A Chemical Model for a Possible Oxidative Rearrangement in the Biosynthesis of Tetranortriterpenes: the Preparation of Methyl 3α-Acetoxy-7-oxoapotirucalla-14,24-dien-21-oate

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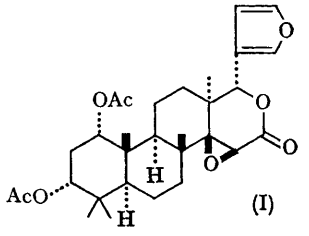
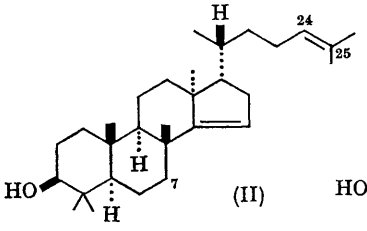
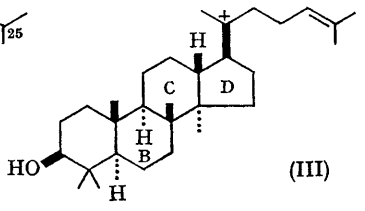
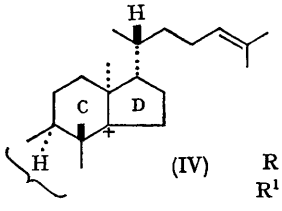
A CURRENT problem of terpenoid biosynthesis is that of the tetranortriterpenes such as khivorin (I),[1] gedunin,[2] and limonin[3] found in the *Meliaceae* and *Rutaceae* families. It was originally suggested[3] that limonin might arise from apoeuphol (II). This could be biosynthesised either directly from squalene *via* the ions (III) and (IV) or *via* butyrospermol (V) or its Δ^8-isomer, euphol, and subsequent migration back of the C-14 methyl group to C-8. Recently it has been suggested[7] that a tirucalla-7,14-dien-3-ol [possibly the 3α-ol (VI)] might be the precursor of the tetranortriterpenes. All the known ones have oxygen at C-7 and when it is present as a hydroxyl group the configuration is α. This suggests that a key step in the biosynthesis is the rearrangement of the 7α,8α-epoxide of a tirucallol (possibly degraded) derivative [*cf.* (IX)] to a 7α-hydroxyapotirucallol derivative [*cf.* (XI)]. Evidence that an oxidative rearrangement of the C-14 methyl group can be brought about was first provided by Spring *et al.*,[5, *cf.* 6] who oxidised dihydrobutyrospermyl acetate with chromic acid to a ketone formulated as a 7-oxo-apoeuphol derivative, although the proposed structure was not proven. A rearrangement of the C-14 methyl group has now been accomplished starting from a 7α,8α-epoxide in the tirucallol series.

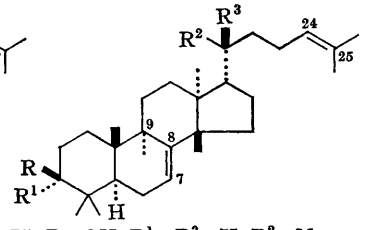
Methyl acetyl-dihydro-α-elemolate (VII) (methyl 3α-acetoxytirucall-7-en-21-oate) on ozonolysis followed by reductive workup with zinc dust readily gave the 7α,8α-epoxide m.p. 130—132°, $[\alpha]_D$ −78°, which was smoothly rearranged with BF_3–Et_2O in benzene to the 7α-hydroxyapo-derivative (XI). This has not yet been obtained crystalline but was homogeneous (t.l.c.) and had the expected n.m.r. spectrum. It was characterised by oxidation to the corresponding ketone (XII), m.p. 160°, $[\alpha]_D$ −140°, when the chemical shift of the C-15 proton changed significantly from τ 4·52 to 4·03 showing the close spatial relationship of the keto-group to the double bond.

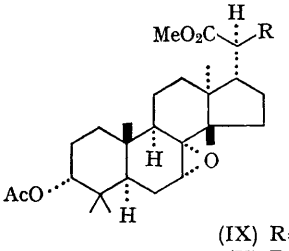










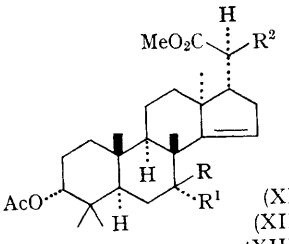


(V) R=OH, R^1=R^3=H, R^2=Me
(VI) R=R^2=H, R^1=OH, R^3=Me
(VII) R=R^2=H, R^1=OAc, R^3=CO_2Me; 24, 25-dihydro
(VIII) R=R^2=H, R^1=OAc, R^3=CO_2Me

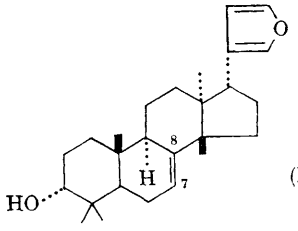
(IX) R=C_6H_{13}
(X) R=C_6H_{11}

Recently we have found that "elemolic acid" from elemi resin is a mixture of *both* the Δ^7-isomer (VIII) and the Δ^8-isomer.[*cf.* 10] Separation of the

isomers is tedious but ozonolysis of the methyl esters from the mixture of acetylated 24,25-dihydro-acids gave an easily separable mixture of the 7α,8α-epoxide (IX) and ketonic material arising from the Δ^8-isomer. Treatment of the acetylated methyl elemolate mixture (Δ^7- and Δ^8-isomers) gave the corresponding admixed 24,25-dibromides. Ozonolysis of these followed by reductive workup with zinc dust, which brought about concomitant debromination, afforded after chromatography, the 7α,8α-epoxide (X), m.p. 127·5—129°, $[\alpha]_D$ −80°, which was rearranged with BF_3–Et_2O/benzene to the 7α-hydroxyapo-derivative (XIII) which was characterised as the corresponding 7-ketone (XIV), m.p. 146—148°, $[\alpha]_D$ −156°. A route is therefore now available to 7α-hydroxyapotirucallol derivatives which should be of potential use both for the preparation of possible biogenetic precurors of the tetranortriterpenes and for the partial synthesis of meliacins. The present pattern of known structures suggests that the furan derivative (XV) and its 7α,8α-epoxide may be key compounds in the biosynthesis. The preparation of these compounds is being attempted.



(XI) R=H, R^1=OH, R^2=C_6H_{13}
(XII) R, R^1=O, R^2=C_6H_{13}
(XIII) R=H, R^1=OH, R^2=C_6H_{11}
(XIV) R, R^1=O, R^2=C_6H_{11}



(XV)

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