perature dihydrolysergamide, as confirmed by m.p. and IR spectrum, was formed. It was therefore apparent that reduction had occurred in the cyclitol side chain rather than in the ergoline nucleus: total acid hydrolysis yielded proline but no phenyl-alanine, as shown by monodimensional electropherogram. These findings ruled out the possible reduction of the tertiary hydroxy group and indicated a modification of the phenylalanine residue[7]. The PMR spectrum[9] (Varian A 60, DMSO-d6) showed the presence of a singlet at 5.68 δ (isolated vinylic proton) and a double doublet at 3.99 and 3.53 δ (non equivalent benzylic protons), whereas the typical triplet at 4.49 δ, present in dihydroergotamine and due to the C'_5–H proton coupled with the benzylic protons, was absent. Catalytic reduction in ethanol with 10% Pd/C at 10 atm gave a dihydroderivative, m.p. 178–180 °C, $[\alpha]_D^{20}$–55° (c=1, Py), whose PMR spectrum no longer showed the presence of the 5.68 δ singlet and the signals due to the benzylic protons were moved up-field in the 3 δ region.

On the basis of the data reported above, structure **II** ($R_1 = CH_3$; $R_2 = CH_2C_6H_5$) has been assigned to the product resulting from the Birch reduction of dihydroergotamine[10]. Furthermore, the presence of a basic labile ene-diamine function justifies both the electrophoretic mobility (twice that of dihydroergotamine at pH 1.9) and the instability in acid conditions.

The reaction has been extended to dihydroergocristine to give **II** ($R_1 = CH(CH_3)_2$; $R_2 = CH_2C_6H_5$), m.p. 160 °C; $[\alpha]_D^{20}$–53° (Py) and to dihydroergocryptine to give **II** ($R_1 = CH(CH_3)_2$; $R_2 = CH_2CH(CH_3)_2$) m.p. 182 °C; $[\alpha]_D^{20}$–50° (Py). The pharmacological activities of the new modified ergot alkaloids will be reported separately by G. Falconi and co-workers.

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Pyrolysis of cannabidiol. Structure elucidation of a major pyrolytic conversion product[1]

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Summary. Pyrolysis of cannabidiol, one of the major constituents of Cannabis sativa, yields a mixture of components. Next to previously identified products, a major conversion product has now been isolated and identified. The unusual and stereospecific route of formation of this compound with altered chromophore is discussed.

Cannabis products are generally administered through the smoking process. As a consequence, pharmacological activities must be ascribed to the components of the smoke, rather than the original plant constituents. In earlier papers[2–6], we discussed the possible influence of the pyrolytic process on the characteristic hemp constituents, the cannabinoids. Particularly cannabidiol (CBD, **I**) was found susceptible for pyrolytic transformations. It was also found that, although CBD in itself shows little or no pharmacological activity, several of its pyrolytic conversion products showed unusual activities like a strong inhibitory effect on prostaglandin biosynthesis, phenomena of general ataxia and nervous reactions in mice[4–6]. In the experimental simulation set-up chosen by us[4,6], pyrolytic treatment of CBD using N_2 as gas-phase converts the pure substance into a mixture of components. Next to previously identified compounds, we were able to isolate one of the major conversion products by repeated chromatography (GC: Rx = 1.43; Rx CBD = 1.00; OV-17 3%. TLC: Rf = 0.45; Rf CBD = 0.60, Rf THC = 0.52; SiO_2 Merck, hexane-ether 4:1).

The mass spectrum of the unknown showed a molecular ion at m/e 314 and a most abundant fragment ion at m/e 271 (product '314/271'). Exact mass measurements of the molecular ion showed the molecular composition to be $C_{21}H_{30}O_2$. The strong resemblance on many of the fragment ions with those occurring in the mass spectra of other '314-cannabinoids'[7] clearly indicated the cannabinoidal nature of product '314/271'. Silylation yielded a product with only one silyl group, molecular ion at m/e 386 (314 + 72), thus indicating that only 1 of the 2 original phenolic OH-groups of CBD was still present.

The IR-spectrum showed absorption for a non-H-bonded OH-group (3609 cm^{-1}). Characteristic absorptions for an isopropenyl group (850, 895 and 900 cm^{-1}) and the geminal Me-groups (1365 and 1380 cm^{-1})[8] were lacking from the spectrum of product '314/271'. Since the IR-spectrum shows no absorption at 3010 cm^{-1}, the olefinic proton at C-2 as present in CBD must be lacking from '314/271' as well. The 100 MHz ^{1}H-NMR-spectrum of

1 Acknowledgments. This research was supported by the Dutch Department of Public Health and Environmental Hygienics. Thanks are due to R. D. van Ooyen who provided technical assistance, Dr M. J. A. de Bie and Dr W. Heerma for valuable discussions, Drs J. W. Marsman and Ir T. Spoormaker for performing PMR experiments.
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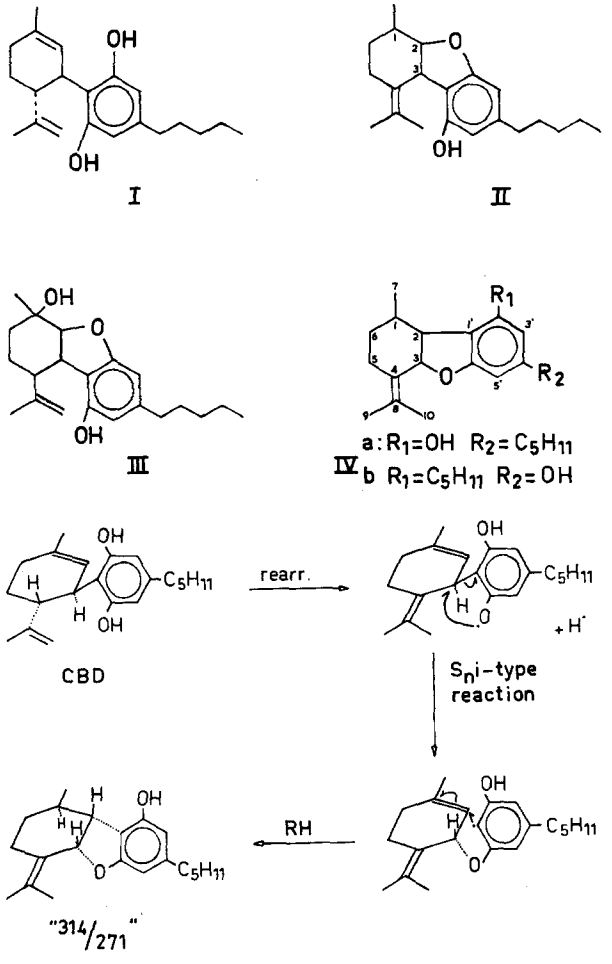
'314/271' showed 2 resonances for the aromatic protons (δ 6.00 and 6.11 ppm), thus suggesting the presence of 2 bonds between the aromatic and terpenoid moiety of the compound. In the case of a single bond as in CBD, identical chemical shifts are observed for the 2 aromatic protons. An OH-proton was found as a broad signal at δ 5.1 ppm. The olefinic nature of a rather down-field



doublet (δ 5.16 ppm) could be excluded by the lack of the required absorptions in the IR-spectrum. This resonance could best be explained by a proton adjacent to at least 2 electronegative centres. Resonances at δ 2.63 ppm (1H, double d, J 6.3 and 9.5 Hz) and δ 2.41 ppm (2H, t, J 7.2 Hz) could be ascribed to a benzylic proton and the α-benzylic protons of the n-pentyl side chain, respectively. Me-resonances of an isopropylidene group were observed at δ 1.75 and 1.82 (d, J 1.8 Hz), the latter showing a rather large homo-allylic coupling. A Me-doublet at δ 1.06 ppm (J 6.3 Hz) was assigned to the C-7 Me-group, thus supporting the disappearance of the C1(2) double bond (C-7 Me of CBD at δ 1.8 ppm). In the first instance, the above data suggested a structure (**II**) similar to cannabielsoin (CBE, **III**)[4]. However, opposing such similarity were the following observations. The resonances of the C-2 and C-3 protons of structure **II** are expected around δ 3.5–3.9 ppm (compare similar resonances in CBE[4] at δ 3.97 and 3.24, respectively). Product '314/271' shows resonances at δ 5.16 and 2.63 ppm, positions which would be in full accord with structures **IVa** or **b**. Formation of e.g. product **IVa** would require cleavage of the original C-C bond as present in CBD between the terpenoid and aromatic moieties. Re-formation of the C-C bond between the 2 moieties could equally result in compound **IVa** or **b**. Results of decoupling experiments, although confirming structure **IV**, are equally applicable to both structures. Irradiation at H-3 (δ 5.16 ppm) with a second radio frequency resulted in a simplification of the double doublet at δ 2.63 ppm into one doublet (J_{12} 9.5 Hz). The Me-doublet at δ 1.82 ppm remained unchanged. However, irradiation at δ 2.07 ppm, the approximate position of the C-5 protons, produced a singlet for the Me-resonance at δ 1.82 ppm. Irradiation at the C-1 proton (δ 1.32 ppm) caused decoupling of the C-7 (δ 1.06 ppm) and C-2 (δ 2.63 ppm) protons, the latter being reduced into a doublet (J_{23} 6.3 Hz).

In order to distinguish between structures **a** and **b**, pyridine and lanthanide induced shifts were studied. Association of pyridine with the phenolic OH-group would result in an asymmetric shift induction of the aromatic protons in the case of structure **IVa**, as opposed by the symmetrical induction which is expected for structure **IVb**. Similar chemical shift changes should result upon addition of lanthanide shift reagent. In both cases unequal chemical shift changes were observed for the aromatic protons, thus favoring structure **IVa** over **IVb**.

Moreover, the NMR-spectrum in C_6D_6 showed an increase in chemical shift difference which is in full accord with observations of Arnone[9]. Product **IVa** can be visualized as originating from CBD as outlined in the figure. The rearrangement of CBD resulting in cleavage of the C3-C1′ bond can best be followed by attack of C1′ at C2. Dreiding models clearly illustrate that attack at C-1, C-8 or C-7 is either impossible or highly unlikely due to steric hindrance. It is also illustrated by the models that attack of C1′ at C2 can only take place from the backside of the molecule as drawn in the figure. Consequently, product **IVa** is expected to be optically active through its internally directed stereospecific route of formation.

Measurement of the optical rotation showed indeed that product '314/271' is optically active; $\alpha_D = -101°$. From the figure it is clear that C-1 and C-2 must have the R-configuration while C-3 has the S-configuration. From the coupling constant J_{12} (9.5 Hz), it can be concluded that H1 and H2 must be preferably diaxial. The proton at C-3 is in the β-position and shows no coupling with the isopropylidene group. The β-protons at C-3 and C-5 are symmetrically positioned relative to the isopropylidene group, and it must thus be concluded that the observed large homoallylic coupling of 1.8 Hz must be ascribed to the α-proton at C-5. This is in full accord with the parallel position between the C5-Hα bond and the p-orbitals of the double bond.

The proposed structure **IVa** is fully supported by the observed mass spectrum. Loss of a C_3H_7 radical resulting in the formation of the intense peak at m/e 271 is in full accord with a similar fragmentation of 4(8)-p-menthene[10], identical in structure to the terpenoid moiety of '314/271'. A peak with a somewhat more pronounced intensity (6–8%) in comparison with other cannabinoids is found at m/e 207. Its elemental composition, $C_{13}H_{19}O_2$, suggests a protonated 2,3-dihydro-4-hydroxy-6-n-pentyl-benzofuran structure. This difference in fragmentation behaviour, as compared to other cannabinoids, can be considered as indicative for the presence of 3 rings in the precursor ions (m/e 314 and 299).

From the above considerations it can be concluded that the pyrolytic product '314/271' from CBD must have the structure (1R, 4^aS, 9^bR)-1,2,3,4,4^a,9b-hexahydro-9-hydroxy-4-isopropylidene-1-methyl-7-pentyldibenzofuran.

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