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The Structure of Angustifoline, an Alkaloid of *Lupinus Angustifolius*, in Solution[1]

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Summary. The ^1H and ^{13}C NMR spectra of the lupin alkaloid *angustifoline* **1** in four solvents (cyclohexane-d_{12}, $CDCl_3$, CD_3CN, and C_6D_6) were assigned using 2D H,H and H,C COSY and 2D J-resolved spectra. The torsional HCCH angles calculated from the vicinal J_{HH} coupling constants are essentially in agreement with those expected for the deformed all-chair conformation with *endo* oriented N(12)–H bond, reported earlier for **1** in the solid state. Some arguments seem to point, however, to a small contribution of other conformations: with ring A deformed in another direction, deformed all-chair with *exo* oriented N(12)–H bond and/or a conformation with ring C in the boat form.

Keywords. Angustifoline; Conformation; NMR, Quinolizidine alkaloids.

Die Lösungsstruktur von Angustifolin, einem Alkaloid aus *Lupinus Angustifolius*

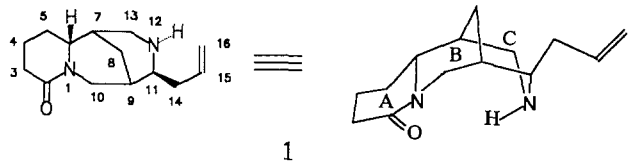
Zusammenfassung. Die ^1H- und ^{13}C-NMR Spektren des Lupinalkaloids Angustifolin (**1**) in vier Lösungsmitteln (Cyclohexan-d_{12}, $CDCl_3$, CD_3CN und C_6D_6) wurden mit Hilfe von H,H-COSY-, C,H-COSY und 2D-*J*-aufgelösten Spektren zugeordnet. Die aus den vicinalen Kopplungskonstanten berechneten Torsionswinkel stimmen mit den für eine *all-chair* Konformation mit *endo*-orientierter N(12)–H-Bindung erwarteten und für **1** im festen Zustand bereits berichteten überein. Es liegen allerdings auch Hinweise auf geringe Beiträge anderer Konformationen vor: deformierter Ring A, verformte *all-chair*-Konformation mit *exo*-orientierter N(12)–H-Bindung und/oder Boot-Konformation von Ring C.

Introduction

(−)-Angustifoline **1** was isolated from *Lupinus angustifolius* [1] and *L. poliphyllus* [2] in the fifties[2]. In the solid state, **1** assumes the deformed all-chair conformation with an axially oriented allyl chain and an axial N12 hydrogen atom [4, 5]. In this paper, we report the results of the analysis of the ^1H and ^{13}C NMR spectra and the geometry of **1** in solution obtained from the HCCH torsional angles calculated from the vicinal coupling constants J_{HH} using the *Haasnoot* equation [6].

[1] Lupin Alkaloids, part 7

[2] We have recently reported an isolation of (+)-angustifoline from *L. albus* seeds [3]



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Results and Discussion

Most of the NMR signals of angustifoline in $CDCl_3$ solution were assigned by means of H,H COSY, H,C COSY, 2D J-resolved, and NOE difference spectra at 300 MHz. To resolve entangled resonances, the 300 MHz spectra of **1** in C_6D_6, CD_3CN and cyclohexane-d_{12} and finally the 600 MHz spectra of **1** in $CDCl_3$ were recorded. Nevertheless, the signals of H(13)-α and H(13)-β as well as H(5)-α and H(5)-β remained second order even at 600 MHz. The chemical shifts and coupling constants of H(13)-α and H(13)-β were estimated roughly from an analysis of the ABMX system, X being involved in other couplings, and checked by a computer simulation [7]. The data are collected in Tables 1, 2, and 3. Table 4 presents the values of HCCH angles calculated from the vicinal J_{HH} coupling constants by means of the *Hassnoot* equation [6] in comparison with those derived from the X-ray analysis [5].

The spectral data are, essentially, not contradictory to the earlier findings as to the conformation of the compound [4, 5]. The HCCH torsional angles calculated from ^{1}H NMR spectra are similar to those obtained from X-ray analysis (Table 4). The chair conformation of ring C and the axial position of the allylic group can be confirmed by the NOE difference spectra (2.6% NOE effect at H(14)-A after irradiation of H(8)-eq). This effect, together with the two H(14) signals, indicates a slowed-down rotation of the allyl methylene group caused by steric hindrance (in the solid state of **1**, the distance H(8)-eq···H(14) is 2.35 Å [5]).

Table 1. ^{13}C chemical shifts of angustifoline (**1**)[a]

C	C_6D_{12}	$CDCl_3$	CD_3CN	C_6D_6
2	167.36	170.04	170.02	169.44
3	33.32	33.24	33.76	34.05
4	21.08	20.20	20.94	21.07
5	28.77	27.97[b]	28.42[c]	28.63
6	60.67	60.29	60.88	60.61
7	34.08	32.79	33.59	33.72
8	28.97	28.07[b]	28.46[c]	28.82
9	32.08	31.25	32.17	32.13
10	48.00	48.09	48.44	48.65
11	57.54	57.02	58.25	57.84
13	42.36	41.92	42.30	42.55
14	38.26	37.58	38.21	38.43
15	136.76	136.14	137.93	137.53
16	115.43	116.47	116.12	116.61

[a] ppm from *TMS*; [b,c] interchangeable

Table 2. ^{1}H chemical shifts of angustifoline (**1**), ppm from TMS[a]

H	C_6D_{12}	$CDCl_3$	CD_3CN	C_6D_6
3α(ax)	2.20	2.35	2.24	2.10
3β(eq)	2.32	2.50	2.28	2.40
4α(eq)	~1.8[b]	1.92	1.84	1.25[c]
4β(ax)	~1.6[b]	1.70	1.79	1.24[c]
5α(ax)	~1.7–1.8[b]	1.80	1.72	1.06[d]
5β(eq)	~1.7–1.8[b]	1.82	1.76	1.09[d]
6(ax)	3.38	3.49	3.45	2.84
7(eq)	1.32	1.52	1.44	0.84
8α(eq)[e]	2.12	2.14	2.09	1.71
8β(ax)[e]	1.51	1.61	1.56	1.35
9(eq)	1.60	1.76	1.65	1.29
10α(eq)	4.70	4.67	4.48	4.83
10β(ax)	2.68	2.89	2.79	2.57
11(eq)	2.79	2.90	2.72	2.76
12(NH)	~1.8[b]	1.63	1.67	1.16
13α(eq)	2.95	3.02	~2.92	~2.70
13β(ax)	2.94	3.01	~2.92	~2.70
14A	2.37	2.42	2.37	~2.3[b]
14B	2.14	2.26	2.21	2.01
15	5.76	5.79	5.81	5.73
16*cis*[f]	4.94	5.06	4.99	~5.01
16*trans*[f]	4.96	5.08	5.04	~5.01

[a] In chloroform-d_3, on the Bruker 600 MHz spectrometer; in all other solvents, on the Varian 300 MHz spectrometer;
[b] rough estimates; [c,d] interchangeable; [e] in ring B; [f] to H(15)

Table 3. H–H coupling constants in angustifoline (**1**) in $CDCl_3$

Coupling constants [Hz]							
3α–3β	17.3	4β–5α	~12.5	7–13β	4.5[c]	11–14A	7.0
3α–4α	6.1	4β–5β	3.5	8α–8β	13.0	11–14B	7.0
3α–4β	12.6	5α–5β		8α[a]–9	3.5	13α–13β[c]	14.0
3β–4α	2.3	5α–6	10.7	8β[b]–9	3.1	14A–14B	14.0
3β–4β	4.7	5β–6	5.0	9–10α	2.3	14A–15	7.0
3β–5β	2.4	6–7	2.6	9–10β	3.5	14B–15	~7.0
4α–4β	12.3	7–8α[a]	5.9	10α–10β	13.6	15–16*cis*	10.2
4α–5α	3.5	7–8β[b]	1.9	10α–8α[a]	2.3	15–16*trans*	17.1
4α–5β	3.5	7–13α	1.7[c]	9–11	1.0–1.4	16*cis*–16*trans*	1.6

[a] equatorial in ring B; [b] axial in ring B; [c] values obtained from the analysis of the AB part of an ABMX system

Table 4. Torsional angles HCCH in angustifoline (**1**)

Angle	X-ray [5]	NMR[a]	Angle	X-ray [5]	NMR[a]
H3αC3C4H4α	50.0	46	H6C6C7H7	−57.6	−59
H3αC3C4H4β	169.7	159	H7C7C8H8α[b]	−49.5	−42
H3βC3C4H4α	−62.6	−65	H7C7C8H8β[c]	69.9	69
H3βC3C4H4β	52.0	53	H8α[b]C8C9H9	56.9	56
H4αC4C5H5α	−62.6	−57	H8β[c]C8C9H9	−63.2	−59
H4αC4C5H5β	54.7	57	H9C9C10H10α	−67.9	−62
H4βC4C5H5α	177.1	165	H9C9C10H10β	58.6	53
H4βC4C5H5β	−65.7	−58	H9C9C11H11	65.2	69 to 74
H5αC5C6H6	168.7	157	H7C7C13H13α	−48.5	−78[d]
H5βC5C6H6	50.8	44	H7C7C13H13β	56.2	46[d]

[a] in $CDCl_3$; [b] equatorial in ring B; [c] axial in ring B; [d] from the analysis of the AB part of an ABMX system

Deshielding of the amine proton (N(12)-H) when compared with those in piperidine and 3-azabicyclo[3.3.1]nonane [8] and in cytisine [9] indicates its predominant *endo* orientation in **1**. This finding is also supported by a solvent effect. The differences in the ^1H and ^{13}C chemical shifts in the NMR spectra of **1** in cyclohexane and in $CDCl_3$ are best explained by assuming weak hydrogen bonds between the lactamic oxygen atom and the amine nitrogen N(12) with chloroform. The formation of the latter is possible only when the lone electron pair is easily accessible [10] which can be fulfilled either in the all-chair conformation with the *endo* N(12)–H bond or in the conformation with the boat ring C. The solvent effects of acetonitrile and benzene on both ^1H and ^{13}C NMR spectra of **1** are consistent with the expectations [11].

Summing up, the main conformer of **1** in solution must then have a structure almost identical to that obtained previously, with axial H(3)-α, H(4)-β, and H(5)-α [5]. There are, however, some data which indicate the possibility of other conformations:

1) Differences in the size of the angles in ring A calculated by both methods (X-ray and NMR, Table 4) indicate a small participation of the conformer with ring A deformed in a different way (with axial H(3)-β, H(4)-α, and H(5)-β) than in the dominant conformer. A similar phenomenon was previously considered for 15-oxosparteine [12, 13] and, as we think, it must occur also in lupanine, which has $J_{5_{ax},6} = 9.2$ Hz (in sparteine with the rigid ring A, 13.2 Hz) [13].

2) The presence of a low intensive "*Bohlmann* band" [14] in the region 2840–2600 cm^{-1} of the IR spectrum of **1** in $CDCl_3$ proves a small contribution of conformations in which α hydrogen atoms are antiperiplanar relative to the N(12) lone electron pair. Such a *Bohlmann* band can occur in the "chair" conformer with *exo* N(12)–H bond (and *endo* lone electron pair). An equilibrium between the *exo* and *endo* position of the hydrogen atom at N(12) also seems to be justified considering the conformation of piperidine [15, 16] or 3-azabicyclo[3.3.1]nonane [8]. The difference in enthalpy between the piperidine conformers with the axial and

the equatorial position of the N–H bond is only about 0.5 kcal/mol [15, 16]. In the case of **1**, *Bratek-Wiewiórowska* explains the unusual predominance of the endo position by the effect of partially negative charge of the oxygen atom of the lactam group [4].

The presence of the *Bohlmann* band could be explained alternatively by assuming a small contribution of the boat ring C with an equatorial N–H bond. This assumption can be supported by the values of $J_{7\,13\alpha}$ and $J_{7\,13\beta}$ (1.7 and 4.5 Hz, respectively), estimated by a computer simulation, which are quite different from those (2.7 and 3.0 Hz) calculated from the X-ray data from the relevant torsional angles *via* the *Haasnoot* equation. The chair-boat conformation of ring C in **1** could be a result of a steric hindrance caused by the allyl substituent at C(11).

In conclusion, the predominant conformation of **1** in solution is similar to that in the solid state, but there are some arguments indicating a contribution of others conformers: with ring A deformed more towards a boat, with an *exo* N(12)–H bond, and perhaps with the boat ring C. The combinations of all these possibilities are also probable.

Experimental Part

(−)-Angustifoline was isolated from *Lupinus angustifolius* using the same method as described for (+)-angustifoline from *L. albus* [3]. Its properties were identical to those reported earlier [1, 2, 3].

The NMR spectra were recorded at ambient temperature on a Varian Gemini 300 spectrometer operating at 300.075 and 75.462 MHz for ^1H and ^{13}C, respectively. The chemical shifts were referenced to internal *TMS*. The 2D H,H – COSY, H,C – COSY, and 2D homonuclear ^1H J-resolved spectra were recorded using standard Varian programs. The NOE difference spectra were obtained by direct subtraction with decoupler offset cycling within a multiplet, with 15 s pre-irradiation. The ^1H NMR, H,H COSY and H,C HMQC spectra of **1** in $CDCl_3$ were recorded also on a Bruker DMX-600 spectrometer operating at 599.87 MHz at ambient temperature using standard Bruker programs.

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