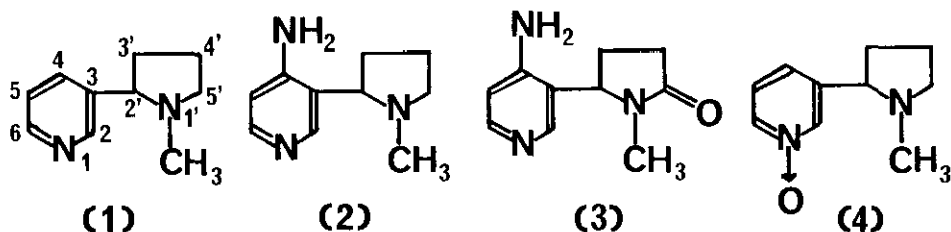


THE SYNTHESSES OF 4-AMINONICOTINE AND 4-AMINOCOTININE

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Abstract - 4-Aminonicotine and 4-aminocotinine were synthesized *via* 4-nitrocotinine-N-oxide, which was obtained by the nitration of cotinine-N-oxide.

Nicotine(1) is the most important component in tobacco, and its chemical and biological properties have been investigated for many years. Several derivatives of 1 which have functional groups on the pyridine ring have been reported.¹⁻⁴ Most of them are the compounds which are functionalized at the 2- and/or 6-position of the pyridine ring. For example, 2- and/or 6-amino-



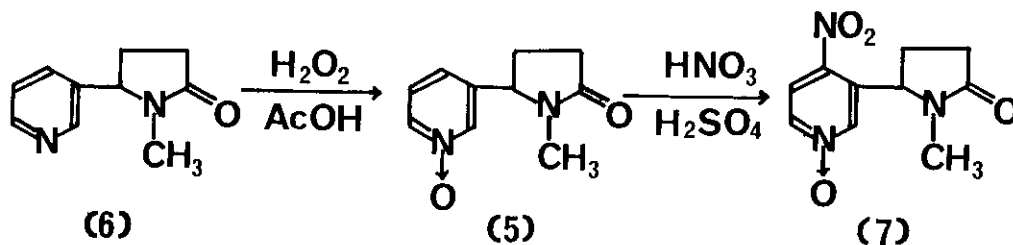
nicotine is easily obtainable by the reaction of 1 with sodium amide.¹ On the other hand, there has been no report concerning the synthesis of the compounds functionalized at 4-position.

In this paper, we wish to report a method to obtain 4-aminonicotine(2) and 4-aminocotinine(3).

The nucleophilicity at 4-position of pyridine is known to be enhanced by the oxidation of the nitrogen to N-oxide,⁵ and the nitration of nicotine-N-oxide(4), which was obtained by the selective reduction of nicotin-N,N'-dioxide with sulfur dioxide,² was attempted. However, the reaction of 4 with fuming nitric acid and concentrated sulfuric acid

underwent mainly the oxidation at the 2'-carbon and acetyl nitrate did not react with 4. Then, in order to avoid the oxidation at the 2'-carbon, we chose to start from cotinine-N-oxide(5).

The reaction of cotinine(6) with hydrogen peroxide in acetic acid gave 5 as white crystals in good yield(>95%). The nitration of 5 was tried under



several conditions, and finally carried out in a mixture of fuming nitric acid and concentrated sulfuric acid at 130°C to give 4-nitrocotinine-N-oxide(7) as yellow needles in 40% yield. The

reduction of 7 was performed with iron powder in acetic acid to give 3 as white crystals.

The reduction of the amide group in 3 was performed with BH₃ in diglyme to give 2 as white crystals after distillation.

The method *via* nitration of 5 was the best for the synthesis of 2. The ¹H and ¹³C NMR spectra of these compounds were listed in Table 1 and Table 2.

EXPERIMENTAL

Cotinine-N-oxide(5) --- To a solution of cotinine(6) (16.2g, 0.1mol) in 50ml of acetic acid was added 10ml of 35% aqueous hydrogen peroxide. The reaction mixture was kept at 70°C for 5 h. Most of the solvent was removed by distillation *in vacuo*, and a small amount of ethanol was added to the concentrate to decompose excess amount of peroxides. The resulting mixture was concentrated *in vacuo*, dissolved in water, neutralized by K₂CO₃, and extracted with chloroform. The extract was washed with aqueous K₂CO₃, dried over Na₂SO₄, and concentrated *in vacuo* to give 18.2g of cotinine-N-oxide(5) as white crystals in 95% yield; mp. 66-68°C

4-Nitrocotinine-N-oxideTable 1 ^1H NMR spectra (ppm from TMS)

(7) --- Cotinine-N-oxide (5) (3.7g, 19mmol) was added slowly to a mix- ture of concentrated H_2SO_4 (40ml) and fuming HNO_3 (40ml). After reflux- ing for 5 h, the re- action mixture was pour- ed over 100g of ice carefully, and neutra- lized by K_2CO_3 , and extracted with chloro- form. The extract was dried over Na_2SO_4 , con- centrated <u>in vacuo</u> , and recrystallized from		1	6	5	7	3	2
	1'	2.18	2.69	2.73	2.83	2.74	2.18
	2'	3.07	4.61	4.54	5.31	4.56	3.16
	3'	1.73	1.91	1.89	1.95	2.15	1.84
		2.21	2.49	2.49	2.85	2.38	2.03
	4'	1.80	2.57	2.57	2.48	2.51	1.84
		1.95	2.57	2.57	2.51	2.56	2.00
	5'	2.31	-	-	-	-	2.22
		3.25	-	-	-	-	3.12
	2	8.54	8.52	8.18	8.02	8.06	8.00
	4	7.68	7.57	7.16	-	-	-
	5	7.22	7.38	7.37	8.12	6.56	6.41
	6	8.48	8.60	8.21	8.18	8.17	8.07

chloroform to give 1.8g

of 4-nitrocotinine-N-oxide(7) (7.6mmol) as yellow needles in 40% yield; mp. 171.5-172.5°C.

4-Aminocotinine(3) --- Iron powder(4.0g) was added to a solution of 4-nitrocotinine-N-oxide(7) (1.8g, 7.6mmol) in 20ml of acetic acid. After refluxing for 5h, excess amount of Fe powder was filtered off, and the filtrate was diluted with water and made basic (pH>12) by NaOH. Redish precipitate was filtered off and the filtrate was extracted with chloroform, dried over Na_2SO_4 , and concentrated in vacuo to give 1.0g of 4-aminocotinine(3) (5.2mmol) as white crystals in 68% yield; mp. 195-196°C. IR:(cm^{-1}) 1377, 1453, 1462, 1600, 1666, 1680 :MASS; (m/z) 191(M+;100), 98(41), 119(53), 120(25), 133(39), 134(45), 148(33), 162(71), 163(34), 176(21): $[\alpha]_D^{25} = -117.9^\circ\text{C}$ (c=2.2, MeOH)

4-Aminonicotine(2) --- 4-Aminocotinine(3) (1.9g, 10mmol) and NaBH_4 (1.9g,

50mmol) was dissolved in 20ml of diglyme, and 8.8g of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (6.3mmol) was added slowly to the solution. After stirring for 4 h at room temperature, the reaction mixture was poured into 30ml of water. Twenty ml of 10% HCl was added to the mixture and the mixture was made basic (pH>12) by NaOH, and extract with chloroform. The extract was concentrated in vacuo, and 1.0g of 4-

Table 1 ^{13}C NMR spectra (ppm from TMS)

	1	6	5	7	3	2
1'	40.30	28.21	28.32	29.06	28.31	40.09
2'	68.82	62.17	61.55	59.10	61.10	70.00
3'	35.24	28.21	27.68	27.12	24.21	30.15
4'	22.65	29.95	29.54	28.61	30.43	22.61
5'	56.93	175.35	175.23	175.46	175.75	56.58
2	149.37	149.60	138.70	139.05	151.00	149.83
3	138.61	136.58	141.26	137.00	117.51	119.27
4	134.57	133.78	123.62	141.42	149.22	152.45
5	123.33	124.02	126.59	123.00	110.79	110.09
6	148.40	148.34	137.71	137.95	149.89	148.86

aminonicotine (2) (5.6mmol) was obtained as white crystals after distillation (bp. 160°C at 2mmHg) in 56% yield; mp. 125-126°C. MASS;(m/z) 177(M+, 22), 84(54), 119(14), 121(42), 134(20), 148(40), 162(100), 176(11): $[\alpha]_{\text{D}}^{25} = -95.2^\circ$ (c=0.7, MeOH)

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