PART - II

OXIDATION REACTION OF SELENIUM DIOXIDE ON LUPANONE

CHAPTER - I

A SHORT REVIEW ON OXIDATION REACTION OF SELENIUM DIOXIDE

A new reaction class was born after the report of Riley et al[1] on the conversion of monocarbonyl compound having an adjacent methylene group or unit to an α-dicarbonyl compound with the help of selenium dioxide. The reagent has found a wide range of application e.g. conversion of a ketone or an aldehyde to an α-dione, allylic oxidation, conversion of monoketone or a 1,4-diketone to an $\alpha\beta$-unsaturated ketone or to an ene-dione. Since the reagent has been used extensively during the course of our several investigations embodied in this thesis, it is but natural to make a short review on the subject - oxidation reactions of selenium dioxide under various conditions.

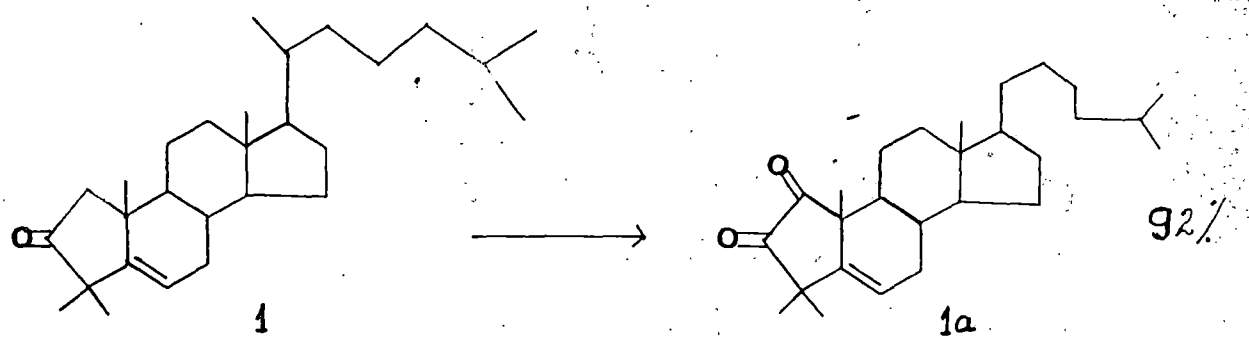
a. Formation of Diones :

As mentioned above ketones and aldehydes containing an adjacent methylene group would react with stoichimetric quantities of selenium dioxide to give α-diketone and keto aldehydes as shown below :

$$CH_3COCH_3 \longrightarrow CH_3COCHO \quad (60\%)$$

$$CH_3CH_2CH_2CHO \longrightarrow CH_3CH_2COCHO \quad (45\%)$$

If the structurel environment of the reactant is such that it avoids any side reaction or competing reactions with the expected route of reaction, then the yield of the product is formed in a considerable amount eg.[2]



1 1a

A-nor-4,4 dimethyl

Cholest-5-ene-3-one

Mechanism :

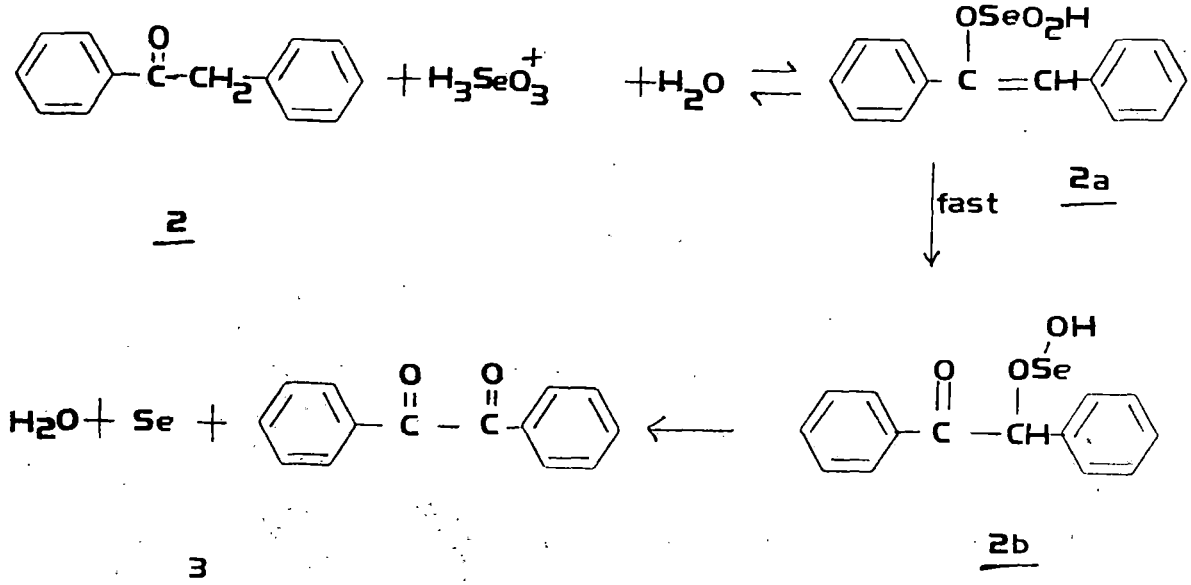
Corey et al[3] studied the oxidation of desoxybenzoin to benzil by SeO_2 (which in aqueous medium present as selenious acid) in 70% HOAc at 89.2°. They observed that the two ortho substituents on the ring adjacent to the carbonyl group did not depress the rate of acid catalysed oxidation nullifying the possibility that carbonyl addition was involved. The rate expression for the oxidation reaction

$$Ph.COCH_2Ph + SeO_2 \longrightarrow Ph.COCO.Ph + Se + H_2O$$

is $$\frac{d[SeO_2]}{dt} = K[SeO_2][Ph.COCH_2Ph][H^+]$$

Replacement of the α-hydrogen of desoxybenzoin by deuterium resulted in a several fold decrease in rate in the acid catalysed process. On the basis of these and other data it was proposed that the rate determining step in the above reaction was the formation of enol selenite ester 2a directly from the ketone by a process mechanistically related to enolization in which the electrophile-nucleophile pairs were $HSeO_2^+$ or $H_3SeO_3^+$ and H_2O (acid catalysed process). The enol selenite ester 2a rearranged to an α-substituted Se(II) ester 2b which decomposed to benzil 3 by 1,2 elimination of (H_2SeO) and selenium (Scheme-1)

Scheme - 1



b. Allylic oxidation :

After a set of experiments on this particular reaction type a general rule has been postulated by Guillemonat[4-8]

(i) The oxidation always occurred alpha to the most substituted end of the double bond.

(ii) When the double bond was in a ring, whenever possible, oxidation occurred within the ring.

(iii) The order of preference for oxidation was $CH_2 > CH_3 > CH$

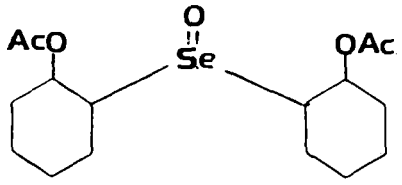
(iv) When the double bond was terminal rather than the expected secondary alcohol or derivative thereof the primary alcohol was formed with the migration of the double bond.

Mechanism of Reaction :

The above mentioned generalisation is not sometime sufficient to explain some experimental findings[9-11] but Guillemonat's studies on the behaviour of selenium dioxide in acetic acid - acetic anhydride led to formation of many useful and still valid generalisation with respect to the site of attack in unsymmetrical alicyclic and acyclic olefins.

Waters[12] has suggested the reaction to proceed via neutral radical species but it seems in contrast to the findings of Sheafer et al[13] that the reaction was unaffected by inhibitors and, therefore, could not be the radical chain. This has received further support from the finding of Trachtenberg et al[14] because the oxisising system could not involve free radical because it could not initiate polymerisation of acrylonitrile under the conditions for this polymerisation to occur which normally rapidly polymerises if a source of free radicals was present.

Wiberg et al[15] isolated 5 (Selenoxide) from the oxidation of cyclohexane in acetic acid - acetic anhydride. Hence he gave a negative view to the postulation of Guillemonat that the organoselenium intermediate was a selenide.



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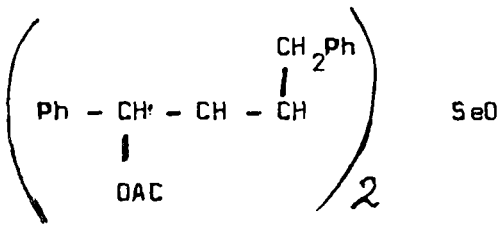
A compound 6 analogus to 5 was isolated by Schaefer et al[13] during the oxidation of 1,3 - diphenyl propene 7. The compound in question very slowly decomposed to 8 to account for the course of oxidation. It was suggested that the path must involve the solvolysis of an allylic selenite ester although the structure of the latter had not been established. A probable reaction path was suggested as below :



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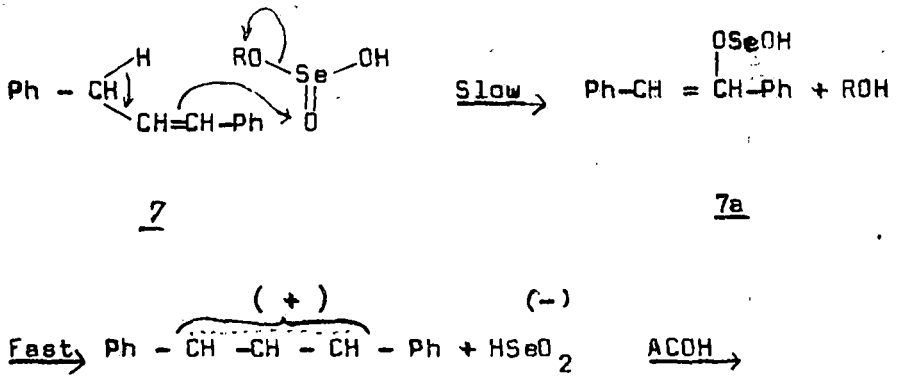
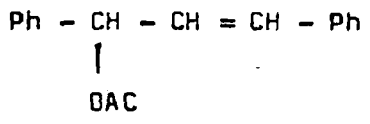
Scheme - II



7 7a



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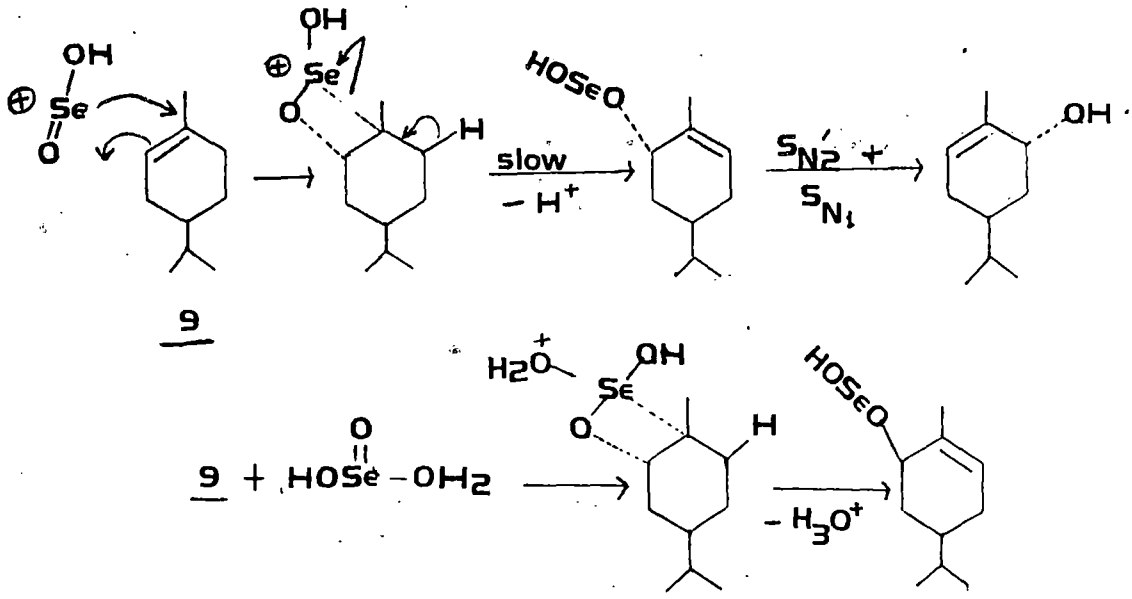
The rapid SN^1 of 7a was in agreement with the observation that 3-deuterium labelled at C-3 showed equilibration of c-1 and C-3. Furthermore, the presence of a final solvolytic step was in agreement with observations on many systems. Thus, one obtained alcohols, acetates and ethers when the selenium dioxide oxidation was performed in water, acetic acid and alcohol respectively[9]-11. Finelly mechanism put forward by Schaefer et al[13] did not explain the stereochemical result.

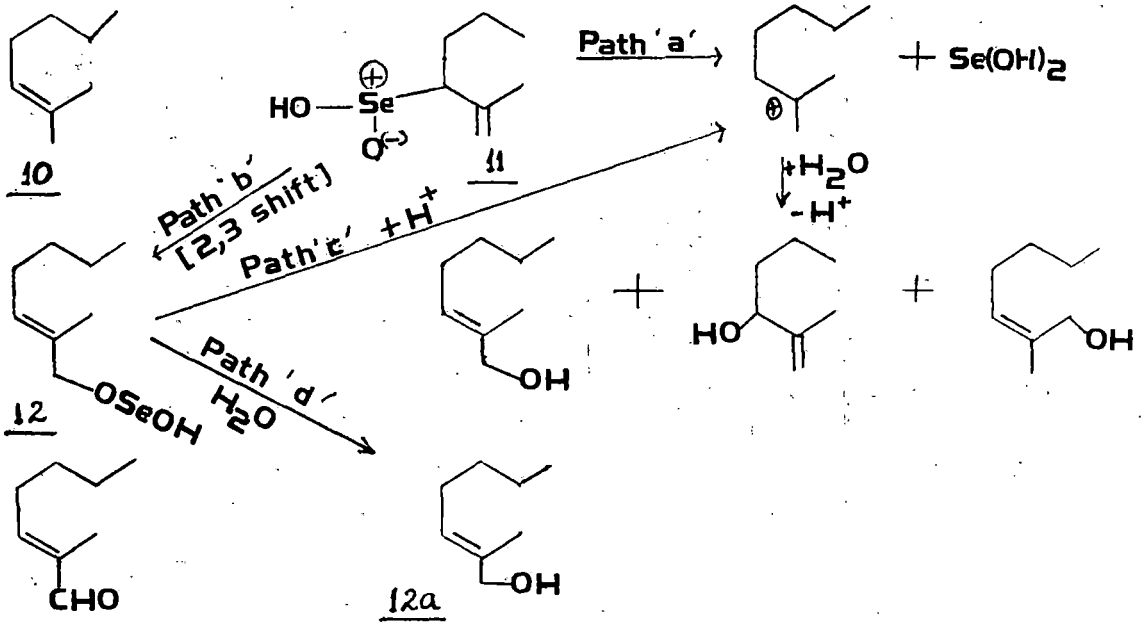
During the oxidation of various cychohexenyl system, Trachtenberg[14] et al proposed the following mechanism to explain the stereochemistry of the product for the oxidation reaction of D(+) - 1 -p-menthane 9.

Scheme - III

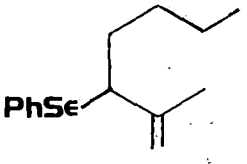


The first step does not imply a converted 2 + 2 cyclo-addition but rather a typical Markowinikoff type electroplilic addition with attack occurring through oxygen to generate positive character at the tertiery carbon followed by cyclisation. Sharpless et at[16] have also proposed a different mechanism for allylic oxidation of olefins. Wiberg et al[15] are of the view that allyl seleninic acid[11] formed initially undergoes solvolysis (scheme IV) to give the products. This mechanism is not fully agreed to by other workers. Because of inertness of benzyl seleninic acid to solvolysis Schaefer[13] and Tractenberg[14] were not in favour of the above mechanism. They proposed a [2,3] sigmatropic rearrangement (path b scheme IV) of allyl seleninic acid 11 to a selenium (II) ester 12 to be more appropriate[16] steps that take place during the oxidation. They[16] suggested that the [2,3] sigmatropic shift indicated in the path b was a facile process

Scheme - IV



Buchi and Wuest[17] established that SeO2 selectively attacked tri-substituted olefins such as 10 to give only the alcohol 12a. The postulation of [2,3] - sigmatropic rearrangement by Sharples et al[16] was further tested by the conversion of allyl phenyl selenide to alcohol 12a.



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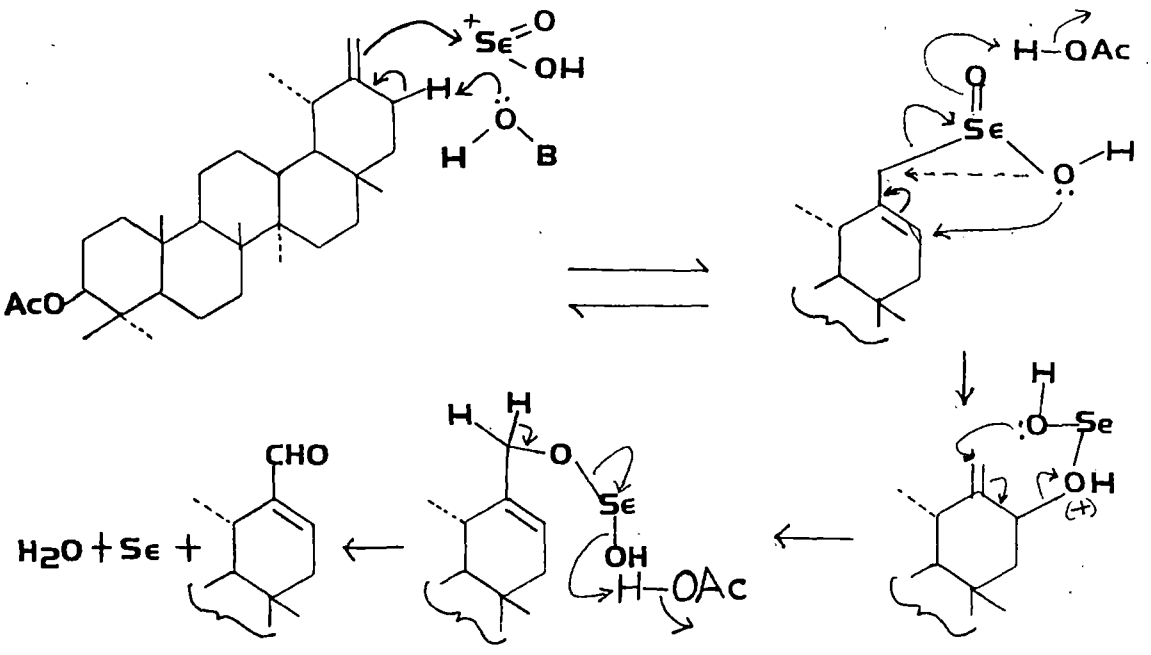
The oxidation of taraxasteryl acetate to 30-oxo-taraxast-20-en-3β-yl acetate (Talapatra et al)[18] was suggested to occur by the following mechanism :

Scheme - V



c. $\alpha\beta$-dehydrogenation of carbonyl compound :

Riley et at[19] reported dehydrogenation of diethyl succinate to a mixture of di and half ester of maleic acid. The conversion of ketones to $\alpha\beta$-unsaturated derivatives by oxidation with selenium dioxide was competive with diketone formation but shielding of α-methylene group by nearby bulky substituents often favoured the formation of $\alpha\beta$-unsaturated ketone e.g. 12-keto steroids afforded $\Delta^{9,11}$-12-ketones upon oxidation with selenium dioxide rather than 11,12-diketones[20-22].

Mechanism of $\alpha\beta$-dehydrogenation

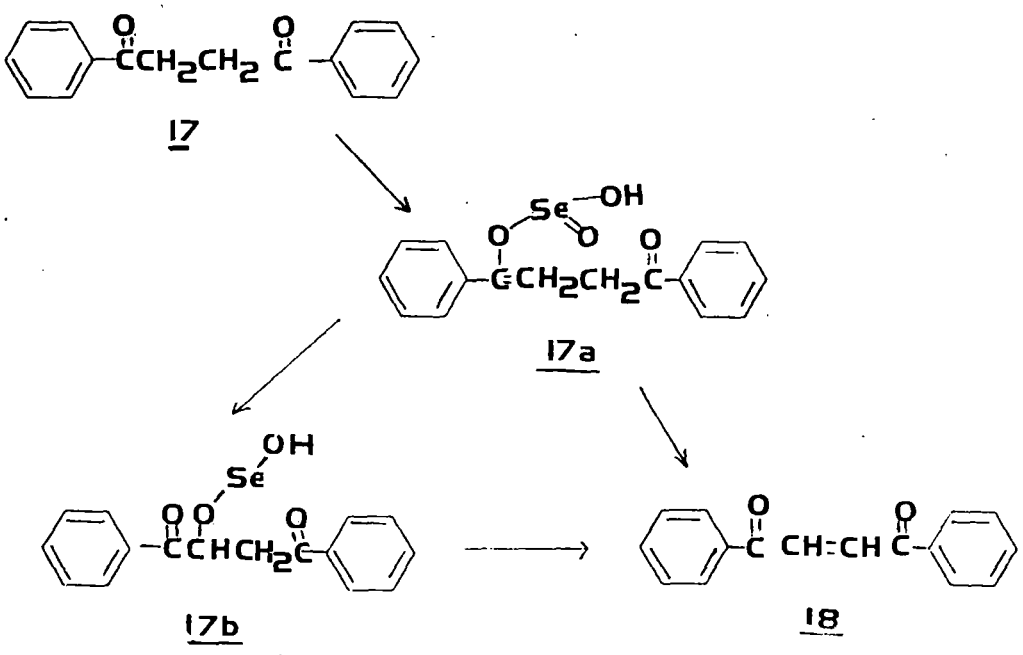
(i) 1,4 - diketones :

Since Riley et al's[1] initial investigation, numerous examples of describing SeO_2 as an oxidant for organic molecules had been reported[23],

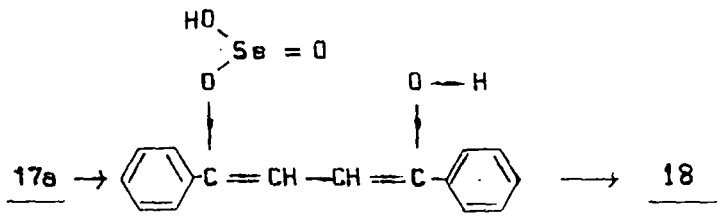
however, little detailed mechanistic information was available. In an effort to understand mechanism of oxidation reaction of 1,4-diketones to 1,4-enediones by SeO_2, Schaefer et al[24] carried out a study of the oxidation of 1,2-dibenzoyl ethane 17 to trans 1,2,-dibenzoyl ethylene 18. In 80% acetic acid - 20% water as solvent, 18 was obtained in 80-85% yield; no 1,4 - diphenyl 1,2,4 - butanetrione 17a could be detected. A kinetic study of the reaction was complicated by the fact that 18 also reacted with seleneous acid, however, the rate of oxidation of 18 was 30 time slower than that of 17. The following mechanism was proposed by Schaefer[24] for the oxidation of 1,2 -dibenzoyl ethane to trans - 1,2 - dibenzoyl ethylene.

Scheme - VI

$$H_2SeO_3 + H^+ \rightleftharpoons H_3SeO_3^+$$



The mechanism involved (i) production of oxidising selenium species $H_3SeO_3^+$, by protonation of selenious acid H_2SeO_3 (ii) rate determining attack of the oxidising selenium species, $H_3SeO_3^+$, on the substrate 17 to give an enol selenenite ester 17a to the product via one of the two pathways. Path A involved rearrangement of 17a to the α-selenium (II) keto ester 17b and then to the product 18 by a rapid 1,2,-elimination of the elements of H_2SeO_2. Of the two possibilities the 1,4 -elimination from enol-selenite ester 17a, was likely since this intermediate contained a doubly activated methylene unit. The latter simply required an enolisation to give the half ester of the dienol 17c which then decomposed to product 18 via bond migration, the driving force being the reduction of the selenium.

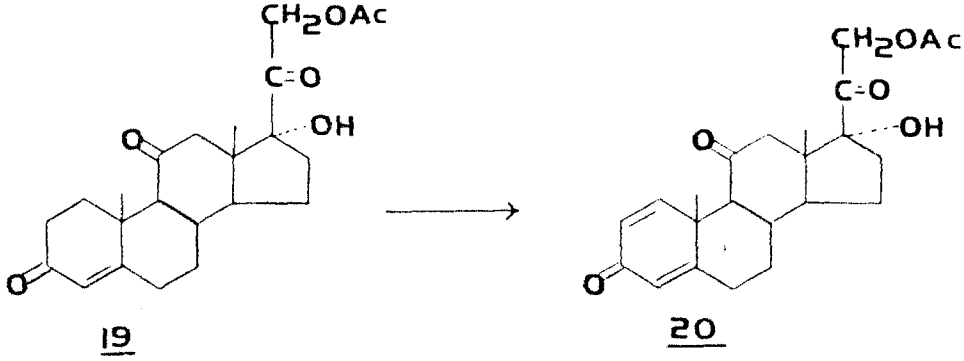


17c

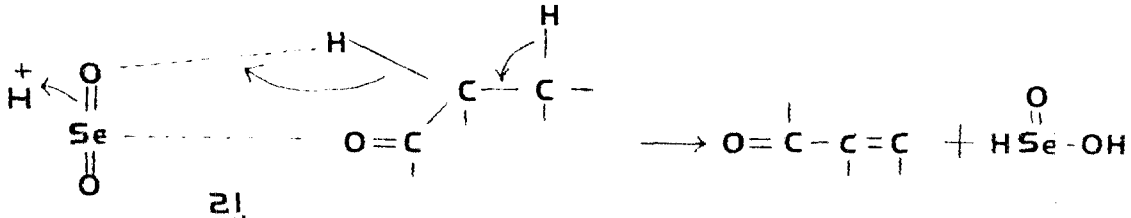
The possibility of 1,2 - elimination of H_2SeO_2 appeared less likely in view of the fact the alternative product of its decomposition 1,4 - diphenyl 1,2,3 - trioxbutane could not be detected[3]. Either a direct 1,4 - elimination from 17a or a rearrangement of 17a to 17b followed by a rapid elimination of the elements of H_2SeO_2 would account for the formation of trans - 1,2 - dibenzoyl ethylene 18.

(ii) Mono Ketones :

While studying the dehydrogenation of an $\alpha\beta$-unsaturated ketone, Langbein[25] obtained a second order rate constant for the Δ^1-dehydrogenation of cortisone acetate 19 to 20, from a plot which contained the concentration of ketone and selenium dioxide. A common intermediate similar to 17a, 17b was suggested to form by direct attack of the oxidant on the ketone, which decomposed to form all possible oxidation products. It was considered more plausible path which did not involve carbon - oxygen bond formation as 21.



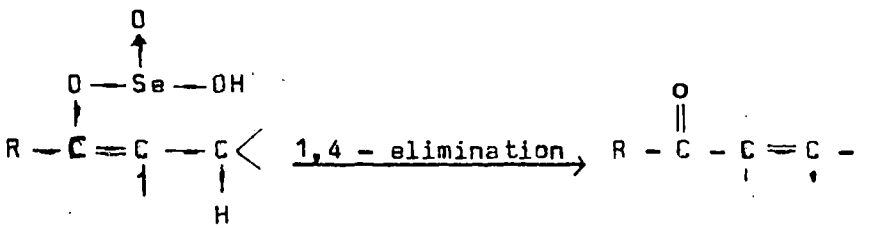
19 20



21

Since conversion of ketone to $\alpha\beta$-unsaturated derivatives by oxidation with selenium dioxide was competitive with diketone formation and this reaction proceeded via an intermediate enol selenite ester, a mechanism for the dehy-

drogenation of a mono ketone was proposed, which involved either concerted 1,4 - elimination from the enol ester 22 or concerted 1,2 - elimination from Se (II) ester 23. These intermediates are similar to 17a and 17b but without a second carbonyl group to activate the β-position and therefore should be less prone to undergo elimination.



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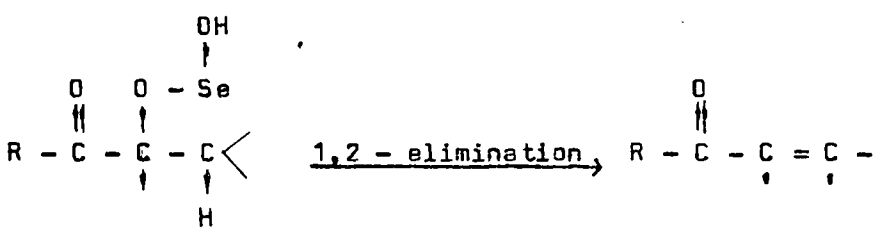
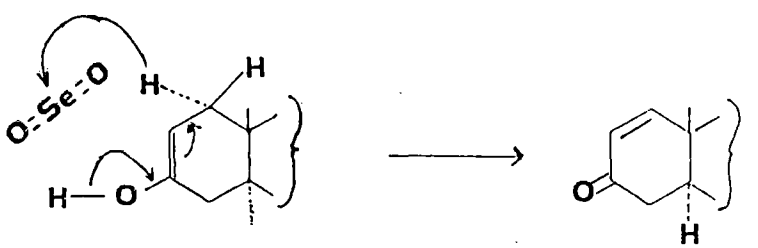


23

Another path, which circumvented the difficulty inherent in 22, would be direct attack on the allylic position in the enol 24, by SeO_2 to remove the hydride ion.

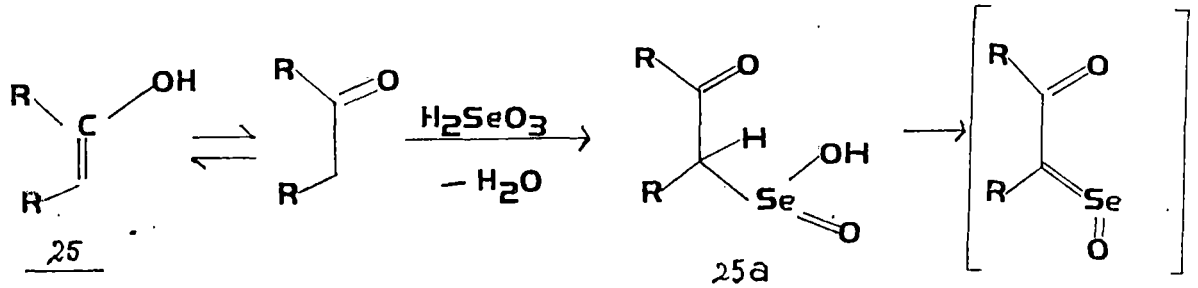


24

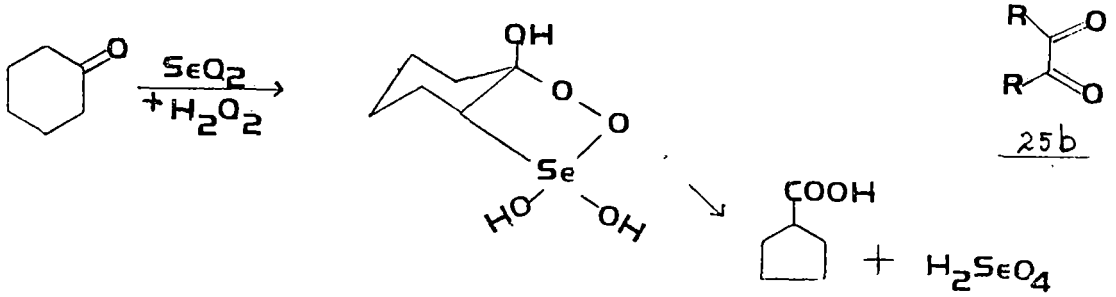
The formation of α-dions by some monoketones and $\alpha\beta$-unsaturated ketones by other is not clearly understood. This is assumed partially due to solvent effect. Tertiary alcohols are normally used to carry out dehydrogenation[26], but the reaction can be affected in acetic acid[27] or in aromatic solvents[28]. α-diones are generally produced while using ethyl alcohol or dioxan[29]. Again shielding of α-methylene group by nearby bulky substitutes often favours the formation of $\alpha\beta$-unsaturated ketones.

Sharpless et al[30] reported that SeO_2 oxidation of ketones and aldehydes to α-diketones and glycols involved an organo selenium species. They proposed that the key intermediate (Scheme VII) in this sequence was the β-keto - seleninic acid 25a formed by the electrophilic attack of selenous acid on the enol 25 which after rearrangement ~~6de~~ afforded 25b. They[30] also suggested that this β-ketoseleninic acid intermediate was responsible for the unusual oxidative rearrangement observed during SeO_2 oxidation of ketones in the presence of H_2O_2 (Scheme VIII)

Scheme VII



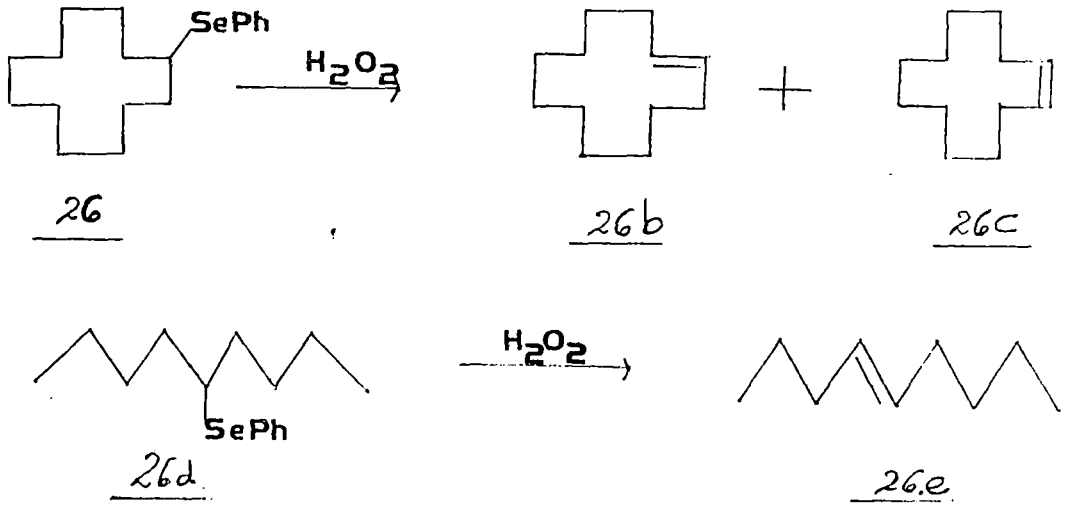
Scheme VIII



However, Uemura et al[31] reported that the treatment of secondary alkyl phenyl selenides with various oxidents (H_2O_2 , m - chloroper-benzoic acid, $NaIO_4$) afforded the corresponding trans alkene highly selective irrespective of the amount of oxidant.

They reexamined the experiment by Sharpless et al[32] on the oxidation of 26a with H_2O_2 (70%) and isolated 26b as the main product together with a small amount of 26c in sharp contrast to their [31] result of quantitative yield of a 1 : 1 mixture of 26b and 26c.

A similar phenomenon was also observed in the oxidation of 5-nonyl phenyl selenide 26d which afforded the corresponding trans alkene (trans-non-4-ene) 26e.



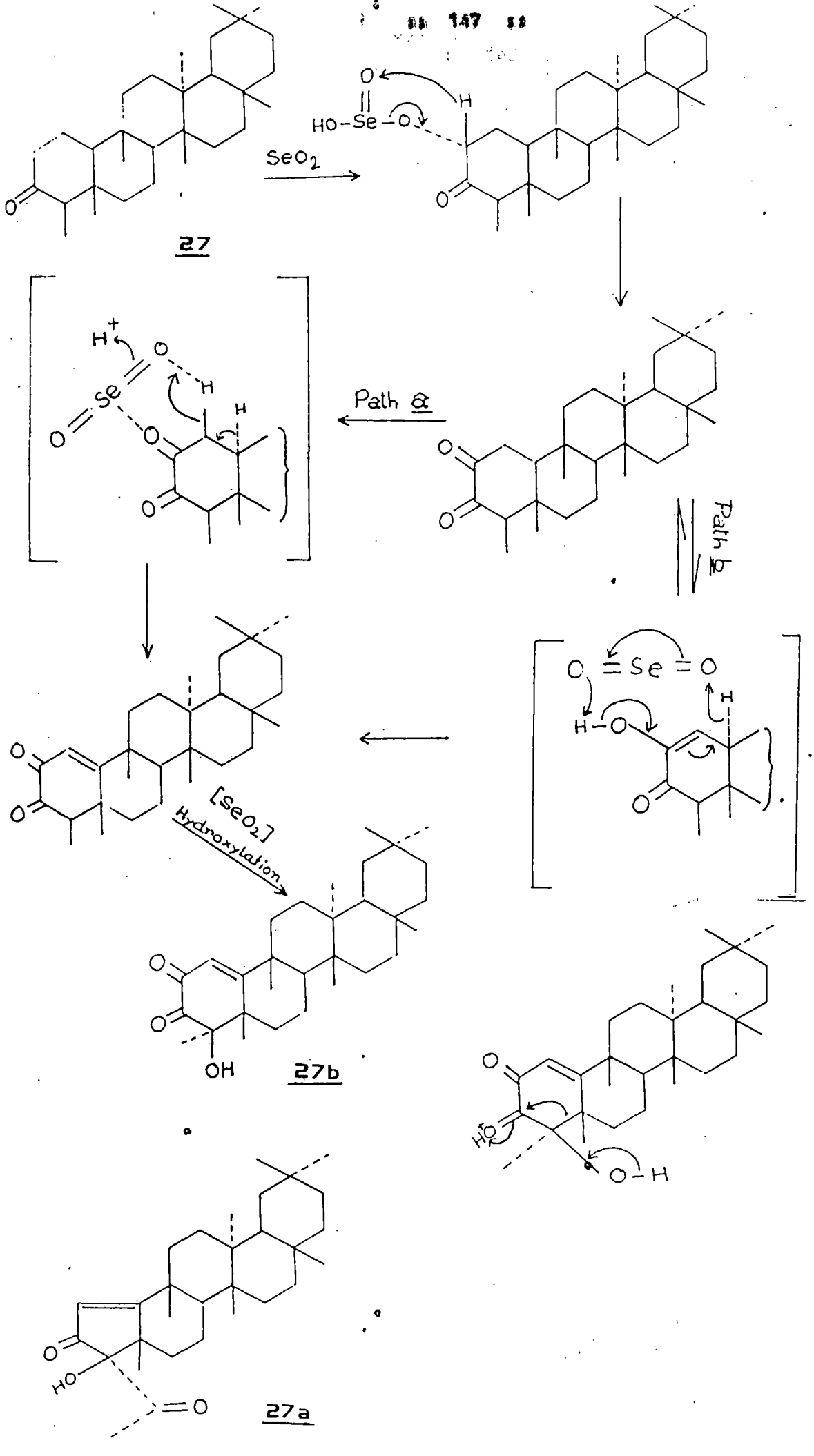
The regiochemical and stereochemical aspects of allylic hydroxylation reactions of Selenium dioxide was studied by Staphenson et al[33]. According to them the mechanism of the reaction in t-butyl alcohol is more complex than predicted by using the ene - [2,3] sigmatropic shift scheme proposed by Sharpless et al[16]. Ionic intermediates bring out stereochemical complexities which can be suppressed in more basic media e.g. t-butyl alcohol/ pyridine. The prefrential formation of trans allylic alcohol products in the reaction is due to staric preferences in the [2,3] sigmatropic migration. The ene step is non-selective.

A few examples of oxidation reactions of SeO_2 on triterpenes are provided in the following paragraphs :

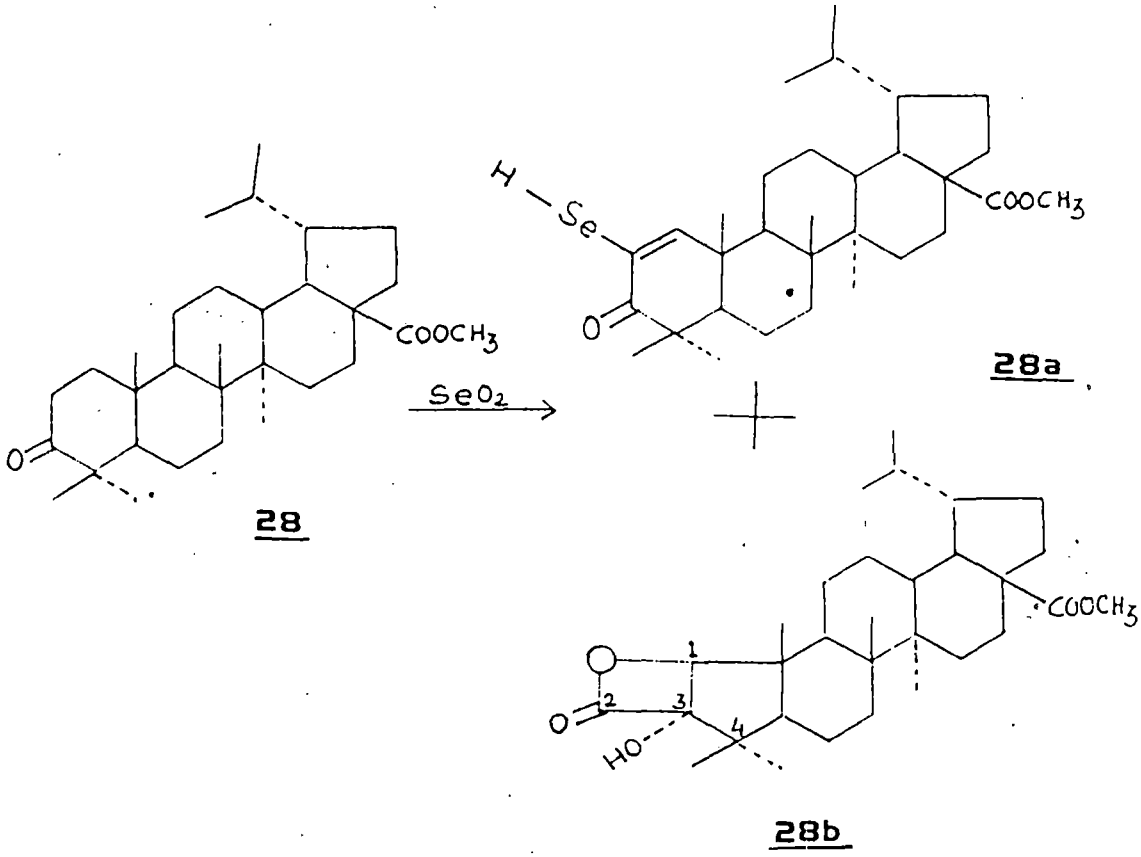
Examples of selenium dioxide oxidation of triterpenes :

Pradhan et al have carried out a series of oxidation reactions on triterpenoids with this reagent which are summarised as follows :

1. Friedlin27 on prolonged heating with selenium dioxide in t-butanol furnishes two oxidised products[34], 3-acetyl -4 nor-friedel-1(10)-en-3β-ol-2-one, 27a and friedel-1(10)-en-4β-ol-2,3-dione, 27b


SeO2
27
Path a
Path b
[SeO2]
Hydroxylation
27b
27a

2. Methyl dihydrobetulonate[35] 28 on prolonged heating with selenium dioxide in t -butenol furnishes lup-28 - carbomethoxy-1(2)-en-3-one-2-seledide, 28a and A-nor-lup-28-carbomethoxy-2-carb-1-olide-3α-ol, 28b.



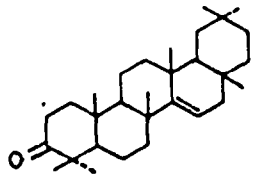
28

28a

28b

3. Taraxerone[36] 29 on prolonged heating with selenium dioxide in t-butanol afford five products, (a) 1(2)°-dehydrotaraxerone 29a, (b) 1(2)-dehydrotaraxe:-3-one-2-selenide 29b, (c) 2-nor-taraxer-1,3-dione 29c, (d) 1(2)-dehydrotaraxerone-2, 2'-seleno-taraxer-1', 3'-dione, 29d and (e) 1,3-dihydroxy-3-carboxy-A-nor-taraxerene, 29e.

Tararerone, SeO_2 mixture reflux with t-butanol for 24 hours under N_2 atmosphere.



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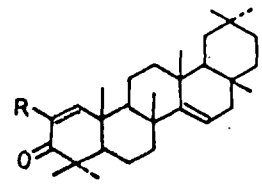
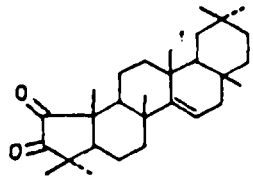
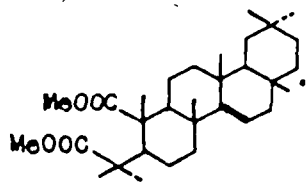
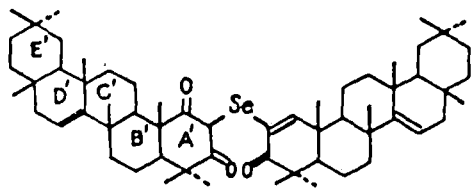


29a, R=H
29b, R=SeH

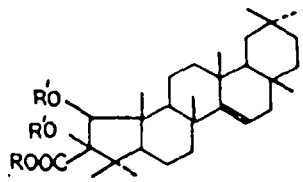


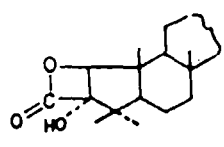


29c



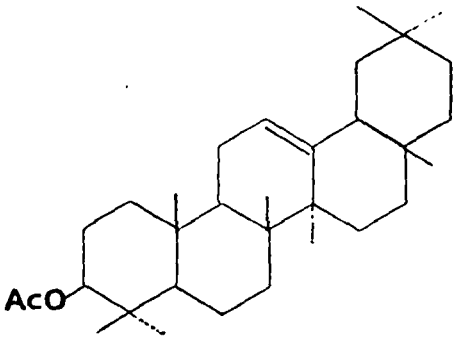
29d



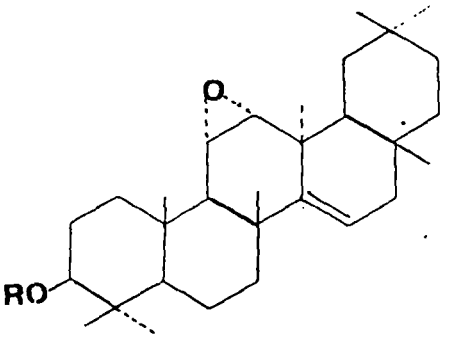


29e, R=R'=H
, R=Me, R'=Ac

4. β -amyrin acetate[37] 30 when refluxed for 60 hrs with selenium dioxide and hydrogen peroxide in t - butanol yields, 11α , 12α -epoxy-taraxer-14-en-3β -yl acetate, 30a 11α , 12α -apoxy-taraxer-14-en-3 β -ol 30b.



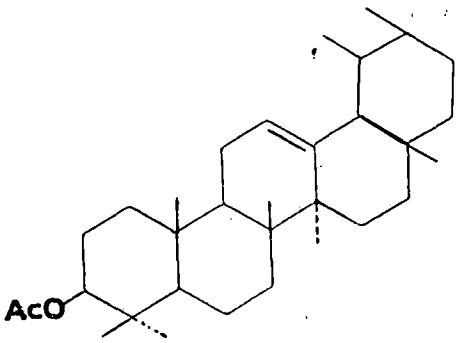
30



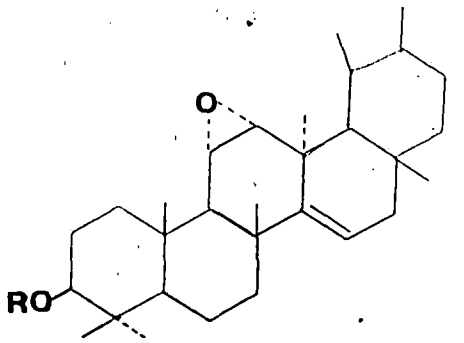
30a , R = Ac

30b , R = H

5. α -amyrin acetate[37] 31 when refluxed with selenium dioxide and hydrogen peroxide in t-butanol affords, 11α, 12α-epoxy-urs-14-en-3β-yl acetate 31a 11α, 12α-epoxy-urs-14-en-3β-ol, 31b.



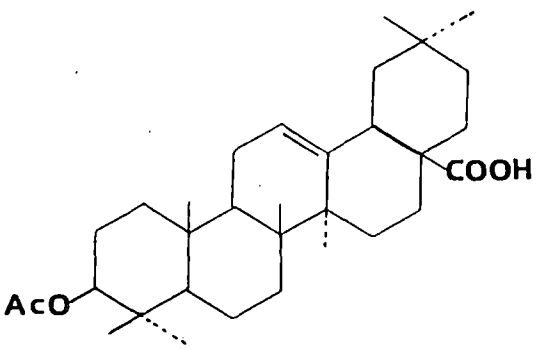
31



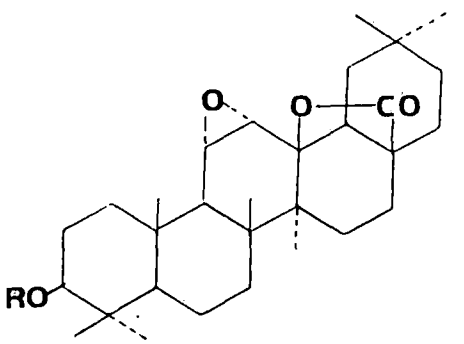
31a , R = Ac

31b , R = H

6. Acetyl oleanolic[37] 32 acid on refluxing with selenium dioxide and hydrogen peroxide gave 11α,12α-epoxy-oleanan-28$\rightarrow$13--olide - 3β-yl acetate, 32a and 11α,12α-epoxy-oleanan-28 $\rightarrow$ 13 - olide-3β-ol, 32b .



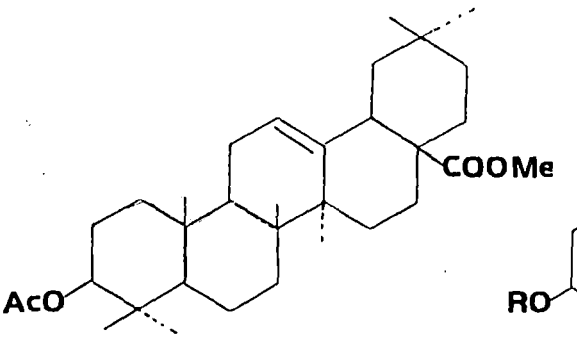
32



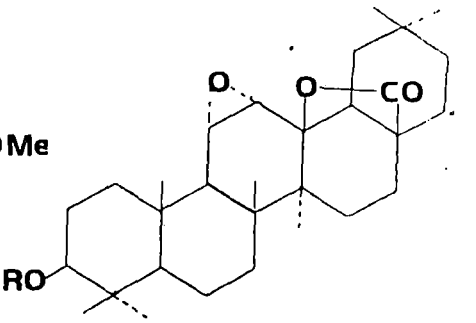
32a , R = Ac

32 b , R = H

7. Methyl acetyl oleaholate 33 when oxidised by selenium dioxide gives 11α,12α-epoxy-oleanan-28 → 13-olide-3β-yl acetate, 33a 11α,12α-epoxy-oleanan-28 → 13-olide-3β-ol, 33b.

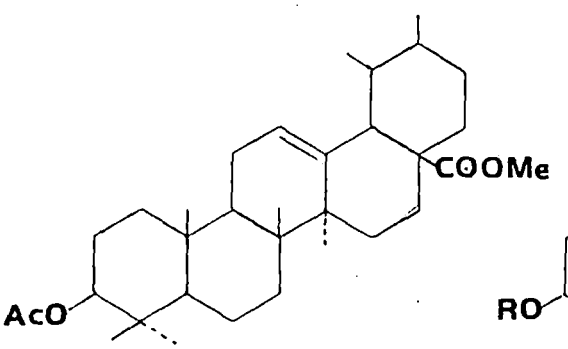


33

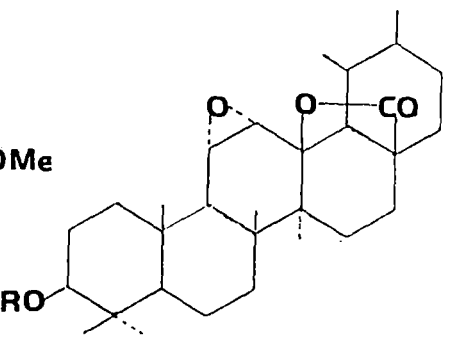


33a, R = Ac
33b, R = H

8. Similarly, methyl acetyl ursolate[37] 34 gave, 11α, 12α-epoxy-urs-28→13-olide-3β-yl acetate, 34a and 11α, 12α-epoxy-urs-28→13-olide-3β-ol, 34b.

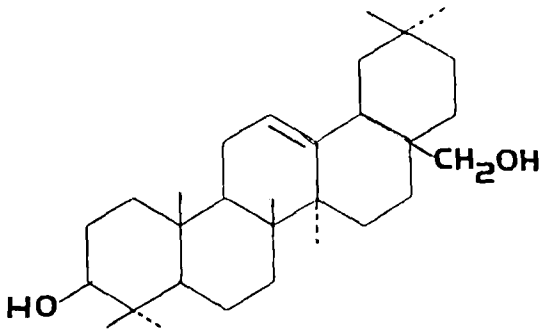


34

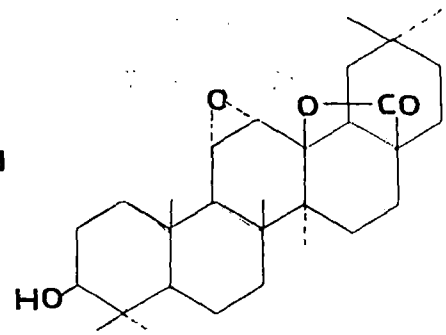


34a, R = Ac
34b, R = H

9. Oxidation of erythrodiol[37] 35 gives, 11α, 12α-epoxy-oleanan-28$\rightarrow$13-olide-3β-ol, 35a.

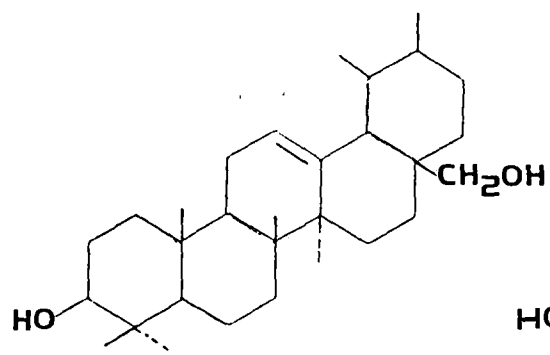


35

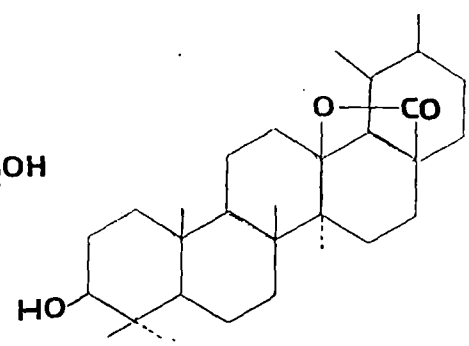


35a

10. Oxidation of uvaol[37] 36 by selenium dioxide gives, 11α-12α-epoxy-urs-28$\rightarrow$13-olide-3β-ol, 36a.

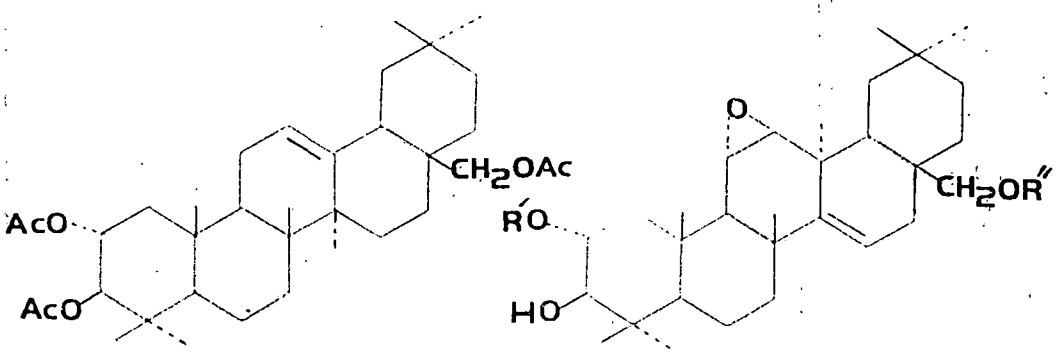


36



36a

11. Oxidation of olean-12-en-2α,3β,28-yl triacetate[37] 37 by selenium dioxide gives 11α,12α-epoxy-taraxer-14-en-3β-ol-28-yl diacetate 37a and 11α,12α-epoxy-taraxer-14-en-2α, 3β-diol-28-yl acetate, 37b.



37

37a, $R' = R'' = Ac$

37b $R' = H, R'' = Ac$

The compound 37 was also expected to furnish a lactone epoxide but did not occur in practice. It may be due to non-proximity of the acetate carbonyl group from the site of carbonium ion.

Thus the triacetate 37 furnished taraxerene derivative only where the functional group at C-28 is not involved.