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Reaction of Aromatic N-Oxides with Dipolarophiles. I. Reaction Products of 3-Picoline 1-Oxide with Phenyl Isocyanate[1]

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The reaction of 3-picoline 1-oxide (VI) with phenyl isocyanate (I) in dimethylformamide at 110° gave the cycloadducts VII and VIII in 33.7 and 24.1% yield, respectively. The reaction at 150° gave 2-anilino-3-methylpyridine (IX) and 2-anilino-5-methylpyridine (X), along with a small amount of VII. Hydrolysis of VII and VIII in alcoholic potassium hydroxide affords IX and X, respectively.

The structures of VII and VIII were discussed in the light of spectroscopic data. IX and X were identified by comparison with the authentic samples prepared by an alternative route.

Since the works of Huisgen first appeared,[3] 1,3-dipolar cycloaddition reaction has found increasingly important uses in organic syntheses, and there have been many reports published on the reactions of aromatic amine oxides[4] as 1,3-dipole with phenyl isocyanate (I) as dipolarophile. For example, the cycloaddition reactions of aromatic amine oxides[4] such as pyridine 1-oxide (II),[5] isoquinoline 2-oxide,[5] phenanthridine 5-oxide (IV),[5,6] phtalazine N-oxide,[7] and quinoxaline N-oxide,[8,9] have been extensively studied. Huisgen and his co-workers[5] showed that the reaction of II and isoquinoline 2-oxide with I afforded 2-anilinopyridine (III) and 1-anilino isoquinoline, respectively. Hayashi[6] also reported similar reaction for IV with I gave 6-anilino derivative (V) in good yield. Our recent paper[10] on the chemical behavior of benzazole N-oxide showed that the reaction of 2-(N-oxido-2-pyridyl)benzothiazoles with I in dimethylformamide (DMF) did not give the corresponding anilino derivatives. In the present paper we will describe the cycloaddition reaction of 3-picoline 1-oxide (VI) with I as a

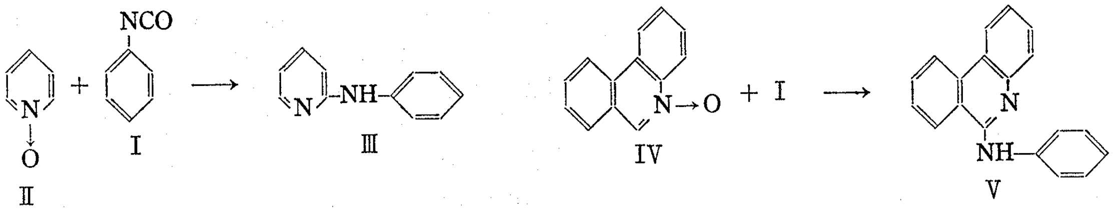

Chart 1

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[1] A part of this work was presented at the Kyushu Local Meeting of the Pharmaceutical Society of Japan, February 1973; Preliminary Communication: T. Hisano, S. Yoshikawa, and K. Muraoka, *Organic Preparations and Procedures International*, **5** (3), 95 (1973).

[2] Location: *Oe-hon-machi, Kumamoto.*

[3] R. Huisgen, *Proc. Chem. Soc.*, **1961**, 357.

[4] E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amusterdam, 1967, p. 256; A.R. Katritzky and J.M. Lagowski, "Chemistry of the Heterocyclic N-Oxides," Academic Press Inc., London, 1971, p. 330.

[5] H. Seidle, R. Huisgen, and R. Grashey, *Chem. Ber.*, **102**, 926 (1969).

[6] E. Hayashi, *Yakugaku Zasshi*, **81**, 1030 (1961).

[7] E. Hayashi and E. Oishi, *Yakugaku Zasshi*, **86**, 576 (1966).

[8] E. Hayashi and Iijima, *Yakugaku Zasshi*, **82**, 1093 (1962).

[9] J.C. Mason and G. Tennant, *J. Chem. Soc. Chem. Comm.*, **1972**, 218.

[10] T. Hisano and H. Koga, *Yakugaku Zasshi*, **91**, 1031 (1971).

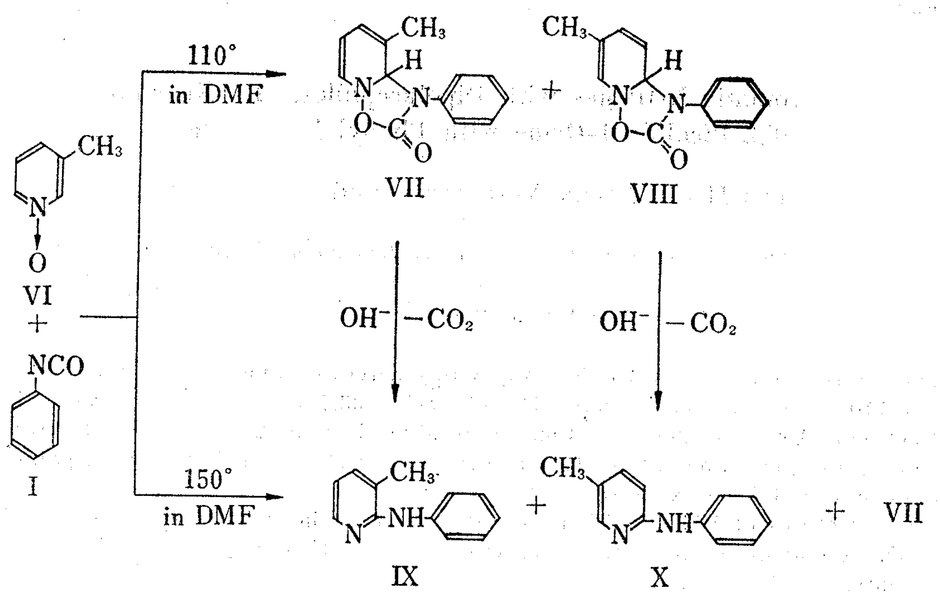


Chart 2

part of our program directed to the reactivity of heterocyclic N-oxides. The reaction has resulted in the formation of two products different from the conventional results, and we have succeeded in separating the cycloadducts VII and VIII, which retained the five membered ring.

VI reacted with I in DMF at 110° to afford the 1: 1 adducts, VII as colorless needles (mp 212°) and VIII as colorless finely needles (mp 142°), in 33.7 and 24.1% yield, respectively. Furthermore, when the reaction was carried out at 150° in the same manner as the above mentioned, the compounds IX as colorless prisms (mp 123°) and X as colorless prisms (mp 115°) were obtained in 29.5 and 23.7% yield along with VII in 3.2% yield and a trace amount of VIII, respectively.

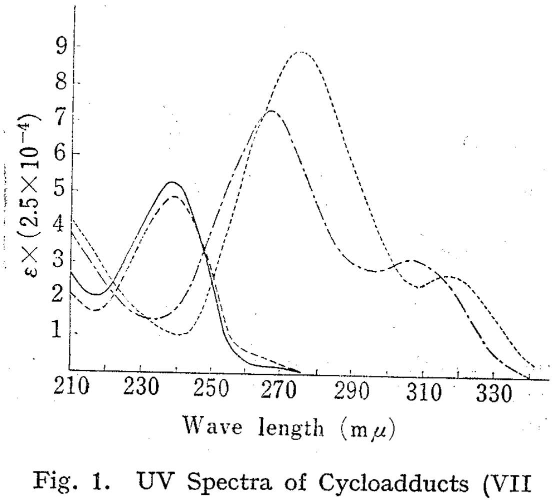


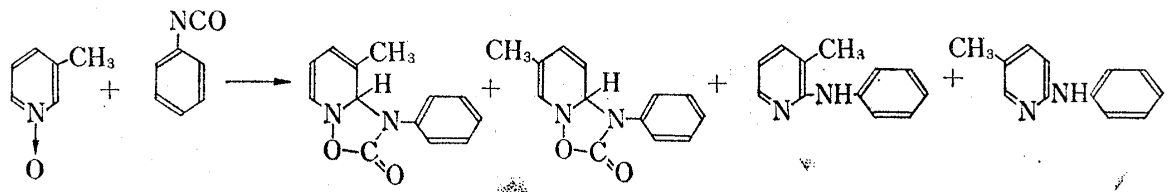
Fig. 1. UV Spectra of Cycloadducts (VII and VIII) and Anilino Compounds (IX and X)

VII: ——— VIII: - - - -
IX: ——— X: ---------

The mass spectra (MS) of VII and VIII showed respective molecular ion peaks at *m/e* 228, and the any results of elemental analyses of both compounds agreed with $C_{13}H_{12}O_2N_2$. The infrared (IR) spectra of VII and VIII exhibited characteristic carbonyl absorptions at 1727 and 1740 cm^{-1}, respectively; neither their compounds displayed bands ascribable to a carboxylic acid group in the 3300 and 2700—2500 cm^{-1} regions. The ultra violet (UV) spectrum of VII (λ_{max}^{EtOH} 234 mμ; log ε=4.11) was similar to that of VIII (λ_{max}^{EtOH} 234.5 mμ; log ε=4.09), while the UV spectrum of IX (λ_{max}^{EtOH} 270 mμ; log ε=4.27) was similar to that of X (λ_{max}^{EtOH} 275.5 mμ; log ε=4.37), as shown in Fig. 1.

Although both VII and VIII are stable to heating in DMF at 150°, they are easily converted by heating in alcoholic potassium hydroxide to IX, mp 122—123°, as colorless prisms and X, mp 114—115°, as colorless prisms, respectively. However, it appears from the viewpoint of their yields that VII is slightly more stable than VIII, as shown in Table II. IX and X were consequently found to be 2-anilino-3-methylpyridine and 6-anilino-3-methyl-

Table I

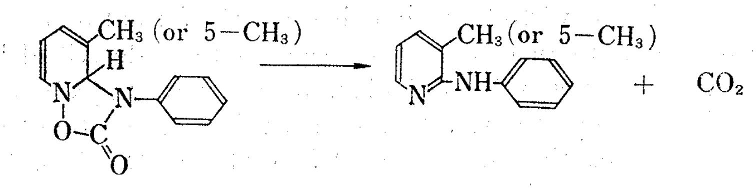


VI I VII VIII IX X

Starting material (mole)		Condition[a)]		Product (%)[b)]			
VI	I	Temp. (°C)	Duration (hr)	VII	VIII	IX	X
0.025	0.025	110	7	15.8	6.1	—	—
0.025	0.050	110	7	33.7	24.1	—	—
0.025	0.050	110	21	13.3	2.1	18.8	19.0
0.025	0.075	110	7	24.5	17.5	—	—
0.025	0.050	150	7	3.2	trace	29.5	23.7

a) used 20 ml of DMF as a solvent
b) based on amount of VI started

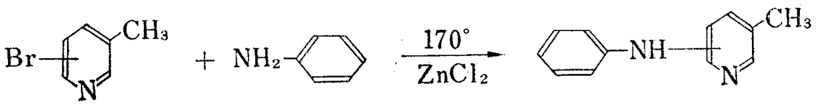
Table II



VII (or VIII) IX (or X)

Temp. (°C)	Reaction condition		Recovery (%)		Product (%)	
	Duration (hr)	Reagent	VII	(VIII)	IX	(X)
150	1	DMF	95	(85)	—	(trace)
150	4	aniline in DMF	<85	(<70)	> 7	(> 5)
150	4	VI in DMF	<90	(<75)	> 4	(> 4)
Reflux	2	5% KOH–EtOH	—	(–)	74	(57)

pyridine by identification in all respects with the authentic samples prepared by the following route.[5)]



2-or 6-bromopicoline 2- or 6-anilinopicoline

In connection with the above mentioned, the structures of VII and VIII were confirmed by nuclear magnetic resonance (NMR) spectroscopy: the NMR spectrum of VII in $CDCl_3$ showed a singlet at 8.42 τ for three methyl protons ($-CH_3$) and a doublet at 4.64 τ for one methine proton (C_2–H) and that of VIII in $CDCl_3$ showed a singlet at 8.07 τ for three methyl protons ($-CH_3$) was broadened and a multiplet at 4.85—5.20 τ for one methine proton (C_2–H).

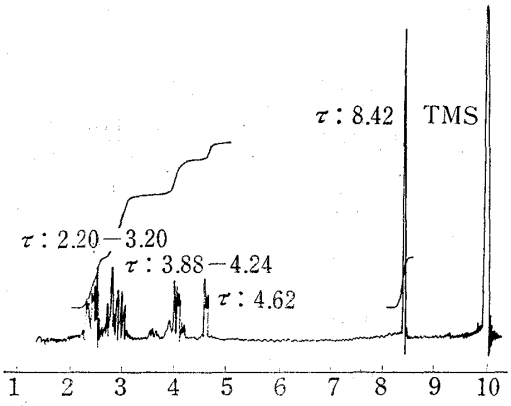


Fig. 2. NMR Spectrum of VII (in $CDCl_3$, 100 Mc)

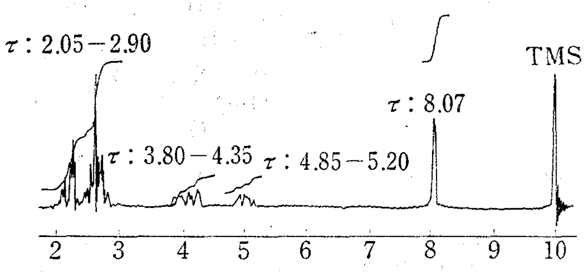


Fig. 3. NMR Spectrum of VIII (in $CDCl_3$, 60 Mc)

Therefore, VII and VIII were concluded to be normal cycloadducts, retaining the five membered ring, and to be isomeric with each other. Elongation of the reaction time at 110° in DMF led to the increase of IX and X and on the contrary the decrease of VII and VIII in yield. The reaction at lower temperature decreased the each yield of all products. Additionally, an excess of I over that required for equimolar addition to VI resulted in an increased yield of their cycloadducts under the reaction condition at 110° for 7 hr, as shown in Table I. It seems that the deoxygenation of VI to 3-picoline disturbs the formation of such cycloadducts, because of isolating 3-picoline as picrate from all the reactions described in Table I.

On the other hand, the reaction of VI with phenylisothiocyanate (XI) has been attempted, according to Seidle,[5] who has reported that a similar reaction of pyridine 1-oxide affords only 2-aminopyridine (III). The reaction of VI with XI at 110° in DMF for 7 hr unexpectedly resulted in the deoxygenation of VI to 3-picoline in 80% yield, instead of the cycloadduct or anilino compound provided by the usual reaction. Even milder reaction conditions resulted in the formation of 3-picoline in about 17% yield.

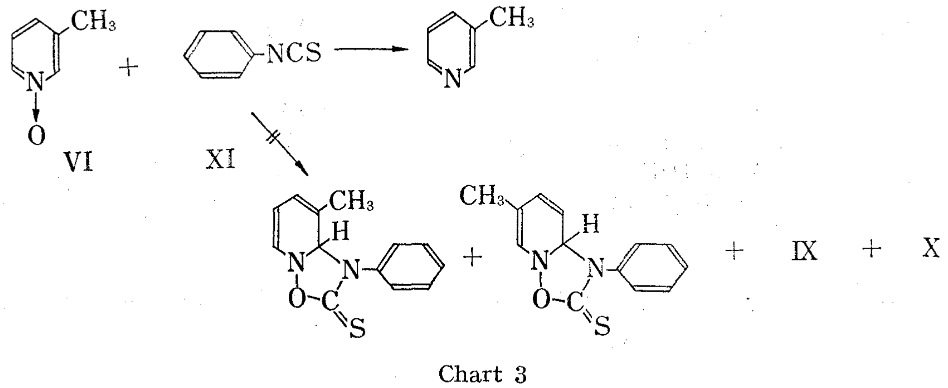


Chart 3

Discussion

The mechanism of 1,3-dipolar cycloaddition has already been reported in detail. In this reaction, the aromaticity of the N-oxide ring is lost during formation of the adduct, and there is a strong driving force to regain this aromaticity by further transformation of the adduct. 1,3-Dipolar cycloaddition of aromatic amine oxides to I is generally followed more or less readily by the elimination of carbon dioxide from the unstable cycloadduct,[11] which is assumed

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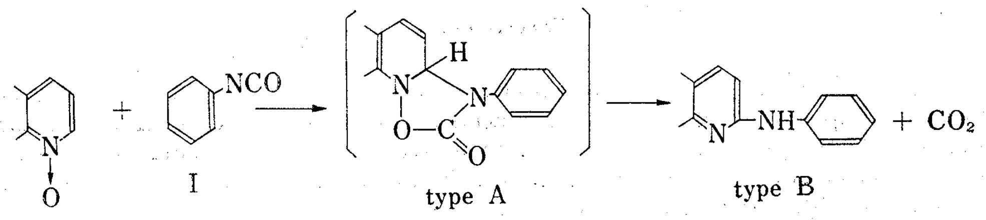
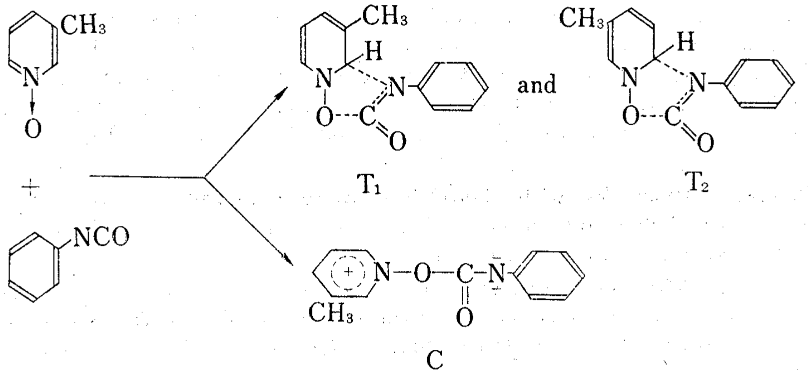
[11] R. Huisgen, *Angew. Chem. Internat. Ed. Engl.*, 2, 589 (1963).

to be formed in this reaction course but has not been isolated. Usually, all the products isolated were not the primary adduct (type A) but anilino compound (type B), as below shown.



Our findings in the reaction of 3-picoline N-oxide with phenylisocyanate are important in two respects. Not only is it the first report, to our knowledge, of the isolation of primary adducts in the cycloaddition of an N-oxide with an isocyanate, but even more interesting is the isolation of two isomeric such adducts. Although the data could be interpreted in terms of two different transition states (T_1 and T_2) leading to VII and VIII, an alternate possibility would involve a stabilized ionic intermediate (C) which could cyclize to either the 2- or the 6-position of the ring.



Although VII is stable to heating to 150° in DMF, VIII is somewhat sensitive to similar temperature with elimination of carbondioxide occurring to some degree to yield X. The fact that both VII and VIII were rather stable to heat suggests that the driving force for rearomatization is not very strong. The formation IX and X from the reaction conducted at 150° is probably due to base-induced decomposition of VII and VIII by weak bases such as 3-picoline-N-oxide or aniline (partial hydrolysis of phenylisocyanate). This point was confirmed by the fact that VII (or VIII) heated to 150° in DMF in the presence of aniline or 3-picoline-N-oxide decomposed to IX (or X).

Although no definite conclusions can be reached at this time, it is clear that the presence of the methyl group at the 3-position has a determining effect on the course of the reaction and that its steric effect is at best extremely small, if not insignificant.

Taylor[12] reported that the treatment of quinazoline 1,3-dioxide derivatives with XI resulted in the formation of quinazoline 1-oxide derivatives in good yield, and presumed the mechanism for the deoxygenation of that reaction. That agreed more or less with our deoxygenation result of VI by use of XI.

From these facts, we conclude that the reaction proceeds stepwise with the formation of the cycloadducts VII and VIII in accordance with the orientation of cyclization of VI

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12) E.C. Taylor, "Topics in Heterocyclic Chemistry," ed. by R.N. Castle, Wiley-Interscience, A Division of John and Sons, Inc., N. Y., 1969, p. 1.

onto I, followed by the elimination of carbon dioxide to anilino compounds (IX and X). The above result in our experiments seems to be the special case and the new behavior of aromatic amine oxides with I.

Experimental

All melting points were uncorrected. IR spectra were recorded on Nippon Bunko DS-301 Infrared Spectrophotometer equipped with a grating. UV spectra were measured in EtOH with Hitachi EPS-3T spectrophotometer. NMR spectra were taken with JNM-MH-100 and JNM-C-60H spectrometer in *ca.* 5% (w/v) solution with tetramethylsilane as an internal standard and chemical shifts were expressed in τ value. MS spectra were taken with JMS-OISG spectrometer.

Reaction of 3-Picoline 1-Oxide (VI) with Phenyl Isocyanate (I) at 110°——To a solution of 2.73 g (0.025 mole) of VI in 20 ml of DMF, 5.96 g (0.050 mole) of I was added dropwise with stirring at room temperature and the mixture was heated in an oil bath at 110° for 7 hr.

a) Separation of VII: After the reaction was over, the reaction mixture was allowed to stand at 0—5° overnight and the colorless crystals deposited were collected by suction and washed with a small amount of cold DMF to give colorless crystals of 1.93 g (33.7%), mp 201—207°. Recrystallization from benzene afforded colorless needles VII, mp 212°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1727 (C=O). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 234 (4.11) (4×10^{-5} mole). Mass Spectrum *m/e*: 228 (M^+), 184 (M^+-CO_2), 183 (M^+-CO_2H). NMR (in $CDCl_3$, 100 Mc): 8.42 (3H, s, -CH_3), 4.64 (1H, d, J=3.5 Hz, C_2-H). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.45; H, 5.39; N, 12.19. Mol. wt. Calcd.: 228. Found: 228 (by mass analysis).

b) Separation of VIII: After the removal of VII, the filtrate was concentrated to one-half of its initial volume under reduced pressure and allowed to stand at 0—5° overnight. Crystals precipitated were collected by suction and washed with a small amount of cold ether to give colorless crystals of 1.88 g (24.1%), mp 139—142°. Recrystallization from benzene afforded colorless finely needles VIII, mp 142°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1740 (C=O). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 234.5 (4.09) (4×10^{-5}mole). Mass Spectrum *m/e*: 228, (M^+) 184 (M^+-CO_2), 183 (M^+-CO_2H). NMR (in $CDCl_3$, 60 Mc): 8.07 (1H, s, broad, -CH_3), 4.85—5.20 (1H, m, C_2-H). *Anal.* Calcd. for $C_{13}H_{12}O_2N_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.45; H, 5.38; N, 12.21. Mol. wt. Calcd.: 228. Found: 228 (by mass analysis).

Reaction of 3-Picoline 1-Oxide (VI) with Phenyl Isocyanate (I) at 150°——To a solution of 2.73 g (0.025 mole) of VI in 20 ml of DMF, 5.96 g (0.05 mole) of I was added dropwise with stirring at room temperature and the mixture was heated in an oil bath at 150° for 7 hr.

a) Separation of VII: After the reaction was over, the mixture was allowed to stand at 0—5° overnight and the colorless crystals deposited were collected by suction and washed with a small amount of cold DMF to give colorless crystals of 0.19 g (3.2%), mp 204—208°. Recrystallization from benzene afforded colorless needles VII, mp 212°.

b) Separation of IX: After the removal of VII, the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in benzene and chromatographed over silica gel (50 g) used benzene as a developing solvent. From the first fraction (100 ml), a colorless crystalline mass of 1.36 g (29.5%) was obtained. Recrystallization from ether gave colorless prisms (IX), mp 122—123°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3280, 3180 (N-H). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 270 (4.27), 310 (3.92) (4×10^{-5}mole). NMR (in $CDCl_3$, 100 Mc): 7.69 (3H, s, -CH_3), 3.48 (1H, s, broad, -NH), 1.88—3.00 (7H, m, pyridine benzene C-H), 1.38 (1H, d-d, J=5.5 Hz, pyridine C_6-H). *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.22. Found: C, 78.11; H, 6.59; N, 15.22. Mol. wt. Calcd.: 184. Found: 184 (by mass analysis).

c) Separation of X: After the elution of IX, from the second fraction (50 ml) a colorless crystalline mass of 1.09 g (23.7%) was obtained. Recrystallization from ether gave colorless prisms (X), mp 114.5—115°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3210, 3150 (N-H). UV $\lambda_{\max}^{\text{EtOH}}$ mμ (log ε): 275.5 (4.37), 320 (3.85) (4×10^{-5}mole). NMR (in $CDCl_3$, 100 Mc): 7.72 (3H, s, -CH_3), 2.20—2.92 (8H, m, pyridine benzene C-H, -NH), 1.57 (1H, s, broad, pyridine C_6-H). *Anal.* Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.22. Found: C, 78.26; H, 6.48; N, 15.16. Mol. wt. Calcd.: 184. Found: 184 (by mass analysis).

Hydrolysis of VII——Refluxing 0.50 g of VII in 5% ethanolic potassium hydroxide for 2 hr, solvent was removed by vacuum distillation. The residue was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and filtered. Removal of the solvent left a residue which was recrystallized from ether to give 2-anilino-3-methylpyridine (IX) of 0.36 g (94%) as colorless prisms, mp 122—123°.

Hydrolysis of VIII——1.0 g of VIII was hydrolyzed under the same condition as in VII. A similar work-up gave 2-anilino-5-methylpyridine (X) of 0.46 g (57%) as colorless prisms, mp 114—115°.

Synthesis of Authentic Samples of IX and X——IX or X was prepared by the reported procedure[5] from 2-bromo-3-methylpyridine or 2-bromo-5-methylpyridine. A mixture of 1.0 g of bromo-methyl-pyridine and 0.54 g of aniline in the presence of 0.95 g of $ZnCl_2$ was heated at 170° for 2 hr. After the reaction was over, the reaction mixture was added 6 ml of 10% Na_2CO_3 solution and was heated at 105° for an additional 2 hr. After cooling and extraction with $CHCl_3$, the $CHCl_3$ layer was dried over anhyd. Na_2SO_4 and filtered.

Removal of solvent left a residue of colorless crystals. Recrystallization from ether gave colorless prisms IX (or X).

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