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Rapid Boulton–Katritzky rearrangement of 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles upon exposure to water and HCl

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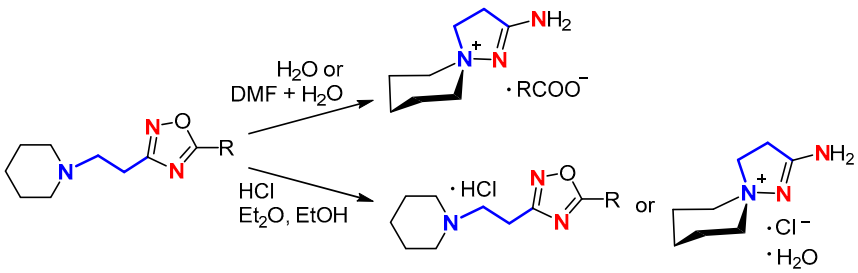


R = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-ClC$_6$H$_4$

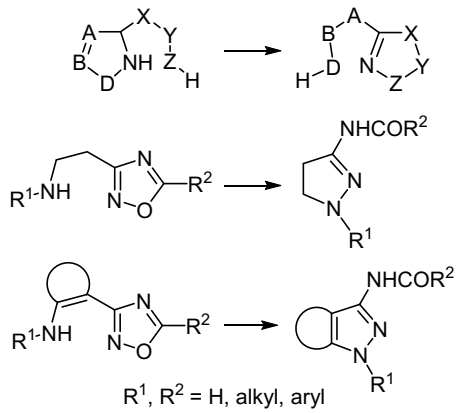
Chemical stability of 3-(2-aminoethyl)-5-substituted 1,2,4-oxadiazoles was studied with respect to Boulton–Katritzky rearrangement, which is known to produce planar pyrazolines and pyrazoles upon heating in DMF at 150°C or without solvent at 240°C. The reactivity of 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles in one type of Boulton–Katritzky rearrangement was observed at room temperature in H_2O, DMF + H_2O, and in the presence of HCl. Hydrolysis of 3,5-disubstituted 1,2,4-oxadiazoles under the first two conditions gave 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates, while the action of HCl on 3,5-disubstituted 1,2,4-oxadiazoles produced their hydrochlorides along with 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate. Thus, the reaction afforded spiropyrazoline compounds instead of products with a planar structure.

Keywords: 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles, spiropyrazolines, Boulton–Katritzky rearrangement, hydrolysis, tendency to regroup.

Our recent interest in 3,5-substituted 1,2,4-oxadiazoles has been motivated by their local anesthetic and antituberculosis properties,[1,2] as well as by some evidence of their antidiabetic activity.[3] Thus, the chemical stability of 1,2,4-oxadiazoles is an area of increased interest. The conversion of these heterocycles *via* Boulton–Katritzky rearrangement, which depends on structural and external factors, has been actively studied. Mononuclear heterocyclic Boulton–Katritzky rearrangement occurs upon heating according to the scheme ABD → XYZ (Scheme 1).[4]

Substituted 1,2,4-oxadiazoles undergo the Boulton–Katritzky rearrangement under forcing conditions (in DMF at 150°C or without solvent at 240°C), forming pyrazolines and pyrazoles with planar structures.[5] The electronic

Scheme 1



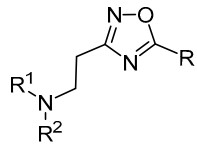
R^1, R^2 = H, alkyl, aryl

properties of aromatic substituents have been reported to affect the Boulton–Katritzky rearrangement of 3-(2-aminoaryl)-1,2,4-oxadiazoles to 3-(acylamino)-1*H*-indazoles to the same extent as the thermal conditions. To avoid the effects of thermal factors in the preparation of rearranged 3-(acylamino)-1*H*-indazoles, reaction conditions including microwave irradiation have been used.[6] Thermal rearrangement of *N*-(1,2,4-oxadiazol-3-yl)hydrazones to 1,2,4-triazole derivatives provided the first example of a triatomic side chain rearrangement involving the NNC sequence of atoms attached to the C-3 atom of 1,2,4-oxadiazoles. The reactions were performed in the absence of solvents and gave high yields of the final products.[7]

Conversion of the (*Z*)-hydrazone of 3-benzoyl-5-phenyl-1,2,4-oxadiazole into the respective triazole was experimentally investigated in aqueous dioxane over the pS^+ range of 5.5(5)–13.9 (pS^+ is an operational proton concentration scale used in dioxane–water).[8a] The uncatalyzed reaction was examined by quantum-chemical calculations according to DFT, using a model system formed by the (*Z*)-hydrazone of 3-formyl-1,2,4-oxadiazole and one or two water molecules. The solvent effects were taken into account by using COSMO (conductor-like screening model) – a continuum model approach for determining the electrostatic interaction of a molecule with solvent.[8b] The course of photochemical Boulton–Katritzky rearrangement was examined depending on structural modifications in the substrate molecules ((*E*)- or (*Z*)-isomers of the arylhydrazones), the influence of substituents in the arylhydrazone moiety, and the substituents at the C-5 atom of the 1,2,4-oxadiazole ring.[9]

The rearrangement rates of eleven (*Z*)-arylhydrazones derived from 5-amino-3-benzoyl-1,2,4-oxadiazole into the respective (2-aryl-5-phenyl-2*H*-1,2,3-triazol-4-yl)ureas were determined in toluene and in aqueous dioxane in the presence of trichloroacetic acid or piperidine at 40°C. The results of acidic catalysis by trichloroacetic acid in both solvents were correlated with the effects of aryl substituents according to the Ingold–Yukawa–Tsuno correlation. When base catalysis by piperidine was used in toluene or aqueous dioxane, a Hammet correlation was observed.[10] A variation of the Boulton−Katritzky rearrangement involving the use of a CNC side chain has been reported, where 3-benzoyl-1,2,4-oxadiazole imines in the presence of strong base afforded novel 4(5)-acylaminoimidazoles.[11]

Previously, we synthesized a series of 5-aryl-3-(2-aminoethyl)-1,2,4-oxadiazoles (Fig. 1). These compounds were apparently stable during the isolation, purification, physicochemical and spectral characterization, as well as storage.[12–15] The molecular structure of a representative member of this series (3-(2-benzimidazol-1-yl)ethyl-5-phenyl-1,2,4-oxadiazole) was confirmed by X-ray structural analysis.[16]

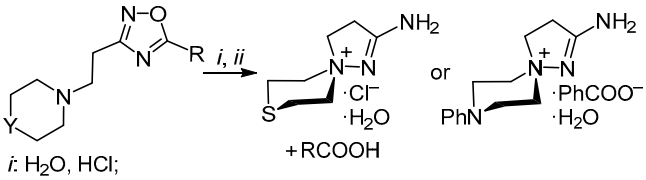


R = 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, Ph, 4-BrC$_6$H$_4$, 3-ClC$_6$H$_4$;
R^{1}R^{2}N = piperidin-1-yl, morpholin-1-yl, benzimidazol-1-yl, thiomorpholin-1-yl, 4-phenylpiperazin-1-yl

Figure 1. Series of 5-aryl-3-(2-amino)ethyl-1,2,4-oxadiazoles.

During our attempts to obtain hydrochlorides of 5-aryl-3-[2-(thiomorpholin-1-yl)ethyl]-1,2,4-oxadiazoles and to grow a single crystal for performing X-ray structural analysis of 5-phenyl-3-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2,4-oxadiazole by prolonged keeping in 2-PrOH in the presence of air moisture we occasionally observed the lability of the investigated 1,2,4-oxadiazoles (Scheme 2).[17,18] Thus, 3-(2-aminoethyl)-5-aryl-1,2,4-oxadiazoles having tertiary amino groups at the β-position of substituent located at the ring position 3 were capable of rearranging to spiropyrazoline compounds. These transformations provided the first examples of spiro compound formation through such rearrangements and could be regarded as a variety of Boulton–Katritzky rearrangement.

Scheme 2

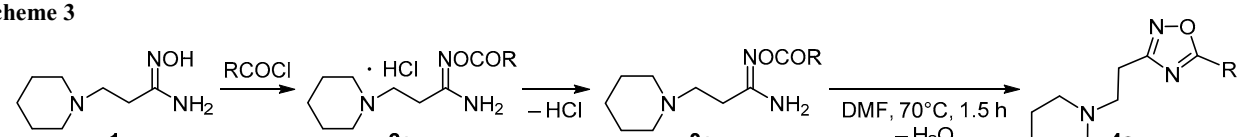


i: H$_2$O, HCl;
Y = S; R = Ph, 4-MeOC$_6$H$_4$, 4-MeC$_6$H$_4$, 4-BrC$_6$H$_4$, 3-ClC$_6$H$_4$;
ii: 2H$_2$O; Y = PhN; R = Ph

In the present work, the Boulton–Katritzky rearrangement of 3,5-disubstituted 1,2,4-oxadiazoles was performed by using the example of 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles **4a**–**e**. 1,2,4-Oxadiazoles **4a**–**e** as crystalline precipitates were obtained by heating of *O*-aroyl-(2-piperidin-1-yl)propioamidoximes **3a**–**e** in DMF at 70°C. An additional amount of products **4a**–**e** were isolated after evaporating of the solvent under oil pump vacuum and treating the residue with acetone (Scheme 3). The synthesis of the starting compounds **1**, **2a**–**e**, **3a**–**e**, and 1,2,4-oxadiazoles **4a**–**e** has been described earlier, where compounds **4a**–**e** were obtainted by dehydration of *O*-aroyl-(2-piperidin-1-yl)propioamidoximes **3a**–**e** by heating in DMF in the presence of molecular sieves.[12]

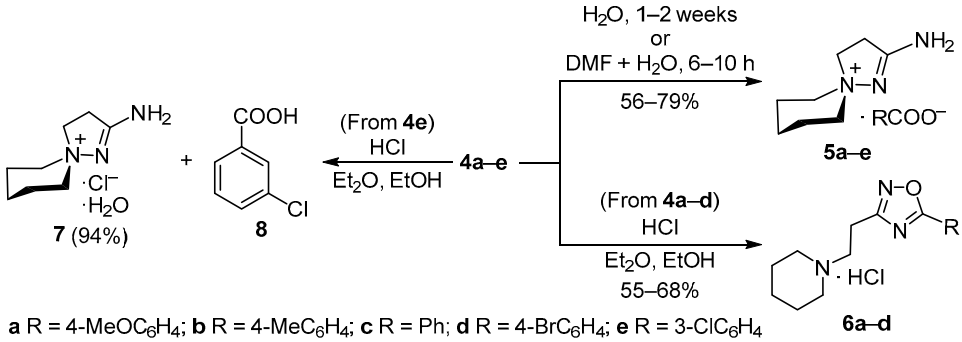
IR spectra of compounds **4a**–**e** contained absorption bands at 1595–1600 (C=C) and 1662–1664 cm^{-1} (C=N). Compounds **4a**–**e** also exhibited absorption at 1358–

Scheme 3



a R = 4-MeOC$_6$H$_4$, **b** R = 4-MeC$_6$H$_4$, **c** R = Ph, **d** R = 4-BrC$_6$H$_4$, **e** R = 3-ClC$_6$H$_4$

Scheme 4



1377 cm^{-1} (C–O), which is a characteristic feature of 1,2,4-oxadiazoles. ^{1}H NMR spectra of 1,2,4-oxadiazoles **4a**–**e** showed peaks in the range of 3.12–3.14 and 3.82 ppm (triplets of α- and β-methylene groups), as well as 3.30–3.36 and 3.42–3.50 ppm (multiplets of two methylene groups bonded to the nitrogen atom of the piperidine heterocycle). Each of the latter signals can be attributed to the axial and equatorial protons of the heterocycle, differentiated by the slow inversion of piperidine ring during the acquisition of NMR spectra.

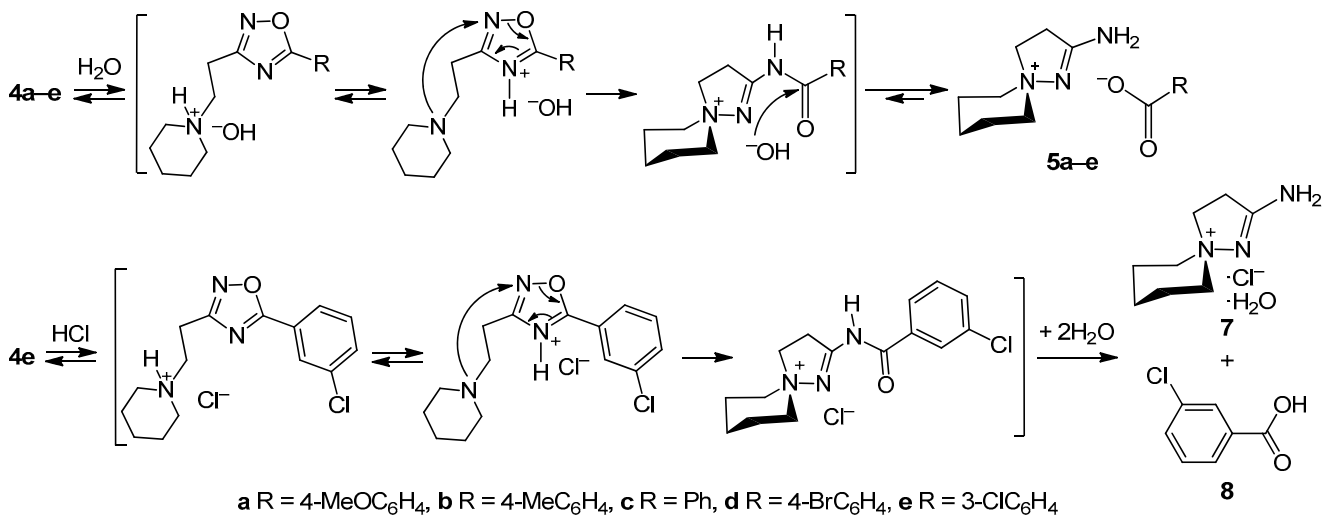
We investigated the behavior of 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles **4a**–**e** in Boulton–Katritzky rearrangement at 25°C in the following media: H_2O, DMF–H_2O, 10:1, and HCl in ether. The transition from 1,2,4-oxadiazoles **4a**–**c** with electron-donating substituents or an unsubstituted phenyl ring to 1,2,4-oxadiazoles **4d**,**e** with electron-withdrawing substituents occurs with a shortening of the regrouping time from 2 weeks to 1 week in the method I and from 10 to 6 h in the method II.

The physicochemical and spectral characteristics of the obtained products, as well as the X-ray diffraction data (see below) indicated that in H_2O and DMF–H_2O 1,2,4-oxadiazoles **4a**–**e** were converted to spiropyrazolines **5a**–**e**, but in ethereal HCl only compound **4e** was converted to spiropyrazoline **7**, while 1,2,4-oxadiazoles **4a**–**d** were recovered in the form of hydrochlorides **6a**–**d**. Spiropyrazolines **5a**–**e** contained the respective benzoate anions, and compound **7** contained chloride as a counterion to the quaternary ammonium cation (Scheme 4).

The formation of compounds **5a**–**e**, **7** can be represented as a series of protonation, proton transfer, and nucleophilic attack steps, effectively constituting hydrolysis during the reaction of 1,2,4-oxadiazoles **4a**–**e** with water and wet HCl (Scheme 5). The comparison of benzoates **5a**–**e** with 1,2,4-oxadiazoles **4a**–**e** revealed that the former have higher melting points (mp 216–238°C) and R_f 0.58–0.78, compared to the latter – mp 206–230°C and R_f 0.47–0.65.

The main distinguishing feature in IR spectra of spiro compounds **5a**–**e** and **7** compared to the IR spectra of 1,2,4-oxadiazoles **4a**–**e** was the presence of symmetric and asymmetric ν(N–H) stretching bands at 3300 and 3500 cm^{-1}, respectively. IR spectrum of chloride hydrate **7** did not contain the characteristic ν(C–O) absorption band of 1,2,4-oxadiazoles at 1358–1377 cm^{-1}. ^{1}H NMR spectra of benzoates **5a**–**e** differed from the spectra of 1,2,4-oxadiazoles **4a**–**e** by the presence of NH_2 proton signal with the integral of 2H at 7.42–7.70 ppm. ^{1}H NMR spectra of 1,2,4-oxadiazole hydrochlorides **6a**–**d** featured the NH^+ proton signals at 12.63–13.20 ppm. ^{1}H NMR spectrum of spiro compound **7** contained the expected proton signals, and no aromatic proton signals were observed. 3-Chlorobenzoic acid (**8**) precipitated during the evaporation of mother liquors obtained after chloride hydrate **7** was collected by filtration.

Scheme 5



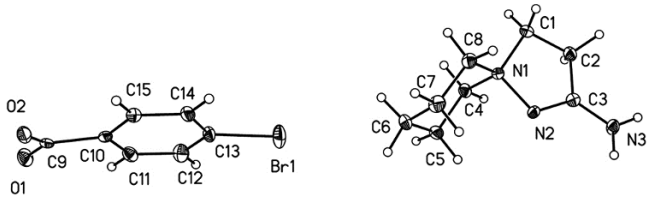


Figure 2. Molecular structure of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromobenzoate (**5d**) with atoms represented by thermal vibration ellipsoids of 50% probability.

After recrystallization of compounds **4a**–**e** from 2-PrOH, only in one case a crystal suitable for X-ray structural analysis could be grown over 9 months. It turned out that a rearrangement and the inclusion of one water molecule in the structure of the resulting spiropyrazoline 4-bromobenzoate occurred, giving hydrate **5d** (Fig. 2). The location of all hydrogen atoms allowed to unambiguously confirm that this structure is a salt, namely, 2-amino-1,5-diazaspiro-[4.5]dec-1-en-5-ium 4-bromobenzoate. It crystallized in chiral space group $P2_1$, and Flack 0.018(6) indicated the correctness of its absolute configuration. The six- and five-membered rings of this cation adopted the conformations of chair and envelope, respectively. The deviation of the C(1) atom from the mean plane of five-membered ring was equal to 0.446(5) Å. The positive charge located on the N(1) atom caused elongation of C(1)–N(1) and N(1)–N(2) bonds compared to the average values for single bonds, which was previously also observed for 2-amino-8-thia-1-aza-5-azoniaspiro[4.5]dec-1-ene,[17] for 1-(*tert*-butyl)-4,5-dihydro-1*H*-pyrazol-1-ium,[19] and for 1,1,3-trimethyl-Δ^2-pyrazolinium ions.[20]

It would be reasonable to assume that the high anti-tuberculosis activity of water-soluble 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles **4a**,**b**,**d** previously observed during prolonged *in vitro* screening experiments was actually due to the rearranged 2-amino-1,5-diazaspiro[4.5]-dec-1-en-5-ium benzoates **5a**,**b**,**d**.[21]

According to the obtained experimental data, the following conclusions can be reached: electron-withdrawing substituents in the phenyl ring accelerate the rearrangement in the series of 5-aryl-3-[2-(piperidin-1-yl)-ethyl]-1,2,4-oxadiazoles; hydrolysis in ethereal HCl occurs immediately, while hydrolysis in DMF–H_2O, 10:1, was faster than in H_2O. Finally, 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles are generally unstable in the presence of acids and bases at room temperature. Thus, there is a significant probability that rearranged products may be present during biological screening experiments with the compounds of this series.

Experimental

IR spectra were obtained on a Thermo Scientific Nicolet 5700 FTIR instrument in KBr pellets. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance III 500 MHz NMR spectrometer (500 and 126 MHz, respectively). The signals of DMSO-d_6 were used as internal reference for ^{1}H NMR (2.50 ppm) and ^{13}C NMR (39.5 ppm) spectra. Elemental analysis was carried out on a CE440 elemental analyzer (Exeter Analytical, Inc., China). Melting points were determined in glass capillaries on a PTP(M) apparatus (Khimlabpribor, Russia). The reaction progress and purity of the obtained products were controlled using Sorbfil (Sorbpolymer, Russia) TLC plates coated with CTX-1A silica gel, grain size 5–17 μm, containing UV-254 indicator. The eluent for TLC analysis was mixture benzene–EtOH, 1:3. The reagents were purchased from different chemical suppliers and were purified before use. The solvents for synthesis, recrystallization, and TLC analysis (ethanol, 2-PrOH, benzene, DMF, acetone, diethyl ether) were purified according to the standard techniques.

5-Aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles have been synthesized earlier.[12]

Dehydration of *N*'-[(aryloxycarbonyl)oxy]-3-(piperidin-1-yl)propanimidamides 3a–e to 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles 4a–e.

5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (4a). A solution of *N*'-{[(4-methoxyphenoxy)-carbonyl]oxy}-3-(piperidin-1-yl)propanimidamide (**3a**) (1.04 g, 3.410 mmol) in dry DMF (10 ml) was heated on an oil bath at 70°C for 1.5 h with TLC control. The obtained crude precipitate of compound **4a** (0.36 g, 1.183 mmol) was filtered at room temperature, and the filtrate was evaporated to dryness under oil pump vacuum at 50°C/ 1 mmHg. The organic residue was treated with dry acetone (10 ml). An additional quantity of 1,2,4-oxadiazole (**4a**) (0.44 g, 1.531 mmol) was collected by filtration. The combined portions of crude compound **4a** were recrystallized from 2-PrOH. Yield 0.50 g (51%), colorless solid, mp 222–224°C, R_f 0.60. IR spectrum, ν, cm^{-1}: 1662 (C=N), 1598 (C=N), 1560 (C=C), 1363 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.60 (2H, m), 1.70–1.78 (2H, m), and 1.85–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.13 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.35 ($2H_{eq}$, m) and 3.43–3.47 ($2H_{ax}$, m, $N(CH_2)_2$); 3.72 (3H, s, *p*-CH_3O); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 6.75 (2H, d, *J* = 8.7, *o*-H Ar); 7.74 (2H, d, *J* = 8.7, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.4; 55.4; 60.7; 64.3; 112.4; 130.9; 135.1; 159.8; 168.6; 168.7. Found, %: C 66.53; H 7.42. $C_{16}H_{21}N_3O_2$. Calculated, %: C 66.88; H 7.37.

3-[2-(Piperidin-1-yl)ethyl]-5-(*p*-tolyl)-1,2,4-oxadiazole (4b) was obtained analogously to compound **4a** from 3-(piperidin-1-yl)-*N*'-{[(*p*-tolyloxy)carbonyl]oxy}propanimidamide (**3b**) (1.30 g, 4.498 mmol) in dry DMF (10 ml). Yield 0.86 g (71%), colorless solid, mp 219–220°C, R_f 0.65. IR spectrum, ν, cm^{-1}: 1662 (C=N), 1595 (C=N), 1550 (C=C), 1359 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.60 (2H, m), 1.69–1.77 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 2.27 (3H, s, *p*-$CH_3$); 3.14 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.30–3.35 ($2H_{eq}$, m) and 3.42–3.50 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0 $C\underline{H}_2N(CH_2)_2$); 7.01 (2H, d, *J* = 8.0, *o*-H Ar); 7.70 (2H, d, *J* = 8.0, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.3; 21.9; 31.5; 60.7; 64.3; 127.9; 129.5; 137.4; 139.7; 168.6; 168.9. Found: C 70.53; H 7.42. $C_{16}H_{21}N_3O$. Calculated, %: C 70.82; H 7.80.

5-Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (4c) was obtained analogously to compound **4a** from *N*'-[(phenoxycarbonyl)oxy]-3-(piperidin-1-yl)propanimidamide (**3c**) (0.73 g, 2.652 mmol) in dry DMF (5 ml). Yield

0.29 g (43%), colorless solid, mp 205–206°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 1663 (C=N), 1598 (C=N), 1553 (C=C), 1377 (C–O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.60 (2H, m), 1.70–1.78 (2H, m), and 1.85–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.36 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.23–7.81 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.6; 60.7; 127.4; 128.4; 129.4; 168.6; 168.9. Found, %: C 70.29; H 7.39. $C_{15}H_{19}N_3O$. Calculated: C 70.01; H 7.44.

5-(4-Bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (4d) was obtained analogously to compound **4a** from *N*'-{[(4-bromophenoxy)carbonyl]oxy}-3-(piperidin-1-yl)propanimidamide (**3d**) (0.98 g, 2.770 mmol) in dry DMF (10 ml). Yield 0.66 g (71%), colorless solid, mp 228–230°C, R_f 0.47. IR spectrum, ν, cm^{-1}: 1662 (C=N), 1598 (C=N), 1547 (C=C), 1358 (C–O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.61 (2H, m), 1.69–1.77 (2H, m), and 1.83–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.35 ($2H_{eq}$, m) and 3.42–3.49 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.41 (2H, d, *J* = 8.0, *o*-H Ar); 7.74 (2H, d, *J* = 8.0, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.5; 60.7; 64.3; 122.1; 130.2; 131.6; 141.4; 167.7; 168.6. Found, %: C 53.71; H 5.46. $C_{15}H_{18}BrN_3O$. Calculated, %: C 53.58; H 5.40.

5-(3-Chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (4e) was obtained analogously to compound **4a** from *N*'-{[(3-chlorophenoxy)carbonyl]oxy}-3-(piperidin-1-yl)propanimidamide (**3e**) (3.94 g, 1.272 mmol) in dry DMF (15 ml). Yield 2.97 g (80%), colorless solid, mp 207–208°C, R_f 0.56. IR spectrum, ν, cm^{-1}: 1664 (C=N), 1600 (C=N), 1557 (C=C), 1360 (C–O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.61 (2H, m), 1.70–1.77 (2H, m), and 1.84–1.91 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.30–3.35 ($2H_{eq}$, m) and 3.44–3.49 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.25–7.78 (4H, m, C_6H_4Cl-*m*). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 127.8; 128.2; 129.2; 129.3; 132.4; 144.6; 167.1; 168.6. Found, %: C 61.71; H 6.46. $C_{15}H_{18}ClN_3O$. Calculated, %: C 61.75; H 6.22.

Hydrolysis of 5-aryl-3-[(2-piperidin-1-yl)ethyl]-1,2,4-oxadiazoles 4a–e in H_2O and in DMF–H_2O to form 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoates 5a–e.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-methoxybenzoate (5a). Method I. 5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4a**) (0.5 g, 1.740 mmol) was dissolved in distilled water (5 ml). The solution was left at room temperature with daily TLC control. After hydrolysis for 2 weeks, the aqueous solution was concentrated under water aspirator vacuum. The organic residue was treated with diethyl ether (10 ml). The hydrolysis product was collected by filtration as a white precipitate, then recrystallized from 2-PrOH. Yield 0.40 g (75%), colorless solid, mp 230–232°C, R_f 0.78. IR spectrum, ν, cm^{-1}: 3500 (NH_2 as), 3300 (NH_2 sy), 1663 (C=N), 1599 (C=C), 1551 (COO^- sy), 1363 (COO^- as). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.60 (2H, m), 1.68–1.78 (2H, m), and 1.82–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.14 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.29–3.36 ($2H_{eq}$, m) and 3.42–3.49 ($2H_{ax}$, m, $N(CH_2)_2$); 3.73 (3H, s, *p*-CH_3O); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 6.75 (2H, d, *J* = 8.7, *o*-H Ar); 7.45 (2H, br. s, NH_2); 7.74 (2H, d, *J* = 8.7, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.4; 55.4; 60.7; 64.3; 112.5; 130.9; 134.7; 160.0; 168.9. Found, %: C 63.11; H 7.30. $C_{16}H_{23}N_3O_3$. Calculated, %: C 62.93; H 7.59.

Method II. 5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)-ethyl]-1,2,4-oxadiazole (**4a**) (0.5 g, 1.740 mmol) was dissolved in DMF (5 ml) and distilled water (0.5 ml). The solution was left at room temperature and checked by TLC at the intervals of 1 h. After hydrolysis for 10 h, the reaction solution was concentrated under water aspirator vacuum and the organic residue was treated with diethyl ether (10 ml). Product **5a** was collected by filtration as a white precipitate, then recrystallized from 2-PrOH. Yield 0.35 g (66%), colorless solid, mp 230–232°C, R_f 0.78. Found, %: C 63.25; H 7.80. $C_{16}H_{23}N_3O_3$. Calculated, %: C 62.93; H 7.59.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-methylbenzoate (5b) was obtained analogously to compound **5a** from 3-[2-(piperidin-1-yl)ethyl]-5-(*p*-tolyl)-1,2,4-oxadiazole (**4b**) (0.5 g, 1.843 mmol). Method I (2 weeks). Yield 0.34 g (64%), colorless solid, mp 227–228°C, R_f 0.75. IR spectrum, ν, cm^{-1}: 3500 (NH_2 as), 3320 (NH_2 sy), 1663 (C=N), 1599 (C=C), 1550 (COO^- sy), 1368 (COO^- as). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.60 (2H, m), 1.70–1.80 (2H, m), and 1.82–1.93 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.13 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.29–3.36 ($2H_{eq}$, m) and 3.41–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.73 (3H, s, *p*-CH_3); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 6.75 (2H, d, *J* = 8.7, *o*-H Ar); 7.44 (2H, br. s, NH_2); 7.70 (2H, d, *J* = 8.7, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 20.1; 22.0; 31.6; 55.4; 60.2; 64.4; 112.6; 130.9; 134.7; 160.0; 168.3. Found, %: C 66.52; H 7.55. $C_{16}H_{23}N_3O_2$. Calculated, %: C 66.41; H 8.01.

Method II (10 h). Yield 0.30 g (56%), colorless solid, mp 227–228°C, R_f 0.75. Found, %: C 66.72; H 8.25. $C_{16}H_{23}N_3O_2$. Calculated, %: C 66.41; H 8.01.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium benzoate (5c) was obtained analogously to compound **5a** from 5-phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4c**) (0.5 g, 1.943 mmol). Method I (2 weeks). Yield 0.39 g (73%), colorless solid, mp 220–222°C, R_f 0.70. IR spectrum, ν, cm^{-1}: 3510 (NH_2 as), 3436 (NH_2 sy), 1663 (C=N), 1598 (C=C), 1554 (COO^- sy), 1377 (COO^- as). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.60 (2H, m), 168–1.77 (2H, m), and 1.83–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.13 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.30–3.35 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.45 (2H, br. s, NH_2); 7.24–7.82 (5H, m, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.5; 60.7; 64.3; 127.4; 130.4; 131.8; 132.2; 167.0; 168.5. Found, %: C 64.95; H 7.30. $C_{15}H_{21}N_3O_2$. Calculated, %: C 65.43; H 7.69.

Method II (10 h). Yield 0.30 g (56%), colorless solid, mp 220–222°C, R_f 0.70. Found, %: C 65.35; H 7.45. $C_{15}H_{21}N_3O_2$. Calculated, %: C 65.43; H 7.69.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromobenzoate (5d) was obtained analogously to compound **5a** from 5-(4-bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4d**) (0.5 g, 1.487 mmol). Method I (1 week).

Yield 0.39 g (74%), colorless solid, mp 237–238°C, R_f 0.58. IR spectrum, ν, cm^{-1}: 3480 (NH_2 as), 3320 (NH_2 sy), 1664 (C=N), 1595 (C=C), 1550 (COO^- sy), 1359 (COO^- as). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.61 (2H, m), 1.70–1.80 (2H, m), and 1.82–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.29–3.36 ($2H_{eq}$, m) and 3.41–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.41 (2H, d, *J* = 7.0, *o*-H Ar); 7.60 (2H, br. s, NH_2); 7.75 (2H, d, *J* = 7.0, *m*-H Ar). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 122.2; 130.3; 131.6; 141.3; 167.8; 168.6. Found, %: C 50.78; H 5.31. $C_{15}H_{20}BrN_3O_2$. Calculated, %: C 50.86; H 5.69.

Method II (6 h). Yield 0.30 g (57%), mp 237–238°C, R_f 0.58. Found, %: C 50.65; H 5.87. $C_{15}H_{20}BrN_3O_2$. Calculated, %: C 50.86, H 5.69.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 3-chlorobenzoate (5e) was obtained analogously to compound **5a** from 5-(3-chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4e**) (0.5 g, 1.714 mmol). Method I (1 week). Yield 0.41 g (77%), colorless solid, mp 214–216°C, R_f 0.68. IR spectrum, ν, cm^{-1}: 3350 (NH_2 as), 3340 (NH_2 sy), 1664 (C=N), 1599 (C=C), 1557 (COO^- sy), 1377 (COO^- as). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.51–1.61 (2H, m), 1.70–1.79 (2H, m), and 1.83–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.11 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.35 ($2H_{eq}$, m) and 3.43–3.47 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.27–7.77 (4H, m, C_6H_4Cl-*m*); 7.42 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.0; 22.0; 31.5; 60.7; 64.3; 127.8; 128.1; 129.2; 129.3; 132.4; 144.9; 166.9; 168.6. Found, %: C 58.56; H 6.14. $C_{15}H_{20}ClN_3O_2$. Calculated, %: C 58.16; H 6.51.

Method II (6 h). Yield 0.42 g (79%), colorless solid, mp 214–216°C, R_f 0.68. Found, %: C 58.55; H 6.35. $C_{15}H_{20}ClN_3O_2$. Calculated, %: C 58.16; H 6.51.

Action of ethereal HCl solution on 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazoles 4a–e to form 5-aryl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochlorides 6a–d or 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (7) and 3-chlorobenzoic acid (8).

5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (6a). 5-(4-Methoxyphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4a**) (0.3 g, 1.044 mmol) was dissolved in a minimum amount of absolute ethanol. Then ethereal HCl solution was added dropwise to pH 2. The resultant white precipitate was triturated with a glass rod and filtered through a micro funnel. Double volume of ether was added to the filtrate. The white precipitate was collected by filtration and combined with the first precipitate. After recrystallization from 2-PrOH, 5-(4-methoxyphenyl)-3-[2-(piperidin-1-yl)-ethyl]-1,2,4-oxadiazole hydrochloride (**6a**) was isolated. Yield 0.23 g (68%), white opaque powder, mp 168–170°C, R_f 0.63. IR spectrum, ν, cm^{-1}: 2850–2450 (N^+–H), 1685 (C=N), 1604 (C=C), 1261 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.62 (2H, m), 1.70–1.80 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.10 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.32–3.38 (4H, m, $N(CH_2)_2$); 3.47 (2H, t, *J* = 7.0, $CH_2C\underline{H}_2N(CH_2)_2$); 3.82 (3H, s, *p*-$CH_3O$); 7.01 (2H, d, *J* = 7.0, *o*-H Ar) and 7.89 (2H, d, *J* = 7.0, *m*-H Ar); 12.63 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9 (2C); 31.5 (2C); 55.9; 60.7; 64.3; 114.3, 123.4, 131.8, 163.5 (6C); 167.4; 168.5. Found, %: C 59.81; H 7.30. $C_{16}H_{22}ClN_3O_2$. Calculated, %: C 59.35; H 6.85.

5-(4-Methylphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (6b) was obtained analogously to compound **6a** from 5-(4-methylphenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4b**) (0.3 g, 1.106 mmol). Yield 0.19 g (56%), white opaque powder, mp 165–168°C, R_f 0.60. IR spectrum, ν, cm^{-1}: 2800–2480 (N^+–H), 1664 (C=N), 1603 (C=C), 1320 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.48–1.63 (2H, m), 1.71–1.81 (2H, m), and 1.83–1.91 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.12 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.33–3.39 (4H, m, $N(CH_2)_2$); 3.47 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.70 (2H, d, *J* = 7.0, *o*-H Ar); 7.90 (2H, d, *J* = 7.0, *m*-H Ar); 13.20 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.2; 22.0; 23.5; 31.6; 60.8; 64.5; 113.4; 123.5; 130.5; 163.5; 167.8; 169.2. Found, %: C 62.72; H 7.45. $C_{16}H_{22}ClN_3O$. Calculated, %: C 62.43; H 7.20.

5-Phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (6c) was obtained analogously to compound **6a** from 5-phenyl-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4c**) (0.3 g, 1.167 mmol). Yield 0.19 g (55%), white opaque powder, mp 237–240°C, R_f 0.57. IR spectrum, ν, cm^{-1}: 2900–2480 (N^+–H), 1664 (C=N), 1603 (C=C), 1321 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.69 (2H, m), 1.72–1.82 (2H, m), and 1.83–1.91 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 2.35 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.32–3.38 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.25–7.83 (5H, m, C_6H_5); 13.18 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.7; 60.9; 64.5; 127.4; 128.4; 129.6; 143.0; 168.7; 169.2. Found, %: C 61.55; H 6.98. $C_{15}H_{20}ClN_3O$. Calculated, %: C 61.32; H 6.86.

5-(4-Bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole hydrochloride (6d) was obtained analogously to compound **6a** from 5-(4-bromophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4d**) (0.3 g, 0.892 mmol) dissolved in absolute EtOH (0.5 ml). Yield 0.22 g (66%), white opaque powder, mp 185–186°C, R_f 0.81. IR spectrum, ν, cm^{-1}: 2900–2554 (N^+–H), 1678 (C=N), 1610 (C=C), 1296 (C–O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.61 (2H, m), 1.70–1.78 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.10 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.36 ($2H_{eq}$, m) and 3.43–3.48 ($2H_{ax}$, m, $N(CH_2)_2$); 3.82 (2H, t, *J* = 7.0, $C\underline{H}_2N(CH_2)_2$); 7.71 (2H, d, *J* = 7.0, *o*-H Ar); 7.86 (2H, d, *J* = 7.0, *m*-H Ar); 13.19 (1H, br. s, $\underline{H}N^+(CH_2)_2$). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 127.4; 130.4; 131.8; 132.2; 167.0; 168.5. Found, %: C 48.78; H 5.31. $C_{15}H_{19}BrClN_3O$. Calculated, %: C 48.34, H 5.14.

2-Amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (7). When ethereal HCl solution was added dropwise to a solution of 5-(3-chlorophenyl)-3-[2-(piperidin-1-yl)ethyl]-1,2,4-oxadiazole (**4e**) (0.3 g, 1.028 mmol) in EtOH (0.5 ml) to pH 2, white precipitate of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium chloride hydrate (**7**) was formed at once and collected by filtration. Yield 0.2 g

(94%), white opaque powder, mp 257–260°C, R_f 0.21. IR spectrum, cm^{-1}: 3338 (NH_2 ν as), 3260 (NH_2 ν sy), 1678 (C=N ν), 1610 (NH_2 δ). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.49–1.61 (2H, m), 1.70–1.78 (2H, m), and 1.84–1.92 (2H, m, $N(CH_2)_2(C\underline{H}_2)_3$); 3.10 (2H, t, *J* = 7.0, $C\underline{H}_2CH_2N(CH_2)_2$); 3.31–3.36 ($2H_{eq}$, m) and 3.45–3.50 ($2H_{ax}$, m, $N(CH_2)_2$); 3.83 (2H, t, *J* = 7.0, $CH_2C\underline{H}_2N(CH_2)_2$); 7.34 (2H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.0; 21.9; 31.5; 60.7; 64.3; 168.5. Found, %: C 46.56; H 8.54. $C_8H_{18}ClN_3O$. Calculated: C 46.26; H 8.74.

3-Chlorobenzoic acid (8) was precipitated during the evaporation of mother liquors obtained after the filtration of choride hydrate **7**. All characteristics of acid **8** corresponded to previously available data.[22]

X-ray diffraction analysis. Inclusion of one water molecule in the structure of 1,2,4-oxadiazole **4d** during its crystallization from 2-PrOH over 9 months gave a single crystal of 2-amino-1,5-diazaspiro[4.5]dec-1-en-5-ium 4-bromobenzoate (**5d**). The intensities of reflections were measured on a Bruker Apex II CCD diffractometer with MoKα radiation (λ 0.71073 Å, graphite monochromator). The crystal ($C_{15}H_{20}BrN_3O_2$, M_r 354.25) was monoclinic, space group $P2_1$, at 120.0 K: *a* 6.5058(5), *b* 7.9245(6), *c* 15.1028(11) Å; β 98.2190(10)°; *V* 770.63(10) $Å^3$; *Z* 2; D_{calc} 1.527 $g·cm^{-3}$; μ 2.675 mm^{-1}. A total of 9361 reflections were measured, 4012 independent (R_{int} 0.0561), final R_1 ($I > 2\sigma(I)$) 0.0259, $wR(F^2)$ 0.0547 (all data), *GOF* 0.897. The structure was solved by direct method and refined by full-matrix least-squares method against F^2. Non-hydrogen atoms were refined in anisotropic approximation. All hydrogen atoms could be located on difference Fourier maps. The H(C) atoms were included in the refinement by the riding model with $U_{iso}(H) = nU_{eq}(C)$, where $n = 1.5$ for methyl groups and 1.2 for the other atoms. All calculations were performed using the SHELXL[23] and OLEX2[24] software suites. The crystallographic dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1496456).

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