THE SELECTIVITY IN N-ALKYLATION OF NICOTINE

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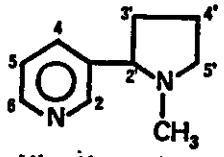
Abstract --- In preference to pyrrolidine, pyridine moiety of nicotine was alkylated by alkyl halides. This preference seemed to result from the difference of steric hinderance around each nitrogen. The reactivity of pyridine moiety was accelerated by the electronic effect of pyrrolidine. The selective alkylation of pyridine appeared to be available for preparation of artificial antigen of nicotine.

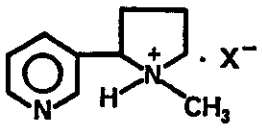
Nicotine (1) has two kinds of tertiary nitrogens, one in pyridine and the other in pyrrolidine. The pKa value of the former is smaller than that of the latter (pKa_1=7.84, pKa_2=3.04).[1] This difference of pKa values suggests that the electrophiles will attack the nitrogen in the pyrrolidine moiety preferentially. In fact, ^{1}H NMR spectrum shows that monohydrochloride or monohydrobromide of 1 has a pyrrolidinium halide structure (2). On the other hand, it was reported that the reaction of 1 with an equimolar amount of methyl iodide led to a mixture of N-methylnicotinium iodide (3) and N'-methylnicotinium iodide (4).[2] This indicates that the N-alkylation occurs competitively and the selectivity does not always depend on the pKa value.

In this paper, we wish to report that the N-alkylation of pyridine moiety in 1 was assisted by the steric and electronic interactions between electrophiles and pyrrolidine moiety. Application of this reaction to the synthesis of artificial antigen of nicotine is also discussed.

To a solution of 5.0 mmol of 1 in 10 ml of methanol or tetrahydrofuran was added dropwise 5.1 mmol of alkyl halide at ice-bath temperature under N_2. The reaction mixture was stirred at room temperature for 48h, and the solvent, unreacted 1, and alkyl halide were distilled off under reduced pressure. The resulting oily mixture was washed with ether, and dried *in vacuo*. The ^{1}H NMR data showed that the residue



Nicotine (1)



(2) X=Cl, Br

Table 1

Reaction of nicotine with alkyl halide

RX	conv. of nicotine (%)		N-alkyl:N'-alkyl
	(a)	(b)	
CH_3I	83.0	84.4	1 : 1
C_2H_5I	29.7	24.5	1 : 0[c]
$n\text{-}C_3H_7I$	21.7	24.0	1 : 0
$iso\text{-}C_3H_7I$	17.6	8.4	1 : 0
$t\text{-}C_4H_9Br$		38.7	—[d]
$PhCH_2Br$		48.4	1 : 0
$BrCH_2CO_2Et$		54.3[e]	1 : 0

a) in THF, rt, 48h b) in MeOH, rt, 48h

c) Treatment of 1 with excess amount of C_2H_5I was reported to lead to N,N'-diethylnicotinium iodide.[3] d) $t\text{-}C_4H_9Br$ was decomposed, and nicotine was converted to 2 (X=Br). e) 24h

was the alkylated nicotine.

The conversion of 1 was analyzed by GLC, and listed in Table 1. The ratio of N-alkylated vs N'-alkylated nicotine was determined by ^1H NMR spectra of the crude reaction products, which were shown in Table 2. The chemical shifts of nicotine moiety in 5~9 were extremely close to those of N-alkylated nicotine (3), but not to those of N'-alkylated derivative (4),[2] and the structures of 5~9 were determined to be N-alkylated derivatives.

The reaction of 1 with ethyl iodide at several temperatures was examined. The conversion of 1 was 85.2% at 97°C for 1.5h, 55.2% at 65°C for 8h, and 24.5% at room temperature for 48h. In each case, N'-ethylnicotinium iodide was not found in the reaction product.

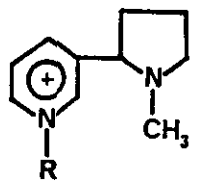
With increasing bulkiness of the alkyl group, the reactivity of alkyl halide decreased; $CH_3I > C_2H_5I > n\text{-}C_3H_7I > iso\text{-}C_3H_7I$. In the case of tert-butyl bromide, the halide was decomposed, and N'-hydronicotinium bromide (2, X=Br) was obtained as the reaction product. The reaction of 1 with ethyl iodide, n-propyl iodide, iso-propyl iodide, benzyl bromide, and ethyl bromoacetate gave N-alkylated nicotines exclusively, while the reaction with methyl iodide led to the mixture of 3 and 4. These results suggested that the selectivity was strongly influenced by steric hinderance rather than the difference of the pKa values. In order to confirm this, a competitive experiment was performed. Treatment of a 1 : 1 mixture of N-methylpyrrolidine (pKa = 10.18)[4] and pyridine (pKa = 5.19)[1] with one equivalent of benzyl bromide in methanol resulted in the formation of a single product of alkylated

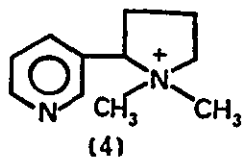
Table 2 ^{1}H NMR chemical shifts (ppm from TMS)

Compound	1	3[2)]	4[2)]	5	6	7	8	9
N'	2.15(s)	2.26(s)	2.87(s)	2.25(s)	2.24(s)	2.27(s)	2.16(s)	2.28(s)
			3.20(s)					
2'	3.07(t)	3.55(t)	5.16(t)	3.66(t)	3.66(t)	3.68(t)	3.56(t)	3.69(t)
3'	1.73,2.21	1.75	2.10	1.69	1.60	1.65	1.60	1.70
4'	1.80,1.95	2.25	2.80	2.25	2.25	2.25	2.25	2.25
5'	2.31,3.25	2.44,3.25	3.90	2.46,3.25	2.50,3.25	2.50,3.40	2.40,3.26	2.43,3.30
2	8.54(s)	9.10(s)	8.87(s)	9.42(s)	9.37(s)	9.28(s)	9.45(s)	9.41(s)
4	7.68(dt)	8.49(dt)	8.12(dt)	8.59(dt)	8.57(dt)	8.58(dt)	8.49(dt)	8.61(dt)
5	7.22	8.12	7.50	8.19	8.18	8.13	8.04	8.12
6	8.48(d)	9.28(d)	8.68(d)	9.47(d)	9.47(d)	9.48(d)	9.61(d)	9.57(d)
N		4.70(s)		5.09(q)	4.96(t)	5.50	6.31(s)	6.27(s)
				1.76(t)	2.11	1.80(d)	7.30	4.28(q)
					1.05(t)		7.70	1.30(t)

The signals are multiplet, unless otherwise specified.

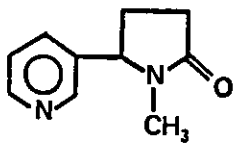
s; singlet d; doublet t; triplet dt; double triplet q; quartet





(4)

R= (3)CH_3, (5)C_2H_5, (6) n−C_3H_7, (7) iso−C_3H_7, (8) CH_2Ph, (9) $CH_2CO_2C_2H_5$



cotinine (10)

N-methylpyrrolidine, and no alkylated pyridine was observed in the ^{1}H NMR spectrum of the crude reaction product. This fact showed that the selectivity of the reaction was governed by the pKa values of reactants, when there is no steric hinderance.

To elucidate the influence of the tertiary nitrogen in pyrrolidine ring on the alkylation, two competitive reactions were performed. A 1 : 1 mixture of 1 and pyridine was treated with one equivalent of benzyl bromide. Although the pKa value of the pyridine nitrogen of 1 is 2.15 units less than that of pyridine and the steric hindrance around the pyridine nitrogen of 1 is not less than that of pyridine, 1 was alkylated predominantly (N-alkylated pyridine : 8 = 1 : 4). This result suggested that the alkylation of pyridine nitrogen in 1 was assisted by the basicity of the nitrogen in the pyrrolidine moiety. To confirm this, in the reaction mentioned above 1 was replaced with cotinine (10) in which the basicity of lactam structure seemed to be negligible. The pKa value of pyridine moiety in 10 (pKa = 4.33)[5] was close to that in 1, and the steric interaction between pyridine and lactam in 10 was considered to be similar to that between pyridine and pyrrolidine in 1. In this case, alkylated pyridine was mainly obtained (N-alkylated pyridine : N-alkylated cotinine = 2 : 1).

The selectivity in N-alkylation of two kinds of tertiary nitrogens in nicotine with alkyl halides was governed by two factors; 1) steric interaction between electrophiles and pyridine or pyrrolidine ring, 2) pKa values. The former factor favored the N-alkylation of pyridine, whereas the latter favored that of pyrrolidine. Furthermore, the reactivity of pyridine was assisted by the basicity of the tertiary nitrogen in pyrrolidine ring.

Although several methods of preparation of artificial antigens of nicotine have been reported,[6~9] the selective N-alkylation in pyridine moiety of nicotine seems to provide a new convenient route to the antigen. N-Carboethoxymethylnicotinium bromide (9) is an example of the intermediate of the antigen, because 9 has a ester group which can conjugate the amino groups of protein potentially. The preparation of other intermediates of the conjugates and their applications for radioimmunoassay of nicotine are under progress.

REFERENCES AND NOTES

1. P. G. Stecher, Ed.,"The Merck Index", Merck and Co., Rahway. N. J. (1976).
2. J. I. Seeman and J. F. Whidby, J. Org. Chem., 41, 3824 (1976).
3. a) A. V. Planta and A. Kekule, Ann. Chem. Pharm., 87, 1 (1853); b) C. von Stahlschmidt, Ann. Chem. Pharm., 90, 218 (1854).
4. J. A. Dean, Ed.,"Lange's Handbook of Chemistry", 11th ed., McGraw-Hill, New York, N. Y.,1973, Tables 5-8.
5. pKa value was measured by titration method.
6. J. J. Langone, H. B. Gjika, and H. V. Vunakis, Biochemistry, 12, 5025 (1973).
7. H. Matsushita, M. Noguchi, and E. Tamaki, Biochem. Biophys. Res. Commun., 57, 1006 (1974).
8. A. Castro and I. Prieto, Biochem. Biophys. Res. Commun., 67, 583 (1975).
9. M. Noguchi, H. Matsushita, and Y. Tsujino, Biochem. Biophys. Res. Commun., 83, 83 (1978).

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