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Note

Cannabis

XIV*. Pyrolysis of cannabidiol —analysis of the volatile constituents

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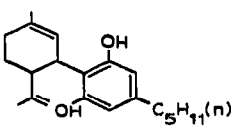
In previous papers in this series[1,2], we expressed our preference for studies on the products obtained after pyrolysis of cannabinoids rather than for those on the pharmacology and chemical nature of the naturally occurring products of *Cannabis sativa* L. The constituents of marihuana and hashish are generally introduced to the organism through smoking processes. The pyrolytic process will induce changes in the plant material and, as a corollary, the pharmacological effects of the pyrolytic products may differ from those of the original material. Our preliminary pharmacological findings[1] actually indicated such differences. In an attempt to identify the pharmacologically active principle in the pyrolyzate of cannabidiol (CBD, I) we have now analyzed the volatile (cracking) products present in the isolated mixture.



(I)

EXPERIMENTAL

The procedures used in the pyrolysis, gas chromatographic purification and silylation were described in detail in Part VIII[1].

Combined gas chromatography–mass spectrometry was carried out using a modified Jeol JMSO7 instrument with a double stage separator. A glass column of dimensions 200 × 0.3 cm I.D. with helium as carrier gas at a pre-pressure 0.6–0–8 kg/cm² was used. The stationary phase was 3% OV-17 on Chromosorb G, AW-DMCS, 80–100 mesh. The injector temperature was 210°, the column temperature

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165° (135° for silylated products), the separator temperature 220° and the ion source temperature 180°. The accelerating voltage was 3.0 kV, the trap current 300 μA and the electron energy 70 eV. The gas chromatograms were obtained by recording the total ion current at 30 eV.

RESULTS AND DISCUSSION

CBD was pyrolyzed with both air and nitrogen as carrier gas. The most volatile constituents of the pyrolyzates collected were separated gas chromatographically (Fig. 1). Silylation and mass spectrometric analysis revealed the molecular weight and the number of hydroxyl groups accessible for silylation.

The analytical results, including those on synthetic reference compounds, and proposed structures of the cracking products are summarized in Tables I and II.

The mass spectrum of compound 2* was identical with that of olivetol. The mass spectra of compounds 4 and 7 have many characteristics in common with those

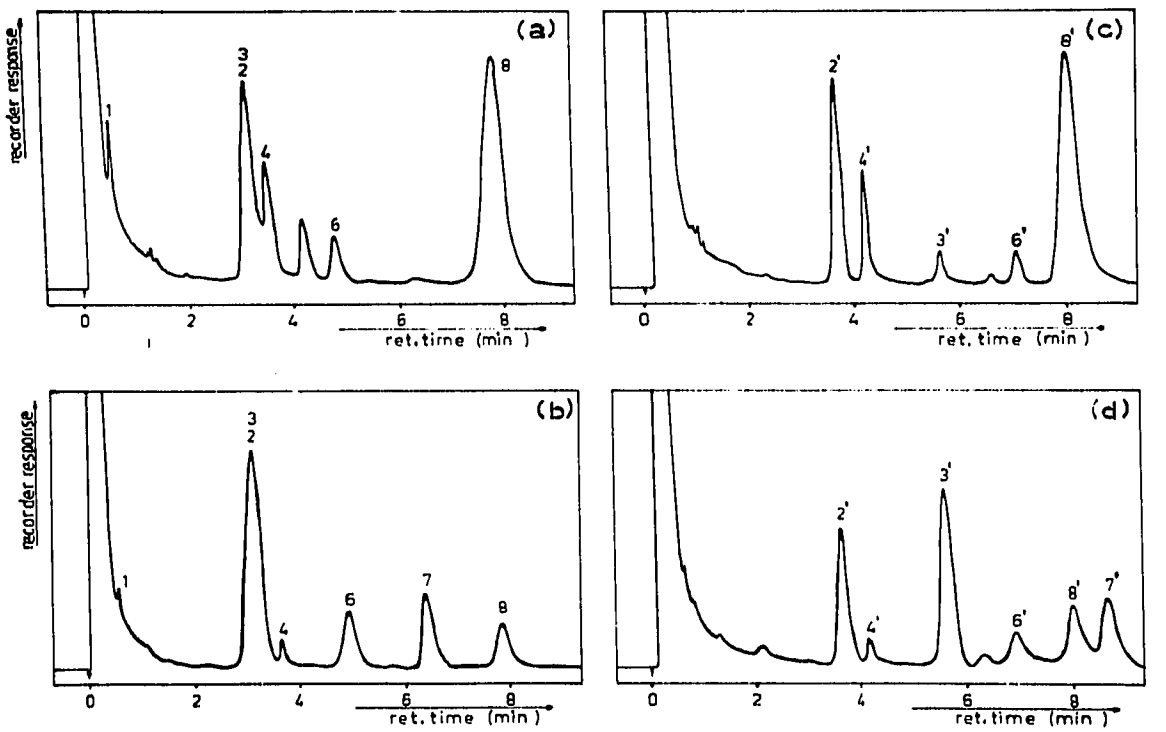
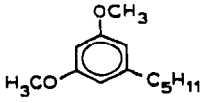
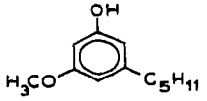
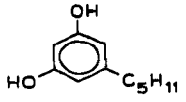
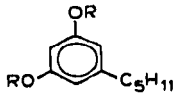
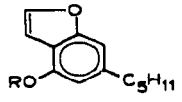
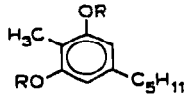
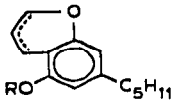
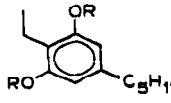
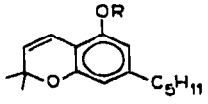


Fig. 1. Gas chromatograms of the most volatile constituents of CBD pyrolyzates. (a), Cracking products from nitrogen pyrolyzate, column temperature: 165°; (b), cracking products from air pyrolyzate, column temperature: 165°; (c), silylated cracking products from nitrogen pyrolyzate, column temperature: 135°; (d), silylated cracking products from air pyrolyzate, column temperature: 135°. The numbers of the peaks refer to the compounds mentioned in the text and in the tables.

* The numbers of the compounds refer to peak numbers in the gas chromatograms shown in Fig. 1.

TABLE I

GAS CHROMATOGRAPHIC DATA OF THE CRACKING PRODUCTS OF CBD AND OF SYNTHETIC REFERENCE COMPOUNDS, AND PROPOSED STRUCTURES

*Peak No.**	*Column temperature (°C)*	*Retention time (min)*	*Relative retention time ($RRT_{CBD} = 1.00$)*	*Number of TMS*** *groups*	*Structure proposed*	*R*
S2'''***	165	1.4	0.04			
S2''***	165	2.3	0.07			
S2	165	3.9	0.11			
1	165	0.6	0.02		?	
1'	135	--				
2	165	3.9	0.11			
2'	135	1.8		2 (180 + 144)		H TMS
3	165	3.9	0.11			
3'	135	5.9		1 (204 + 72)		H TMS
4	165	4.4	0.12			
4'	135	4.6		2 (194 + 144)		H TMS
5	165	5.2	0.14		?	
5'	135	--				
6	165	5.8	0.16			
6'	135	7.4		1 (218 + 72)		H TMS
7	165	6.9	0.20			
7'	135	9.5		2 (208 + 144)		H TMS
8	165	7.7	0.22			
8'	135	8.6		1 (246 + 72)		H TMS

* The peak numbers correspond to the chromatograms in Fig. 1.
** TMS = trimethylsilyl.
*** Synthetically derived from olivetol by CH_3I/Ag_2O.

TABLE II

PRINCIPAL IONS AND RELATIVE INTENSITIES IN THE ELECTRON IMPACT MASS SPECTRA AT 70 eV

Peak No.	*Principal ions and relative intensities*
S2‴	208 (19%), 166 (21%), 165 (13%), 153 (15%), 152 (100%), 151 (17%), 91 (18%), 77 (24%)
S2″	194 (27%), 152 (12%), 151 (11%), 139 (8%), 138 (100%), 137 (30%), 107 (6%), 91 (13%)
S2	180 (24%), 138 (14%), 137 (11%), 125 (11%), 124 (100%), 123 (32%), 95 (6%), 91 (8%), 77 (8%)
1	188 (16%), 132 (17%), 131 (100%), 115 (12%), 91 (9%)
1′	—
2	180 (22%), 138 (16%), 137 (10%), 125 (10%), 124 (100%), 123 (28%), 95 (9%), 91 (15%), 77 (11%)
2′	324 (18%), 309 (10%), 282 (24%), 281 (14%), 270 (15%), 269 (40%), 268 (100%), 253 (13%)
3	204 (35%), 162 (5%), 161 (18%), 149 (14%), 148 (100%), 147 (82%), 91 (32%)
3′	276 (30%), 261 (8%), 235 (7%), 222 (16%), 221 (100%), 220 (40%), 205 (18%)
4	194 (30%), 152 (15%), 151 (14%), 139 (14%), 138 (100%), 137 (42%), 123 (21%), 91 (16%)
4′	338 (25%), 296 (20%), 295 (10%), 283 (26%), 282 (100%), 268 (15%), 267 (18%)
5	230 (28%), 215 (34%), 187 (6%), 174 (16%), 173 (100%), 131 (22%), 130 (19%), 115 (10%)
5′	—
6	218 (26%), 162 (40%), 161 (100%), 147 (14%), 91 (18%)
6′	290 (45%), 247 (20%), 245 (18%), 234 (75%), 233 (100%), 219 (25%), 161 (30%), 115 (35%)
7	208 (16%), 166 (9%), 165 (11%), 153 (8%), 152 (100%), 151 (11%), 123 (18%), 91 (10%)
7′	352 (4%), 351 (3%), 338 (30%), 337 (100%), 208 (15%)
8	246 (11%), 232 (14%), 231 (100%), 189 (7%), 174 (30%), 91 (10%)
8′	318 (8%), 304 (30%), 303 (100%), 246 (15%), 184 (20%), 183 (35%)

of the synthetic products S2″ and S2‴, respectively. The spectra of S2″ and S2‴, however, lack the intense fragment ion at *m/e* 123 that is present in those of compounds 4 and 7. The latter fragment is probably a dihydroxytropylium ion.

Similar indications were obtained by gas chromatography. Compounds S2″ and S2‴ possessed the expected retention times compared with olivetol and predicted by Vree *et al.*[3]. Products 4 and 7, however, showed retention times considerably longer than those of S2″ and S2‴. Thus the mass spectra and retention times pointed to the presence of phenolic hydroxyl groups, and silylation experiments conclusively confirmed this structural feature.

The most abundant ions in the spectra of compounds 4 and 7 correspond to the loss of butene, which supports the presence of the intact *n*-pentyl side-chain in these cracking products. Completion of the structures of compounds 4 and 7 can now be achieved only by substitution of the remaining three positions of the aromatic ring. As the products were obtained by pyrolysis of CBD, it is most likely that compounds 4 and 7 are 2-methyl- and 2-ethylolivetol, respectively.

Compound 3 has a molecular ion at *m/e* 204 and is considered to have the same structure as the *m/e* 204 fragment ion in the spectrum of cannabielsoin[1] because of the striking resemblance between their fragmentation. In this respect, it is also noteworthy that the formation of cannabielsoin takes place in the "air" pyrolyzate. Fig. 1 shows clearly the larger amount of compound 3 present in the "air" pyrolyzate compared with the "nitrogen" pyrolyzate, and compound 3 can thus be considered to be formed primarily through pyrolytic degradation of cannabielsoin.

The presence of the *n*-pentyl side-chain in compound 3 was shown by the high intensity fragment at *m/e* $(M - 56)^+$ (loss of butene), and silylation proved the presence of only one (phenolic) hydroxyl group.

Comparison of the spectra of compounds 6 and 3 strongly suggests a common basic structure, differing by one methylene group. An unambiguous assignment of the position of the additional methylene group, based exclusively upon a mass spectrum, cannot be made, however.

The fragmentation pattern of compound 8 corresponds to a great extent with the mass spectra of several cannabinoids of molecular weight 314 in the region from *m/e* 246 downwards. Therefore, the structure of compound 8 is assumed to be identical with that of the fragment ion at *m/e* 246 in CBD. The formation of a mono-trimethylsilylated derivative (8') indicates the presence of only one (phenolic) hydroxyl group. Elimination of one of the *geminal* methyl groups yields the base peak at *m/e* 231. The structure and the formation of this ion has been discussed earlier[4] and it is worth mentioning that the higher intensity ratio, $I_{m/e\ 174}/I_{m/e\ 231}$, of compound 8 (*ca.* 30%) compared with this ratio (*ca.* 10%) for cannabinoids of molecular weight 314 can be expected on account of the higher internal energy content of the precursor ion of *m/e* 231. Further, the formation of compound 8 is an illustration of the parallel between the thermolytic and mass spectrometric fragmentation[5].

It seems necessary for additional spectrometric data to be collected in order that reliable structural proposals for products 1 and 5 can be made. However, preliminary assays for further purification proved to be extremely difficult and substantial further work is required.

Preliminary pharmacological assays (to be published elsewhere) on the volatile constituents of the CBD pyrolyzate revealed no significant effects. However, recent work by Burnstein *et al.*[6] on the inhibition of the biosynthesis of prostaglandins by naturally occurring cannabinoids included the assay on olivetol in the tests. It was found that olivetol showed high inhibitory activity in the assays considered. Our finding that olivetol represents a substantial amount of the volatile products formed by pyrolysis of CBD may therefore be of further pharmacological interest.

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REFERENCES

1 F. J. E. M. Küppers, R. J. J. Ch. Lousberg, C. A. L. Bercht, C. A. Salemink, J. K. Terlouw, W. Heerma and A. Lavèn, *Tetrahedron*, 29 (1973) 2797.
2 R. J. J. Ch. Lousberg and C. A. Salemink, *Pharm. Weekbl.*, 108 (1973) 1.
3 T. B. Vree, D. D. Breimer, C. A. M. van Ginneken and J. M. van Rossum, *J. Chromatogr.*, 74 (1972) 209.
4 J. K. Terlouw, W. Heerma, P. C. Burgers, G. Dijkstra, A. Boon, H. F. Kramer and C. A. Salemink, *Tetrahedron*, 30 (1974) 4243.
5 M. P. David and J. F. W. McOmie, *Tetrahedron Lett.*, 16 (1973) 1361.
6 S. Burstein, E. Levin and C. Varanelli, *Biochem. Pharmacol.*, 22 (1973) 2905.