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^{1}H NMR SPECTROSCOPY AND CONFORMATIONAL ANALYSIS OF *N*-BENZYLIMIDAZOLIDINES

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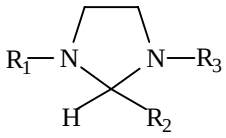
Abstract-^{1}H NMR spectra of a series of 1-benzyl- and 1,3-dibenzylimidazolidines are analyzed and correlated with their conformational features. The spectra are assigned on the basis of chemical shifts and proton coupling constant values, and confirmed by NOESY spectra. C_2-Unsubstituted imidazolidines (**1, 9**) show a fast inversion of the nitrogen atoms. By contrast, 1,2,3-trisubstituted imidazolidines display a preferential conformation with a transoid orientation of the N_1, N_3, and C_2 substituents.

INTRODUCTION

The biological importance of imidazolidines as synthetic models of the coenzyme N^5,N^{10}-methylenetetrahydrofolic acid and for the pharmacological activity displayed by some of these compounds has been pointed out in previous manuscripts.[1,2] Our present interest on the synthesis and characterization of *N*-benzylimidazolidines is based on the potential antimicrobial and antifungal activities of these substances. Preliminary studies have indicated that this type of imidazolidines has important antimicotic activity *in vitro.* Due to the structural specificity commonly exhibited by pharmacological agents, a sound structure-activity study of imidazolidines requires a systematic description of, at least, the relative substituent orientation within the molecule. We report here the ^{1}H NMR spectra of a series of imidazolidines substituted with benzyl groups on one or both nitrogen atoms (Table 1), and discuss their conformational implications. The assignments are carried out largely by considering the dependence of proton chemical shifts and coupling constant values with the orientation of the nitrogen lone electron pair, and confirmed by NOESY experiments recorded at 600 MHz.

Table 1

Imidazolidines (**1-13**)



Compound	R_1	R_2	R_3
1	*p*-$CH_3OC_6H_4CH_2$	H	*p*-$CH_3OC_6H_4CH_2$
2	*p*-$CH_3OC_6H_4CH_2$	CH_3	*p*-$CH_3OC_6H_4CH_2$
3	*p*-$CH_3OC_6H_4CH_2$	$CH{=}CHC_6H_5$	*p*-$CH_3OC_6H_4CH_2$
4	*p*-$CH_3OC_6H_4CH_2$	C_6H_5	*p*-$CH_3OC_6H_4CH_2$
5	*p*-$CH_3OC_6H_4CH_2$	*m*-$NO_2C_6H_4$	*p*-$CH_3OC_6H_4CH_2$
6	$C_6H_5CH_2$	C_6H_5	$C_6H_5CH_2$
7	$C_6H_5CH_2$	*p*-$CH_3OC_6H_4$	$C_6H_5CH_2$
8	*p*-$ClC_6H_4CH_2$	*m*-ClC_6H_4	*p*-$ClC_6H_4CH_2$
9	*p*-ClC_6H_4	H	$C_6H_5CH_2$
10	*p*-ClC_6H_4	C_6H_5	$C_6H_5CH_2$
11	*p*-$NO_2C_6H_4$	C_6H_5	$C_6H_5CH_2$
12	*p*-$NO_2C_6H_4$	*o*-ClC_6H_4	$C_6H_5CH_2$
13	*p*-$NO_2C_6H_4$	*p*-$CH_3OC_6H_4$	$C_6H_5CH_2$

RESULTS AND DISCUSSION

C_2-Unsubstituted Imidazolidines (**1**, **9**)

The 300 MHz ^{1}H-NMR spectra of imidazolidines (**1**) (Table 2) and (**9**) (Table 3) recorded at room temperature show single peaks for the C_2 and benzyl methylene protons indicating signal average over all possible conformations. Thus, the imidazolidine ring is undergoing rapid exchange (in the NMR time scale) with inversion of both nitrogen atoms and rapid rotation along the *N*-CH_2Ar bond. In the case of compound (**1**), proton signals of the ethylenediamine moiety (hydrogen Hb-e) are isochronous and resonate at 2.35 ppm. In contrast, due to the N_1 and N_3 substitution with different groups, these proton signals are resolved in the spectrum of **9** and appear as two triplets. By comparison with compounds

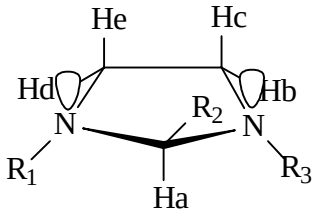
studied previously,[2] the triplet at 3.10 ppm is assigned to the methylene adjacent to the *N*-benzyl group (Hb,c) and the signal at 3.40 ppm to the protons neighboring the *N*-phenyl group (Hd,e). Conjugation of the *p*-chlorophenyl group with the nitrogen lone electron pair causes a deshielding of protons flanking the *N*-aryl group, namely Ha, Hd, and He. Such conjugation is reflected also in the shielding experienced by the *ortho* protons of the aromatic moiety, which resonate at 6.40 ppm.

Symmetric 1,2,3-Trisubstituted Imidazolidines (**2-8**) (Table 2)

The introduction of a C_2-substitution abolishes the magnetic equivalence previously observed for the geminal protons of the ethylenediamine moiety (Hb-He). As a consequence, each compound has an AA´XX´ spin system that results in the presence of a centrosymmetric multiplet, with the appearance of two double double doublets (compounds **2, 5-8**) or of two double triplets (compounds **3,** and **4**) with a $\Delta\delta$ of 0.60-0.65 ppm. This spectroscopic feature must be linked to the existence of a preferred conformer in solution, with different shielding constant for the Hb(d) and Hc(e) protons. The analysis of possible conformers that result from the inversion of pyramidal nitrogens indicates that an *anti*-periplanar arrangement of the substituents at the nitrogen atoms and the group at C_2 is sterically favored.

The chemical shift difference between the AA´ and XX´ proton signals is attributed to their relative orientation with respect to the nitrogen lone electron pair. Based on the shielding effect of a pair of electrons in *trans* and of an alkyl group in *cis*,[3] the upfield signals in the spectra, at around 2.40 ppm, are assigned to the Hb and Hd protons of the ethylenediamine moiety. Accordingly, the signals centered at 3.00 ppm originate from the Hc and He protons located in *cis* to the pair of electrons in all the series (Scheme 1).

Scheme 1



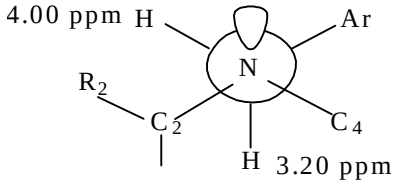
Taking compound (**2**) as reference, aryl or cinnamyl substitution of the C_2-alkyl group (**3-8**) causes a small paramagnetic shift of the Hb-d signals, which is larger for the protons in *cis* to the C_2 substituent, namely Hc and He. This effect must be attributed to the perpendicular orientation of the C_2 substituent to the C_4-C_5 bond and the imidazolidine ring. We have observed this effect previously in the spectra of 1,3-diarylimidazolidines.[2]

The heteronuclear $^1J_{C-H}$ coupling constant of carbon atoms in position alpha to a nitrogen also allows the determination of the orientation of the nitrogen lone electron pair.[5] During the structural characterization of other imidazolidines having different C_2 substitutions, $^1J_{C-H}$ values around 135 Hz were ascribed to a *trans* orientation between the Ha proton and nitrogen lone electron pair.[2,6,7] In the present case of symmetrically 1,2,3-trisubstituted imidazolidines,[8] the C_2 signal is a doublet with a $^1J_{C-H}$ coupling constant of 135.0 Hz. supporting the orientation depicted in Scheme 1.

Like it was observed for other *N*-benzylimidazolidines,[9] the benzylic methylene protons of compounds (**2**-**8**) are chemically non-equivalent. They exhibit chemical differences ($\Delta\delta$) of 0.40-0.80 ppm and $^2J_{H-H}$ around 13 Hz, conforming a spin system of quasi-first order. This diasterotopicity is caused by the presence of the prochiral center C2.[10]

Following the criteria described previously for the ethylene protons, upfield signals (δ *ca.* 3.10 ppm) must be assigned to the hydrogen atoms in *trans* to the nitrogen lone-electron pair. This conformational preference is depicted in Scheme 2.

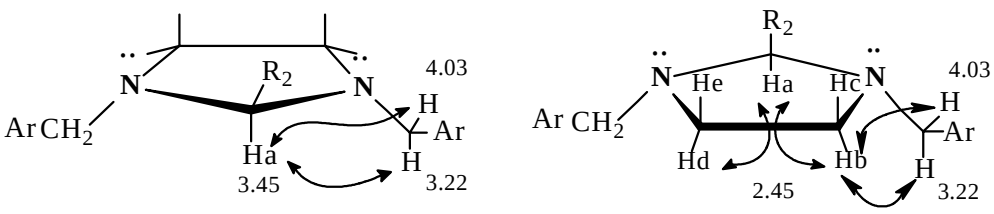
Scheme 2



Focusing on the C_2 position, we observe that aryl moiety substitution (compounds **4**-**8**) of a methyl group (compound **2**) results in a diamagnetic shift of the benzyl signals, which is more pronounced for the protons in *cis* to the nitrogen lone electron pair. As shown in Scheme 2, these protons are closer to the aryl group at C_2 and, therefore, more affected by its shielding effects.[11]

Spectral assignment of compounds (**2**-**8**), which was based in the analysis of coupling constants and chemical shifts, is supported further by several cross-peaks observed in a NOESY spectrum of **3** (1s mixing time). The main NOE interactions are summarized in Scheme 3.

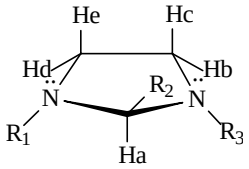
Scheme 3



Compound (**3**)

Table 2

^{1}H-NMR Spectra of 1,3-Dibenzylimidazolidines (**1-8**) [a]



Comp.	Ha	Hb-d	Hc-e	CH_2-Ar	Aromatics	Others
1	3.45 (s)	2.35 (s)		3.60 (s)	6.85 (dd, J_1=6.52, J_2= 2.05, *p*-$CH_3OC_6H_4$, *meta* H), 7.25 (dd, dd, J_1=6.52, J_2= 2.05, *p*-$CH_3OC_6H_4$, *ortho* H)	3.85 (s,OC*H*$_3$)
2	3.05 (q) J=5.38	2.35 (ddd) J_1=14.74, J_2=10.30, J_3=8.68	2.95 (ddd)	3.21 (d), 4.00 (d) J=12.74	6.81 (dd, J_1=6.59, J_2= 2.08, *p*-$CH_3OC_6H_4$, *meta* H), 7.30 (dd, J_1=6.59, J_2= 2.08, *p*-$CH_3OC_6H_4$, *ortho* H)	3.79 (s, OC*H*$_3$) 1.30 (d, J=5.38, CHC*H*$_3$)
3	3.45 (d) J=7.99	2.45 (dt) J_1=13.95, J_2=8.97	3.05 (dt)	3.22 (d), 4.03 (d) J=12.97	6.80 (dd, J_1=6.59, J_2= 2.19, *p*-$CH_3OC_6H_4$, *meta* H), 7.27 (m, *p*-$CH_3OC_6H_4$, *ortho* H, and C_6H_5, *para* H), 7.35 (t, J=7.65, C_6H_5, *meta* H), 7.50 (d, J=7.32, C_6H_5, *ortho* H)	3.80 (s, OC*H*$_3$), 6.20 (dd, J_1=15.96, J_2= 7.99, C*H*=CHAr), 6.61 (d, J= 15.96, CH=C*H*Ar)
4	3.82 (s)	2.45 (dt) J_1=12.52, J_2=8.12	3.10 (dt)	3.10 (d), 3.65 (d) J=12.72	6.79 (dd, J_1=6.81, J_2= 2.20, *p*-$CH_3OC_6H_4$, *meta* H), 7.15 (dd, J_1=6.81, J_2= 2.20, *p*-$CH_3OC_6H_4$, *ortho* H), 7.35 (m, C_6H_5, *meta* and *para* H), 7.63 (dd, J_1=8.13, J_2= 1.64, C_6H_5, *ortho* H)	3.78 (s, OCH_3)
5	3.94 (s)	2.55 (ddd) J_1=14.95, J_2=10.05, J_3=8.64	3.20 (ddd)	3.29 (d), 3.67 (d) J=12.73	6.70 (dd, J_1=6.81, J_2= 1.98, *p*-$CH_3OC_6H_4$, *meta* H), 7.10 (dd, J_1=6.81, J_2= 1.98, *p*-$CH_3OC_6H_4$, *ortho* H), 7.50 (t, J= 7.81, *m*-$NO_2C_6H_4$, *meta* H), 7.90 (d, J=7.46, *m*-$NO_2C_6H_4$, H *ortho*), 8.25 (dd, J_1=7.48, J_2= 1.76 *m*-$NO_2C_6H_4$, *para* H), 8.45 (t, J=1.80, *m*-$NO_2C_6H_4$, *ortho* H).	3.75 (s, OCH_3)
6	3.85 (s)	2.50 (ddd) J_1=14.80, J_2=10.02, J_3=8.08	3.19 (ddd)	3.21 (d), 3.80 (d) J=12.91	7.20 (m, $CH_2C_6H_5$), 7.40 (m, C_6H_5, *meta* and *para* H), 7.65 (dd, J_1=6.67, J_2= 1.82 C_6H_5, *ortho* H).	
7	3.70 (s)	2.40 (ddd) J_1=14.61, J_2=10.03, J_3=8.50	3.10 (ddd)	3.10 (d), 3.70 (d) J=13.08	6.85 (dd, J_1=6.67, J_2=2.06, *p*-$CH_3OC_6H_4$, *meta* H), 7.20 (m, $CH_2C_6H_5$), 7.50 (dd, J_1=6.67, J_2=2.06, *p*-$CH_3OC_6H_4$, *ortho* H).	3.75 (s, OCH_3)
8	3.82 (s)	2.49 (ddd) J_1=14.76, J_2=10.31, J_3=8.30	3.15 (ddd)	3.21 (d), 3.70 (d) J=13.14	7.20-7.60 (m, 12H).	-

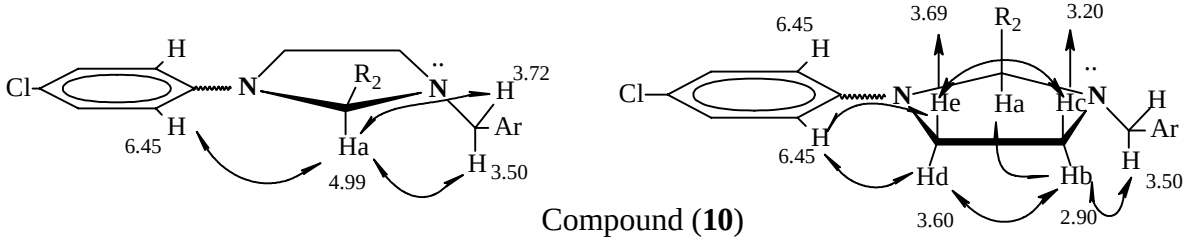
[a] For compounds (**2-8**) Hc,e are *cis* to R_2 and *trans* to R_1 and R_3.

Asymmetric *N*-Benzylimidazolidines (**10-13**) (Table 3)

In comparison to the previous series, the Ha signal undergoes a large paramagnetic shift (*ca*.1-1.75 ppm) that must be ascribed, mainly, to the aryl substitution of the benzyl group at N_1 and also to conformational features of each compound. Protons of the ethylenediamine moiety appear as two isolated multiplets at δ *ca.* 2.90 and 3.20 ppm, each of them corresponding to one hydrogen, and one (or two) additional multiplets at 3.60-3.80 ppm that which account for the other two protons of the ring.

In a 600 MHz NOESY spectrum of compound (**10**), the Ha proton (δ 4.99 ppm) shows correlation with both benzylic protons (Scheme 4), revealing a *transoid* orientation between the substituents at the C_2 and N_3 positions. Other interactions observed in the same spectrum provide the complete assignment of the ethylene hydrogens. NOE cross-peaks correlate the multiplets resonating at 3.60 ppm and 3.69 ppm with the *ortho* protons of the *p*-chlorophenyl group, allowing the assignment of these signals to the C_5 methylene protons (Hd and He) and establishing the fast inversion rate of the *N*-aryl atom.[13] The Ha proton displays an NOE interaction with the signal at 2.90 ppm, which in turn interacts with a benzylic proton at 3.50 ppm. Therefore, the multiplet at 2.90 ppm is assigned to the Hb proton of the imidazolidine ring, in *cis* to the benzyl group, and the remaining signal at 3.20 ppm to Hc. Further support for this assignment is the correlation observed between Hc and the multiplet at 3.69 (He) and the presence of a strong NOE peak between the geminal Hb-Hc protons. This interpretation supersedes our previous assignment, based solely in coupling constants, where the 2.90 ppm signal had been attributed to the Hc proton.[2]

Scheme 4

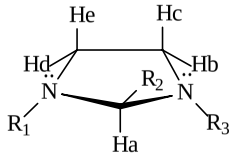


Compound (**10**)

As it was observed for the symmetrically substituted imidazolidines, benzyl methylene protons in compounds (**10-13**) are anisochronous. Diasterotopicity in these compounds is attributed to the presence of the C_2 chiral center. However in this case, the chemical shift differences between benzylic protons is notably smaller than in the previous series (Δδ *ca.* 0.20 ppm). Comparing compounds (**6**) and (**10**), we observe a down field shift for the hydrogen assigned in *trans* to the nitrogen lone-electron pair. This effect may be associated with the presence of the N_1-aryl group that would mainly affect the benzylic proton (δ 3.50 ppm) directed toward the imidazolidine ring (Scheme 5). Heteronuclear $^1J_{C2\text{-}H}$ constants for the series of asymmetrically substituted imidazolidines[14] are around 145 Hz, a value systematically larger that those observed for the 1,3-dibenzylimidazolidines. This difference suggest a positive contribution of

Table 3

^{1}H-NMR Spectra of 1-Aryl-3-benzylimidazolidines (**9-13**) [a]

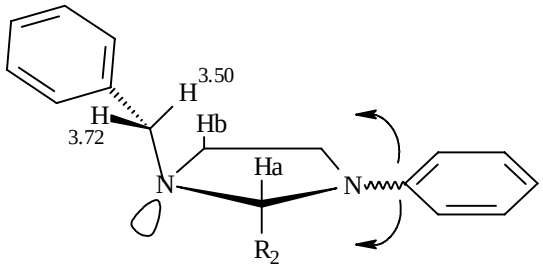


Comp.	Ha	Hb-e	CH_2-Ar	Aromatics	Others
9	4.00 (s)	3.10 (t, J=6.25, Hb,c), 3.40 (t, J=6.25, Hd,e)	3.75 (s)	6.40 (d, J=8.15, *p*-ClC_6H_4, *ortho* H), 7.20 (d, J=8.15, *p*-ClC_6H_4, *meta* H), 7.40 (s, C_6H_5).	
10	4.99 (s)	2.90 (ddd, J_1=10.40, J_2=6.30, J_3=6.40, Hb), 3.20 (dt, J_1=10.40, J_2=5.27, Hc) 3.60 (m, Hd), 3.69 (m, He)	3.50 (d), 3.72 (d) J= 12.20	6.45 (dd, J_1=6.70, J_2=1.97, *p*-ClC_6H_4, *ortho* H), 7.10 (dd, J_1=6.70, J_2=1.97, *p*-ClC_6H_4, *meta* H), 7.30-7.40 (m, C_2-C_6H_5, CH_2-C_6H_5).	
11	5.19 (s)	2.95 (dt J_1=10.30, J_2=6.10, Hb), 3.15 (dt, J_1=10.30, J_2=6.45, Hc) 3.70-3.82 (m, Hd,e)	3.56 (d), 3.70 (d) J=12.91	6.42 (d, J=9.20, *p*-$NO_2C_6H_4$, *ortho* H), 7.15-7.40 (m, C_2-C_6H_5, CH_2-C_6H_5), 8.05 (d, J=9.20, *p*-$NO_2C_6H_4$, *meta* H).	
12	5.20 (s)	2.90 (dt, J_1=10.98, J_2=6.59, Hb), 3.20 (dt, J_1=10.98, J_2=5.71, Hc) 3.65-3.81 (m, Hd,e)	3.70 (d), 3.90 (d) J=12.95	6.40 (d, J=9.22, *p*-$NO_2C_6H_4$, *ortho* H), 7.10-7.40 (m, *o*-ClC_6H_4, CH_2-C_6H_5), 8.05 (d, J= 9.22, *p*-$NO_2C_6H_4$, *meta* H).	
13	5.10 (s)	2.91 (dt, J_1=9.88, J_2=6.37, Hb), 3.20 (dt, J_1=9.88, J_2=6.50, Hc) 3.69-3.80 (m, Hd,e)	3.51 (d), 3.65 (d) J=12.93	6.42 (d, J=9.03, *p*-$NO_2C_6H_4$, *ortho* H), 6.85 (d, J=8.41, *p*-$CH_3OC_6H_4$, *meta* H), 7.19 (d, J=8.41, *p*-$CH_3OC_6H_4$, *ortho* H), 7.21-7.40 (m, C_6H_5), 8.05 (d, J=9.03 *p*-$NO_2C_6H_4$, *meta* H)	3.78 (s, OCH_3)

[a] For the compounds (**10-13**) Hb are *cis* to R_3 and *trans* to R_2

the *N*-aryl electron pair in *cis* to the C_2-Ha bond, which results from the fast inversion of the nitrogen as it was reported previously for 1,2-diaryl-3-methylimidazolidines.[2]

Scheme 5



EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected temperature readings. NMR spectra were recorded on a Bruker MSL spectrometer operating at 7.05 *T*. Typically, samples were dissolved in deuterochloroform to a 0.10 M concentration. Chemical shift values are reported relative to internal TMS. J values are given in Hertz (Hz). Phase-sensitive NOESY (1s mixing time) spectra were recorded at 27ºC on a Varian Inova spectrometer (14.1 *T* field strength) using the hypercomplex method.[15] Data sets consisted of 4096 and 500 complex points in the t2 and t1 dimensions, respectively. Time domain data in both dimensions were multiplied by shifted sine-bell functions.

MS spectra (EI) were recorded with a GC-MS Shimadzu QP-1000 spectrometer operating at 20 eV. TLC analyses were carried out on aluminum sheets silica gel 60 F_{254} using a benzene-methanol mixture (9:1) as solvent.

Imidazolidines (**1-13**).

Compounds (**1-5**),[16] (**6**),[17] (**9**),[1] and (**10**)[2] were synthesized following procedures reported previously. Purity was ascertained by TLC analysis.

Compounds (**7**, **8**) and (**11-13**) were obtained by reacting equimolar amounts of the corresponding *N*,*N'*-disubstituted ethylenediamine and aldehyde in ethanol under reflux.

1,3-Dibenzyl-2-(*p*-methoxyphenyl)imidazolidine (**7**)

mp 89ºC (Ethanol), ms: *m/z* 358 ($M^{+\cdot}$).

Anal. Calcd for $C_{24}H_{26}N_2OCl_3$: C, 80.41; H, 7.31; N, 7.81. Found : C, 80.36; H, 7.38; N, 7.77.

1,3-Di(*p*-chlorobenzyl)-2-(*m*-chlorophenyl)imidazolidine (**8**)

mp 83ºC (Ethanol), ms: *m/z* 431($M^{+\cdot}$).

Anal. Calcd for $C_{23}H_{21}N_2Cl_3$: C, 63.98; H 4.90; N, 6.49. Found : C 64.01; H 4.76; N, 6.61.

1-Benzyl-2-phenyl-3-(*p*-nitrophenyl)imidazolidine (**11**)

mp 122ºC (Ethanol); *m/z* 359 ($M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{21}N_3O_2$: C, 73.52; H. 5.89, N, 11.69. Found : C,73.65; H. 5.72; N. 11.78.

1-Benzyl-2-(*o*-chlorophenyl)-3-(*p*-nitrophenyl)imidazolidine (**12**)

mp 127ºC (Ethanol); ms: *m/z* 393 ($M^{+\cdot}$).

Anal. Calcd for $C_{22}H_{20}N_3O_2Cl$: C 67.09; H5.12; N. 10.67. Found : C 67.20; H, 5.06; N, 10.83.

1-Benzyl-2-(*p*-methoxyphenyl)-3-(*p*-nitrophenyl)imidazolidine (**13**)

mp 124ºC; ms: *m/z*: 389 ($M^{+\cdot}$).

Anal. Calcd for $C_{23}H_{23}N_3O_3$: C, 70.93; H. 5.95; N, 10.79. Found : C 70.77; H. 6.07; N, 10.87.

ACKNOWLEDGEMENTS

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REFERENCES AND NOTES

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3. In azacycloalkanes, the shielding of hydrogens alpha to nitrogen atoms by a lone electron pair in *trans* and a methyl group in *cis* has been widely documented.[4]
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