ISSN 1070-4280, Russian Journal of Organic Chemistry, 2011, Vol. 47, No. 8, pp. 1190–1193. © Pleiades Publishing, Ltd., 2011.
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Synthesis of 1,3-Dialkyl-5-(hetaryl-1-yl)-1,3-dihydrobenzimidazol-2-ones

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Received December 28, 2010

Abstract—Reactions of 5-amino-1,3-dialkyl-1,3-dihydrobenzimidazol-2-ones with 2,5-dimethoxytetrahydrofuran and 2,6-dimethyl-γ-pyranone led to the formation of 1,3-dialkyl-1,3-dihydro-5-(pyrrol-1-andл)benzimidazol-2-ones and 1-(1,3-dialkyl-2-oxo-1,3-dihydrobenzimidazol-5-yl)-2,6-dimethylpyridin-4-ones.

DOI: 10.1134/S1070428011080112

Versatile and pronounced biological action in the series of benzimidazole derivatives promotes the search for the methods of synthesis of new compounds of this class aiming at the investigation of their pharmacological properties and designing drugs on their basis. The structure of drugs like mebendazole, omeprazole, misolastin, pantoprazole, telmisartan, domperidone consists of a benzimidazole fragment linked through C or N atoms with alkyl (aralkyl) and hetaryl moieties [1]. Pyrrole and pyridine fragments also constitute fragments of a number of pharmaceuticals: antibiotics, enzymes, etc. [2]. The combination of these factors determined the target of this study as the synthesis of new benzimidazol-2-one derivatives containing at the C^5 atom of the benzene ring pyrrole or pyridine fragments for the subsequent investigation of their biological properties.

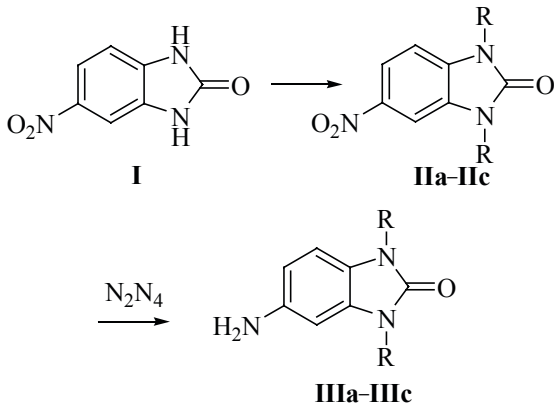
The known Clauson-Kaas reaction of alkyl(aryl) amines with 2,5-dimethoxytetrahydrofuran results in the formation of 1-alkyl(aryl)pyrroles [3]. It seemed reasonable to bring into the reaction with 2,5-dimethoxytetrahydrofuran 1,3-dialkyl-substituted 5-amino-1,3-dihydrobenzimidazol-2-ones.

As the initial compound for the synthesis of N^1,N^3-dialkyl derivatives of 5-amino-1,3-dihydrobenzimidazol-2-one we applied the benzimidazol-2-one [4].

The nitration of benzimidazol-2-one with a mixture of concn. nitric and sulfuric acids gave 5-nitro-1,3-dihydrobenzimidazol-2-one (**I**) [5]. By the alkylation of nitro compound **I** with dimethyl sulfate, diethyl sulfate, and benzyldimethylphenylammonium chloride N^1,N^3-dialkyl substituted 5-nitro-1,3-dihydrobenzimidazol-2-ones **IIa–IIc** were obtained in 57–65% yields (Scheme 1). The composition and structure of nitro compounds **IIa–IIc** are confirmed by elemental analysis and ^{1}H NMR spectra. In the ^{1}H NMR spectra of nitro compounds **IIa–IIc** alongside the singlet of H^4 proton (7.77–8.09 ppm), doublets of protons H^6 (7.97–8.08 ppm) and H^7 (6.90–7.39 ppm) the signals appear of the methyl, ethyl, and benzyl groups at the atoms N^1, N^3 of the benzimidazole ring.

1,3-Dialkyl-substituted 5-amino-1,3-dihydrobenzimidazol-2-ones **IIIa–IIIc** were obtained by the reduc-

Scheme1.



R = Me (**a**), Et (**b**), Bn (**c**).

tion of nitro compounds **IIa–IIc** with hydrazine hydrate in 43–67% yields. In the ^{1}H NMR spectra of the amines alongside the singlet of H^4 proton (6.29–6.52 ppm), doublets of the vicinal protons H^6 (6.60–6.89), H^7 (6.35–6.50 ppm) and the signals of the alkyl groups the protons of the amino group give rise to signals at 5.10–5.21 ppm.

In the reaction of amines **IIIa–IIIc** with 2,5-dimethoxytetrahydrofuran under the conditions of Clauson-Kaas reaction [3] 1,3-dialkyl-1,3-dihydro-5-(pyrrol-1-yl)benzimidazol-2-ones **IVa–IVc** were obtained in 48–66 % yields (Scheme 2). In the ^{1}H NMR spectra of compounds **IVa–IVc** alongside the signals of the alkyl groups of the imidazole fragment, the singlet of H^4 proton (6.99–7.82 ppm), the doublets of the vicinal protons H^6 (7.13–8.02) and H^7 (6.95–7.05 ppm) of the benzene ring the triplet signals appear of the protons $H^{3'}$, $H^{4'}$ and $H^{2'}$, $H^{5'}$ of the pyrrole ring in the region 6.27–6.40 and 7.04–7.35 ppm.

It is known that the reaction of alkyl(aryl)amines with 2,6-dimethyl-γ-pyranone affords 1-alkyl-(aryl)-substituted 2,6-dimethylpyridin-4-ones [6]. The reaction under similar conditions between 5-amino-1,3-dialkyl-1,3-dihydrobenzimidazol-2-ones **IIIa–IIIc** with 2,6-dimethyl-γ-pyranone led to the formation of condensation products **Va–Vc** in 72–78% yields (Scheme 2). The ^{1}H NMR spectra of compounds obtained contain the signals of protons of alkyl groups at the atoms N^1 and N^3 of the imidazole fragment, the singlet of H^4 proton (6.31–6.44 ppm), the doublets of the vicinal protons H^6 (6.68–6.81), H^7 (6.37–6.49 ppm) of the benzene ring, and also singlets of protons H^3, $H^{5'}$ (6.09–7.37) and the methyl groups at $C^{2'}$ and $C^{6'}$ (2.26–2.28 ppm) of the pyridine ring.

The computer estimation of the biological activity of the synthesized compounds **IVa–IVc, Va–Vc** applying PASS 4.2 (Prediction of Activity Spectra of Substance) program indicates that these compound may possess antihypertensive activity as antagonists of angiotensin of II subtype, and also may be antagonists of β-1-adrenoreceptors.

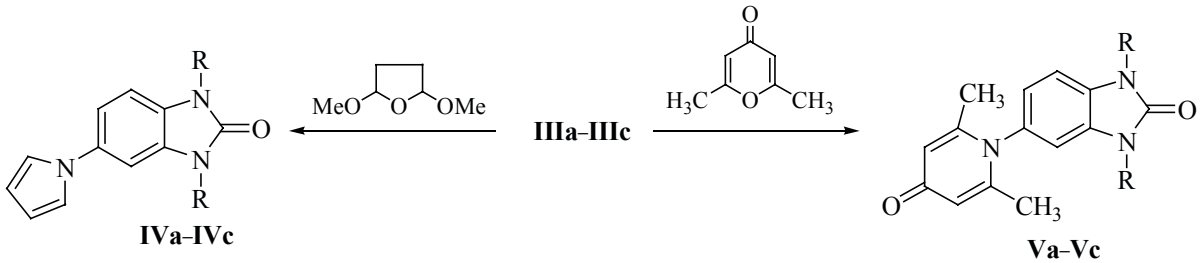
EXPERIMENTAL

^{1}H NMR spectra were registered on a spectrometer Bruker Avance II 400 at operating frequency 400 MHz, internal reference HMDS. The purity and homogeneity of compounds synthesized was checked by TLC on Silufol UV-254 plates, eluents ethanol, chloroform, spots detection in iodine vapor or under UV irradiation.

1,3-Dimethyl-5-nitro-1,3-dihydrobenzimidazol-2-one (IIa). To a solution of 3.3 g (82.5 mmol) of NaOH in 70 ml of water at vigorous stirring was added 6.7 g (37.4 mmol) of compound **I**. Then at room temperature was slowly added 7.8 ml (81.7 mmol) of dimethyl sulfate. After 2 h the separated light-yellow precipitate was filtered off, washed with cold water, and recrystallized from 20% acetic acid. Yield 5 g (65%), mp 202–204°C (204–205°C [7]). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.40 s (6H, N^1CH_3, N^3CH_3), 7.39 d (1H, H^7, J 9.3 Hz), 8.08 d (1H, H^6, J 9.3 Hz), 8.09 s (1H, H^4). Found, %: C 51.95; H 4.32; N 20.12. $C_9H_9N_3O_3$. Calculated, %: C 52.17; H 4.38; N 20.28.

5-Nitro-1,3-diethyl-1,3-dihydrobenzimidazol-2-one (IIb). To a solution of 10 g (55.8 mmol) of 5-nitro-1,3-dihydrobenzimidazol-2-one (**I**) in 100 ml of DMF was added 16.6 g (167.5 mmol) of potassium carbonate. After 0.5 h at room temperature while vigorous stirring was added by portions within 1 h 20 ml (125.5 mmol) of diethyl sulfate, then the mixture was heated for 14 h at 90–95°C and evaporated in a vacuum on a water bath. The reaction product was extracted from the dry residue with benzene, the solvent was distilled off. Yield 7.3 g (56%), mp 125–127°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.43 t (6H, $N^1CH_2\underline{CH_3}$, $N^3CH_2\underline{CH_3}$), 4.04 q (4H, $N^1\underline{CH_2}CH_3$, $N^3\underline{CH_2}CH_3$), 7.09 d (1H, H^7, J 8.6 Hz), 7.95 s (1H, H^4), 8.14 d (1H, H^6, J 8.6 Hz). Found, %: C 55.98;

Scheme 2.



R = Me (**a**), Et (**b**), Bn (**c**).

H 5.51; N 17.69. $C_{11}H_{13}N_3O_3$. Calculated, %: C 56.16; H 5.57; N 17.86.

1,3-Dibenzyl-5-nitro-1,3-dihydrobenzimidazol-2-one (IIc). In 10 ml of 20% water solution of NaOH was dissolved 4.5 g (2.5 mmol) of 5-nitro-1,3-dihydrobenzimidazol-2-one (**I**) at room temperature. At stirring 14.5 g (58.5 mmol) of benzyldimethylphenylammonium chloride in 15 ml of water was added, the mixture was heated at boiling for 7 h, *N,N*-dimethyaniline was removed by steam distillation. On cooling the separated precipitate was filtered off, washed with cold water, dried, and crystallized from 2-propanol. Yield 5.0 g (57%), mp 164–166°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.16 s (4H, $N^1\underline{CH_2}C_6H_5$, $N^3\underline{CH_2}C_6H_5$), 6.90 d (1H, H^7, *J* 8.6 Hz), 7.23–7.31 m (10H, $N^1CH_2\underline{C_6H_5}$, $N^3CH_2\underline{C_6H_5}$), 7.77 s (1H, H^4), 7.97 d (1H, H^6, *J* 8.6 Hz). Found, %: C 70.12; H 4.71; N 11.54. $C_{21}H_{17}N_3O_3$. Calculated, %: C 70.18; H 4.77; N 11.69.

5-Amino-1,3-dialkyl-1,3-dihydrobenzimidazol-2-ones IIIa–IIIc. To 25 mmol of compound **IIa–IIc** was added 30 ml of hydrazine hydrate, and the reaction mixture was heated in an argon flow for 14 h at 115–120°C. Then excess hydrazine hydrate was distilled off, the residue was dissolved in water and cooled. The separated precipitate was filtered off, dried, and recrystallized from an appropriate solvent.

5-Amino-1,3-dimethyl-1,3-dihydrobenzimidazol-2-one (IIIa). Yield 43%, mp 135–136°C (benzene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.40 s (3H, N^1CH_3), 3.41 s (3H, N^3CH_3), 5.21 br.s (2H, NH_2), 6.42 s (1H, H^4), 6.50 d (1H, H^7, *J* 8.2 Hz), 6.80 d (1H, H^6, *J* 8.2 Hz). Found, %: C 60.83; H 6.21; N 23.56. $C_9H_{11}N_3O$. Calculated, %: C 61.00; H 6.26; N 23.71.

5-Amino-1,3-diethyl-1,3-dihydrobenzimidazol-2-one (IIIb). Yield 63%, mp 175–176°C (benzene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.28 t (6H, $N^1CH_2\underline{CH_3}$, $N^3CH_2\underline{CH_3}$), 3.85 q (4H, $N^1\underline{CH_2}CH_3$, $N^3\underline{CH_2}CH_3$), 6.43 d (1H, H^7, *J* 8.2 Hz), 6.52 s (1H, H^4), 6.89 d (1H, H^6, *J* 8.2 Hz). Found, %: C 64.25; H 7.31; N 20.31. $C_{11}H_{15}N_3O$. Calculated, %: C 64.37; H 7.37; N 20.47.

5-Amino-1,3-dibenzyl-1,3-dihydrobenzimidazol-2-one (IIIc). Yield 67%, mp 132–134°C (2-propanol). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.10 br.s (2H, NH_2), 5.20 s (4H, $N^1\underline{CH_2}C_6H_5$, $N^3\underline{CH_2}C_6H_5$), 6.29 s (1H, H^4), 6.35 d (1H, H^7, *J* 8.2 Hz), 6.60 d (1H, H^6, *J* 8.2 Hz), 7.32 s (10H, $N^1CH_2\underline{C_6H_5}$, $N^3CH_2\underline{C_6H_5}$). Found, %: C 76.46; H 5.74; N 12.63. $C_{21}H_{19}N_3O$. Calculated, %: C 76.57; H 5.81; N 12.76.

1,3-Dialkyl-1,3-dihydro-5-(pyrrol-1-yl)benzimidazol-2-ones IVa–IVc. To a dispersion of 1.2 mmol of compound **IIIa–IIIc** in 2–3 ml of glacial acetic acid was added 1.2 mmol of 2,5-dimethoxytetrahydrofuran, then the mixture was heated for 0.5 h at 130°C, the excess acetic acid was distilled off to dryness, the residue was ground in warm hexane. The precipitate was filtered off and recrystallized from an appropriate solvent.

1,3-Dimethyl-1,3-dihydro-5-(pyrrol-1-yl)benzimidazol-2-one (IVa). Yield 66%, mp 151–152°C (heptane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.45 s (6H, N^1CH_3, N^3CH_3), 6.35 t (2H, $H^{3',4'}$), 6.98 d (1H, H^7, *J* 8.0 Hz), 6.99 s (1H, H^4), 7.04 t (2H, $H^{2',5'}$), 7.13 d (1H, H^6, *J* 8.0 Hz). Found, %: C 68.54; H 5.71; N 18.37. $C_{13}H_{13}N_3O$. Calculated, %: C 68.71; H 5.77; N 18.49.

1,3-Diethyl-1,3-dihydro-5-(pyrrol-1-yl)benzimidazol-2-one (IVb). Yield 48%, mp 115–117°C (heptane). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (6H, $N^1CH_2\underline{CH_3}$, $N^3CH_2\underline{CH_3}$), 4.00 q (4H, $N^1\underline{CH_2}CH_3$, $N^3\underline{CH_2}CH_3$), 6.40 t (2H, $H^{3',4'}$), 7.05 d (1H, H^7, *J* 8.5 Hz), 7.06 s (1H, H^4), 7.08 t (2H, $H^{2',5'}$), 7.15 d (1H, H^6, *J* 8.5 Hz). Found, %: C 70.52; H 6.65; N 16.30. $C_{15}H_{17}N_3O$. Calculated, %: C 70.56; H 6.71; N 16.46.

1,3-Dibenzyl-1,3-dihydro-5-(pyrrol-1-yl)-benzimidazol-2-one (IVc). Yield 52%, mp 165–168°C (2-прОпаНОл). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5,20 s (4H, $N^1\underline{CH_2}C_6H_5$, $N^3\underline{CH_2}C_6H_5$), 6.27 t (2H, $H^{3',4'}$), 6.95 d (1H, H^7, *J* 8.5 Hz), 7.35 t (2H, $H^{2',5'}$), 7.40 br.s (10H, $N^1CH_2\underline{C_6H_5}$, $N^3CH_2\underline{C_6H_5}$), 7.82 s (1H, H^4), 8.02 d (1H, H^6, *J* 8.5 Hz). Found, %: C 78.97; H 5.52; N 10.95. $C_{25}H_{21}N_3O$. Calculated, %: C 79.13; H 5.58; N 11.07.

1-(1,3-Dialkyl-2-oxo-1,3-dihydrobenzimidazol-5-yl)-2,6-dimethylpyridin-4-ones Va–Vc. A mixture of 10 mmol of 5-amino-1,3-dialkyl-1,3-dihydrobenzimidazol-2-one **IIIa–IIIc** and 10 mmol of 2,6-dimethyl-γ-pyranone was heated at 120–125°C over 6–8 h. On cooling the melt was ground in petroleum ether (bp 60–80°C), the precipitate was isolated and crystallized from heptane.

1-(1,3-Dimethyl-2-oxo-1,3-dihydrobenzimidazol-5-yl)-2,6-dimethylpyridin-4-one (Va). Yield 78%, mp 90–92°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.28 s (6H, $C^{2'}CH_3$, $C^{6'}CH_3$), 3.38 s (3H, $N^{1'}CH_3$), 3.39 s (3H, $N^{3'}CH_3$), 6.10 s (2H, $H^{3',5'}$), 6.41 s (1H, H^4), 6.49 d (1H, H^7, *J* 8.2 Hz), 6.78 d (1H, H^6, *J* 8.2 Hz). Found, %: C 67.66; H 5.98; N 14.64. $C_{16}H_{17}N_3O_2$. Calculated, %: C 67.83; H 5.05; N 14.83.

1-(1,3-Diethyl-2-oxo-1,3-dihydrobenzimidazol-5-yl)-2,6-dimethylpyridin-4-one (Vb). Yield 72%, mp 127–128°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.33 t (6H, $N^1CH_2\underline{CH}_3$, $N^3CH_2\underline{CH}_3$), 2.27 s (6H, $C^{2'}CH_3$, $C^{6'}CH_3$), 3.90 q (4H, $N^1\underline{CH}_2CH_3$, $N^3\underline{CH}_2CH_3$), 6.09 s (2H, $H^{3',5'}$), 6.44 s (1H, H^4), 6.47 d (1H, H^7, *J* 8.2 Hz), 6.81 d (1H, H^6, *J* 8.2 Hz). Found, %: C 69.24; H 6.73; N 13.35. $C_{18}H_{21}N_3O_2$. Calculated, %: C 69.43; H 6.80; N 13.49.

1-(1,3-Dibenzyl-2-oxo-1,3-dihydrobenzimidazol-5-yl)-2,6-dimethylpyridin-4-one (Vc). Yield 81%, mp 87–89°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.26 s (6H, $C^{2'}CH_3$, $C^{6'}CH_3$), 5.12 s (4H, $N^1\underline{CH}_2C_6H_5$, $N^3\underline{CH}_2C_6H_5$), 6.12 s (10H, $N^1CH_2\underline{C}_6\underline{H}_5$, $N^3CH_2\underline{C}_6\underline{H}_5$), 6.31 s (1H, H^4), 6.37 d (1H, H^7, *J* 8.0 Hz), 6.68 d (1H, H^6, *J* 8.0 Hz), 7.37 s (2H, $H^{3',5'}$). Found, %: C 77.03; H 5.71; N 9.48. $C_{28}H_{25}N_3O_2$. Calculated, %: C 77.22; H 5.79; N 9.65.

REFERENCES

1. Shvaika, Ol., *Osnovi sintezu likars'kikh rechovin ta ïkh promizhnikh produktiv* (Principles of Synthesis of Drugs and Their Intermediates), Donets'k, 2004.
2. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2010, p. 1216.
3. Elming, N. and Clauson-Kaas, N., *Acta Chem. Scand.,* 1952, vol. 6, p. 867.
4. Efros, L.S., Porai-Koshits, B.A., and Farbenshtein, S.G., *Zh. Obshch. Khim.,* 1953, vol. 23, p. 1691.
5. Efros, L.S. and El'tsov, A.V., *Zh. Obshch. Khim.*, 1957, vol. 27, p. 127.
6. Dorofeenko, G.N., Zvezdina, E.A., Zhdanova, M.P., and Barchan, I.A., *Khim. Geterotsikl. Soedin*., 1973, vol. 12, p. 1682.
7. Efros, L.S. and El'tsov, A.V., *Zh. Obshch. Khim*., 1958, vol. 28, p. 141.