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Dedicated to the memory of
Professor Mircea D. Banciu (1941–2005)

N-α-CYANO DERIVATIVES OF SOME *N*-BENZYL AZACYCLOALKANES

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Endocyclic (**1**) and exocyclic (**2**) (*i.e*., CN at the aliphatic ring-carbon and in the benzylic position, respectively) *N*-α-cyano derivatives of *N*-benzylmorpholine, -piperidine, -pyrrolidine, -piperazine, and *N*,*N'*-dibenzylpiperazine were prepared and their ^{1}H- and ^{13}C-NMR spectral properties tabulated and discussed. Careful analysis of the NMR spectra revealed that the CN group in **1** is essentially *a*xially located. Semiempirical AM1 calculations supported the experimentally found conformation and gave the *cis*-1-(*e*)-benzyl-2-(*a*)-cyano stereoisomers as being the most stable ones. Broadening of the NMR signals belonging to the aliphatic ring-protons or -carbons in **2** was ascribed to the fast chair-chair interconversion of the aliphatic ring and/or to the presence of the chiral Ph-*C*H-CN carbon atom.

INTRODUCTION

During our works on the RuO_4-mediated oxidation of aliphatic tertiary amines in the presence of NaCN,[1-3] we found the corresponding *N*-α-cyano derivatives as main reaction products. For instance, working with *N*-benzyl azacycloalkanes, two types of such nitriles were present, depending on the functionalized *N*-α-site: endocyclic (*i.e.*, CN at the aliphatic ring-carbon) and exocyclic (*i.e*., CN in the benzylic position).[1,3] The identification was made by comparison of the ^{1}H- and ^{13}C-NMR spectra of the respective oxidation mixtures registered before to and after addition of unambiguously synthesized nitriles. We wish to report now details about the synthesis of some *N*-α-cyanoazacycloalkanes and to discuss more deeply their NMR features. Our attention will be focused on the compounds **1A-E** and **2A-F** (Chart 1), resulted from the RuO_4-oxidation[1,3] of *N*-benzylmorpholine, -piperidine, -pyrrolidine, -piperazine, and *N*,*N'*-dibenzylpiperazine (**3A-E**, respectively).

For comparison purposes, we depicted in Chart 1 the formulae of **4A-B**,[4,5] **5A-B**,[4,5] and **6A**,[6] from the literature. It is necessary to add here that the numeration in Chart 1 follows the IUPAC rules for all compounds, unless for **1A**, **1C**, **2A**, and **2C**. However, to facilitate the comparison between various NMR chemical shifts, the same type of numeration was adopted for these four compounds. The same reason determined us to keep the designations "*a*xial" and "*e*quatorial" for the pyrrolidine ring-protons in **1C** and **2C**, although they have real meanings for a six-membered ring only. In addition, only chair conformations were considered for the aliphatic, six-membered rings in **1A-B**, **1D-E**, **2A-B**, and **2D-F**, because no particular stereoelectronic needs are present that would force them to adopt boat or twisted conformations.[7] The NMR data of **4A-B**, **6A**, and of other 2-cyanopiperidines have been interpreted so far in terms of chair conformation too (see below).

RESULTS AND DISCUSSION

Nitriles **1A-C** and **2A-C** were from our earlier work[1] and were synthesized according to published procedures.[4,8-10] Compounds **1D-E** were obtained from 2,3-dibromopropionitrile and *N*-benzyl- or *N*,*N'*-

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dibenzylethylenediamine, respectively, by adapting the method of Omodei-Salé and Toja.[11] Nitriles **2D-F** were prepared by condensation of benzaldehyde with the corresponding piperazine derivative, in the presence of NaCN. To our best knowledge, **1D-E** and **2D-F** are all new compounds.[12]

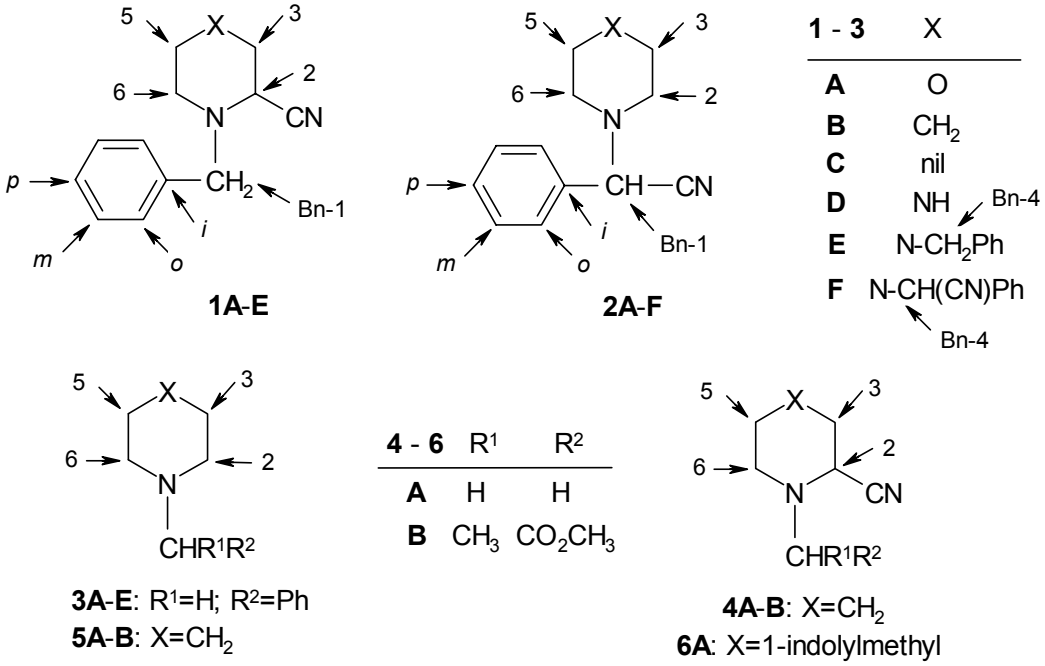

Chart 1

All nitriles discussed in this paper presented a weak IR absorption band around 2240 cm^{-1}, due to the CN group. Barely discernible CN-absorption bands were encountered several times for analogous nitriles.[4,13] The NMR spectra were by far more indicative, as shown below.

Before going into details, some considerations are needed. As both 1-benzyl and 2-cyano substituents in **1A-D** can adopt either *a*xial or *e*quatorial positions, these compounds could exist as two *cis*/*trans* diastereoisomers. Moreover, *cis*-**1A**, -**1B**, and -**1D** could be (*e*)-benzyl-(*a*)-cyano- and/or (*a*,*e*)-conformers. Similarly, the *trans* isomer could have, almost in principle, either an (*e*,*e*)- or an (*a*,*a*)-conformation. The case of **1E** is more complicated, because the additional 4-benzyl substituent induces the possible existence of four diastereoisomers [*cis* (1,2)-*trans* (2,4), *cis*-*cis*, *trans*-*cis*, and *trans*-*trans*], each of them having two conformations. Analogously, **2A-B** and **2D** might be mixtures of 1-(*e*)- and 1-(*a*)-conformers and **2E-F** of 1,4-*cis*/*trans* isomers (four conformers). Additionally, all **1A-E** and **2A-F** should be mixtures of *R*/*S*-enantiomers, as a consequence of the presence of chiral C-2 or benzylic carbon, respectively.

The ^{1}H- and ^{13}C-NMR spectral features of **1A-E** and **2A-F** are presented in Tables 1 and 2, respectively. The assignments were made from two-dimensional NMR experiments, including the long-range ^{1}H-^{13}C heteronuclear correlation. Multiplicity of proton signals is abbreviated as br-broad singlet, d-doublet, dd-doublet of doublets, m-multiplet, qd-quartet of doublets, s-singlet, t-triplet, and td-triplet of doublets. The interproton coupling constants (*J*) are quoted in Table 1 as their absolute values;[14] only absolute values are given and discussed throughout this paper. We reported previously[1] the ^{1}H- and ^{13}C-NMR characteristics of **1A-C** and **2A-C**, but without discussion. The NMR features found by us for **2B** (^{13}C-NMR: Table 2, entry 7) and **2C** (^{1}H-NMR: Table 1, entry 8) agreed well with the corresponding literature data.[4,15] However, our ^{1}H-NMR features of **2B** (Table 1, entry 7) resulted to be slightly different from those claimed elsewhere.[4] Erroneous (^{1}H) or incomplete (^{13}C) NMR spectral data of **2A** have been published very recently.[10,16]

A. Endocyclic derivatives 1A-E

All **1A-E** presented the benzyl protons as AB quartets [Table 1; entries 1-5 (column 2) and footnote *i*]. This anisochronicity is due to the asymmetry induced by the 2-cyano group. More telling was the aliphatic part of the NMR spectra, as presented and discussed in the following.

The ^{1}H-NMR spectrum of **1A** (Table 1, entry 1) was sufficiently resolved to allow full assignment of the observed multiplets. Thus, the doublet at 3.49 ppm was ascribed to H-2, because it was the sole proton in the molecule showing long-range heteronuclear coupling with *both* cyano and benzylic carbon atoms (*i.e.*, 115.3 and 60.2 ppm, respectively; Table 2, entry 1). At the same time, the ^{1}H-^{1}H homonuclear correlation revealed the coupling between H-2 and other two protons (*i.e.*, H-3). These last protons appeared as two distinct 1H-multiplets (3.58 and 3.93 ppm) and were attached on the same carbon atom (*i.e.*, C-3 at 67.6 ppm; Table 2, entry 1). The higher electronegativity of O-4 *vs.* that of N-1 was responsible for the deshielding of H-5 (multiplets at 3.61 and 3.86 ppm) relative to H-6 (multiplets at 2.61 and 2.69 ppm). The same effect was encountered for the corresponding carbon atoms (C-5 at 66.5, C-6 at 48.9 ppm).

Table 1

^{1}H-NMR data (400 MHz, δ, ppm, *J* in Hz, $CDCl_3$, 25°C)[a] of **1A-E**,[b] **2A-F**,[c] **4A-B**,[d] and **6A**[e]

Entry	Compd.	Bn-1	H-2	H_a-6	H_e-6	H_a-3	H_e-3	H_a-5	H_e-5
0	1	2	3	4	5	6	7	8	9
1.	**1A**[f]	3.65[g]	3.49d *(3.2)*	2.69td *(11.6; 3.2)*	2.61d *(11.6)*	3.58dd *(11.2; 3.2)*	3.93d *(11.2)*	3.61td *(11.2; 3.2)*	3.86d *(11.2)*
2.	**1B**[f]	3.57[g]	3.68t *(3.2)*	2.38td *(11.4; 2.8)*	2.74d *(11.4)*	1.48-1.83m (6H)[h]			
3.	**1C**[f]	3.70[g]	3.59m	2.5m (1H) + 2.84m (1H)		1.83m (2H) + 2.0m (2H)			
4.	**1D**	3.57[g]	3.54d *(2.4)*	2.43td *(11.6; 2.4)*	2.63d *(11.6)*	2.92dd *(13.0; 2.4)*	3.05d *(13.0)*	2.78td *(11.6; 2.4)*	2.91d *(11.6)*
5.	**1E**[i]	3.56[g]	3.49d *(2.0)*	2.58-2.60m (2H)		2.20dd *(11.2; 2.0)*	2.80d *(11.2)*	2.17td *(11.2; 4.2)*	2.68dd *(11.2; 1.7)*
6.	**2A**[f]	4.82s	2.58t (4H; *4.6*)			3.65-3.78m (4H)			
7.	**2B**[f,j]	4.82s	2.45-2.57m (4H)			1.53-1.68m (4H)			
8.	**2C**[f]	4.98s	2.64br (4H)			1.82br (4H)			
9.	**2D**	4.80s	2.47br (4H)			2.75-2.90m (4H)			
10.	**2E**[k]	4.84s	2.50br (4H)			2.62br (4H)			
11.	**2F**	4.89s	2.63br (8H)						
12.	**4A**		3.75br	2.35-2.85m (2H)		1.40-1.85m (6H)[h]			
13.	**4B**		3.90br	2.40-3.05m (2H)		1.30-2.10m (6H)[h]			
14.	**6A**		3.80t *(4.0)*	2.20td *(12.8; 2.8)*	2.70td *(3.6; 12.0)*	1.62td *(12.0; 4.2)*	[l]	1.35qd *(12.0; 4.2)*	[l]

[a] Numeration as in Chart 1. Absolute *J* values are quoted (in *italics*) in the order of cited multiplicity. [b] The aromatic protons give a 5H-multiplet at 7.2-7.4 ppm. [c] The aromatic protons yield a 3H-multiplet (7.28-7.45 ppm, H_{meta}+H_{para}) and a 2H-doublet (7.53 ppm, *J*=7 Hz, H_{ortho}). [d] Data at 60 MHz from ref. 4 with our assignments. [e] Data at 200 MHz with Authors' assignments (ref. 6). [f] Data from ref. 1. [g] Center of an AB quartet with J_{AB}=13.0 (**1A**, **1C**-**E**) or 13.2 Hz (**1B**) and Δν=0.16 (**1A**, **1C**) or 0.15 ppm (**1B**, **1D**-**E**). [h] Including the two H-4 protons. [i] The Bn-4 protons appear as an AB quartet centered at 3.46 ppm (J_{AB}=13.1 Hz, Δν=0.11 ppm). [j] The two H-4 protons resonate within 1.42-1.52 ppm. [k] The Bn-4 protons give an AB quartet centered at 3.52 ppm (J_{AB}=13.1 Hz, Δν=0.05 ppm). [l] Both H_e-3 and H_e-5 gave a multiplet extended over 1.74-2.07 ppm.

Considering the well-known order of magnitude of the interproton coupling constants in a cyclohexane-like ring (i.e., $J_{gem} \sim J_{a,a} >> J_{a,e} > J_{e,e}$),[17] it was possible to ascribe the observed multiplets to axial or equatorial protons, as shown in Table 1 (entry 1). At the same time, some *J* values for the aliphatic ^{1}H-^{1}H coupling in **1A** could be written: $J_{6a,6e} \sim J_{6a,5a} \sim J_{5a,5e} \sim$ 11.2-11.6, $J_{6a,5e} \sim J_{6e,5a} \sim J_{2e,3a} \sim$ 3.2, and $J_{3e,3a}$ = 11.2 Hz. Although the signals' shapes and the derived coupling constants suggest an average spectrum, we note that H-2 is significantly coupled to practically only one adjacent H-3, with 3.2 Hz. This value rather corresponds to an *e*-*a* relationship, suggesting therefore an equatorial H-2; otherwise, a doublet of doublets (like H_a-3) or even a doublet with $J \sim$ 11-13 Hz should be seen.[17] In other words, the 2-cyano group seems to be essentially axially located. This implies that **1A** could be either a *cis*-(1-*e*, 2-*a*)- and/or a *trans*-(1-*a*, 2-*a*)-isomer.

Additional information was obtained by the AM1 semiempirical method,[18] by taking the calculated heat of formation (ΔH_f) as a criterion of stability. According to these calculations, *cis*-(1-*e*, 2-*a*)-**1A** is the most stable from all possible four conformers. For instance, it is by 4.4 kJ/mole more stable than *cis*-(1-*a*, 2-*e*)-**1A**. At the same time, *trans*-**1A** is more stable as the (1-*e*, 2-*e*)-conformer than the (1-*a*, 2-*a*)-one ($\Delta\Delta H_f$= 6.2 kJ/mole). In other words, if **1A** contains most probably an axial CN, as indicated by the NMR spectrum, its structure could be best described by a *cis*-(1-*e*, 2-*a*)-structure. However, because the theoretical results must be taken with due caution, we do not exclude some contribution of the *cis*-(1-*a*, 2-*e*)-conformer.

Table 2

^{13}C-NMR data[a] (100 MHz, δ, ppm, $CDCl_3$, 25°C) of the nitriles **1A-E**, **2A-F**, and **4A-B**

Entry	Compd.	Bn-1	C-2	C-6	C-3	C-5	C-4	CN	Aromatics
1.	**1A**[b]	60.2	51.7	48.9	67.6	66.5	-	115.3	127.8, 128.5, 128.7, 135.7 (*i*)
2.	**1B**[b]	60.3	51.7	49.2	28.2	24.6	20.1	116.2	127.2 (*p*), 128.1 (*m*), 128.6 (*o*), 136.6 (*i*)
3.	**1C**[b]	56.4	53.0	51.1	29.4	21.7	-	117.8	127.3, 128.3, 128.7, 137.5 (*i*)
4.	**1D**	60.5	52.3	49.6	47.8	45.0	-	116.1	127.6 (*p*), 128.5 (*o*), 129.0 (*m*), 136.2 (*i*)
5.	**1E**[c]	58.9	50.9	48.2	53.0	51.2	-	115.2	126.2, 126.7, 127.3, 127.5, 127.7, 128.1, 135.5 (*i*), 136.5 (*i*)[d]
6.	**2A**[b]	62.4	49.9		66.6		-	115.2	128.0 (*o*), 128.8 (*m*), 129.1 (*p*), 132.5 (*i*)
7.	**2B**[b]	62.8	50.8		25.7		23.8	115.5	127.7, 128.5, 128.9, 134.5 (*i*)
8.	**2C**[b]	59.1	50.1		23.3		-	115.9	127.4, 127.5, 128.5, 134.1 (*i*)
9.	**2D**	61.7	49.9br		44.7		-	114.7	127.1 (*o*), 127.9 (*p*), 128.0 (*m*), 132.2 (*i*)
10.	**2E**[e]	62.1	49.5br		52.6		-	115.5	127.0, 127.9, 128.2, 128.7, 128.8, 129.0, 133.0 (*i*), 137.9 (*i*)[d]
11.	**2F**	61.9	49.3br				-	115.2	127.8 (*o*), 128.8 (*m*), 129.0 (*p*), 132.6 (*i*)
12.	**4A**[f]		54.4	50.8	28.4	24.5	19.5	116.1	
13.	**4B**[f,g]		50.2, 49.8	46.0, 45.5	29.4, 28.8	24.7	20.3, 20.0	117.1, 116.2	

[a] Numeration as in Chart 1. [b] Data from ref. 1. [c] The Bn-4 carbon appears at 60.9 ppm. [d] C_{ipso} of 4-benzyl ring. [e] The Bn-4 carbon resonates at 62.7 ppm. [f] Data at 15 MHz from ref. 5 with Authors' assignments. [g] Two isomers are present (see text).

The piperidine ring-protons of **1B** (Table 1, entry 2) resonated in four regions. The most deshielded one, a 1H-triplet at 3.68 ppm, was ascribed to H-2, for the same reason as in **1A**. Its apparent multiplicity could be interpreted as a doublet of doublets with identical coupling constants (*i.e.*, $J_{2e,3a} = J_{2e,3e} = 3.2$ Hz). A similar case was found for the analogous proton in **6A** (entry 14).[6] Therefore, H-2 in **1B** resulted to be of equatorial type. The triplet of doublets centered at 2.38 and the doublet at 2.74 ppm could be ascribed to H_a-6 and H_e-6 ($J_{6a,6e} = J_{6a,5a} = 11.4$, $J_{6a,5e} = 2.8$ Hz), respectively, both being deshielded with respect to H-3, H-4, and H-5 due to the closer proximity of the electron-withdrawing N-1 atom. Protons H-6 showed long-range heteronuclear coupling with the benzylic carbon atom (60.3 ppm; Table 2, entry 2). Unfortunately, extensive signal overlapping precluded any determination, by simple inspection, of the chemical shifts and multiplicities for H-3, H-4, and H-5, all resonating within 1.48-1.83 ppm. However, the 2D-NMR experiments suggested 1.79, 1.71, 1.67, 1.53, 1.61, and 1.51 ppm for H_e-3, H_a-3, H_e-4, H_a-4, H_e-5, and H_a-5, respectively. As in the case of **1A**, the AM1 method[18] indicated *cis*-(1-*e*, 2-*a*)-**1B** as being the most stable conformer. Analogous or different structures have been proposed in the literature for other 2-cyanopiperidines. These will be presented later in this section.

All aliphatic protons of the pyrrolidine derivative **1C** (Table 1, entry 3) gave distinct chemical shifts. For instance, H-2 appeared as an unresolved 1H-multiplet at 3.59 ppm with width at half-height (W_H) of 7 Hz. However, as pertinent data on the pyrrolidine-like protons' coupling constants are still lacking, it was not possible to be more specific. The AM1 method[18] indicated a more stable *cis*-isomer than the *trans*-one (by 3 kJ/mole).

Unlike **1B-C**, the ^{1}H-NMR spectra of piperazine derivatives **1D-E** (Table 1, entries 4 and 5, respectively) were better resolved. Consequently, full assignment was possible, unless for H-6 in **1E**. Thus, from the two H-3 protons of **1D** (2.92 and 3.05 ppm), only the former was significantly coupled with the H-2 doublet at 3.54 ppm ($J_{2e,3a} = 2.4$ Hz). This resembles to the previously discussed case of H-2 in **1A**. Inspection of the ^{1}H-NMR data of **1D** allowed assignments for all remaining significant coupling constants: $J_{6a,6e} \sim J_{6a,5a} \sim J_{5a,5e} \sim 11.6$, $J_{6a,5e} \sim J_{6e,5a} \sim 2.4$, and $J_{3a,3e} = 13.0$ Hz. As for **1A-B**, the axial location of the 2-CN group seemed to be favored again. According to AM1 calculations,[18] this is the most stable conformer of **1D**. In fact, *trans*-(1-*e*, 2-*e*)-, *trans*-(1-*a*, 2-*a*)-, and *cis*-(1-*a*, 2-*e*)-**1D** resulted to be *less* stable by 3.3, 5, and 6.7 kJ/mole, respectively. An analogous situation occurred also for **1E**, both spectra and calculations indicating an axial CN group and a possible *cis*-relationship between it and 1-benzyl. The preferred conformation of the 4-benzyl substituent remains, however, unspecified, although the AM1 method indicated a slightly more stable 4-(*e*)-conformer [*i.e.*, *cis*, *trans*-(1-*e*, 2-*a*, 4-*e*)].

Our NMR data of **1B** can be compared with those given in literature for the similar compounds **4A-B**[4,5] and **6A**.[6] The spectral features of the last three nitriles were included in Table 1 (entries 12-14) and Table 2 (entries 12 and 13). No ^{13}C-NMR characteristics were offered for **6A**.[6] When missing, the assignments were made by us, by analogy with our data of **1B**. Unfortunately, the reported ^{1}H-NMR characteristics[4] of **4A-B**

are quite vague. For instance, no W_H values have been offered for the H-2 broad signals. It is worth mentioning that the two sets of ^{13}C-NMR data obtained for the ring-carbons of **4B** were assigned by Koskinen and Lounasmaa[5] to *cis* and *trans* isomers, but without additional specification. In a sharp contrast with our data of **1B**, they claimed also that *e*-CN was the preferred conformation in both isomers of **4B**. Accordingly, **4B** would be a mixture of *trans*-(1-*e*, 2-*e*)- and *cis*-(1-*a*, 2-*e*)-conformers. The Authors based this statement on the comparison of δ_C increments observed on passing from **5B** to **4B** with those originated when an *a*- or *e*-CN group is introduced into the cyclohexane molecule. Two sets of δ_C increments[19,20] are available in the last case. We chose those[19] used by Koskinen and Lounasmaa,[5] in order to have the same reference. The comparison is presented in Table 3, where the data of **4A/5A**,[5] **1B/3B**,[21] **1A/3A**,[21] **1D/3D**,[3] and **1E/3E**,[21] calculated by us, have been included too.

Table 3

Influence of 2-CN group on the NMR δ_C of piperidine-like carbon atoms

Entry	Observed carbon[a]	Differences in δ_C ($CDCl_3$, ppm)[b] Predicted[c] for 2-*a*-CN	2-*e*-CN	Experimental data for the pairs **4B/5B**[d]	**4A/5A**[e]	**1B/3B**[f]	**1A/3A**[f]	**1D/3D**[f]	**1E/3E**[f]
0	1	2	3	4	5	6	7	8	9
1	C-2	0	+1	+0.1; -0.3 (-0.1)	-1.8	-2.5	-1.7	-2.1	-2.2
2	C-3	-1	+3	+3.6; +3.0 (+3.3)	+2.5	+2.5	+0.6	+1.8	-0.1
3	C-4	-5	-2	-3.7; -4.0 (-3.85)	-4.4	-3.1	-	-	-
4	C-5	-1	-2	-1.1; - (-1.1)	-1.4	-1.1	-0.5	-1.0	-1.9
5	C-6	-5	-2	-4.6; -4.1 (-4.35)	-5.4	-5.0	-5.5	-4.8	-4.9

[a] Numeration as in Chart 1. [b] A sign minus signifies a shielding effect. [c] Values from ref. 19 for cyanocyclohexanes/cyclohexane pairs. [d] Single values for each of the two isomers of **4B** *vs.* **5B** (ref. 5); mean values in parenthesis. [e] Calculated using the data of ref. 5. [f] Calculated with the data of **1A**-**B** and **1D**-**E** from Table 2 and with those of **3A**-**B** and **3E** from ref. 21; for **3D** see ref. 3.

More in details, the Authors[5] compared the mean values of column 4 with those predicted for *a*- and *e*-cyanocyclohexane/unsubstituted cyclohexane pairs (columns 2 and 3, respectively). They argued that the +3.3 ppm mean increment of $\delta_{C\text{-}3}$ (entry 2, column 4) is highly indicative for an *e*-CN conformation in **4B**, because it matched better the +3 ppm increment (entry 2, column 3) than that of -1 ppm (entry 2, column 2). However, looking at all mean values listed in column 4, it results that the incriminated increment of $\delta_{C\text{-}3}$ is the only one resembling to the *e*-cyanocyclohexane/cyclohexane pair. All other increments of entries 1 and 3-5 (column 4) fit better the corresponding data of *a*-cyanocyclohexane/cyclohexane pair (column 2). The same holds true for the increments of **4A/5A** (column 5). In our opinion, the conformational deductions of Koskinen and Lounasmaa[5] are quite wrong, just because reasoning on a four-item fit is always more convincing than that based on one-item concordance only. More importantly, the principle itself of this comparison can be seriously questioned. In fact, the ^{13}C-chemical shifts of the parent **5B**, used as a reference for **4B**, belong to an unknown mixture of 1-(*a*)- and 1-(*e*)-**5B**. Accordingly, a reliable comparison should be based on δ_C's of single conformers only.

With all these objections in mind, we still applied the same type of reasoning to **1B**/**3B**. The derived δ_C increments (Table 3, column 6) clearly indicate an essentially *axial* position for the 2-CN group in **1B**, as suggested also by the corresponding ^{1}H-NMR spectrum and AM1 theoretical calculations. The same is true for the pairs **1A**/**3A**, **1D**/**3D**, and **1E**/**3E** (columns 7-9, respectively). We must add here that 4-(1-indolylmethyl)-1-methyl-2-carbonitrilepiperidine (**6A**) exists as a 1-(*e*)-2-(*a*)-4-(*e*)-isomer only.[6] The sterically demanding indolylmethyl group occupies the equatorial position and prevents the molecule to float between more structures. In the corresponding ^{1}H-NMR spectrum (Table 1, entry 14), the equatorial H-2 proton appears at 3.8 ppm as an apparent triplet with J = 4 Hz (*i.e.*, $J_{2e,3e} = J_{2e,3a}$), just like the analogous proton of our **1B**. The other J's (*i.e.*, $J_{3a,3e} = J_{3a,4a} = J_{5a,5e} = J_{5a,4a} = J_{5a,6a} \sim J_{6a,6e} \sim$ 12-13, $J_{5e,6a} \sim J_{5a,6e} \sim J_{5e,6e} \sim$ 2.8-3.6 Hz.) are similar to the corresponding values presented before by **1A**-**B** and **1D**-**E**. Analogous axial preference of a cyano group in other 2-cyanopiperidines has been claimed many other times.[22,23]

In principle, our method of synthesis of **1D**-**E** is not regiospecific. However, it is known that a 11.9/1 mixture (calculated on the isolated yields) of 1-benzyl-4-methyl-2-carbonitrilepiperazine/-3-carbonitrilepiperazine resulted from 2,3-dibromopropionitrile and *N*-benzyl-*N'*-methylethylenediamine.[11] Consequently, starting

from *N*-benzylethylenediamine, mixtures of 2-CN (*i.e.*, **1D**) and 3-CN derivatives might be obtained. Actually, we isolated only **1D** and all attempts to separe its 3-CN isomer from the respective mother liquors or to put it in evidence by NMR were unfruitful. However, the modest yield of **1D** might hide the concomitant formation of 3-CN derivative, although in a presumably much lower amount. Obviously, only one endocyclic nitrile (*i.e.*, **1E**) can result from the symmetrical *N*,*N'*-dibenzylethylenediamine.

We did not expect any stereospecificity for the aforementioned method of synthesis of **1D-E**. Accordingly, mixtures of *cis* and *trans* stereoisomers might account for these compounds. However, the experimental NMR data and AM1 calculations suggested that **1D-E** are mainly *cis*-(1,2)-isomers with an axial cyano group. In other words, the adopted synthesis might have some stereospecificity, but, at this moment of our research, we are far from a precise statement. A future study[24] should clarify if epimerization[22,23] at the C-2 level did occur during the work-up or sample purification. A particular attention should be also paid to the optical purity of the synthesized nitriles.[24] In fact, as mentioned before, **1A-E** have a chiral C-2 carbon atom and, consequently, they must exist as *R*/*S*-enantiomers. Similar enantiomerism should be also shown by **2A-F** because of the presence of chiral benzylic carbon atom.

B. Exocyclic derivatives 2A-F

Compounds **2A-E** presented the Bn-1 proton as a 1H-singlet around 4.9 ppm, strongly deshielded by three adjacent electron-withdrawing substituents: N atom, CN group, and phenyl ring [Table 1, entries 6-10 (column 2), respectively]. Only one 2H-singlet (at 4.89 ppm) was observed for the identical Bn-1 and Bn-4 protons (see Chart 1) of **2F** (entry 11). The aliphatic ring-protons H-2 and H-6 of **2A-F**, as well as H-3 and H-5, are identical by symmetry. They gave multiplets and/or broad singlets, as a consequence of two factors acting in the same direction, namely (i) chair-chair interconversion of the aliphatic ring, a process too rapid at room temperature for the NMR time scale, and (ii) the asymmetry induced by the chiral benzylic carbon atom. The relative broadening of the C-2+C-6 carbon signals in **2D-F** (Table 2, entries 9-11, respectively) might be due mainly to (ii).

Protons H-2+H-6 appeared in **2A** as a resolved 4H-triplet (Table 1, entry 6). The corresponding coupling constant (*i.e.*, 4.6 Hz) was identical to that in the parent *N*-benzylmorpholine (**3A**).[21] Clearly, H_a-2 and H_e-2 are indistinguishable in both **2A** and **3A**. To the contrary, H-3+H-5 in **2A** covered a wider zone than that in **3A**, indicating that some difference between axial and equatorial protons began to exist. Analogous signal enlargement occurred for all aliphatic protons in **2B** (entry 7), when compared with the corresponding protons in *N*-benzylpiperidine (**3B**).[21] Both **3A-B** are mixtures of *e*- and *a*-conformers and this is true also for **2A-B**. However, the mentioned spectral differencies suggest that *e*/*a* ratios could be instead slightly different in **2A-B** *vs*. those in **3A-B**. In fact, taking the **2A**/**3A** pair as an example, the AM1 method[18] indicated that *e*-**3A** is more stable by 2.75 kJ/mole than *a*-**3A**, but *e*-**2A** by 5.25 kJ/mole than *a*-**2A**. In other words, the percentage of *e*-conformer in the average NMR spectrum of **2A** might be higher than that of *e*-**3A** in the corresponding spectrum of **3A**. Analogous situation occurred for the **2B**/**3B** pair. This is not surprising, because the cyanobenzyl group in **2A-B** is larger than the benzyl substituent in **3A-B** and it would prefer into a higher extent to occupy the more stable *e*-location.

Extensive signal broadening of all aliphatic ring-protons in **2C-F** precluded any discrimination between axial and equatorial hydrogen atoms (Table 1, entries 8-11, respectively). Interestingly, the Bn-4 benzylic protons in **2E** (see Chart 1), an AB quartet centered at 3.52 ppm (see footnote *k* of Table 1), felt the remote asymmetry due to the chiral 1-substituent. The aliphatic ring-protons in **2F** yielded an unique, relatively broad 8H-singlet at 2.63 ppm (entry 11), resembling to the case of structurally similar *N*,*N'*-dibenzylpiperazine (**3E**).[21] All these data are consonant to the existence of **2A-F** as mixtures of rapidly interconverting 1-*e*- and 1-*a*-conformers.

CONCLUSIONS

Two types of *N*-α-cyanoazacycloalkanes derived from *N*-benzylmorpholine, -piperidine, -pyrrolidine, -piperazine, and *N*,*N'*-dibenzylpiperazine were unambiguously synthesized and characterized by ^{1}H- and ^{13}C-NMR spectroscopy. They differed by the location of the cyano group, namely at the aliphatic ring-carbon (**1**) or in the benzylic position (**2**). The NMR features of **1** were rather consistent with 2-(*a*xial)-cyano-structures.

Semiempirical AM1 calculations supported this deduction and favored the *cis*-(1-*e*-benzyl, 2-*a*-cyano) conformers. The benzyl protons in **1** appeared as AB quartets due to the CN-induced asymmetry. The NMR characteristics of **2** indicated the existence of both 1-*e* and 1-*a* conformers. The aliphatic protons of **2** gave multiplets and/or broad singlets, as a consequence of chair-chair interconversion of the aliphatic ring, a process too rapid at room temperature for the NMR time scale, and/or of the asymmetry induced by the chiral Ph-*C*H-CN atom. The latter factor could be the main responsible for the broadening of the aliphatic (*N*-α)-*C* carbon signals in some **2**.

EXPERIMENTAL PART

General. Melting points were taken on a Boetius hot plate and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were registered on a Bruker Avance DRX 400 instrument. Chemical shifts are quoted in Tables 1 and 2 relative to internal (CH_3)$_4$Si (0 ppm) and CDCl$_3$ (77.01 ppm), respectively. IR spectra were taken in $CHCl_3$ with an UR-20 Carl Zeiss Jena spectrophotometer.

Materials and warnings. *N*-Benzylethylenediamine, *N,N'*-dibenzylethylenediamine, 2,3-dibromopropionitrile, and anhydrous piperazine were used as purchased from Aldrich. $CDCl_3$ was supplied by ITIMCD (Cluj-Napoca, Roumania). Compounds **1A**-**C**[1] and **2A**-**C**,[1] as well as *N*-benzylpiperazine (**3D**),[21,25] were from our earlier works. Syntheses of new **1D**-**E** and **2D**-**F** are presented below; their ^{1}H- and ^{13}C-NMR spectral properties were quoted in Tables 1 and 2, respectively. All newly prepared compounds presented satisfactory elemental analyses (± 0.3%) for C, H, and N. Sodium cyanide was used to prepare **2D**-**F**. **Caution!** Sodium cyanide is highly toxic. Care should be taken to avoid direct contact of the chemical or its solutions with the skin, and impervious gloves should be worn to handle the reagent.

1-Benzyl-2-carbonitrilepiperazine (**1D**). To a stirred solution of 2,3-dibromopropionitrile (0.5 mL; 4.5 mmole) in benzene (10 mL) was added dropwise, at room temperature, a solution of *N*-benzylethylenediamine (675 mg; 4.5 mmole) and Et_3N (1.4 mL; 10.1 mmole) in 10 mL of benzene. The mixture was stirred and heated at reflux for three hours. The precipitated white solid (Et_3N.HBr, 1.62 g; 99% of the theoretical amount) was separated by filtration and the filtrate was washed with water, anhydrized (Na_2SO_4), and then freed from solvent *in vacuo*. The residue was triturated with a little ether and the resulted colorless solid was recrystallized from petroleum ether (bp 60-90°C) to give 0.5 g (yield 55%) of **1D**, melting at 98-99°C.

1,4-Dibenzyl-2-carbonitrilepiperazine (**1E**) was prepared similarly to **1D**, starting from *N,N'*-dibenzylethylenediamine (2.16 g; 9 mmole). After cooling at room temperature, the precipitated solid (Et_3N.HBr, 2.94 g; 90% of the theoretical amount) was filtered off and the filtrate was washed with water, anhydrized (Na_2SO_4), and then freed from solvent *in vacuo*. The residue (2.55 g) was triturated with aqueous 1M HCl (22 mL) and the resulted solid (1.22 g) was separated by filtration. Acidic water was extracted with $CHCl_3$ and the organic layer left another portion (0.81 g) of the same solid after solvent evaporation. The remaining aqueous solution, after basification and $CHCl_3$-extraction, gave back 0.22 g (0.9 mmole; 10% recovery) of the starting ethylenediamine derivative. The combined solids (2.03 g) separated before were treated with aqueous NaOH and taken up in CH_2Cl_2. The anhydrized (Na_2SO_4) organic layer was freed from solvent to leave **1E** (1.82 g; 77% yield, calculated with respect to the reacted substrate), as colorless crystals melting at 44-47ºC. The analytical sample had mp of 47-49ºC after recrystallization from petroleum ether (bp 30-60ºC).

2-(1-Piperazinyl)-2-phenylacetonitrile (**2D**) and **1,4-piperazinediylbis[2-(2-phenylacetonitrile)]** (**2F**). To 0.94 mL (9.4 mmole) of benzaldehyde, a 35.5% $NaHSO_3$ solution (1.95 mL, 9.4 mmole) was added, followed by 5 mL of water in order to facilitate the stirring. To this mixture, 0.81 g (9.4 mmole) of anhydrous piperazine was added and the new mixture was stirred for 30 minutes at room temperature. A solution of NaCN (0.5 g; 10.2 mmole) in 2 mL of water was added and the whole mixture was stirred for one hour at 50ºC. The heterogeneous mixture was extracted with 5x10 mL of $CHCl_3$ and the combined organic layers were washed with 3×10 mL of aqueous HCl (3.6%) to give organic (I) and aqueous (II) mixtures. Mixture I was washed with some NaOH solution, anhydrized (Na_2SO_4), and evaporated to leave 0.44g (yield 30%, calculated with respect to benzaldehyde as a limiting reagent) of **2F** as colorless crystals melting at 112-114ºC after recrystallization from ethanol.

Mixture II was basified with NaOH and extracted with $CHCl_3$. The new organic extract, anhydrized over Na_2SO_4, was evaporated *in vacuo* to give colorless crystals of **2D** (1g; yield 53%, calculated with respect to piperazine as a limiting reagent), melting at 65-67ºC after recrystallization from petroleum ether (bp 30-60°C).

2-(4-Benzyl-1-piperazinyl)-2-phenylacetonitrile (**2E**). (A) It was obtained analogously to **2D**+**2F**, employing 1.04 g (5.91 mmole) of **3D**. The cooled reaction mixture was filtered from some white solid and then extracted with 2×5 mL of CH_2Cl_2. The organic layer, anhydrized (Na_2SO_4) and freed from solvent *in vacuo*, gave 1.15 g (yield 67%) of **2E**, as colorless crystals melting at 98-100°C (from petroleum ether, bp 60-90°C). (B) The method indicated[10] for **2A** was followed, starting from **3D**, benzaldehyde, sodium cyanide, and a little $CoCl_2$. The yield in **2E** was 65%.

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REFERENCES

1. H. Petride, C. Drăghici, C. Florea and A. Petride, *Central Eur. J. Chem.*, **2004**, *2*, 302-322.
2. H. Petride, O. Costan, C. Drăghici, C. Florea and A. Petride, *ARKIVOC*, **2005**, *(x)*, 18-32 (http://www.arkat-usa.org/ark/journal/2005/I10_Balaban/1275/AB-1275B.pdf).

3. H. Petride, O. Costan, C. Florea and A. Petride, in preparation.
4. A. Koskinen and M. Lounasmaa, *Tetrahedron*, **1983**, *39*, 1627-1633.
5. A. Koskinen and M. Lounasmaa, *Heterocycles*, **1983**, *20*, 563-569.
6. J. Bosch, M. Feliz and M. L. Bennasar, *Tetrahedron*, **1984**, *40*, 1419-1424.
7. A boat conformation might be eventually considered for more encumbered substrates, like the *trans*-*N*-*tert*-butyl analog of **1**. See for example R. Lafrance, J. P. Aycard, J. Berger and H. Bodot, *Org. Magn. Reson.*, **1976**, *8*, 95-101.
8. T. K. Yang, S. T. Yeh and Y. Y. Lay, *Heterocycles*, **1994**, *38*, 1711-1715.
9. H. Moehrle and R. Feil, *Tetrahedron*, **1971**, *27*, 1033-1041.
10. S. K. De, *Beilstein J. Org. Chem.*, **2005**, *1*:8 (http://bjoc.beilstein-journals.org/content/1/1/8).
11. A. Omodei-Salé and E. Toja, *Farmaco*, **1975**, *30*, 650-665.
12. Compound **1E** is mentioned in the literature, but without physical characterization or details about its preparation (see T. Morie, S. Kato, H. Harada, N. Yoshida, I. Fujiwara and J. Matsumoto, *Chem. Pharm. Bull.*, **1995**, *43*, 1137-1147).
13. See for instance, G. N. Walker, A. R. Engle and R. J. Kempton, *J. Org. Chem.*, **1972**, *37*, 3755-3770.
14. It is well known that all vicinal interproton coupling constants ($J_{a,a}$, $J_{a,e}$, $J_{e,e}$) in cyclohexane-like structures are positive, but J_{gem} is large and negative.
15. A. Jonczyk, D. Lipiak and T. Zdrojewski, *Tetrahedron*, **1990**, *46*, 1025-1038.
16. The Author (see reference 10) recognized his mistake (personal communication).
17. In absolute values, $J_{gem} \sim J_{a,a}$, $J_{a,e}$, and $J_{e,e}$ are in the ranges of 8-13, 2-6, and 1-4 Hz, respectively. Always, $J_{a,e} \geq J_{e,e}$. See for instance, L. M. Jackman and S. Sternhell, *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, Oxford, 2nd edition, **1969**, pp. 275 and 288.
18. J. J. P. Stewart, *QCPE* 581.
19. E. Breitmaier and W. Voelter, *^{13}C NMR Spectroscopy: Methods and Applications in Organic Chemistry*, Verlag Chemie, Weinheim, 2nd edition, **1978**, p. 210 (Table 4.59). A regrettable error occurred. According to the indicated literature (see H. J. Schneider and V. Hoppen, *Tetrahedron Lett.*, **1974**, 579-582), the δ_C increments of C-α (our C-2) given in Table 4.59 should be inverted.
20. H. J. Schneider and V. Hoppen, *J. Org. Chem.*, **1978**, *43*, 3866-3873.
21. H. Petride, A. Corbu, O. Costan, C. Florea, V. Marin, A. Petride and E. Şerban, *Rev. Roum. Chim.*, **2005**, *50*, 633-640.
22. M. Bonin, J. R. Romero, D. S. Grierson and H. P. Husson, *Tetrahedron Lett.*, **1982**, *23*, 3369-3372.
23. M. Bonin, R. Besselièvre, D. S. Grierson and H. P. Husson, *Tetrahedron Lett.*, **1983**, *24*, 1493-1496.
24. H. Petride, work in progress.
25. M. Căproiu, C. Florea, C. Galli, A. Petride and H. Petride, *Eur. J. Org. Chem.*, **2000**, 1037-1043.