THE SYNTHESIS OF 5′-ALKYLNICOTINES

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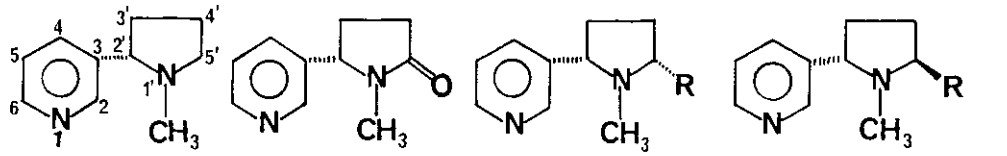
Abstract - The reaction of cotinine(2) with alkyl lithium followed by the reduction with $NaBH_3CN$ in acidic methanol gave cis and trans-5′-alkylnicotines(3 and 4). The stereochemistry of the products was discussed.

To understand the biological activities of nicotine(1), the synthesis of its analogues for the development of structure-activity relationship is important. Although several alkylnicotines have been prepared from this point of view,[1] as to 5′-alkylnicotines only 5′-dimethylnicotine has so far been obtained.[2] In this paper, we wish to report the synthesis of 5′-monoalkylnicotines. The stereochemistry will also be mentioned.

The reaction of cotinine(2) with alkyl lithium followed by the reduction with sodium cyanoborohydride in acidic methanol gave 5′-monoalkylnicotine. The yield and the stereoselectivity were listed in Table 1. The alkylation of 2



1 2 3a;R=Me d; Ph 4a;R=Me d; Ph
b; Et e; i-Pr b; Et e; i-Pr
c; n-Bu f; t-Bu c; n-Bu

with methyl, ethyl, n-butyl, isopropyl and phenyl lithium gave cis- and trans-5′-alkylnicotines (3 and 4) in moderate yields. With tert-butyl lithium, cis-isomer only was isolated in very low yield.

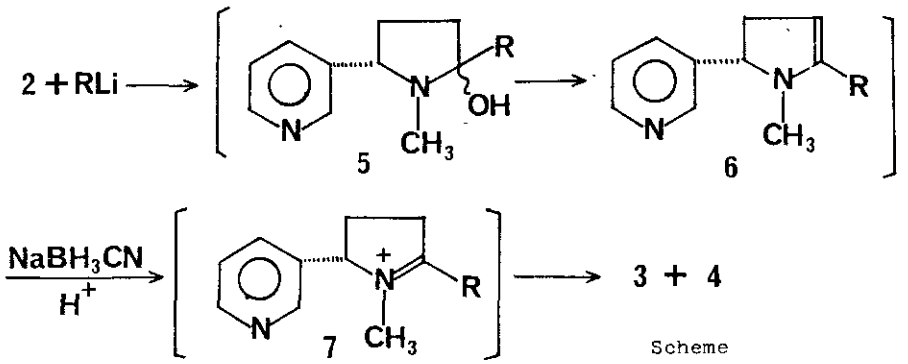
The relative configurations of 3 and 4 were confirmed by the NMR analysis. The assignments of individual resonances in these compounds shown in Table 2 and

Table 3 were made by H-H and C-H decoupling methods. As shown in Table 2, the chemical shifts of 5′-proton in 4 were observed at lower field than those in 3. Since 5′-α(pseudo equatorial)-proton in 1 is assigned to the lower field resonance than 5′-β(pseudo axial)-proton,[3] 3 and 4 were assumed to have pseudo axial and pseudo equatorial protons, respectively. This explanation was further supported by ^{13}C NMR analysis. As shown in Table 3, the chemical shifts of 2′- and 5′-carbons in 3 were observed at lower field than those in 4. This difference was explained to be caused by the steric effect from 5′-substituent. An axial substituent causes higher field shift of α and γ carbons than an equatorial one in cyclohexane ring.[4] Therefore, the 5′- substituents in 3 and 4 were considered to be pseudo equatorial and pseudo axial, respectively. Two possible conformations of cis-5′-alkyl isomer were anticipated, but the conformation of pyridine ring and alkyl group being both pseudo equatorial was more stable than that being both pseudo axial. Then the compounds possessing 5′-pseudo axial proton and pseudo equatorial substituent, that is 3, were cis-isomers.

Table 1 The yield and stereoselectivity

substituent		yield(%)	3 : 4 (%)
a	methyl	68	78 : 22
b	ethyl	47	82 : 18
c	n-butyl	70	82 : 18
d	phenyl	66	90 : 10
e	isopropyl	54	90 : 10
f	tert-butyl	9	100 : 0

As shown in Table 1, cis-isomers were predominantly obtained, and the stereoselectivity increased with an increase in the bulkiness of 5′-alkyl



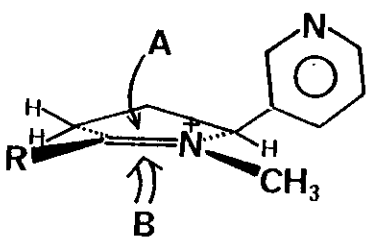
Scheme

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

	1*	3a	4a	3b	4b	3c	4c	3d	4d	3e	4e	3f
1′	2.18	2.11	2.16	2.11	2.16	2.11	2.15	2.01	1.92	2.10	2.15	2.31
2′	3.07	3.24	3.72	3.24	3.80	3.23	3.80	3.44	4.14	3.31	4.14	3.51
3′	1.73	1.66	1.76	1.60	1.76	1.61	1.76	1.81	1.96	1.53	1.78	1.59
	2.21	2.10	2.37	2.08	2.32	2.08	2.30	2.23	2.54	2.05	2.48	1.97
4′	1.80	1.57	1.58	1.60	1.57	1.56	1.67	1.81	1.96	1.67	1.52	1.77
	1.95	1.98	2.24	1.96	2.12	1.95	2.14	2.23	2.54	1.72	2.27	1.92
5′	2.31	2.42	3.41	2.31	3.02	2.33	3.07	3.44	4.14	2.39	3.29	2.43
	3.25	-	-	-	-	-	-	-	-	-	-	-
6′	-	1.21	1.06	1.38	1.21	1.32	1.22	-	-	1.91	1.93	-
	-	-	-	1.74	1.95	1.71	1.65	-	-	-	-	-
7′	-	-	-	0.95	0.91	1.36	1.34	7.45	7.46	0.93	0.94	0.94
	-	-	-	-	-	-	-	-	-	0.95	0.95	-
8′	-	-	-	-	-	1.37	1.37	7.35	7.34	-	-	-
9′	-	-	-	-	-	0.93	0.93	7.27	7.27	-	-	-
2	8.54	8.53	8.51	8.54	8.50	8.53	8.49	8.65	8.54	8.55	8.54	8.61
4	7.68	7.74	7.65	7.71	7.61	7.70	7.61	7.83	7.64	7.71	7.53	7.77
5	7.22	7.25	7.25	7.23	7.24	7.24	7.24	7.27	7.27	7.23	7.24	7.23
6	8.48	8.49	8.48	8.48	8.48	8.47	8.47	8.51	8.51	8.47	8.47	8.47

* see reference 3

groups; tert-butyl > iso-propyl = phenyl > methyl = ethyl = n-butyl. This reaction is presumed to proceed as shown in Scheme. The reaction of 2 with alkyl lithium gives hydroxy derivative(5), which is dehydrated to enamine derivative(6) in acidic media.[5] It is well known that the reduction of enamine by sodium cyanoborohydride in acidic media proceeded via iminium salt. Therefore the reduction of 6 proceeds via iminium intermediate(7). As shown in Figure, a



Figure

Table 3 ^{13}C NMR chemical shift (ppm from TMS)

	1*	3a	4a	3b	4b	3c	4c	3d	4d	3e	4e	3f
1′	40.3	38.5	35.1	39.0	35.2	39.0	35.2	38.7	35.5	39.1	39.2	43.9
2′	68.8	70.0	64.5	70.0	65.4	70.0	64.8	69.1	65.7	69.8	68.9	71.6
3′	35.2	33.2	31.9	33.8	33.0	33.6	33.1	34.2	33.5	34.6	34.7	36.3
4′	22.7	32.0	29.9	29.2	28.9	29.7	29.4	34.1	33.3	23.7	23.7	26.9
5′	56.9	62.4	58.6	68.2	65.1	67.1	63.6	71.7	68.1	71.2	71.2	74.7
6′	-	19.6	14.9	27.0	22.2	34.2	29.5	144.0	143.2	29.3	29.2	36.2
7′	-	-	-	10.3	11.1	28.5	29.1	127.5	128.0	15.5	15.5	27.2
	-	-	-	-	-	-	-	-	-	20.1	20.0	-
8′	-	-	-	-	-	23.3	23.2	128.5	128.4	-	-	-
9′	-	-	-	-	-	14.3	14.3	127.2	127.2	-	-	-
2	149.4	149.7	149.8	149.6	149.9	149.7	149.8	149.6	149.8	149.6	149.6	149.5
3	138.6	139.8	139.8	139.9	139.9	139.8	139.8	139.8	139.8	140.1	140.1	140.1
4	134.6	135.2	135.2	135.0	135.3	135.1	135.3	135.0	135.3	134.9	135.4	134.6
5	123.3	123.7	123.6	123.6	123.5	123.7	123.6	123.7	123.5	123.6	123.2	123.5
6	148.4	148.7	148.6	148.5	148.6	148.7	148.6	148.6	148.7	148.5	148.3	148.4

* see reference 3

hydride attacks C=N double bond from side B predominantly to give 3, because side A is hindered by 2′-pyridine ring.

EXPERIMENTAL

2′S,5′S-5′-Methylnicotine(3a) and 2′S,5′R-5′-Methylnicotine(4a) --- To a solution of cotinine(2) (5mmol, 0.9g) in 20ml of ether was added dropwise 6mmol of methyl lithium in 10ml of ether at 0°C. The reaction mixture was stirred at room temperature. After 1 h, dil. HCl was added to the mixture, made basic with $NaHCO_3$, and extracted with ether. The extract was dried over Na_2SO_4, and concentrated in vacuo. The resulting oil was dissolved in 20ml of methanol, and a trace of bromocresol green (pH 3.8-5.4) was added followed by

the addition of a 2N solution of HCl in methanol until the color turned yellow. Then 0.33g(5mmol) of $NaBH_3CN$ was added with stirring, and the methanolic HCl was added dropwise to maintain the yellow color. After stirring at room temperature for 1h, the solution was poured into 20ml of 0.1N NaOH, saturated with NaCl and extracted with ether. The extract was dried over Na_2SO_4, an concentrated in vacuo to give a mixture of 2'S,5'S- and 2'S,5'R-5'-methylnicotine(3a and 4a). These diastereomers were separated by a reversed phase column chromatography (ODS; 22mm ϕ x 50cm; CH_3OH : H_2O = 4 : 1), and 0.47g(53%) of 3a and 0.13g(15%) of 4a were obtained. (3a): mass(m/z); 176(M+; 7), 98(22), 118(7), 130(35), 147(6), 161(100), 162(10), 175(5): Found: m/z, 176.1322. Calcd for $C_{11}H_{16}N_2$: M, 176.1314: $[\alpha]_{546}^{25}$ -96.4° (c=0.6, MeOH); (4a): mass(m/z); 176(M+; 10), 98(18), 118(7), 130(41), 147(12), 161(100), 162(11), 175(8): Found: m/z, 176.1325. Calcd for $C_{11}H_{16}N_2$: M, 176.1314: $[\alpha]_{546}^{25}$ -65.2° (c=0.23, MeOH).

2'S,5'S-5'-Ethylnicotine(3b) and 2'S,5'R-5'-Ethylnicotine(4b) --- The reaction of 2 with ethyl lithium was carried out in a similar manner as described above. After separation, 0.37g(39%) of 2'S,5'S-5'-ethylnicotine(3b) and 0.08g(8%) of 2'S,5'R-5'-ethylnicotine(4b) were obtained. (3b): mass(m/z); 190(M+; 2), 118(7), 130(23), 161(100), 162(11): Found: m/z, 190.1433. Calcd for $C_{12}H_{18}N_2$: M, 190.1471: $[\alpha]_D^{25}$ -40.7° (c=1.15, MeOH); (4b): mass(m/z); 190(M+; 4), 118(7), 130(42), 161(100), 162(15): Found: m/z, 190.1450. Calcd for $C_{12}H_{18}N_2$: M, 190.1471: $[\alpha]_D^{25}$ -65.5° (c=0.33, MeOH).

2'S,5'S-5'-n-Butylnicotine(3c) and 2'S,5'R-5'-n-Butylnicotine(4c) --- The reaction of 2 with n-butyl lithium was carried out in a similar manner as described above. After separation, 0.57g(53%) of 2'S,5'S-5'-n-butylnicotine (3c) and 0.19g(18%) of 2'S,5'R-5'-n-butylnicotine(4c) were obtained. (3c): mass(m/z); 218(M+; 1), 92(4), 118(5), 130(6), 161(100), 171(10), 217(1): Found: m/z, 218.1761. Calcd for $C_{14}H_{22}N_2$: M, 218.1783: $[\alpha]_D^{25}$ -37.6° (c=1.9, MeOH); (4c): mass(m/z); 218(M+; 2), 118(3), 130(29), 161(100), 162(11), 217(1): Found: m/z, 218.1759. Calcd for $C_{14}H_{22}N_2$: M, 218.1783: $[\alpha]_D^{25}$ -85.1° (c=0.1, MeOH).

2'S,5'R-5'-Phenylnicotine(3d) and 2'S,5'S-5'-Phenylnicotine(4d) --- The reaction of 2 with phenyl lithium was carried out in a similar manner as

described above. After separation, 0.71g(59%) of 2'S,5'R-5'-phenylnicotine(3d) and 0.08g(7%) of 2'S,5'S-5'-phenylnicotine(4d) were obtained. (3d): mass(m/z); 238(M+; 21), 91(8), 118(13), 130(15), 160(96), 161(100), 195(4), 209(15), 237(33): Found: m/z, 238.1493. Calcd for $C_{16}H_{18}N_2$: M, 238.1470: $[\alpha]_D^{25}$ -8.3° (c=6.1, MeOH); (4d): mass(m/z); 238(M+; 30), 91(12), 118(16), 130(17), 160(100), 161(79), 195(9), 209(33), 237(30): Found: m/z, 238.1441. Calcd for $C_{16}H_{18}N_2$: M, 238.1470: $[\alpha]_{546}^{25}$ -88.9° (c=1.26, MeOH).

2'S,5'R-5'-Isopropylnicotine(3e) and 2'S,5'S-5'-Isopropylnicotine(4e) --- The reaction of 2 with isopropyl lithium was carried out in a similar manner as described above. After separation, 0.48g(48%) of 2'S,5'R-5'-isopropylnicotine (3e) and 0.06g(6%) of 2'S,5'S-5'-isopropylnicotine(4e) were obtained. (3e): mass(m/z); 204(M+; 1), 118(5), 130(50), 161(100), 162(17), 189(1), 203(1): Found: m/z, 204.1611. Calcd for $C_{13}H_{20}N_2$: M, 204.1626: $[\alpha]_D^{25}$ -29.5° (c=0.6, MeOH); (4e): mass(m/z); 204(M+; 1), 118(7), 130(45), 161(100), 162(11), 189(3): Found: m/z, 204.1650. Calcd for $C_{13}H_{20}N_2$: M, 204.1626: $[\alpha]_D^{25}$ -15.0° (c=0.08, MeOH).

2'S,5'R-5'-tert-Butylnicotine(3f) --- The reaction of 2 with tert-butyl lithium was carried out in a similar manner as described above. After separation 0.10g(9%) of 2'S,5'R-5'-tert-butylnicotine(3f) was obtained. mass(m/z); 218(M+; 0.02), 130(25), 161(100), 162(9), 203(5): Found: m/z, 203.1547. Calcd for $C_{13}H_{19}N_2$: M - CH_3, 203.1548: $[\alpha]_D^{25}$ -76.0° (c=0.5, MeOH).

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