Synthesis and Structure of New *N*-Bromobenzyl Bis-quinolizidine Derivatives

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Abstract: New potentially biologically active *N*-bromobenzyl derivatives of α-isosparteine and 2-methylsparteine were obtained. Newly obtained compounds were characterized by IR and NMR spectroscopy. The structure of the new compounds in solution was proposed.

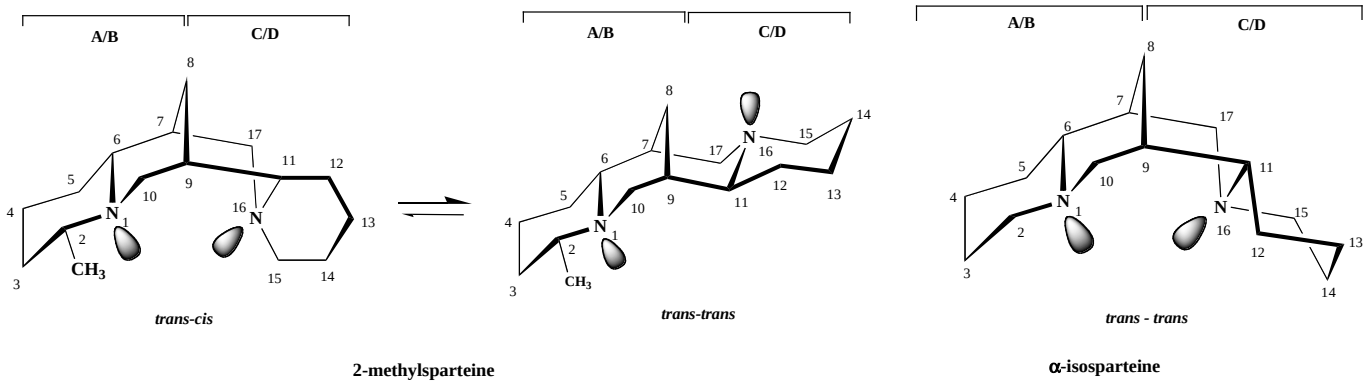
Keywords: Bromobenzyl derivatives, IR and NMR spectroscopy, sparteine derivatives, sparteine stereoisomers.

INTRODUCTION

Quinolizidine alkaloids make one of the most abundant groups of alkaloids distributed within the *Leguminosae*. It is known that bis-quinolizidine alkaloids are characterized and distinguished by their valuable pharmacological properties as they show antihypersensitive, antiinflammatory, antidepressant, antiarrhythmic, diuretic and hypoglicemic activity [1-5]. It has been found that chemical modification of bis-quinolizidine molecules can strongly influence their potential biological activity.

As a continuation of our studies aimed at the determination of the influence of a substituent introduced to a bis-quinolizidine molecule on the stereochemistry, and properties of this system we obtained new potentially biologically active *N*-bromobenzyl-substituted bis-quinolizidine derivatives. The preparation and X-ray crystallographic analysis of the benzyl quaternary salt of sparteine were described earlier by Yoshizawa and co-workers [6]. Gadepalli and co-workers describe the synthesis and X-ray analysis of (+)-6-benzyl-17-oxosparteine [7]. As the object of our research we chose conformationally stable α-isosparteine (**1**) and conformationally flexible 2-metylsparteine (**2**).

Of the sparteine diastereoisomers, α-isosparteine is practically conformationally homogeneous with the most stable *trans-trans* full-chair conformer whereas, the skeleton of 2-methylsparteine (similarly as sparteine) is very flexible, so sparteine and its 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 (Scheme **1**).



Scheme 1. The conformational-configurational arrangements and atom numbering of α-isosparteine and 2-methylsparteine.

RESULTS AND DISCUSSION

Treatment of α-isosparteine (or 2-methylsparteine) with 3 equivalents of *o*-(*m*-, *p*-)bromobenzyl bromides in MeOH afforded the *N*16-*o*-(*m*-, *p*-)bromobenzyl-α-isosparteinium (or 2-methylsparteinium) bromide (Scheme **2**).

The yields of the reactions 2-methylsparteine with *o*-(*m*-, *p*-)bromobenzyl bromides are almost the same (74-78%), while the yields of the reactions of α-isosparteine with *o*-(*m*-, *p*-)bromobenzyl bromides depend on the position of bromine atom in aromatic ring. This fact is connected with all-chair structure of the alkaloid.

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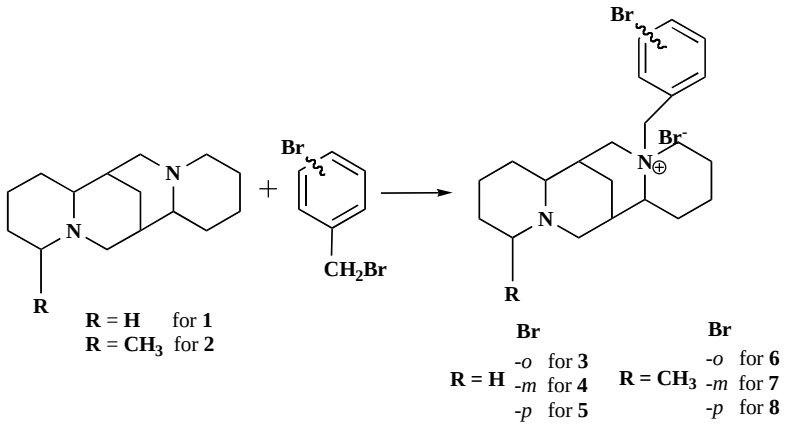


Scheme 2.

All compounds were characterized on the basis of spectral studies. Their structures were determined by comparison of their spectral data with those of α-isosparteine and 2-methylsparteine. The IR spectra of quinolizidine alkaloids have the characteristic so-called "*trans-band*" region (*T-band*, 2840-2600 cm^{-1}). The "*trans*-band" region in the spectrum of the α-isosparteine comprises three main absorption maxima at about 2793, 2758 and 2735 cm^{-1} [8], which result from the fact that the axial hydrogen atoms at C2, C6, C10 and C11, C15, C17 are in position *trans* in relation to the lone pairs on the nitrogen atoms at the N1 and N16. The attachment of a bromobenzyl group to one nitrogen atom changes the type and intensity of the *trans* band complex – only one absorption band is present near 2800 cm^{-1}. The *T-band* of 2-methylsparteine consists of one maximum near 2790 cm^{-1} [9]. IR spectrum of **2** in $CDCl_3$ solution shows within the 2200-2100 cm^{-1} region an additional band arising from C-D stretching vibration of $CDCl_3$ molecule associated with the nitrogen atom N16. The appearance of this band supports the claim that in solution ring C of 2-methylsparteine exists in boat conformation, which is equivalent to a "transoidal" arrangement of N1 and N16. The attachment of a bromobenzyl group to the N16 results in the disappearance of the absorption at 2790 cm^{-1} and appearance of a new absorption band at 2815 cm^{-1}. Also the absorption band assigned to the interaction of nitrogen atom N16 with $CDCl_3$ molecule disappears. The IR spectra of all new compounds show additional bands characteristic of bromobenzyl substituents.

The set of eight signals assigned to the alkaloid in the ^{13}C NMR spectra of **3-5** is correctly reproduced by the symmetric structure of α-isosparteine. Additional signals assigned to the bromobenzyl are observed at: 63.7 ppm ($-CH_2$) and 122.0-140.0 ppm (aromatic ring). The presence of a bromobenzyl substituent has practically no influence on the change in the chemical shifts of carbon atoms α-isosparteine. The only differences in the NMR spectra of compounds **3-5** appear in the region corresponding to the benzyl group substituted with a bromine atom at *-ortho*, *-metha*, and *-para* positions. Similarly, the differences in the NMR spectra of compounds **6-8** are also related to different substitution of benzyl group. Therefore, Table **1** presents the chemical shift of carbon and hydrogen atoms in the spectra of the representative derivatives of α-isosparteine and 2-methylsparteine with *p*-bromobenzyl substituent (compounds **5** and **8**, respectively).

^{13}C chemical shifts for C2, C3, C5, C6, C7 and C10 carbon atoms of *N*16-bromobenzyl-2-methylsparteinium salts approximate the analogous values of 2-methylsparteine (Table **1**). This result corroborates the presence of chemically unchanged A and B rings preserving the *trans*-quinolizidine form in *N*16-bromobenzyl salts. The deshielding influence of the benzyl substituent on *N*16 nitrogen of the alkaloid considered causes a down-field shift of the signals assigned to α carbons, i.e. C11, C15, C17 as compared with the respective 2-methylsparteine δ_C values. The change in the chemical shift of the carbon atom C13 by over 8 ppm testifies to the boat-chair conformation of C/D rings with *cis* fusion. The position of a bridge carbon signal C8 is diagnostic of the conformation of the two fused B/C rings in the sparteine skeleton. According to the criterion of Bohlmann and Zeisberg for the one carbon bridge in the bicyclo[3.3.1] moiety, this resonance is expected to move downfield in the sequence boat/boat, chair/boat, chair/chair [10,11]. For 2-methylsparteine (chair/boat) this resonance occurs at about 27.5 ppm (theor. 26.1 ppm); for α-isosparteine (chair/chair) at 36.4 ppm (theor. 35.4 ppm) [11]. These values are in agreement with the values obtained for *N*-bromobenzyl derivatives: 28.8 ppm for 2-methylsparteinium salts and 33.2 ppm for α-isosparteinium salts.

The assignments of the ^1H NMR signals to particular protons were achieved by two-dimensional methods, ^1H-^{13}C HETCOR and ^1H-^1H COSY.

The signals of protons connected with the C11, C15 and C17 carbons appear within the range $3.70 > \delta_H > 3.00$ ppm. A characteristic singlet appearing in the range 4.60-4.70 ppm was assigned to the aliphatic protons in the benzyl moiety attached to the nitrogen atom. The signals from aromatic protons are in the range 7.0 – 8.0 ppm.

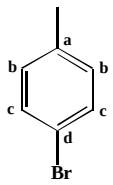
EXPERIMENTAL SECTION

General Techniques

The IR spectra were recorded by means of a FT-IR Bruker 113v spectrometer ($CDCl_3$ solution). The ^1H and ^{13}C NMR spectra were measured on a Varian Gemini 300 spec-

Table 1. NMR Spectroscopic Data of α-isosparteine, 2-methylsparteine and their Bromobenzyl Derivatives 5 and 8 (in $CDCl_3$)

Carbon Atom	α-isosparteine (1) [12]		*N-p*-bromobenzyl-α-isosparteine (5)		2-methylsparteine (2) [13]		*N*16-*p*-bromobenzyl--2-methylsparteine (8)	
	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H	δ_C	δ_H
2	57.2	1.72 2.70	56.5	1.70 2.65	58.0	1.89	57,5	2.08
3	25.3	1.63 1.48	25.2	1.65 1.50	35.3	1.51 1.21	34,3	1.30 1.50
4	24.9	1.23 1.71	24.8	1.20 1.80	24.5	1.64 1.64	23,3	1.65 1.30
5	30.0	1.59 1.24	29.3	1.60 1.65	30.2	1.25 2.08	30,1	1.35 1.35
6	66.3	1.89	66.2	1.95	66.2	1.74	66,4	1.90
7	35.6	1.45	33.7	1.45	33.8	1.85	33,7	1.95
8	36.4	1.52 1.52	33.2	1.50 1.50	27.5	1.10 2.11	28,8	1.50 2.30
9	35.6	1.45	33.7	1.85	36.4	1.54	33,7	1.95
10	55.8	1.99 2.90	55.9	2.00 2.85	57.3	1.70 2.93	56,7	1.85 2.93
11	66.3	1.89	66.2	3.00	64.4	2.03	73,6	3.10
12	30.0	1.59 1.24	29.3	1.60 1.30	34.7	1.42 1.53	26,4	2.70 1.45
13	24.9	1.23 1.71	24.8	1.25 1.70	24.9	1.32 1.66	16,2	1.35 1.65
14	25.3	1.63 1.48	25.2	1.60 1.50	26.0	1.48 1.63	22,9	2.45 1.55
15	57.2	1.72 2.70	56.5	3.35 3.15	55.3	1.61 2.78	65,0	3.65 3.15
17	55.8	1.89 2.90	55.9	3.60 3.45	53.5	2.35 2.68	61,7	3.70 3.40
$-CH_2$	-	-	63.7	4.65	-		63.7	4.65
$-CH_3$	-	-	-	-	21.3	1.01	20.7	1.05
a	-	-	134.9	-	-	-	135.5	-
b	-	-	128.6	7.24	-	-	128.6	7.57
c	-	-	131.3	7.14	-	-	131.6	7.29
d	-	-	120.8	-	-	-	121.3	-



trometer at 300.13 and 75.462 MHz, respectively and at ambient temperature, using ~0.5 M solution in $CDCl_3$, TMS as internal reference. Elemental analysis was carried out by means of a Perkin-Elmer 2400 CHN automatic device.

2-Methylsparteine was obtained by the reaction of 2-oxosparteine with methyllithium [9]. α-Isosparteine was obtained according to literature [14].

General procedure for preparation of *N*-bromobenzyl bis-quinolizidines

To a methanol solution consisting of 1 mmol of the alkaloid [**1** (234 mg) or **2** (248 mg)] *o-(m-, p-)*bromobenzyl bromide (747 mg; 3 mmol) was added. The reaction mixture was stirred at room temperature. Completion of the reaction was controlled by TLC examination [MeOH:$(CH_3)_2$

$CO:NH_4OH$ 1:1:0.5 v/v). Then half of the solvent volume was evaporated under vacuum and 5 ml of acetone was added. The oils obtained were dried under pressure in a desiccator above P_2O_5.

N-o-bromobenzyl-α-isosparteinium bromide (**3**) Yellow oil. Yield: 41.7%. Anal. Calcd. for $C_{22}H_{32}N_2Br_2$: C, 54.54; H, 6.61; N, 5.79. Found: C, 54.48; H, 6.48; N, 5.59.

N-m-bromobenzyl-α-isosparteinium bromide (**4**) Yellow oil. Yield: 88.8%. Anal. Calcd. for $C_{22}H_{32}N_2Br_2$: C, 54.54; H, 6.61; N, 5.79. Found: C, 54.62; H, 6.65; N, 5.64.

N-p-bromobenzyl-α-isosparteinium bromide (**5**) Yellow oil. Yield: 61.5%. Anal. Calcd. for $C_{22}H_{32}N_2Br_2$: C, 54.54; H, 6.61; N, 5.79. Found: C, 54.60; H, 6.72; N, 5.81.

16N-o-bromobenzyl-2-methylsparteinium bromide (**6**) Yellow oil. Yield: 78.1%. Anal. Calcd. for $C_{23}H_{34}N_2Br_2$: C, 55.42; H, 6.83; N, 5.62. Found: C, 55.54; H, 6.78; N, 5.54.

16N-m-bromobenzyl-2-methylsparteinium bromide (**7**) Yellow oil. Yield: 75.9%. Anal. Calcd. for $C_{23}H_{34}N_2Br_2$: C, 55.42; H, 6.83; N, 5.62. Found: C, 55.40; H, 6.81; N, 5.68.

16N-p-bromobenzyl-2-methylsparteinium bromide (**8**) Yellow oil. Yield: 74.8%. Anal. Calcd. for $C_{23}H_{34}N_2Br_2$: C, 55.42; H, 6.83; N, 5.62. Found: C, 55.46; H, 6.90; N, 5.56.

CONCLUSION

Six new potentially biologically active compounds were prepared with good yields using a simple alkylation reaction. The yield of the reaction depends on the alkaloid and the position of bromine (*o*-, *m*-, *p*-) in bromobenzyl bromide. The compounds synthesized were fully characterized by NMR and IR methods. The attachement of a bromobenzyl substituent to the α-isosparteine skeleton does not change the alkaloid structure, while in the 2-methylsparteine molecule, the bromobenzyl groups at N16 induces a change in the C/D rings positions from *trans* to *cis*.

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CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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