139. ^{13}C-NMR Spectra of Cannabinoids

Part 2[1])

Side-Chain Substituted Tetrahydrocannabinols and Synthetic Intermediates

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Summary

The ^{13}C-NMR spectra of eight semi-synthetic side-chain substituted cannabinoids and of eight synthetic intermediates were analyzed in detail. Assignments of the signals are based on their chemical shifts, splitting patterns in ^{1}H-off-resonance decoupling experiments, incremental calculations, and model considerations.

Introduction. – We have reported the analysis of the ^{13}C-NMR spectra of several semi-synthetic cannabinoids substituted in the dibenzopyrane moiety [1]. These compounds were grouped around $\Delta^{9(11)}$-tetrahydrocannabinol (= $\Delta^{9(11)}$-THC), a cannabinoid model compound devoid of psychotropic activity in the rhesus monkey [2]. The major objective of our investigations being the elucidation of the molecular mechanism of action of the psychotropically active cannabinoid Δ^{9}-THC, $\Delta^{9(11)}$-THC was employed to differentiate non-specific, lipophilicity-mediated effects which Δ^{9}- and $\Delta^{9(11)}$-THC share from specific, receptor-mediated effects which should be unique to Δ^{9}-THC [3]. The next step was the synthesis of 17,18-didehydro-Δ^{8}-THC **8** *via* 18-bromo-Δ^{8}-THC **7** as precursor for [17,18-$^{3}H_2$]-Δ^{8}-THC in order to conduct binding studies to the putative THC receptor. As tools for the characterization of this receptor, cannabinoid affinity gels were developed employing 17-methyl-Δ^{8}-THC-18-oic acid **2** as affinity ligand, and the synthesis [4] and some biological properties [5] of the corresponding *N*-ethyl amide **6** which represents the closest approximation to the final affinity unit were reported. The *Scheme* summarizes the structural formulas of the intermediates and cannabinoids involved in the syntheses of 17,18-didehydro-Δ^{8}-THC **8** and the amides **5** and **6** (*cf.* [4]) for which we now report also the ^{13}C-NMR data.

The assignments of the ^{13}C-NMR signals are based on general ^{13}C-NMR shift theory [6], ^{1}H-off-resonance decoupling, and incremental calculations [7].

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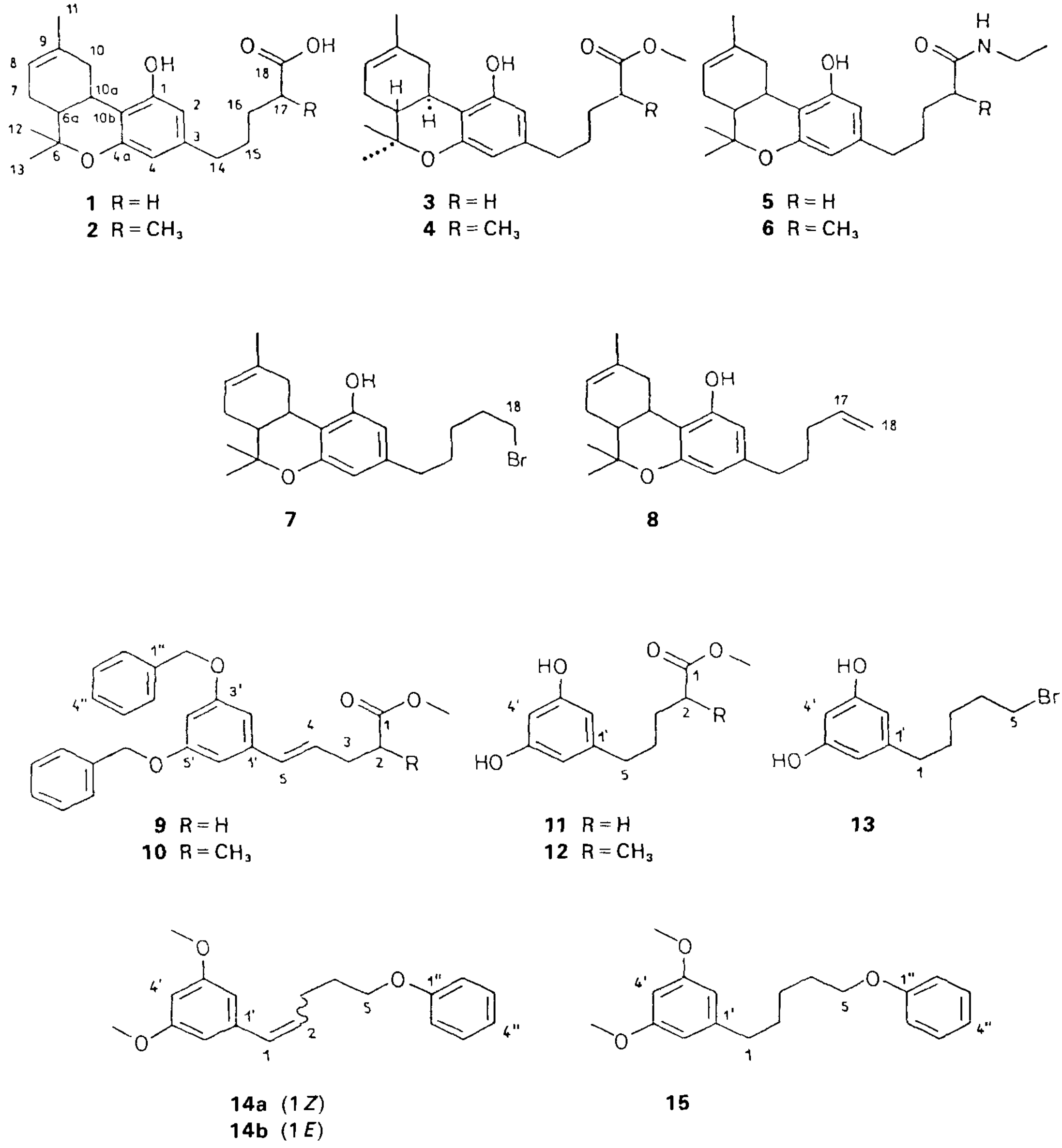
[1]) Part 1: see [1].

[2]) Deceased on February 15th, 1984.

Scheme



1 R = H
2 R = CH_3

3 R = H
4 R = CH_3

5 R = H
6 R = CH_3

7

8

9 R = H
10 R = CH_3

11 R = H
12 R = CH_3

13

14a (1*Z*)
14b (1*E*)

15

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 proton-noise and off-resonance decoupling. All spectra were recorded in $CDCl_3$ solution at 300 K with more than 240 ppm sweep width.

Table 1. *^{13}C-NMR Shifts (in ppm Downfield from Me_4Si) and Splitting Pattern of Cannabinoid Compounds.* Predicted shifts in parentheses.

C	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	155.0 *s*	155.9	155.2	155.1	155.9	155.8	154.9	154.8
2	107.7 *d*	107.6	107.6	107.6	107.8	107.8	107.7	107.6
3	141.6 *s*	141.6	141.5	141.7	141.4	141.6	142.1	142.2
4	109.9 *d*	109.8	109.6	109.9	109.0	109.4	110.1	110.1
4a	154.8 *s*	154.8	154.7	154.9	154.6	154.8	154.9	154.7
6	76.7 *s*	76.6	76.6	76.6	76.5	76.6	76.7	76.7
6a	44.9 *d*	44.9	44.8	44.9	45.0	45.1	44.9	44.8
7	27.9 *t*	27.9	27.8	27.9	27.9	28.0	27.8	27.9
8	119.3 *d*	119.3	119.2	119.3	119.1	119.2	119.3	119.3
9	134.7 *s*	134.7	134.7	134.7	134.9	135.0	134.7	134.7
10	36.0 *t*	36.0	35.8	36.1	36.4	36.1	36.1	36.0
10a	31.6 *d*	31.6	31.5	31.6	31.6	31.8	31.6	31.5
10b	110.9 *s*	110.9	110.8	110.8	110.9	110.9	110.8	110.6
11	23.4 *q*	23.3	23.4	23.3	23.3	23.4	23.4	23.5
12	27.4 *q*	27.5	27.5	27.5	27.5	27.6	27.5	27.5
13	18.4 *q*	18.4	18.4	18.4	18.4	18.5	18.5	18.5
14	34.9 *t* (35.0)	35.1 *t* (35.5)	34.9 *t* (35.0)	35.2 *t* (35.5)	35.0 *t* (34.6)	35.4 *t* (35.1)	35.1 *t* (35.5)	34.8 *t* (35.3)
15	30.1 *t* (28.3)	28.2 *t* (27.9)	30.2 *t* (28.3)	28.4 *t* (27.9)	30.2 *t* (27.9)	28.5 *t* (27.5)	29.9 *t* (30.0)	30.0 *t* (31.1)
16	24.3 *t* (24.2)	33.1 *t* (31.2)	24.5 *t* (24.2)	33.4 *t* (31.2)	25.3 *t* (24.8)	33.9 *t* (31.8)	27.8 *t* (27.9)	33.3 *t* (32.2)
17	33.9 *t* (33.3)	39.1 *d* (39.0)	35.9 *t* (35.8)	39.3 *d* (41.5)	35.9 *t* (35.2)	41.5 *d* (40.9)	33.5 *t* (33.6)	138.6 *d* (138.1)
18	179.8 *s*	182.1 *s*	174.5 *s*	177.4 *s*	173.7 *s*	176.9 *s*	32.7 *t* (32.4)	114.6 *t* (114.4)
CH_3–C(17)		16.8 *q* (15.0)		17.0 *q*		17.9 *q* (15.0)		
CH_3–O			51.5 *q*	51.4 *q*				
$\mathrm{N}\mathit{C}\mathrm{H_2CH_3}$					34.4 *t*	34.4 *t*		
$\mathrm{NCH_2}\mathit{C}\mathrm{H_3}$					14.6 *q*	14.8 *q*		

Table 2. *^{13}C-NMR Shifts (in ppm Downfield from Me_4Si) and Splitting Pattern of Synthetic Intermediates.* Predicted shifts in parentheses.

C	**9**	**10**	**11**	**12**	**13**	**14a**	**14b**	**15**
1	173.0 *s*	176.2 *s*	175.6 *s*	178.6 *s*	35.5 *t* (35.5)	132.0 *d*	130.5 *d*	36.1 *t* (35.5)
2	33.9 *t* (33.9)	39.6 *d* (41.7)	35.1 *t* (36.0)	39.4 *d* (41.5)	29.9 *t* (30.0)	129.6 *d*	130.1 *d*	28.8 *t* (30.7)
3	23.9 *t* (25.3)	32.3 *t* (34.4)	24.3 *t* (24.1)	33.0 *t* (31.2)	27.7 *t* (27.9)	25.1 *t* (28.7)	28.7 *t* (28.7)	25.5 *t* (25.5)
4	129.9 *d*	129.6 *d*	30.1 *t* (29.8)	28.2 *t* (28.6)	33.7 *t* (33.6)	29.4 *t* (31.0)	29.2 *t* (31.0)	30.8 *t* (32.7)
5	130.7 *d*	130.7 *d*	33.8 *t* (35.0)	35.3 *t* (35.5)	32.6 *t* (32.4)	67.0 *t* (67.1)	66.8 *t* (67.1)	67.3 *t* (62.5)
1′	139.0 *s*a)(138.1)	139.2 *s*a) (138.1)	145.0 *s* (145.0)	144.9 *s* (145.0)	145.7 *s* (145.0)	139.2 *s* (137.9)	139.6 *s* (137.9)	144.7 *s* (144.5)
2′,6′	108.0 *d* (104.7)	105.1 *d* (104.7)	108.0 *d* (108.0)	107.9 *d* (108.0)	108.3 *d* (108.0)	106.7 *d* (103.9)	103.9 *d* (103.9)	106.5 *d* (105.5)
3′,5′	159.7 *s* (157.0)	159.8 *s* (157.0)	156.6 *s* (156.0)	156.7 *s* (156.0)	156.4 *s* (156.0)	160.4 *s* (157.8)	160.7 *s* (157.8)	160.4 *s* (159.4)
4′	100.8 *d* (95.2)	101.0 *d* (95.2)	105.5 *d* (100.2)	100.6 *d* (100.2)	100.5 *d* (100.2)	98.7 *d* (95.6)	99.2 *d* (95.6)	97.5 *d* (96.3)
1″	136.9 *s*a)(141.5)	137.0 *s*a) (141.5)				158.9 *s* (158.7)	158.9 *s* (158.7)	158.8 *s* (158.7)
2″,6″	127.2 *d* (127.1)	127.4 *d* (127.1)				114.4 *d* (113.8)	114.4 *d* (113.8)	114.2 *d* (113.8)
3″,5″	128.4 *d* (128.5)	128.5 *d* (128.5)				129.3 *d* (129.4)	129.3 *d* (129.4)	129.5 *d* (129.4)
4″	127.7 *d* (127.3)	127.8 *d* (127.3)				120.4 *d* (120.4)	120.4 *d* (120.4)	120.1 *d* (120.4)
CH_3–C(2)		16.5 *q* (15.3)		16.7 *q* (16.1)				
OCH_3	51.3 *q*	51.4 *q*	51.9 *q*	51.8 *q*		55.0 *q*	55.0 *q*	
O$CH_2C_6H_5$	69.9 *t* (69.0)	70.1 *t* (69.0)						

a) Assignments based on integral area of the resp. signals.

Discussion. The ^{13}C-NMR data of compounds **1–8** (all with (6a*R*,10a*R*)-configuration; **2**, **4**, and **6**: 17*RS*) are summarized in *Table 1*. All eight molecules share an identical tetrahydrodibenzopyrane moiety, and the signals of the respective ^{13}C-atoms appear within ± 0.5 ppm at the same position as those of the parent compound Δ^8-THC [1]. The chemical shifts of the side chain C-atoms (C(14) to C(18)) were estimated using the *Grant-Paul* relation [6] considering compounds **1**, **3**, and **5** as butane, **2**, **4**, **6**, and **7** as pentane, and **8** as propane derivatives.

A set of increments (Z) for the complete tetrahydrodibenzopyrane moiety was obtained by comparing the ^{13}C-NMR chemical shifts of pentane and Δ^8-THC: $Z_\alpha = 22.0$, $Z_\beta = 8.3$, $Z_\gamma = -2.6$, and $Z_\delta = 0.2$ ppm. Employing the reported Z-values for $-COOH$, $-COOR$, $-CONR_2$, $-HC{=}CH_2$, $-Br$, and the necessary steric corrections, the predicted δ-values (see *Table 1*) suffice to assign the observed signals to the corresponding C-atoms. All assignments are confirmed by the off-resonance splitting patterns of the resp. signals.

The ^{13}C-NMR data of the synthetic intermediates **9–15** are given in *Table 2*. The observed chemical shifts of compounds **11–13** and **15** agree well with the values obtained by incremental calculations. For the spectra of the olefinic compounds **9**, **10**, **14a**, and **14b**, the calculations prove sufficient to locate all signals arising from aliphatic and aromatic C-atoms, but fail with the olefinic C-atoms, the predicted values differing as much as 6 ppm from the observed ones. Since of all four compounds the ^{1}H-NMR signals of the respective olefinic protons are less than 0.5 ppm apart (*cf.* [4]), selective frequency decoupling could not be employed. Therefore, the assignments for the olefinic C-atoms are based on theoretical considerations: according to the ^{1}H-NMR spectra [4], the olefinic double bond of both compounds **9** and **10** is in *trans*-configuration. Except for the CH_3-group at C(2), **9** and **10** are identical. Thus, the ^{13}C-NMR chemical shift increment induced by the introduction of this CH_3-group when going from **9** and **10** should influence the position of the signal of the γ-carbon atom C(4) but not the one arising from the δ-carbon atom C(5). Therefore, the signals at 130.7 ppm in **9** and at 130.7 ppm in **10** are assigned to C(5) and the signals at 129.9 ppm (**9**) and 129.6 ppm (**10**) to C(4). For compound **14**, spectra of both the *cis*-(**14a**) and *trans*-form (**14b**) were recorded. According to the *Dreiding* models of **14a** and **14b**, C(2) of **14a** is twisted out of the plane of the aromatic ring by at least 50°. Compared to **14b**, this places C(2) and especially C(3) of **14a** into the aromatic shielding cone, shifting the signals of these C-atoms 0.5 and 3.6 ppm upfield. Since conjugation is interrupted, C(1) and C(2')/C(6') are deshielded by 1.5 and 2.8 ppm, respectively.

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