Revue Roumaine de Chimie, **2006**, *51*(5), 413–423

Dedicated to the memory of
Professor Maria Brezeanu (1924–2005)

E/*Z* ISOMERISM OF SOME DIFORMAMIDES

Horia PETRIDE,* Constantin DRĂGHICI, Cristina FLOREA, Maria MAGANU and Silvia UDREA

"Costin D. Nenitzescu" Center of Organic Chemistry, Spl. Independenței 202-B, P.O. 35, Box 108,
RO-050461, Bucharest, Roumania, fax: (+40)-21-3121601, e-mail: hpetride@cco.ro

Received February 22, 2006

N,*N'*-Diformylethylenediamine derivatives of the general formula R^1-N(CHO)-CH_2CH_2-N(CHO)-R^2 [R^1=R^2=benzyl (**1**); R^1=benzyl, R^2=H (**2**); R^1=benzyl, R^2=benzoyl (**3**); R^1=R^2=H (**4**); R^1=R^2=benzoyl (**5**); R^1=H, R^2=benzoyl (**6**)] were synthesized and fully characterized by ^{1}H- and ^{13}C-NMR spectroscopy, including NOE experiments. Restricted rotation about the C-N amide bonds determined the existence of *E*/*Z* isomers. At room temperature, **1** presented three stereoisomers (48/45/7%), **2** four (5.5/58.5/3/33%), each of **3** or **6** two (60/40 and 88/12%, respectively), but **4** and **5** one species only. The preferred conformations of (benzyl)N-CHO (in **1**-**3**) and HN-CHO (in **2** and **6**) moieties were *E* and *Z*, respectively.

INTRODUCTION

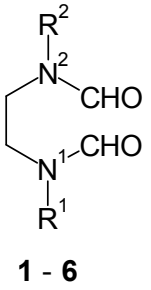
During our studies on the RuO_4-mediated oxidation of tertiary amines,[1a-b] the NMR spectroscopy was successfully used to identify the various reaction products. Small amounts of the expected, pure compounds were added to the respective reaction mixtures and their NMR spectra compared to those formerly registered. Working with 1,4-dibenzyl- and 1-benzylpiperazine as substrates,[1c] the acyclic derivatives **1**-**6** (formulae in Chart 1) with an *N*,*N'*-diformylethylenediamine skeleton seemed to be formed. To clarify this, a complete knowledge of the NMR features of **1**-**6** is strongly needed. We report in this paper the unambiguous synthesis of **1**-**6**, together with their full ^{1}H- and ^{13}C-NMR spectral characterization. For the sake of simplicity and clarity, we labeled by 1 and 2 superscripts the nitrogen atoms of **1**-**6** in Chart 1, as well as in coming Charts 2 and 3.

As shown below, **1**-**3** and **6** presented *E*/*Z* isomerism at room temperature due to slow rotation(s) about the C-N amide bond(s). This rotation is by far the most studied case of a topomerization-diastereomerization process not only because the substrates are readily available and the respective motion is quite often of large amplitude, but especially because of its biochemical implications.[2] It is worth mentioning that the amide linkage is probably the most important functional group to life processes. As part of proteins and enzymes, amide bonds are the building blocks of a series of important naturally occurring compounds that includes glycoproteins and sphingolipids, as well as synthetic polyamides and pharmaceuticals. The key structural features of amides, especially the hindered rotation about the C-N bond have long been known. The corresponding literature is very rich in experimental data[3] and theoretical studies.[3f-i, 4] The rotation is governed by both inductive and steric effects provided by substituents around the C-N bond.[5] Usually, the rotation barriers are high enough for the NMR-time scale and the two isomers/amide bond can be seen even at room temperature.[6] Generally speaking, this seems to be our case too, but a detailed discussion is needed.

RESULTS

Compounds **1** and **2** were previously prepared by formylation of the corresponding diamines with formic acid.[7, 8] We repeated this procedure and found it inadequate for **2**, because of partial hydrolysis[9] occurred during

the aqueous washings of the crude reaction mixture. Replacement of formic acid by ethyl formate proved to be the method of choice to obtain both **1** and **2** in high yields. Derivative **4** was prepared similarly.[10]



1 - 6

1 - 6	R^1	R^2
1	Bn	Bn
2	Bn	H
3	Bn	Bz
4	H	H
5	Bz	Bz
6	H	Bz

Bn=benzyl

Bz=benzoyl

Chart 1

Diformamide **3** was synthesized by benzoylation of the N^2-$SiMe_3$ derivative of **2**, generated *in situ* from **2** and chlorotrimethylsilane. Compound **5** was obtained analogously, starting from **4**, chlorotrimethylsilane (two equivalents), and benzoyl chloride (two equivalents). When the last reaction was performed with up to one equivalent of benzoyl chloride, a mixture of **5** and of another compound was obtained (~1/2, molar; by NMR). If silylation and benzoylation were repeated starting from this mixture, only **5** was obtained. On these bases, we ascribed to the major, unknown compound the structure **6**. Unfortunately, our efforts to isolate **6** failed. To our knowledge, the diformamides **3**, **5**, and **6** are new compounds.

All **1**-**6** were fully characterized by ^{1}H- and ^{13}C-NMR spectroscopy, in $CDCl_3$ (acetone-d_6 for **4**) as a solvent and at room temperature. The respective results were collected in Tables 1 and 2, respectively, where the chemical shifts were expressed in ppm (δ scale). For solutions in $CDCl_3$, they were measured relatively to internal (CH_3)$_4$Si (δ_H=0) and $CDCl_3$ (δ_C=77.01). In the case of **4**, both ^{1}H- and ^{13}C-chemical shifts were related to the solvent peaks (δ_H=2.05; δ_C=29.8 and 206.3 ppm). Because **6** was not obtained in a pure state, its NMR data (see below) must be considered as preliminary results.

The previously reported[8] ^{1}H-NMR spectral features of **1** and **2** are too vague or even wrong and, consequently, not useful to our purposes. Let us analyze first the case of **1**. Only ranges have been given for the protons of **1** in $CDCl_3$, namely 3.14-3.36 (m, 4H, CH_2-CH_2), 4.28-4.45 (m, 4H, CH_2-Ph), 7.08-7.36 (m, 10H, Ph), and 7.88-8.26 ppm (m, 2H, CHO).[8] Working in the same solvent and at a higher magnetic field, we obtained the spectrum presented in Fig. 1, where the integrals were arranged in order to correspond to values requested by the molecular formula.[11] The four ^{1}H-zones were now more resolved and allowed full assignment when correlated with the corresponding ^{13}C- and two-dimensional NMR data, as follows.

Zone (a). The 4H/molecule CH_2-CH_2 zone (3.16-3.39 ppm) appeared as a singlet at δ 3.38 and as two triplets (J = 5.6 Hz) centered at 3.29 and 3.19 ppm, in relative integrals' ratios of 1.80/0.96/1.25. The unusual shape of the last triplet suggested a superposition of a triplet, centered at 3.19 ppm, with a singlet at 3.17 ppm. Indeed, two CH_2 carbon atoms corresponded to these triplet+singlet ^{1}H-signals, namely those resonating at 43.55 and 45.33 ppm, respectively. It results that four types of CH_2 protons were present in this zone: two as singlets (3.38 and 3.17 ppm) and two as triplets (3.29 and 3.19 ppm). These triplets being coupled between them (^{1}H-^{1}H correlation), they should belong to the same molecular species and should have equal integrals (*i.e.*, 0.96). Therefore, the singlet at 3.17 ppm might correspond to about 1.25-0.96 = 0.29H/molecule of **1**. These considerations suggest that **1** could be present as three stereoisomers: one asymmetric (**1A**; the ethylene protons give two distinct triplets) and two symmetric (**1B**, major, and **1C**, minor; the ethylene protons yield only one singlet/isomer). Considering that each triplet of **1A** corresponds to 2H/isomer and the singlet of **1B** (or **1C**) to 4H/isomer, it results that the ratios **1A**/**1B**/**1C** could be 0.48/0.45/0.07.

Zone (b). The benzyl protons' region (4.3-4.5 ppm; total integral of 4H/molecule of **1**) consisted of three distinct singlets occurring at δ 4.31, 4.46, and 4.48, respectively. However, the last one possesses a shoulder at about 4.49 ppm (see Fig. 1), that is again four types of benzyl protons are present, as confirmed also by their direct correlation with four CH_2 carbon atoms (δ_C 52.23, 50.77, 45.33, and 46.03, respectively). The four singlets belong surely to benzyl protons, as indicated by their ^{1}H-^{13}C long-range correlation with four quaternary aromatic carbon atoms (C_{ipso}). No such correlation presented the ethylene protons of zone (a). The integrals of benzyl protons' singlets (from right to left in Fig. 1) were in the 0.96/~1.90/~0.88/~0.29 ratios

(not shown in Fig. 1). Accordingly, we ascribe the singlets at δ 4.31 and 4.48 to **1A**, the singlet at δ 4.46 to **1B**, and the shoulder at 4.49 ppm to **1C**.

Zone (c). The formyl protons' zone (7.91-8.30 ppm) contained four singlets (δ_H 7.91, 8.01, 8.26, and 8.30 ppm), as expected, in 0.14/0.48/0.90/0.49 ratios. This suggests that the peaks at 8.01 and 8.30 ppm belong to the asymmetric isomer **1A**, the singlet at 8.26 to **1B**, and that at 7.91 ppm to **1C**. The respective ^{13}C-signals showed long-range correlation with the corresponding benzyl [zone (b)] and C*H*$_2$-C*H*$_2$ [zone (a)] protons. For instance, the peak at δ_C 163.00 (δ_H 8.30) felt the singlet at δ_H 4.31 and the triplet at 3.29 ppm.

Zone (d). The aromatic region (7.10-7.40 ppm) was more complex, but its up-field part could be rationalized as being formed by one distinct doublet (δ 7.15; J = 6.4 Hz) and two partially overlapped doublets [δ 7.20 (J_{app} = 6.0 Hz) and 7.21 (J_{app} = 6.8 Hz)]. Four *C*H carbon atoms corresponded to these doublets: δ_C 127.58 to δ_H 7.15, 128.31 to 7.20, 127.63 and 128.44 to 7.21 ppm. At the same time, the three ^{1}H-doublets were long-range correlated with the four benzyl carbon atoms of zone (b). Taking into consideration also their ^{1}H-integrals and -shapes (Fig. 1), the three doublets in question were assigned to aromatic *ortho* protons, as follows: on the one hand, δ_H 7.15 and 7.20 to H_{ortho} of the two distinct phenyl groups of asymmetric **1A** and, on the other hand, δ_H 7.21 to H_{ortho} of the two identical phenyl rings of symmetric **1B** *plus* those belonging to the two identical phenyl groups of symmetric **1C**. Obviously, H_{meta} and H_{para} of all types of phenyl rings resonated in the 7.25-7.40 ppm region. Eight peaks were expected for the corresponding C_{meta} and C_{para} carbon atoms, but only seven were observed. From these, the peak at 128.82 ppm had the highest relative intensity and might belong to C_{meta} of **1B**.

Summing up all the considerations expressed before, the ^{1}H- and ^{13}C-NMR features of **1A-C** could be assigned as quoted in Tables 1 and 2 (entries 1), respectively.

The following ^{1}H-NMR data and assignments have been reported[8] for the asymmetrically *N*,*N'*-disubstituted diformamide **2**, in acetone-d_6: 3.06 (s, 1H, NH), 3.24-3.36 (m, 4H, CH_2-CH_2), 4.51-4.54 (m, 2H, C*H*$_2$-Ph), 7.29-7.32 (m, 5H, Ph), 8.06-8.34 (m, 2H, CHO). Clearly, an amide NH proton cannot resonate at such a high magnetic field, unless mixed with the adventitious water peak.

Table 1
^{1}H-NMR data of compounds **1-6**[a,b]

Compd.	Chemical shifts (400 MHz, δ, ppm, *J* in Hz, $CDCl_3$, 25°C) and assignments[c]
1[d]	**1A** (*E*,*Z*):[e] 3.19 (t, *J* 6.4, 2H,[f] N^2-CH_2), 3.29 (t, *J* 6.4, 2H, N^1-CH_2), 4.31 (s, 2H, N^1-Bn), 4.48 (s, 2H,[f] N^2-Bn), 7.15 (d, *J* 6.4, 2H, H_{ortho} of *Ph*-CH_2-N^1), 7.20 (d, J_{app} 6.0, 2H,[f] H_{ortho} of *Ph*-CH_2-N^2), 8.01 (s, 1H, N^2-CHO), 8.30 (s, 1H, N^1-CHO); **1B** (*E*,*E*):[e] 3.38 (s, 4H, C*H*$_2$-C*H*$_2$), 4.46 (s, 4H, Bn), 7.21 (d, J_{app} 6.8, 4H,[f] H_{ortho}), 8.26 (s, 2H, CHO); **1C** (*Z*,*Z*):[e] 3.17 (s, 4H,[f] C*H*$_2$-C*H*$_2$), 4.49 (sh, 4H,[f] Bn), 7.21 (d, J_{app} 6.8, 4H,[f] H_{ortho}), 7.91 (s, 2H, CHO); **1A-C**:[g] 7.25-7.40 (m, 6H, H_{meta}+H_{para}).
2[h]	**2A** (*E*,*E*):[e] 3.25 (q,[i] *J* 6.0, 2H,[f] N^2-CH_2), 4.45 (s, 2H, Bn), 6.55 (br s, 1H, NH),[j] 7.18 (d, *J* 7.2, 2H,[f] H_{ortho}), 7.86 (d,[k] *J* 11.7, 1H, N^2-CHO), 8.33 (s, 1H, N^1-CHO); **2B** (*E*,*Z*):[e] 3.39-3.42 (m, 4H, CH_2-CH_2), 4.46 (s, 2H, Bn), 6.70 (br s, 1H, NH),[j] 7.18 (d, *J* 7.2, 2H,[f] H_{ortho}), 8.10 (d,[k] *J* 1.6, 1H, N^2-CHO), 8.32 (s, 1H, N^1-CHO); **2C** (*Z*,*E*):[e] 3.23 (q,[i] *J* 6.0, 2H,[f] N^2-CH_2), 4.56 (s, 2H,[f] Bn), 6.91 (br s, 1H, NH),[j] 7.25 (d, *J* 7.2, 2H,[f] H_{ortho}), 7.76 (d,[k] *J* 11.7, 1H, N^2-CHO), 8.20 (s, 1H, N^1-CHO); **2D** (*Z*,*Z*):[e] 4.56 (s, 2H,[f] Bn), 6.84 (br s, 1H, NH),[j] 7.25 (d, *J* 7.2, 2H,[f] H_{ortho}), 8.15 (s, 2H, N^1-CHO+N^2-CHO); **2A-D**:[g] 3.30-3.39 (m, 1.49H, CH_2-CH_2 of **2D** and N^1-CH_2 of **2A**+**2C**), 7.28-7.39 (m, 3H, H_{meta}+H_{para} of **2A-D**).
3[l]	**3A** (*E*):[e] 3.50 (t, *J*≈5.6, 2H, N^1-CH_2), 4.02 (t, *J*≈5.6, 2H, N^2-CH_2), 4.44 (s, 2H, Bn), 8.18 (s, 1H, N^1-CHO), 8.82 (s, 1H, N^2-CHO); **3B** (*Z*):[e] 3.37 (t, *J* 6.0, 2H, N^1-CH_2), 3.97 (t, *J* 6.0, 2H, N^2-CH_2), 4.57 (s, 2H, Bn), 8.07 (s, 1H, N^1-CHO), 8.87 (s, 1H, N^2-CHO); **3A-B**:[g] 7.16-7.36 (m, 5H, *Ph*-CH_2), 7.37-7.52 (m, 5H, *Ph*-CO).
4[m]	3.37 (s, 4H, CH_2), 8.14 (s, 2H, CHO).
5	4.27 (s, 4H, C*H*$_2$-C*H*$_2$), 7.47 (t, *J* 7.2, 4H, H_{meta}), 7.51-7.58 (m, 6H, H_{ortho}+H_{para}), 8.90 (s, 2H, CHO).
6[n]	**6A** (*Z*):[e] 3.63 (q,[i] *J* 5.6, 2H, N^1-CH_2), 4.09 (t, *J* 5.6, 2H, N^2-CH_2), 6.28 (br s, 1H, NH),[j] 8.16 (d,[k] *J* 1.2, 1H, N^1-CHO), 8.92 (s, 1H, N^2-CHO); **6B** (*E*):[e] 3.55 (q,[i] *J* 6.2, 2H, N^1-CH_2), 4.04 (t, *J* 6.2, 2H, N^2-CH_2), 6.18 (br s, 1H, NH),[j] 8.02 (d,[k] *J* 12.2, 1H, N^1-CHO), 8.95 (s, 1H, N^2-CHO).

[a] See Charts 2-3 for the *E*/*Z* isomerism of **1-3** and **6**. Only one species was seen for **4** and **5**. [b] For the meaning of N^1 and N^2 see Charts 1-3. [c] Bn stands for benzyl protons. [d] **1A**/**1B**/**1C** = 48/45/7%. [e] The integrals are intended for the considered isomer. [f] Calculated value (see text). [g] The integrals are intended for the mixture of isomers. [h] **2A**/**2B**/**2C**/**2D** = 5.5/58.5/3/33%. [i] Triplet with D_2O. [j] Vanishes with D_2O. [k] Singlet with D_2O. [l] **3A**/**3B** = 60/40%. [m] In acetone-d_6. [n] Preliminary data obtained from a 1/2 (molar) mixture of **5**/**6** (**6A**/**6B** = 88/12%).

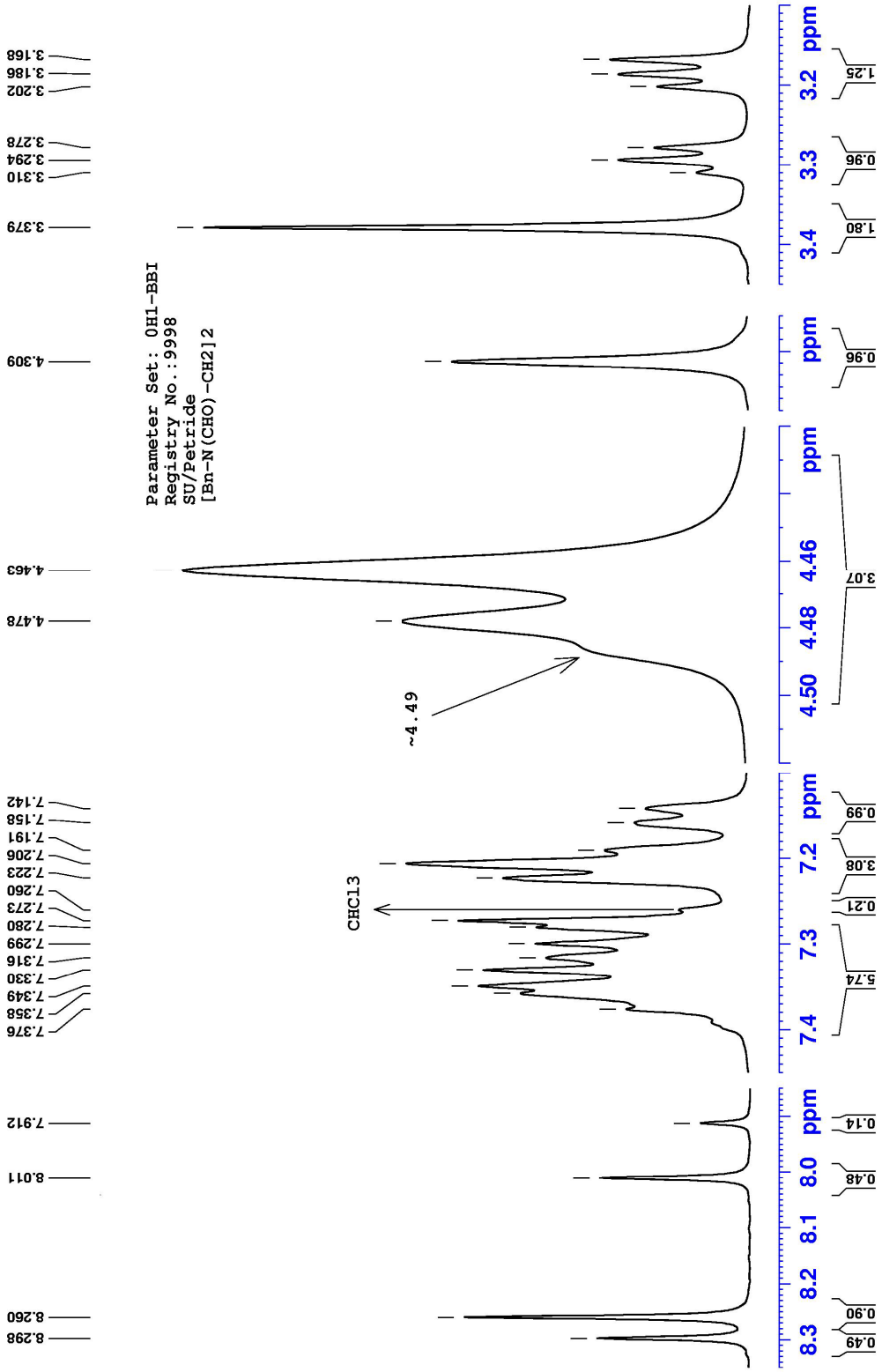


Fig. 1 – Experimental PMR spectrum of 1 (400 MHz, CDCl3, 25 deg).

Table 2

^{13}C-NMR data of compounds **1**-**6**[a]

Compd.	Chemical shifts (100 MHz, δ, ppm, $CDCl_3$, 25°C) and assignments[b]
1[c]	**1A** (*E*,*Z*): 40.92 (N^1-CH_2), 43.55 (N^2-CH_2), 45.33 (N^2-Bn), 52.23 (N^1-Bn), 127.58 (C_{ortho} of *Ph*-CH_2-N^1), 128.31 (C_{ortho} of *Ph*-CH_2-N^2), *135.38* (of *Ph*-CH_2-N^2), *136.09* (of *Ph*-CH_2-N^1), 162.66 (N^2-CHO], 163.00 (N^1-CHO); **1B** (*E*,*E*): 37.71 (*C*H_2-*C*H_2), 50.77 (Bn), 127.63 (C_{ortho}), 128.82 (C_{meta}), *135.65*, 163.27 (CHO); **1C** (*Z*,*Z*): 45.33 (*C*H_2-*C*H_2), 46.03 (Bn), 128.44 (C_{ortho}), *135.90*, 162.63 (sh, CHO); **1A-C** (CH): 127.67, 128.00, 128.24, 128.66, 128.87, 129.04.
2[d]	**2A** (*E*,*E*): 39.35 (N^2-CH_2), 43.40 (N^1-CH_2), 52.39 (Bn), *135.48*, 163.50 (N^1-CHO), 164.72 (N^2-CHO); **2B** (*E*,*Z*): 35.93 (N^2-CH_2), 41.26 (N^1-CH_2), 51.51 (Bn), 127.54 (C_{ortho}), 128.94 (C_{meta}), *135.37*, 161.76 (N^2-CHO), 164.02 (N^1-CHO); **2C** (*Z*,*E*): 39.81 (N^2-CH_2), 45.94 (Bn), 47.83 (N^1-CH_2), 163.41 (N^1-CHO), 164.85 (N^2-CHO); **2D** (*Z*,*Z*): 35.65 (N^2-CH_2), 45.52 (Bn), 45.94 (N^1-CH_2), 128.00 (C_{ortho}), *135.95*, 161.88 (N^2-CHO), 163.34 (N^1-CHO); **2A-D** (CH): 127.75, 127.92, 128.07, 128.21, 128.26, 128.39, 128.76, 128.84, 129.01.
3[e]	**3A** (*E*): 36.92 (N^2-CH_2), 39.35 (N^1-CH_2), 50.63 (Bn), 127.66 (C_{ortho} of *Ph*-CH_2), 128.22 (C_{para} of *Ph*-CH_2), 131.98 (C_{para} of *Ph*-CO), *133.30* (of *Ph*-CO), *135.62* (of *Ph*-CH_2), 163.71 (N^1-CHO), 164.45 (N^2-CHO), 172.29 (Ph-*C*O); **3B** (*Z*): 37.82 (N^2-CH_2), 43.68 (N^1-CH_2), 45.09 (Bn), 127.79 (C_{para} of *Ph*-CH_2), 128.45 (C_{ortho} of *Ph*-CH_2), 132.60 (C_{para} of *Ph*-CO), *132.77* (of *Ph*-CO), *136.10* (of *Ph*-CH_2), 162.67 (N^1-CHO), 164.03 (N^2-CHO), 172.10 (Ph-*C*O); **3A-B** (CH): 128.84, 128.93, 128.99, 129.18.
4[f]	38.8 (*C*H_2-*C*H_2), 163.5 (CHO).
5	38.91 (*C*H_2-*C*H_2), 128.56 (C_{ortho}), 128.88 (C_{meta}), 131.87 (C_{para}), *133.32*, 164.74 (CHO), 172.45 (Ph-*C*O).
6[g]	**6A**: 37.0 (N^1-CH_2), 39.9 (N^2-CH_2), 128.6 (C_{ortho}), 129.0 (C_{meta}), 132.3 (C_{para}), *133.0*, 161.8 (N^1-CHO), 164.5 (N^2-CHO), 172.7 (Ph-*C*O); **6B**: 39.6 (N^1-CH_2), 40.4 (N^2-CH_2), 128.9, 129.1, 130.5 (C_{para}), *132.6*, 164.2 (N^2-CHO), 165.2 (N^1-CHO), 172.5 (Ph-*C*O).

[a] See footnotes *a* and *b* of Table 1. [b] Bn stands for benzyl carbons. The value of aromatic C_{ipso} is given in *italics*. [c-g] See footnotes *d*, *h*, *l*, *m*, and *n* of Table 1, respectively.

In our hands, **2** proved to exist in $CDCl_3$ as a mixture of four isomers (**2A**/**2B**/**2C**/**2D** = 5.5/58.5/3/33%). Assignment of the observed signals was made similarly to the previously discussed case of **1** and is presented in Tables 1 and 2 (entries 2). For instance, the NH proton appeared as four distinct broad signals, at 6.55 (**2A**), 6.70 (**2B**), 6.84 (**2D**), and 6.91 ppm (**2C**), very different from the single value given previously.[8] Moreover, the N^2-CHO protons in **2A**-**C** were doublets, by coupling with the adjacent NH proton (^{1}H-^{1}H correlation and D_2O-deuteration). The corresponding coupling constants were large (11.7 Hz) in **2A** and **2C**, but small (1.6 Hz) in **2B**. We note also that both N^1-CHO and N^2-CHO formyl protons belonging to **2D** merged into one peak, at δ 8.15, which corresponded to two carbon atoms, located at 163.34 and 161.88 ppm. Although its half-height width was somewhat greater than that of the formyl proton of **2B** at 8.32 ppm, it was not truly resolved, but became sharper after adding D_2O into the analyzed sample. This suggested that N^2-C*H*O of **2D** could be also coupled with the adjacent NH by a small *J* value. Interestingly, during the hydrolysis of **2**,[9] the singlet at δ 8.15 was sometimes split into two equally populated, partially overlapped signals at about δ 8.16 (sharp singlet; N^1-CHO) and 8.15 ppm (doublet with *J* of 1.2 Hz; N^2-CHO). The benzyl protons of **2C**-**D** resonated both at 4.56 ppm.

The C*H*$_2$-C*H*$_2$ protons of **2** covered a wide zone (3.20-3.42 ppm), which could be divided into three parts: (i) 3.20-3.29, (ii) 3.29-3.39, and (iii) 3.39-3.42 ppm. The first region (seven peaks) was rationalized as two unequally populated, partially overlapping quartets with *J* of 6.0 Hz. The quartets belong to the CH_2-N^2 protons of **2A** and **2C**, located at 3.25 and 3.23 ppm, respectively. Suppression of their coupling with NH by addition of D_2O transformed the quartets into triplets (*J* 6.0 Hz) (five peaks in total). Unfortunately, the complexity of the remaining (ii) and (iii) zones precluded any assignment by simple inspection. However, useful indications were offered by the 2D-NMR experiments. They indicated that both N^1-CH_2 and N^2-CH_2 protons of **2B** are centered at about 3.40 ppm. Moreover, the same types of protons in **2D** could resonate at 3.32 and 3.36 ppm, respectively. At the same time, the multiplet due to N^1-CH_2 of **2A** might be centered at δ 3.37 and that of **2C** at about 3.35 ppm. In other words, it results that, on the one hand, all CH_2-CH_2 protons of **2B** are located in zone (iii) and, on the other hand, in the region (ii) lay CH_2-CH_2 of **2D**, as well as the N^1-CH_2 protons of **2A** and **2C**. This explains why the integrated areas of zones (i)-(iii) corresponded to 0.17, 1.5, and 2.33H/molecule of **2**, respectively.

All types of carbon atoms belonging to **2A**-**D** were seen (Table 2, entry 2), unless C_{ipso} of the minor isomer **2C**, probably because of its too low relative intensity. As for **1**, assignment of the aromatic CH carbons was possible in few cases only.

Only two stereoisomers (**3A**/**3B**=60/40%) were found by NMR for the diformamide **3** (Tables 1 and 2, entries 3). Interestingly, the C*H*$_2$-C*H*$_2$ protons presented different coupling constants and shapes in the two isomers. Thus, the two triplets of **3A** were poorly resolved ($J \approx 5.6$ Hz) in pure **3**, but "normally" resolved ($J = 6.0$ Hz)[9] in impure compound. In both cases, the analogous two triplets of **3B** behaved normally ($J = 6.0$ Hz). As indicated by ^{1}H-^{13}C long-range correlation, the most deshielded signals at δ_H 8.82 and 8.87 ppm belong surely to N^2-CHO formyl protons in **3A**-**B**, respectively. For instance, both Ph-*C*O (δ_C 172.3) and N^2-*C*HO (δ_C 164.5) carbon atoms in **3A** felt the triplet at δ_H 4.02. As in the case of **1** or **2**, rationalization of the observed chemical shifts due to the remaining aromatic protons and carbons was more difficult. Thus, only ranges could be ascribed to benzyl- and benzoyl-ring protons [7.16-7.36 (m, 5H, *Ph*-CH$_2$), 7.37-7.52 (m, 5H, *Ph*-CO)], regardless the isomer.

NMR spectra of **4** and **5** showed the presence of one species only, but two isomers were found for **6** (**6A**/**6B** = 88/12%) (Tables 1 and 2, entries 4-6, respectively). From the point of view of N-C*H*O, **6** resembled to **2** and **3**. Thus, the N^1-CHO formyl proton appeared as doublets in both **6A**-**B**, but *J*'s for the coupling with the adjacent NH proton were very different: small in the major isomer (1.2 Hz, like N^2-CHO in **2B**), but large in the minor one (12.2 Hz, similarly to N^2-CHO in **2A** or **2C**). On the other hand, the N^2-CHO proton resulted to be the most deshielded one of the entire molecule of **6** (**6A**: 8.92; **6B:** 8.95 ppm), just as the corresponding protons N^2-CHO of **3A**-**B** did. The formyl protons of symmetric **5** (8.90 ppm) behaved analogously. Although the δ_H values of **4**, a compound insoluble in $CDCl_3$, were similar to those of **2**, no reliable comparison could be made because of different solvents employed.

DISCUSSION

Compounds **1**, **2**, and **4** have two amide functions/molecule and, consequently, could exist as four *E*/*Z* isomers, just as depicted for **1** and **2** in Chart 2, where the first (*E* or *Z*) letter corresponds to the N^1-CHO conformation. Analogously, **3** and **6** might show eight isomers, but **5** sixteen stereoisomers. Actually, because R^1 = R^2 (see Chart 1), **1** and **4** could show only three species, their (*E*,*Z*)- and (*Z*,*E*)-isomers being identical.[12] Up to twelve distinct isomers are possible for **5**, for the same reason (*i.e.*, R^1 = R^2). We will analyze below each case a part.

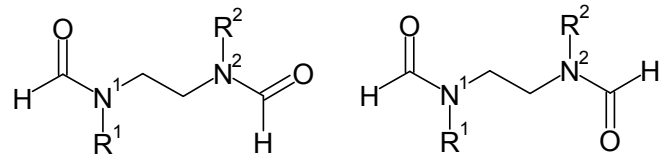
Three species (**1A**-**C**) were really observed in the NMR spectra of **1**. Inspection of the structural formulae of **1** in Chart 2 revealed that only the (*E*,*Z*)≡(*Z*,*E*)-isomer is asymmetric and, therefore, it should correspond to **1A**≡**1D**. Let **1A** be the structure of this isomer. Consequently, the symmetric **1B**-**C** would have the symmetric (*E*,*E*)- and (*Z*,*Z*)-structures, but not necessarily in this order. Two questions arise: (i) which NMR chemical shifts are due to (*E*)-N^1-CHO and which to (*Z*)-N^2-CHO moieties of **1A**, and (ii) which are the real structures of **1B** and **1C**? The correct responses came from experiments exploiting the Nuclear Overhauser Effects (NOE) and the same technique was used for **2** and **3**. All NOE results were collected in Table 3 and are discussed below. Values higher than 5% were considered only. With one exception, NOE values were modest (*i.e.*, 6-12%), indicative for mobile **1**-**3**, most probably through low-energy demanding rotations about the C-C and H$_2$C-N single bonds.

Under NOE conditions, the formyl proton of **1A** at δ 8.01 felt the triplet at δ 3.19, but not the benzyl singlet at δ 4.48. Conversely, irradiation of the other formyl proton of **1A** (δ 8.30) did not enhance the δ 3.29-integral, but that of benzyl protons at δ 4.31 (Table 3, entry 1). This means that the N^1-CHO and N^2-CHO amide bonds of **1A** have (*E*)- and (*Z*)-conformation, respectively, and the observed NMR chemical shifts can be safely assigned as quoted in Tables 1 and 2 (entries 1).

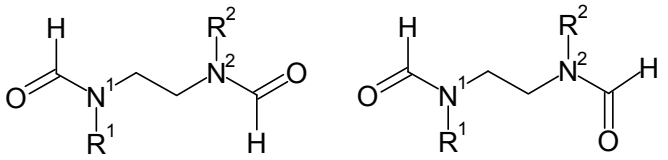
At the same time, irradiation of the 8.26 ppm-singlet of **1B** did not influence the 3.38 ppm-integral, but enhanced that of benzyl protons at δ 4.46 (Table 3, entry 2). On the contrary, irradiation of the δ 7.91-signal of **1C** enhanced by 25% the δ 3.17-integral and had no effect on that of δ 4.49 (entry 3). Taking into account the previous considerations on **1A**, these data are consonant to (*E*,*E*)- and (*Z*,*Z*)-conformation for **1B**-**C**, respectively, as depicted in Chart 2.

Semiempirical MO calculations at the PM3 level[13] indicated that the heats of formation (ΔH_f) of (*E*,*Z*)- and (*Z*,*Z*)-**1** are bigger than that of (*E*,*E*)-**1** by 2.72 and 8.03 kJ/mole, respectively. If ΔH_f is taken as the criterion of stability, it emerges that the theoretical stability order of these isomers is (*E*,*E*)≥(*E*,*Z*)>(*Z*,*Z*). This could be considered as matching our experimental findings [*i.e.*, (*E*,*Z*)/(*E*,*E*)/(*Z*,*Z*)=48/45/7%]. In fact, the

difference between the calculated ΔH_f's of (*E*,*Z*)- and (*E*,*E*)-**1** is too small and seems indicate a rather similar stability, which is in accord with the experimental evidence.



1A (*E*,*Z*) **1B** (*E*,*E*)
2A (*E*,*E*) **2B** (*E*,*Z*)



1C (*Z*,*Z*) **1D** (*Z*,*E*) = **1A**
2C (*Z*,*E*) **2D** (*Z*,*Z*)

Chart 2

As presented in the preceding section, diformamide **2** was a mixture of four isomers (**2A**-**D**). Taking into account the *J* value of the coupling within the N^2*H*-C*H*O fragment it was possible to assign an *E*-conformation to the N^2-CHO amide bond in **2A** and **2C** and a *Z*-one in **2B** and **2D**. In the first case, the large *J* value indicated an *anti*-relationship (*i.e.*, *E*-conformation) between the indicated protons. Analogously, the small *J* value suggested a *syn*-relationship in the latter case (*i.e.*, *Z*-conformation). This is well documented in the literature[14] and the simple example of *N*-benzylformamide[15] is highly indicative.

Table 3

NOE experiments on **1**-**3**

Entry	Isomer	Irradiated	Observed signals, ppm (*NOE*, %)	
		signal, ppm	Ph-C*H*$_2$	C*H*$_2$-C*H*$_2$
1.	**1A**	8.01	4.48 (-)	3.19 (*12*)
		8.30	4.31 (*8*)	3.29 (-)
2.	**1B**	8.26	4.46 (*11*)	3.38 (-)
3.	**1C**	7.91	4.49 (-)	3.17 (*25*)
4.	**2B**	8.32	4.46 (*10*)	3.39-3.42 (-)
		8.10	4.46 (-)	3.39-3.42 (-)
5.	**2D**	8.15	4.56 (-)	3.30-3.39 (*6*)
6.	**3A**	8.18	4.44 (*10*)	4.02 (-); 3.50 (-)
		8.82	4.44 (-)	4.02 (-); 3.50 (-)
7.	**3B**	8.07	4.57 (-)	3.97 (-); 3.37 (*6*)
		8.87	4.57 (-)	3.97 (-); 3.37 (-)

Which would be the conformations about the other amide bond (*i.e.*, N^1-CHO) of **2A**-**D**? NOE experiments enlightened only partially this question. Thus, irradiation at 8.32 ppm of **2B** determined a 10% enhancement of the δ 4.46-integral and had no effect on the ethylene protons region (Table 3, entry 4). The opposite situation occurred when the formyl proton at δ 8.15 of **2D** was irradiated (entry 5). At the same time, irradiation at 8.10 ppm of **2B** did not influence benzyl or ethylene protons (entry 4), as expected for a (*Z*)-N^2-CHO. These data indicated that **2B** and **2D** are (*E*,*Z*)-, and (*Z*,*Z*)-isomers, respectively, as depicted in Chart 2 and quoted in Tables 1 and 2 (entries 2).

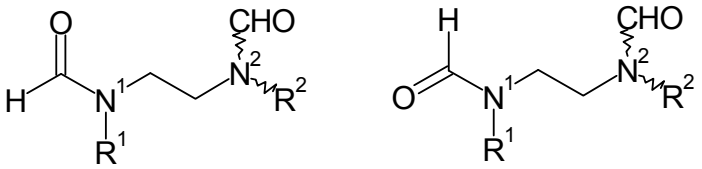
No significant nuclear Overhauser enhancements were obtained for the remaining isomers **2A** and **2C**. Conformational assignment for N^1-CHO was achieved in these cases by analogy with **1A**-**C**. Thus, the

molecules of **1A-C** and **2A-D** might be seen as unions of two moieties, namely HOC-N^1R^1-CH_2 and CH_2-N^2R^2-CHO. Judging on the NMR data of **1A-C**, **2B**, and **2D** from Tables 1 and 2, we tried to see what kind of variations suffer δ_H and δ_C of the N-methylene groups in one moiety, when the second moiety changes in conformation. Conversely, the δ_H and δ_C variations were observed also within the moiety of which conformation is changing, maintaining constant that of the second moiety. These variations were calculated for both types of N-methylene groups (*i.e.*, benzylic and N-CH_2-CH_2), but the data on the benzylic one were more telling, as presented below.

On passing from *E*- to *Z*-conformation in one moiety of the indicated compounds, the Ph-CH_2 group of the second, conformationally constant moiety showed $\Delta\delta_H$ between –0.15 and +0.01 ppm and $\Delta\delta_C$ between –0.3 and +1.5 ppm. Reversing the point of observation, the benzylic protons were *deshielded* ($\Delta\delta_H$ = 0.02-0.18 ppm) and the corresponding carbon atoms *shielded* ($-\Delta\delta_C$ = 5.4-6.2 ppm) on passing from *E*- to *Z*-conformation, providing that the second molecular moiety had preserved its conformation. These opposite effects on the δ_H and δ_C variations have precedents in the literature,[16] the most obvious examples being those of *N*,*N*-dimethylformamide[17] and *N*-benzylformamide.[15] From these variations it emerges that only $\Delta\delta_C$ can be safely used to predict conformations in our case. Indeed, highly negative $\Delta\delta_C$ might indicate an *E*→*Z* transformation within the observed moiety.

This criterion was applied to **2A** and **2C**. On passing from **2B** to **2A** or **2C**, $\Delta\delta_C$ of Ph-CH_2 was +0.9 and –5.6 ppm, respectively. According to the aforementioned deductions, the N^1-CHO conformation in **2A** should be the same as that in **2B** (*i.e.*, *E*), but changed in **2C** (*i.e.*, *Z*). At the same conclusion one may arrive by considering the $\Delta\delta_C$ values for **2D**→**2A** or **2D**→**2C**. All these data suggest that **2A** and **2C** are (*E*,*E*)- and (*Z*,*E*)-isomers, respectively. No PM3-calculations were made for **2A-D** (or **4**, or **6**), because the semiempirical methods give erratic results when applied to N-monosubstituted amides. Their relative energies and molecular geometries could be instead correctly predicted using more sophisticated MO methods.[3f]

In the case of **3A**, NOE irradiation of the singlet at δ 8.18 affected the benzyl protons (at 4.44 ppm) and not the other N^1-methylene group (triplet at δ 3.50) (Table 3, entry 6). The inverse situation held when the singlet at δ 8.07 of **3B** was irradiated (entry 7). Therefore, the N^1-CHO amide bond in **3A-B** has *E*- and *Z*-conformation, respectively (Chart 3). At the same time, no NOE was seen for δ 4.02 or 3.97 when the signals at δ 8.82 (entry 6) or 8.87 ppm (entry 7) were irradiated, respectively, suggesting that the N^2-C*H*O proton in **3A-B** is not so close to the N^2-CH_2 hydrogen atoms. This could be due to (i) a freely rotating formyl group, (ii) a particular conformation about the CH_2-N^2 single bond, or (iii) an (*E*)-N^2-CHO conformation. On the other hand, we could tentatively exclude the (*Z*,*Z*)-conformation of PhCO-N^2-CHO imide moiety, because of the unfavorable dipole-dipole interaction between the two coplanar carbonyl groups lying in the same direction,[18] which in our case is not counterbalanced by an extra stabilization (*i.e.*, chelation, etc).[19] These speculations seem to favor (*Z*)- and/or (*E*)-PhCO-N^2, but only (*E*)-N^2-CHO. However, we are sure only of the conformations about the N^1-CHO bond. As NMR data on model compounds are missing, our experimental features of **3A-B** were not sufficient to establish the conformations about the other two amide bonds of these species (Chart 3).



3A (*E*) **3B** (*Z*)
6A (*Z*) **6B** (*E*)

Chart 3

A similar discussion can be made for the PhCO-N^2-CHO moiety in **6A-B**. As concerns the N^1-CHO conformation in **6A-B**, these species are (*Z*)- and (*E*)-isomers, respectively (Chart 3), as indicated by the *J*'s values within the *H*N^1-C*H*O fragment (Table 1, entry 6).

More intriguing are the cases of **4** and **5**, which presented only one species. Accordingly, their NMR spectra could be due either to a particular isomer ('frozen' rotations) or to an average of more isomers, when the rotations about the amide C-N bonds are too rapid for the NMR-time scale. Unfortunately, NOE experiments on **4**-**6** failed and this was the reason for which they have not been included in Table 3. More data are needed to clarify the real structures of **3**-**6**. For instance, low-temperature NMR experiments could be especially useful in these cases. However, the NMR data of Tables 1 and 2 are entirely sufficient for the purpose of this paper.

CONCLUSIONS

Diformamides with the general formula R^1-N(CHO)-CH_2CH_2-N(CHO)-R^2 [R^1 = R^2 = benzyl (**1**); R^1 = benzyl, R^2 = H (**2**); R^1 = benzyl, R^2 = benzoyl (**3**); R^1 = R^2 = H (**4**); R^1 = R^2 =benzoyl (**5**); R^1 = H, R^2 = benzoyl (**6**)] were synthesized and fully characterized by NMR spectroscopy. At room temperature, compounds **1** and **2** presented all possible *E*/*Z* isomers, that is three for **1** [**1A**/**1B**/**1C** = (*E*,*Z*)/(*E*,*E*)/(*Z*,*Z*) = 48/45/7%] and four for **2** [**2A**/**2B**/**2C**/**2D** = (*E*,*E*)/(*E*,*Z*)/(*Z*,*E*)/(*Z*,*Z*) = 5.5/58.5/3/33%]. In all these isomers, the first (*E* or *Z*) letter corresponds to the conformation around the R^1*N*-*C*HO bond. In the same conditions, **3** presented two isomers [**3A**/**3B** = (*E*)/(*Z*) = 60/40%] due to the hindered rotation about the (benzyl)N-CHO bond. Similarly, the two isomers observed for **6** [**6A**/**6B** = (*Z*)/(*E*) = 88/12%] were due to the slow rotation about the H*N*-*C*HO bond. Both **4** and **5** existed as one species only, which could be either a single isomer or an averaged mixture of freely rotating isomers. The preferred conformation of (benzyl)*N*-*C*HO was *E* (in **1**-**3**) and that of the H*N*-*C*HO amide bond was *Z* (in **2** and **6**).

EXPERIMENTAL

General. Melting points were taken on a Boetius hot plate and are uncorrected. NMR spectra were registered at 25ºC on a Bruker Avance DRX 400 instrument. IR spectra were taken with an UR-20 Carl Zeiss Jena spectrophotometer. MS data were obtained on a QMD100 apparatus (Carlo Erba Instruments; EI, 70 eV) coupled with a HRGC-5300 gas chromatograph, equipped with a VF-5ms (methylsilicone) capillary column (30 m × 0.25 mm), using helium as a carrier gas and a programmed column temperature (between 120-290°C with a rate of 10°C/min and then isothermally). The retention times of **1**, **2**, **3**, **5**, and **6** were 20.1, 13.8, 20.6, 20.3, and 13.6 min, respectively.

Materials. *N*-Benzyl- and *N*,*N'*-dibenzylethylenediamine (from Aldrich), as well as ethyl formate and ethylenediamine (from Merck), were used as purchased. Triethylamine (Merck) was stored over KOH pellets. Dichloromethane (Chemical Company, Iassy, Roumania) was distilled from P_4O_{10} just before use. $CDCl_3$ and acetone-d_6 were purchased from ITIMCD (Cluj-Napoca, Roumania). Compounds **1**-**5** gave satisfactory (±0.3%) elemental analyses for C, H, and N.

***N*,*N'*-Dibenzyl-*N*,*N'*-1,2-ethanediylbisformamide** (**1**). (A) *N*,*N'*-Dibenzylethylenediamine (2.35 mL; 0.01 mol) was mixed with excess ethyl formate (19.3 mL; 0.24 mol) and the whole mixture was refluxed for 30 hours. Volatile materials (ethanol and unreacted ethyl formate) were eliminated *in vacuo* and the solid residue was recrystallized from a benzene/hexane mixture to afford 2.6 g (yield 88%) of **1**, as colorless crystals melting at 99-101°C (lit.[8] mp 99-100°C). (B) When the formylation was performed with formic acid,[7, 8] the yield in **1** was about 75%.
IR spectrum (CH_2Cl_2, ν_{CO}): 1681 cm^{-1}.
MS spectrum [m/z, relative intensity (%)]: 296 (0.35, M^+), 267 (5), 161 (9.9), 91 (100), 65 (6.3).

***N*-Benzyl-*N*-(2-formylaminoethyl)formamide** (**2**). (A) It was obtained similarly to **1**, starting from *N*-benzylethylenediamine and excess ethyl formate. After elimination of the volatile materials at the water pump, the residue was distilled at reduced pressure and the viscous fraction boiling at 225-227ºC/1.33 hPa (lit.[8] bp 240ºC/2.67 hPa) retained (yield 74%). (B) When the formylation was carried out with formic acid in benzene,[8] some of **2** must be recovered by CH_2Cl_2 extraction from the aqueous washings, the distillation repeated in order to separate **2** from its hydrolysis products,[9] and the yield dropped to about 45%.
IR spectrum (CH_2Cl_2, ν): 1682 (CO), 3437 cm^{-1} (NH).
MS spectrum [m/z, relative intensity (%)]: 206 (0.15, M^+), 177 (9.5), 161 (7.7), 148 (4.5), 106 (5), 92 (11), 91 (100), 65 (7.4), 58 (4.5).

***N*-Formyl-*N*-(2-benzylformylaminoethyl)benzamide** (**3**). To a stirred solution of **2** (1.3 g; 6.3 mmol) and Et_3N (0.9 mL; 6.5 mmol) in 10 mL of CH_2Cl_2, a solution of chlorotrimethylsilane (0.8 mL; 6.3 mmol) in 5 mL of CH_2Cl_2 was added dropwise at room temperature and the mixture was stirred for another 1.5 hours. A solution of benzoyl chloride (0.75 mL; 6.4 mmol) in 5 mL of CH_2Cl_2 was added gradually and the whole mixture heated at reflux for 1.5 hours. The homogeneous mixture was washed with water and alkaline ($NaHCO_3$) water. The separated organic layer was anhydrized over Na_2SO_4 and the solvent removed *in vacuo* to leave a solid. It was recrystallized from ethanol to afford pure **3** (1.17 g; 60% yield), as colorless crystals melting at 115-117°C.
IR spectrum (CH_2Cl_2, ν_{CO}): 1682 (strong) and 1724 cm^{-1} (medium).

MS spectrum [m/z, relative intensity (%)]: 310 (1, M^+), 281 (9.7), 177 (5.3), 161 (22.5), 148 (14), 132 (6), 106 (11.9), 105 (65), 92 (10.7), 91 (100), 77 (6.8), 65 (6.3), 51 (5.3).

***N,N'*-1,2-Ethanediylbisformamide** (**4**). A solution of ethylenediamine (1.5 mL; 22.5 mmol) and HCO_2Et (15 mL; 0.186 mol) was refluxed until no more solid separated (about 10 hours).[10a] The solid was recovered by filtration, washed with ether and then recrystallized from EtOAc to give pure **5** (2.28 g; 87% yield), as colorless crystals melting at 109-111°C (lit.[10b] mp 110-112°C).
IR spectrum (KBr, ν): 1680 (large), 3230 cm^{-1} (large).

***N,N'*-Diformyl-*N,N'*-1,2-ethanediylbisbenzamide** (**5**). (A) To a heterogeneous mixture of **4** (348 mg; 3 mmol) and Et_3N (0.9 mL; 6.5 mmol) in dichloromethane (20 mL) was added dropwise, under magnetic stirring and at room temperature, a solution of chlorotrimethylsilane (0.8 mL; 6.3 mmol) in dichloromethane (5 mL). The whole mixture was refluxed for 30 minutes and then cooled. Benzoyl chloride (0.7 mL; 6 mmol) in 5 mL of dichlorometane was added gradually and the mixture was refluxed for one hour. After cooling at about 5°C, cold water was added and the organic layer separated, anhydrized (Na_2SO_4), and then freed from the solvent to leave a solid residue. This was purified by recrystallization from an anhydrous ethanol/anhydrous ether mixture to afford colorless crystals of **5** (0.75 g, yield 78%). No reliable melting point could be given, because of its too high reactivity towards atmospheric water.[9] For the same reason, it should be kept in a dessicator, under vacuum. (B) The same procedure as before was followed starting from a 1/2 (molar) mixture of **5**/**6** (see below), but the amounts of reagents were diminished accordingly. Only **5** resulted, in 85% yield (based on **6**).
IR spectrum (CH_2Cl_2, ν_{CO}): 1685 (medium), 1725 cm^{-1} (strong).
MS spectrum [m/z, relative intensity (%)]: 324 (0.04, M^+), 147 (8.2), 106 (8.7), 105 (100), 77 (23.9), 51 (5).

Generation of *N*-formyl-*N*-(2-formylaminoethyl)benzamide (**6**). The previous procedure A used for **5** was followed, but only one equivalent of benzoyl chloride (*i.e.*, 0.35 mL; 1.5 mmol) was added. The solid residue obtained after solvent evaporation proved to be a mixture of two compounds (1/2, molar; by NMR), from which **5** was identified by pure sample addition. The NMR data of the unknown, major compound corresponded to those expected for **6** (Tables 1 and 2, entries 6). Additional amount of **6** could be isolated from the aqueous washings by continuous extraction with CH_2Cl_2, but it was more impure because of hydrolysis.[9] Attempts to isolate **6** by fractional recrystallization or by column chromatography failed, its hydrolysis products being obtained only.
MS spectrum [m/z, relative intensity (%)]: 220 (0.7, M^+), 147 (12.8), 134 (10.2), 106 (7.9), 105 (100), 77 (30.1).

ACKNOWLEDGEMENTS. This work was supported by the *Roumanian Academy* and by the Roumanian *Ministry of Education and Research* (grant n. 4-232/2004).

REFERENCES

1. a) H. Petride, C. Drăghici, C. Florea and A. Petride, *Cent. Eur. J. Chem.*, **2004**, *2*, 302-322; b) 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); c) H. Petride, C. Drăghici, C. Florea and A. Petride, *Cent. Eur. J. Chem.*, **2006**, *4*, published online on Aug. 30, 2006.
2. G. Fischer, B. Wittmann-Liebold, K. Lang, T. Kiefhaber and F. Schmid, *Nature*, **1989**, *337*, 446-448; S. L. Schreiber, *Science*, **1991**, *251*, 238-287; C. T. Walsh, L. D. Zydowsky and F. D. McKeon, *J. Biol. Chem.*, **1992**, *267*, 13115-13118; R. K. Harrison and R. L. Stein, *J. Am. Chem. Soc.*, **1992**, *114*, 3467-3471; K. P. Lu, S. D. Hanes and T. A. Hunter, *Nature*, **1996**, *380*, 544-547; Y. Ikeura, Y. Ishichi, T. Tanaka, A. Fujishima, M. Murabayashi, M. Kawada, T. Ishimura, I. Kamo, T. Doi and H. Natsugari, *J. Med. Chem.*, **1998**, *41*, 4232-4239; G. S. Hamilton and J. P. Steiner, *J. Med. Chem.*, **1998**, *41*, 5119-5143; C. Cox and T. Lectka, *Acc. Chem. Res.*, **2000** *33*, 849-858.
3. a) M. B. Robin, F. A. Bovey, H. Basch, "The Chemistry of Amides", J. Zabicky (Ed.), Interscience Publishers, London, 1970, Chapter 1, especially pp. 7-40; b) R. C. Neuman, Jr. and V. Jonas, *J. Org. Chem.*, **1974** *39*, 925-928; c) L. K. Leung, D. G. Antonovic, V. E. Vajs, N. D. Stoianovic, A. D. Nikolic and S. D. Petrovic, *J. Mol. Struct.*, **1992** *266*, 255-258; d) M. B. Pinto, "Acyclic Organonitrogen Stereodynamics", J. B. Lambert, Y. Takeuchi (Eds.), VCH Publishers, New York, 1992, chapter 5, pp. 149-175; e) I. P. Gerothanassis, A. Troganis and C. Vakka, *Tetrahedron*, **1995**, *51*, 9493-9500; f) M. Avalos, R. Babiano, J. L. Barneto, J. L. Bravo, P. Cintas, J. L. Jimenez and J. C. Palacios, *J. Org. Chem*., **2001**, *66*, 7275-7282; g) G. Bartoli, S. Grilli, L. Lunazzi, M. Massaccesi, A. Mazzanti and S. Rinaldi, *J. Org. Chem*., **2002**, *67*, 2659-2664; h) R. A. Bragg, J. Clayden, G. A. Morris and J. H. Pink, *Chem. Eur. J*., **2002**, *8*, 1279-1289; i) M. Avalos, R. Babiano, J. L. Barneto, P. Cintas, F. R. Clemente, J. L. Jimenez and J. C. Palacios, *J. Org. Chem*., **2003**, *68*, 1834-1842.
4. See for instance, M. Feigel and T. Strassner, *THEOCHEM*, **1993**, *102*, 33-48; L. P. Olson, Y. Li, K. N. Honk, A. J. Kresge and L. J. Schaad, *J. Am. Chem. Soc.*, **1995** *117*, 2992-2997; H. J. Lee, M. H. Lee, Y. S. Choi, H. M. Park and K. B. Lee, *THEOCHEM*, **2003**, *631*, 101-110; Y. Jean, I. Demachy, A. Lledos and F. Maseras, *THEOCHEM*, **2003**, *632*, 131-144; Y. K. Kang and H. S. Park, *THEOCHEM*, **2004**, *676*, 171-176.
5. M. D. Wunderlich, L. K. Leung, J. A. Sandberg, K. D. Meyer and C. H. Yoder, *J. Am. Chem. Soc.*, **1978**, *100*, 1500-1503; C. H. Yoder and R. D. Gardner, *J. Org. Chem.*, **1981**, *46*, 64-66.
6. W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **1970**, *70*, 517-551; H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **1970**, *9*, 219-235; M. Oki, *Top. Stereochem.*, **1983**, *14*, 1-81; M. Oki, "Applications of Dynamic NMR Spectroscopy to Organic Chemistry", VCH Publishers, Deerfield Beach, FL, 1986, pp. 43-54 and 161-164.
7. E. F. Curragh and H. B. Henbest, A. Thomas, *J. Chem. Soc.*, **1960**, 3559-3563.
8. C. Vetuschi, N. Tangari, M. Giovine, C. Franchini and V. Tortorella, *Farmaco*, **1992**, *47*, 599-605.
9. H. Petride, O. Costan, C. Florea and S. Udrea, *Rev. Roum.Chim.*, **2006**, *51*, 245-253.
10. a) I. B. Romanova, M. T. Tolibov and N. M. Feiershtein, *Uzb. Khim. Zh.*, **1971**, *15*, 43-46; b) F. F. Blicke and C. J. Lu, *J. Am. Chem. Soc.*, **1950**, *74*, 3933-3934.

11. The integral of the residual $CHCl_3$ peak at 7.26 ppm is overestimated.
12. Several other rotamers could be drawn if the rotations about the H_2C-N and C-C single bonds are considered. Semiempirical PM3 calculations indicated that *anti*-$(N^1)H_2C$-$CH_2(N^2)$ rotamers of **1** (as depicted in Chart 2) have the lowest heats of formation and, presumably, are the most stable. The same was assumed as being true for **2**-**6**.
13. J. J. P. Stewart, *J. Comput. Chem.*, **1989**, *10*, 209-220.
14. In (*Z*)- and (*E*)-*N*-monosubstituted formamides, the *H*N-C*H*O protons are coupled with about 2 and 12 Hz, respectively. See for instance, L. A. La Planche and M. T. Rogers, *J. Am. Chem. Soc.*, **1964**, *86*, 337-341; A. J. R. Bourn, D. G. Gillies and E. W. Randall, *Tetrahedron*, **1964**, *20*, 1811-1818; M. Liler, *J. Chem. Soc. (B)*, **1971**, 334-338.
15. At room temperature, *N*-benzylformamide presents two isomers in $CDCl_3$ (*Z*/*E*=85/15%). The main NMR features (personal results) are the following, where the values belonging to the *Z*-isomer are underlined. δ_H: 4.31+4.38 (d+d, *J* 6.0, 0.3+1.7H, CH_2-Ph), 6.09+6.20 (br s+br s, 0.15+0.85H, NH), 8.03+8.13 [d (*J* 12.0)+s, 0.15+0.85H, CHO]; δ_C: 42.05+45.59 (*C*H_2-Ph), 137.44+137.56 (C_{ipso}), 161.08+164.69 (CHO). See also, C. J. Pouchert and J. Behnke, "The Aldrich Library of ^{13}C and ^1H FT NMR Spectra", Aldrich Chemical Company, Inc., 1993, vol. 2, spectrum n. 1359B, but the value of (*E*)-C_{ipso} is missing.
16. See for instance, G. Szalontai and A. Vass, *Acta Chim. Acad. Sci. Hung.*, **1979**, *102*, 413-421; J. Llinares, R. Faure, E. J. Vincent and J. Elguero, *Spectrosc. Lett.*, **1981**, *14*, 423-430; H. Petride, *Rev. Roum. Chim.*, **1994**, *39*, 547-561.
17. F. A. L. Anet and A. J. R. Bourn, *J. Am. Chem. Soc.*, **1965**, *87*, 5250-5251; M. Moriyasu, A. Kato and Y. Hashimoto, *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 939-940.
18. V. Král and Z. Arnold, *Coll. Czech. Chem. Commun.*, **1977**, *42*, 3455-3463; V. Král and Z. Arnold, *Coll. Czech. Chem. Commun.*, **1980**, *45*, 80-91; V. Král and Z. Arnold, *Coll. Czech. Chem. Commun.*, **1980**, *45*, 92-103.
19. A. A. Petrov, S. M. Esakov and B. A. Ershov, *Zh. Org. Khim.*, **1974**, *10*, 1988-1989.