# PART 2

# STUDIES IN REDUCTION

## 1. INTRODUCTION

Dissolving metal reductions provide a most important method for the reductive modifications of organic molecules, either in the presence of a proton donor or followed by a treatment with proton donor. Although this method of reduction which was among the first reductions of organic compounds, discovered some 130 years ago, has been overshadowed by more universal catalytic hydrogenation and metal hydride reduction for some classes of compounds, there remains a substantial group of dissolving metal reductions that are currently used synthetically because of advantages offered in selectivity or stereoselectivity. The metals commonly involved include the alkali metals - Li, Na, and K as well as Ca, Zn, Fe, Mg, and Sn. A review of dissolving metal reductions is available.[1]

In catalytic hydrogenation, the reaction between gaseous hydrogen and an organic compound takes place only at the surface of a catalyst which adsorbs both the hydrogen and the organic molecule and thus facilitates their contact.

It is believed that at the surface of a catalyst the organic compounds react with individual atoms of hydrogen which become attached successively through a half-hydrogenated intermediate[2]. Because the attachment takes place at a definite time interval reactions such as hydrogen - hydrogen (or hydrogen-deuterium) exchange, cis/trans isomerism and even allylic bond shift occur. Nevertheless the time interval between the attachment of the two hydrogen atoms must be extremely short since catalytic hydrogenation is often stereospecific and usually gives predominantly cis-products (where feasible) resulting from the approach of hydrogen from the less hindered side of the molecule. However,

different and sometimes even contradictory results have been obtained over different catalysts and under different conditions[3].

A serious shortcoming of catalytic hydrogenation, the inability to reduce selectively the carbonyl function of ketones, acids, esters, and amides in the presence of carbon-carbon double bonds, has led to the wide spread use of certain complex metal hydrides for reduction of carbonyl groups[4].

Metal hydrides act as nucleophiles in which hydride anion attacks the places of lowest electron density.

Hydrides and complex hydrides tend to approach the molecule of a compound to be reduced from the less hindered side (steric approach control). If relatively uninhibited function is reduced the final stereochemistry is determined by the stability of the product (product development control). In addition, torsional strain in the transition state affects the steric outcome of the reduction. However, the contribution of the latter effect (product stability) to the stereochemical outcome of the reduction has been disputed[5]. Since the reductions with hydrides and complex hydrides are very fast, it is assumed that transition states develop early in the reaction; and consequently steric approach is more important than the stability of the product. But the determination of which side of the molecule is more accessible is at times difficult.

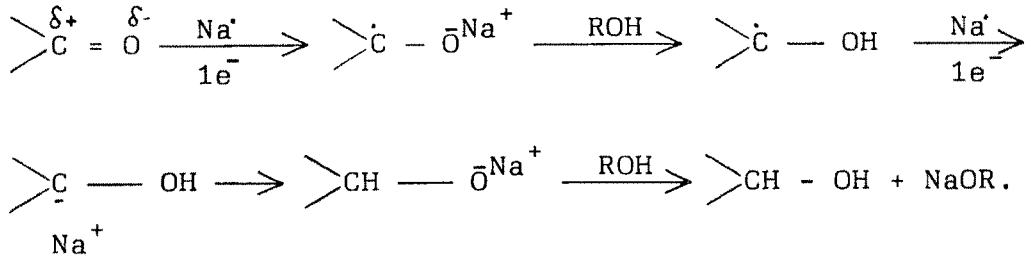
Dissolving metal reductions are better considered as internal electrolytic reductions[6,7] in which an electron is transferred from the metal surface (or from the metal in solution) to the organic molecule to be reduced. The reducing powers of metals parallel their relative electrode potentials, i.e.

the potential developed when the metal is in contact with a normal solution of its salt. Metals with large negative potentials, such as Li(-2.9), K(-2.9), Na(-2.7), and Ca(-2.8) are able to reduce almost anything, even carbon-carbon double bonds. Metals with low potentials e.g. Fe(-0.44) and Sn(-0.14) can reduce only strongly polar groups, such as nitro group, but generally not carbonyl group.

The alkali metals have been used in liq. ammonia (b.p. -33°, the Birch reduction[8]), low molecular wt. aliphatic amines[9], in hexamethylphosphoramide[10], as very dilute solutions in ethers as 1,2-dimethoxy ethane[11] or as solutions in ether or tetrahydrofuran or certain alkali metal (K and Cs) complexes with macrocyclic polyethers[12] (crown ethers[13]). The majority of dissolving metal reductions are carried out in the presence of proton donors, most frequently methanol, ethanol, and t-butanol (Birch reduction). The function of these donors is to protonate the intermediate anion radicals and thus to cut down undesirable side reactions, such as dimerization of radical anion and polymerization. Other proton sources, such as N-ethyl aniline, ammonium chloride, and others are used less often. Co-solvents, such as tetrahydrofuran help increase mutual miscibility of the reaction components.

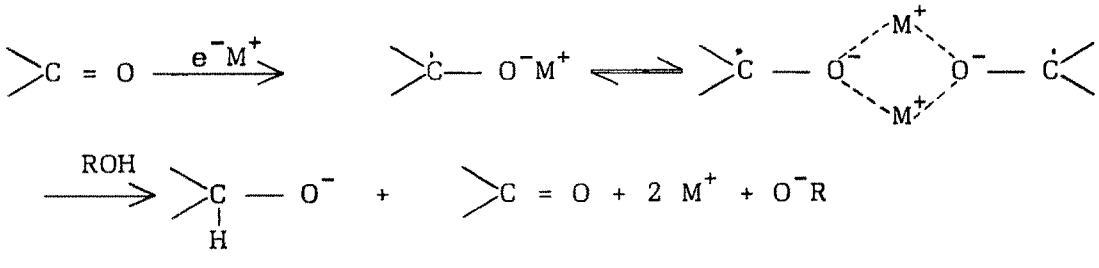
Many reductions with sodium are carried out in boiling alcohols : in methanol (b.p. 64°), ethanol (b.p. 78°), butanol (b.p.117-118°), and isoamyl alcohol (b.p. 132°). Reductions carried out by adding sodium to a compound in boiling alcohols require large excesses of sodium and alcohols. A better and convenient procedure to carry out such reductions is to add stoichiometric quantity of an alcohol and a compound in toluene or xylene to a mixture of toluene or xylene and calculated amount of a dispersion of molten sodium[14].

The mechanism universally accepted for sodium/alcohol reduction is the one proposed by House[1] wherein $e^-$, $H^+$, $e^-$, $H^+$ path is followed as shown in scheme - 1.



Scheme - 1 . Mechanism of ketone reduction ($e^-$, $H^+$, $e^-$, $H^+$, path)

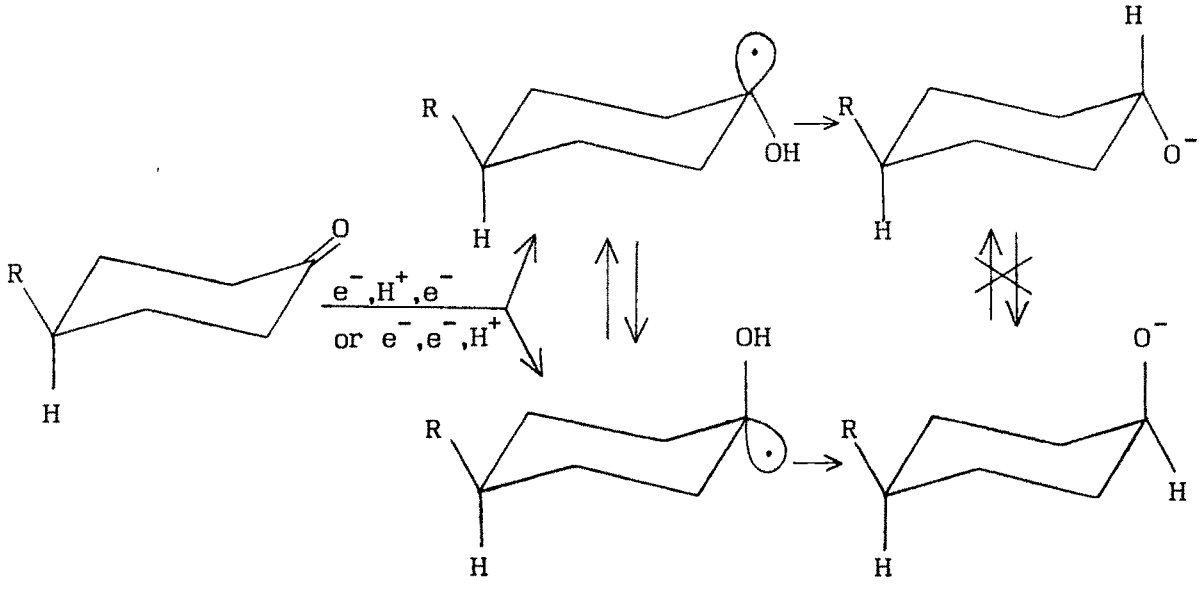
However, it is interesting to discuss the stereochemistry of reduction of cyclic and bicyclic ketones. A review article[15] presents a useful survey of the earlier theories relating to alkali metal/ammonia reductions of ketones. The review concludes with the observation that the stereochemistry of reductions is dependent on very subtle variations in the structure of an assumed dimeric 'quadrupole ion' intermediate as shown in scheme - 2.



Scheme - 2 . Reduction of ketone through ketyl dimer.

Very recently Pradhan[16] has reviewed the mechanism and stereochemistry of reductions of saturated cyclic ketones with sodium/alcohol.

It was Barton who generalized that Na/alcohol reduction of cyclohexanone would invariably afford mixtures of product alcohols rich in thermodynamically more stable epimer[17a]. He suggested the direct reduction of the ketonic carbonyl group to a tetrahedral, vicinal, dianion in which oxygen atom adopted the more stable orientation. Protonation of the dianion at the carbon would afford thermodynamically more stable alcohol as major product[17b,18-20].



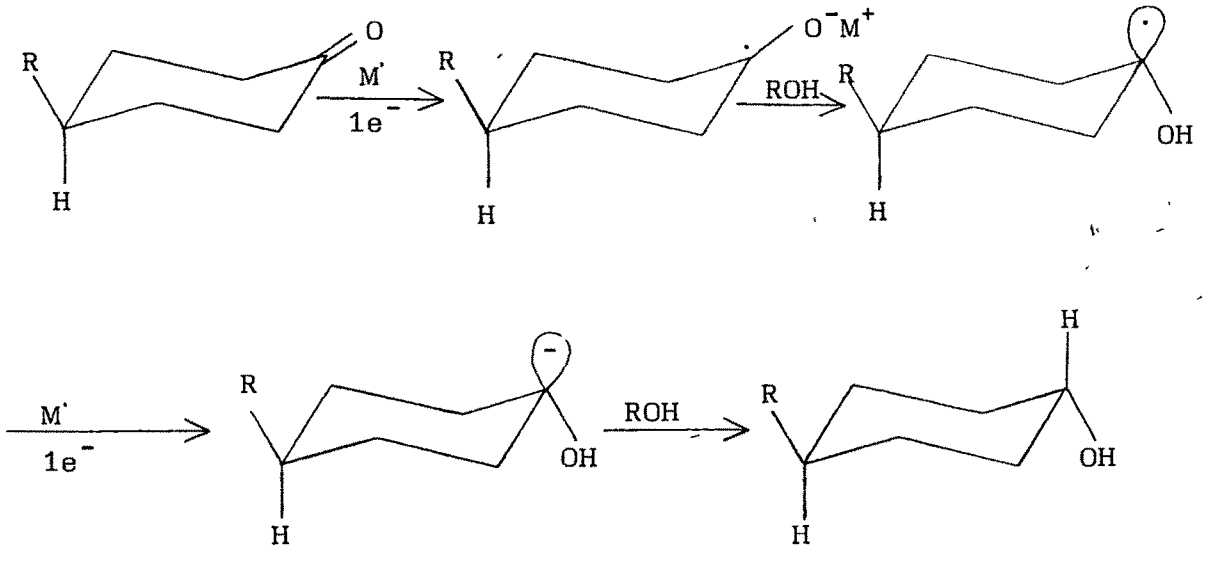

Scheme - 3. Barton's mechanism of cyclohexanone reduction.

The most striking feature of this mechanism is that protonation occurs with the retention of configuration and that it proceeds at equal rates so that the transition state energy differences for protonation correspond to ground state energy differences between two carbanions.

Based on the assumption that equilibration occurs at the carbanion stage,

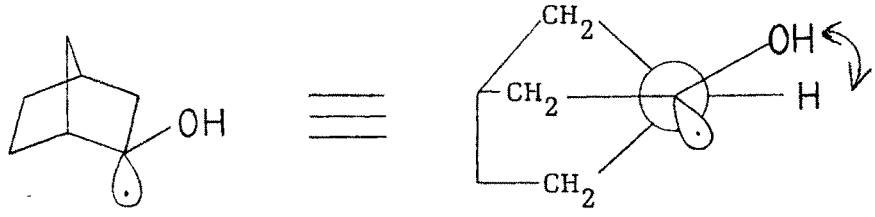
the reduction of camphor should give endo-borneol and norcamphor should give exo-norborneol. The latter, however gives endo-norborneol[21].

To account for the formation of equatorial alcohol in cyclohexanone reduction, House[1] assumed that ketone first adds an electron to give a ketyl radical anion. This is presumed to be planar. Protonation on oxygen is postulated to give a pyramidal ketyl and is considered to take-up the more stable 'configuration' before being reduced and protonated. The sequence is followed as shown in scheme - 4.

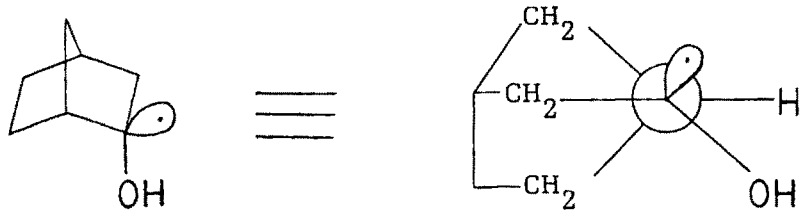



Scheme - 4. House's mechanism of cyclohexanone reduction.

Formation of less stable endo-norborneol from norcamphor on dissolving metal reduction has been explained on the basis of steric interference and torsional strain present in various conformations of the intermediate radical or anion in which the angle bonds to carbon atoms 1 and 4 are distorted. The conformations of two intermediates are illustrated in structures I and II.




I Torsional strain in exo-hydroxy norbornyl radical.




II endo-Hydroxy norbornyl radical.

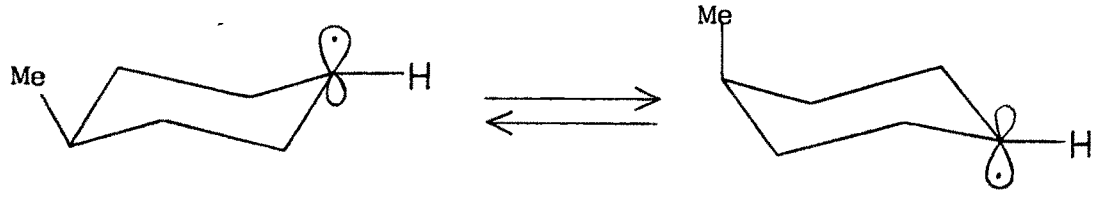
The torsional strain present in intermediate I (arrow) leading to the more stable exo-alcohol is diminished in intermediate II leading to endo-alcohol, the major product of reduction.

However, two objections are raised in the above explanation (1) the same torsional effect that makes the ketyl with -OH group bent in the endo-direction more stable should have made endo-norborneol (wherein the radical lobe is replaced by a C-H bond) more stable than exo-norborneol. The other objection is that the replacement of -OH group by H should have removed the torsion and consequently the exo-selectivity. Yet exo-selectivity at radical sites persists for 2-norbornyl radicals and is well documented[22].

Pradhan[16,23] employs the orbital extension theory as proposed by Fukui[24] which is based on the concept that an otherwise planar radical becomes somewhat pyramidalized due to a 'neighbouring group effect'. Under the influence of a vicinal $\sigma$- bond and provided the said bond does not lie in the nodal plane of p-orbital, rehybridization occurs. The direction of the orbital mixing in determined by the phases of the orbitals allowed to mix. According to him, the strained $\sigma$- bond joining C 1-C 7 in norbornyl radical (Str.III) ensures resulting modified C 2 p orbital corresponding to a partial extension to exo-direction.


III Norbornyl radical according to Fukui[24]

However, in a stable chair conformation the axial orbital extension in due to the interaction with C 2 - C 3 and C 5 - C 6 bonds in the 4-methyl cyclohexan-1-yl radical (Str.IV).




IV 4-Methyl cyclohexan-1-yl radical.

It is noteworthy in Str.IV that orbital containing the single electron (SOMO) is extended in the axial direction in both conformers.

Experimental evidence for pyramidal geometry around the radical centre C atom of some 2-norbornyl type of radicals has been given by Kawamura[25].

Another explanation is given by Dewar[26] which is based on $\sigma$- conjugation that the radical hybridizes in order to get benefit of conjugation with $\sigma$- orbitals on the same carbon. This also supports the concept of $\sigma$- framework linked rehybridization including Fukui concept, which assigns stereochemistry to orbital extension, i.e. to a single species of minimum energy in the cyclohexyl and the 2-norbornyl radicals.

ESR evidence also supports the existence of a similar partially pyramidalized single species in unsymmetrical molecules[27]. Thus, 2-norbornyl ketyl is assigned a conformation in which the hydroxyl group is bent in the endo-direction. Although in the fully pyramidalized alcohol, endo-norborneol is destabilised relative to exo-norborneol because of the steric repulsion by other three endo-hydrogens. But, in case of 2-norbornyl ketyl the angle of bending relative to the plane containing C 1, C 2, and C 3 is far short of the 54° required for a tetrahedral arrangement. Therefore, the 'quasi-endo' hydroxyl in the ketyl does not encounter the same steric repulsion by the three endo-hydrogens that the hydroxyl of endo-norborneol does.

In fact Lloyd[28] using variable temperature ESR studies has shown that 1-hydroxy-4-t-butylcyclohexyl radical is also a single species with the ring 'frozen' in chair conformation and the -OH group in the 'quasi-equatorial' position. However, for 1-hydroxy-4-methylcyclohexyl and 1-hydroxycyclohexyl

radicals non-polar radical sites have been confirmed and that they invert between chair conformations through a high energy intermediate that is likely a twist boat form.

Hence it has been postulated[23] that whenever the orbital extension is predominantly in one direction as in the axial direction in cyclohexyl ketyl and in the exo-direction in 2-norbornyl ketyl as well as 2-bronyl ketyl, a secondary alcohol is produced by attachment of hydrogen from the same direction provided the reaction is carried out in the presence of large excess of proton donors of sufficient acidity.

It is concluded that it is Fukui effect which places C-O bond of the ketyl nearly antiperiplanar to the bonds, determines the conformation[29].

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19. Proton transfer from oxygen to the carbanion should be facile through (a) intermediacy of alcohol, (b) mutual transfer between two molecules, and/or (c) through a bridged intermediate.

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27. Symmetrical molelcules such as formaldehyde yields ketyls which are expected to have two identical non-planar conformations of minimum energy [Y.Ellinger, R.Subra, A.Rassat, J.Douady, and G.Berthier, J.Am.Chem.Soc. 97, 476 (1975)]. The estimated energy barrier of 0.875 k cal/mol. is so low that with unsymmetrical molecules even if two minima exist, the higher energy one will hardly be distinguishable.

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# SECTION 1

# REDUCTION OF KETONES, ESTERS, AND OXIMES USING $Na/Al_2O_3$ AND ALCOHOL

# REDUCTION OF KETONES, ESTERS, AND OXIMES USING $Na/Al_2O_3$ AND ALCOHOL.

## Abstract

Sodium on alumina is described and evaluated as convenient off-the-shelf reagent for efficient reduction of ketones, esters, and oximes. $Na/Al_2O_3$ can be effectively used to afford thermodynamically more stable alcohols from substituted cyclohexanones.

## 1. INTRODUCTION

Alkali metals have been used as reactants in organic chemistry since about 1870. The use of finely divided metal suspended in hydrocarbon is mentioned in 1902 by J.W.Bruhl. A development in organic chemistry since 1946 is the use of alkali-metal in the form of a stable dispersions of very small particles, size ranging from 1 to 20 microns. In these dispersions the total metallic surface area is so large that an entirely new set of reactions becomes possible and those reactions carried out before with larger particles are now more rapid, convenient, and of higher yield. Use of sodium dispersions in various organic reactions has been compiled by Fatt and Tashima[1].

The concept of utilizing reagents adsorbed on inert inorganic supports for organic syntheses is not new. Catalytic hydrogenations and dehydrogenations and numerous other processes which occur at metal and other solid surfaces can properly be classified as examples supported reagents, albeit of transitory nature. The effectiveness of inorganic supports in the reactions appear to be due to (1) an increase in the effective surface area for reaction and (2) making the reactants relatively less unstable thus lowering energy of activation of the reaction. The supported reagents offer more advantages over their unsupported counterparts because (1) they are more selective (2) they can be used under milder conditions and (3) they are convenient in use.

The synthetic utility of such reagents, however, is readily demonstrable. Many reactions can be carried out cleanly, rapidly and in high yield under mild conditions using supported reagents whereas attempts to carry out the

same reactions with unsupported reagents frequently either fail or result in the formation of mixture of products.

A review on organic reactions on alumina surface has been published by Posner[2] which deals mainly with reagents supported on alumina. Other two reviews are also published which describe in detail the synthetic utility of supported reagents[3,4]. The common supports used are $Al_2O_3$, $SiO_2$, graphite, C, etc. A review of various supported reagents and their synthetic uses is given by Singh[5].

Pines and Haag[6] were the first to report sodium dispersion on alumina and to study its induced activity and selectivity for the isomerization of monoolefins. Later on, it has been exploited for a number of reactions.

The isomerization of monoolefins to thermodynamically more stable olefins has been effected with sodium dispersed on alumina prepared from molten sodium[7], sodim/alumina containing sodium hydroxide[8], potassium carbonate[9], sodium/alumina prepared from ammonia solution[10], containing potassium hydroxide[11], sodium/alumina partially deactivated with tert. butyl alcohol[12], sodium/alumina prepared by evaporation of sodium on alumina[13], and with sodium on carbon[14].

Conjugated dienes[15], triene[16], and terminal acetylenes[17] are also prepared using $Na/Al_2O_3$ from their corresponding non-conjugated dienes, triene, and allenes, respectively.

Sodium/alumina is also very effective in isomerizing optically active amines[18].

Disproportionation is effected on $Na/Al_2O_3$ [19] and Na/graphite[20]. Other reactions, such as hydrogenation[21,22], dehydrogenation[23,24], dimerization[25,26], polymerization[27], condensation[28,29], and alkylation[30,31,32] are performed using sodium supported on inert materials.

Although much more mechanistic work must be done before a detailed picture of the solid support emerges, the alumina probably lowers the entropy of activation when a reactant and reagent are adsorbed close to each other and in the proper orientation for chemical reaction[33]. Another important function of alumina probably is to activate the reactant and/or the reagent[34].

Thus we see the tremendous applicability of sodium supported reagents in organic synthesis. The present objective of study is to prepare sodium/alumina from molten sodium and to protect it with wax so that it could be used as convenient off-the-shelf reagent to effect reduction of a variety of compounds, e.g. ketones, esters, oximes, etc.

## 2. PRESENT WORK

Sodium, because of its low cost, typical alkali-metal behaviour, and ease of preparation in dispersed form, is the most widely used alkali metal. Lithium is the second most widely used alkali metal but trials far behind sodium. Potassium is much more reactive than sodium or lithium and is dangerous to handle in dispersed form.

A convenient procedure for the reduction of cycloheptanone with sodium dispersions in toluene and isopropyl alcohol has been reported by S.Dev[35]. The reaction, however, takes more time and preparation of sodium dispersion is a tedious process especially at small scale. Here we have devised a procedure by which sodium dispersed on alumina can be preserved for a long time (checked for 6 months) without losing its efficiency. The activity of which was evaluated for the reduction of cyclic ketones, esters, and oximes.

In the reduction of low molecular wt. ketones, such as cyclohexanone, removal of high boiling solvent, such as toluene always causes a problem and there is a chance of losing material, hence we optimised the conditions in solvent ether and tetrahydrofuran. However, tetrahydrofuran was preferred because of its water misciblity and higher dissolving power for alkoxide formed in the reaction.

Sodium was also supported on carbon which was found to be less effective than sodium/alumina.

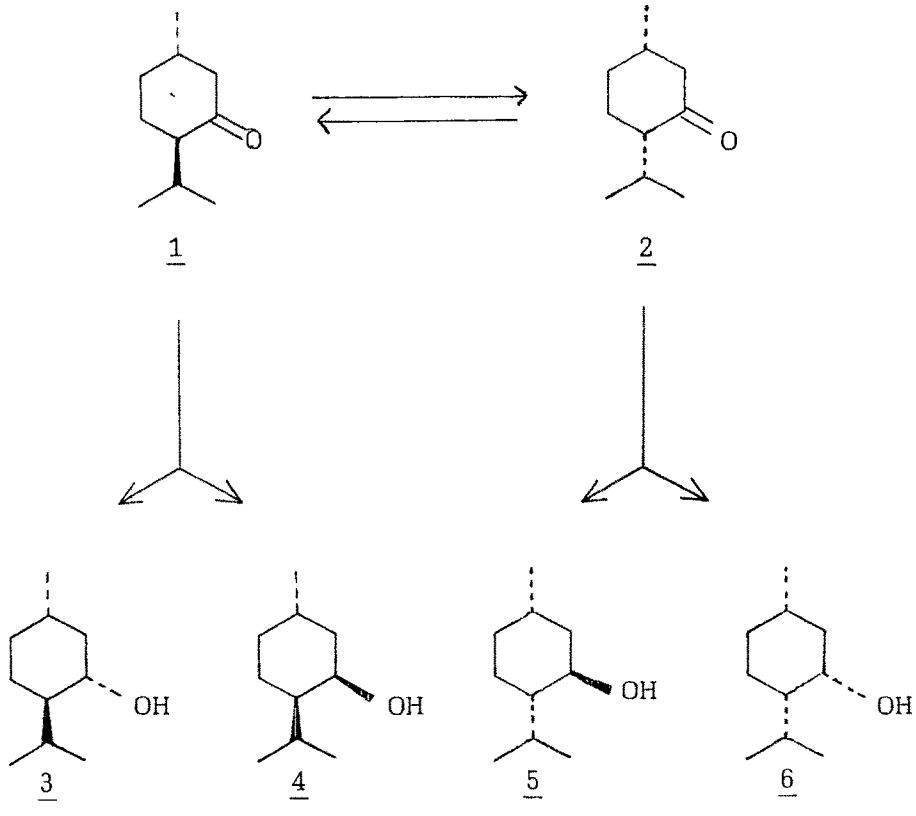
The sodium dispersion on alumina (3-4 mole equivalent calculated for active sodium present) was used and washed with dry light petroleum and dispersed in THF followed by addition of ketone-alcohol mixture. It was refluxed for 4-5 hours. However, the reductions of esters and oximes were carried out using toluene as solvent.

## 3. RESULTS AND DISCUSSION

### 3.1 Reduction of menthone and 2-methyl cyclohexanone.

Menthone(±)( $>95\%$) on reduction with $Na/Al_2O_3$ - alcohol gave all possible isomers. However, the ratios of axial vs equatorial alcohols were different with different alcohols. Reduction in tert-butyl alcohol gave more of the equatorial alcohol than iso-propyl alcohol. The results are summarized in Table-1.

The formation of four isomers from menthone can only be explained if menthone (1) epimerizes to isomenthone (2). The reduction of 1 will give menthol (3) and neomenthol (4) while reduction of 2 will give isomenthol (5) and neoisomenthol (6).

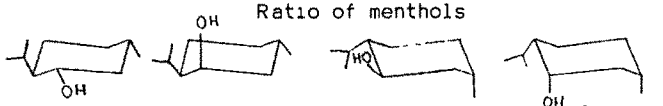



1 2

3 4 5 6

## TABLE - 1

Reduction of menthone using $Na/Al_2O_3$ and alcohol.

| Sr. No. | Reagents: Sodium dispersion | Gm eq. | Alcohol | Solvent | Reaction condns: Temp. (°C) | Time (h) | GC: Convn (%) | Recov. (%) | Ratio of menthols:  3 | 4 | 5 | 6 | Yield (%) | Unreacted (%) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 01. | Na | 3 | i-PrOH | Toluene | 110° | 3 | 100 | 86.5 | 55.7 | 18.4 | 22.0 | 2.4 | 86.5 | |
| 02 | " | " | " | THF | 69° | 4 | 100 | 86 | 69.0 | 1.7 | 22.0 | 5.1 | 86.0 | |
| 03. | $Na/Al_2O_3$ | 3 | MeOH | THF | 69° | 5 | 46.5 | 85 | 73.7 | 3.2 | 15.2 | 7.7 | 39.5 | 53.4 |
| 04. | " | " | i-PrOH | THF | 69° | 5 | 90 | 82 | 54.8 | 23.5 | 10.4 | 11.1 | 73.8 | 10.0 |
| 05. | " | " | " | " | " | 12 | 96 | 82 | 54.3 | 27.2 | 11.7 | 6.7 | 78.7 | 4.0 |
| 06. | " | 4 | i-PrOH | " | " | 5 | 99 | 85 | 65.2 | 19.1 | 13.0 | 2.6 | 84.1 | 1.0 |
| 07. | " | 3 | t-BuOH | " | " | 5 | 62.7 | 85 | 75.9 | 1.4 | 18.9 | 3.6 | 53.3 | 37.3 |
| 08. | " | " | " | " | " | 12 | 79 | 80 | 76.0 | 2.7 | 20.3 | 0.9 | 63.2 | 21.0 |
| 09. | " | 4 | " | " | " | 5 | 79.8 | 85 | 75.1 | 2.5 | 17.8 | 4.5 | 67.8 | 20.2 |

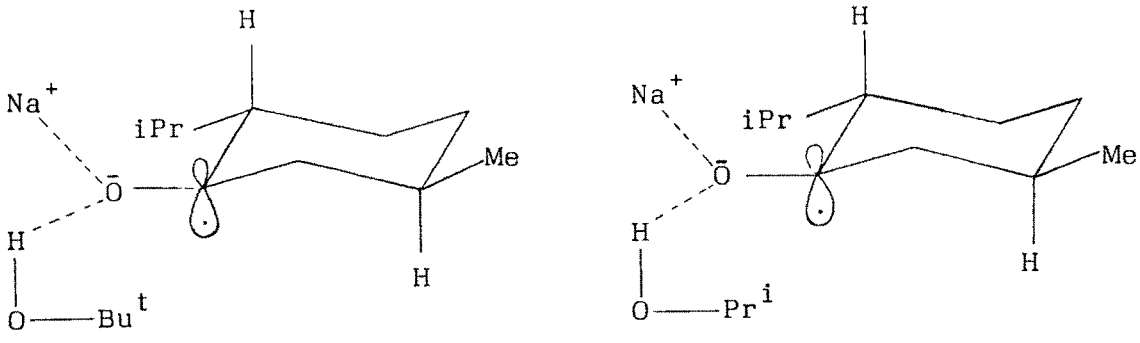
Note : Corrected for 100 % alcohol content.

In fact, it has been found that under basic conditions menthone epimerizes to equilibrated mixture of 1 and 2. And because of their difference in free energy the equilibrium constant is close to 2.3 so that equilibrium corresponds to about 70% 1 and 30% 2[36,37]. In order to ensure it menthone was epimerized with sodium in THF without adding alcohol and it was found that epimerization was complete in less than one hour.

The results shown in Table-1 also indicate that the formation of 3 and 4 is 78-84% and that of 5 and 6 is 22-16%. The ratio of 3+4 versus 5+6 comes to 3.5-5.0 : 1. This would mean that epimerization occurred before reduction.

Furthermore, it is interesting to note that the formation of equatorial alcohol 3 and 5 and axial alcohol 4 and 6 depends on the proton source (alcohol) used. In case of isopropanol the equatorial alcohol is 54-65% 3 and 10-13% 5, and that of axial alcohol 19-27% 4 and 3-11% 6 (the ratio of 3 vs 4 is 2-3.4 : 1 and 5 vs 6 is 1-5.0 : 1). But with t-butanol as proton donor equatorial alcohol is much more 75-76% 3 and 18-20 % 5 compared to axial alcohol 1.4-2.7% 4 and 1-4.5% 6 (the ratio of 3 vs 4 is 28-54.0 : 1 and 5 vs 6 is 5-22.0 : 1).

Such effect of proton donors can be explained on the basis of their acidities. Formation of more stable (eq.-OH) isomer in case of t-butanol might be because of weaker hydrogen bonding (pK 19.0) which is a weaker Lewis acid than isopropanol (pK 18.0)[38]. (Str.I)




Str. I

It will result in greater pyramidalization of ketyl radical anion in t-butanol than isopropanol leading to increased amount of the major alcohol (eq.-OH) in the former relative to the latter.

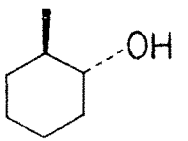
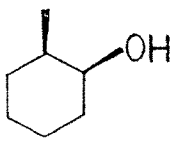
Reduction of 2-methyl cyclohexanone also produced trans-alcohol as major product which is thermodynamically more stable. However, selectivity was higher for tert-butyl alcohol. Table-2 summarizes the results.

### 3.2 Reduction of camphor and fenchone.

The reduction of the bicyclic ketones with $Na/Al_2O_3$ gave endo-alcohol as major product. Again, tert-butyl alcohol showed more selectivity than isopropyl alcohol. The results are summarized in Table - 3.

TABLE - 2

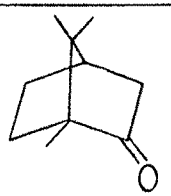
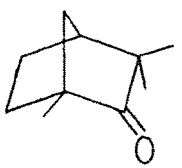
Reduction of 2-methyl cyclohexanone using $Na/Al_2O_3$ and alcohol in THF as solvent at 69°C.

| Sr. No. | Reagents | | | Reaction Time (Hrs) | GC | | Ratio of alcohols   | | Yield % | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|
| | Sodium dispersion | Gm eq. | Alcohol | | Convn (%) | Recov. (%) | | | | |
| 01. | Na | 3 | i-PrOH | 4.0 | 100 | 85.0 | 85.8 | 13.3 | 85 | |
| 02. | $Na/Al_2O_3$ | 4 | i-PrOH | 5.0 | 100 | 84.0 | 81.6 | 17.6 | 84 | |
| 03. | $Na/Al_2O_3$ | 4 | t-BuOH | 5.0 | 90 | 86.0 | 94.7 | 5.2 | 77.4 | 10 % unreacted |

Note : Calculated for 100 % alcohol content.

TABLE - 3

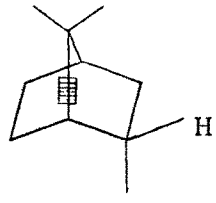
Reduction of camphor and fenchone with $Na/Al_2O_3$ and alcohol in THF as solvent at 69°C.

| Sr. No. | Substrate | Reagents: Na dispersion | Gm eq. | Alcohol | Reactn. Time (Hrs) | GC: Convn. (%) | GC: Recov. (%) | Ratio of alcohols: endo- | Ratio of alcohols: exo- | Yield % | Unreacted. % |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 01. |  | Na | 3 | i-PrOH | 4 | 86.5 | 89.1 | 87.2 | 12.8 | 77.0 | 13.5 |
| 02. | | $Na/Al_2O_3$ | 4 | i-PrOH | 5 | 72.3 | 85.0 | 74.5 | 25.5 | 61.4 | 27.7 |
| 03. | | $Na/Al_2O_3$ | 4 | t-BuOH | 5 | 58.3 | 86.0 | 83.6 | 16.4 | 50.1 | 41.7 |
| 04. |  | Na | 3 | i-PrOH | 4 | 96.2 | 88.0 | 58.6 | 41.6 | 84.6 | 3.8 |
| 05. | | $Na/Al_2O_3$ | 4 | i-PrOH | 5 | 94.4 | 85.0 | 55.8 | 44.1 | 80.2 | 5.6 |
| 06. | | $Na/Al_2O_3$ | 4 | t-BuOH | 5 | 91.8 | 85.0 | 60.4 | 39.5 | 78.0 | 8.2 |

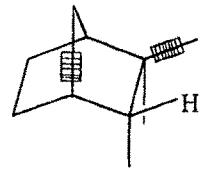
Note: Calculated for 100 % alcohol content.

The mechanism of saturated bicyclic ketones reduction has been of much discussion because different results have been obtained with different metals and alcohols in ammonia[39-41].

Recently, Pradhan et al.[42], employing FMO extension theory have explained that in case of camphor and fenchone, the ketyl pair derived by reduction of both camphor and fenchone, the SOMO is extended in the exo-direction. And according to them, whenever, there is extension of orbital in one direction predominantly, a secondary alcohol is produced by attachment of hydrogen from the same direction. Hence following alcohols are supposed to be major.




endo-borneol




endo-fenchol

σ-bond which is responsible for stereoelectronic stabilization of the specific ketyl conformation.

In case of camphor and fenchone the dominant stereoelectronic effect is due to more highly substituted single bond since its HOMO is higher in energy.

### 3.3 Reduction of $\alpha$ , $\beta$ -unsaturated ketones.

Carvone, isophorone, and 2,5,6-trimethyl cyclohex-2-en-1-one were reduced using Na and $Na/Al_2O_3$ and isopropyl alcohol as proton source. In all the

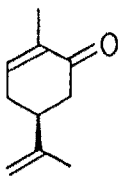
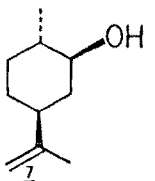
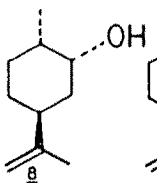
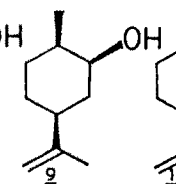
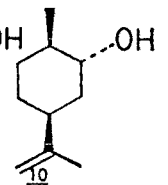
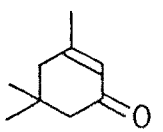
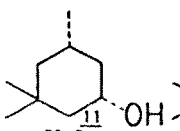
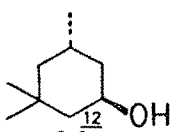
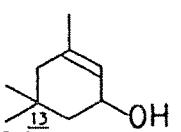
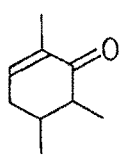
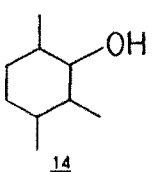
three ketones, fully saturated alcohols were obtained which were rich in thermodynamically more stable isomer. Table-4 summarizes the results.

Lawrence and Hogg[43] also obtained the four isomers of dihydrocarveols from carvone. The isolated double bond was not affected during reaction. However, we do not agree with their data reported for neoisodihydrocarveol (9; IR 3390 $cm^{-1}$, C-OH) and neodihydrocarveol (8; IR 3390 $cm^{-1}$, C-OH) which can not be same for 9 and 8 because stereochemistry at CHOH is opposite. Rather it should be less for 9 than 8 because C-OH is equatorial in the former and axial in the latter. In accordance with the literature for cyclohexanols, ax.-OH group should absorb at higher frequency ($\sim$3600 $cm^{-1}$) than eq.-OH group ($\sim$3590 $cm^{-1}$)[44]. Our idea is further supported by PMR data. The chemical shift of CHOH is 3.53 and coupling constant is 10.5 Hz for 9 which supports C-OH group to be equatorial. Had it been axial as in case of 8, the chemical shift ( $\delta$ ) of CHOH should have been further lower and J value should have been 0-5 Hz[45] [8, ( $\delta$ ) CHOH 3.82 ppm, J=2.5 Hz.]. NMR and IR of these isomers are shown in Figs. 1-6.

The stereochemistry 11 and 12 is fully consistent with the reported data[46,47a]. PMR and IR are shown in Figs.7-12. Reduction of 2,5,6-trimethylcyclohex-1-en -2-one afforded a mixture of 8 fully saturated alcohols as confirmed by NMR and IR. Their separation by prep. GLC could not be possible. Although one compound which was major reduction product was separated, but the stereochemistry of this compound could not be ascertained from the available spectral data at hand[47a,b]. A review article has been written by Caine[48] on the reduction of $\alpha$ , $\beta$ -unsaturated ketones with alkali-metal/ammonia. Barton

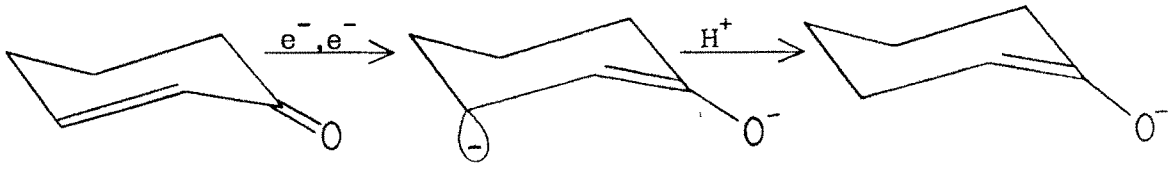
TABLE - 4

Reduction of carvone, isophorone, and 2,5,6-trimethylcyclohex-2-en -1-one using $Na/Al_2O_3$ and isopropyl alcohol in THF as solvent.

| Sr. No. | Substrate / reagent | Reactn. Time (Hrs) | Convn. (%) | Recov. (%) | Product(s) % | | | | Yield (%) | Unreacted (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| |  | | | |  7 |  8 |  9 |  10 | | |
| 01. | Na | 4 | 93.0 | 61.6 | 69.3 | 9.6 | 16.5 | 1.9 | 57.2 | 7.0 |
| 02. | $Na/Al_2O_3$ | 4 | 96.0 | 58.4 | 59.1 | 20.4 | 18.3 | 1.9 | 56.0 | 4.0 |
| |  | | | |  11 |  12 |  13 | | | |
| 03. | Na | 4 | 64.9 | 60.0 | 78.8 | 2.6 | 18.4 | | 40.5 | 35.1 |
| 04. | $Na/Al_2O_3$ | 8 | 60.0 | 62.0 | 72.0 | 10.3 | 15.0 | | 37.2 | 40.0 |
| |  | | | |  14 | | | | | |
| 05. | Na | 4 | 100 | 62.8 | 100 | | | | 62.8 | - |
| 06. | $Na/Al_2O_3$ | 4 | 100 | 62.1 | 100 | | | | 62.5 | - |

Note: Products calculated for 100% alcohol content.

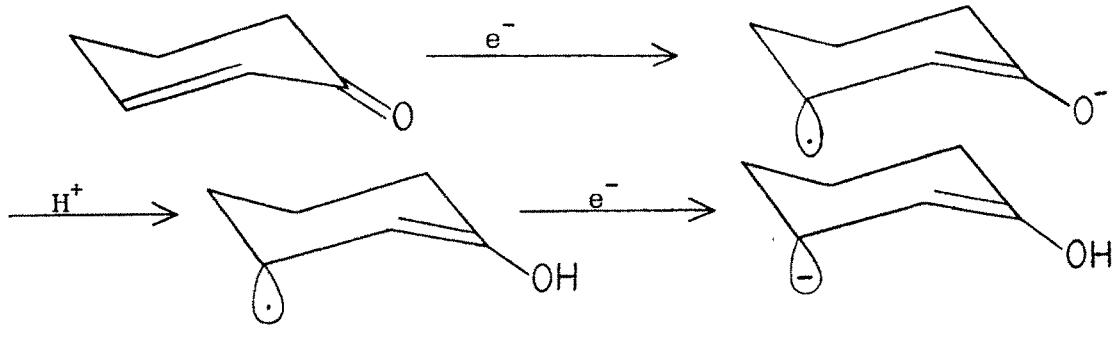
and Robinson[49] proposed a dianion mechanism as part of one of the earliest studied on stereochemistry of $Li/NH_3$ reduction of $\alpha,\beta$ -unsaturated ketones as shown in scheme - 1.




Scheme - 1. Barton's dianion mechanism of reduction $\alpha,\beta$ -unsaturated ketone.

The carbanions were expected to take up the more stable configuration prior to protonation with retention of configuration.

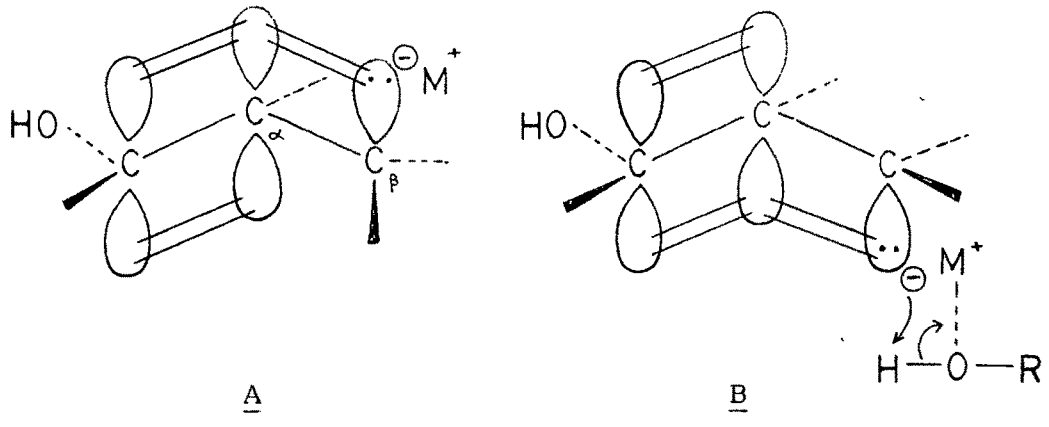
The other explanation is given by House[50] in which first step is the addition of an electron to give a 1,4-radical anion. The subsequent steps are expected to be fast leading to an enolate ion as shown in scheme - 2.




Scheme - 2. House's mechanism of $\alpha,\beta$ -unsaturated ketone reduction.

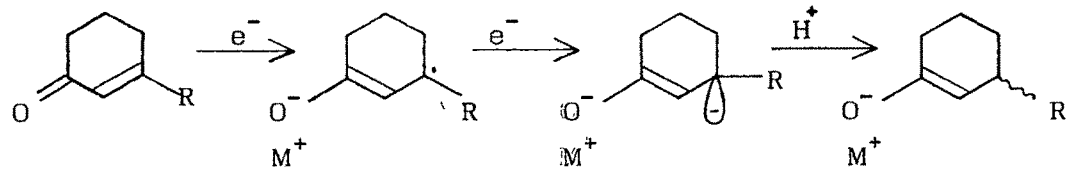
The third step consists of protonation of dianion by $NH_3$ in the Barton's mechanism and the addition of an electron to the SOMO in the House's mechanism.

Based on other experiments House[51] modified the above mechanism and suggested that allylic carbanions are pyramidal[52] rather than planar, especially when associated with metal cation.The anions are stabilized by overlap of the carbanion $sp^3$ orbital with the adjacent $\pi$ -orbital of the double bond so that conformation A is favoured energetically with respect to other conformations obtained by rotation about the $C_\alpha$ - $C_\beta$ bond. According to him A can equilibrate (by rotation, inversion, or both) morerapidly than they are protonated and that atleast the protonations of these anions which have a metal counter ion with simple alcohols in relatively polar media occur with retention of configuration as shown in structure B.




A B

Thus, the stereochemical outcome at the $\beta$ -carbon in these reductions will be determined by the allylic anion (or perhaps its precursor, the allylic radical) adopting the conformation of lowest energy prior to protonation. Hence, the possible mechanism of $\alpha$ , $\beta$ - unsaturated ketones will be as follows (scheme - 3).




Scheme - 3. Mechanism of reduction of $\alpha$ , $\beta$ -unsaturated ketones.

## 3.4 Reduction of esters

Ethyl palmitate, methyl oleate, ethyl benzoate, and ethyl phenyl acetate were reduced to their corresponding primary alcohols in 65-70% isolated yields. The results are summarized in Table - 5.

**TABLE - 5**

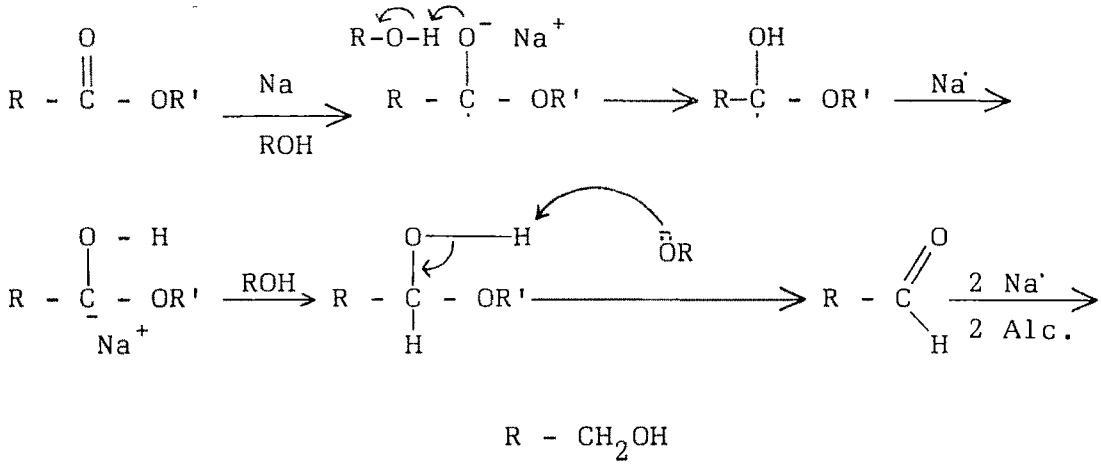
Reduction of esters to primary alcohols using $Na/Al_2O_3$ and t-BuOH in toluene as solvent at 110°C for 5½ hours.

| Sr. No. | Substrate | Product | GC | |
|---|---|---|---|---|
| | | | Convn. (%) | Isolated yield(%) |
| 01. | $CH_3(CH_2)_4$ COOEt | $CH_3(CH_2)_{14}CH_2OH$ | 100 | 70.0 |
| 02. | $CH_3(CH_2)_7CH{=}CH(CH_2)_7COOMe$ | $CH_3(CH_2)_7CH{=}CH(CH_2)_7CH_2OH$ | 100 | 68.00 |
| 03. | $C_6H_5COOEt$ | $C_6H_5CH_2OH$ | 100 | 66.0 |
| 04. | $C_6H_5CH_2COOEt$ | $C_6H_5$ $CH_2CH_2OH$ | 100 | 65.0 |

Note : The reported yields of alcohols from esters on reduction with Na/alcohol vary from 65-70 %[53,54].

It can be noted from the results that $Na/Al_2O_3$ is equally good for the reduction of esters, too.

The mechanism of ester reduction with sodium/alcohol is supposed to take place in two steps via the formation of aldehyde[53] as shown in scheme - 4 .

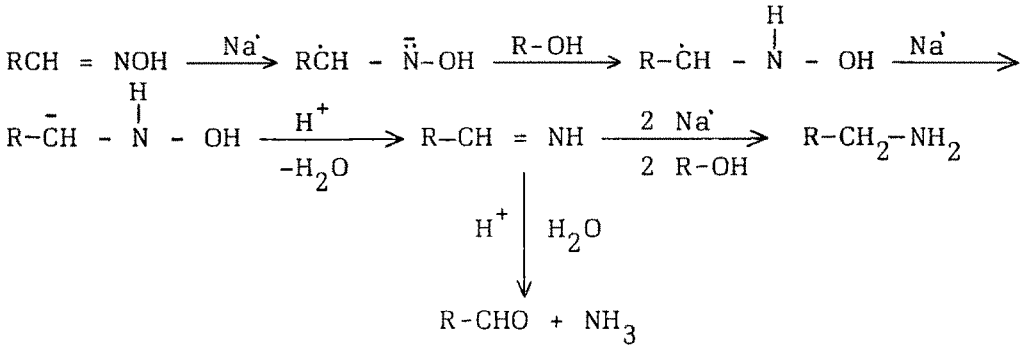


Scheme 4. Mechanism of reduction of esters to alcohols.

### 3.5 Reduction of Oximes

$Na/Al_2O_3$ effectively reduced oximes of cyclohexanone (I), cyclopentanone (II), benzophenone (III) and benzaldehyde (IV) to their corresponding amines, respectively. The conversions were 100% for I,II, and IV, although recoveries of amines were low, i.e. 50 - 60 %. The reduction of III gave some hydrolyzed product also. Table - 6 summarizes the results.

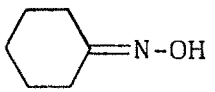
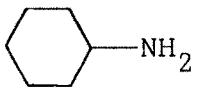
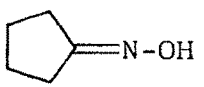
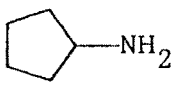
The mechanism of oxime reduction follows via imine formation[55] as shown in scheme - 5 .



Scheme 5. Mechanism of reduction of oximes to amines.

**TABLE - 6**

Reduction of oximes using $Na/Al_2O_3$ and isopropyl alcohol in toluene at 110°C for 5 hours.

| Sr. No. | Substrate | Product | Yield (%) | Reported yield with Na/alc. | Other products | Unreacted (%) |
|---|---|---|---|---|---|---|
| 01 |  |  | 50 | 50-60[55] | - | - |
| 02 |  |  | 53 | 50-60[55] | - | - |
| 03 | $C_6H_5-C(=NOH)-C_6H_5$ | $C_6H_5-CH(NH_2)-C_6H_5$ | 36 | 35-40[56] | $C_6H_5-C(=O)-C_6H_5$ (28.0%) | 36.00% |
| 04 | $C_6H_5-CH=N-OH$ | $C_6H_5-CH_2NH_2$ | 60 | 60-65[55] | - | - |

## 4. CONCLUSIONS

It is concluded from this study that :

(1) Reduction of substituted cyclohexanones with $Na/Al_2O_3$ /alcohol gives more of thermodynamically stable alcohol (eq.-OH). Yet selectivity is higher when t-butanol is used as proton donor than isopropanol.

(2) Bicyclic ketones could be reduced to endo-alcohols selectively.

(3) Esters and oximes could be reduced to primary alcohols and primary amines, respectively, in high yields.

(4) $Na/Al_2O_3$ is more effective and selective than Na dispersion. Moreover, the former is convenient off - the - shelf reagent ready to use.

## 5. EXPERIMENTAL

All m.ps and b.ps are uncorrected. Pet ether refers to light petroleum fraction b.p. 60-80°. Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use[57]. Toluene was refluxed over sodium and kept over sodium wire. Isopropyl alcohol and t-butyl alcohol were dried over CaO and kept over 4A molecular sieves. $Na/Al_2O_3$ was washed several times ( $\sim$ 6) with anhydrous pet ether before use. Diethyl ether was used for the extraction of product. All solvent extracts were finally washed with brine and dried ($Na_2SO_4$).

TLC was carried out on silica gel layers (0.25 mm containing 15.0% gypsum and activated at 110-115°(2 h); visualization : conc. $H_2SO_4$ aq.spray or 0.5% aq. $CuCl_2$ (for oximes)[58] followed by heating $\sim$100°/5 min.

The following instruments were used for spectra/analytical data : Perkin-Elmer infrared spectrophotometer, model 267; Perkin-Elmer model R 32 (90 MHz), NMR spectrometer; Hewlett-Packard 5712 A and 7624 A gas chromatographs [(for analytical purpose): ss columns; 360 cmsX0.6 cm; support 60-80 mesh chromosorb W; stationary phase 10% SE 30, 10% CW, or 10% P(DEGS);carrier gas $H_2$ or $N_2$; (for preparative purpose): ss column, 360 cmsX1.0 cm; support 60-80 mesh chromosorb W; stationary phase 20% CW; carrier gas $H_2$ 80 ml/min; equipped with TCD, Col.130°, 20 $\mu$l each injection.]

IR spectra were recorded as smears. All PMR spectra were recorded with 15-20% solution in $CCl_4$ (unless stated contrary) with TMS as internal reference; signals are reported in ppm ( $\delta$ ); while citing PMR data the following abbreviations have been used : s, singlet; d, doublet; t, triplet;

m, multiplet; b, broad.

**Preparation of $Na/Al_2O_3$**[59]

To a flame dried assembly containing 500 ml round bottomed flask equipped with an efficient hershberg stirrer, a condenser, a thermowell, and $N_2$ inlet, was charged 37.5 g alumina (mesh 80-200) and activated at 220°±10° for 2 hours with stirring under oxygen free dry $N_2$ . The temperature was then lowered to 145-165° and 12.5 g shining sodium pieces were added slowly over a period of $\sim$ 10 minutes. Sodium melted at that temperature and temperature shot upto 185°C. It was controlled by putting off heating source and maintained at 165°C. It was stirred slowly for 5-10 minutes so that sodium should not splash on the wall of flask, and then vigorously for 2 hours. Thus a bluish black or dark black free flowing powder was obtained. Now the temperature was lowered to 100° and 6.25 g (7.0 ml, 12.5 % by wt.) molten wax (m.p. 50-60°) was added and vigorous stirring resumed for one hour. It was then cooled to room temperature and a black free flowing powder transferred into a wide mouth dry bottle. Throughout the experiment $N_2$ was continuously purged ( wt.of $Na/Al_2O_3$ was 54.0 g).

**Estimation of active sodium in $Na/Al_2O_3$**

It is based on measurement of hydrogen gas released by the reaction of sodium and an alcohol. The raction was carried out in a standard apparatus commonly used for estimation of LAH.

The following procedure was followed.

(1) 1.0-1.5 g $Na/Al_2O_3$ ($W_1$) was weighed in a 50 ml 2 necked round bottomed flask fitted with a bulb shaped suction adopter and rubber septum joint.

(2) The flask was attached to the system and magnetic stirrer was placed under flask.

(3) 5.0 ml dry pet ether was charged into the flask with the help of a syringe and stirred for 2 minutes. The water level in the burette was set at 100 ml. ($V_3$)

(4) Dry methanol (10 ml) was then added slowly over a period of 10-15 minutes. A vigorous reaction starts and hydrogen starts collecting in burette. The temperature of flask was controlled by maintaining the temperature of bath.

(5) The stirring was continued until there was evolution of hydrogen ($\sim$20 min). The final reading was noted down ($V_4$).

(6) The wt. of active sodium or percentage of active sodium on alumina was calculated by the following equations.

(i) $$V_2 = \frac{22.4 \times (273 + t)}{273}$$

(ii) $$W_2 = \frac{2 \times M \times (V_3 - V_4)}{V_2}$$

(iii) $$\% \text{ Active Na} = \frac{W_2}{W_1} \times 100$$

Where, t = room temperature, $V_2$ = volume of $H_2$ at temp. t, M = molecular of wt. of Na (23), $W_2$ = actual wt. of active sodium present in the sample, $V_3$ = initial reading of burette, $V_4$ = final reading of burette, and $W_1$ = wt. of sample of $Na/Al_2O_3$.

**A representative example of ketone reduction**

4.5 g $Na/Al_2O_3$ (21.0 % active Na, 0.94; 0.04 g atom) was weighed in a dry three necked 50 ml round bottomed flask fitted with a condenser, a thermal well, $N_2$ inlet, and a pressure equilibrated addition funnel. It was washed with pet ether (10 ml x 6) and finally with THF (10 ml x 2) and dispersed in THF (30 ml). A mixture of menthone (1.54 g, 0.01 mol.) and isopropanol (2.4 g, 0.04 mol.) or t-butanol (3.96 g, 0.04 mol.) was added slowly at such a rate that smooth refluxing was maintained (5-10 minutes). The reaction mixture was then stirred vigorously and refluxed for 5-6 hours at 67-9°C; cooled to 0-5° and excess sodium was destroyed cautiously with ice water. The slurry was filtered to discard alumina and filtrate was extracted with ether (10 ml x 6). The combined solvent extracts were washed with water (15 ml x 3) and brine (10 ml x 2), and dried over anhyd. $Na_2SO_4$. Removal of solvent furnished 1.32 g (85 %) product which after distillation was analyzed by GLC.

However, reduction of ketones with sodium and alcohol was performed by first preparing sodium sand in refluxing toluene as described by S.Dev[35] and then replacing it with THF as given above.

Spectral data of some isomeric alcohols obtained after reduction of $\alpha$ , $\beta$ unsaturated ketones.

1. Dihydrocarveol (7)

IR (neat)(Fig.1) : 3340, 3080, 1645, 1450, 1372, 1072, 1050, 1017, 928, 887, 848 $cm^{-1}$.

NMR (Fig.2) : Me (3H, s, 1.05 ppm), Me-C=C(3H, s, 1.70 ppm), CHOH

(1H, m, 2.86-3.3 ppm), CH=C (2H, s, 4.64 ppm).

2. Neodihydrocarveol (8)

IR (neat)(Fig.3) : 3400, 3080, 1644, 1450, 1372, 1260, 1212, 1012, 995, 976, 950, 885, 800 $cm^{-1}$.

NMR (Fig.4) : Me(3H, s, 0.97 ppm ), Me C=C(3H, s, 1.70 ppm,) CHOH (1H, bs, 3.82 ppm), CH=C (2H, s, 4.60 ppm)

3. Neoisodihydrocarveol (9)

IR (neat)(Fig.5) : 3350, 3080, 1645, 1450, 1375, 1069, 1036, 1020, 1004, 930, 917, 888 $cm^{-1}$.

NMR (Fig.6) : Me(3H, d, 0.905 ppm, J=7.0 Hz), Me-C=C(3H, s, 1.72 ppm) CHOH (1H, td, 3.69 ppm, $J_1$=10.5 Hz, $J_2$= 4.5 Hz), CH=C(2H, s, 4.67 ppm).

4. cis - 3,3,5-trimethylcyclohexanol (11)

IR (neat)(Fig.7) : 3320, 1460, 1365, 1180, 1150, 1080, 1030, 905 855 $cm^{-1}$.

NMR (Fig.8) : Me(9H, two singlets, 0.89 ppm and 0.93 ppm), CHOH (1H, m, 3.4-3.9 ppm).

5. cis - 3,3,-trans-5-trimethylcyclohexanol (12).

IR (neat)(Fig.9) : 3630, 3400, 1455, 1363, 1335, 1263, 1215, 1185, 1080, 1050, 1020, 1000, 955 $cm^{-1}$

NMR (Fig. 10) : Me(9H, three singlets, 0.86, 0.92, and 1.09 ppm) CHOH (1H, b, 3.9-4.18 ppm).

6. Isophorol (13)

IR (neat)(Fig.11) : 3330, 3040, 1675, 1455, 1438, 1362, 1130, 1045, 1020, 995, 950, 820 $cm^{-1}$.

NMR (Fig.12) : Me (6H, two singlets, 0.89 ppm and 0.99 ppm), Me-C=C (3H,s,1.66 ppm), CHOH (1H,m, 3.9-4.3 ppm), CH=C (1H,bs,5.37 ppm).

7. 2,3,6-Trimethyl cyclohexanol (14)

IR (neat) : 3350, 1460, 1375, 1120, 1060, 1040, 1020, 980 $cm^{-1}$.

NMR : Me (9H, d, 0.97 ppm, J=4.0 Hz), CHOH (1H, m, 2.4-2.8 ppm),

**Reduction of esters**

Esters were prepared from corresponding acids and ethanol in the presence of p-toluene sulphonic acid as catalyst. However, ethylphenyl acetate was prepared from benzyl cyanide and rectified spirit in the presence of conc. $H_2SO_4$[60].

3.30 g $Na/Al_2O_3$ (0.69 g Na, 0.03 g atom; 21.0% active Na) was washed with dry pet ether (10 ml x 6) and finally with dry toluene (10 ml x 2) and dispersed in 50 ml toluene. A mixture of ethyl palmitate (1.42 g, 0.005 mole) and t-butyl alcohol (2.22 g, 0.03 g mole) was added slowly to the reaction flask with stirring at such a rate that smooth refluxing was maintained (5-10 min). The reaction mixture was additionally stirred for 5½ hours at 110°C or till reaction was complete. The reaction was stopped and excess sodium destroyed with ice water after chilling the flask (0-5°C). Work-up was followed as described for the reduction of ketones. 0.84 g 1-hexadecanol (70%) was obtained after distillation.

**Reduction of oximes**

Oximes of cyclohexanone, cyclopentanone, benzaldehyde, and benzophenone were prepared according to the standard procedure of Vogel[61].

Reduction of oximes was carried out with $Na/Al_2O_3$ (7 gm equivalents ) and iso-propanol (7 gm eq.) in refluxing toluene for 3-4 hours. After the reaction was over as monitored by TLC, it was quenched with ice-water and $Al_2O_3$ filtered out. The filtrate was acidified with 50% aq. HCl to a pH of 2-3 and mixture of toluene and water was stripped off by distillation (up to nearly

dryness). The solid was treated with 40% aq. KOH solution in order to hydrolyze amine hydrochloride into amine until it dissolved completely. Amine was extracted 6 times with 15 ml ether. Removal of solvent furnished the crude liquid which was distilled to get the required amine in 40-60% yield.

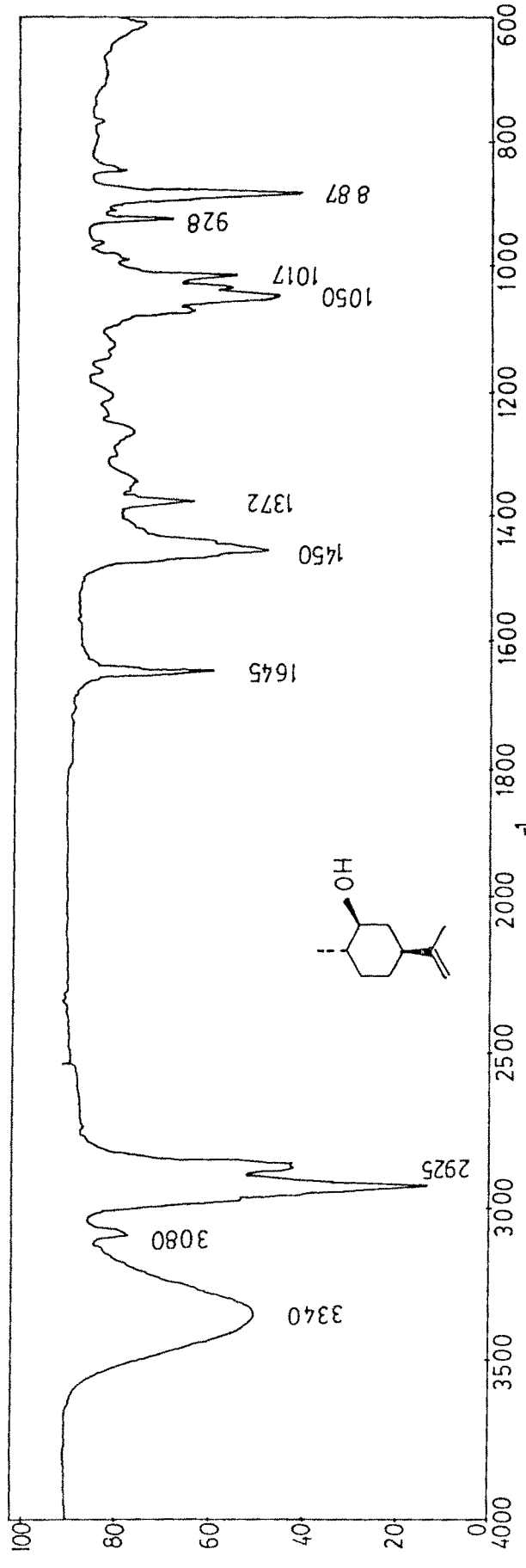



Fig. 1 - IR spectrum of Dihydrocarveol

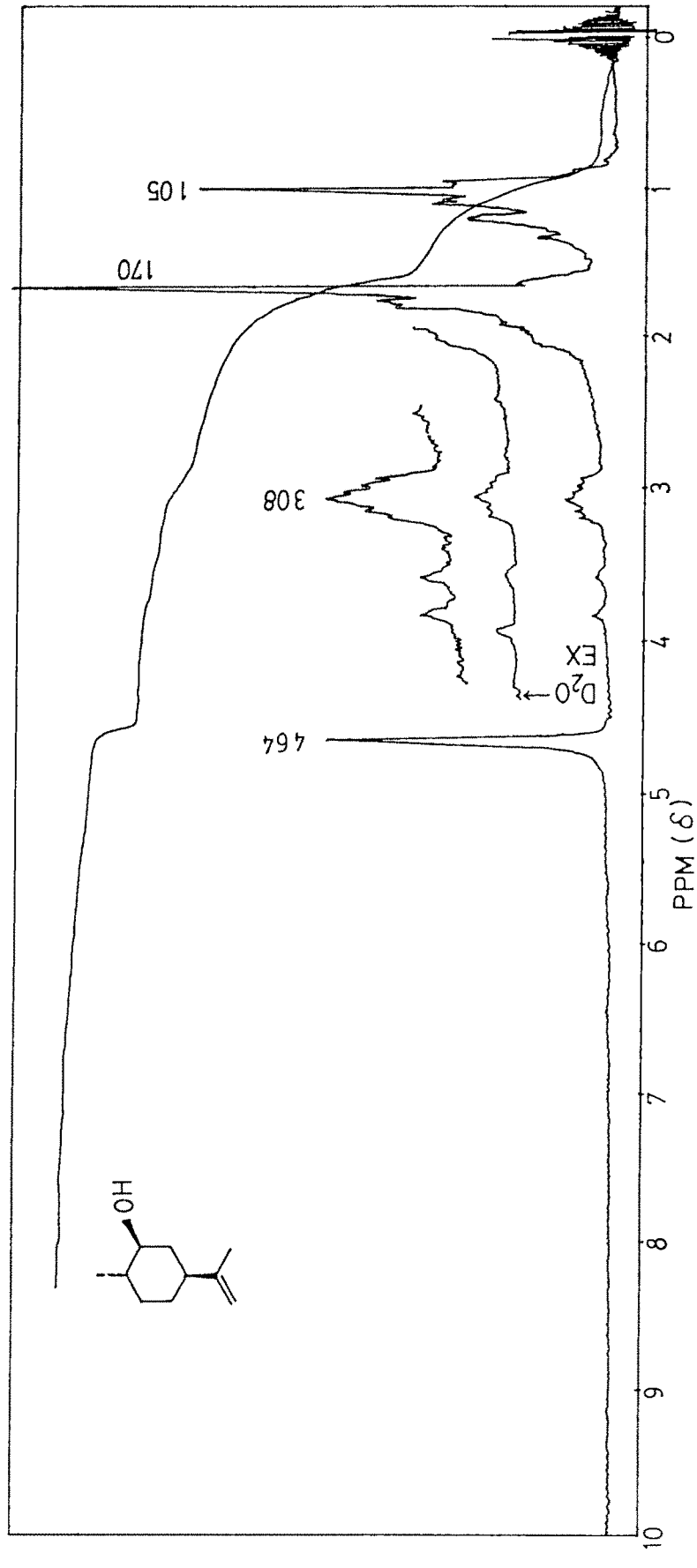



Fig. 2 - NMR spectrum of Dihydrocarveol.

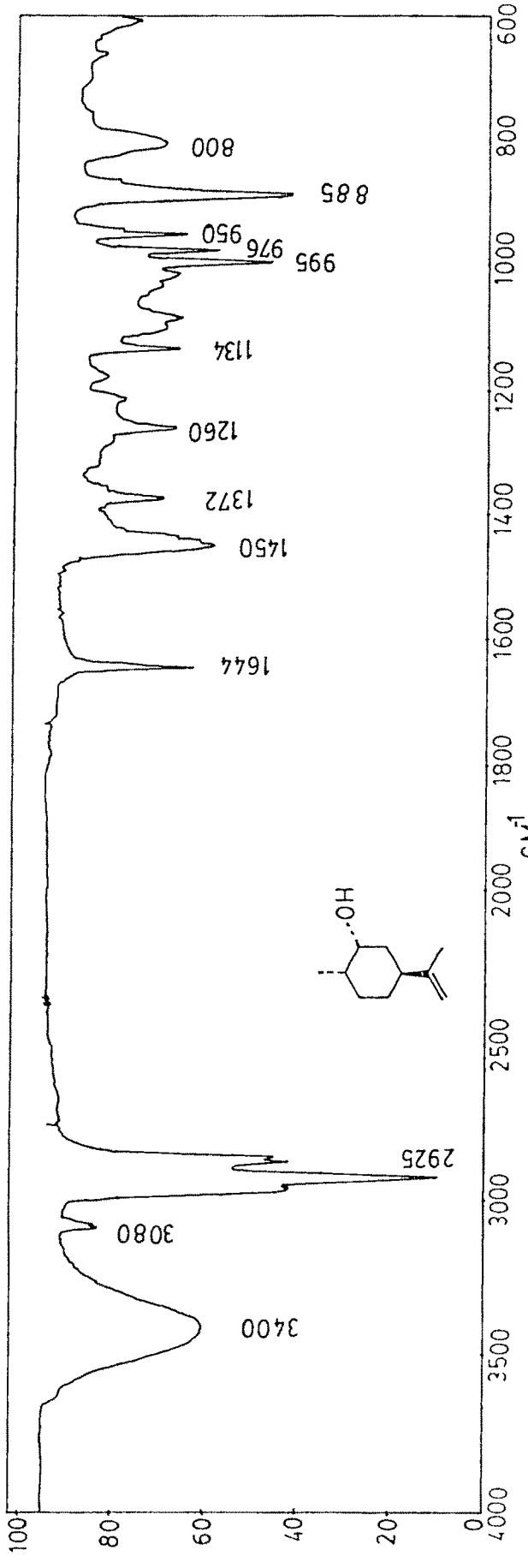



Fig. 3 - IR spectrum of Neodihydrocarveol

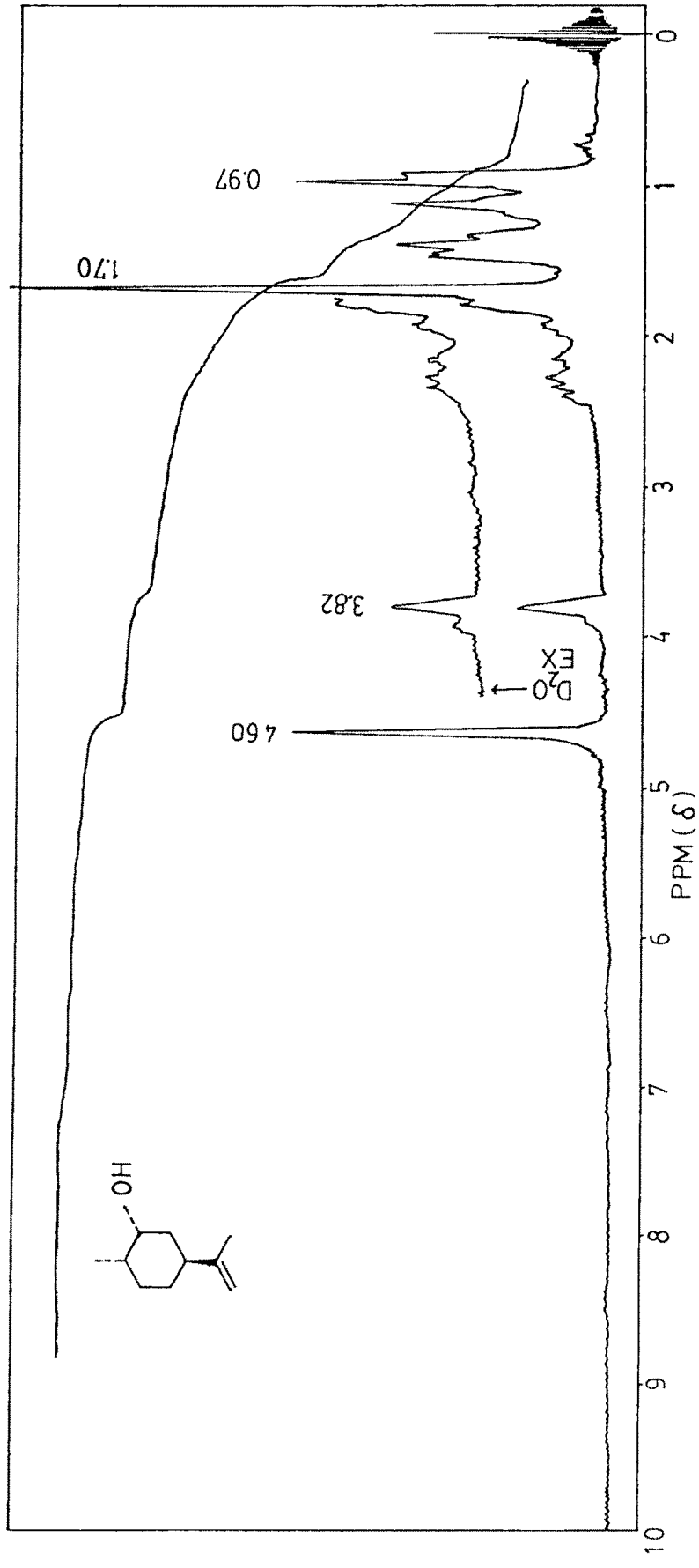



Fig. 4 - NMR spectrum of Neodihydrocarveol.

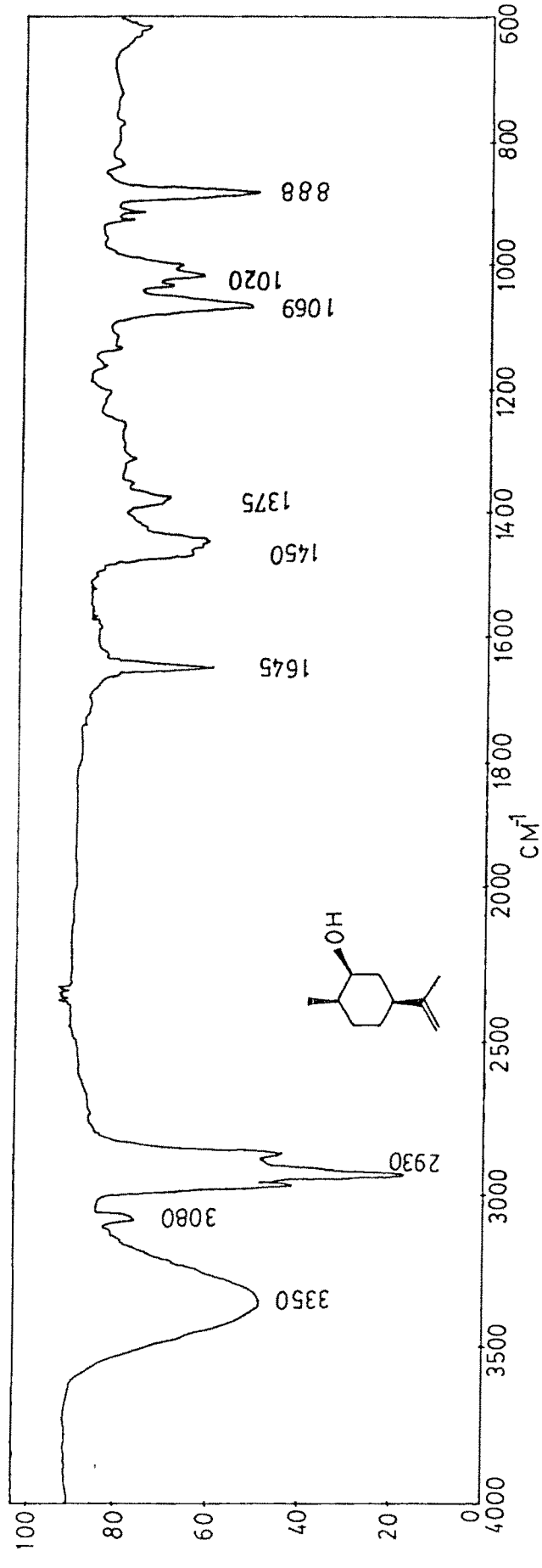



Fig. 5 - IR spectrum of Neoisodihydrocarveol.

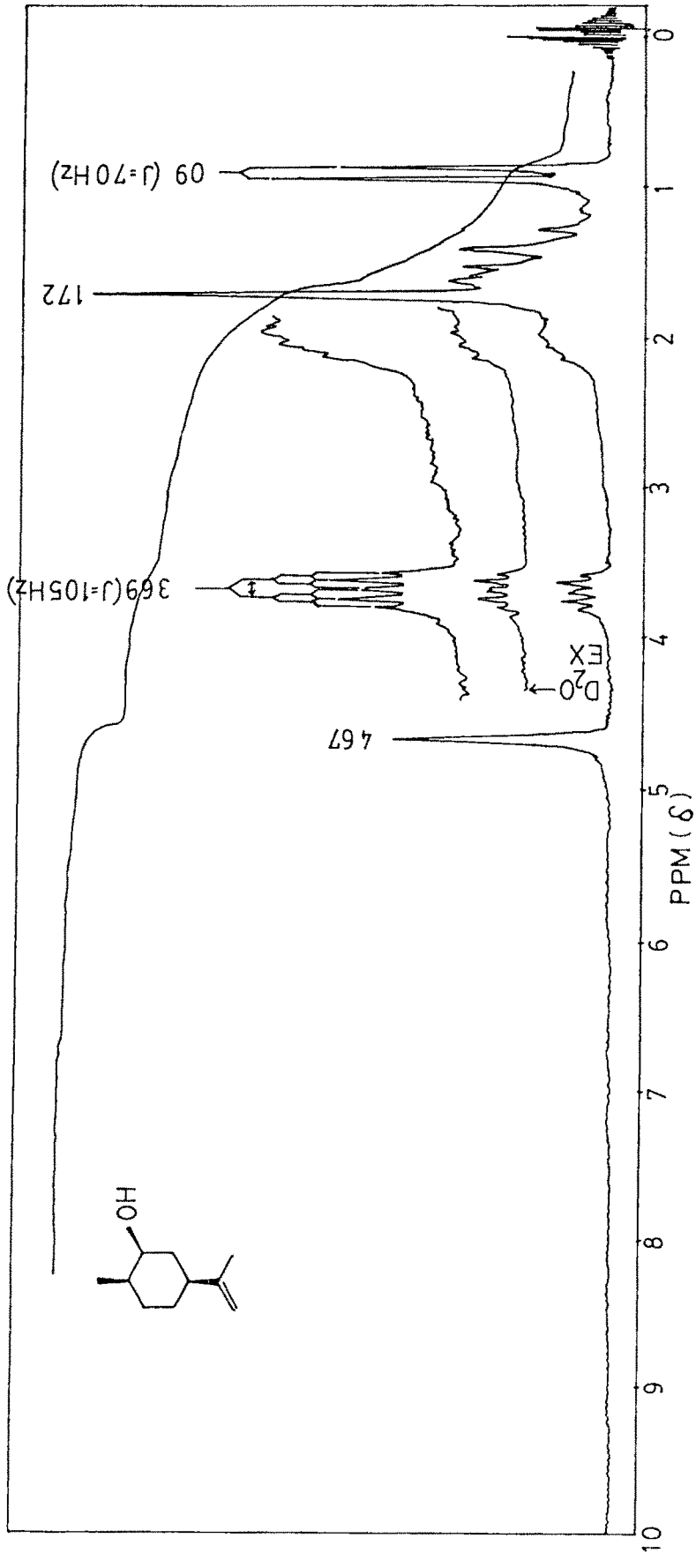



Fig. 6 - NMR spectrum of Neoisodihydrocarveol.

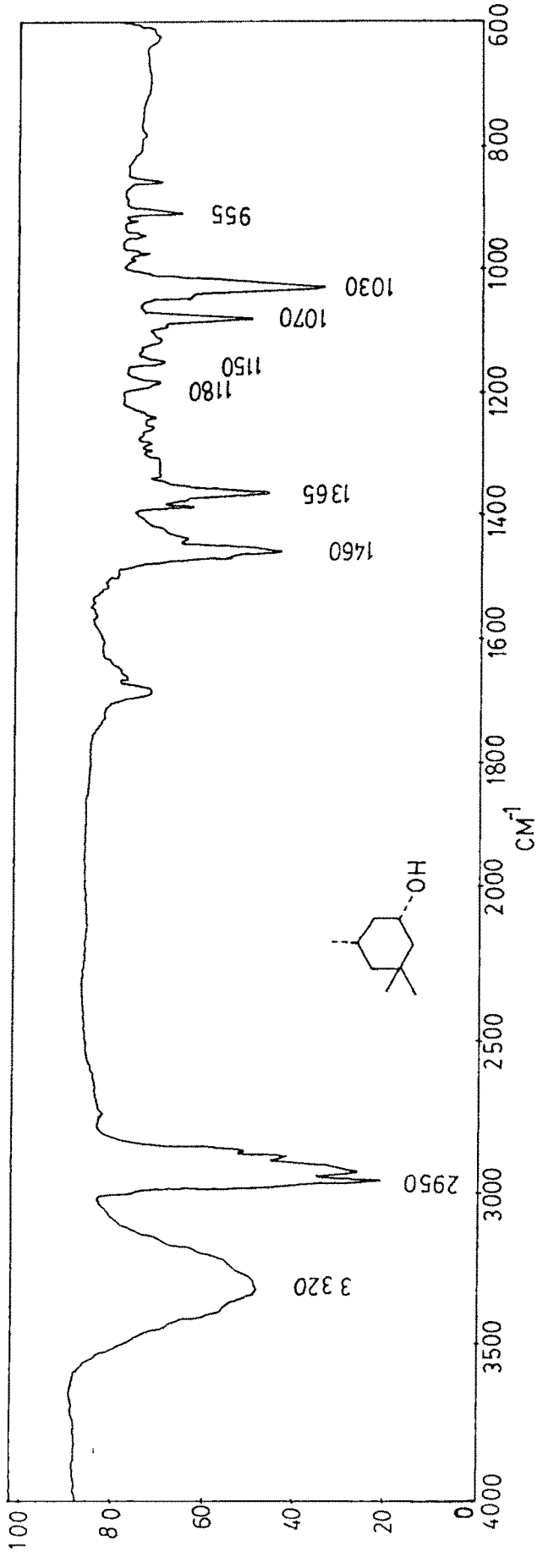



Fig. 7 - IR spectrum of cis 3,3,5-Trimethyl cyclohexanol

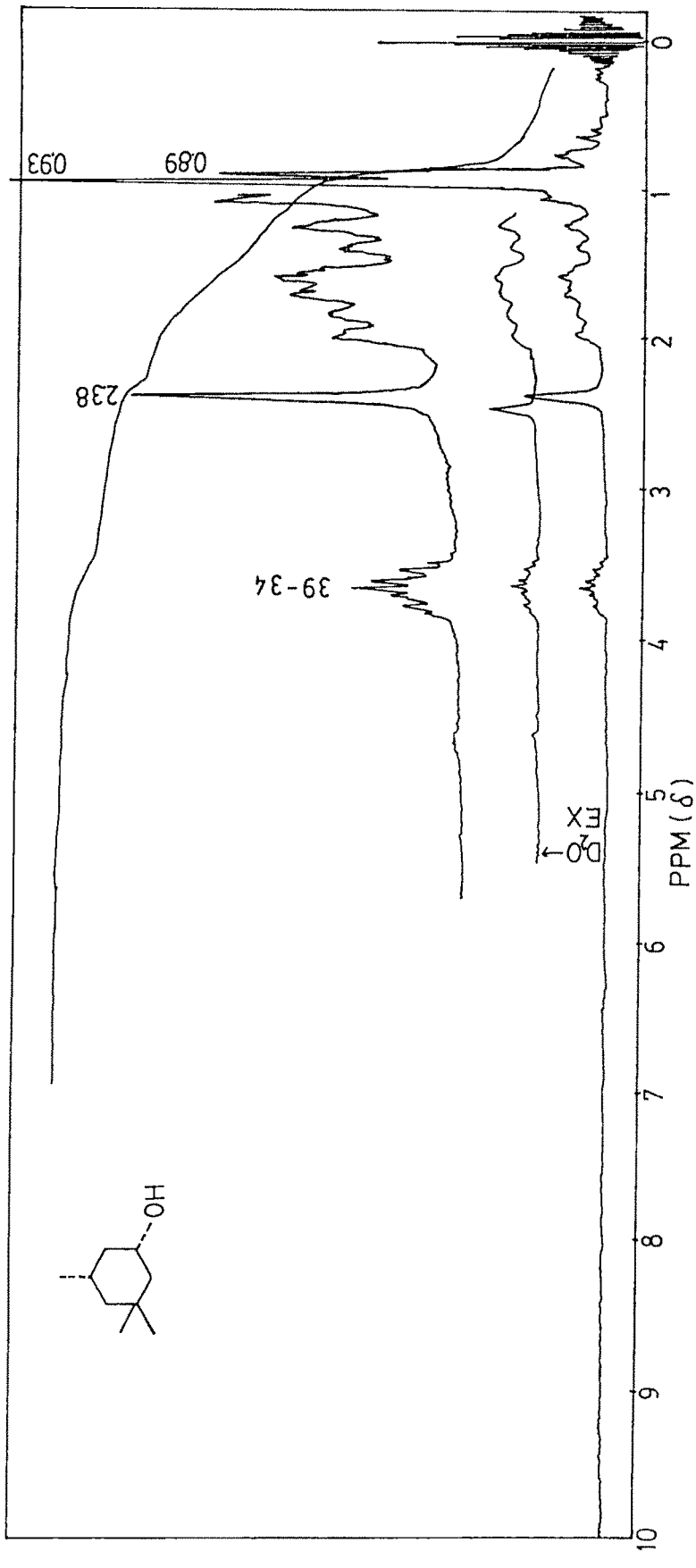



Fig. 8 - NMR spectrum of cis 3,3,5-Trimethyl cyclohexanol

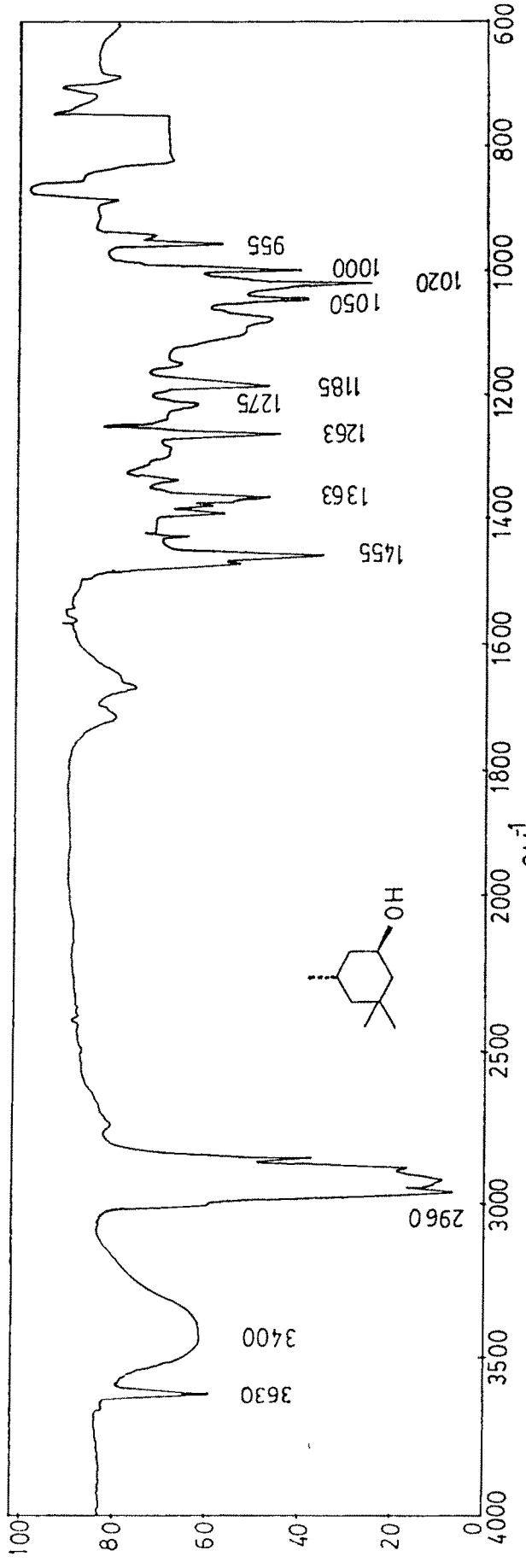



Fig. 9 - IR spectrum of cis 3,3-trans-5-Trimethyl cyclohexanol.

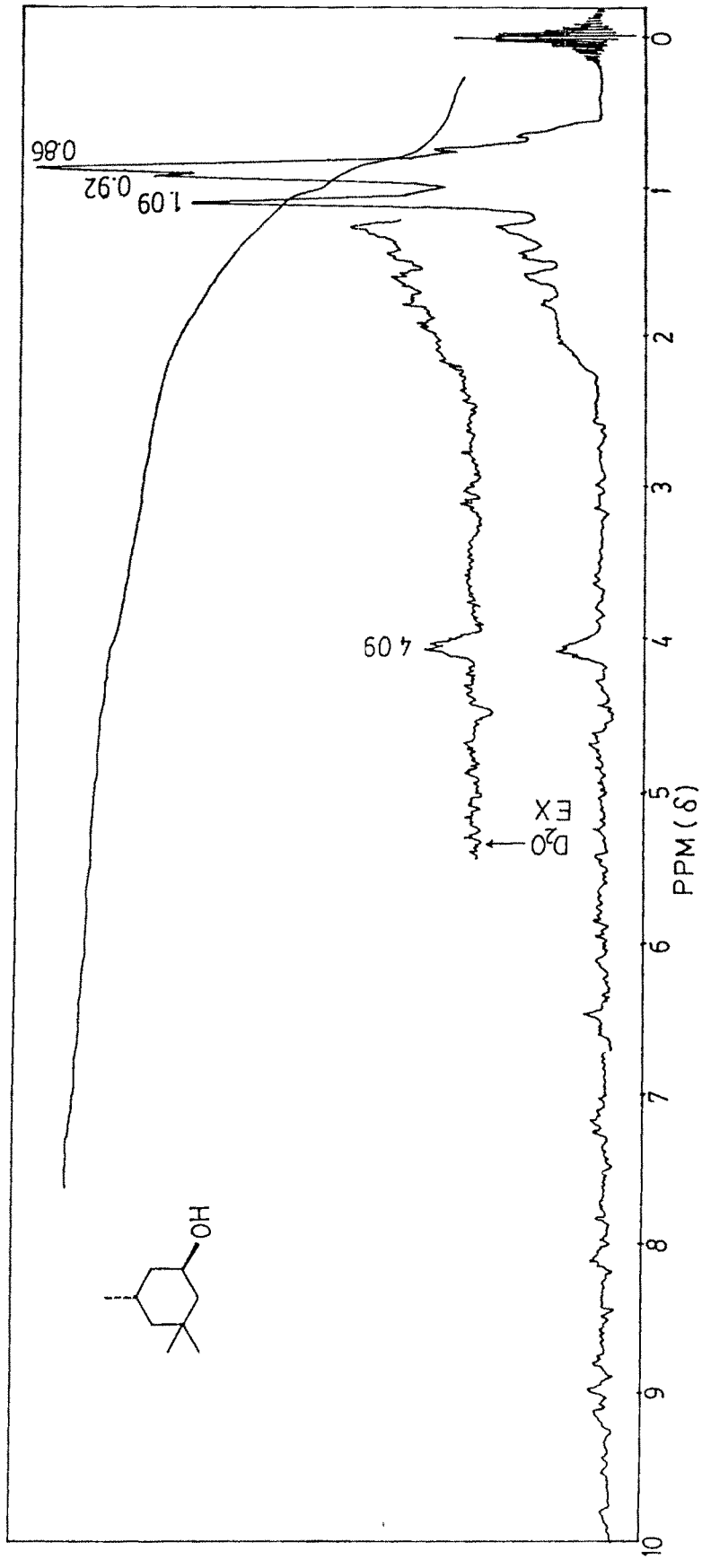



Fig. 10 - NMR spectrum of cis 3,3-trans-5-Trimethyl cyclohexanol.

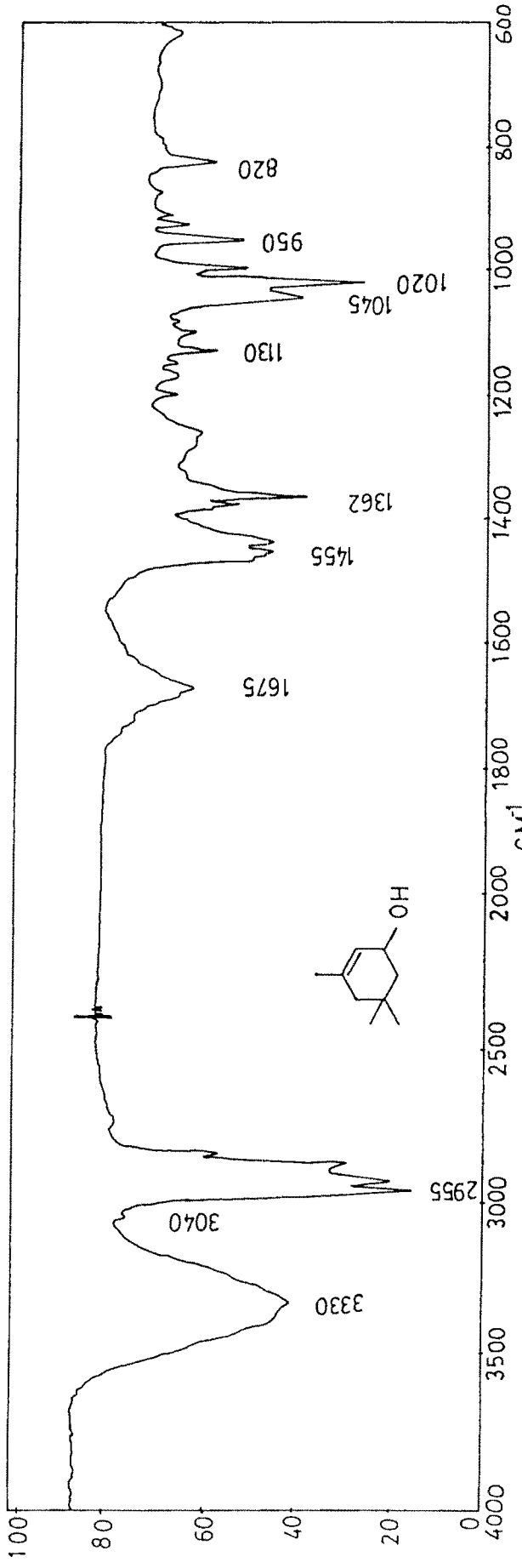



Fig. 11 - IR spectrum of Isophorol

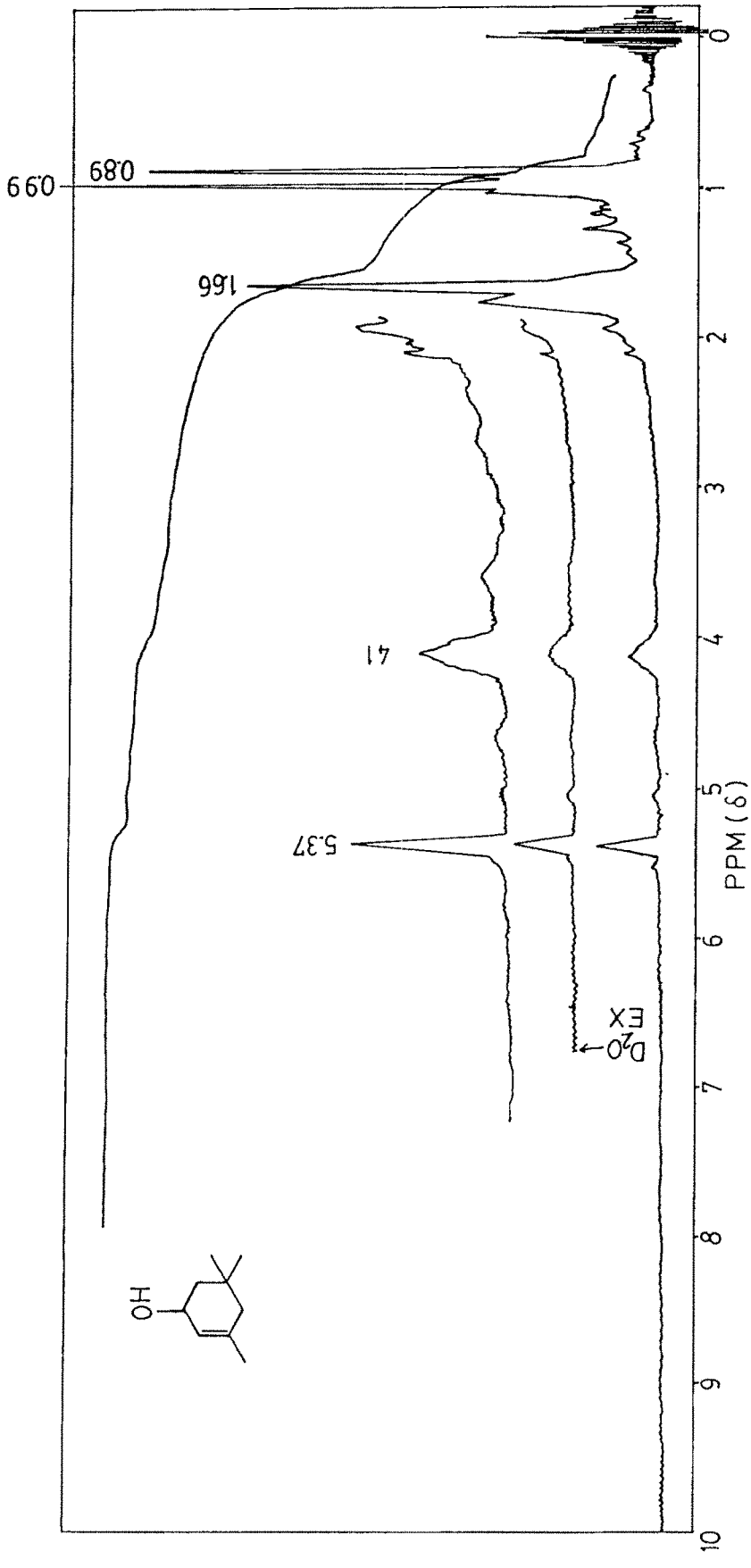



Fig. 12 - NMR spectrum of Isophorol

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# SECTION 2

# REDUCTIVE COUPLING
# OF
# KETONES WITH OLEFINS

# REDUCTIVE COUPLING OF KETONES WITH OLEFINS.


## Abstract

The intramolecular and intermolecular reductive condensation of ketones with olefins has been investigated using $Na/Al_2O_3$/alcohol in N-methyl pyrrolidone. It provides a simple and effective method for the preparation of tert-alcohol.

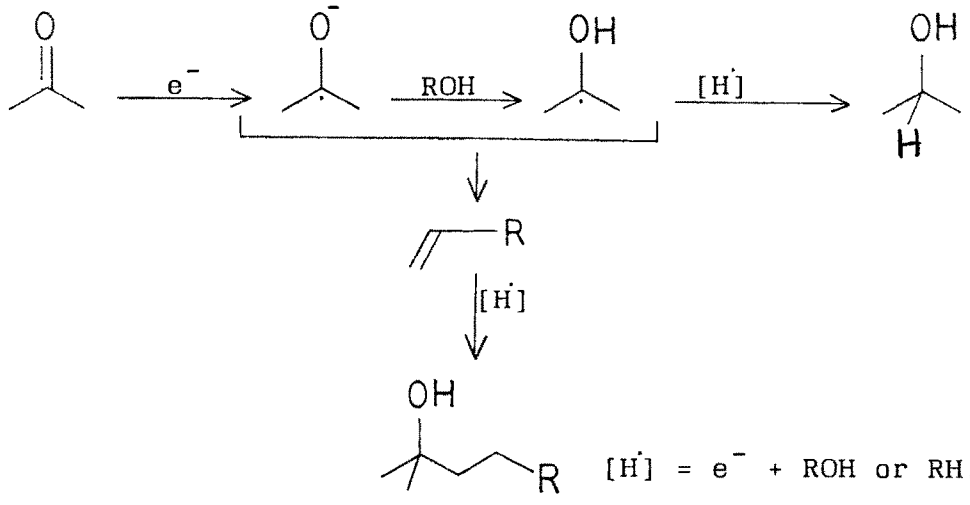
## 1. INTRODUCTION

It has long been known that free radicals may add to olefinic double bonds. The alkyl radicals so formed may undergo further reactions, such as abstraction of hydrogen or halogen. The 'abnormal' peroxide catalyzed addition of HBr to olefins is an early example of this type of phenomenon[1].

Radical addition to carbon-carbon double bonds can also occur intramolecularly. Such reactions lead to cyclization products and are of interest both in synthesis and for mechanistic problems they pose[2,3].

Whitesides[4] has reported intermolecular reductive coupling of ketones with olefins using sodium/N-ethyl pyrrolidone. Thus, stirring 1-hexene with sodium in NEP at 25° with 2-heptanone in presence of excess t-butyl alcohol gave 6-methyl 6-hydroxydodecane in 66% yield. No condensation product was observed in liquid ammonia-ether, but modest yields were obtained in ethylene diamine-ether (6%), HMPA (10%), and in N,N-diethyl acetamide (40%).

The mechanism suggested by him involves the addition of the intermediate ketyl anion or hydroxy radical derived from one electron reduction of the ketone to the exo-carbon of the terminal olefin. This intermediate alkyl radical could undergo subsequent reduction by single-electron transfer and protonation or by hydrogen atom abstraction from any one of several good hydrogen donors that are present. The ketyl anion or $\alpha$-hydroxy radical that does not add appears to suffer reduction to the secondary alcohol by these same sequences (Scheme - 1).




Scheme - 1. Reductive coupling of ketone with olefin.

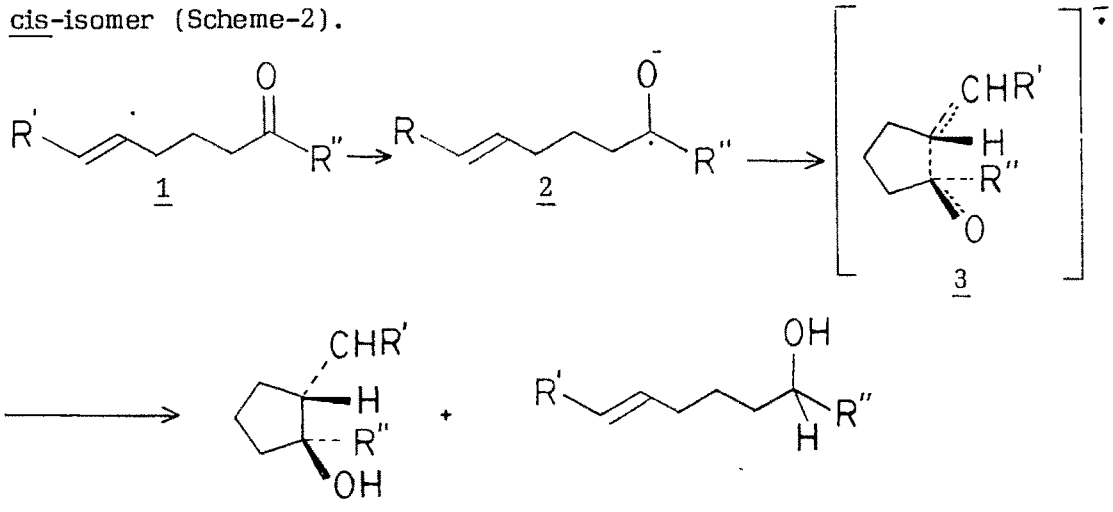
One interesting aspect of his mechanism is that the species attacking the mono-substituted olefin does so at the terminal carbon as it is typical for both electrophilic and alkyl radical attacks but not for carbanion attack.

Using similar conditions, he also reports intramolecular cyclization of 6-hepten -2-one to 1,2-dimethyl cyclopentanol in $\sim$ 65% yield. No attack at the terminal position to give a cyclohexanol was observed.

Shono[5] has prepared 5 - and 6 -membered tertiary alcohols by electrochemical cyclization of non-conjugated enones under protic [1:9 (v/v) methanol/dioxane-tetra ethyl ammonium p-toluene sulphonoate or aprotic conditions (anhydrous DMF - tetraethyl ammonium p-toluene sulphonoate].

The reductive cyclization showed remarkable regio- and stereoselectivities in which the reaction always took place between the inner carbon atom of the double bond and the carbonyl carbon atom, and the product was exclusively cis-isomer.

Shono explains that the first electron transfer from the cathode to the starting olefinic ketone 1 generates a radical anion species 2 which subsequently interacts with the olefinic part. In the cyclic intermediate 3 which is formed by the interaction of radical anion with the inner carbon atom of the double bond, both the oxygen atom and -CHR' group carry some negative charge which keeps both moieties away from each other and brings about the formation of cis-isomer (Scheme-2).




Scheme - 2. Intramolecular cyclization[5]

Ketone-olefin[6,7] and ketone-alkyne[8] reductive coupling by dissolving metal mixtures has been observed previously only in stereochemically rigid systems.

It seems rather difficult to explain why the hexenyl radical should add more rapidly to the substituted end of the double bond rather than to the other end, the terminal one. It is clear that the stability of the radical that is formed in the addition step is not the deciding factor.

It has been suggested[9] that interaction of the unpaired electron with the lowest unoccupied orbital of the unsaturated system is the important factor in free

radical addition reactions. Bond formation should therefore occur at that end of the double bond more readily approached vertically by the attacking radical.

On the lines proposed by Hoffmann[10], Beckwith[11] further explains orbital symmetry control in cyclization of hept-6-en-2-yl radical that the transition state for alkyl radical to an olefinic bond involves interaction of the half filled p-orbital with the vacant $\pi^*$ orbital. Hyperconjugative mixing of the former with adjacent CH $\sigma$ and $\sigma^*$ orbitals produces a modified delocalized orbital which is of similar symmetry to the acceptor $\pi^*$ orbital. Thus, in the transition state, 5, leading to cis-disubstituted product there is a secondary attractive interaction between the alkyl substituent and the olefinic bond which is not available in transition state 4 for trans-cyclization (Fig.1).

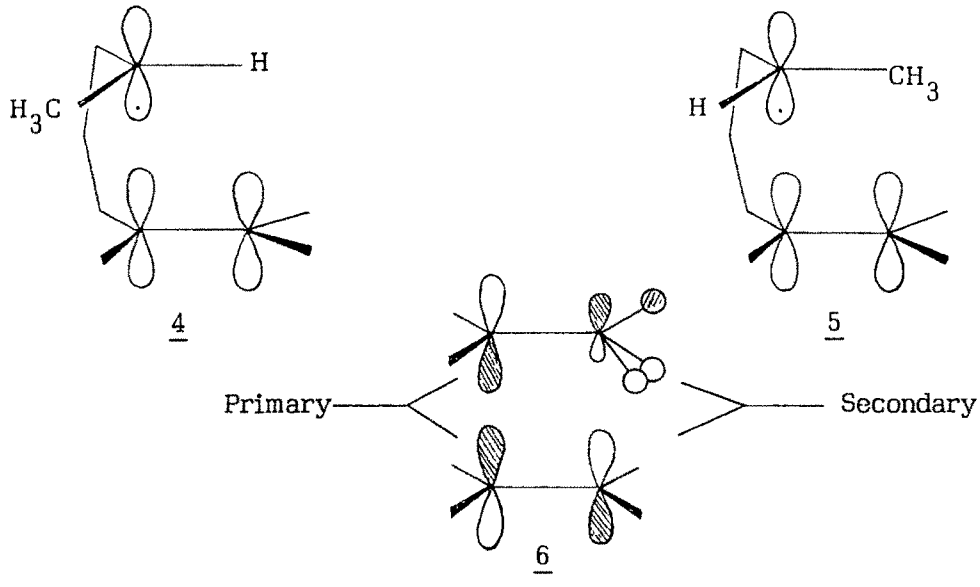



Fig. 1. Orbital symmetry control in cyclization of hept-6-en-2-yl radical.

However, he has pointed out that such interactions should be important only in highly exothermic reactions where the transition state occurs at large separation of the reaction partners.

Pradhan et al.[12] have argued the explanation given by Beckwith and proposed that primary interactions should be SOMO-HOMO based on ionization potential values[13], calculations by Fukui[14] of the reaction of methyl radical with ethylene, and MINDO-3 calculations by Dewar[15] of the same reaction.

Baldwin[16] has concluded that favoured ring closures are those in which the length and nature of the linking chain enables the terminal atoms to achieve the required trajectories to form the final ring bond. The disfavoured cases require severe distortion of bond angles and distances to achieve such trajectories, consequently alternative reaction pathways, if available, dominate.

## 2. PRESENT WORK

Intermolecular reductive coupling of a ketone with olefin is reported by Whitesides[4].

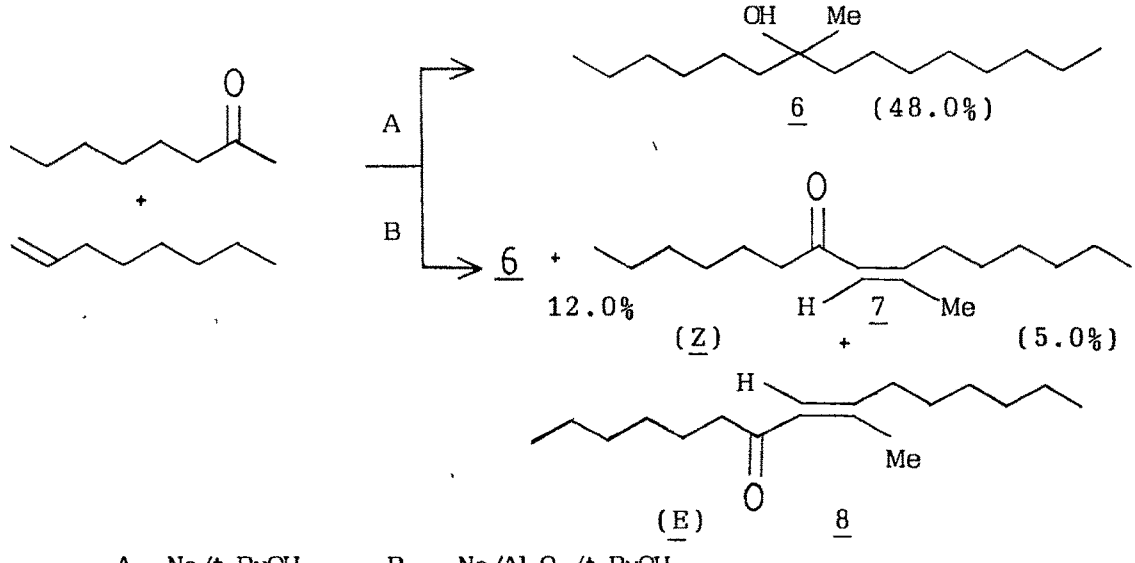
We have utilized $Na/Al_2O_3$ in N-methyl pyrrolidone in order to synthesise 7-methyl-7-hydroxy pentadecane (6) from 2-octanone and 1-octene in presence of t-butanol.

By adopting similar conditions 2-(4-pentenyl) cyclohexanone (9) has also been reductively cyclized to 2-methyl bicyclo [4.4.0] decan-1-ol (10).

## 3. RESULTS AND DISCUSSION

Stirring 1-octene with sodium in N-methyl pyrrolidone at 32°C with 2-octanone in presence of t-butanol for 5.0 hours furnished 7-methyl-7-hydroxy pentadecane (6). The conversion was 48.0% but the isolated yield (after distillation and chromatography) was only 34.0%. The other compounds were 1-octene (26.0%) and 2-octanol (25.0%).

However, on repeating the same experiment with $Na/Al_2O_3$ in place of sodium, only 17.0% condensation product was obtained which, after column chromatography was found to contain 6 (12.0%) and a mixture of aldol condensation products 7+8 (Fig.2). An attempt to increase the yield of condensation product by providing reaction longer time did not appreciably improve it. The total conversion was 22.0 - 24.0 % even after 12 hours of stirring.




A Na/t-BuOH, B $Na/Al_2O_3$/t-BuOH

Fig. 2. Reductive coupling of 2-octanone with 1-octene.

IR and NMR spectra of 6 are shown in figures 5 and 6, respectively. The formation of Z-9-methyl-8-pentadecen-7-one(7) and E-9-methyl-8-pentadecen-7-one (8) could have taken place by aldol type of condensation in presence of base (alkoxide formed as a result of reaction of Na with t-BuOH). The dehydration then must have been facilitated on alumina surface which contains both acidic and basic sites (Fig.3).

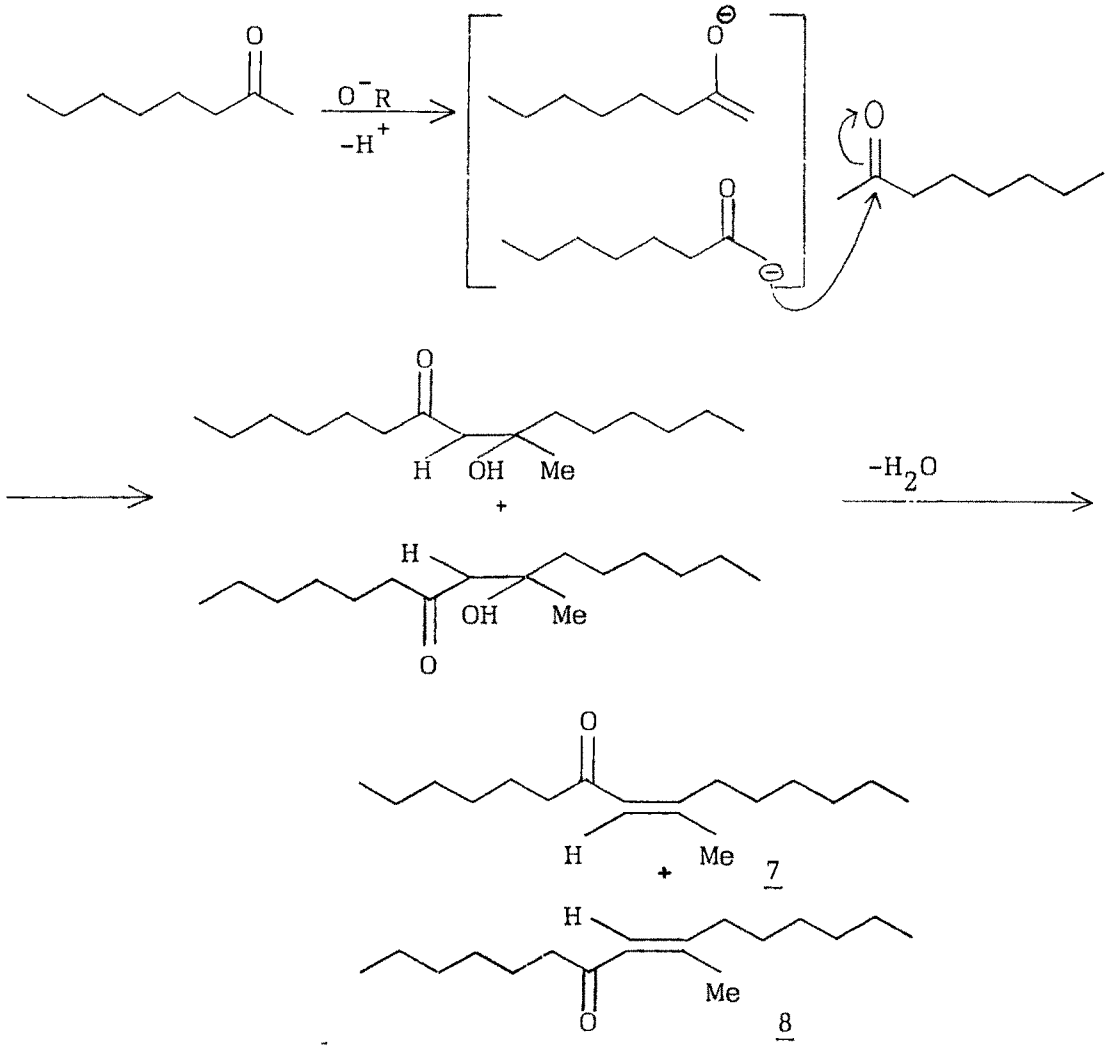
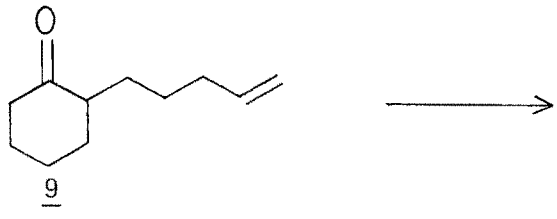



Fig. 3. Formation of aldol condensation products.

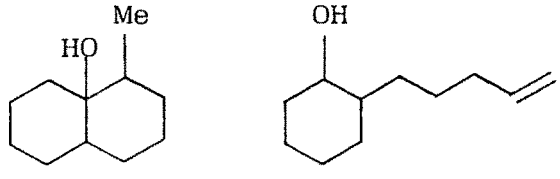
The structures of 7 and 8 were confirmed by NMR and IR. In compound 7 olefinic methyl appeared at $\delta$ 1.82 ppm which in 8 it displayed at 2.08 ppm ( $\delta$ ) due to deshielding effect of carbonyl group[17,18]. The spectral data of these compounds is presented in Figs. 7-12.

**Reductive cyclization**

Reductive cyclization of 2-(4-pentenyl)cyclohexanone (9) was carried out by using Na/t-butanol and $Na/Al_2O_3$/t-butanol in N-methyl pyrrolidone at 32°C for 5.0 hours, separately. The conversion was complete in each case but the ratio of products was somewhat different as shown in Fig. 4.



9




10 11

| | | | |
|---|---|---|---|
| 1. | Na | 66.2 % | 33.8 % |
| 2. | $Na/Al_2O_3$ | 52.7 % | 47.3 % |

Fig. 4. Reductive cyclization of 2-(4-pentenyl) cyclohexanone .

The compound 10 showed two major peaks on analysis by GLC. Column chromatography afforded two compounds. But NMR and IR of two showed that each was a mixture of isomers, which did not resolve on GLC and could not be separated by column chromatography. Thus, it can be presumed that 10 could be a mixture of all possible four isomers viz. trans-anti, trans-syn, cis-anti, and cis-syn 1-methyl-9-decalol[19]. Thus, stereochemistry of cyclized product could not be assigned.

## 4. CONCLUSIONS

1. $Na/Al_2O_3$ is an effective reagent for intermolecular reductive coupling of ketone and olefin.

2. It is equally effective for intramolecular reductive condensation which leads to cyclized product, a reaction of synthetic importance.

## 5. EXPERIMENTAL

All b.ps. are uncorrected. Pet ether refers to light petroleum fraction b.p. 60-80°. N-methyl pyrrolidone was distilled from $CaH_2$ under reduced pressure. t-Butyl alcohol was distilled from sodium metal under nitrogen. Reactants such as olefins and ketones were purified by fractional distillation. All the reactions were carried out in a flame-dried glass ware under an inert atmosphere of oxygen free nitrogen. All solvent extracts were finally washed with brine and dried (anhydr. $Na_2SO_4$).

Silica gel for chromatography (-100, +200 mesh) was obtained from Bhavna Chemicals, Vallabh Vidyanagar (Guj.) (Gr.II A + II B), 10% $AgNO_3$-silica gel was prepared according to the standard procedure[20]. TLC was carried out on silica gel layers (0.25 mm) containing 15% gypsum and activated at 110-115° (2 h); visualization : conc. $H_2SO_4$ spray followed by heating ~100°/5 min.

The following instruments were used for spectral/analytical data : Perkin-Elmer model 267 Infrared spectrophotometer; Perkin-Elmer model 402 ultraviolet spectrophotometer; Perkin-Elmer model R 32 (90 MHz) NMR spectrometer: Varian Mat CH 7 mass spectrometer (75 eV, direct inlet system); Hewlett-Packard model 5712 A gas chromatograph (ss coloumn 180 cms x 0.6 cm, 10% CW and 10% SE 30, support 60-80 mesh chromosorb W; carrier gas $H_2$). All PMR spectra were recorded with 15-20% solution in $CCl_4$ (unless otherwise stated) with TMS as internal reference ; signals are reported in ppm ( $\delta$ ); while citing $^1$H-NMR data following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. While summarizing mass spectral data, besides the molecular ion, ten most abundant ions (m/e) are reported with their relative intensities.

**Reductive coupling of 2-Octanone with 1-octene.**

4.0 g $Na/Al_2O_3$ (18% active Na, 0.70 g, 0.03 g atom) was taken in a predried 50 ml round bottomed flask fitted with a condenser, pressure equilibrated addition funnel and $N_2$ inlet, and washed with dry n-pentane (10ml x 6) with stirring. The solvent was withdrawn with the help of dropper and last traces of solvent were removed by gently warming the flask while purging the nitrogen. N-methyl pyrrolidone (20 ml) was added and stirred for 40 min; dark red colour developed. The 1-octene (0.672 g, 0.006 mole) was added and stirred for 10 min. The 2-octanone (0.768 g, 0.006 mole) and t-butyl alcohol (3.6 g, 0.48 mole) were added slowly to the vigorously stirred mixture over a period of 1 hour and the mixture stirred an additional 4 hours at 32°. Later on it was cooled to 0-5° and unreacted sodium was cautiously treated with ice water and filtered. The filtrate was extracted with pentane (10ml x 6) and combined extracts were washed with three 15 ml volumes of water. The solution was dried over anhyd. $Na_2SO_4$. After removal of solvent and fractional distillation 0.3206 g (15.4%, b.p. 70°/0.5 mm Hg) condensation product was obtained, and 12% was residue. The condensation product showed 2 peaks on GC which were separated by column chromatography over silica gel/II (25.0 g, 17.0 cms x 1.8 cms; elution with 2% EtOAc in pet. ether, 50 ml cuts.)

| Fr. No. | Vol. | Eluent | Eluate | Wt. in gms. |
|---|---|---|---|---|
| 01. | 200 ml | Pet ether | Impurities | 0.024 |
| 02. | 250 ml | 2% EtOAc in pet ether. | Colourless oil | 0.096 |
| 03. | 450 ml | .. do .. | .. do .. | 0.150 |

Fraction 1 was discarded

Fraction 2 was found to be a mixture of $\alpha,\beta$ - unsaturated ketones.

Fraction 3 was identified as t-alcohol (6)(isolated yield 8.5%)

IR (neat)(Fig.5) : 3400, 1470, 1380, 1150, 920, 730 $cm^{-1}$.

NMR (Fig.6) : Me(6H, d, 0.87 ppm, J = 6.0 Hz), Me-C-OH (3H, s, 1.05 ppm), $CH_2$-, -CH (24H, bs, 1.1-1.5 ppm).

The mixture of $\alpha,\beta$ -unsaturated ketones (0.24 g) was separated by column chromatography over 10% $AgNO_3$-silica gel (7.5 g, 25.0 cms x 1.0 cm; elution with pet ether, 10 ml cuts).

| Fr. | Vol. | Eluent | Eluate | Wt. in gms. |
|---|---|---|---|---|
| 01. | 50 ml | Pet ether | Compd 7 | 0.060 |
| 02. | 20 ml | Pet ether | Mixt. of 7+8 | 0.015 |
| 03. | 50 ml | Pet ether | Compd 8 | 0.100 |
| 04. | 60 ml | Pet ether | Mixt. of 8+Others | 0.020 |
| 05. | 90 ml | Pet ether | Mixt. | 0.010 |

Fraction 1 was identified to be Z-9-methyl-8-pentadecen-7-one (7).

IR(neat)(Fig.7): 1690, 1620, 1455, 1375, 1135, 1020, 800, 725 $cm^{-1}$.

NMR (Fig.8) : Me (6H, t, 0.90 ppm, J=6.0 Hz), Me-C=C (3H, s, 1.82 ppm), $CH_2$-C=C- (2H, t, 2.3 ppm, J=7.0 Hz), $CH_2CO$-(2H,t, 2.5 ppm, J=7.5Hz), CH=C(1H, s, 5.92 ppm) (Lit.[17])

Mass (Fig.9) : m/e 238($M^+$, 86.7%), 182 (74.8%), 168 (63.5%), 153 (100%), 113 (50.3%), 98 (100%), 83 (52.2%), 69 (100%), 55 (100%).

Fraction 3 was characterized as E-9-methyl-8-pentadecen-7-one (8).

IR(neat)(Fig.10) : 1690, 1620, 1470, 1380, 1135, 1075, 730 $cm^{-1}$.

NMR (Fig.11) : Me (6H, t, 0.90 ppm, J=6.0 Hz), Me-C=C(3H,s,2.08 ppm), $CH_2$ - C=C (2H, t, 2.07 ppm, J=6.0 Hz), $CH_2$ -CO-(2H, t, 2.3 ppm, J=7.0 Hz), CH=C (1H, s, 5.92 ppm) (Lit.[17]).

Mass (Fig.12) : m/e 238 ($M^+$, 41.5%), 181(27.9%), 168(89.3%), 154(46.8%), 153(100%), 98(100%), 83(44.6%), 68(62.5%), 55(54.4%).

**Reductive cyclization of 2-(4-pentenyl) cyclohexanone (9)**

Compound 9 was prepared by alkylation of cyclohexanone according to the procedure of Conia[21]. 4-Pentene-1-bromo for this reaction was synthesized according to Smith[22] from 4-penten-1-ol[23] and $PBr_3$.

4.0 g $Na/Al_2O_3$ (18.0% active Na, 0.7 g, 0.03 g atom) was washed with n-pentane and stirred with N-methyl pyrrolidone (20ml) for 40 min. 9 (0.332 g, 0.002 mol.) and t-butanol (1.8 g, 0.24 mol.) were added slowly to the vigorously stirred mixture at 30°C over a period of 1 h; stirring was continued for another 4.0 h. Usual work-up furnished 0.2805 g (85.0%) product which on analysis by GLC showed it to be a mixture of four compounds. The mixture was separated by column chromatography over silica gel/II (10.0 g, 31.0 cms x 1.0 cm; elution with 1.0% EtOAc in pet ether, 10 ml cuts)

After rejecting 60 ml of first eluate ( pet ether, 5 mg), the next 10 ml x 8 of solvent (1% EtOAc in pet ether) eluted 100 mg of 10. The next 10 ml x 4 of eluate gave a mixture of other isomers of 10 (45 mg). This was followed by compound 11 (90 mg, 10 ml x 9).

2-Methyl bicyclo (4.4.0) decan-1-ol (10)

IR (neat) : 3400, 1450, 1380, 1260, 1165, 1100, 960, 940, 860, 800 $cm^{-1}$. (Lit.[5]).

NMR : Me (3H, 0.95 ppm, J=6.8 Hz), $CH_2$ -, -CH-(18H, b, 1.1-2.6 ppm). (Lit.[5]).

2-(4-pentenyl) cyclohexanol (11)

IR (neat) : 3400, 3080, 1640, 1450, 1265, 1130, 1060, 1020, 980, 910 $cm^{-1}$ (Lit.[5]).

NMR : $CH_2$-, -CH- (15H, b, 0.63-2.48 ppm), CHOH(1H, bm, 2.93-3.4 ppm), $CH_2$=C(2H, m, 4.77-5.17 ppm), -CH=C(1H, m, 5.48-6.06 ppm)(Lit.[5]).

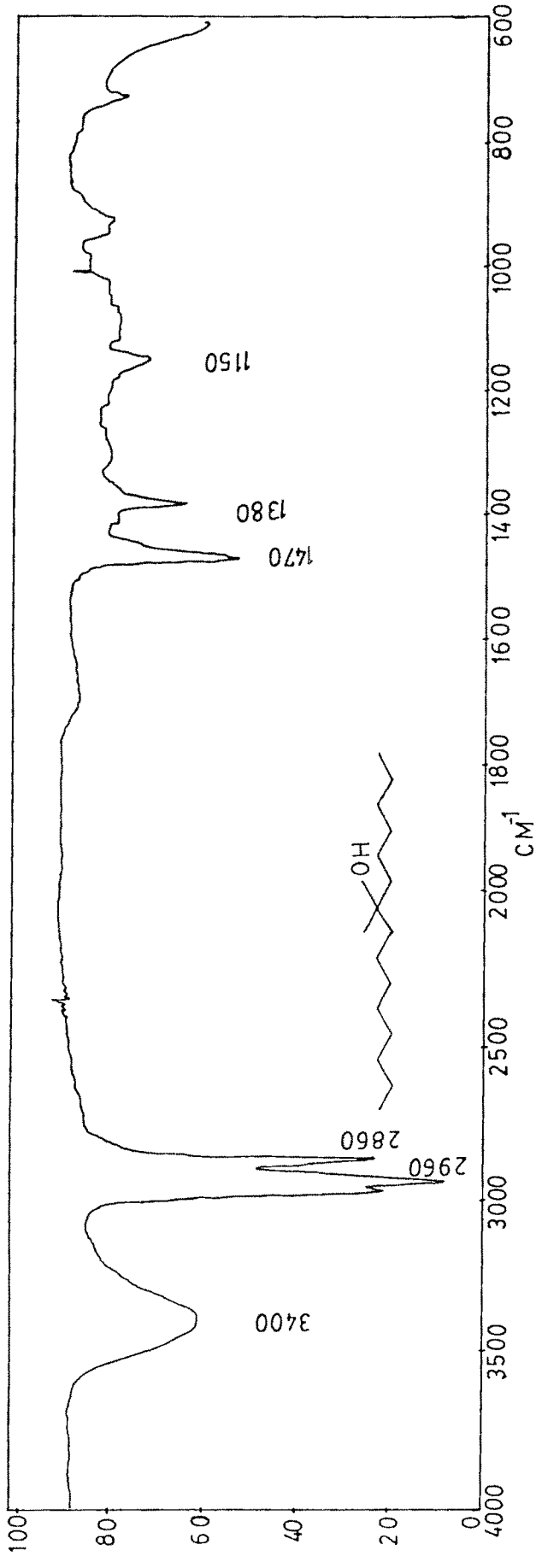



Fig. 5 - IR spectrum of 7-Methyl-7-hydroxy pentadecane

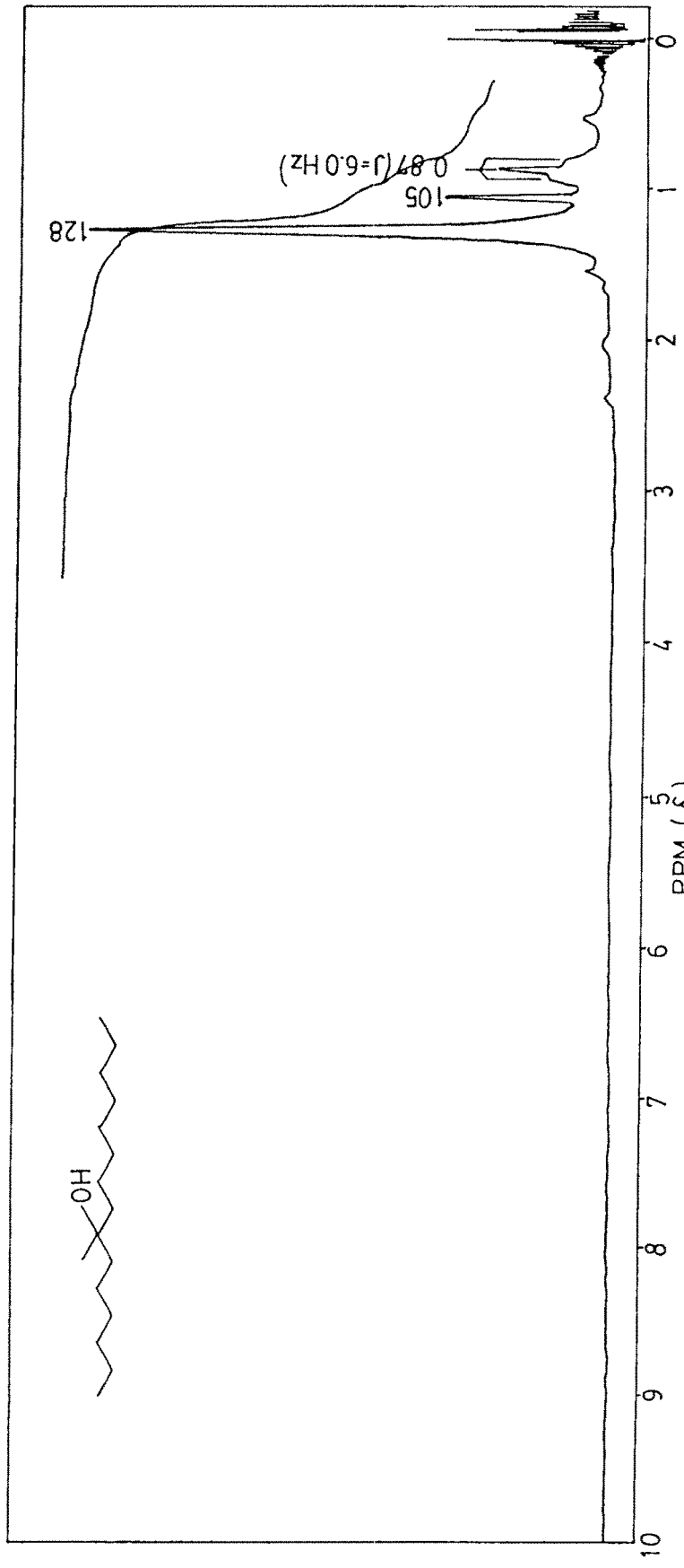



Fig. 6 - NMR spectrum of 7-Methyl-7-hydroxy pentadecane

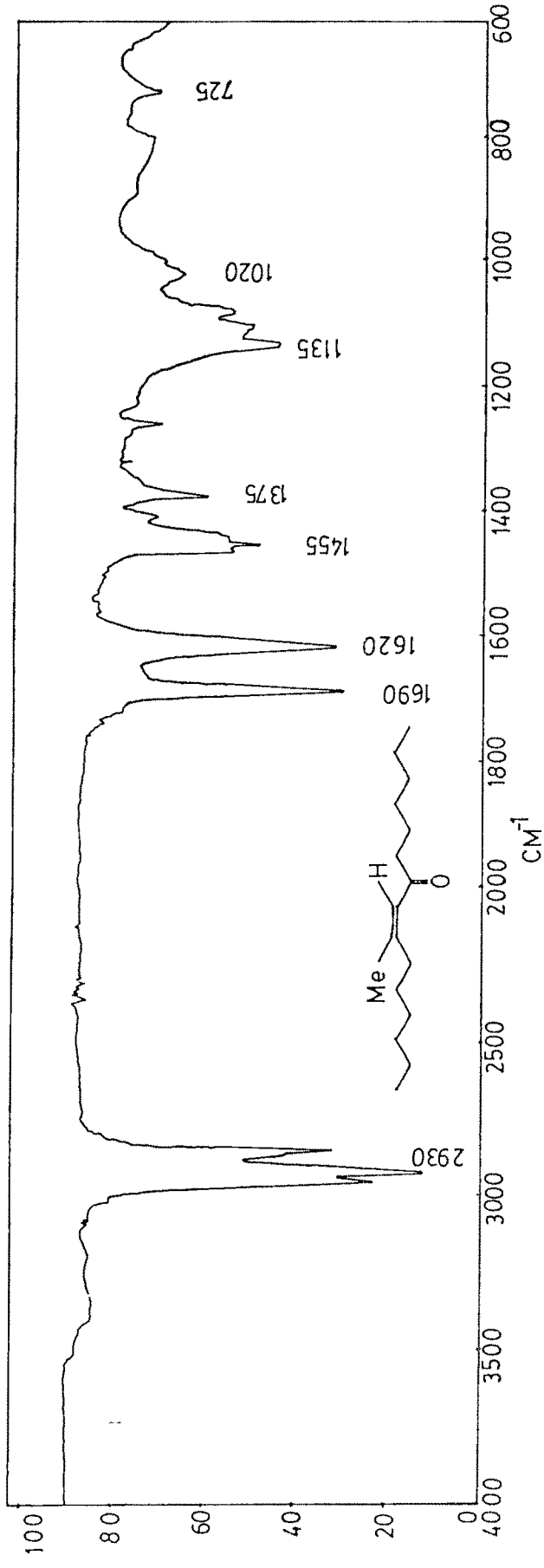



Fig. 7 - IR spectrum of Z-9-Methyl-8-pentadecen-7-one

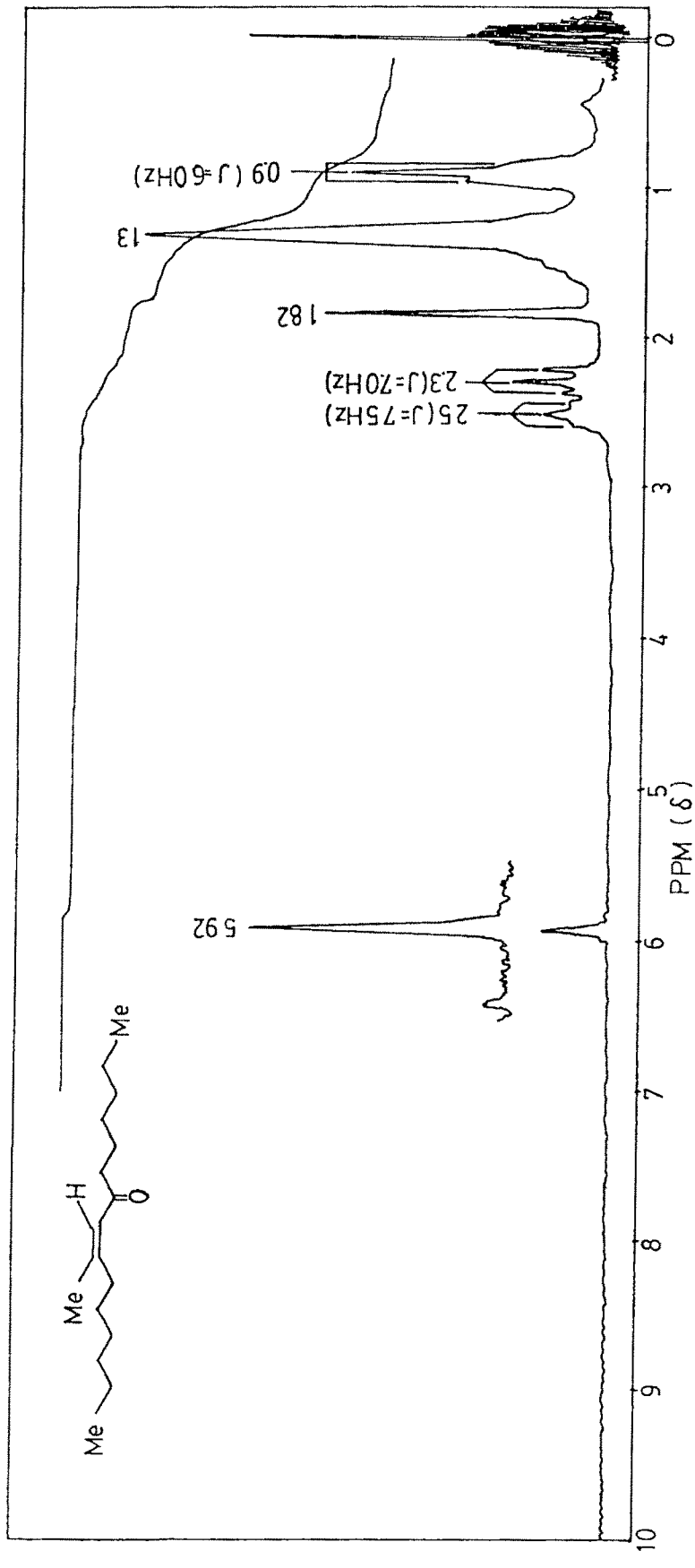



Fig. 8 - NMR spectrum of Z-9-Methyl-8-pentadecen-7-one

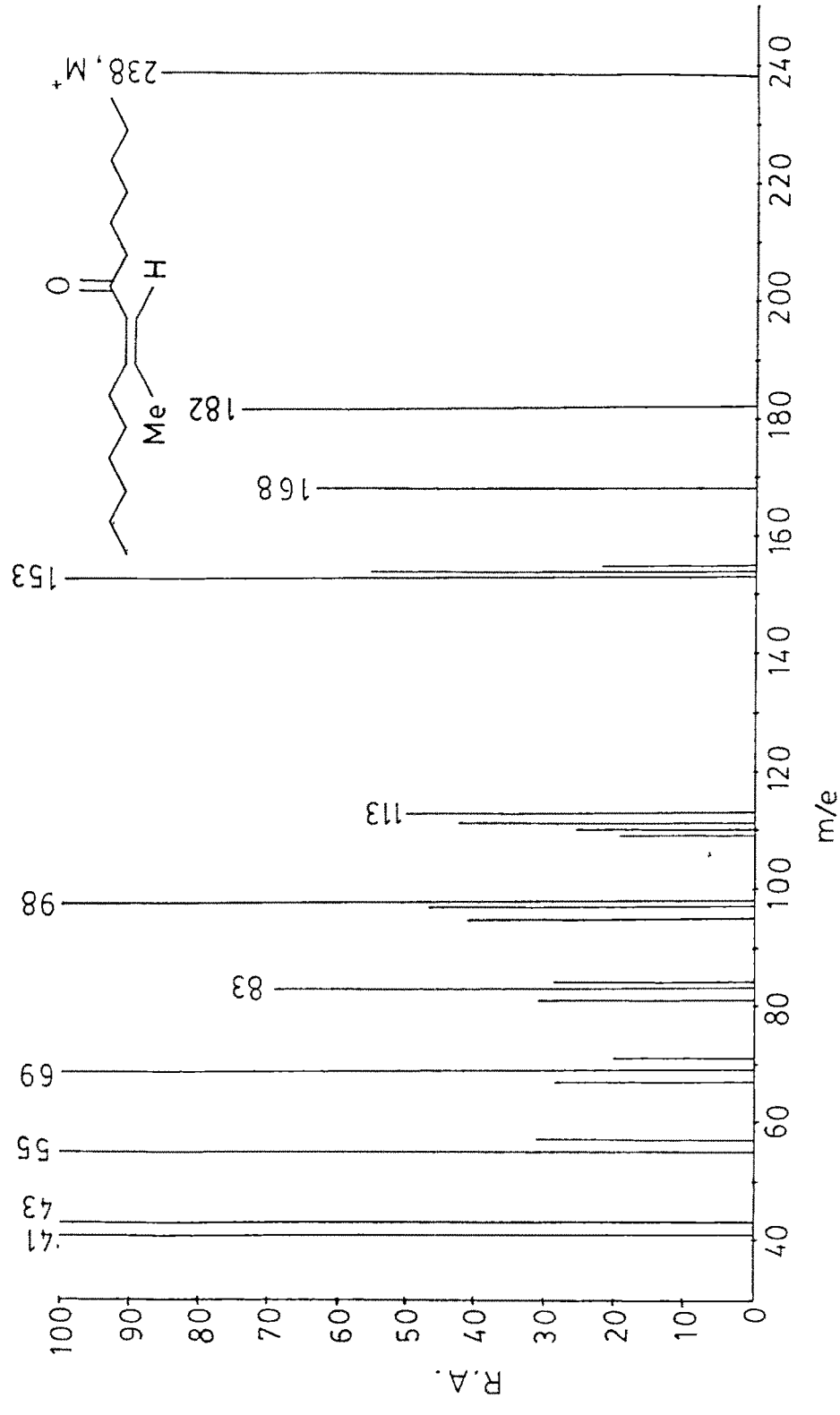



Fig. 9 - Mass spectrum of Z-9-Methyl-8-pentadecen-7-one (7)

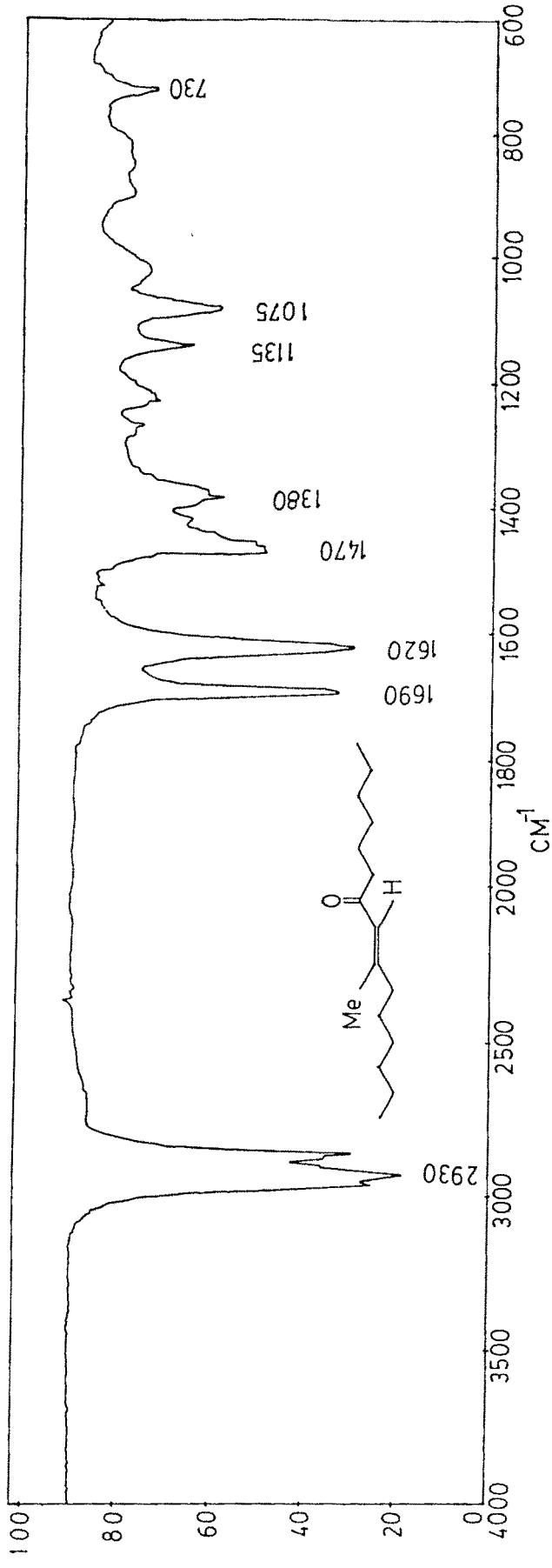



Fig. 10 - IR spectrum of E-9-Methyl-8-pentadecen-7-one

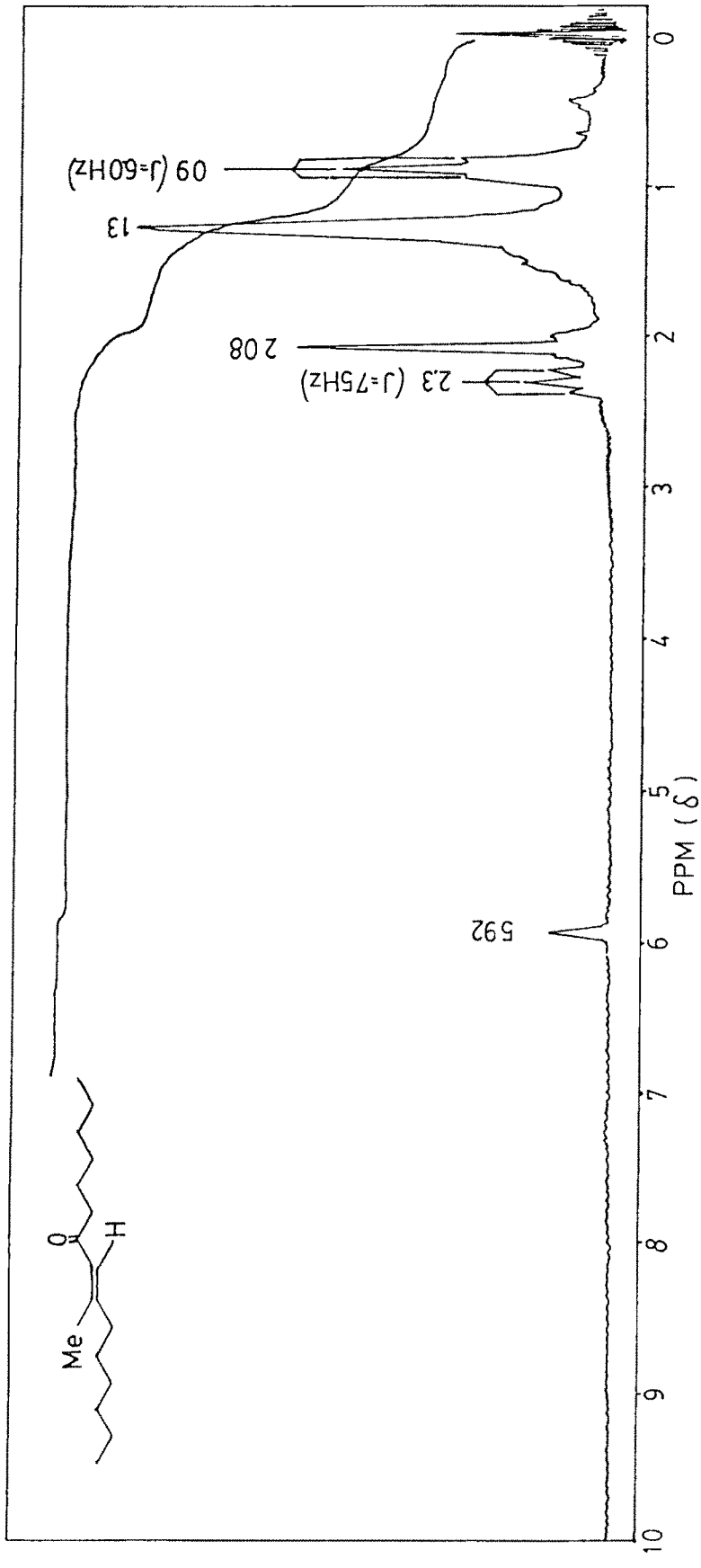



Fig. 11 - NMR spectrum of E-9-Methyl-8-pentadecen-7-one

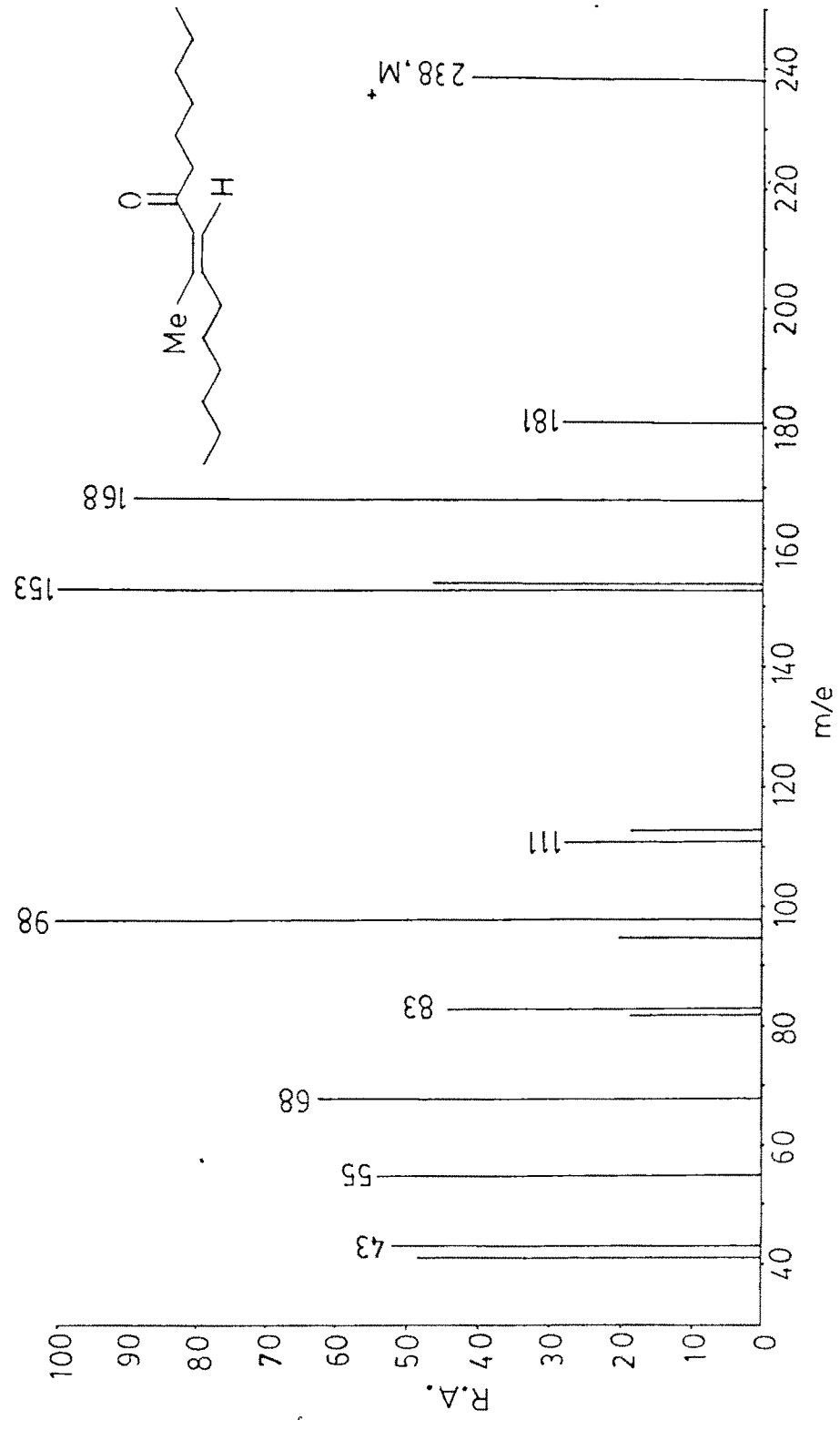



Fig. 12 - Mass spectrum of E-9-Methyl-8-pentadecen-7-one (8)

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