ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 7, pp. 1045–1048. © Pleiades Publishing, Inc., 2006.
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Synthesis of New Modified Aza Heterocycles on the Basis of 5-(2-Chloro-1-nitroalkyl)-3-phenyl- and 5-(2-Chloro-1-nitroalkyl)-3-methyl-1,2,4-oxadiazoles

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Received November 2, 2005

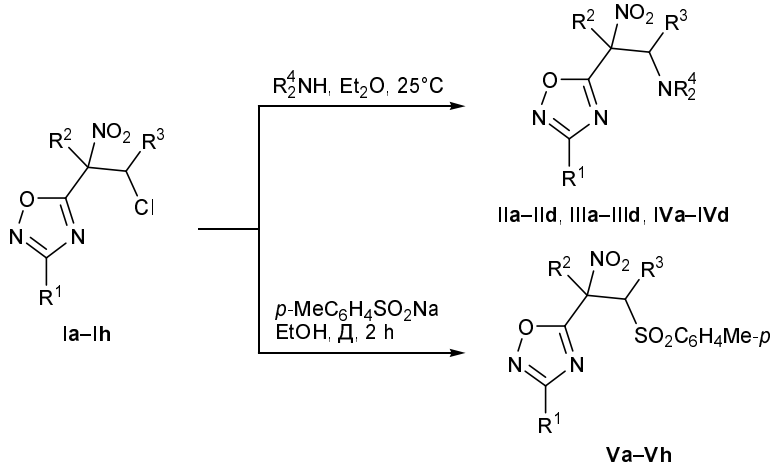
Abstract—3-Phenyl- and 3-methyl-5-(2-chloro-1-nitroalkyl)-1,2,4-oxadiazoles reacted with piperidine, pyrrolidine, and morpholine to give the corresponding 5-(2-amino-1-nitroalkyl) derivatives, while their reactions with sodium *p*-toluenesulfinate led to the formation of 2-[3-methyl(or phenyl)-1,2,4-oxadiazol-5-yl]-2-nitroethyl *p*-tolyl sulfones.

DOI: 10.1134/S1070428006070207

The problem of oxadiazole modification is the matter of increased interest; in some cases, modification of oxadiazole derivatives enhances their physiological activity or reduces side effects [1, 2]. There are limited published data on modification of 1,2,4-oxadiazoles; for example, Brizzi et al. [3] reported on the replacement of the chlorine atom in 3-aryl-5-chloromethyl-1,2,4-oxadiazole by pyrimidinyl- or pyridinylsulfanyl group. No such reactions were described so far for oxadiazoles having a nitroethyl moiety in position *5* of the heteroring. It should be noted that nonfused polynitrogen-containing heterocyclic compounds on the basis of 1,2,4-oxadiazole attract strong interest as intermediate products for the synthesis of various polyfunctional compounds [4] and pharmacological agents with a broad spectrum of activity [5, 6].

The present communication reports on the synthesis of polynuclear nonfused azoles in which two heterorings are linked through a nitroethyl fragment with a view to obtain new heterocyclic compounds of the oxadiazole series. One version of such synthesis includes modification of 5-(2-chloro-1-nitroethyl)-3-phenyl-1,2,4-oxadiazoles **Ia**–**Id** via reaction with piperidine, pyrrolidine, or morpholine. Nucleophilic replacement of the chlorine atom in **Ia**–**Id** by the amine residue readily occurred at 25°C to give previously unknown 5-[1-nitro-2-piperidino(or pyrrolidin-1-yl, or morpholino)ethyl]-3-phenyl-1,2,4-oxadiazoles

Scheme 1.



I–**V**, R^1 = Ph (**a**–**d**), Me (**e**–**h**); R^2 = NO_2, R^3 = H (**a**, **e**), Me (**b**, **f**); R^2 = CO_2Et, R^3 = H (**c**, **g**), Me (**d**, **h**); **II**, R^4_2N = piperidino; **III**, R^4_2N = 1-pyrrolidinyl; **IV**, R^4_2N = morpholino.

II–IV (Scheme 1) whose structure was confirmed by IR and ^{1}H NMR spectroscopy. The best yields of the target products were obtained when the reaction was performed in anhydrous diethyl ether using 3 equiv of the corresponding cyclic amine. The IR spectra of compounds **IIc**, **IId**, **IIIc**, **IIId**, **IVc**, and **IVd** contained absorption bands belonging to the ester carbonyl group (1770–1775 cm^{-1}) and medium-intensity absorption at 1620–1630 cm^{-1} due to C=N bond in the oxadiazole ring (cf. [7]). A set of medium and weak bands in the regions 1560–1570, 1440–1460, and 1360–1400 cm^{-1} was assigned to stretching vibrations of the 1,2,4-oxadiazole ring, and bands in the region 910–930 cm^{-1}, to its in-plane bending vibrations [7]. Absorption bands in the regions 1410–1425, 1360–1380, and 1060–1080 cm^{-1} were attributed to stretching vibrations of the oxadiazole =N–O fragment, in keeping with the data of [8]. Antisymmetric and symmetric vibrations of the nitro group in compounds **IIa**, **IIb**, **IIIa**, **IIIb**, **IVa**, and **IVb** appeared at 1600 and 1300 cm^{-1}, respectively; the difference in their frequencies is 250 cm^{-1} which is smaller by 20 cm^{-1} than the corresponding difference in the spectra of initial azoles **Ia** and **Ib** [9]. These data may be interpreted in terms of a stronger donor effect of the amino group introduced into the nitroethyl fragment. Replacement of one α-nitro group by ethoxycarbonyl leads to further decrease of the difference between the frequencies of antisymmetric and symmetric stretching vibrations of the remaining nitro group in compounds **IIc**, **IId**, **IIIc**, **IIId**, **IVc**, and **IVd** to 215 cm^{-1}; presumably, the reason is weaker electron-withdrawing effect of the ethoxycarbonyl group as compared to nitro group {$\sigma(CO_2Et) = 0.46$, $\sigma(NO_2) = 0.78$ [10]}.

Molecules **II–IV** (**a–d**) consist of three proton-containing fragments. In the ^{1}H NMR spectra of these compounds, protons in the aromatic ring give rise to unresolved multiplets in the δ region 7.52–7.75 ppm. Signals from the methylene protons of the nitroethyl fragment in compounds **IIa**, **IIc**, **IIIa**, **IIIc**, **IVa**, and **IVc** appear at δ 4.02–4.35 ppm. A quartet at δ 4.11–4.44 ppm in the spectra of **IIb**, **IId**, **IIIb**, **IIId**, **-IVb**, and **IVd** was assigned to the CH proton in the bridging moiety. These signals are displaced upfield relative to those typical of initial compounds **Ia–Id** [9, 11]. Signals from the amine residues appeared in the spectra as complex multiplets in a strong field; their position did not contradict the data of [12].

Oxadiazoles **Ia–Ih** reacted with sodium *p*-toluenesulfinate to give the corresponding sulfones **Va–Vh** (Scheme 1). Compounds **Va–Vh** showed in the IR spectra absorption bands due to stretching vibrations of the nitro groups (almost in the same regions as in the spectra of the initial chloro derivatives) and those typical of SO_2 group at 1300 and 1150 cm^{-1} [$\nu_{as}(SO_2)$ and $\nu_s(SO_2)$, respectively]. The ^{1}H NMR spectra of sulfones **Va–Vh** were consistent with the assumed structure; they contained signals from protons in the *p*-tolyl fragment.

Thus the results of the present study showed that the halogen atom in 5-(2-chloro-1-nitroethyl)-1,2,4-oxadiazoles is highly reactive and that it can readily be replaced by amino or sulfonyl group in reactions with piperidine, pyrrolidine, morpholine, or sodium *p*-toluenesulfinate. The resulting compounds may possess practically important properties.

EXPERIMENTAL

The IR spectra were recorded on an IKS-29 spectrophotometer from solutions in chloroform with a concentration of 40 mg/ml (film thickness 0.1 mm). The ^{1}H NMR spectra were measured on a Tesla BS-487C spectrometer (80 MHz) from solutions in acetone-d_6 using HMDS as internal reference. The purity of the products was checked by TLC on Silufol UV-254 plates using acetone–hexane (2:3) as eluent; development with iodine vapor.

Chlorine-containing 5-(1-nitroethyl)-3-phenyl-1,2,4-oxadiazoles **Ia–Id** were synthesized previously according to the procedures described in [9, 11]. Sodium *p*-toluenesulfinate was prepared by reduction of *p*-toluenesulfonyl chloride with zinc in alkaline medium [13].

5-(1-Nitroethyl)-3-phenyl-1,2,4-oxadiazoles II–IV (*general procedure*). A solution of 9 mmol of freshly distilled piperidine, pyrrolidine, or morpholine in 10 ml of anhydrous diethyl ether was added to a solution of 3 mmol of oxadiaxole **Ia–Id** in 20 ml of the same solvent. The mixture was kept for 48 h at 25°C, the precipitate was filtered off, the solvent was removed from the filtrate under reduced pressure, and the residue was subjected to chromatography on a glass column (10×500 mm) charged with activated silica gel (Silicagel 100/400 μm) using benzene (**IIa**, **IIb**, **IIIa**, **IIIb**, **IVa**, **IVb**) or chloroform as eluent (**IIc**, **IId**, **IIIc**, **IIId**, **IVc**, **IVd**).

1-[2,2-Dinitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethyl]piperidine (IIa). Yield 57%, n_D^{20} = 1.5346. ^{1}H NMR spectrum, δ, ppm: 7.52 m (5H, H_{arom}), 4.43 s

(2H, CH_2), 2.73 t (4H, CH_2), 1.52 m (6H, CH_2). Found, %: C 51.53; H 5.07; N 20.09. $C_{15}H_{17}N_5O_5$. Calculated, %: C 51.87; H 4.90; N 20.17.

1-[1-Methyl-2,2-dinitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl]piperidine (IIb). Yield 62%, n_D^{20} = 1.5410. ^{1}H NMR spectrum, δ, ppm: 7.56 m (5H, H_{arom}), 4.44 q (1H, CH), 2.69 t (4H, CH_2), 1.55 d (3H, CH_3), 1.45 m (6H, CH_2). Found, %: C 52.82; H 5.20; N 19.27. $C_{16}H_{19}N_5O_5$. Calculated, %: C 53.19; H 5.26; N 19.39.

Ethyl 2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-piperidinopropanoate (IIc). Yield 55%, n_D^{20} = 1.5535. ^{1}H NMR spectrum, δ, ppm: 7.72 m (5H, H_{arom}), 4.52 q (2H, OCH_2), 4.02 s (2H, CH_2), 2.75 t (4H, CH_2), 1.53 m (6H, CH_2), 1.32 t (3H, CH_3). Found, %: C 57.41; H 5.75; N 14.83. $C_{18}H_{22}N_4O_5$. Calculated, %: C 57.76; H 5.88; N 14.97.

Ethyl 2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-piperidinobutanoate (IId). Yield 55%, n_D^{20} = 1.5580. ^{1}H NMR spectrum, δ, ppm: 7.75 m (5H, H_{arom}), 4.55 q (2H, OCH_2), 4.11 q (1H, CH), 2.73 t (4H, CH_2), 1.50 d (3H, CH_3), 1.46 m (6H, CH_2), 1.35 t (3H, CH_3). Found, %: C 58.36; H 6.25; N 14.19. $C_{19}H_{24}N_4O_5$. Calculated, %: C 58.76; H 6.19; N 14.43.

5-[1,1-Dinitro-2-(1-pyrrolidinyl)ethyl]-3-phenyl-1,2,4-oxadiazole (IIIa). Yield 61%, n_D^{20} = 1.5238. ^{1}H NMR spectrum, δ, ppm: 7.56 m (5H, H_{arom}), 4.35 s (2H, CH_2), 2.75 t (4H, CH_2), 1.63 m (4H, CH_2). Found, %: C 50.08; H 4.55; N 20.84. $C_{14}H_{15}N_5O_5$. Calculated, %: C 50.45; H 4.51; N 21.02.

5-[1,1-Dinitro-2-(1-pyrrolidinyl)propyl]-3-phenyl-1,2,4-oxadiazole (IIIb). Yield 60%, n_D^{20} = 1.5302. ^{1}H NMR spectrum, δ, ppm: 7.54 m (5H, H_{arom}), 4.43 q (1H, CH), 2.76 t (4H, CH_2), 1.64 m (4H, CH_2), 1.53 d (3H, CH_3). Found, %: C 51.75; H 4.86; N 20.03. $C_{15}H_{17}N_5O_5$. Calculated, %: C 51.87; H 4.90; N 20.17.

Ethyl 2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)]-3-(1-pyrrolidinyl)propanoate (IIIc). Yield 53%, n_D^{20} = 1.5424. ^{1}H NMR spectrum, δ, ppm: 7.58 m (5H, H_{arom}), 4.50 q (2H, OCH_2), 4.02 s (2H, CH_2), 2.74 t (4H, CH_2), 1.66 m (4H, CH_2), 1.33 t (3H, CH_3). Found, %: C 56.59; H 5.48; N 15.42. $C_{17}H_{20}N_4O_5$. Calculated, %: C 56.67; H 5.56; N 15.56.

Ethyl 2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)]-3-(1-pyrrolidinyl)butanoate (IIId). Yield 65%, n_D^{20} = 1.5473. ^{1}H NMR spectrum, δ, ppm: 7.54 m (5H, H_{arom}), 4.52 q (2H, OCH_2), 4.12 q (1H, CH), 2.76 t (4H, CH_2), 1.65 m (4H, CH_2), 1.52 d (3H, CH_3), 1.32 t (3H, CH_3). Found, %: C 57.58; H 5.76; N 14.88. $C_{18}H_{22}N_4O_5$. Calculated, %: C 57.76; H 5.88; N 14.97.

4-[2,2-Dinitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethyl]morpholine (IVa). Yield 62%, n_D^{20} = 1.5360. ^{1}H NMR spectrum, δ, ppm: 7.71 m (5H, H_{arom}), 4.35 s (2H, CH_2), 3.58 t (4H, CH_2), 2.74 t (4H, CH_2). Found, %: C 48.05; H 4.23; N 19.02. $C_{14}H_{15}N_5O_6$. Calculated, %: C 48.13; H 4.30; N 20.06.

4-[1-Methyl-2,2-dinitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl]morpholine (IVb). Yield 54%, n_D^{20} = 1.5405. ^{1}H NMR spectrum, δ, ppm: 7.74 m (5H, H_{arom}), 4.42 q (1H, CH), 3.54 t (4H, CH_2), 2.80 t (4H, CH_2), 1.51 d (3H, CH_3). Found, %: C 49.44; H 4.62; N 26.31. $C_{15}H_{17}N_5O_6$. Calculated, %: C 49.59; H 4.68; N 26.45.

Ethyl 3-morpholino-2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)]propanoate (IVc). Yield 55%, n_D^{20} = 1.5549. ^{1}H NMR spectrum, δ, ppm: 7.70 m (5H, H_{arom}), 4.52 q (2H, OCH_2), 4.02 s (2H, CH_2), 3.52 t (4H, CH_2), 2.73 t (4H, CH_2), 1.35 t (3H, CH_3). Found, %: C 54.12; H 5.24; N 14.76. $C_{17}H_{20}N_4O_6$. Calculated, %: C 54.26; H 5.32; N 14.89.

Ethyl 3-morpholino-2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)]butanoate (IVd). Yield 57%, n_D^{20} = 1.5572. ^{1}H NMR spectrum, δ, ppm: 7.72 m (5H, H_{arom}), 4.56 q (2H, OCH_2), 4.11 q (1H, CH), 3.55 t (4H, CH_2), 2.70 t (4H, CH_2), 1.53 d (3H, CH_3), 1.34 t (3H, CH_3). Found, %: C 55.24; H 5.56; N 14.21. $C_{18}H_{22}N_4O_6$. Calculated, %: C 53.38; H 5.64; N 14.36.

3-Phenyl(or methyl)-5-[1-nitro-2-(*p*-tolylsulfonyl)ethyl]-1,2,4-oxadiazoles Va–Vh (*general procedure*). Sodium *p*-toluenesulfinate, 3 mmol, was added in two portions to a solution of 3 mmol of compound **Ia**–**Ih** in 50 ml of anhydrous ethanol. The mixture was stirred for 2 h at 50°C and was left to stand for 48 h at room temperature. The solvent was removed under reduced presure, the residue was treated with diethyl ether (2×10 ml), the extract was evaporated, and the residue was subjected to chromatography on a 10× 500-mm column charged with activated silica gel (Silicagel 100/400 μm) using chloroform as eluent.

2,2-Dinitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-ethyl 4-tolyl sulfone (Va). Yield 48%, mp 135°C. ^{1}H NMR spectrum, δ, ppm: 7.15–7.70 m (9H, H_{arom}), 3.96 s (2H, CH_2), 2.33 s (3H, CH_3). Found, %: C 48.95; H 3.46; N 13.54. $C_{17}H_{14}N_4O_7S$. Calculated, %: C 48.80; H 3.35; N 13.40.

1-Methyl-2,2-dinitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)ethyl 4-tolyl sulfone (Vb). Yield 54%, mp 151°C.

^{1}H NMR spectrum, δ, ppm: 7.12–7.68 m (9H, H_{arom}), 4.10 q (1H, CH), 2.32 s (3H, CH_3), 1.52 d (3H, CH_3). Found, %: C 50.16; H 3.82; N 13.07. $C_{18}H_{16}N_4O_7S$. Calculated, %: C 50.00; H 3.70; N 12.96.

Ethyl 2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-(4-tolylsulfonyl)propanoate (Vc). Yield 50%, mp 120°C. ^{1}H NMR spectrum, δ, ppm: 7.05–7.72 m (9H, H_{arom}), 3.75 s (2H, CH_2), 4.55 q (2H, OCH_2), 2.30 s (3H, CH_3), 1.35 t (3H, CH_3). Found, %: C 54.03; H 4.35; N 9.31. $C_{20}H_{19}N_3O_7S$. Calculated, %: C 53.93; H 4.27; N 9.44.

Ethyl 2-nitro-2-(3-phenyl-1,2,4-oxadiazol-5-yl)-3-(4-tolylsulfonyl)butanoate (Vd). Yield 53%, mp 132°C. ^{1}H NMR spectrum, δ, ppm: 7.12–7.70 m (9H, H_{arom}), 3.83 q (1H, CH), 4.54 q (2H, OCH_2), 2.31 s (3H, CH_3), 1.50 d (3H, CH_3), 1.30 t (3H, CH_3). Found, %: C 55.01; H 4.63; N 9.04. $C_{21}H_{21}N_3O_7S$. Calculated, %: C 54.90; H 4.58; N 9.15.

2-(3-Methyl-1,2,4-oxadiazol-5-yl)-2,2-dinitroethyl 4-tolyl sulfone (Ve). Yield 43%, mp 91–93°C. ^{1}H NMR spectrum, δ, ppm: 7.12–7.65 m ($4H_{arom}$), 3.95 s (2H, CH_2), 2.54 s (3H, CH_3), 2.31 s (3H, CH_3). Found, %: C 40.56; H 3.48; N 15.62. $C_{12}H_{12}N_4O_7S$. Calculated, %: C 40.45; H 3.37; N 15.73.

1-Methyl-2-(3-methyl-1,2,4-oxadiazol-5-yl)-2,2-dinitroethyl 4-tolyl sulfone (Vf). Yield 52%, mp 124°C. ^{1}H NMR spectrum, δ, ppm: 7.10–7.62 m (4H, H_{arom}), 4.05 q (1H, CH), 2.53 s (3H, CH_3), 2.32 s (3H, CH_3), 1.52 d (3H, CH_3). Found, %: C 42.25; H 3.86; N 15.04. $C_{13}H_{14}N_4O_7S$. Calculated, %: C 46.16; H 3.78; N 15.14.

Ethyl 2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-nitro-3-(4-tolylsulfonyl)propanoate (Vg). Yield 40%, mp 79–81°C. ^{1}H NMR spectrum, δ, ppm: 7.10–7.63 m (4H, H_{arom}), 3.76 s (2H, CH_2), 4.52 q (2H, OCH_2), 2.51 s (3H, CH_3), 2.30 s (3H, CH_3), 1.32 t (3H, CH_3). Found, %: C 47.08; H 4.53; N 10.83. $C_{15}H_{17}N_3O_7S$. Calculated, %: C 46.99; H 4.44; N 10.97.

Ethyl 2-(3-methyl-1,2,4-oxadiazol-5-yl)-2-nitro-3-(4-tolylsulfonyl)butanoate (Vh). Yield 51%, mp 104°C. ^{1}H NMR spectrum, δ, ppm: 7.15–7.65 m (4H, H_{arom}), 3.85 q (1H, CH), 4.54 q (2H, OCH_2), 2.50 s (3H, CH_3), 2.31 s (3H, CH_3), 1.51 d (3H, CH_3), 1.30 t (3H, CH_3). Found, %: C 48.46; H 4.68; N 10.49. $C_{16}H_{19}N_3O_7S$. Calculated, %: C 48.36; H 4.79; N 10.58.

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