CHAPTER - II

SYNTHESES OF SANTALENES, SANTALOLS & ALLIED PRODUCTS

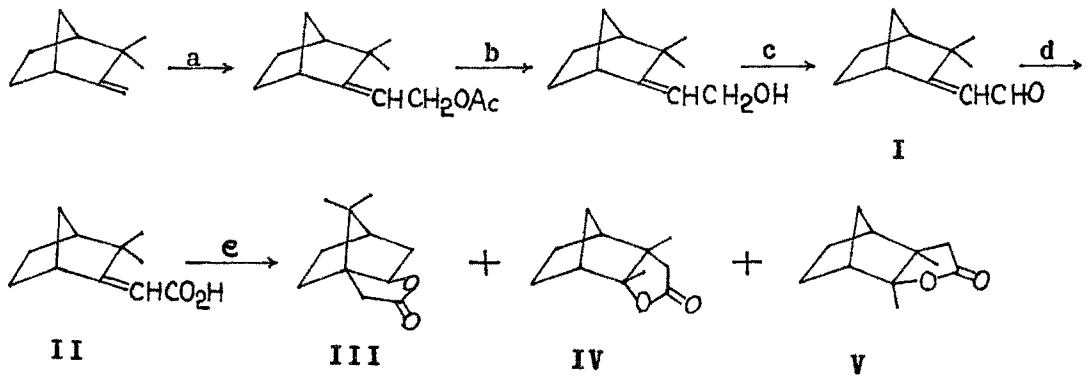
INTRODUCTION

Most of the characteristic fragrance of the valued East Indian sandalwood (Santalum album Linn.)oil is traditionally attributed to its high α-santalol and β-santalol contents (~90%). The minor constituents include sesquiterpene hydrocarbons (α-santalene, β-santalene, epi-β-santalene, α-curcumene, β-curcumene, and possibly β-farnesene) as well as minute amounts of relatively volatile substances: these are santene[1],borneol[1], and isovaleraldehyde[1]. Other minor constituents of the oil are tricyclo-eka-santalal[2], exo-norbicyclo-ekasantalal[3],and 11-methyl-7-oxa-tetracyclo[6.3.1.$0^{1,6}$ $0^{4,11}$] dodecane[2]. E.Demole et al[4] isolated and characterized 36 new constituents including 4 novel substances, viz.,santalone,4-methylcyclohexa-1,3-dien-1-yl methyl ketone, 5,6-dimethyl-5-norbornen-exo-2-ol, and (E)-5-(2,3-dimethyl-3-nortricyclyl)-pent-3-en-2one. The other constituents identified[4] were 1-furfurylpyrrole and 10 phenols accompanied by 17 mono-and sesquiterpene derivatives. Some of these new constituents were also synthesized[4].

In view of the increasing and continued importance of α- and β-santalols in the realm of odour, our objective was to evolve a commercially viable syntheses of these compounds.

9-Hydroxymethyl camphene(IX), prepared earlier by Vaughan[5]

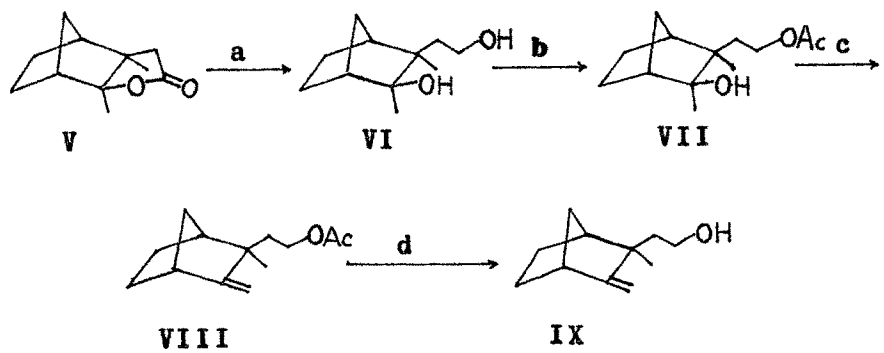
according to schemes given in Fig.1, appeared a suitable starting



Reagents: (a) $(CH_2O)_3$ + Ac_2O+AcOH (b) KOH/EtOH
(c) 8N CrO_3 in H_2SO_4-H_2O (d) Air (e) HCO_2H or CF_3CO_2H or H_2SO_4

Fig.1(a): LACTONIZATION OF CAMPHENE-8-CARBOXYLIC ACID(II)

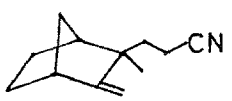
material for our syntheses of β-and α-santalols and related compounds for (a) IX can be readily and cheaply prepared from abundantly available camphene and (b) IX is suitably functionalized for further elaboration to either 9-cyanomethyl camphene(X)



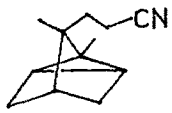
Reagents: (a) LAH/ether (b) Ac_2O/pyridine (c) $SOCl_2$/pyridine
(d) KOH/EtOH

Fig.1(b): DEGRADATION OF THE EXO-LACTONE(V)

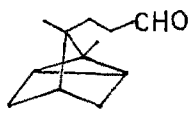
or 9-formyl camphene(XIII). 9-Cyanomethyl camphene(X) has been converted by Willis[6] in his stereospecific synthesis to (±)- β-santalol and its hydrogenated analogues, whereas the tricyclic analogue(XI) of 9-cyano compound(X) has been stereospecifically converted via the corresponding aldehyde(XII) into (±)- α-santalol by Corey[7].



X



XI



XII

In the light of above, if cyano compounds (X) and (XI) can successfully be synthesized(which in fact have been synthesized by us and form the subject matter of this Chapter) then, this would complete the syntheses of β- and α-santalols.

Besides this, another successful approach that has been followed by us for the synthesis of β-santalene(XVII) and its double bond isomer includes the addition of a C_3+C_1 chain (derived from acetone and CH_3I, respectively) to the C_{11} block (9-hydroxymethyl camphene, IX) as depicted in Fig.2. In above approach, it was thought that 9-hydroxymethyl camphene(IX)

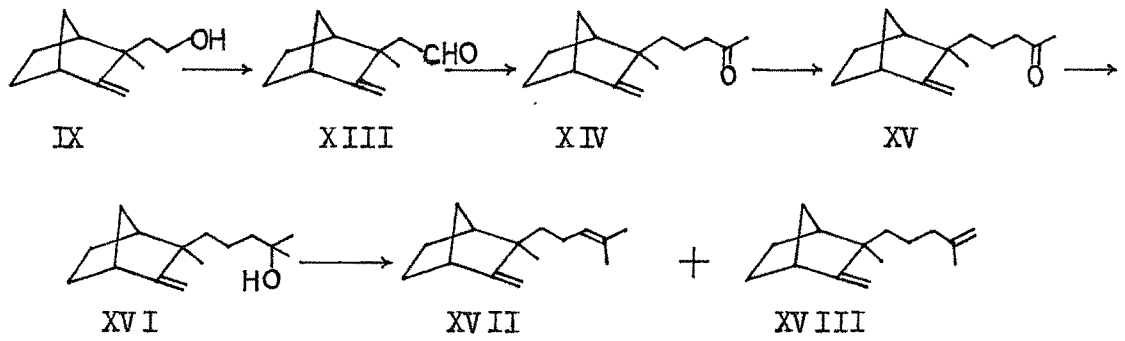
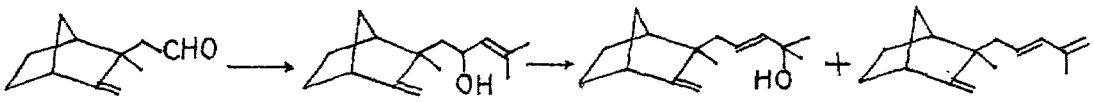


FIG.2: SYNTHESIS OF β-SANTALENE(XVII)

would undergo aldol condensation[8] with acetone to give α, β-unsaturated ketone(XIV) as a result of concomitant dehydration, which(XIV) then would be converted into a tertiary alcohol(XVI) (as shown in Fig.2). Dehydration of alcohol(XVI) would give β-santalene(XVII) and also, possibly, other double bond isomer (XVIII). In practice, this indeed was found to be the case.

In another possible approach, it was thought that if an allylic alcohol(XIX) can be obtained from 9-formyl camphene, then, by using one of the known methods[9(a-f)] for allylic deoxygenation, it should be possible to synthesize β-santalene.

However, in an attempt to make the allylic alcohol(XIX) by



XIII XIX XX XXI

carrying out Grignard reaction on 9-formyl camphene, we only isolated a tertiary alcohol(XX) and its dehydration product (XXI).

Now, we describe the details of steps of our syntheses under the subheads which represent the final product of that step.

8-FORMYL CAMPHENE(I)

Vaughan prepared[5] 8-formylcamphene in three steps(vide supra) in a 47% overall yield. We first aimed at (i) improving the yield of 8-formyl camphene and also (ii) cutting down the number of steps, if possible. The Vilsmeier formylation reaction[10] is well known for its simplicity, efficiency, and also excellent yields, hence we decided to apply the same on camphene.

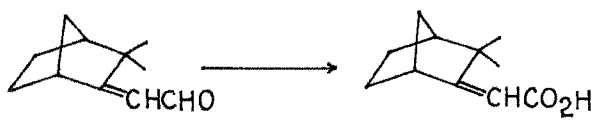
I

On careful literature survey it was found that Jutz and Muller, in 1967, reacted[11] camphene with the Vilsmeier reagent ($DMF+POCl_3$) and isolated 8-formylcamphene in 81% yield. When this reaction was carried out under the reaction conditions in which N,N-dimethylaniline had been formylated[cf 10(b)], the yield could be improved to 88%. The product from its spectral characteristics (IR,UV,PMR) was identical with those of Jutz and Muller[11] and Vaughan et al[5].

CAMPHENE-8-CARBOXYLIC ACID(II)

Camphene-8-carboxylic acid(II) was prepared[5] by Vaughan by exposure of 8-formylcamphene to air. Essentially the same

procedure was followed by us for preparing(II) in ~90% crude yield. However, we have found that 8-formyl camphene(I) undergoes this oxidation much faster when its ethereal solution is exposed than when it is exposed as such(with no solvent). The product was recrystallized from n-hexane(m.p. 122-124°; lit.[5] mp.122-124°, 85% yield). The product from its IR spectrum(1645, 1680 and 2500-2700 cm^{-1}), U.V absorption spectrum(λ_{max}^{EtOH} 235 nm, $\epsilon = 1.12 \times 10^4$) and PMR spectrum(viz. absence of aldehydic signal at ~9.7 ppm) was, once again, identical with that of Vaughan et al[5].



I II

LACTONIZATION OF CAMPHENE-8-CARBOXYLIC ACID

When camphene-8-carboxylic acid(II) is treated[5] with an acid, a lactone mixture consisting of III, IV and V is produced. The structures to these lactones have been delineated by Vaughan et al[5] by spectral and chemical degradation experiments. The composition of the lactone mixture depends[5] upon the particular acid used, the reaction temperature, and also the reaction time (TABLE 1).

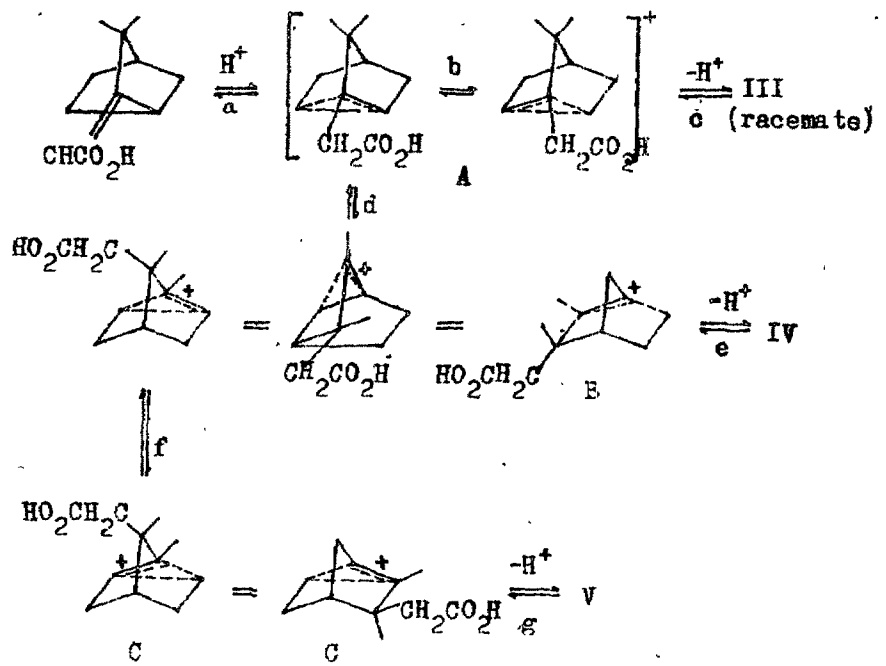
TABLE 1

LACTONES FROM CAMPHENE-8-CARBOXYLIC ACID

CONDITIONS	TIME	LACTONE III, %	LACTONE IV, %	LACTONE V,%
	1 hour	28.2	18.8	
	2 "	31.1	25.2	
90% HCOOH, 100°C	6 "	20.5	41.9	?
	4 days	09.9	73.1	?
	10 "	06.5	81.0	?
	14 "		84.5	15.5
	2 hour	09.0		
	6 "	12.3	01.7	
CF_3COOH, 25°C	16 "	23.8	03.2	
	2 days	50.0	09.4	
	6 "	46.4	42.8	
	15 "	26.4	73.6	
	25 "		100.0	Trace
CF_3CO_2H, 72°C	3.5 "		79.4	21.6
	0.5 hour		92.0	09.0
10% H_2SO_4 in HCOOH	3.0 "		57.0	43.0
	6.5 "		37.0	63.0
50% H_2SO_4, 150°C	0.5 "		47.0	53.0
	2.0 "		25.6	74.4
95% H_2SO_4, 0°C	6.0 "		11.0	89.0

Examination of Table 1 demonstrates that camphene-8-carboxylic acid(II) is first converted into lactone III, which is then transformed into the lactone IV with passage of time. Lactone V appears much later in the reaction sequence and is the only important product when sulphuric acid is present. Control experiments confirm[5] the reaction sequence II→III→IV→V. Protonation of acid II is a rate-determining step, which triggers the Wagner-Meerwein rearrangement and accompanying 6,2-hydride shift, which culminate in the formation of lactone III.

LACTIONIZATION-REARRANGEMENTS



STEPS : a, protonation and bridging; b, 2,6-hydride shift (+A→+A); c, ring closure and deprotonation (A→III); d, exo-metnyl snift (A→B); e, ring closure and deprotonation (B→IV); f, 2,6-hydride shift (B→C); g, ring closure and deprotonation (C→V)

Since, only racemic products(lactones) are obtained, and since rate control appears to be vested in protonation of II, it is assumed that reaction b is a relatively rapid one, reaction c being slower than b but faster than a, i.e., that lactone III is the primary, kinetically controlled product.

Lactone IV can be formed from II or from III and so it is postulated[5] that, under the reaction conditions used, IV is thermodynamically more stable than III, while the energy barrier in reactions d and e is higher than that in reaction a-c. Otherwise, IV would have formed more readily than III.

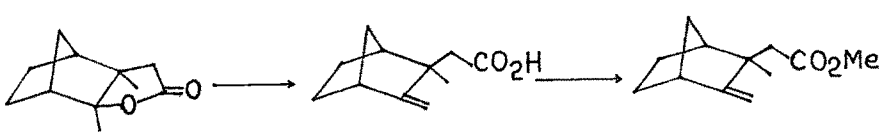
Since V does not revert into other members of the series, it is assumed[5] that, under conditions leading to its formation, V is the most stable lactone and that the energy barrier in reactions f and g is still higher than that in reactions d and e, i.e., the thermodynamic stabilities of the acid(II) and the lactones (III-V) are in the order II < III < IV < V and the energy barriers for the conversions are in the order II → III < III → IV < IV-V.

When we repeated this work to make the lactones(IV and V), our observations were at variance with those of Vaughan et al[5]. Though these authors[5] do not specify the concentration of sulphuric acid in terms of w/w or w/v, we found that when the reaction is carried out at 0^{o} for 6 hours using 95%(w/v) sulphuric acid the ratio of endo- to exo- lactone is 1:3,

whereas with 95%(w/w) H_2SO_4 this changes to 1:12; the reported[5] ratio of endo- to exo- lactone under unspecified concentration is 1:8. It was further observed that when the reaction is continued for 10 hours, endo- to exo- lactone ratio is 1:16. On further increase in the reaction time, this ratio does not change.

CLEAVAGE OF EXO-LACTONE(V)

Now, with an objective to transform the exo-lactone(V) into 9-hydroxymethyl camphene and also cutting down the number of steps in Vaughan's degradation procedure[5], we first sought to open the lactone ring with diethylene glycol-sodium hydroxide[12] because of its dehydrative cleavage action. The product, after being esterified with diazomethane and purified by column chromatography(SiO_2/II, eluted with benzene, tlc monitoring), analyzed for $C_{12}H_{18}O_2$ (M^+= m/e 194). Its IR spectrum (Fig.3) (1740 cm^{-1}, CO_2Me; 3070, 1660 and 888 cm^{-1}, characteristic of exomethylene grouping) and PMR spectrum (Fig.4) (>C=CH_2:2s,2H, 4.70 and 4.44 ppm; CO_2Me: s, 3H, 3.56 ppm; a quaternary methyl: s, 3H, 1.13 ppm) showed it to be the desired compound (XXII).



V XXII

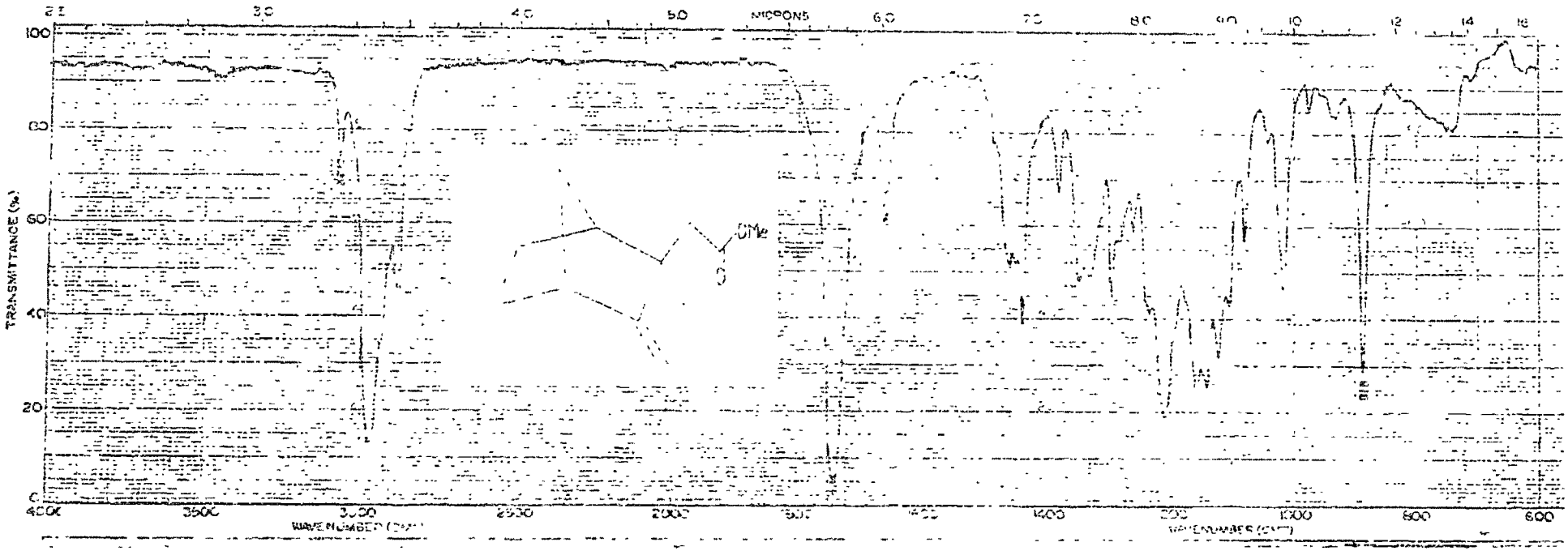


FIG.3: IR SPECTRUM OF 9-CARBOMETHOXY CAMPHENE(XXII)

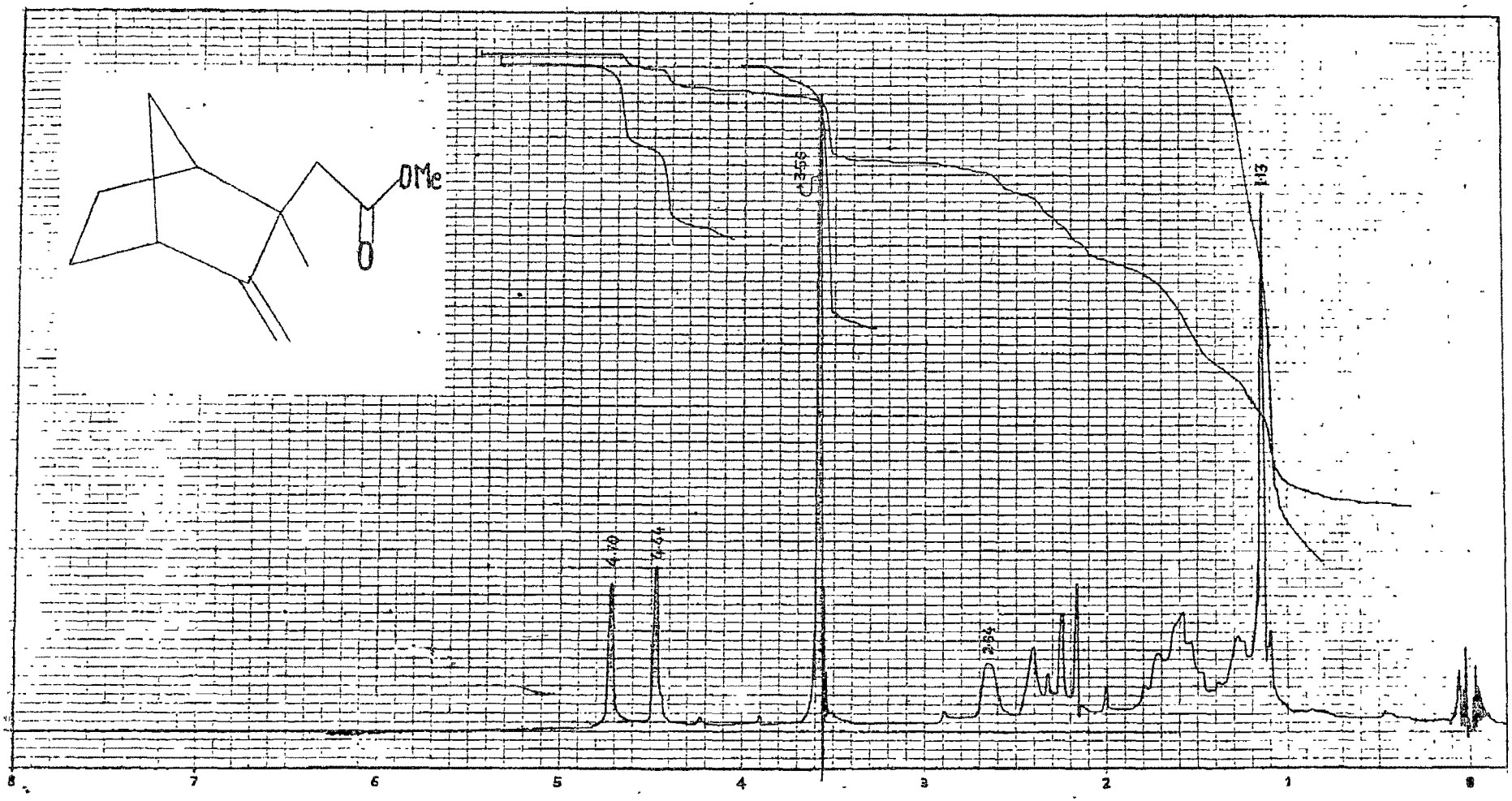


FIG.4: PMR SPECTRUM OF 9-CARBOMETHOXY CAMPHENE(XXII)

Because the overall yield of the above process (V→XXII) was only 40%, this procedure of cleaving the lactone was abandoned. p-Toluenesulphonic acid and alcohol in benzene at reflux temperature is known[6,13] to cleave δ-lactones. We have tried this on our the γ-lactone(V) but with no success. This failure could probably be due to the very strong thermodynamic stability of γ-lactones. We finally followed Vaughan's lithium aluminum hydride cleavage method[5] to get (VI).

V VI

We carried out LAH reduction in THF instead of ether[5]. The reaction mixture was worked up by destroying the excess of LAH with THF aqueous (1:1, 15 ml being used for 1 g of LAH used) followed by diluting with water and extracting with chloroform. The product,crystallized from n-hexane(m.p. 98-101°; lit[5] m.p. 97-100°C),was, from its IR spectrum(3240 cm^{-1}, OH), PMR spectrum ($\underline{CH_2}OH$: m, 2H, 3.68 ppm) and mass spectrum (M^+=m/e 184), identical with the diol obtained by Vaughan et al[5].

To keep the 9-hydroxymethyl group intact during the next step of dehydration, it is important to protect this hydroxyl function. This was accomplished by acetylation given below:

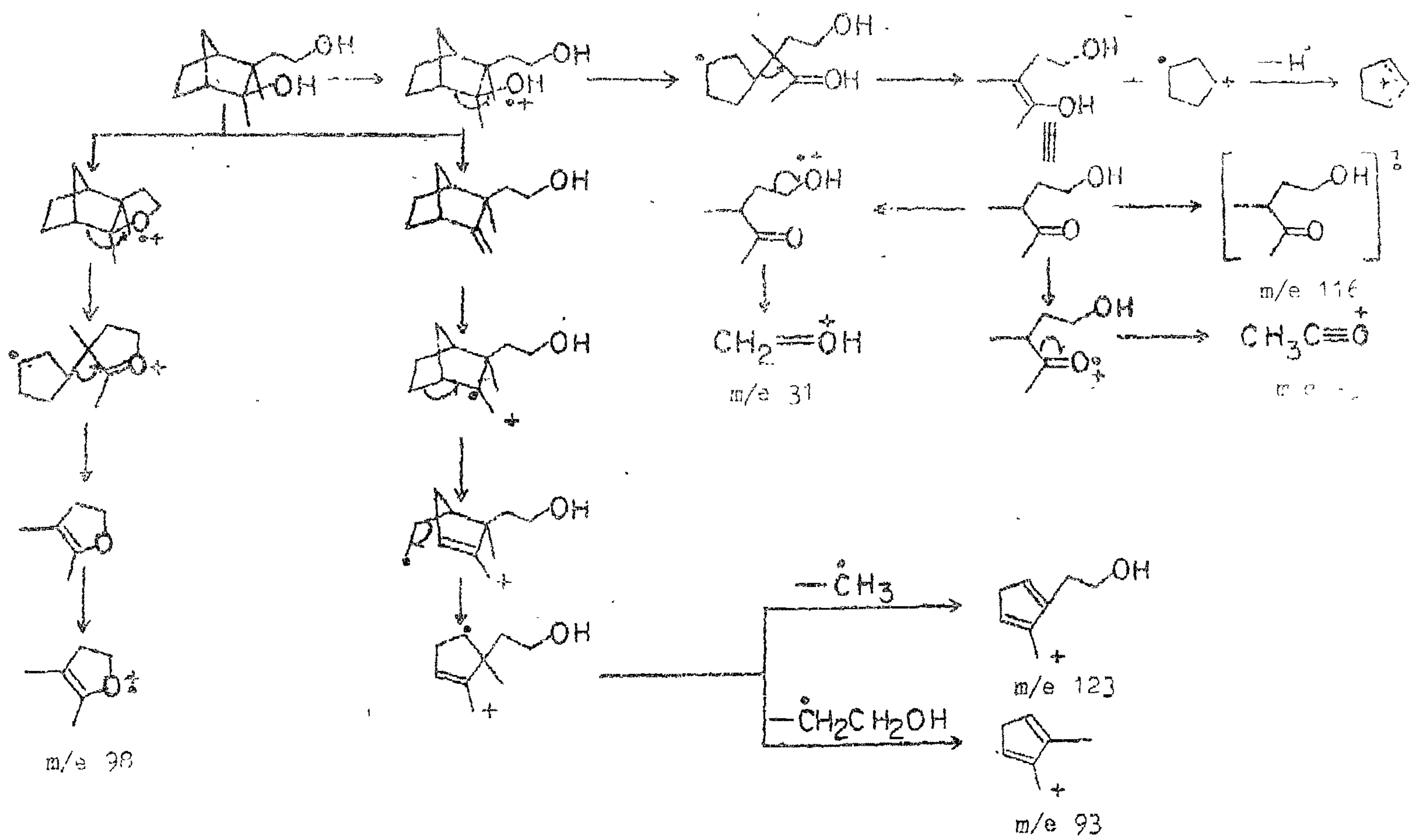
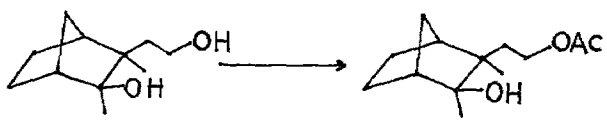


CHART 1:MASS SPECTRAL FRAGMENTATION PATTERN OF THE DIOL(VI)

THE MONOACETATE(VII)

The diol, which has a primary and a tertiary hydroxyl group, was next converted into a monoacetate(VII) using acetic anhydride-pyridine in 98% yield. The monoacetate was, from its IR spectrum(3510 cm^{-1}, OH; 1725 cm^{-1}, $OCOCH_3$) and PMR spectrum ($\underline{CH_2}OAc$: m, 2H, 4.05 ppm; $OC\underline{OCH_3}$:s, 3H,1.96 ppm), readily characterized as VII.



VI VII

THE OLEFIN-ACETATE(VIII)

Though number of reagents are known for dehydration of a tertiary alcohol(e.g.alumina[14], boric acid[15], $BF_3.Et_2O$[16], N-bromoacetamide-pyridine-SO_2[17], diketene[18],DMSO[19], florisil[20], $FeCl_3$ on SiO_2[21], HBr,mesylchloride-SO_2[22], naphthalene-β-sulphonic acid[23], oxalic acid[24], phenylisocyanate[25], $POCl_3$-pyridine[26], $SOCl_2$-pyridine[27], $KHSO_4$[28], p-toluene sulphonic acid[29] and p-tosyl-chloride[30]) but in our case acidic reagents cannot be used as these may lead to rearrangement products arising from a carbonium ion of the type depicted below:

Hence, we looked for only those reagents which are used in neutral or slightly basic conditions.

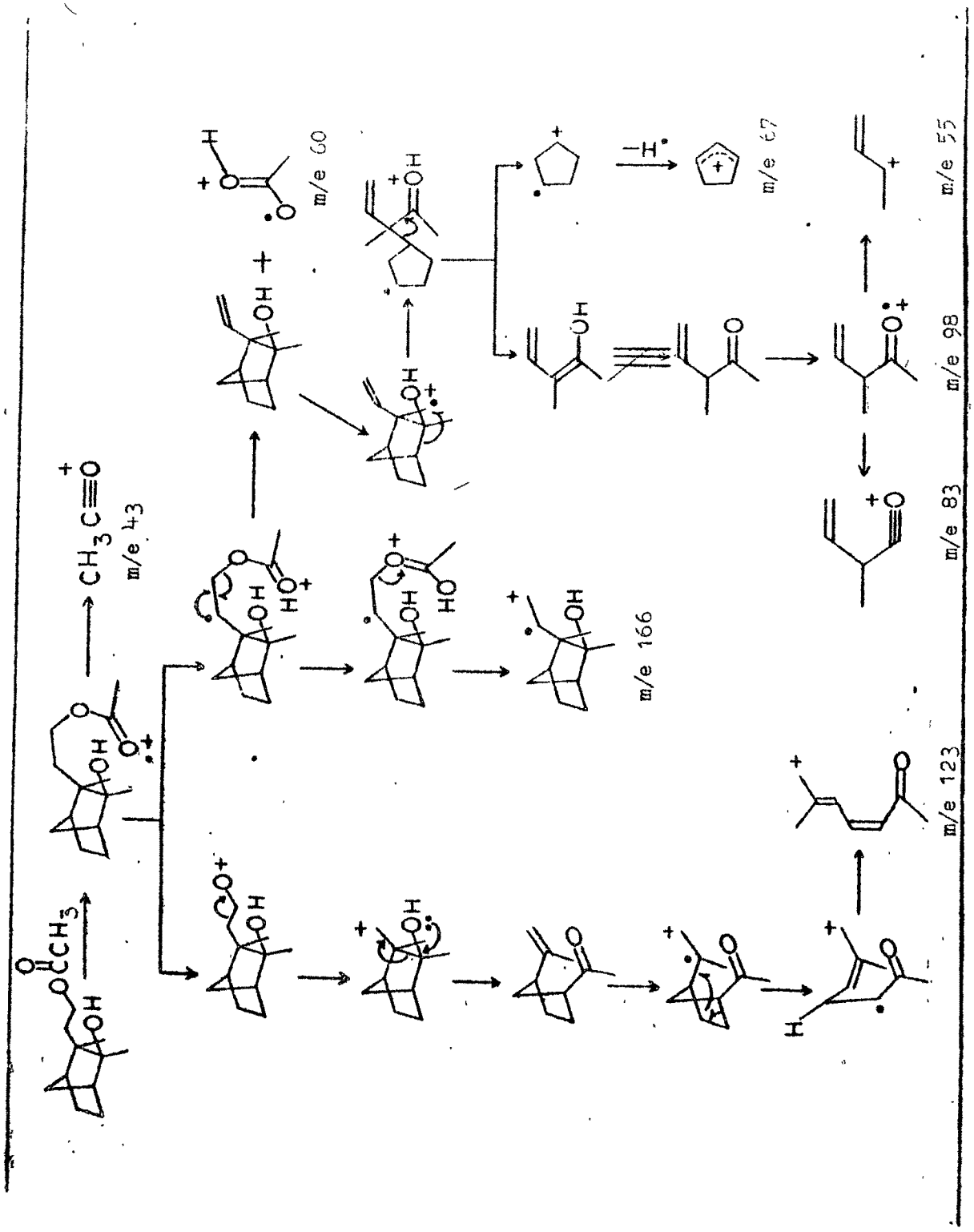


CHART 2: MASS SPECTRAL FRAGMENTATION OF THE MONO-ACETATE(VII)

The monoacetate(VII), on refluxing with $POCl_3$-pyridine[26] for 5 hours, gave, after usual work up, a crude product from which only ~40% material could be distilled(rest was a residue which was not investigated further). The distillate, however, was, from its PMR, exclusively the required olefin acetate(VIII).

The monoacetate, when adsorbed on alumina[14] impregnated with pyridine(2%) followed by slow vacuum distillation (in bulb[31]), yielded a distillate which consisted of ~30% of the desired olefin acetate(VIII) and ~70% of an unidentified product.

Dehydration with $FeCl_3/SiO_2$[21] gave, as expected, a complex mixture of rearrangement products(tlc, pmr), along with little of the required 9-acetoxymethyl camphene(VIII).

Dehydration with thionyl chloride-pyridine[27] at temperatures of 25°, 0°, and -5°C was unsatisfactory in view of the complexity of the product mixture (tlc). Because the product mixture gave a +ve Beilstein test for chlorine containing components, it was thought reasonable to go for still lower temperatures and also to use excess of pyridine. Finally, with a large excess of pyridine and at temperatures of -20° to -15° for the first two hours and then at ~30° for ~16 hours, this reagent worked satisfactorily. The product was purified by column chromatography(SiO_2/II, eluted with benzene, tlc monitoring) and was, thus, obtained in ~80% yield.

VII VIII

The structure(VIII) for the olefin-acetate was confirmed from its IR spectrum (3060,1660 and 880 cm^{-1}—characteristic of exocyclic methylene grouping) and PMR spectrum($>C=\underline{CH_2}$: 2s,2H, 4.74 and 4.47 ppm).

THE OLEFIN-ALCOHOL(IX):

Treatment of the olefin-acetate(VIII) with 10% KOH in ethanol gave 9-hydroxymethylcamphene(IX) in almost quantitative yield. The product was characterized as (IX) from its IR spectrum (3630 cm^{-1},OH; 3075,1660 and 885 cm^{-1}—exocyclic methylene group), PMR spectrum ($>C=\underline{CH_2}$: 2s, 2H, 4.70 and 4.44 ppm; $-CH_2\underline{CH_2}OH$: t, 2H, 3.60 ppm) and Mass spectrum (M^+= m/e 166).

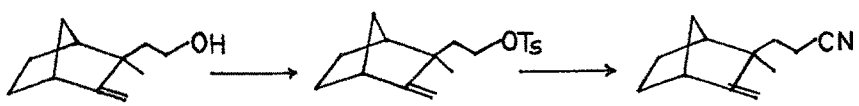
VIII IX

After removing ethanol from the reaction mixture, it is necessary to neutralize it very carefully with dilute HCl in order to avoid complications arising from the carbonium ion(vide supra) resulting from protonation of the exo-cyclic double bond at lower pH values. In fact, in one of our experiments, when the reaction mixture was acidified to pH-5, only rearrangement products(not investigated) were obtained.

Having prepared the 9-hydroxymethyl camphene, the problem of converting it into 9-cyanomethyl camphene(X) and its tricyclic analogue(XI) was taken up first. Also, having earlier faced the problem of rearrangement under acidic conditions, we were always on a look out for either neutral or basic reaction conditions.

9-CYANOMETHYL CAMPHENE(X)

9-Cyanomethyl camphene was readily prepared from 9-hydroxy methyl camphene (IX) by treating[32] the tosylate(XXII^{A}) from IX with NaCN in dimethyl formamide at 100°C for ~5 hours in 95% overall yield. The product from its IR spectrum (Fig.5)



IX XXII A X

(2250 cm^{-1}, -C≡N; 3070, 1660 and 885 cm^{-1}, >C=CH$_2$), PMR spectrum (Fig 6) (>C=CH$_2$: 2s,2H, 4.80 and 4.48 ppm; -CH$_2$CH$_2$CN:

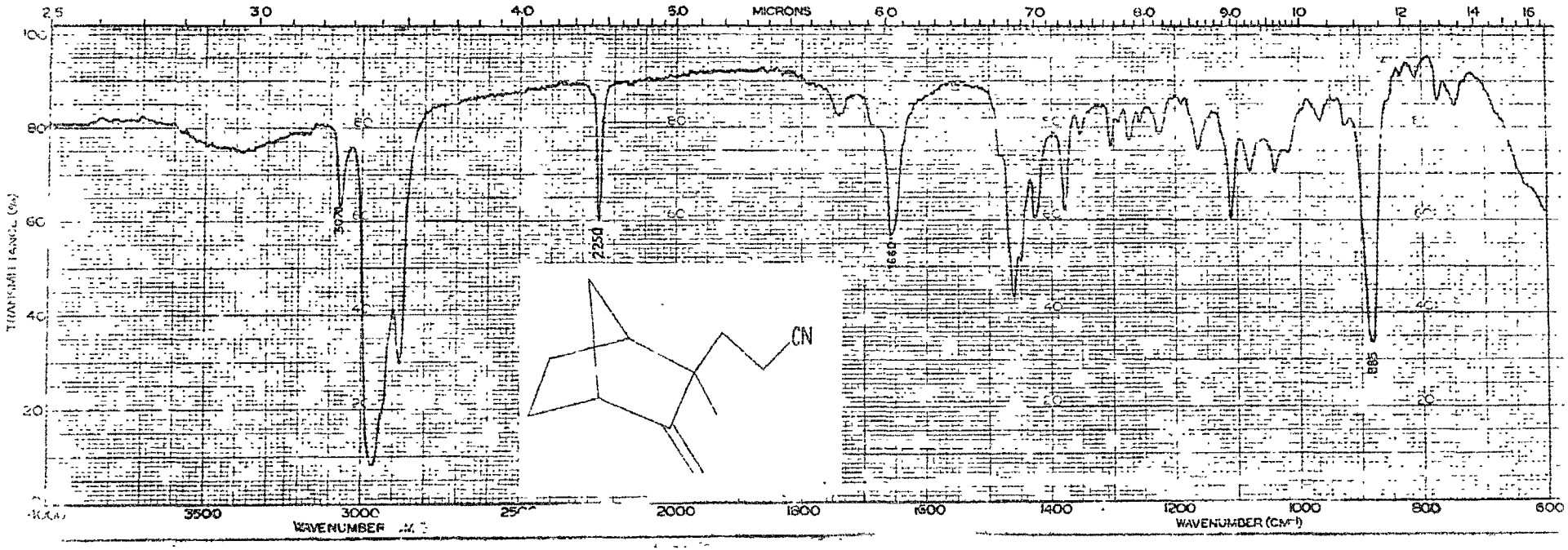


FIG.5: IR SPECTRUM OF 9-CYANOMETHYL CAMPHENE(X)

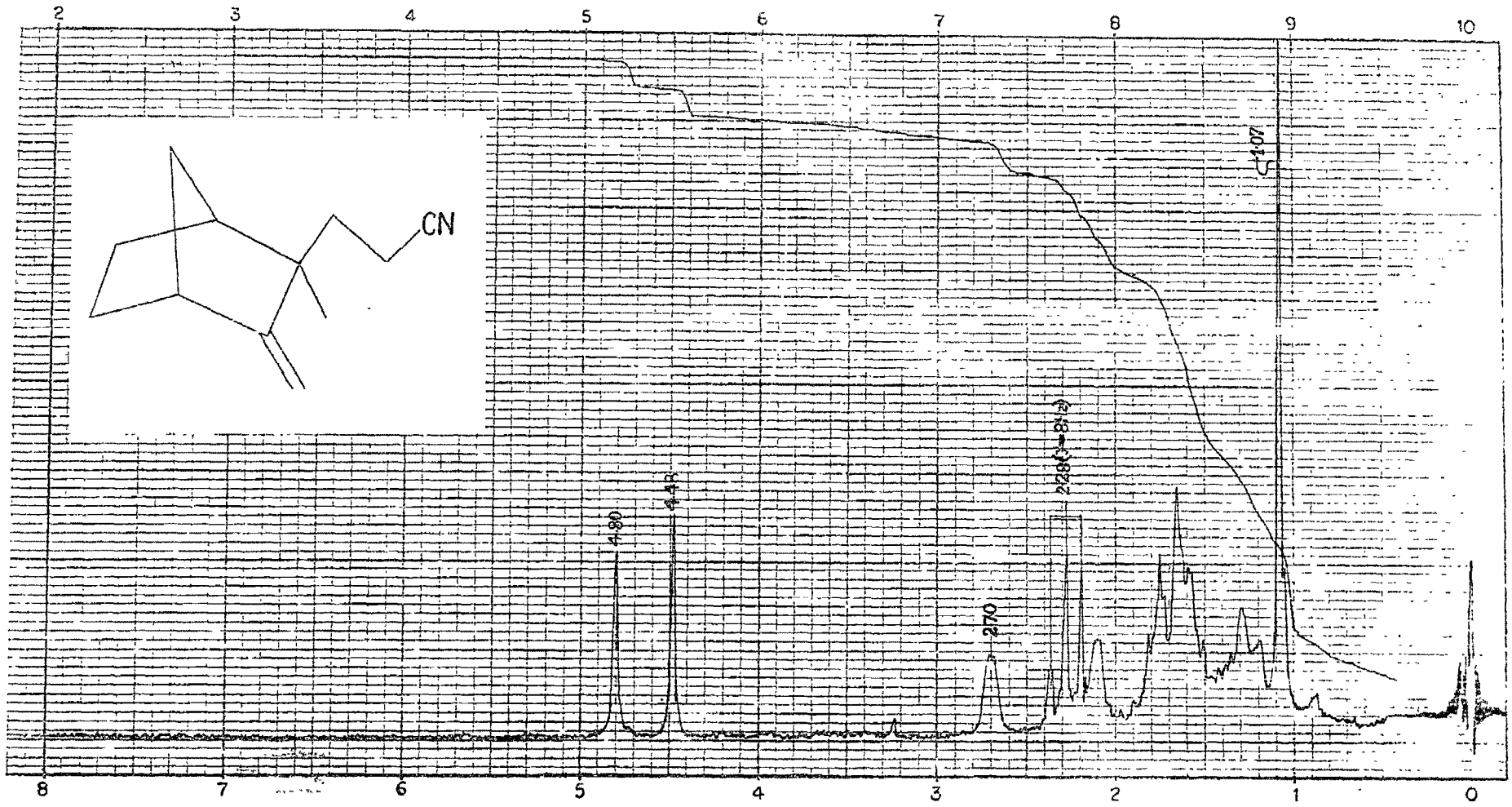
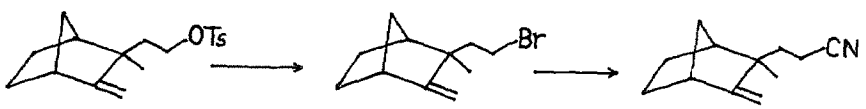


FIG.6: PMR SPECTRUM OF 9-CYANOMETHYL CAMPHENE(X)

t, 2H, 2.28 ppm) and Mass spectrum (M^+= m/e 175) was readily characterized as (X).

The nitrile (X) could also be prepared by treating 9-bromomethyl camphene with NaCN in DMSO at ~100° for 5 hours. 9-Bromomethyl camphene was readily obtainable from the tosylate (XXIIA) by reacting it with NaBr in either 2-butanone or DMSO in ~85 and ~95% yields respectively. The bromide (XXIII) could readily be identified from its



XXIIA XXIII X

PMR spectrum (Fig 7) ($-CH_2\underline{CH_2}Br$:t, 2H, 3.33 ppm) and Mass spectrum (M^+ = m/e 229).

THE TRICYCLIC NITRILE(XI)

The nitrile(X) on treatment with H_3PO_4-dioxan(details given in the following chapter) at reflux temperature for 30 hours yields a mixture comprising 3 components having retention times (in seconds) 186(19.35%), 228(34.4%) and 247(46.25%) in its gas chromatogram.

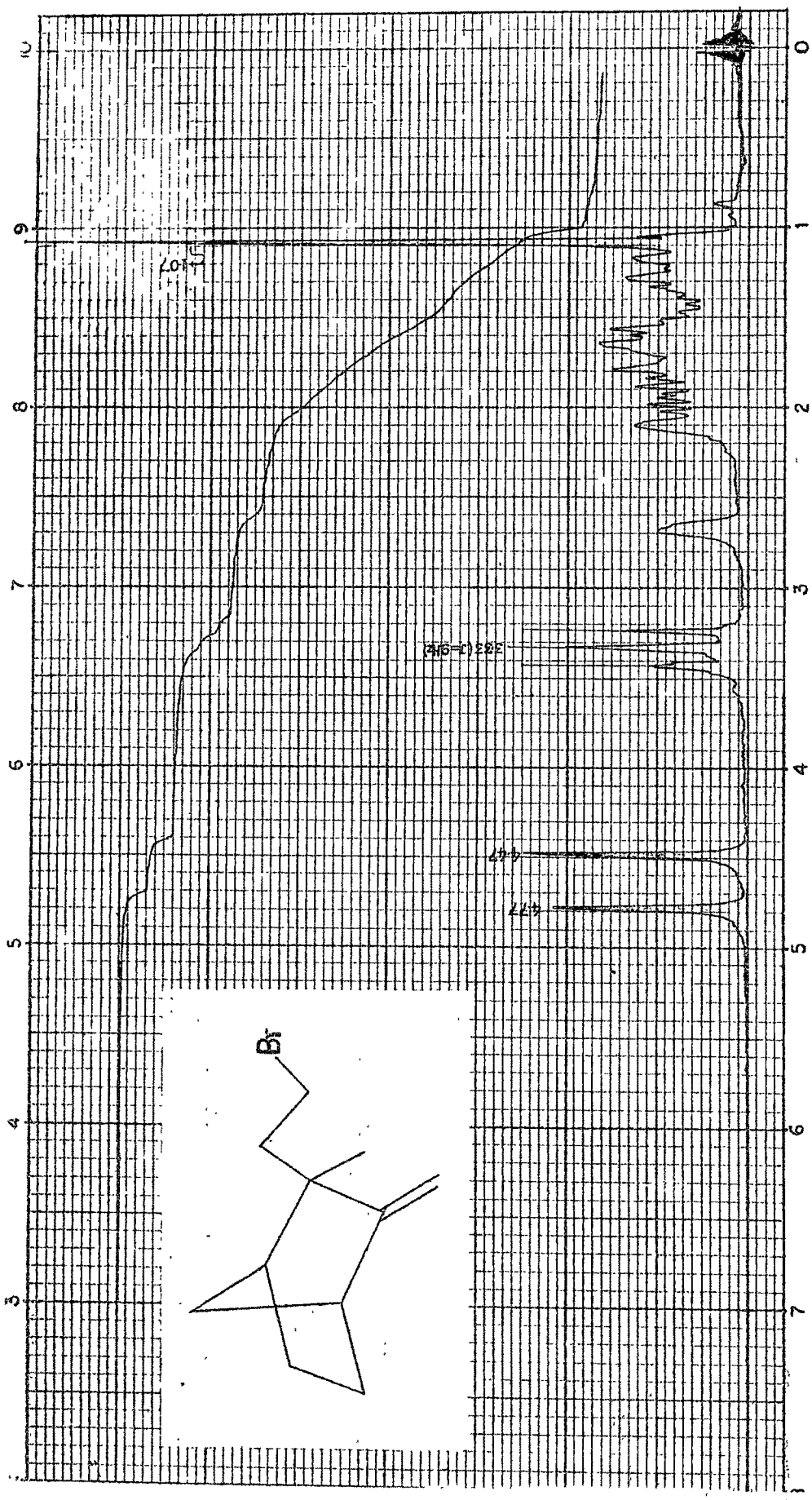
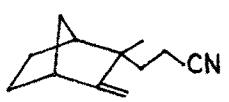


FIG.7 : PMR SPECTRUM OF 9-BROMOMETHYL CAMPHENE(XXIII)

The compound having retention time 247 seconds was easily characterized as the starting nitrile(X) by (a) coinjection of starting olefin nitrile(X) and the reaction mixture in glc and (b) comparing the PMR spectra of mixture and the starting material.

The compound of retention time 186 seconds was readily isolated in a state of purity by chromatography on $AgNO_3$ impregnated SiO_2/II(eluted with benzene) and characterized as the desired nitrile(XI) from its IR spectrum (Fig. 8) (absence of 880 cm^{-1} hand and appearance of strong absorption at 2250 cm^{-1} due to -CN group) and PMR spectrum (Fig.9) (disappearance of exocyclic methylene protons at 4.80 and 4.48 ppm and also emergence of a quaternary methyl signal at 0.85 ppm).

The third component of retention time 228 seconds, in its PMR spectrum displayed a quaternary methyl signal at 1.11 ppm; this value is 0.04 ppm higher than that for quaternary methyl in olefin nitrile (X). The fact that no skeletal rearrangement has taken place is revealed by its PMR spectrum (Fig 10) in which the bridge head protons at 2.70 and 2.10 ppm and the exocyclic methylene protons at 4.76 and 4.50 ppm remain unchanged. Because <u>exo</u>methyls appear 0.03 ppm down filed as compared to <u>endo</u> methyls(compare β-santalene and epi-β-santalene)[33], this compound must be as depicted in (XXIV).



XXIV

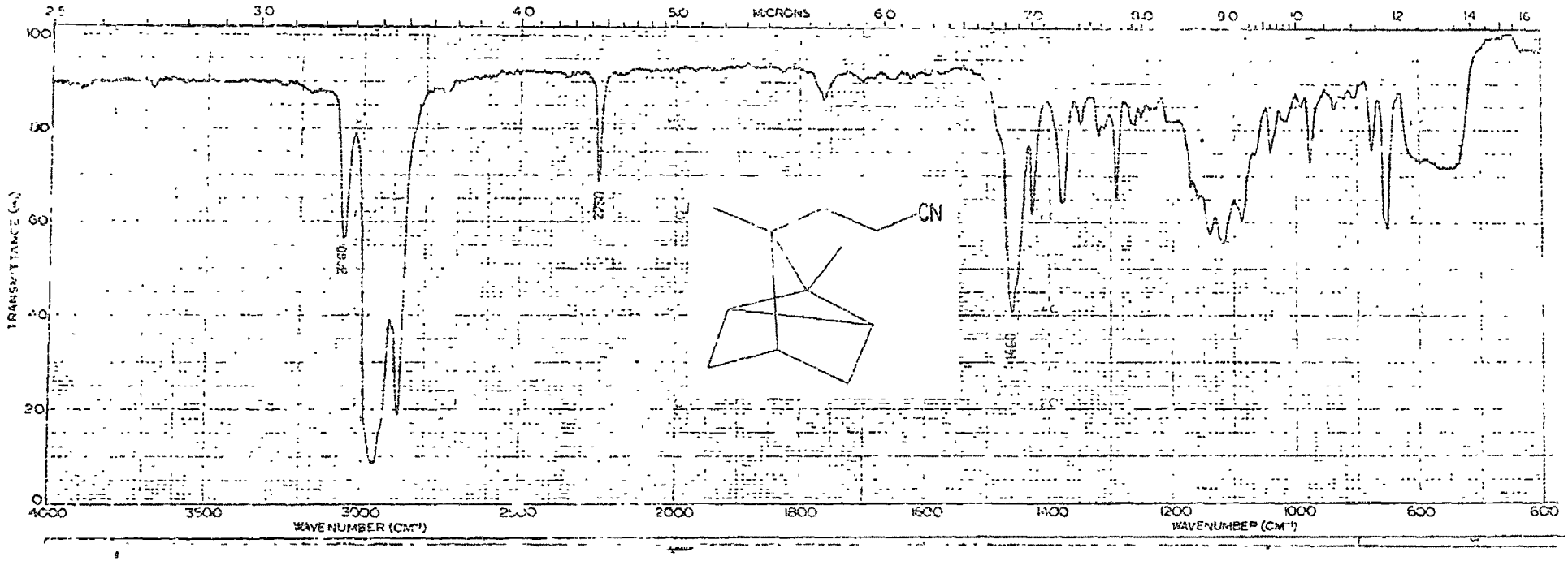


FIG.8: IR SPECTRUM OF THE TRICYCLIC NITRILE(XI)

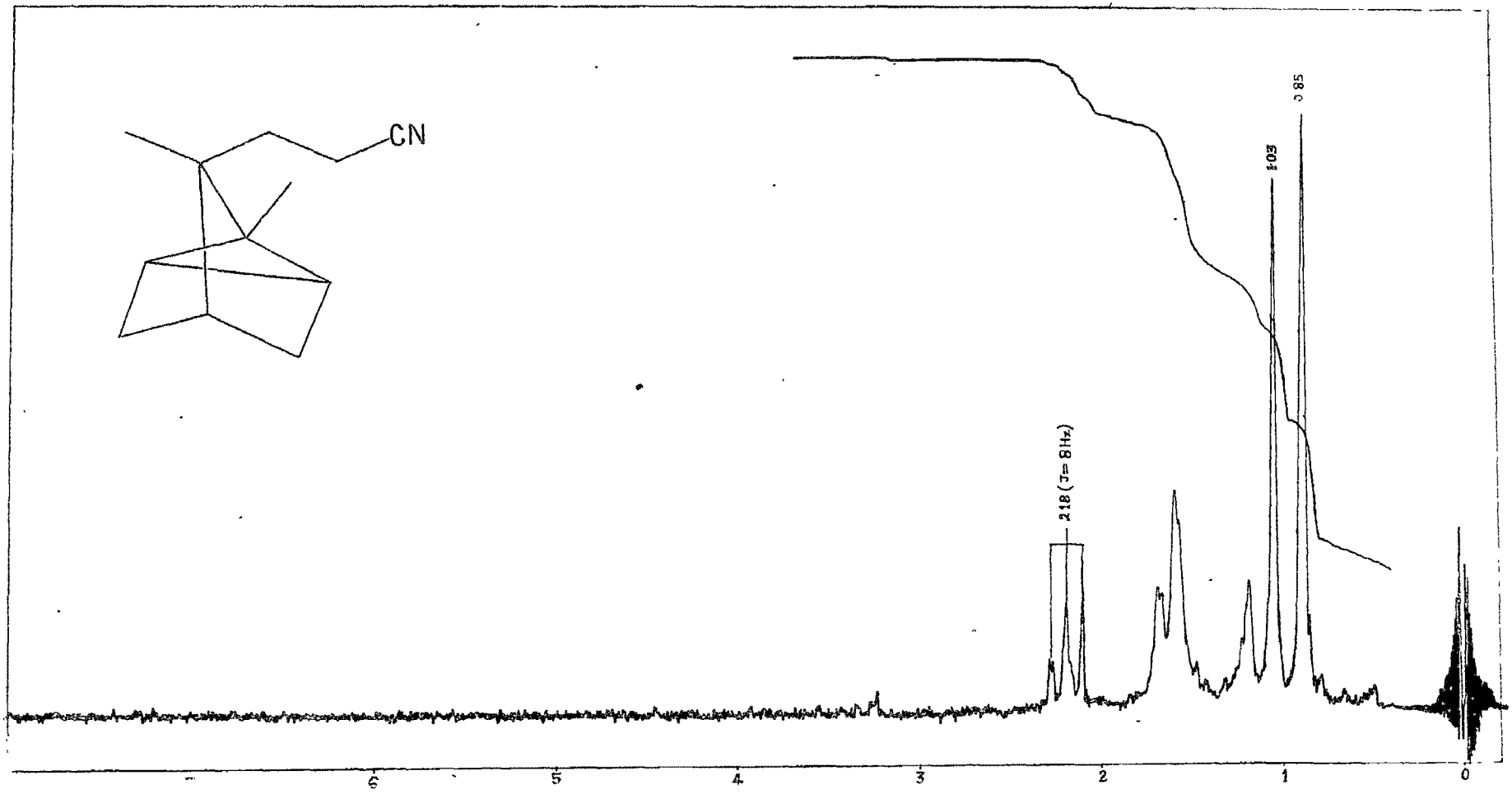


FIG.9: PMR SPECTRUM OF THE TRICYCLIC NITRILE(XI)

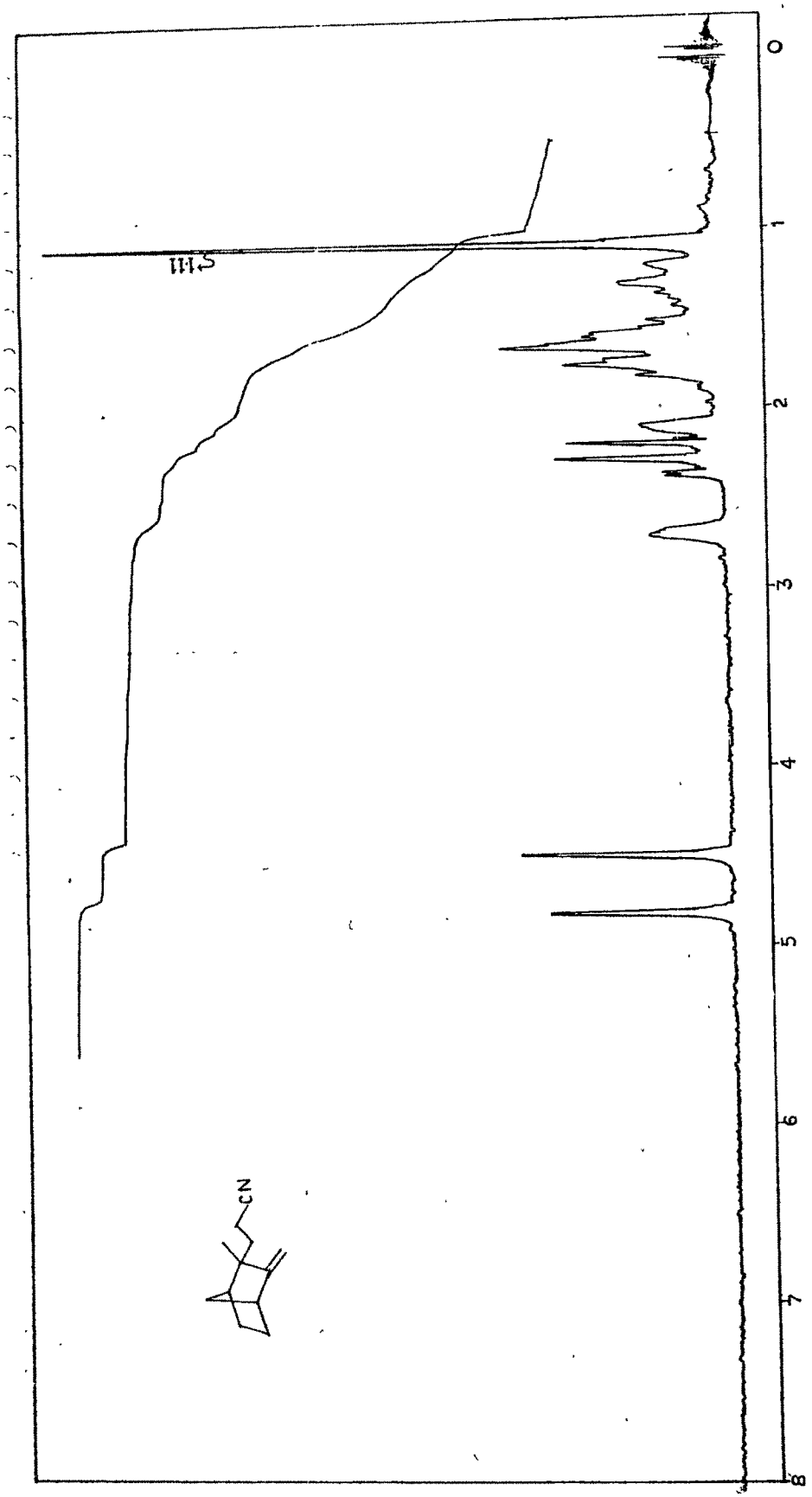


FIG.10: PMR SPECTRUM OF 10-CYANOMETHYL CAMPHENE(XXIV)

A mechanism leading to the formation of (XXIV) from (X) has been proposed in the following chapter.

β-SANTALENE AND ITS DOUBLE BOND ISOMER

Now, the objective was to synthesize β-santalene on the lines depicted in Fig.2. The additional 4 carbon chain has been added in a (3+1) manner onto the C_{11} unit of 9-hydroxymethyl camphene. Here, the C_3 unit is derived from acetone and the C_1 unit from methyl iodide.

THE OLEFIN-ALDEHYDE(XIII)

Though a number of reagents (e.g.,Sarret reagent[34], Cornforth reagent[35], CrO_3-dimethyl formamide[36], and dimethyl sulphoxide[37]) are known for oxidizing a primary alcohol to the corresponding aldehyde, we have been interested particularly in using pyridinium chlorochromate[38] in view of (i) its easy preparation[38] in quantitative yield, (ii) its neutral behaviour and (iii). the excellent yields of the products. Pyridinium chlorochromate oxidation of 9-hydroxymethyl camphene in dichloromethane at ~30°C for 2 hours furnished a product in ~97% yield, which was, from its IR spectrum (Fig.11)(1730 cm^{-1}, -CHO) and PMR spectrum (Fig.12)(-CH_2C<u>H</u>O:t,1H,9.68 ppm), the

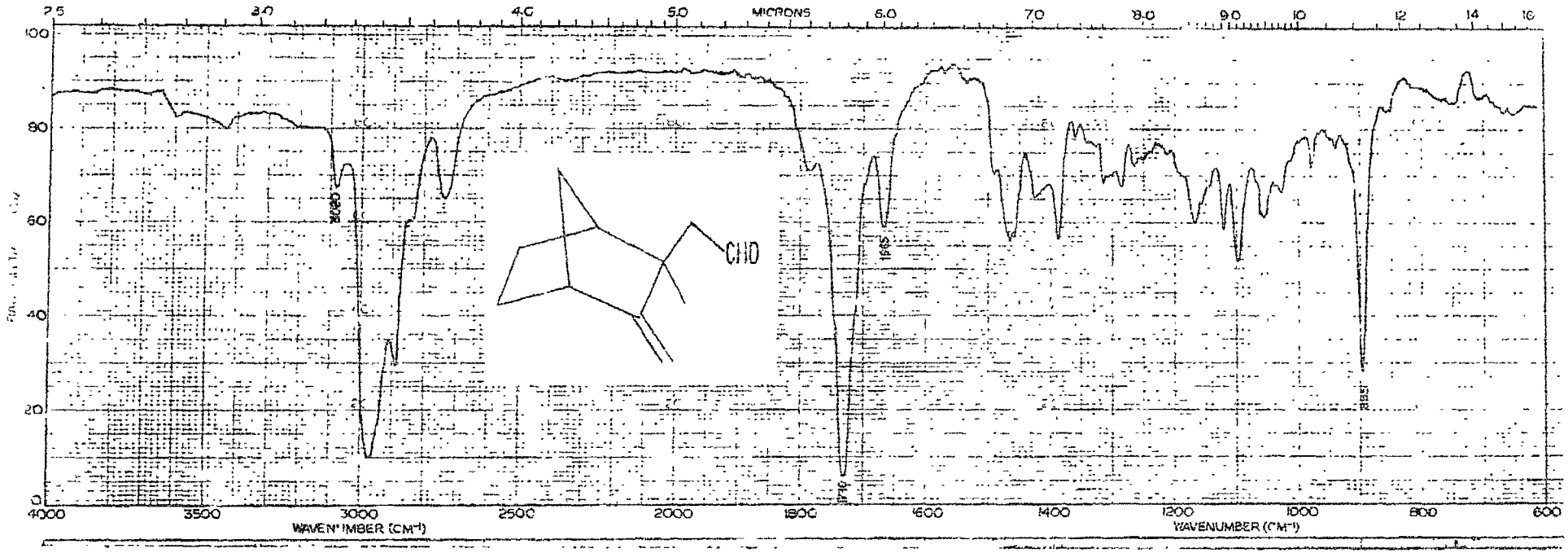


FIG. 11: IR SPECTRUM OF 9-FORMYL CAMPHENE(XIII)

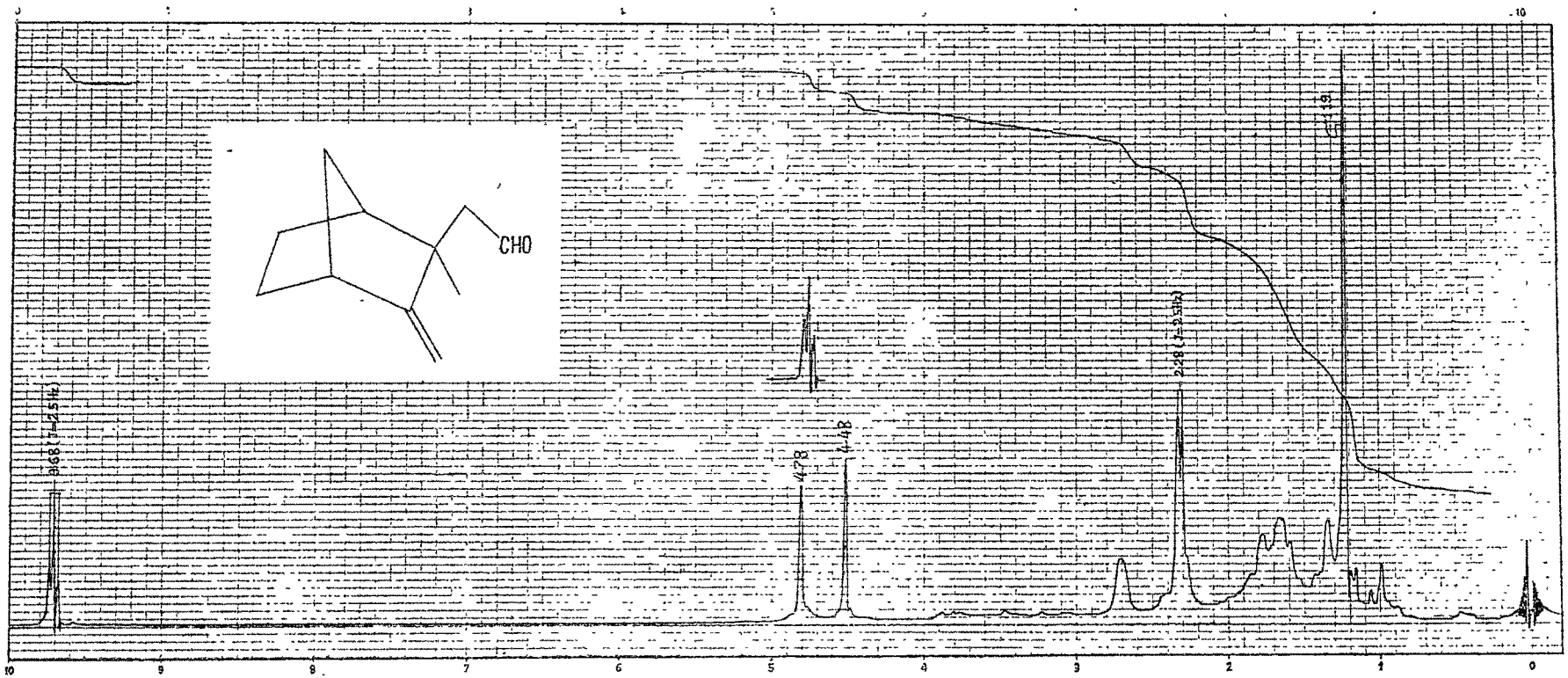
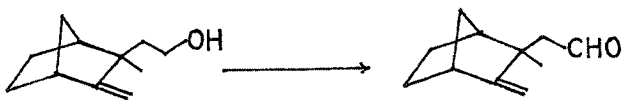


FIG.12: PMR SPECTRUM OF 9-FORMYL CAMPHENE(XIII)

desired aldehyde(XIII).



IX XIII

THE α-, β-UNSATURATED KETONE(XIV)

Aldol condensation[8] of aldehydes with ketones is a generally low yielding and somewhat complex reaction. Under the alkaline conditions in which it is carried out, it gives rise to some side products. Under suitable conditions, the extent of the side products can be minimised[8] and the yield of the desired product increased.

When the aldehyde(XIII) was added in several portions over a period of 2.5-3 hours to a mixture of acetone and NaOH maintained at 50-52°C, a product, obtained after chromatography over SiO_2/II (eluted with benzene, tlc monitoring) in ~70% yield, was, from its IR spectrum (Fig 13)(1675 cm^{-1}, characteristic of α-, β-unsaturated acyclic ketones),U.V.absorption spectrum(λ_{max}^{EtOH} 228 nm, ε 1.342×10^4), PMR spectrum (Fig.14)(-$COCH_3$:s,3H, 2.16 ppm; $-CH_2-CH=CH-CO$: m, 1H,6.68 ppm; $-CH_2CH=CHCO-$:td, 1H,5.96 ppm), and Mass spectrum (M^+=m/e 204), the desired α-, β-unsaturated ketone(XIV).

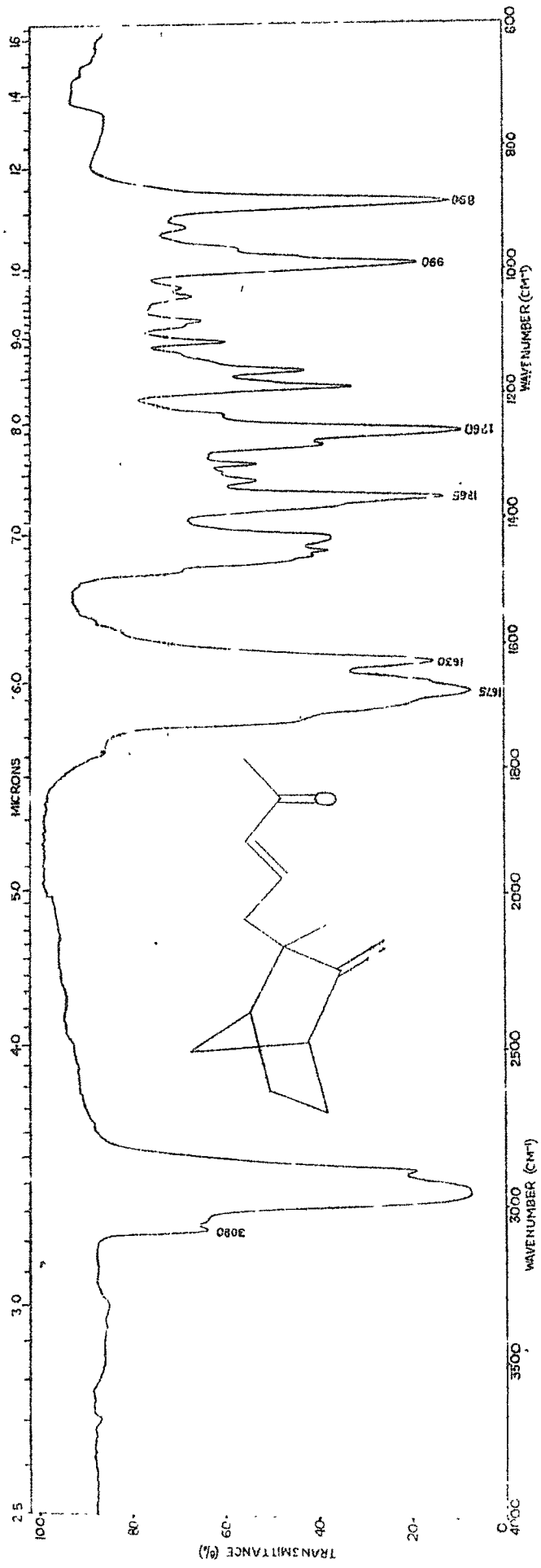


FIG.13: IR SPECTRUM OF THE UNSATURATED KETONE (XIV)

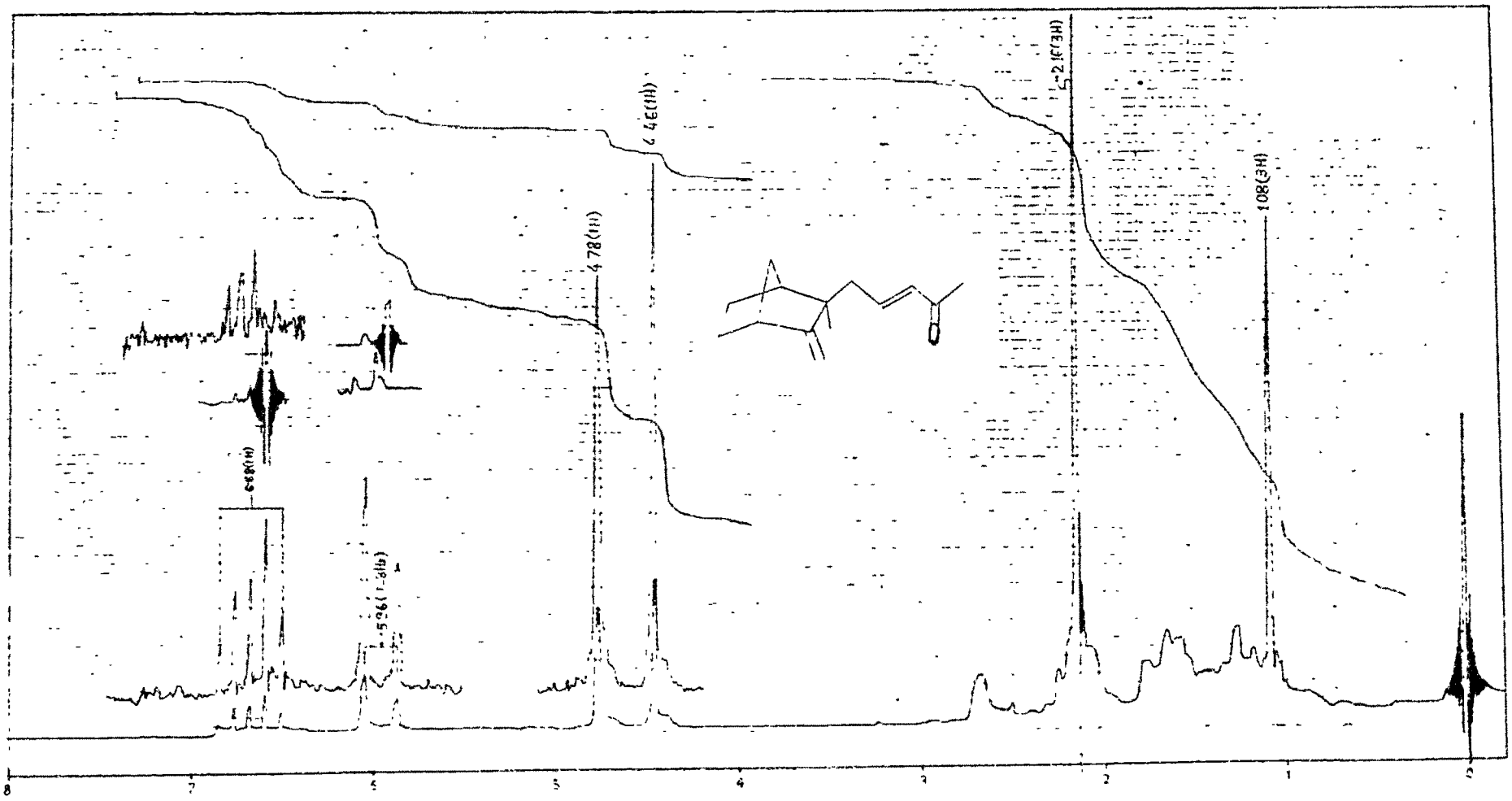


FIG.14: PMR SPECTRUM OF THE UNSATURATED KETONE(XIV)

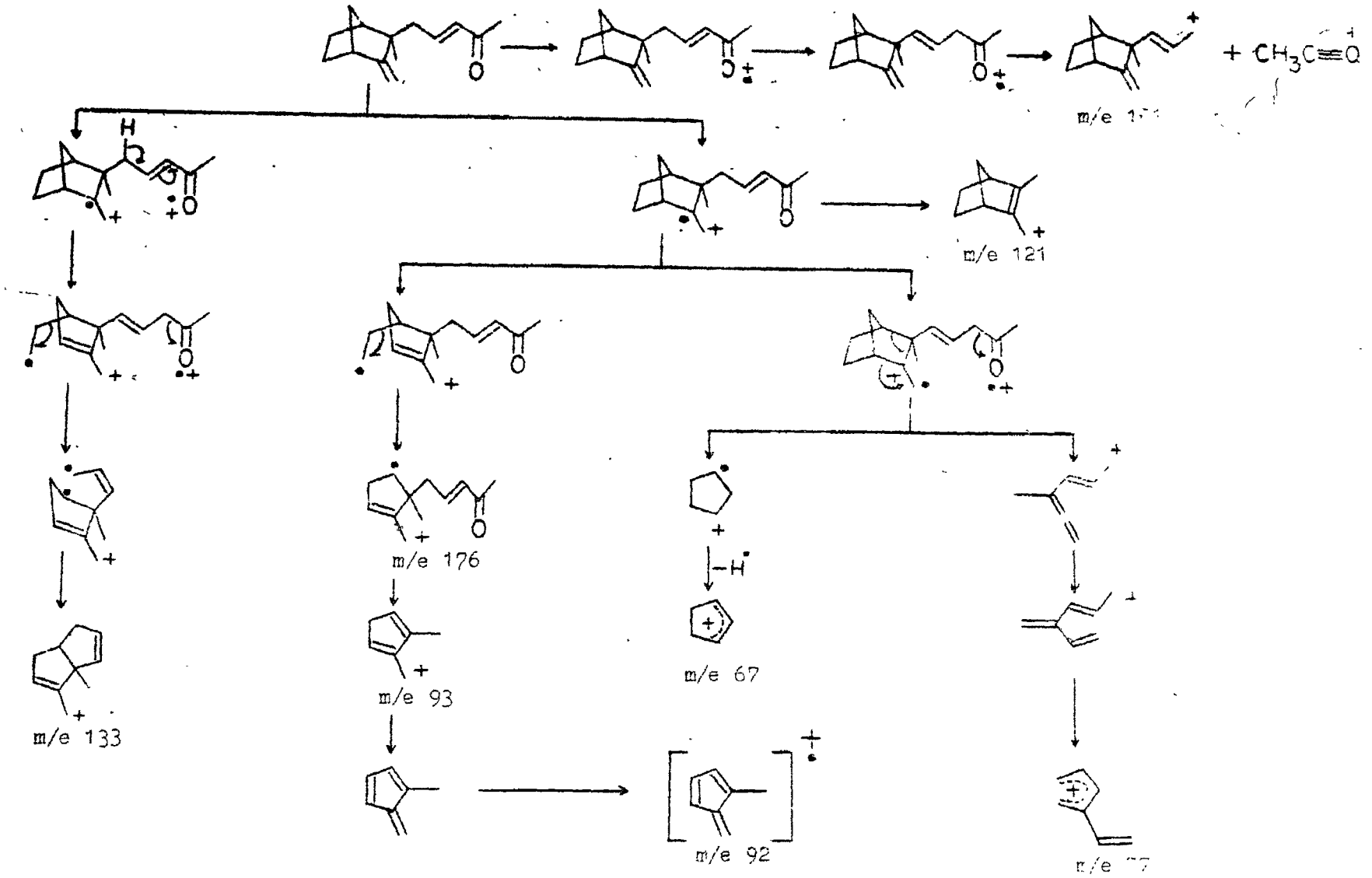
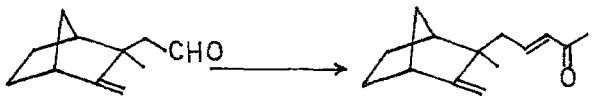


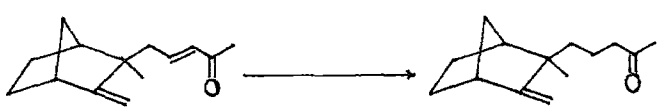
CHART 3: MASS SPECTRAL FRAGMENTATION OF THE UNSATURATED KETONE (XIV)



XIII XIV

THE SATURATED KETONE(XV)

Though several reagents(e.g.,Zn-AcOH[39], LAH-Cu_2I_2[40], and Li-liquid NH_3[41]) are known for this type of reduction, we preferred to use Li-NH_3 for its (i) simplicity,(ii)being cheapest of the reagents, and (iii) products obtained in almost quantitative yields. Li-liquid ammonia reduction of (XIV) was carried out in the usual fashion[42](at -35°C for 2 hours; work-up by NH_4Cl[42]). The product obtained after distillation was, from its IR spectrum (Fig.15) (1725 cm^{-1},-$COCH_3$; 3075,1660 and 885 cm^{-1}, a characteristic of the exo-methylene grouping). PMR spectrum (Fig. 16) (-$COCH_3$:s, 3H, 2.03 ppm; -$CH_2CH_2COCH_3$: t,2H,2.3 ppm) and Mass spectrum (M^+=m/e 206), readily characterized as the saturated ketone(XV).



XIV XV

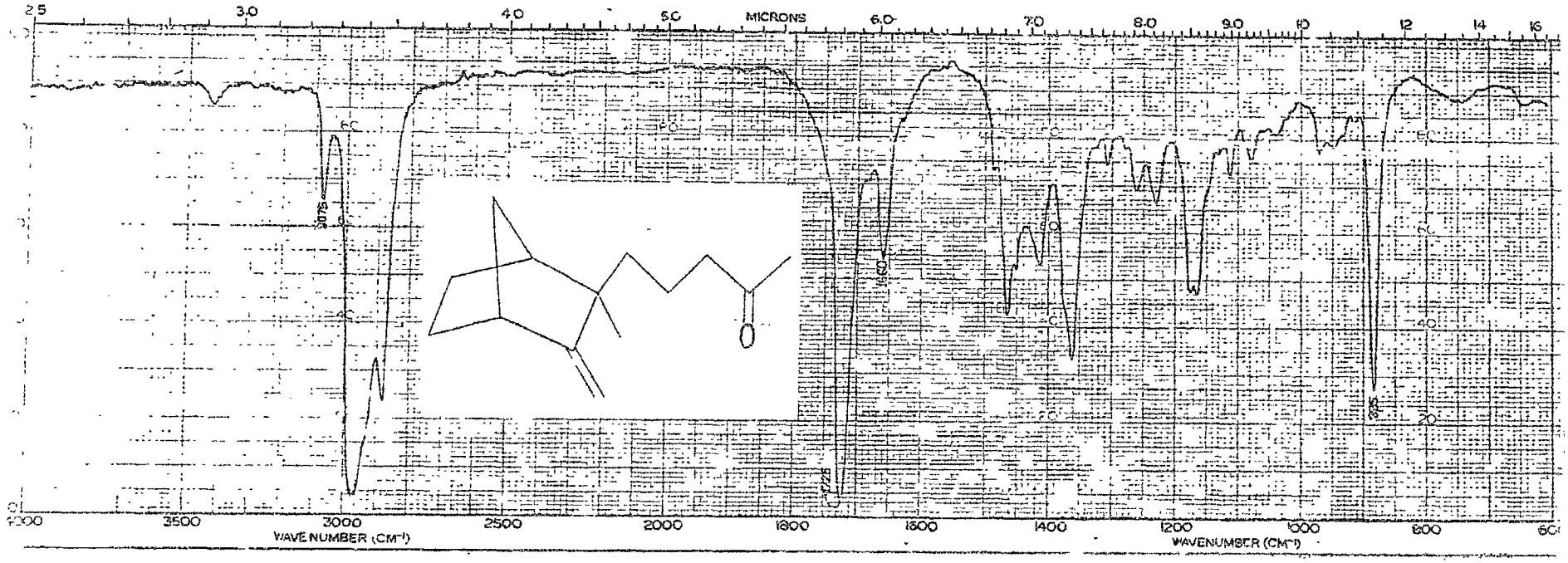


FIG.15: IR SPECTRUM OF THE SATURATED KETONE(XV)

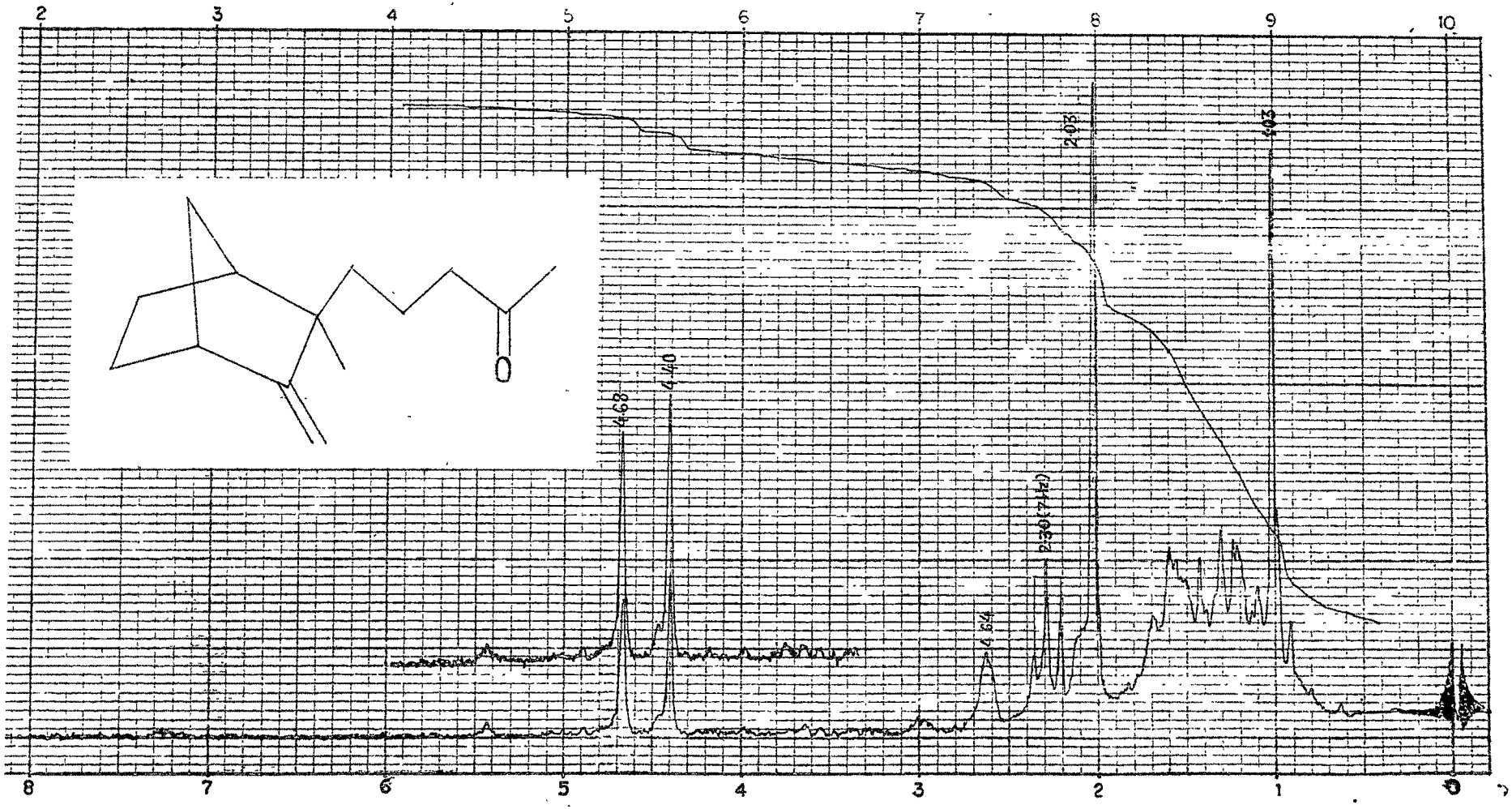


FIG.16: PMR SPECTRUM OF THE SATURATED KETONE(XV)

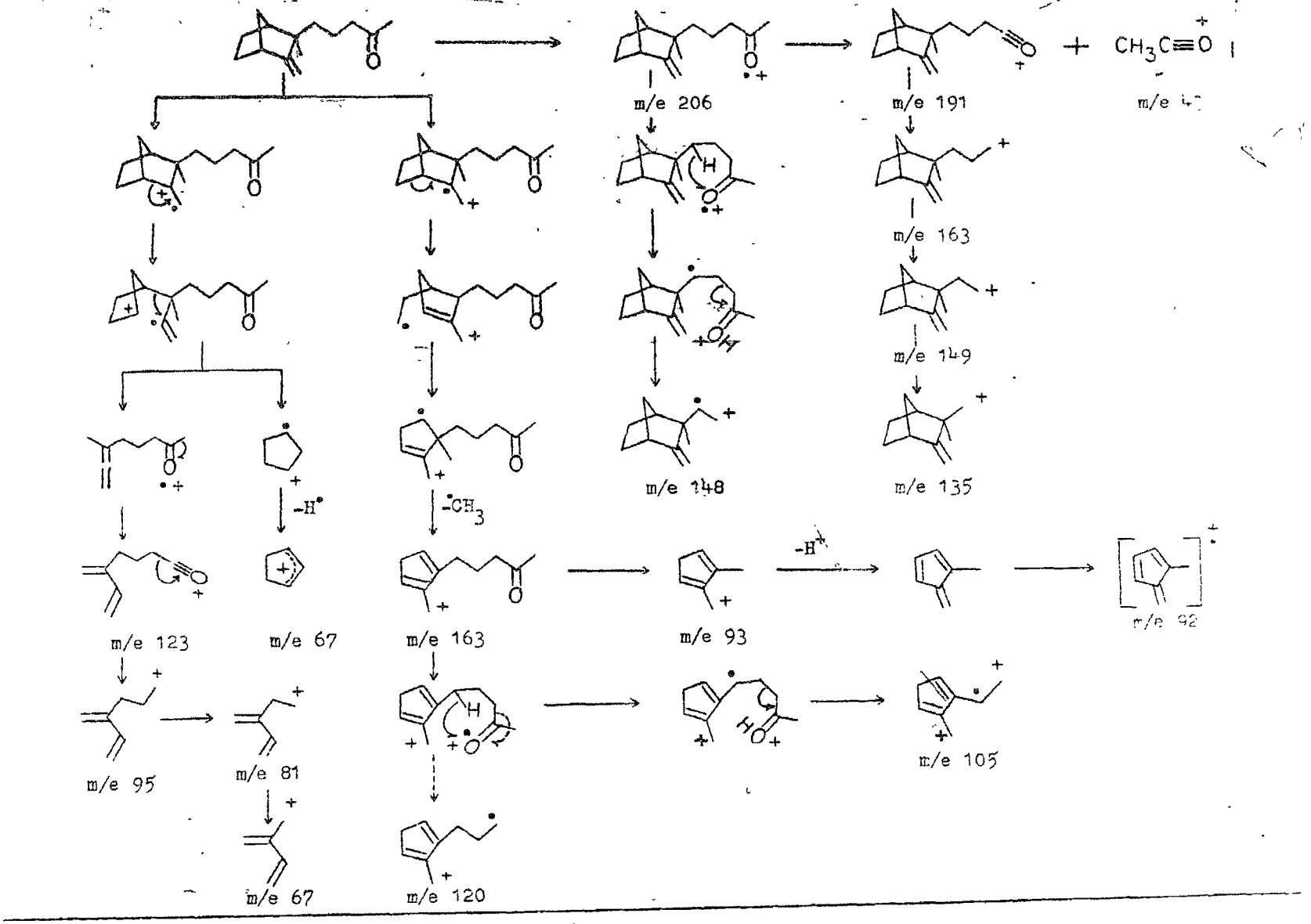


CHART 4: MASS SPECTRAL FRAGMENTATION OF THE OLEFIN-KETONE (XV)

β-SANTALENE(XVII) AND ITS DOUBLE BOND ISOMER(XVIII)

The saturated ketone(XV) via the tertiary carbinol(XVI) can be converted into β-santalene and its double bond isomer by its dehydration.

The tertiary carbinol(XVI) can be prepared from the saturated ketone(XV) by reaction using either MeLi or MeMgX (X=Cl,Br,I). For economic reasons,we preferred Grignard reaction. Treatment of (XV) with MeMgI and the usual work up furnished the product (tlc pure) in ~90% yield. Spectral data, e.g., IR spectrum (Fig.17) (3620 cm^{-1}, OH) and PMR spectrum (Fig.18) (Me_2C-OH:s, 6H, 1.10 ppm), confirmed that this was the desired carbinol(XVI).

Though number of reagents are available for dehydration of tertiary alcohols(these are listed under "OLEFIN-ACETATE-VIII" of this chapter) we carried out dehydration using $SoCl_2$/pyridine where the rearrangements are minimal. Dehydration under the conditons as reported earlier(for olefin-acetate-VIII in this chapter) furnished a mixture of two compounds(glc,10% carbowax, 12', 170°C). One having retention time 84 seconds(46%), by (a) coinjection technique in glc and (b) comparison of PMR of the mixture with authentic sample, was characterized as targetted β-santalene(XVII). The other compound having retention time 78 seconds(~54%) was, by elimination of signals due to β-santalene in the PMR spectrum of the mixture, suspected to be the double

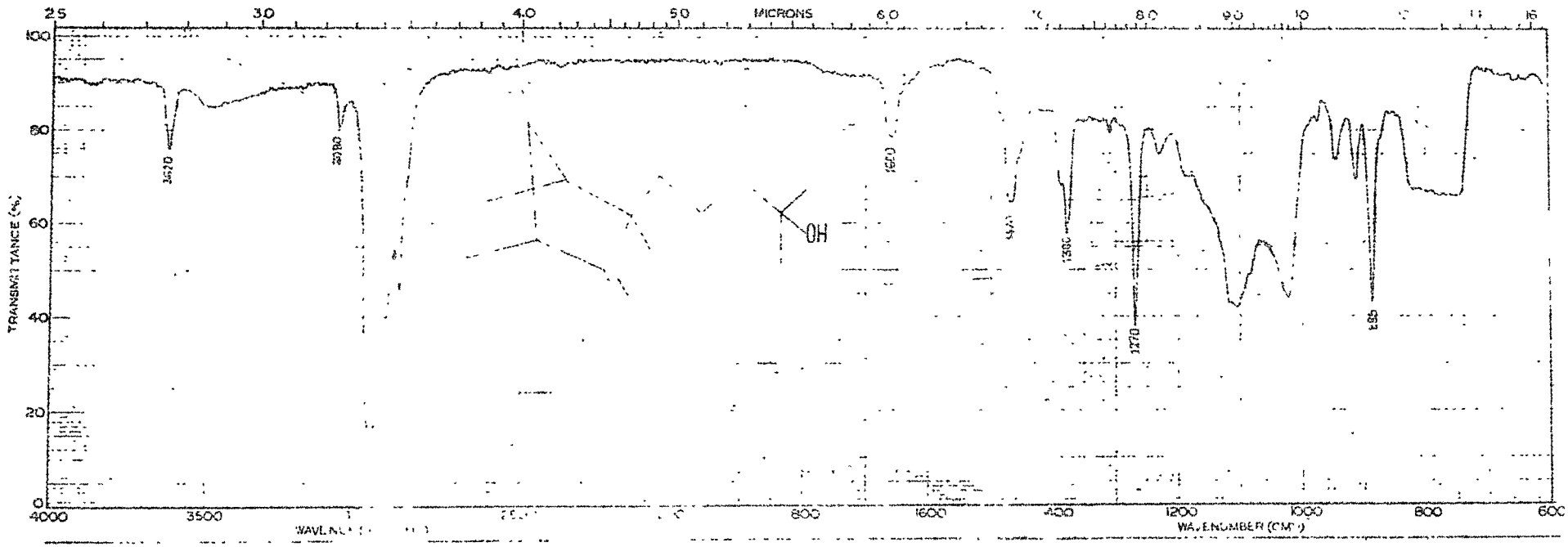


FIG.17: IR SPECTRUM OF THE TERTIARY CARBINOL(XVI)

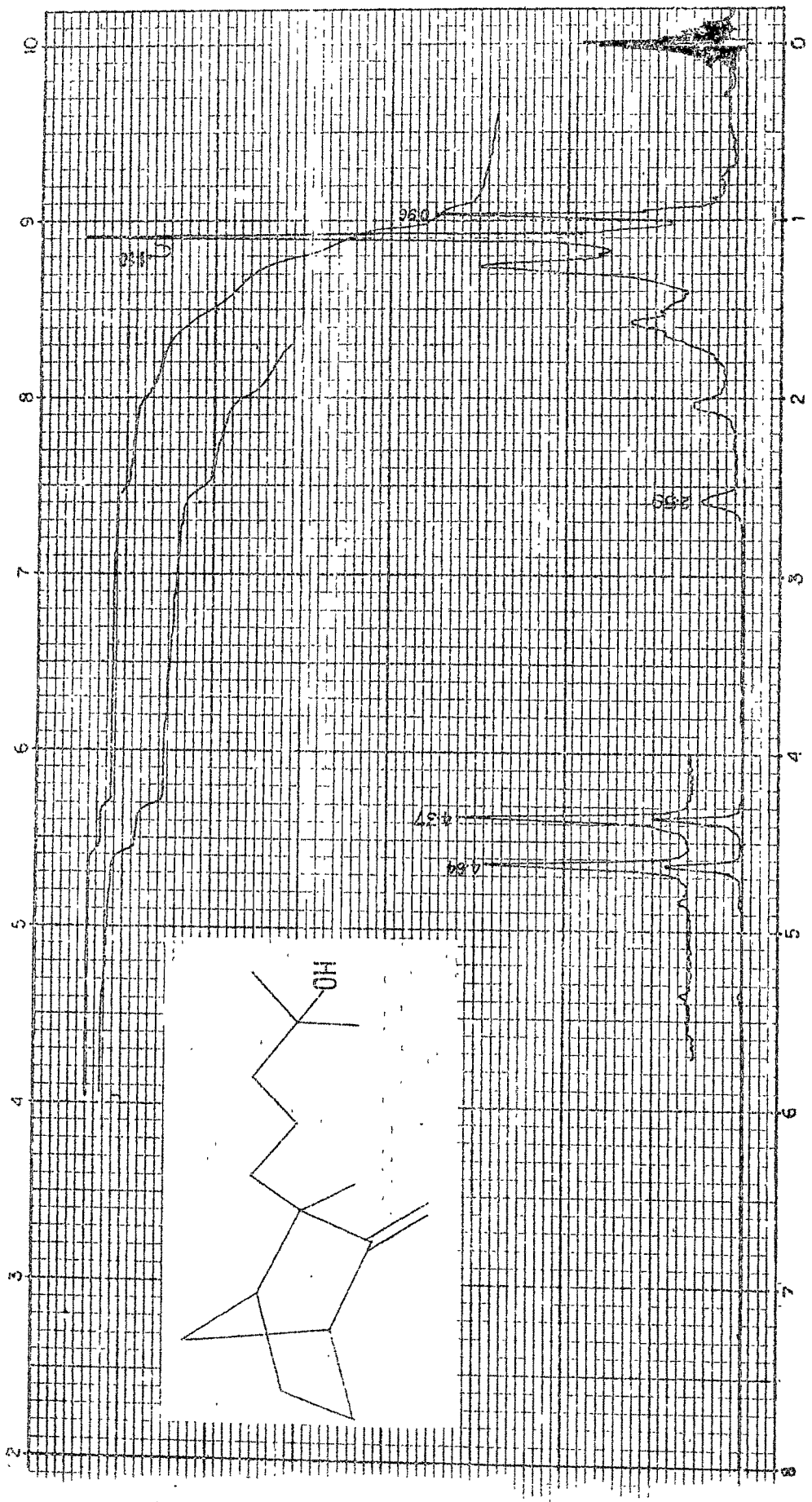
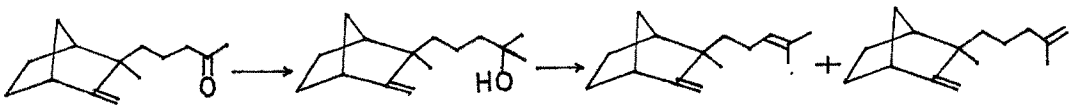


FIG.18: PMR SPECTRUM OF THE TERTIARY CARBINOL(XVI)

bond isomer(XVIII) of (XVII).



XV XVI XVII XVIII

THE ALCOHOL(XX)

We next turned to synthesize the aforementioned allylic tertiary alcohol(XX), a material having potential of becoming a very good substitute for sandalwood oil.

The aldehyde(XIII) was treated with 0.2 molar excess of β,β-dimethyl vinyl magnesium bromide[43] in tetrahydrofuran. Excess of the Grignard reagent was decomposed with calculated amount of saturated NH_4Cl aqueous solution. The product was shown by glc(Fig.19) to be a mixture of at least 6 components, viz. compound corresponding to peak 1(6.06%). 2(14.90%), 3(44.84%), 4(10.14%), 5(12.30%), and 6(11.7%). Compounds corresponding to peaks 3 and 4 were isolated in a state of purity by preparative glc(20% SE-30, 12', 170°).

Compound corresponding to peak no.3, from its IR spectrum (Fig. 20)(3060,1655,885 cm^{-1} for exo-cyclic methylene grouping and 1605 cm^{-1}- a characteristic of 1,3-diene system), U.V. absorption spectrum (λ_{max}^{EtOH} 2.32 nm, ϵ 1.4544 x 10^4, again a

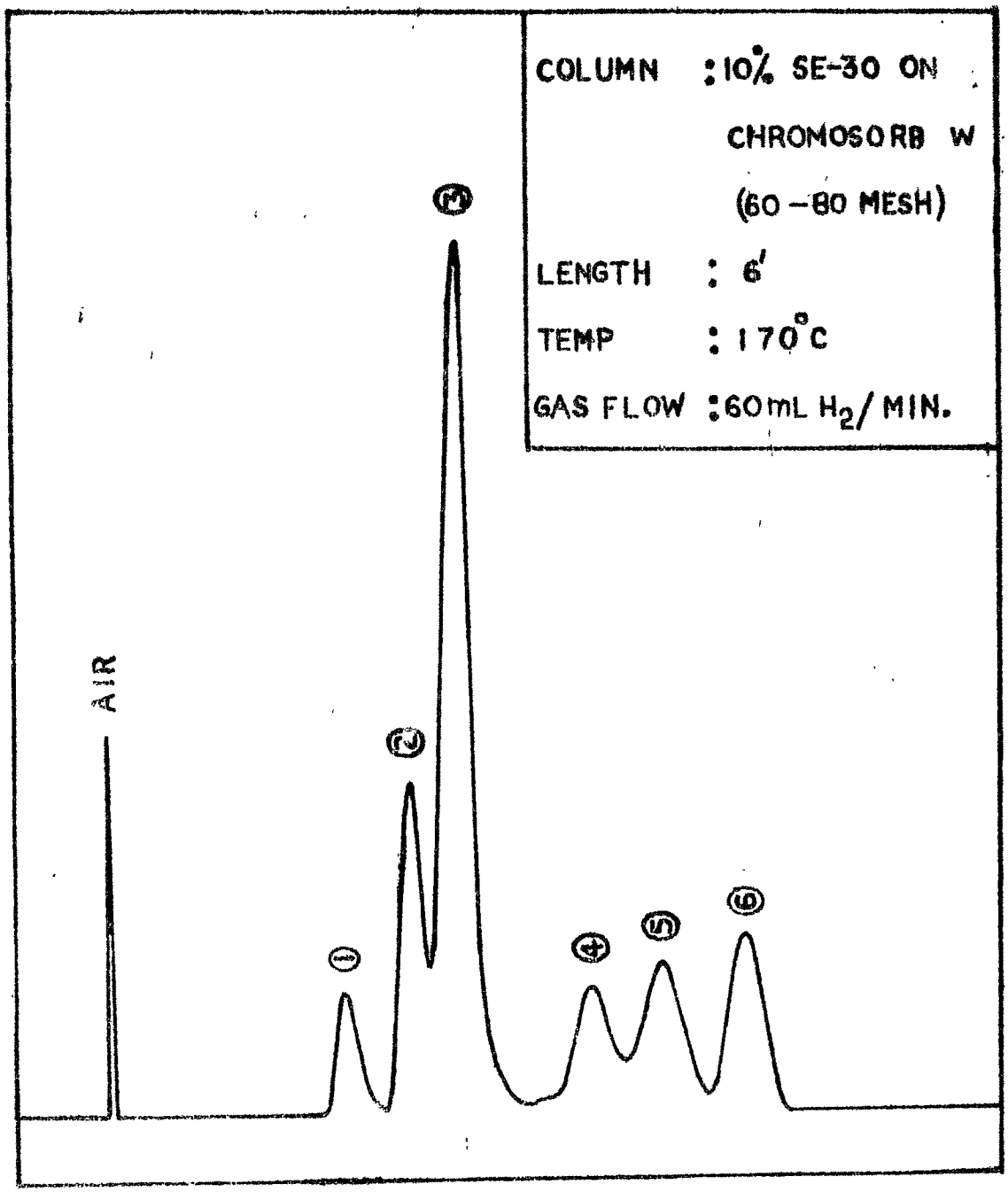

COLUMN : 10% SE-30 ON CHROMOSORB W (60 – 80 MESH)
LENGTH : 6'
TEMP : 170°C
GAS FLOW : 60 mL H_2 / MIN.
AIR
1
2
3
4
5
6

FIG .19

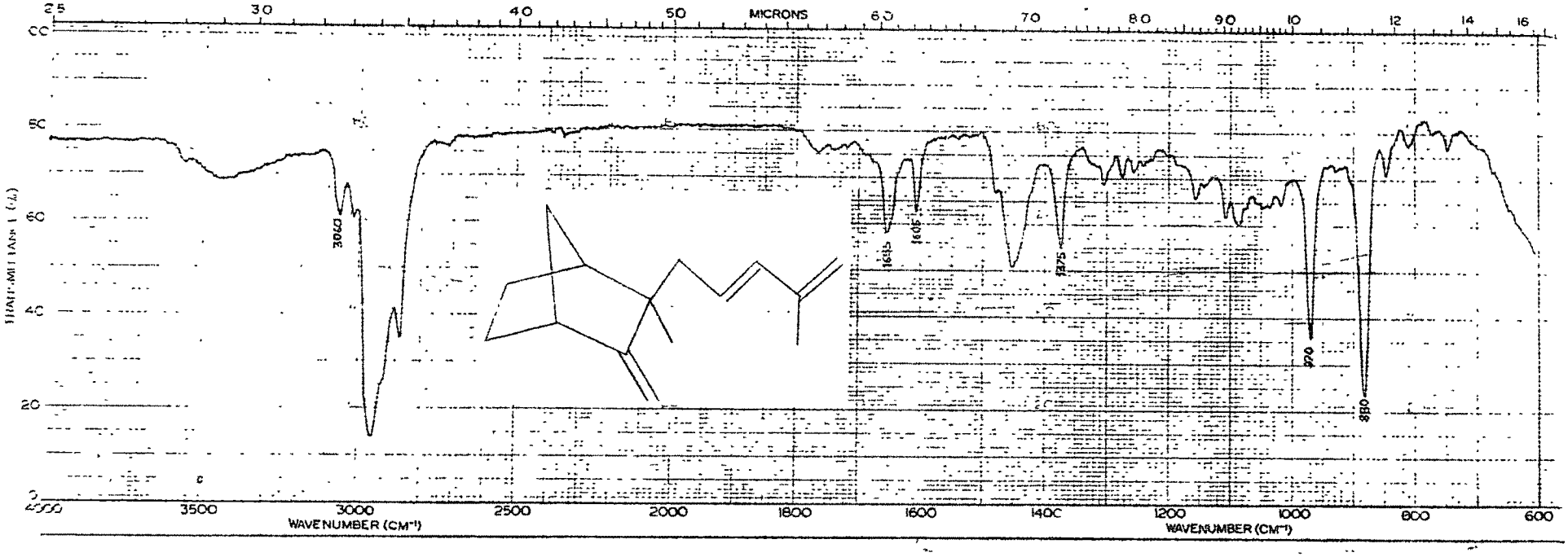


FIG.20: IR SPECTRUM OF THE 1,3-DIENE(XXI)

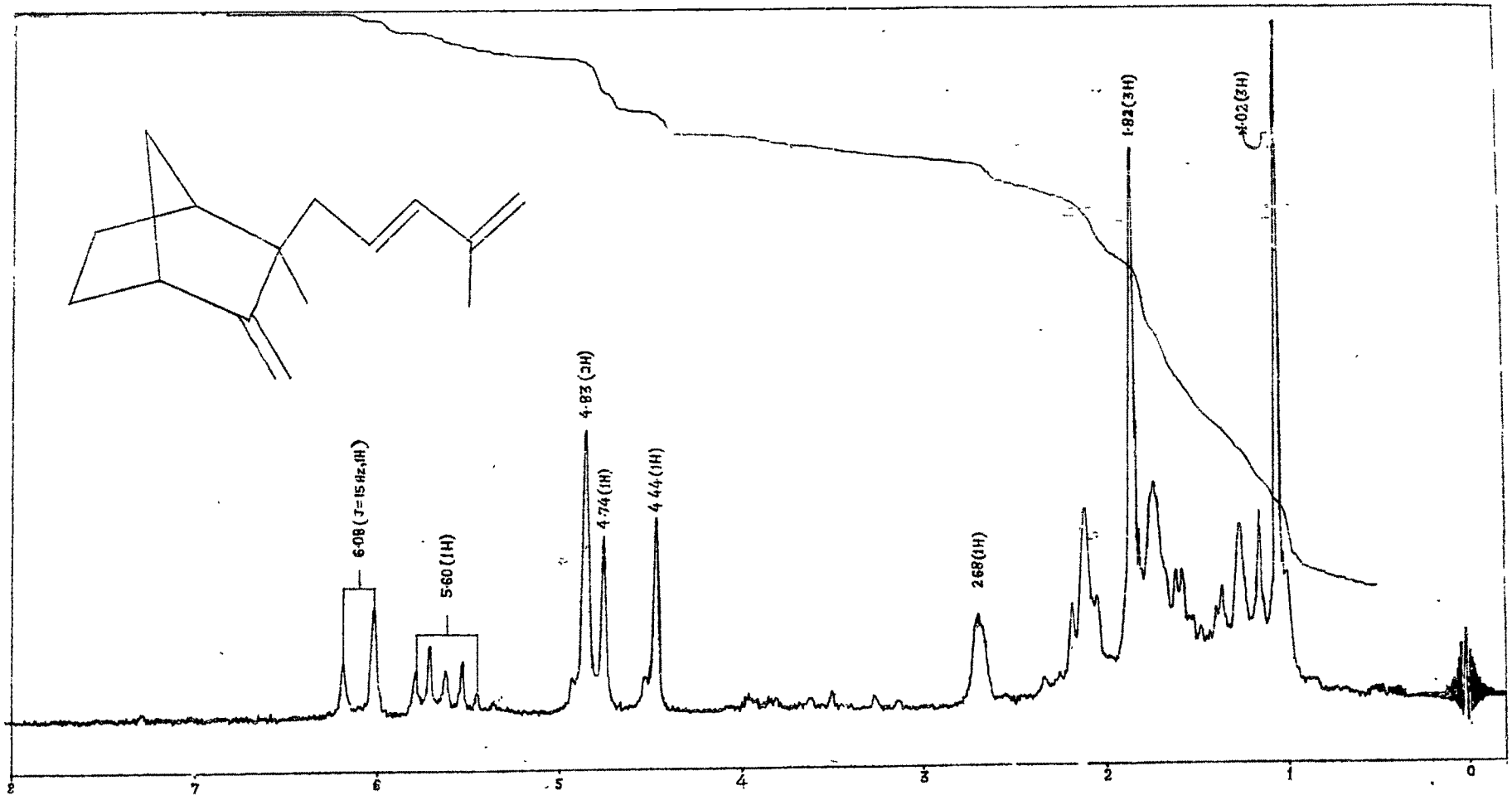
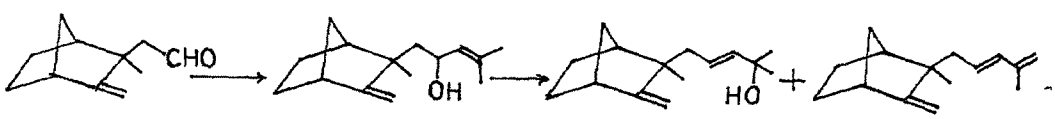


FIG.21: PMR SPECTRUM OF THE 1,3-DIENE(XXI)

characteristic of 1,3-diene system) and PMR spectrum (Fig.21) (>C=$\underline{CH_2}$:2s, 2H, 4.74 and 4.45 ppm; -CH=CH-C(Me)=$\underline{CH_2}$: s,2H, 4.83 ppm;-CH=$\underline{CH}$-C(Me)=CH_2: d, 1H,6.08 ppm;-$\underline{CH}$=CH-C(Me)=CH_2; m,1H, 5.6 ppm; C=C-C($\underline{Me}$)=C:s, 3H, 1.82 ppm), was characterized as the 1,3-diene(XXI).

Compound corresponding to peak No.4 was, from its IR spectrum(Fig.22) (3620 cm^{-1},OH) and PMR spectrum (Fig.23) (>C=$\underline{CH_2}$:2s, 2H, 4.73 and 4.43 ppm; -$\underline{CMe_2}$OH:s, 6H,1.27 ppm; -C($\underline{H}$)=C($\underline{H}$)-C: m, 2H, 5.58 ppm), readily identified as the allylic tertiary alcohol(XX).



XIII XIX XX XXI

As one would expect,(XIX) is the primary product of the reaction which upon hydrolytic work-up undergoes allylic rearrangement to furnish the tertiary carbinol(XX).
The 1,3-diene (XXI) could arise from this carbinol(XX) by dehydration under the work-up conditions.

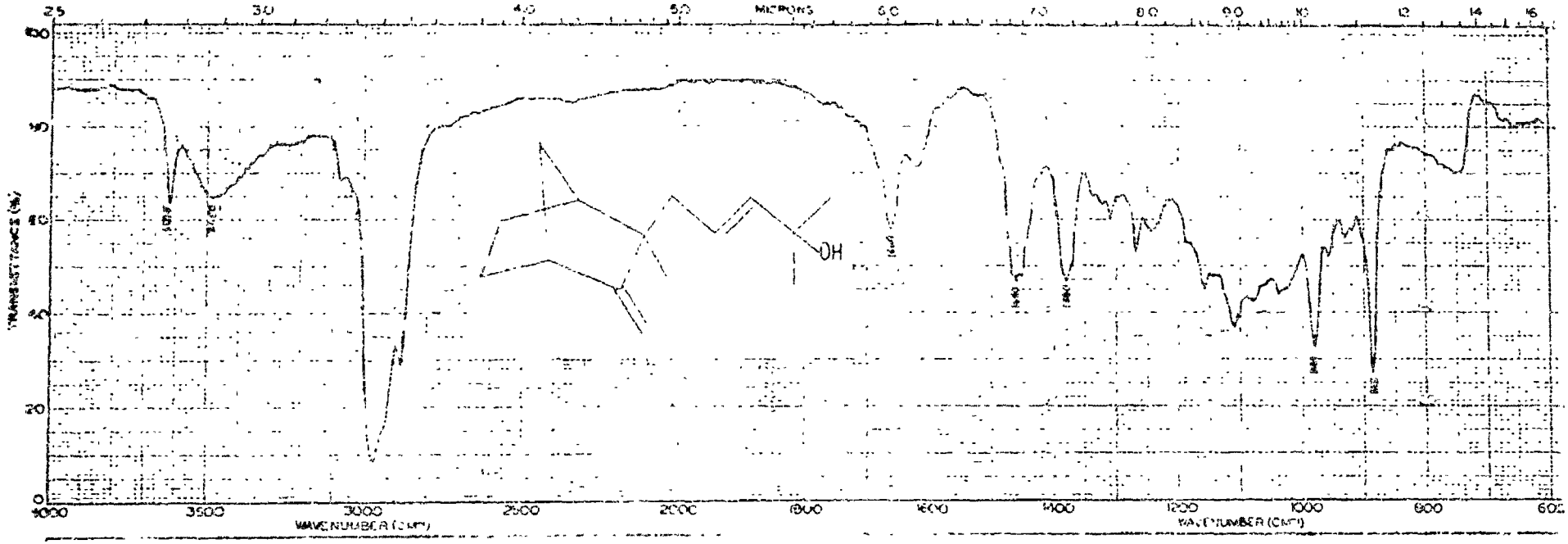


FIG.22: IR SPECTRUM OF THE α, β-UNSATURATED TERTIARY CARBINOL(XX)

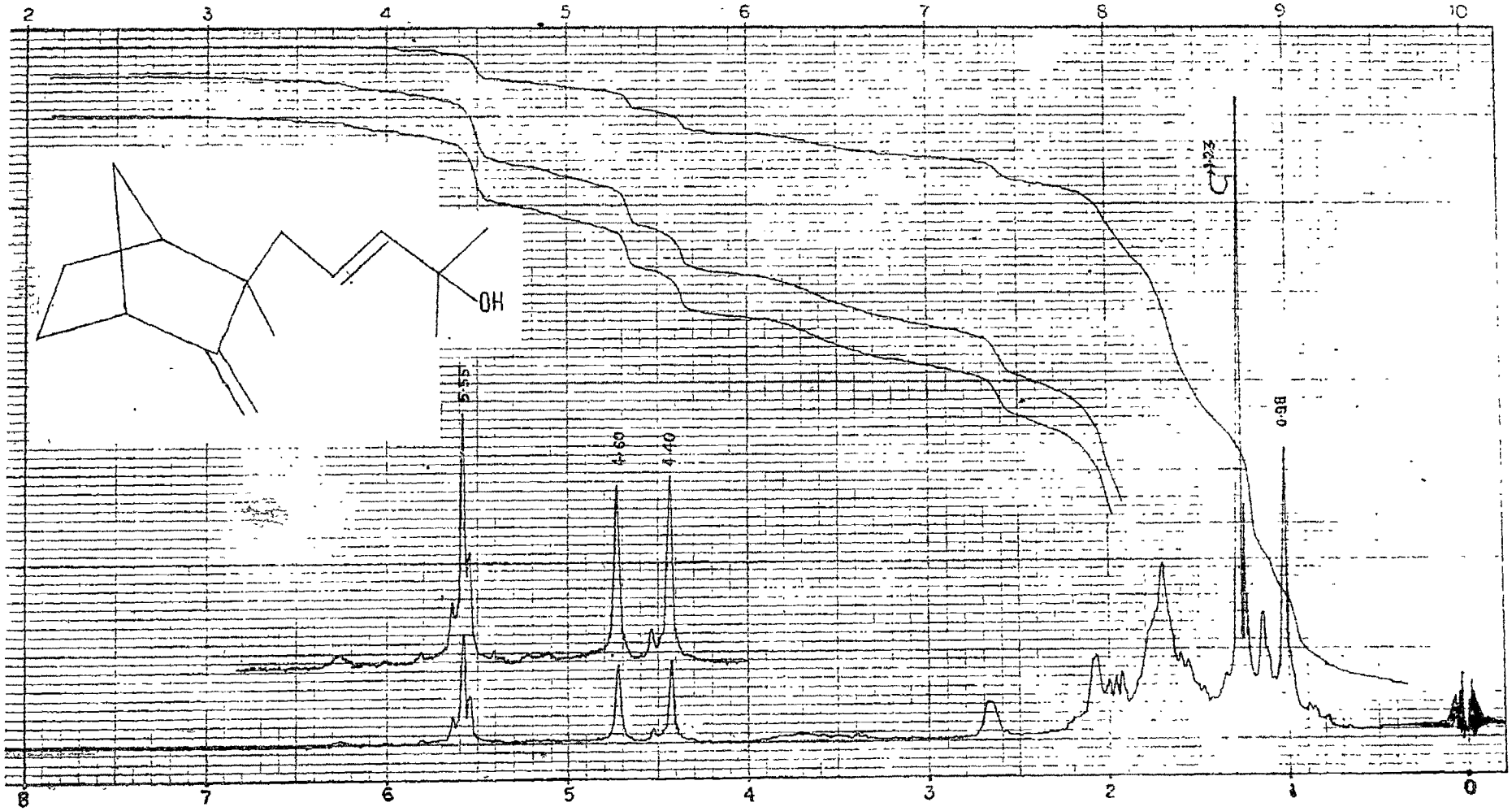


FIG.23: PMR SPECTRUM OF THE α, β-UNSATURATED TERTIARY CARBINOL (XX)

EXPERIMENTAL

GENERAL REMARKS: All mps and b.ps are uncorrected. Petroleum ether refers to the fraction, b.p. 60-80°, unless otherwise stated. All solvent extracts were finally washed with saturated brine solution before drying over anhydrous Na_2SO_4. Optical rotations were measured in absolute EtOH on a Schmidt-Haensch electronic polarimeter model polatronic 1.

The silicagel for column chromatography was 100-200 mesh, was activated at 120-125°(8-10 hours) and then standardized [R.Hernandez, R.Hernandez Jr and L.R.Axelrod, Analyt. Chem., 33 370 (1961)]. The alumina for column chromatography was 100-200 mesh, was activated at 400°(6 hrs) and then standardized [H.Brockmann and H.Schodder, Chem. Ber. 74 73 (1940)].TLC was carried out on silica gel or silica gel-$AgNO_3$(15%) layers (0.3 mm) containing 15% plaster of Paris and activated at 120-125° for an hour; Concentrated H_2SO_4 used as the visualization agent. Chromatographic separations were monitored by TLC.

IR spectra were recorded as smears(liquids) or nujol mulls(solids) or in $CHCl_3$ or CCl_4 on Perkin-Elmer IR spectrophotometer, model 267. U.V.spectra were taken on a Perkin-Elmer UV-VIS spectrophotometer, model 402 in 95% ethanol solution. PMR spectra were taken with 10-20% solution in $CCl_4/CDCl_3$ with TMS as the internal standard on Perkin-Elmer NMR spectrometer model R-32(90 MHz);

signals are recorded in ppm(δ) relative to TMS as zero. While citing PMR data, following abbreviations have been used: s, singlet; d, doublet; t,triplet;q,quartet;m,multiplet; b,broad etc. Mass spectra were recorded on a Varian Mat CH-7 mass spectrometer using an ionizing energy of 76 eV and a direct inlet system.

GLC were run on Hewlett-Packard gas chromatograph, model 5712A, using a 360/180 cm x 0.6 cm aluminum column packed with 10% carbowax 20 M/ SE-30 on 60-80 mesh Chromosorb W for analytical purposes and model 7624A, using a 360 cm x 0.9 cm aluminum column packed with 20% carbowax 20 M/SE-30 on 45-60 mesh Chromosorb W for preparative use; H_2(60 ml/min) was used as carrier gas.

8-FORMYL CAMPHENE(I)

Freshly distilled phosphoryl chloride(4.3 ml, b.p.106-107°C) was dropwise added to cold DMF(14.5 ml, -10 to -8°C, ice-salt bath) under stirring. After the addition was over (30 minutes), stirring,under cooling, was continued for an additional 30 minutes. Now, a solution of camphene(5.80 g) in DMF (5 ml) was added at such a rate that the temperature never exceeded 10°C (30 minutes). The reaction mixture was allowed to come to room temperature(30°C) and the stirring

at this temperature (30°C) continued for 4 hours. It was next refluxed for 8 hours when it set to a solid mass. Crushed ice(15 g) was added and the contents brought to pH 6 by adding saturated NaOAc aqueous solution. It was extracted with ether (15 ml x 3) and the combined extract washed with brine (15 ml x 2). Drying and solvent removal gave the crude product (7.1 g), which on distillation furnished 8-formyl camphene(6.8 g, ~88% yield, b.p. 128-130°/ 12 torr). GLC: 98% pure (10% carbowax, 12', 200°C).

CAMPHENE-8-CARBOXYLIC ACID(II)

8-Formyl camphene (16.4 g, 100 m moles) in ether (40 ml) was exposed to air for 4 days when the semi-solid mass was dissolved in ether (40 ml) and extracted with 10% NaOH aqueous (15 ml x 3). The alkaline extract was washed with ether (20 ml x 2) to remove any neutral material and then acidified with dilute HCl when the acid separated. It was taken up in ether (40 ml) and washed with water (10 ml x2) and brine (10 ml x1). Drying and solvent removal gave crude camphene-8-carboxylic acid (16.2 g, m.p.118-120°C) which was crystallized from n-hexane(25 ml) (15.2 g, ~85% yield, m.p. 122-124°C, lit[5] m.p. 122-124°C).

IR SPECTRUM: 1645, 1680, and 2500-2700 cm^{-1}($>C=C-CO_2H$), UV.ABSORPTION SPECTRUM: λ_{max}^{EtOH} 235 nm, ϵ 1.12 x 10^4. PMR SPECTRUM: $>C=C(\underline{H})-CO_2H$(s, 1H, 5.36 ppm), $>C(\underline{H})-\dot{C}=$(bs,1H, 3.97 ppm) and two quaternary methyls(s,6H, 1.07 ppm).

THE ENDO- AND EXO- LACTONES (IV AND V)

Camphene-8-carboxylic acid (1.8 g, 10 m moles) was added to ice-cold 95% H_2SO_4 aq(w/w, 10 ml) and shaken till the acid dissolved (30 minutes). After keeping it at 0°C for 10 hours, it was poured onto crushed ice(30 g) and extracted with ether (10 ml x 2). The combined extract was washed with water(7ml x2) and brine (7 ml x 1). Drying and solvent removal gave a white crystalline residue (1.78 g, ~99% yield, glc: endo-/exo- ratio = 1: 16) which was recrystallized from n-hexane(5 ml)(1.65 g, ~92% yield, endo-/ exo- ratio = 1:22, m.p. 150-152°C). Two more recrystallizations from n-hexane made the above ratio (1:22) reach 1:107(1.4 g, ~78% yield, m.p.155-158°C, lit[5] m.p. 157-161°C).

IR SPECTRUM : 1765 cm^{-1} (a γ-lactone). PMR SPECTRUM: $>C(\underline{Me})-CH_2CO$(s,3H, 1.0 ppm), $>C(\underline{Me})-OCO-$(s,3H,1.2 ppm), and $-\underline{CH_2}COO$(s, 2H, 2.04 ppm).

The above endo-exo-(=1:16) lactones' mixture (1g) was chromatographed over silica gel/IIA(100 g, 60 cm x2 cm) and

eluted with pet-ether containing increasing proportions of benzene when a pure sample of the endo-lactone(IV, 30 mg) was obtained.

IR SPECTRUM: 1760 cm^{-1} (γ-lactone). PMR SPECTRUM: >C(Me)CH_2CO(s, 3H, 1.14 ppm) and >C(Me)OCO-(s,3H,1.28 ppm).

THE DIOL(VI)

A solution of the exo-lactone(V,2.50 g, 14 m moles) in THF (10 ml) was dropwise added to a stirred slurry of LAH (0.76 g, 20 m moles) in THF (10 ml) under nitrogen atmosphere. After the addition was over (30 minutes), the reaction mixture was refluxed for 5 hours. Excess of LAH was destroyed by using THF aqueous (1:1, 15 ml being used for 1 g of LAH used) and the solution decanted. The white mass in the flask was shaken with chloroform(10 ml x 2) and decanted to the original aqueous organic phase. It was diluted with water (40 ml) and extracted with chloroform (20 ml x 3). The combined chloroform layer was washed with water (15 ml x 2) and brine (15 ml x 1). The residue (2.43 g, gum) left after drying and solvent evaporation was crystallized from n-hexane(5 ml) to give the white crystalline diol (VI, 2.3 g, 90% yield, m.p. 96-100°C, lit[5] m.p. 97-100°C)

IR SPECTRUM: 3240 cm^{-1}(OH). PMR SPECTRUM: >C(Me)-CH_2- (s, 3H, 0.9 ppm), >C(Me)OH (s, 3H, 1.17 ppm) and -CH_2CH_2OH (m, 2H, 3.68 ppm). Analyzes for C, 71.96%; H,10.57%. $C_{11}H_{20}O_2$ requires: C, 71.74%; H, 10.87%.

ALCOHOL-ACETATE(VII)

Diol(VI, 10.25 g) was dissolved in a solution of Ac_2O (20 ml) in dry pyridine(40 ml) and and kept at 25-30°C for 18 hours. The reaction mixture was poured onto crushed ice(100g) and extracted with ether (30 ml x 4). The combined extract was washed successively with 5% HCl aqueous (30 ml x 3), water (30 ml x 3) and brine (30 ml x 1). Drying and solvent removal furnished a residue (13.3 g) which,on distillation,furnished a colourless mobile liquid, the alcohol-acetate(VII, 12.3g, 96% yield, b.p. 115°C/ 0.3 torr, n_D^{30} 1.4877).

IR SPECTRUM: 3510, 1365 and 1120 cm^{-1}(OH); 1725 cm^{-1}(-OAc). PMR SPECTRUM: -CH_2OAc (m, 2H, 4.05 ppm), -OCOMe(s, 3H, 1.96 ppm), >C(Me)-CH_2(s,3H,0.86 ppm), and >C(Me)OH(s,3H,1.13 ppm). MASS SPECTRUM: important ions at m/e 166(M^+-60), 151(10%), 138(26%), 123(71%), 98(79%),95(28%),67(29%),and 43(100%). Found: C, 69.24; H,9.68. $C_{13}H_{22}O_3$ requires: C,69.03; H,9.73.

THE OLEFIN-ACETATE(VIII)

A solution of thionyl chloride (0.595 g, 5 m moles) in dry pyridine (5 ml) was added to a solution of the mono-acetate (VII, 0.565 g, 2.5 m moles) in pyridine (5 ml) at -20° to -15°C during 50 minutes under stirring. Stirring was continued at this temperature (-20° to -15°C) for another 90 minutes and then left as such at room temperature (25-30°C) for 16 hours. It was poured into ice-water (40 ml) and extracted with ether (10 ml x 4). The combined extract was washed successively with 5% HCl aqueous (10 ml x 3), water (10 ml x 2), and brine (10 mlx1). Solvent was removed and the residue (0.51 g) chromatographed over SiO_2/IIB(6 g, 12 x 1.1 cm) and eluted with benzene containing increasing proportions of ethylacetate. 2% EtOAc in benzene (20 ml x 3) eluted the olefin-acetate(VIII, 0.42g, ~80% yield, b.p.82-83°/0.3 torr). GLC: >99% pure (10% SE-30, 6', 160°C).

IR SPECTRUM: 1745 cm^{-1}(OAc); 3060,1660 and 880 cm^{-1}(>C=CH_2) PMR SPECTRUM: >C=$\underline{CH_2}$(2s, 2H, 4.74 and 4.47 ppm), -$\underline{CH_2}$OAc (t, 2H, 4.05 ppm, J=7.5 Hz), -OCO$\underline{Me}$(s, 3H, 1.96 ppm), and a quaternary methyl(s,3H,1.1 ppm).

THE OLEFIN-ALCOHOL(IX)

Ethanolic KOH (10%, 15 ml) was added to the olefin-acetate (VIII,0.245 g, 1.18 m moles) and kept at room temperature(~30°C) for 16 hours. Ethanol was removed under reduced pressure(130mm)

and the residue diluted with water (10 ml). 5% HCl aqueous was slowly added to this till neutral (pH-7). This was extracted with ether (5 ml x 3) and the combined extract washed successively with water (5 ml x 2) and brine (5 ml x 1). Drying and solvent removal gave a residue (0.21 g) which on distillation furnished the olefin-alcohol(IX, 0.196 g, >99% yield, b.p. 93-96°/1.5 torr, n_D^{30} 1.5007) GLC: ~97% pure (10% SE-30, 6', 160°C).

IR SPECTRUM 3630 cm^{-1}(OH); 3075. 1660 and 885 cm^{-1}(>C=CH_2). PMR SPECTRUM: >C=$\underline{CH_2}$(2s, 2H, 4.70 and 4.44 ppm), -$CH_2\underline{CH_2}$OH(t, 2H, 3.6 ppm, J = 7 Hz), and a quaternary methyl(s,3H,1.05 ppm). MASS SPECTRUM: important ions at m/e 166(M^+), 122(49%), 121(28%), 94(100%), 93(38%), 79(29%), 67(11%),41(11%) and 31(6%). Found: C,79.72; H,10.52, $C_{11}H_{18}O$ requires: C,79.52; H, 10.84.

THE OLEFIN-NITRILE(X)

(a) p-Toluene sulphonyl chloride(3.82 g, 20 m moles) was added to a 3-5°C cooled solution of olefin-alcohol(IX,1.66 g, 10 m mols) in pyridine (10 ml) and kept at ~5°C for 20 hours. The content was dumped in ice-water(40 ml) and extracted with ether(10 ml x 3). The combined extract was washed successively with cold 5% HCl aqueous (10 ml x 3), water (10 ml x 3) and brine (10 ml x 1). Drying and solvent removal gave the crude tosylate (XXIIA,3.1 g, ~97% yield).

PMR SPECTRUM: >C=$\underline{CH_2}$(2s, 2H, 4.75 and 4.42 ppm), -$\underline{CH_2}$OTs(t, 2H, 4.05 ppm, J=7 Hz), aromatic protons(m, 4H, 7.28-7.37 and 7.7-7.8 ppm), Ar-$\underline{Me}$(s, 3H, 2.46 ppm) and a quaternary methyl(s, 3H, 1.02 ppm).

The above crude tosylate (3.1 g , ~10 m moles) was heated with NaCN (0.98 g, 20 m moles) in DMF(10 ml) at 100°C for 5 hours, When it was dumped in water (30 ml) and extracted with ether (10 ml x 3). The combined extract was washed with water (10 ml x 1) and brine(10 ml x1). The residue (1.62 g), left after solvent evaporation,furnished,on distillation,the olefin-nitrile(X, 1.57 g, ~95% yield, b.p. bath 90°/0.3 torr). GLC: 97% pure (10% carbowax, 12', 190°C).

IR SPECTRUM: 2250 cm^{-1}(-CN) and 3070, 1660 and 885 cm^{-1} (>C=CH_2). PMR SPECTRUM: >C=$\underline{CH_2}$(2s, 2H, 4.80 and 4.48 ppm), >C($\underline{H}$)-C=(bs,1H,2.7 ppm), -$CH_2\underline{CH_2}$CN (t, 2H, 2.28 ppm, J=8Hz) and a quaternary methyl(s, 3H, 1.07 ppm). MASS SPECTRUM: important ions at m/e 175(M^+,8%, 160(6%), 146(5%),121(100%), 105(17%), 93(76%), 79(49%) and 67(18%).

(b) The tosylate (XXIIA,6.2 g, ~20 m moles) was heated with NaBr (4.12 g, 40 m moles) in DMSO (15 ml) at 100°C. After the reaction was over (5 hours, tlc monitoring), it was poured into ice-water(50 ml) and extracted with ether(20 mlx3).

The combined extract was washed with water (15 ml x 2) and brine (15 ml x 1). Drying and solvent removal gave the crude product(4.34 g) which, when distilled, gave the olefin-bromide(XXIII, 4.28 g, ~96% yield, b.p. 87-88°/0.5 torr, n_D^{30} 1.5167 GLC: >98% pure (10% SE-30, 6', 200°C).

IR SPECTRUM: 3070, 1660 and 890 cm^{-1} ($>C=CH_2$). PMR SPECTRUM: $>C=\underline{CH_2}$(2s, 2H, 4.77 and 4.47 ppm), $-CH_2\underline{CH_2}Br$(t, 2H, 3.33 ppm, J=8.5 Hz), $>C(\underline{H})-\dot{C}=$(bs, 1H, 2.68 ppm), $>C(\underline{H})-\dot{C}-C$ (bs, 1H, 2.1 ppm) and a quaternary methyl(s,3H, 1.07 ppm). MASS SPECTRUM: important ions at m/e 229 (M^+), 149(3%),122(65%), 121(100%), 105(13%), 94(39%), 93(74%), 91(31%), 79(46%), and 77(28%).

The olefin-bromide (XXIII, 1.15 g, 5 m moles) was treated with NaCN (0.5 g, 10 m moles) in DMF(10 ml) at 108 for 6 hours. The reaction mixture was worked up as above. Distillation of the residue(0.9 g) gave the olefin-nitrile(X, 0.83 g, ~95% yield, b.p. bath 90°/0.3 torr).

9-FORMYL CAMPHENE (XIII)

9-Hydroxymethyl camphene (IX, 166 mg, 1 m mole) in CH_2Cl_2(2 ml) was added in one lot to a stirred suspension of pyridinium chloro-chromate(324 mg, 1.5 m moles) and NaOAc (25 mg, 0.3 m moles) in CH_2Cl_2. After stirring for

2 hours at room temperature(~30°C) 4 ml of dry ether was added and the supernatant liquid decanted from the black gum. The gum was washed with ether (3 ml x 3) whereupon it became a brown grannular solid. The combined organic solution was passed through a short pad (1.5 cm) of celite. Distillation of the residue left after solvent evaporation gave the olefin aldehyde (XIII, 132 mg, ~93% yield, b.p.bath 110-115°/ 0.5 torr).

IR SPECTRUM 1730 cm^{-1}(-CHO) and 3080, 1665 and 895 cm^{-1} >C=CH_2). PMR SPECTRUM: -CH_2C<u>H</u>O(t,1H, 9.68 ppm, J= 2.5 Hz), >C=<u>CH_2</u>(2s, 2H, 4.78 and 4.48 ppm), -<u>CH_2</u>CHO (d,2H, 2.28 ppm, J= 2.5 Hz) and quaternary methyl (s, 3H,1.19 ppm).

<u>THE α-, β-UNSATURATED KETONE (XIV)</u>

A solution of 9-formyl camphene(XIII, 0.108 g, 0.66 m moles) in acetone (1.5 ml) was added in several portions to a stirred solution of NaOH(0.015 g, 0.375 m moles) in acetone(1:1, 3 ml) at 50-52°C. After the addition was over (100 minutes), stirring at 50-52° was continued for an hour. Acetone was distilled off, the residue diluted with water (10 ml) and neutralized with calculated quantity of acetic acid (0.0225 g, 0.375 m moles). It was extracted with ether(5 ml x3) and the combined extract washed with water (5 ml x 2) and brine

(5 ml x 1). The crude product (0.115 g), obtained after drying and solvent evaporation, was chromatographed over SiO_2/IIB(4 g, 16 cm x 0.8 cm) and eluted with pet-ether containing increasing proportions of ethylacetate when the unsaturated ketone (XIV, 0.093 g, 70% yield, b.p. bath 120-125°/0.5 torr) GLC : 97% pure (10% carbowax, 12', 200°C).

IR SPECTRUM: 1675 cm^{-1} ($-C=C-COCH_3$) and 3080 and 890 cm^{-1} ($>C=CH_2$). U.V ABSORPTION SPECTRUM: λ_{max}^{EtOH} 228 nm, ϵ = 1.34×10^4. PMR SPECTRUM : -CH=CH-CO(m,1H,6.68 ppm), -CH=CH-CO (td, 1H, 5.96 ppm, J= 8 Hz), $>C=CH_2$(2s,2H, 4.78 and 4.46 ppm) $-COCH_3$(s, 3H, 2.16 ppm) and a quaternary methyl (s,3H, 1.08 ppm). MASS SPECTRUM : important ions at m/e 204(M^+,9%), 176(4%), 161(7%), 121(100%), 105(19%), 93(72%), 91(34%), 79(52%), 77(32%), 67(14%),and 43(49%). Found C, 82.50; H,10.05. $C_{14}H_{20}O$ requires: C, 82.35; H, 09.80.

THE OLEFIN-KETONE(XV)

A solution of the α-, β-unsaturated ketone (XIV, 0.052g, 0.25 m moles) in dry dioxan and ether (each 1 ml) was added dropwise to a stirred solution of lithium (0.012 g, 1.7 m moles) in liquid ammonia (10 ml). After the addition was over(20 minutes), it was further stirred for 30 minutes. Solid NH_4Cl(0.08 g, 1.5 m moles) was added and the ammonia allowed

to evaporate. Water(10 ml) was added to the residue and extracted with ether(5 ml x 2). Drying and solvent evaporation gave the product(0.052 g) which upon distillation furnished the desired olefin-ketone(XV, 0.048 g, ~93%yield, b.p. bath 125-130°(0.5 torr). GLC: 98% pure (10% carbowax, 12', 200°C).

IR SPECTRUM: 1725 cm^{-1} (>C=O) and 3075, 1660 and 885 cm^{-1} (>C=CH_2). PMR SPECTRUM: >C=$\underline{CH_2}$(2s, 2H, 4.68 and 4.40 ppm), >C($\underline{H}$)-C=(bs, 1H, 2.64 ppm), -$\underline{CH_2}$COMe(t,2H,2.3 ppm, J=7 Hz), -CO$\underline{Me}$(s, 3H, 2.03 ppm) and a quaternary methyl(s,3H, 1.03 ppm), MASS SPECTRUM : m/e 206(M^+,7%), 191(2%), 122(100%),121(94%), 120(15%), 107(12%), 105(14%), 93(82%), 85(36%),79(43%) and 67(7%). Found : C, 81.10; H,10.55. Calculated for $C_{14}H_{22}O$: C, 81.55: H,10.68.

THE OLEFIN-ALCOHOL(XVI)

A solution of the olefin-ketone(XV, 0.053 g, 0.25 m moles) in ether (5 ml) was added dropwise to a 0.2 molar excess of methyl magnesium iodide(prepared from 0.008 mg Mg and MeI) in ether under stirring at 3-5°C. After the addition was over (20 minutes), the reaction mixture was further stirred at the same temperature (3-5°C) for 30 minutes and then at ~30°C for an hour. Brine (2 ml) was added to the reaction mixture and the organic phase separated from the aqueous portion.

Drying and solvent evaporation gave the crude olefin-alcohol (XVI, 0.0552 g, 95% yield, tlc pure).

IR SPECTRUM: 3620 cm^{-1}(OH) and 3080,1660 and 885 cm^{-1}(>C= CH_2). PMR SPECTRUM >C=$\underline{CH_2}$(2s, 2H, 4.64 and 4.37 ppm), >C($\underline{H}$)-C=(bs, 1H, 2.59 ppm), -C($\underline{Me_2}$)OH(s,6H, 1.1 ppm) and a quaternary methyl(s, 3H, 0.96 ppm).

β-SANTALENE (XVII)

A solution of thionyl chloride (0.04 ml) in pyridine (2 ml) was added dropwise to a stirred solution of the tertiary carbinol (XVI, 0.054 g, 0.25 m moles) in dry pyridine(3 ml) at -20° to -15°C. After the addition was over (20 minutes), the stirring was continuted at the same temperature(-20° to -15°C) for an hour and then left as such at ~30°C for 15 hours. It was poured into ice-water (15 g) and extracted with ether (7 ml x3). The combined extract was washed successively with cold 5% HCl aqueous (5 ml x 3), water (5 ml x 2) and brine (5 ml x 1). Drying and solvent evaporation yielded a material (0.05 g) whichw as distilled (0.040 g, ~80% yield, b.p.bath 130-135°/0.5 torr) and analyzed by glc. Mixed injection of this material and of β-santalene(natural, isolated from s andalwood oil) showed this product to consist of β-santalene(~46%) and one more component (~54%), probably the double bond

isomer(XVIII). This analysis was supported by the mixture's PMR spectrum also.

THE OLEFIN-ESTER(XXII)

NaOH(0.5085 g, 12.7 m moles) and diethylene glycol (5.1 ml) were heated to 170-180°(oil-bath temperature) when a part of it distilled out. The resulting thick slurry was equivalent to 2.3 m moles NaOH.

Lactone(V, 1.0 g, 5.56 m moles) and the above reagent 2.3 m moles were heated first to 245±5°C for 2 hours and then to 210° for 6 hours under slow nitrogen flow. It was now allowed to cool to room temperature and then poured into water (25 ml). It was neutralized with dilute HCl and extracted with ether (10 ml x 2). The combined extract was washed with water (7 ml x 2) and brine (7 ml x 1). Drying and solvent removal gave the crude product (1.424 g).

A portion of the above crude product(0.20 g) was esterified with diazomethane and the distilled product(0.072g, b.p. bath 100-110°/0.3 torr) was chromatographed over SiO_2/IIA(7.5 g, 20 cm X 0.7 cm) when elution with benzene (60 ml) gave the pure olefin ester(XXII, 0.061 g, overall yield = ~40%, b.p. bath 100-105°/0.3 torr) GLC: 96% pure (10% carbowax, 12', 200°C.

THE ALCOHOL (XX) AND THE 1,3-DIENE(XXI)

A solution of the olefin aldehyde (XIII, 0.656 g, 4 m moles) in THF (5 ml) was added dropwise to 0.2 molar excess of the Grignard reagent from β,β -dimethyl vinyl bromide (prepared by using 117 mg Mg and 550 mg β,β -dimethyl vinyl bromide) at 5-10°C. After the addition was over (30 minutes), stirring at the same temperature(5-10°C)was continued for an hour and was then gently refluxed for 30 minutes. This was allowed to cool to room temperature and decomposed with saturated NH_4Cl aqueous solution(1 ml). The organic layer was dried and the solvent removed under reduced pressure (150 torr). The crude product (0.9 g),on distillation,furnished a material (0.72 g, b.p. bath 120-130°/0.3 torr) which when analyzed by glc(10% SE-30, 6', 170°C) was found to be a mixture of at least 6 components. Compounds corresponding to peaks 3 and 4 (Fig 19) were isolated pure by preparative glc(20% SE-30, 12', 170°) and identified as (XXI) and (XX), respectively.

REFERENCES

1. E.Gildemeister and Fr.Hoffmann, Die atherischen Ole. Vol IV, p 571, Akademie Verlag, Berlin 1956.
2. H.C.Kretschmar, Z.I.Barneis and W.F.Erman, Tetrahedron Letters, 37(1970).
3. T.Gibson and Z.I.Barneis, Tetrahedron Letters, 2207(1972).
4. F.Demole, C.Demole and P.Enggist, Helv.Chim.Acta 59 737(1976).
5. W.R.Vaughan, J.Wolinsky, R.R.Dueltgen, S.Grey and F.S. Seichter, J.Org.Chem, 35 400(1970).
6. P.Christenson and Brian J.Willis, J.Org.Chem.,44 2012(1979).
7. E.J.Corey and H.Yamamoto, J.Am.Chem.Soc., 92 226(1970).
8. A.T.Nielsen and W.J.Houlihan in Organic Reactions Vol. 16, p. 1-438.
9. (a) E.J.Corey and K.Achiwa, J.Org.Chem. 34 3667(1969).
   (b) E.W.Collington and A.I.Meyers, J.Org.Chem. 36 3044(1971).
   (c) R.M.Magid, O.S.Fruchey and W.L.Hohnson,Tetrahedron Letters 2999(1977).
   (d) H.C.Brown and S.Krishnamurthy, J.Org.Chem 34 3918(1969).
   (e) H.M.Bell, C.W.Vanderslice and A.Spehar, J.Org.Chem. 34 3923(1969).
   (f) P.Kocovsky and V.Cerny, Collect. Czech.Chem.Commun. 44 246(1979).
10. (a) A.Vilsmeier and A.Haack,Chem. Ber, 60B 119(1927).
    (b) E.Campaigne and W.L.Archer, Org.Synth Coll.Vol.4, 331(1963).

(c) G.F.Smith, J.Chem. Soc., 3842(1954); P.N.James and H.R.Snyder, Org.Synth. Coll Vol.4,539(1963).

(d) D.Burn, Chem. Ind., 870(1973).

11. C.Jutz and W.Muller, Chem. Ber., 100 1536(1967).

12. R.Sobti and Sukh Dev, Tetrahedron,30 2927(1974).

13. A.B.Upadye, M.S.Wadia, V.V.Mhaskar and Sukh Dev, Tetrahedron, 26 4177(1970); A.B.Upadhye, M.S.Wadia, V.V.Mhaskar and Sukh Dev, Tetrahedron, 28 1933(1972).

14. (a) E.Von Rudloff, Can.J.Chem., 39 1860(1961).

(b) E.J.Corey and A.G.Hortmann, J.Am.Chem.Soc. 87 5736(1965).

15. (a) W.Brandenberg and A.Galat, J.Am.Chem.Soc., 72 3275(1950).

(b) J.R.B.Campbell, A.M.Islam, and R.A.Raphael, J.Chem.Soc., 4096(1956).

(c) O.L.Chapman and G.W.Borden, J.Org.Chem., 26 4193(1961).

16. H.Heymann and L.F.Fieser, J.Am. Chem. Soc., 73 5252(1951).

17. (a) A.Drake, A.Fonken, and R.B.Haward, British patent 790,452; C.A. 52 14722i(1958).

(b) W.J.Wechter and G.Slomp, J.Org.Chem., 27 2549(1962).

(c) H.A.Drake, R.B.Howard, and A.E.Fonken,U.S.patent 3,005,834; C.A 52 14722i (1958).

18. C.Frisell and S.O.Lawesson, Arkiv Kemi, 17 401(1961).

19. V.J.Traynelis and W.L.Hergenrother, J.Org.Chem., 29 221(1964).

20. R.H.Bible, Jr. and N.W.Atwater, J.Org. Chem. 26 1336(1961).

21. E.Keinan and Y.Mazur, J.Org. Chem.,43 1020(1978).

22. G.G.Hazen and D.W.Rosenberg, J.Org.Chem,29 1930(1964).

23. E.P.Kohler, M.Tishler, H.Polter, and H.T.Thompson, J.Am.Chem.Soc.,61 1057(1939).

24. R.B.Carlin and D.A.Constantine, J.Am.Chem.Soc. 69 50(1947).

25. W.Oroshnik, G.Karmas, and A.D.Mebane, J.Am.Chem.Soc., 74 295(1952).

26. L.H.Sarett, J.Am.Chem.Soc., 71 2443(1949).

27. (a) W.S.Allen and S.Bernstein, J.Am.Chem.Soc.,77 1028 (1955).

(b) S.Bernstein, R.H.Lenhard, W.S.Allen, M.Heller, R.Littell, S.M.Stelar, L.I.Feldman, and R.H.Blank, J.Am.Chem. Soc., 78 5693(1956).

28. (a) H.H.Inhoffen, H.Siemer, and K.D.Mohle,Annalen, 585 126(1954).

(b) C.G.Overberger and J.H.Saunders, Org.Synthesis., Coll. Vol 3, 204(1955).

29. (a) F.Sondheimer, R.Mechoulam, and M.Sprecher, Tetrahedron, 20 2473(1964).

(b) E.Wenkert and T.E.Stevens, J.Am.Chem.Soc., 78 2318(1956).

30. O.Wintersteiner and M.Moore, J.Am.Chem.Soc., 65 1503, 1507(1943).

31. K.M.Saplay, J.Chem.Educ. 57 124(1980).

32. (a) M.S.Newman and T.Otsuka, J.Org.Chem., 23 797(1958).
(b) M.S.Hewman and R.M.Wise, J.Am.Chem.Soc. 78 450(1956).

33. F.A.Bovey, NMR Data Tables for Organic Compounds, Vol 1 Interscience Publishers, New York, 1967.

34. G.I.Poos, G.E.Arth, R.E.Beyler, and L.H.Sarett, J.Am.Chem. Soc., 75 422(1953).

35. R.H.Cornforth, J.W.Cornforth, and G.Popjak, Tetrahedron 18 1351(1962).

36. G.Snatzke, Chem. Ber, 94 729(1961).

37. K.E.Pfitzner and J.G.Moffatt, J.Am.Chem.Soc., 85 3027 (1963); definitive papers, J.Am.Chem.Soc., 87 5661, 5670(1965).

38. E.J.Corey and I.W.Suggs, Tetrahedron Letters, 2647(1975).

39. (a) A.Windaus, Chem.Ber, 39 2249(1906).
(b) L.F.Fieser and J.E.Herz, J.Am.Chem.Soc.,75 121(1953).
(c) J.G.St.C.Buchanan and P.D.Woodgate, Quart.Rev.,23 522(1969).

40. E.C.Ashby and J.J.Lin, Tetrahedron Letters, 4453(1975).

41. (a) A.J.Birch and H.Smith, Quart. Rev., 13 17(1958).
(b) G.W.Watt, Chem. Rev, 46 317(1950).
(c) J.L.Dye, Accts. Chem.Res., 1 306(1968).
(d) G.S.R.Subbarao and N.S.Sundar, J.Chem.Res(S) 282(1979).

42.(a) Gilbert Stork and S.D.Darling, J.Am.Chem.Soc., 86 1761(1964).

(b) F.Sondheimer, O.Mancera, G.Rosenkranj, and C.Djerassi, J.Am.Chem.Soc., 75 1282(1953).

43. H.Normant in Advances in Organic Chemistry Vol II, Interscience Publishers, New York, 1960.

SUMMARY

9-Cyanomethyl camphene, which has earlier been converted into (±) β-santalol by using a set of very straightforward and standardized reactions, has been prepared from 9-hydroxymethyl camphene in two/three steps. 9-Hydroxymethyl camphene has also been converted into an allylic tertiary carbinol which has a potential of becoming a good substitute for sandalwood oil. β-Santalene along with its double bond isomer has been synthesized through a twelve step sequence using the readily available camphene as the starting material.