Notes

Chem. Pharm. Bull.
15(4) 515～517 (1967)

UDC 547.551.2.07 : 547.821.4.07

Seiji Miyano, Akiko Uno, and Nobuhiro Abe: Syntheses of N-Pyridylmethylanilines and Its Reaction Mechanism.

(*Faculty of Pharmaceutical Sciences, Fukuoka University*[*1])

(Received June 7, 1966)

In the initial paper[1] one of the authors described the preparation of N-(2-pyridylmethyl)aniline (II, R=phenyl, R′=2-pyridyl) and its derivatives from various aromatic amines and 2-pyridinemethanol (I, R′=2-pyridyl) in the presence of potassium hydroxide. The present paper concerns the proof provided for the reaction mechanism and the extension of the same general synthetic procedure to prepare N-(4-pyridylmethyl)aniline (II, R′=4-pyridyl) and derivatives.

$$\text{R-NH}_2 + \underset{\text{I}}{\text{R}'\text{-CH}_2\text{OH}} \xrightarrow{\text{KOH}} \underset{\text{II}}{\text{R-NH-CH}_2\text{-R}'} + \text{H}_2\text{O}$$

Chart 1.

The reaction may be explained by condensation of aniline with 2-pyridinealdehyde which is present in 2-pyridinemethanol as an impurity[*2] to form a Schiff's base, N-(2-pyridylmethylene)aniline (III), and subsequent reduction of III with 2-pyridinemethanol to give N-(2-pyridylmethyl)aniline (II) as a final product, the 2-pyridinealdehyde formed being reused to the first step (Chart 2).

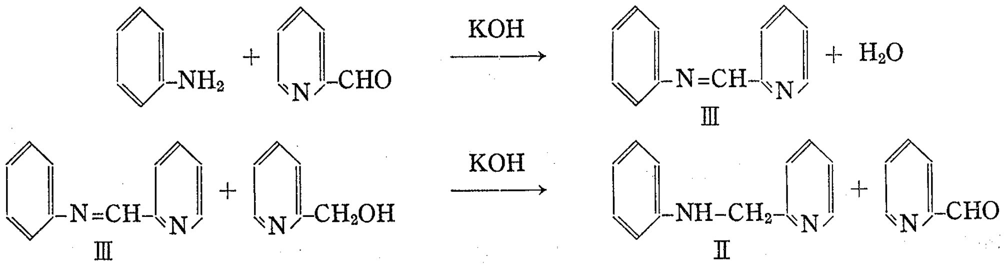

Chart 2.

Evidence in support of the reaction path was presented by the following observations.

1) In the present study we observed that in several instances in which freshly distilled 2-pyridinemethanol was employed no reaction was initiated,[*3] whereas with some old samples of 2-pyridinemethanol the vigorous reaction rapidly ensued. Addition of a small amount of 2-pyridinealdehyde likewise induced the violent reaction. These observations suggest that trace of 2-pyridinealdehyde might be essential for the initiation of this reaction according to the first stage of the proposed mechanism.

2) The reduction of N-(2-pyridylmethylene)aniline (III) to II was achieved by means of 2-pyridinemethanol and potassium hydroxide under the procedure condition.

[*1] Nanakuma, Fukuoka (宮野成二，宇野昭子，安倍宣博).

[*2] Although no attempt to detect 2-pyridinealdehyde was made, it is very likely that old samples of 2-pyridinemethanol contains trace of 2-pyridinealdehyde as benzaldehyde in benzyl alcohol.

[*3] This phenomena is in accordance with the Sprinzak's description which no reaction was initiated when benzaldehyde-free benzyl alcohol was used in benzylation of fluorene; Y. Sprinzak: J. Am. Chem. Soc., **78**, 466 (1956).

1) S. Miyano: This Bulletin, **13**, 1135 (1965).

Table I. Preparation of N-(4-Pyridylmethyl)anilines

Amine	Amine (g.)	4-Pyridine-methanol (g.)	KOH (g.)	Final[a)] temp. (°C)	Yield[b)] (g.)	Yield[b)] (%)
Aniline	9.3	12.3	0.9	230	6.5	35.3
p-Toluidine	5.4	5.5	0.45	240	4.0	40.4
p-Anisidine	8.6	7.6	0.72	260	6.8	45.3
p-Phenetidine	6.9	6.0	0.45	270	6.7	58.8
2-Aminopyridine	9.4	10.9	0.9	260	6.6	35.7
o-Toluidine	5.4	5.5	0.45	240	2.5	25.3

a) Bath temperature at which the reaction was discontinued.
b) Yields are based on amines.

Table II. Preparation of N-(2-Pyridylmethyl)anilines

Amine	Amine (g.)	2-Pyridine-methanol (g.)	KOH (g.)	Final[a)] temp. (°C)	Yield[b)] (g.)	Yield[b)] (%)
o-Toluidine	10.7	12.0	0.9	230	11.0	55.6
o-Anisidine	6.2	6.0	0.45	230	5.4	50.0
o-Phenetidine	6.9	6.0	0.45	230	5.3	46.5
α-Naphthylamine	6.0	7.2	0.45	240	9.3	79.5
o-Phenylenediamine	3.2	7.7	0.6	225	6.2	72.1

a) Bath temperature at which the reaction was discontinued.
b) Yields are based on amines.

Table III. N-Pyridylmethylanilines[a)]

	b.p. (°C/mm. Hg)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N
N-(2-Pyridylmethyl)-*o*-toluidine picrate	153∼158/4[b)]	147 (decomp.)	$C_{19}H_{17}O_7N_5$	53.39/53.60	4.01/4.08	16.39/16.74
N-(2-Pyridylmethyl)-*o*-anisidine picrate	173∼176/7[b)]	144 (decomp.)	$C_{19}H_{17}O_8N_5$	51.47/51.81	3.87/3.89	15.80/16.01
N-(2-Pyridylmethyl)-*o*-phenetidine		102∼104	$C_{14}H_{16}ON_2$	73.65/73.57	7.06/6.85	12.27/12.16
N-(2-Pyridylmethyl)-α-naphthylamine picrate	211∼213/6[b)]	172 (decomp.)	$C_{22}H_{17}O_7N_5$	57.02/57.36	3.70/3.82	15.11/15.30
N,N′-Bis-(2-pyridylmethyl)-*o*-phenylenediamine	235∼243/7	75	$C_{18}H_{18}N_4$	74.45/74.81	6.25/6.20	19.30/19.19
N-(4-Pyridylmethyl)aniline		103∼104	$C_{12}H_{12}N_2$	78.23/77.77	6.57/6.34	15.21/15.13
N-(4-Pyridylmethyl)-*o*-toluidine	165∼167/3	75∼ 76	$C_{13}H_{14}N_2$	78.75/78.47	7.12/6.85	14.13/14.30
N-(4-Pyridylmethyl)-*p*-toluidine	162∼166/4	74	〃	78.75/78.78	7.12/6.91	14.13/14.35
N-(4-Pyridylmethyl)-*p*-anisidine	184∼186/4	78∼ 80	$C_{13}H_{14}ON_2$	72.87/72.69	6.59/6.39	13.08/13.12
N-(4-Pyridylmethyl)-*p*-phenetidine	192∼193/4	103∼105	$C_{14}H_{16}ON_2$	73.65/73.76	7.06/7.17	12.27/11.98
N-(4-Pyridylmethyl)-2-aminopyridine	166∼167/4	109∼111	$C_{11}H_{11}N_3$	71.33/71.04	5.99/5.57	22.69/22.74

a) All the compounds can be purified by recrystallization from aqueous ethanol.
b) Boiling points of free bases.

In view of the earlier report²⁾ that deoxygenation of pyridine 1-oxide was readily effected by means of 2-pyridinemethanol and potassium hydroxide to give pyridine and 2-pyridinealdehyde,*4 a few drops of pyridine 1-oxide was added to the reaction media, thus providing 2-pyridinealdehyde as an initiating agent. The reaction proceeded smoothly as expected. Because of the difficult accessibility of pyridinealdehyde use of pyridine 1-oxide is greatly to be preferred. The reaction was thus extended to the preparation of N-(4-pyridylmethyl)anilines which were obtained in moderate yields (Table I) and some new derivatives of 2-analogs were also prepared (Table II). Physical constants and microanalyses of them were shown in Table III.

Experimental

General Procedure for Synthesis of N-(4-Pyridylmethyl)anilines——As a typical run, preparation of N-(4-pyridylmethyl)-*p*-phenetidine (II, R=*p*-ethoxyphenyl, R′=4-pyridyl) is illustrated. A mixture of 6.9 g. (0.05 mole) of *p*-phenetidine, 6 g. (0.055 mole) of 4-pyridinemethanol, and 0.45 g. (0.008 mole) of KOH placed in a distilling flask was heated together with 0.01 g. of pyridine 1-oxide on an oil-bath. The temperature was raised gradually to 220° around which the reaction became vigorous and water started to distil. The water separated amounted to 0.8 ml. (theoretical amount: 0.9 ml.). After the reaction subsided and the water evolution ceased the heating was discontinued and the mixture was neutralized with 10% HCl and extracted twice with $CHCl_3$. After drying over anhyd. K_2CO_3, the extract was stripped of solvent and distilled *in vacuo*. Thus was obtained 6.7 g. (58.8%) of the product, b.p. 192~193°/4 mm., which solidified to a pale-yellow prism, m.p. 103~105° (from aq. EtOH). IR ν_{max}^{KBr} cm^{-1}: 3289 (>NH).

N-(2-Pyridylmethyl)anilines——The procedure employed was essentially the same with that reported in an earlier paper¹⁾ for the preparation of II except that a small amount of pyridine 1-oxide was added.

Reduction of N-(2-Pyridylmethylene)aniline——A mixture of 5.45 g. (0.05 mole) of 2-pyridinemethanol and 1 g. (0.018 mole) of KOH was heated at 120°. When KOH came into solution 1.8 g. (0.01 mole) of N-(2-pyridylmethylene)aniline (III) was added and the mixture was heated to 175° at which the vigorous reaction started. After 0.5 ml. of water distilled over 20 min. the whole mixture solidified to light-yellow mass which was dissolved in water and extracted with ether. The ethereal layer was washed with water, dried over anhyd. K_2CO_3, and the solvent was removed. The residual solid was recrystallized from petr. ether to give 1.5 g. (82.4%) of N-(2-pyridylmethyl)aniline (II, R=phenyl, R′=2-pyridyl) as light-yellow prisms, m.p. 53~54°, undepressed upon admixture with the sample obtained by the procedure above and having an identical infrared spectrum. IR ν_{max}^{KBr} cm^{-1}: 3279 (>NH).

---

*4 Finally separated as potassium picolinate as a result of Cannizzaro reaction. See ref. 2).

2) S. Miyano: This Bulletin, **14**, 663 (1966).