PART-I

OXIDATION OF PENTACYCLIC TRITERPENOIDS HAVING DOUBLE BONDS AT C-2 AND C-3 POSITIONS WITH SELENIUM DIOXIDE IN TERTIARY BUTANOL CONTAINING HYDROGEN PEROXIDE.

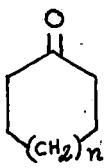
CHAPTER-I

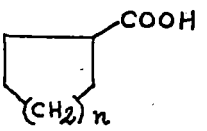
A SHORT REVIEW ON REACTIONS OF SELENIUM-DIOXIDE IN PRESENCE OF HYDROGEN-PEROXIDE.

The selenium dioxide(SeO_2) catalysed reaction of hydrogen peroxide (H_2O_2)has been widely used for performing various oxidative transformations. A brief description of some oxidative transformations are summerised below.

Seguin[1] prepared trans cyclohexanediol free of cis-compound from cyclohexene using H_2O_2 in presence of SeO_2 and also prepared 1,2 diols cyclopentadiene from cyclopentadiene.

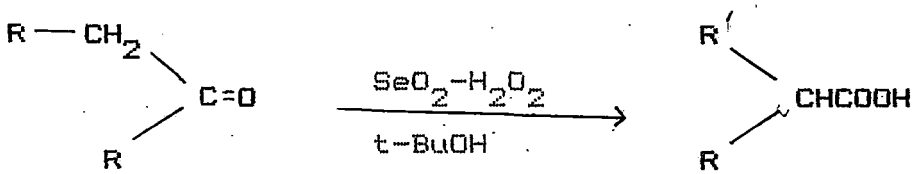
Curtis et al[2] used SeO_2, as catalyst in presence of hydrogen peroxide to oxidise acrolein and methacrolein to monomeric acrylic and methacrylic acids and suggested that at first selenious acid oxidised to selenenic acid with H_2O_2 than that selenenic acid reacted with acrolein to give acrylic acid and selenious acid. Payne et al[3] investigated the oxidation of cycloheptanone,cyclohexanone and cyclo pentanone with SeO_2 in presence of H_2O_2 and anticipated that the cyclic ketones might undergo the well known reaction with SeO_2 giving α-diketones with H_2O_2 serving merely to oxidise selenium metal back to dioxide. They[3] observed that along with other competing reactions,all three ketones underwent oxidative ring contraction to cyclohexane, cyclopentane and cyclobutane carboxylic acids in 34,32 and 23% yields, respectively.





n = 2, 34%
n = 1, 32%
n = o, 23%

Sonoda et al[4] studied oxidation of aliphatic ketones, RCH_2COR' with H_2O_2 in presence of SeO_2 in tertiary butanol solvent(t-BuOH) and got carboxylic acids,RRCHCOOH accompanied by rearrangment of alkyl groups.



Where R = H, R′ = R = alkyl group

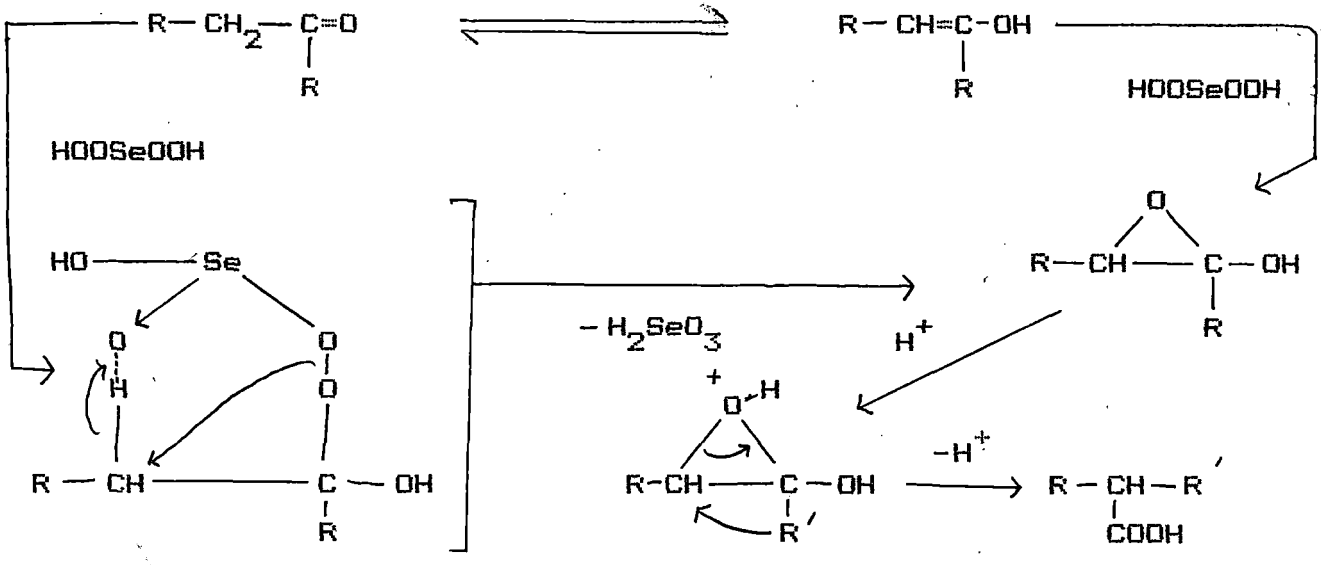
They[4] used acetone, methyl ethyl ketone, methyl-n-propyl ketone, and diethyl ketone as starting material. They suggested that the main rearrangement observed was due to migration of the alkyl group having smaller number of carbon atoms to the α-carbon atom of the larger number of carbon atoms; to the small one also occurred in some degree. These workers shared the view of Hughes and Martin[5] who proposed the formation of peroxy selenious acid **1** from SeO_2 by the action of H_2O_2.

$$SeO_2 + H_2O_2 \rightleftharpoons HOOSeOOH$$

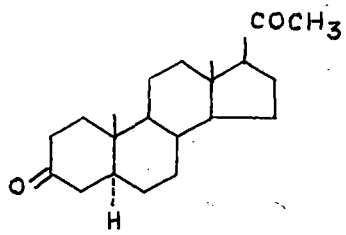
1

The following mechanism was presumed by these workers as shown in scheme -I

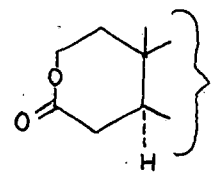
SCHEME-I



Caspi et al[6,7] reported that steroidal 3-Ketones in the 5α and 5β-series with H_2O_2 in presence of SeO_2 gave ring-A contracted acids and products of bond scission on either side of the carbonyl group. The compound with A/B - trans junctions, 17β- acetoxy 5α- androstan -3-one **2a** gave lactone **3** and two carboxylic acids **4** and **5**. The oxidation of 17β-acetoxy -5β- androstan -3- one **2b**, gave lactone **6** as single product.



2a = 5α, 2b = 5β,



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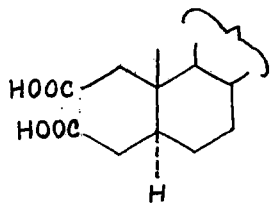

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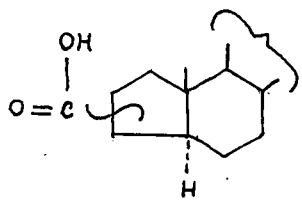

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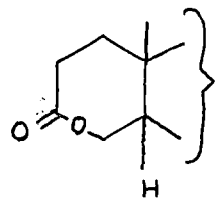
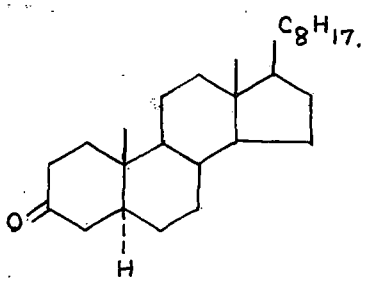


6,

Jerussi et al[8] studied the oxidation reaction of 5α-cholestan-3-one 7 with selenenic acid and 30% H_2O_2 in tertiary butanol. They found a complex mixture of acids which on esterification gave 2α- carbomethoxy -A-nor- 5α- cholestane, 8 in 35% yield, 3β- carbomethoxy-A-nor-5α- cholestane 9 in 4% yield and methyl 2,3-seco-5α-cholestane 2,3 - dioate 10a in 8% yield.



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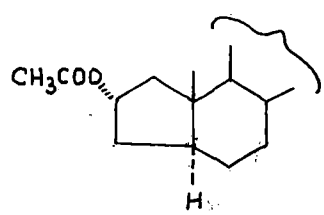

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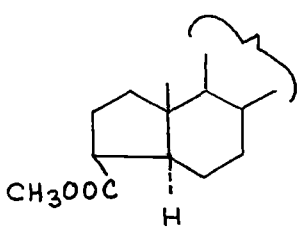

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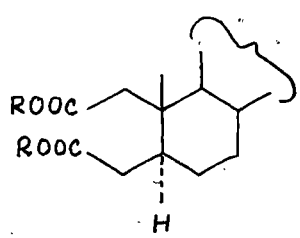
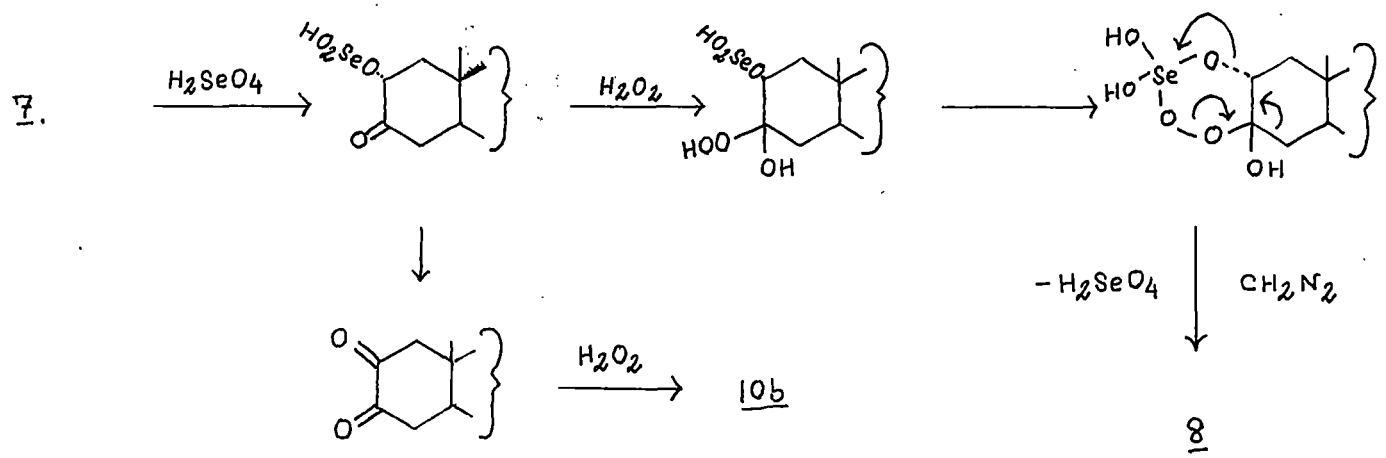


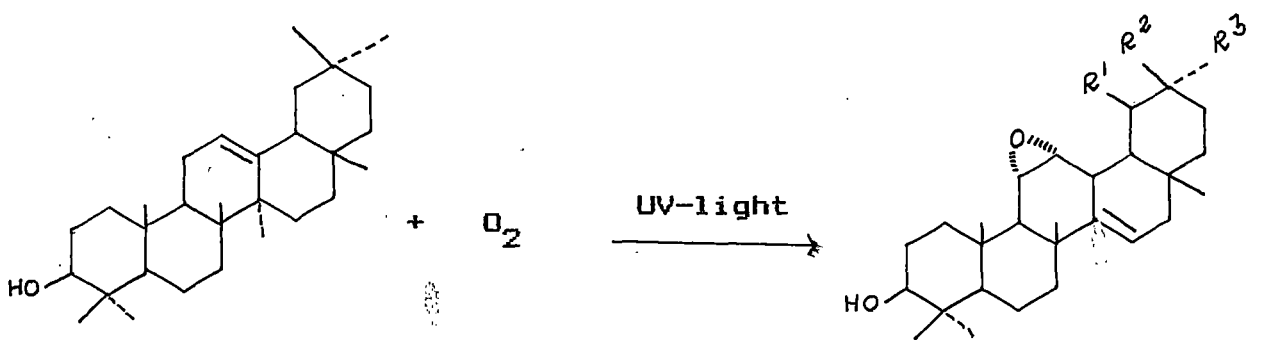
10a, R=CH_3, 10b, R=H.

The mechanism proposed by Jerussi et al[8] are summerised in the Scheme -II

SCHEME-II



Corey et al[9] reported the formation of a new photoxidation product 12, obtained by irradiation of acidified ethanolic solution of β-amyrin 11 for 2-3 weeks with Ultra - Violet Lamp (through pyrex glass)



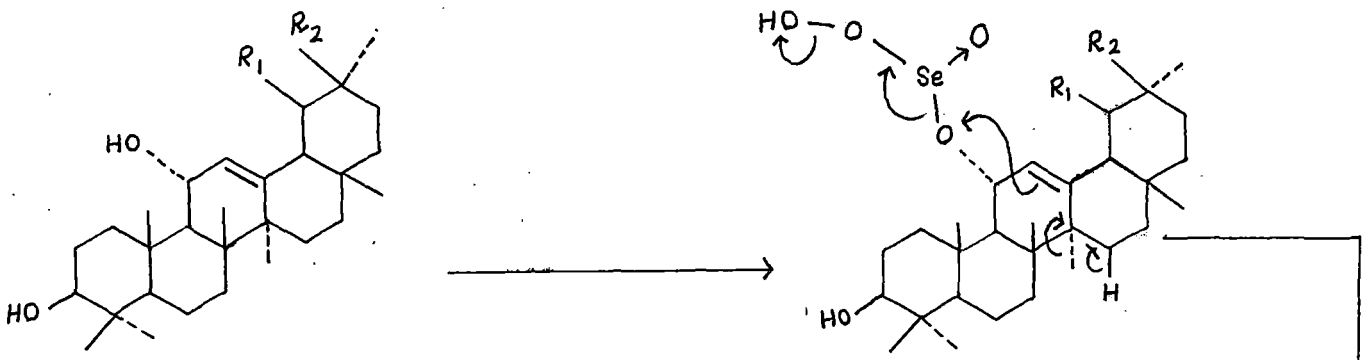
11, 12, R_1= CH_3, R_2=H, R_3= CH_3.

13, R_1= H, R_2= CH_3, R_3 = CH_3.

They[9] also reported the formation of 13 in small amount by photoxidation of α-amyrin and establised the structure as 13 by chemical and spectral analysis.

They[9] further synthesised the compounds 12/13 from olean

12-en-3β,11α-diol **14a** / Urs-12-en-3β,11α-diol **14b** by treatment with a mixture of hydrogen peroxide and selenious acid in t-BuOH. The mechanism first proposed was as follows:-

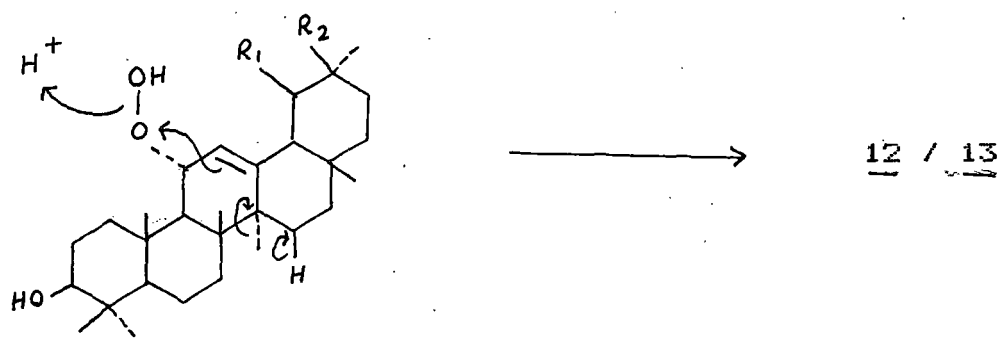


14a, R_1 = H, R_2 = CH_3

14b, R_1 = CH_3, R_2 = H

12 / **13**,

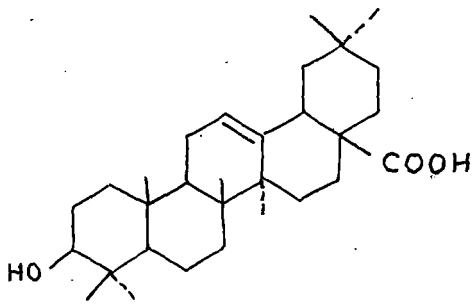
However, this was shown not to be the actual mechanism of the formation **12**/**13** from 3β,11α-diol **14a**/**14b** from the fact that the reaction of the 11-epimeric 12-en-3β,11β-diol with the same reagent also afforded the same product **12**/**13** and not the epimeric epoxide. It evidently shows that the C_{11}-O bond is broken during the reaction. This suggested an alternative mechanism in which the isomeric diols furnish the same C-11,12,13 allylic cation which reacts with the peroxide to form 12-en-3β-ol-11α - hydroperoxide **15**. This in turn undergoes acid catalysed O-O bond fission and carbon rearrangment to give **12**/**13**



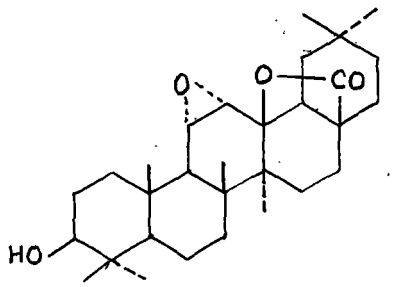
15,

They suggested[9] that selenious acid merely functioned as an acid catalyst and could be replaced by other acids.

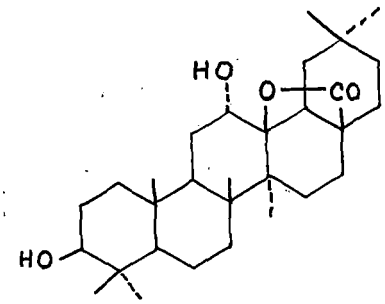
Kitagawa et al[10] studied the photoxidation of oleanolic acid 16 and reported two products 17,18 together with starting material.



16,

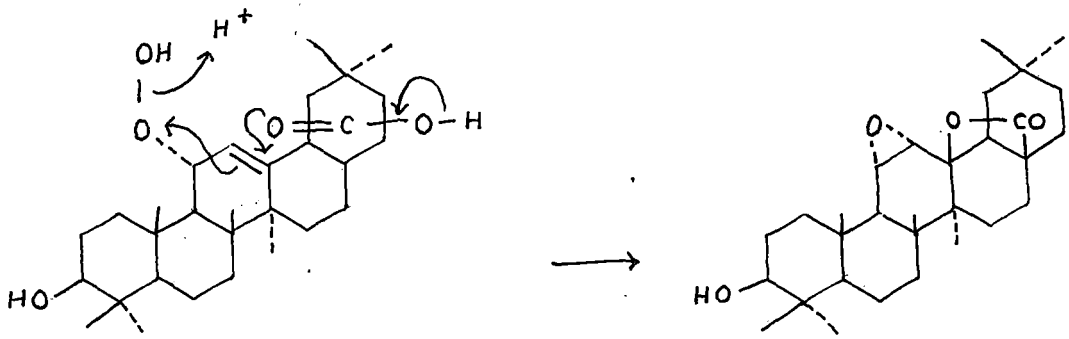


17,



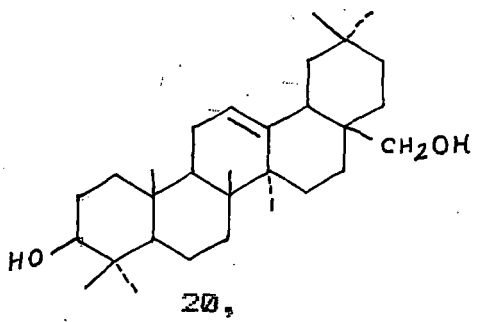
18,

They[10] suggested that the formation of 17 from 16 took place via hypothetical intermediate 19 in which carboxylic function at C-17 was participating .

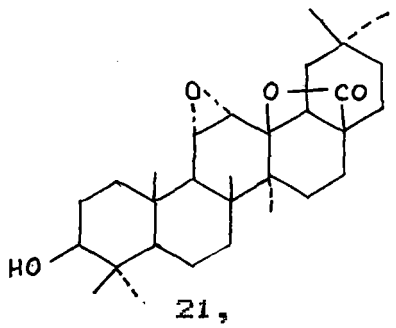


19, 18,

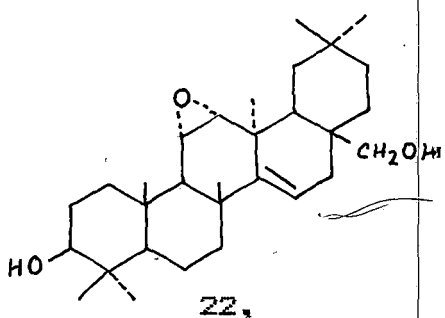
Irradiation of erythrodiol 20 for 100 hours afforded two products 21 and 22 together with starting material.



20,

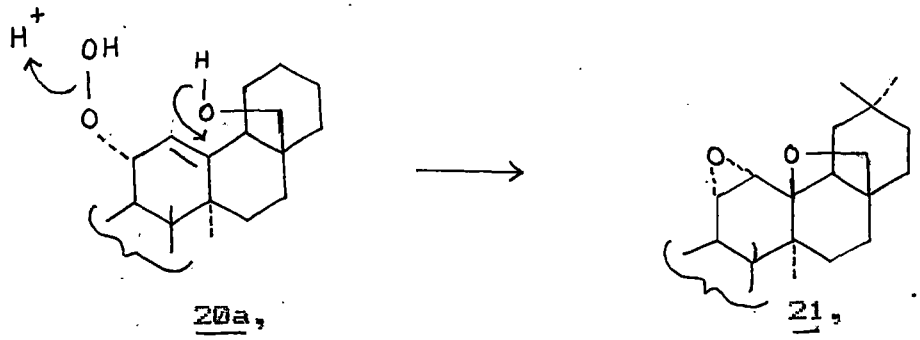


21,



22,

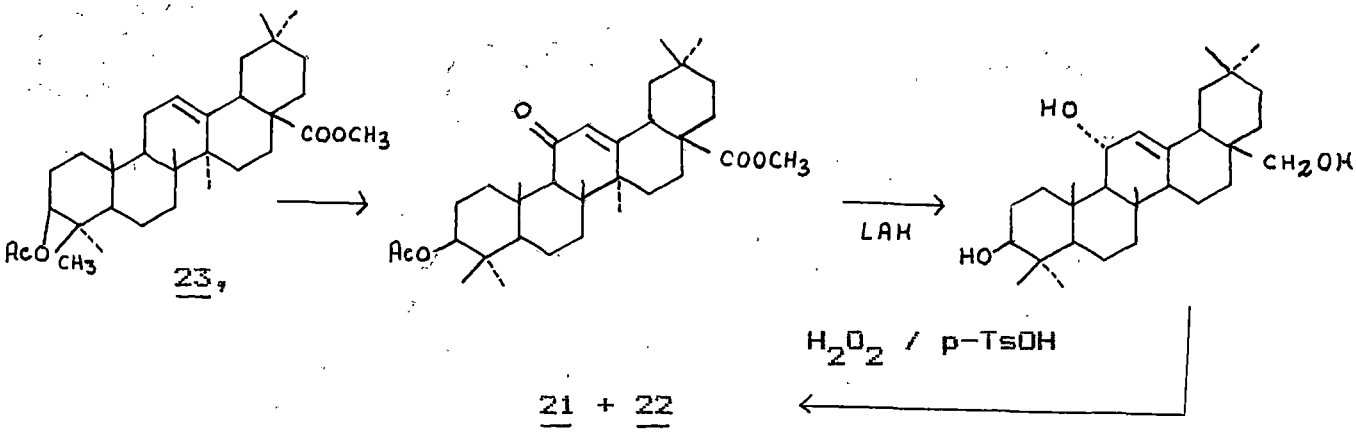
They[11] suggested that the formation of 21 from 20 took place via intermediate 20a in which unshared electron pair of 17β-CH_2OH was participating



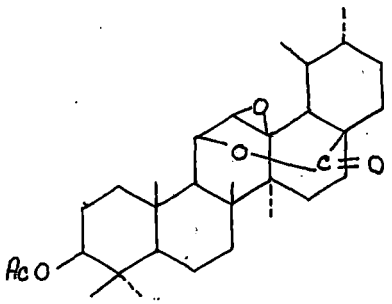
20a, 21,

Kitagawa et al [12] synthesised 21 and 22 from methyl-3-O-acetyl oleanolate 23. as shown in the scheme-III

SCHEME-III



Jeger et al[13] studied the action of H_2O_2 on ursolic acid acetate 24a in hot glacial acetic acid and reported the isolation of three compounds designated as U_1 ($C_{32}H_{48}O_5$), U_2 ($C_{32}H_{50}O_5$), U_3 ($C_{32}H_{50}O_5$) and assigned the structures 25 and 26 for U_1 and U_3 respectively and did not assign any structure for U_2. But Simonsen et al[14] disapproved *structure* 25 for U_1 and suggested the structure 27 or 28 for U_1 without providing any positive evidence in support of their proposition. So Majumder et al[15] reinvestigated this work and isolated U_1, U_2 and methylester of U_3. They revised the structure of U_1 and established the structures of U_2 and U_3 from spectral and chemical analysis.



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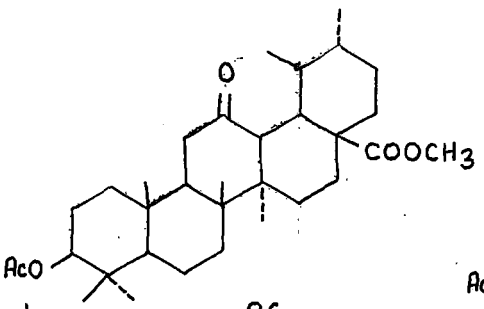

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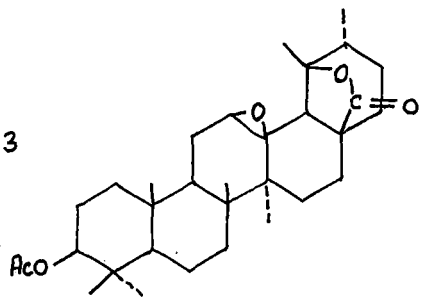

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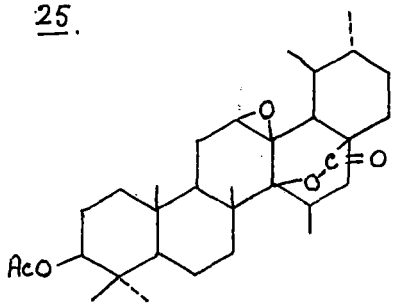

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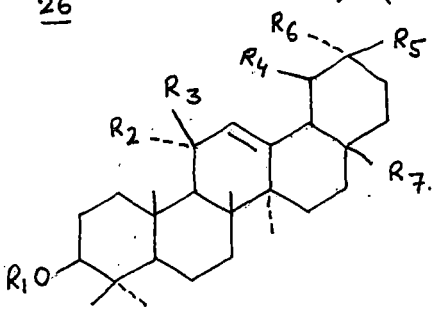


24a, R_1 = Ac, R_2 = R_3 = R_5 = H
R_4 = R_5 = Me, R_7 = COOH

24b, R_1 = Ac, R_2 = R_3 = R_4 = H
R_5 = R_6 = Me; R_7 = COOH

24c, R_1 = R_2 = R_3 = R_5 = H
R_4 = R_6 = Me, R_7 = CH_2OH

24d, R_1 = R_2 = R_3 = R_5 = H
R_4 = R_6 = Me, R_7 = CH_2OAc

24e, R_1 = Ac, R_2 = R_3 = R_5 = H.
R_4 = R_6 = Me, R_7 = CH_2OH.

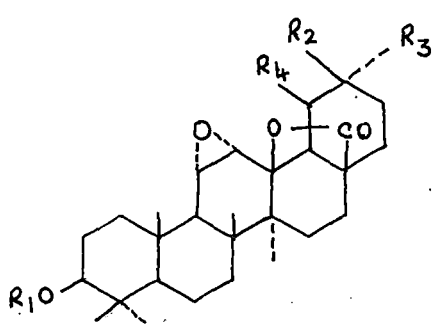
24f, R_1 = Ac, R_2 = R_3 = R_5 = H.
R_4 = R_6 = Me, R_7 = CH_2OAc.

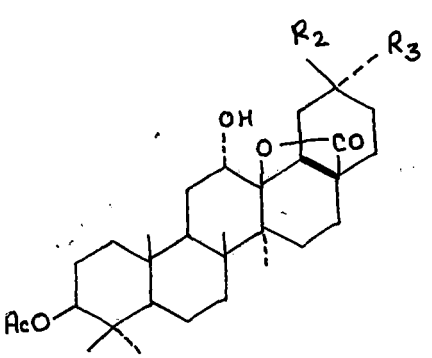
24g, R_1 = Ac. R_2 = R_3 = R_4 = H.
R_5 = R_6 = Me, R_7 = CH_2OH

24h, R_1 = R_2 = R_3 = R_4 = H.
R_5 = R_6 = Me, R_7 = CH_2OAc

24i, R_1 = Ac, R_2 = R_3 = R_4 = H, R_5 = R_6 = Me, R_7 = CH_2OAc.

Majumder et al[15] suggested structure 3β-acetoxy 11α-12α epoxy ursan--28-oic-13(28)-lactone **29a** for U_1 ;
3β-acetoxy-12α-hydroxy-ursane-28-oic-13 (28)-lactone **30a** for U_2 and **26** for U_3 from PMR and other physical data.



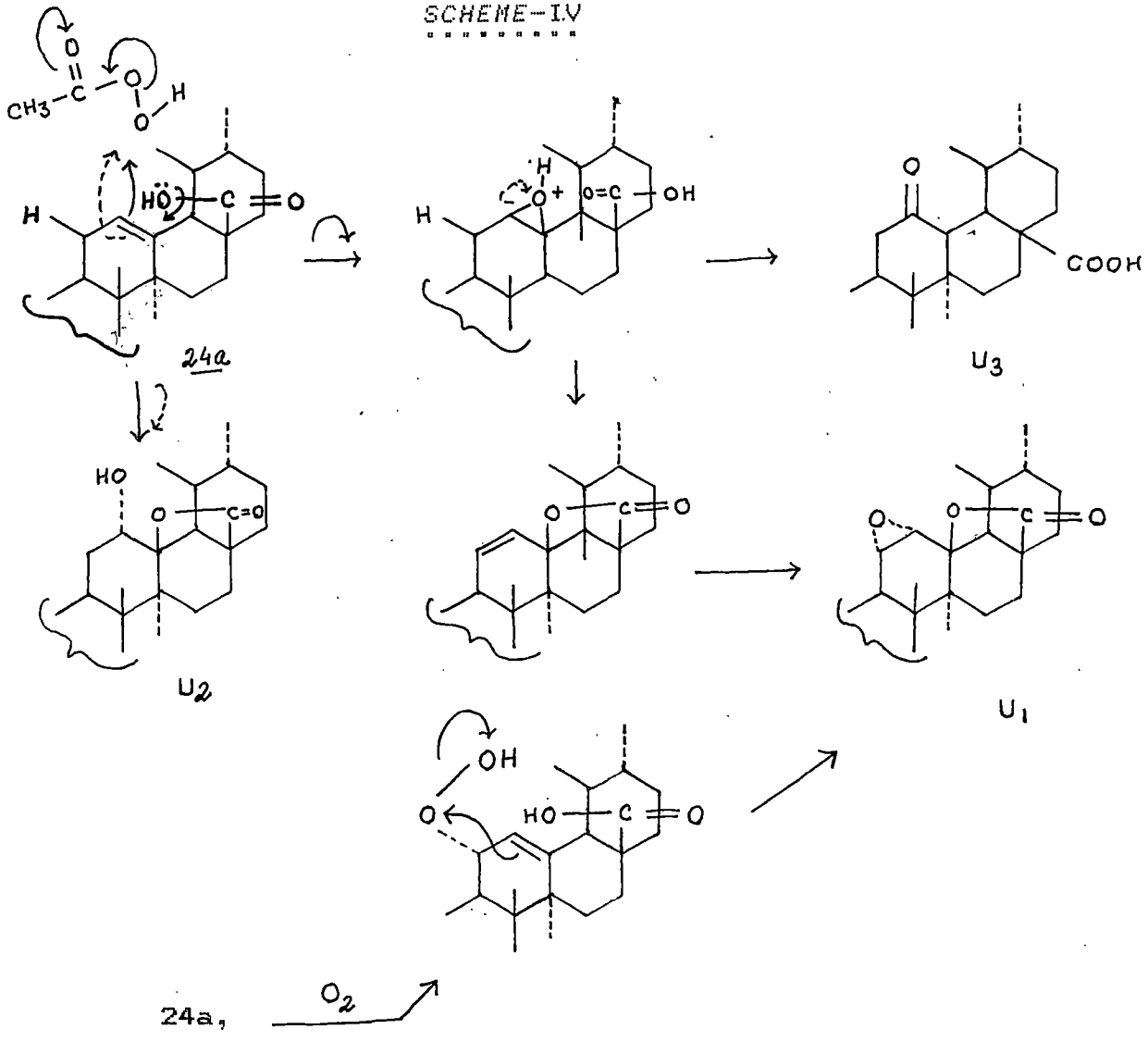


29a, R_1 = Ac, R_3 = H, R_2 = R_4 = Me,
29b, R_1 = Ac, R_2 = H, R_3 = R_4 = Me

30a, R_2 = H, R_1 = R_3 = Me
30b, R_1 = H, R_2 = R_3 = Me

Majumder et al[15] suggested the following mechanism for the formation of U_1, U_2, and U_3 as shown in Scheme IV

SCHEME-IV

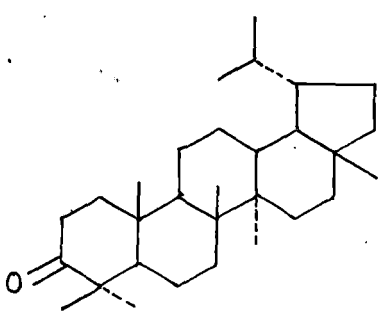


After isolation of products **29a**, **30a** and **26** from ursolic acid acetate **24a** the action of H_2O_2 in boiling acetic acid. Majumder et *al*[16] carried out this reaction to oleanolic acid acetate **24b** and isolated. epoxy γ-lactone **29b** and 12 hydroxy γ-lactone **30b** but keto dihydro derivative was absent. They[16] suggested that the presence of keto dihydro derivative **26** in case of **24a** and the absence of keto dihydro derivative in case of oleanolic acid acetate **24b** was due to the additional steric effect of 19-methyl group in **24a**.

Based on the assumption that 17-CH_2OH group in the ursane and oleanane systems might undergo necleophilic participation like

17-carboxyl functions in this systems, Majumder et al[16] carried out H_2O_2-AcOH reaction with uvaol **24c** and erythrodiol **20**. In case of **24c** three products were 28-O-acetyl uvaol **24d**, 3-O-acetyl Uvaol **24e** and 3,28-O,O-diacetyl uvaol **24f**, similarly **20**, gave **24g**, **24h**, and **24i**. The total absence of any oxidation product in the reaction of **24c** and **20** with H_2O_2 -AcOH established the significant role played by the C_{17}- carboxyl group in initiating oxidative transformation of **24a** and **24b**. They [16] finally suggested that for any appreciable oxidation with H_2O_2 to be initiated by the 12,13-double bond in the ursane and Oleanane skeleta, *the presence of 17-carboxyl group was an essential requirement*.

The SeO_2 catalysed reaction of H_2O_2 on pentacyclic triterpene 3-ketone was studied by Pradhan et al[17]. They[17] observed that lupanone **31** on oxidation with molar proporation of H_2O_2 and catalytic amount of SeO_2 in t-BuOH afforded lup-1-ene-3-one[19] **32**, 2α-carboxyl-A-nor-lupane[20] **33** and 2,3 seco-lupane dicarboxylic acid **34**; with excess H_2O_2 **31** furnished 4, 23,24 tri-nor-lupane 3 5 olide, a δ- lactone **35** together with [21] **34**



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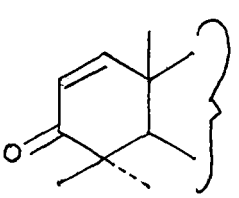

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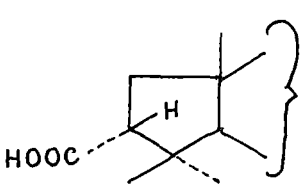

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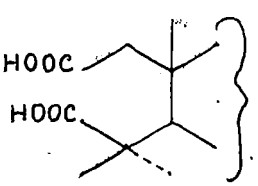

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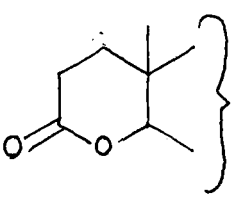
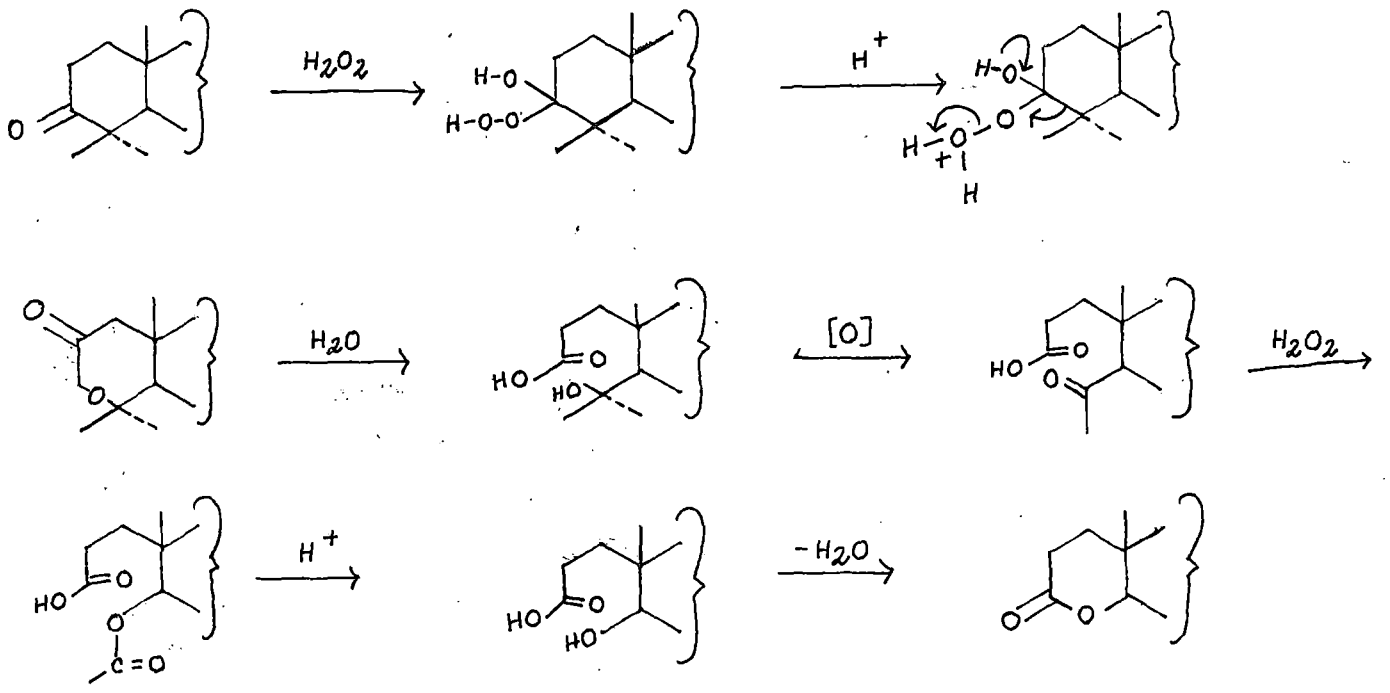


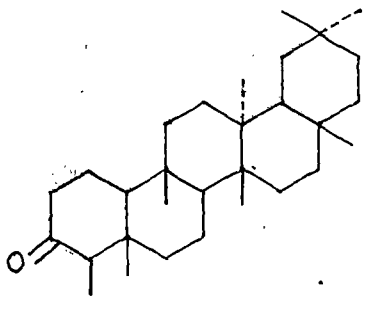
35,

Pradhan et al[17] suggested the following mechanism for the formation of δ-lactone 35 shown in scheme-V

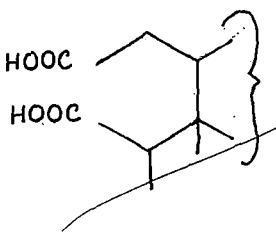
SCHEME-V



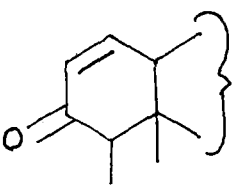
Pradhan et al[18] performed similar reactions of H_2O_2-SeO_2 in t-BuOH on friedlin 36 and reported the isolation of 2,3 seco-friedlinic acid 37, 2α- carboxy-A-nor-friedlin 38 and a δ-lactone.39.



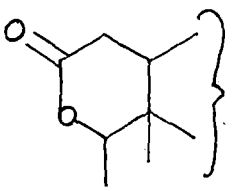
36.



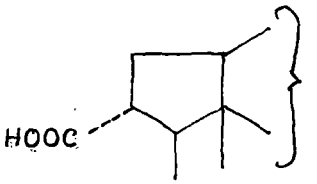
37.



36d.



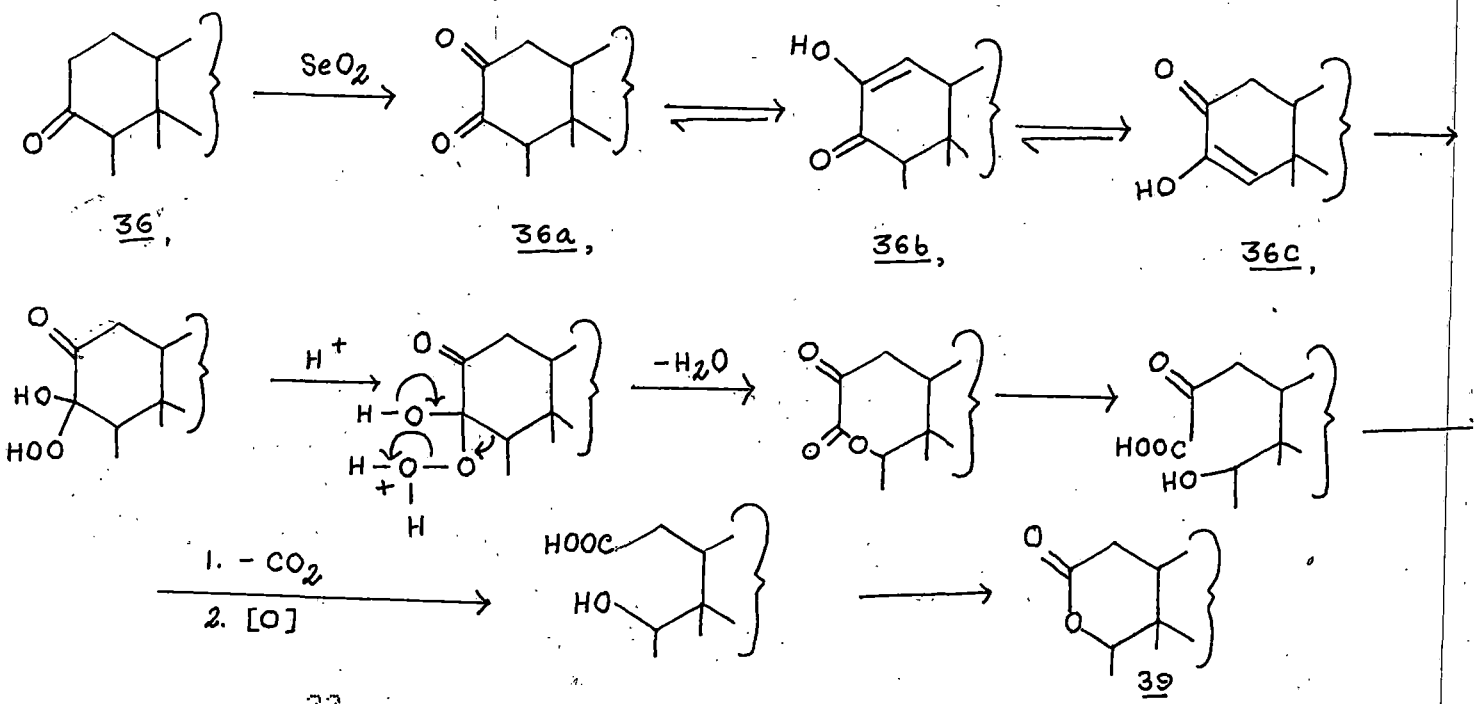
39



38

The mechanism suggested by Pradhan et al[18] shown in scheme-VI. They suggested that the formation of δ-lactone 39 proceeded via the formation of the diketone 36a [⇌ diosphenol ⇌ 36b ⇌ 36c]

SCHEME -VI

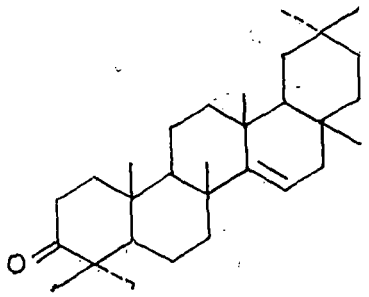


36, 36a, 36b, 36c, 39

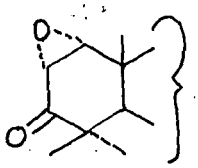
Anjaneyulu et al[22] reinvestigated the oxidation of friedlin 36 with H_2O_2-SeO_2 in t-BuOH and reported the formation of friedel-1-ene-3-one 36d and friedelolactone 39 along with 37 and 38 already reported by Pradhan et al[18].

Pradhan et al[23] extended the reaction to taraxerone 40,a 3-keto triterpenoid having a trisubstituted double bond. They[22] reported that 40 on oxidation with H_2O_2 in presence of SeO_2 in t-BuOH afforded 1α ,2α-epoxide 41, 4, 23, 24-tri-nor-taraxerene 3 5 olide, a δ- lactone 42 and taraxerene-ε-lactone 43 from neutral part and 2α-carboxyl-A-nor-taraxerene 44 together with taraxerene 3,4 seco-dicarboxylic acid 45 from acid part. The formation of the products 41,42,43,44,45 shows that in SeO_2 oxidation of taraxerone 40,no migration of 14-15 double bond took place. They concluded from previous studies and present observations that the δ-lactones were

formed irrespective of the presence of methyl groups at C-4 position. Further isolation of ε-lactone 43 supported the mechanism of formation of δ-lactone via the ε-lactone. They also suggested that the epoxide 41 was most probably formed via Δ^{1-2} unsaturated ketone.



40,



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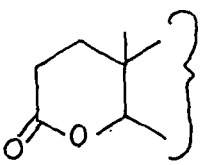
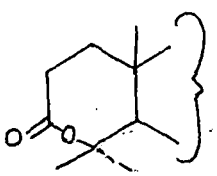


42



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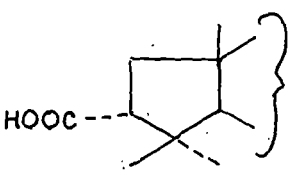

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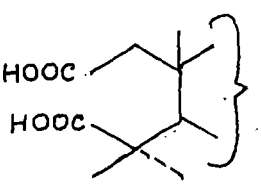
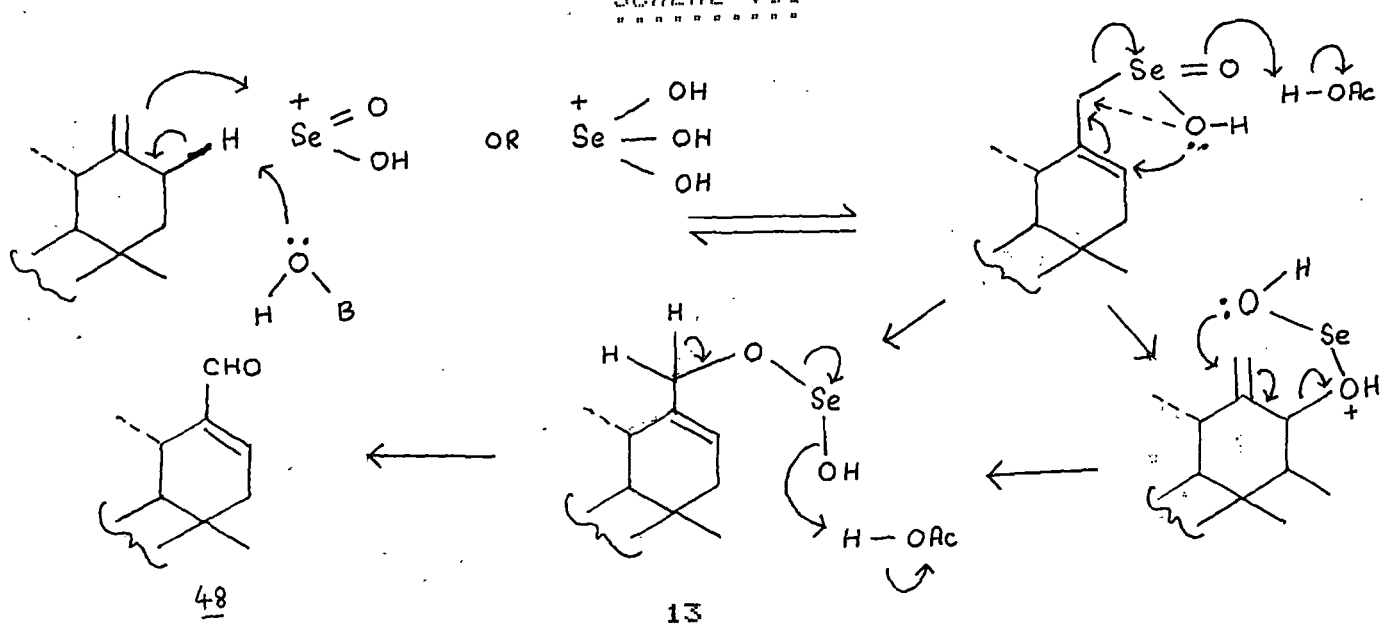


45.

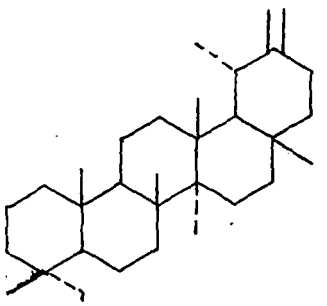
Talapatra et al[24] explained oxidation of taraxastene 46 and ψ-taraxastene 47 to give the corresponding aldehyde 48 on the basis of mechanism shown in scheme-VII

SCHEME-VII

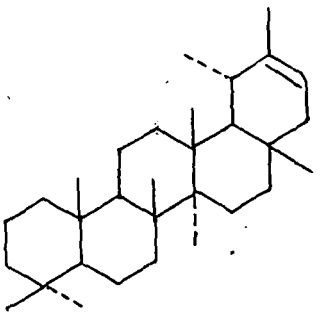


48

13

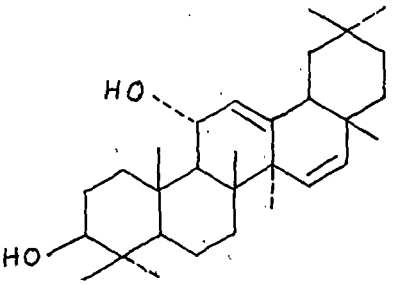


46,

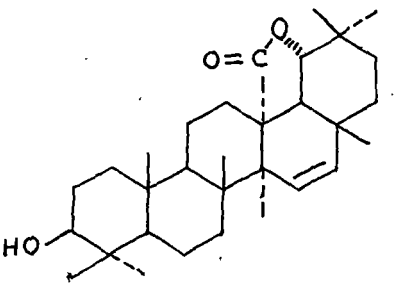


47,

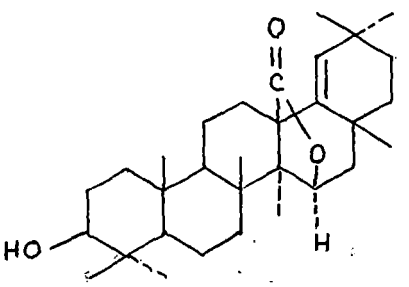
Pradhan et al[25] carried out the reaction of olean-12,15,dien 3,11-diol **48a** with H_2O_2 p-toluene sulphonic acid under identical condition of Corey et al[9] with a view to produce the multiflorenol derivative **51**. But they[26] isolated to isomeric γ-lactones identified as 3β-acetates of C_{12}-nor-olean-15(16)-en-13α-carb$\rightarrow$19α-olide **49** and C_{12}-nor-olean-18 (19)-en-13β-carb$\rightarrow$15β-olide **50**.



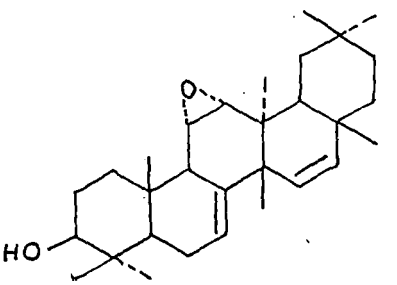
48a



49,

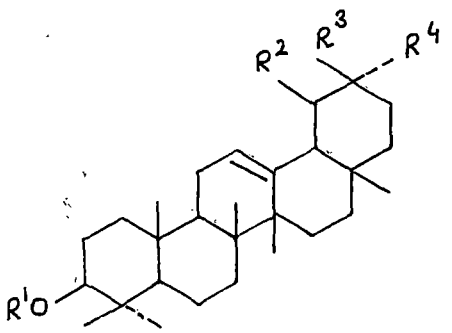


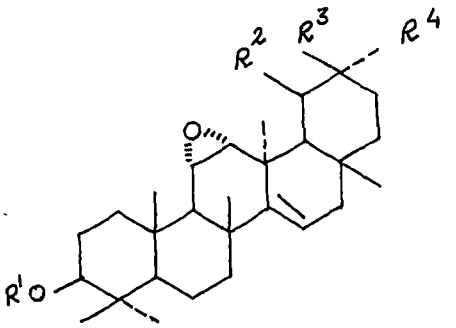
50,



51,

Pradhan et al[26] studied the reaction of SeO_2-H_2O_2 on β-amyrin acetate 51 in t-BuOH and reported two compounds as 11α,12α-epoxy-taraxer-14-en-3β-yl acetate 52 and 11α,12α-epoxy-taraxer-14-en-3β-ol 53 while on similar treatment, α-amyrin acetate 54 furnished 11α,12α-epoxy-urs-14-en-3β-yl acetate 55 and 11α,12α-epoxy-urs-14-en-3β-ol 56

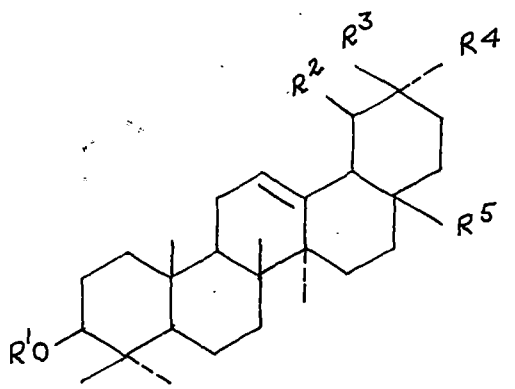


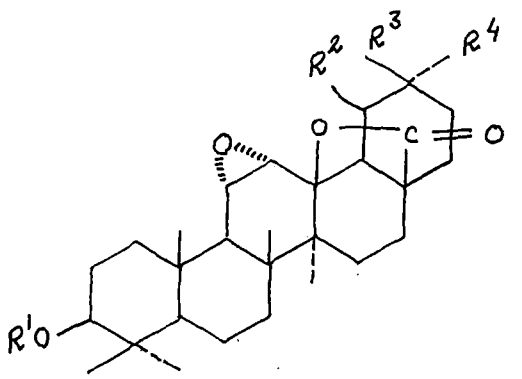


51, R^1=Ac, R^2=H, R^3=R^4=CH_3
54, R^1=Ac, R^4=H, R^2=R^3=CH_3

52, R^1= Ac, R^2= H, R^3=R^4=CH_3
53, R^1= R^2= H, R^3= R^4= CH_3
55, R^1=Ac, R^4= H, R^2= R^3=CH_3
56, R^1=R^4=H, R^2=R^3=CH_3

They[26] studied the action of SeO_2-H_2O_2 on acetyl oleanolic acid 57 and acetyl methyl oleanolate 58 in t-BuOH and isolated 11α,12α-epoxy-oleanan-28 13-olide-3β-yl acetate 59 and 11α,12α-epoxy-oleanan-28 13-olide 3β-ol 60. Under similar condition methyl acetyl ursolate 61 afforded two compounds identified as 11α,12α-epoxy-urs-28 13-olide -3β-yl acetate 62 and 11α,12α-epoxy-urs-28→13-olide-3β-ol 63.





57, R^1=Ac, R^2=H, R^3=R^4=CH_3, R^5=COOH

58, R^1=Ac, R^2=H, R^3=R^4=CH_3, R^5=$COOCH_3$

61, R^1=Ac, R^4=H, R^2=R^3=CH_3, R^5=$COOCH_3$

65, R^1=R^2=H, R^3=R^4=CH_3, R^5=CH_2OH

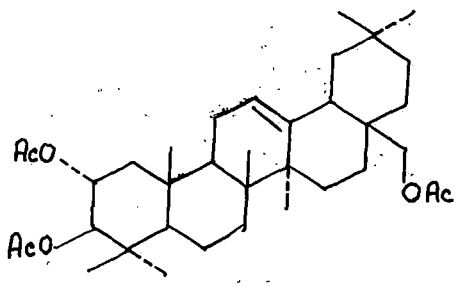
59, R^1=Ac, R^2=H, R^3=R^4=CH_3

60, R^1=R^2=H, R^3=R^4=CH_3

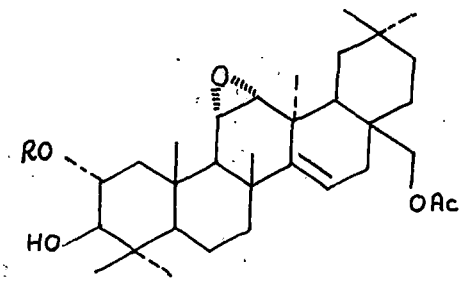
62, R^1=Ac, R^4=H, R^2=R^3=CH_3

63, R^1=R^4=H, R^2=R^3=CH_3

Pradhan et al[27] also carried out the reaction on erythrodiol **65** when the product **60** was formed whereas similar oxidation on the tri-acetate **66** furnished the epoxy derivatives **67** and **68** only.



66,



67, R = Ac

68, R = H

from these reactions they concluded:-

(1) the reaction is identical to the photochemical oxidation in the formation of 11,12, epoxide.

(2) the C-17 Carbomethoxy group as well as the CH_2OH group at the C-17 position is also involved in the formation of 28 13 lactone ring.

(3) the primary-CH_2OAc group at C-17 do not undergo hydrolysis where as the secondary -CHOAc group partially hydrolyses to -CHOH group under the reaction condition.