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CONFORMATIONS OF TWO ISOMERIC MORPHOLINOETHYL-1,2,4-TRIAZOLES

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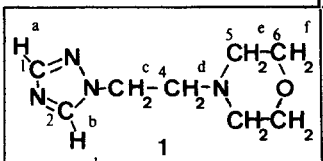
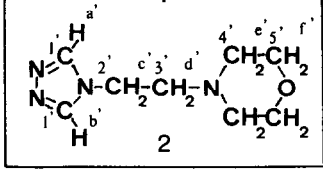
In the field of our work on histamine-like substances[2,3], we prepared two isomeric morpholinoethyl-1,2,4-triazoles: the 1-(2-morpholinoethyl)-1,2,4-triazole 1 and the 4-(2-morpholinoethyl)-1,2,4-triazole 2. It was necessary to determine the conformation of 1 and 2 in solution to establish the possible relationships between their molecular structure and their pharmacodynamical activity on specific receptor sites[4].

The 1-substituted compound 1 was prepared by cyclisation of a mixture of 3-dimethylamino-2-azaprop-2-en-ylidendimethylammonium chloride[5,6] and morpholinoethylhydrazine. The cyclising condensation of formylhydrazine with 2-morpholinoethylisothiocyanate gave the 4-(2-morpholinoethyl)-1,2,4-Δ-2-triazoline-5-thione and the hydrogenolysis of the thione group led to 2.

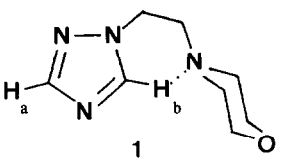
The ^{1}H NMR spectra of 1 and 2 in CCl_4 are strictly similar (table I). If the non-equivalence of the protons a and b of 1 could correspond to the dissymetry of the molecule[7], we could expect the corresponding protons a' and b' for 2 to be equivalent.

	^{1}H NMR (δ in ppm)			^{13}C NMR (δ in ppm) Broad band spectrum	
	CCl_4 Int. ref.: TMS	$CDBr_3$	D_2O (dihydrochlorides) Int. ref.: $(CH_3)_3Si(CH_2)_3SO_3Na$		
 1	(a) 7.70;s;i=1	7.90;s;i=1	8.78;s;i=1	(1)	146.94 and 144.86
	(b) 8.08;s;i=1	8.24;s;i=1	9.66;s;i=1	(2)	
	(c) 4.20;t;i=2	4.32;t;i=2	3.93;t;i=2	(3)	47.64
	(d) 2.70;t;i=2	2.80;t;i=2	3.80;t;i=2	(4)	56.74
	(e) 2.40;m;i=4	2.45;m;i=4	3.55;m;i=4	(5)	65.87
	(f) 3.52;m;i=4	3.65;m;i=4	4.98;m;i=4	(6)	54.69
 2	(a') 7.70;s;i=1	8.30;s;i=2	7.48;s;i=2	(1')	146.40
	(b') 8.08;s;i=1				
	(c') 4.20;t;i=2	4.22;t;i=2	3.98;t;i=2	(2')	43.64
	(d') 2.70;t;i=2	2.72;t;i=2	3.72;t;i=2	(3')	57.39
	(e') 2.40;m;i=4	2.53;m;i=4	3.51;m;i=4	(4')	66.22
	(f') 3.52;m;i=4	3.67;m;i=4	4.90;m;i=4	(5')	55.01

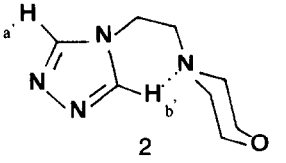
$J_{cd} = J_{c'd'} = 6$ Hz

Table I

We can explain the identical shifts for a and a' on one hand and for b and b' on the other hand by the establishment of a hydrogen-bonding between b (or b') and the morpholinic nitrogen atom, giving analogous structure for 1 and 2 (scheme I).

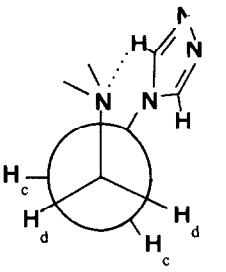


1



2

Scheme I



Scheme II

This postulated configuration is in accordance with the dihedral angle between vicinal protons of the side chain determined by the way of Karplus relationship[8]. The $^{3}J_{cd}$ datum (6 Hz) corresponds to a theoretical dihedral angle value of 30° (scheme II). In this configuration, it is possible to evaluate the distance C-H···N (d≈1,5 Å) corresponding to a strong hydrogen-bonding[9]. This spatial interaction disappears when a more polar solvent is used, the protons a' and b' becoming equivalent for 2 but a and b remaining different for 1; the example of $CDBr_3$ as a ^{1}H NMR solvent is given in table I. Similar features are noted when the nitrogen atom of morpholin is protonated: the above mentioned hydrogen-bonding cannot then exist; the C-H free from chelation undergoes the isotopic exchange with D_2O, illustrating so the acidic character of this proton (table I, ^{13}C NMR).

REFERENCES AND NOTES

1 Researcher at INSERM, present address: Unité U 16, Place de Verdun, 59045 Lille Cedex (France)

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