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Reference Data

^{1}H and ^{13}C NMR Spectra of Pyrido[2,3-*b*]pyrazines and Pyrido[2,3-*b*]pyrazine-*N*-oxides

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^{1}H and ^{13}C NMR spectral data for several pyrido[2,3-*b*]pyrazines and pyrido[2,3-*b*]pyrazine-*N*-oxides are reported. The chemical shift assignments were based on 1D-NOE, gradient HSQC and gradient HMQC experiments for some model compounds.

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INTRODUCTION

In the context of research on antagonists at the glycine site of the NMDA receptor as neuroprotective drugs after an ischaemic insult, series of pyrido[2,3-*b*]pyrazines (**1A**–**27A**) and pyrido[2,3-*b*]pyrazine-*N*-oxides (**1B**–**21B**) were synthesized.[1] All these derivatives showed good affinity for the glycine binding site[2] and, among them, the product **12B** was extremely effective in reducing neuronal damage.[3] In this paper we report ^{1}H and ^{13}C NMR spectral data for compounds **1A**–**27A** (Tables 1 and 2) and **1B**–**21B** (Tables 3 and 4). Structures and numbering are reported in Fig. 1.

EXPERIMENTAL

All ^{1}H NMR spectra were recorded at room temperature at 300 MHz on a Varian VXRS-5000 spectrometer. ^{13}C NMR spectra were recorded at room temperature either on a Bruker AC-200F spectrometer at 50.3 MHz (**4A**, **8A**, **17A**, **19A** and **4B**) or on a Varian VXRS-5000 spectrometer at 75.4 MHz (other compounds). For all the spectra 5 mm NMR tubes were used. Deuterated dimethyl sulphoxide was used as a solvent and the chemical shifts were referenced to residual solvent signals (2.50 and 39.5 ppm for ^{1}H and ^{13}C, respectively).

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About 0.015 M solutions were prepared for compounds **1A**–**27A**, whereas saturated solutions (normally less than 0.01 M) were used for compounds **1B**–**21B**, owing to the very low solubility showed by this class of products.

^{1}H NMR spectra were recorded with spectral width 4800 Hz, pulse angle 45° and acquisition time 4 s. Typical conditions for recording ^{13}C NMR spectra at 75.4 MHz were spectral width 19 kHz, pulse angle 45° and acquisition time 1.15 s, and at 50.3 MHz spectral width 12.5 kHz, pulse angle 45° and acquisition time 2.6 s.

1D-NOE experiments were carried out using standard Varian softwares.

Gradient HSQC and gradient HMQC experiments were recorded on a Varian Unity-Plus 500 MHz spectrometer. The conditions used for phase-sensitive gradient-enhanced one-bond HSQC were spectral width *ca.* 7000 Hz in t_1 and *ca.* 3500 Hz in t_2, 512 increments in t_1 with two scans and 2048 data points per t_1 value and gradient combination of $1:-1$. After zero filling in the t_2 dimension, a 90° shifted sine-squared window function was applied before Fourier transformation in both dimensions, leading to a final data matrix of 512 × 2048. The conditions used for absolute value gradient-enhanced long-range HMQC were spectral width *ca.* 8500 Hz in t_1 and *ca.* 3500 Hz in t_2, 512 increments in t_1 with 64 scans per t_1 value and gradient combination of $2:2:-1$. After zero filling in the t_1 dimension, 90° shifted sine and sine window functions were applied before Fourier transformation in the t_2 and t_1 dimensions, respectively, leading to a final data matrix of 1024 × 2048.

RESULTS AND DISCUSSION

Proton chemical shifts for pyrido[2,3-*b*]pyrazines (**1A**–**27A**) and pyrido[2,3-*b*]pyrazine-*N*-oxides (**1B**–**21B**) are given in Tables 1 and 3, respectively. As expected, the aromatic protons are influenced by their position in the rings and by the effect of substituents.

The assignment of the two NH protons in the pyrido[2,3-*b*]pyrazines (**1A**–**27A**) was done by means of 1D-NOE experiments recorded for some model compounds (**6A**, **20A**, **26A** and **27A**): the NOE observed between the methyl group at C-8 and the NH proton in position 1 allowed the assignment of this NH upfield with respect to the other in position 3 and the methyl signals in compounds **26A** and **27A** (6,8-dimethyl derivatives) could be distinguished. Then, such an NH assignment was considered reproducible for all compounds of class **A**.

For almost all of the *N*-oxides (**1B**–**21B**), only one of the NHs appeared very broad, and this behaviour was reasonably due to the *N*-oxide function effect. Moreover, some 1D-NOE experiments (**6B** and **14B**) allowed the confirmation of this hypothesis. The assignment of the NH protons in all compounds was also confirmed by the analysis of long-range correlation over three bonds observed in gradient HMQC experiments (**1A**, **1B**, **26A** and **27A**).

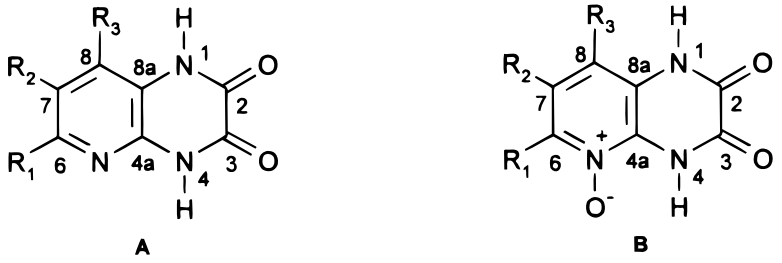

Figure 1. Structures and numbering of series **A** and **B** compounds.

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Table 1. ^{1}H NMR chemical shifts (δ, ppm with respect to residual DMSO, 2.50 ppm) of pyrido[2,3-*b*]pyrazines **A**

No.	R_1	R_2	R_3	H-1	H-4	H-6	H-7	H-8	Others
1A	H	H	H	11.97	12.32	8.07	7.13	7.46	
2A	H	CH_3	H	11.95	12.24	7.91		7.26	2.27
3A	H	Cl	H	12.03	12.47	8.15		7.44	
4A	H	I	H	11.85	12.44	8.24		7.69	
5A	H	CF_3	H	13.0–12.0		8.44		7.61	
6A	H	Cl	CH_3	11.60	12.41	8.11			2.42
7A	H	Br	CH_3	11.57	12.40	8.18			2.43
8A	H	I	CH_3	11.52	12.37	8.33			2.46
9A	H	Cl	n-C_5H_{11}	11.67	12.40	8.09			2.89 (2H), 1.40 (6H), 0.87 (3H)
10A	H	CF_3	Cl	12.0	12.8	8.45			
11A	Cl	H	H	12.05	12.5		7.19	7.45	
12A	Cl	Cl	H	12.8–11.8				7.55	
13A	Cl	Cl	n-C_5H_{11}	11.76	12.57				2.93 (2H), 1.40 (6H), 0.87 (3H)
14A	Cl	CF_3	H	12.17	12.88			7.73	
15A	Cl	Br	H	11.8	12.6			7.62	
16A	Cl	Br	CH_3	11.65	12.57				2.49
17A	n-C_3H_7	Cl	H	12.6–11.6				7.39	2.73 (2H), 1.63 (2H), 0.91 (3H)
18A	n-C_5H_{11}	Cl	H	11.93	12.35			7.39	2.74 (2H), 1.6–1.3 (6H), 0.85 (3H)
19A	CH_3	I	H	11.90	12.35			7.75	2.55
20A	Cl	Cl	CH_3	11.68	12.58				2.47
21A	CH_3	H	H	11.90	12.24		6.99	7.36	2.40
22A	H	H	CH_3	11.48	12.28	7.95	7.00		2.37
23A	Cl	I	H	12.00	12.57			7.77	
24A	H	I	Cl	11.73	12.54	8.39			
25A	n-C_3H_7	Cl	CH_3	11.50	12.30				R_1: 2.75 (2H), 1.64 (2H), 0.92 (3H). R_2: 2.40
26A	CH_3	I	CH_3	11.46	12.31				R_1: 2.63. R_3: 2.51
27A	CH_3	Cl	CH_3	11.52	12.33				R_1: 2.47. R_2: 2.42

Table 2. ^{13}C NMR chemical shifts (δ, ppm with respect to residual DMSO, 39.50 ppm) of pyrido[2,3-*b*]pyrazines A

No.	R_1	R_2	R_3	C-2	C-3	C-4a	C-6	C-7	C-8	C-8a	Others[c]
1A	H	H	H	154.75	155.86	139.13	141.96	118.71	122.23	121.71	
2A	H	CH_3	H	154.90	155.68	137.09	141.99	127.98	122.43	121.30	17.28
3A	H	Cl	H	154.67	155.64	138.33	139.76	124.35	121.26	122.93	
4A	H	I	H	154.44	155.61	138.64	146.82	84.64	128.85	123.38	
5A[a]	H	CF_3	H	154.50	155.94	142.50	138.56	119.56	118.27	122.07	123.68
6A	H	Cl	CH_3	155.08	155.29	137.83	140.06	125.83	130.27	121.48	13.71
7A	H	Br	CH_3	155.26	155.39	138.37	142.60	116.72	131.87	121.69	16.64
8A	H	I	CH_3	155.30		138.92	148.18	93.98	134.74	121.12	21.93
9A	H	Cl	n-C_5H_{11}	155.14	155.53	138.23	140.46	125.55	134.48	121.09	30.78, 26.51, 27.57, 21.92, 13.84
10A[a]	H	CF_3	Cl	154.90	155.47	143.56	139.52	117.43	124.27	121.30	122.77
11A	Cl	H	H	154.53	155.78	139.08	141.13	118.23	125.38	121.22	
12A	Cl	Cl	H	154.45	155.58	137.91[b]	138.08[b]	121.58	124.16	122.71	
13A	Cl	Cl	n-C_5H_{11}	155.15	155.35	139.02	137.33	120.74	137.86	122.49	30.74, 27.32, 27.95, 21.91, 13.83
14A[a]	Cl	CF_3	H	154.22	155.81	141.72	138.05	116.89	122.10	121.39	122.29
15A	Cl	Br	H	155.13	156.44	139.65	139.15	109.97	127.27	123.83	
16A	Cl	Br	CH_3	154.76–154.73		140.28	137.07[b]	114.41	135.30[b]	120.36	17.98
17A	n-C_3H_7	Cl	H	154.50	155.64	137.59	150.19	122.95[b]	120.96	122.25[b]	35.75, 21.34, 13.65
18A	n-C_5H_{11}	Cl	H	154.56	155.71	137.66	150.48	122.91[b]	120.99	122.33[b]	33.77, 27.67, 30.87, 21.86, 13.81
19A	CH_3	I	H	154.42	155.74	138.52	151.33	86.91	131.12	120.80	27.22
20A	Cl	Cl	CH_3	155.09–155.07		138.69	136.89	122.82	133.77	121.06	15.26
21A	CH_3	H	H	154.64	155.91	138.29	150.66	117.98	122.86	119.18	23.06
22A	H	H	CH_3	155.36	155.59	138.74	141.76	120.76	132.81	120.32	16.58
23A	Cl	I	H	154.27	155.55	139.05	143.83	85.57	133.18	122.33	
24A	H	I	Cl	155.14	155.33	139.83	148.27	90.61	130.42	120.87	
25A	n-C_3H_7	Cl	CH_3	155.20		136.63	150.35	124.57	130.87	119.50	36.69, 21.17, 13.73 (R_1), 14.34 (R_3)
26A	CH_3	I	CH_3	155.30	155.43	137.87	152.08	96.74	135.87	118.04	29.31 (R_1), 23.18 (R_3)
27A	CH_3	Cl	CH_3	155.21		136.46	147.11	124.83	130.81	119.43	22.25 (R_1), 14.26 (R_3)

[a] Typical $^1J_{CF} \approx 270$ Hz, $^2J_{CF} \approx 32$ Hz, $^3J_{CF} \approx 4$–7 Hz.
[b] Interchangeable assignment.
[c] The assignment of carbons in n-C_3H_7 and n-C_5H_{11} groups is given starting from the —CH_2— directly attached to the aromatic ring to the final —CH_3.

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Table 3. ^{1}H NMR chemical shifts (δ, ppm with respect to residual DMSO, 2.50 ppm) of pyrido[2,3-*b*]pyrazine-*N*-oxides **B**

No.	R_1	R_2	R_3	H-1	H-4	H-6	H-7	H-8	Others
1B	H	H	H	12.13	12.5–11.8	8.08	7.05	7.12	
2B	H	CH_3	H	12.11	12.5–11.5	8.00		6.87	2.24
3B	H	Cl	H		12.3	8.39		7.06	
4B	H	I	H	12.2	12.6–11.4	8.39		7.26	
5B	H	CF_3	H		12.8–11.8	8.64		7.20	
6B	H	Cl	CH_3	11.76	12.5–11.5	8.43			2.37
7B	H	Br	CH_3		12.6–11.6	8.47			2.38
8B	H	I	CH_3	11.63	12.5–11.5	8.51			2.42
9B	H	Cl	*n*-C_5H_{11}	11.81	12.5–11.5	8.41			2.85 (2H), 1.38 (6H), 0.87 (3H)
10B	H	CF_3	Cl	12.53	12.8–11.8	8.66			
11B	Cl	H	H	12.27	12.5–12.0		7.05	7.46	
12B	Cl	Cl	H	12.25	12.6			7.19	
13B	Cl	Cl	*n*-C_5H_{11}	11.87	12.4				2.92 (2H), 1.36 (6H), 0.87 (3H)
14B	Cl	CF_3	H	12.32	13.0–12.4			7.36	
15B	Cl	Br	H		12.4			7.30	
16B	Cl	Br	CH_3	11.79	12.4				2.48
17B	*n*-C_3H_7	Cl	H	12.12	13.0–11.8			7.08	2.97 (2H), 1.60 (2H), 0.93 (3H)
18B	*n*-C_5H_{11}	Cl	H		12.6–11.6			7.08	2.98 (2H), 1.57 (2H), 1.31 (4H), 0.86 (3H)
19B	CH_3	I	H	12.03	12.4–11.8			7.40	2.63
20B	Cl	Cl	CH_3	11.85	12.4				2.42
21B	*n*-C_5H_{11}	Cl	Cl		12.6–11.8				3.04 (2H), 1.57 (2H), 1.32 (4H), 0.86 (3H)

Reference Data

Table 4. ^{13}C NMR chemical shifts (δ, ppm with respect to residual DMSO, 39.50 ppm) of pyrido[2,3-*b*]pyrazine-*N*-oxides **B**

No.	R_1	R_2	R_3	C-2–C-3	C-4a	C-6	C-7	C-8	C-8a	Others[c]
1B	H	H	H	154.69–154.41	132.53	131.99	118.51	111.74	124.22	
2B	H	CH_3	H	154.86–154.26	130.39	131.68	128.48	112.44	123.69	17.32
3B	H	Cl	H	154.82	132.68	130.82	123.39	111.55	124.58	
4B	H	I	H	154.60–154.29	132.71	136.79	81.32	119.20	124.95	
5B[a]	H	CF_3	H	154.49–154.45	135.72	129.55	120.20	107.43	124.59	122.32
6B	H	Cl	CH_3	155.29–153.57	131.73	130.40	122.84	120.50	124.36	13.22
7B	H	Br	CH_3	155.39–153.73	132.08	132.50	113.94	122.71	122.05	16.16
8B	H	I	CH_3	155.26–153.68	132.19	137.15	89.83	121.44	124.89	21.36
9B	H	Cl	*n*-C_5H_{11}	155.55–153.65	132.01	130.64	122.56	124.20[b]	124.85[b]	30.62, 26.02, 27.81, 21.96, 13.85
10B[a]	H	CF_3	Cl	154.78–153.98	136.77	130.51	117.80	112.22	123.61	121.47
11B	Cl	H	H	154.46–154.31	134.11	133.01	118.75	112.01	122.78	
12B	Cl	Cl	H	154.39–154.34	132.90	133.69	122.27[b]	111.97	122.41[b]	
13B	Cl	Cl	*n*-C_5H_{11}	155.34–153.86	132.97		120.69	125.65	123.13	30.59, 27.35, 27.66, 21.95, 13.83
14B[a]	Cl	CF_3	H	154.55–154.08	132.02	136.59	118.24	109.03	121.98	121.55
15B	Cl	Br	H	154.50–154.41	134.19		110.67	114.71	122.79	
16B	Cl	Br	CH_3	155.15–153.93	134.26	132.96	114.67	120.94	123.17	17.91
17B	*n*-C_3H_7	Cl	H	154.53–154.37	132.17	142.67	121.82	111.37	123.19	28.95, 18.75, 13.73
18B	*n*-C_5H_{11}	Cl	H	154.63–154.50	132.27	142.99	121.86	111.45	123.12	30.94, 24.82, 27.04, 21.77, 13.75
19B	CH_3	I	H	154.45–154.35	132.74	142.73	85.37	119.77	122.54	20.72
20B	Cl	Cl	CH_3	155.05–153.76	132.72[b]	132.64[b]	121.32	120.94	123.32	14.59
21B	*n*-C_5H_{11}	Cl	Cl	155.05–154.05	132.85	143.81	120.34	114.41	122.24	30.93, 24.71, 28.25, 21.77, 13.75

[a] Typical $^1J_{CF} \approx 270$ Hz, $^2J_{CF} \approx 32$ Hz, $^3J_{CF} \approx 4$–7 Hz.
[b] Interchangeable assignments.
[c] The assignment of carbons in *n*-C_3H_7 and *n*-C_5H_{11} groups is given starting from the —CH_2— directly attached to the aromatic ring to the final —CH_3.

Reference Data

The chemical shifts for the carbon atoms of compounds **1A–27A** and **1B–21B** are reported in Tables 2 and 4, respectively. The assignments were based on $^{1}H–^{13}C$ one-bond connectivities using gradient HSQC experiments and on $^{1}H–^{13}C$ long-range correlations over three bonds using gradient HMQC experiments in model compounds **1A** and **1B**. All the other carbon spectra were assigned by comparison with these, taking into account the effect of substituents. The assignment of C-2 upfield with respect to C-3 in compounds **1A–27A** derived from the —NH—(CO)—CO— three-bond heterocorrelation in **1A**.

Further confirmation for the assignments were obtained by both gradient HSQC and HMQC heterocorrelation experiments on some other compounds (**26A** and **27A**).

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References

1. A. Cugola, D. Donati, M. Guarneri, F. Micheli, A. Missio, A. Pecunioso, A. Reggiani, G. Tarzia and V. Zanirato, *Biorg. Med. Chem. Lett.* **6**, 22, 2749 (1996) and references cited therein.
2. H. Kishimoto, J. R. Simon and M. H. Aprison, *J. Neurochem.* **37**, 1015 (1981).
3. J. A. Hunter, R. A. Green and A. J. Cross, *Trends Pharmacol. Sci.* **16**, 123 (1995).