Monatshefte für Chemie 115, 597—603 (1984)

Monatshefte für Chemie
Chemical Monthly

2 D-NMR of Natural Products, Part V[1] Structure Elucidation and Complete ^{1}H- and ^{13}C-Assignment of Resin Acid Derivatives

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(Received 5 October 1983. Accepted 27 October 1983)

Application of 2 D-NMR-techniques including heteronuclear 2 D-J-resolved spectroscopy and ^{1}H—^{13}C-2 D-shift correlation is used to assign the ^{1}H- and ^{13}C-resonances of resin acid derivatives.

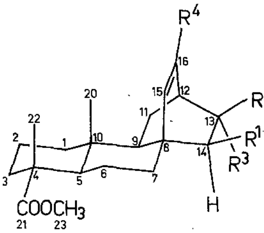
(Keywords: 2 D-NMR; 2 D-J-Resolved NMR spectroscopy; ^{1}H—^{13}C-*Shift correlation; Diterpene acids)*

2 D-NMR von Naturprodukten, 5. Mitt.: Strukturaufklärung und komplette ^{1}H- *und* ^{13}C-*Zuordnung von Harzsäure-Derivaten*

2 D-NMR-Methoden (2 D-J-resolved-Spektren, ^{1}H—^{13}C-Shiftkorrelationsspektren) erlauben die Zuordnung der ^{1}H- und ^{13}C-Signale von Harzsäurederivaten.

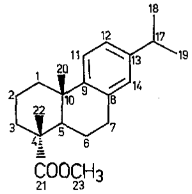
Introduction

During our attempts to use resin acids as precursors for the synthesis of steroids we have studied various *Diels-Alder*-adducts of levopimaric acid[2,3]. One of the main problems in the course of this work is the characterization of reaction products by NMR. Even using highfield NMR-spectrometers, the analysis of the proton spectra of complex natural compounds like resin acids is not possible with conventional methods. In these cases 2 D-NMR-techniques have proved to be very useful for obtaining additional information[4,5]. We have used several of these modern techniques simultaneously to get an unambiguous assignment of the ^{1}H- and ^{13}C-resonances of compounds **2**, **3** and **4**.



	R^1	R^2	R^3	R^4
1	$-\underset{O}{\underset{\Vert}{C}}-O-\underset{O}{\underset{\Vert}{C}}-$		$-H$	$-CH(CH_3)_2$
2	$-\underset{O}{\underset{\Vert}{C}}-\overset{\vert}{O}-\underset{O}{\underset{\Vert}{C}}-$		$-H$	$\underset{17}{-\overset{\overset{18}{CH_2}}{\overset{\Vert}{C}}}-\underset{19}{CH_3}$
3	$-COOCH_3$	$-H$	$-COOCH_3$	$-CH(CH_3)_2$
4	$-COOCH_3$	$-H$	$-COOCH_3$	$-CBr(CH_2Br)_2$

5



For the sake of clarity we have used the same numbering system for compounds **1** to **5**.

Results and Discussion

The assignment of the ^1H- and ^{13}C-resonances of compounds **2**–**4** is given in Tables 1 and 2, respectively, and will be discussed in detail. For the sake of clarity the shifts of compounds **1** and **5** are also listed in the tables[5,6]. The assignment of **5** was checked by 2D-NMR-experiments and is in full agreement with literature.

Compound 2

The assignment of the carbons 15, 18 and 21 is possible by shift arguments and multiplicity information from a J-modulated ^{13}C-spectrum. The anhydride carbons and the two remaining singuletts at 137.9 and 140.6 ppm could not be assigned unambiguously.

The aliphatic region of the ^{13}C-spectrum consists of 18 well separated lines. The signal at 51.0 ppm is due to the ester-methyl group. The methyl group attached to C-17 can be easily detected in the SFORD-

Table 1. ^{13}C-*Chemical shifts of compounds* **1**–**5** *in* C_6D_6; δ-*values are in ppm from TMS* (± 0.05); ^{a,b,c} *shift values may be interchanged*

	1	2	3	4	5
1	38.1	37.9	37.8	37.6	38.4
2	17.3	17.3	17.4	17.4	18.9
3	37.2	37.2	37.1	37.0	37.1
4	47.2	47.2	47.4	47.2	47.8
5	49.6	49.5	49.7	49.4	45.4
6	22.0	22.0	22.3	22.1	22.2
7	35.2	34.9	35.3	34.6	30.4
8	40.4	41.0	41.7	42.2	147.3
9	53.1	53.2	54.8	55.1	134.8
10	37.7	37.6	38.0	37.8	37.2
11	27.2	26.3	23.9	24.5	124.5
12	35.8	33.0	36.3	36.8	124.2
13	45.7	45.6	49.1	48.8	145.8
14	53.0	52.8	54.5	55.5	127.3
15	125.4	129.1	125.0	134.7	—
16	148.1	141.9^{a}	148.2	138.9	—
17	33.0	139.3^{a}	33.1	67.0	34.0
18	20.1^{a}	112.9	20.6	38.9^{a}	24.3
19	20.7^{a}	19.7	20.6	37.4^{a}	24.3
20	17.0	17.0	17.1	17.2	16.9
21	178.4	178.4	178.5	178.3	178.3
22	15.5	15.2	16.3	16.1	25.3
23	51.6	51.6	50.9^{a}	51.1^{b}	51.5
24	172.6^{b}	171.9^{b}	174.2^{b}	173.2^{c}	—
25	170.8^{b}	170.8^{b}	173.8^{b}	173.0^{c}	—
26	—	—	51.5^{a}	51.5^{b}	—
27	—	—	51.5^{a}	51.8^{b}	—

spectrum by its large residual splitting. The proton signal of Me-22 is shifted highfield by the anisotropy of the C-15/C-16-double bond, thus yielding the assignment of C-20 and C-22 via the 2D-^{1}H-^{13}C-shift correlation.

In the ^{1}H-spectrum the protons H-7 eq, H-12, H-13 and H-14 show characteristic splitting patterns and are well separated. The shift correlation spectrum therefore allows the assignment of C-7, C-12, C-13 and C-14. C-7 gives in turn the resonance position of H-7 ax.

The assignment of the remaining tripletts in the lowfield region of the ^{13}C-spectrum (C-1 and C-3) is possible because of the characteristic highfield shift of H-1 ax[5]. The assignment of the remaining ^{13}C-signals was done by comparing spectra of **1** and **2**, yielding the shift values of all protons by the shift correlation experiment.

Compound **3**

The ^{1}H-spectrum shows an isopropyl group and two further aliphatic methyl groups. The corresponding ^{13}C-resonances can be detected via the shift correlation experiment using the same arguments for the assignment of H-22 and H-20 as above.

Table 2. ^{1}H-*Chemical shifts of compounds* **1**–**5** *in* C_6D_6; δ-*values are in ppm from TMS* (±*0.01*); [a,b,c] *shift values may be interchanged*

	1	**2**	**3**	**4**	**5**
1 eq	1.03	0.97	1.14	1.12	2.12
1 ax	0.63	0.61	0.68	0.63	1.38
2	1.18–1.25	1.17–1.26	~ 1.2	~ 1.2	~ 1.4
3 eq	1.50	1.52	1.47	1.46	1.58
3 ax	1.77	1.74	1.80	1.68	1.83
5	1.71	1.75	1.81	1.75	2.32
6	1.18–1.25	1.17–1.26	~ 1.3	~ 1.2	1.40/1.73
7 eq	2.54	2.54	1.78	1.91	2.74
7 ax	1.53	1.50	1.71	1.53	2.74
9	0.77	0.96	1.35	1.41	—
11 eq	0.73	0.73	0.93	1.12	—
11 ax	0.98	0.80	1.67	1.62	7.13
12	2.74	3.28	2.92	3.14	7.02
13	2.30	2.35	2.87	3.05	—
14	1.53	1.97	3.06	3.11	6.86
15	5.23	5.56	5.48	5.72	—
17	2.08	—	2.30	—	2.74
18	0.85[a]	4.88/5.19	1.07	3.79/3.93[b]	1.19
19	0.86[a]	1.58	1.07	3.90/4.05[b]	1.19
20	1.15	1.13	1.20	1.17	1.27
22	0.26	0.22	0.46	0.45	1.10
23	3.40	3.40	3.40	3.23[c]	3.35
26	—	—	3.51	3.38[c]	—
27	—	—	3.51	3.34[c]	—

H-12, H-13 and H-14 are separated from all other ^{1}H-resonances, thus giving easily the corresponding carbon signals. Ring opening of the anhydride causes a highfield shift of H-7 eq while C-7 remains unaffected. Irradiation at H-12 gives the resonance position of the protons at C-11, leading to an assignment of the carbon atom itself. C-1 and C-3 can be differentiated by the corresponding ^{1}H-chemical shifts. The assignment of the residual resonances was done in analogy to the other compounds.

Compound 4

The ^{13}C-spectrum of **4** shows several groups of resonances with nearly identical shift values. Therefore ^{13}C-multiplicity assignment was performed by a ^{13}C—^{1}H-J-resolved experiment (Fig. 1).

The ^{1}H-spectrum of 4 exhibits two overlapping AB-systems near 4 ppm which correspond to H-18 and H-19 giving the shifts of C-18 and C-19. The assignment of the carbons and protons at positions 12, 13 and 14 was done in the usual manner. The ^{1}H-resonance of H-7 eq is well separated giving C-7 and in turn H-7 ax via the shift correlation spectrum (Fig. 2). Me-22 appears in the ^{1}H-spectrum at highest field leading to the assignment of C-22. Discrimination of C-1 and C-3 is possible by the highfield shift of H-1 ax leading to the assignment of C-1 and C-3. The remaining three tripletts (C-2, C-6 and C-11) could be assigned by comparison of **4** with the other compounds (see Table 1). The low-field singulett at 67.0 ppm belongs to C-17, the two dubletts for C-5 and C-9 are found at 49.4 ppm and 55.1 ppm, respectively.

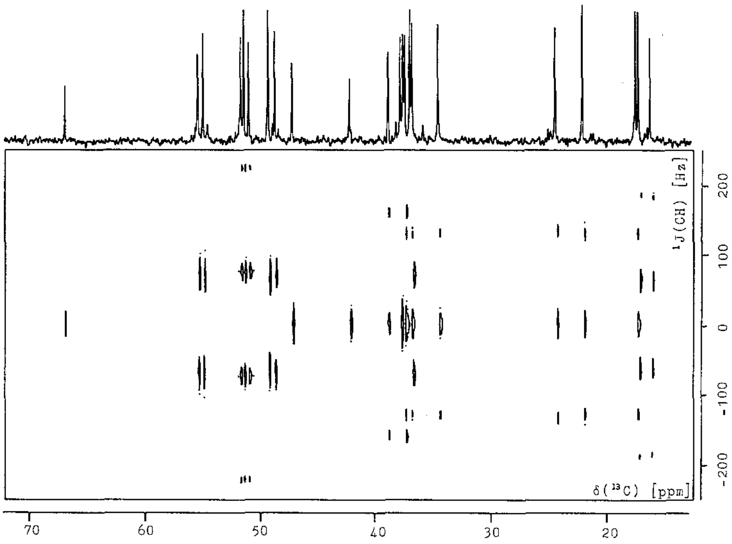


Fig. 1. ^{13}C—^{1}H-J-resolved NMR spectrum of 4 in C_6D_6

Comparing the ^{13}C-shifts of compounds **1**–**4** one finds that the shifts of carbons 9, 11, 13 and 14 are sensitive to the orientation of the carbonyl groups attached to the C-ring. Introduction of a C=C-double bond in position 17 induces a lowfield shift for C-15 and a highfield shift for C-

16[7]. The structure determination of compound **4** was mainly based on the results of the 2D-NMR-shift correlation. The influence of the Br-substitution on the ^{13}C-shifts can be seen by comparing the shift values of **3** and **4**. Only the two olefinic carbons are shifted considerably (C-15: 10 ppm to low field, C-16: 10 ppm to high field). This is probably due to electronic and steric interactions with the Br-atoms. The ^{1}H-shifts reveal no big influence of the Br-substituents on the surrounding protons. Only the equatorial hydrogens attached to the C-ring are shifted slightly to lower field in compound **4**.

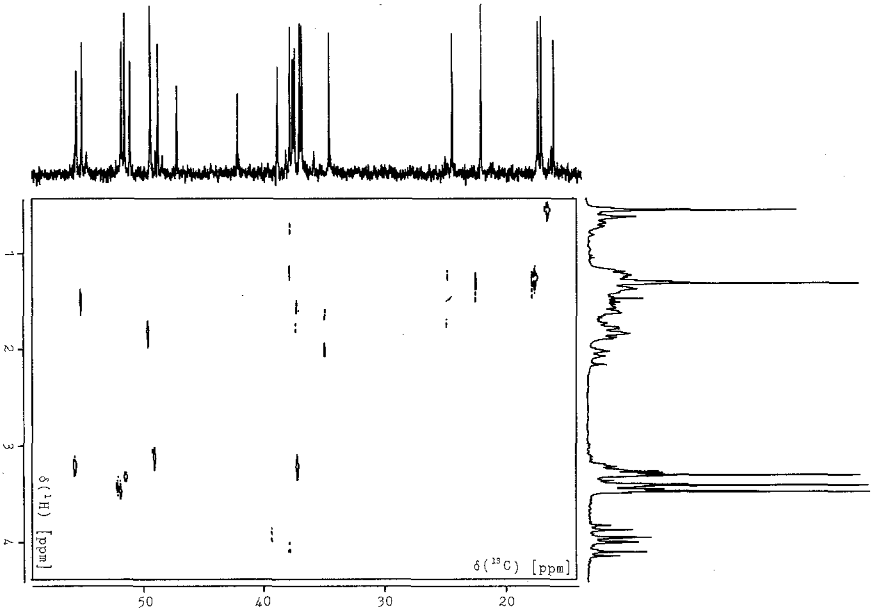


Fig. 2. ^{13}C—^{1}H-shift correlation spectrum of **4** in C_6D_6

Finally we have computed theoretical shift values with a computer program from a ^{13}C-data bank[8]. Theoretical and experimental shift values have been in excellent agreement.

Acknowledgements

We are grateful to the *Fonds zur Förderung der wissenschaftlichen Forschung* for providing the NMR-spectrometer (Project No. 4009). *H. S.* is grateful to Fa. Krems-Chemie (Krems/Donau) for financial support.

Experimental

The syntheses of compounds **1**–**5** have been described elsewhere[3,9,10].

All NMR-measurements were performed on a Bruker WM 250 NMR spectrometer equipped with an 80 K ASPECT-2000 computer running the DISNMRP-program[11]. Sample tubes of 5 mm diameter have been used. The deuterium resonance of the solvent provided the field-frequency-lock.

Typical parameters were:

^{1}H

$SW = 2\,500$ Hz; digital resolution: 0.3 Hz; $PW = 1\,\mu$s (15°); $NS = 32$—64; $T = 298$ K; concentration: approx. 0.02 *M*.

^{13}C

$SW = 16\,000$ Hz; digital resolution: 1 Hz; $PW = 5\,\mu$s (30°); $NS = 500$–2 000; $T = 303$ K; concentration: approx. 0.4 *M*.

J-Modulated ^{13}C-*Spin-Echo*

Pulse sequence: D 1-π/2-τ(DO)-π-τ(BB)-FID; $SW = 16\,000$ Hz; $NS = 500$–2 000; PW (90°) $= 16\,\mu$s; $T = 303$ K; $\tau = 7.5$ ms for $J = 133$ Hz; recycle delay: 2.5 s.

Heteronuclear 2 D-J-Resolved Spectrum

Pulse sequence: D 1-π/2 (PH 1, BB)-t_1/2-π(PH 2, DO)-t_1/2-FID (BB); $SW_1 = \pm 125$ Hz; $SW_2 = 4\,000$ Hz; $NS = 144$; $T = 303$ K; recycle delay: 2.5 s; data matrix: 2 K × 128.

^{1}H—^{13}C-*Shift Correlation*

Pulse sequence: D 1-π/2 (PH 1, ^{1}H)-t_1/2-π (PH 3, ^{13}C)-t_1/2-Δ_1-π/2 (PH 2, ^{1}H)-π/2 (PH 4, ^{13}C)-Δ_2-FID (BB); $SW_1 = \pm 500$ to ± 900 Hz; $SW_2 = 3\,000$ to 8 000 Hz; $NS = 160$–640; $T = 303$ K; PW (π/2, ^{13}C) $= 18\,\mu$s; PW (π/2, ^{1}H) $= 17\,\mu$s; recycle delay: 2.5 s; data matrix: 2 K (4 K) × 128 (256); $\Delta_1 = 4$ ms; $\Delta_2 = 2.67$ ms.

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