PART - B

A SYNTHESIS OF PYROCURZERENONE

ABSTRACT

Acylation of m-cresyl methyl ether with succinic anhydride in presence of anhydrous aluminium chloride gave β-(2-methyl-4-methoxy)ᴐbenzoyl propionic acid (5.3a) as a major product which on Clemmensen reduction gave 4-(2-methyl-4-methoxyphenyl)ᴐbutyric acid (5.5a). The PPA cyclization of this acid (5.5) gave 5-methyl-7-methoxy-1-tetralone (5.6) and 5-methoxy-7-methyl 1-tetralone (5.7), the former being the major one.

The formylation of tetralone (5.6) with ethyl formate, in presence of sodium methoxide gave 2-hydroxymethylene-5-methyl-7-methoxy-1-tetralone (5.8). The tetralone (5.8) was converted into it's thioether (5.9) with n-butyl-mercaptan and then desulphurised with W-2 Raney nickel to give 2,5-dimethyl-7-methoxy-1-tetralone (5.10), an essential intermediate for the synthesis of pyrocurzerenone.

Demethylation of tetralone (5.10=7.1) with aluminium iodide gave 2,5-dimethyl-7-hydroxy-1-tetralone (7.2). The phenolic tetralone (7.2) was treated with bromoacetone to furnish the corresponding acetonyloxy tetralone (7.3). The cyclization of (7.3) with trifluoroacetic acid as well as PPA gave the desired naphthofuranone (7.4). Naphthofuranone (7.4) on reduction with sodium borohydride followed by dehydration of the resultant alcohol (7.5) with p-Ts as well as iodine gave pyrocurzerenone (7.6).

p-TSA

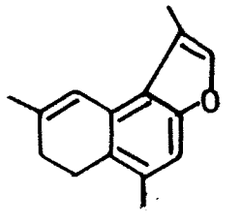
INTRODUCTION

Pyrocurzerenone [6,7-dihydro-1,5,8-trimethylnaphtho (2,1-b) furan] (1.1) claimed to be the first furocadinane sesquiterpenoid was isolated[1] from rhizomes of *Curcuma zedoaria* Roscoe. It's structure was deduced mainly on the basis of spectral data and by an interesting pyrolytic transformation involving a double Cope rearrangement by which curzerenone (1.2) and it's epimer (1.3) gave pyrocurzerenone.

The UV spectrum of pyrocurzerenone (λ_{max} : 233, 239, 249, 283 and 293 nm) (Log ϵ 4.75, 4.72, 4.62, 4.4 and 4.4) suggests the presence of benzofuran further conjugated with an ethylene bond. The PMR spectrum showed the presence of α-hydrogen (7.10) and β-methyl (2.31) on furan ring. It also showed the presence of aromatic methyl (2.25), methyl on ethylenic linkage (1.92) and four allylic hydrogens (2.0 to 2.75). The aromatic hydrogen appeared at (6.91) and hydrogen on ethylenic linkage at (6.69). Further, the occurrence of an intramolecular nuclear overhauser effect was observed between β-methyl of furan (2.31) and hydrogen on ethylenic linkage (6.69) demonstrating that both are very close in space.

In the pyrolytic transformation of curzerenone to pyrocurzerenone, a preliminary Cope rearrangement was presumed to give furanodienone which further undergoes a second Cope rearrangement followed by dehydration to give pyrocurzerenone. The furanocadalene (1.5) must be getting formed from pyrocurzerenone by transfer of hydrogen, to another molecule of pyrocurzerenone or to the starting substance curzerenone.

CHART-1



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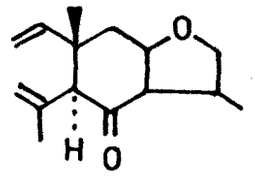

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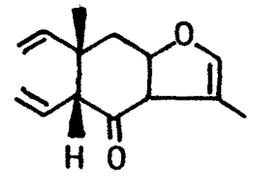

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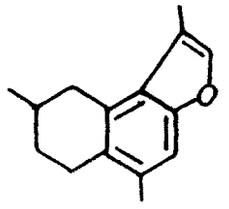

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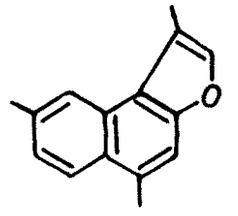

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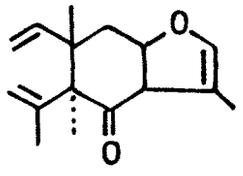
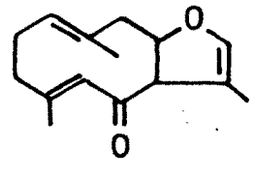
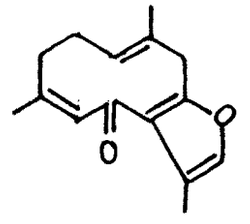
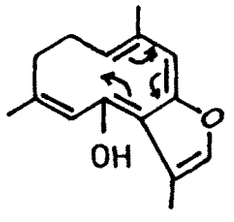


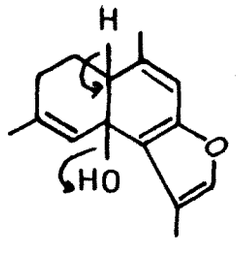
(2)

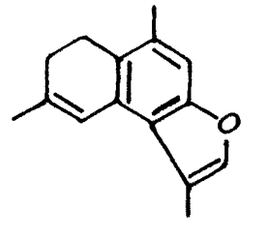
Cope rearrangement











The structure of pyrocurzerenone (1.1) and it's pyrolytic disproportionation products dihydropyrocurzerenone (1.4) and furocadalene (1.5) was substantiated by it's synthesis[2] [Chart-3] by V. Vishwanath and G.S.K. Rao. The second total synthesis of curzerenone, it's epimer and pyrocurzerenone has also been reported[3] via 2-methyl furan annulation reaction using 1-nitro-1 (phenyl thio)propene in a crucial step [Chart-4].

Pyrocurzerenone (2.1) is structurally related to furanoeremophilane, 1-oxo-9-desoxycacalol (2.2), cacalol (2.3) and cacalone (2.4) isolated from the leaf extract of Bolivian *Senecio serratifolis*[4] and Mexican shrub *Cacalia decomposita*[5] respectively.

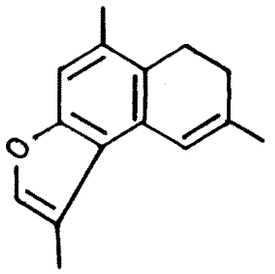
Our earlier studies ref. on the synthesis of 1-oxo-9-desoxycacalol using β-benzoyl propionic acid (2.5) as a starting material prompted us to undertake the synthesis of pyrocurzerenone from the same intermediate β-keto acid (2.5).

PRESENT WORK

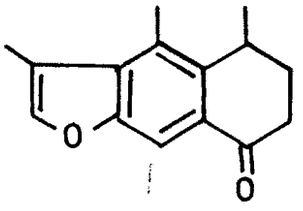
Friedel-Craft's acylation of m-cresyl methyl ether with succinic anhydride[6] in presence of anhydrous aluminium chloride gave β-(2-methyl-4-methoxy) benzoyl propionic acid (5.3a). This was suspected to contain a small impurity of *ortho* acylated product viz. β-(2-methoxy-4-methyl) benzoyl propionic acid (5.3b), as the melting point of recrystallised acid did not match perfectly with the one reported earlier[6b]. With a view to checking the purity of acid, small amount of acid (5.3) was converted into it's methyl ester (5.4) using methanol sulphuric acid. The examination of TLC of the ester (5.4) showed two close spots. One (nearly 10%) with higher R_f value appeared like

From what

CHART-2



(1)



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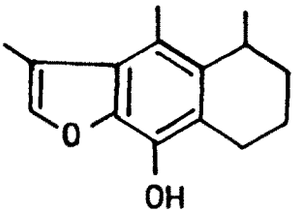

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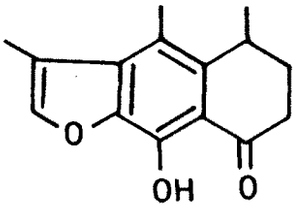

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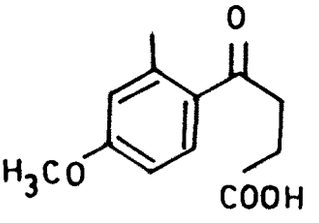

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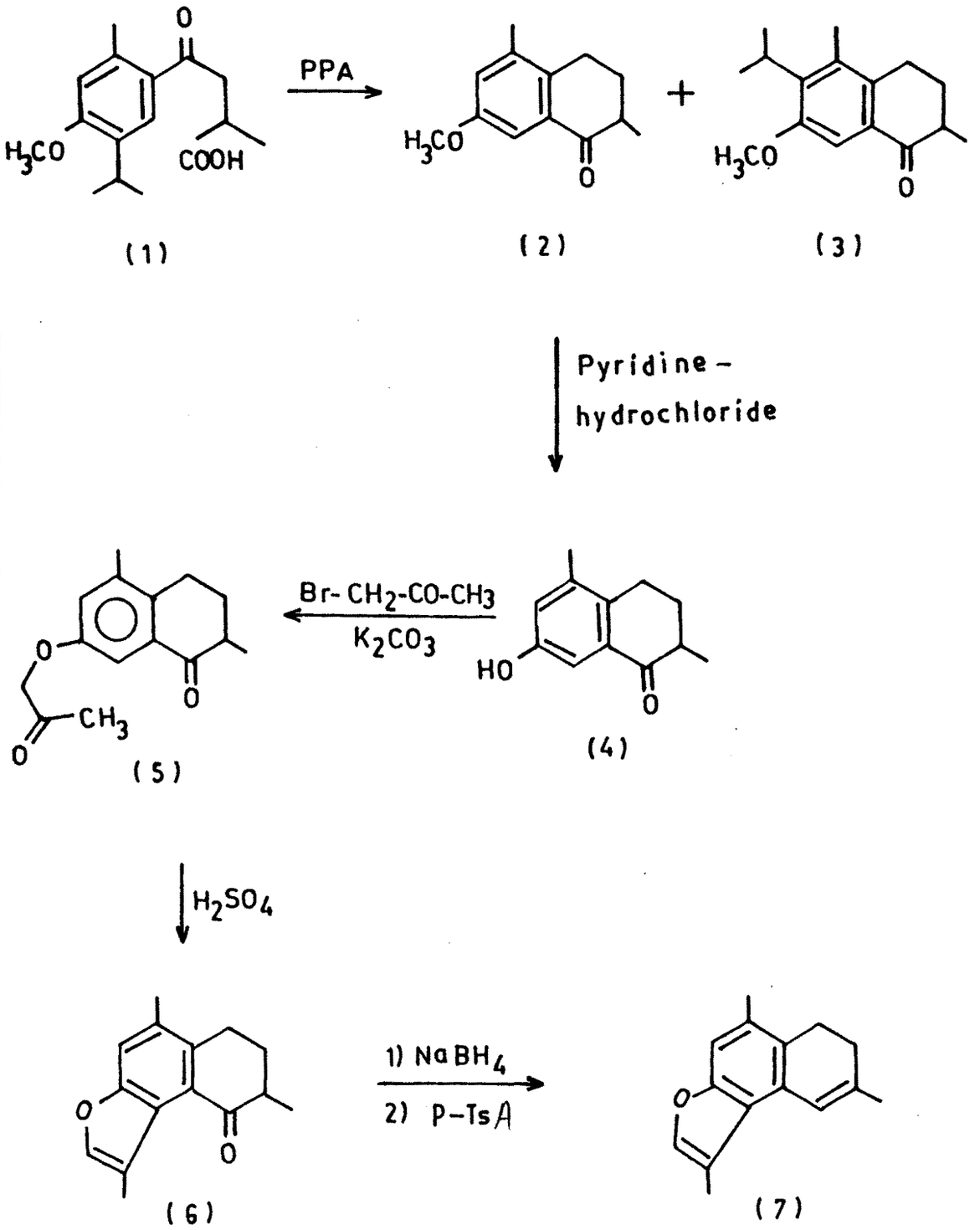
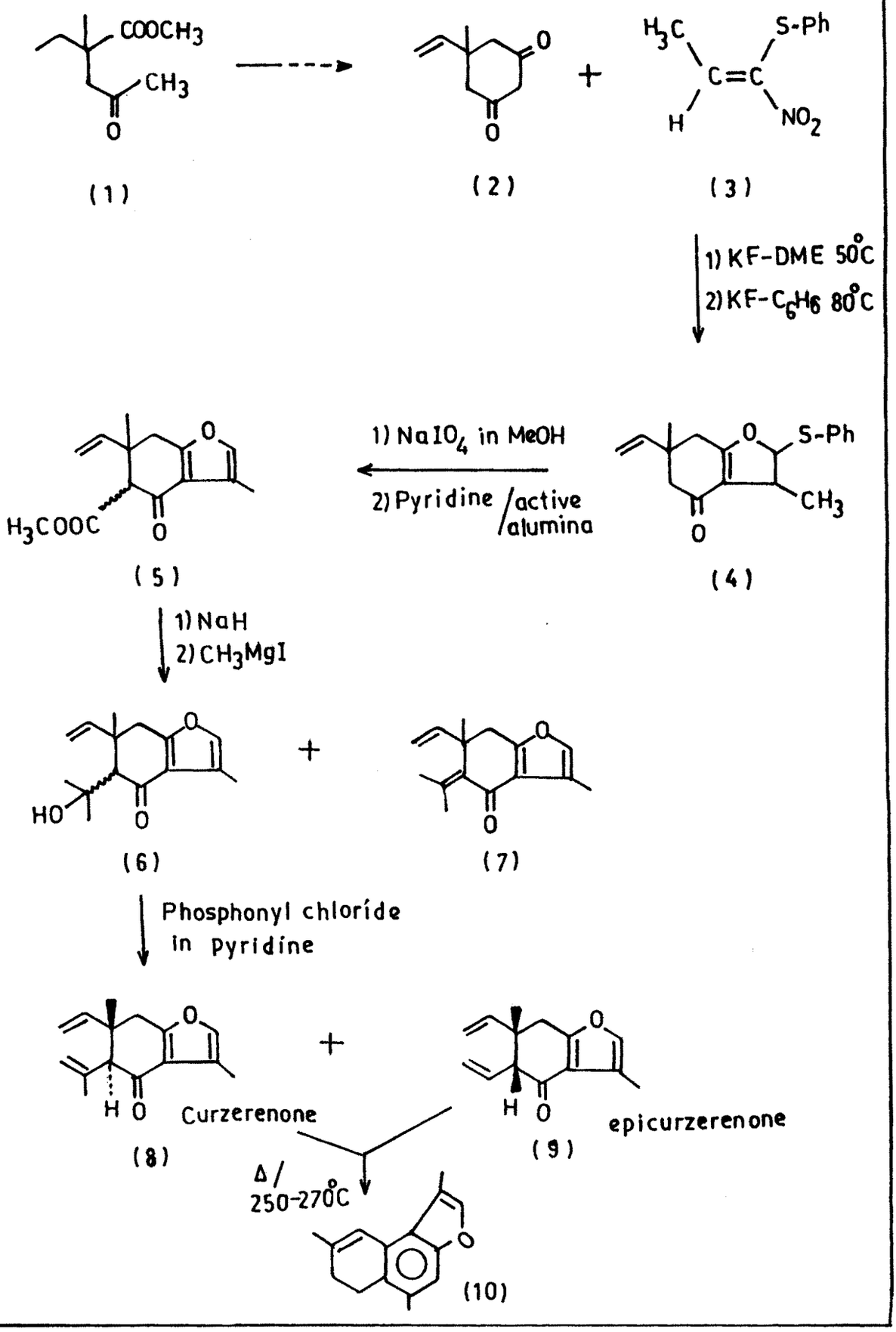
CHART-3



V. Vishwanath and G.S.K. Rao's synthesis of Pyrocurzerenone .

CHART-4

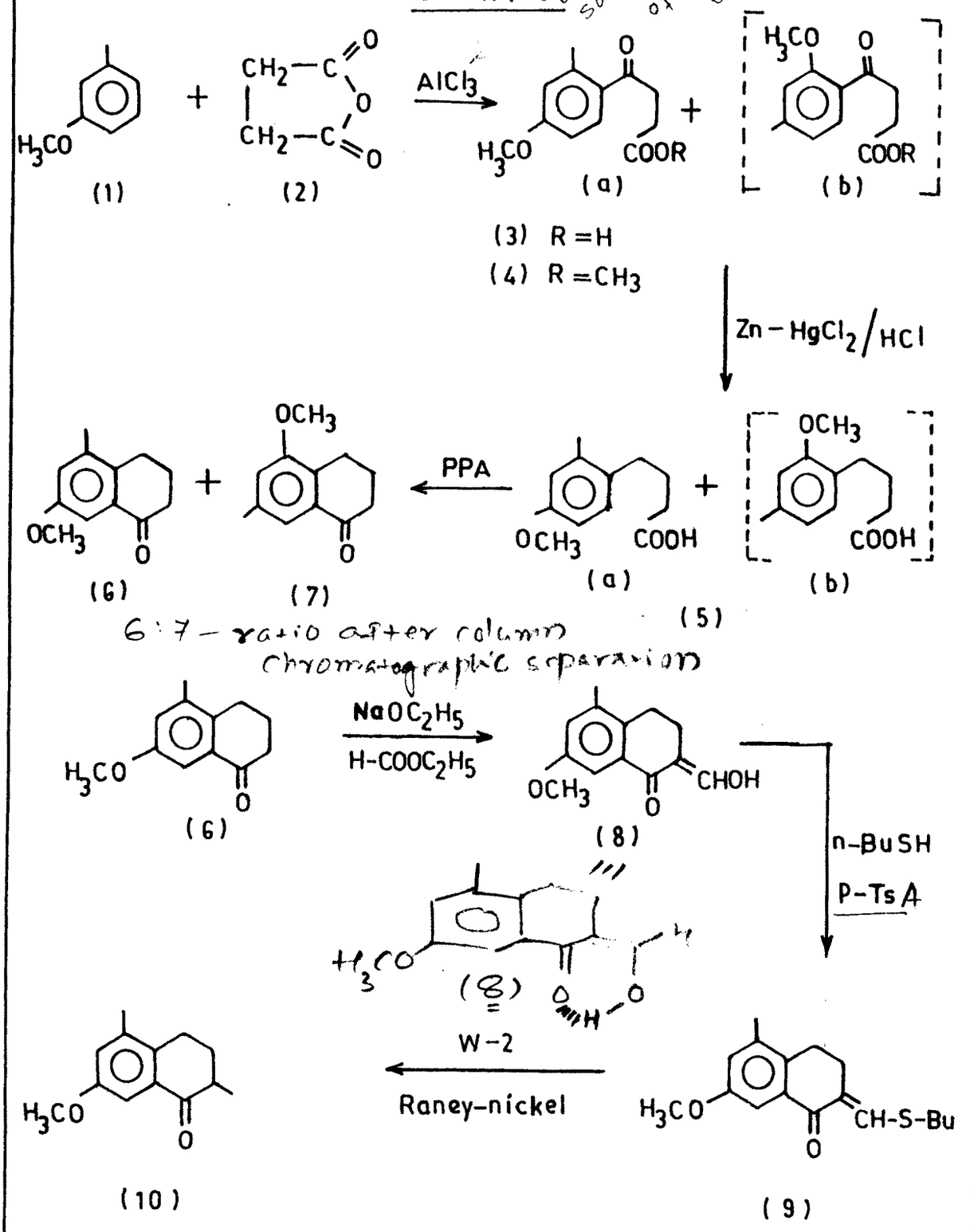

COOCH3
CH3
O
(1)
O
O
(2)
H3C
S-Ph
C=C
H
NO2
(3)
1) KF-DME 50°C
2) KF-C6H6 80°C
O
S-Ph
CH3
O
(4)
1) NaIO4 in MeOH
2) Pyridine /active alumina
O
H3COOC
O
(5)
1) NaH
2) CH3MgI
O
HO
O
(6)
+
O
O
(7)
Phosphonyl chloride in pyridine
O
H O
Curzerenone
(8)
+
O
H O
epicurzerenone
(9)
Δ/ 250-270°C
O
(10)

a cap over the other spot of major component (nearly 90%) with lower R_f value. The methyl ester (5.4) was separated on preparative TLC plates and the major component was identified to be the methyl ester, of *para* acylated product (5.3a) on the basis of spectral evidence. It showed a strong ester carbonyl peak at 1725 and a ketone carbonyl at 1680 cm^{-1} in the IR spectrum (fig.1). The PMR spectrum (fig.2) exhibited the signals due to aromatic methyl, ester methyl and methoxyl group at 2.26, 3.72 and 3.85 respectively. The ketomethylene appeared as a triplet at 3.26 while the methylene group adjacent to ester also appeared as a triplet at 2.76. Two aromatic protons *ortho* to methoxyl group appeared as a multiplet at 6.78 and the proton *meta* to methoxyl group appeared as a doublet at 7.78. The downfield shift for aromatic methyl (δ 2.6) is indicative of *ortho* ketonic group. No attempt was made to separate *ortho* and *para* succinoylated products (5.3a & 5.3b) at this stage.

Clemmensen reduction[7] of the acid (5.3) yielded 4-(2-methyl-4-methoxyphenyl) butyric acid (5.5a) which was expected to contain small amount of 4-(2-methoxy-4-methylphenyl) butyric acid (5.5b). The melting point of reduced acid was in close agreement with that reported earlier[8]. The acid (5.5) was cyclised with polyphosphoric acid[9] to give 5-methyl-7-methoxy-1-tetralone (5.6) as major component along with small amount of 5-methoxy-7-methyl-1-tetralone (5.7). The two tetralones were separated effectively by column chromatography and their structures confirmed spectroscopically. The IR spectrum (fig.3) of tetralone (5.6) showed a strong peak at 1680 cm^{-1}, for aromatic ketone. The PMR spectrum (fig.4) showed a multiplet for homobenzylic methylene group at 2.2, a singlet for aromatic

AlCl3 with some demethylation of -OCH3 to -OH will also be seem in product mixture.

CHART-5



methyl at 2.3, a multiplet for ketomethylene and benzylic methylene group at 2.7, a singlet at 3.9 for aromatic methoxyl group, two broad singlets for aromatic protons *ortho* and *para* to methyl group at 7.0 and 7.5 respectively. The proton appearing at 7.5 must have been deshielded due to the presence of *peri* carbonyl group. The enlargement of aromatic signals in PMR spectrum showed them to be sharp doublets with a small coupling constant of 2 Hz, which is in perfect agreement with their *meta* disposition.

The IR spectrum of tetralone (5.7, fig.5) and PMR spectrum (fig.6) were very much similar to that for tetralone (5.6). This was assigned the structure 5-methoxy-7-methyl-1-tetralone, as it was obtained in minor amount. This is in agreement with the fact that, during succinoylation *ortho* acylated product was present but to a minor extent, though literature[10] reports the formation of single component (*para* acylated product).

The next strategy towards the synthesis was to monoalkylate the ketone (5.6) to (5.10). Several methods are reported in the literature[11] for alkylation of ketones. The method involving the use of sodium hydride and methyl iodide[12] may yield the desired mono methylated ketone (5.10) along with the bis-alkylated product, which is undesired. The conversion of tetralone (5.6) into it's enamine followed by alkylation was another option but yields reported in similar alkylation[13] have been poor.

A number of methods have been used to improve selectivity in the alkylation in high yields and to reduce the amount of polyalkylation. One widely used procedure is to introduce temporarily an activating group at α-position to stabilise the corresponding enolate anion. This group is removed

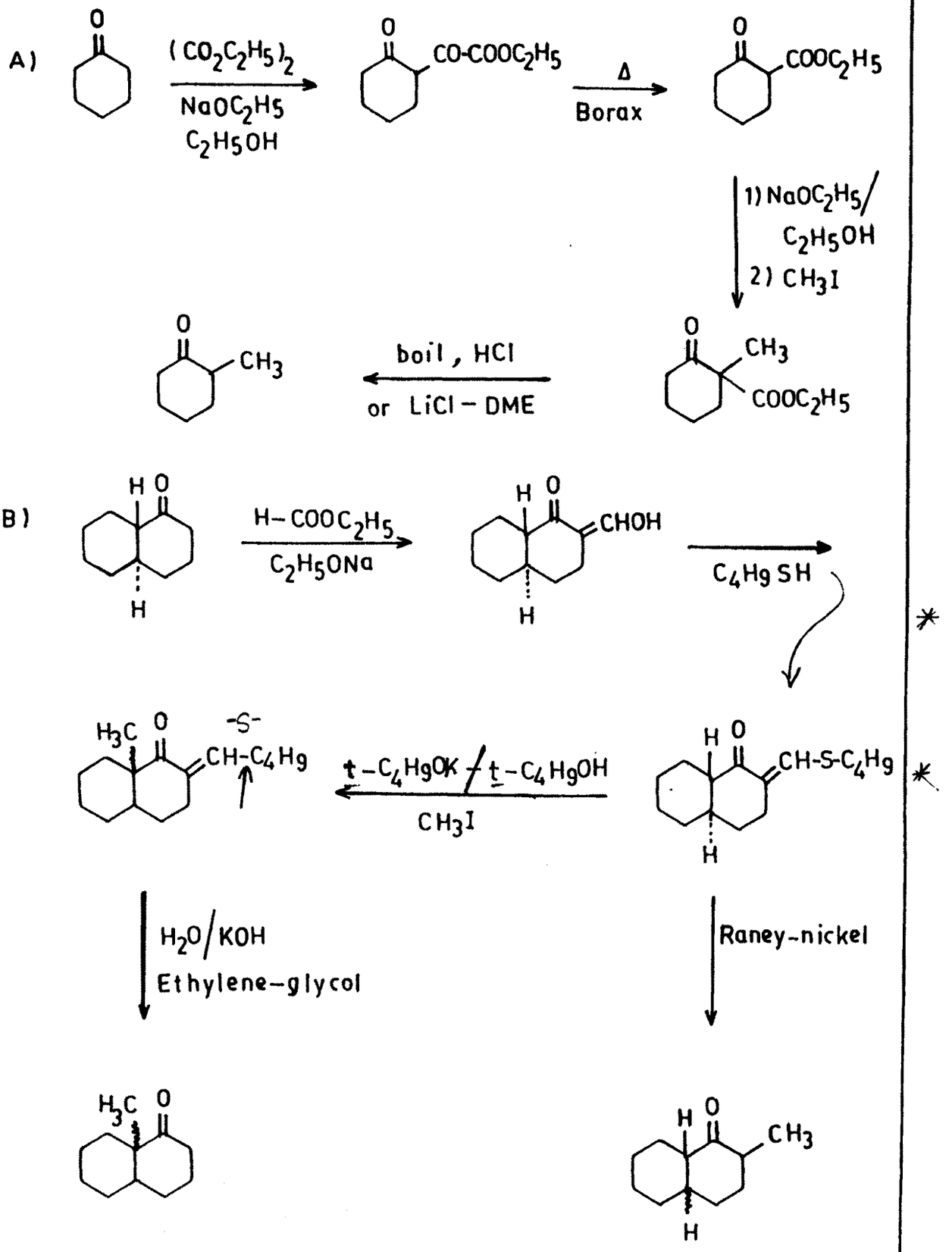
later after the alkylation has been effected. Common activating groups used for this purpose are ethoxycarbonyl, ethoxyoxalyl and formyl group. Thus for e.g. to prepare 2-methyl cyclohexanone from cyclohexanone, the best procedure is to go through the 2-ethoxycarbonyl derivative, which is easily obtained from the ketone by reaction with ethyl carbonate or by condensation with diethyl oxalate followed by decarbonylation. Now, the conversion into enolate ion with a base such as sodium ethoxide takes place exclusively at the doubly activated position. Methylation of such 2-ethoxy carbonyl derivative with methyl iodide and removal of β-ketoester group with acid or base gives 2-methyl cyclohexanone, free from polyalkylated products [Chart-6A].

Another technique is to acylate the ketone with ethyl formate and to transform the resulting formyl group or hydroxymethylene substitutent into a group that is stable to base, such as enamine, an enol ether or an enol thioether. The enol thioether on reduction with Raney nickel gives exclusively monoalkylated product. Instead of one, if two α-positions are available, one of the α-position can be blocked by the same technique of conversion to an enol-thioether. This group is removed later after alkylation is effected at other α-position [Chart-6B].

We planned the conversion of tetralone (5.6) by formylation to it's hydroxymethylene derivative (5.8), then into it's thioenol ether (5.9), followed by Mozingo desulphurization with W-2 Raney nickel to get the methylated ketone (5.10)[14].

The tetralone (5.6) was formylated with ethyl formate in presence of sodium methoxide. The formylation proceeds smoothly and the formylated

CHART-6


A)
$(CO_2C_2H_5)_2$
$NaOC_2H_5$
C_2H_5OH
CO-COOC$_2$H$_5$
Δ
Borax
COOC$_2$H$_5$
1) $NaOC_2H_5$/ C_2H_5OH
2) CH_3I
CH$_3$
COOC$_2$H$_5$
boil, HCl
or LiCl – DME
CH$_3$
B)
H–COOC$_2$H$_5$
C_2H_5ONa
CHOH
C_4H_9SH
t-C_4H_9OK / t-C_4H_9OH
CH_3I
CH-S-C$_4$H$_9$
H_2O/KOH
Ethylene-glycol
Raney-nickel
CH$_3$

product remains in it's enolic form (5.8) as evidenced by it's PMR specturm (fig.7). The PMR spectrum exhibited two singlets for aromatic methyl and methoxyl group at 2.3 and 3.9 respectively. It also showed, two clear triplets with J=7 Hz for homobenzylic methylene at 2.55 and for benzylic methylene at 2.8. Two aromatic *meta* coupled protons appeared as two sharp doublets (J=2 Hz) at 6.95 and 7.4. A broad singlet at 8.2 was due to the olefinic proton and a highly deshielded enolic proton appeared at 14.6.

The appearance of triplet for homobenzylic methylene clearly indicated the enolic form of formylated product (5.8).

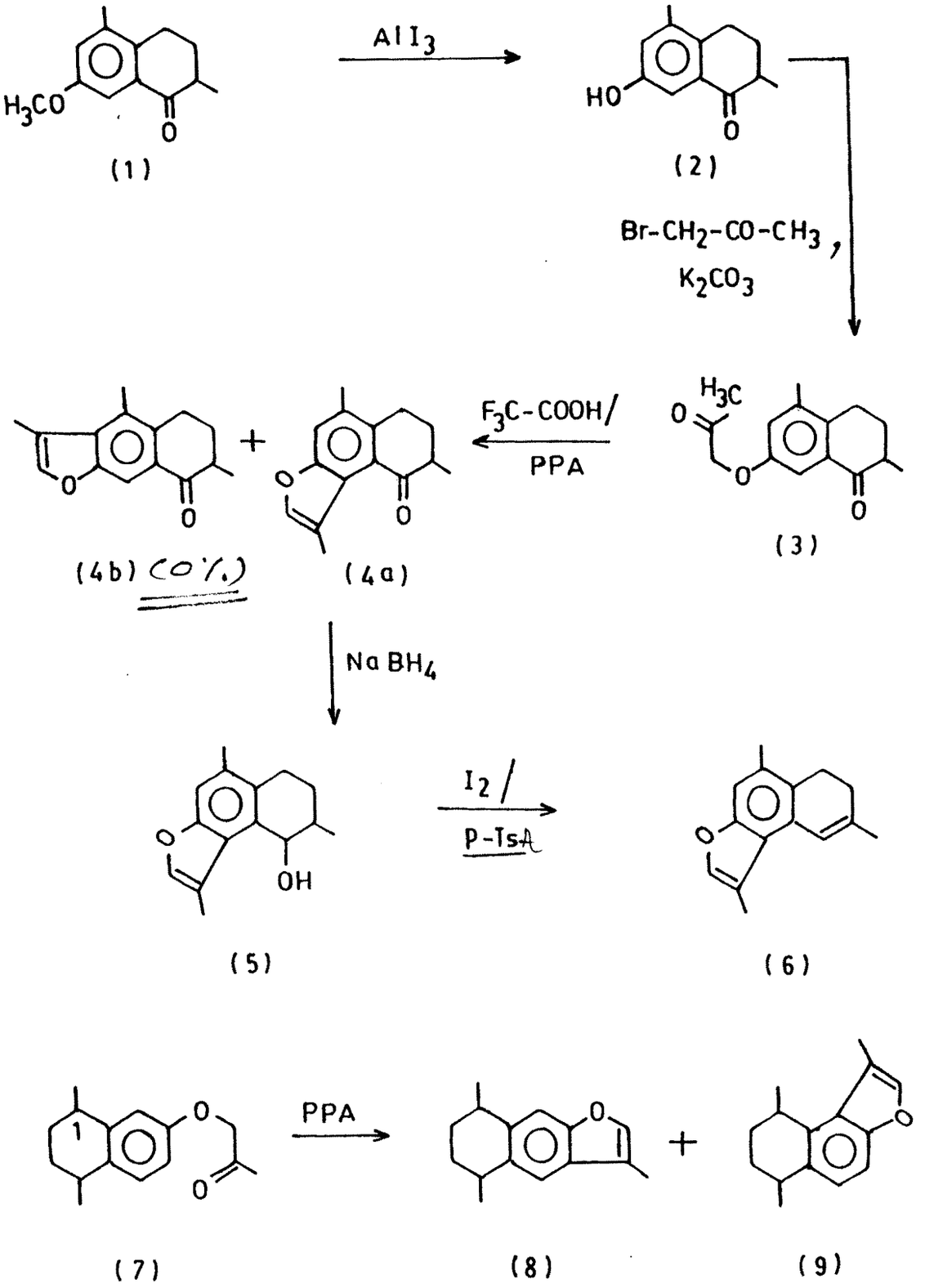
The hydroxymethylene tetralone (5.8) was refluxed with n-butyl mercaptan in presence of para-toluenesulphonic acid which gave 2-butyl thiomethylene derivative (5.9). The IR spectrum (fig.8) showed peaks at 1650 (ketone), 1560 (thiomethylene group) cm^{-1}. The PMR spectrum (fig.9) exhibited a triplet of δ 0.9 (J=7Hz) for aliphatic methyl group (from butyl chain), a multiplet for six protons, four from butyl chain and two from homobenzylic methylene appeared as at 1.6 while four protons, two from benzylic methylene and two from thiomethylene group appeared as a multiplet between 2.7 to 3.0, two sharp singlets at 2.3 and 3.9 were due to aromatic methyl and methoxyl group respectively and two aromatic *meta* coupled protons appeared as doublets (J=2Hz) at 7.0 and 7.5 respectively. The olefinic proton appeared at 7.8 as a singlet.

2-Butyl thiomethylene derivative (5.9) was subjected to Mozingo desulphurisation with W-2 Raney nickel[15] to yield desired 2,5-dimethyl-7-methoxy-1-tetralone (5.10). The conversion of (5.6) to (5.10) takes place in

high yield (~80%) and possibility of bis-alkylated product is no more. The IR spectrum (fig.10) of this methylated ketone showed a peak at 1680 cm^{-1} for ketone carbonyl while PMR spectrum (fig.11) indicated two singlets at 2.2 and 3.9 for aromatic methyl and methoxyl group respectively, a characteristic doublet for secondary methyl group appeared at 1.25, a multiplet at 1.9 was due to homobenzylic methylene and that between 2.5 to 3.0 was due to benzylic methylene and methine proton. Two broad singlets at 7.0 and 7.5 were due to aromatic protons *ortho* and *para* to methyl group respectively. The appearance of a doublet at 1.25 was a clear indication for the formation of monoalkylated product.

The next step was the demethylation of methoxy tetralone (5.10=7.1). This was initially achieved using pyridine hydrochloride[2] which involved heating of (7.1) with pyridine hydrochloride at a high temperature of about 200°C. This introduced several polymeric and coloured impurities which were undesired at this stage. Hence, demethylation was achieved using aluminium iodide[16] at moderate temperature and in excellent yields. There was little formation of coloured as well as polymeric impurities. The phenolic tetralone (7.2) so prepared showed peaks at 3400 (hydroxyl) and 1670 (ketone) cm^{-1} in it's IR spectrum (fig.12). The PMR spectrum (fig. 13) exhibited a doublet at 1.25 for secondary methyl group, a multiplet at 1.8 for homobenzylic methylene group, and at 2.2 for benzylic methylene group, a sextet at 2.9 for methine proton, a singlet at 2.3 for aromatic methyl, a broad singlet at 5.7 for hydroxyl proton and two broad singlets at 7.10 and 7.60 for aromatic protons *ortho* and *para* to methyl group respectively.

CHART-7


AlI3
H3CO
HO
(1)
(2)
Br-CH2-CO-CH3,
K2CO3
F3C-COOH/
PPA
H3C
(4b) (20%)
(4a)
(3)
NaBH4
OH
I2 /
P-TsA
(5)
(6)
PPA
(7)
(8)
(9)

The phenolic tetralone (7.2) was treated with bromoacetone[17] in presence of potassium carbonate to yield the acetonyloxy tetralone (7.3). The IR spectrum (fig.14) indicated the absence of phenolic hydroxyl group. It showed two peaks at 1725 and 1680 cm^{-1} characteristic for the presence of saturated and aromatic ketones respectively. The PMR spectrum (fig.15) exhibited a doublet at 1.25 for secondary methyl, a multiplet at 1.9 for homobenzylic methylene, a triplet at 2.5 for benzylic methylene, a sextet at 2.9 for methine proton, a sharp singlet for six protons of keto methyl and aromatic methyl group at 2.2, a singlet at 4.65 for methylene group attached to oxygen and ketonic group, two broad singlets at 7.1 and 7.35 for aromatic protons *ortho* and *para* to methyl group respectively.

The acetonyloxy tetralone (7.3) was cyclized using PPA as well as trifluoroacetic acid to yield the naphthofuranone (7.4). The IR spectrum (fig.16) showed the presence of aromatic ketone 1685cm^{-1} and the absence of saturated ketone. The PMR spectrum (fig.17) showed a doublet at 1.25 for secondary methyl group, two singlets at 2.3 and 2.4 for aromatic methyl and furan methyl respectively and a singlet at 7.5 (two protons) for aromatic proton *ortho* to methyl group and that from furan ring.

The disappearance of a singlet for aromatic proton (δ 7.1, fig.15) clearly indicates that, cyclization has taken place but it tempts to conclude that, during cyclization second isomer (7.4b) might have been formed instead of (7.4a). Infact, it is quite known that during such cyclization aromatic proton signals get shifted to downfield positions. If cyclization of (7.3) would have yielded (7.4b) the signal due to proton *peri* to carbonyl would have been shifted to still downfield position (~7.8 to 8.0) but it has not so

happened. Thus, cyclization of acetonyloxy tetralone (7.3) has yielded (7.4a) and not (7.4b). Beyond this spectral assumption, the fact has also been proved earlier on the basis of synthetic evidence[2].

During cyclization of (7.3), the presence of keto group at position-1 must be responsible for exclusive formation of (7.4a) as there are reports in the literature[18] for the formation of mixture of isomers, when there is no keto group at position-1 (7.7 → 7.8+7.9).

The naphthofuranone (7.4) was reduced with sodium borohydride to yield secondary alcohol (7.5) in quantitative yield. The IR spectrum of the alcohol (7.5, fig.18) showed a peak at 3450 cm^{-1} (hydroxyl) and absence of peak at 1680 cm^{-1}. The alcohol on heating with a crystal of iodine as well as with para toluenesulphonic acid gave pyrocurzerenone (7.6). The PMR spectrum (fig.19) exhibited a singlet at 2.0 for methyl group, a singlet at 2.38 (6H) was due to aromatic methyl and furan methyl group, three broad singlets at 6.65, 6.9 and 7.1 were due to olefinic proton, aromatic proton and proton from furan ring respectively. This spectral data is in complete agreement with that reported earlier[1,2] for pyrocurzerenone.

In conclusion, we have completed * the third 11-step synthesis of pyrocurzerenone with ___ % over-all yield by taking the partial advantage from first synthesis.

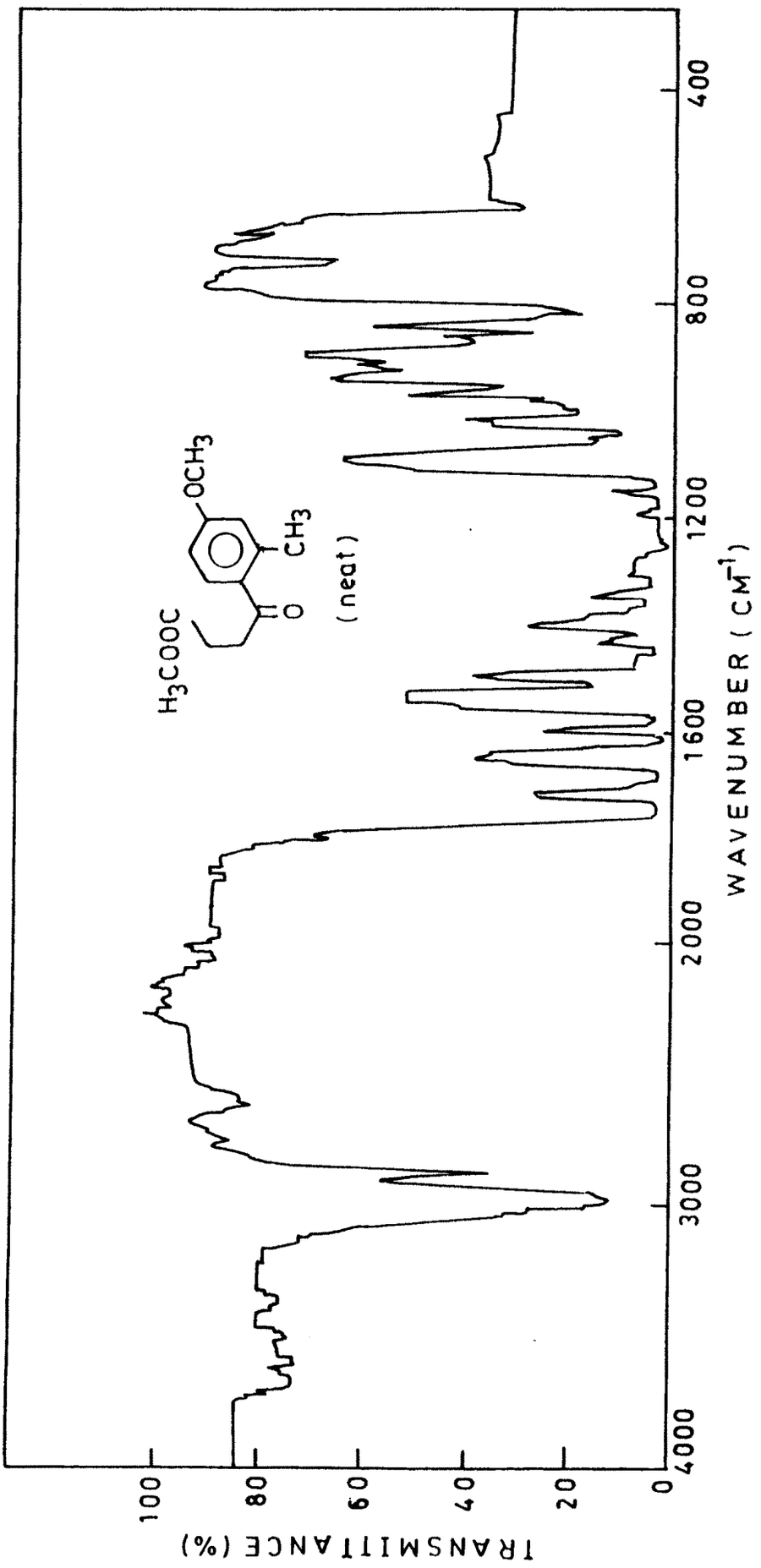

TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3000
2000
1600
1200
800
400
WAVENUMBER (CM⁻¹)
H3COOC
OCH3
CH3
O
(neat)

Fig. 1

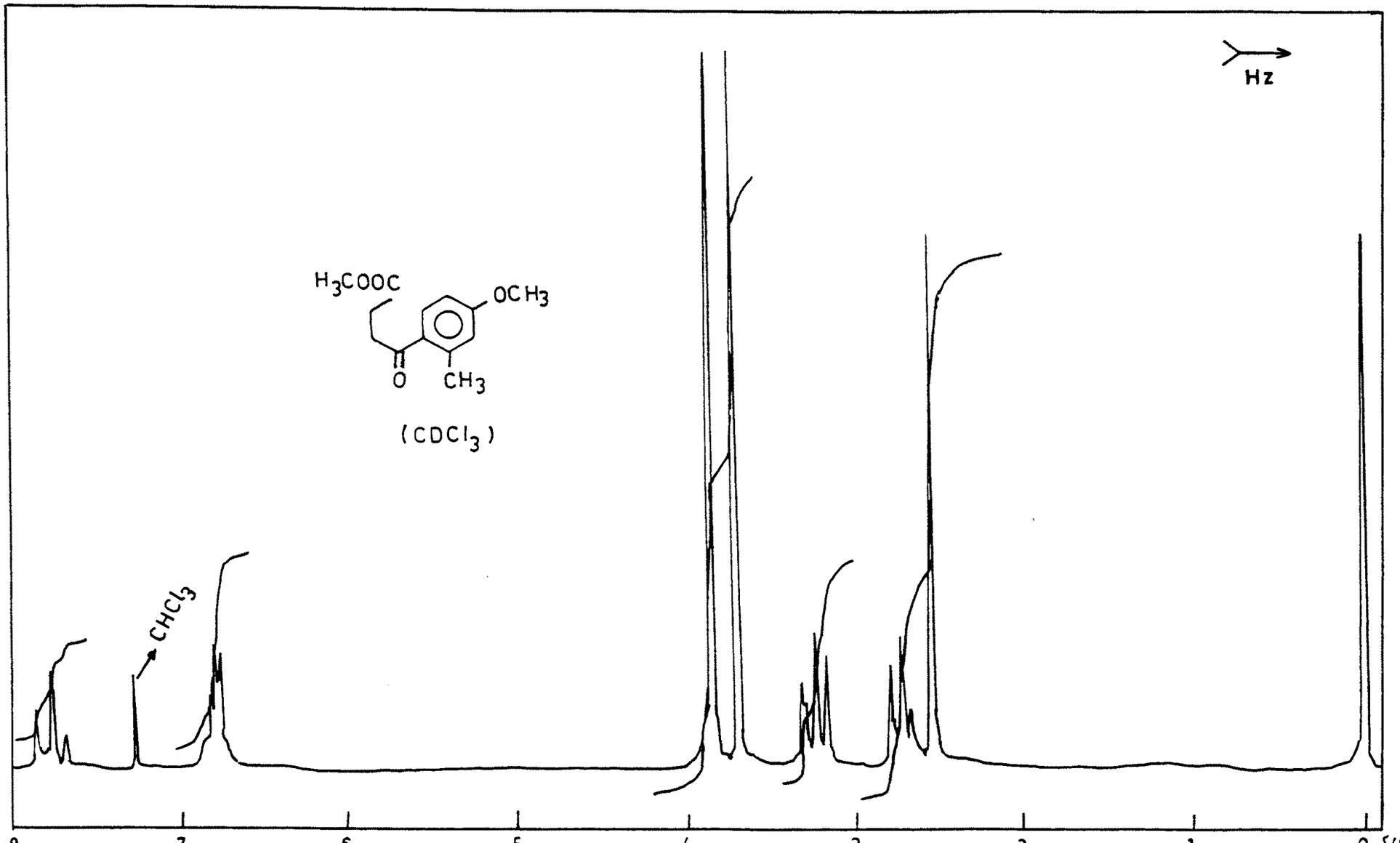


Fig. 2

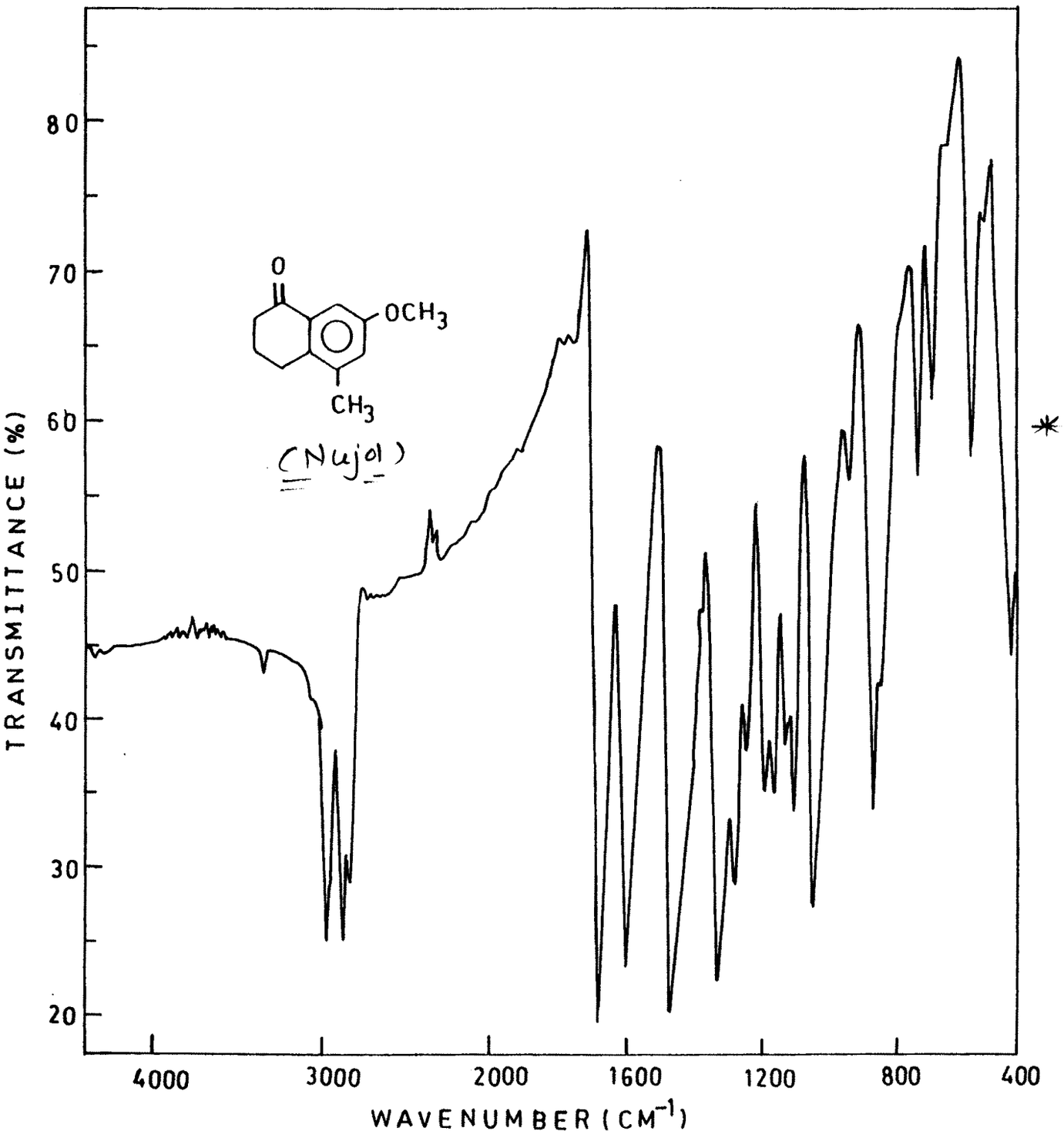

TRANSMITTANCE (%)
80
70
60
50
40
30
20
4000
3000
2000
1600
1200
800
400
WAVENUMBER (CM⁻¹)
O
OCH3
CH3
(Nujol)

Fig. 3

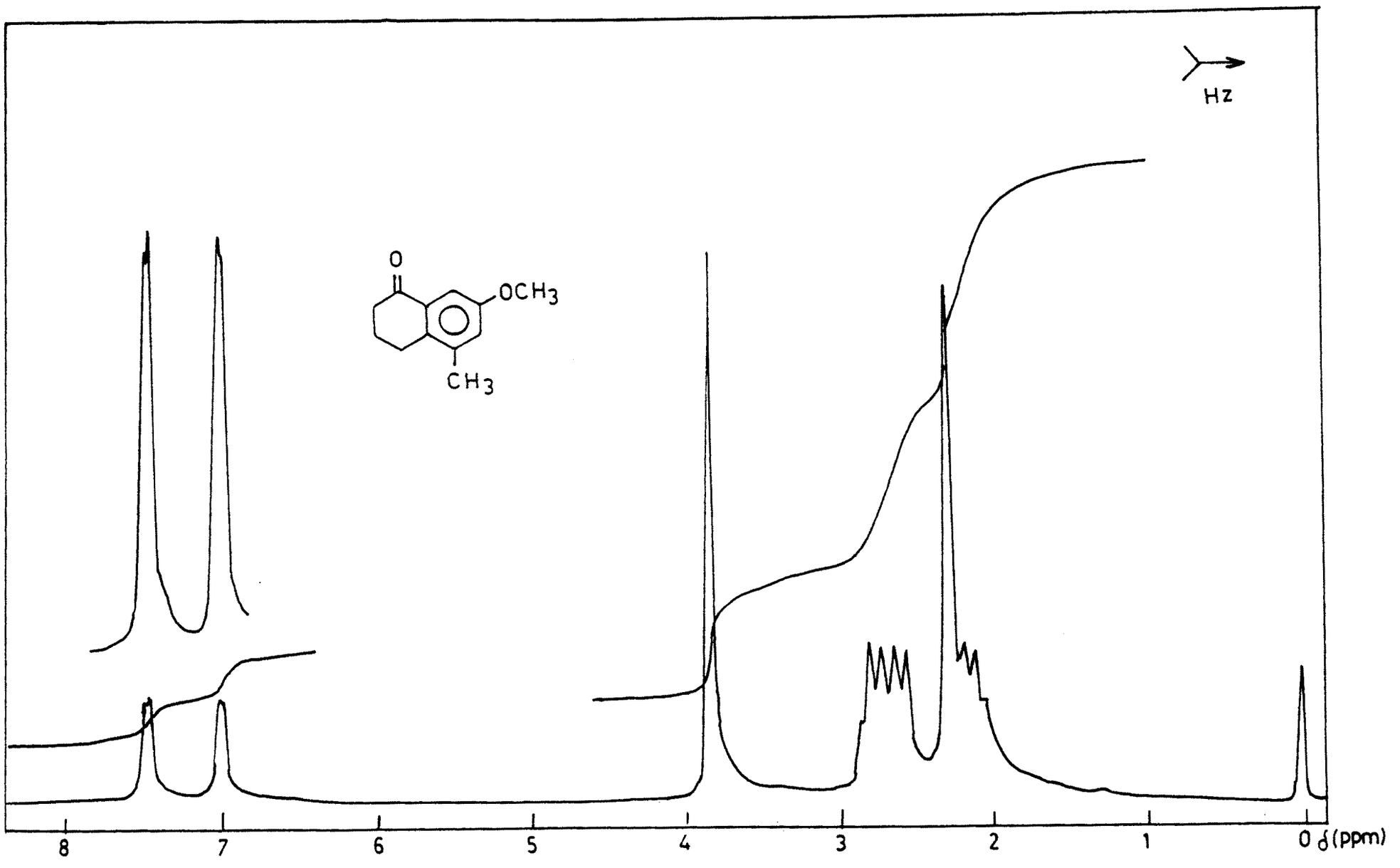


Fig. 4

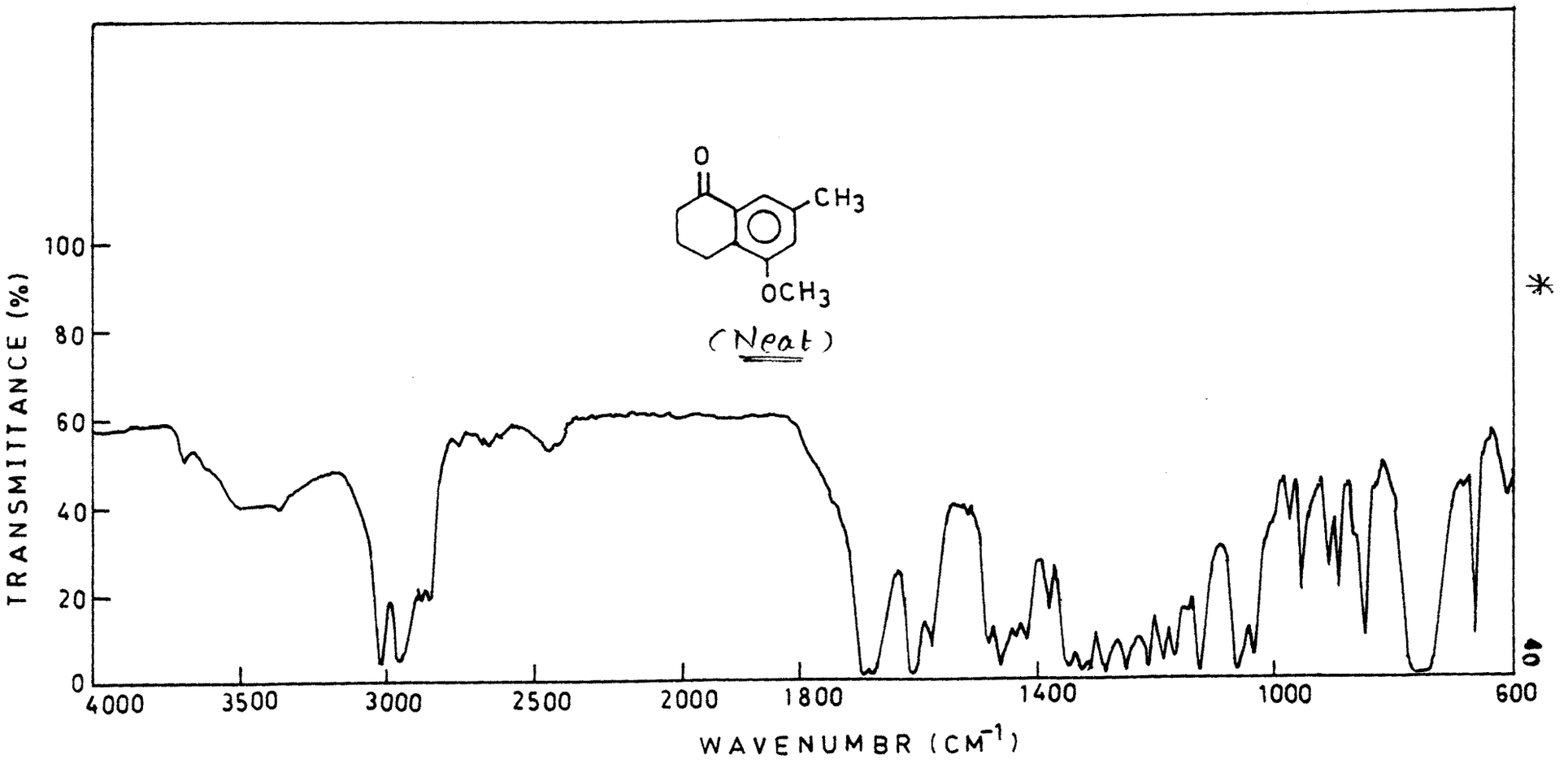

O
CH3
OCH3
(Neat)
TRANSMITTANCE (%)
100
80
60
40
20
0
4000
3500
3000
2500
2000
1800
1400
1000
600
WAVENUMBR (CM-1)

Fig. 5

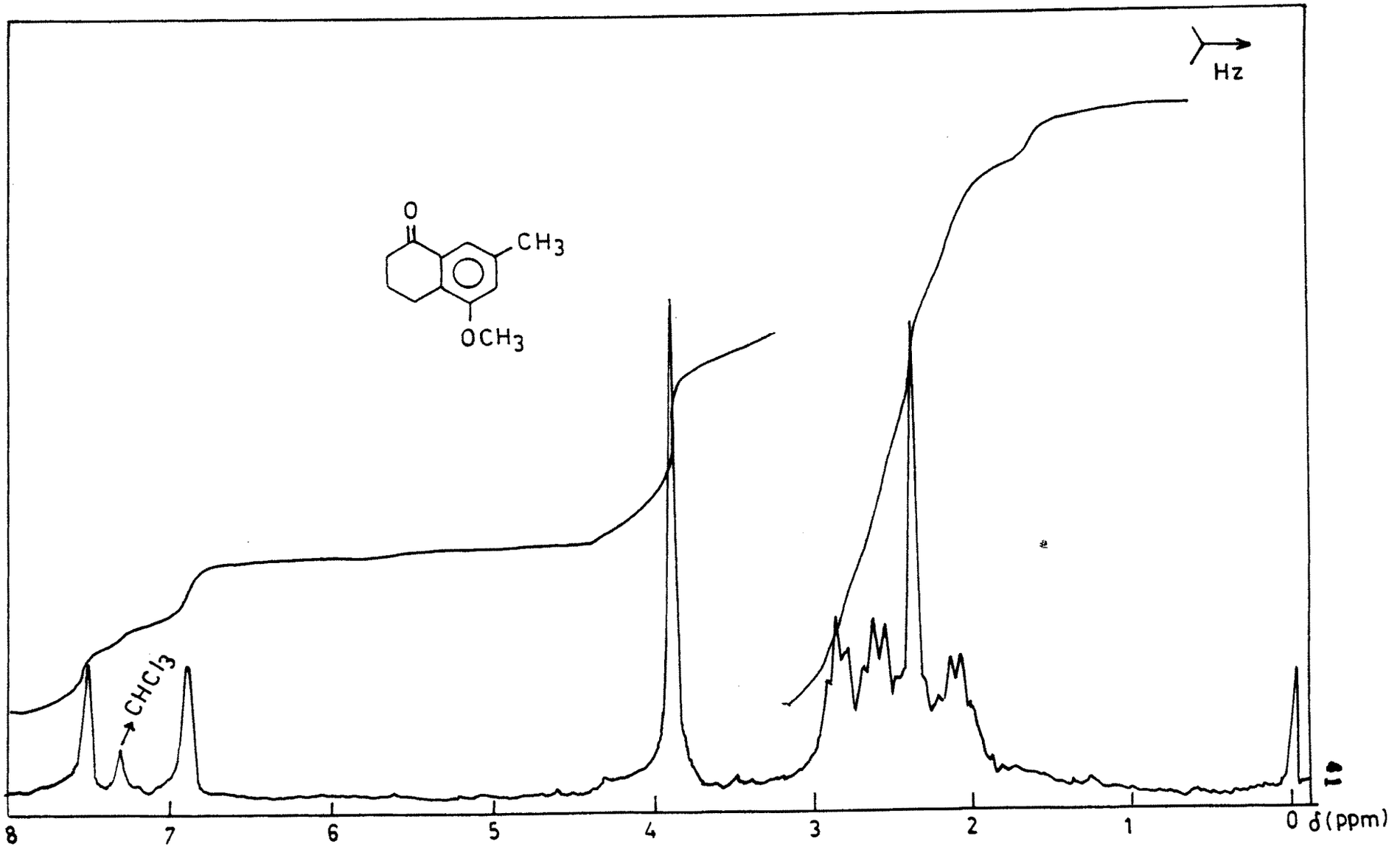


Fig. 6

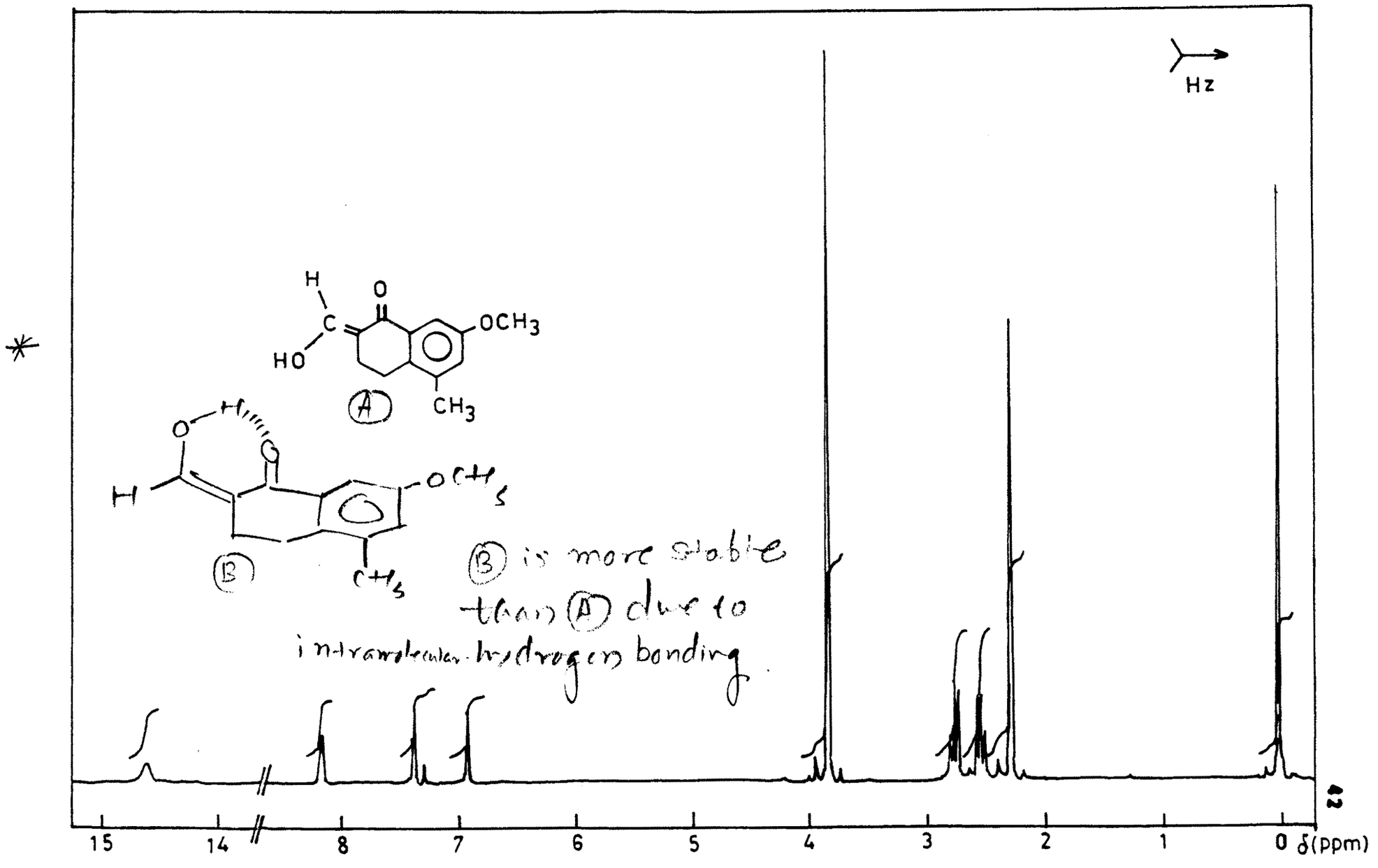

Hz
H
O
C
HO
OCH3
CH3
A
O
H
O
H
OCH3
CH3
B
B is more stable than A due to intramolecular hydrogen bonding
15
14
8
7
6
5
4
3
2
1
0
δ(ppm)

Fig. 7

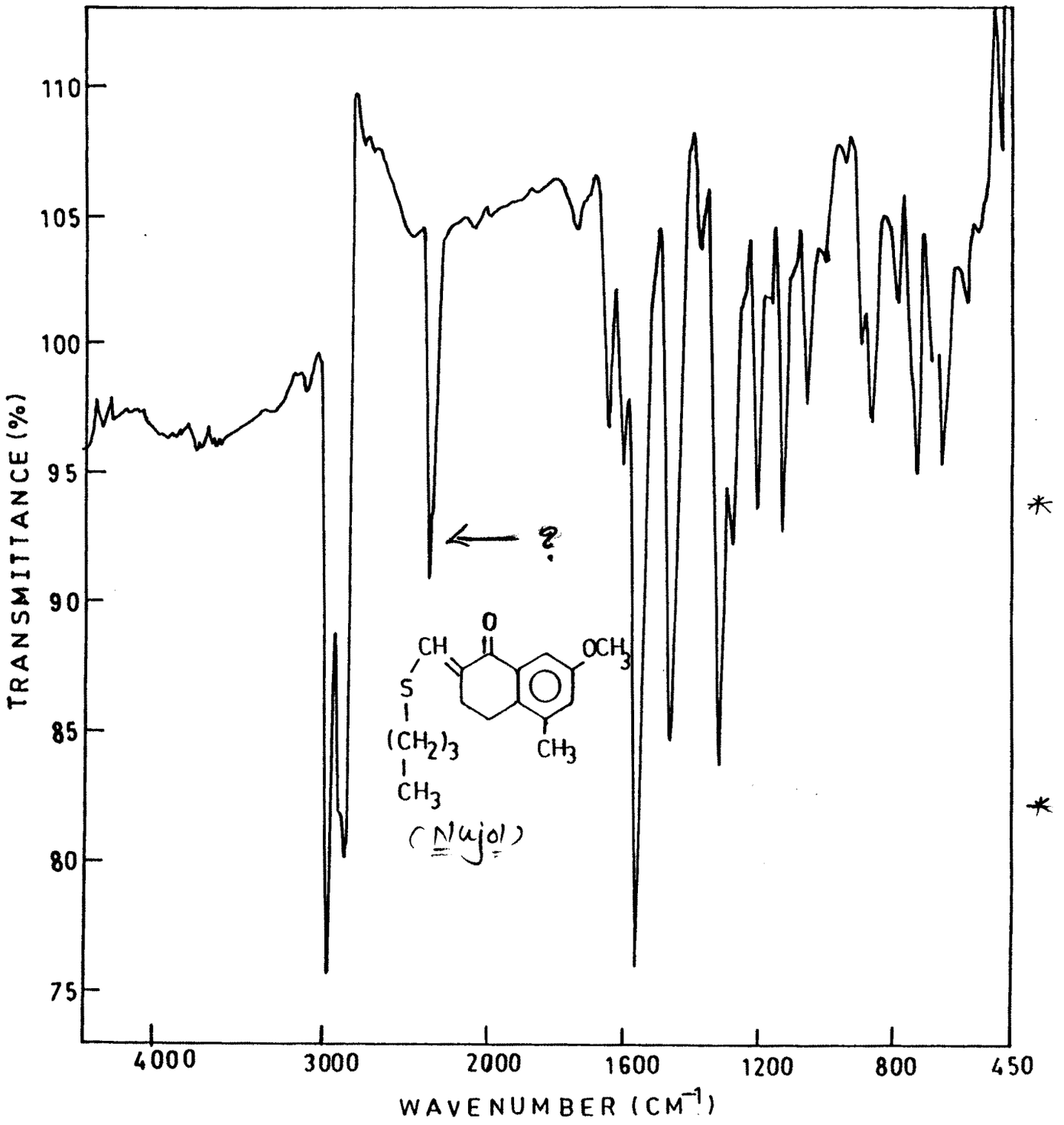

110
105
100
95
90
85
80
75
TRANSMITTANCE (%)
4000
3000
2000
1600
1200
800
450
WAVENUMBER (CM⁻¹)
?
O
CH
OCH3
S
(CH2)3
CH3
CH3
(Nujol)
*
*

Fig. 8

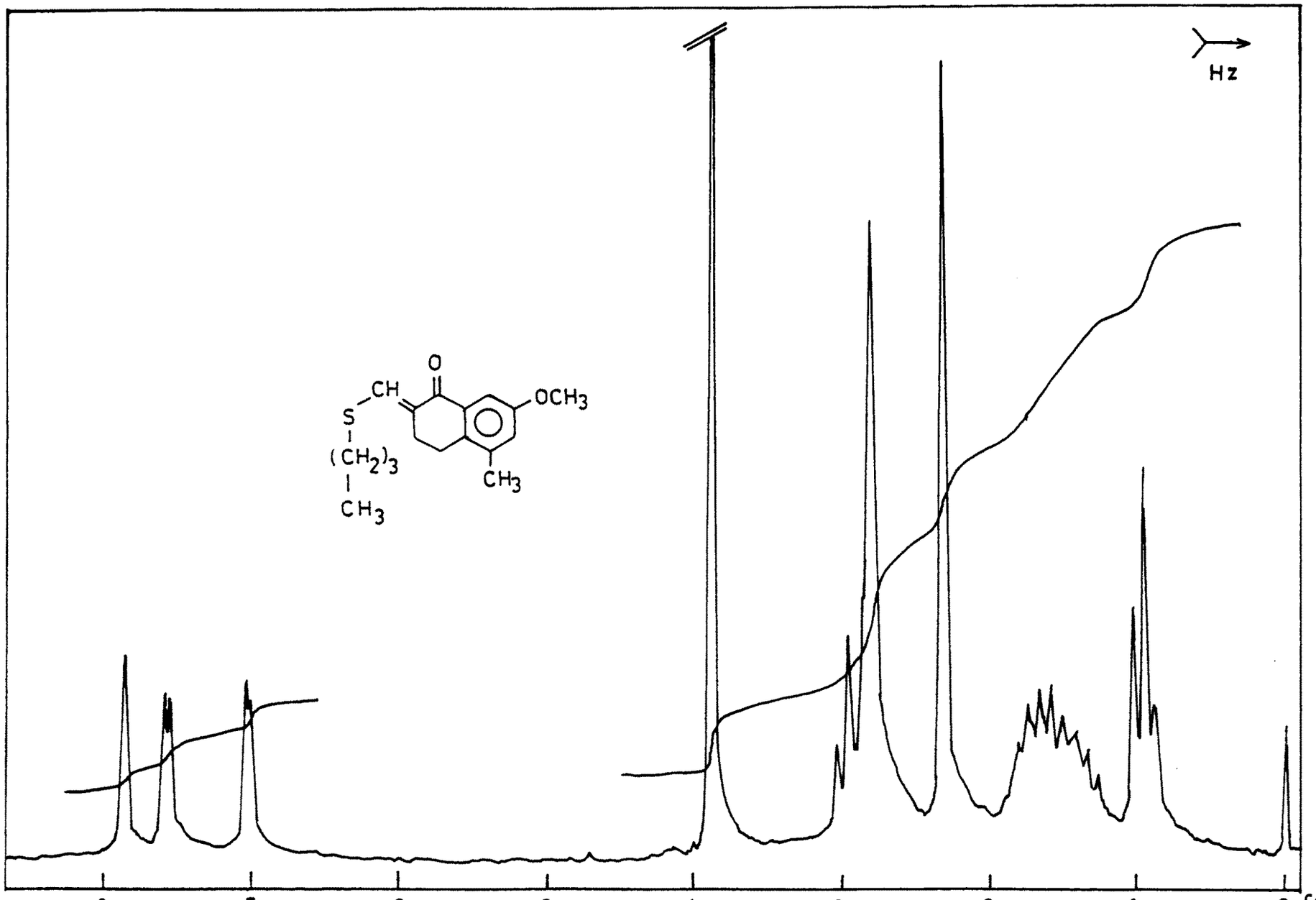


Fig. 9

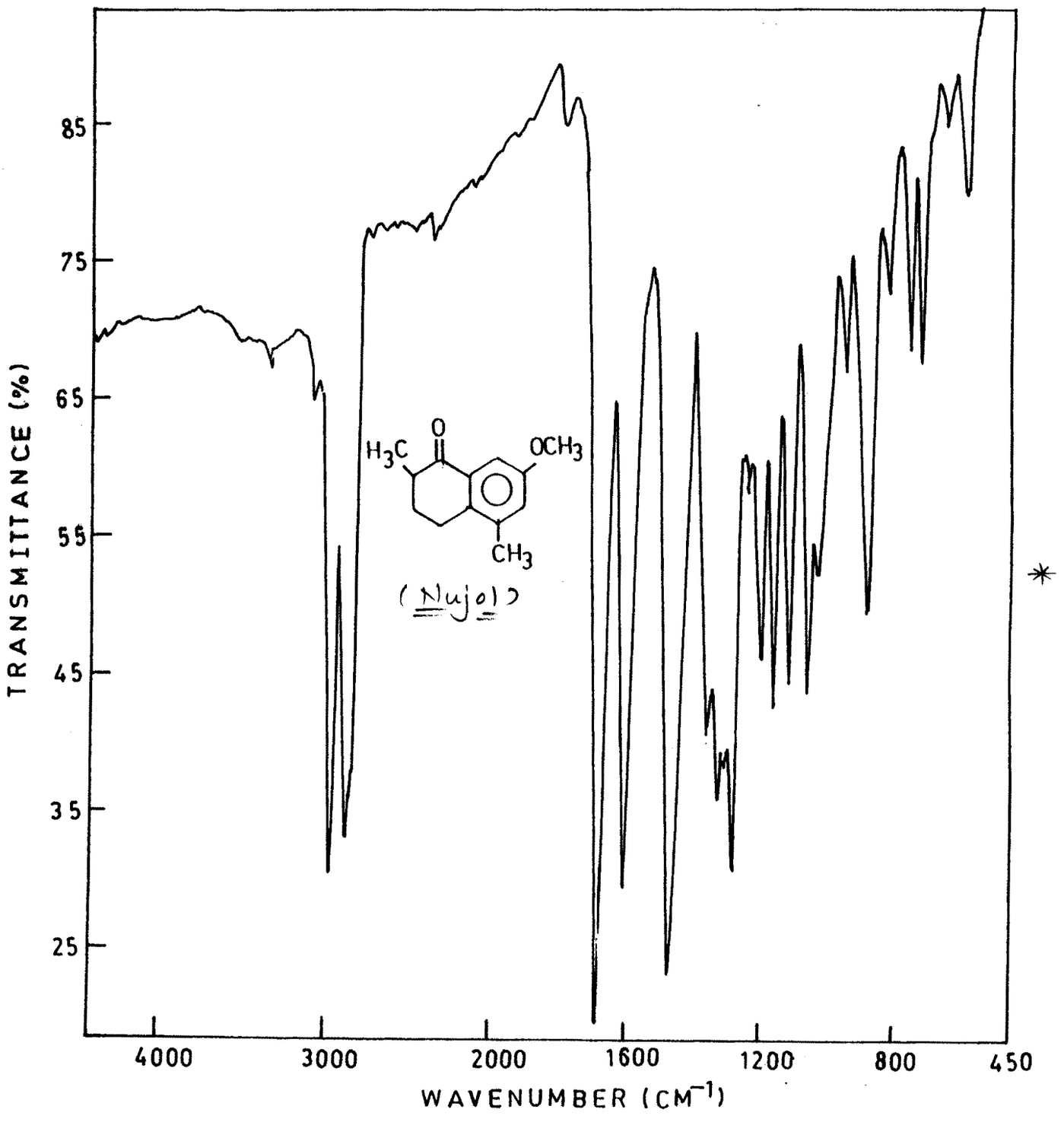

TRANSMITTANCE (%)
85
75
65
55
45
35
25
4000
3000
2000
1600
1200
800
450
WAVENUMBER (CM⁻¹)
H3C
O
OCH3
CH3
(Nujol)

Fig. 10

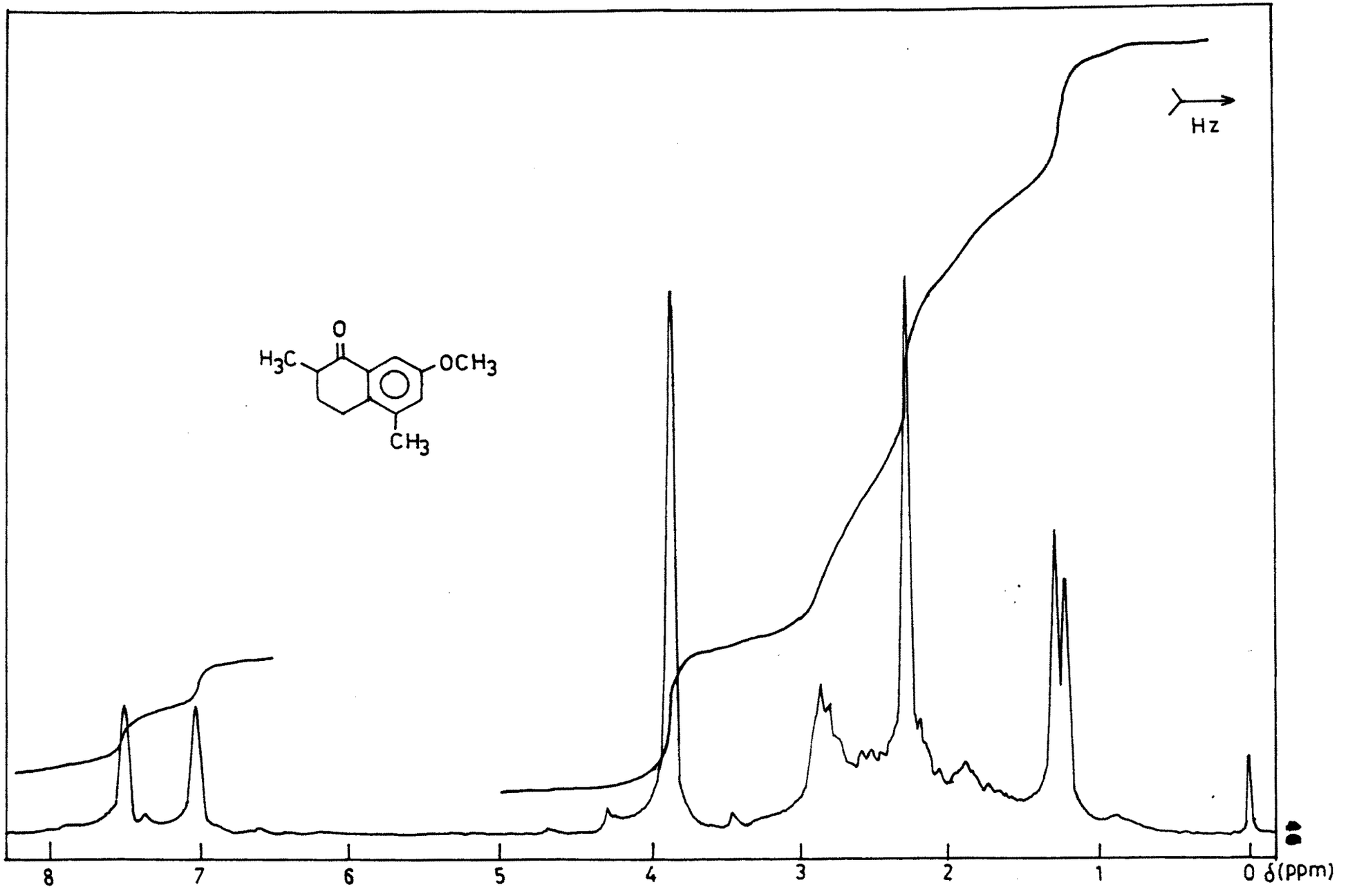


Fig. 11

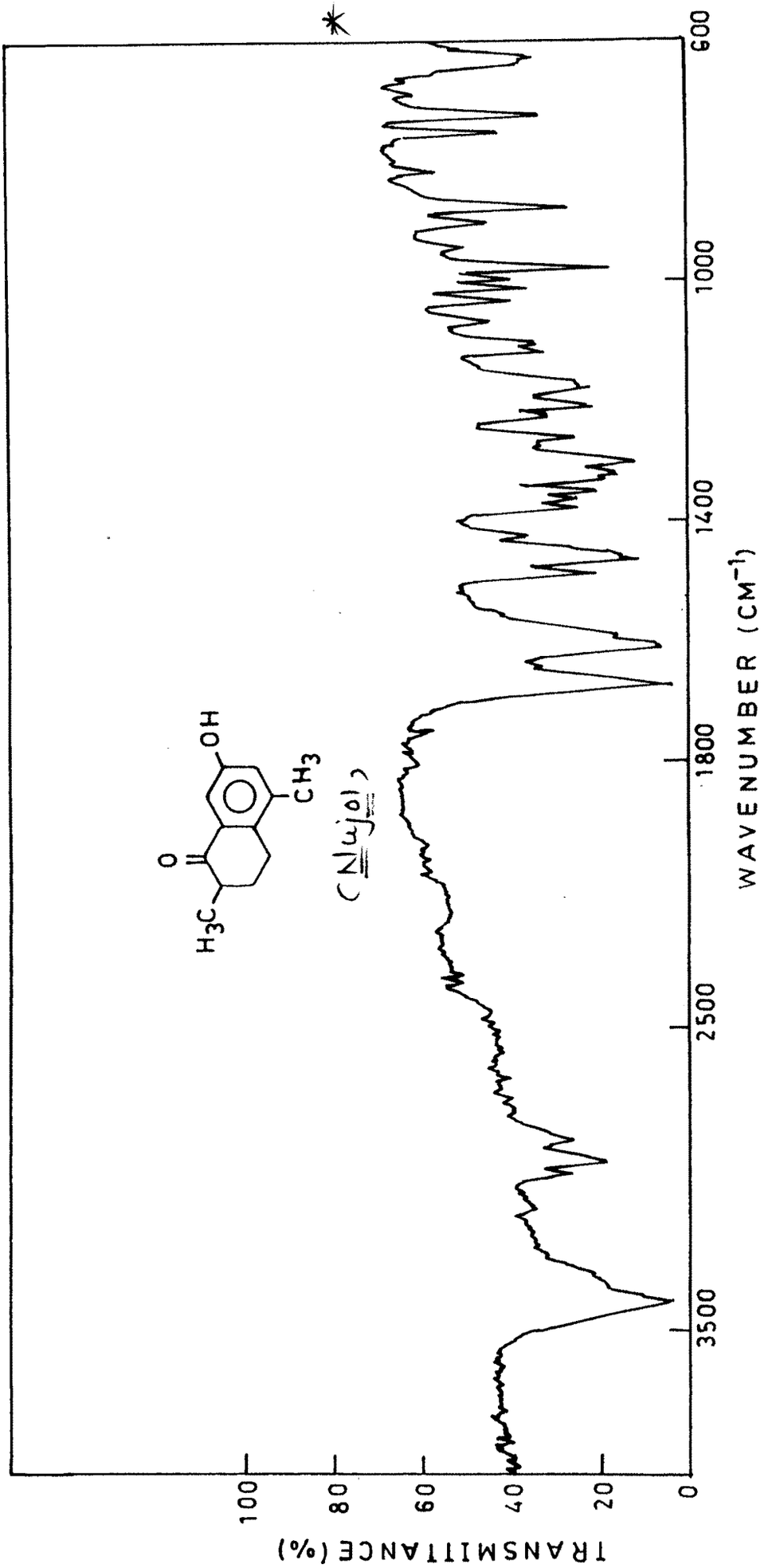

TRANSMITTANCE (%)
100
80
60
40
20
0
3500
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
OH
CH3
O
H3C
(Nujol)

Fig. 12

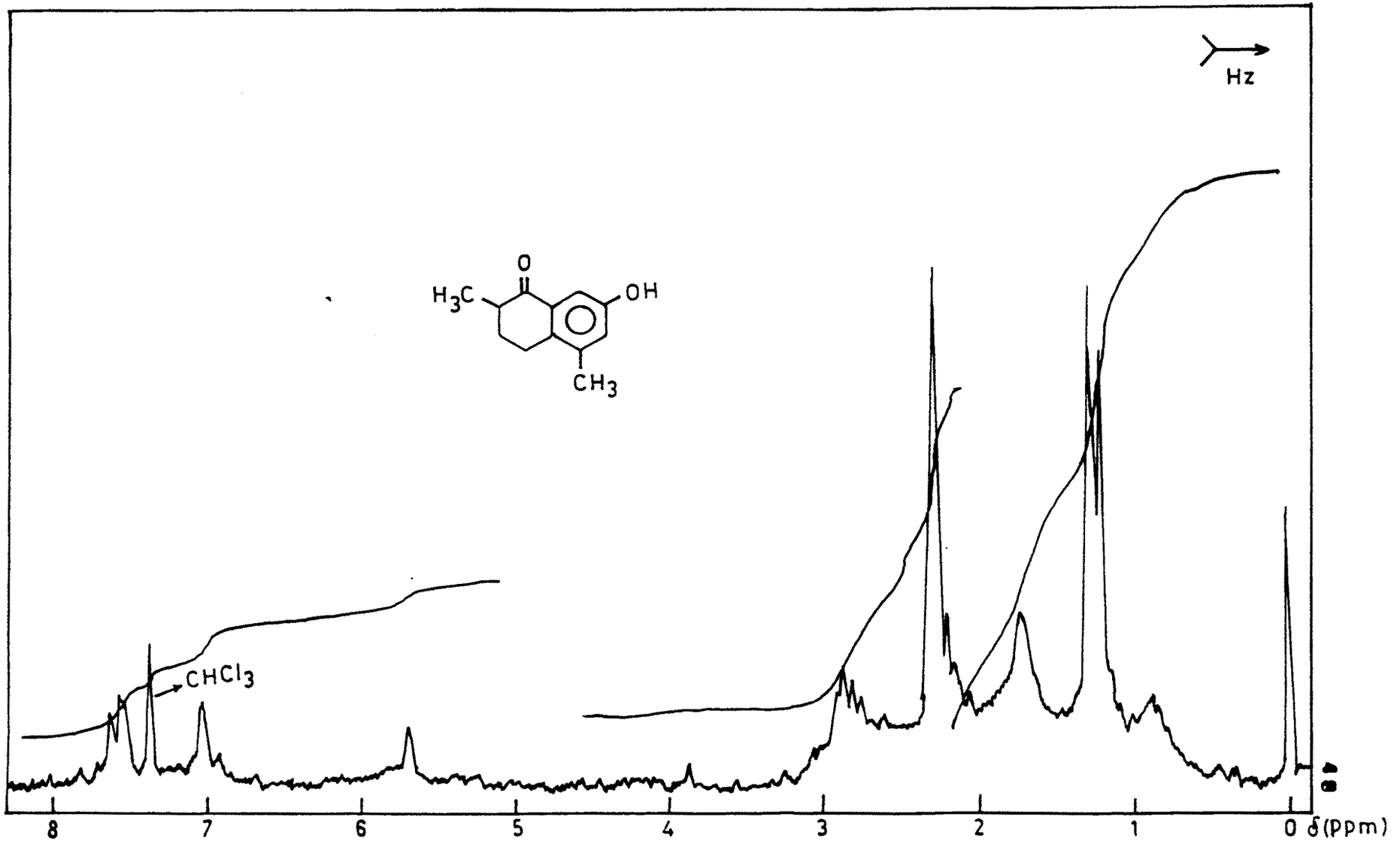


Fig. 13

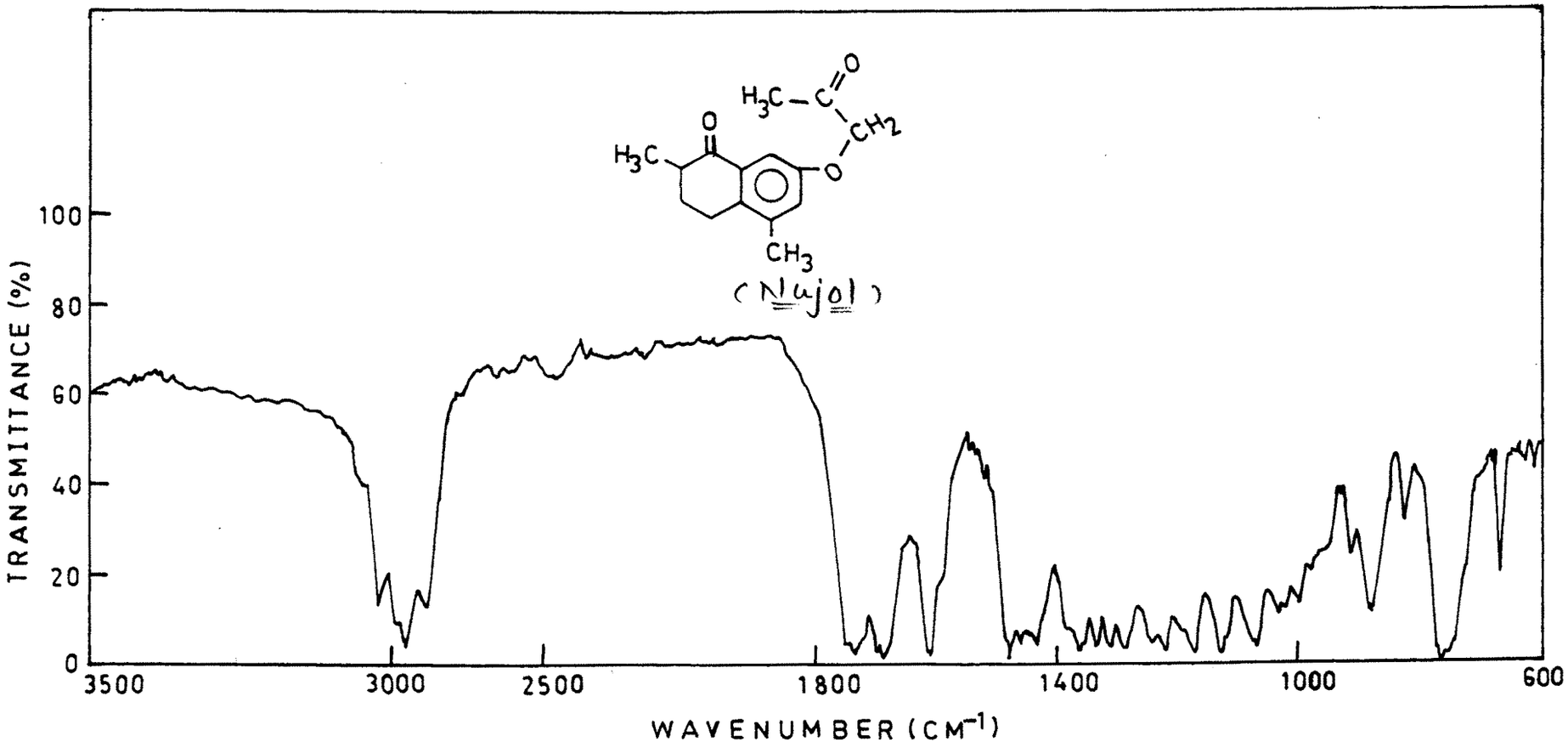

TRANSMITTANCE (%)
100
80
60
40
20
0
3500
3000
2500
1800
1400
1000
600
WAVENUMBER (CM⁻¹)
(Nujol)

Fig. 14

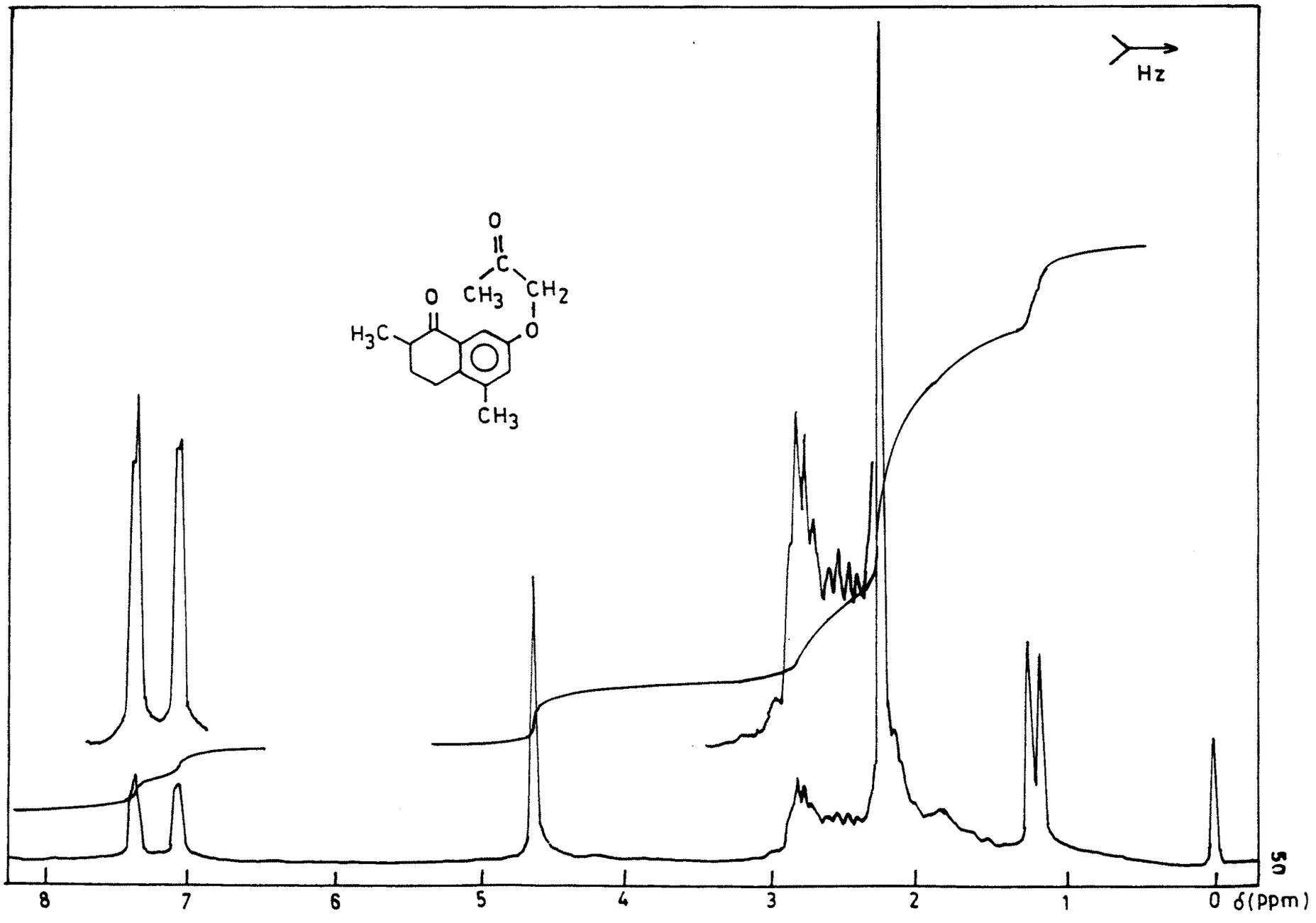


Fig. 15

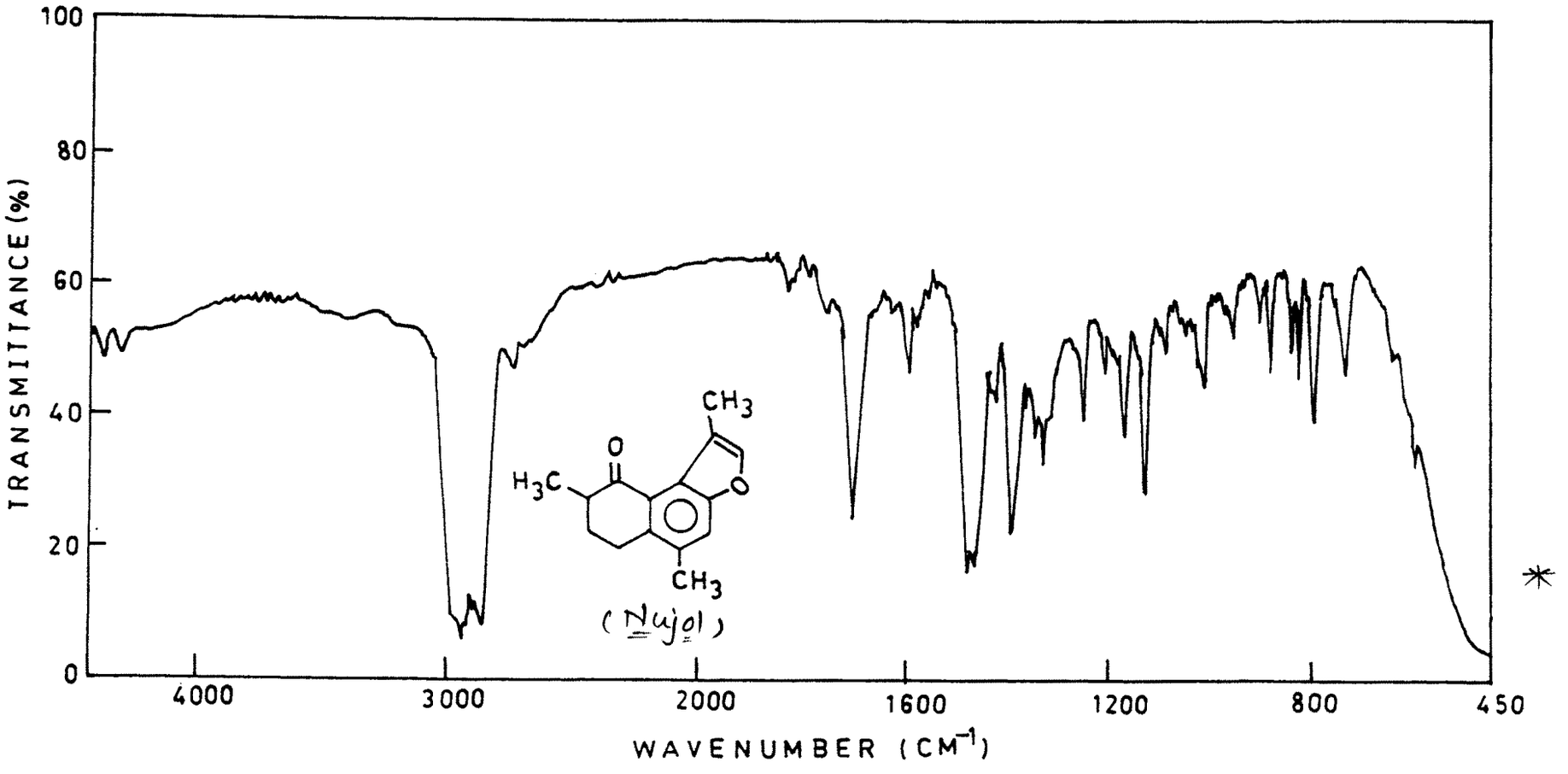

100
80
60
40
20
0
TRANSMITTANCE (%)
4000
3000
2000
1600
1200
800
450
WAVENUMBER (CM⁻¹)
CH3
O
H3C
O
CH3
(Nujol)

Fig . 16

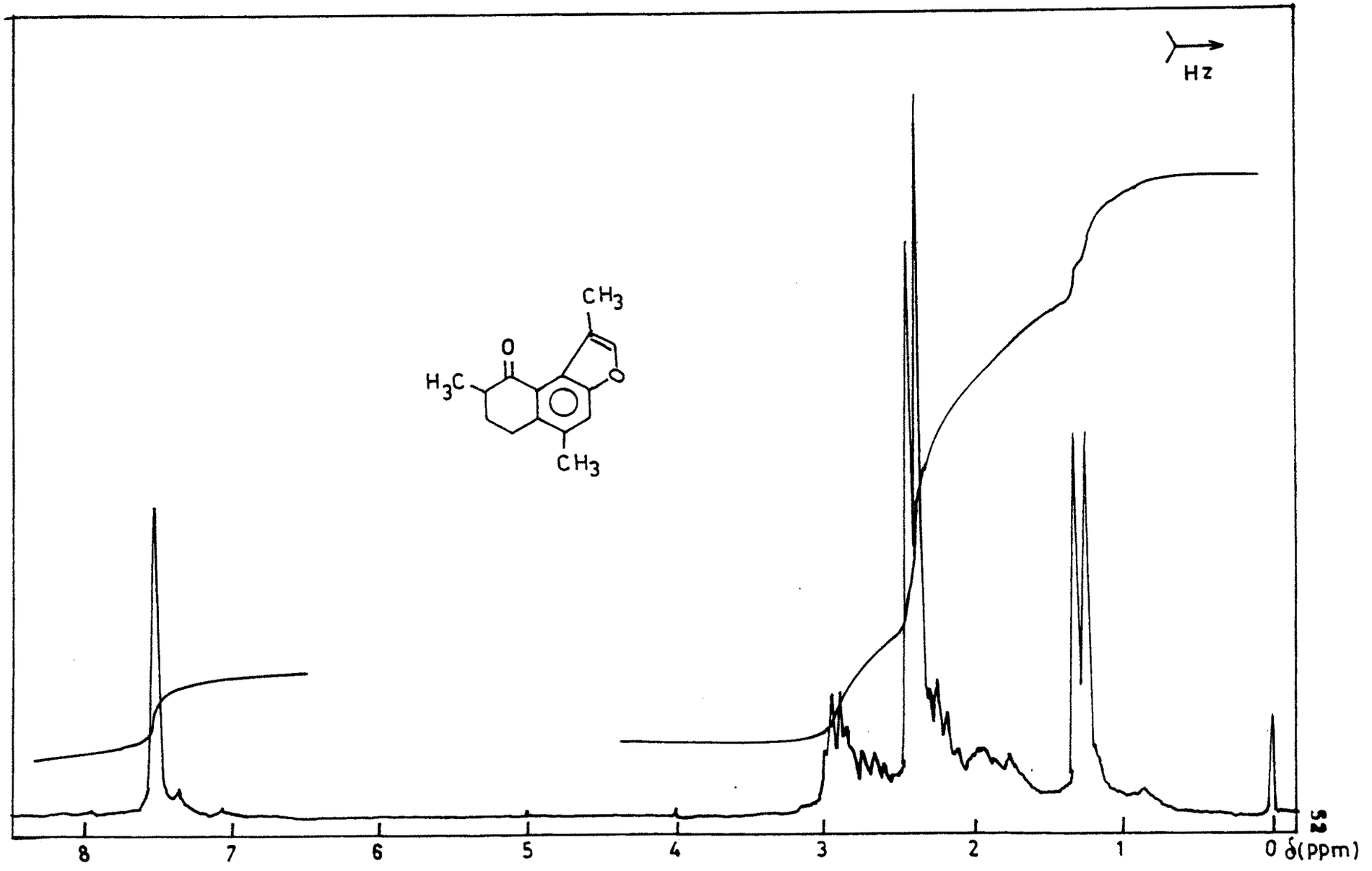


Fig. 17

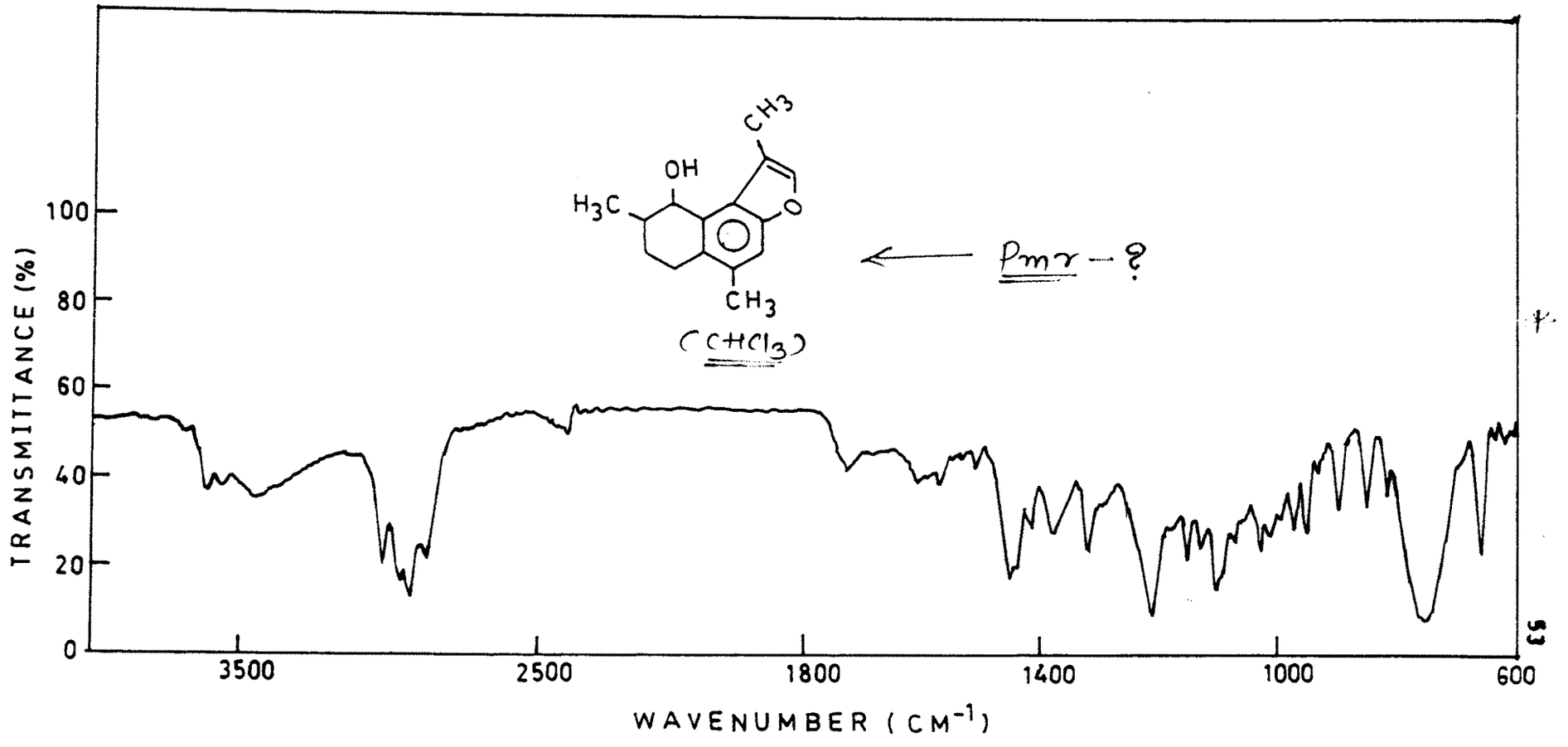

TRANSMITTANCE (%)
100
80
60
40
20
0
3500
2500
1800
1400
1000
600
WAVENUMBER (CM^{-1})
OH
H_3C
CH_3
O
CH_3
(CHCl$_3$)
← Pmr - ?

Fig. 18

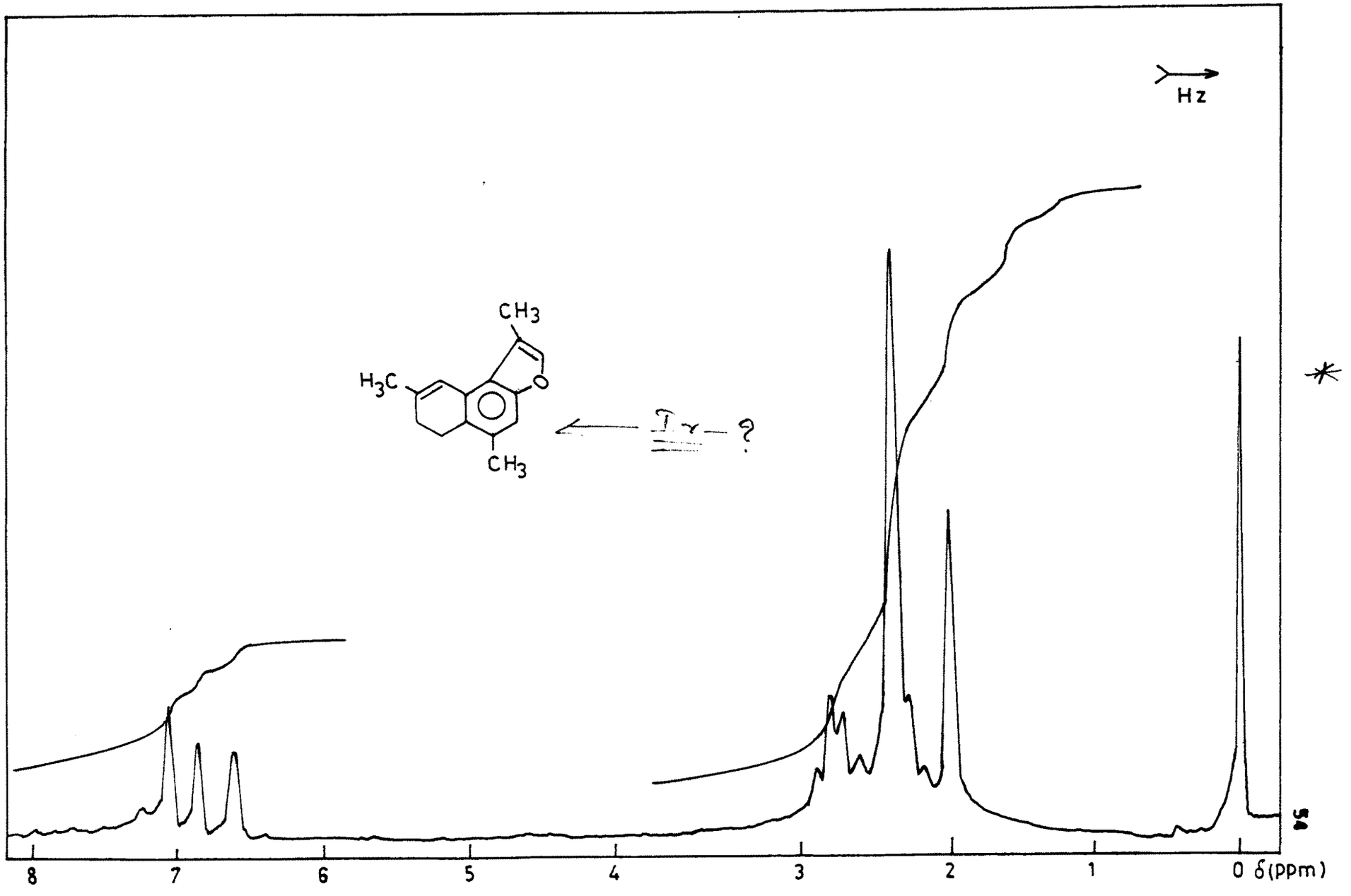


Fig. 19

EXPERIMENTAL

m-Cresol (K and L), anhydrous aluminium chloride, orthophosphoric acid, phosphorus pentoxide and all solvents (S.D's); n-butymercaptan, nickel-aluminium alloy and sodium borohydride (E. Merck, Germany); while zinc wool (BDH) and silica gel (Qualigens) were used.

m-Cresyl methyl ether (5.1)

To a stirred solution of m-cresol (188 g) in 10% sodium hydroxide (800 ml) was added below 20°C dimethyl sulphate (188 ml) during two hours. The reaction mixture was refluxed for three hours and left overnight. The organic layer was separated, washed with dilute sulphuric acid, water, 10% sodium hydroxide, water and then dried over anhydrous calcium chloride. It was finally filtered and distilled to yield m-cresyl methyl ether (130 g), b.p. 174-175°C (Lit.[8] 176°C). Yield ___ %.

Succinic anhydride (5.2)

The mixture of succinic acid (178 g) and acetic anhydride (285 ml) was heated on water bath till clear solution resulted. It was heated further for two hours and left overnight. The reaction mixture was cooled in ice and separated succinic anhydride was filtered at pump. The crystals were washed with ice water, dry ether and finally dried in air to yield succinic anhydride (112 g), m.p. 119°C (Lit.[8] 119-120°C). Yield ___ %.

β-(2-Methyl-4-methoxy) benzoyl propionic acid (5.3a)

To a stirred suspension of succinic anhydride 5.2 (100 g, 1 mole) in nitrobenzene (450 ml) was added with stirring below 5°C, anhydrous aluminium chloride (200 g, 1.49 mole) in small lots during 1.5 hour. The reaction mixture was stirred at room temperature for 20 minutes and then m-cresyl methyl ether 5.1 (86 g, 0.70 mole) was added dropwise during seven hours. The stirring was continued for an additional hour and mixture was left overnight. It was decomposed by cautious addition of iced hydrochloric acid (1:1) and nitrobenzene was removed by steam distillation to yield crude, red coloured acid residue. It was dissolved in saturated solution of sodium carbonate and alkali layer was extracted with benzene (to remove coloured and polymeric impurities). The alkali phase on acidification with hydrochloric acid (1:1) gave desired acid, 5.3 which was filtered and dried (140 g). It was purified by crystallisation from hot water, to get pure 5.3 (100 g) m.p. 127-128°C (Lit.[6b] m.p. 136-137°C). Yield ___ %.

Note : 1) The trials showed that the yield of acid depends upon the rate of addition of m-cresyl methyl ether. It should be as slow as possible.

2) Even after two recrystallisations, there was no change in the m.p. of acid hence with a view of checking the purity of acid, small amount was esterified with methanol and sulphuric acid.

Methyl β-(2-methyl-4-methoxy) benzoyl propionate (5.4a)

The above acid 5.3 (1.0 g) was refluxed with methanol (15 ml) and con. sulphuric acid (6 drops) for eight hours. The routine work-up for ester furnished the propionate 5.4 (0.730 g), m.p. 48-50°C. Yield ___ %.

The examination of the TLC of the ester showed two close spots. Second spot of minor component (nearly 10%, of *ortho* isomer) appearing like a cap over the first spot of major component (nearly 90%, of *para* isomer). For identification purpose ester (5.4) was separated over four preparative TLC plates (pet. ether + ethyl acetate, 9:1 as mobile phase) and major component (lower R_f) was identified spectrally. IR (neat, fig.1) : 1725 (ester), 1680 (ketone) cm^{-1}; PMR ($CDCl_3$, fig. 2) : 2.60 (3H, s, Ar-CH_3), 2.76 (2H,t, J=7 Hz, -CO-CH_2-$\underline{CH_2}$), 3.26 (2H, t, J=7 Hz, -CO-$\underline{CH_2}$-CH_2), 3.72 (3H, s, - $COOCH_3$), 3.85 (3H,s, Ar-OCH_3), 6.78 (2H,m, Ar-H *ortho* to -OCH_3) and 7.78 (1H, d, J=8 Hz, Ar-H *meta* to -OCH_3).

4-(2-Methyl-4-methoxyphenyl) butyric acid (5.5a)

A mixture of zinc wool (170 g), mercuric chloride (19.0 g), water (300 ml) and con. hydrochloric acid (8 ml) was shaken together in 2 lit. r.b. flask for 20 minutes. The clear solution was decanted and following materials were added : water (75 ml), con. HCl (175 ml), toluene (260 ml) and the keto acid 4.3 (50 g). The mixture was refluxed for 40 hours. During heating, after every eight hours, con. HCl (25 ml) was added. After heating, organic layer was separated and aqueous layer extracted with ether. The combined organic extract was washed with water, dried over anhydrous calcium chloride and solvent removed to yield desired reduced acid 5.5a (39 g), m.p. 73-74°C (Lit.[8] 75-76°C). Yield ___ %.

5-Methyl-7-methoxy-1-tetralone (5.6) and 5-Methoxy-7-methyl-1-tetralone (5.7)

To a stirred solution of polyphosphoric acid [prepared from phosphorous pentoxide (40 g) and orthophosphoric acid (25 ml)] was added the above reduced acid 5.5a (6.0 g) at room temperature and then reaction mixture was heated with stirring at 95°C for 45 minutes. The cooled reaction mixture was decomposed using ice water and extracted with ether. The ether extract was washed with water, dilute sodium hydroxide, again with water, dried over anhydrous sodium sulphate and ether removed to furnish mixture of tetralones 5.6 and 5.7 (3.8 g). Yield ___ %.

The examination of TLC showed two close spots, one with lower R_f value was major (*para* -isomer, 5.6) and other with higher R_f value was minor (*ortho*-isomer, 5.7).

Large scale preparation of tetralones was carried out by following the same procedure : Reduced acid (25 g) was cyclised to yield a mixture of tetralones 5.6 and 5.7 (15.150 g). The mixture of tetralones was separated by column chromatography over silica gel (250 g). Slow elution with carbon tetrachloride gave fraction-I (2.8 g) while elution with benzene gave fraction-II (6.7 g). Yield ___ % .

Fraction - II : 5-Methyl-7-methoxy-1-tetralone (5.6)

M.P. 59°C (Lit.[9] m.p. 57-57.5°C); IR (nujol, fig.3) : 1680 (C=O) cm^{-1}; PMR ($CDCl_3$, fig.4) : 2.2 (2H,m, Ar-CH_2-$\underline{CH_2}$), 2.30 (3H,s, Ar-CH_3), 2.7 (4H, m, J=7 Hz, Ar-CO-$\underline{CH_2}$ and Ar-CH_2), 3.90 (3H, s, Ar-OCH_3), 7.0 (1H, bsAr-H *ortho* to -CH_3) and 7.5 (1H, bs, Ar-H *para* to -CH_3).

Fractioin - 1 : 5-Methoxy-7-methyl-1-tetralone (5.7)

IR (neat, fig.5) : 1680 cm^{-1}; PMR ($CDCl_3$, fig.6) : 2.2 (2H, m, J=7 Hz, Ar-CH_2-$\underline{CH_2}$), 2.35 (3H, s, Ar-CH_3), 2.6 (2H, t, J=7 Hz, Ar-CO-$\underline{CH_2}$), 2.9 (2H, t, J=7 Hz,Ar-CH_2),3.9(3H,s, Ar-OCH_3), 6.9 (1H, bs, Ar-H *ortho* - OCH_3) and 7.55 (1H, bs, Ar-H *para* to -OCH_3).

2,5-Dimethyl-7-methoxy-1-tetralone (5.10) :

a) 2-Hydroxymethylene-5-methyl-7-methoxy-1-tetralone (5.8)

To an ice cold suspension of sodium methoxide (15 g, 0.27 mole) in dry benzene (120 ml) under nitrogen atmosphere was added dropwise, with stirring the above tetralone 5.6 (6.0 g, 0.031 mole) in benzene (10 ml), followed by ethyl formate (25 ml, 0.31 mole), The mixture was stirred overnight and diluted with water. The separated benzene layer was washed with water and then with 5% sodium hydroxide. The combined alkaline extract on acidification furnished the hydroxymethylene tetralone 5.8. It was extractred with ether, washed with water, dried over anhydrous sodium sulphate and then ether removed to yield 5.8 (5.6 g). The material got solidified on cooling and examination of TLC showed it to be almost pure. m.p.68-69°C (chloroform + pet.ether).PMR($CDCl_3$ fig.7) : 2.3(3H, s,Ar-CH_3), 2.55 (2H, t, J=7 Hz, Ar-CH_2-$\underline{CH_2}$), 2.8 (2H, t, J=7 Hz, Ar-CH_2), 3.9 (3H,s, Ar-OCH_3), 6.95 (1H, d, J=2 Hz, Ar-H *ortho* to -CH_3), 7.4 (1H, d, J=2 Hz, Ar-H *para* to -CH_3), 8.2 (1H, bs, Ar-CO-C = $\underline{CH}$-OH) and 14.6 (1H, bs, -C=CH-$\underline{OH}$).

b) 2-Butylthiomethylene-5-methyl-7-methoxy-1-tetralone (5.9)

To the solution of above hydroxymethylene tetralone 5.8 (5.0 g, 0.025 mole) in dry benzene (50 ml) was added n-butylmercaptan (3.0 ml, 0.031 mole) and a trace of p-toluenesulphonic acid. The reaction mixture was refluxed azeotropically till no more water gets collected (six hours). The cooled reaction mixture was diluted with benzene. The benzene extract was washed with water, dilute sodium hydroxide, again with water, dried over anhydrous sodium sulphate and benzene removed firstly on water bath and then under vacuum to get expected thioether 5.9 (4.8 g), m.p. 67°C. IR (nujol, fig.8) : 1650 (ketone carbonyl) and 1560 (=CH-S-R) cm^{-1}; PMR ($CDCl_3$, fig.9): (6H, m, J=7Hz, CH_3-$\underline{CH_2}$-$\underline{CH_2}$-CH_2 and Ar-CH_2-$\underline{CH_2}$), 2.3 (3H, s, Ar-CH_3), 2.7 to 3.0 (4H, m, J=7Hz, =CH-S-$\underline{CH_2}$ and Ar-CH_2), 3.9 (3H, s, Ar-OCH_3), 7.0 (1H,d, J=3.5 Hz, Ar-H *ortho* to -CH_3), 7.5 (1H, d, J=3.5 Hz, Ar-H *para* to -CH_3) and 7.8 (1H,s, -C = $\underline{CH}$-Bu).

c) 2,5-Dimethyl-7-methoxy-1-tetralone (5.10)

i) Preparation of W-2 Raney-nickel[7] :

To a solution of sodium hydroxide (195 g in 800 ml of distilled water) contained in a beaker equipped with a mechanical stirrer and cooled to 10°C was added nickel-aluminium alloy (160 g) in small portions and maintaining the temperature about 30°C (nearly three hours are required). When evolution of hydrogen becomes slow, the beaker was heated on steam bath for eight hours. During this heating volume of the solution was maintained constant by frequent addition of distilled water. After heating, nickel was allowed to settle

down and most of the liquid was decanted. To it 10% sodium hydroxide (250 ml) was added and mixture stirred for five minutes and allowed to settle. The alkali was decanted and the spongy nickel obtained was washed by suspension in distilled water and decantation method repeatedly until washings are neutral to litmus. It was further washed with distilled water for twenty to thirty times so as to remove alkali completely from nickel surface. Then it was washed with 95% ethanol (3x150 ml) and finally kept suspended in absolute ethanol (80 ml).

ii) To a suspension of W-2, Raney nickel (80 g) in absolute alcohol (80 ml) was added the above thioether 5.9 (4.5 g) in absolute ethanol (20 ml). The mixture was rapidly heated with stirring to 65-70°C for one hour. The catalyst was filtered using G-2 gooch crucible and then washed with boiling ethanol (3x50 ml). From the combined alcohol extract, alcohol was removed under vacuum and residue taken up in ether. The ether extract was washed with water, dried over anhydrous sodium sulphate and ether removed to obtain the desired methylated ketone 5.1 (4.2 g). The material was chromatographed over column of silica gel (100 g) and elution with benzene gave the pure methylated ketone (2.8 g), m.p. 50°C (Lit.[2] m.p. 51-52°C). IR (nujol, fig.10): 1680 cm^{-1}; PMR ($CDCl_3$, fig. 11) : 1.25 (3H,d, J=7.0 Hz, Ar-COCH-$\underline{CH_3}$), 1.9 (2H,m, Ar-CH_2-$\underline{CH_2}$), 2.2 (3H, s, Ar-CH_3), 2.5 to 3.0 (3H, m, Ar-$\underline{CH_2}$-CH_2-$\underline{CH}$-CH_3), 3.9 (3H, s, Ar-OCH_3), 7.0 (1H, bs, Ar-H *ortho* to -CH_3), and 7.5 (1H, bs, Ar-H *para* to -CH_3).

2,5-Dimethyl-7-hydroxy-1-tetralone (7.2)

a) Using pyridine hydrochloride :

2,5-Dimethyl-7-methoxy-1-tetralone 5.10 = 7.1 (1.4 g) was demethylated by heating with pyridine hydrochloride (15 g) at 180-190°C for three hours. On cooling, the reaction mixture was diluted with water and then extracted with ether. The ether extracted was washed repeatedly with water, dried over anhydrous sodium sulphate and ether removed to yield the impure phenolic tetralone 7.2 (1.320 g). The material on chromatography over silica gel (60 g) gave the pure phenolic tetralone 7.2 (0.620 g), m.p. 168°C (Lit.[2] m.p. 171 - 172°C). IR (nujol, fig. 12) : 3400 (phenolic -OH), 1670 (C=O) cm^{-1}. PMR ($CDCl_3$, fig. 13) : 1.25 (3H,d, J=7 Hz, Ar-CO-CH-$\underline{CH_3}$), 1.8 (2H,q, J=7 Hz, Ar-CH_2-$\underline{CH_2}$), 2.2 (2H, m, Ar-$\underline{CH_2}$), 2.3 (3H, s, Ar-CH_3), 2.9 (1H, sexlet, J=7 Hz, Ar-CO-$\underline{CH}$-CH_3), 5.7 (1H, bs, Ar-$\underline{OH}$), 7.0 (1H, bs, Ar-H *ortho* to -CH_3) and 7.60 (1H, bs, Ar-H *para* to -CH_3).

b) Using aluminium iodide :

To a stirred solution of methylated ketone 5.10 = 7.1 (3.8 g) in dry acetonitrile (60 ml) was added in small amounts aluminium iodide (7.0 g) and the mixture was refluxed on water bath for four hours (completion of reaction was monitored by TLC). The reaction mixture was poured into ice-water. The solution was decolourised by addition of aqueous sodium thiosulphate and then extracted with dilute sodium hydroxide (3x30 ml). Acidification of alkaline phase gave desired phenolic tetralone which was re-extracted with ether. The routine work up yielded the phenol 7.2 (3.3 g).

The compound 7.2, so prepared was identical in every respect with the one prepared using pyridine hydrochloride and the yield of phenol obtained by demethylation with aluminium iodide was found to be far superior. The phenol so obtained was used as such for the next step.

2,5-Dimethyl-7-acetonyloxy-1-tetralone (7.3)

The phenolic tetralone 7.2 (3.1 g) and freshly distilled bromoacetone (5.0 ml) in dry acetone (50 ml) were refluxed in presence of anhydrous potassium carbonate (4 g) on a water bath for eight hours. The completion of reaction was monitored by TLC. After completion, reaction mixture was diluted with water and extracted with ether. Ether extract was washed with water, dilute sodium hydroxide, again with water, dried and ether removed to get a gummy solid (3.7 g) which was chromatographed over silica gel (80 g). Elution with benzene gave the pure acetonyloxy tetralone 7.3 (1.8 g) which solidified on cooling; m.p. 71°C (Lit.[2] m.p. 72-73°C). IR (nujol, fig. 14) : 1735 (CH_3-C = O) and 1685 (C=O) cm^{-1}; PMR ($CDCl_3$, fig. 15) : 1.25 (3H, d, J=7 Hz, -CH-$\underline{CH_3}$), 1.9 (2H, m, Ar-CH_2-$\underline{CH_2}$), 2.5 (2H, t, J=7 Hz, Ar-$\underline{CH_2}$), 2.9(1H, sextet, J=7 Hz, -$\underline{CH}$-CH_3), 2.2 (6H,s, Ar-CH_3 and CO-CH_3), 4.65 (2H, s, Ar-O-$\underline{CH_2}$), 7.1 (1H, bs, Ar-H *ortho* to -CH_3) and 7.35 (1H, bs, Ar-H *para* to -CH_3).

1,5,8-Trimethyl-7,8-tetrahydronaphtho (2,1-b) furan (6H)-one 7.4

i) Using polyphosphoric acid :

To a solution of polyphosphoric acid [prepared from phosphorous pentoxide (31.0 g) and orthophosphoric acid (21 ml)] was added the above acetonyloxy tetralone 7.3 (1.0 g) and reaction mixture was stirred at room

temperature for two hours. It was decomposed using ice water and extracted with ether. The ether extract was washed with water, dilute sodium hydroxide, water, dried and ether removed to yield a gummy product 7.4 (1.050 g). This was chromatographed over silica gel (30 g). Elution with pet. ether gave the pure naphthofuranone 7.4 (0.360 g), m.p. 76°C (Lit.[2] m.p. 78-79°C). IR (nujol, fig. 16) : 1685 (ketone) cm^{-1}; PMR ($CDCl_3$, fig. 17) : 1.25 (3H,d, J=7 Hz Ar-CO-CH-$\underline{CH_3}$), 2.25 (2H, q, J=7 Hz, Ar-CH_2 - $\underline{CH_2}$), 2.30 (3H,s, Ar-CH_3), 2.40 (3H,s, furan CH_3), 2.7 (2H,m, Ar-$\underline{CH_2}$), 2.9 (1H, sextet, J=7 Hz - CO-$\underline{CH}$-CH_3), 7.5 (2H, bs, Ar-H, and furan $\underline{H}$).

ii) <u>Using trifluoroacetic acid</u> :

To a solution of trifluoroacetic acid (15 ml) was added acetonyloxy product 7.3 (0.400 g) slowly with stirring. The reaction mixture was refluxed for eight hours. After cooling, trifluoroacetic acid was removed under vacuum and the residue was extracted with ether. It was then washed with water, aqueous sodium carbonate, water, dried and ether removed to yield the naphthofuranone 7.4 (0.300 g) identical in all respects (m.p., TLC and PMR) to that obtained by PPA cyclisation.

<u>1,5,8-Trimethyl-6,7-dihydronaphtho [2,1-b] furan (pyrocurzerone) 7.6</u>

i) To the stirred solution of above naphthofuranone 7.4 (0.300 g) in alcohol (15 ml) was added sodium borohydride (0.300 g) and reaction mixture left overnight. It was decomposed by pouring into saturated solution of ammonium chloride and then extracted with ether. Ether extract was repeatedly washed with water, dried and ether removed to yield the

Yield — %.

naphthofuranol 7.5 (0.270 g) as a liquid. The alcohol 7.5 being almost pure, it was used as such for next step. IR ($CHCl_3$, fig. 18) : 3450 cm^{-1}. PMR - ?

ii) a) To the solution of above alcohol 7.5 (0.250 g) in benzene (10 ml), p-toluenesulphonic acid (0.050 g) was added and mixture refluxed for thirty minutes. The reaction was monitored by TLC and on completion, the reaction mixture was diluted with ether and ether extract was washed with aqueous sodium carbonate, dried and ether removed to yield a gummy material (0.220 g). This was purified over four preparative TLC plates, using pet. ether as mobile phase, to yield pure pyrocurzerenone 7.6 (0.06g), m.p. 73-74°C (Lit.[2] m.p. 77-78°C); PMR ($CDCl_3$, fig. 19) : 2.0 (3H, s, allylic CH_3), 2.38 (6H,s, Ar-CH_3 & furan -CH_3), 6.65 (1H, bs, olefinic H), 6.90 (1H, bs, Ar-H) and 7.1 (1H, bs, furan-H). Yield — %. IR - ?

b) To the solution of above alcohol 7.5 in benzene was added a small crystal of iodine and refluxed for four hours on water bath. It was decomposed by pouring into ice-water and extracted with ether. Ether extract was washed with water, with very dilute sodium thiosulphate, water, dried and ether removed to yield a sticky material. The examination of TLC and PMR spectrum showed it to be identical with the pyrocurzerenone 7.6 prepared by dehydration of alcohol 7.5 with para-toluenesulphonic acid.

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