CHAPTER II

A short review on Δ^{14}-Taraxerene triterpenoids

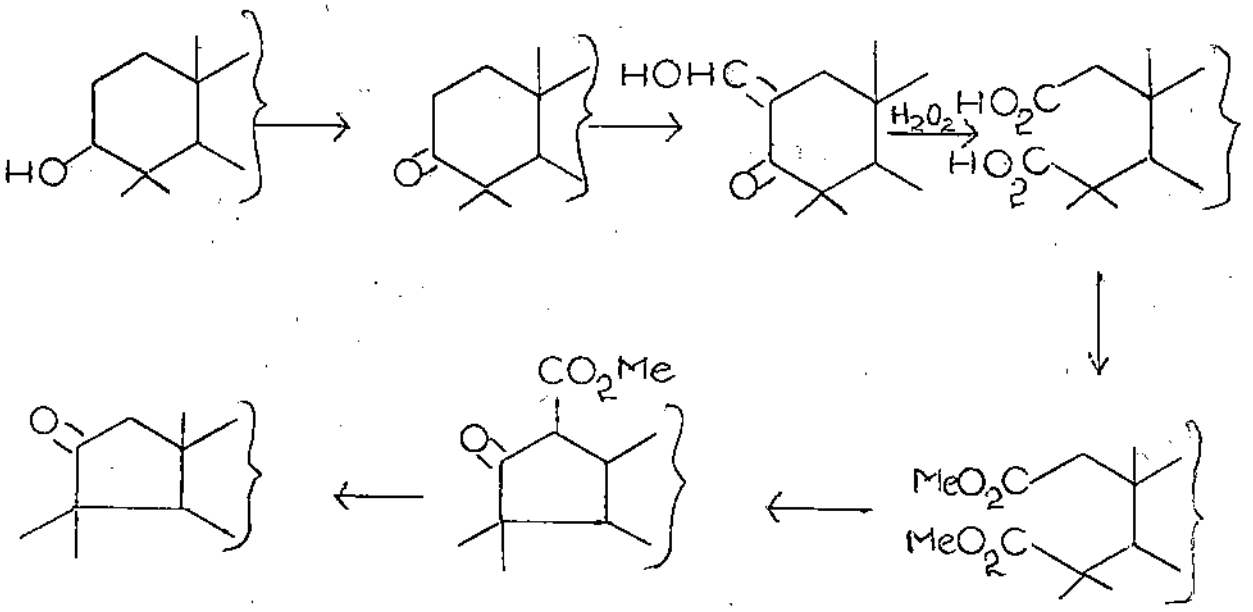
1. Taraxerol and Taraxerone:

An alcohol named taraxerol was first isolated from Taraxacum officinale[2,2a] and also from the bark of Litsea dealbata[3]. The alcohol alnulin[4-7] was isolated from the bark of grey older. These two alcohols were shown to be identical in 1950 by Jeger and co-workers[9]. In 1945 Takeda[8,10,11] isolated an alcohol, skimmiol from Skimmia japonica and latter suggested that it might be identical with taraxerol. This was confirmed by Brooks[12].

The triterpenoid nature of taraxerol was proved by Burrows[2,12] and also by Takeda and his collaborators[13,14]. On selenium dehydrogenation 1.2:3:4-tetramethylbenzene, 2:7-dimethyl, 1:2:7-trimethyl, and 1:2:5:6-trimethyl naphthalene were isolated. 1:8-dimethylpicene was also obtained and these facts suggested a general relationship to amyrins with normal triterpenoid rings A and B. The presence of unsaturation in taraxerol was shown by conversion of the unsaturated acetate to an epoxide $C_{32}H_{52}O_3$, m.p. 257-60°, $(\alpha)_D$ + 47.3° with perbenzoic acid, yielding on hydrolysis the hydroxy oxide $C_{30}H_{50}O_2$, m.p. 203-206°, $(\alpha)_D$ + 37.6°. The unsaturation was probably present as the group $>C=CH$ (IR band at 814 cm^{-1}). In cyclohexane-glacial acetic acid in the presence of platinum oxide Takeda claimed to have hydrogenated taraxerol to dihydrotaraxerol $C_{30}H_{52}O$, m.p. 261-2°, $(\alpha)_D$ + 47.3°.

The nature and environment of the hydroxyl group in taraxerol was proved by oxidation of taraxerol with CrO_3-Py to taraxerone $C_{30}H_{48}O$, m.p. 238-40°, $(\alpha)_D$ + 8° and in part by the reactions given below (Chart I). These reactions showed the secondary nature of

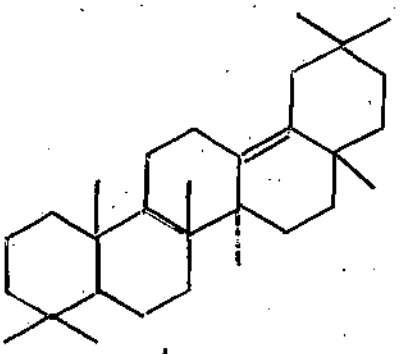
Chart I



hydroxyl group and also the occurrence of the hydroxyl group in a six membered ring.

That taraxerol belongs to β-amyrin group was proved by Takeda[10] and subsequently by Jeger[9]. Clemmensen reduction of taraxerone gave a hydrocarbon m.p. 190-91°, $(\alpha)_D$ - 34°, identical with δ-amyrene 1. Pyrolysis of taraxeryl benzoate at 340° gave amongst other products, a small amount of doubly unsaturated compound which on hydrogenation with the saturation of one of the double bond gave δ-amyrene 1. From this and other work Takeda was led to the conclusion reasonable at that time, that taraxerol was olean-18-en-3β-ol 2.

This proposal was invalidated[15] latter when this structure was assigned to germanicol 2.



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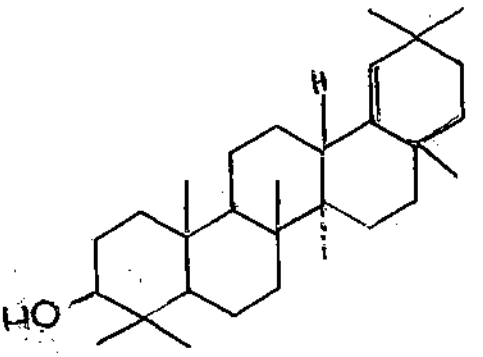

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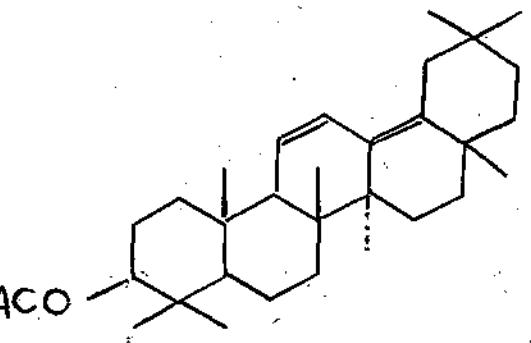
Oxidation of taraxeryl acetate with selenium dioxide gave two isolable products, olean-11:13(18)-dienyl acetate 3, m.p. 226°, $(\alpha)_D$ - 58°, λmax 242 mμ, log ε 4.35; 250 mμ, log ε 4.4; 259 mμ, log ε 4.2 and the diene dione 4, m.p. 237-40°, $(\alpha)_D$ - 90°, λmax 276 mμ, log ε 4.1. These results established decisively the presence of the hydroxyl group at C-3. Now with the clearly made proviso that no skeletal change had taken place during the selenium dioxide oxidation, the structure 5 was proposed for taraxerol after elimination of already assigned structures.



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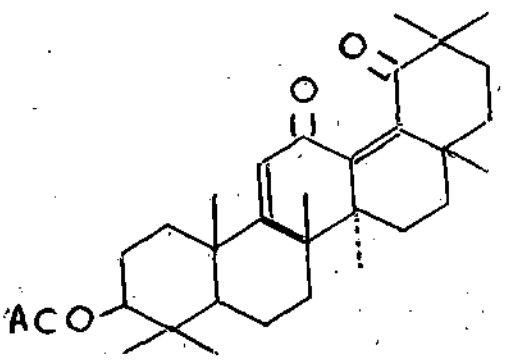

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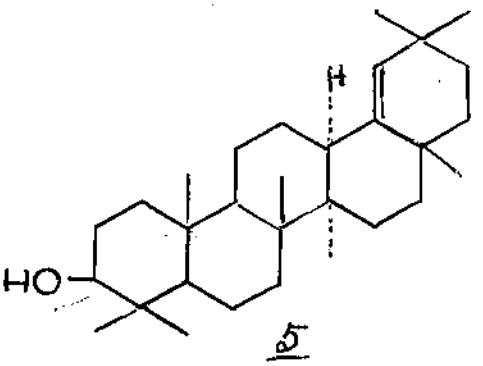

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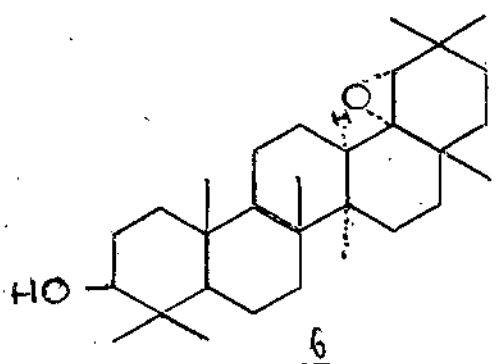
If 5 was indeed the correct structure then the oxide derived would be 6 and the unsaturated alcohol (as was claimed by Takeda) would be 7. But 7 is an allylic alcohol and as such would be unlikely to survive in the conditions of its genesis. A further objection raised was that the formation of a small amount of olean-2:12-diene on dry distillation of taraxeryl benzoate, as reported by Takeda, would require the migration of the double bond at 18:19 past the thermodynamically more stable 13(18) position to the less stable 12:13 position leaving, also, the less stable configuration at C_{18}.



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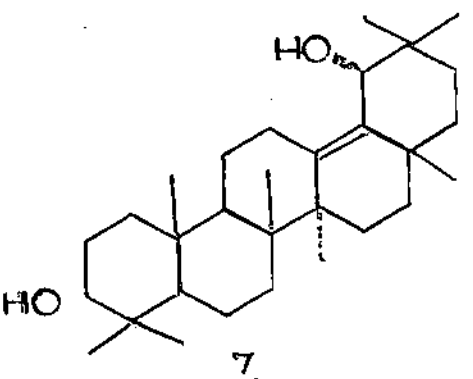

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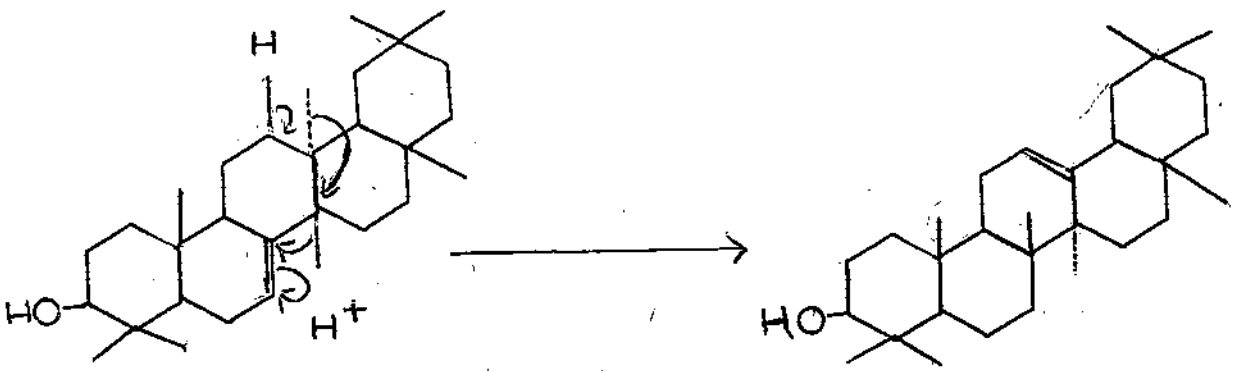
When a suspension of taraxeryl acetate in acetic acid at 90° was treated with hydrochloric acid, in a very short time an excellent yield of β-amyrin acetate was obtained. These results were

indicative that, in the formation of oleanane derivatives from taraxerol, a rearrangement had taken place.

Since rearrangement has led to the β-amyrin structure taraxerol cannot already possess it. Two possibilities, at least, then presented themselves, 8 and 9. The conversion of 8 to β-amyrin could be viewed as protonation of the double bond with concerted methyl migration from C_{14} and C_{13} as represented below. This is strongly reminiscent of euphenol→ isoeuphenol rearrangement[16]. A similar rearrangement for 9 is also possible. The formulation 9 was preferred because of certain analogies with previous work on β-amyrin series[17].



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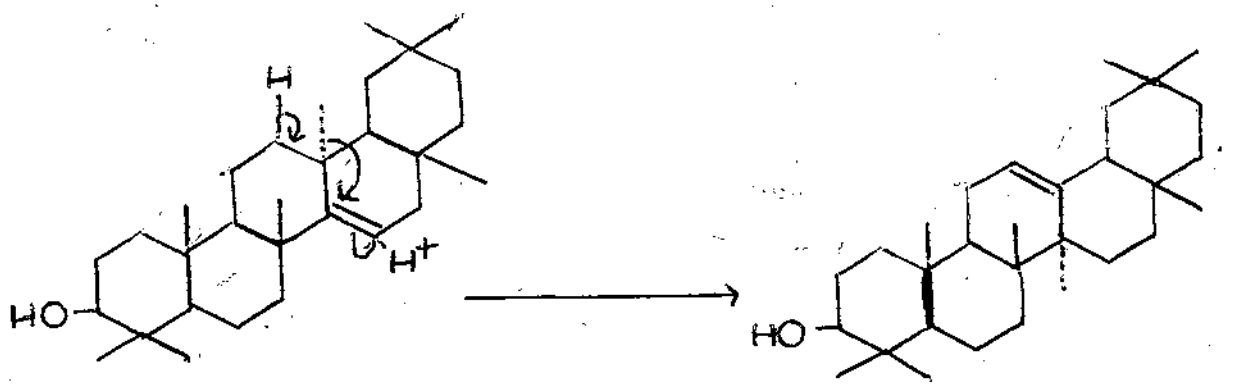

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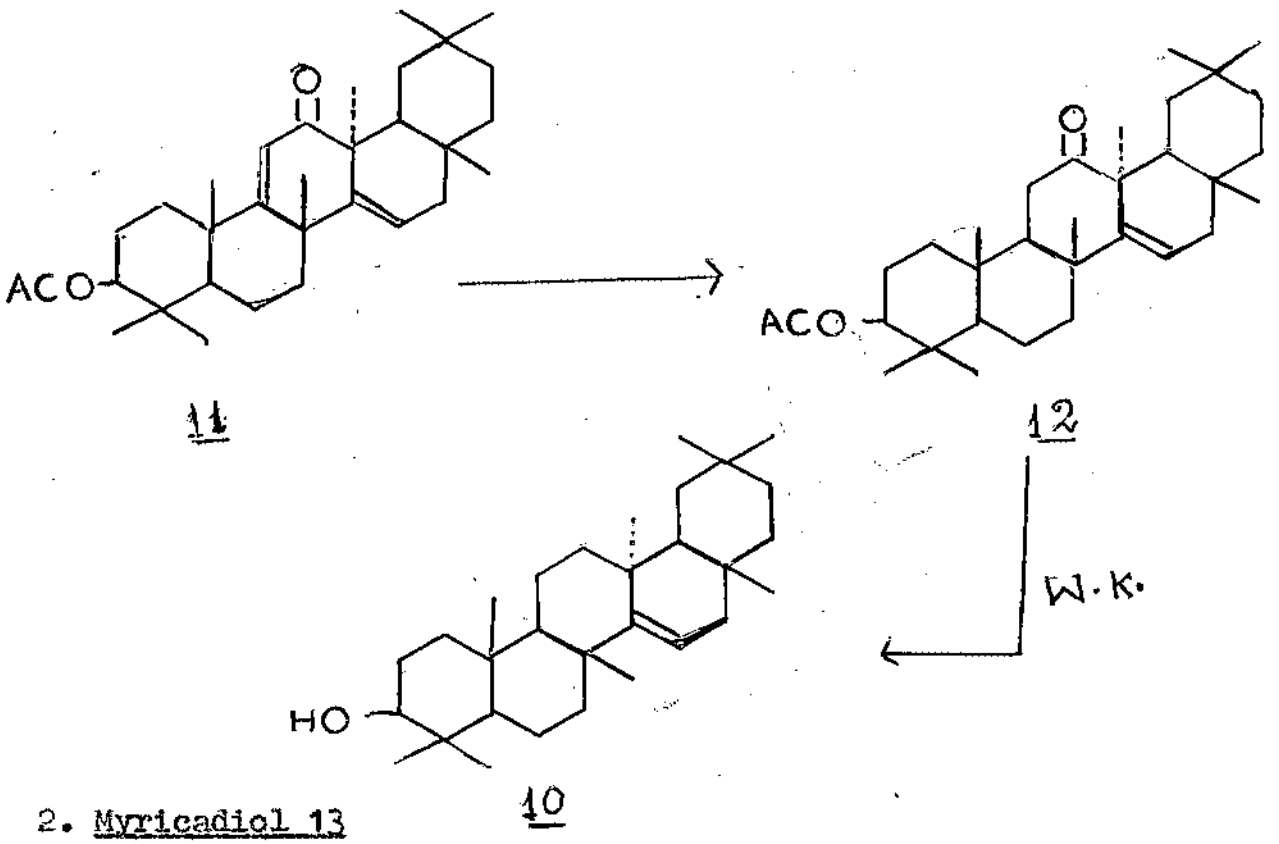
Those analogies stimulated Spring and his collaborators[18] to attempt the partial synthesis of 10. Reduction of the double bond in 12-keto-iso-oleana-$\Delta^{9(11):14(15)}$-dienyl acetate 11[19] using lithium and liquid ammonia afforded 12-keto-iso-olean-Δ^{14}-enyl acetate 12, $C_{32}H_{50}O_3$, m.p. 298-300°, $(\alpha)_D$ - 30°, λ max 206 mμ, log ε 3.63. The removal of the carbonyl group required a forcing variant of the Wolff-Kishner reduction[20]. The product was taraxerol 10.



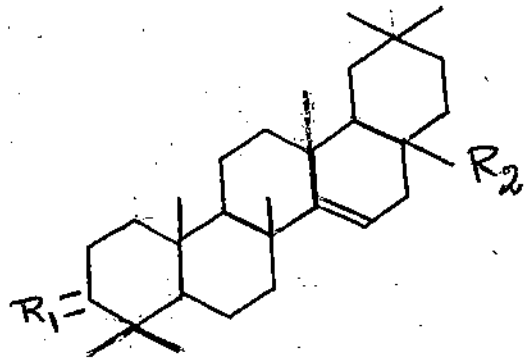
11 12 10

2. Myricadiol 13

From the bark of Myrica gale Ryabinin and Matyukhina[21] isolated a triterpene diol, myricadiol $C_{30}H_{50}O_2$, m.p. 273-4°, which has been assigned structure 13, on the basis of the following arguments. It gave a diacetate, $C_{34}H_{54}O_4$, m.p. 256-58° $(\alpha)_D$ + 1°. Oxidation of myricadiol with chromium trioxide-pyridine gave myriconal 14, an oxo-aldehyde, $C_{30}H_{48}O_2$ m.p. 256-57°, (disemicarbazone m.p. 298°, bis-2,4-

dinitrophenyl hydrazone m.p. 247°). Treatment of the latter with diethylene glycol, N_2H_4 and KOH gave taraxerene m.p. 241-2°, which was also prepared from taraxerone by similar Wolff-Kishner reduction. The latter on being treated with HCl-chloroform gave olean-12-ene m.p. 161.5-162.5°. Acid isomerisation of myricadiol diacetate with acetic acid - hydrochloric acid mixture gave erythrodiol diacetate, $C_{34}H_{54}O_4$, m.p. 184.5-85.5°, $(\alpha)_D$ + 60°, which on hydrolysis gave erythrodiol[22] m.p. 231.5°-32.5°, $(\alpha)_D$ + 83°. Myricadiol evidently conteined a primary and a secondary hydroxyl group as indicated by the spectrum of the oxidation product described above and evidently was taraxen-14-ene-3β-28-diol.

Myricadiol was also isolated from the bark of Myrica esculenta by Dhar and Agarwal[23]. Recently Bose and Paul[24] isolated myricadiol and have recorded the mass spectra of the compound.



13 R_1 = H (OH,β), R_2 = CH_2OH

14 R_1 = O , R_2 = CHO

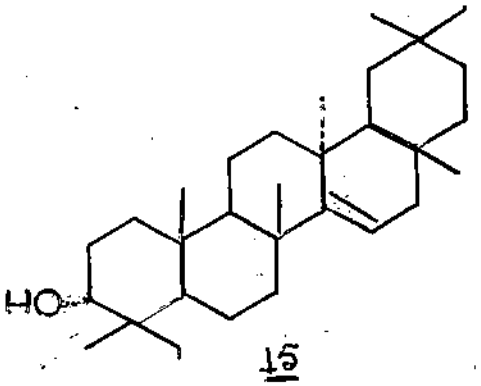
3. Myriconol 14

The Russian authors[25,26] also isolated another new triterpene $C_{38}H_{48}O_2$ m.p. 288°, from the bark of Myrica gale. The structure 14

was assigned to it. Myriconal gave an acetate $C_{32}H_{50}O_3$ m.p. 304-5° and a 2,4-dinitrophenyl hydrazone, m.p. 250°. On lithium aluminium hydride reduction it furnished myricadiol 13, showing thereby that it must be represented either as 14-taraxerene-28-ol-3 one or 14-taraxerene-3-ol-28-al 14. The decision in favour of structure 14 was made on the basis of the IR spectrum which showed clearly an aldehyde peak.

4. Epi-taraxerol 15

Recently Khastgir and Bose[27] reported the isolation of epi-taraxerol 15 m.p. 261-2°, $(\alpha)_D$ - 22.6° from Macaranga denticulata, and this appears to be the first report for the isolation of epitaraxerol from plant sources. Epi-taraxerol gave an acetate, m.p. 161-62°, $(\alpha)_D$ - 41°. On oxidation with chromium trioxide-pyride, it gave taraxerone m.p. 238-40°. Meerwin-Pondorff reduction of taraxerone following the method of Paton et al.[28] furnished both epitaraxerol m.p. 261-2° and taraxerol m.p. 275-6°. The epi-taraxerol, thus obtained and its acetate were identical with epi-taraxerol and its acetate respectively isolated by Bose and Khastgir. Reduction of taraxerone with sodium and iso-amyl alcohol also gave epi-taraxerol and taraxerol identical with those isolated from the plant sources described above. By sodium and isoamyl alcohol reduction of taraxerone Takeda[29,30] obtained an isomeric alcohol which he named iso-taraxerol, m.p. 267-69°, $(\alpha)_D$ + 11.9°, acetate m.p. 205-7° $(\alpha)_D$ - 21.8° and was thought to be the 3-epimer of taraxerol. In view of Khastgir and Bose's work Takeda's epi-taraxerol was probably a mixture of triterpenes.



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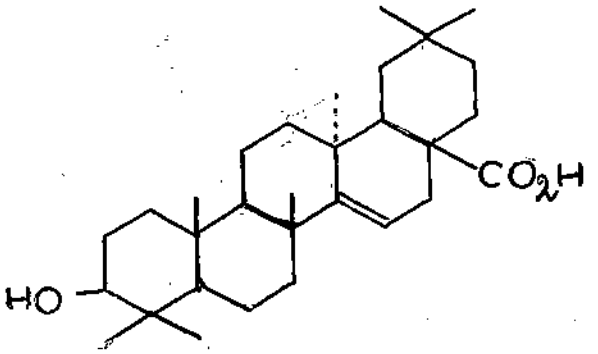
5. Aleuritolic acid, 16

Aleuritolic acid 16, $C_{30}H_{48}O_3$, m.p. 300-302°, has recently been isolated by the present author from the acidic fraction of the bark and stem of Aleurites montana. The details regarding its chemistry is reported in the next chapter (chapter III).



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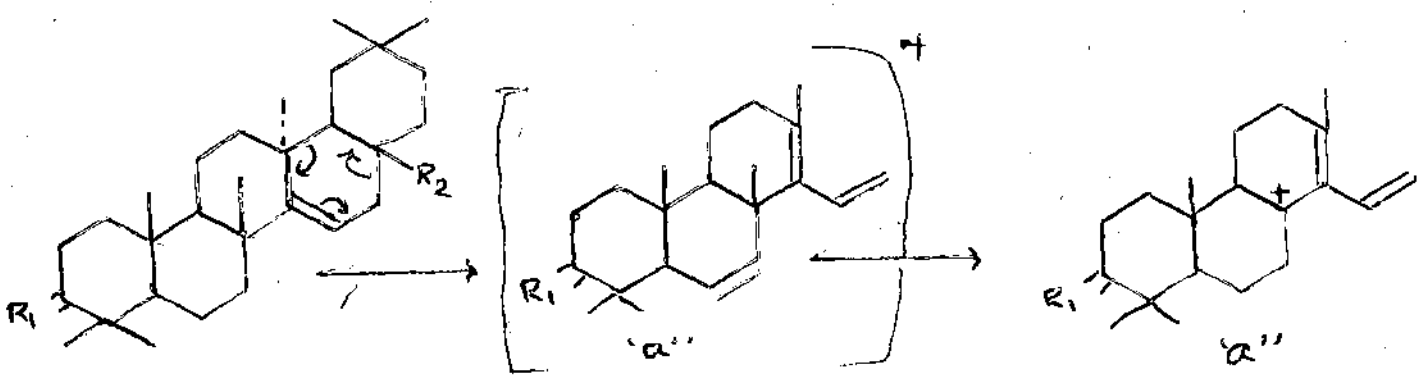
A review on the mass spectra of Δ^{14}-taraxerene

Mass spectra of Δ^{14}-taraxerene: The spectra of three compounds of this class, namely taraxerone 17, taraxerol 18 and myricadiol diacetate 19 have been measured by Djerassi and co-workers[31], thus offering the necessary labels for assigning structure to the major fragments.



17, R_1 = O ; R_2 = CH_3

18, R_2 = H, (OH,β), R_2 = CH_3

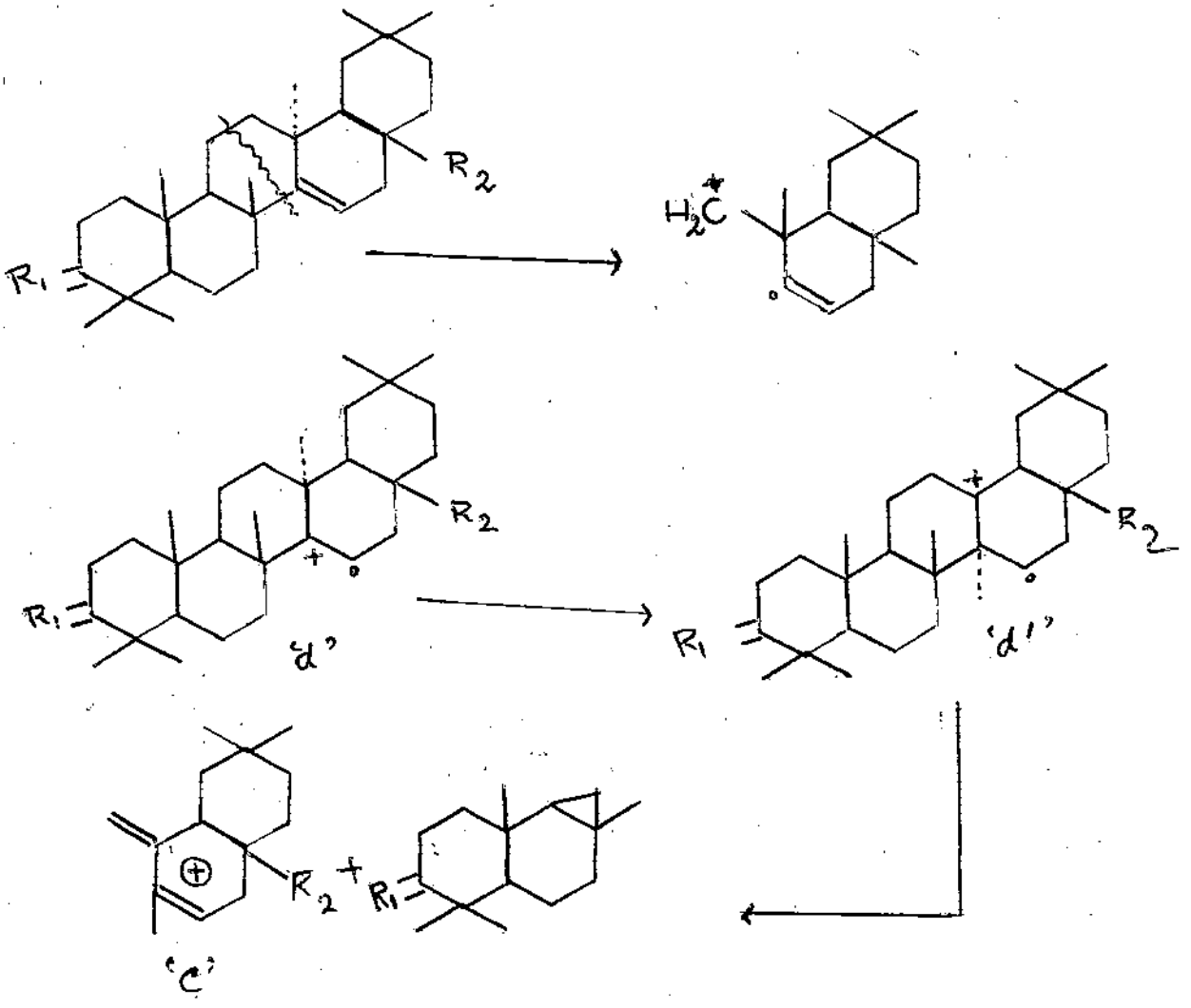
19, R_1 = H, (-OAc,β), R_2 = CH_2OAc

In these molecules a similar retro-Diels-Alder decomposition was observed as was the case with Δ^{12}-unsaturated derivatives, except that collapse of ring D rather than ring C occurred. This cleavage process was actually observed, the charge remaining with the diene portion, comprising the rings A, B and C. The resulting fragment 'a' exhibits a mass of m/e 300 in the case 17, 302 for 18 and 344 for 19 depending upon the C_3- substituent. Ion 'a' is accompanied by a satellite peak 15 mass units lower, which is formed by the loss of a methyl group, probably the allylically activated one at C-8 ('a'). The spectrum of 18 exhibited additional peaks due to the loss of H_2O and (H_2O + CH_3) respectively from species 'a', while that of 19 showed (a-CH_3COOH) and (a' -CH_3COOH) ion peaks.

In addition to species 'a' and its further decomposition products, the spectra of 17 and 18 showed a very abundant fragment at m/e 204 (c). This cleavage product, therefore, cannot contain ring A but must be derived from ring D and E, which had been verified by the

spectrum of 12, which showed a small peak at m/e 262 (c), but an abundant one at m/e 202 (c-CH_3COOH). Furthermore, fragment 'c' loses the substituent at C-17 giving rise to a fragment 'c' -CH_3 for 17 and 18 and 'c' -CH_2OAc for 19 (m/e 189 = 'c'). The formation of the fragment 'c' corresponded to the cleavage of 11-12 and 8-14 bonds as indicated by the wavy line (Chart II). But it is difficult to visualise the driving force of this fragmentation as this would involve rupture of a bond next to a double bond and cleavage of a bond between two secondary carbon atoms, rather than next to the quaternary C-13 center. Furthermore, the resulting ion would not be a very favourable species, since it contains a primary carbonium ion and a radical on a double bond.

CHART II



A more acceptable mechanism was also proposed by assuming that in the molecular ion the missing electron is preferentially removed from the carbon-carbon double bond (d), migration of the C-13 methyl group yielded the radical ion 'd'. Fission of 11-12 and 8-14 bonds gave the stable diene 'c'. However, no experimental proof was available and it was emphasised that many factors influenced the formation of a fragment ion, release of strain and stability of the final product being among the important ones.

Biogenesis

The tetra and pentacyclic triterpenes which may differ from each other in the carbon skeleton, in the position of a double bond or in configuration can be derived from squalene with all their structural and configurational details rests on the assumption of a few reasonable postulates:

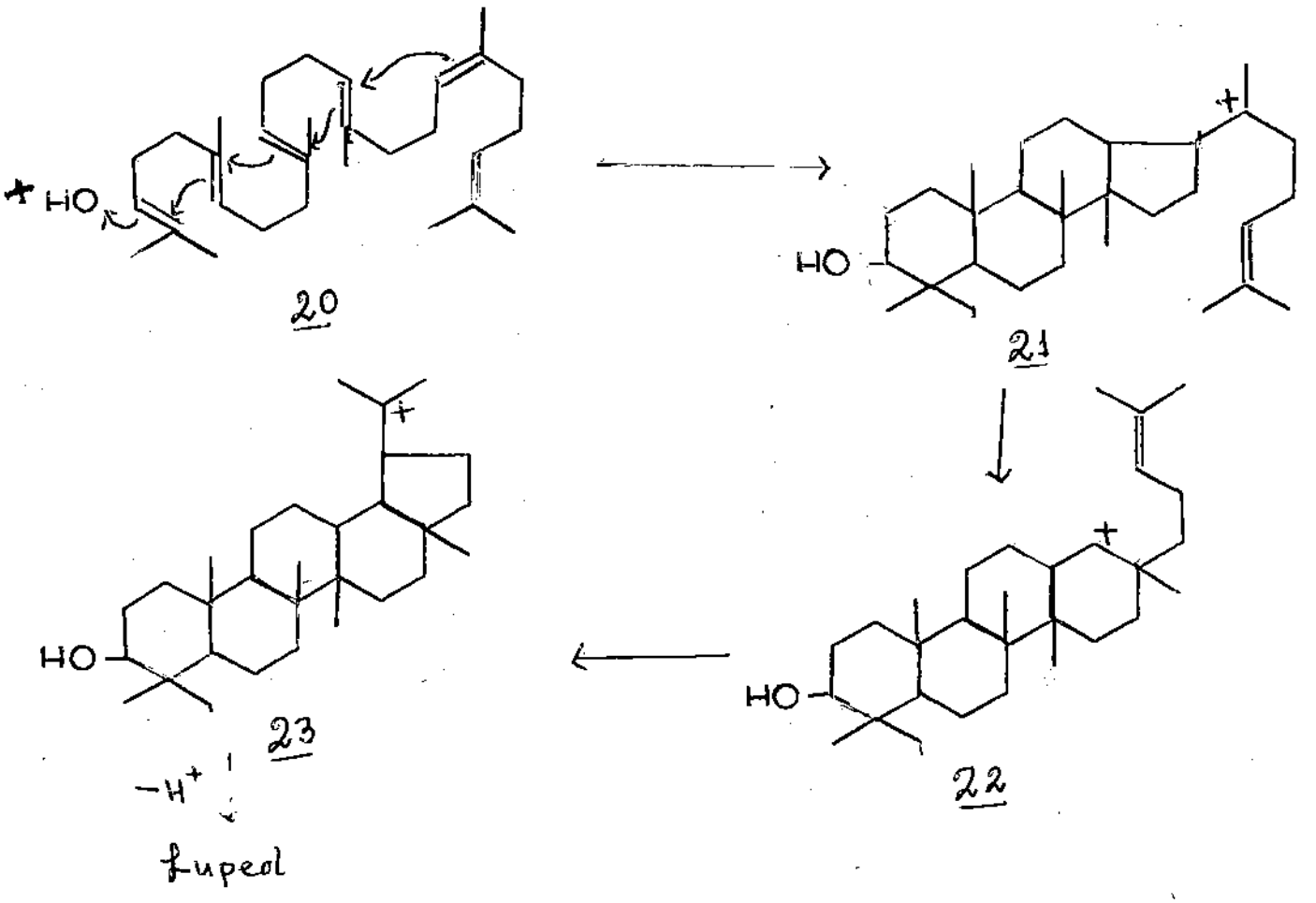
(1) The cyclization of squalene[32,33,34] takes place in the all-trans configuration and in a well defined sequence of chair and boat conformation.

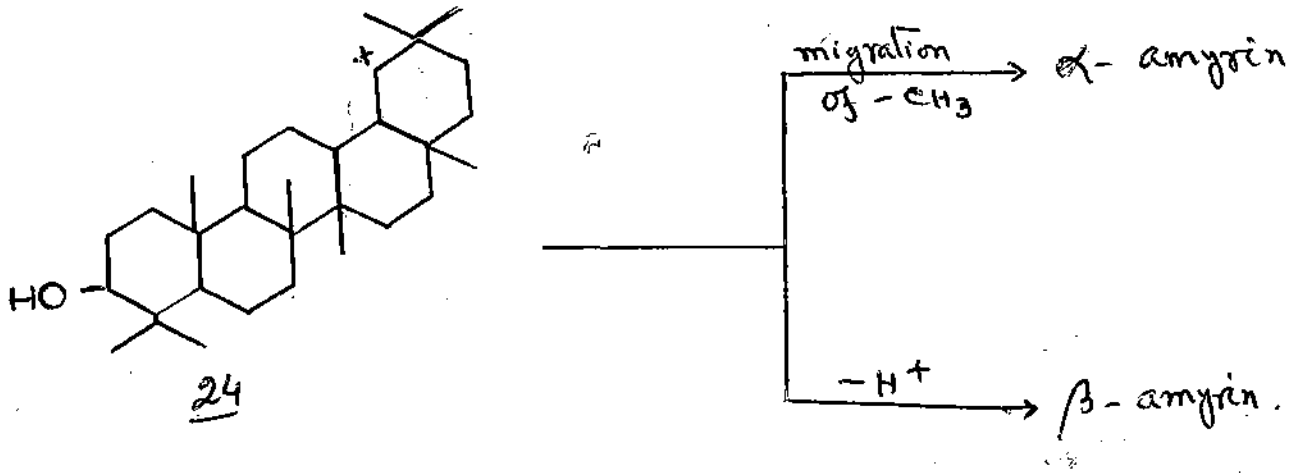
(2) The transformation from squalene[20] to the triterpenes[35] proceeds according to the rules of anti-planar cationic 1,2-addition, 1,2-rearrangement and 1,2-elimination.

(3) All steps on the route from squalane to the final product proceed in a non-stop reaction.

The biological cyclisation of squalene was considered to be initiated by the attack of a formal cation $OH^{(+)}$. Thereupon

cyclisation should proceed synchronously to completion. The formal cation 21 which leads to lanosterol by hydrogen and methyl shifts, could be converted by a rearrangement involving (C_{16}) to the formal cation 22. A further cyclisation of the latter to 23 and elimination of hydrogen would produce lupeol. The intermediate 23 could in turn rearrange to 24 and thus give rise to β-amyrin. The migration of a methyl group in 24 would lead to the formation of α-amyrin. It should be emphasised that these biogenetic schemes are based on generally accepted reaction mechanism. The proposed rearrangements and methyl shifts follow the rules of the Wagner-Meerwein rearrangement. This also provides an explanation of the structural variation of ring E in the pentacyclic triterpenes.





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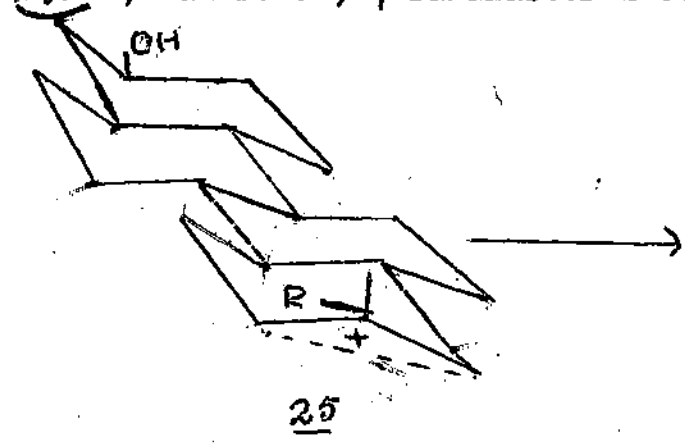
The structure of triterpenes with the correct configuration by the use of above mechanism was established by Ruzicka[36] and was confirmed by the work of Eschenmoser and Arigoni[37]. In nature it is the enzyme system that is responsible for the formation of one enantiomer of this racemate.

Cyclisation of all-trans-squalene in Chair-Boat-Chair-Boat conformation furnished lanosterol[38-41]. Cyclisation of all trans-squalene in Chair-Chair-Chair-Boat conformational sequence lead to 15 basic tetracyclic and pentacylcic triterpenes representatives.

All the pentacyclic triterpenes are derived from the nonclassical cation 25 by cyclisation of the long side-chain in its boat conformation. The intermediate 26 so produced gives rise to lupeol 27 by elimination of hydrogen. On the other hand the formation of all triterpenes with a six membered ring E requires the rearrangement of the same ring E in the intermediate 26 to a chair conformation 28.

These triterpenes exist in two structural types. One type is characterised by the presence of gem-dimethyl groups in ring E (e.g. Germanicol, δ-amyrin, β-amyrin, Taraxerol etc), whereas in the other type ring E carries two isolated methyl groups (e.g. Taraxasterol, α-amyrin, Bauerenol, ψ-Taraxasterol etc.).



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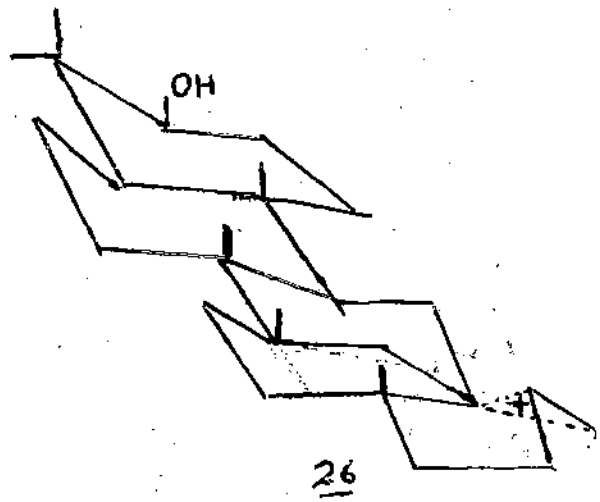

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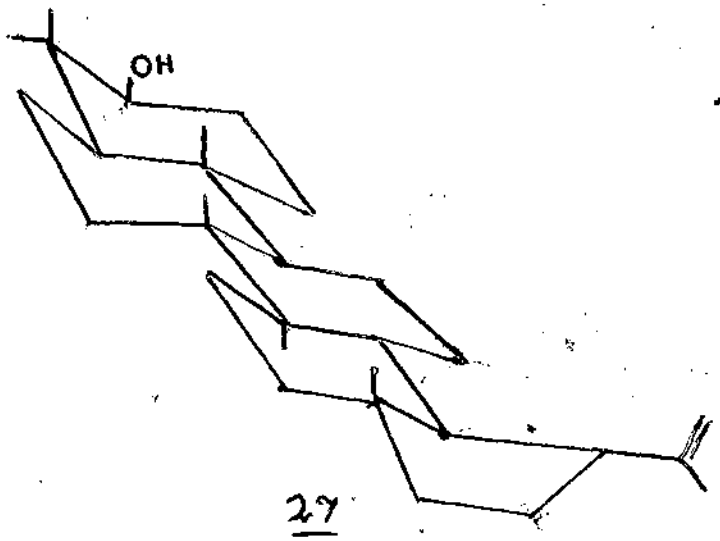

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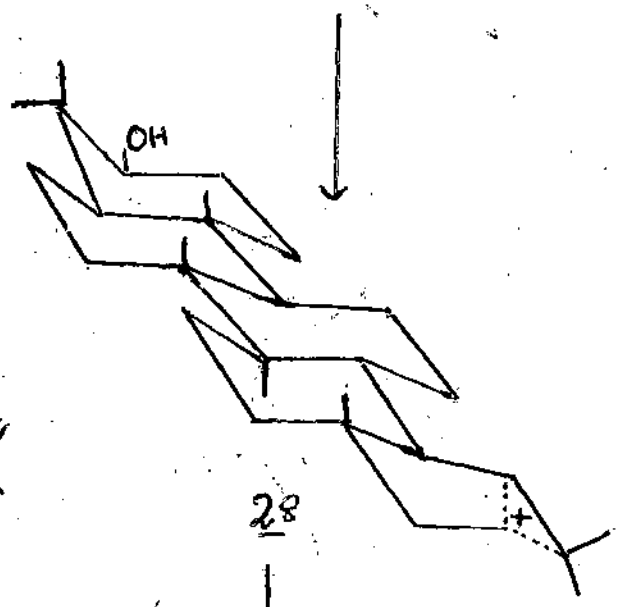

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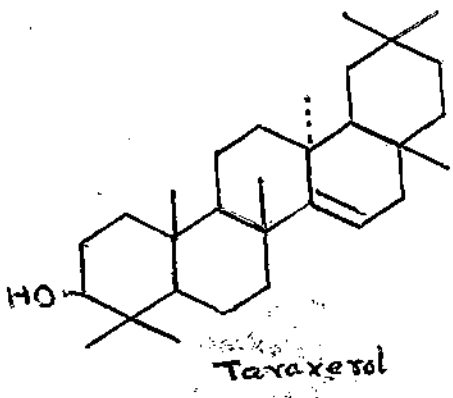
H, 18α → 19α
H, 13β → 18β
Me, 14α → 13α

$-H^+$, 15β

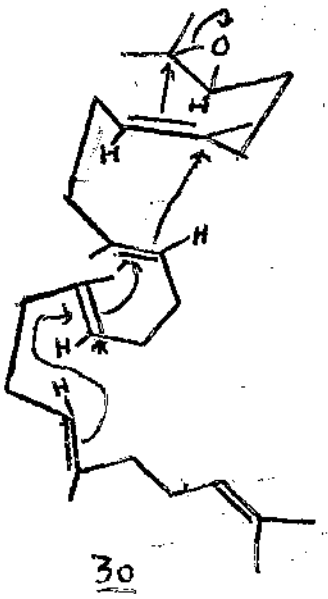


Taraxerol

From the bridged cation 28 by hydrogen shifts and hydrogen elimination gives pentacyclic triterpenes like germanicol, δ-amyrin and β-amyrin with the gem dimethyl groups in ring E[42,43]. The formation of the triterpenes taraxerol requires the shifts of methyl groups in addition to further hydrogen shifts.

Recently[44,45,46] it has been demonstrated that 2,3-oxido squalene 29 can be biosynthesised enzymatically and also can act as a precursor for natural triterpene source of lanosterol and cholesterol. Lanosterol is synthesised in the mammalian liver from 2,3-oxido squalene 29 under the influence of an enzyme, 2,3-oxidosqualene-sterol cyclase, which can be obtained from liver microsomes in a partially purified water soluble form[47]. The separation of the squalene-to-sterol conversion into discrete oxidation and cyclization steps suggests a similar possibility for the biosynthesis of pentacyclic triterpenes. It has now been shown recently[45] that 2,3-oxidosqualene is indeed a precursor of β-amyrin in Pisum sativum and that the cyclizing enzyme can be obtained in water soluble form. Experimentation with C^{14} labelled 2,3-oxidosqualene led to the isolation of β-amyrin[45]. It has also been shown that the original epoxy oxygen is retained as the 3β-hydroxyl group[44] in the product. The mechanism proposed for this cyclization[44] of 29 to lanosterol is given in the chart below 30→ → 33 (Chart III).

CHART III



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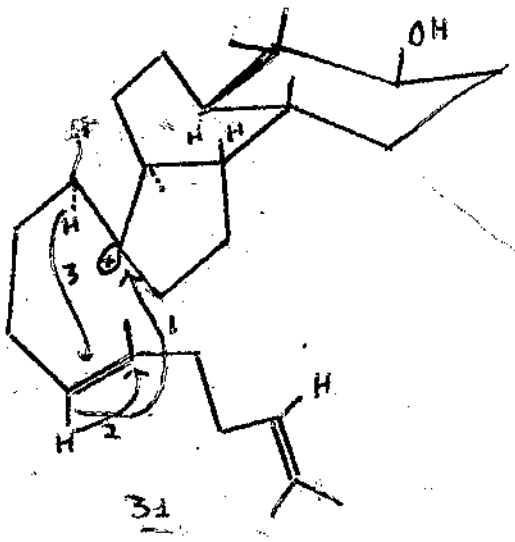

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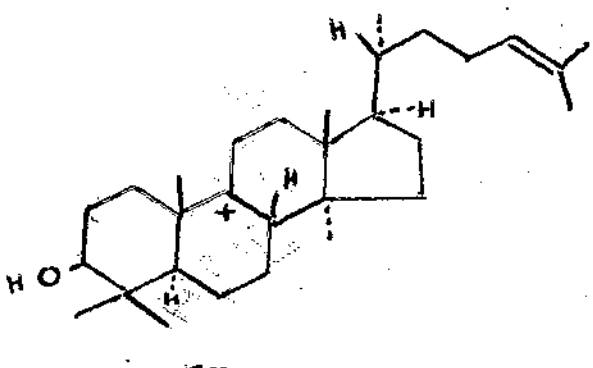

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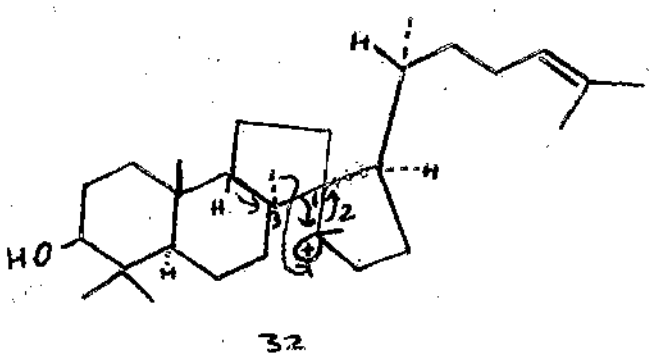

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