1-BENZYL-1,2,3,4-TETRAHYDROISOQUINOLINES. ^{1}H NMR CONFORMATIONAL STUDIES AND ROTATIONAL BARRIERS

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ABSTRACT

The conformational preferences of a series of 1-benzyl-1,2,3,4-tetrahydroisoquinolines (norlaudanosine and coclaurine analogues) were investigated with the aid of their 1H NMR spectra and NOESY experiments, coupled with ab initio theoretical studies to estimate energy barriers among the various stable conformers of these systems. The secondary amines prefer an extended conformation, while the N-alkylated derivatives prefer a semi-folded one, with considerable freedom to exchange between both forms. A third, folded conformation, although not much higher in energy, is relatively inaccessible.

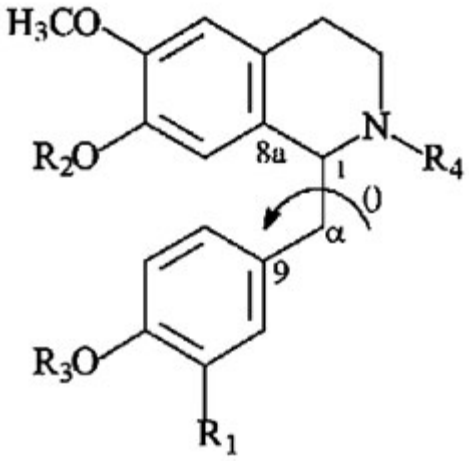
KEYWORDS: 1-benzyl-1,2,3,4-tetrahydroisoquinolines; conformation; NMR studies; RHF/6-31g(d,p) calculations.

INTRODUCTION

In early studies of the 1H NMR spectra of 1-benzyl-1,2,3,4-tetrahydroisoquinoline (BTHIQ) alkaloids, it was noted that when the nitrogen atom is methylated the H-8 resonance is shifted upfield from the expected value, sometimes to $\delta < 6$ ppm.[1-4] This effect was attributed to the shielding of H-8 by the benzyl ring, which, as a consequence of the bulk of the N-methyl group, was assumed to prefer an orientation placing it close to the tetrahydroisoquinoline aromatic ring. Rather strong shielding by the unsubstituted 1-benzyl group has been noted more recently for 7-benzyloxy- and 7-hydroxy-BTHIQ's.[5] In agreement with the foregoing, (R)-(-)-armepavine and (S)-(-)-norarmepavine, whose absolute configurations had been demonstrated by chemical transformations,[6,7] show opposite optical rotatory dispersion spectra.[8] It is now common knowledge that (R)-N-unsubstituted BTHIQ's are dextro- and their (S) counterparts are levorotatory, while the opposite obtains for their N-substituted congeners.

Access to particular pharmacophoric BTHIQ conformers is a prerequisite for these compounds to be able to elicit specific biological responses. As a result of the sustained interest in the pharmacology of natural and synthetic BTHIQ's, particularly as dopaminergic agents and smooth muscle relaxants,[5,9] we considered it timely to study the conformational freedom of these flexible molecules using the powerful experimental and theoretical methodologies developed since the pioneering NMR studies were carried out.

In this paper we report the results of the conformational analysis of norlaudanosine (1, tetrahydropapaverine or THP: 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline) and its N-methyl (laudanosine), -ethyl and -n-propyl derivatives, along with some coclaurine (2) derivatives such as N- and/or O-substituted 1-(4-hydroxybenzyl)-7-hydroxy-6-methoxy-1,2,3,4-tetrahydroisoquinolines. To this end we carried out NMR studies including NOESY experiments at 300 MHz (^{1}H) and 75 MHz (^{13}C), as well as RHF/6-31g(d,p) [10] potential energy calculations on the internal rotation for these molecules along the torsional angle q, defined by atoms C-9/C-α/C-1/C-8a.



EXPERIMENTAL

All solvents were of analytical grade. Papaverine hydrochloride, the phenylacetic acids and all alkyl iodides were purchased from Aldrich. Vanillin was from Fluka. The NMR spectra were recorded with a Bruker AMX-300 instrument at 300 MHz (1H) or 75 MHz (^{13}C), in $CDCl_3$ for the bases and D_2O for the salts. The experiments carried out to confirm the structures, for complete signal assignment and for conformational analysis, were mainly one-dimensional ^{1}H and ^{13}C spectra, DEPT experiments, and 2-D experiments such as ^{1}H-^{1}H COSY, NOESY and heteronuclear HMBC and HMQC using standard Bruker software.

Chemistry

Norlaudanosine (1) was prepared following the method of Pyman,[11] laudanosine (1a) was prepared by $NaBH_4$ reduction of papaverine methiodide,[12] and derivatives 1b-1c were prepared by direct N-alkylation of 1 with the respective alkyl iodides using a modification of a method described by Chiou et al.[13] Briefly, a solution of 1 was refluxed with the corresponding alkyl iodide and $NaHCO_3$ in MeCN for 2 days, the free bases were purified by column cromatography and the salts were crystallized from ethanol/ether. In this way the following compounds were prepared:

±)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (1); (norlaudanosine). Obtained in 68 % yield, mp 212-215 ºC (lit.[11] m.p. 217-219 ºC). δ_H 6.69 (1H, s, H-5), 6.62 (1H, s, H-8), 6.78 (1H, d, J 1.4 Hz, H-10), 6.86 (1H, d, J 8.1 Hz, H-13), 6.82 (1H, dd, J 8.1, 1.4 Hz, H-14), 4.16 (1H, dd, J 9.2, 4.4 Hz, H-1), 3.90 (3H, s, O-Me), 3.88 (6H, s, 2 ´ O-Me), 3.86 (3H, s, O-Me), 3.19 (1H, dd, J 13.7, 4.4 Hz, H-α), 2.88 (1H, dd, J 13.7, 9.3 Hz, H-α '), 3.24 (1H, dd, J 12.6, 5.5 Hz, H-3), 2.94 (1H, m, J 5.3, 12.6, 5.3 Hz, H-3'), 2.8 (1H, dd, J 16.3, 5.5 Hz, H-4), 2.7 (1H, m, J 15.7, 5.3, 5.5 Hz, H-4'). δ_C 58.7 (C-1), 41.8 (C-3), 27.0 (C-4), 127.3 (C-4a), 113.3 (C-5), 151.2 (C-6), 150.9 (C-7), 114.9 (C-8), 131.1 (C-8a), 126.1 (C-1'), 115.1 (C-2'), 125.1 (C-6'), 149.4 (C-3'), 150.6 (C-4'), 116.3 (C-5'), 41.3 (C-α), 58.6 (O-CH_3), 58.6 (O-CH_3), 58.5 (O-CH_3), 58.4 (O-CH_3).

±)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-N-methyl-1,2,3,4-tetrahydroisoquinoline (1a); (laudanosine). Obtained in 78 % yield, mp 200-202 ºC (lit.[12] m.p. 201-203 ºC). δ_H 6.59 (1H, s, H-5), 6.07 (1H, s, H-8), 6.61 (1H, d, J 1.8 Hz, H-10), 6.77 (1H, d, J 8.1 Hz, H-13), 6.64 (1H, dd, J 8.2, 1.8 Hz, H-14), 3.85 (3H, s, O-Me), 3.84 (3H, s, O-Me), 3.79 (3H, s, O-Me), 3.58 (3H, s, O-Me), 3.69 (1H, dd, J 7.6, 5.0 Hz, H-1), 3.14 (1H, dd, J 13.6, 5.0 Hz, H-α), 2.78 (1H, dd, J 13.6, 7.6 Hz, H-α '), 3.16 (1H, dd, J 15.8, 5.4 Hz, H-3), 2.84 (1H, dd, J 15.8, 5.4 Hz, H-3'), 2.75 (1H, dd, J 5.8, 5.4 Hz, H-4), 2.59 (1H, m, J 16.0, 5.3 Hz, H-4'), 2.54 (3H, s, N-Me). δ_C 56.3 (C-1), 40.8 (C-3), 25.9 (C-4), 126.5 (C-4a), 112.1 (C-5), 149.2 (C-6), 149.9 (C-7), 112.2 (C-8), 129.1 (C-8a), 124.9 (C-1'), 113.6 (C-2'), 123.1 (C-6'), 145.2 (C-3'), 148.6 (C-4'), 115.3 (C-5') 39.3 (C-α), 57.5 (O-CH_3), 57.3 (O-CH_3), 57.2 (O-CH_3), 57.4 (O-CH_3), 41.9 (N-CH_3).

±)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-N-ethyl-1,2,3,4-tetrahydroisoquinoline (1b); (N-ethylnorlaudanosine). Obtained in 80 % yield, mp 164-167 ºC (lit.[14] m.p. 167-169 ºC). δ_H 6.56 (1H, s, H-5), 6.00 (1H, s, H-8), 6.62 (1H, d, J 1.7 Hz, H-10), 6.76 (1H, d, J 8.6 Hz, H-13), 6.63 (1H, dd, J 8.6, 1.7 Hz, H-14), 3.85 (3H, s, O-Me), 3.84 (3H, s, O-Me), 3.83 (1H, dd, J 7.9, 5.3 Hz, H-1), 3.79 (3H, s, O-Me), 3.56 (3H, s, O-Me), 3.19 (1H, m, J 6.9, 11.5, 6.9 Hz, H-3), 3.1 (1H, dd, J 13.4, 5.3 Hz, H-a), 2.91 (1H, dd, J 11.5, 6.9 Hz, H-3'), 2.83 (1H, dd, J 16.1, 6.9 Hz, H-4), 2.75 (1H, dd, J 13.4, 7.9 Hz, H-α '), 2.7 (2H, q, J 7.1 Hz, N-CH_2-CH_3), 2.51 (m, H-4'), 1.13 (3H, t, J 7.1 Hz, N-CH_2-CH_3). δ_C 59.3 (C-1), 42.7 (C-3), 28.0 (C-4), 129.4 (C-4a), 114.2 (C-5), 153.2 (C-6), 150.9 (C-7), 116.7 (C-8), 133.4 (C-8a), 128.0 (C-1'), 117.5 (C-2'), 125.5 (C-6'), 149.2 (C-3'), 150.1 (C-4'), 118.2 (C-5'), 42.3 (C-α), 58.8 (O-CH_3), 58.7 (O-CH_3), 58.5 (O-CH_3), 58.4 (O-CH_3), 47.6 (N-CH_2CH_3), 38.4 (N-CH_2CH_3).

±)-1-(3,4-Dimethoxybenzyl)-6,7-dimethoxy-N-propyl-1,2,3,4-tetrahydroisoquinoline (1c); (N-propylnorlaudanosine). Obtained in 75 % yield, mp 194-197 ºC (lit.[14] m.p. 206-207 ºC). δ_H 6.56 (1H, s, H-5), 6.03 (1H, s, H-8), 6.63 (1H, d, J 1.8 Hz, H-10), 6.77 (1H, d, J 8.6 Hz, H-13), 6.64 (1H, dd, J 8.6, 1.8 Hz, H-14), 3.85 (3H, s, O-Me), 3.83 (3H, s, O-Me), 3.81 (3H, s, O-Me), 3.78 (1H, dd, J 7.6, 5.6 Hz, H-1), 3.58 (3H, s, O-Me), 3.23 (1H, m, J 5.5, 12.0, 8.0 Hz, H-3), 3.1 (1H, dd, J 13.4, 5.7 Hz, H-α), 2.89 (1H, dd, J 12.0, 5.5 Hz, H-3'), 2.86 (1H, m, J 14.6, 5.5, 8.0 Hz, H-4), 2.75 (1H, dd, J 13.4, 7.6 Hz, H-α '), 2.49 (1H, dd, J 14.6, 5.5 Hz, H-4'), 2.39 (2H, t, J 7.4 Hz, N-CH_2-CH_2-CH_3), 1.54 (2H, sex, J 7.4 Hz, N-CH_2-CH_2-CH_3), 0.88 (3H, t, J 7.4 Hz, N-CH_2-CH_2-CH_3). δ_C 56.9 (C-1), 41.7 (C-3), 29.2 (C-4), 127.8 (C-4a), 114.7 (C-5), 144.7 (C-6), 144.0 (C-7), 108.6 (C-8), 130.8 (C-8a), 129.5 (C-1'), 118.5 (C-2'), 130.4 (C-6'), 149.6 (C-3'), 151.2 (C-4'), 114.0 (C-5'), 40.5 (C-α), 56.0 (O-CH_3), 55.7 (O-CH_3), 55.5 (O-CH_3), 55.3 (O-CH_3), 41.9 (N-$CH_2CH_2CH_3$), 38.7 (N-$CH_2CH_2CH_3$), 35.5 (N-$CH_2CH_2CH_3$).

Most of the non-N-alkylated coclaurine derivatives (2, 3, 4, 5, 6, 7 and 8) were prepared following the method of Teitel & Brossi,[15] which led to the desired products in acceptable yields. All N-alkylated derivatives of coclaurine (compounds 2a, 2b, 3a, 3b, 4a, 5a, 6a, 6b, 7a, 8a, 8b, 8c) were prepared from the corresponding BTHIQ (2, 3, 4, 5, 6, 7, or 8) as described above for N-alkylnorlaudanosines. The mixtures were purified by column cromatography and the salts were crystallized from ethanol/ether. The preparation of 12-O-benzylcoclaurine (9) was achieved via selective O-debenzylation of 7,12-O,O'-dibenzylcoclaurine (7) in the presence of $SnCl_4$.[16] Details of the preparation of these compounds and their properties have been published recently.[17]

Quantum Chemical Studies

Full geometry optimizations were carried out in order to rationalize the internal mobility of the molecules inferred from the NOESY experiments. These calculations were performed at the RHF/6-31g(d,p) level of theory, implemented in the Gaussian 98 package of programs, revision A3.[10] In order to find points lying on a minimum energy path on the potential energy surface, the RHF/6-31g(d,p) calculations were carried out allowing complete geometry optimization. The potential energy surface scan was carried out around the C-1/C-α bond (θ). These values were driven between 0º and 360º with a 10º grid.

RESULTS AND DISCUSSION

The structures of all norlaudanosine (1) and coclaurine (2) derivatives prepared and studied in this work are shown below. Table 1 lists all derivatives with the corresponding ring and substituent numbering.

Table 1. Tetrahydroisoquinoline derivatives studied in this work.

Compound	R_1	R_2	R_3	R_4
1	OCH_3	CH_3	CH_3	H
1a	OCH_3	CH_3	CH_3	CH_3
1b	OCH_3	CH_3	CH_3	CH_2CH_3
1c	OCH_3	CH_3	CH_3	$(CH_2)_2CH_3$
2	H	H	H	H
2a	H	H	H	CH_3
2b	H	H	H	CH_2CH_3
3	H	CH_3	H	H
3a	H	CH_3	H	CH_3
3b	H	CH_3	H	CH_2CH_3
4	H	H	CH_3	H
4a	H	H	CH_3	CH_3
5	H	CH_3	CH_3	H
5a	H	CH_3	CH_3	CH_3
6	H	Bn	H	H
6a	H	Bn	H	CH_3
6b	H	Bn	H	CH_2CH_3
7	H	Bn	Bn	H
7a	H	Bn	Bn	CH_3
7b	H	Bn	Bn	CH_2CH_3
7c	H	Bn	Bn	$(CH_2)_2CH_3$
8	H	Bn	CH_3	H
8a	H	Bn	CH_3	CH_3
9	H	H	Bn	H

Bn ≡ $C_6H_5CH_2$-

The reduction of papaverine with Sno, as described originally by Pyman,[11] was the key reaction to obtain

norlaudanosine (1) together with pavine, needed for other studies. Laudanosine (1a) was prepared by $NaBH_4$ reduction of papaverine methiodide.[12] The direct N-alkylation of norlaudanosine with higher alkyl groups was initially attempted following the method of Chiou et al.[13] However, the use of Na_2CO_3 in methanol led to considerable amounts of Hoffmann elimination products, a drawback that was circumvented by the alternative use of $NaHCO_3$ in acetonitrile. Under these conditions no elimination products were observed, even after prolonged reaction times, and the N-alkylated compounds 1b and 1c were obtained with higher yields (80-90%). Teitel and Brossi's methodology [15] afforded acceptable yields of coclaurine derivatives 2-8. These syntheses were followed when necessary by N-alkylation as above. 12-O-Benzylcoclaurine (9) was prepared by $SnCl_4$-catalyzed O-debenzylation of 7,12-O,O'-dibenzylcoclaurine (7).[16]

In order to confirm the suggestion previously put forward by different authors,[1-4, 18] that N-alkylation of the secondary nitrogen of BTHIQ alkaloids leads to significant conformational changes in these molecules, we carried out a systematic investigation of the spectral behavior of all the norlaudanosine and coclaurine derivatives prepared by us.

A preliminary comparison of the 1H NMR spectra of norlaudanosine and its hydrochloride, laudanosine, N-ethylnorlaudanosine and N-n-propylnorlaudanosine was carried out with the results shown in Table 2.

Table 2. Selected ^1H chemical shifts (ppm) and coupling constants (Hz) of norlaudanosine hydrochloride, its free base (1), laudanosine (1a), N-ethyl- (1b) and N-n-propylnorlaudanosine (1c).

Compound	1 HCl [a]	1 [b]	1a [b]	1b [b]	1c [b]
	δ	δ	δ	δ	d
1H	(3J)	(3J)	(3J)	(3J)	(3J)
H-8	6.40	6.62	6.07	6.00	6.03
H-1	4.74 (7.2)	4.16 (9.2; 4.4)	3.69 (7.6; 5.0)	3.83 (7.9; 5.3)	3.78 (7.6; 5.6)
H-α	3.27 (14.0; 7.4)	3.19 (13.7; 4.4)	3.14 (13.6; 5.0)	3.09 (13.4; 5..3)	3.10 (13.4; 5.7)
H-α'	3.21 (14.0; 7.4)	2.88 (13.7; 9.2)	2.78 (13.6; 7.6)	2.74 (13.4; 7.9)	2.75 (13.4; 7.6)
O-CH_3	3.64	3.86	3.58	3.56	3.58
O-CH_3	3.78	3.88	3.78	3.78	3.80
O-CH_3	3.86	3.88	3.84	3.83	3.83
O-CH_3	3.87	3.90	3.85	3.84	3.85

[a] in D_2O.

[b]in $CDCl_3$.

All chemical shift and coupling assignments were confirmed by ^1H-^1H COSY experiments.

Aside from the expected deshielding of the protons on carbon atoms directly bonded to nitrogen, arising from N-protonation, additional differences are evident between the spectra of norlaudanosine hydrochloride and the free base. A more exhaustive comparison of these two spectra was therefore carried out, as shown in Table 3.

Table 3. Spectral assignments of norlaudanosine (1) and its hydrochloride.

^1H	1 [a,b]	1 HCl [a,c]
H-5	s, 6.69	s, 6.92
H-8	s, 6.62	s, 6.40
H-10	d, 6.78 (1.4)	s, 6.78 (1.5)
H-13	d, 6.86 (8.1)	d, 7.02 (8.2)
H-14	dd, 6.82 (8.1; 1.4)	dd, 6.86 (8.2; 1.6)
H-1	dd, 4.16 (9.2; 4.4)	t, 4.7 (7.2)
H-α	dd, 3.19 (13.7; 4.4)	dd, 3.27 (14.0; 7.4)
H-α ’	dd, 2.88 (13.7; 9.2)	dd, 3.21 (14.0; 7.4)
H-3	dd, 3.24 (12.6; 5.5)	dd, 3.56 (13.2; 6.5)
H-3’	ddd, 2.94 (5.3;12.6; 5.3)	dd, 3.45 (12.7; 6.5)
H-4d	dd, 2.80 (16.3; 5.5)	t, 3.0 (6.3)
H-4’d	ddd, 2.70 (15.7; 5.3 ; 5.5)	
O-CH_3	s, 3.90	s, 3.87
O-CH_3	s, 3.88	s, 3.86
O-CH_3	s, 3.88	s, 3.78
O-CH_3	s, 3.86	s, 3.64

[a] All chemical shift (in ppm) and coupling constant (in Hz) assignments were confirmed by ^1H-^1H COSY experiments; [b] spectrum recorded in $CDCl_3$; [c] spectrum recorded in D_2O; [d] the H-4 signals in the spectrum of laudanosine hydrochloride could not be distinguished.

An interesting observation from the ^1H NMR spectra of the benzyl derivatives of coclaurine was the loss of magnetic equivalence of the methylene hydrogen atoms of the OCH_2Ph group attached to C-7, when the nitrogen atom was alkylated. In contrast, the methylene hydrogen resonances of the benzyloxy group attached to C-12 were not affected by alkyl substitution of the nitrogen, both protons remaining magnetically equivalent. The changes in behavior of these benzyl derivatives are presented in Table 4.

Table 4. Chemical shifts and geminal coupling constants for the methylene protons of the benzyl substituent in R_2 or R_3 of coclaurine derivatives 6 and 7.

Compound	δ (multiplicity)	^3J
6	5.12 (s)	
6a	4.75 (dd)	12.3
6b	4.81 (dd)	11.9
7	4.77 (s); 5.09 (s)	
7a	4.75 (dd); 4.96 (s)	12.1
7b	4.81 (dd); 4.93 (s)	12.0
7c	4.77 (dd); 4.86 (s)	12.6

Table 5 lists the chemical shifts of H-8 and H-1 of all the compounds, allowing a comparison to be made between coclaurine and its N-alkylated derivatives. In general, a pattern of behavior similar to that of the N-alkyl derivatives of norlaudanosine (Table 2) was seen.

Table 5. Chemical shifts for H-8 and H-1 of coclaurine derivatives 2-9.

Compound	H-8	H-1
2	6.60	3.92
2a	6.01	3.75
2b	6.07	3.78
3	6.52	4.15
3a	6.12	3.81
3b	5.95	3.84
4	6.52	3.99
4a	6.05	3.59
5	6.55	4.09
5a	6.07	3.58
6	6.62	4.09
6a	6.08	3.71
6b	6.06	3.89
7	6.60	4.05
7a	6.04	3.59
7b	6.09	3.70
7c	6.01	3.68
8a	6.53	4.01
8b	6.08	3.75

9	6.57	4.07

The most conspicuous changes observed in the spectra of the secondary amines upon N-alkylation were: 1. an upfield shift of the H-8 resonance; 2. a change in the multiplicity of the methylene singlet of the C-7 benzyloxy substituent, which becomes a doublet of doublets upon N-alkylation; 3. an upfield shift of the C-7 methoxyl signal in the norlaudanosine series. These features are illustrated in Figures 1-3, which allow comparison of the spectra of three N-alkylated products (1a, 6a, and 7a) with those of the corresponding secondary amines (1, 6, and 7). The observed changes were general, as can be seen in the data of Table 2 and Table 4, where the signals corresponding to H-8, the C-7 methoxyl group or the methylene protons of the benzyloxy substituent at C-7 are given for all N-alkylated compounds and their unalkylated counterparts.

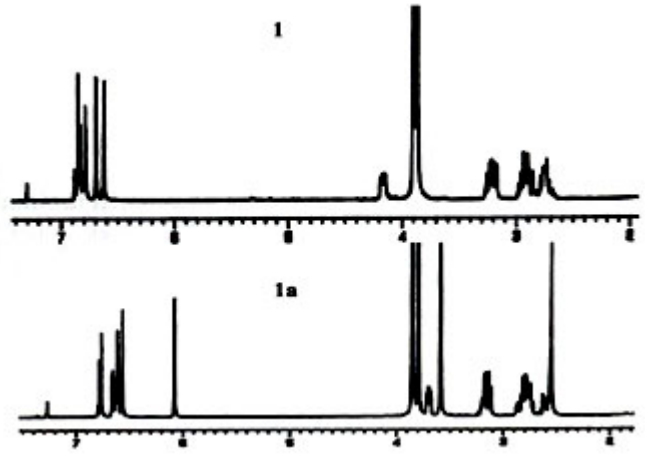


Fig. 1. ^{1}H NMR spectra of compounds 1 and 1a.

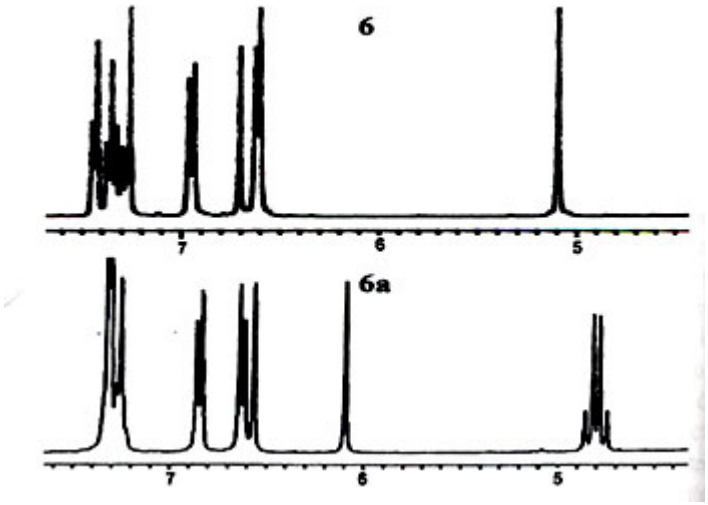


Fig. 2. ^{1}H NMR spectra of compounds 6 and 6a.

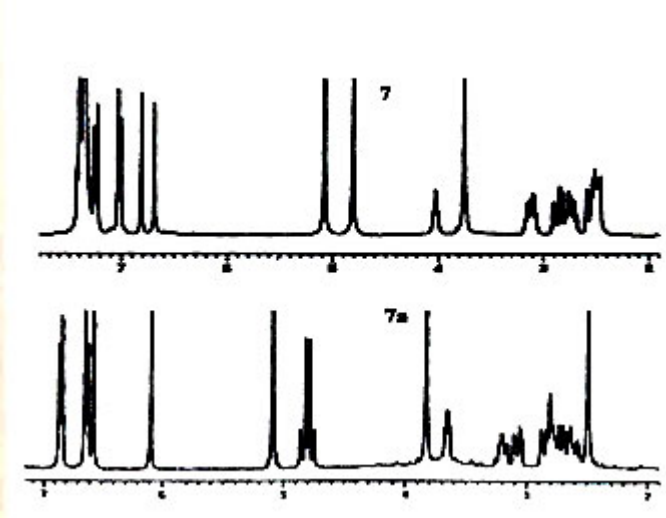


Fig. 3. ^{1}H NMR spectra of compounds 7 and 7a.

The NOESY experiments show that in the cases of the O-benzylated compounds with alkylated nitrogen, NOE's can be seen between H-8 and the methylene protons of the C-7 benzyloxy substituent along with H-11 and H-13 of the 1-benzyl group. On the contrary, when the nitrogen atom is not alkylated, these NOE's are absent. These spectral changes may be rationalized in terms of conformational changes that take place upon N-alkylation of both norlaudanosine and coclaurine and its derivatives. Both systems may exist in three stable conformations: an "extended" one, a "folded" and a "semi-folded" structure (Figure 4). These conformations may be characterized by the dihedral angle q formed by C-9, C-α, C-1 and C-8a.

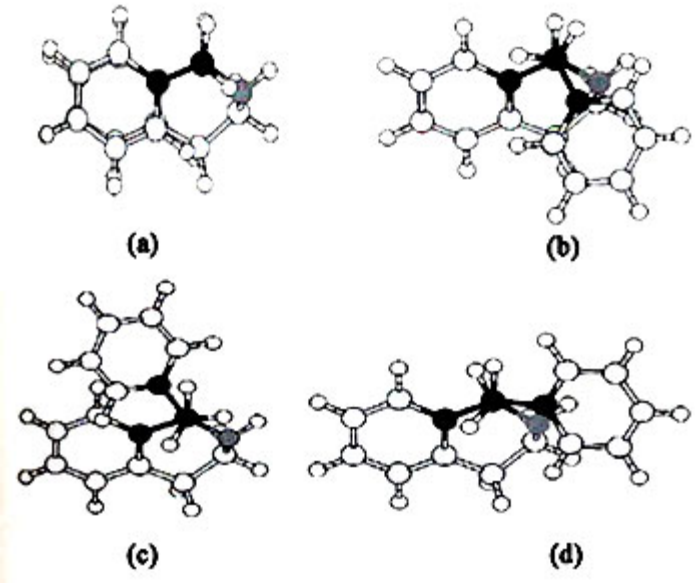


Fig. 4. Eclipsed (a), folded (b), semi-folded (c), and extended (d) conformations of 1-benzyl-1,2,3,4-tetrahydroisoquinoline, after geometry optimization at the RHF/6-61g(d,p) level.

Following previous suggestions, we might envisage a change from the most stable, extended conformation of the secondary amine derivatives toward a semi-folded structure when the secondary nitrogen is alkylated. This is borne out by the observed spectral changes. In a semi-folded conformation both H-8 and the C-7 methoxyl hydrogens are shielded by the 1-benzyl group, with the resulting upfield shift of their signals. This interpretation is reinforced by the observation that the two equivalent methylene protons of 7-benzyloxy substituent in the secondary amines

become non-equivalent in the N-alkylated derivatives. The resulting doublet of doublets, with a characteristic coupling constant of 12.3 Hz, points to a loss of mobility of this methylene group due to steric hindrance by the neigboring C-1 benzyl group in the semi-folded conformation. This interpretation was been confirmed by NOESY experiments, where NOE's can be seen between H-11 and H-13 on one hand, and the C-7 methyleneoxy group on the other.

In order to confirm this view, we resorted to theoretical calculations which might help us compare the relative stabilities of all conformers. Therefore, an ab initio theoretical study of the relative stabilities of several conformations of BTHIQ and some N-alkyl derivatives was performed. The relative rotational energies calculated at the RHF/6-31g(d,p) level as a function of the C-9/C-α/C-1/C-8a angle (θ) in the BTHIQ molecule are illustrated in Figure 5, where the zero energy value corresponds to the overall minimum which occurs at θ = 180º (the extended conformation) in agreement with the NMR NOESY results. Two other minima lie in troughs 1.2 and 1.7 kcal mol-1 above the global minimum at θ values of 70º and 300º, corresponding to the folded and semi-folded conformations, respectively. The barriers separating the absolute minimum from the semi-folded conformer and from the folded one are 4.6 and 7.0 kcal mol-1, respectively.

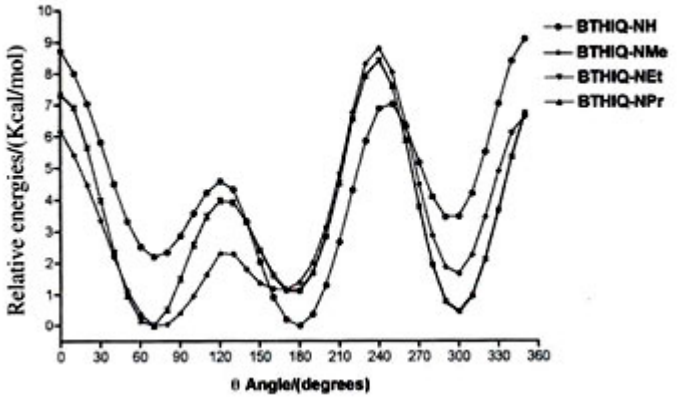


Fig. 5. Relative energies calculated for 1-benzyl-1,2,3,4-tetrahydroisoquinoline conformations as a function of the dihedral angle θ formed by atoms C-9, C-α, C-1 and C-8a. Calculations were performed at 10º intervals, with complete geometry optimization of the rest of the molecule. Note that the curves for the N-ethyl- and N-propyl derivatives are practically identical.

Figure 5 also shows the relative RHF/6-31g(d,p) rotational energy around θ for the N-alkylated derivatives of BTHIQ. It can be seen that the curves show three minima at similar q values to those shown by BTHIQ, but with the global minimum at 70º, corresponding to the semi-folded conformation. The other two local minima correspond to an extended and a folded conformation, with θ = 180º and 290º, respectively. The former lies 1.2 kcal mol-1 above the global minimum for all three derivatives, while the latter lies 0.4 kcal mol^{-1} (for the N-ethyl and -propyl analogues) or 1.6 kcal mol-1 (for the N-methyl compound) above the global minimum. The second minimum is separated from the first by an internal energy barrier of 1.4 (for the N-methyl derivative) or 2.9 kcal mol^{-1} (for the N-ethyl and -propyl derivatives), and from the third by an 7.6-7.3 kcal mol^{-1} barrier. This indicates that exchange between the extended and semi-folded conformations is freer in the N-substituted derivatives than in BTHIQ itself. For the N-methyl analogue, the semi-folded and extended conformations should therefore be quite densely populated and in rapid equilibrium with each other. On the other hand, for the N-ethyl and N-propyl counterparts, although the internal energy difference between the extended and semi-folded conformers again barely exceeds 1.1 kcal mol^{-1}, the height of the barrier suggests a slower rate of exchange of these two forms. In all cases, however, the folded conformer is not easily accessible, even when it is not energetically disfavored. It is noteworthy that the potential energy profiles of the N-ethyl and N-propyl derivatives are almost indistinguishable.

In summary, it may be gathered from the diagrams that in the case of the unalkylated compound the extended

conformation (θ ca. 180º) is the most stable. For the N-alkylated compounds, the semi-folded conformations (θ ca. 70º) are preferred. In all these BTHIQ derivatives, exchange between the extended and semi-folded conformations is fairly easy, but the folded conformation is relatively inaccessible.

Early spectral studies of BTHIQ alkaloids had suggested, from the significant shifts of the C-8 proton resonances to higher field in the N-methylated compounds, that methylation of the nitrogen atom should lead to conformational changes in the molecule.[1,2] Comparison of the ^{1}H NMR spectra of norlaudanosine and its hydrochloride indicates that the conformation of the molecule may be affected by the the presence of an additional proton bound to the nitrogen atom. The signals corresponding to H-8 and the C-7 OCH_3 group in the free base (δ 6.62 and 3.86, respectively) are shifted upfield (to δ 6.40 and 3.64, respectively) in the hydrochloride (see Table 3). This may be the result of a small shielding effect by the benzyl group in the salt. In the salt, in D_2O, the vicinal coupling constants (^{3}J) between H-1, H-α and H-α' are equal (7.4 Hz), indicating that the two methylene protons should form, on the average, the same dihedral angle with H-1. In the free base, however, in $CDCl_3$, the two coupling constants are different (9.2 and 4.4 Hz), as can be seen in Table 3. These observations are in agreement with calculations in vacuo that predict the semi-folded conformation to be more stable for the hydrochloride, a trend which should be reinforced for the strongly solvated salt in D_2O.

The spectral analysis of the N-alkylnorlaudanosines indicates that alkylation of the nitrogen atom shifts the equilibria toward the folded conformations more than mere N-protonation. This may be deduced from the gradual shielding of H-8, as one proceeds from norlaudanosine (δ 6.62) to its hydrochloride (δ 6.40) and its N-alkylated derivatives (δ ≈ 6.00). This shows that the 1-benzyl ring is on the average closer to H-8 in the N-alkyl compounds than in the salt or the free base. The same conclusion may be drawn from an analysis of the gradual shielding of the C-7 methoxyl protons, if their chemical shifts in the free base (δ 3.86), in the salt (δ 3.64) and in the N-alkylated derivatives (δ ≈3.60) are compared. These experimental results show that, for the N-alkylnorlaudanosines, the predominant conformation should be the semi-folded form, whereas the extended conformation should be the preferred one for the free norlaudanosine base. These conclusions are supported by the theoretical conformational analysis, which predicts the extended conformation to be more stable than the semi-folded one when the nitrogen is not alkylated, with the opposite situation occurring when it is. An important trend that emerges from the theoretical analysis is the substantial decrease in the stability differences between the extended and semi-folded conformations in the series of N-alkylated derivatives, indicating that these forms should interconvert quite freely.

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