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Nucleophilic Addition to Schiff Base. II.[1] Addition of Phenols to N-(2-Pyridylmethylene)anilines

Seiji Miyano, Nobuhiro Abe, Akiko Abe and Kazuko Hamachi

Faculty of Pharmaceutical Sciences, Fukuoka University[2]

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A nucleophilic addition of phenol to N-(2-pyridylmethylene)aniline (I) is described. Electron density around carbon atom ortho to phenolic hydroxyl group and acidity of phenol are the two factors governing the outcome of the reaction. The effects of structural variation of Schiff base on its reactivity are also discussed. Extension of the reaction involved addition of 8-hydroxyquinoline to the Schiff base (I).

In a recent communication[1] from this Laboratory it was demonstrated that phenols underwent addition reaction to N-(2-pyridylmethylene)aniline (I) under mild conditions to yield N-(2-hydroxyphenyl-2-pyridylmethyl)anilines (II). This reaction is of particular interest since there seems to be no report of phenol addition to ordinary Schiff bases. The publications dealing with addition of nucleophilic agents to Schiff bases, especially N-benzylideneaniline (III,R=H), are numerous. Additions of amines[3-6] and thiols[7-9] are widely studied in recent years. Addition of active methylene compounds such as ethyl acetoacetate,[10] pyruvic acid,[11] and nitromethane[12] to N-benzylideneaniline has long been known. More recently one report concerning to addition of ketones[13] appeared.

However, our attempts to bring about adduct formation of phenol to III (R=H) failed. The reaction of phenol with N-benzylideneaniline analogs (III) where polarization of carbon–nitrogen double bond is enhanced by the presence of powerful electron-attracting group such as *o*- and *p*-nitro group (III, R=*o*- and *p*-NO_2) was explored with wholly unpromising results, no product being isolated.

The situation is changed when N-(2-pyridylmethylene)aniline is employed in place of N-benzylideneaniline derivatives: I underwent a facile addition with phenols to give N-(2-hydroxyphenyl-2-pyridylmethyl) anilines (II) in moderate to good yields.

The ease of formation of II is due, primarily, to the enhanced electron deficiency of Schiff base carbon[14] of N-(2-pyridylmethylene) aniline which is influenced by the inherent electron-attracting nitrogen of pyridine nucleus. However, in the light of this striking distinction

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[1] The paper published by S. Miyano and N. Abe *Tetrahedron Letters*, **1970**, 1909 represents Part I of this series.

[2] Location: *Nanakuma, Fukuoka.*

[3] A. Kirgal and E. Reiter, *Chem. Ber.*, **60**, 666 (1927).

[4] R. Jaunin and R. Holl, *Helv. Chim. Acta*, **41**, 1783 (1958).

[5] J. Goerdeler and H. Ruppert, *Chem. Ber.*, **96**, 1630 (1963).

[6] G.W. Stacy, B.V. Ettling and A.J. Papa *J. Org. Chem.*, **29**, 1537 (1964).

[7] G.W. Stacy and R.J. Morath, *J. Am. Chem. Soc.*, **74**, 3885 (1952).

[8] H. Gilman, J.L. Towle and R.K. Ingham, *J. Am. Chem. Soc.*, **76**, 2920 (1954).

[9] G.W. Stacy, R.I. Day and R.J. Morath, *J. Am. Chem. Soc.*, **77**, 3869 (1955).

[10] R. Schiff and C. Bertini, *Ber.*, **30**, 601 (1897).

[11] R.E. Lutz, P.S. Bailey, M.T. Clark, J.F. Codington, A.J. Deinet, J.A. Freek, G.H. Harnest, N.H. Leake, T.A. Martin, R.J. Rowlett, Jr., J.M. Salsbury, N.H. Shearer, Jr., J.D. Smith and J.W. Wilson, III, *J. Am. Chem. Soc.*, **68**, 1813 (1946).

[12] C.H. Hurd and J.S. Strong, *J. Am. Chem. Soc.*, **72**, 4813 (1950).

[13] A.H. Blatt and N. Gross, *J. Org. Chem.*, **29**, 3306 (1946).

[14] In the present paper, carbon of –CH=N– of Schiff base is referred to as "Schiff base carbon" rather than "azomethine carbon" which we used in the previous communication (see 1).

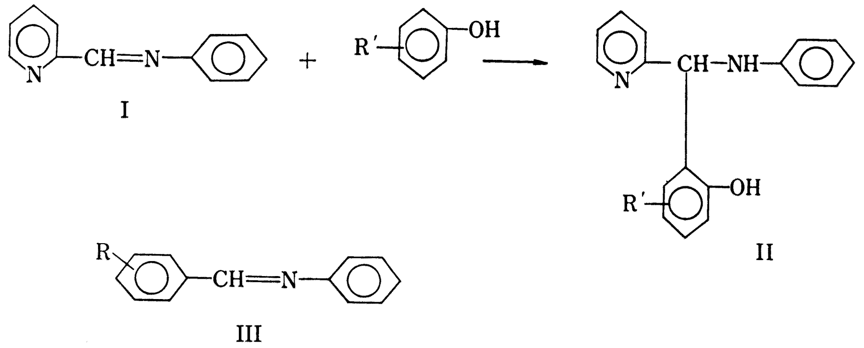

Chart 1

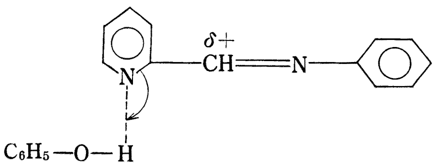

Chart 2

between reactivities of I and *o*- and *p*-nitrobenzylideneaniline (III, R=*o*- and *p*-NO_2) it seems very likely[15] that electron deficiency around Schiff base carbon is enhanced by the formation of intermolecular hydrogen bond between basic nitrogen of pyridine nucleus and phenolic hydroxyl to such a degree that addition is brought about under very mild conditions (Chart 2).

By the simplest procedure reaction is complete by merely refluxing the benzene solution of I and phenol for a few hours. The proof for the structure (II) was provided by microanalyses and infrared (IR) spectra which showed broad band at 3200—2400 cm^{-1} (intramolecular hydrogen bonded OH) and a single sharp band at 3430—3370 cm^{-1} (secondary amine). Production of violet color with ferric chloride solution also proved the presence of phenolic hydroxyl group.

Yields varied widely with diverse nature and position of side chain substituents of phenol (Table I). Phenols of type IV (R=OCH_3, OC_2H_5) which are sufficiently active with two electron-releasing groups gave adducts in good yields, whereas with *m*-hydroxyacetophenone (IV, R=$COCH_3$) and methyl *m*-hydroxybenzoate (IV, R=$COOCH_3$) in which electron-attracting group such as $COCH_3$ and $COOCH_3$ exerts its influence to adjacent position no adduct was obtained. With resorcinol (IV, R=OH) and *m*-aminophenol (IV, R=NH_2) only resinous products resulted presumably because of their unusually high reactivities. Of particular interest is the behavior of phenols carrying ortho substituted proton-accepting group where intramolecular hydrogen bond exists: *o*-hydroxyacetophenone (V), and methyl salicylate (VI) failed to react. *o*-Hydroxyanisole (VII) gave only poor results, whereas no-chelating *o*-cresol and phlorol (*o*-ethylphenol) afforded adducts in good yields, 67% and 57%, respectively (Table I).

However, we have observed that *o*-chlorophenol (VIII) in which intramolecular hydrogen bonding is more pronounced[16] than that of VII gave better result (41%, Table I). This seemingly odd behavior can be attributable to the ready formation of intermolecular hydrogen bonding[17] (IX) between Schiff base nitrogen and more acidic (than VII) phenolic hydroxyl of VIII which is a key step of the reaction as described below, and the poor result with VII

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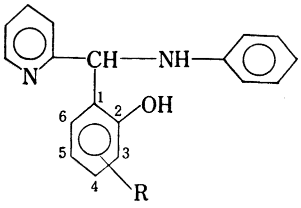
15) On intermolecular hydrogen bonding between basic nitrogen of pyridine nucleus and phenolic hydroxyl a quite many reports appeared *e.g.*, Y. Sato, *Nippon Kagaku Zasshi*, **79**, 1384 (1958). However, resulting activation of carbon at 2-position by the presence of this type of hydrogen bonding has not been mentioned.

16) A.W. Baker and A.T. Shulgin, *J. Am. Chem. Soc.*, **80**, 5358 (1958).

17) J. Weinstein and E. McIninch, *J. Am. Chem. Soc.*, **82**, 6064 (1960).

TABLE I. N-(2-Hydroxyphenyl-2-pyridylmethyl) anilines (II)



R	mp (°C)$^{a)}$	Yield (%)$^{b)}$	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
H	150—152$^{c)}$	63	needle	$C_{18}H_{16}ON_2$	78.23	5.84	10.14	78.19	5.71	10.16
3-CH_3	80— 85$^{c)}$	67	needle	$C_{19}H_{18}ON_2$	78.59	6.25	9.65	78.24	6.30	9.82
4-CH_3	187—188$^{d)}$	84	powder	$C_{19}H_{18}ON_2$	78.59	6.25	9.65	78.38	6.12	9.37
5-CH_3	121—125$^{c)}$	43	prism	$C_{19}H_{18}ON_2$	78.59	6.25	9.65	78.20	6.15	9.45
3-C_2H_5	96— 97$^{e)}$	62	prism	$C_{20}H_{20}ON_2$	78.92	6.62	9.20	78.54	6.73	9.16
3-OCH_3	156—157$^{e)}$	12	needle	$C_{19}H_{18}O_2N_2$	74.49	5.92	9.15	74.25	5.98	9.05
4-OCH_3	158—159$^{e)}$	72	needle	$C_{19}H_{18}O_2N_2$	74.49	5.92	9.15	74.10	5.88	8.95
5-OCH_3	133—135$^{e)}$	44	prism	$C_{19}H_{18}O_2N_2$	74.49	5.92	9.15	74.51	5.95	9.02
4-OC_2H_5	125$^{c)}$	71	needle	$C_{20}H_{20}O_2N_2$	74.97	6.29	8.74	74.77	6.43	8.31
5-$COOCH_3$	160—161$^{e)}$	54	powder	$C_{20}H_{18}O_3N_2$	71.84	5.43	8.38	72.23	5.47	8.04
5-$COCH_3$	155—157$^{e)}$	40	needle	$C_{20}H_{18}O_2N_2$	75.45	5.70	8.80	75.43	5.71	8.51
3-Cl	149—150$^{e)}$	41	needle	$C_{18}H_{15}ON_2Cl$	69.56	4.87	9.01	69.42	4.93	8.99
4-Cl	170—172$^{e)}$	61	needle	$C_{18}H_{15}ON_2Cl$	69.56	4.87	9.01	69.51	4.93	8.91
5-Cl	151—152$^{e)}$	50	prism	$C_{18}H_{15}ON_2Cl$	69.56	4.87	9.01	69.78	5.00	9.08

a) Melting points of all products listed tend to rise several degrees (3—5°) when allowed to stand at room temperature for a week.

b) Reaction times were limited to four hours. Yield of N-(2-hydroxyphenyl-2-pyridylmethyl)aniline (R=H) increased to 80% when the reaction time was extended to nine hours. Consequently these yields may subject to change when reactions are run for a longer period of time.

c) recrystallized from ethanol

d) recrystallized from acetone

e) recrystallized from methanol

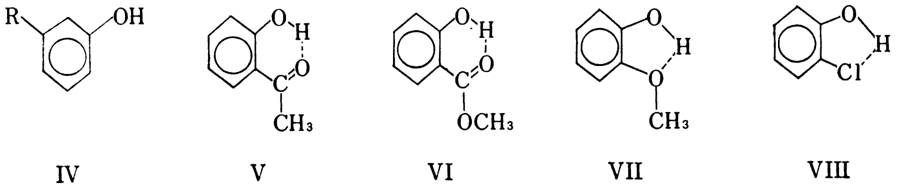


Chart 3

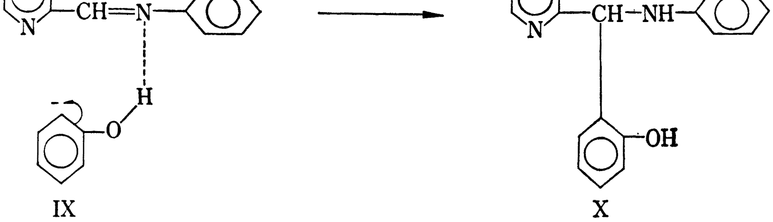


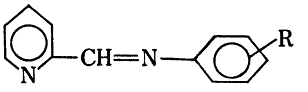
Chart 4

can largely be due to the low degree of acidity of phenolic hydroxyl group rather than chelation in VII.

These observations suggest that two structural factors of addendum, *i.e.*, reactivity of ortho position of phenolic hydroxyl group and acidity of phenol, are influential in governing the outcome of the addition reaction.

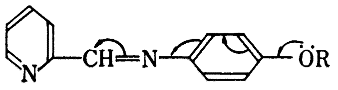
The reaction can be considered to proceed according to the route shown in Chart 4: intermolecular hydrogen bonding (IX) forms between Schiff base nitrogen and phenolic hydroxyl group, the resulting electron deficiency around Schiff base nitrogen promotes activation of Schiff base carbon (IX) on which nucleophilic attack of phenol takes place (IX→X). The poor results obtained with V and VI are consistent to their inabilities to form key intermediate IX because of the strong chelation in their molecule.

It was of further interest to observe the effects of varying the substituents on benzene ring attaching to Schiff base nitrogen. A remarkable distinction was observed between the reactivities of *ortho*-alkoxy- and *para*-alkoxy-substituted Schiff bases, XI and XII. Schiff



XI : R=o-OCH$_3$, o-OC$_2$H$_5$

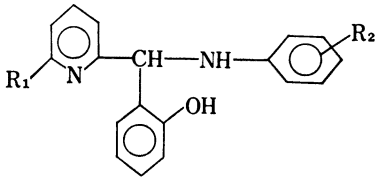
XII : R=p-OCH$_3$, p-OC$_2$H$_5$



XIII

Chart 5

Table II. Effects of Varying the Substituents on Phenyl Group attaching to Schiff Base Nitrogen



R_1	R_2	mp (°C)[a,b]	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	o-CH$_3$	124—125	48	$C_{19}H_{18}ON_2$	78.59	6.25	9.65	78.14	6.46	9.63
H	p-CH$_3$	133—134	28	$C_{19}H_{18}ON_2$	78.59	6.25	9.65	78.42	6.34	9.62
H	o-OCH$_3$	169—170	82 69[c]	$C_{19}H_{18}O_2N_2$	74.49	5.92	9.15	74.42	5.62	9.15
H	o-OC$_2$H$_5$	155—157	77 78[c]	$C_{20}H_{20}O_2N_2$	74.97	6.29	8.71	75.29	6.20	8.68
H	o-Cl	167—168	66 71[c]	$C_{18}H_{15}ON_2Cl$	69.56	4.87	9.01	69.33	4.63	8.71
H	p-Cl	135—137	36	$C_{18}H_{15}ON_2Cl$	69.56	4.87	9.01	69.45	5.01	8.72
CH$_3$	H	130—131	59[d]	$C_{19}H_{18}ON_2$	78.59	6.25	9.65	78.25	6.03	9.66
CH$_3$	o-OCH$_3$	169—170	66[d]	$C_{20}H_{20}O_2N_2$	78.97	6.29	8.74	75.36	6.11	8.73
CH$_3$	o-OC$_2$H$_5$	144—145	60[d]	$C_{21}H_{22}O_2N_2$	75.42	6.63	8.38	75.21	6.74	8.44
CH$_3$	o-Cl	141	50[d]	$C_{19}H_{17}ON_2Cl$	70.25	5.28	8.63	70.10	5.29	8.85

[a] All products are obtained as colorless prisms.

[b] All products are recrystallized from methanol except N-(2-hydroxyphenyl-2-pyridylmethyl)-o-anisidine (R_1=H, R_2=o-OCH$_3$) which is purified by recrystallization from EtOH-acetone.

[c] Obtained from reaction of N,N'-(2-pyridylmethylene)-bis-aniline (XIV) with phenol.

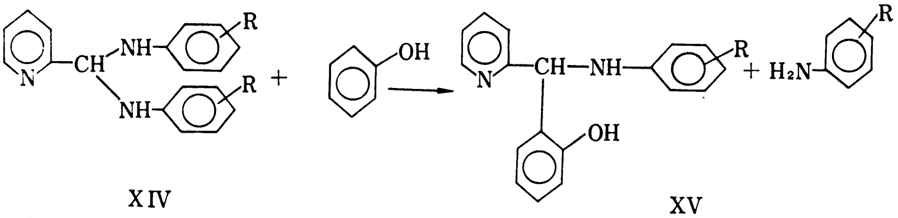
[d] These yields are recorded when the reaction mixtures are stood at room temperature for two weeks.

bases with ortho substituent (XI) react readily while those with para substituent fail to react. (Table II)

The poor reactivities of XII can be explained in terms of mesomeric effect of *p*-alkoxy group: electron-releasing effect of *p*-methoxy or *p*-ethoxy group exerts its deactivating influence on Schiff base carbon as shown in structure XIII in which coplanar configuration between -CH=N- and the attaching benzene ring is maintained in such a degree as to allow the mesomeric effect pass through the molecule. In contrast, yields of the adduct with *ortho* substituted Schiff base XI are excellent and this may be attributed to the lack of mesomeric effect of *o*-alkoxy group to be rendered to Schiff base carbon. Unlike its *p*-alkoxy counterpart (XII) steric factors involved in XI oppose coplanar configuration between -CH=N- and the ring and this prevents the mesomeric interaction of alkoxy group.

Whether the yields which are even higher (82 and 77%, respectively) than that with I (66%) may be due to the ortho effect of *o*-alkoxy group or not could not be determined merely from these two reactions.

In three experiments (XI, R=*o*-OCH_3, *o*-OC_2H_5 and *o*-Cl) varying the substituents on phenyl group the adducts were also obtained from reaction of N,N'-(2-pyridylmethylene)-bis-anilines[18] (XIV) with phenol (Chart 6).

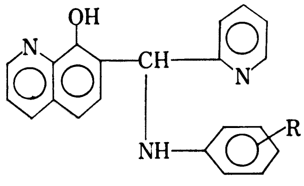


XIV
(R = *o*-OCH_3, *o*-OC_2H_5 and *o*-Cl)

XV

Chart 6

Table III. 7-(Anilino-2-pyridylmethyl)-8-hydroxyquinolines



R	mp (°C)	Yield (%)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	127—128	86	prism	$C_{21}H_{17}ON_3$	77.04	5.23	12.84	77.19	5.39	12.78
o-CH_3	135—137	85	light yellow prism	$C_{22}H_{19}ON_3$	77.39	5.61	12.31	77.10	5.63	12.24
p-CH_3	146—147	82	prism	$C_{22}H_{19}ON_3$	77.39	5.61	12.31	77.25	5.37	11.94
o-OCH_3	174—175	85	prism	$C_{22}H_{19}O_2N_3$	73.93	5.36	11.76	73.88	5.35	11.60
p-OCH_3	137—138	70	prism	$C_{22}H_{19}O_2N_3$	73.93	5.36	11.76	73.88	5.05	11.77
o-OC_2H_5	163—164	91	yellow prism	$C_{23}H_{21}O_2N_3$	74.37	5.70	11.31	74.45	6.07	10.95
p-OC_2H_5	160—161	46	prism	$C_{23}H_{21}O_2N_3$	74.37	5.70	11.31	74.02	5.39	11.11
o-Cl	169—171	68	needle	$C_{21}H_{16}ON_3Cl$	69.71	4.46	11.61	70.06	4.18	11.47
p-Cl	140—141	81	prism	$C_{21}H_{16}ON_3Cl$	69.71	4.46	11.61	69.39	4.25	11.52

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[18] S. Miyano, N. Abe and A. Abe, *Chem. Pharm. Bull.* (Tokyo), **18**, 511 (1970).

The reaction just reported was successfully extended to 8-hydroxyquinolines. The adducts, 7-(anilino-2-pyridylmethyl)-8-hydroxyquinolines are given in Table III. As compared with phenol addition, the procedure is even simpler: an ethanolic solution of equivalent amounts of Schiff base and 8-hydroxyquinoline is allowed to stand at room temperature and yields are good to excellent.

Experimental

Preparation of N-(2-Hydroxyphenyl-2-pyridylmethyl)anilines (II) (Table I)——The preparations of II do not require individual descriptions since the variations in the procedure are not great except the preparation of N-(2-hydroxy-4-methoxyphenyl-2-pyridylmethyl)aniline.

In a typical example, a solution of 0.011 mole of N-(2-pyridylmethylene)aniline (I) and 0.016 mole of phenol in 100 ml of benzene is refluxed for 4 hours. Crystals separated upon standing are collected and purified by recrystallization. Three adducts (Table I, R=5-$COOCH_3$, 5-$COCH_3$, and 5-Cl) which did not crystallize out by this procedure was secured by removal of benzene *in vacuo*, followed by addition of a small amount of methanol.

N-(2-Hydroxy-4-methoxyphenyl-2-pyridylmethyl)aniline (Table I, R=4-OCH_3)——A solution of 2.0 g (0.011 mole) of N-(2-pyridylmethyl)aniline (I) and 2.1 g (0.016 mole) of *m*-methoxyphenol (IV, R=OCH_3) in 50 ml of benzene is allowed to stand at room temperature for 40 hours. Reaction is exothermic. Filtration gave 1.8 g of the product, mp 158—159° as colorless crystals. Evaporation of the mother liquor gives 0.6 g of additional product. Yield 2.4 g (72%).

Experiments to observe the Effects of Varying the Substituents on Benzene Ring attached to Schiff Base Nitrogen (Table II)——The following two methods for the preparation of N-(2-hydroxyphenyl-2-pyridylmethyl)-*o*-anisidine (XV, R=*o*-OCH_3) are illustrative.

From N-(2-Pyridylmethylene)-*o*-anisidine and Phenol——A solution of 2.12 g (0.01 mole) of XIV and 1.4 g (0.015 mole) of phenol in 10 ml of benzene is refluxed for 4 hours. Removal of benzene gave 2.5 g (82%) of XV (R=*o*-OCH_3). Recrystallization from methanol affords a colorless prism melting at 169—170°.

From N,N′-(2-Pyridylmethylene)-bis-*o*-anisidine (XIV) and Phenol (Chart 6)——XIV is prepared according to our method.[18] A solution of 3.35 g (0.01 mole) of XIV and 1.4 g (0.015 mole) of phenol in 10 ml of benzene is refluxed for 4 hours. Evaporation of the solvent followed by recrystallization from methanol gave 2.12 g (69%) of XV (R=*o*-OCH_3).

General Procedure for the Preparation of 7-(Anilino-2-pyridylmethyl)-8-hydroxyquinolines——To a solution of Schiff base (0.01 mole) in 20 ml of ethanol is added 0.01 mole of 8-hydroxyquinoline and the resulting nearly clear solution is allowed to stand at room temperature for a week. The deposited crystals are collected. One recrystallization gave pure products.

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