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THE STRUCTURE OF RUPESTROL - A NEW SESQUITERPENOID FROM VERBESINA RUPESTRIS (URB.) BLAKE

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We report here the structural elucidation of a new sesquiterpene, rupestrol, which occurs naturally as its orthocinnamate (1) and cinnamate (2) esters in Verbesina rupestris.

Rupestrol orthocinnamate (1), $C_{24}H_{32}O_5$, m/e 400 (M^+), m.p. 206-207°, had a trans-styrene unit [λ_{max} 250 nm (ε 22,000), ν_{max} 1656,1587,1572,970, 750 and 700 cm^{-1}, δ (d_6-DMSO) 6.22 and 6.90 (1H each, AB system, J_{AB} 16.5 Hz), 7.39 (5H, m, aromatic H)] and two secondary hydroxy groups [ν_{max} 3400 cm^{-1}, δ 4.67 (1H, d, J 1.5 Hz) and 4.82 (1H, d, J 2.0 Hz) vanishing on treatment with D_2O]. On mild acid treatment, it afforded rupestrol cinnamate (2) $C_{24}H_{34}O_6$, m.p. 222-224°, λ_{max} 221 and 278.5 nm (ε 12,300 and 20,600), ν_{max} 3175, 1724, 1631 and 990 cm^{-1}, δ (d_6-DMSO) 6.68 and 7.73 (1H each, AB system, J_{AB} 16 Hz), 7.55 (5H, m, aromatic H). Basic hydrolysis of (2) gave cinnamic acid together with the parent sesquiterpene rupestrol (3), $C_{15}H_{28}O_5$, m.p. 206-207°, $[\alpha]_D$ + 11°, ν_{max} 3150 cm^{-1}. The NMR spectra of rupestrol and its derivatives indicated the presence of one tertiary and two secondary methyl groups.

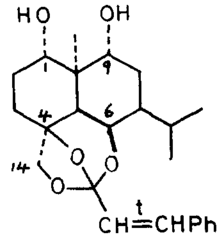
Acetylation of (2) with acetic anhydride-pyridine gave the amorphous triacetate (4), ν_{max} 3460, 1725 cm^{-1}, δ ($CDCl_3$) 4.20 and 4.58 (1H each, d, J 12 Hz, CH_2O-), 4.08(OH), 5.61 (1H, dd, J 11, 3 Hz, H-6) and 4.73-5.06 (2H, m, H-1 and H-9). Hydrolysis of (4) with one mole of potassium hydroxide in methanol (reflux, 2 hr) afforded the diacetate (5), $C_{19}H_{32}O_7$, m.p. 185-186°, ν_{max} 3350, 1724 cm^{-1}, δ 3.84 (2H, bs, $C\underline{H}_2OH$), 4.44 (1H, m, H-6), 4.65-5.09 (2H, m, H-1 and H-9).

Rupestrol cinnamate is inert to periodic acid. However, periodate oxidation of the diacetate (5) gave the ketone (7) as a gum, ν_{max} 3350, 1724 cm^{-1}, δ 2.70 (1H, d, J 10.5 Hz, H-5), 4.32 (1H, dd, sharpening on deuterium exchange, J 10.5, 4 Hz, H-6). The vicinal couplings of H-6 indicate a diaxial relationship with H-5 and a small dihedral angle relationship with H-7. These assignments were confirmed in the NMR spectrum of the derived acetate (8), $C_{20}H_{30}O_7$, m.p. 137-138°, ν_{max} 1725 cm^{-1} which had δ 2.94 (1H, d, J 11.5 Hz, H-5), 5.11 (1H, dd, J 11.5, 5 Hz, H-6), 5.35 (1H, dd, J 11, 4.5 Hz, H-1) and 5.23 (1H, dd, J 7.5, 3.5 Hz, H-9).

With acetone and anhydrous copper sulphate, (5) gave the acetonide (6), m.p. 152-153°, ν_{max} 3400, 1736 cm^{-1}, in which protons on carbon bearing oxygen were clearly resolved. A singlet (2H) at δ 4.00 could be ascribed to H-14; a double doublet (J 8, 4 Hz) at 4.23 (which sharpened on deuterium exchange) to H-6. Two other double doublets at δ 4.64 (J 8, 5 Hz) and 5.05 (J 5.5, 2.5 Hz) must be attributed to H-1 and H-9. Oxidation of the acetonide (6) or the triol (5) with Jones reagent yielded the ketone (9), $C_{22}H_{34}O_7$, m.p. 184-186°, ν_{max} 1733, 1718 cm^{-1}, δ 1.38 (6H, s, acetonide $C\underline{H}_3$), 3.75 and 4.90 (1H each, AB system, J 7.5 Hz, $-C\underline{H}_2O-$), 3.03 (1H, s, H-5), 4.90-5.45 (2H, m, H-1 and H-9).

Treatment of (9) with 60% aqueous acetic acid gave the amorphous diol (10), ν_{max} 3300, 1735, 1695 cm^{-1}, δ 2.83 (1H, s, H-5), 3.55 and 4.30 (1H each, AB system, J 11.5 Hz, $C\underline{H}_2OH$) which on oxidation with sodium periodate afforded the β-diketone (11), $C_{18}H_{26}O_6$, m.p. 101-102°, λ_{max} 290.5 nm (ε 9,700) shifting on addition of base to 309.5 nm (ε 12,300), ν_{max} 1727, 1578 cm^{-1}, δ 4.83-5.10 (2H, m, H-1 and H-9), 16.74 ($O\underline{H}$ of enolic form).

The above evidence confirms that rupestrol is a pentahydroxy sesquiterpene of the eudesmane type with hydroxy groups at C-4, C-14 and C-6 and two other secondary alcohols. The multiplicities of the protons at the bases of the acetates in (6) and (8) require that each has two adjacent protons



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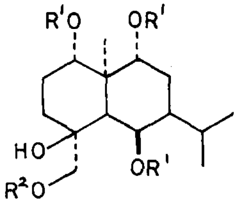
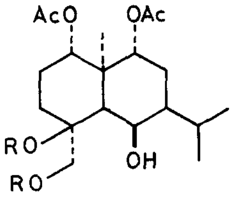


2 R^1=H, R^2=cinnamoyl

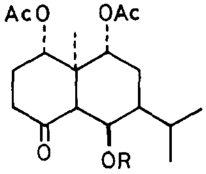
3 R^1=R^2=H

4 R^1=Ac, R^2=cinnamoyl



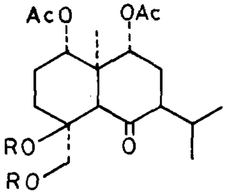
5 R=H

6 R=CMe_2



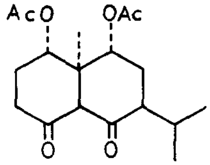
7 R=H

8 R=Ac



9 R=CMe_2

10 R=H



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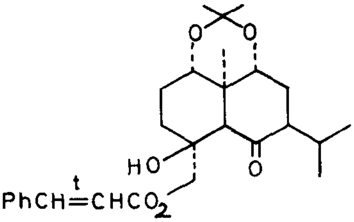

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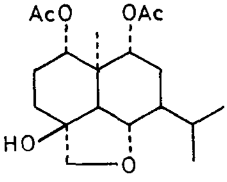

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and confirm the location of the secondary alcohols at C-1 and C-9: C-3 is excluded by the inertness of (2) to periodic acid (see above). The location of the hydroxy groups at C-1 and C-9 was further supported by the isolation of the keto acetonide (12) $C_{27}H_{36}O_6$, from Jones oxidation of (2). This had UV and IR bands characteristic of the cinnamate moeity and the structure was confirmed by the NMR spectrum: δ 1.46 and 1.55 (3H each, s, acetonide $C\underline{H}_3$), 2.56 (1H, s, H-5), 4.50 and 5.10 (1H each, AB system, J 12 Hz, $-C\underline{H}_2O-$), 3.10 (1H, O$\underline{H}$, disappearing on D_2O exchange).

The relative configuration at C-4 was revealed by the preparation of the ether (13), $C_{19}H_{30}O_6$, m.p. 164-165°, by the treatment of (5) with anhydrous cupric sulphate-conc. sulphuric acid. The NMR spectrum of (13) showed H-6 as a well resolved triplet (J 5.3 Hz) at δ 4.26 indicating that H-6 is now equatorial. Thus the ether linkage at C-6 and the C-4 - C-14 bond must both be axial.

The absolute configuration of rupestrol was disclosed by the CD curve of the ketone (8) ($\Delta\varepsilon_{294\ nm}$ +1.99). Further evidence for the stereochemistry of rupestrol will be discussed in the full paper.

Rupestrol is thus revealed as a highly oxygenated *enantio*-eudesmane containing the rare oxygenation at C-9.[1] Eudesmane sesquiterpenes have also been isolated from *Verbesina virginica*.[2]

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