THE STEREOSELECTIVE OXIDATION OF 1-BENZYLNICOTINIUM BROMIDE TO ITS 1′-N-OXIDE

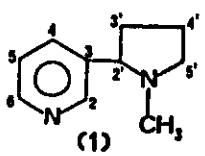
Makoto Shibagaki*, Hajime Matsushita, and Hajime Kaneko
Central Research Institute, The Japan Tobacco & Salt Public Corporation
6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan

Abstract —— 1′-N-oxidation of 1-benzylnicotinium bromide(4) was studied. Among the oxidizing agents examined, peroxomolybdate and peroxotungstate gave the cis- and trans-1′-N-oxides(5 and 6) in the ratio of 1 : 14 and 1 : 15, respectively.

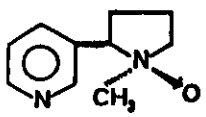
There have been some reports concerning the stereochemistry of 1′-N-oxidation of nicotine(1)[1-4]. The oxidation of 1 with aqueous hydrogen peroxide gave a mixture of the cis- and trans-1′-N-oxides(2 and 3) in a ratio of 1 : 2.3.[1] The oxidation with m-chloroperbenzoic acid(m-CPBA) gave the same compounds in a ratio of 1 : 2.[2] It is interesting that peroxomolybdate or peroxotungstate, which are obtained in situ by adding alkali molybdate(VI) or tungstate(VI) to aqueous hydrogen peroxide, respectively, accelerated the oxidation and favored the formation of 2.[4] Thus a 2.7 : 1 ratio of 2 to 3 was observed when 0.8 molar equivalent of sodium molybdate(VI) was added to aqueous hydrogen peroxide. In this paper, we wish to report the stereochemistry of 1′-N-oxidation of 1-benzylnicotinium bromide(4)[5] by means of these oxidizing agents.

The results are listed in Table 1. The ratio of cis (5) to trans (6) was determined by N-methyl signals in ^{1}H NMR spectra of the products.[6]

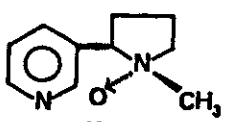
As shown in Table 1, peroxomolybdate or peroxotungstate led to an excellent stereoselectivity favoring the formation of trans-1′-oxide(6) in contrast to the case of 1. Although it is not clear how resinous substances which lowered the yield of



(1)



(2)



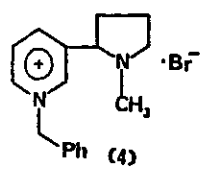
(3)

Table 1 Oxidation of 4

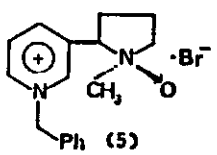
Oxidizing agent [a]	Solv.	Temp.(°C)	Time(h)	Conv.(%)	Yield(%)	5 : 6
H_2O_2	4	H_2O	0	24	33	31	1 : 2.5
H_2O_2	4	H_2O	25	24	60	60	1 : 3
H_2O_2	4	H_2O	40	4	50	47	1 : 2.7
K_2MoO_4 [b]	1	H_2O	25	1	100	45	1 : 14
K_2MoO_4 [b]	0.5	H_2O	25	1	100	36	1 : 13
K_2WO_4 [b]	1	H_2O	25	1	100	49	1 : 15
m-CPBA	1.2	CH_2Cl_2	25	1	60	50	1 : 0.38
m-CPBA	1.2	CH_3OH	25	1	19	19	1 : 2.3

a) molar ratio of oxidizing agent to 4

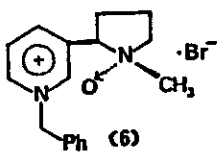
b) 4 equivalent of H_2O_2 was added to the reaction mixture.



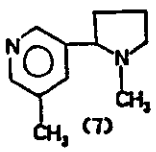
(4)



(5)



(6)



(7)

the oxides were produced in these cases, the stereoselectivities were not caused by the selective degradation of cis-1′-N-oxide (3). This was confirmed by the following fact. After a treatment of a mixture of 5 and 6 in the ratio of 1 : 0.38 with peroxomolybdate under the same condition as the oxidation of 4, the ratio of 5 to 6 was not changed (5 : 6 = 1 : 0.4).

It has been reported that the stereochemistry of 1′-N-methylation of 1 is not affected by a methyl substituent at it's 5-position; that is, the ratio of cis- to trans-1′-methylation in 5-methylnicotine(7) is almost the same as in 1.[7] Analogously, the steric effects of the 1-N-benzyl group in 4 on 1′-N-oxidation may be negligible. In fact, 10% aqueous hydrogen peroxide at several reaction temperatures afforded the ratio of 5 to 6, similar to that obtained in the case of 1. The high stereoselectivity for the formation of 6 can be explained by assuming that molybdate or tungstate anion is first attracted to

Table 2 ^{13}C NMR chemical shifts of 5 and 6[8]

	N-CH3	2′	3′	4′	5′	2	3	4	5	6
5	41.07	70.03	32.88	23.81	58.62	153.16	147.49	146.90	127.07	148.19
6	55.75	78.16	30.60	22.17	72.60	153.33	148.24	147.13	129.99	150.70

	CH2-Ph	Ph
5	66.87	131.57~136.49
6	66.98	131.45~135.72

the quaternary pyridine nitrogen and then attacks the pyrrolidine nitrogen. In such a mechanism, the trans conformer of 4 which has the pyridine ring and the lone pair of the pyrrolidine nitrogen on the same side of the pyrrolidine ring would be more susceptible to the attack of the oxidizing agents to afford 6.

Although it is very interesting, the reason for solvent dependence of the stereoselectivity in m-CPBA oxidation is not clear at present.

EXPERIMENTAL

Oxidation with hydrogen peroxide --- To a solution of 5 mmol of 1-benzylnicotinium bromide(4) in 20 ml of water was added 20 mmol of 35% aqueous hydrogen peroxide. The reaction mixture was stirred for 1 day at 25°C, and 1g of Pd-Al_2O_3 was added to the mixture to decompose excess hydrogen peroxide. After filtration, the filtrate was passed through a short column of C_{18} hydrocarbon coated silica to remove resinous substances. The eluate was concentrated in vacuo to give a brown oil. The ratio of cis (5) to trans (6) was determined by ^1H NMR analysis of the oil in D_2O. The oxidations at other temperatures were performed in a similar manner.

^1H NMR(δ)[8]; cis-1′-N-oxide: 2.30~2.86(4H, m), 2.88(3H, s), 3.80~4.04(2H, m), 4.98~5.22(1H, m), 6.04(2H, s), 7.40~7.70(5H, m), 8.32(1H, dd, J=7Hz and 8Hz), 8.94(1H, d, J=8Hz), 9.14(1H, d, J=7Hz), 9.40(1H, s)

trans-1′-N-oxide: 2.30~2.88(4H, m), 3.20(3H, s), 3.80~4.04(2H, m), 4.98~5.22(1H, m), 6.04(2H, s), 7.40~7.70(5H, m), 8.32(1H, dd, J=7Hz and 8Hz), 8.94(1H,

d, J=8Hz), 9.14(1H, d, J=7Hz), 9.40(1H, s)

Oxidation with peroxomolybdate or peroxotungstate --- To a solution of 5 mmol of **4** in 20 ml of water were added 20 mmol of 35% aqueous hydrogen peroxide and 5 mmol of potassium molybdate(VI) at 0°C. The reaction mixture was stirred for 1h at 25°C, and was passed through an anion exchange resin columm(Dowex 1-X4) to remove molybdate. The eluant was concentrated in vacuo and then a small amount of ethanol was added to the concentrate. The resulting solid of potassium salt was filtered off, and the ethanol layer was diluted with water and treated with a short column in a similar manner as described above. Oxidation by a half amount of peroxomolybdate or by peroxotungstate was proceeded in a similar manner.

Oxidation with m-chloroperbenzoic acid --- To a solution of 5 mmol of **4** in 20 ml of dichloromethane was added 6 mmol of m-chloroperbenzoic acid at 0°C. The reaction mixture was stirred for 1h at 25°C, and extracted with water. The water extract was washed with dichloromethane, and was treated in a similar manner as described above. The oxidation in methanol as a solvent was performed in a similar manner described above.

REFERENCES

1) A. W. Johnson, T. J. King, and J. R. Turner, J. Chem. Soc., 1958, 3230.

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

3) A. H. Beckett, P. Jenner, and J. W. Gorrod, Xenobiotica, 1973, **3**, 557.

4) S. Brandange, L. Lindblom, and D. Samuelsson, Acta Chem. Scand., 1977, **B31**, 907.

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

6) The ^{1}H NMR spectra of **5** and **6** were identical with those of the benzylated products of **2** and **3**, respectively.

7) J. I. Seeman, H. V. Secor, C. G. Chavdarian, E. B. Sanders, R. L. Bassfield, and J. F. Whidby, J. Org. Chem., 1981, **46**, 3040.

8) ppm from DSS in D_2O.

Received, 1st August, 1983