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**SHORT COMMUNICATIONS**

# Alkylation of Hydroxy Derivatives of 3-(4-Methoxyphenyl)-1,2,4-oxadiazoles with Chloromethyloxirane

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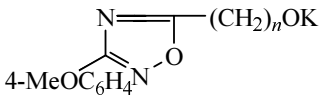
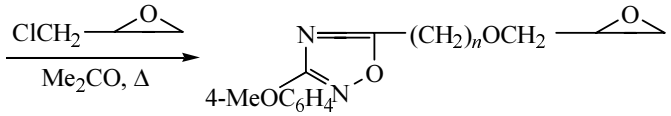
Development of new fresh opportunities for chemical modification of 1,2,4-oxadiazoles attracts considerable attention first of all due to the search for promising approaches to preparation of synthetic analogs of the known physiologically active substances [1] or to revealing new hidden equivalents of pharmacophore groups in the naturally occurring compounds [2]. In particular, incorporation of an oxirane substituent into indole or other fragments followed by cleavage of the oxirane ring in the cycloadducts provided a possibility to prepare a number of β-adrenoblockaders (for instance, Pindolol, Atenolol) possessing high sympathomimetic activity (antianginal, antiarrhythmic, antihypertensive effect) [3]. Taking into consideration that the 1,2,4-oxadiazole ring possesses a wide range of pharmacological activity [4, 5] development of new modified systems including this structure is an urgent task.

Aiming at extending the variety of polyfunctional 1,2,4-oxadiazoles containing valuable biologically active groups and at performing subsequent pharmacological screening we studied the possibility of direct introduction of an oxirane moiety into a number of hydroxy derivatives of 1,2,4-oxadiazoles. The method underlies a reaction

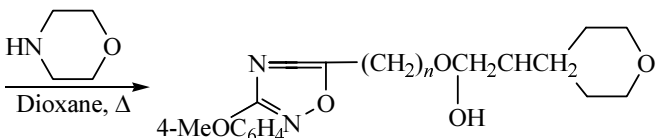



**I, II**




**III, IV**

**III** or **IV**




**V, VI**

$n$ = 0 **(I, III, V),** 1 **(II, IV, VI).**

of chloromethyloxirane with potassium salts of 3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-ol (**I**) or [3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methanol (**II**). We established that alkylation of oxadiazoles **I** and **II** with chloromethyloxirane provided previously unknown 3-(4-methoxyphenyl)-5-(oxiran-2-ylmethoxy)-1,2,4-oxadiazole (**III**) from compound **I** and 3-(4-methoxyphenyl)-5-[(oxiran-2-ylmethoxy)methyl]-1,2,4-oxadiazole (**IV**) from compound **II**.

Reaction products **III** and **IV** were characterized by elemental analysis and $^1$H NMR spectra. Reaction of adducts **III** and **IV** with morpholine in anhydrous dioxane occurred with the cleavage of the oxirane ring in keeping with the Krasusky rule [6] and afforded 1-{[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]oxy}-3-morpholinopropan-2-ol (**V**) or 1-{[3-(4-methoxyphenyl)-1,2,4-oxadiazol-5-yl]methoxy}-3-morpholinopropan-2-ol (**VI**) respectively. The structure of compounds **V** and **VI** was established using IR and $^1$H NMR spectra. The observed direction of recyclization is probably due to the presence of an oxygen exhibiting *–I*-effect at the oxirane ring.

Hence this study resulted in developing of a synthesis of 1,2,4-oxadiazoles connected to an oxirane fragment forming a part of the structure of a number of alkaloids from the atropine group. A possibility is also demonstrated to transform these substances into compounds

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interesting as structural analogs of cardioselective $\beta_1$-adrenoblockaders.

**Reaction of 1,2,4-oxadiazoles I and II with chloromethyloxirane.** To a solution of 10 mmol of compound **I** [7] or **II** [8] in 20 ml of ethanol at 0 ± 5°C was added equimolar quantity of potassium ethylate, the reaction mixture was kept for 0.5 h at 5°C, the precipitate was filtered off, washed with cold ethanol, and dried. Then the potassium salts of oxadiazoles **I** or **II** were dispersed in 100 ml of acetone, and an equimolar amount of chloromethyloxirane was added. The reaction mixture was heated at reflux for 5 h, the precipitate was filtered off, the solvent was evaporated, and the residue was subjected to chromatography on a column (10 × 500 mm) packed with activated silica gel of the grade Silicagel 100/400m, eluent for compounds **III** and **IV** benzene.

**3-(4-Methoxyphenyl)-5-(oxiran-2-ylmethoxy)-1,2,4-oxadiazole (III).** Yield 78%, $n_D^{20}$ 1.4860. $^1$H NMR spectrum, δ, ppm: 2.67 d ($CH_2$), 3.04 m (CH), 3.82 s ($CH_3O$), 4.45 d ($CH_2$), 7.82–6.93 m ($C_6H_4$). Found, %: C 57.82; H 4.64; N 11.05. $C_{12}H_{12}N_2O_4$. Calculated, %: C 58.06; H 4.84; N 11.29.

**3-(4-Methoxyphenyl)-5-[(oxiran-2-ylmethoxy)-methyl]-1,2,4-oxadiazole (IV).** Yield 74%, $n_D^{20}$ 1.4820. $^1$H NMR spectrum, δ, ppm: 2.65 d ($CH_2$), 3.05 m (CH), 3.80 s ($CH_3O$), 4.43 d ($CH_2$), 4.66 s ($CH_2$), 7.80–6.92 m ($C_6H_4$). Found, %: C 59.26; H 5.17; N 10.48. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.34; N 10.69.

**Reaction of 3-(4-methoxyphenyl)-5-(oxiran-2-ylmethoxy)-1,2,4-oxadiazoles (III and IV) with morpholine.** To a solution of 5 mmol of oxadiazole **III** or **IV** in 50 ml of anhydrous dioxane was added 5 mmol of freshly distilled morpholine, the reaction mixture was heated on a water bath for 6 h. The solvent was evaporated under reduced pressure, the residue was subjected to chromatography as described above, eluent chloroform.

**1-{[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-oxy}-3-morpholinopropan-2-ol (V).** Yield 56%, $n_D^{20}$ 1.5340. IR spectrum, ν, cm$^{-1}$: 3530 (OH). $^1$H NMR spectrum, δ, ppm: 2.75 t ($CH_2$), 3.18 d ($CH_2$), 3.56 t ($CH_2$), 3.80 s ($CH_3O$), 4.46 d ($CH_2$), 4.78 m (CH), 5.23 d (OH), 7.78–6.90 m ($C_6H_4$). Found, %: C 57.13; H 6.08; N 12.35. $C_{16}H_{21}N_3O_5$. Calculated, %: C 57.31; H 6.27; N 12.54.

**1-{[3-(4-Methoxyphenyl)-1,2,4-oxadiazol-5-yl]-methoxy}-3-morpholinopropan-2-ol (VI).** Yield 58%, $n_D^{20}$ 1.5356. IR spectrum, ν, cm$^{-1}$: 3530 (OH). $^1$H NMR spectrum, δ, ppm: 2.74 t ($CH_2$), 3.15 d ($CH_2$), 3.53 t ($CH_2$), 3.82 s ($CH_3O$), 4.45 d ($CH_2$), 4.68 C ($CH_2$), 4.77 m (CH), 5.21 d (OH), 7.80–6.90 m ($C_6H_4$). Found, %: C 58.24; H 6.41; N 11.84. $C_{17}H_{23}N_3O_5$. Calculated, %: C 58.45; H 6.59; N 12.03.

IR spectra were recorded on spectrophotometer IKS-29 from solutions in chloroform. $^1$H NMR spectra were registered on spectrometer Tesla BS-487C (80 MHz) in acetone-$d_6$, internal reference HMDS.

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