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A COMPOUND LINKING MELIANES* WITH MELIACINS

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Recently we have reported studies on the constituents of two Melia species: M. azedarach L.[1] and M. azadirachta L.[2] From the fruit of the former, compounds having an unaltered tirucallane type skeleton only, have been isolated and identified, while from the seed oil of M. azadirachta (Nim oil), compounds having carbon skeletons of both tirucallane and the meliacin[3] types have been identified. The latter possess a carbocyclic apoeuphol type skeleton with a β-oriented methyl group at C_8 and an α-oriented acetoxyl group at C_7[2]. We now report the isolation of a new compound having structure (Ia), from M. azedarach L. fruit. Since (Ia) could not be obtained in a pure form from the plant, purification was accomplished through acetylation and separation on thick layer chromatoplates to yield the crystalline acetyl derivative (Ib); m.p. 169-171°; $[\alpha]_D$ -3.0°(chlorof.c 0.1). Elemental analysis and the molecular ion peak in the mass spectrum, M^+ 512, indicated an empirical formula of $C_{32}H_{48}O_5$. The n.m.r. spectrum of (Ib) shows signals corresponding to seven tertiary methyl groups in the molecule, two of which are at lower field δ 1.70 and 1.65 related to the vinylic methyl groups attached to C_{25} as is the case in flindissol[4], the vinylic proton at C_{24} being at δ 5.15 (m). That (Ib) is the monoacetyl derivative is clearly indicated by the single methyl signal of the acetate group at δ 2.07, the C_3 proton signal being centered at δ 4.50 (dd). The other signals are as follows: δ 5.35 (t) 15-H; δ 4.10 (m) (2H) for 23-H and 7-H (β-oriented); δ 1.70, 1.65, 1.36, 0.94, 0.87, 0.83 and 0.80 for 7 x CH_3 signals; U.V. end absorption, at 200 mμ (ε 11,300); $\nu_{max}^{CHCl_3}$ 1776 for the five membered ring lactone in the side chain and 1720 cm^{-1} for the acetate.

Oxidation of (Ib) with Jones reagent in acetone solution at room temperature afforded the 7-keto derivative (Ic), m.p. 206-208°; M^+ 510; U.V. end absorption, at 205 mμ (ε 11,400); ν_{max}^{KBr} 1776, 1720 cm^{-1} for cyclohexanone and acetate. In the n.m.r. spectrum

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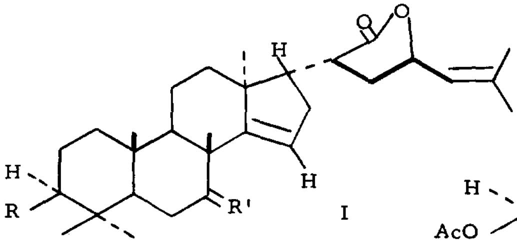
*We propose the name of melianes for the group of compounds having a tirucallane type skeleton with an oxygenated ring system in the side chain as found in the Meliaceae.



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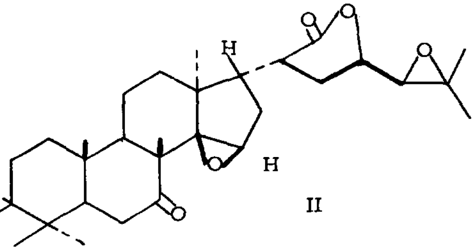
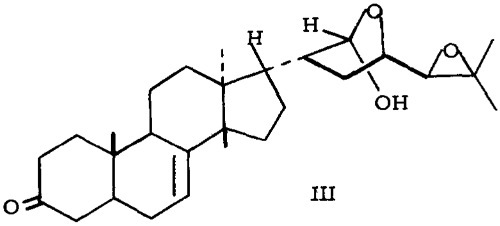


II

a. R=β-OH; α-H
R'=α-OH; β-H

b. R=β-OAc; α-H
R'=α-OH; β-H

c. R=β-OAc; α-H
R'=O



III

of (Ic) the signal of the vinylic C_{15}-H now appears at lower field δ 5.49 (t) while of the two ovelapping C_7-H and C_{23}-H, only that of the latter remains. Thus, of the two signals at δ 4.10 (m) in (Ib), one is related to the proton geminal to a hydroxyl group which, being secondary and not acetylatable, has to be in a hindered position. The problem was now to locate this hydroxyl group and determine its relationship to the double bond.

Oxidation of a Δ^7-11-OH or alternatively a $\Delta^{9(11)}$-7-OH compound under the acidic conditions of the reaction, would have obviously led to the corresponding α, β-unsaturated ketone with the double bond at 8-9 being tetrasubstituted (carbonyl at 7 or 11)[5]. Thus, in the n.m.r. spectrum of (Ic) the second vinylic proton, in either of the proposed cases, would have disappeared. Since this signal continues to persist after the oxidation, it can be concluded that the relationship of the hydroxyl group to the double bond is not as proposed above. Further evidence was obtained through the elimination of the hydroxyl group with thionyl chloride in dry pyridine solution. In this reaction no $\Delta^{7,9(11)}$ diene derivative with its characteristic absorption in the ultra-violet spectrum[6] was formed. This leaves two other possibilities only, the double bond being at C_{14-15} and the hydroxyl group either at

C_7 or C_{11}. Oxidation of the hydroxyl group to the corresponding ketone (Ic) induced a downfield shift in the n.m.r. spectrum of the C_{15}-H, and therefore a hydroxyl group at C_{11} can be eliminated since such a shift is expected when a C_7 hydroxyl is oxidized to the ketone. Epoxidation of (Ic) with perbenzoic acid afforded the diepoxy derivative (II); m.p. 238-240°; $[\alpha]_D$ -4.0°(chlorof. c 0.1); M^+ 542; U.V. end absorption, at 200 mμ (ε 5600); ν_{max}^{KBr} 1776, 1720 cm^{-1}. The n.m.r. spectrum of (II) shows the following signals: δ 4.15 (m) 23-H; δ 2.95 (narrow doublet) 15-H; δ 2.85 (d)(J=7 Hz)24-H; δ 1.31 (2 x CH_3), 1.21, 1.29, 0.98, 0.90, 0.87 (5 x CH_3). Indeed, the appearance of the epoxidic proton as a narrow doublet is good evidence for an epoxide at 14-15, most probably β-oriented[7]. The second epoxide ring introduced in the molecule, was shown to be located at position 24-25 in the side chain, by the signal of the two geminal methyl groups at C_{25} now appearing at δ 1.31. The epoxidic proton at C_{24} appears as a doublet centered at δ 2.85 (J=7 Hz). These resonances for both the methyl groups and epoxidic proton are identical with those of the corresponding protons in melianone[1] (III).

We have previously reported[8] the conversion of a 7α,8α-epoxy-melianone derivative by opening of its epoxide ring with stannic chloride and concomitant C_{14}-β methyl migration to C_8 (β-oriented) to form a 7α-hydroxy-Δ^{14} derivative possessing then an apoeuphol type skeleton. This transformation gave rise to the postulation that the meliacins could have been derived through a secondary biogenetical transformation of a 7α,8α-epoxy intermediate by opening of the oxirane ring. Thus, the isolation of (Ia) from natural sources, having an unaltered tirucallane side chain and an apoeuphol type skeleton, indeed, supports such a postulation. Therefore (Ia) may be looked upon as a link between the melianes and the meliacins.

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