PART II

AUTOXIDATION OF FRIEDELIN

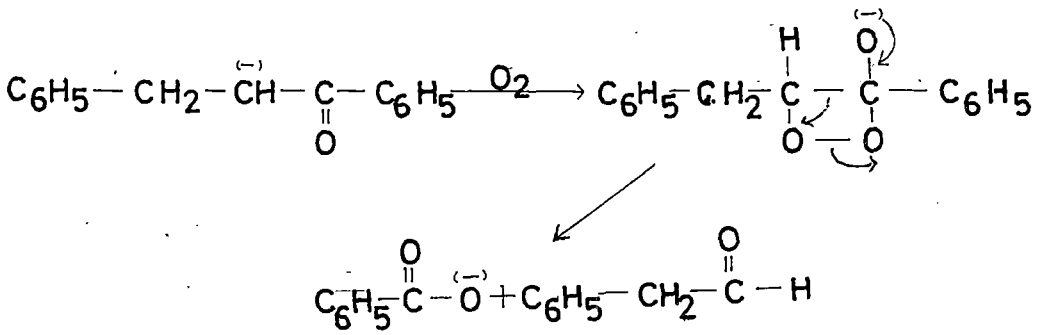
CHAPTER - I

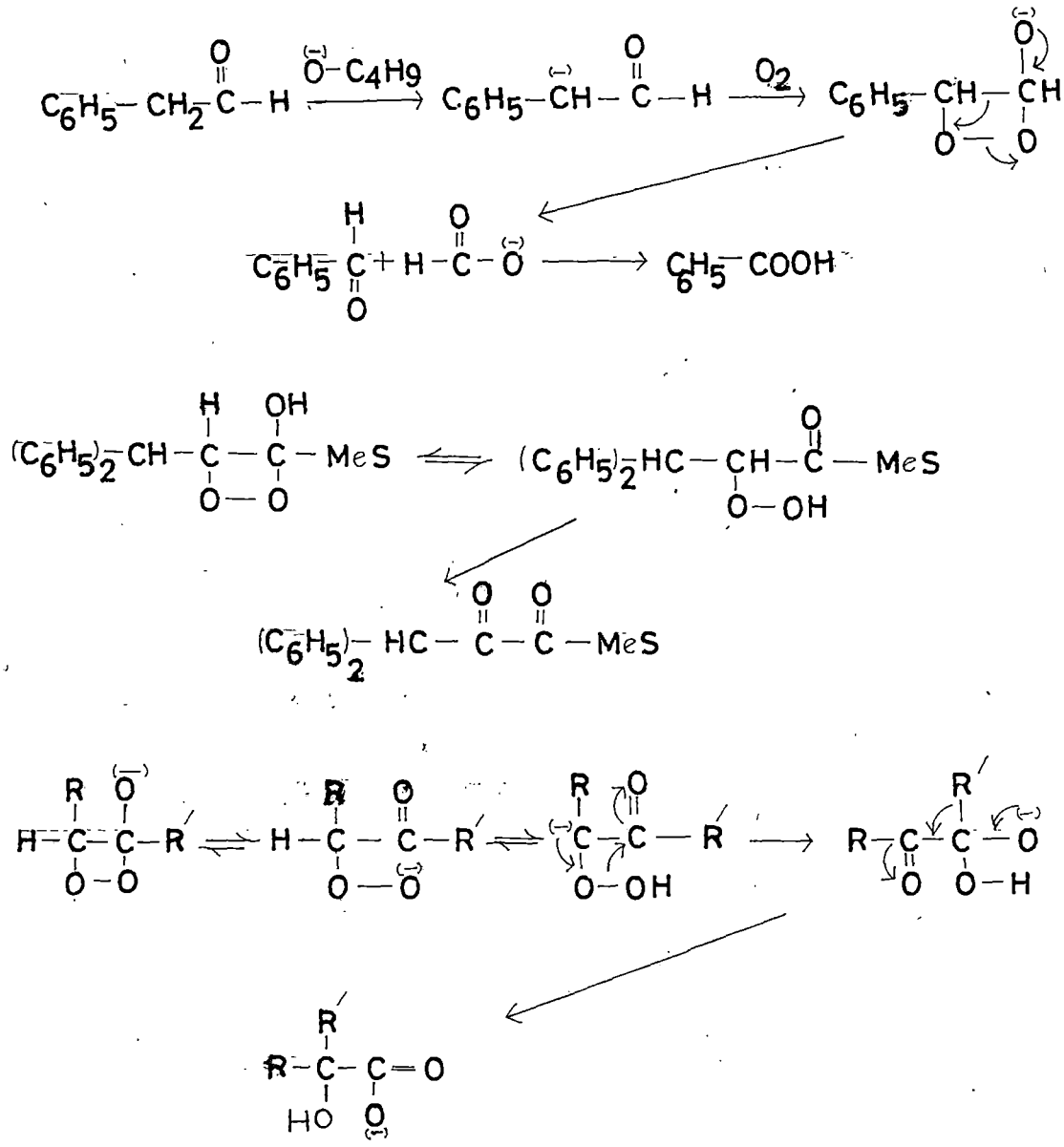
A short review on autoxidation and isomerisation in ring A in triterpenoids.

The term autoxidation actually applies to any oxidation with atmospheric oxygen. Autoxidation, a slow oxidation process affected by oxygen (e.g. air) at moderate temperature are catalysed by light and small quantities of catalyst, notably the oxides and oil soluble salts of heavy metals as well as by various peroxidic substances. Again, it can be markedly retarded by mere traces of oxidisable organic substances, such as phenols and amines.

Woodward et al[1] studied the autoxidation of quinone to quininic acid in a boiling solution of potassium enolate in benzene and by Doering[2] in presence of tertiary butoxide. Doering et al also studied the autoxidation of ketones and isolated diketones, dicarboxylic acids and lactols[3]. The formation of various products was explained on the basis of addition of oxygen molecule on the enolate double bond to form the four membered cyclic hydroxy peroxide as shown in the Scheme I.

Scheme - I



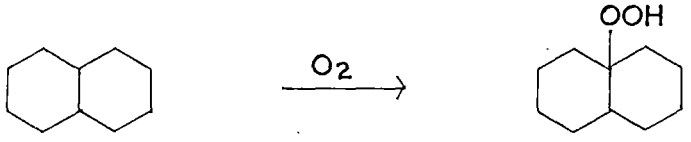


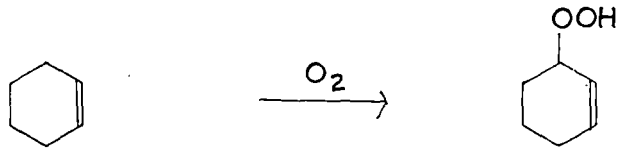
The atmospheric oxidation of a C-H bond to a C-O-O-H group is called autoxidation[4].

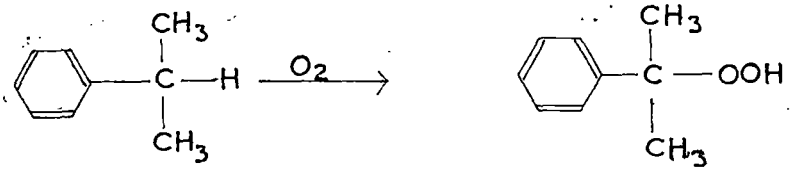
$$R\text{-}H + O_2 \longrightarrow R\text{-}O\text{-}OH$$

The reaction occurs when compounds are allowed to stand in air and is catalysed by light, so that unwanted oxidations may be greatly slowed by keeping the compounds in dark places. The hydroperoxides produced often react further, to alcohols, ketones and more complicated products, so that the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield.

The reaction may be carried out successfully at tertiary (to a lesser extent secondary) allylic[5], and benzylic R. The following are actual examples.







Another susceptible position is aldehydic C-H, but the per acids so produced are not easily isolated, since they are converted to the corresponding carboxylic acids.

$$R - \underset{\displaystyle H}{\overset{|}{C}} = O \xrightarrow{O_2} R - C - O - OH$$

The actual direct oxidation product in the case of aldehyde is the per acid RCO_3H, which with another molecule of aldehyde disproportionates to give two molecules of acid[6].

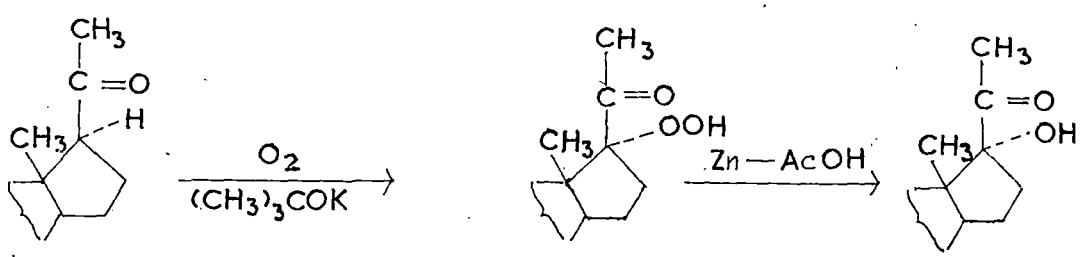
In the early sixties Gersmann et al[7] studied the autoxidation of ketones and esters to hydroperoxides using potassium tertiary butoxide as catalyst.

Hanna and Ourisson[8] reported the autoxidation of several cyclic ketones in hexamethyl phosphotriamide in the presence of potassium tertiary butoxide. The reaction was found to proceed in accordance with the previously proposed mechanism in which the initial formation of an α-hydroperoxy ketone is followed by transformation into an α-ketol and then to an α-diketone, attack of the α-diketone followed by decarboxylating fragmentation, cleavage into a keto acid or an aldehyde acid or rapid oxidation of the aldehyde acid.

Hendry et al[9] found that the initial oxidation of cyclohexane gave mostly cyclohexyl hydroperoxide and gave cyclohexanol and cyclohexanone as chain termination products.

The hydroperoxide was converted directly to ketone on further reaction.

It was found by Barton et al[10] that when a 20-keto steroid was shaken with oxygen in the presence of ptassium tertiary butoxide in tertiary butanol it was oxidised to the 17α-hydroperoxide, which could not be reduced to the 17α-alcohols with zinc and acetic acid. Under the identical conditions[11], 3-keto-5β-steroids were oxidised to 4-hydroxy-Δ^4-3-ketones, the 5α-isomers were oxidised to the 2-ketones (enolic forms) and cholestenones was oxidised to diosterol-1 in low yields. Since in each case attack was at the site of enolisation, oxygen evidently attacked the enolate ion.



In view of the fact that Chapter II deals with autoxidation of triterpenoid, it will be of interest to make a brief review of autoxidation of some triterpenoids.

1. Oxidation in ring A in Euphol.

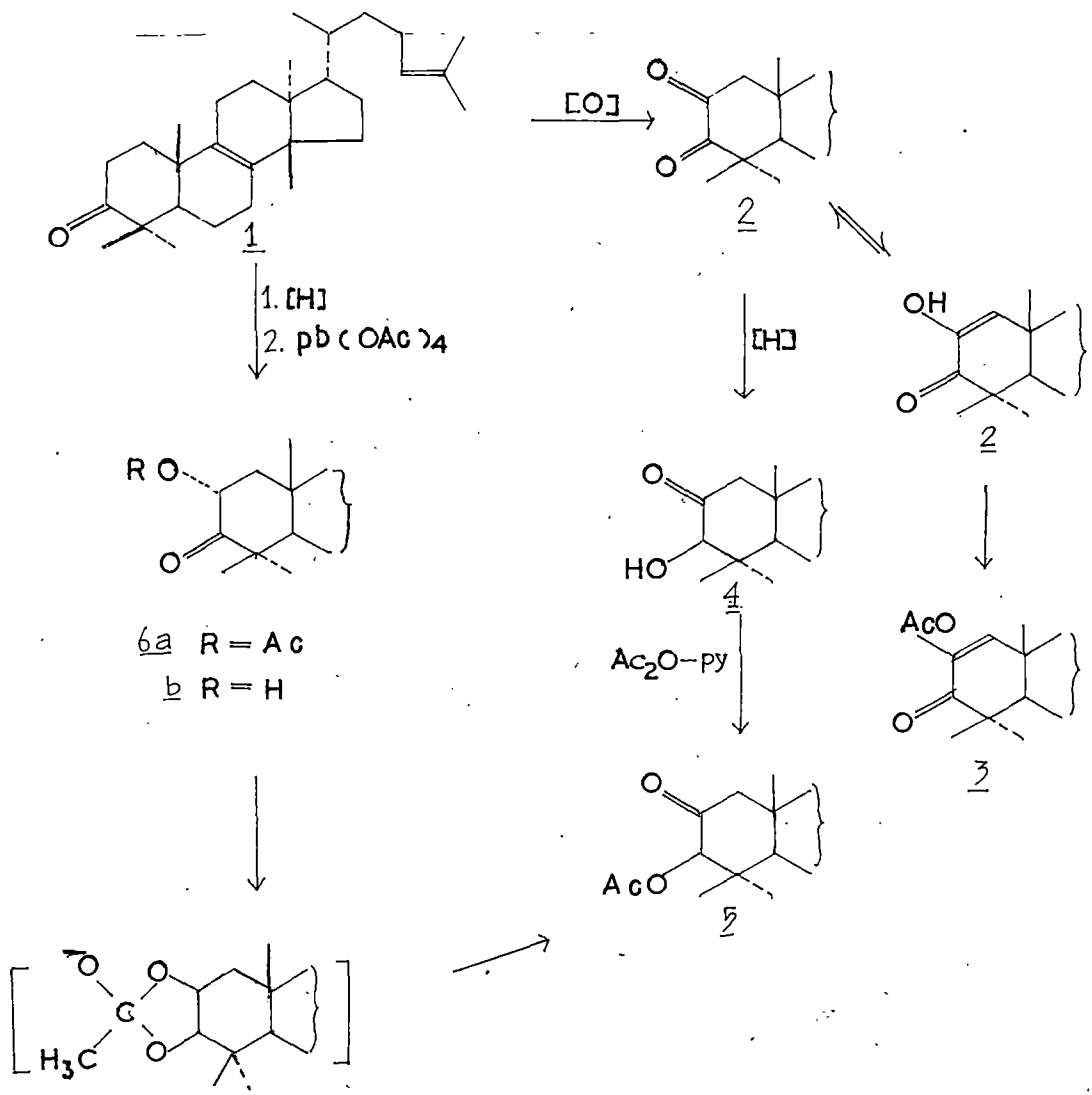
Lavie and co-workers[13] studied the autoxidation of

euphadiene-3-one, 1 and the results of their work are summarised as follows.

Euphadiene-3-one, 1 was oxidised by shaking in oxygen in t-butanol saturated with potassium t-butoxide[10,12]. A tautomeric mixture of diketone and the corresponding diosphenol 2 (two spots on chromatoplate) was produced by absorbing one mole of oxygen, uv, λ_{max} 269 nm, (ϵ = 7900), IR ν_{max} 1715, 1672 and 1653 cm^{-1}. ^1H NMR of the compound 2 showed a singlet at δ 3.60 due to vinylic proton at C-1 upon acetylation, a diosphenol acetate 3 was obtained. UV and IR showed values λ_{max} 236 nm, ν_{max} 1764 cm^{-1}. ^1H NMR showed singlet at δ 3.02 due to C-1 proton.

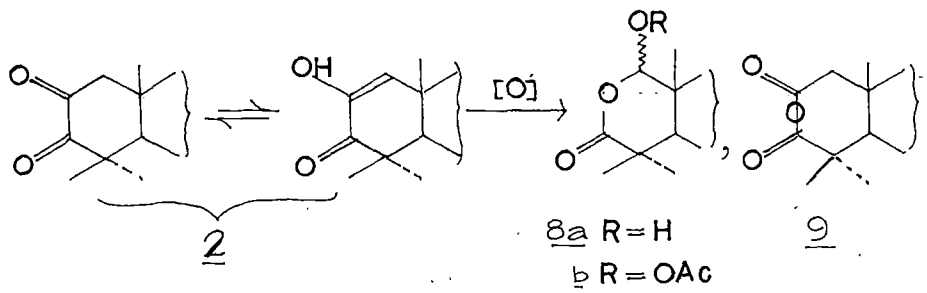
On hydrogenation of the diosphenol 2 over palladium on charcoal, a non-crystallisable homogeneous solid was obtained. IR showed ν_{max} 1712 cm^{-1}. ^1H NMR of the compound showed values at δ 5.95 accounting for one hydrogen and two AB type doublet centred at δ 7.69 and 7.35, accounting for two hydrogens. Acetylation of the compound gave a crystalline keto acetate IR ν_{max} 1742, 1730 cm^{-1}. ^1H NMR showed peak at δ 4.95 for one proton and a broad peak at δ 7.50 integrating for two protons. From the above spectral studies structure 4 and 5 was proposed for the hydroxy ketone and the keto acetate respectively. 2α-equatorial acetoxy derivative 6a was prepared by the reaction of dihydro-derivative of 1 with lead tetraceate in acetic acid in the presence of boron trifluoride[14]. The product 6a showed IR band

at 1742 and 1730 cm^{-1} and the ^1H NMR spectra showed a quartet of lines centred at δ 4.3 (J_{ae} = 6.5 cps and J_{aa} = 13.0 cps) for the C-2 proton but no signals for protons α-to keto function.



The isomerisation of 2α-equatorial-acetoxy ketone 6 into the isomer 5 was also observed and they proposed that migration proceeded through the cylic intermediate 7[15]. Acid hydrolysis of 6a afforded a compound which has been assigned the 2α-equatorial hydroxy-3-keto derivative 6b on the basis of its IR, ν_{max} 1718 cm^{-1}.

During the process of autoxidation, a second mole of oxygen was absorbed and the product isolated was identified as the lactol 8a, ν_{max} 1710 and 1107 cm^{-1}. ^1H NMR showed peak at δ 4.40, the corresponding acetate 8b (R = Ac) showed a sharp peak at δ3.58 indicating the absence of neighbouring proton. The formation of the lactol was interpreted through the formation of ring A seco-2-nor aldehydo carboxylic acid, which cyclized upon acidification. The loss of a carbon atom (C-2) in the process and the formation of the heterocyclic six membered ring were shown unequivocally by the ^1H NMR spectrum of the substance. Indeed a characteristic singlet related to C-1 proton was found atδ5.60; this peak was not sharp due to coupling with the proton of the adjacent hydroxyl group. However, upon acetylation, the signal in the lactol acetate 8b was found to be shifted down field to 6.42 as sharp peak. It was therefore, decided that no proton was present neighbouring the C-1 hydrogen as would be expected from a lactol derived from a 2,3 seco aldehydo acid.

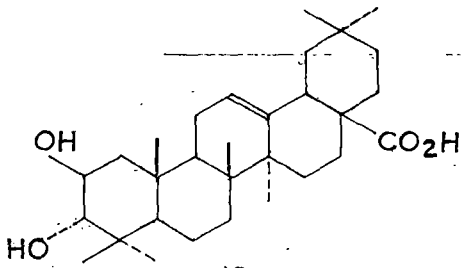


It is noteworthy that a substance, identified as the anhydride, 9, was also formed during the autoxidation. The formation of the anhydride 9 was explained by the initial formation of an α-hydroperoxy ketone and its cleavage to seco-2-aldehyde-3-carboxylic acid either by a four membered ring intermediate mechanism[3] or by an alternative peroxide mechanism[16]. The aldehyde under the basic reaction condition, is subsequently oxidised to a carboxylic group thus forming the 2,3-seco dicarboxylic acid, which upon cyclization formed the anhydride 9.

2. Oxidation of ring A in oleanolic acid.

In connection with their work to confirm the structure of bredemolic acid, 10 and crategolic acid 11 Tschesche and co-workers[17,18] performed the autoxidation of ring A in methyl oleanonate, 12. Methyl oleanonate was stirred in t-butanol containing potassium metal at 25-50°, with simultaneous introduction of oxygen.

The reaction mixture on acidification and usual working up gave an amorphous solid for which they proposed the structure 13 , methyl-2,3-dioxo-olean-12-en-28-oate, m.p. 130-35°, $[\alpha]_D$ 104° ± 4°. Sodium borohydride reduction of 13 gave methyl 2α-, 3α-dihydroxy-12-en-olean-28-oate, 14, which on oxidation with Kiliani solution gave a mixture of several compounds in which 10% of 13 was found to present as was shown by its uv spectrum.



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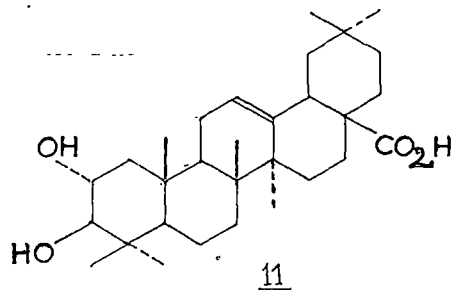

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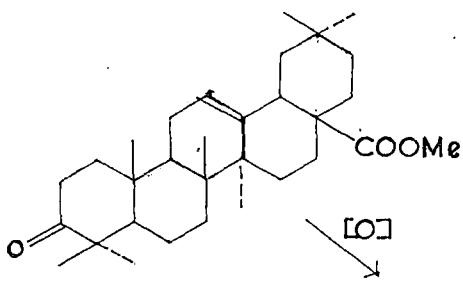

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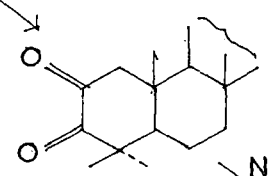
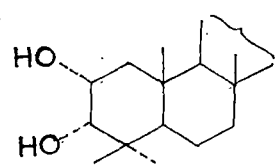
[O]



13

$NaBH_4$



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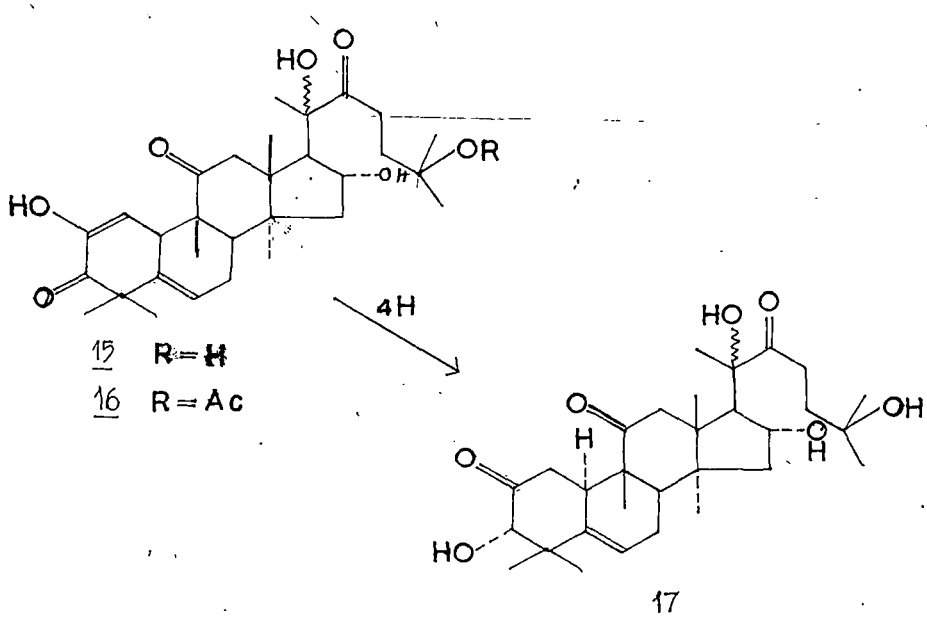
3. Isomerisation in ring A of the cucurbitacins.

Lavie and co-workers[19,20] reported that hydrogenation of the disophenol containing cucurbitacins, viz. elatericin B 15 and elaterin 16 resulted in 1,4 addition of hydrogen during the process of hydrogenation. ^{1}H NMR of the hydrogenation product elatericin B was found to show a singlet at δ 6.02 and that of its diacetate a sharp peak at δ 5.00. This observation clearly pointed to the fact that the proton linked to the carbon to which the acetoxy group is also attached had no neighbouring protons and can not, therefore, be at C-2. The ^{1}H NMR spectra could be explained if it was considered that 1, 4 addition of hydrogen to the diosphenol system took place, resulting in the conversion of Δ^{1-2}-hydroxy-3-keto to a 2-keto-3-hydroxy system 17.

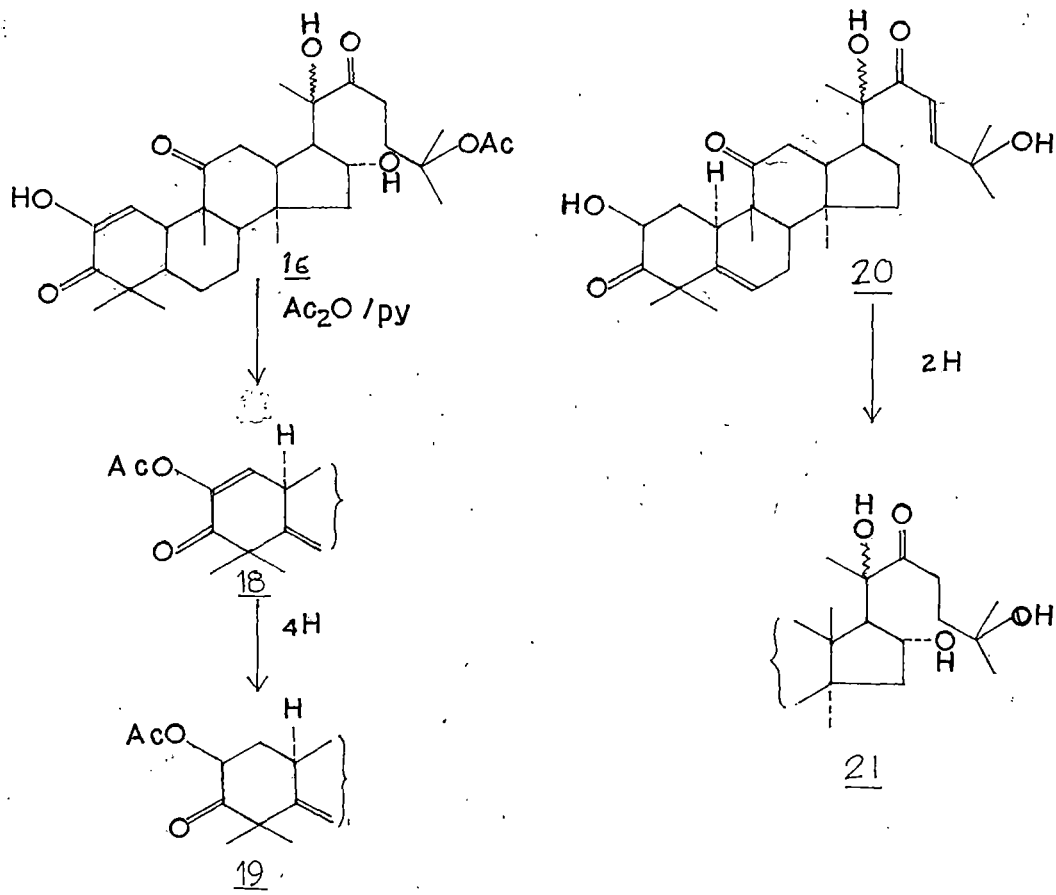


15 R=H
16 R=Ac

17

Elatericin B diacetate 18, on hydrogenation formed the 2β-equatorial-acetoxy-3-keto derivative 19 by a normal 1, 2 addition of hydrogen. This compound showed a quartet of lines related to the 2-α axial proton which is centred at δ 4.4 (J_{aa}= 13.5 cps, J_{ae} = 5.1 cps).

The isomerisation of 2-acetoxy-3 keto derivative 19 on basic alumina column as well as on acidic column was studied. In both the cases the material recovered from the column showed that it had remain unchanged.



The ORD curves of dihydro elatericin A 21 and tetrahydro elatericin B 19 were also interpreted. Cotton effect curves of both 2- and 3- keto derivatives were found to be positive, with the amplitude of the 2-keto derivative being larger than that of the keto form. The same results were observed also in the case of the 3-keto steroids[21] and the oxomanoyl oxide series[22]. The inverted stereochemistry of cucurbitacins at C-10 resulting in a mirror image of the C-10, β-analog, should give rise to a negative cotton effect but instead the two compounds displayed positive cotton effect.

This can be interpreted as due to the presence of two additional carbonyl chromophore, one in particular at C-11 displaying a large amplitude, which counteracts thereby the inverted rotation of the keto group in ring A as should be expected. The result is a lower positive value instead of a negative one. The peak for dihydro elatericin A 21 (3-keto) at $(\alpha)_{325}$ + 2200° is larger than that of tetrahydro elatericin B 17 (2-keto) $(\alpha)_{325}$ + 1558°. In both the cases the keto group was flanked by an equatorial (OH) substituent which is either likely to increase the cotton effect or to render no change at all.

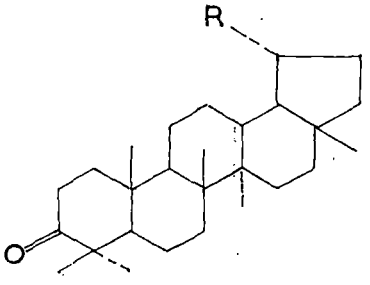
In order to obtain pure tetrahydro elatericin B 18, alkaline hydrolysis of tetrahydro elatericin B diacetate 19 was attempted but the reaction resulted in the formation of dihydro elatericin B 21[23], λ_{max} 267 nm, ϵ = 5700, positive ferric

chloride colouration (characteristic of diosphenol). Tetrahydro elatericin B diacetate 21 on alkaline hydrolysis yielded the same dihydro elatericin B 20. The alkali induced autoxidation of α-hydroxy ketone in elatericin was also studied[24] and was found to occur at much slower rate.

4. Oxidation in ring A in Lupeol.

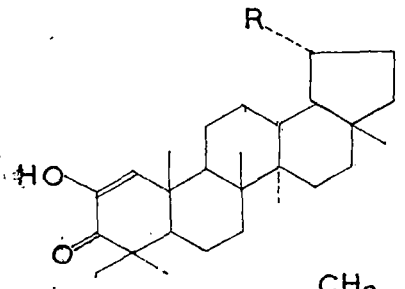
Ganguly et al[25] carried out the oxidation of Lupenone 22 and Lupanone 23 to the corresponding diosphenol 24 and 25 respectively by passing oxygen in dry tertiary butyl alcohol containing potassium tertiary butoxide. Diosphenol 25 on hydrogenation afforded a non crystalline alcohol which on hydrogenation afforded a non crystalline alcohol which on acetylation yielded the keto acetate, 26.

The structure 26 was assinged to the keto acetate by examining its ^{1}H NMR spectra. ^{1}H NMR spectra of compound 26 showed a sharp peak at δ 4.95 which was ascribed to the C-3 proton.



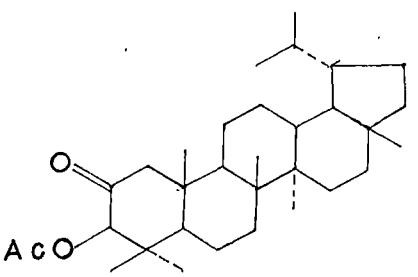
22 R= $-C(=CH_2)-CH_3$

23 R= $-C(CH_3)_2-CH_3$



24 R= $-C(=CH_2)-CH_3$

25 R= $-C(CH_3)_2-CH_3$



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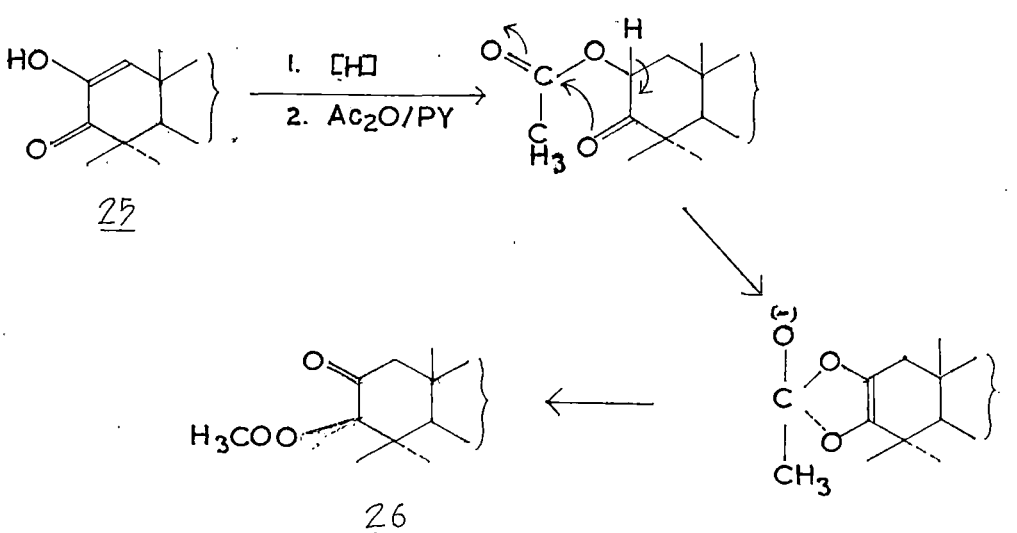
Formation of 26 from 25 was explained by the mechanism shown below.



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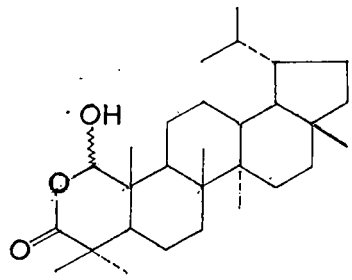
26

Diosphenol 25 on ozonisation gave a neutral compound $C_{29}H_{48}O_3$, whose structure was assigned as 27 on the basis of mode of formation, spectral characterisation and elemental analysis. Diosphenol 24 was cleaved by alkaline hydrogen peroxide to the dicarboxylic acid $C_{30}H_{48}O_4$. The acid was converted into the dimethyl ester 28, which on refluxing with alcoholic alkali yielded a neutral crystalline compound 29.



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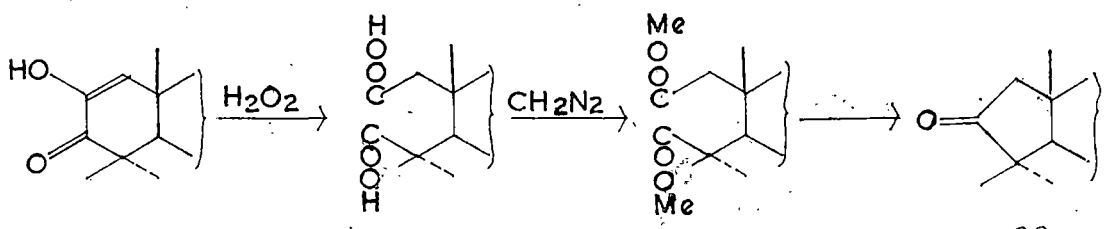


24 28 29

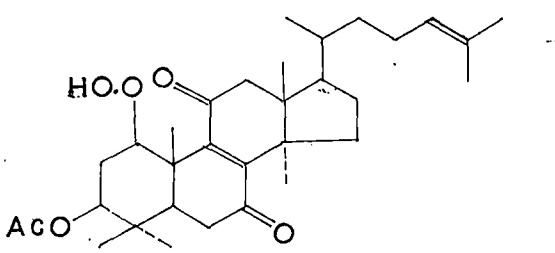
5. Autoxidation of Lanostenyl acetate

Horn and ILse[26] stated that lanostenyl acetate in ethyl acetate was extensively converted into a mixture of 7-hydroperoxy and 7,11-dihydroperoxy lanostenyl acetate by treatment with gaseous oxygen at 50° for 48 hours.

After that Scotney and Truter[27] found that the oxidation of lanostenyl acetate in ethylacetate at 50° after 14 days was a mixture of at least eight peroxides. The two most plentiful peroxides were recovered and shown to be 7β -and 11β -hydroperoxy lanostenyl acetates. The structure of 7β -hydroperoxy-lanostenyl acetate was obtained by reducing it with sodium borohydride to 7β -hydroxy lanostenyl acetate. The structure of 11β -hydroperoxide was proved by converting it to 11-oxo-lanostenyl acetate with ferrous ion. Further more, Lithium aluminium hydride reduction of the 11-hydroperoxide afforded one product, which was identical with 11β -hydroxylanostenol.

Autoxidation of 7, 11-dioxolanost-8-enyl-3β -acetate in cyclohexane at 40° proceeded via 1β -hydroperoxy-7, 11-dioxo-lanostenyl acetate to 1, 7, 11-trioxolanost-8-enyl acetate[28]. The location of ketone at 1-position was deduced from the behaviour of the trione acetate with alkali. With alkali 1, 7, 11-trioxo lanost-8-enyl acetate yielded 1,7,11-trioxolanosta-2, 8 diene and it had been derived from the trione acetate by

elimination of the 3β-acetate group and the formation of a conjugated unsaturated grouping (30, 31, 32). That the precursor for the trione is a monohydroperoxide of 7, 11-dioxo-lanostenyl acetate was established by the fact it was deomcposed by ferrous ion to 1,7,11-trioxolanostenyl acetate.



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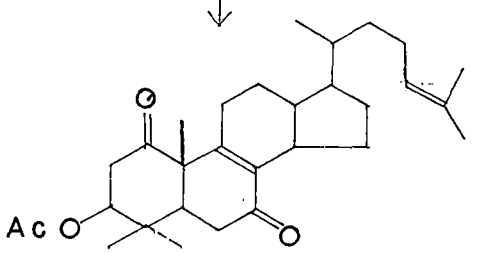

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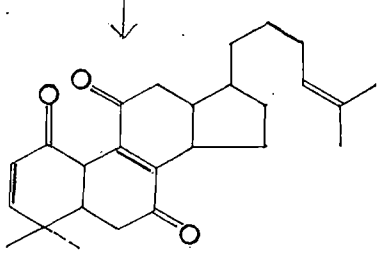


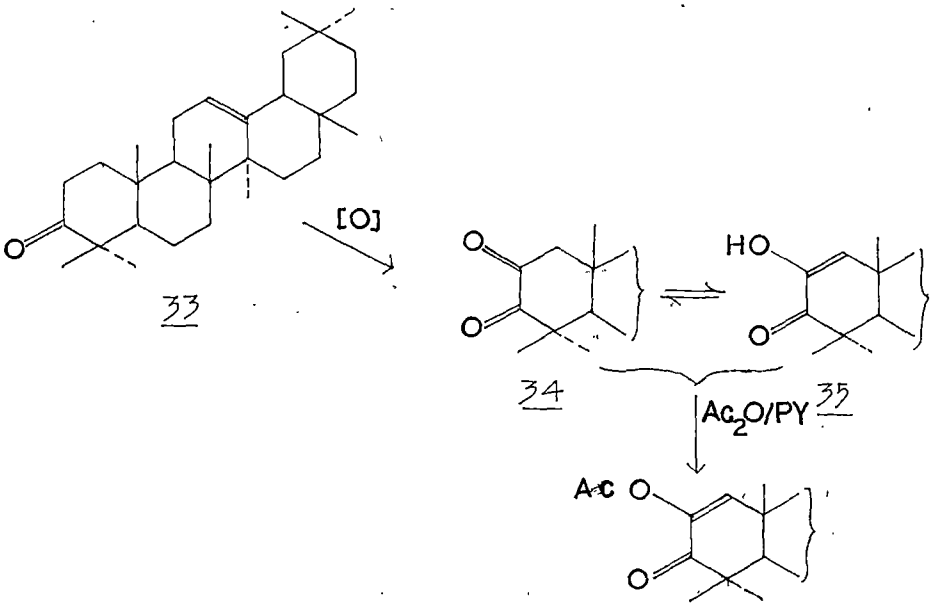
32

In an experiment a solution of lanost-8-en-3β-yl acetate in cyclohexane at 40^{o} was oxidised by passing oxygen through it[28a]. After twelve months treatment the neutral fraction was examined and was found to contain at least sixteen components. From the R_f values several compounds have been identified e.g. 1,7,11-trioxolanostenyl acetate, 1,7,11-trioxolanosta-2,8-diene. Besides these, 15β-hydroxy-7-oxo, 15α-hydroxy-7-oxo-, 7, 15-dioxo- and 11, 15-dioxo-lanosten-3β-yl acetate were also identified.

6. Autoxidation of β-amyrone

In an attempt to introduce more oxygen functions in a triterpenoid molecule Khastgir et al[29] studied the autoxidation of β-amyrone (which unlike euphol does not contain any double bond in 8, 9 position).

The introduction of an oxygen function α- to the C-3 carbonyl group was carried out by stirring β-amyrone in an atmosphere of oxygen in dry tertiary butanol containing potassium tertiary butoxide. One mole of oxygen was rapidly absorbed by the compound giving a α-diketone derivative, m.p. 200-2^{o}, $[\alpha]_D$ + 124.27^{o}. The compound showed two spots on the chromatoplate indicating the presence of a mixture of two compounds. The compound showed positive ferric chloride colouration. Its uv spectra exhibited maxima at 270 nm, ϵ 7932. IR showed peaks at 1100, 1650, 1670, 1716, 2960 and 3570 cm^{-1}. These data established that the compound was a tautomeric mixture of diketone 34 and the diosphenol 35.

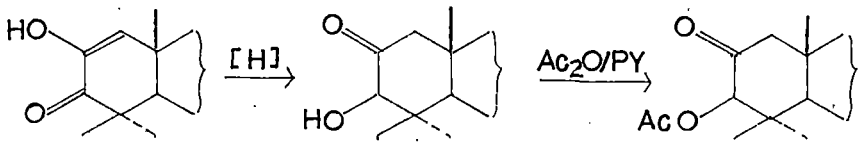


33 34 35 36

However, acetylation of the above compound with acetic anhydride and pyridine at room temperature gave the corresponding acetate 36, m.p. 172-73°, $[\alpha]_D$ + 107.69, uv absorption at λ_{max} 236 nm. IR absorption at ν_{max}^{nujol} 1205, 1685, 1720, 2950 cm^{-1}.

These spectral data clearly established the structure 35 and 36 for the diosphenol and diosphenol acetate respectively.

In order to prepare the α-hydroxy ketone derivative in ring A, catalytic hydrogenation of the diosphenol 35 was investigated and several interesting results were obtained. Hydrogenation of diosphenol 35 in presence of 10% palladium - on charcoal catalyst yielded 2-keto-3-hydroxy compound 37 which on acetylation afforded the corresponding acetate 38.

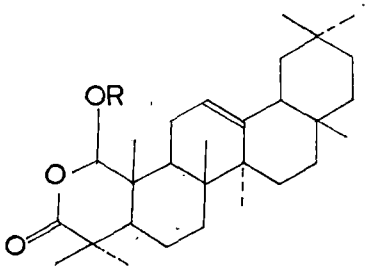


35 37 38

The formation of 3-hydroxy-2 keto derivative 37 during the process of hydrogenation was explained by Khastgir et al as in the following way. During the process of hydrogenation a rear attack of the hydrogen from the less hindered side of the molecule might take place resulting in the formation of the 2-hydroxyl group in β-axial orientation. It is known that the conformation of ring A in triterpenoids as well as in 4,4-dimethyl steroids[30-32] are dependent on the 1, 3 homoannular interactions of the methyl groups at C-4 and C-10.

Therefore, the C-2 β-axial hydroxyl group which could be formed by rear attack of hydrogen would produce further 1, 3-diaxial interactions resulting in a great strain in the molecule. The strain could be released by ready conversion to 3-hydroxy-2 keto derivative, 37, through enlisation of the 2 β-hydroxy-3-keto derivatives.

During the process of autoxidation, a second mole of oxygen was absorbed by the diosphenol 35, which resulted in the formation of a lactol, 39 (1-hydroxy-2-oxo-β-amyrone), m.p. 262-5°, $[\alpha]_D$ + 66.66°. The formation of such a lactol had already been described and was interpreted through the formation of a ring A seco-2-nor-aldehydo carboxylic acid which cyclizes upon acidification[33]. Acetylation of 39 with acetic anhydride-pyridine gave an acetate 40 m.p. 186-8°, $[\alpha]_D$ + 117.64°.



39 R = H
40 R = Ac

7. Autoxidation of Moretanone

Moretanone, 41, obtained by hydrogenation of Moretenone[34] was autoxidised by passing oxygen through a suspension of moretanone, 41, in dry tertiary butanol containing K-tert-butoxide[35], which resulted in the formation of corresponding diosphenol 42. Acetylation of diosphenol afforded the diosphenol acetate 43. Disophenol acetate 43 on hydrogenation in presence

of palladium charcoal catalyst in ethanol solution gave the reduced product 44, m.p. 179-81°. Diosphenol 42 on hydrogenation in presence of palladium on charcoal catalyst in ethanol solution gave a solid 45 m.p. 181-83°, which on acetylation afforded the corresponding acetate 46 m.p. 264-67°. The acetate 43 on isomerisation by absorbing it on basic alumina column was converted to the stable 2-keto moretanylacetate structure 45a.