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Effect of hydroxy groups on conformational equilibrium in bis-quinolizidine systems

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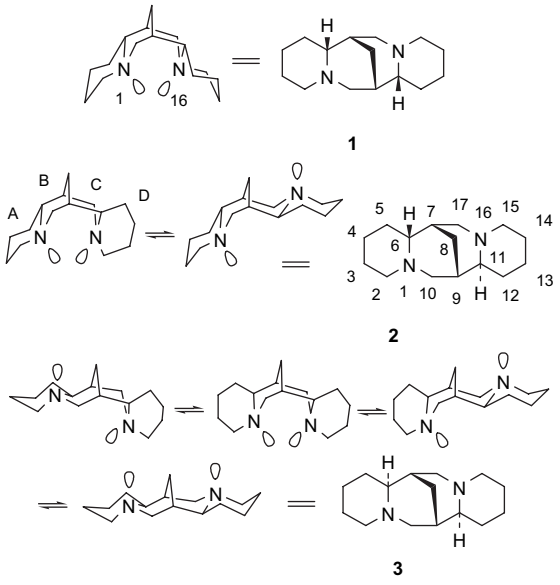
Abstract

A review of the 99 ^{13}C NMR spectra of 72 hydroxy, methoxy or ester derivatives of alkaloids with the sparteine skeleton has been made. An improved method of determination of the conformer fractions in conformational equilibria in bis-quinolizidine compounds of sparteine type has been used to estimate the energy of the hydroxy group effect at various positions. The effect can be explained by intermolecular hydrogen bonds.

Keywords: Sparteine; Quantitative method of conformational equilibrium determination; ^{13}C NMR spectroscopy; ^{1}H NMR spectroscopy

1. Introduction

Quinolizidine alkaloids make one of the most abundant groups of alkaloids distributed within the Fabaceae (Leguminosae). Of the three sparteine diastereoisomers, α-isosparteine (**1**) is practically conformationally homogeneous. According to DFT calculations, the energy difference between the most stable trans–trans full-chair conformer and the conformer with the boat conformation of ring C is 5.9 kcal mol^{-1} (there is only 4.7×10^{-3}% of the less abundant conformer).[1] In contrast, the skeleton of sparteine (**2**) is very flexible, so sparteine derivatives can assume a conformation with ring C either a boat (the boat conformer) or a chair (the chair conformer), or occur in conformational equilibrium. The skeleton of β-isosparteine (**3**) is also very flexible[1] but there is scarce information on the conformation of **3** and its derivatives.[1,2]



The majority of bis-quinolizidine alkaloids with the sparteine skeleton occurs in conformational equilibrium in solution. In order to determine the fractions of conformers in equilibrium, we have proposed a method based on NMR spectroscopic data.[3–8]

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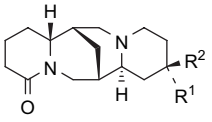
Two years ago, we published our new X-ray, NMR and IR studies of the conformation of 13α-hydroxylupanine (**4**) and 13β-hydroxylupanine (**5**) in the solid phase and in solution.[9] In the solid state the molecules of both 13-hydroxylupanines assume the chair conformation unlike most related compounds. For example, lupanine (**6**), which is lacking the hydroxy group occurs in the solid in the boat conformer.[10] In $CDCl_3$ solution of **4** or **5**, an equilibrium exists and it is shifted towards the dominant boat form, whose fraction amounts to ca. 85%. We explained such an unexpected and very interesting inversion of conformational preference by changes in the systems of intermolecular hydrogen bonds. In the solid, a bond between the lactam C═O group and the OH group of the neighbouring molecule stabilizes the chair conformer—as follows from both X-ray diffraction results and IR (KBr) spectrum. In $CDCl_3$ solution, this bond is retained only in a small population of molecules and three novel bonds arise: OH group with N16 atom of the neighbouring molecule and two bonds with the solvent—those of the lactam C═O group and N16 atom, whose presence is detected in the IR spectrum.[9] The change in the conformation preference of both 13-hydroxylupanine epimers demonstrates how sensitive the sparteine system is to even a little change in the factors influencing the conformation.

We use a handbook[11,6] equation

$$F_C = \frac{\delta_{exp} - \delta_C}{\delta_B - \delta_C} \quad (1)$$

where F_C is the fraction of the chair conformer, δ_{exp} is the experimental chemical shift of the appropriate C atom (or coupling constant), δ_B is the chemical shift of the same atom in the boat conformer (or model compound **2**), and δ_C is the chemical shift of the same atom in the chair conformer (or model compound 5,6-didehydromultiflorine **7**).

We tried to corroborate our results with other methods. Unfortunately, the molecular mechanics methods failed. Some non-quantitative results were obtained using IR spectroscopy, especially in the Bohlmann band region.[9] Recently, the confirmation of some results was delivered in the papers by Galasso et al.[1,12–14] who used the density functional theory (DFT) calculations with the B3LYP hybrid functional. Results for conformational equilibria very similar to ours were obtained for lupanine (**6**),[6,12] 2,13-dioxosparteine (**8**)[5,12] and multiflorine (**9**).[6,14] Therefore, we think it is the first calculation method, which gives results consistent

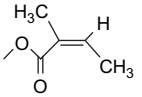


4 R^1 = OH, R^2 = H

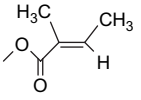
5 R^1 = H, R^2 = OH

6 R^1 = H, R^2 = H

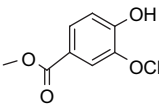
33 R^1 = H, R^2 = OCH_3



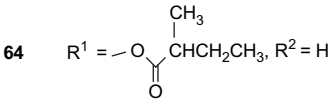
37 R^1 = , R^2 = H



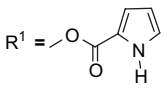
41 R^1 = , R^2 = H



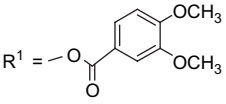
42 R^1 = , R^2 = H



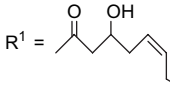
64 R^1 = , R^2 = H



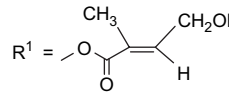
65 R^1 = , R^2 = H



66 R^1 = , R^2 = H



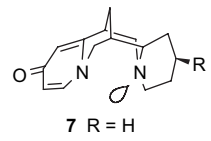
67 R^1 = , R^2 = H



68 R^1 = , R^2 = H

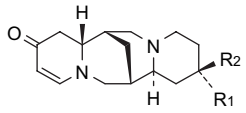
Our method of determination of the fraction of a conformer makes use of the NMR spectrum parameters that are especially sensitive to conformation changes and possibly independent of any factors other than conformational ones.[3,4,6] Of the few parameters that were originally taken into account,[4] the chemical shifts of C(12) and C(14) atoms and $J_{H7-H17\beta}$ coupling constants were eventually chosen.[6]

with experimental ones for the conformational equilibria. Very recently, Galasso et al. published the results for 5,6-didehydromultiflorine (**7**).[14] According to them, the fraction of the boat conformation in the equilibrium is about 9.13%—the conformational equilibrium is not shifted towards the dominant chair conformation as much as we had assumed.



7 R = H

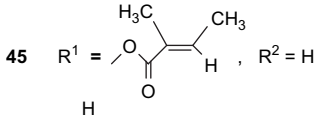
46 R = OH



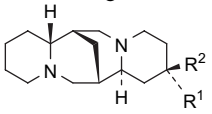
9 R^1 = H, R^2 = H

43 R^1 = OH, R^2 = H

44 R^1 = H, R^2 = OH



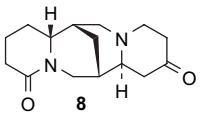
45 R^1 = , R^2 = H



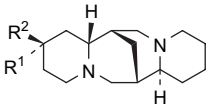
13 R^1 = OH, R^2 = H

14 R^1 = H, R^2 = OH

59 R^1 = $OCOCH_3$, R^2 = H



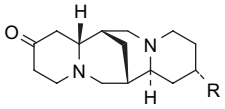
8



10 R^1 = OH, R^2 = H

11 R^1 = H, R^2 = OH

12 R^1 = CH_3, R^2 = OH



15 R = H

27 R = OH

The method we have hitherto applied is relatively accurate for compounds with a small amount of the chair conformer but can be less accurate for those with a large fraction of this conformer. We realized that our procedure would be more precise if we took into consideration the Galasso group's results. Our new results are presented in Section 2.

This paper is also an attempt at compilation of conformational equilibrium data for various hydroxy derivatives of sparteine. We try to find out how the hydroxy substituent in different positions of the sparteine skeleton influences the equilibrium and what is the change in the free enthalpy of the equilibrium caused by this substituent. The hydroxy group was chosen because it is probably the most common substituent occurring in the known bis-quinolizidine alkaloids. We have also some experience with the subject as besides the article on 13-hydroxylupanines[9] we have also published papers on 4-hydroxysparteines (**10**,**11**),[15] 4*S*-4-hydroxy-4-methyl-2,3-didehydrosparteine (**12**)[16] and 13-hydroxysparteines (**13**,**14**).[17]

2. Results and discussion

To discuss the influence of hydroxy groups attached to the skeleton of bis-quinolizidine alkaloids, we gathered all available ^{13}C NMR spectra of their hydroxy, ether and ester derivatives (Table 1) and some ^{1}H NMR (Table 2) and IR spectroscopic data useful for the stereochemical considerations. As for ^{13}C NMR, some data were collected by Mikhova and Duddeck,[18] however, they were incomplete and are out of date now.

If the results of the calculations performed by Galasso's group are correct, δ_{C12}=34.78 ppm for sparteine (**2**)[6] must correspond to 99.68% of the boat conformer[1] and δ_{C12}= 22.24 ppm for 5,6-didehydromultiflorine (**7**)[6] to 9.13% of this conformer.[14] The difference in the chemical shifts of C12 in **2** and **7** equals to 12.54 ppm must then correspond to 90.55% of the conformer amount. The difference in the chemical shifts of C12 for pure chair and boat conformers (100%) must be equal to **13.85 ppm**—this is our new $\delta_B-\delta_C$ value. The new value of the C12 chemical shift for the model of the boat conformer must be **34.89 ppm** and the new value of the C12 chemical shift for the model of the chair conformer is **21.04 ppm**. The detailed equation for the fraction of the boat conformation derived from the chemical shift of C12 becomes now

$$F_{C12}=\frac{34.89-\delta_{C12}}{34.89-21.04}=\frac{34.89-\delta_{C12}}{13.85} \tag{1a}$$

In a similar way, we can express the equations for the chemical shift of C14

$$F_{C14}=\frac{26.04-\delta_{C14}}{26.04-18.21}=\frac{26.04-\delta_{C14}}{7.83} \tag{1b}$$

and the $J_{H7-H17\beta}$ coupling constant

$$F_{C14}=\frac{10.8-J_{H7-H17\beta}}{10.8-1.9}=\frac{10.8-J_{H7-H17\beta}}{8.9} \tag{1c}$$

Of the above three parameters, the ^{13}C chemical shifts are much more accurate.[†] Actually, there is no compound whose diagnostic parameters depend only on conformational factors; even distant substituents can influence the geometry of ring D and intermolecular hydrogen bonds involving the N1 atom or a hydroxy group at position 13 can change the electron density of carbon atoms, so *the results obtained for the conformational equilibria are only approximations*. Also the $J_{H7-H17\beta}$ coupling constant can be affected by a substituent (but rather in the vicinity of C7 and C17 atoms). Nevertheless, we have determined some conformational equilibria in bis-quinolizidine alkaloids to quite a good accuracy. The confirmation of the method's correctness is the similarity of the results obtained for different parameters[6] and for some compounds—also the results of Galasso's DFT calculations.

Our new results of conformer fraction determination seem to be more reliable than the former ones obtained without

[†] The mathematical accuracy (spectral line resolution) can be different for different spectra; it depends on the number of points in the spectrum and the width of the spectral window and is correlated with the frequency of the spectrometer. For instance, in the 75.46 MHz ^{13}C NMR spectrum of 13β-hydroxylupanine (**5**), the spectral line resolution amounts to 22,573 Hz (=299.144 ppm)/67,720 points=0.0044 ppm/point. In the 600 MHz ^{1}H NMR spectrum of **5**, the spectral line resolution is 0.084 Hz≈0.1 Hz.

Table 1
^{13}C NMR chemical shifts in hydroxy derivatives of sparteine and related compounds ($CDCl_3$ if not mentioned otherwise)

Compound	Carbon atom																Ref.
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17	Others	
10	53.81	34.43	69.33	38.71	63.78	32.74	27.14	35.89	60.94	64.30	35.02	24.78	25.71	55.38	53.25		15
11	52.58	32.26	64.65	35.85	59.17	32.23	27.37	35.55	61.37	64.09	33.37	24.51	24.51	55.19	49.17		15
20	55.2	25.8	24.5	29.8	64.6	43.2	73.9	40.4	60.3	63.6	36.0	24.5	26.1	54.9	52.9		25
25	57.1	25.1	24.7	29.4	65.2	37.2	44.6	71.6	62.5	67.7	25.3	24.3	25.0	55.4	57.2		25
25	55.98	25.56	24.61	28.61	65.37	33.73	26.27	68.97	68.78	68.26	36.51	24.80	25.29	55.71	53.12		28
26	56.2	25.8	24.6	29.3	66.3	33.0	28.1	32.7	62.3	67.7	70.7	31.4	19.8	55.0	52.9		25
26	56.2	25.8	24.6	28.8	66.4	32.7	29.3	33.0	62.2	66.9	70.9	31.3	19.9	54.8	52.8		22
13	56.2	25.7	24.7	29.3	66.5	35.6	27.4	33.1	61.7	57.2	41.7	64.6	32.8	49.2	53.2		25
13	56.12	25.77	24.69	29.28	66.41	32.98	27.43	35.48	61.63	57.25	41.54	65.01	32.76	49.13	53.18		17
59	56.3	26.0	24.8	29.5	66.5	35.7	27.4	33.3	61.9	58.3	38.4	68.8	29.5	49.8	53.1		25
59	56.21	25.79	24.66	29.39	66.41	33.02	27.30	35.34	61.66	58.08	37.80	68.53	29.67	49.61	52.72		58
14	56.27	25.92	24.75	29.40	66.45	33.12	27.48	35.81	61.66	61.86	43.57	69.34	35.24	52.83	52.61		17
12	137.61	103.73	68.53	42.66	59.67	31.72	27.06	35.48	57.35	64.28	34.35	24.80	25.69	55.52	52.73	CH_3, 31.72	59
12[a]	137.74	107.57	68.82	43.83	60.62	32.93	28.02	36.93	58.10	64.82	35.44	26.02	26.92	56.30	53.63	CH_3, 32.93	59
28	172.1	67.6	26.9	22.3	59.5	33.4	26.9	34.3	42.7	63.5	31.5	24.4	23.6	55.0	51.3		31
28	172.05	67.53	26.67	22.32	59.26	33.66	26.93	34.27	47.23	63.17	31.54	23.78	24.50	54.84	51.31		30
29	166.86	69.98	25.36	21.63	60.30	32.90	26.65	34.90	47.15	63.50	33.16	24.43	24.98	55.30	52.13	CO, 169.89; Me, 21.63	30
30	173.6	67.9	24.4	26.2	61.5	34.4	27.1	32.1	47.7	64.0	33.2	24.2	25.0	55.3	52.7		33
30	172.9	67.3	26.6	23.6	60.8	31.5	25.7	33.8	47.0	63.3	32.6	23.9	24.4	54.6	52.1		32
32	171.5	70.9	70.3	26.3	57.8	34.0	32.5[b]	31.7	48.3	64.1	30.2	24.4	24.3	55.4	52.1	C1′, 167.8; C2′, 127.8; C3′, 139.2; C4′, 15.5; C5′, 20.1	33
35	172.0	33.2	19.2[c,d]	32.2	85.5	37.5	15.9[d]	34.3	42.5	64.3	34.2	24.1	24.1	55.3	54.1		36
35	171.6	33.1	19.4[c,d]	32.4	85.5	37.8	15.8[d]	34.5	42.8	63.9	34.1	24.4	24.6	55.2	54.3		60
35	171.6	33.1	15.9[c]	32.5	85.7	38.0	19.4	34.2	42.8	63.9	34.1	24.5	24.6	55.2	54.4		37
35[e]	174.3	33.8	16.6[c]	35.1	86.7	39.3	20.2	36.1	44.0	65.7	33.5	28.7	25.5	56.6	55.4		38
60	172.3	32.8	17.2	32.0	89.5	35.8	19.8	34.3	42.9	63.6	34.1	24.2	24.6	55.1	53.6	OMe, 49.3	37
61	171.2, 162.9[f]	33.0, 116.9[f]	20.6, 138.8[f]	38.1, 104.6[f]	87.1, 150.5[f]	32.3, 35.3[f]	19.4, 25.7[f]	35.1, 28.3[f]	42.9, 49.9[f]	63.8, 62.1[f]	34.3	24.4, 61.0[f]	24.7, 46.1[f]	55.2	54.4		37
36	171.5	33.0	19.5	27.3	61.0	31.9	27.9	32.1	47.0	66.7	70.6	30.9	19.8	55.0	52.5		40
4		32.9	19.6	26.6	60.8	34.2	27.3	31.6	46.8	57.0	39.9	64.0	32.4	49.2	52.4		25
4[g]	171.2	33.7	20.3	27.2	61.1	32.6	27.8	35.3	47.3	57.7	40.6	64.5	33.2	49.9	52.8		42
4	170.9	32.9	19.6	26.6	60.8	34.2	27.3	31.6	46.8	57.0	39.9	64.0	32.4	49.2	52.4		61
4[e]	171.9	32.9	19.4	26.3	60.7	33.8	27.3	31.9	46.6	57.4	39.5	63.7	31.2,	49.4	52.2		43
4	171.69	32.84	19.35	27.19	60.73	31.97	26.31	33.87	46.59	57.14	39.48	63.68	31.21	49.27	52.15		30
4[h]	172.3	32.4	18.9	26.8	60.7	31.8	25.9	33.8	46.6	56.7	39.2	67.9	30.9	49.0	52.2		44
4	172.3	32.4	18.9	26.8	60.7	31.8	25.9	33.8	46.6	56.7	39.2	63.6	30.9	49.0	52.2		45
4	171.19	33.09	19.78	27.46	60.86	32.40	26.62	34.30	46.75	57.11	40.17	64.46	31.73	49.16	52.43		9
37	171.33	32.90	19.83	26.31	60.50	33.85	27.56	32.68	46.81	58.87	35.09	67.84	28.33	49.86	51.49	C1′, 166.25; C2′, 126.45; C3′, 139.61; C4′, 14.74; C5′, 18.96	52

(*continued on next page*)

Table 1 (*continued*)

Compound	Carbon atom																Ref.
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17	Others	
37	170.9	32.9	19.6	26.5	60.6	34.0	27.4	32.2	46.6	57.9	36.4	67.7	28.8	49.8	52.0	C1′, 167.4; C2′, 128.2; C3′, 137.6; C4′, 16.0; C5′, 20.8	33
38	173.8	67.7	24.3	26.1	61.2	33.5	27.2	32.2	49.7	57.8	35.8	67.9	28.3	47.8	51.7	C1′, 167.3; C2′, 128.1; C3′, 137.5; C4′, 15.9; C5′, 20.7	33
38[i]	173.8	67.7	24.3	26.1	61.3	33.6	27.2	32.2	47.8	57.9	35.8	67.9	28.3	49.7	51.7	C1′, 167.3; C2′, 128.1; C3′, 137.6; C4′, 15.9; C5′, 20.7	51
40	173.7	67.9	24.6	27.5	60.4	40.9	72.7	39.2	45.1	58.1	38.9	66.6	29.7	49.6	52.4	C1′, 167.2; C2′, 128.0; C3′, 137.7; C4′, 16.0; C5′, 20.8	33
40[i]	173.7	67.9	24.6	27.5	60.4	40.9	72.7	39.2	46.3	58.1	38.9	66.6	29.7	49.6	52.4	C1′, 167.2; C2′, 128.0; C3′, 137.7; C4′, 16.0; C5′, 20.8	51
62	174.0	68.0	24.7	27.5	60.5	40.9	72.7	39.2	46.2	57.0	42.0	63.7	32.7	48.6	52.4		51
63	171.5	32.9	19.8	27.7	59.5	41.3	73.1	39.3	45.4	56.7	42.0	63.4	32.1	48.5	52.3		51
39	171.0	32.7	19.7	27.6	59.3	41.0	72.9	39.2	45.1	57.6	38.9	66.5	29.6	49.3	52.1	C1′, 167.1; C2′, 127.9; C3′, 137.7; C4′, 15.8; C5′, 20.6	33
41	171.14	33.01	19.66	26.37	60.63	33.80	27.50	32.81	46.69	58.25	35.89	67.73	28.30	49.93	51.49	C1′, 167.10; C2′, 128.76; C3′, 137.63; C4′, 14.47; C5′, 12.16	52
42	171.26	33.04	19.73	26.54	60.66	34.12	27.50	32.44	46.78	58.17	36.43	68.43	28.71	49.85	51.86	OMe, 56.04; C1′, 170.98; C2′, 123.03; C3′, 137.63; C4′, 152.86; C5′, 148.55; C6′, 110.37; C7′, 111.85	52

64	170.93	33.01	19.46	26.81	60.62	33.66	27.36	31.94	46.41	58.91	35.75	67.54	27.52	50.42	51.51	C1′, 167.19; C2′, 41.07; C3′, 26.55; C4′, 11.30; C5′, 16.74	52
65[e]	171.6	33.1	19.5	26.6	60.7	34.2	27.3	32.6	46.9	57.6	36.1	68.0	28.7	49.9	52.1	C18, 160.2; C19, 122.9; C21, 123.4; C22, 110.3; C23, 116.1	43
66	171.0	33.0	19.7	27.5	60.6	32.4	26.5	34.0	46.7	58.2	36.6	68.3	28.6	49.9	51.8	C1′, 123.0; C2′, 111.9; C3′, 148.6; C4′, 153.0; C5′, 110.4; C6′, 123.7; C7′, 165.6; Me 56.0	45
67	171.7	32.9	19.3	27.3	60.8	32.4	26.4	33.9	46.7	57.6	36.4	67.7	29.0	50.2	52.7	C1′, 171.5; C2′, 41.7; C3′, 68.4; C4′, 35.4; C5′, 124.1; C6′, 134.4; C7′, 20.7; C8′, 14.2	45
68	172.0	32.7	18.9	26.3	60.6	33.8	27.0	32.2	46.7	57.5	37.3	67.3	28.9	50.5	53.1	C1′, 166.8; C2′, 127.1; C3′, 143.2; C4′, 60.0; C5′, 12.4	62
5		33.0	19.6	26.7	58.7	34.5[d]	27.4	32.6[d]	46.9	61.3	41.5	69.6	33.8	51.5	53.0		25
5[h]	171.9	32.9	19.4	27.4	60.7	31.8	26.2	34.0	46.6	61.8	40.5	67.9	32.8	52.9	51.0		44
5	171.9	32.9	19.4	27.4	60.7	31.8	26.2	34.0	46.6	61.8	40.5	67.9	32.8	52.9	51.0		45
5	171.25	32.42	19.50	27.31	60.57	32.24	26.62	34.35	46.71	61.17	41.56	68.97	33.84	52.78	51.49		9
33	171.3	32.8	19.4	27.3	60.5	32.4	26.6	34.4	46.7	61.1	37.6	77.4	30.1	52.7	51.3	OCH_3, 55.4	35
34[k]	169.7	42.0	63.2	35.8	57.3	32.7	26.9	34.0	47.2	60.7	36.1	77.5	29.0	52.3	50.2	OCH_3, 55.3	35
69[k]	171.1	74.0	68.7	31.9	57.9	32.2	26.7	33.9	48.3	61.2	36.6	77.5	29.4	52.7	50.7	OCH_3, 55.4	35
18[e]	56.74	26.75	25.46	30.65	67.60	33.75	27.05	35.27	62.19	66.46	36.00	63.08	28.76	65.00	67.00		26
19	171.6	33.6	20.4	28.3	62.8	33.0	26.3	34.3	47.8	65.7	36.0	62.5	28.5	63.1	66.1		26
70	173.8	68.2	26.3	24.5	61.6	33.9	27.4	32.2	47.8	57.3	39.6	64.3	31.5	49.3	52.3		61
70	173.8	68.0	24.4	26.2	61.6	33.9	27.4	32.2	47.8	57.0	39.8	64.6	31.6	49.0	52.3		51
71	173.2	68.0	27.3	24.5	61.3	32.4	26.3	33.7	47.9	57.8	35.4	68.0	28.1	49.6	51.3	C1′, 167.4; C2′, 129.2; C3′, 137.1; C4′, 14.4; C5′, 12.1	63
73	173.7	24.4	67.8	26.2	61.3	33.5	27.2	32.2	47.9	57.9	35.7	68.1	28.0	51.4	49.8	C18, 160.2; C19, 122.8; C21, 123.1; C22, 110.5; C23, 115.8	65

(*continued on next page*)

Table 1 (*continued*)

Compound	Carbon atom															Ref.
	2	3	4	5	6	7	8	9	10	11	12	13	14	15	17	Others	
74[l]	172.7	32.8	19.2	26.8	61.1	31.7	27.3	30.8	47.1	60.9	72.8	66.9	27.1	49.4	52.3		43
75	178.6	34.5	20.7	25.3	65.3	32.5	27.8	32.3	49.1	63.1	70.5	69.8	28.8	52.3	53.4	C18, 163.3; C19, 123.5; C21, 128.2; C22, 113.1; C23, 119.7	43
31	171.47	73.77	68.42	26.58	58.24	34.30	32.97[b]	31.95	48.26	63.98	31.69	24.82	24.53	55.33	52.56		34
76[l]	173.8	75.6	69.6	27.1	59.5	35.3	31.8[b]	33.4	49.9	58.7	39.9	65.3	34.2	50.3	53.0		43
76	173.8	75.6	69.6	27.1	59.3	35.3	31.8[b]	33.4	49.9	58.7	39.9	65.3	34.2	50.3	53.0		66
77[e]	171.8	74.3	68.0	26.5	57.7	33.4	27.5	32.2	48.3	57.4	34.6	68.4	32.4	49.4	50.5	C18, 160.8; C19, 122.9; C21, 123.4; C22, 110.3; C23, 116.1	43
77	171.8	74.3	68.0	26.5	57.7	33.4	27.5	32.2	48.3	57.4	34.6	68.4	32.4	49.4	50.5	C18, 160.8; C19, 122.9; C21, 123.4; C22, 110.3; C23, 116.1	66
78	170.9	70.7	70.3	30.1	57.2	31.9	26.4	33.6	48.2	61.0	36.2	77.4	29.1	52.4	50.3	OMe, 55.3; C1′, 167.1; C2′, 127.4; C3′, 138.7; C4′, 15.7; C5′, 20.4	67
79	171.1	32.6	19.2	32.7	58.8	43.6	26.7	32.2	47.9	53.9	29.8	26.0	18.4	72.3	168.9		68
80	170.69	32.98	19.86	26.97	59.52	43.46	25.02	34.84	47.22	60.41	33.74	25.25	25.76	51.62	85.75		16
27	54.7	41.1	206.5	47.6	64.9	35.2	27.6	33.1	61.0	56.0	40.3	63.8	32.2	50.1	54.7		29
49[e]	42.7	25.1	24.8	29.1	59.4	32.4	22.6	43.2	172.9	52.0	29.3	65.3	25.1	47.8	46.1		43
81[e]	42.6	24.8	22.6	26.0	59.2	32.4	22.6	43.1	172.0	52.6	29.1	69.0	25.1	48.3	45.9	C18, 160.5; C19, 122.8; C21, 123.2; C22, 110.1; C23, 115.7	43
82	42.8	25.0	24.7	29.3	59.9	32.3	22.9	43.8	172.8	53.2	27.2	67.3	23.1	49.1	47.3	C1′, 167.3; C2′, 128.7; C3′, 138.2; C4′, 14.7; C5′, 12.9	29
83	72.1	30.3	25.0	28.1	58.3	31.7	22.2	43.3	172.3	59.0	23.9	25.0	19.1	54.1	53.3		69
50	40.7	21.1	21.4	101.8	138.6	35.2	21.6	43.6	171.2	52.6	29.8	64.1	26.7	48.6	53.7		69
54	72.24	26.46	16.51	103.97	136.46	36.46	28.02	71.41	174.68	64.09	16.31[c]	25.14	18.81	53.64	51.57		28
55	73.16	24.78	17.04	101.89	137.26	36.84	25.88	77.80	169.59	62.49	16.76[c]	25.19	18.94	53.75	52.13	$C{=}O_{ac}$, 169.50; Me, 21.09; $C{=}O_{ac}$, 169.27; Me, 21.28	28

58[m]	72.95[n]						25.36[n] or 26.78[n] or 28.24[n]	71.48[n]			16.38[c,n], or 16.12[c,n]		19.10[c]		52.31[n] or 53.95[n]		28
56	73.32	24.90	16.62	101.73	137.56	36.87	25.13	78.19	169.60	61.62	16.65[c]	25.02	18.87	53.85	52.35	C=O_{ac}, 169.12; Me, 21.08; C=O_{ac}, 168.82; Me, 21.29	28
84[m]	75.12[n]						25.12[n] or 25.43[n]	79.03[n]			16.63[c,n]		18.84[c]		52.30[n]		28
51	72.84	25.55	16.93	102.96	136.84	35.59	21.53	44.50	172.90	58.49	23.18	26.89	19.30	54.33	53.57		28
53	73.42	24.91	16.93	101.98	138.36	35.68	21.19	44.27	171.97	58.37	22.41	25.54	18.94	54.28	53.57	C=O_{ac}, 169.66; Me, 21.19	28
52[m]	71.97[n]						21.70[n]				22.92[n]		19.02[n]		53.00[n] or 54.12[n]		28
43	155.6	98.0	192.4	39.0	59.8	31.0	25.4	33.6	57.2	56.1	37.0	64.3	30.0	48.4	50.1		70
43	155.33	98.99	192.32	39.55	60.41	31.48	25.74	34.13	57.49	56.56	37.71	64.96	30.61	48.65	50.55		54
45	155.1	98.8	192.5	39.6	60.1	31.4	25.7	33.8	57.5	57.3	33.7	68.4	26.9	49.3	49.7	C1′, 167.3; C2′, 129.2; C3′, 137.1; C4′, 14.4; C5′, 12.1	56
44	155.8	98.9	192.3	39.2	58.0	31.6	25.3	32.4	57.1	61.2	38.9	69.2	31.2	51.2	52.3		69
46[e]	142.87	117.68	180.47	116.32	156.91	33.48	21.46	36.36	59.22	57.05	29.80	66.32	26.33	48.98	52.56		54
46[e]	142.8	117.2	178.9	116.2	154.7	31.6	21.6	35.2	59.1	57.2	29.9	65.3	26.0	49.1	52.4		71
85[e]	142.5	117.9	179.2	115.9	155.9	31.6	20.2	32.1	61.1	64.1	25.1	63.9	23.4	64.0	68.2		71
86[e]	63.0	56.9	196.4	159.8	176.2	29.6	34.4	32.8	62.1	58.0	33.4	63.8	29.3	49.1	52.7		72
87	163.5	116.8	138.7	104.5	151.5	35.3	22.8	31.8	48.4	56.6	26.2	69.2	20.6	51.4	52.2	C=O_{ac}, 170.5; Me, 21.4	73
88[e]	165.3	116.5	141.3	107.6	153.6	36.5	22.0	33.4	53.2	64.0	31.8	70.7	30.4	67.6	47.4	CHOH, 67.5; CH_3, 20.0	38
48	163.6	116.5	138.9	105.0	151.8	35.2	20.4	31.8	51.5	65.3[n,o]	29.0	55.8[n,o]	25.7	47.8	52.1		74
48[e]	165.7	117.0	141.0	108.0	153.1	36.3	20.8	33.3	52.9	57.6[c]	30.0	65.7	26.1	48.9	52.8		38
47[e]	165.5	116.6	141.3	107.8	153.8	36.7	21.2	34.4	53.1	62.7	32.6	70.6	29.2	53.4	53.4		38

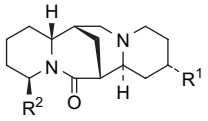
[a] Spectrum recorded in C_6D_6.
[b] Erroneous assignment or α-isosparteine system.
[c] γ-*gauche* Effect.
[d] Should be interchanged.
[e] Spectrum recorded in CD_3OD.
[f] Cytisine moiety.
[g] Spectrum recorded in C_5D_5N.
[h] The authors erroneously interchanged the epimers. The right one is given here.
[i] Data corrected relative to those presented in Ref. 33.
[k] Signals were referenced to $CDCl_3$ solvent.
[l] Spectrum recorded in D_2O+DCl system.
[m] Signals not assigned in the original paper.
[n] Dubious values.
[o] Probably the signals should be interchanged (there is a γ-*gauche* effect on C11 atom).

Table 2
^{1}H NMR parameters important to the stereochemistry determination of the bis-quinolizidine derivatives

Compound	J[a] (Hz)	$\Delta\delta$[b] or δ_{OH} (ppm)	Ref.
(−)-4α-Hydroxysparteine (**10**)		1.02	15
(−)-4β-Hydroxysparteine (**11**)	9.8	0.95	15
(+)-12α-Hydroxy-sparteine [(+)-retamine] (**26**)		0.14[c]	22
13α-Hydroxysparteine (**13**)	10.7	0.98	17
13α-Acetoxysparteine (**59**)		0.96	58
13β-Hydroxysparteine (**14**)	10.7	0.96	17
4*S*-4-Hydroxy-4-methyl-2,3-didehydrosparteine (**12**)			59
4*S*-4-Hydroxy-4-methyl-2,3-didehydro-sparteine (**12**)[d]	11.0		59
3α-Hydroxylupanine (**28**)		0.95	31
3α-Hydroxylupanine (**28**)	10.5	0.84	30
3α-Acetoxylupanine (**29**)	9.0	0.93	30
3β-Hydroxylupanine (**30**)	10.15		33
3β-Hydroxylupanine (**30**)	Large	0.91	32
(−)-3β-Hydroxy-4α-angeloyloxylupanine (sessifoline) (**32**)	10.2	0.98	33
6β-Hydroxylupanine (**35**)		0.26	60
(−)-6α-Methoxylupanine (**60**)	7.4[c]		37
(+)-12α-Hydroxylupanine (**36**)	11.2[c]	0.78	40
13α-Hydroxylupanine (**4**)	10.0	1.01	30
13α-Hydroxylupanine (**4**)	10.0	0.84	44
13α-Hydroxylupanine (**4**)	10.1	0.84	45
13α-Hydroxylupanine (**4**)	9.9	0.90	9
(+)-13α-Angeloyloxy-lupanine (**37**)	10.4	1.15–0.95	33
(−)-3β-Hydroxy-13α-angeloyloxylupanine (cajanifoline) (**38**)	9.2	0.85	33
(+)-13α-(3′,4′-Dimethoxy-benzoyl)-oxylupanine (cineverine) (**66**)		0.93	45
(+)-13α-(3′-Hydroxy-*cis*-oct-5-enoyl)-oxylupanine (cineroctine) (**67**)		0.97	45
13β-Hydroxylupanine (**5**)	9.0		44
13β-Hydroxylupanine (**5**)	9.8	0.88	45
13β-Hydroxylupanine (**5**)	8.9	0.85	9
13β-Methoxylupanine (**33**)		0.83	35
4α-Hydroxy-13β-methoxylupanine (**34**)	8.0	0.77	35
3β,4α-Dihydroxy-13β-methoxylupanine (**69**)	8.4	0.82	35
13α-Hydroxysparteine *epi-N*(16)-oxide (**18**)[f]	9.9	2.13	26
13α-Hydroxylupanine *epi-N*-oxide (**19**)	10.2	2.06	26
(−)-3β-Hydroxy-13α-tigloyloxylupanine (**71**)	8.9	0.83–0.80, δ_{OH} 3.83	63
(−)-3β-Hydroxy-13α-tigloyloxylupanine (**71**)		0.83, δ_{OH} 3.89	64
4β,13α-Dihydroxy-lupanine (**72**)		δ_{OH} 3.30	65
(+)-3β,4α-Dihydroxy-lupanine(lebeckianine) (**31**)	9.8		34
3β,4α-Dihydroxy-13α-*O*-(2′-pyrrolyl-carbonyl)-lupanine (calpaurine) (**77**)	2.2[c]	0.79	66
(−)-4α-Angeloyloxy-3β-hydroxy-13β-methoxy-lupanine (**78**)	2.1[c]	0.8	67
(+)-15β-Hydroxy-2,17-dioxosparteine [(+)-15β-hydroxy-17-oxolupanine] (**79**)		0.20–0.39	68
17β-Hydroxylupanine (**80**)		1.07	16
13α-Hydroxy-4-oxosparteine (**27**)		0.71–0.74	29
(−)-13α-Tigloyloxyaphylline (**82**)	8.2[c]		29
(+)-2β-Hydroxyaphylline (**83**)	8.9[c]	0.37	69
(+)-13α-Hydroxyaphyllidine (**50**)	2.6	0.06–0.20	69
(+)-2(*S*)ax-9(*R*)-Dihydroxyaphyllidine (**54**)	2.7	0.22	28
(+)-2(*S*)ax-9(*R*)-Diacetoxyaphyllidine (**55**)	2.5	0.81[c]	28
(+)-2(*R*)eq-9(*R*)-Diacetoxyaphyllidine (**56**)	3.2	0.85[c]	28
(−)-2(*R*)-Hydroxyaphyllidine (argyrolobine) (**51**)	2.9	0.24	28
(+)-2(*R*)-Acetoxyaphyllidine (**53**)	3.0	0	28
(−)-13α-Hydroxymultiflorine (**43**)	3.3[c]	0.46–0.61	69
(−)-13α-Hydroxymultiflorine (**43**)	8.4	0.87	4
(−)-13β-Hydroxymultiflorine (**44**)	3.2[c]	0.30–0.55	69
(−)-13α-Hydroxy-5,6-didehydromultiflorine *N*-oxide (**85**)[e]	11[f]	0.21–0.59	71
(−)-13α-Hydroxy-15α-(1-hydroxyethyl)anagyrine (clathrotropine)[e] (**88**)	2.0		38

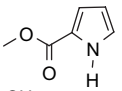
[a] $J_{H7-H17\beta}$.
[b] $\Delta\delta=\delta_{H8\alpha}-\delta_{H8\beta}$.
[c] Dubious values.
[d] Spectrum recorded in C_6D_6.
[e] Spectrum recorded in CD_3OD.
[f] Conceivably provided the boat conformation of ring C and a cis-juncture of rings C/D.[75]

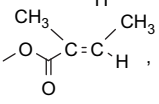
taking into consideration the DFT calculations.[‡] The differences between the old and the new results for the fraction of the chair conformer usually give small differences in the free enthalpy (ΔG) value but for some compounds they are quite distinct. For instance, for aphylline (**16**), the decrease in the fraction of the chair conformer from 98.7 to 90.2% determined for C12 atom gave a decrease in ΔG value from -2.56 to -1.31 kcal mol^{-1} (it was the greatest change in ΔG value for compounds studied. For C14 atom in aphylline, the new result of 92.5% of the chair conformer gave ΔG value of -1.49 kcal mol^{-1} (the former determination was unreasonable being above 100%), while the Galasso's value for ΔE is -1.6 kcal mol^{-1}.[12] So the new value seems to be much more reasonable than the former.



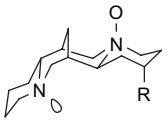
16 R^1 = H, R^2 = H

49 R^1 = OH, R^2 = H

81 R^1 =  , R^2 = H

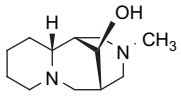
82 R^1 =  , R^2 = H

83 R^1 = H, R^2 = OH



18 R = OH

19 R = H



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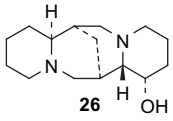
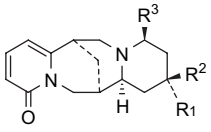


26

For preparing this paper, we reviewed 99 ^{13}C NMR spectra of 72 hydroxy or esters or alkyloxy derivatives of sparteine, 3 spectra were not assigned (Table 1). We found only six X-ray analyses for five relevant compounds[19–22,9] (NMR spectroscopic data are available only for three of them). Almost all IR data were only a part of compounds' characterization and bring very little information on the conformation of compounds. As for the ^{1}H NMR spectra, the most important conformational information comes from the J_{H7-H17} coupling constants. Bohlmannn et al.[23] noted that the chemical shift of H8β amounting to about 1.0 ppm is typical of the predominance of the boat conformer. In our opinion, a better stereochemical parameter is the difference in the chemical shifts of H8α and H8β protons (the denomination is valid for ring B)



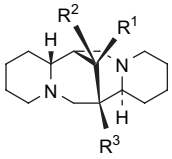
17 R^1= H, R^2 = H, R^3= H

47 R^1= H, R^2 = OH, R^3 = H

48 R^1 = OH, R^2 = H, R^3 = H

87 R^1 = $OCOCH_3$, R^2 = H, R^3 = H

88 R^1 = H, R^2 = OH, R^3 = $CH(OH)CH_3$



20 R^1 = OH, R^2 = H, R^3 = H

21 R^1 = H,R^2 = OH, R^3 = H

22 R^1 = $OCOCH_3$, R^2 = H,R^3 = H

23 R^1 = H,R^2= $OCOCH_3$, R^3 = H

25 R^1 = H,R^2 = H, R^3 = OH

[‡] The quality of the conformational equilibria determination can be measured by the difference between the highest and the lowest results for the fraction of the chair (or boat) conformer obtained for the same compound using different parameters. For 17 compounds, this difference decreased as a result of taking into account the corrections for energy difference calculated by Galasso et al. for the boat and chair conformers of sparteine (**2**)[1] and 5,6-didehydromultiflorine (**7**),[14] for 7 compounds it increased and for 2 it remained the same. For five compounds, for which the chemical shifts of C12 and C14 atoms have the value smaller than those in 5,6-didehydromultiflorine (**7**) (and were not known at the moment of our original publication[6]), the results became reasonable (formerly they were above 100% and their discussion was impossible). The improvement (or deterioration) was rather small and was greater for the compounds with the equilibrium shifted towards the dominant chair conformers.

as an auxiliary criterion of conformation. We reported a similar dependence for some tricyclic quinolizidine–piperidine compounds previously.[8] Now, we can corroborate for the greater number of compounds that the less is the difference, the greater is the fraction of the chair conformer. However, this relation does not have a quantitative character. These two ^{1}H NMR parameters, $J_{H7-H17\beta}$ coupling constant and the difference in the chemical shifts of both bridge H8α and H8β protons, are included in Table 2.

If we are evaluating the influence of a hydroxy group on the conformational equilibrium, we must choose compounds fulfilling the following criteria:

Table 3
Energetic relations in some hydroxy derivatives of sparteine

Compd	C(12)				C(14)				$J_{H7-H17\beta}$				DFT $\Delta E^{d,g}$	Ref.
	δ^a	Fr.[b]	$\Delta G^{c,d}$	$\Delta\Delta G^{d,e}$	δ^a	Fr.[b]	$\Delta G^{c,d}$	$\Delta\Delta G^{d,e}$	J^f	Fr.[b]	ΔG^c	$\Delta\Delta G^{c,d}$		
Std[h]	34.89	0			26.04				10.8	0				
Std[h]	21.04	100			18.21	100			1.9	100				
2	34.78	0.79	**2.86**		25.96	1.02	**2.71**		10.8	0			**3.4**[i]	6
10	34.43	3.3	2.00	−0.86	25.71	4.2	1.85	−0.86						15
11	33.37	11.0	1.24	−1.62	24.51	19.5	0.84	−1.87	9.8	11.2	1.23	−1.23		15
20	36.0	~0[k]			26.1	~0[k]								25
25	36.51[l]				25.29	9.6	1.33	−1.38						28
12	34.35	3.9	1.90		25.69	4.5	1.81							59
26	70.7[m]				19.8[n]									25
6	33.5	10.0	**1.30**		25.3	9.5	**1.33**		10.0	9.0	**1.37**		**1.4**[o]	6
28	31.54	24.2	0.68	−0.62	24.50	19.7	0.83	−0.50	10.5[p]	3.4				30
29	33.16	12.5	1.15	−0.15	24.98	13.5	1.10	−0.23	9.0[p]	20.2	0.81	−0.58		30
30	32.6	16.5	0.96	−0.34	24.4	20.9	0.79	−0.54						32
35	34.1	5.7	1.66	+0.36	24.6	18.4	−0.88	−0.45	7.8[p,q]	33.7	0.40			60
60	34.1	5.7	1.66	+0.36	24.6	18.4			7.4[p]	38.2				37
61	34.3	4.3	1.84	+0.54	24.7	16.4	0.96							37
4	40.17, 33.41[r]	10.7	1.26	−0.04	31.73, 25.03[r]	12.9	1.13	−0.20	9.9	10.1	1.29	−0.08	1.45[s]	9
5	41.56, 32.77[r]	15.3	1.01	−0.29	33.84, 24.66[r]	17.6	0.91	−0.42	8.9, 9.0[t]	21.3, 20.2[t]	0.77, 0.81[t]	−0.60		9
33	37.6				30.1									35
80	33.74	8.3	1.42	+0.12	25.76	3.6	1.95	+0.62	—					16
9	31.76	22.6	**0.73**		23.98	26.3	**0.61**		8.8	22.5	**0.73**		**0.73**[u]	6
43	37.71, 30.95[r]	28.4	0.55	−0.20	30.61, 23.91[r]	27.2	0.58	−0.03	8.4	27.0	0.59	−0.14		54
44	38.9, 30.1[r]	34.6	0.38	−0.35	31.2, 22.9[r]	40.1	0.24	−0.37	3.2[p]					69
7	22.24	91.3	**−1.39**		18.87	91.6	**−1.41**		2.7	91.0	**−1.37**		**−1.36**[u]	6
46[v]	29.80, 23.04[r]	85.6	−1.06	+0.33	26.33, 19.63[r]	81.9	−0.86	+0.55						54
16	22.4	90.2	**−1.31**		18.8	92.5	**−1.49**						**−1.6**[o]	
83	23.9	79.4	−0.80	+0.51	19.1	88.6	−1.21	0.28	8.9[p]	21.3				69
49[v]	29.3, 22.5[r]	89.5	−1.27	+0.04	25.1, 18.4[r]	97.6	−2.19	−0.70						43
57	23.3	83.7	**−0.97**		19.2	87.4	**−1.15**		3.5	82.0	**−0.90**			
51	23.18	84.6	−1.01	−0.04	19.30	86.1	−1.08	+0.07	2.9	88.8	−1.23	−0.33		28
53	22.41	90.1	−1.31	−0.34	18.94	90.7	−1.35	−0.20	3.0	87.6	−1.16	−0.26		28
58	16.38[n,x] or 16.12[n,x]				19.10	88.6	−1.21	−0.06						28
56	16.65n				18.87	91.6	−1.41	−0.26	3.2	85.4	−1.05	−0.15		28
84	16.63n				18.84	92.0	−1.45	−0.30						28
52	22.92	86.4	−1.09	+0.13	19.02	89.7	−1.28	−0.13						28
54	16.31n				18.81	92.3	−1.47	−0.32	2.7	91.0	−1.37	−0.47		28
55	16.76n				18.94	90.7	−1.35	−0.20	2.5	93.3	−1.56	−0.66		28
50	29.8, 23.0[r]	85.4	−1.05	−0.08	26.7, 20.0[r]	77.1	−0.72	+0.43	2.6	92.1	−1.45	−0.55		69
17	22.5	89.5	**−1.27**		19.0	89.9	**−1.29**		3.0	87.6	**−1.16**		**−1.57u**	
48[v]	30.0, 23.2[r]	84.4	−1.00	+0.27	26.1, 19.4[r]	84.8	−1.02	+0.27						38
47[v]	32.6, 23.8[r]	80.1	−0.82	+0.45	29.2, 20.0[r]	77.1	−0.72	+0.57						38

15	34.37	3.8	**1.91**		25.66	4.9	**1.76**	10.7	1.1	2.66		**2.3**[o]	15
27	40.3,[x] 33.5,[r,x] 41.1,[x] 34.3[r,x]	10.0, 4.3	1.30[x], 1.84[x]	−0.61[x], −0.07[x]	32.2, 25.5[f]	6.9	1.54	−0.20					29

[a] Chemical shift, ppm from TMS.
[b] Fraction of the chair conformer, percent.
[c] Free enthalpy.
[d] kcal mol^{-1}.
[e] The difference in free enthalpy between a given hydroxy derivative and its *parent compound*.
[f] Coupling constant $J_{H7-H17\beta}$, Hz.
[g] The difference in energy between the boat and the chair conformers calculated by means of DFT method.[1,12–14]
[h] Standard, see the text.
[i] Ref. 1.
[k] The boat conformation stabilized by an intramolecular O–H···N16 hydrogen bond.
[l] γ-Effect from 9-OH group.
[m] α-Effect from OH group.
[n] γ-*gauche* Effect from OH group.
[o] Ref. 12.
[p] Value probably incorrectly determined.
[q] Ref. 37.
[r] With a correction for the hydroxy group.
[s] Calculated by Mr. J. Włodarczak, Faculty of Chemistry, Adam Mickiewicz University, Poznan.
[t] Ref. 44.
[u] Ref. 14.
[v] Spectrum recorded in CD_3OD solution.
[x] Ambiguous attribution, original spectrum not assigned.

(1) The ^{13}C NMR chemical shifts of C12 and C14 and/or the $J_{H7-H17\beta}$ coupling constant for a given compound as well as for its parent compound (i.e., the analogous compound without the hydroxy or ester or ether group) are available. The NMR spectra of these two compounds must have been recorded essentially in the same solvent (usually in $CDCl_3$).
(2) The data must seem reasonable (especially many $J_{H7-H17\beta}$ coupling constant seems to have been wrongly determined). When more than one dataset for a given compound is available, those, which seem to be the best have been chosen.
(3) The ^{13}C NMR chemical shifts of C12 and C14 are little or not influenced by factors other than conformational ones[§] or, as for 13α- and 13β-hydroxy derivatives, an appropriate correction for the hydroxy group effect can be used. The correction is equal to the difference between the chemical shifts of C12 or C14 atom in 13α-hydroxysparteine (**13**) or 13β-hydroxysparteine (**14**)[17] and those in sparteine (**2**).[6]

The relevant data are given in Table 3. The data for the parent compounds are also included in the same table. The data were used for the calculation of the fraction of the boat conformer F_B (Eqs. 1a–1c) as well as for the calculation of the equilibrium constant $K=F_B/F_C$ (F_C is for the fraction of the chair conformer$=1-F_B$), which was subsequently used to find the free enthalpy ΔG:

$$\Delta G = -RT \ln K \tag{2}$$

The ΔG value for a given compound was compared with that of its parent compound ΔG_P. The difference $\Delta G - \Delta G_P$ is denoted as $\Delta\Delta G$. It should be a quantitative measure of the hydroxy group effect, which shifts the equilibrium and is probably realized by a system of intermolecular hydrogen bonds with the neighbouring molecule (or molecules) of the same compound and/or with the solvent molecules.

The correctness of the procedure could be confirmed by a similarity of the ΔG values calculated using our method and ΔE values reported by Galasso et al., for some of the alkaloids, which are our parent compounds [a very good agreement was obtained for multiflorine (**9**) and 5,6-didehydromultiflorine (**7**),[14] quite a good agreement for lupanine (**6**),[12] less consistency for 4-oxosparteine (**15**),[12] aphylline (**16**)[12] and anagyrine (**17**)[14]] as well as a consistency of the ΔG values for the same compound calculated on the basis of different parameters. For some compounds, the ΔG values obtained on the basis of one parameter differ from those calculated using the other two ones. The reasons could be an incorrectly determined parameter or some atypical changes in the geometry of the molecule.

We divided the data for the hydroxy derivatives into two groups. The first one—the data for the sparteine derivatives without substituents affecting directly the chemical shifts of C12 and C14 atoms and the second group—of those for which

[§] In reality, even a distant substituent can change the geometry of ring D or a hydrogen bond involving N16 nitrogen atom or OH group can change the electron density on C12 and C14 atoms.

the corrections for substituents in the close vicinity of C12 and C14 atoms must be made. As to the latter, we have no data for getting the corrections for substituents at skeleton atoms other than those at C13 atom.

As for the first group, it can be divided into subgroups depending on the parent compound.

2.1. Compounds with sparteine skeleton and without lactam groups

In a sparteine system, we have reasonable results only for both 4-hydroxy derivatives (**10**,**11**) of sparteine. The hydroxy group in a sparteine system causes a shift of the conformational equilibrium larger than that in these sparteine derivatives, which have the functional groups involving the N1 lone electron pair into a mesomerism. Of the two compounds, the 4-hydroxy group affects the equilibrium in the axial β epimer (**11**) more than that in the equatorial α one (**10**).[15]

The observation of the molecular model of sparteine suggests that the basic centre more easily accessible to a possible hydrogen bond with the solvent or with hydroxy group of the neighbouring molecule is the N16 atom in the boat conformation. On the other hand, there is a known effect of so-called 'intramolecular catalysis' manifested, e.g., by an increase in the basicity of sparteine and related diamines compared with that of monoamines.[24] A similar cooperation of the two basic centres in sparteine derivatives forming an intermolecular hydrogen bond with hydroxy group of the neighbouring molecule can be responsible for an increase in the chair conformer fraction in the conformational equilibrium.

We also have results for 13-hydroxysparteine epimers **13** and **14**.[17] As we detected the effect of 4-hydroxy groups, it is probable that also the hydroxy group in position 13 (analogous to position 4, γ to the nitrogen atom in the external ring) can affect the equilibrium but we cannot determine the conformational equilibrium in **13** and **14** either from C12 and C14 atoms chemical shifts or from the diagnostic $J_{H7-H17\beta}$ coupling constant (see above). The corrections derived from the comparison of the C12 and C14 chemical shifts in the NMR spectra of 13-hydroxysparteine epimers **13** and **14** and sparteine (**2**) used for the determination of the equilibria in some 13α and 13β-hydroxy compounds work quite well, which confirms that the possible equilibrium shift caused by 13-hydroxy group in **13** and **14** can be neglected.¶

The NMR spectral data for 8α-hydroxysparteine (**20**) do not allow determination of conformational equilibrium. The ^{13}C signals of C12 and C14 are shifted downfield relative to the relevant signals in the spectrum of sparteine. The conformational equilibrium in 8α-hydroxysparteine is probably shifted towards the absolute domination of the boat conformer caused by the intramolecular hydrogen bond C8–O–H···:N16. Such a hydrogen bond is postulated by Bohlmann on the basis of different chemical shifts of protons attached to C8 atom in 8α-hydroxysparteine (**20**) (3.41 ppm) and in 8β-hydroxysparteine (**21**) (4.34 ppm) as well as in their acetyl derivatives 8α-acetoxysparteine (**22**) (2.53 ppm) and 8β-acetoxysparteine (**23**) (5.28 ppm).[23] A similar hydrogen bond shifting the conformational equilibrium towards the domination of the boat conformation occurs, e.g., in *anti*-(±)-11-methyl-7,11-diazatricyclo-[7.3.1.$0^{2,7}$]tridecan-13-ol (**24**) in chloroform solution but not in methanol solution.[27] Withdrawal of the electrons from the carbon atoms neighbouring N16 due to hydrogen bonding could be the reason for the downfield shift of the C12 and C14 signals.

As for 9-hydroxysparteine (**25**), chemical shift of C12 atom cannot be used for the determination of the conformational equilibrium because the hydroxy group shifts the C12 signal downfield[28] (γ effect, which is possible only in the boat conformation; greater fraction of the chair conformer would cause an upfield shift). The chemical shift of C14 is consistent with the 9.6% of chair conformer fraction but we have no other data to corroborate such a determination.

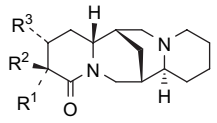
(+)-12α-Hydroxysparteine (retamine, **26**) occurs in the boat conformation in the solid.[22] The axial OH group is involved in a hydrogen bond with the N16 atom of the neighbouring molecule. Both C12 and C14 chemical shifts cannot be used for the determination of the conformational equilibrium: the hydroxy group produces α-effects on C12 and γ-*gauche* effect on C14. There is no doubt that the boat conformation predominates in possible conformational equilibrium in solution.[22] We tried to determine the effect of the hydroxy group on the shift of the conformational equilibrium in 13α-hydroxy-4-oxosparteine (**27**).[29] The results obtained by us for the determination of the equilibrium in its parent compound—4-oxosparteine (**15**) (1.8–1.9 kcal mol^{-1}),[15] are somewhat different from those calculated for this compound by Galasso et al. (2.3 kcal mol^{-1})[12] but the difference is not dramatic. The effect of 13α-hydroxy group is difficult to determine because of uncertainty of the spectral data[29] but probably it is small and amounts to about −0.07 to −0.20 kcal mol^{-1}.

2.2. Lactams and other sparteine derivatives with delocalized lone electron pair of N1 nitrogen atom

Our determination of conformational equilibrium in lupanine is quite consistent with that of Galasso et al.[12] In 3α-hydroxylupanine (**28**), the axial hydroxy group shifts the equilibrium by about −0.5 to −0.6 kcal mol^{-1}[30,31] (we reject the result for $J_{H7-H17\beta}$ coupling constant as it seems unreasonable) to about 20–24% of the chair conformer fraction, while the ester group in 3α-acetoxylupanine (**29**)[30] by ca. −0.2 kcal mol^{-1} to about 13% of the chair conformer. It could be explained by assuming that the hydroxy group is involved

¶ We tried to obtain corrections for the 13α-hydroxy group effect by comparing chemical shifts of C12 and C14 atoms in 13α-hydroxysparteine *epi-N*-oxide (**18**) and sparteine *epi-N*-oxide (**19**), which are rigid and conformationally homogeneous.[26] However, the conformational equilibria in 13α-hydroxy derivatives of lupanine, multiflorine, etc. obtained using these corrections were strongly unreasonable. Probably the hydroxy group in *N*-oxides is involved in a stronger hydrogen bond with *N*-oxide group of the neighbouring molecule, which withdraws electrons from C12 and C14 atoms in 13α-hydoxysparteine *epi-N*-oxide (**18**) more than that in 13α-hydroxysparteine (**13**).

in an intermolecular hydrogen bond or a series of bonds, which cannot be formed with the ester moiety. The presence of a hydrogen bond is manifested by the value of 3414 and 3133 cm^{-1} for the associated OH groups and 1640[30,31] and 1605 cm^{-1}[31] for lactam C=O in IR spectrum (in $CHCl_3$). It means that one of the hydrogen bonds shifting the conformational equilibrium could be the one between the OH group and the lactam oxygen atom of the neighbouring molecule. In the IR spectrum of 3α-acetoxylupanine (**29**) the bands assigned to the stretching vibrations of the OH group are lacking and the band assigned to the carbonyl group is at about 1630 cm^{-1}.[30] The carbonyl group can be solvated by $CHCl_3$. The data available in the literature do not provide evidence confirming the formation of any hydrogen bond involving OH and N16 atom of the neighbouring molecules of **28**.



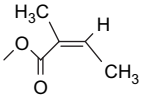
28 R^1 = OH, R^2 = H, R^3 = H

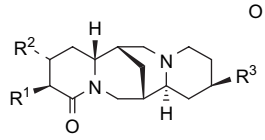
29 R^1 = $OCOCH_3$, R^2 = H, R^3 = H

30 R^1 = H, R^2 = OH, R^3 = H

31 R^1 = H, R^2 = OH, R^3 = OH

32 R^1 = H, R^2 = OH, R^3 =

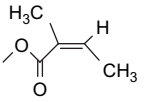




34 R^1 = H, R^2 = OH, R^3 = OCH_3

69 R^1 = OH, R^2 = OH, R^3 = OCH_3

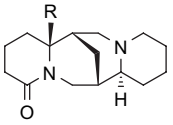
78 R^1 = OH, R^2 =



, R^3 = OCH_3

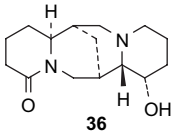
In 3β-hydroxylupanine (**30**),[32] the equatorial hydroxy group shifts the equilibrium by about −0.3 to −0.5 kcal mol^{-1} to about 16–21% of the chair conformer. This shift could be accomplished by means of an intermolecular hydrogen bond between the lactam oxygen atom and the hydroxy group, which is corroborated by the bands at 3479 cm^{-1} (ν OH) and 1633 cm^{-1} (ν C=O).[33] It is not clear to us why the axial group shifts the conformational equilibrium to a greater extent than the equatorial one.

We have no data for 4-hydroxylupanines but we can compare the appropriate ^{13}C chemical shifts in 3β-hydroxylupanine (**30**)[32,33] and 3β,4α-dihydroxylupanine (lebeckianine, **31**)[33,34] if the structure of the latter compound, as well as that of (−)-3β-hydroxy-4α-angeloyloxy-lupanine (sessilifoline, **32**), was elucidated properly—the chemical shift of C8 carbon atom is atypical of the sparteine skeleton compound and resembles rather the chemical shift of C8 atom in compounds with an α-isosparteine skeleton.[25] The chemical shift of C14 is uncertain but the signal of C12 carbon atom is shifted upfield by about 0.9 or 1.5 ppm. It can be of some significance and it means that the conformational equilibrium is shifted towards a greater amount of the chair conformer (ca. 23%, ΔG=−0.63 kcal mol^{-1} relative to −0.34 kcal mol^{-1} for 3β-hydroxylupanine, **30**, provided **31** does not have the skeleton of α-isosparteine). It is qualitatively consistent with the ability of the 4α-hydroxy group to shift the conformation in 4α-hydroxysparteine and can be explained in a similar way: by assuming the formation of an intermolecular hydrogen bond connecting the 4α-hydroxy group with N16 nitrogen atom (besides a similar bond involving the 3β hydroxy group). The energy of this bond is equal to about 0.3 kcal mol^{-1}. Qualitatively, a similar effect on the conformational equili-



35 R = OH

60 R = OCH_3



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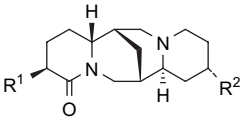
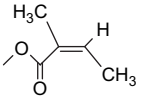
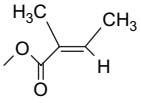


38 R^1 = OH, R^2 =



70 R^1 = OH, R^2 = OH

71 R^1 = OH, R^2 =



brium is caused by the 4α-hydroxy group in 13β-methoxylupanine (**33**)[35] system. In 4α-hydroxy-13β-methoxylupanine (**34**),[35] the fraction of the chair conformer must be significantly greater than that in the parent 13β-methoxylupanine (the signal of C12 atom is in 4α-hydroxy derivative shifted upfield by 1.5 ppm while the signal of C14 atom by 1.1 ppm relative to the positions in the spectrum of 13β-methoxylupanine). As we cannot determine a correction for the 13β-methoxy group (lupanine is not conformationally homogeneous), it is impossible to give an exact value of this fraction and the exact value of $\Delta\Delta G$.

There are several ^{13}C NMR spectra reported for 6-hydroxylupanine (**35**) differing in some details.[22,36–38] All of them when used for the determination of conformational equilibrium give unreasonable results. The difference in the percentage of the conformers calculated by putting the ^{13}C chemical shifts of C12 and C14 carbon atoms to the relevant Eq. 1a or

1b, respectively, could be explained by a possible distortion of the molecular geometry of compound.‖

Similarly as for retamine (**26**), for its 2-oxo analogue (**36**),[40] the conformational equilibrium cannot be determined because of the effects of the axial 12α-hydroxy group on the diagnostic carbon atoms. The $J_{H7-H17\beta}$ coupling constant amounts to 11.2 Hz but is determined on the basis of the triplet resulting from averaging of the geminal and vicinal coupling constants. Thus, we can only say that the conformational equilibrium is strongly shifted to the predominance of the boat conformer.

Both 13α- and 13β-hydroxylupanine (**4** and **5**) occurs in the chair conformation in the solid.[41,9] This rather rarely met conformation of the bis-quinolizidine free base alkaloids is caused by intermolecular OH···O=C–N1′ hydrogen bond with the neighbouring molecule.

There are many ^{13}C NMR data on 13α-hydroxylupanine (**4**),[9,25,30,42–45] which are sometimes inconsistent, even when recorded in the same solvent ($CDCl_3$). The reason is probably the quality of the deuterated chloroform, i.e., its contamination with DCl, which increases during storage, especially with dissolved basic alkaloids.[46] We have decided to use our own data, which seem to us quite reliable. Relative to the situation in the solid, in solution almost complete inversion of the conformational preference occurs: there is only about 10–13% of the chair conformer at equilibrium. The reason for the inversion is the appearance of another system of intermolecular hydrogen bonds: the population of the molecules involved in the OH···O=C–N1′ hydrogen bond with the neighbouring molecule is relatively small, instead there are many intermolecular hydrogen bonds between the carbonyl group or N16 atom with the solvent. The changes relative to lupanine are rather small (about −0.04 to 0.20 kcal mol^{-1}) and are probably caused by additional hydrogen bonds between the OH group and the N16 atom of the neighbouring molecule. The hydrogen bonds are manifested by the shift in the position of the relevant bands in IR spectra of 13α-hydroxylupanine in $CDCl_3$: associated OH group bands (concentration dependent), Bohlmann bands,[9,47,48] so-called deuterium bond[9,49,50] and bathochromic shifting of the carbonyl bond compared with that in the solid.[9]

Similar inversion of the conformational preference in solution, relative to the solid state, occurs in 13β-hydroxylupanine (**5**)[9,50] and the system of hydrogen bonds is similar to that in 13α-hydroxylupanine (**4**). The fraction of the chair conformer in the conformational equilibrium in solution in **5** is a little greater than that in **4** and the free enthalpy changes are greater too (about −0.3 to −0.6 kcal mol^{-1}). The reason seems to be a better steric accessibility of the equatorial hydroxy group in **5** facilitating the formation of a hydrogen bond with N16 atom of the neighbouring molecule in the chair conformation relative to the situation in **4**.

Although we do not have a correction for 13β-methoxy group, the similarity of the ^{13}C NMR spectrum of 13β-methoxylupanine (**33**)[35] to our spectrum of 13β-hydroxylupanine[9] (except for the signals of atoms in positions α and β to the substituent) allows us to conclude that their conformational equilibria and skeleton geometry are essentially the same. The minute difference in the chemical shifts of C3 atoms in the spectra of both compounds can be (but do not have to be) an indication that the lactam oxygen atom in the hydroxy derivative is involved in a weak hydrogen bond (but there is no difference in chemical shifts of the carbonyl carbon atom).

Substitution of 13α-hydroxy group by an ester group usually changes the ^{13}C NMR spectrum only to a very small extent. Only chemical shifts of the carbon atoms adjacent to the ester group differ significantly from those in the parent alcohol. The change is regular and very similar in different 13α-hydroxy derivatives, e.g., 13α-angeloyloxylupanine (**37**), 3β-hydroxy-13α-angeloyloxylupanine (cajanifoline, **38**), 8α-hydroxy-13α-angeloyloxylupanine (cryptanthine, **39**), 3β,8α-dihydroxy-13α-angeloyloxylupanine (pearsonine, **40**): for C13 by about −2.9 to −3.7 ppm, for C12 and C14 by about 3.0–4.0 ppm and for C11 and C15 by about −0.6 to 1.1 ppm[51] or different esters, e.g., 13α-tigloyloxylupanine (**41**) and 13α-vanillyloxylupanine (**42**) for which the chemical shifts of the appropriate carbon atoms are almost the same.[52] They are consistent with the handbook changes for secondary alcohols and esters.[53] The changes are too subtle to discuss their dependence on the conformational changes relative to the parent alcohol—anyway, they must be very small.

The 13-hydroxy group influences the multiflorine (**9**) skeleton in a very similar way as that of lupanine (**6**). In α epimer (**43**),[54] it shifts the conformational equilibrium by about −0.03 to −0.20 kcal mol^{-1} while in β epimer (**44**)[55] the equilibrium shift involves the energy change by about −0.35 kcal mol^{-1}. The ^{13}C NMR spectrum of 13α-tigloyloxymultiflorine (**45**) is similar to that of 13α-hydroxymultiflorine (**43**) [but not as close as the spectra of 13β-hydroxylupanine (**5**) and 13β-methoxylupanine (**33**)]. It means that some little changes in the conformation of **33** relative to that of 13α-hydroxymultiflorine (**43**) are possible.

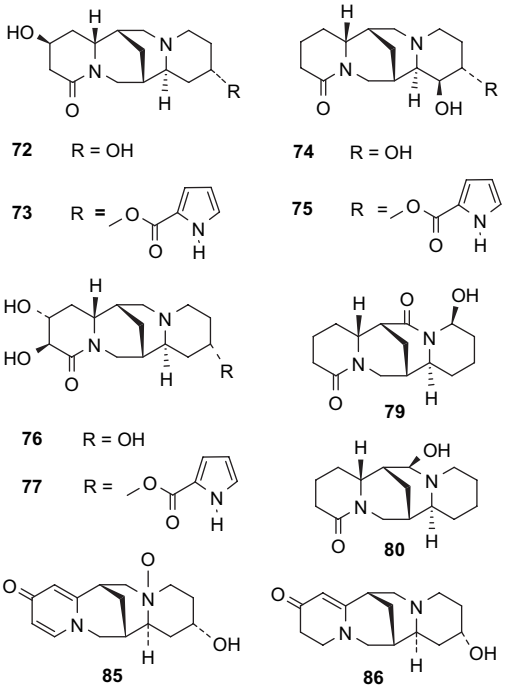
In 13α-tigloyloxymultiflorine (**45**), changes in the chemical shifts of C11–C15 carbon atoms relative to those in 13α-hydroxymultiflorine (**43**) are almost exactly the same as the relevant changes in the respective derivatives (**41** and **13**) of lupanine.[56]

As for 13α-hydroxy-5,6-didehydromultiflorine (**46**) and the two 13-hydroxyanagyrine (**47** and **48**) epimers as well as 13α-hydroxyaphylline (virgiline, **49**), we are only able to approximate the possible influence of the hydroxy group because their spectra were recorded in deuterated methanol due to their poor solubility in chloroform, while the spectra of their parent compounds were recorded in chloroform. In 13α-hydroxy-5,6-didehydromultiflorine (**46**),[54] the axial hydroxy group seems to shift the conformational equilibrium in the opposite direction than in the case of compounds in which the boat

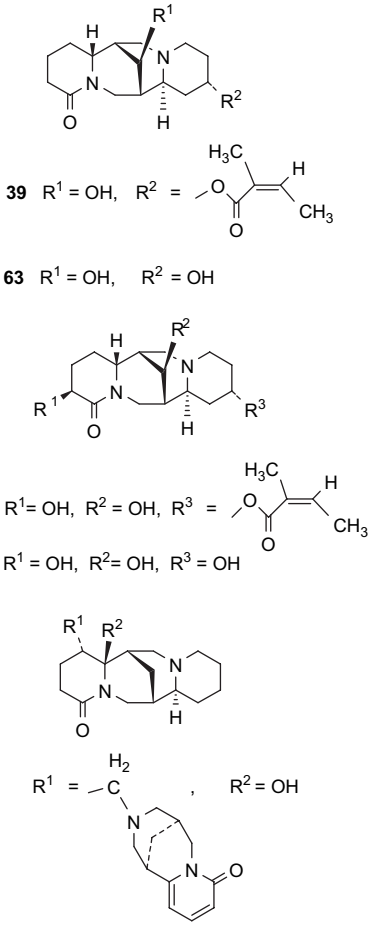
‖ According to our molecular mechanics calculations,[39] among the greatest changes in geometry 6-hydroxylupanine relative to that of lupanine are those in the distances between the carbonyl lactam group and the diagnostic C12 and C14 carbon atoms (distances C2—C12 and O2—C12 are by 0.08 and 0.12 Å, respectively, shorter in 6-hydroxylupanine (**35**) than in lupanine (**6**) while the distances C2—C14 and O2—C14 are shorter by 0.15 and 0.20 Å, respectively).

conformer predominates. If the solvent effect is neglected, the hydroxy group diminishes the fraction of the chair conformer from about 91% in 5,6-didehydromultiflorine to about 82–86% in its 13α-hydroxy derivative. It corresponds to the free enthalpy change by about 0.33–0.55 kcal mol^{-1}. The 13-hydroxy group in anagyrine (**17**), another compound occurring in mostly chair conformation, acts in a similar way. The axial (here 13β) hydroxy group causes a decrease in the fraction of the chair conformer from about 90% in anagyrine to about 85% in 13β-hydroxyanagyrine (baptifoline, **48**)[38] (the free enthalpy change amounts to about 0.27 kcal mol^{-1}) while the equatorial 13α-hydroxy group to about 77–80% in 13α-hydroxyanagyrine (epibaptifoline, **47**)[38] (free enthalpy change amounts to about −0.45 to −0.57 kcal mol^{-1}). As for 13α-hydroxyaphylline (virgiline, **49**),[43] the result obtained using C12 atom chemical shift is different from the result determined using C14 atom chemical shift. The more reliable C12 atom result suggests only very little changes[43] in conformational equilibrium relative to the parent aphylline (**16**).[57] The quantitative determination for all hydroxy derivatives with the predominance of the chair conformer may be distinctly inaccurate due to the solvent effect but the direction of the conformational change seems to be beyond doubt.

In 13α-hydroxyaphyllidine (**50**, axial hydroxy group), the direction of changes in the conformation equilibrium cannot be determined because of the differences in the results obtained using different parameters.[55]



Such an influence of 13-hydroxy groups on the conformational equilibrium could be explained by their probable association with N16 atom of the neighbouring molecules on both sides—*endo* and *exo*. In compounds occurring mainly



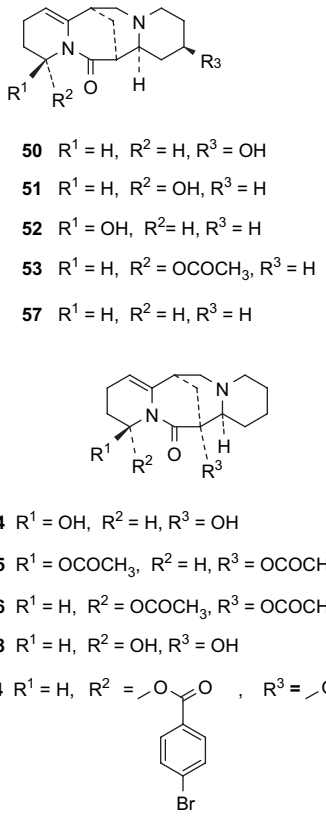


Table 4
Changes in the conformational equilibrium induced by hydroxyl or ester substituents

Position of substituent	Substituent		Parent compound	Reasons postulated	Remarks
	OH group	Ester group			
2ax	**D**, 0.3−0.5 kcal mol^{-1} Very small		Aphylline (**16**) Aphyllidine (**57**)	Steric hindrance?	
2eq	Very small	**I**, −0.3 kcal mol^{-1}	Aphyllidine (**57**)	Steric hindrance?	
3ax	**I**, −0.6 kcal mol^{-1}	**I**, −0.2 kcal mol^{-1}	Lupanine (**6**)	Intermol. h.b. h.b. with solvent	
3eq	**I**, −0.3 to −0.5 kcal mol^{-1}		Lupanine (**6**)	Intermol. h.b.	
4ax	**I**, −1.2 to −1.9 kcal mol^{-1} −0.3 kcal mol^{-1}		Sparteine (**2**) 3β-Hydroxylupanine (**30**)	Intermol. h.b. Intermol. h.b.	
4eq	**I**, −0.9 kcal mol^{-1}		Sparteine (**2**)	Intermol. h.b.	
6ax			Lupanine (**6**)	Distortion of the sparteine skeleton	
8eq[a]	D		Sparteine (**2**)	Intramol. h.b.	
9eq	**I**, −1.4 kcal mol^{-1}		Sparteine (**2**)	Intermol. h.b.?	γ-*gauche* ef. on C12
12ax	Small?				α ef. on C12, γ-*gauche* ef. on C14
13ax	A small **I**, 0 to −0.2 kcal mol^{-1}, **D**, +0.3 to +0.6 kcal mol^{-1}		Lupanine (**6**), multiflorine (**9**), 4-oxosparteine (**15**), 5,6-didehydromultiflorine (**7**), anagyrine (**17**)	Intermol. h.b.	
13eq	**I**, −0.3 to −0.6 kcal mol^{-1}, **D**, +0.45 to +0.6 kcal mol^{-1}		Lupanine (**6**), multiflorine (**9**), anagyrine (**17**)	Intermol. h. b.	
17ps eq	?		Lupanine (**6**)	Intermol. h.b.	γ-*gauche* ef. on C12 and on C14

Abbreviations: **D**, decrease in the chair conformer fraction; **I**, increase in the chair conformer fraction; h.b., hydrogen bond; ef., effect; intermol., intermolecular; intramol, intramolecular.
[a] In ring B.

in the boat conformation, the conformational equilibrium is shifted away from the boat form and in compounds occurring mainly in the chair conformation, there is a similar shift away from the chair form. As association of the hydroxy groups with the carbonyl group of the neighbouring molecule is also conceivable, such an interaction can be easier with the equatorial hydroxy group. Probably in the lupanine system in the chair conformation, the geometry of the molecule affords a possibility of cooperation of the lactam group with the lone electron pair of N16 nitrogen atom in intermolecular hydrogen bond formation with the hydroxy group of the neighbouring molecule.

In both epimers of 2-hydroxy derivatives of aphyllidine (**51** and **52**), the changes induced by the hydroxy group are very small,[28] while the equatorial acetoxy group in **53** seems to shift the equilibrium towards increasing chair conformer fraction.[28] In (+)-2(*S*),9(*R*)-dihydroxyaphyllidine (**54**) and its diacetoxy derivative (**55**) as well as in (+)-2(*R*),9(*R*)-diacetoxyaphyllidine (**56**) the fraction of the chair conformer increases a little compared with the parent aphyllidine (**57**)[28] while in (+)-2(*R*),9(*R*)-dihydroxyaphyllidine (**58**) it seems unchanged or changed very little.[28] It is difficult to explain such results. Perhaps the hydroxy group in position 2 is so sterically hindered that it is not able to produce a hydrogen bond with the carbonyl group or N16 atom of the neighbouring molecule but it can form an intramolecular hydrogen bond with the lactam group. The acetoxy group is more accessible but lacks the proton, which could be involved in a hydrogen bond.

3. Conclusions

A review of 96 assigned ^{13}C NMR spectra of 69 hydroxy, methoxy or ester derivatives (plus 3 unassigned spectra) of alkaloids with sparteine skeleton was made. We presented also a method of determination of conformational equilibria in bis-quinolizidine compounds with the sparteine skeleton. The method was improved owing to taking into consideration the DFT calculations of Galasso's group. The variants, which involve ^{13}C chemical shift of C12 and C14 carbon atoms give more reliable percentages of the boat or chair conformer fraction and free enthalpy determination. Less accurate but also useful is the variant based on the use of the $J_{H7-H17\beta}$ coupling constant. The reviewed ^{13}C NMR spectral data seem to be of variable quality (probably due to aged $CDCl_3$ contaminated by DCl), which could be a reason for misinterpretation and improper steric conclusions. Another reason for little precision of the conformational equilibrium determination in some cases could be a change in the electron density of the diagnostic C12 and C14 carbon atoms induced by a hydrogen bond involving the N16 nitrogen atom. The best knowledge of the conformational equilibrium can be achieved when the three variants of NMR results are compared with some other non-quantitative methods: differences in the H8α and H8β protons' chemical shifts, the chemical shift of C8 carbon atom as well as the conformationally dependent IR bands (Bohlmann band, deuterium band, associated hydroxyl stretching vibration bands and carbonyl stretching vibration bands).

The influence of the hydroxide group on the equilibrium (Table 4) is more distinct in sparteine than that in lupanine and multiflorine and their derivatives as well as the sparteine derivatives with pyridone moiety. The reason could be a possibility of stronger cooperation of the two basic centres on N1 and N16 atoms, which can increase the strength of a bifurcated hydrogen bond with the hydroxy group of the neighbouring molecule and shift the equilibrium towards the greater fraction of the chair conformer. In lactams such a cooperation is also possible but is much weaker. In compounds, which have a quasi-aromatic ring A, this cooperation can be neglected. Usually, a change in the conformational equilibrium is more distinct in compounds, which have the hydroxy group in positions more available for hydrogen bond formation.

A difference in the effect of the hydroxy group and the effect of the ester group in positions 2ax (in aphyllidine) and 3eq (in lupanine) is observed. The reason could be the difference in the system of intermolecular hydrogen bonds. The effects of both groups in position 13ax seem to be very similar, perhaps because the hydroxy group changes the conformational equilibrium only to a small extent.

References and notes

1. Galasso, V.; Asaro, F.; Berti, F.; Kovač, B.; Habuš, I.; Sacchetti, A. *Chem. Phys.* **2003**, *294*, 155.
2. Skolik, J.; Podkowińska, H. *Zesz. Nauk. Akad. Ekonomiczej Poznań, Ser. I* **1991**, *198*, 109.
3. Wysocka, W.; Brukwicki, T. *J. Mol. Struct.* **1992**, *265*, 143.
4. Brukwicki, T.; Wysocka, W.; Nowak-Wydra, B. *Can. J. Chem.* **1994**, *72*, 193.
5. Wysocka, W.; Brukwicki, T. *Pol. J. Chem.* **1995**, *70*, 1295.
6. Wysocka, W.; Brukwicki, T. *J. Mol. Struct.* **1996**, *385*, 23.
7. Brukwicki, T.; Przybył, A.; Wysocka, W.; Sośnicki, J. *Tetrahedron* **1999**, *55*, 14501.
8. Wysocka, W.; Brukwicki, T. *Tetrahedron* **2003**, *59*, 8597.
9. Borowiak, T.; Wolska, I.; Wysocka, W.; Brukwicki, T. *J. Mol. Struct.* **2005**, *753*, 27.
10. Doucerain, H.; Chiaroni, A.; Riche, C. *Acta Crystallogr., Sect. B* **1976**, *32*, 3213.
11. Wehrli, F. W.; Wirthlin T. *Interpretation of Carbon-13 NMR Spectra*, Polish edition; P.W.N.: Warszawa, 1985; p 210 (Eq. 5.4).
12. Galasso, V.; Asaro, F.; Berti, F.; Kovač, B.; Habuš, I.; De Risi, C. *Chem. Phys.* **2004**, *301*, 33.
13. Galasso, V.; Asaro, F.; Berti, F.; Przybył, A. K.; Włodarczak, J.; Wysocka, W.; Habuš, I.; Kovač, B. *Chem. Phys.* **2005**, *314*, 25.
14. Galasso, V.; Przybył, A. K.; Christov, V.; Asaro, F.; Kovač, B.; Zangrando, E. *Chem. Phys.* **2006**, *325*, 365.
15. Wysocka, W.; Przybył, A. *Monatsh. Chem.* **2001**, *132*, 973.
16. Thiel, J.; Boczoń, W.; Wysocka, W. *Monatsh. Chem.* **2000**, *131*, 1073.
17. Brukwicki, T.; Włodarczak, J.; Wysocka, W. *J. Mol. Struct.* **2007**, *832*, 90.
18. Mikhova, B.; Duddeck, H. *Magn. Reson. Chem.* **1998**, *36*, 779.
19. Garbarczyk, J.; Kałuski, Z.; Bratek-Wiewiórowska, M. D.; Skolik, J.; Wiewiórowski, M. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1974**, *22*, 651.
20. Kałuski, Z.; Garbarczyk, J.; Gusev, A. I.; Struchkov, Yu. T.; Skolik, J.; Wiewiórowski, M. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1977**, *25*, 347.
21. Vermin, W. J.; de Kok, A. J.; Romers, C.; Radema, M. H.; van Eijk, J. L. *Acta Crystallogr., Sect. B* **1979**, *35*, 1839.
22. Abdel-Halim, O.; Sekine, T.; Halim, A. F.; Abdel-Fattah, H.; Saito, K.; Ogata, K.; Murakoshi, I. *Phytochem. Anal.* **1995**, *6*, 302.
23. Bohlmann, F.; Schumann, D.; Arndt, Ch. *Tetrahedron Lett.* **1965**, 2705.
24. Wiewiórowski, M.; Skolik, J. *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **1963**, *11*, 69.

25. Bohlmann, F.; Zeisberg, R. *Chem. Ber.* **1975**, *108*, 1043.
26. Brukwicki, T.; Wysocka, W. *J. Mol. Struct.* **2003**, *647*, 275.
27. Balázs, B.; Nemes, P.; Scheiber, P.; Tóth, G. *J. Mol. Struct.* **1999**, *475*, 153.
28. Arslanian, R. L.; Harris, G. H.; Stermitz, F. R. *J. Org. Chem.* **1990**, *55*, 1204.
29. Mohamed, M. H.; Mohamed, K. M.; Hassanean, H. A.; El-Moghazy, S. A. *Pharmazie* **1999**, *54*, 778.
30. Al-Tel, T. H.; Sabri, S. S.; Abu Zarga, M. H.; Pervin, A.; Shah, Z.; Atta-ur-Rahman; Rycroft, D. S. *Phytochemistry* **1991**, *30*, 2393.
31. Proksa, B.; Uhrin, D.; Uhrinová, S.; Grossmann, E.; Selenge, D.; Batsuren, D. *Collect. Czech. Chem. Commun.* **1990**, *55*, 1257.
32. Touché, A.; Courtois, D.; Frèche, J.-P.; Bromet, N.; Djedaïni-Pilard, F.; Perly, B.; Guillaumet, G.; Rollin, P. *J. Agric. Food Chem.* **1997**, *45*, 2148.
33. Verdoorn, G. H.; van Wyk, B.-E. *Phytochemistry* **1990**, *29*, 1297.
34. van Wyk, B.-E.; Verdoorn, G. H. *Biochem. Syst. Ecol.* **1989**, *17*, 225.
35. Veitch, N. C.; Goodwin, B. L.; Kite, G. C.; Simmons, M. S. J. *Phytochemistry* **1997**, *45*, 847.
36. Asres, K.; Phillipson, J. D.; Mascagni, P. *Phytochemistry* **1986**, *25*, 1449.
37. Wang, Y.-H.; Li, J.-S.; Jiang, Z.-R.; Kubo, H.; Higashiyama, K.; Ohmiya, S. *Chem. Pharm. Bull.* **2000**, *48*, 641.
38. Sagen, A.-L.; Gertsch, J.; Becker, R.; Heilmann, J.; Sticher, O. *Phytochemistry* **2002**, *61*, 975.
39. *HyperChem® Release 7.1 for Windows®*; Hypercube: Gainesville, FL, 2003.
40. Abdel-Halim, O.; Saito, K.; Halim, A.; Abdel-Fattah, H.; Murakoshi, I. *Phytochemistry* **1992**, *31*, 3251.
41. See Ref. 20.
42. Gołębiewski, W. M.; Spencer, I. D. *Can. J. Chem.* **1985**, *63*, 716.
43. Asres, K.; Gibbons, W. A.; Phillipson, J. D.; Mascagni, P. *Phytochemistry* **1986**, *25*, 1443.
44. Veen, G.; Schmidt, C.; Witte, L.; Wray, V.; Czygan, F.-C. *Phytochemistry* **1992**, *31*, 4343.
45. Van Rensen, I.; Wray, V.; Witte, L.; Canto, P.; Greinwald, R.; Veen, G.; Veit, M.; Czygan, F.-C. *Phytochemistry* **1994**, *35*, 421.
46. Wysocka, W.; Brukwicki, T. Unpublished Results.
47. Bohlmann, F. *Angew. Chem.* **1957**, *69*, 641.
48. Bohlmann, F. *Chem. Ber.* **1958**, *91*, 2157.
49. Wiewiórowski, M.; Lompa-Krzymień, L. *Roczniki Chem.* **1970**, *44*, 845.
50. Wiewiórowski, M.; Lompa-Krzymień, L. *Roczniki Chem.* **1969**, *43*, 1219.
51. Verdoorn, G. H.; van Wyk, B.-E. *Phytochemistry* **1991**, *30*, 3631.
52. Hussein, R. A.; Kinghorn, A. D.; Molyneux, R. J. *J. Nat. Prod.* **1988**, *51*, 809.
53. Wehrli, F. W.; Wirthlin T. *Interpretation of Carbon-13 NMR Spectra*, Polish edition; P.W.N.: Warszawa, 1985; p 51.
54. Wysocka, W.; Brukwicki, T. *Planta Med.* **1991**, *57*, 579.
55. Mohamed, M. H.; Hassanean, H. A. *Phytochemistry* **1997**, *46*, 365.
56. Takamatsu, S.; Saito, K.; Murakoshi, I.; Ohmiya, S. *J. Nat. Prod.* **1991**, *54*, 477.
57. Duddeck, H.; Skolik, J.; Majchrzak-Kuczyńska, U. *Khim. Geterocykl. Soed.* **1995**, 1026.
58. Brukwicki, T. Unpublished Results.
59. Thiel, J.; Wysocka, W.; Boczoń, W. *Monatsh. Chem.* **1995**, *126*, 233.
60. Abdel-Halim, O. *Phytochemistry* **1995**, *40*, 1323.
61. Murakoshi, I.; Yamashita, Y.; Ohmiya, S.; Otomasu, H. *Phytochemistry* **1986**, *25*, 521.
62. Nasution, M.; Kinghorn, A. D. *Phytochemistry* **1993**, *32*, 1603.
63. Saito, K.; Suzuki, H.; Yoshiaki, Y.; Murakoshi, I. *Phytochemistry* **1994**, *36*, 309.
64. Olivier, M.; Renault, J.-H.; Richard, B.; Moretti, C.; Zèches-Hanrot, M. *Fitoterapia* **2001**, *72*, 583.
65. Asres, K.; Phillipson, J. D.; Mascagni, P. *Planta Med.* **1986**, *31*, 302.
66. Mascagni, P.; Gibbons, W. A.; Asres, K.; Phillipson, J. D.; Niccolai, N. *Tetrahedron* **1987**, *43*, 149.
67. Nuzillard, J.-M.; Connolly, J. D.; Delaude, C.; Richard, B.; Zèches-Hanrot, M.; Le Men-Olivier, L. *Tetrahedron* **1999**, *55*, 11511.
68. Mohamed, M. H.; Ibraheim, Z. Z.; Abdallah, O. M.; Murakoshi, I. *Phytochemistry* **1994**, *37*, 1751.
69. See Ref. 55.
70. Mohamed, M. H.; Saito, K.; Kadry, H. A.; Khalifa, T. I.; Ammar, H. H. *Phytochemistry* **1991**, *30*, 3111.
71. Mohamed, M. H. *Bull. Pharm. Sci., Assiut Univ.* **1998**, *21*, 55.
72. Mohamed, M. H.; Koskinen, A. M. P.; Kamel, M. S. *Bull. Pharm. Sci., Assiut Univ.* **1995**, *18*, 55.
73. Saito, K.; Takamatsu, S.; Murakoshi, I.; Ohmiya, S.; Otomasu, H. *J. Nat. Prod.* **1989**, *52*, 1032.
74. Kennelly, E. J.; Flynn, T. J.; Mazzola, E. P.; Roach, J. A.; McCloud, T. G.; Danford, D. E.; Betz, J. M. *J. Nat. Prod.* **1999**, *62*, 1385.
75. Thiel, J.; Boczoń, W.; Fiedorow, P.; Jasiewicz, B.; Knychała, M. *J. Mol. Struct.* **2002**, *642*, 15.