SUMMARY

The work embodied in the present thesis has been divided into Four Parts.

PART - I

PHOTOCHEMICAL SYNTHESIS OF THE NATURALLY OCCURRING TRITERPENE LACONTE, 3β-HYDROXY LUPAN-28, 13β-OLIDE AND CHIROPTICAL (CD) MEASUREMENT OF THIS AND RELATED LACTONES

CHAPTER - I

In this chapter a short review on the mechanism of intramolecular cyclization of alcohols by oxidation with Pb(IV) acetate or by hypohalite reaction, is described.

CHAPTER - II

This chapter gives a short review on the triterpene lactones of lupane series.

CHAPTER - III

In this chapter photochemical synthesis of the naturally occurring triterpene lactone, 3β-hydroxy lupan-28, 13β-olide, stereochemistry of isopropyl group at C-19 and the chiroptical measurements (CD) of this and related lactones are described.

Section A

This section deals with the photochemical synthesis of the naturally occurring triterpene lactone, 3β-hydroxy lupan-28, 13β-olide X.

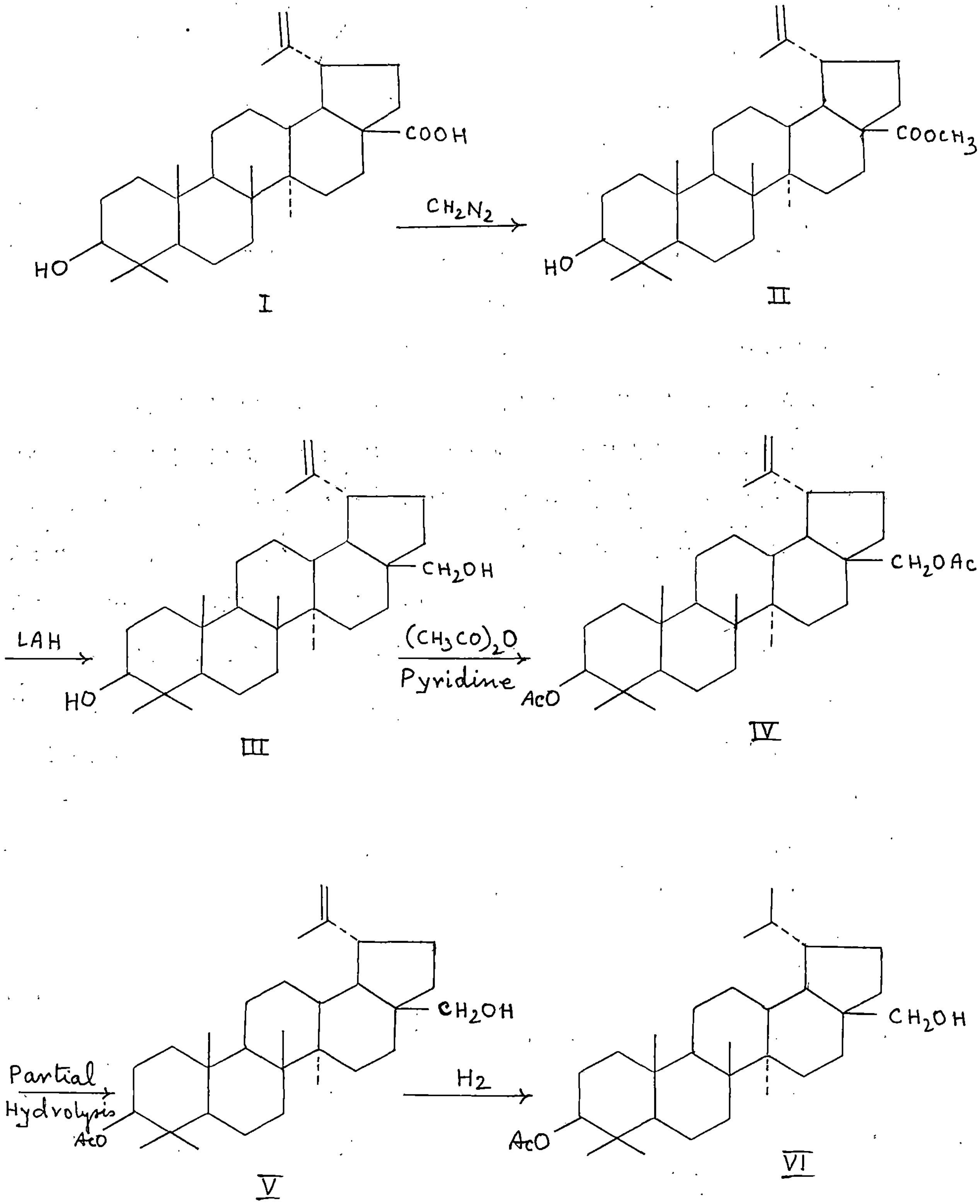
Methyl betulinate II, obtained by esterification of betulinic acid I, on $LiAlH_4$ reduction gave betulin III, $C_{30}H_{50}O_2$, m.p. 258-59°, $[\alpha]_D$ + 16°, which on acetylation with acetic anhydride-pyridine gave betulin diacetate IV, $C_{34}H_{54}O_4$, m.p. 223-24, $[\alpha]_D$ + 20°. This betulin diacetate IV on partial hydrolysis with 0.05 N KOH using 1.2 mole equivalent in methanolic solution afforded 3β acetoxy betulin V which on catalytic hydrogenation with Pd - charcoal in ethyl acetate gave the key intermediate, 3β-acetoxy dihydrobetulin VI, m.p. 256-8°, $[\alpha]_D$ - 4.2°, ν_{max} 3420 (OH), 1740 and 1260 (OAc) cm^{-1}, PMR : δ 0.73-1.12 (7 saturated CH_3), 2.03 (3H, s, OAc), 3.36 + 3.72 (2H, d, $-C\underline{H}_2OH$) and 4.58 (1H, m, $\underline{H}$-C-OAc).

This key intermediate VI was irradiated for 3 hours with 250W tungsten lamp separately under three different reaction conditions: (1) lead tetraacetate alone in cyclohexane, (2) lead tetraacetate + $CaCO_3$ + I_2 in cyclohexane and (3) mercuric oxide + I_2 in carbon tetrachloride.

In cases 1 and 2, same type of distribution of products VII and VIII was observed while in case of 3 only ether VIII was obtained. The less polar product VII eluted in petroleum ether : benzene (4:1) analysed for $C_{31}H_{50}O_2$ (M^+ 454), m.p. 158-64°, $[\alpha]_D$ + 21.4°; ν_{max} 1720, 1245 (acetate), 900 and 860 (olefin) cm^{-1}; PMR : δ .75-1.00, 2.05 (3H, s, acetate), 4.5 (1H, m, $\underline{H}$-C-OAc) and 5.14 (1H, m, vinylic proton). Its GLC behaviour and spectral characteristics indicated it to be a mixture of unsaturated hydrocarbons resulting from the oxidative removal of $-CH_2OH$ from C-17.

The more polar material VIII eluted by petroleum ether : benzene (3:2) was analysed for $C_{32}H_{52}O_3$ (M^+ 484) m.p. 192-4°, $[\alpha]_D$ + 17°; ν_{max} 1040 (ether), 1745, 1255 (acetate); PMR : δ .76-1.00 (7 saturated CH_3), 2.05 (3H, S, -OAc), 3.44 and 3.60 (2H, $-\overset{|}{\underset{|}{C}}-C-CH_2-$, J_{gem} = 8.1 Hz), 4.5 (1H, m, $H-\overset{|}{\underset{|}{C}}-OAc$). This ether VIII on chromic acid oxidation in acetic acid afforded tertiary γ-lactone IX, $C_{32}H_{50}O_4$ (M^+ 498), m.p. 315°, $[\alpha]_D$ + 86°; ν_{max} 1762 (γ-lactone), 1720, 1240 (acetate) cm^{-1}; PMR : δ .76-1.00 (7 saturated CH_3), 1.98 (3H, S, $-OCOCH_3$) and 4.42 (1H, m, $H-\overset{|}{\underset{|}{C}}-OAc$) which on hydrolysis gave the hydroxy lactone X, m.p. 321°, $[\alpha]_D$ + 60°. X did not show peak around δ 4 but showed a peak at δ 80.9 ($-\overset{|}{\underset{|}{C}}-O-$, a singlet, carbon atom of tertiary lactone termination) in ^{1}H NMR and ^{13}C NMR respectively - an observation which firmly established tertiary lactone structure in X. X on Jones oxidation afforded the keto lactone XI. The physical constants and spectroscopic properties of the hydroxy lactone X and the corresponding acetoxy lactone IX and keto lactone XI are very similar to those of the naturally occurring 3β-hydroxy lupan 28, 13β-olide, m.p. 325°, $[\alpha]_D$ + 63.4° and its acetoxy m.p. 319-320° and keto derivatives m.p. 328-330°, $[\alpha]_D$ + 70° obtained from Dillania Indica by Banerjee et al (Phytochemistry, 14, 1447, 1975). The reaction sequence has been illustrated as follows:

(IV)


COOH
HO
I
CH2N2
COOCH3
HO
II
LAH
CH2OH
HO
III
(CH3CO)2O
Pyridine
CH2OAc
AcO
IV
Partial
Hydrolysis
CH2OH
AcO
V
H2
CH2OH
AcO
VI

(V)

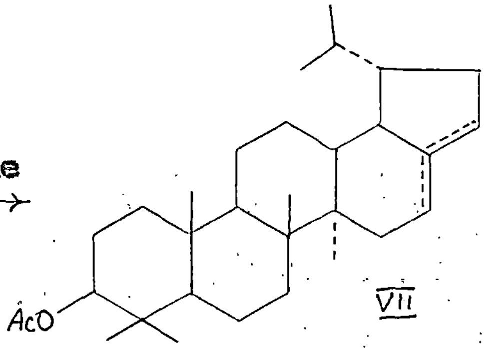
VI $\xrightarrow{\text{Pb(OAc)}_4 \text{ in cyclohexane}}$

or $Pb(OAc)_4$

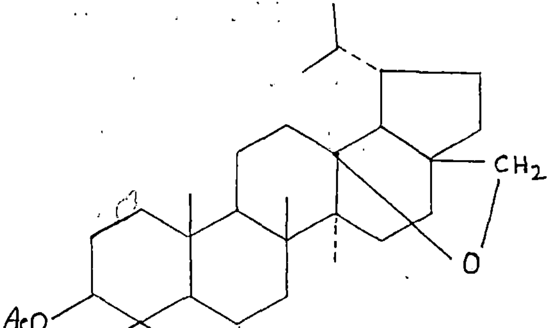
+ $CaCO_3$

+ I_2

in cyclohexane


VII

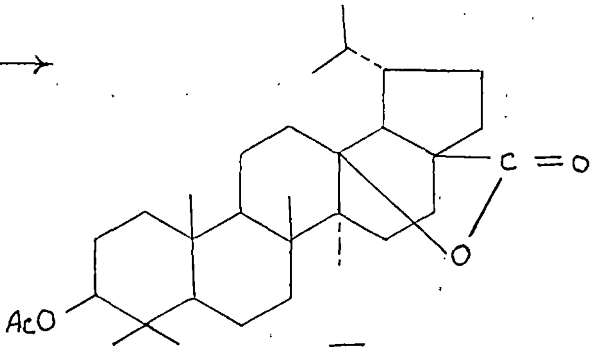
+



VIII

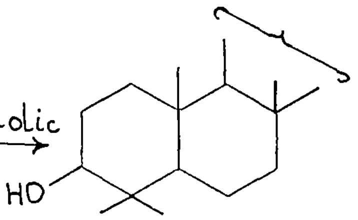
VI $\xrightarrow[\text{in Carbon tetrachloride}]{HgO + I_2}$ VIII

VIII $\xrightarrow[\text{acetic acid}]{CrO_3 \text{ in}}$

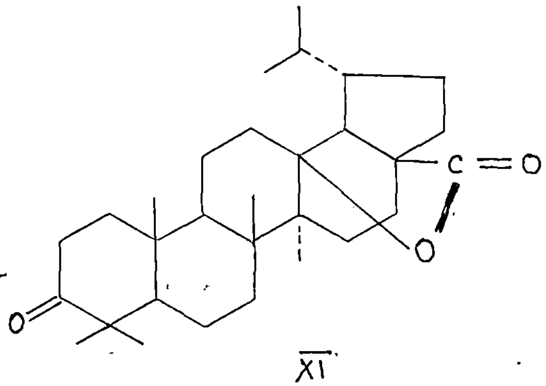


IX

IX $\xrightarrow[\text{KOH}]{\text{Methanolic}}$


X

$\xrightarrow[\text{Oxidation}]{\text{Jones}}$



XI

Section B

This section deals with the stereochemistry of the isopropyl group at C-19. Since in no step of the sequence α-orientation of the C-19 isopropenyl group (isopropyl in dihydro derivative) of betulinic acid I was affected, this synthesis proved unequivocally the α-stereochemistry of isopropyl substituent at C-19 in X, i.e in the naturally occurring 3β- hydroxy Lupan 28, 13β - olide.

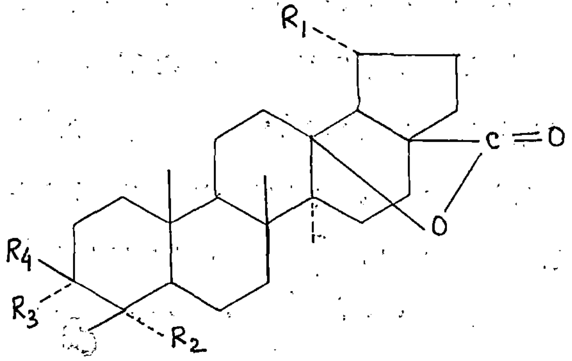
Section C

This section deals with the chiroptical measurement (CD) of the lactone X and related lactones.

Very recently from our laboratory the synthesis of (G. Dutta and S.N.Bose, Tetrahedron Letters, 29, 5807, 1988) the authentic C-28, 19β-lactone XII and C_{28}, 13β -lactone XIII and measurements of their CD spectra have been reported.

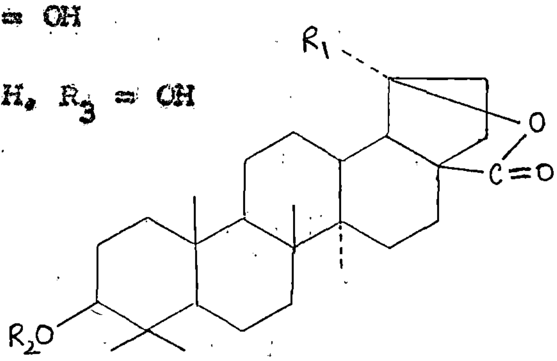
Both the synthetic lactone XII and the lactone XIV obtained by Hg(II) acetate oxidation [Baddeley et al, Tetrahedron, 25, 1643 (1969), Adhikary et al, J. Chem. Soc. (C), 1030 (1970), Vystrcil and Blecha, Coll. Czech. Chem. Commun., 35, 3309 (1970)] exhibited negative CD with maxima at 216 nm ($\Delta\epsilon = -3.6$) and at 217 nm ($\Delta\epsilon = -6.05$) respectively. On the other hand, the synthetic lactone XIII and the lactone X obtained photochemically both showed positive CD having maxima at 219 nm ($\Delta\epsilon = 3.19$) and at 220 nm ($\Delta\epsilon = 1.04$) respectively. CD spectrum ($\Delta\epsilon = 2.32$ at 217 nm) of another naturally occurring lupane triterpene, epicaltholide XV having C-28, 13β-lactone [Bhandari and Rastogi, Phytochemistry, <u>23</u>, 1699 (1984) _7 was also recorded by us. Thus CD data provided convincing physical evidence in support of C-28, 13β -lactone structure for X and XV.

/This part of the work has been published by us : Organic photochemistry, Part II. Photochemical Synthesis of the Naturally Occurring Triterpene Lactone, 3β -hydroxy lupan-28, 13β -olide, S.K.Nag and S.N. Bose, Tetrahedron Letters, <u>30</u>, 2855 (1989). A photo copy of the reprint has been attached at the end of the thesis_7.



XIII $R_1 = R_3 = H, R_2 = CH_3, R_4 = OH$

XV R_1 = isopropyl, $R_2 = R_4 = H, R_3 = OH$



XII $R_1 = R_2 = H$

XIV R_1 = isopropyl, R_2 = Ac

<u>CHAPTER - IV</u>

Experimental portion has been described in this chapter.

PART - II

LEAD (IV) ACETATE OXIDATION OF TRITERPENOID 3-KETOHYDRAZONES

CHAPTER - I

This chapter gives a short review on the lead (IV) acetate oxidation of steroid and triterpenoid keto hydrazones.

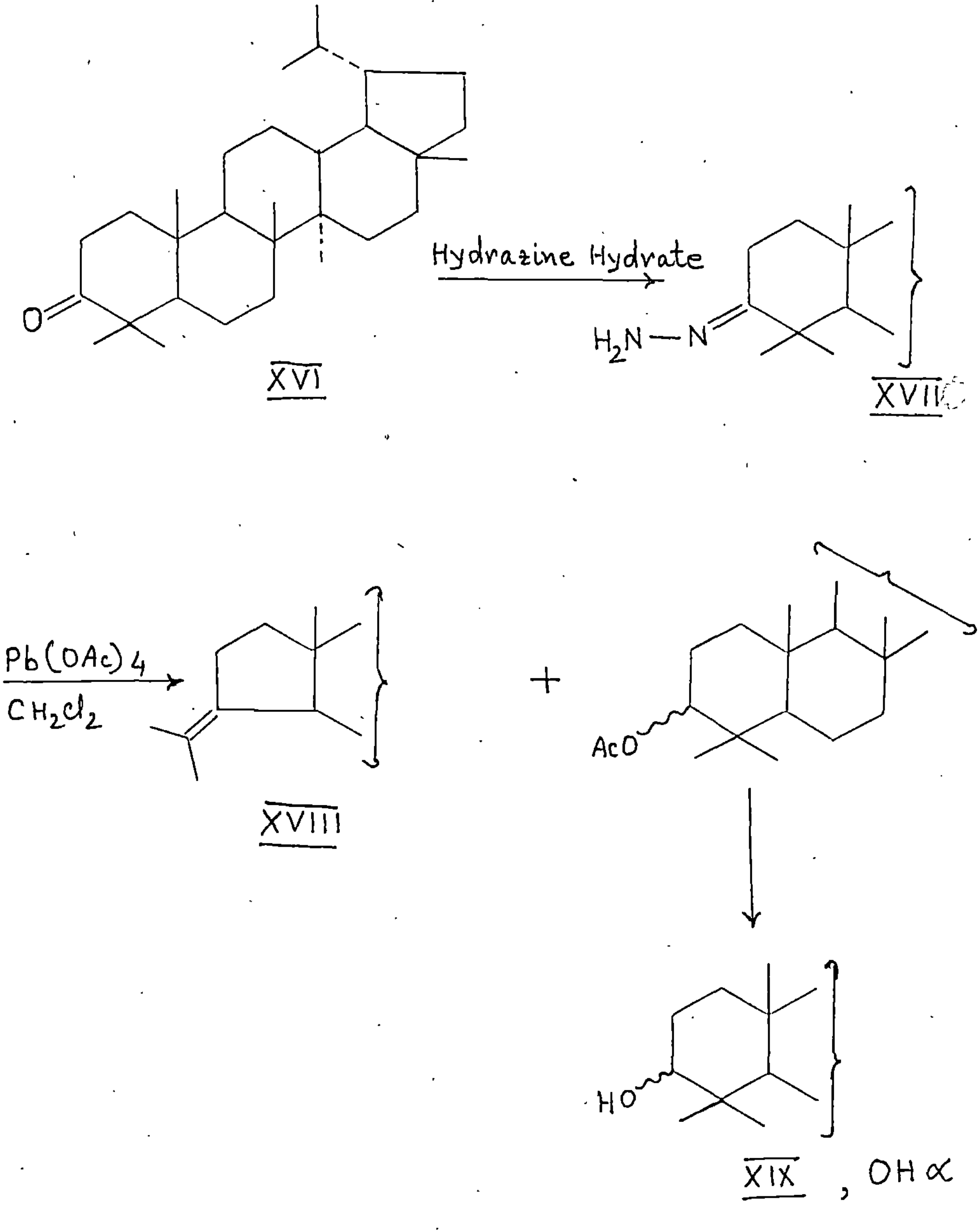
CHAPTER - II

This chapter describes lead (IV) acetate oxidation of triterpenoid 3-ketohydrazones.

Section A

This section deals with lead (IV) acetate oxidation of lupanone hydrazone, a triterpene bearing 4, 4-dimethyl 3 keto moiety.

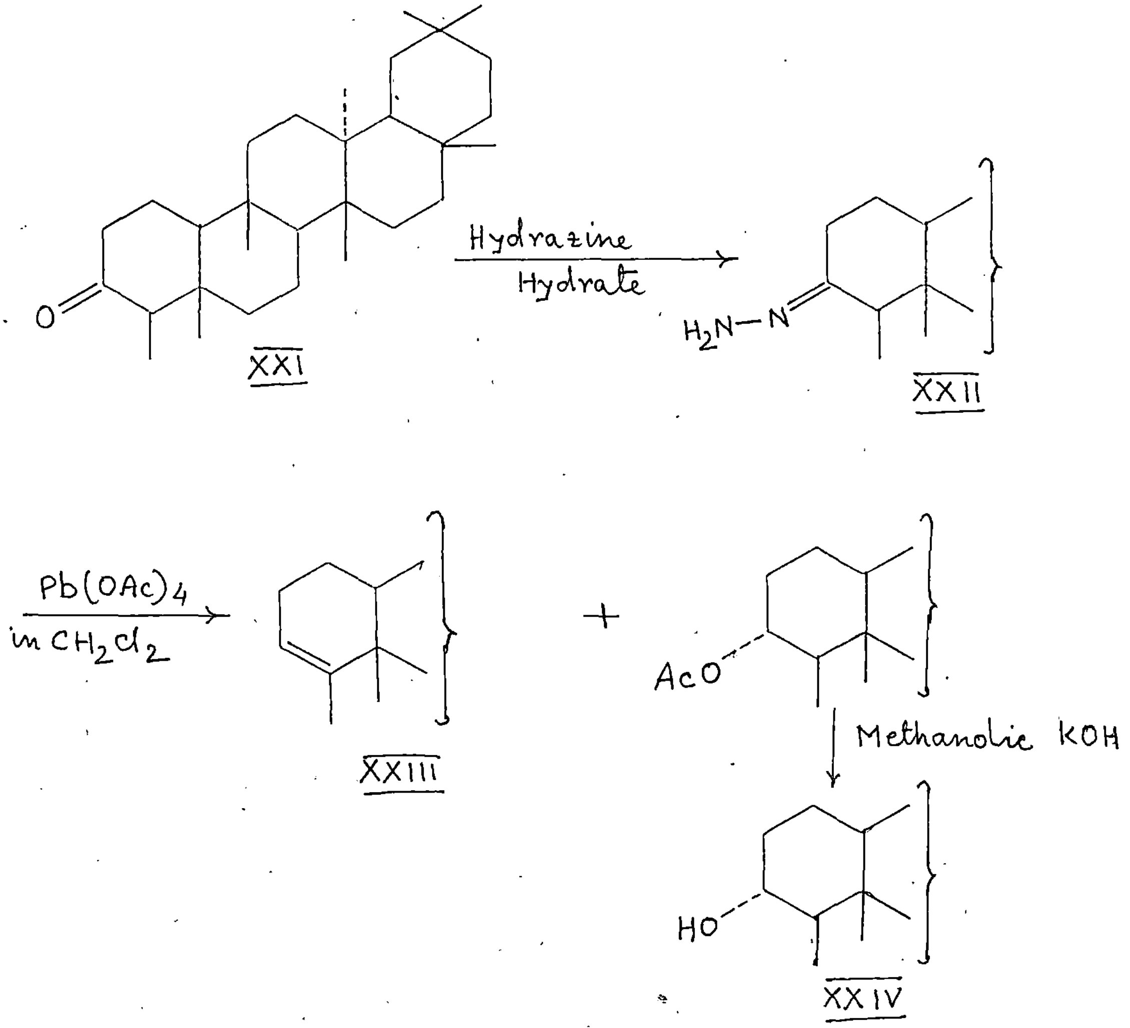
Lupanone XVI, m.p. 208°, $[\alpha]_D$ + 15° on treatment with hydrazine hydrate in anhydrous diethylene glycol afforded lupanone hydrazone XVII. The compound XVII was subjected to lead (IV) acetate oxidation in dichloromethane solvent according to the procedure of Barton et al (D.H.R. Barton, J.F. McGhie and P.L. Batten, J. Chem. Soc. (C), 1033, 1970). For efficient and smooth separation the reaction mixture was saponified with 5% methanolic KOH for 2 hours. On chromatography the saponified material furnished olefin 3-Isopropylidene-A-nor-lupane XVIII, Lupan-3α-ol XIX and lupan-3β-ol XX. The olefin XVIII showed m.p. 198, $[\alpha]_D$ - 19.7°, $C_{30}H_{50}$ (M^+ 410); PMR : δ .71-1.17 (6 saturated CH_3), ~~2.05~~ 1'73 (3H, S) and ~~2.15~~ 1'65 (3H, S) (isopropylidene methyls). It developed yellow colouration with TNM. This olefin XVIII was not identical with lup-2-ene obtained by $POCl_3$ reaction of lupanol but identical with PCl_5 reaction product of lupanol. The reaction path $\overset{i}{\text{w\cancel{a}s}}$ shown below:



Section B

This section deals with lead (IV) acetate oxidation of Friedelin hydrazone, a triterpene bearing 4-methyl 3-keto moiety.

Friedelin XXI on treatment with hydrazine hydrate in anhydrous diethylene glycol afforded friedelin hydrazone XXII which on lead tetraacetate oxidation according to the procedure of Barton et al same as described in section A followed by saponification and chromatography afforded the olefin, Δ^3 ~~friedelin~~ friedelene XXIII and the alcohol friedelan-3α-ol XXIV. The olefin XXIII was found to be identical with the product obtained by $POCl_3$ dehydration of friedelan-3β-ol. The products were characterised by spectral data and comparison with authentic samples. The reaction sequence is described below:



Section C

In this section the effect of substituents in ring A of the triterpenes and also steroid as regards products distribution has been discussed.

Section D

In this section evidence for the reactive intermediate involved in the olefin formation has been presented. Based on mercury (II) oxide oxidation of hydrazones and Bamford-Stevens reaction of the corresponding tosylhydrazones carbocation has been postulated as the precursor of the olefin formation [This part of our work has been accepted for publication : Lead (IV) Acetate Oxidation of Triterpenoid 3-ketohydrazones, S.K. Nag and S.N. Bose, Indian J. Chem., 29B, 000, 1990].

A photo copy of the galley proof of the accepted paper has been attached at the end of the thesis.

CHAPTER - III

Experimental portion has been described in this chapter.

PART - III

PARTIAL SYNTHESIS OF METHYL 2α, 3α-DIHYDROXY LUPAN-28-OATE FROM BETULINIC ACID

CHAPTER - I

This chapter gives a short review on the triterpenoid 2,3-dihydroxy 28-carboxylic acids.

CHAPTER - II

This chapter deals with the partial synthesis of methyl 2α, 3α-dihydroxy lupan-28-oate from betulinic acid, the dihydro methyl ester derivative of the naturally occurring 2α, 3α-dihydroxy lup 28(29)en-28-oic acid XXV [Phytochemistry, 24, 1337 (1985)].

Section A

This section describes the aims and objective of the present work.

Section B

This section describes the partial synthesis of methyl 2α, 3α-dihydroxy lupan-28-oate from betulinic acid.

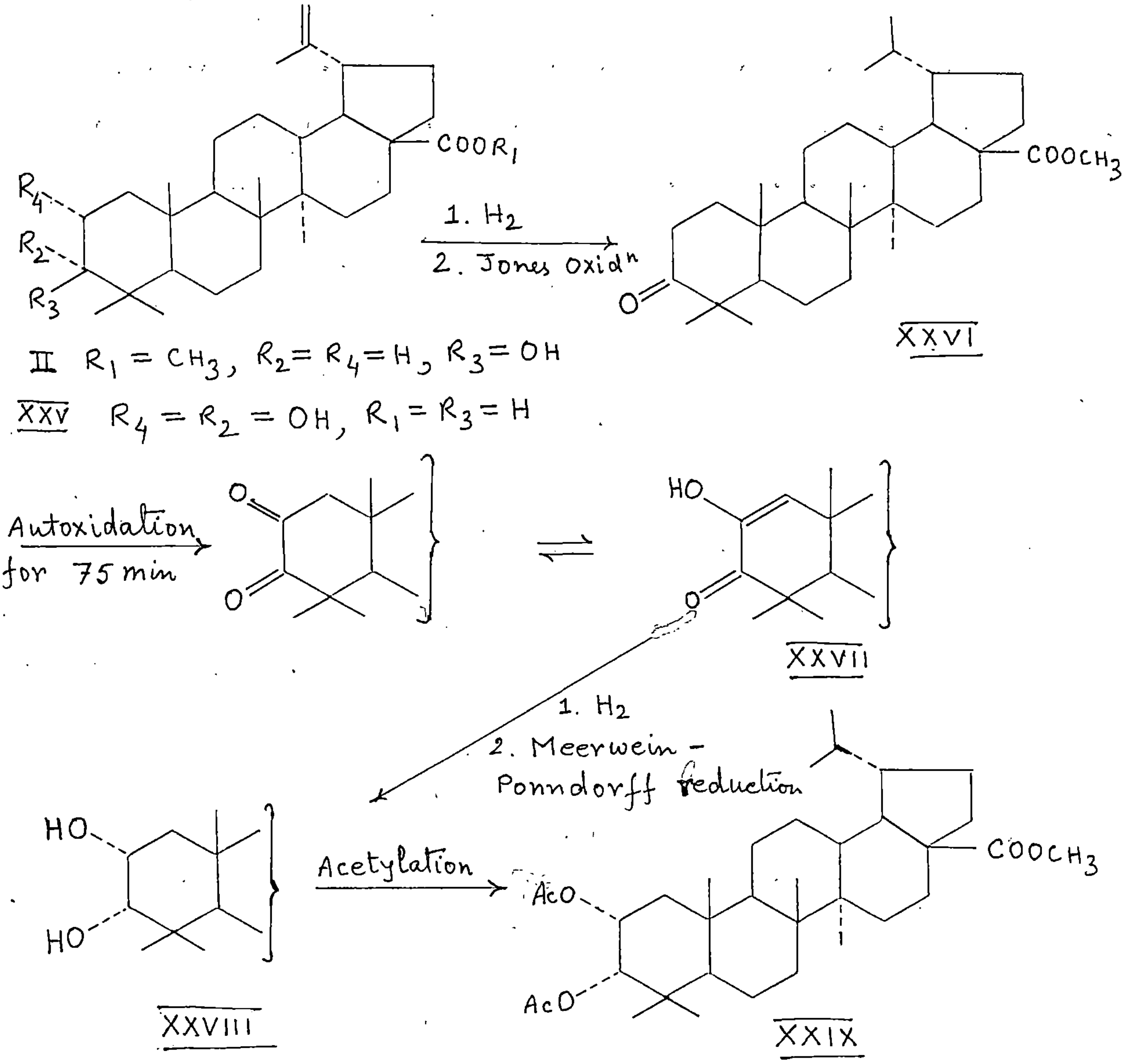
Methyl dihydrobetulonate XXVI which was obtained by hydrogenation followed by Jones oxidation of the methyl betulinate II, on autoxidation for 75 min gave the diosphenol XXVII, m.p. 131-33°, $[\alpha]_D$ - 1.96°, λ_{max} 270 mμ (ϵ, 7932) in methanol, λ_{max} 310 mμ in KOH containing methanol.

Hydrogenation of diosphenol ~~XXIV~~ XXVII followed by Meerwein-Ponndorff reduction furnished a crystalline solid diol XXVIII, $C_{31}H_{52}O_4$, m.p. 215°, ν_{max} 3420 (OH), 1730 ($-COOCH_3$) cm^{-1}; PMR : δ .69-1.01 (7 saturated CH_3), 3.39 (1H, d, J = 3Hz, $\underline{H}-C_3-OH$), 3.95 (1H, ddd, J = 12, 4, 3 Hz) and 3.66 (3H, s, $-COOCH_3$). Acetylation with acetic anhydride-pyridine afforded the diacetate XXIX, $C_{35}H_{56}O_6$ (M^+ 572), m.p. 198-200°; ν_{max} 1740, 1260 (acetate)cm^{-1};

^1H NMR : δ 0.78–0.91 (7 saturated CH_3), 1.89 and 2.04 (3H, s, $-OCOCH_3$), 4.94 (1H, d, J = 3 Hz, $H-C_3-OAc$), 5.19 (1H, ddd, J = 11, 4, 3 Hz, $H-C_2-OAc$), 3.58 (3H, s, $-COOCH_3$).

^1H NMR observations of the diol ~~XXV~~ XXVIII and its acetate ~~XXVI~~ XXIX are quite in accord with their 2α, 3α-stereochemical assignments reported very recently [Phytochemistry 28, 1703 (1989)] for triterpenes 2, 3 diols.

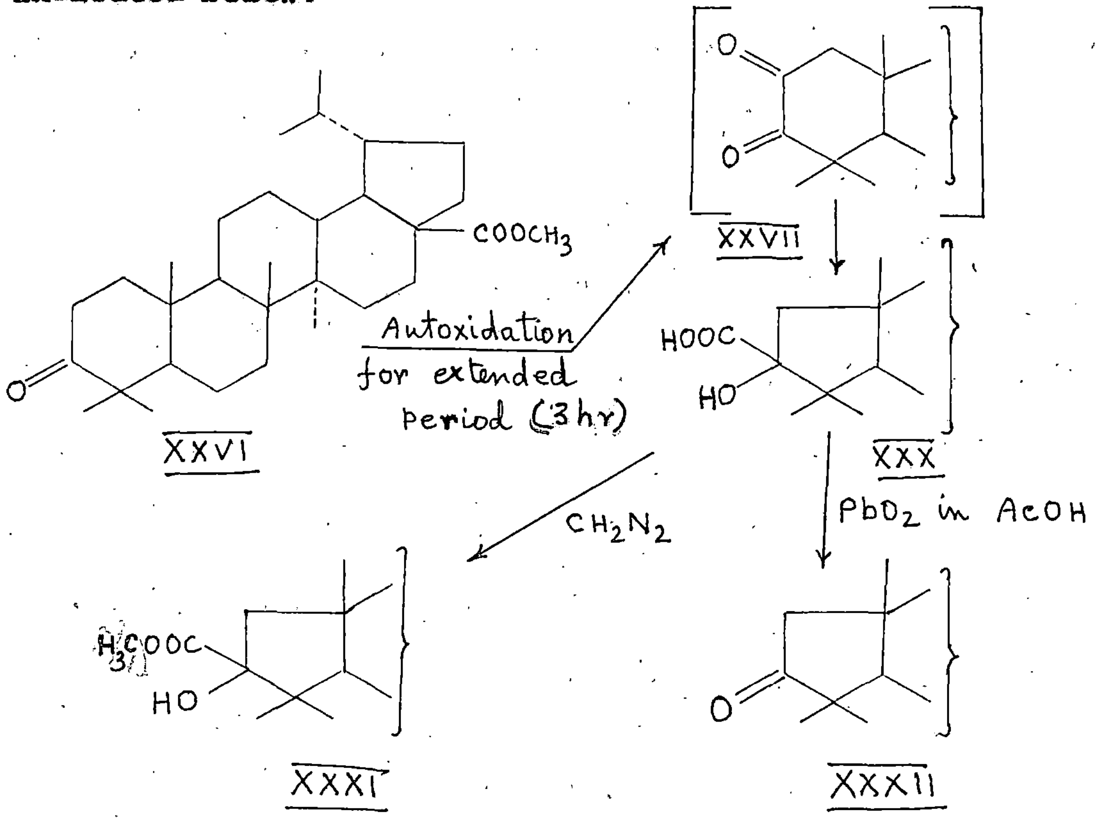
The reaction sequence is illustrated below:



Section C

This section describes an interesting one-step combined autoxidation and benzilic acid rearrangement of methyl dihydrobetulonate XXVI when autoxidation has been carried out for an extended period.

The rearrangement gave a product XXX, m.p. 255-56°; ν_{max} 3440, 3340, 1720 cm^{-1} which has been assigned α-hydroxy carboxylic acid structure XXX. The compound XXX on esterification gave the product XXXI which has been characterised as α-hydroxy ester. The compound XXX on treatment with PbO_2 in acetic acid gave the product XXXII, m.p. 179-80°, $[\alpha]_D$ 75.4°; ν_{max} 1735 cm^{-1} (unresolved band for cyclopentanone and ester) having identical m.p., rotation and IR spectra as those reported in the literature for methyl decarboxydehydrodihydroceanothate (P. de Mayo and A.N. Starratt, Can. J. Chem., 40, 788, 1962). The reaction path is indicated below:



CHAPTER - III

Experimental portion has been described in this chapter.

PART - IV

REINVESTIGATION ON THE BENZENE EXTRACT OF THE BARK OF BISCHOFIA JAVANICA (EUPHORBIACEAE)

CHAPTER - I

In this chapter morphological feature of the plants of Euphorbiaceae family, Bischofia species and Bischofia javanica blume is described.

CHAPTER - II

In this chapter isolation of betulinic acid as acidic constituent and epi-friedelanol acetate, friedelin, β-sitosterol, friedelanol and an unsaturated pentacyclic nor triterpene dihydroxy ketone as neutral constituents from benzene extract of the bark of Bischofia javanica blume is described.

Section A

This section deals with the extraction of the bark of *Bischofia javanica*.

Section B

This section deals with the chromatography of the neutral part of the benzene extract of *Bischofia javanica*.

Sections C, D, E and F deal with the isolation and characterization of epi-friedelanol acetate, friedelin, β-sitosterol and friedelan-3α-ol respectively.

Section G

This section deals with the isolation of an unsaturated pentacyclic nor triterpene dihydroxy ketone.

The compound m.p. 295°, analysed for $C_{29}H_{46}O_3$ (M^+ 442 m/z), ν_{max} 3500 (OH), 1720 (CO) cm^{-1}. This on acetylation furnished a diacetate m.p. 228°, $C_{33}H_{50}O_5$(M^+ 526 m/z), ν_{max} 1740 (composite of acetate and ketone), 1250 (acetate) cm^{-1}. ^{1}H NMR analysis of the diacetate showed seven saturated methyl groups and suggested one primary and one secondary acetoxy group in the molecule. It gave positive triterpene and unsaturation tests. ^{13}C NMR of the diacetate confirmed the presence of an olefinic double bond, besides showing the presence of one keto carbonyl, one- CH_2OAc, one-CHOAc groups and 26 Sp^3 hybridized carbon atoms. Observations so far made suggested the compound to be an unsaturated pentacyclic nor triterpene keto diol.

Further work for the complete characterization of the compound is in progress.

Section H

This section deals with the isolation and identification of betulinic acid from acid part of the extraction of *Bischofia javanica*.

CHAPTER - III

Experimental portion has been described in this chapter.