Cannabis XVII*
Pyrolysis of cannabidiol. Structure elucidation of two pyrolytic conversion products

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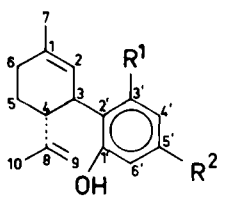
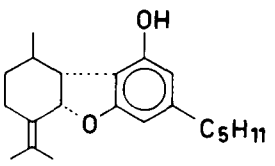
Abstract. Pyrolysis of cannabidiol in a nitrogen atmosphere, which was shown to be a good model for the smoking process, yields a mixture of compounds. Next to the previously described major rearrangement product **2** we have now isolated and identified two more compounds formed by rearrangement processes: 2-[2-(*p*-tolyl)propyl]olivetol (**3**) and 4-(3,4-*trans*-*p*-mentha-1,8-dien-3-yl)olivetol (**1b**).

In previous articles in this series[1–5] several products formed by pyrolytic treatment of cannabidiol (CBD, **1a**) have been described. Until recently emphasis had been given to pyrolysis in air. Since we demonstrated that pyrolysis in nitrogen is a good model experiment for the smoking of cannabinoids[5] the products present in the nitrogen pyrolysate of CBD have been studied in more detail. The main product of CBD under this condition was earlier identified as (1*R*,4a*S*,9b*R*)-1,2,3,4,4a,9b-hexahydro-9-hydroxy-4-isopropylidene-1-methyl-7-pentyldibenzofuran (**2**)[4], a rather unusual product in which there has been a rearrangement of the original carbon skeleton.



1a: $R^1 = OH$, $R^2 = C_5H_{11}$
1b: $R^1 = C_5H_{11}$, $R^2 = OH$



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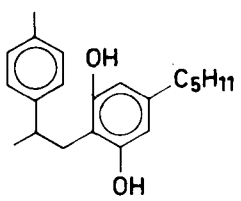

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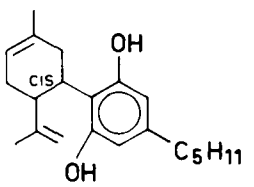

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In this paper we wish to report on two more products: 2-[2-(*p*-tolyl)propyl]olivetol (**3**) and 4-(3,4-*trans*-*p*-mentha-1,8-dien-3-yl)olivetol (**1b**: abnormal CBD). These products provide further examples of rearrangements between the olivetol and terpene moiety of the starting material CBD.

Results and discussion

Analysis of the nitrogen pyrolysate of CBD using combined gas-chromatography/mass-spectrometry (GCMS) showed that the tail of the peak with relative retention time (*Rx*) 1.71 (*Rx* CBD = 1.00), which was identified as cannabinol consisted of an unknown product with a relatively simple mass-spectrum with molecular ion at *m/e* 312 (18%) and most abundant fragment ion at *m/e* 193 (product "312/193"). Further fragment ions are observed at *m/e* 149 (4%), 137 (5%), 136 (10%), 119 (67%) and 91 (17%). This product could be isolated by repeated chromatography (GLC: *Rx* = 1.75; OV-17 3%. TLC: *Rf* = 0.43; *Rf* CBD = 0.71, *Rf* tetrahydrocannabinol = 0.65; SiO_2 Merck, hexane/ether 4 : 1). Exact mass measurement of the molecular ion revealed the elemental composition: $C_{21}H_{28}O_2$. Metastable measurements by the defocussing technique of Jennings showed that the fragment-ion *m/e* 193 is directly formed from the molecular ion. The metastable/daughter ion intensity ratio for this transition is very small (0.05%) indicating a simple cleavage reaction. Upon trimethylsilylation a product with molecular ion at *m/e* 456 (312 + 2 × 72) was obtained which shows the presence of two hydroxyl groups. The IR spectrum of "312/193" (in CCl_4) shows both a free OH absorption (3606 cm^{-1}) and a broadened OH absorption (3524 cm^{-1}). The characteristic absorptions of an isopropenyl (890 and 3090 cm^{-1}) were absent. The 100 MHz PMR spectrum of "312/193" in CCl_4 shows a singlet at 6.97 ppm (4H). In pyridine, this signal is split into two doublets at 7.46 ppm (2H, J = 8.0 Hz) and 7.08 ppm (2H, J = 8.0 Hz). From this finding, together with the presence of an aromatic methyl absorption at 2.28 ppm (3H), it can be deduced that the original C(1)–C(6) terpene ring in CBD is transformed into a *para*-substituted aromatic ring. These data indicate that the olivetol moiety in "312/193" has shifted to the original isopropenyl group. An absorption at 5.99 ppm (2H) results from two equivalent aromatic protons of the olivetol moiety, which is in agreement with the presence of two OH groups giving rise to a very broad absorption at 4.0 ppm (2H). A complicated multiplet at 2.5–3 ppm (3H) is ascribed to benzylic protons, while the α- and ω-protons of the *n*-pentyl side chain absorb at 2.37 ppm (2H, J = 8 Hz) and 0.88 ppm (3H, J = 6 Hz), respectively. A doublet at 1.27 ppm (3H, J = 7 Hz) results from a methyl group coupled to one benzylic proton, since irradiation at 2.74 ppm results in a collapse of the doublet to a singlet. The above-mentioned considerations are in excellent agreement with structure **3**: 2-[2-(*p*-tolyl)propyl]-olivetol.

* Part XVI, see ref. 6.

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[3] *F. J. E. M. Küppers, C. A. L. Bercht, C. A. Salemink, R. J. J. Ch. Lousberg, J. K. Terlouw* and *W. Heerma*, J. Chromatogr. **108** (2), 375 (1975).
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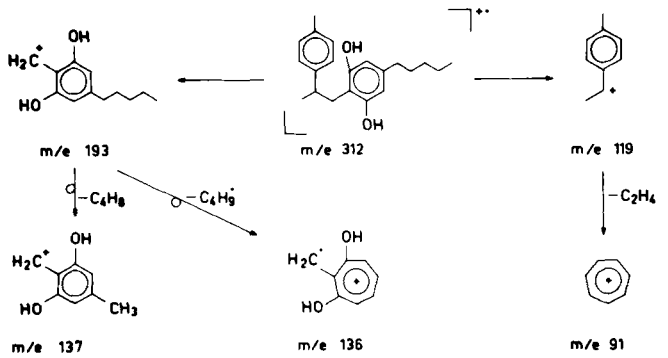

Fig. 1. Proposed fragmentation mechanism for compound "312/193".

The proposed fragmentation pathway for "312/193" is outlined in Fig. 1; the major fragmentation will be a simple cleavage of the bibenzylic bond of the molecular ion giving rise to the most abundant ions *m/e* 193 and *m/e* 119.

Further proof for the proposed structure **3** was obtained by the synthesis of this compound, which is described in the accompanying paper. During the preparative GLC isolation of "312/193" the peak corresponding to CBD (*Rx* = 1) was collected separately. Using preparative TLC another unknown was isolated which in the GC(MS) apparently was hidden under the bulky peak of CBD (GLC: *Rx* = 0.96; OV-17 3%. TLC: *Rf* 0.10; *Rf* CBD = 0.48; SiO_2 Merck, hexane/ether 4 : 1). The mass spectrum of this product shows a molecular ion at *m/e* 314 and most abundant ion at *m/e* 175 (product "314/175"). The elemental composition of the molecular ion was determined by exact mass measurement: $C_{21}H_{30}O_2$. Silylation resulted in the formation of the disilylated derivative (M^+ = 458 = 314 + 2 × 72) showing the presence of two hydroxyl groups. The very informative IR spectrum (in CCl_4) supported the presence of the OH groups (3620 and 3460 cm^{-1}), while the characteristic absorptions of the isopropenyl group are still present: 3080, 900 and 890 cm^{-1}. An absorption at 850 cm^{-1} may be indicative of the presence of a trisubstituted double bond.

The 100 MHz PMR spectrum of "314/175" in $CDCl_3$ shows a striking resemblance with those of CBD[7] and Δ 4(5) CBD[2]: 6.29 (s, br, 1H, temperature dependent), 6.19 (s, 2H), 6.00 (s, br, 1H, temperature dependent), 5.50 (s, br, 1H), 4.63 (s, br, 1H), 4.45 (s, br, 1H) 3.52 (d, br, $J \simeq 9.7$ Hz, 1H) 0.7–2.7 (mult, br, 22H, especially: 1.80 (s, br, 3H), 1.53 (s, br, 3H), 0.90 (t, J = 6 Hz, 3H)) ppm. Upon addition of C_6D_6 the aromatic protons are split into an AB pattern ($J \simeq 2.5$ Hz), which at higher temperatures collapses to a singlet, the coalescence point being about 60°C (compare CBD 20°C), indicating a higher steric hindrance between the benzene ring and the terpene moiety in "314/175" compared with CBD. These solvent and temperature experiments also suggest the equivalence of the aromatic protons. Based on these data, product "314/175" was originally identified as 3,4-*cis*-Δ1(6)CBD (**4**). However, this assignment was ruled out by comparison with the spectroscopical data of compound **4** recently synthesized by *Handrick* et al.[8]. On the other hand, the analytical data for "314/175" are also applicable to abnormal CBD (**1b**), assuming that the aromatic protons in "314/175" are chemically not equivalent despite their appearance as a singlet in the PMR spectrum. Comparison with the literature data of this compound, earlier synthesized by *Petrzilka* et al.[9], confirm the identity of the pyrolytic product "314/175" with **1b***. As can be seen from structure **1b** the terpene moiety has shifted from C(2) to C(4') of the olivetol ring.

It may be expected that further rearrangement-products will be found upon more detailed analysis of the pyrolysate mixture, since the C(3)–C(2') bond in CBD can be cleaved easily and the olivetyl radical, which is probably an intermediate, is relatively stable.

Acknowledgement

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* This product was originally also identified by the same authors as a *cis*-cannabidiol[10]. Although the data for product **1b** given by *Petrzilka* et al.[9] do not rigidly prove the position of the double bond (*i.e.* Δ1(2) or Δ1(6)) and the substitution of the olivetol moiety (*i.e.* at C(2') or C(4'), the derivatisation reactions with **1b** described by *Razdan* et al.[11] and the preparation of several analogues reported by *Cardillo* et al.[12] leave no doubt about the assigned structure **1b**.

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