SUMMARY

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

A. The first part (Part I) consists of investigations carried out on the benzene extract of the bark of Sapium sebiferum Roxb. (Euphorbiaceae).

B. The second part (Part II) describes preparation of diosphenols in ring A of triterpenoids and confirmation of the structure of baccatin

C. The third part (Part III) deals with an approach to the total stereospecific synthesis of C_{11} -acid, a degraded product of Abietic acid.

A. PART - I

CHAPTER - I

In this chapter the morphological features of "Euphorbiaceae family" is described.

CHAPTER - II

Section A:

This section gives a short review on dihydroxy triterpenic acids.

Section B:

This section deals with a short review on the mass spectra of Δ^{14} -taraxerene moiety.

Section C:

This section provides a short review on the biogenesis of triterpenoids with special emphasis on Friedo oleananes.

CHAPTER - III

Section A:

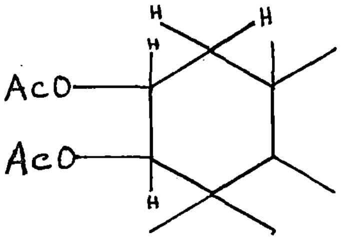
This section deals with the reinvestigations on the acid part of benzene extract of the bark of Sapium sebiferum Roxb. and the isolation of Sebiferic acid, the isolation and identification of Aleuritolic acid and the isolation of a new triterpenic acid, Sebiferenic acid, $C_{30}H_{48}O_4$ (2α-hydroxy aleuritolic acid), m.p. 325° (decomp) have been described. The name Sebiferenic acid has been proposed by the author after the name of the species from which it has been isolated for the first time.

Section B:

The section deals with the structure elucidation of this new triterpenic acid, sebeferenic acid. It gave positive Liebermann-Burchard test showing that the compound to be a triterpene. Sebeferenic acid on esterification with diazomethane formed a methyl ester, $C_{31}H_{50}O_4$, m.p. 253-254°. The presence of a double bond in it was shown by positive tetranitromethane colour test and by the consumption of 1 mole of perbenzoic acid. The double bond resisted hydrogenation in presence of palladium-on-charcoal catalyst under normal conditions. This experiment indicated that the double bond was most probably present in a hindered position. The IR spectrum of this methyl ester showed peaks at 3380 (broad -OH), 1730 (carbomethoxy) and at 820 cm^{-1} (trisubstituted double bond) Hydrolysis of methyl ester with alkali was attempted but the recovery of the starting material indicated the hindred nature of ester group i.e. carboxyl group in the original acid was probably at a tertiary position.

The elemental analysis of the methyl ester showed the molecular formula to be $C_{31}H_{50}O_4$. On acetylation with Ac_2O/Py, the methyl ester afforded the diacetyl methyl ester, $C_{35}H_{54}O_6$, m.p. 224-226°. The IR spectrum showed the absence of peak in hydroxyl region but instead showed peak at 1725 (broad, $OCOCH_3$, $-CO_2CH_3$) and 1250 cm^{-1} ($-OCOCH_3$). Thus it was concluded that the methyl ester of the acid contains acylable hydroxyl group. From the molecular formula of the methyl ester and the diacetyl methyl ester, it was concluded that the new acid is a pentacyclic triterpenoid. PMR spectrum of acetyl methyl ester showed peak at 5.50 ppm (multiplet), accounting for one vinyl proton, suggesting the presence of a trisubstituted double bond; at 1.98 (a sharp singlet) and 2.04 ppm due to two acetate methyls; a sharp singlet at 3.58 ppm due to the ester methyl and several sharp signals between 0.85 to 1.05 ppm due to seven tertiary methyls.

PMR spectrum showed also that methine protons at 4.7 and 5.05 ppm as a doublet and a triplet of doublets. Different absorption of these two protons (attached to acetate bearing carbons) suggested that they are situated in different chemical environments. This might arise from the coupling of one of these protons with two nearby methylene protons. This part of the spectrum corresponded to the X-part of the ABXY type of spectrum shown in case of four protons attached to adjacent carbons in the system (1).



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If we assume that one of the acetate functions is situated as in all triterpene at C-3 of the A ring of the triterpene nucleus then PMR data could easily be correlated by placing the other acetyl group at C-2. Appearance of C-3 proton with unsymmetrical doublet at 4.7 ppm having the coupling constant (J = 10 Hz) showed that C-2 and C-3 protons are in trans diaxial arrangement and consequently 2α, 3β diequatorial configuration of the acetate groups as in 2. This type of splitting is reminiscent of these observed in case of methyl dihydroalphitolate diacetate, baccatin diacetate and methyl crategolate diacetate. Hence sebeferenic acid must have the two hydroxyl groups in 2α, 3β (trans diequatorial) configuration as in 3

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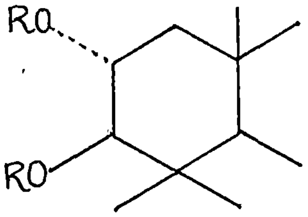


2) R = Ac
3) R = H

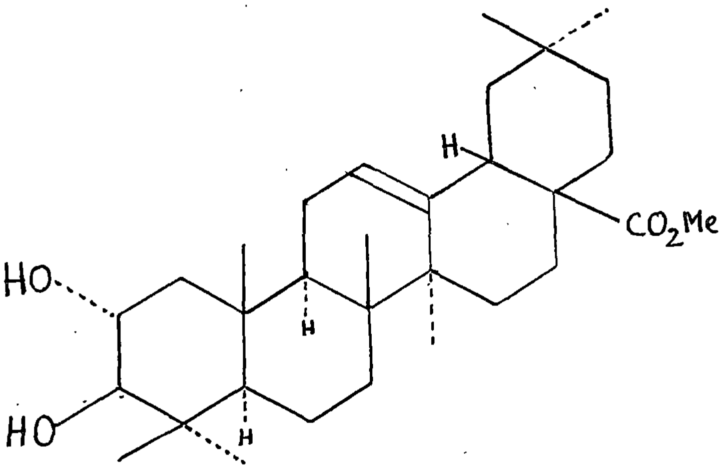
^{13}C NMR spectrum of acetyl methyl ester showed that the peaks at 170.57 and 170.31 ppm are consistent with the presence of two acetate carbonyls. The peaks at 116.79 and 160.10 ppm are characteristic of a double bond to a ring junction (160.10 ppm) with a proton on the other olefinic carbon (116.79 ppm). The peaks at 80.62 and 69.96 ppm are due to the CH groups to which the acetates are attached.

^{13}C NMR spectrum showed that the peak at 178.25 ppm is the carbonyl of a carbomethoxy group; and confirmed the presence of 35 carbon atoms in the molecule.

The total number of methyl groups is found to be ten, so there are seven tertiary methyl groups, two acetate methyls and one carbomethoxy.

The off resonance noise decoupled spectrum gives sharp lines for non-protonated (singlet) carbons. From this we can see that there are six quaternary carbons (two coincide at 38.94 ppm) in addition to three carbonyl carbons and the doubly bonded carbon at ring junction.

The acetyl methyl ester of the acid on heating with HCl-acetic acid on a water bath for fifteen minutes afforded a compound, $C_{35}H_{54}O_6$, m.p. 166-168°, $[\alpha]_D$ 24°. This on hydrolysis with methanolic alkali afforded a compound, $C_{31}H_{50}O_4$, m.p. 220-222°, $[\alpha]_D$ 36°. This was found to be identical throughout the IR region with that of authentic methyl crategolate 4 (maslinate) [supplied by Prof. P. Sengupta as a gift]. Moreover, the mixed m.p. showed no depression as well as Co-tlc was found to be same.



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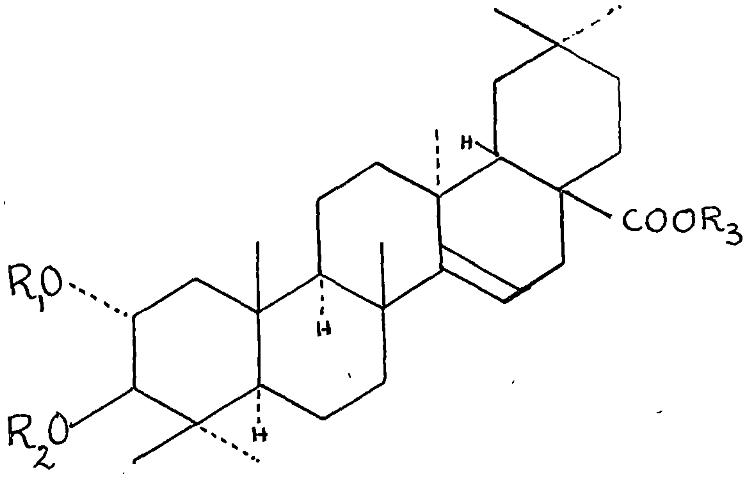
Thus it could be concluded that sebeferenic acid contains a modified oleanane skeleton with the position and stereochemistry of hydroxyl groups (secondary) at C-2 (OH, α) and at C-3 (-OH, β) and the position of the carboxyl group at C-17.

The position of the double bond has been established from the mass fragmentation pattern of the methyl ester and the acetyl methyl ester of this sebeferenic acid which agree in all respects with the fragments as reported by

Djerassi[37] for Δ^{14}-taraxerene moiety. Thus the new acid, sebeferenic acid could be represented as 5, its methyl ester as 6 and the acetyl methyl ester as 7



5, $R_1 = R_2 = R_3 = H$

6, $R_1 = R_2 = H$, $R_3 = CH_3$

7, $R_1 = R_2 = Ac$, $R_3 = CH_3$

*CHAPTER V deals with the investigation of the neutral part of the benzene extract of Sapium sebiferum Roxb.

*CHAPTER IV deals with the experimental section.

B. PART - II

CHAPTER - I

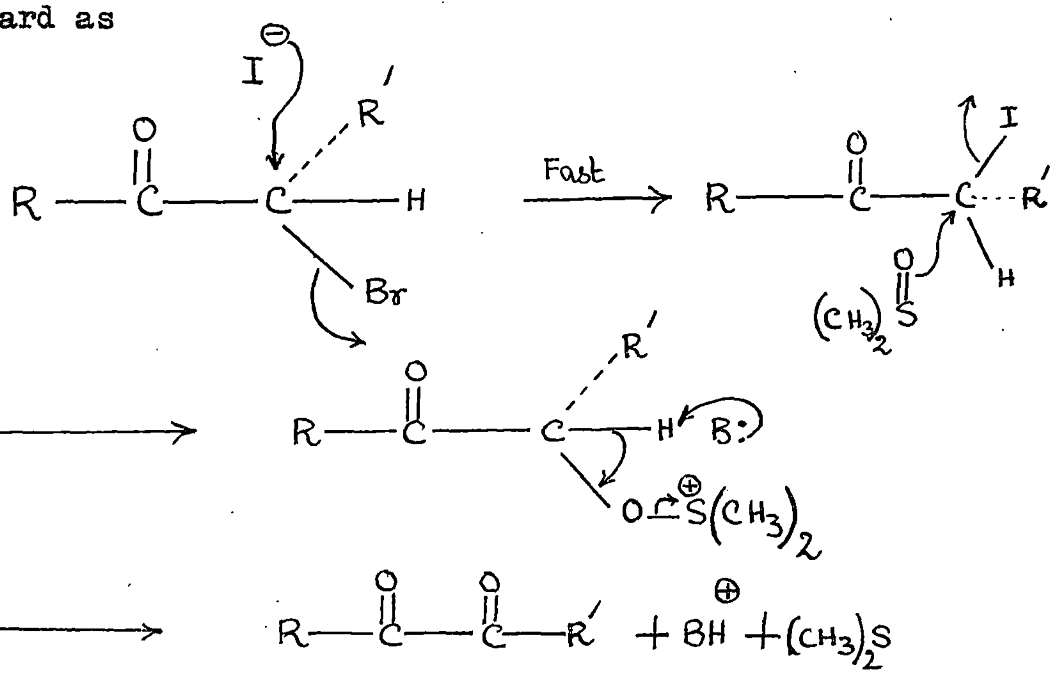
This chapter comprises a short review on general methods for the preparation of α-diketones.

CHAPTER - II

Section A:

This section deals with a novel method for the preparation of ring A diosphenol of lupanone.

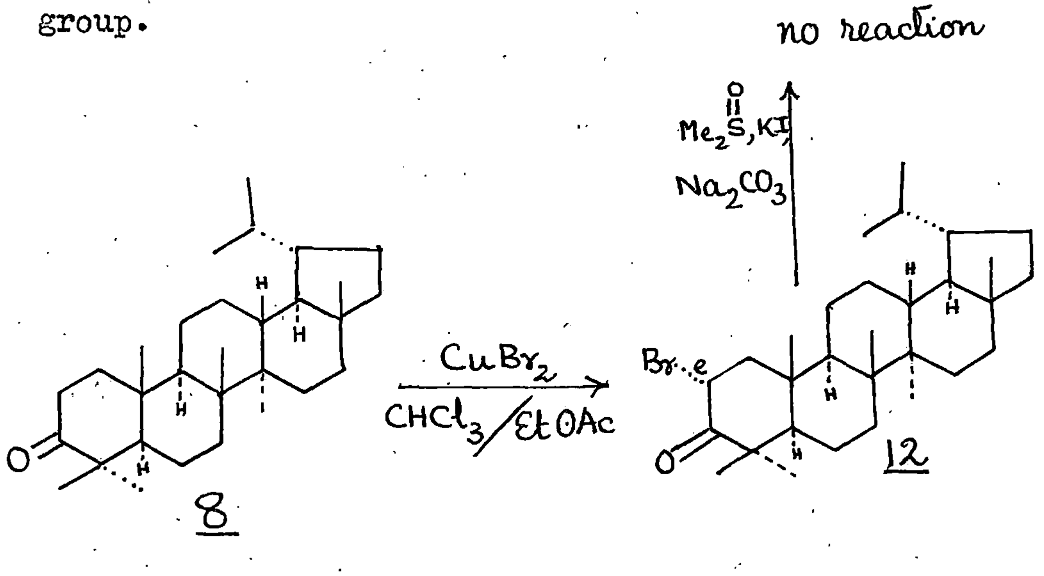
An attempt was made to apply the iodide catalysis oxidation of 2-bromolupanone 12, m.p. 226-227°, $[\alpha]_D$ -20.6° (prepared by refluxing lupanone 8 with cupric bromide in presence of chloroform and ethyl acetate mixture) with dimethyl sulfoxide. The reaction failed due to the fact that as DMSO oxidation required SN_2 attack by the sulfoxide oxygen at brominated carbon, it is sensitive to the steric environment of that center. The mechanism could be put forward as



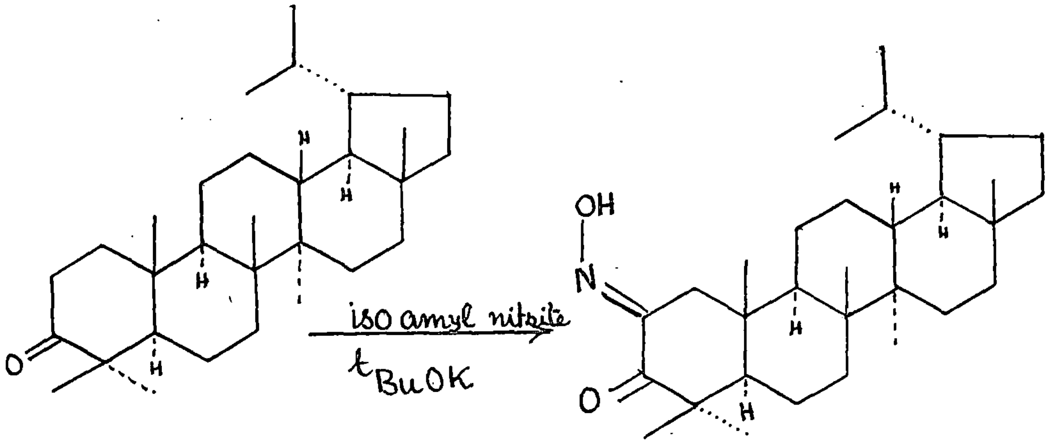
Thus reaction could be feasible if the halogen atom (Br) assumed the axial conformation with respect to carbonyl group in case of 2-bromo lupanone.

It is known that the special spatial relationship of the carbonyl function in cyclohexanone to the equatorial and axial groups on the adjacent (α) carbon gives rise certain peculiarities in the infrared spectra of these compounds when the substituent is a polar group such as halogen. In the infrared spectra, the carbonyl stretching frequency is increased by the nearly parallel dipole of an equatorial α-halogen by about 20 cm^{-1}, whereas the dipole of an axial α-halogen is so oriented that it leaves the carbonyl stretching frequency nearly the same as in the unsubstituted ketone.

Infrared spectrum of 2-bromo lupanone 12 clearly showed an increase of carbonyl stretching frequency by about 20 cm^{-1} from that of lupanone 8 indicating thereby that the bromine atom is equatorial in respect of carbonyl group.



The introduction of C-2 carbonyl group in lupanone 8 was then carried out as follows.



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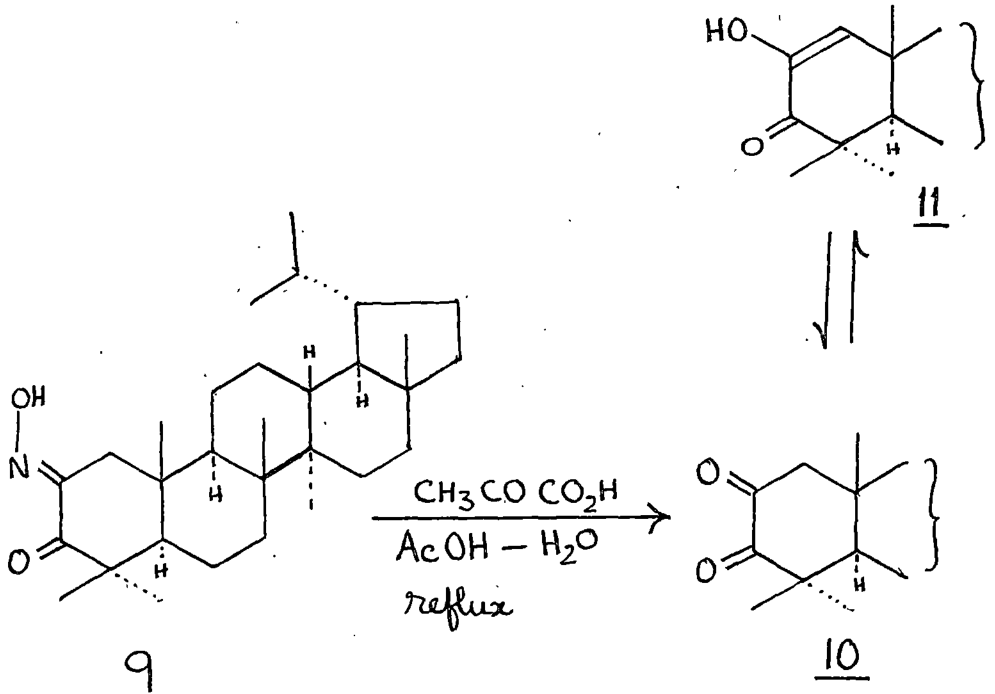
Lupanone 8 in presence of potassium tert. butoxide was stirred with freshly prepared isoamyl nitrite which after acidification followed by purification by column chromatography and crystallisation afforded 2-oximino lupanone 9 m.p. 260° $[\alpha]_D$ 72.34° . IR showed bands at 1700 ($>C = O$), 1615 ($C = N$) and 3240 cm^{-1} (N-OH) respectively. UV spectra showed absorption maxima at 240 nm ($\log \epsilon = 4.1$) and an alkali shift at 291 nm (log ϵ = 4.3). Further confirmation of the structure of 2-oximino lupanone <u>9</u> came from the mass fragmentation pattern.

Hydrolysis of 2-oximino lupanone was effected with freshly distilled pyruvic acid in presence of dilute acetic acid to the corresponding α -diketone derivative <u>10</u>, m.p. 210-213°, $[\alpha]_D$ 24.75°. This produced intense violet coloration with neutral ferric chloride solution. This showed two spots on the chromatoplate indicating the tautomeric mixture of the diketone <u>10</u> and the diosphenol <u>11</u>. IR showed bands at 3440, 1660 and at 1640 cm^{-1}. UV spectrum showed absorption maxima at 272 nm (log ϵ = 3.69) and an alkali shift 324 nm (log ϵ = 3.56).



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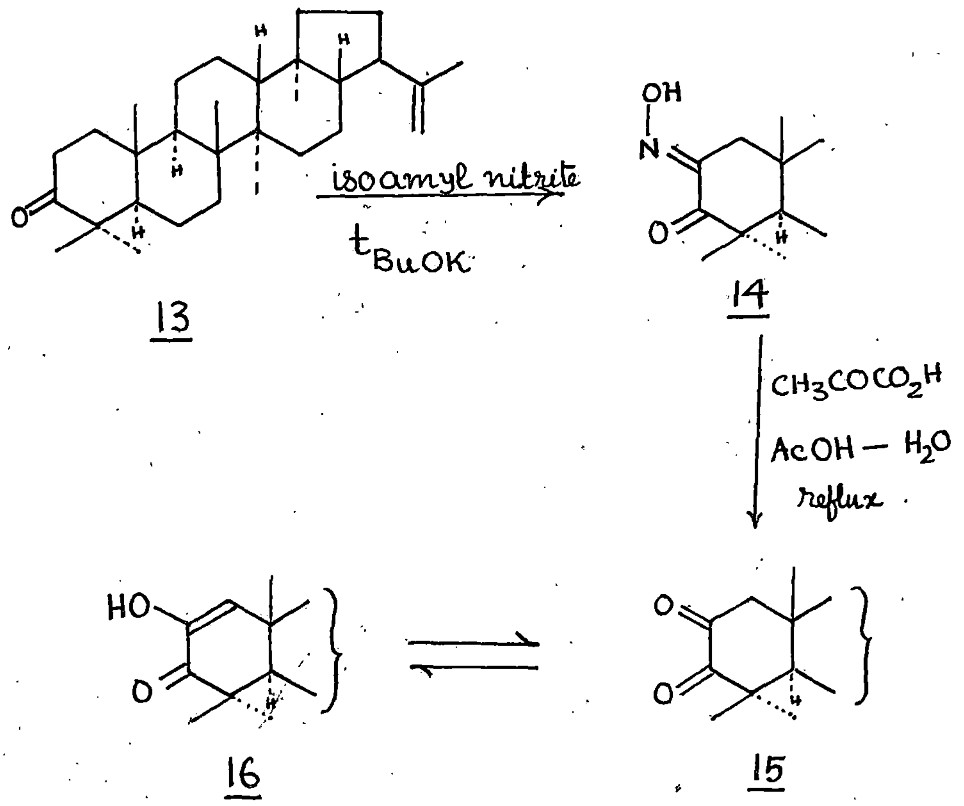
<u>10</u>

Section B:

This section deals with the preparation of ring A diosphenol of moretenone by the above method.

Moretenone 13 (isolated from the benzene extract of the bark of *Sapium sebiferum* Roxb.) m.p. 198-199°, $[\alpha]_D$ 50° in presence of potassium tert. butoxide was stirred with freshly prepared isoamyl nitrite which after acidification and purification by means of column chromatography and crystallisation afforded 2-oximino moretenone 14, m.p. 255-256°. IR showed band at 1700 ($>C = O$), 1605 ($C = N$), 3200 cm^{-1} (N-OH) and at 875 cm^{-1} ($\overset{CH_3}{>}C = CH_2$) respectively. Its UV spectra showed absorption maxima at 240 nm ($\log \epsilon = 4.06$) and an alkali shift at 290 nm ($\log \epsilon = 4.08$) respectively.

This on hydrolysis with freshly distilled pyruvic acid in presence of dilute acetic acid afforded the corresponding α-diketone derivative 15 m.p. 155-158°. This compound indicated two spots on the chromatoplate indicating the tautomeric mixture of the keto 15 and diosphenol 16 forms. It developed intense violet colour with neutral ferric chloride solution. Its UV spectra showed absorption maxima at 270 nm ($\log \epsilon = 3.52$) and an alkali shift at 327 nm ($\log \epsilon = 3.41$). IR exhibited bands at 3420, 1700 and 1660 cm^{-1} respectively.

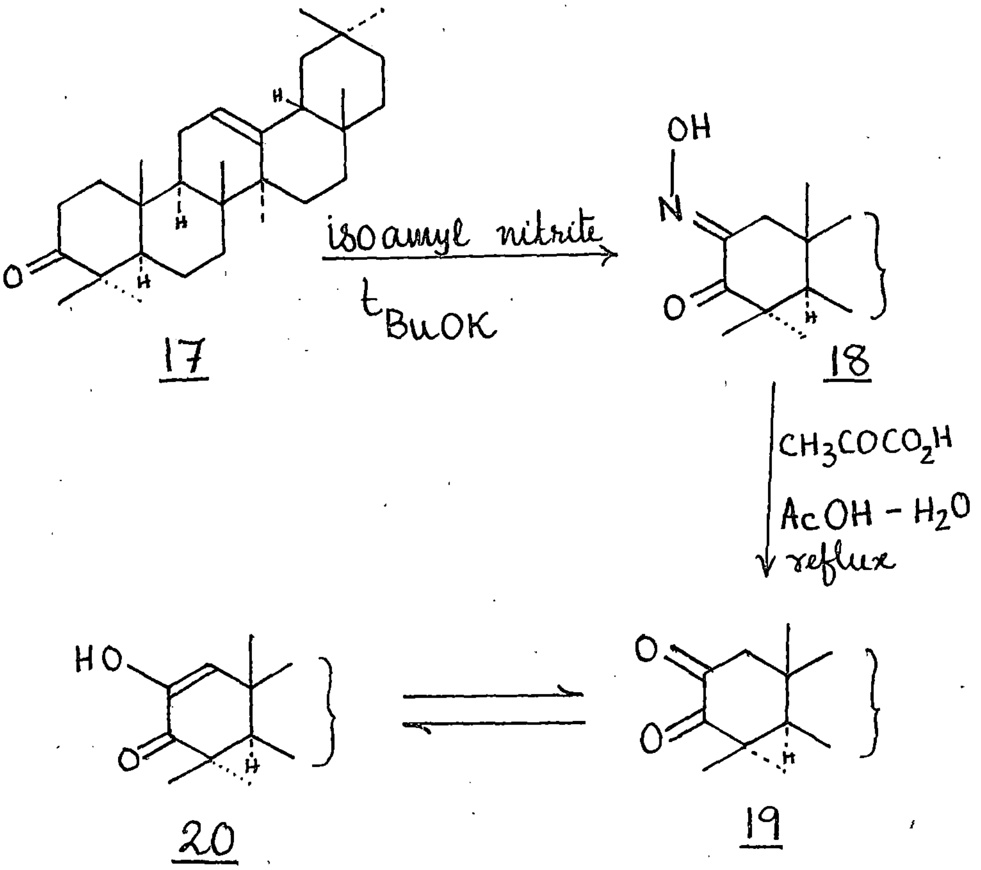


Section C:

This section deals with preparation of ring A diosphenol of β-amyrone via oximino ketone.

β-amyrone 17, m.p. 174-176°, $[\alpha]_D$ 105.6°, obtained by acid isomerisation of taraxerone m.p. 238-240°, $[\alpha]_D$ 10.8° in presence of potassium tert. butoxide was stirred with freshly prepared isoamyl nitrite which after acidification and column chromatography yielded 2-oximino β-amyrone 18 m.p. 200-205°. IR exhibited bands at 3400 (N-OH), 1700 ($>C=O$), and at 1620 cm^{-1} ($C=N$). Its UV spectra showed absorption maxima at 238 nm and an alkali shift at 289 nm respectively.

This was hydrolysed with freshly distilled pyruvic acid in presence of dilute acetic acid to the α-diketone derivative <u>19</u> m.p. 200-202°, $[\alpha]_D$ 124.27°. It produced intense violet colour with neutral ferric chloride solution. This compound developed two spots on the chromatoplate indicating a mixture of two components for both the keto <u>19</u> and the diosphenol <u>20</u> forms. IR showed bands at 3400, 1710 and at 1660 cm^{-1}. Its UV spectra exhibited absorption maxima at 270 nm ($\log \epsilon = 3.90$) and an alkali shift at 328 nm ($\log \epsilon = 3.84$) respectively.



Section D:

This section deals with partial synthesis of the degraded product from a nor-triterpene, baccatin, starting from oleanolic acid.

Treatment of baccatin 21 m.p. 228-229°, $[\alpha]_D$-9.09° with methanolic alkali gave the homoannular conjugated diene 22, $C_{29}H_{46}O_2$ and this on acetylation afforded the diene diacetate 23, $C_{33}H_{50}O_4$. Treatment of the latter with a mixture of hydrochloric acid and acetic acid gave a compound 24, $C_{33}H_{50}O_4$, m.p. 189-190°. The UV absorptions of the compound λ_{max}^{MeOH} 237 (ϵ, 27000), 244(ϵ, 28,300) and 252 nm (ϵ, 20,200) thereby suggesting the presence of a heteroannular conjugated system of the rearranged product. The NMR spectrum (100 MHz) of the rearranged product showed signals at 0.85 - 1.14 ppm (7 tertiary methyl groups), 1.96, 2.0 ppm (6H, 2-$OCOCH_3$) unsymmetrical doublet at 4.64, 4.75 ppm (H on acetoxy bearing C-3), quartet of doublets at 4.95, 5.03, 5.08, 5.2 ppm (H on acetoxy bearing C-3) and 5.46 ppm (1H, vinyl proton). The mass spectrum of the rearranged product showed significant peaks at m/e 510 (M^+), 495 (M^+ -15), 450 (M^+ -60), 435 (M^+ -60-15), 390 (M^+ -60-60), 375 (M^+ -60-60-15), 308, 202, 188. On the basis of these data, the structure of the rearranged product was assigned to be 2α, 3β-diacetoxy-28-nor-oleana-12, 17 diene 24 by Khastgir[38,39].

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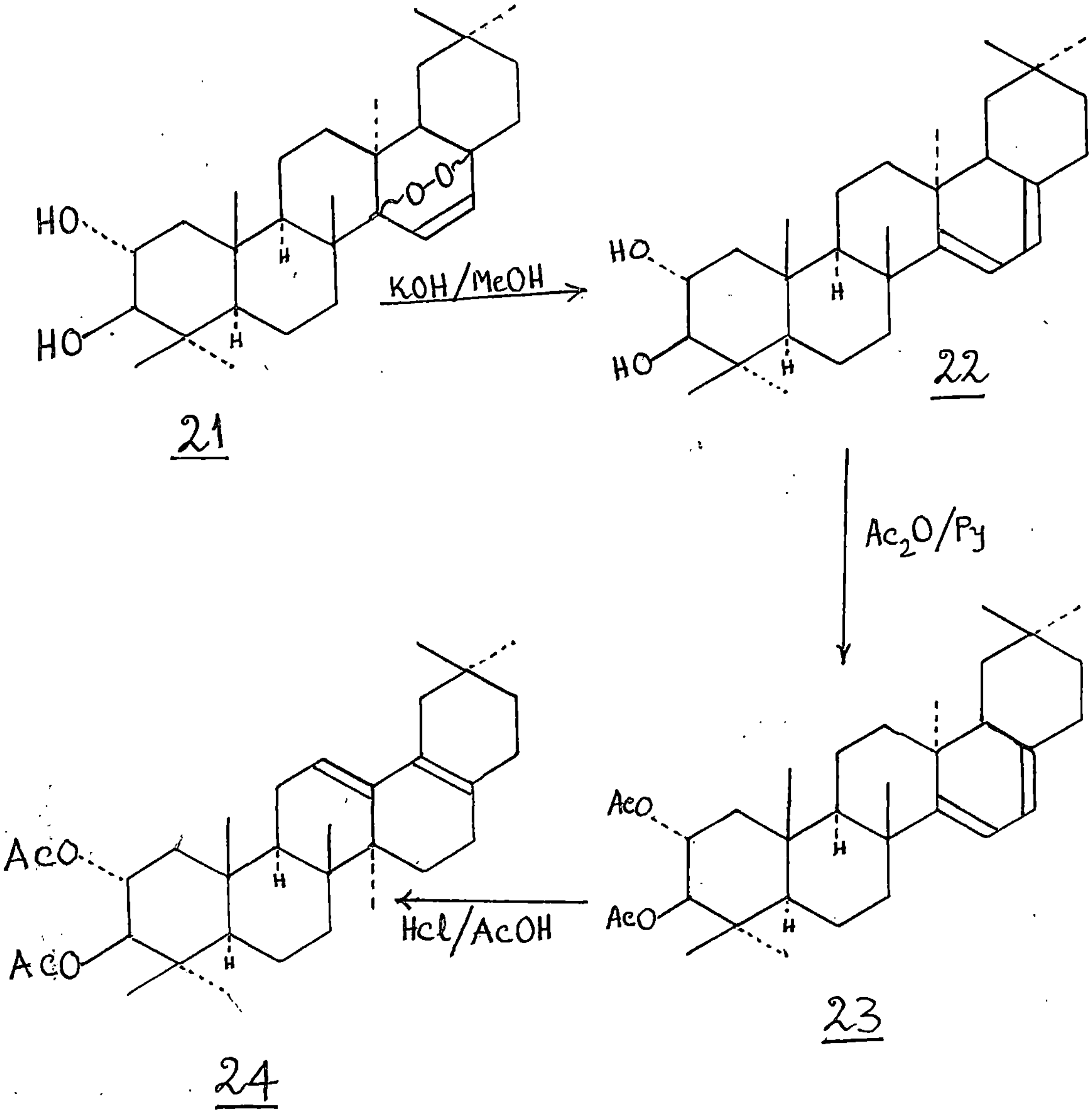
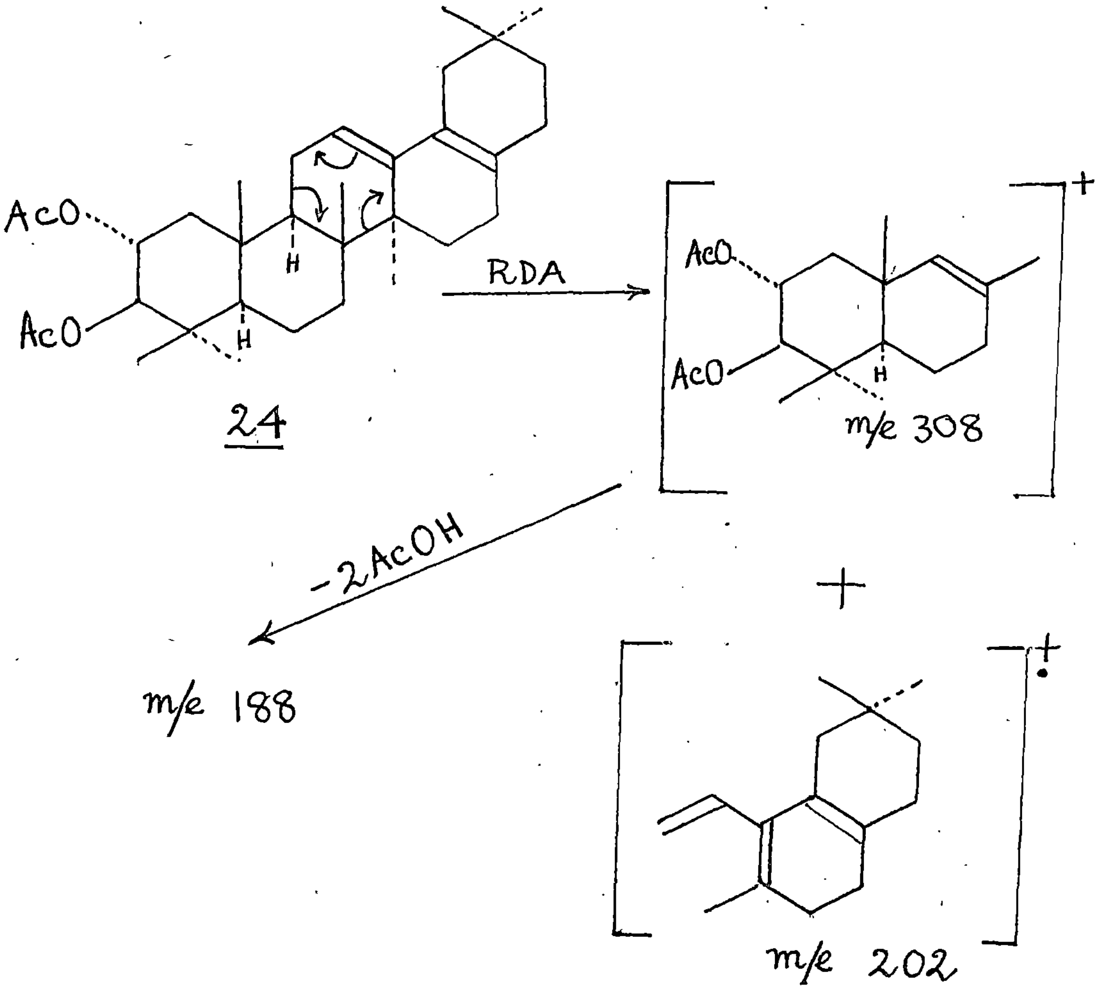
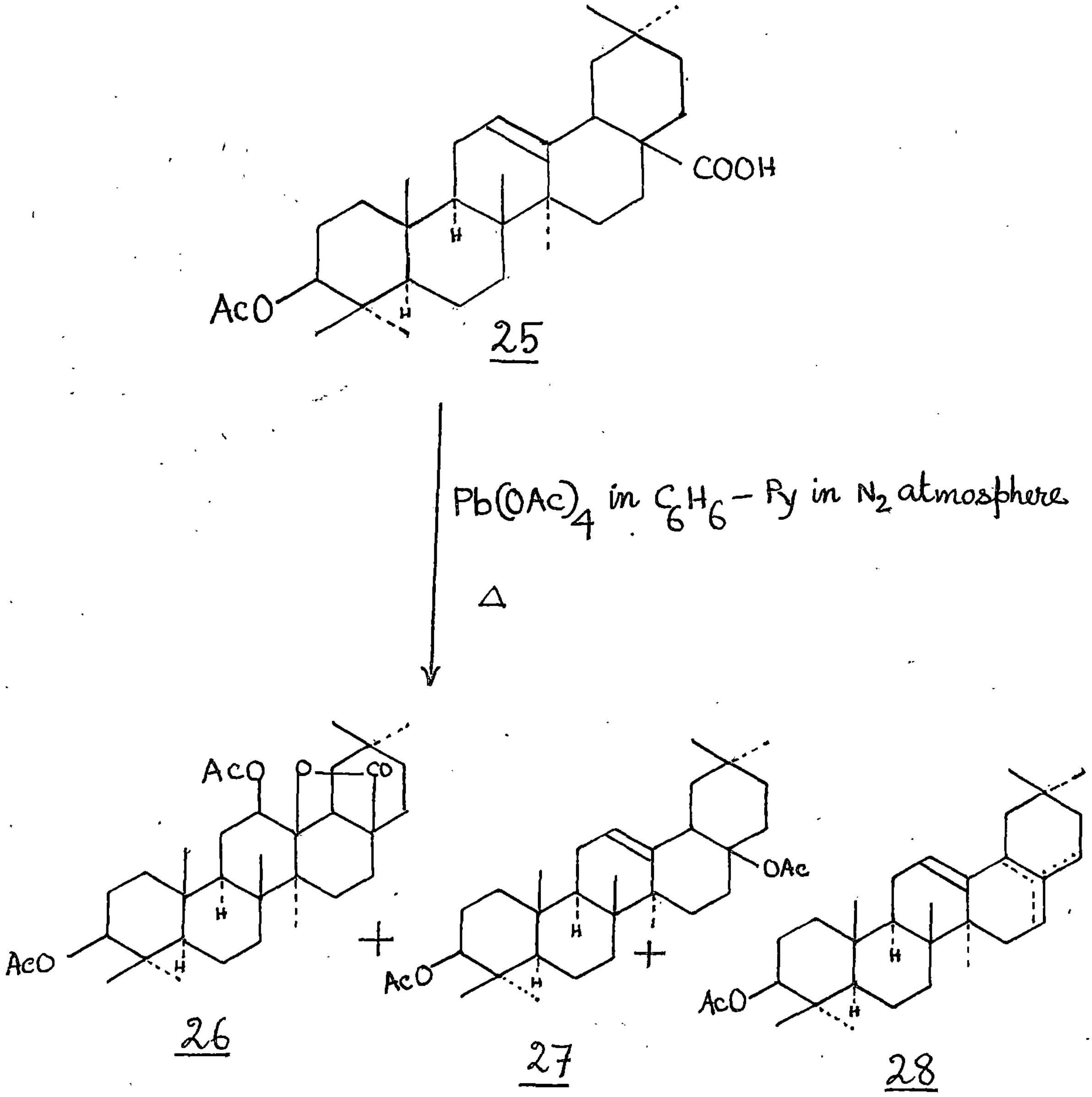

HO
HO
H
H
~O-O~
21
KOH/MeOH
HO
HO
H
H
22
Ac2O/Py
AcO
AcO
H
H
23
HCl/AcOH
AcO
AcO
H
H
24

The mass fragmentation pattern of the rearranged product 24 was explained as follows.



In order to correlate the above observation, Khastgir et al[38,39] prepared a similar system starting from acetyl oleanolic acid.

Oxidative decarboxylation of acetyl oleanolic acid 25 with lead tetraacetate by the method of Cambie et al[41] gave the lactone diacetate 26, the diacetate 27 and the mixture of monoacetates represented by 28.



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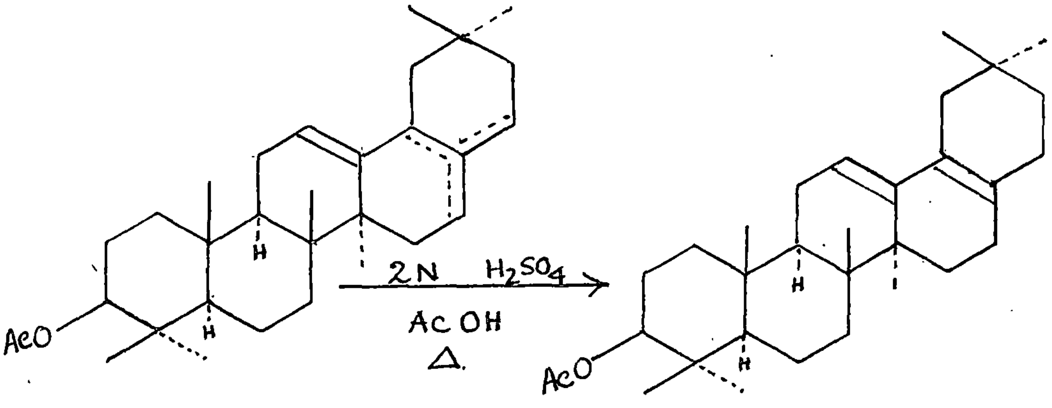
28

When the mixture of monoacetates 28 was heated with 2(N)H_2SO_4 in acetic acid it rearranged to single thermodynamically more stable heteroannular conjugated diene monoacetate 29 m.p. 177-78°, IR: ν_{max}^{nujol} 1710, 1245 cm^{-1} (acetate), UV: λ_{max}^{MeOH} 237 (ϵ 27,090), 243 (ϵ 29,180), 252 nm (ϵ 25,530). The NMR spectrum of this compound showed signals at 0.82, 0.92, 1.15 (21H, seven tertiary methyl groups); 2.01 (3H, $-OCOC\underline{H}_3$), doublet at 4.74, 4.82 ($\underline{H}$ - C_3-$OCOCH_3$) and 5.45 (1H, vinyl proton) ppm. On this basis the structure 29 was assigned to the rearranged product by Khastgir *et al*[39].



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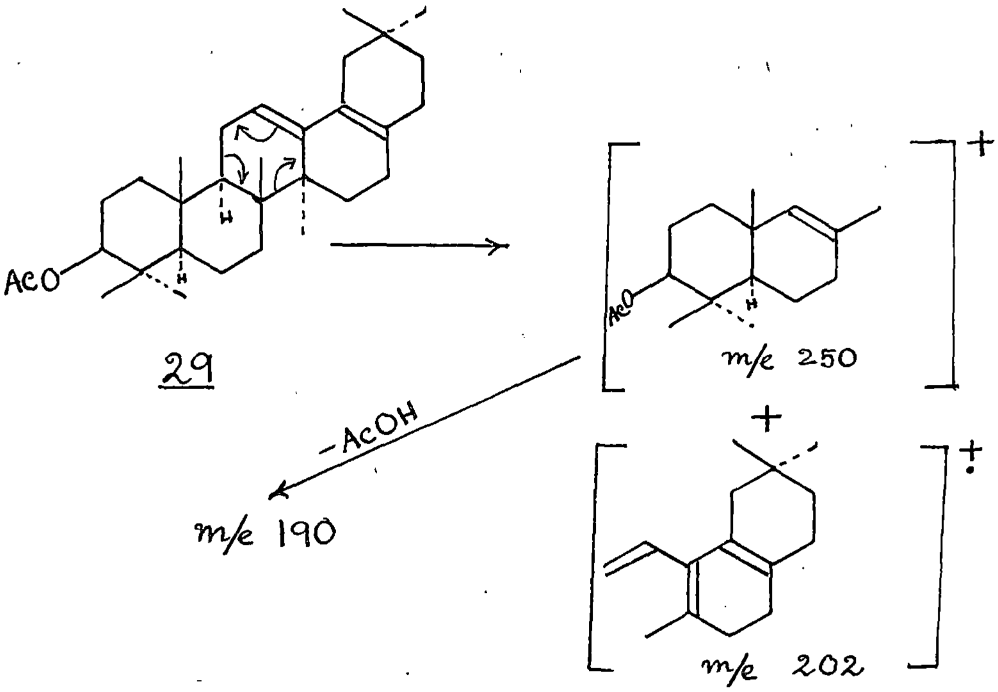
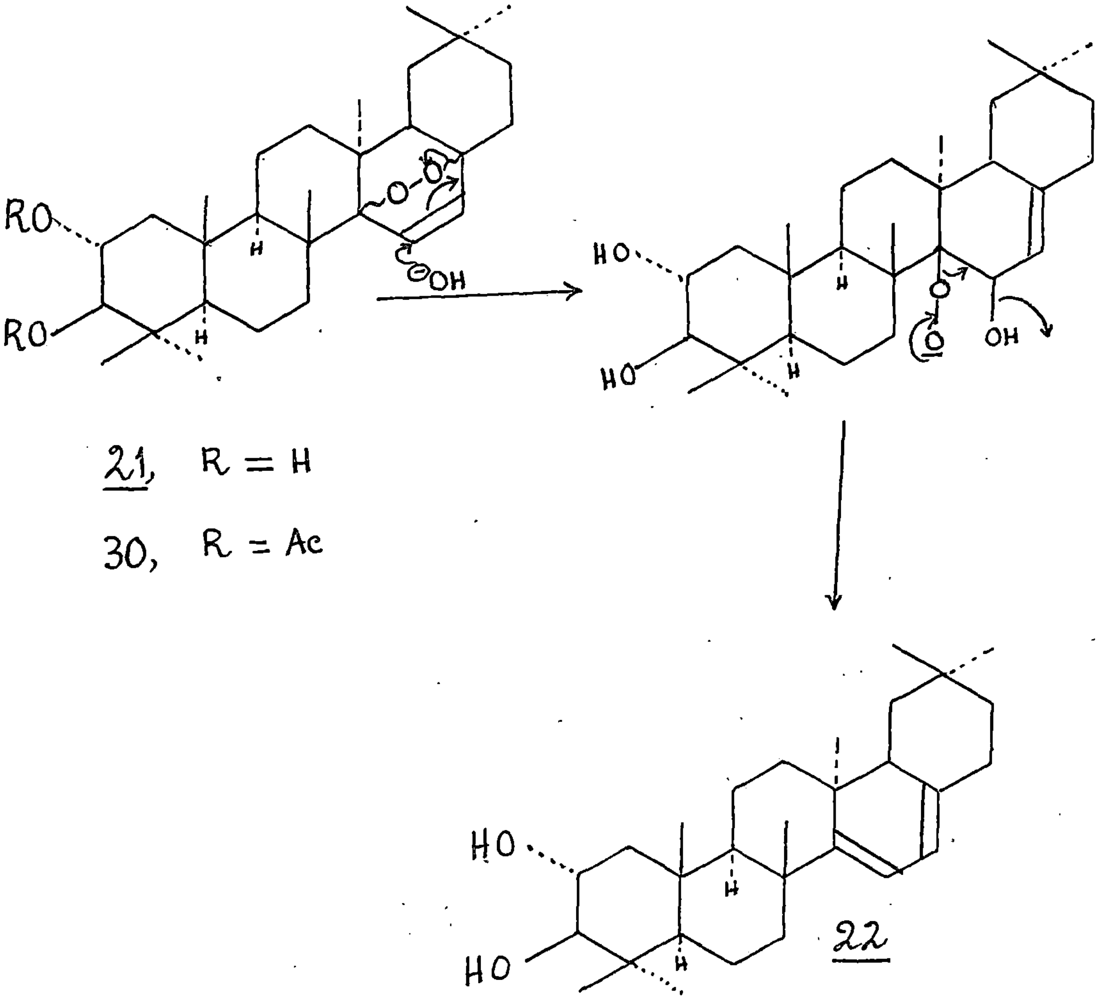
29

If the peaks at m/e 202 and 188 are indeed the diagnostic of structure <u>24</u>, it is expected that <u>29</u> which has the same skeleton as that of <u>24</u> should exhibit peaks at m/e 202 and 190 corresponding to the following fragmentation.



In accordance with the above expectation the mass spectrum of <u>29</u> showed prominent peaks at m/e 452 (M^+), 437 (M^+ -15), 392 (M^+-60), 377 (M^+-60-15), 202 and 190. Hence the structure <u>24</u> for the rearranged diene diacetate was confirmed which in turn confirms the structure <u>22</u> for the homoannular conjugated diene obtained by the alkali treatment of baccatin which must have structure <u>21</u>

Khastgir et al[39] have also proposed a probable mechanism for the transformation of baccatin 21 or its diacetate 30 to the homoannular conjugated diene 22 by the treatment with methanolic alkali as shown below.

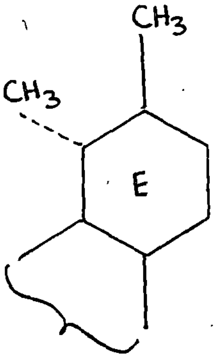


21, R = H

30, R = Ac

22

Though the structure of baccatin 21 had been correlated by comparing the mass fragmentation pattern of its degraded product i.e. 2α, 3β-diacetoxy-28-nor-oleana-12, 17 diene 24 with that of 3β- acetoxy-28-nor-oleana-12, 17 diene 29 a degraded product from acetyl oleanolic acid, it was felt pertinent to correlate further by chemical evidence. Because of the fact that the presence of an ursane-type E ring such as shown in 31 in the heteroannular diene 24 (and consequently in baccatin) could also explain the mass fragmentation pattern and other physical data to a fair degree of accuracy. It was therefore, thought that it was necessary to prove that 24 (and consequently baccatin) indeed contained an oleanane-type E ring as shown in 32.



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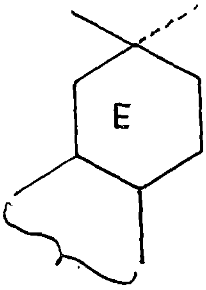

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In order to establish the structure of baccatin by chemical evidenee, the rearranged heteroannular diene diacetate 24 obtained from degradation of baccatin had been further degraded to 2α, 3β dihydroxy-28-nor-oleana-12, 17 diene 33, $C_{29}H_{46}O_2$, m.p. 192-195°. IR showed significant bands at 3240 (-OH), 1055, 830 cm^{-1}. UV showed absorptions at λ_{max}^{MeOH} 237 (ϵ, 25,000), 244 (ϵ, 26,200) and 252 nm (ϵ, 20,100). This on oxidation with Jone's reagent gave 2,3-dioxo-28-nor-oleana-12, 17 diene 34, $C_{29}H_{44}O_2$, m.p. 205-206°. UV showed absorption maxima at λ_{max}^{MeOH} 237, 244, 252 and 271 nm and an alkali shift at 326 nm. IR spectrum exhibited significant bands at 3400, 1700 and at 1650 cm^{-1}. It developed itense violet colour with neutral ferric chloride solution indicating the presence of diosphenol system 35.

3β-acetoxy-28-nor-oleana-12, 17 diene 29 that might contain minor amount of 27 (obtained from acetyl oleanolic acid) was then hydrolysed with potassium tertiary butoxide and dimethyl sulfoxide following the method of Chang and Wood[42] so as to hydrolyse both C-3 and C-17 acetoxy groups for easy separation which was then chromatographed and crystallised to give 3β-hydroxy-28-nor-oleana-12, 17 diene 36 as major product, $C_{29}H_{50}O$, m.p. 182-183°. UV spectrum showed absorptions at λ_{max}^{MeOH} 237 (ϵ 8150), 244 (ϵ 8340), 252 (ϵ 8020) nm. IR spectrum exhibited significant peak at ν_{max}^{nujol} 3380 cm^{-1} (-OH). This was oxidised by chromium trioxide-pyridine complex to 3-oxo-28-nor-oleana-12, 17 diene 37, $C_{29}H_{48}O$, m.p. 110-112°. IR exhibited band at ν_{max}^{nujol} 1700 cm^{-1} ($>C = O$). This on treatment with isoamyl nitrite in presence of potassium tert. butoxide afforded 2-oximino-3-oxo-28-nor-oleana-12, 17 diene 38, m.p. 220-225° which could not be crystallised from any usual solvent.

IR spectrum of this crude compound exhibited bands at ν_{max}^{nujol} 3200 (N-OH), 1700 ($>C = O$), 1635 ($C = N$) cm^{-1}. This was hydrolysed with freshly distilled pyruvic acid in presence of dilute acetic acid to give 2,3-dioxo-nor-oleana-12, 17 diene 34 m.p. 205-206°. This was found to be identical throughout the IR region with that of the degraded product 34 from baccatin. The mixed melting point showed no depression of melting point as well as the G-tlc was same. This confirmed the carbon skeleton of baccatin to belong to the oleanane series.

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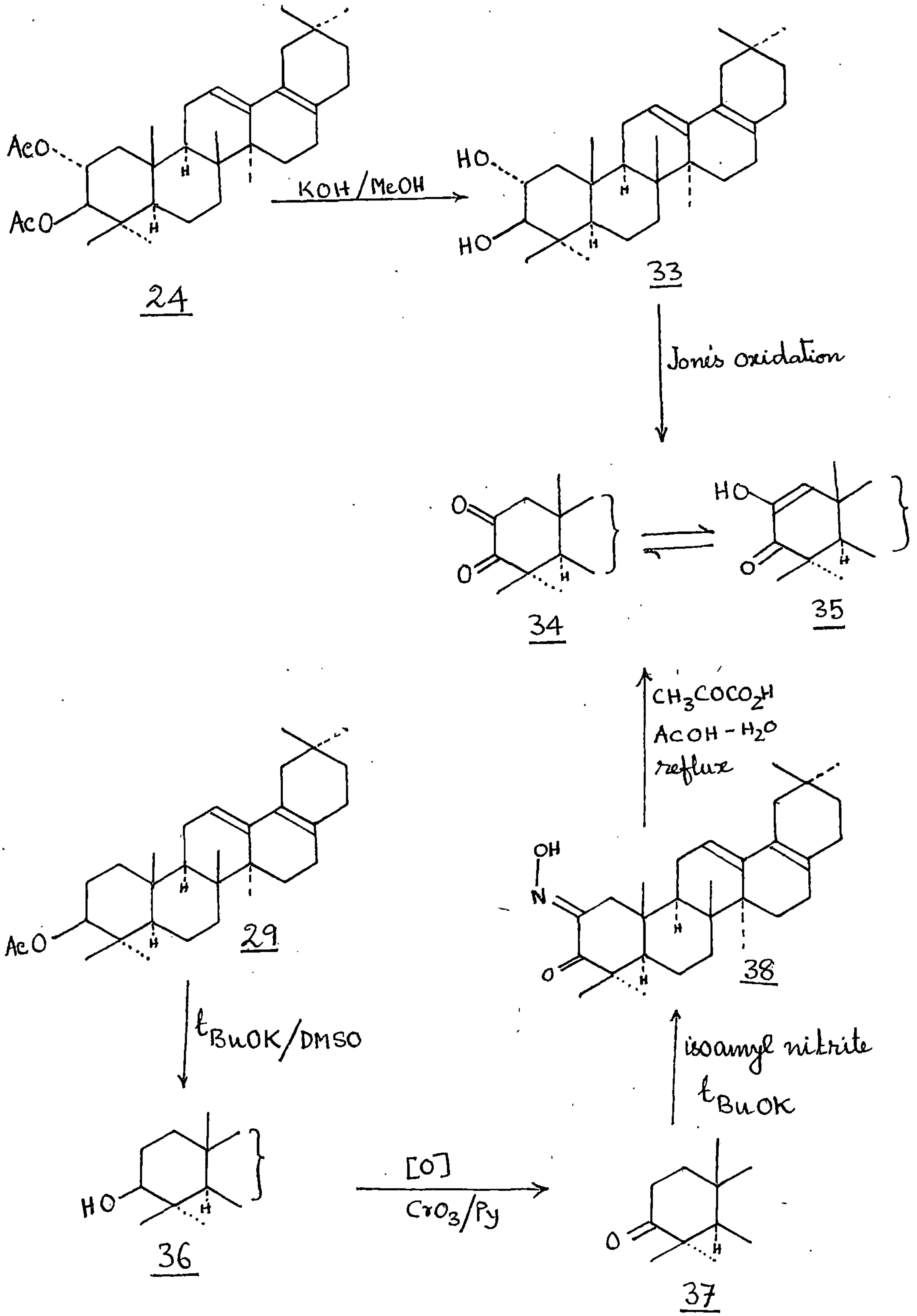
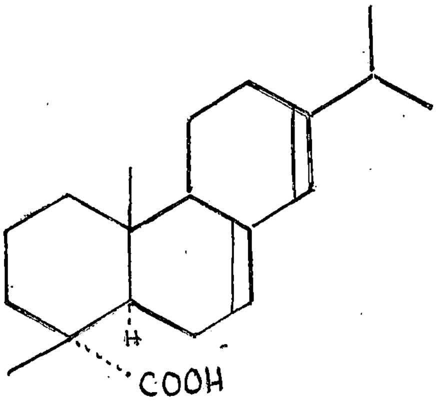

AcO
AcO
H
H
24
KOH/MeOH
HO
HO
H
H
33
Jone's oxidation
O
O
H
34
HO
O
H
35
CH$_3$COCO$_2$H
AcOH - H$_2$O
reflux
AcO
H
H
29
tBuOK/DMSO
OH
N
O
H
H
38
isoamyl nitrite
tBuOK
HO
H
36
[O]
CrO$_3$/Py
O
H
37

CHAPTER -III describes the experimental section.

C. PART - III deals with attempted total synthesis of C_{11}-acid 39 a degraded product of abietic acid 40



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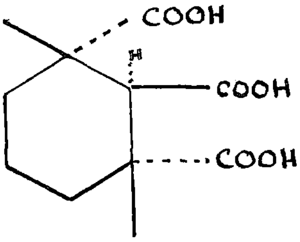

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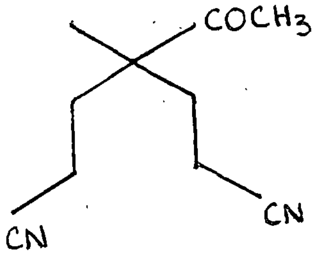
Section B deals with the scope~~s~~ of the present work which is briefed as follows.

Bruson et al prepared 4-methyl-4-acetyl-pimelonitrile 41 by cyanoethylation of ethyl methyl ketone in presence of methanolic potassium hydroxide. The pimelonitrile 41 thus obtained on hydrolysis with potassium hydroxide followed by acidification afforded the diacid 42 which on oxidation with calcium hypochlorite (80% available chlorine H.T.H. quality) furnished the triacid 43.



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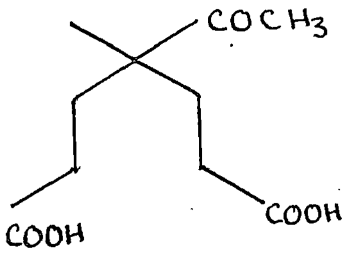

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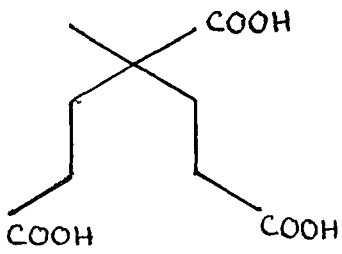
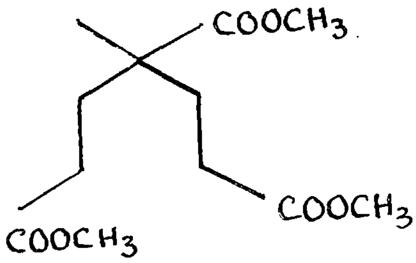
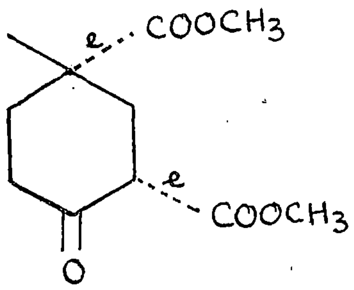


43

The triacid 43 is expected that on esterification with diazomethane it would result the triester 44. This on Dieckmann cyclisation should provide us the β -keto ester 45.



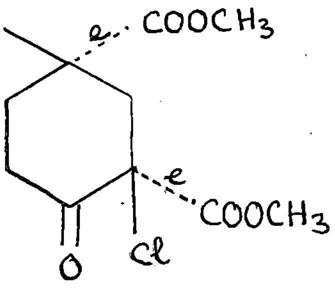
44



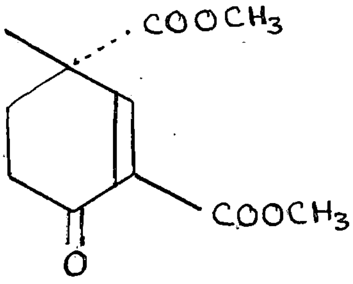
45

Examination of Drieding model of β-keto ester 45 favours the conformation as indicated above.

Stereoselective halogenation of 45 with sulphuryl chloride would provide us the chloro keto ester 46. This on dehydrohalogenation with base collidine is expected to result the $\alpha\beta$ unsaturated ketone 47.

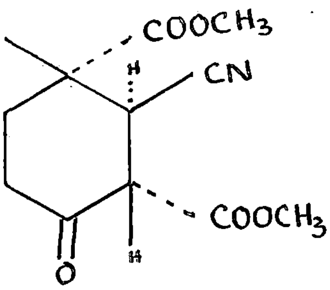


46

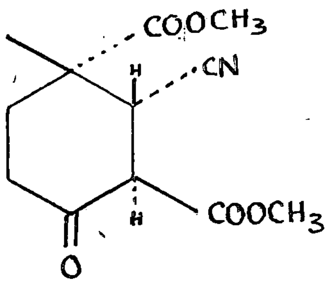


47

Hydrocyanation of 47 with potassium cyanide in presence of ammonium chloride and dimethyl formamide would result a pair of stereoisomers 48 and 49. The desired isomer 48 is expected to be predominant[14b].

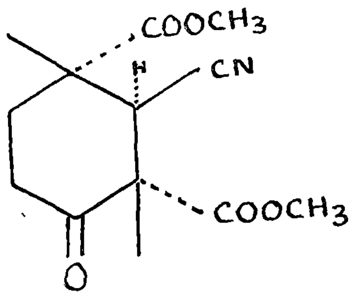


48



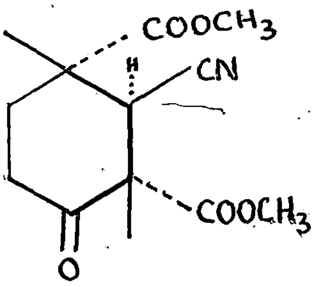
49

After separating 48, introduction of angular methyl group could be carried out by treatment of 48 with methyl iodide in presence of base. Thus 50 would result.

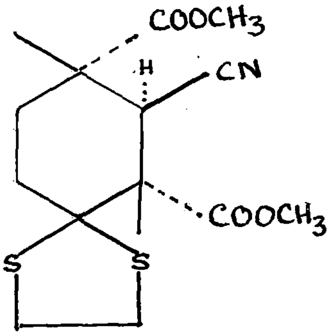


50

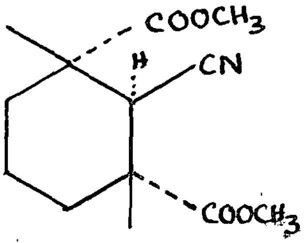
Reduction of carbonyl group to methylene group from the β-keto cyano ester 50 may be carried out by treatment of 50 with ethane dithiol followed by desulphurisation with Raney Nickel. Thus 51 would be obtained.



50

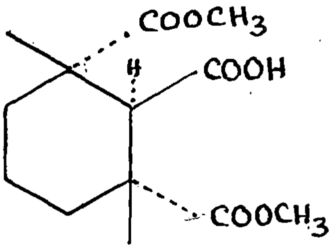


50a



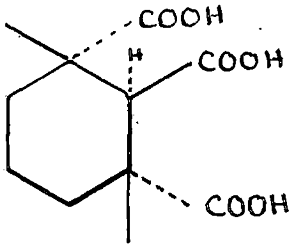
51

51 on hydrolysis with alkali followed by acidification should furnish 52.



52

52 on hydrolysis with dimethyl sulfoxide in presence of potassium tert. butoxide followed by acidification is expected to give C_{11} -acid 53, identical with the degraded product of abietic acid.



53

CHAPTER - II describes the attempted synthesis of C_{11}-acid, a degraded product of abietic acid.

Cyanoethylation of ethyl methyl ketone with freshly redistilled acrynitrile in presence of methanolic potassium hydroxide furnished 4-acetyl 4-methyl pimelonitrile 41 m.p. 67°C. IR showed significant bands at 2230 ($C \equiv N$ stretching), 1700 ($>$C = 0 stretching)cm^{-1}. This on hydrolysis afforded the diacid i.e. γ -methyl γ-acetyl pimelic acid 42 m.p. 125°C. IR showed bands at 1715 (due to $>$C = 0 stretching of -COOH group) 1690 ($>$C = 0 stretching due to another -COOH group), 3020-2610 cm^{-1} (broad O-H stretching). As calcium hypochlorite (HTH quality containing 80%

available chlorine) used by Bruson et al was not available, we oxidised the diacid 42 to triacid 43 by sodium hypobromite and the yield of triacid 43 was found to be better. The triacid 43 on crystallisation from nitromethane afforded colourless crystals m.p. 112°. This on esterification with diazomethane yielded the triester 44 having b.p. 170-72° at 4.5 nm of Hg. TLC showed a single spot. IR showed broad peak at 1720 cm^{-1} (due to $\rangle C = O$ stretching of three carbomethoxy groups).

^1H NMR (90 MHz) spectrum of triester 44 exhibited signals at 1.1 ppm for one methyl group (tert.), two multiplets centred at 2.22 and 1.88 ppm for the two α methylene protons and the other two β methylene protons respectively with respect to terminal carbomethoxy groups. The three carbomethoxy methyl groups appeared at 3.65 ppm as singlet integrated for nine protons.

Dieckmann cyclisation of triester 44 with sodium hydride resulted the β-keto ester 45 having b.p. 132-35° at 2.5 mm of Hg. It produced intense violet colour with neutral ferric chloride solution.

IR showed band at 2940 (due to intramolecular hydrogen bonding between ester $\rangle C = O$ and the enolic hydroxyl group), 1735 cm^{-1} (due to $\rangle C = O$ stretch of the carbomethoxy group).

^1H NMR spectrum (90 MHz) of β-keto ester 45 exhibited signals at 1.2 ppm for one methyl group (tertiary), multiplets centred at 2.4 ppm for methylene proton adjacent to carbonyl group; multiplets centred at 3.22 ppm for one methine proton adjacent to carbonyl group and carbomethoxy bearing carbon atom and two sharp singlets one at 3.65 ppm for one carbomethoxy group attached to carbon bearing methyl group and the other at 3.72 ppm for one carbomethoxy group adjacent to carbonyl group, 2.75 ppm for methylene protons at C-3 and 2.09 ppm for methylene protons at C-5.

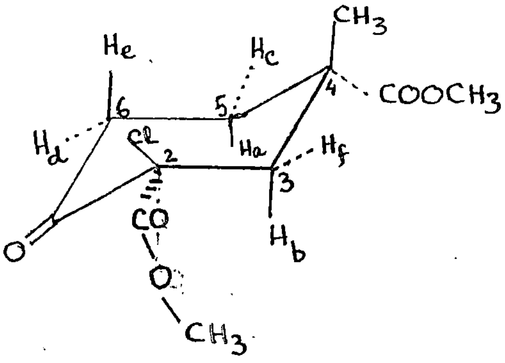
Introduction of halogen (Cl) to the more substituted carbon atom α to carbonyl group was carried out by treatment of the β-keto ester <u>45</u> with freshly distilled sulphuryl chloride in presence of dry carbon tetrachloride. After usual work up a gummy colourless solid was obtained. This was chromatographed over active silica gel column. Petrol+benzene (9:1) elute afforded a colourless solid. TLC showed a single spot. This on multicrystallisation from methanol afforded fine needle shaped crystals m.p. 100°C of 2-chloro-4-methyl cyclohexanone 2:4 dimethyl dicarboxylate <u>46</u>.

This gave positive Beilstein test for halogens. Infrared spectrum of the compound showed significant band at 1720 cm^{-1} (due to $>C=O$ stretch of carbomethoxy group).

80 MHz ^1H NMR spectra of the α chloro keto ester <u>46</u> showed a strong peak due to a tertiary methyl group at 1.25 (3H, $C\underline{H}_3$) ppm, at 3.67 (3H, $COOC\underline{H}_3$) ppm due to

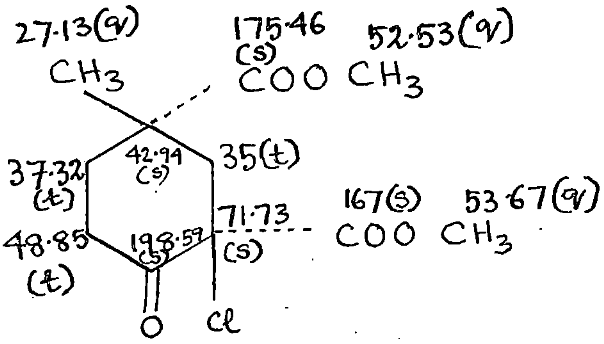
carbomethoxy group attached to the carbon atom bearing methyl group and at 3.72 (3H, $COOCH_3$) ppm due to carbomethoxy group attached to carbon atom bearing chlorine.

Figure 10 indicated the axial (H_e) and equatorial (H_d) protons of carbon atom 6 at 3.04 and 2.59 ppm respectively. It also showed the axial (H_a) and equatorial (H_c) protons of carbon atom 5 at 1.67 and 2.4 ppm respectively. It further showed the axial (H_b) and equatorial protons (H_f) of carbon atom 3 at 2.09 and 3.34 ppm respectively. From the coupling constants of the system ABCDEF, the coupling constants (J) of AB (0.00), AC (14.00), AD (4.50), AE (13.69), AF (0.00), BC (0.00), BD (0.00), BE (0.00), BF (14.30), CD (3.79), CE (5.69), CF (3.00), DE (15.00), DF (0.00) and EF (0.00) clearly deduced the conformation of α-chloro keto ester molecule 46 as indicated below (A)



A

^{13}C NMR spectra of the compound 46 showed that there are eleven carbon atoms in the molecule. The ^{13}C peaks of the α-chloro keto ester 46 are assigned in the structure B given below.



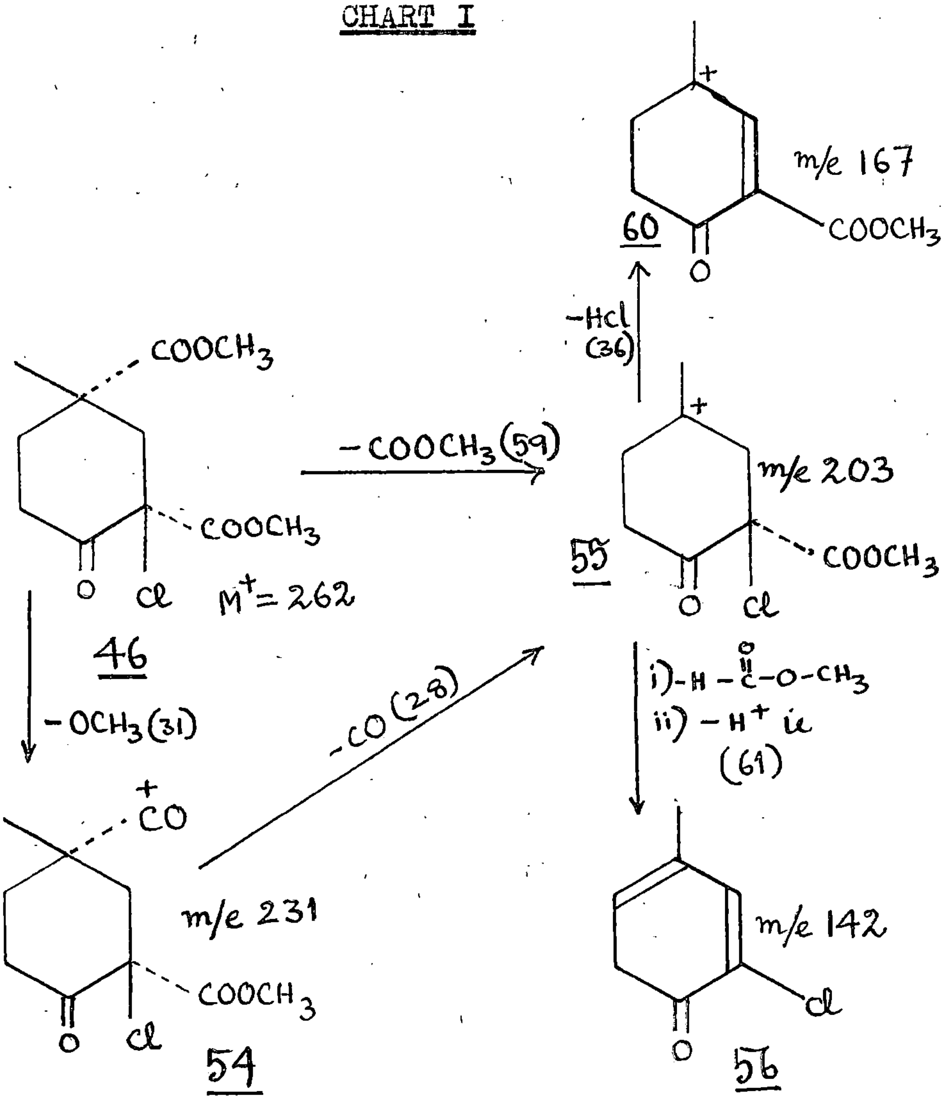
B

s = singlet, t = triplet

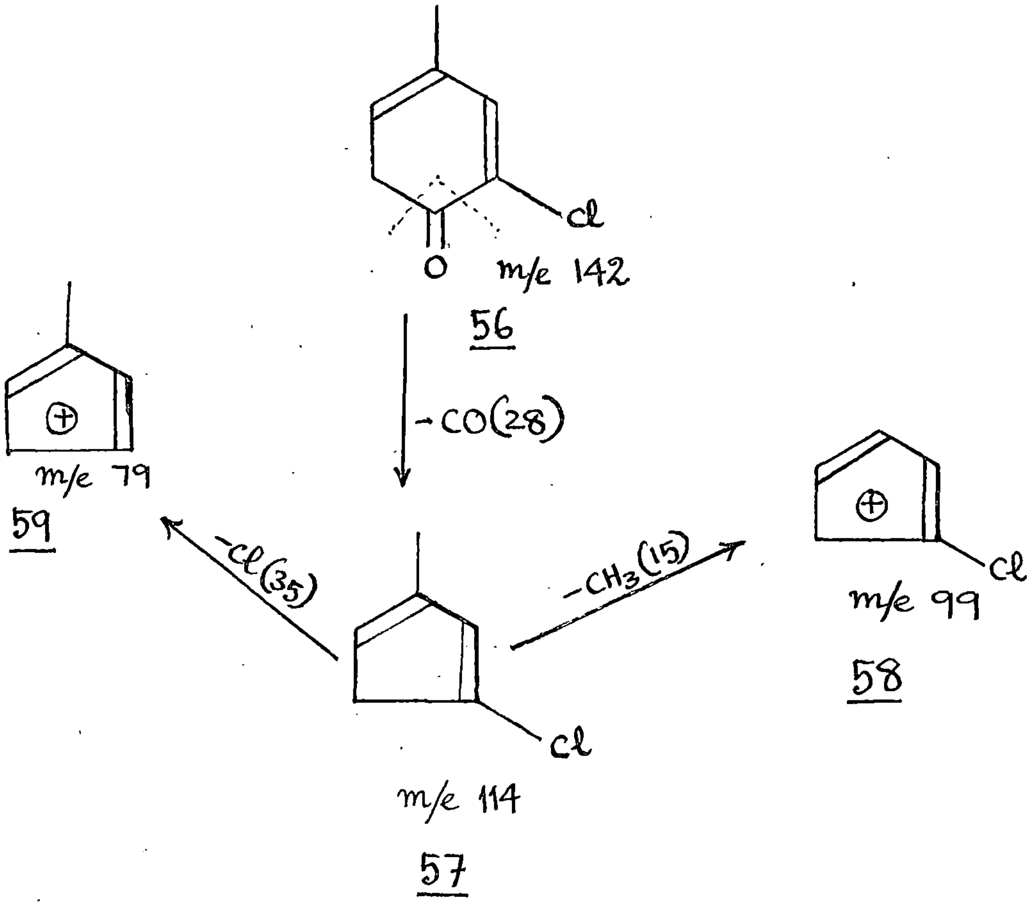
q = quartet.

The molecular ion of the α-chloro keto ester 46 has been found to be (M^{+} = 262) by the chemical ionisation method (methane ionisation). Ion peak at m/e 231 due to fragment 54 formed by the loss of -OCH$_3$ (i.e. 31 mass unit) from the molecular ion. Fragment 54 lo~~o~~ses CO to furnish the fragment 55 which is also obtained by the loss of carbomethoxy group (59) from the molecular ion to give ion peak at m/e 203. The peak at m/e 142 arises due to fragment 56. Further loss of CO (28) results fragment 57 responsible for the ion peak at 114. Loss of a methyl radical (mass unit 15) gives the fragment 58 responsible for the ion peak at m/e 99. Loss of chlorine (35) from m/e 114 affords fragment 59 responsible for the ion peak at m/e 79. Loss of HCl (36) from the ion peak at m/e 203 resulted the most abundant fragment 60 responsible for the ion peak at m/e 167. The mass fragmentation pattern of the α chloro keto ester 46 has been depicted in the following Chart I.

CHART I



(XXXXI)



The α-chloro keto ester was gradually heated to reflux with collidine at 145-150° under nitrogen atmosphere when a sudden evolution of CO$_2$ gas (the gas collected in balloon was passed through lime water which turned milky) due to decarboxylation with simultaneous separation of collidine N-methyl chloride occurred. After usual work, it was distilled when a liquid having b.p. 142-158° at 5.5 mm of Hg was obtained. This showed UV absorption at 231 and 247 nm characteristic of $\alpha\beta$ unsaturated carbonyl compounds. TLC showed three spots with one spot prominent. The liquid gave positive Beilstein test for halogens.

80 MHz ^1H spectrum of the liquid showed strong peak due to tertiary methyl group at 1.22 ppm and a carbomethoxy peak at 3.7 ppm. A pair of doublets at 4.6 ppm (J = 13 Hz) is due to CH bonded to chlorine ortho to carbonyl group and the triplets centred at 1.75 ppm which has the same spacing (J = 13 Hz) as the larger spacing in the pair of doublets suggesting that these protons are coupled together with 13 Hz coupling constant. Since coupling this large requires a 180° dihedral angle it is concluded that the two adjacent protons are axially oriented.

The lines centred at 2.8 ppm are due to C-3 equatorial hydrogen which has coupling constant 12 Hz (geminal with C-3 axial protons) and 6 Hz (vicinal with C-2 axial proton).

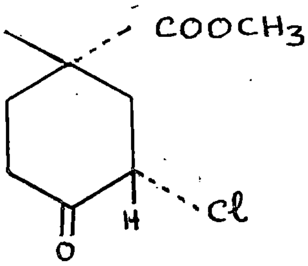
The complexity of methoxyl region and methyl region suggests that the liquid is a mixture of compounds with one predominant species present to 50-60 percent.

The ^{13}C NMR spectra confirms this view.

The NMR data obtained are consistent with the following structure <u>61</u>.

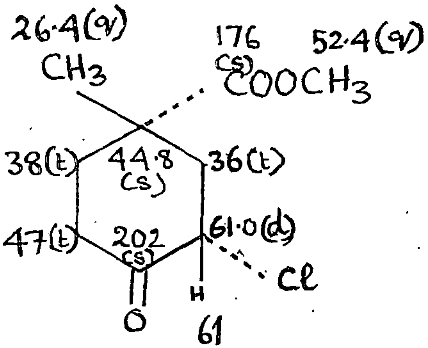
(XXXXIII).

for the predominant species



61

The ^{13}C peaks of 61 are assigned as below



61

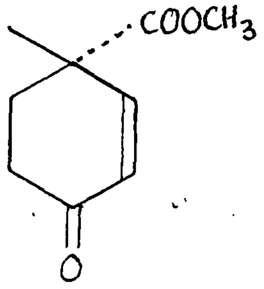
s = singlet

t = triplet

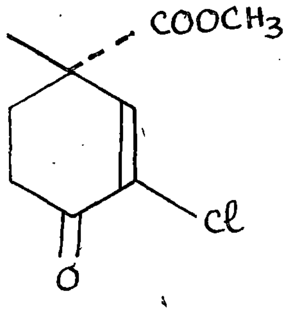
q = quartet

d = doublet

The small lines between 130 and 150 ppm are all doublets, hence they are protonated double bonded carbons. These are due to possible side products 62 and 63 present as minor components in the mixture which would be responsible for the UV absorptions of 231 and 247 nm respectively.

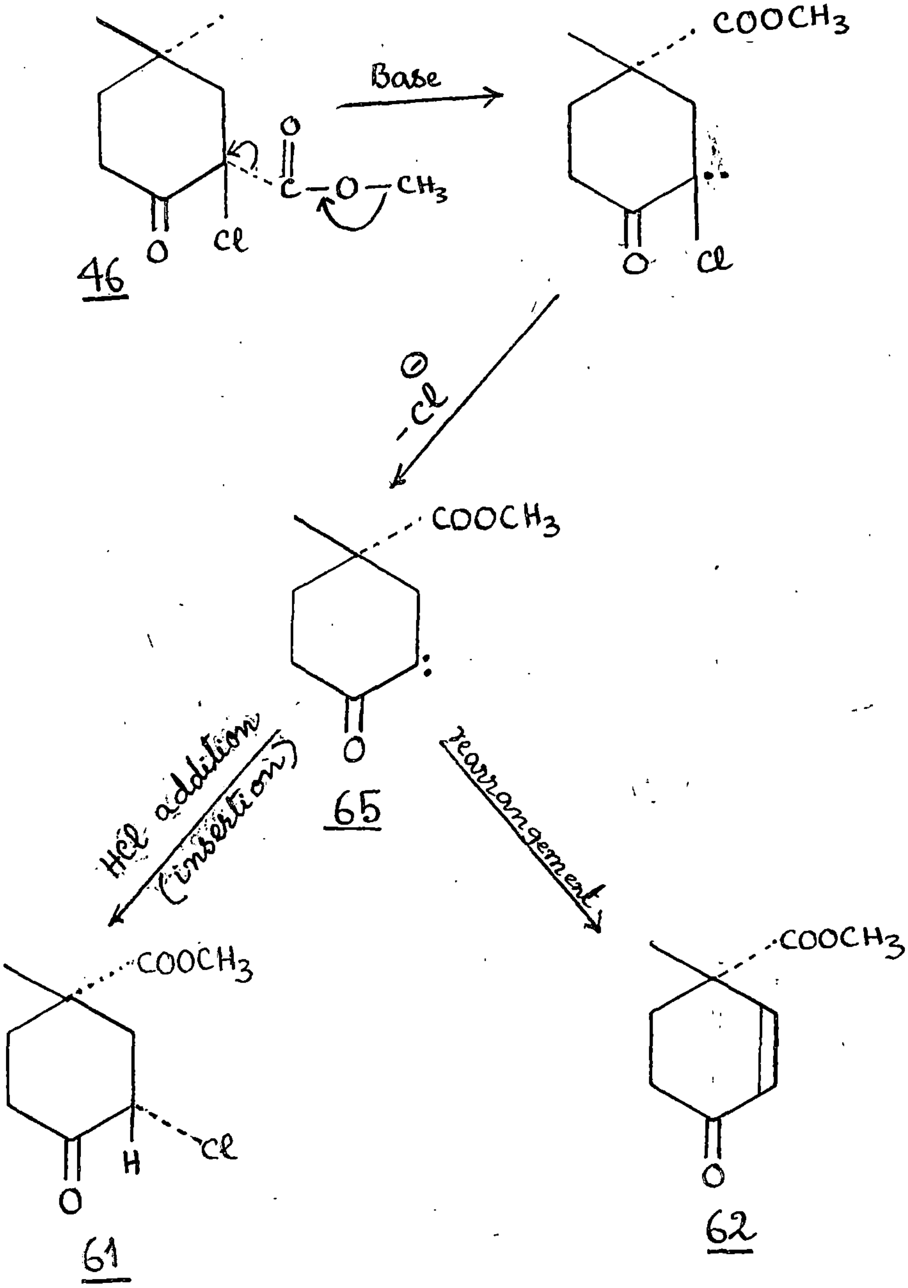


62



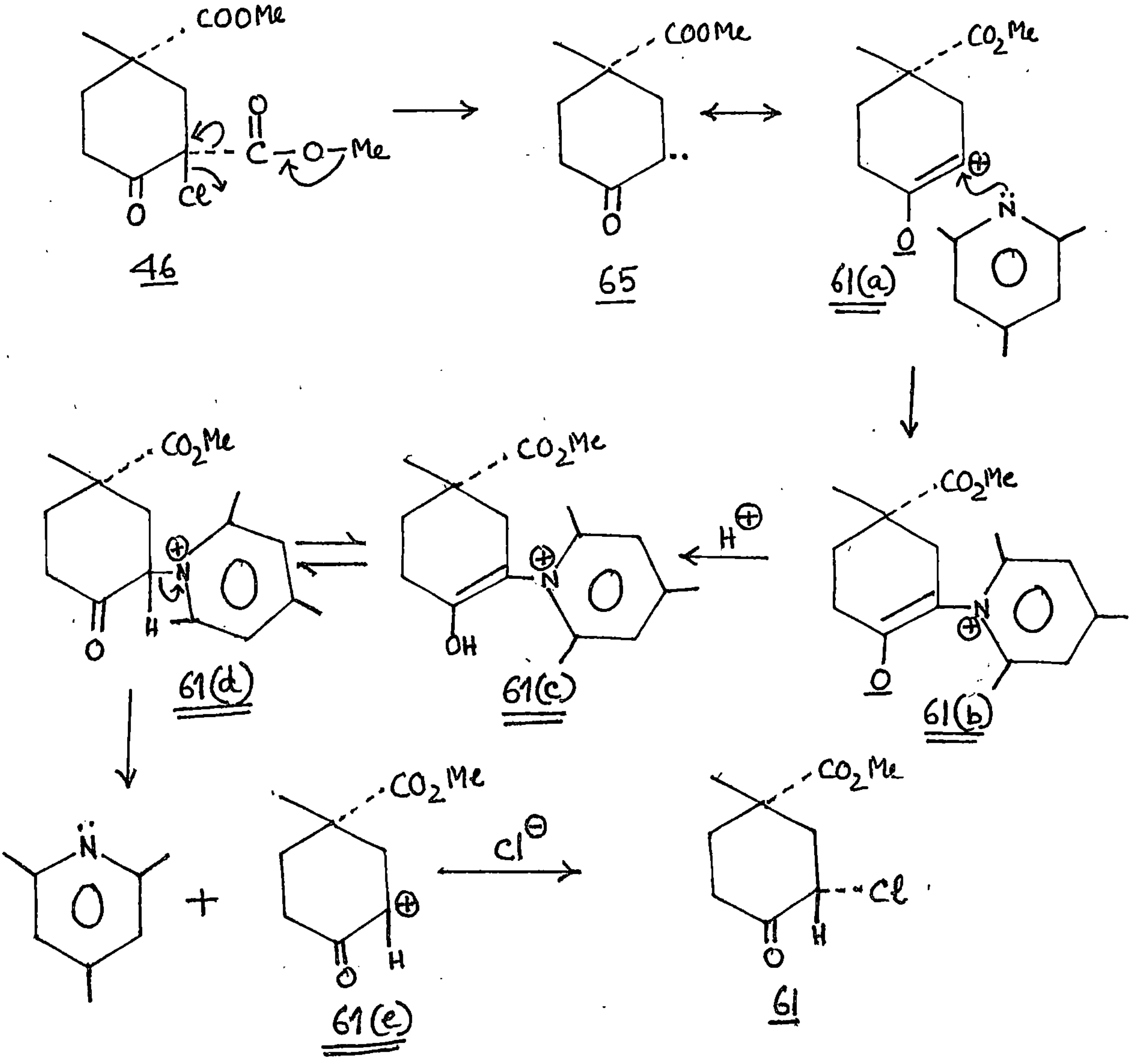
63

The plausible mechanism for the formation of major product 61 and the minor product 62 has been explained through carbene intermediate 65 as follows:



Addendum 1

A more plausible mechanism for the formation of α-chloro ketone 61 may be via the formation of dipolar ion 61(a) which in presence of collidine will behave as an electrophile to give the corresponding dipolar ion 61(b). This salt may be stable enough to react with dil HCl to form the enol 61(c) which may tautomerise to the keto form 61(d). Intermediate 61(d) eventually loses collidine to form the carbonium ion 61(e) which will react with chloride ion to form 61.



Further, the appearance of minor peaks in the mass spectrum at 202 and 144 confirms the existence of minor products <u>63</u> and <u>62</u> respectively. The mass fragmentations for the main product <u>61</u> ($M^+ = 204$) and the minor product <u>63</u> ($M^+ = 202$) are also discussed.

<u>CHAPTER III</u> describes the experimental section.