PART — II

ACTION OF HYDROGEN PEROXIDE ON TRITERPENOID ALLYLIC ALCOHOLS

CHAPTER—I

A SHORT REVIEW ON SOME OXIDATIVE REACTIONS OF PENTACYCLIC TRITERPENOIDS

In Organic Chemistry oxidative reaction can not be well defined very easily like in inorganic chemistry i.e. loss of electrons or increase in oxidation number. While electrons are directly transferred in some organic oxidation reactions the mechanism of most of these reactions do not involve a direct electron transfer. While considering for oxidation number it is easy to apply in some cases. As for example the oxidation number of carbon in CH_4 is -4, in most cases attempts to apply the concept lead to fractional values or apparent absurdities. Thus carbon in propane has an oxidation number of - 2.67 and in butane of - 2.5, though organic chemists considered these two compounds as being in different oxidation states. An improvement could be made by assigning different oxidation states to different carbon atoms in a molecule, depending on what is bonded to them. As for example two carbon atoms in acetic acid are obviously in different oxidation states. Assumption would be required to explain the phenomena since the oxidation number of an atom in a molecule is assigned on the basis of the oxidation numbers of the atoms attached to it. Then the Organic Chemists defined oxidation as the conversion of a functional group in a molecule from one category to a higher one. Most oxidation in Organic Chemistry involve a gain of oxygen or a loss of hydrogen.

We have carried out reactions of hydrogen peroxide, which is known as an oxidising agent, on triterpenoids. It has been found that triterpenoids undergo molecular rearrangements with very simple reagents. Some important rearrangements take place under various oxidative conditions e.g. with mercuric acetate, lead tetracetate, chromic acid, organic peracids, hydrogen peroxide etc. Photochemical Oxidation and autoxidation on triterpenoids have also been observed. The following is a brief review of different transformational reactions on triterpenoids with the help of different oxidative reagents.

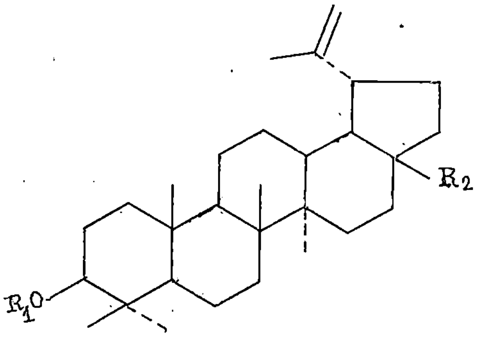
1. Mercuric acetate reaction in the lupane series[3,4]:

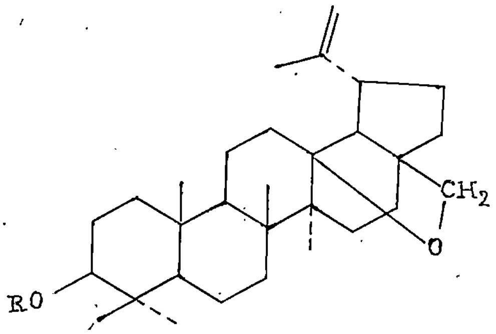
It has been found that mercuric acetate was used widely for the dehydrogenating agent for introducing an ethylenic double bond in conjugation with an existing double bond in the field of steroids.

Biedebach *et al*[1,2] first reported the Hg (II) acetate oxidation on pentacyclic triterpenes of lupane series.

Betulin and lupeol formed dehydro compounds of unknown structure. Since their esters also underwent dehydrogenation but not their dihydro derivatives, it was concluded that this dehydrogenation was associated with the presence of an olefinic bond.

Allison and coworkers[5] carried out mercuric acetate oxidation on betulin **1a** and isolated a cylic ether **2a**, IR ν max 1630, 836 cm^{-1} (Vinylidine group). NMR spectrum of the corresponding acetate **2b** exhibited peaks at 63 and 89 cps ($-C-CH_2-O$). Hydrogenation of **2b** followed by oxidation gave a lactone **3b**, IR ν max 1770 cm^{-1} (γ -lactone).

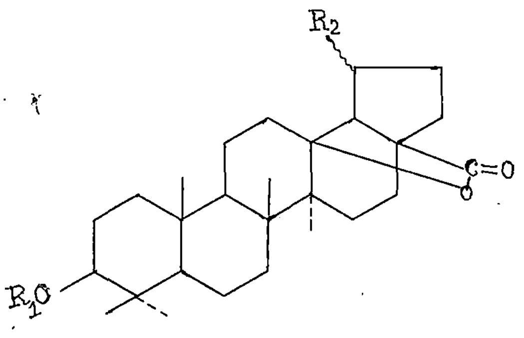




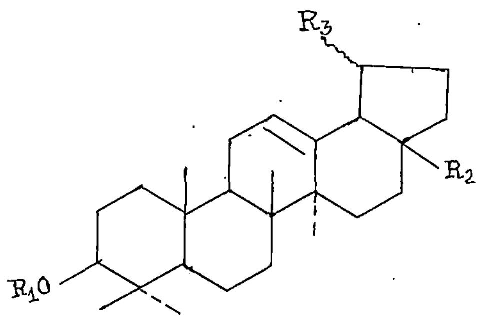
1a $R_1 = H$, $R_2 = CH_2OH$
1b $R_1 = Ac$, $R_2 = COOH$
1c $R_1 = Ac$, $R_2 = COOCH_3$
1d $R_1 = Ac$, $R_2 = CH_2OAC$

2a $R = H$
2b $R = AC$

The authors advanced the following arguments in favour of their structure **3b** for the lactone. The termination of the lactone could be at 13, 15, 19 or 21 position. Lithium aluminium hydride reduction product of **3b** on acetylation produced a diacetate and not a triacetate, thus excluding positions 15 and 21 for the lactone termination and it was thought that one of the hydroxyl groups was tertiary in nature. The smooth dehydration of the diacetate with $POCl_3$ - pyridine confirmed the tertiary nature of the third hydroxyl group and the product obtained in this reaction was assigned structure **4e**, λ max 203 nm (ϵ 7900), IR ν max 1650 and 3050 cm^{-1}. The decision



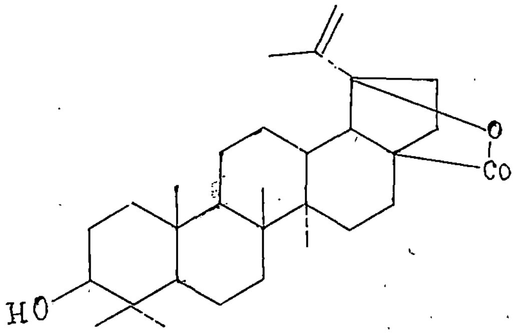
3a, R_1=Ac, R_2=isopropenyl
3b, R_1=Ac, R_2=isopropyl
3c, R_1=H , R_2=isopropenyl



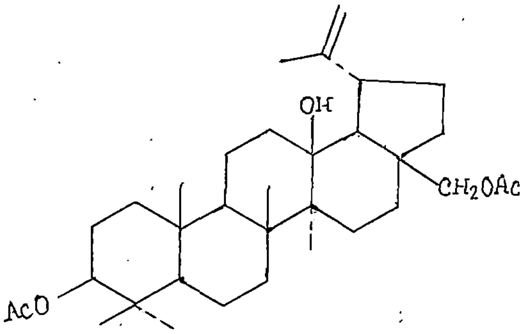
4a, R_1=Ac ,R_2=CO_2Me ,R_3=isopropenyl
4b, R_1=Ac ,R_2=CO_2Me ,R_3=isopropyl
4c, R_1=H ,R_2=CO_2H ,R_3=isopropyl
4d, R_1=Ac ,R_2=CH_2OAc ,R_3=isopropenyl
4e, R_1=Ac ,R_2=CH_2OAc ,R_3=isopropyl
4f, R_1=Ac ,R_2=CH_3 ,R_3=isopropyl

regarding the lactone termination was made on the basis of experiments with betulinic acid and its methyl ester. Acetyl betulinic acid 1b with Hg (ic) acetate oxidation gave a γ-lactone assigned as 3a, IR ν max 1792 cm^{-1}, which on hydrogenation gave the same dihydrolactone 3b as that obtained from betulin. Consequently the lactone termination and the other linkage in 2b must be at the same point, either at C—13 or C—19. The lactone 3a was found to be different from thurberogenin which was assigned the C—17—C—19 lactone structure by Djerassi et al[6] in 1955. Nonidentity of thurberogenin with this lactone lead Allison and coworkers[5] to assign structure 3a (13 - 17 lactone) for the lactone.

It was found that when 3β-acetoxy methyl betulinate 1c on similar oxidation with Hg (ii) acetate gave an unconjugated diene λ max 208 nm (ϵ 7100), IR ν max 3078, 1634, 901 - ($C = CH_2$), 1730, 1250 cm^{-1} ($—O.COCH_3$) and was assigned structure 4a. The corresponding hydrogenated product 4b, λ max 205 nm (ϵ 5300), ν max 878 cm^{-1}, on hydrolysis with sodium ethoxide gave the acid 4c. The later on treatment with hydrogen chloride in chloroform gave the lactone 3c. Betulin diacetate 1d on Hg (ii) acetate oxidation gave a nonconjugated diene assigned as structure 4d, which was also prepared from the ester 4a and the lactone 3a. Reduction of the ester 4a with lithium aluminium hydride gave a diol which on acetylation gave the same dienyl acetate 4d. When the lactone 3a was reduced by lithium aluminium hydride and then acetylation of the product gave the acetoxy alcohol 5. The acetoxy alcohol on dehydration gave the dienyl acetate 4d. Since 4d was formed by dehydration of the tertiary hydroxyl group at C—13 and after hydrogenation of it gave 4e, which showed no IR band for vinylidine group. But UV absorption of the compound showed a maxima at λ_{max} 206 nm (ϵ 7900), it was confirmed that the double bond was trisubstituted and should be placed at 12—13 position.



Thurberogenin 7



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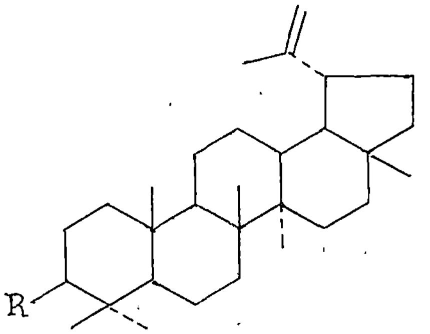
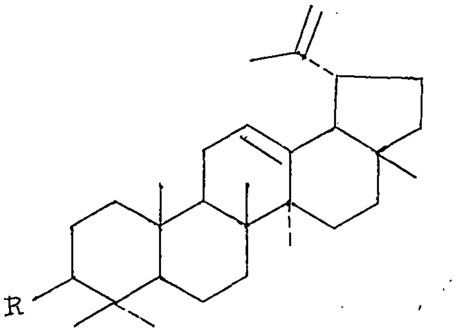
The authors also claimed that Hg (ic) acetate oxidation of lupeol 6a, lupenyl acetate 6b lupenyl benzoate 6c, lupenone 6d and α -lupene 6e under the same condition introduced a double bond at C, 12—13 position, the resultant



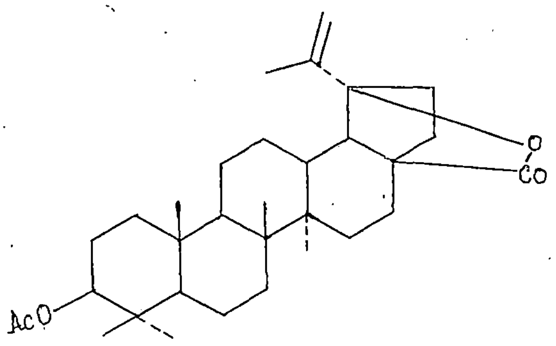


6a, R = OH
6b, R = OAc
6c, R = OBz
6d, R = O
6e, R = H

7a, R = OH
7b, R = OAc
7c, R = OBz
7d, R = O
7e, R = H

products being 7a, 7b, 7c, 7d and 7e respectively. The structure of the compound was evident from UV and perbenzoic acid titration.

Baddeley and his coworkers[7] proposed the structure of the lactone obtained from acetyl betulinic acid 1b would be like 8 and not as 3a.



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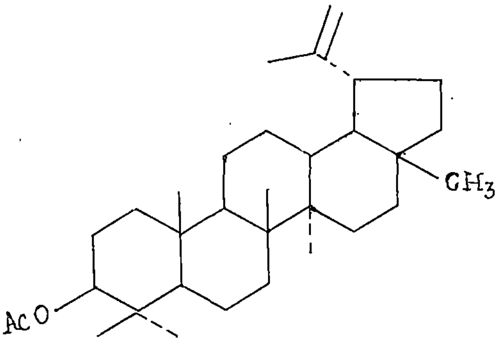
Almost simultaneously Baddeley *et al*[8] and Mclean and his coworkers[9] independently put forward spectroscopic and chemical evidences showing conclusively that in absence of any reactive substituent at C—17, mercuric acetate oxidation introduced a tetrasubstituted conjugated double bond at C—18, 19. Thus, **9** would produce **10** on mercuric acetate oxidation.



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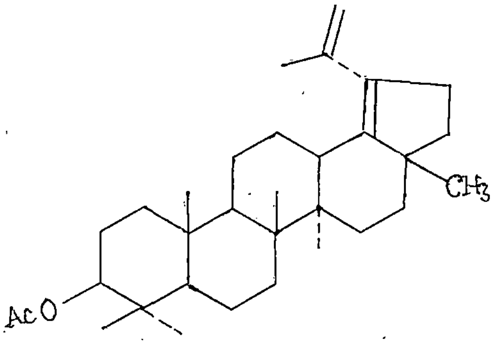

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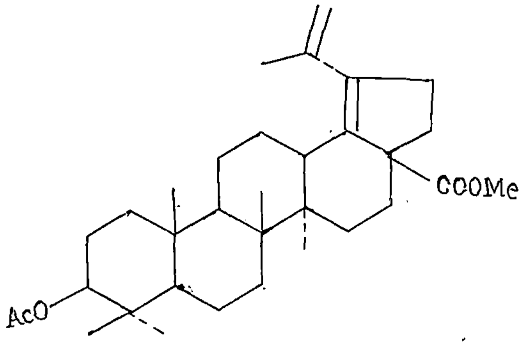
The structure of **10** was proved by the UV absorption of the compound for a conjugated diene system. It was again showed by Baddeley[10] the product of mercuric acetate oxidation on **1c**, to be **11**.



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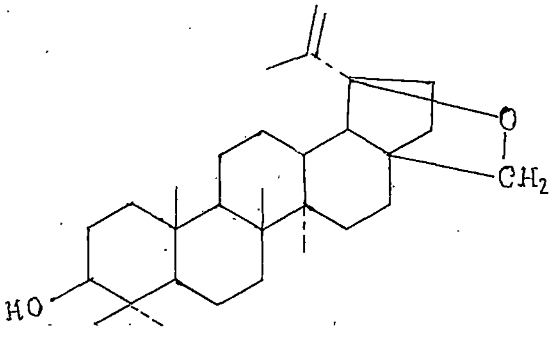

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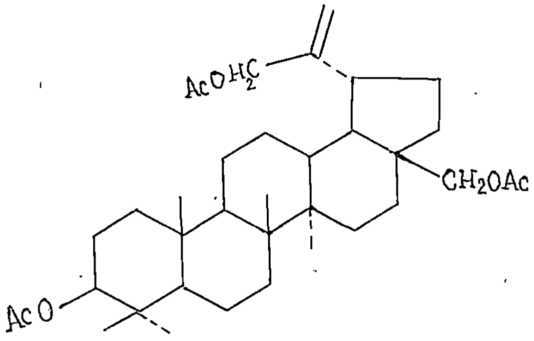
The structure of **11** was proved by its UV absorption for conjugated dienesystem and also by degradative evidence.

Vystroil *et al*[11] have shown that the primary product of oxidation of betulin **1a** with Hg (ic) acetate has got the structure **12** and not the **2a** proposed earlier by Allison *et al*[5].

2. Lead tetraacetate reaction on some triterpenoids:

Lead tetraacetate was found to be an useful oxidising agent in the field of terpenes. It has been used in many important transformation of pentacyclic triterpenes.

While studying in the lupane series which contain an isopropenyl double bond has two allylic position at C—19 and C—30. It was expected that one of these two allylic positions could be oxidised[12—15] by the reagent. It has been demonstrated[16] that in these compounds the C—30 position was so reactive that it reacted with lead tetraacetate in glacial acetic acid and the alternative C—19 position remained unaffected. Thus betulin diacetate 1d and lupeol acetate 6b gave products showing that only the C—30 position was attacked and the compounds 13 and 14 were isolated.



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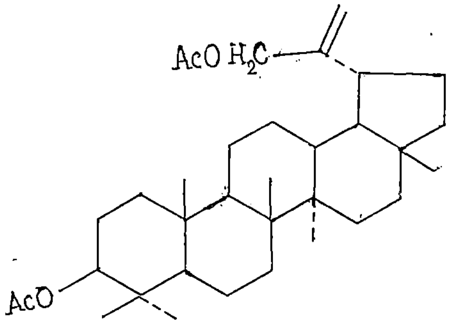

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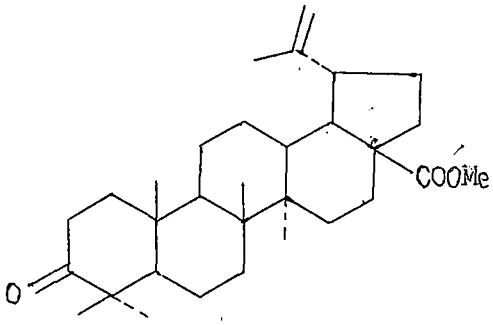
It was found that if the C—3 position of the triterpene occupied by a Keto functional group instead of a hydroxyl or acetate functional group the attack of acetoxy was found solely at C—2 position, not at C—30 position. When methyl betulonate 15 and methyl ursonate 16 was reacted with lead tetraacetate it was found that the corresponding 2α-acetoxy 3-keto compounds[17] were obtained which were assigned as 17 and 18.



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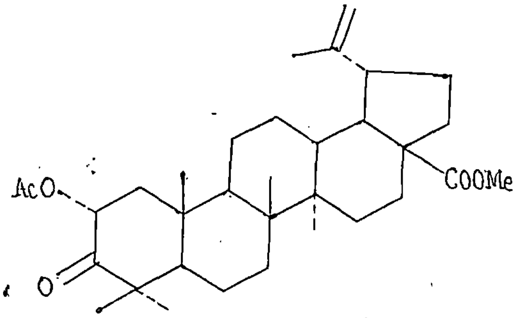

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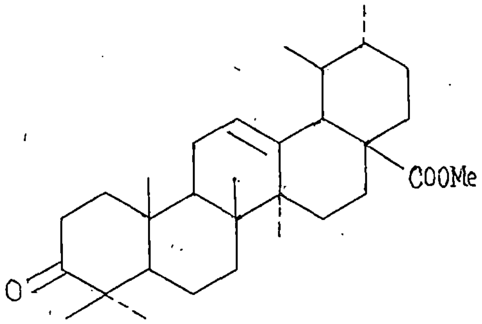

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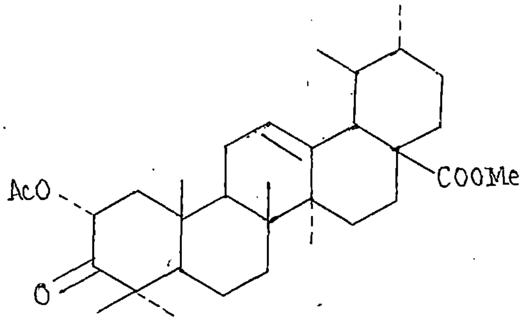

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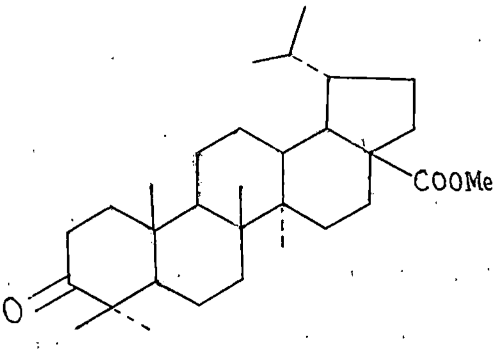
It was thought that the introduction of acetoxy group at C—2 position instead of C—30 was based on the fact that the α-hydrogens at C—2 position was much more reactive than the allylic hydrogens at C—19 or C—30 position due to the presence of a keto group at C—3 position.

It was also found that methyl dihydroalphitolate could be synthesised starting from betulinic acid[18].

Introduction of acetoxy group at the C—2, α -position to 3-oxo group of methyl-3-oxo-dihydrobetulonate 19, could be done very easily by lead tetraacetate[19] to form 20.



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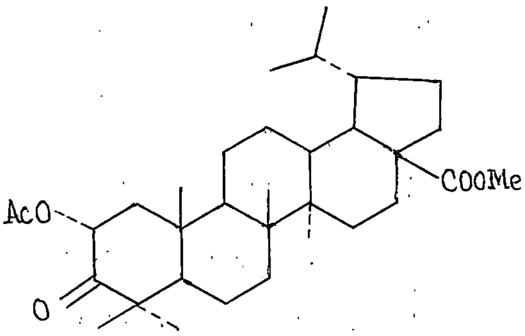

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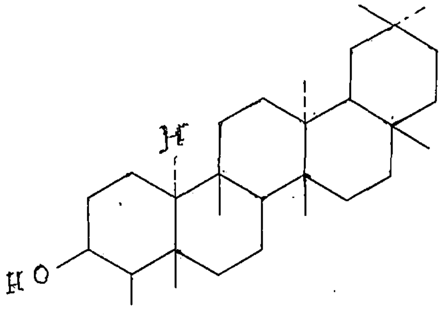
It was considered that in this reaction there was the formation of enol[20]. This enol was expected to give the desired product when attacked from less hindered α -side of the molecule. Under mild condition[21] in which boron trifluoride catalyst was used, an acetoxy ketone was obtained.

So, lead tetraacetate is a very useful reagent for the introduction of 2 α -oxygen function in 3 keto pentacyclic triterpenes.

Fukuda and coworkers[22] observed the action of lead tetraacetate in the presence of iodine and calcium carbonate under irradiation on 3β-friedelanol 21 produced a γ-lactone 22. The product was established by different physical methods.



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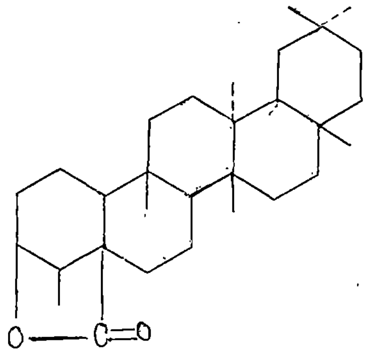

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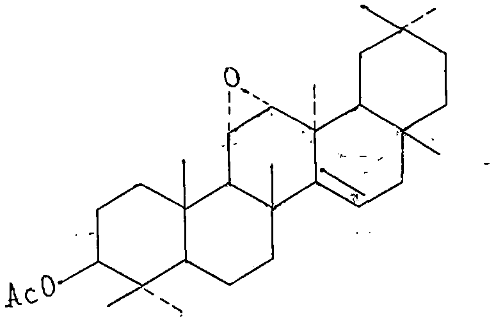
3. Oxidation of chromic acid on pentacyclic triterpene:

Chromic acid has got very good oxidising property in organic chemistry. With the help of this reagent various types of conversion occur among the pentacyclic triterpenes.

Conversion of epoxytaraxerol[23] to the multiflorenol series involved the oxidative rearrangement of the acetate 23 using chromic acid in the presence of a strong acid. These were conditions which in general seem to be less favourable to over-all allylic oxidation to a conjugated enone and relatively more favourable to the formation of epoxides, glycols, or their further transformational products[24,25]. The product of the oxidation of the acetate 23 was dioxidoketo acetate $C_{32}H_{48}O_5$, the structure of which was assigned as 24. The structure of 24 was established on the basis of physical and chemical evidences.



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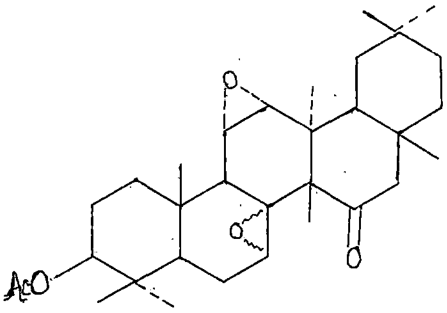

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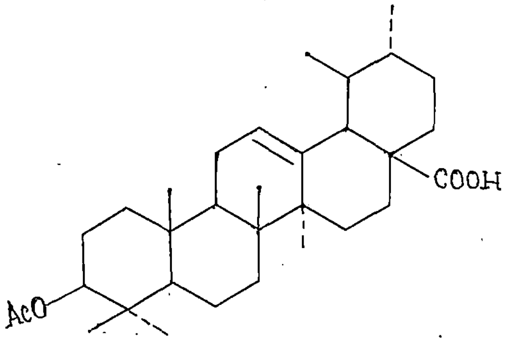
Spring and coworkers[26,27,28] have observed that when ursolic acid acetate 25 was treated with chromic acid in refluxing 97% acetic acid then introduction of 11-keto compound i.e. 3β-acetoxy-11-oxo ursolic acid 26 was obtained. The compound has got a clear UV absorption in the region 225 nm for the presence of a α-β unsaturated ketone.



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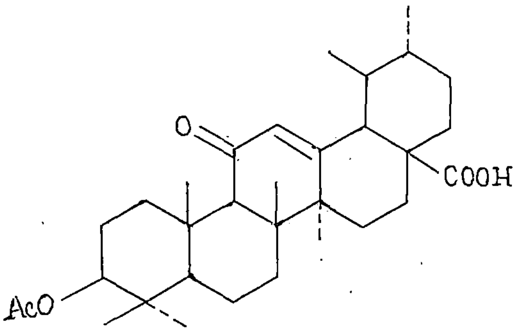

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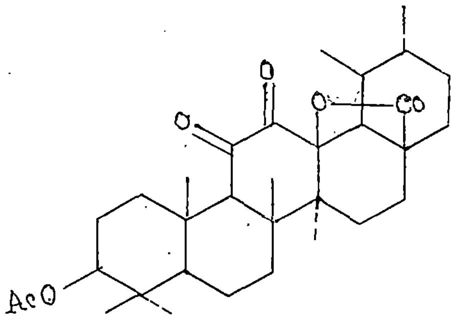
The other product of the reaction was too much interesting for the lactone with a di-one system in the molecule. The compound was formulated as 3 β -acetoxy-11, 12-dioxo ursan-28-oic—13-18-lactone 27. The structure was proved by chemical and physical evidences.



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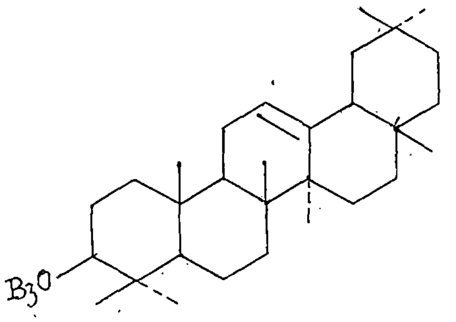
4. Reaction of triterpenoids with organic peracids:

Several transformation reactions were done with the help of organic peracide like peracetic acid, perbenzoic acid and m-chloro perbenzoic acid on the pentacyclic triterpenes. The products obtained in different cases were found to be interesting in all respects.

Treatment of β-amyrin benzoate 28 with perbenzoic acid in chloroform at 0° afforded epoxy compound[29]. The compound so obtained was assigned as 3β-benzoyloxy-12β-13-epoxy oleanane 29.



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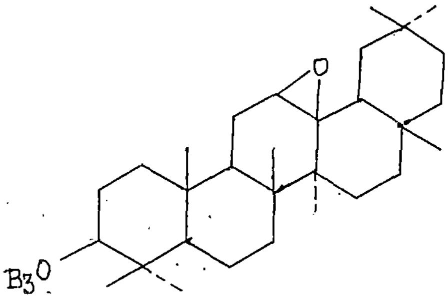

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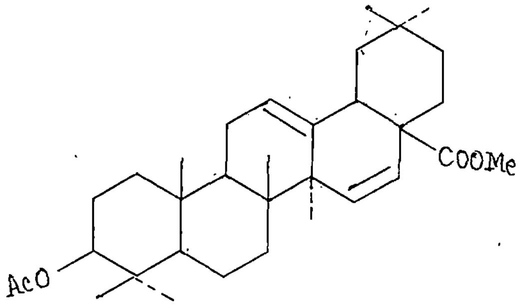
Barton and his coworkers[30] observed that when methyl 3β-acetoxy olean-12,15-dien-28-oate 30 was treated with perbenzoic acid (1.0 mol eq.) it formed an epoxy compound.

The compound so obtained was formulated as methyl 3β-acetyl-12β,13-epoxyolean-15-en-28-oate 31.



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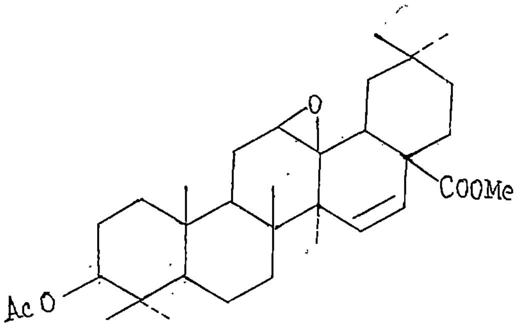

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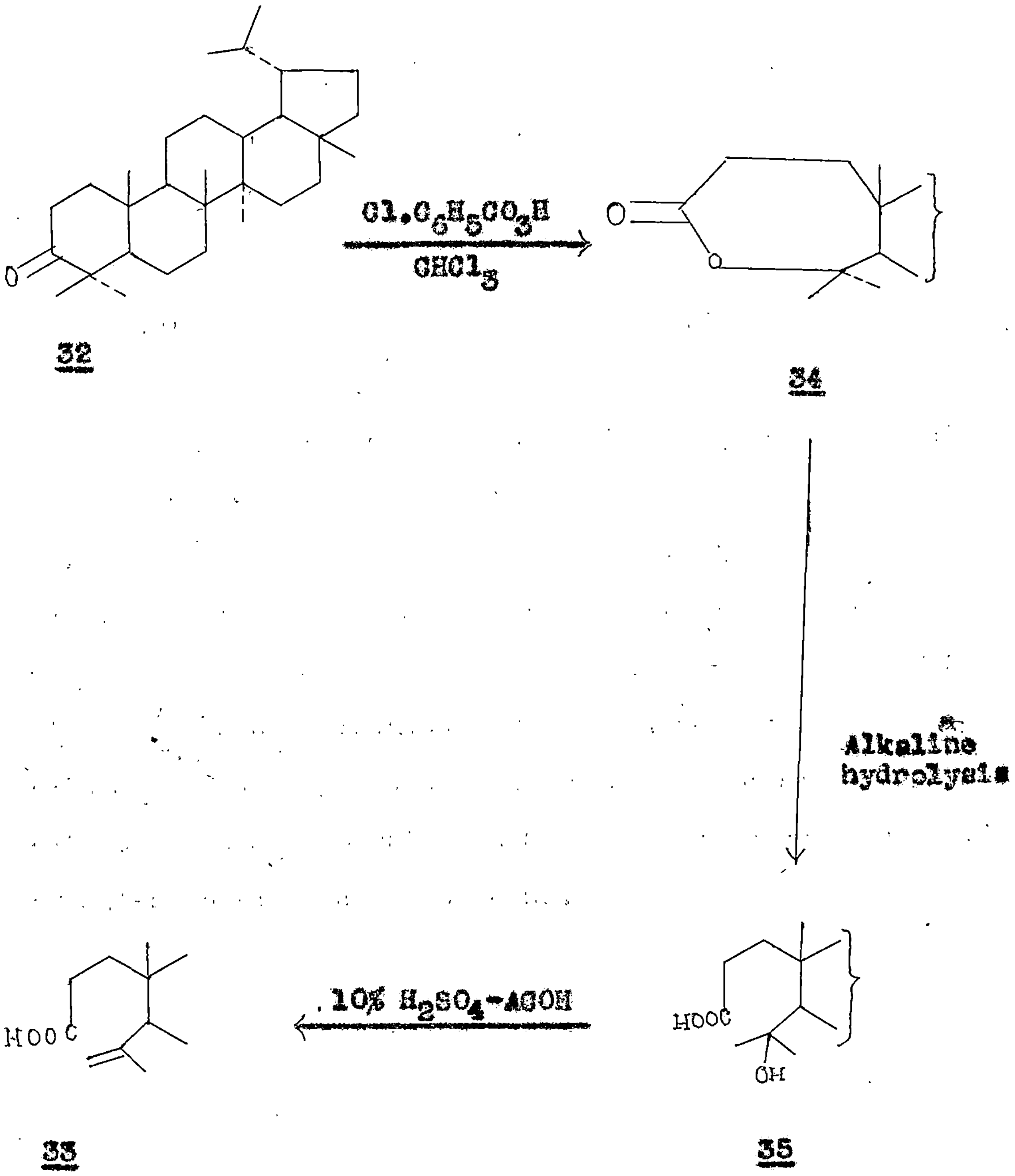
Another example of reaction of perbenzoic acid was the conversion of lupanone 32 to isodihydrocanaric acid 33. The product 33 was obtained[31] when lupanone 32 was treated with m-chloroperbenzoic acid in chloroform followed by alkaline hydrolysis of the product 4-oxa-A-homo-lupan-3-one 34 whereby ring A cleaved to yield 3,4-seco-lupan-4-ol-3-oic acid 35 which dehydrated with 10% sulphuric acid + acetic acid to give 33. So using this route (Scheme—1) synthesis of 3,4-seco acids could be done.

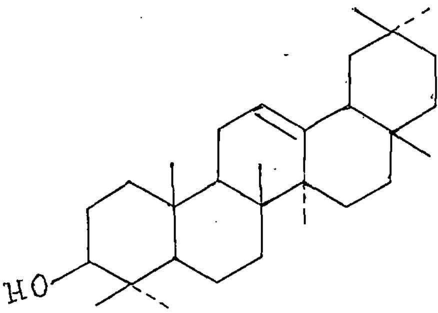
Scheme—1


32
$Cl.C_6H_5CO_3H$
$CHCl_3$
34
Alkaline hydrolysis
HOOC
OH
35
$10\%\ H_2SO_4-AcOH$
HOOC
33

5. Action of hydrogen peroxide on pentacyclic triterpenes:

Hydrogen peroxide was found to be a very interesting oxidising reagent in the field of triterpenoids which formed different types of rearrangement products.

While studying the photooxidating reaction on α and β amyrins Corey et al[23] observed that Olean-12-en-3 ol 36 produced epoxy taraxerol 37.



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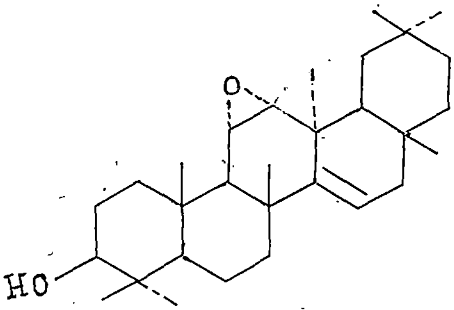

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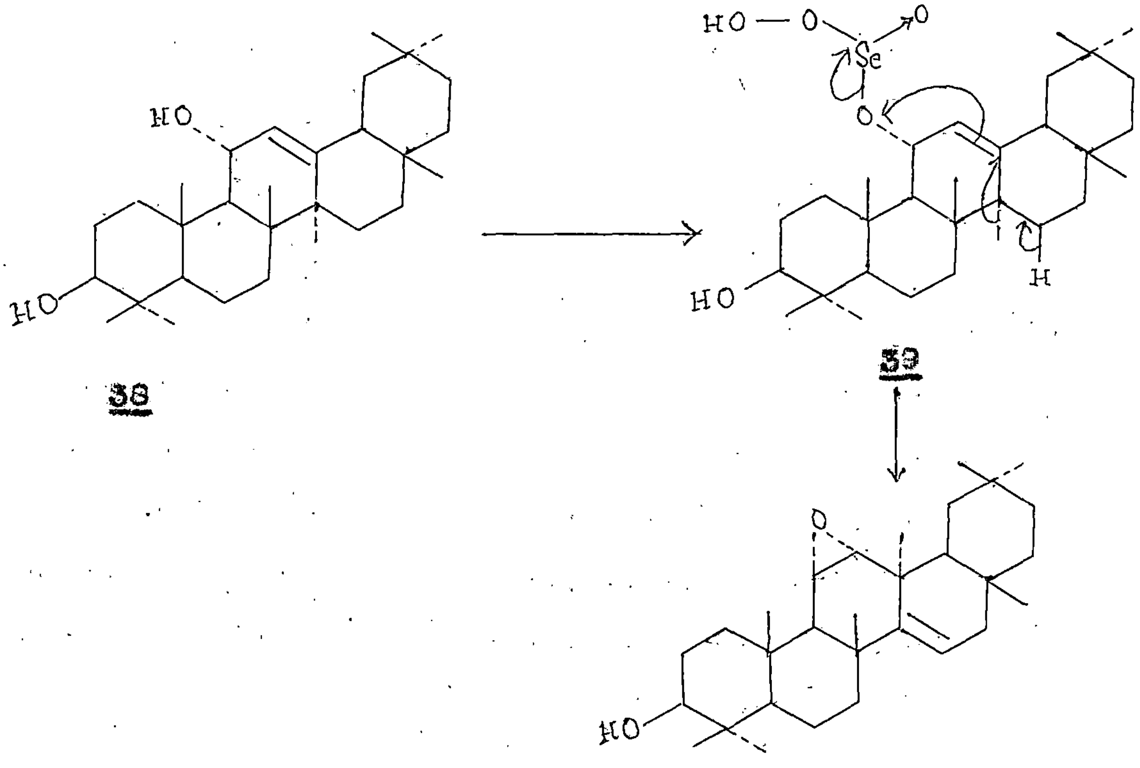
The structure of the epoxy taraxerol was established by the authors by different chemical and physical evidences. They observed that there was a skeletal change from more stable β-amyrin to taraxerene system. In the conversion of 36 to 37a therefore, there was an intrinsic driving force which would overcome the energetically unfavourable change in the arrangement of carbon and hydrogen and the skeletal rearrangement could be considered as powered by the oxidation. The former could be affected by mere application of a suitable catalytic agent. While studying in β-amyrin series they obtained the same epoxy compound.

While studying individually with α-amyrin series for the synthesis of 37, the first successful experiment involved the oxidation of olean-12-en-3 β,11 α-diol 38 with a mixture of hydrogen peroxide and selenous acid in tert. butyl alcohol. This experiment produced 37 in 50—60% yield. The pathway which was first considered was the formation of the intermediate 39 as shown in Scheme—2.

Scheme—2



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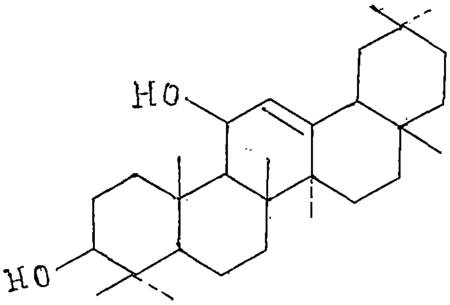
However, this was shown not to be the actual mechanism of the formation of 37 from 3β, 11α-diol 38 from the fact that the reaction of the 11-epimeric olean-12-en-3β, 11β-diol 40 with the hydrogen peroxide and selenous acid reagent also afforded the same epoxide 37 and not the epimeric epoxide.



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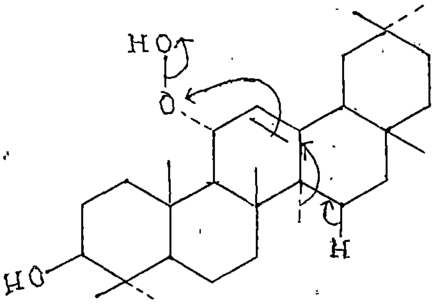
So, evidently the C-11-O bond was broken during the reaction. They suggested an alternative mechanism in which the isomeric diols 38 and 40 yield the same C-11, 12, 13 allylic cation which reacts with the peroxide to form olean-12-en-3β-ol, 11α-hydroperoxide 41.



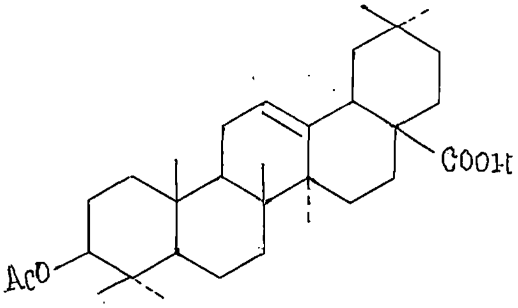
41

This hydroperoxide 41 in turn would undergo acid catalysed O—O fission and carbon rearrangement to give 37.

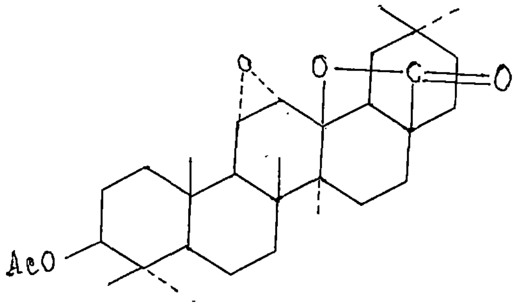
As expected from the above-mentioned fact it was found selenous acid merely functioned as an acid catalyst and the reaction could be done in presence of other acids like p-toluene sulfonic acid.

The reaction was extended to α -amyrin analogue ursan-12-en-3β , 11α-diol and observed similar type of products being formed.

Majumder and coworkers[32] reported that when oleanolic acid acetate 42, was treated with H_2O_2 in presence of boiling acetic acid and epoxy γ -lactone 43 and 12-hydroxy-γ -lactone 44 was formed.



42



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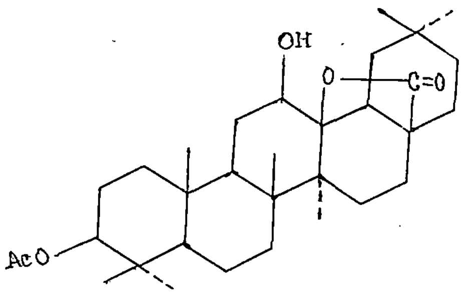
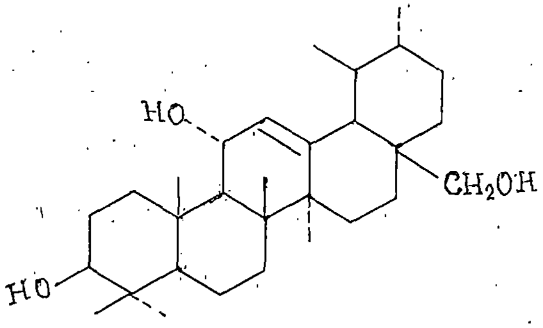
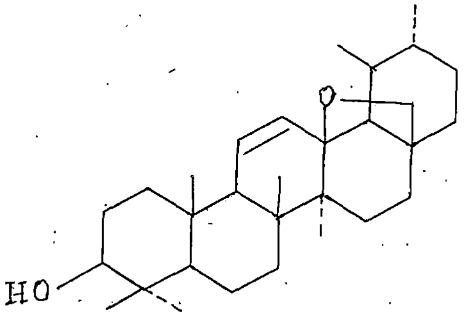


44

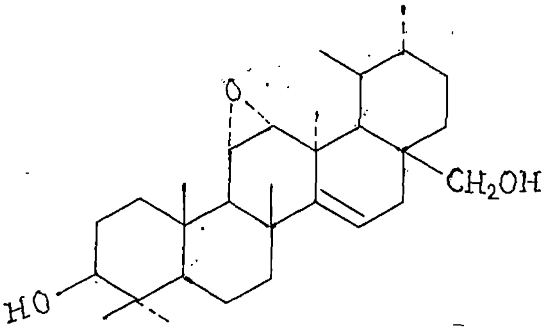
The similar type of reaction also observed in the case of ursane skeleton. It was observed that when 45 was treated with H_2O_2/TSOH, 46 and 47 were formed.



45

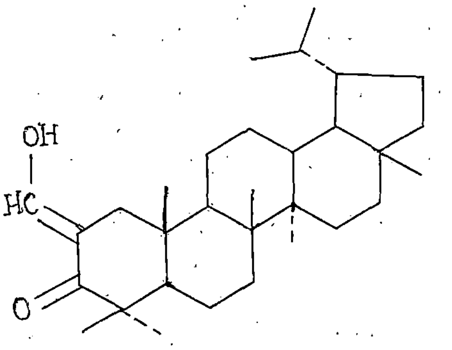


46

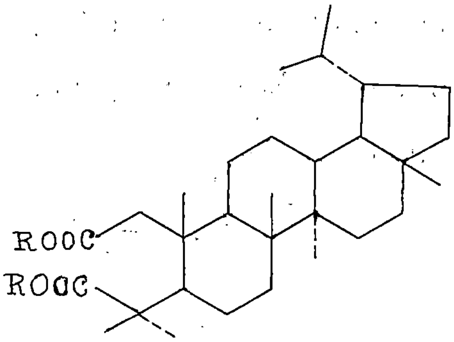


47

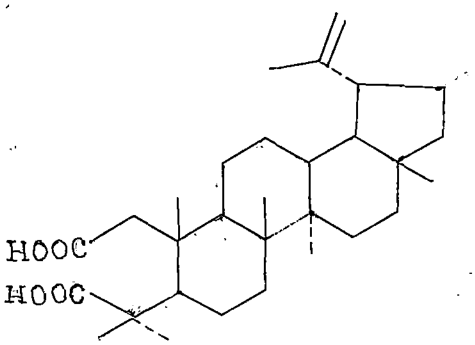
Another example of interest was the action of hydrogen peroxide on triterpenoids containing a hydroxymethylene ketone function. It has been observed that in absence of βγ-unsaturation and especially in alkaline media[33,34] oxidative cleavage occurred producing 2,3-secodiacids. Thus the ketone 48 gave exclusively the diacid[35] 48a, characterised as the ester 48b which was also obtained from 49 by catalytic hydrogenation[36].



48



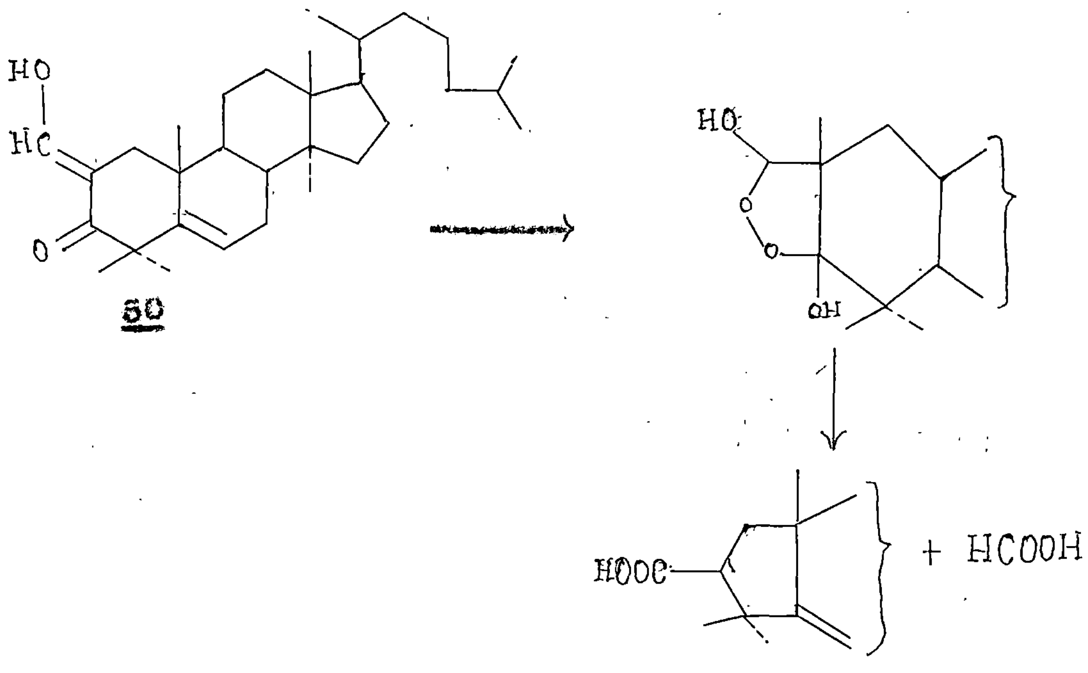
48a R = H
48b R = CH_3



49

It has been found that the ring contraction occurred in the presence of a β-γ-unsaturation. Thus hydroxymethylene anhydro dihydro litsomentone 50 would undergo rearrangement[37] in presence of hydrogen peroxide in alkaline media producing 51 as shown in Scheme—3.

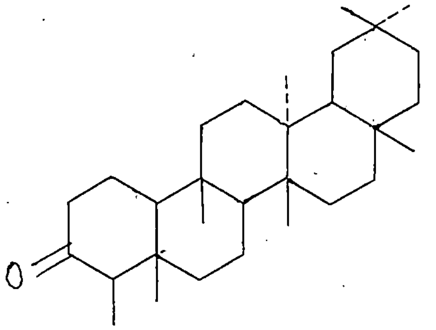
Scheme—3



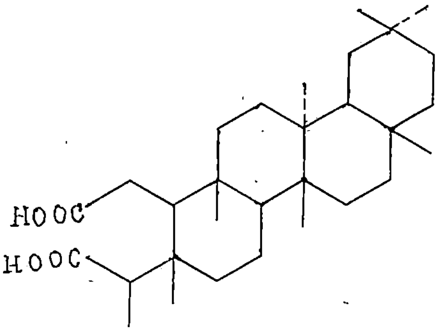
50

51

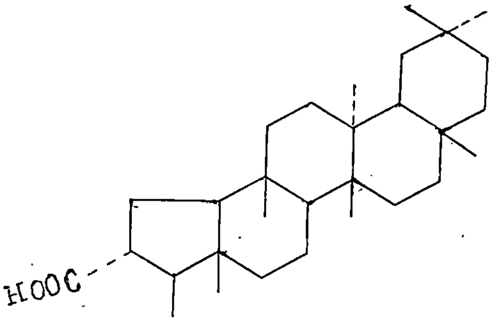
Pradhan *et al*[38] observed that when friedelin 52 was treated with hydrogen peroxide and selenium dioxide in tertiary butanol, a number of products were formed which were assigned structures 53,54,55.



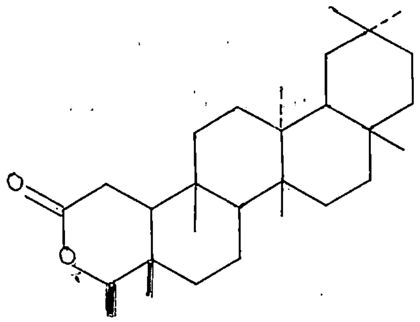
52



53



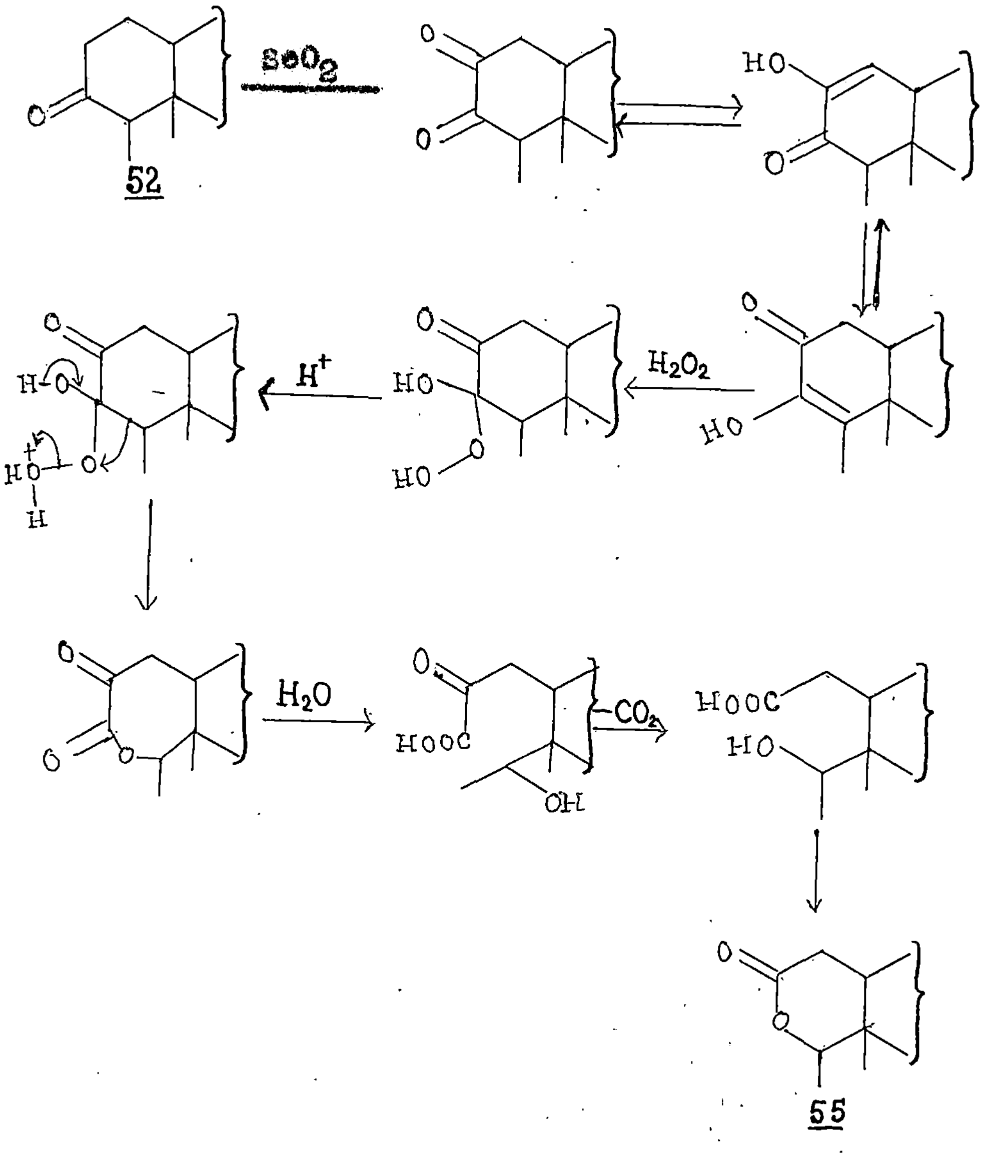
54



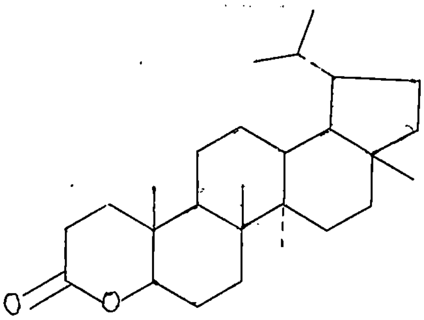
55

The products were characterised by making different derivatives and from the physical evidences. The interesting product 55 was found to be lactone. The mechanism of formation of the lactone was summerised in Scheme—4 as follows:

Scheme—4



The authors[39] also did the reaction on lupanone 56 and isolated the lactone 57.

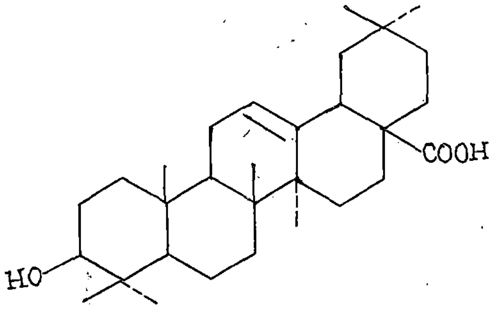


57

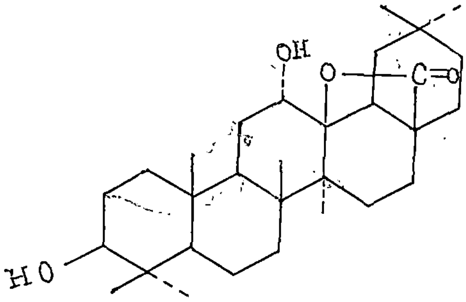
6. Photochemical oxidation on triterpenoids:

I. Kitigawa, K. Kitazawa and I. Yosioka[40] while working on biogenetic type photochemical conversion of plant observed that when oleanolic acid 58 in ethanolic solution was irradiated for 80 hours with occasional shaking afforded two lactones-one was 13α-hydroxy oleanolic lactone 59 while the other was the epoxy lactone which was assigned structure 60.

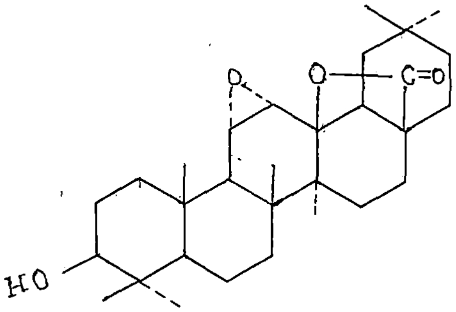
The structure of the compounds was established by the chemical and physical evidences.



58

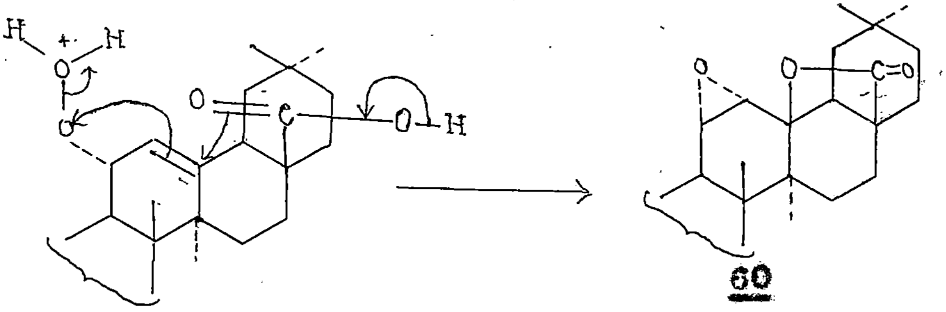


59



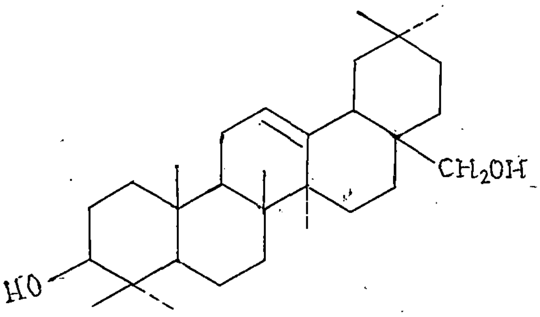
60

The mechanism of formation of the epoxy lactone was given following the Corey's[23] path as follows:

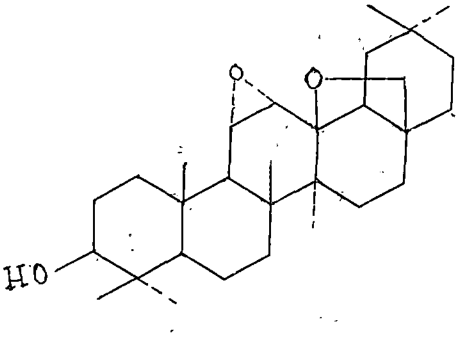


60

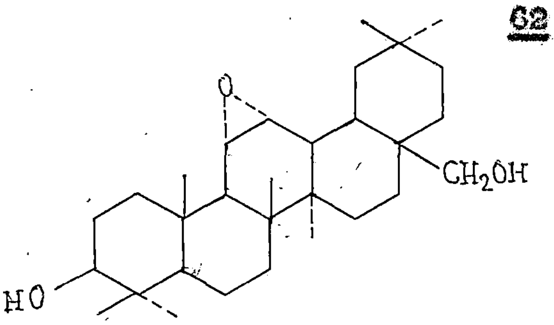
The reaction was extended in the case of erythrodiol 61 which possessed a 17β -CH_2OH function in place of 17β -COOH found in oleanolic acid 58. Here also two compounds 62 and 63 were isolated. One was an epoxy ether type of product 62 while the other product was characterised as the epoxy compound 63.



61

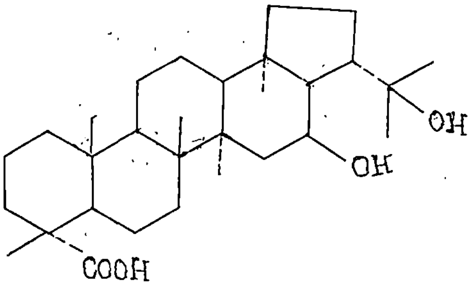


62

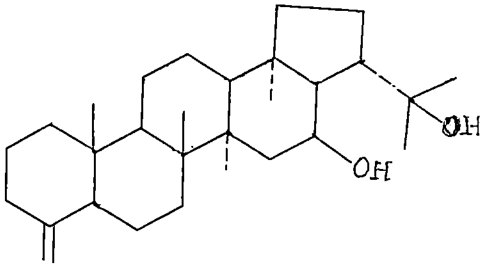


63

In a parallel examination[41] it was found that the introduction of a terminal methylene group could be done with the photooxidation method. It was observed that when leucotylic acid 64 was irradiated by mercury lamp at low pressure for 83 hours it yielded two products. The structure of the first compound was assigned as 65 where there was an introduction of terminal methylene at C—4 position which appeared as a biogenetic precursory system.

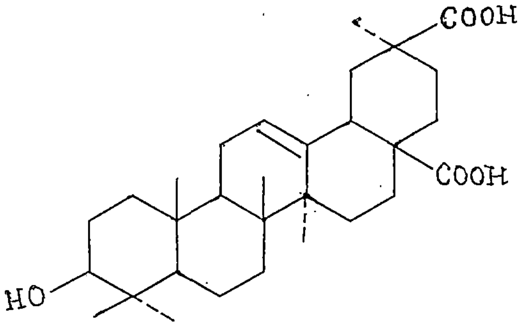


64

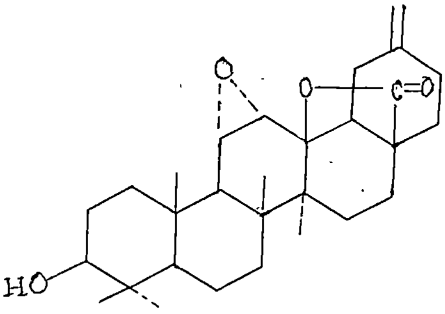


65

Taking this idea they have prepared eupteleogenin 66 from spergulagenic acid 67.



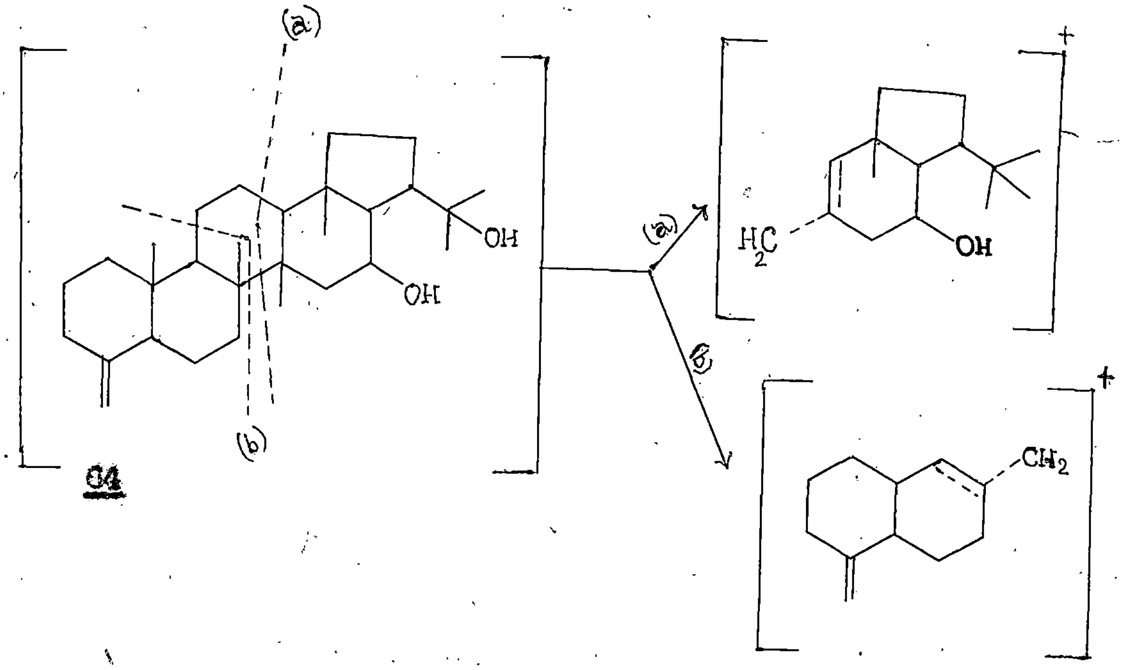
66



67

The structure of 64 was confirmed by its mass fragmentation pattern.

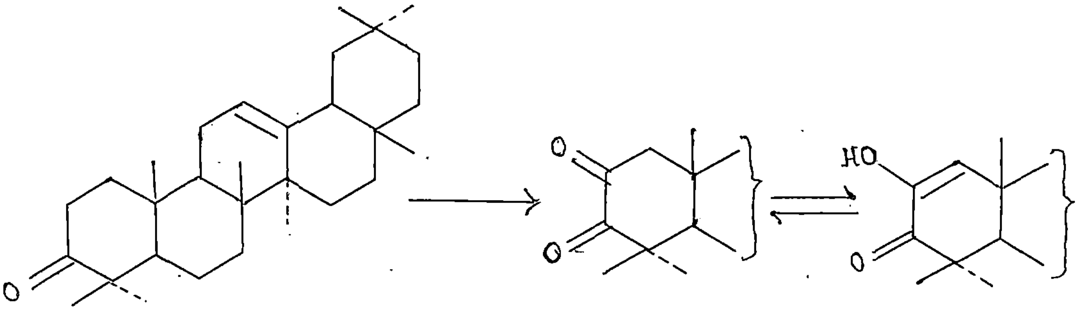
Scheme—6



7. Autoxidation on triterpenoids:

Khastgir and coworkers[42] studied autoxidation in ring A of β-amyrone. When β-amyrone 68 was oxidised by passing oxygen through its suspension in tertiary butyl alcohol containing potassium tertiary butoxide gave diosphenol 69a and 69b. The structure of the compound was established by its physical and chemical evidences.

Scheme—7



68 69a 69b