Complete assignments ^{1}H and ^{13}C NMR spectral data of four anabaseine derivatives

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The anabaseine derivatives 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline, 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline and 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline were prepared either by demethylation with HBr or by reduction with different reagents, $NaBH_4$ and H_2/PtO_2 from 6,7-dimethoxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline, as starting material. The structures have been fully assigned by the combination of one- and two-dimensional experiments.

KEYWORDS: ^{1}H NMR; ^{13}C NMR; HMQC; HMBC; anabaseine; 1-(pyridin-3-yl)-3,4-dihydroisoquinoline

INTRODUCTION

Neuronal nicotinic receptors have attracted much interest during the past few years, largely due to the discovery that the Alzheimer's brain loses many of its nicotinic receptors by the time of death.[1,2] Anabaseine (3-(3,4,5,6-tetrahydropyridin-2-yl)pyridine) **(1)** (Fig. 1) was initially isolated from a marine worm, but has subsequently been found in certain species of ants.[3,4] As with nicotine, anabaseine enhances passive avoidance behavior in nucleus basalis-lesioned rats[5] and has been extensively studied for its potential activity on nicotinic acetylcholine receptors (nAChR).[6]

In this paper, we describe the structure determination, conducted entirely by the use of NMR spectroscopy, and the complete chemical shift assignments of the ^{1}H and ^{13}C NMR spectra of four anabaseine derivatives afforded from 6,7-dimethoxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline **(2)**[7] as potential nicotinic agonists. This was achieved through the concerted application of gradient-enhanced[8] experiments such as HMQC and HMBC.[9,10]

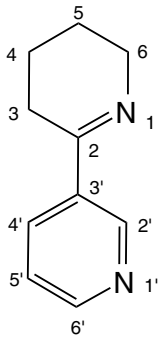

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Figure 1. Structure of (3-(3,4,5,6-tetrahydropyridin-2-yl)pyridine) – anabaseine (**1**).

The investigated alkaloids can be separated into three groups (see Scheme 1): (i) two 1-(pyridine-3-yl)-3,4-dihydroisoquinoline **(2, 3)**; (ii) one 1,2,3,4-tetrahydro-1-(pyridine-3-yl)isoquinoline **(4)**; and (iii) 1,2,3,4-tetrahydro-6,7-dimethoxy-1-(piperidin-3-yl)isoquinoline **(5)**. All ^{1}H signals could be assigned unequivocally on the basis of the ^{1}H-^{1}H COSY spectra. However, the complexity of the coupling patterns in the ^{1}H NMR spectra owing to the presence of several neighboring methylenes and methines made it necessary to apply HMQC and HMBC techniques for the direct unequivocal assignment of the heteronuclear correlations.

RESULTS AND DISCUSSION

The anabaseine derivatives were prepared by using 6,7-dimethoxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline **(2)** as starting material. Demethylation of the *O*-7-CH_3 group of **2** by heating with HBr/AcOH should give a catechol derivative. However, an expected product was characterized as 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline **(3)**.

Several reduction methods were used in order to explore the reactivity of the substituted isoquinoline derivatives with a pyridine ring at C-1. By using $NaBH_4$ in MeOH as solvent, 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline **(4)** was obtained in high yield, and the mild catalytic hydrogenation under PtO_2 as catalyst led to the complete reduction of both the pyridine ring and the imine bond; the product obtained was 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline **(5)**. The complete assignments of the NMR spectra of **2–5** are summarized in Tables 1 and 2. The synthetic route of the different anabaseine derivatives are shown in Scheme 1.

The ^{1}H NMR spectra of compounds **2–4** were analyzed with the aid of ^{1}H,^{1}H COSY and HMQC. For **2**, the signals of aromatic protons were easily assigned to C-5 and C-8 with values of $\delta = 6.70$ and 6.79 ppm, respectively. The methine proton H-8 of **4** at $\delta = 6.15$ ppm shows a significant shielding as compared to **2**, **3** and **5** owing to the loss of planarity of the imine-pyridine system. The protons at the pyridine ring for the compounds **2–4** were assigned unequivocally with the aid of HMBC; the correlations are given in Table 2. The aromatic H-6′ of **4** with $\delta = 8.51$ (*dd*, $J = 4.1$ Hz) is moderately shielded with respect to **2** and **3**; this may be due to the larger basicity of the secondary amine nitrogen atom. The methoxyl groups at C-6 and C-7 are differently influenced by the neighboring aromatic systems. Thus, the *O*-6-CH_3 protons show no major change in all compounds, while the *O*-7-CH_3 protons of **4** are somewhat shielded ($\delta = \delta 3.61$ ppm). This fact may be attributed to the lack of conjugation due to the reduction of the imine group (sp^3 carbon at C-1). The methylene protons of the dihydroisoquinoline framework of **2** and **3**, as well as the methine H-1 in the tetrahydroisoquinoline derivatives **4** and **5** were easily assigned by analyzing the HMBC spectra. So, the methylene group at C-4 of **2** and **3,** and the methine proton at C-1 in **4** and **5** were identified by long-range correlation with H-3, H-5 and H-8. Likewise, H-3′ of **5** was assigned unequivocally by correlation with H-2′ and H-5′ as well as with H-1.

The ^{13}C NMR spectra of all anabaseine derivatives revealed eight carbon resonances; two methylenes, two aromatic methines and four quaternary carbon atoms in the isoquinoline moiety. The remaining resonances for all derivatives varied according to the degree of hydrogenation. Thus, ^{1}H,^{13}C correlations were useful starting points for the assignment of each carbon (Table 2). For instance, C-3 of **2** and **3** resonate at $\delta = 47.61–47.74$ ppm while for **4** and **5** the signals are at $\delta = 41.70–42.23$ ppm being affected by the strong shielding of the tetrahydro-system. Once the signals were identified, the four additional methylene carbons of 1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**5**) were assigned by HMBC.

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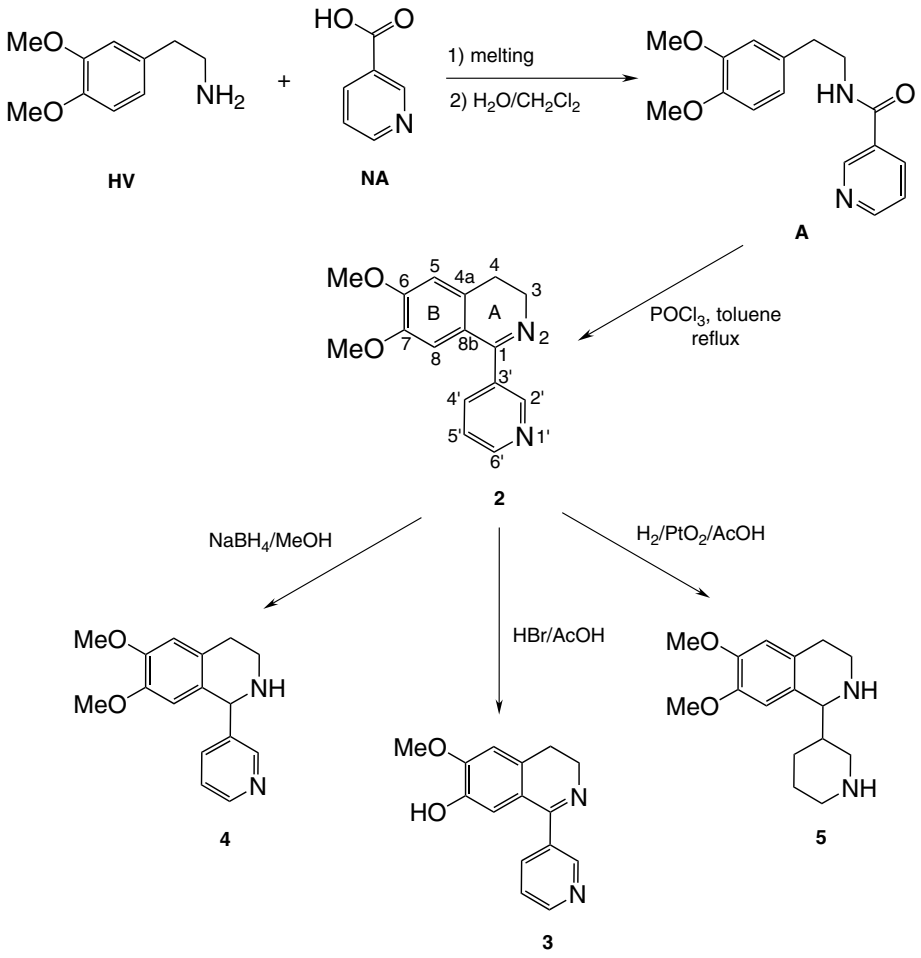

Scheme 1. Syntheses of 1-(pyridine-3-yl)-3,4-dihydroisoquinoline derivatives (**2** and **3**), 6,7-dimethoxy-1-(pyridine-3-yl)-1,2,3,4-tetrahydroisoquinoline (**4**) and 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**5**).

Table 1. ^{1}H chemical shifts δ[a], signal multiplicities and J(H,H) (in Hz) of 6,7-dimethoxy-1-(pyridine-3-yl)-3,4-dihydroisoquinoline (**2**), 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (**3**), 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**4**) and 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**5**)

Position	**2**	**3**	**4**	**5**
1	–	–	5.07	3.99; m
3α/3β	3.83; t, $J = 7.4$	3.71; t, $J = 7.6$	3.06–3.17; m	2.86–3.13; m
4α/4β	2.74; t, $J = 7.4$	2.67; t, $J = 7.6$	2.74–2.91; m	2.57–2.72; m
4a	–	–	–	–
5	6.79	6.95	6.62	6.52
6	–	–	–	–
7	–	–	–	–
8	6.70	6.59	6.15	6.70
8a	–	–	–	–
2′	8.83; d, $J(2', 4') = 1.3$	8.68; d, $J(2', 4') = 1.6$	8.54; d, $J(2', 4') = 1.1$	–
2′α/2′β	–	–	–	2.63; m
3′	–	–	–	2.35; m
4′	7.94; dd, $J(4', 5') = 7.8$	7.90; dd, $J(4', 5') = 8.1$; $J(5', 6') = 2.0$	7.53; d, $J(4', 5') = 7.8$	–
4′α/4′β	–	–	–	1.81; m
5′	7.37; dd, $J(4', 5') = J(5', 6') = 6.1$	7.50; dd, $J(4', 5') = J(5', 6') = 6.3$	7.22; dd, $J(4', 5') = J(5', 6') = 5.7$	–
5′α/5′β	–	–	–	1.65; m
6′	8.68; dd, $J(6', 5') = 4.8$; $J(5', 4') = 1.5$	8.66; dd, $J(6', 5') = 4.8$; $J(5', 4') = 1.6$	8.51; d, $J(6', 5') = 4.1$	–
6′α/6′β	–	–	–	2.57; m
O-6-CH_3	3.94	3.85	3.85	3.87
O-7-CH_3	3.73	–	3.61	3.80
OH-7	–	9.20; bs[b]	–	–

[a] In ppm from TMS.
[b] bs = broad singlet.

Table 2. ^{13}C chemical shifts $\delta(^{13}C)$ of 6,7-dimethoxy-1-(pyridine-3-yl)-3,4-dihydroisoquinoline (**2**), 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (**3**), 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**4**) and 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (**5**)[a]

	2		**3**		**4**		**5**	
Position	$\delta(^{13}C)$	HMBC[b]	$\delta(^{13}C)$	HMBC[b]	$\delta(^{13}C)$	HMBC[b]	$\delta(^{13}C)$	HMBC[b]
1	164.36	3, 8, 2′, 4′	164.07	3, 8, 2′, 4′	58.80	3, 8, 2′, 4′	58.26	3, 8, 2′, 3′, 4′
3	47.74	4	47.61	4	41.70	1, 4	42.23	1, 4
4	25.82	3, 5	25.53	3, 5	29.00	3, 5	29.45	3, 5
4a	132.50	3, 4, 5, 8	130.63	3, 4, 5, 8	127.70	1, 3, 4, 5, 8	128.11	3, 4, 5, 8
5	110.87	4	111.77	4	111.60	4	111.70	4
6	151.28	5, 8, *O*-6-CH_3	150.54	5, 8, *O*-6-CH_3	147.90	5, 8, *O*-6-CH_3	147.30	5, 8, *O*-6-CH_3
7	147.31	5, 8, *O*-7-CH_3	145.14	5, 8	147.30	5, 8, *O*-7-CH_3	147.30	5, 8, *O*-7-CH_3
8	110.48		114.77		110.60	1	109.05	1
8a	120.97	4, 5, 8	120.89	4, 5, 8	128.40	1, 4, 5, 8	128.40	1, 5, 8, 3′
2′	149.78	4′, 6′	149.61	4′6′	150.30	1, 4′, 6′	45.98	1, 3′, 4′, 6′
3′	134.77	2′, 5′	134.64	2′, 5′	140.00	1, 2′, 5′	40.16	1, 2′, 5′
4′	136.17	2′, 6′	136.51	2′, 6′	136.40	1, 2′, 6′	27.82	1, 2′, 6′
5′	123.16	6′	123.66	6′	123.5	6′	24.63	3′, 6′
6′	150.29	2′, 4′, 5′	150.50	2′, 4′, 5′	149.00	2′, 4′, 5′	45.39	2′, 4′
O-6-CH_3	56.04	–	56.16	–	55.86	–	56.05	–
O-7-CH_3	56.16	–	–	–	55.89	–	55.77	–

[a] In ppm from TMS.
[b] ^{13}C,^{1} H HMBC connectivities.

EXPERIMENTAL

Synthesis of 6,7-dimethoxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (2)

A mixture of nicotinic acid (**NA**) and homoveratrylamine (**HV**) was heated for 2 h. Then, the mixture was poured onto water and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and the solvent evaporated to give the amide **A,** which was cyclized by a Bischler–Napieralski reaction to give **2** (4.74 g, 75% yield from amide). IR (KBr, ν, cm^{-1}): 1636 (C═N). MS m/z (%): 268.2 (M^+, 100).

Synthesis of 6-methoxy-7-hydroxy-1-(pyridin-3-yl)-3,4-dihydroisoquinoline (3)

Compound **2** (1.2 g, 4.48 mmol) was dissolved in a AcOH/HBr mixture and heated to 100 °C with stirring for 5 h. Then, the organic residue was diluted in water, neutralized with NH_4OH and extracted with CH_2Cl_2. The extracts were dried with Na_2SO_4, concentrated *in vacuo* and subjected to silica gel flash chromatography with dichloromethane-methanol (9 : 1, v/v) as eluant affording **3** as yellow needles (0.680 g, 60% yield). IR (KBr, ν, cm^{-1}): 3427 (OH), 1639 (C═N). MS m/z (%): 254.25 (M^+, 100).

Synthesis of 6,7-dimethoxy-1-(pyridin-3-yl)-1,2,3,4-tetrahydroisoquinoline (4)

Compound **2** (0.37 g, 1.4 mmol) was dissolved in 50 ml of MeOH and small portions of $NaBH_4$ were added at room temperature. The mixture was stirred for 1 h, poured onto water and its pH was adjusted to 8–9 with AcOH. Then, it was extracted with dichloromethane, dried and concentrated *in vacuo*. The crude residue was purified by column chromatography dichloromethane-methanol (9 : 1) as eluant to give **4** as brown oil (0.310 g, 83% yield). IR (KBr, ν, cm^{-1}): 3384 (NH). MS m/z (%): 270.25 (M^+, 100).

Synthesis of 6,7-dimethoxy-1-(piperidin-3-yl)-1,2,3,4-tetrahydroisoquinoline (5)

Compound **2** (0.3 g, 1.12 mmol) was dissolved in 50 ml of AcOH and hydrogenated at room temperature for 24 h at 80 psi over PtO_2. The colorless solution was diluted with 100 ml water, neutralized with NH_4OH and extracted with CH_2Cl_2. The organic extract was dried over Na_2SO_4 and concentrated to dryness to give **5** as brown oil (0.102 g, 33% yield). IR (KBr, ν, cm^{-1}): 3437 (NH). MS m/z (%): 276.2 (M^+, 100).

NMR spectroscopy

^1H and ^{13}C NMR spectra were acquired using a Bruker AVANCE DRX 300 spectrometer operating at 300.13 and 75.47 MHz, respectively. All measurements were performed at a probe temperature of 300 K, using solutions of compounds **2–5** in $CDCl_3$ (15–21 mg ml^{-1}) containing tetramethylsilane (TMS) as an internal standard. All two-dimensional spectra were acquired with a Bruker inverse 5 mm z-gradient probe. ^1H NMR spectra were obtained with 32 scans in a spectral width of 5.000 Hz using a 90° flip angle (11 μs) and 2 s relaxation delay. The one-dimensional carbon spectrum was obtained with a spectral width of 17.900 Hz with 3 s between transients and the 90° pulse was 9 μs.

The HMQC spectra were recorded using standard Bruker software (inv4gstp). These spectra were collected with 512 × 512 data points, a data acquisition of 4 scans × F_2 and 256 increments in t_1. Spectral widths of 3000 Hz and 13.000 Hz were employed in the F_2 (^1H) and F_1 (^{13}C) domains, respectively. Data were processed using Qsine functions for weighting in both dimensions. The HMBC spectra were obtained using the inv4gslplrnd pulse sequence in the Bruker software and collected with 512 × 512 data points, a data acquisition of 10 scans × F_2 and 256 increments in t_1. The spectral widths were 3.000 Hz (F_2) and 13.000 Hz (F_1) and the delays Δ_1 and Δ_2 were set to 3.45 and 65 ms, respectively. Data were processed using an exponential window in F_2 with a line broadening of 0.3 Hz and a Qsine window in F_1.

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