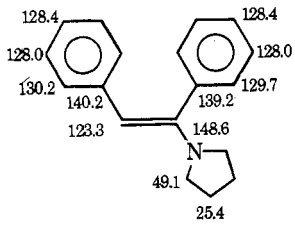


Registry No.—**10a,** 58268-19-2; **10b,** 58268-20-5; **10c,** 58268-21-6; **12,** 58268-22-7; **13a,** 58268-23-8; **13b,** 58268-24-9; **19,** 58268-25-0; **34,** 2866-82-2; *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate HCl, 58268-26-1; *threo*-1,2-diphenyl-2-(*N*-*n*-butylamino)ethyl acetate, 58268-27-2; 1,2-diphenyl-1-pyrrolidinoethane, 58268-28-3.

References and Notes

(1) H. Euler, *Chem. Zentralbl.*, **74,** 1165 (1903).
(2) H. Euler, *Justus Liebigs Ann. Chem.*, **330,** 280 (1903).
(3) C. L. Bumgardner, K. S. McCallum, and J. P. Freeman, *J. Am. Chem. Soc.*, **83,** 4417 (1961).
(4) W. Rundel and E. Muller, *Chem. Ber.*, **96,** 2528 (1963).
(5) R. D. Clark and G. K. Helmkamp, *J. Org. Chem.*, **29,** 1316 (1964).
(6) G. Drefahl, K. Ponsold, and B. Schoenekker, *Chem. Ber.*, **97,** 2014 (1964).
(7) R. M. Carlson and S. Y. Lee, *Tetrahedron Lett.*, 4001 (1969).
(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 159.
(9) W. L. Mock and P. A. H. Isaac, *J. Am. Chem. Soc.*, **94,** 2749 (1972).
(10) P. A. S. Smith and R. N. Loeppky, *J. Am. Chem. Soc.*, **89,** 1147 (1967).
(11) G. E. Hein, *J. Chem. Educ.*, **40,** 181 (1963).
(12) W. Lijinsky, L. Keefer, E. Conrad, and R. Van de Bogart, *J. Natl. Cancer Inst.*, **49,** 1239 (1972).
(13) N. H. Cromwell, G. V. Hudson, R. A. Wankel, and P. J. Vanderhorst, *J. Am. Chem. Soc.*, **75,** 5385 (1953); G. J. Buist and H. J. Lucas, *ibid.*, **79,** 6157 (1957).
(14) J. D. McCown, Ph.D. Thesis, University of Iowa, 1968.
(15) D. Seebach and D. Enders, *Angew. Chem., Int. Ed. Engl.*, **14,** 15 (1975).
(16) M. E. Munk and Y. K. Kim, *J. Org. Chem.*, **30,** 3705 (1965).
(17) R. Dulou, E. Elkik, and A. Veillard, *Bull. Soc. Chim. Fr.*, 967 (1960).
(18) R. Huisgen, E. Funke, H. Gotthardt, and H. L. Panke, *Chem. Ber.*, **104,** 1532 (1971).
(19) R. W. Hoffmann and K. R. Eicken, *Chem. Ber.*, **102,** 2987 (1969).
(20) G. P. Rizzi, *J. Org. Chem.*, **35,** 2069 (1970).
(21) J. Collin, *Bull. Soc. R. Sci. Liege*, **23,** 201 (1954).
(22) S. S. Dubou and A. M. Khokhlova, *Zh. Obshch. Khim.*, **34,** 1961 (1964).
(23) G. Schroll, R. G. Cooks, P. Klemmensen, and S. O. Luwesson, *Ark. Kemi*, **28,** 413 (1967).
(24) T. Axenrod and G. W. A. Milne, *Chem. Commun.*, 67 (1968).
(25) J. W. ApSimon and J. D. Cooney, *Can. J. Chem.*, **49,** 1367 (1971).
(26) P. S. Pregosin and E. W. Randall, *Chem. Commun.*, 399 (1971).
(27) A detailed interpretation of the mass spectrum of **13a** may be obtained by writing the principal author.
(28) A. A. Polyakova et al., *Zh. Org. Khim.*, **3,** 836 (1967).
(29) R. N. Loeppky, R. Christiansen, and D. H. Smith, unpublished results.
(30) S. Hunig, G. Buttner, J. Cramer, L. Geldern, H. Hansen, and E. Lucke, *Chem. Ber.*, **102,** 2093 (1969).
(31) R. E. Lutz, J. A. Freek, and R. S. Murphey, *J. Am. Chem. Soc.*, **70,** 2015 (1948).
(32) T. W. J. Taylor, J. S. Owen, and D. Whittaker, *J. Chem. Soc.*, 206 (1938).
(33) "Tables for the Identification of Organic Compounds", C. D. Hagman, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1960, p 68.
(34) R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 142.
(35) R. N. Haszeldine and B. J. H. Mattison, *J. Chem. Soc.*, 4172 (1955).
(36) R. L. Schriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds", Wiley, New York, N.Y., 1964, p 142.
(37) Reference 36, p 254.
(38) Reference 33, p 71.
(39) Reference 34, p 329.
(40) Reference 33, p 101.
(41) Reference 33, p 97.

The Configuration[1] of Nicotine. A Nuclear Magnetic Resonance Study

Jerry F. Whidby and Jeffrey I. Seeman*

Philip Morris Research Center, P.O. Box 26583, Richmond, Virginia 23261

Received July 29, 1975

Radiofrequency irradiation of the *N*-methyl group in nicotine at pD values of 11.0, 5.0, and 0.8 caused nuclear Overhauser enhancements (NOE) of the pyridyl protons and the C-2′ and C-5′ protons on the pyrrolidine ring. However, irradiation of the *N*-methyl group at 3.13 ppm of nicotine in trifluoroacetic acid solution (TFA) did not cause an NOE on the pyridyl protons but rather on the C-2′ and C-5′*β* protons. In TFA, the rate of deprotonation of nicotinium diacid salts is slow compared to the NMR time scale, and the peak at 3.13 ppm is attributed to the nicotinium salt in which the *N*-methyl group is trans to the pyridine ring. A second singlet at 2.82 ppm is attributed to the nicotinium salt in which the *N*-methyl group is cis to the pyridine ring. These assignments were established by NMR studies in mixtures of TFA–TFA-*d*. These results are interpreted in terms of nitrogen protonation–deprotonation–pyramidal inversion equilibria and the complexities of NOE studies on configurationally mobile systems. The rates of inversion and proton relaxation are considered. It is estimated that nicotine-free base exists with its *N*-methyl group preferentially (90.9 ± 0.9%) trans to the pyridine ring by gas-phase kinetic quenching experiments.

The configuration[1] of nicotine and nicotine acid salts has been a topic of concern for many years.[2-9] Nicotine structural analysis indicates two unknown features: the orientation of the *N*-methyl group and the relative position of the pyridine and pyrrolidine rings. Experimental determination of these two structural parameters is complicated by the likelihood of low energy barriers to change.[10] We now report the results of our studies which show that the preferred (>90%) configuration of the *N*-methyl group in nicotine is 1′ (*R*) (i.e., trans to the pyridine ring) under a variety of experimental conditions.

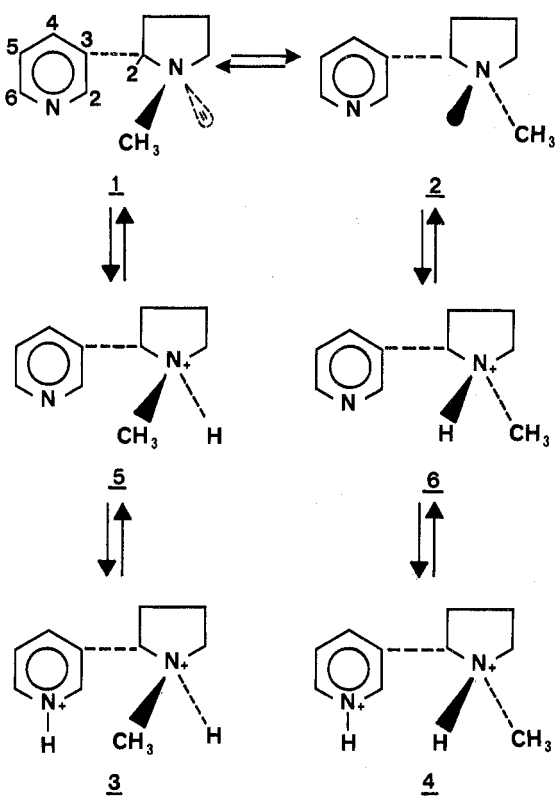
Recently, Chynoweth, Ternai, Simeral, and Maciel[8] concluded on the basis of their NMR studies of nicotine in $CDCl_3$ and D_2O "that the N-methyl group is preferentially on the same side of the pyrrolidine ring as the pyridine ring". That conclusion[8] contrasted with perturbative configuration interaction calculations performed by Pullman, Courriere, and Coubeils,[7a] which indicated that 1 (see Scheme I) was approximately 4 kcal/mol more stable than **2**.[11] Other investigators[2-4] based their configurational assignments on (1) steric evaluations using space-filling models or (2) demethylation studies of nicotine *N*′-oxide. Any conclusion based on these latter two criteria meets with severe criticism.[12] Finally, Koo and Kim[5] have reported the x-ray analysis of a crystal of nicotine dihydriodide in which the *N*-methyl group was in a trans configuration with respect to the pyridine ring (cf. **3**). However, the crystalline sample was undoubtedly prepared under conditions in which the equilibria shown in Scheme I were operative, and it is theoretically possible that a minor component, or one of a number of components, crystallized. In addition, conclusions based on x-ray data of a solid cannot necessarily be applied to the conformation or configuration of the same molecule in solution, especially if protonation–deprotonation reactions are occurring in solution.[14]

Table I. NOE Studies of Nicotine[c]

Sample description	Figure	Position irradiated, ppm	Proton irradiated[d]	Position observed, ppm	Proton observed	% enhancement[e]
pD 11.0[a]	1	2.16	N-CH_3 of	8.52	2,6	10.8
			1 ⇄ 2	7.98	4	10.0
pD 5.0[a]	2	2.88	N-CH_3 of	8.69	2,6	5.9 (4)[b]
			5 ⇄ 6		4	10.9 (10)[b]
pD 0.8[a]	3	2.98	N-CH_3 of	9.00	2,4,6	8.1
			3 ⇄ 4	4.00	5′α	5
				3.58	5′β	5
Trifluoroacetic acid-*d*	4	3.13	N-CH_3 of **3**[d]	9.36	2,4,6	0
				4.90	2′	13
				4.28	5′α	3
				3.58	5′β	11
22% DCl	*f,g*	3.13	N-CH_3 of **3**[d]	9.36	2,4,6	0
				4.90	2′	12.5
				4.28	5′α	3
				3.58	5′β	11

[a] Acidity was adjusted with D_2SO_4 in D_2O. [b] Data from ref 8. [c] See Experimental Section for instrumental details. [d] See text for discussion of assignments. [e] Enhancements reported are based on total number of protons in the multiplet observed and not on the number of protons expected to be enhanced. [f] Essentially identical with Figure 4. [g] Similar results were found with concentrated DCl.

Scheme I



Note that rotation of one ring with respect to the other effectively interchanges the spatial orientation of H_2 and H_4 with respect to the pyrrolidine ring.

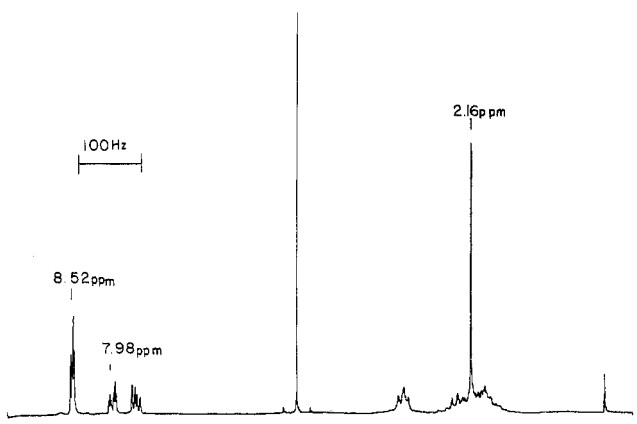


Figure 1. NMR spectra of nicotine, pD 11, at 100 MHz.

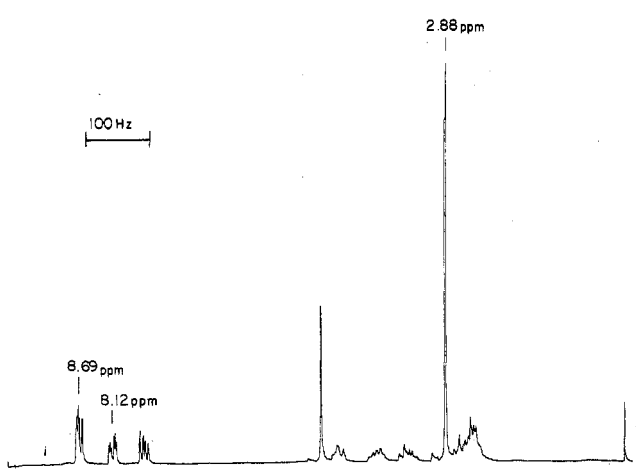


Figure 2. NMR spectra of nicotine, pD 5.0, 100 MHz. At this pD, only the pyrrolidine nitrogen is protonated.

Results and Discussion

A knowledge of the intramolecular distance between the *N*-methyl group and the pyridine ring would be sufficient to uniquely determine the cis-trans nature of the *N*-methyl group in nicotine. Recently, the intramolecular nuclear Overhauser effect (NOE) has been utilized to determine intramolecular distances between atoms.[15] This technique measures an area change of the NMR signal of one atom when a second radiofrequency field is applied at the resonance frequency of another atom. Since the magnitude of the area increase is strongly dependent on the intramolecular distance between the atoms involved ($1/r^6$ dependency), structural information is often obtainable.

Ternai et al.[8] attempted to utilize the intramolecular NOE data from nicotine to determine structural information. Table I summarizes their results and includes our data as well (see Figures 1–4). At pD ≥0.8, irradiation of the *N*-methyl group clearly results in a substantial NOE signal enhancement of the 2- and 4-pyridyl protons. Molecular models indicate that

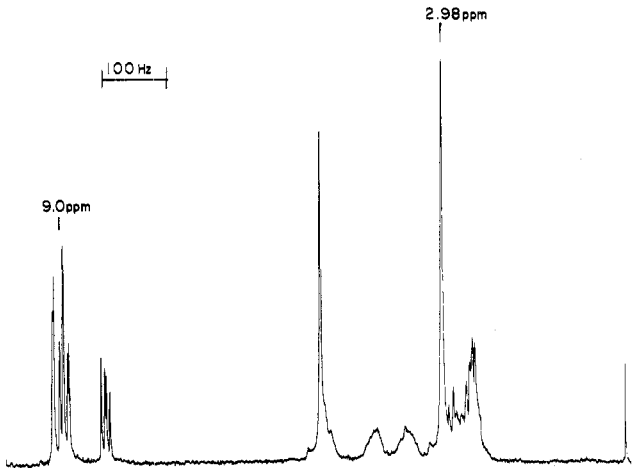


Figure 3. NMR spectra of nicotine, pD 0.8, at 100 MHz. At this pD, both nitrogens are protonated but deprotonation is extremely rapid compared to the NMR time scale.

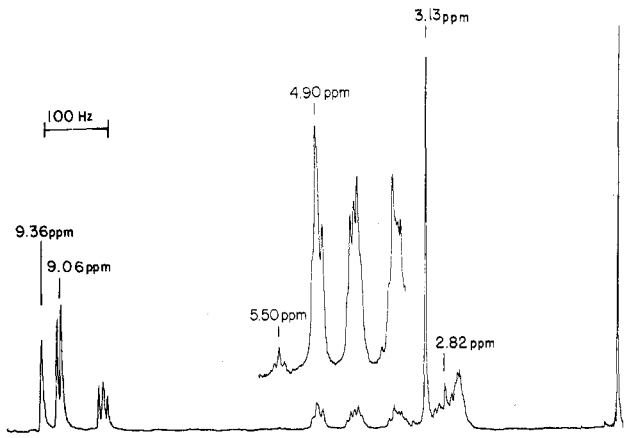
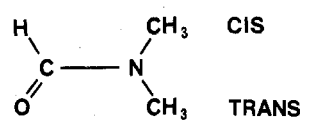


Figure 4. NMR spectra of nicotine in trifluoroacetic acid-*d* at 100 MHz. In this solvent, both nitrogens are protonated and deprotonation is slow compared to the NMR time scale.

only in **2** is the methyl group of nicotine-free base sufficiently close to the pyridine ring protons to cause an NOE. These considerations led Ternai et al.[8] to conclude that **2** is the predominant stereoisomer of nicotine-free base in solution.

However, for systems in which conformational or configurational equilibria are possible, the rate of interchange must be considered. This was elegantly demonstrated by Saunders and Bell,[16] who considered the NOE of dimethylformamide (**7**). At 90 °C, the two methyl signals are separated by 0.15



7

ppm; however, NOE studies showed that irradiation of each signal independently resulted in equal enhancements (28%) of the formyl proton. It is expected that the methyl group cis to the formyl proton should show an NOE and that the trans methyl group is too distant to cause an enhancement. Indeed, at 31 °C, the NOE for the trans methyl was almost zero, but as the temperature was raised the enhancement increased to the limiting value of 28%. This phenomenon is explained by (1) spin saturation of the trans methyl group; (2) temperature-dependent rotation about the amide linkage, thereby effectively interchanging methyl groups; and (3) spin–spin interaction and NOE enhancement. Thus, in a mobile system, the observation of an NOE is not sufficient evidence on which to base conformational or configurational preference.[15,16]

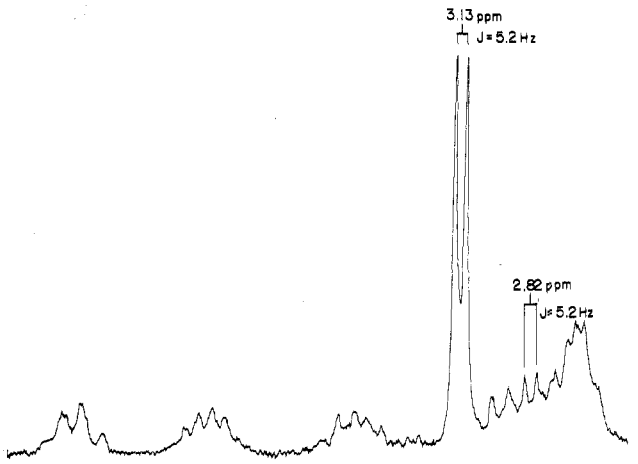
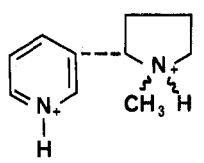


Figure 5. NMR spectra of nicotine in trifluoroacetic acid at 100 MHz.

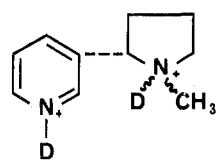
These considerations indicate that the observed NOE enhancements of nicotine discussed above (see Table I, pD ≥0.8) could be a phenomenological effect of a conformationally or configurationally mobile system. We, therefore, investigated the NOE of nicotine at various acidities since it is well known[17] that the rate of deprotonation and nitrogen inversion can be markedly decreased by increasing acid concentration.

The NMR of nicotine in trifluoroacetic acid-*d* (TFA-*d*) is shown in Figure 4. In this solvent, the rates of deprotonation (**4** → **6** → **2** and **3** → **5** → **1**) have been slowed considerably. Indeed, careful inspection of Figure 4 reveals a singlet at 2.82 ppm which can be attributed to the methyl group in **4** in addition to a singlet at 3.13 ppm for the methyl group in **3**. Accumulation of multiple repetitive scans of nicotine in TFA-*d* allows the observation of a multiplet at 5.50 ppm which corresponds to the proton at C-2′ of **4** in addition to a multiplet at 4.90 ppm for the C-2′ proton in **3**.[24]

To establish that the resonance at 2.82 ppm is due to the methyl group in **4**, the NMR of nicotine was run in TFA (Figure 5) and in mixtures of TFA-*d* and TFA (Figure 6). The methyl group of **8** should appear as a doublet while the methyl group of **9** should be a singlet. The combination of **8** and **9** in



8



9

solution produces a triplet (the combination of a singlet and a doublet) at 3.13 ppm and a triplet at 2.82 ppm (Figure 6) in which the ratio of the doublet area to the singlet area is equal to the ratio of TFA to TFA-*d* (see Figure 6).[24]

Thus, increasing the acidity of the nicotine solution effectively freezes out, relative to the NMR time scale, the two diastereomeric nicotine acid salts, **3** and **4**. The similarities of this to the often utilized variable-temperature NMR experiments are readily apparent.

Table I shows the results of NOE experiments performed on the nicotine–strong acid mixtures. Irradiation of the *N*-methyl group singlet at 3.13 ppm resulted in no area enhancement in the pyridyl proton region, indicating that the methyl group at 3.13 ppm is trans to the pyridine ring, i.e., this methyl group is from **3**. However, large NOE (>11%) were observed for two of the three protons α to the prrrolidine nitrogen (4.90 and 3.58 ppm) when the 3.13-ppm singlet was irradiated.

The multiplet at 4.90 ppm was assigned to the C-2′ proton of **3** using both decoupling experiments and chemical shift

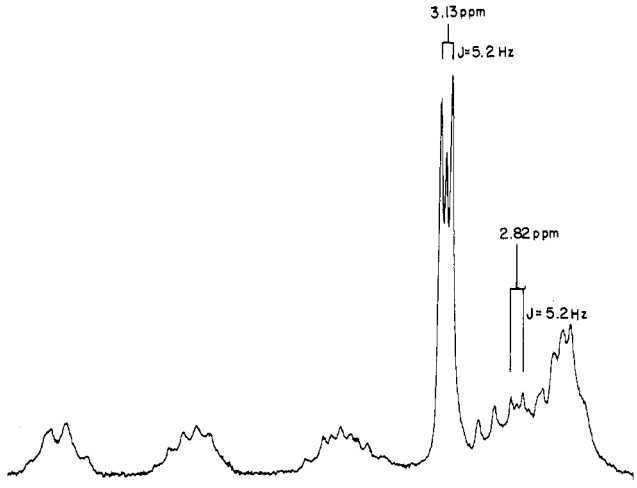


Figure 6A. NMR spectra of nicotine in 2.5:1 trifluoroacetic acid–trifluoroacetic acid-*d* at 100 MHz.

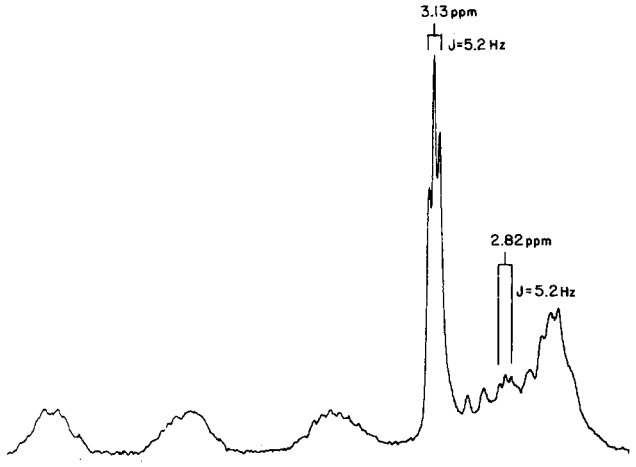
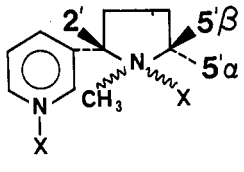


Figure 6B. NMR spectra of nicotine in 1:1 trifluoroacetic acid–trifluoroacetic acid-*d* at 100 MHz.

evaluations. When a decoupling frequency was applied to the C-3′ and C-4′ proton region, the multiplet at 4.90 ppm was simplified to a doublet with a coupling constant of 8.8 Hz due to coupling with the proton on the protonated nitrogen (H–C–N–H coupling). Under these decoupling conditions, multiplets at 3.58 and 4.28 ppm approximated somewhat complex ABM patterns due to geminal coupling and H–C–N–H coupling. The signal at 3.58 ppm was assigned to the C-5′β proton



X=H,D or nitrogen lone pair

10

(cf. **10**) because of the observed NOE. Furthermore, quantitative NMR shift analysis of nicotine with increasing acid concentration confirm these assignments. The observation of an NOE for the C-2′ and C-5′β protons and the failure to observe an NOE for the pyridyl or C-5′α protons confirm the assignment of the 3.13-ppm singlet as the resonance from the methyl group of **3**.

An NOE enhancement in the pyridyl protons was observed when the minor methyl group singlet at 2.82 ppm was irradiated, but evaluation of this NOE is hampered since the pyrrolidine resonances appear in the 2.5–3.2-ppm region and an NOE would be expected from these protons on the pyridyl protons.

Further confirmation of the trans configuration of the major isomer can be obtained by considering the relative chemical shifts of the large (3.13 ppm) and small (2.82 ppm) methyl groups and the large (4.90 ppm) and small (5.50 ppm) C-2′ protons in the **3**–**4** mixture. Examination of space-filling models reveals that in the cis orientation, the methyl group is much closer to the face of the pyridine ring than in the trans orientation in which the methyl group appears to be almost antiperiplanar to the pyridine ring. The anisotropic magnetic field generated by the circulating π electrons in the aromatic ring would therefore be expected to shield the cis methyl group near the face of the pyridine ring, resulting in an upfield shift for that methyl group.[18a] In fact, this is observed for the smaller methyl group, i.e., the methyl group in **4**. A similar argument can be made for the relative positions of the C-2′ proton and the *N*-methyl group, since it is established that a methyl group is capable of shielding protons in close proximity to itself.[18b] Comparing **3** and **4**, the methyl group is closer to the C-2′ proton in **3** than in **4**, and the C-2′ proton of **3** would be expected to be upfield relative to the C-2′ proton of **4**.

The NOE experiments in strong acid were also performed in 22% DCl and 38% DCl (see Table I). The results obtained in these solvents were essentially identical with the NOE found (or not found) in TFA. These duplicate experiments were necessary to evaluate the possible complications of TFA as solvent in NMR relaxation studies. It is known[19] that the ^{19}F dipoles of the solvent TFA are large and could provide a competing relaxation mechanism for the pyridine ring protons, thereby short-circuiting any excess polarization of these protons produced by saturating the *N*-methyl group. However, the similarity of the results in the nonfluorinated solvents and the observation of NOE for some of the protons in TFA-*d* mitigate against this complication.

These results reemphasize the importance of considering rate processes in NOE measurements involving systems possessing configurational or conformational mobility. In the case at hand, saturation of the *N*-methyl resonance will result in an NOE for the pyridine protons only if these protons are relaxed to a significant extent by the methyl protons. For nicotine, an NOE would be observed even if the methyl group spends only a very small portion of its time in the cis orientation, given the simultaneous condition that relaxation by other mechanisms is insufficient to completely relax the methyl group when it is trans to the pyridine ring.[15]

This explanation applies when nitrogen inversion is rapid relative to $1/T_{1,\text{trans}}$ for the methyl proton, otherwise the methyl protons would have sufficient time to return to spin equilibrium. This is the case for nicotine in neutral, basic, or mildly acidic solutions. For example, we have determined that $1/T_{1,\text{trans}}$ is 0.75 s^{-1} in concentrated DCl solution. Proton relaxation rates are commonly slow. We have attempted to freeze out nicotine using low-temperature NMR techniques, but even at −145 °C (in CF_2Cl_2) we observed no line broadening of the *N*-methyl group. Nitrogen atomic inversion is well known to be a very facile process,[17a] and E_a for related *N*-alkyl pyrrolidines have been found to be less than 12 kcal/mol, and should be even more facile a process for nicotine owing to steric acceleration of inversion.[17a] The fact that the acidity of the nicotine medium must be very high in order to slow down the **3** ⇄ **4** interconversion (see above) is indicative of an exceedingly low E_a.[20]

At the other extreme, the observation of two methyl groups and two C-2′ protons in the nicotine–TFA-*d* solutions clearly indicates that the deprotonation–inversion–protonation processes have been slowed down considerably. However, the

observation of two sets of signals is not inherently sufficient to make transfer of spin saturation inefficient. The time scales for NOE and collescence phenomenon are different. Coalescence is related to the frequency difference of the protons in their different orientations while NOE phenomena are related to the T_1 of these protons.[16]

We have evaluated the low inversion rate conditions in four fashions. First, when the nicotine–DCl mixture is irradiated at 4.90 ppm, corresponding to the C-2′ proton in **3**, no decrease in the area of the multiplet at 5.50 ppm corresponding to the C-2′ proton of **4** was observed. Thus, spin saturation is not transferred under these conditions from **3** to **4**. Apparently, the relaxation time is short enough *not* to allow transfer of saturation.

Second, when the nicotine–DCl mixture was irradiated at 3.13 ppm (cf. above), only the C-2′ and C-5′β protons were enhanced. The C-5′α proton did not show an NOE. If the deprotonation–inversion–protonation processes were occurring with an overall rate of the same order of magnitude of the rate of relaxation, an NOE would have been expected for all three of these protons (cf. experiments of nicotine pD 0.8).

Third, when a sample of nicotine is treated with 1:1 D_2SO_4–TFA-*d*,[21] a mixture of diastereomers **9** is formed. Subsequent treatment with 1:1 H_2SO_4–TFA allows a crude determination of the deprotonation–inversion rate by an analysis of the rate of transformation of **9** → **8**. After 120 h, no NMR evidence for the formation of **8** was observed. Under these conditions, the deprotonation–inversion rate is many orders of magnitude slower than $1/T_{1,\text{trans}}$.

Fourth, when a crystalline sample of isomerically pure *trans*-nicotine dihydriodide (**3**)[14] was dissolved in concentrated DCl, H–D exchange at the pyrrolidine nitrogen was observed by following the disappearance of the doublet and appearance of the singlet at 3.13 ppm, i.e., **8** → **9**. This H–D exchange was essentially complete after 1 h. However, even after 4 h, *cis*-nicotine dideuterioiodide was not formed under these conditions, as judged by the absence of both the C-2′ proton at 5.50 ppm and the *N*′-methyl group at 2.82 ppm. Upon addition of D_2O to this solution (to form approximately 22% DCl), a significant quantity (~10%) of **4** formed within 15 min. Thus, in concentrated DCl, a solvent less acidic than either TFA, sulfuric acid, or TFA–sulfuric acid mixtures used above, the nicotinium salt is capable of deprotonation to form the amine followed by reprotonation *without* nitrogen inversion. This is not unexpected as the rate constant for nitrogen inversion is slower than the rate constant for protonation.

Thus, the accumulated evidence proves that **3** and **4** formed in the nicotine–concentrated DCl or TFA mixtures have rates of deprotonation and inversion sufficiently less than their respective $1/T_1$'s, thereby satisfying the conditions necessary for the NOE studies at low interconversion rates.

The ratio of **3**:**4** can be used to determine the ratio of **1**:**2** if protonation to form **3** and **4** occurs faster than deprotonation and inversion.[22] Kinetically controlled protonation conditions can be met since (1) protonation can be made effectively irreversible by adjusting the acidity of the solution and (2) by quenching the amine with acid in the gas phase. The former criterion has been demonstrated in TFA-*d*–D_2SO_4 by measuring the conversion of **9** → **8**. The latter condition removes the objection of reversible protonation at the interface of the acidic and basic phases during the mixing process.

A dilute stream of nicotine vapor in argon was mixed with hydrogen chloride gas. A solid, crystalline mass of nicotine dihydrochloride **8** was formed at the region of mixing and this was treated with D_2SO_4–TFA-*d* (1:20) under anhydrous conditions. The failure to observe **9** after 20 h proves that the deprotonation–inversion processes do not interfere with this analysis. Careful integration of the C-2′ protons of **3** and **4** allowed determination of the ratio **3**:**4** = **1**:**2** = 10:1. Thus, nicotine in the vapor phase is 90.9 ± 0.9% **1**.

The relative concentrations of **1**–**6** (cf. Scheme I) under various conditions may well be important in the evaluation of the chemical behavior of nicotine. However, this work is also pertinent to the conformational and configurational analysis of many other alkaloid bases which possess a substituted nitrogen atom capable of facile pyramidal inversion.[23] Spectroscopic techniques are well geared to solving the complex questions of conformational and configurational analysis, but caution is the keynote in any such analysis.

In summary, we have demonstrated (1) that nicotine exists 90% in the 1′ (*R*) configuration; and (2) that the use of the NOE for determining nitrogen configuration must be evaluated under slow inversion conditions relative to the appropriate relaxation conditions.[24]

Experimental Section

The NMR spectra of nicotine (5% v/v) at various acidities were recorded on a Varian XL-100 operating at 100 MHz. The spectrometer was operated in the pulse Fourier transform mode, using a Digilab data system (FTS/NMR-3) and pulse unit. The samples used for the NOE measurements were thoroughly degassed by at least five freeze–pump–thaw cycles. The power from the decoupler was held at a minimum since the pyrrolidine proton resonances were close to the *N*-methyl resonance. The pD of the D_2O–nicotine solutions was determined on a Corning Digital 110 line operated pH meter standardized with NBS buffer solutions.

Acknowledgment. The authors gratefully acknowledge the encouragement of Dr. T. S. Osdene during the course of this work. Helpful discussions with Drs. W. F. Gannon, E. B. Sanders, and T. P. Pitner are also acknowledged with pleasure.

Registry No.—**1**, 58407-29-7.

References and Notes

(1) (a) Although seemingly a matter of semantics, the orientation of the *N*-methyl group relative to the pyridine ring in nicotine is properly described in terms of configurational rather than the uniformly used conformational label. Even though no bonds are broken in the nitrogen inversion process, a net change in configuration results. Conformation usually connotes "one of the infinite number of momentary arrangements of the atoms in space that result from the rotation about single bonds",[1b] and the pyramidal inversion process is more complicated than a simple rotational process. However, configuration involves the three dimensional arrangement in space of the atoms around a chiral center, in this case the nitrogen atom.[1c] There are numerous examples of misnomer in the current literature involving nitrogen conformational and configurational terminology. Two molecules which differ *only* by the process of nitrogen pyramidal inversion are properly termed configurational isomers. (b) E. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962, p 87. (c) *ibid.*, p 124.
(2) J. C. Craig, N. Y. Mary, N. L. Goldman, and L. Wolf, *J. Am. Chem. Soc.*, **86**, 3866 (1964).
(3) T. R. Simpson, J. C. Craig, and W. D. Kumler, *J. Pharm. Sci.*, **56**, 708 (1967).
(4) L. B. Kier, *Mol. Pharmacol.*, **4**, 70 (1968).
(5) (a) C. H. Koo and H. S. Kim, *Daehan Kwahak Kwoejee*, **9**, 134 (1965); *Chem. Abstr.*, **65**, 6431*e* (1966); (b) C. Chothia and P. Pauling, *Proc. Natl. Acad. Sci. U.S.A.*, **65**, 477 (1970).
(6) M. Ohashi, I. Morishima, and T. Yonezawa, *Bull. Chem. Soc. Jpn.*, **44**, 576 (1971).
(7) (a) B. Pullman, P. Courriere, and J. L. Coubeils, *Mol. Pharmacol.*, **7**, 397 (1971); (b) B. Testa and P. Jenner, *Ibid.*, **9**, 10 (1973); (c) R. J. Radna, D. L. Beveridge, and A. L. Bender, *J. Am. Chem. Soc.*, **95**, 3831 (1973).
(8) K. R. Chynoweth, B. Ternai, L. S. Simeral, and G. E. Maciel, *Mol. Pharmacol.*, **9**, 144 (1973).
(9) M. S. Cushman, Ph.D. Thesis, University of California, San Francisco, 1973.
(10) H. Kessler, *Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970), and references cited therein.
(11) The free energy difference, $\Delta F°$, at 25 °C of 4 kcal/mol implies that for an equilibrium of isomers, the more stable isomer is present to the extent of almost 99.9%.
(12) For example, in the demethylation studies on nicotine *N*′-oxide, no mention of the possibility of diastereoisomerism was considered.[2] Indeed, two nicotine *N*′-oxides are known.[13]
(13) A. H. Beckett, P. Jenner, and J. W. Gorrod, *Xenobiotica*, **3**, 557 (1973).
(14) We have found that treatment of nicotine in ether with an excess of dry hydrogen iodide led to a heavy white precipitate which gave colorless needles when crystallized from methanol. The NMR spectrum of this material in TFA-*d* indicates that it is pure **3** dihydriodide. J. Seeman and J. F. Whidby, unpublished results.

(15) (a) R. A. Bell and J. K. Saunders, *Top. Stereochem.*, **7**, 1 (1973); (b) J. H. Noggle and R. E. Schirmer, "The Nuclear Overhauser Effect", Academic Press, New York, N.Y., 1971.
(16) J. K. Saunders, and R. A. Bell, *Can. J. Chem.*, **48**, 512 (1970).
(17) (a) J. B. Lambert, *Top. Stereochem.*, **6**, 19 (1971); (b) V. K. Pogorelyi and I. P. Gragerov, *Russ. Chem. Rev.*, **39**, 875 (1970); (c) D. Eustace and E. Grunwald, *J. Am. Chem. Soc.*, **96**, 7171 (1974).
(18) (a) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", Pergamon Press, Oxford, 1972, p 94; (b) E. Breuer and D. Melumad, *J. Org. Chem.*, **38**, 1601 (1973), and references cited therein.
(19) Reference 15b, p 31.
(20) (a) W. R. Morgan and D. E. Leyden, *J. Am. Chem. Soc.*, **92**, 4527 (1970); (b) M. Saunders and F. Yamada, *ibid.*, **85**, 1882 (1963).
(21) For a discussion of the Hammett acidity function for this solvent, see H. H. Hyman and R. A. Garber, *J. Am. Chem. Soc.*, **81**, 1847 (1959).
(22) (a) M. J. T. Robinson, *J. Chem. Soc., Chem. Commun.*, 844 (1975); (b) P. J. Crowley, M. J. T. Robinson, and M. G. Ward, *ibid.*, 825 (1974), and references cited therein; (c) J. McKenna, *Tetrahedron*, **30**, 1555 (1974).
(23) For an early excellent use of this technique, see G. L. Closs, *J. Am. Chem. Soc.*, **81**, 5456 (1959).
(24) **Noted Added in Proof.** We have prepared nicotine-*3',3',4',4',5',5'-d*$_6$. NMR analysis of this substance in TFA-*d* substantiates our assignments for **3** and **4** (see Figures 4–6).

Novel Synthesis of Imidazole Derivatives from 1-Phenyl-1,2-propanedione and Methylguanidine

Tamio Nishimura* and Koji Kitajima

Department of Chemistry, School of Hygienic Sciences, Kitasato University, Asamizodai, Sagamihara-shi, Japan

Received December 2, 1975

The reaction of 1-phenyl-1,2-propanedione (I) with methylguanidine (II) at −10 °C yielded 2-amino-4,5-dihydroxy-1,5-dimethyl-4-phenylimidazoline (IIIa) in methanol and 2-amino-4,5-dihydroxy-1,4-dimethyl-5-phenylimidazoline (IIIb) in ethanol. Catalytic hydrogenation of the reaction mixture of I and II in methanol produced 2-methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc). IIIa and IIIb were converted to 2-amino-5-chloromethyl-1-methyl-4-phenyl- and 2-amino-4-chloromethyl-1-methyl-5-phenylimidazoles (Va and Vb) by concentrated hydrochloric acid treatment. Va and Vb produced 2-amino-1,5-dimethyl-4-phenyl- and 2-amino-1,4-dimethyl-5-phenylimidazoles (VIa and VIb) by catalytic hydrogenation and 2-amino-5-ethoxymethyl-4-phenyl- and 2-amino-4-ethoxymethyl-5-phenylimidazoles (VIIa and VIIb) by ethanolysis. 2-Amino-5-hydroxymethyl-1-methyl-4-phenylimidazole (VIIIa) was obtained by hydrolysis of Va in dilute hydrochloric acid.

We have previously reported that 2-(disubstituted amino)-4-methyl-5-phenyl-4*H*-imidazoles, produced in good yields by the reaction of 1-phenyl-1,2-propanedione with 1,1-disubstituted guanidines in methanol at −10 °C, are useful as intermediates for synthesizing various 2-(disubstituted amino)imidazoles.[1] We have now explored the synthesis of 2-amino-1-methyl- and 2-methylaminoimidazoles by the application of this method to methylguanidine.

The reaction of 1-phenyl-1,2-propanedione (I) and methylguanidine (II) in methanol at −10 °C yielded a white powder, mp 54.5–55 °C dec (A-1), with molecular formula $C_{11}H_{15}N_3O_2{\cdot}CH_3OH$. This material showed absorption bands at 1650 and 1570 cm^{-1}, which may be assigned to a 4*H*-imidazole ring.[1] When the reaction mixture was hydrogenated in the presence of Pt catalyst without isolation of A-1, 2-methylamino-4(5)-methyl-5(4)-phenylimidazole (VIc) was obtained. The NMR spectrum of VIc exhibited a doublet for the *N*-methyl protons due to coupling with the proton on the same nitrogen atom. Ir and mass spectral and elemental analyses were consistent with this structure. Accordingly, one of the possible structures for A-1 was 2-methylamino-4*H*-imidazole (IV) but this structure was inconsistent with the observed mass spectral fragmentation pattern. The mass spectrum of A-1 lacked the $M^+ - C_6H_5CN$ fragment ion characteristic for 2-(disubstituted amino)-4*H*-imidazoles.[1] The abundant ions in the mass spectrum of A-1 were those of *m/e* 105 (22%, $C_6H_5C{\equiv}O^+$) and 104 (59%, $C_6H_5C{\equiv}N^+H$). Neither ion is conspicuous in 2-(disubstituted amino)-4*H*-imidazoles[1] but the former ion is abundant in 2-alkyl-4,5-dihydroxyimidazolines.[2] The mass spectral behavior of the latter compound is consistent with the fact that they are liable to decompose to starting materials.[3,4] The above spectral evidence strongly suggests 4,5-dihydroxyimidazoline (IIIc) as the structure of A-1; however, additional evidence did not support this structure, but rather the structure IIIa. Measuring NMR and uv spectra of A-1 was impossible because of quick decomposition of A-1 in the usual solvents, although they are obvious methods of establishing the structure of A-1.

Reaction of I and II in ethanol rather than methanol unexpectedly gave a different unstable compound, mp 45–47 °C dec (B-1). The abundance (86%) of the *m/e* 105 ion in the mass spectrum of B-1 together with elemental and ir analysis suggests either IIIa or IIIb as its structure. The structures of A-1 and B-1 were unraveled from the following series experiments. Treatment of B-1 hydrochloride (prepared by treating B-1 with a small amount of concentrated hydrochloric acid at −10 °C) with concentrated hydrochloric acid at room temperature gave a new compound B-2 as colorless prisms, mp 251 °C dec. The ir, NMR, and mass spectral and elemental analyses of B-2 were consistent with 1-methylimidazole Va or Vb. Treatment of A-1 with concentrated hydrochloric acid at −10 °C and then at room temperature precipitated colorless needles, mp 238–240 °C dec (A-2). On the basis of elemental and spectral data, A-2 was determined to be Va or Vb but isomeric to B-2. The NMR spectrum of A-2 showed an NCH_3 absorption at δ 3.73, which is consistent with that reported for the 1-methyl protons in 1-methylimidazoles (δ 3.42–4.05).[5] The chemical shift of *N*-methyl protons on the 2-amino nitrogen in 2-(disubstituted amino)imidazoles is reported to be δ 2.96–3.30.[1] Moreover, the ir spectrum of A-2 showed a medium peak at 1540 cm^{-1} (δ NH_2).

Hydrogenation of A-1 in the presence of Pt catalyst yielded pale yellow prisms, mp 225 °C dec (A-3). Similar treatment of B-2 afforded yellow plates, mp 226–227 °C dec (B-3). The NMR NCH_3 proton signals for these substances were consistent with the 1-methylimidazole structure. However, in their mass spectra, the relative intensity of the *m/e* 118 ($C_6H_5C{\equiv}N^+CH_3$) fragment ion was 8.3% in B-3 but only 1.2% in A-1. On the other hand, the *m/e* 56 ($CH_3C{\equiv}N^+CH_3$) ion was observed (13%) in A-3 but not in B-3. On the basis of these observations, it was established that A-3 is 2-amino-1,5-dimethyl-4-phenylimidazole (VIa) and B-3 is 2-amino-1,4-