evaporated, and the off-white residue recrystallized from aqueous ethanol and sublimed at 60 °C (10 torr) to yield 1.47 g (81%) of white, crystalline **16**: mp 38–40 °C; ^{1}H NMR as shown in Table I.

Anal. Calcd for $C_9H_8Cl_5N$: C, 35.12; H, 2.60; N, 4.55. Found: C, 35.09; H, 2.70; N, 4.91.

Acknowledgment. This investigation was supported in part by NIH Grant GM 19212 for which we are grateful. The National Science Foundation Research Instrument Grant CHE 76-05683 for the purchase of the Bruker WH-90DS FT-NMR spectrometer is gratefully acknowledged. We also thank Dr. J. T. Joseph for the operation of the spectrometer.

Registry No. 1, 57802-40-1; 5, 65392-20-3; 7, 77630-22-9; 9, 77630-23-0; 10, 77630-24-1; 12, 77630-25-2; 14, 77647-94-0; 16, 77630-26-3; cyclopentadiene, 542-92-7; cyclopentene, 142-29-0; cyclohexadiene, 592-57-4; cyclohexene, 110-83-8; *trans*-piperylene, 2004-70-8.

Steric and Conformational Effects in Nicotine Chemistry[1]

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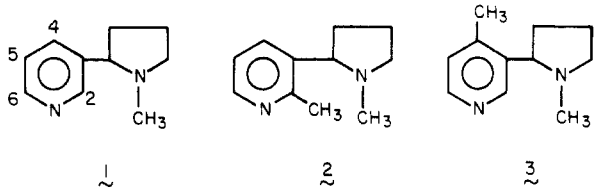
The stereoselectivity of iodomethylation of nicotine and seven nicotine analogues having pyridine alkyl groups was determined by using ^{13}C NMR. Alkylation at the pyridine (N) and at the pyrrolidine (N′) nitrogens was observed. Two modes of N′-iodomethylation occur, cis and trans to the pyridine ring. N′-Iodomethylation occurs regioselectively cis to the pyridine ring for all compounds examined. The N/N′ and N'_{cis}/N'_{trans} ratios for the nicotinoids were evaluated with regard to (1) the orientation of the *N′*-methyl group in the free base, (2) conformational properties of the pyridine ring with respect to the pyrrolidine ring, and (3) steric hindrance and buttressing effects on the pyridine nitrogen. The Curtin–Hammett principle and the Winstein–Holness equation are used to analyze these reactions.

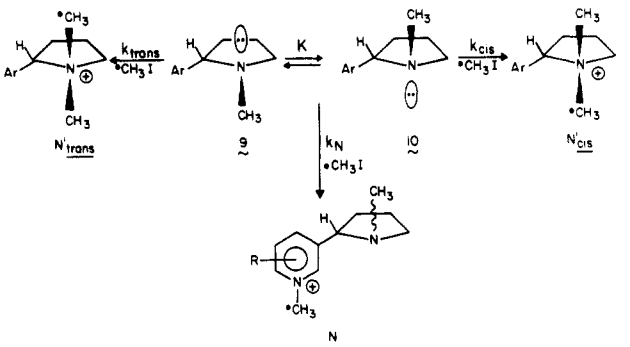
Recently, we and others have observed that 2-methylnicotine (**2**) and 4-methylnicotine (**3**) were both significantly less active than nicotine (**1**) in a variety of pharmacological tests, while 6-methylnicotine retained full nicotinic activity.[1,2,3a,b] The pyridine methyl groups in **2** and **3** are likely not only to alter the reactivity of their respective pyridine nitrogen atoms but also to affect the compounds' ground-state conformational profile. As part of our studies on the pharmacology of nicotine and related compounds, we have prepared[4] a large number of pyridine substituted nicotinoids (**2–8**). We now report results on the iodomethylation of these nicotinoids aimed at evaluating the effect of structure and conformation on nitrogen reactivity in these heterocycles.



Results and Discussion

Each compound was alkylated with 0.7–0.8 equiv of $^{13}CH_3I$ at 0.1–0.6 M in acetonitrile-d_3 6–15 times. Long pulse delays and small pulse flip angles were used in obtaining ^{13}C NMR spectra of the alkylation products in order to minimize the effect of differences in ^{13}C relaxation times (see Experimental Section for complete details).[5] Figures 1 and 2 show ^{13}C and ^{1}H NMR spectra of the total reaction mixture from the alkylation of nicotine with $^{13}CH_3I$. Figure 1 shows three resonances, the relative ratios of which relate directly to the relative rates of the three modes of nicotine alkylation: N (pyridine), N'_{cis} (pyrrolidine attack cis to the pyridine ring), and N'_{trans} (pyrrolidine attack trans to the pyridine ring) (cf. Scheme I). In all cases, the pyridine quaternary methyl carbon appears as a broad singlet while the pyrrolidine quaternary methyl carbons appear as triplets because of ^{14}N coupling of the more symmetrical quaternary nitrogen of the dimethylpyrrolidinium iodide.

Scheme I



A definitive assignment of these methyl resonances was made on the basis of a series of nuclear Overhauser enhancement (NOE) experiments. Table I indicates the results of one such experiment. For example, irradiation of the N'_{cis}-methyl protons of purified *N′*-methylnicotinium iodide in acetonitrile at δ 2.94 results in enhancements of the H_2 and H_4 pyridine protons as well as a small en-

(1) For the previous paper in this series, see: Seeman, J. I.; Dwyer, W. R. Jr.; Osdene, T. S.; Sanders, E. B.; Secor, H. V., submitted for publication.

(2) Sanders, E. B.; Secor, H. V.; Seeman, J. I. U.S. Patent 4 155 909, 1979; U.S. Patent 4 220 781, 1980.

(3) (a) Haglid, F. *Acta Chem. Scand.* **1967**, *21*, 329. (b) Haglid, F. *Acta Pharm. Suec.* **1967**, *4*, 117. (c) Leete, E.; Leete, S. A. S. *J. Org. Chem.* **1978**, *43*, 2122.

(4) (a) Seeman, J. I. *Synthesis*, **1977**, 498. (b) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *J. Org. Chem.* **1978**, *43*, 324. (c) Seeman, J. I.; Secor, H. V.; Whidby, J. F.; Bassfield, R. L. *Tetrahedron Lett.* **1978**, 1901. (d) Sanders, E. B.; Secor, H. V.; Seeman, J. I. *J. Org. Chem.* **1976**, *41*, 2658.

(5) Crowley, P. J.; Robinson, M. J. T.; Ward, M. G. *Tetrahedron*, **1977**, *33*, 915.

0022-3263/81/1946-3040$01.25/0

Table I. Nuclear Overhauser Enhancement Experiments[a]

compd	proton irradiated	proton(s) obsd			
		2	4	2′	5′
N'-methylnicotinium iodide[b]	N'_{trans} (δ 3.27)	<1	<1	7.1	5.1
	N'_{cis} (δ 2.94)	8.5	7.9	<1	5.9
nicotine bis(deuteriotrifluoroacetate)[c]	N′ (δ 3.13)	<1	<1	13	3 (α), 11 (β)
	N′ (δ 2.83)[d]				

[a] See ref 6. Values are given as percents. [b] In D_2O. [c] Prepared by addition of nicotine to trifluoroacetic acid-*d* in an NMR tube. [d] This resonance is that of the minor (<10%) isomer having the N′-CH_3 group cis to the pyridine ring (cf. ref 6). NOE experiments were not performed for the minor isomer due to its low concentration.

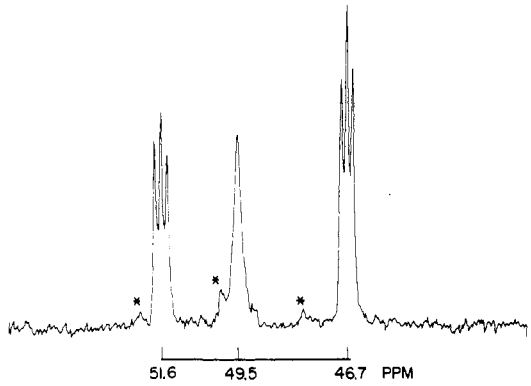


Figure 1. ^{13}C NMR spectrum (25.0 MHz) of the total reaction mixture of nicotine and 0.75 equiv of $^{13}CH_3I$. The asterisks refer to the methyl carbons of the dialkylated product, nicotine dimethiodide.

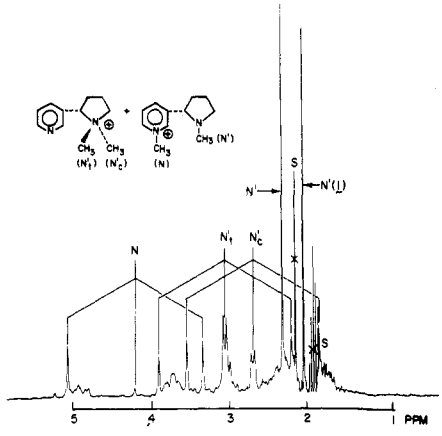


Figure 2. ^1H NMR spectrum (80 MHz) of total reaction mixture of nicotine and 0.75 equiv of $^{13}CH_3I$. The complex patterns for each of the N'-methyl groups are because of the presence of diastereomers due to unsymmetrical isotopic labeling. N′(1) refers to unreacted nicotine. The resonances at ca. δ 1.9 and 2.2 result from the solvent and are labeled "S".

hancement of the $H_{5'}$ pyrrolidinyl protons but no enhancement of the $H_{2'}$ pyrrolidinyl proton. The diastereotopic $H_{5'}$ pyrrolidine protons have overlapping resonances in acetonitrile, and differential NOEs were not observable. Similarly, irradiation of the N'_{trans}-methyl protons at δ 3.27 results in enhancements of the $H_{2'}$ and $H_{5'}$ pyrrolidinyl protons but no enhancements of the pyridine protons. The N'_{cis}- and not the N'_{trans}-methyl protons can, in theory, relax the H_2 and H_4 pyridine protons; each of the N'_{cis}- and the N'_{trans}-methyl protons can relax one $H_{5'}$ proton, though the major relaxation mode for the $H_{5'}$ protons should be their mutual relaxation.[6]

Chemical shift comparisons of N'-methylnicotinium iodide with the diastereomeric nicotine bis(trifluoroacetates) in TFA-*d* are shown in Table I. We have previously assigned the N'-methyl groups of the two salts by NOE studies, and these data are also included in Table I.[6]

Table II. ^{13}C NMR Chemical Shifts of Quaternary N^+-CH_3 Resonances[a]

alkylated derivatives of	shift, ppm		
	N[b]	N'_{cis}[c]	N'_{trans}[c]
nicotine (1)	49.5	46.7	51.6
2-methylnicotine (2)	47.9	47.1	51.9
4-methylnicotine (3)	49.0	47.1	51.8
5-methylnicotine (4)	49.2	46.8	51.6
6-methylnicotine (5)	47.1	46.5	51.4
2,6-dimethylnicotine (6)		47.1	51.8
4,6-dimethylnicotine (7)	46.6	47.0	51.8
5,6-dimethylnicotine (8)	48.1	46.7	51.6

[a] Some minor concentration dependence for the chemical shifts were noted on occasion. All spectra were obtained in CD_3CN. [b] Broad singlet. [c] Triplet.

A feature clearly evident from Figure 2 is the observation of ^1J(C–H) and ^3J(C–N^+–C–H) couplings. These heteronuclear couplings are generally not observed in ^1H NMR spectra due to the low natural abundance of ^{13}C but are observed here because of the incorporation of one ^{13}C atom per monomethiodide molecule. Thus, Figure 2 is a composite spectrum of four compounds, nicotine, the "two" N'-methiodides, and the N-methiodide. The heteronuclear coupling constants are approximately ^1J = 150 Hz and ^3J = 7 Hz.[7] The proton resonances for the "composite" pyrrolidine N'-methyl carbons can have five lines, two due to a large ^1J coupling, two due to a smaller ^3J coupling, and one resulting from alkylation with $^{12}CH_3I$, present due to a 5–10% impurity in the $^{13}CH_3I$.[8] Similarly, the pyridine quaternary methyl hydrogens have three lines, two due to ^1J coupling and one due to the N^+–$^{12}CH_3$ species. The stereoselectivities observed in the ^1H spectra can be readily correlated to that seen in the ^{13}C spectra, and the ^1H spectra were used to confirm the ^{13}C NMR results. Thus, for the iodomethylation products of nicotine the upfield pentet (Figure 2), assigned as the methyl group cis to the pyridine ring on the basis of the NOE experiments, has the ^1J = 165 Hz doublet significantly larger in area than the ^3J = 7 doublet, from which it can be concluded that the downfield ^1H NMR N'-methyl resonance corresponds to the downfield ^{13}C NMR resonance. Thus, the more upfield carbon triplet (Figure 1) can be assigned to the *cis*-N'-methyl and the lowfield triplet the *trans*-N'-methyl group.

In all cases studied the ^{13}C shift of the pyridine methyl carbon was in the 46.6–49.5-ppm range, while the cis pyrrolidine methyl carbon was in the 46.5–47.1-ppm range

(6) Whidby, J. F.; Seeman, J. I. *J. Org. Chem.* **1976**, *41*, 1585.

(7) For another study involving long-range heteronuclear coupling in nicotine, see: Pitner, T. P.; Seeman, J. I.; Whidby, J. F. *J. Heterocycl. Chem.* **1978**, *15*, 585.

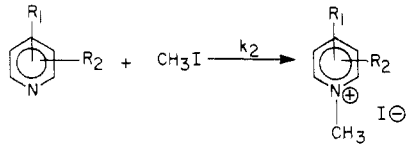
(8) Isotopic purity of the $^{13}CH_3I$ is approximately 90% (Merck).

Table III.[a] Relative Rates of Competitive Iodomethylation of Nicotine and Nicotine Analogues[b]

compd	N'_{cis}/N'_{trans} ratio	N'/N ratio	rel N/N' ratio
nicotine (1)	1.50 ± 0.11	2.66 ± 0.36	1
2-methylnicotine (2)	1.27 ± 0.18	2.31 ± 0.12	1.15
4-methylnicotine (3)	1.16 ± 0.05	0.33 ± 0.03	8.1
5-methylnicotine (4)	1.48 ± 0.24	2.15 ± 0.17	1.2
6-methylnicotine (5)	1.62 ± 0.06	8.0 ± 0.33	0.33
2,6-dimethylnicotine (6)	1.64 ± 0.23	>50	<0.05
4,6-dimethylnicotine (7)	1.40 ± 0.10	0.92 ± 0.08	2.9
5,6-dimethylnicotine (8)	1.75 ± 0.10	8.9 ± 0.60	0.31

[a] See Scheme I for explanation of terms. [b] See Experimental Section for additional details.

Table IV. Relative Rate of Pyridine Iodomethylation[a,b]



compd	k_2 (rel)	compd	k_2 (rel)
pyridine	1	2,4-dimethylpyridine	0.92
2-methylpyridine	0.43	2,5-dimethylpyridine	0.82
3-methylpyridine	1.7	2,6-dimethylpyridine	0.040
4-methylpyridine	2.1	3,4-dimethylpyridine	3.4
2,3-dimethylpyridine	0.43	3,5-dimethylpyridine	2.6

[a] Data from ref 10. [b] At 25.00 ± 0.01 °C in acetonitrile. Note that for pyridine, $k_2 = 3.18 \pm 0.08 \times 10^{-4}$.

and the trans pyrrolidine methyl carbon in the 51.4–51.9-ppm range (see Table II). Further confirmation of this correlation was readily obtained by comparison of the ^1H, ^2H, and ^{13}C spectra of the mixture resulting from, e.g., the reaction of nicotine with CD_3I. In this case, the carbon resonance for a CD_3 residue is considerably less intense than the corresponding resonance for a CH_3 residue due to the shorter relaxation time of a carbon bound to a deuterium atom relative to the same carbon bound to a hydrogen atom.

Competitive Nitrogen Alkylation Results. The relative rates of product formation of nicotine[9] and the nicotine analogues examined herein are reported in Table III. Also listed are the ratios of N'/N attack (where N refers to pyridine alkylation and N' to total pyrrolidine alkylation) and N'_{cis}/N'_{trans} attack (where N'_{cis} and N'_{trans} refer to pyrrolidine alkylation cis and trans to the pyridine ring, respectively).

Of particular interest to us was the determination of the effect of pyridine methyl substitution on reactivity at both nitrogen atoms. In order to assess these features, it is constructive to compare the relative rates of product formation shown in Table III with the relative rate constants of iodomethylation of pyridine, the three picolines, and the six lutidines in acetonitrile (cf. Table IV). In terms of pyridine alkylations,[10-12] alkyl substituents at both the β- and γ-positions cause significant rate enhancements which are relatively independent of the steric size of the alkyl group. On the other hand, α substituents are rate decelerating with the more bulky substituents effecting a greater rate retardation.

Chart I

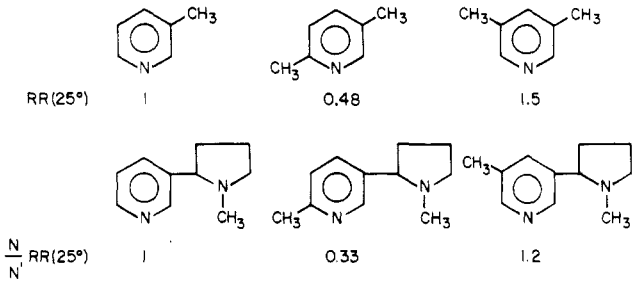
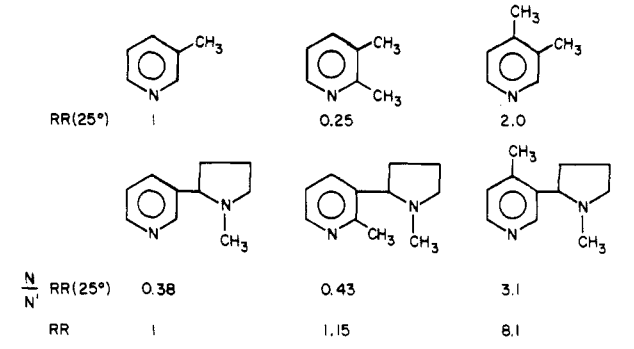


Chart II



Do these generalizations apply to the nicotine systems? Assuming that substitution at C_5 or C_6 has a minimal effect on the rate of N' product formation, one can calculate that, relative to nicotine, the rate constant for pyridine alkylation is 0.33 times slower for 6-methylnicotine (5) and 1.2 times faster for 5-methylnicotine (4). These results are consistent with the picoline results (see Chart I).

The N/N' ratio for 2-methylnicotine (2) is 0.43, slightly more than that of nicotine (0.38) and significantly more than the ratio (0.33) found for the 6-methyl isomer (5) (see Chart II and Table III). Thus, the 2-methyl group must decrease the rate of N'-alkylation of 2. Although the actual rate constants for pyrrolidine alkylation can be determined only when the ratio of free base nitrogen invertomers is known,[4c] one can estimate that the 2-methyl substituent causes an overall 4.6-fold N' rate retardation, a figure which is arrived at by a comparison of the relative rates of 3-methylpyridine and 2,3-dimethylpyridine. Similarly, 3,4-dimethylpyridine reacts 2.0 times faster than 3-methylpyridine; N/N' for 4-methylnicotine is 3.1, which implies ca. a 4.1-fold rate retardation for N'-alkylation of 3 relative to nicotine.

The greater than 4-fold decrease in the relative rate of pyrrolidine nitrogen iodomethylation caused by a pyridine methyl group α to the pyrrolidine ring is an interesting example of steric hindrance in a conformationally mobile system. To place this deceleration in perspective, it is of value to compare this 4-fold decrease to that observed in the classic example of steric hindrance in the Menschutkin reaction. 2-Methylpyridine iodomethylates only half as fast as pyridine and one-fourth as fast as 4-methylpyridine, and these examples are without the conformational freedom and spatial relationships found in 2 and 3.[10,11]

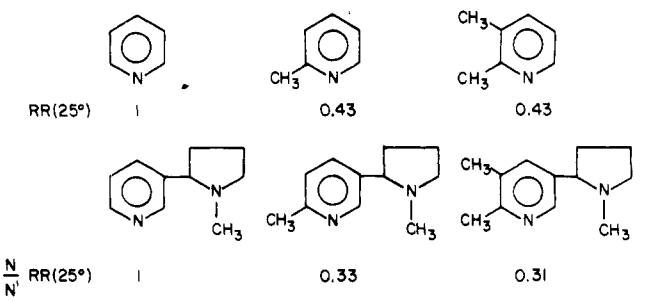
(9) For a preliminary report on the iodomethylation stereoselectivity of nicotine, see ref 4c.

(10) (a) Curtis, K.; DeNagel, D.; Galzerano, R.; Seeman, J. I., unpublished results. (b) Seeman, J. I.; Galzerano, R.; Curtis, K.; Schug, J. C.; Viers, J. N., manuscript submitted for publication.

(11) (a) Brown, H. C.; Cahn, A. *J. Am. Chem. Soc.* **1955**, *77*, 1715. (b) Brown, H. C. *J. Chem. Soc.* **1956**, 1248.

(12) (a) Fischer, A.; Galloway, W. J.; Vaughn, J. *J. Chem. Soc.* **1965**, 3591. (b) Clarke, K.; Rothwell, K. *Ibid.* **1960**, 1885.

Chart III



The buttressing effect noted in the iodomethylation of 2,3-dimethylpyridine[10] is also seen in the iodomethylation of 5,6-dimethylnicotine (8) which has an N/N′ ratio almost identical with that found for 6-methylnicotine (5) and one-fourth that found for 5-methylnicotine (4) (see Chart III).

Iodomethylation of 2,6-dimethylnicotine (6) led to <2% pyridine alkylation. A number of factors are operating in this case: α,α-dipyridine substitution decreases N-alkylation in a manner analogous to that found for 2,6-dimethylpyridine; 2,3-dialkylpyridine substitution may decrease N alkylation by a buttressing effect; i.e., the net steric effect of a 2,3-disubstituted pyridine ring is greater than the "sum" of the effects of the individual substituents derived by examining the 2-substituted and 3-substituted pyridine compounds independently.

A comparison (cf. Chart I) between the pairs of compounds 3-methylpyridine/2,5-dimethylpyridine and nicotine/6-methylnicotine indicates that the N/N′ ratio for 6-methylnicotine relative to nicotine is lower that the rate of 2,5-dimethylpyridine relative to 3-methylpyridine (0.33 < 0.48). This suggests that the 6-methyl substituent is increasing the rate of N′-alkylation. Similarly, a comparison between 3-methylpyridine/3,5-dimethylpyridine and nicotine/5-methylnicotine indicates a decreased N/N′ ratio (1.5 > 1.2) (cf. Chart I) as does a comparison between pyridine/2,3-dimethylpyridine and nicotine/5,6-dimethylnicotine (0.43 > 0.30) (cf. Chart III). It thus appears that alkyl substitution at C_5 and/or C_6 of nicotine *increases* the relative rate of N′ alkylation.

Conformational Effects on N′ Reactivity. As indicated above, the pyridine methyl group in both 2-methylnicotine and 4-methylnicotine decreases the overall rate of pyrrolidine nitrogen alkylation. Nicotine and its analogues discussed herein are conformationally mobile; the *N*-methyl moiety is inverting rapidly, the two rings rotate with respect to each other, and the pyrrolidine ring itself has numerous low-energy motions available. In order to analyze steric effects in these systems, one must first attempt to evaluate the role played by these numerous conformations and their dynamic interchange play.

The role of conformational freedom on chemical reactivity (cf. eq 1) can be analyzed quantitatively by use

$$A_1 \overset{k_{21}}{\leftarrow} A_2 \overset{K}{\rightleftarrows} A_3 \overset{k_{34}}{\rightarrow} A_4 \quad (1)$$

$$A_4/A_1 = K(k_{34}/k_{21}) \quad (2)$$

$$k_{W\text{-}H} = k_{21}x_2 + k_{34}x_3 \quad (3)$$

of the Curtin–Hammett (C–H) principle (eq 2) and the Winstein–Holness equation (eq 3).[13-15] In eq 1–3, K refers to the ground-state equilibrium distribution of $A_2 \rightleftarrows A_3$, x_i refers to mole fraction of the ith reacting conformation, and $k_{W\text{-}H}$ refers to the total empirical reaction rate constant.[15b]

For a molecule which exists in numerous reacting conformations, $k_{W\text{-}H}$ is equal to the sum of the product of the rate constants for each particular conformation (k_i) times the mole fraction of each conformation (x_i; eq 4).[15b] This

$$k_{W\text{-}H} = \sum x_i k_i \quad (4)$$

population-weighted rate constant has the net effect of increasing the influence on the rate constant of more populated conformations.

Molecular models indicate significant increases in the steric component of the potential energy of nicotine when its pyridine–pyrrolidine ring conformations are within the dihedral angle C_4–C_3–C_2–$C_{3'}$ of 180° ± 20° or 0° ± 20°. The additional pyridine methyl group of **2** and **3** renders conformations having torsional angles of 180° ± 20° and 0° ± 20°, respectively, particularly unstable and, as a consequence, relatively unpopulated, due to cross-ring interactions.

Literature reports[6,16] and our preliminary INDO calculations[1] support these observations. One would anticipate even more significant steric interactions in these dihedral angle ranges for the *N*′-methyl invertomers, those in which the *N*′-methyl group is cis to the pyridine ring. These destabilizations would be even more magnified in either N'_{cis} or N'_{trans} transition-state structures (Scheme I) having conformations of similar dihedral angles. This being the case, the relative population of ground-state conformational isomers having the C_4–C_3–C_2–$C_{3'}$ dihedral angle within the range of either 180° ± 20° or 0° ± 20° is expected to be small, and the analogous transition-state structures would be even less favored over other transition states.

The four-fold decrease in rate of N′ alkylation for **2** and **3** must reflect a time average of all the reacting conformations. Although we have just demonstrated that conformations having the pyridine methyl group spatially close to the pyrrolidine ring would be energetically unfavorable in the ground state (reflecting low populations, x_i), a significant rate decrease is observed. According to this analysis, the observed reaction rate constant must be affected by a decrease in the rate constants of the more stable conformations. Yet, it is these conformations which do not possess significantly destabilizing ring–ring interactions.

This apparent inconsistency can be resolved by considering the time constants of two molecular motions: (1) the rate of rotation about the C–C bond connecting the pyridine and pyrrolidine rings and (2) the relative rate of

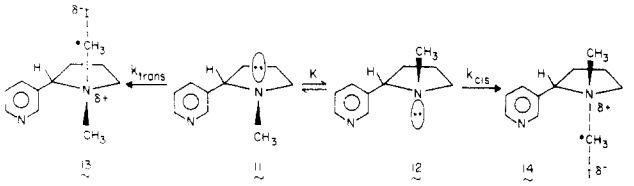
(13) Eliel, E. L.; Allinger, N. L.; Angyl, S. J.; Morrison, G. A. "Conformational Analysis"; Wiley-Interscience: New York, 1965; pp 27–35, 47–50.

(14) (a) Seeman, J. I.; Farone, W. A. *J. Org. Chem.* **1978**, *43*, 1854. (b) Seeman, J. I.; Sanders, E. B.; Farone, W. A. *Tetrahedron* **1980**, *36*, 1173.

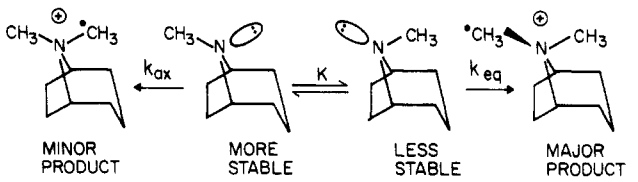
(15) (a) A more detailed discussion of these points is presented in our work involving the alkylation of 1-methyl-2-(2-alkylphenyl)pyrrolidines: Seeman, J. I.; Secor, H. V.; Hartung, H.; Galzerano, R. *J. Am. Chem. Soc.* **1980**, *102*, 7741. (b) Strictly speaking, x_i refers to the mole fraction of the ith component of the ground-state conformational mixture at $t = 0$. Since $k_{23}, k_{32} \gg k_{21}, k_{34}$ for eq 1, the C-H/W-H approximations are valid and $[A_3]/[A_2] = K$ throughout the course of the reaction. However, as products A_1 and A_4 build up during the reaction, x_i cannot refer to the mole fraction of the ith component since the concentration of products must be taken into account. Perhaps, x_i would better refer to the fraction of the ith reactant with regard to all the reactants.

(16) (a) Kier, L. B. *Mol. Pharmacol.* **1968**, *4*, 70. (b) Lee, I.; Park, D. H. *Taehan Hwahakhoe Chi.* **1978**, *22*, 195; *Chem. Abstr.* **1979**, *90*, 6592. (c) Radna, R. J.; Beveridge, D. L.; Bender, A. L. *J. Am. Chem. Soc.* **1973**, *95*, 3831. (d) Pullman, B.; Courriere, P.; Coubeils, J. L. *Mol. Pharmacol.* **1971**, *7*, 397. (e) Testa, B.; Jenner, P. *Ibid.* **1973**, *9*, 10. (f) Pitner, T. P.; Edwards, W. B., III; Bassfield, R. L.; Whidby, J. F. *J. Am. Chem. Soc.* **1978** *100*, 246. (g) Whidby, J. F.; Edwards, W. B., III; Pitner, T. P. *J. Org. Chem.* **1979**, *44*, 794. (h) Pitner, T. P.; Whidby, J. F.; Edwards, W. B., III *J. Am. Chem. Soc.* **1980**, *102*, 5149.

Scheme II



Scheme III



approach of the alkylating reagent and the substrate. The observation that a C_2 or a C_4 pyridine methyl group retards pyrrolidine alkylation indicates that pyridine–pyrrolidine ring–ring rotation is occurring many times on the potential energy surface(s) reflecting the transition-state structures. That is, rapid ring–ring rotation appears to have the effect of allowing minor, highly energetic conformations to play a significant role in the overall kinetics. One cannot analyze the system as a series of conformations, each reacting completely independent of each other.[15]

Stereoselectivity of Pyrrolidine Alkylation. The rato N'_{cis}/N'_{trans} is the relative amount of pyrrolidine alkylation cis/trans to the pyridine ring. This ratio can be related (1) to the difference in the free transition-state energies of the pyrrolidine quaternization reactions or (2) to the product of the invertomer equilibrium constant (K) and the ratio of the invertomer alkylation rate constants (eq 5;[14] see Scheme I).

$$\frac{N'_{cis}}{N'_{trans}} = K\frac{k_{cis}}{k_{trans}} = \exp(-\Delta\Delta G^{\ddagger}/RT) \qquad (5)$$

Examination of Table III indicates that N'_{cis}/N'_{trans} ratios are very similar for all the compounds examined and have a mean value of 1.48 ± 0.20. As shown by eq 5, N'_{cis}/N'_{trans} is determined by the two independent rate constants and one equilibrium constant shown in Scheme I. The equilibrium constant K reflects the difference in free energies between the two substrates, **9** and **10**. Consider the case of nicotine illustrated in Scheme II. The pyridine ring is the only substituent which removes the symmetry from the N'-methylpyrrolidine ring (and from the two N'-alkylation transition states). The equilibrium is heavily in favor of **12**, i.e., $K \gtrsim 10$.[6] The second ratio, k_{cis}/k_{trans}, reflects the decelerating effect of a substituent on the N-methylpyrrolidine ring caused by steric interference. For nicotine, the pyridine ring sterically hinders cis pyrrolidine alkylation (k_{cis}) relative to trans pyrrolidine alkylation (k_{trans}). Since cis alkylation predominants (N'_{cis}/N'_{trans} ratio of 1.5), the value of k_{cis}/k_{trans} must be greater than $1/K$; i.e., for iodomethylation, the α substituent has more effect on the equilibrium constant than on the ratio of the two rate constants.

An alternate description of this stereoselectivity involves an examination of the diastereomeric transition states again illustrated in Scheme II. According to eq 5, since more cis alkylation is obtained, the cis transition state is preferred. The difference between these two transition states involves a pairwise comparison of two effects: the already bonded pyrrolidine N'-CH_3 in **13** and **14** interacting with the other pyrrolidine substituents and the attacking iodomethane moiety interacting with the pyrrolidine substituents. These two related analyses imply that nicotine's already bonded N'–CH_3 group has a larger steric requirement than the $N'^{\delta+}\cdots CH_3\cdots I^{\delta-}$ group in the transition state.[4c]

Throughout these discussions, we have not focused on the importance of solvation. Clearly, Scheme II is incomplete without inclusion of solvent molecules, and any discussion of pyrrolidine nitrogen alkylation stereoselectivity[17,18] (cf., e.g., eq 5) is incomplete without considering the effect of solvent on K, k_{cis}, and k_{trans}. Arnett and Reich have recently reported their results of a most careful analysis of kinetic and thermodynamic parameters in pyridine quaternizations.[17] They presented a very detailed account of the alkylation transition state, in which bond formation between nitrogen and carbon is only partially completed but bond rupture between the "transferring alkyl group and the leaving group with solvent reorganization is nearly complete".[17]

For the purposes of this discussion, the moiety "$CH_3\cdots I^-$" in Scheme II represents a group of atoms in which considerable bond breakage has already occurred between the methyl carbon and the iodide and considerable solvation of a highly organized form has taken place. One effect of this solvation is the net increase in the effective size of the iodide anion. However, the regiochemistry of the observed pyrrolidine nitrogen iodomethylation favors cis attack and reflects the *net* free energy effect of solvation of the equilibrating invertomers, the two transition states, and the steric effect of the already bonded methyl group. Increasing the size of the alkylating group (e.g., from iodomethane to iodoethane to benzyl bromide) could then reverse the regiochemistry at the pyrrolidine nitrogen.[19a] This seems to imply that the regiochemistry is determined by the spatial requirements of the alkylating reagent rather than by solvation phenomena alone. Of course, these transition-state factors are not independent; the position of the transition state is very dependent on reaction rate which relates to reagent size, leaving group facility, and solvation. We are currently examining these matters more fully.

Examination of the literature reveals that in almost all instances the stereoselectivity of *methylation* of tertiary *methylamines* results in a preponderance in attack from the more stable invertomer. This includes methylation of 2- and 4-substituted piperidines,[4c,18a] 2-substituted pyrrolidines,[4c,19] aziridines,[20] 4,4-disubstituted piperidines,[18f] *trans*-decahydroquinolines,[18] 4-aza-5α-cholestanes,[18a,21] and camphidines.[18e] This is neither an obvious nor necessary experimental result, for as discussed above, those steric factors which control the value of the equilibrium constant K also determine, *in an inverse fashion*, the value of the ratio of the alkylation rate constants, k_{34}/k_{21} (compare Scheme II and eq 1–3). The net effect of the above

(17) Arnett, E. M.; Reich, R. *J. Am. Chem. Soc.* **1980**, *102*, 5892.
(18) (a) McKenna, J. *Top. Stereochem.* **1970**, *5*, 275–308. (b) Bare, T. M.; Hershey, N. D.; House, H. O.; Swain, C. G. *J. Org. Chem.* **1972**, *37*, 997. (c) Kawazoe, Y.; Tsuda, M. *Chem. Pharm. Bull.* **1967**, *15*, 1405. (d) Baker, V. J.; Blackburne, I. D.; Katritzky, A. R.; Kolinski, R. A.; *J. Chem. Soc., Perkin Trans. 2* **1974**, 1557. (e) Brown, D. R.; Lygo, R.; McKenna, J.; McKenna, J. M.; Hutley, B. G. *J. Chem. Soc. B* **1967**, 1184. (f) House, H. O.; Tefertiller, B. A.; Pitt, C. G. *J. Org. Chem.* **1966**, *31*, 1073 and previous papers in this series.
(19) (a) Solladié-Cavallo, A.; Solladié, G. *Tetrahedron Lett.* **1972**, 4237. (b) For a study involving the alkylation of hydroxy or (carboalkoxy)-pyrrolidines, the stereoselectivity being complicated by the unknown effect of these highly polar substituents, see: Mandava, N.; Fodor, G. *Justus Liebigs Am. Chem.* **1970**, *741*, 167.
(20) Rivoirard, E.-M.; Baret, P.; Boucherle, A.; Gey, C.; Pierre, J.-L. *J. Heterocycl. Chem.* **1979**, *16*, 327 and references cited therein.
(21) McKenna, J.; McKenna, J. M.; Tulley, A.; White, J. *J. Chem. Soc.* **1965**, 1711.

counterbalancing phenomena is to minimize the variability in the value of the A_4/A_1 ratio, i.e., to cause the ratio of products to "hover" above unity. That the methylation of most tertiary methylamines occurs predominantly from the more stable nitrogen invertomer indicates that the already bonded N–CH_3 group has a larger steric requirement than the $N^{\delta+}\cdots CH_3\cdots I^{\delta-}$ group in the transition state.[4c]

However, there are a few notable exceptions to this theme, e.g., methylation of *N*-methyltropine analogues.[22] In these cases, selectivity favors attack from the less stable invertomer, i.e., attack from the isomer in which the N–CH_3 group is axial with respect to the tropine six-membered ring[22,23] (see Scheme III). For tropines, the already bonded N–CH_3 group appears to have a smaller steric requirement than the $N^{\delta+}\cdots CH_3\cdots I^{\delta-}$ group in the transition state.[24,25]

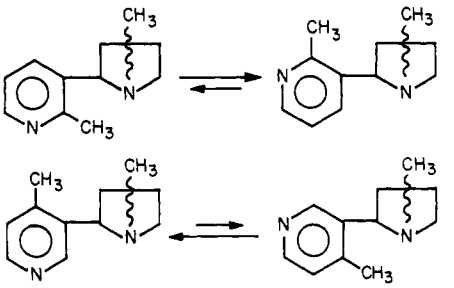
This analysis contrasts sharply with recent evaluations of tropane alkylation stereoselectivity. For example, Mundy suggested that tropanes alkylate preferentially axially because "steric interactions on the pyrrolidine ring side of the molecule are considerably less than on the piperidine side".[26] Mundy's analysis fails to consider the pairwise comparison of the two phenomena, the ground-state and transition-state interactions (cf. eq 6). Thus,

$$\frac{\text{major product}}{\text{minor product}} = K\frac{k_{eq}}{k_{ax}} \text{ (cf. Scheme III)} \qquad (6)$$

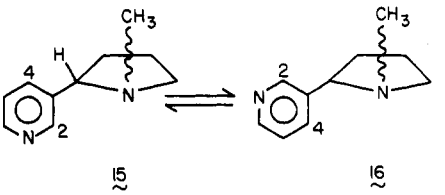
a priori, one cannot easily speculate which of two interactions will be more sterically demanding, those involving the attacking reagent or those involving the already bonded nitrogen substituent. The answer requires a detailed evaluation of the individual reaction rate constants, k_{eq} and k_{ax}, along with K.

Katritzky has shown that the rate constant for equatorial iodomethylation of *N*-methyltropane is significantly faster than equatorial alkylation of 1-methyl-4-phenylpiperidine while axial tropane alkylation is slower than that for this piperidine.[27] This suggests that equatorial tropane iodomethylation has an earlier transition state and less advanced charge separation than axial tropane alkylation. An earlier equatorial transition state implies that the iodomethane moiety would have a small net effective size in the equatorial transition state while it would have a larger effective size in the axial transition state. This phenomenon would have no effect on K, the ground-state equilibrium constant of the tropane-free base invertomers, but would have a significant effect on k_{ax}/k_{eq}, decreasing the ratio of rate constants by the greater net effective size of the iodomethane moiety in the axial transition state.

Scheme IV



Ring–Ring Stereoelectronic Effects. Nicotine exists in two energy minima illustrated by **15** and **16** in which the plane of the two rings are perpendicular.[1,16,29,30] We were interested in determining if any difference in chemical properties could be ascribed to the two major conformations $(N\text{–}N')_{syn}$ and $(N\text{–}N')_{anti}$, **15** and **16**, respectively. We considered one approach to this subject, namely, an evaluation of the alkylation stereoselectivity of the methylated nicotinoids.



15 **16**

INDO calculations[1] support conclusions based on molecular models that, for any nicotine analogue having a methyl group at C_2 and/or C_4, significant nonbonded interactions occur between the pyridine methyl moiety and the cis pyrrolidine nitrogen substituent (either the *N*-methyl group or the $N^{\delta+}\cdots CH_3\cdots I^{\delta-}$ group in the transition state). This would imply that $(N\text{–}N')_{syn}$ orientations would be less stable than $(N\text{–}N')_{anti}$ orientations for 2-methylnicotine, and the reverse would be obtained for 4-methylnicotine (cf. Scheme IV). On the basis of Winstein–Holness considerations (eq 1),[13] the alkylation kinetics and hence the alkylation stereoselectivity would be affected by the population of each of the reactive forms. We were interested in determining if biasing in favor of, or against, the $(N\cdots N')_{anti}$ conformations would have an observable effect on the N'_{cis}/N'_{trans} ratio. Full analysis of the effect of these interactions on nicotine iodomethylation would require consideration of the time course of alkylation over all conformational changes and is beyond the scope of the present work. However, we have shown that structural variations in the aryl group of 1-methyl-2-arylpyrrolidines can effect N'-alkylation stereoselectivity and reactivity.[31]

The N'_{cis}/N'_{trans} ratio for 2-methylnicotine (**2**) is identical, within experimental error, with that found for 4-methylnicotine (**3**). Because 4-methylnicotine alkylates preferentially at the pyridine nitrogen, however, the absolute values of N'_{cis} and N'_{trans} were low for **3**. We therefore wanted to examine the N'_{cis}/N'_{trans} ratio for an-

(22) For results pertinent to the conformations of tropane compounds, see: (a) Schneider, H.-J.; Sturm, L. *Agnew. Chem., Int. Ed. Engl.* **1976**, *15*, 545; (b) Closs, G. L. *J. Am. Chem. Soc.* **1959** *81*, 5456; (c) Appleton, D. C.; McKenna, J.; McKenna, J. M.; Sims, L. B.; Walley, A. R. *Ibid.* **1976**, *98*, 292.

(23) For reviews of tropane alkylations, see: (a) Fodor, G.; Frehel, D.; Cooper, M. J.; Mandava, N. In "Conformational Analysis"; Chiurdoglu, G., Ed.; Academic Press: New York 1971; pp 73–91; (b) Bottini, A. T. In "Selective Organic Transformations"; Thyagarajan, B. S., Ed.; Wiley: New York, 1970; Vol. 1, pp 89–142. See also: (c) Fodor, G.; Medina, J. D.; Mandava, N. *Chem. Commun.* **1968**, 581; (d) Fodor, G.; Chastain, R. V., Jr.; Frehel, D.; Cooper, M. J.; Mandava, N.; Gooden, E. L. *J. Am. Chem. Soc.* 1971, *93*, 403.

(24) For another example of an unusual alkylation stereoselectivity which can be analyzed using these concepts, see: Gassman, P. G.; Heckert, D. C. *Tetrahedron* **1965**, *21*, 2725.

(25) Another example which seemingly contradicts the piperidine alkylation literature[18] but may be rationalized by consideration of alternate conformations is found in: Iorio, M. A.; Casy, A. F. *Gazz. Chim. Ital.* **1974**, *104*, 1243.

(26) Otzenberger, R. D.; Lipkowitz, K. B.; Mundy, B. P. *J. Org. Chem.* **1974**, *39*, 319.

(27) Jones, R. A. Y.; Katritzky, A. R.; Mente, P. G. *J. Chem. Soc. B* **1970**, 1210.

(28) Simpson, T. R., Jr.; Craig, J. C.; Kumler, W. D. *J. Pharm. Sci.* **1967**, *56*, 708.

(29) Ohashi, M.; Morishima, I.; Yonezawa, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 576.

(30) (a) Koo, C. H.; Kim, H. S. *Taehan Hwahakhoe Chi.* **1965**, *9*, 134; *Chem. Abstr.* **1965**, *65*, 6431e. (b) Chothia, C.; Pauling, P. *Proc. Natl. Acad. Sci. U.S.A.* **1970**, *65*, 477. (c) Kim, H. S.; Jeffrey, G. A. *Acta Crystallogr. Sect. B* **1971**, *B27*, 1123.

(31) Seeman, J. I.; Whidby, J. F. Centennial Meeting of the American Chemical Society, San Francisco, CA, Sept 3, 1976; American Chemical Society: Washington, DC; Abstr. No. ORGN 224.

other compound having a 4-methyl substituent but which alkylated to a greater extent at its pyrrolidine nitrogen. To solve this problem, 4,6-dimethylnicotine was prepared. We anticipated that the additional methyl group at C_6 would decrease the rate of pyridine alkylation without significantly affecting pyrrolidine alkylation (cf. the results for 6-methylnicotine and the discussion above), thereby allowing an estimate of the N'_{cis}/N'_{trans} ratio for 4-methylnicotine. In this event, alkylation of 4,6-dimethylnicotine did result in an increased N'/N ratio allowing an accurate measure of the N'_{cis}/N'_{trans} ratio.

As shown in Table III, the value of N'_{cis}/N'_{trans} for 2-methylnicotine was identical, within experimental error, with that found for 4,6-dimethylnicotine. Indeed, given the similarity of the N'_{cis}/N'_{trans} ratios found for the series 1–8, we are hesitant to suggest that any significant distinction can be made in the regioselectivity of pyrrolidine iodomethylation. Thus, for iodomethylation, no stereoelectronic controlling factor ascribable to N···N' orientation is observed.

Summary

This work has examined the effect of a variety of steric and conformational features on the alkylation chemistry of nicotine and nicotine analogues. Methyl groups at C_2 or C_4 of nicotine were found to substantially reduce the relative rate of pyrrolidine (N') alkylation. This result indicates significant ring–ring mobility in the alkylation transition states; i.e., the time constant for alkylation is longer than the time constant for ring–ring rotation. Methyl groups at C_4 and C_5 increase the relative rate of pyridine (N) alkylation but at C_2 and C_6 retard N alkylation. N'-Alkylation can occur cis and trans to the pyridine ring (N'_{cis} and N'_{trans}, respectively), and the ratio N'_{cis}/N'_{trans} is very similar, within experimental variation, for all the compounds studied. Since the value of $N'_{cis}/N'_{trans} = 1.5$ which is >1, the already bonded N'–CH_3 has a greater steric requirement than the $N'^{\delta+}\cdots CH_3\cdots I^{\delta-}$ in the alkylation transition state. Buttressing effects are observed in the case of 5,6-dimethylnicotine. Methyl groups at C_5 and C_6 appear to increase the rate of N'-alkylation relative to nicotine.

Experimental Section

Methods and Materials. ^1H and ^{13}C NMR spectra were obtained on either a Varian XL-100 NMR spectrometer equipped with a Digilab NMR-3 FT accessory or a Bruker WP-80 spectrometer operated in the FT mode. Infrared spectra were obtained on a Perkin-Elmer Model 283B or Model 621 spectrophotometer. Mass spectra were obtained on a Du Pont 21-490 GC/MS/DS. All reactions were run under a dry nitrogen atmosphere. Gas chromatography was carried out on a Bendix 2300 instrument using 5 ft × 0.25 in. stainless-steel columns packed with 5% SE-30 on Chromosorb G-HP. Microanalyses were performed by Galbraith Laboratories. TLC analyses were run on silica gel GF plates by using $CHCl_3/EtOH/NH_4OH$ (85:14:1). The following compounds were obtained commercially: 6-methylnicotinic acid (Ash-Stevens), 5-methylnicotinonitrile (Reilly Tar & Chemical Corp.).

Methyl 6-Methylnicotinate.[32] 6-Methylnicotinic acid (50 g, 0.375 mol) was added to a refluxing solution of 25 mL of concentrated sulfuric acid in 250 mL of methanol and stirred at reflux for 3 h. An additional 250 mL of methanol was added, and the resultant mixture was heated at reflux for an additional 18 h. The reaction mixture was allowed to cool and was concentrated under vacuum to a slurry which was added to a cold solution of 80 g of sodium bicarbonate in 450 mL of water. Further concentration removed most of the methanol. The resultant turbid mixture was extracted with methylene chloride, and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated, giving 43.5 g of a tan oil which was distilled; bp 94–95 °C (ca. 20 torr). The material crystallized on being allowed to stand: mp 32–33 °C (lit.[32] mp 32 °C); ^1H NMR ($CDCl_3$) δ 9.08 (d, J = 2.5 Hz, 1), 8.13 (dd, J = 10, 2.5 Hz, 1), 7.28 (d, J = 10 Hz, 1), 3.93 (s, 3), 2.62 (s, 3).

6-Methylmyosmine. To a solution of 46.5 mL (0.33 mol) of diisopropylamine in 500 mL of ether under nitrogen at −70 °C was added 113 mL (0.247 mol) of n-butyllithium in hexane.[33a] To the prepared lithium diisopropylamide (LDA) was added 41.5 mL (0.265 mol) of N-(trimethylsilyl)pyrrolidinone, and the solution was stirred at −70 °C for 15 min. To this solution was then added 25.0 g (0.165 mol) of methyl 6-methylnicotinate with 25 mL of ether. The resultant yellow mixture was allowed to gradually warm to room temperature and stirred as such overnight. The mixture was cooled in an ice bath, and 33 mL of water was added. The ether layer was decanted, additional ether was added, and the decantion process was repeated two more times. To the aqueous layer was added 165 mL of concentrated HCl and the resultant solution refluxed overnight. The acidic solution was washed with ether, concentrated on the rotary evaporator, cooled in an ice bath, and basified with 50% aqueous KOH. The aqueous mixture was extracted with ether (3 × 150 mL), and the combined ether layers were dried (Na_2SO_4) and evaporated to give 18.49 g of yellow solid. Distillation of this material afforded 16.4 g (62%) of light yellow, solid 6-methylmyosmine, bp 85–87 °C (0.03 torr). Recrystallization from ethyl acetate afforded an analytical sample: mp 75–76 °C; ^1H NMR ($CDCl_3$) δ 8.83 (d, J = 2 Hz, 1), 8.01 (dd, J = 8, 2 Hz, 1), 7.15 (d, J = 8 Hz, 1), 4.03 (m, 2), 2.89 (m, 2), 2.58 (s, 3), 2.0 (m, 2).

Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.49. Found: C, 74.83; H, 7.64; N, 17.27.

6-Methylnornicotine. To a solution of 12.58 g (0.0783 mol) of 6-methylmyosmine, 8.1 g (0.129 mol) of sodium cyanoborohydride, and a trace of bromocresol green indicator in 500 mL of methanol under nitrogen was added enough 2 N HCl/methanol such that the color of the solution turned from blue to yellow. As the color reverted to blue, additional acid was added to effect the change back to yellow. This process was repeated until the color remained yellow. The solution was allowed to stir for several hours, and 6 N aqueous HCl was then added to destroy excess sodium cyanoborohydride. The mixture was concentrated and basified. Routine ether extraction and workup afforded the crude product. Distillation provided 12.01 g (94%) of 6-methylnornicotine as a colorless oil: bp 80–82 °C (0.025 torr); dipicrate, mp 182–183 °C; ^1H NMR ($CDCl_3$) δ 8.43 (d, J = 2 Hz, 1), 7.55 (dd, J = 8, 2 Hz, 1), 7.03 (d, J = 8 Hz, 1), 4.03 (t, J = 7 Hz, 1), 2.78–3.28 (m, 2), 2.49 (s, 3), 2.08 (br s, NH, 1), 1.33–2.25 (m, 4).

Anal. Calcd for $C_{22}H_{20}N_8O_{14}$ (dipicrate): C, 42.59; H, 3.25; N, 18.06. Found: C, 42.69; H, 3.24; N, 18.07.

6-Methylnicotine (5). A mixture of 4.35 g (0.0269 mol) of 6-methylnicotine, 7 mL of 40% aqueous formaldehyde, and 8 mL of formic acid was heated at reflux for 12 h under nitrogen. After the mixture cooled, 2.0 mL of concentrated hydrochloric acid was added, and the mixture was concentrated. After being washed with ether, the aqueous layer was basified with 10 mL of 50% aqueous potassium hydroxide and extracted with ether (twice) and methylene chloride (once). The combined organic layers were dried (sodium sulfate) and evaporated to an oil. Distillation afforded 3.83 g (81%) of 6-methylnicotine: bp 63–65 °C (0.025 torr); ^1H NMR ($CDCl_3$) δ 8.43 (d, J = 2 Hz, 1), 7.58 (dd, J = 8, 2 Hz, 1), 7.08 (d, J = 8 Hz, 1), 3.03 (t, J = 8 Hz, 1), 3.1–3.09 (m, 1), 2.53 (s, 3), 2.14 (s, 3), 1.5–2.43 (m, 5).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.06; H, 9.20; N, 15.83.

The method of Borch[33b] was also successfully utilized to prepare 6-methylnicotine (5) from 6-methylnornicotine. Haglid reported an alternative preparation of 6-methylnicotine from the radical methylation of nicotine.[3a,b] This procedure results in a mixture of 2-methyl-, 4-methyl-, and 6-methylnicotine as well as unreacted starting material. To date, there is no report of a preparative

(32) Campbell, A. D.; Chan, E.; Chooi, S. Y.; Deady, L. W.; Shanks, R. A. *Aust. J. Chem.* **1971**, *24*, 377.

(33) (a) This condensation reaction is modeled after: Hu, M. W.; Bondinell, W. E.; Hoffmann, D. *J. Labelled Compd.* **1974**, *10*, 79; (b) Borsch, E. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673.

procedure for the isolation of large quantities of pure 6-methylnicotine from this mixture.

4-Methylnicotine (3) was prepared from methyl 4-methylnicotinate[34] by the same procedure shown above for 6-methylnicotine. This compound was spectrally identical with that reported in the literature.[3c]

Methyl 5-Methylnicotinate.[35] 5-Methylnicotinonitrile (57.07 g, 0.5 mol) was added to 125 mL of water containing 210 mL of concentrated sulfuric acid. The resulting mixture was heated at 130 °C for 18 h and allowed to cool to 65 °C, at which point 450 mL of methanol was added over a 1.5-h period. The resulting mixture was held at 65 °C for 6.5 h, allowed to cool to room temperature slowly, and added with cooling to 200 mL of water containing 450 g of sodium bicarbonate. After there was no further gas evolution, the mixture was extracted five times with 250 mL of ether, and the combined ethereal layers were dried ($MgSO_4$) and concentrated. The residue was recrystallized from boiling pentane, yielding 60 g of methyl 5-methylnicotinate: mp 47–48 °C (lit.[35] mp 45–46 °C); ^1H NMR ($CDCl_3$) δ 9.08 (d, J = 2 Hz, 1), 8.66 (d, J = 2 Hz, 1), 8.16 (m, 1), 3.98 (s, 3), 2.44 (d, J = 0.5 Hz).

Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.69; H, 5.98; N, 9.28.

5-Methylnicotine (4) was prepared from methyl 5-methylnicotinate by the same procedure shown above for 6-methylnicotine: ^1H NMR ($CDCl_3$) δ 8.34 (m (approximate d), J = 2 Hz, 2), 7.53 (t (barely resolved), 1), 3.05 (t, J = 7 Hz, 1), 2.93–3.4 (m, 1), 2.34 (s, 3), 2.19 (s, 3), 1.44–2.5 (m, 5).

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.95; H, 9.15; N, 15.90. Found: C, 74.98; H, 9.50; N, 16.04.

Methyl 4,6-Dimethylnicotinate. A solution containing 125 mL of water, 210 mL of concentrated sulfuric acid, and 80 g of 4,6-dimethylnicotinonitrile[36] was heated at reflux for 18 h. The reaction mixture was cooled to 50 °C, and 450 mL of methanol was added over 2 h. The resultant solution was heated at 65 °C for 6.5 h, allowed to cool slowly overnight, and added to 1 L of water containing 300 g of sodium bicarbonate. Additional potassium carbonate was added until the mixture was alkaline. The resulting mixture was extracted with ether, and the combined ethereal layers were dried ($MgSO_4$) and concentrated under vacuum to yield 55.06 g of a yellow solid, which afforded 49.30 g of product on distillation; bp 53–60 °C (0.005 mm). The distillate spontaneously crystallized: mp 44–45 °C; ^1H NMR δ ($CDCl_3$) 8.96 (br s, 1), 7.02 (br s, 1), 3.95 (s, 3), 2.62 (s, 3), 2.59 (s, 3); IR (Nujol) 1720, 1285 (aryl ester), 1600, 1485, 1444 (aromatic ring), 2925 and 2855 cm^{-1} (aromatic CH_3).

Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.75; H, 6.91; N, 8.52.

4,6-Dimethylnicotine (7) was prepared from methyl 4,6-dimethylnicotinate by the same procedure discussed in detail for 6-methylnicotine: dipicrate, mp 240–241 °C; ^1H NMR ($CDCl_3$) δ 8.56 (s, 1), 6.90 (s, 1), 3.09–3.43 (m, 2), 2.49 (s, 3), 2.30 (s, 3), 2.19 (s, 3), 1.50–2.44 (m, 5).

Anal. Calcd for $C_{12}H_{18}N_2$: C, 75.74; H, 9.53; N, 14.72. Found: C, 75.58; H, 9.65; N, 14.52.

Ethyl β-Amino-α-methylcrotonate. A mixture of 30 g (0.208 mol) of ethyl 2-methylacetoacetate (Aldrich) and 50 mL of 28% aqueous ammonium hydroxide was stirred for 16 h at room temperature. The mixture was cooled in an ice bath, and the white, crystalline product was filtered, washed with water, and air-dried. Recrystallization from hexane afforded 9.49 g (32%) of product: mp 47.5–49.5 °C; ^1H NMR ($CDCl_3$) δ 5.0–7.13 (br, NH_2, 2), 4.13 (q, J = 7 Hz, 2), 1.93 (s, 3), 1.75 (s, 3), 1.28 (t, J = 7 Hz, 3).

Ethyl 2,4-Dihydroxy-5,6-dimethylnicotinate. To a solution of 0.098 mol of sodium ethoxide in ethanol (prepared from 2.25 g of sodium in 50 mL of ethanol) in a Teflon-lined 125-mL capacity Parr bomb was added 14.5 mL (0.0955 mol) of diethyl malonate. To this was added 13.65 g (0.0955 mol) of ethyl β-amino-α-methylcrotonate. The bomb was sealed and heated in an oven at 140 °C for 9 h. The solid sodium salt of the product was filtered, washed with ethanol and ether, and air-dried. The material was then dissolved in water and acidified with acetic acid. The resultant white solid was filtered, washed with water, and oven dried to yield 10.16 g (51%) of product: mp 216–221 °C (lit.[37] mp 222 °C); ^1H NMR ($CDCl_3$) δ 13.68 (br s, D_2O exchangeable H, 1), 12.53 (br s, D_2O exchangeable H, 1), 4.43 (q, J = 7 Hz, 2), 2.35 (s, 3), 1.98 (s, 3), 1.44 (t, J = 7 Hz, 3).

Ethyl 2,6-Dichloro-5,6-dimethylnicotinate. A mixture of 10.16 g (0.048 mol) of ethyl 2,4-dihydroxy-5,6-dimethylnicotinate and 53 mL (0.576 mol) of phosphorus oxychloride was heated in a 125-mL capacity Teflon-lined Parr bomb at 120 °C for 6 h. The mixture was concentrated to a small volume, and 100 mL of absolute ethanol was added. After being refluxed for 1 h, the solution was concentrated, and to it was carefully added 200 mL of saturated aqueous sodium bicarbonate. The mixture was extracted with chloroform (2 × 100 mL), and the combined extracts were washed with 50 mL of saturated aqueous sodium chloride. Evaporation of the chloroform afforded a solid which was crystallized from 95% ethanol. A second crop was obtained from the mother liquor to give a combined yield of 8.25 g (69%) of product, mp 83–86 °C. Recrystallization gave an analytical sample: mp 87–88 °C; ^1H NMR ($CDCl_3$) δ 4.46 (q, J = 7 Hz, 2), 2.56 (s, 3), 2.35 (s, 3), 1.41 (t, J = 7 Hz, 3); IR ($CHCl_3$) 1740 cm^{-1}; electron-impact mass spectrum, m/e 247, 249 (M^+).

Anal. Calcd for $C_{10}H_{11}Cl_2NO_2$: C, 48.41; H, 4.47; Cl, 28.58; N, 5.65. Found: C, 48.49; H, 4.31; Cl, 28.76; N, 5.63.

Ethyl 5,6-Dimethylnicotinate. A mixture of 8.25 g (0.0333 mol) of ethyl 2,6-dichloro-5,6-dimethylnicotinate, 2.373 g (0.0134 mol) of palladium chloride, 7.0 g (0.0854 mol) of sodium acetate, and 120 mL of absolute ethanol was shaken with hydrogen at 50 psi in a Parr apparatus for 22 h. The mixture was filtered through Celite and evaporated, and the resulting residue was dissolved in 100 mL of ether and washed with saturated aqueous sodium bicarbonate (2 × 50 mL) and 50 mL of saturated aqueous sodium chloride. The ethereal layer was dried (magnesium sulfate) and evaporated to a clear, lightly colored oil. Bulb to bulb distillation [oven temperature 85–95 °C (0.1 torr)] afforded 4.49 g (75%) of product as a clear, colorless oil: picrate, mp 180–182 °C; ^1H NMR ($CDCl_3$) δ 8.94 (d, J = 2 Hz, 1), 8.01 (d, J = 2 Hz, 1), 4.39 (q, J = 7 Hz, 2), 2.56 (s, 3), 2.34 (s, 3), 1.4 (t, J = 7 Hz, 3); IR (film) 1722 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}N_4O_9$ (picrate): C, 47.07; H, 3.95; N, 13.72. Found: C, 47.04; H, 4.08; N, 13.72.

5,6-Dimethylnicotine (8) was prepared from ethyl 5,6-dimethylnicotinate by the same procedure discussed in detail for 6-methylnicotine: dipicrate, mp 235–240 °C dec; ^1H NMR ($CDCl_3$) δ 8.23 (d, J = 2 Hz, 1), 7.44 (d, J = 2 Hz, 1), 3.25 (m, 1), 3.01 (t, J = 8 Hz, 1), 2.49 (s, 3), 2.28 (s, 3), 2.15 (s, 3), 1.50–2.56 (m, 5).

Anal. Calcd for $C_{24}H_{24}N_8O_{14}$ (dipicrate): C, 44.45; H, 3.73; N, 17.28. Found: C, 44.59; H, 3.75; N, 17.03.

2-Methylnicotine (2) and 2,6-Dimethylnicotine (6). Each of these compounds was prepared by a [2,3]-sigmatropic rearrangement of the corresponding 1-methyl-1-1(2-picolyl)-2-cyanopyrrolidinium halide as previously reported.[4b]

Product Ratio Alkylation Experiments. Typically, 10–25 mg of 1–8 was dissolved in ca. 0.2 mL of anhydrous acetonitrile-d_3 in an NMR tube. Following equilibration at 25.00 ± 0.01 °C, a solution of iodomethane-^{13}C (**Caution**: cancer suspect agent!) in acetonitrile-d_3 was added via syringe to the equilibrated amine solution. The resultant mixture was allowed to stand at 25.00 ± 0.01 °C for >14 h before NMR analysis. Because of the potential for different relaxation rates, a delay period of >6 s (usually 8–20 s) was used between successive acquisitions. In order to be certain that the ^{13}C NMR integrations accurately reflected the stereochemistry of the alkylations, we examined each iodomethylation experiment using at least two different delay times, including 10 and 20 s. The integrations obtained for these two delay times were statistically indistinguishable. Figure 3 (see supplementary material) illustrates the spectra obtained for the alkylation of nicotine by using a delay time of 10 and 20 s; subtraction of one spectrum from the other (the difference spectrum

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of these two spectra, also shown in Figure 3) results in a spectrum indistinguishable from the baseline. To further assure meaningful results, a pulse flip angle of ca. 30° was chosen in the integration experiment. As shown by eq 7, the observed intensity is related

$$M_\tau = M_0 \frac{1 - \exp(-\tau/T_1)}{1 - \exp(-\tau/T_1)\cos\alpha} \quad (7)$$

to both the delay time (τ) and the pulse flip angle (α), where M_τ is the measured intensity and M_0 is the absolute intensity.[38] Table V (see supplementary material) lists the ratio M_τ/M_0 for delay times of 1–5 T_1's and pulse flip angles of 4–90 s. These experiments indicate that the data reported in Table III are valid.[39] Typically 100 acquisitions were collected for each spectrum, and at least three (averaging nine throughout this work) alkylations were performed for each compound. The deviations were typically less than 10%. ^1H and ^{13}C NMR spectra were obtained for each alkylation reaction, and excellent correlations were observed for the two methods.

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Registry No. 1, 54-11-5; 1 *N*-methyl iodide derivative, 77647-89-3; 1 *cis*-*N'*-methyl iodide derivative, 77647-90-6; 1 *trans*-*N'*-methyl iodide derivative, 77647-91-7; 2, 77698-47-6; 2 *N*-methyliodide derivative, 77629-25-5; 2 *cis*-*N'*-methyl iodide derivative, 77629-26-6; 2 *trans*-*N'*-methyl iodide derivative, 77629-27-7; 3, 13270-57-0; 3 *N*-methyl iodide derivative, 77629-28-8; 3 *cis*-*N'*-methyl iodide derivative, 77629-29-9; 3 *trans*-*N'*-methyl iodide derivative, 77629-30-2; 4, 77629-31-3; 4 *N*-methyl iodide derivative, 77629-32-4; 4 *cis*-*N'*-methyl iodide derivative, 77629-33-5; 4 *trans*-*N'*-methyl iodide derivative, 77629-34-6; 5, 13270-56-9; 5 *N*-methyl iodide derivative, 77629-35-7; 5 *cis*-*N'*-methyl iodide derivative, 77629-36-8; 5 *trans*-*N'*-methyl iodide derivative, 77629-37-9; 6, 77698-94-3; 6 *cis*-*N'*-methyl iodide derivative, 77629-38-0; 6 *trans*-*N'*-methyl iodide derivative, 77629-39-1; 7, 77629-40-4; 7 *N*-methyl iodide derivative, 77629-41-5; 7 *cis*-*N'*-methyl iodide derivative, 77629-42-6; 7 *trans*-*N'*-methyl iodide derivative, 77629-43-7; 8, 77629-44-8; 8 *N*-methyl iodide derivative, 77629-45-9; 8 *cis*-*N'*-methyl iodide derivative, 77629-46-0; 8 *trans*-*N'*-methyl iodide derivative, 77629-47-1; 8 dipicrate, 77629-48-2; methyl 6-methylnicotinate, 5470-70-2; 6-methylnicotinic acid, 3222-47-7; *N*-(trimethylsilyl)pyrrolidinone, 14468-90-7; 6-methylmyosmine, 77629-49-3; 6-methylnornicotine, 77629-50-6; 6-methylnornicotine dipicrate, 77647-92-8; methyl 4-methylnicotinate, 33402-75-4; 5-methylnicotinonitrile, 42885-14-3; methyl 5-methylnicotinate, 29681-45-6; methyl 4,6-dimethylnicotinate, 69971-44-4; 4,6-dimethylnicotinonitrile, 6623-21-8; ethyl β-amino-α-methylcrotonate, 14369-90-5; ethyl 2-methylacetoacetate, 609-14-3; ethyl 2,4-dihydroxy-5,6-dimethylnicotinate, 77629-51-7; diethyl malonate, 105-53-3; ethyl 2,4-dichloro-5,6-dimethylnicotinate, 77629-52-8; ethyl 5,6-dimethylnicotinate, 77629-53-9; ethyl 5,6-dimethylnicotinate picrate, 77629-54-0.

Supplementary Material Available: Table V (normalized ^{13}C intensity as a function of pulse flip angle and delay time) and Figure 3 (^{13}C NMR spectrum of the reaction mixture of nicotine and 0.75 equiv of $^{13}CH_3I$) (4 pages). Ordering information is given on any current masthead page.

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(39) For a pulse flip angle of 30°, Table V indicates that 97.95% of the intensity of the ^{13}C resonance will be measured by using a delay time of $2T_1$. Of course, longer delay times will increase the normalized measured intensity relative to 100%. Preliminary results (obtained with Dr. J. Wooten) indicate that the quaternary pyrrolidine methyl carbon T_1's are ca. 1.5 and the pyridine methiodine methyl carbon T_1's are ca. 4 s. We estimate that our integrations incorporate 98–99.9% of the theoretical areas.

Rates and Mechanism of the Alkaline Hydrolysis of a Sterically Hindered Phosphinate Ester. Partial Reaction by Nucleophilic Attack at Carbon[1]

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The alkaline hydrolysis of the sterically hindered phosphinate ester, methyl diisopropylphosphinate, has been studied in water. At 100 °C, the rate constant is 5.3×10^{-5} M^{-1} s^{-1}, $\Delta S^* = -15$ gibbs, and $\Delta H^* = 23.6$ kcal/mol. Mass spectrometric and NMR determination of the point of reaction in oxygen-18 labeled water indicates that there is approximately 75% attack of hydroxide ion at the phosphorus atom, resulting in cleavage of the P–O bond, and 25% attack at the methyl carbon, resulting in cleavage of the C–O bond.

Although dissociative, unimolecular mechanisms have been observed in displacements at phosphorus through metaphosphate intermediates,[2-5] associative reactions are greatly preferred. We observed that phosphinic acids, R_2PO_2H, do not form phosphinylium ions, R_2PO^+, in sulfuric acid or oleum,[6] conditions under which carboxylic acids form acylium ions.[7] In a solvolytic study of phosphinyl chlorides, $R_2P(O)Cl$, we found clear evidence for associative mechanisms of reaction except for di-*tert*-butylphosphinyl chloride which reacts exceedingly slowly by a unimolecular mechanism;[8] in this case, the associative pathway for reaction appears to be ruled out by the high steric hindrance around the phosphorus atom. The high preference for associative reactions appears to be a result of the weak multiple bonds to phosphorus in a unimo-

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