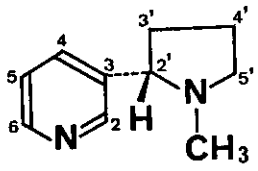
# BASE-CATALYZED RACEMIZATION OF NICOTINE

Yasuko Tsujino, Saizo Shibata, Akio Katsuyama, Takuro Kisaki,
and Hajime Kaneko
Central Research Institute, The Japan Tobacco & Salt Public
Corporation, 6-2 Umegaoka, Midori-ku, Yokohama, Kanagawa 227, Japan

Abstract — Catalytic activities of various bases on the racemization of nicotine were investigated. S-(-)-Nicotine was completely racemized by refluxing with a catalytic amount of potassium-t-butoxide for a short time. Thus, a facile preparation method of racemic nicotine was provided.

It is interesting to elucidate the biological activities of R-(+)-nicotine from the viewpoint of better understanding of these of natural S-(-)-nicotine, particularly in its relation to the specific receptors in the central nervous system. However, probably because of the difficulties of obtaining pure R-(+)-nicotine, there have been relatively little reports on this subject.[1] One of the problems is the optical resolution of (±)-nicotine, and another is the preparation of (±)-nicotine. As to the former, Aceto et al.[1] recently obtained pure R-(+)-nicotine by using a combination of (+)-tartaric acid and di-p-toluoyl-(-)-tartaric acid. R-(+)-nicotine was also obtained from (±)-nicotine by a stereoselective microbial degradation of S-(-)-nicotine.[2] Because the synthesis of (±)-nicotine is tedious, the racemization of natural (-)-nicotine seems most practical for the preparation of (±)-nicotine. Racemization of (-)-nicotine by heating its organic or inorganic salts has been reported.[3] In this method, a prolonged heating at high temperature in a sealed tube was required, and the recovery of (±)-nicotine was not satisfactory because of degradation and polymerization. Thus, the development of more useful procedure has been required.




S-(−)-Nicotine

Here we wish to report base-catalyzed facile racemization of nicotine. Natural S-(-)-nicotine was heated with a catalytic amount of various bases, and the optical rotation of the recovered nicotine was measured. The results are shown in Table 1.

Table 1. Effects of Various Bases on Racemization of (-)-Nicotine

| | Base | Base/Nicotine (mol%) | Temp. (°C) | Time (min) | Racemization[a] yield (%) |
|---|---|---|---|---|---|
| 1 | MeONa | 15.0 | 247[b] | 10 | 2.9 |
| 2 | MeONa | 4.5 | 247 | 10 | 2.5 |
| 3 | MeOK | 4.5 | 247 | 10 | 34.4 |
| 4 | EtONa | 4.5 | 247 | 10 | 3.0 |
| 5 | EtOK | 4.5 | 247 | 10 | 60.0 |
| 6 | t-BuONa | 4.5 | 247 | 10 | 4.5 |
| 7 | t-BuOK | 4.5 | 247 | 10 | 100.0 |
| 8 | t-BuOK | 4.5 | 70 | 100 | 2.3 |
| 9 | t-BuOK | 4.5 | 150 | 100 | 9.8 |
| 10 | t-BuOK -HMPA[c] | 4.5 | 150 | 10 | 100.0 |
| 11 | NaH | 4.5 | 247 | 10 | 9.2 |
| 12 | KH | 4.5 | 247 | 10 | 23.3 |
| 13 | $NaNH_2$ | 4.5 | 247 | 10 | 27.5 |

a) measured by optical rotation
b) b.p. of nicotine
c) 2.5 ml of HMPA was added to 1.62 g of nicotine.

Among the bases examined, potassium t-butoxide (t-BuOK) was most effective. Thus, after 10 minutes reflux with 4.5 mol% of t-BuOK, nicotine was distilled to give a completely racemized specimen in over 95% recovery. A combination of t-BuOK and hexamethylphosphoramide (HMPA) was more effective, but this was not practical because the separation of the nicotine and HMPA was tedious.

The influences of the alkoxyl groups and the counter ions on the racemization were quite obvious. The catalytic activities were in the order of $t\text{-BuO}^- > \text{EtO}^- > \text{MeO}^-$, and potassium ion was far more effective than sodium ion. Although in the series of the alkoxides the basicity of each catalyst seemed to relate to the catalytic activity, NaH, KH and $NaNH_2$ were not so effective as expected from their rather strong basicities.

The racemization rate was measured in the case of t-BuOK. Result is shown in Fig.1. The racemization rate was found to obey good first-order kinetics.

A deuterium exchange experiment was also carried out. Mixture of (-)-nicotine,

t-BuOK and t-BuOD was heated at 250°C for 1 hr in an autoclave. The optical rotation of recovered nicotine was 0°, and its mass spectrum showed an $M^+$ peak at m/z 167 and a base peak at m/z 85. In its $^1$H-NMR spectrum (400 MHz) signals at $\delta$ 8.54, 8.48, 7.68, 7.22 and 3.07 became very weak. These facts suggested that both 2'-proton of pyrrolidine ring and pyridine protons were deuterated. Other protons of pyrrolidine ring were not deuterated. A base-catalyzed deuterium exchange of 3-methylpyridine was examined in the same manner. The peak at m/z 100 ($M^+$) in the mass spectrum showed that all protons in the molecule were deuterated.

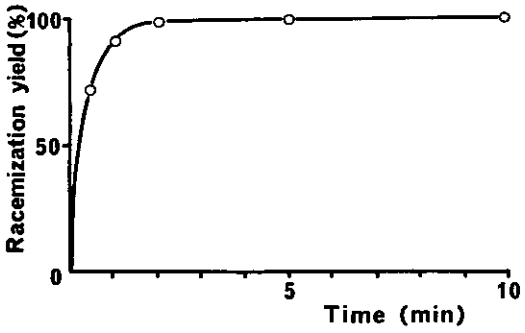



Fig.1. Racemization Rate of (-)-Nicotine
condition : nicotine + 4.5 mol% t-BuOK, reflux

From the fact that N'-methyl group of nicotine was not deuterated and the methyl group of 3-methylpyridine was deuterated, the base-catalyzed racemization of nicotine was concluded to proceed by the extraction of 2'-proton assisted by the electronic effect of the pyridine ring.

## EXPERIMENTAL

Materials Commercially available S-(-)-nicotine was dried over $CaH_2$ and distilled under reduced pressure. $[\alpha]_D^{25}$ -136.4° (c=10, MeOH). MeOK, EtOK and t-BuONa were prepared from corresponding alcohols and metal hydrides. Other bases were commercially available.

Optical rotation Optical rotation was measured in MeOH solution using a JASCO DIP-181 polarimeter.

Racemization of nicotine A typical example is as follows. Base (0.45 mmol) was added to nicotine (1.62 g, 10 mmol) and the mixture was refluxed for 10 min. It was then cooled, and the nicotine was recovered by a bulb to bulb distillation under reduced pressure. A semi-large scale experiment was done in the same manner using 16.2 g of nicotine and 0.5 g of t-BuOK. After a distillation under reduced pressure, 15.6 g of the nicotine which showed single peak in a gas chromatography was recovered (96.3% recovery). In the case of t-BuOK-HMPA system, after the reaction, the mixture was acidified with 6N HCl and extracted 10 times with $CHCl_3$

to remove the HMPA completely. The aqueous layer was made alkaline with aq. NaOH and extracted with ether. The ether layer was dried over $Na_2SO_4$ and distilled under reduced pressure to give the nicotine.

Racemization rate To a refluxing nicotine (1.94 g, 12 mmol) was added 0.06 g of t-BuOK (0.54 mmol) all at once through the reflux condenser. After 30 sec, the mixture was cooled rapidly with water, and brine was added to the mixture. Extraction with ether followed by a bulb to bulb distillation gave pure nicotine, of which optical rotation was measured. In the same manner, racemization after 1 min and 5 min were also examined.

Deuterium exchange A mixture of nicotine (243 mg, 1.5 mmol), t-BuOD (4.5 g, 60 mmol) and t-BuOK (112 mg, 1.0 mmol) was heated at 250°C for 1 hr in an autoclave. The nicotine was recovered from the reaction mixture by a bulb to bulb distillation under reduced pressure.

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