Spectroscopic Analysis of Imidazolidines. Part II: ^{1}H NMR Spectroscopy and Conformational Analysis of 1,2 and 1,3-Diarylimidazolidines

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^{1}H NMR spectra of a series of 1,2 and 1,3-diarylimidazolidines are analyzed and correlated with their conformational features. Results were interpreted on the basis of chemical shifts and coupling constants of hydrogen atoms and confirmed by 1D nOe difference experiments. 1,3-Diarylimidazolidines (**1-7**) show a fast inversion of the *N*-aryl nitrogen in all studied cases. 1,2-Diaryl-3-methyl (or benzyl) imidazolidines (**8-13**) display a preferential conformation with a transoid orientation of N_3 and C_2 substituents.

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Introduction.

The importance of imidazolidines as synthetic models of the coenzyme N^5,N^{10}-methylenetetrahydrofolic acid was pointed out in our previous work of this series [1]. Besides, the synthesis and study of this type of compounds present interest from a chemical point of view as synthetic intermediates of cyclic and acyclic compounds with the ethylenediamine structural unit. Thus, dehydrogenation of imidazolidines leads to 1*H*-4,5-dihydroimidazolium salts [2] and their selective reduction to *N*,*N*,*N'*-trisubstituted ethylenediamines [3]. Imidazolidines have also been studied as plant-protective agents [4] and as regards their insecticide [5] and pharmacological activity, which is closely related to the substitution type. Accordingly, a large number of these compounds with diverse properties such as estrogenic activity [6] and mammary tumor inhibition [7], as well as antimycotic [8] and antiinflammatory agents [9], have been described in the literature.

The study of conformational features and substituent orientation in molecules of biological interest has been the object of several investigations in order to elucidate structure-activity correlations. However, data on imidazolidine conformation studies are scarce in the literature and limited to substituted 1,3-dialkyl compounds [10-13].

In this work we present the conformational analysis by ^{1}H NMR spectroscopy of a series of 1,2 and 1,3-diaryl substituted imidazolidines **1-13** (Table I) with potential pharmacological activity. The assignment was mainly carried out considering the orientational dependence of nitrogen lone electron pair on chemical shifts [14] and coupling constants of hydrogen atoms of the heterocyclic ring and confirmed by 1D nOe difference experiments.

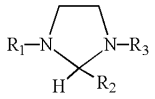
Results and Discussion.

1,3-Diarylimidazolidines (**1-7**) (Table II).

^{1}H NMR spectra at room temperature of compounds **1-5** show isochronicity of ethylene hydrogens of the heterocyclic ring and those of C_2 appearing as two singlets at *ca.* δ 3.50 ppm (Hb-e) and 4.50 ppm (Ha), practically independent of the substituent on the phenyl group. As in 1,3-dimethylimidazolidine [10], these features are consistent with fast *N*-inversion at room temperature. Besides, in our case a more rapid inversion of the nitrogens linked to phenyl groups was to be expected due to conjugation of the nitrogen electron pair with such groups, thus stabilizing the transition state of the process [16].

Table I

Imidazolidines **1-13**

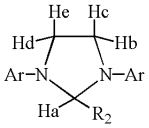


Compound	R_1	R_2	R_3
1	C_6H_5	H	C_6H_5
2	*p*-ClC_6H_4	H	*p*-ClC_6H_4
3	*p*-$CH_3C_6H_4$	H	*p*-$CH_3C_6H_4$
4	*p*-$CH_3OC_6H_4$	H	*p*-$CH_3OC_6H_4$
5	*p*-$C_2H_5OC_6H_4$	H	*p*-$C_2H_5OC_6H_4$
6	C_6H_5	CH_3	C_6H_5
7	C_6H_5	C_6H_5	C_6H_5
8	C_6H_5	C_6H_5	CH_3
9	*p*-$CH_3OC_6H_4$	C_6H_5	CH_3
10	*p*-$CH_3C_6H_4$	C_6H_5	CH_3
11	*p*-ClC_6H_4	C_6H_5	CH_3
12	*p*-$NO_2C_6H_4$	C_6H_5	CH_3
13	*p*-ClC_6H_4	C_6H_5	$CH_2C_6H_5$

Compound **6** with a methyl group on C_2 presents spectroscopic features similar to the previous compounds. Instead, the introduction of a phenyl group in the same position (compound **7**) causes magnetic nonequivalence of the geminal hydrogens of the ethylenediamine moiety, originating a centrosymmetric multiplet corresponding to AA'BB' system with two multiplets centered at δ 3.70 and 3.90 ppm. The observed difference should be ascribed to the presence of the C_2-phenyl group, causing a general paramagnetic shift of the Hb-d attributable to the perpendicular orientation of this group to the C_4-C_5 bond and the imidazolidine ring, the more affected hydrogens being those in position *cis* to the benzene nucleus (Hc,e) [17].

Table II

^{1}H NMR Spectra of 1,3-Diarylimidazolidines **1-7**

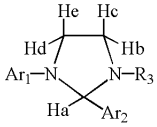


Compound	Ha	Hb	Hc	Hd	He	Ar	R_2
1	4.70 (s) [a]		3.50 (s)			6.60-6.80 (m), C_6H_5, 2 *ortho* and *para* H 7.30 (dd), C_6H_5, 2 *meta* H	[b]
2	4.45 (s) [a]		3.50 (s)			6.45 (dd), *p*-ClC_6H_4, 2 *ortho* H 7.15 (dd), *p*-ClC_6H_4, 2 *meta* H	[b]
3	4.55 (s) [a]		3.56 (s)			6.50 (d), *p*-$CH_3C_6H_4$, 2 *ortho* H 7.10 (d), *p*-$CH_3C_6H_4$, 2 *meta* H 2.30 (s), *p*-$CH_3C_6H_4$	[b]
4	4.55 (s) [a]		3.60 (s)			6.55 (d), *p*-$CH_3OC_6H_4$, 2 *ortho* H 6.88 (d), *p*-$CH_3OC_6H_4$, 2 *meta* H 3.70 (s), CH_3	[b]
5	4.50 (s) [a]		3.55 (s)			6.70 (d), *p*-$C_2H_5OC_6H_4$, 2 *ortho* H 6.91 (d), *p*-$C_2H_5OC_6H_4$, 2 *meta* H 3.90 (q), CH_2O 1.42 (t), CH_3	[b]
6	5.40 (q)		3.60 (s)			6.60-6.80 (m), C_6H_5, 2 *ortho* and *para* H 7.30 (m), C_6H_5, 2 *meta* H	1.30 (d), CH_3
7 [c]	6.00 (s)	3.70 (m)	3.90 (m)		3.70 (m)	3.90 (m)6.70 (m), C_6H_5, 2 *ortho* and *para* H 7.40 (m), C_6H_5, 2 *meta* H	7.20-7.30 (m), C_6H_5

[a] This signal corresponds to two protons. [b] For this compounds R_2=H correspond to Ha. [c] In this compound Hb,d and Hc,e are *trans* and *cis* to C_2–phenyl respectively.

Table III

^{1}H NMR Spectra of 1,2-Diaryl-3-methyl (or benzyl) imidazolidines **8-13** [a]



Compound	Ha	Hb	Hc	Hd	He	Ar_1	Ar_2	R_3
8 [b]	4.52 (s)	2.73 (dt)	3.30 (ddd)	3.60 (ddd)	3.75 (ddd)	6.40-6.60 (m), C_6H_5, 2 *ortho* and *para* H 7.30 (m), C_6H_5, 2 *meta* H	7.40 (s), C_6H_5	2.20 (s), CH_3
9 [c]	4.62 (s)	2.81 (dt)	3.30 (ddd)	3.62 (ddd)	3.81 (ddd)	6.60 (d), *p*-$CH_3OC_6H_4$, 2 *ortho* H 6.90 (d), *p*-$CH_3OC_6H_4$, 2 *meta* H 3.75 (s), CH_3O	7.50 (s), C_6H_5	2.30 (s), CH_3
10 [d]	4.48 (s)	2.80 (dt)	3.35 (ddd)	3.65 (ddd)	3.80 (ddd)	6.40 (d), *p*-$CH_3C_6H_4$, 2 *ortho* H 7.40 (d), *p*-$CH_3C_6H_4$, 2 *meta* H 2.40 (s), CH_3	7.35 (s), C_6H_5	2.25 (s), CH_3
11 [e]	4.50 (s)	2.77 (dt)	3.28 (ddd)	3.60 (ddd)	3.75 (ddd)	6.50 (dd), *p*-ClC_6H_4, 2 *ortho* H 6.90 (dd), *p*-ClC_6H_4, 2 *meta* H	7.20-7.30 (m) C_6H_5	2.25 (s), CH_3
12 [f]	4.66 (s)	2.75 (dt)	3.26 (ddd)	3.63 (ddd)	3.78 (ddd)	6.51 (d), *p*-$NO_2C_6H_4$, 2 *ortho* H 8.10 (d), *p*-$NO_2C_6H_4$, 2 *meta* H	7.40 (s), C_6H_5	2.35 (s), CH_3
13 [g]	5.00 (s)	3.20 (dt)	2.90 (ddd)	3.60 (m)	3.75 (m)	6.45 (dd), *p*-ClC_6H_4, 2 *ortho* H 7.10 (dd), *p*-ClC_6H_4, 2 *meta* H	7.30-7.40 (m) C_6H_5 7.30-7.40 (m), CH_2-C_6H_5	3.55 (d) and 3.75 (d),CH_2-C_6H_5 [h]

[a] Hb,d are *cis* to R_3 and *trans* to R_2. Hc,e are *trans* to R_3 and *cis* to R_2. [b] $^2J_{Hb\text{-}Hc}$ = 9.75 Hz, $^2J_{Hd\text{-}He}$= 8.50 Hz, $^3J_{Hb\text{-}Hd}$ = 7.30 Hz, $^3J_{Hb\text{-}He}$ = 7.30 Hz, $^3J_{Hc\text{-}Hd}$ = 6.50 Hz, $^3J_{Hc\text{-}He}$ = 4.20 Hz. [c] $^2J_{Hb\text{-}Hc}$ = 9.75 Hz, $^2J_{Hd\text{-}He}$ = 8.60 Hz, $^3J_{Hb\text{-}Hd}$ = 7.27 Hz, $^3J_{Hb\text{-}He}$ = 7.27 Hz, $^3J_{Hc\text{-}Hd}$ = 6.60 Hz, $^3J_{Hc\text{-}He}$ = 4.28 Hz. [d] $^2J_{Hb\text{-}Hc}$ = 9.70 Hz, $^2J_{Hd\text{-}He}$ = 8.50 Hz, $^3J_{Hb\text{-}Hd}$ = 7.32 Hz, $^3J_{Hb\text{-}He}$ = 7.32 Hz, $^3J_{Hc\text{-}Hd}$ = 6.50 Hz, $^3J_{Hc\text{-}He}$ = 4.30 Hz. [e] $^2J_{Hb\text{-}Hc}$ = 9.65 Hz, $^2J_{Hd\text{-}He}$ = 8.63 Hz, $^3J_{Hb\text{-}Hd}$ = 7.35 Hz, $^3J_{Hb\text{-}He}$ = 7.35 Hz, $^3J_{Hc\text{-}Hd}$ = 6.60 Hz, $^3J_{Hc\text{-}He}$ = 4.35 Hz. [f] $^2J_{Hb\text{-}Hc}$ = 9.75 Hz, $^2J_{Hd\text{-}He}$ = 8.60 Hz, $^3J_{Hb\text{-}Hd}$ = 7.35 Hz, $^3J_{Hb\text{-}He}$ = 7.35 Hz, $^3J_{Hc\text{-}Hd}$ = 6.60 Hz, $^3J_{Hc\text{-}He}$ = 4.30 Hz. [g] $^2J_{Hb\text{-}Hc}$ = 10.40 Hz, $^2J_{Hd\text{-}He}$ = 8.50 Hz, $^3J_{Hb\text{-}Hd}$ = 6.30 Hz, $^3J_{Hb\text{-}He}$ = 6.30 Hz, $^3J_{Hc\text{-}Hd}$ = 6.40 Hz, $^3J_{Hc\text{-}He}$ = 5.27 Hz, [h] $^2J_{H\text{-}H}$ = 12.20 Hz.

1,2-Diaryl-3-methylimidazolidines (**8-12**) (Table III).

In all ^1H NMR spectra, this imidazolidine series shows the Ha signal as a singlet at *ca.* δ 4.50 ppm. Unlike 1,3-dialkylimidazolidines [11] no long range coupling constants ($^4J_{H-H}$) are observed.

Hb-e appear as four separate signals, each one corresponding to a symmetrical multiplet, whose geminal and vicinal coupling constants were calculated directly from the spectrum. Signal assignment was made for 1-*p*-methylphenyl-3-methyl-2-phenylimidazolidine (**10**) whose ethylene hydrogens resonate at 2.80, 3.35, 3.65 and 3.80 ppm.

The analysis of geminal coupling constants allows grouping the geminal hydrogen atoms of the ethylenediamine moiety in two pairs: 2.80 and 3.35 ppm ($^2J_{Hb-Hc}$ = 9.70 Hz) and 3.65 and 3.80 ppm ($^2J_{Hd-He}$ = 8.50 Hz). Consistently with this assignment in the HMQC spectrum, the signals at lower frequency correlated with the one corresponding to a carbon atom (δ 55.7 ppm) and resonances at 3.65 and 3.80 ppm to the other ethylene carbon (δ 48.4 ppm). Taking as reference compound **3** and 1,3-dimethylimidazolidine [19], the two resonances at lower frequency were initially assigned to the hydrogen atoms adjacent to the *N*-CH_3 group, and the other two to the ones adjacent to the *N*-C_6H_5 group. Differential assignment of geminal protons was made on the basis of vicinal coupling constants and the influence of the nitrogen lone electron pair [21]. The signals at 3.35 and 3.80 ppm present a remarkably low $^3J_{H-H}$ (4.30 Hz), which was assigned to the *cis* vicinal coupling between the hydrogen atoms *cis* to the *N*-CH_3 lone electron pair (Hc,He), as occurs in 1,3-dialkylimidazolidines [11], whereas the Hb presents J*cis* and J*trans* of a similar value.

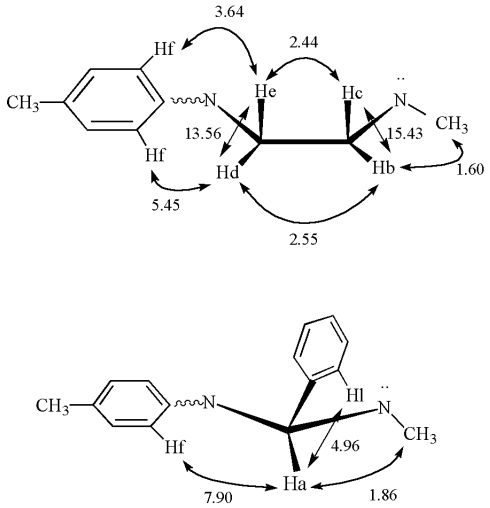
The preferential spatial orientation of the *N*-CH_3 group is also reflected in signal multiplicity and heteronuclear coupling constants $^1J_{C-H}$, since the signal assigned to C_4 appears as a doublet of doublet with two coupling constants of *ca.* 134 and 143 Hz corresponding to Hb and Hc (*trans* and *cis* to the lone electron pair) respectively [22]. These values agree with those reported by other authors for *N,N'*-dialkylimidazolidines [11,12]. Instead, C_5 signal multiplicity (t, $^1J_{C5-H}$ = 142.3 Hz) is consistent with *N*-aryl features (see below).

The relative orientation of the phenyl group on C_2 was determinated and the previous assignments confirmed by a ^1H NMR 1D nOe difference spectrum of compound **10**, whose correlations are shown in Scheme I. Correlation between the *N*-methyl group with Ha and Hb indicates the *cis* orientation of both, showing the transoid relationship of the substituent on C_2 and the *N*-CH_3 in the preferred (averaged) conformation. Correlation between both Hd and He with *N*-aryl *ortho* hydrogens indicates a fast *N*-inversion with a marked sp2 nitrogen hybridization.

1-Benzyl-3-*p*-chlorophenyl-2-phenylimidazolidine (**13**).

The ^1H NMR spectrum of 1-benzyl-3-*p*-chlorophenyl-2-phenylimidazolidine (**13**) presents the Hb-d as four signals

Scheme 1



at δ 2.90, 3.20, 3.60 and 3.75 ppm and a benzyl geminal anisochronism (N-CH_2-Ar, Δδ = 0.20 ppm, $^2J_{H-H}$ = 12.20 Hz), due to the presence of the chiral center C_2 [13].

Since the signals at δ 3.60 and 3.75 ppm remained practically unchanged as regards the similar *N*-methyl derivative **11**, they were assigned to the Hd,e (adjacent to the *N*-*p*-chlorophenyl). Due to partial overlapping of these signals with those of the benzyl methylene, the corresponding coupling constants could not be evaluated in this case. On the other hand, the signals at 2.90 and 3.20 ppm ($^2J_{H-H}$ = 10.40 Hz) were analyzed in detail and assigned respectively to Hc and Hb, unlike the previous compounds. The resonance at 2.90 ppm (ddd) is assigned to Hc due to the presence of a vicinal coupling constant of lower value (5.27 Hz), associated to coupling between the hydrogens located *cis* to the *N*-benzyl nitrogen lone electron pair, as happens in the previous series (compounds **8-12)**. The signal at 3.20 ppm is assigned to the Hb (*cis* to the benzyl group), as it presents vicinal *cis* and *trans* coupling constants of similar value. The Hb signal underwent a 0.5 ppm paramagnetic shift attributable to the loss of shielding of the methyl in position *cis* [14] when substituted by a benzyl group. A similar effect is observed in the Ha signal, also showing a *ca.* 0.5 ppm paramagnetic shift with regard to imidazolidines **8-12**. These spectroscopic features suggest a *trans* relationship between *N*-benzyl lone electron pair and the Ha atom. Therefore, a preferential transoid pattern of the groups on C_2 and N_3 (phenyl and benzyl respectively) is proposed, similar to that of the previous series.

EXPERIMENTAL

Melting points were taken on a Büchi capillary apparatus and were uncorrected. The ^1H NMR spectra of compounds **1-13** were obtained on a Bruker MSL 300 MHz spectrometer using deuteri-

ochloroform as solvent and the standard concentration of samples was 0.10 *M*. The nOe difference experiments were performed by presaturation of the signal and substraction of the FID of the control spectrum from the FID on irradiation. The nOe difference spectra were recorded for saturation time of 2 seconds and irradiation power levels between 30 and 36 dB below 2W depending on the selectivity required. The HMQC spectrum was acquired using a Bruker AVANCE DRX 300 spectrometer. Chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Signals are quoted as: s (singlet), d (doublet), dd (double doublet), td (triple doublet), ddd (double double doublet), t (triplet), q (quartet) and m (multiplet). J values are given in Hertz (Hz). Mass spectra (EI) were recorded using a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. Analytical tlc was carried out on Silica Gel 60 F_{254}. Reagents, solvents and starting materials were purchased from standard sources and purified according to literature procedures.

Imidazolidines **1-13**.

Compounds **1**, **3** and **5** [23], **2** [24], **4** [25], **6** [26], **7** [27], **8-11** [3] and **12** [28] were prepared following literature procedures.

Purity was ascertained by tlc experiments employing five different solvent mixtures.

1-Benzyl-3-(*p*-chlorophenyl)-2-phenylimidazolidine (**13**).

Compound **13** was synthesized from *N*-benzyl-*N´*-(*p*-chlorophenyl)ethylenediamine [29] (0.1 mmol) and benzaldehyde (0.1 mmol) in ethanol (10 mL) to yield 295 mg (85%), mp 95° (ethanol); ms: m/z 348 (M^+).

Anal. Calcd. for $C_{22}H_{21}ClN_2$: C, 75.74; H, 6.07; N, 8.03. Found: C, 75.68; H, 5.99; N, 8.18.

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