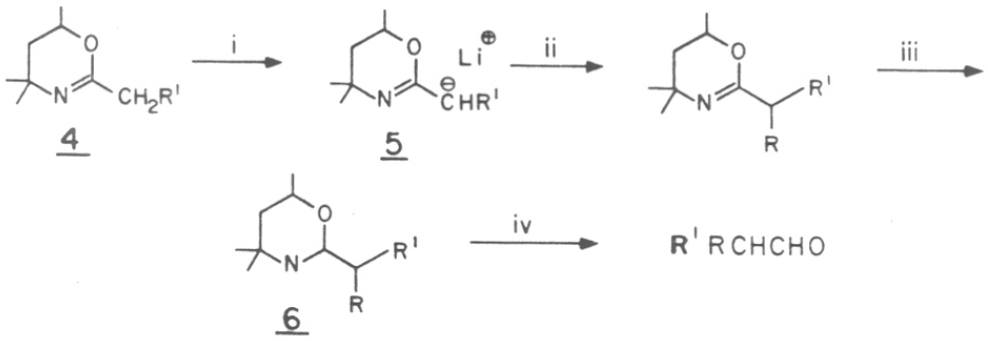
There are several reports in literature wherein alkyl halides can be converted to aldehydes. For example Grignard reagents prepared from alkyl halides have been formylated by reaction with N,N-dialkyl formamides[5,6]. A different route employs treatment of Grignard with 1,1,3,3-tetramethyl butyl isocyanate and hydrolysis of the resultant metallated aldimine.[7]

There are few reports in the literature regarding the conversion of alkyl halide to aldehydes homologated with a two extra carbon atoms.

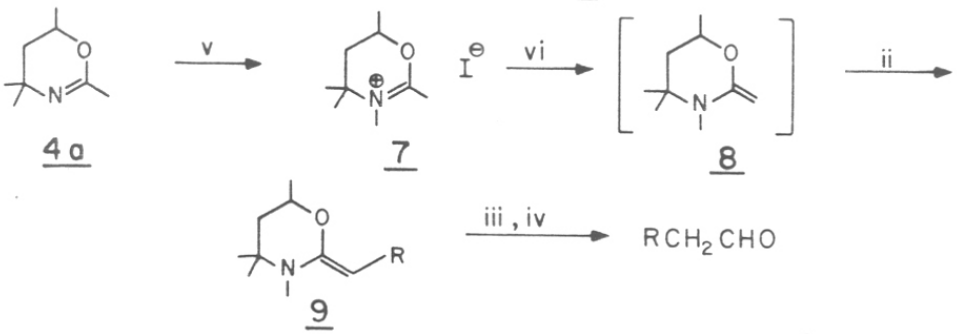
A.I. Meyers[8] has developed a range of versatile aldehyde syntheses based on the production and subsequent hydrolysis of tetrahydro-oxazines. In one such synthesis an alkyl halide is converted into aldehyde containing two more carbon atoms. In this process dihydro-4H-1,3-oxazine 4 is prepared from nitrile and 2-methyl pentane 2,4-diol. 4 on lithiation with n-BuLi gave lithiated species 5 which upon subsequent reaction with alkyl halide and sodium borohydride gave tetrahydro oxazine derivative 6, which was then hydrolyzed to the aldehyde (Chart I, Scheme I).

CHART I

SCHEME I

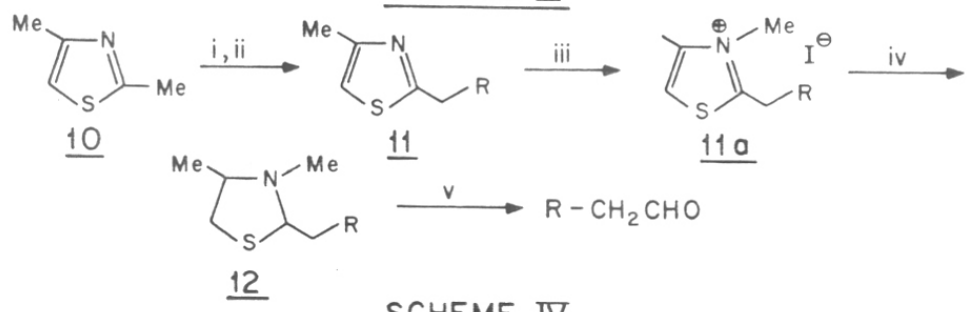


SCHEME II

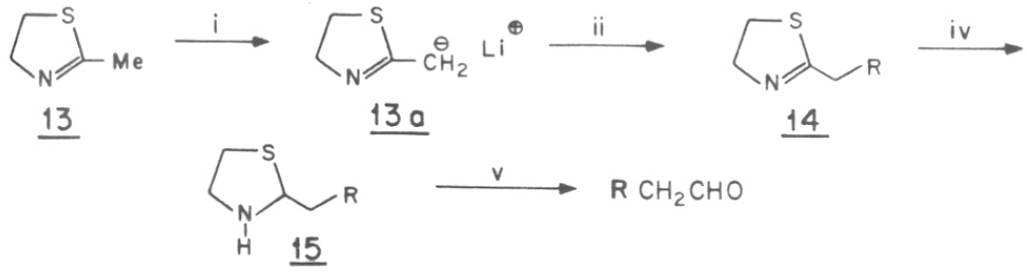


Reagents : i) n-Buli , ii) R−X , iii) $NaBH_4$, iv) $H_3O^{\oplus}$, v) MeI , vi) NaH / DMF

SCHEME III



SCHEME IV



Reagents : i) n-Buli , ii) R-X , iii) $(CH_3)_3O^{\oplus}BF_4^{\ominus}$, SO_2 , iv) $NaBH_4$, v) $HgCl_2$, H_2O

In an another approach[9] Meyer et.al. have reported a method wherein 1,3-oxazine 4a formed methiodide salt 7 on reaction with methyl iodide. 7 was transformed into ketene N,O-acetal 8 by treatment with sodium hydride in dimethyl formamide (DMF). Alkylation of 8 with various alkyl halide gave alkylated product 9. Reaction of 9 with sodium borohydride and subsequent hydrolytic cleavage gave aldehyde (Chart I, Scheme II).

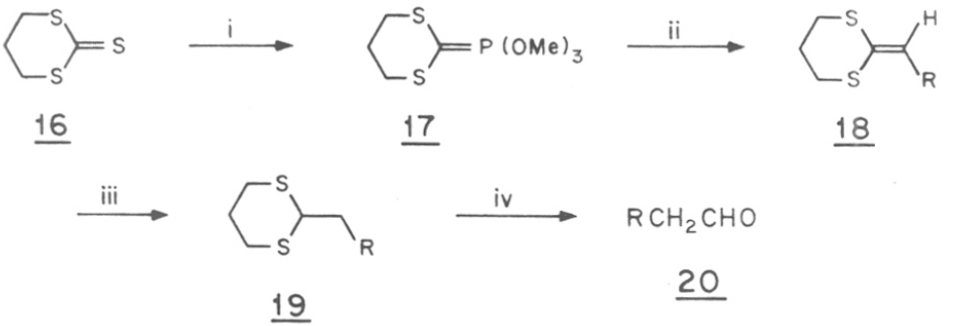
Altman[10] reported a method based on lithiation technique. This method takes advantage of the hydrolysis of thiazolidines on treatment with mercuric chloride catalyst. 2,3-Dimethyl-1,3-thiazoline 10 on lithiation and subsequent quenching with alkyl halide gave alkylated product 11. 11 was transformed to tetrahydro derivative 12 upon reaction with sodium borohydride, which on hydrolysis yielded aldehyde (Chart I, Scheme III).

A modified version of above method[11] by Meyers starts with 2-methyl-2-thiazoline 13. 13 was transformed to alkylated derivative 14 via intermediate lithiated species 13a. 14 was reduced to tetrahydro derivative 15. The latter was cleaved to the aldehyde by treatment with mercuric chloride in aqueous acetonitrile (Chart I, Scheme IV).

So far we have seen the methods by which one can get aldehydes depending upon the availability of lithiated species and its subsequent reaction with alkyl halides.

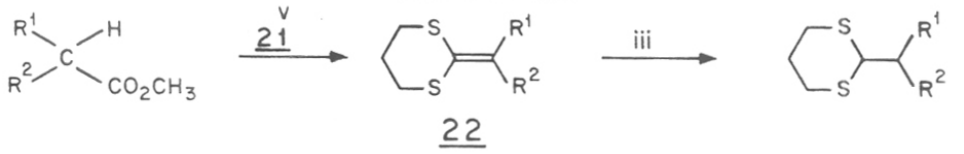
CHART II

SCHEME I



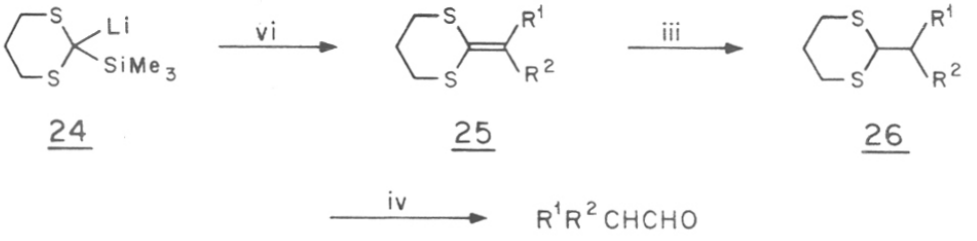
16 17 18 19 20

SCHEME II



22 23

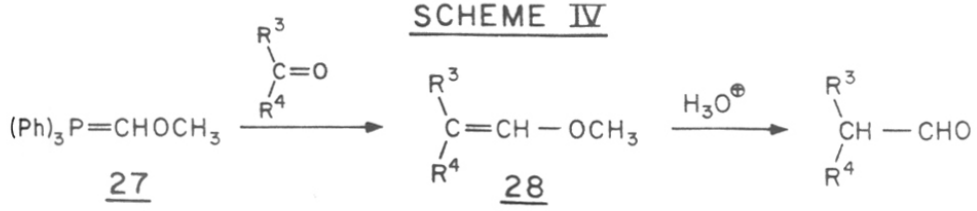
SCHEME III



24 25 26

Reagents : i) $P(OMe)_3$, ii) R − CHO , iii) CF_3CO_2H , Et_3SiH ,
iv) HgO , v) $(Me)_2AlS(CH_2)_3SAl(Me)_2$, vi) R^1COR^2

SCHEME IV



27 28

Prof. Corey developed few aldehyde synthesis. In one such synthesis[12], 1,3-dithiacyclohexan-2-thione 16 reacts with trimethyl phosphite to give 1,3-dithiacyclohexylidinetrimethoxyphosphorane 17, which reacts with aldehyde to form ketene thioacetal 18, which is transformed to 19 and subsequently to aldehyde 20 (Chart II, Scheme I).

Another approach developed by Corey[13] makes use of the ready availability of bis(dimethyl aluminium)-1,2-ethane dithiolate 21. 21 reacts with various esters to give ketene thioacetal 22, which on workup gave aldehydes 23 (Chart II, Scheme II).

Carey et. al.[14] synthesis of these aldehydes starts from 2-lithio-2-trimethylsilyl-1,3-dithiane 24. 24 reacts with aldehydes or ketones to afford ketene thioacetal 25. Protonation-hydride transfer reaction using trifluoroacetic acid and triethyl silane transform 25 to 26 and deprotection of 26 gives aldehyde (Chart II, Scheme III).

Phosphorane 27 reacts with an aldehyde or ketone to give enol ether 28, which underwent hydrolysis to aldehydes (Chart II, Scheme IV).

PRESENT WORK

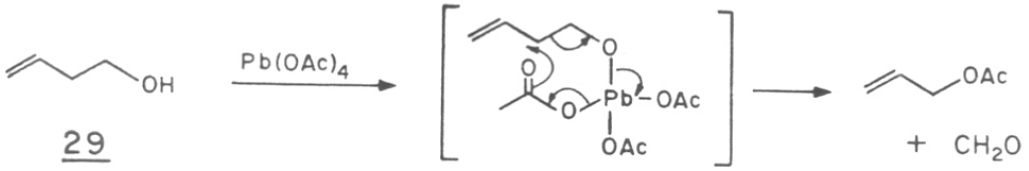
In view of the importance of aldehydes in natural product and synthetic chemistry, we have developed a new route for the synthesis of aldehydes.

There have been various reports in literature that homoallylic alcohols can be easily fragmented on treatment with lead tetraacetate[16,17]. Moon and Lodge[18] have carried out the reaction of lead tetraacetate on 3-buten-1-ol 29 and they obtained a product derived from the cleavage reaction (Chart III, Scheme I). The driving force for the formation of this product was explained due to the enhanced stability of the intermediate allyl radical. This work was further supported by the fact that 2-phenylethanol 30 also gave a product as a result of cleavage reaction to give benzylacetate and formaldehyde (Chart III, Scheme II). In this particular case one gets the formation of benzyl radical 31.

Wheeler and Brande[19] also reported that steroid alcohol 32 on hypoiodite reaction gave the cleavage product 33 and benzyl iodide 34. Benzyl iodide 34 is formed from benzyl radical (Chart III, Scheme III). Recently we have synthesised aromatic aldehydes[20], based on the fragmentation of appropriate homobenzylic alcohols 35 (Chart III, Scheme IV).

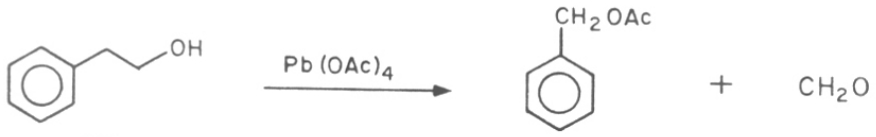
CHART III

SCHEME I

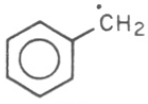


29

SCHEME II

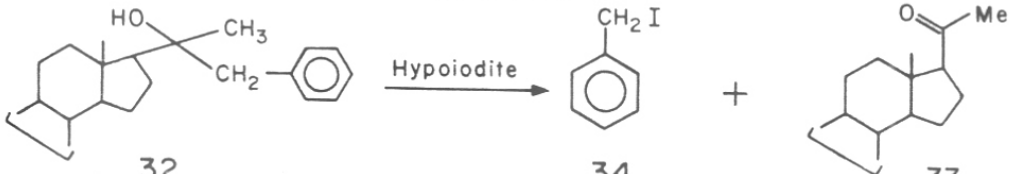


30



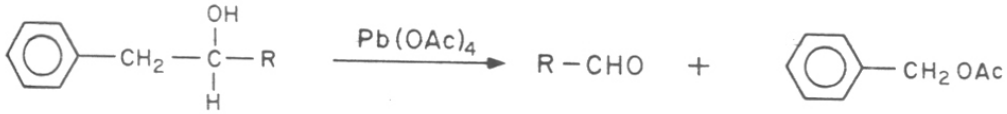
31

SCHEME III



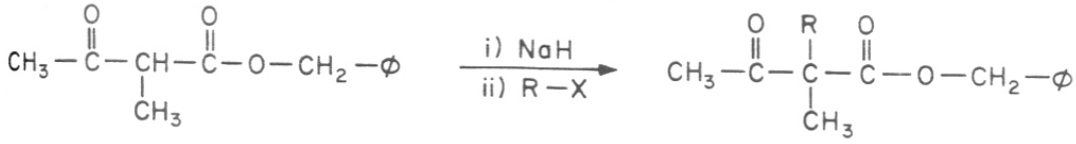
32 34 33

SCHEME IV



35

SCHEME V



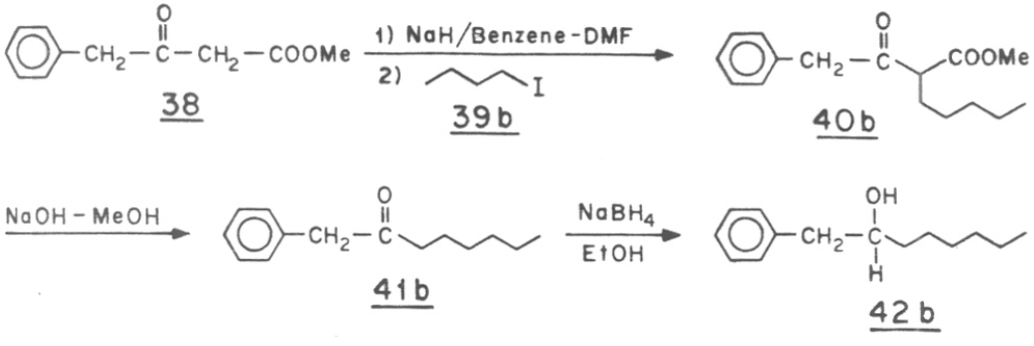
36 37

In a study designed to broaden the scope of fragmentation reaction we have developed a route (Chart V) by which alkyl halides can be converted into aldehydes having two additional carbon atoms.

Burgsthaler et.al[21] have reported that β-keto ester 36, can be alkylated with alkyl halides in the presence of sodium hydride in benzene/DMF to give the alkylated ester 37 in 90% yield (Chart III, Scheme V). We have observed that methyl-3-oxo-4-phenylbutanoate 38 reacts with iodopentane 39b under identical experimental conditions of Burgsthaler's procedure to give 40b. (Chart IV, Scheme I). The identity of 40b was established through elemental analysis and NMR. The NMR spectrum of 40b showed signals at δ 3.46 (1H, t, J=7 Hz, -CO-CH) and 3.7 (2H, s, Ar-CH_2-CO). Saponification of 40b in methanolic sodium hydroxide gave 41b. In this particular reaction the ester group first gets hydrolysed to give β-keto acid, which then easily decarboxylates to give 41b (Chart IV, Scheme II). The NMR spectrum of 41b displayed signals at 2.36 (2H, t, J=6 Hz, -CO-CH_2-) and 3.63 (2H, s, Ar-CH_2-CO-). The benzyl ketone 41b was transformed into secondary homobenzylic alcohol 42b using sodium borohydride in ethanol. The NMR spectrum of 42b showed signals at δ 2.66 (2H, t, J=6 Hz, Ar-CH_2-CH-) and 3.7 (1H, m, -CHOH). The alcohol 42b was also characterised from IR spectral

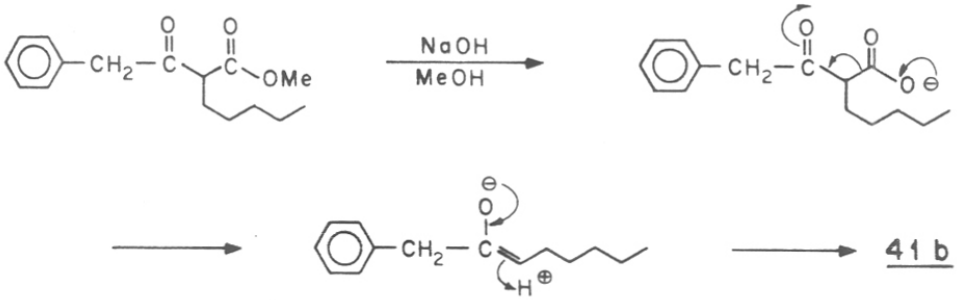
CHART IV

SCHEME I



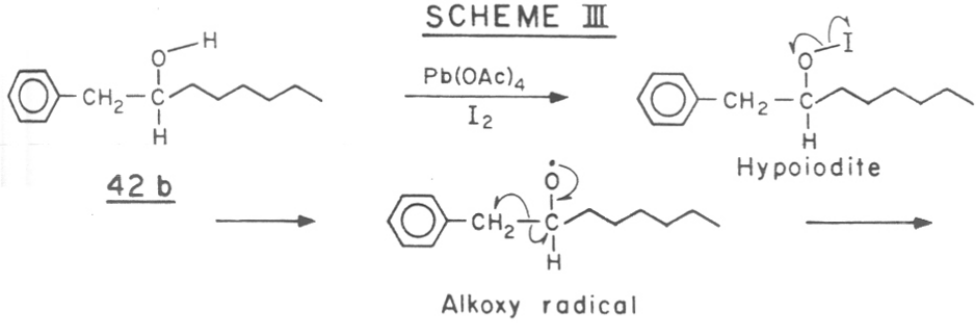
38 → 40b (39b) → 41b → 42b → 43b + 44

SCHEME II

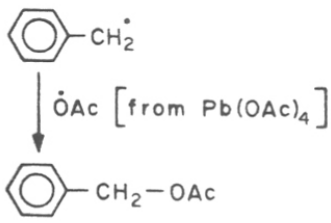


→ 41b

SCHEME III



42b → 43b + 44



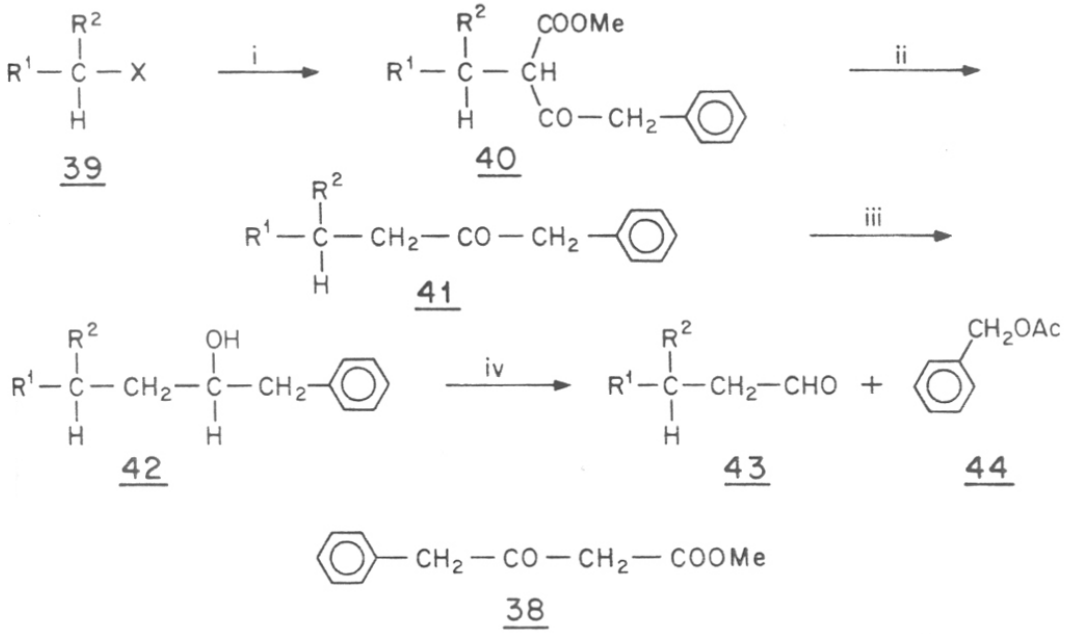
data and showed the disappearance of carbonyl band (1706 cm^{-1}) and appearance of band at 3571 cm^{-1} (hydroxyl stretching). Alcohol 42b on heating with lead tetraacetate in the presence of iodine[16,23] underwent fragmentation to furnish in satisfactory yield the aldehyde 43b.

A probable mechanism involving hypoiodite as a reaction intermediate for the transformation of 42b to aldehyde 43b is given in Chart IV, Scheme III. Benzyl acetate 44 is chief by product in this homobenzylic alcohol fragmentation. A large boiling point difference between benzyl acetate 44 and heptanal 43b enabled us a very efficient separation of aldehyde from benzyl acetate. 43b was characterized as 2,4-Dinitrophenylhydrazone. The identity of 43b was further established by direct comparison with heptanal (heptaldehyde) by means of GLC studies.

At the alkylation step one can use either primary bromides or iodides. Better results were obtained by using iodides. In the case of secondary halides[+] the iodo compound has to be employed for getting satisfactory yield. On the identical lines alkyl halide 39a and 39c-e were transformed to aldehydes 43a and 43c-e.

[+]Successful alkylation and further reactions were carried out on 2-iodo octane by D.G. Talekar and A.S. Rao - personal communication.

CHART V



39 40 41 42 43 44 38

Reagents : i) 38, NaH/benzene-DMF , ii) NaOH — MeOH

iii) $NaBH_4$/EtOH , iv) $Pb(OAc)_4$ - I_2/benzene

FOR ALL COMPOUNDS IN THE SERIES

Compound	R^1	R^2	X
a		H	Cl
b	n-C_4H_9	H	I
c	n-C_6H_{13}	H	Br
d	n-$C_{13}H_{27}$	H	I
e	n-$C_{15}H_{31}$	H	I

EXPERIMENTAL PROCEDURE

Methyl-3-oxo-4-phenyl butanoate (38)

To a stirred mixture of Meldrums acid[24] (10 g, 0.07 M), pyridine (12.6 g, 0.154 M) and dichloro-methane (30 ml) at 0° was added a solution of phenyl acetylchloride[25] (12 g, 0.077 M) in dichloro-methane (20 ml) for a period of 0.5 hour. The mixture stirred at 0° for one more hour and at room temperature for 1.5 hours. The dichloromethane layer was washed with water, 10% solution of hydrochloric acid, brine, dried and evaporated to give brown residue. The residue without purification was dissolved in methanol (75 ml) and refluxed for 3 hours. The excess methanol was removed and the residue was extracted with ether (3x100 ml). The etheral layer was washed with water, brine, dried and evaporated to give the product, which on distillation under vacuum gave 38 (12.0 g, 80%), b.p. 120°/1.5 mm.

GENERAL METHOD FOR ALKYLATION

1-Phenyl-3-carbomethoxy-2-octanone 40b

A solution of β-keto ester 32 (1.92 g, 0.01 M) was added to a stirred suspension of sodium hydride (0.24 g, 0.01 M) in benzene (20 ml) and dimethyl formamide (4 ml) over a period of half hour at room temperature. Subsequently iodo pentane 39b (2.0 g, 0.01 M) was added

and the reaction mixture was heated at 45-50° for 24 hours and then at 80° for 24 hours. The reaction mixture poured into water. The benzene layer was separated and aqueous layer extracted with benzene (2x50 ml). The combined benzene extracts were washed with water, brine and dried. The residue obtained after the evaporation of benzene was chromatographed[26] on a column of alumina (Grade II). The alumina was eluted successively with (i) Petroleum ether (ii) Petroleum ether + 10% benzene (iii) Petroleum ether + 30% benzene (iv) Petroleum ether + 50% benzene (v) benzene. The fraction eluted out with petroleum ether + 30% benzene was 40b (1.83 g, 70%), R_f = 0.50 (85: 15 mixture of petroleum ether + acetone and with respect to 38. 38 showed R_f = 0.26 in the same solvent system.

IR spectrum (liquid film) showed bands at 1739 cm^{-1} (carbonyl of ester), 1701 cm^{-1} (carbonyl of ketone).
NMR spectrum (CCl_4) showed signals at τ 3.46 (1H, t, J=7 Hz, -CO-C<u>H</u>-), 3.60 (3H, s, -OC<u>H</u>$_3$), 3.7 (2H, s, -C<u>H</u>$_2$-CO-), 7.2 (5H, s, aromatic protons).
Analysis: Found C, 73.15; H, 8.45.
$C_{16}H_{22}O_3$ requires C, 73.25; H, 8.45.

1-Phenyl-3-carbomethoxy-2-decanone 40c

Alkylation was done in an identical manner to give 40c (60%), R_f = 0.52 (85:15 mixture of petroleum ether + acetone).

IR spectrum (liquid film) showed bands at 1736 cm^{-1} (carbonyl of ester), 1706 cm^{-1} (carbonyl of ketone).

NMR spectrum (CCl_4) showed signals at τ 3.36 (1H, t, J=6 Hz, -CO-C<u>H</u>-), 3.53 (3H, s, -OC<u>H</u>$_3$), 3.6 (2H, s, C<u>H</u>$_2$-CO-), 7.06 (5H, s, aromatic protons).

Analysis: Found C, 74.74; H, 9.03.

$C_{18}H_{26}O_3$ requires C, 73.44; H, 9.03.

1,4-Diphenyl-3-carbomethoxy-2-butanone 40a

Alkylation was done in an identical manner as given for procedure 40b to give 40a (62%), R_f = 0.38 (85:15 mixture of petroleum ether + acetone).

IR spectrum (liquid film) showed bands at 1742 cm^{-1} (ester carbonyl) and 1712 cm^{-1} (keto carbonyl).

NMR spectrum (CCl_4) showed signals at τ 3.06 (2H, d, J=7 Hz, -CH-C<u>H</u>$_2$-Ar), 3.5-3.6 (5H, OC<u>H</u>$_3$ and Ar-C<u>H</u>$_2$-CO), 3.76 (1H, t, J = 6 Hz, -C<u>H</u>-CH$_2$), 7.1 (10H, aromatic protons).

Analysis: Found C, 76.34; H, 6.57.

$C_{18}H_{18}O_3$ requires C, 76.57; H, 6.43.

1-Phenyl-3-carbomethoxy-2-heptadecanone 40d

Alkylation was performed in the identical manner to give 40d (76%), R_f = 0.60 (85:15 mixture of petroleum ether + acetone).

IR spectrum (liquid film) showed bands at 1745 cm^{-1} (ester carbonyl) and 1710 cm^{-1} (keto carbonyl).

NMR spectrum (CCl_4) showed signals at τ 3.45 (1H, t, J= 6 Hz, -C<u>H</u>-CH_2), 3.68 (3H, s, -OC<u>H</u>$_3$), 3.72 (2H, s, -C<u>H</u>$_2$-CO-), 7.08 (5H, s, aromatic protons).

Analysis: Found C, 76.91; H, 10.49.

$C_{25}H_{40}O_3$ requires C, 77.27; H, 10.38.

1-Phenyl-3-carbomethoxy-2-nonadecanone 40e

Alkylation in a similar manner gave 40e (84%), R_f = 0.54 (85:15 mixture of petroleum ether + acetone). IR spectrum (liquid film) showed bands at 1739 cm^{-1} (ester carbonyl) and 1712 cm^{-1} (keto carbonyl). NMR spectrum (CCl_4) showed signals at τ 0.8-1.26 (33H, methylene and methyl of side chain), 3.53 (1H, t, J = 6 Hz, -C<u>H</u>-CH_2), 3.63 (3H, s, -OC<u>H</u>$_3$), 3.7 (2H, s, -C<u>H</u>$_2$-CO-), 7.1 (5H, s, aromatic protons).

Analysis: Found C, 77.66; H, 10.50.

$C_{27}H_{44}O_3$ requires C, 77.83; H, 10.65.

GENERAL PROCEDURE FOR HYDROLYSIS

1-Phenyl-2-octanone 41b

A mixture of keto ester 40b (1.0 g; 0.0038 M) in methanol (12 ml) sodium hydroxide (1.4 g; 0.035 M) and water (4 ml) was heated under reflux for 3 hours, poured into water and extracted with ether (4x50 ml). The combined ether extracts were washed with water, brine, dried and concentrated. Distillation of the residue under vacuum

furnished 41b (0.726 g, 93%); b.p. 165°(bath)/1.3 mm.

IR spectrum (liquid film) showed band at 1706 cm^{-1} (carbonyl).

NMR spectrum (CCl_4) showed signals at τ 2.36 (2H, t, J = 6 Hz, -CO-CH_2), 3.63 (2H, s, Ar-CH_2-CO-), 7.16 (5H, s, aromatic protons).

Analysis: C, 82.41; H, 9.91.

$C_{14}H_{20}O$ requires C, 82.30; H, 9.87.

1-Phenyl-2-decanone 41c

Hydrolysis as given for procedure 41b gave 41c (91%), b.p. 168° (bath)/1 mm.

IR spectrum (liquid film) showed band at 1715 cm^{-1} (carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.9-1.26 (15H, methylene and methyl of side chain), 2.4 (2H, t, J=6 Hz, -CO-CH_2), 3.6 (2H, s, Ar-CH_2-CO), 7.13 (5H, s, aromatic protons).

Analysis: C, 82.96; H, 10.32.

$C_{16}H_{24}O$ requires C, 82.70; H, 10.64.

1,4-Diphenyl-2-butanone 41a

Hydrolysis as given for procedure 41b gave 41a (91%), m.p. 41-42° (Lit.[27] m.p. 43°).

IR spectrum (Nujol) showed band at 1718 cm^{-1} (carbonyl).

NMR spectrum (CCl_4) showed signals at τ 2.66 (4H, m, -CO-CH_2-CH_2-Ar), 3.53 (2H, s, Ar-CH_2-CO-), 7.-7.2 (10H, broad singlet, aromatic protons).

1-Phenyl-2-heptadecanone 41d

Hydrolysis as given for procedure 41b gave 41d (93%), m.p. 45-6° (recrystallised from methanol). IR spectrum (Nujol) showed band at 1715 cm^{-1} (carbonyl)

NMR spectrum (CCl_4) showed signals at δ 0.9-1.26 (29H, methylene and methyl of aliphatic side chain), 2.33 (2H, t, J = 6Hz, CH_2-CH_2-CO-), 3.5 (2H, s, -CO-CH_2-Ar), 7.13 (5H, s, aromatic protons).

Analysis: C, 83.65; H, 11.54.

$C_{23}H_{38}O$ requires C, 83.57; H, 11.59.

1-Phenyl-2-nonadecanone 41e

Hydrolysis as given for procedure 41b gave 41e (95%), m.p. 53-54° (recrystallized from methanol). IR spectrum (Nujol) showed band at 1718 cm^{-1} (carbonyl).

NMR spectrum (CCl_4) showed signals at δ 0.83-1.3 (33H, methylene and methyl of aliphatic side chain), 2.33 (2H, t, J=6 Hz, -CH_2-CO-), 3.56 (2H, s, -CO-CH_2-Ar), 7.2 (5H, s, aromatic protons).

Analysis: C, 83.54; H, 11.93.

$C_{25}H_{42}O$ requires C, 83.73; H, 11.81.

GENERAL PROCEDURE FOR SODIUM BOROHYDRIDE REDUCTION

1-Phenyl-2-octanol 42b

Sodium borohydride (0.304 g, 0.008 M), was added to a stirred solution 41b (1.5 g, 0.0073 M) in ethanol (30 ml) and water (3 ml). The mixture was stirred at room temperature for 15 hours, diluted with water and extracted with ether (3x50 ml). The ether extract was washed with water, brine, dried and concentrated. The residue was chromatographed over alumina (Grade II). The alumina was eluted wi out with (i) petroleum ether (ii) petroleum ether + 10% benzene (iii) petroleum ether + 30% benzene (iv) petroleum ether + 50% benzene. The fraction eluted out with petroleum ether + 50% benzene was 42b (1.37 g, 92%).

IR spectrum (liquid film) showed band at 3571 cm^{-1} (hydroxyl group).

NMR spectrum (CCl_4) showed signals at τ 2.66 (2H, q, J = 6 Hz, Ar-$\underline{CH_2}$-CH-), 3.7 (1H, m, -$\underline{C}$HOH), 7.2 (5H, s, aromatic protons).

Analysis: C, 81.52; H, 10.86.

$C_{14}H_{22}O$ requires C, 81.50; H, 10.75.

1-Phenyl-2-decanol 42c

Reduction by sodium borohydride in a manner as given for procedure 42b gave 42c (92%), m.p. 38-39° (Lit.[28] m.p. 37.7-8.5°).

IR spectrum (Nujol) showed band at 3534 cm^{-1} (hydroxyl group).
NMR spectrum (CCl_4) showed signals at τ 0.9-1.6
(17H, methyl and methylene of aliphatic side chain),
2.63 (2H, q, J = 6 Hz, Ar-CH_2-CH-), 3.66 (1H, m, -CHOH),
7.06 (5H, s, aromatic protons).

1,4-Diphenyl-2-butanol 42a

Reduction by sodium borohydride in a similar manner as given for procedure 42b gave 42a (98%), m.p. 43-44° (Lit.[27] m.p. 44°).

IR spectrum (Nujol) showed band at 3509 cm^{-1} (hydroxyl group).
NMR spectrum (CCl_4) showed signals at τ 1.53 (1H, broad singlet OH, exchangeable with D_2O), 1.7 (2H, m, -CH_2-),
2.63 (4H, m, Ar-CH_2), 3.66 (1H, m, -CH-OH),
7.1 (10H, s, aromatic protons).

1-Phenyl-2-heptadecanol 42d

Reduction in a similar manner as given for procedure 42b gave 42d (88%), m.p. 62° (Lit.[28] m.p. 63-64°).
IR spectrum (Nujol) showed band at 3574 cm^{-1} (hydroxyl group).
NMR spectrum (CCl_4) showed signals at τ 0.9-1.3
(31H, methylene and methyl of aliphatic side chain),
2.7 (2H, m, -CH_2-Ar), 3.66 (1H, m, -CHOH), 7.06
(5H, s, aromatic protons).

Analysis: C, 82.98; H, 11.97.
$C_{23}H_{40}O$ requires C, 83.06; H, 12.13.

1-Phenyl-2-nonadecanol 42e

Reduction in a similar manner gives 42e (96%), m.p. 66° (Lit.[28] m.p. 68°).

IR spectrum (Nujol) showed band at 3534 cm^{-1} (hydroxyl group).

NMR spectrum (CCl_4) showed signals at τ 0.83-1.28 (35H, methylene and methyl of aliphatic side chain), 2.68 (2H, m, $-C\underline{H}_2-Ar$), 3.71 (1H, m, $-C\underline{H}OH$), 7.12 (5H, s, aromatic hydrogen).

Analysis: C, 83.30; H, 12.03

$C_{25}H_{44}O$ requires C, 83.26; H, 12.30.

GENERAL PROCEDURE FOR FRAGMENTATION

Heptanal 43b

A mixture of alcohol 42b (3.0 g, 0.014 M), benzene (20 ml), iodine (2.21 g; 0.017 M) and lead tetraacetate (13.3 g, 0.03 M) was heated under reflux with stirring for 6 hours and then cooled to room temperature. The excess of lead tetraacetate was destroyed by adding ethylene glycol (5 ml). The benzene layer was washed with aqueous sodium thiosulfate solution, water, brine, dried and the solvent evaporated. The residue was fractionally distilled using a Vigreux column (length 7 cm). The fraction with b.p. 93-95°/80 mm (Lit.[29] b.p. 80-84°/65 mm),

(yield 0.92 g, 56%) was composed almost exclusively of heptanal 43b identified by comparison of GLC, IR and NMR with an authentic sample.

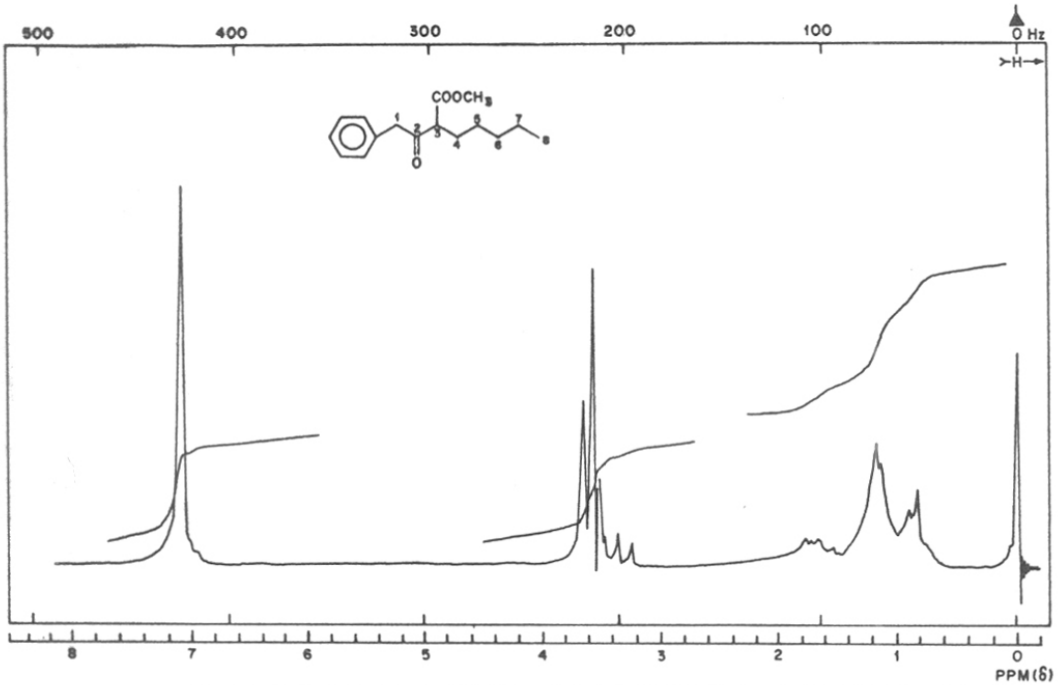
Identical repetition of above procedure on the remaining alcohols 42a, 42c-e gave as expected the aldehydes 43a, 43c-e whose properties and yields are summarized in the Table -1.

Table 1 : Aldehydes 43a-e synthesised

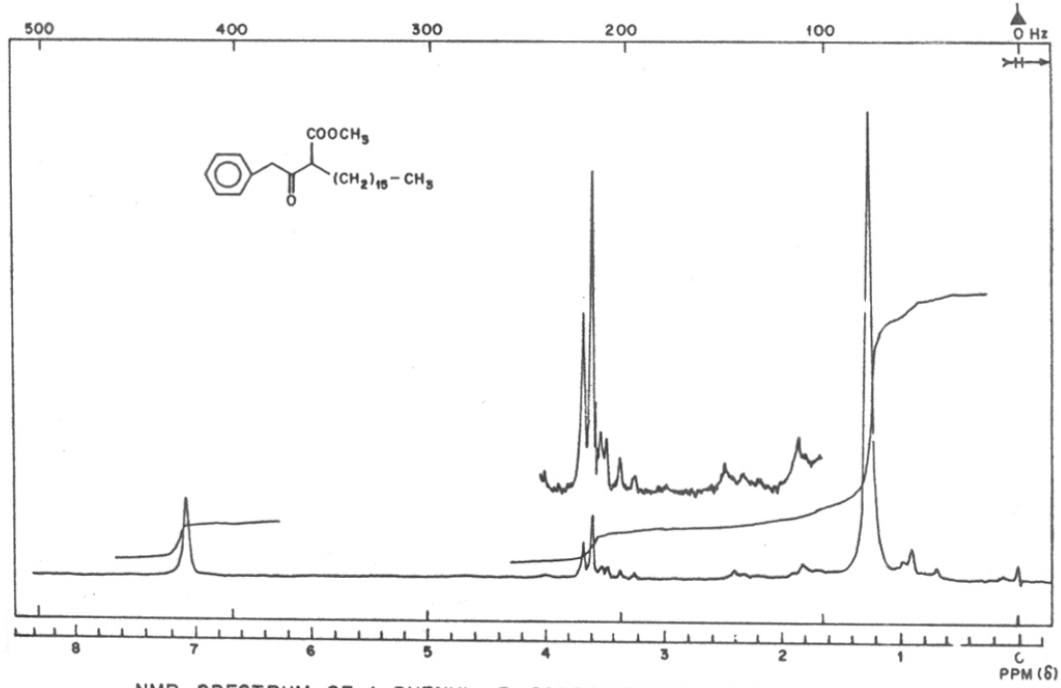
Entry	Yield [a,b] %	M.p. (°C) of 2,4-dinitrophenyl hydrazone	Lit. m.p. of 2,4-dinitrophenyl hydrazone
43a	58	148°	144-5° [30]
43b	56	-	-
43c	58	102-4°	105° [31]
43d	51	104-6°	105-106° [32]
43e	58	105°	106.5-107° [29]

a. Yields for all compounds, except 43b were based on the 2,4-dinitrophenyl hydrazone isolated; in the case of compound 43b the yields are based on GLC data.

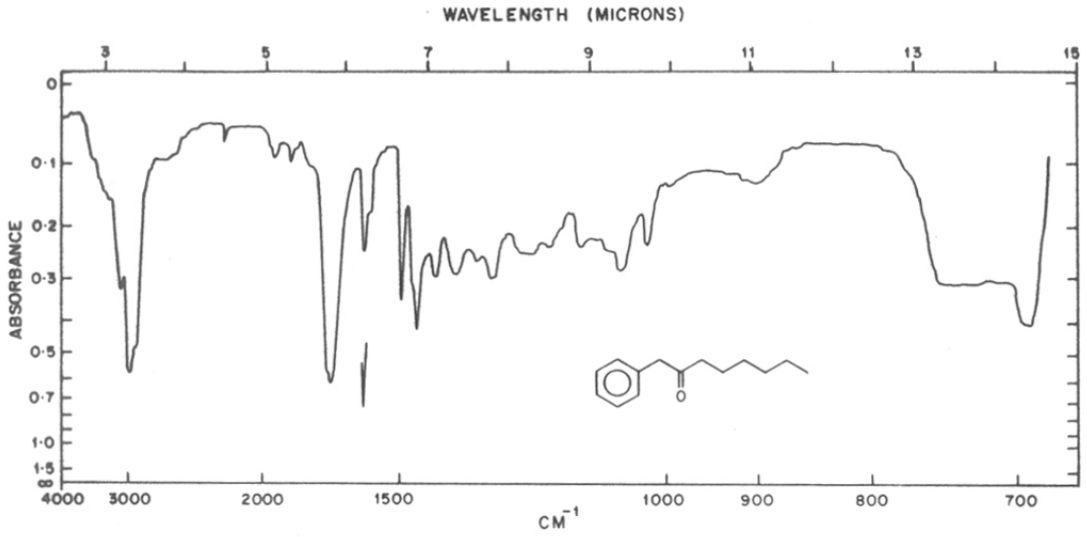
b. The identity of 43b was also established by comparison of GLC with authentic sample.



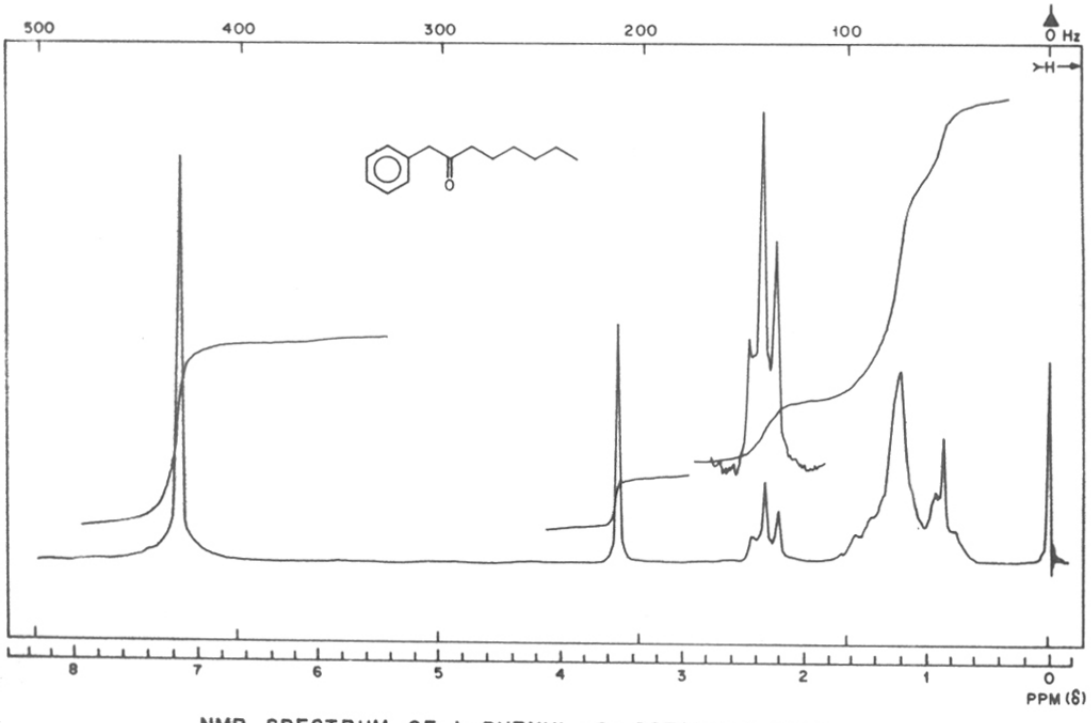
NMR SPECTRUM OF 1-PHENYL-3-CARBOMETHOXY-2-OCTANONE.(40b)



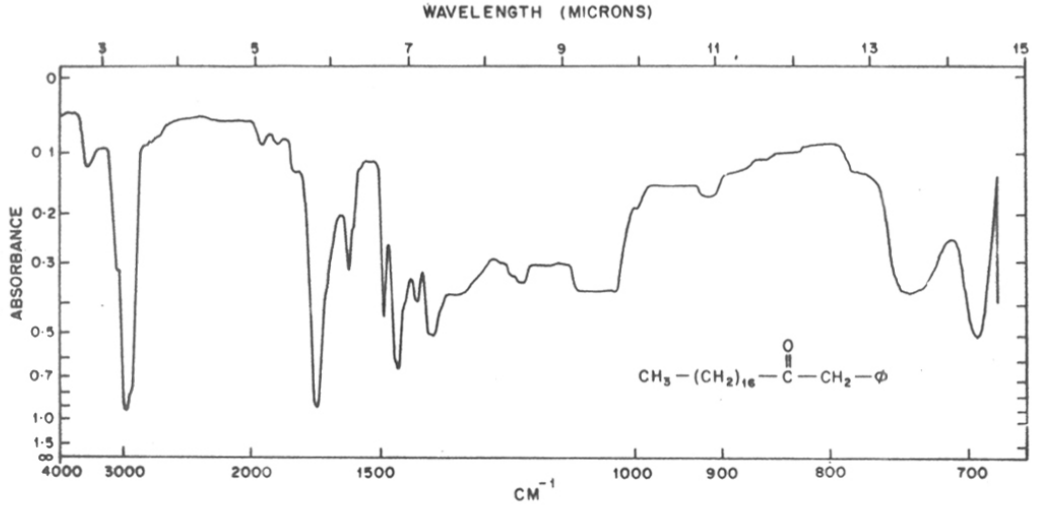
NMR SPECTRUM OF 1-PHENYL-3-CARBOMETHOXY-2-NONADECANONE.(40e)



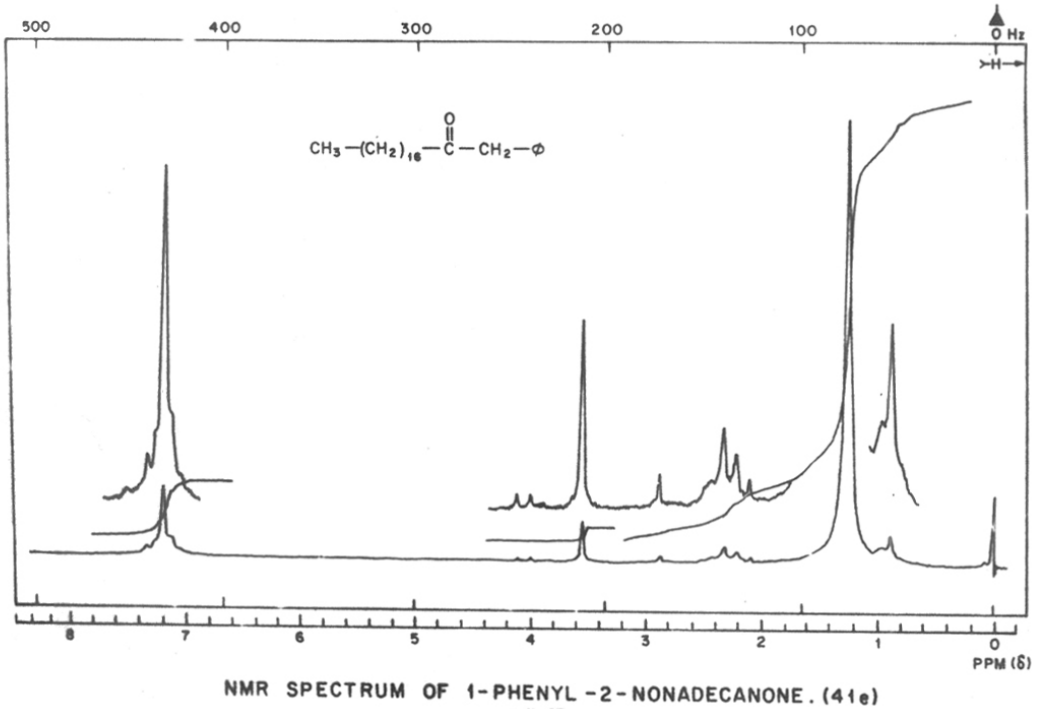
IR SPECTRUM OF 1-PHENYL-2-OCTANONE. (41b)



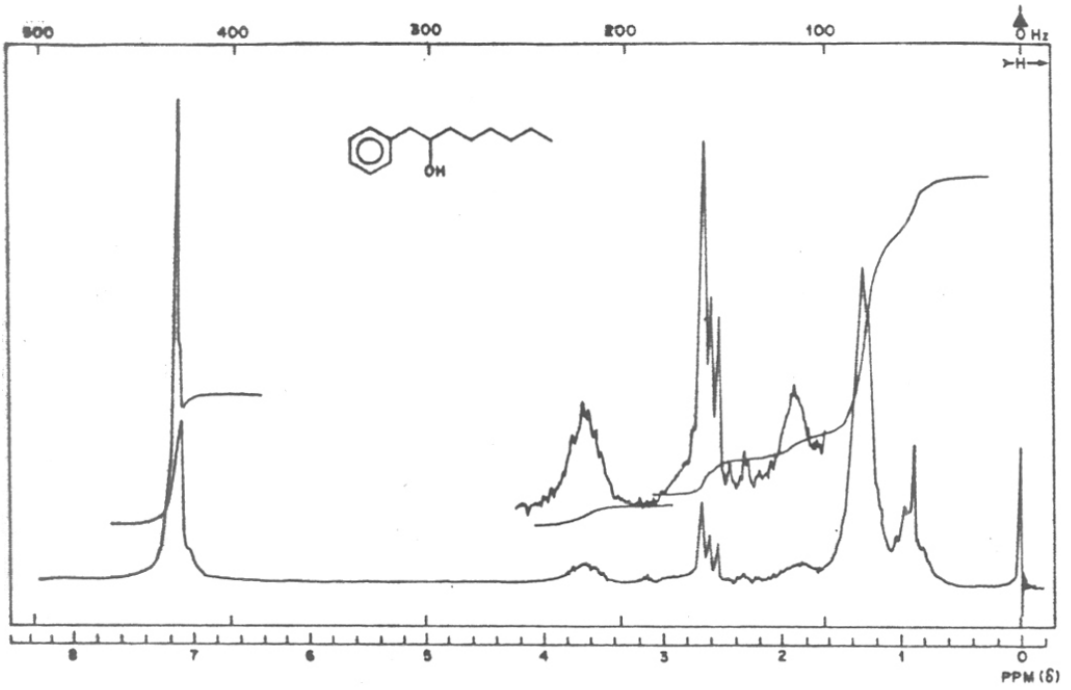
NMR SPECTRUM OF 1-PHENYL-2-OCTANONE. (41b)



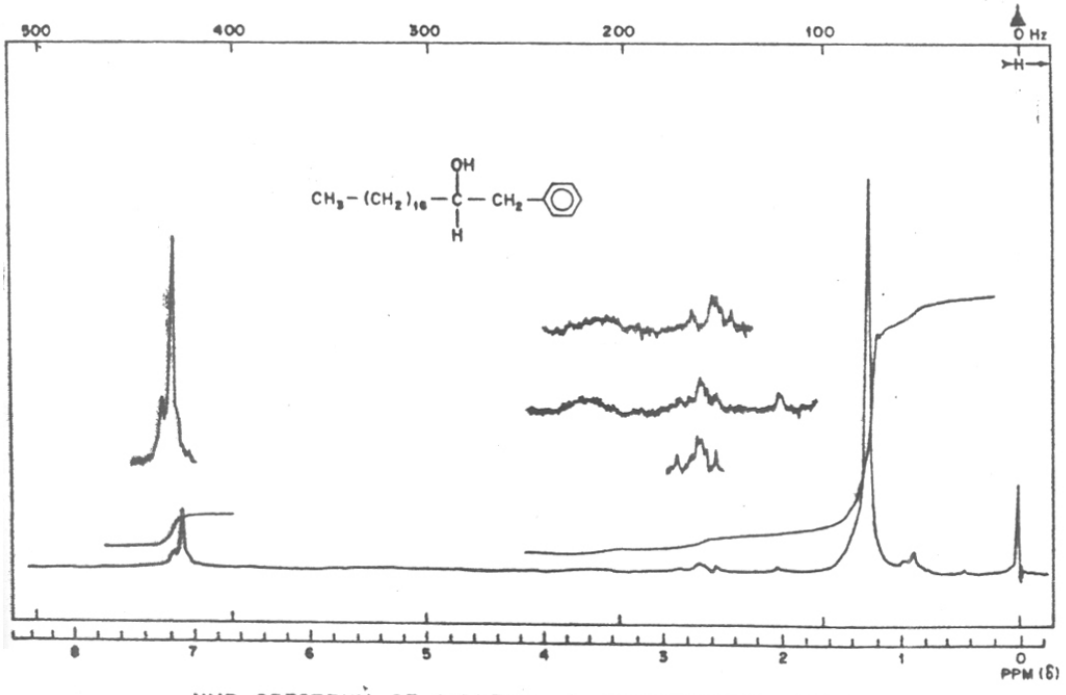
IR SPECTRUM OF 1-PHENYL-2-NONADECANONE. (41e)



NMR SPECTRUM OF 1-PHENYL-2-NONADECANONE. (41e)



NMR SPECTRUM OF 1-PHENYL-2-OCTANOL. (42b)



NMR SPECTRUM OF 1-PHENYL-2-NONADECANOL. (42e)

REFERENCES

1. D. Seebach and M. Kolb, Chem.Ind.(London), 687 (1974).
2. D.A. Evans and G.C. Andrews, Acc.Chem.Res., 7, 147 (1974).
3. H.E. Nursten, Rep.Prog.Appl.Chem., 56, 622 (1971).
4. K. Eiter, Pure Appl.Chem., 41, 201 (1975).
5. O. Bayer, in Houben-Weyl 'Methoden der Organischen Chemie', Thieme, Stuttgart, 4th edn., 1954, Vol.VII, part 1.
6. J. Carnduff, Quart.Rev., 20, 169 (1966).
7. H.M. Walborsky, W.H. Morrison and G.E. Niznik, J.Amer.Chem.Soc., 92, 6675 (1970).
8. A.I. Meyers, A. Nabeya, H.W. Adickes and I.R. Politzer, J.Am.Chem.Soc., 91, 763 (1969).
9. A.I. Meyers and N. Nazarenko, J.Am.Chem.Soc., 94, 3243 (1973).
10. L.J. Altman and S.L. Richheimer, Tet.Lett., 4709 (1971).
11. A.I. Meyers, R. Munavu and J.Durandetta, Tet.Lett., 3929 (1972).
12. E.J. Corey and G. Markl, Tet.Lett., 3201 (1967).
13. E.J. Corey and A.P. Kozikowski, Tet.Lett., 925 (1975).
14. F.A. Carey and A.S. Court, J.Org.Chem., 37, 1926 (1972).
15. S.L. Levine, J.Am.Chem.Soc.,80, 6150 (1958).
16. K. Heusler and J. Kalvoda, Angew.Chem.Int.Edn., 3, 525 (1964).
17. K. Shankaran and A.S. Rao, Ind.J.Chem., 18B, 507 (1979).
18. S. Moon and J.M. Lodge, J.Org.Chem., 29, 3453 (1969).
19. E.A. Brande and O.H. Wheeler, J.Chem.Soc., 320 (1955).
20. K. Shankaran and A.S. Rao, Synth.Comm., 10, 573 (1980).
21. A.W. Burgsthaler, M.E. Sanders, C.G. Shaefer and L.O. Weigel, Synthesis, 405 (1977).

22. Y. Oikawa, K. Sugano and O. Yonemitsu, J.Org.Chem., 43, 2087 (1978).

23. Z. Majerski and J. Janjotovic, Tet.Lett., 20, 3977 (1979).

24. D. Davidson and S.A. Bernhardt, J.Am.Chem.Soc., 70, 3426 (1948).

25. M.S. Newman and D.E. Reid, J.Org.Chem., 23, 665 (1958).

26. It is not essential to purify the keto ester by chromatography. Crude esters as such can be employed for the preparation of the corresponding ketones.

27. R. Cornubert and H.C. Eggert, Bull.Soc.Chim.Frac., 522 (1954).

28. S. Hersek, Istanbul Univ.Fen.Falkmecm.Seric., 31, 39 (1966). Also see Chem.Abs., 69, 43554a (1968).

29. P.J.C. Kramer and H. Van Duin, Rec.Trav.Chem. 73, 63 (1954).

30. I. Heilbron, "Dictionary of Organic Compounds", Vol.IV, Oxford Press, New York, N.Y., 1965, p.2712.

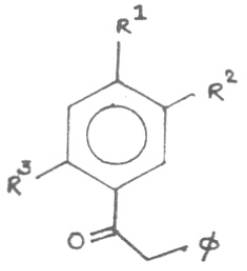
31. T. Haga, Nippon Kagaku Zasshi, 81, 948 (1960). Also see Chem.Abs., 56, 311f (1962).

32. J.A. Knight and H.D. Zook, J.Amer.Chem.Soc., 74, 4560 (1952).

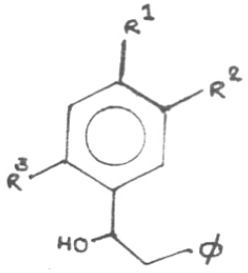
CHAPTER IIIA : A CONVENIENT METHOD FOR THE SYNTHESIS OF AROMATIC ALDEHYDES

Summary

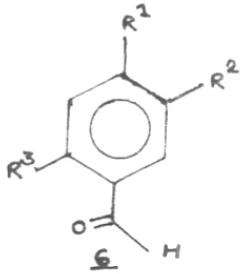
A convenient route for the preparation of aromatic aldehydes is described in this Chapter. Benzyl ketones 4 obtained by Freidel-Craft's acylation were reduced to homobenzylic alcohols 5. 5 underwent a ready fragmentation to give aromatic aldehydes 6.



4



5



6

Introduction

Aromatic aldehydes are colourless or pale yellow, water-immisicible, liquids or solids with low melting points and are generally volatile in steam. Many members of the series have characteristic odours; benzaldehyde itself, which occurs in nature in the leaves of kernels of apricots and peaches has an odour of bitter almonds. Phenolic aldehydes, such as salicylaldehyde and their ethers such as vanillin and piperonal, also have good odours and are synthesised on a large scale for use in the flavouring and perfumery industries.

Benzaldehyde is also an important industrial material, being used in the food, beverage, and pharmaceutical industries as a flavouring and in the fine chemicals industry as intermediate in the synthesis of other perfumery and flavouring chemicals (e.g. cinnamaldehyde). Benzaldehyde and many other substituted benzaldehydes (e.g. o-chloro-benzaldehyde, o-formylbenzene sulphonic acid) are intermediates in the synthesis of triphenylmethane dyestuffs which are used extensively in the paper, printing and synthetic fibre industries.

Synthesis of aromatic aldehydes

The methods of introduction of the formyl group into the aromatic ring are numerous and are discussed in detail below.

Synthesis of aromatic aldehydes by oxidation of methyl group.

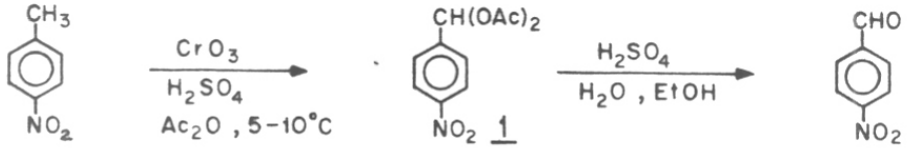
Chromium trioxide in acetic anhydride is a reagent of choice for the conversion of methyl substituted aromatics to aldehydes. In this method further oxidation of aldehydes to acid is prevented by the formation of the intermediate diacetate 1 which is stable to the reaction conditions. Hydrolysis in aqueous ethanol gives the aldehyde in good yield[1,2] (Chart I, Scheme I). A similar transformation, which can be accomplished using chromyl chloride as the oxidising agent, is known as the Etard reaction[3]. The reaction is carried out using carbon tetrachloride or carbon-disulphide as solvent (Chart I, Scheme II). More recently the oxidising agent ammonium cerium (IV) nitrate has been used to perform this transformation under mild conditions in high yields[4,5,6] (Chart I, Scheme III). The use of manganese oxide[7] and selenium oxide[8] have been also reported in few cases.

Synthesis of aromatic aldehydes from halomethyl compounds

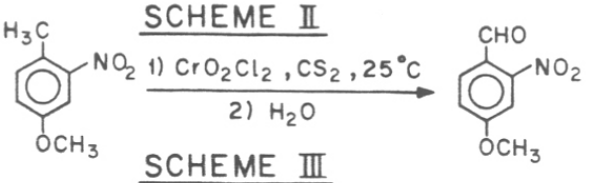
This group of synthetic method represents an important class of reaction, since the halomethylated aromatics are readily available starting materials, formed either by the halogenation of methyl aromatics (e.g. using N-halosuccinimides) or by direct halomethylation (using formaldehyde-hydrogen chloride).

CHART I

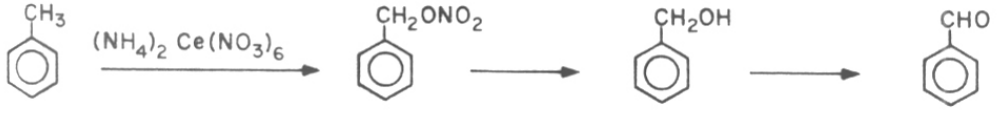
SCHEME I



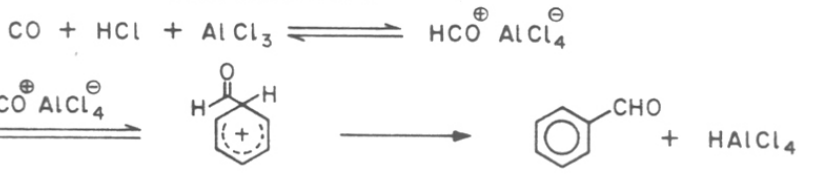
SCHEME II



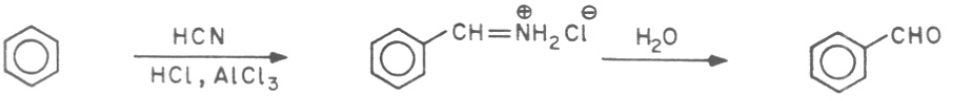
SCHEME III



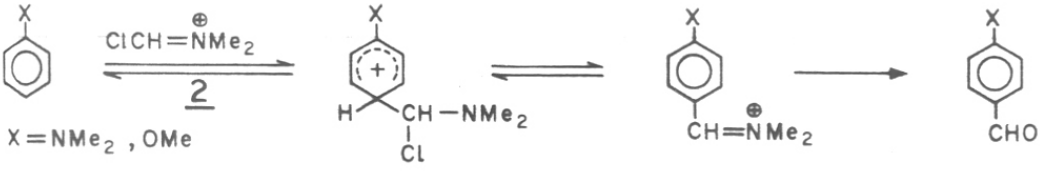
SCHEME IV



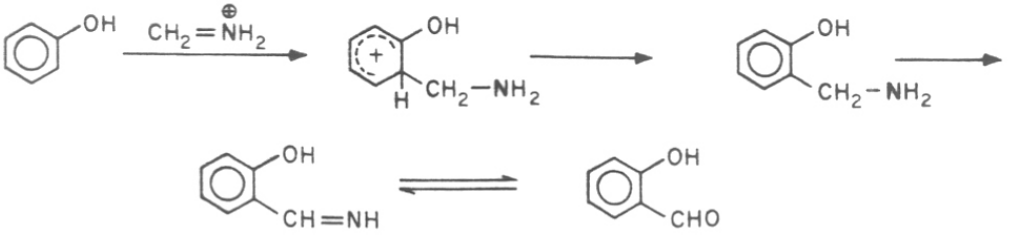
SCHEME V



SCHEME VI



SCHEME VII



The older methods of converting $CH_2X \rightarrow CHO$ such as the Sommelet[9] and Krohnke[10] process are indirect but give good overall yields. The practical advantage of these indirect method is that there is no need to purify the lachrymatory, unstable and often carcinogenic halomethyl starting material. More recently, however, specific oxidising agents such as dimethyl sulfoxide[11], pyridine N-oxides[12], sodium salt of 2-nitropropane[13] (called the Hass reaction), mercuric and silver nitrate[14] have been used successfully to transform halomethyl compounds to aldehydes.

Other methods of preparation of aromatic aldehydes

Gatterman-Koch reaction

Gatterman-Koch reaction[15,16] is a method of inserting CO into an aromatic C-H bond using HCl and typical Friedel-Crafts catalysts, such as aluminium chloride (Chart I, Scheme IV).

Gatterman reaction

Since the Gatterman-Koch reaction fails with phenols and phenol ethers, Gatterman developed a second formylation method involving the reaction of the aromatic substrate with HCN and HCl, usually in the presence of a Lewis acid[17] (Chart I, Scheme V).

Vilsmeier-Haack reaction

Formylation of electron rich aromatics using N,N-dimethylformamide (DMF), and phosphorus oxychloride ($POCl_3$) is known as Vilsmeier-Haack reaction[18]. Reaction between DMF and $POCl_3$ gives a reactive species 2, which react with electron rich aromatic systems (Chart I, Scheme VI) to give aldehydes.

Duff reaction

Reaction of electron-rich aromatics such as phenols and aromatic amines with hexamethylenetetramine in the presence of glycerol or acetic acid is referred to as Duff's reaction[19] (Chart I, Scheme VII).

Reimer-Tiemann reaction

Reaction of electron rich aromatics and hetero-aromatics, such as phenol using chloroform and alkali is known as the Reimer-Tiemann reaction[20] (Chart II, Scheme I).

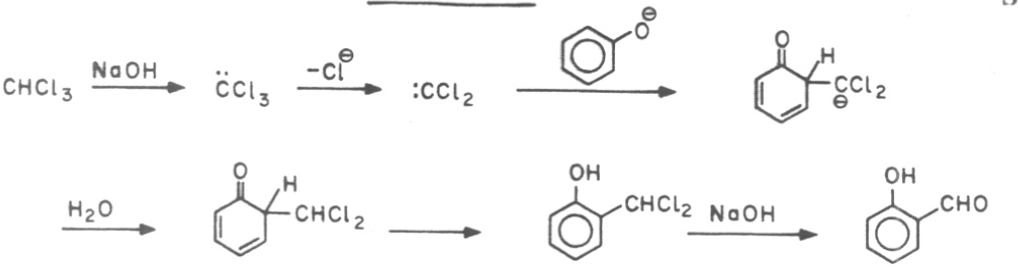
New methods for aromatic aldehyde synthesis

P.G. Gassman discovered a method[21] by which formyl group can be introduced ortho to phenol. A crucial step in this reaction was that a [2,3] -sigmatropic shift is used to form the new carbon-carbon bond (Chart II, Scheme II).

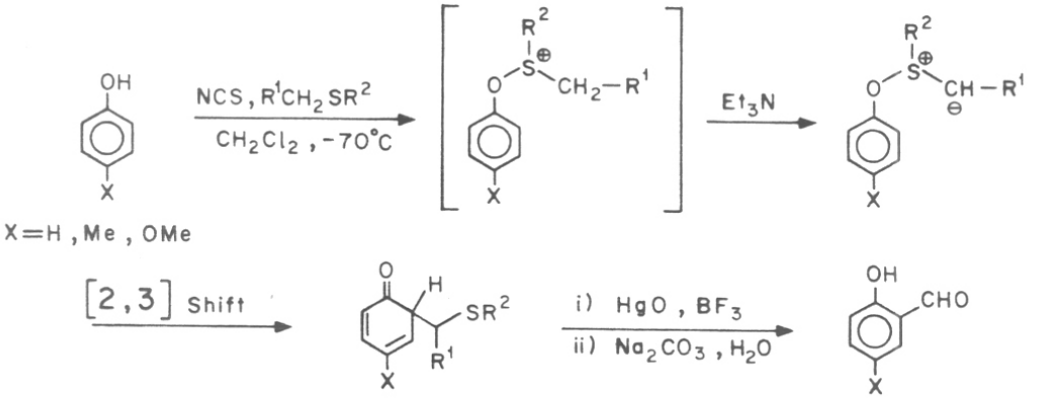
M.V. Bhatt developed a method based on the fact that amidomethyl group is preferentially brominated even

CHART II

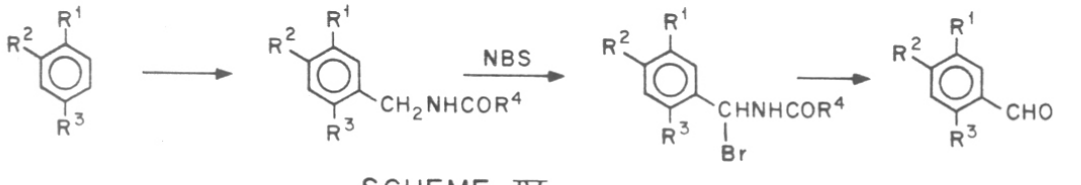
SCHEME I



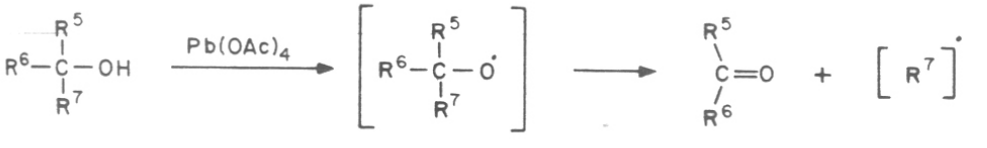
SCHEME II



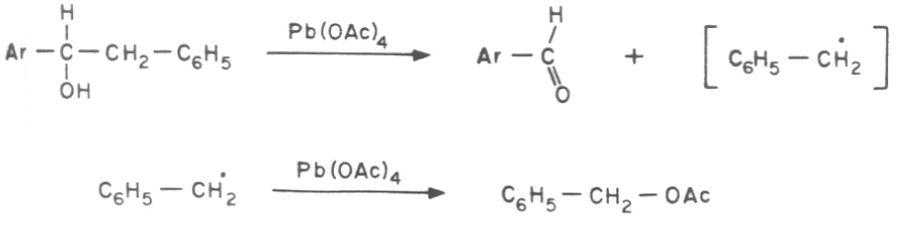
SCHEME III



SCHEME IV



SCHEME V



in the presence of methyl group. This bromination is brought about by N-bromosuccinimide (NBS). Subsequent dehydrobromination and hydrolysis gave aldehydes (Chart II, Scheme III).

PRESENT WORK

Though a variety of methods[23,24,25] are available for the synthesis of aldehydes, this area continues to attract attention[21,22] since the aldehydes are important intermediates in synthetic organic chemistry. Our work in synthetic chemistry is directed towards the development of new methods and reactions. In this Chapter we present a new route for the synthesis of aromatic aldehydes.

Several examples of the fragmentation of alcohols on treatment with lead tetraacetate to furnish carbonyl compounds according to Chart I, Scheme IV, are reported.

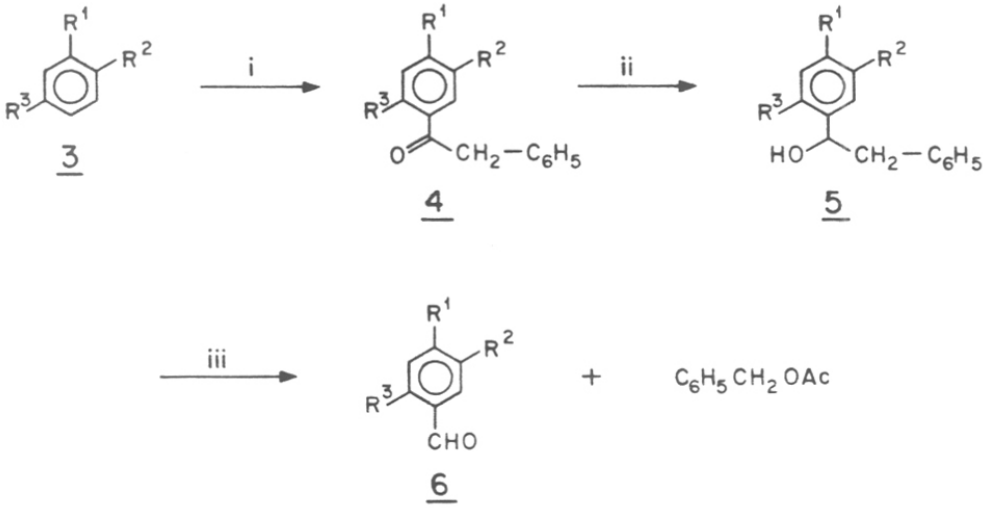
This reaction is particularly facile when the substrates are homoallylic alcohols since the fragmentation to carbonyl compounds also leads to the formation of stable allylic radicals. Hence we anticipated that secondary homobenzylic alcohols would readily fragment to furnish aromatic aldehydes according to Chart II, Scheme V, since the relatively stable benzyl radicals are formed as intermediates. Benzyl ketones 4 are readily available compounds. They are prepared generally by the Friedel-Craft's acylation of the corresponding aromatic hydrocarbon with phenyl acetic acid in which case the acylating agent was polyphosphoric acid or phenyl acetyl chloride using $AlCl_3$ as Lewis acid.

All the benzyl ketones 4a-g (Chart III) used by us are known compounds. 1-(4-Methoxy phenyl)-2-phenyl ethanone 4c was prepared by polyphosphoric acid reaction as given in literature[28]. The remaining benzyl ketones 1-(2,5-dimethoxy phenyl)-2-phenyl ethanone 4a, 1-(4-methyl phenyl)-2-phenyl ethanone 4b, 1-(2,4-dimethoxy phenyl)-2-phenyl ethanone 4d, 1-(3,4-dimethoxy phenyl)-2-phenyl ethanone 4f and 1-(4-chlorophenyl)-2-phenyl ethanone 4g were obtained by similar reaction and are known[29-33] in the literature.

The alcohols 5a-g were obtained by performing sodium borohydride reduction in ethanol at room temperature on benzyl ketone 4a-g. All the alcohols are known in the literature i.e. 5b [34], 5c [35], 5d [36], 5e [31] and 5g [34]. Melting points were in agreement with literature values. In the case of new alcohols 5a and 5f satisfactory elemental analysis and structure assigned are in agreement with NMR and IR spectra. IR spectrum of 5a showed band at 3571 cm^{-1} (OH stretching). Similarly 5f showed 3448 cm^{-1} (OH stretching).

Having obtained the homobenzylic alcohols 5a-g it was now only left to subject them to fragmentation reaction with lead tetraacetate. This was brought about by stirring the mixture of homobenzylic alcohols, lead tetraacetate in refluxing benzene.

CHART III



Reagents : i) $C_6H_5CH_2COCl$ / $AlCl_3$ or $C_6H_5CH_2CO_2H$ / Poly phosphoric acid.
ii) $NaBH_4$/EtOH , iii) $Pb(OAc)_4$

FOR ALL COMPOUNDS IN THE SERIES

Entry	R^1	R^2	R^3
a	H	OMe	OMe
b	CH_3	H	H
c	OMe	H	H
d	OMe	H	OMe
e	OMe	OMe	H
f	OMe	NO_2	H
g	Cl	H	H

Synthesis of aldehydes **6** a–g.

The aldehydes 6a-g thus obtained were characterized by IR and NMR spectra. The identities of the aldehydes 6a, 6b, 6c, 6e and 6g have been confirmed by comparing GLC behaviour with authentic samples. 6b was characterized as its 2,4-dinitrophenyl hydrazone (see Table).

In these fragmentation reactions benzyl acetate is formed as by-product. In all cases except 6b the aldehydes could be separated from the accompanying benzyl acetate by fractional distillation. Though the route presented here involves three steps, it is attractive since all the three steps are comparatively easy to carry out and proceed in good yields. The good advantage of our method is that the secondary homobenzylic alcohols 5a-g being solid, it gives an opportunity to employ the pure alcohol for fragmentation.

EXPERIMENTAL PROCEDURE

1-(2,5-Dimethoxyphenyl)-2-phenyl ethanone 4a

To a mixture of phenyl acetic acid (3 g, 0.022 M), polyphosphoric acid (prepared from 50 g of P_2O_5 + 21 g of phosphoric acid) was added 3a (3.0 g, 0.022 M) at 70-75° for about 10-15 minutes with vigorous stirring and the temperature slowly raised to 95° and maintained for about 1.5 hours. The mixture was cooled and poured into ice cold water (200 ml) and extracted with ether (3x100 ml). The etheral layer was washed with water, 10% solution of sodium bicarbonate, brine, dried and evaporated to give the residue which on distillation under vacuum gave 4a (4.8 g, 87%), b.p. 190° (bath)/0.7 mm. On keeping 4a slowly solidified to give m.p. 47° (Lit.[29] m.p. 49°).

1-(4-Methoxy phenyl)-2-phenyl ethanone 4b

Starting from phenyl acetic acid (3.0 g, 0.022 M), polyphosphoric acid (50.0 g, P_2O_5 + 21.0 g H_3PO_4) and toluene 3b (2.0 g, 0.022 M) and employing the method given above (see preparation of 4a) ketone 4b (3.8 g, 84%), m.p. 108° (Lit.[30] m.p. 109-111°) was obtained.

1-(4-Methoxy phenyl)-2-phenyl ethanone 4c

Starting from phenyl acetic acid (13.0 g, 0.022 M), polyphosphoric acid (50.0 g, P_2O_5 + 21.0 g H_3PO_4) and anisole 3c (2.2 g, 0.022 M) and employing the method given

above (see preparation of 4a) ketone 4c (3.6 g, 74%), m.p. 74° (Lit.[28] m.p. 74-5°) was obtained.

1-(2,4-Dimethoxy phenyl)-2-phenyl ethanone 4d

Starting from phenyl acetic acid (3.0 g, 0.022 M), polyphosphoric acid (50.0 g P_2O_5 + 21.0 g H_3PO_4) and resorcinol dimethyl ether 3d (3.0 g, 0.022 M) and employing the method given above (see preparation of 4a) ketone 4d (4.4 g, 80%), m.p. 46° (Lit.[36] m.p. 45-6°) was obtained.

1-(3,4-Dimethoxy phenyl)-2-phenyl ethanone 4e

Starting from phenyl acetic acid (3.0 g, 0.022 M), polyphosphoric acid (50.0 g P_2O_5 + 21.0 g H_3PO_4) and catechol dimethyl ether 3e (3.0 g, 0.022 M) and employing the method given above (see preparation of 4a) ketone 4e (4.1 g, 73%), m.p. 84° (Lit.[31] 82-3°) was obtained.

1-(3-Nitro-4-methoxy phenyl)-2-phenyl ethanone 4f

This compound was prepared as given in the literature[32].

1-(4-Chlorophenyl)-2-phenyl ethanone 4g

This compound was prepared as given in the literature[33].

PREPARATION OF ALCOHOLS

1-(2,5-Dimethoxy phenyl)-2-phenyl ethanol 5a

A mixture of 4a (2.5 g, 0.01 M), sodium borohydride (0.38 g, 0.01 M), ethanol (50 ml) and water (10 ml) stirred at room temperature for 3 hours and then extracted with

ether (2x50 ml). The etheral layer was washed with water, dried and evaporated to give 5a (2.4 g, 94%), recrystallised from petroleum ether. M.p. 55-6°.

IR spectrum (Nujol) showed bands at 3571 cm^{-1} (hydroxyl stretching).

NMR spectrum (CCl_4) showed signals at τ 2.83 (2H, d, J=6 Hz, $-CH_2-$), 3.63 (3H, s, $-OCH_3$), 3.7 (3H, s, $-OCH_3$), 5.0 (1H, m, -CHOH), 6.6 (2H, s, aromatic protons at C-3 and C-4), 6.7 (1H, s, C-6 aromatic proton), 7.0 (5H, s, aromatic protons).

Analysis: Found: C, 74.49; H, 7.00.

$C_{16}H_{18}O_3$ requires C, 74.39; H, 7.00.

1-(4-Methyl phenyl)-2-phenyl ethanol 5b

5b was prepared in the same manner given above (see procedure 5a). M.p. 68° (Lit.[34] m.p. 66.8-68.2°).

1-(4-Methoxy phenyl)-2-phenyl ethanol 5c

Procedure similar to 5a gave 5c (93%), m.p. 57° (Lit.[35] m.p. 58°).

1-(2,4-Dimethoxy phenyl)-2-phenyl ethanol 5d

5d was prepared in the same manner as in 5a to give 5d (90%), m.p. 43° (Lit.[36] m.p. 42-44°).

1-(3,4-Dimethoxy phenyl)-2-phenyl ethanol 5e

Following procedure similar to 5a gave 5e (93%), m.p. 69-70° (Lit.[31] m.p. 68-70°).

1-(3-Nitro-4-methoxy phenyl)-2-phenyl ethanol 5f

Prepared according to procedure given as under 5a to give 5f (82%), m.p. 68-70°.

IR spectrum (Nujol) showed bands at 3448 cm^{-1} (OH, stretching), 1515 and 1340 cm^{-1} (NO_2 group).

NMR spectrum (CCl_4) showed signals at τ 2.88 (2H, d, J=6 Hz, $-C\underline{H}_2-$), 3.83 (3H, s, $-OC\underline{H}_3$), 4.8 (1H, t, J = 6 Hz, $-\underline{CH}OH$), 7.5 (1H, s, aromatic proton ortho to nitro group).

Analysis: Found C, 66.04; H, 5.62.

$C_{15}H_{15}NO_4$ requires C, 65.92; H, 5.53.

1-(4-Chloro-phenyl)-2-phenyl ethanol 5g

Prepared in the similar manner as in 5a to give 5g (96%), b.p. 140°/0.5 mm (Lit.[34] b.p. 213°/20 mm).

GENERAL PROCEDURE FOR FRAGMENTATION REACTION

p-Anisaldehyde 6c

A mixture of 5c (6.85 g, 0.03 M), dry benzene (120 ml) and lead tetraacetate (33.3 g, 0.075 M) was heated under reflux with stirring for 6 hours and subsequently cooled to room temperature. The excess of lead tetraacetate was destroyed by adding ethylene glycol. The benzene layer was washed with water, brine, dried and the solvent was evaporated. The residue was fractionally distilled using a vigreux column (length 6 inches). The fraction with

b.p. 55-60°/1.4 mm (yield 2.8 g) was composed almost entirely of benzyl acetate identified by comparison of GLC, IR and NMR with those of an authentic sample. The residue left after removal of benzyl acetate was distilled with bulb-to-bulb distillation unit to furnish p-anisaldehyde 6c, b.p. 71°/1.4 mm (yield 2.6 g) Lit.[20] b.p. 93-4°/4-5 mm. The identity of the product 6c was confirmed by comparison of GLC, IR and NMR with an authentic sample.

Similarly alcohols 5a, 5b, 5d, 5e, 5f and 5g were transformed to aldehydes 6a, 6b, 6d, 6e, 6f and 6g (see Table -1).

Table 1 : Aldehydes 6a-g synthesised

Entry	Yield %	M.p. or b.p./mm	Lit. m.p. or b.p./mm.
6a	55	107°/0.7 mm	154°/18 mm [37]
6b	53	a	-
6c	63	71°/1-4 mm	93-4°/4-5 mm [39]
6d	50	138°/0.7 mm	110°/0.1 mm [40]
6e	48	43°	44° [41]
6f	66	82-84°	84° [42]
6g	50	44-46°	45° [43]

The IR and NMR spectra of the products were in agreement with the structures assigned. The identities of aldehydes 6a, 6b, 6c, 6e and 6g have been confirmed by comparing GLC behaviour with authentic samples.

a. Characterized as 2,4-dinitrophenyl hydrazone, m.p. and mixed m.p. with authentic sample 255°.[38]

REFERENCES

1. T. Nishimura, Org.Synth.Coll.Vol. 4, 713 (1963).
2. S.V. Lieberman and R. Conner, Org.Synth.Coll. Vol. 2, 441 (1943).
3. W.H. Hartford and M. Darrin, Chem.Rev., 58, 1 (1958).
4. L. Syper, Tet.Lett., 4493 (1966).
5. W.S. Trahanovsky and I.B. Young, J.Org.Chem., 31, 2035 (1966).
6. W.S. Trahanovsky, L.B. Young and G.L. Brown, J.Org.Chem., 32, 3865 (1967).
7. C.S. Markel, J.H. Sannders and C.G. Overberger, J.Amer.Chem.Soc., 68, 1085 (1946).
8. J.S. Gillespie Jr., S.P. Acharya, D.A. Shamblee and R.E. Davis, Tetrahedron, 31, 3 (1975).
9. S.J. Angyal, Org.Reactions, 8, 197 (1954).
10. P. Krohnke, Angew.Chem.Intnat.Edn., 2, 380 (1963).
11. N. Karnblum, W.J. Jones and G.J. Anderson, J.Amer.Chem.Soc., 81, 4113 (1959).
12. R.E. Manning and F.M. Schaefer, Tet.Lett., 213 (1975).
13. H.B. Hass and M.L. Bender, J.Amer.Chem.Soc., 71, 1767 (1949).
14. A. McKillop and M.E. Ford, Synth.Comm., 4, 45 (1974).
15. G.A. Olah and S.J. Kuhn in "Friedel-Crafts and related reaction", Ed. G.A. Olah, Interscience, New York, 1964, Vol.3, part 2, Chapter 38.
16. N.N. Crounse, Org.Reactions, 5, 290 (1949).
17. W.E. Truce, Org.Reactions, 9, 37 (1957).
18. S. Seshadri, J.Sci.Ind.Res.India, 32, 128 (1973).
19. J.C. Duff and V.I. Furness, J.Chem.Soc., 1159 (1952).
20. H. Wynberg, Chem.Rev., 60, 169 (1960).
21. P.G. Gassman and D.R. Amick, Tet.Lett., 889, 3463 (1974).

22. M.B. Gopinathan and M.V. Bhatt, Tet.Lett., 3875 (1979).

23. I.T. Harrison and S. Harrison, "Compendium of organic synthetic methods", Interscience Publishers (John Wiley and Sons), New York, N.Y., 1971, p.132.

24. S.F. Martin, Synthesis, 633 (1979).

25. C.A. Buehler and D.E. Pearson, "Survey of organic synthesis", Vol.II, Interscience Publications, (John-Wiley and Sons), New York, N.Y., 1977, p.480.

26. K. Heusler and J. Kalvoda, Angew.Chem.Internat.Edn., 3, 525 (1964).

27. K. Shankaran and A.S. Rao, Ind.J.Chem., 18B, 507 (1979).

28. J.S. Buck and W.S. Ide, J.Am.Chem.Soc., 54, 3012 (1932).

29. T.R. Ingale, N.L. Phalnikar and B.V. Bhide, J.Ind.Chem.Soc., 26, 569 (1949).

30. R.N. Mcdonald and P.A. Schwab, J.Am.Chem.Soc., 85, 820 (1963).

31. P. Bercot and M.B. Valteroni, Compdt.Rendus, 260, 3099 (1965).

32. O. Behoghel and H. Ratz, Ber., 72, 1257 (1939).

33. M.S. Newman and D.E. Reid, J.Org.Chem., 23, 665 (1958).

34. A. Feldstein and C.A. Vander West, J.Am.Chem.Soc., 76, 1626 (1954).

35. S.S. Ienkins, J.Am.Chem.Soc., 54, 1155 (1932).

36. G.M. London and D.S. Noyce, J.Am.Chem.Soc., 91, 1433 (1969).

37. A. Neuberger, J.Bio.Chem., 43, 599 (1948).

38. E.L. Niedzielski and F.F. Nord, J.Am.Chem.Soc., 63, 1462 (1941).

39. K.A. Bogadanov, Masloboino-zhirovaya Prom., 18, 20 (1953).

40. A.H. Sonners, R.J.Michael and A.W. Wegton, J.Am.Chem.Soc., 74, 5446 (1952).

41. J. Weijland, E. Tashijian and M. Tishler, J.Am.Chem.Soc., 69, 2070 (1947).

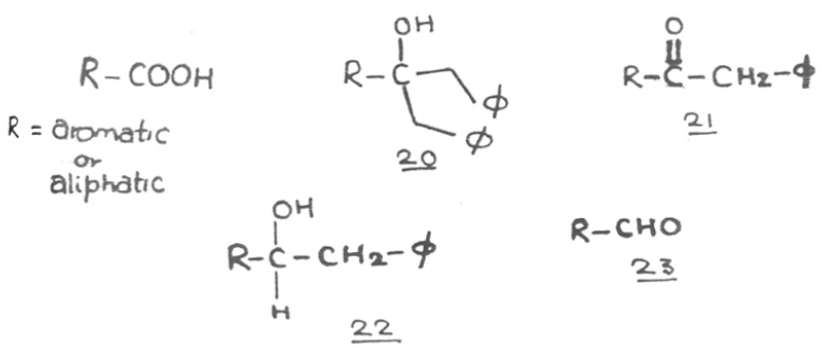
42. L.E.Hinkel, E.E. Ayling and N.H.Morgan, J.Chem.Soc., 1112 (1932).

43. L.E. Hinket, E.E. Ayling and J.H. Beynon, J.Chem.Soc., 1877 (1925).

CHAPTER IIIB : FRAGMENTATION STUDIES ON HOMOBENZYLIC ALCOHOLS USING LEAD-TETRAACETATE AND CERIC AMMONIUM NITRATE : A METHOD FOR THE CONVERSION OF ACID TO ALDEHYDE GROUP

Summary

This Chapter deals with the comparative study of fragmentation of different tertiary homoallylic alcohols under variety of experimental conditions. The outcome of such a study was the conversion of acid into an aldehydic function. In general esters of acid (R = aromatic or aliphatic) were transformed to tertiary homobenzylic alcohol 20. It was found out that when R (aromatic), the reagent of choice for fragmentation of 20 was ceric ammonium nitrate to give benzyl ketone 21, and when R (aliphatic) the reagent of choice was lead tetraacetate-iodine to afford benzyl ketone 21. 21 was reduced to secondary homobenzylic alcohols 22 by using sodium borohydride in ethanol. 22 (R = aromatic) gave aldehyde 23 (aromatic) with lead tetraacetate and when 22 (R = aliphatic) gave aldehydes 23 (aliphatic) with lead tetraacetate-iodine.



Introduction

Aldehydes occupy a central position in the series of oxidation level found among organic compounds. They may act as electrophiles and also by removal of α-proton give rise to nucleophilic anions. This variety of possible reaction makes them potentially very valuable intermediates, but complicates their synthesis, since they are often unstable particularly in basic and oxidising media. Examples are however widespread in nature and exhibit widely differing but often highly important physiological activity e.g. glucose 1, pyridoxyl phosphate 2, streptomycin 3 etc. (Chart I).

In recent years several excellent reagents are available for the selective transformations. A range of different metal hydrides with various degree of selectivity has been introduced over the last two decades. These reagents have been extensively used for the synthesis of aldehydes by the partial reduction of carboxylic acids. and its derivatives. Reviews on these metallic hydrides have been published[1,2]. It is the purpose of this brief review in this Chapter to give an impression that this transformation is still getting predominent importance in synthetic organic chemistry. An attempt is made here to give methods that have appeared in the past few years. The transformation of aromatic as well as aliphatic acids

to corresponding aldehydes will be discussed.

Aliphatic aldehydes from acids and their derivatives

In order to reduce acids to corresponding aldehydes, it is usually necessary to convert the acids into a more nucleophilically labile derivatives. However there are some exceptions to this. For e.g. lithium-methyl amine reduction[3] and diamino-aluminium hydrides[4] are known to reduce acids to aldehydes. Methyl esters are reduced to aldehydes by diamino aluminium hydrides[5] and sodium bis-(methoxy ethoxy)aluminium hydride[2]. In some cases acyl malonic esters can be reduced by sodium borohydride under conditions such that retro-aldol fission of the product leads directly to the aldehydes[6]. Thiol esters, RCOSR are reduced to aldehydes by treatment with Raney nickel[7]. Quite a variety of tertiary amides have been reduced to aldehydes with lithium aluminium hydride[2], but more recently the simple N,N-dimethyl amides have been used with lithium bis-(ethoxy)aluminium hydride or alkoxy aluminium hydride as the reactant[2].

Nordin[8] synthesised 2-oxazoline derivatives 1 from acids. 1 was methylated to give 2-oxazoline methiodides 2, which underwent reduction with sodium borohydride in methanol to give dihydro-2-oxazoline derivative 3. 3 on acid hydrolysis gave aldehydes (Chart I, Scheme I).

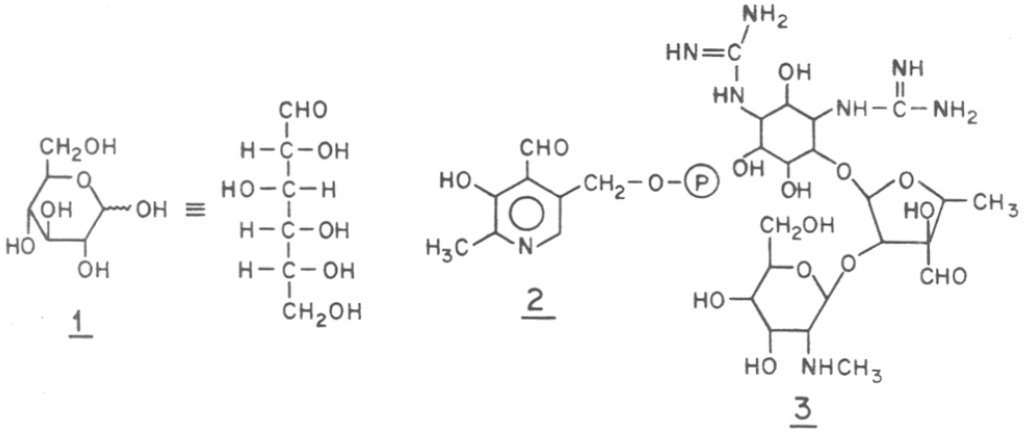
Doleschall[9,10] developed a very simple and efficient method based on the availability of triazolium salt 4. Methanolic solution of these salts are reduced with sodium borohydride to give dihydro triazole 5. 5 was decomposed in aqueous sulfuric acid to give the desired aldehydes (Chart I, Scheme II).

In Meyer's synthesis[11] of aldehydes, 5,6-dihydro-1,3-oxazines 7 saved as precursor to aldehydes. The conversion of 7 to aldehydes was brought about by controlled sodium borohydride (at -40°C) reduction to 7a, followed by acidic work-up. One advantage of above method is avoidance of the strongly reducing lithium aluminium hydride (Chart I, Scheme III).

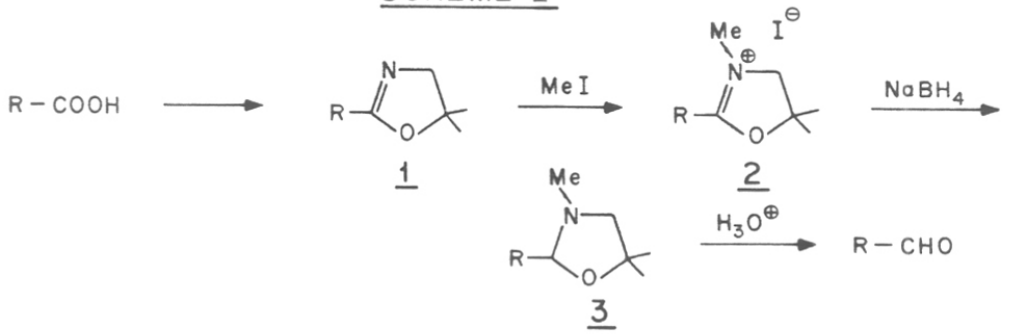
Watanabe et al.[12] provided a method by which acyl chloride was converted to acyl carbonyl ferrate 8, by treatment with disodium tetracarbonyl ferrate 7b. 8, after quenching with acetic acid furnished corresponding aldehydes in high yields (Chart I, Scheme IV).

Disodium tetracarbonyl ferrate 7b is also shown to react with various anhydrides[13] to give acyl carbonyl ferrates 8, which are then converted to aldehydes by quenching with acetic acid (Chart II, Scheme I). The above procedure was later modified[14] by taking carboxylic ethyl carbonic anhydride 9 and disodium tetracarbonyl ferrate 7b (Chart II, Scheme II).

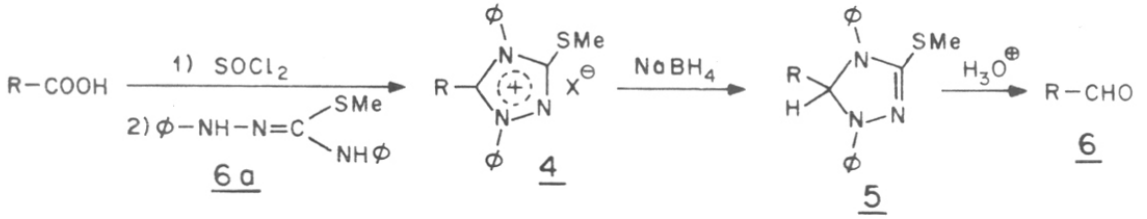
CHART I



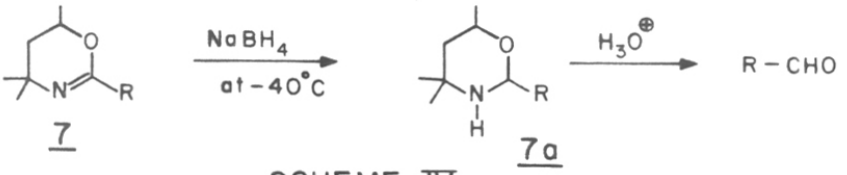
SCHEME I



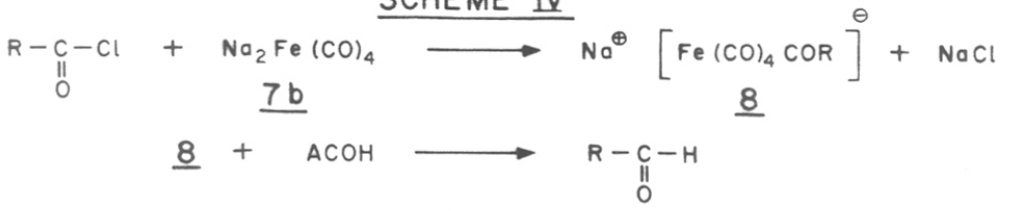
SCHEME II



SCHEME III



SCHEME IV



It was shown that the combination of triethylsilane and transition metal (Pd) reduces acid chlorides to aldehydes, however α-branching in the alkyl group of acid lowers the yield of aldehyde[15] (Chart II, Scheme III).

A different approach by Fujita et al.[16,17,18] involves conversion of carboxylic acids into their 2-thiazoline-2-thiol esters 10, which on reduction with di-isobutyl aluminium hydride (DIBAH) gives aldehydes (Chart II, Scheme IV).

Brown et al.[19] have developed a method involving rapid reduction of carboxylic acid with borane-dimethyl sulfide, followed by oxidation of the resultant trialkoxyboroxine with pyridinium chlorochromate in refluxing dichloromethane furnished aldehydes (Chart II, Scheme V).

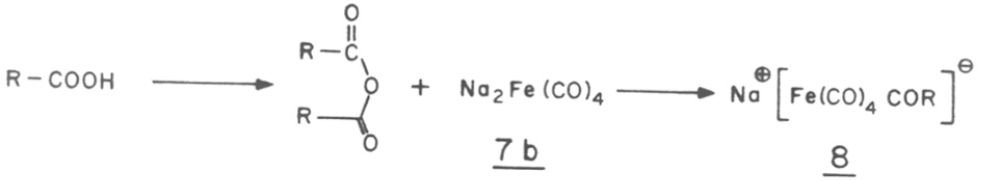
Aromatic aldehydes from acids and their derivatives

An early review[20] in this subject discussed seven methods for the conversion of acids or their derivatives to aldehydes, but these methods have been superceded by reduction using complex metal hydrides which are selective and experimentally easier to carry out. Hence these methods will be discussed briefly.

A modified version of Rosenmund reduction[21], developed by scientists at Hoffman-La-Roche converts

CHART II

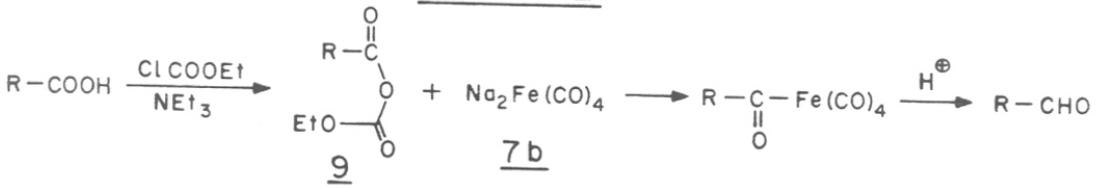
SCHEME I



7b

8

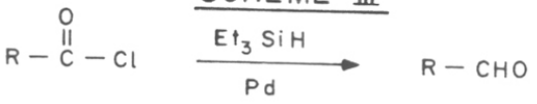
SCHEME II



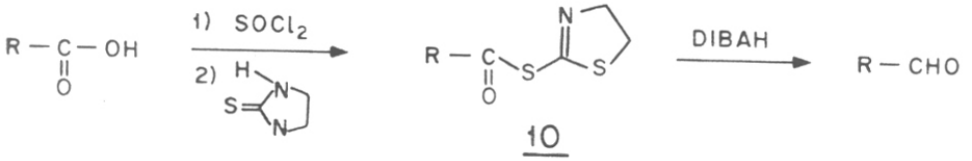
9

7b

SCHEME III

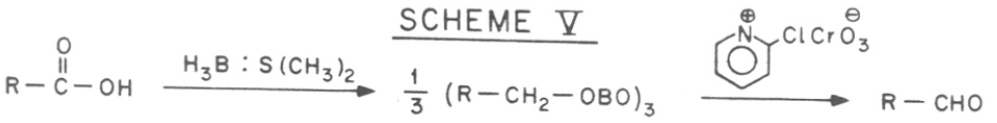


SCHEME IV

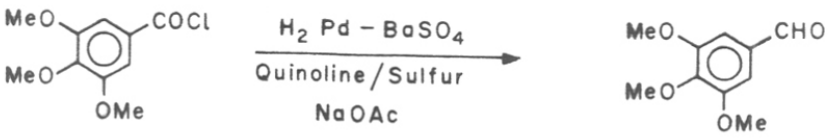


10

SCHEME V



SCHEME VI



aromatic acid chloride to aldehyde in the presence of catalyst. The catalyst usually palladium or barium sulfate, is poisoned with a suitable additive e.g. quinoline-sulfur.(This is done to reduce the activity of the catalyst to try to prevent over reduction). Sodium acetate is also used to scavenge the hydrochloric acid liberated during the process (Chart II, Scheme VI).

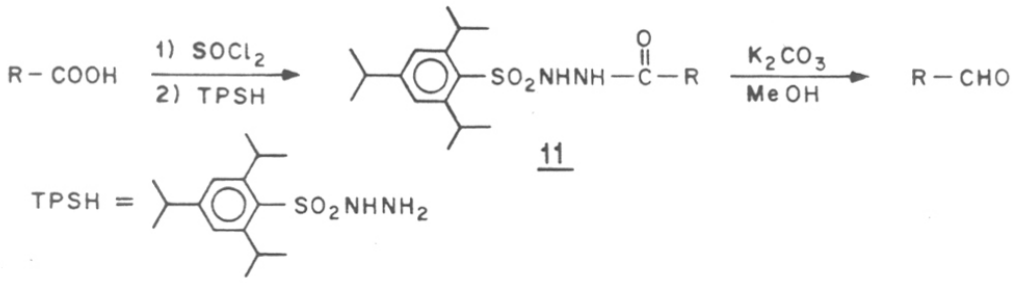
Indirect methods for converting aromatic acid chlorides to aldehydes include the hydrolysis of Weisserts compounds[20], reductive desulphurization of thiol esters using Raney nickel[20], the Sonn-Muller method via imidoyl chlorides[20] and the McFadyen-Stevans reaction[20].

Reese et al.[22] reported a modified McFadyen-Stevans reaction. Use of 2,4,6-triisopropylbenzenesulphonyl hydrazide (TPSH) instead of toluene-p-sulphonyl hydrozide leads to much milder conditions with an efficient separation of aromatic aldehydes (Chart III, Scheme I). 11 was prepared by allowing acid chlorides to react with TPSH. 11 decomposed on reflux with anhydrous potassium carbonate in methanol to give aldehydes.

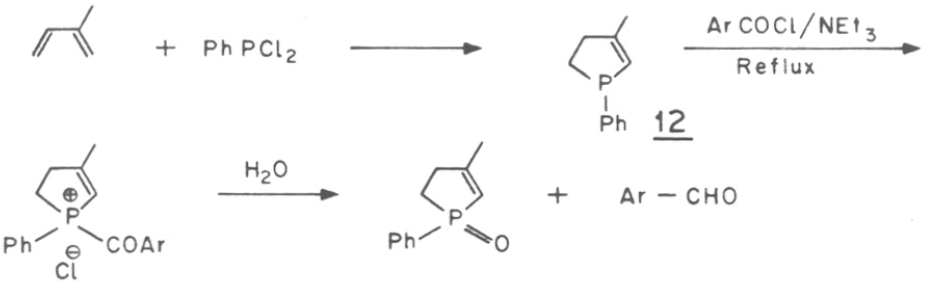
An alternative reagent which is suitable only for the synthesis of aromatic and hetero-aromatic aldehydes is the phospholene 12, readily prepared from isoprene and dichlorophenyl phosphine. Reaction of 12 with aroyl chlorides gives a salt 13, which is hydrolysed by water to give the aldehydes in good yield[23] (Chart III, Scheme II).

CHART III

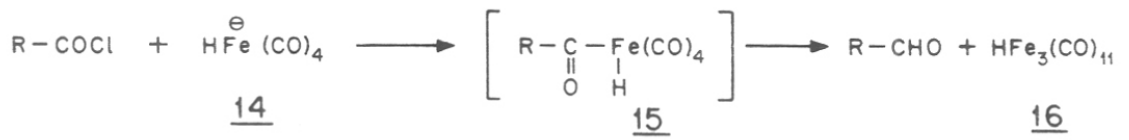
SCHEME I



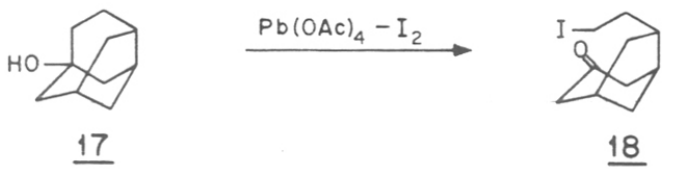
SCHEME II



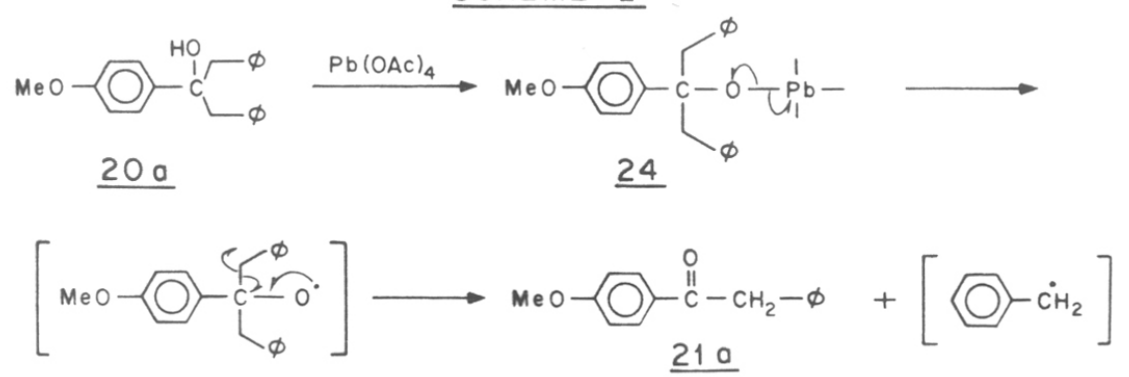
SCHEME III



SCHEME IV



SCHEME V



Hydridotetracarbonylferrate anion 14 reacts with acid chlorides to generate the aldehydes[24] and the salt of known hydridotriironundecarbonyl 16. Acyl hydride complex 15 is the intermediate for these reactions (Chart III, Scheme III).

Another closely related reaction to above is reduction of acid chlorides with $Na_2Fe(CO)_4$ as reported by Watanabe and co-workers[12] (Chart I, Scheme IV).

PRESENT WORK

Having come to realize that the partial reduction of acids to aldehydes continues to enjoy the popularity of synthetic organic chemist, we decided to devise a new route for the same. Our strategy for this transformation involves three steps. Namely,

1) Conversion of esters (of aromatic and aliphatic acid) to benzyl ketones.
2) Transformation of benzyl ketones to homobenzylic alcohols.
3) Fragmentation of homobenzylic alcohols to aldehydes.

Several methods are known in the literature for the synthesis of benzyl ketones[25], because of their importance in medicinal chemistry. Our method for the synthesis of benzyl ketones involves the transformation of ester 19a and 19h to tertiary homobenzylic alcohol 20a and 20h by performing Grignard reaction with benzylmagnesium chloride. The alcohols 20a and 20h can lead to benzyl ketone 21a and 21h by fragmentation reaction (Chart V).

It was reported by us[26] that secondary homobenzylic alcohols can be readily fragmented to give aldehydes (Eqn.I)

$$Ar\text{-}CH_2\text{-}\underset{H}{\overset{OH}{\underset{|}{\overset{|}{C}}}}\text{-}R \xrightarrow{Pb(OAc)_4} Ar\text{-}CH_2\text{-}OAc + R\text{-}CHO \qquad (I)$$

using lead tetraacetate in refluxing benzene.

It appears reasonable to expect that tertiary homobenzylic alcohol 20a should fragment (in good yields) more readily than the secondary homobenzylic alcohol (Eqn.I) for two reasons,

(1) Since the alcohol is tertiary other types of oxidations can be suppressed*.

(2) The presence of bulky substituents on the hydroxyl bearing carbon results in steric strain which can be relieved by ejection of one of the benzyl substituents.

However the tertiary alcohol 20a was virtually recovered unchanged on heating with lead tetraacetate in refluxing benzene. Lead tetraacetate and pyridine in refluxing benzene also did not bring about fragmentation of 20a to benzyl ketone 21a. It is well known that pyridine is known to catalyze such lead tetraacetate reactions[27].

Majerski et al.[28] have fragmented alcohol 17 to ketone 18 in the presence of lead tetraacetate-iodine (Chart III, Scheme IV). The identical conditions as given by above reference, were also tried out to bring

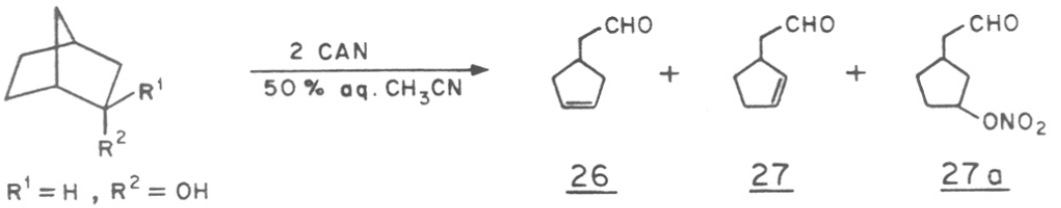
---

* It is known in the literature that secondary alcohols can be oxidised [27] to ketones in the presence of LTA.

R-CHOH-R' → R-CO-R'

CHART IV

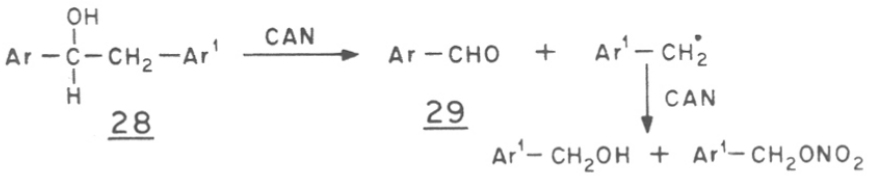
SCHEME I



$R^1 = H$, $R^2 = OH$

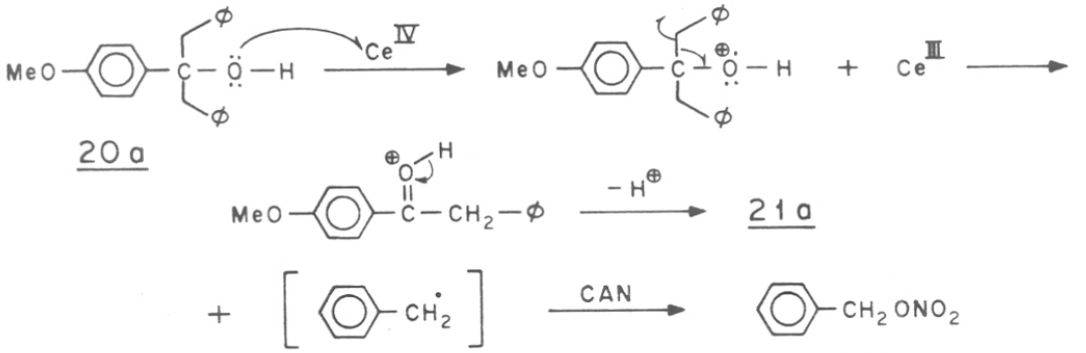
$R^1 = OH$, $R^2 = H$

25 26 27 27a

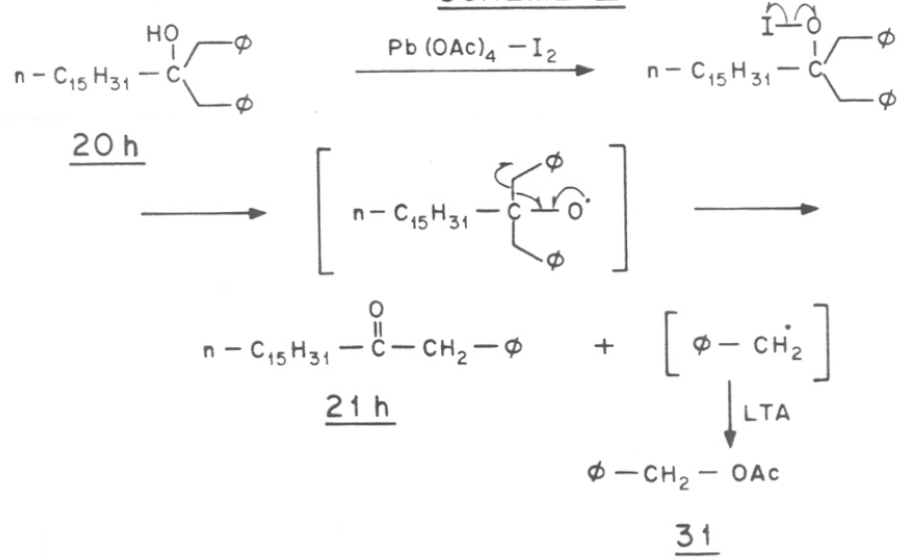


28 29 30

SCHEME II



SCHEME III



about the fragmentation of alcohol 20a to ketone 21a. The reaction indeed succeeded, however the yields were very low. These experiments suggested that probably the alcohol 20a is not transformed to the required reactive intermediate 24 due to steric hindrance (Chart III, Scheme V).

Trahanovsky et al.[29] reported that oxidation of either exo or endo-2-norboranol 25 with 2 equivalents of ceric ammonium nitrate (CAN) in 50% aqueous acetonitrile at 50° gave 3 and 4-cyclopentane acetaldehydes 26 and 27 along with 27a (Chart IV, Scheme I). In another experiment[30] alcohol 28 was fragmented to 29 by using ceric ammonium nitrate (CAN) (Chart IV, Scheme I).

We took advantage of above mentioned reference[29,30] and the same conditions were performed on alcohol 20a. Excellent yields of benzyl ketone 21a (77%) were obtained with ceric ammonium nitrate (CAN) in acetonitrile. Hence this procedure was utilized for the preparation of benzyl ketones 21b-e from tertiary homobenzylic alcohol 20b-e. Mechanism involving single electron transfer for the above fragmentation reaction has been described (Chart IV, Scheme II). Benzyl nitrate 30 (formed by the reaction of benzyl radical and CAN) is the by-product in these reactions. An efficient separation of 21a from 30 can be affected by passing through alumina column. 30 is eluted

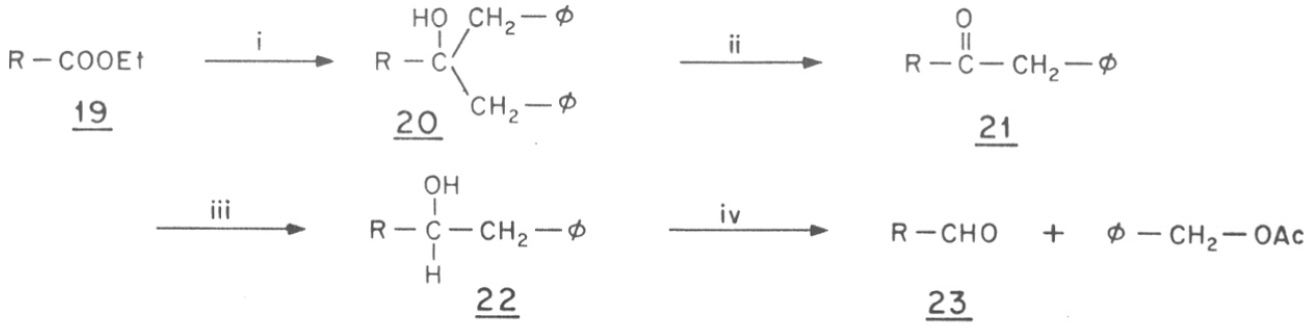
out with petroleum ether and the benzyl ketone are eluted with petroleum ether + 50% benzene (see experimental).

The benzyl alcohols 22a-e were obtained by carrying out sodium borohydride reduction on ketones 21a-e. Alcohols 21a-e were fragmented to aldehydes by the procedure described by us[26].

The alcohol 20h did not fragment to give benzyl ketone 21h when ceric ammonium nitrate in acetonitrile was used[29]. However, satisfactory yields of benzyl ketone 21h was obtained when lead tetraacetate-iodine was employed. A mechanism showing hypoiodites as intermediates is described in Chart IV, Scheme III. Benzyl acetate 31 formed as by-product can be removed by distillation under vacuum. The undistilled residue was then chromatographed over alumina to give 21h (see experimental). Hence this procedure was employed for the preparation of benzyl ketones 21f, 21g and 21i also from alcohols 20f, 20g and 20i.

The benzyl ketones 21f-i were reduced with sodium borohydride in ethanol to give homobenzylic alcohols 22f-i. Heating secondary homobenzylic alcohol 22h with lead tetraacetate-benzene did not prove satisfactory for the preparation of aldehyde 23h, showing that 22h is far less reactive than 22a. However when heated with lead tetraacetate-benzene in the presence of iodine[28], the

CHART V



Reagents : i) $\phi - CH_2 - MgCl$ / Ether ii) $Pb(OAc)_4 - I_2$/Benzene or $(NH_4)_2\ Ce(NO_3)_6$/Acetonitrile

iii) $NaBH_4$ /EtOH iv) LTA – I_2 / Benzene

FOR ALL THE COMPOUNDS IN THE SERIES

ENTRY→	a	b	c	d	e	f	g	h	i
R	MeO–C6H4–	Me–C6H4–	Cl–C6H4–	H–C6H4–	Me / C6H4	n-C_6H_{13}	n-$C_{13}H_{27}$	n-$C_{15}H_{31}$	n-$C_{17}H_{35}$

alcohol 22h furnished the aldehyde 23h in satisfactory yields. This procedure was found suitable for the preparation of aldehydes 23f, 23g and 23i from alcohols 22f, 22g and 23i.

The alcohols 20a-i were prepared by the action of benzylmagnesium chloride on the ethyl esters 19a-i.

The systematic studies described here provide a convenient route for the preparation of aldehydes and benzyl ketones. Incidentally the transformation aliphatic ester → 20 → 21 → 22 → 23 carried out by us in the course of this work constitute a route for the conversion of aliphatic acids to the corresponding aldehydes. The experiments carried out in this study together with previous work (Chapter IIIa) provide a route for the conversion of aromatic acids to the corresponding aldehydes.

EXPERIMENTAL PROCEDURE

2-(4-Methoxy phenyl)-1,3-diphenyl propan-2-ol 20a

To a well stirred solution of benzylmagnesium chloride (prepared from magnesium (2.04 g, 0.085 g atom) and benzyl chloride (10.7 g, 0.085 M) was added a solution of 19a (5.0 g, 0.03 M) in 25 ml ether at 0°. The mixture stirred for 20 hours at room temperature and quenched by adding saturated solution of ammonium chloride at 0°. The ether layer was separated and aqueous layer extracted with ether (2x50 ml). The combined ether extracts were washed with water, brine, dried and evaporated to give a solid, which upon recrystallization from petroleum ether gave 20a (7.8 g, 83%), m.p. 91-92°.

IR spectrum (Nujol) showed band at 3636 cm^{-1} (OH stretching).

NMR spectrum (CCl_4) showed signals at δ 1.63 (1H, s, OH exchanges on addition of D_2O), 3.06 (4H, q, J_{AB} = 14 Hz, $C\underline{H}_2$-Ar), 3.6 (3H, s, $OC\underline{H}_3$), 6.6-7.0 (14H, m, aromatic protons).

Analysis: Found C, 82.73; H, 6.97.

$C_{22}H_{22}O_2$ requires C, 82.98; H, 6.96.

Alcohol 20b-e were prepared in the similar manner given above.

2-(4-Methyl phenyl)-1,3-diphenyl propan-2-ol 20b

M.p. 81-2° (recrystallised from petroleum ether).
IR spectrum (Nujol) showed band at 3523 cm^{-1} (for OH).
NMR spectrum (CCl_4) showed signals at τ 2.23 (3H, s, $C\underline{H}_3$-Ar), 3.1 (4H, q, J_{AB}= 14 Hz, $C\underline{H}_2Ar$), 7.0-7.2 (14H, m, aromatic protons).

Analysis: Found C, 87.53; H, 7.35
$C_{22}H_{22}O$ requires C, 87.37; H, 7.33.

2-(4-Chloro-phenyl)-1,3-diphenyl propan-2-ol 20c

M.p. 80-1° (recrystallised from petroleum ether).
IR spectrum (Nujol) showed band at 3536 cm^{-1} (for OH).
NMR spectrum (CCl_4) showed signals at τ 1.7 (1H, s, OH, exchangeable on addition of D_2O), 3.06 (4H, q, J_{AB}= 13 Hz, $C\underline{H}_2$-Ar), 6.8-7.2 (14H, m, aromatic protons).

Analysis: Found C, 78.59; H, 6.00.
$C_{21}H_{19}ClO$ requires C, 78.12; H, 5.89.

1,2,3-Triphenyl propan-2-ol 20d

M.p. 84-5° (recrystallised from petroleum ether).
IR spectrum (Nujol) showed band at 3571 cm^{-1} (for OH).
NMR spectrum (CCl_4) showed signals at τ 1.66 (1H, s, OH, exchanges on addition of D_2O), 3.06 (4H, q, J_{AB} = 14 Hz, $C\underline{H}_2$-Ar), 6.6-7.1 (14H, m, aromatic protons).

Analysis: Found C,87.21; H, 7.03.
$C_{21}H_{20}O$ requires C, 87.46; H, 6.99.

2-(2-Methyl phenyl)-1,3-diphenyl propan-2-ol 20e

B.p. 176°(bath)/0.3 mm.

IR spectrum (liquid film) showed band at 3550 cm^{-1} (for hydroxyl).

NMR spectrum (CCl_4) showed signals at τ 2.36 (3H, s, $C\underline{H}_3$-Ar), 3.16 (4H, q, J_{AB}= 13 Hz, $C\underline{H}_2$-Ar), 6.7-7.1 (14H, m, aromatic protons).

Analysis: Found C, 86.92; H, 7.14.

$C_{22}H_{22}O$ requires C, 87.37; H, 7.33.

GENERAL PROCEDURE FOR FRAGMENTATION BY CERIC AMMONIUM NITRATE.

1-(4-Methoxy phenyl)-2-phenyl ethanone 21a

To 20a (1.0 g, 0.0031 M) in acetonitrile (4 ml) was added ceric ammonium nitrate (3.4 g, 0.0062 M) in acetonitrile (1 ml) and water (5 ml). The mixture was warmed upto 50-55° and maintained at hot temperature till the orange yellow colour of ceric ammonium nitrate disappeared (about 10 minutes). The mixture was then diluted with water (50 ml) and extracted with ether (3x25 ml). The ether layer was washed with water, dried and concentrated to give a syrup. This syrup was chromatographed over alumina (30.0 g, Grade II). The alumina column was eluted successively with (i) petroleum ether (ii) petroleum ether + 10% benzene (iii) petroleum ether + 50% benzene.

The fraction eluted with petroleum ether + 50% benzene was composed entirely of 21a (0.537 g, 77%), m.p. 72-73° (Lit.[31] m.p. 74-75°).

Similarly alcohols 20b-e gave benzyl ketones 21b-e (see Table 1).

Table 1 : Benzyl ketones 21a-e synthesised

Name	Compound	M.p. or b.p.	Lit. m.p. or b.p.	Yield %
1-(4-Methoxy phenyl) -2-phenyl ethanone	21a	72-3°	74-5° [31]	77
1-(4-Methyl phenyl) -2-phenyl ethanone	21b	109°	109-111° [32]	87
1-(4-Chloro phenyl) -2-phenyl ethanone	21c	106-7°	106-7° [33]	81
1-Phenyl-2-ethanone	21d	52-3°	55-6° [34]	85
1-(2-Methyl phenyl) -2-phenyl ethanone	21e	158°/8 mm	172-3/ 10 mm [35]	79

Conversion of benzyl ketones to homobenzylic alcohols and to aldehydes have been already discussed in Chapter IIIa.

GENERAL PROCEDURE FOR CONVERSION OF ALIPHATIC ACIDS TO ALDEHYDES

1-Phenyl-2-benzyl-heptadecan-2-ol 20h

To a well stirred solution of benzylmagnesium chloride [prepared from magnesium (2.5 g, 0.105 g atom) and benzyl chloride (13.25 g, 0.105 M)] was added ethyl palmitate 19h (10.0 g, 0.035 M) in ether (30 ml) at 0°. The mixture left stirred at room temperature for 20 hours and then quenched with saturated solution of ammonium chloride at 0°. Ether layer was separated from aqueous layer. Aqueous layer was extracted with ether (2x100 ml). The combined ether extract was washed with water, brine, dried and evaporated to give viscous liquid weighing (12.2 g, 83%).

The IR spectrum (liquid film) showed band at 3509 cm^{-1} (OH, stretching).

NMR spectrum (CCl_4) showed signals at τ 0.96-1.33 (31H, methylene and methyl of aliphatic side chain), 2.73 (4H, s, $-C\underline{H}_2-Ar$), 7.2 (10H, s, aromatic protons).

For analytical purpose the sample 20h was purified by preparative layer chromatography. (PLC plate was prepared from SiO_2 in a slurry made from distilled water). The plate was developed in petroleum ether + 10% ethyl acetate.

Analysis: Found C, 84.84; H, 11.07

$C_{30}H_{46}O$ requires C, 85.24; H, 10.97.

Similarly alcohols 20f, 20g and 20i were prepared from the esters 19f, 19g and 19i. The properties and other features of above mentioned alcohols are outlined in the Table 2 and Table 3.

Table 2 - Alcohols 20f-i synthesised

Name	Molecular Formula	Yield %	Microanalysis	
			Found	Requires
1-Phenyl-2-benzyl-octan-2-ol (20f)	$C_{21}H_{28}O$	80	C 85.31 H 9.46	85.08 9.52
1-Phenyl-2-benzyl-pentadecan-2-ol (20g)	$C_{28}H_{42}O$	81	C 84.93 H 10.61	85.22 10.73
1-Phenyl-2-benzyl-heptadecan-2-ol (20h)	$C_{30}H_{46}O$	83	C 84.84 H 11.07	85.24 10.97
1-Phenyl-2-benzyl-nonadecan-2-ol (20i)	$C_{32}H_{50}O$	78	C 85.08 11.31	85.27 11.18

Table 3 - NMR values of alcohol 20f-i

Compound	NMR shift
20f	0-9-1.2 (13H, methylene and methyl of aliphatic side chain), 2.7 (4H, s, $-CH_2-Ar$), 7.0 (10H, s, aromatic protons).
20g	0.95-1.26 (27H, methylene and methyl of aliphatic side chain), 2.73 (4H, s, $-CH_2-Ar$), 7.13 (10H, s, aromatic protons).
20h	0.96-1.33 (31H, methylene and methyl of aliphatic side chain), 2.73 (4H, s, $-CH_2-Ar$), 7.2 (10H, s, aromatic protons).
20i	0.98-1.3 (35H, methylene and methyl of aliphatic side chain), 2.7 (4H, s, $-CH_2-Ar$), 7.13 (10H, s, aromatic protons).

1-Phenyl-2-heptadecanone 21h

A mixture of alcohol 20h (1.0 g, 0.0023 M), dry benzene (30 ml), iodine (0.588 g, 0.0023 M) and lead tetraacetate (2.4 g, 0.0055 M) was heated under reflux with stirring for 6 hours and then cooled to room temperature. The excess of lead tetraacetate was destroyed by adding ethylene glycol. The benzene layer was washed with aqueous sodium thiosulphate solution, water, brine, dried and the solvent removed; from the resulting product, benzyl acetate was distilled out by heating in a distillation apparatus under vacuum (10 mm) and raising the bath temperature to 100°. The undistilled material was chromatographed over alumina (30.0 g, Grade II). The alumina column was eluted with petroleum ether to yield 21h (0.410 g, 57%), m.p. 45-6°.

IR spectrum (Nujol) showed band at 1724 cm^{-1} (for carbonyl).

NMR spectrum (CCl_4) showed signals at τ 2.3 (2H, t, J = 7 Hz, $C\underline{H}_2$-CO-), 3.56 (2H, s, -$C\underline{H}_2$-Ar), 7.1 (5H, s, aromatic protons).

Analysis: Found C, 83.65; H, 11.54.

$C_{23}H_{38}O$ requires C, 83.57; H, 11.59.

Following the similar procedure alcohols 20f, 20g and 20i were transformed to benzyl ketones 21f, 21g and 21i. The properties of benzyl ketones are being present in the Table 4.

Table 4 - Benzyl ketones 21f-i synthesised

Compound	Molecular Formula	Yield %	M.p.	Microanalysis Found	Requires
1-Phenyl-2-octanone (21f)	$C_{14}H_{20}O$	51	165°/ 1 mm	C 82.41 H 9.91	82.30 9.80
1-Phenyl-2-pentadecanone (21g)	$C_{21}H_{34}O$	55	215°/ 0.6 mm	C 83.01 H 11.41	83.38 11.33
1-Phenyl-2-heptadecanone (21h)	$C_{23}H_{38}O$	57	45-6°	C 83.65 H 11.54	83.57 11.59
1-Phenyl-2-nonadecanone (21i)	$C_{25}H_{40}O$	58	53-4°	C 83.54 H 11.93	83.73 11.81

The IR and NMR spectral details on the benzyl ketones are being given in Table 5.

Table 5 - NMR and IR spectral properties of 21f, 21g and 21i

Compound	IR (cm^{-1}) for carbonyl	NMR (δ)
21f	1712	0.9-1.3 (11H, methyl and methylenes of aliphatic side chain), 2.33 (2H, t, J=6 Hz, CH_2-$\underline{CH_2}$-CO-), 3.63 (2H, s, -$\underline{CH_2}$-Ar), 7.16 (5H, s, aromatic protons).
21g	1709	0.9-1.23 (25H, methyl and methylenes of aliphatic side chain), 2.3 (2H, t, J=6Hz, CH_2-$\underline{CH_2}$-CO-), 3.5 (2H, s, -$\underline{CH_2}$-Ar), 7.06 (5H, s, aromatic protons).
21i	1709	0.83-1.23 (33H, methyl and methylene of aliphatic side chain), 2.36 (2H, t, J=6Hz, CH_2-$\underline{CH_2}$-CO-), 3.56 (2H, s, $\underline{CH_2}$-Ar), 7.2 (5H, s, aromatic protons).

1-Phenyl-2-heptadecanol 22h

A mixture of 21h (1.0 g, 0.003 M), sodium borohydride (0.114 g, 0.003 M), ethanol (15 ml) and water (2 ml) were magnetically stirred for 4 hours at room temperature and then diluted with excess of water (25 ml). The mixture extracted with ether (2x50 ml). The ether layer was washed with water, brine, dried and evaporated to give solid residue which on recrystallization with petroleum ether gave 22h (0.909 g, 91%), m.p. 62° (Lit.[36] m.p. 63.1-64.2°).

IR spectrum (Nujol) showed band at 3448 cm^{-1} (OH stretching). NMR spectrum (CCl_4) showed signals at 0.93-1.33 (31H, methyl and methylene of aliphatic side chain), 2.7 (2H, m, $-CH_2-Ar$), 3.6 (1H, m, -CHOH), 7.03 (5H, s, aromatic proton).

Analysis: Found C, 82.98; H, 11.97.

$C_{23}H_{40}O$ requires C, 83.06; H, 12.13.

The remaining alcohols 22f, 22g and 22i were prepared in the same manner. The properties of these alcohols are being presented in Table 6.

Table 6 - Alcohols 22f, 22g and 22i synthesised

Compound	Yield %	M.p./b.p.	Lit. m.p./b.p.	Microanalysis Found	Requires
22f	92	a	a	C 81.52 H 10.86	81.50 10.75
22g	85	52-3°	55° [36]	C 82.66 H 12.20	82.83 11.92
22i	96	66°	68-9° [36]	C 82.85 H 12.03	83.26 12.30

[a - purified by column chromatography].

Characteristic band in IR and signals in NMR for the alcohols 21f, 21g and 21i are given in Table 7.

Table 7 - NMR and IR spectral details on 21f, 21g and 21i

Compound	IR (cm^{-1}) for hydroxyl	NMR (δ)
21f	3571	0.93-1.36 (13H, methyl and methylenes of aliphatic side side chain), 2.65 (2H, m, $C\underline{H}_2$-Ar), 3.7 (1H, m, -C<u>H</u>OH), 7.2 (5H, s, aromatic protons).
21g	3548	0.9-1.3 (27H, methyl and methylenes of aliphatic side chain), 2.63 (2H, m, $C\underline{H}_2$-Ar), 3.63 (1H, bm, -C<u>H</u>OH), 7.03 (5H, s, aromatic protons).
21i	3548	0.8-1.23 (35H, methyl and methylenes of aliphatic side chain), 2.7 (2H, m, -$C\underline{H}_2$-Ar), 3.71 (1H, m, -C<u>H</u>OH), 7.1 (5H, s, aromatic protons).

Hexadecanal 23h

A mixture of 22h (1.0 g, 0.003 M),dry benzene (15 ml), iodine (0.768 g, 0.003 M) and lead tetraacetate (3.1 g, 0.007 M) was heated under reflux with stirring for 4 hours and then cooled to room temperature. The excess of lead tetraacetate was destroyed by adding ethylene glycol. The benzene layer

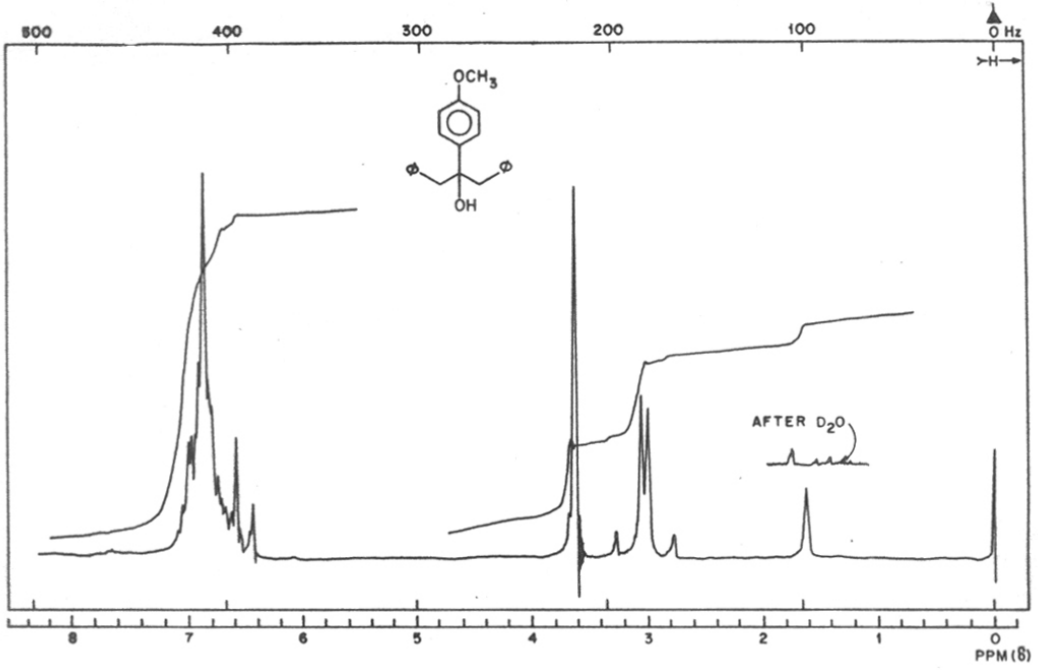
was washed with aqueous sodium thiosulphate solution, water, brine, dried and the solvent evaporated. To the residue which weighed (1.2 g) was added 2,4-dinitrophenyl hydrazone (1.1 g) in ethanol (10 ml). The mixture was boiled for few minutes and left for crystallization. On cooling the yellow-crystals of 2,4-dinitrophenyl hydrazone of hexadecanal 23h separated out as shining particle (0.630 g, 67%), m.p. 104-6° (Lit.[37] m.p. 105-6°).

The similar experimental conditions were performed on the alcohols 22f, 22g and 22i to furnish the corresponding aldehydes 23f, 23g and 23i respectively. The yield and m.ps. of 2,4-dinitrophenyl hydrazones of above derivatives are given in Table 8.

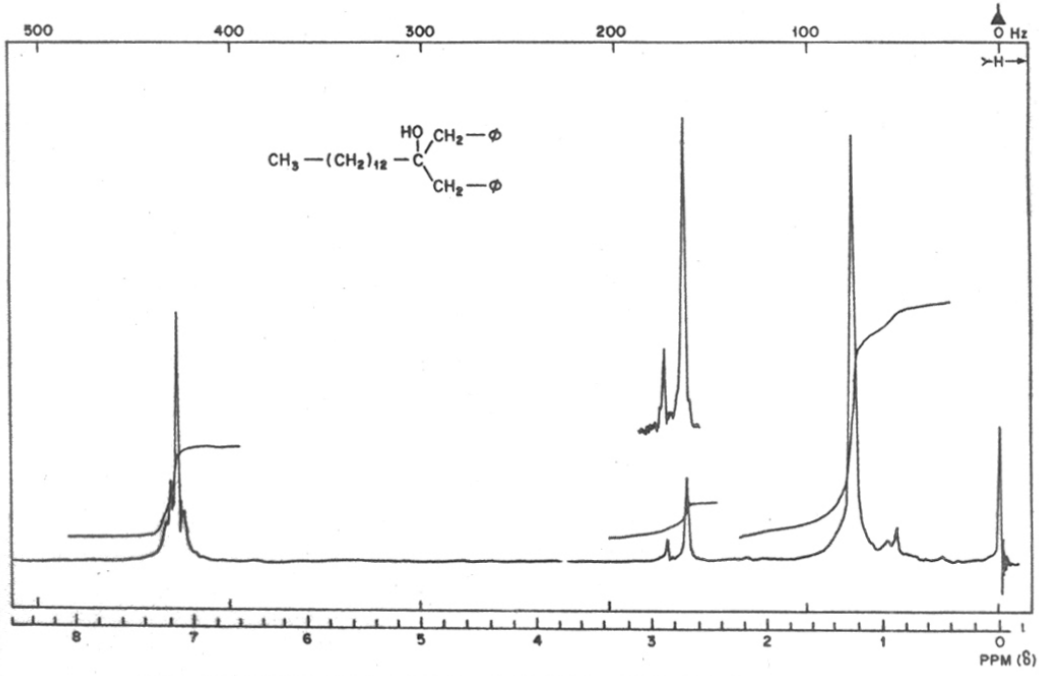
Table 8 - Aldehydes 23f-i synthesised

Compound	Yield %	m.p. of 2,4-DNP	Lit. m.p. of 2,4-DNP
23f	56	-	-
23g	58	105°	106-7° [39]
23h	67	104-6°	105-6° [37]
23i	58	103-5°	106.5-107° [38]

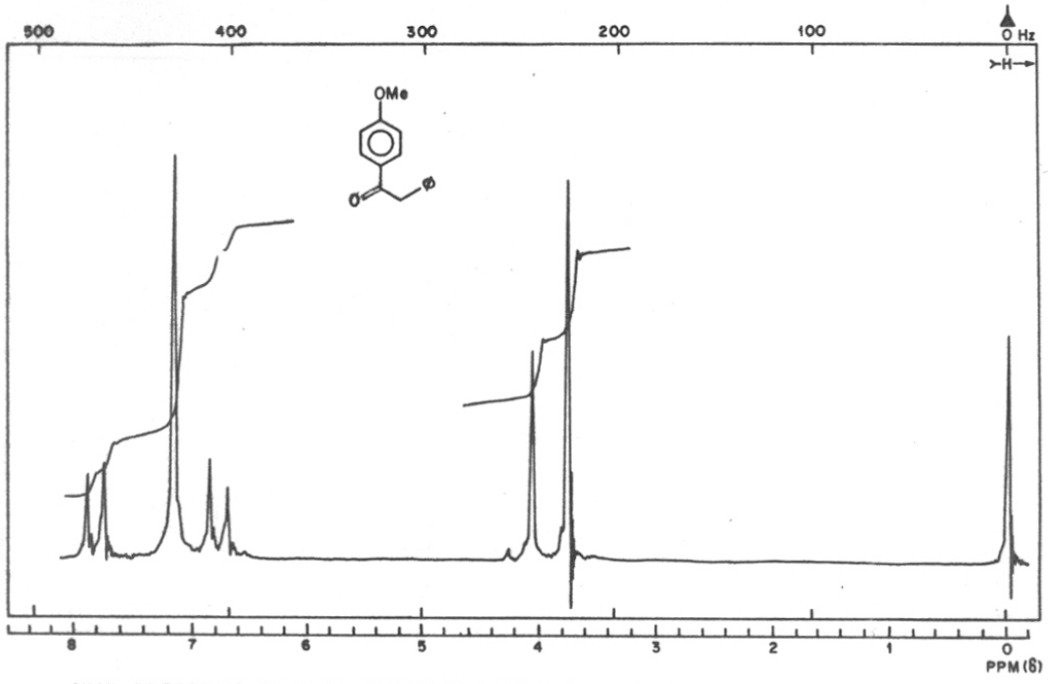
The identity and yield of 23f was established on the basis of GLC comparison with authentic sample of heptanal.



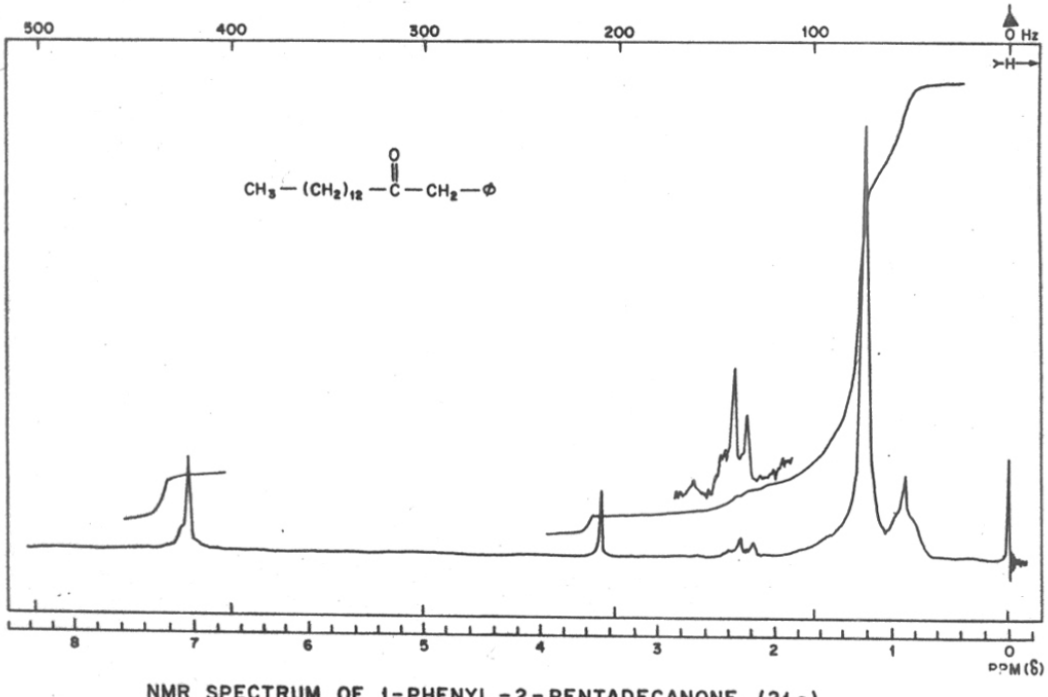
NMR SPECTRUM OF 2-(4-METHOXY PHENYL)-1,3-DIPHENYLPROPAN-2-OL.(20a)



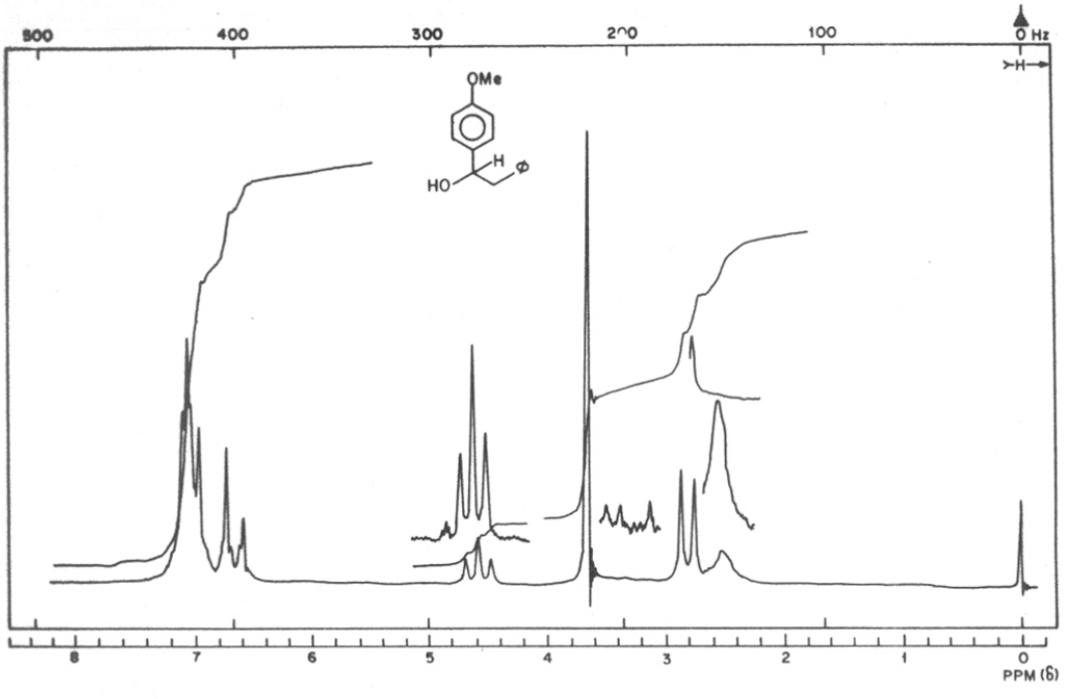
NMR SPECTRUM OF 1-PHENYL-2-BENZYL-PENTADECAN-2-OL.(20g)



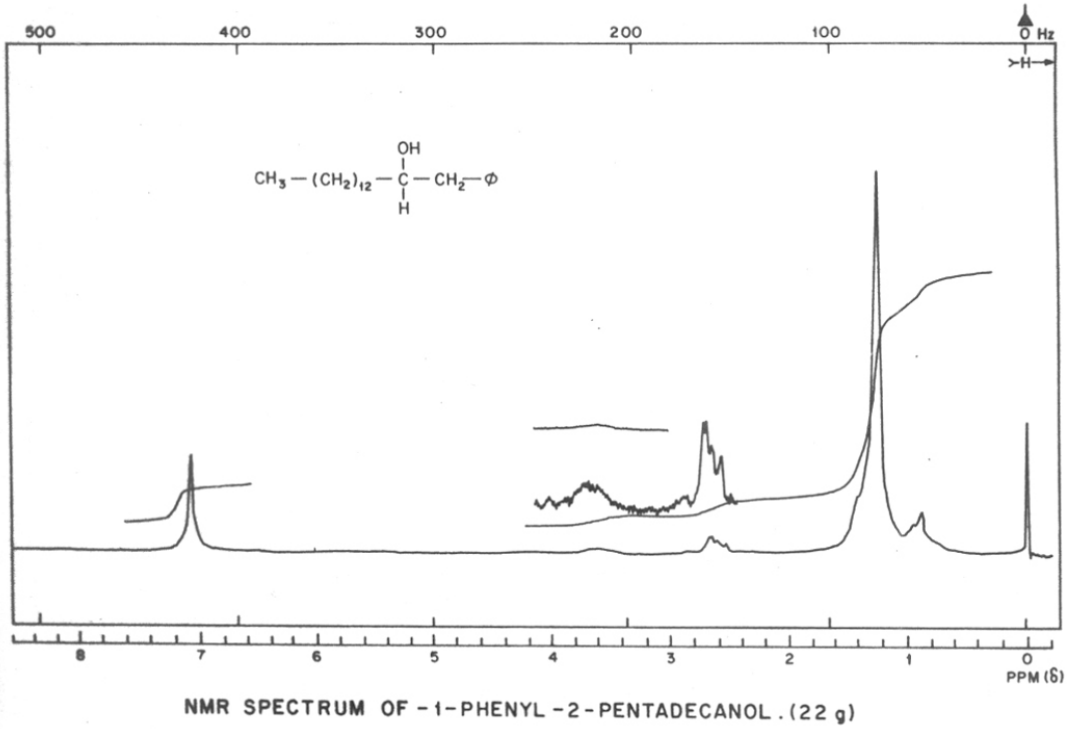
NMR SPECTRUM OF 1-(4-METHOXY PHENYL)-2-PHENYL ETHANONE.(21a)



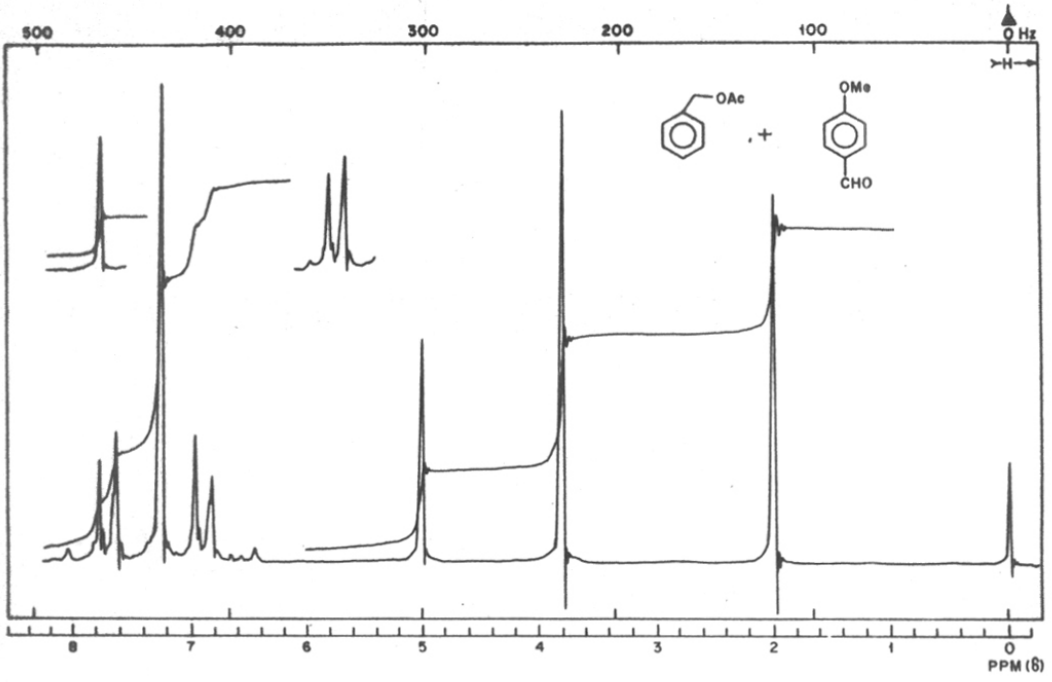
NMR SPECTRUM OF 1-PHENYL-2-PENTADECANONE. (21g)



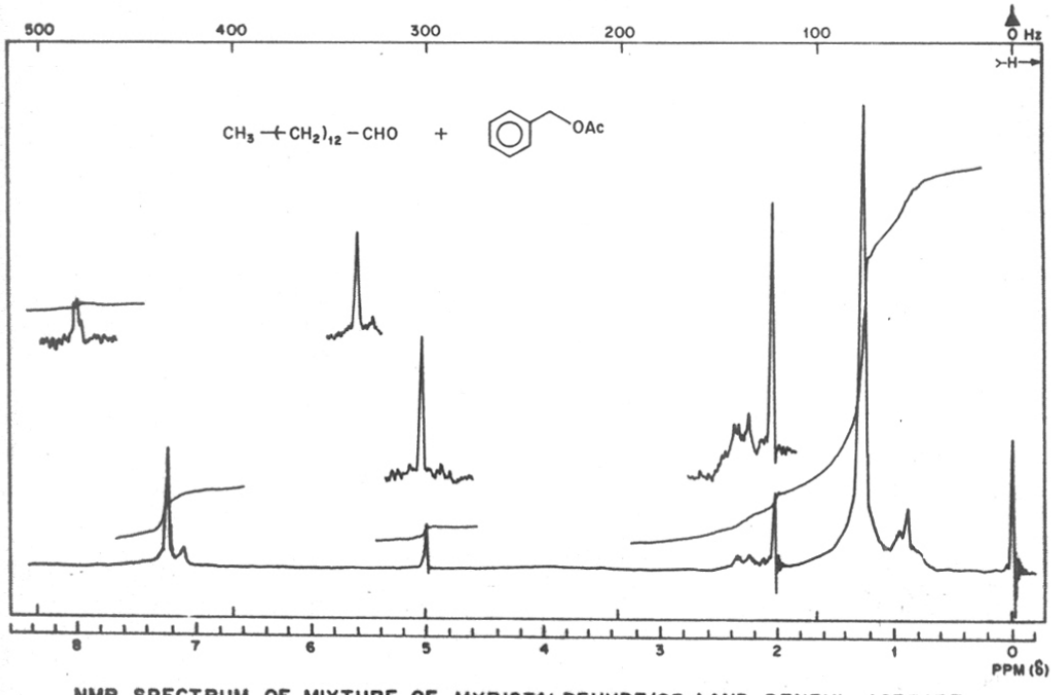
NMR SPECTRUM OF 1-(4-METHOXY PHENYL)-2-PHENYL ETHANOL.(22 a)



NMR SPECTRUM OF -1-PHENYL-2-PENTADECANOL. (22 g)



NMR SPECTRUM OF MIXTURE OF p-ANISALDEHYDE (23a) AND BENZYL ACETATE.



NMR SPECTRUM OF MIXTURE OF MYRISTALDEHYDE (23g) AND BENZYL ACETATE.

REFERENCES

1. J. Carnduff, Quart.Review, 20, 169 (1966).

2. J. Malek and M. Cerny, Synthesis, 217 (1972).

3. A.O. Badenbaugh, J.H. Badenbaugh, W.A. Bergin and J.D. Adkins, J.Am.Chem.Soc., 92, 5774 (1970).

4. M. Muraki and T. Mukaiyama, Chem.Letts., 1447 (1974).

5. M. Muraki and T. Mukaiyama, Chem.Letts., 215 (1975).

6. H. Muxfeldt, W. Rogalski and G. Klananberg, Chem.Ber.,98, 3040 (1965).

7 a) E. Mosettig, Org.Reactions, 8, 218 (1954).

b) H. Hanptmann and W.F. Walter, Chem.Rev., 62, 375 (1962).

c) G.R. Pettit and E.E. Van Tamelan, Org.Reactions, 12, 389 (1962).

8. I.C. Nordin, J.Heterocyclic Chem., 3, 531 (1966).

9. G. Doleschall, Tet.Lett., 2649 (1974).

10. G. Doleschall, Tet.Lett., 681 (1975).

11. A.I. Meyers, A. Nabeya, H.W. Adickes, I.R. Politzer, G.R. Malone, A.C. Kovelesky, R.L. Nolen and R.C. Portney, J.Org.Chem., 38, 36 (1973).

12. T. Mitsudo, T. Okajima, Y. Yakegami, M. Tanaka, Y. Watanabe and K. Yamamoto, Bull.Chem.Soc.Japan, 44, 2569 (1971).

13. Y. Watanabe, M. Yamashita, T. Mitsudo, M. Igami and Y. Takegami, Bull.Chem.Soc.Japan, 48, 2490 (1975).

14. Y. Watanabe, M. Yamashita, T. Mitsudo, M. Igami, K. Tomi and Y. Takegami, Tet.Letts., 1063 (1975).

15. J.D. Citron, J.Org.Chem., 34, 1977 (1969).

16. Y. Nagao, K. Kawabata and E. Fujita, J.C.S.Chem.Commu., 330 (1978).

17. T. Izawama and T. Mukaiyama, Chem.Letts., 1443 (1977).

18. N. Nagao, K. Kawabata, K. Seno and E. Fujita, J.C.S. Perkin I, 2470 (1980).

19. H.C. Brown, C.G. Rao and S.V. Kulkarni, Synthesis, 704 (1979).

20. E. Mosettig, Org.Reactions, 8, 218 (1954).

21. A.I. Rachlin, H, Gurien and D.P. Wagner, Org.Synth., 51, 8 (1971).

22. C.B. Reese, P. Grice and C.C. Dudman, Tet.Lett., 21, 3175 (1980).

23. D.G. Smith and D.J.H. Smith, J.C.S. Chem.Comm., 459 (1975).

24. T.E. Cole and R. Petit, Tet.Letts., 781 (1977).

25. K.J. Divakar and A.S. Rao, Ind.J.Chem., 14B, 704 (1976) and references cited therein.

26. K. Shankaran and A.S. Rao, Synth.Comm., 10, 573 (1980).

27. M. Lj.Mihailovic, Z. Maksimovic, D. Jeremic, Z. Cikovic, A. Milovanovic and Lj. Lorenc, Tetrahedron, 21, 1395 (1965).

28. Z. Majerski and J. Janjotovic, Tet.Lett., 3977 (1979).

29. W.S. Trahanovsky, P.J. Flash and L.M. Smith, J.Am.Chem.Soc., 91, 5068 (1969).

30. W.S. Trahanovsky and P.M. Nave, J.Am.Chem.Soc., 90, 4775 (1968).

31. J.S. Buck and W.S. Ide, J.Am.Chem.Soc., 54, 3012 (1932).

32. R.N. McDonald and P.A. Schwab, J.Am.Chem.Soc., 85, 820 (1963).

33. M.S. Newman and D.E. Reid, J.Org.Chem., 23, 665 (1958).

34. C.F.H. Allen and N.E. Barker, Org.Syn., 156, Collective Volume II.

35. I. Heilbron, "Dictionary of Organic Compounds", Vol.IV, Oxford Press, New York, N.Y., 1965, 2291.

36. S. Hersek, Istanbul Univ.Fen.Falkmecm.Seric., 31, 39 (1966), also see Chem.Abst., 69, 43554a (1968).

37. J.A. Knight and H.D. Zook, J.Amer.Chem.Soc., 74, 4560 (1952).

38. P.J.G. Kramer and H. Van Duin, Rec.Trav.Chim., 73, 63 (1954).

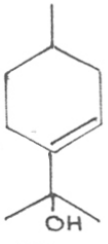
39. J. Kiss, G. Fodor and D. Banji, Helv.Chim.Acta., 37, 1471 (1954).

CHAPTER IV : USE OF DIELS-ALDER REACTION IN THE SYNTHESIS OF TERPENOID INTERMEDIATES

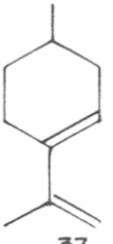
Summary

A new method for the preparation of p-menth-3-en-8-ol 36 and p-menth-$\Delta^{3,8(9)}$-diene 37 will be presented. Our main objective was to synthesise acetate 32, such that 32 on hydrolysis will afford homoallylic alcohol 28, which may be readily fragmented to acetoxy aldehyde 29. The aldehyde 29 can be then transformed to sesquicarane derivative 31.

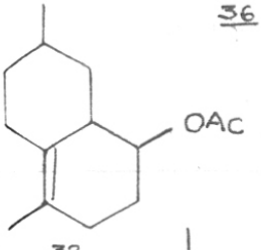
Two different methods for 32 by applying Diels-Alder reaction were investigated. In one of the methods the diene 37 reacted with ethyl acrylate to give 38, which on hydrolysis gave 39. 39 was transformed to 32. In another approach diene 37 was reacted with vinyl acetate to give 32. Merits and demerits of above two Diels-Alder reaction will be discussed.



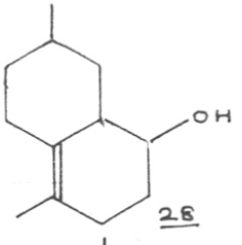
36



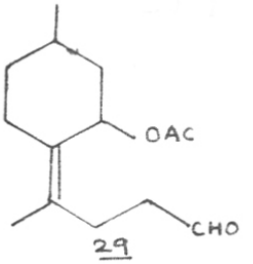
37



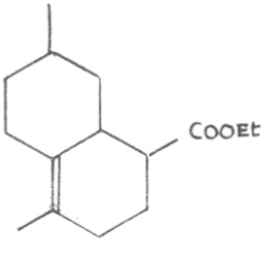
32



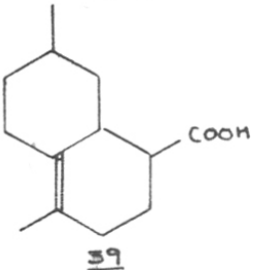
28



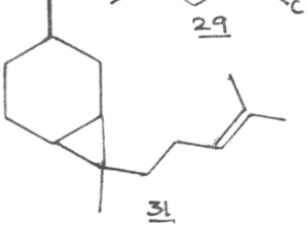
29



38



39



31

Introduction

The combination of conjugated dienes with olefins is only a special case of the more general reaction of cycloaddition in the formation of the six-membered ring, two new σ-bonds are formed at the expense of two π-bonds (Equation I).

[I]

Other examples of cycloaddition are epoxidation, carbene addition, dimerization of olefins to cyclobutane derivatives and 1,3-dipolar addition reactions[1-3].

The Diels-Alder reaction[4-8], which is a thermal (4+2) cycloaddition, provides a very useful, though indirect method for the formation of mono and poly-cycles containing six-membered rings. The reaction involves 1,4-addition of an alkene (a dineophile) to a conjugated diene. The simplest example being the addition of ethylene to butadiene to give cyclohexene. This particular example is a poor one since the yield is low, but it does illustrate the general point that, where a six-membered ring can be constructed in this way. Conversion of the product into the cycloalkane can be readily achieved by hydrogenation.

Addition occurs much more easily when the dineophile bears electron-withdrawing groups. A noteworthy feature of the Diels-Alder reaction is the great variety of the compounds which may serve as dineophiles. The compounds that have been employed as dineophiles fall into one of the following categories.

1. CH_2=CHA

   A = CHO, CO_2H, CO_2CH_3, $CO_2C_2H_5$, COCl, $COCH_3$, COϕ, CN, NO_2, C_6H_5, CH_2OH, CH_2X, CH_2NH_2, CH_2CN, CH_2CO_2H, CH_2NCS, $OCOCH_3$, $SC_6H_4CH_3$, SO_2R, X, H.

2. C_6H_5CH=CHA

   A = CHO, CO_2H, CO_2CH_3, $CO_2C_2H_5$, $COCH_3$, COC_6H_5

3. CH_2 = CA_2

   A = $CO_2C_2H_5$, CN, $COCH_3$, X.

4. ACH = CHA

   A = CO_2H, COCl, CO_2CH_3, $CO_2C_2H_5$, $COCH_3$, COC_6H_5, X.

5. Quinones.

6. AC ≡ CA

   A = CO_2H, CO_2CH_3, $CO_2C_2H_5$, COC_6H_5, C_6H_5, H.

More reactive dineophiles usually contain the C=C-C=O or the C≡C-C=O system. Other unsaturated groups

such as CN, NO_2 or SO_2 promote the addition. Ketenes do not react with dienes in Diels-Alder reactions.

The types of dienes which have been employed and examples of each type are shown below.

Acyclic dienes

Butadiene, alkylbutadienes, arylbutadienes, alkoxybutadienes, silyloxy-butadienes, etc.

Alicyclic compounds

Wholly alicyclic dienes - cyclopentadiene, cyclohexadiene, α-phellandrene, cycloheptadiene.

Alicyclic-acyclic compounds

1-Vinyl cyclohexene, 1-vinyl-3,4-dihydronaphthalenes, 1-ethynyl-6-methoxy-3,4-dihydronaphthalene.

Bicyclic compounds - Bicyclohexenyl etc.

Aromatic compounds

Wholly aromatic compounds - anthracene, 9-bromoanthracene etc.

Aromatic-alicyclic compounds

1-Vinyl naphthalene styrene, methylene anthrone.

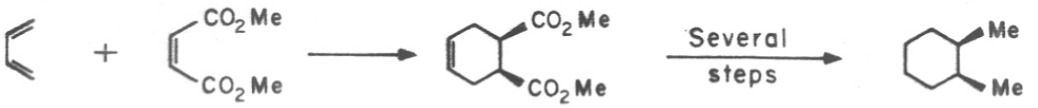
Heterocyclic compounds

Furans, 2-methylfuran, isobenzofuran, etc.

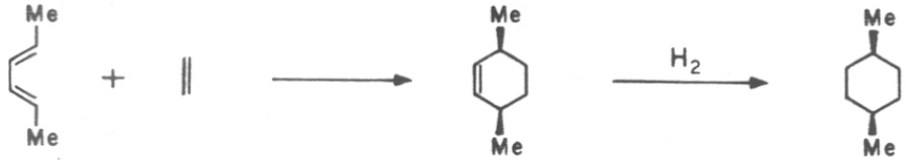
Another reason why this reaction is so useful in organic synthesis is its high stereospecificity. The

CHART I

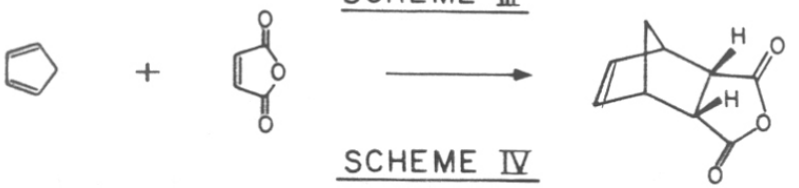
SCHEME I



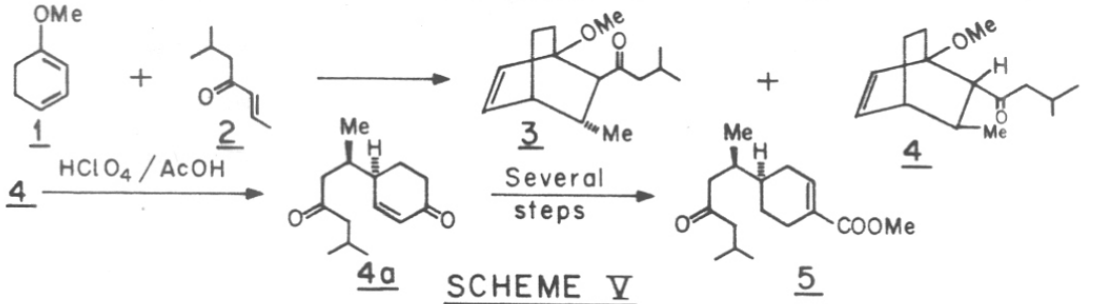
SCHEME II



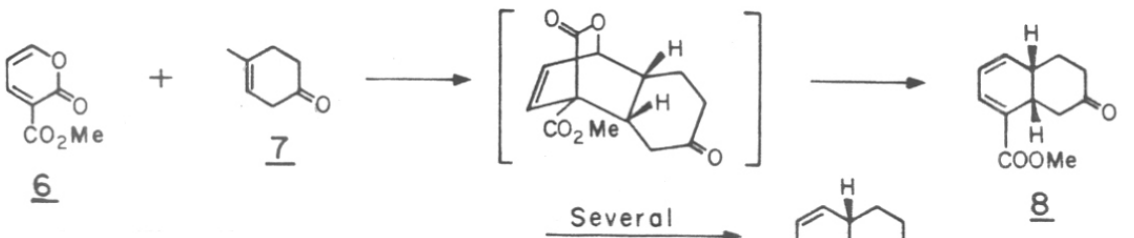
SCHEME III



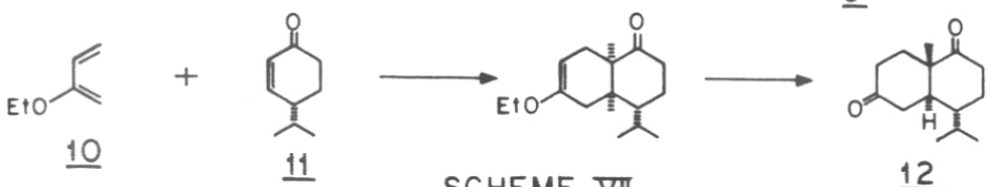
SCHEME IV



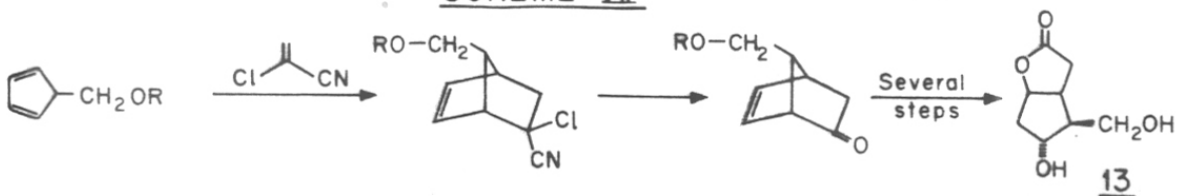
SCHEME V



SCHEME VI



SCHEME VII



The configuration of the diene and dineophile are retained in the adduct. Thus addition of cis-dimethyl maleate and butadiene gives a cis-substituted cyclohexene (Chart I, Scheme I). With the retention of configuration in the dineophile, the groups can be subsequently removed or reduced to alkyl group (Chart I, Scheme I). That retention of configuration in the diene, if substituted occurs is shown by the product obtained from ethylene and trans-trans-hexa-2,4-diene (Chart I, Scheme II). Thus if one wished to use these reaction as routes to 1,2 and 1,4-dimethylcyclohexanes, the configuration of the products are established at the cycloaddition stage. Another feature of Diels-Alder reaction which is important in determining the stereochemistry of bicyclic and bridged-ring carbocycles is the preference for endo addition. Thus for example cyclopentadiene reacts with maleic anhydride to give exclusively endo-product (Chart I, Scheme II).

Applications of Diels-Alder reaction in natural product synthesis.

Application of Diels-Alder reaction in natural products synthesis amply demonstrates its stereo and regiospecificity. An attempt is made here to single out instances wherein the Diels-Alder reaction played a crucial role.

Juvabion 5 was synthesised by Birch[9] et al. involving reaction of diene 1 and dineophile 2 to give 3 and 4. 4 underwent acid catalyzed ring opening to give intermediate 4a, which was transformed to juvabion 5 involving several steps (Chart I, Scheme IV).

Corey et al. have synthesised[10] occidentalol 9 by the reaction of diene 6 and dineophile 7 to afford 8. 8 was transformed into 9 involving series of steps (Chart I, Scheme V).

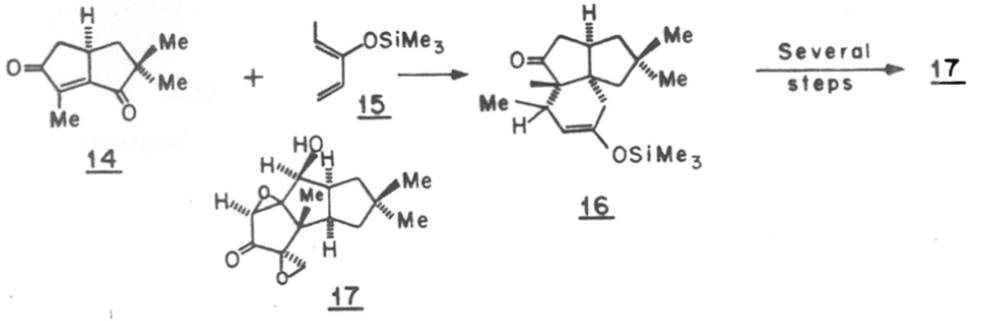
Dikatone 12 is an important synthetic intermediate to many cadenanes, was prepared by carrying out Diels-Alder reaction of 10 and 11 (Chart I, Scheme VI).

A general and stereocontrolled synthesis of all the prostaglandins in the naturally occurring forms from common intermediate 13 has been developed by Corey[12-15]. The key intermediate 13 was synthesised by an efficient route involving diene and dineophile to give [2,2,1]-heptane system (Chart I, Scheme VII).

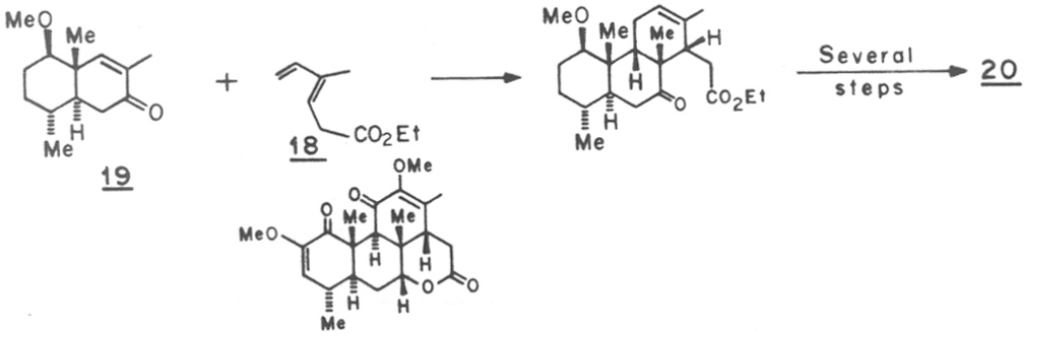
Recently Danishefsky[16] et al. have synthesised dl-coriolin 17 based on the availability of intermediate 16. Intermediate 16 was synthesised by Diels-Alder reaction of diene 15 and dineophile 14 (Chart II, Scheme I).

CHART II

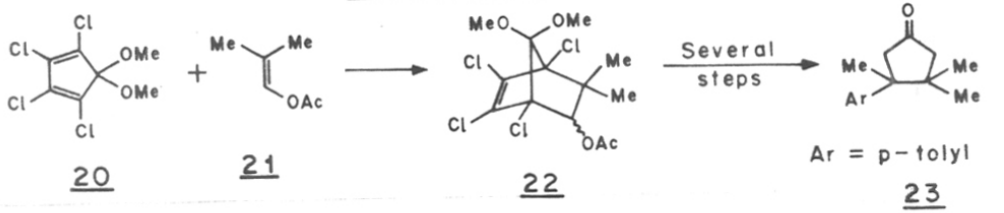
SCHEME I



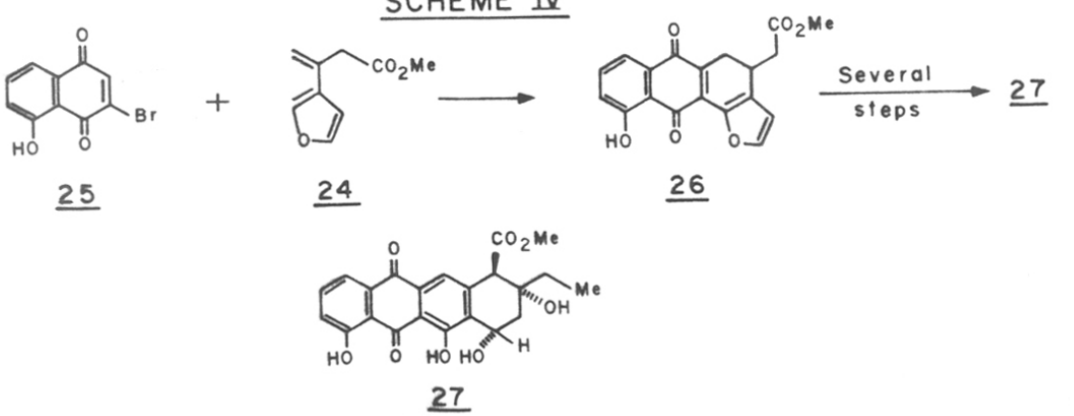
SCHEME II



SCHEME III



SCHEME IV



Greico et al. during the synthesis of dl-quassin 20 employed a Diels-Alder strategy involving diene 18 and dineophile 19 as a key reaction[17] (Chart II, Scheme II).

β-Cuparanone 23 was synthesised[18] involving the interaction of diene 20 and dineophile 21 to give intermediate 22 which was then transformed to 23 (Chart II, Scheme III).

Kishi's[19] synthesis of anthracycline antibiotics aklavin, starts from diene 24 and dineophile 25 to give the key intermediate 26, which was transformed to aclavin precursor 27 (Chart II, Scheme IV).

Latest trend of research in this area continuous to be in the field of Intramolecular Diels-Alder Reaction symbolized as IMDA. In this case the diene and dineophile are built within the molecule so as to synthesise effectively a variety of interesting natural products and bridged polycyclic systems. In properly designed system added advantages in terms of ease of reaction, regio and stereoselectivity may occur. The synthetic applications of IMDA have been reviewed recently[20,21].

PRESENT WORK

In our previous Chapters we saw how a homoallylic alcohol under suitable experimental conditions[22-24] can be fragmented to yield aldehydes, benzyl ketones etc. On this basis we argued that the alcohol 28, which is secondary homoallylic alcohol can be fragmented to give 29. 29 can be then transformed to enone 30 and then to sesquicarane derivatives 31[25,26].

We present here in the synthesis of acetate 32 by two different routes employing Diels-Alder reaction. 32 can be transformed to 28, which is key precursor to 29. Hence 32 is a potential intermediate for sesquicarane derivatives.

p-Mentha-$\Delta^{3,8(9)}$-diene 37 required for Diels-Alder reaction was synthesised in the manner given in the Chart III, Scheme I. Although there are several methods reported in the literature[27,34,35] for the synthesis of 37, our method was based on the availability of starting materials. 4-Methyl cyclohexanone 33 was converted to cyanohydrin followed by dehydration in the presence of thionyl chloride-pyridine gave 1-cyano-4-methyl-cyclohex-1-ene 34[28]. Saponification of 34 gave acid 34a[29]. Esterification of 34a in the presence of methanol and sulphuric acid catalyst gave 1-carbomethoxy-4-methyl-cyclohex-1-ene 35. 35 when reacted with excess of

methylmagnesium iodide gave p-menth-3-en-8-ol 36. 36 is known in the literature as a minor product formed as a result of epoxide ring opening reactions[30,31]. Alcohol 36 is naturally occurring and has been isolated from seto mint oil[32]. The route described above 33 → 34 → 35 → 36 constitutes a convenient route for the same.

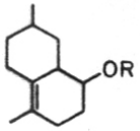
Von-Rudloff[33] reported that heating an alcohol under reflux at 200-300° from 1 to 6 hours in the presence of twice its weight of neutral alumina which contained 2% pyridine, gave satisfactory yield of alkene. Following the above procedure we could bring about dehydration of alcohol 36 to diene 37 in about 90% yield. The NMR spectrum of diene 37 showed signals at δ 0.97 (3H, d, J = 6 Hz, CH_3-CH), 1.83 (3H, s, CH_3-C=C), 4.6 (2H, m, C=CH_2) and 5.6 (1H, m, vinyl H).

The diene 37 was condensed* with ethyl acrylate to yield the adduct 38 (Chart III, Scheme II) in about 50% yield. This was brought about by heating 37 and ethyl acrylate for 48 hours at 85-90°. The IR spectrum of 38

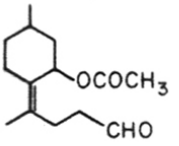
---

* Andersen et al.[35] have carried out the reaction of diene 37 with acrolein and analysed the stereochemistry of aldehydic groups in the reaction products. Buttery and Ling have also carried out the reaction[36] of diene 37 and methyl acrylate.

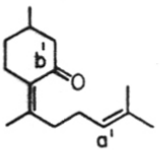
CHART III



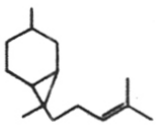
28 R = H
32 R = $COCH_3$



29

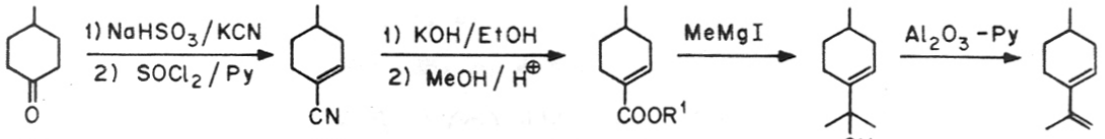


30



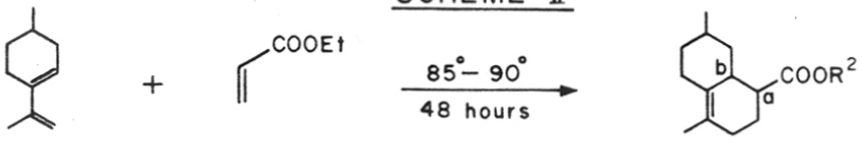
31

SCHEME I



33 34 34a R^1=H 35 R^1=CH_3 36 37

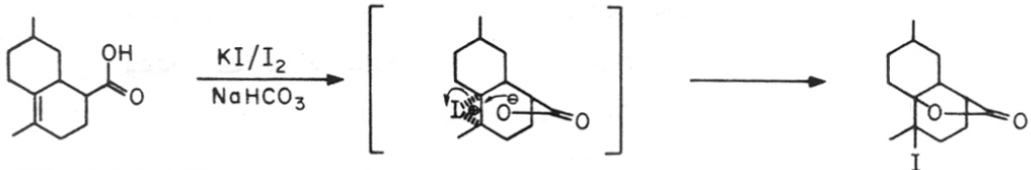
SCHEME II



37

38 R^2=Et
39 R^2=H
40 R^2=Me

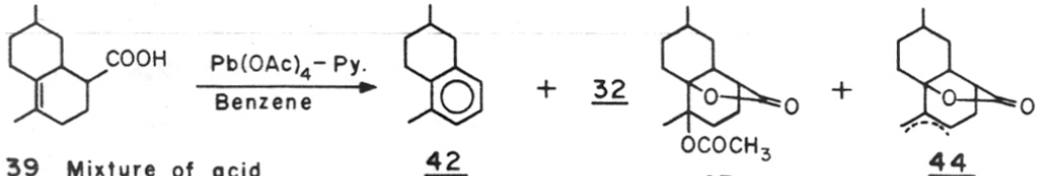
SCHEME III



39 Solid acid

41

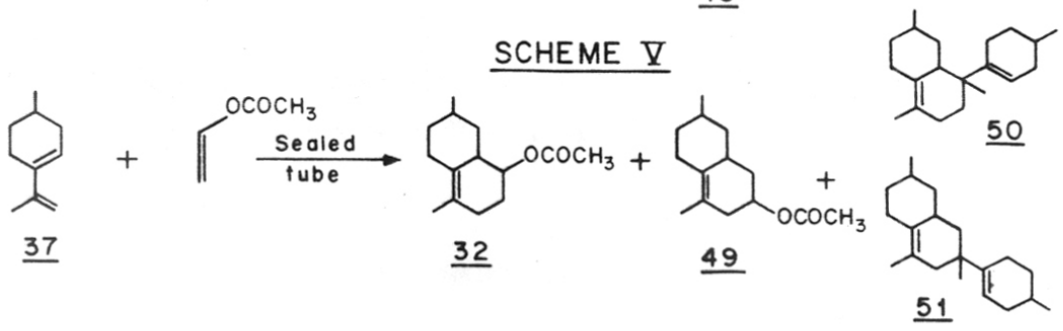
SCHEME IV



39 Mixture of acid

42 + 32 + 43 + 44

SCHEME V



37 32 49 50 51

showed a band at 1739 cm^{-1} for ester carbonyl. NMR spectrum of 38 showed signals at τ 1.1 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.23 (3H, t, J=6 Hz, $C\underline{H}_3$-CH_2), 1.6 (3H, s, CH_3-C=C) and 4.03 (2H, q, J = 6 Hz, -$C\underline{H}_2$-CH_3). The GLC analysis of 38 showed two peaks in the ratio of 60:40. Ester 38 could be a mixture of stereoisomers (38 has 3 asymmetric carbons and hence 4 racemates are possible). 38 was saponified to acid 39. From the stereoisomeric mixture of acids, a petroleum ether insoluble acid was isolated as solid. This solid acid which had m.p. 135-8° showed in IR a band at 1701 cm^{-1} for carbonyl of carboxylic acid. The NMR spectrum of solid acid showed signals at τ 1.13 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH), 1.66 (3H, s, $C\underline{H}_3$-C=C). The solid acid has the carboxylic group axially oriented. This was proved by iodolactonization[36] to give iodolactone 41 (Chart III, Scheme III). The lactone 41 in the IR showed band at 1786 cm^{-1} for γ-lactone. The NMR spectrum of 41 showed signals at τ 1.1 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH), 2.0 (3H, s, $C\underline{H}_3$-C-I), 2.96 (1H, q, $J_{ea} = J_{ee} = 3H_2$, -C$\underline{H}$-CO-O). Further the solid acid was characterized as solid methyl ester 40, m.p. 56-7°, which showed in IR a band at 1736 cm^{-1} for ester carbonyl. The NMR spectrum of 40 (solid) showed signals at τ 1.03 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.6 (3H, s, $C\underline{H}_3$-C=C), 3.57 (3H, s, -O-$C\underline{H}_3$).

We realized that this mixture of acids will not disturb our further studies, since the asymmetric centres at the carbon bearing carboxylic group (carbon-a) and tertiary allylic hydrogen bearing carbon (carbon-b) in the mixture of acids 39, will be converted to the product 30, where the carbon-a' (derived from carbon-a) and carbon-b' (derived from carbon-b) are trigonal centres.

Having obtained acid 39, it was now left to transform 39 into acetate 28. There are several reports in the literature[37] whereby carboxylic group can be transformed to acetoxy group. This transformation which is known as oxidative substitution can be brought about by heating a mixture of acid and lead tetraacetate in the presence of pyridine in refluxing benzene. The same was performed on acid 39 in refluxing benzene for 3 hours (Chart III, Scheme IV). After work-up the product so obtained was separated by column chromatography over alumina. The column was eluted successively with (i) petroleum ether (ii) petroleum ether + 3% ethyl acetate (iii) petroleum ether + 5% ethyl acetate (iv) petroleum ether + 10% ethyl acetate.

The fraction eluted with petroleum ether was identified as 42. The NMR spectrum of 42 showed

signals at τ (1.04 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 2.2 (3H, s, $C\underline{H}_3$-Ar), 2.63 (4H, m, $C\underline{H}_2$-Ar), 6.88 (3H, s, aromatic protons). The fraction eluted with petroleum ether + 3% ethyl acetate was acetate 32. The acetate 32 in the IR spectrum showed bands at 1742 and 1235 cm^{-1} for acetate group. NMR spectrum of 32 showed signals at τ 1.03 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.6 (3H, s, CH_3-C=C), 2.0 (3H, s, -O-CO-$C\underline{H}_3$), 4.5 (1H, m, -$C\underline{H}$OAc). The fraction eluted with petroleum ether + 5% ethyl acetate was assigned structure 43 on the following grounds. The IR spectrum of 43 showed bands at 1770 cm^{-1} for γ-lactone and 1739 cm^{-1} for acetate group. The NMR spectrum of 43 showed signals at τ 1.0 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.5 (3H, s, -$C\underline{H}_3$-C-O), 2.0 (3H, s, -OCO$C\underline{H}_3$). The fraction eluted with petroleum ether + 10% ethyl acetate as indicated by NMR was inseparable double bond isomers 44.

A brief genesis for the formation of mixture of 42, 32, 43 and 44 is shown in Chart IV, Scheme I. The acid 39 forms lead tetraacetate complex 39a. The complex such as 39a in general is less stable and more reactive than lead tetraacetate itself, hence dissociates to give 45 via 39b. 45 by loosing an electron gets oxidised to carbonium ion species 46. Trapping of 46 by acetoxy anion explains the formation of 32. Alternatively

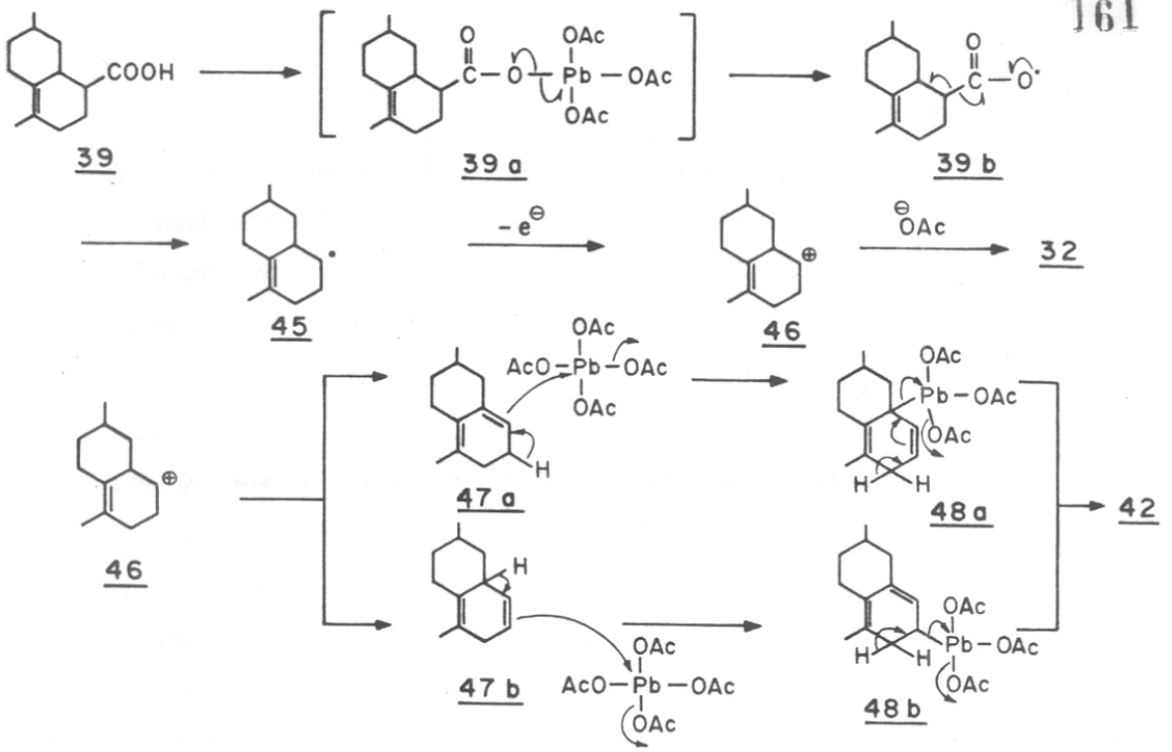
46 can loose proton either way to give conjugated diene 47a or non-conjugated diene 47b. By means of lead tetraacetate 47a is converted to 48a and 47b to 48b. It is very likely that 47b is more reactive and hence potential reactive intermediate for the formation of 42. This is because if one assumes diene 47a to be reactive species, in the next step for the formation of 48a, one has destroyed the conjugation. However from the transformation 47b to 48b, a non-conjugated diene 47b is transformed to conjugated complex 48b, which may be the driving force for this reaction. 48b is further oxidised to 42. The lactones 43 and 44 are probably derived from an acid 39 where the carboxylic group assumes axial orientation. In this case the lead atom is attacked by double bond (Pb - behaves as electrophile) and then followed by lactonization involving carboxylic group (Chart IV, Scheme II).

In conclusion, oxidative substitution with lead tetraacetate is not a good method for the preparation of 32 for two reasons. (i) The yield of 32 is low (about 27%). (ii) Formation of side products 42, 43 and 44. Hence an alternative method was sought for preparing 32.

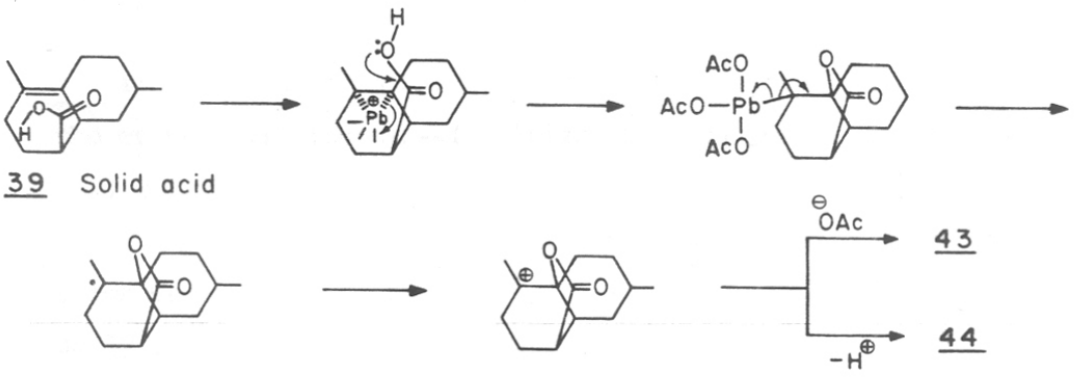
Heating diene 37 with vinyl acetate in a sealed tube for 72 hours gave a mixture of 32 and 49 in equal

CHART IV

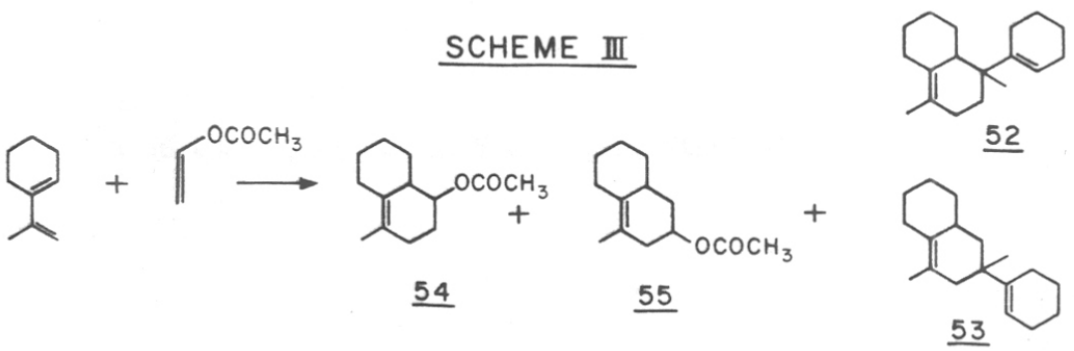
SCHEME I



SCHEME II



SCHEME III



proportion (Chart III, Scheme V). 32 and 49 could not be separated through column chromatography from each other because they had same R_f value. However the presence of 32 was established by direct GLC comparison with 32 obtained through lead tetraacetate reaction as discussed above. Wharton et al.[38] have studied the reaction of isopropenyl-cyclohexene and vinyl acetate (Chart IV, Scheme III). Two products 54 and 55 were obtained. Hence we assume that the second peak during comparative GLC studies from the reaction of p-mentha-$\Delta^{3,8(9)}$-diene and vinyl acetate may be the product 49. Thin layer chromatography showed that apart from 32 and 49, a less polar fast moving component is present (SiO_2 plate and developed in petroleum ether + 10% ethyl acetate). The total product from Diels-Alder reaction was chromatographed over alumina (Grade II) and the column was successively eluted with (i) petroleum ether (ii) petroleum ether + 3% ethyl acetate (iii) petroleum ether + 5% ethyl acetate. The fraction eluted with petroleum ether was identified as 50 or 51. That 50 or 51 is a dimer of 37 was shown by mass spectrum, wherein M^+ corresponded to 272. The next intense peak that was prominent was due to M-136 (Retro Diels-Alder fragmentation). The hydrocarbon (dimer) 50 or 51 analysed for $C_{20}H_{32}$. The NMR spectrum of 50 or 51 showed signals at τ 0.77-1.1 (9H, m, CH_3-), 1.56 (3H, s, CH_3-C=C), 5.2 (1H, m, vinyl H).

Hence Diels-Alder reaction of p-mentha-$\Delta^{3,8(9)}$-diene 37 and vinyl acetate is not a good method for getting 32 for the following reasons. (i) The reaction is not regiospecific and leads to the formation of unwanted isomer 49. (ii) Besides the side products 50 and(or) 51 decrease the value of this work. Wharton et al.[38] have carried out a similar reaction and they apparently did not get any dimerized product of the type 52 or 53.

Having obtained acetate 32, alcohol 28 was formed by saponification of 32. 28 in IR spectrum showed band at 3448 cm^{-1} for OH stretching and NMR spectrum showed signals at τ 1.1 (3H, d, J=6 Hz, CH_3-CH), 1.66 (3H, s, CH_3-C=C), 2.9 (1H, bm, OH, exchanges with D_2O), 3.3 (1H, m, CHOH).

The secondary homoallylic alcohol 28 was subjected to fragmentation by heating with lead tetraacetate in refluxing benzene. The aldehyde 29 was not formed, since the NMR spectrum of reaction product did not show a signal for aldehydic proton for 29 in the region of 9-10 τ.

EXPERIMENTAL PROCEDURE

1-Cyano-4-methyl-cyclohex-1-ene 34

4-Methyl cyclohexanone 33 (43 ml, 0.35 M) was added over a period of 30 minutes, to an ice cold solution of sodium bisulfite (55.0 g, 0.52 M) in 105 ml H_2O. Then potassium cyanide (34.0 g, 0.52 M) in 105 ml of water was added slowly to the cooled temperature and stirred overnight. The mixture was extracted with ether (3x200 ml). The ether layer was washed with water, brine, dried and concentrated to give (31.9 g, 65%) of cyanohydrin. Without purification the cyano-hydrin was stirred in pyridine (49 ml, 0.56 M) at 0° under nitrogen. Thionyl chloride (43.8 ml, 0.6 M) was then added dropwise. The solution warmed to room temperature and stirred overnight. The mixture then poured into 500 ml of water, pH adjusted to 4 with 1N NaOH and extracted with ether (3x150 ml). The ether layer was washed with water, brine, dried and evaporated to give residue, which on distillation furnished 34 (22.1 g, 80%), b.p. $138^{\circ}/20$ mm (Lit.[28] b.p. $118^{\circ}/11$ mm).

IR spectrum (liquid film) showed bands at 2222 cm^{-1} (nitrile group), 1639 cm^{-1} (double bond).

NMR spectrum (CCl_4) showed signals at τ 1.0 (3H, d, J=6 Hz, $\underline{CH}_3$-CH), 1.4-2.0 (3H, m, $\underline{CH}_2$ and $\underline{CH}$-), 2.33 (4H, m, allylic $\underline{CH}_2$), 6.4 (1H, m, vinyl H).

1-Carboxylic-4-methyl-cyclohex-1-ene 34a

A mixture of 34 (12.0 g, 0.11 M), ethanol (75 ml), potassium hydroxide (7.3 g, 1.1 M) and water (12 ml) refluxed for 10 hours and ethanol removed. The mixture was cooled, diluted with water and extracted with ether (2x150 ml). The ether extract was discarded and the aqueous part was acidified with 10% hydrochloric acid and extracted with ether (2x100 ml). The ether layer was washed with water, brine, dried and concentrated to give a solid, which on recrystallization from benzene gave 34a (11.2 g, 73%). M.p. 132° (Lit.[29] m.p. 132-3°).

1-Carbomethoxy-4-methyl cyclohex-1-ene 35

A mixture of 34a (14.0 g, 0.1 M), methanol (30 ml) and sulfuric acid (3 drops) refluxed for 4 hours. The reaction mixture (TLC indication) poured into water and extracted with ether (3x50 ml). The ether layer was washed with water, 10% solution of sodium bicarbonate, 10% solution of hydrochloric acid, brine, dried and evaporated to give residue, which on distillation under vacuum furnished 35 (13.8 g, 90%), b.p. 153°(bath)/44 mm.
The IR spectrum (liquid film) showed band at 1667 cm^{-1} (conjugated carbonyl).
The NMR spectrum (CCl_4) showed signals at τ 1.0 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH-), 1.3-1.83 (3H, m, $C\underline{H}_2$ and -C$\underline{H}$-), 2.3 (4H, m, allylic $C\underline{H}_2$), 3.6 (3H, s, -OC$\underline{H}_3$), 6.6 (1H, m, vinyl H).

p-Menth-3-en-8-ol 36

To a etheral solution of methylmagnesium iodide (43.0 g, 0.26 M, prepared from 37.0 g of MeI and 6.0 g of magnesium) was added a solution of 35 (10.g, 0.065 M) in ether (20 ml) at 0°. The mixture kept at the same temperature for 1 hour and then at room temperature for 24 hours. The reaction was quenched by adding saturated solution of ammonium chloride at 0°. The ether layer was separated and aqueous layer extracted with ether (2x50 ml). The combined ether layer was washed with water, 10% solution of sodium thiosulfate, brine, dried and evaporated to give the alcohol 36 (9.8 g, 98%). A small amount of sample was distilled to give pure 36, b.p. 123°(bath)/1.1 mm.

IR spectrum (liquid film) showed bands at 3509 and 1149 cm^{-1} (tertiary OH).

NMR spectrum (CCl_4) showed signals at 0.96 (3H, d, J = 6 Hz, CH_3-CH), 1.3 (6H, s, CH_3 on carbon bearing hydroxyl group), 1.43-2.33 (7H, m, CH_2 and CH_2), 5.7 (1H, m, vinyl H).

Analysis: Found C, 77.65; H, 11.83.

$C_{10}H_{18}O$ requires C, 77.86; H, 11.76.

p-Menth-$\Delta^{3,8(9)}$-diene 37

In a distillation unit containing Al_2O_3 (20.0 g, prepared by mixing neutral alumina (19.6 g) and pyridine (0.4) g) and alcohol 36 (10.0 g) was immersed in a metallic

bath maintained at a temperature of 300-20°. The dehydrated product which distills along with the water was collected. The distilled product was extracted with ether (50 ml). The ether layer was washed with water, brine, dried and evaporated to give the crude 37, which on distillation under vacuum gave pure 37 (8.0 g, 91%), b.p. 135°(bath)/40 mm.

IR spectrum (liquid film) showed bands at 1600 and 877 cm^{-1} ($C=CH_2$).

NMR spectrum (CCl_4) showed signals at τ 0.97 (3H, d, J=6 Hz, $\underline{CH_3}$-CH-), 1.83 (3H, s, $\underline{CH_3}$-C=C), 4.6 (2H, m, C=C$\underline{H_2}$), 5.6 (1H, m, vinyl H).

Analysis: Found C, 88.02; H, 11.93.

$C_{10}H_{16}$ requires C, 88.16; H, 11.84.

1,2,3,5,6,7,8,8a-Octahydro-1-carboethoxy-4,7-dimethyl-$\Delta^{4(4a)}$-naphthalene 38

A mixture of diene 37 (5.4 g, 0.04 M), ethyl acrylate (5.0 g, 0.05 M) and hydroquinone (0.2 g) heated in the nitrogen atmosphere for 48 hours at 90°. After the reaction was complete, excess of ethyl acrylate was removed under suction (50 mm). The residue obtained was distilled. The fraction with b.p. 145°(bath)/3.5 mm was identified as 38 (4.6 g, 50%).

IR spectrum (liquid film) showed bands at 1742 cm^{-1} (carbonyl of ester), 1695 cm^{-1} (tetra substituted double bond).

NMR spectrum (CCl_4) showed signals at τ 1.1 (3H, d, J=6 Hz, $C\underline{H}_3$-CH-), 1.23 (3H, t, J = 6 Hz, $C\underline{H}_3$-CH_2), 1.6 (3H, s, $C\underline{H}_3$-C=C), 4.03 (2H, q, J = 6 Hz, $C\underline{H}_2$-CH_3).

Analysis: Found C, 76.28; H, 10.50.

$C_{15}H_{24}O$ requires C, 76.22; H, 10.24.

1,2,3,5,6,7,8,8a-Octahydro-1-carboxyl-4,7-dimethyl-$\Delta^{4(4a)}$-naphthalene 39

A mixture of ester 38 (6.6 g, 0.03 M), methanol (60 ml), sodium hydroxide (1.2 g, 0.3 M) and water (5 ml) refluxed for 6 hours and the excess of methanol removed by suction. The mixture was cooled, diluted with water and extracted with ether (2x50 ml). The ether layer was rejected. The aqueous layer was acidified with 10% solution of hydrochloric acid and extracted with ether (2x100 ml). The ether extract was washed with water, brine, dried and evaporated to give crude acid 39 (5.8 g, 93%). From the above mixture of acids a petroleum ether insoluble acid weighing 2.3 g was isolated. This solid acid was recrystallised from ethanol (2.0 g) to give solid 39. m.p. 135-8°.

IR spectrum (Nujol) showed band at 1701 cm^{-1} (carbonyl).

NMR spectrum (CCl_4) showed signals at τ 1.13 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH), 1.66 (3H, s, CH_3-C=C).

Analysis: Found C, 73.45; H, 10.14.

$C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27.

Iodolactonization of solid acid 39

To a mixture of solid acid 39 (0.160 g, 0.00077 M), and sodium bicarbonate (5 ml, 0.5 M) was added a solution of iodine (0.317 g, 0.0024 M), potassium iodide (1.33 g, 0.008 M) in water (3 ml) at 0°. The flask was wrapped in a black cloth and the mixture stirred for 24 hours at room temperature. The mixture was diluted with water and extracted with ether (2x50 ml). The ether layer was washed with water, 10% solution of sodium thiosulfate, brine, dried and evaporated to give residue, which on recrystallization from petroleum ether gave pale yellow crystals of 41 (0.257 g, 90%), m.p. 92°.

IR spectrum (Nujol) showed band at 1786 cm^{-1} (γ-lactone).
NMR spectrum (CCl_4) showed signals at τ 1.1 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH-), 2.0 (3H, s, $C\underline{H}_3$-CH-I), 2.96 (1H, q, $J_{ea} = J_{ae} = 3$ Hz, -C$\underline{H}$-CO-O-).

Analysis: Found C, 46.58; H, 5.61.
$C_{13}H_{19}IO$ requires C, 46.71; H, 5.43.

The solid acid 39 was further characterized as its methyl ester 40 (93%), m.p. 56-7°.
The IR spectrum (Nujol) showed band at 1736 cm^{-1} (carbonyl)
NMR spectrum (CCl_4) showed signals at τ 1.03 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH), 1.6 (3H, s, $C\underline{H}_3$-C=C), 3.57 (3H, s, -O$C\underline{H}_3$).

Analysis: Found C, 75.38; H, 9.84.
$C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97.

Lead tetraacetate reaction on mixture of acid 39

A mixture of acid 39 (3.5 g, 0.017 M) lead tetraacetate (15.5 g, 0.035 M), pyridine (2.8 g, 0.035 M) and benzene (75 ml) refluxed for 6 hours. The mixture was cooled and the excess of lead tetraacetate destroyed by adding ethylene glycol. The benzene layer was washed with water, 10% sodium bicarbonate solution, brine, dried and solvent removed to give the product, which on distillation under vacuum furnished 2.26 g of mixture of products (as indicated by TLC chromatography). The above product was chromatographed over column of alumina (Grade II, 70.0 g) and eluted successively with (i) petroleum ether (ii) petroleum ether + 3% ethyl acetate (iii) petroleum ether + 5% ethyl acetate (iv) petroleum ether + 7% ethyl acetate. The fraction eluted with petroleum ether was identified as 1,2,3,4-tetrahydro-2,5-dimethyl naphthalene 42 (0.375 g, 15%), b.p. 165°(bath)/35 mm.

IR spectrum (liquid film) showed bands at 1600 and 1460 cm^{-1} (aromatic ring), 763 cm^{-1} (C-H bending aromatic).

NMR spectrum (CCl_4) showed signals at τ 1.04 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH-), 2.2 (3H, s, $C\underline{H}_3$-Ar), 2.63 (4H, m, $C\underline{H}_2$-Ar), 6.88 (3H, s, aromatic protons).

Analysis: Found C, 89.86; H, 10.12.

$C_{12}H_{16}$ requires C, 89.94; H, 10.06.

The fraction eluted with petroleum ether + 3% ethyl acetate was identified as 1,2,3,4,5,6,7,8,8a-octahydro-1-acetoxy-4,7-dimethyl-$\Delta^{4(4a)}$-naphthalene 32 (0.973 g, 27%), b.p. 125°(bath)/2.5 mm.

IR spectrum (liquid film) showed bands at 1742 and 1235 cm^{-1} (carbonyl of acetate).

NMR spectrum (CCl_4) showed signals at τ 1.03 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH), 1.6 (3H, s, CH_3-C=C), 2.0 (3H, s, -O-CO-$C\underline{H}_3$), 4.5 (1H, m, -C$\underline{H}$-OAc).

Analysis: Found C, 75.78; H, 9.91.

$C_{14}H_{22}O_2$ requires C, 75.63; H, 9.97.

The fraction eluted with petroleum ether + 5% ethyl acetate was lactone 43 (0.344 g, 8%).

IR spectrum (liquid film) showed bands at 1770 cm^{-1} (γ-lactone), 1739 cm^{-1} (carbonyl of acetate).

NMR spectrum (CCl_4) showed signals at τ 1.0 (3H, d, J = 6 Hz, $C\underline{H}_3$-CH-), 1.5 (3H, s, $C\underline{H}_3$-C-O), 2.0 (3H, s, -OCOCH_3).

Analysis: Found C, 67.48; H, 8.37.

$C_{15}H_{22}O_4$ requires C, 67.64; H, 8.33.

The fraction eluted with petroleum ether + 7% ethyl acetate was mixture of lactones 44 (0.210 g, 6%).

IR spectrum (liquid film) showed bands at 1786 cm^{-1} (γ-lactone), 1667 cm^{-1} (tri-substituted) alkene).

NMR spectrum (CCl_4) showed signals at τ in the vinylic region 4.8 (2H, m, $=CH_2$), 5.45 (1H, m, =C$\underline{H}$).

Diels-Alder reaction of p-menth-$\Delta^{3,8(9)}$-diene 37 and vinyl acetate

A mixture of diene 37 (4.8 g, 0.035 M), vinyl acetate (3.0 g, 0.035 M) and hydroquinone (0.150 g) heated at 190° for 72 hours in a sealed tube. The tube cooled to room temperature and excess of vinyl acetate removed on a water bath. The residue transferred to a distillation unit and distilled under vacuum to give a mixture of several products (3.5 g, 45%) indicated by thin layer chromatography (plate prepared from SiO_2 and developed in petroleum ether + 10% ethyl acetate). The total distilled product of Diels-Alder reaction was chromatographed over alumina (Grade II, 150.0 g) and eluted successively with (i) petroleum ether (ii) petroleum ether 5% ethyl acetate (ii) petroleum ether + 10% ethyl acetate.

The fraction eluted with petroleum ether was identified as 50 or 51 (1.3 g, 54%), b.p. 145°(bath)/0.15 mm. IR spectrum (liquid film) showed bands at 2985 cm^{-1} (C-H stretching), 1449 cm^{-1} (C-H bending).

NMR spectrum (CCl_4) showed signals at τ 0.77-1.1 (9H, m, CH_3-), 1.56 (3H, s, CH_3-C=C), 1.9-2.2 (9H, m, allylic methylene and methine protons), 5.2 (1H, m, vinyl H).

Analysis: Found C, 88.00; H, 11.78.

$C_{20}H_{32}$ requires C, 88.16; H, 11.84.

The fraction eluted with petroleum ether + 5% ethyl acetate was identified as 32 and(or) 49 (1.7 g, 22%), b.p. 102°(bath)/0.4 mm.

IR spectrum (liquid film) showed band at 1745 cm^{-1} (acetate carbonyl).

NMR spectrum (CCl_4) showed signals at τ 0.9-1.1 (3H, m, $C\underline{H}_3$-), 1.66 (3H, s, $C\underline{H}_3$-C=C), 2.0 (3H, -O-CO-$C\underline{H}_3$), 4.5-4.8 (1H, m, -C$\underline{H}$OAc).

1,2,3,5,6,7,8,8a-Octahydro-1-hydroxy-4,7-dimethyl-$\Delta^{4(4a)}$-naphthalene 29.

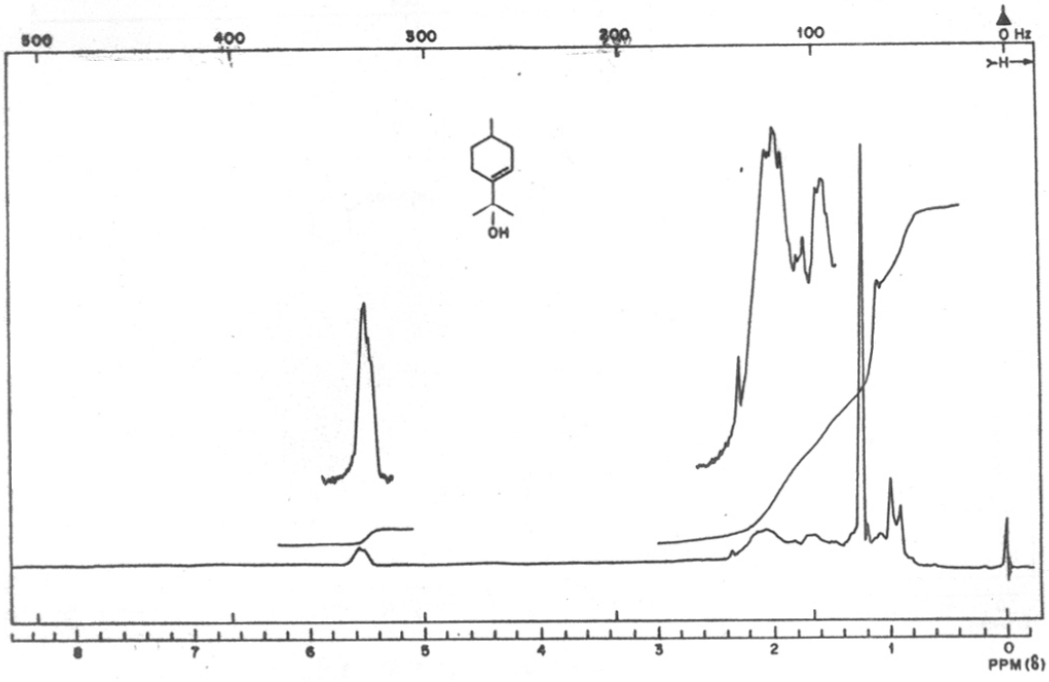
A mixture of 32 (0.700 g, 0.0031 M), sodium hydroxide (1.2 g, 0.031 M), methanol (15 ml) and water (2 ml) refluxed for 3 hours. The mixture cooled and poured into ice-cooled water and extracted with ether (2x25 ml). The ether extract was washed with water, brine, dried and evaporated to give residue, which on distillation gave 29 (0.493 g, 88%), b.p. 143°(bath)/0.5 mm.

IR spectrum (liquid film) showed band at 3448 cm^{-1} (hydroxyl stretching).

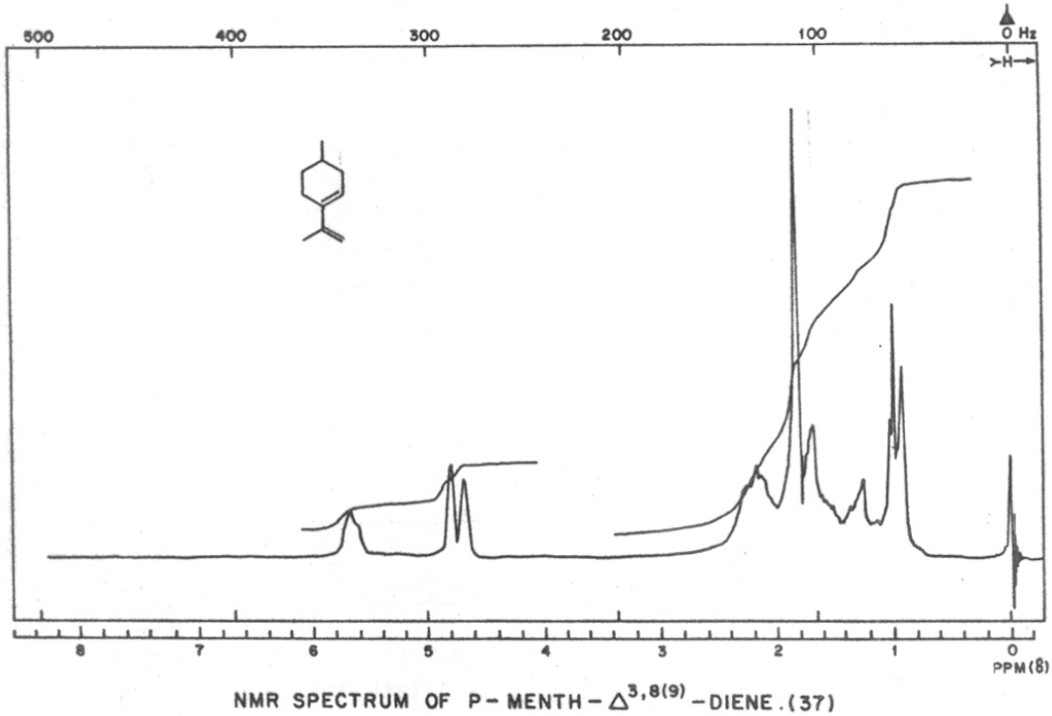
NMR spectrum (CCl_4) showed signals at τ 1.1 (3H, d, J=6 Hz, $C\underline{H}_3$-CH), 1.66 (3H, s, $C\underline{H}_3$-C=C), 2.9 (1H, bm, OH, exchanges with D_2O) and 3.3 (1H, m, -C$\underline{H}$OH).

Analysis: Found C, 79.73; H, 11.05.

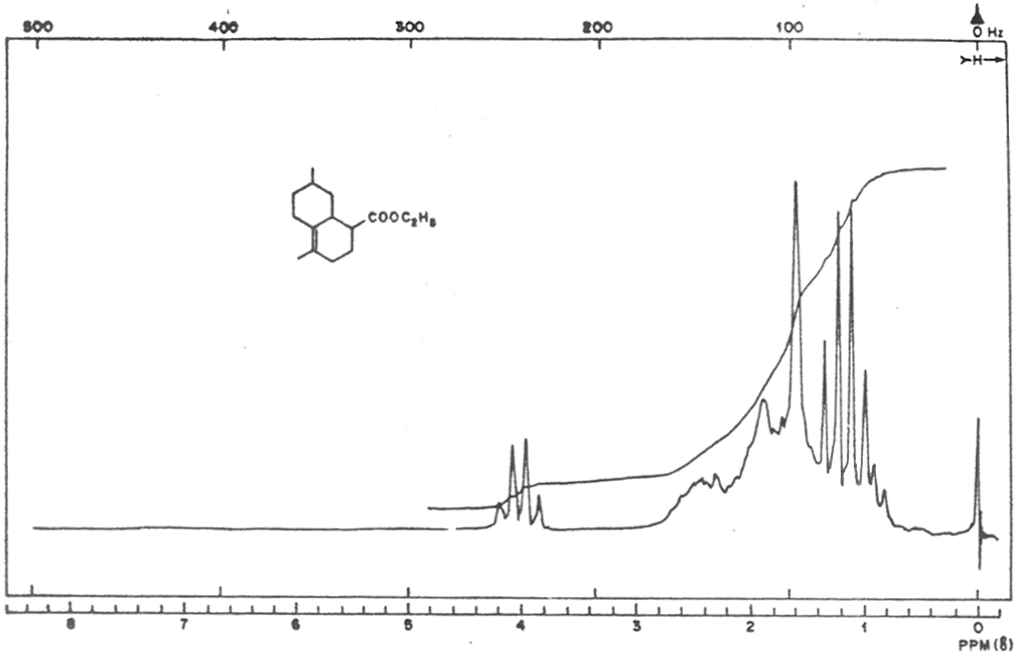
$C_{12}H_{16}O$ requires C, 79.94; H, 11.18.



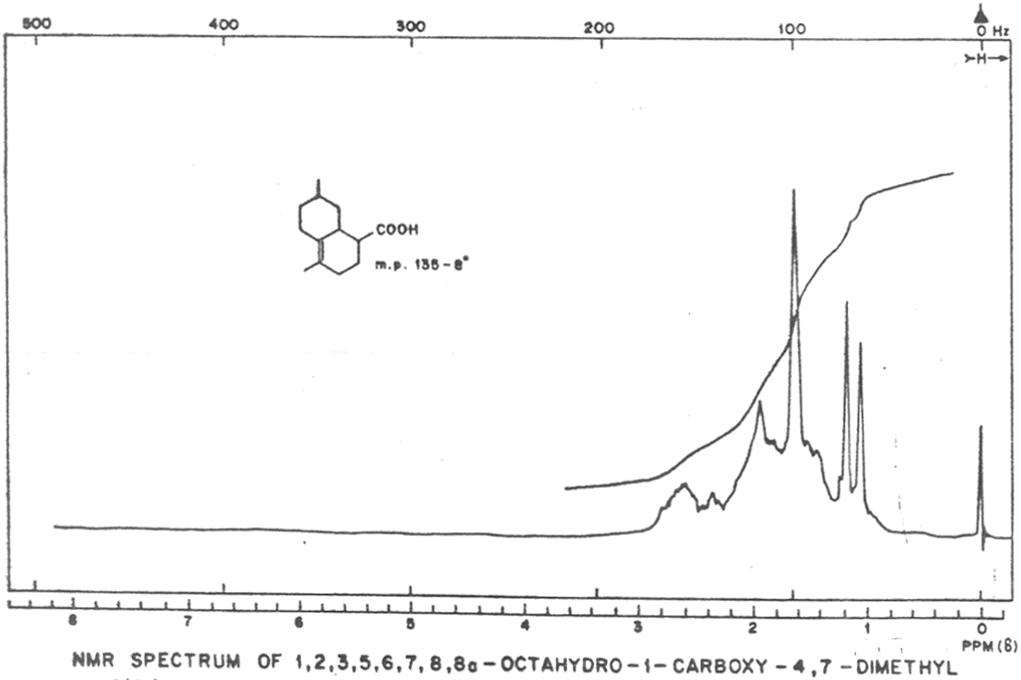
NMR SPECTRUM OF P-MENTH-8-EN-3-OL. (36)



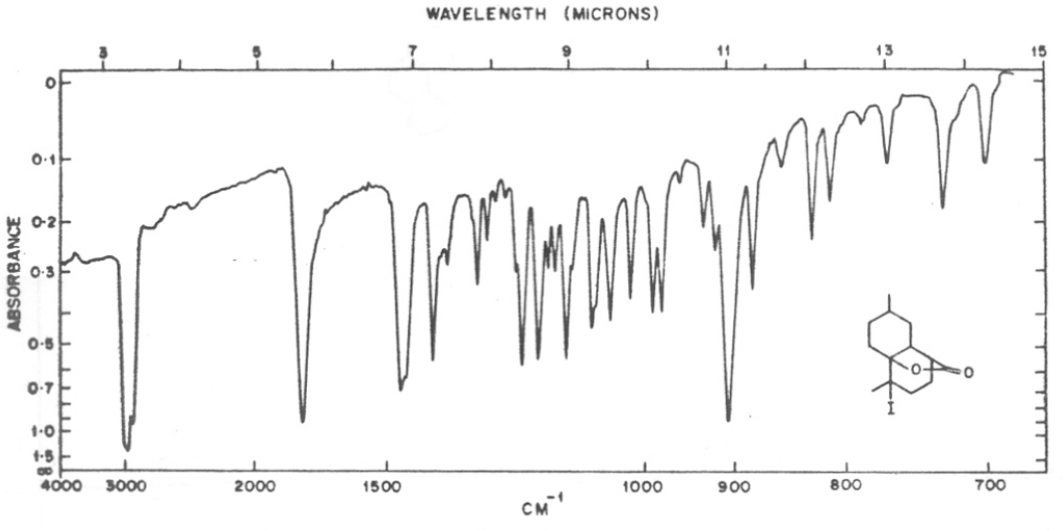
NMR SPECTRUM OF P-MENTH-$\Delta^{3,8(9)}$-DIENE. (37)



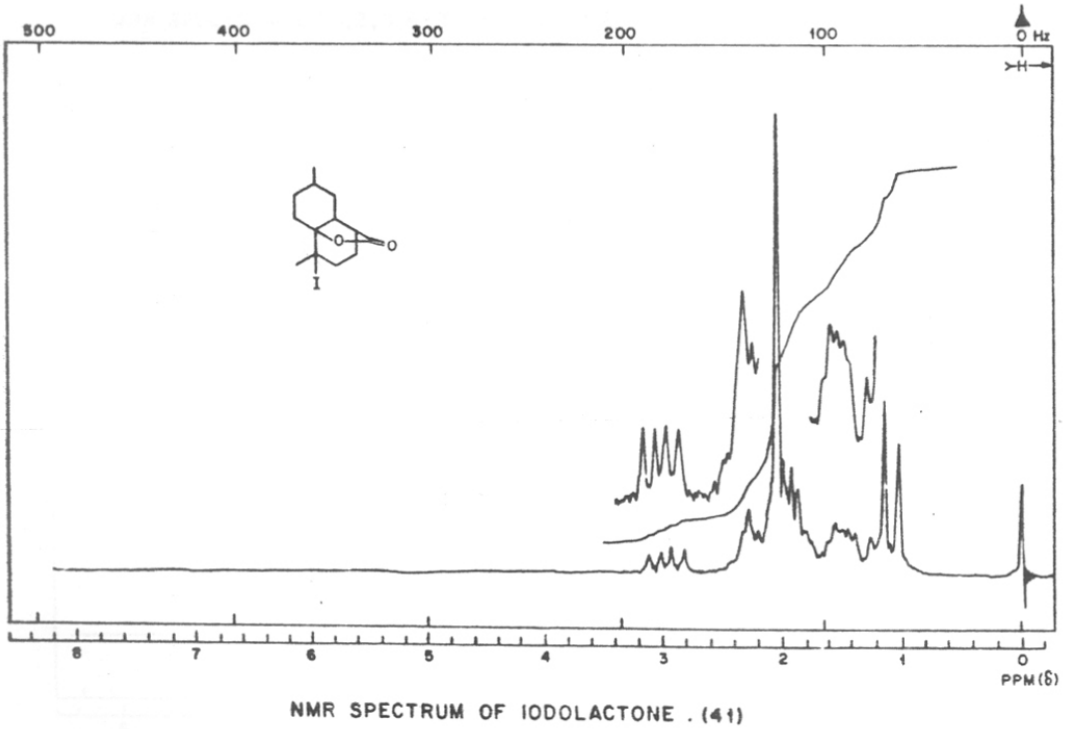
NMR SPECTRUM OF 1,2,3,5,6,7,8,8a - OCTAHYDRO - 1 - CARBOETHOXY - 4,7 - DIMETHYL - $\Delta^{4(4a)}$ - NAPHTHALENE . (38)



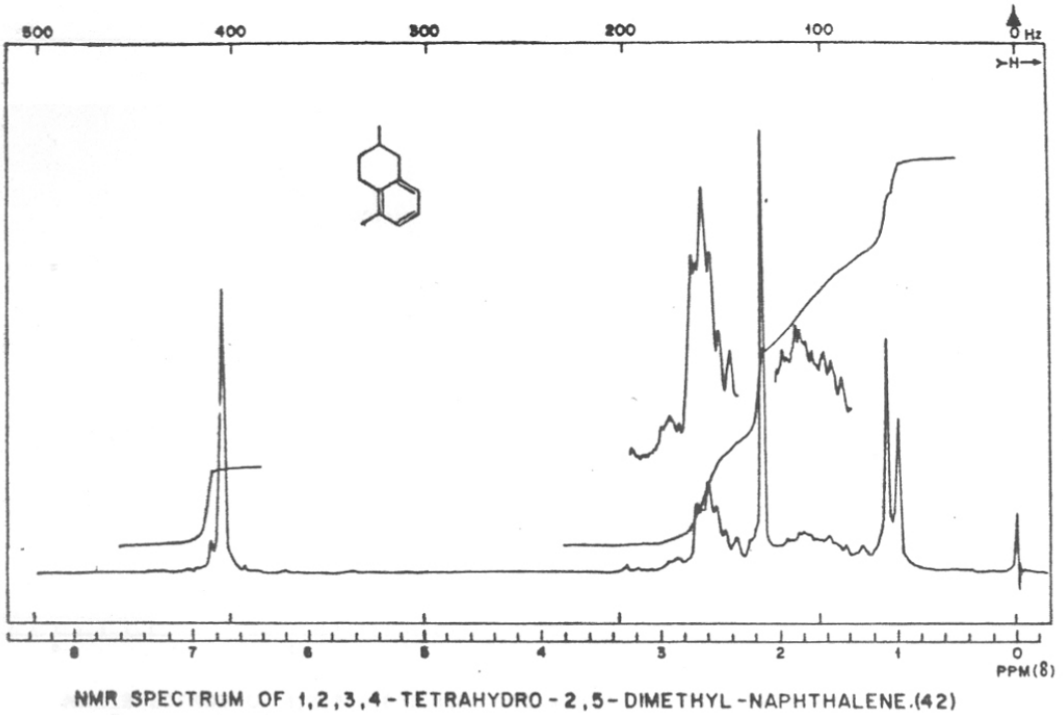
NMR SPECTRUM OF 1,2,3,5,6,7,8,8a - OCTAHYDRO - 1 - CARBOXY - 4,7 - DIMETHYL - $\Delta^{4(4a)}$ - NAPHTHALENE . (39)



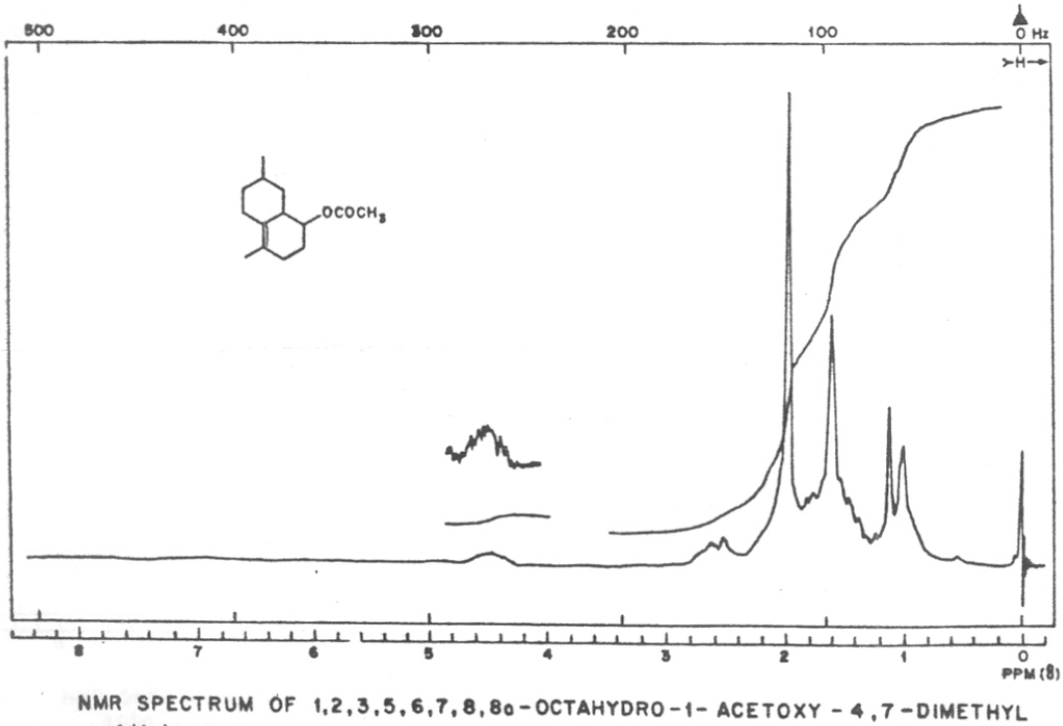
IR SPECTRUM OF IODOLACTONE . (41)



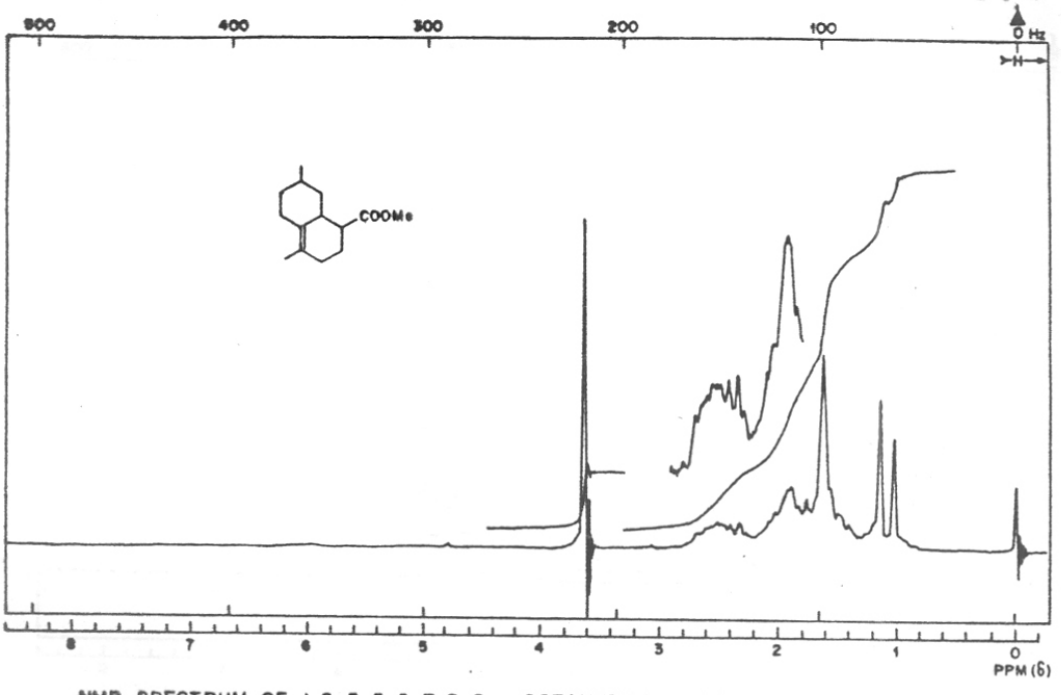
NMR SPECTRUM OF IODOLACTONE . (41)



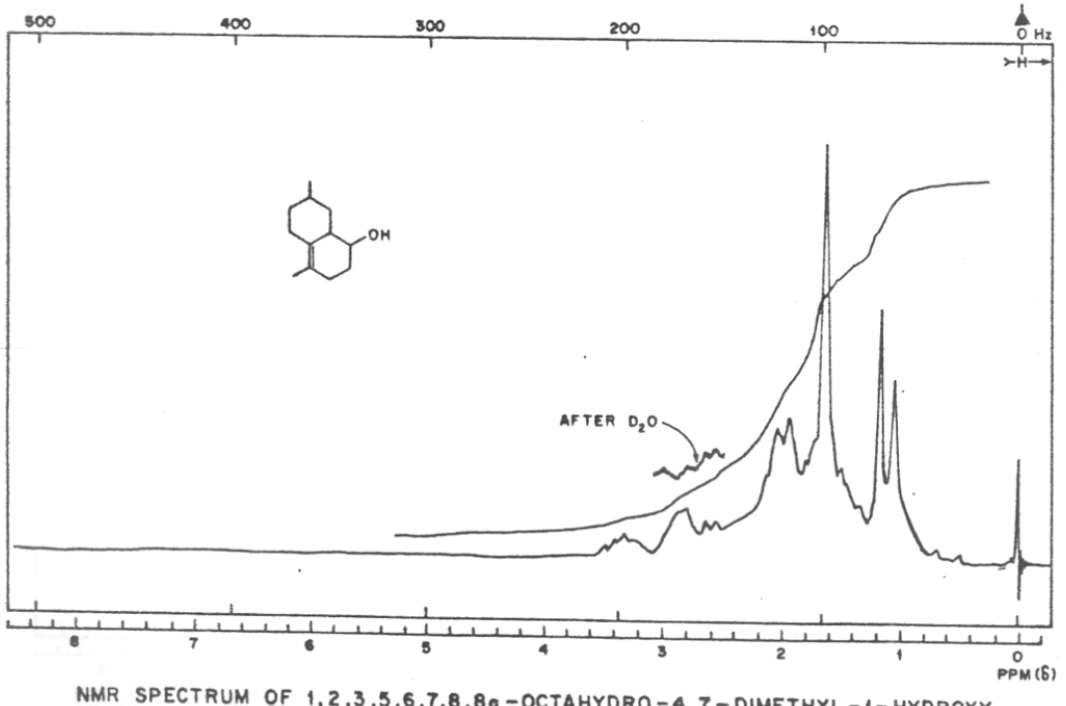
NMR SPECTRUM OF 1,2,3,4-TETRAHYDRO-2,5-DIMETHYL-NAPHTHALENE.(42)



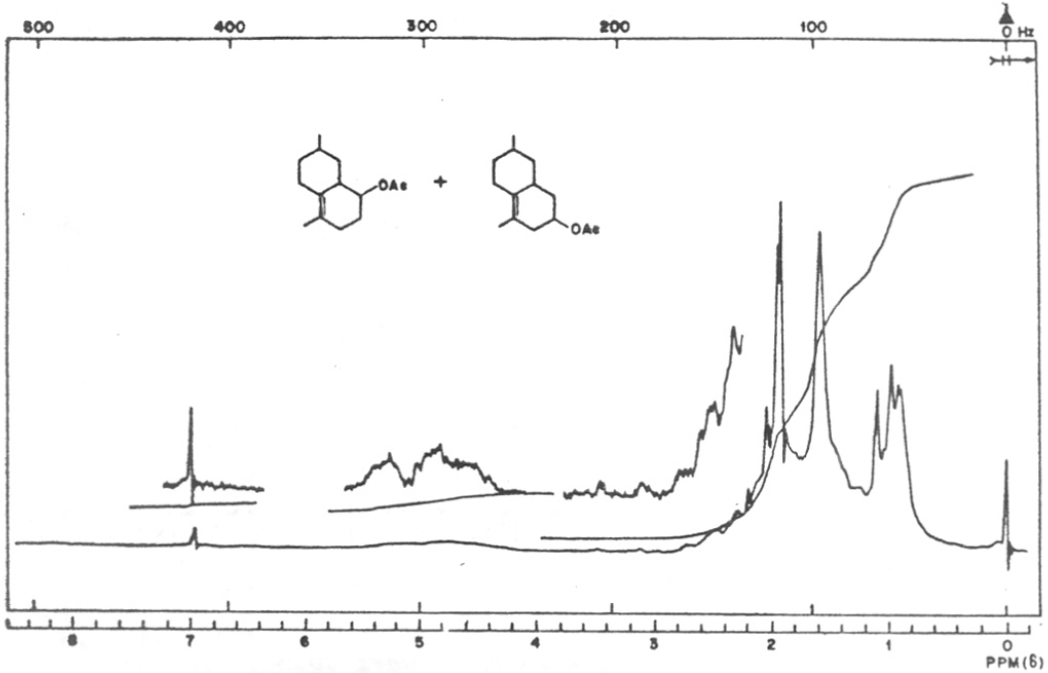
NMR SPECTRUM OF 1,2,3,5,6,7,8,8a-OCTAHYDRO-1-ACETOXY-4,7-DIMETHYL $-\Delta^{4(4a)}-$ NAPHTHALENE.(32)



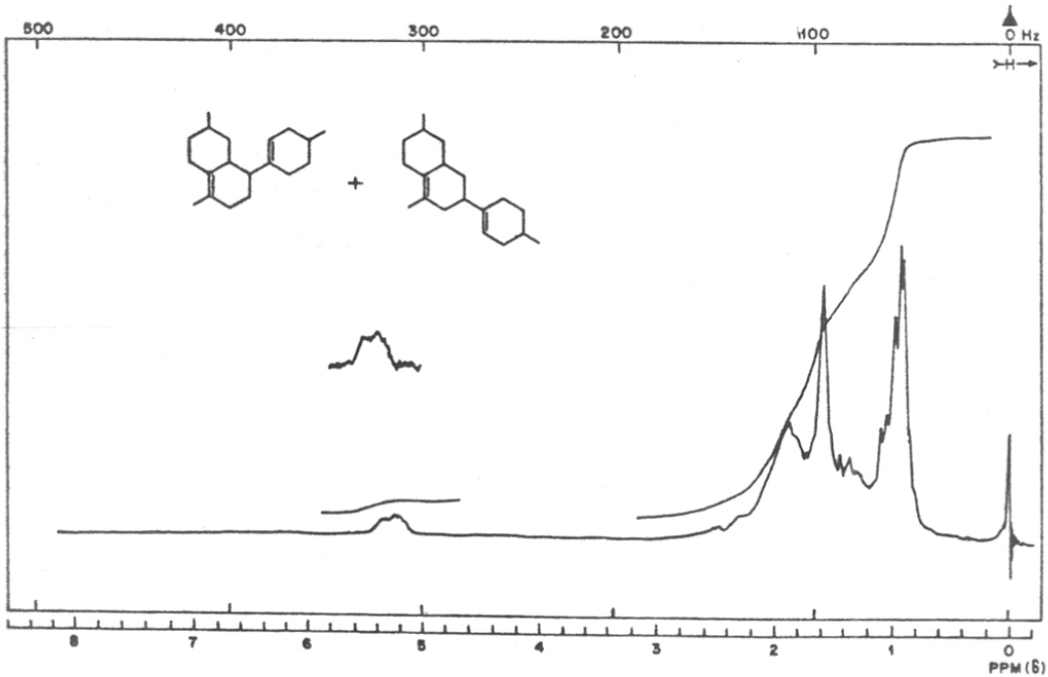
NMR SPECTRUM OF 1,2,3,5,6,7,8,8a-OCTAHYDRO-1-CARBOMETHOXY-4,7 DIMETHYL-$\Delta^{4(4a)}$-NAPHTHALENE. (40)



NMR SPECTRUM OF 1,2,3,5,6,7,8,8a-OCTAHYDRO-4,7-DIMETHYL-1-HYDROXY-$\Delta^{4(4a)}$-NAPHTHALENE. (28)



NMR SPECTRUM OF MIXTURE OF (32) + (49).



NMR SPECTRUM OF MIXTURE OF (50) + (51).

REFERENCES

1. R. Huisgen, R. Grashey and J. Saner in S. Patai: The Chemistry of Alkenes, Interscience, London, 1964, p.739.
2. R. Huisgen, Angew.Chem., 75, 604, 702 (1963).
3. R. Huisgen, Angew.Chem.Internat.Edit., 2, 565, 633 (1963).
4. M.C. Kloetzel, Org.Reactions, 4, 1 (1948).
5. H.L. Holmes, Org.Reactions, 4, 61 (1948).
6. L.W. Butz and A.W. Rytina, Org.Reactions, 5, 136 (1949).
7. J.L. Ripoll, A. Rouessac and F. Rouessac, Tetrahedron, 34, 19 (1978).
8. J.G. Martin and R.K. Hill, Chem.Rev., 61, 537 (1961).
9. A.J. Birch, P.L. Macdonald, V.H. Powell, J.Chem.Soc.C, 1469 (1970) and Tet.Lett., 351 (1969).
10. E.J. Corey and D.S. Watt, Tet.Lett., 4651 (1972).
11. M.D. Soffer and L.A. Burk, Tet.Lett., 211 (1970).
12. E.J. Corey, T.K. Schaaf, W. Huber, U. Koelliker and N.M. Weinshanker, J.Am.Chem.Soc., 92, 397 (1970).
13. E.J. Corey, S.M. Albonico, U. Koelliker, T.K. Schaaf and R.K. Varma, J.Am.Chem.Soc., 93, 1491 (1971).
14. E.J. Corey and R.K. Varma, J.Am.Chem.Soc., 93, 7319 (1971).
15. E.J. Corey, J.S. Bindra, A. Grodski, and T.K. Schaaf, J.Am.Chem.Soc., 95, 7522 (1973).
16. S. Danishefsky, R. Zamboni, M. Kahu and S.E. Jane, J.Am.Chem.Soc., 102, 2097 (1980).
17. P.A. Grieco, S. Ferrino and G. Vidari, J.Am.Chem.Soc., 102, 7586 (1980).
18. M.E. Jung and C.D. Radcliffe, Tet.Lett., 21, 4397 (1980).
19. B.A. Pearlman, J.M. McNamara, J. Hasan, S. Hatakayama, H. Sekizaki and Y. Kishi, J.Am.Chem.Soc., 103, 4248 (1981).

20. W. Oppolzer, Angew.Chem.Int.Edn.Engl., 16, 10 (1977).

21. G. Brieger and J.N. Bennett, Chem.Rev., 80, 63 (1980).

22. K. Shankaran and A.S. Rao, Ind.J.Chem., 18B, 507 (1979).

23. K. Shankaran and A.S. Rao, Synth.Comm.,10, 573 (1980).

24. K. Heusler and J. Kalvoda, Angew.Chem.Int.Edn., 3, 525 (1964).

25. Y. Ohta and Y. Hirose, Tet.Lett., 1251 (1968).

26. R.M. Coates and J.E. Shaw, J.C.S.Chem.Comm., 315 (1968).

27. D.H.R. Barton, M. Bolton, P.D. Magnus, K.G. Marathe, G.A. Poulton and P.J. West, J.Chem.Soc., Perkin I, 1574 (1973).

28. G.A. Kraus and K. Frazier, J.Org.Chem., 45, 4823 (1980).

29. M. Qudrat-I-Khuda and S.K. Ghosh, J.Ind.Chem.Soc., 17, 19 (1940).

30. E.H. Eschinasi, J.Org.Chem., 35, 1598 (1970).

31. E.H. Eschinasi, J.Org.Chem., 35, 2010 (1970).

32. T. Nagasawa, K. Umemoto, T. Tsukeya and M. Shiga, J.Agri.Chem.Soc.,Japan, 49, 217 (1975).

33. E.Von-Rudloff, Can.J.Chem., 39, 1860 (1961).

34. N.H. Andersen, D.W. Ladner and A.L. Moore, Synth.Comm., 8, 437 (1978).

35. R.G. Buttery and L.C. Ling, J.Agric.Food Chem., 25, 291 (1977).

36. S. Torii, T. Kunitomi and T. Okamoto, Bull.Chem.Soc.Japan, 47, 2349 (1974).

37. E.J. Corey and J. Caronona, J.Am.Chem.Soc., 85, 165 (1963).

38. P.S. Wharton and B.T. Aw, J.Org.Chem., 31, 3787 (1966).

APPENDIX

1. Synthesis of 3,7-dimethyl-6-oxo-octanoic acid, K. Shankaran and A.S. Rao, Ind.J.Chem., 18B, 507 (1979).

2. A convenient route for the preparation of aromatic aldehydes, K. Shankaran and A.S. Rao, Synth.Comm., 10, 573 (1980).

3. Synthesis of 2,6-dimethyl-1,6-heptadien-3-ol acetate: A probable bio-genetic precursor of the pheromone 2,6-dimethyl-1,5-heptadien-3-ol acetate, K. Shankaran and A.S. Rao (accepted for publication in Ind.J.Chem.).

4. Synthesis of aldehydes and benzyl ketones through fragmentation of homobenzylic alcohols, K. Shankaran, D.G. Talekar and A.S. Rao (accepted for publication in Synthetic Communications).

5. Transformation of alkyl halides to aldehydes having two additional carbon atoms, K. Shankaran, D.G. Talekar and A.S. Rao (accepted for publication in Ind.J.Chem.).