

# S U M M A R Y

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

## PART-I

REINVESTIGATION ON THE FERN OLEANDRA NERIFOLIA CAV. HOOK:  
ISOLATION AND STRUCTURE ELUCIDATION OF A NEW TRITERPENE,  
29-ETHOXYHOPANE.

### Chapter-I:

In this chapter the morphological features of the fern Oleandra nerifolia Cav. Hook is described.

### Chapter-II:

#### Section A:

This section gives a short review on the chemical constituents of ferns of Oleandraceae family.

#### Section B:

This section gives a short review on the structure of dryocrassol isolated from the Aspidiaceous fern.

### Chapter-III:

This chapter deals with the present investigations on the neutral part of the benzene extract of the fern Oleandra nerifolia

(ii)

and the isolation of a new triterpene, 29-ethoxyhopane along with fillicene, nerifoliol and  $\beta$ -sitosterol.

#### Chapter-IV:

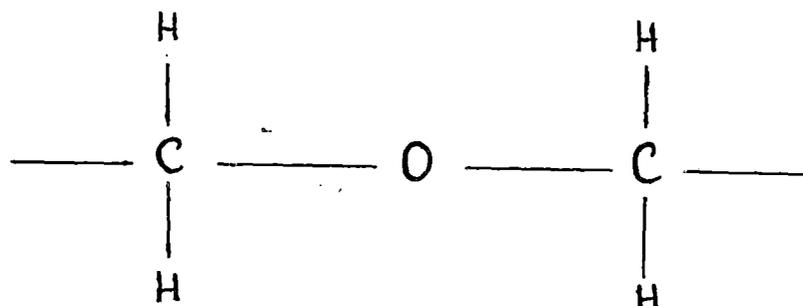
In this chapter the structure elucidation of the new triterpene, 29-ethoxyhopane, isolated from the neutral part of the benzene extract of the fern Oleandra nerifolia is described in detail.

#### Section A:

This section deals with the establishment of the structure of the new triterpene.

The new triterpene, 29-ethoxyhopane,  $C_{32}H_{56}O$ , m.p. 179-80°,  $(\alpha)_D^{20}$  27.16° gave positive Libbermann-Burchard test but did not give any colour with tetra-nitromethane indicating thereby that it was a saturated triterpene. The IR spectrum of the new triterpene  $C_{32}H_{56}O$ , showed bands at 1105  $cm^{-1}$  indicating that the oxygen function was probably present as an ether linkage. The NMR spectrum showed signals between  $\delta$  0.7 to 0.95 (seven methyl groups) and a broad multiplet in the region  $\delta$  2.8 to 3.6 (four protons). The NMR band in the region  $\delta$  2.8 to 3.6 indicated the presence of an ether linkage. The new triterpene, thus, contains an ether linkage and the grouping like (I)

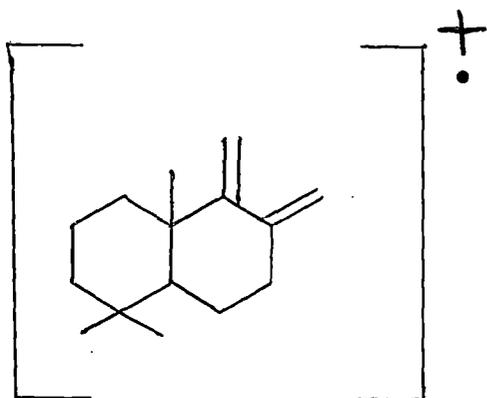
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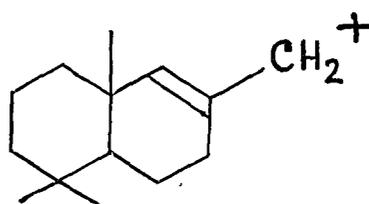
(I)

From an analysis of the molecular formula, the new triterpene was shown to be pentacyclic in nature.

The mass spectrum of the triterpene showed peaks at  $m/e$  456 ( $M^+$ ), 441 ( $M^+ - CH_3$ ), 411 ( $M^+ - OCH_2CH_3$ ), 396 ( $M^+ - CH_3 - OCH_2CH_3$ ), 369 ( $M^+ - CH(CH_3)CH_2OC_2H_5$ ), 235, 204, 191, 175 and 147. The peaks at  $m/e$  235, 204 and 191 were characteristic of hopane or lupane type triterpene. The peaks at  $m/e$  204 and 191 were explained as arising due to the formation of species (II) and (III) respectively.



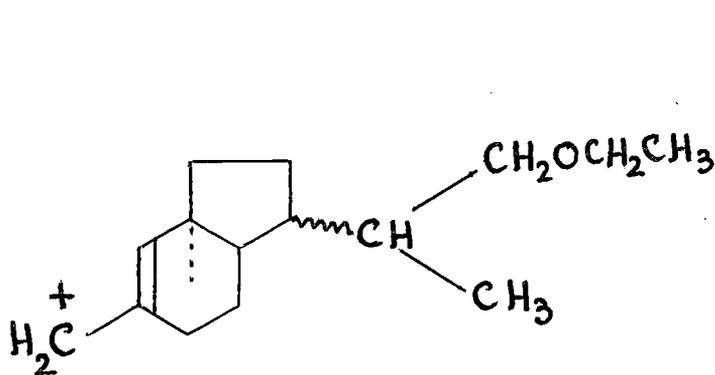
(II)



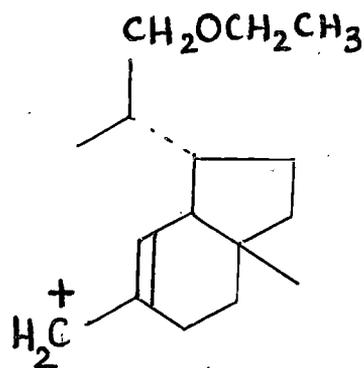
(III)

(iv)

The peak at  $m/e$  235 was explained as arising due to the species (IV) or (V) depending on whether a hopane or lupane type of nucleus was present.



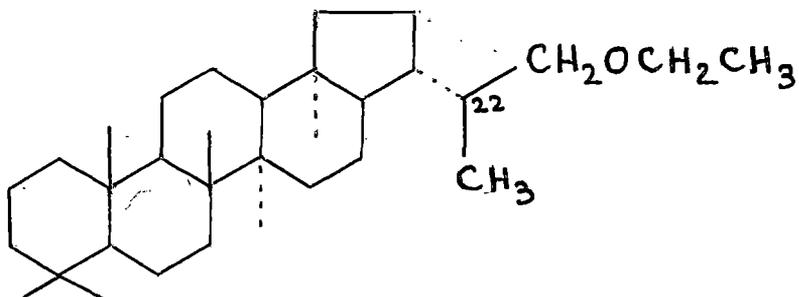
(IV)



(V)

Further loss of  $(CH_3 + OCH_2CH_3)$  and  $(CH \begin{matrix} \swarrow CH_2OCH_2CH_3 \\ \searrow CH_3 \end{matrix} + H)$  units from (IV) or (V) gave peaks at  $m/e$  175 and 147, respectively. Thus the mass spectra gave a detailed insight into the structure of the new triterpene. However, it did not prove whether a hopane, lupane, or isohopane type of nucleus was present in the triterpene. Since the new triterpene was found to occur with nerifoliol, containing a hopane type of nucleus, it appeared reasonable from biogenetic considerations that the same hopane type of nucleus was involved in the formation of the new triterpene in the fern. On the basis of these considerations, structure (VI) was proposed for the new triterpene.

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(VI)

A detailed study of the NMR spectra (80 MHz) of the triterpene confirmed the presence of the grouping (VII) in the triterpene.



VII

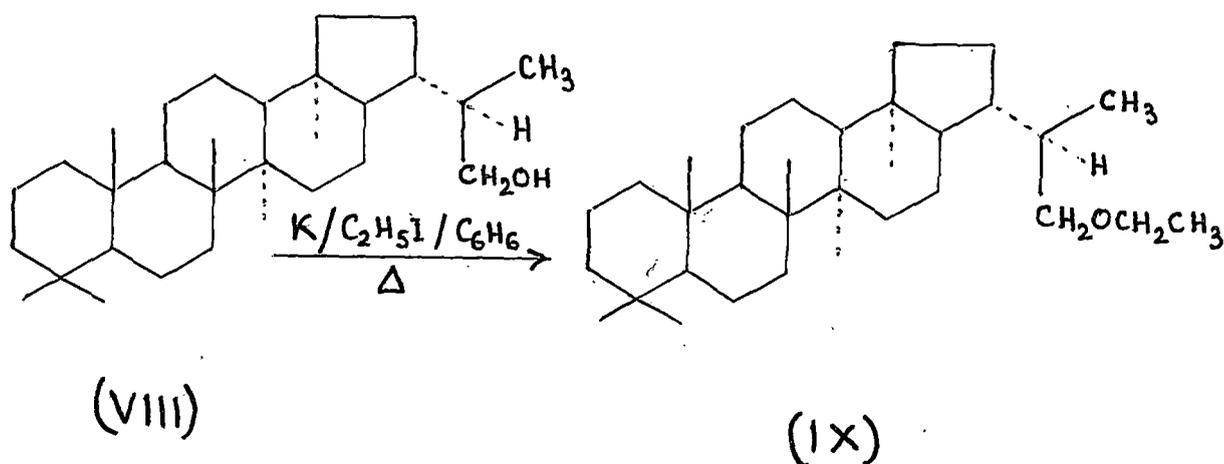
### Section B:

This section deals with the confirmation of the proposed structure (VI) of the triterpene by chemical evidences and settlement of the stereochemistry at C-22 and the complete stereo-structure of the triterpene. The chemical correlation studies described in this section were of two kinds (I) Partial

(vi)

synthesis of the new triterpene from a known triterpene, and  
(II) Conversion of the new triterpene into a known triterpene.

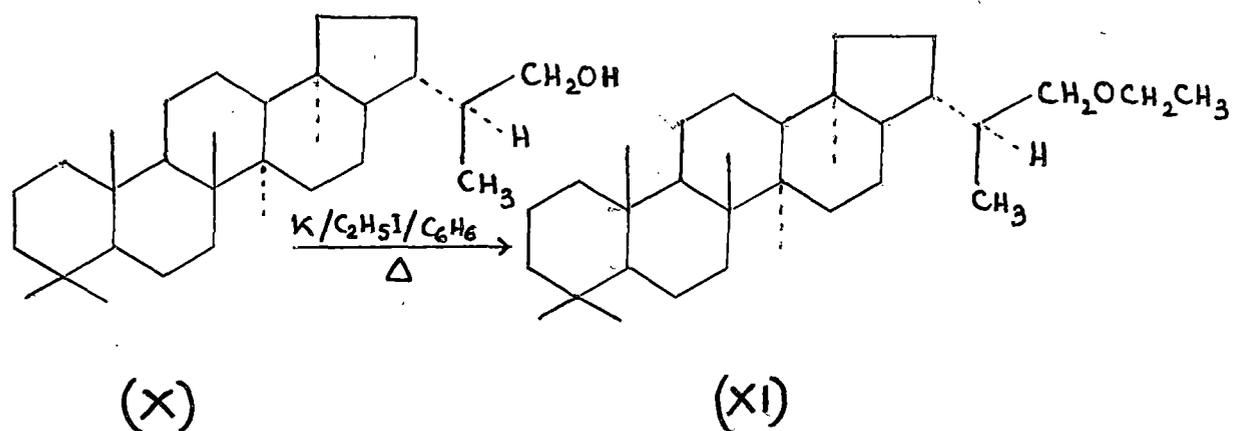
Nerifoliol (hopan-29-ol), (VIII) was converted into its ethyl ether (IX) by refluxing with potassium metal and ethyl iodide in benzene.



The reaction product was found to be identical in all respects with the new triterpene isolated from Oleandra nerifolia.

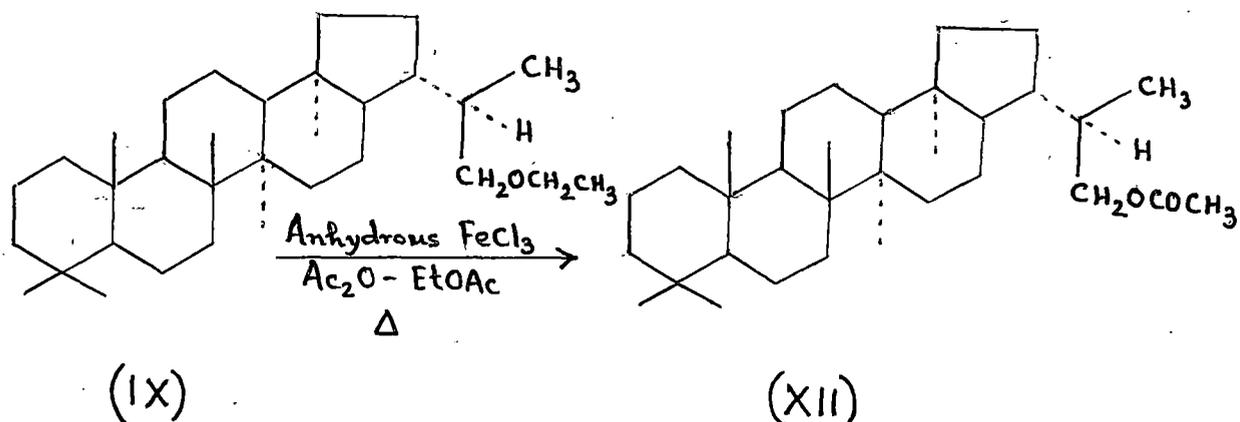
In this connection it may be mentioned that dryocrassol (hopan-30-ol), (X) was also converted into its ethyl ether (XI) by the same procedure.

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The reaction product, however, was found to be distinctly different from the new triterpene isolated from Oleandra nerifolia.

The new triterpene was also converted into nerifoliol acetate (XII) by ~~oxidation~~<sup>reaction</sup> with anhydrous ferric chloride in acetic anhydride-ethyl acetate mixture.



(viii)

The above observation confirmed the proposed structure (VI) for the new triterpene. Furthermore, nerifoliol possessed the 22-R configuration. It was, therefore, evident that the new triterpene did also possess the 22-R configuration. Thus the new triterpene was shown to be 29-ethoxyhopane (IX).

#### Chapter-V:

Experimental portion has been described in this chapter.

### PART-II

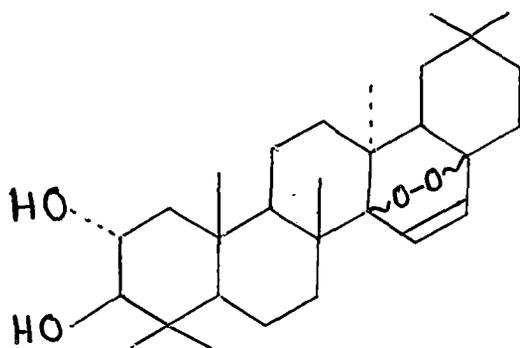
#### PARTIAL SYNTHESIS OF 2 $\alpha$ , 3 $\beta$ -DIACETOXY-28-NOR OLEANA-12, 17-DIENE: CONFIRMATION OF THE STRUCTURE OF BACCATIN:

#### Chapter-I:

This chapter gives a short review on the structure elucidation of baccatin.

The benzene extract of the bark of Sapium baccatum Roxb. afforded the new nor-triterpene baccatin, along with taraxerone, taraxerol, 1-hexacosanol,  $\beta$ -sitosterol, 3, 3'-di-O-methyl ellagic acid and 3-acetoxy aleuritolic acid. From the physical and chemical data of baccatin and its various degradation products, the structure (XIII) was proposed for baccatin.

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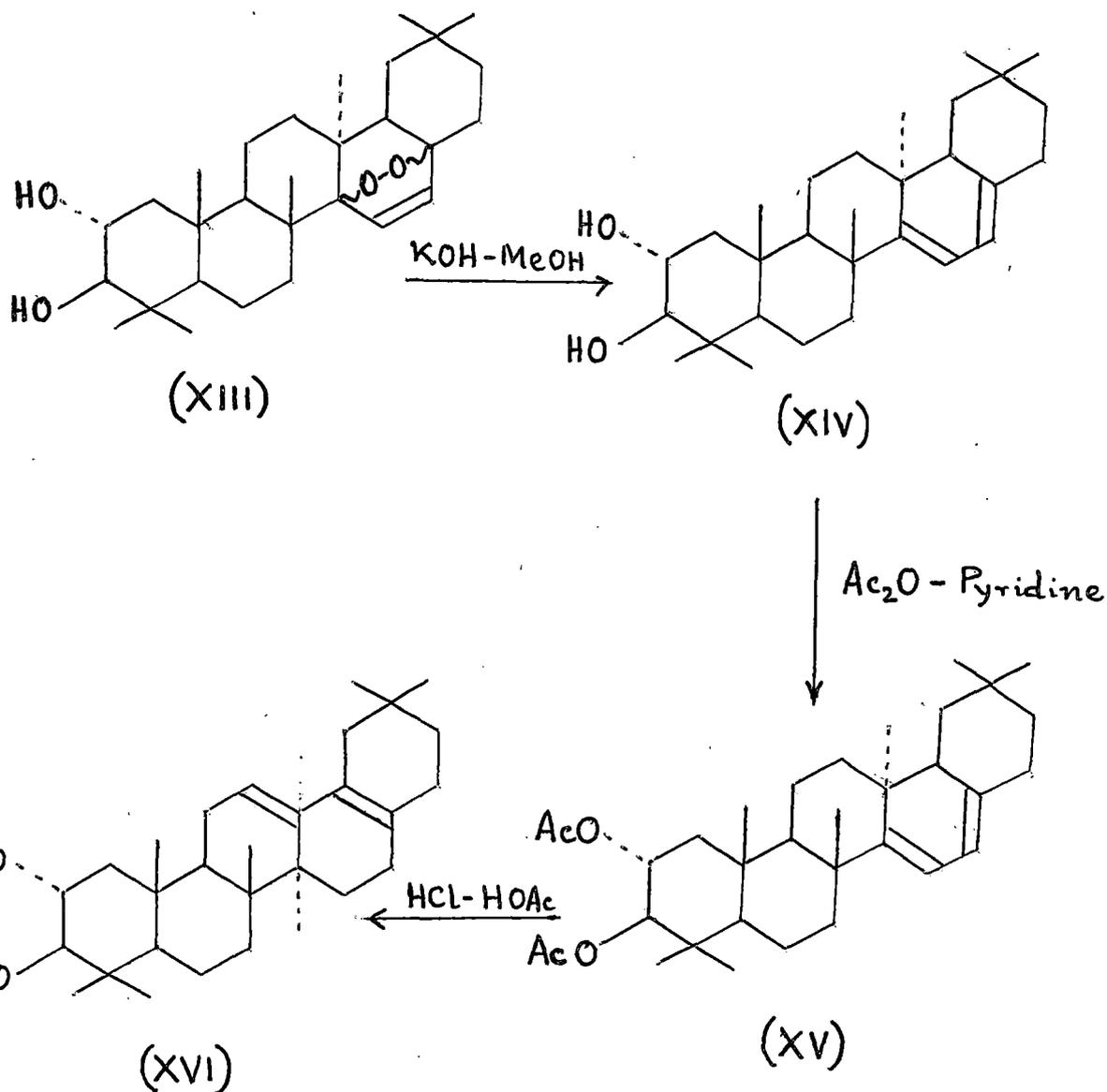


(XIII)

The presence of a taraxerene nucleus in baccatin was suggested mainly from biogenetic considerations; because of its occurrence with other triterpenes containing taraxerene nucleus.

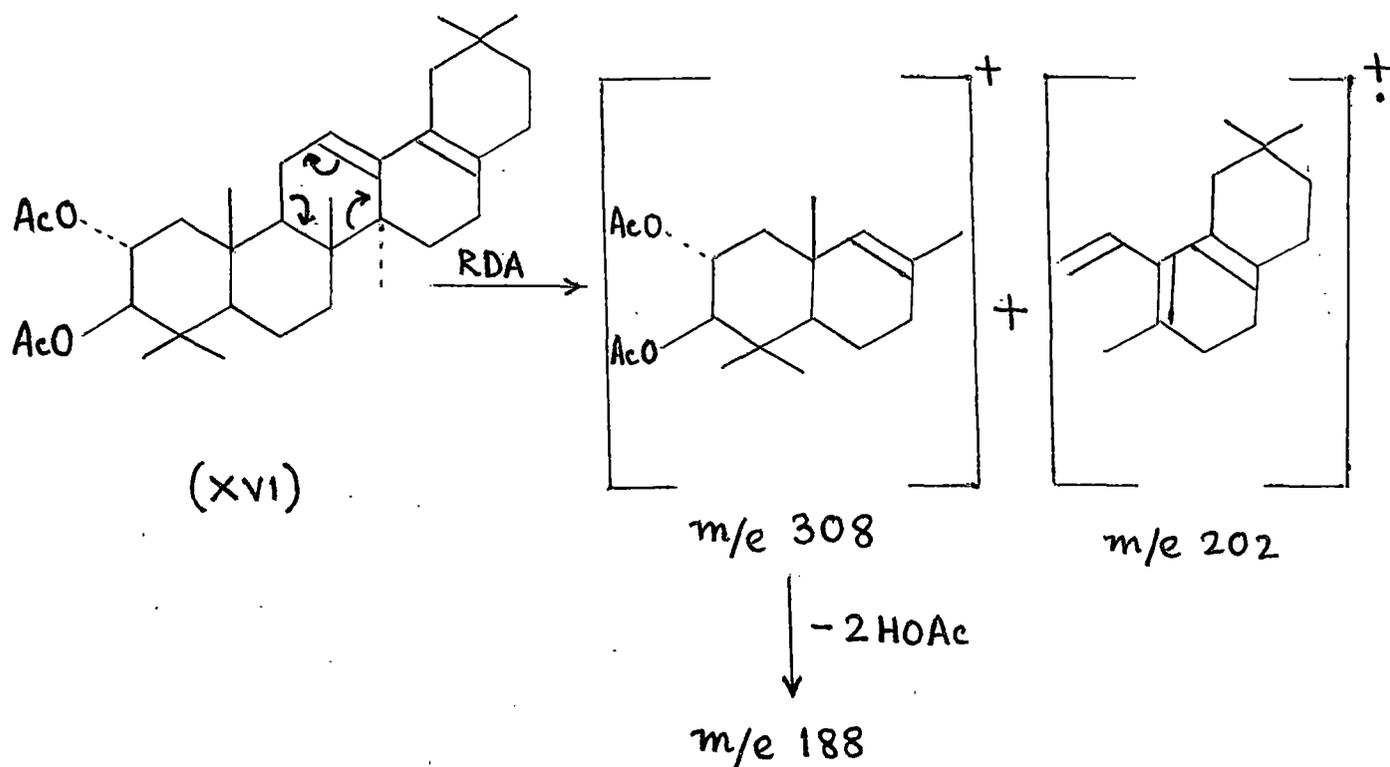
Methanolic alkali treatment of baccatin afforded a homoannular diene-diol. The corresponding diacetate, on acid treatment, isomerised to a heteroannular diene-diacetate. The structure  $2\alpha, 3\beta$ -diacetoxy-28-nor-oleana-12, 17-diene (XVI) was proposed for this heteroannular diene-diacetate from physical data especially from its mass fragmentation pattern. The reactions were schematised as follows:

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The mass peak at  $m/e$  308, 202 and 188 of the heteroannular diene-diacetate was explained in the light of the following fragmentation.

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From this mass fragmentation pattern, the structure (XVI) for the heteroannular diene-diacetate was established. This, in turn, confirmed the structure (XIII) for baccatin.

### Chapter-II:

This chapter describes a successful partial synthesis of  $2\alpha, 3\beta$ -diacetoxy-28-nor oleana-12, 17-diene. The synthetic

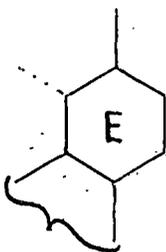
compound was shown to be identical with the heteroannular diene-diacetate previously obtained from the degradation of baccatin. This, in turn, confirmed the structure (XIII) for baccatin. This chapter was subdivided into two sections.

Section A:

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

A critical analysis showed that a few conclusions regarding the structure elucidation of baccatin required further confirmation.

The presence of a taraxerene nucleus in baccatin was suggested mainly from biogenetic consideration and this was supported by the structure (XVI) for the heteroannular diene diacetate obtained from it. However, all the physical and chemical data of the heteroannular diene diacetate could be explained with a fair degree of accuracy by assuming the presence of an ursane-type E ring (XVII) also in it and consequently in baccatin.



(XVII)

Furthermore, the presence of a  $2\alpha$ ,  $3\beta$ -diol system, suggested from NMR spectra, in baccatin required chemical proof.

From these considerations it was thought that a partial synthesis of  $2\alpha$ ,  $3\beta$ -diacetoxy-28-nor oleana 12, 17-diene from a known triterpene, namely, crategolic acid, and subsequent demonstration of its identity with the heteroannular diene diacetate obtained from baccatin would remove the ambiguity and, in turn, would confirm the proposed structure (XIII) of baccatin.

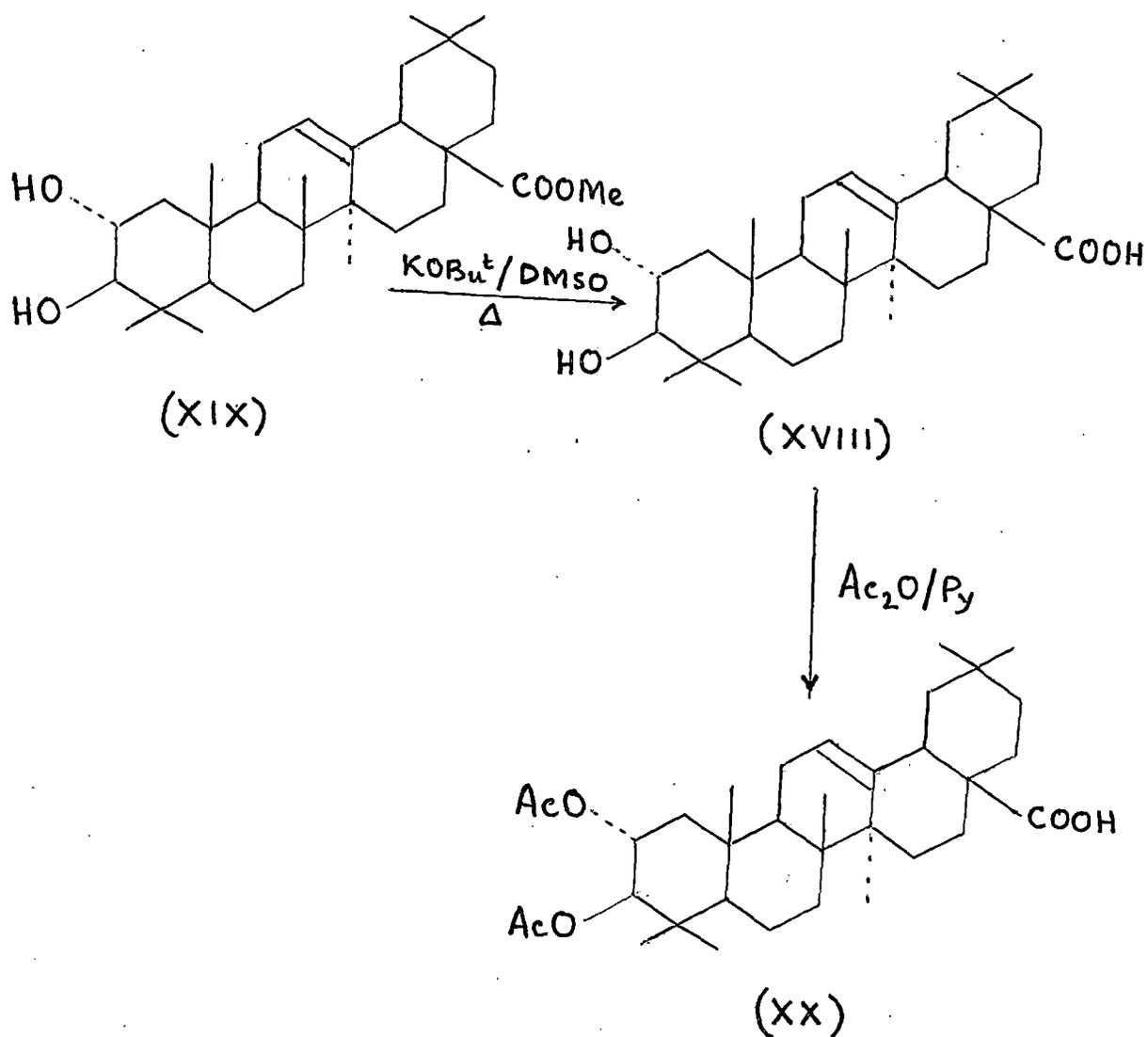
#### Section B:

This section describes a successful partial synthesis of  $2\alpha$ ,  $3\beta$ -diacetoxy-28-nor oleana-12, 17-diene.

Benzene extract of the flowers of Eugenia Jambolana Lam was separated into acidic and neutral portions. Chromatography of the crude acid mixture gave Crategolic acid (XVIII) m.p.  $266-69^{\circ}$ . The yield of pure crategolic acid by this method was very poor. The crude acid mixture on esterification followed by chromatography afforded methyl crategolate (XIX), m.p.  $224-27^{\circ}$ ,  $(\alpha)_D^{25} 36^{\circ}$ . Hydrolysis of methyl crategolate with potassium tertiary butoxide in dimethyl sulfoxide gave crategolic acid identical with the acid obtained earlier. On acetylation,

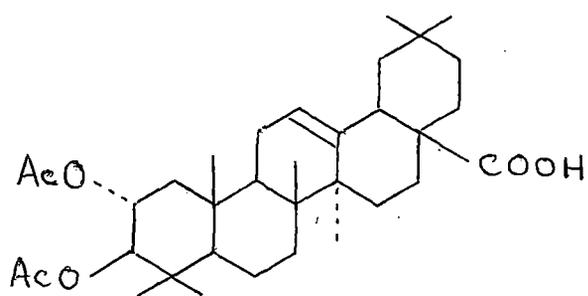
(xiv)

crategolic acid gave crategolic acid diacetate (XX), m.p. 234-37°,  $(\alpha)_D^{31}$ .



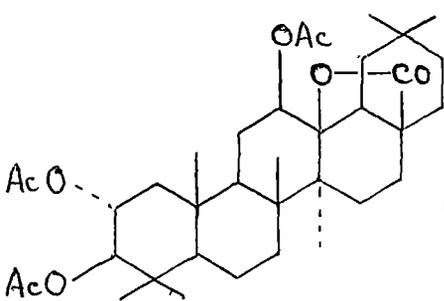
(xv)

Oxidative decarboxylation of crategolic acid diacetate gave a mixture of products.

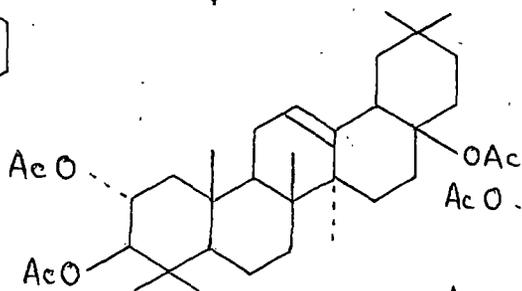


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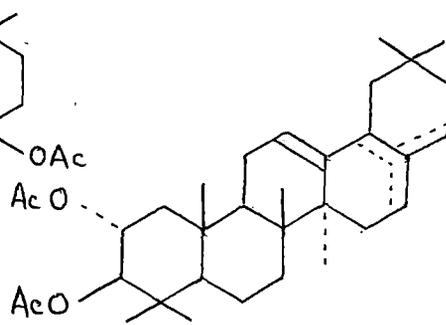
$Pb(OAc)_4 / C_6H_6 - Py / \Delta / N_2 Atmos.$



(xxi)



(xxii)

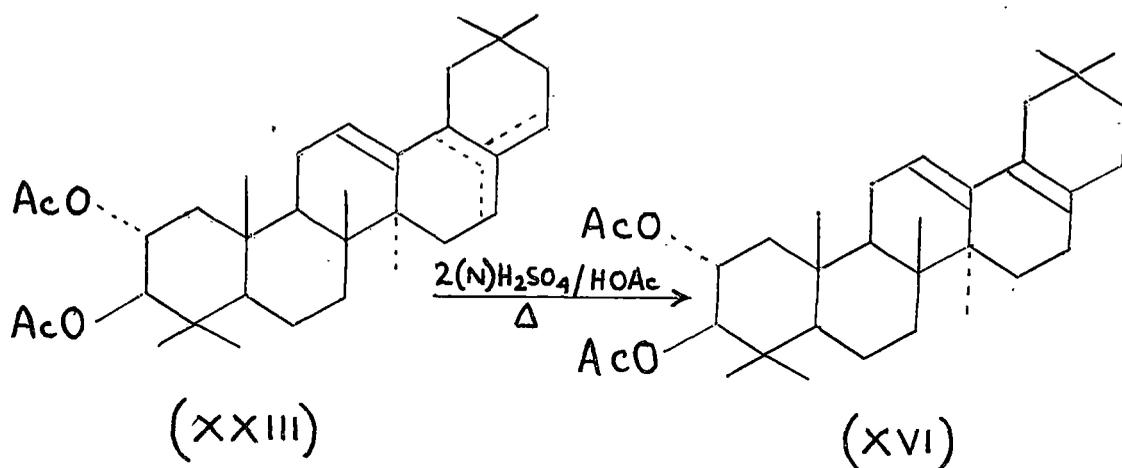


(xxiii)

(xvi)

Chromatography of the reaction product led to the successful separation of the mixture of diene-diacetates,  $C_{33}H_{50}O_4$ , represented by (XXIII), m.p.  $114-170^\circ$ , (TLC- three spots), IR  $\nu_{\max}^{\text{nujol}}$  1740, 1240  $cm^{-1}$ , UV  $\lambda_{\max}^{\text{MeOH}}$  237 ( $\epsilon$  9510), 244 ( $\epsilon$  10,050), 252 nm ( $\epsilon$  7590). The UV absorption spectra indicated that some amount of heteroannular conjugated diene was also present in the diene diacetate mixture.

On treatment with  $2(N)H_2SO_4$  in acetic acid the mixture of the diene diacetates was isomerised completely into the conjugated system,  $2\alpha, 3\beta$ -diacetoxy-28-nor oleana-12, 17-diene, (XVI), m.p.  $189-90^\circ$ , IR  $\nu_{\max}^{\text{nujol}}$  1745, 1650(W), 1255, 1220  $cm^{-1}$ , UV  $\lambda_{\max}^{\text{MeOH}}$  237 ( $\epsilon$  27,000), 244 ( $\epsilon$  28,300), 252 nm ( $\epsilon$  20,200).



(xvii)

The synthetic  $2\alpha, 3\beta$ -diacetoxy-28-nor-oleana-12, 17-diene (XVI) was found to be identical in all respects with the heteroannular diene-diacetate (XVI) previously prepared from the degradation of baccatin (XIII).

This unambiguous synthesis thus confirmed the proposed structure (XVI) of heteroannular diene diacetate obtained from baccatin and showed that it indeed contain<sup>ed</sup> an oleanane type E ring and a  $2\alpha, 3\beta$ -diacetoxy system. These confirmed the proposed structure (XIII) of baccatin.

#### Chapter-III:

Experimental portion has been described in this chapter.

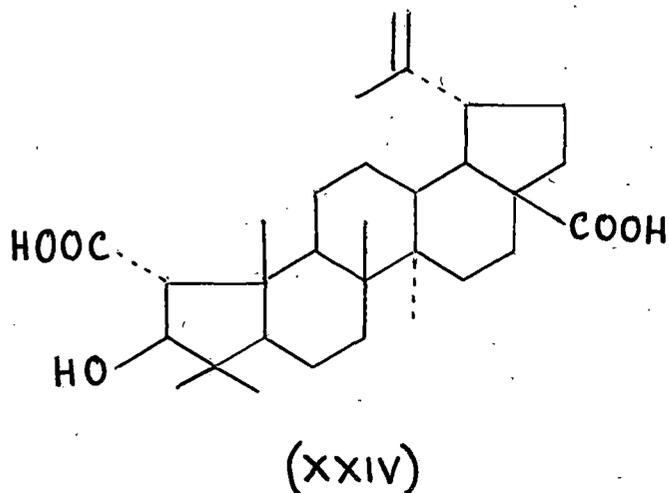
### PART-III

#### PARTIAL SYNTHESIS OF ALL THE FOUR STEREOISOMERS OF DIMETHYL DIHYDROCEANOATE STARTING FROM BETULINIC ACID.

#### Chapter-I:

This chapter gives a short review on the isolation, structure elucidation and stereochemistry of ceanothic acid (XXIV).

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This chapter is divided into three sections.

Section A:

This section describes the isolation of ceanothic acid.

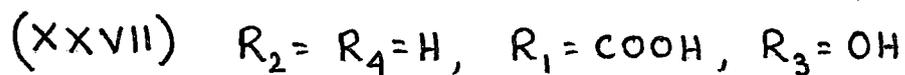
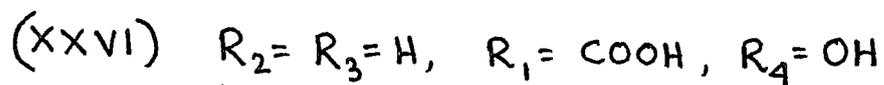
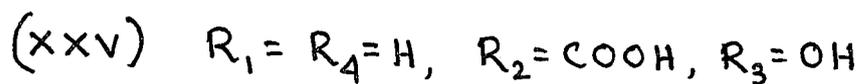
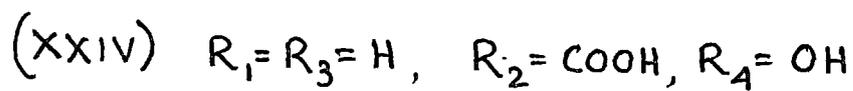
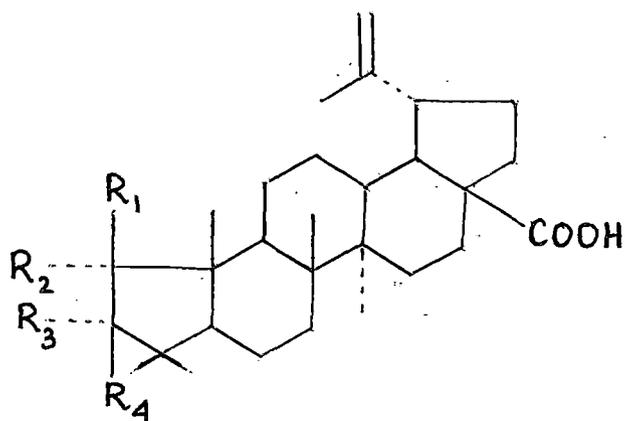
Section B:

This section deals with the structure elucidation of ceanothic acid.

Section C:

This section describes the establishment of the stereochemistry of ceanothic acid (XXIV) and its other three stereoisomers (XXV), (XXVI) and (XXVII).

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### Chapter-II:

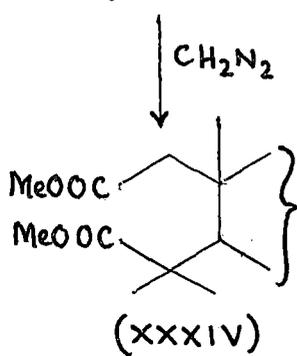
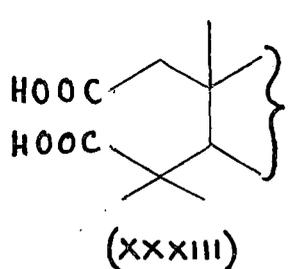
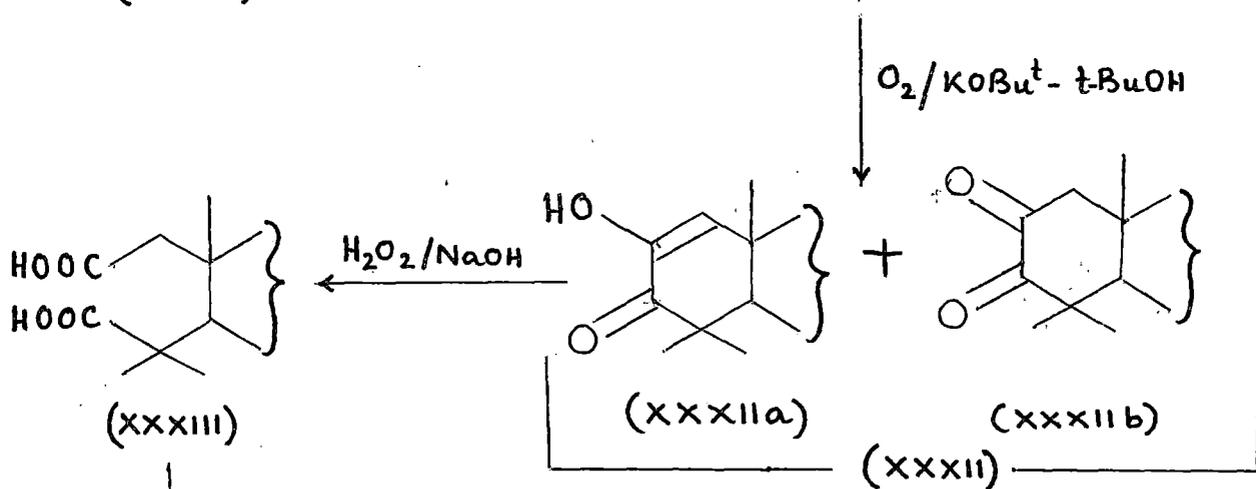
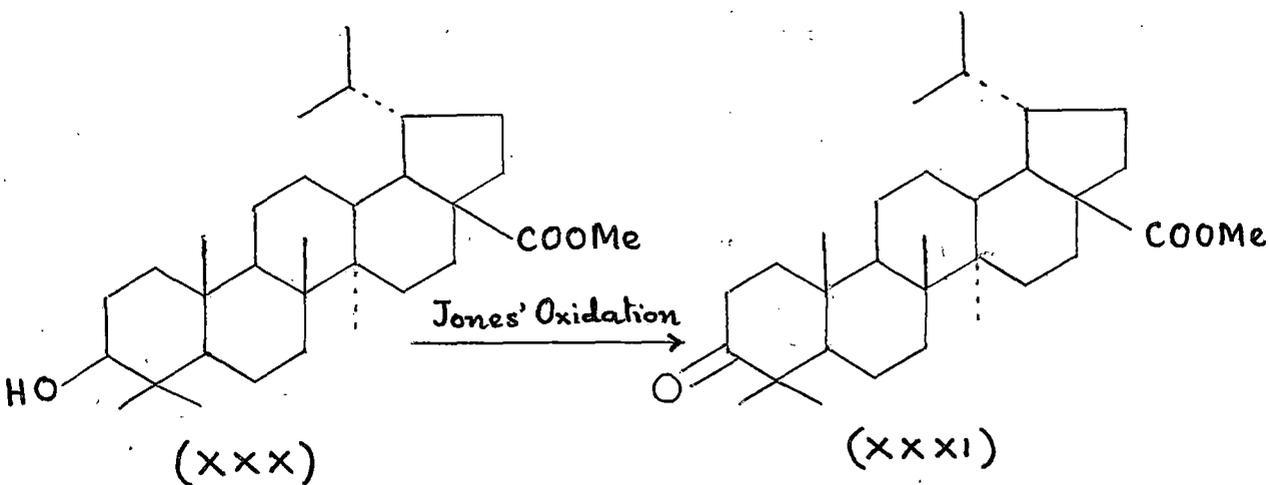
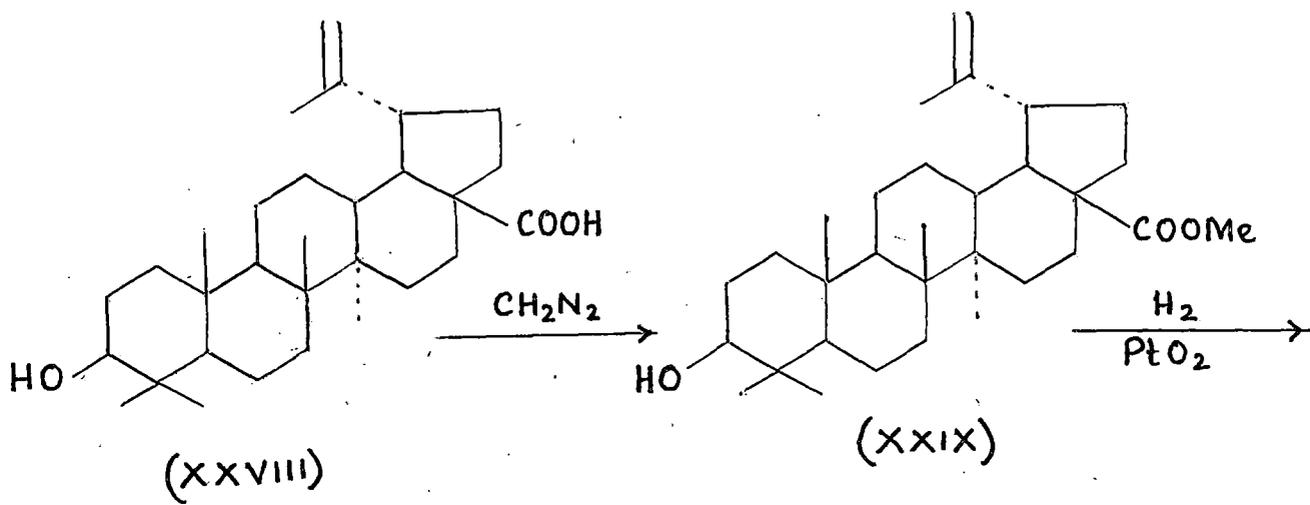
This chapter gives a short review on the previous attempts towards the partial synthesis of ceanothic acid and its stereoisomers.

Chapter-III:

This chapter describes a successful partial synthesis of all the four stereoisomers of dimethyl dihydroceanothate starting from betulinic acid.

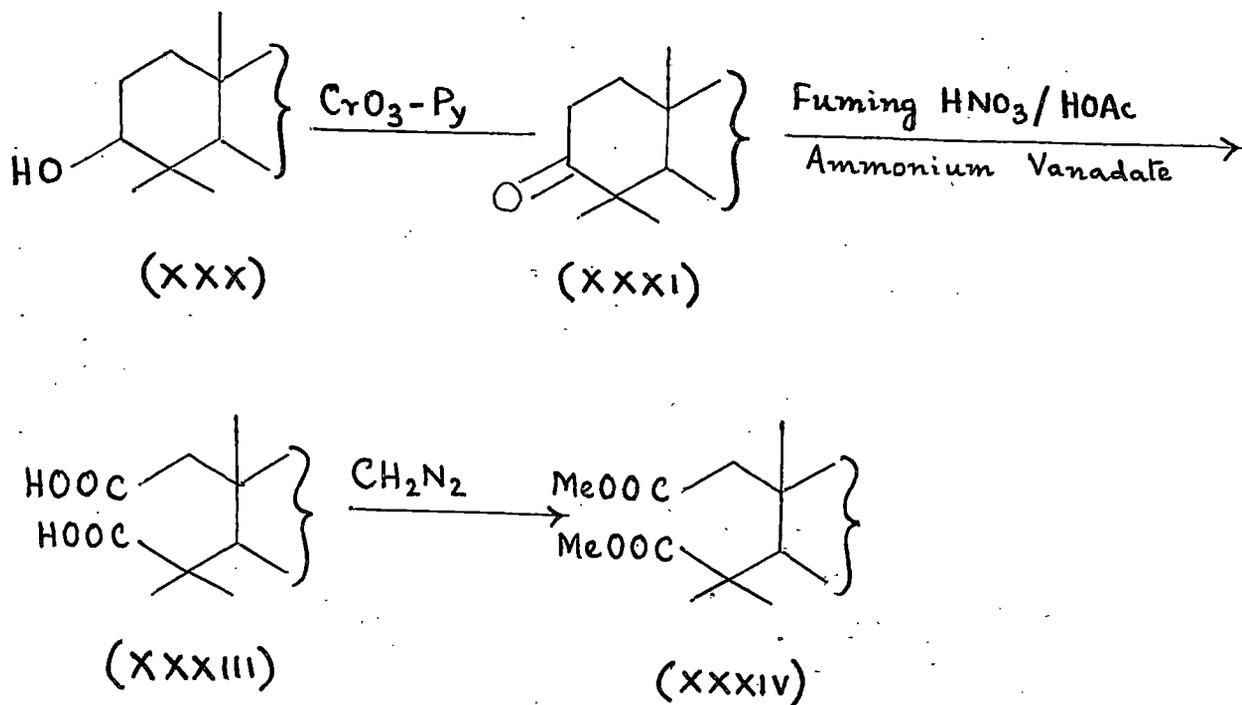
Betulinic acid (XXVIII) extracted from the acid part of the benzene extract of the bark of Bischofia Javonica Blume on esterification gave methyl betulinate (XXIX), m.p. 223-24°,  $(\alpha)_D^{25}$ . Hydrogenation of methyl betulinate (XXIX) afforded methyl dihydrobetulinate (XXX), m.p. 236-38°. Jones' oxidation of methyl dihydrobetulinate (XXX) afforded methyl dihydrobetulonate (XXXI), m.p. 191-93°,  $(\alpha)_D^{25}$  8°. Autoxidation of the latter by dry oxygen in presence of potassium tertiary butoxide in tertiary butanol afforded a solid, m.p. 131-33°,  $(\alpha)_D^{25}$  -1.96°, IR  $\nu_{\max}^{\text{nujol}}$  3460, 1730, 1670, 1650, 860  $\text{cm}^{-1}$ , UV  $\lambda_{\max}^{\text{MeOH}}$  269 nm ( $\epsilon$ , 7532). In this solid the diosphenol (XXXIIa) was in equilibrium with the  $\alpha$ -diketone (XXXIIb). Alkaline hydrogen peroxide oxidation of this equilibrium mixture (XXXII) afforded the A-seco acid (XXXIII), m.p. 175-77°, IR  $\nu_{\max}^{\text{nujol}}$  1710 and 1680  $\text{cm}^{-1}$ . Esterification of the A-seco acid (XXXIII) yielded the trimethyl ester (XXXIV), m.p. 146-47°, IR  $\nu_{\max}^{\text{nujol}}$  1745 and 1725  $\text{cm}^{-1}$ .

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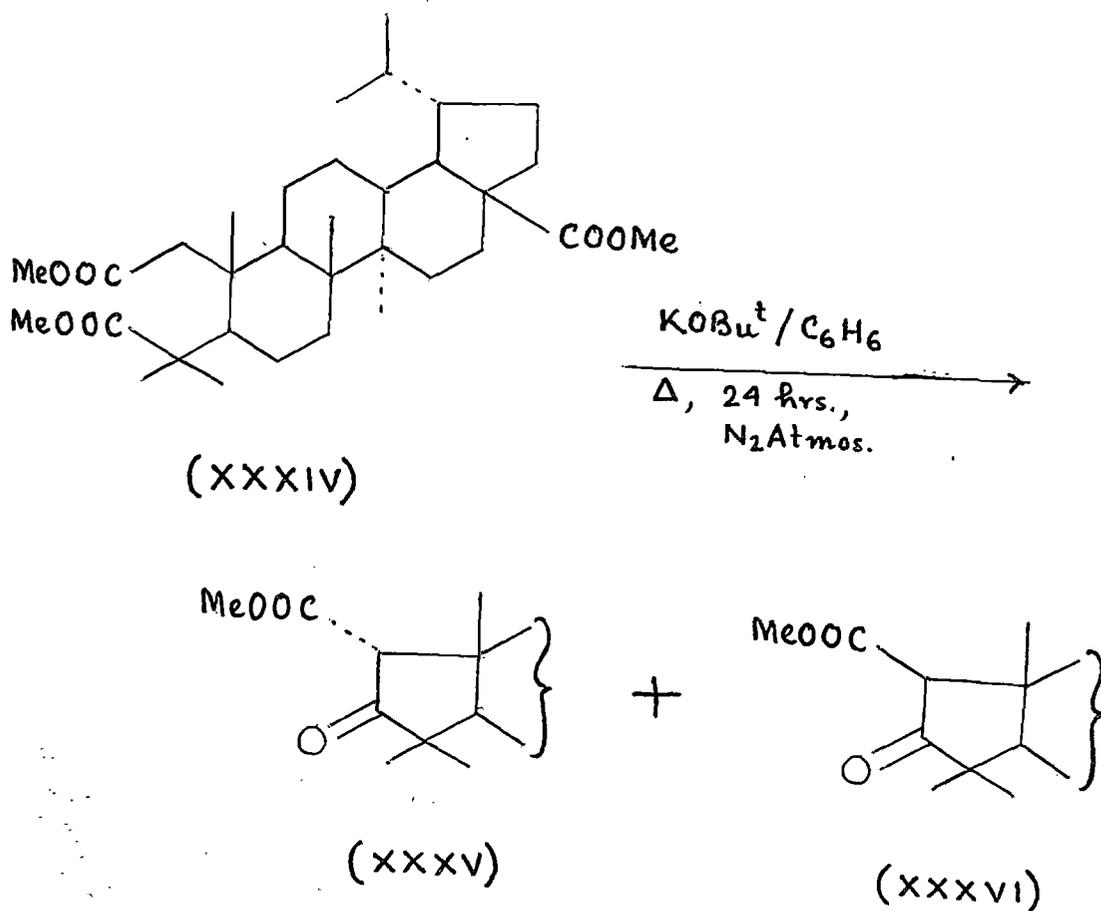
(xxii)

The overall yield of the trimethyl ester (XXXIV) by the above method was low. Finally a better method was also developed. Oxidation of methyl dihydrobetulinate (XXX) with anhydrous Chromium trioxide-Pyridine complex afforded methyl dihydrobetulonate (XXXI) in very good yield. Methyl dihydrobetulonate (XXXI) was directly converted into A-seco acid (XXXIII) by oxidation with fuming nitric acid in acetic acid in presence of ammonium vanadate as catalyst. Subsequent esterification of the A-seco acid then afforded the trimethyl ester (XXXIV) in fairly good overall yield.



(xxiii)

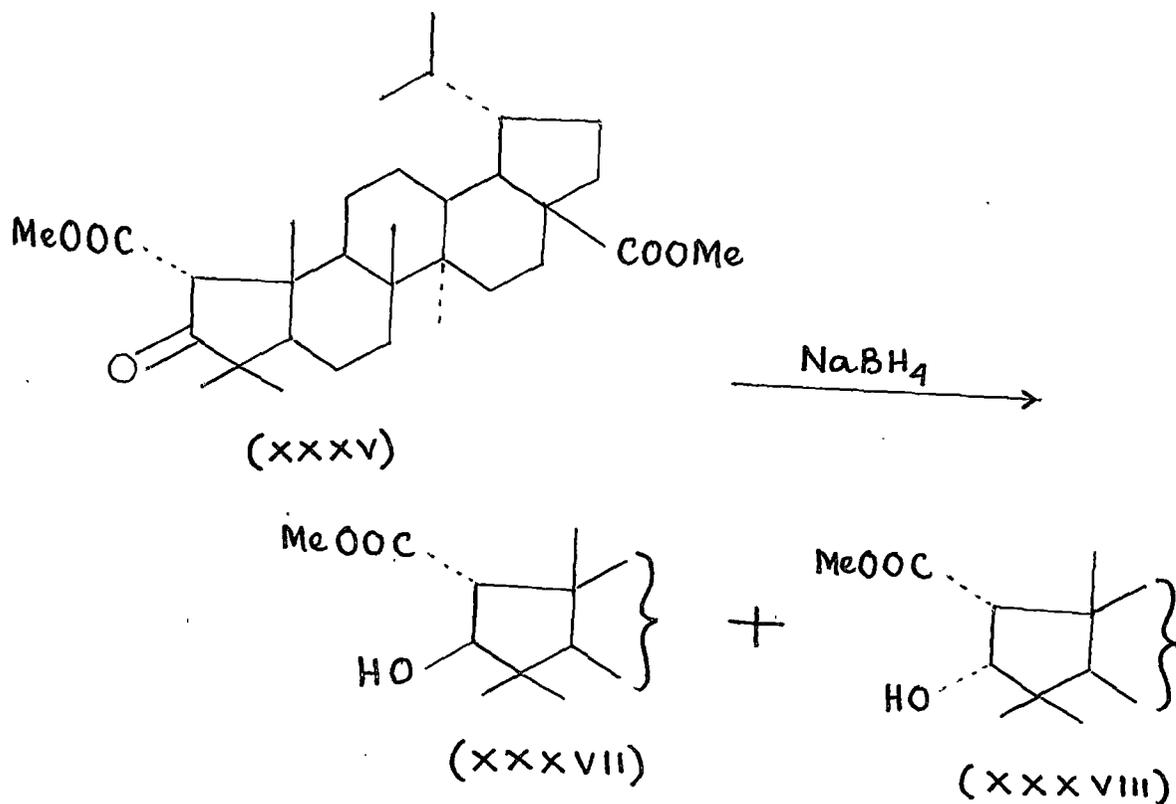
Dieckmann condensation of the trimethyl ester (XXXIV) with potassium-tertiary butoxide in benzene under nitrogen atmosphere followed by chromatographic separation afforded methyl-2 $\alpha$ -methoxycarbonyl-3-oxo-A(1)-norlupan-28-oate (XXXV), m.p. 191-93 $^{\circ}$ , ( $\alpha$ )<sub>D</sub> 89 $^{\circ}$ , IR  $\nu_{\text{max}}^{\text{nujol}}$  1755, 1725  $\text{cm}^{-1}$  and its epimer methyl-2 $\beta$ -methoxycarbonyl-3-oxo-A(1)-norlupan-28-oate (XXXVI), m.p. 175-77 $^{\circ}$ , ( $\alpha$ )<sub>D</sub> 42 $^{\circ}$ , IR  $\nu_{\text{max}}^{\text{nujol}}$  1750, 1720  $\text{cm}^{-1}$ .



Sodium borohydride reduction of the  $\beta$ -ketoester (XXXV) in methanol-dioxan solution gave a mixture of two compounds. The

(xxiv)

reaction product, on chromatography, first eluted a solid, m.p. 261-63°, ( $\alpha$ )<sub>D</sub> 22°, IR  $\nu$ <sub>max</sub><sup>nujol</sup> 3540, 1730, 1710  $\text{cm}^{-1}$  which was found to be identical in all respects with an authentic specimen of dimethyl dihydroceanothate  $\left[ \text{methyl-3}\beta\text{-hydroxy-2}\alpha\text{-methoxycarbonyl-A(1)-norlupan-28-oate} \right]$  (XXXVII). Further elution with the same solvent afforded its C-3 epimer, methyl-3 $\alpha$ -hydroxy-2 $\alpha$ -methoxycarbonyl-A(1)-norlupan-28-oate (XXXVIII), m.p. 140-42°, IR  $\nu$ <sub>max</sub><sup>nujol</sup> 3560, 1745, 1705  $\text{cm}^{-1}$ . Confirmation of this structure by NMR is in progress.

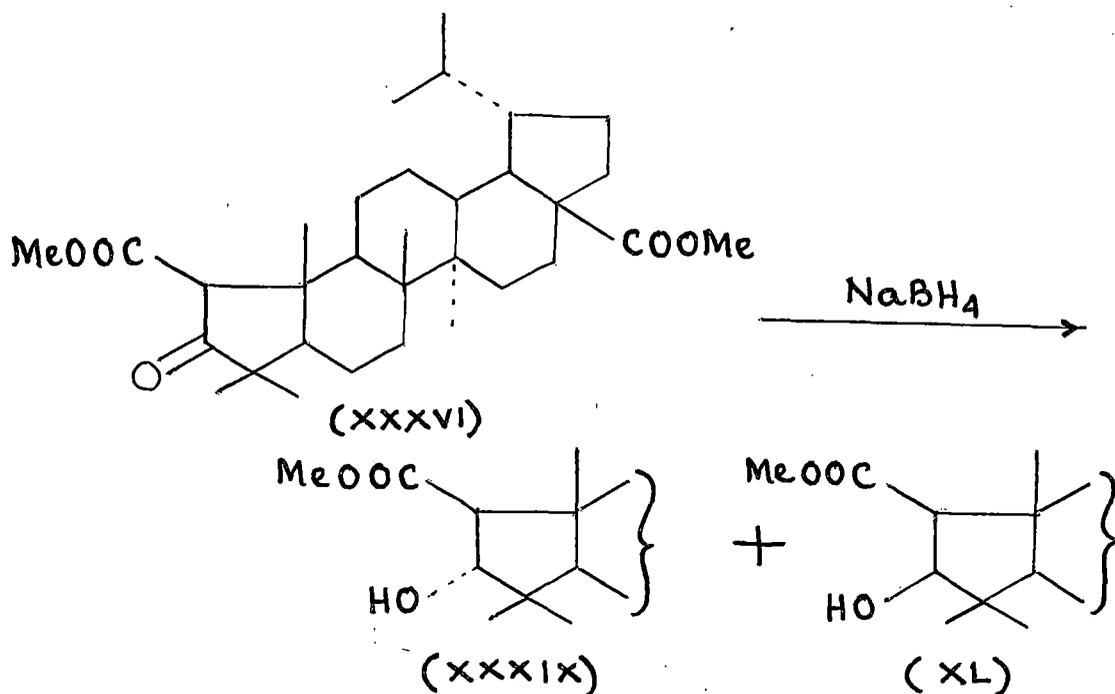


Sodium borohydride reduction of the other  $\beta$ -ketoester (XXXVI) also gave a mixture of two compounds. Chromatography on

(xxv)

neutral alumina first eluted a solid A  $C_{32}H_{52}O_5$ , m.p. 202-203<sup>o</sup>, IR  $\nu_{\max}^{\text{nujol}}$  3490, 1730, 1695  $cm^{-1}$ ,  $^1H$ -NMR (80  $MHz$ )  $\delta$  0.7 to 1.1 (seven methyl groups), 2.1 (1H,  $OH$ ), 3.06 (1H doublet,  $J = 7.0 H_z$ ,  $CH-CO_2Me$ ), 3.65 (3H singlet,  $COOCH_3$ ), 3.7 (3H singlet,  $COOCH_3$ ) and 4.18 (1H doublet,  $J = 7.0 H_z$ ,  $CHOH$ ). Further elution with more polar solvent afforded another solid B,  $C_{32}H_{52}O_5$ , m.p. 174-76<sup>o</sup>, IR  $\nu_{\max}^{\text{nujol}}$  3540, 1740, 1690  $cm^{-1}$ ,  $^1H$ -NMR (80  $MHz$ )  $\delta$  0.7 to 1.1 (seven methyl groups), 2.35 (1H doublet,  $J = 7.2 H_z$ ,  $CH-CO_2Me$ ), 2.8 (1H doublet,  $J = 4.5 H_z$ ,  $OH$ ), 3.65 (3H singlet,  $COOCH_3$ ), 3.7 (3H singlet,  $COOCH_3$ ), 4.02 (1H multiplet,  $CHOH$ ). The above physical data indicated that the solids A and B were C-3 epimeric alcohols which fact was also evident from their methods of preparation. The assignment of conformations were done from the fact that the proton on C-2 in A was shifted downfield to  $\delta$  3.06 indicating thereby that the proton at C-2 and the hydroxyl group at C-3 in this compound A was on the same side of the ring, i.e., A was methyl-3 $\alpha$ -hydroxy-2 $\beta$ -methoxycarbonyl-A(1)-norlupan-28-oate (XXXIX). Consequently B was methyl-3 $\beta$ -hydroxy-2 $\beta$ -methoxycarbonyl-A(1)-norlupan-28-oate (XL).

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Additional support for the above interpretation was found in the fact that, although the solution used for <sup>1</sup>H-NMR of (XL) was comparatively dilute, the signal for OH group was found further downfield than that in (XXXIX). This indicated the presence of an intramolecular hydrogen bond in (XL), which could only occur when the OH and COOMe groups were on the same side of the ring as in (XL). The <sup>13</sup>C-NMR spectra also supported the above structural assignments.

#### Chapter-IV:

Experimental portion has been described in this chapter.