THE SYNTHESES OF 4-AMINONICOTINE AND 4-AMINOCOTININE

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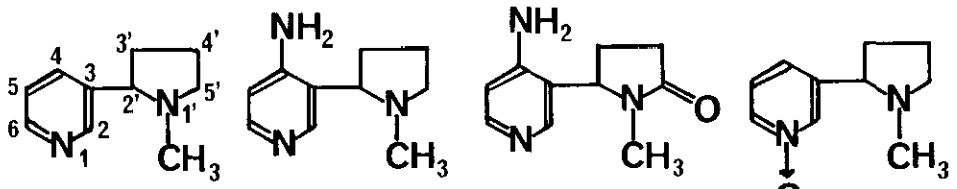
Abstract - 4-Aminonicotine and 4-aminocotinine were synthesized via 4-nitrocotinine-N-oxide, which was obtained by the nitration of cotinine-N-oxide.

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-



(1) (2) (3) (4)

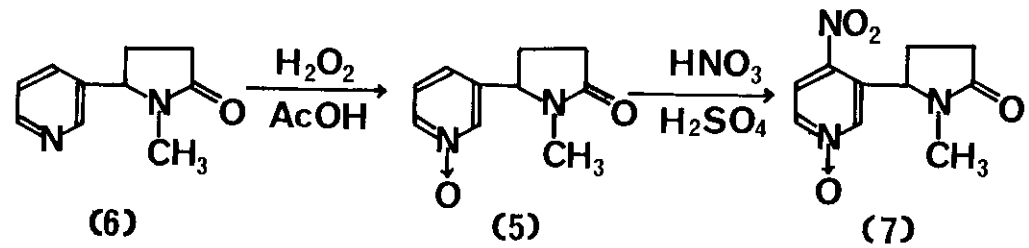
nicotine is easily obtainable by the reaction of 1 with sodium amide.[1] On the other hand, there has been no report concerning the synthesis of the compounds functionalized at 4-position.

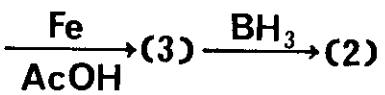
In this paper, we wish to report a method to obtain 4-aminonicotine(2) and 4-aminocotinine(3).

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 BH_3 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 ^{13}C 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 K_2CO_3, and extracted with chloroform. The extract was washed with aqueous K_2CO_3, dried over Na_2SO_4, and concentrated in vacuo to give 18.2g of cotinine-N-oxide(5) as white crystals in 95% yield; mp. 66-68°C

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

	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

4-Nitrocotinine-N-oxide (7) --- Cotinine-N-oxide (5) (3.7g, 19mmol) was added slowly to a mixture of concentrated H_2SO_4(40ml) and fuming HNO_3(40ml). After refluxing for 5 h, the reaction mixture was poured over 100g of ice carefully, and neutralized by K_2CO_3, and extracted with chloroform. The extract was dried over Na_2SO_4, concentrated *in vacuo*, and recrystalized from 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 bacic (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°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 $BF_3 \cdot Et_2O$(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 bacic (pH>12) by NaOH, and extract with chloroform. The extract was concentrated in vacuo, and 1.0g of 4-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): $[\alpha]_D^{25}$= -95.2° (c=0.7, MeOH)

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

REFERENCES

1) H. E. Tschitschibabin and A. W. Kirssanow, Chem. Ber., 1924, 57, 1163

2) J. D. Phillipson and S. S. Handa, Phytochemistry, 1975, 14, 2683

3) M. Shibagaki, H. Matsushita, S. Shibata, A. Saito, Y. Tsujino, and H. Kaneko, Heterocycles, 1982, 19, 1641

4) H. Matsushita, M. Noguchi and E. Tamaki, Biochem. Biophys. Res. Comm., 1974, 57, 1006

5) E. Ochiai, "Aromatic Amine Oxides"; Elsevier: New York, 1967; H. Saito and M. Hanada, Heterocycles, 1979, 12, 475; H. Tanida, T. Irie and Y. Hayashi, J. Org. Chem., 1984, 49, 2527

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