

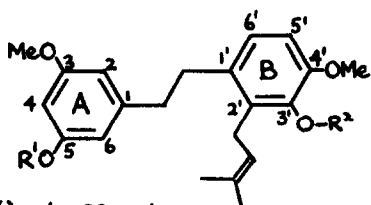
DIHYDROSTILBENES OF THAILAND CANNABIS.

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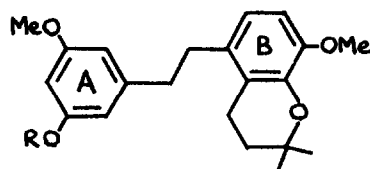
Because of continuing reports of effects such as estrogenic activity and teratogenicity caused by Cannabis¹, there is interest in natural components, other than cannabinoids, which may contribute to the pharmacological profile. From Thailand-high Δ^1 -THC-type Cannabis sativa leaf (16 weeks from germination) we have isolated (470mg/Kg) a new compound, needles from ether-hexane, m.p.112-113^o. The compound, C₂₁H₂₆O₄, obsd. M⁺ 342.1833, named canniprene, is formulated as dihydrostilbene (1).

Canniprene (dull purple-red with Fast Blue Salt B) contained two hydroxyls which could be trimethylsilylated (M⁺486). It had λ_{\max} (EtOH) 206 (43,000), 224i(11,400), 277i(2,400) and 281(2,400)nm, ν_{\max} (KBr) 3368br, 1627, 1598 and 1497cm⁻¹, and electron impact cleaved it into two fragments C₁₃H₁₇O₂, m/e 205.1250(100%) and C₈H₉O₂, m/e 137(20%), each fragment carrying one silylatable hydroxyl. This suggested a substituted bibenzyl and confirmation was found in the nmr. The bismethylene bridge resonated at δ 2.81(s,4H) and two aromatic methoxyls were present at 3.80(s,3H) and 3.90(s, 3H), along with two hydroxyls (D₂O exchange), one broad, 4.91, the other sharp 5.70. The presence of a prenyl residue was shown by benzylic resonance at 3.40(d,2H,J7Hz), an olefinic proton at 5.16(br.tr.,1H,J,7,~1Hz), and two olefinic methyls at 1.70(sl.br.,3H) and 1.79(3H). Three aromatic protons resonated as a multiplet 6.2-6.41 and the pattern of this, and the dimethyl ether (below), showed meta-coupling : a resorcinol monomethyl ether structure was assigned to ring-A and a further aromatic resonance at 6.71(2H) (appearance of a singlet) was assigned to ring-B.

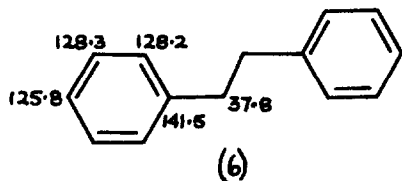
Canniprene gave a dihydroderivative m.p.112-113^o, M⁺344.1988, and



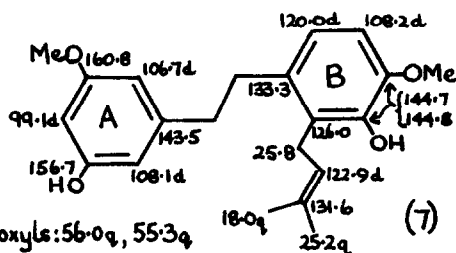
- (1) $R^1 = R^2 = H$
 (2) $R^1 = R^2 = Ac$
 (3) $R^1 = R^2 = Me$



- (4) $R = H$
 (5) $R = Ac$

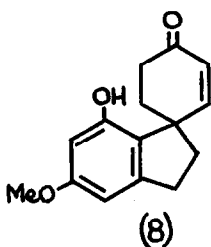


(6)

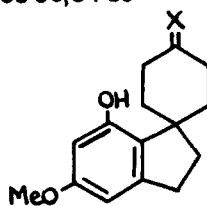


Methoxyls: 56.0q, 55.3q
 Bridge: 38.0t, 34.3t

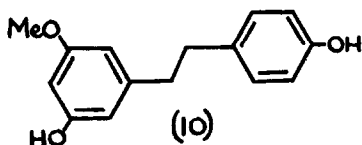
(7)



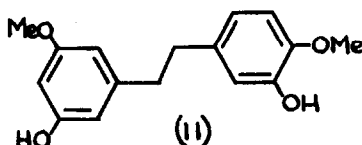
(8)



- (9a) $X = O$
 (9b) $X = \begin{matrix} H \\ | \\ OH \end{matrix}$



(10)



(11)

when treated with 1% BF_3 cyclised to (4) [chroman: δ 2.65 (t, 2H, J 8Hz), 1.83 (t, 2H, J 8Hz), 1.38 (6H)], showing the relationship of the prenyl to one hydroxyl. The sharp hydroxyl of (1) (5.70) disappeared, suggesting it might be bonded to an adjacent methoxyl. Chroman (4) formed an acetate (5), m.p. 70-71°. The relationship of the two aromatic protons in ring-B became clear when canniprene was converted into a diacetate (2), M^+ 426.2029, as the two B ring protons now appeared as an AB quartet 6.77 (d, 1H, J 8Hz) and 7.00 (d, 1H, J 8Hz), and are clearly ortho. In accordance with the placing of the prenyl, the olefinic proton of the latter shifted upfield (0.14 δ) on acetylation and there was a smaller upfield shift (0.07 δ) on one of the methoxyls (3.83 and

3.80). Canniprene formed a dimethyl ether (3) (NaH/MeI), $M^+370.2146$ and again ring-B protons formed an AB quartet 6.64(d,1H, $\underline{J}7\text{Hz}$) and 6.80(d,1H, $\underline{J}7\text{Hz}$). In canniprene these protons have identical chemical shifts.

The ordering of substituents on ring-B was explored by ^{13}Cmr . Making the restriction of o-coupled protons in ring-B, and adjacent positioning of prenyl and hydroxyl, there are six arrangements. Working from a framework of ^{13}C -resonances for (6), and using substituent constants², the 2'-prenyl, 3'-OH, 4'-OMe arrangement gave best agreement between calculated sets and experimental values, as on (7). Recently, Bosch et al.³ have reported a dihydrostilbene in Mexican Cannabis, similar to canniprene, but isomeric. No m.p. or chemical work are included, and though ^1Hmr , ir and ms data are listed, structural argument is not given.

Quantitative glc shows Thailand Cannabis leaves, 6 weeks after germination, to contain 0.01% of canniprene (dry wt) and, after 15 weeks, 0.14%. Occurring with canniprene in our older plant material were the Known dehydrocannabispiran⁴ (cannabispirenone)⁵ (8) (61mg/Kg, isolated), m.p.172.5-173.5°; cannabispiran⁴ (cannabispirone)⁵ (9a) (4mg/Kg), identical with the hydrogenation product of (8), and cannabispiranol⁶ (9b) (18mg/Kg), m.p.179-182°.

Two simpler dihydrostilbenes were also isolated. The first, $\text{C}_{15}\text{H}_{16}\text{O}_3$, $M^+244.1140$ (2mg/Kg dry wt) cleaved on ms into two fragments m/e 137(8%) and 107(100%), each cleavage fragment carrying one hydroxyl (silylation): the only other substituent was a methoxyl (δ 3.73). The aromatic protons divide into two groups, one 6.2-6.4(3H) similar to those of ring-A in (1) and models; the remainder 6.69(d,2H, $\underline{J}8\text{Hz}$), 7.01(d,2H, $\underline{J}8\text{Hz}$), form two identical AB quartets leading to (10). Dihydrostilbene (10) is known⁷ synthetically and is the putative precursor of spirocompounds (8)-(9), likely to be formed biosynthetically by intramolecular oxidative phenol coupling. Other natural isomers of (10) are the batatasins-III and -IV.⁷

The third dihydrostilbene ($\sim 5\text{mg/Kg}$), needles m.p.133-134°, $M^+274.1232$, cleaved on electron impact apparently into halves m/e 137 and each carried one hydroxyl (silylation). Four benzylic protons resonate at 2.80 and the molecule is not symmetrical about the bismethylene bridge (methoxyls 3.74 and

3.88). Ring-A shows the pattern of m-alkylated-resorcinol protons (3H), whilst those of ring-B form a multiplet (3H) near 6.74. The oxygenation pattern of dihydrostilbenes (1) and (10) is typical of compounds of mixed phenylalanine-acetate derivation and (11) is a reasonable proposal. Both dihydrostilbenes apparently occur in Mexican Cannabis³ and these are the first reports of dihydrostilbenes in Cannabis.

All nmr spectra are reported for CDCl₃ solutions. We thank the MRC for support and the SRC for use of spectroscopic equipment.

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