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PAPERS

Dedicated to Professor Dr. ALEXANDRU T. BALABAN, member of the Roumanian Academy on the occasion of his 75th anniversary

COMPETITIVE AMIDE HYDROLYSIS IN MONO- AND DIFORMYLATED ETHYLENEDIAMINES

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Alkaline hydrolysis of formylated ethylenediamines of the general structure R^1-N(X)-CH_2CH_2-N(CHO)-R^2 (R^1, R^2 = H, benzyl, benzoyl; X = H, CHO) was studied in mild conditions. Breaking of the N-C amide bonds took place easily for HN-CHO or (benzoyl)N-CHO, hardly for (benzyl)N-CHO, and did not occur at all for N-COPh. Generally speaking, the various amide bonds underwent hydrolysis according to the following qualitative order of increasing reactivity: PhCO-N(H or alkyl)(alkyl or CHO) << HCO-N(alkyl)$_2$ < HCO-NH(alkyl) <<HCO-N(H or alkyl)(COPh). Reactions with benzaldehyde of various hydrolysis-derived amines were also investigated and found to give Schiff bases and/or imidazolidines, according to the particular substrate structure. The ^{1}H- and ^{13}C-NMR features of all compounds of interest are presented and discussed. Hindered rotation about the C-N amide bond(s) caused *E*/*Z* isomerism in mono- and diformylated derivatives.

INTRODUCTION

Similarly to the behavior of other *N*-benzylazacycloalkanes,[1a] preliminary investigation[1b] on the RuO_4-mediated oxidation of 1,4-dibenzyl- and 1-benzylpiperazine suggested the formation, along with benzaldehyde, of the acyclic diformamides **1A-E** (formulae in Scheme 1). They were accompanied also by other compounds, which could derive from them during the reaction mixture work-up, by hydrolysis. Therefore, these last compounds are not true oxidation products, but their presence could be indicative for the previous formation of **1A-E**. To clarify this point, we decided to study the hydrolysis of **1A-E** in conditions as close as possible to those employed for the RuO_4-oxidation mixtures work-up. As presented in the next Section *A*, a qualitative reactivity order resulted for the hydrolysis of various types of amide bonds in **1A-E**. Despite the vast experimental data on the amide hydrolysis (including enzymatic) existing in the literature,[2,3] few competitive reactions have been undertaken since now.[4-7] Our paper shows that there is much work to do even in this apparently overstudied field.

Some of the hydrolysis products are primary or secondary amines. During the RuO_4-mediated oxidation, they are formed in the presence of benzaldehyde and, consequently, could react with it. This was the reason that suggested us to study these reactions too. The respective results will be presented later in Section *B*.

Identification of the RuO_4-oxidation reaction products was[1a] and should be[1b] mainly achieved by ^{1}H- and ^{13}C-NMR spectroscopy. Consequently, particular attention was paid now to the NMR features of all hydrolysis- and benzaldehyde-derived products (Section *C*).

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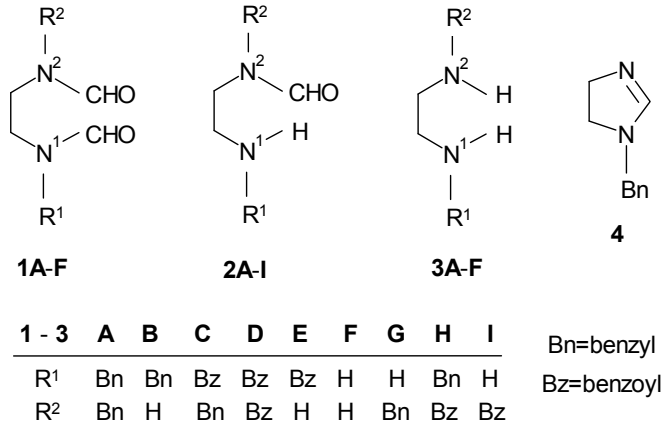
RESULTS AND DISCUSSION

A. Hydrolysis experiments

The formulae of the possible hydrolysis products (*i.e.*, **1F**, **2A-I**, and **3A-F**) originating from **1A-E**, as well as that of **4**, are shown in Scheme 1. To gain in clarity, we labeled by 1 and 2 superscripts the two nitrogen atoms in **1-3**. Imidazoline **4** was found as a minor reaction product during the preparation of some diformylated compounds (see Experimental Part). It probably resulted by thermal cyclodehydration of monoformylated intermediates of type **2**.[8]



1 - 3	A	B	C	D	E	F	G	H	I
R^1	Bn	Bn	Bz	Bz	Bz	H	H	Bn	H
R^2	Bn	H	Bn	Bz	H	H	Bn	Bz	Bz

Scheme 1

Table 1

Hydrolysis of some formamides

Entry	Substrate	Reaction conditions[a]	Time (hr)	Substrate conversion (%)[b]	Hydrolysis products (yield, %)[c]
0	1	2	3	4	5
1.	**1A**	*A* or *B*	6	0	no reaction
2.	**1B**	*A*	6	31	**2B** (22), **2G** (71.5), **3B** (6.5)
3.	**1B**	*B*	2	29	**2B** (21.5), **2G** (72.5), **3B** (6)
4.	**2B**+**2G**[d]	*B*	2	35 (**2B**), 11 (**2G**)	**3B** (100)[e]
5.	**1C**	*A*	2	10	**2C** (100)
6.	**1C**	*B*	2	55	**2C** (100), $PhCO_2H$ (<0.2)
7.	**2C**	*A* or *B*	6	0	no reaction
8.	**1D**	*B*	1	70	**3D** (100)
9.	**1D**	*B*	0.5	30	**2D** (38), **3D** (62)
10.	**1D**+**1E**[f]	*B*	1	68 (**1D**), 100 (**1E**)	**3D** (100), **2E** (50), **3E** (50)
11.	**2E**	*B*	1	48	**3E** (100)

[a] *A*: substrate/CH_2Cl_2/NaOH/H_2O = 1/10/10/10 (mmole/mL/mmole/mL), room temperature; *B*: as in *A*, but benzyltriethylammonium bromide (0.1 mmole/mmole of substrate) was added too. [b] Calculated with respect to its initial amount. [c] Relative to the corresponding reacted substrate. [d] **2B**/**2G**/**3B**=44/51/5% (molar). [e] Cumulated yield. [f] **1D**/**1E**=1/2 (molar).

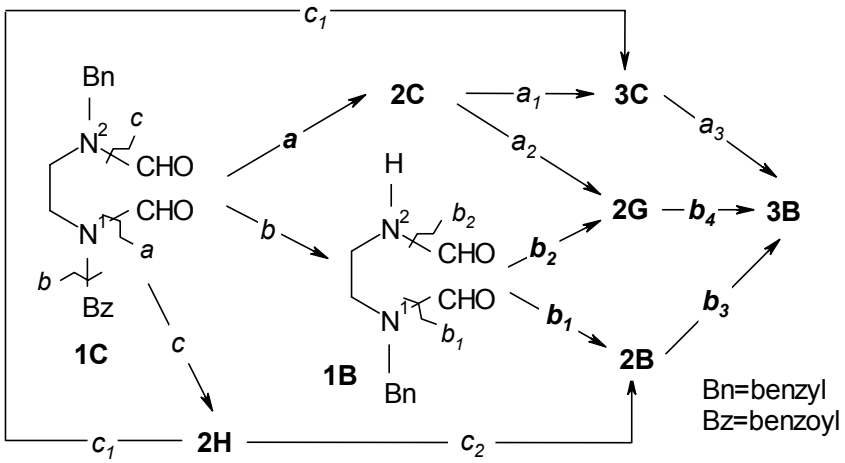
Hydrolysis experiments were performed at room temperature, in heterogeneous mixtures of CH_2Cl_2/aqueous NaOH, and for 0.5-6 hours. These mild conditions mimic those adopted for the RuO_4-oxidation mixtures work-up.[1,9] It is conceivable that the reaction occurs at the interface of the two phases, namely aqueous and organic, where the nucleophile (HO^-) and the substrate are present, respectively. Therefore, besides the presumably different substrate reactivity, the ease of the hydrolysis could be highly dependent on the mixing degree of the two phases. Accordingly, two sets of hydrolysis experiments were performed, that is without or in the presence of a surfactant [benzyltriethylammonium bromide (BTEAB)].

The most important results are summarized in Table 1 and discussed below using Schemes 2 and 3. The effectively observed hydrolysis paths were typed in **bold** within these schemes and in the main text.

Hydrolysis of the symmetrically substituted diformamide **1A** would give in a first stage the monoformamide **2A** and, subsequently, the diamine **3A**. Each step involves the expelling of a formic acid molecule as a formate anion. This reaction sequence was not found experimentally, the diamide **1A** being recovered unaltered, even in the presence of BTEAB (Table 1, entry 1).

Diformamide **1B** might be initially hydrolyzed to **2B** and/or **2G**, depending on the cleaved amide bond: N^1-CHO and/or N^2-CHO (Scheme 2, routes $\boldsymbol{b_1}$ and/or $\boldsymbol{b_2}$, respectively). Both intermediates should give the same diamine **3B**, as a final reaction product (routes $\boldsymbol{b_3}$ and $\boldsymbol{b_4}$). All these reactions seem to occur really. Thus, after six hours of reaction, **2B**, **2G**, and **3B** were all identified in the reaction mixture (Table 1, entry 2). In the presence of BTEAB, a similar result was obtained after two hours of reaction (entry 3). Because the amount of **3B** was relatively low, we can speculate about the HN-CHO/(benzyl)N-CHO reactivity ratio in **1B**. Thus, two hypothetical limiting cases might be considered for the reaction of entry 3: (i) all **3B** resulted from **2G** and (ii) **3B** resulted from **2B** only. Using the data of entry 3, we obtained (**2G**+**3B**)/**2B** = 3.65 in the first case and **2G**/(**2B**+**3B**) = 2.64 in the second. Therefore, the calculated reactivity ratio HN-CHO/(benzyl)N-CHO for **1B** could lie between these two values. Unfortunately, distinct hydrolysis of **2B** or **2G** could not be studied because they were not obtained separately (see Experimental). However, working with a 0.86/1 mixture of **2B**/**2G**, it was possible to see their hydrolysis to **3B** (entry 4). We note that (benzyl)N-CHO in **2G** resulted to be 3.2 times *less* reactive than HN-CHO in **2B** (entry 4, column 4: 35/11=3.18). This experimental value is within the range calculated before (*i.e.*, 2.64-3.65) for the reactivity ratio HN-CHO/(benzyl)N-CHO in **1B**. Consequently, a value close to 3.2 could be advanced too for the mentioned reactivity ratio in **1B**.

These results imply that an *N*-monoalkylated formamide could undergo hydrolysis more easily than an *N*,*N*-dialkylated one (*i.e.*, N^2-CHO in **2B** and **2G**, respectively). This is well documented in the literature and it was ascribed as originating from the different energies required to reach the tetrahedral intermediate in the rate-determining step.[2] The N^1-CHO function is of an *N*,*N*-dialkylated formamide type in both **1A**-**B**, but showed very different reactivity. This cannot be explained yet with the data at hand. A more extensive study on the hydrolysis paths $\boldsymbol{b_1}$-$\boldsymbol{b_4}$ will be published soon.[1b]

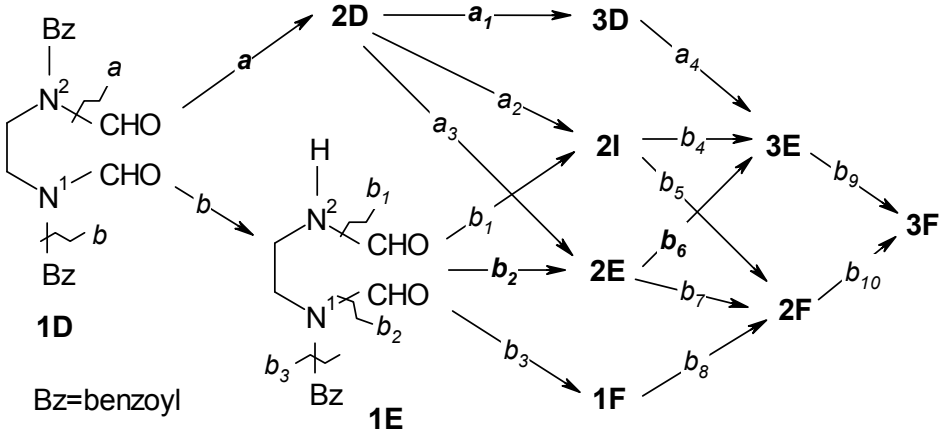


Scheme 2

Hydrolysis of **1C** might be, almost in principle, more complicated, because it contains three types of amide bonds prone to be broken. Thus, in a first stage, cleavage of N^1-CHO, PhCO-N^1, and/or N^2-CHO bonds of **1C** could give the diamides **2C**, **1B**, and/or **2H**, respectively (Scheme 2, routes *a*-*c*, resp.). Subsequent hydrolysis of these diamides would yield the monoamides **3C** [from **2C** (route a_1) and/or **2H** (route c_1)], **2G** [from **1B** (route b_2) and/or **2C** (route a_2)], and/or **2B** [from **1B** (route b_1) and/or **2H** (route c_2)]. All these monoamides should give the same final hydrolysis product, namely the diamine **3B**. In our

reaction conditions, the hydrolysis mixture obtained from **1C** contained **2C** as a practically single reaction product (Table 1, entries 5 and 6). No other NMR signals, attributable to **2H**, **1B**, or their possible hydrolysis products, were observed in the respective reaction mixtures' spectra. This means that only the route ***a*** was followed during the hydrolysis of **1C**. Because of these results, we did not synthesize further **2H**. We checked also the behavior of **2C** and found its inertness in our reaction conditions (entry 7). At a higher conversion of **1C**, a very small amount of benzoic acid was also found (entry 6). This does not change our previous conclusions on the active hydrolysis route of **1C**, but, at the same time, it suggests that alternative pathways (*i.e.*, *b*) could be also followed in more drastic reaction conditions.

Although belonging to the same general type of an *N*,*N*-disubstituted amide, the N^1-CHO group in **1A** is unlike that in **1C** because of the different nature of one N^1-substituent, namely benzyl and benzoyl group, respectively. The higher reactivity towards hydrolysis of N^1-CHO in **1C** *versus* that in **1A** might be ascribed to the different electronic effects provided by the incriminated substituents: electron-withdrawing in **1C**, but electron-releasing in **1A**. In fact, it is known that electron-withdrawing *N*-substituents accelerate the amide hydrolysis rate.[2] On the other hand, the data of entries 5 and 6 of Table 1 show that, within the imidic moiety of **1C** (*i.e.*, PhCO-N^1-CHO), the formyl group is much more able to undergo hydrolysis than the benzoyl one. This behavior has some precedents in the literature. Thus, *N*-formylbenzamide (*i.e.*, PhCO-NH-CHO), a compound very similar to the imidic moiety of **1C**, proved to be stable in pure water, but very easily hydrolysable in dilute NaOH aqueous solution. In this last case, only benzamide resulted,[5,6] that is the HN-CHO bond was broken and not PhCO-NH. A similar result was obtained during the mild alkaline hydrolysis of *N*-acetylsalicylamide.[7]



Scheme 3

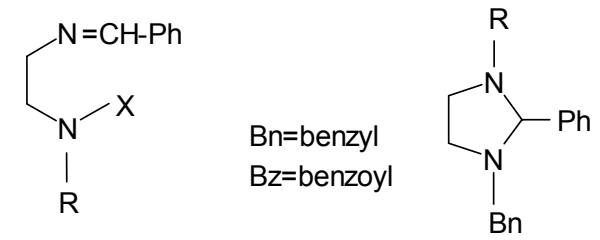
In principle, the hydrolysis of **1D** could follow the general Scheme 3, but, taking into account the previously discussed behavior of **1C**, the route *b* seems unlikely. In fact, after one hour, the unique reaction product found was **3D** (Table 1, entry 8), meaning that the active routes have been ***a*** and a_1. When the hydrolysis mixture was worked-up after a shorter reaction time (entry 9), the NMR spectra indicated the presence, besides **3D**, of another compound, which was not **1E**, **2E**, nor **3E**. Its NMR features (see Tables 2 and 3 in Section *C*), as well as its disappearance at longer reaction time with concomitant enhancement of the amount of **3D**, suggested the structure **2D**. Attempts to synthesize **2D** failed, but its transient formation during the hydrolysis of **1D** is not doubtful.

Compound **1E** was not obtained in a pure state, but mixed with **1D**.[10] Looking at Scheme 3, it results that the hydrolysis of **1E** can be really studied even in this case, because the expected routes b_1-b_{10} (from **1E**) do not interfere with *a* and a_1 (from **1D**). The reaction mixtures derived from **1D**+**1E** showed the formation, along with **3D**, of **2E** and **3E** (Table 1, entry 10). Additional experiment starting from **2E** confirmed its unique transformation into **3E** (entry 11). Accordingly, the hydrolysis of **1E** occurred only through the reaction paths b_2 and b_6. This was the reason that allowed us not to synthesize further and study **1F**, **2F**, or **2I**.

Summing up all information of this Section, it results that an amide bond may be hydrolyzed in mild alkaline conditions according to the following qualitative order of increasing reactivity: PhCO-N(H or alkyl)(alkyl or CHO) << HCO-N(alkyl)$_2$ < HCO-NH(alkyl) << HCO-N(H or alkyl)(COPh).

B. Reactions with benzaldehyde

As presented before, the mild hydrolysis of **1A-E** gave mono- and/or diamines. According to the substitution degree at the aminic nitrogen atom level and selecting only the amines effectively observed in Section *A*, the monoamines can be divided into primary (**2G**, **3E**) and secondary (**2B**). Analogously, the experimentally found **3B** can be seen as a (N^2)-primary-(N^1)-secondary diamine. Although not found in the hydrolysis mixtures of **1A**, we attached **3A** to the diamines' group, as an example of a secondary-secondary derivative. In all these compounds, the aminic *N*-substituents (if any) are of alkyl type. From these four kinds of amines, only the secondary monoamines cannot react efficiently with benzaldehyde. Consequently, we will discuss below the reactions of benzaldehyde with the remaining three types of amines. The formulae of the expected reaction products are shown in Scheme 4.



5: R=Bz, X=H
6: R=Bn, X=CHO
8: R=Bn, X=H

7: R=Bn
9: R=H

Scheme 4

It is well known that primary monoamines react easily with benzaldehyde to yield the corresponding Schiff bases. In fact, starting from **3E** or **2G**, the azomethine compounds **5**[11] and **6** were obtained, respectively (see Experimental Part).

It is also known that *N*-alkyl- or *N*,*N'*-dialkylethylenediamines react with benzaldehyde to give Schiff bases and/or imidazolidines.[12] For instance, only imidazolidine **7** could result from the N^1,N^2-dialkylated diamine **3A**. At the same time, starting from the N^1-monoalkylated diamine **3B,** both **8** and **9** are expected as reaction products. These predictions were entirely confirmed by our experiments (see Experimental Part). For instance, only **7** was obtained from **3A**, but a 1/2 mixture of **8**/**9** resulted from **3B**. Compound **7** was cited by Chapuis and his co-workers,[12] but without any details about preparation or characterization. We repeated its preparation in order to cover this gap. Derivatives **6-9** are all new compounds. Unfortunately, **6**, **8**, and **9** were obtained mixed with other compounds and all attempts to isolate them were unsuccessful. Their presence was deduced from the corresponding NMR spectra.

C. NMR spectra

As mentioned in the Introduction, the various RuO_4-oxidation reaction products obtained from 1-benzyl- and 1,4-dibenzylpiperazine should be identified especially by NMR spectroscopy.[1b] Accordingly, we considered highly necessary to have at hand the ^{1}H- and ^{13}C-NMR features of all compounds studied in this paper. The corresponding data are tabulated in Tables 2 and 3. The ^{1}H- and ^{13}C-NMR chemical shifts are expressed in ppm (δ scale) and were measured relatively to internal (CH_3)$_4$Si (δ_H=0 ppm) and the *C*DCl$_3$ peak (δ_C=77.01), respectively. Proton signal multiplicity is abbreviated as s-singlet, d-doublet, dd-doublet of doublets, t-triplet, td-triplet of doublets, q-quartet, m-multiplet, br-broad singlet, ABq-AB quartet. The assignments were made by two-dimensional NMR experiments, including the long-range ^{1}H-^{13}C heteronuclear correlation.

Table 2

^{1}H-NMR data[a] of compounds of interest

Compd.	Chemical shifts (400 MHz, δ, ppm, *J* in Hz, $CDCl_3$) and assignments[b]
2B[c,d]	2.77+2.78 (t+t, *J*=5.6, 2H, CH_2-N^1), 3.33+3.38 (q[e]+q,[e] *J*=5.6, 2H, CH_2-N^2), 3.77+3.78 (s+s, 0.3+1.7H, Bn), 6.99 (br, 0.85H, N^2H),[f] 8.02+8.14 [d (*J*=11.0)[g]+d (*J*=1.2),[g] 0.15+0.85H, N^2-CHO].
2C[c]	3.42 (t, *J*=5.6, 0.58H, CH_2-N^2), 3.49+3.52 [q (*J*=5.6)[e]+s, 3.32H, CH_2-N^1 and CH_2-CH_2], 4.47+4.59 (s+s, 1.42+0.58H, Bn), 6.86 (t, *J*=5.6, 0.29H, NH),[f] 7.23+7.27 (d+d, *J*=7.4, 1.42+0.58H, H_{ortho} of *Ph*-CH_2), 7.29-7.35 [m, 3.71H, H_{meta}+H_{para} of *Ph*-CH_2 and NH (at about 7.33)[f]], 7.37+7.41 (t+t, *J*=7.4, 2H, H_{meta} of *Ph*-CO), 7.46+7.48 (t+t, *J*=7.4, 1H, H_{para} of *Ph*-CO), 7.70+7.79 (d+d, *J*=7.4, 0.58+1.42H, H_{ortho} of *Ph*-CO), 8.12+8.34 (s+s, 0.29+0.71H, N^2-CHO).
2D[d]	3.73 (q,[e] *J*=5.6, 2H, N^1-CH_2), 4.14 (t, *J*=5.6, 2H, N^2-CH_2), 8.89 (s, 1H, N^2-CHO).
2E[c]	3.46+3.52 (q[e]+m,[e] *J*~5.4, 0.24+1.76H, CH_2-N^2), 3.54 (m,[e] *J*~5.4, 2H, CH_2-N^1), 6.67 (br, 1H, N^2H),[f] 7.22 (br, 1H, N^1H),[f] 7.36+7.43 (t+t, *J*=7.6, 2H, H_{meta}), 7.49 (t, *J*=7.4, 1H, H_{para}), 7.77+7.80 (d, *J*=7.6, 2H, H_{ortho}), 8.01+8.19 [d (*J*=12.0)[g]+d (*J*=1.2),[g] 0.12+0.78H, N^2-CHO].
2G[c,d]	2.77+2.78 (t+t, *J*=6.0, 2H, CH_2-N^1), 3.21+3.31 (t+t, *J*=6.0, 1.06+0.94H, CH_2-N^2), 4.43+4.54 (s+s, 0.94+1.06H, Bn), 8.23+8.32 (s+s, 0.53+0.47H, N^2-CHO).
3B	1.75 (br, 3H, N^1H+N^2H_2),[f] 2.66 (t, *J*=6.0, 2H, CH_2-N^1), 2.77 (t, *J*=6.0, 2H, CH_2-N^2), 3.77 (s, 2H, Bn), 7.20-7.33 (m, 5H, Ph).
3C	2.0 (br, 1H, N^2H),[f] 2.80 (t, *J*=5.6, 2H, CH_2-N^2), 3.47 (q,[e] *J*=5.6, 2H, CH_2-N^1), 7.18 (br, 1H, N^1H),[f] 7.20-7.30 (m, 5H, *Ph*-CH_2), 7.35+7.43+7.76 (t+t+d, *J*=7.2, 2+1+2H, H_{meta}+H_{para}+H_{ortho} of *Ph*-CO).
3D[h]	3.84 (s, 4H, CH_2-CH_2), 7.47+7.60+7.71 (t+t+d, *J*=7.5, 4+2+4H, H_{meta}+H_{para}+H_{ortho}).
3E	1.69 (s, 2H, N^2H_2),[f] 2.83 (t, *J*=5.6, 2H, CH_2-N^2), 3.41 (q,[e] *J*=5.6, 2H, CH_2-N^1), 7.33+7.42+7.80 (t+t+d, *J*=7.6, 2+1+2H, H_{meta}+H_{para}+H_{ortho}), 7.74 (br, 1H, N^1H).[f]
4	3.15 (t, *J*=10, 2H, CH_2-N-Bn), 3.80 (td, *J*=10 and 1.6, 2H, CH_2-N=CH), 4.29 (s, 2H, Bn), 7.00 (t, *J*=1.6, 1H, N=CH).
5	3.75 (br, 2H, CH_2-NH), 3.77 (br, 2H, CH_2-N=CH), 7.20 (br, 1H, NH),[f] 7.25-7.45 (m, 6H, H_{meta}+H_{para} of *Ph*-CO and *Ph*-CH), 7.69 (d, *J*=7.6, 2H, H_{ortho} of *Ph*-CH), 7.78 (d, *J*=7.6, 2H, H_{ortho} of *Ph*-CO), 8.25 (t, *J*=1.3, 1H, CH=N).
6[c,d]	3.54+3.57 (t+t, *J*=5.6, 1.08+0.92H, CH_2-N-CHO), 3.64+3.78 (td+td, *J*=5.6 and 1.4, 1.08+0.92H, CH_2-N=CH), 4.48+4.58 (s+s, 0.92+1.08H, Bn), 7.68+7.73 (dd+dd, *J*=7.6 and 2.0, 1.08+0.92H, H_{ortho} of *Ph*-CH=N), 8.04+8.25 (t+t, *J*=1.4, 0.54+0.46H, CH=N), 8.21+8.30 (s+s, 0.54+0.46H, CHO).
7	2.40-2.54+3.09-3.22 (m+m, 2+2H, CH_2-CH_2), 3.18+3.78 [d+d (ABq), J_{AB}=13.2, 2+2H, Bn], 3.83 (s, 1H, CH), 7.12-7.27 (m, 5H, *Ph*-CH_2), 7.32+7.38+7.64 (t+t+d, *J*=7.4, 1+2+2H, H_{para}+ H_{meta}+ H_{ortho} of *Ph*-CH).
8[d]	2.93 (t, *J*=5.2, 2H, CH_2-NH), 3.71 (t, *J*=5.2, 2H, CH_2-N=CH), 3.79 (s, 2H, Bn), 8.24 (s, 1H, CH=N).
9[d]	2.27-2.37+3.06-3.18 (m+m, 1+1H, CH_2-NH), 3.00-3.02+3.06-3.18 (m+m, 1+1H, CH_2-N-Bn), 3.11+3.78 [d+d (ABq), J_{AB}=13.0, 1+1H, Bn], 4.17 (s, 1H, CH), 7.57 (d, *J*=7.2, 2H, H_{ortho} of *Ph*-CH).

[a] Data useful in product identification are listed only. Coupling constants *J* are given in the order of cited multiplicity. [b] Bn stands for benzylic protons. [c] Two unequally populated *E*/*Z* isomers are present; the values belonging to the major one are underlined. [d] Data derived from mixtures of compounds (see Experimental Part). [e] Triplet with D_2O. [f] Vanishes with D_2O. [g] Singlet with D_2O. [h] In a $CDCl_3$/trifluoroacetic acid mixture.

Table 3

^{13}C-NMR data[a] of compounds of interest

Compd.	Chemical shifts (100 MHz, δ, ppm, $CDCl_3$) and assignments[b]
2B[c,d]	37.3+40.1 (CH_2-N^2), 47.6+47.8 (CH_2-N^1), 53.1+53.3 (Bn), *139.2*+*139.5*, 161.5+164.8 (CHO).
2C[c]	37.8+38.9 (CH_2-N^1), 41.6+46.3 (CH_2-N^2), 45.6+51.8 (Bn), 126.8(sh)+126.9 (C_{ortho} of *Ph*-CO), 127.5+128.1 (C_{ortho} of *Ph*-CH_2), 127.8 (C_{para} of *Ph*-CH_2), 128.3+128.5 (C_{meta} of *Ph*-CH_2), 128.8+129.0 (C_{meta} of *Ph*-CO), 131.4+131.6 (C_{para} of *Ph*-CO), *133.83*+*133.87* (of *Ph*-CO), *135.4*+*136.4* (of *Ph*-CH_2), 163.3+164.5 (N^2-CHO), 167.6+167.9 (N^1-CO).
2D[d]	38.6 (N^1-CH_2), 39.9 (N^2-CH_2), 164.5 (N^2-CHO), 167.9 (N^1-CO), 172.7 (N^2-*C*O-Ph).
2E[c]	38.2+41.5 (CH_2-N^2), 40.2+40.8 (CH_2-N^1), 126.9+127.7 (C_{ortho}), 128.3+128.4 (C_{meta}), 130.7+131.5 (C_{para}), *133.8*+*133.9*, 162.7+165.2 (N^2-CHO), 168.3+168.5 (N^1-CO).
2G[c,d]	38.9+39.2 (CH_2-N^1), 44.5+49.6 (CH_2-N^2), 45.4+51.6 (Bn), *135.8*+*136.3*, 163.2+163.5 (N^2-CHO).
3B	41.5 (CH_2-N^2), 51.7 (CH_2-N^1), 53.7 (Bn), 126.8 (C_{para}), 128.0 (C_{ortho}), 128.2 (C_{meta}), *140.2*.
3C	39.5 (CH_2-N^1), 47.9 (CH_2-N^2), 53.4 (Bn), 126.98 (C_{ortho} of *Ph*-CO), 127.04 (C_{para} of *Ph*-CH_2), 128.1 (C_{ortho} of *Ph*-CH_2), 128.40 (C_{meta} of *Ph*-CH_2), 128.42 (C_{meta} of *Ph*-CO), 131.25 (C_{para} of *Ph*-CO), *134.6* (of *Ph*-CO), *140.0* (of *Ph*-CH_2), 167.7 (CO).
3D[e]	40.5 (CH_2), 127.2 (C_{ortho}), 129.2 (C_{meta}), *131.3*, 133.5 (C_{para}), 172.3 (CO).
3E	41.0 (CH_2-N^2), 42.4 (CH_2-N^1), 126.7 (C_{ortho}), 128.0 (C_{meta}), 130.9 (C_{para}), *134.2*, 167.8 (CO).
4	47.8 (Bn), 47.9 (CH_2-N-Bn), 54.4 (CH_2-N=CH), *136.9*, 157.4 (N=CH).
5	40.5 (CH_2-NH), 59.9 (CH_2-N=CH), 126.7 (C_{ortho} of *Ph*-CO), 127.9 (C_{ortho} of *Ph*-CH), 128.2 (C_{meta} of *Ph*-CO), 128.3 (C_{meta} of *Ph*-CH), 130.6 (C_{para} of *Ph*-CH), 131.0 (C_{para} of *Ph*-CO), *134.3* (of *Ph*-CO), *135.6* (of *Ph*-CH), 162.5 (CH=N), 167.4 (CO).
6[c,d]	43.4+47.9 (CH_2-N-CHO), 46.3+52.7 (Bn), 59.29+59.35 (CH_2-N=CH), *135.6*+*136.0* (of *Ph*-CH=N), 128.17+128.23 (C_{ortho} of *Ph*-CH=N), 131.0+131.9 (C_{para} of *Ph*-CH=N), *136.3*+*136.7* (of *Ph*-CH_2), 162.6+163.2 (CH=N), 163.1+163.5 (CHO).
7	50.6 (CH_2-CH_2), 56.8 (Bn), 88.9 (CH), 126.7+128.0+128.5 (CH of *Ph*-CH_2), 128.1+128.3+129.5 (CH of *Ph*-CH), *139.1* (of *Ph*-CH_2), *140.3* (of *Ph*-CH).
8[d]	49.4 (CH_2-NH), 53.7 (Bn), 61.2 (CH_2-N=CH), *136.1* (of *Ph*-CH=N), *140.3* (of *Ph*-CH_2), 161.9 (CH=N).
9[d]	44.6 (CH_2-N-Bn), 52.4 (CH_2-NH), 56.5 (Bn), 83.0 (CH), 127.7 (C_{ortho} of *Ph*-CH), *136.1* (of *Ph*-CH), *139.5* (of *Ph*-CH_2).

[a] Data useful in product identification are listed only. [b] Bn stands for benzylic carbons. The value of aromatic C_{ipso} is given in *italics*. [c-e] See footnotes *c*, *d*, and *h* of Table 2, respectively.

The NMR data of **1A-E** are missing from Tables 2 and 3, because we already reported them.[10] We remember here that **1A-B** presented all possible *E*/*Z* stereoisomers, that is three and four, respectively, but **1C** and **1E** only those derived from the hindered rotation about N^2-CHO.[10] The easily available data[13] of **3A** were omitted too from Tables 2 and 3. In order to have a complete NMR characterization, the ^{1}H-NMR spectral features of **3E** were instead maintained in Table 2, even if similar to those reported elsewhere.[14]

Monoformamides **2B**, **2C**, **2E**, and **2G** presented two *E*/*Z* isomers, meaning that the hindered rotation about the N^2-CHO amide bond was slow enough for the NMR-time scale at room temperature.[10,15] As for **1C-E**,[10] we did not see distinct isomers due to the rotation about the N-COPh bond(s) in **2C-E** or about N^2-CHO in **2D**. This signifies that either (i) the registered spectrum was an average one (*i.e.*, free rotation) or (ii) only one particular isomer was present (*i.e.*, "frozen" rotation). A choice between them is not possible with the present data, but low-temperature NMR experiments might enlighten these cases. For **2B** and **2E**, it was easy to assign *Z*- and *E*-conformation to the HN^2-CHO group in the major and minor isomer, respectively. This became possible because of the quite different coupling constants (*J*) between the adjacent NH and CHO protons. In fact, it is known[10,16] that *J* is small (~2 Hz) for a *syn*-N*H*-C*H*O relationship (*i.e.*, *Z*-conformation), but large (~12 Hz) for an *anti*-one (*i.e.*, *E*-conformation). It emerges that the preferred conformation of N^2-CHO in **2B** and **2E** is *Z*.

By analogy with our previous data,[10] we assigned *E*- and *Z*-conformation to the N^2-CHO bond in the major and minor isomer of **2C**, respectively. For **2C** and other similar cases,[17] the N^2-CH_2(Ph) methylene protons were deshielded and the corresponding carbon atoms shielded on passing from *E*- to *Z*-conformation. If these opposite shifts are taken for granted, we are forced to assign a *Z*-conformation to N^2-CHO in the major isomer of **2G**. In other words, the preferred conformation of the discussed amide bond could be *E* in **2C** (*E*/*Z*=71/29%), but *Z* in **2G** (*E*/*Z*=47/53%), although in a quite relatively smaller degree.

A case similar to **2G** seems to be that of **6**. According to the aforementioned deductions, the *Z*-conformation of N-CHO in **6** was slightly preferred too (*E*/*Z*=46/54%). We note also that the CH_2-N=C*H* protons in both *E*/*Z* isomers of **6** were long-range coupled with 1.4 Hz. The same type of coupling was seen in a cyclic Schiff base, the imidazoline **4**.

Equally interesting were the NMR data of imidazolidines **7** and **9**. In both compounds, the benzyl protons appeared as AB quartets with J_{AB} of about 13 Hz. This anisochronicity can be ascribed to the existence of the asymmetrically substituted *C*H-Ph carbon atom.

CONCLUSIONS

Mild alkaline hydrolysis of compounds of general formula R^1-N(X)-CH_2CH_2-N(CHO)-R^2 (R^1, R^2 = H, benzyl, benzoyl; X = H, CHO) occurred at the N-CHO function only. The formamide moiety was easily hydrolyzed if it is of NH-CHO or (benzoyl)N-CHO type, but the (benzyl)N-CHO bond was broken more hardly. The following qualitative order of increasing reactivity resulted: PhCO-N(H or alkyl)(alkyl or CHO) << HCO-N(alkyl)$_2$ < HCO-NH(alkyl) << HCO-N(H or alkyl)(COPh). According to their particular structures, some of the amines formed by hydrolysis reacted with benzaldehyde to afford Schiff bases and/or imidazolidines. All hydrolysis- and benzaldehyde-derived compounds were unambiguously synthesized and fully characterized by NMR spectroscopy. In the NMR spectra at room temperature, some of these compounds presented *E*/*Z* isomerism due to the hindered rotation about the N-CHO amide bond. The preferred conformations were (*Z*)-NH-CHO and (*E*)-(benzyl)N-CHO, but for two compounds the (*Z*)-(benzyl)N-CHO conformation was slightly more stable than the (*E*)-one. In the case of imidazolidines, the N-CH_2-Ph protons were anisochronous in the corresponding NMR spectra, because of the asymmetry induced by the chiral N-*C*-N carbon atom.

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EXPERIMENTAL PART

General. Melting points were taken on a Boetius hot plate and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were registered either on a Varian Gemini A 300A apparatus or on a Bruker Avance DRX 400 instrument.

Materials. Diformamides **1A-E** were from our earlier work.[10] Commercial **3A-B** (from Aldrich) and **3F** (from Merck) were used as purchased. $CDCl_3$ was supplied by ITIMCD (Cluj-Napoca, Roumania). Compounds **3D**,[18] **4**,[8] and **5**[11] were prepared according to the indicated procedures. The ^{1}H- and ^{13}C-NMR spectral features of all compounds of interest were included in Tables 2 and 3, respectively. Derivatives **2C**, **2E**, **3C**-**E**, **4**, **5**, and **7** presented satisfactory (±0.3%) elemental analyses for C, H, and N.

Generation of *N*-(2-benzylaminoethyl)formamide (2B) and *N*-benzyl-*N*-(2-aminoethyl)formamide (2G). An equimolecular mixture of **3B** and HCO_2Et in CH_2Cl_2 as a solvent was refluxed for 20 hours. Solvent evaporation (max. bath temperature of 40°C, water pump) left a viscous residue which consisted of a 39/42/4.5/5.5/9% (molar) mixture of **2B**/**2G**/**4**/**3B**/**1B** (by NMR). The calculated yield (**2B**+**2G**+**4**+2***1B** *vs.* introduced HCO_2Et) was about 95%. The residue was partitioned between $CHCl_3$ and dilute aqueous HCl. The separated aqueous phase was carefully basified with saturated aqueous $NaHCO_3$ until pH 6, extracted with CH_2Cl_2, and the organic layer separated, dried (Na_2SO_4), and evaporated to afford a 44/51/5% (molar; by NMR) liquid mixture of **2B**/**2G**/**3B**. The recovery yield was about 60%. Monoamides **2B** and **2G** proved to be thermally sensitive. Attempts to isolate them by distillation gave complex mixtures containing various amounts of imidazoline **4**.

***N*-(2-Benzylformylaminoethyl)benzamide (2C)**. A mixture of **3C** (0.9 g, 3.54 mmole) and excess ethyl formate (5 mL, 62 mmole) was heated at reflux for 10 hours. The residue obtained after solvent evaporation was triturated with ether and recrystallized from $CHCl_3$/ether to give 0.7 g (yield 70%) of **2C**, as colorless crystals melting at 100-101°C.

Generation of *N*-formyl-*N*-(2-benzoylaminoethyl)benzamide (2D). Compound **1D**[10] (322 mg; 1 mmole) was hydrolyzed for 30 minutes in the conditions specified in Table 1 (entry 9) and the reaction mixture was worked-up as described below. The NMR spectra in $CDCl_3$ as a solvent indicated the presence of **2D** in a 38% yield (calculated with respect to the reacted **1D**), along with unreacted **1D** and some **3D**. It was not possible to isolate **2D**, because of its too high reactivity towards water giving always **3D**.

***N*-(2-Formylaminoethyl)benzamide (2E)** was prepared in an 82% yield from **3E** and excess ethyl formate, as described for **2C**. Colorless crystals melting at 104-105°C (from EtOAc) (lit.[19] mp 105-106°C).

***N*-(2-Benzylaminoethyl)benzamide (3C)**. Reduction of **5**[11] with excess $NaBH_4$ in methanol gave **3C** (yield 85%). It was purified through its hydrochloride, melting at 206-207°C after recrystallization from 2-propanol (lit.[11] mp 206-208°C).

***N*-(2-Aminoethyl)benzamide (3E)** was obtained by heating, at 90-95°C (internal temperature) and for 33 hours, a mixture of ethyl benzoate and a three-fold molar excess of ethylenediamine (**3F**), as suggested in the literature.[20,21] The evaporation residue was treated with $CHCl_3$ and the insoluble **3D** (yield 15%, based on ethyl benzoate) separated by filtration. Chloroform was eliminated *in vacuo* and the resulted crude **3E** was purified through its hydrochloride, as indicated elsewhere.[22] The oily free base **3E**, obtained in a 50% over-all yield (relative to ethyl benzoate), was soluble in $CHCl_3$. It should be kept under nitrogen in tightly closed vessels, because it rapidly absorbs CO_2 from the air to afford a crystalline carbonate (lit.[23] mp 132-140°C, with decomposition), sparingly soluble in $CHCl_3$. Attempts to distillate **3E** gave partially or totally 2-phenyl-2-imidazoline.[20,24]

Generation of *N*-benzyl-*N*-(2-benzylideneaminoethyl)formamide (6). (A) The previously obtained mixture of **2B**/**2G**/**3B** was heated with benzaldehyde in benzene. Solvent evaporation left a residue of which NMR spectra indicated the presence of **6** instead of **2G**. Attempts to isolate **6** were unsuccessful. (B) The crude 1/2 mixture of **8**/**9** (see below) was refluxed for 4 hours with a large excess of HCO_2Et. Evaporation gave a yellow liquid in which the corresponding formamides, namely **6** and the *N*-formyl derivative of **9**, were present (NMR results). Attempts to separate them were unfruitful.

1,3-Dibenzyl-2-phenylimidazolidine (7) was obtained in an 85% yield by azeotropic distillation with benzene of the requested water amount liberated from a stoichiometric mixture of **3A** and benzaldehyde. Colorless crystals melting at 98-99°C (from ethanol).

Generation of *N*-benzyl-*N'*-benzylidene-1,2-ethanediamine (8) and 1-benzyl-2-phenylimidazolidine (9). An equimolar mixture of **3B** and benzaldehyde was refluxed in benzene until all formed water separated in the Dean-Stark apparatus. The residue obtained after solvent evaporation consisted of a 1/2 mixture of **8**/**9** (cumulated yield of about 90%; by NMR). Attempts to isolate them by fractional recrystallization, distillation, or by column chromatography failed.

Hydrolysis experiments. One mmole of substrate was dissolved in 10 mL of CH_2Cl_2 and 10 mL of an aqueous 1 M NaOH solution was then added. Occasionally, 27 mg (0.1 mmole) of benzyltriethylammonium bromide (BTEAB) were added too to the reaction mixture before starting the stirrer. The heterogeneous mixture was magnetically stirred at room temperature and for the desired reaction time. The two layers were separated (*Note 1*) and the aqueous phase was continuously extracted with CH_2Cl_2. The new organic layer was combined with the older one, anhydrized (Na_2SO_4), and the solvent evaporated at the water pump to leave the residue I. The alkaline aqueous layer was acidified with HCl and continuously extracted with CH_2Cl_2. Treatment of the organic layer as before gave the residue II. Residues I and II were separately dissolved in $CDCl_3$ (*Note 2*) and analyzed by NMR (*Note 3*) in the presence of a known amount of cyclohexane, as an internal standard for the integrals' measurement. When possible, the amounts of the various reaction products, calculated from the NMR spectra, were corrected by blank experiments concerning the same work-up as before, but applied to synthetic mixtures of compounds. Residue II contained all benzoic acid (if formed).

Note 1. When starting from **1D** or **1D**+**1E**, most of **3D** precipitated during the reaction, as a white solid. It was recovered by filtration, before separating the two layers.

Note 2. If the residue I contains **3D**, the first NMR analysis in $CDCl_3$ as a solvent was followed by a second one in a $CDCl_3$/CF_3COOH mixture.

Note 3. In the case of **3E**-containing residue I, the NMR analysis should be performed immediately, to avoid the fast transformation of **3E** into its $CDCl_3$-insoluble carbonate.[23]

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