The Natural Occurrence of Melianodiol and its Diacetate in *Samadera madagascariensis* (Simaroubaceae): Model Experiments on Melianodiol directed towards Simarolide

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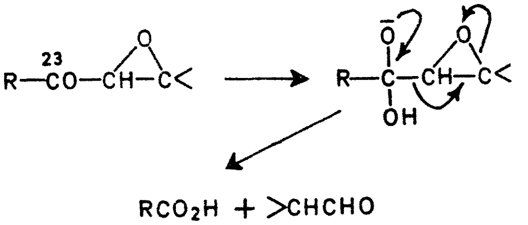
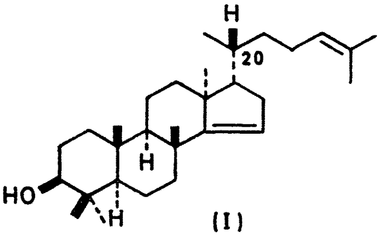
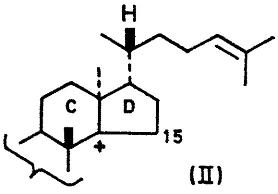
Summary "From *Samadera madagascariensis* melianodiol and its diacetate have been isolated; biogenetic experiments directed towards simarolide have been carried on melianodiol."

The triterpenoid biogenetic pathway for the quassinoids (C_{20} compounds related to quassin) has been experimentally verified[1] using labelled mevalonate lactone. A current problem of the biosynthesis of the quassinoids and of the limonoids (C_{26} compounds related to limonin) remains that of their tetracyclic triterpenoid precursor. It was originally suggested that the limonoids[2] and the quassinoids[3,4] might arise from apoeuphol (I). This could be biosynthesised either directly from squalene 2,3-oxide *via* the cationic intermediate (II) and subsequent loss of a proton from C-15,[5,6] or, alternatively, *via* Δ^7-euphol or its 20α-isomer, Δ^7-tirucallol (III), and subsequent back-migration of the C-14 methyl group to C-8;[2] this skeletal rearrangement (apoeuphol type rearrangement) could be triggered by oxidative attack of the nuclear double bond of the Δ^7-isomer of euphol or tirucallol (III). The second biogenetic hypothesis is supported by the occurrence of a number of side-chain oxygenated tirucall-7-ene derivatives (melianes[7]) in the Meliaceae and Rutaceae families from which limonoids have been isolated.





(I)



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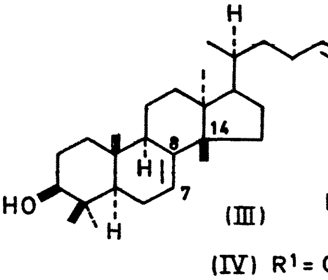

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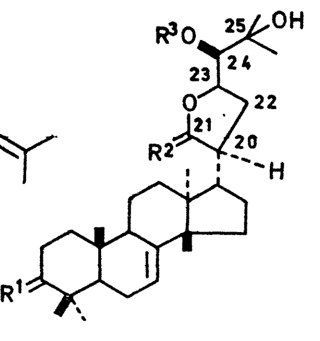
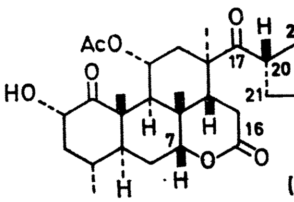


(IV) $R^1 = O; R^2 = \alpha\text{-OH},\beta\text{-H}; R^3 = H$
(V) $R^1 = O; R^2 = \alpha\text{-OAc},\beta\text{-H}; R^3 = Ac$
(VI) $R^1 = O; R^2 = O; R^3 = H$

We now report the isolation from *Samadera madagascariensis* (Jussieu) of melianodiol (IV) and its diacetate (V), tirucall-7-ene derivatives, found for the first time in a

Simaroubaceous plant. Furthermore, the conversion of the side-chain of (IV) into a γ-lactone by a three-step synthesis, the apoeuphol type rearrangement of the corresponding 7,8-α-epoxido derivative and the transformation of ring D into an $\alpha\beta$-unsaturated δ-lactone are described.

According to Capuron,[8] *Samadera madagascariensis* J. is identical to *Samadera indica* Gaert. Actually, we isolated, from the alcoholic extract of the former Simaroubaceae, samaderin B and C, the major C_{19}-quassinoids of *Samadera indica*.[9]



(VII)

From the petrol extract of the twigs and leaves of *Samadera madagascariensis* two crystalline compounds were isolated by chromatography. The more polar product, $C_{30}H_{48}O_5$ (M^+ 488), m.p. 219—222°, $[\alpha]_D$ −39°,† was identified as melianodiol (IV) on the following grounds. Its i.r. spectrum showed a band at 1700 cm^{-1} and its c.d. curve shows a negative Cotton effect ($\Delta\epsilon$ = − 0·7 at 296 nm) of the same sign and magnitude as that of odoratone which has a carbonyl grouping at C-3. The n.m.r. spectrum showed the presence of seven methyl signals between 0·7 and 1·4 p.p.m.; at low field there are 4 protons: multiplet (1H) at 3·2 p.p.m. simplifying to a doublet (J = 2 Hz) on exchange with D_2O (24-H), multiplet (1H) at 4·5 p.p.m. (23-H) and a multiplet (2H) at 5·3 p.p.m. (21-H and 7-H).

The hemiacetal structure was proved by oxidation with silver carbonate,[11] yielding the γ-lactone (VI), $C_{30}H_{46}O_5$ (M^+ 486), m.p. 200—203°, $[\alpha]_D$ − 130°, characterized by a band at 1775 cm^{-1} and by the disappearance of the C-21 proton signal. In addition to the hydroxy-group of the hemiacetal, compound (IV) possesses a secondary and a tertiary hydroxy-group which are involved in an α-glycol grouping as shown by periodic acid oxidation of the lactone (VI) and by acetylation of (IV). The latter reaction affords the diacetate (V), $C_{34}H_{52}O_7$ (M^+ 572), m.p. 204—206°, $[\alpha]_D$ +36°‡ which still shows OH absorption and a down-field shift of 24-H and 21-H.

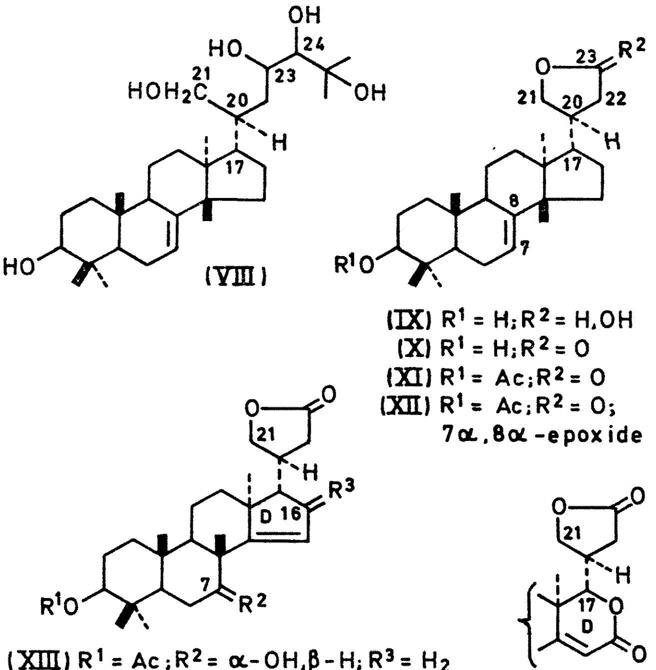
The diacetate (V) was found to be identical to the less polar compound isolated from the petrol extract of *Samadera madagascariensis*.

The suggested structures of the compounds under discussion have been confirmed by direct comparison with authentic samples of melianodiol (IV) and its corresponding lactone (VI).

Melianodiol (IV) has been previously obtained by acid-catalysed opening of the epoxide of melianone (24,25-epoxide corresponding to melianodiol) and isolated from *M. azedarach*.[12] The simultaneous occurrence of both melianodiol and its diacetate in *Samadera madagascariensis* indicates that the former is not an artefact produced by the isolation procedure.

In model experiments directed towards simarolide (VII), the only known C_{25}-quassinoid, melianodiol (IV) has been converted into an analogous C_{26} γ-lactone by the following reactions: the pentaol (VIII)[12] obtained from melianodiol (IV) with sodium borohydride, was cleaved by sodium metaperiodate to the hemi-acetal (IX), $C_{26}H_{42}O_3$ (M^+ 402), m.p. 204—208°, $[\alpha]_D$ −23°. Oxidation with silver carbonate[11] leads then to compound (X), $C_{26}H_{40}O_3$ (M^+ 400), m.p. 212—214°, $[\alpha]_D$ −54°, with a γ-lactone [ν(CO) at 1775 cm^{-1}] such as is found in simarolide (VII). Upon acetylation the compound affords the monoacetate (XI), $C_{28}H_{42}O_4$ (M^+ 442), m.p. 219—222°, $[\alpha]_D$ −29°.

It has been suggested previously[13] that the potential C-23 carboxyl group of simarolide (VII) might arise from a 23-keto-24,25-epoxide:



(VIII)

(IX) R¹ = H; R² = H,OH
(X) R¹ = H; R² = O
(XI) R¹ = Ac; R² = O
(XII) R¹ = Ac; R² = O; 7α,8α-epoxide

(XIII) R¹ = Ac; R² = α-OH,β-H; R³ = H₂
(XIV) R¹ = Ac; R² = O; R³ = H₂
(XV) R¹ = Ac; R² = α-OAc,β-H; R³ = H₂
(XVI) R¹ = Ac; R² = α-OAc,β-H; R³ = O

(XVII)

However, transformations similar to that shown in (VIII) → (X) may occur in nature.

According to one of the biogenetic hypotheses,[6] the quassinoids as well as the limonoids, which are all oxygenated at C-7, could arise by the formation of the 7α,8α-epoxide of a tirucall-7-ene derivative followed by rearrangement to a 7α-hydroxy-Δ^{14}-apo-derivative.§ Such transformations have now been carried out on compound (XI) following the procedure of Buchanan *et al.* [15] When (XI) was treated with monoperphthalic acid in dry ether at 0° for 48 h it yielded the 7α,8α-epoxide (XII), $C_{28}H_{42}O_5$ (M^+ 458), m.p. 222—225°, $[\alpha]_D$ −59° which rearranged with boron trifluoride etherate to give the apo-compound (XIII), $C_{28}H_{42}O_5$ (M^+ 458), m.p. 244—252° $[\alpha]_D$ −73°.

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† All the optical rotations were measured in $CHCl_3$ and the n.m.r. spectra were measured in $CDCl_3$.

‡ All compounds gave satisfactory elemental analyses and possessed the expected spectral properties.

§ An oxidative rearrangement of a 7-ene-derivative to a 7-oxo-apo-compound is excluded since the incorporation experiments with [2-^{3}H]mevalonate into glaucarubinone showed that the label at C-7 was retained in this quassinoid.[14]

Treatment of compound (XI) with *m*-chloroperbenzoic acid leads to the 7,8;9,11-diepoxide, whereas with *p*-nitroperbenzoic acid a mixture of the epoxide (XII) and the rearranged apo-compound (XIII) was obtained.

Upon oxidation at 0° with Jones' reagent the latter compound gives the ketone (XIV), $C_{28}H_{40}O_5$ (M^+ 456), m.p. 238—242°, $[\alpha]_D$ $-111°$ and upon acetylation it affords the diacetate (XV), $C_{30}H_{44}O_6$ (M^+ 500), m.p. 178—181°, $[\alpha]_D$ $-80°$, which, upon treatment with chromic acid in acetone, smoothly oxidises to the $\alpha\beta$-unsaturated ketone (XVI), $C_{30}H_{42}O_7$ (M^+ 514), λ_{max} 240 nm (log $\epsilon = 3{\cdot}97$). When submitted to a Baeyer–Villiger oxidation the latter yields the $\alpha\beta$ unsaturated lactone (XVII), $C_{30}H_{42}O_8$ (M^+ 530), m.p. 257—260°, $[\alpha]_D$ $-34°$, λ_{max} 225 nm, [n.m.r.: 5 methyl groups (singlets at 0·77, 0·85, 0·97, 1·08, and 1·25 p.p.m.), two acetate groups (singlets at 2 and 2·05 p.p.m.), 3-H, 17-H, and 21-H (multiplet, 4H, centred at 4·42 p.p.m.), 7-H (triplet at 5·08 p.p.m.), and 15-H (singlet at 6·18 p.p.m.)].

The isolation of side-chain oxygenated tirucall-7-ene derivatives from a Simaroubaceous plant as well as the transformations we report are clearly relevant to the biogenetic schemes that have been suggested for the quassinoids.

We thank Dr. T. G. Halsall for a gift of melianodiol and its corresponding lactone (VI), Dr. B. C. Das for discussion of the mass spectra, and Mrs. L. Alais for the n.m.r. spectral measurements.

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