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CANNABICITRAN: A NEW NATURALLY OCCURRING TETRACYCLIC DIETHER FROM LEBANESE *CANNABIS SATIVA**

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Key Word Index—*Cannabis sativa*; hashish; cannabinoids; cannabicitran; citrylidene-cannabis.

Abstract—A new cannabinoid, cannabicitran, was isolated from Lebanese hashish. This component was found to be identical to synthetic citrylidene-cannabis.

INTRODUCTION

SINCE the first complete structure elucidation of a natural cannabinoid, cannabinol, by Adams *et al.*,[1] many cannabinoids have been isolated and identified.[2,3] Their structures were determined by spectroscopic methods and final confirmation was in many cases provided by their synthesis.[4,5]

During our research[6] on the chemical composition of Lebanese hashish, we established the natural occurrence of cannabinol methyl ether and cannabidiol monomethyl ether among many well-known cannabinoids. These components were found in some of the counter-current distribution fractions of the hexane-soluble part of the hashish by means of GC–MS. Together with these ethers, we discovered a previously unidentified *n*-pentyl-cannabinoid with a retention time close to that of cannabidivarinol(CBD-C_3). The present paper reports the isolation and structure elucidation of this product.

RESULTS AND DISCUSSION

The unknown cannabinoid was obtained by repeated column chromatography on silica of the last counter-current distribution fractions of an ethanolic extract of Lebanese hashish. Its TLC R_f value was 0·71 (precoated silica gel plates Merck, eluted twice with petrol.

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* Part IX in the series 'Cannabis'. For Part VIII see Küppers, F. J. E. M., Lousberg, R. J. J. Ch., Bercht, C. A. L. Salemink, C. A., Terlouw, J. K., Heerma, W. and Lavèn, A. (1973) *Tetrahedron* **29**, 2797.

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b.p. 60–80/Et_2O, 4:1). The colour reaction after moderate heating with an alkaline solution of Fast Blue Salt B was pink. On GLC, the relative retention time was found to be 0·63, using cannabidiol as the internal standard (1·00).

The IR spectrum of the compound did not show hydroxyl absorptions. Therefore, it was tentatively concluded that the two oxygen-functions which normally occur in the olivetol-part of cannabinoids were present as ether functions. The presence of the olivetol moiety was revealed by its MS which showed the base peak *m/e* 231, an indicative fragment for this type of compound. Except for cannabigerol, all the neutral *n*-pentyl-cannabinoids (M 314) have one of the two oxygen atoms of the olivetol moiety free and the other is present as an internal ether. Therefore, the molecular ion at *m/e* 314 suggests that the above mentioned ether functions are present as internal ether functions with the terpene moiety. The presence of these ether functions were further supported by the presence of strong absorptions at 1130 and 1065 cm^{-1}. Except for two absorptions at 1620 and 1585 cm^{-1}, generally ascribed to vibrations of the aromatic ring of the olivetol moiety, no further indications could be found for the presence of olefinic or vinylic bonds in the molecule.

The 75 eV MS strongly resembled that of cannabichromene and cannabicyclol,* but the relative intensities of *m/e* 314, 299, 271 and 258 were greater in the isolated product (see Table 1). Moreover, under the same conditions, the MS of the isolated compound showed mass fragments at *m/e* 246 and 243, which are lacking from the spectra of cannabichromene and cannabicyclol.

TABLE 1. RELATIVE INTENSITIES OF SOME FRAGMENT IONS OF THE MS OF CANNABICHROMENE, CANNABICYCLOL AND THE ISOLATED COMPOUND

	Cannabichromene		Cannabicyclol		Isolated compound	
m/e	75 eV	20 eV	75 eV	20 eV	75 eV	30 eV
314	2	8·5	4	15	14	100
299	3	3	4	3	4·5	11
271	1·5	1	2	1	8	7
258		1		1	6·5	7
246					4	3·5
243					5·5	2·5
232	19	21	18	19	14·5	11·5
231	100	100	100	100	100	76

The 100 M Hz PMR spectrum (in CCl_4 with TMS as the internal standard) showed, among others, resonances at δ 0·88 (*t*, *J* 6·0 Hz, 3 H) (ω-CH_3), 0·94 (*s*, 3 H), 1·30 (*s*, 3 H), 1·44 (*s*, 3 H), 2·44 (*t*, *J* 7·0 Hz 2 H) (benzylic protons), 2·75 (*m*, 1 H) and 6·11 (*dd*, *J* 1·0 Hz, 2 H) ppm. It should be noted that the absence of olefinic and vinylic resonances is in good support of the IR observations.

The above spectroscopic data were the same as those of a known synthetic product, obtained by the dehydrogenation of cannabigerol with chloranil[7] or by pyridine-catalysed condensation of olivetol with citral.[8,9] Crombie and Ponsford called this compound citrylidene-cannabis (**1**). For reference purpose, citrylidene-cannabis was synthesized by treating natural cannabichromene with pyridine[5] and the synthetic and natural products

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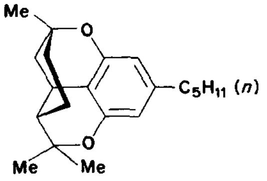
* The RR_t of cannabichromene and cannabicylol are 0·96 and 0·79, respectively.

[7] MECHOULAM, R., YAGNITINSKY, B. and GAONI, Y. (1968) *J. Am. Chem. Soc.* **90**, 2418.

were identical (R_f and MS). Crombie and Pomford[8] earlier predicted that citrylidene-cannabis would eventually be found as natural product. In accord with these authors, we now propose the name cannabicitran for the natural product.



(1) Cannabicitran

The citran moiety is not an unusual feature among plant compounds, e.g. bruceol, a product isolated by Duffield *et al.*[10] from *Eriostemon brucei* or more recently the rubramin-chalcone and its analogue, desbenzylidenrubramin, synthesized by Montero and Winternitz[11] during the structure elucidation of products from rose-wood *Aniba rosaeodora* Ducke. This is, however, the first finding of this structural feature among natural cannabinoids.

EXPERIMENTAL

A Becker 409 gas chromatograph with a FID was used. A 1·80 m glass column, i.d. 4 mm, was packed with 2% OV17 on Chromosorb G AW-DMCS 100–120 mesh. Injector 240°, column 245°, detector 310°, carrier gas N_2, flow 30 ml/min. The MS were recorded on a modified JEOL MS 07 with a double stage separator. A 1·80 m glass column, i.d. 2·5 mm, was packed with 3% OV17 on Chromosorb G AW-DMCS 80–100 mesh. Injector 210°, column 200°, separator 240°, ion source 180°, carrier gas He, flow 25 ml/min. The gas chromatogram was recorded by the total ion current at 30 eV. The trap current was 300 μA, the accelerating voltage 3·0 kV.

The residue of the ethanolic extract of Lebanese hashish was dissolved in petrol b.p. 60–80°Et_2O (1:1) (10 ml for 1 g of residue). The soln was shaken with 3% aqu. KOH and 2% $NaHSO_3$ and next with 5% aq. H_2SO_4. The organic layer was separated, dried and concentrated to a thick syrup. From this residue, 35 g was transferred into the first step of a 100 step counter current apparatus,[6] using petrol. b.p. 60–80°/petrol. b.p. 80–110°/MeOH/H_2O (5:5:9:1). After 130 steps, the fractions 75–100 were combined and concentrated. The remaining oil was dissolved in Et_2O, dried and concentrated again, yielding 10 g of an oil which possessed the typical hashish odour. This oil was chromatographed on a silica gel column (75 × 3 cm); the eluent was petrol. 60–80/Et_2O (9:1). The collected 1-hr-fractions 53–59 were combined and concentrated. The residue (1·6 g) was re-chromatographed on a column (120 × 2 cm) of the same type; the eluent was petrol b.p. 60–80/Et_2O (99:1). The fractions were tested by GLC and those fractions which only contained the component with RR_t 0·63 were combined and concentrated, yielding 37·5 mg cannabicitran as a yellowish oil.

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