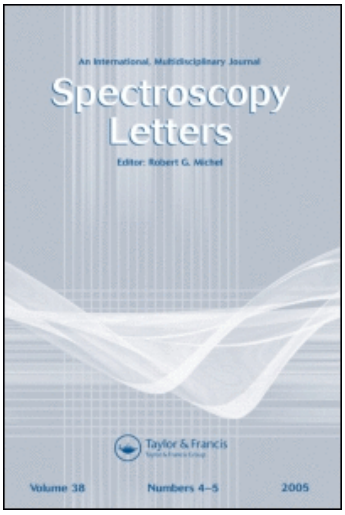

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Determination of the Stereochemistry of Substituted 4-(Sulfo- and Sulfonamidoalkyl) piperidine-2-carboxylic Acids with H NMR, COSY, and Homonuclear NOE Experiments

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DETERMINATION OF THE STEREOCHEMISTRY OF SUBSTITUTED 4-(SULFO- AND SULFONAMIDOALKYL) PIPERIDINE-2-CARBOXYLIC ACIDS WITH ^{1}H NMR, COSY, AND HOMONUCLEAR NOE EXPERIMENTS

Key Words : NMDA, competitive antagonists, (sulfo- and sulfonamidoalkyl) piperidine-2-carboxylic acids, ethyl 4-(hydroxyalkyl)piperidine-2-carboxylates, ^{1}H NMR spectra, Homonuclear NOE.

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ABSTRACT

Basically the aim of this work is to define the accurate configuration of 4-substituted (sulfo- and sulfonamidoalkyl)piperidine-2-carboxylic acids which have been conceived as potential NMDA antagonists. ^{1}H NMR and 2D NMR (COSY)

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followed by qualitative Homonuclear NOE have led to the assignement of the (±) cis and (±) trans configuration of the whole family's compounds.

INTRODUCTION

Numerous NMDA receptor antagonists have been described these last years[1,2]. Several of them were found active both against epilepsy[3], ischemia[4] and as neuroprotectors[5]. CGS-19755 [4-(phosphonomethyl)piperidine-2-carboxylic acid][6] and LY-257883[7] were among the most potent and promising compounds.

We have focussed our attention on sulfonic anologs e.g. 4-(sulfo- and sulfonamido alkyl)piperidine-2-carboxylic acid dervatives as potential NMDA receptors antagonists[8,9](fig.1). The key compounds in the preparation of this family were the ethyl-4-(hydroxy alkyl)piperidine-2-carboxylates (scheme I).

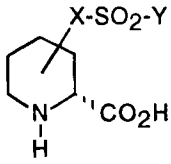
These compounds were obtained by catalytic reduction of the corresponding ethyl 4-(hydroxyalkyl)pyridine-2-carboxylate in AcOH with PtO_2 as catalyst. Unexpectedly enough both (±) cis and (±) trans isomers where obtained for n = 1 and 2.

^1H NMR and COSY experiments permitted to attribute the stereochemistry of compounds **1a** and **1b**, however for **2a** and **2b** additional Homonuclear NOE were needed.

EXPERIMENTAL

The ^1H NMR spectra and NOE experiments were recorded at 20°C in 5 mm tube on a Bruker AC 200 spectrometer with a proton operating frequency of 200.13 Mhz and referenced to the $CDCl_3$ or D_2O signal.

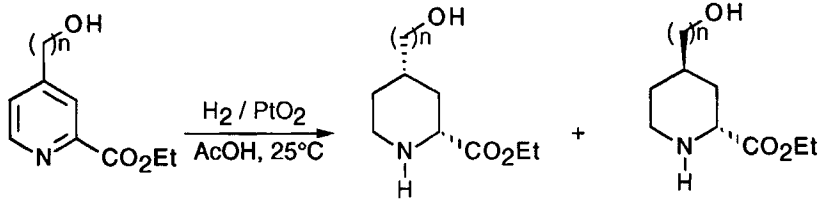
Experiments in NOE difference spectroscopy were achieved on samples prealably filtered and degassed. The NOE is measured according to the method of Bell and Saurders[10].



X : $(CH_2)_n$, n = 1, 2
$CH(OH)CH_2$
$CH(Cl)CH_2$
$(CH_2)_nCH=CH$, n = 0, 1

Y : OH, NMe_2, NHEt

FIG. 1.

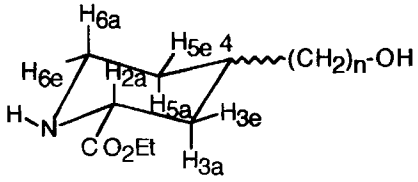


n =1 **1a** 55% **1b** 45%
n =2 **2a** 66% **2b** 34%

Scheme I.

TABLE 1.

Chemical Shifts ^1H δ (ppm) of Compounds **1a**, **1b**, **2a** and **2b**.



n = 1 (**1a** and **1b**)
n = 2 (**2a** and **2b**)

Compd	H_{2a}	H_{3a}	H_{3e}	H_4	H_{5a}	H_{5e}	H_{6a}	H_{6e}
1a	3.02	0.95	1.49	1.96	0.95	1.49	2.61	3.20
1b	3.12	0.92	1.57	1.97	1.05	1.57	2.60	3.28
2a	3.29	1.07	2.04	1.65	1.07	1.65	2.61	3.13
2b	3.29	1.07	2.04	1.65	1.07	1.65	2.61	3.13

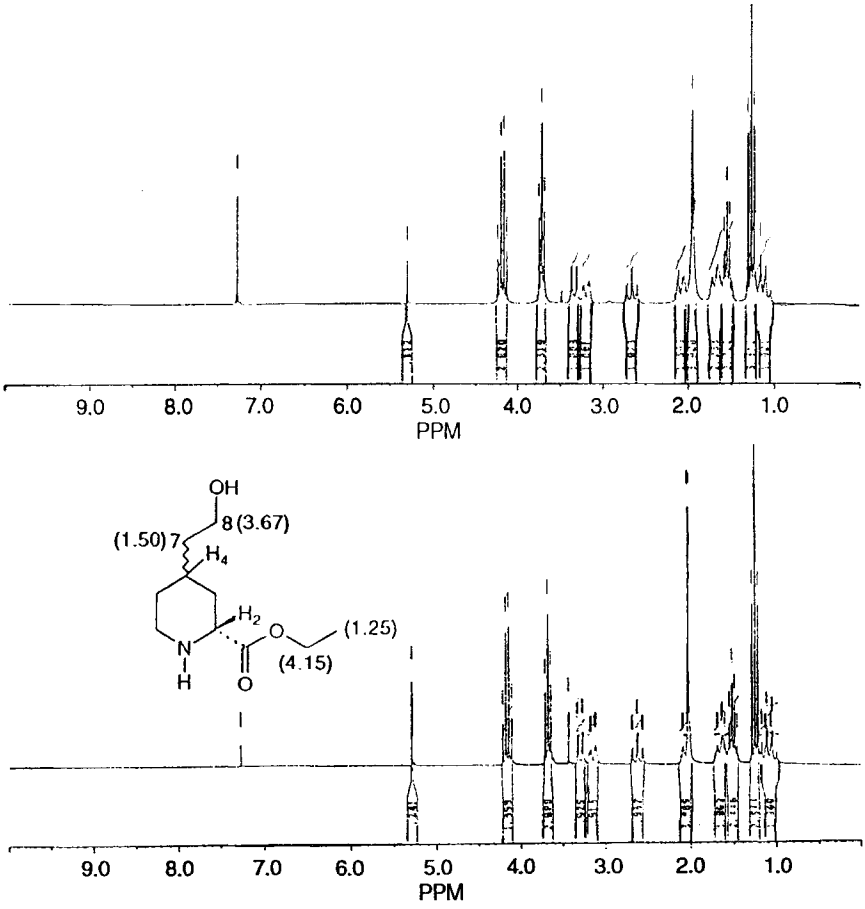


FIG. 2. ^{1}H NMR Spectra of Compounds **2a** and **2b** in $CDCl_3$

RESULTS AND DISCUSSION

The assignement of (±) cis and (±) trans configurations of compounds **1a**, **1b**, **2a** and **2b** was based on ^{1}H NMR spectra assuming a chair conformation for these derivatives. Selective irradiations were helpful to achieve the accurate configuration of all protons (table 1, fig.2).

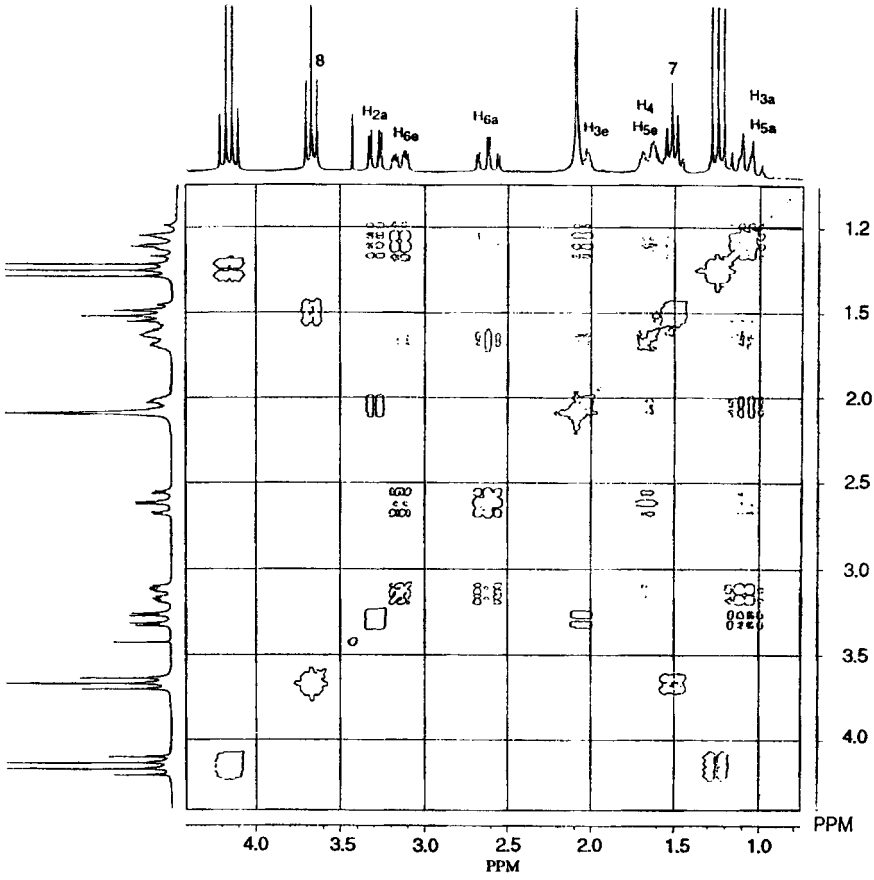


FIG. 3. COSY Spectra of Compound **2b**

2D ^{1}H NMR were in agreement with the initial interpretations. The COSY spectrum of compounds **2b** (fig.3) is given as an example.

- Coupling constants measured on the H_2 proton (J = 12.0, 3.0 Hz) of compounds **1a**, **1b**, **2a** and **2b** indicate an axial position.

- coupling constants measured at 1.96 and 1.97 ppm for **1a** (J = 12.02, 3.0 Hz) and **1b** (J = 3.0, 2.2 Hz) indicate respectively an axial and an equatorial position

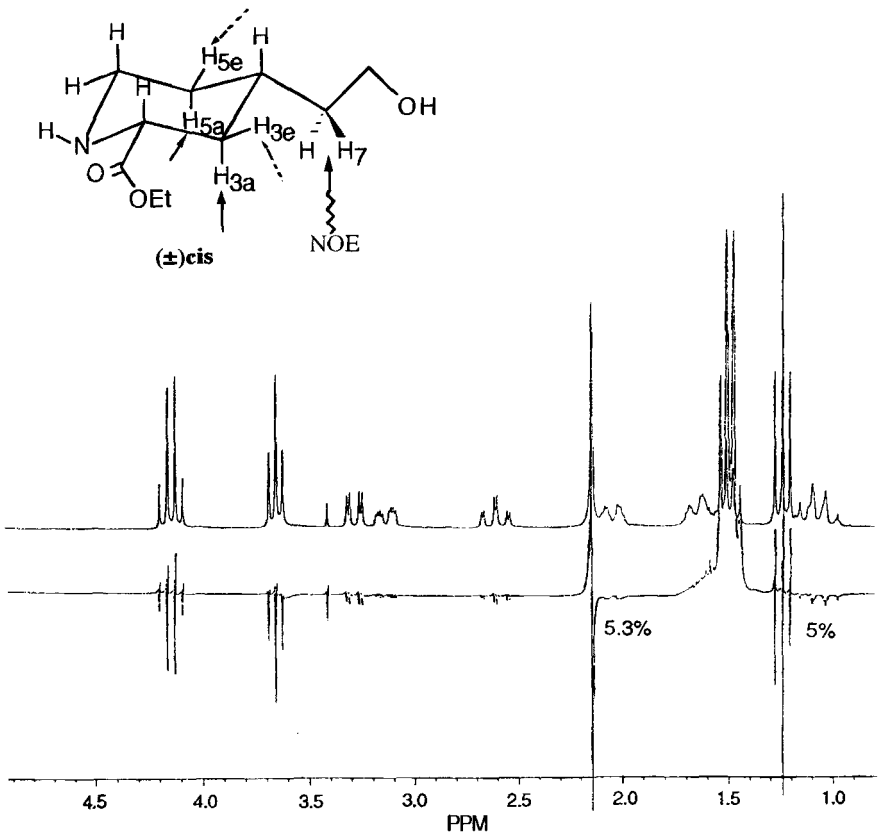


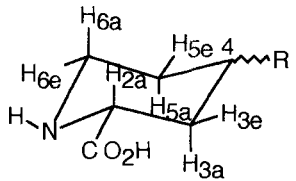
FIG. 4.

for H_4 and consequently a (±) cis configuration for **1a** and a (±) trans configuration for **1b**.

- the signal at 1.65 ppm for **2a** or **2b** corresponds to protons H_4 and H_{5e}. The coupling constant associated to this signal (J = 12-13 Hz) did not permit to attribute the configuration of H_4,because the geminal coupling between H_{5a} and H_{5e} and the vicinal H_{4a}, H_{5a} coupling are identicals. This assignment was achieved by Homonuclear NOE. Selective irradiations of H_7 protons of **2a** and **2b** indicate a

TABLE 2.

Chemical Shifts δ ^{1}H (ppm) of the Disubstituted-2,4-Piperidine Derivatives.



Compd	R	Stereochem.	H_{2a}	H_{3a}	H_{3e}	H_4	H_{5a}	H_{5e}	H_{6a}	H_{6e}
3a	CH_2SO_3H	(±)cis	3.63	1.32	2.36	2.02	1.32	2.02	2.87	3.33
3b	$(CH_2)_2SO_3H$	(±)cis	3.37	1.15	2.11	1.72	1.15	1.72	2.79	3.25
3c	$(CH_2)_2SO_2NMe_2$	(±)cis	3.50	1.18	2.14	1.80	1.18	1.80	2.80	3.27
3d	$CH(OH)CH_2SO_2NHEt$	(±)cis	3.07	0.88	1.79	1.44	0.88	1.44	2.32	2.88
3e	$CH(Cl)CH_2SO_2NHEt$	(±)cis	3.32	1.31	2.12	1.71	1.31	1.71	2.68	2.91
4a	$CH{=}CH\text{-}SO_2NMe_2$*	(±)cis	3.75	1.42	2.26	1.89	1.42	1.89	2.87	3.34
4b	$CH_2CH{=}CH\text{-}SO_2NMe_2$*	(±)cis	3.52	1.14	2.32	2.01	1.14	2.01	2.79	3.22
4c	$CH_2CH{=}CH\text{-}SO_2NMe_2$*	(±)trans	3.56	1.16	2.33	2.03	1.16	2.03	2.81	3.24

* : Z configuration

mutual relationship between H_{3a}, H_{5a} and H_{3a} for **2b** (NOE effect of 5% for H_{3a}, H_{5a} and 5,3% for H_{3e}, for H_{5e} the NOE effect could not be observed because of its vicinity with H_7). These data are only in ageement with a (±) cis stereochemistry (fig 4).

On the contrary irradiation of H_7 for **2a** has no effect on H_{3a}, H_{5a} and H_{5e} and only a weak one on H_{2a} and H_{6a}. Consequently the stereochemistry of **2a** is (±) trans.

The above results were used to assign unambigously the accurate stereochemistry of a series of compounds derived from **1a**, **1b**, **2a** and **2b**. The data are gathered in table 2.

CONCLUSION

Basically the aim of this study is to define the exact configuration of disubstituted-2,4-piperidines. A previsional survey has been undertaken from the ^1H and 2D spectra analysis. The qualitative study with Homonuclear NOE effect leads to the assignement of the accurate configuration and reveal a good coherence with the previsional study.

We have also observed that in the all series of 2,4-disubstituted piperidines, the shielding of piperidine protons varies in the decreasing order of $H_{2a} > H_{6e} > H_{6a} > H_{3e} > H_4$, $H_{5e} > H_{3a}$, H_{5a}. Consequently this observation can be used as an easy method to assign the configuration of these compounds.

REFERENCES

1.Watkins J.C.,Olverman H.J., Agonists and antagonists for excitatory amino acid receptors. Trends in Neurosci. 1987, 10 (7), 265-272.

2. George P., Frost J., Carter C., Scatton B., Benavides J., NMDA receptor antagonists-potential agents for the therapy of stroke and head trauma. Actual. Chim. Thér., 1994 - 21é série, 45-67.

3. Meldrum B.S., Possible therapeutic applications of antagonists of excitatory aminoacid neurotrasmitters. Clin. Sci. , 1985, 68, 113-122.

4. Simon R.P., Swan J.H., Griffiths T., Meldrum B.S., Blackade of N-methyl-D-aspartate receptors may protect against iscemic damage in the brain. Science, 1984, 226, 850-852.

5. Wüllfert E., Stratégies de recherches pharmaceutiques dans la maladie d'Alzheimer. J. Pharm. Belg., 1991, 46, 67-77.

6. Lehmann J., Chapman A.G., Meldrum B.S., Hutchinson I., Tsai C., Wood P.L., CGS-19755 is a potent and competitive antagonist at NMDA-type receptors. Euro. J. Pharmacol. 1988, 154, 89-93.

7. Ornstein P.L., Schaus J.M., Chambers J.W., Huster D.L., Leander J.D., Wong D., Paschal J. W.,Jones N.D., Deeter J.B., Synthesis and pharmacology of a series of 3- and 4-(Phosphonoalkyl)pyridine- and piperidine-2-carboxylic acids : Potent N-methyl-D-aspartic acid receptor antagonists. J. Med. Chem. 1989, 32, 827-833.

8. El hadri A., Maldivi P., Leclerc G., Rocher J.P., Syntheses, Activity and Modeling studies of 3- and 4-(sulfo and sulfonamidoalkyl)pyridine and piperidine-2-carboxylic acid derivatives as analogs of NMDA receptor antagonists. BioMed. Chem. (submitted).

9. El hadri A., Leclerc G., A convenient synthesis of 4-(sulfomethyl)piperidine-2-carboxylic acid : NMR assignement. J. Heterocycl. Chem., 1993, 30, 631-635.

10. Bell R.A., Saurders J.K., Nuclear Overhauser effect. Can. J. Chem., 1970, 48, 1114-1122.

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