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THE FIRST QUANTITATIVE DETERMINATION OF CONFORMATIONAL EQUILIBRIUM IN QUINOLIZIDINE-PIPERIDINE ALKALOIDS

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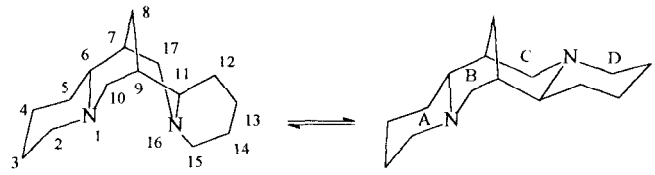
Abstract. The fraction of the conformer with the boat ring C in the conformational equilibrium in *N*-methyl-angustifoline (**7**) in chloroform and benzene solutions was determined to be ca. 34% using coupling constant $J_{7\text{-}13\beta}$. In angustifoline (**5**) $J_{7\text{-}13\beta}$ could not be determined directly from the spectra; a simulation gave the result of 4.25 Hz corresponding to ca. 23% of the boat conformer. In tetrahydrorhombifoline (**6**), rings B and C have a chair conformation. Low temperature ^{13}C NMR measurements seem to corroborate these results qualitatively. Factors influencing conformational equilibria are discussed.

Key words: quinolizidine-piperidine alkaloids, conformational equilibrum, NMR spectroscopy.

Introduction

Most of the four-ring bis-quinolizidine alkaloids of sparteine (**1**) type as well as some of the 3,7-diazabicyclo[3.3.1]nonane derivatives (bispidine, **2**, which can be considered as composed of rings B and C of **1**) exist in solution as mixtures of conformers [1,2]. It is also conceivable that also some tricyclic quinolizidine-piperidine alkaloids (which consist of rings A, B and C of **1**) should occur as mixtures of conformers with ring C in a chair or a boat conformation.



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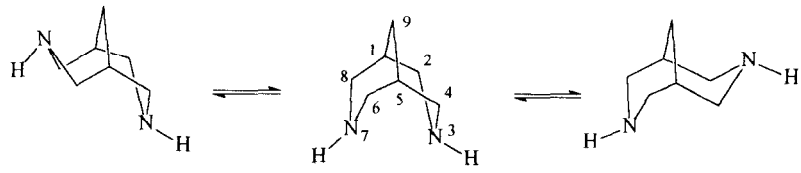

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For the tetracyclic alkaloids, we can use quite precise criteria of

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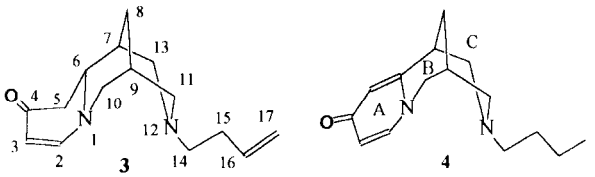
conformation: ^{13}C chemical shifts of the atoms C12 and C14 (in ring D). These atoms are exposed to the γ-synclinal (γ-gauche) effects from the atoms C8 and C17 in the chair conformers but not in the boat ones [1]. A less precise criterion is the ^{1}H-^{1}H coupling constant of the bridgehead proton and the proton at the next carbon atom (between the bridgehead C atom and the nitrogen atom) from the β-side. In the alkaloids with the sparteine skeleton the coupling constant is denoted as $J_{7\text{-}17\beta}$. If ring C is a chair, $J_{7\text{-}17\beta}$ is small, if it is a boat, $J_{7\text{-}17\beta}$ takes a value from above 10 Hz. The intermediate values indicate the conformational equilibria. For many tetracyclic alkaloids the three criteria are in good agreement [1]. Unfortunately, for the bi- and tricyclic compounds only the third criterion is valid; in tricyclic ones it is denoted as $J_{7\text{-}13\beta}$.

Recently, we discussed the conformational equilibria and geometry of some tricyclic quinolizidine-piperidine alkaloids [1,3]. Seco(11,12)-12,13-didehydromultiflorine (**3**), seco-(11,12)-5,6-didehydromultiflorine (**4**), and cytisine assume practically exclusively the conformation with ring C in the chair form. Up untill now, the conformation of angustifoline (**5**) has not been fully resolved. The fact that the Bohlmann band ("trans" band) [4] in the IR spectrum is only trace, seems to indicate a substantial domination of the chair conformation of ring C with the endo N-H bond in **5**. The presence of the band can be related not only to a low contribution of the boat conformation of ring C, but also to the co-occurrence of the chair form with the exo N-H bond and the endo lone electron pair. The chemical shift of H8β in **5** could indicate a certain contribution of the boat conformer [1]. Unfortunately, a strong coupling between H13α and H13β prevents determination of the coupling constant H7-H13β. In earlier work we gave a value of 4.5 Hz as a tentative result following from a simulation of part of the spectrum performed by M.Popenda [4]. This value was also an argument for the presence of conformational equilibrium in angustifoline.



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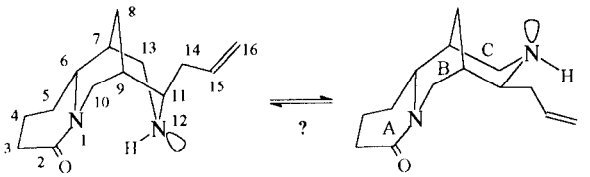

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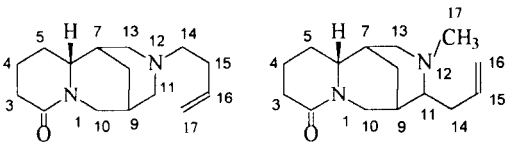
In this work we come back to the problem of angustifoline's conformation in the new context – in the light of data on two other quinolizidine-piperidine alkaloids of similar structure: tetrahydrorhombifoline (**6**) and N-methylangustyfoline (**7**).



6 **7**

Tetrahydrorhombifoline was first isolated from the seeds of *Lupinus angustifolius* by Bohlmann et al. [6]. They also determined the structure of **6**

Bratek-Wiewiórowska proved that the IR spectra of **6** and some of its deuterated derivatives are in agreement with those expected for the compound in the all-chair conformation [7]. NMR, especially ^{1}H NMR is a more accurate method of stereochemical investigation. Unfortunately, the results of Bohlmann and Schumann [8,9] obtained by means of a 100 MHz spectrometer, allowed assignment of only a small number of the signals. A ^{13}C NMR spectrum of **6** was published but not assigned [10].

N-Methylangustifoline (**7**) was obtained for the first time by methylation of **5** by Knöfel and Schütte [11]. Much later, it was proved to occur as a trace alkaloid in *Lupinus polyphyllus* [12]. On the basis of the Bohlmann band in the IR spectra of **7** and its deuterated derivatives, Bratek-Wiewiórowska suggested the occurrence of conformational equilibrium in **7**, and estimated the contribution of its conformer as about 10 % [7]. Bratek-Wiewiórowska also published an 80 MHz ^{1}H NMR spectrum of **7** in which only a few signals could be separated and assigned [13]. As far as we know, no ^{13}C NMR spectrum of **7** has been published yet.

Results

^{13}C NMR signals in **6** and **7** were assigned on the basis of the spectra of similar compounds [3], verified by ^{13}C-^{1}H COSY spectra and are shown in Table 1.

Table 1. ^{13}C NMR chemical shifts of tetrahydrorhombifoline (**6**), angustifoline (**5**) and N-methylangustifoline (**7**) in $CDCl_3$ and C_6D_6 (ppm from TMS)

C atom	**6** $CDCl_3$	**5** $CDCl_3$	**7** $CDCl_3$	**6** C_6D_6	**5** C_6D_6	**7** C_6D_6
2	168.86	170.04	169.62	167.78	169.44	168.48
3	32.99	33.53	32.88	33.53	34.05	33.34
4	20.07	20.20	19.83	20.45	21.07	20.26
5	27.94	27.97	27.75	28.23	28.63	28.02
6	58.79	60.29	59.65	58.56	60.61	59.42
7	33.98	32.79	33.43	34.31	33.72	33.90
8	33.43	28.07	26.90	33.83	28.82	27.22
9	29.21	31.25	30.29	29.62	32.13	30.94
10	46.33	48.09	47.32	46.33	48.65	47.48
11	59.23	57.02	63.90	59.19	57.84	64.03
13	53.98	41.92	50.81	54.38	42.55	50.81
14	58.15	37.58	30.59	58.70	38.43	30.16
15	31.40	136.14	135.90	31.88	137.53	136.34
16	137.02	116.72	116.50	137.42	116.61	116.34
17	115.08		Me 42.32	115.44		Me 42.46

9 [19]: Me 46.88

Most of the ^1H signals were assigned to the particular protons in **6** using mainly ^1H-^1H COSY and ^{13}C-^1H COSY methods. Some interpretation problems stemming from the second order character of the spectra and overlapping of signals appear in two regions: from 1.10 to 1.45 ppm with signals from 7 protons and from 1.95 to 2.15 ppm with signals from 3 protons. These were also resolved using the J-resolved spectra. The assignment of the majority of signals was verified by means of NOESY spectra. The NOESY spectra allowed us to distinguish some equatorial protons from axial ones, among them very important for the stereochemical considerations H11β and H13β from H11α and H13α, respectively. The spectra of **6** recorded in other solvents were solved in a similar manner. Chemical shifts of all protons in **6** in $CDCl_3$ and C_6D_6 are presented in Table 2.

Table 2. ^1H NMR chemical shifts of tetrahydrorhombifoline (**6**), angustifoline (**5**) and N-methylangustifoline (**7**) in chloroform-d and benzene-d_6 (ppm from TMS)

H atom	**6**[a]	**5**[b]	**7**	**7 – 5**[c]	effect of methyl group[d]	**6**	**5**	**7**
		chloroform-d					benzene-d_6	
3α	2.27	2.35	2.30			2.19	2.10	2,12
3β	2.43	2.50	2.43			2.44	2.40	2,40
4α	1.84	1.92	ca. 1.8			1.37	1.25	1.35
4β	ca. 1.66	1.70	1.66			1.22	1.24	1.19
5α	ca. 1.7-1.9	1.80	ca. 1.7-1.8			1.37	1.06	1.22
5β	ca. 1.7-1.9	1.82	ca. 1.7-1.8			1.15	1.09	1.16
6	3.47	3.49	3.40	-0.09	-0.06	2.90	2.84	2.82
7	1.66	1.52	1.72	+0.20	+0.19	1.00	0.84	1.12
8α	ca.1.8	2.14	2.00	-0.14	-0.14[e]	1.31	1.72	1.71
8β	ca. 1.7	1.61	1.44	-0.17	-0.35[e]	1.23	1.35	1.01
9	1.92	1.76	1.88	+0.12	+0.19	1.41	1.29	1.62
10α	4.68	4.67	4.57	-0.10	-0.33	4.95	4.83	4.89
10β	2.81	2.89	2.74	-0.15	-0.06	2.57	2.57	2.55
11α	2.95	2.90	2.54	-0.36	-0.51	2.74	2.76	2.52
11β	ca.2.2	-	-			1.85	-	-
13α	3.17	3.02	2.49	-0.53	-0.51	2.79	ca. 2.70	2.23
13β	2.02	3.01	2.69	-0.32	-0.70	1.67	ca. 2.70	2.34
14A	ca. 2.1-2.3	2.42	ca. 2.31	-0.11		2.08	ca. 2.30	ca. 2,10
14B	ca. 2.1-2.3	2.26	2.17	-0.09		2.00	2.01	1.97
15	ca . 2.15	5.79	5.72			2.10	5.73	5.57
16cis	5.79	5.06	5.03			5.86	5.01	4.98
16trans		5.02	4.96				5.08	5.04
17cis	4.95					5.05		
17trans	5.02		Me 2.21			5.06		Me 2.04

[a] recorded with Varian Gemini 300 MHz spectrometer; [b] recorded with Bruker DMX-600 MHz spectrometer, ref. 5; [c] difference between the chemical shifts of appropriate protons of **7** and **5**; [d] difference between the chemical shifts of appropriate protons of **9** [16] and **8** [17]; [e] the values could be interchanged.

The majority of the coupling constants were read out directly from the spectra taken in $CDCl_3$ and benzene-d_6, some of them from the 2D J-resolved spectra. All vicinal coupling constants in rings B and C were found except for those involving H8β (axial in ring B; they should be treated as tentative ones). The signal of H8β is superimposed on that of H4β. Unfortunately, of the coupling constants of protons of ring A, only a few are available because of poor data on H4α, H4β, H5α, and H5β. The known coupling constants are presented in Table 3.

The vicinal coupling constants of the protons of rings B and C were used to obtain HCCH dihedral angles from Karplus-like equation according to Haasnoot et al. [14]. The results are included in Table 3.

The majority of ^{1}H signals in the spectrum of 7 can be easily assigned from the spectra ^{13}C, ^{1}H COSY and ^{1}H, ^{1}H COSY. The problems start with the assignment of the following signals:

- H5ax and H5eq, which lie very close to each other and are second order signals,
- H4eq, which lies close to other signals,
- H3ax i H14A, which overlap and are second order signals.

In the spectrum taken in benzene we could assign all signals except that of H14A. Some of the signals of α and β protons were distinguished thanks to the NOESY spectra: the couplings H6/H10ax, H6/H8ax, H10ax/H8ax and H8eq/H13ax allowed a distinction of the relevant protons including H13α and H13β.

The chemical shifts of ^{1}H in the spectra of **7** in benzene and chloroform are given also in Table 3.

^{13}C NMR spectra were recorded at various temperatures from 195 K to the room temperature. As two of the signals in **6** (C6 and C11) are superimposed at 295 K and at low temperature they are not, it was necessary to record a DEPT spectrum at 195 K.

Discussion

Tetrahydrorhombifoline (**6**) and *N*-methylangustifoline (**7**) join angustifoline (**5**) in a logical series. They have the same structure of a three-ring skeleton with a lactam group in ring A and the trans-quinolizidine arrangement of the A/B rings, and differ in the substituents at ring C.

Angustifoline (**5**) is a secondary amine and its IR spectrum shows a poor and low-intense trans band (Bohlmann band). Wiewiórowska assumed the lack of the Bohlmann band [7], and thus she concluded that **5** takes the conformation with the chair ring C, the endo (axial) N-H bond and the exo lone electron pair. The compounds **6** and **7** are tertiary amines, **6** has an *N*-butenyl chain at N12, while **7** – has an exo methyl group and an endo free electron pair. Angustifoline (**5**) and its N-methyl derivative (**7**) have an axial allyl substituent at 11β.

These differences are manifested in the ^{13}C and ^{1}H NMR spectra.

Table 3. ^{1}H -^{1}H coupling constants in tetrahydrorhombifoline[a] (**6**) and N-methylangustifoline[b] (**7**) in solution (Hz) and HCCH torsional angles[c] in tetrahydrorhombifoline in chloroform-d solution

Proton coupled	coupling constant (Hz) 7	**6**	some HCCH torsional angles in **6** HCCH angle	value (grades)
3α-3β	17.0	17.0[b]		
3α-4α		5.9[b]		
3α-4β		12.5[b]		
3β-4α		4.9[b,d]		
3β-4β		2.3[b,d,e]		
3β-5β		2.3[b,e]		
4α-4β	12.4	14.4? 13.0?[b,d]		
4β-5α		13.0[b,d]		
5α-5β		ca.14		
5α-6	ca 10	10.3	H5αC5C6H6	154
5β-6	5.3	4.3	H5βC5C6H6	49
6-7	2.5	3.0	H6C6C7H7	-56
7-8α[f]	3.7	3.4[e]	H7C7C8H8α	-57
7-8β[f]	3.0	4.8? 2.7?[b,d]	H7C7C8H8β	48[g]
7-13α	3.0	3.2	H7C7C13H13α	-55
7-13β	5.1	2.4	H7C7C13H13β	62
8α-8β	12.5	12.3		
8α[f]-9	3.7	3.4[e]	H8αC8C9H9	57
8α-10α	2.2	2.2		
8β[f]-9	3.0	4.8? 2.7?[b,d]	H8βC8C8H9	-62[g]
9-10α	2.1	2.2	H9C9C10H10α	-64
9-10β	3.6	3.5	H9C9C10H10β	53
10α-10β	13.5	13.5		
10β-11β		2.4		
9-11α	2.3	2.6	H9C9C11H11α	60
9-11β		2.4	H9C9C11H11β	-62
11α-11β		10.7		
11α-13α		1.7		
13α-13β	11.9	11.4		
11α-14A	3.7			
11α-14B	9.3			
14A-14B	13.9			
14A-15	6.0			
14B-15	8.3			
14B-16	1.1			
15-16		6.2		
15-16cis[h]	10.2			
15-16trans[h]	16.8			
16-17cis[h]		10.3		
16-17trans[h]		16.9		

[a] in $CDCl_3$ solution, if not stated otherwise; [b] in C_6D_6; [c] from the Haasnoot equation, cf. [14]; [d] uncertain assignment; [e] the value could be averaged; [f] in ring B; [g] values could be interchange; [h] proton trans or cis to H15 in **7** or H16 in **6**.

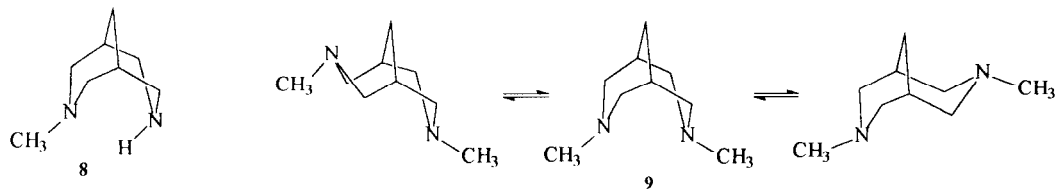
a) ^{13}C NMR spectra.

The signals assigned to the carbon atoms forming ring A and to the majority of atoms from ring B in compounds **5**, **6** and **7**, do not differ significantly, Table 1. Part of the spectrum of tetrahydrorhombifoline corresponding to rings B and C and the butenyl chain is very similar to the corresponding fragments of the spectra of seco(11,12)-12,13-didehydromultiflorine (**3**), which suggests a similar conformation. Significant differences in the chemical shifts ascribed to C8 in tetrahydrorhombifoline (**6**) and angustifoline (**5**) as well as N-methylangustifoline (**7**) are mainly a result of the γ-synclinal effect induced by the allyl carbon atom C14 in **5** and **7**. The lack of substituent at N12 in **5** accounts for the difference in the chemical shifts of C11 and C13 in **5** and **6** or **7**, and also for the difference in the chemical shift of C14 in **5** and **7**. The effect of the N-methyl group may also explain the differences in the chemical shifts of C8 in **5** and in **7** (in the system piperidine – N-methylpiperidine the α, β and γ effect of the methyl group is +8.9, -1.3 and -1.5 ppm, respectively [15]). The differences in the ^{13}C chemical shifts after taking into account these effects are so small that they can hardly be considered in the aspect of changes in the conformations.

b) ^{1}H NMR spectra

The chemical shifts of protons from ring A and some of the protons from ring B (H6, H10α, H10β) are very similar in the spectra of **5**, **6** and **7**, (Table 2), which is a consequence of a structural similarity of rings A and B in these compounds and in particular – the presence of a lactam group. The fragments of the ^{1}H NMR spectrum assigned to the protons from ring C and the n-butenyl chain in **6** are very similar to the corresponding fragments of the spectra of seco(11,12)-12,13-didehydromultiflorine (**3**) [3], which confirms the chair conformation of ring C in **6**.

Also similar are the chemical shifts of the allyl group protons in the spectra of **5**, **7** and those of the protons from the allyl fragment in butenyl group in **6**. The chemical shifts of protons belonging to ring C are different in the spectra of **5**, **6** and **7**. The differences in the chemical shifts of the corresponding protons in **5** and **7** can be explained by the effect of *N*-methyl group. We have estimated this effect analysing the spectra of certain derivatives of bispidine. In *N*-methylbispidine (3-methyl-3,7-diazabicyclo[3.3.1]nonane, **8**) the *N*-methyl group



affects the chemical shift in both *N*-methylpiperidine and piperidine ring. Therefore, we estimated the effect from a comparison of the chemical shifts of protons from *N,N'*-dimethylbispidine (3,7-dimethyl-3,7-diazabicyclo-

[3.3.1]nonane, **9**) [16] and **8** [17]. The results of the estimation are given in Table 2. We are aware of the fact that the model compounds are not the ideal ones (better were not available) as *N*-methylbispidine (**8**) has a double-chair conformation [17], while dimethylbispidine (**9**) is at the conformational equilibrium with a contribution of about 22% of the boat-chair form [17]. The chemical shift of the majority of protons in the spectra of *N*-methylangustifoline can be explained by the effect of the methyl group, Table 2. An important exception is the chemical shift of H13β. As follows from the studies on conformational equilibria in bis-quinolizidine alkaloids, the chemical shift of the analogous proton (H17β) in the compounds of the sparteine (**1**) skeleton is particularly sensitive to conformational changes [18].

The paramagnetic shifts of the signals corresponding to H8α in **5** and **7** with respect to that in **6** can be accounted for by the overcrowding effect caused by a close distance of one of the protons from the allyl group (H14B), which is reflected by the presence of the cross-peaks of H8α/H14B in the NOESY spectra of **5** and **7.**

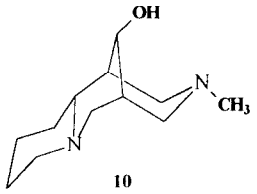
The differences in the chemical shifts of H8α in **5** and **7** can be explained by the effect of methyl group. Even if there is the overcrowding effect related to the differences in the conformational equilibria in **5** and **7**, it is too small to be considered.

In the bis-quinolizidine alkaloids with the boat conformation of ring C, the chemical shift of H8β is of about 1 ppm, while in the compound with the chair conformation H8β gives the resonance at a lower field [19]. This observation seems to be valid for the quinolizidine–piperidine compounds as well. The values of the chemical shift of H8β may be used as a criterion testifying that the greatest contribution of the boat form is in **7**, lower in **5** and the lowest in **6**.

The coupling constants ^{1}H-^{1}H between the protons from the rings B and C of tetrahydrorhombifoline (**6**) (Table 3) take values similar to those obtained for all-chair compounds **3** and **4**. In particular the $J_{7\text{-}13\beta}$ = 2.5 Hz (in some spectra 2.4 Hz) and $J_{7\text{-}11\beta}$ =2.5 Hz testify to a practically exclusive chair conformation of the ring C in **6**. This fact enables the calculation of the HCCH torsional angles (Table 3) from the modified Karplus equation [14]. The angles are comparable to their correspondents in **3** and **4** and prove the presence of a rather regular chair ring C.

In *N*-methylangustfoline (**7**) the coupling constant $J_{7\text{-}13\beta}$ is 5.1 Hz, which means that **7** is at a conformational equilibrium. To calculate the ratio of conformers the values of coupling constants of pure conformers are needed. The method, which we developed for four-ring compounds of the sparteine skeleton, assumes that for the boat conformer the coupling constant corresponding to $J_{7\text{-}13\beta}$ in the three-ring compounds is 10.8 Hz, while for the chair conformer it is 2.7 Hz. If these data were used for **7**, the contribution of the boat conformer would be 29.6%. However, the three-ring compounds should have their own specific models of both conformers. The lowest value of $J_{7\text{-}13\beta}$ in this class of compounds is 2.3 Hz for **3** and **4** [3], and this value should be assumed as characteristic of the chair conformer. It is more difficult to propose a value characteristic of the boat conformer. The only trans-quinolizidine-piperidine compound of the boat ring C known to us, i.e.

13α-hydroxy-11-methyl-7,11-diazatricyclo[7.3.1.$0^{2,7}$]tridecane (**10**) has coupling constants (according to traditional numeration for alkaloids) $J_{7\text{-}13\beta}$ and $J_{9\text{-}11\beta}$ equal to 9.5 Hz [20]. In our opinion these values are too low for pure boat conformation, so it seems probable that **10** occurs at a conformational equilibrium with a small contribution of the chair conformer. We would like to propose a tentative value of $J_{7\text{-}13\beta}$ for the boat conformer as 10.6 Hz which is the same as for the bicyclic compounds of the bispidine skeleton [2]. Assuming this value, the contribution of the boat conformer in **7** is estimated as 33.7%.



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Because of such a high contribution of the less abundant conformer the calculation of the torsional HCCH angles in **7** is pointless.

From among the angustifoline derivatives for which the coupling constants have been determined, in *N*-carboxymethyl ester of angustifoline the value of $J_{7\text{-}13\beta}$ is 3.0 Hz, while in *N*-formyloangustifolinie - 3.5 Hz [12][1]. For pure angustifoline we were not able to determine $J_{7\text{-}13\beta}$ even at a frequency of 600 MHz [5]. Thanks to the Lorentzian to Gaussian transformation we could obtain the fragment of the spectrum containing the H13α and H13 signals, which was possible to simulate. The simulation performed by the NMRSIM23 [21] program gave the value of $J_{7\text{-}13\beta}$ equal to 4.25 Hz, which corresponds to a contribution of 23.5% of the boat conformer in **5** (assuming the model values of 2.3 Hz and 10.6 Hz for the chair and boat conformers, respectively). A similar value of $J_{7\text{-}13\beta}$, equal to 4.03 Hz was obtained when using the program DAISY [22], and the contribution of the boat conformer in **5** which would correspond to this value was ~ 20.8%.

The molecular modelling [23] and the Haasnoot [14] equation lead to overestimated values of the coupling constants $J_{7\text{-}13\beta}$ i $J_{9\text{-}11\beta}$ for tetrahydrhorombifoline (**6**). The value of $J_{7\text{-}13\beta}$ calculated for **5** and **7** is close to that of **6**, which means that the actual value of $J_{7\text{-}13\beta}$ for the chair conformer of **5** and **7** should also be close to 2.5 Hz. Therefore, much higher experimental values of $J_{7\text{-}13\beta}$ provide a qualitative proof of the presence of a conformational equilibrium in **5** and **7**.

The ^{1}H-^{1}H NOESY spectra provide evidence for the prevalence of the chair conformer in **5**, **6** and **7** in the form of cross-peaks H8α/H13β, H8α/H11β (in **6**) or H8α/H14B (in **5** and **7**). On the other hand, no characteristic signals, whose appearance might prove its presence, are related to the boat conformation.

c) Temperature spectra

The temperature spectra were taken in deuterated methanol and deuterated chloroform. In methanol we reached 195 K, while in chloroform 220 K, unfortunately we were not able to reach the temperature of coalescence. In the spectra of **6** no significant signal broadening was observed. In the spectrum of angustifoline (**5**) at 195 K the signal assigned to C14 was broadened, while in that of N-methylangustyfoline (**7**) broadened were the signals from C13 and C14.

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[1] In ref. 12 no differentiation of α and β protons was given. Other possible values: 2.0 and 2.5 Hz, respectively.

When there are no temperature induced conformational changes in a rigid hydrocarbon, with increasing temperature its ^{13}C NMR spectrum reveals a small deshielding effect, up to 0.0060 ppm/ degree [24]. A heteroatom may reverse the direction of changes for α carbon atoms, while its effect on β carbon atoms is small and on γ carbon atoms it is practically unnoticed. A greater deshilding effect at β- and γ- carbon atoms or the appearance of the shielding effect with increasing temperature (disregarding the effect on TMS) are interpreted as due to a change in conformation or in the case of conformational mixture a change in its composition [24]. In tetrahydrorhombifoline only one atom, C11 shows a shielding effect, but it is an α carbon atom with respect to the nitrogen atom. All other atoms important from the conformational point of view show a deshilding effect and only the effect of C7 is slightly greater than that assumed for compounds of uniform conformation (0.0082 ppm/ degree). Thus, it can be assumed that **6** has a uniform conformation or its conformational changes are very small. For angustifoline all atoms from rings B and C as well as C14 show the deshielding effect whose value for C13 is 0.0081ppm/degree, and for C9 even 0.0162 ppm/degree. These effects by themselves are not a strong evidence for conformational changes, however, considered together with the other effects it may indicate the inhomogeneous conformation of **5**.

Significant changes with increasing temperature are observed in the spectra of N-methylangustifoline. A few C atoms show a significant deshielding effect, which were the maximum for C7 and C8, by about 0.0110 ppm/deg. Two atoms show the shielding effect which is small for C13 (at the α position relative to the nitrogen atom) and may not be convincing but for C14 it is significant (Fig. 1). This atom is particularly sensitive to conformational changes, in the chair conformation it assumes an axial position, while in the boat conformation – an equatorial one.

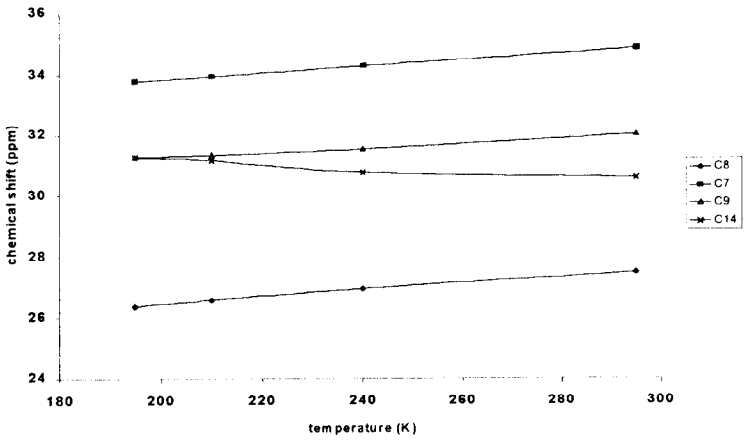

Fig. 1. Temperature dependence of ^{13}C chemical shifts of some C atoms in N-methylangustifoline (**7**) (CD_3OD solution).

Conclusions

Tetrahydrorhombifoline (**6**) was proved to occur in a practically pure and quite regular conformation with chair rings B and C. Impossibility of determination of all coupling constants of ring A protons does not allow a discussion of the geometry and conformation of this ring.

There is increasing evidence suggesting a conformational inhomogeneity of angustifoline (**5**) . As follows from the simulation of the second order fragment of the spectrum including the signals from protons H13α and H13β at room temperature the contribution of the boat conformer in **5** is ~ 23.5%. This value should be verified by measurement of $_{7\text{-}13\beta}$ directly from the spectrum. Unfortunately, as yet all attempts at separation of the signals assigned to H13α and H13β, with different solvents and with a spectrometer of the frequency of 600 MHz, have failed and a further increase in the spectrometer frequency does not seem to solve the problem. A possible solution would be analysis of the ^{1}H NMR spectrum of the compound specifically deuterated at the position 13α, which is, however, very difficult to synthesise.

N-methylangustifoline (7) occurs as a mixture of conformers with a contribution of about 30% of the boat conformer (33.7% using the assumed model values). A qualitative confirmation of conformational inhomogeneity of **7** is the temperature change in the chemical shifts of ^{13}C and probably a chemical shift of H8β.

The reason for the occurrence of **7** and probably **5** at conformational equilibrium is the destabilising interaction H8α···H14B. As follows from the calculations by the MMPMI program [23], the distance between these atoms in **7** is 2.39 Å, and in **5** endo – 2.25 Å, which would suggest a greater contribution of the boat conformer in **5** than in **7** and this is contrary to the experimental results. Therefore, there must be an additional effect which would explain a greater contribution of the boat conformer in **7**. As we suppose it could be the interaction of the amine endo H12 with O2 in **5** suggested by Bratek-Wiewiórowska [7], which is also responsible for a significant prevalence of the endo N-H form to the exo N-H form in **5**.

Experimental

Both tetrahydrorhombifoline (**6**) and *N*-methylangustifoline (**7**) were obtained from angustifoline (**5**) (extracted from *Lupinus angustifolius*) according to the method described by Bratek-Wiewiórowska [25] and was characterised as in ref. 7 and 25.

IR spectra were recorded with Perkin Elmer 580 and Bruker FTIR 113v spectrometers.

The ^{1}H and ^{13}C NMR spectra (including ^{1}H-^{1}H COSY and ^{13}C-^{1}H COSY) of tetrahydrorhombifoline in $CDCl_3$ were recorded with a Varian 300 Gemini spectrometer at 300 MHz and at 75.462 MHz, respectively. The NMR spectra of tetrahydrorhombifoline (**6**) in C_6D_6, $(CD_3)_2CO$ and CD_3OD solution, angustifoline (**5**) in C_6D_6 and $CDCl_3$, as well as N-methylangustifoline (7) in $CDCl_3$, C_6D_6 and CD_3OD were recorded at 295 K on Bruker Avance 400 spectrometer equipped with an 5 mm 1H/BB - inverse probe head, operating at 400.13 and 100.62 MHz for ^{1}H and ^{13}C respectively. ^{1}H spectra were measured using 32 pulses with an acquisition time of 16s. The 90° pulse width was 7.8 μs. The 30° pulse width (2.6 μs) was used. The spectral width was 8224 Hz and the digital resolution was 0.063 Hz per point. ^{13}C spectra

(including DEPT-45, 90, 135) were recorded using a 30° (9.2 μs) pulse, 1024 transients, spectral width 31850 Hz, acquisition time 2.06 s, delay time 1s and digital resolution 0.48 Hz per point. The 90° pulse for ^{13}C measurement was 9.2 μs. For standard ^{13}C spectra the 30° (3.0 μs) pulse was applied. Deuteriated solvents were used as an internal lock. All chemical shifts were determined relative to internal TMS. Two-dimensional spectra were acquired using standard Bruker software. Heteronuclear correlation (^{13}C, ^{1}H COSY) was adjusted for 145 Hz. In ^{1}H, ^{1}H NOESY experiment the mixing time 0.9 s was used. Enhanced resolution spectrum was obtain by Lorentzian to Gaussian transformation (LB = - 2.5, GB = 0.8) using Bruker software for PC.

Simulation of the H13α/H13β fragment of the ^{1}H NMR spectrum (in $CDCl_3$):

(a) NMRSIM program [21]: frequency 400.13 MHz, number of points 6584 (covering also signals for H8β and H7), line width 0.9 Hz, δ H7 1.510 ppm, δ H8β 1.590 ppm, δ H13α 3.00865 ppm, δ H13β 2.99095 ppm, $J_{7\text{-}13\alpha}$ = 2.58 Hz, $J_{7\text{-}13\beta}$ = **4.25** Hz, $J_{13\alpha\text{-}13\beta}$ = 14.025 Hz, $J_{7\text{-}8\beta}$ = 2.95 Hz, $J_{8\beta\text{-}13\alpha}$ = 1.91 Hz, $J_{6\text{-}13\beta}$ = 0.00 Hz,
standard devition 0.051.

(b) DAISY program [22]: frequency 400.13 MHz, number of points 986, resolution 0.063 Hz/point, δ H7 594.72 Hz, δ H8β 632.26 Hz, δ H13α 1204.1152 Hz, δ H13β 1196.9.024 Hz, $J_{7\text{-}13\alpha}$ = 2.34 Hz, $J_{7\text{-}13\beta}$ = **4.03** Hz, $J_{13\alpha\text{-}13\beta}$ = -13.66 Hz, $J_{7\text{-}8\beta}$ = 1.77 Hz, $J_{8\beta\text{-}13\alpha}$ = 2.60 Hz, standard devition 0.097.

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