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N-Alkylation of Aromatic Amines by Means of Alcohol. III.[1] New Syntheses of N-Pyridylmethyleneaniline and Related Compounds

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A new synthesis of N-(2-pyridylmethylene)aniline (I) is described. The method consists of heating a mixture of 2-pyridinemethanol, aniline, and nitrobenzene in the presence of potassium hydroxide. Extension of the reaction to some related compounds was made. By-products accompanied with *ortho*-substituted derivatives of I were characterized as pyridylmethylene-bis-amines.

Study of the synthesis of title compounds is part of a continuing study of syntheses of N-pyridylmethylaniline and related compounds.

In spite of their relatively simple structures, only two syntheses of N-(2-pyridylmethylene)-aniline(I) and derivatives have been reported. One[3] involves dehydration between aniline and 2-pyridinealdehyde and the other[4] dehydration between *p*-nitrosodimethylaniline and picoline methiodide. Though the former method seems to be more general, it is still limited by lack of simple methods of preparation of pyridinealdehyde.

In previous publications[1] from this laboratory it was demonstrated that when aniline was condensed with 2-pyridinemethanol in the presence of potassium hydroxide the reaction proceeded through intermediary N-(2-pyridylmethylene)aniline (I) to give N-(2-pyridylmethyl)-aniline (II) as a final product:

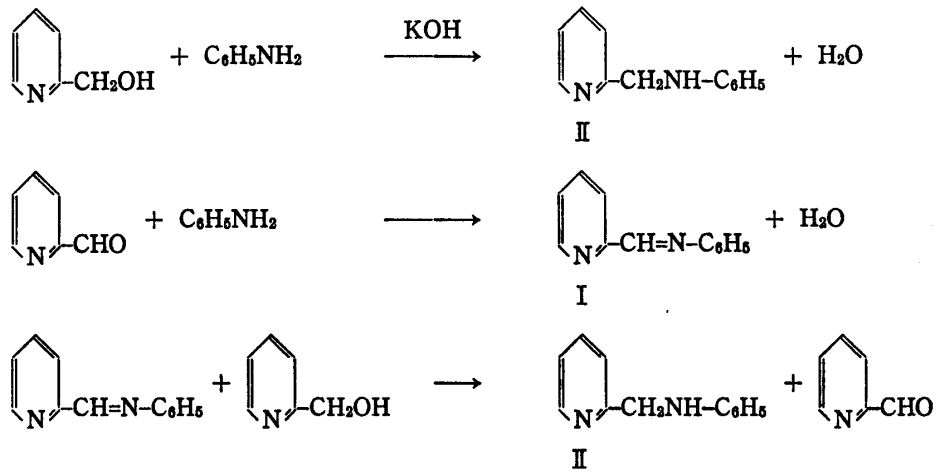


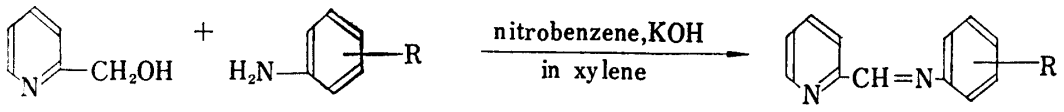
Chart 1

In the light of this observation it appeared quite likely that in the presence of sufficient amount of oxidizing agent to convert all of the pyridinemethanol to pyridinealdehyde, the

1) The paper published by S. Miyano, A. Uno, and N. Abe, *Chem. Pharm. Bull.* (Tokyo), **15**, 515 (1967) represents part II of this series. For part I, see S. Miyano, *ibid.*, **13**, 1135 (1965).
2) Location: *Nanakuma, Fukuoka.*
3) U. Hörlein, *Ber.*, **87**, 463 (1954).
4) A. Kaufmann and L.G. Vallette, *Ber.*, **45**, 1743 (1912).

reaction would be interrupted in the first step and the Schiff base (I) result as a primary product.

On this conceptual basis, nitrobenzene was added dropwise as an oxidizing agent to the reactants with the expectation that the pyridinealdehyde as soon as it is formed would be stabilized by condensation with aniline and its derivatives to form Schiff base (III) (Chart 2).



R=H,CH_3,OCH_3,OC_2H_5,Cl III

Chart 2

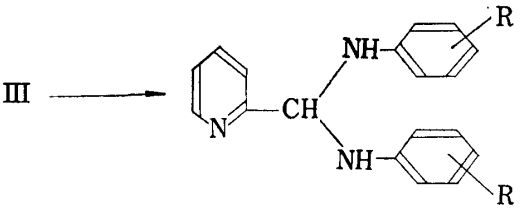
Xylene was used as solvent and water was removed during the reaction; the use of xylene maintains the temperature well below that range of 225—240° which is considered to be the temperature of the reaction. Interrupting the reaction sequence is thus assured.

This concept was apparently well-founded since the desired N-(2-pyridylmethylene)-aniline (I) and its hitherto unknown derivatives were obtained in one step. Extension of the reaction resulted in preparation of N-(4-pyridylmethylene)aniline, N-(6-methyl-2-pyridylmethylene)anilines and their derivatives (Table I). The yields are moderate to excellent. The azomethines thus obtained were identified by microanalyses and infrared spectra which showed absorption within the range of 1619—1634 cm^{-1}. N-Benzylidenanilines show similar absorption in the region 1613—1637 cm^{-1}.[5-7]

Although no systematic attempt has been made to determine optimum reaction conditions, aniline was always used in excess. When 50% excess aniline was employed in the condensation with 2-pyridinemethanol yield of the product (I) was approximately twice those with equimolar quantity of aniline.

It is notable that the yields of azomethines from *ortho*-substituted anilines[8] are generally lower than those of *p*-isomers which may be ascribed to the instability of these azomethines. Actually *ortho*-substituted azomethines often gave wrong analyses (Table I) in spite of the careful and repeated purifications. After standing for several hours at room temperature the weak infrared absorption band at 1713 cm^{-1} regions arising from carbonyl invariably appeared in all samples of *ortho*-substituted azomethines in contrast to the absence of carbonyl band when the measurement was made without delay on the samples as obtained. The carbonyl band suggests the presence of 2-pyridinealdehyde, one of the hydrolysates of the azomethine.

The odd behavior was well illustrated by N-(2-pyridylmethylene)-*o*-phenetidine[9] (III, R=*o*-OC_2H_5) which, originally obtained as a liquid, developed a crystalline precipitate on standing overnight at room temperature. The purified crystals showed a secondary amino band at 3425 cm^{-1} in the infrared. This and microanalytical data suggest the material to be N,N'-(2-pyridylmethylene)-bis-*o*-phenetidine (IV, R=*o*-OC_2H_5).



IV : R= *o*-OCH_3, *o*-OC_2H_5

Chart 3

5) J. Fabian, M. Legrand, and P. Poirier, *Bull. Soc. Chim. France*, **1956**, 1499.
6) L.E. Clougherty, J.A. Sousa, and G.M. Wyman, *J. Org. Chem.*, **22**, 462 (1957).
7) M. Nakamura, K. Komatsu, Y. Gondo, K. Ohta, and Y. Ueda, *Chem. Pharm. Bull.* (Tokyo), **15**, 585 (1967).
8) Azomethines with *o*-substituent in benzene ring.
9) Liquid azomethine, bp 154—157° (3 mmHg).

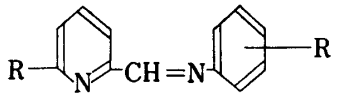
Another example was N-(2-pyridylmethylene)-*o*-anisidine (III, R=*o*-OCH_3) which affords N,N'-(2-pyridylmethylene)-bis-*o*-anisidine (IV, R=*o*-OCH_3) as a crystalline solid at room temperature. However, other *o*-substituted azomethines when kept at room temperature for longer periods of time gave only syrupy material, no formation of crystalline azomethine being observed.

The formation of IV can be explained by the ready hydrolysis[10] of *ortho*-substituted azomethine with subsequent addition of the resulting *o*-phenetidine to III (Chart 3). This route was substantiated by the preparation of IV by allowing a mixture of *o*-phenetidine and freshly prepared III to stand at room temperature. The exothermic reaction soon occurred and the mixture solidified within a period of several minutes. The crystalline solid proved to be identical with IV by mixed melting point determination, and comparison of their infrared spectra.

Experimental

Material——All amines except *o*- and *p*-chloroanilines were purified by distillation before use. 2-Pyridinemethanol was prepared by rearrangement of 2-picoline 1-oxide[11–13] in the presence of acetic anhydride

Table I. N-(2-Pyridylmethylene)anilines[a]



R	R'	mp[b] (°C)	bp (°C) (mmHg)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H	H	39—40	157—158 (8)[c]	62.1	$C_{12}H_{10}N_2$	79.09	5.53	15.38	79.06	5.48	15.52
H	*o*-CH_3	26.5—27	140—144 (6)	65.3	$C_{13}H_{12}N_2$	79.56	6.16	14.28	78.65[d]	6.05	14.11
H	*m*-CH_3	47	157—158 (6)	61.2	$C_{13}H_{12}N_2$	79.56	6.16	14.28	79.87	6.21	14.05
H	*p*-CH_3	58.5—59	152—155 (6)	76.5	$C_{13}H_{12}N_2$	79.56	6.16	14.28	79.69	6.24	14.33
H	*o*-OCH_3		162—175 (5)	51.9	$C_{13}H_{12}ON_2$	73.56	5.70	13.20	73.04[d]	6.06	13.75[d]
H	*p*-OCH_3	40	179 (5)	67.0	$C_{13}H_{12}ON_2$	73.56	5.70	13.20	73.76	5.55	13.14
H	*o*-OC_2H_5		160—164 (6)	48.9	$C_{14}H_{14}ON_2$	74.31	6.24	12.38	72.59[d]	6.38	13.00[d]
						74.31	6.24	12.38	72.37[d]	6.15	11.69[d]
H	*p*-OC_2H_5	58.5—59	174—178 (7)	78.3	$C_{14}H_{14}ON_2$	74.31	6.24	12.38	74.41	6.04	12.29
H	*o*-Cl		157—162 (7)	43.6	$C_{12}H_9N_2Cl$	66.52	4.19	12.93	65.59[d]	4.62	12.29[d]
H	*p*-Cl	65—66	167—172 (7)	62.4	$C_{12}H_9N_2Cl$	66.52	4.19	12.93	66.82	4.22	12.98
CH_3	H		140—145 (6)	73.0	$C_{13}H_{12}N_2$	79.56	6.16	14.28	78.01[d]	6.25	14.01
CH_3	*o*-CH_3	39	156—161 (7)	54.7	$C_{14}H_{14}N_2$	79.96	6.70	13.32	80.21	6.73	13.37
CH_3	*p*-CH_3	68	150—160 (7)	76.1	$C_{14}H_{14}N_2$	79.96	6.70	13.32	80.06	6.67	13.35
CH_3	*o*-OCH_3	49—50	175—177 (7)	44.6	$C_{14}H_{14}ON_2$	74.31	6.24	12.38	73.81[d]	5.93	13.09[d]
CH_3	*p*-OCH_3	48	187—192 (7)	77.4	$C_{14}H_{14}ON_2$	74.31	6.24	12.38	74.69	6.03	12.02
CH_3	*o*-OC_2H_5	83—85	153—157 (3)	40.8	$C_{15}H_{16}ON_2$	74.97	6.71	11.66	75.37	6.74	11.51
CH_3	*p*-OC_2H_5	75	188—194 (7)	59.5	$C_{15}H_{16}ON_2$	74.97	6.71	11.66	75.11	6.63	11.63

a) Two syntheses of N-(4-pyridylmethylene)anilines are described in Experimental Section.
b) All crystalline materials listed were recrystallized from ligroin.
c) lit.[9] bp 165 (13 mmHg) No melting point was reported.
d) As has been described in discussion section, the *o*-substituted compounds are unstable and often gave wrong analytical values in spite of the careful and repeated purifications. They are likely to undergo hydrolysis at room temperatures and, in two instances, subsequent formation of IV results. These microanalyses were usually made one or two days after purifications.

10) The hydrolysis was apparently brought about by the action of atmospheric moisture since no formation of a crystalline (IV) was observed when the sample was kept free from moisture.
11) G. Kobayashi and S. Furukawa, *Pharm. Bull.* **1**, 347 (1953).
12) V. Boekelheide and W.J. Linn, *J. Am. Chem. Soc.*, **76**. 1286 (1954).
13) O.H. Bullitt and J.T. Maynard, *J. Am. Chem. Soc.*, **76**. 1370 (1954).

followed by hydrolysis of the resulting 2-pyridinemethanol acetate. 4-Pyridinemethanol and 6-methyl-2-pyridinemethanol were prepared[14] *via* essentially the same route.

Preparation of N-(2-Pyridylmethylene)aniline and Its Derivatives——The procedure is illustrated below for the preparation of N-(2-pyridylmethylene)aniline (I). The constants and analyses are given in Table I.

In a three-necked flask fitted with a mechanical stirrer, dropping funnel and a Dean–Starke water separator was placed a suspension of 2 g of KOH, 27.9 g (0.299 mole) of aniline, and 21.8 g (0.199 mole) of 2-pyridinemethanol in 100 ml of dry xylene. The mixture was heated under stirring until all the KOH was brought into solution. To the heated solution (bath temperature: 150—155°) was added dropwise[15] 24.6 g (0.199 mole) of nitrobenzene in 15 min and the vigorous stirring was continued for 1 hr[16] during which H_2O collected in the trap amounted to 6.8 ml (94.4% of the theoretical). H_2O was added to dissolve the separated inorganic material and the upper organic layer was washed with H_2O and extracted with three portions of 10% HCl. The combined acid extracts were neutralized with K_2CO_3, extracted twice with ether, and ether extracts dried over anhydrous K_2CO_3. Removal of ether followed by fractional distillation gave light-yellow oil boiling at 157—158° (8 mmHg) which solidified to light-yellow prisms, melting at 39—40° (from ligroin). Yield 22.6 g (62.1% based on 2-pyridinemethanol). IR ν_{max}^{KBr} cm^{-1}: 1623 (C=N). In a run in which equimolar quantity of aniline was used, the yield dropped to 31.7%.

N-(2-Pyridylmethylene)-*o*-phenetidine (III, R=*o*-OC_2H_5)——The procedure is essentially the same with that of N-(2-pyridylmethylene)aniline except that the separation of the product in pure state is cumbersome. To a refluxing mixture of 5 g of KOH, 41.1 g (0.299 mole) of *o*-phenetidine, 21.8 g (0.199 mole) of 2-pyridinemethanol in 100 ml of dry xylene was added carefully 24.6 g (0.199 mole) of nitrobenzene. The reaction mixture was worked up as before. The vacuum distillation gave 20.6 g (45.6%) of N-(2-pyridylmethylene)-*o*-phenetidine boiling at 160—164° (6 mmHg). A fore-run, unreacted excess *o*-phenetidine, was recovered. In spite of repeated fractionations the carbon content was low in two analyses (Table I). IR ν_{max}^{liq} cm^{-1}: 1634 (C=N). When this substance was kept at room temperature overnight it became syrupy and crystals gradually separated from the solution, and the product was isolated by simply filtering off the crystals. Recrystallization from ligroin gave IV (R=*o*-OC_2H_5) as a colorless prism, mp 70—71°. IR ν_{max}^{KBr} cm^{-1}: 3425 (>NH).

Anal. Calcd. for $C_{22}H_{25}O_2N_3$: C, 72.70; H, 6.93; N, 11.56. Found: C, 72.77; H, 7.06; N, 11.64.

N,N'-(2-Pyridylmethylene)-bis-*o*-phenetidine (IV, R=*o*-OC_2H_5)——A mixture of 1.73 g (0.126 mole) of *o*-phenetidine and 2.86 g (0.126 mole) of N-(2-pyridylmethylene)-*o*-phenetidine (III, R=*o*-OC_2H_5) was allowed to stand at room temperature. An exothermic reaction set in and the mixture virtually solidified in a period of 20 min. After trituration with cold ether the crystalline solid was recrystallized from ligroin to give 4.27 g (93.0%) of N,N'-(2-pyridylmethylene)-bis-*o*-phenetidine as colorless prisms, mp 70—71°, identical with a sample obtained in the preceding experiment with respect to mixture melting point and IR spectrum.

N,N'-(2-Pyridylmethylene)-bis-*o*-anisidine (IV, R=*o*-OCH_3)——A mixture of 1 g (0.008 mole) of *o*-anisidine and 1.7 g (0.008 mole) of N-(2-pyridylmethylene)-*o*-anisidine (III, R=*o*-OCH_3) was allowed to stand at room temperature. The resulting solid was worked up as in IV (R=*o*-OC_2H_5). 2.4 g (88.9%) of IV (R=*o*-OCH_3) was obtained as colorless prisms, mp 72—73.5° (from ligroin). On admixture with the sample obtained on merely standing N-(2-pyridylmethylene)-*o*-anisidine (III, R=*o*-OCH_3), no melting point depression was observed.

N-(4-Pyridylmethylene)aniline——The procedure is practically the same as in the preparation of N-(2-pyridylmethylene)aniline (I). To a refluxing mixture of 1 g of KOH, 18.6 g (0.199 mole) of aniline, 10.9 g (0.099 mole) of 4-pyridinemethanol in 70 ml of dry xylene was added dropwise 12.3 g (0.099 mole) of nitrobenzene in 15 min. The resulting mixture was stirred and refluxed for 1 hr during which 2.4 ml (66.7% of the theoretical) of H_2O was removed. Working up of the reaction mixture in the usual manner gave 6.5 g (35.9%) of N-(4-pyridylmethylene)aniline, boiling at 148—152° (6 mmHg). The oil soon solidified to light-yellow scales, mp 72—74° (from ligroin).

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.38. Found: C, 78.59; H, 5.52; N, 15.53.

In exactly the same fashion, from 1.5 g of KOH, 10.7 g (0.099 mole) of *p*-toluidine, 5.5 g (0.05 mole) of 4-pyridinemethanol, and 6.2 g (0.049 mole) of nitrobenzene there was obtained 3.6 g (36.6%) of N-(4-pyridylmethylene)-*p*-toluidine, bp 160—169° (6 mmHg). The oil solidified to light yellow plates, mp 99.5° (from ligroin).

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.17; N, 14.27. Found: C, 79.31; H, 6.04; N, 14.24.

14) G. Kobayashi, S. Furukawa, and Y. Kawata, *Yakugaku Zasshi*, 74, 790 (1954).
15) Addition of nitrobenzene in one portion caused vigorous reaction and bumping resulted.
16) Bath temperature was maintained at 170—175° throughout.