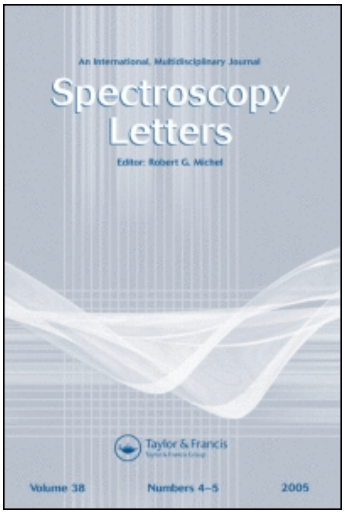

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N → N′ ACYL MIGRATION IN AN ETHYLENEDIAMINE DERIVATIVE: ISOLATION AND NMR CHARACTERIZATION OF A REACTION INTERMEDIATE

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ABSTRACT

The isolation and characterization by ^{1}H and ^{13}C-NMR spectroscopy of a reaction intermediate in a rearrangement with acyl migration in an ethylenediamine derivative is presented.

Key Words: ^{1}H and ^{13}C-NMR spectroscopy; Intermediate isolation; Intramolecular aminolysis of amides; Acyl migration; Carbinolamine; Dihydroimidazolium ion.

INTRODUCTION

Type **I** cyclic hemiorthoamides have been proposed as intermediates in the hydrolysis of 1*H*-4,5-dihydroimidazolium salts **1** (n = 2) [1–3] and their homologues [3,4] (Scheme 1), which are related to N^5, N^{10}-methenyl-tetrahydrofolic

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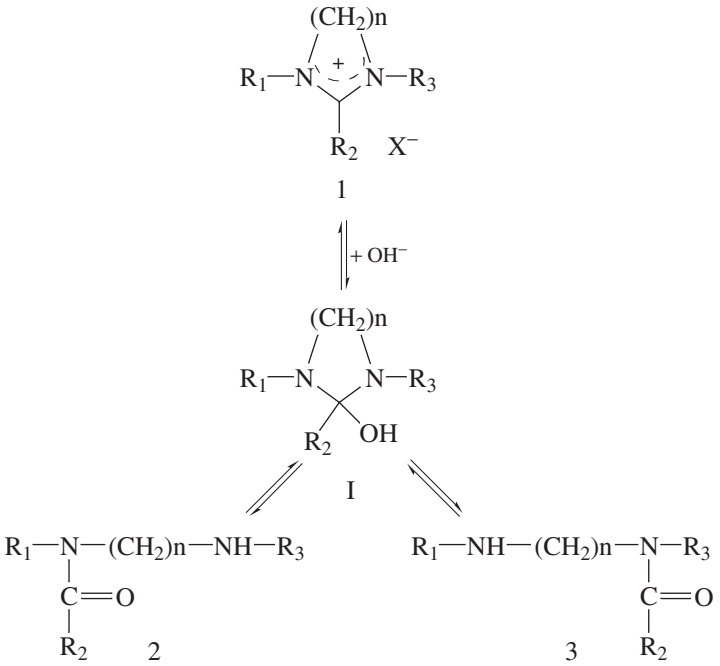

Scheme 1.

acid, an important cofactor that participates in the transfer of single-carbon units at formic acid oxidation level [5,6].

Due to the presence of hydroxyl hydrogen carbinolamines **I** cleave spontaneously and in regiospecific fashion when nitrogen substituents are dissimilar, giving rise to *N*-acylalkylenediamines (**1** → **2** or **3**). These carbinolamine pseudobases have also been proposed as intermediates in intramolecular transfer of acyl groups in alkylenediamine derivatives (**2** → **3** or vice versa), in neutral or alkaline medium (Scheme 1) [3,4,7]. In the study of involved reaction mechanisms, detection or evidence of this intermediate type is crucial. However, this is hindered by the ready opening of the carbinolamine subsequent to a prototropic process mediated by the oxianion or by the protonated carbinolamine [2], depending on the experimental *p*H value [8]. Despite such limitations, the lifetime of such compounds has allowed some cases to be detected by UV spectroscopy [3,7,10]. However, as far as we know, the isolation and characterization of this intermediate type by NMR spectroscopy has not been reported in any case [11].

In this work we present the isolation and characterization by ^{1}H and ^{13}C-NMR of the intermediate involved in the intramolecular aminolysis reaction leading to the migration of a benzoyl group in an ethylenediamine derivative (**2a** → **3a**, Scheme 2).

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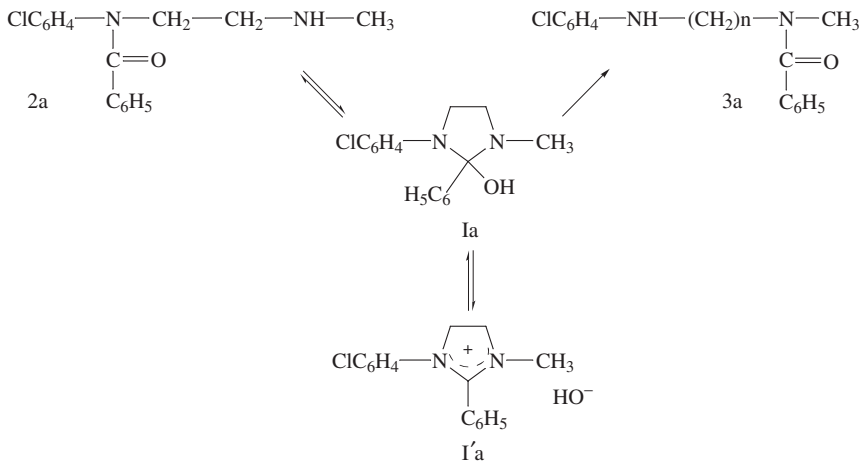

Scheme 2.

EXPERIMENTAL

The ^{1}H and ^{13}C-NMR spectra were recorded on a Bruker MSL 300 MHz using deuteriochloroform as solvent. Chemical shifts are quoted in parts per million (δ) downfield from an internal tetramethylsilane reference. The presence of exchangeable protons was confirmed by the use of deuterium oxide. Proton signals are quoted as: s (singlet), bs (broad singlet), d (doublet), t (triplet), bt (broad triplet) and m (multiplet).

Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

N-Benzoyl-*N*-(*p*-chlorophenyl)-*N*′-methylethylenediamine (**2a**) was obtained by hydrolysis of 1-(*p*-chlorophenyl)-3-methyl-2-phenyl-1*H*-4,5-dihydroimidazolium iodide (**1a**) according to literature [12]. The oil obtained shows the presence of compound **2a** as the main product with small amounts of *N*-benzoyl-*N*′-(*p*-chlorophenyl)-*N*-methylethylenediamine (**3a**) [12]. In order to accomplish complete transformation **3a** → **2a**, a solution of the above mixture 1×10^{-2} M in 5% H_2SO_4 was prepared, and thermostated at 25° C ± 0.1 for at least one week.

Sample Preparation and Chromatographic Experiments

An aliquot (20 ml) of **2a** solution (1×10^{-2} M in 5% H_2SO_4) was treated with solid sodium carbonate to *p*H 8.

Reaction was monitored (TLC) employing Aluminium sheets (Silica Gel 60 $F_{254+366}$) and using chloroform-methanol (8:2, v/v) as eluent. Compounds **2a** and

3a purified to analytical grade were employed as standards. Appropriate UV light was used to locate the separated spots.

Preparative thin layer separations (PLC) were carried out by centrifugally accelerated radial chromatography using Chromatotron model 7924T. The rotors were coated with Silica Gel 60 PF_{254} and the layer thickness was 2 mm. Separation was achieved applying compound **2a** in aqueous solution at *p*H 8 (10 ml), prepared as indicated above, with *ca*. 50 hs. of reaction time. The plate was carefully dried and eluted with a gradient of chloroform-methanol (9:1 to 7:3). The eluted fractions were concentrated to dryness at 20°C with nitrogen flow.

RESULTS AND DISCUSSION

With the purpose of detecting, isolating and characterizing by NMR spectroscopy a type **I** carbinolamine intermediate in reactions leading to N → N′ acyl transfer in *N*-acylalkylenediamines, *N*-benzoyl-*N*-(*p*-chlorophenyl)-*N*′-methylethylenediamine (**2a**) was chosen as starting product. To such end, a sample of this compound in aqueous solution at *p*H 8 was allowed to react, while it was monitored by TLC using chloroform-methanol (8:2) as eluent. Initially, compound **2a** alone was detected (Rf *ca*. 0.25). One hour later there were traces of a new spot of lower Rf (*ca*. 0.05) that increased in intensity as the reactant diminished and the final product **3a** became detectable (Rf 0.80). At 48-50 hs of reaction time, the greatest intensity of the lower Rf product was observed, which coexisted with **2a** and **3a**. In roughly 7 days the transformation into **3a** was complete (Scheme 2).

The separation of the compounds present in a sample with 50 hs reaction time was carried out by preparative centrifugally accelerated radial chromatography. Three bands were obtained, analyzed by ^{1}H-NMR spectroscopy and the spectra compared with those of authentic samples of compounds **2a** and **3a**, as well as of related 1*H*-4,5-dihydroimidazolium iodide **1a** [12] and 1-(*p*-chlorophenyl)-3-methyl-2-phenylimidazolidine **4** [13] (Table 1).

The ^{1}H-NMR spectrum of the first eluted band corresponds to compound **3a**, presenting the *N*-CH_3 signal at 3.00 ppm, and the methylene groups *a* and *b* at 3.40 and 3.85 ppm respectively (Table 1). The latter two signals present characteristically as wide triplets with a poorly defined partition mainly due to the presence of two rotamers subsequent to electronic delocalization of benzamide [14]. The aromatic hydrogens of the *p*-chloroaniline ring resonate at 6.60 and 7.10 ppm (doublets), displaying the shielding effect typical of aniline *ortho* hydrogens.

The ^{1}H-NMR spectrum of the compound isolated from the second fraction corresponds to the starting benzamide **2a** presenting the N-CH_3 at 2.40 ppm, the signals of the methylene hydrogens as sharp triplets at 2.70 and 4.00 ppm (hydrogens *b* and *a* respectively) and the aromatic hydrogens as a complex multiplet at 7.00-7.40 ppm.

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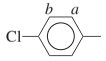
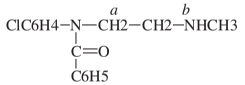
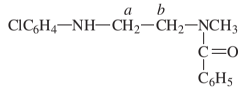
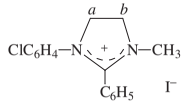
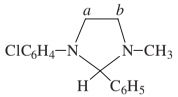
Table 1. 1H-MNR Spectra [δ (ppm)] of Compounds **1a**, **2a**, **3a**, **4**, and **I′a**

Compound	N-CH_3	CH_2a	CH_2b			Others
2a 	2.40, s	4.00, t	2.70, t	7.00–7.40, m		1,85, bs (NH)
3a 	3.00, s	3.40, bt	3.85, bt	6.60, d (*a*) 7.10, d (*b*)	7.00–7.40, m	3.50, bs (NH)
1a 	3.20, s	4.40–4.60, m (centrosymmetric)		7.10, d (*b*) 7.31, d (*a*)	7.30–7.40, m (*d*) 7.50, t (*e*) 7.70, d (*c*)	
4 	2.30, s	2.70, m; 3.30, m; 3.60, m; 3.90, m		6.40, d (*a*) 6.90, d (*b*)	7.30–7.50, m	4.60, s (C_2-H)
I′a	3.30, s	4.40–4.60, m (centrosymmetric)		7.80, d (*c*) 7.20–7.60, m		

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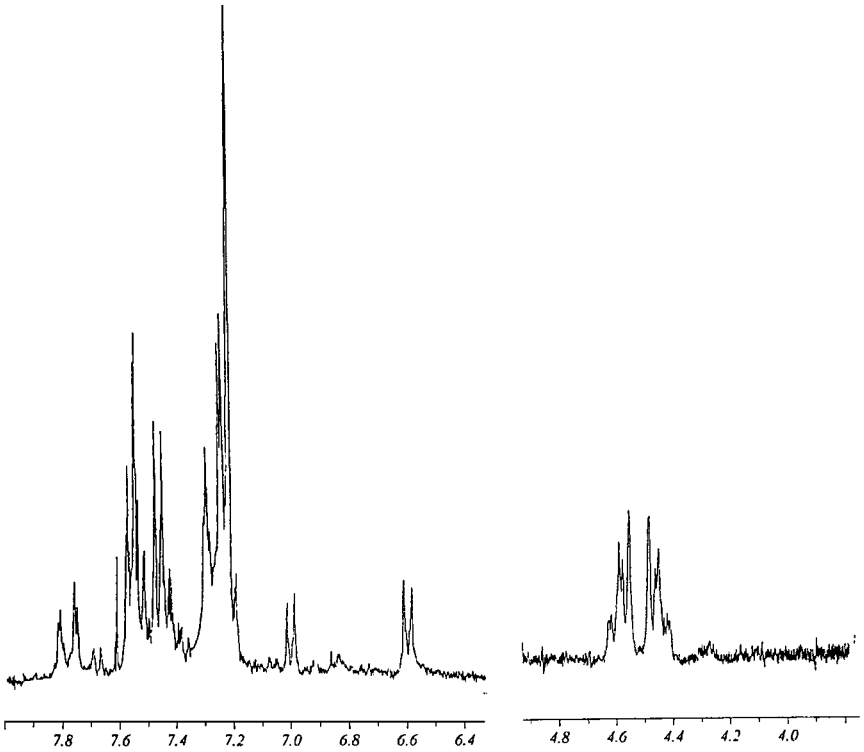

Figure 1. [1]H-NMR spectrum of the isolated intermediate (deuteriochloroform).

In the spectrum of the third fraction (Figure 1), there are three characteristic signals that suggest the presence of the dihydroimidazolium cation and are taken as evidence of the **I′a** form (Scheme 2), namely, N-CH_3 at 3.30 ppm, the ethylene group as a centrosymmetric multiplet at 4.40-4.60 ppm and one aromatic hydrogen at 7.80 ppm.

The ethylene multiplet is slightly differentiated into two multiplets and corresponds to a AA′BB′ coupling system; chemical shifts to lower fields regarding compounds **2a**-**4** clearly indicate the marked electronic deficit at heterocyclic ring level. Within the aromatic moiety of the spectrum, the doublet at 7.80 ppm is assigned to *ortho* hydrogen of the C_2 phenyl group, which also appears in the corresponding 1*H*-4,5-dihydroimidazolium salt [15]. Besides, this spectrum discloses a doublet at 6.60 ppm and a N-CH_3 group at 2.30 ppm compatible with an imidazolidine structure suggesting the presence of the carbinolamine **Ia**. Although these signals could be associated respectively to amides **3a** and **2a**, the presence of acyclic alkylenediamines in this fraction was ruled out, since in the spectral

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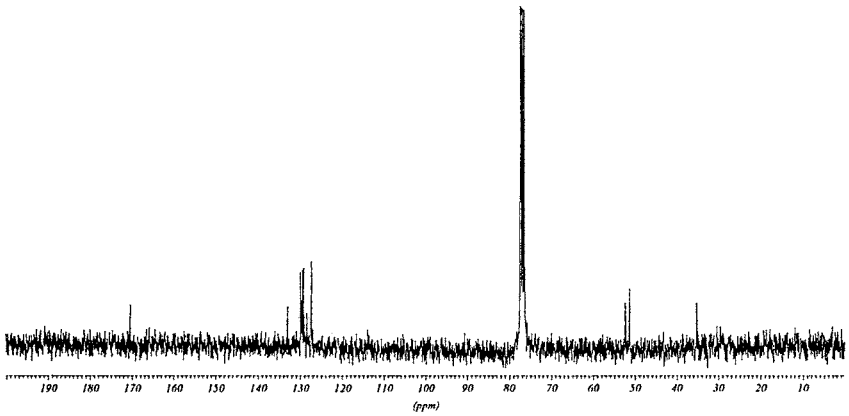
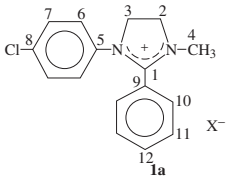


Figure 2. ^{13}C-NMR spectrum of the isolated intermediate (deuteriochloroform).

range from 3.80 to 4.40 ppm there are no signals corresponding to the methylene hydrogens either in **2a** or in **3a** (4.00 and 3.85 ppm respectively).

The ^{13}C-NMR spectrum (Figure 2) of the third fraction displays the signals corresponding to the **I′a** species, which are in agreement with those of 1*H*-4,5-dihydroimidazolium iodide **1a** [15] (Figure 2, Table 2). Due to the weaker sensitivity of ^{13}C-NMR spectra and to the low concentration of the **Ia** species, in this

Table 2. ^{13}C-NMR Spectra [δ (ppm)] of Compound **1a** and the Intermediate **I′a**



1a

Compound	C_1	C_2	C_3	C_4	Others
1a (X^-=I^-)	163.5	51.3	52.4	35.3	5,8: 134.3, 135.0 9: 121.5 6,7,10-12: 127.7, 129.1, 129.5, 129.6, 132.5
I′a (X^-=OH^-)	170.4	51.3	54.4	35.3	127.3, 128.4, 129.0, 129.2, 129.5, 129.9, 132.9

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fraction no **Ia** signals are detected.

Taking into account our results, a cyclic structure wherein under the conditions of spectroscopic analysis (Cl_3CD) an ionic species (imidazolinium hydroxide **I′a**) coexists with a covalent one as carbinolamine **Ia**, is proposed for the isolated reaction intermediate (Scheme 2). This supports the contention that these two compounds are in anionotropic equilibrium [16]. However, to the best of our knowledge, it is the first case in which both species are detected simultaneously.

ACKNOWLEDGMENTS

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