Cannabichromene, a New Active Principle in Hashish[1]

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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).

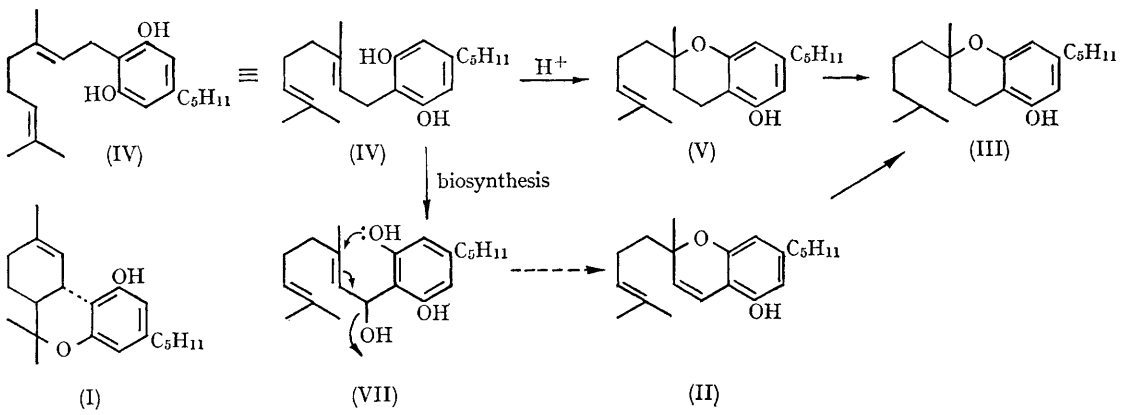
Chromatography of a hexane extract of hashish on Florisil yielded the following identified compounds (in order of increasing polarity): cannabidiol,[5] Δ^1-tetrahydrocannabinol,[3] cannabinol, cannabichromene (1·5% of the total extract) and cannabigerol.[6] The fractions containing cannabichromene were re-chromatographed twice and distilled. Purity was established by thin-layer chromatography. Cannabichromene (II), $C_{21}H_{30}O_2$, λ_{max}(EtOH) 228, 280 mμ (ϵ, 25·100, 8900); $[\alpha]_D(CHCl_3)$ $-9°$; mol. weight (mass spectrum) 314; two double bonds] gives a crystalline 3,5-dinitrophenylurethane [m.p. 106—107°; $[\alpha]_D(CHCl_3)$ $-1·5°$]. 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) [λ_{max} (EtOH) 281, 275 mμ (ϵ, 1250, 1230); $[\alpha]_D(CHCl_3)$ $-2·3°$; 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: cannabigerol[6] (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 (±)-(III) (3,5-dinitrophenylurethane, m.p. 125—128°). The n.m.r., ultraviolet, and infrared spectra of (±)-(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.



(*Received, November 23rd,* 1965; *Com.* 732.)

[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 $\Delta^{1(6)}$-isomer[1] 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.