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Note

Cannabis

VII*. Identification of cannabinol methyl ether from hashish

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The structures of most of the cannabinoids, the phenolic components of the resin of hemp (*Cannabis sativa* L.), of which cannabinol, $\Delta^{1,2}$-tetrahydrocannabinol and cannabidiol are the most abundant, were elucidated by spectroscopic measurements on the pure compounds[1]. Vree and co-workers[2,3] described for the first time the determination of the structure of cannabinoids by means of combined gas chromatography–mass spectrometry. Their method permitted the identification of many of the *n*-propyl and methyl homologues of the normal *n*-pentylcannabinoids without previous isolation, by comparison of the mass fragmentograms of the compounds.

By using this method, we were able to identify one of the minor constituents of a hashish sample as cannabinol methyl ether (CBNM). The natural occurrence of $\Delta^{1,2}$-tetrahydrocannabinol methyl ether seems likely.

EXPERIMENTAL

A 5-g amount of the residue of an ethanolic extract of Lebanese hashish was subjected to a 130-step counter-current distribution (each tube contained 50 ml). The solvent system used consisted of light petroleum (boiling range 60–80°)–light petroleum (boiling range 80–110°)–methanol–water (5:5:9:1)[4]. After the distribution, the fractions were concentrated under reduced pressure (below 25°) and the residue was dissolved in ether and dried. The filtered solution was concentrated and submitted to gas chromatography–mass spectrometry.

An LKB 9000 combined gas chromatograph–mass spectrometer was used. Glass columns, 1.50 m long and 4 mm I.D., were packed with 3% OV-17 on Gas-Chrom Q, 60–80 mesh. The temperature of the oven was 200°; the separator 220°; and the ion source 250°. Repetitive mass spectra were taken at 20, 18, 16, 14, 12 and 10 eV during the elution of a component from the gas chromatograph, recorded by

* For Part VI, see C. A. L. Bercht, R. J. J. Ch. Lousberg, F. J. E. M. Küppers and C. A. Salemink, *Phytochemistry*, in press.

total ion current at 20 eV. The trap current was 60 μA and the acceleration potential was 3.5 kV.

Cannabinol methyl ether and $\Delta^{1,2}$-tetrahydrocannabinol methyl ether were prepared by dissolving CBN or $\Delta^{1,2}$-THC in a small amount of ether, adding an excess of methyl iodide and silver oxide and stirring the mixture for several hours. The solution was filtered and concentrated under reduced pressure.

RESULTS

The mass spectra of the components of some of the 130 counter-current fractions studied revealed some of the minor constituents. The mass fragmentograms of these components were compared with those of known compounds, such as cannabidiol (CBD) and cannabinol (CBN)[2]. Peak No. 25 in the gas chromatogram of fraction 37–39 (Fig. 1) gave an M^+ of *m/e* 324, whereas the base peak was at *m/e* 309. The great resemblance of its mass fragmentogram with that of the CBN homologues[5] strongly suggested that this component was the methyl ether of cannabinol. Evidence for the correctness of this conclusion was obtained by synthesis of cannabinol methyl ether from natural cannabinol. The synthetic compound possessed the same GLC retention time (1.24 compared with 1.00 for CBD-C_5 as the internal standard) and the same mass fragmentogram as the natural component.

The monomethyl ether of cannabidiol was also detected. Fraction 10–12 con-

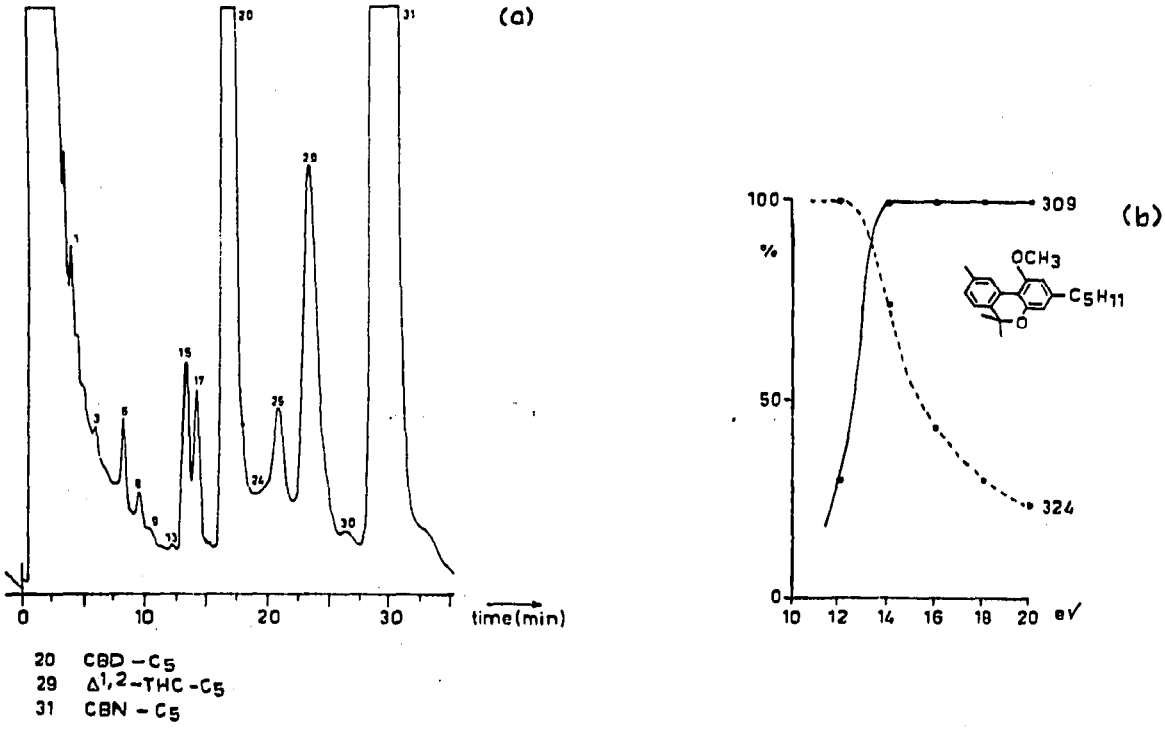

Fig. 1. Gas chromatogram of the counter-current fraction 37–39 (a) and mass fragmentogram of peak 25 (b). CBD, THC and CBN are cannabidiol, tetrahydrocannabinol and cannabinol, respectively.

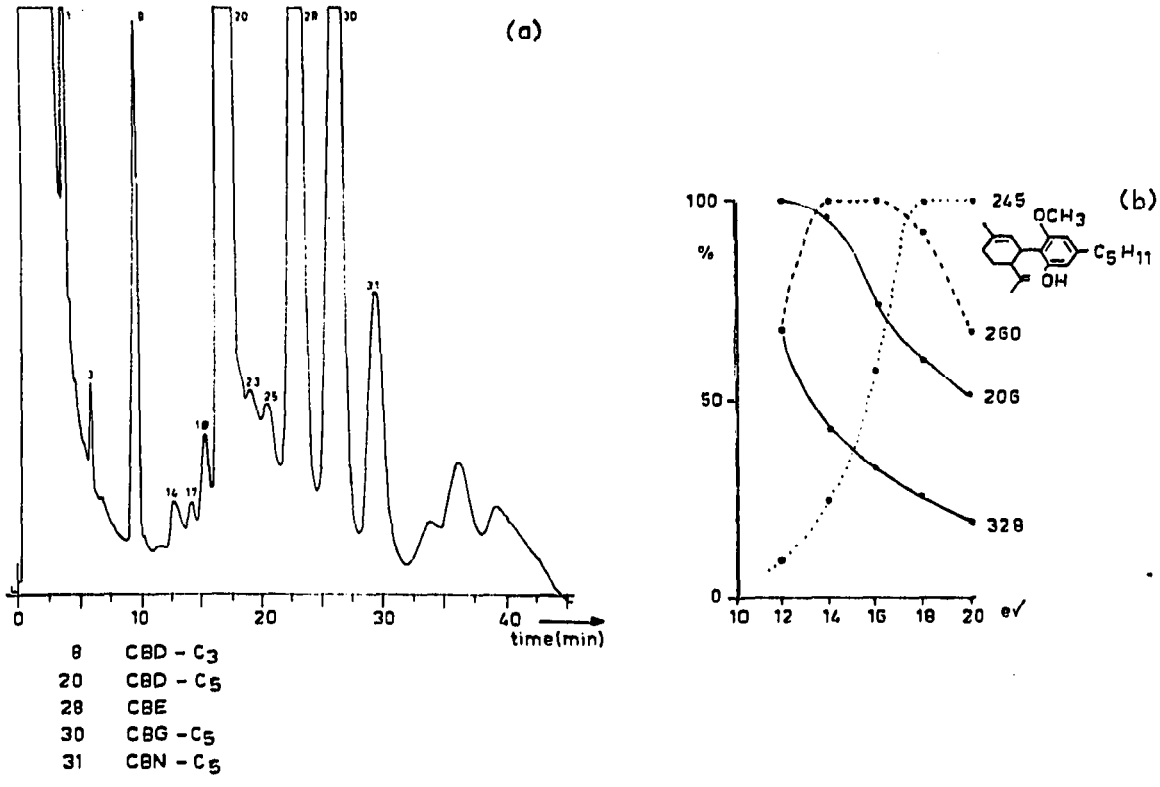

Fig. 2. Gas chromatogram of the counter-current fraction 10–12 (a) and mass fragmentogram of peak 14 (b). CBE and CBG are cannabielsoin and cannabigerol, respectively.

tained a component with a relative retention time 0.76 and a mass fragmentogram similar to that of CBD (Fig. 2). The latter finding confirmed the results of Shoyama *et al.*[6], who reported the isolation of this compound from Japanese hemp.

It seems likely that the methyl ether of $\Delta^{1,2}$-tetrahydrocannabinol is also present as a natural product. Unfortunately, the relative retention time of this compound, as measured on the synthetic methyl ether, is 1.14, which is in the region that in most chromatograms is generally obscured by large amounts of cannabidiol. Other chromatographic separations are in progress in order to separate CBD from the fractions that might contain $\Delta^{1,2}$-tetrahydrocannabinol methyl ether.

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