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SHORT COMMUNICATIONS

Synthesis of New *C*-Alkyl-*N*-pyridoxylmethylbenzimidazoles

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Abstract—The reactions of pyridoxal monoimine based on *ortho*-phenylenediamine with aliphatic aldehydes results in the formation of new *C*-alkyl-*N*-pyridoxylmethylbenzimidazoles.

Keywords: pyridoxal, azomethines, diimines, heterocyclization, benzimidazoles

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Benzimidazole derivatives occupy an important place in the search for and creation of new biologically active substances. The benzimidazole fragment is a component of fungicidal drugs [1], as well as drugs used for treatment of arterial hypertension, gastric and duodenal ulcer, erosive gastritis, and some diseases of nervous system [2, 3]. Generally, the above applies to *C*-alkyl-*N*-benzylated derivatives. The synthesis of *N*,C-dialkylated and *C*-aryl-*N*-benzylated derivatives by reacting *ortho*-phenylenediamine with aromatic or aliphatic aldehydes in a 1 : 2 ratio has been reported earlier. As a rule, the reactions are carried out in the presence of a catalyst (lactic acid [4], trifluoroacetic acid [5], copper salt [6], zinc chloride [7], indium oxide [8], ionic liquid [9]), as well as under the action of ultrasound [10].

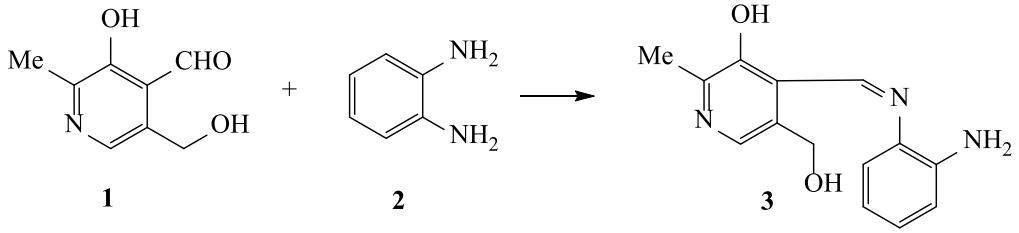
The reactions of pyridoxal with alkylenediamines afforded the corresponding bisazomethines as a sole product regardless of the conditions, ratio and nature of the initial aldehydes [11, 12]. There is only one example describing the use of aromatic diamines in this reaction: pyridoxal hydrochloride reacts with *ortho*-phenylenediamine in a methanol solution in the presence of potassium hydroxide to produce monoimine **3** [13]. We assumed that *C*-alkyl-*N*-pyridoxal-methylated benzimidazoles, analogs of known drugs, can be obtained through the reaction of monoimine **3** with aliphatic aldehydes.

At the first stage, 4-{[(2-aminophenyl)imino]methyl}-5-(hydroxymethyl)-2-methylpyridin-3-ol **3** was obtained by the reaction of neutral pyridoxal with *ortho*-phenylenediamine in 88% yield (Scheme 1).

The presence of a free amino group in compound **3** allows it to react with various aliphatic aldehydes.

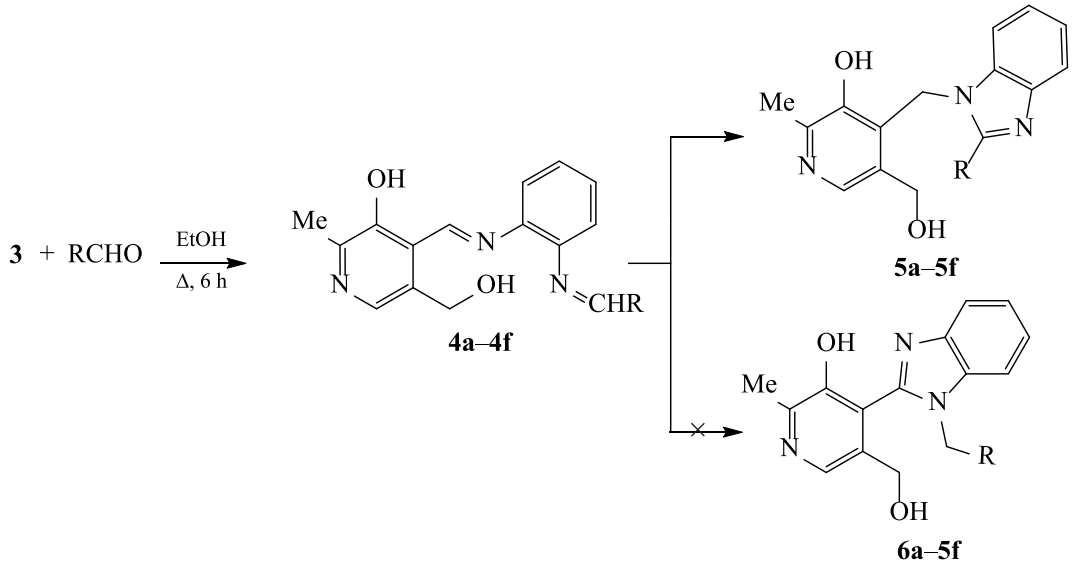
The reactions of *ortho*-phenylenediamine with aliphatic aldehydes have been known to afford symmetric diimines, which undergo cyclization to the corresponding benzimidazoles [14]. We assumed that non-symmetrical bisazomethines **4a**–**4f** formed by reacting imine **3**

Scheme 1.



1 **2** **3**

Scheme 2.

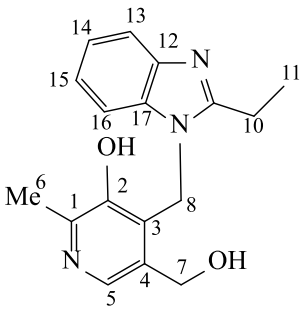


R = C_2H_5 (**a**), *n*-C_3H_7 (**b**), C_5H_{11} (**c**), C_6H_{13} (**d**), C_7H_{15} (**e**), $C_{11}H_{23}$ (**f**).

with aliphatic aldehydes can undergo intramolecular heterocyclization involving one of two nonequivalent nitrogen atoms of the azomethine fragments, which is accompanied by 1,3-migration of protons to the carbon of the pyridoxal or alkyl fragment. As a result, benzimidazoles **5a**–**5f** or **6a**–**6f** can be formed. In their molecules, the methylene group is a linker between the benzimidazole fragment and pyridoxal (**5a**–**5f**) or alkyl (**6a**–**6f**) moiety (Scheme 2). It was found that the reactions of aliphatic aldehydes with monoimine **3** lead to the regioselective formation of benzimidazoles **5a**–**5f**.

Structure of compounds **5a**–**5f** was confirmed by means of two-dimensional NMR spectroscopy techniques. Structure of compound **5a** in a solution was established on the basis of 2D correlation NMR experiments. First, using a ^1H–^1H COSY experiment, individual spin systems (H^{16}–H^{15}–H^{14}–H^{13}, H^{10}–H^{11} and H^7–OH, Scheme 3) were revealed. Then, based on

Scheme 3.



5a

the DEPT and ^1H–^{13}C HSQC spectroscopy data, the methylene protons and the corresponding carbon atoms were detected. The correlations observed in the ^1H–^{13}C HMBC spectra made it possible to identify the signals of the pyridoxal fragment (for example, correlations H^7/C^5, H^6/C^2, H^5/C^3, H^5/C^1), and then to confirm its link with the benzimidazole fragment through the CH_2 group (H^8/C^2, H^8/C^4 and H^8/C^{17}, H^8/C^9).

To clarify the heterocyclization conditions, the reaction mixture of monoimine **3** with propionaldehyde was kept in ethanol at 20°C for 7 days when monitored by MALDI mass spectrometry and ^1H NMR spectroscopy. According to the data obtained, benzimidazole **5a** is also formed as a result of the reaction.

In conclusion, effective method for the synthesis of *C*-alkyl-*N*-pyridoxylmethylbenzimidazoles, analogs of known biologically active compounds, was proposed.

4-{[(2-Aminophenyl)imino]methyl}-5-(hydroxymethyl)-2-methylpyridin-3-ol (3). To a suspension of 0.95 g (6 mmol) of pyridoxal in 20 mL of ethanol was added with stirring 0.61 g (6 mmol) of *o*-phenylenediamine. The reaction mixture was stirred for 10 h at room temperature. The precipitate formed was filtered off and dried. Yield 1.28 g (88%), mp 197–200°C (mp 182–184°C [13]). IR spectrum, ν, cm^{-1}: 1620 (C=N), 3332 (NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.45 s (3H, CH_3), 4.77 s (2H, CH_2O), 5.42 s (2H, NH_2), 6.67–7.21 m (4H, Ph), 7.99 s (1H, CH_{Py}), 9.09 s (1H, CH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 19.22, 58.97, 116.28, 117.35,

119.35, 120.98, 129.31, 133.82, 133.96, 138.65, 143.47, 148.48, 153.33, 159.03. Mass spectrum (MALDI-TOF), *m/z*: 258 $[M + H]^+$. Found, %: C 65.00; H 6.21; N 16.31. $C_{14}H_{15}N_3O_2$. Calculated, %: C 65.34; H 5.89; N 16.33.

General procedure for the preparation of benzimidazoles 5a–5f. A mixture of 1.2 mmol of monoimine **3** and 1.2 mmol of the corresponding aliphatic aldehyde in 10 mL of ethanol was refluxed for 6 h. After cooling, the solvent was partially removed in vacuum, and then 10 mL of diethyl ether was added to the residue. The precipitate was separated, washed with diethyl ether and dried under vacuum.

4-{(2-Ethyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-5-(hydroxymethyl)-2-methylpyridine-3-ol (5a). Yield 0.31 g (88%), mp 246–247°C. IR spectrum (KBr), ν, cm^{-1}: 1615 (C=N), 3186 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 1.30 t (3H, CH_3 *J* = 7.5), 2.37 s (3H, CH_3), 2.92 q (2H, CH_2, *J* = 7.5), 4.38 s (2H, CH_2), 5.27 s (1H, OH), 5.46 s (2H, CH_2O), 7.02 d. t (1H, Ph, *J* = 7.5, 1.3), 7.08 d. t (1H, Ph, *J* = 7.5, 1.3), 7.19 d (1H, Ph, *J* = 7.8), 7.53 d (1H, Ph, *J* = 7.8), 8.00 s (1H, CH_{Py}), 9.02 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 11.89, 20.38, 20.76, 39.50, 59.22, 110,69, 118.77, 121.30, 121.71, 128.89, 134.60, 135.77, 140.15, 142.70, 146.64, 149.99, 157.23. Mass spectrum (MALDI-TOF), *m/z*: 298 $[M + H]^+$. Found, %: C 68.45; H 6.66; N 14.81. $C_{17}H_{19}N_3O_2$. Calculated, %: C 68.65; H 6.45; N 14.13.

5-(Hydroxymethyl)-2-methyl-4-{(2-propyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}pyridine-3-ol (5b). Yield 0.29 g (81%), mp 209–211°C. IR spectrum (KBr), ν, cm^{-1}: 1615 (C=N), 3167 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.95 t (3H, CH_3, *J* = 7.4), 1.74 q (2H, CH_2, *J* = 7.4), 2.37 s (3H, CH_3), 2.87 t (2H, CH_2, *J* = 7.7), 4.36 s (2H, CH_2), 5.26 s (1H, OH), 5.46 s (2H, CH_2O), 6.99–7.04 m (1H, Ph), 7.05–7.09 m (1H, Ph), 7.20 d (1H, Ph, *J* = 8.0), 7.51 d (1H, Ph, *J* = 7.9), 7.99 s (1H, CH_{Py}), 9.05 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.31, 20.38, 20.84, 29.28, 39.54, 59.22, 110.76, 118.75, 121.36, 121.70, 128.94, 134.66, 135.65, 140.01, 142.73, 146.65, 150.03, 156.22. Mass spectrum (MALDI-TOF), *m/z*: 312 $[M + H]^+$. Found, %: C 69.45; H 6.66; N 13.81. $C_{18}H_{21}N_3O_2$. Calculated, %: C 69.42; H 6.81; N 13.50.

5-(Hydroxymethyl)-2-methyl-4-{(2-pentyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}pyridine-3-ol (5c). Yield 0.27 g (68%), mp 196–199°C. IR spectrum (KBr), ν, cm^{-1}: 1615 (C=N), 3194 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.87 q (3H, CH_3, *J* = 6.7), 1.20–1.40 m (4H, CH_2), 1.62–1.77 m (2H, CH_2), 2.37 d (3H, CH_3, *J* = 4.3), 2.86 t (2H, CH_2, *J* = 7.7), 4.34 s (2H, CH_2), 5.25 s (1H, OH), 5.47 d (2H, CH_2O, *J* = 7.3), 7.03 t (1H, Ph, *J* = 7.5), 7.07 t (1H, Ph, *J* = 7.4), 7.23 d (1H, Ph, *J* = 8.1), 7.51 d (1H, Ph, *J* = 7.9), 7.99 s (1H, CH_{Py}), 9.03 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.35, 20.40, 22.37, 27.17, 27.32, 31.53, 39.49, 59.23, 110.76, 118.77, 121.37, 121.71, 128.93, 134.68, 135.74, 140.10, 142.75, 146.64, 149.93, 156.38. Mass spectrum (MALDI-TOF), *m/z*: 340 $[M + H]^+$. Found, %: C 70.45; H 7.66; N 11.81. $C_{20}H_{25}N_3O_2$. Calculated, %: C 70.76; H 7.44; N 12.08.

4-{(2-Hexyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-5-(hydroxymethyl)-2-methylpyridine-3-ol (5d). Yield 0.29 g (71%), mp 193–195°C. IR spectrum (KBr), ν, cm^{-1}: 1612 (C=N), 3170 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.86 t (3H, CH_3, *J* = 6.8), 1.21–1.30 m (4H, CH_2), 1.32 q (2H, CH_2, *J* = 7.2), 1.61–1.72 m (2H, CH_2), 2.37 d (3H, CH_3, *J* = 4.3), 2.86 t (2H, CH_2, *J* = 7.7), 4.34 s (2H, CH_2), 5.23 s (1H, OH), 5.46 s (2H, CH_2O), 7.03 t (1H, Ph, *J* = 7.6), 7.07 t (1H, Ph, *J* = 7.5), 7.23 d (1H, Ph, *J* = 8.0), 7.51 d (1H, Ph, *J* = 7.8), 7.98 s (1H, CH_{Py}), 9.00 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.42, 20.41, 22.52, 27.37, 27.46, 29.01, 31.51, 39.49, 59.24, 110.76, 118.77, 121.37, 121.71, 128.93, 134.69, 135.76, 140.08, 142.76, 146.64, 149.96, 156.38. Mass spectrum (MALDI-TOF), *m/z*: 354 $[M + H]^+$. Found, %: C 71.45; H 7.66; N 11.81. $C_{21}H_{27}N_3O_2$. Calculated, %: C 71.34; H 7.71; N 11.89.

4-{(2-Heptyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}-5-(hydroxymethyl)-2-methylpyridine-3-ol (5e). Yield 0.40 g (93%), mp 155–158°C. IR spectrum (KBr), ν, cm^{-1}: 1614 (C=N), 3054 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.86 t (3H, CH_3, *J* = 6.8), 1.21–1.30 m (6H, CH_2), 1.32 q (2H, CH_2, *J* = 7.2), 1.61–1.72 m (2H, CH_2), 2.37 d (3H, CH_3, *J* = 4.3), 2.86 t (2H, CH_2, *J* = 7.7), 4.34 s (2H, CH_2), 5.23 s (1H, OH), 5.46 s (2H, CH_2O), 7.03 t (1H, Ph, *J* = 7.6), 7.07 t (1H, Ph, *J* = 7.5), 7.23 d (1H, Ph, *J* = 8.0), 7.51 d (1H, Ph, *J* = 7.8), 7.98 s (1H, CH_{Py}), 9.00 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.42, 20.40, 22.56, 27.36, 27.49, 28.93, 29.30, 31.70, 39.49, 59.23, 110,77, 118.76, 121.37, 121.71, 128.93, 134.68, 135.75, 140.03, 142.74, 146.64, 149.97, 156.37. Mass spectrum (MALDI-TOF), *m/z*: 368 $[M + H]^+$. Found, %: C 71.45; H 7.66; N 11.81. $C_{22}H_{29}N_3O_2$. Calculated, %: C 71.89; H 7.97; N 11.44.

5-(Hydroxymethyl)-2-methyl-4-{(2-undecyl-1*H*-benzo[*d*]imidazol-1-yl)methyl}pyridine-3-ol (5f).

Yield 0.26 g (53%), mp 146–148°C. IR spectrum (KBr), ν, cm^{-1}: 1615 (C=N), 3214 (OH). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 0.79–0.94 m (3H, CH_3), 1.25 s (16H, CH_2), 1.67 t (2H, CH_2, *J* = 7.3), 2.37 d (3H, CH_3, *J* = 4.3), 2.86 t (2H, CH_2, *J* = 7.7), 4.34 d (2H, CH_2, *J* = 4.0), 5.25 d (1H, OH, *J* = 5.4), 5.46 s (2H, CH_2O), 6.99–7.12 m (2H, Ph), 7.29–7.15 m (1H, Ph), 7.51 d. d (1H, Ph, *J* = 7.6, 1.4), 7.99 s (1H, CH_{Py}), 9.02 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.42, 20.41, 22.58, 27.36, 27.48, 29.20, 29.28, 29.33, 29.46, 29.50, 29.52, 31.79, 39.48, 59.23, 110,75, 118.76, 121.36, 121.70, 128.92, 134.67, 135.75, 140.12, 142.76, 146.65, 149.90, 156.37. Mass spectrum (MALDI-TOF), *m/z*: 424 $[M + H]^+$. Found, %: C 73.45; H 8.66; N 9.81. $C_{26}H_{37}N_3O_2$. Calculated, %: C 73.71; H 8.82; N 9.92.

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 instrument [399.9 (^1H), 100.6 MHz (^{13}C)]. IR spectra (mineral oil) were registered a Bruker Vector-22 spectrometer. Elemental analysis was performed on a Euro-3000 (C, H) instrument.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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