to a cyclobutanone; the MS has 2 main peaks at 69 and 138 m/e arising from fragmentations a and b respectively; fragment a shows that the first isoprene unity is not implied in the cyclization, while fragment b is indicative of the presence of a [3.2.0]-bicycloheptenone system, from which a methylcyclopentadiene molecule is easily lost. In the NMR-spectrum it is possible to show the isopropylidene moiety (2 methyl signals at 1.60 and 1.65 δ with a long range coupling to a proton on double bond at 5.0 δ), a vinyl methyl at 1.72 δ coupled with a second proton on double bond at 5.3 δ; again, there is a multiplet at 3.85 δ for the proton on the ring junction adjacent to the carbonyl group and a tertiary methyl at 1.05 δ.

The relative stereochemistry shown in structure **IV** is based mainly on the study of molecular models[7,8]: the cyclization of the ketene, initially formed from farnesic acid, on the central double bond of the molecule leaves the tertiary methyl group on the opposite side of the hydrogens of the ring junction if the double bond has an E configuration, whereas the same methyl is cis to the hydrogens of the junction if the double bond has a Z configuration.

To confirm this point, we have repeated the reaction starting from a mixture of 2-cis,6-cis- and 2-trans,6-cis-farnesic acids. GLC analysis[9] of the crude mixture shows again 3 main products; the retention times of 2 of them (as well as their MS) coincide with those of **V** and **VI**, whereas the compound of higher volatility has a retention time slightly different from that of **IV**.

Structure **VII** has been attributed to this new compound: its IR and NMR are very similar to those of compound **IV** as well as most of the NMR-spectrum. The only meaningful difference is the chemical shift of the tertiary methyl, which, in this case, is at 1.20 δ. These data are in agreement with a different shielding effect of the π-electrons of the double bond of the ring on the tertiary methyl: when this is trans to the junction as in **IV**, it falls very near to the lobes of the double bond, when it is cis it lies well outside the influence of these electrons. The structure of **V** and **VI** derives immediately from their physicochemical data. While this work was in progress, a paper appeared in a Japanese journal[10] concerning the cyclization of farnesic acid chlorides with Lewis acids. The authors obtain mainly mono- and dichlorinated compounds such as **VIII**; on dehydrochlorination with LiCl they obtain a mixture of compounds which we found identical with **V** and **VI**.

Another compound having a very low retention time in GLC is always present in the reaction mixture, although in very small amounts. Structure **IX** has been attributed to it on the basis of the following data: UV-spectrum with a maximum at 242 nm (ε=11,000), IR with aromatic bands at 3030 cm^{-1}, MS with the molecular ion at 200 m/e and main fragments at 157, 132, 91, 69 m/e. In the NMR-spectrum, a 4-protons double doublet due to aromatic protons at 7.0 and a methyl on benzene ring at 2.28 δ are easily recognizable; furthermore there are 2 vinyl protons at 4.85 and 5.05 δ and 3 vinyl methyls at 1.50 (3H) and 1.62 δ (6H). The biological activity of the compounds so far obtained is now under investigation.

7 We have confirmed the suggestion made by Erman and coll.[8] that also in the conditions described for the synthesis of filifolone, an unsaturated ketene first cyclize to a [3.1.1]-bicycloheptenone system and then rearranges to the [3.2.0]-bicycloheptenone system. This and other related results will be discussed in a following paper.

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Ergot alkaloids modified in the cyclitol moiety

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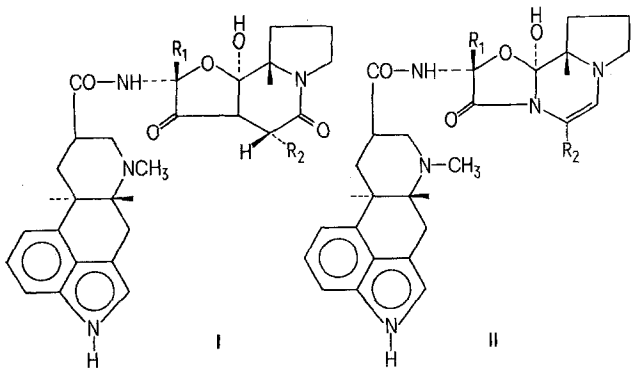
Summary. Birch reduction of 9,10-dihydroergot alkaloids (**I**) yields a compound to which structure **II** is assigned.

In recent years the preparation, via total synthesis, of ergot alkaloids modified in the cyclitol moiety, has been intensively investigated[1]; however no attempt has been so far made to modify directly the peptide residue of the natural alkaloids. In the present note we report the selective reduction of the 6′ carbonyl group of 9,10-dihydroergot alkaloids (**I**) by litium in liq. ammonia to give the 6′-desoxy-5′, 6′-didehydroderivatives (**II**).



Portionwise treatment of dihydroergotamine (**I**; R_1 = CH_3; R_2 = $CH_2C_6H_5$) (10.3 mmoles) in liq. NH_3 (900 ml) with litium (30 mmoles) at −35 °C yielded a new compound, less polar than the starting material, that still gave a blue color with the Van Urk reagent, thus indicating that the indole nucleus, contrary to the expectations, had been unaffected[2]. Minor by-products were also present as shown by TLC, but since with this reagent they gave a yellowish-green color typical for the 2,3-dihydroergolines[5], they were not further investigated.

The new compound, purified by chromatography on silicagel column (60% yield; m.p. 207–208 °C; $[\alpha]_D^{20}$ −50°, Py) had a molecular formula $C_{33}H_{37}N_5O_4$ corresponding to a loss of the 1 oxygen atom from dihydroergotamine, the mass spectrum[6] showed a peak at m/e 269 (dihydrolysergamide) and 298 (reduced cyclol moiety), and on treatment with a dilute solution of oxalic acid at room tem-

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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