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LETTERS TO THE EDITOR

A Convenient Approach to Synthesis of Benzoxazol-2-ylglycine and Benzothiazol-2-ylglycicne Derivatives

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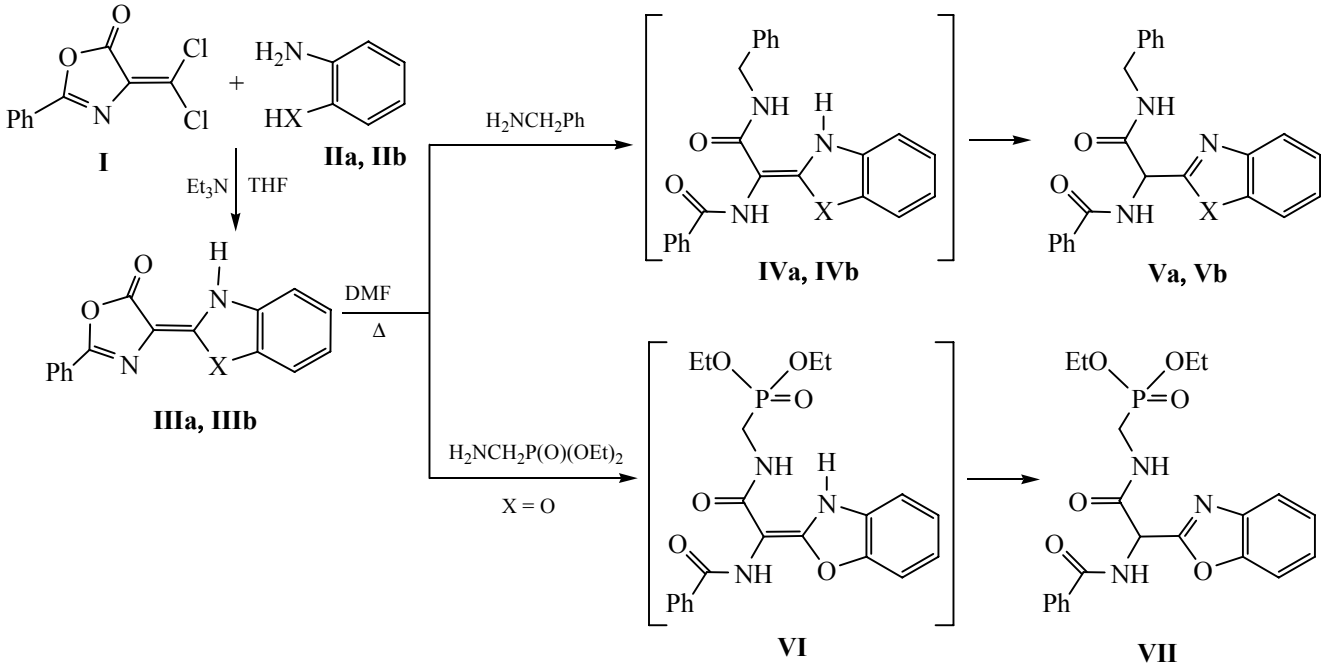
Introduction of pharmacophore heterocyclic moieties into the peptide chain is of particular interest because it results in a promising new bioregulators [1] with a significant anticonvulsant, neuropathic and analgesic activity [2–6], and also oxytocin antagonists [7]. However, the functionalization of α-amino acids with electron-acceptor heterocycles is a challenging task, due to their ease of decarboxylation. This substantially limits the use of such amino acids in peptide synthesis.

In this work, we developed a convenient approach to the synthesis of glycine derivatives, which were modified at the α-position with benzoxazol-2-yl and benzothiazol-2-yl moieties. For the first time we used for this purpose available 2-phenyl-4-dichloromethylene-5(4*H*)-oxazolone [8], which was involved into the reactions sequence: **I** → **III** → **V** or **VII**. The reaction **I** → **III** has been previously described by an example of 2-aminothiophenol [9], and all the other reaction were investigated by us for the first time. The



X = O (**IIa–Va**), S (**IIb–Vb**).

final step in this process is the cleavage of oxazolones **III** with benzylamine or diethyl aminomethylphosphonate to form intermediates **IV** and **VI** followed by prototropic isomerization into the products **V** and **VII**.

Compound **VII** is of particular interest since it belongs to the class of phosphonopeptide mimetics [10, 11].

The assumed structures of the new compounds are in a good agreement with the data of ^{1}H NMR and IR spectroscopy. Thus, in the IR spectrum of compound **IIIa** there are two intensive absorption bands at 1713 and 1655 cm^{-1} belonging to the stretching vibration of the bonds C=O and C=N of oxazolone ring. The ^{1}H NMR spectra of products **V** and **VII** contain characteristic two doublet signals of the protons of NH–CH group at 6.13–6.23 and 9.42–9.46 ppm

It should be noted that attempts to obtain such structure with benzothiazol-2-yl moiety have been made earlier, but the target compound was not isolated in a pure form [12–14]. Only dipeptides containing quinolin-2-yl, pyridin-2-yl, and 4-pyrimidin-2-yl moieties in the peptide chain have been synthesized [15].

Thus, we have developed a new convenient method for the synthesis of benzoxazol-2-yl- and benzothiazol-2-ylglycine derivatives, which was applied to obtain a phosphonopeptide mimetic containing benzoxazol-2-yl moiety in the side chain.

2-Phenyl-4-(2,3-dihydrobenzo[1,3]oxzol-2-ylidene)-1,3-oxazol-5-one (IIIa). To a suspension of 0.008 mol of compound **I** in 40 ml of tetrahydrofuran under cooling with ice water and stirring was added 1.7 g (0.017 mol) of triethylamine and a solution of 0.5 g (0.004 mol) of 2-aminophenol in 50 ml of tetrahydrofuran within 1 h. The mixture was stirred for 4 h and kept for 24 h at 20–25°C. The precipitate was filtered off, and the filtrate was evaporated in a vacuum to dryness. The residue was purified by recrystallization from acetonitrile. Yield 70%, mp 259–261°C. IR spec-trum, ν, cm^{-1}: 1655 (C=N), 1713 (C=O), 3228 (NH). Mass spectrum, *m*/*z*: 279 $[M + 1]^+$. Found, %: C 69.17; H 3.48; N 10.14. $C_{16}H_{10}N_2O_3$. Calculated, %: C 69.06; H 3.62; N 10.07.

2-Phenyl-4-(2,3-dihydrobenzo[1,3]thiazol-2-ylidene)-1,3-oxazol-5-one (IIIb) was obtained by the described method [9].

***N*-(Benzoxazol-2-ylbenzylcarbamoylmethyl)benzamide (Va).** To a solution of 0.002 mol of compound **IIIa** in 40 ml of dioxane was added 0.23 g (0.0021 mol) of benzylamine. The mixture was heated at 65–70°C for 5 h (TLC monitoring) and evaporated in a vacuum to dryness. The residue was purified by recrystallization from benzene. Yield 80%, mp 162–163°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 1640 (C=O), 3310 (N–H). ^{1}H NMR spectrum, δ,ppm: 4.43 d (2H, CH_2, $^3J_{HH}$ 5.2 Hz), 6.13 d (1H, CH, $^3J_{HH}$ 7.0 Hz), 7.25–8.00 m (14H, $2C_6H_5$, C_6H_4), 9.03 br. s (1H, NH), 9.46 d (1H, NH, $^3J_{HH}$ 7.0 Hz). Mass spectrum, *m*/*z*: 386 $[M + 1]^+$. Found, %: C 71.36; H 4.82; N 10.98. $C_{23}H_{19}N_3O_3$. Calculated, %: C 71.67; H 4.97; N 10.90.

***N*-(Benzothiazol-2-ylbenzylcarbamoylmethyl)benzamide (Vb)** was prepared similarly from oxazolone **IIIb**. Yield 82%, mp 184–185°C. IR spectrum, ν, cm^{-1}: 1633 (C=O, shoulder), 3277 (NH). ^{1}H NMR spectrum, δ, ppm: 4.31–4.54 m (2H, CH_2), 6.23 d (1H, CH, $^3J_{HH}$ 7.2 Hz), 7.26–8.11 m (14H, $2C_6H_5$, C_6H_4), 9.08 br. s (1H, NH), 9.45 br. s (1H, NH). Mass spectrum, *m*/*z*: 402 $[M + 1]^+$. Found, %: C 68.56; H 4.62; N 10.65; S 7.89. $C_{23}H_{19}N_3O_2S$. Calculated, %: C 68.81; H 4.77; N 10.47; S 7.99.

Diethyl [(2-benzoxazol-2-yl)-2-benzoylaminoacetylamino)methyl]phosphonate (VII). To a solution of 0.002 mol of compound **IIIa** in 40 ml of dioxane was added 0.34 g (0.0021 mol) of the freshly prepared aminomethylphosphonic acid diethyl ester [16]. The mixture was heated at 65–70°C for 6 h (TLC monitoring). The solvent was evaporated in a vacuum, and the residue was purified by recrystallization from acetonitrile. Yield 88%, mp 134–135°C. IR spectrum, ν, cm^{-1}: 962 (P–OCC), 1027 (POC), 1211 (P=O), 1650 (C=O, shoulder), 3230 (NH). ^{1}H NMR spectrum, δ, ppm: 1.17–1.21 m (6H, $2OCH_2\underline{CH_3}$), 3.66–3.77 m (2H, CH_2), 3.99–4.06 m (4H, $O\underline{CH_2}CH_3$), 6.18 d (1H, CH, $^3J_{HH}$ 8.0 Hz), 7.43–7.97 m (9H, C_6H_5, C_6H_4), 8.98 t (1H, NH, $^3J_{HH}$ 5.0 Hz), 9.42 d (1H, NH, $^3J_{HH}$ 8.0 Hz). ^{31}P NMR spectrum: δ_p 22.9 ppm. Mass spectrum, *m*/*z*: 446 $[M + 1]^+$. Found, %: C 56.39; H 5.36; N 9.57; P 6.81. $C_{21}H_{24}N_3O_6P$. Calculated, %: C 56.63; H 5.43; N 9.43; P 6.95.

The IR spectra were recorded on a Vertex 70 instrument from KBr pellets. The NMR spectra were obtained on a Bruker AVANCE DRX-500 spectrometer operating at 500.07 (^{1}H) and 202.43 MHz (^{31}P) and using DMSO-d_6 as a solvent; chemical shifts are reported relative to internal reference TMS or external reference 85% phosphoric acid. GC-MS spectra were recorded on a liquid chromatograph-mass spectrometer system HPLC Agilent 1100 Series equipped with a

diode array with a mass selective detector Agilent LC\MSD SL [column Zorbax SB-C18 (1.8 μm 4.6 × 15 mm, PN 821975-932); acetonitrile–water (95:5) with the addition of 0.1% trifluoroacetic acid (A) or 0.1% aqueous trifluoroacetic acid (B), eluent flow 3 ml min^{-1}, injection volume 1 μL; UV detecting at 215, 254, 265 nm; chemical ionization at atmospheric pressure (APCI), scan range *m*/*z* 80–1000. Melting points were measured on a Fisher-Johns instrument.

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