

β -Cannabispiranol: A new non-cannabinoid phenol from *Cannabis sativa* L.¹E. G. Boeren, M. A. Elsohly, C. E. Turner² and C. A. Salemink³*Research Institute of Pharmaceutical Sciences, School of Pharmacy, University of Mississippi, University (Mississippi 38677, USA), 6 December 1976*

Summary. An ethanol extract of *Cannabis sativa* L. afforded upon partitioning and repeated chromatography a new non-cannabinoid phenol [7'-hydroxy-5'-methoxy-spiro-(cyclohexane-1,1'-indan)-4 β -ol](**IIIa**), named β -cannabispiranol.

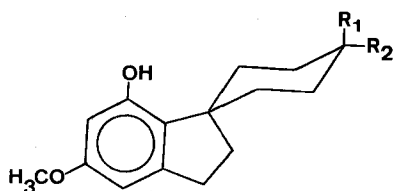
Cannabispiran structure (**I**) as determined by X-ray crystallography⁴ represented a new class of compounds discovered in cannabis. In a previous communication⁵ we have reported the isolation of cannabispiran (**I**) and dehydrocannabispiran (**II**) from an ethanolic extract of a South African variant of cannabis grown in Mississippi. Further examination of the above extract resulted in the isolation of a new related compound 7'-hydroxy-5'-methoxy-spiro-(cyclohexane-1,1'-indan)-4 β -ol which we named β -cannabispiranol (**IIIa**). The structure of **IIIa** is the subject of this report.

β -cannabispiranol (**IIIa**), m.p. 179–183°C, RRT 0.32⁶; C₁₅H₂₀O₃ (M⁺. 248) was optically inactive. The UV spectrum showed peaks at $\lambda_{\max}^{\text{MeOH}}$ 207 (log ϵ 3.85) and 221 nm (3.82). The IR spectrum (KBr) showed bands at 3440 (OH), 3190 (OH), 2910 (CH), 2845 (OCH), 1625 and 1595 (C=C_{Ar}), but no carbonyl absorption. The ¹HNMR showed a singlet at δ 3.60 (3H) (OCH₃), 2 aromatic protons at δ 6.10 (s) and 2 protons at δ 3.05 and δ 7.95 which were exchangeable with D₂O. Most important was a pentet at δ 3.98 (1H J=3Hz) assigned to -CHOH-. Treatment of **IIIa** with acetic anhydride in pyridine yielded a diacetate (**IIIb**), m.p. 127–128°C; RRT 0.58; which showed IR bands at 1763 and 1731 cm⁻¹ (aromatic and aliphatic acetates respectively)⁷. The mass spectrum showed prominent ions at m/e 332 (16%) (M⁺) (for C₁₉H₂₄O₅); 290 (85%) (M-H₂C=C=O)⁺; 272 (28%) (M-CH₃COOH)⁺; 230 (85%) (M-H₂C=C=O - H₃CCOOH)⁺; 189 (61%); 187 (16%) and 176 (100%). In addition to the acetate methyls at δ 2.10 (3H, s), 2.31 (3H, s), the ¹HNMR showed a pentet at δ 5.05 (1H) assigned to -CHOAc-. These data suggested that **IIIa** might be a dihydroderivative of cannabispiran (**I**). This was proven to be the case by reduction of cannabispiran with NaBH₄ in MeOH which resulted in the formation of 2 isomeric products in a 1:4 ratio (by GLC analysis) with RRT 0.32 and 0.36. TLC of the reaction product showed 2 spots (R_f 0.43 and 0.55, CHCl₃-EtOAc, 1:1), the less polar of which was the major component. Separation was achieved by chromatography on silica gel G

column using the previous TLC solvent system. The most polar isomer (RRT 0.32, R_f 0.43) was found to be identical with the natural product **IIIa** (TLC, m.p., IR and MS).

The isomer **IVa** (RRT 0.36) had m.p. 176°C and similar spectral data to **IIIa**. The ¹HNMR however, showed that H_a was overlapping with the methoxy signal. Thus **IVa** was acetylated (acetic anhydride in pyridine) to give a diacetate **IVb**, m.p. 85–86°C; RRT 0.48 and ν max (KBr) 1770 and 1735 cm⁻¹. The ¹HNMR (CDCl₃) of **IVb** showed 2 acetate methyls at δ 2.00 (3H, s) and δ 2.25 (3H, s) and most important was a broad multiplet between δ 4.33 and 4.91 (1H) assigned to the proton under the acetoxy group H_b. Based on the ¹HNMR of **IIIa** and **IVa** and their acetates **IIIb** and **IVb** the hydroxyl group on the cyclohexane ring of **IIIa** was assigned the axial position and the hydrogen H_a the equatorial position. The equatorial H_a couples with the neighboring axial and equatorial hydrogens with the same coupling constant resulting in a pentet J=3Hz. On the other hand **IVa** was assigned an equatorial OH and axial H. The ¹HNMR of **IVb** showed proton H_b as a broad multiplet as a result of coupling with 2 axial protons and 2 equatorial protons on both sides with different coupling constants.

Upon building a Dreiding model of **IIIa** and **IVa** it was found that the molecules had a plane of symmetry which bisects the indan nucleus and which explains the optical inactivity of both compounds. This is the first report of β -cannabispiranol in nature.



- I** R₁ + R₂ = = 0
II R₁ + R₂ = = 0, Δ α , β to carbonyl group
IIIa R₁ = OH, R₂ = H_a
IIIb R₁ = OAc, R₂ = H_a
IVa R₁ = H_b, R₂ = OH
IVb R₁ = H_b, R₂ = OAc

- 1 Acknowledgments. Supported by contract HSM-42-70-109 and grant DA-00928-01 from the National Institute on Drug Abuse as well as the Research Institute of Pharmaceutical Sciences. The authors are grateful to Mrs Glenda Lewis for running the GC analyses and to Dr Stephen Billets for running the Mass Spectra. Cannabis Herbarium specimens are stored in the Herbarium, Department of Pharmacognosy, School of Pharmacy, University of Mississippi, USA.
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- 3 Laboratory of Organic Chemistry, State University of Utrecht, the Netherlands.
- 4 T. Ottersen, A. Aasen, F. S. El-Ferally and C. E. Turner, Chem. Comm. 1976, 580.
- 5 F. S. El-Ferally, M. A. Elsohly, E. G. Boeren, C. E. Turner, T. Ottersen and A. Aasen, Tetrahedron, submitted for publication.
- 6 All gas chromatographic analyses were performed on a 2% OV-17 column at 210°C using androst-4-ene-3,17-dione as the internal standard as described by C. E. Turner and K. Hadley, J. pharm. Sci. 62, 251 (1973).
- 7 K. Nakanishi, in: Infrared Absorption Spectroscopy-Practical, p. 42. Holden-Day Inc., San Francisco 1962.