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Seiji Miyano[*1] : Syntheses of N-(2-Pyridylmethyl)aniline and its Derivatives.

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In connection with other studies now underway in this laboratory N-(2-pyridylmethyl)-aniline (I) and its derivatives were desired. I was first synthesized by catalytic hydrogenation of N-(2-pyridylmethylene)aniline[1] (II), a Schiff's base between aniline and 2-pyridinealdehyde. But this method is limited to the availability of the pyridinealdehyde that is less accessible than aromatic aldehyde.

On the other hand, preparation of N-benzylaniline by N-benzylation of aromatic amines by means of benzyl alcoholic potassium hydroxide has been reported[2~3] and the mechanism shown by Sprinzak.[4]

In view of these reports the method which appeared to be the most promising was a condensation between 2-pyridinemethanol (III), a pyridine analog of benzyl alcohol, and appropriate aromatic amines.

This paper deals with the preparation of I and its derivatives as an extension of Sprinzak's benzylation method.

The procedure consists in heating the mixture of aniline and 2-pyridinemethanol with potassium hydroxide at a temperature of 225~240° (Procedure A). Elimination of water as it is formed is advantageous to accelerate the reaction (Table I). A series of I and its para-substituted homologues were obtained in good yield (Table II). With *p*-phenylenediamine each amino group reacted with 2-pyridinemethanol and N,N′-bis(2-pyridylmethyl)-*p*-phenylenediamine is formed. The extension of this reaction involves the condensation of 2-pyridinemethanol with 2-aminopyridine in a similar manner to give the corresponding secondary amine (IV).

TABLE I. Preparation of N-(2-Pyridylmethyl)anilines According to Procedure A[a]

Amine	Amine (g.)	2-Pyridine-methanol (g.)	KOH (g.)	Final temp. (°C)[b]	Yield	
					(g.)	(%)[c]
Aniline	9.3	12.0	0.9	235	11.5	62.5
p-Toluidine	7.5	7.7	0.5	225	6.9	49.7
p-Anisidine	6.2	7.0	0.45	225	8.6	71.2
p-Phenetidine	4.5	3.5	0.2	240	5.1	68.2
β-Naphthylamine	1.2	1.2	0.1	237	1.0	51.0
p-Phenylenediamine	3.2	7.7	1.2	235	6.1	72.6
2-Aminopyridine	4.7	5.5	0.45	225	3.8	41.2

a) Preparation according to Procedure B, see Experimental.
b) The bath temperature at which reaction was stopped.
c) These per cent yields are based on amines. No attempt has been made to determine the optimum conditions or maximum yields for the reaction.

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1) U. Hörlein : Ber., **87**, 463 (1954).

2) E.F. Pratt, F.J. Frazza : J. Am. Chem. Soc., **76**, 6174 (1954).

3) I. Hirao, M. Hayashi : Yakugaku Zasshi, **74**, 853 (1954).

4) Y. Sprinzak : J. Am. Chem. Soc., **78**, 3207 (1956); Org. Syntheses, **38**, 3 (1958).

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Table II. N-(2-Pyridylmethyl)anilines

Compounds	m.p.[a] (°C)	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
N-(2-Pyridylmethyl)aniline	47∼ 49[b]	78.23	6.57	15.21	78.40	6.48	14.92
N-(2-Pyridylmethyl)-*p*-toluidine	41∼ 43[c]	78.75	7.12	14.13	78.83	7.28	14.17
N-(2-Pyridylmethyl)-*p*-anisidine	74∼ 75[d]	72.87	6.59	13.08	72.90	6.81	12.93
N-(2-Pyridylmethyl)-*p*-phenetidine	72∼ 73[d]	73.65	7.06	12.27	73.57	6.89	12.21
N-(2-Pyridylmethyl)-β-naphthylamine	82∼ 83[d,e]	82.02	6.02	11.96	81.91	6.43	11.60
N,N′-bis(2-Pyridylmethyl)-*p*-phenylenediamine	152∼153[d]	74.45	6.25	19.30	74.87	6.55	19.92
2-(2-Pyridylmethylamino)-pyridine	53∼ 54[f]	71.33	5.99	22.69	71.69	5.94	22.40

[a] All the compounds can be purified by recrystallization from aqueous ethanol.
[b] b.p. 137∼140°/3 mm. [c] b.p. 150∼152°/3 mm.
[d] Obtained as crystals when chloroform was removed from the extracts in working up the reaction mixture.
[e] Sealed capillary tube was used for the measurement of melting point, otherwise no definite melting point was recorded.
[f] b.p. 151∼153°/3 mm.

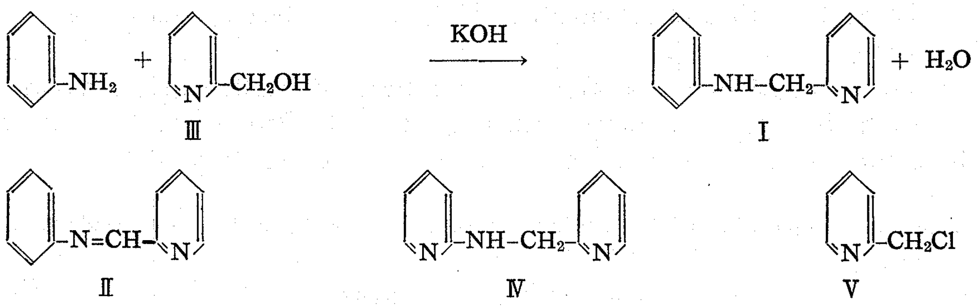

Chart 1.

Infrared spectrum of I shows the presence of a single absorption at 3378 cm^{-1} characteristic of a secondary amino band. Proof for the structures (I) and (IV) was also provided by alternate syntheses under milder condition which consist of condensing 2-chloromethylpyridine (V) with aniline and 2-aminopyridine in the presence of anhydrous potassium carbonate and sodamide, respectively (Procedure B).

Since 2-pyridinemethanol is readily available by rearrangement of 2-picoline 1-oxide in the presence of acetic anhydride followed by hydrolysis of the resulting 2-pyridinemethanol acetate[5,6] this reaction provides a convenient route for the synthesis of I and its derivatives.

Experimental

Two different procedures are illustrated below for the preparation of N-(2-pyridylmethyl) aniline (I) and 2-(2-pyridylmethylamine)pyridine (IV). The constants and analyses of the products are given in Table II.

N-(2-pyridylmethyl)aniline (I). Procedure A——A mixture of 9.3 g. (0.1 mole) of aniline, 12 g. (0.11 mole) of 2-pyridinemethanol and 0.9 g. (0.016 mole) of KOH is heated to boiling by means of an oil bath and refluxed to cause slow distillation of water. The residual slurry which solidified on standing for several minutes was triturated with water and neutralized with dilute hydrochloric acid. The resulting mixture was extracted with chloroform, the chloroform layer dried over anhydrous K_2CO_3 and the solvent

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[5] G. Kobayashi, S. Furukawa: This Bulletin, **1**, 347 (1953).
[6] V. Boekelheide, W. J. Linn: J. Am. Chem. Soc., **76**, 1286 (1954).

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removed by distillation. Vacuum distillation of the residue gave 11.5 g. (62.5%) of I, b.p. 137~140°/3 mm. which solidified on cooling to light-tan prisms, m.p. 47~49°(from EtOH). The picrate was formed in 96% EtOH solution, m.p. 154~155° (decomp.). *Anal.* Calcd. for $C_{12}H_{12}N_2 \cdot 2C_6H_3O_7N_3$: C, 44.83; H, 2.82; N, 17.30. Found : C, 44.52; H, 3.11; N, 16.93.

Procedure B——To the boiling mixture of 33 g. (0.36 mole) of freshly distilled aniline, 8.5 g. (0.062 mole) of anhydrous K_2CO_3 and 75 ml. of dry benzene is added with stirring 12 g. (0.094 mole) of freshly distilled 2-chloromethylpyridine. The addition required fifteen minutes during which the reaction mixture turned red. Stirring and refluxing were continued for five hours and water was added to separate into two layers. The upper layer was dried over anhydrous Na_2SO_4, the solvent removed and the residue distilled *in vacuo*. After the fore-run of excessive aniline yellow viscous liquid came over between 151° and 152° at 8 mm. and solidified on cooling. Yield 9.2 g. (52.8% based on 2-chloromethylpyridine).

2-(2-Pyridylmethylamino)pyridine (IV). Procedure A——A mixture of 4.7 g. (0.05 mole) of 2-aminopyridine, 5.5 g. (0.05 mole) of 2-pyridinemethanol and 0.45 g. (0.008 mole) of KOH was boiled on an oil-bath at 225°. The heating required about forty minutes and 1.6 ml. of water was separated. The mixture was worked up as in I. The product distilled at 152~153°/3 mm. and weighed 3.8 g. (41.2%). It solidified to light-tan prisms, m.p. 53~54°. The picrate was formed in 96% EtOH solution, m.p. 202~204° (decomp.). *Anal.* Calcd. for $C_{11}H_{11}N_3 \cdot 2C_6H_3O_7N_3$: C, 42.92; H, 2.64; N, 19.60. Found : C, 42.92; H, 2.90; N, 19.55.

Procedure B——A solution of 6 g. (0.063 mole) of 2-aminopyridine in 40 ml. of dry toluene was added to a suspension of 2.7 g. (0.069 mole) of sodamide in 10 ml. of dry toluene. The mixture was stirred and refluxed for two hours, heating discontinued and a solution of 8 g. (0.063 mole) of 2-pyridinemethanol in 20 ml. of dry toluene added dropwise. The material was further stirred and refluxed for four hours and worked up in the usual way. Distillation *in vacuo* yielded 8.2 g. (69.5%) of a dark yellow liquid, b.p. 151~153°/3 mm. which solidified upon standing overnight. Purified from aqueous EtOH, it formed light-yellow prisms, m.p. 53~54°.

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