PART II

Studies on Autoxidation: Isomerisation in ring A in β-amyrone

PART II

CHAPTER I

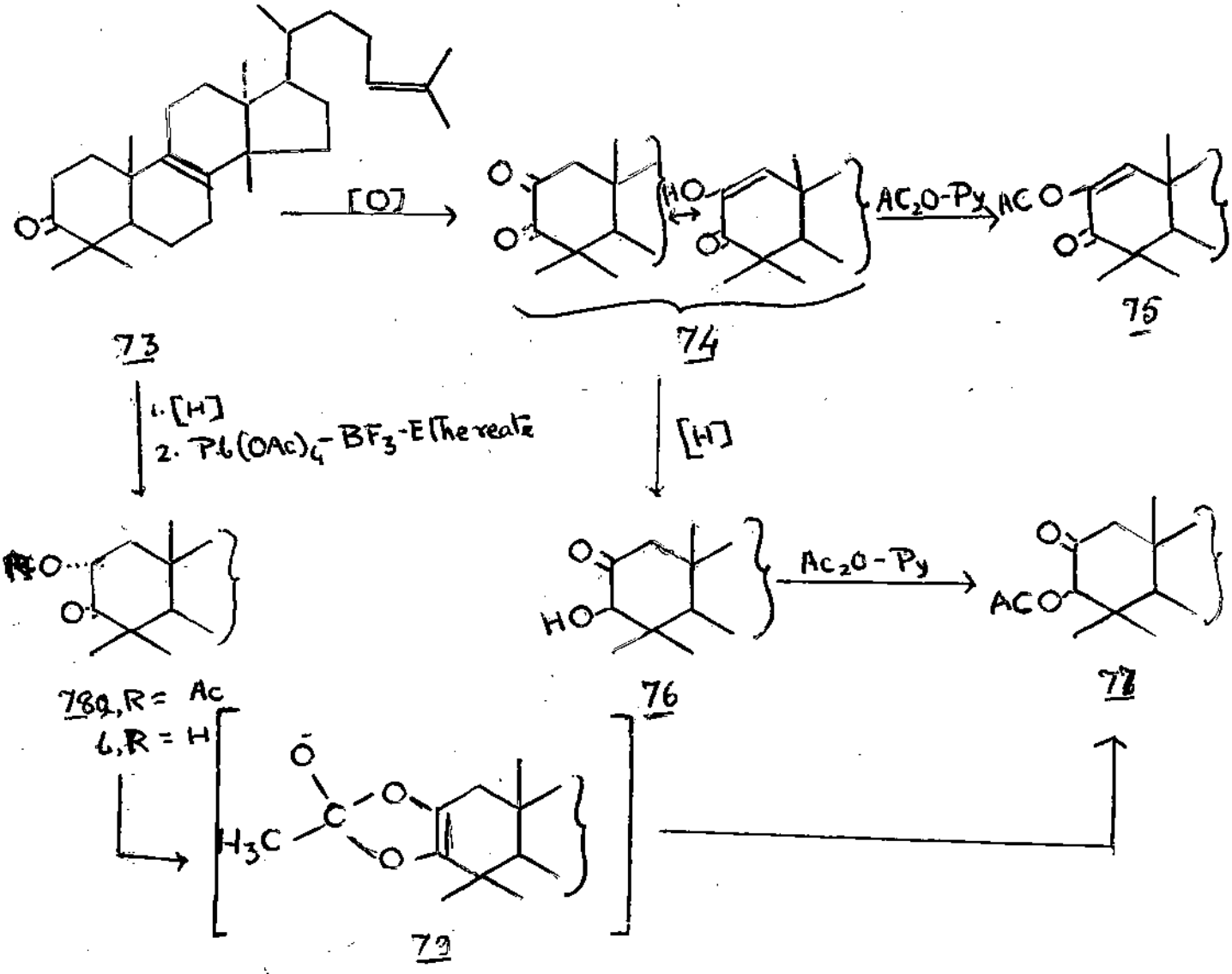
A short review on autoxidation and isomerisation in ring A in triterpenoids

1. Oxidation in ring A in Euphol

Lavie and co-workers[1] studied the autoxidation of euphadiene-3-one 73 and the results of their work are summarised as follows. Euphadiene-3-one 73 was oxidised by shaking in oxygen in t-butanol saturated with potassium t-butoxide[2,3]. A tautomeric mixture of diketone and the corresponding disophenol 74 (two spots on chromatoplate) was produced by absorbing one mole of oxygen, UV, λ max 269 mμ, (ϵ = 7,900), IR, ν max 1715, 1672 and 1653 cm^{-1}. NMR of the compound 74 showed a singlet at τ=3.60 due to vinylic proton at C-1. Acetylation gave the corresponding acetate, UV, λ max 236 mμ, ϵ=9,000; IR, ν max 1764 cm^{-1}. NMR showed a singlet at τ = 3.02 due to C-1 proton.

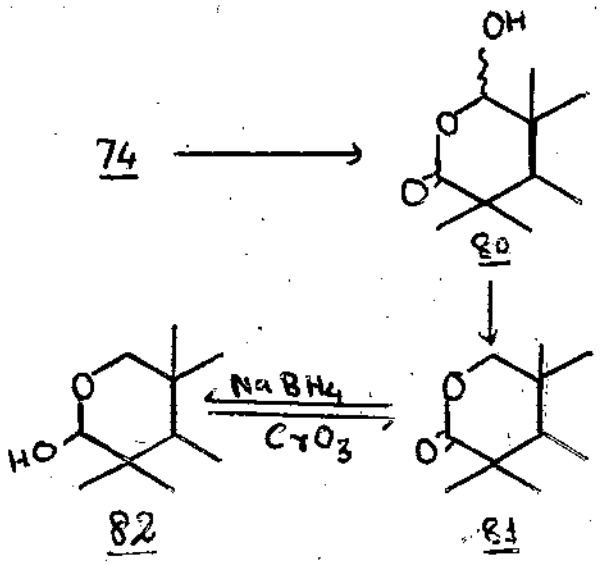
On hydrogenation of the diosphenol 74 over palladium-on-charcoal (two moles of hydrogen were absorbed-one mole to reduce the side chain double bond and the second mole to reduce the enolic double bond) a non-crystallisable homogeneous solid, IR, ν max 1712 cm^{-1}, NMR, singlets at τ = 5.95 accounting for one hydrogen and two AB type doublet centered at τ = 7.69 and 7.35 accounting for two hydrogens, were obtained. Upon acetylation a crystalline keto

acetate was obtained, νmax 1742 and 1730 cm^{-1}, NMR singlet at τ= 4.95 for one hydrogen and a broad peak at τ = 7.50 accounting for two hydrogens. From the above spectral properties structure 76, and 77 was proposed for the hydroxy ketone and the keto acetate respectively. 2α-equatorial-acetoxy derivative 78a was prepared by the reaction of dihydro derivative of 73 with lead tetraacetate in acetic acid in the presence of boron trifluoride[4]. The product 78a showed IR band at 1742 and 1730 cm^{-1} and the NMR spectra showed a quartet of lines centered at τ = 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 a keto function.



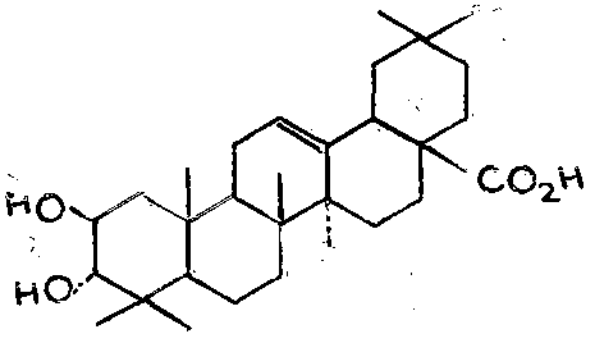
The isomerisation of 2α-equatorial-acetoxy ketone 28a into the isomer 27 was also observed and they proposed that the migration proceeded through the cyclic intermediate 29[5]. Acid hydrolysis of 28a afforded a compound which has been assigned the 2α-equatorial hydroxy 3-keto derivative 28b on the basis of its IR, νmax 1718 cm^{-1}.

During the process of autoxidation a second mole of oxygen was absorbed and the product isolated was identified as the lactol 80, (R=H) νmax 1710 and 1107 cm^{-1} NMR peak at τ = 4.40, the corresponding acetate 80 (R = Ac) showed a sharp peak at τ=3.58, 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 cyclizes upon acidification. Further confirmation of the structure 80 for the lactol was obtained by reducing it with sodium borohydride in the presence of one mole of potassium hydroxide. Two products, a δ -lactone 81, νmax 1739 cm^{-1} (no absorption in the hydroxylic region) and a hemiacetal 82, νmax 3450 and 1068 cm^{-1} (no absorption in the carbonyl region) were obtained. NMR spectra of the hemiacetal 82 showed two doublets of an AB type centered at τ = 6.69 and 6.09 (J_{AB} = 11 cps, related to C-1 protons), peak at τ = 5.66 (related to C-3 proton adjacent to hydroxyl group) which shifted downfield at τ = 4.71 in the corresponding acetate[6]. The hemiacetal 82 on oxidation with chromium trioxide gave the lactone 81 whereas the lactone on sodium borohydride reduction gave back the hemiacetal 82.



2. Oxidation of ring A in oleanolic acid

In connection with their work to confirm the structure of bredemolic acid 83 and crategolic acid 84 Tschesche and co-workers[7,8] performed the autoxidation of ring A in methyl oleanonate 85. 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 86, methyl-2,3-dioxo-olean-12 en-28-oate, m.p. 130-35°, $(\alpha)_D$ 104° ± 4°. Sodium borohydride reduction of 86 gave methyl 2α, 3α-dihydroxy-12-en-olean-28-oate 87 which on oxidation with kiliani solution gave a mixture of several compounds in which 10% of 86 was found to present as was shown by its UV spectrum.



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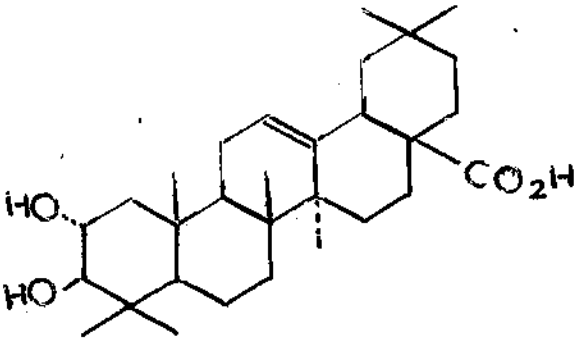

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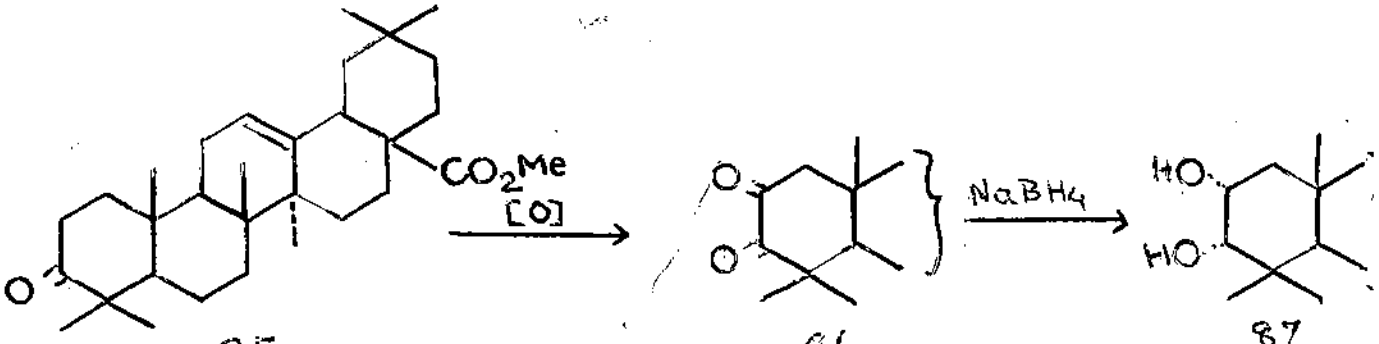

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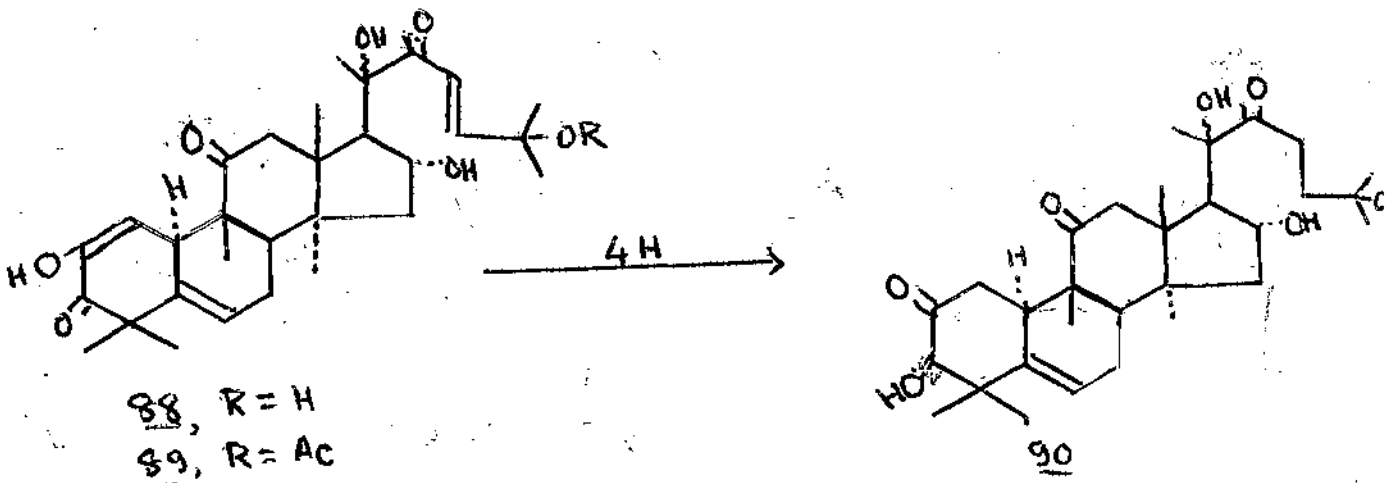
3. Isomerisation in Ring A of the cucurbitacins

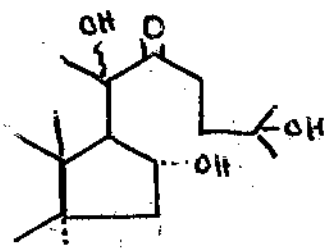
Lavie and co-workers[9,10] reported that hydrogenation of the diosphenol containing curcurbitacins, namely elatericin B 88 and elaterin 89 resulted in 1,4-addition of hydrogen during the process of hydrogenation. The NMR spectrum of hydrogenation product of elatericin B was found to show a singlet at $\tau = 6.02$ and that of its diacetate a sharp one at $\tau = 5.00$. 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 cannot, therefore, be at C-2. The 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^4-2-hydroxy-3-keto to a 2-keto-3-hydroxy system 90.



88, R = H
89, R = Ac

90



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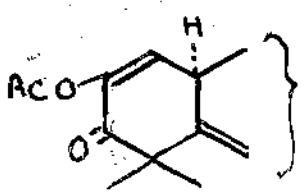

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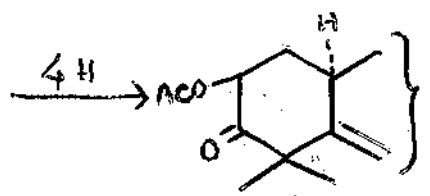

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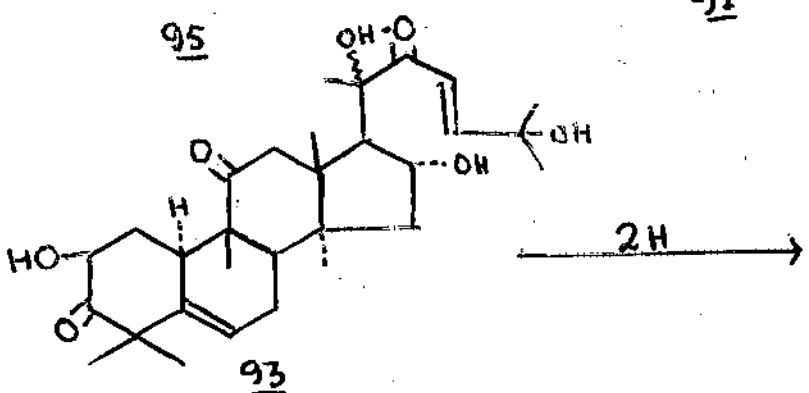

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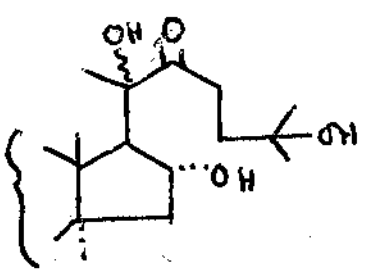

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Elatericin B diacetate 91, on hydrogenation formed the 2β-equatorial-acetoxy-3 keto derivative 92, by a normal 1,2-addition of hydrogen. This compound showed a quartet of lines related to the 2α-axial proton which is centered at $\tau = 4.4$ ($J_{aa} = 13.5$ cps;

J_{ae} = 5.1 cps). The isomerisation of 2-acetoxy-3 keto derivative 92 on basic column of alumina as well as on acidic column was studied. In both the cases the material recovered from the columns showed that it had remained unchanged.

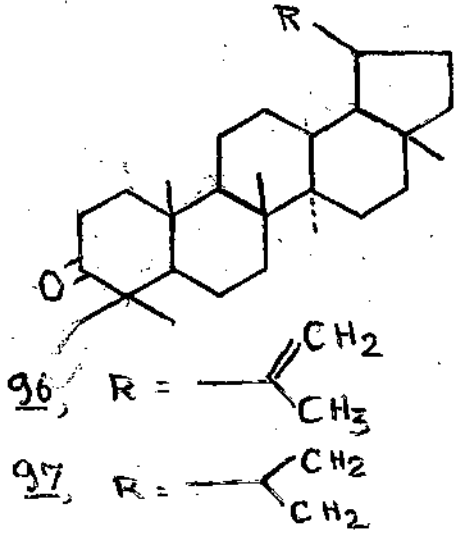
The ORD curves of dihydro elatericin A 94 and tetrahydro elatericin B 90 were also interpreted. Cotton effect curves of both 2- and 3-keto derivatives were found to be positive, with the amplitude of the 2-keto derivative being larger than that of the 3-keto form. The same results were also observed in the case of 2- and 3-keto steroids[11] and the oxomanoyl oxide series[12]. 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 curves. 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 94 (3 keto) at $(\alpha)_{325}$ + 220°, is larger, than that of tetrahydroelatericin B 90 (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.

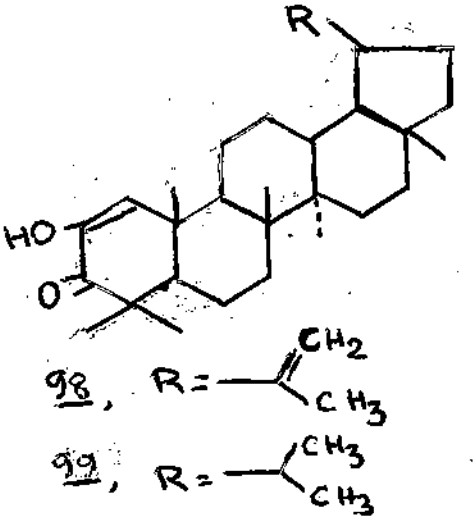
In order to obtain pure tetrahydroelatericin B 95, alkaline hydrolysis of tetrahydroelatericin B diacetate 92 was attempted but

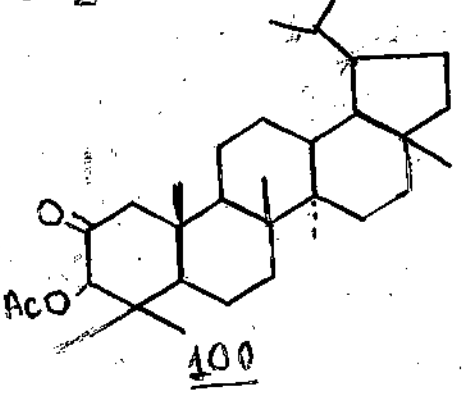
the reaction resulted in the formation of dihydroelatericin B 93[13], λmax 267 mμ, ε = 5700, positive ferric chloride coloration (characteristic of diosphenol). Tetrahydroelatericin B diacetate 94 on alkaline hydrolysis yielded the same dihydroelatericin B 93. The alkali induced autoxidation of α-hydroxy ketone in elatericin was also studied[14] and was found to occur at much slower rate.

4. Oxidation in ring A in Lupeol

Ganguly and co-workers[15] carried out the oxidation of lupeone 96 and lupanone 97 to the corresponding diosphenols 98 and 99 respectively by passing oxygen in dry t-butyl alcohol containing potassium tertiary butoxide. Diosphenol[22] on hydrogenation afforded a non-crystalline alcohol which on acetylation yielded the keto-acetate 100. The structure 100 was assigned to the keto-acetate by examining its NMR spectra (a sharp singlet at δ = 4.95 ascribed to the C_3 proton).







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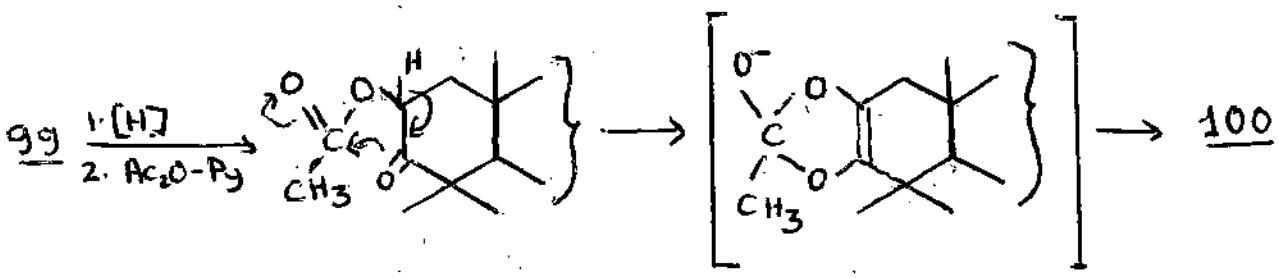
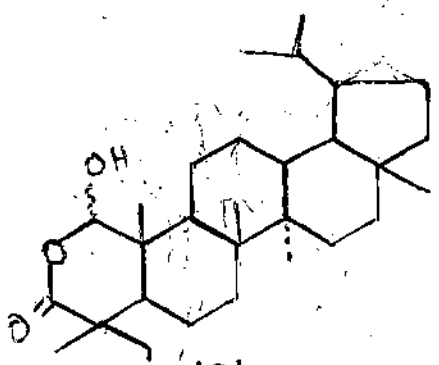


Formation of 100 from 99 was explained by the mechanism shown in Chart I. Diosphenol 99 on ozonisation gave a neutral compound $C_{29}H_{48}O_3$, whose structure was assigned as 101 on the basis of mode of formation, spectral characteristics and elemental composition. Diosphenol 98, was cleaved by alkaline hydrogen peroxide to the dicarboxylic acid ~~121~~ $C_{30}H_{48}O_4$. The acid was converted into the dimethyl ester 102, which on refluxing with alcoholic alkali yielded a neutral crystalline compound 103.



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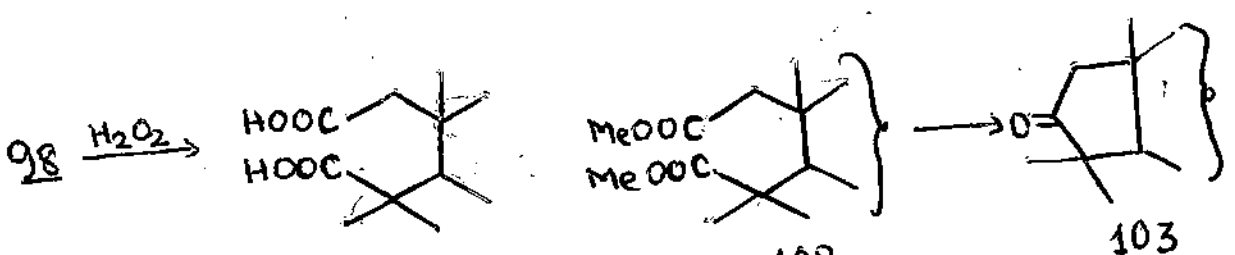

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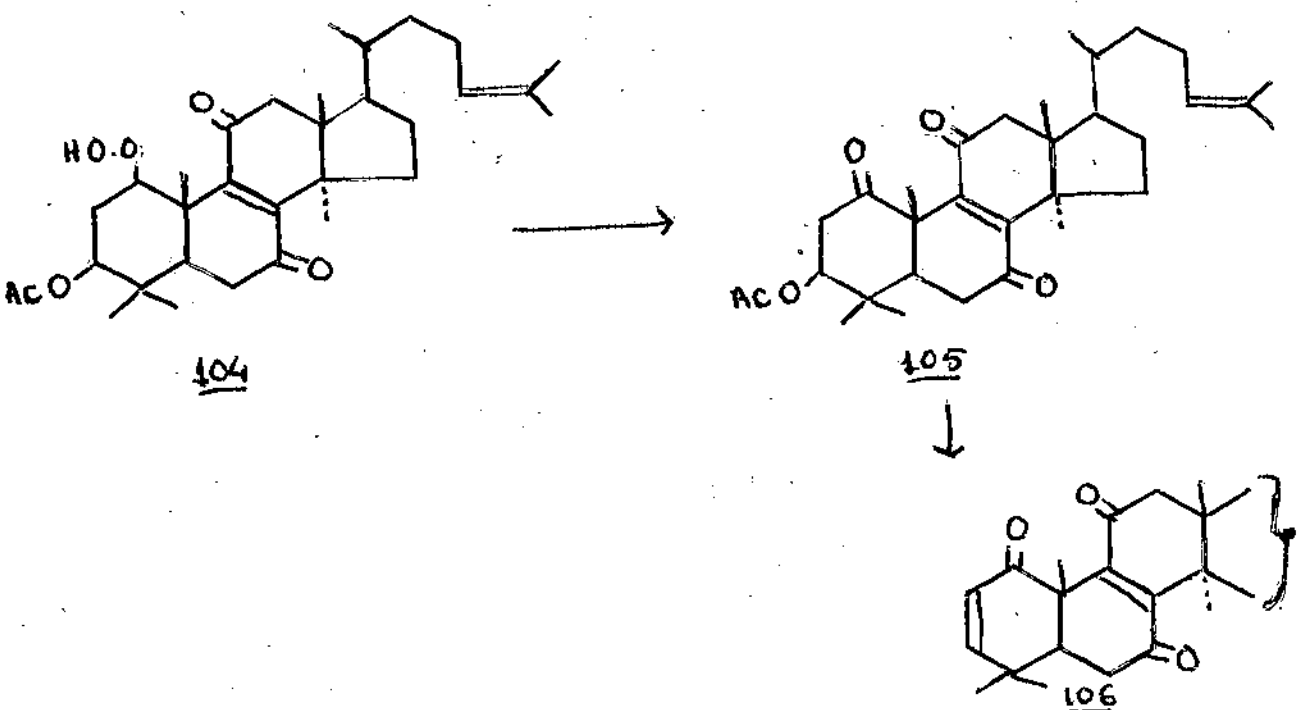
5. Autoxidation of Lanostenyl acetate

Horn and Ilse[16] stated that lanostenyl acetate in ethyl acetate was extensively converted into a mixture of 7-hydroperoxy- and 7,11-dihydroperoxy lanostenyl acetates by treatment with gaseous oxygen at 50° for 48 hours. After that Scotney and Truter[17] found that the autoxidation of lanostenyl acetate in ethyl acetate at 50° after 14 days was a mixture of at least eight per-oxides (laminar chromatography). The two most plentiful peroxides were recovered and shown to be 7β- and 11β- hydroperoxylanostenyl acetates. The structure of 7β-hydroperoxy-lanostenyl acetate was obtained by reducing it with sodium borohydride to 7β- hydroxylanostenyl acetate. The structure of 11β-hydroperoxide was proved by converting it to 11-oxo-lanostenyl acetate with ferrous ion. Furthermore, 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-dioxolanostenyl acetate to 1,7,11-trioxolanost-8-enyl acetate[18]. The location of ketone at 1-position was deduced from the behaviour of the trione acetate with alkali. With alkali 1,7,11-trioxolanost-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 (104 → 105 → 106). That the precursor for the trione is a mono-hydroperoxide of 7,11-dioxolanostenyl acetate 34 was established by the fact it was decomposed by ferrous ion to 1,7,11-trioxolanostenyl acetate.



In an experiment a solution of lanost-8-en-3β-yl acetate in cyclohexane at 40° was oxidised by passing oxygen through it[19]. After twelve months treatment the neutral fraction was examined and was found to contain at least sixteen components. From the R_f values several components 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-lanostan-3β-yl acetate were also identified.