RECENT STUDIES IN NICOTINE CHEMISTRY. CONFORMATIONAL ANALYSIS, CHEMICAL REACTIVITY STUDIES, AND THEORETICAL MODELING§

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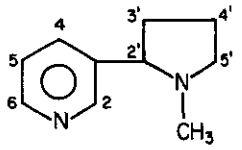
Abstract - The synthesis in our laboratories of a wide variety of nicotine analogues has served as the basis for a range of chemical investigations. We have examined the effect of substituents on nicotine's structure, conformation, and chemical reactivity. The methylation of nicotine and a wide variety of nicotine analogues has been studied. Three modes of alkylation are observed: pyridine and pyrrolidine, the latter occurring either cis or trans to the pyridine ring. The results of these alkylations are evaluated in terms of the Curtin-Hammett principle and the Winstein-Holness equation. Attention is focused on the effect of conformation on chemical reactivity. Ground state and transition state reactivity modes of the Menschutkin reaction are presented.

I. INTRODUCTION

Nicotine (1) is undoubtedly the most well known tobacco constituent to the lay person, if not the only constituent known to both the tobacco consumer and nonconsumer alike. This alkaloid, which has received more scientific attention than any other compound isolated from tobacco,[1-6] was the subject of a comprehensive review article over forty years ago.[3]



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Nicotine has a long and splendid history (see Table I).[3] Nicotine was named after Jean Nicot, a French ambassador to Portugal, who in the mid-sixteenth century is said to have introduced tobacco seed and leaf to the royal courts of France. Nicotine was first isolated in 1828,

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TABLE I. Selected Important Events in the Chemical History of Nicotine

1828	First Isolated
1893	Correct Structure Proposed
1895	First Synthesis
1925	Determination of Absolute Confuguration
1928	First "Modern" Synthesis
1935	"Bibliography of Nicotine" by USDA listing 6000 publications
1940	Major Summary of Nicotine Chemistry in Chemical Reviews
1950-1980's	Biosynthetic Studies
1976-1980's	Elucidation of Nicotine's Conformation
1970-1980's	Synthesis of Nicotine Analogues

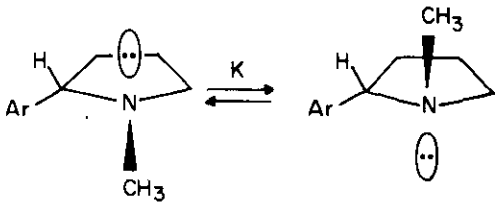
before the isolation of such other important alkaloids as codeine, atropine, papavarine and physostigmine. The correct structure of 1 was proposed by Pinner in 1893 and it was first synthesized by Pictet in 1895. The chemical literature of the nineteenth century is replete with reference to nicotine's reactivity. For example, the famous August Kekulé reported the ethylation of nicotine in 1853,[7] some twelve years before he proposed the structure of benzene.

Nicotine clearly has had a life of its own, independent of its inherent relationship with tobacco and tobacco products. There have been many interesting chemical results which originated during studies on nicotine and related compounds. One of our goals was the development of structure-reactivity relationships for nicotine analogues, from which we could evaluate a wide variety of physical and chemical reactivity features. Consequently, we prepared various series of nicotinoids having substituents in critical positions on the nicotine ring periphery and/or modifications in the ring system itself. Following to some extent the chronological development of our work, we shall first discuss the structure of nicotine, placing primary emphasis on conformational properties, followed by a presentation of our chemical reactivity results.

II. THE CONFORMATION OF NICOTINE

Specification of nicotine's conformation requires definition of three stereochemical features: (a) the orientation of the pyrrolidine N'-methyl group relative to the pyridine ring (cis as in 2, trans as in 3); (b) the conformation of the pyrrolidine ring; and (c) the orientation of the pyridine ring relative to the pyrrolidine ring, described by the dihedral angle $\tau(H_{2_\beta}{}'C_2{}'C_3C_2)$. By conformation we mean "any one of the infinite number of momentary arrangements of the atoms in space that result from rotation about single bonds."[8] If we keep to this definition, it may be argued that the orientational properties of the N'-methyl group in nicotine is a configurational question, not a conformational one.[9] This is a subtlety about which there remains some

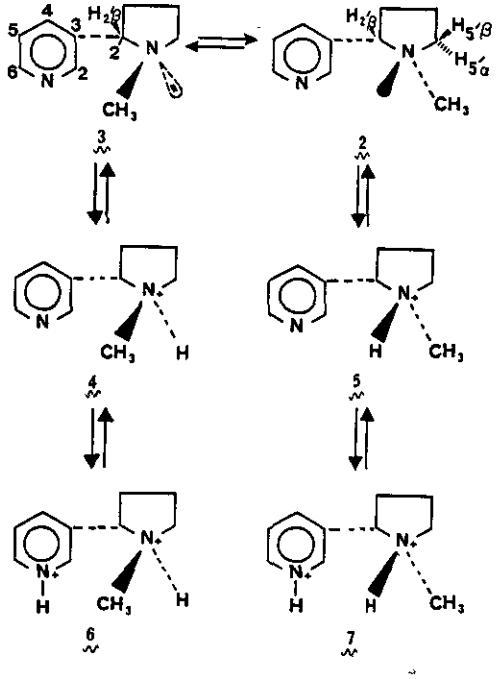
debate among practicing stereochemists, and we will not concern ourselves about it in this context.[10,11]



2 ~ 3 ~

A. The Orientation of the N'-Methyl Group

In the x-ray analyses of both nicotine dihydroiodide[12] and nicotine-salicylic acid complex (1:1),[13] the N'-methyl group was found to be trans to the pyridine ring, as in 6. However, this result does not necessarily reflect solution or gas phase conformational propensities, since it is well known that crystal lattice forces are not always suitable models for alternate environments. Furthermore, the crystalline samples were undoubtedly prepared under conditions in which the equilibrium between 6 and 7 were operative (c.f. Scheme I), and it is theoretically possible that the acid salt of a minor component could have crystallized preferentially.



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.

A number of theoretical studies have also suggested that the N'-methyl group is trans, at least for an isolated molecule in the gas phase.[14-19] That 3 would be more stable than 2 is intuitively reasonable on the basis of steric hindrance. However, Chynoweth, Ternai, Simeral and Maciel reported in the first solution phase experimental data on this subject "that the N-methyl group is preferentially on the same side of the pyrrolidine ring as the pyridine ring."[20] Their study involved the observation of an intramolecular nuclear Overhauser effect (NOE) on the protons attached to C_2 and C_4 (H_2 and H_4 respectively) when the resonance of the N'-methyl group was irradiated. Chynoweth, et al. based their conclusion on three factors: (a) the observation of the NOE; (b) an NOE can be observed only when the proton of the irradiated resonance and the proton of the observed resonance are spatially closed to each other; and (3) the N'-methyl group is close to H_2 and H_4 in 7 but not in 6.[20]

One factor which Chynoweth, et al. did not consider was the effect of the nitrogen inversion process on the NOE experiments.[20] Scheme I illustrates the equilibria involved. Let us assume that 3 is the more stable isomer. If nitrogen inversion ($2 \rightleftarrows 3$) is fast relative to $1/T_1(3)$, where T_1 is the proton relaxation time, then during the NOE experiment, there would be sufficient time for the methyl group of 3 to invert to 2 prior to relaxation and return to spin equilibrium. The net effect could be the observation of an NOE even though the resonance irradiated was that for the N'-methyl group in 3 and not 2! Alternatively, the major isomer could be 2 as concluded by Chynoweth, et al., though based on inconclusive information.[9,20]

To differentiate between these two alternatives, we determined the NOE for nicotine under conditions in which the rates of interconversion $2 \rightleftarrows 3$ were much slower than $1/T_1(3)$.[9] This condition was obtained when nicotine was dissolved in a very strong acid (e.g., trifluoroacetic acid), resulting in the diprotonated nicotine salts 6 and 7 (see Scheme I and Fig. 1). Under these conditions, we established that deprotonation at the pyrrolidine nitrogen was very slow on the NMR timescale, and certainly considerably slower than $1/T_1(3)$. Table II indicates that no NOE was observed at the resonances of H_2 or H_4 when the N'-methyl group resonance was irradiated in the mixture of 6+7 (TFA-d), though significant enhancements were observed for the resonances of $H_2'_\beta$ and $H_5'_\beta$. The lack of enhancements at the resonances of H_2 and H_4 implies that the N'-methyl group is trans to the pyridine ring. The observed enhancements at the resonances of $H_2'_\beta$ and $H_5'_\beta$ could only be obtained if the N'-methyl group were cis to $H_2'_\beta$ and $H_{5'_\beta}$, consistent with the methyl group being trans (6) to the pyridine ring.[9]

It is well known that protonation of amines like nicotine with strong acids is diffusion controlled and thus faster than nitrogen inversion. Accordingly, the observation that 6 is the major diprotonated isomer implies that 3 is the major free base isomer. In fact, barring the well-documentated experimental difficulties associated with kinetic quenching of amines, the ratio

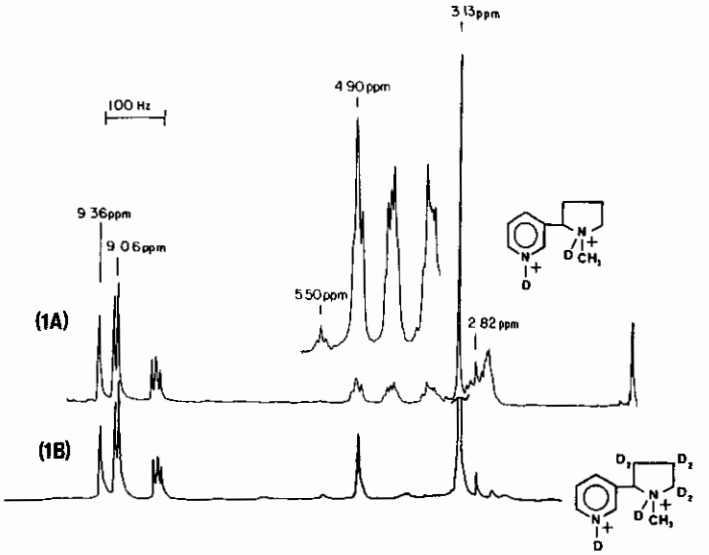


Figure 1. NMR spectra of nicotine (Figure 1A) and nicotine-3',3',4',4',5',5'-d_6 (Figure 1B) in trifluoroacetic acid-d at 100 MHz. In this solvent, both nitrogens are protonated and deprotonation is slow compared to the NMR time scale. From reference 9.

TABLE II. NOE Studies of Nicotine

sample description	proton irradiated	proton observed	% enhancement[a]
pD 11.0[b]	N-CH_3 of 2 ⇄ 3	2,6	10.8
		4	10.0
pD 5.0[b]	N-CH_3 of 4 ⇄ 5	2,6	5.9 (4[c])
		4	10.9 (10[c])
pD 0.8[b]	N-CH_3 of 6 ⇄ 7	2,4,6	8.1
		5'α	5
		5'β	5
Trifluoroacetic acid-d	N-CH_3 of 6	2,4,6	0
		2'β	13
		5'α	3
		5'β	11
22% DCl	N-CH_3 of 6	2,4,6	0
		2'β	12.5
		5'α	3
		5'β	11

[a] Enhancements reported are based on total number of protons in the multiplet observed and not on the number of protons expected to be enhanced. Data from ref. 9. [b] Acidity was adjusted with D_2SO_4 in D_2O. [c] Data in parantheses from ref. 20.

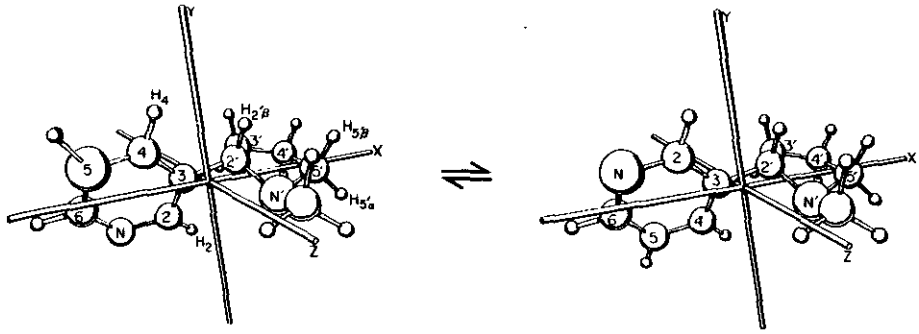


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Figure 2. The most probable solution conformations of nicotine. Note that "α" and "β" refer to the stereochemistry of the pyrrolidine hydrogens or pyrrolidine substituents, as indicated in 8. (See references 23 and 29.)

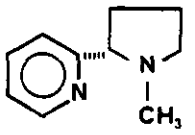
6:7 is equal to the ratio 3:2.[21,22] The former ratio could be obtained by assigning specific resonances for both 6 and 7; e.g., for the resonances of $H_2'_\beta$ and N'-CH_3. We obtained additional evidence by preparing nicotine-3',3',4',4',5',5'-d_6 and subjecting it to the kinetic quenching procedures discussed above. These results are illustrated in Figures 1A and 1B and Table II. On this basis, we concluded that the major isomer, 3, was present to an extent >90% in nicotine.[9]

B. Pyrrolidine Ring Conformation

While pyrrolidine ring geometries are available for nicotine dihydroiodide[12] and nicotine: salicylic acid complex[13] from their respective x-ray analyses, this information may not be transferable to solution phase conformations and may be somewhat unreliable due to the errors associated with locating hydrogen atoms by x-ray methods, especially for large compounds containing halogen atoms. During the last twenty years, conformational information has become available by evaluation of NMR proton-proton coupling data using Karplus-type relationships.

Pitner, et al. reported in 1978 the analysis of the seven spin (seven attached protons) pyrrolidine ring system of nicotine.[23] By obtaining NMR spectra for a number of specifically deuterated nicotines, they were able to assign the chemical shifts and relevant coupling constants for nicotine itself. From these evaluations, they concluded that nicotine's pyrrolidine ring exists in an envelope conformation with $H_2'_\beta$ and $H_{5'_\alpha}$ protons in a pseudo axial orientation, with $H_3'_\alpha$ and $H_4'_\alpha$ eclipsed, and $H_3'_\beta$ and $H_4'_\beta$ eclipsed, as indicated in Fig. 2.[23] There are at least three reservations that tag along with these conclusions: (a) the Karplus equations are empirical and depend on the choice of coefficients used; (b) the treatment assumes that there are not a number of equally stable minimum energy conformations on a rather flat ground state potential energy surface; and (c) there are no significant bond angle distortions in the pyrrolidine ring which affect the validity of the Karplus equations.

Whidby, Edwards, and Pitner subsequently reported similar analyses of two nicotine analogues, 2-isonicotine (10) and 4-isonicotine (11) using deuterated derivatives to obtain chemical shifts and coupling constants.[24] Interestingly, although 1, 10 and 11 have different physical and chemical properties, their vicinal and long-range coupling constants indicated that they have virtually identical conformations in $CDCl_3$ solution.[24]



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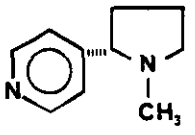

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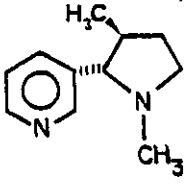
Recently, we obtained ^1H NMR spectra for a series of additional nicotine analogues at high field (300 and 360 MHz) which resulted in separate resolved resonances for each of the pyrrolidine ring protons. Analyses of these spectra have led to information regarding the effect of substitutents on pyrrolidine ring conformations, given the same three reservations mentioned above.[25] In addition, for nicotine itself, this work has resulted in chemical shifts and coupling constants identical to those reported by Pitner et al.;[23] thereby mutually confirming each other's experimental techniques.

There have been additional investigations directed at discerning information regarding nicotine's pyrrolidine ring conformation. Ohashi, Morishima and Yonezawa have reported a lanthanide induced shift (LIS) study of nicotine,[26] and Castagnoli and Cushman have disclosed analogous LIS experiments on trans-3'-methylnicotine (12).[27] In both cases, significantly greater shifts were observed for the pyridyl ring protons rather than for the pyrrolidine ring protons, even though in both 1 and 12, the pyrrolidine nitrogen is significantly more basic than the pyridine nitrogen. Since the magnitudes of the LIS are dependent on the distance between the lanthanide atom and the protons, the lanthanide atom in both cases must be complexing with the respective pyridine nitrogen. Steric inhibition to complexation at the more basic site thus foils the use of this technique to the application under discussion in this section. Interestingly, we examined the LIS of the related N-methylnicotinium iodide (13) and found that complexation occurs



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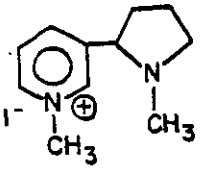

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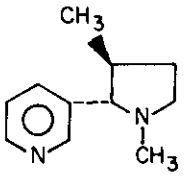
at the quaternary N-methylpyridinium site.[28] This curious result established that the counter-ions of quaternary ammonium salts are powerful LIS donors, stronger than for amines like N,N-dimethyldodecylamine and N-methyldodecylamine.

C. Pyridine-Pyrrolidine Ring-Ring Orientations

As part of their careful analysis of the high resolution spectrum of nicotine, Pitner, et al. observed a small but finite (<0.05 Hz) long-range coupling between $H_2'_\beta$ and H_6; they also observed an NOE of 9 ± 2 and 5 ± 2% for $H_2'_\beta$ upon saturation of the resonances of H_2 and H_4, respectively.[23] On the basis of these results, they suggested that the pyridine-pyrrolidine ring-ring orientation was perpendicular, i.e., dihedral angle $\tau(H_2'_\beta C_2' C_3 C_2)$ is 0° and/or 180° (see Fig. 2).[23] Subsequently, Pitner, Whidby and Edwards determined the ^{13}C NMR spin-lattice relaxation times (T_1's) of nicotine and analyzed these in terms of anisotropic rotational diffusion constants.[29] A number of very interesting conclusions were made, one being that inter-ring rotation is slower than overall molecular tumbling in chloroform solution, since the experimental relaxation times for C_2 and C_4 differed by more than could otherwise be accounted for. By assuming a fixed geometry for the pyridine and pyrrolidine rings as determined by previous results, they calculated the ^{13}C T_1's for different values of $\tau(H_2'_\beta C_2, C_3 C_2)$. A comparison of $T_{1,calcd}$ with $T_{1,obsd}$ for all of these dihedral angles indicated that the best fit obtained is for 9 (τ=0°), and this fit was far superior to that obtained for 8 (τ=180°). On this basis, they concluded that "the most probable ring-ring orientation is . . .τ=0°" (9, c.f. Figure 2).[29]

Of course, conformational preferences are not "all or nothing" as described previously in the introduction to Section II. A number of theoretical studies have reported the potential energy of nicotine as a function of $\tau(H_2'_\beta C_2, C_3 C_2)$. Invariably, minima are found in the region of 0° and 180°, extending, as part of energy wells, some 20° on each side.[14-19] The most recent calculations on nicotine, those of Dwyer using the INDO algorithm[14] and of Lee and Park using both ETH and CNDO,[19] indicate that these two minima are of nearly equal energy. Given the limitations of these algorithms, we can only conclude that nicotine is likely to be significantly populated in both forms, 8 and 9, shown in Figure 2. This conclusion is not inconsistent with the Pitner, et al. results[29] as they "had no feeling for how sensitive the fit [of $T_{1,obsd}$ vs. $T_{1,calcd}$] is to population distribution."[30]

We recently compared the effect of substituents on the periphery of nicotine's ring systems on the energy as a function of dihedral angle.[14] Using the INDO algorithm, we calculated that a methyl substituent at C_5, C_6 or $C_{3'_\beta}$ in 5-methyl, 6-methyl, and trans-3'-methylnicotine (14, 15 and 12) respectively had little effect on the overall shape or energetics of rotation about C_3-$C_{2'}$. However, a methyl group at either C_2, C_4 or $C_3'_\alpha$ in 2-methyl, 4-methyl and cis-3'-methylnicotine (16, 17 and 18) led to significant changes in rotational barriers though the energy minima



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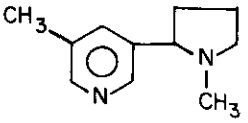

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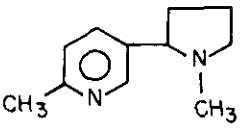

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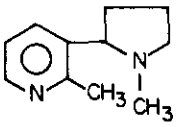

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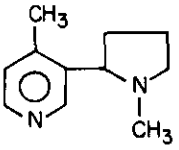

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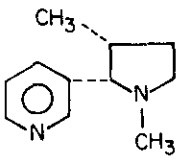

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TABLE III. INDO Calculated Parameters of Nicotine and Nicotine Analogues[a]

	τ (degrees)[b,c]		rotational barriers[d,e]	ΔH_o[e,f]
compound	minima	maxima	(kcal/mole)	(kcal/mol)
nicotine (1)	340/160	0/220	13.5/14.0	0.05
2-methylnicotine (16)	160/340	60/220	33.2/23.3	1.8
4-methylnicotine (17)	340/160	240/300	39.7/26.2	2.4
5-methylnicotine (14)	340/160	220/0	13.5/14.0	0.05
6-methylnicotine (15)	340/160	0/220	13.5/14.0	0.05
cis-3'-methylnicotine (18)	160/340	240/60	60.3/58.8	0.02
trans-3'-methylnicotine (12)	340/160	0/220	13.5/14.0	0.05

[a] Reference 14 and R. W. Dwyer, unpublished results. [b] $\tau = \tau(H_{2'_\beta}, C_2, C_3C_2)$ dihedral angle. Clockwise rotation of the pyrrolidine ring relative to the pyridine ring is in the "positive" sense. [c] For each pair, the lower energy conformation is listed first. [d] The order corresponds to lower energy minimum to lower energy maximum, followed by higher minimum to higher maximum. [e] Complete geometry optimization was not attempted, and these unrealistically high energy barriers are in part due to the "rigid rotor" model as well as to the approximations inherent in the INDO algorithm. [f] Energy differences separating the two minima.

remained essentially at ca. 0° and 180°. See Table III. Examination of molecular models indicates that the cross-ring interaction of a C_2- or a C_4-methyl group on the pyrrolidine ring in 16 and 17 is very similar to the cross-ring interaction of the $C_3'_\alpha$-methyl group on the pyridine ring in 18. The results in Table III are probably valid as trends in this closely related series, but one cannot push their quantitative capabilities, given the approximate nature of the INDO method and its difficulty in treating tertiary amines.

We await the development of force fields which incorporate parameters suitable for both pyridine nitrogen atoms and pyrrolidine nitrogen atoms so that more reliable calculational results may be available using molecular mechanics procedures.

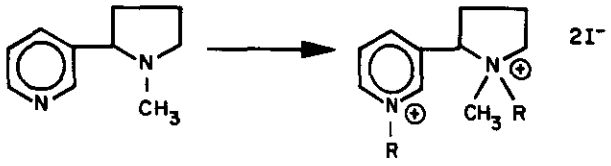
III. THE CHEMICAL REACTIVITY OF NICOTINE AND NICOTINE ANALOGUES

We felt that it was essential to characterize the chemical "personalities" of nicotine and its analogues as part of our structure-reactivity studies. There is no question that the nitrogen atoms of nicotine and its analogues represent the most significant structural functionality, from a chemical reactivity and a physical property point-of-view. We therefore desired to quantify in some fashion the nucleophilicity of nicotine's two nitrogen atoms, and to compare these parameters with the same features of important nicotine analogues. To achieve these goals, we decided to choose a specific chemical reaction which we could apply to each of our analogues from which chemical reactivity information could be extracted. This reaction had to possess the following features:

1. The reaction should take place exclusively at the nitrogen atoms by the same well-known mechanism for all compounds studied.
2. The reaction should be uncomplicated by side reactions, and it should be irreversible.
3. The products should be stable and clearly distinguishable from the starting materials.
4. The reaction should be readily quantifiable by standard, reliable kinetics procedures.
5. For meaningful comparisons, the reaction rates for the different analogues should vary over a wide range of reactivity.

Based on these considerations, we chose to study the methylation of these nicotinoids. The Menschutkin reaction is one of the most well studied in all of organic chemistry, and it has provided an experimental basis for the understanding of many controlling factors in chemical reactivity.[31]

We were not, of course, the first to be interested in the alkylation of nicotine. v. Planta and Kekule[7] in 1853 and von Stahlschmidt[32] in 1854 reported the alkylation of nicotine with excess iodoethane and iodomethane and obtained nicotine diethiodide (19) and nicotine dimethiodide (20) respectively (eq 1). These early studies were aimed at determining the number and type of nitrogen atoms in nicotine with structure determination as a goal.

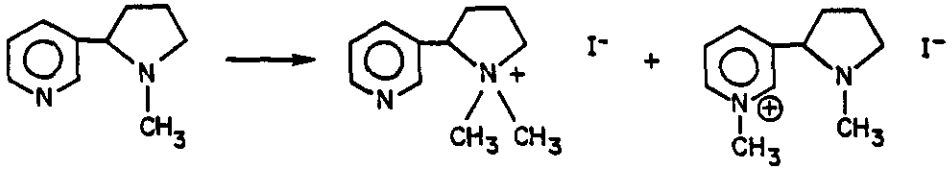


(1)

19, R = Et
20, R = Me

1853 Kekule
1854 von Stahlschmidt

Many years later, Pictet and Genequand[33] in 1897 reported the preparation of the two monomethiodides of nicotine, N-methylnicotinium iodide (13) and N'-methylnicotinium iodide (21). This latter work proved to be of significant interest to many subsequent investigators, in part because it proved extremely difficult to repeat the original experimental procedures.[34]



(2)

21 13

We[35] repeated the 1897 experimental conditions[33] and subjected the crude reaction mixtures of nicotine and iodomethane (eq 2) in either methanol or acetonitrile to ^{1}H NMR analysis. The resultant NMR spectrum from a typical experiment is shown in Figure 3A. Note that in this experiment, less than one equivalent (0.75 equiv.) of iodomethane was used in order to minimize the formation of the dialkylation product, nicotine-N,N'-dimethiodide (20). Clearly, too many methyl singlets are observed. We showed that the product consists of ca. 2.5:1 mixture of 21 + 13 and not of only 21 as previously reported.[33,34] Because of fortuitous solubility properties (nicotine is soluble in water, ether, and chloroform; N-methylnicotinium iodide is soluble in water and chloroform but insoluble in ether; and N'-methylnicotinium iodide is soluble in water but insoluble in both ether and chloroform), the preparation of purified quantities of both mono-

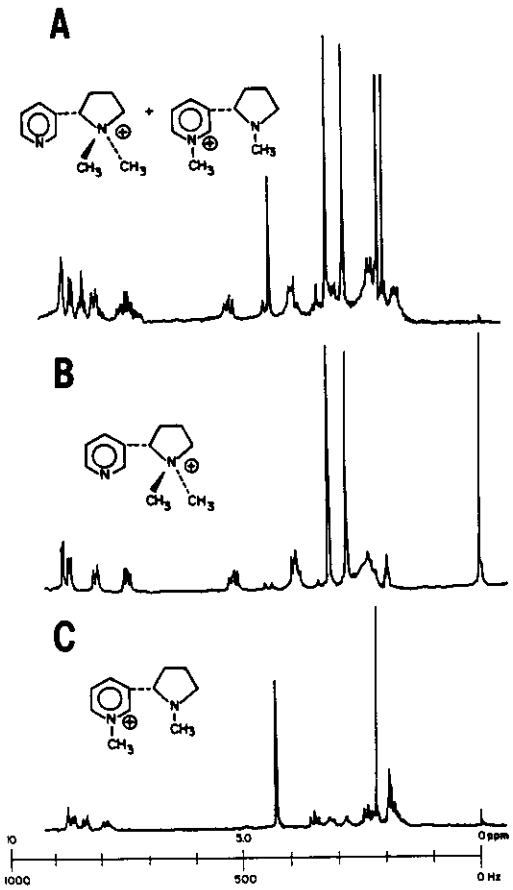
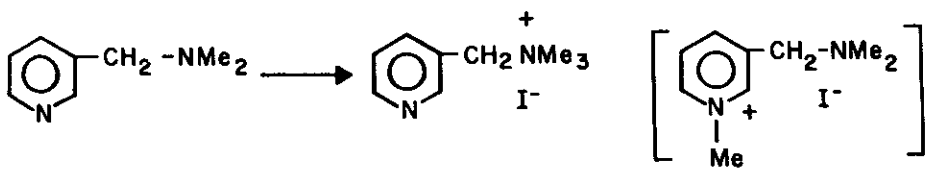


Figure 3. (A) NMR spectra of total crude reaction product of nicotine and 0.75 equiv of iodomethane in acetonitrile in the presence of sodium carbonate at 100 MHz. The singlets are the N'-methyl groups of nicotine (1), 13, and 21. (B) NMR spectra of N'-methylnicotinium iodide 21 in acetonitrile-d_3 at 100 MHz. (C) NMR spectra of N -methylnicotinium iodide (13) in acetonitrile-d_3 at 100 MHz. From reference 35.

methiodides turns out to be a rather simple experimental task -- once it is recognized that the product is a mixture of the two compounds.[35] See Figures 3B and 3C.

The formation of N-methylnicotinium iodide (13) in this alkylation is quite remarkable, since the pyridine nitrogen of nicotine is some three orders of magnitude less basic than its pyrrolidine nitrogen (Table IV). That the rate of the Menschutkin reaction is significantly dependent on nitrogen basicity can be shown by the fact that methylation of the nicotine analogue, N,N-dimethyl-3-aminomethylpyridine (22) was found to yield only one methiodide, 23, to the exclusion of 24 (eq 3).[35] As shown in Table IV, the pK_a's of nicotine and 22 are nearly identical, supporting our suggestion that steric factors associated with nicotine's pyrrolidine ring decrease the nucleophilicity of its pyrrolidine nitrogen.

Also listed in Table IV are the pK_a's for a number of compounds which are found as substructures of nicotine. Note that the pK_a of the pyrrolidine nitrogen of nicotine is substantially smaller than that of N-methylpyrrolidine (25) and its methyl and phenyl substituted derivatives 26-27. As can be seen in Table IV, the presence of an aromatic



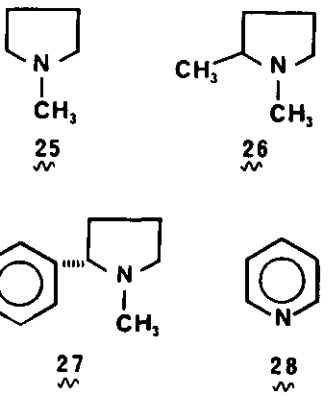
(3)

22 23 24

TABLE IV. pK_a Values of Nicotine and Selected Analogues[a]

compound	pK_{a1}	pK_{a2}
nicotine (1)	7.8	3.0
N,N-dimethyl-3-aminomethylpyridine (22)	7.8	3.1
1-methyl-2-phenylpyrrolidine (27)	9.3	
N-methylpyrrolidine (25)	10.	
1,2-dimethylpyrrolidine (26)	10.	
pyridine (28)	5.2	

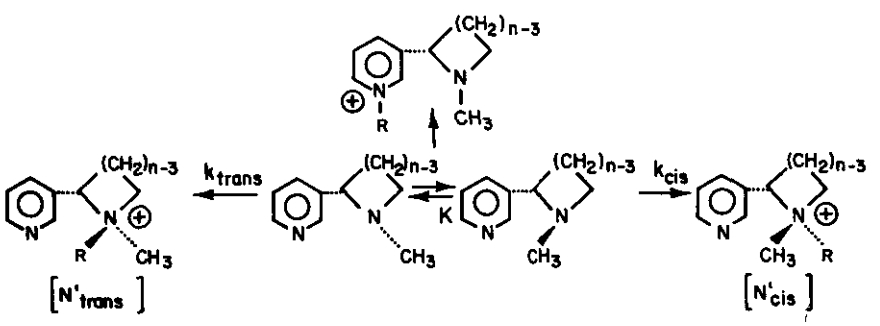
[a] From reference 35.



group α to a pyrrolidine's nitrogen atom clearly has substantial electronic and steric effects, reflected by both pK_a's and alkylation rates. More recently, Kaneko and colleagues studied the select of nicotine alkylations with alkyl halides more bulky than iodomethane.[36] They observed regiospecific N-alkylation (pyridine alkylation) for ethyl iodide, isopropyl iodide, n-propyl iodide, benzyl bromide and ethyl bromoacetate.[36] Apparently, N'-alkylation of nicotine is more sensitive to increasing steric effects than N-alkylation.

The alkylation of nicotine is actually more complicated than indicated in eq 2. Recall that the N'-methyl group in 1 is rapidly inverting, and that nicotine is more appropriately described as an interconverting set(s) of conformers 2 ⇄ 3. By extension of the results shown in Scheme I, we can expect that nicotine can be alkylated via three paths and not two as implied in eq 2: on the pyrrolidine nitrogen, both cis and trans to the pyridine substituent; and on the pyridine nitrogen (see Scheme II).[9,37,38]

SCHEME II



29, n=4
1, n=5 (Nicotine)
30, n=6 (N'-Methylanabasine)
31, n=7

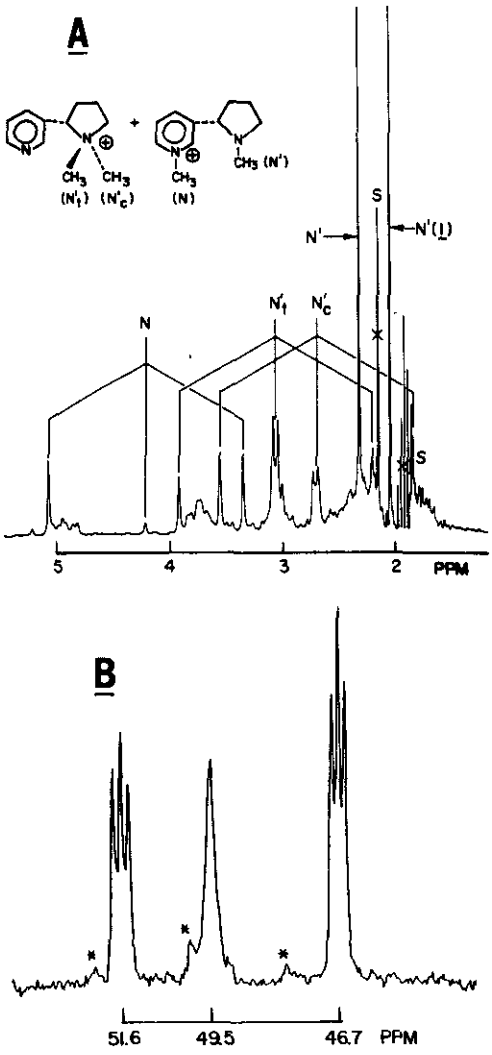


Figure 4.

(A) Upfield portion of the ^{1}H NMR spectrum (80 MHz) of total reaction mixture of nicotine and 0.75 equiv of $^{13}CH_3I$. The complex patterns for each of the N'-methyl groups are because of the presence of diastereomers due to unsymmetrical isotopic labeling. N'(1) refers to unreacted nicotine. The resonances at ca. δ 1.9 and 2.2 result from the solvent and are labeled "S".

(B) ^{13}C NMR spectrum (25.0 MHz) of the total reaction mixture of nicotine and 0.75 equiv of $^{13}CH_3I$. The asterisks refer to the methyl carbons of the dialkylated product, nicotine dimethiodide. From reference 37.

Experimentally, the relative rates of the three corresponding methylation pathways can be readily determined if one uses isotopically labeled reagents, e.g., $^{13}CH_3I$ or CD_3I. The ^{13}C and ^{1}H NMR spectra of a typical example of the methylation-^{13}C of nicotine is shown in Figure 4. The ^{1}H NMR spectrum (Figure 4A) is quite complex, due to ^{13}C-^{1}H couplings that are not observed when examining the ^{1}H NMR spectra of compounds which have natural isotopic abundances. However, even this complex spectrum is readily understood in combination with the ^{13}C NMR spectrum of the same material and with the ^{1}H NMR spectrum of the analogous reaction mixture obtained with $^{12}CH_3I$. In all the cases we have examined, the ^{13}C resonance of the pyridinium-$^{13}\underline{C}H_3$ resonances appears as a broad singlet while the pyrrolidinium-$^{13}\underline{C}H_3$ resonances each appears as a sharp triplet, presumably due to the more symmetrical nature of a quaternary pyrrolidinium salt. Careful integration of the three resonances in Figure 4B results in the relative rates of $N:N'_{cis}:N'_{trans}$ alkylation (see Scheme II). We note that the assigment of the two pyrrolidine-$^{13}\underline{C}H_3$ resonances is based on double resonance studies and NOE experiments, in a fashion similar to the assignments of nicotine diacid salts illustrated in Table II.[37,38]

The relative rates of alkylation of nicotine and a series of nicotine analogues are shown in Table V. A number of interesting conclusions regarding the relative nucleophilicities of the nitrogen atoms in these molecules result from careful analysis of these data.

TABLE V. Relative Rates of Competitive Methylation of Nicotine and Nicotine Analogues[a]

compound	N'_{cis}/N'_{trans}	N'/N	N/N'(rel)	reference
nicotine (1)	1.5	2.7	1	b
2-methylnicotine (16)	1.3	2.3	1.2	b
4-methylnicotine (17)	1.2	0.33	8.1	b
5-methylnicotine (14)	1.5	2.2	1.2	b
6-methylnicotine (15)	1.6	8.0	0.33	b
2,6-dimethylnicotine (32)	1.6	>50	<0.05	b
4,6-dimethylnicotine (33)	1.4	0.92	2.9	b
5,6-dimethylnicotine (34)	1.8	8.9	0.31	b
1-methyl-2-(3-pyridyl)azetidine (29)	2.4	12.	0.23	c
1-methyl-2-(3-pyridyl)piperidine (30)	10	1.2	2.2	c
1-methyl-2-(3-pyridyl)-1-azacyclo-heptane (31)	0.6	0.91	2.9	c
1-methyl-2-(2-pyridyl)pyrrolidine (10)	2.0	>100	<0.027	d
1-methyl-2-(4-pyridyl)pyrrolidine (11)	1.1	1.5	1.8	d

[a] See Scheme II for explanation of terms. Alkylations were performed at ca. 25°C with ca. 0.8 equiv. iodomethane to minimize overalkylation. N and N' refer to alkylation direction. Estimated error in alkylation ratios is 10%. [b] Reference 37. [c] Reference 38. [d] Unpublished results.

(1) The ratio of N'_{cis}/N'_{trans} remains essentially constant (within experimental error) for all the methyl-substituted nicotines. However, the stereoselectivity of N'-methylation is significantly altered when either the saturated ring size is changed (e.g., 29-31) or when the connection between the pyridine and pyrrolidine rings is changed (10-11). Sophisticated conformational analysis is required to explain these results, for a knowledge of K, k_{cis} and k_{trans} is necessary. The Curtin-Hammett principle[11,39] (eq 4) describes the relationship between product ratio for a

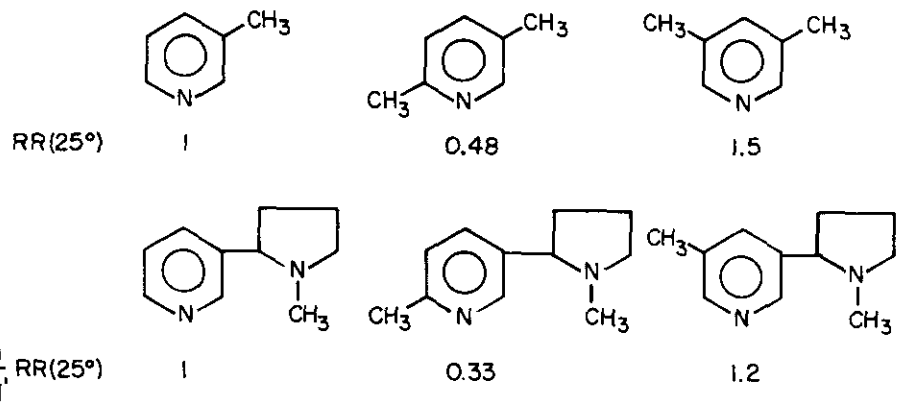
$$\frac{N'_{cis}}{N'_{trans}} = K \frac{k_{cis}}{k_{trans}} = \exp(-\Delta G^{\neq}_{TS}/RT) \qquad (4)$$

compound which exists in two rapidly interconverting conformations (e.g., $2 \rightleftarrows 3$), each of which slowly reacts to form a unique product (e.g., N'_{trans} and N'_{cis} respectively, Scheme II).

(2) For compounds bearing methyl groups close to nicotine's pyridine nitrogen [e.g., 2,6-dimethylnicotine (32)], methylation at N is slowed down relative to N'-alkylation. A methyl group at C_5 (e.g., 14) causes an enhancement of N-methylation. These results are consistent

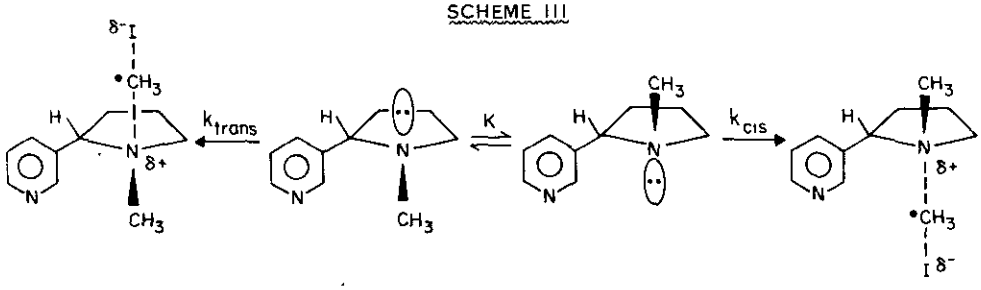
with the known reactivity effects of alkyl groups on the Menschutkin reaction of substituted pyridines[31] (*see Chart I for a comparison* of relative methylation rates).

CHART 1



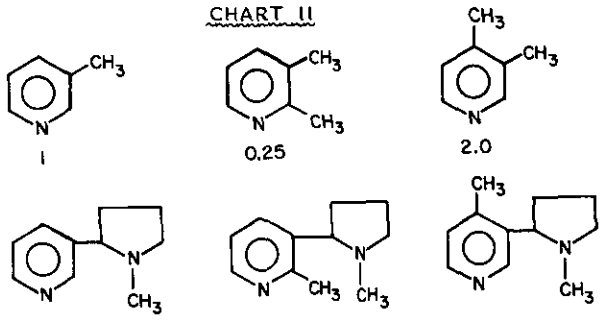
Perhaps the most unusual result is the reactivity difference in the set of 1-methyl-2-(z-pyridyl)pyrrolidines, where "z" refers to the point of attachment of the pyrrolidine ring to the pyridine ring in 1, 10 and 11.[38] *For these three compounds,* (a) *steric effects* should be nearly identical since they are no additional ring substituents; and (b) previous NMR results, discussed in Section II,B above, indicates their pyrrolidine rings have *identical conformations. The varia-*tion in N'_{cis}/N'_{trans} must be due to electronic effects in the respective alkylation transition states (TS), illustrated in Scheme III for nicotine. Examination of molecular models indicates that dipole:dipole interactions between the pyridine moiety and the pyrrolidine $N'\text{---}CH_3\text{---}I^-$ moiety can be either attractive or repulsive, depending on the position of the pyridine nitrogen and the conformational features of the ring system. This analysis predicts that N'_{cis}/N'_{trans} should decrease in the order 10 → 1 → 11, and the total rate of reaction should also decrease in the same order: both of these predictions match the experimental observations.[37,38]

SCHEME III



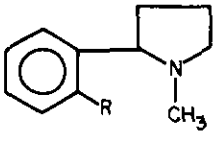
(3) Methyl groups at C_2 and/or C_4 of nicotine (e.g., 16, 17 and 33) hinder pyrrolidine (N') methylation.[37] As illustrated in Chart II, 2,3-lutidine and 3,4-lutidine react at 0.25 and 2.0 times the rate of 3-picoline. If the C_2- and C_4-methyl groups of 2-methylnicotine and 4-methylnicotine effected only N-alkylation, then their N-rates relative to nicotine would be approximately 0.25 and 2.0 respectively. However, the experimental values are 1.15 and 8.1, respectively, indicating that the C_2-and C_4-methyl groups either (a) enhance N-alkylation or (b) hinder N'-alkylation by a factor of ca. four-fold.

CHART II



We felt that it was important to establish the reasons for this unpredicted reactivity, and to accomplish this goal, we decided to examine a series of analogues which focused attention on substituent effects at nicotine's C_2 and C_4 position. The compounds chosen for this study were the 1-methyl-2-(2-alkylphenyl)pyrrolidines 35-39.[39]

35, R = H
36, R = Me
37, R = Et
38, R = i-Pr
39, R = t-Bu



A particular advantage of studying 35-39 is their lack of a pyridine nitrogen, thereby simplifying the reaction to alkylation by two paths, N'_{cis} and N'_{trans} (see Scheme IV).

SCHEME IV

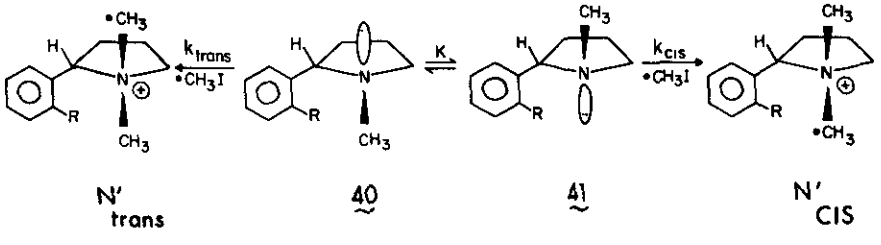


TABLE VI. Observed Total Rates Constant, Product Stereoselectivity, and Ground-State Equilibrium Distribution of 35-39[a]

compound	$10^4 k_{obsd}$	k_{obsd} (rel)	N'_{cis}/N'_{trans}	K
R=H (35)	30. ± 0.6	24	1.7±0.02	>17
$R=CH_3$ (36)	7.6±0.08	6.1	1.4±0.02	>30
$R=CH_3CH_2$ (37)	6.2±0.02	4.9	1.3±0.05	>30
$R=(CH_3)_2CH$ (38)	5.3±0.07	4.2	1.3±0.03	>30
$R=(CH_3)_3C$ (39)	1.3±0.06	1	0.38±0.01	>40

[a] See Scheme IV and eq 4-7. From reference 39.

Our principle goal was the determination of k_{cis} and k_{trans} for 35-39, thereby establishing by extrapolation the underlying features controlling the nucleophilicity of 2-methyl- and 4-methylnicotine. Two equations are available which allow for the derivation of k_{cis} and k_{trans}, the Curtin-Hammett principle (eq 4) and the Winstein-Holness equation (eq 5).[11,39] Note that k_{obsd}

$$k_{obsd} = (k_{cis} K + k_{trans})/(K + 1) \quad (5)$$

is the total observed reaction rate constant. *Taken together, these two equations can be solved* for k_{cis} (eq 6) and k_{trans} (eq 7) in terms of K, the ground state equilibrium distribution for

$$k_{cis} = k_{obsd} [(K+1)/K][P/(P+1)] \quad (6)$$

$$k_{trans} = k_{obsd} [(K+1)/(P+1)] \quad (7)$$

where $P = N'_{cis}/N'_{trans}$

each compound, k_{obsd} and N'_{cis}/N'_{trans}. We have previously described the methodologies for the experimental determinations of K and the reaction product ratio (c.f. Section II,A). The total observed reaction rate constant was determined conductometrically, a very simple procedure given that the starting materials are neutral molecules and the products are quaternary ammonium salts. Note that k_{obsd} is experimentally obtained for a Scheme III system in the same fashion as if the reaction were simply pyridine and iodomethane.

Table VI lists the experimental values for k_{obsd}, K, and N'_{cis}/N'_{trans}. We emphasize that three experiments were needed to determine these three parameters, a kinetic quenching experiment, a kinetics experiment, and an ^{13}C NMR experiment.[39] As these three experiments were run under different conditions, their combined usage is an assumption in this study. We emphasize that the values of K are to be regarded as approximate, given that it is very difficult to obtain precise values for equilibrium distributions which are considerably skewed. In addition,

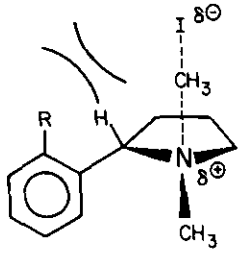
TABLE VII. Calculated Methylation Rate for 35-39

compound	$10^5 k_{cis}$	k_{cis}(rel)	$10^3 k_{trans}$	k_{trans}(rel)
R=H (35)	200	71	20	5.0
R=CH_3 (36)	46	16	9.8	2.5
R=CH_3CH_2 (37)	36	13	8.0	2.0
R=$(CH_3)_2CH$ (38)	30	11	6.9	1.7
R=$(CH_3)_3C$ (39)	2.8	1	4.0	1

[a] See Scheme IV and eq 6-7. From reference 39.

we have confirmed earlier studies which indicate complications can occur in amine quenching studies with strong acid,[21,22] and that the values for k are best to be considered as lower limits.

Substitution of the data in Table VI into eq 6-7 leads to the values of k_{cis} and k_{trans} shown in Table VII. It is evident that alkyl substituents on the benzene ring significantly hinder pyrrolidine nitrogen alkylation, especially for methylation of the trans (k_{cis}) or major conformational isomer 41 (Scheme IV). A reactivity range for k_{cis} of over seventy-fold is calculated. Small but definite steric hindrance is noted for alkylation trans to the aromatic ring, a significant feature given the distance between the aromatic substituent and the iodomethane moiety in this TS (see 42).



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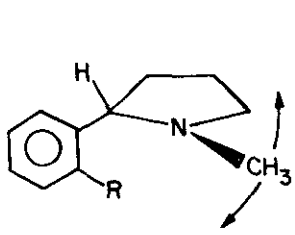
These results are particularly significant for two reasons:

(1) The alkyl substituents are remote from the reaction site (N') yet the effects are considerable. For comparison, consider the archetypal example of steric hindrance in the Menschutkin reaction: pyridine methylates only twice as rapidly as does 2-methylpyridine, even though the methyl group is directly attached to C_2.[31] On the other hand, k_{trans}(36) is approximately two times less reactive than k_{trans}(35).

(2) These steric effects are being observed in a conformationally mobile system. The phenyl group is capable of rotating the bulky substituents "out-of-the-way" of the incoming iodomethane molecule if, in fact, steric hindrance results in destabilizing energetics.

To analyze these two seemingly contradictory features, we consider three important conformational processes: nitrogen inversion (43), rotation about the bond connecting the two rings (44), and rotation about the phenyl substituent (45). The last process suggests the division of 35-39 into essentially three groups, based on the symmetry or lack of symmetry of the aromatic substituent: 35, 36-38, and 39.



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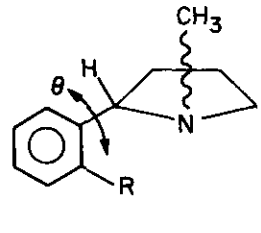

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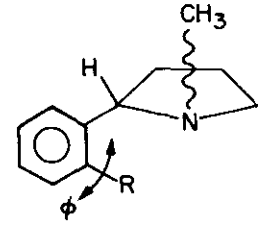

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In order for the alkyl substituents in 36-39 to affect the reaction rate constants, they must sterically interfere with the collision of the amine with the iodomethane. From the studies on the orientation of the pyridine ring relative to the pyrrolidine ring of nicotine (Section II,C), it is likely that there are two energy minima associated with 44, one in which the alkyl substituent is pointed away from the pyrrolidine nitrogen and one in which it is pointed toward the nitrogen. Even though the latter represents a relatively unstable conformation, as evidenced by the significant alkylation rate depression, it must be sufficiently "populated" to affect the rate. The rates of the conformational processes indicated in 43-45 are faster than the rates of alkylation. Conformations which are energetically unfavorable and are not significantly populated will nevertheless hinder the alkylation reaction. For more details of this argument and the possible importance of enthalpic and solvent effects, the reader is referred to the original literature.[37,39]

IV. THEORETICAL STUDIES ON THE MENSCHUTKIN REACTION

The Menschutkin reaction of substituted nicotinoids has served us well in the understanding of the effects of substituents on the chemical and physical properties of these compounds (see Section III). It is not always possible to determine experimentally some of the fundamental properties which we are interested in having in hand. For example, it is a rather unlikely challenge to measure the methylation rate constant for pyridine nitrogen alkylation of 2,6-dimethylnicotine (32) since, as shown in Table V, an overwhelming preponderance of pyrrolidine methylation occurs. Alternatively, we may have insufficient material for physical organic chemical studies. How then do we obtain a measure of a chemical or physical property if that property is not measurable or if the compound is unavailable?

TABLE VIII. Steric Accessibility Factor and Geometric Parameters[a] of 2-Substituted Pyridines

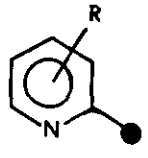
compounds	k_{rel}	S[b]	d_{NH}[a,c] (A)	θ[b,d] (deg)
2-picoline	1	1	2.596	117.01
2,3-lutidine	1.0	0.59	2.537	114.23
2,4-lutidine	2.1	1.0	2.595	117.07
2,5-lutidine	1.9	1.1	2.601	117.36
2-methyl-3-ethylpyridine	1.1	0.51	2.523	113.59
2-methyl-5-ethylpyridine	2.6	1.2	2.603	117.45
2-methyl-3-isopropylpyridine	1.2	0.49	2.515	113.15
2-methyl-5-isopropylpyridine	2.8	1.2	2.604	117.50
2-methyl-3-t-butylpyridine	0.77	0.27	2.452	110.30
2-methyl-5-t-butylpyridine	3.0	1.1	2.605	117.64
2,3-cyclopentenopyridine	4.4	2.6	2.924	127.12
2,3-cyclohexenopyridine	2.6	1.5	2.688	117.44
2,3-cycloheptenopyridine	0.70	0.41	2.473	114.12

[a] Geometries obtained via complete MINDO/3 energy minimization calculations. From references 40-42. [b] $S = k_{rel}/k_{calcd}$. k_{calc} was derived using LFER. The deviation of S from unity is a measure of kinetic nonadditivity. [c] Distance from pyridine nitrogen to closest hydrogen on C_{2_α}. [d] $N\text{-}C_2\text{-}C_{2_\alpha}$ angle.

Theoretical calculations have often provided the answer, or at least, an answer to such a conundrum. In this section, we shall cover two aspects of our current work in the area of nicotine-related theoretical calculations, though we briefly commented on other such studies in Section II. Because of the complexity of the nicotine structure, we decided to begin our analysis with the theoretical modeling of the Menschutkin reaction with substructures of the nicotine molecule: substituted pyridines and pyrrolidines. This is a rather fortunate choice of compounds since there is available a large literature data bank on the alkylation of pyridines[31] in addition to the kinetic information we were able to obtain.

A. Correlation of Kinetic Effects with Ground State Molecular Geometries[40-42]

As a first step in this work, we decided to focus attention on a well recognized steric effect in the Menschutkin reaction, the role of pyridine α-substitution (c.f. 46). As the alkyl



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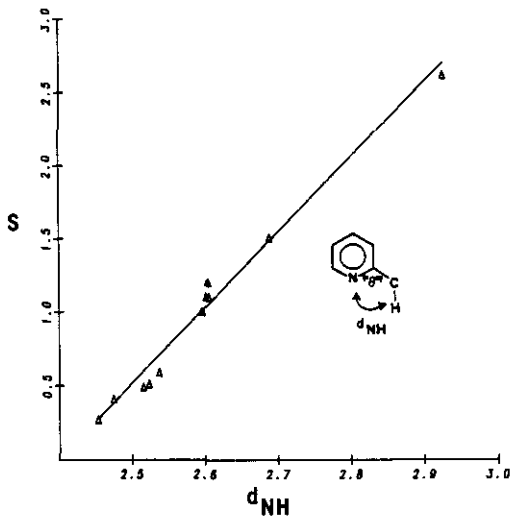


Figure 5. Relationship between S and d_{NH}. From references 40-41.

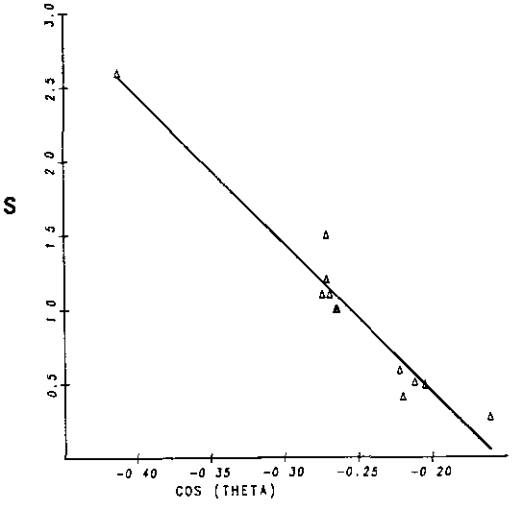
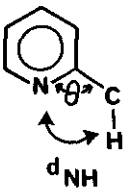


Figure 6. Relationship between S and θ. From references 40-41.

group increases in size in 46, the overall rate of methylation drops considerably. We decided to quantify this effect in terms of structural features, i.e., bond lengths and bond angles, which had previously received only qualitative attention.[40-42]

We performed complete MINDO/3 energy minimization for a series of 2-alkylpyridines listed in Table VIII. We then correlated two structural parameters which we anticipated would be related to reactivity differences (θ, the $\angle NC_2C_{2_\alpha}$; and d_{NH}, the distance between the pyridine nitrogen and the closest C_{2_α}-hydrogen atom) with the reactivity of these compounds. See 47 for the definition of θ and d_{NH}. As a measure of reactivity, we defined the steric factor S which quantifies the deviation of each rate constant from kinetic additivity, as indicated in Table VIII.



47

The reactivity differences illustrated by k_{rel} and S in Table VIII are the result of very subtle geometrical effects. We were evidently able to model these effects as illustrated by the excellent correlations which were obtained (eq 8-9) as seen in Figures 5-6.

$$S = 5.16\ d_{NH} - 12.4 \quad (8)$$

[r = 0.983, n = 13, p = 0.00001, std. dev. of residuals = 0.118]

$$S = -10.0\ (\cos\theta) - 1.56 \quad (9)$$

[r = 0.964, n = 13, p = 0.00001, std. dev. of residuals = 0.017]

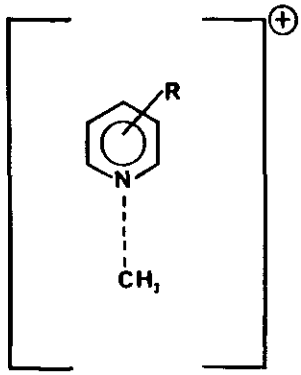
This study represents one of the first examples of quantifying kinetic effects, and especially nonadditive kinetic effects, with ground state geometries. For example, the many illuminating reports of the use of linear free energy relationships (e.g., Taft steric parameters, E_S) for the quantification of steric effects all fail to directly consider the structural consequences of the substituents.[43] Indeed, in LFER studies, substituents are treated as "black boxes" and bond length and bond angle effects are not treated.

We have also studied the effect of substituents on alkylpyridine and N-methylpyridinium cation geometry and energetics using the MINDO/3 algorithm.[42] These studies illuminate the geometry and energy changes during the course of pyridine methylation, in that the pyridines are starting materials and the N-methylpyridinium cations are the products in the reactions.

B. Transition State "Models" for the Menschutkin Reaction[44,45]

While the ground state model described above nicely illustrates some of the geometrical implications of steric effects, it is not suitable for compounds bearing either no C_{2_α} substituent (e.g., 3,4-lutidine and 4-aminopyridine) or those with two C_{2_α} substituents (e.g., 2,6-diisopropylpyridine). We therefore developed a transition state (TS) "model" which has been found to have predictive and correlative capabilities.

From the ground state model, we had calculated the total energy, E_{FB}, for a number of pyridine free bases.[40,41] We defined a TS model as shown by 48 in which a CH_3^+ cation was



48

placed 1.88 Å from the pyridine molecule (d_{NC_M}). We then performed MINDO/3-complete energy minimization on the resulting supermolecule, optimizing all parameters except for the 1.88 Å

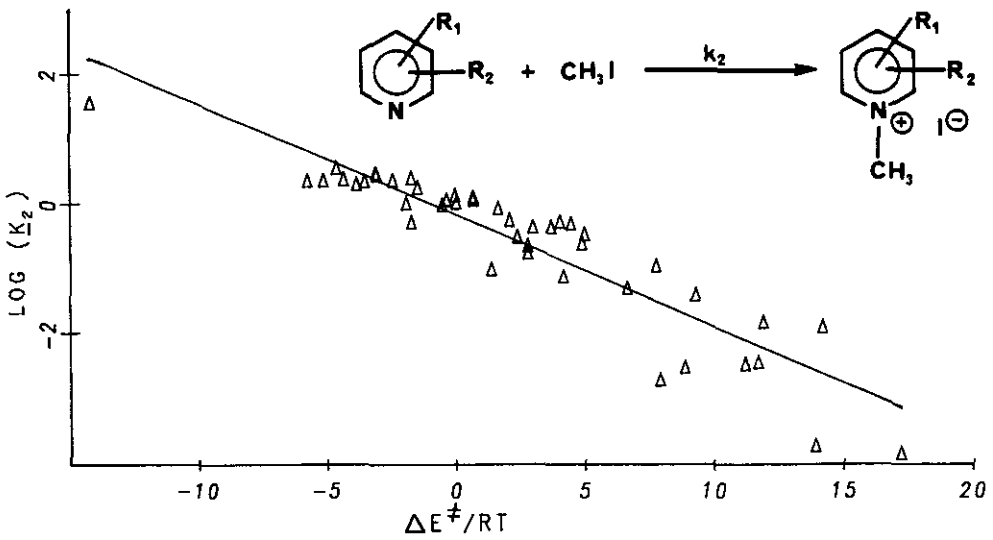


Figure 7. Relationship between the logarithm of the experimental methylation rate constants [*log*(k_2)] *and the MINDO/3-derived* activation energies. From references 44-45.

d_{NC_M}. A transition state energy, E_{TS}, was then calculated for each pyridine-CH_3^+ complex. Subtracting E_{FB} from E_{TS} for each pyridine resulted in an activation energy for our model from which $\Delta E^{\neq}$ relative to pyridine was calculated (c.f. eq 10-11). This process was performed for

$$\delta E^{\neq} = E_{TS} - E_{FB} \tag{10}$$

$$\Delta E_i^{\neq} = \delta E_i^{\neq} - \delta E_{pyridine}^{\neq} \tag{11}$$

forty four pyridines having both alkyl and heterosubstituents which incorporated a range in reactivity of over five orders in magnitude. Included in the series of compounds studied were 2-, 3-, and 4-monosubstituted pyridines (R = methyl, ethyl, isopropyl, and tert-butyl), as well as 2,3-, 2,4-, 2,5- and 2,6-dialkylpyridines (including those listed in Table VIII and 2,6-diethylpyridine and 2,6-diisopropylpyridine). We obtained an excellent correlation between the MINDO/3-derived activation energies and the common logarithm of the experimental methylation rate constants, as shown in Figure 7 and eq 12.

$$log\ (k_2) = -0.171\ (\Delta E^{\neq}/RT) - 0.192 \tag{12}$$

[r = 0.921, n = 44, p = 0.00001, std. dev. of residuals = 0.459]

Because of this highly significant correlation, we have confidence in drawing conclusions regarding substituent-induced effects in the pyridine alkylation geometry. This work has led to a better understanding of nonadditive kinetics and the structural features which operate in such

systems. Further discussion of these points are outside the scope of the current report, and the interested reader is referred to the original literature.[44,45]

V. OVERVIEW OF RESULTS

In the above sections, we have summarized some of the recent chemical studies on nicotine and a variety of nicotine analogues. Based on this work, we can make the following observations and conclusions:

1. Nicotine exists primarily in a conformation in which (a) the N'-methyl group is trans to the pyridine ring; (b) the pyrrolidine ring is in an envelope conformation, as illustrated in Figure 2; and (c) the relative orientation of the pyridine and pyrrolidine rings is essentially orthogonal.

2. Nicotine methylates competititvely at both the pyrrolidine and pyridine ring nitrogen atoms even though the pyrrolidine nitrogen (N') is considerably more basic. The pyridine ring significantly decreases pyrrolidine nitrogen nucleophilicity, by decreasing its basicity and by increasing steric hindrance.

3. Pyrrolidine methylation occurs cis and trans to the pyridine ring, with a slight preference to cis alkylation. Alkylation with alkyl halides larger than iodomethane results in pyridine quaternized products regiospecifically.

4. Placement of methyl groups on the pyridine ring of nicotine significantly alters the chemical reactivity of the resulting analogues. Substitution at C_2 and/or C_4 decreases pyrrolidine nitrogen reactivity by decreasing N'-accessibility. This is an unusual example of steric hindrance in a conformationally mobile system.

5. The methylation of the analogues has been thoroughly evaluated by determination of the individual reaction rate constants for pyrrolidine nitrogen alkylation (k_{cis} and k_{trans}, see Scheme II and IV) for the 1-methyl-2-(2-alkylphenyl)pyrrolidines. The Curtin-Hammett principle and the Winstein-Holness equation were used to analyze these kinetic systems. Three conformational processes are responsible for the significant rate effects observed: nitrogen inversion, aromatic ring-pyrrolidine ring rotation, and substituent-aromatic ring rotation.

6. Steric effects in the Menschutkin reaction of substituted pyridines have been quantified in terms of structural features (bond lengths and bond

angles). This represents one of the first studies which quantifies reactivity with molecular geometry.

7. A reactivity model for the methylation of pyridines has been developed. A wide range in chemical reactivity (over five orders in magnitude) were successfully correlated with this transition state model. Included in the series of pyridines were both unhindered (4-aminopyridine and 3,4-dimethylpyridine) and highly hindered (2,6-diisopropyl- and 2-tert-butylpyridine) substrates.

These results clearly indicate that a knowledge of conformation is essential for an understanding of the chemical personality of nicotine and its analogues. Although nicotine is seemingly a simple molecule, of rather low molecular weight and incorporating few functional groups, it is also clear that its "fundamental" chemical and physical properties are like golden nuggets, carefully secluded from prospecter-chemists.

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