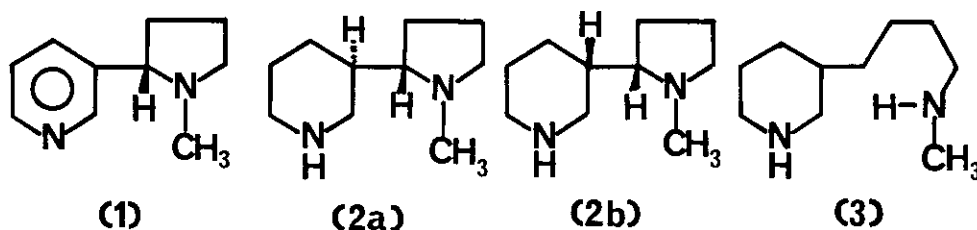


THE SYNTHESIS OF 2'S,3R- AND 2'S,3S-HEXAHYDRONICOTINE

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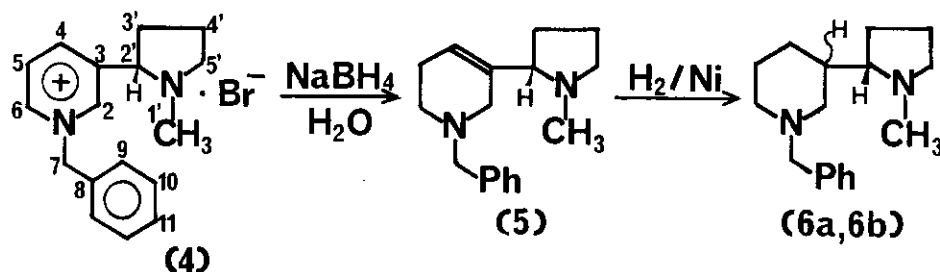
Abstract - The reduction of 1-benzylnicotinium bromide(4) with NaBH_4 led to 1-benzyl-1,2,5,6-tetrahydronicotine(5), and the catalytic reduction of 5 over Raney nickel gave 2'S,3R- and 2'S,3S-1-benzylhexahydronicotine(6a,6b) in the ratio of 4 : 1 at room temperature. The debenzylations of 6a and 6b were carried out by the catalytic reduction over palladium on charcoal to give 2'S,3R- and 2'S,3S-hexahydronicotine(2a,2b), respectively. The configurations of 2a and 2b were determined by NMR spectra.

In the study of the biological activities of compounds structurally related to nicotine(1), hexahydronicotine(2) is one of the interesting compounds. 2 was first obtained by the reduction of 1 with sodium in ethanol.¹ The catalytic reduction of 1 over platinum or nickel has also been reported.² However, these

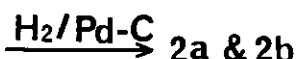


reductions required rather drastic conditions, and the products were always accompanied by a fair amount of octahydronicotine(3). Furthermore, the separation of the two diastereomers of 2 has not been reported.

In this paper we wish to report a new synthetic method for 2'S,3R- and 2'S,3S-hexahydronicotine. The determination of the configurations of these



diastereomers will also be reported.



The reduction of 1-benzylpyridinium bromide(4)³ with sodium borohydride afforded 1-benzyl-1,2,5,6-

tetrahydronicotine(5) in an 80% yield. The catalytic reduction of 5 over Raney nickel gave 1-benzylhexahydronicotine as a mixture of two diastereomers(6a and 6b). Although the separation of the debenzylated products(2a and 2b) was unsuccessful, that of 6a and 6b was carried out efficiently by a reversed phase column chromatography (ODS).

Thus, 6a and 6b were obtained from the reaction mixture in 72% and 23% yields, respectively. The debenzylations of 6a and 6b were carried out by the catalytic reduction over 5% palladium on charcoal, and the yields of 2a and 2b were 95% and 90%, respectively.

Relative configurations of 2a and 2b were confirmed by ¹³C NMR analysis. The assignments of individual resonances in 2a, 2b, 5, 6a, and 6b shown in Table 1 and Table 2 were estimated by two dimensional shift correlated spectroscopy (COSY) and two dimensional heteronuclear correlated spectroscopy

Table 1 ¹³C NMR chemical shifts
(ppm from TMS)

	2a	2b	6a	6b	5
1'	41.4	41.5	41.3	41.4	40.4
2'	69.4	68.7	69.2	68.7	71.9
3'	27.3	27.0	26.7	26.4	30.3
4'	22.5	22.8	22.4	22.7	22.3
5'	57.8	57.6	57.7	57.6	56.7
2	47.4	51.2	55.2	58.7	52.0
3	39.1	39.6	37.9	38.3	136.6
4	29.5	25.1	28.8	24.4	121.7
5	26.6	26.4	25.8	25.6	25.8
6	47.4	47.5	53.9	54.8	49.5
7	-	-	63.7	64.0	62.6
8	-	-	138.7	138.9	138.5
9	-	-	128.0	128.3	128.1
10	-	-	129.0	129.4	129.1
11	-	-	126.7	127.0	126.8

analysis.

The most remarkable difference in the chemical shifts between 2a and 2b was recognized at 2- and 4-carbon. This fact was presumed to be caused by the difference of the steric effect of pyrrolidine ring on these two carbons. If the cyclopentane ring is attached to 3-position in piperidine ring, the γ -effect on 2- and 4-carbon must be equal. The substituent chemical shift (SCS) was applied to 3-methylpiperidine (7)⁴ to estimate the difference of the γ -effect. Three kinds of the chemical shifts of 2- and 4-carbon were calculated by the use of the additive parameters⁵ of the saturated carbon and the amino substituents at the methyl group in 7, which were listed in Table 3. As shown in Table 3, the chemical shifts of 2-carbon in 2a and 2b were close to the calculated ones estimated by the two amino and the two methyl substituents, respectively. Similarly, those of 4-carbon in 2a and 2b were close to the calculated ones estimated by the two methyl and the two amino substituents, respectively. These results suggested that 1'-nitrogen had stronger steric effects on 2-carbon than 4-carbon in 2a and on 4-carbon than 2-carbon in 2b.

These estimations were supported by ¹H NMR analysis. As shown in Table 2, the chemical shifts of equatorial protons on 2-carbon in 2a and 6a were shifted to

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

	<u>2a</u>	<u>2b</u>	<u>6a</u>	<u>6b</u>	<u>5</u>
1'	2.29	2.28	2.28	2.26	2.20
2'	1.98	1.99	2.02	1.98	2.48
3'	1.59	1.59	1.61	1.57	1.67
	1.71	1.70	1.70	1.67	1.83
4'	1.65	1.66	1.64	1.63	1.67
	1.67	1.67	1.66	1.68	1.67
5'	2.11	2.11	2.10	2.10	2.07
	3.02	3.04	3.01	3.02	3.06
2	2.38	2.38	1.81	1.77	2.92
	3.04	2.99	2.94	2.80	3.03
3	1.72	1.68	1.88	1.84	-
4	1.15	1.15	1.02	1.00	5.65
	1.68	1.78	1.64	1.70	-
5	1.47	1.47	1.55	1.53	2.13
	1.68	1.70	1.69	1.66	2.13
6	2.50	2.52	1.80	1.83	2.42
	3.01	3.03	2.79	2.84	2.57
7	-	-	3.37	3.45	3.52
	-	-	3.63	3.50	3.62
9	-	-	7.29	7.30	7.34
10	-	-	7.28	7.29	7.28
11	-	-	7.20	7.23	7.22

lower field in comparison with those in 2b and 6b, and those on 4-carbon in 2b and 6b were also shifted to lower field. These facts were presumed to be caused by the deshielding effect of the lone pair of 1'-nitrogen.

If the bond of 2'- and 3-carbons rotated rapidly, the difference of the chemical shifts of 2- and 4-carbon between 2a and 2b should disappear. The pyrrolidine and piperidine rings in both 2a and 2b, as well as

nicotine,⁶ can be regarded to have the fixed conformation, in which 2- and 4-carbon were close to 1'-nitrogen and 3'-carbon in 2a, respectively. Similarly, 2- and 4-carbon were close to 3'-carbon and 1'-nitrogen in 2b, respectively. This observation was supported by the coupling constant of 13.2Hz between the 2'- and 3-proton in both 2a and 2b and the dihedral angle was assumed to be approximately 0° or 180°. Thus, four probable conformations for 2a and 2b were proposed as shown in Figure 1. It is apparent that the conformation of A and C have smaller steric repulsions between the pyrrolidine and piperidine ring than B and D. From above mentioned discussion, we conclude

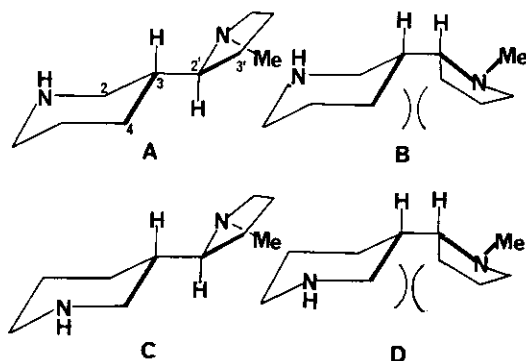


Figure 1

Table 3 ¹³C NMR chemical shifts
(ppm from TMS)¹⁾

	τ	cal. ²⁾	cal. ³⁾	cal. ⁴⁾	<u>2a</u>	<u>2b</u>
2	56.0	51.0	48.4	45.8	47.4	51.2
4	35.0	30.0	27.4	24.8	29.5	25.1

1) τ -effects of methyl and amino group are -2.5 and -5.1 ppm, respectively.

2) estimated by two methyl groups.

3) estimated by a methyl and an amino group

4) estimated by two amino groups.

that the configuration of 2a is A and that of 2b is C, that is, 2a is 2'S,3R-hexahydronicotine and 2b is 2'S,3S-hexahydronicotine, because 1'-nitrogen is close to 2-carbon in 2a and to 4-carbon in 2b.

This conclusion was su-

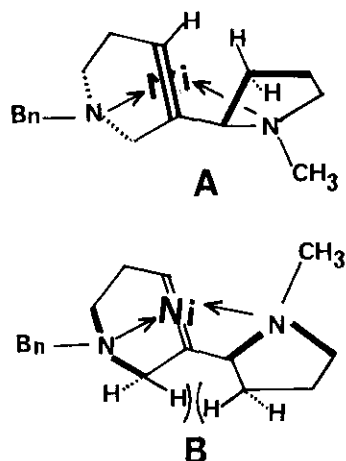


Figure 2

ported by the selectivity in the catalytic reduction of **5** over Raney nickel. In this reduction, we assumed that two nitrogens in **5** coordinated to nickel and that hydrogen attacked the unsaturated carbons from the same side of the coordinated nickel. As a result, two possible conformations of the transition states were considered. As shown in Figure 2, the steric repulsion between 2- and 3'-protons in B is larger than that between 4 and 3'-protons in A. Therefore, the reduction

proceeds through the conformation A predominantly, and 2'S,3R-hexahydronicotine is given as the major product.

EXPERIMENTAL

1-Benzyl-1,2,5,6-tetrahydronicotine (5) --- To a stirring solution of 1-benzylpyridinium bromide (**4**) (6.7g, 20mmol) in 80ml of water was added slowly 3.8g of NaBH₄ (100mmol) at room temperature. After 1h, 15ml of 6N HCl was added, and the resulting mixture was made basic (pH>11) with NaOH, and extracted with ether. The extract was dried over Na₂SO₄, and concentrated *in vacuo* to give 1-benzyl-1,2,5,6-tetrahydronicotine (**5**) (4.1g, 80%) after distillation (153°C, 2mmHg). MASS(m/e); 256(M⁺; 76), 91(100), 199(89), 212(89), 255(89); [α]_D²⁵ -52.9° (c=0.31 MeOH).

2'S,3R- and 2'S,3S-1-Benzylhexahydronicotine (6a and 6b) --- To a suspension of 0.8g of Raney nickel (R-4) in 60ml of methanol was added 1-benzyl-1,2,5,6-tetrahydronicotine (**5**) (4.1g, 16mmol). The reaction mixture was stirred under hydrogen at room temperature and atmospheric pressure. After 10h, nickel was filtered off, and the filtrate was concentrated *in vacuo* to give a mixture of 2'S,3R- and 2'S,3S-1-benzylhexahydronicotine (**6a** and **6b**). These diastereomers were separated by a reversed phase column chromatography (ODS; 22mm ϕ x 50cm; MeOH : H₂O = 3 : 1), and 2.8g(72%) of **6a** and 0.9g(23%) of **6b** were obtained.

MASS(m/e); (6a): 258(M⁺; 16), 84(100), 91(26), 167(9), 186(26); (6b): 258(M⁺; 11), 84(100), 91(27), 167(11), 186(16).

2'S,3R-hexahydronicotine(2a) --- To a solution of 2'S,3R-1-benzylhexahydronicotine(6a) (2.8g, 11mmol) in 10ml of ether was passed HCl gas. The resulting HCl salt of 6a was filtered, and was added to a suspension of 5% Pd-C (0.2g) in 45ml of methanol. The reaction mixture was stirred under hydrogen at room temperature and atmospheric pressure. After 4h, Pd-C was filtered off, and the filtrate was concentrated in vacuo. The resulting oil was dissolved in water, made basic(pH>11) with NaOH, and extracted with ether. The extract was dried over Na₂SO₄, concentrated in vacuo, and the resulting crystals were recrystallized by petroleum ether at -10°C to give 2'S,3R-hexahydronicotine(2a) (1.8g, 95%) as white crystals; mp 41-42°C. MASS(m/e); 168(M⁺; 6), 84(100), 96(5), 110(3); [α]_D²⁵ -51.2 (c=0.3, MeOH).

2'S,3S-hexahydronicotine(2b) --- The debenzylation of 2'S,3S-1-benzylhexahydronicotine(6b) (0.9g, 3.5mmol) proceeded in a similar manner mentioned above to give 2'S,3S-hexahydronicotine(2b) (0.5g, 90%) as a colorless oil. MASS(m/e); 168(M⁺; 4), 84(100), 96(4), 110(4); [α]_D²⁵ -37.1° (c=0.05, MeOH).

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