

A NUCLEOPHILIC ADDITION OF PHENOLS TO N-(2-PYRIDYLMETHYLENE)ANILINE

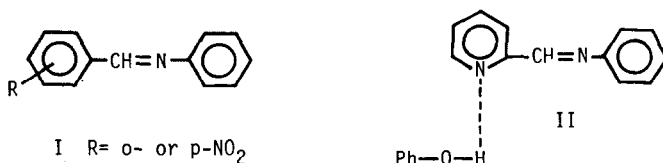
Seiji Miyano and Nobuhiro Abe

Department of Pharmaceutical Sciences, Fukuoka University, Fukuoka, Japan

(Received in Japan 16 March 1970; received in UK for publication 8 April 1970)

Among the various publications dealing with addition of nucleophilic agents, such as amines¹⁻³, active methylene compounds⁴, and thiols⁵⁻⁷, to N-benzylideneaniline there appears to be no report on addition of phenol to the Schiff base. Actually our attempt to add phenol to N-benzylideneaniline failed. With the Schiff base (I) where polarization of carbon-nitrogen double bond is enhanced by the presence of powerful electron-attracting group such as o- and p-nitro group, the addition of phenol was also unsuccessful, only starting materials being recovered.

It has now been observed that phenol underwent a facile addition to N-(2-pyridylmethylene)-aniline (II)⁸ to afford N-(2-hydroxyphenyl-2-pyridylmethyl)aniline (VII). The proof for the structure was provided by microanalyses and IR spectra which showed broad band at $3200-2400\text{ cm}^{-1}$ (intramolecular hydrogen bonded OH) and a single sharp band at $3430-3370\text{ cm}^{-1}$ (secondary amine). Production of violet color with ferric chloride solution also proved the presence of phenolic hydroxyl group.



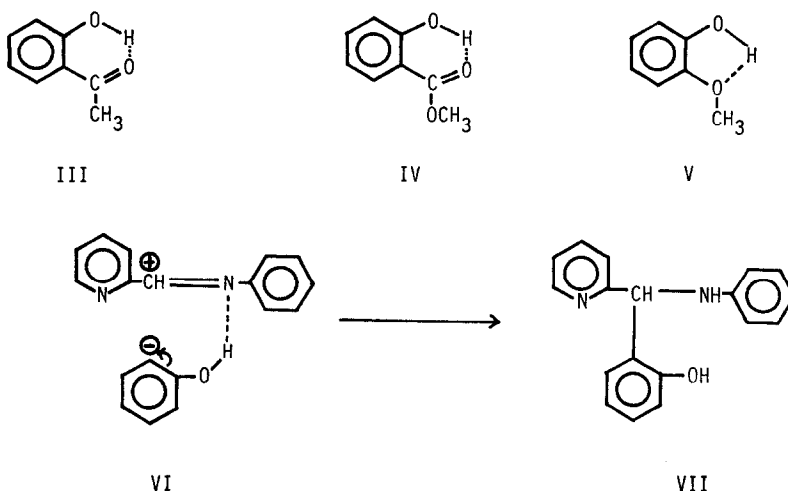
The greater reactivity of II can be attributed, for the most part, to the inherent electron-attracting nature of pyridine nucleus which makes carbon of carbon-nitrogen double bond (called hereafter as "azomethine-carbon") sufficiently active. However, in view of the direct contrast between the reactivities of N-(2-pyridylmethylene)aniline (II) and o- and p-nitrobenzylideneaniline (I) there might be another factor involved in phenol addition to II.

Thus, for the rationalization of unusually high activity of II, the formation of

intermolecular hydrogen bond between basic nitrogen of pyridine nucleus and phenolic hydroxyl, and subsequent promotion of electron deficiency around "azomethine-carbon" is proposed.

Addition usually proceeds without complication by refluxing the benzene solution of azomethine and phenol for a few hours. Yields varies widely with diverse nature and position of side chain substituents of phenol. (Table I) The presence of two electron-releasing groups made *m*-methoxyphenol so active that the adduct was obtained in 72% yield by merely allowing the reactants to stand at room temperature. Of particular interest is the behavior of phenols with ortho-substituted proton-accepting group where intramolecular hydrogen bond exists: *o*-Hydroxyacetophenone (III), and methyl salicylate (IV) failed to react. *o*-Hydroxyanisole (V) gave only poor result (12%), whereas *no*-chelating *o*-cresol afforded adduct in fairly good yield (67%). (Table I)

On the other hand, Weinstein and McIninch⁹ presented the evidence which showed the existence of intermolecular hydrogen bond between phenolic hydroxyl and "azomethine-nitrogen". The present reaction is, therefore, considered to be initiated by the formation of intermolecular hydrogen bond (VI) between phenol and *N*-(2-pyridylmethylene)aniline. The resulting electron deficiency around "azomethine-nitrogen" promote activation of "azomethine-carbon" on which nucleophilic attack of phenol occurs. (VI \rightarrow VII)



Accordingly, the poor results encountered with III, IV, and V in which intramolecular hydrogen bond is pronounced are apparently due to the inability of these compounds to form

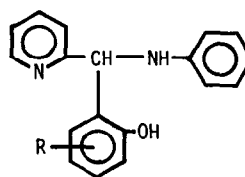
intermolecular hydrogen bond with "azomethine-nitrogen". To our knowledge this is the first example of addition of phenol to Schiff base.

The following procedure for the preparation of N-(2-hydroxyphenyl-2-pyridylmethyl)-aniline (VII) is illustrative: A solution of 2 g (0.011 mole) of N-(2-pyridylmethylene)-aniline and 1.5 g (0.016 mole) of phenol in 10 ml of benzene was refluxed for 4 hours. Recrystallization of the product which separated on standing overnight gave 1.9 g (63%) of VII as colorless needles, m.p. 150-152. IR $\nu_{\text{N-H}}$: 3405 cm^{-1} , $\nu_{\text{O-H}}$: 2400-3100 cm^{-1} .

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_2\text{O}$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.19; H, 5.84; N, 10.16.

Table I

N-(2-Hydroxyphenyl-2-pyridylmethyl)anilines



R	M.p., °C ^a	Yield, %
H	150-152	63
3-CH ₃	78-79	67
4-CH ₃	176-181	84
5-CH ₃	123-125	43
3-OCH ₃	131-133	12
4-OCH ₃ ^b	158-159	72
5-OCH ₃	132-134	44
3-COOCH ₃	-----	0
5-COOCH ₃	157-159	54
3-COCH ₃	-----	0
5-COCH ₃	155-157	40

^aAll products were recrystallized from methanol.

^bObtained by allowing a solution of 2 g of N-(2-pyridylmethylene)aniline and 2.1 g of m-methoxyphenol in 10 ml of benzene to stand at room temperature for 40 hours.

REFERENCES

1. R.Jaunin and R.Holl, Helv.Chim.Acta., 41, 1783 (1958)
2. J.Goerdeler and H.Ruppert, Chem.Ber., 96, 1630 (1963)
3. G.W.Stacy, B.V.Ettling and A.J.Papa, J.Org.Chem., 29, 1537 (1964)
4. A.H.Blatt and N.Gross, J.Org.Chem., 29, 3306 (1964)
5. G.W.Stacy and R.J.Morath, J.Am.Chem.Soc., 74, 3885 (1952)
6. H.Gilman, J.L.Towle and R.K.Ingham, J.Am.Chem.Soc., 76, 2920 (1954)
7. G.W.Stacy, R.I.Day and R.J.Morath, J.Am.Chem.Soc., 77, 3869 (1955)
8. N-(2-Pyridylmethylene)aniline (II) and its analogs were prepared by condensation between 2-pyridinealdehyde and aromatic amines or the reaction of 2-pyridinemethanol with aromatic amines in the presence of potassium hydroxide and nitrobenzene; S.Miyano and N.Abe, Chem.Pharm.Bull., 18, 520 (1970)
9. J.Weinstein and E.McIninch, J.Am.Chem.Soc., 82, 6064 (1960)