Hindered Rotation in Substituted 1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinolines[1]

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Received May 23, 1969

Abstract: Conformational information concerning 1- and 2-substituted 1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines can be obtained by examination of the proton magnetic resonance (pmr) spectra of a suitable series of these compounds. The pmr spectra of 1,2,3,4-tetrahydro-2-acetyl-6,7-dimethoxyisoquinoline and its C-1 derivatives indicate the presence of unequal populations of two conformers at room temperature. The rates of exchange between the conformers were, in several cases, obtained from a match of experimental line widths (expanded sweeps) and calculated line widths as derived from the Gutowsky–Holm line shape equation. In the case of 1-benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline the rates were obtained from the methoxy, acetyl, and aromatic resonances and each gave Arrhenius activation energies of 20.6 ± 0.5 kcal/mole. The collective data for this series suggest that the two conformations observed reflect the two minimum energy conformations of N,N-disubstituted amides resulting from rotation of the N-acetyl group. This conclusion, as well as that concerning the value of the activation energy for the exchange process, differs markedly from that previously reached. Finally, in 2-substituted 1-(*o*-aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolines, the location of the C-1 benzyl group appears to be a function of the size of the substituent in the 2 position.

While the general theory of nuclear magnetic resonance (nmr) as applied to equilibrating systems is well established,[3-5] the accuracy of the thermodynamic parameters resulting from use of the resonance experiment depends upon not only the experimental and calculated spectra, but also the approximations used to obtain the calculated spectra and the means by which the two are compared.[6,7]

In obtaining the calculated spectra, the complete Gutowsky–Holm equation[4] may be utilized providing T_2, the spin–lattice relaxation time, is known. However, for most systems, particularly those involving two or more functional groups, a simple means of accurately measuring T_2 does not exist, and hence errors often intrude. Nonetheless, a modified T_2 may be approximated from the line width at slow exchange, or in the absence of exchange, and the value may or may not include the inhomogeneity of the field. Alternatively, a large value of T_2 may be assumed and linear plots of log k *vs.* $1/T$°K are observed if the values corresponding to very slow exchange are excluded.

In addition, calculated spectra suggest that the difference in chemical shift between the two sites ($\Delta\delta_{AB}$) remains constant until overlap occurs while in actuality, for most cases, the overlap extends to approximately 10–15° below the coalescence temperature. As a consequence, the rate of change of $\Delta\delta_{AB}$ with temperature below the beginning of coalescence must be established and the extrapolated value used in the calculations. Utilization of this technique obviates the necessity for accurate measurements of $\Delta\delta_{AB}$ under conditions of overlap where additional complications due to unequal isomer populations are also present.

It is, of course, possible to utilize peak separations below the coalescence temperature when $\Delta\delta_{AB}$ is independent of temperature and the separation is large. However, as has been vividly pointed out[7] line shape measurements, although more difficult to obtain, are more reliable since they are less sensitive to changes in $\Delta\delta_{AB}$ and more sensitive to changes in τ, the mean lifetime (in seconds) of the molecule before inversion occurs. Therefore, we have used corrected line widths (see Experimental Section) in matching experimental and computer simulated spectra, inspection of which indicates that small changes in $\Delta\delta_{AB}$ produce no significant alteration in the over-all shape or width of the line.

The omission of at least some of these precautions appears to be well illustrated by our recent report[1b] of a 7.8-kcal/mole barrier for conformer interconversion in the system 1-benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**1**). As suggested by Roberts[8] we have repeated our initial study and extended it to include compounds **1–4** and, because of their synthetic interest, **5–7**.[9]

Results and Discussion

The 100-MHz spectrum of **1**, in chloroform-*d* ($CDCl_3$), at 40°, is presented in Figure 1. Figure 2 presents the 100-MHz spectrum of **1** in chlorobenzene

(1) Preliminary accounts of portions of this work have appeared: (a) D. R. Dalton, M. P. Cava, and K. T. Buck, *Tetrahedron Lett.*, 2687 (1965); (b) G. Fraenkel, M. P. Cava, and D. R. Dalton, *J. Amer. Chem. Soc.*, **89**, 329 (1967); (c) presented, in part, at the Second Natural Products Conference, Mona, Jamaica, Jan 1968.

(2) (a) Department of Chemistry, Temple University, Philadelphia, Pa., 19122; (b) ARCO Chemical Co., Division of The Atlantic Richfield Co., Glenolden, Pa. 19036.

(3) H. S. Gutowsky, D. W. McCall, and C. P. Slichter, *J. Chem. Phys.*, **21**, 279 (1953).

(4) H. S. Gutowsky and C. H. Holm, *ibid.*, **25**, 1228 (1956).

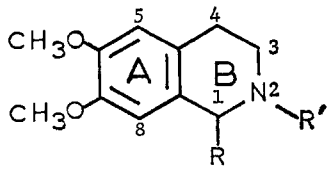
(5) H. M. McConnell, *ibid.*, **28**, 430 (1958).

(6) A. Allerhand, H. S. Gutowsky, J. Jones, and R. A. Meinzer, *J. Amer. Chem. Soc.*, **88**, 3185 (1966).

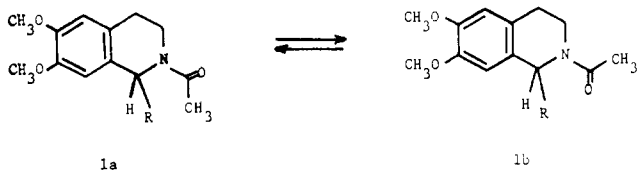
(7) J. D. Roberts, *Chem. Brit.*, **2**, 529 (1966).

(8) J. D. Roberts, private communication.

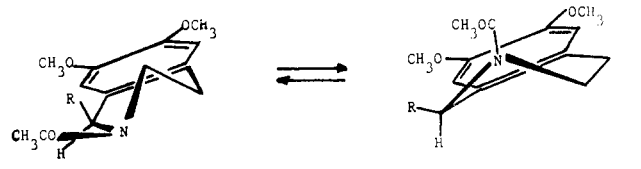
(9) The structures **1c** through **1h** are all related, *e.g.* flipping of the B ring and inversion at nitrogen of **1c** generates the mirror image of **1e** while flipping of the B ring of **1g** gives the mirror image of **1f**. Thus, it is clear that if inversion through nitrogen and ring inversion are fast, the only process that can be attributed to the system which results in the observed spectra is that of hindered acetyl rotation.



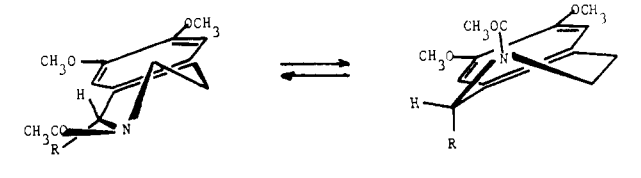
1, R = $-CH_2C_6H_5$; R′ = $-COCH_3$
2, R = $-C(CH_3)_3$; R′ = $-COCH_3$
3, R = $-CH_3$; R′ = $-COCH_3$
4, R = $-H$; R′ = $-COCH_3$
5, R = $-CH_2C_6H_4NH_2$-(*o*); R′ = $-H$
6, R = $-CH_2C_6H_4NH_2$-(*o*); R′ = $-CH_3$
7, R = $-CH_2C_6H_4NH_2$-(*o*); R′ = $-CH_2C_6H_5$



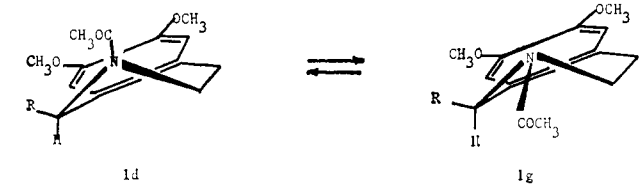
1a 1b



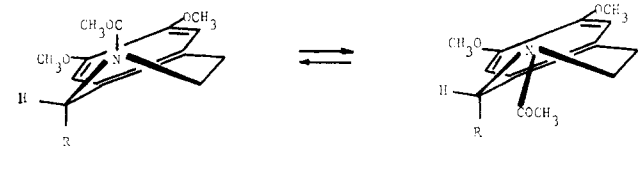
1c 1d



1e 1f



1d 1g



1f 1h

(C_6H_5Cl), at 40°, the solvent used for high-temperature studies. Minor solvent differences are observed but the results are quite similar to those previously reported.[1b] It is clear from these spectra, as it was earlier, that two sets of resonances for the protons at C-1, C-5, and C-8 as well as the methoxyls at C-6 and C-7 and the acetyl group are present.

A priori, these signals might arise from (i) rotation of the acetyl group about the C–N bond (**1a** ⇄ **1b**); (ii) inversion of the saturated ring (**1c** ⇄ **1d** and **1e** ⇄ **1f**); inversion through nitrogen (**1d** ⇄ **1g** and **1f** ⇄ **1h**); or (iv) combinations of all of these processes. Now, recent reports indicate that inversion through nitrogen in a five- or six-membered ring is probably too fast for detection by the nmr method[10,11] and that the rate of ring inversion is also large.[12] On this basis, and on the results of this work (*vide infra*) the spectra observed at room temperature are assigned to the process **1a** ⇄ **1b**.

Figure 3 presents representative experimental line shapes for the acetyl and methoxyl resonances of compound **1** with change in temperature. Table I presents the pmr parameters for compound **1** in the temperature range 40–130°. The line widths of the acetyl and methoxyl resonances as obtained from sweep widths of 100 Hz and corrected for the inhomogeneity of the field and some portion of T_2 by subtraction of the $W_{1/2}$ of the CH_2Cl_2 resonance are included.

Table I. Change in Line Separation ($\Delta\delta$), Line Width, and Mean Lifetime (τ) with Temperature for 1-Benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**1**)

Temp, °C	Acetyl resonance — (corrected line width)[a] $\Delta\delta_{1a-1b}$	**1a**	**1b**	τ	Methoxyl resonance — (corrected line width)[a] $\Delta\delta_{1a-1b}$	**1a**	**1b**	τ
40	41.4	0.5	0.7	0.35	21.4	0.5		0.30
50	40.0	0.8	1.2	0.18		0.9		0.16
60	38.4	2.0	2.6	0.061		1.9		0.078
70	36.6	4.1	5.8	0.032		4.2		0.030
80	33.0	8.4	11.4	0.010				
90							6.6	0.0042
100		12.8		0.0024			3.5	0.0025
110		6.2		0.0012			1.8	0.0013
120		2.8		0.00055			0.6	0.0004
130		1.4		0.00025			0.4	0.0003

[a] Line width a half-height ($W_{1/2}$) minus the line width ($W_{1/2}$) of dichloromethane (CH_2Cl_2) at the same temperature.

In Table I, τ is defined by

$$\tau = \frac{\tau_A \tau_B}{\tau_A + \tau_B} \tag{1}$$

and is related to the rate constants K_A and K_B by

$$\frac{1}{\tau} = \frac{K_A}{P_B} = \frac{K_B}{P_A} \tag{2}$$

where P_A and P_B are the mole fraction populations of isomers **1a** and **1b**, respectively.[13] At 40°, for compound **1**, the ratio $P_A:P_B$ is 60:40.

Figure 4 presents a plot of log K *vs.* $1/T$°K which yields an Arrhenius activation energy of 20.6 ± 0.5 kcal/mole. The thermodynamic parameters—ΔF^*_{373}, the free energy of activation and ΔH^*_{373}, the enthalpy of activation—were calculated from their relationship to the rate of the reaction.[14] The values obtained are, respectively, 19.9 ± 0.5 and and 19.9 ± 0.5 kcal/mole.

For compound **2**, the pmr spectrum (Figure 5) in chlorobenzene (C_6H_5Cl) at 40° shows similarities to the spectrum of **1** under the same conditions. Here, the

(10) A. T. Bottini and J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 5126 (1958); **80**, 5203 (1958).
(11) J. E. Anderson and J. M. Lohm, **89**, 81 (1967).
(12) W. A. Thomas in "Annual Review of NMR Spectroscopy," Vol. 1, E. F. Mooney, Ed., Academic Press, New York, N. Y., 1968, p 58 ff.
(13) K. C. Ramey, J. F. O'Brien, I. Hasagawa, and A. E. Borchert, *J. Phys. Chem.*, **69**, 3418 (1965).
(14) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1965).

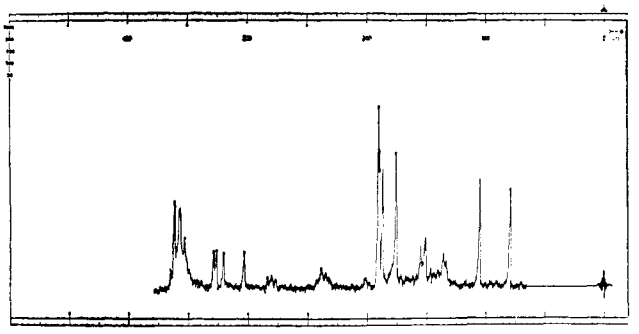


Figure 1. The spectrum of 1-benzyl-2-acetyl-1,2,3,4-tetrahydro 6,7-dimethoxyisoquinoline (**1**) in chloroform-*d* ($CDCl_3$) at 40°.

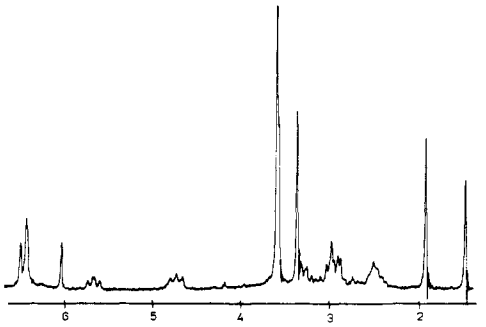


Figure 2. The spectrum of 1-benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**1**) in chlorobenzene (C_6H_5Cl) at 40°.

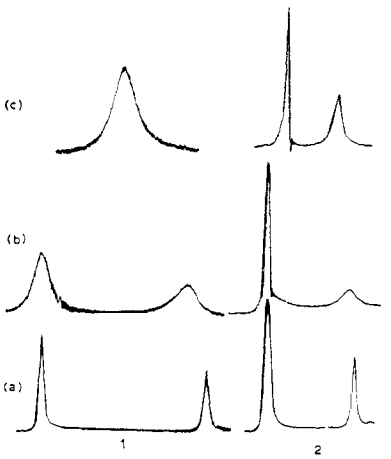


Figure 3. The acetyl resonances (1) and the methoxyl resonances (2) for 1-benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**1**) in chlorobenzene (C_6H_5Cl) at (a) 40°, (b) 70°, and (c) 110°.

known steric requirements of the *t*-butyl group[14] make it highly unlikely that it is other than equatorially fixed, implying again that the two conformers observed result from the amide energy minima.[15]

However, there are also differences between the spectra of **1** and **2** which affect the accuracy of the measurement of experimental parameters. Thus, the ratio of the isomers of compound **2** is *ca.* 78:22 (compared to 60:40 for compound **1**) as determined from examination of the respective areas of the acetyl resonances. Confirmation of this ratio by examination of the C-8 proton resonances (successful for **1a–1b**) fails with compound **2**.

(15) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *J. Amer. Chem. Soc.*, **89**, 4910 (1967).

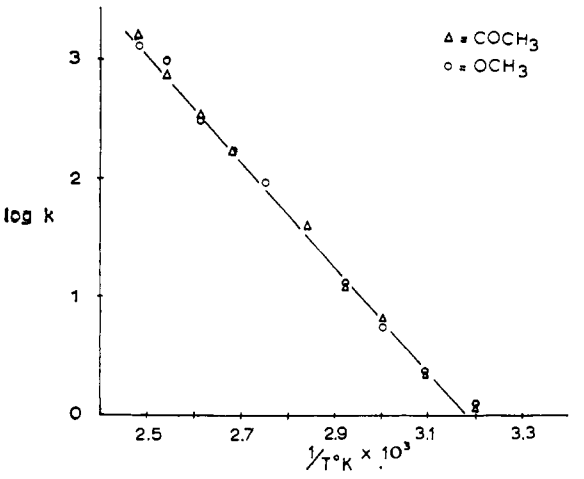


Figure 4. A plot of log *k* *vs.* $1/T$°K for the methoxyl (○) and N-acetyl (△) resonances for compound **1**.

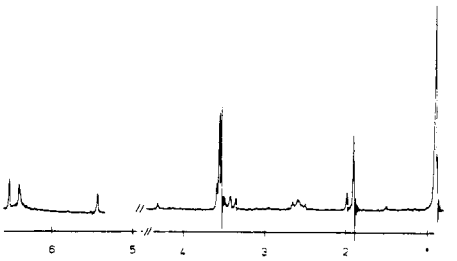


Figure 5. The spectrum of 1-*t*-butyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**2**) in chlorobenzene (C_6H_5Cl) at 40°.

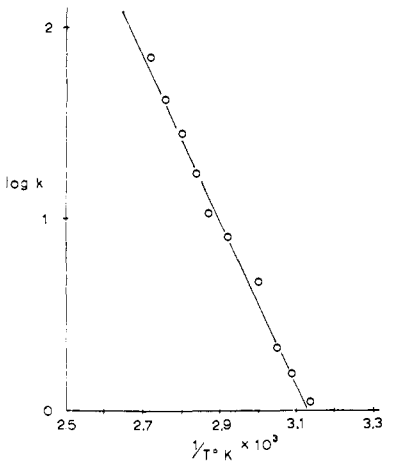


Figure 6. A plot of log *k* *vs.* $1/T$°K for the N-acetyl (○) resonances for compound **2**.

This is attributed to the fact that the substituent benzene ring at C-1 in compound **1** significantly deshields the proton at C-8 in one conformation resulting in ready observation and measurement of the respective signals whereas similar deshielding is absent in compound **2**.

Table II presents the experimental parameters for compound **2** in the temperature range 40–95°. In this case, the complications discussed above permitted use of the acetyl resonance only and the data resulting are plotted in Figure 6. The Arrhenius activation energy is 20.4 ± 0.5 kcal/mole and the thermodynamic parameters, similar to those found for compound **1**, are

Table II. Change in Line Separation ($\Delta\delta$), Line Width, and Mean Lifetime (τ) with Change in Temperature for 1-*t*-Butyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**2**)

Temp, °C	$\Delta\delta_{A-B}$	Acetyl resonance (corrected line width)[a] 2a	2b	τ
45	8.1	1.35	0.36	0.210
50	7.7	2.19	0.49	0.141
55	7.4		0.68	0.105
60	6.5		1.33	0.049
70		2.08		0.028
75		2.20		0.021
80		1.68		0.0128
85		1.12		0.008
90		0.74		0.0055
95		0.46		0.0031

[a] Line width at half-height ($W_{1/2}$) minus the line width ($W_{1/2}$) of dichloromethane (CH_2Cl_2) at the same temperature.

resonances for the C-1 protons. However, the room temperature spectrum of **4** (Figure 8) shows only two singlet resonances (δ 4.46 and 4.55 ppm) for the protons at C-1, in a ratio of *ca.* 60:40, which coalesce to a single line at 80°. At no temperature was an AB pattern observed. Process i clearly describes the observed results. However, the broadening of the C-1 protons by the nitrogen severely restricts the accuracy of the quantitative measurement of these signals.

Finally, Table III presents the pmr parameters for compounds **5**–**7**. Here it is clearly seen that increasing the size of the substituent on the 2 position results in movement of the benzene ring of the benzyl group at C-1 toward the A ring, *i.e.*, the angle subtended by the planes of rings A and C (θ, Figure 9) increases while the angle ϕ, Figure 9, decreases.

Table III. Pmr Spectral Parameters for Compounds **5**–**7**

Compd	H_5 resonance, ppm from TMS	H_8 resonance, ppm from TMS	Methoxyl 6 and 7, ppm from TMS	$\Delta\nu_{methoxyls}$, Hz	$\Delta\nu_{hydrogens}$, Hz
5	6.59	6.59	3.77 and 3.82	3.0	0.0
6	6.56	6.26	3.65 and 3.81	7.8	18.6
7	6.61	6.16	3.61 and 3.84	13.8	27.0

$\Delta H^*_{363} = 19.5 \pm 0.05$ kcal/mole and $\Delta F^*_{363} = 17.6 \pm 0.5$ kcal/mole.

The activation enthalpies of *ca.* 20 kcal/mole for compounds **1** and **2** are quite similar to those reported for a number of amides.[16]

Additional confirmation of the proposed process is obtained by examination of the 100-MHz spectra of compounds **3** and **4**, Figures 7 and 8, respectively.

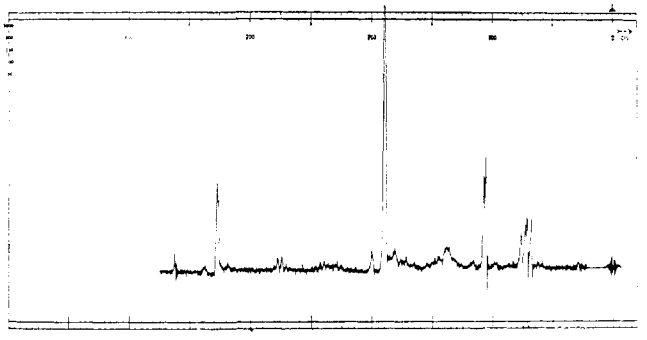


Figure 7. The spectrum of 1-methyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**3**) in chlorobenzene (C_6H_5Cl) at 40°.

The spectrum of **3**, in $CDCl_3$, clearly shows, again, the presence of two isomers (ratio *ca.* 45:55) through the presence of two acetyl resonances and the pair of doublets (J = 5.5 Hz) due to the methyl at C-1.

The spectral characteristics of compound **4** (Figure 8) clearly demonstrate that the processes ii, iii, and iv *vide supra* cannot be detected by the nmr experiment for the isoquinolines considered in this study. Thus, if more than one process were involved, the spectrum of **4**, in the slow exchange limit, would be expected to show AB-type

(16) J. W. Emsley, J. Feeney, and L. H. Sutcliff, "High Resolution NMR Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, p 556 ff. A first-order approximation, carried out according to F.-H. Marquard, *Chem. Ind.* (London), 1788 (1967), yields E_a = 21.6 kcal/mole for the acetyl methyl collapse.

These data lend support to the contention[17] that ring-closure reactions, by whatever mechanism, involving these compounds will proceed with enhanced yields when the substituent on nitrogen is large.

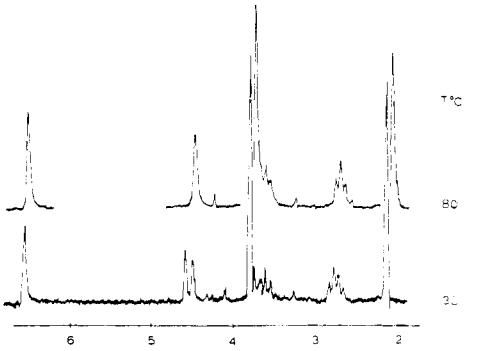


Figure 8. The spectrum of 2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (**4**) in chloroform-*d* ($CDCl_3$) at (a) 40° and (b) 80°.

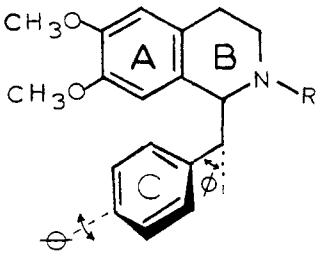


Figure 9. The change in angles resulting from an increase in the size of the substituent on nitrogen in the 2-substituted 1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline system.

(17) M. P. Cava and D. R. Dalton, *J. Org. Chem.*, **31**, 1281 (1966).

Experimental Section

Pmr spectra were measured with Varian A-60, A-60A, and HA-100 spectrometers equipped with variable temperature probes and accessories. Chloroform-*d* ($CDCl_3$) and chlorobenzene (C_6H_5Cl) were used as solvents and tetramethylsilane was included as an internal standard and field lock.

A computer program, written in Fortran IV for an IBM 1800 computer, which utilized the Gutowsky–Holm line equation, was used to generate line shapes for a given relaxation time. The experimental line widths less T_2 of methylene chloride were computed to give the rate constant at a given temperature. Plots of log k *vs.* $1/T$°K (see Discussion) were used to obtain the activation energies.

For all compounds, whether previously reported or not, microanalyses were obtained from Schwartzkopf Microanalytical Laboratory, Woodside, N. Y., and Micro-Analysis, Inc., Wilmington, Del. Melting points were obtained on a Fisher-Johns block or a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Beckman IR-5A spectrophotometer.

1-Benzyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (1) was prepared as previously noted.[1b]

1-*t*-Butyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (2) was prepared by a modification of the procedure of Craig, *et al.*[18] The amine, prepared as noted,[18] was acetylated with acetyl chloride in pyridine and recrystallized from benzene–heptane (1:1).

Anal. Calcd for $C_{17}H_{25}NO_3 \cdot 0.5H_2O$: C, 67.97; H, 8.72; N, 4.66. Found: C, 68.14; H, 8.92; N, 4.65.

1-Methyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (3), mp 100–101° (lit.[19] mp 100–101°), was prepared according to Hromatka, *et al.*,[19] and recrystallized from hexane.

2-Acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (4) was prepared as previously noted.[1b]

1-(2′-Aminobenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (5) was prepared according to the procedure of Weisbach and Douglas,[20] mp (hydrochloride) 257–258° dec (lit.[20] mp 256–257° dec).

1-(2′-Ambinobenzyl)-2-methyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (6) was prepared according to the procedure of Gulland and Haworth,[21] mp 95–96°, hydrochloride mp 240° dec (lit.[21] mp 243–244° dec).

1-(2′-Aminobenzyl)-2-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (7) was prepared according to the procedure of Weisbach and Douglas,[20] mp 120° (lit.[20] mp 112–114°).

Acknowledgment. This investigation was supported, in part, by Public Health Service Research Grant CA 08841 from the National Cancer Institute.

(18) P. N. Craig, F. P. Nabenhauer, P. M. Williams, E. Macko, and J. Toner, *J. Amer. Chem. Soc.*, 74, 1316 (1952).

(19) O. Hromatka, W. Graf, and M. Knollmüller, *Monatsh. Chem.*, 97, 19 (1966).

(20) J. A. Weisbach and B. Douglas, *J. Org. Chem.*, 27, 3738 (1962).

(21) J. M. Gulland and R. D. Haworth, *J. Chem. Soc.*, 581 (1928).

Nuclear Magnetic Resonance Spectroscopy. Slow Nitrogen Inversion in an Acyclic Substituted Hydrazine[1a]

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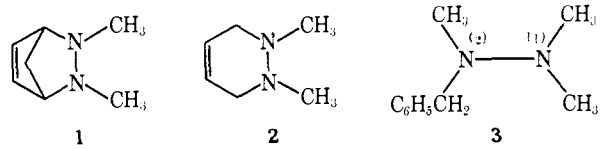
Received March 7, 1969

Abstract: Changes which were found to occur in the proton nmr spectrum of benzyltrimethylhydrazine at low temperatures are discussed in terms of hindered rotation about the nitrogen–nitrogen bond and slow nitrogen inversion. It is concluded that, below −130°, inversion of the nitrogen atom bearing the benzyl group is slow on the nmr time scale. The barrier to inversion is calculated to be 6.8 kcal/mol, which is substantially lower than the barriers found for cyclic and bicyclic hydrazines or for group V analogs of hydrazine.

Recently, there have been several studies of nitrogen inversion in cyclic and bicyclic hydrazine derivatives.[2-9] At about −60°, nitrogen inversion is slow on the nmr time scale for compounds of types **1**[3] and **2**.[9]

The barriers to nitrogen inversion in these substances are substantial, and it is perhaps surprising that there has been no report of barriers to nitrogen inversion of acyclic alkylhydrazines. Clearly, knowledge of such barriers is important for an understanding of those found in the cyclic compounds.

Some time ago we reported studies of the inversion rates of nitrogen atoms bearing electronegative substituents,[10] among which was benzyltrimethylhydrazine (**3**). No significant change in the proton nmr spectrum of **3** was observed on cooling to −70°. We have now extended our examination to much lower temperatures, and report here the changes observed.



1 2 3

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