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Communication

NMR Spectra of Sparteine N1-oxide and α-Isosparteine N-oxide

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Abstract: Sparteine N1-oxide and α-isosparteine N-oxide were prepared and their structures determined for the first time by ^{1}H- and ^{13}C-NMR spectroscopy using two-dimensional techniques. The N-oxide effects were also calculated.

Keywords: Sparteine, α-isosparteine, N-oxides, NMR spectroscopy, DFT calculations.

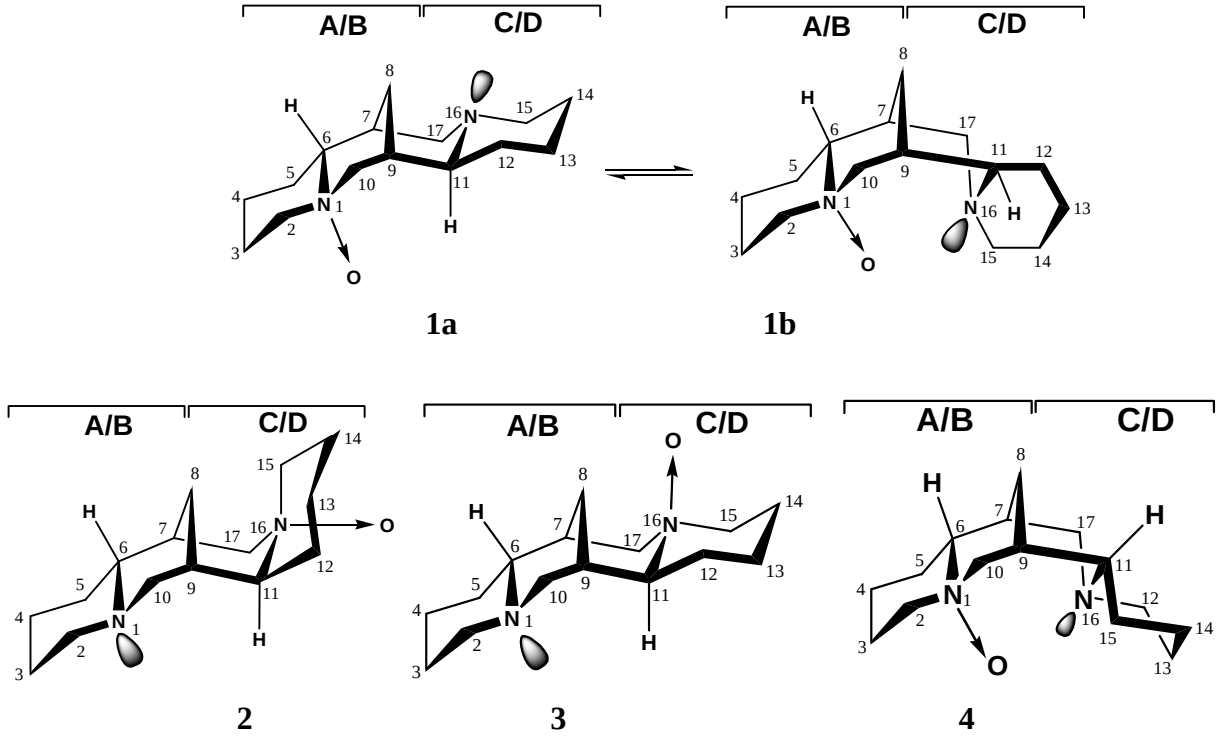
Introduction

The wide use of quinolizidine alkaloids in chemistry is related first of all with a possibility of configurational-conformational changes that could take place in the bis-quinolizidine skeleton. Naturally occurring (–)-sparteine is an equilibrium mixture in which the conformer possessing a boat ring C and trans junction of rings C/D predominates [1-4]. On the other hand, the less stable all-chair conformer participates in complex formation [5-7]. The compound α-isosparteine, consisting of two trans-quinolizidine systems, exists solely in an all-chair conformation, and similarly in the free base form [8] and in metal complexes [5-7,9,10]. As a continuation of our study on the complex forming ability of bis-quinolizidine alkaloids [6,7,9,10], the choice of N-oxides as ligands was made. We have already obtained the complexes of sparteine N16-oxides with lithium [11] and zinc [12] salts. This time the subject of our study was the synthesis of the complexes of sparteine N1-oxide, sparteine epi-N-oxide and α-isosparteine N-oxide.

NMR spectroscopy is known to permit observation of conformational changes taking place in the structure of the ligands during complexation reactions. Moreover, a comparison of the chemical shifts of carbon atoms and protons of the initial alkaloid and the complex formed, enables determination of the effects of complexation. The present work is a continuation of our studies on the structural investigation of bis-quinolizidine alkaloids [13-17]. The NMR data of sparteine N16-oxide and

sparteine epi-N-oxide have been presented before [11,18]. In this paper we present the NMR spectra of sparteine N1-oxide and α-isosparteine N-oxide. For each of them the N-oxide effects were determined. The two conformers of sparteine form three isomeric mono N-oxides: sparteine N1-oxide (**1**), sparteine N16-oxide (**2**) and sparteine epi-N-oxide (**3**). In the reactions of sparteine with H_2O_2 a 1:3 mixture of the two sparteine N-oxides: sparteine N_1-oxide and sparteine N16-oxide is obtained [19,20]. Sparteine N1-oxide (**1**) occurs in a chair-boat type equilibrium involving inversion of the lone pair on the N16 atom [20]; the N16-oxide of sparteine (**2**), previously thought to adopt the all chair conformation, has been found recently to have ring C in a boat conformation and a *cis* C/D ring junction [21]. Sparteine epi-N-oxide (**3**) has the C ring boat conformation and must be obtained by $NaBH_4$ reduction of lupanine N-oxide [20]. α-Isosparteine N-oxide (**4**) has a conformation identical to that of the free base (Figure 1) [19].

Figure 1. Chemical structures of sparteine N-oxides **1**-**3** and α-isosparteine N-oxide (**4**).



Results and Discussion

In order to obtain the NMR spectra of the two conformers of the N1-oxide of sparteine (**1a** and **1b**), the NMR spectra were measured in two solvents: $CDCl_3$ and DMSO-d_6. The NMR spectrum of sparteine N1-oxide recorded in DMSO-d_6 solution is typical of that expected for pure **1a** conformer, while the spectrum recorded in $CDCl_3$ seems to be that of sparteine N1-oxide hydrochloride (all-chair conformation) since in its ^{1}H-NMR spectrum the signal of the "acid" proton appears at 17.5 ppm.

The ^{1}H- and ^{13}C-NMR data for sparteine N1-oxide (conformer **1a**), sparteine N1-oxide hydrochloride (**1**-HCl) and free base of sparteine are collected in Table 1. The N-oxide effect can be derived as a difference in the chemical shifts of the appropriate carbon atoms in N-oxide and its basic amine. This effect is superimposed by the solvent effect as the solvent is changed from $CDCl_3$ (free base of

sparteine) into DMSO-d_6 (sparteine N1-oxide). The ^{13}C chemical shifts for C7, C8, C9, C12, C13, C14 and C15 carbon atoms of conformer **1a** approximate the analogous δ_C values of sparteine [22]. This result corroborates the presence of chemically unchanged C and D rings preserving the *trans*-quinolizidine form in the N-oxide. The deshielding influence of the N-oxide function, generated on the N1 nitrogen of the alkaloid considered, causes a down-field shift of the α carbons, i.e. C2 ($\Delta\delta_C$ = 13.4 ppm), C6 ($\Delta\delta_C$ = 4.3 ppm) and C10 ($\Delta\delta_C$ = 8.7 ppm), as compared with respective sparteine δ_C values.

Table 1. ^{13}C- and ^{1}H-NMR chemical shifts of sparteine, sparteine N1-oxide (conformer **1a**) and sparteine N1-oxide hydrochloride (**1**-HCl) (δ in ppm).

C	Sparteine [see ref. 22] $CDCl_3$		Sparteine N1-oxide (1a) DMSO-d_6		N-oxide effects	Sparteine N1-oxide hydrochloride (1-HCl) $CDCl_3$		N-oxide and protonation effects
	δ_C	δ_H	δ_C	δ_H	$\Delta\ \delta_C$	δ_C	δ_H	$\Delta\ \delta_C$
2	56.0	1.79	69.4	4.80	+13.4	66.9	5.00	+10.9
		2.53		3.10			3.41	
3	25.6	1.38	19.9	1.35	–5.7	20.3	1.65	–5.3
		1.38		2.35			2.18	
4	24.5	1.05	23.1	1.30	–1.4	21.8	1.85	–2.7
		1.55		1.60			1.85	
5	29.1	1.24	26.0	1.35	–3.1	24.3	1.45	–4.8
		1.12		2.25			2.20	
6	66.3	1.58	70.6	3.20	+4.3	72.9	4.70	+6.6
7	32.9	1.69	32.1	1.95	–0.8	33.8	2.10	+0.9
8	27.4	0.90	26.1	1.25	–1.3	24.0	1.45	–3.4
		1.91		2.15			2.15	
9	35.9	1.32	35.5	1.60	–0.4	34.2	2.10	–1.7
10	61.8	1.84	70.5	4.15	+8.7	70.9	4.50	+9.1
		2.38		3.10			3.30	
11	64.2	1.83	57.8	3.70	–6.4	58.4	3.05	–5.8
12	34.5	1.35	35.2	1.10	+0.7	24.5	1.45	–10.0
		1.21		1.40			1.90	
13	24.6	1.15	24.3	2.30	–0.3	23.2	2.50	–1.4
		1.55		1.15			1.45	
14	25.8	1.43	24.8	1.50	–1.0	18.4	1.50	–7.4
		1.43		1.60			2.18	
15	55.2	1.86	53.9	2.60	–1.3	51.8	2.90	–3.4
		2.63		2.00			2.00	
17	53.4	2.20	48.4	2.40	–5.0	43.9	2.60	–9.5
		2.54		3.80			3.20	

Analysis of the chemical shifts given in Table 1 shows that the conformational changes are observed for the bis-quinolizidine skeleton in sparteine N1-oxide hydrochloride on passing from the free base to the N-oxide salt. The γ-gauche effects which usually accompany a conformational change from boat-chair to all-chair [23] are observed at carbon atoms C12 ($\Delta\delta_C$ = 10.0 ppm), C14 ($\Delta\delta_C$ = 7.4 ppm) and C17 ($\Delta\delta_C$ = 9.5 ppm). The conformational changes are superimposed by the N-oxide effect

assuming the greatest values for the carbon atoms in the α position with respect to the N-oxide group: C2 (+10.9 ppm), C6 (+6.6 ppm) and C10 (+9.1 ppm).

The β–effect influencing the secondary carbon atoms in the outer ring (A) is negative, amounting to –5.7 and –3.1 ppm for **1a** and –5.3 and –4.8 ppm for 1-HCl. In the inner ring (B), the oxidation effects on on the tertiary carbon atoms differ only slightly from 0. The γ-effect in the outer ring amounts to ca. –1.4 ppm (**1a**) and –2.7 ppm (**1**-HCl), in the inner rings (B and C), it amounts ca. –1.3, –5.0, –6.4 ppm for the boat conformer 1a and –3.4, –5.8 and –9.5 ppm for the hydrochloride salt. In the proton spectra, the greatest N-oxidation effect is observed for C2, C6 and C10 (Table 1). The protons connected with these carbons appear within the range $5.00 > \delta_H > 3.10$. The NMR spectra of α-isosparteine N-oxide and the free base of α-isosparteine are shown in Table 2. The spectra of both compounds display the ^{13}C chemical shift of C8 characteristic of the α-isosparteine skeleton structure (32.8 ppm for α-isosparteine and 31.7 ppm for the N-oxide).

Table 2. ^{13}C- and ^{1}H-NMR chemical shifts of α-isosparteine and α-isosparteine N-oxide (δ in ppm)

C	α-isosparteine DMSO-d_6		α-isosparteine N-oxide (4) DMSO-d_6		N-oxide effects
	δ_C	δ_H	δ_C	δ_H	$\Delta\,\delta_C$
2	55.5	1.76	66.5	3.42	+11.0
		2.74		3.50	
3	23.8	1.75	19.9	1.60	–3.9
		1.40		2.02,	
4	22.9	1.24	21.8	1.44	–1.1
		1.70		1.76	
5	28.0	1.69	23.8	1.70	–4.2
		1.19		1.40	
6	65.7	1.86	72.9	3.74	+7.2
7	32.1	1.45	32.4	2.07	+0.3
8	32.8	1.31	31.7	1.80	–1.1
		1.52		2.00	
9	32.1	1.31	33.0	2.18	+0.9
10	55.7	2.04	65.5	3.74	+9.8
		2.96		3.74	
11	65.7	1.86	60.6	2.68	–5.1
12	28.0	1.69	27.4	1.60	–0.6
		1.19		1.74	
13	22.9	1.24	22.6	1.44	–0.3
		1.70		1.76	
14	23.8	1.75	23.3	2.16	–0.5
		1.40		1.40	
15	55.5	1.76	52.4	2.48	–3.1
		2.74		3.08	
17	55.7	2.04	50.7	2.58	–5.0
		2.96		3.00	

The relatively rigid skeleton of α-isosparteine allows us to determine the N-oxide effects more precisely than in the flexible sparteine. The α N-oxide effect for the metine carbon atom (C6) is +7.2 ppm, and for methylene carbon atoms (C2, C10) +11.0 and + 9.8 ppm, respectively, while the value of the N-oxide β effect on carbon atoms C3, C5, C7 and C9 range from –4.2 to +0.9 ppm. The γ-effect in the A ring amounts to ca. –1.1 ppm. In the rings B and C, it is generally greater and amounts to ca. –5.1 ppm. Chemical shift changes (from –0.6 to –3.1 ppm) are noted on the carbon atoms of ring D. These changes follow mainly from the presence of the N-O group. It seems probable that the effect of a slight change in the geometry of the molecule involving greater deformation of rings B and C than that of ring A (following an elongation of the N-C bonds as a result of introducing the N^+–O^- function) is imposed on the direct N-oxidation effect in the inner rings. In the proton spectra, the greatest N-oxidation effect (Table 2) is for H6 ($\Delta\delta_H$ = 1.88 ppm). Other large effects are those on the α-axial protons (above 1.70 ppm). Also significant are the effects on α-equatorial protons (0.80 ppm).

The conformational assignment for compounds **1a, 1**-HCl and **2** was also carried out by comparison of the experimental ^{13}C-NMR chemical shifts with those predicted by DFT/CSGT shielding calculations. The results of these calculations for the optimized structures, together with the experimental values are listed in Table 3. The correlation coefficient (R^2) for carbon chemical shifts is 0.97 for **1a**, 0.98 for **1**-HCl and 0.98 for **2**. The results suggest that the structures of the N-oxides investigated in solution and under vacuum are the same.

Table 3. Comparison of CSGT chemical shifts (δ, in ppm) calculated at the DFT level of theory for sparteine N1-oxide (conformer **1a**), sparteine N1-oxide hydrochloride (**1**-HCl) and α-isosparteine N-oxide (**2**).

C	δ exper. (1a)	δ theor. (1a)	$\Delta\delta_C$ (1a)	δ exper. (1-HCl)	δ theor. (1-HCl)	$\Delta\delta_C$ (1-HCl)	δ exper. (2)	δ theor. (2)	$\Delta\delta_C$ (2)
C2	69.4	72.2	2.8	66.9	66.3	–0.6	52.4	48.9	–3.8
C3	19.9	21.3	1.4	20.3	17.9	–2.4	23.3	23.4	0.1
C4	23.1	23.0	–0.1	21.8	21.4	–0.4	22.6	23.4	0.8
C5	26.0	27.1	1.1	24.3	26.2	1.9	27.4	28.9	1.5
C6	70.6	70.3	–0.3	72.9	70.9	–2.0	60.6	57.5	–3.1
C7	32.1	33.3	1.2	33.8	31.2	–2.6	33.0	34.0	1.0
C8	26.1	23.4	–2.7	24.0	22.3	–1.7	31.7	33.3	1.6
C9	35.5	35.0	–0.5	34.2	32.5	–1.7	32.4	33.4	1.0
C10	70.5	71.8	1.3	70.9	67.3	–3.6	50.7	45.5	–5.2
C11	57.8	60.8	3.0	58.4	62.9	4.5	72.9	71.8	–1.1
C12	35.2	34.4	–0.8	24.5	25.4	0.9	23.8	23.5	–0.3
C13	24.3	26.6	2.3	23.2	22.9	–0.3	21.8	23.5	1.7
C14	24.8	21.5	–3.3	18.4	17.6	–0.8	19.9	19.6	–0.3
C15	53.9	53.2	–0.7	51.8	53.1	1.3	66.5	69.4	2.9
C17	48.4	52.2	3.8	43.9	45.9	2.0	65.5	65.9	0.4

Conclusions

The NMR data of sparteine N1-oxide and α-isosparteine N-oxide have been presented. The spectrum of sparteine N1-oxide recorded in DMSO-d_6 solution is typical of that expected for the boat conformer **1a**, while the spectrum recorded in $CDCl_3$ solution turned out to be a spectrum of sparteine N1-oxide hydrochloride (in the all chair conformation **1b**). The similarity of the conformation of **1a** and **4** to that of their free bases allowed us to determine the N-oxidation effect better than previously possible.

Experimental

General

The ^{1}H- and ^{13}C-NMR spectra (including ^{1}H-^{1}H COSY, ^{13}C-^{1}H COSY) were measured on a Varian 300 Mercury spectrometer operating at 300.13 and 75.462 MHz, respectively, and at ambient temperature, using ~0.5 M solutions in $CDCl_3$ and DMSO-d_6 with TMS as internal reference. The conditions of the spectra recording were: ^{13}C NMR: acquisition time 1.5 s; spectral width 23 000 Hz; number of points 69 000. ^{1}H NMR: acquisition time 3.0 s; spectral width 9000 Hz; number of points 45 000 (**1a, 2**), 70 000 (**1**-HCl). ^{1}H-^{1}H Cosy 90-90: relax. delay 1.0 s; acquisition time 0.170 s (**1a**, **2**), 0.250 s (**1**-HCl); spectral width and 2D width 6 330 Hz (**1a**), 4160 Hz (**1**-HCl), 5700 Hz (**2**); 16 repetitions (**1a**), 32 repetitions (**1**-HCl, **2**); 256 increments (**1**-HCl), 512 increments (**1a**, **2**). ^{13}C-^{1}H COSY: relax. delay 0.9 s; acquisition time 0.180 s (**1a**, **2**), 0.250 s (**1**-HCl); spectral width 4160 Hz (**1**-HCl), 5700 (**2**), 6300 (**1a**); 2D width 2 2630 Hz; 32 repetitions (**1a**), 64 repetitions (**1**-HCl, **2**); 2 x 256 increments (**1**-HCl), 2 x 512 increments (**1a**, **2**).

Syntheses

Sparteine N1-oxide (**1**) was prepared by oxidation with 30% aqueous H_2O_2 in methanol of the alkaloid freed from commercial (–)-sparteine sulphate pentahydrate (Aldrich), according to a previously described method [20].

α-Isosparteine N-oxide (**4**). α-Isosparteine (234 mg) was dissolved in methanol (6 mL) and 30% aqueous hydrogen peroxide (4 mL) was added. The reaction was complete after 1 day (TLC). A small amount of palladium on asbestos was added to decompose excess H_2O_2 and filtered off after 12 h. The solvents were evaporated under reduced pressure giving a white crystalline product. Yield: 64%. Elemental analysis: calcd. (%) for $C_{15}H_{28}N_2O$: C, 67.16; H, 10.45; N, 10.45. Found: C, 67.24; H, 10.38; N, 10.46.

DFT calculations

The ^{13}C-NMR absolute shielding constants (σ values) were calculated at the B3LYP/DFT level with the continuous set of gauge transformations (CSGT) method using the (6)6-311+G basis set. The

calculated magnetic shieldings were converted into the δ chemical shifts using the calculated ^{13}C absolute shieldings in TMS (177.3) at the same level of theory [3].

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Sample Availability: Contact the author.