Crystal and Molecular Structure of Withanolide E, a New Natural Steroidal Lactone with a 17α-Side-chain

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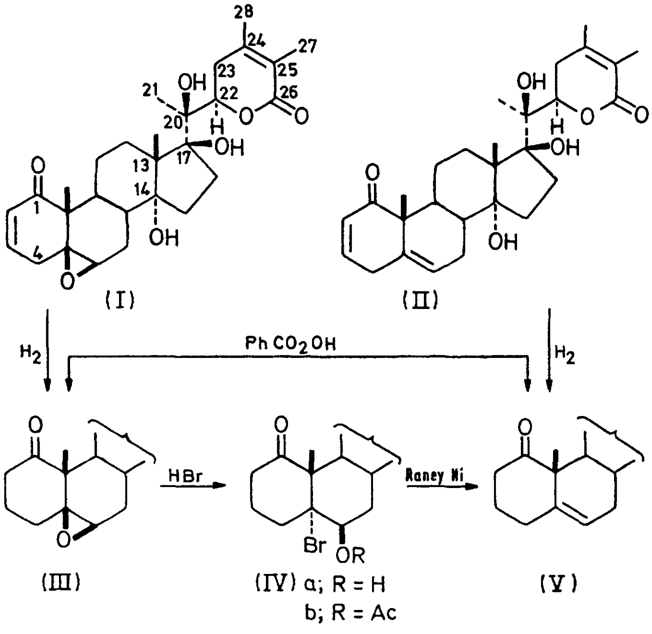
Summary An *X*-ray analysis of withanolide E, a new steroidal lactone isolated from *Withania somnifera* Dun. chemotype III, (14α,17β,20α-trihydroxy-5β,6β-epoxy-1-oxo-17*S*,20*S*,22*R*-witha-2,24-dienolide) has disclosed that the side-chain possesses the unusual 17α-orientation.

The withanolides are a series of naturally occurring steroidal lactones having an ergostane skeleton. Out of the nine new withanolides isolated so far from *Withania somnifera* Dun. chemotype III (Solanaceae),[1] growing in Israel, two have now been found to possess the unusual 17α-oriented side-chain.



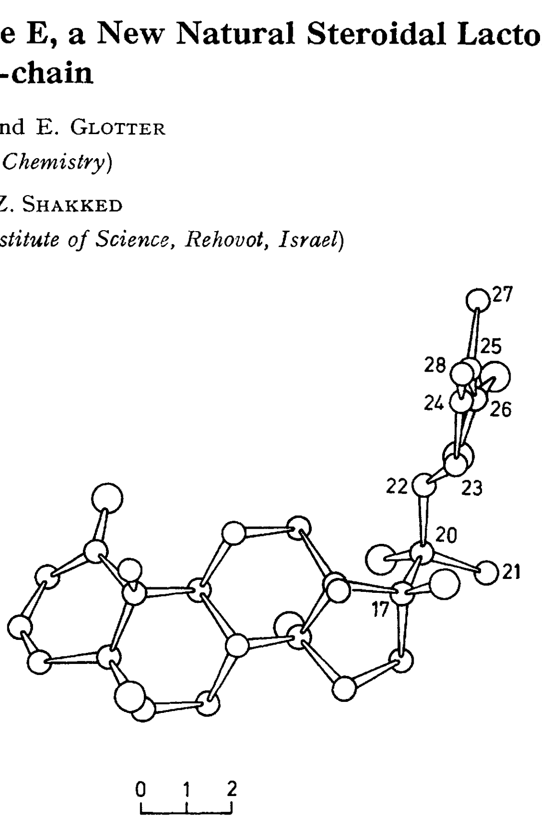


Figure. *Withanolide E, shown in the best plane of the steroid skeleton.* O *atoms are drawn slightly larger than* C *atoms.*

Withanolide E (I), $C_{28}H_{38}O_7,2H_2O$, *M* 522·6, m.p. 167—168° (acetone), ν_{max} 1675 cm^{-1}, λ_{max} 223 nm (ϵ 17,000), exhibits n.m.r. signals for three tertiary methyl groups as well as for protons assigned to the ring-A αβ-unsaturated ketone, the 5β,6β-epoxide and the side-chain δ-lactone. C.d. measurements confirmed the *cis*-junction of rings A/B and the 22*R*-configuration (λ_{max} 340 and 255nm, $\Delta\epsilon$ +1·69 and +4·05, respectively). The fragmentation pattern of (I) and its companion withanolide F (II) under electron impact and the lack of n.m.r. signals for protons α to a hydroxy-group clearly indicated the presence of three tertiary hydroxy-groups.

Crystal data: space group $P2_12_12_1$; a = 15·252(5), b = 13·098(7), c = 13·298(4) Å; U = 2656·6 Å; D_m = 1·306

$\pm$ 0·04, Z = 4, D_c = 1·307 g cm^{-3}. Intensity data were collected with Mo-K_α radiation by the balanced filter technique on a Siemens automatic diffractometer controlled by an IBM 1800 on-line computer. The structure was solved by a multi-solution direct method[2] and refined anisotropically by a block-diagonal least-squares programme to R = 0·06.

According to this analysis, withanolide E is 14α,17β,20α-trihydroxy-5β,6β-epoxy-1-oxo-17*S*,20*S*,22*R*-witha-2,24-dienolide, with a boat-like conformation for ring A, a distorted half-chair for ring B, and a normal chair for ring C; ring D has an envelope form in which C(14) is the out-of-plane atom.

Catalytic hydrogenation of (I) afforded the 2,3-dihydro-derivative (III) m.p. 264—265° (ethanol), the c.d. curve (λ_{max} 295 nm, $\Delta\epsilon$ −4·18) being in agreement with the β-orientation of the epoxide ring. Treatment of the latter with HBr in acetone at −12° afforded the 5α-bromo-6β-hydroxy-derivative (IVa) characterised as the corresponding acetate (IVb), m.p. 239° (dec.). Heating (IVb) under reflux in the presence of Raney nickel induced the elimination of the 5-bromo- and 6-acetoxy-substituents with the formation of a trisubstituted double bond (Δ^5, 6-H signal δ 5·52), the product (V) being identical with the 2,3-dihydro-derivative of withanolide F (II). Epoxidation of (V) with perbenzoic acid (1 equiv.) proceeded stereoselectively to yield (III). Compounds (I) and (II) are thus interrelated.

(*Received*, 12*th May* 1972; *Com.* 811.)

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[1] A. Abraham, I. Kirson, E. Glotter, and D. Lavie, *Phytochemistry*, 1968, **7**, 957.

[2] G. Germain and M. Woolfson, *Acta Cryst.*, 1968, **B24**, 91.