SYNTHESIS AND CONFORMATIONAL ANALYSIS OF NEW 17-ALKYL DERIVATIVES OF LUPANINE AND THEIR PERCHLORATE SALTS

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New 17-alkyl derivatives of lupanine and their perchlorate salts have been synthesised. Substituents at C-17 are introduced by treatment of C(17)=N(16) immonium perchlorate **2** with alkylmagnesium compounds. NMR spectra of the new compounds have been taken to study the chemical shift changes caused by the introduced alkyl substituents, ethyl and butyl. In 17-alkyl derivatives (17-ethyl- (**3**) and 17-butyllupanine (**4**)) the substituent is equatorially oriented. All the lupanine derivatives analysed have the same structure, i.e. ring C in a boat conformation. The reaction of 17-butyllupanine (**4**) and 17-cyanolupanine (**5**) with methyllithium has led to 17-butyl-2-methyl-2,3-didehydrosparteine (**6**), 17-butyl-2-methylsparteine (**7**) and 17-cyano-2-methyl-2,3-didehydrosparteine (**8**).

Keywords: Bisquinolizidine alkaloids; Lupanine derivatives; Grignard reaction; Alkyl substituents; NMR spectroscopy; IR spectroscopy; Tertiary amines.

As a continuation of our study of the stereochemistry of bisquinolizidine alkaloids, we report in this paper on the reaction of carbinolamine – 17-hydroxylupanine (**1**). Edwards has synthesised this compound by the reaction of silver oxide with lupanine[1], Wiewiórowski and Legocki by the oxygenation of the parent alkaloid by means of a mercuric acetate/ETDA complex[2]. Thiel and co-workers have described the formation of 17-hydroxylupanine as a result of DDQ effect on lupanine and determined the spatial structure of the alkaloid[3]. It is known that carbinolamine converts to C(17)=N(16) immonium perchlorate upon treatment with $HClO_4$. This salt, when treated with KCN or a Grignard reagent, affords with good yields the 17-substituted lupanine derivatives.

As a continuation of our study of configurational-conformational dynamics of bisquinolizidine and its derivatives we obtained (by Grignard reaction) two new derivatives with ethyl and butyl substituents at the carbon atom C-17 that could later be used as a substrate in the reaction with organolithium compounds similarly to the recently obtained 17-methyl-

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and 17-isopropyllupanine[4]. 17-Isopropyllupanine gives only monoperchlorate; for lupanine and 17-methyllupanine it has been possible to obtain diperchlorates, in which the proton acceptors are the amino nitrogen atom N-16 and the oxygen atom of the lactam group[5,6]. This result has prompted us to continue investigation of protonation of 17-alkyl substituted lupanines.

EXPERIMENTAL

The IR spectra were recorded on an FT-IR Bruker IFS 113v spectrometer (film, KBr pellets or $CDCl_3$ solution). The ^{13}C NMR, ^1H NMR, ^1H-^1H COSY, ^1H-^{13}C COSY and DEPT spectra were measured on a Varian Gemini 300 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. Electron-impact mass spectra were taken on an AMD 402 spectrometer at standard parameters. Elemental analysis was carried out on a Perkin–Elmer 2400 CHN automatic device.

17-Ethyllupanine (**3**) and 17-Butyllupanine (**4**)

Grignard reagent was prepared from magnesium (150 mg, 6.2 mmol), ethyl bromide (1.0 ml, 13.4 mmol) and diethyl ether (20 ml) (or magnesium (220 mg, 9.0 mmol) and butyl bromide (1.6 ml, 14.9 mmol)). A suspension of immonium perchlorate **2** (520 mg, 1.5 mmol) was added to Grignard reagent solution and the reaction mixture was heated under reflux for 4 h. After standing overnight aqueous ammonium chloride solution was added until a clear organic layer was obtained. The layers were separated and aqueous one was extracted exhaustively with diethyl ether (Dragendorff's test). The extract was dried over KOH pellets, filtered and concentrated under reduced pressure.

The obtained oil of 17-ethyllupanine (**3**) crystallised. Recrystallisation from methanol gave white crystals of **3** (335 mg, 81%), m.p. 278–280 °C. EI-MS, *m/z*: 276 [M^+]. For $C_{17}H_{28}N_2O$ (276.4) calculated: 73.87% C, 10.21% H, 10.13% N; found: 73.90% C, 9.85% H, 9.78% N. For NMR see Table I.

17-Butyllupanine (**4**) was obtained as an oil (415 mg, 91%). EI-MS, *m/z*: 304 [M^+]. For $C_{19}H_{32}N_2O$ (304.5) calculated: 74.95% C, 10.59% H, 9.20% N; found: 74.92% C, 10.41% H, 9.66% N. For NMR see Table I.

17-Ethyllupaninium Perchlorate (**3·HClO$_4$**) and 17-Butyllupaninium Perchlorate (**4·HClO$_4$**)

Compound **3** (138 mg, 0.5 mmol) (or 150 mg (0.5 mmol) of **4**) was dissolved in MeOH (10 ml) and a 60% perchloric acid solution in methanol (1:4 v/v) was added until a slightly acidic pH was reached. A white powder precipitated. Recrystallisation from methanol gave white crystals of **3·HClO$_4$** (141 mg, 75%), m.p. 291–292 °C. For $C_{17}H_{28}N_2O{\cdot}HClO_4$ (376.9) calculated: 54.18% C, 7.76% H, 7.43% N; found: 54.40% C, 8.10% H, 7.10% N. For NMR see Table II. White crystals of **4·HClO$_4$** (161 mg, 80%), m.p. >430 °C. For $C_{19}H_{32}N_2O{\cdot}HClO_4{\cdot}H_2O$ (423.0) calculated: 53.96% C, 8.34% H, 6.62% N; found: 54.34% C, 8.57% H, 6.30% N. For NMR see Table II.

TABLE I
NMR data of C-17 lupanine derivatives ($CDCl_3$; δ, ppm; *J*, Hz); substituent effect in italics[a]

Carbon atom	17-Ethyllupanine (**3**)		17-Butyllupanine (**4**)		17-Cyanolupanine (**5**)	
	δ_C (DEPT)	δ_H multiplicity *J*	δ_C(DEPT)	δ_H multiplicity *J*	δ_C(DEPT)	δ_H multiplicity *J*
2	171.3		171.2		171.3	
	–0.1		*–0.2*		*–0.1*	
3	33.0 (CH_2)	*2.49 m	32.9 (CH_2)	*2.40 m	32.8 (CH_2)	*2.59 m
	–0.1	*2.30 m	*–0.2*	*2.30 m	*–0.3*	*2.59 m
4	19.8 (CH_2)	*1.62 m	19.6 (CH_2)	*1.66 m	19.4 (CH_2)	*1.72 m
	+0.1	*1.88 m	*–0.1*	*1.85 m	*–0.3*	*1.90 m
5	27.0 (CH_2)		26.9 (CH_2)	*1.68 m	27.1 (CH_2)	*1.62 m
	+0.2		*–0.1*	*1.70 m	*+0.3*	*1.96 m
6	60.8 (CH)	3.26 bs	59.8 (CH)	3.30 bs	59.7 (CH)	3.40 dd?,
	–0.2		*–1.2*		*–1.3*	*10.8, 2.0*
7	38.7 (CH)	1.70 m	39.2 (CH)	1.68 m	39.2 (CH)	2.40 m
	+6.3		*+6.7*		*+6.8*	2.0
8	27.2 (CH_2)		26.9 (CH_2)	*1.18	25.2 (CH_2)	1.34 m (ax)
	–0.3		*–0.6*	*2.14	*–2.3*	2.32 m (eq)
9	35.7 (CH)	1.60	35.6 (CH)	1.60 bs	34.2 (CH)	1.68 m, 2.4
	+0.8		*+0.7*		*–0.7*	
10	46.5 (CH_2)	2.48 (ax),	46.4 (CH_2)	2.42 (ax),	46.4 (CH_2)	2.50 dd (ax),
	–0.3	4.42 dt (eq),	*–0.4*	4.38 dt (eq),	*–0.4*	*13.3, 2.5*
		13.0, 2.5, 2.2		*12.9, 2.5, 2.2*		4.45 dt (eq),
						13.3, 2.4, 2.2
11	63.2 (CH)	1.55, bs	63.1 (CH)	1.50 bs	62.9 (CH)	1.74 m
	–1.0		*–1.1*		*–1.3*	
12	33.0 (CH_2)	*1.60 m	34.8 (CH_2)	*1.60 m	33.5 (CH_2)	*1.57 m
	–0.5	*1.60 m	*+1.3*	*1.60 m	*0.0*	*1.57 m
13	24.9 (CH_2)		24.8[b] (CH_2)	*1.20 m	24.9 (CH_2)	*1.64 m
	+0.4		*+0.3*	*1.20 m	*+0.4*	*1.64 m
14	26.1 (CH_2)		26.0 (CH_2)	*1.50 m	24.3 (CH_2)	*1.30 m
	+0.9		*+0.8*	*1.50 m	*–0.9*	*1.74 m
15	51.6 (CH_2)	1.50 (ax)	51.6 (CH_2)	1.48	53.9 (CH_2)	1.98 m (*ax*), 11.2
	–0.4	3.02 (eq)	*–0.4*	3.00	*–1.7*	3.30 m (*eq*), 11.2
17	60.2 (CH)	1.88	60.7 (CH)	3.22	52.9 (CH)	2.95 d (*ax*), 3.7
	+7.3		*+7.2*		*0.0*	–
-CN	–	–	–	–	120.9	–
$-CH_2$	–	–	34.8	*1.58	–	–
$-CH_2$	–	–	23.2[b]	*1.22	–	–
$-CH_2$	27.4	1.24	24.5[b]	*1.30	–	–
$-CH_3$	6.8	0.85 t, *7.3*	13.9	0.91 t, *7.0*	–	–

[a] (+) Upfield shift; (–) downfield shift (relative to lupanine); (*) δ_H values extracted from the HET-COR spectrum. Substituent effects were calculated by subtracting the chemical shifts of individual carbon atoms of lupanine from the values of the chemical shifts of the corresponding carbon atoms in lupanine derivatives. [b] Assignment uncertain, can be interchanged.

TABLE II

NMR data of perchlorate salts of C-17 lupanine derivatives (DMSO-d_6; δ, ppm; *J*, Hz); protonation effect in italics[a]

Carbon atom	Perchlorate salt of 17-ethyllupanine 3·$HClO_4$		Perchlorate salt of 17-butyllupanine 4·$HClO_4$	
	δ_C (DEPT)	δ_H, multiplicity, *J*	δ_C (DEPT)	δ_H, multiplicity, *J*
2	170.6	–	171.0	
	–0.7		*–0.2*	
3	32.5 (CH_2)	*2.26	32.5 (CH_2)	*2.26
	–0.5	*2.20	*–0.4*	*2.20
4	19.2 (CH_2)	*1.54	19.1 (CH_2)	*1.54
	–0.6	*1.72	*–0.5*	*1.72
5	26.3 (CH_2)	*1.52	26.3 (CH_2)	*1.72
	–0.7	*1.52	*–0.6*	*1.52
6	59.0 (CH)	3.37ax	59.1 (CH)	3.37 ax
	–1.8		*–0.7*	
7	35.8 (CH)	2.00, bs	36.6 (CH)	2.00, bs
	–2.9		*–2.5*	
8	24.3 (CH_2)	*2.00	24.2 (CH_2)	*2.00
	–2.9	*1.62	*–2.7*	*1.62
9	32.8 (CH)	1.90, bs	32.8 (CH)	1.90, bs
	–2.9		*–2.8*	
10	44.7 (CH_2)	2.51 ax	44.8 (CH_2)	2.51 ax
	–1.8	4.31, d (eq), *13.4*	*–1.6*	4.31, d (eq), *13.4*
11	64.0 (CH)	2.46 ax	64.0 (CH)	2.46 ax
	+0.8		*+0.9*	
12	30.8 (CH_2)	*1.94	30.9 (CH_2)	*1.94
	–2.2	*1.72	*–3.9*	*1.72
13	22.7[b] (CH_2)	*1.80	22.4[c] (CH_2)	*1.80
	–2.2	*1.80	*–2.4*	*1.80
14	24.1[b] (CH_2)	*2.08	25.5 (CH_2)	*2.08
	–2.0	*1.58	*–0.5*	*1.58
15	51.7 (CH_2)	2.88, d? (ax), *12.5, 3.30*	51.9 (CH_2)	2.88, d? (ax), *12.5, 3.30*
	+0.1	3.71, d? (eq), *12.0*	*+0.3*	3.71, d? (eq), *12.0*
17	63.2 (CH)	3.00 (ax)	62.5 (CH)	3.00 (ax)
	+0.3		*+1.8*	
-CH_2	–	–	31.1	1.70
			–3.7	
-CH_2	–	–	22.2[c]	
			–1.0	
-CH_2	22.4	1.78	22.7[c]	
	–5.0		*–1.8*	
-CH_3	8.3	0.94, t, 7.4	13.8	0.92, t, *7.4*
	+1.5		*–0.1*	

[a] (+) Upfield shift; (–) downfield shift; (*) δ_H values extracted from the HET-COR spectrum. Protonation effects were calculated by subtracting the chemical shifts of individual carbon atoms of lupanine derivatives as free bases from the values of the chemical shifts of the corresponding carbon atoms in the corresponding perchlorate. [b,c] Assignment uncertain, can be interchanged.

17-Cyanolupanine (**5**)

Immonium salt (**2**; 346 mg, 1.0 mmol) was dissolved in water (25 ml) and then KCN (99 mg, 1.5 mmol) was added and heated at 100 °C for 2 h. After cooling, the precipitate was filtered off, and the reaction mixture was extracted with diethyl ether (Dragendorff's test). The ethereal extract was dried with KOH pellets and evaporated to dryness under reduced pressure. The obtained oil crystallised. Recrystallisation from methanol gave white crystals of **5** (200 mg, 74%), m.p. 120–123 °C. EI-MS, *m/z*: 273 [M^+]. For $C_{16}H_{23}N_3O$ (273.4) calculated: 70.30% C, 8.48% H, 15.37% N; found: 70.18% C, 8.37% H, 15.12% N. For NMR see Table I.

17-Butyl-2-methyl-2,3-didehydrosparteine (**6**) and 17-Cyano-2-methyl-2,3-didehydrosparteine (**8**)

A solution of 17-butyllupanine (**4**; 150 mg, 0.5 mmol) (or 17-cyanolupanine (**5**; 273 mg, 1 mmol)) in diethyl ether (10 ml) was added to 1.4 M methyllithium ethereal solution (4 ml, 5.6 mmol) (or 6 ml, 8.4 mmol) and diethyl ether (30 ml) under argon. Toluene (10 ml) was added and the reaction mixture was heated to about 70 °C. The reaction progress was controlled by TLC. The reaction mixture was left at room temperature overnight. Then the reaction flask was placed in an ice bath and water (5 ml) was added with stirring. The organic layer was extracted with 2 M HCl (3 × 15 ml portions), the combined acid layers were made alkaline with 50% KOH and, after cooling, extracted exhaustively with diethyl ether. The extract was dried over KOH pellets, filtered and concentrated under reduced pressure. The resulting oil (149 mg, 80%) was crude 17-butyl-2-methyl-2,3-didehydrosparteine (**6**). EI-MS, *m/z*: 302 [$M]^+$. (Or 255 mg (94%) of 17-cyano-2-methyl-2,3-didehydrosparteine (**8**). EI-MS, *m/z*: 271 [$M]^+$.)

Reduction of 17-Butyl-2-methyl-2,3-didehydrosparteine (**6**) to 17-Butyl-2-methyl-sparteine (**7**) and 17-Cyano-2-methyl-2,3-didehydrosparteine (**8**) to 2-Methylsparteine (**9**)

Compound **6** (149 mg, 0.5 mmol) (or **8** (255 mg, 0.95 mmol)) was dissolved in MeOH (15 ml). After cooling, $NaBH_4$ (35 mg, 0.92 mmol) was added portionwise. The mixture was heated at 45 °C for 60 min, a few drops of AcOH were added to decompose the excess of the reducing agent, and then MeOH was evaporated under reduced pressure. The obtained oil was alkalinised with 50% KOH and extracted with diethyl ether. The ether solution was dried with KOH pellets and evaporated under reduced pressure. The oily residue was crystallised from MeOH. Yield 127 mg (85%) of **7**, m.p. 97–99 °C. EI-MS, *m/z*: 304 [M^+]. For $C_{20}H_{36}N_2$ (304.5) calculated: 78.88% C, 11.92% H, 9.20% N; found: 78.56% C, 11.72% H, 9.18% N. For NMR see Table III. (Or 210 mg (90%) of **9**, m.p. 49–51 °C; lit.[7] gives m.p. 49–51 °C. EI-MS, *m/z*: 248 [M^+].)

RESULTS AND DISCUSSION

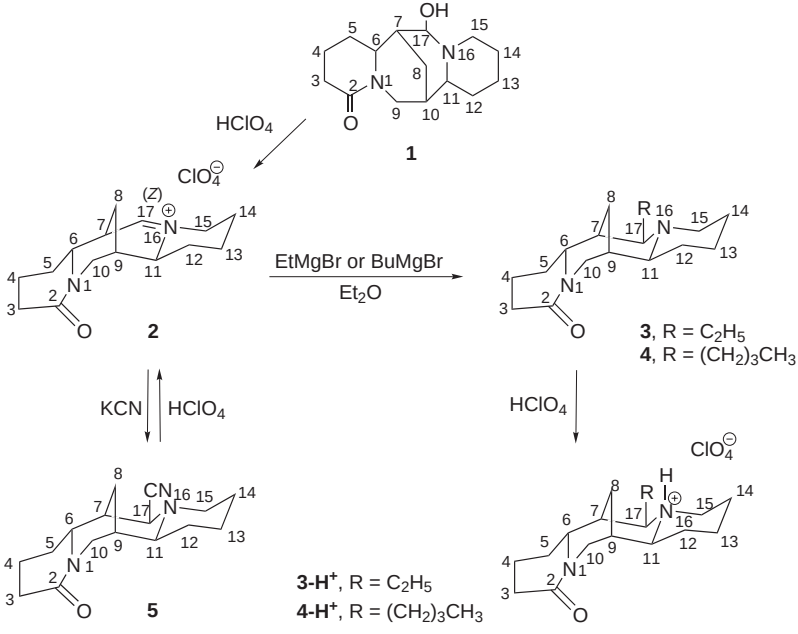
*17-Ethyllupanine (**3**) and 17-Butyllupanine (**4**) and Their Perchlorates*

Immonium salt **2** treated with Grignard reagents (Mg turnings, ethyl or butyl bromide) affords the crude bases in good yields: 17-ethyl- (**3**) and 17-butyllupanine (**4**) (Scheme 1). The structure and conformation of

TABLE III
NMR data of 17-butyl-2-methylsparteine (**7**) ($CDCl_3$; δ, ppm)

Carbon atom	δ_C (DEPT)	δ_H
2	57.4	1.86
	(CH)	
3	35.4	*1.25
	(CH_2)	*1.25
4	25.6	*1.30
	(CH_2)	*1.30
5	30.4	*1.18
	(CH_2)	*1.26
6	66.2	1.92 ax
	(CH)	
7	41.2	1.40
	(CH)	
8	27.9	*2.08
	(CH_2)	*1.05
9	37.2	1.56
	(CH)	
10	58.5	1.72 ax
	(CH_2)	2.86
11	64.2	1.86
	(CH)	
12	35.4	*1.50
	(CH_2)	*1.50
13	25.4	*1.45
	(CH_2)	*1.45
14	26.5	*1.52
	(CH_2)	*1.48
15	52.0	1.42
	(CH_2)	3.15
17	60.0	3.25
	(CH)	
2-CH_3	21.2	1.10
17-CH_2	34.9	1.56
-CH_2	22.8	1.20
-CH_2	23.5	1.30
-CH_3	14.2	0.92

17-alkyl substituted sparteines have been studied by IR and NMR methods. The absorption bands appearing in the spectra of quinolizidine and its derivatives in the 2840–2600 cm^{-1} region (trans bands) are assigned to the stretching vibrations of one or more axially oriented C_α–H bonds. The intensity and shape of the band depend on the number of these bonds and their steric environment in the molecule. Lupanine (2-oxosparteine), the most common of sparteine lactams, occurs in two conformations, of which the boat-chair form is favoured[8]. The lone electron pair on the nitrogen



SCHEME 1

atom N-1 takes part in the lactim-lactam mesomerism. The band complex in the 2840–2600 cm^{-1} region of lupanine consists of two main bands at 2808 and 2761 cm^{-1} which are assigned to $\nu_{C\alpha-H(ax)}$ vibrations in methylene groups at C-15 and C-17 [9,10]. The IR spectra of lupanine, 17-ethyl- and 17-butyllupanine are very similar. The three aminolactams occur in the same transoidal arrangements in which the C/D fragment occurs in boat-chair conformation. We could expect some differences in the profile and intensity of the T-band, although in all three cases it is generated by three C_α–H bonds at N-16. These differences are caused by equatorial substituents at C-17, which modulate the T-band generated by $\nu_{C17-H(ax)}$. When two

hydrogen atoms are at C-17, the T-band forms a doublet and when $H_{(eq)}$ is substituted with an alkyl group, then it forms a singlet whose position is affected by the character of the substituent (near 2800 cm^{-1}). The single band assigned to the carbonyl group is in its normal position at 1600 cm^{-1}. Moreover, the IR spectra of **3** in $CDCl_3$ solution show an intense band at 2250 cm^{-1} assigned to the 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 **3** is in a boat conformation, which is equivalent to a transoidal arrangement of N-1 and N-16.

The newly obtained compounds, when treated with $HClO_4$, give only monosalts. The monoprotonated cations occur in the "transoidal" form with ring C in boat form slightly deformed by the substituent at C-17. In the IR spectra the trans band disappears, like in the spectra of lupanine and 17-isopropyllupanine perchlorates, because the lone electron pair on N-16 is involved in the protonation. The band assigned to ν_{Cl-O} of the ClO_4^- group is at 1100 cm^{-1}. The bands assigned to $\nu_{\equiv N^+-H}$ occur at 3100 cm^{-1}. Further information on the structure of the new compounds was derived from their NMR spectra. From the data given in Table I it is clearly evident that the free bases of **3** and **4** in solution have also the ethyl and butyl substituents in equatorial positions, stabilising the C boat conformation of the molecule. The α-substituent effect of the ethyl group in **3** and that of butyl in **4** on C-17 is +7.3 ppm relative to lupanine itself. The β-substituent effects on C-7 are observed in **3** (+6.3 ppm) and **4** (+6.7 ppm). According to the concept of Beierbeck and Saunders, the upfield shift of –4.0 ppm for C-15 in **3** and **4** is due to the elimination of the 1,3 interaction of equatorial H atoms at C-17 and C-15 [11]. This is in agreement with the diamagnetic effect of equatorial CH_3 at C-2 in 2-methylsparteine, observed at C-10 [12]. The remaining chemical shifts of **3** and **4** are very close to those of lupanine, indicating that the substituent at C-17 does not change the lupanine conformation. The parent alkaloids – lupanine and 17-ethyl- and 17-butyllupanines, have $H\text{-}10_{(eq)}$ strongly deshielded by the synperiplanar amide carbonyl group; the chemical shifts are 4.42 and 4.38 ppm for **3** and **4**, respectively. For lupanine, chemical shift is 4.80 ppm [13,14]. No γ-gauche effects which usually accompany a change in the conformation from boat-chair to all-chair[15,16] are observed on the carbon atoms C-12, C-14 and C-17. In monosalts, the nitrogen atoms N-16 have positive charge. As a consequence, shift changes are observed on protons at C-11, C-15 and C-17. The chemical shift values for all these protons are above 2.40 ppm. The calculated protonation effects are given in Table II, their values varying

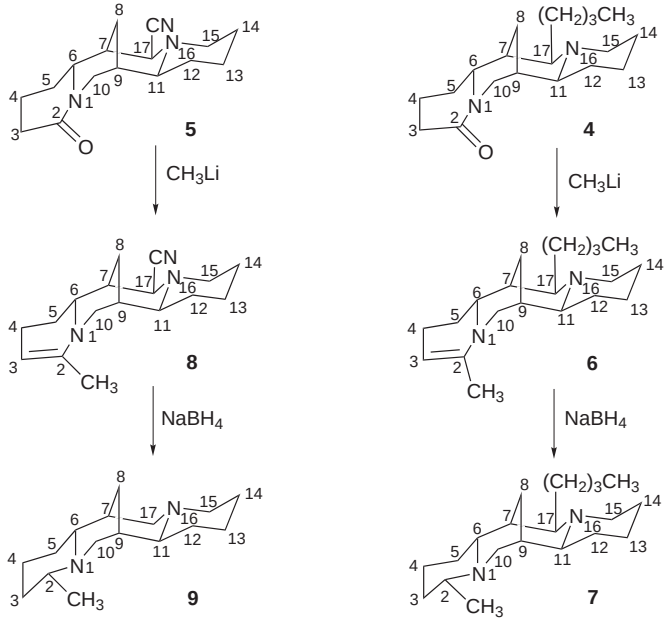
between –3.9 and +3.0 ppm. These values are also affected by replacement of $CDCl_3$ solvent by DMSO-d_6. Similarly to free bases, the H-$10_{(eq)}$ signal appears at 4.30 ppm. The acidic protons resonate at 8 ppm.

*Reaction of 17-Butyllupanine (**3**) and 17-Cyanolupanine (**5**) with Methyllithium*

Lupanine derivatives are a group of compounds that are convenient substrates for further modifications of the sparteine molecule. Particularly interesting is 17-cyanolupanine (**5**) because of the presence of a substituent with strong proton-acceptor properties. Compound **5** was obtained according to the methods described previously, by the reaction of the immonium salt **2** with KCN [17] (Scheme 1). Santamaria and co-workers have synthesised this compound by photooxidation of lupanine under nitrogen atmosphere[18–20]. However, the authors have given only the chemical shifts of selected carbon atoms and protons. The spatial structures of these compounds have not yet been investigated. The two-dimensional NMR spectra recorded in this work permitted the assignment of chemical shifts for all carbon atoms and protons. As follows from the data in Table I, chemical shifts of the carbon atoms of **5** are similar to those reported for lupanine[13], except for the carbon atoms in a close vicinity of the substituted carbon atom. Substituent effects given in Table I are calculated in accordance with lupanine. No α-substituent effect at C-17 has been observed; the β effect of the cyano group at C-7 is +6.8 ppm and the γ-substituent effect observed at the carbon atoms C-6, C-11 and C-15 is –1.3 ppm for C-6 and C-11, and –1.7 ppm for C-15. Similarly to **3** and **4**, 17-cyanolupanine (**5**) shows strongly deshielded H-$10_{(eq)}$ (δ 4.45 ppm). The boat conformation of ring C and the equatorial position of the CN substituent have been confirmed by the IR spectrum analysis. The IR spectrum (KBr) presents the band assigned to the carbonyl group at 1648 cm^{-1} and to the cyano group at 2238 cm^{-1}. Because of delocalisation of the lone electron pair at the nitrogen atom N-16 caused by a negative induction effect of the substituent in the α position, the intensity of the trans band is reduced and this band appears as a residual. The substituent with a negative induction effect plays a different role from that of the oxygen atom in the α position, which, as a result of lactam mesomerism, eliminates the trans band. The trans band of 17-cyanolupanine absorption occurs at 2815 and 2840 cm^{-1}.

17-Butyllupanine and 17-cyanolupanine in reaction with methyllithium give new unsaturated sparteine derivatives: 17-butyl-2-methyl-2,3-didehydrosparteine (**6**) and 17-cyano-2-methyl-2,3-didehydrosparteine (**8**)

(Scheme 2). IR spectra of **6** and **8** (film) revealed a band characteristic of the C=C bond near 1655 cm^{-1}. The double bond between C-2 and C-3 eliminates the contribution of the trans axial hydrogen atom at C-2 to the trans band, whose structure is thus simplified. Only one band at 2800 cm^{-1} is observed. In the spectrum of **8** there is also a band assigned to the cyano group at 2219 cm^{-1}. The reaction products proved very unstable and that was why they were so difficult to analyse by NMR. Although the spectra taken in a $CDCl_3$ solution were blurred, it was possible to identify the signal assigned to the methyl group at 20 ppm, the signal assigned to the CN group (for **8**) at 119.3 ppm and the signals assigned to the carbon atoms C-2 and C-3, connected with a double bond; for C-2 the chemical shift was near 142 ppm, and for C-3 it was near 98 ppm. Because of the products instability, they were treated with sodium borohydride (Scheme 2). IR spectrum of 17-butyl-2-methylsparteine (**7**) shows 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 alkaloid molecule (nitrogen atom N-16). The butyl group at C-17 appears the element stabilizing the boat-chair system of C/D rings. Newly obtained sparteine derivative **7** has the same configurational-conformational system as



SCHEME 2

recently obtained disubstituted sparteine derivatives: trans A/B chair/chair, trans C/D boat/chair. In the NMR spectrum of **7** we found chemical shifts close to those of 2,17-dimethylsparteine[4] exept those in the nearest vicinity of the C-17 substituents (see Table III). The methyl group at C-2 is equatorial (≈21.2 ppm). The preservation of the boat conformation of ring C is confirmed by the absence of high-field shift of the signals of C-11, C-12 and C-14. The boat conformation of ring C is also reflected by the value of the chemical shift of the signal assigned to H-$15_{(eq)}$ in the new compound above 3.0 ppm. This 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.

The product of the reduction reaction of **8** was identified by analyses of the IR, NMR and MS spectra. In the IR spectrum there was no band assigned to the cyano group. The trans band was compared with the analogous band of 2-methylsparteine[7] and the ^{13}C NMR spectra of the two compounds were also compared. The comparative analysis indicated that the reaction product was 2-methylsparteine (**9**). This identification was confirmed by the analysis of the mass spectrum showing a molecular ion M^+ 248 coming from **9**.

As expected, the ethyl and butyl groups introduced into the "labile" fragment of lupanine at C-17 at the equatorial position stabilise the "transoidal" arrangement of both nitrogen atoms in the four-ring skeleton. Both compounds give only monoperchlorates.

From among the four 17-alkyl aminolactams compared (alkyl = methyl, ethyl, isopropyl, butyl), only 17-methyllupanine gives a diperchlorate salt. It means that the proton-acceptor properties of the lactam group oxygen atom depend on the size of the substituent introduced at the carbon atom C-17.

CALCULATIONS

In the our study, we used several semi-empirical methods supplied within the HyperChem program[21] for prediction of geometry. The geometry optimisation was performed with the Polak–Ribiere conjugate gradient algorithm, and convergence limit of 0.001 kcal/mol. All the calculations performed in this study refer to isolated molecule in vacuo. The initial input geometry for the semi-empirical calculation was obtained by means of the MM+ molecular mechanic program for gas phase.

The results of AM1, PM3, MNDO and MINDO3 calculations for **3**–**5** are collected in Table IV, and the corresponding structures are shown in Fig. 1.

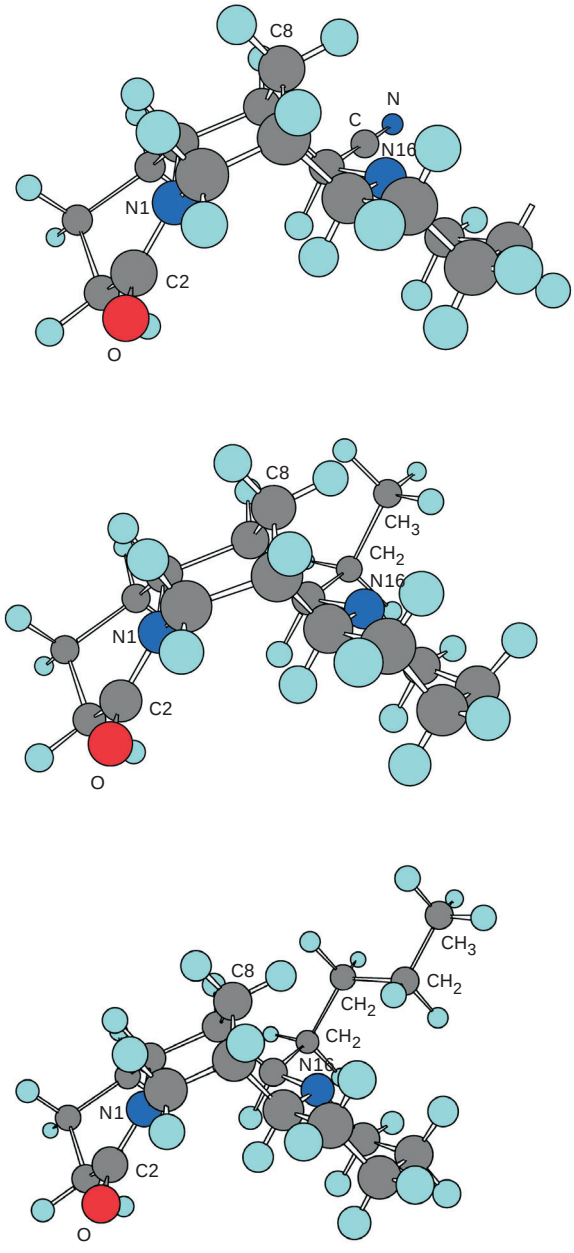


FIG. 1
Molecular structures of: a 17-cyano- (**5**), b 17-ethyl- (**3**) and c 17-butyllupanine (**4**)

TABLE IV
Calculated energies (in kcal/mol) for structures **3**–**5** relative to the energy of lupanine

Compound	AM1	PM3	MNDO	MINDO3
17-Cyanolupanine (**5**)	194.83	192.66	192.09	203.39
17-Ethyllupanine (**3**)	557.21	558.48	548.49	548.47
17-Butyllupanine (**4**)	1117.55	1118.62	1105.03	1108.20

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