

Cannabichromene, a New Active Principle in Hashish¹

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It is generally assumed that the active principles of hashish are double bond or stereochemical isomers of tetrahydrocannabinol.² Recently we were indeed able to isolate, elucidate the structure of, and synthesize the active Δ^1 -tetrahydrocannabinol (I).³ However we have been unable to detect the presence of any additional tetrahydrocannabinols in hashish.⁴

We now report the isolation of a second active constituent which is of a different structural type. For this new component we suggest the name cannabichromene and assign structure (II).

Chromatography of a hexane extract of hashish on Florisil yielded the following identified compounds (in order of increasing polarity): cannabidiol,⁵ Δ^1 -tetrahydrocannabinol,³ cannabinol, cannabichromene (1.5% of the total extract) and cannabigerol.⁶ The fractions containing cannabichromene were re-chromatographed twice and distilled. Purity was established by thin-layer chromatography. Cannabichromene (II), $C_{21}H_{30}O_2$, $\lambda_{\max}(\text{EtOH})$ 228, 280 $m\mu$ (ϵ , 25,100, 8900); $[\alpha]_D(\text{CHCl}_3)$ -9° ; mol. weight (mass spectrum) 314; two double bonds] gives a crystalline 3,5-dinitrophenylurethane [m.p. 106–107°; $[\alpha]_D(\text{CHCl}_3)$ -1.5°]. The ultraviolet spectrum

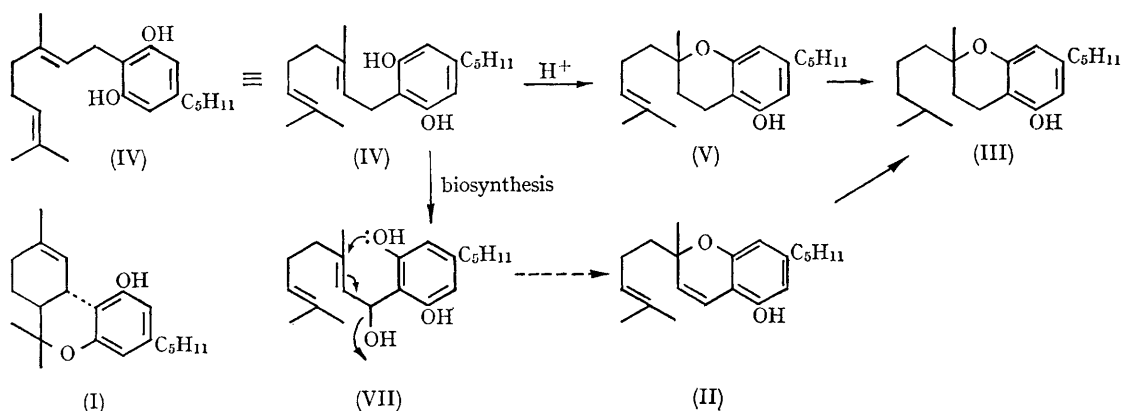
of (II) indicates conjugation of one of the double bonds with the ring and is compatible with the spectra of similar chromenes derived from resorcinol derivatives.⁷ The n.m.r. spectrum indicates that (a) the two aromatic protons are magnetically nonequivalent (δ , 5.97, 6.15) and that one of the methyl groups on the terpene moiety is α to an oxygen atom (δ , 1.32 singlet), thus determining the point of attachment of the ether-oxygen atom, the other oxygen atom being in a free phenolic group; (b) two of the olefinic protons are not flanked by any hydrogen atoms (sharp AB pattern; δ , 5.44, 6.60; J_{AB} , 10 c./sec.); (c) the second double bond is in an isopropylidene grouping (two methyl groups, δ , 1.58, 1.62; one olefinic proton; δ , 5.05). The findings are compatible only with structure (II).

Corroboration of structure (II) was obtained by catalytic hydrogenation of cannabichromene to (–)-tetrahydrocannabichromene (III) [$\lambda_{\max}(\text{EtOH})$ 281, 275 $m\mu$ (ϵ , 1250, 1230); $[\alpha]_D(\text{CHCl}_3)$ -2.3° ; δ , 1.20 (methyl group α to an oxygen atom), 5.98, 6.10 (two nonequivalent aromatic protons), no olefinic protons or olefinic methyl groups; 3,5-dinitrophenylurethane of (III), m.p. 125–128°]. (±)-Tetrahydrocannabichromene (III) was synthesized as follows: cannabigerol⁶ (IV) on boiling

with toluene-*p*-sulphonic acid in benzene gave (V), which is isomeric with the starting material. The chromane (V) [δ , 1.25 (one methyl group α to an oxygen atom), 1.60, 1.65 (two olefinic methyl groups), 6.00, 6.12 (two nonequivalent aromatic protons)] on catalytic hydrogenation yielded ($\pm$)-(III) (3,5-dinitrophenylurethane, m.p. 125–128°). The n.m.r., ultraviolet, and infrared spectra of ($\pm$)-(III) and (–)-(III) are identical.

In Nature cannabichromene is probably formed from cannabigerol (IV) through 8-hydroxycannabigerol (VII). This hypothetical biogenetic intermediate has been postulated by us^{3b} in the formation of cannabidiol and Δ^1 -tetrahydrocannabinol (I) *via* a different cyclisation path.

When administered to a dog cannabichromene caused sedation and ataxia.



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¹ Hashish, Part VIII. For Part VII see: Y. Gaoni and R. Mechoulam, *Tetrahedron*, in the press.

² *Inter alia*, (a) F. Korte and H. Sieper in "Hashish, Its Chemistry and Pharmacology," Ciba Foundation Study Group, No. 21, Churchill, London, 1965, p. 15; (b) L. S. Goodman and A. Gilman, New York, 1955, p. 171; (c) A. R. Todd, *Experientia*, 1946, **2**, 55.

³ (a) Y. Gaoni, and R. Mechoulam, *J. Amer. Chem. Soc.*, 1964, **86**, 1646; (b) R. Mechoulam, and Y. Gaoni, *J. Amer. Chem. Soc.*, 1965, **87**, 3273.

⁴ In view of the easy conversion of Δ^1 -tetrahydrocannabinol into the Δ^1 (⁶)-isomer¹ the presence of the latter in hashish should be expected. In our samples however it is absent.

⁵ R. Mechoulam and Y. Shvo, *Tetrahedron*, 1963, **19**, 2073.

⁶ Y. Gaoni, and R. Mechoulam, *Proc. Chem. Soc.*, 1964, 82.

⁷ H. Fukami, M. Nakayama, and M. Nakajima, *Agric. and Biol. Chem. (Japan)*, 1961, **25**, 247; R. Ghosh, A. R. Todd, and S. Wilkinson, *J. Chem. Soc.*, 1940, 1124; H. Asahina, *Bull. Narcotics*, 1957, **9** (No. 4), 17.