Tetrahedron Letters No. 7, pp 661 - 664.
0040-4039/79/0208-0661$02.00/0

ISOLATION OF CANNABISPIRADIENONE AND CANNABIDIHYDROPHENANTHRENE. BIOSYNTHETIC RELATIONSHIPS BETWEEN THE SPIRANS AND DIHYDROSTILBENES OF THAILAND CANNABIS

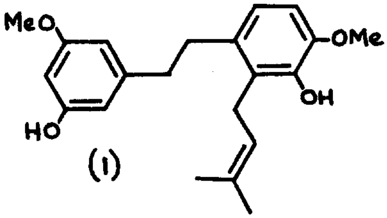
Leslie Crombie, W.Mary L.Crombie and Sally V. Jamieson
Department of Chemistry, The University,
Nottingham, NG7 2RD

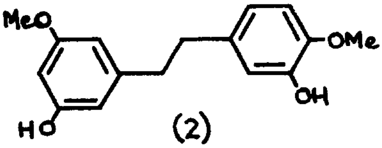
We have recently reported the isolation of three dihydrostilbenes (1)-(3), apparently of mixed shikimate-acetate derivation, from Thailand high-Δ'-THC type *Cannabis sativa* leaf (16 weeks from germination).[1] Also found in that investigation were cannabispirone (7), cannabispiranol (8) and cannabispirenone (6). We have now discovered in this plant specimen the hitherto unknown cannabispiradienone (5), the key product which would be formed by internal oxidative coupling of the dihydrostilbene (3), via (4). In addition a new 9,10-dihydrophenanthrene, cannabidihydrophenanthrene (9), the first compound of this class to be found in *Cannabis* and related to (5) by a dienone-phenol rearrangement, has been isolated.

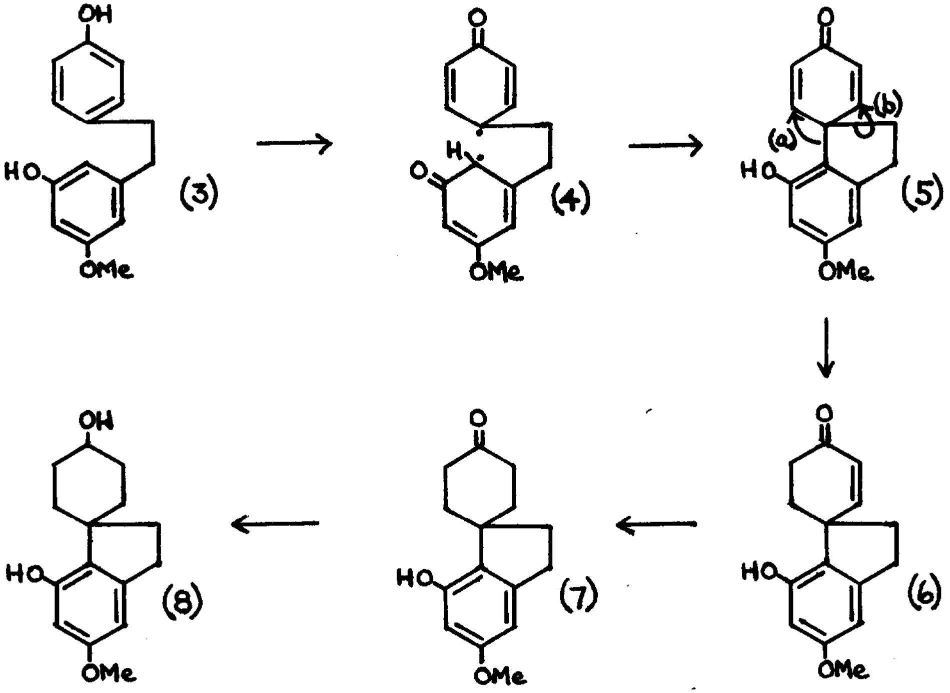
Cannabispiradienone (6 mg/Kg isolated), m.p. 174-176° (decomp.), $C_{15}H_{14}O_3$, obsd. M^+242.0945, gave a pink-purple with Fast Blue Salt B and contained one hydroxyl (trimethylsilyl derivative M^+314) and a conjugated ketone (ν_{max}KBr, 1654 cm^{-1}). The R_f in ether/n-hexane (3:1) was 0.32 (cannabispirenone 0.44). In the nmr spectrum ($CDCl_3$) there were two *m*-coupled aromatic protons at δ6.21 and 6.45 (*J*, ∿2Hz), an aromatic methoxyl (3.80) and hydroxyl (5.35, D_2O exchange). The four protons of the spiro-bismethylene bridge formed two triplets (3.09 and 2.28) and the remaining four protons formed two degenerate AB-systems at 6.37d(2H) and 6.98d(2H), *J*, 10Hz. This leads to structure (5), supported by uv data λ_{max} (EtOH) 212(28,600), 239.5(23,100), 277(3,100), 285(3,050) and 307i(600)nm.

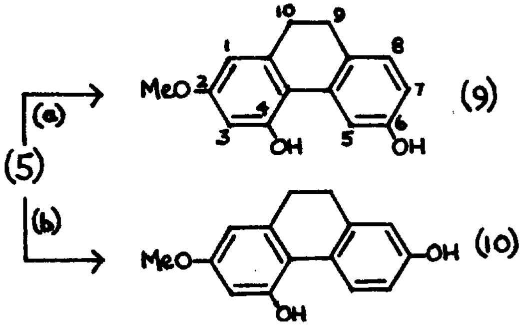
For confirmation, cannabispiradienone (5) was hydrogenated to cannabispirone) (cannabispiran) (7), the structure of which is known from X-ray data[2] (mixed m.p., spectral and chromatographic comparison). Cannabispirenone (dehydrocannabispiran)[2] (6), m.p. 172.5-173.5° (methyl ether m.p. 117-118°) was also hydrogenated to (7), whilst cannbispiranol[3] m.p. 190-192° (acetate m.p. 133-135°) was oxidised to the latter using pyridinium chlorochromate. This links together chemically the structures of the four spirans we have isolated from Thailand *Cannabis*.

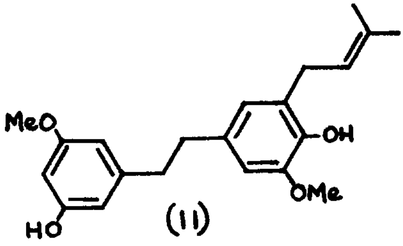
On the evidence of co-occurrence in one and the same plant specimen, a


(1)

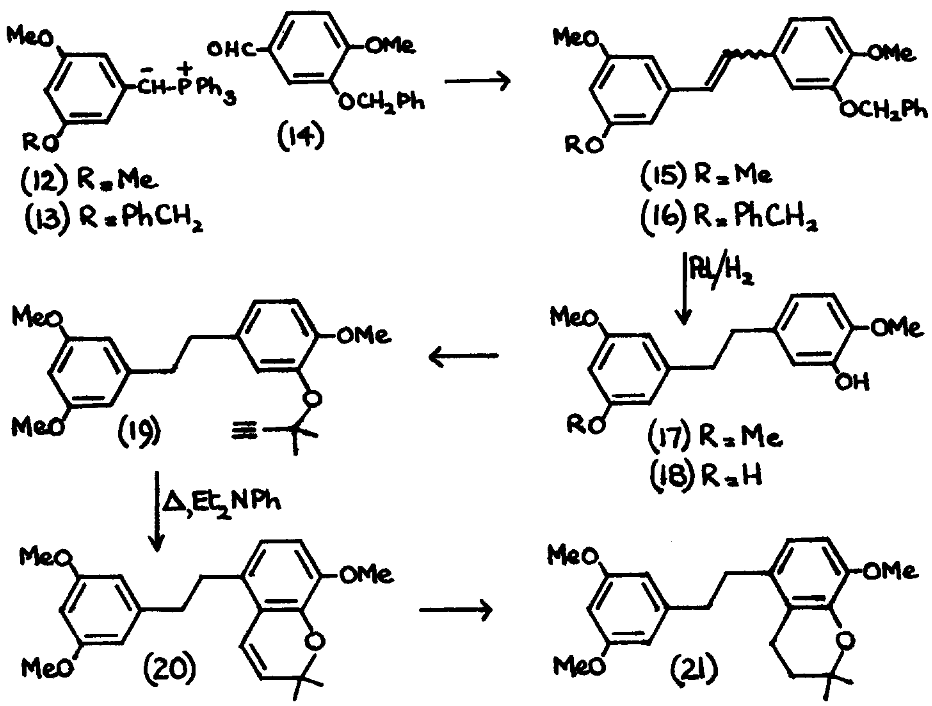

(2)






(11)

biosynthetic sequence (3) → (8) can be entertained. The substitution of the shikimate-derived ring of (3) is p-coumaric in pattern, whereas that of (1) and (2) is isoferulic in type: a different 'starter' may be involved in the polyketide development of the latter compounds though elaboration could proceed from (3). Prenylation in (1) is probably a late event. Spirans (5), (7) and



(8) have mirror planes of symmetry but cannabispirenone (6) is optically active $[\alpha]^{21.5}_{D}$ -156.4°(EtOAc), supporting an enzyme-mediated origin.

Cannabidihydrophenanthrene (20 mg/Kg), $C_{15}H_{14}O_3$ (M^+242.0950) contained two hydroxyls (trimethylsilylation, M^+386), had a uv spectrum characteristic of a 9,10-dihydrophenanthrene,[4] λ_{max}(EtOH)220, 265sh, 274, 301 and 310 nm, and gave a purple FBSB colour. In the nmr spectrum (D_6-acetone) there were two hydroxyls at δ8.52 and 7.83 (D_2O exchange), one methoxyl (3.70), m-coupled protons assigned to C-1 and C-3 (6.45d, 6.24d, *J*, 2.5Hz), four bridge methylene protons (2.7) and an AB-quartet due to the C-8 and C-7 protons respectively (7.02d, *J* 7.5 and 6.58dd, *J*, 7.5 and 2.5). The C-7 proton is also *m*-coupled to the characteristically deshielded[4] C-5 proton at 7.94d, *J*, 2.5. This leads to structure (9) which is related to (5) by dienone-phenol rearrangement, migrating bond (a), as opposed to (b): the latter would give the isomer (10). On keeping cannabispiradienone (5) at its m.p. it thermally rearranged to a substituted 9,10-dihydrophenanthrene, λ_{max} 221,266,276,301 and 309 nm, having a closely similar R_f and mass spectrum to (9). The status of cannabidihydrophenanthrene as a natural product or artefact therefore requires further investigation.

Since a dihydrostilbene (11) has very recently been reported in Mexican *Cannabis*,[5] we have confirmed the structure of our canniprene (1)[1] synthetically.

Wittig reaction between (12) and the benzyl protected aldehyde (14) gave a cis-trans-mixture of stilbene (15). Catalytic hydrogenation and hydrogenolysis gave (17) which was converted into the dimethylpropargyl ether (19). Claisen rearrangement and cyclisation led to the chromen (20), hydrogenated to chroman (21). The latter is readily obtainable from natural canniprene (1) by treatment with 1% BF_3 and methylation: the natural and synthetic specimens were identical in all respects (m.p. and mixed m.p. 113-114°, and spectral comparison). Through the kindness of Professor Salemink, we have compared his compound from Mexican *Cannabis*[5] with our canniprene and find that they are identical: he has independently revised his structure from (11) to (1) and we thank him for this information. The structure of dihydrostilbene (2)[1] was also confirmed by synthesis using ylid (13) and aldehyde (14). The cis-trans-stilbene (16) was hydrogenated and debenzylated to give (18), identical with natural (2).

We thank the MRC for support, and the SRC for spectroscopic instrumentation.

References

1. L. Crombie and W.M.L. Crombie, *Tetrahedron Letters*, 1978, 4711.
2. F.S. El-Feraly, M.A. Elsohly, E.G. Boeren, C.E. Turner, T. Ottersen and A. Aasen, *Tetrahedron*, 1977, *33*, 2373. C.A.L. Bercht, J.P.C.M. van Dongen, W. Heerma, R.J.J. Ch. Lousberg and F.J.E.M. Küppers, *Tetrahedron*, 1976, *32*, 2939.
3. E.G. Boeren, M.A. Elsohly, C.E. Turner and C.A. Salemink, *Experientia*, 1977, *33*, 848.
4. R.M. Letcher and L.R.M. Nhamo, *J.Chem.Soc.(C)*, 1971, 3070; *J.C.S. Perkin I*, 1972, 206, 2941.
5. J.J. Kettenes-van den Bosch and C.A. Salemink, *Receuil, J.Roy.Neth.Chem. Soc.*, 1978, *97*, 221.

(Received in UK 4 December 1978)