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# Recyclization of 2-Methoxy-5-morpholino-1,3-oxazole-4-carbonitrile by Benzylamine, Phenethylamine, and Phenylhydrazine

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**Abstract**—Reaction of 2-methoxy-5-morpholino-1,3-oxazole-4-carbonitrile with benzylamine, phenethylamine and phenylhydrazine results in the new substituted 5-amino-2,3-dihydro-1*H*-imidazol-2-ones.

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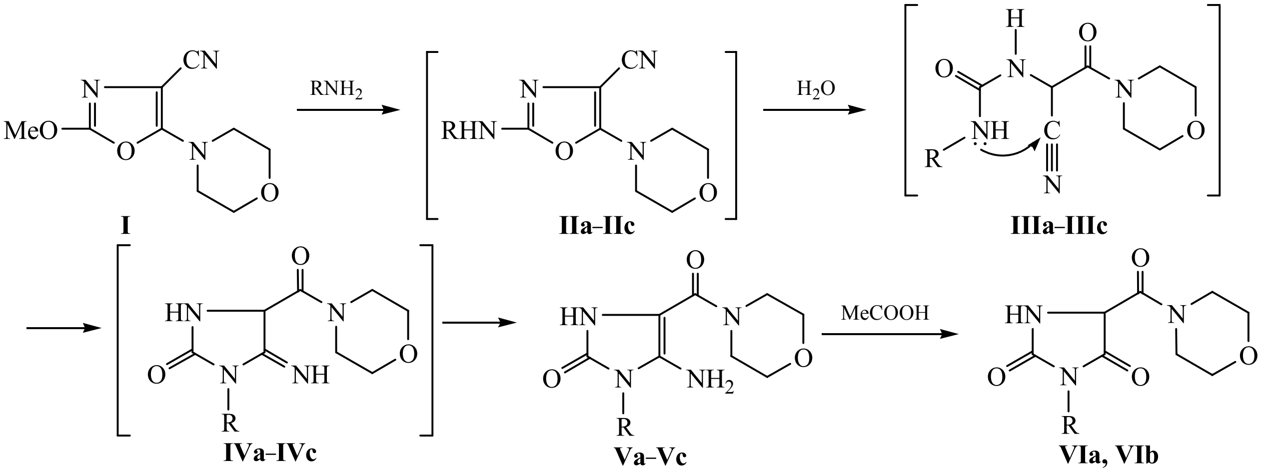
It is known that 2-alkyloxy- and 2-aryloxybenzoxazoles react readily with aliphatic amines to give 2-aminobenzoxazole derivatives [1–3]. As 2-alkyl(aryl)-substituted 5-aminodialkyl-1,3-oxazole-4-carbonitriles are stable to the action of nitrogen nucleophiles [4 ], using this reaction makes commercially available 2-methoxy-5-morpholino-1,3-oxazole-4-carbonitrile **I** [5] a promising synthone for the synthesis of novel diaminooxazole derivatives, exhibiting a wide range of biological activity [6–8]. However, secondary aliphatic amines did not react with **I** even in boiling organic solvents. In the case of primary aliphatic amines, hydrazine, and methylhydrazine, under the same conditions a complex mixture of products was formed, and we failed to isolate individual compounds from it. Only in the cases of oxazole **I** interaction with benzylamine, phenethylamine and phenylhydrazine, it was possible to isolate individual products from the mixture containing more than 6 substances (according to GC–MS data). The optimal reaction conditions were boiling the starting materials for 3 h in the *n*-butanol–water mixture (95:5) at the reagents ratio of 1:1.1. Under such conditions, the substituted 5-amino-4-[(morpholin-4-yl)carbonyl]-2,3-dihydro-1*H*-imidazol-2-ones **Va**–**Vc** were isolated with moderate yields.

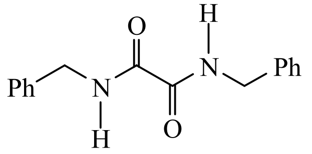
A possible mechanism of the formation of compounds **V** involved substitution of the methoxy group with the nitrogen nucleophile, oxazole ring opening by the action of water, and subsequent cyclization to form



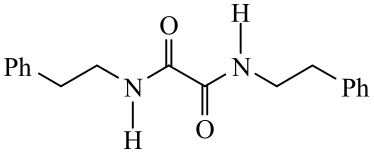
**II–VI**, R = $PhCH_2$ (**a**), $Ph(CH_2)_2$ (**b**), PhNH (**c**).

2-imidazolone **IV** derivatives or their prototropic forms **V**. Similar behavior of 2-amino-1,3-thiazoles, being rearranged into 2-mercapto-1,3-imidazoles in the presence of bases, has been reported [9, 10].

The complexity of the studied reaction was confirmed by isolating of oxalic acid bisamides **A** and **B** with yield of 4–5% after continuous heating of a mixture of compound **I** with benzylamine and phenethylamine in *n*-butanol.



**A**



**B**

The products **Va**–**Vc** were new representatives of the 5-aminoimidazol-2-ones class. Their composition and structure were confirmed by elemental analysis data and spectroscopic methods including GC–MS. In particular, in the IR spectra of the substituted 5-amino-4-[(morpholin-4-yl)-carbonyl]-2,3-dihydro-1*H*-imidazol-2-ones **Va**–**Vc** (as compared with that of the starting 2-methoxy-5-morpholino-1,3-oxazole-4-carbonitrile **I**) the nitrile group signal at 2220–2230 cm$^{-1}$ [5] disappeared, and the intense absorption bands at 3100–3300 cm$^{-1}$ appeared, assigned to NH and NH$_2$ groups. Additionally, the structure of compounds **V** was confirmed by transformation of imidazol-2-ones **Va** and **Vb** into 3-alkyl-5-[(morpholin-4-yl)carbonyl]imidazolidine-2,4-diones **VIa** and **VIb**, a well known reaction of aminohydantoines [11, 12]. However, an unambiguous determination of the structure of substituted 5-amino-4-[(morpholin-4-yl)-carbonyl]-2,3-dihydro-1*H*-imidazol-2-ones **V** and 3-alkyl-5-[(morpholin-4-yl)-carbonyl]imidazolidine-2,4-diones **VI** was performed using the comparative complex (NOESY, COSY, HSQC, HMBC, HSQC, and HMBC) NMR analysis of compounds **Va** and **VIa**. The main correlations and assignments of their $^1$H and $^{13}$C signals are shown in Figs. 1 and 2, and full set of the found correlations is given in Tables 1 and 2, respectively.

Cross-peaks in the NOESY spectra of compound **Va** (7.27 ↔ 4.82, 7.27 ↔ 6.18, 4.82 ↔ 6.18, and 9.76 ↔ 3.39) as well as those in the HMBC spectra (4.82 → 142.20, 4.82 → 151.04, 4.82 → 127.57, 4.82 → 137.67, 9.76 → 151.04, 9.76 → 142.20, and 9.76 → 91.15) clearly revealed that it contained 2,3-dihydro-1*H*-imidazol-2-one ring with the corresponding set of substituents (Fig. 1). Numerous cross-peaks in the NOESY (7.27 ↔ 7.33, 7.27 ↔ 4.56, 5.58 ↔ 8.51, 5.58 ↔ 3.68, 5.58 ↔ 3.78, 5.58 ↔ 3.41, and 5.58 ↔ 3.63) and HMBC (4.56 → 157.42, 4.56 → 163.62,

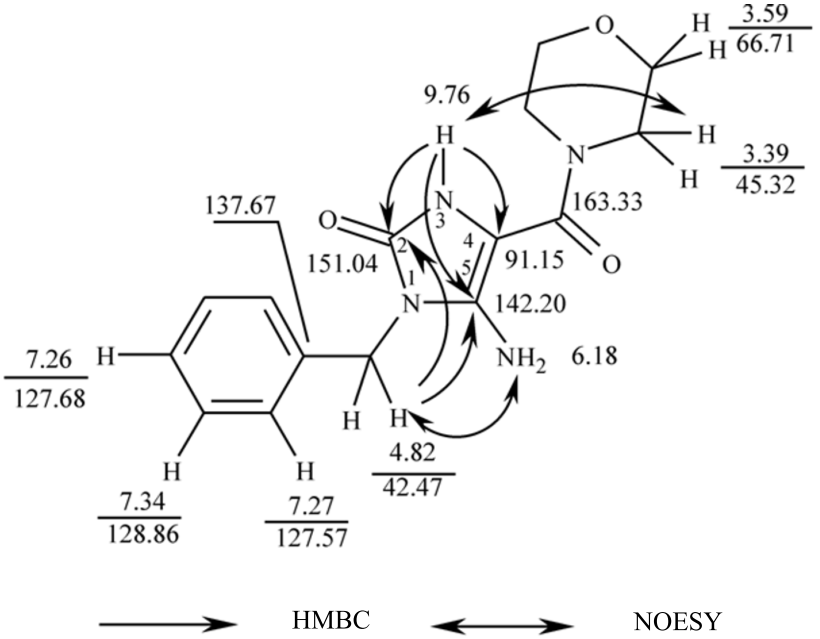


**Fig. 1.** Main correlations and the signals assignments (ppm) in the $^1$H and $^{13}$C NMR spectra of **Va**.

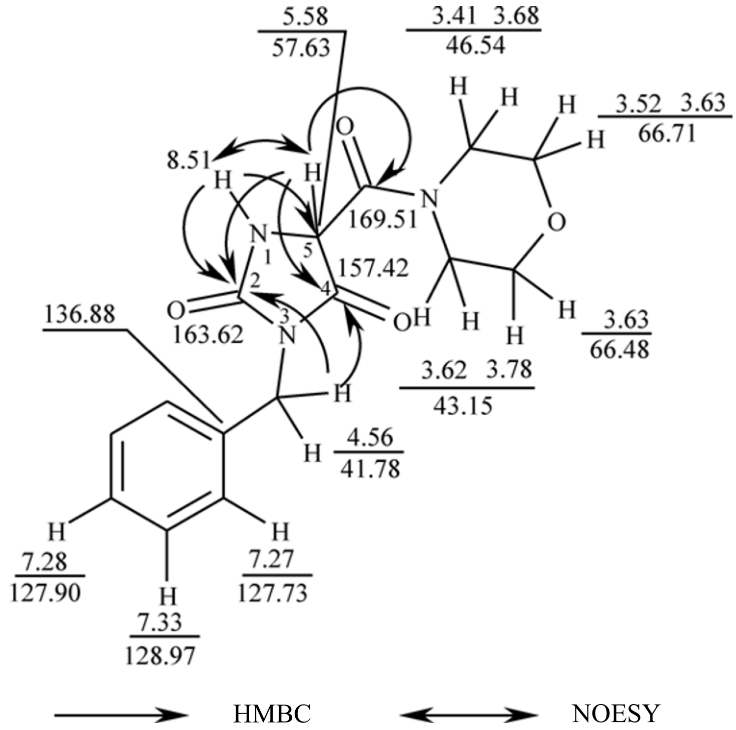


**Fig. 2.** Main correlations and the signals assignments (ppm) in the $^1$H and $^{13}$C NMR spectra of **VIa**.

4.56 → 127.73, 4.56 → 136.88, 8.51 → 163.62, 8.51 → 157.42, 8.51 → 57.63, 5.58 → 163.62, 5.58 → 157.42, and 5.58 → 169.51) spectra of **VIa** reliably indicated that its molecule contained imidazolidine-2,4-dione system with benzyl and (morpholin-4-yl)carbonyl substituents (Fig. 2). It should be noted that in the HMBC spectrum of compound **VIa** in the region of morpholine moiety resonance a complex poorly resolved pattern was observed making the signal assignment somewhat sophisticated, however, that part of the spectrum was not of primary importance for the structure elucidation.

Thus, we demonstrated a new use of the substituted 2-methoxy-1,3-oxazole-4-carbonitriles for synthesis of 5-aminoimidazol-2-ones; the screening of such products for biological activity will likely reveal prospective regulatory compounds [13, 14].

**Table 1.** Correlations found in the COSY, NOESY, HSQC, and HMBC NMR spectra of compound **Va**[a]

| $\delta_H$, ppm | $\delta_H$, ppm | | $\delta_C$, м. д. | |
|---|---|---|---|---|
| | COSY | NOESY | HSQC | HMBC |
| 7.26 | 7.34 | 7.34 | 127.68 | 127.57 |
| 7.34 | 7.26, 7.27 | 7.26, 7.27 | 128.86 | 128.86, 137.67 |
| 7.27 | 7.34, 4.82 | 7.34, 4.82, 6.18 | 127.57 | 126.68, 126.57, 42.47 |
| 4.82 | 7.27 | 7.27, 6.18 | 42.47 | 142.20, 151.04, 127.57, 137.67 |
| 6.18 | – | 7.27, 4.82 | – | 91.15 |
| 9.76 | – | 3.39 | – | 151.04, 142.20, 91.15 |
| 3.39 | 3.59 | 3.59, 9.76 | 45.32 | 45.32, 163.33 |
| 3.59 | 3.39 | 3.39 | 66.71 | 66.71 |

[a] The signals assignments for compound **Va** are shown in Fig. 1.

**Table 2.** Correlations found in the COSY, NOESY, HSQC and HMBC NMR spectra of compound **VIa**[a]

| $\delta_H$, ppm | $\delta_H$, ppm | | $\delta_C$, ppm | |
|---|---|---|---|---|
| | COSY | NOESY | HSQC | HMBC |
| 7.28 | 7.33 | 7.33 | 127.90 | 127.73 |
| 7.33 | 7.28, 7.27 | 7.28, 7.27 | 128.97 | 128.97, 136.88 |
| 7.27 | 7.33, 4.56 | 7.33, 4.56 | 127.73 | 127.90, 127.73, 41.78 |
| 4.56 | 7.27 | 7.27 | 41.78 | 157.42, 163.62, 127.73, 136.88 |
| 8.51 | 5.58 | 5.58 | – | 163.62, 157.42, 57.63 |
| 5.58 | 8.51 | 8.51, 3.68, 3.78, 3.41, 3.63 | 57.63 | 163.62, 157.42, 169.51 |
| 3.41 | 3.68, 3.63, 3.52 | 3.68, 3.63, 3.52 | 46.54 | – |
| 3.68 | 3.41, 3.63, 3.52 | 3.41, 3.63, 3.52 | 46.54 | – |
| 3.52 | 3.41, 3.63, 3.68 | 3.41, 3.63, 3.68 | 66.71 | – |
| 3.63 | 3.41, 3.52, 3.68 | 3.41, 3.52, 3.68 | 66.71 | – |
| 3.62 | 3.78, 3.63 | 3.78, 3.63 | 43.15 | – |
| 3.78 | 3.62, 3.63 | 3.62, 3.63 | 43.15 | – |
| 3.63 | 3.62, 3.78 | 3.62, 3.78 | 66.48 | – |

[a] The signals assignments for compound **VIa** are shown in Fig. 2.

## EXPERIMENTAL

IR spectra of the compounds in the form of KBr pellets were recorded with Vertex 70 instrument. $^1$H and $^{13}$C NMR spectra of DMSO-$d_6$ solutions were recorded with Bruker AVANCE DRX-500 spectrometer operating at 500 and 125 MHz, respectively, TMS being used as internal standard. GC–MS spectra were recorded with HPLC Agilent 1100 Series liquid chromatography–mass spectrometry system equipped with a diode array with an Agilent LC\MSD SL mass selective detector. Experimental conditions were as follows: Zorbax SB-C18 column, 1.8 μm × 4.6 × 15 mm (PN 821975-932); solvent **A**: acetonitrile–water (95:5), 0.1% trifluoroacetic acid; solvent **B**: 0.1% aqueous trifluoroacetic acid; eluent flow 3 ml min$^{-1}$, injected volume 1 μl, UV detectors – 215, 254, and 285 nm; chemical ionization at atmospheric pressure (APCI), scan range *m*/*z* 80–1000. Melting points were measured with Fisher-Johns instrument.

2-Methoxy-5-morpholino-1,3-oxazole-4-carbonitrile **I** was prepared as described in [5].

***N*-Substituted 5-amino-4-[(morpholin-4-yl)carbonyl]-2,3-dihydro-1*H*-imidazol-2-ones (Va–Vc).** The corresponding amine or phenylhydrazine (5.5 mmol) was added to a suspension of 1.05 g (5 mmol) of compound **I** in 10 ml of *n*-butanol. The reaction mixture was refluxed for 3 h, and then kept for 12 h at 20–25°C. Precipitate formed was filtered off, washed with *n*-butanol, and recrystallized from ethanol.

**5-Amino-1-benzyl-4-[(morpholin-4-yl)carbonyl]-2,3-dihydro-1*H*-imidazol-2-one (Va).** Yield 28%, mp 210–212°C. IR spectrum, ν, cm$^{-1}$: 1633 (C=O), 1715 (C=O), 3032–3396 (NH, NH$_2$). Found, %: C 59.46; H 6.15; N 18.36. $C_{15}H_{18}N_4O_3$. Calculated, %: C 59.59; H 6.00; N 18.53. *M* 302.

**5-Amino-4-[(morpholin-4-yl)carbonyl]-1-(2-phenylethyl)-2,3-dihydro-1*H*-imidazol-2-one (Vb).** Yield 37%, mp 193–195°C. IR spectrum, ν, cm$^{-1}$: 1634 (C=O), 1710 (C=O), 3128–3383 (NH, NH$_2$). $^1$H NMR spectrum, δ, ppm: 2.84 t (2H, CH$_2$, $^3J_{HH}$ 7.6 Hz), 3.40–3.47 m (4H, 2CH$_2$, morpholine), 3.55–3.61 m (4H, 2CH$_2$, morpholine), 3.76 t (2H, CH$_2$, $^3J_{HH}$ 7.6 Hz), 6.18 s (2H, NH$_2$), 7.20–7.32 m (5H, $C_6H_5$), 9.65 s (1H, NH). $^{13}$C NMR spectrum, $\delta_C$, ppm: 34.29, 40.54, 45.30, 66.69, 90.99, 126.83, 128.80, 129.27, 138.75, 142.17, 150.74, 163.36. Found, %: C 60.46; H 6.19; N 17.96. $C_{16}H_{20}N_4O_3$. Calculated, %: C 60.75; H 6.37; N 17.71. *M* 316.

**5-Amino-4-[(morpholine-4-yl)carbonyl]-1-(phenylamino)-2,3-dihydro-1*H*-imidazol-2-one (Vc).** Yield 21%, mp 229–231°C. IR spectrum, ν, cm$^{-1}$: 1644 (C=O), 1707 (C=O), 3056–3444 (NH, NH$_2$). $^1$H NMR spectrum, δ, ppm: 3.40–3.45 m (4H, 2CH$_2$, morpholine), 3.60–3.67 m (4H, 2CH$_2$, morpholine), 5.98 s (2H, NH$_2$), 6.57–6.63 m (2H, C$_6$H$_5$), 6.80–6.87 m (1H, C$_6$H$_5$), 7.17–7.24 m (2H, C$_6$H$_5$), 8.64 s (1H, NH), 9.80 s (1H, NH). $^{13}$C NMR spectrum, δ$_C$, ppm: 45.36, 66.71, 88.55, 113.02, 120.45, 129.42, 141.80, 147.74, 149.77, 163.23. Found, %: C 55.56; H 5.39; N 23.01. $C_{14}H_{17}N_5O_3$. Calculated, %: C 55.44; H 5.65; N 23.09. *M* 303.

**3-Alkyl-5-[(morpholine-4-yl)carbonyl]imidazolidine-2,4-diones (VIa, VIb).** A solution of 2 mmol of compound **Va** or **Vb** in 10 ml of acetic acid was refluxed for 2 h upon stirring. After cooling, the solvent was removed under vacuum. The precipitate was washed with a small amount of water and recrystallized from ethanol.

**3-Benzyl-5-[(morpholine-4-yl)carbonyl]imidazolidine-2,4-dione (VIa).** Yield 82%, mp 151–153°C. IR spectrum, ν, cm$^{-1}$: 1649 (C=O), 1719 (C=O), 1786 (C=O), 3074–3294 (NH). Found, %: C 59.56; H 5.78; N 14.01. $C_{15}H_{17}N_3O_4$. Calculated, %: C 59.40; H 5.65; N 13.85. *M* 303.

**5-[(Morpholine-4-yl)carbonyl]-3-(2-phenylethyl)-imidazoline-2,4-dione (VIb).** Yield 86%, mp 127–129°C. IR spectrum, ν, cm$^{-1}$: 1631 (C=O), 1711 (C=O), 1771 (C=O), 3162–3222 (NH). $^1$H NMR spectrum, δ, ppm: 2.81 br.s (2H, CH$_2$), 3.63–3.72 m (10H, 4CH$_2$, morpholine, CH$_2$), 5.47 s (1H, CH), 7.19–7.28 m (5H, C$_6$H$_5$), 8.40 s (1H, NH). $^{13}$C NMR spectrum, δ$_C$, ppm: 33.80, 40.56, 43.11, 46.49, 57.49, 66.48, 66.71, 126.87, 128.90, 129.14, 138.51, 157.38, 163.44, 169.33. Found, %: C 60.48; H 6.20; N 13.15. $C_{16}H_{19}N_3O_4$. Calculated, %: C 60.56; H 6.03; N 13.24. *M* 317.

***N*,*N'*-Dialkylethanediamides (A, B)**. The corresponding amine (5.5 mmol) was added to a suspension of 1.05 g (5 mmol) of compound **I** in 10 ml of *n*-butanol. The mixture was refluxed for 3 h and then kept for 12 h at 20–25°C. The precipitate formed was filtered off. The mother liquor was additionally refluxed for 24 h and cooled to room temperature. The precipitate formed was washed with a small amount of water and recrystallized from ethanol.

***N*,*N'*-Dibenzylethanediamide (A).** Yield 5%, mp 208–210°C (213–215°C [15], 221–222°C [16]). IR spectrum, ν, cm$^{-1}$: 1654 (C=O), 3288 (NH). $^1$H NMR spectrum, δ, ppm: 4.33 d (4H, 2CH$_2$, $^3J_{HH}$ 2.4 Hz), 7.21–7.33 m (10H, 2C$_6$H$_5$), 9.31 t (2H, 2NH, $^3J_{HH}$ 6.2 Hz). $^{13}$C NMR spectrum, δ$_C$, ppm: 42.91, 127.39, 127.85, 128.77, 139.21, 160.62. Found, %: C 71.48; H 6.10; N 10.25. $C_{16}H_{16}N_2O_2$. Calculated, %: C 71.62; H 6.01; N 10.44. *M* 268.

***N*,*N'*-Bis(2-phenylethyl)ethanediamide (B).** Yield 4%, mp 181–183°C (184–185°C [17], 186–188°C [18]). IR spectrum, ν, cm$^{-1}$: 1654 (C=O), 3307 (NH). $^1$H NMR spectrum, δ, ppm: 2.79 t (4H, 2CH$_2$, $^3J_{HH}$ 7.5 Hz), 3.35–3.40 m (4H, 2CH$_2$), 7.18–7.33 m (10H, 2C$_6$H$_5$), 8.75 t (2H, 2NH, $^3J_{HH}$ 5.8 Hz). $^{13}$C NMR spectrum, δ$_C$, ppm: 35.08, 40.06, 126.63, 128.81, 129.05, 139.58, 160.33. Found, %: C 72.78; H 6.97; N 9.55. $C_{18}H_{20}N_2O_2$. Calculated, %: C 72.95; H 6.80; N 9.45. *M* 296.

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