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SOME *N*-MONO- AND *N*, *N*'-DISUBSTITUTED DERIVATIVES OF 2-PIPERAZINECARBONITRILE

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Five new 4-R^1-mono- and 1-R^1-4-R^2-disubstituted derivatives (R^1, R^2 = benzyl, benzoyl) of 2-piperazinecarbonitrile were synthesized and fully characterized by PMR and CMR spectral methods. By comparison with model compounds, a preferred axial position was advanced for the cyano group. Substitution of the aminic hydrogen atom by a benzyl or benzoyl group affected the NMR chemical shifts of all piperazine atoms. Careful spectral analysis gave the respective $\Delta\delta_H$ and $\Delta\delta_C$ increments, useful in stereochemical assignments. The protons in α with respect to the introduced *N*-benzyl group were shielded by about 0.4 ppm and the corresponding carbons deshielded by about 6 ppm. The most affected were the axial *N*-α-protons ($\Delta\delta_H \sim 0.55$ ppm). If the *N*-substituent was benzoyl, the piperazine *N*-α-protons were largely deshielded, especially those *pseudo*-equatorially located (by 1.0-1.1 ppm). The NMR shifts were interpreted in terms of through-bond (*i.e.*, inductive) and through-space effects exerted by the introduced *N*-substituent.

INTRODUCTION

During our studies on the RuO_4-catalyzed oxidation of *N*-benzyl- or *N*-benzoylpiperazine in the presence of NaCN,[1] the corresponding *N'*-α-CN derivatives seemed to be formed. This derived from the careful analysis of the NMR spectra of crude reaction mixtures. Owing to the mechanistic implications, we need to know unequivocally the NMR features of these α-aminonitriles. We report in this paper the unambiguous synthesis of the desired compounds and their NMR characterization.

Starting from 2-piperazinecarbonitrile (**1**) and considering benzyl and benzoyl groups as *N*-substituents, the structures **2**-**9** can be formally derived (Chart 1). A part the previously[2] studied **2** and **3**, the remaining derivatives **4**-**9** resulted to be new compounds. As shown below, only **4**-**8** were successfully obtained in pure state (Section A). The PMR and CMR spectra of **1** and **4**-**8** were studied in detail with full assignments (Section B).

RESULTS AND DISCUSSION

A. Synthesis

The parent compound of the studied series, 2-piperazinecarbonitrile (**1**), was obtained from its dihydrochloride (**1.2HCl**), which was prepared at its turn from ethylenediamine and 2-chloroacrylonitrile, as described in the literature.[3] Analogous treatment of *N*-benzyl- or *N*,*N'*-dibenzylethylenediamine afforded the benzylated piperazines **2** or **3**, respectively, in yields around 80%. Both **2** and **3** were previously obtained by us[2] by using 2,3-dibromopropionitrile as a CN-containing reaction partner. However, the present method proved to give cleaner reaction mixtures, easier work-up protocol and better yields. This was probably mainly due to the higher purity of the starting nitrile. In fact, commercial 2-chloroacrylonitrile is 99% pure, but 2,3-dibromopropionitrile only 90%, the main impurity being 3-bromopropionitrile (~ 5%).

It is known[4] that the condensation of *N*-benzyl-*N'*-methylethylenediamine with 2,3-dibromopropionitrile yields 1-benzyl-4-methyl- *and* 4-benzyl-1-methyl-2-piperazinecarbonitrile, in an isolated ratio of 11.9/1. Accordingly, both isomers **2** and **4** were expected to be formed from the analogous reaction of *N*-benzylethylenediamine. However, in our hands, 1-benzyl-2-piperazinecarbonitrile (**2**) resulted only, regardless the nature of the starting nitrile (*i.e.*, 2,3-dibromopropionitrile or 2-chloroacrylonitrile). Consequently, the desired 4-benzyl-2-piperazinecarbonitrile (**4**) was prepared by another method, namely by treating **1** with benzyl chloride. Although the reaction mixture

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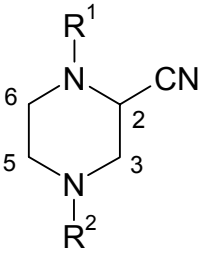
proved to be quite complex, compound **4** was the main reaction product when the benzylation was performed in ethanol and in the presence of $NaHCO_3$ as a base. It was isolated by column chromatography.



1 - 9

Bn = benzyl
Bz = benzoyl

	R^1	R^2
1	H	H
2	Bn	H
3	Bn	Bn
4	H	Bn
5	Bn	Bz
6	Bz	Bn
7	H	Bz
8	Bz	Bz
9	Bz	H

Chart 1

Benzoylation of **2** or **4** with benzoyl chloride and in the presence of triethylamine as an HCl-scavenger yielded the expected benzamide (*i.e.*, **5** or **6**, respectively). Similar reaction with **1** as a starting amine gave mixtures of **7**-**9**, but their isolation was complicated by the presence of Et_3N or its hydrochloride. Although 1,4-dibenzoyl-2-piperazinecarbonitrile (**8**) was the main reaction product, the method was abandoned, owing to the too laborious work-up required. However, **8** and a monobenzoyl derivative of **1** were successfully isolated from the reaction mixture obtained from **1** and benzoyl chloride under modified Schotten-Baumann conditions. We ascribed to the monobenzoylated derivative the structure of 4-benzoyl-2-piperazinecarbonitrile (**7**). This was substantiated on its NMR features (see later), but a conclusive proof came from the nature of its *N'*-benzylated derivative, proved to be **5** and not **6**. In all benzoylation attempts of **1**, the crude reaction mixtures contained also another minor compound, believed to be **9**, but we were unable to isolate it.

All nitriles **1**-**8** presented barely discernible IR absorption band around 2230 cm^{-1} due to the CN group. This is a common situation for many aliphatic nitriles.[5-7] The NMR spectra of **1**-**8** were by far more indicative, as presented and discussed in the next section.

B. NMR Spectra

The ^{1}H- and ^{13}C-NMR characteristics of **1**-**8** (in $CDCl_3$) were listed in Tables 1 and 2, respectively, together with our assignments. The chemical shifts were quoted with respect to those of internal $Si(CH_3)_4$ ($\delta_H = 0$ ppm) and $CDCl_3$ ($\delta_C = 77.36$ ppm),[8] respectively. The spectral features of **1.2HCl** (in D_2O) were appended too in Tables 1 and 2. In this case, the proton chemical shifts were related to that of the residual H_2O, taken at 4.76 ppm. For all compounds, the assignments were made by two-dimension NMR (2D-NMR) experiments, including the ^{1}H-^{13}C long-range heterocorrelation. All these data are new, except those already reported by us[2] belonging to **2** and **3**. Equally known[3] are the ^{1}H-NMR characteristics of **1.2HCl**, but our data were slightly different, as presented below. Actually, this was the reason which suggested us to include the spectral features of **1.2HCl** in Tables 1 and 2.

The following ^{1}H-NMR data have been reported so far for **1.2HCl** (in D_2O, δ scale, $J_{H,H}$ in Hz), without assignements: 4.72 (t, J = 4.0, 1H), 3.57 (dd, J = 12.0 and 4.0, 2H), 3.2-3.4 ppm (m, 4H).[3] It seems therefore that the mentioned chemical shifts belong to H-2, $H_{A,B}$-3, and $H_{A,B}$-5 + $H_{A,B}$-6, respectively. Generally speaking, these chemical shifts are all high-field shifted by about 0.2 ppm than our data (Table 1, entry 1). We do not pay much attention to this shift, since the Authors[3] did not specify the reference employed. In our case, the 2D-NMR experiments showed the sole C*H* proton in the molecule (*i.e.*, H-2; δ_H = 4.96 ppm) as being connected to the carbon atom resonating at 43.3 ppm (*i.e.*, C-2). The chemical shifts belonging to the other protons and carbons (all of CH_2 type) were assigned similarly. At variance with the literature data,[3] the complex multiplet due to the two H-3 protons (3.71-3.83 ppm) could be rationalized as two overlapping doublets of doublets, centered at 3.76 and 3.78 ppm.

They have in common a large coupling constant of 14.5 Hz, ascribed by us to $^2J_{3A,3B}$, the constant of geminal[9] coupling between H_A-3 and H_B-3. The other coupling constants are smaller, of similar magnitude, but different (*i.e.*, 4.6 and 5.4 Hz). These should be the vicinal coupling constants[10] with H-2. In fact, irradiation of the H-2 signal transformed the 3.71-3.83 ppm-region into two partially overlapping doublets. Obviously, $^2J_{3A,3B}$ was not affected in this case. Interestingly, the signal of H-2 in **1.2HCl** was a triplet with J = 5.0 Hz and not the required doublet of doublets with $^3J_{2,3A}$ = 5.4 and $^3J_{2,3B}$ = 4.6 Hz. We note however that the experimental value of 5 Hz is the mean of the expected values. In other words, the signal of H-2 might be a masked doublet of doublets, provided the difference of 0.8 Hz between the two coupling constants was too small to be seen in our experimental conditions. A similar situation was presented by the analogous protons in **4** (see later).

In principle, the piperazines **1**-**4** could be mixtures of several conformers. Thus, confining our discussion only to the more stable chair conformation for the piperazine ring, compounds **1**, **2** (or **4**), and **3** could be present as two, four, and eight conformers, respectively. They derive from the different axial (*a*) or equatorial (*e*) locations of CN (for **1**-**4**) and benzyl group(s) (for **2**-**4**). More specifically, compound **1** might be 2-*a*- (**1A**) and/or 2-*e*-piperazinecarbonitrile (**1B**), as depicted in Chart 2. The structures of the conformers of **2**-**4** can be easily deduced. As the syntheses of **1**-**4** were not stereospecific, at least in principle, the conformers with *a*-CN *and* those with *e*-CN could result for all compounds **1**-**4**. The sterically demanding benzyl groups in **2**-**4** might occupy the equatorial position, but an axial location can not be excluded *a priori* at least for R^1 = benzyl in **2** or **3**, due to the mutual interaction with the vicinal CN group. Moreover, the passage from a conformer to another could be easy if the energetic barrier to be climbed is not so high. For instance, the *N*,*N'*-unsubstituted piperazine **1** could fluctuate between **1A** and **1B**. Therefore, several conformers of **1**-**4** might be present during their NMR investigation, either as a synthetic result or as a dynamic equilibrium.

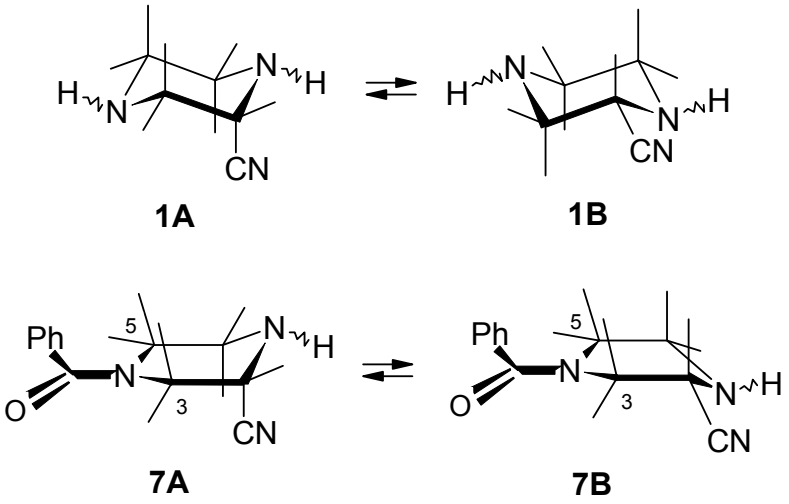


Chart 2

The case of the benzoylated derivatives **5**-**8** could be more complicated, owing to the hindered rotation about the N-CO amide bond. It is well-known that this rotation is usually slow enough for the NMR-time scale (*i.e.*, the barrier to rotation is sufficiently high), thus allowing the concomitant existence of both *E* and *Z* isomers. The interested nitrogen atom is no longer of sp^3 pyramidal type as in **1**-**4**, but more flattened, tending to become of sp^2 planar type. This means that the piperazine ring in **5**-**8** has a *pseudo*-chair conformation, as depicted in Chart 2 for *Z*-**7**. In this particular case, the hydrogen atoms in positions 3 and 5 are no more true axial and equatorial protons. This might influence their interproton coupling constants, since, among other factors, the dihedral angles are different with respect to those in a true chair conformation. These considerations, as well as those of the precedent paragraph, suggested us to label the piperazine ring-protons in **1**-**8** as H_A or H_B and not as H_a or H_e (Table 1). All these stereochemical considerations will serve us to interpret properly the experimental NMR features discussed below.

Table 1

^{1}H-NMR data[a] (300 MHz, $CDCl_3$, δ, ppm, 25°C, $J_{H,H}$ in Hz)[b] of compounds **1-8** and assignments[c]

Entry	Compd.	H-2	H_A-3 + H_B-3	H_A-5 + H_B-5	H_A-6 + H_B-6	Bn[d]
1.	**1.2HCl**[e]	4.96t (*5.0*)	H_A + H_B: 3.71-3.83m H_A: 3.76dd (*14.5, 5.4*) H_B: 3.78dd (*14.5, 4.6*)	H_A + H_B: 3.39-3.63m	H_A + H_B: 3.39-3.63m	-
2.	**1**	3.85t (*3.3*)	H_A + H_B: 3.00d (*3.3*)	H_A: 2.71-2.80m (~ 2.76[f]) H_B: 2.85-2.89m (~ 2.87[f])	H_A: 2.93-3.03m (~ 2.98[f]) H_B: 2.71-2.80m (~ 2.76[f])	-
3.	**2**[g]	3.54d (*2.4*)	H_A: 2.92dd (*13.0*, *2.4*) H_B: 3.05d (*13.0*)	H_A: 2.78ddd (*11.6*, *11.6*, *2.4*) H_B: 2.91d (*11.6*)	H_A: 2.43ddd (*11.6*, *11.6*, *2.4*) H_B: 2.63d (*11.6*)	3.57 (*13.0*; 0.14)
4.	**3**[g]	3.49d (*2.0*)	H_A: 2.20dd (*11.2*, *2.0*) H_B: 2.80d (*11.2*)	H_A: 2.17ddd (*11.2*, *11.2*, *4.2*) H_B: 2.68dd (*11.2*, *1.7*)	H_A + H_B: 2.58-2.60m	3.56 (*13.0*; 0.15)[h] 3.46 (*13.1*; 0.11)[i]
5.	**4**	3.88t (*3.5*)	H_A: 2.38dd (*11.4*, *3.9*) H_B: 2.75dd (*11.4*, *3.1*)	H_A: 2.24ddd (*11.2*, *9.7*, *3.2*) H_B: 2.63ddd (*11.2*, *3.3*, *1.1*)	H_A: 3.13ddd (*11.9*, *9.7*, *3.3*) H_B: 2.81ddd (*11.9*, *3.2*, *1.1*)	3.49 (*13.3*; 0.09)
6.	**5**	3.55br	H_A: 3.13br H_B: 4.1-4.8br	H_A: 3.00br H_B: 4.1-4.8br	H_A: 2.56ddd (*11.8*, *11.8*, *3.3*) H_B: 2.72br	3.60 (*13.0*; 0.19)
7.	**5**[j]	3.56br	H_A: 3.14dd (*13.4*, *3.2*) H_B: 4.0-4.3br (~ 4.20[f])	H_A: 2.99ddd (*13.0*, *11.8*, *3.6*) H_B: 4.0-4.3br (~ 4.17[f])	H_A: 2.57ddd (*11.8*, *11.8*, *3.4*) H_B: 2.71dm (J_{app}=*12.1*)	3.61 (*13.0*; 0.17)
8.	**6**	5.3-5.7br	H_A: 2.32dm (J_{app}=*11.0*) H_B: 3.10dm (J_{app}=*11.6*)	H_A: 2.16ddd (*11.4*, *11.4*, *3.2*) H_B: 2.85 dm (J_{app}=*11.5*)	H_A: 3.4-3.6br H_B: 3.8-4.2br	3.61 (*13.4*; 0.09)
9.	**6**[j]	5.40br	H_A: 2.32dd (*11.9*, *3.5*) H_B: 3.10d (*11.9*)	H_A: 2.17ddd (*11.8*, *11.7*, *3.3*) H_B: 2.86d (*11.7*)	H_A: 3.48ddd (*13.2*, *11.8*, *3.5*) H_B: 3.90br d (J_{app}=*12.0*)	3.61 (*13.4*; 0.09)
10.	**7**	3.9-4.0br	H_A: 3.36dd (*13.3*, *3.3*) H_B: 4.2-4.6br	H_A: 3.1-3.3m H_B: 4.2-4.6br	H_A: 3.1-3.3m H_B: 2.6-2.9br	-
11.	**7**[j]	3.94t (*3.3*)	H_A: 3.40dd (*13.3*, *3.3*) H_B: 3.96-4.17br (~ 4.11[f])	H_A: 3.16ddd (*10.2, 10.2, 2.9*) H_B: 3.96-4.17br (~ 4.01[f])	H_A: 3.09ddd (*10.2, 10.2, 2.4*) H_B: 2.83-2.89m (~ 2.86[f])	-
12.	**8**	5.4-5.6br	H_A: 3.25-3.37br d H_B: 4.2-4.9br	H_A: 2.9-3.1br t H_B: 4.2-4.9br	H_A: 3.4-3.55br t H_B: 3.9-4.15br	-
13.	**8**[j]	5.46br	H_A: 3.26dd (*13.8*, *3.5*) H_B: 4.3-4.5br (~ 4.43[f])	H_A: 2.96ddd (*13.2*, *12.5*, *3.3*) H_B: 4.3-4.5br (~ 4.37[f])	H_A: 3.45ddd (*13.2*, *12.9*, *3.4*) H_B: 4.06dm (J_{app}=*13.0*)	-

[a] When present, the aromatic protons give a multiplet in the region 7.2-7.55 ppm. [b] Absolute values of *J*'s are given only (in parenthesis, in *italics*). [c] Bn stands for benzylic protons; br means a broad singlet, unless otherwise noted. [d] Center of an AB quartet; J_{AB} (Hz, in *italics*) and Δν (ppm) are given in parenthesis. [e] In D_2O as a solvent. [f] Center of a broad signal, as deduced from 2D-NMR experiments. [g] Data from ref. 2. [h] Values of R^1. [i] Values of R^2. [j] Data at 62°C.

Table 2

^{13}C-NMR data[a] (75 MHz, $CDCl_3$, δ, ppm, 25°C) of compounds **1-8** and assignments

Entry	Compd.	C-2	C-3	C-5	C-6	CN	Bn[b]	CO	Aromatic C's (*o*, *m*, *p*, *i*)
1.	**1.2HCl** [c]	43.3	43.7	42.3	40.4	115.1	-	-	-
2.	**1**	46.9	48.4	45.6	43.5	119.6	-	-	-
3.	**2** [d]	52.7	48.2	45.4	50.0	116.5	60.9	-	128.0 (*p*), 128.9 (*o*), 129.4 (*m*), 136.6 (*i*)
4.	**3** [d]	51.3	53.4	51.6	48.6	115.6	59.3,[e] 61.3[f]	-	126.6, 127.1, 127.7, 127.9, 128.1, 128.5, 135.9 (*i*),[e] 136.9 (*i*)[f]
5.	**4**	46.7	54.8	53.0	43.2	119.8	62.7	-	127.5 (*p*), 128.6 (*o*), 129.1 (*m*), 137.7 (*i*)
6.	**5**	51.7	[g]	[g]	48.8	114.9	60.3	171.4	127.5, 128.4 (*p*), 128.9, 129.0, 129.5, 130.3 (*p*), 135.1 (*i*), 135.9 (*i*)
7.	**5** [h]	51.9	47.3br	44.5br	48.9	114.9	60.4	171.4	127.6, 128.4 (*p*), 128.9, 129.1, 129.5, 130.3 (*p*), 135.4 (*i*), 136.2 (*i*)
8.	**6**	[i]	54.0	52.4	[i]	117.3	62.1	170.6	127.5, 127.9 (*p*), 128.9, 129.0, 129.2, 131.0 (*p*), 134.1 (*i*), 137.0 (*i*)
9.	**6** [h]	45.7br	54.1	52.3	42.8br	117.2	61.8	170.6	127.4, 127.7 (*p*), 128.7, 128.9, 129.1, 130.7 (*p*), 133.8 (*i*), 136.8 (*i*)
10.	**7**	46.2	[g]	[g]	42.2	118.2	-	171.2	127.3 (*o*), 128.8 (*m*), 130.1 (*p*), 135.0 (*i*)
11.	**7** [h]	46.2	46.9br	43.0br	42.5	118.1	-	171.0	127.1 (*o*), 128.6 (*m*), 130.1 (*p*), 135.2 (*i*)
12.	**8**	[i]	~ 48br	~ 44br	[i]	116.0	-	171.0, 171.6	127.58, 127.63, 129.1, 129.3, 130.8 (*p*), 131.5 (*p*), 133.8 (*i*), 134.5 (*i*)
13.	**8** [h]	[i]	47.4br	43.9br	[i]	115.9	-	170.9, 171.6	127.5, 127.6, 129.0, 129.3, 130.7 (*p*), 131.4 (*p*), 133.7 (*i*), 134.4 (*i*)

[a] A broad signal is abbreviated as br. [b] Benzylic carbon. [c] In D_2O as a solvent. [d] Data from ref. 2, recalculated for δ_{CDCl3} = 77.36 ppm. [e] Value of R^1. [f] Value of R^2. [g] Very broad signal at 42-50 ppm. [h] Data at 62°C. [i] Unobserved.

The PMR data of the free base **1** (Table 1, entry 2) showed the H-2 signal (3.85 ppm) as a doublet (J = 3.3 Hz), coupled with the doublet at 3.00 ppm (*i.e.*, H_A-3 + H_B-3). Actually, the latter doublet is overlapped with a multiplet, the whole region (2.93-3.03 ppm) being equivalent to 3H/molecule. We suspected first that both H_A-3 and H_B-3 resonate accidentally at the same place, but their geminal coupling is still present. Accordingly, the doublet at 3.00 ppm would be a masked doublet of doublets with an AB-quartet appearance. This was wrong, since the irradiation at 3.85 ppm transformed the 3.00 ppm-doublet into one sharp singlet and not in two singlets separated by a presumably large geminal coupling constant. Therefore, both H-3 protons of **1** are equivalent, not only magnetically but also stereochemically. The other protons of the molecule presented complex multiplets, rationalization of which was impossible. However, the 2D-NMR experiments indicated their approximate locations, as quoted in Table 1 (entry 2). For instance, the C-6 peak (43.5 ppm) was directly correlated with the H-multiplets centered at 2.76 and 2.98 ppm (*i.e.*, $H_{A,B}$-6) and long-range correlated with the H-2 triplet (3.85 ppm). Assignments of chemical shifts for H_A and H_B in positions 5 and 6 became clear only after comparison with other similar compounds (see below). These data suggest the existence of both conformers **1A** and **1B**. Consequently, at least at this stage of our discussion, the subscripts A and B do not mean axial and equatorial protons, respectively. However, which of the two conformers is more stable? A possible response will be given later.

As previously reported,[2] the PMR data of the piperazine ring-protons in **2** and **3** (Table 1, entries 3 and 4, respectively) were fully rationalized. Judging from the J's values, the data were interpreted as indicating a main axial location for the 2-CN group. We will extend below this discussion on other similar compounds.

All six piperazine CH_2-protons in **4** were magnetically different (Table 1, entry 5). For instance, the protons in position 3 appeared as two distinct doublets of doublets, centered at 2.38 (H_A-3) and 2.75 ppm (H_B-3). Considering the values of the implied coupling constants, one could ascribe $^2J_{3A,3B}$ = 11.4, $^3J_{2,3A}$ = 3.9, and $^3J_{2,3B}$ = 3.1 Hz. Since usually $^3J_{a,e} > {}^3J_{e,e}$,[10] it seems that H_A-3 and H_B-3 are axially and equatorially located, respectively. Protons H-3 being coupled to H-2, the signal of H-2 would be a doublet of doublets too. However, as in the case of **1.2HCl**, H-2 in **4** appeared as a triplet with J = 3.5 Hz, suggesting that $^3J_{2,3A} = {}^3J_{2,3B}$ = 3.5 Hz. Again, this value is the arithmetic mean of those required [*i.e.*, (3.1+3.9)/2 = 3.5]. From the J's values within the C(2)*H*-C(3)H_AH_B molecular fragment one could ascribe for H-2 a preferred equatorial orientation. Otherwise, it should give a clear doublet of doublets with one large coupling constant (*i.e.*, $^3J_{2,3A} \geq 10$ Hz). At the same time, the aspects of the signals belonging to H_A-3 and H_B-3 should be quite different than those experimentally observed. Thus, H_A-3 should give either a doublet of doublets with two large coupling constants ($^3J_{2,3A}$ and $^2J_{3A,3B}$) or a well-spaced triplet, if $^3J_{2,3A} = {}^2J_{3A,3B}$.

Looking at the other piperazine protons of **4**, the following assignments could be made: $^2J_{5A,5B}$ = 11.2, $^2J_{6A,6B}$ = 11.9, $^3J_{5A,6A}$ = 9.7, $^3J_{5A,6B}$ = 3.2, $^3J_{5B,6A}$ = 3.3, and $^3J_{5B,6B}$ = 1.1 Hz. Considering the well-known[10] order of magnitude $^2J_{gem} \approx {}^3J_{a,a} >> {}^3J_{a,e} \geq {}^3J_{e,e}$, it results that all H_A and H_B are merely axial and equatorial protons, respectively. Therefore, an axial preference is implied for the 2-CN substituent in **4**.

The benzyl protons in **2**-**4** gave AB quartets (Table 1, last column, entries 3-5, respectively). This anisochronicity is due to the asymmetry induced by the 2-CN group. The same situation held in the case of the monobenzoylated derivatives **5** (entries 6 and 7) and **6** (entries 8 and 9).

It is known that the introduction of a cyano substituent into the cyclohexane molecule influences all carbon chemical shifts, depending not only by the relative distance from the point of attachment but also by the axial or equatorial CN-location.[11] To the extent of which the respective $\Delta\delta_C$ increments are valid also for the piperazine ring, one could assign[2] the conformation of **1**-**4** by comparison of the respective CMR data (Table 2, entries 2-5, respectively) with those of the model compounds **10**,[12] **11**,[13] and **12**[14] (Chart 3). For a correct calculation, two structures (**11A**-**B**) were depicted for 1-benzylpiperazine (**11**), differing by atoms' numbering only. The comparison is offered in Table 3.

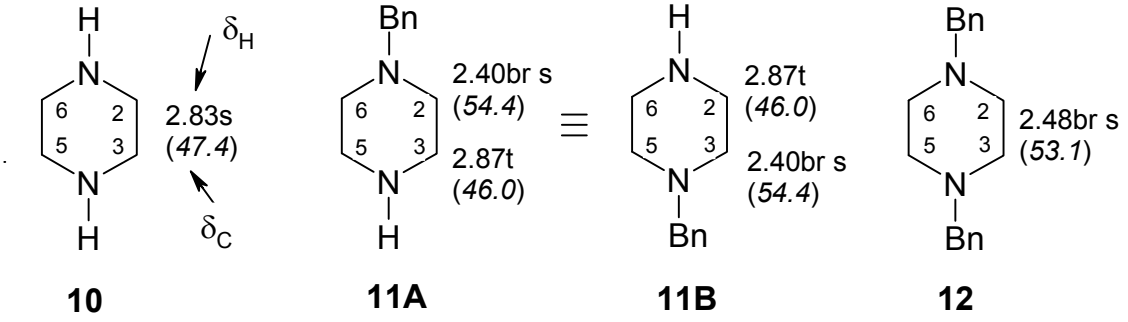


Chart 3

Taking into consideration the data of the pairs **2**/**11A** and **3**/**12** (Table 3, columns 6 and 7, respectively), it results that three (from the possible four) $\Delta\delta_C$'s are much more likely to an axial CN group in both **2** and **3**. The data of the **1**/**10** and **4**/**11B** pairs are less conclusive. For instance, the **1**/**10** pair (column 5) show two items (entries 1 and 4) in accord with *a*-CN, one item (entry 3) in agreement with *e*-CN, and one item (entry 2) just in the middle of the presumed range of values. In the case of the **4**/**11B** pair (column 8), two $\Delta\delta_C$'s (entries 2 and 3) seem sustaining for **4** an *a*-CN conformation, but the remaining two (entries 1 and 4) an *e*-CN one. As reported previously,[2] semiempirical AM1-MO calculations[15] showed that from the four isomers possible for **2** (eight for **3**) that having a 1-*e*-benzyl-2-*a*-CN conformation is the most stable. This derived from the comparison of the corresponding heats of formation (ΔH_f), taken as a criterion of stability. Analogous calculations for **1** showed the 2-*a*-CN-isomer (**1A**) as being more stable by about 2 kcal/mol than the *e*-one (**1B**). On the contrary, in the case of **4**, both isomers 2-*a*-CN-4-*e*-benzyl (**4A**) and 2-*e*-CN-4-*e*-benzyl (**4B**) presented practically the same AM1-computed ΔH_f. Similar ΔH_f values were obtained by using the newly parameterized version RM1.[16] However, the 2007-version of MNDO semiempirical MO method (*i.e.*, PM6)[16] gave somewhat different results: **1A** was more stable than **1B** [$\Delta\Delta H_f = \Delta H_f$ (**1B**) - ΔH_f (**1A**) = 3.3 kcal/mol], as expected, but also **4A** with respect to **4B** ($\Delta\Delta H_f$ = 4.4 kcal/mol). Therefore, the data of Table 3 and the MO calculations rather indicate that **1**-**4** are all mixtures of 2-*a*- (major) and 2-*e*-CN (minor) isomers, but the molar fraction of the axial isomer might follow the qualitative increasing order of **1** ≤ **4** < **2** ~ **3**.

Table 3

Influence of the CN group on the δ_C values of piperazine carbon atoms

Entry	Observed carbon[a]	Differences in δ_C ($CDCl_3$, 25°C, ppm)[b]					
		Predicted for:		Experimental data[c] for the pairs:			
		2-*a*-CN[d]	2-*e*-CN[d]	**1**/**10**	**2**/**11A**	**3**/**12**	**4**/**11B**
0	1	2	3	5	6	7	8
1.	C-2	0	+1	-0.5	-1.7	-1.8	+0.7
2.	C-3	-1	+3	+1.0	+2.2	+0.3	+0.4
3.	C-5	-1	-2	-1.8	-0.6	-1.5	-1.4
4.	C-6	-5	-2	-3.9	-4.4	-4.5	-2.8

[a] The CN group is always attached in position 2 (see Charts 1 and 3). [b] A sign minus signifies an up-field shift. [c] Calculated with the data of Table 2 (for **1**-**4**) and Chart 3 (for **10**-**12**). [d] Values from ref. 11 for the *a*- or *e*-cyanocyclohexane/cyclohexane pairs.

In the PMR and CMR spectra of the benzoyl derivatives **5**-**8** (Tables 1 and 2, respectively), taken at the apparatus temperature (*i.e.*, 25°C in entries 6, 8, 10, and 12, respectively), the piperazine protons and carbons presented broad signals. Moreover, some carbon chemical shifts are missing at all (*e.g.*, C-2 in **6** and **8**). These facts were inferred to the hindered rotation about the N-CO amide bond (*i.e.*, *E*/*Z* isomerism), slow enough for the NMR-time scale, as expected.[17-20] Much more intelligible spectra were obtained by forcing the N-CO bond to rotate faster (*i.e.*, by increasing the sample temperature to 62°C) (entries 7, 9, 11, and 13). For instance, the signals of H_A-3, H_A-5, and H_A-6 in **5** were all resolved at 62°C, thus enabling the assignment of some coupling constants:

$^2J_{3A,3B}$ = 13.4, $^3J_{2,3A}$ = 3.2, $^2J_{5A,5B}$ = 13.0, $^3J_{5A,6A}$ = $^2J_{6A,6B}$ = 11.8, $^3J_{5A,6B}$ = 3.6, $^3J_{5B,6A}$ = 3.4 Hz (Table 1, entry 7). Unfortunately, the signals of H_B's were still broad at 62°C and this was the case also for that of H-2. Similar characteristics presented the compounds **6**-**8**. The signal of H-2, a triplet at 3.95 ppm with $^3J_{2,3A}$ = $^3J_{2,3B}$ = 3.3 Hz, was somewhat resolved only in **7** (Table 1, entry 11).

Sample temperature increase accelerates not only the N-CO bond rotation in **5**-**8**, but also the *pseudo*-chair ↔ *pseudo*-chair equilibrium in both *Z* (*e.g.*, **7A** ↔ **7B** in Chart 2) and *E* isomers. Clearly, a higher temperature would favor the less stable conformer. However, the comparison of PMR data at 25°C with those at 62°C indicated that the mentioned equilibrium was not significantly perturbed. In fact, the values of δ_H's belonging to the piperazine protons in **5**-**8** were practically the same, whatever was the employed temperature (compare entries 6/7, 8/9, 10/11, and 12/13 of Table 1). Moreover, the aspects of the multiplets belonging to H_A-6 in **5**, H_A-5 in **6**, and H_A-3 in **7**, all resolved even at 25°C, did not significantly change on passing to 62°C. By way of consequence, the differences between the PMR features at 25°C and 62°C could be merely due to the benzoyl group rotation.

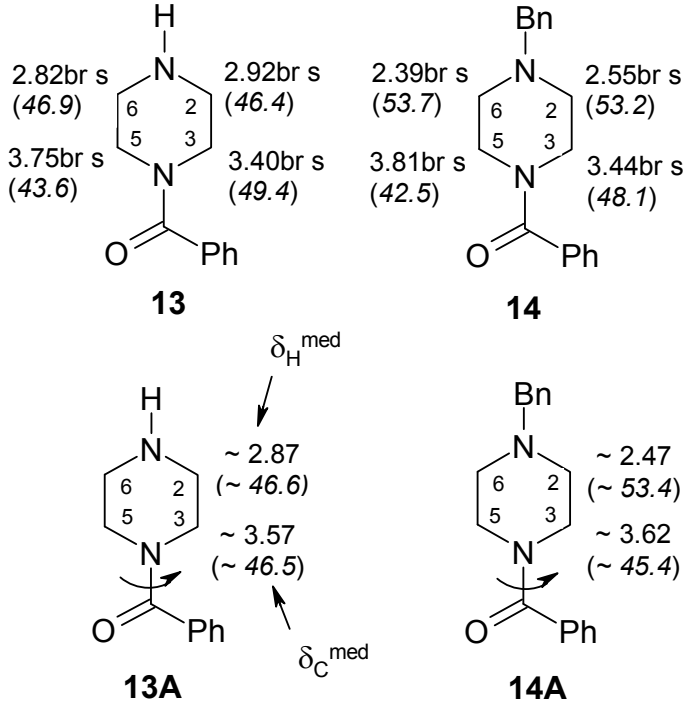


Chart 4

Broadening of H- and/or C-signals and the lack of multiplicities in the PMR spectra are common features for many related compounds. We chose as examples the benzoylated piperazines **13** and **14** (Chart 4). At 25°C,[14] they presented broad singlets for the piperazine protons, as indicated. The rotation about the N-CO amide bond is sufficiently slow at 25°C, explaining the differentiation between H-3 and H-5 or between H-2 and H-6. Knowing that (i) the CH_2-N-CO protons *syn* to the oxygen atom are deshielded relatively to those in an *anti* relationship and (ii) the opposite is true for the corresponding *C*H_2-N-CO carbon atoms, it was easy to make the quoted assignments. At 62°C, the rotation about the N-CO bonds becomes faster and mediated δ_H^{med} and δ_C^{med} values were observed for the species **13A** and **14A** (Chart 4).

Substitution of the aminic hydrogen atom by R (R = benzyl or benzoyl) affected differently the NMR chemical shifts of piperazine protons and carbons. Taking the appropriate pairs of compounds and using the data of Tables 1 and 2, as well as those of Charts 3 and 4, the $\Delta\delta_H$ and $\Delta\delta_C$ increments of Table 4 resulted. They were listed from left to right in order of the increasing distance between the observed position and the point of substitution. In other words, the position α (with respect to *N*-R) preceded the position β. When the piperazine ring is 2-CN-substituted, two distinct α positions must be considered. We noted them by α

and α', where α corresponds to the atom bearing the CN group. Analogously, positions β and β' resulted in this case (*i.e.*, C-β and C-β' are connected to C-α and C-α', respectively). Whenever possible, separate increments for H_A and H_B were calculated for the CH_2 protons. They were accompanied by their arithmetic mean (columns 3, 5, 7, 9). In all comparisons involving the 6-protons in **3** (2.58-2.60 ppm), the $\Delta\delta_H$ increments were less reliable, since no distinct chemical shifts were observed for these protons. In this case, the mean value of 2.59 ppm was considered for both H_A-6 and H_B-6.

Another type of mean increments was listed in entries 8 (for R = benzyl) and 15 (for R = benzoyl) of Table 4. It refers to the mean of all $\Delta\delta_H$ and $\Delta\delta_C$ increments, calculated for all considered pairs of compounds and for each position with respect to the introduced substituent. Each mean is accompanied by its range. From this point of view, many means are less useful owing to their unacceptably large ranges. In the case of the PMR data of CH_AH_B protons, three kinds of mean values were quoted, namely for H_A, for H_B *and* for their mean value. Unfortunately, distinction between H_A and H_B was possible in few cases only. However, entries 8 and 15 contain all necessary information. Since **1**-**8** could be present as many species, as discussed before, the mean values of $\Delta\delta_H$'s quoted in columns 3, 5, 7, and 9 (entries 8 and 15) might be more informative. From them, those of columns 3 and 5 presented narrow ranges and, consequently, resulted to be more confident. For the same reason, from the means of $\Delta\delta_C$'s (entries 8 and 15; columns 10-13), those quoted in columns 10 and 11 (entry 8) were more useful only.

On passing from *N*-H to *N*-benzyl piperazines (Table 4, entry 8), the protons in positions α and α' were *shielded* by about 0.4 ppm (mean value; columns 3 and 5) and the corresponding carbons *deshielded* by about 6 ppm (columns 10 and 11). The mediated $\Delta\delta_H$ and $\Delta\delta_C$ increments of the atoms in positions β and β' were of relatively smaller magnitudes and scattered and, consequently, of minor practical importance. When the two α- or α'-protons resonated distinctly one from the other, that in an axial position (*i.e.*, H_A) suffered an up-field shift of about 0.5 ppm, bigger than that of 0.3 ppm found for the proton in an equatorial location (entry 8, columns 2 and 4). These NMR α- or α'-shifts can be ascribed to the electronreleasing inductive (+I) effect of the benzyl group. Like other alkyl substituent, it pushes the bonding electrons more deeply into the direction of the observed protons. In other words, the C-H bond becomes relatively more polarized (*i.e.*, $C^{\delta+}$-$H^{\delta-}$). This occurs always when an N-*H* aminic proton is substituted by an alkyl group, but no quantification has been made till now in the piperazine series.

These effects served us to assign properly the chemical shifts of H_A and H_B in positions 5 and 6 of **1**, as quoted in Table 1 (entry 2). As an example, if 2.76 and 2.98 ppm would correspond to H_A-6 and H_B-6 in **1**, the $\Delta\delta_H$ increments for the pair **2**/**1** would be -0.33 and -0.35, respectively, and not -0.55 and -0.13 ppm, as calculated in Table 4 (entry 3, column 4). The new values are in contradiction with those of other similar pairs of compounds (Table 4, column 4; entries 4, 6, or 7). In other words, even no structural motivation exists, the rule stating a higher deshielding effect on H_A-6 with respect to that on H_B-6 would be no longer obeyed.

If a benzoyl group is introduced at the piperazine *N*-atom (Table 4, entries 9-14), all aliphatic protons are *deshielded*, those in *N*-α- or *N*-α'-positions more significantly (mean value of about 0.74 ppm; entry 15, columns 3 and 5). These low-field shifts are mainly due to the formal *N*-positivation through the amide function particular structure (*i.e.*, O=C-N ↔ $O^{\delta-}$-C=$N^{\delta+}$). When distinction between H_A and H_B protons was possible (entries 11-14), it appeared that the freely rotating benzoyl group deshielded more those *pseudo*-equatorially located (*i.e.*, H_B), by about 1.1 ppm, to be compared to the shift of about 0.5 ppm found for the corresponding *pseudo*-axial protons (entry 15, columns 2 and 4). This suggests that the through-space influence of the strongly deshielding oxygen atom is felt more by H_B than by H_A (both in *N*-α- or *N*-α'-positions). The corresponding $\Delta\delta_C$ increments (entry 15, columns 10-13) are generally small and negative, but no clear rule can be developed since the respective values are too scattered, as mentioned before. Consequently, only the discussed PMR data are more indicative in this case.

All these considerations could be useful in NMR assignments connected to the stereochemistry of the piperazine ring. The NMR shifts found for axial and equatorial α- or α'-protons should be considered as minimal, because our data were not based on single conformers' study (*i.e.*, "frozen" conformation).

Table 4

Effect of the *N*-R substituent on the PMR and CMR chemical shifts of piperazine atoms ($CDCl_3$, 25°C)

Entry	Pair of compounds	$\Delta\delta_H$ (ppm, in *italics*)[a] at the position: α [b] values [c]	α [b] mean[d]	α' [b] values [c]	α' [b] mean[d]	β [b] values [c]	β [b] mean[d]	β' [b] values [c]	β' [b] mean[d]	$\Delta\delta_C$ (ppm, in *italics*)[a] at the position: α [b] value [c]	α' [b] value [c]	β [b] value [c]	β' [b] value [c]
0	1	2	3	4	5	6	7	8	9	10	11	12	13
						R = benzyl							
1.	**11A/10**	2A:[e] *-0.43* 2B:[e] *-0.43*	*-0.43*	6A:[e] *-0.43* 6B:[e] *-0.43*	*-0.43*	3A:[e] *+0.04* 3B:[e] *+0.04*	*+0.04*	5A:[e] *+0.04* 5B:[e] *+0.04*	*+0.04*	2: *+7.0*	6: *+7.0*	3: *-1.4*	5: *-1.4*
2.	**12/11A**	3A:[e] *-0.39* 3B:[e] *-0.39*	*-0.39*	5A:[e] *-0.39* 5B:[e] *-0.39*	*-0.39*	2A:[e] *+0.08* 2B:[e] *+0.08*	*+0.08*	6A:[e] *+0.08* 6B:[e] *+0.08*	*+0.08*	3: *+7.1*	5: *+7.1*	2: *-1.3*	6: *-1.3*
3.	**2/1**	2B: *-0.31*	-	6A: *-0.55* 6B: *-0.13*	*-0.34*	3A: *-0.08* 3B: *+0.05*	*-0.02*	5A: *+0.02* 5B: *+0.04*	*+0.03*	2: *+5.8*	6: *+6.5*	3: *-0.2*	5: *-0.2*
4.	**3/2**	3A: *-0.72* 3B: *-0.25*	*-0.48*	5A: *-0.61* 5B: *-0.23*	*-0.42*	2B: *-0.05*	-	6A: *+0.16*[f] 6B: *-0.04*[f]	*+0.06*	3: *+5.2*	5: *+6.2*	2: *-1.4*	6: *-1.4*
5.	**4/1**	3A: *-0.62* 3B: *-0.25*	*-0.43*	5A: *-0.52* 5B: *-0.24*	*-0.38*	2B: *+0.03*	-	6A: *+0.15* 6B: *+0.05*	*+0.10*	3: *+6.4*	5: *+7.4*	2: *-0.2*	6: *-0.3*
6.	**3/4**	2B: *-0.39*	-	6A: *-0.54*[f] 6B: *-0.22*[f]	*-0.38*	3A: *-0.18* 3B: *+0.05*	*-0.07*	5A: *-0.07* 5B: *+0.05*	*-0.01*	2: *+4.6*	6: *+5.4*	3: *-1.4*	5: *-1.4*
7.	**5**[g]/**7**[g]	2B: *-0.38*	-	6A: *-0.52* 6B: *-0.15*	*-0.33*	3A: *-0.26* 3B: *+0.09*	*-0.09*	5A: *-0.17* 5B: *+0.16*	*0.00*	2: *+5.7*	6: *+6.4*	3: *+0.4*	5: *+1.5*
8.	mean[h] of Δδ's:	A: *-0.54±0.17* B: *-0.34±0.09*	*-0.43±0.05*	A: *-0.51±0.11* B: *-0.26±0.15*	*-0.38±0.05*	A: *-0.08±0.14* B: *+0.04±0.07*	*-0.01±0.08*	A: *+0.03±0.17* B: *+0.05±0.10*	*+0.04±0.05*	*+6.0±1.3*	*+6.6±1.0*	*-0.8±0.9*	*-0.6±1.5*
						R = benzoyl							
9.	**13A**[g]/**10**	3A:[e] *+0.74* 3B:[e] *+0.74*	*+0.74*	5A:[e] *+0.74* 5B:[e] *+0.74*	*+0.74*	2A:[e] *+0.04* 2B:[e] *+0.04*	*+0.04*	6A:[e] *+0.04* 6B:[e] *+0.04*	*+0.04*	3: *-0.9*	5: *-0.9*	2: *-0.8*	6: *-0.8*
10.	**14A**[g]/**11A**	3A:[e] *+0.75* 3B:[e] *+0.75*	*+0.75*	5A:[e] *+0.75* 5B:[e] *+0.75*	*+0.75*	2A:[e] *+0.07* 2B:[e] *+0.07*	*+0.07*	6A:[e] *+0.07* 6B:[e] *+0.07*	*+0.07*	3: *-0.6*	5: *-0.6*	2: *-1.0*	6: *-1.0*
11.	**7**[g]/**1**	3A: *+0.40* 3B: *+1.11*	*+0.75*	5A: *+0.40* 5B: *+1.14*	*+0.77*	2B: *+0.09*	-	6A: *+0.11* 6B: *+0.10*	*+0.10*	3: *-1.5*	5: *-2.6*	2: *-0.7*	6: *-1.0*
12.	**5**[g]/**2**	3A: *+0.22* 3B: *+1.15*	*+0.68*	5A: *+0.21* 5B: *+1.26*	*+0.73*	2B: *+0.02*	-	6A: *+0.14* 6B: *+0.08*	*+0.11*	3: *-0.9*	5: *-0.9*	2: *-0.8*	6: *-1.1*
13.	**6**[g]/**4**	2B: *+1.52*	-	6A: *+0.35* 6B: +1.09	*+0.72*	3A: *-0.06* 3B: *+0.35*	*+0.15*	5A: *-0.07* 5B: *+0.23*	*+0.08*	2: *-1.0*	6: *-0.4*	3: *-0.7*	5: *-0.7*
14.	**8**[g]/**7**[g]	2B: *+1.52*	-	6A: *+0.36* 6B: *+1.20*	*+0.78*	3A: *-0.14* 3B: *+0.32*	*+0.09*	5A: *-0.20* 5B: *+0.36*	*+0.08*	2: -	6: -	3: *+0.5*	5: *+0.9*
15.	mean[i] of Δδ's:	A: *+0.53±0.26* B: *+1.13±0.39*	*+0.73±0.03*	A: *+0.47±0.24* B: *+1.03±0.26*	*+0.75±0.03*	A: *-0.02±0.09* B: *+0.15±0.17*	*+0.09±0.05*	A: *+0.01±0.17* B: *+0.15±0.16*	*+0.08±0.03*	*-1.0±0.4*	*-1.1±1.1*	*-0.6±0.7*	*-0.6±1.0*

[a] A sign minus signifies a shielding effect. [b] With respect to the *N*-R nitrogen atom (see also text). [c] The position considered in calculation is indicated below, according to the numbering depicted in Charts 1 (for **1-8**), 3 (for **10-12**), and 4 (for **13A**, **14A**). [d] Arithmetic mean of the values of H_A and H_B. [e] H_A is undistinguishable from H_B. [f] Less reliable value (see text). [g] The data at 62°C were used. [h] Calculated with the data of the respective column (entries 1-7). [i] Calculated with the data of the respective column (entries 9-14).

EXPERIMENTAL PART

General. Melting points were taken on a Boetius hot plate and are uncorrected. FT-IR spectra were registered on a Brucker Vertex 70 apparatus. The relative intensities of the IR absorption bands were abbreviated as vs (very strong), s (strong), m (medium), w (weak), and vw (very weak). NMR spectra were obtained with a Varian Gemini A 300A spectrometer. Column chromatography was performed on glass columns packed with silica gel 60 (70-230 mesh, Merck), eluted either with AcOEt/*n*-hexane (1/3, v/v) (eluant 1) or with *n*-hexane/methanol (1/3, v/v) (eluant 2). Thin layer chromatography (TLC) was carried out on silica gel 60 F_{254} plastic sheets (Merck), eluted with the same mixtures as before; the spots were visualized by an UV lamp.

Materials. *N*-Benzylethylenediamine, *N,N'*-dibenzylethylenediamine, 2-chloroacrylonitrile (all from Aldrich), benzyl chloride, and benzoyl chloride (both from Merck) were used as purchased. Triethylamine (Merck) was stored over KOH pellets. The newly obtained compounds **4**-**8** gave satisfactory (± 0.3%) elemental analyses for C, H and N. They were characterized by IR (see below) and NMR (see text) spectral methods.

2-Piperazinecarbonitrile (**1**). 2-Piperazinecarbonitrile dihydrochloride[3] (**1.2HCl**; 0.92 g, 5 mmol) was dissolved in water (10 mL), the solution made basic (pH ~ 9) with solid $NaHCO_3$ (0.9 g, 10.7 mmol) and then continuously extracted with $CHCl_3$. The separated organic layer was anhydrized over KOH, the solvent removed *in vacuo* and the resulted oily free base **1** weighted (0.47-0.5 g, 85-90% recovery) and analyzed.

FT-IR spectrum (neat, cm^{-1}): 3330 + 3255 (vs + vs, large, ν_{NH}), 2226 (vw, ν_{CN}), 1672 (m, large), 1448 (s).

1-Benzyl-2-piperazinecarbonitrile (**2**). To an anhydrous benzene solution (15 mL) containing *N*-benzylethylenediamine (1.88 mL, 12.5 mmol) and triethylamine (1.75 mL, 12.6 mmol), 2-chloroacrylonitrile (1 mL, 12.5 mmol) dissolved in anhydrous benzene (5 mL) was added dropwise, at room temperature and under mechanical stirring. The mixture was stirred for 8 hours and then left undisturbed after night. The deposited white solid (Et_3N.HCl; 1.6 g, 93% of the theoretical value) was filtered off and the clear filtrate was washed with water, anhydrized over KOH, and freed from solvent *in vacuo*. The solid residue (2.24 g; mp 86-95°C) was recrystallized from *n*-hexane to give 1.99 g (yield 79%) of colorless crystals of **2**, identical (mixed mp, IR and NMR spectra) to the sample prepared previously[2] with 2,3-dibromopropionitrile instead of 2-chloroacrylonitrile.

FT-IR spectrum (solid, cm^{-1}): 3342 (vs, ν_{NH}), 1659 (m), 1492 (s).

1,4-Dibenzyl-2-piperazinecarbonitrile (**3**) was obtained similarly to **2**, starting from *N,N'*-dibenzylethylenediamine. Yield: 82%. Same mp, IR and NMR spectra as those previously reported.[2]

FT-IR spectrum (solid, cm^{-1}): 1665 (m, large), 1491 (w), 1449 (m).

4-Benzyl-2-piperazinecarbonitrile (**4**). 2-Piperazinecarbonitrile (**1**; 0.5 g, 4.5 mmol) was dissolved in ethanol (25 mL) and solid $NaHCO_3$ (1 g, 11.9 mmol) suspended in. To this mixture, a solution of benzyl chloride (0.52 mL, 4.5 mmol) in ethanol (10 mL) was added dropwise at room temperature and under stirring. The heterogeneous mixture was refluxed for one hour under vigorous stirring, chilled at room temperature, filtered and the clear filtrate evaporated to dryness at the water pump. Column chromatography (eluant 1) of the residue (*Note*) afforded oily **4** (0.3 g; yield 33%). The chromatographic process was monitored by TLC (R_f = 0.7 for **4**).

Note. According to the NMR analyses, the residue contains **4** (major), **2**, and another (unknown) compound. The approximate molar ratios would be **4**/**2**/unknown ~ 5/2/1.

FT-IR spectrum (neat, cm^{-1}): 3337 (m, large, ν_{NH}), 2227 (vw, ν_{CN}), 1669 (m).

4-Benzoyl-1-benzyl-2-piperazinecarbonitrile (**5**).

(A) To a stirred solution of **2** (0.5 g, 2.49 mmol) and Et_3N (0.4 mL, 2.9 mmol) in anhydrous benzene (15 mL), benzoyl chloride (0.29 mL, 2.5 mmol) in anhydrous benzene (5 mL) was added dropwise within 5 min. The whole mixture was stirred for another 30 min at room temperature, then refluxed for one hour and chilled at room temperature. The deposited solid (Et_3N.HCl) was filtered off, the clear filtrate washed with aqueous Na_2CO_3 (10%) and anhydrized over Na_2SO_4. The residue obtained after benzene evaporation was recrystallized from benzene/ether to give 0.67 g (yield 88%) of **5**, as colorless crystals melting at 95-96°C.

(B) Analogously to the preparation of **4** from **1**, treatment of **7** with an equivalent amount of benzyl chloride, in ethanol and in the presence of $NaHCO_3$, gave **5** in 55% yield. To avoid the benzoyl group hydrolysis, the reaction was performed at room temperature only (reaction time of 3 hours).

FT-IR spectrum (solid, cm^{-1}): 1634 (vs, amide I band), 1456 + 1427 (m + m, amide II band), 1290 (m, amide III band).

1-Benzoyl-4-benzyl-2-piperazinecarbonitrile (**6**) was obtained similarly to **5** (method A), starting from **4** instead of **2**. Yield 85%. Colorless crystals melting at 46-48°C (from benzene/ether).

FT-IR spectrum (solid, cm^{-1}): 1644 (vs, amide I band), 1447 + 1405 (m + m, amide II band), 1293 (m, amide III band).

4-Benzoyl-2-piperazinecarbonitrile (**7**) and **1,4-dibenzoyl-2-piperazinecarbonitrile** (**8**). Dihydrochloride **1.2HCl** (475 mg, 2.58 mmol) was dissolved in water (20 mL) and **1** was generated *in situ* by adding solid $NaHCO_3$ (650 mg, 7.75 mmol). To the clear solution resulted, benzoyl chloride (BzCl; 0.3 mL, 2.58 mmol) was added and the whole mixture was vigorously stirred at room temperature until the odor of benzoyl chloride disappeared (about 1.5 h). The deposited solid 1 (*Note 1*) was recovered by filtration, the filtrate made basic to pH 8.5 with $NaHCO_3$, and continuously extracted with CH_2Cl_2. The organic layer was anhydrized ($MgSO_4$) and freed from solvent *in vacuo*. The waxy residue (*Note 2*) was column-chromatographed (eluant 2), the convenient fractions combined, the solvents removed, and the residue re-chromatographed. The suitable fractions (pure by TLC) gave 166 mg of oily **7** (yield 30%, calculated with respect to BzCl). Solid 1 was washed with 5% aqueous Na_2CO_3 solution and recrystallized from ethanol to afford 170 mg of **8** (yield 41%, calculated with respect to BzCl), as colorless crystals melting at 135-136°C.

Note 1. Solid 1 consists of a mixture of **8** and benzoic acid, in about 2.5/1 molar ratio (by NMR).

Note 2. A part **7** and unreacted **1**, it contains traces of **8** and of another compound, presumably **9** (by NMR). On TLC, the compounds **1**, **7** and **8** had R_f values of 0.5, 0.7 and 0.8, respectively.

FT-IR spectrum (neat, cm^{-1}) of **7**: 3317 (m, large, ν_{NH}), 2229 (vw, ν_{CN}), 1623 (vs, amide I band), 1428 (s, amide II band), 1285 (m, amide III band).

FT-IR spectrum (solid, cm^{-1}) of **8**: 1633 (vs, amide I band), 1447 + 1401 (m + s, amide II band), 1288 + 1262 (m + m, amide III band).

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10. For substituted cyclohexanes in chair conformation, the absolute values of $^2J_{gem} \sim {}^3J_{a,a}$, $^3J_{a,e}$, and $^3J_{e,e}$ are in the ranges of 8-13, 2-6, and 1-4 Hz, respectively. Always, $^3J_{a,e} \geq {}^3J_{e,e}$. 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.
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