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^{15}N NMR SPECTROSCOPY OF ANNULATED Δ^2-PYRAZOLINES AND Δ^2-1,2,4-TRIAZOLINES

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Abstract – Enantiopure Δ^2-pyrazolines and Δ^2-1,2,4-triazolines fused to the 1,4-benzodiazepine moiety, as well as Δ^2-pyrazolines annulated to the 1,5-benzoxazocine moiety (racemic) or inserted in a *bis*-1,3-pyrazolophane skeleton (enantiopure) were investigated through ^{15}N NMR spectroscopy in natural abundance. Nitrogen chemical shifts were determined by (1D)-INEPT experiments, while proton-nitrogen scalar coupling were obtained through 2D-*J*-HMBC experiments.

Due to the occurrence of nitrogen atoms in a huge number of heterocyclic rings, their study through ^{15}N NMR spectroscopy may appear as a logical consequence in order to obtain a better knowledge of their own structures. As a matter of fact, increasing attention have been payed to this interesting topic[1] and, in particular, the chemical shifts of some ^{15}N-enriched azoles have been investigated by ^{15}N NMR spectroscopy.[2] Several efforts have also been made in studying ^{15}N NMR of azoles in natural abundance.[3] Within this field, early papers by Elguero and coworkers[4] are concerned to simple Δ^2-pyrazoline derivatives, while our recent work[5] deals with the spectroscopic data of a series of 1-(4-substituted)phenyl-3-methoxycarbonyl-5-ethoxycarbonyl-Δ^2-pyrazolines. Having firmly established the basic spectroscopic features of simple Δ^2-pyrazolines within the frame of ^{15}N NMR spectroscopy, we turned our attention to the study of annulated Δ^2-pyrazolines and Δ^2-1,2,4-triazolines, namely 3,3a-dihydropyrazolo[1,5-*a*][1,4]benzodiazepine-4(6*H*)-ones **1** and [1,2,4]triazolo[4,3-*a*][1,4]benzo-diazepinones **2** (Figure 1), in natural abundance. These heterocyclic skeletons are particularly attracting since they belong to the class of annulated 1,4-benzodiazepines, which occupy a prominent place among drugs for the treatment of CNS disturbances.[6] Some significant representatives are alprazolam, a common anxiolytic agent,[7] and flumazenil[8] which belongs to the family of cognition enhancers. Other interesting Δ^2-pyrazolines annulated to the 1,5-benzoxazocine moiety (compounds **3** and **4**, racemic) or inserted in a

bis-1,3-pyrazolophane skeleton (compound **5**, enantiopure) have also been investigated.

In order to gain deeper insights about the spectroscopic features of compounds **1**-**5** we undertook their comprehensive ^{15}N NMR analyses.

All the substrates **1**-**5** submitted to ^{15}N NMR analyses (Figure 1) were synthesised *via* nitrilimine cycloaddition onto the appropriate dipolarophile. Nitrilimine intermediates were generated *in situ* by treating the corresponding hydrazonoyl chloride with silver carbonate as the basic agent, according to a procedure developed in our laboratory.[9]

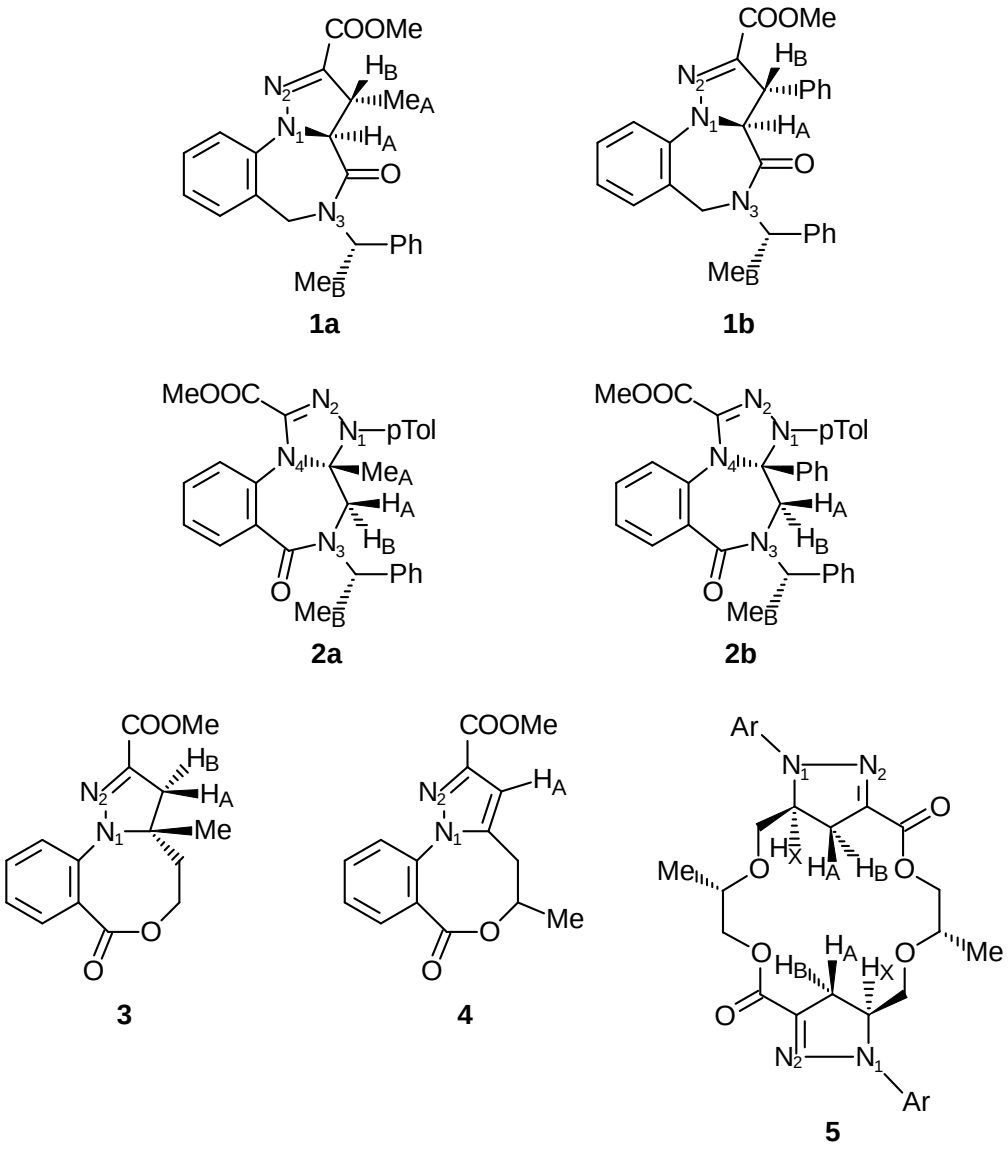

Figure 1. Formulae of compounds **1**-**5** (pTol = *para*-tolyl).

In the cases where a chiral pendant is present a stereoselective cycloaddition took place giving mixtures of the possible enantiopure diastereoisomers.[10] In the present paper we examined the spectral properties of the major diastereoisomers **1a,b**, **2a,b** and **5** in the enantiopure form, whose absolute configurations are

depicted in Figure 1 and were assigned previously on the basis of X-ray diffractometric analyses.[11] As far as racemic substrates **3** and **4** are concerned, their structure were assigned unambiguously by analytical and spectral data.[12]

All the experiments reported in the present paper were performed in natural abundance thus avoiding the synthesis of ^{15}N-enriched compounds. Futhermore, the lack of ^{15}N labeled atoms did not lead to excessive time-consuming experiments.

The ^{15}N nuclear shielding values of compounds **1-5**, which resulted from (1D)-INEPT pulse sequences, are given in Table 1. It is known that nitrogen chemical shift (δN) of some aromatic azoles can be affected by the solvent,[13] however these changes occur because of explicit hydrogen bondings which are clearly absent in the present case. Hence, all experiments were performed in $CDCl_3$ as the solvent, while sample concentration was always 0.25 M.

Table 1. ^{15}N chemical shifts of compounds **1-5**.[a]

Compound	δN_1	δN_2	δN_3	δN_4
1a	- 224.52	- 29.60	- 241.22	—
1b	- 225.05	- 29.67	- 241.52	—
2a	- 236.61	- 101.31	- 243.87	- 274.23
2b	- 240.41	- 100.78	- 244.30	- 279.29
3	- 217.70	- 7.56	—	—
4	- 163.90	- 59.04	—	—
5	- 217.02	- 21.25	—	—

[a]0.25 M in $CDCl_3$.

According to Table 1, the chemical shift values of N_1 and N_2 vary due to their hybridisation. It is apparent that sp^2-hybridised N_2 falls downfield with respect to sp^3-hybridised N_1. In other words N_2 atoms appear strongly deshielded with respect to N_1, a result which agrees with the known chemical shifts of both sp^2 and sp^3 nitrogens of simple heterocycles.[14] Some fluctuation in the N_2 chemical shift values appears from Table 1 according to their chemical environment. In particular, sp^2-hybridised N_2 contained in the 1,2,4-triazoline ring of **2a**,**b** appears shielded with respect to their counterparts in the pyrazoline ring of compounds **1a**,**b**. Such a behaviour is hardly rationalisable on the basis of simple inductive and hybridisation effects. In fact, it may be recalled that some nitrogens experience an upfield shift due to the dominance of the increase in molecular-plane shielding over the decrease in the out-of-plane shielding.[15] This latter statement can be applied to the present case since structures of compounds **1a** and **2a** provided by X-ray crystallographic analysis show better planarity for the 1,2,4-triazoline ring. Compounds **1a,b** and **2a,b** display both N_1 and N_3 or N_3 and N_4, respectively, whose chemical shifts are difficult to assign

unambiguosly on the basis of the above-mentioned (1D)-INEPT experiment. In the case of such compounds 2D-HMBC experiments were required to attain this latter purpose. As far as racemic benzoxazocine-annulated pyrazoles **3** and **4** are concerned, their N_1 and N_2 chemical shifts finds a rationale in the light of the above considerations. The N_1 and N_2 chemical shifts of enantiopure *bis*-1,3-pyrazolophane **5** just match with that observed in the case of simple Δ^2-pyrazolines.[5]

Next, we measured the $^{15}N_x$-C-C-H scalar couplings of compounds **1**-**5** by means of 2D-*J*-HMBC experiments. The ^3J values reported in Table 2 encompasses the range 3.3-4.2 Hz in the case of compounds **1**-**4**, which are consistent with literature data.[16] As far as *bis*-1,3-pyrazolophane **5** is concerned, larger values of ^3J were observed, namely between 6.0 and 6.2 Hz. It needs to be underlined the perfect agreement between these latter data and those previously found for simple Δ^2-pyrazolines.[5]

Table 2. ^3J values of compounds **1**-**5**.[a]

Type of ^3J	Compound						
	1a	**1b**	**2a**	**2b**	**3**	**4**	**5**
N_1-H_A	—	—	3.8	3.5	3.6	3.4	6.0
N_1-H_B	3.8	3.5	—	—	3.6	—	6.0
N_1-H_X	—	—	—	—	—	—	6.1
N_1-Me_A	—	—	3.7	—	3.9	—	—
N_2-H_A	3.4	3.4	—	—	4.1	4.2	6.2
N_2-H_B	3.6	3.6	—	—	4.1	—	6.2
N_3-Me_B	5.6	3.7	3.9	3.7	—	—	—
N_4-H_A	—	—	3.7	3.6	—	—	—
N_4-Me_A	—	—	3.3	—	—	—	—

[a]In $CDCl_3$.

Novel ^{15}N NMR spectroscopic data, namely chemical shifts and scalar coupling constants, have been obtained for some enantiopure Δ^2-pyrazolines and Δ^2-1,2,4-triazolines fused to the 1,4-benzodiazepine moiety, as well as for racemic pyrazolo[1,5-*a*][5,1]benzoxazocines or enantiopure *bis*-1,3-pyrazolophane.

EXPERIMENTAL

Compounds **1a**,**b**,[11a] **2a**,**b**,[11b] **3**,[12a] **4**,[12b] and **5**[11c] are known in the literature.

^{15}N NMR spectroscopic experiments.

NMR spectra were acquired on a Bruker Avance 400 MHz (40.557 MHz for ^{15}N) or on AMX 300 MHz (30.424 MHz for ^{15}N) spectrometer, both equipped with a 5 mm inverse z-gradient probe.

^{15}N chemical shifts were measured *via* (1D)-INEPT experiments, which were recorded over a range of

300 ppm with a *J* value of 4 Hz and a relaxation delay of 2 s.

The 2D-HMBC spectra are recorded with a *J* value of 4 Hz, spectral width of 300 ppm in F1 dimension, a relaxation delay of 1.5 s; data matrices of 1024 x 256 points (eight scans) were zero filled in F1 dimension to 1024 points.

J_{H-N} long range were recorded by means of 2D-*J*-HMBC experiment of samples in $CDCl_3$ solution, with the following parameters: relaxation delay 4.0 s, scaling factor SF = 23, *J* = 4 Hz, 16 scans.

In all experiments nitromethane was used as reference of ^{15}N chemical shifts (δ = 0 ppm).

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