ISSN 1070-4280, Russian Journal of Organic Chemistry, 2017, Vol. 53, No. 6, pp. 873–878. © Pleiades Publishing, Ltd., 2017.
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Synthesis of Substituted 2-(2-Oxopyrrolidin-1-yl)acetamides

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Received March 17, 2017

Abstract—The reaction of chloroacetamide with 2 equiv of γ-aminobutyric acid potassium salts provides a convenient method for the synthesis of substituted 4-[(2-amino-2-oxoethyl)amino]butanoic acids. Alkylation products of 2-aminoacetic and 3-aminopropanoic acid with chloroacetamide were isolated. Thermal cyclization of substituted 4-[(2-amino-2-oxoethyl)amino]butanoic acids afforded 2-(2-oxopyrrolidin-1-yl)acetamides.

DOI: 10.1134/S1070428017060100

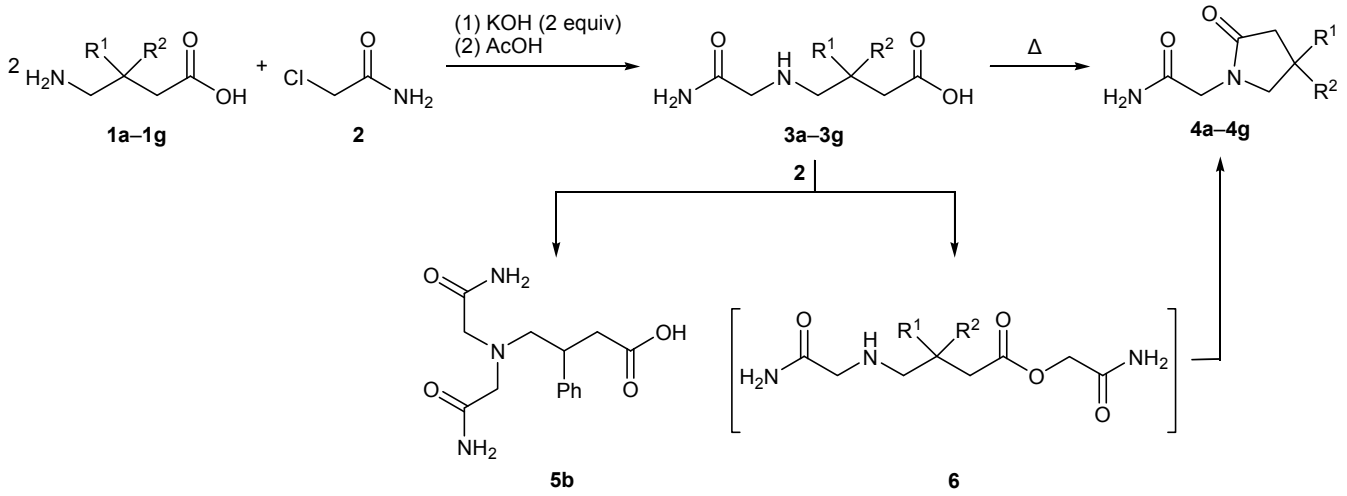
2-(2-Oxopyrrolidin-1-yl)acetamide derivatives are known as biologically active compounds exhibiting psychotropic and cerebroprotective effects [1]. Medicinals based on 2-(2-oxopyrrolidin-1-yl)acetamide are widely used for the treatment of central nervous system and cerebrovascular disorders [2]. Among these, the most widely known are 2-(2-oxopyrrolidin-1-yl)acetamide (Piracetam) and 2-(2-oxo-4-phenylpyrrolidin-1-yl)acetamide (Phenylpiracetam) which have been discovered in the second half of the XXth century [3, 4]. Interest in 2-(2-oxopyrrolidin-1-yl)acetamide derivatives has continued until now, and development of new efficient laboratory and large-scale procedures for the synthesis of substituted 2-(2-oxopyrrolidin-1-yl)acetamide is a topical problem.

Known methods for the synthesis of 2-(2-oxopyrrolidin-1-yl)acetamide derivatives are generally based on the alkylation of pyrrolidin-2-ones with haloacetic acid esters in the presence of sodium hydride, metal alkoxides, or lithium diisopropylamine, as well as of trimethylsilyl derivatives, followed by ammonolysis [5–11]. An alternative method is intramolecular acylation of *N*-substituted 4-aminobutanoic acid esters prepared by condensation of 4-halobutanoyl chlorides with glycine esters [12] or 2-aminobutanamides [13]. The alkylation of 4-aminobutanoic acids with haloacetamides has been reported. The resulting *N*-substituted 4-aminobutanoic acid esters were converted to 2-(2-oxopyrrolidin-1-yl)acetamides by thermal cyclization in organic solvents [13, 14]. These procedures have some essential drawbacks, the main of which is difficult isolation of the target compounds. Therefore, special methods are necessary for purification of the products, which reduces the efficiency of the synthesis.

In this work, the alkylation of 3-substituted 4-aminobutanic acids **1a**–**1g** with chloroacetamide (**2**) was carried out by preliminarily converting acids **1** to potassium salts in aliphatic alcohols (methanol, ethanol, propan-2-ol, or their mixtures), adding 0.5 equiv of chloroacetamide (**2**), and heating the reaction mixture at 65–75°C for 3–4 h. After cooling and removal of unreacted acid **1** and potassium chloride by filtration, acidification of the filtrate with acetic acid afforded pure 3-substituted 4-[(2-amino-2-oxoethyl)amino]butanoic acids **3a**–**3g** whose subsequent thermal cyclization in a high-boiling solvent (anisole or *o*-xylene) gave 2-(2-oxopyrrolidin-1-yl)acetamides **4a**–**4g** (Scheme 1).

The use of sodium hydroxide was inappropriate since 4-aminobutanoic acid sodium salts are poorly soluble in alcohols. The solvent and its amount were selected taking into account the solubility of the initial compounds, target products, and by-products. Excess potassium salt of acid **1** with respect to **2** (ratio **1**:**2** ≥ 2:1) was taken for the following reasons. It is known that alkylation of amino acids may be accompanied by formation of *N*,*N*- and *N*,*O*-dialkyl derivatives (in our case, compounds **5** and **6**). 4-Aminobutanoic acid esters with aliphatic alcohols were reported to undergo intramolecular cyclization to pyrrolidinones [13, 14].

Scheme 1.



R^1 = H, R^2 = H (**a**), Ph (**b**), 2,4-$Cl_2C_6H_3$ (**c**), 4-ClC_6H_4 (d), 4-$MeOC_6H_4$ (e), 3-$O_2NC_6H_4$ (**f**); R^1R^2 = $(CH_2)_5$ (**g**).

Obviously, cyclization of **6** in alcohol at 26–65°C yields 2-(2-oxopyrrolidin-1-yl)acetamides **4**, as follows from the HPLC/MS data.

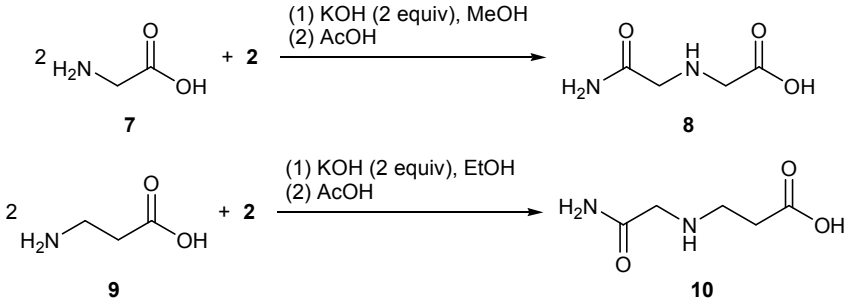
Thus, excess potassium salt partially suppresses side formation of compounds **5** and **6** and acts as a base which neutralizes liberated hydrogen chloride. As a result, initial amino acid **1** is formed. It is poorly soluble in alcohols and precipitates from the reaction mixture. After purification from potassium chloride, it can be reused. Acid **3** is also poorly soluble in alcohol and is precipitated by acidification with acetic acid, whereas by-product **5** and compound **4** arising from *N*,*O*-bis(2-amino-2-oxoethyl) derivative **6** remain in solution.

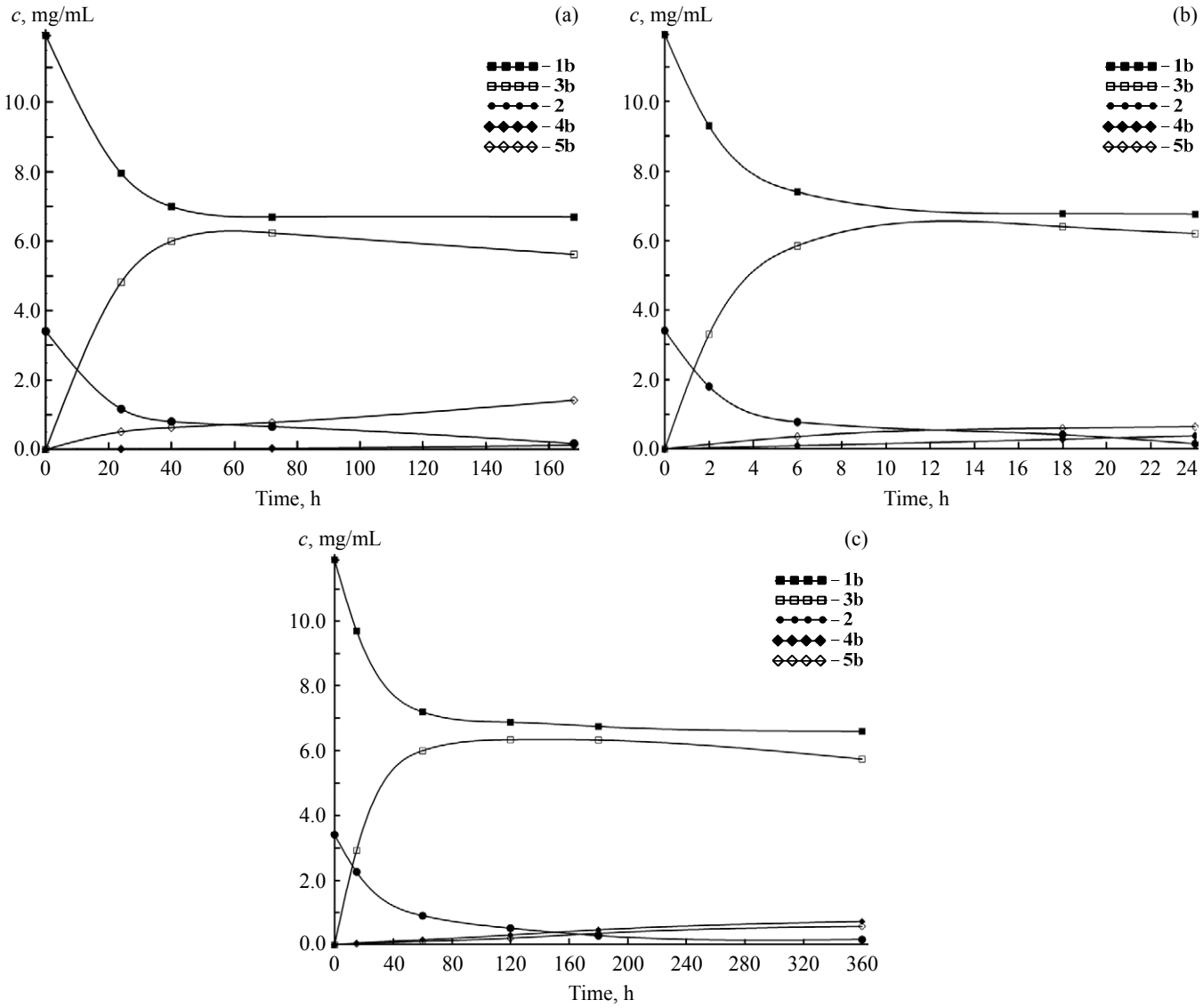
The kinetics of the formation of 4-[(2-amino-2-oxoethyl)amino]-3-phenylbutanoic acid (**3b**) were studied as follows. The reaction mixture was kept for different periods of time (15 min to 168 h) at a specified temperature (26, 45, or 65°C) and diluted with a 10-fold volume of cold distilled water. The resulting mixture was filtered, and a 1-mL sample of the filtrate was withdrawn and frozen with dry ice. Samples were then analyzed by HPLC/MS according to a developed procedure. Figure shows variations of the concentrations of the initial compounds and products with time at different temperatures.

Most part of initial amino acid **1b** is converted to **3b** during the first hour at 65°C, and then the rate of alkylation sharply decreases. After 3 h, the fraction of **3b** begins to decrease due to formation of by-products, while the concentrations of **5b** and **4b** increase. Lowering the temperature to 45°C reduces the reaction rate, so that the time necessary to achieve the maximum concentration of **3b** increases to 14 h. The corresponding time at 26°C is 55 h.

The reaction selectivity depends on the temperature conditions. At 26°C, compound **3b** is consumed mainly for the formation of *N*,*N*-disubstituted derivative **5b**, whereas raising the temperature to 65°C favors formation of pyrrolidone **4b**, which indicates prevalence of *O*-alkylation. The yields of 3-substituted 4-[(2-amino-2-oxoethyl)amino]butanoic acids **3** were

Scheme 2.





Variation of the concentrations of the initial compounds and products in the reaction mixture during the reaction of 4-amino-3-phenylbutanoic acid (**1b**) with chloroacetamide (**2**) at (a) 26, (b) 45, and (c) 65°C.

50–80%, and of the cyclization products, 2-(2-oxopyrrolidin-1-yl)acetamides **4**, 70–97%.

In order to extend the scope of the described reaction, chloroacetamide was reacted with aminoacetic acid (**7**) and 3-aminopropanoic acid (**9**) that are homologous to 4-aminobutanoic acid. As a result, [(2-amino-2-oxoethyl)amino]acetic acid (**8**) and 3-[(2-amino-2-oxoethyl)amino]propanoic acid (**10**) were obtained in 50 and 70% yield, respectively (Scheme 2).

In summary, substituted 2-(2-oxopyrrolidin-1-yl)-acetamides can readily be synthesized according to the proposed procedure which is suitable not only for laboratory but also for large-scale applications. The rate of formation of 4-[(2-amino-2-oxoethyl)amino]-3-phenylbutanoic acid and qualitative and quantitative compositions of the products were found to depend on the reaction conditions (temperature and time), and optimal conditions were determined. *N*-(2-Amino-2-oxoethyl) derivatives of substituted 4-aminobutanoic acids and its nearest homolog, 3-aminopropanoic acid, were isolated for the first time. The structure of the isolated compounds was confirmed by ^{1}H and ^{13}C NMR spectra and elemental analyses.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III UltraShield Plus spectrometer (400 MHz). HPLC/MS analyses were done with

a Thermo Fisher Scientific TSQ Quantum Access MAX instrument [Zorbax SB-18 column, 150× 2.10 mm, grain size 1.8 μm; column temperature 35°C; sample compartment temperature 5°C; eluents 0.1% aqueous formic acid (for HPLC) and acetonitrile (for gradient HPLC); gradient elution]. Detailed procedure for studying the kinetics of formation of compound **3b** is available from the authors by e-mail. The elemental analyses were obtained using a Thermo Scientific FLASH 2000 CHNS analyzer. The melting points were measured on a melting point apparatus equipped with an electric heater (measurement range 20–360°C).

Compounds 3a–3f (*general procedure*). Amino acid **1a**–**1f**, 1 mol, was added to a solution of 1 mol of potassium hydroxide in ethanol or ethanol–propan-2-ol (2:1) (8 mL per gram of amino acid), and the mixture was heated to 65–75°C and stirred until complete dissolution. Chloroacetamide, 0.5 mol, was added to the resulting solution, the mixture was stirred for 3–4 h at 65–75°C and cooled to room temperature, and the precipitate of potassium chloride and initial amino acid was filtered off and washed with alcohol. The filtrate was acidified with glacial acetic acid (0.5 mol), the mixture was stirred until complete crystallization, and the precipitate was filtered off, washed with alcohol, and dried at a temperature not higher than 75°C.

4-[(2-Amino-2-oxoethyl)amino]butanoic acid (3a). Solvent ethanol–propan-2-ol, 2:1. The filtrate containing potassium 4-[(2-amino-2-oxoethyl)amino]-butanoate was acidified with 2 equiv of acetic acid, and compound **3a** separated from the solution as an acetic acid salt. Yield 62–64%. Recrystallization from methanol gave amino acid **3a** as colorless prisms, mp 150–151°C (from MeOH). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.87 quint (1H, CH, J = 8.0 Hz), 2.26 t (2H, CH_2, J = 8.0 Hz), 3.04 t (2H, CH_2, J = 8.0 Hz), 3.84 s (2H, CH_2). Found, %: C 44.87; H 7.49; N 17.39. $C_6H_{12}N_2O_3$. Calculated, %: C 44.99; H 7.55; N 17.49.

4-[(2-Amino-2-oxoethyl)amino]-3-phenylbutanoic acid (3b). Solvent ethanol. Yield 62–64%, colorless prisms, mp 148–149°C (from aqueous acetone). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.48–2.63 m (2H, CH_2), 3.33–3.44 m (3H, CH_2, CH), 3.73–3.77 m (2H, CH_2), 7.30–7.32 m (3H, H_{arom}), 7.36–7.40 m (2H, H_{arom}). Found, %: C 60.94; H 6.76; N 11.81. $C_{12}H_{16}N_2O_3$. Calculated, %: C 61.00; H 6.83; N 11.86.

4-[(2-Amino-2-oxoethyl)amino]-3-(2,4-dichlorophenyl)butanoic acid (3c). Solvent ethanol–propan-2-ol, 2:1. Yield 50–51%, light brown prisms, mp 147–150°C (decomp.; from H_2O). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.50–2.65 m (2H, CH_2), 3.34 d (2H, CH_2, J = 4.0 Hz), 3.82 s (2H, CH_2), 3.94 quint (1H, CH, J = 8.0 Hz), 7.30–7.36 m (2H, H_{arom}), 7.51 s (1H, H_{arom}). Found, %: C 47.15; H 4.56; N 9.11. $C_{12}H_{14}Cl_2N_2O_3$. Calculated, %: C 47.23; H 4.62; N 9.18.

4-[(2-Amino-2-oxoethyl)amino]-3-(4-chlorophenyl)butanoic acid (3d). Solvent ethanol. Yield 52–53%, colorless prisms, mp 142.5–144.5°C (decomp., from MeOH). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.39–2.56 m (2H, CH_2), 3.27–3.39 m (3H, CH_2, CH), 3.70–3.79 m (2H, CH_2), 7.23 d (2H, H_{arom}, J = 6.0 Hz), 7.34 d (2H, H_{arom}, J = 6.0 Hz). Found, %: C 53.18; H 5.49; N 10.28. $C_{12}H_{15}ClN_2O_3$. Calculated, %: C 53.24; H 5.58; N 10.35.

4-[(2-Amino-2-oxoethyl)amino]-3-(4-methoxyphenyl)butanoic acid (3e). Solvent ethanol–propan-2-ol (2:1). Yield 68–70%, colorless prisms, mp 137–140°C (decomp., from MeOH). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.40–2.56 m (2H, CH_2), 3.24–3.38 m (3H, CH_2, CH), 3.71–3.80 m (2H, CH_2), 3.76 s (3H, CH_3), 6.95 d (2H, H_{arom}, J = 4.0 Hz), 7.24 d (2H, H_{arom}, J = 4.0 Hz). Found, %: C 58.54; H 6.74; N 10.46. $C_{13}H_{18}N_2O_4$. Calculated, %: C 58.63; H 6.81; N 10.52.

4-[(2-Amino-2-oxoethyl)amino]-3-(3-nitrophenyl)butanoic acid (3f). Solvent ethanol–propan-2-ol (2:1). Yield 69–71%, light brown prisms, mp 151–153°C (from H_2O). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.49–2.68 m (2H, CH_2), 3.36–3.45 m (2H, CH_2), 3.56 quint (1H, CH, J = 8.0 Hz), 3.76–3.85 m (2H, CH_2), 7.58 t (1H, H_{arom}, J = 8.0 Hz), 7.71 d (1H, H_{arom}, J = 4.0 Hz), 8.14 d (1H, H_{arom}, J = 4.0 Hz), 8.19 br.s (1H, H_{arom}). Found, %: C 51.28; H 5.32; N 14.88. $C_{12}H_{15}N_3O_5$. Calculated, %: C 51.24; H 5.38; N 14.94.

(1-{[(2-Amino-2-oxoethyl)amino]methyl}cyclohexyl)acetic acid (3g). Solvent propan-2-ol. After addition of all reactants, the mixture was heated for 4 h at 75°C, the resulting suspension was cooled to room temperature, the precipitate of potassium chloride was filtered off, and the filtrate was diluted with two volumes of acetone, acidified with acetic acid, cooled to –5°C, and left to stand for 24 h at that temperature. The precipitate of initial [1-(aminomethyl)cyclohexyl]-acetic acid was filtered off and washed with acetone, the filtrate was concentrated to 25% of the initial volume under reduced pressure, the residue was cooled to –5°C and kept for 24 h, and the crystalline solid was filtered off and washed with acetone. Yield 79–80%, white prisms, mp 142–143°C (from acetone). ^{1}H NMR spectrum (D_2O), δ, ppm: 1.28–1.49 m (10H, C_5H_{10}), 2.31 s (2H, CH_2), 3.25 s (2H, CH_2), 3.95 s (2H, CH_2).

Found, %: C 57.80; H 8.72; N 12.19. $C_{11}H_{20}N_2O_3$. Calculated, %: C 57.87; H 8.83; N 12.27.

Compounds 4a–4g (*general procedure*). A suspension of 5 g of **3a**–**3g** in 30 mL of anisole or *o*-xylene was heated with stirring until it became homogeneous with simultaneous removal of water by distillation. The mixture was allowed to cool down, and the precipitate was filtered off, washed with propan-2-ol, and dried.

2-(2-Oxopyrrolidin-1-yl)acetamide (4a). Solvent anisole. Yield 70–75%, white prisms, mp 152–153°C (from *i*-PrOH); published data: mp 151.5–152.5 [3], 150–153°C [11]. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.01 quint (2H, CH_2, J = 8.0 Hz), 2.39 t (2H, CH_2, J = 8.0 Hz), 3.43 t (2H, CH_2, J = 8.0 Hz), 3.92 s (2H, CH_2).

2-(2-Oxo-4-phenylpyrrolidin-1-yl)acetamide (4b). Solvent anisole. Yield 95–97%, white prisms, mp 130–131°C (from *i*-PrOH); published data: mp 132°C [4], 129.5–130.5°C [5]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.38–2.45 m (1H, H_{eq}), 2.66–2.73 m (1H, H_{ax}), 3.40–3.44 m (1H, H_{eq}), 3.62 quint (1H, CH, J = 8.0 Hz), 3.73–3.78 m (1H, H_{ax}), 3.83 s (2H, CH_2), 7.10 br.s (1H, NH_2), 7.22–7.27 m (1H, H_{arom}), 7.33 d (4H, H_{arom}, J = 2.0 Hz), 7.42 br.s (1H, NH_2).

2-[4-(2,4-Dichlorophenyl)-2-oxopyrrolidin-1-yl]-acetamide (4c). Solvent *o*-xylene. Yield 91–95%, light brown plates, mp 156–158°C (from EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.34–2.40 m (1H, H_{eq}), 2.72–2.78 m (1H, H_{ax}), 3.43–3.47 m (1H, H_{eq}), 3.78–3.88 m (3H, H_{ax}, CH_2), 3.98 quint (1H, CH, J = 8.0 Hz), 7.02 br.s (1H, NH_2), 7.37 d (1H, H_{arom}, J = 4.0 Hz), 7.39 br.s (1H, NH_2), 7.48 s (1H, H_{arom}), 7.64 d (1H, H_{arom}, J = 4.0 Hz). Found, %: C 50.11; H 4.13; Cl 24.59; N 9.68. $C_{12}H_{12}Cl_2N_2O_2$. Calculated, %: C 50.19; H 4.21; Cl 24.69; N 9.76.

2-[4-(4-Chlorophenyl)-2-oxopyrrolidin-1-yl]-acetamide (4d). Solvent anisole. Yield 90–91%, colorless prisms, mp 138–140°C (from *i*-PrOH); published data [6]: mp 133–136°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.36–2.43 m (1H, H_{eq}), 2.66–2.72 m (1H, H_{ax}), 3.39–3.43 m (1H, H_{eq}), 3.63 quint (1H, CH, J = 8.0 Hz), 3.73–3.78 m (1H, H_{ax}), 3.78–3.86 m (2H, CH_2), 7.03 br.s (1H, NH_2), 7.32–7.37 m (5H, H_{arom}, NH_2).

2-[4-(4-Methoxyphenyl)-2-oxopyrrolidin-1-yl]-acetamide (4e). Solvent *o*-xylene. Yield 90–93%, colorless prisms, mp 118–120°C (from *i*-PrOH); published data [7]: mp 117–118°C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.35–2.42 m (1H, H_{eq}), 2.61–2.68 m (1H, H_{ax}), 3.37–3.41 m (1H, H_{eq}), 3.56 quint (1H, CH, J = 8.0 Hz), 3.69–3.74 m (1H, H_{ax}), 3.75 s (3H, OCH_3), 3.81 s (2H, CH_2), 6.85 d (2H, H_{arom}, J = 4.0 Hz), 7.00 br.s (1H, NH_2), 7.23 d (2H, H_{arom}, J = 4.0 Hz), 7.35 br.s (1H, NH_2).

2-[4-(3-Nitrophenyl)-2-oxopyrrolidin-1-yl]acetamide (4f). Solvent anisole. Yield 94–95%, light brown prisms, mp 172–174°C (from EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.45–2.55 m (1H, H_{eq}), 2.73–2.80 m (1H, H_{ax}), 3.47–3.53 m (1H, H_{eq}), 3.77–3.91 m (4H, H_{ax}, CH_2, CH), 7.05 br.s (1H, NH), 7.40 br.s (1H, NH), 7.63 t (1H, H_{arom}, J = 8.0 Hz), 7.84 d (1H, H_{arom}, J = 4.0 Hz), 8.10 d (1H, H_{arom}, J = 4.0 Hz), 8.24 br.s (1H, H_{arom}). Found, %: C 54.66; H 4.87; N 15.85. $C_{12}H_{13}N_3O_4$. Calculated, %: C 54.75; H 4.98; N 15.96.

2-(3-Oxo-2-azaspiro[4.5]decan-2-yl)acetamide (4g). Solvent *o*-xylene. Yield 83%, colorless prisms, mp 141.5–142.5°C (from *i*-PrOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32–1.59 m (10H, C_5H_{10}), 2.12 s (2H, CH_2), 3.16 s (2H, CH_2), 3.73 s (2H, CH_2), 6.97 br.s and 7.31 br.s (1H each, NH_2).

4-[Bis(2-amino-2-oxoethyl)amino]-3-phenylbutanoic acid (5b) was synthesized according to the procedure described above for compounds **3** using **3b** as amino acid substrate and ethanol as solvent. The filtrate was acidified with concentrated aqueous HCl to pH 4, the precipitate was filtered off, and the filtrate was evaporated to dryness. The residue was dissolved in a minimum amount of methanol, the solution was filtered, and the product was precipitated by slowly adding an equal volume of propan-2-ol. The precipitate was filtered off and dried at 75°C. Acid **5b** was characterized as sodium salt. Yield 65–70%, colorless prisms flowing on exposure to air, mp 171–173°C. ^{1}H NMR spectrum (D_2O), δ, ppm: 2.31–2.37 m and 2.49–2.54 m (1H each, CH_2), 2.76–2.90 m (2H, CH_2), 3.08–3.25 m (5H, CH_2, CH), 7.19–7.33 m (5H, H_{arom}). Found, %: C 53.26; H 5.67; N 13.24. $C_{14}H_{18}N_3NaO_4$. Calculated, %: C 53.33; H 5.75; N 13.33.

[(2-Amino-2-oxoethyl)amino]acetic acid (8) was synthesized as described above for compounds **3** using methanol as solvent. Yield 50%, colorless prisms, mp 192–194°C (decomp., from DMF). ^{1}H NMR spectrum (D_2O), δ, ppm: 3.60 s (2H, CH_2), 3.88 s (2H, CH_2). ^{13}C NMR spectrum (D_2O), δ_C, ppm: 47.38 and 48.98 (CH_2), 168.51 ($CONH_2$), 170.92 (COOH). Found, %: C 36.29; H 6.01; N 21.13. $C_4H_8N_2O_3$. Calculated, %: C 36.36; H 6.10; N 21.20.

3-[(2-Amino-2-oxoethyl)amino]propanoic acid (10) was synthesized as described above for compounds **3** using ethanol as solvent. Yield 70–71%, colorless prisms, mp 189–190°C (decomp., from DMF). ^{1}H NMR spectrum (D_2O), δ, ppm: 2.53 t (CH_2, J = 8.0 Hz), 3.21 t (2H, CH_2, J = 8.0 Hz), 3.86 s (2H, CH_2). ^{13}C NMR spectrum (D_2O), δ, ppm: 32.25, 44.61, 47.50 (CH_2); 168.46 ($CONH_2$), 177.86 (COOH). Found, %: C 40.99; H 6.81; N 19.12. $C_5H_{10}N_2O_3$. Calculated, %: C 41.09; H 6.90; N 19.17.

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