

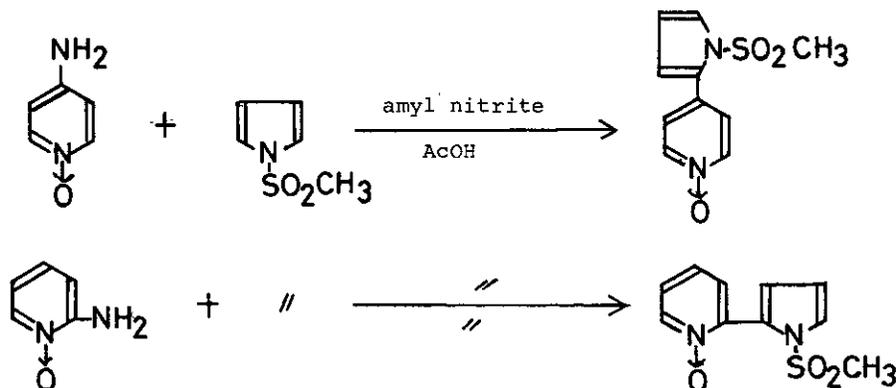
A NEW SYNTHESIS OF NORNICOTYRINE¹Seitaro Saeki,[•] Takaaki Hayashi, and Masatomo Hamana²

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Abstract — The reaction of 3-aminopyridine 1-oxide (1) and 1-methanesulfonylpyrrole (2) with amyl nitrite in acetic acid gave 1-methanesulfonyl-2-(1-oxido-3-pyridyl)pyrrole (3), which was converted into nornicotyrine (4) by successive treatment with phosphorous tribromide and sodium hydroxide solution.

We recently reported that the pseudo-Gomberg reaction³ of 4-aminopyridine 1-oxide with aromatic hydrocarbons by means of amyl nitrite smoothly occurs in acetic acid to afford 4-arylpyridine 1-oxides⁴. It was further found that reactions of 4- and 2-aminopyridine 1-oxides with 1-methanesulfonylpyrrole also readily proceed under the same conditions to give the corresponding 2-substituted pyrroles as shown below, while the reaction with pyrrole itself or 1-methylpyrrole causes only resinification^{4,5}.

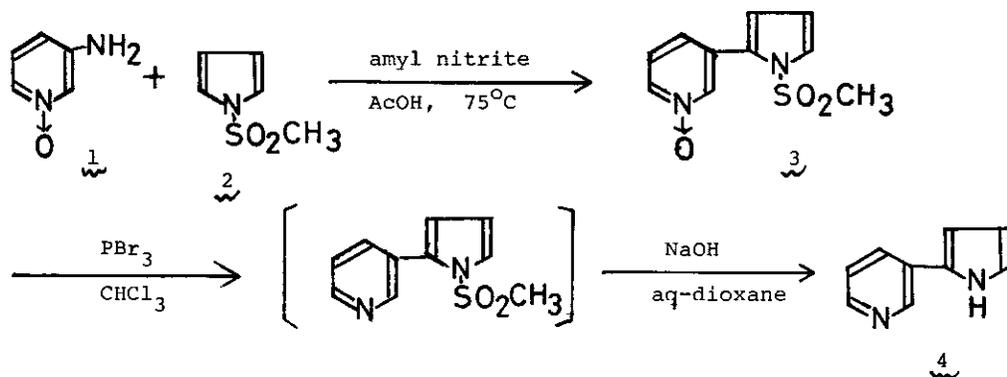


This paper describes a novel synthesis of nornicotyrine⁶ using the reaction of 3-aminopyridine 1-oxide (1) with 1-methanesulfonylpyrrole (2) under the same conditions as the key step.

The reaction of 3-aminopyridine with 2 was first attempted under the same conditions, but no coupling product was obtained, not unexpectedly, similarly to the reaction of 4- or 2-aminopyridine⁴, 2 being recovered almost quantitatively. On the other hand, the reaction of 3-aminopyridine 1-oxide (1) with 2 was found to proceed smoothly as was expected. Thus, amyl nitrite (1.28 eq) was added to a solution of 1 and 2 (10 eq) in acetic acid warmed at 75°C, and the reaction mixture was stirred for 1 h at the same temperature to give 1-methanesulfonyl-2-(1-oxido-3-pyridyl)pyrrole (3), colorless needles, mp 133-135°C, in 57.6% yield after purification by chromatography on silica gel.

Deoxygenation of 3 was easily effected by treatment with phosphorous tribromide in chloroform under reflux, and the resulting product was hydrolyzed at 60°C with an aqueous dioxane solution of sodium hydroxide to afford nornicotyrine (4), colorless needles, mp 97-98°C, in 87% yield; the overall yield of 4 from 1 is about 50%.

The analytical data, and the IR, ¹H-NMR and mass spectra of 3 and 4 were in full agreement with the respective structures.



As for the synthesis of nornicotyrine, Pictet and Crépiux⁶ described, in early 1895, that 1-(3-pyridyl)pyrrole formed by dry distillation of a mixture of 3-aminopyridine and mucic acid underwent rearrangement to nornicotyrine upon pyrolysis through a red heated tube, but they did not record its yield. The conditions are too much drastic and this process is apparently of little value for the preparative method of nornicotyrine.

EXPRIMENTAL

All melting points are uncorrected. IR spectra were recorded on a JASCO IR-E spectrometer. $^1\text{H-NMR}$ spectra were measured with a JEOL PS-100 spectrometer at 100 M Hz using TMS as internal reference. Mass spectra were obtained on a JMS 01SG spectrometer. Column chromatography was performed on Merk Silica Gel 60 PF₂₅₄.

1-Methanesulfonyl-2-(1-oxido-3-pyridyl)pyrrole (3) — A solution of 3-aminopyridine 1-oxide (1, 0.22 g, 2 mmol) and 1-methanesulfonylpyrrole (2, 2.9 g, 20 mmol) in AcOH (40 ml) was warmed at 75°C under stirring, and amyl nitrite (0.3 g, 2.58 mmol) was added slowly. Stirring was continued at the same temperature for 1 h, and the reaction mixture was concentrated under reduced pressure, made alkaline with 10% Na₂CO₃ solution and extracted with CH₂Cl₂. The extract was concentrated, and the residue was chromatographed on silica gel with n-hexane, CH₂Cl₂ and MeOH. The eluate with n-hexane-CH₂Cl₂ (2:1) gave unchanged 2 (2.41 g) and that with CH₂Cl₂-MeOH (35:1) afforded 0.247 g (57.6%) of 3 colorless needles, mp 133-135°C (diisopropyl ether). Anal. Calcd for C₁₀H₁₀N₂O₃S: C, 50.26; H, 4.22; N, 11.72. Found: C, 50.32; H, 4.31; N, 11.68. MS m/e: 238 (M⁺). IR) $\text{Nujol}_{\text{max}}^{-1}$: 1602 (C=N), 1581 (C=C), 1250 (N-O). $^1\text{H-NMR}$ (CDCl₃) δ : 8.16-8.36 (2H, m, Py-H₂, H₆), 7.20-7.56 (3H, m, Py-H₄, H₅, Pyrr-H₅), 6.40-6.50 (2H, m, Pyrr-H₃, H₄).

Nornicotyrine (4) — To an ice-cooled solution of 3 (0.476 g, 3.3 mmol) in CHCl₃ (40 ml) was added PBr₃ (2 g), and then the solution was refluxed for 5 h. The cooled solution was treated with 10% Na₂CO₃ solution to destroy excess PBr₃ and POBr₃ formed during the reaction. The CHCl₃ layer was separated and dried over MgSO₄. The residue from the CHCl₃ layer was warmed at 60°C for 5 h with a mixture of 10% NaOH solution (20 ml) and dioxane (20 ml). The reaction mixture was concentrated under reduced pressure, a small amount of water was added and extracted with CHCl₃. The residue from the CHCl₃ extract was chromatographed on silica gel with CH₂Cl₂-MeOH (100:1) to give 0.251 g (87%) of 4, colorless needles, mp 97-98°C (diisopropyl ether-n-hexane). Anal. Calcd for C₉H₈N₂: C, 75.0; H, 5.55; N, 19.44. Found: C, 74.97; H, 5.59; N, 19.43. MS m/e: 144 (M⁺). IR) $\text{Nujol}_{\text{max}}^{-1}$: 1602 (C=N), 1580 (C=C). $^1\text{H-NMR}$ (CDCl₃) δ : 9.62 (1H, bs, Pyrr-NH), 8.79 (1H, d, J_{2,4}=2.4 Hz, Py-H₂), 8.38 (1H, dd, J_{4,6}=1.9 Hz, J_{5,6}=4.8 Hz, Py-H₆), 7.76 (1H, dt, J_{4,5}=8.0 Hz, J_{4,6}=1.9 Hz, J_{2,4}=2.4 Hz, Py-H₄), 7.23 (1H, dd, J_{4,5}=8.0 Hz, J_{5,6}=4.8 Hz, Py-H₅), 6.90 (1H, m, Pyrr-H₅), 6.59 (1H, m, Pyrr-H₄), 6.32 (1H, m, Pyrr-H₃).

REFERENCES AND NOTE

1. Part LXXVIII in the series "Studies on Tertiary Amine Oxides". For part LXXVII, see Ref. 4.
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