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LETTERS TO THE EDITOR

To the 80th Anniversary of B.I. Ionin

Pyridoxal-Derived Schiff's Bases

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Over the past few decades synthesis of functionalized derivatives of pyridoxal (vitamin B_6) and study of their biological activity have received a great deal of interest [1–3]. Among these compounds, mono- and bis-azomethines of pyridoxal occupy an important place [4–6]. In practice, pyridoxal hydrochloride is often used since free pyridoxal is unstable and undergoes irreversible fast transformation.

Reaction of pyridoxal hydrochloride with sodium bicarbonate affords free pyridoxal **I** (mp 191°C).

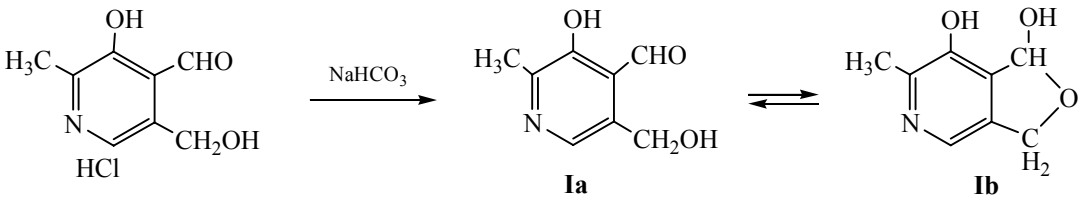
The available data on the structure of pyridoxal are contradictory: either cyclic hemiacetal form **Ib** [7, 8] or the aldehyde **Ia** [9] have been suggested as possible alternatives (Scheme 1).

Since azomethines are usually obtained in alcoholic or aqueous medium, we examined ^{1}H NMR spectra of pyridoxal recorded in D_2O and MeOH-d_4 solutions. Analysis of the spectral data indicated the existence of pyridoxal in hemiacetal form in those solvents, being further supported by the absence of carbonyl group absorption in the IR spectrum.

Pyridoxal is known to react readily with primary aliphatic and aromatic amines to form the corresponding azomethines that may exist in two tautomeric forms as well: the aminoacetal and the aldimine [1].

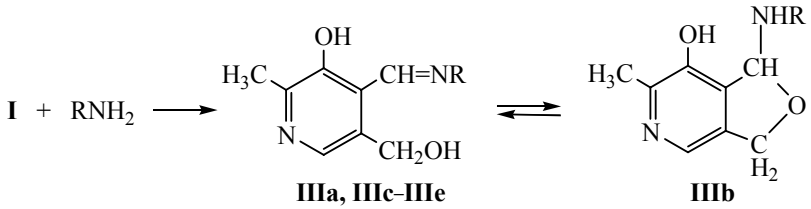
Different substituents at the nitrogen atom can preferentially stabilize one of the tautomeric forms. According to our data, the aniline-derived azomethine **III** existed in the aldimine form. Its IR spectrum contained an absorption band at 1613 cm^{-1} assigned to the C=N bond. The ^{1}H NMR spectrum contained a singlet at 9.35 ppm corresponding to the methine proton. Substitution of the phenyl group with pyridyl stabilized the aminoacetal form **IIIb** as evidenced by the presence of absorption band at 3201 cm^{-1} (N–H) in the IR spectrum and the absence of the methine proton (CH=N) signal in the ^{1}H NMR spectrum.

Scheme 1.



Ia **Ib**

Scheme 2.



R = Ph (**a**), C_5H_4N (**b**), *S*-(–)-CH(Me)Ph (**c**), *R*-(+)-CH(Me)Ph (**d**), *ortho*-$C_6H_4CH_2OH$ (**e**).

Next, we prepared optically active azomethines **IIIc** and **IIId** starting from *R*-(+)- and *S*-(–)-phenylethylamine, respectively; the products can later be used for targeted synthesis of optically active functional derivatives. Azomethine **IIId**, bearing *ortho*-positioned hydroxymethyl group in the aromatic moiety, is of interest for macrocyclic structures preparation. According to ^{1}H NMR spectra, compounds **IIIc** and **IIId** existed in the aldimine form in solution (Scheme 2).

3-Hydroxy-5-(hydroxymethyl)-2-methylisonicotinoaldehyde (I). A solution of 2.42 g of sodium hydrocarbonate in 15 mL water was added upon stirring to a solution of 5.86 g of pyridoxal hydrochlochloride in 10 mL of H_2O. Light-yellow precipitate was formed almost immediately. The reaction was accompanied by gas evolution. The reaction mixture was stirred during 1 h. The precipitate was filtered off; the benzene solution was refluxed with a Dean–Stark trap to remove water and then dried under vacuum (0.02 mmHg) during 1 h. Yield 4.52 g (94%), mp 191°C. ^{1}H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 2.41 s (3H, CH_3), 5.00 d (1H^a, CH_2, $^2J_{HH}$ 13.3), 5.18 d (1H^b, CH_2, $^2J_{HH}$ 13.3), 6.50 s (1H, CH), 7.50 c (1H, CH_{Ar}).

5-(Hydroxymethyl)-2-methyl-4-[(phenylamino)methyl]pyridin-3-ol (IIIa). Aniline (0.93 g) was added dropwise to a suspension of 1.67 g of pyridoxal in 15 mL of ethanol. Orange precipitate was filtered off, washed with anhydrous ethanol and with diethyl ether, and dried. Yield 1.35 g (55.8%), mp 178–179°C. IR spectrum, ν, cm^{-1}: 1613 (C=N). ^{1}H NMR spectrum (acetone-d_6), δ, ppm: 2.47 s (3H, CH_3), 4.51 s (1H, OH), 4.93 s (1H^a, CH_2O), 4.94 s (1H^b, CH_2O), 7.34–7.54 m (5H, Ph), 8.01 s (1H, CH_{Ar}), 9.35 s (1H, CH), 13.76 s (1H, OH). Mass spectrum: *m*/*z* 242 $[M]^+$. Found, %: C 69.94; H 5.63; N 10.95. $C_{14}H_{14}N_2O_2$. Calculated, %: C 69.42; H 5.79; N 11.57.

6-Methyl-1-(pyridin-2-ylamino)-1,3-dihydrofuro-[3,4-*c*]pyridin-7-ol (IIIb). A mixture of 1.94 g of pyridoxal and 1.1 g of α-aminopyridine in 20 mL of ethanol was stirred during 12 h. Then the precipitate was filtered off, washed with ethanol and diethyl ether, and dried. Yield 1.49 g (52.8%), mp 179–180°C. IR spectrum, ν, cm^{-1}: 3201 (N–H). ^{1}H NMR spectrum (DMSO-d_6, 20°C), δ, ppm: 2.36 s (3H, CH_3), 4.92 d (1H^a, CH_2O, $^2J_{HH}$ 11.6), 5.06 d (1H^b, CH_2O, $^2J_{HH}$ 11.6), 6.61 d.t (1H, CH, $^3J_{HH}$ 8.4), 6.63–6.66 m (1H, Py), 6.88 d.d (1H, NH, $^3J_{HH}$ 7.7), 7.44–7.49 m (2H, Py), 7.93 s (1H, CH_{Ar}), 8.05–8.07 m (1H, Py), 10.23 s (1H, OH). Mass spectrum: *m*/*z* 243 $[M]^+$. Found, %: C 63.93; H 5.78; N 17.20. $C_{13}H_{13}N_3O_2$. Calculated, %: C 64.20; H 5.35; N 17.28.

4-[*S*-(–)-(1-Phenylethylimino)methyl]-5-(hydroxymethyl)-2-methyl-4-pyridin-3-ol (IIIc). A mixture of 1.0 g of pyridoxal, 0.72 g of *R*-(+)-1-phenylethylamine, and 10 mL of ethanol was stirred at 20°C during 1 day, and then evaporated. The residue was washed with a mixture of diethyl ether and hexane (1:1), and dried. Yield 1.38 g (85%), mp 101–102°C, $[\alpha]_D^{20}$ –119.7° (*c* 0.5, acetone). IR spectrum, ν, cm^{-1}: 1632 (C=N), 3152 (OH). ^{1}H NMR spectrum (acetone-d_6, 20°C), δ, ppm: 1.66 d (3H, CH_3, $^3J_{HH}$ 6.7), 2.43 s (3H, CH_3), 4.47 s (1H, OH), 4.78 q (1H, CHPh, J_{HH} 6.6), 4.82 s (2H, CH_2O), 7.29–7.48 m (5H, Ph), 7.94 s (1H, CH_{Ar}), 9.17 s (1H, CH=), 14.12 br. s (1H, OH). Mass spectrum: *m*/*z* 270 $[M]^+$. Found, %: C 70.85; H 6.41; N 10.48. $C_{16}H_{18}N_2O_2$. Calculated, %: C 71.11; H 6.67; N 10.37.

4-[*R*-(+)-(1-Phenylethylimino)methyl]-5-(hydroxymethyl)-2-methyl-4-pyridin-3-ol (IIId) was obtained similarly from 1.00 g of pyridoxal, 0.72 g of *S*-(–)-1-phenylethylamine, and 10 mL of ethanol. Yield 1.34 g (82.7%), mp 101–102°C, $[\alpha]_D^{20}$ 117.2° (*c* 0.5, acetone). IR spectrum, ν, cm^{-1}: 1632 (C=N), 3152 (OH). ^{1}H NMR spectrum (acetone-d_6, 20°C), δ, ppm: 1.66 d (3H, CH_3, $^3J_{HH}$ 6.7), 2.43 s (3H, CH_3), 4.48 s (1H, OH), 4.78 q (1H, CHPh, J_{HH} 6.6), 4.82 s (2H, CH_2O), 7.29–7.48 m (5H, Ph), 7.94 s (1H, CH_{Ar}), 9.17 s (1H, CH=), 14.12

br.s (1H, OH). Mass spectrum: *m*/*z* 270 $[M]^+$. Found, %: C 70.85; H 6.41; N 10.48. $C_{16}H_{18}N_2O_2$. Calculated, %: C 71.11; H 6.67; N 10.37.

5-(Hydroxymethyl)-4-{[2-(hydroxymethyl)phenylimino]methyl}-2-methylpyridin-3-ol (IIIe). A mixture of 1.64 g of pyridoxal, 1.21 g of 2-aminobenzyl alcohol, and 15 mL of methanol was heated at 60°C during 1 h. The precipitate was filtered off, washed with diethyl ether, and recrystallized from ethanol–petroleum ether mixture (1 : 1). Yield 2.57 g (96.3%), mp 197–198°C. IR spectrum, ν, cm^{-1}: 1607 (C=N). ^1H NMR spectrum (DMSO-d_6, 20°C), δ, ppm: 2.36 s (3H, CH_3), 4.68 s (1H_a, CH_2O), 4.77 s (1H_b, CH_2O), 5.24 s (1H, CH_2O), 5.41 s (1H, CH_2O), 7.34–7.56 m (4H, Ph), 7.99 s (1H, CH_{Ar}), 9.12 s (1H, CH=N), 13.80 s (1H, OH). Mass spectrum: *m*/*z* 273 $[M + H]^+$. Found, %: C 66.81; H 6.04; N 10.26. $C_{15}H_{16}N_2O_3$. Calculated, %: C 66.18; H 5.88; N 10.29.

IR spectra were recorded with a Vector-22 Bruker instrument (400–3600 cm^{-1}, KBr pellets). ^1H NMR spectra were registered using an Avance 600 spectrometer operating at 600.13 with residual proton signals of the deuterated solvent as reference. Mass spectra (MALDI-TOF) were taken using an Ultraflex III TOF/TOF Bruker instrument (*p*-nitroaniline as matrix).

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