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Novel Reaction of Aminopyridines with Glyoxal and Formaldehyde; Synthesis of 4,8-Di (N-aminopyridyl) 2,6-dioxa 4,8-diazabicyclo[3.3.0]octane, 6,8-Di(N-aminopyridyl) 2,4-dioxa 6,8-diazabicyclo[3.3.0]octane and X-Ray Structural Study of Related 1,3-Di(N-aminopyridyl) 4,5-dihydroxy imidazolidine.

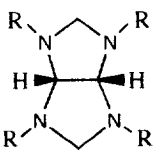
S. Morteza F. Farnia*, Ali Kakanejadifard and Dawood Soudbar

Department of Chemistry, University of Tehran, Tehran, Iran
e-mail: MFARNIA @ Khayam.ut.ac.ir

Abstract: Condensation of 2-aminopyridine with glyoxal proceeds with high selectivity to a mixture of meso and dl diol 7 to be easily transformed into the corresponding bicyclooctane 2a and 3a with formaldehyde and acetonitrile as solvent. In water, however, the reaction selectively produces imidazolidine 4a. Based on NMR analysis, the major diastereomers were assigned as syn derivatives. X-ray crystal structure of 4a shows a planar configuration for imidazolidine ring, in line with two anomeric effects, first a strong $n_N \rightarrow \sigma^*_{C\text{-}O}$ interaction and second a weak $n_O \rightarrow \sigma^*_{C\text{-}N}$ one. A network of hydrogen bonding between pyridyl nitrogens and hydroxy hydrogens forms a pattern of twelve atom in a chair-like conformation.

INTRODUCTION

Addition of benzylamine and arylamines to glyoxal and formaldehyde is a well known studied reaction used for the synthesis of tetraazabicyclo[3.3.0]octanes[1-5]. In our preceeding papers, we reported on selective synthesis of arylamine derivatives 1b-1c and studied the structure of Phenylamine 1c by X-ray diffraction to reveal cis configuration at the ring juncture[2-4].



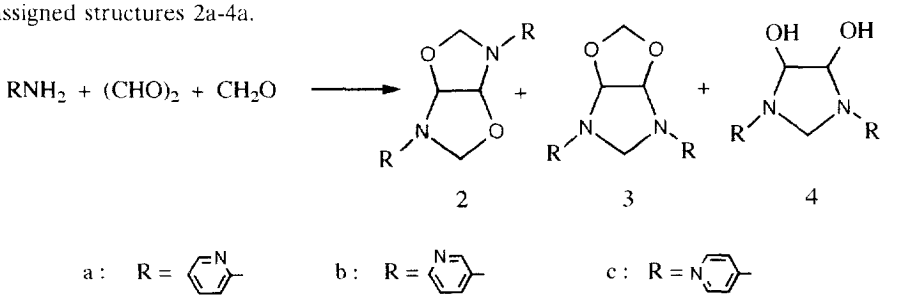
1a	R = Alkyl-
1b	R = $ArCH_2$-
1c	R = Ar-
1d	R = Acyl-

Molecules containing anomeric effect in N-C-N system has been the subject of extensive study during the last two decades. Results for N-C-N units of 1c are consistent with two interactions; first, aromatic conjugation with ring nitrogens and second a strong $n_N \rightarrow \sigma^*_{C\text{-}N}$ anomeric effect generally accepted as "negative hyperconjugation"[4,6-8]. The occurance of these effects in a system influences many structural and electronic properties. Molecules containing O-C-N system had also been studied and shown to contain two unequal anomeric effects: a strong $n_N \rightarrow \sigma^*_{C\text{-}O}$ anomeric interaction and a weak $n_O \rightarrow \sigma^*_{C\text{-}N}$ one[9]. In this article we describe selective condensation of aminopyridines, glyoxal and

formaldehyde to extend our studies of polyoxaazapolycyclic amines. In addition, reactivities, solvation and anomeric interactions based on structural analysis of X-ray diffraction data are discussed.

RESULTS AND DISCUSSION

When 2-aminopyridine (2 mole equiv.) is added to aqueous glyoxal (1 mole equiv.) and formaldehyde (2 mole equiv.) in ethanol at 0-5°C, a homogeneous solution results from which white precipitates starts depositing in a few hours. These precipitates proved to be a mixture mp 140-147°C and are assigned structures 2a-4a.



When condensation was proceeded in acetonitrile solvent at 0°C using formic acid catalyst with stoichiometric quantities of amine, formaldehyde and glyoxal a white precipitate of 4,8-di(2-aminopyridyl) 2,6-dioxa 4,8-diazabicyclo[3.3.0]octane (2a) forms, mp 161.5-162°C (78.5% yield) and a correct elemental analysis for $C_{14}H_{14}N_4O_2$. The IR spectrum lack both amine and carbonyl absorptions. The electron impact mass spectrum reveals a weak molecular ion at m/z 270. Characteristic of the proton spectra is a singlet at δ 5.05 for the cis-bridgehead CH protons. The ring methylene signals appear as an AB quartet at δ 5.44-6.11 (J=6.7 Hz). Supernatant liquid of this reaction was concenterated to give an oily liquid, when triturated with acetonitrile yielded white pure crystals, mp 181-181.5°C (8.5% yield). We have assigned to this compound 6,8-di(2-aminopyridyl) 2,4-dioxa 6,8-diazabicyclo[3.3.0]octane (3a), based on the following observations. First, it gives the correct elemental analysis for $C_{14}H_{14}N_4O_2$ and it lacks NH and CO absorptions in the IR spectra. Mass spectrum reveals a molecular ion peak at m/z 270. In the ^1H NMR spectrum there are a singlet at δ 6.22 for methinic protons and two AB quartet patterns for the two ring methylene moieties at δ 5.01-5.27 (ABq, J=6.2 Hz) and 4.82-5.15 (ABq, J=0.9 Hz).

We next proceeded the reaction at 0°C with stoichiometric quantities of amine, glyoxal and formaldehyde in water instead of acetonitrile without formic acid catalyst. Under these conditions, a solid precipitated from the reaction mixture mp 117°C (91.36% yield). Surprisingly, this product was 1,3-di(2-aminopyridyl) 4,5-dihydroxy imidazolidine (4a) based on the following observations. The IR spectra showed a sharp stretch for OH at 3311 cm^{-1} and lack NH and CO absorptions. The EI mass spectrum showed molecular ion peak at m/z 258 and elemental analysis is consistent for $C_{13}H_{14}N_4O_2$. Characteristics of the proton spectra are a singlet at δ 5.04 for the ring CH_2 hydrogens and a doublet for methinic protons at δ 5.39-5.48 (J=6.63 Hz). The hydroxy signals appear as a doublet centered near δ 6.01-6.097 (J=6.63 Hz). Upon addition of D_2O to the NMR sample, the hydroxy signals disappeared and methinic ring protons quickly collapsed into a singlet at δ 5.45. The crystal structure of 4a was solved to confirm the stereochemistry and determine the overall molecular conformation. Details regarding the data collection and structure solution and refinement are presented in the Experimental Section. The atomic coordinates and thermal parameters are given in the supplementary

pages. Figure 1 shows a computer generated view of 4a with atom numbering and a plot of the rings. The hydrogens at the ring juncture are plotted in figure 1 to more clearly show trans configuration.

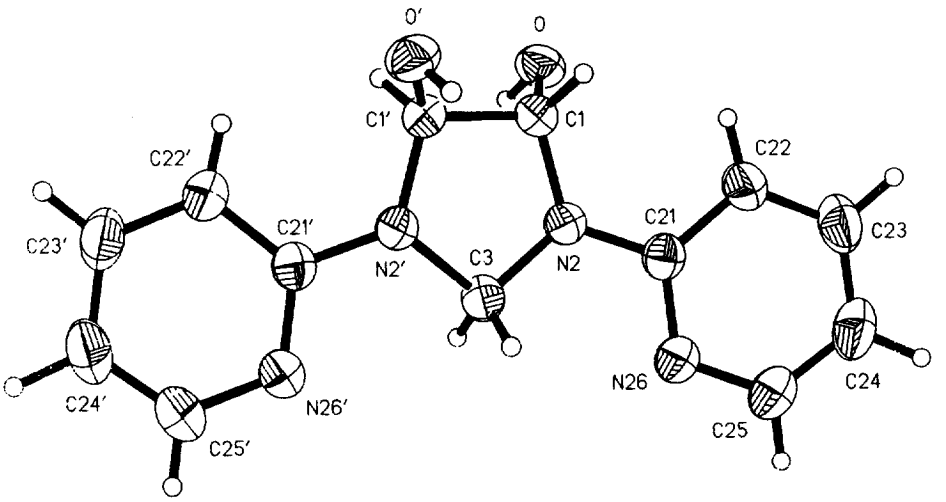
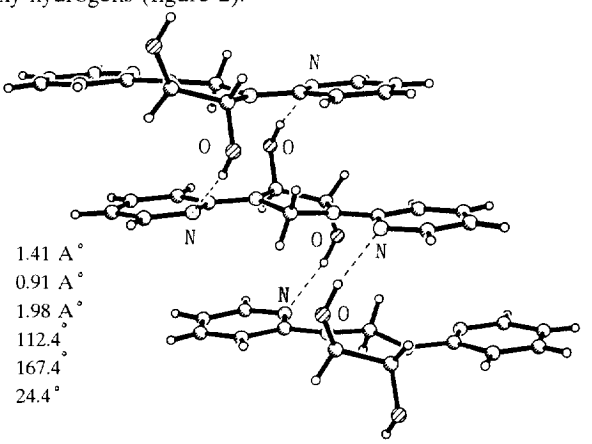


Figure 1. X-ray crystal structure of 4a. Selected bond lengths (Å) and angles (°): C1-N2 1.436(2), C21-N2 1.373(2), C3-N2 1.454(2), C1-C1' 1.540(2), C1-O 1.409(2), C3-N2' 1.454(2), C1-N2-C21 123.9(1), C3-N2-C21 120.9(1), C1-N2-C3 114.3(1), N2-C3-N2' 102.2(1), N2-C1-C1' 104.5(1), O-C1-N2 113.7(1).

There are unusual structural features in the molecule. The C1, C3 and C21 bond lengths to N2 are smaller than usual value of 1.48 Å. The ring bond angles N2-C3-N2' and N2-C1-C1' are shortened and C1-N2-C21, C3-N2-C21 and C1-N2-C3 deviate significantly from 109° and are all rather large. It is most noteworthy that both pyridyl rings lie in the plane of the central ring (torsion angle involving the atoms C1-N2-C3-N2' and C1'-C1-N2-C3 are -2.1° and 5.1° respectively). The central imidazolidine ring is essentially planar with maximum deviation of 7.2° from the mean plane comprised of the atoms C1-N2-C3-N'2-C1'.

A three dimensional net-work of hydrogen bonds exists in the crystal of 4a between the pyridyl nitrogen atoms and hydroxy hydrogens (figure 2).



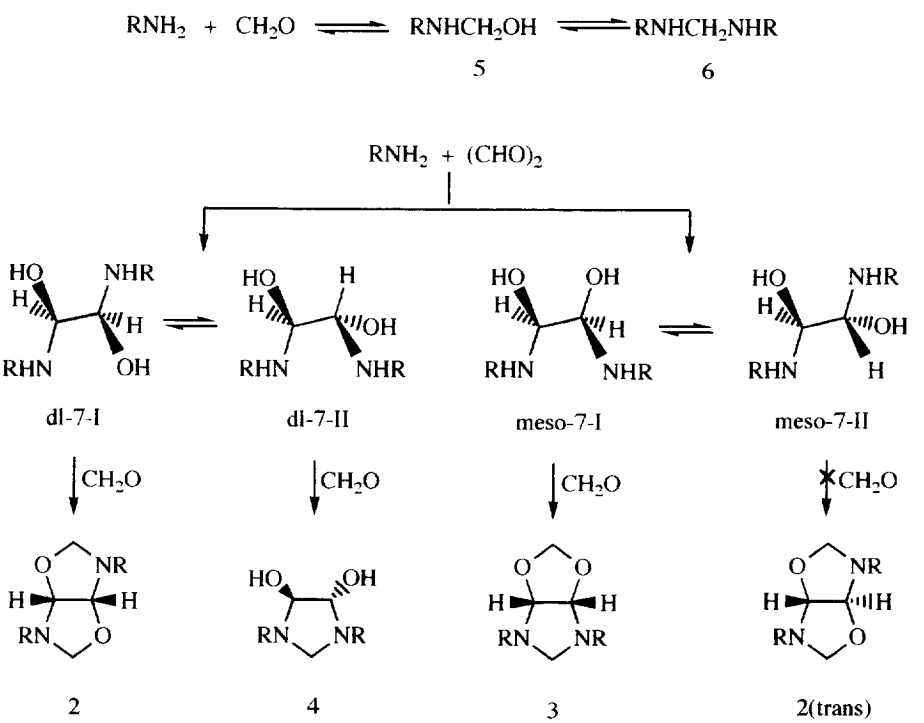
C-O	1.41 Å
O-H	0.91 Å
H ... N	1.98 Å
C-O-H	112.4°
O-H ... N	167.4°
C-O-H ... N	24.4°

Figure 2. Hydrogen bonding scheme in 4a.

This alcohol-amine complementarity forms a pattern of hydrogen bonds in a twelve atom chair-like conformation, probably due to two torsion angles O-C1-N2-C21 and C1-N2-C21-N26 24.4° and 180° respectively. In solution however, hydrogen bonding prevents exchange of hydroxy hydrogens to permit coupling CH (methinic) and OH protons.

Short C-O and C-N bonds as well as tightened N2-C3-N2′ bond angle (102.2°) leads to an anticipated anomeric effect in O-C-N moiety due to two cross hyperconjugation from $n_{N_2} \rightarrow \sigma^*_{C\text{-}O}$ and $n_O \rightarrow \sigma^*_{C\text{-}N}$. Back donation of electrons from nitrogens drastically decrease nitrogen pyramidality leading to an increase p character of the 1p,s.

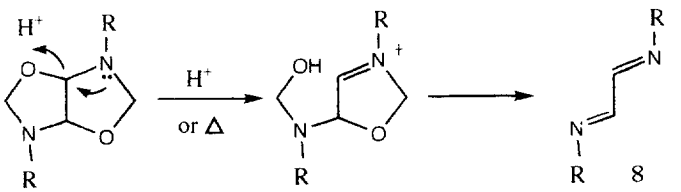
One of the major differences between reactivity of aminopyridines is that, condensation of 3-aminopyridine with glyoxal and formaldehyde in acetonitrile gives polymers, whereas in water white precipitates of 2b are formed. On the contrary 4-aminopyridine in water gives 4c as the major product. The reaction of 2-aminopyridine in acetonitrile produce 2a and 3a, whereas in water hydroxy imidazoldine 4a is formed. A reaction mechanism which accounts for all the observed products is presented in scheme 1. Available data from the present investigation as well as previous work on the condensation of amines with glyoxal, suggest that the mechanism of this reaction involves first the formation of intermediate diol 7 (independently generated at 0°C, Experimental Section).



Scheme I

Studies indicate that intermediate 7 is generated in situ in two configurations dl (major) and meso (minor), the conformations of each are equilibrating very fast; hence the relative stability of each conformer may effect the direction of equilibrium. We believe differing products formed in the reactions in acetonitrile and water from dl-7 are due to the modes of trapping of the reversibly formed intermediate, the conformational equilibria of which are likely to be solvent dependent. Thus in acetonitrile as solvent the conformer dl-7-I is much lower in energy leading to product 2 with formaldehyde. Whereas in water the conformer dl-7-II has a more favorable activation energy to proceed to trans dihydroxy imidazolidine 4. In addition, the reaction of conformer meso-7-I with formaldehyde proceeds preferably through a low energy transition state to more stable product 3 relative to a high energy, high strained path to unstable trans isomer of 2. While considering Curtin-Hammett principle that accounts for product distribution, the fact that the compounds are all produced by precipitation from the reaction mixture, indicates that solubility factors might play a role in orientation of products. The investigation also rules out the involvement of intemediate 6 in the reaction, as condensation with glyoxal failed to give similar products.

When solutions of 7 in water or acetonitrile exposed to the atmosphere, decompose to diimmine 8 as evidenced by the presence of CH signal at δ 8.2 ppm. Addition of small amounts of formic acid to solutions of 2a (~ 10%) accelerated the decomposition to a half-life of 10 minutes or less. O-protonation provides a low energy path for ring opening of 2a and 4a:



CONCLUSIONS

The compounds described here represent a novel class of bicyclooctanes that were synthesized in a one-step/ one-pot reaction in high yields from readily available starting materials. To the best of our knowledge, formation of 2a-4a is the first example of solvent mediated regioselective ring formation of bicyclooctanes by ethanediol-7 generated in situ. The present study related to new class of compounds having negative hyperconjugation in the ring system and are the first such structures described with parallel anomeric interaction in O-C-N and N-C-N units.

EXPERIMENTAL SECTION

General. All commercially available chemical reagents were used without further purification. Melting points were determined with an Electrothermal model 9100 apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 4300 spectrometer. NMR spectra were recorded with a Brucker 80MHZ instrument. Mass analysis of the product was conducted with a Shimadzu-QP 1000 EX and Finnigan matt 8430 GC-MS instruments. Elemental analyses were carried out with a C,H,N,O Rapid-Heraeus apparatus.

Synthesis of 4,8-di(2-aminopyridyl) 2,6-dioxa 4,8-diazabicyclo[3.3.0] octane (2a) and 6,8- di (2-aminopyridyl) 2,4 -dioxa 6,8 -diazabicyclo [3.3.0] octane (3a). To a stirred solution of 2-aminopyridine (1.88 g, 20 mmol) and formic acid (0.05 g of 98% aqueous solution, 1.1 mmol) in acetonitrle (40 ml) at 0-5°C, is slowly added glyoxal (1.45 g of 40% aqueous solution, 10 mmol). To the resulting mixture formaldehyde (1.6 g of 37% aqueous solution, 20 mmol) was added in five minutes. The solution was stirred at 0-5°C for 5 hours until white precipitates were formed. The mixture was filtered and precipitates were washed with cold ethanol to give 2a, 2.11 g (78.5% yield). Recrystallization from ethanol gave white crystals of 2a, mp 161.5-162°C (dec.). ^{1}H NMR (DMSO d_6) δ: 6.6-8.18 (m, 8H, pyridyl CH), 5.44-6.11 (ABq, 4H, J=6.7 Hz, CH_2 ring), 5.05 (S, 2H, CH ring); ^{13}C NMR (DMSO d_6) δ: 155.01, 147.94, 137.36, 113.67, 107.66, 85.64 (CH), 62.13 (CH_2); CH_2 carbon signal is negative in Dept ^{13}C NMR; M/Z (%): 270 (1.0), 107(42.5), 106(87.5), 78(100). Calculated for $C_{14}H_{14}N_4O_2$: C, 62.22; H, 5.19; N, 20.74. Found: C, 62.12; H, 5.21; N, 20.81. The filterate was concentrated to an oily residue and dissolved in acetonitrile (2ml). Cooled the solution to give white crystals of 3a, 0.23 g (8.5% yield). Recrystallization from acetonitrile yielded white pure crystals mp 181-181.5°C. ^{1}H NMR (DMSO d_6) δ: 6.75-8.27 (m, 8H, pyridyl CH), 6.22 (S, 2H, CH), 5.01-5.27 (ABq, 2H, J=6.2 Hz, N-CH_2-N), 4.82-5.15 (ABq, 2H, J=0.9 Hz, O-CH_2-O); ^{13}C NMR ($CDCl_3$) δ: 155.09, 148.08, 138.23, 115.65, 108.24, 93.66 (CH_2-N), 87.93 (CH), 64.55 (CH_2-O); M/Z: 270. Calculated for $C_{14}H_{14}N_4O_2$: C, 62.22; H, 5.19; N, 20.74. Found: C, 62.19; H, 5.19; N, 20.71.

Synthesis of 1,3-di(2-aminopyridyl) 4,5-dihydroxy imidzolidine (4a). To a stirred solution of 2-aminopyridine (1.88 g, 20 mmol) in water (30 ml) at 0-5°C was added dropwise, glyoxal (1.45 g of 40% aqueous solution, 10 mmol) and formaldehyde (0.81 g of 37% aqueous solution, 10 mmol). After ten hours of stirring at 0-5°C the mixture was filtered and white precipitates washed with cold water to give 4a, 2.36 g (91.36% yield). Recrystallization from ethanol gave white pure crystals of 4a, mp 117°C (dec.). IR (KBr) 3311 cm^{-1} (OH); ^{1}H NMR (DMSO d_6) δ: 6.65-8.18 (m, 8H, pyridyl CH), 6.01-6.097 (d, 2H, J=6.63 Hz, OH) 5.39-5.48 (d, 2H, J=6.63 Hz, CH), 5.04 (S, 2H, CH_2); ^{13}C NMR (DMSO d_6) δ: 155.4, 148.46, 138.77, 114.99, 108.74, 85.92 (CH), 62.63 (CH_2); M/Z: 258. Calculated for $C_{13}H_{14}N_4O_2$: C, 60.46; H, 5.43; N, 21.70. Found: C, 60.35; H, 5.42; N, 21.68.

Synthesis of 4,8-di (3-aminopyridyl) 2,6-dioxa 4,8-diazabicyclo[3.3.0]octane (2b). To a stirred solution of 3-aminopyridine (1.88 g, 20 mmol) and formic acid (0.05 g 98% solution, 1.1 mmol) in water (40 ml) at 5-10°C was added dropwise glyoxal (1.45 g of 40% solution, 10 mmol) and formaldehyde (1.624 g of 37% solution, 20 mmol). The solution was stirred at 5-10°C for 5 hours. The precipitates were filtered and washed with cold ethanol, 1.56 g (57% yield). Recrystallization from ethanol gave 1.45 g white crystals of 2b, mp 159.7-160°C. ^{1}H NMR (DMSO d_6) δ: 6.83-8.18 (m, 8H, pyridyl CH), 5.37-6.20 (ABq, 4H, J=7.2 Hz, CH_2), 4.61 (S, 2H, CH); ^{13}C NMR (DMSO d_6) δ: 140, 138.92, 135.23, 123.59, 119.57, 86.13 (CH), 62.64 (CH_2); M/Z: 272 (M+2), 270 (M^+). Calculated for $C_{14}H_{14}N_4O_2$: C, 62.22; H, 5.19; N, 20.74. Found: C, 62.20; H, 5.25; N, 20.82.

Synthesis of 1,3-di(4-aminopyridyl)4,5-dihydroxy imidazolidine (4c). Preparation was performed similar to 4a, 1.98 g (73.13% yield), mp 110°C (dec.). IR (KBr) 3246 cm^{-1} (OH); ^{1}H NMR (DMSO d_6) δ: 6.59,8.19 (dd, 8H, J=5.49 Hz, pyridyl CH), 5.84 (S, 2H, OH), 5.29 (S, 2H, CH), 5.04 (S, 2H, CH_2); ^{13}C NMR (DMSO d_6) δ: 149.4, 107.9, 102, 84.4 (CH), 78.27 (CH_2); M/Z: 258. Calculated for $C_{13}H_{14}N_4O_2$: C, 60.46; H, 5.43; N, 21.70. Found: C, 60.37; H, 5.41; N, 21.71.

Synthesis of N,N' -methylene-bis(3-aminopyridyl) (6b). To a stirred solution of 3-aminopyridine (0.94 g, 10 mmol) in 10 ml water, was added dropwise formaldehyde (0.4 g of 37% aqueous solution, 5 mmol) at 5-10°C. The solution was stirred at 5-10°C for two hours until white precipitates were formed. Precipitate were filtered and washed with cold ethyl ether to give 0.95 g titled compound (95.6% yield). Recrystallization from acetonitrile, gave white pure crystals mp 178.3-178.5°C. IR (KBr), 3240 cm^{-1}; ^1H NMR (DMSO d_6) δ: 7.04-8.08 (m, 8H, pyridyl CH), 6.54-6.68 (t, 2H, J=5.76, NH), 4.48-4.63 (t, 2H, J=5.76, CH_2); ^{13}C NMR (DMSO d_6) δ: 137.47, 135.5, 123.54, 118.31, 51.68 (CH_2); M/Z: 200. Calculated for $C_{11}H_{12}N_4$: C, 44; H, 6; N, 28. Found: C, 43.96; H, 6.01; N, 28.02. When 6b reacted with glyoxal, compounds 2b or 4b were not observed.

Synthesis of 1,2-di(2-aminopyridyl)1,2-dihydroxyethanol (7a). This compound was prepared by the method of Kliegman and Barnes[10]. 0.98 g (79.67% yield) mp 100°C (dec.). IR (KBr) 3590-3500 cm^{-1} (OH), 3244 cm^{-1} (NH); ^1H NMR (DMSO d_6) δ: 6.51-8.1 (m, 8H, pyridyl CH), 6.38 (S, 2H, CH), 5.2-5.9 (m, 4H, NH and OH). On standing at room temperature for one hour, signals at δ 5.2-5.9 and 6.38 disappear and a new signal at δ 8.2 (S, 2H, CH=N-) appear. Precipitates of 7a when reacted with formaldehyde in acetonitrile, give product 2a and in water as solvent white precipitates of 4a are formed.

X-Ray Structure Analysis of 4a: A colorless prismatic crystal with dimension 0.18 × 0.22 × 0.28 mm was used for data collection on a Siemens P4 diffractometer with graphite monochromated MoK_α radiation (λ = 0.71073 Å). $C_{13}H_{14}N_4O_2$, FW=258.3, monoclinic crystals in a C2/c space group, a=12.490(2), b=12.244(2), C=8.439(2) Å, β=111.83(2)°, V=1197.9(4) $Å^3$, Z=4, D_x=1.432 $Mg.m^{-3}$, μ=0.101 mm^{-1}, F(000)=544, T=296 K. Of the 2272 total reflections, 1055 were unique, R_{int}=0.124. The structure was solved by direct methods (Siemens SHELXTL PC) and refined by full-matrix least-squares (isotropic refinement of the molecule and location of remaining non-hydrogen atoms from a difference Fourrier and subsequent anisotropic refinement on all atoms; H atoms were found after high-angle refinement in a difference Fourrier and their positions included in the final stages of refinement), 111 variables, wR=0.0621 for all data, R(F)=0.0359 for 858 observed data with F>6.0 σ (F), goodness-of-fit 1.11, Δ_{rmax}= 0.24, Δ_{rmin}=-0.12 e $Å^{-3}$. Atomic coordinates and temperature factors, bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

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