Cannabivarichromene, a New Cannabinoid with a Propyl Side Chain in Cannabis

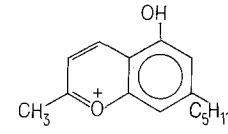
Recent investigations on *Cannabis sativa* L. preparations such as hashish and marihuana have shown that the major cannabinoids Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD) and cannabinol (CBN) can be accompanied by their propyl homologues[1-3] (Δ^9-tetrahydrocannabivarol, cannabidivarol, cannabivarol) and by their methyl homologues[4] (Δ^9-tetrahydrocannabiorcol, cannabidiorcol, cannabiorcol). Detection and identification of these homologues besides the normal pentyl cannabinoids could be greatly facilitated by means of varying the electron energy in combined gas chromatography – mass spectrometry[5]. Rather than using trivial names for the cannabinoids, we prefer abbreviations such as Δ^9-THC, CBD, CBN, and then add the term -C1, -C3 or -C5, corresponding to the methyl-, the *n*-propyl-, or *n*-pentyl side chain, respectively. This indicates the differences as well as the similarities between the homologues.

We now wish to report the occurrence in hashish and marihuana of the propyl homologue of cannabichromene (CBC–C3), for which we suggest the name cannabivarichromene.

Materials and methods. Samples of hashish from different origins were obtained from police seizures. Marihuana samples were grown at the facilities in Groningen from seeds of unknown origin.

Extraction procedures were described previously[6]. Thin layer chromatography (TLC) was done on Silica gel GF 254 (Merck), layer thickness 0.25 mm. Solvent systems were benzene in combination with a trough with 10 ml of 25% ammonia at the bottom of the chamber, or cyclohexane on dimethylformamide impregnated plates[7]. All solvents were reagent grade. Development in unsaturated chambers to a height of 15 cm over the starting points. Visualization under UV-light of 254 nm, or with a 0.5% solution of *o*-dianisidine tetrazolium chloride (Fast blue salt B, Merck). Combined gas chromatography – mass spectrometry (GLC–MS) was performed on an LKB 9000 instrument as described previously[5].

Results and discussion. TLC of an Asian hashish extract (further details on its origin unknown) showed 2 unusual, intense cannabinoid spots besides the major components Δ^9-THC–C5, CBD–C5, CBN–C5, Δ^9-THC–C3, CBD–C3 and CBN–C3. This is illustrated in Figure 1, in which the unusual spots are designated 1 and 3. By means of combined GLC–MS and by comparison with an authentic sample, spot number 1 could be identified as cannabichromene (CBC–C5). Its mass fragmentograph is given in Figure 2A. At low energies (10–11 eV), the molecular ion of mass 314 is the base peak, but at higher energies mass fragment 231 becomes the base peak with the molecular ion peak decreasing to about 10% at 20 eV. Fragment 231 is due to the chromenyl ion.



Direct GLC–MS of the whole sample did not provide adequate information on the identity of spot number 3, as this component did not separate completely from CBD–C3 on the OV 17 column used. We therefore isolated component 3 by preparative TLC, using the benzene-ammonia system as solvent. GLC–MS of the fraction thus obtained gave the mass fragmentogram of Figure 2B. This mass fragmentogram is identical in shape with that of Figure 2B, but its mass fragments are a factor 28 less than those of CBC–C5. As we know that under the conditions used the main fragmentation takes place in the alicyclic ring system instead of in the alkyl side chain[5], it follows that the ring systems of the molecules are identical for Figures 2A and 2B.

Hence, the component with fragments 28 less than CBC–C5 must represent the CBC–homologue with a propyl side chain (CBC–C3; M = 286). We suggest the name cannabivarichromene for this cannabinoid, as it can be considered to be derived from the dihydroxyphenol divarinol. The chromatographic behaviour of CBC–C3 relative to CBC–C5 is in agreement with that of other propyl cannabinoids[6]. In TLC the separation order of the propyl and pentyl homologues are exactly the same, but the propyl homologues move slower than their corresponding pentyl homologues.

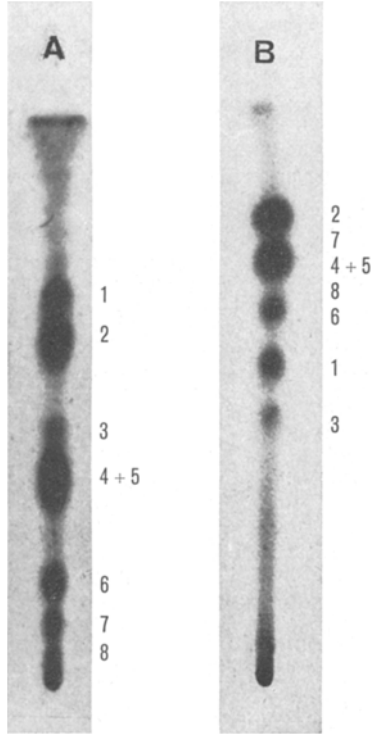


Fig. 1. Thin layer chromatograms of an Asian hashish extract. A) Solvent cyclohexane on a dimethylformamide impregnated plate. B) Solvent benzene with a throug containing 10 ml 25% ammonia at the bottom of the chamber. 1 = CBC-C5; 2 = Δ^9-THC-C5; 3 = CBC-C3; 4 = Δ^9-THC-C3; 5 = CBN-C5; 6 = CBN-C3; 7 = CBD-C5; 8 = CBD-C3.

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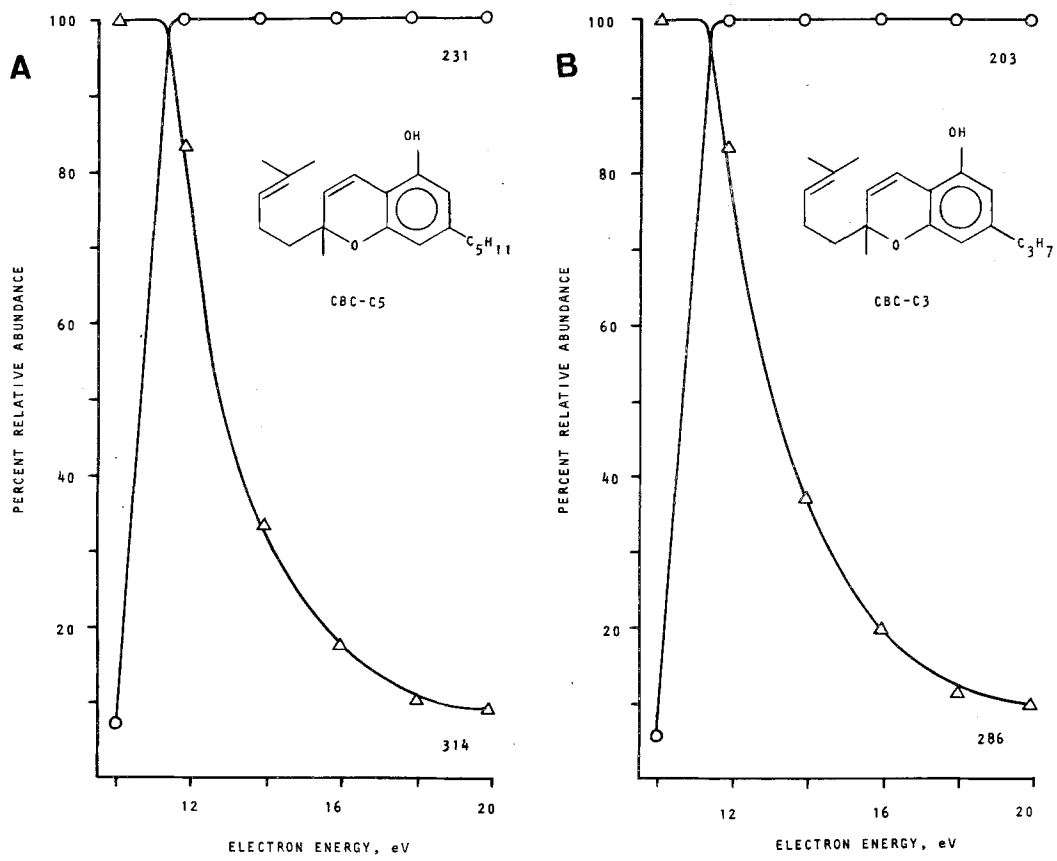

Fig. 2. A) Mass fragmentogram of CBC-C5. B) Mass fragmentogram of CBC-C3.

The isolated CBC–C5 and CBC–C3 fractions were unstable in normal daylight. After 2 weeks, in the course of which the solutions in chloroform were kept at 4 °C, both showed a decomposition product. The Rf-values and the retention times[8] of the products indicated that CBC–C5 decomposed into cannabicyclol (CBY–C5) and CBC–C3 into the corresponding propyl homologue, CBY–C3. Work on a definite identification of the decomposition products is being carried out. The photochemical conversion of CBC–C5 into CBY–C5 has been described[9], but the present finding suggests that the conversion can salo take place in daylight.

The occurrence of CBC–C5 and CBC–C3 in nature seems to depend on the origin of the sample. In most samples we have investigated so far, the two cannabinoids were minor components in comparison to Δ^9–THC–C5, CBD–C5, CBN–C5 and their propyl homologues. The present Asian sample, however, had rather high quantities of CBC–C5 and CBC–C3. In addition, the sample contained small amounts of their respective acids.

It is still uncertain wheter CBC–C5 and CBY–C5 are natural plant constituents or whether they arise from decompositions after harvesting[9,10]. By analogy, this would also hold for CBC–C3 and CBY–C3. However, the occurrence of CBC–C5 and CBC–C3 is not restricted to hashish or marihuana alone. A recent sample of fresh Cannabis leaves showed fairly large quantities of CBC–C5 and lesser amounts of CBC–C3. The only two other cannabinoids in this sample were Δ^9–THC–C5 and Δ^9–THC–C3. This may indicate that the cannabichromenes are genuine plant constituents.

Investigations on the activity of CBC–C5 has shown the component to be inactive in the dog ataxia- or monkey behavioural tests[10], contrary to earlier findings[11]. Unfortunately, our Asian hashish sample was too small to isolate suitable amounts of CBC–C3 to carry out activity tests[12].

Zusammenfassung. Es wurde ein neuer Vertreter aus der Gruppe der psychotrop wirkenden Inhaltsstoffe im Haschisch indischer Herkunft gefunden. Es handelt sich um Cannabivarichromen, als Homologa mit einer Propyl-Seitenkette des Cannabichromens.

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