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MENSCHUTKIN REACTION STEREOSELECTIVITIES OF NICOTINE AND RELATED COMPOUNDS[1]

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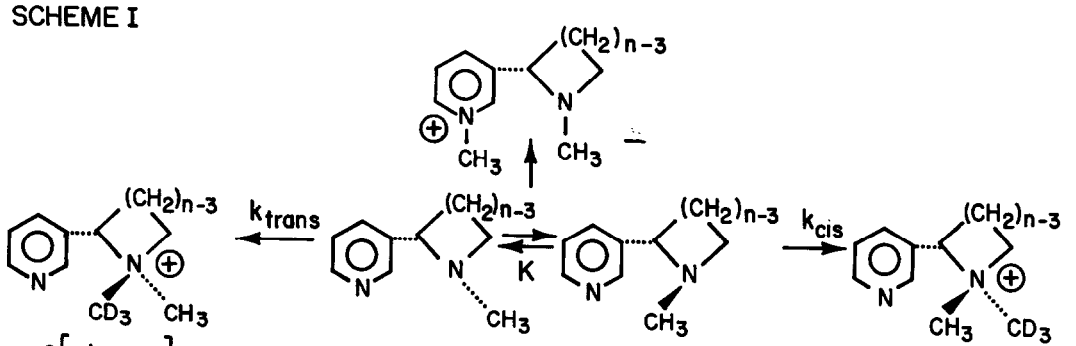
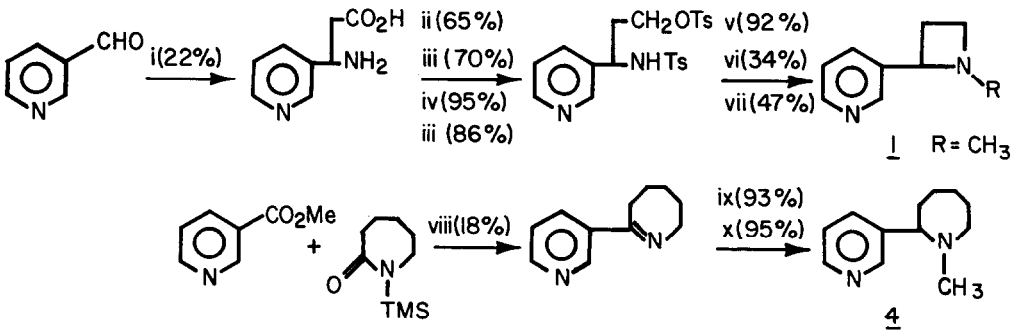
Recently we reported that iodomethylation of nicotine (2) led to the formation of N'-methylnicotinium iodide (5, n=5) and N-methylnicotinium iodide (6, n=5) (Scheme I) in a ratio of 2.2:1.[2] This example of competitive nitrogen alkylation was interesting in that iodomethylation of the nicotine analogue 3-N,N-dimethylaminomethylpyridine (7) resulted in the formation of only 3-N,N,N-trimethylammoniummethylpyridine (8).[2] The two major controlling factors in the Menschutkin reaction are nitrogen basicity and steric constraints in the transition state.[3] Because the pK_A's of nicotine and 7 are nearly identical, we suggested that constraining the aliphatic nitrogen of nicotine into a pyrrolidine ring caused steric inhibition in the transition states which lead to N'-attack.[2]

SCHEME I



To further examine the stereochemical factors in nicotine alkylation, we have prepared[4] three additional N-methyl-2-(3-pyridyl)azacycloalkanes (1,3, and 4) as shown in Scheme II and have examined their quaternization with CD_3I. This constitutes the first report of the alkylation stereoselectivity of either N-alkylazetidines or N-alkylazacycloheptanes.[3]

SCHEME II

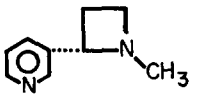
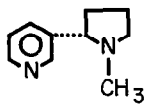
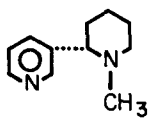
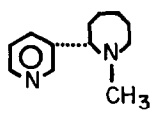


i, malonic acid, NH_4OAc
ii, H^+/EtOH
iii, TsCl/pyr
iv, LAH
v, KO^{t}Bu
vi, $[C_{10}H_8]^{\cdot}Na^+$/gylme
vii, $CH_2O/NaBH_3CN$
viii, $[(CH_3)_2CH]_2NLi$, then H^+
ix, $NaBH_3CN$
x, CH_2O, HCO_2H

Each compound was independently treated with CH_3I, CD_3I and $^{13}CH_3I$. The alkylation selectivities (Table 1) were determined by a combination of ^1H, ^2H, and ^{13}C nmr experiments.[4] Assignments for the methyl groups were made in the following way. In all four cases, the pyridyl-N-methyl ^{13}C resonance occurred at 71.9 ppm. A detailed NOE experiment on purified N'-methylnicotinium iodide allowed a definitive ^1H nmr assignment of the two N'-methyl groups.[5,6] A correlation between these N'-methyl proton resonances and the corresponding ^{13}C resonances was made by a comparison of the relative ^1H and ^{13}C resonance intensities of the N'-methyl groups of 5 (n=5) and N'-methylnicotinium iodide obtained from the reaction of nicotine with CD_3I and CH_3I, respectively. The ^{13}C methyl resonances of 5 (n=6) were assigned using the well-established relationship $\delta_{ax}-\delta_{eq}=-10$ ppm for piperidines.[7] The assignments of the N'-methyl group resonances for 5 (n=4 and 7) were made on the consistent observation that the *cis* methyl resonance appeared more upfield than the *trans* in both the ^{13}C and ^1H nmr spectra for all compounds studied.

Inspection of Table 1 clearly indicates a pronounced variation in both the ratio of N'/N attack and N'_{cis}/N'_{trans} attack. As with nicotine, 1, 3, and 4 all show competitive pyridine alkylation although the $pK_{a_1} > pK_{a_2}$. It is interesting to note that the azetidine 1 has the greatest percentage of N' alkylation. The relative rates of aliphatic nitrogen alkylation can be obtained from the N'/N ratios since the rate of pyridine nitrogen alkylation in these compounds is likely to be nearly identical.[8] Thus, these N-methyl-2-arylazacycloalkanes exhibit the following relative N' iodomethylation rates: azetidine, 13.0; pyrrolidine, 2.4; piperidine, 1.3; and homopiperidine, 1.

Table 1.[a] Iodomethylation Selectivities and Spectral Assignments of 1-4.

		Alkylation Ratios (^{13}C Chemical Shift)					
		N	N'_{cis}	N'_{trans}	pK_{A_1}	$\frac{N'}{N}$	$\frac{N'_{cis}}{N'_{trans}}$
	1	1 (49.2)	8.3 (46.9)	3.5 (53.4)	8.07	11.8	2.4
	2	1 (49.2)	1.4 (46.5)	0.82 (51.1)	7.9	2.2	1.7
	3	1 (49.2)	1.1 (43.8)	0.11 (54.1)	8.04	1.2	10
	4	1 (49.2)	0.35 (48.4)	0.56 (54.0)	8.38	0.91	0.6

[a]All alkylations were performed at *ca.* 25°C with *ca.* 0.8 equiv. iodomethane in order to avoid overalkylation. N and N' refer to alkylation direction. Estimated error in alkylation ratios is 10%.

The ratio N'_{cis}/N'_{trans} for these compounds is dependent on both the equilibrium distribution of the free base configurational isomers and the relative rates of *cis*- and *trans*-alkylation and is described by the Curtin-Hammett approximation [$N'_{cis}/N'_{trans}=K(k_{cis}/k_{trans})$].[9] For compounds 1-3, *cis* attack predominates. It is tempting to suggest that the alkylation stereoselectivities of these 2-aryl substituted cyclic amines are controlled by the same steric phenomena, that being the interaction between the aliphatic nitrogen substituent(s) and the two rings. The equilibrium constant K (see Scheme I) reflects primarily the destabilizing interaction between the N'-methyl group and the ring constituents; the ratio k_{cis}/k_{trans} reflects a decrease in k_{cis} (relative to N-methylpyrrolidine iodomethylation) due to the destabilizing interaction between the ring substituents and the $N^{\delta+}---CH_3---I^{\delta-}$ in the alkylation transition state. Since *cis* alkylation predominates, $K(k_{cis}/k_{trans})>1$ requiring $K>(k_{trans}/k_{cis})$. Thus, the already bonded N-CH_3 has a larger steric requirement[9b] than $N^{\delta+}---CH_3---I^{\delta-}$. A simple Curtin-Hammett analysis cannot be made for compounds such as 4 where numerous conformations are reacting, but a pairwise analysis of the reacting nitrogen invertomers of 4 should be examined in light of the above inequality generalization.

A complete analysis of these systems requires a knowledge of the equilibrium distribution of stereoisomers[10] and the reaction rate constant of each of these.[11] Kinetic studies and the preparation of the requisite labelled materials[12] are curcurently being undertaken.

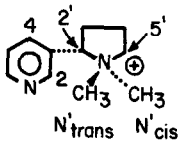
References and Notes

(1) For the previous paper in this series, see E. B. Sanders, H. V. Secor, and J. I. Seeman, J. Org. Chem., 43, 324 (1978).

(2) J. I. Seeman and J. F. Whidby, J. Org. Chem., 41, 3824 (1976).

(3) For reviews of the Menschutkin reaction, see (a) J. McKenna, Topics in Stereochemistry, 5, 275 (1970); (b) A. T. Bottini in "Selective Organic Transformations", Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1970, pp. 89-142; (c) Note that the iodomethylation of N-t-butyl-3-hydroxyazetidine was studied [E. L. McGandy, H. N. Berman, J. W. Burgnen, II, and R. L. van Etten, J. Am. Chem. Soc., 91, 6173 (1969)] but the role of the hydroxy group in this case was unspecified [*c.f.*, R. Wylde, J. G. Saeluzika and M. Lanfumey, J. Org. Chem., 40, 1308 (1975)].

(4) Full details of the preparation of these compounds and the spectral analyses performed will be reported elsewhere. For the synthesis of azetidine 1 and analogous compounds, see H. V. Secor and W. B. Edwards, III, in preparation. We thank Mr. Dominick Quagliato for valuable technical assistance.



Proton Irradiated		Proton(s) Observed 2	4	2'	5'
N'_{trans}	(δ 3.27)	<1%	<1%	7.1%	5.1%
N'_{cis}	(δ 2.94)	8.5%	7.9%	<1%	5.9%

(6) Our results confirm those made previously for 2-phenyl-N,N-dimethylpyrrolidinium iodide based on chemical shift analogies [*c.f.*, A. Solladié-Cavallo and G. Solladié, Org. Mag. Resonance, 7, 18 (1975)].

(7) (a) A. J. Jones, C. P. Beeman, M. U. Hasan, A. F. Casy and M. A. Hassan, Can. J. Chem., 54, 126 (1976); (b) E. L. Eliel and F. W. Vierhapper, J. Am. Chem. Soc., 97, 2424 (1975) and references cited therein.

(8) (a) H. C. Brown and A. Cahn, J. Am. Chem. Soc., 77, 1715 (1955); (b) ^{13}C chemical shifts are well-known to be very dependent on steric congestion. Our observation that the ^{13}C pyridyl-$\underline{C}H_3$ resonances of 6 (n=4-7) are identical suggests that the no significant steric differences are caused by ring size variation going from the azetidine to the homopiperidine.

(9) (a) For a complete analysis of Curtin-Hammett/Winstein-Holness kinetics, including an exact solution, see J. I. Seeman and W. F. Farone, J. Org. Chem., in press; (b) The same conclusion can be reached by an evaluation of the relative free energies of the two alkylation transition states. See also A. Solladié-Cavallo and G. Solladié, Tetrahedron Lett., 4237 (1972).

(10) J. F. Whidby and J. I. Seeman, J. Org. Chem., 41, 1585 (1976).

(11) V. J. Baker, I. D. Blackburne and A. R. Katritzky, J. Chem. Soc., Perkin II, 1557 (1974) and references cited therein.

(12) P. J. Crowley, M. J. T. Robinson and M. G. Ward, Tetrahedron, 33, 915 (1977)