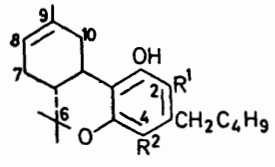
C-Glucosidation of Δ^8-Tetrahydrocannabinol

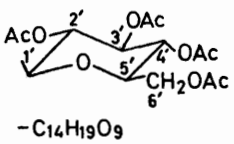
By K. BAILEY* and D. VERNER
(*Research Laboratories, Food and Drug Directorate, Tunney's Pasture, Ottawa* K1A 0L2, *Canada*)

Summary The reaction of Δ^8-tetrahydrocannabinol with α- or β-glucose penta-acetate gave a novel product considered to be 2-(β-tetra-acetylglucosyl)-Δ^8-tetrahydrocannabinol.

Δ^8-TETRAHYDROCANNABINOL (I) was treated with β-glucose penta-acetate in benzene containing boron trifluoride etherate. Work-up and column chromatography (silica gel, chloroform) gave the chief product (57%) as a sticky glass. The analytical sample was obtained by preparative t.l.c. (silica gel, 1% methanol in chloroform) as a sticky powder. The same product was isolated in lower yield using α-glucose penta-acetate. Mild alkali or acid hydrolysis removed the acetate functions and (I) was not detected (t.l.c.) in the hydrolysate.

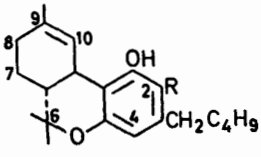


(I) $R^1 = R^2 = H$
(II) $R^2 = H, R^1 = C_{14}H_{19}O_9$
(III) $R^1 = H, R^2 = C_{14}H_{19}O_9$



$-C_{14}H_{19}O_9$

Structure (II) or (III) is suggested for the product on spectroscopic evidence. Comparison with our and published[1] n.m.r. spectra showed that there was new aromatic substitution and that the skeleton of (I) was unchanged. The n.m.r. spectrum (60 MHz, in $CDCl_3$ with internal Me_4Si) showed δ 7·55 (s, O*H*, exchanged with D_2O), 6·20 (s, Ar*H*),



(IV) R = H
(V) $R = CONHC_6H_3(NO_2)_2$
(VI) $R = H, OH = OCONHC_6H_3(NO_2)_2$

5·55—5·10 (m, complex of 8-H, 2′-H, 3′-H, and 4′-H), 4·80 (d, *J* 9, 1′-H), 4·29 and 3·90 (overlapping multiplets of 6′-H and 5′-H), 2·13, 2·05, 1·99, and 1·72 (4 s, $OCOCH_3$), 1·70 (s, 9-CH_3), 1·36 and 1·05 (2 s, 6β- and 6α-CH_3) with appropriate overall integration ratios, although there is considerable signal overlap. The presence of one aromatic and one hydroxy-proton was thus proved. The anomeric proton position and observed coupling are consistent with the range for *C*-substituted aryl β-glucosyl compounds,[2] and the high-field $OCOCH_3$ signal is appropriate for the acetate function at 2′.[2] The u.v. spectrum in EtOH had λ_{max} 286 shifted to 299 nm on adding 1 drop of NaOH solution, confirming that the OH group was phenolic. [Similar treatment of (I) shifts the λ_{max} from 276/283 to 287/293 nm,

but of (I) methyl ether does not change the λ_{max} at 276/280 nm.]

The i.r. spectrum in CCl_4 had λ_{max} 3410 (OH), 3030 (ArH), 1760 (OAc), 1620, 1575, 1240, and 1040 cm^{-1}. The spectrum of (I) at 6% concentration has bands due to free and intermolecularly hydrogen-bonded OH at 3600 and 3350 cm^{-1}, respectively. A dilution i.r. study of the glucoside showed that the band at 3410 cm^{-1} was unchanged in the concentration range 5—0·004% in CCl_4, and therefore arose from an intramolecularly hydrogen-bonded hydroxy-group. This result favours structure (II) over (III) since intramolecular bonding of the 2-OH to an oxygen of the 3-glucosyl residue is possible only in (II).

The production of a *C*-glucoside in the presence of a phenolic group was unexpected. However, the reactivity of cannabinoids toward electrophilic attack on the aromatic ring has been observed in the reaction of (IV) with 3,5-dinitrobenzoyl azide, which produced the amide (V) together with the urethane (VI),[3] and was exploited in the preparation of cannabinoid acids from cannabinoids using methylmagnesium carbonate.[4] It should be considered when investigating the mode of action and metabolic processes in cannabinoids.

(*Received, October 18th,* 1971; *Com.* 1800.)

[1] R. A. Archer, D. B. Boyd, P. V. Demarco, I. J. Tyminski, and N. L. Allinger, *J. Amer. Chem. Soc.*, 1970, **92**, 5200.
[2] B. Gentili and R. M. Horowitz, *J. Org. Chem.*, 1969, **33**, 1571.
[3] Y. Gaoni and R. Mechoulam, *J. Amer. Chem. Soc.*, 1971, **93**, 217.
[4] R. Mechoulam and Z. Ben-Zvi, *Chem. Comm.*, 1969, 343.