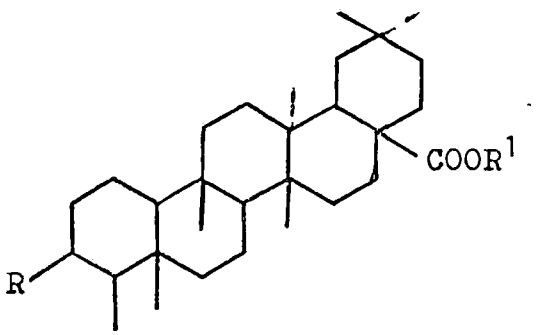
CHAPTER - II

STUDIES ON THE REDUCTIVE ACTION OF POTASSIUM HYDROXIDE IN DIETHYLENE GLYCOL ON TRITERPENOID KETONES AND NON-TERPENOID KETONE

INTRODUCTION:

During the hydrolysis of 3-keto-methyl trichadenate[13] 1 with potassium hydroxide in diethylene glycol we observed that the 3-keto functional group of the triterpenoid being converted to epimeric alcohols (viz. trichadenic acid A and B[13]) 1a and 1b.



1, R = O, $R^1 = CH_3$

1a, R = , R^1 = H

1b, R = , R^1 = H

A survey of literature showed that there were many oxidation - reduction (equilibration) type of reaction using various types of alkoxides. In all these cases alkoxides were separately prepared by the addition of active metals to the alcohols except in the case of reactions reported by Barton[11] and Halsall[12]. In order to examine the validity of the reaction on other keto compounds we carried out the reaction on a series of triterpenoid ketones (Entries 1-7) and one non-terpenoid ketone (Entry-8) as shown in Table - 1.

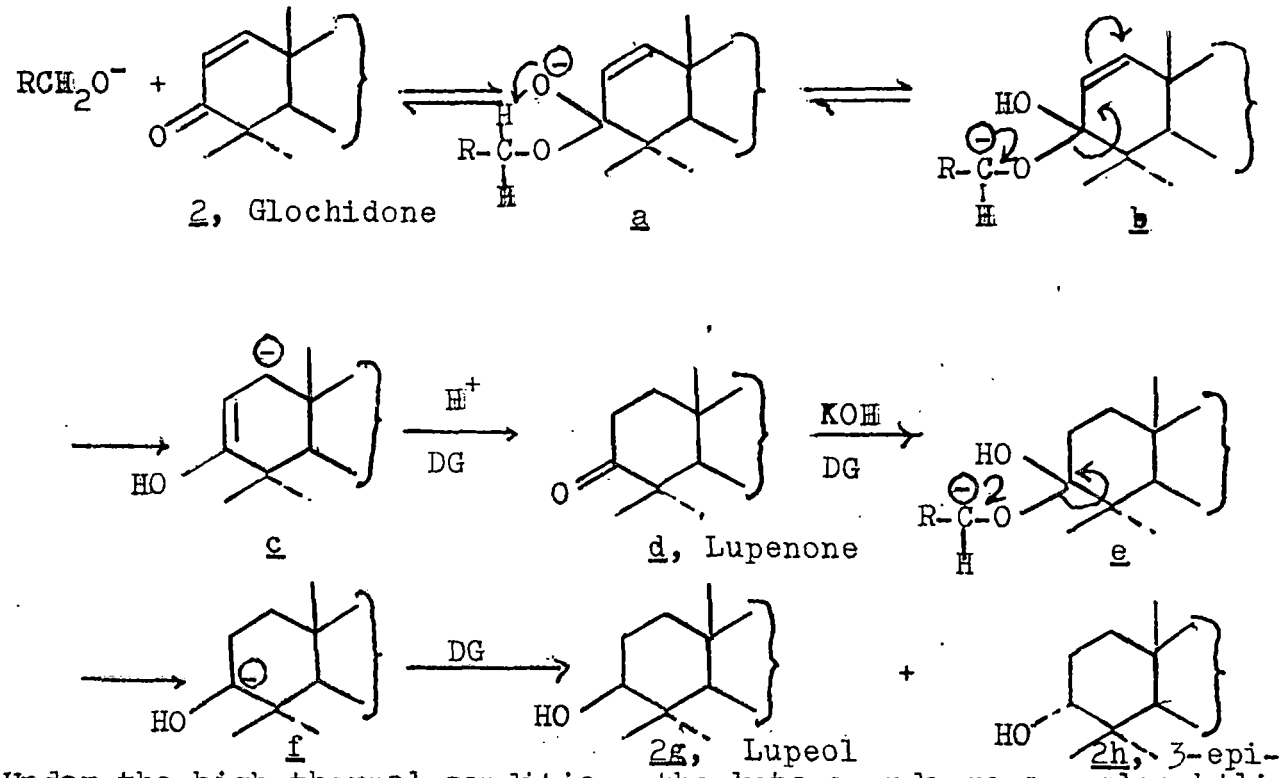
Table - 1

Entry No.	Ketones	Product (Yield in%)
1.	Methyl Trichadonate[13]	Trichadenic acid-A[13] 1a(50) and Trichadenic acid-B 1b (15)
2.	Friedelin[14]	Friedelanol[14] (45) and epi-friedelanol[14] (20)
3.	Moretenone[15]	Moretenol[15] (50) and epi-moretenol (15)
4.	Taraxerone[14]	Taraxerol[14] (50) and epi-taraxerol[6] (15)
5.	β-amyrone[19]	β-amyrin[19] (50) and epi- -amyrin[14] (15)
6.	Lupenone[19]	Lupeol[14] (50) and epi-lupeol[14] (15)
7.	Glochidone[16] (2)	Lupeol[14] 2g (40) and epi-lupeol[14] 2 (15) and lupenone 2d (8)
8.	Benophenone	Benzhydrol (90)

The reaction was carried out at higher temperature. At the high temperature of the reaction mixture, potassium hydroxide probably forms potassium-glycoxide with diethylene glycol. The glycoxide so formed may reduce the ketone in a cyclic mechanism that may be considered parallel to the action of aluminium-alkoxides in the case of Meerwein-Ponndorf - Verley reduction[16]; but in the latter case the reduction of α,β -unsaturated ketones furnish only the allylic alcohols[17], whereas in the present case the entry 7 shows that along with the keto group, the α,β-unsaturation is also reduced which cannot

be explained by the cyclic mechanism. A most probable mechanism for this reduction may follow the route as depicted in the Scheme I :

Scheme I



Under the high thermal condition, the ketone undergoes nucleophilic /ol attack by the anionic glycoxide to form the intermediate anion a that undergoes proton shift forming the carbanion intermediate b; elimination of glycol aldehyde from b furnishes the tautomeric carbanion c which subsequently acquires a proton from the solvent, the glycol to form the saturated ketone h. The isolation of a small amount of the ketone, lupenone from the reaction mixture as shown in entry 7 of table 1 confirms the proposed mechanism. Further nucleophilic attack by the glycoxide anion on the saturated ketone in a similar path furnishes

the intermediate anion d which ultimately affords the epimeric alcohols, 2g and 2h

CONCLUSION :

From the above observation we find that ketones are reduced to the epimeric alcohols by potassium hydroxide and diethylene glycol and the formation of the equatorial isomers predominate the less thermodynamically stable axial isomers.

EXPERIMENTAL :

Melting points are uncorrected IR spectra were run in KBr disc. in Beckman-20 and UV spectra were recorded in ethanol in Beckman DU-2 spectrometers. Mass spectra were run in JMS-300 instrument. All the rotations were determined in $CHCl_3$ solution. Column chromatography were performed in silica gel (BDH 60-120 mesh) and TLC were run on plates coated with silica gel G and were developed in iodine chamber. All the analytical samples were routinely dried for 36 hr in vacuo. Petrol used had the boiling point 60-80^{o} and the ether extracts were dried over anhydrous $NaSO_4$.

Treatment of methyl trichadonate 5 with KOH diethylene glycol : Preparation of trichadenic acid-A 1a and trichadenic acid B 1b.

A mixture of methyl trichadonate (0.5g) and KOH (2g) in diethylene glycol (50 ml) was heated in a r.b. flask (100 ml) in a heating mantel initially without condenser till all the moisture escaped from the mixture. When the temperature rose above 160^{o} in the

vapour phase, the condenser was fitted in the r,b. flask and the mixture was refluxed for 2 hr. The mixture was then cooled, acidified with dil. HCl and extracted with ether. The ether extract was washed with water, dried and the solvent was remered by distillation. The residue (0.45g) was chromatographed over silica gel column (1.5g). The following solvents were used for chromatography.

Table - 2

Eluent	Fractions 100 ml each	Residue on evaporation
Petrol	1 - 4	Nil
Petrol-benzene (4:1)	5 - 8	Nil
Petrol:benzene (3:2)	9 - 12	Nil
Petrol:benzene (2:3)	13 - 20	Nil
Petrol:benzene (1:4)	21 - 25	Nil
Benzene	26 - 30	Nil
Benzene:solvent ether (4:1)	31 - 40	White solid m.p. 280-85°
Benzene:solvent ether (7:3)	41 - 50	White solid m.p. 325-30°

Further elution with more polar solvents did not afford any solid material.

Isolation of trichadenic acid A. 1a

Fractions 31-40 (Table -2) were mixed. The residue (65 mg) was crystallised from chloroform-methanol to afford crystals of trichadenic acid-A, m.p. 289-90°.

IR (nujol) : 3410, 1688 cm^{-1}

Mass : 458 $[M]^+$

$[\alpha]_D$: +23°

Acetylation of trichadenic acid-A. 1a :

25 mg of the hydroxy acid 1a was dissolved in 2 ml pyridine. This was treated with 2 ml of acetic anhydride. The reaction mixture was kept on water bath for 4 hrs. It was cooled and poured into ice cold water and extracted with solvent ether. The ethereal layer was washed several times with water and then dried over anhydrous sodium sulphate. Removal of solvent afforded a gummy mass (25 mg) which was chromatographed over silica gel (7 gms) column. The following solvents were used for elution.

Table - 3

Eluent	Fraction collected 50 ml each	Residue on evaporation
Petrol	1-4	Nil
Petrol:benzene (4:1)	5-8	Nil
Petrol : benzene (3:2)	9-12	Nil
Petrol:benzene (1:4)	13-18	White solid

Further elution with more polar solvents did not afford any solid material.

Isolation of O-acetyl trichadenic acid-A

Fractions 13-18 (Table - 3) were mixed. The residue (25 mg) was crystallised from $CHCl_3$ - MeOH to afford crystals of O-acetyl trichadenic acid m.p. 251-52°.

IR(Nujol) : 1740, 1688, 1240

Mass : 500 (M^+)

$[\alpha]_D$: +27°

Acetate was identified as O-acetyl trichadenic acid (α-acetyl) by m.m.p., Co-IR and Co-TLC with an authentic sample.

Isolation of trichadenic acid-B 1b :

Fractions 41-50 (Table -2) were mixed. The residue (0.2g) was crystallised from chloroform-methanol to afford crystals of trichadenic acid 1b m.p. 334-35°.

IR (nujol) : 3425, 1690 cm^{-1}

Mass : 458

$[\alpha]_D$: +41°

Acetylation of trichadenic acid-B : 1b:

Acetate derivative prepared by Ac_2O-Py method as described before. m.p. of acetate derivate 27071°.

IR (nujol) : 1725, 1690, 1240 cm^{-1}

Mass : 500 (M^+)

$[\alpha]_D$: +50°

The acetate was identified as 3β-O-acetyl trichadenic acid by m.m.p, Co-IR and Co-TLC.

Treatment of friedelin with KOH - diethylene glycol: Preparation of epi-friedelanol and friedelanol:

A mixture of friedelin (0.5g) and KOH (2g) in diethylene glycol (50 ml) was boiled in a r.b. flask (100 ml) in a heating mantel without condenser till the temperature of the escaping vapour started registering temperature above 160° when the condenser was fitted in. The mixture was allowed to reflux for 2 hr and then cooled. The mixture was then acidified with dil HCl, extracted with ether, washed the extract with water and dried (Na_2SO_4). The solvent was removed and the residue (0.45g) was chromatographed over silica gel (15g). The following solvents were used for chromatogram.

Table - 4

Eluent	Fractions 100 ml each	Residue on evaporation
Petrol	1-5	Nil
Petrol : benzene (4:1)	6-15	White solid
Petrol : benzene (3:2)	16-20	Nil
Petrol : benzene (2:3)	21-30	White Solid

Further elution with more polar solvents did not afford any solid material.

Isolation of epifriedelanol:

Fractions 6-15 (Table - 4) were mixed. The residue (0.1g) was crystallised from $CHCl_3$ - MeOH to afford crystals of epi-friedelanol m.p. 278-80°.

IR (nujol) : 3610 cm^{-1}

Mass : 428 (M^+)

$[\alpha]_D$: $+20^\circ$

Acetyl derivative of epi-friedelanol was prepared by Ac_2O-Py method.

m.p. : $291-92^\circ$

IR (nujol) : 1730, 1240 cm^{-1}

Mass : 470 (M^+)

$[\alpha]_D$: 38°

The acetyl derivative was found identical (m.m.p.) Co-IR and Co-TLC) with an authentic sample of epi-friedelanol acetate.

Isolation of friedelanol:

Fractions (21-30) were mixed. The residue (0.2g) was crystallised from $CHCl_3$-MeOH to afford crystals of friedelanol, m.p. $300-302^\circ$.

IR (nujol) : 3620 cm^{-1}

Mass : 428 (M^+)

$[\alpha]_D$: $+18^\circ$

Acetyl derivative of friedelanol was prepared by Ac_2O-Py method.

m.p. : $315-16^\circ$

IR : 1730, 1240 cm^{-1}

$[\alpha]_D$: -10°

Acetyl derivative was found identical with an authentic sample of friedalanol acetate by comparison of their m.p., TLC and IR spectra

Treatment of moretone with KOH-diethylene glycol: Preparation of epi-meretenol and meretenol:

Meretenone - (0.5g) and KOH (2g) was mixed with diethylene glycol (50 ml) taken in a.r.b. flask (100 ml) and heated as described before. The solid (0.45g) obtained after usual work up was chromatographed over silica gel (15g). The following solvents were used.

Table - 5

Eluent	Fractions 100 ml each	Residue on evaporation
Petrol	1-5	Nil
Petrol : benzene (4:1)	6-15	White solid
Petrol : benzene (3:2)	16-20	Nil
Petrol : benzene (2:3)	21-30	White solid

Further elution with more polar solvents did not afford any solid material.

Isolation of epi-moretenol:

Fractions 6-15 (Table - 5) were mixed. The residue (65 mg) was crystallised from $CHCl_3$-MeOH to afford crystals of epi-moretenol m.p. 223-24°.

IR (nujol) : 3460, 3080, 1640, 890 cm^{-1}

Mass : 426 (M^+)

$[\alpha]_D$: - 2°

epi-moretenol was acetylated by Ac_2O-Py.

Acetate derivative was crystallised from $CHCl_3$-MeOH

m.p. 231-32°

IR (nujol) : 3070, 1725, 1640, 890 cm^{-1}

Mass : 468 (M^+)

$[\alpha]_D$: -18°

The acetate was identical (m.m.p., Co-IR and Co-TLC) with an authentic sample of epi-moretenyl acetate.

Isolation of moretenol:

Fractions 21-30 (Table - 5) were mixed together. The residue (0.1g) was crystallised from $CHCl_3$-MeOH to afford crystals of moretenol, m.p. 228-30°.

IR (nujol) : 3480, 3070, 1640, 890 cm^{-1}

Mass : 426 (M^+)

$[\alpha]_D$: +27°

moretenol was acetylated by Ac_2O-Py. Acetate derivative was crystallised from $CHCl_3$-MeOH m.p. 276-78°.

IR (nujol) : 3070, 1725, 1640, 1250, 885 cm^{-1}

Mass : 468 (M^+)

$[\alpha]_D$: +20°

Acetate was identified as moretenyl acetate by comparison of m.m.p., IR and TLC with an authentic sample.

Treatment of taraxerone with KOH-diethylene glycol: Preparation of epi-taraxerol and taraxerol

A mixture of taraxerone (0.5g) and KOH (2g) in diethylene glycol (50 ml) was refluxed for 2 hr as described before. The solid (0.45g) obtained after usual work up was absorbed in a silica gel chromatogram (15g). The following solvents were used for chromatogram.

Table - 6

Eluent	Fractions 100 ml each	Resicue on evaporation
Petrol	1-4	Nil
Petrol : benzene (4:1)	6-15	White solid
Petrol : (3:2)	16-20	Nil
Petrol : benzene (2:3)	21-30	White solid

Further elution with more polar solvents did not afford any solid material.

Isolation of epi-taraxerol:

Fractions from 6-15 (Table - 6) were mixed. The residue (75 mg) was crystallised from $CHCl_3$-MeOH to afford crystals of epi-taraxerol m.p. 262-64°.

IR (nujol) : 3470, 810 cm^{-1}

Mass : 426 (M^+)

$[\alpha]_D$: -18°

Acetyl derivative of epi-taraxerol was prepared by Ac_2O-Py method.

m.p.	: 202-203°
IR (nujol)	: 1730, 1240, 820 cm^{-1}
Mass	: 468 (M^+)
$[\alpha]_D$	: -25°

The acetyl derivative was found identical (m.m.p., Co-IR and Co-TLC) with an authentic sample of epi-taraxeryl acetate.

Isolation of taraxerol:

Fractions from 21-30 (Table - 6) were mixed. The residue (0.25g) was crystallised from $CHCl_3$-MeOH to afford crystals of taraxerol - m.p. 278-79°.

IR (nujol)	: 3460, 815 cm^{-1}
Mass	: 426 (M^+)
$[\alpha]_D$	: +3°

The solid on acetylation with Ac_2O-Py method formed acetate of m.p. 297-99°.

IR (nujol)	: 1730, 1240, 820 cm^{-1}
Mass	: 468 (M^+)
$[\alpha]_D$	: +8°

The acetate was identical (m.m.p., Co-IR, Co-TLC) with an authentic specimen of taraxeryl acetate.

Treatment of β-amyrone with KOH - diethylene glycol : Preparation of epi-β-amyrin and β-amyrin:

A mixture of β-amyrone (0.5g) and KOH (2g) in diethylene glycol (50 ml) was refluxed as described before. The solid (0.45g) obtained after usual work-up was crhomatographed over silica gel (15g). The following solvents were used for elution.

Table - 7

Eluent	Fractions 100 ml each	Residue on evaporation
Petrol	1-4	Nil
Petrol : benzene (4:1)	6-15	White solid
Petrol : benzene (3:2)	16-20	Nil
Petrol : benzene (2:3)	21-30	White solid

Further elution with more polar solvents did not give any solid material.

Isolation of epi β-amyrin

Fraction from 6-15 (Table - 7) were mixed. The residue (75 mg) was crystallised from $CHCl_3$-MeOH to afford crystals of epi β-amyrin m.p. 220-22°.

IR (nujol) : 3540, 820 cm^{-1}

Mass : 426 (M^+)

$[\alpha]_D$: +70°

Its acetate was prepared by Ac_2O-Py method. m.p. 125-26°

IR (nujol) : 1730, 1240, 810 cm^{-1}

Mass : 468 (M^+)

$[\alpha]_D$: +55°

The acetate was found to be identical with an authentic epi β- amyrin acetate by m.m.p., Co-IR, Co-TLC.

Isolation of β-amyrin:

Fractions from 21-30 (Table - 7) were mixed. The residue (0.25g) was crystallised from $CHCl_3$-MeOH to afford crystals of β-amyrin. m.p. 197-98°.

IR (nujol) : 3500, 810 cm^{-1}

Mass : 426 (M+)

$[\alpha]_D$: +80°

Acetyl derivative of β-amyrin was prepared by Ac_2O - Py method.

m.p. : 237-38°

Mass : 468 (M+)

IR (nujol) : 1730, 1240, 820 cm^{-1}

$[\alpha]_D$: +79°

The acetate was identical (m.m.p., Co-IR and Co-TLC) with an authentic sample of β-amyrin acetate.

Treatment of Lupenone with KOH-diethylene-glycol: Preparation of epi-lupeol and lupeol.

A mixture of lupenone (0.5g) and KOH (2g) in diethylene glycol (50 ml) was refluxed for 2 hrs as described before. The product (0.45g)

obtained after usual work-up was chromatographed over silica gel (15g). The following solvents were used for elution.

Table - 8

Eluent	Fractions 100 ml each	Residue on evaporation
Petrol	1-8	White solid
Petrol : benzene (4:1)	9-14	Nil
Petrol : benzene (3:2)	15-25	White solid

Further elution with more polar solvents did not afford any solid material.

Isolation of epi-lupeol

Fractions from 1-8 (Table - 8) were mixed. The residue (75 mg) was crystallised from $CHCl_3$-MeOH to afford crystals of epi-lupeol m.p. 200-201°

IR (nujol) : 3320, 3060, 1640, 880 cm^{-1}

Mass : 426 (M+)

$[\alpha]_D$: +17°

Epi-lupeol was acetylated by Ac_2O-Py. Acetate derivative was crystallised from $CHCl_3$-MeOH, m.p. 159-60°.

IR (nujol) : 3060, 1730, 1640, 1250, 880 cm^{-1}

Mass : 468 (M^+)

$[\alpha]_D$: -5°

The acetate was identical (m.m.p., Co-IR and Co-TLC) with an authentic sample of epi-lupenyl acetate.

Isolation of Lupeol:

Fractions from 15-25 (Table - 8) were mixed. The residue (0.25g) was crystallised from $CHCl_3$-MeOH to afford crystals of lupeol m.p. 214-16°.

IR (nujol) : 3340, 1640, 890 cm^{-1}

Mass : 426 (M^+)

$[\alpha]_D$: +26°

Lupeol was acetylated by Ac_2O - Py. Acetate derivative was crystallised from $CHCl_3$-MeOH, m.p. 215-17°.

IR (nujol) : 1730, 1640, 1240, 880 cm^{-1}

Mass : 468 (M^+)

$[\alpha]_D$: +20°

The acetate was identical (m.m.p., Co-IR and Co-TLC) with an authentic sample of lupenyl acetate.

Treatment of Glochidone with KOH-diethylene glycol: Preparation of lupenone, epi-lupeol and lupeol:

A mixture of glochidone (0.5g) and KOH (2g) in diethylene glycol (50 ml) was refluxed for 2 hrs as described before. The product (0.45g) obtained after usual work up was absorbed in a column of silica gel (15g). The following solvents were used for elution.

Table - 9

Eluent	Fractions 100 ml each	Residue on evaporation
Petrol	1-5	White solid
Petrol	6-10	White solid
Petrol : benzene (4:1)	11-15	Nil
Petrol : benzene (3:2)	16-25	White solid

Further elution with more polar solvents did not give any solid material.

Isolation of lupenone:

Fractions from 1-5 (Table - 9) were mixed. The residue (0.04g) was crystallised from $CHCl_3$-MeOH, m.p. 168-69°.

IR (nujol) : 1700, 1640, 880 cm^{-1}

Mass : 424 (M^+)

UV : No absorption between 220 to 270 nm.

The solid was identified as lupenone by comparison of m.p., IR and TLC with an authentic specimen.

Isolation of epi-lupeol:

Fractions from 6-10 (Table - 9) were mixed. The residue (0.08g) was crystallised from $CHCl_3$-MeOH, m.p. 199-200°.

IR	: 3320, 3060, 1640, 880 cm^{-1}
Mass	: 426 (M^+)
$[\alpha]_D$	: $+18^\circ$

The solid was directly compared with an authentic sample of epi-lupeol and was found identical.

Isolation of lupeol:

Fractions from 16-25 (Table - 9) were mixed. The residue (0.2g) was crystallised from $CHCl_3$-MeOH, m.p. 215-16°.

IR (nujol)	: 3340, 1640, 890 cm^{-1}
Mass	: 426 (M^+)
$[\alpha]_D$	: $+24^\circ$

The acetate prepared by Ac_2O-Py.

m.p.	: 214-15°
IR (nujol)	: 1730, 1640, 1240, 880 cm^{-1}
Mass	: 468 (M^+)
$[\alpha]_D$	:

The acetate was found identical (m.m.p., Co-IR and Co-TLC) with an authentic specimen of lupenyl acetate.

Treatment of Benzophenone-with KOH-diethylene glycol: Preparation of benzhydrol:

A mixture of benzophenone (0.5g) and KOH (2g) in diethylene glycol (50 ml) was refluxed for 2 hr as in the previous cases. After

usual work up the solid (0.45g) was chromatographed over silica gel (15g). The following solvents were used for elution.

Table - 10

Elution	Fractions 100 ml each	Residue on evaporation
Petrol	1-5	Nil
Petrol : benzene (4:1)	6-10	Nil
Petrol : benzene (3:2)	11-15	Nil
Petrol : benzene (2:3)	16-30	White solid

Further elution of more polar solvents did not give any solid material.

Isolation of benzhydrol:

Fractions from 16-30 (Table - 10) were mixed. The residue (0.4g) was crystallised from $CHCl_3$-MeOH afford crystals of m.p. 67-68°.

IR (nujol) : 3350, 1605, 1280, 1050, 1030, 940, 920, 860, 765, 750, 700 cm^{-1}

Mass : 168 (M^+)

The solid was found identical (m.m.p., Co-IR and Co-TLC) with an authentic sample of benzhydrol.

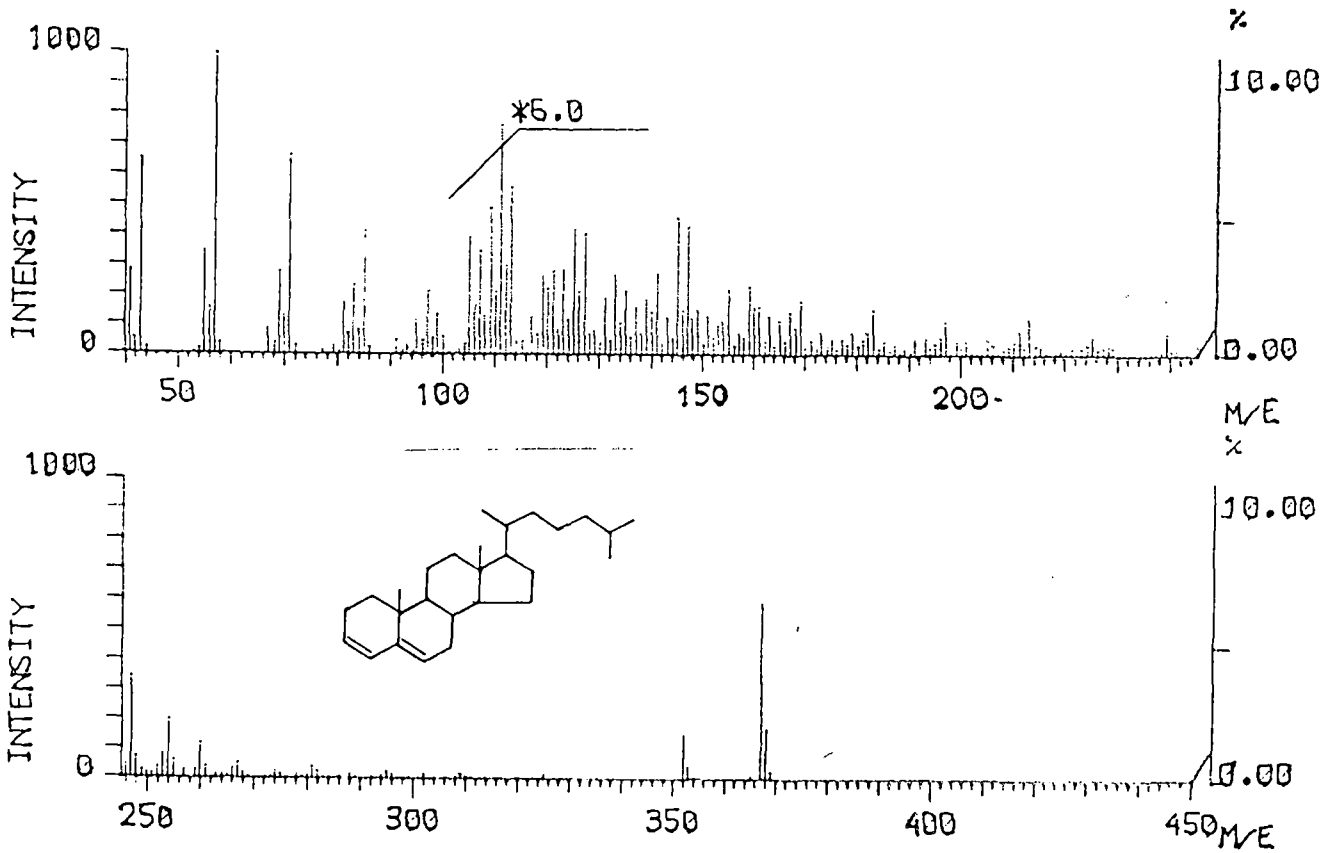


Fig. 1 MS spectrum of Cholesta-3,5-diene.

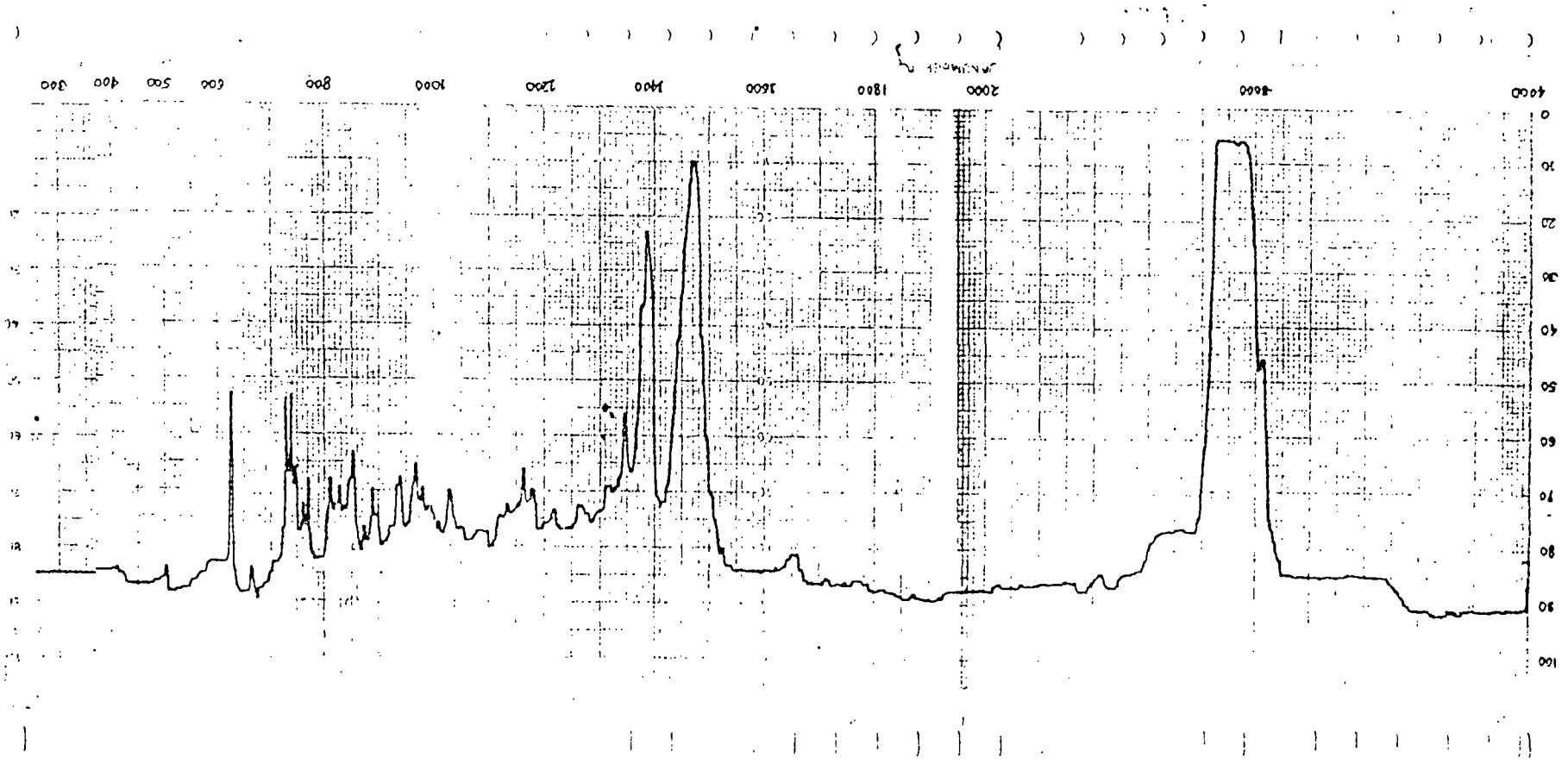


Fig. 2 IR spectrum of Cholesta-3,5-diene.

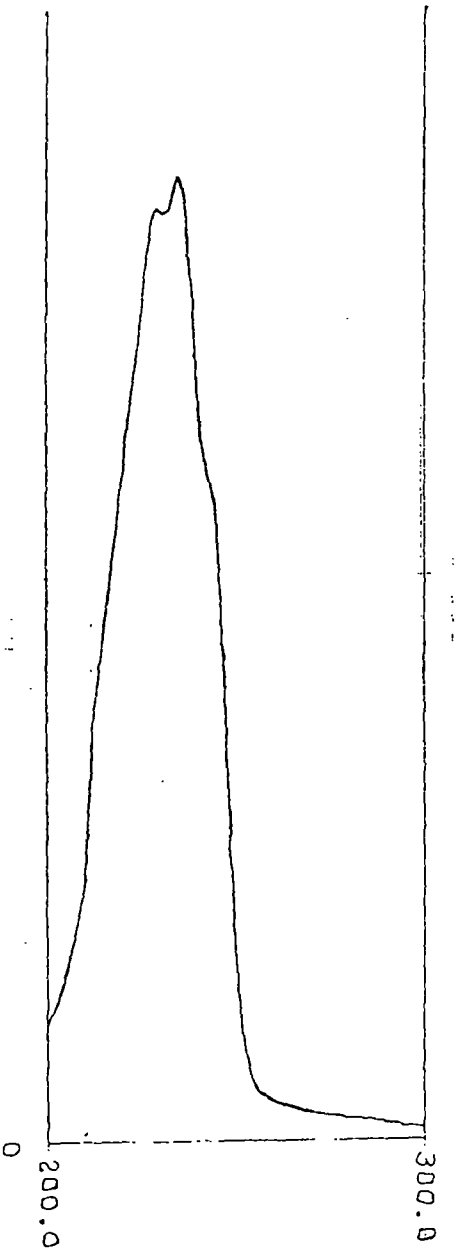


Fig. 3 UV spectrum of Cholesta-3,5-diene.