PART III

Studies on autoxidation : A new method for the synthesis of isomeric Δ^{12}-oleanene-2,3-diols.

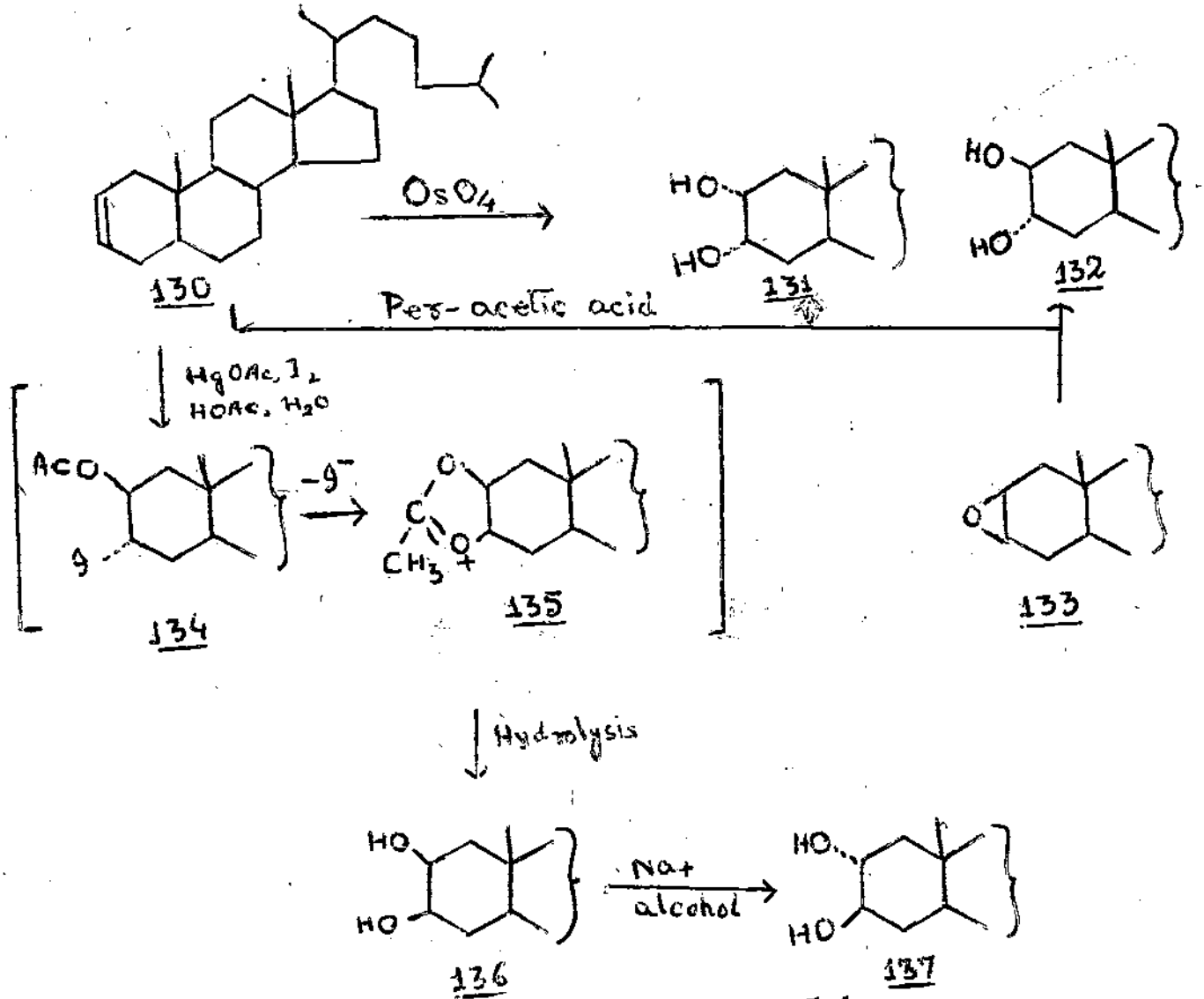
PART III

CHAPTER I

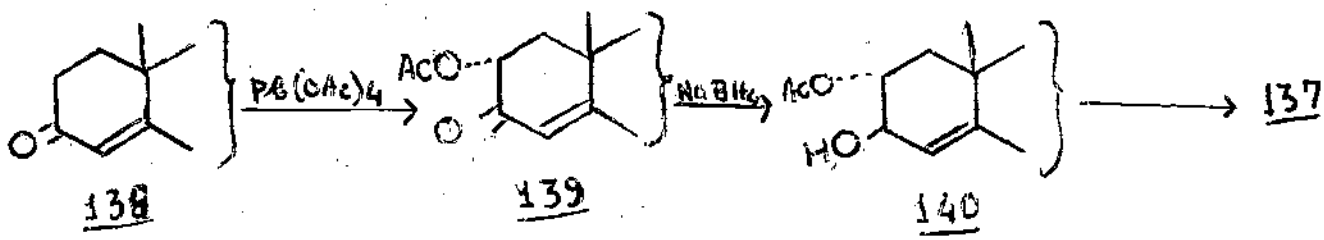
Studies on autoxidation of β-amyrone : Synthesis of isomeric Δ^{12}-oleanene 2,3-diols

Section A

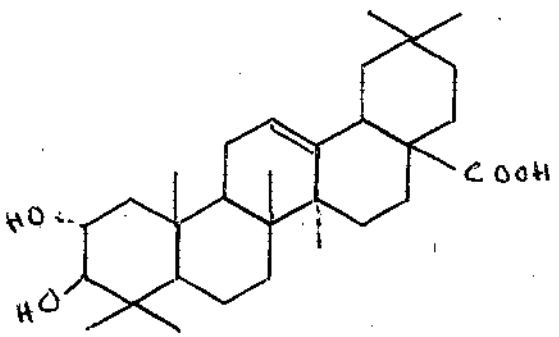
Introduction: In the course of elucidation of the configurations of sapogenins containing a 2,3-diol system, methods were developed for production of the four possible isomers in this series. By methods largely developed in this connection, the four cholestane 2,3-diols have also been prepared[1,2]. Δ^2-cholestene 130 affords the 2α, 3α-diol 131 on reaction with osmium tetroxide and give the 2β, 3α-diol 132 on oxidation with peracetic acid and subsequent hydrolysis[1-3]. The same diol 132 also results on diaxial opening of 2α, 3α- or 2β, 3β- oxidocholestanes. The 2β, 3β-diol 136 has also been prepared[1,2] according to Winstein and Buckles[4] by treatment of Δ^2-cholestene with silver acetate, iodine and moist acetic acid. The reaction probably involves formation of a cyclic 2α, 3β-iodonium ion, which on acetolysis with inversion at C_2 gives 134. Expulsion of iodide ion with inversion at C-3 forms a resonant oxonium-carbonium ion 135 which leads to a monoacetate which again on hydrolysis gives 136. Since the diol 136 has one axial substituent at C-2 it is epimerised by treatment with sodium in ethanol at 180° to the diequatorial 2α, 3β-diol 137. Diol 137 was also obtained from cholestenone 138, which reacts with lead tetra-acetate to give in about 10%



yield a product 139 having 2α-acetoxy group[5,6]. Reduction of 139 with sodium borohydride and hydrogenation gave the 2α, 3β-diol.



Tschesche and co-workers[7] in connection with their work to confirm the structure of crateogolic acid[141] and bredemolic acid 142 has reported the successful synthesis of all the four stereoisomeric 2,3-dihydroxy derivatives of oleanolic acid, starting from oleanolic acid by following essentially the methods described above. Methyl olean-2,12-diene-28-oate 143 on treatment with osmium tetroxide afforded a mixture of Methyl 2α, 3α-dihydroxy-12-olean-28-oate 144 m.p. 258-60° and 2β, 3β-isomer 145 m.p. 278-82°. The 2β, 3α- isomer 146 m.p. 247-49° was prepared by performic acid oxidation of 143 and the IR spectra of this compound was found to be identical with an authentic sample of 146. The Me-2α, 3β dihydroxy-olean 12-en-28-oate



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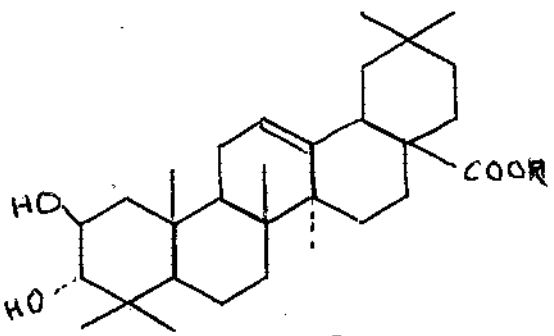
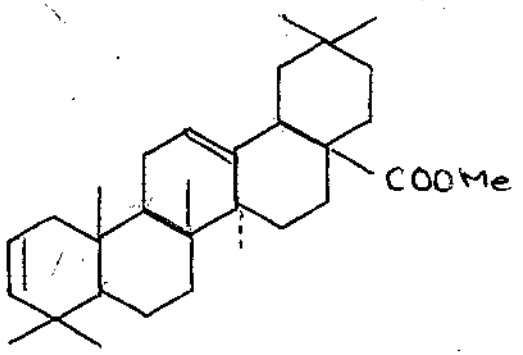


142, R = H

146, R = Me



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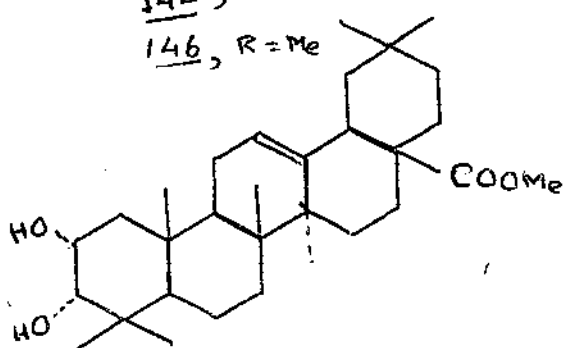

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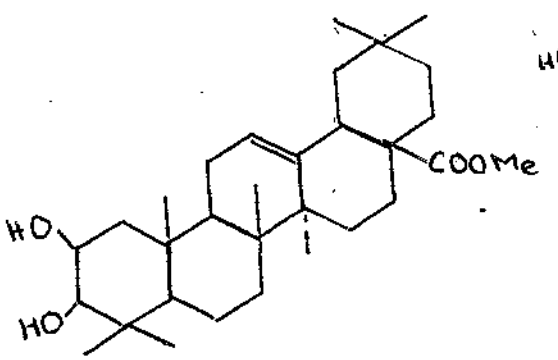

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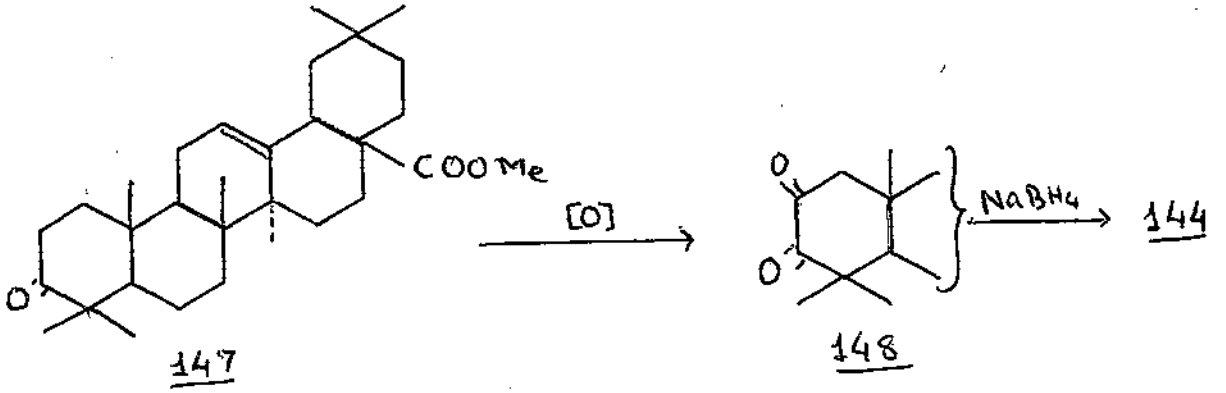
was prepared by isomerising the 2α, 3α-isomer 144 by treatment with sodium in ethanol at 180° for 36 hours. The product isolated was found to be identical with an authentic specimen of methyl crategolate. These authors also oxidised methyl oleanonate 147 by passing oxygen through a solution of it containing potassium tertiary butoxide in tertiary butanol. Me-2,3-dioxo-olean-12 en-28-oate 148 was isolated which on reduction with sodium borohydride afforded methyl-2α, 3α-dihydroxy derivative 144.



147 148

They also prepared the acetonide derivatives of all the four isomeric diols and commented that unlike the steroid series acetonide formation cannot be used as an argument for the presence of 2,3-cis-vicinal diols.

A new method for the synthesis of isomeric Δ^{12}-oleanene 2,3-diols and discussion on its structures:

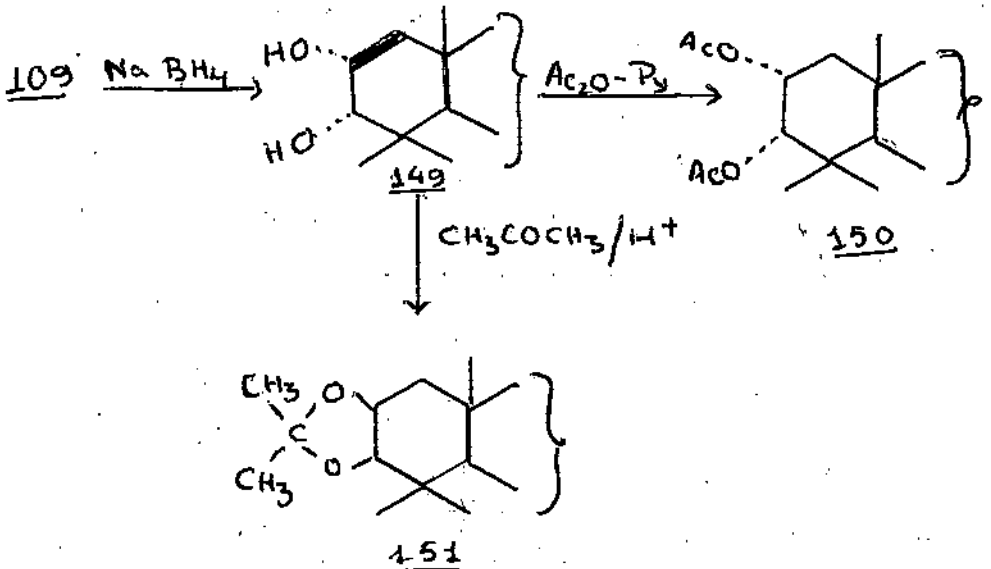
A number of 2,3-isomeric diols of triterpenoids have been isolated from natural sources. In order to develop a new general method for the preparation of isomeric 2,3-diols of triterpenes, we thought that the diosphenol obtained by autoxidation of β-amyrone may be

successfully utilised as a suitable starting material. This goal has been realised and the detailed discussion is presented below.

Section B : Synthesis of Δ^{12}-oleanene 2α, 3α-diol 149

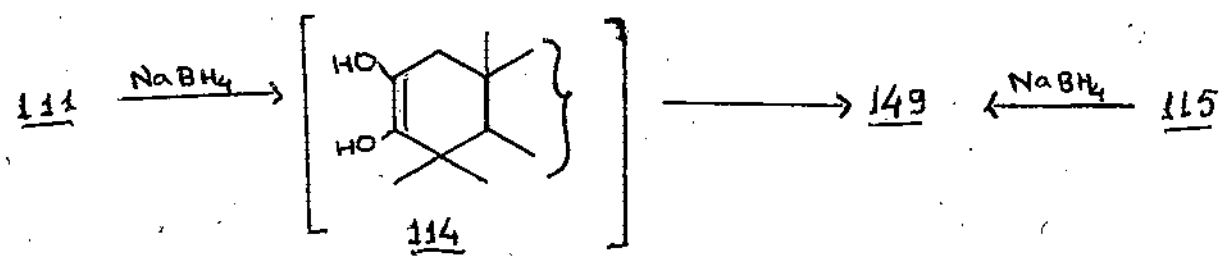
Autoxidation of β-amyrone 107 gave the diosphenol 109 m.p. 200-202°, $(\alpha)_D$ + 124.27° (for details see part II of this thesis, page 79). Sodium borohydride reduction of 109 gave a compound 149, m.p. 240-42°, $(\alpha)_D$ + 101.88°. IR, ν_{max}^{nujol} 3420, 2950, 1460, 1275, 1250, 1060, 1025, 998, 835 cm^{-1}, which on acetylation with acetic anhydride-pyridine afforded a crystalline compound 150, m.p. 221-22°, $(\alpha)_D$ + 83.63°, IR, ν_{max}^{nujol} 2960, 1725 (acetate), 1485, 1455, 1385, 1370, 1255 (acetate) cm^{-1}. Analysis of the sodium borohydride reduced product and its diacetate corresponded to the molecular formulae $C_{30}H_{50}O_2$ and $C_{34}H_{54}O_4$ respectively. NMR spectra of the compound 149 (fig. 14) showed a sharp singlet at 3.43 ppm indicating that the hydroxyl group at C-3 is axial associated with an equatorial proton (H_e). The equatorial nature of the hydrogen at C-3 can also be visualised from its coupling constant (J_{ea} = 3.6 cps) which indicates the presence of an equatorial-axial coupling. A broad multiplet at 3.98 ppm is probably a double triplet due to its being from an axial proton (H_a-2) which has one axial-axial and two equatorial-axial couplings (J_{ae} = 4.5 cps and J_{aa} = 11.5 cps). The diacetate of above reduced product also showed the same pattern of NMR peaks (fig. 15) but being more prominent and shifted to lower fields by the acetates. It showed sharp doublet at 4.61, 4.65 ppm accounting for the C-3 equatorial proton having a coupling constant (J_{ea} = 4.2 cps). The proton

at C-2 exhibited a doublet of a multiplet at 5.34 ppm. These NMR observations of the diol and its diacetate are quite in accord with the assignment of 2α, 3α-orientation as shown in structure 149 and 150.



Compound 149 on treatment with acetone in presence of catalytic amount of P-toluene sulfonic acid gave an acetonide derivative 151, m.p. 180-82°, $(\alpha)_D$ + 102.56°.

2-keto-β-amyrin 111 obtained by hydrogenation of diosphenol 109 (part II of this thesis, page 81) in presence of 10% palladium-on-charcoal catalyst, on reduction with sodium borohydride afforded a crystalline solid m.p. 239-40°, identical in all respects with the 2α, 3α-diol 149 described earlier. We have already established earlier (part II of this thesis) that hydrogenation of diosphenol 109 gave a 3β-hydroxy-2-keto compound. Sodium borohydride reduction would be expected to furnish a 2β, 3β-diol or 2α, 3β-diol or a mixture of 2α, 3β and 2β, 3β-diols. However, 2α, 3α-diol 149 could



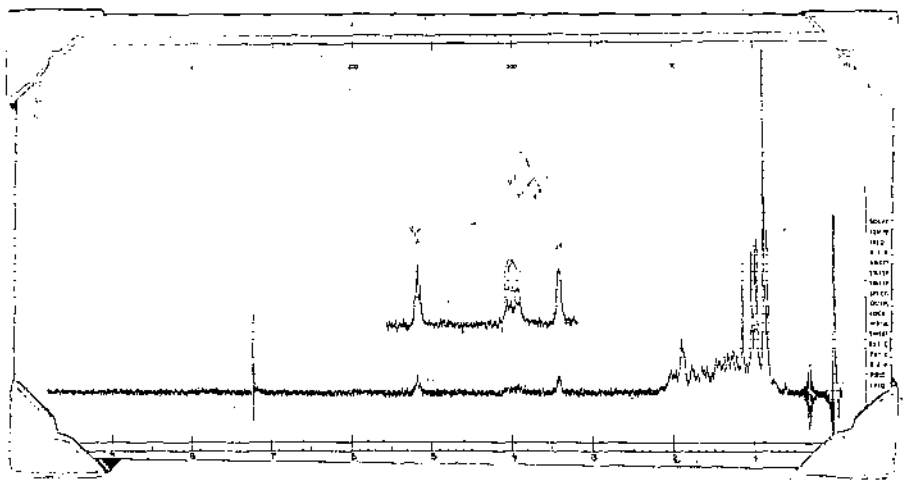


Fig. 14 : NMR spectra of α,α-diol.

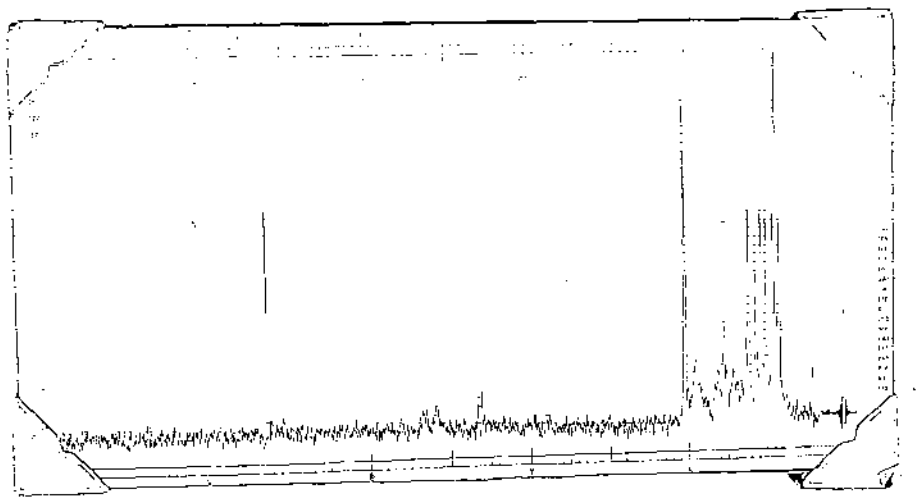


Fig. 15 : NMR spectra of α,α-diol diacetate.

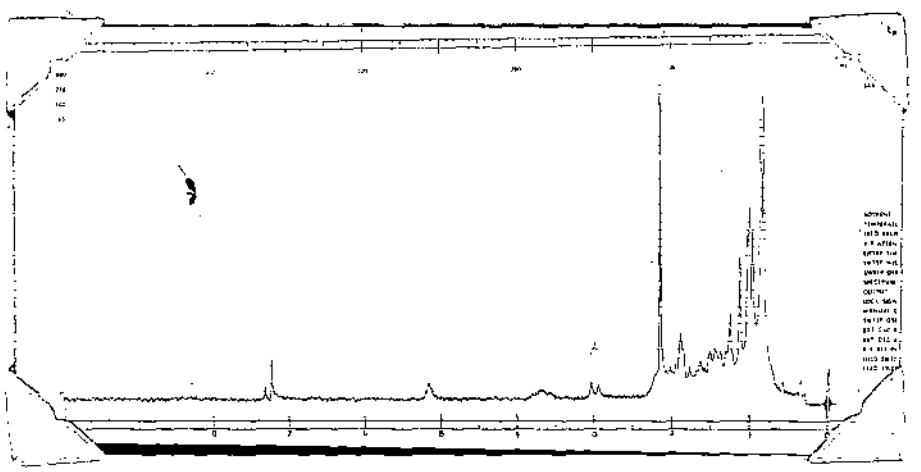
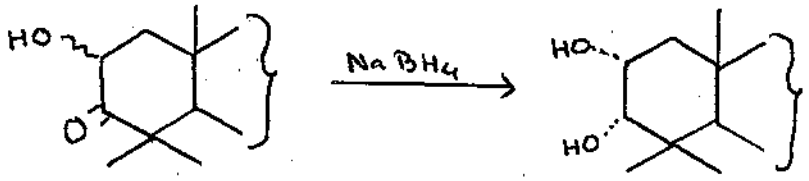


Fig. 16 : NMR spectra of α,β-diol.

only be isolated which can be explained if it is assumed that the reduction proceeds via the enediol 114 intermediate.



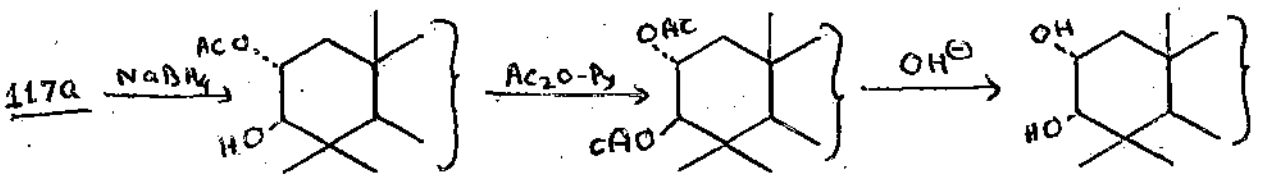
115 149

2-hydroxy-β-amyrone 115 obtained by potassium tertiary butoxide treatment of 111 (part II of this thesis, page 83) also on similar reduction with sodium borohydride gave the same 2α, 3α-diol 149.

Section C : Synthesis of Δ^{12}-oleanene 2α, 3β-diol 154

Diosphenol acetate 110 on hydrogenation in presence of 10% palladium-on-charcoal catalyst gave 2α-acetoxy-β-amyrone 117a (part II of this thesis, page 95). Sodium borohydride reduction of 18,19,110, in dioxan solution buffered at P_H-8 to reduce isomerisation gave the crystalline 2α-acetoxy-β-amyrin m.p. 246-48°. The latter on acetylation afforded the 2α, 3β-diacetate 152, m.p. 216-18°, $(\alpha)_D$ + 73.42° which on alkaline hydrolysis gave the corresponding 2α, 3β-diol 154 m.p. 202-4°, $(\alpha)_D$ + 60°. The diequatorial 2α, 3β-configuration of the hydroxyl groups in the diol 154 was unequivocally confirmed by

examination of the NMR spectra of the diol 154 (fig. 16) and its diacetate 153. The NMR spectra of the diol 154 gives rise to an unsymmetrical doublet near 2.94 and 3.14 ppm (J_{aa} = 10 cps). This unsymmetrical doublet arises due to coupling with C-2 proton. The 10 cps coupling between these protons implies a trans diaxial arrangement of the C-2 and C-3 proton[11]. The C-2 proton is further coupled to the methylene protons at C-1, and the signal for it is discerned as a quartet of doublets centered at 3.74 ppm (X part of an ABXY). A similar pattern of δ-values have been observed for methyl maslinate and other triterpenoids with identical ring A[12]. The NMR spectrum of its diacetate 153 showed the same pattern shifted to lower fields due to the acetate groups.



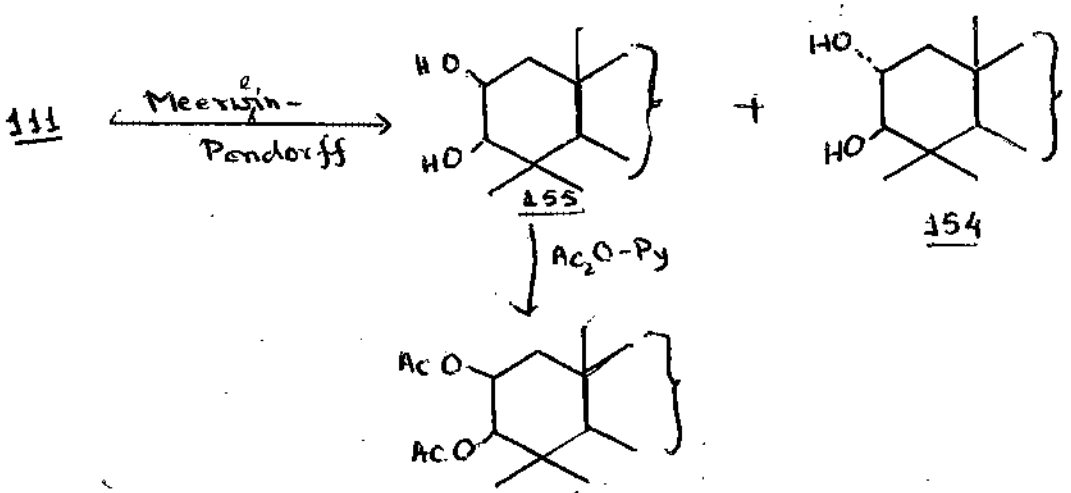
152 153 154

Lithium aluminium hydride reduction of 117a gave a mixture of diols (TLC showed two spots). Chromatography of the mixture gave two different diols, the major fraction had m.p. 239-40° and was found to be identical with 2α, 3α-diol 149. The other diol obtained in 10% yield was identified as 2α, 3β-diol 154.

2α, 3β-diol on treatment with acetone in presence of catalytic amount of p-toluene sulfonic acid gave an acetonide m.p. 173-4°.

Section D : Synthesis of Δ^{12}-oleanene 2β, 3β-diol 155

Meerwein-Ponndorff reduction of 2-keto-β-amyrin furnished a crystalline solid which exhibited two distinct spots on a chromatoplate. Chromatography of the solid first eluted a solid compound which after crystallisation from methanol and chloroform mixture afforded a crystalline solid 155, m.p. 278-80°, $(\alpha)_D$ + 71.28°, ν_{max} 3420, 2960, 1450, 1370, 1350, 1040 cm^{-1}, in 92% yield which on acetylation with pyridine-acetic anhydride afforded an acetate 156, m.p. 280-82°, + 40.77°. The second solid obtained from the chromatogram in about 6% yield had m.p. 202-4°. The solid was found to be



identical with 2α, 3β-diol 154 by m.m.p. and IR comparison of its diacetate. The stereochemistry of the hydroxyl groups of the diol 155 has been assigned as 2β, 3β as depicted in 155 on the basis of chemical and physical evidences described below.

Epi-β-amyrin prepared by Meerwein-Ponndorff reduction of β-amyrone following Paton's method[13] on dehydration with $POCl_3$ and pyridine gave $\Delta^{2,12}$-olean diene 152[14]. The diene 152 was treated

with osmium tetroxide in pyridine solvent and the product obtained after chromatography melted at 262-70° and showed two spots on chromatoplate. The separation of this two components could not be successfully accomplished by column chromatography. However, careful fractional crystallisation of the mixture from chloroform-methanol mixture afforded first a diol having m.p. 278-80°, as the major component (90%). From the mother liquor a second diol having m.p. 239-41° was obtained as a minor product (8%). The latter compound has been identified as the 2α, 3α-diol 149 from its m.m.p. and I.R. comparison with the 2α, 3α-diol described earlier. The major diol m.p. 278-80°, $(\alpha)_D$ + 69.35° afforded a diacetate 156 m.p. 280-82° and both of them were found to be identical with the diol and the diacetate respectively obtained by the Meerwein Pondorff reduction of 2-keto-β-amyrin 111 described above (m.m.p. and IR comparison fig. 19). Since osmylation can only afforded two cis isomers, the diol of m.p. 278-80° 155 and its diacetate 156 m.p. 280-82° must have 2β, 3β-configuration as depicted in formulae 155 and 156 respectively.

NMR observations of the diol 155 and its diacetate 156 are quite in accord with their 2β, 3β stereochemical assignments. The NMR spectrum of the diol 155 (fig. 17) showed broad peak at 3.2 ppm associated with the C-3 proton (H_a). The C-2 proton couples with the C-3 proton and the C-1 methylene protons resulting in two equatorial axial and one equatorial-equatorial couplings and the signal for this is discerned as a doublet at 4.06 and 4.1 ppm. In the NMR spectrum of its diacetate 156 (fig. 18), the peak associated with

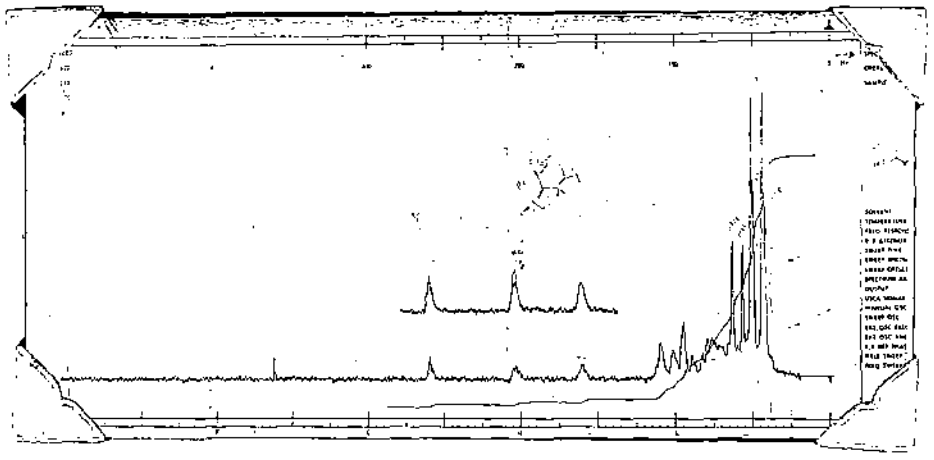


Fig. 17 : NMR spectra of β,β-diol

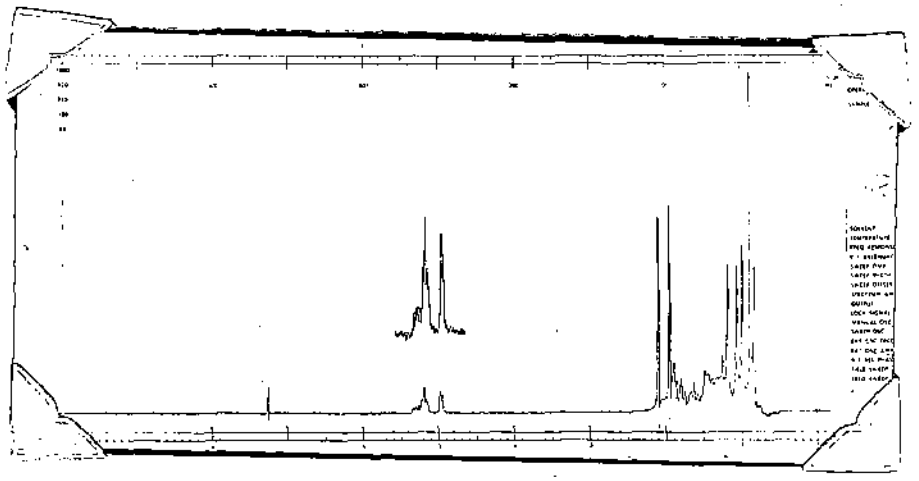


Fig. 18 : NMR spectra of β,β-diol diacetate.

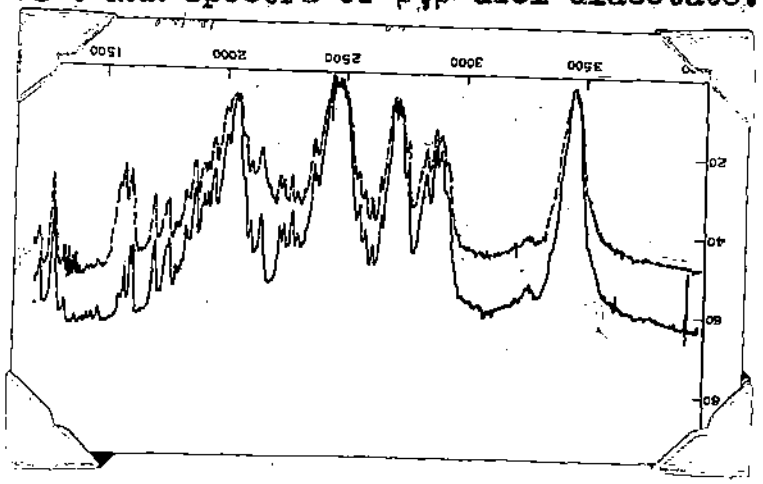
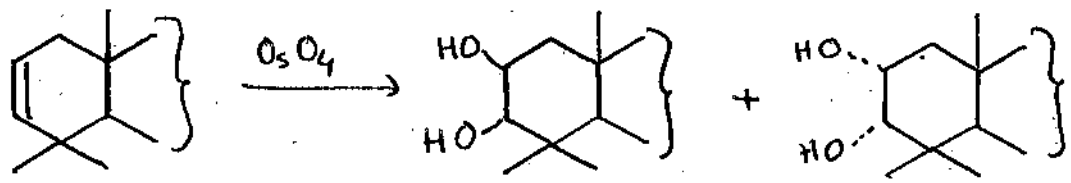


Fig. 19 : IR comparison
β,β-diol obtained by Meerwin Pondorff method (solid line).

β,β-diol obtained by Osmium tetroxide treatment of β-amyrilene II (dotted line).

the C-3 axial proton is shifted to lower field giving rise to a sharp doublet at δ3.94 and δ3.98 ppm (J_{ea} = 3.2 cps) and C-2 proton (H_e)



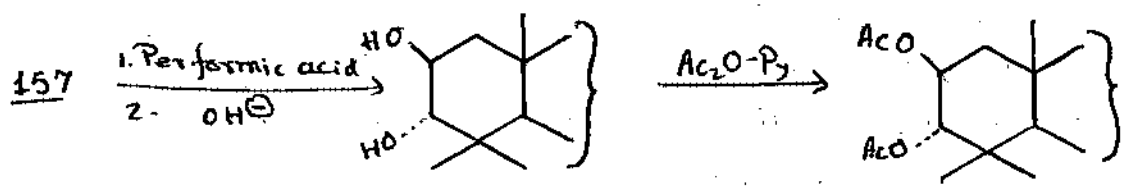
157 155 149

gives rise to a quartet of a doublet at 5.26, 5.28, 5.3 and 5.34 ppm (J_{ea} = 2 cps, J_{ee} = 2.5 cps). The assignments of the stereochemistry at positions 2 and 3 of the hydroxyl groups are once again supported by the observed coupling constants.

The diol 155 on treatment with acetone in presence of catalytic amount of p-toluene sulfonic acid gave an acetonide m.p. 199-200°, $(\alpha)_D$ + 97.73°.

Section E : Synthesis of Δ^{12}-oleanene 2β, 3α-diol

The sterically most unstable 2β, 3α-diol (axial-axial) was prepared by the known method described in the literature[1,2,3]. The method involved the oxidation of $\Delta^{2,12}$-olean diene 157 with performic acid and subsequent hydrolysis of the ester with alkali solution. By following the above procedure on 157 crystalline //



158 159

solid, m.p. 250-2° $(\alpha)_D$ + 120°, was obtained and has been assigned 2β, 3α-diol structure 158 by analogy with previous work in the literature[1,2,3,7]. IR spectra of the diol showed peaks at 3560, 2980, 1455, 1375, 1040, 1018 cm^{-1}. Acetylation of the diol with acetic anhydride and pyridine afforded the crystalline 2β, 3α-diacetate 159, m.p. 161-63°.

The acetonide derivative could not be prepared for want of material.

It may be pointed out that all the isomeric diols in the series furnished acetonide derivatives, which is in agreement with the observation of Tschesche et al.[7]

The melting points and rotations of the isomeric diols, their diacetates and their acetonide derivatives has been shown in the table I.

Table I

Δ^{12}-oleanene 2,3-diols

	Diol		Diacetate		Acetonide derivatives	
	m.p.	$(\alpha)_D$	m.p.	$(\alpha)_D$	m.p.	$(\alpha)_D$
2α, 3α	240-42°,	+101.88°	221-22°	+83.63°	180-82°,	+102.50°
2β, 3β	278-82°,	+71.28°	180-82°	+40.77°	199-201°,	+ 97.73°
2α, 3β	202-4°,	+60.00°	216-18°	+73.42°	173-4°	-
2β, 3α	250-52°,	+120°	161-63°	-	-	-