Isomeric Nicotines. Their Solution Conformation and Proton, Deuterium, Carbon-13, and Nitrogen-15 Nuclear Magnetic Resonance

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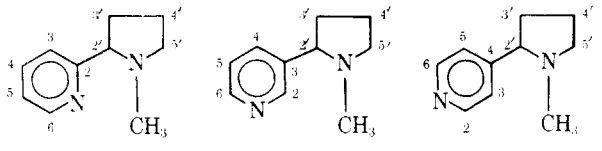
Complete ^1H, ^{13}C, and ^{15}N assignments are presented for 2-nicotine (**2**) and 4-nicotine (**4**) as well as ^2H assignments of selectively deuterated **2** and **4** derivatives. The ^2H chemical shifts of the deuterated derivatives allow assignment of ^1H resonances to specific protons and provide starting chemical shifts for analysis of the severely overlapping pyrrolidine ^1H resonances. The three-, four-, and five-spin pyrrolidine ^1H spectra of these analogues are less complex to analyze than the corresponding seven-spin spectra of **2** and **4**. The Karplus parameters obtained from the ^1H analyses indicate an envelope conformation for both **2** and **4**. Analysis of the long-range coupling constants between H(2′) and the pyridine protons suggests a perpendicular spatial arrangement of the pyridine and pyrrolidine rings for both **2** and **4**. A comparison is made between the solution conformations of **2** and **4** and the conformation of 3-nicotine (**3**).

An essential component of the continuing effort to relate the structure and conformation of biomolecules to their physiological function has been the study of the effect of altering molecular structure upon physiological activity. Thus, whereas 3-nicotine (**3**)[1] exhibits cholinergic activity, this property is either severely attenuated or lacking entirely for 2-nicotine (**2**) or 4-nicotine (**4**).[2] Since the nicotinic receptor very likely requires a precise spatial arrangement for the atoms of the binding molecule, the loss in activity of **2** and **4**



2 **3** **4**

could be explained by changes in location within the molecular framework of atoms responsible for binding at the active site, or alternatively by conformational or electronic changes induced by the structural variations. In this paper we compare the solution conformation of **2, 3, and 4,** to determine if the variation in activity is reflected in conformations.

In a previous paper we examined the conformation of **3** by ^1H and ^2H NMR.[3] Analysis of the pyrrolidine ^1H resonances in terms of a Karplus dihedral angle relationship[4,5] revealed that the principal solution conformer is one in which the five-membered ring assumes an envelope conformation. The long-range coupling constants between H(2′) and the pyridine protons are consistent with a perpendicular arrangement of the pyridine and pyrrolidine rings, the C(2′)–H(2′) bond and the pyridine moiety being coplanar.

We adopt a similar approach in the present study to interpret the conformation of **2** and **4** in terms of ^1H spectral parameters. In addition ^{13}C and ^{15}N NMR assignments for **2** and **4** as well as ^2H assignments for selectivity deuterated analogues are presented.

Experimental Section

^1H (100 MHz), ^2H (15.4 MHz), ^{13}C (25.2 MHz), and ^{15}N (10.1 MHz) NMR spectra were obtained with a Varian XL-100 equipped with the Gyrocode Observe option and operating in the pulse-Fourier transform mode. The spectrometer utilizes a Digilab data system and pulse programmer. All samples were 0.205 (±1%) molal in $CDCl_3$ (Stohler) except those for ^{15}N which were neat. ^1H and ^{13}C spectra of **2** and **4** were obtained with 5-mm tubes (Wilmad). The selectively deuterated samples for ^1H and ^2H (50 transients) NMR were trapped from a Bendix Model 2300 gas chromatograph directly in 2-mm NMR capillaries (Wilmad); the appropriate weight of $CDCl_3$ was added to the capillary; and then the capillary was flushed with N_2 and sealed. ^1H and ^{13}C spectra are referenced to internal tetramethylsilane (Me_4Si). The deuterium resonance of $CDCl_3$ serves as a secondary chemical shift reference in ^2H NMR spectra; the chemical shift of this deuteron (7.30 ppm) was determined by measuring the ^1H chemical shift of the corresponding proton of the residual $CHCl_3$ in the same sample.[6] Field/frequency stabilization was provided by a ^2H internal solvent lock for ^1H and ^{13}C spectra of **2** and **4**, and by a ^{19}F external lock for ^2H and ^1H spectra of samples in 2-mm tubes. ^{15}N spectra were obtained in 12-mm tubes with a D_2O capillary providing the external lock. ^{15}N chemical shifts are referenced to neat CH_3NO_2[7] whose resonance position was determined using the same D_2O lock system at identical spectrometer frequency settings.

^1H NMR spectra were analyzed with the LAOCOON-3 computer program. The maximum standard deviations in the chemical shifts and coupling constants of fitted spectra were 0.17 Hz for the pyrrolidine protons and 0.02 Hz for the pyridine protons. These deviations are larger than obtained in the previous study, because the broad ^{19}F external lock allowed some field drift during accumulation of spectra.

The syntheses of **2, 4,** and their selectively deuterated analogues have been reported.[8]

Results

^{13}C assignments for **3** in $CDCl_3$ have been reported.[9,10] We have confirmed these assignments at 0.2 m (Table I). The pyrrolidine ^{13}C resonances of **2** and **4** can be assigned readily by analogy with those resonances of **3**.

The pyridine C(2), C(4), and C(6) resonances of **2** can be assigned by analogy with 2-picoline,[11] since these peaks are well separated (Table I). However, the C(3) and C(5) resonances nearly overlap, so chemical shift analogies cannot be used. In cases such as this, we have used the assignment technique of selective long-range ^1H decoupling.[10] By comparison with 2-picoline,[12] the coupling between C(3) and H(2′) should be significant, whereas the coupling between C(5) and H(2′) should be very small. Upon selective irradiation of H(2′),

Table I. ^{13}C NMR Chemical Shifts[a]

	2-nicotine (**2**)[c]	3-nicotine (**3**)[b,d]	4-nicotine (**4**)[e]
C(2)	162.45	149.37	149.69
C(3)	121.28	138.61	122.41
C(4)	136.40	134.57	152.76
C(5)	121.88	123.33	122.41
C(6)	148.94	148.40	149.69
C(2′)	72.32	68.82	70.27
C(3′)	33.63	35.24	35.19
C(4′)	22.87	22.65	22.81
C(5′)	56.93	56.93	56.98
CH_3	40.46	40.30	40.52

[a] ppm downfield from Me_4Si. [b] References 9 and 10. [c] Registry no., 23950-04-1. [d] Registry no. 54-11-5. [e] Registry no. 5860-66-2.

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Table II. ^{15}N NMR Chemical Shifts[a]

	2-nicotine	3-nicotine[b]	4-nicotine
pyridine nitrogen	−63.6	−60.9	−64.5
pyrrolidine nitrogen	−330.1	−327.6	−329.4

[a] ppm relative to external CH_3NO_2. The negative sign indicates upfield shift.[7] [b] Measured previously by R. L. Lichter and J. D. Roberts.[13]

Table III. Pyridine ^1H Spectral Parameters of 2-Nicotine and 4-Nicotine

2-Nicotine

		coupling constants, Hz			
	σ, ppm	H(4)	H(5)	H(6)	H(2′)
H(3)	7.425	7.90	1.22	0.96	−0.32
H(4)	7.644		7.53	1.72	0.29
H(5)	7.135			4.91	−0.24
H(6)	8.548				0.0

4-Nicotine

		coupling constants, Hz			
	σ, ppm	H(3)	H(5)	H(6)	H(2′)
H(2)	8.537	5.09	0.95	0.0	0.20
H(3)	7.277		1.61	0.95	−0.52
H(5)	7.277			5.09	−0.52
H(6)	8.537				0.20

Table IV. Pyrrolidine ^1H and ^2H Chemical Shifts (ppm) of 2-Nicotine

		^1H		
	^2H	2-nicotine-3′,3′-d_2[b]	2-nicotine-4′,4′-d_2[c]	2-nicotine-5′,5′-d_2[d]
2′	3.32		3.321	3.316
$3'_a$[a]	1.85		1.837	1.845
$3'_b$	2.28		2.262	2.275
$4'_a$	1.85	1.814		1.822
$4'_b$	1.97	1.954		1.962
$5'_a$	2.41	2.356	2.363	
$5'_b$	3.27	3.252	3.251	
CH_3	2.23	2.241	2.246	2.241

[a] Subscripts a and b refer respectively to high-field and low-field chemical shifts of protons attached to a specific carbon. [b] Registry no., 68582-53-6. [c] Registry no. 68582-54-7. [d] Registry no., 68582-55-8.

Table V. Pyrrolidine ^1H Coupling Constants (Hz) of 2-Nicotine[d]

	$3'_a$	$3'_b$	$4'_a$	$4'_b$	$5'_a$	$5'_b$
2′	8.23[c] 8.45[b]	8.16[c] 8.30[b]	—	—	—	0.50
$3'_a$	- - -	−12.60[c] −12.81[b]	5.48	10.60	—	—
$3'_b$	- - -	- - -	9.29	5.40	—	—
$4'_a$	- - -	- - -	- - -	−12.39[c] −12.30[a]	8.30	2.10
$4'_b$	- - -	- - -	- - -	- - -	9.68	8.15
$5'_a$	- - -	- - -	- - -	- - -	- - -	−8.98[b] −8.97[a]

[a] Measured for 2-nicotine-3′,3′-d_2. [b] Measured for 2-nicotine-4′,4′-d_2. [c] Measured for 2-nicotine-5′,5′-d_2. [d] — indicates long-range coupling constant not resolvable and - - - indicates table redundancy or same proton.

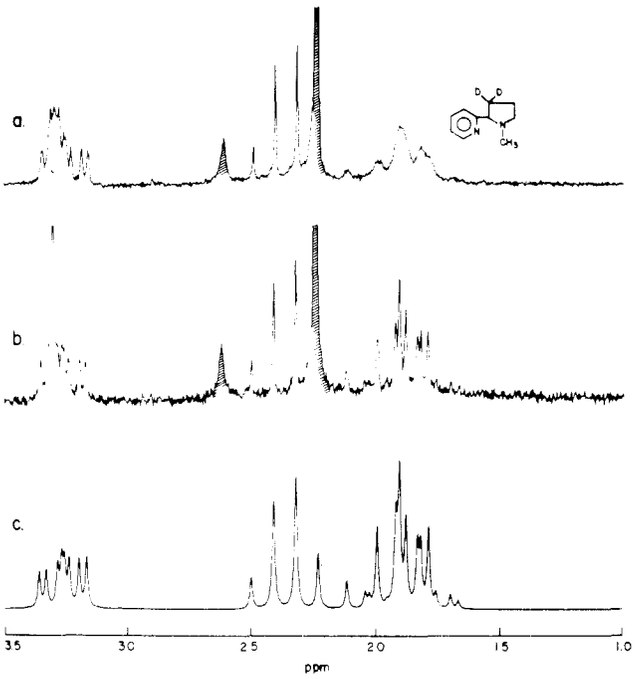


Figure 1. (a) Pyrrolidine ^1H resonances of 2-nicotine-3′,3′-d_2. (b) Deuterium decoupled spectrum. (c) Computer fitted spectrum minus CH_3 resonance.

we only see perturbation of the resonances of the upper field carbon, indicating that this carbon is C(3).

The pyridine C(2) and C(6) carbons of **4** are adjacent to the nitrogen and therefore resonate at lower field than C(3) and C(5) (Table I). The C(4) resonance is distinguished from the other aromatic peaks since it is lower in intensity; the resonance corresponds to only one carbon, and since it bears no directly attached proton, its spin–lattice relaxation time is increased and its nOe (nuclear Overhauser effect) is diminished.

^{15}N chemical shifts of **2**, **3**,[13] and **4** are presented in Table II. The pyridine nitrogen resonance positions reflect similar chemical shift substituent effects as obtained in ^{14}N and ^{15}N studies of the analogous picolines.[14a,b] The pyrrolidine nitrogen chemical shifts exhibit the same dependence as do the 3′ carbons on the position of attachment of the pyrrolidine ring to the pyridine ring.

The pyridine ^1H resonances of **2** and **4** can be assigned (Table III) by examining the coupling constants obtained for each proton from the LAOCOON analysis, since the constants are characteristic for protons at specific ring positions of 2- and 4-substituted pyridines.[15] Since H(2′) couples with the pyridyl protons, it is included in the analysis of this region of the spectrum. The small long-range coupling constants, $J_{2',5}$ of **2** and both $J_{2',2}$ and $J_{2',6}$ of **4**, were determined from the extent of narrowing of the corresponding pyridine resonances upon irradiation of H(2′) of **2** and of **4**. Careful computer simulation of these resonances using the decoupled line width yielded the coupling constants in Table III. The estimated error using this technique is ±0.05 Hz.

The seven-spin pyrrolidine regions of the ^1H spectra of **2** and **4** are complicated due to extreme overlap, making analysis difficult. This difficulty can be circumvented by obtaining ^1H spectra of specifically deuterated analogues, which reduce the seven-spin analyses to more tractable three-, four- and five-spin analyses. In addition, the ^2H NMR chemical shifts of these analogues (Tables IV and V) provide excellent estimates[3,16–18] of the corresponding proton chemical shifts, as well as allowing assignment of ^1H resonances to protons on specific carbons. A typical analysis is illustrated in Figure 1 for 2-nicotine-3′,3′-d_2; the broadening of ^1H resonances in-

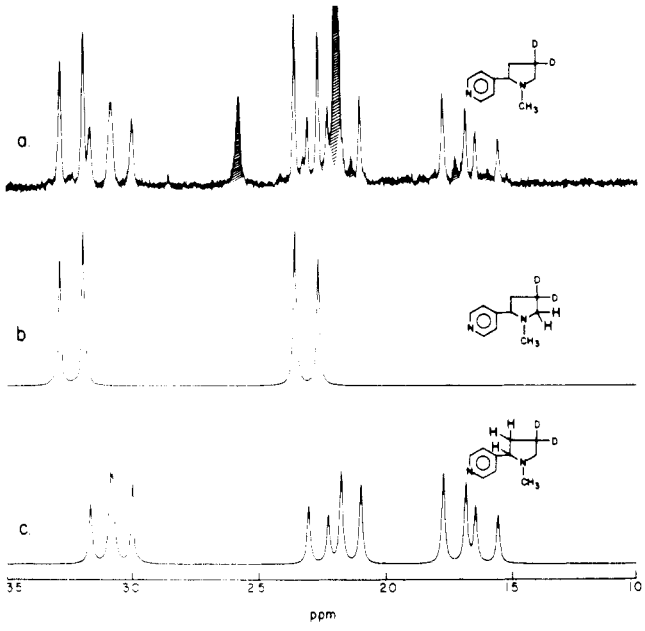


Figure 2. (a) Deuterium decoupled pyrrolidine ^1H resonances of 4-nicotine-*4′,4′*-d_2. Computer fitted (b) H(5′) resonances and (c) H(2′) and H(3′) resonances minus CH_3 resonance.

Table VI. Pyrrolidine ^1H and ^2H Chemical Shifts (ppm) of 4-Nicotine

		^1H		
	^2H	4-nicotine-*3′,3′*-d_2[b]	4-nicotine-*4′,4′*-d_2[c]	4-nicotine-*5′,5′*-d_2[d]
2′	3.09		3.073	3.079
$3'_a$[a]	1.69		1.673	1.682
$3'_b$	2.23		2.193	2.207
$4'_a$	1.85	1.804		1.800
$4'_b$	1.95	1.927		1.928
$5'_a$	2.33	2.319	2.311	
$5'_b$	3.24	3.236	3.230	
CH_3	2.18	2.190	2.190	2.190

[a] Subscripts a and b refer respectively to high- and low-field chemical shifts of protons attached to a specific carbon. [b] Registry no., 68582-56-9. [c] Registry no., 68630-27-3. [d] Registry no., 68582-57-0.

duced by ^2H scalar coupling (Figure 1a) is removed by irradiating the ^2H resonances (Figure 1b). Shown in Figure 1c is the spectrum generated from the computer fit data in Tables IV and V. The same approach is taken for 4-nicotine-*4′,4′*-d_2 (Figure 2, Tables VI and VII). Spectral parameters obtained in a similar manner are shown in Tables IV and V for 2-nicotine-*4′,4′*-d_2 and 2-nicotine-*5′,5′*-d_2 and in Tables VI and VII for 4-nicotine-*3′,3′*-d_2 and 4-nicotine-*5′,5′*-d_2.

Discussion

Pyrrolidine Ring Conformation. Although in five-membered ring systems there is often a great deal of internal conformational mobility, the presence of substituents, such as a methyl group and a pyridine ring, can reduce significantly the populations of sterically hindered conformers. In our earlier study of **3**,[3] it was determined that the principal solution conformation of the pyrrolidine ring was an envelope, presumably resulting, at least in part, from the tendency of the trans pyridine and *N*-methyl moieties[19] to adopt equatorial orientations and minimize steric interactions. A comparison between the vicinal coupling constants of **3** on the one hand and **2** and **4** on the other (average coupling constants shown in Table VIII) suggests that similar conformational

Table VII. Pyrrolidine ^1H Coupling Constants (Hz) of 4-Nicotine[d]

	$3'_a$	$3'_b$	$4'_a$	$4'_b$	$5'_a$	$5'_b$
2	8.91[c]	7.51[c]	—	—	—	0.50
	8.86[b]	7.81[b]				
$3'_a$	- - -	−12.48[c]	5.83	10.71	—	—
		−12.81[b]				
$3'_b$	- - -	- - -	9.55	5.63	—	—
$4'_a$	- - -	- - -	- - -	−12.60[c]	8.29	2.15
				−12.55[a]		
$4'_b$	- - -	- - -	- - -	- - -	9.77	8.13
$5'_a$	- - -	- - -	- - -	- - -	- - -	−9.15[b]
						−9.19[a]

[a] Measured for 4-nicotine-*3′,3′*-d_2. [b] Measured for 4-nicotine-*4′,4′*-d_2. [c] Measured for 4-nicotine-*5′,5′*-d_2. [d] — indicates long-range coupling constants not resolvable. - - - indicates table redundancy or same proton.

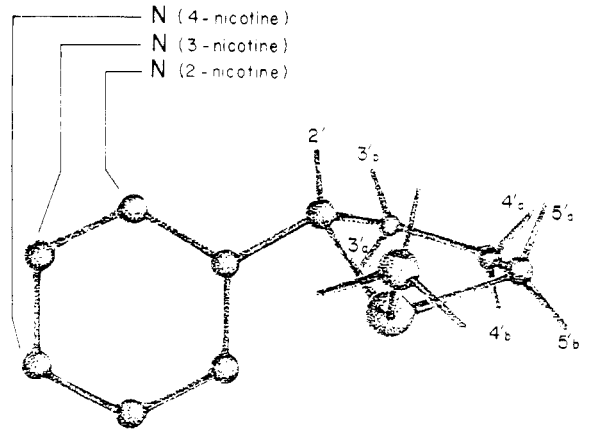


Figure 3. The conformation of 2-nicotine (**2**), 3-nicotine (**3**), and 4-nicotine (**4**) in which $\Theta = 0°$.

determinants are operative in these three compounds.

Employing the Karplus parameters determined for **3**,[3] we can obtain estimates of the pyrrolidine ring dihedral angles, ϕ, of both **2** and **4** ($J = A\cos^2\phi + 2$; $A = 7.8$, $0 < \phi < 90°$; $A = 10.5$, $90° < \phi < 180°$). The vicinal coupling $J_{4'a,5'b}$ ($\simeq 2.1$ Hz) yields a dihedral angle near 95° for the corresponding H–C–C–H sequence of **2** and **4** (refer to Figure 3). This means that H($5'_a$) adopts an axial orientation. Since this proton is trans to the nitrogen lone pair (as indicated by its higher field resonance position relative to H($5'_b$)[20-23]), the lone pair is axial and the methyl group equatorial. The symmetry of the coupling constants between the 3′ and 4′ hydrogens (Table VIII) suggests an eclipsed orientation for these hydrogens; significant deviation from this orientation would not allow each of the 3′ and 4′ protons to exhibit a similar pair of coupling constants to protons on the other carbon ($\simeq 5.5$, 10 Hz). The large 2′,3′ couplings are consistent with an axial orientation of the 2′ proton. Assignment of resonances to each proton on a given carbon (Figure 3) follows directly from a consideration of the above coupling constants.[3] In our study of **3** no attempt was made to describe the minor conformers present, because of the approximate nature of the Karplus parameters, and because the small $J_{4'a,5'b}$ and large values for both $J_{2',3'a}$ and $J_{2',3'b}$ indicated a preponderance of one isomer. A similar approach is taken in the present study.

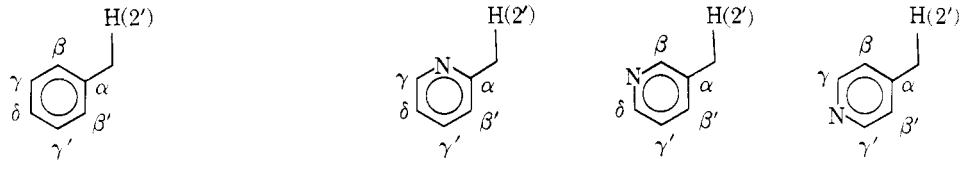
Table VIII summarizes the average coupling constants for **2**, **3**, and **4**. The torsional angles (χ) calculated from Karplus parameters determined previously[3] are also shown (χ is defined viewing the carbon–carbon bond end on with the lower numbered carbon nearest the viewer; clockwise rotation of the

Table VIII. Comparison of the Pyrrolidine ^1H Coupling Constants (Hz) and Calculated Torsional Angles

J	2-nicotine	χ, deg	3-nicotine[a]	χ, deg	4-nicotine	χ, deg
$2',3'_a$	8.36	24 ± 4	8.99	27 ± 3	8.88	28 ± 5
$2',3'_b$	8.23		7.96		7.66	
$3'_a,3'_b$	−12.70		−12.77		−12.64	
$3'_a,4'_a$	5.48	0 ± 11	5.68	0 ± 7	5.83	0 ± 10
$3'_a,4'_b$	10.60		10.92		10.71	
$3'_b,4'_a$	9.29		9.67		9.55	
$3'_b,4'_b$	5.40		5.43		5.63	
$4'_a,4'_b$	−12.34		−12.48		−12.62	
$4'_a,5'_a$	8.30	−27 ± 2	8.30	−27 ± 3	8.29	−27 ± 3
$4'_a,5'_b$	2.10		2.19		2.15	
$4'_b,5'_a$	9.68		9.68		9.77	
$4'_b,5'_b$	8.15		7.93		8.13	
$5'_a,5'_b$	−8.97		−9.16		−9.17	

[a] Reference 3. The solvent used in ref 3 was 33% $CFCl_3$ and 67% $CDCl_3$; however, the spectra of 3-nicotine in the mixed solvent and in $CDCl_3$ are virtually identical.

Table IX. Comparison of Calculated and Observed ^1H–^1H Long-Range Coupling Constants (Hz)



2 **3** **4**

coupling constant	calcd[a] at Θ[b] = 0°	90°	180°	obsd 2-nicotine	3-nicotine[c]	4-nicotine
$2',\beta$ (^4J)	−0.34	−1.47	−0.58		−0.51	−0.52
$2',\beta'$ (^4J)	−0.58	−1.47	−0.34	−0.32	−0.48	−0.52
$2',\gamma$ (^5J)	0.23	0.89	0.83	0.0		0.20
$2',\gamma'$ (^5J)	0.83	0.89	0.23	0.29	0.35	0.20
$2',\delta$ (^6J)	−0.08	−1.22	−0.08	−0.24	−0.20	

[a] Calculated for a methyl proton of toluene.[24] [b] Θ is the H(2′)–C(2′)–C(α)–C(β) dihedral angle. Θ = 0° shown in table. [c] For the present study, the pyridine coupling constants of **3** were redetermined in $CDCl_3$, using the technique described in this paper for the small coupling $2',\delta$.

carbon farthest away produces a positive χ). Although the large $3'_a,4'_b$ couplings indicate a $\chi_{3',4'}$ near zero, they are not used to determine the average $\chi_{3',4'}$, since these couplings fall slightly outside the limits of the Karplus parameters which are most consistent with the remainder of the coupling constants. As would be expected from the similarity between the coupling constants obtained for **2, 3,** and **4,** the χ values predicted for each compound indicate virtually identical conformations for their pyrrolidine rings.

Relative Orientation of Pyridine and Pyrrolidine Rings. The long-range ^1H–^1H coupling between aromatic protons and exocyclic protons is sensitive to the spatial relationship between these nuclei. The dependence of these couplings upon rotation about the exocyclic bond has been observed experimentally and calculated theoretically.[24,25] Shown in Table IX are the observed coupling constants for **2, 3,** and **4** and computed coupling constants for the exocyclic proton of toluene at three angles (the dependence at intermediate angles is monotonic) abstracted from a more complete table by Wasylishen and Shaefer[24] (the Greek lettering system is chosen to simplify discussion by emphasizing the isopositional nature of the aromatic hydrogens of toluene, **2, 3,** and **4**). Θ is defined as the H(2′)–C(2′)–C(α)–C(β) dihedral angle. Although the calculated data shown are for a nonheterocyclic ring, calculations on the corresponding picolines[26] indicate only minor differences between coupling constants for toluene and those for the picolines. It is clear from Table IX that the best agreement occurs at $\Theta \simeq 0°$ or $\Theta \simeq 180°$. The small values of the five-bond coupling, $J_{2',\gamma}$ of **2** and **4**, and $J_{2',\gamma'}$ of **4** probably result from attenuation by the adjacent nitrogen atom of the σ contribution to the long-range coupling. It has been noted previously that the nitrogen can alter this σ contribution,[25,27] but the π contribution to long-range coupling should remain unaltered. Thus, the low values of these five- and six-bond couplings, all of which should have large π contributions for Θ values significantly divergent from 0 or 180°, point very strongly to coplanarity of the H(2′)–C(2′) bond and the pyridine ring, making the two rings perpendicular to each other.

Conclusion

The ^1H–^1H vicinal and long-range coupling constant of **2, 3,** and **4** are consistent with virtually identical solution conformations, so that the position of pyridine ring substitution has very little influence, if any, on the conformation of these molecules. The pyrrolidine ring assumes an envelope conformation with the pyridine ring and methyl group equatorial, and the two ring systems adopt a perpendicular orientation relative to one another. So that, insofar as the solution conformation is retained at the nicotinic receptor site, the lack of cholinergic activity of **2** and **4** cannot be explained by variations in conformation. The differences could result either from varying spatial placement of atoms such as the pyridine and pyrrolidine nitrogen which may bind to precisely situated sites at the receptor, or from electronic changes affecting factors such as nitrogen basicity. The possibility remains,

however, that the factors determining solution conformation are completely overridden by binding constraints placed on the nicotines as they approach the active site resulting in different conformations for **2, 3,** and **4** at the active site. Future studies such as this on more complex model systems or directly on nicotines interacting with nicotinic receptors will undoubtedly shed more light on the fascinating picture of the mechanisms of cholinergic activity.

Acknowledgments. The authors wish to thank Dr. R. Wasylishen for helpful discussions of the conformational dependence of long-range coupling in aromatic systems. We are grateful to Mr. R. L. Bassfield for preparing the three-dimensional figure of the nicotines.

References and Notes

(1) The prefix number in 2-nicotine (**2**), 3-nicotine (**3**), and 4-nicotine (**4**) designates the pyridine ring position at which the pyrrolidine ring is attached. The boldface numbering system is chosen to correspond with the position of substitution for convenience in reading.
(2) We thank Professor Avram Goldstein and C. Romano for making available to us these unpublished results.
(3) T. P. Pitner, W. B. Edwards III, R. L. Bassfield, and J. F. Whidby, *J. Am. Chem. Soc.*, **100,** 246 (1978).
(4) M. Karplus, *J. Chem. Phys.*, **30,** 11 (1959).
(5) M. Karplus, *J. Am. Chem. Soc.*, **85,** 2870 (1965).
(6) The resonance of $CDCl_3$ must be used with caution as a secondary ^2H chemical shift standard. Its position can be influenced strongly by the solute, as is well known for $CHCl_3$. Since concentration was carefully controlled in the present study, the chemical shift of $CHCl_3$ and hence $CDCl_3$ was constant for all samples.
(7) P. R. Srinivasan and R. L. Lichter, *J. Magn. Reson.*, **28,** 227 (1977).
(8) D. F. Glenn and W. B. Edwards III, *J. Org. Chem.*, **43,** 2860 (1978).
(9) W. O. Crain, Jr., W. C. Wildman, and J. D. Roberts, *J. Am. Chem. Soc.*, **93,** 990 (1971).
(10) T. P. Pitner, J. I. Seeman, and J. F. Whidby, *J. Heterocycl. Chem.*, **15,** 585 (1978).
(11) P. C. Lauterbur, *J. Chem. Phys.*, **43,** 360 (1965).
(12) Y. Takeushi, *Org. Magn. Reson.*, **7,** 181 (1975).
(13) Measured previously by R. L. Lichter and J. D. Roberts, *J. Am. Chem. Soc.*, **94,** 2495 (1972).
(14) (a) M. Witznowski, T. Saluvere, L. Stefaniak, and H. Januszewski, *Mol. Phys.*, **23,** 1071 (1972); (b) A. J. DiGiola, G. T. Furst, L. Psota, and R. L. Lichter, *J. Phys. Chem.*, **82,** 1644 (1978).
(15) J. W. Emsley, J. Feeney, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy", Pergamon Press, New York, 1966, p 797.
(16) J. M. Briggs, L. F. Farnell, and E. W. Randall, *Chem. Commun.*, 70 (1973).
(17) P. Diehl in "Nuclear Magnetic Resonance of Nuclei Other than Protons", T. Axenrod and G. A. Webb, Ed., Wiley, New York, 1974, p 275.
(18) H. H. Mantsch, H. Saito, and I. C. P. Smith, *Prog. Nucl. Magn. Reson. Spectrosc.*, **11,** 211 (1977).
(19) J. F. Whidby and J. I. Seeman, *J. Org. Chem.*, **41,** 1585 (1976).
(20) M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Bressi, *J. Am. Chem. Soc.*, **86,** 3364 (1964).
(21) H. Booth and J. H. Little, *Tetrahedron*, **23,** 291 (1967).
(22) E. Breuer and D. Melumad, *J. Org. Chem.*, **38,** 1681 (1973).
(23) H. Nakanishi and O. Yamamoto, *Tetrahedron*, **30,** 2115 (1974).
(24) R. Wasylishen and T. Schaefer, *Can. J. Chem.*, **50,** 1852 (1972).
(25) J. B. Rowbotham and T. Schaefer, *Can. J. Chem.*, **50,** 2344 (1972).
(26) We thank Dr. R. Wasylishen for making available to us these calculations.
(27) J. B. Rowbotham, R. Wasylishen, and T. Schaefer, *Can. J. Chem.*, **49,** 1799 (1971).

Conformation of Dihydropyran Rings. Structures of Two 3,4-Dihydro-2*H*,5*H*-pyrano[3,2-*c*][1]benzopyran-5-ones

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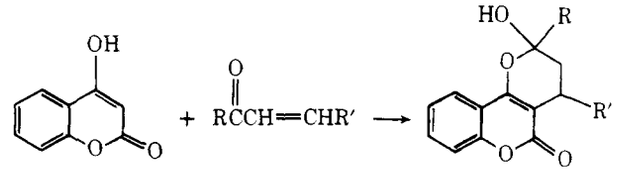
The crystal structures of *cis*-2-hydroxy- and *trans*-2-methoxy-2,4-dimethyl-3,4-dihydro-2*H*,5*H*-pyrano[3,2-*c*]-[1]benzopyran-5-one have been determined. The half-chairs of the dihydropyran rings are distorted toward the e,f and d,e diplanar (sofa) forms, respectively. The long endocyclic C–O bonds (cis, 1.475, 1.473 Å; trans, 1.459 Å) result from conjugation of the dihydropyran ring unsaturation with the coumarin carbonyl group. In each compound, the axial anomer is found. In solution, the hydroxy compound exists as a mixture of diastereomeric hemiketal and the open-chain keto forms. The *cis*-methyl ketal interconverts between alternate half-chair conformations, while the *trans*-methyl ketal has a preferred conformation similar to that found in the crystal.

For dihydropyran rings, a natural point of reference is cyclohexene, with a half-chair (symmetry C_2) ground state conformation[1] and a rather flat pseudorotation potential amounting to only 1–2 kcal/mol to reach the 1,2-diplanar (sofa) form,[2] in consequence in part of a remarkably slight initial dependence of the 1,3-diaxial contact distances on distortion of the half-chair.[2–4] Dihydropyrans lack the cyclohexene symmetry and one of the diaxial contacts, but still retain conformations close to the half-chair.[5–7] The 1,2-diplanar form is found in other ring systems most commonly in which the unsaturation conjugates with an adjacent endocyclic atom.[8–10] Such a conformation could be approached in nonrigid dihydropyrans to which steric and anomeric effects simultaneously contribute. These features are evident in the Michael addition products of certain α,β-unsaturated ketones with 4-hydroxycoumarin, which may exist as hemiketals.[11] Warfarin (*trans*-4-phenyl-3,4-dihydro-2-hydroxy-2-



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