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PHENOLIC PROTON TRANSFER TO THE 1,2 DOUBLE BOND IN THE MOLECULAR ION OF *trans*-1,2-TETRAHYDROCANNABINOL

T. B. VREE
Department of Pharmacology, University of Nijmegen. Geert, Grooteplein Noord 21, The Netherlands

and

N. M. M. NIBBERING*
Laboratory for Organic Chemistry, University of Amsterdam, Nieuwe Achtergracht 129, The Netherlands

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Abstract—It is known that the molecular ion of *trans*-1,6-tetrahydrocannabinol (1,6-THC) with *m/e* 314 decomposes *via* a retro Diels-Alder reaction to fragment *m/e* 246, which then loses a Me radical to give the ion *m/e* 231 (*cf* Scheme 1).[1]

A similar breakdown is found for *trans*-1,2-tetrahydrocannabinol (1,2-THC), suggesting a shift of the double bond from the 1,2 to the 1,6 position in its molecular ion.

Methylation of the phenolic OH group in *trans*-1,2-tetrahydrocannabinol however, shows that the phenolic proton transfer to the 1,2 double bond (*cf* Scheme 2) is much more important (~35–80%) than simple double bond migration (~20%; Scheme 3) in the formation of fragment *m/e* 231.

INTRODUCTION

In the cannabinoids Cannabidiol (CBD) and *trans*(3,4)-1,6-tetrahydrocannabinol (1,6-THC) the electron-impact induced retro Diels-Alder reaction of the cyclohexenyl ring is the main fragmentation process. This decomposition results in fragment *m/e* 246 and subsequent loss of a Me group gives fragment *m/e* 231. A retro Diels-Alder reaction in 1,2-, 2,3- and 3,4-THC cannot generate *m/e* 246.[1]

In the mass spectrum of *trans*(3,4)-1,2-tetrahydrocannabinol (1,2-THC; see for its structure Fig. 1) however, the fragment *m/e* 231 has a considerable relative intensity (~50%) at 20 eV. Budzikiewicz[2] suggested an isomerisation of 1,2-THC into 1,6-THC prior to a retro Diels-Alder reaction.

In the present paper we show by use of *ortho*- and *para*-1,2-THC and their methylated homologues that this isomerisation is of limited importance and that the fragmentation process is triggered by an intramolecular proton transfer from the phenol moiety to the 1,2 double bond.

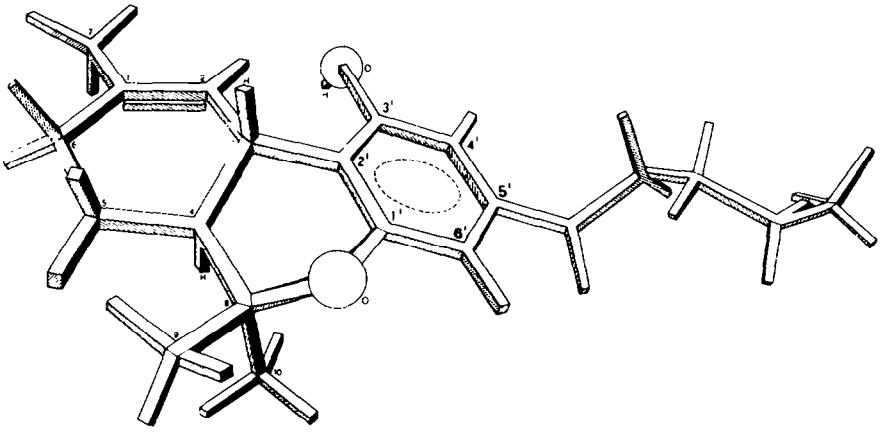


Fig 1. *trans*(3,4)-*para*-1,2-THC-C_5. C_5 refers to the number of carbon atoms of the side-chain; in *trans*(3,4)-*ortho*-1,2-THC-C_5 the side-chain and phenolic OH group are positionally interchanged.

RESULTS AND DISCUSSION

A retro Diels-Alder reaction of the molecular ion *m/e* 314 of *trans*-1,2-THC (*ortho* and *para*; for structure see Fig 1) should not result in the loss of C_5H_8 (*m/e* 246) and subsequent elimination of a Me radical (*m/e* 231), as will be seen by comparison with the retro Diels-Alder fragmentation of the isomeric *trans*-1,6-THC (*cf* Scheme 1 and Table 1).

Nevertheless, the intensity of fragment *m/e* 231 appears to be rather high in the mass spectra of *trans-ortho-* and *trans-para*-1,2-THC as can be deduced from Table 2.

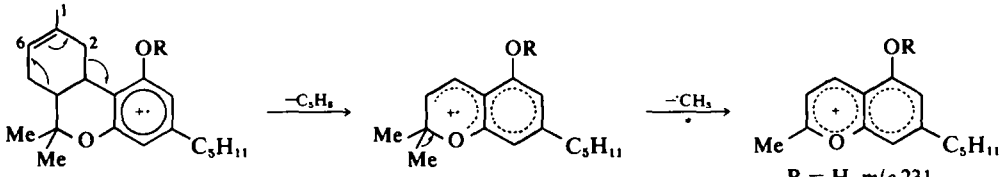
Furthermore, this fragment appears to be generated from *m/e* 246 (m* 246→231, calcd. 216·7, obsd. 217).

We have considered two possibilities for its formation:

(1) There is a shift of the double bond from the 1,2 position to the 1,6 position in the molecular ion of *trans*-1,2-THC, as proposed by Budzikiewicz[2] and well-known in unsaturated alicyclic ring systems.[3]

(2) The phenolic proton is transferred to the 1,2 double bond *via* the π-orbital of the aromatic ring, so that the alicyclic ring can be opened in a way, entailing the loss of C_5H_8. A recent D- and ^{18}O-labelling study of *m*-hydroxybenzylalcohol[4] has shown, that in its molecular ion the phenolic proton is transferred *via* the π-orbital to the benzylic hydroxyl group, suggesting that such a process is quite feasible in the present case.

When the phenol group is methylated a large drop in intensity of fragment *m/e* 245 (= 231 + 14) is observed, thus supporting the proton transfer in *trans-ortho-* and *trans-para*-1,2-THC (Table 2). It is important to note, that the most abundant frag-



SCHEME 1. Rationalization of the formation of *m/e* 231 (*m/e* 245) from the molecular ion of *trans-para*-1,6-THC, involving a retro Diels-Alder reaction and subsequent expulsion of a Me radical.

Table 1. Partial mass spectra of *trans-ortho-* and *trans-para*-1,6-THC and their methyl ethers at 20 eV*

Fragment	*m/e*	*ortho*-1,6	*ortho*-1,6-Me	*para*-1,6	*para*-1,6-Me
M	314 (328)	100	100	100	100
M-15	299 (313)	15	19	13	13
M-43	271 (285)	60	70	25	22
M-56	258 (272)	27	21	40	32
M-68	246 (260)	10	5	17	22
	243 (257)	2	1	5	5
	231 (245)	65	60	60	75

*See for the structure of *trans-para*-1,6-THC Scheme 1. In *trans-ortho*-1,6-THC the side-chain and phenolic OH group are interchanged.

Table 2. Partial mass spectra of *trans-ortho-* and *trans-para*-1,2-THC and their methyl ethers at 20 eV*

Fragment	*m/e*	*ortho*-1,2	*ortho*-1,2-Me	*para*-1,2	*para*-1,2-Me
M	314 (328)	100	100	100	100
M-15	299 (313)	55	77	63	62
M-43	271 (285)	32	42	30	17
M-56	258 (272)	25	31	27	26
M-68	246 (260)	10	3	5	2
	243 (257)	10	5	20	5
	231 (245)	72	15	40	16

*See for the structures Fig. 1.

ment ion *m/e* 231, generated from the isomers with the double bond in 1,6 position (*trans-ortho-* and *trans-para*-1,6-THC) *via* the retro Diels-Alder route given in Scheme 1, shifts to *m/e* 245 upon methylation of the phenol group but *without* a drop of intensity (*cf* Table 1).

These experiments therefore prove that the phenolic proton plays an essential role in the formation of *m/e* 231 from the molecular ions of *trans-ortho-* and *trans-para*-1,2-THC, supporting possibility 2 (*vide supra*). This has been rationalized in Scheme 2.

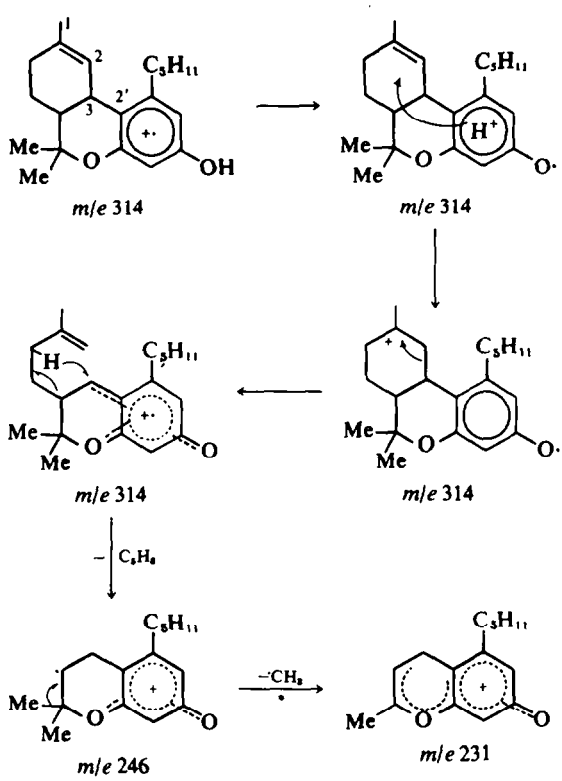
After transfer of the phenolic proton to the π-orbital of the aromatic ring it may shift from position 2' to position 2 (1-3 shift) due to the coplanarity of both π electron systems (Fig 1).

A similar shift can hardly occur or is perhaps even impossible in *cis*(3,4)-1,2-THC-C_5, where these π electron systems are practically perpendicular to each other (Fig 2); this indeed explains the very low relative intensity of *m/e* 231 (11% at 20 eV), observed in that case.[5]

However, methylation of the phenol group in *trans-ortho-* and *trans-para*-1,2-THC does not inhibit completely the formation of *m/e* 245 (Table 2), so that some isomerization of the 1,2 double bond must occur as suggested by Budzikiewicz[2] and visualized in Scheme 3 (possibility 1, *vide supra*).

From the intensities of the peaks *m/e* 231 and *m/e* 245 in the spectra of *trans-ortho*-1,2-THC and its methylated analogue (*cf* Table 2), it can be calculated, that ~80% of *m/e* 231 is generated by internal protonation, i.e. the phenolic proton transfer, whereas the contribution of the isomerization of the double bond is ~20%, assuming that the latter is not influenced by methylation.

This assumption appears to be reasonable, as no difference is found for the intensity of *m/e* 245, de-



SCHEME 2. Rationalization of the formation of *m/e* 231 from the molecular ion of *trans-ortho*-1,2-THC, induced by a phenolic proton transfer *via* the π-orbital of the aromatic ring to the 1,2-double bond.

rived from *trans-ortho-* and *trans-para*-1,2-THC methyl ether (~15%, *cf* Table 2).

After correction for the contribution of this isomerization (~15%) the relative intensities of

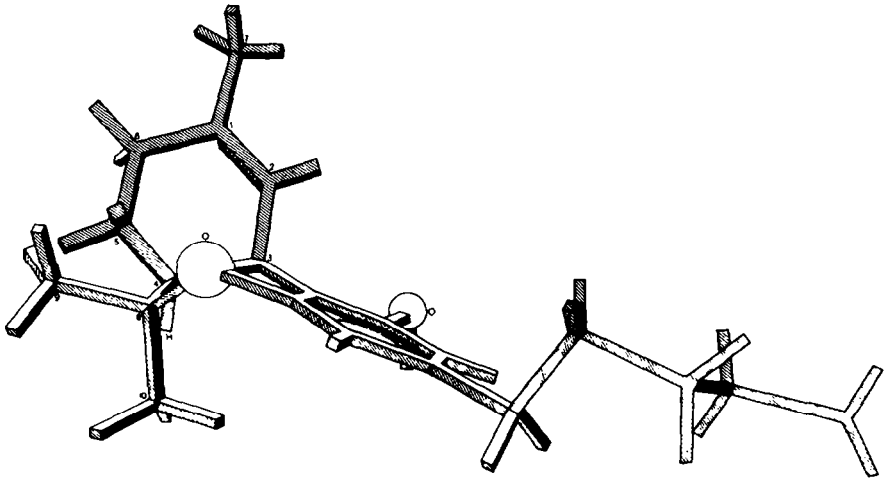
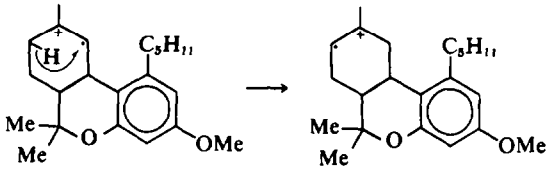


Fig 2. *cis*(3,4)-*para*-1,2-THC-C_5. C_5 refers to the number of carbon atoms of the side-chain; in *cis*(3,4)-*ortho*-1,2-THC-C_5 the side-chain and phenolic hydroxyl group are positionally interchanged.

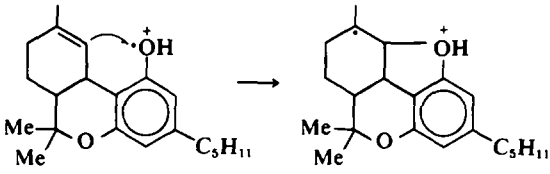


SCHEME 3. Rationalization of the isomerization of the molecular ion of *trans-ortho*-1,2-THC to that of *trans-ortho*-1,6-THC.

m/e 231 from *trans-ortho-* and *trans-para*-1,2-THC appear to be 57% and 24%, resp. (*cf* Table 2).

Such a significant difference is not observed for the relative intensities of *m/e* 231 from *trans-ortho-* and *trans-para*-1,6-THC (*cf* Table 1). Thus, it seems that the internal protonation in *trans-para*-1,2-THC is reduced, presumably due to the position of the phenol group, as methylation does not influence the isomerization of the 1,2 double bond (*vide supra*).

A possible explanation is, that the phenolic O atom in *trans-para*-1,2-THC attacks the 1,2 double bond, before or after phenolic proton transfer to the π-orbital of the aromatic ring, generating an ion with four fused rings (Scheme 4; note the difference with Scheme 3, where isomerization of the 1,2 double bond is rationalized by assumption of charge-localization in the alicyclic ring).



SCHEME 4. Bond formation in the molecular ion of *trans-para*-1,2-THC.

This bond formation destroys the 1,2 double bond, so that the phenolic proton cannot be transferred anymore to the alicyclic ring, and this is of course impossible in the molecular ion of *trans-ortho*-1,2-THC. In the formation of *m/e* 231 from *trans-para*-1,2-THC we may therefore distinguish three factors, i.e. ~35% internal protonation, ~20% isomerization of the 1,2 double bond and ~45% bond formation. It is interesting to note that the discussed internal protonation is also blocked when the phenolic OH group is converted to an ether function with trimethylchlorosilane, trichloroacetylchloride or heptafluoroburytic anhydride.

Additional evidence for the internal protonation as given in Scheme 2 can in principle be obtained from specific deuterium labelling in the phenolic hydroxyl group. Unfortunately, a complicated mixture of d_0, d_1, d_2, d_3 and even d_4 molecules was obtained upon deuteration in the GLC column as well as in the ion source by exchange with D_2O (Experimental).

EXPERIMENTAL

An L.K.B. 9000 gas chromatograph-mass spectrometer combination was used in this study. All compounds examined were first separated at a column of 3% OV 17 at 180° and subsequently subjected to mass spectrometric analysis. Further conditions were: separator temperature 240°; ion source 290°; emission current 4 A; trap current 60 μ A; accelerating voltage 3·5 kV.

During the elution of a compound from the column, monitored by the total ion current at 20 eV, mass spectra were taken at 20 eV in order to have predominantly the four main routes of fragmentation (*cf* Tables 1 and 2).

In the deuterium exchange experiments two alternative procedures were performed:

(1) D_2O was passed (4 times) through the GLC column prior to injection of the THC mixture.

(2) D_2O was introduced (4 times) into the ion source by means of the heated inlet system, followed by admittance of the THC mixture *via* the (H_2O treated) GLC column.

Samples. A sample of synthetic THC appeared to contain 4 compounds, which could be separated by GLC using a column of 3% OV 17.[6]

Their mass spectra were very similar: they all showed a molecular ion peak at *m/e* 314 and further the peaks at *m/e* 299, 271, 258, 246, 243 and 231. Comparison with spectra, reported in the literature[1,2] revealed that two compounds did have the double bond in the 1,6 position. Saturation of the 4 compounds with H_2/PtO_2 at 1 atm resulted in two compounds.[6] Their mass spectra showed a molecular ion peak at *m/e* 316, establishing that they were hexahydrocannabinols. One of these mass spectra was identical with that, published by Budzikiewicz.[2]

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