SYNTHESIS AND CONFORMATIONAL ANALYSIS OF DISUBSTITUTED SPARTEINE DERIVATIVES

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Synthesis of disubstituted sparteine derivatives and their diperchlorate salts was performed. Their IR and NMR spectra were analysed to determine the structure of these compounds, as well as the substituent and the protonation effects. It was shown that both unsaturated (2,17β-dimethyl-2,3-didehydrosparteine (**12**), 17β-isopropyl-2-methyl-2,3-didehydrosparteine (**13**)) and saturated (2,17β-dimethylsparteine (**14**), 17β-isopropyl-2-methylsparteine (**15**)) newly obtained sparteine derivatives have the same configurational-conformational system: *trans* A/B chair/chair, *trans* C/D boat/chair. The methyl and the isopropyl (both equatorial) groups at C-17 appear the elements stabilizing the boat-chair system of the C/D rings, which does not change either on the introduction of the second substituent to the opposite quinolizidine system (the A/B rings) or on protonation. The protonation of the free bases obtained gives only disalts. The atoms undergoing the protonation are either C-3 and N-16 in **12** and **13** or both nitrogen atoms (N-1 and N-16) in **14** and **15**. The methyl group introduced on the carbon atom C-2 takes equatorial position, as in 2-methylsparteine (**2**).
Keywords: Bis-quinolizidine alkaloids; Sparteine derivatives; IR spectroscopy; NMR spectroscopy; Chiral saturated heterocycles; Tertiary amines.

It is well known that the basic bis-quinolizidine system – sparteine (**1**), is made of four rings, two of which (A/B) form a double-chair system of *trans*-quinolizidine relatively resistant to conformational-configurational changes. The second system of rings (C/D) is much more susceptible to inversion on nitrogen atom N-16 and it may occur in *trans* boat-chair or *cis* double-chair conformation (see Fig. 1).

The hitherto performed studies on the effect of substituents introduced stereoselectively into the molecule of sparteine on the structure, properties and configurational-conformational equilibrium were confined to the monosubstituted bis-quinolizidine only (exclusively, in the A/B ring system or in the C/D ring system). In the beginning, the α,β-unsaturated >C(2)=C(3)< system has been incorporated into the A/B ring system of sparteine (**1**), and a methyl (**2**), phenyl (**3**) or *p*-tolyl (**4**) substituent was ad-

ded at the position of C-2. It turned out that neither the double bond nor the substituent induced significant configurational-conformational changes in the molecule, nor did protonation of these systems bring about such an effect; in each case only disalts were obtained[1a,1b]. Also the saturated derivatives: 2-methyl- (**5**), 2-phenyl- (**6**) and 2-(*p*-tolyl)sparteine (**7**) maintained the same C/D rings system (*trans* boat-chair) as the parent enamines. Changes in the configurational-conformational system were caused only by protonation of these compounds. The C/D ring system changed into a *cis* all-chair with an intramolecular hydrogen bond[1c,1d]. Other monosubstituted bis-quinolizidines are 14,15-didehydro-15-phenylsparteine (**8**) and 15-phenylsparteine (**9**). Compound **8** occurs in *trans* A/B–*cis* C/D configuration and adopts an all-chair conformation. Two crystalline salts were obtained[1e,1f] from the compounds monoperchlorate and dihydrochloride (depending on the influence of anion). Reduction of **8** yields 15-phenylsparteine (**9**) which exhibits a *transoidal* arrangement of nitrogen atoms. Upon its protonation, monoperchlorate with an intramolecular hydrogen bond is formed, and nitrogen atom N-1 is protonated (*cisoidal* arrangement of nitrogen atoms)[1e]. It has also been found that the methyl or isopropyl group, introduced selectively on C-17β (17β-methylsparteine (**10**), 17β-iso-

SPARTEINE
(**1**)

trans A/B – *cis* C/D
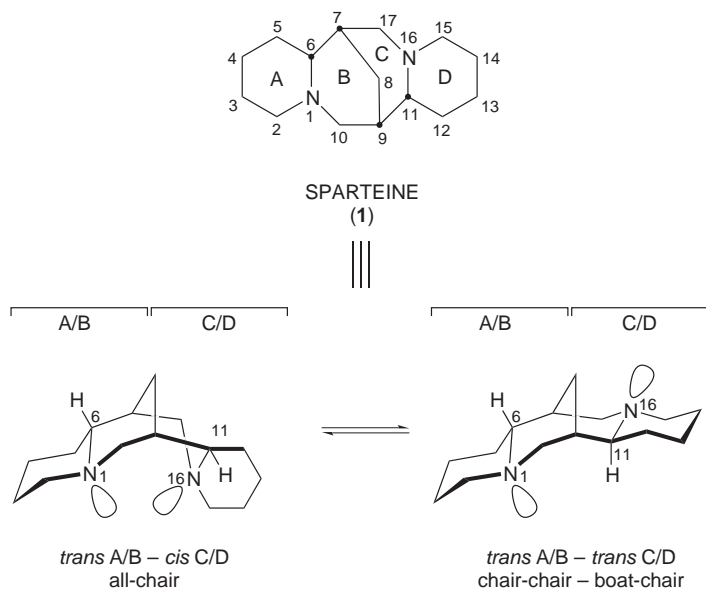all-chair

trans A/B – *trans* C/D
chair-chair – boat-chair

FIG.1
Conformation of sparteine

propylsparteine (**11**), Fig. 2), is an effective "anchor" against full stabilisation of the *transoidal* arrangement of N-1 and N-16 (*trans* boat-chair C/D ring system) which is present also in disalts[2,3].

Sparteine has recently received widespread interest as a chiral ligand in asymmetric synthesis. On the other hand, chemical transformations of the alkaloid itself have attracted much less attention. As a continuation of our study of configurational-conformational dynamics of bis-quinolizidine and its derivatives it seemed reasonable to extend our investigation on disubstituted: 2- and 17-disubstituted derivatives of sparteine. We have obtained 2,17β-dimethyl-2,3-didehydrosparteine (**12**), 17β-isopropyl-2-methyl-2,3-didehydrosparteine (**13**), 2,17β-dimethylsparteine (**14**), 17β-isopropyl-2-methylsparteine (**15**) and their diperchlorate salts.

EXPERIMENTAL

IR spectra (ν, cm^{-1}) were recorded with a Brücker FTIR 113v spectrometer; film or 0.4 M solutions in CDCl$_3$ or CD$_3$CN. ^{13}C and ^{1}H NMR (DEPT, HETCOR, COSY) measurements (δ, ppm; *J*, Hz) were carried out on a Varian 300 Gemini spectrometer at 300 MHz and at ambient temperature, using ≈0.5 M solutions in CDCl$_3$ or in DMSO-d_6, TMS as internal reference. EI mass spectra were recorded on an AMD-Intectra GmbH (Harpstedt) D-27243 Model 402 two-sector mass spectrometer. The pK_a measurements (in acetonitrile) were measured potentiometrically. A pX-processor PM-600 pH meter was used. Optical rotations were measured with a Perkin–Elmer 243B polarimeter and [α]$_D$ values are given in 10^{-1} deg cm^2 g^{-1}.

2,17β-Dimethyl-2,3-didehydrosparteine (**12**) and Its Diperchlorate Salt (**12**·2HClO$_4$)

Methyllithium in diethyl ether (1.6 M solution; 6 ml, 9.6 mmol) was added to diethyl ether (30 ml) under argon. Then a solution of 17β-methyllupanine (**16**; 524 mg, 2 mmol) in di-

2, R = CH$_3$
3, R = C$_6$H$_5$
4, R = p-tolyl

5, R = CH$_3$
6, R = C$_6$H$_5$
7, R = p-tolyl
9, R^2 = C$_6$H$_5$
10, R^3 = CH$_3$
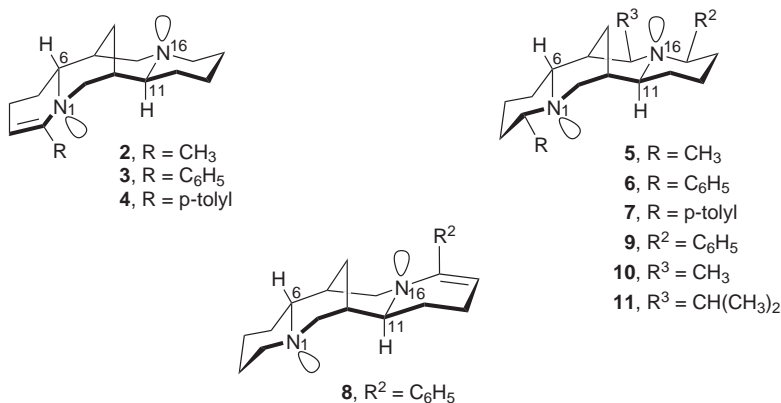**11**, R^3 = CH(CH$_3$)$_2$

8, R^2 = C$_6$H$_5$

Fig. 2
Conformation of sparteine derivatives

ethyl ether (10 ml) was introduced into this solution. Toluene (10 ml) was added and the reaction mixture was heated to about 70 °C. Progress of the reaction was controlled by TLC on plastic plates covered with silica gel with a mixture of MeOH–acetone–NH_4OH (10:10:1, v/v) as developing phase. The spots were detected by Dragendorff's reagent (D.R.). The mixture was kept at room temperature overnight. The reaction flask was placed in an ice bath and water (5 ml) was added with stirring. The aqueous layer was extracted with diethyl ether. The extract was dried over KOH, filtered and concentrated under reduced pressure. The resultant oil (16 mg) was crude 2,17β-dimethyl-2,3-didehydrosparteine (**12**). The upper layer (organic) was extracted with 2 M HCl (3 × 15 ml portions); the combined acidic layers were placed once more in the separating funnel, made alkaline with 50% KOH and (after cooling) extracted exhaustively with diethyl ether. The extract was dried over KOH, filtered and concentrated under reduced pressure. A yellowish oil was obtained. Combined oils of **12** (400 mg, 77%); $[\alpha]_D^{20}$ –1.03 (c 1, MeOH). IR: see Fig. 3. For $C_{17}H_{28}N_2$ (260.5) calculated: 78.46% C, 10.76% H, 10.76% N; found: 78.63% C, 10.76% H, 10.79% N.

Because of instability of **12**, the resulting oil was transformed into diperchlorate salt. Compound **12** (130 mg, 0.5 mmol) was dissolved in MeOH (5 ml) and treated with $HClO_4$–MeOH (1:4, v/v) solution to pH about 3. The resultant substance was recrystallized from methanol affording white crystals of **12**·2HClO$_4$ (140 mg, 51%), m.p. 256–259 °C; $[\alpha]_D^{20}$ –0.67 (c 1, MeOH). NMR: see Table I. For $C_{17}H_{28}N_2 \cdot 2HClO_4 \cdot H_2O$ (478.5) calculated: 42.59% C, 6.74% H, 5.84% N; found: 42.45% C, 6.40% H, 5.59% N.

2,17β-Dimethylsparteine (**14**)

Compound **12** (260 mg, 1 mmol) was dissolved in MeOH (15 ml). After cooling, $NaBH_4$ (40 mg, 1.1 mmol) was added portionwise. The mixture was heated at 45 °C for 60 min, a few drops of AcOH was added to decompose the excess of reducing agent, and then, MeOH was evaporated under reduced pressure. The obtained oil was alkalized with 50% KOH and extracted with diethyl ether. The ether solution was dried with KOH pellets, evaporated under pressure and oily residue was crystallized from MeOH. White crystalline **14** was obtained (210 mg, 80%), m.p. 72–74 °C; $[\alpha]_D^{20}$ –0.84 (c 1, MeOH). IR: see Fig. 4. NMR: see Table II. pK_a: see Table IV. EI-MS, m/z: 262 [M$^+$]. For $C_{17}H_{30}N_2$ (262.5) calculated: 77.76% C, 11.54% H, 10.67% N; found: 76.68% C, 11.95% H, 10.50% N.

17β-Isopropyl-2-methyl-2,3-didehydrosparteine (**13**) and Its Diperchlorate Salt (**13**·2HClO$_4$)

Ethereal 1.6 M solution of CH_3Li (5 ml, 8 mmol) was added to a solution of 17β-isopropyl-lupanine (**17**; 524 mg, 2 mmol) in anhydrous diethyl ether (10 ml). The same procedure as for preparation of compound **12** was used. A yellowish oil of **13** was obtained (450 mg, 78%); $[\alpha]_D^{20}$ –0.38 (c 1, MeOH). IR: see Fig. 3. For $C_{19}H_{32}N_2$ (288.5) calculated: 79.09% C, 11.20% H, 9.71% N; found: 79.37% C, 11.43% H, 9.81% N.

Compound **13** (144 mg, 0.5 mmol) was dissolved in MeOH (5 ml) and treated with $HClO_4$–MeOH (1:4, v/v) solution to pH about 3. The resultant substance was recrystallized from methanol giving white crystals of **13**·2HClO$_4$ (140 mg, 57%), m.p. 260–262 °C; $[\alpha]_D^{20}$ –0.17 (c 1, MeOH). NMR: see Table I. For $C_{19}H_{32}N_2 \cdot 2HClO_4 \cdot H_2O$ (507.5) calculated: 44.97% C, 7.16% H, 5.52% N; found: 44.87% C, 6.99% H, 5.28% N.

17β-Isopropyl-2-methylsparteine (**15**)

The same procedure as for preparation of 2,17β-dimethylsparteine (**14**) was used here. Compound **13** (288 mg, 1 mmol) was dissolved in MeOH (15 ml), after cooling, NaBH₄ (45 mg, 1.2 mmol) was added. Colourless oil of **15** was obtained (203 mg, 70%); $[\alpha]_D^{20}$ −0.03 (*c* 1, MeOH). IR: see Fig. 4. NMR: see Table II. pK_a: see Table IV. EI-MS, *m/z*: 290 [M⁺]. For $C_{19}H_{34}N_2$ (290.6) calculated: 78.54% C, 11.82% H, 9.64% N; found: 78.19% C, 12.19% H, 9.60% N.

Preparation of Diperchlorate Salt of (**14**) and (**15**)

Compound **14** (131 mg, 0.5 mmol) (or **15** (145 mg, 0.5 mmol)) was dissolved in MeOH (10 ml) and a mixture of HClO₄–MeOH (1: 4, v/v) was added until a slightly acidic solution was obtained. Then, diethyl ether was added until the first turbidity was observed. White crystals of **14**·2HClO₄ were obtained (138.5 mg, 60%), m.p. 134–135 °C; $[\alpha]_D^{20}$ −0.53 (*c* 1, MeOH). IR: see Fig. 5. NMR: see Table III. For $C_{17}H_{30}N_2 \cdot 2HClO_4 \cdot H_2O$ (479.4) calculated: 42.32% C, 7.05% H, 5.81% N; found: 42.20% C, 7.38% H, 5.92% N. **15**·2HClO₄ (207 mg, 60%), m.p. 250–255 °C; $[\alpha]_D^{20}$ −0.01 (*c* 1, MeOH). IR: see Fig. 5. NMR: see Table III. For $C_{19}H_{34}N_2 \cdot 2HClO_4 \cdot 2H_2O$ (525.5) calculated: 43.26% C, 7.66% H, 5.31% N, found: 43.33% C, 7.83% H, 5.51% N.

RESULTS AND DISCUSSION

Unsaturated Derivatives and Their Salts

2,17β-Dimethyl-2,3-didehydrosparteine (**12**) and 17β-isopropyl-2-methyl-2,3-didehydrosparteine (**13**) were obtained in a reaction of a proper lactam (17β-methyllupanine (**16**) or 17β-isopropyllupanine (**17**)) with methyllithium (see Scheme 1). Compounds **12** and **13** are highly unstable oils quickly decomposing in air. Their IR spectra (film) revealed the bands characteristic of isolated and conjugated >C=C< bonds at 1650 cm⁻¹. Further information about the structure of **12** and **13** were gained from the analysis of "trans-band" (T-band, or Bohlman's band) in the 2840–2600 cm⁻¹ region of IR spectra. These T-bands were compared with the proper T-bands observed for 2-methyl-2,3-didehydrosparteine (**2**) and sparteine (**1**) the latter being frequently treated as a reference standard for this group of compounds. The T-band of sparteine reveals two absorption peaks at about 2800 and 2760 cm⁻¹. The T-bands of **2**, **12** and **13** are very similar showing the main maxima at about 2780 (**2**), 2794 (**12**) and 2785 cm⁻¹ (**13**). The differences between T-bands of sparteine and new compounds are a consequence of the absence of the trans-axial hydrogen atom at C-2 in the last two compounds. This, in turn, results in a significant simplification of the IR spectrum in the T-band region. The similarity of the position of this

band in **2**, **12** and **13** may testify to the fact that the last two compounds have the same arrangement of rings C/D as it has already been determined for **2**. The obtained diperchlorate salts of **12** and **13** are white crystalline substances, similarly to the diperchlorate of 2-methyl-2,3-didehydro-sparteine (**2**·2HClO$_4$). In the analysis of IR spectra of **12**·2HClO$_4$ and **13**·2HClO$_4$, the IR spectra of diperchlorate salt of **2**·2HClO$_4$ were used as a reference. Preliminary analysis of IR spectra of these salts in CD$_3$CN solutions confirmed the absence of bands characteristic of the >C=C< bond for both compounds. Instead of protonation of nitrogen atoms N-1 and N-16, as in the case of sparteine (**1**), in the discussed case the atoms C-3 and N-16 were protonated. This leads to the formation of an immonium system >C(2)=N(1)$^+$< with protonated atom N-16. The absence of a signal in the classic region of the immonium band (1670–1700 cm^{-1}) is related to the presence of the methyl substituent at C-2. We also observed the absence (or evident disappearance) of the trans band due to the lack of free electron pairs at the nitrogen atoms N-1 and N-16. The well-shaped band at 3080 cm^{-1} for **12**·2HClO$_4$ and 3090 cm^{-1} for **13**·2HClO$_4$ is assigned to the stretching vibrations of ≡N(16)$^+$–H associated with the perchlorate anion[4].
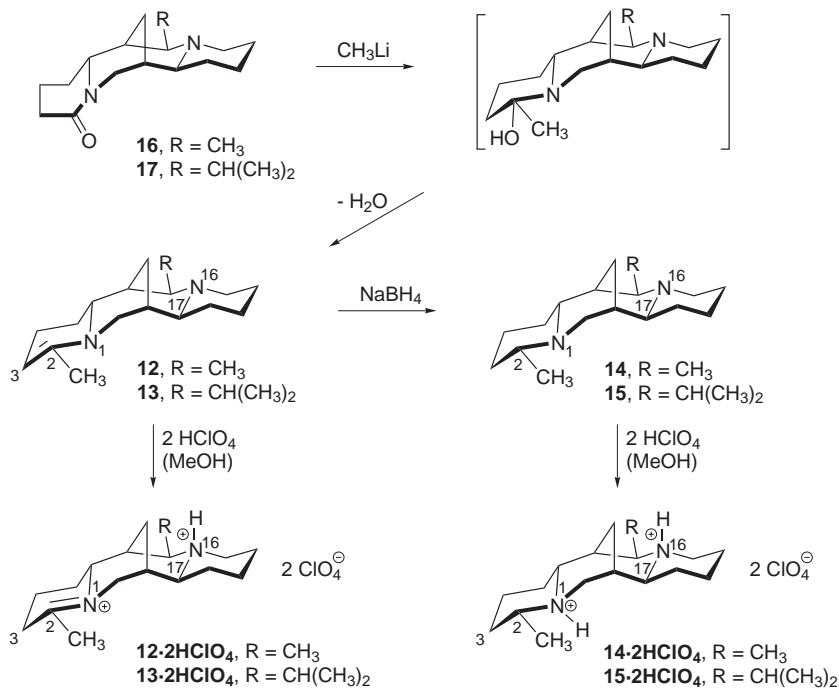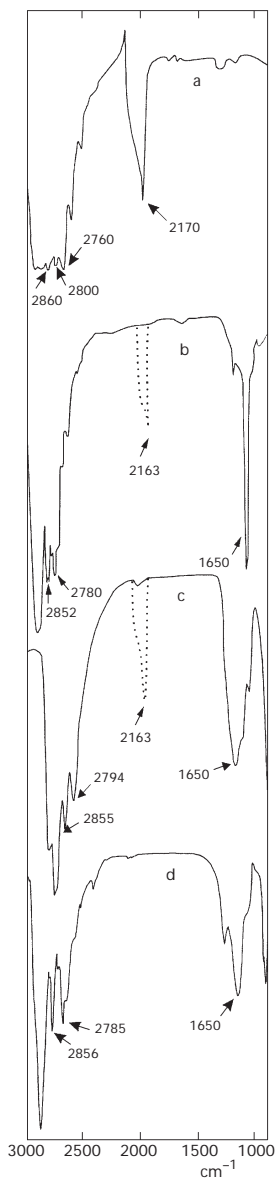

SCHEME 1

F<small>IG</small>. 3

The IR spectra of: a sparteine (CDCl$_3$) (**1**), b 2-methyl-2,3-didehydrosparteine (**2**) (film), c 2,17β-dimethyl-2,3-didehydrosparteine (**12**) (film), d 17β-isopropyl-2-methyl-2,3-di-dehydrosparteine (**13**) (film)

TABLE I

NMR chemical shifts (DMSO-d_6) of diperchlorate salts of 2,17β-dimethyl-2,3-didehydrosparteine (**12**·2ClO$_4$) and 17β-isopropyl-2-methyl-2,3-didehydrosparteine (**13**·2HClO$_4$) (substituent effect; + upfield shift, – downfield shift)

Position	**12**·2HClO$_4$		**13**·2HClO$_4$	
	δ_C, ppm	δ_H, ppm	δ_C, ppm	δ_H, ppm
2	194.7	–	194.8	–
	+139.5		+139.6	
3	35.8	3.07[a]	35.9	3.07[a]
	+13.6	3.09[a]	+13.7	3.09[a]
4	15.8	1.50[a]	16.1	1.78[a]
	–6.4	1.50[a]	–6.1	1.60[a]
5	24.6	1.83eq[a]	25.4	2.83eq[a]
	–1.8	1.60ax[a]	–1.0	2.70ax[a]
6	63.9	3.76ax	63.9	4.90ax
	–1.4		–1.4	
7	39.3	2.20eq	32.2[b]	3.45eq
	+10.7		+3.6	
8	22.7	2.10eq[a]	20.4	2.90eq[a]
	+0.5	1.85ax[a]	–1.8	1.85ax[a]
9	33.4	2.10eq	33.1[b]	3.15eq
	+1.9		+1.6	
10	55.4	3.46[a]	55.2	4.46[a]
	–1.1	3.46[a]	–1.3	5.40[a]
11	63.9	2.70ax	67.0	4.10ax
	+1.6		+4.7	
12	31.2	2.05eq[a]	30.3	2.00eq[a]
	+0.4	1.59ax[a]	–0.5	1.60ax[a]
13	22.4	1.70eq[a]	22.0	2.80eq[a]
	+0.8	1.40ax[a]	+0.4	2.45ax[a]
14	22.2	1.76eq[a]	22.6	1.50[a]
	0.0	1.60ax[a]	+0.4	1.50[a]
15	50.8	3.47ax	51.9	3.85ax
	–3.4	4.46eq	–2.3	4.80eq
17	57.2	3.12ax	62.2	3.65ax
	+9.1		+14.1	
2-CH$_3$	25.4	2.50	25.5	3.46
17-CH$_3$	19.3	1.37	–	–
-CH$_3$	–	–	14.6	1.95
-CH	–	–	26.6	3.46
-CH$_3$	–	–	19.4	1.90

[a] δ_H values extracted from the HET-COR spectrum; [b] the values could be interchanged.

All the assumptions concerning the structure of diperchlorates **12**·2HClO$_4$ and **13**·2HClO$_4$ have been confirmed by analysis of NMR spectra and their comparison with the spectra of diperchlorates of sparteine (**1**·2HClO$_4$) and 2-methyl-2,3-didehydrosparteine (**2**·2HClO$_4$) (see Table I). Substituent effects and changes in hybridization are calculated by subtracting chemical shifts of individual carbon atoms of sparteine diperchlorate from the chemical shifts of the corresponding carbon atoms in **12**·2HClO$_4$ and **13**·2HClO$_4$. New disalts have the same conformation as those of sparteine and 2-methyl-2,3-didehydrosparteine diperchlorate, *i.e.* the boat conformation in ring C. This is concluded by the lack of negative γ-gauche effects on the carbon atoms C-12, C-14 and C-17, which are known to accompany a change in the conformation from the boat-chair *trans*-quinolizidine to the all-chair *cis*-quinolizidine[5]. Both compounds are immonium salts having a double bond between N-1 and C-2. This is indicated by a large positive effect of about +139 ppm for C-2. These effects are mainly a consequence of the changed hybridization of C-2 from sp^3 in sparteine to sp^2 in the investigated disalts. The effect of introducing a double bond is modified by the effect of the substituent – a methyl group. On carbon atoms C-3 we can observe the β effect owing to the double bond (>C=N$^+$<) and the substituent (about +14 ppm). Distinct negative γ effects, related to the elimination of 1,3 diaxial proton interaction are observed on C-4 (about –6.5 ppm). Because of the presence of positive charge on the two nitrogen atoms, we observe low-field shifts of the signals assigned to the protons bonded to C-6, C-10, C-11 and C-15. The signals assigned to the axial hydrogen atoms at the carbon atom C-17 are in a lower field (δ 3.12 and 3.65 ppm) than in the disalt **2**·2HClO$_4$ (δ 2.62 ppm)[5].

Saturated Derivatives and Their Salts

The disubstituted sparteine derivatives, 2,17β-dimethylsparteine (**14**) and 17β-isopropyl-2-methylsparteine (**15**), were obtained by reducing **12** and **13** with NaBH$_4$. Most data on the structure of these compounds were obtained from a comprehensive analysis of IR spectra of **12**, **13** and **5**, **10**, **11** (CDCl$_3$) in the following ranges: 2300–2000 cm^{-1} (association with CDCl$_3$ molecule) and 2840–2600 cm^{-1} (T-band). IR spectra of **5**, **10** and **14** show within the 2200–2100 cm^{-1} region an intense band arising from C–D stretching vibrations of CDCl$_3$ molecules, associated with the easily accessible basic centre of the alkaloids molecule (nitrogen atom N-16). This supports the hypothesis that ring C in **14**, similarly as in **5** and **10**, exists in boat conformation, which is equivalent to a *transoidal* arrangement of N-1 and N-16 in all

cases. This band is not observed in the spectrum of **15**. As it is well known, the nature of the T-band observed in IR spectra of quinolizidine alkaloids depends on the conformational-configurational arrangement present in the molecule[6,7]. The T-band in the IR spectrum of **14** and **15** is similar to that in the IR spectra of **5**, **10** and **11**. Thus it can be concluded that newly obtained compounds like **5**, **10** and **11** occur in the following conformational system: *trans* A/B (chair/chair)–*trans* C/D (boat/chair). In 2,17β-dimethylsparteine the two nitrogen atoms N-1 and N-16 are protonated. In the spectrum of this compound, the trans band disappears and the bands assigned to $v_{\equiv N^+-H}$ occur, similarly as in the spectrum of **10**·2HClO$_4$ at 3070 cm^{-1}.

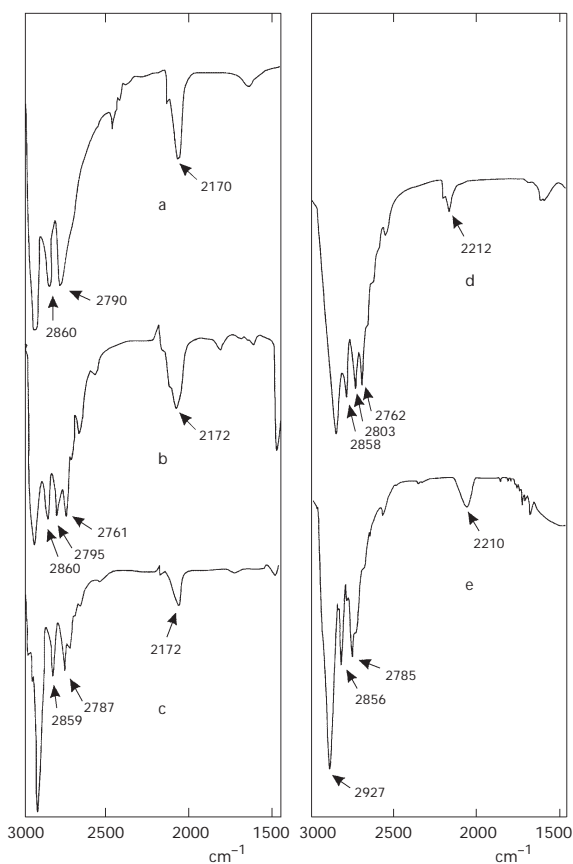
F ig. 4

The IR spectra (in CDCl$_3$) of: a 2-methylsparteine (**5**), b 17β-methylsparteine (**10**), c 2,17β-dimethylsparteine (**14**), d 17β-isopropylsparteine (**11**), e 17β-isopropyl-2-methylsparteine (**15**)

A similar situation takes place in **15**·2HClO$_4$. Its spectrum recorded in solution (CD$_3$CN) reveals the absorption bands at 3105 and 3084 cm^{-1}.

In the NMR spectrum of **14** and **15** we found chemical shifts close to those of sparteine (**1**) except those in the nearest vicinity of the substituents (see Table II). Consequently, **14** and **15** have the same conformation as sparteine, with ring C in boat form. The methyl group at C-2 is equatorial since no γ-gauche effects are observed in ring A on C-3 and C-6. In accordance with this, the methyl substituent resonates at a much lower field (≈21.0 ppm) than it would be expected for an axial methyl substituent[8,9]. Another fact testifying to the preservation of the boat conformation of the ring C is the absence of high-field shift of the signals due to the carbon atoms C-11, C-12 and C-14. The boat conformation of ring C is also reflected by the values of the chemical shift of the signal assigned to H-15eq in the new compounds above 3.0 ppm (δ 2.63 ppm for sparteine). This shift

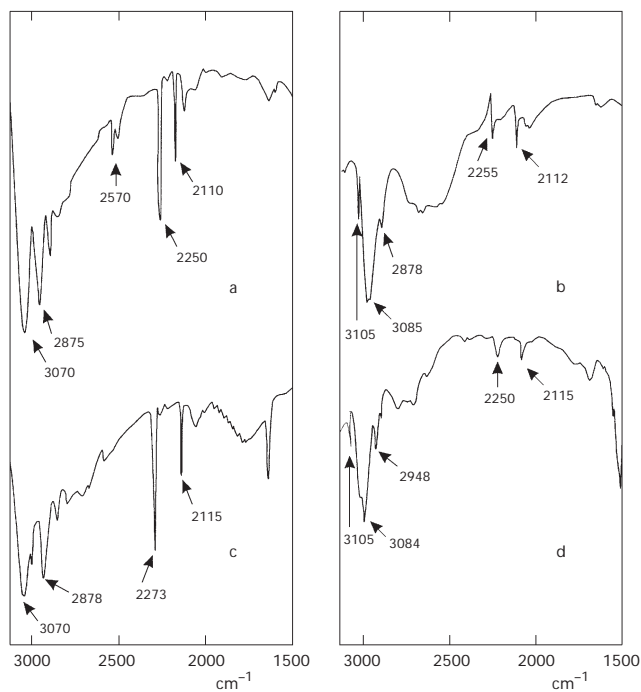FIG. 5
The IR spectra of diperchlorate salt (in CD$_3$CN) of: a 17β-methylsparteine (**10**·2HClO$_4$), b 17β-isopropylsparteine (**11**·2HClO$_4$), c 2,17β-dimethylsparteine (**14**·2HClO$_4$), d 17β-isopropyl-2-methylsparteine (**15**·2HClO$_4$)

TABLE II

NMR chemical shifts (CDCl$_3$) of 2,17β-dimethylsparteine (**14**) and 17β-isopropyl-2-methyl-sparteine (**15**) (substituent effect; + upfield shift, – downfield shift)

Position	14		15	
	δ_C, ppm	δ_H, ppm	δ_C, ppm	δ_H, ppm
2	58.4	1.92ax	58.9	1.86ax
	+2.4		+2.9	
3	35.4	1.34ax[a]	35.3	1.50[a]
	+9.8	1.49eq[a]	+9.7	1.50[a]
4	25.4[b]	1.50[a]	24.9	1.65[a]
	+0.9	1.50[a]	+0.4	1.65[a]
5	30.2	1.24ax[a]	31.3	1.23[a]
	+1.1	1.42eq[a]	+2.2	1.23[a]
6	66.3	1.79ax	66.6	1.80ax
	0.0		+0.3	
7	43.7	1.36eq	34.7	1.52eq
	+10.8		+1.8	
8	27.4	2.02eq	28.7	1.92eq
	0.0	0.96ax	+1.3	1.00ax
9	37.2	1.50eq	36.9	1.45eq
	+1.3		+1.0	
10	57.2	1.69ax	57.7	1.69ax
	–4.6	2.91eq	–4.1	2.92eq
11	64.9	1.92ax	64.2	2.10ax
	+0.7		0.0	
12	35.4	1.49eq[a]	36.0	1.46eq[a]
	+0.9	1.23ax[a]	+1.5	1.30ax[a]
13	24.8[b]	1.55eq[a]	25.7	1.66[a]
	+0.2	1.26ax[a]	+1.1	1.66[a]
14	26.4	1.55[a]	26.8	1.56[a]
	+0.6	1.55[a]	+1.0	1.56[a]
15	52.0	1.66ax	52.2	1.70ax
	–3.2	3.18eq	–3.0	3.20eq
17	56.7	2.30ax	63.9	2.20ax
	+3.3		+10.5	
2-CH$_3$	21.2	1.01	21.3	1.00
17-CH$_3$	23.0	1.07	–	–
-CH$_3$	–	–	20.2	0.80
-CH	–	–	28.6	2.18
-CH$_3$	–	–	15.5	0.85

[a] δ_H values extracted from the HET-COR spectrum; [b] the values could be interchanged.

TABLE III

NMR chemical shifts (DMSO-d_6) of diperchlorate salts of 2,17β-dimethylsparteine (**14**·2HClO$_4$) and 17β-isopropyl-2-methylsparteine (**15**·2HClO$_4$) (protonation effect; + upfield shift, – downfield shift)

Position	(**14**-2H$^+$)			(**15**-2H$^+$)		
	δ_C, ppm	R, ppm	δ_H, ppm	δ_C, ppm	R, ppm	δ_H, ppm
2	56.4	+1.2	3.31ax	63.5	+8.3	3.35ax
	–2.0			+4.6		
3	31.4	+9.2	2.22[a]	30.8	+8.6	2.00[a]
	–4.0		2.22[a]	–4.5		2.00[a]
4	21.7[b]	–0.5	2.31eq[a]	22.2[b]	0.0	1.85eq[a]
	–3.7		1.72ax[a]	–2.7		1.54ax[a]
5	26.5	+0.1	1.86ax[a]	27.5	+1.1	1.52ax[a]
	–3.7		2.45eq[a]	–3.8		1.67eq[a]
6	63.1	–2.2	3.18ax	62.6	–2.7	3.20ax
	–1.8			–4.0		
7	38.5	+9.9	2.08eq	32.0	+3.4	2.10eq
	–5.2			–2.7		
8	22.8	+0.6	1.64eq	23.2	+1.0	1.84eq
	–4.6		1.46ax	–5.5		1.56ax
9	32.2	+0.7	2.10eq	31.0	–0.5	2.34eq
	–5.0			–5.9		
10	53.0	–3.5	2.95ax	53.0	–3.5	2.95ax
	–4.2		3.74eq	–4.7		3.75eq
11	65.4	+3.1	3.28ax	66.4	+4.1	3.26ax
	–0.9			+2.2		
12	31.5	+0.7	1.93eq[a]	31.1	+0.5	1.90eq[a]
	–3.9		1.65ax[a]	–4.7		1.65ax[a]
13	21.9[a]	+0.3	2.35eq[a]	22.4[b]	+0.8	1.82eq[a]
	–2.9		1.78ax[a]	–3.3		1.50ax[a]
14	22.5[b]	+0.3	1.79ax[a]	22.6[b]	+0.4	1.48ax[a]
	–3.9		2.28eq[a]	–4.2		1.80eq[a]
15	51.7	–2.5	2.64ax	52.7	–1.5	2.72ax
	–0.3		3.81eq	+0.5		3.95eq
17	63.3	+15.2	3.36ax	65.7	+17.6	3.30ax
	+6.6			+1.8		
2-CH$_3$	17.2	–	1.30	17.5	–	1.30
	–4.0			–3.8		
17-CH$_3$	19.3	–	1.38	–	–	–
	–3.7					
-CH$_3$	–	–	–	19.7	–	0.88
				–0.5		
-CH	–	–	–	26.5	–	2.48
				–2.1		
-CH$_3$	–	–	–	14.3	–	0.95
				–1.2		

[a] δ_H values extracted from the HET-COR spectrum; R, substituent effect; [b,c] the values could be interchanged.

can be explained by the effect of the neighbouring nitrogen atom N-16 and magnetic anisotropy of its free electron pair and the presence of a substituent at C-17. A similar effect can be noted for H-10eq neighbouring the nitrogen atom N-1. Similarly as in the case of disalts of unsaturated derivatives, no γ-gauche effects are observed on the carbon atoms C-12, C-14 and C-17, which usually accompany a change in the conformation from boat-chair to all-chair. The protonation of the two nitrogen atoms in both disalts is evidenced by a change in the values of the chemical shifts of the substituents in their vicinity. The protonation effects were calculated by subtracting chemical shifts of individual carbon atoms of sparteine derivatives as free bases from the chemical shifts of the corresponding carbon atoms in desalts (see Table III).

Additional information about new disubstituted sparteine derivatives **14** and **15** may be obtained from analysis of their pK_a values performed in CH_3CN (compounds **12** and **13** are very unstable). The reference values are pKa for sparteine (**1**) and 2-methylsparteine (**5**). For sparteine (**1**), the value of pK_a is relatively high – 17.50 units. The introduction of methyl group in position C-2 causes a reduction of the basicity of the parent system by 4.45 pK_a, whereas the presence of another substituent at C-17 increases the basicity of the system by 1.80 pK_a in **14** and by 0.37 pK_a in **15**. Hence, a significantly greater basicity of the dimethyl derivative **14** relative to that of 17β-isopropyl-2-methylsparteine (**15**) is a result of the presence of a bulky isopropyl group in the latter compound. The basicity of **15** is very similar to that of unsubstituted sparteine (**1**).

All compounds mentioned in Table IV have *trans* boat/chair system of their C/D rings. The protonation of both **14** and **15** gives disalts. Moreover, disalt can be also obtained on protonation of sparteine and, similarly to sparteine, the first proton in **14** is attached relatively fast. The disalt of **14**

TABLE IV
The values of pK_a for sparteine (**1**), 2-methylsparteine (**5**), 2,17β-dimethylsparteine (**14**) and 17β-isopropyl-2-methylsparteine (**15**). ΔpK_a = pK_a(sparteine derivatives) – pK_a(sparteine)

Compound	pK_a	ΔpK_a
Sparteine (**1**)	17.50	–
2-Methylsparteine (**5**)	13.05	–4.45
2,17β-Dimethylspartein (**14**)	19.30	+1.80
17β-Isopropyl-2-methylsparteine (**15**)	17.87	+0.37

with a partly shielded nitrogen atom N-16 forms the fastest, while that of **15** – with a significantly shielded nitrogen atom N-16 – takes the longest time to form.

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