79. ^{13}C-NMR. Spectra of Natural and Semi-synthetic Cannabinoids

by **Michael Binder, Ingo Franke** and **Burkhard Schmidt**
Institut für Physiologische Chemie

and **Wolfgang Dietrich**
Analytische Chemie, SC-Abteilung, Ruhr-Universität Bochum, Postfach 102148, D-4630 Bochum 1

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Summary

The ^{13}C-NMR. spectra of one natural and ten semi-synthetic cannabinoids were analyzed in detail. Assignements of the signals are based on their chemical shifts, splitting patterns in ^{1}H-off-resonance decoupling experiments and comparison with ^{13}C-NMR. data of related cannabinoids. With some compounds final assignements were made by selective ^{1}H-decoupling experiments and incremental calculations.

Introduction. - ^{13}C-NMR. Spectroscopy is now a powerful technique for identification and structure elucidation of natural products. Since our work involves the syntheses of cannabinoids and cannabinoid model compounds as tools for the elucidation of the molecular mechanism of action of the psychotropic constituents of the drugs hashish and marihuana, derived from the indian hemp (*Cannabis sativa* L.), namely (6a*R*, 10a*R*)-Δ^9-tetrahydrocannabinol (=Δ^9-THC) and (6a*R*, 10a*R*)-Δ^8-tetrahydrocannabinol (=Δ^8-THC, **1**), we became interested in the ^{13}C-NMR. spectra of natural cannabinoids and their semi-synthetic derivatives.

So far two detailed investigations on ^{13}C-NMR. spectra of cannabinoids and related compounds have been published by *Wenkert et al.* [1] and *Archer et al.* [2]. These studies were mainly concerned with the analysis of Δ^9-THC, Δ^8-THC **1**, their synthetic isomers (6a*S*, 10a*R*)-Δ^8-THC, $\Delta^{6a(10a)}$-THC, the parent phenol of **9** and several isomers of "THC" in which the positions of the phenolic hydroxyl group and the pentyl side chain are reversed.

We now report the analysis of the ^{13}C-NMR. spectra of the compounds **1** to **11** (all 6a*R*, 10a*R*).

Of these eleven compounds only the data of Δ^8-THC **1** have been published [2] and, for comparison, they are included in the *Table*. The assignements of the ^{13}C-NMR. signals are based on general ^{13}C-NMR. shift theory [3] [4], ^{1}H-off-resonance decoupling, selective frequency ^{1}H-off-resonance decoupling experiments, incremental calculations and comparison to the data of *Wenkert et al.* [1] and *Archer et al.* [2].

Since our synthetic work will be reported elsewhere the *Scheme* summarizes the structural formulas of the compounds and the routes by which they were obtained.

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Table. *^{13}C-shifts* (in ppm downfield from $Si(CH_3)_4$) *and splitting pattern of cannabinoid compounds*

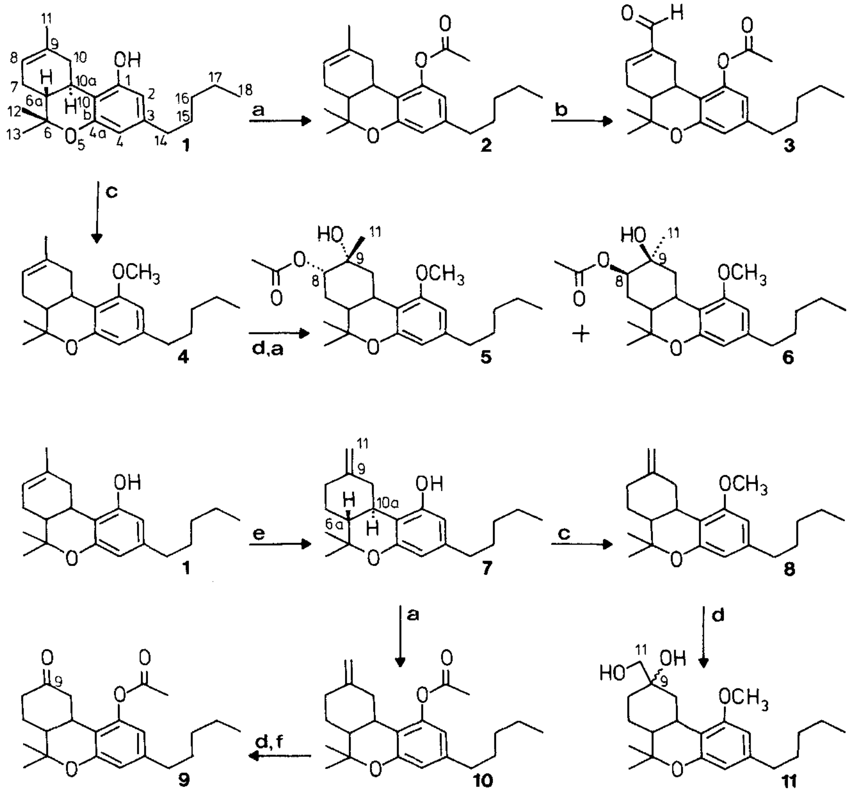
C	**1**[a]	**1**[b]	**2**	**3**	**4**	**5** ($CDCl_3$)	**5** (C_6D_6)	**6** ($CDCl_3$)	**6** (C_6D_6)	**7**	**8**	**9**	**10**	**11**
1	154.6*s*	155.0*s*	149.7*s*	149.7*s*	158.9*s*	158.8*s*	159.3*s*	158.7*s*	159.3*s*	154.7*s*	158.9*s*	149.2*s*	149.6*s*	158.5*s*
2	107.6*d*	108.0*d*	114.2*d*	114.7*d*	102.9*d*	103.1*d*	103.4*d*	103.2*d*	103.3*d*	107.8*d*	103.1*d*	115.3*d*	115.3*d*	103.1*d*
3	142.4*s*	142.7*s*	142.6*s*	141.4*s*	142.3*s*	142.8*s*	142.7*s*	143.0*s*	142.9*s*	142.7*s*	142.6*s*	143.5*s*	142.9*s*	142.8*s*
4	109.8*d*	110.1*d*	115.2*d*	115.3*d*	110.2*d*	110.2*d*	111.1*d*	110.2*d*	111.1*d*	109.8*d*	110.1*d*	114.5*d*	114.2*d*	110.3*d*
4a	154.4*s*	154.7*s*	154.5*s*	154.2*s*	154.3*s*	154.5*s*	155.5*s*	154.4*s*	155.3*s*	154.7*s*	154.6*s*	154.2*s*	154.6*s*	154.4*s*
6	76.3*s*	77.0*s*	76.7*s*	76.6*s*	76.2*s*	76.3*s*	76.1*s*	76.2*s*	76.0*s*	77.0*s*	76.7*s*	76.9*s*	77.0*s*	76.6*s*
6a	44.8*d*	45.0*d*	44.6*d*	44.6*d*	45.1*d*	47.1*d*	47.4*d*	42.6*d*	43.1*d*	48.7*d*	48.9*d*	47.4*d*	48.8*d*	49.2*d*
7	27.8*t*	28.0*t*	27.7*t*	27.0*t*	27.9*t*	29.0*t*	29.3*t*	29.8*t*	30.0*t*	28.8*t*	28.9*t*	26.6*t*	28.7*t*	25.3*t*
8	119.1*d*	119.4*d*	119.6*d*	148.7*d*	119.2*d*	78.0*d*	78.1*d*	76.4*d*	76.3*d*	34.8*t*	34.9*t*	40.5*t*	34.5*t*	35.0*t*
9	134.5*s*	134.8*s*	133.7*s*	143.3*s*	134.8*s*	71.2*s*	71.0*s*	71.3*s*	71.2*s*	148.2*s*	148.7*s*	209.5*s*	147.9*s*	73.1*s*
10	35.9*t*	36.1*t*	36.1*t*	29.0*t*	36.2*t*	41.2*t*[c]	41.5*t*	39.5*t*[c]	40.1*t*	38.8*t*	39.1*t*[c]	45.8*t*	39.5*t*	39.2*t*
10a	31.5*d*	31.7*d*	31.8*d*	31.5*d*	31.8*d*	30.1*d*	30.5*d*	32.5*d*	32.9*d*	36.5*d*	36.8*d*	34.8*d*	36.9*d*	32.3*d*
10b	110.4*s*	110.8*s*	115.9*s*	114.7*s*	111.8*s*	110.1*s*	110.9*s*	110.0*s*	110.7*s*	109.8*s*	111.0*s*	113.9*s*	115.3*s*	110.3*s*
11	23.4*qa*	23.6*qa*	23.4*qa*	193.3*d*	23.5*qa*	27.9*qa*	27.7*qa*[c]	24.9*qa*	25.3*qa*[c]	108.8*t*	108.6*t*		108.7*t*	66.7*t*
12	27.5*qa*	27.6*qa*	27.4*qa*	27.4*qa*	27.5*qa*	27.7*qa*	27.7*qa*[c]	27.8*qa*	27.8*qa*[c]	27.6*qa*	27.8*qa*	27.6*qa*	27.5*qa*	27.8*qa*
13	18.4*qa*	18.6*qa*	18.4*qa*	18.4*qa*	18.4*qa*	19.2*qa*	19.1*qa*	18.8*qa*	18.7*qa*	18.9*qa*	18.9*qa*	18.8*qa*	19.0*qa*	18.9*qa*
14	35.4*t*	35.5*t*	35.3*t*	35.4*t*	36.0*t*	36.1*t*	36.4*t*	36.1*t*	36.4*t*	35.3*t*	35.9*t*	35.2*t*	35.3*t*	36.0*t*
15	30.5*t*	30.7*t*	30.4*t*	30.4*t*	30.7*t*	30.8*t*	31.3*t*	30.8*t*	31.3*t*	30.4*t*	30.7*t*	30.4*t*	30.4*t*	30.8*t*
16	31.5*t*	31.7*t*	31.4*t*	31.0*t*	31.6*t*	31.7*t*	31.8*t*	31.7*t*	31.8*t*	31.5*t*	31.6*t*	31.4*t*	31.5*t*	31.7*t*
17	22.5*t*	22.6*t*	22.4*t*	22.5*t*	22.5*t*	22.6*t*	22.9*t*	22.6*t*	22.9*t*	22.4*t*	22.5*t*	22.4*t*	22.4*t*	22.6*t*
18	14.0*qa*	14.1*qa*	13.9*qa*	14.0*qa*	14.0*qa*	14.1*qa*	14.2*qa*	14.1*qa*	14.2*qa*	13.9*qa*	14.0*qa*	13.9*qa*	13.9*qa*	14.1*qa*
$\mathrm{O}\mathit{C}\mathrm{H}_3$					54.9*qa*	55.2*qa*	54.9*qa*	55.2*qa*	54.8*qa*		55.1*qa*			55.2*qa*
$\mathrm{O}\mathit{C}\mathrm{OCH}_3$			168.7*s*	169.2*s*		170.3*s*	169.3*s*	170.7*s*	170.0*s*			168.9*s*	168.7*s*	
$\mathrm{OCO}\mathit{C}\mathrm{H}_3$			21.1*qa*	21.3*qa*		21.3*qa*	20.6*qa*	21.3*qa*	20.6*qa*			21.1*qa*	21.1*qa*	

[a] Values of [2].

[b] Values of this work.

[c] Signal assignement confirmed by selective decoupling.

Scheme



a	$(CH_3CO)_2O$/pyridine	d	OsO_4/pyridine/$NaHSO_3$
b	SeO_2	e	h·v
c	CH_3I/K_2CO_3/DMF	f	H_5IO_6

Analysis of the ^{13}C-NMR. spectra. – *Experimental.* The measurements were performed at 62.9 MHz on a *Bruker* WM-250 NMR. spectrometer by use of conventional proton noise and off-resonance decoupling. In some special cases selective decoupling technique was applied to ensure assignements. All spectra were recorded in $CDCl_3$ solution at 300 K (concentrations: 0.25 to 0.50 mol/l) with more than 240 ppm sweep width. The spectra of compounds **5** and **6** were recorded both in $CDCl_3$ and C_6D_6.

Discussion. Within 0.4 ppm the δ values of all C-atoms of Δ^8-THC (**1**) are in good agreement with those reported [2].

The spectrum of Δ^8-THC acetate (**2**) shows no major changes in the chemical shifts of the isoprenoid part of the molecule and of the pentyl side chain. As can be seen from the *Table* the chemical shifts of the side chain C-atoms generally remain unaffected throughout the whole series of compounds thus confirming the original assignements of these signals by *Archer et al.* [2] based on the study of deuteriated 1-phenylpentanes. C(4a) is deshielded by 5.1 ppm (calc. 6.2) as is C(1) (6.2; calc.

6.2 ppm). The signal of C(10b) is shifted upfield by 5.3 ppm (calc. 3.9) and C(3) shows a downfield shift of 5.1 ppm (calc. 5.3).

In comparison to compound **2** the spectrum of the aldehyde **3** displays major differences in the isoprenoid region. C(11) gives rise to a doublet at 193.3 ppm, C(8) is strongly deshielded (148.7 ppm) and C(9) leads to a singlet at 143.3 ppm, while C(10) is shielded by 7.1 ppm ($\delta = 29.0$ ppm) owing probably to *van der Waals* contact of the protons at C(10) and the electrons of the aldehyde O-atom.

Δ^8-THC methyl ether **4** reveals the expected shifts of the aromatic ring C-atoms. Compared to the parent compound **1**, C(1) is deshielded by 3.9 ppm (calc. 4.4) and C(2) is shielded by 5.1 ppm (calc. 2.4) while the other signals remain unaffected.

$\Delta^{9(11)}$-THC (**7**) is isoelectronic to the phenol parent of **9** that has been studied by *Archer et al.* [2] and the comparison to the published data was helpful in assigning the ^{13}C signals of **7**. By decoupling, C(9) gives rise to a singlet at 148.2 ppm, C(11) to a triplet at 108.8 ppm. C(10), coming close to the plane of the aromatic ring leads to a triplet at 38.8 ppm, and the signal of the other allylic C-atom, C(8), appears as a triplet at 34.8 ppm. This assignement was confirmed by selective decoupling at the position of H_α-C(10) (3.63 ppm; ^1H-NMR. spectrum of **8** in $CDCl_3$) of $\Delta^{9(11)}$-THC methyl ether (**8**) which makes the triplet at 39.1 ppm collapse to a doublet but leaves the triplet of C(8) at 34.9 ppm unchanged. Compared to Δ^8-THC (**1**) C(10a) and C(6a) in **7** are deshielded by 4.8 and 3.7 ppm respectively. No significant changes in the positions of the other signals were observed.

In going from $\Delta^{9(11)}$-THC (**7**) to its methyl ether (**8**) or acetate (**10**) the same changes in the chemical shifts of the aromatic C-atoms were evident as in the Δ^8-THC series **1**, **4** and **2**.

Both diol monoacetates **5** and **6** were obtained from Δ^8-THC methyl ether (**4**) by reaction with OsO_4 followed by acetylation of the hydroxyl group at C(8). The configurations at C(9) and C(8) were established unequivocally from the ^1H-NMR. spectra of the compounds. Since in both compounds the isoprenoid ring is fixed in a rigid chair conformation, the splitting pattern of the signal of H–C(8) was used to differentiate between **5** and **6**. The proton at C(8) of 8α-acetoxy-9α-hydroxy-hexahydrocannabinol methyl ether (**5**) gives rise to a doublet of doublets centered at 4.7 ppm due to a large *trans*-diaxial coupling to H_α–C(7) ($J = 11$ Hz) and a synclinar coupling of 5 Hz to H_β–C(7). In 8β-acetoxy-9β-hydroxy-hexahydrocannabinol methyl ether (**6**) the signal of H–C(8) appears as a triplet at 4.9 ppm due to equal synclinar couplings of 3 Hz to the protons at C(7). The ^1H-NMR. spectra of **5** and **6** yield further information that was used in selective decoupling experiments to confirm assignements of ^{13}C-signals. Selective decoupling at the positions of H_α–C(10), 3.21 ppm in **5** and 3.07 ppm in **6** ($CDCl_3$) led to the identification of the C(10) signal in both compounds and decoupling of the methyl protons at C(12), 1.30 ppm in **5** and 1.26 ppm in **6** (C_6D_6) allowed differentiation between the ^{13}C signals of C(12) and C(11).

The ^{13}C-NMR. spectra of **5** and **6** revealed no major changes in the chemical shifts of the aromatic ring and side chain C-atoms compared to Δ^8-THC methyl ether (**4**). By decoupling, C(9) in compound **5** gives rise to a singlet at 71.2, this signal being at 71.3 ppm in **6**. The signal of C(10) appears as a triplet at 41.2 ppm in **5** and 39.5 ppm in **6** as confirmed by selective decoupling of Hα–C(10). The doublet of C(6a) in the spectrum of **6** (42.2 ppm) is shielded by the axial acetoxy group at C(8) compared to **5** (47.1 ppm). Since in $CDCl_3$ solution the signals of C(8) and C(6) could not be differentiated owing to superposition on the solvent signal both spectra were recorded in C_6D_6. C(8) gave rise to a doublet at 78.1 ppm in **5** and 76.3 ppm in **6** and C(6) led to singlets at 76.1 in **5** and 76.0 ppm in **6**. Selective decoupling of H–C(12) resulted in the collapse of the quartets at 27.7 ppm in **5** and 27.8 ppm in **6**. In **6** the signal at 25.3 ppm retained its splitting pattern and consequently must arise from C(11). The shielding of C(11) by 2.4 ppm in **6** compared to **5** is in agreement with the change in the configuration of this C-atom from equatorial to axial and is complemented by simultaneous deshielding of the protons at C(11) in the ^1H-NMR. spectra of **5** and **6** where the respective signals appear at 1.20 and 1.42 ppm.

The assignement of the signals of diol **11** is based on their off-resonance decoupling splitting patterns given in the *Table* and requires no further discussion. Since only one of the epimeric diols was obtained, no assignement of the configuration at C(9) can be made.

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