ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 5, pp. 779–781. © Pleiades Publishing, Ltd., 2013.
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SHORT COMMUNICATIONS

Condensation of Amino Derivatives of Benzimidazol-2-ones and Imidazo[4,5-*b*]pyridin-2-ones with 2,6-Dimethyl-γ-pyrone in Acetic Acid

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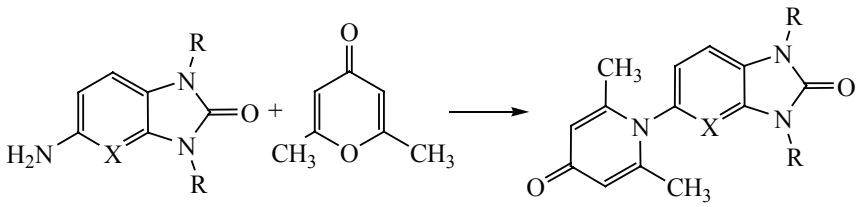
Received April 4, 2012

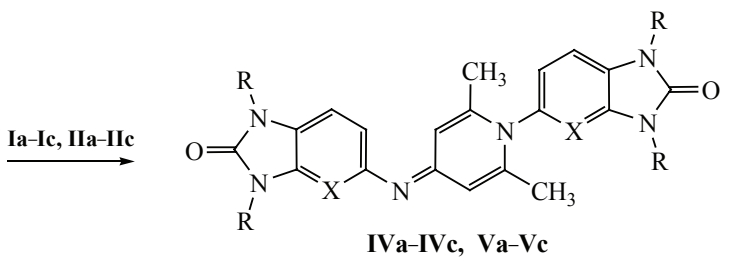
DOI: 10.1134/S107042801305031X

Derivatives of benzimidazole and of imidazo[4,5-*b*]-pyridine attract attention as potential biologically active compound of antiviral, antitumor, antimicrobial, antisecretory, cytostatic, antihistamine, and antiulcer action [1]. This class compounds can also serve as initial substances for the synthesis of new drugs [2].

The goal of this study was the synthesis of new derivatives of benzimidazole and its azaanalog, imidazo-[4,5-*b*]pyridine, for the subsequent investigation of their biological properties. We formerly obtained by melting 5-amino-1,3-dialkyl-1,3-dihydro-2*H*-benzimidazol-2-ones with 2,6-dimethyl-γ-pyrone at the molar ratio 1 : 1 1-substituted 2,6-dimethylpyridine-4-ones [3]. It was interesting to examine the direction of the reaction of amino derivatives of benzimidazole and imidazo[4,5-*b*] pyridine with 2,6-dimethyl-γ-pyrone at the molar ratio 2 : 1 in a polar solvent.

We selected as initial amines 5-amino-1,3-dialkyl-1,3-dihydro-2*H*-benzimidazol-2-ones **Ia–Ic** [3] and 5-amino-1,3-dialkyl-1,3-dihydro-2*H*-imidazo[4,5-*b*] pyridin-2-ones **IIa–IIc** [4]. The condensation of compounds **Ia–Ic**, **IIa–IIc** with 2,6-dimethyl-γ-pyrone (**III**) in the glacial acetic acid afforded the corresponding benzimidazolyliminopyridinylbenzimidazolones **IVa–IVc** and their 4-azaanalogs **Va–Vc** in 50–68% yields. The reaction apparently occurs via the recyclization of





I, IV, VI, X = CH, R = Me (**a**), Et (**b**), Bn (**c**); **II, V, VII**, X = N, R = Me (**a**), Et (**b**), Bn (**c**).

the ring of γ-pyrone **III** under the action of the heterocyclic amine **I** or **II** into the corresponding γ-pyridone **VIa–VIc**, **VIIa–VIIc** that undergoes the condensation with the second amine molecule.

The composition and structure of compounds **IVa–IVc**, **Va–Vc** are confirmed by the data of elemental analyses and ^{1}H NMR spectra. The ^{1}H NMR spectra of compounds **IVa–IVc** in DMSO-d_6 contain the doubled signals of the N^1- and N^3-alkyl groups of the imidazole fragment, doubled singlets of the proton H^4 (7.43– 7.51 ppm), and doublet signals of the vicinal protons H^6, H$^{6'}$, H^7, H$^{7'}$ (7.08–7.16 and 7.03–7.07 ppm) of the benzene ring, and also singlets of the protons H^{10}, H^{12} (9.86–9.90 ppm) and methyl groups at the atoms C^{9,13} of the pyridone ring (1.98–2.02 ppm). In the ^{1}H NMR spectra of compounds **Va–Vc** in DMSO-d_6 also doubled signals are present of N^1- and N^3-alkyl groups of the imidazole fragment, doubled doublets of the vicinal protons H^6, H$^{6'}$, H^7, H$^{7'}$ (7.79–7.86 and 7.48–7.54 ppm) of the pyridine ring, and also singlets of protons H^{10}, H^{12} (10.31–10.42 ppm) and of methyl groups in the positions *9* and *13* of the pyridone ring (2.06–2.12 ppm).

The downfield position of the signals of protons H^{10} and H^{12} (9.88–10.42 ppm) in the spectra of compounds **IVa–IVc**, **Va–Vc** is apparently caused by the formation of hydrogen bonds between DMSO-d_6 and quinoid protons CH. In $CDCl_3$ these signals shift to the region 7.86–7.81 ppm (for compounds **Vb, Vc** Δδ is 2.43– 2.50 ppm). This assumption is confirmed also by the similar shift of the signals of related protons in the spectrum of the intermediate **VIa** (Δδ 2.93 ppm).

The computer estimation of the virtual biological activity of the synthesized compounds **IVa–IVc**, **Va–Vc** applying the PASS 4.2 program (Prediction of Activity Spectra of Substance) indicated that these compounds may possess the antiphlogistic and hypertensive activity, and also may be inhibitors of muramyl-tetrahydropeptide carboxypeptidase [5].

^{1}H NMR spectra were registered on a spectrometer Bruker Avance II 400 at operating frequency 400 MHz in DMSO-d_6 and $CDCl_3$, internal reference TMS. The individuality of compounds obtained was checked by TLC on Silufol UV-254 plates (eluents ethanol, chloroform, development in iodine vapor or under UV irradiation).

Compounds IVa–IVc, **Va–Vc.** A mixture of 1 mmol of compound **Ia–Ic**, **IIa–IIc** and 0.5 mmol of 2,6-dimethyl-γ-pyrone in 6 ml of glacial acetic acid was heated at 120–125°C for 6 h. The solution was evaporated in a vacuum at heating on a water bath. The dry residue was triturated in water. The precipitate was filtered off and recrystallized from an appropriate solvent.

5-{2,6-Dimethyl-4-[(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)imino]pyridin-1-(4*H*)-yl}-1,3-dimethyl-1,3-dihydro-2*H*-benzimidazol-2-one (IVa). Yield 50%, mp 197–200°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.02 s (6H, C^{9}CH$_3$, C^{13}CH$_3$), 3.27 s (12H, N^{1}CH$_3$, N^{3}CH$_3$, N$^{1'}$CH$_3$, N$^{3'}$CH$_3$), 7.03 d (2H, H^7, H$^{7'}$, *J* 8.0 Hz), 7.11 d (2H, H^6, H$^{6'}$, *J* 8.0 Hz), 7.51 s (2H, H^4, H$^{4'}$), 9.88 s (2H, H^{10}, H^{12}). Found,%: C 67.67; H 5.90; N 18.85. $C_{25}H_{26}N_6O_2$. Calculated,%: C 67.86; H 5.92; N 18.96.

5-{2,6-Dimethyl-4-[(1,3-diethyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)imino]pyridin-1(4*H*)-yl}-1,3-diethyl-1,3-dihydro-2*H*-benzimidazol-2-one (IVb). Yield 55%, mp 84–86°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.14 t (12H, N^{1}CH$_2$<u>CH$_3$</u>, N^{3}CH$_2$<u>CH$_3$</u>, N$^{1'}$CH$_2$<u>CH$_3$</u>, N$^{3'}$CH$_2$<u>CH$_3$</u>, *J* 4.0 Hz), 1.98 s (6H, C^{9}CH$_3$, C^{13}CH$_3$), 3.76 q (8H, N^1<u>CH$_2$</u>CH$_3$, N^3<u>CH$_2$</u>CH$_3$, N$^{1'}$<u>CH$_2$</u>CH$_3$, N$^{3'}$<u>CH$_2$</u>CH$_3$, *J* 7.2 Hz), 7.04 d (2H, H^7, H$^{7'}$, *J* 12.0 Hz), 7.08 d (2H, H^6, H$^{6'}$, *J* 12.0 Hz), 7.51 s (2H, H^4, H$^{4'}$), 9.90 s (2H, H^{10}, H^{12}). Found, %: C 69.50; H 6.85; N 16.78. $C_{29}H_{34}N_6O_2$. Calculated, %: C 69.86; H 6.87; N 16.85.

5-{2,6-Dimethyl-4-[(1,3-dibenzyl-2-oxo-2,3-dihydro-1*H*-benzimidazol-5-yl)imino]pyridin-1-(4*H*)-yl}-1,3-dibenzyl-1,3-dihydro-2*H*-benzimidazol-2-one (IVc). Yield 64%, mp 155–157°C (2-propanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.01 s (6H, C^{9}CH$_3$, C^{13}CH$_3$), 5.09 s (8H, N^1<u>CH$_2$</u>C$_6$H$_5$, N^3<u>CH$_2$</u>C$_6$H$_5$, N$^{1'}$<u>CH$_2$</u>C$_6$H$_5$, N$^{3'}$<u>CH$_2$</u>C$_6$H$_5$), 7.07 d (2H, H^7, H$^{7'}$, *J* 8.0 Hz), 7.16 d (2H, H^6, H$^{6'}$, *J* 8.0 Hz), 7.31–7.37 m (20H, N^{1}CH$_2$C$_6$<u>H$_5$</u>, N^{3}CH$_2$C$_6$<u>H$_5$</u>, N$^{1'}$CH$_2$C$_6$<u>H$_5$</u>, N$^{3'}$CH$_2$C$_6$<u>H$_5$</u>), 7.43 s (2H, H^4, H$^{4'}$), 9.86 s (2H, H^{10}, H^{12}). Found, %: C 77.87; H 5.64; N 11.12. $C_{49}H_{42}N_6O_2$. Calculated, %: C 78.80; H 5.67; N 11.25.

5-{2,6-Dimethyl-4-[(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)imino]-pyridin-1(4*H*)-yl}-1,3-dimethyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (Va). Yield 53%, mp >250°C (water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.12 s (6H, C^{9}CH$_3$, C^{13}CH$_3$), 3.35 s (6H, N^{1}CH$_3$, N$^{1'}$CH$_3$), 3.36 s (6H, N^{3}CH$_3$, N$^{3'}$CH$_3$), 7.51 d (2H, H^7, H$^{7'}$, *J* 8.0 Hz), 7.86 d (2H, H^6, H$^{6'}$, *J* 8.0 Hz), 10.42 s (2H, H^{10}, H^{12}). Found, %: C 61.97; H 5.41; N 25.19. $C_{23}H_{24}N_8O_2$. Calculated, %: C 62.15; H 5.44; N 25.21.

5-{2,6-Dimethyl-4-[(1,3-diethyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)imino]pyridin-1(4*H*)-yl}-1,3-diethyl-1,3-dihydro-2*H*-imidazo-[4,5-*b*]pyridin-2-one (Vb). Yield 58%, mp 158–160°C (water). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.23 t (12H, $N^1CH_2\underline{CH}_3$, $N^3CH_2\underline{CH}_3$, $N^{1'}CH_2\underline{CH}_3$, $N^{3'}CH_2\underline{CH}_3$, J 8.0 Hz), 2.07 s (6H, C^9CH_3, $C^{13}CH_3$), 3.86 q (8H, $N^1\underline{CH}_2CH_3$, $N^3\underline{CH}_2CH_3$, $N^{1'}\underline{CH}_2CH_3$, $N^{3'}\underline{CH}_2CH_3$, J 6.7 Hz), 7.54 d (2H, H^7, $H^{7'}$, J 8.0 Hz), 7.81 d (2H, H^6, $H^{6'}$, J 8.0 Hz), 10.32 s (2H, H^{10}, H^{12}); ($CDCl_3$): 1.38 t (12H, $N^1CH_2\underline{CH}_3$, $N^3CH_2\underline{CH}_3$, $N^{1'}CH_2\underline{CH}_3$, $N^{3'}CH_2\underline{CH}_3$, J 4.0 Hz), 2.27 s (6H, C^9CH_3, $C^{13}CH_3$), 3.98 q (8H, $N^1\underline{CH}_2CH_3$, $N^3\underline{CH}_2CH_3$, $N^{1'}\underline{CH}_2CH_3$, $N^{3'}\underline{CH}_2CH_3$, J7.2 Hz), 7.23 d (2H, H^7, $H^{7'}$, J 8.0 Hz), 7.89 s (2H, H^{10}, H^{12}), 7.98 d (2H, H^6, $H^{6'}$, J8.0 Hz). Found, %: C 64.58; H 6.42; N 22.23. $C_{27}H_{32}N_8O_2$. Calculated, %: C 64.78; H 6.44; N 22.38.

5-{2,6-Dimethyl-4-[(1,3-dibenzyl-2-oxo-2,3-dihydro-1*H*-imidazo[4,5-*b*]pyridin-5-yl)imino]-pyridin-1(4*H*)-yl}-1,3-dibenzyl-1,3-dihydro-2*H*-imidazo[4,5-*b*]pyridin-2-one (Vc). Yield 68%, mp 210–212°C (ethanol). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.06 s (6H, C^9CH_3, $C^{13}CH_3$), 5.08 s (8H, $N^1\underline{CH}_2C_6H_5$, $N^3\underline{CH}_2C_6H_5$, $N^{1'}\underline{CH}_2C_6H_5$, $N^{3'}\underline{CH}_2C_6H_5$), 7.27–7.33 m (20H, $N^1CH_2C_6\underline{H}_5$, $N^3CH_2C_6\underline{H}_5$, $N^{1'}CH_2C_6\underline{H}_5$, $N^{3'}CH_2C_6\underline{H}_5$), 7.48 d (2H, H^7, $H^{7'}$, J 8.0 Hz), 7.79 d (2H, H^6, $H^{6'}$, J 8.0 Hz), 10.31 s (2H, H^{10}, H^{12}); ($CDCl_3$): 2.21 s (6H, C^9CH_3, $C^{13}CH_3$), 5.09 s (4H, $N^1\underline{CH}_2C_6H_5$, $N^{1'}\underline{CH}_2C_6H_5$), 5.14 s (4H, $N^3\underline{CH}_2C_6H_5$, $N^{3'}\underline{CH}_2C_6H_5$), 7.04 d (2H, H^7, $H^{7'}$, J 8.0 Hz), 7.32–7.35 m (30H, $N^1CH_2C_6\underline{H}_5$, $N^3CH_2C_6\underline{H}_5$, $N^{1'}CH_2C_6\underline{H}_5$, $N^{3'}CH_2C_6\underline{H}_5$), 7.81 s (2H, H^{10}, H^{12}), 7.86 d (2H, H^6, $H^{6'}$, J 8.0 Hz). Found, %: C 75.12; H 5.31; N 14.85. $C_{47}H_{40}N_8O_2$. Calculated, %: C 75.38; H 5.38; N 14.96.

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