Determination of Rotational Barriers of Carbon-Carbon Bonds in 2-Arylpiperidines

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Carbon-carbon sp^3-sp^2 rotational barriers of 3,3-dimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidones and their ethylene ketals have been evaluated using nmr techniques. The conformation of **1** hydrochloride has been studied by NOE determinations. Values found for the hydrochlorides of the title compounds are discussed in terms of equilibria with free bases and nitrogen inversion.

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The conformation of phenylpiperidines with methyl substituents on the α position concerning the phenyl group has been recently studied due to the possible relationship between the conformation of these compounds and their analgesic activity [1]. Thus, the presence of the phenyl group in a nearly right angle disposition with respect to the piperidine ring has been described for 1,3-dimethyl-4-phenyl-4-piperidinols [2] and for 1,3,4-trimethyl-4-phenylpiperidines [3].

In the context of our studies on 2-aryl-4-piperidones [4] and their application as intermediates to the synthesis of benzomorphan analogues [5], we have observed that in the aromatic zone of the ^1H nmr spectrum (60 MHz) of 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (**1**) hydrochloride, in deuteriochloroform solution, two signals at δ 6.40 and 7.60 appeared, thus reflecting the magnetic non equivalence of *ortho* aromatic protons. Moreover, these signals experimented noteworthy variations in their chemical shift when changing the solvent polarity. Thus, addition of several drops of tetradeuteriomethanol decreased the difference of chemical shift between both signals, whereas when using deuterium oxide as solvent they collapsed as a broad singlet at δ 6.90.

It was also observed that under identical conditions in the aromatic zone of nmr spectrum of 1,5,5-trimethyl analogue **2**, only a singlet at δ 7.15 appeared.

These facts suggested the existence of restricted rotation around the C_2-Ar bond due to the steric interactions between aromatic protons and methyl groups of the piperidine ring.

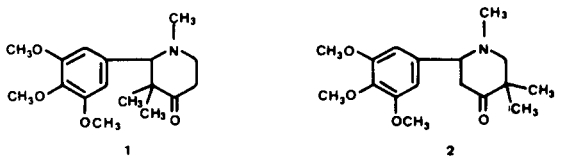

Figure 1

Although restricted rotation around simple Csp^2-Csp^2 bonds has been widely studied [6], there are few examples in which Csp^3-Csp^2 rotational barriers are high enough to be observed in ^1H nmr spectra situations of restricted rotation at room temperature [7].

In this work we expose the results obtained from the conformational analysis and the C_2-Ar bond rotational barrier studies made on the hydrochloride of 2-aryl-4-piperidone **1** as well as for its free base. Moreover, in order to evaluate the effect of the *N*-methyl group over the above rotational barrier, we have studied the nmr spectra of 3,3-dimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (**5**) at variable temperature. Finally, the results obtained in the above examples have been extended to the study of the corresponding 4,4-ethylenedioxy derivatives **4** and **6**.

Results and Discussion.

Preparation of compounds **1**, **4**, **5** and **6** required for our study has been carried out by a Mannich-like cyclization from 3,3-ethylenedioxy-4-methyl-*N*-(3,4,5-trimethoxy-

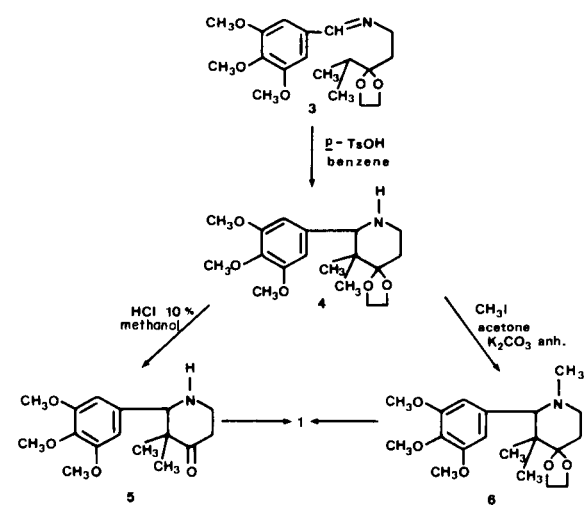

Figure 2

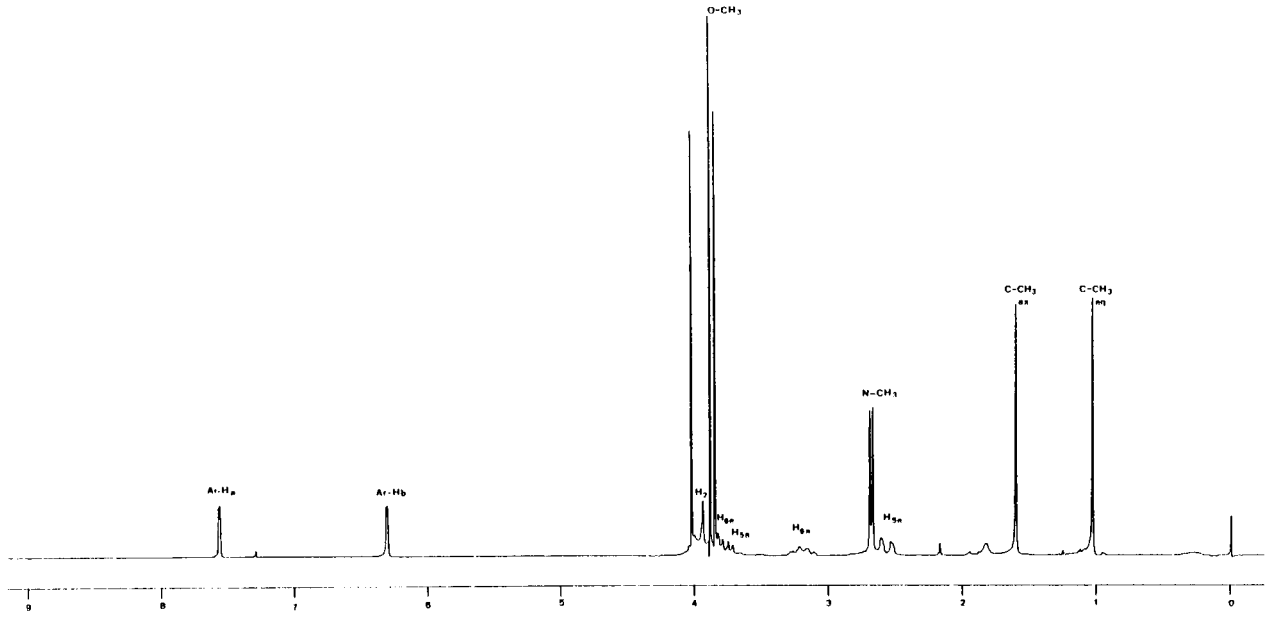

Figure 3. ^{1}H-nmr spectra of 1,3,3-trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (**1**) hydrochloride at 200 MHz in deuteriochloroform.

benzylidene)pentylamine (**3**). The yield of this cyclization improved when using *p*-toluenesulfonic acid instead of hydrogen chloride as previously described [4c].

In the ^{1}H nmr spectra (200 MHz) of **1** hydrochloride two singlets at δ 1.03 and 1.61 corresponding to the equatorial and axial methyl groups, respectively, can be observed. This chemical shift difference concordates with the greater deshielding effect promoted by the nitrogen free electron pair over the axial methyl group [8]. It can also be observed that the three methoxy groups show differentiated chemical shifts, at δ 3.85, 3.89, and 4.02, which indicate the influence of different environments for them. Finally, in the aromatic zone two doublets (J = 2 Hz) appear at δ 6.31 and 7.56, due to the two phenyl protons.

Assignment of piperidine protons signals has been effected from double resonance experiments and by comparison with model structures [9]. The coupling constants observed for these protons are in agreement with those of the simulated spectra for them.

The absence of geometrical distortion in the chair conformation of **1** hydrochloride could be confirmed by calculation of the dihedral angle ψ according to Lambert [10]. Thus, for values of 7.5 and 3.5 Hz corresponding to J_{trans} and J_{cis} we obtained values of 2.15 for R constant and 57.5° for the rotation angle. According to the conformational disposition described for 3-methyl-4-phenyl-4-piperidinol [2] we postulate the preference of the phenyl group in a nearly right angle disposition with respect to the piperidine ring. This proposed conformation is supported by next evidences. Thus, the study of NOE's of the strategic groups (Table 1) reveals not only the system conformation but also permits the assignment of the chemical shifts corresponding to the Ha and Hb aromatic protons and the two *meta* methoxyl groups and confirms the preliminary assignment of C-CH_3 axial and equatorial signals. Thus, when irradiating the signal at δ 7.56 enhancement (5-8%) of the methoxy group **a** and the piperidine axial methyl was observed. When irradiating the proton at δ 6.31 a similar effect was observed over **b** methoxy, piperidine equatorial methyl, and methine protons.

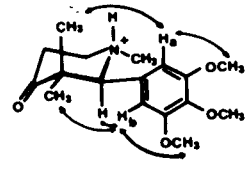

Figure 4. Proposed conformation for **1** hydrochloride showing some of the observed NOE's.

The analysis of variable temperature spectra using DMSO-d_6 as solvent have shown that in the studied temperature interval (20°-170°) there is no coalescence of the aromatic signals. However, at 162° the coalescence of the two *meta* methoxy groups was observed (Figure 5). The temperature dependence was measured by the line-width method at coalescence temperature [11]. From Tc 162° and $\Delta\nu$ 12.7 Hz an apparent $\Delta G^{\ddagger}$ for the conformational equilibrium showed in Figure 6 was calculated to be 96 KJ mol^{-1}.

Table 1

Nuclear Overhauser Effect in **1** Hydrochloride

Irradiated proton		Observed proton							
		Ar-H δ 7.56	Ar-H δ 6.31	O-CH_3 δ 4.02	C_2-H δ 3.91	O-CH_3 δ 3.89	O-CH_3 δ 3.85	C-CH_3 δ 1.61	C-CH_3 δ 1.03
Ar-H	δ 7.56	Irr	+	+			+	+	
Ar-H	δ 6.31	+	Irr		+		+		+
C-CH_3	δ 1.61	+						Irr	+
C-CH_3	δ 1.03		+		+		+	+	Irr

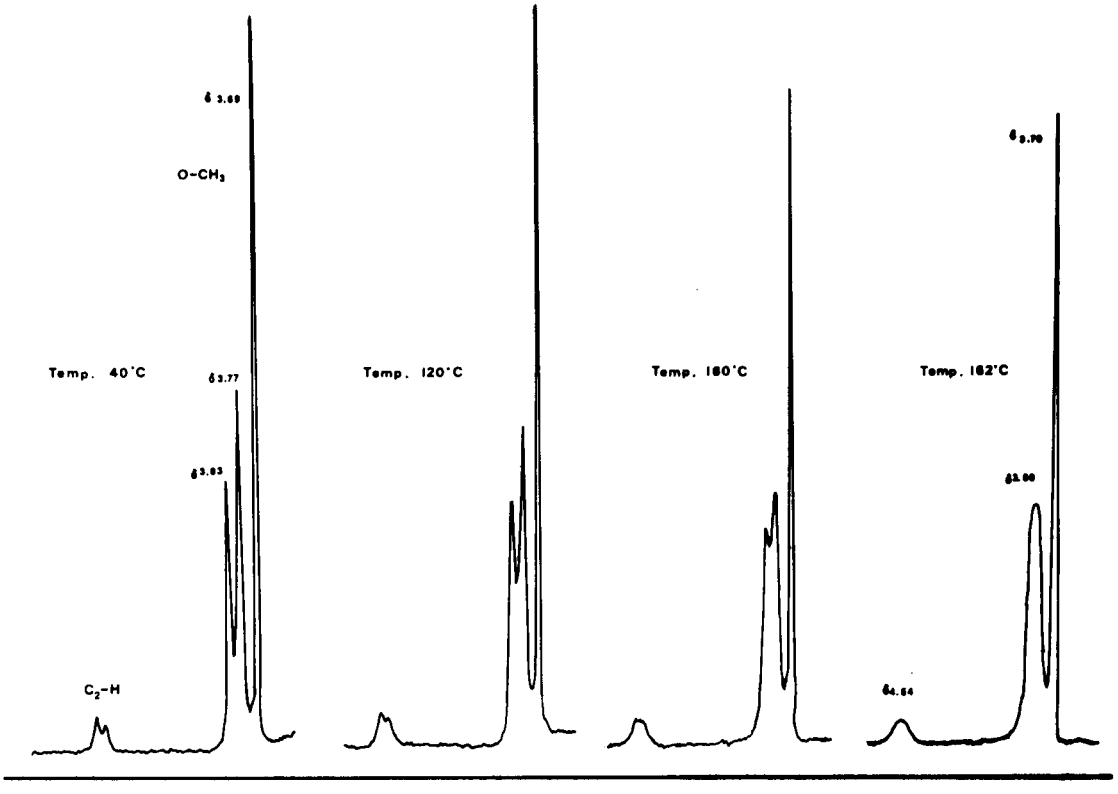

Figure 5. Partial ^1H nmr spectra of **1** hydrochloride at 200 MHz in DMSO-d_6 at various temperatures.

The modification of the methine proton signal, which appears as a doublet at room temperature (J = 8 Hz), was also observed, becoming a wide signal (δ 4.54) at 162°.

When the spectrum of **1** hydrochloride was recorded in DMSO-d_6 solution containing two drops of deuterium oxide, the signals corresponding to the methoxy protons coalesce at 85°. Consequently, it is possible to question if the experimental $\Delta G^{\ddagger}$ value corresponds exclusively to the process indicated in Figure 6 or is the resultant of several steps in which the protonation-deprotonation of the corresponding salt participates.

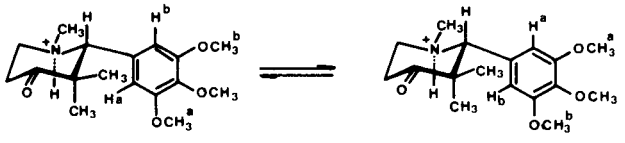

Figure 6

The rotational barrier determination of the C_2-Ar bond in this kind of system is difficult due to the simultaneous presence of several dynamic processes: i) the aryl group rotation around C_2-Ar bond, ii) the nitrogen atom inversion, iii) the piperidine ring inversion, and iv) the possibility of hydrochloride-free base equilibrium. These different processes are represented in Figure 7.

In order to avoid the possible equilibrium between hydrochlorides and free bases, the hydrochloride of 2-aryl-4-piperidone (**1**) has been studied at variable temperature in deuterium chloride-deuterium oxide (*p*D 0.2). The observed coalescence temperature for the aromatic protons was 65° and the rotational barrier 71 KJ mol^{-1}.

2-Aryl-4-piperidone (**1**) shows in its ^1H nmr spectrum at room temperature only one signal at δ 6.43 for the two magnetically equivalent aromatic protons. In Figure 8 the

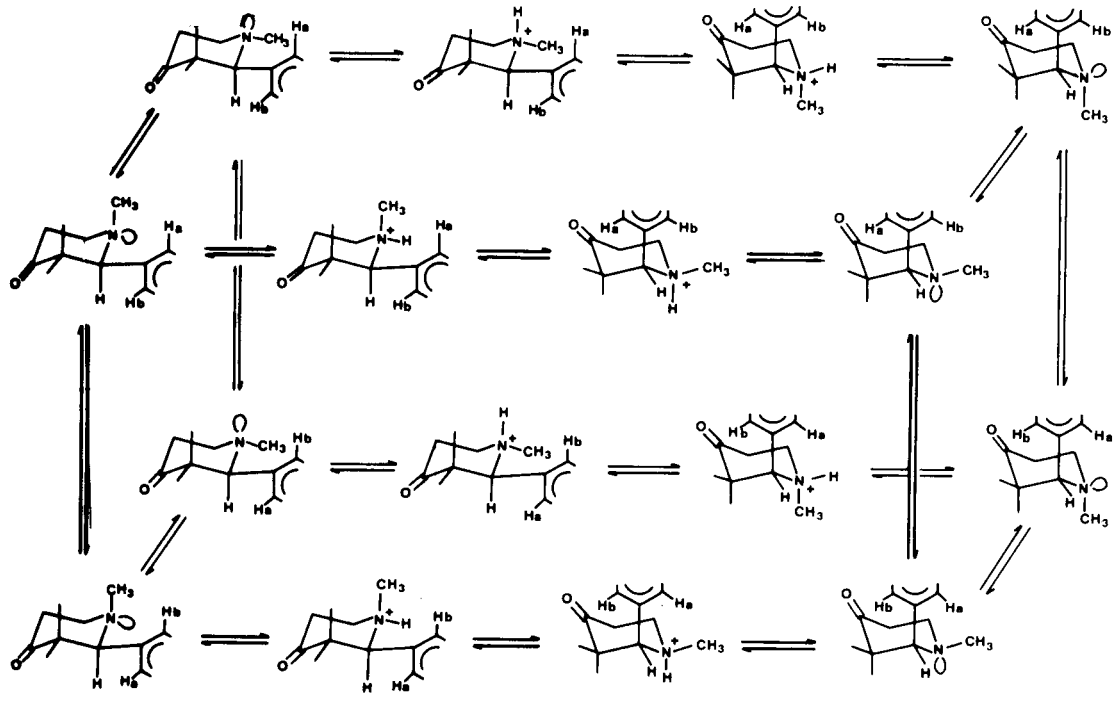

Figure 7. Equilibrium processes implicated in the rotation about C_2-Ar bond. Some equilibrium arrows have been omitted in order to facilitate its understanding.

Table 2

NMR Data of 2-Aryl-4-piperidones **1** and **5** and Their Ethylene Acetals **4** and **6**

Compound No.	Solvent	Observed proton	δ_a	δ_b	T (°C)	$\Delta\delta$ (Hz)	T_c (°C)	K_c (s^{-1})	$\Delta G_c^{\ddagger}$ (KJ mol^{-1})
1	$CDCl_3$	Ar-H	6.68	6.32	−57	70.8	−7	161.4	54
1·HCl	DMSO-d_6	O-CH_3	3.77	3.70	19.8	12.7	162	28.5	96
4·HCl	$CDCl_3$	Ar-H	7.07	6.33	−44	148.6	−32.5	338.8	47
5·HCl	$CDCl_3$	Ar-H	7.23	6.35	−51.5	176.0	−27.7	394.2	47
6	$CDCl_3$	Ar-H	6.58	6.36	−36.2	44.9	−38.6	98.9	64

temperature dependence of both aromatic protons is represented. In this case the coalescence temperature is reached at −7°, with a δ_a 6.68 and δ_b 6.32 at −57°; these figures yield an activation energy of 54 KJ $mole^{-1}$. As it was expected, this rotational barrier is smaller (42 KJ mol^{-1}) than that obtained for the corresponding hydrochloride. This can be explained by considering that in the base, the C_2-Ar bond rotation is favoured in the conformation in which the *N*-methyl group adopts an axial position, decreasing the interactions with the aromatic nucleus in comparison when this group is equatorial.

In order to establish the influence of the *N*-methyl group over the above rotational barrier, the corresponding *N*-unsubstituted piperidone **5** was studied. Its nmr spectrum at 20° shows only one signal at δ 6.60 for the aromatic protons. This signal does not suffer any variation in the range of temperature until −40°. In the same interval no variation for the singlet at δ 3.87 corresponding to the *meta* methoxyl group was observed.

However, in the hydrochloride a singlet appears at δ 6.72, which becomes a wide signal at −27.7° (coalescence temperature) and two signals with a chemical shift difference of 176 Hz at −51.1°. The rotational barrier calculated in this case is 47 KJ mol^{-1}, smaller than that of **1** hydrochloride. The difference of 49 KJ mol^{-1} indicates the effect exerted by the *N*-methyl group over the C_2-Ar bond rotation.

Finally, we have also studied the rotational barriers around the C_2-Ar bond in the 4,4-ethylenedioxy derivatives **4** and **6** with the results indicated in Table 2.

Conclusion.

The problematic of the factors influencing the rotation-

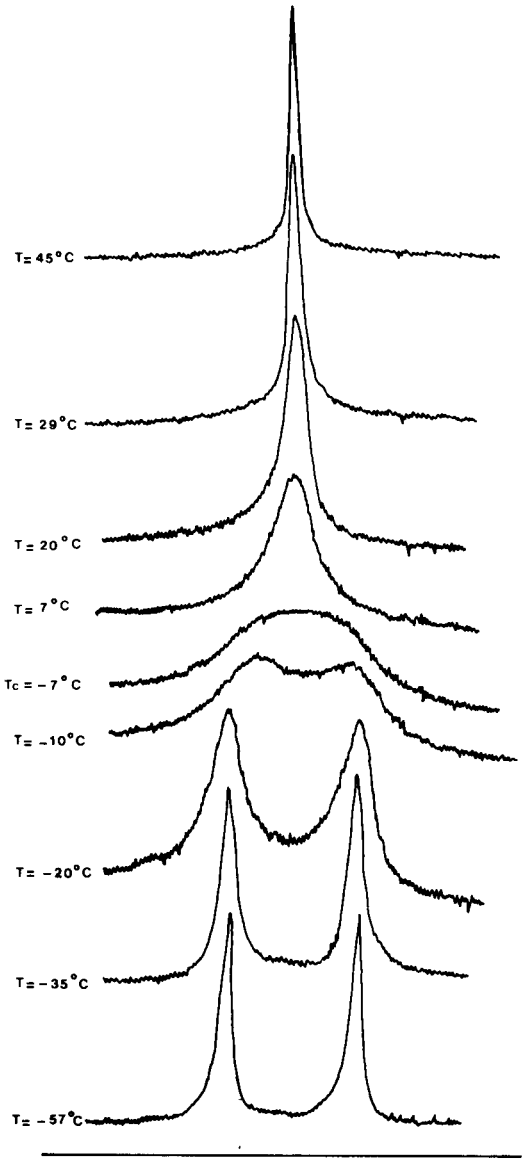

Figure 8

al barriers in 2-arylpiperidines α methyl substituted is obviously complex. However, the piperidines studied in this work have showed to be a very convenient system for the study of carbon-carbon sp^3-sp^2 rotational barriers. The possible equilibria with the free bases advises a prudent interpretation of the data obtained from the hydrochlorides exclusively in terms of rotational barriers. Comparison of the experimental measurements of related compounds in different polarity and *p*H conditions allows to circumvent this problem. Finally, mapping of the molecule by NOE determinations have proved to be very valuable in determining the more stable conformations of these compounds.

EXPERIMENTAL

All ^{1}H nmr spectra were recorded on a Varian XL-200 spectrometer with the lock channel activated at the tetramethylsilane (TMS) and operating in FT mode. The 90° pulse width at 200 MHz was *ca.* 6.5 μs. The proton NOE measurements were made by the Delta sequence. Pre-irradiation times in NOE experiments were 1-2 s. Spectral simulations were made by using the LAOCOON 3 program. Temperature variable measurements were determined before recording a spectrum by using a standard methanol or glycol sample.

3,3-Dimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone Ethylene Acetal (**4**).

A stirred mixture of 3,3-ethylenedioxy-4-methyl-*N*-(3,4,5-trimethoxybenzylidene)pentylamine (**3**) (17 g, 50.4 mmoles) [4c] and anhydrous *p*-toluenesulfonic acid (8.2 g, 43.4 mmoles) in 250 ml of anhydrous benzene was refluxed for 18 hours. The cooled mixture was poured into a 20% aqueous potassium carbonate solution and extracted with benzene. The extracts were washed with 20% aqueous potassium carbonate solution, dried, and evaporated to yield 12 g (82%) of ethylene ketal [4] which was purified by column chromatography through silica gel (chloroform as eluent).

3,3-Dimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (**5**).

A solution of 1.5 g (4.45 mmoles) of ethylene ketal **4**, 15 ml of 20% hydrochloric acid, and 10 ml of methanol was stirred at reflux temperature for 2 hours. After cooling the solution was concentrated, basified with solid potassium carbonate, and extracted with chloroform. The organic extracts were dried and evaporated to give 1.05 g (81%) of piperidone **5**.

1,3,3-Trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone Ethylene Acetal (**6**).

A solution of 3.4 g (10 mmoles) of ethylene ketal **4**, 75 ml of anhydrous acetone, 1.4 g (10 mmoles) of methyl iodide, and 3 g of anhydrous potassium carbonate was stirred at 0° for one hour. After filtration and evaporation 3.2 g (93%) of ethylene ketal **6** were obtained.

1,3,3-Trimethyl-2-(3,4,5-trimethoxyphenyl)-4-piperidone (**1**).

Operating as above from 1 g (3.4 mmoles) of piperidone **5**, 30 ml of anhydrous acetone, 0.5 g (3.4 mmoles) of methyl iodide, and 1 g of anhydrous potassium carbonate, 0.9 g (90%) of piperidone **1** were obtained; ^{1}H nmr (deuteriochloroform): 1.03 (s, 3H, CH_3 eq), 1.61 (s, 3H, CH_3 ax), 2.58 (ddd, J 13, 3, 1 Hz, 1H, H_{5e}), 2.67 (d, 3H, NCH_3), 3.18 (dddd, J 14, 14, 10, 3, Hz, 1H, H_{6a}), 3.75 (ddd, J 13, 14, 4 Hz, 1H, H_{5a}), 3.80 (ddd, J 14, 4, 1 Hz, 1H, H_{6e}), 3.85 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.91 (d, J 10 Hz, 1H, C_2-H), 4.02 (s, 3H, OCH_3), 6.31 (d, J 2 Hz, 1H, ArH), 7.56 (d, J 2 Hz, 1H, ArH), 11.50 (b, 1H, NH).

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