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NMR Spectroscopic Studies on Peptide Alkaloids ^{1}H and ^{13}C Spectra of Zizyphin A and Frangulanin

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^{1}H and ^{13}C studies of the styrylamine mojety in the 13-membered cyclopeptide alkaloid zizyphin A and the 14-membered cyclopeptide alkaloid frangulanin are reported.

(Keywords: Cyclopeptide alkaloids, partially relaxed ^{1}H-NMR spectra; $^{1}J_{^{1}H^{13}C}$-Coupling constants)

NMR-Spektroskopische Untersuchungen an Peptid-Alkaloiden. ^{1}H- und ^{13}C-Spektren von Zizyphin A und Frangulanin

Es werden ^{1}H- und ^{13}C-spektroskopische Untersuchungen des 13-gliedrigen Cyclopeptidalkaloids Zizyphin A und des 14-gliedrigen Cyclopeptidalkaloids Frangulanin beschrieben.

Introduction

Cyclopeptide alkaloids are particularly common in plants of the *Rhamnaceae* family, but they have also been found in *Sterculiaceae*, *Rubiaceae*, *Urticeae*, *Hymenocardiaceae* and *Celastraceae*[1,2]. They have an alkoxystyrylamin group as common structural unit in a 13-, 14- or 15-membered heterocyclic ring system. Recently growing interest in the conformation of cyclic peptides has also induced NMR-investigations of these compounds. Up to now only a few ^{13}C-NMR-studies of cyclopeptide alkaloids have been reported in the literature[3–6].

UV spectra of these alkaloids show a different behaviour, dependent on the ring size, indicating substantial conjugation of the enamine residue with the aromatic ring in the 13- and 14-membered molecules[4].

As our first assignment[3] of the carbon resonances of the styrylamin

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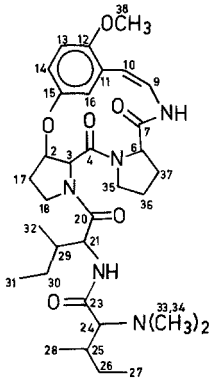
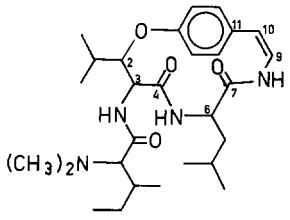
unit in frangulanin[12] (**2**) was based on solvent induced shifts and tentatively concerning the carbons in the double bond[3] we have reinvestigated the styrylamin resonances of **2** and zizyphin A (**1**)[7–9]. No exhaustive ^{1}H-NMR study on **1** has been reported so far; we therefore studied the ^{1}H-NMR-Spectrum of this compound in order to gain information from {^{1}H} — ^{13}C — double resonance experiments.



(1)



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Results and Discussion

^{1}H-NMR Studies on Zizyphin A (**1**)

The ^{1}H-NMR-spectrum of **1** is shown in Fig. 1, the assignment of the ^{1}H-resonances is given in Table 1. The resonances of the styrylamino group are remarkable different from the corresponding resonances of **2** (Tab. 2). The vinylic protons have a larger vicinal coupling constant in **1** indicating a less strained structure, what is supported by the larger coupling of the NH proton to the vinylic hydrogen.

In the region from 5.22 to 4.00 ppm the resonances of six protons appear. These can be assigned to the hydrogens in positions 2, 3, 6, 35, 18 and 21. As several lines in this region are overlapping, we used partially relaxed spectra to make the splitting pattern of single protons visible. This technique has been used earlier with frangulanin (**2**)[10,11,13] and is based on the fact, that the protons in position 3 and 6 have longer relaxation times, than the other three (Fig. 2). The protons in positions 18 and 35 have in turn been assigned by ^{1}H-^{13}C double resonance experiments. The assignment of the methylresonances has also been made by means of partially relaxed spectra.

The absorption of the $N(CH_3)_2$-group at ambient temperature is very broad, showing restricted motion of the side chain. A similar

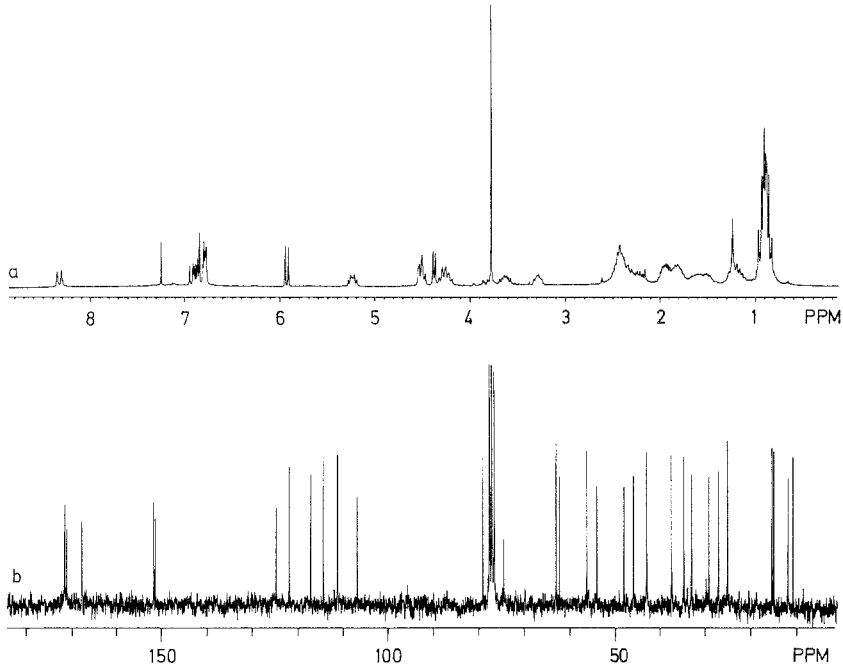

Fig. 1. *a* 250 MHz ^{1}H spectrum of **1**; *b* 62.9 MHz ^{13}C spectrum of **1**

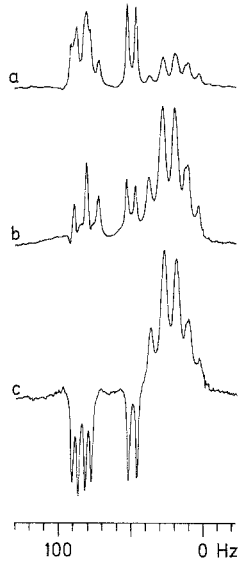

Fig. 2. Partially relaxed ^{1}H spectra of **1** (4.0-4.5 ppm); *a* normal spectrum; *b* 0.5 s after 180°-puls; *c* 0.25 s after 180°-puls. Traces *b* and *c* show clearly the splitting pattern of the overlapping resonances of the protons 6 and 21

Table 1. ^1H *and* ^{13}C-NMR *data for zizyphin A* (**1**) *in* $CDCl_3$ $\Delta\delta = (\delta_{CDCl_3} - \delta_{CD_3OD})$

Position	^{13}C/ppm	$\Delta\delta$	^1H/ppm	J/Hz
1	79.1	—1.1	5.26	(2,3) 5.8; (2, 17 a, b) 6.0; 9.5
2				
3	63.1	—1.3	4.39	(2,3) 5.8
4	171.2*			
5				
6	62.3	—1.5	4.50	(6,37 a, b) 4.2; 9.0
7	167.9	—2.4		
8			8.36	(8,9) 12.2
9	121.9	0.1	6.93	(1.10) 8.7; (8,9) 12.2
10	106.9	—3.5	5.95	(9, 10) 8.5
11	124.8	—0.5		
12	151.4	—1.2		
13	111.4	—1.4	6.89	(13, 14) 10.0
14	117.2	—1.4	6.82	(13, 14) 10.0
15	151.7	—1.2		
16	111.3	—0.9	6.82	
17	32.9	—0.7	a 2.5; b 2.5	
18	45.9	—0.9	a 4.25; b 3.65	
19				
20	171.6*			
21	54.1	—1.5	4.50	(21, 29) 8.5; (21, 22) 8.5
22			7.15	
23	171.9*			
24	74.5	0.2	2.4	
25	37.4	—0.3	1.2—1.9	
26	27.1	0.2	1.2—1.9	
27	11.9	0.0	0.96	(26, 27) 7.3
28	15.4	—0.1	0.92	(25, 28) 6.7
29	34.6	—0.6	1.95	
30	25.1	—0.8	1.2—1.9	
31	10.8	0.0	0.88	(30, 31) 7.0
32	15.0	—0.5	0.91	(32, 28) 6.7
33	43.0	—0.6	2.45	
34	43.0	—0.6	2.45	
35	48.0		a 4.35; b 3.28	
36	25.1	—0.8	a 1.95; b 1.95	
37	29.2	—0.9	a 1.95; b 1.95	
38	56.3	—0.5	3.80	

* Interchangeable.

behaviour is known from lasiodine B which also contains a proline residue and exists as a mixture of *cis* and *trans* isomers[6]. Recording the spectrum at 348 K gives a sharp $N(CH_3)_2$-singulet and shows temperature shifts of this signal and the NH-22 resonance. No changes of the signals from the hydrogens situated at the macrocyclic ring are observed. The resonance position of H-24 was located by selective ^1H-^{13}C decoupling at 2.4 ppm.

The ^{13}C Spectrum of Zizyphin A (**1**) *and Frangulanin* (**2**)

The assignment of the ^{13}C resonances of **1** is mainly based on ^1H-^{13}C-double resonance experiments and is presented in Table 1. It is in full agreement with that of *Shamma* et al.[4], who used chemical shifts and multiplicities.

The signals of the carbons 24, 33 and 34 are remarkably broadened indicating restricted motion, thus supporting the results from the ^1H-high-temperature measurements. The carbonylresonance at 171.9 ppm is very broad too and could therefore be assigned to the CO group in position 23. Recording the spectrum in CD_3OD shows different shifts mainly for the carbons in the 13-membered macrocycle thus indicating a solvent induced conformational change of the rigid ringsystem (Tab. 1).

In order to check our first tentative assignment of the olefinic carbons in the styrylamin group of **2**, we performed selective decoupling experiments, irradiating the protons of the double bond. As a result of these experiments, our previous assignment[3] has to be corrected. The new values are given in Table 2. These shifts are in good agreement with

Table 2. ^1H *and* ^{13}C-NMR-*parameters of the styrylamine mojety in ziziphin A* (**1**) *and frangulanin* (**2**)

osition	Zizyphin A (**1**)				Frangulanin (**2**)			
	^1H/ppm	$^3J_{^1H^1H}$/Hz	^{13}C/ppm	$^1J_{^1H^{13}C}$/Hz	^1H/ppm	$^3J_{^1H^1H}$/Hz	^{13}C/ppm	$^1J_{^1H^{13}C}$/Hz
;	8.36	12.2			6.40	6.4		
)	6.93	8,7; 12.2	121.9	181.3	6.43	7.1; 6.4	126.0	184.3
)	5.95	8.7	106.9	166.5	6.57	7.1	126.7	165.8

the shifts given for the styrylamin group of the 14-membered alkaloids discarin B, discarin A and lasiodine B[6]. The signals of the styrylamin carbons in the 13-membered alkaloid **1** exhibit shifts predicted for a conjugated double bond[14]; on the other hand different shifts in the 14-membered alkaloids indicate a decreased conjugation. The large spin

spin coupling ($^1J_{^1H^{13}C}$) of C-9 is not influenced by the twisting of the double bond in the more strained 14-membered macrocycle. This coupling can be used to assign the ^{13}C-resonance of this carbon.

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Experimental

The isolation and purification of Frangulanin (**2**) has been described elsewhere[15].

The NMR-spectra have been recorded on a Bruker WM 250-NMR spectrometer equipped with an 80 K Aspect 2000 computer. Typical parameters are:

^1H: Aquisition time: 3.27 s; pulswidth: 1 μs (20°); number of transients: 40–120.

^{13}C: Aquisition time: 1.08 s; pulswidth: 4 μs (25°).

Usually 10000 transients for noise decoupled spectra were accumulated over a 15 kHz sweep using 32 K of memory. For the gated decoupled spectra up to 55000 responses have been accumulated.

The concentration was 0.1 *M*, tetramethylsilan (*TMS*) was used as internal reference and the deuterium resonance of the solvent provided the field frequency lock signal. Assigned carbon shifts marked with an asteriks may be interchanged.

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