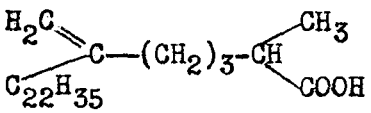
CHAPTER-II

A SHORT REVIEW ON 3,4-SECO TRITERPENE ACIDS

1. Nyctanthic Acid, $C_{30}H_{48}O_2$, m.p. 222°, $[\alpha]_D$ +91° was originally isolated by Vasistha[4] in 1938 from Nyctanthes arobor-tristis Linn. and was named "Nycosterol". He suggested the molecular formula $C_{27}H_{44}O_2$ for it. Turnbull and coworkers[5] gave the molecular formula $C_{30}H_{48}O_2$ and suggested that it was a triterpenoid acid containing two double bonds. Infrared spectra showed that one of them was present as a vinylidene group (=CH_2, ν_{max} 1634, 890 cm^{-1}) and the other as a trisubstituted double bond (ν_{max} 809-810 cm^{-1}). The methyl ester of the acid could be easily hydrolysed as in the case of methyl ester of polyporenic acid[6]. The formation of a diphenylethylene derivative (λ_{max} 252 mμ) from the methyl ester of nyctanthic acid suggested that the acid contained grouping $-CH_2-COOH$ or $>CH.COOH$. On the basis of the above observations structure 1 was suggested for nyctanthic acid. The correct structure 2 was put forward by Whitham[7] from chemical evidences and biogenetic considerations.



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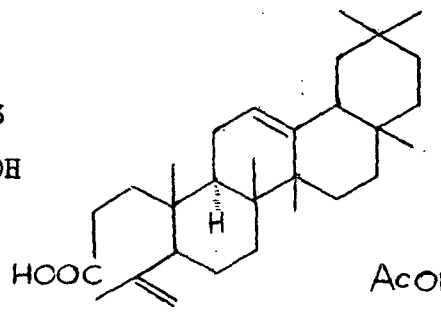

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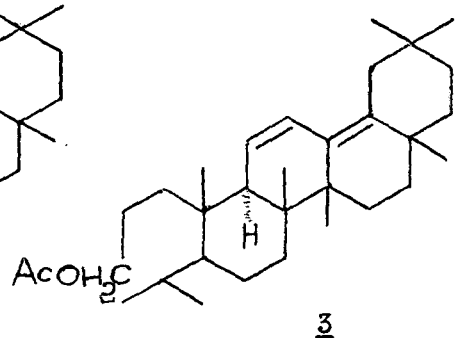
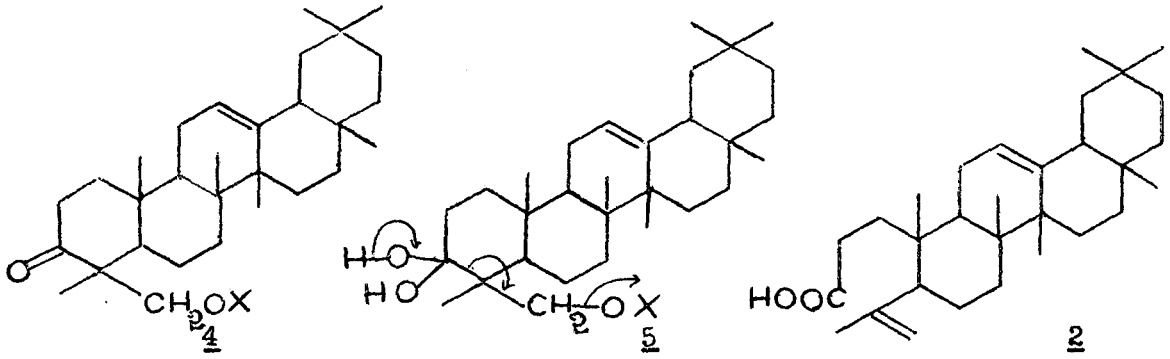


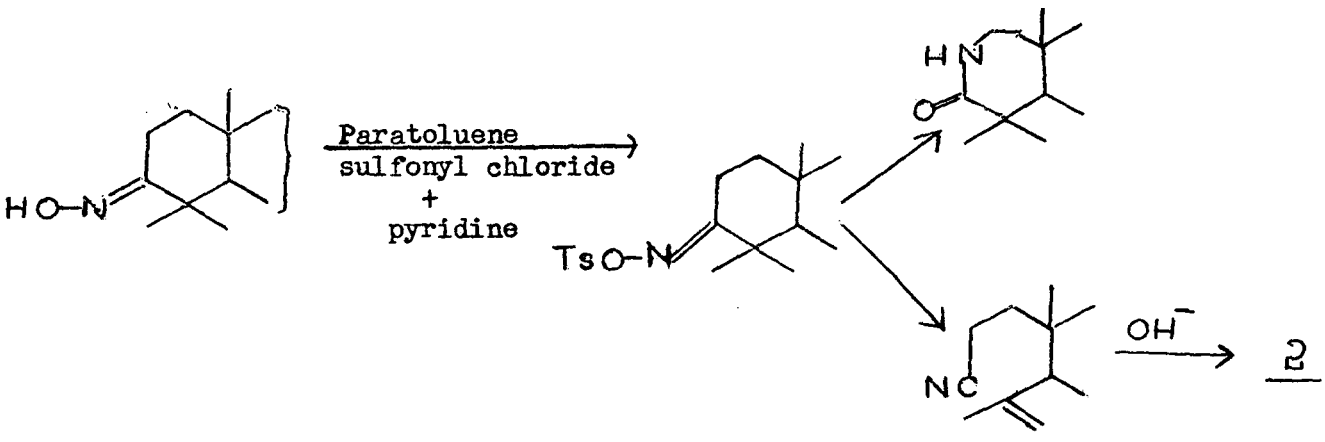
3

In accordance with the above structure 2 the vinylidene group could only be hydrogenated readily to give dihydroderivative 2a, the other trisubstituted

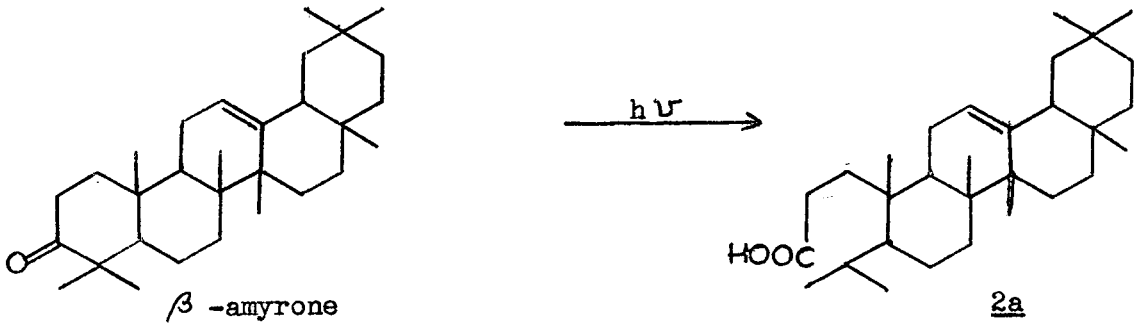
double bond being inert to hydrogenation. The environment of this double bond was shown to be same as in β-amyrin. SeO_2-oxidation of the acetate of the alcohol obtained by LAH reduction of dihydromethylnyctanthate yielded the diene 3, $C_{32}H_{52}O_2$, m.p. 133.5-5°, $[\alpha]_D$ -74° having UV_{max} at 243, 251 and 260 mμ characteristic of olean-11,13(18)-diene system. The large negative M_D difference (ΔM_D-682) accompanying the dehydrogenation is in close agreement with the corresponding value in the case of β-amyrin acetate (ΔM_D-697). The tetracyclic structure 2, which possesses all the features necessary to explain the chemical reactions of nyctanthic acid was also acceptable from biogenetic point of view. The biogenetic origin of nyctanthic acid 2 was postulated as derived from the β-amyrin derivative 4 by the sequence shown below:



Finally, structure 2 was confirmed by its partial synthesis by Beckmann rearrangement of β-amyroneoxime as shown below :

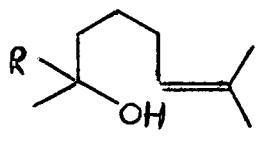


The same structure 2 was deduced by Arigoni and coworkers[8] on biogenetic grounds and by photochemical synthesis of 2a starting from β-amyrone.



β-amyrone 2a

2. Dammarenolic Acid, $C_{30}H_{50}O_3$, m.p. 138-42°, $[\alpha]_D$ +43° was isolated by Mills and Werner[9] from "Pole Bold Indonesian Dammar". IR spectra showed peaks at 3620 cm^{-1} (tert.-OH group, no acetate was formed), 3070 (-COOH), 1640, and 895 ($=CH_2$) cm^{-1}. On hydrogenation it gave a tetrahydro derivative. CrO_3 oxidation of the ester gave acetone and the tris-nor-lactone 7 which suggested that the side chain must be present as in 6. The structure 8 was finally established by Arigoni and coworkers[8] from chemical and physical evidences.



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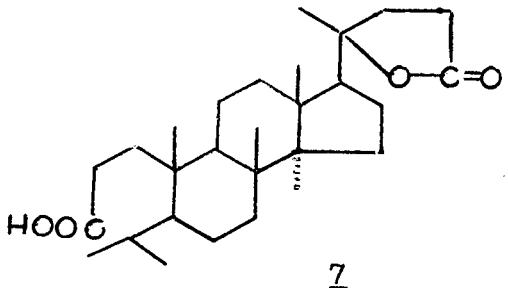

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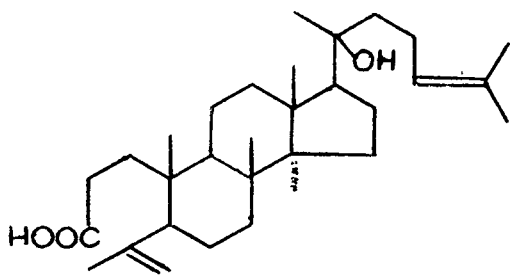

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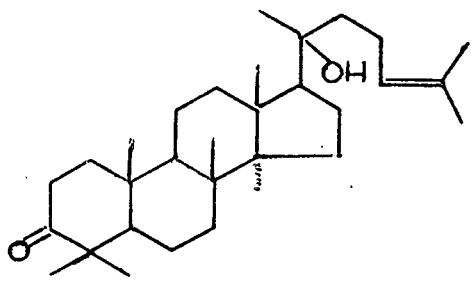
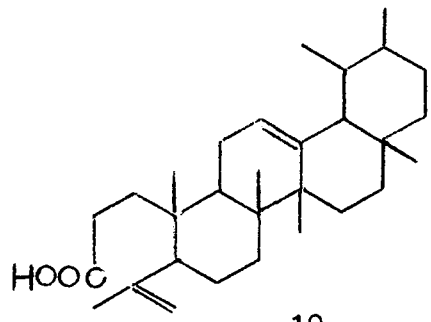


9

They put forward the following new scheme for the biogenetic formation of dammarenolic acid.

The structure 8 was supported by partial synthesis of 7 by photochemical oxidation[8,10] of the γ-lactone obtained from hydroxy dammarenone-II, 9.

3. Roburic Acid, $C_{30}H_{48}O_2$, m.p. 181-2°, $[\alpha]_D$ +78° was isolated together with nyctanthic acid by Mangani and Belardini[11] from common Oak (Quercus robur). Its structure 10 was suggested by these workers on the basis of physical and chemical data and by analogy of its occurrence with nyctanthic acid.

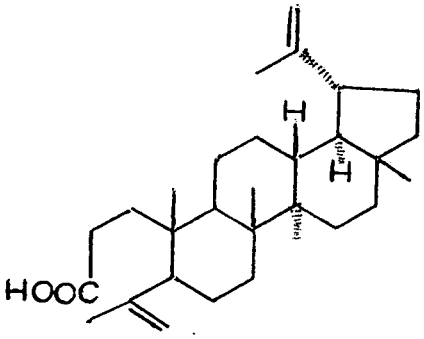


10

The IR spectra showed peaks at 1640 cm^{-1} and 900 cm^{-1} indicating the presence of $C=CH_2$ group. This was confirmed by NMR spectrum where there are peaks at 5.34 τ and 5.16 τ ($=CH_2$) and in addition a peak corresponding to another vinyl proton is present at 4.85 τ . On catalytic hydrogenation it yielded dihydroroburic acid which still shows a peak at 4.85 τ in its NMR indicating the presence of the inert 12,13 double bond. Dihydroroburic acid was found to be identical to 3,4-seco-urs-12-ene-3 carboxylic acid prepared by Arigoni and coworkers[8]. That roburic acid actually has structure 10

was proved by its partial synthesis from α-amyrone oxime by following the method of Whitham[7] and Klinot[12].

4. Canaric Acid, $C_{30}H_{48}O_2$, m.p. 215-16°, $[\alpha]_D$ +56.5° was first isolated in 1925 by T.G.H.Jones and F.Berry-Smith[13] from Canarium muelleri and assigned the molecular formula $C_{28}H_{45}(?)O_2$ to it. Later in 1964 Carman and Cowley[14] reinvestigated the compound and gave the correct molecular formula $C_{30}H_{48}O_2$. They assigned the 3,4-seco structure 11 to it on the basis of IR and NMR studies and chemical evidences. The IR spectra exhibited two bands at 895 and 875 cm^{-1} assignable to two asymmetrically disubstituted ethylene functions. These two bands disappeared on hydrogenation of the compound. The NMR spectra showed a complex of four vinyl protons between 5.1 and 5.5 τ , two methyl groups located on double bonds (8.26, 8.31 τ) and four additional methyl groups (8.92, 9.04, 9.15, 9.20 τ). The tetrahydro derivative showed only eight methyl groups between 8.95 and 9.25 τ. The physical and chemical reactions of canaric acid are in confirmaty with the assigned structure 11 derived from lupeol via lupenone 11a. This structure was confirmed by partial synthesis[7,12] from the oxime of lupenone 11a.



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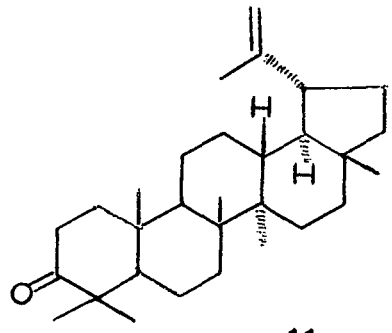
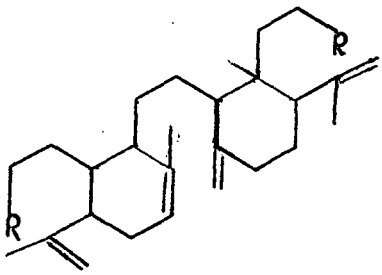


11a

5. Lansic Acid, $C_{30}H_{46}O_4$, m.p. 182-4°, $[\alpha]_D$ -7° was isolated by Kiang and coworkers[15] from the fruits of Lansium domesticum (Maliaceae). It is a dibasic acid 12a which afforded the dimethyl ester 12b on esterification. LAH reduction gave diol 12c, which furnished a diacetate 12d. Hydrogenation

of 12c gave octahydrodiol 13a which gave the diacetate 13b. Spectroscopic studies of these compounds led to structure 12a for lansic acid.

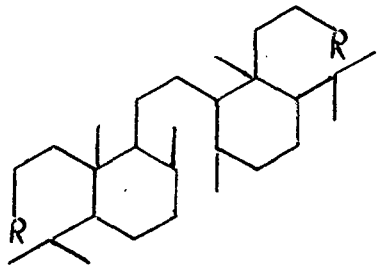


12a; R = COOH

12b; R = $COOCH_3$

12c; R = CH_2OH

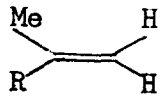
12d; R = CH_2OAc



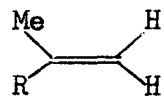
13a; R = CH_2OH

13b; R = CH_2OAc

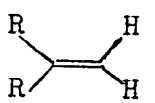
100 Mc NMR spectrum of the methyl ester 12b showed signals attributable to two tertiary methyls at 0.73 and 0.81 ppm; three olefinic methyls at 1.66, 1.68 and 1.76 ppm; two methoxy carboxyl methyls at 3.51 and 3.50 ppm and seven olefinic protons at 4.65-4.95 (6H) and 5.34 ppm (1H). Irradiation at 1.68 ppm caused the six olefinic protons to be coupled from the allylic protons as well as the olefinic methyl groups so that the complex signal around 4.8 ppm arising from six protons was reduced to three pairs of doublets thus suggesting the three moieties 14-16. Moreover, irradiation of the 1.76 ppm methyl signal converted the broad olefinic peak at 5.34 ppm (1H) to a singlet, thus indicating the presence of 17.

1.66  (d, J - 1.5)

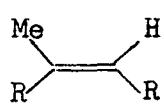
14

1.68  (J - 2.2)

15

 (d, J - 2.2)

16

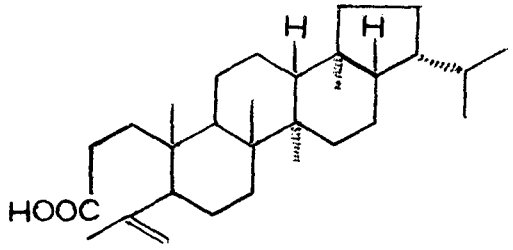
1.76  (br, S)

17

The above structures were supported by NMR spectra of lansic acid derivatives; for example, the spectrum of the octahydrodiol 13a showed two pairs of isopropyl doublets (centered at 0.87 and 0.77 ppm both with J, 6.6 cps), two secondary methyl doublets centered at 0.73 ppm, J, 6.1 cps and 0.89 ppm with J, 7.5 cps respectively; two tertiary methyl singlets (overlapping at 0.74 ppm). These results coupled with the mass spectra of compounds 12a-12d fully corroborated 12a assigned to it.

Thus lansic acid may be considered to have arisen biogenetically from onocerin group of triterpenesin which both rings A and E have undergone cleavage of the type encountered in ring A of nyctanthic acid, dammarenolic acid etc.

6. Sebiferic acid, 19a, $C_{30}H_{48}O_2$, m.p. 178-80°, $[\alpha]_D$ +28.57° has recently been isolated by the present author from the acidic fraction of the bark and stem of Sapium sebiferum Roxb. The details regarding its chemistry is reported in the next chapter (Chapter-III).

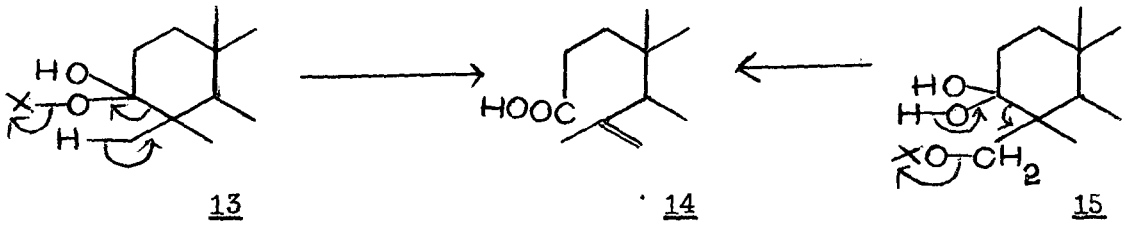


19a

Biogenesis

D. Arigoni and coworkers[8] postulated that oxygen atom which is present in almost all the triterpenoids at C-3 might be present as carboxyl group in dammarenolic acid, which might result from the cleavage of normal triterpenoid

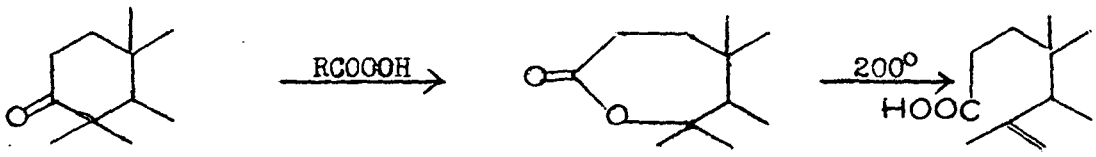
3-ketone according to the biogenetic process illustrated in 13 (X = a suitable electro negative departing group) or equivalent process (13 ⟶ 14).



13 14 15

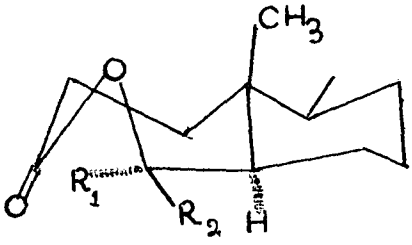
G.H. Whitham[7] speculated that nyctanthic acid might be formed biogenetically by ring opening of a suitable β-amyrin derivative to give the functional group of nyctanthic acid. As the naturally occurring oleanane derivative oxygenated at C-23 or C-24 are well known, an attractive biogenetic sequence leading from 3-oxo-precursor to the desired type of compound was proposed by the author[7] as in (15 ⟶ 14) where OX^- is a suitable leaving group.

A.I.Laskin and coworkers[16] postulated the formation of natural seco acids via ε-lactones and they[7] succeeded in preparing 3,4-seco-8,24(28)-eburicadiene-4-ol-3,21-dioic acid from eburicoic acid by cultivating Glomerella fusarioides. Recently, David Rosenthal and coworkers[8] justified the above possibility of their biogenetic sequence of formation by carrying out the pyrolysis of ε-lactones prepared by Baeyer-Villiger oxidation of 3-keto compounds of steroids with no methyl substituent in the 4 position, with 4α and 4β monomethyl substituent and 4α,β dimethyl substituents. Only in the case of ε-lactones obtained from 3-keto 4,4-dimethyl compounds they obtained the seco compounds of the type 14.



14

It seems that it is essential to explain why seco acids with mono substituent or no substituent at C-4 position as in the case of steroids, has not yet been isolated from natural sources. The following[28] is the explanation for it: there are two possible, readily interconvertible chair conformations for the ϵ -lactone system under consideration. In the conformation 16 the 4β substituent R_2 is in a 1,3-diaxial relationship with regard to C-19 methyl group, whereas in conformation 17, R_2 is equatorially situated. On the other hand, conformation 17 involves some interactions between the 4α substituent R_1 and the carbonyl group at position 3 as well as with the axial-H atoms at C-1 and C-5. In the unsubstituted lactone and probably also in the 4α-methyl derivative it is likely that the latter factors combine to stabilise conformation 16. However the presence of a β-oriented methyl group at C-4 would be expected to overcome this interaction and force the lactone ring into conformation 17 in which case the hydrogen atoms of 4α-methyl group R_1 are perfectly oriented for a facile intramolecular cyclic transition to the olefinic acid 14 as shown in 17a.



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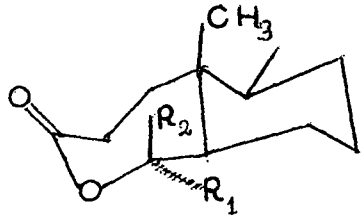

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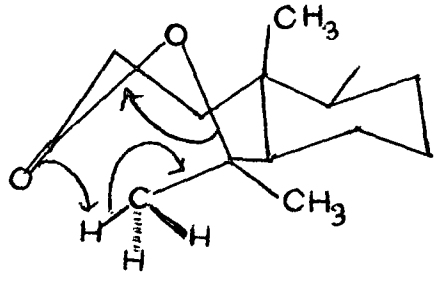
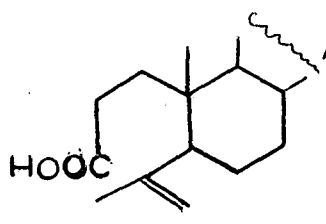


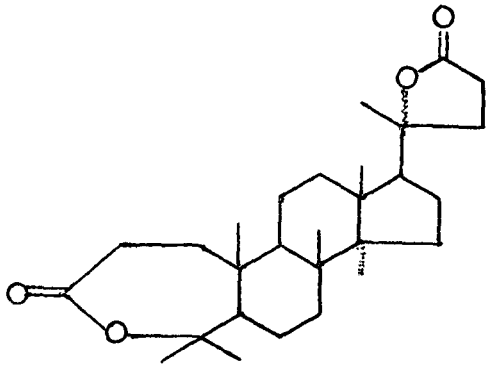
17a



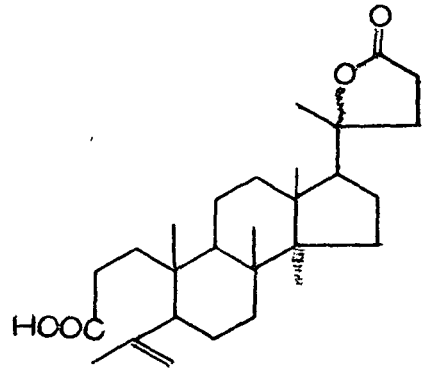
14

The above considerations receive support from NMR spectra of the various ϵ -lactones with or without substituents at C-4. As a consequence of the above considerations it is evident that methylene group in the cleavage product 14 be derived exclusively from the 4α-methyl group.

A striking demonstration of the expected selectivity of this pyrolytic elimination reaction was provided by the conversion of the dilactone 18a into the unsaturated acid 18b without opening of the γ-lactone.



18a



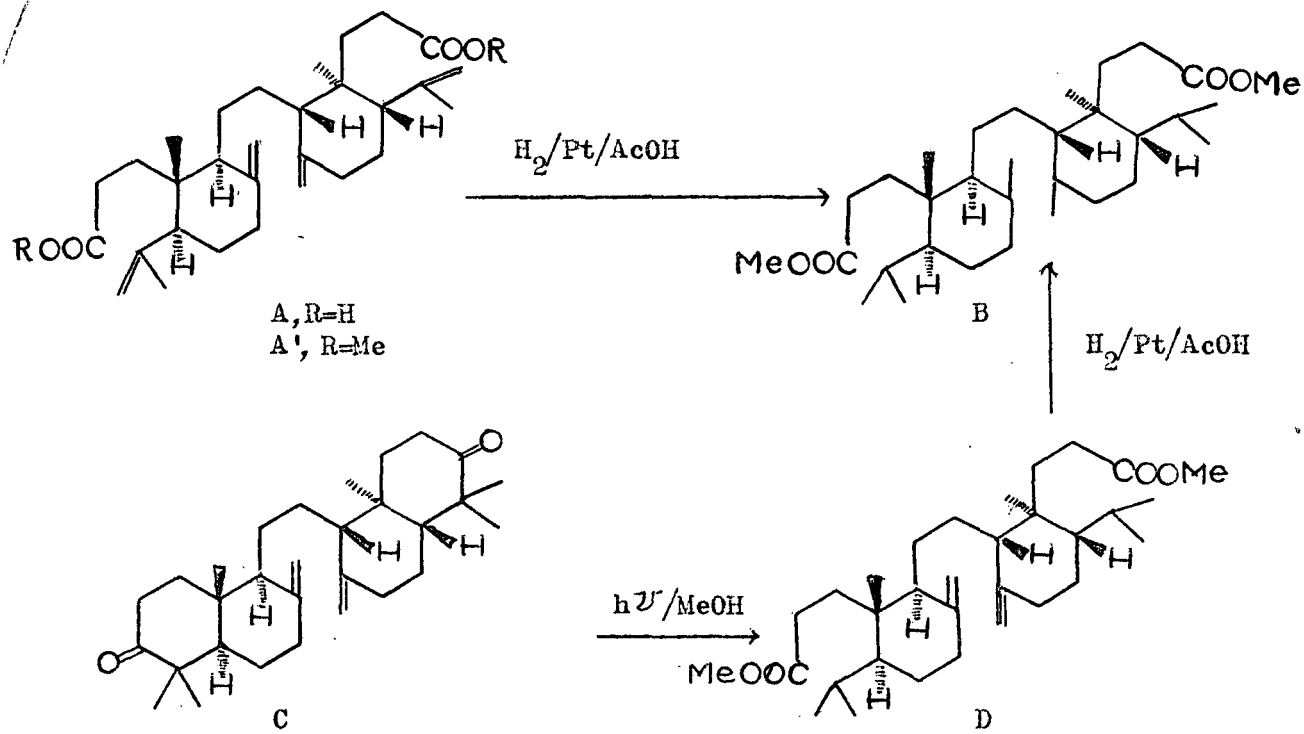
18b

Hence from the above findings and explanations it is quite plausible that the 3-4 seco acids that have been isolated might be formed in nature via ϵ -lactones derived from the 3-keto triterpenoids.

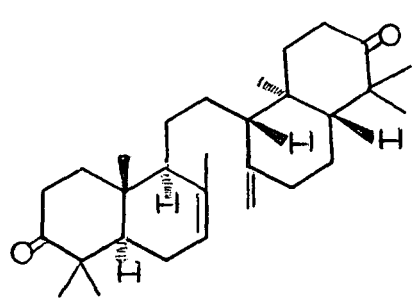
It is quite interesting from the biogenetic point of view that three different compounds of isohopane series - moretenone, moretenol and 3-epi-moretenol[19,20,21] have been isolated from neutral fraction of the same plant, Sapium sebiferum and that the seco-acid, sebiferic acid is also present in the same plant. Hence, sebiferic acid might result from moretenone via ϵ -lactone as discussed by Rosenthal et al[18].

ADDENDUM

Recently* K. Habaguchi et al correlated lansic acid with α-onocerin and established the stereochemistry of lansic acid as A.



α-Onoceradienedione C was irradiated for 6 hours with a 450W high-pressure mercury lamp to give the oily methyl ester D as the major product. Hydrogenation of the product D afforded the fully saturated ester B identical with octahydro methyl lansate obtained from methyl lansate A'. From the petroleum extract a minor constituent E was isolated which is probably a precursor in the biosynthesis of lansic acid.



E

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* K.Habaguchi, M.Watanabe, Y.Nakadaira, K.Nakanishi, A.K.Kiang and F.Y.Lim. Tetrahedron Letters, 34,3731,1968.