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Synthesis of Amino Polycarboxylic Acids of the Adamantane Series

E. A. Ivleva,* I. M. Tkachenko, V. S. Gavrilova, and Yu. N. Klimochkin

Samara State Technical University, ul. Molodogvardeiskaya 244, Samara, 443100 Russia
**e-mail: elena.a.ivleva@yandex.ru*

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Abstract—The Ritter reaction of dibasic carboxylic acids of the adamantane series with carboxy and carboxymethyl groups attached to bridgehead carbon atoms afforded a number of amino polycarboxylic acids.

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Restriction of conformational mobility of molecules is a widely used technique of medicinal chemistry. This technique ensures synthesis of peptidomimetics that are synthetic analogs of cell peptides of high molecular complexity with improved activity parameters [1–3]. Search for new conformationally rigid amino acid analogs constitutes a topical field of research [4–12] since incorporation of conformationally rigid acid residues into peptide chain provides some advantages from the viewpoint of molecular design of peptidomimetics.

Adamantane and its derivatives occupy a particular place among conformationally rigid structural units. Due to specific properties of the adamantane skeleton, amino acids derived therefrom offer a number of advantages. Despite relatively large molecular weight, their molecules are fairly compact due to conformational rigidity and are highly lipophilic, which makes them capable of penetrating hematoencephalic barrier [13–15]. Therefore, amino acids of the adamantane series are quite attractive for the synthesis of peptidomimetic molecular assemblies.

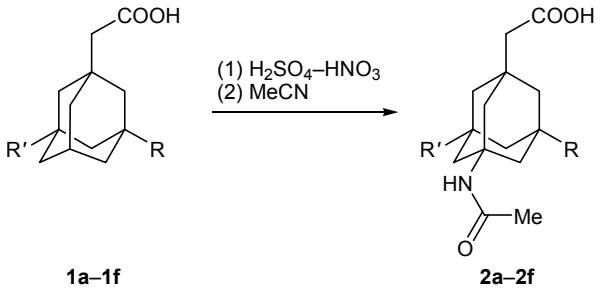
Methods of fine organic synthesis allowing design of molecules with desired structure and geometric parameters have been developed to a sufficient extent [16–18]. However, only a few publications are available on the use of adamantane amino acids in the synthesis of peptidomimetics [19–22] because of the lack of convenient methods for the preparation of such acids containing several carboxy groups.

Amino acids of the adamantane series can be synthesized by acid hydrolysis of acetylamino derivatives [21, 23, 24] that are available via the Ritter reaction [25]. In this reaction, both adamantane carboxylic acids [21, 24, 26] and the corresponding acid chlorides [27–29] can be used as starting compounds. An alternative synthetic approach to acetylamino derivatives is based on photoinitiated oxidation of adamantane-1-carboxylic acid with ceric ammonium nitrate (CAN) in acetonitrile [30]. The presence of electron-withdrawing substituents on the adamantane skeleton sharply reduces the reactivity of such compounds due to low stability of carbocations with the cationic center in the bridgehead position, so that possible ways of functionalization of these substrates are limited [31, 32].

In continuation of our studies on functionalization of deactivated cage substrates [33, 34], we have developed a synthetic approach to amino polycarboxylic acids of the adamantane series which may be regarded as GABA analogs [21, 35–37] and used as building blocks in the molecular design of peptidomimetics with required geometric parameters.

As starting compounds we used 3-carboxymethyladamantane-1-carboxylic acids **1a**–**1c** [33] and (adamantane-1,3-diyl)diacetic acids **1d**–**1f** [38] which were brought into the Ritter reaction to obtain acetylamino derivatives **2a**–**2f** (Scheme 1). Due to the presence of two carboxy groups in initial molecules **1d**–**1f**, the reactions required harsh conditions. Successful oxidation of the tertiary C–H bond in adamantane skeleton was achieved with the use of 5 equiv of fuming nitric acid in 98% sulfuric acid. The yield of **2a**–**2f** in 96% sulfuric acid was lower, whereas the reactions in 90–94% H_2SO_4 afforded only hydroxy derivatives

Scheme 1.



1a–1f **2a–2f**

R = COOH, R′ = H (**a**), Me (**b**), Et (**c**); R = CH_2COOH, R′ = H (**d**), Me (**e**), Et (**f**).

[34]. The oxidation was carried out at room temperature (3 h), acetonitrile was then added, and the mixture was kept for 3 h; acetylamino derivatives **2a**–**f** were isolated in 42–90% yield. The structure of **2a**–**2f** was confirmed by spectral data and elemental analyses. Compounds **2a**–**2f** displayed a signal of the NH proton in the region δ 7.38–7.45 ppm of the ^{1}H NMR spectra. The adamantane carbon atom linked to nitrogen resonated in the ^{13}C NMR spectra at δ_C 52–53 ppm.

Acetamides **2a**–**2f** were converted to amino acids **3a**–**3f** by prolonged heating (40–70 h) in boiling aqueous HCl (Scheme 2). The hydrolysis of **2d**–**2f** was accompanied by partial substitution of the amino group in **3d**–**3f** by chlorine with formation of chloro derivatives **4a**–**4c**. The formation of **4a**–**4c** is determined by high stability of the bridgehead carbocation generated by relatively facile dissociation of the C–N bond and subsequent addition of chloride ion as external nucleophile [28]. No by-products were detected in the hydrolysis of acetylamino derivatives **2a**–**2c**. In the ^{13}C NMR spectra of amino acids **3a**–**3f**, signal of the CNH_3^+ carbon atom was observed at δ_C 52.60–53.27 ppm. The corresponding carbon signal of **4a**–**4c** (CCl) was located at δ_C 70.00–70.40 ppm.

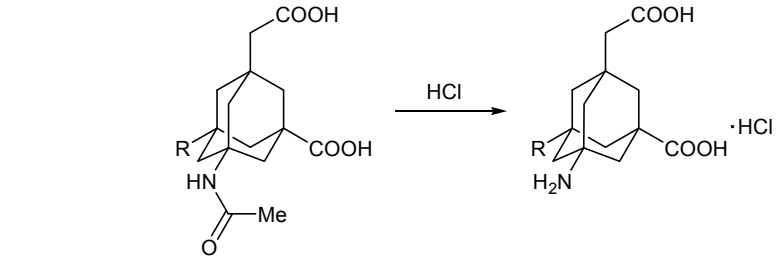
The synthesis of amino acids of the adamantane series opens the way to design of conformationally rigid peptidomimetics with improved activity parameters. Directed variation of the lipophilicity of the cage fragment in combination with modification of functional group polarity by known methods and development of new molecular design methods could give rise to a broad spectrum of initial compounds with required molecular geometry.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM ECX-400 spectrometer (400 MHz for ^{1}H) using DMSO-d_6 as solvent. The IR spectra were measured in KBr on a Shimadzu IR Affinity-1 spectrometer. The elemental analyses were obtained on a Euro Vector 3000 EA analyzer with L-cystine as standard.

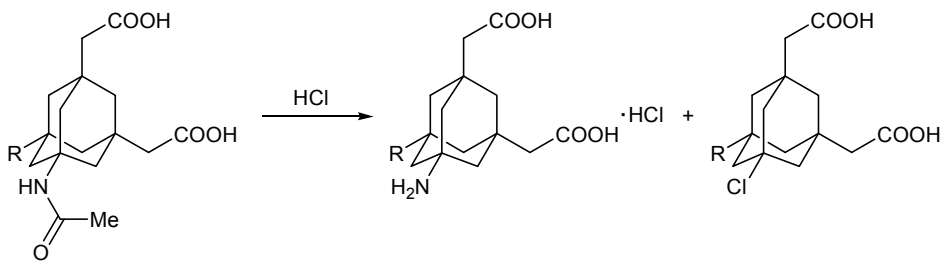
3-(Acetamido)-5-(carboxymethyl)adamantane-1-carboxylic acid (2a). 3-(Carboxymethyl)adamantane-

Scheme 2.



2a–2c **3a–3c**

R = H (**a**), Me (**b**), Et (**c**).



2d–2f **3d–3f** **4a–4c**

2d, **3d**, **4a**, R = H; **2e**, **3e**, **4b**, R = Me; **2f**, **3f**, **4c**, R = Et.

1-carboxylic acid (**1a**), 3.0 g (0.013 mol), was dissolved in 25 mL of 98% sulfuric acid, and 2.7 mL (0.063 mol) of fuming nitric acid was added dropwise with stirring at such a rate that the temperature of the mixture did not exceed 20°C. When the addition was complete, the mixture was kept for 3 h at that temperature, and 4.6 mL (0.088 mol) of acetonitrile was added dropwise with stirring, maintaining the temperature not higher than 25°C. The mixture was stirred for 3 h at room temperature and poured onto 100 g of ice. After 24 h, the product was filtered off and recrystallized from glacial acetic acid–water–acetone (5:5:2). Yield 2.56 g (67%), colorless crystals, mp 147–149°C [21].

Compounds **2b**–**2f** were synthesized in a similar way.

5-(Acetamido)-3-(carboxymethyl)-7-methyladamantane-1-carboxylic acid (2b) was synthesized from 3 g (0.012 mol) of 3-(carboxymethyl)-5-methyladamantane-1-carboxylic acid (**1b**) and 4.3 mL (0.083 mol) of acetonitrile using 2.5 mL (0.06 mol) of fuming nitric acid and 25 mL of 98% sulfuric acid. Yield 2.56 g (67%), colorless crystals, mp 233–236°C (from AcOH–H_2O–Me_2CO, 5:5:2). IR spectrum, ν, cm^{-1}: 3352 (NH), 2927, 2862 (CH_{Ad}), 1724, 1624 (C=O). ^1H NMR spectrum, δ, ppm: 0.81 s (3H, CH_3), 1.14–1.22 m (2H, CH_2, Ad), 1.30–1.39 m (2H, CH_2, Ad), 1.44–1.61 m (6H, CH_2, Ad), 1.70 s (3H, CH_3), 1.83 (2H, CH_2, Ad), 2.04 s (2H, C**H**$_2$COOH), 7.43 s (1H, NH), 12.06 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 24.20 (CH_3), 30.14 (CH_3), 32.30, 34.86, 41.45 (CH_2), 42.21 (CH_2), 43.10, 44.41 (CH_2), 44.50 (CH_2), 46.77 (CH_2), 47.32 (CH_2), 47.61 (CH_2), 52.76, 169.41, 172.84, 177.95. Found, %: C 62.16; H 7.53; N 4.56. $C_{16}H_{23}NO_5$. Calculated, %: C 62.12; H 7.49; N 4.53.

5-(Acetamido)-3-(carboxymethyl)-7-ethyladamantane-1-carboxylic acid (2c) was synthesized from 3 g (0.011 mol) of 3-(carboxymethyl)-5-ethyladamantane-1-carboxylic acid (**1c**) and 4.1 mL (0.079 mol) of acetonitrile using 2.5 mL (0.060 mol) of fuming nitric acid and 25 mL of 98% sulfuric acid. Yield 1.70 g (48%), colorless crystals, mp 224–226°C. IR spectrum, ν, cm^{-1}: 3352 (NH), 2939, 2854 (CH_{Ad}), 1715, 1689 (C=O). ^1H NMR spectrum, δ, ppm: 0.72 t (3H, CH_3, J = 7.36 Hz), 1.11–1.20 m (4H, CH_2, Ad), 1.28–1.38 m (2H, C**H**$_2$CH$_3$), 1.44–1.62 m (6H, CH_2, Ad), 1.70 s (3H, CH_3), 1.84 s (2H, CH_2, Ad), 2.03 (2H, CH_2), 7.45 (1H, NH), 8.09 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 7.57 (CH_3), 24.20 (CH_3), 34.70, 34.91, 35.32 (CH_2), 41.77 (CH_2), 42.10 (CH_2), 42.54 (CH_2), 42.92, 44.26 (CH_2), 44.73 (CH_2), 45.19 (CH_2), 47.42 (CH_2), 52.75, 169.42, 172.86, 178.06. Found, %: C 63.18; H 7.83; N 4.37. $C_{17}H_{25}NO_5$. Calculated, %: C 63.14; H 7.79; N 4.33.

[5-(Acetamido)adamantane-1,3-diyl]diacetic acid (2d) was synthesized from 3 g (0.012 mol) of (adamantane-1,3-diyl)diacetic acid (**1d**) and 4.3 mL (0.083 mol) of acetonitrile using 2.5 mL (0.060 mol) of fuming nitric acid and 30 mL of 98% sulfuric acid. The mixture was poured onto 223 g of ice. Yield 1.6 g (42%), colorless crystals, mp 229–232°C (from AcOH). IR spectrum, ν, cm^{-1}: 3325 (NH), 2912, 2858 (CH_{Ad}), 1732, 1658 (C=O). ^1H NMR spectrum, δ, ppm: 1.31–1.43 m (4H, CH_2, Ad), 1.64–1.71 m (8H, CH_2, Ad), 1.87 s (3H, CH_3), 1.98 s (4H, CH_2), 2.05 s (1H, CH, Ad), 7.38 s (1H, NH), 8.60 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 24.20 (CH_3), 29.45 (CH), 34.55, 40.02 (CH_2), 40.72 (CH_2), 45.25 (CH_2), 46.15 (CH_2), 47.87 (CH_2), 52.36, 169.29, 172.86. Found, %: C 62.15; H 7.52; N 4.57. $C_{16}H_{23}NO_5$. Calculated, %: C 62.12; H 7.49; N 4.53.

[5-(Acetamido)-7-methyladamantane-1,3-diyl]-diacetic acid (2e) was synthesized from 3.0 g (0.012 mol) of (5-methyladamantan-1,3-diyl)diacetic acid (**1e**) and 4.3 mL (0.083 mol) of acetonitrile using 2.5 mL (0.060 mol) of fuming nitric acid and 30 mL of 98% sulfuric acid. The mixture was poured onto 223 g of ice. Yield 2.70 g (70%), colorless crystals, mp 215–218°C (from Me_2CO). IR spectrum, ν, cm^{-1}: 3333 (NH), 2904, 2854 (CH_{Ad}), 1732, 1658 (C=O). ^1H NMR spectrum, δ, ppm: 0.78 s (3H, CH_3), 1.09–1.34 m (6H, CH_2, Ad), 1.49 s (2H, CH_2, Ad), 1.62 s (4H, CH_2, Ad), 1.69 s (3H, CH_3), 1.99 s (4H, CH_2), 7.39 s (1H, NH), 11.58 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 24.17 (CH_3), 30.25 (CH_3), 32.39, 35.03, 44.53 (CH_2, Ad), 45.47 (CH_2, Ad), 46.85 (CH_2, Ad), 47.52 (CH_2, Ad), 47.79 (CH_2), 53.00, 169.25, 172.86. Found, %: C 63.17; H 7.82; N 4.36. $C_{17}H_{25}NO_5$. Calculated, %: C 63.14; H 7.79; N 4.33.

[5-(Acetamido)-7-ethyladamantane-1,3-diyl]-diacetic acid (2f) was synthesized from 3.0 g (0.010 mol) of (5-ethyladamantane-1,3-diyl)diacetic acid (**1f**) and 3.6 mL (0.070 mol) of acetonitrile using 2.1 mL (0.050 mol) of fuming nitric acid and 25 mL of 98% sulfuric acid. The mixture was poured onto 223 g of ice. Yield 3.0 g (90%), colorless crystals, mp 224–226°C (from AcOH). IR spectrum, ν, cm^{-1}: 3340 (NH), 2966, 2904 (CH_{Ad}), 1724, 1672 (C=O). ^1H NMR spectrum, δ, ppm: 0.71 t (3H, CH_3, J = 7.32 Hz), 1.07–1.37 m (8H, CH_2, Ad, C**H**$_2$CH$_3$), 1.47 s (2H, CH_2, Ad),

1.63 s (4H, CH_2, Ad), 1.69 s (3H, CH_3), 2.00 (4H, CH_2), 7.40 (1H, NH), 11.57 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 7.61 (CH_3), 24.18 (CH_3), 34.86, 35.03, 35.41 (CH_2), 44.33 (CH_2), 44.87 (CH_2), 45.35 (CH_2), 45.80 (CH_2), 47.63 (CH_2), 53.00, 169.26, 172.87. Found, %: C 64.11; H 8.11; N 4.19. $C_{18}H_{27}NO_5$. Calculated, %: C 64.07; H 8.07; N 4.15.

3-Carboxy-5-(carboxymethyl)adamantan-1-aminium chloride (3a). A mixture of 4.0 g (0.014 mol) of compound **2a**, 48 mL of 36% aqueous HCl, and 16 mL of water was refluxed for 64 h. The mixture was evaporated, the oily residue was dissolved in anhydrous acetone, and the solution was left to stand for crystallization. Yield 2.88 g (69%), colorless crystals, mp 249–251°C [21].

Compounds **3b** and **3c** were synthesized in a similar way.

3-Carboxy-5-(carboxymethyl)-7-methyladamantan-1-aminium chloride (3b) was obtained from 1.7 g (0.006 mol) of **2b** in a mixture of 13 mL of 36% aqueous HCl and 6 mL of water (reaction time 70 h). Yield 0.85 g (47%), colorless crystals, mp 259–261°C. IR spectrum, ν, cm^{-1}: 3051 (NH^+), 2951, 2858 (CH_{Ad}), 1701 (C=O). ^1H NMR spectrum, δ, ppm: 0.86 s (3H, CH_3), 1.22–1.74 m (12H, CH_2, Ad), 2.10 (2H, CH_2), 8.29 br.s (3H, NH_3^+), 12.19 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 29.60 (CH_3), 32.45, 34.87, 40.46 (CH_2), 41.63 (CH_2), 43.02 (CH_2), 43.85 (CH_2), 45.57 (CH_2), 46.61 (CH_2), 46.83 (CH_2), 52.96, 172.65, 177.16. Found, %: C 55.39; H 7.34; N 4.65. $C_{14}H_{22}ClNO_4$. Calculated, %: C 55.35; H 7.30; N 4.61.

3-Carboxy-5-(carboxymethyl)-7-ethyladamantan-1-aminium chloride (3c) was obtained from 1.9 g (0.006 mol) of **2c** in a mixture of 13 mL of 36% aqueous HCl and 6 mL of water (reaction time 70 h). Yield 0.80 g (42%), colorless crystals, mp 236–238°C. IR spectrum, ν, cm^{-1}: 3010 (NH^+), 2927, 2858 (CH_{Ad}), 1716 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 t (3H, CH_3, J = 7.36 Hz), 1.14–1.76 m (14H, CH_2, Ad, CH_2), 2.10 s (2H, CH_2) 8.34 s (3H, NH_3^+), 12.24 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 7.50 (CH_3), 34.71, 34.82 (CH_2), 35.12, 40.74 (CH_2), 41.48 (CH_2), 41.93 (CH_2), 42.84, 43.13 (CH_2), 43.33 (CH_2), 44.44 (CH_2), 46.70 (CH_2), 53.03, 172.63, 177.24. Found, %: C 56.73; H 7.65; N 4.45. $C_{15}H_{24}ClNO_4$. Calculated, %: C 56.69; H 7.61; N 4.41.

3,5-Bis(carboxymethyl)adamantan-1-aminium chloride (3d). A mixture of 2.0 g (0.006 mol) of **2d** and 40 mL of 36% aqueous HCl was refluxed for 40 h. The mixture was evaporated, the oily residue was dissolved in acetic acid, and the solution was left to stand for crystallization. The precipitate (compound **4a**) was filtered off, and the filtrate was evaporated to isolate compound **3d**. Yield 1.0 g (51%), colorless crystals, mp 194–196°C. IR spectrum, ν, cm^{-1}: 3032 (NH^+), 2912, 2862 (CH_{Ad}), 1716 (C=O). ^1H NMR spectrum, δ, ppm: 1.35–1.39 m (6H, CH_2, Ad), 1.61–1.66 m (6H, CH_2, Ad), 2.03 s (4H, CH_2), 2.08 s (1H, CH, Ad), 8.22 s (3H, NH_3^+), 12.08 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 29.00 (CH), 34.51, 39.02 (CH_2), 39.94 (CH_2), 43.90 (CH_2), 45.45 (CH_2), 47.21 (CH_2), 52.63, 172.62. Found, %: C 55.38; H 7.33; N 4.64. $C_{14}H_{22}ClNO_4$. Calculated, %: C 55.35; H 7.30; N 4.61.

Compounds **3e** and **3f** were synthesized in a similar way.

3,5-Bis(carboxymethyl)-7-methyladamantan-1-aminium chloride (3e) was obtained by heating 1.0 g (0.003 mol) of **2e** in 25 mL of 36% aqueous HCl for 45 h. The oily residue was dissolved in glacial acetic acid. Yield 0.42 g (43%), colorless crystals, mp 199–200°C. IR spectrum, ν, cm^{-1}: 3010 (NH^+), 2926, 2912, 2854 (CH_{Ad}), 1701 (C=O). ^1H NMR spectrum, δ, ppm: 0.81 s (3H, CH_3), 1.06–1.38 m (8H, CH_2, Ad), 1.56 s (4H, CH_2, Ad), 2.04 s (4H, CH_2), 8.27 s (NH_3^+). ^{13}C NMR spectrum, δ_C, ppm: 29.77 (CH_3), 32.52, 35.03, 43.25 (CH_2), 44.81 (CH_2), 45.71 (CH_2), 46.90 (CH_2), 47.10 (CH_2), 53.21, 172.63. Found, %: C 56.72; H 7.64; N 4.44. $C_{15}H_{24}ClNO_4$. Calculated, %: C 56.69; H 7.61; N 4.41.

3,5-Bis(carboxymethyl)-7-ethyladamantan-1-aminium chloride (3f) was obtained by heating 1.3 g (0.0038 mol) of **2f** in 25 mL of 36% aqueous HCl for 45 h. The oily residue was dissolved in glacial acetic acid. Yield 0.55 g (43%), colorless crystals, mp 254–255°C. The yield of **3f** increased to 64% when the reaction was carried out in 5% aqueous HCl. IR spectrum, ν, cm^{-1}: 3008 (NH^+), 2962, 2854 (CH_{Ad}), 1701 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 t (3H, CH_3, J = 7.08 Hz), 1.11–1.19 m (6H, CH_2, Ad, CH_2CH_3), 1.24–1.28 m (1H, CH, Ad), 1.35–1.37 m (3H, CH, Ad), 1.58 s (4H, CH_2, Ad), 2.06 s (4H, CH_2), 8.27 s (3H, NH_3^+), 12.08 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 7.57 (CH_3), 34.89, 34.95 (CH_2), 35.24, 43.33 (CH_2), 43.58 (CH_2), 44.69 (CH_2), 45.14 (CH_2), 47.00 (CH_2), 53.27, 172.64. Found, %: C 57.95; H 7.94; N 4.26. $C_{16}H_{26}ClNO_4$. Calculated, %: C 57.91; H 7.90; N 4.22.

The solid products filtered off from acetic acid solutions in the synthesis of **3d**–**3f** were washed with water and dried. We thus isolated compounds **4a**–**4c**.

(5-Chloroadamantane-1,3-diyl)diacetic acid (4a). Yield 18%, colorless crystals, mp 205–207°C. IR spectrum, ν, cm^{-1}: 2935, 2912 (CH_{Ad}), 1716 (C=O). ^1H NMR spectrum, δ, ppm: 1.35–1.49 m (8H, CH_2, Ad), 1.84–1.92 m (4H, CH_2, Ad), 2.04 s (4H, CH_2), 2.15 s (1H, CH, Ad), 12.01 br.s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 31.44 (CH), 36.77, 39.46 (CH_2), 44.77 (CH_2), 46.24 (CH_2), 47.04 (CH_2), 51.26 (CH_2), 70.00, 172.66. Found, %: C 58.68; H 6.71. $C_{14}H_{19}ClO_4$. Calculated, %: C 58.64; H 6.68.

(5-Chloro-7-methyladamantane-1,3-diyl)diacetic acid (4b). Yield 10%, colorless crystals, mp 215–216°C. IR spectrum, ν, cm^{-1}: 2935, 2908, 2858 (CH_{Ad}), 1697 (C=O). ^1H NMR spectrum, δ, ppm: 0.82 s (3H, CH_3), 1.11–1.40 m (6H, CH_2, Ad), 1.66 s (2H, CH_2, Ad), 1.82 s (4H, CH_2, Ad), 2.05 s (4H, CH_2), 12.01 s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 29.65 (CH_3), 34.84, 37.10, 44.11 (CH_2), 46.60 (CH_2), 46.73 (CH_2), 50.52 (CH_2), 52.92 (CH_2), 70.04, 172.66. Found, %: C 59.94; H 7.07. $C_{15}H_{21}ClO_4$. Calculated, %: C 59.90; H 7.04.

(5-Chloro-7-ethyladamantane-1,3-diyl)diacetic acid (4c). Yield 15%, colorless crystals, mp 224–225°C. IR spectrum, ν, cm^{-1}: 2931, 2854 (CH_{Ad}), 1701 (C=O). ^1H NMR spectrum, δ, ppm: 0.73 t (3H, CH_3, J = 7.32 Hz), 1.12–1.42 m (8H, CH_2, Ad, C**H**$_2$CH$_3$), 1.65 s (2H, CH_2, Ad), 1.84 s (4H, CH_2, Ad), 2.07 s (4H, CH_2), 12.01 s (2H, COOH). ^{13}C NMR spectrum, δ_C, ppm: 7.60 (CH_3), 34.92 (CH_2), 36.95, 37.57, 44.17 (CH_2), 44.41 (CH_2), 46.82 (CH_2), 50.57 (CH_2), 50.86 (CH_2), 70.41, 172.68. Found, %: C 61.08; H 7.39. $C_{16}H_{23}ClO_4$. Calculated, %: C 61.05; H 7.36.

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