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PYROLYSIS OF CANNABIDIOL. STRUCTURE ELUCIDATION OF FOUR PYROLYTIC PRODUCTS

F. J. E. M. KÜPPERS, C. A. L. BERCHT, C. A. SALEMINK and R. J. J. CH. LOUSBERG*
Laboratory of Organic Chemistry, State University of Utrecht, The Netherlands

and

J. K. TERLOUW and W. HEERMA
Laboratory of Analytical Chemistry, State University of Utrecht, The Netherlands

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Abstract—Pyrolysis of cannabidiol in nitrogen atmosphere affords at least six more products with longer GC-retention times than CBD, next to unconverted CBD. Two of these could be identified as Δ1(2)THC and CBN Two further products were investigated and their mass spectrometrical fragmentations and structures are proposed.

In the preceeding paper[1] we described the volatile products of pyrolysis of cannabidiol (CBD). A main product formed during pyrolysis using air as gas phase was earlier identified as cannabielsoin.[2] We now wish to report on the structure of four more products of pyrolysis of CBD.

It had been observed that changing the nature of the gas phase which was used during pyrolysis considerably influenced the yield of the various compounds in the pyrolysates (Fig. 1). Combined gas chromatography-mass spectrometry (GCMS) revealed the structural identity between the products present in the two differently obtained pyrolysates. It was thus concluded that compound **10** (Fig. 1) could best be isolated and identified[2] from the air-pyrolysate. The nitrogen-pyrolysate seemed a better source for the isolation of the products **9** and **11–15** (Fig. 1). GCMS measurements identified product **11** (Rx = 1·32; Rx CBD = 1·00) as Δ1(2)THC.[3] Product **15** (Rx = 1·63) was identified as cannabinol.[4] The peak at Rx = 1·42 represented at least three products with molecular weights 314, 312 and 310 as was found by recording several spectra in one and the same gas chromatographic peak.

Through a combination of prolonged preparative gas and TLC, products **9** (Rx = 1·22) and **12** (Rx = 1·42) could be obtained in pure form. Their mass spectra are presented in Fig. 2. The mass spectrum of compound **9** showed its most abundant ions at *m/e* 314 (34%) and 108 (100%) and will therefore from hereon be designated as compound "314/108". For similar reasons, product **12** will be referred to as compound "314/272".

Compound "314/108" was further studied by mass spectrometry. Exact mass measurement of the fragment ion and molecular ion at *m/e* 108 and 314, respectively, showed their composition to be C_8H_{12} and $C_{21}H_{30}O_2$. The mass spectrum of the silylated derivative revealed the presence of one (phenolic) OH group. Comparison of the mass spectrum of "314/108" with those of the M.W. 314 cannabinoids CBD, Δ1(6)THC, Δ8(9)isoTHC and cannabichromene, clearly illustrates that the fragmentation of "314/108" is substantially different from the normally observed fragmentation patterns. The above mentioned four cannabinoids, although structurally quite different, give mass spectra with major fragment ions at *m/e* 193, 231, 246, 258, 271 and 299.[5] The main fragmentation of the molecular ion in the "314/108" compound is the elimination of a $C_{13}H_{18}O_2$ neutral moiety which results in the most abundant ion at *m/e* 108. A metastable peak at *m/e* 37·1 supports the occurrence of this fragmentation.

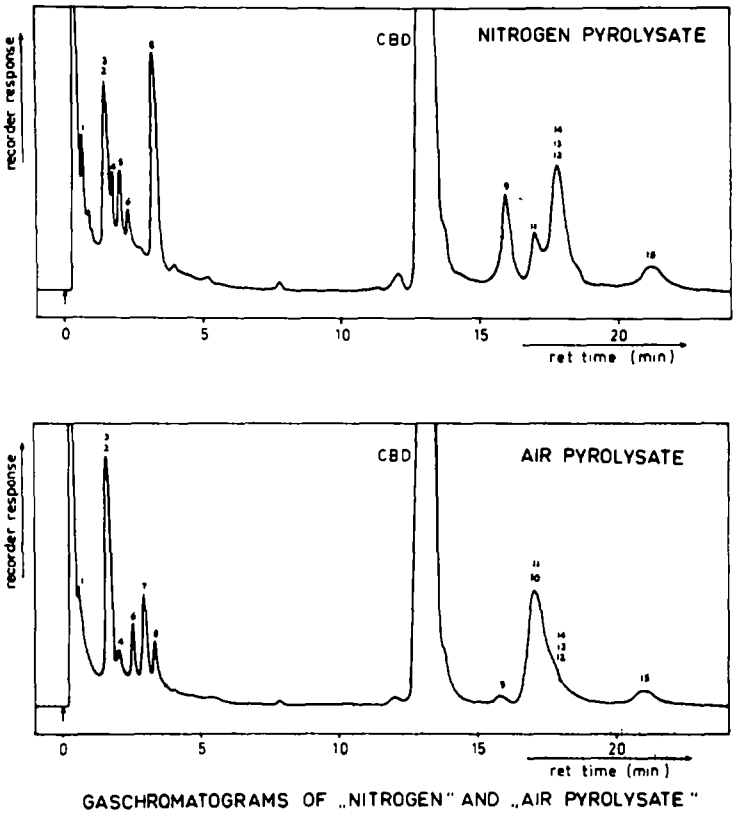
The 220-MHz PMR spectrum of "314/108" showed no resonances in the 4·3–5·8 ppm region for the olefinic- and end-vinylic protons, which were present in the starting material (CBD).[6] A single Me resonance at 0·79 ppm indicated the presence of a bridge-head Me group by its—among cannabinoids—unusual high-field position. The temperature-dependant broad signal of the phenolic OH proton was found at 4·21 ppm. A Me group α to oxygen (1·43 ppm) appears as a singlet and must thus be attached to a non-proton bearing C atom. Two triplets at 0·91 (3H) and 2·41 (2H) and multiplets between 1·00–2·20 ppm proved the presence of the n-pentyl side-chain.

The IR spectrum further confirmed the presence of a non-H-bonded OH group (3608 cm^{-1}). No absorption resulting from an iso-propylidene group (880 and 895 cm^{-1})[7] or geminal Me groups (1365 and 1380 cm^{-1})[7] were observed. Based upon the above data we propose the formation and structure of compound "314/108" as given in Fig. 3.

The fragmentation upon electron impact can be visualized to take place according to the mechanism as outlined in Fig. 4.

The purified component "314/272" was first studied by mass spectrometry. A remarkable aspect of its spectrum was the large stability of the molecular ion. Exact mass measurements revealed the following composition of some of the fragment ions at *m/e* 314 ($C_{21}H_{30}O_2$), 272 ($C_{18}H_{24}O_2$) and 257 ($C_{17}H_{21}O_2$). A metastable ion at 235·6 confirmed the direct formation of the fragment ion at *m/e* 272 from the molecular ion by loss of the neutral fragment C_3H_6. Loss of a Me radical affords the fragment ion at *m/e* 257 from that at *m/e* 272. The metastable ion at *m/e* 242·8 further confirmed this transition.

Silylation yielded a product with two trimethylsilyl groups, molecular ion at *m/e* 458 (314 + 2 × 72). The fragmentation of this compound gives an intense fragment



GASCHROMATOGRAMS OF „NITROGEN" AND „AIR PYROLYSATE"

Fig. 1

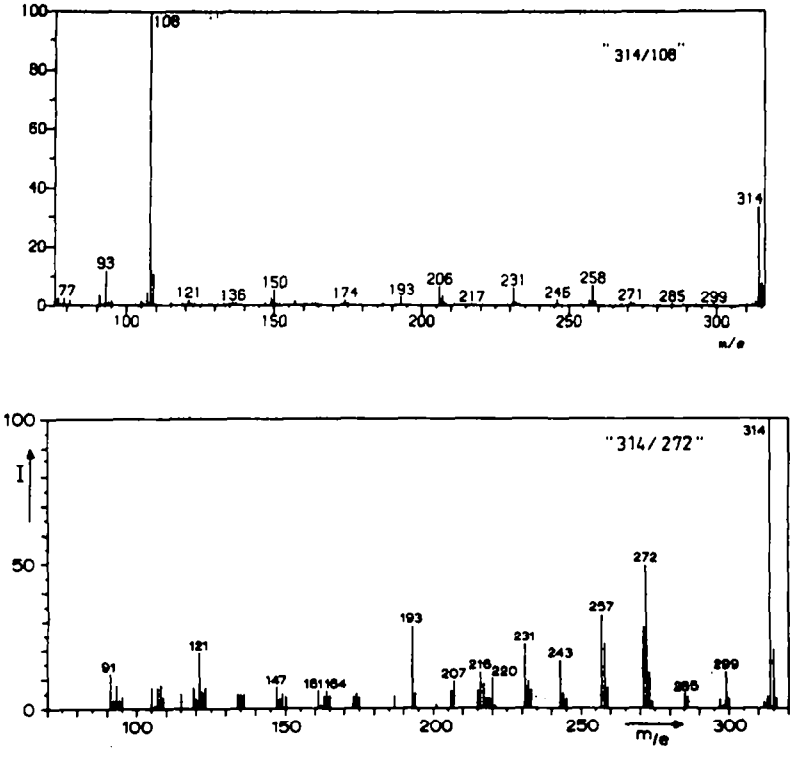


Fig. 2

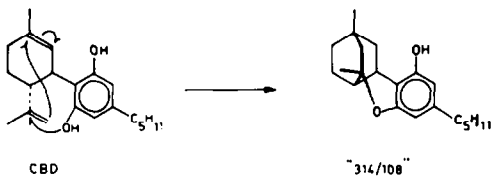


Fig. 3

GCMS measurements were carried out on a modified JEOL JMS 07 instrument under the conditions as described in the preceeding paper. HRP mass spectra were measured with an AEI-MS 902 mass spectrometer, nominally operating at 70 eV electron energy and 50–70° ion chamber temp. Samples were introduced via the direct inlet system. Elemental compositions were derived from element lists obtained by on line measurements with the AEI-MS 902-Argus 500 computer combination at a dynamic resolving power of 10,000. All transitions were metastable confirmed.

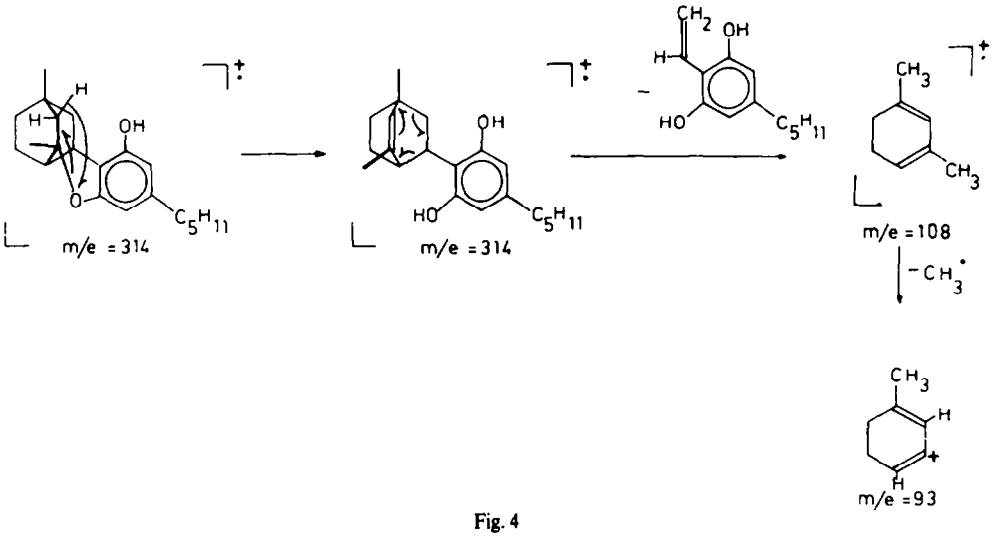


Fig. 4

ion at m/e 337 ($193+2\times72$), which corresponds to the aromatic moiety of the molecule bearing two trimethylsilylated phenolic OH groups (see also proposed fragmentation mechanism, Fig. 5).

The 220-MHz PMR spectrum of product "314/272" gave a superimposed Me doublet and triplet centered at 0·91 ppm. The triplet was assigned to the n-pentyl side chain. A Me singlet at 1·91 ppm was ascribed to the Me group attached to the isopropylidene system (compare similar resonance from CBD at 1·80 ppm).[6] The benzylic protons appear at 2·40 ppm as a triplet. A broad doublet at 3·62 ppm was assigned to the similar C-3 proton in CBD. In compound "314/272" a trans coplanar C-2 proton couples with a large coupling constant (J 11 Hz), while a second proton gives smaller coupling (J 2 Hz). Two singlets at 4·75 and 5·04 ppm could best be assigned to the methylene protons of the iso-propylidene group. The relatively large chemical shift difference of the two protons must be due to the decreased flexibility of the system to which the isopropylidene group is attached. A broad resonance at 5·84 ppm must be ascribed to one olefinic proton. Two aromatic protons appear as one broadened singlet at 6·04 ppm.

The above data obtained on product "314/272" are all in good agreement with its structure as Δ4(5)CBD (Fig. 5).

Its fragmentation is proposed to proceed along the lines given in Fig. 5.

The IR spectrum shows the required two absorptions for the H- and non-H-bonded phenolic hydroxyls at 3480 and 3518 cm^{-1} as is equally observed in the spectrum of CBD. The isopropylidene group was further confirmed by the medium to strong absorption at 890 cm^{-1}.[7]

EXPERIMENTAL

Instrumentation. Pyrolysis was carried out by using the instrument and the conditions as described in part VIII of this series.[2]

PMR spectra were recorded on a Varian HR-220 instrument, using CCl_4 as solvent and TMS as internal standard. IR spectra were taken with a Perkin-Elmer 257 IR spectrophotometer.

Isolation of compound "314/108". Approximately 100 consecutive pyrolyses of 3·5 mg CBD yielded 150 mg nitrogen-pyrolysate. This material dissolved in 0·75 ml CH_3OH was subjected to preparative gas chromatography in 4–5 μl aliquots. Thus, 4·5 mg of the required compound (GLC Rx = 1·22; Rx CBD = 1·00) was collected in 75% pure form. Subsequently, preparative TLC was applied, using SiO_2 (Merck "Fertigplatten") plates (20 × 20 cm) and eluant light petroleum–diethyl ether (9:2) (three consecutive runs over 15 cm). The area between R_f = 0·69 and 0·75 was removed from the plate and the adsorbent extracted three times with diethyl ether, yield 1·3 mg "314/108" (97% by GLC); PMR 0·79 (s, 3H), 0·91 (t, 3H), 1·43 (s, 3H), 1·0–2·2 (m, 15H), 2·41 (t, 2H), 2·93 (br, d, 1H), 4·21 (s, 1H), 5·95 (s, 1H), 6·06 (s, 1H); IR: 3608 (s), 2960 (s), 2930 (s), 2860 (s), 1630 (m), 1455 (w), 1430 (ms), 1380 (m), 1355 (m) cm^{-1}.

Isolation of compound "314/272". During the preparative gas chromatographic isolation of product "314/108" a second fraction was collected (Rx = 1·42, 72% GLC). This fraction, 6·3 mg, was similarly purified by prep. TLC as described above. The area between R_f = 0·7 and 0·82 contained the required product and extraction of the adsorbent yielded 1·5 mg of compound "314/272". (91·8% by GLC), PMR: 0·91 (t, 3H), 0·94 (d, 3H), 1·0–1·85 (m, 11H), 1·91 (s, 3H), 2·4 (t, 2H), 3·62 (br. d, 1H), 4·2–4·6 (br. s, 1H), 4·75 (s, 1H), 5·04 (s, 1H), 5·84 (s, 1H), 6·04 (br. s, 2H), 5·8–6·1 (br. s, 1H); IR: 3618 (s), 3480 (s), 2960 (s), 2930 (s), 2865(m), 1635 (s), 1445 (s), 1220 (s), 980 (ms), 880 (m).

Silylation procedure. A soln of 0·25 ml bis (trimethylsilyl) trifluoroacetamide (+1% trimethylchlorosilane) in 1 ml hexane was added to solns of "314/108" and "314/272". After 1 hr at 60° GCMS analysis of the mixtures showed complete mono- and disilylation of "314/108" and "314/272", respectively.

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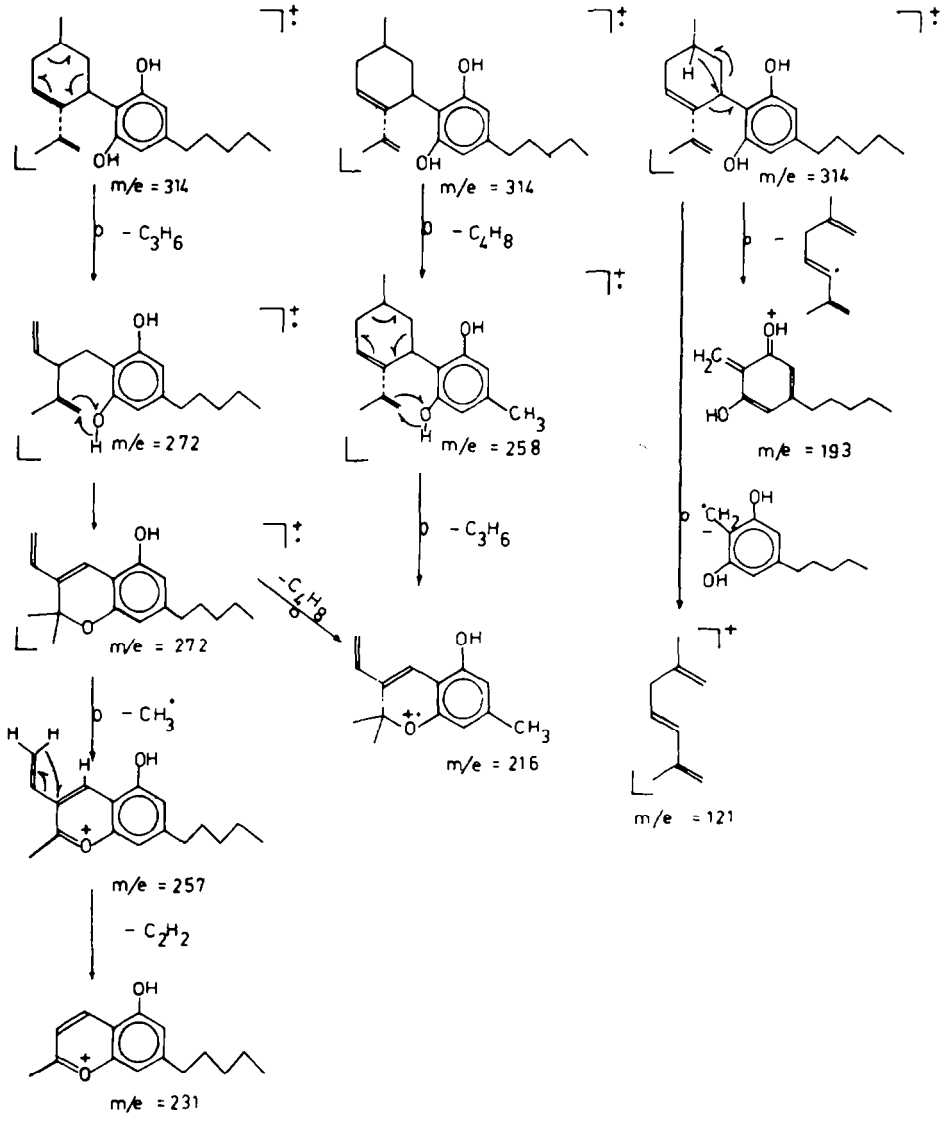

Fig. 5.

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