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HASHISH:[1] SYNTHESIS OF A NOVEL Δ^9-TETRAHYDROCANNABINOL (THC) ANALOG

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Treatment of cannabinoid diacetate (2b) with N-bromosuccinimide gave the brominated product 2c in excellent yield, which with base formed a novel cannabinoid 3b. The structure was confirmed by ^{13}C n.m.r. and ^{1}H n.m.r. nuclear Overhauser enhancement spectral studies.

In recent years several publications have appeared on the natural constituents of Cannabis sativa L (marijuana).[2] It is well known that Δ^9-tetrahydrocannabinol (THC,1) is the primary psychoactive constituent of the plant and that the closely related ring-opened analog, cannabidiol (CBD, 2a) is much less active as a behavioral agent.[2]

Treatment of Δ^9-THC acetate with N-bromosuccinimide[3] results mainly in the regioselective bromination at C(8), whereas we have found that similar treatment with CBD diacetate 2b gives the C(10) brominated product 2c[4] in 81% isolated yield. Reaction of 2c with one equivalent of NaCN in DMSO formed a new cannabinoid in good yield[4] which could be easily isolated by a simple chromatography (5% EtOAc-Hexane); n.m.r. ($CDCl_3$), δ 0.88 (t, 3, 5' -CH_3), 1.68 (s, 3, 12-CH_3), 2.18 (s, 3, $COCH_3$), 2.86 (m, J 10.9, 3.4Hz, 1, 7a-H), 3.43 (m, J 10.9Hz, 1, 11a-H), 4.62 (bs, 2, 6-H_2), 4.89 (d, 2, 13-CH_2), 5.49 (bs, 1, 11-H), 6.58, 6.65 (2d, J 2Hz, 2, 2-H, 4-H). On the basis of these data, this compound was tentatively assigned the novel oxepin structure 3a. It was also found that in the above reaction, when the quantity of NaCN was increased to two equivalents, a different but similar compound, with no n.m.r. signal at δ 2.18 ($COCH_3$), was formed in nearly quantitative yield; mass spectrum M^+ 312.2068 (calculated for $C_{21}H_{28}O_2$, 312.2089). It was assigned the corresponding phenol structure 3b. In addition, compound 3b was also obtained in quantitative yield on treatment of 2c with Na_2CO_3 in methanol at r.t. for 3 hr., which on acetylation (Ac_2O/pyr. at 20°C), formed 3a. It appears that these compounds (3a and 3b) are being formed by attack of the phenolate ion on the allyl bromide system in 2c with loss of bromide ion. The CN^- is thus primarily deacetylating the resorcinol in 2c.

The structure of the novel cannabinoid 3a was confirmed by the ^{13}C n.m.r. and ^{1}H n.m.r. nuclear Overhauser enhancement (NOE) spectral studies. The skeletal framework was established from the ^{13}C n.m.r. spectral assignments based on model systems Δ^9-THC (1)[5] and CBD (2a).[6]

Compound 3a showed the following ^{13}C n.m.r. spectral data: ($CDCl_3$), δ (p.p.m.) 149.42 (C-1) 118.62 (C-2), 142.56 (C-3), 119.72 (C-4), 157.88 (C-4a), 77.21 (C-6), 149.14 (C-7), 43.46 (C-7a), 28.58 (C-8), 30.43 (C-9), 133.17 (C-10), 124.85 (C-11), 40.62 (C-11a), 125.55 (C-11b), 23.50 (C-12), 111.41 (C-13),

35.18 (C-1'), 30.53 (C-2'), 31.47 (C-3'), 22.46 (C-4'), 13.94 (C-5'), 169.48, 20.49 ($COCH_3$).

The assignments of the ^{13}C signals for the n-pentyl side chain [C (1)' to C (5)'], C (8), C (9), C (10), C (11) and the vinyl methyl C (12) are all straight forward and are derived from 1[5] and 2a[6]. The presence of the acetyl is indicated by the resonances at 169.48 and 20.49 p.p.m.[8] and explains the downfield shift of C (2), C (4), C (11b) and the upfield shift of C (1)[9,10] compared to 1 and 2a. The presence of signals in 3a, indicating (i) a methylene ether carbon (77.21 p.p.m.) similar to C (6) in Δ^9-THC (i.e. 77.10 p.p.m.)[5], (ii) a quarternary olefinic carbon (149.14 p.p.m.) and an exo-methylene carbon (111.41 p.p.m.) as in CBD 2a (i.e. 149.19 and 110.91 p.p.m. respectively)[6] are only compatible with an oxepin structure as shown. The differences in the values of the chemical shifts of the two bridgehead centers C (7a) and C (11a) in 3a as compared to 1 (45.70, 33.63 p.p.m.) and 2a (46.26, 37.15 p.p.m.) are explained in terms of the formation of the unusual seven-membered oxepin ring in 3a.

The NOE data as derived from the ^1H homonuclear double resonance experiments established the position of the vinylic double bond and the stereochemistry of the ring junction. The double irradiation of the 3H resonance at δ 1.70 (vinyl methyl) transforms the broad resonance at δ 5.49 into a sharp 3.4Hz doublet and causes a 28% NOE in the latter absorption. Therefore, the peak at δ 5.49 was assigned to H (11). The double irradiation of H (11) resonance eliminates 3.4Hz splitting from the multiplet at δ 3.43. Hence, it was designated to the bridgehead H (11a). The double irradiation of H (11a) resonance eliminates a large 10.9Hz coupling pattern in the signal at δ 2.86. The latter absorption is thus assigned to the adjacent bridgehead hydrogen atom H (7a). The presence of large coupling (10.9Hz) between H (7a) and H (11a) as well as the absence of any NOE between them establishes their trans diaxial relationship and assigns their orientations as β and α respectively.

As far as we are aware, this is the first example of a Δ^9-THC analog with an oxepin ring, although other cannabinoids containing an oxepin ring have been reported[11] including one from our laboratory[12].

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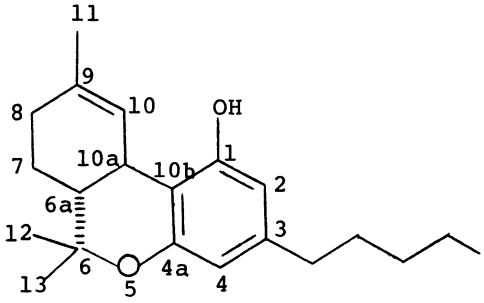
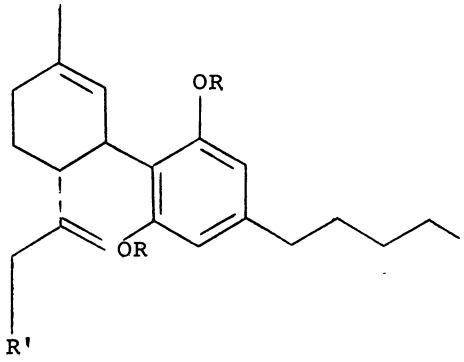
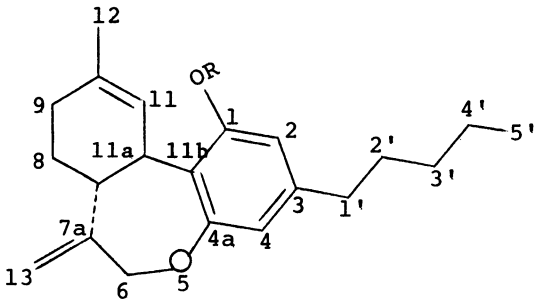


1 Δ^9-THC



2 a. R=H, R'=H
b. R=Ac, R'=H
c. R=Ac, R'=Br



3 a. R=Ac
b. R=H

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