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To the 85th Anniversary of birthday of late Yu.G. Gololobov

Synthesis of α-Imino Derivatives of 1-Adamantylacetic and (3-Hydroxy-1-adamantyl)acetic Acids

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Abstract—α-Imino derivatives of 1-adamantylacetic and (3-hydroxy-1-adamantyl)acetic acids were synthesized. Isopropyl esters of 1-adamantyl-glycine and 3-hydroxy-1-adamantyl-glycine were prepared by hydrogenation of the corresponding oximes on Raney nickel.

Keywords: adamantane, imino derivatives, 1-adamantyl-glycine, 3-hydroxy-1-adamantyl-glycine

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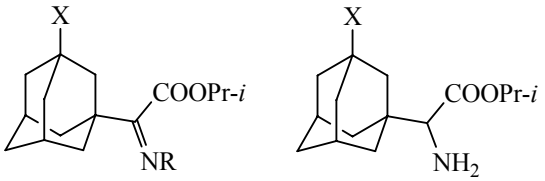
Nitrogen-containing adamantane derivatives are widely used in the treatment of neurodegenerative disorders, viral infections, and type 2 diabetes [1]. Introduction of adamantane moiety into the molecule of biologically active compound in some cases enhances its bioavailability and resistance to hydrolytic enzymes (amidases, esterases) [2–5]. One of the promising fields of the use of adamantyl-containing amino acids is the modification of biologically active peptides [6–8]. However, nitrogen-containing adamantane derivatives find the widest application as antiviral drugs, many of which (amantadine, rimantadine, tromantadine) are utilized in medical therapy [1, 9–13].

Initially it was believed that only aminoadamantane derivatives exhibit antiviral activity, while other classes of compounds have been much less studied. We have previously shown that adamantane derivatives of other classes like heterocyclic compounds and hydrazides show high antiviral activity [14–17]. In addition, antiviral activity of oximes and other imine derivative of adamantane series is known [18]. Of particular interest are amino and imino derivatives of adamantane containing other functional groups which allow their further modification. For example, 1-adamantyl-glycine and its derivatives possess antiviral activity towards influenza virus A [19].

The aim of this work was to develop method for the preparation of α-imino-α-amino derivatives of 1-adamantylacetic acid as compounds with potential antiviral activity and precursors for the synthesis of saxagliptin antidiabetic drug [20].



1a–**1f** **2a**, **2b**

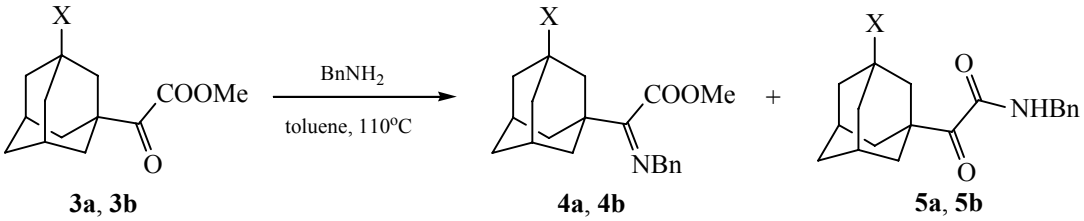
1, X = H, R = Bn (**a**); X = OH, R = Bn (**b**); X = H, R = OH (**c**); X = OH, R = OH (**d**); X = H, R = NH_2 (**e**); X = OH, R = NH_2 (**f**); **2**, X = H (**a**); X = OH (**b**).

Synthesis of α-imino derivatives was performed starting from 2-(1-adamantyl)-2-oxoacetic and 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acids.

The reaction between ketones and amines resulting in imino derivative is well known, but in the case of substrates containing multiple reaction sites it is complicated by the occurrence of side reactions. We found that methyl esters **3a** and **3b** reacted with benzylamine to form a mixture of the corresponding ketimines **4a**, **4b** and amides **5a**, **5b** in the ratio of 1 : 1 (Scheme 1).

The use of isopropyl ester of the corresponding acids provides selective reaction occurring at the carbonyl group.

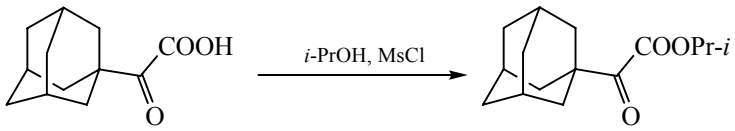
Scheme 1.



3a, **3b** **4a**, **4b** **5a**, **5b**

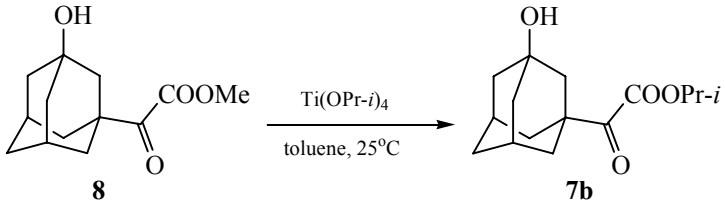
X = H (**a**), OH (**b**).

Scheme 2.



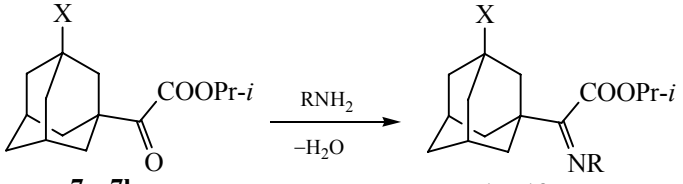
6 **7a**

Scheme 3.



8 **7b**

Scheme 4.



7a, **7b** **1a–1f**

7, X = H (**a**); X = OH (**b**); **1**, X = H, R = Bn (**a**); X = OH, R = Bn (**b**); X = H, R = OH (**c**); X = OH, R = OH (**d**); X = H, R = NH_2 (**e**); X = OH, R = NH_2 (**f**).

Isopropyl 2-(1-adamantyl)-2-oxoacetate **7a** was prepared by reacting acid **6** with isopropanol in the presence of methanesulfonyl chloride (Scheme 2).

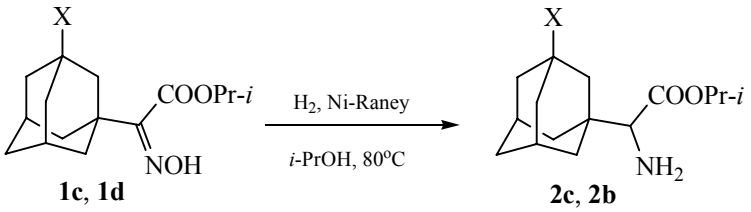
An attempt of the synthesis of isopropyl 2-(3-hydroxy1-adamantyl)-2-oxoacetate **7b** directly from compound **7a** by its hydroxylation in the presence of concentrated sulfuric and nitric acids in various conditions was unsuccessful due to the lability of isopropyl esters in a strongly acidic medium.

Isopropyl ester **7b** was prepared by reacting methyl ester **8** with titanium isopropoxide at room temperature in anhydrous toluene (Scheme 3).

α-Imino derivatives **1a**–**1f** were obtained by reacting esters **7a** and **7b** with benzylamine, hydrazine hydrate, and hydroxylamine, respectively (Scheme 4).

The reaction of esters **7a** and **7b** with benzylamine proceeded in toluene and resulted in the quantitative formation of the corresponding ketimines **1a** and **1b**. Oximes **1c** and **1d** (62–63% after recrystallization) were prepared by heating the esters **7a** and **7b** in a mixture with sodium acetate and hydroxylamine hydrochloride in methanol. Hydrazones **1e** and **1f** were synthesized by reacting esters **7a** and **7b** with hydrazine hydrate in isopropanol in a 50% yield after recrystallization.

Scheme 5.



1c, **1d** **2c**, **2b**

Synthesis of isopropyl esters of 1-adamantylglycine **2a** and (3-hydroxy-1-adamantyl)-glycine **2b** was performed by hydrogenating the corresponding oximes on Raney nickel (Scheme 5).

In summary, we synthesized a number of new α-imino-derivatives of esters of 1-adamantylacetic and (3-hydroxy-1-adamantyl)acetic acids with potential antiviral activity. High selectivity of the reaction of 2-(1-adamantyl)-2-oxoacetic and 2-(3-hydroxy-1-adamantyl)-2-oxoacetic acids was achieved by the use of isopropyl esters. Isopropyl ester of 1-adamantylglycine and (3-hydroxy-1-adamantyl)-glycine were prepared by hydrogenation of the corresponding oximes on Raney nickel.

EXPERIMENTAL

Elemental analysis was performed on an EuroVector EA 3000 analyzer. IR spectra were recorded on a Shimadzu IRAffinity-1 instrument from KBr pellets. NMR spectra ($CDCl_3$) were registered on a Jeol JNM-ECX400 spectrometer [399.78 (^{1}H) and 100.53 MHz (^{13}C)]. Mass spectra were obtained on a Finnigan Trace DCQ gas chromatography-mass spectrometer using SGE BPX-5 capillary column (30 m × 0.32 mm) at the energy of ionizing electrons of 70 eV.

Methyl 2-(1-adamantyl)-2-oxoacetate **3a** and methyl 2-(3-hydroxy1-adamantyl)-2-oxoacetate **3b** were obtained as described in [21].

Isopropyl 2-(1-adamantyl)-2-oxoacetate (7a). To a mixture of 30 g (0.14 mol) of 2-(1-adamantyl)-2-oxoacetic acid **6**, 28.6 g (0.36 mol) of pyridine and 18.5 g (0.31 mol) of 2-propanol in 66 mL of THF cooled to –5°C was added by portions 19.8 g (0.17 mol) of methanesulfonyl chloride. The stirring was continued, and the temperature was allowed to slowly rise to room temperature. The mixture was kept overnight, then poured into 1 L of saturated sodium hydrogen carbonate water solution, stirred for 30 min, and extracted with chloroform (2 × 250 mL). The extract was washed with sodium hydrogen carbonate solution and evaporated. The residue was dissolved in petroleum ether, washed subsequently with 5% acetic acid (100 mL), aqueous sodium hydrogen carbonate solution (2 × 100 mL) and water (50 mL), dried over sodium sulfate, and evaporated in a vacuum. Yield 26.3 g (73%). IR spectrum, ν, cm^{-1}: 2980, 2908, 2852, 1728, 1708, 1301, 1143, 1006. ^{1}H NMR spectrum, δ, ppm: 1.29 d (6H, CH_3, $^3J_{HH}$ 8.5 Hz), 1.67–1.70 m (6H, Ad), 1.86 br.s (6H, Ad), 2.01 br.s (3H, Ad), 5.12–5.14 septet (1H, CH, $^3J_{HH}$ 8.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.8 (CH_3, *i*-Pr), 27.6 (CH_2, Ad), 36.4 (CH_2, Ad), 37.3 (CH, Ad), 44.9 (C, Ad), 69.9 (CH, *i*-Pr), 164.00 (COO), 202.03 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 250 $[M]^+$, 193 (10), 163 (10) $[AdCO]^+$, 135 (100) $[Ad]^+$, 107 (7), 93 (10), 79 (8), 67 (15). Found, %: C 71.92; H 8.91. $C_{15}H_{22}O_3$. Calculated, %: C 71.97; H 8.86.

Isopropyl 2-(3-hydroxy-1-adamantyl)-2-oxoacetate (7b). To a solution of 7.0 g (0.03 mol) of methyl 2-(3-hydroxy-1-adamantyl)-2-oxoacetate **8** in 50 mL of anhydrous toluene was added 7.4 g (0.03 mol) of titanium(IV) isopropoxide while stirring under argon atmosphere. The resulting homogenic solution was kept at room temperature for 2 days. Then to the mixture was added 5 mL of water, and stirring was continued for 30 min. The reaction mixture was filtered. The organic layer was separated, and the aqueous layer was extracted with toluene. The combined toluene extracts were dried over sodium sulfate and evaporated in a vacuum. Yield 4.35 g (63%). IR spectrum, ν, cm^{-1}: 3406, 2920, 2858, 1724, 1708, 1300, 1149, 1068. ^{1}H NMR spectrum, δ, ppm: 1.28 d (6H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.56–1.77 m (12H, Ad), 2.26 br.s (2H, Ad), 5.10–5.14 septet (1H, CH, $^3J_{HH}$ 6.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 21.7 (CH_3, *i*-Pr), 30.1 (CH, Ad), 34.9 (CH_2, Ad), 36.2 (CH_2, Ad), 44.2 (CH_2, Ad), 44.6 (CH_2, Ad), 48.3 (C, Ad), 68.3 (COH, Ad), 70.3 (CH, *i*-Pr) 163.6 (COO), 200.3 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 266 $[M]^+$, 179 (8), 152 (10), 151, 133 (7), 107 (12), 95 (26), 93 (36), 91 (12), 43 (27). Found, %: C 67.59; H 8.39. $C_{15}H_{22}O_4$. Calculated, %: C 67.65; H 8.33.

Isopropyl 2-(1-adamantyl)-2-(benzylimino)-acetate (1a). A mixture of 0.52 g (2.0 mmol) of ester **7a**, 0.24 g (2.3 mmol) of benzylamine in 20 mL of toluene, and 10 mg of *p*-toluenesulfonic acid was refluxed with a Dean–Stark trap for 24 h. After the reaction completed, the solvent was evaporated in a vacuum. Yield 0.65 g. IR spectrum, ν, cm^{-1}: 3010, 2978, 2906, 2850, 1720, 1670, 1520. ^1H NMR spectrum, δ, ppm: 1.34 d (6H, CH_3, $^3J_{HH}$ 6.2 Hz), 1.74–1.75 m (6H, Ad), 1.92–1.93 m (6H, Ad), 2.06–2.07 m (3H, Ad), 4.55 s (2H, CH_2), 5.24–5.27 septet (1H, CH, $^3J_{HH}$ 6.2 Hz), 7.30–7.34 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.9 (CH_3, *i*-Pr), 27.7 (CH_2, Ad), 36.8 (CH_2, Ad), 40.1 (CH, Ad), 57.7 (CH_2, Bn), 69.1 (CH, *i*-Pr), 126.9 (*o*-C, Ph), 127.8 (*p*-C, Ph), 128.4 (*m*-C, Ph), 139.3 (*ipso*-C, Ph), 165.7 (COO), 171.8 (C=N). Mass spectrum, *m/z* (I_{rel}, %): 339 $[M]^+$ (28), 296 (5), 252 (28), 135 (5), 91 (100). Found, %: C 77.79; H 8.67; N 4.09. $C_{22}H_{29}NO_2$. Calculated, %: C 77.84; H 8.61; N 4.13.

Isopropyl 2-(benzylimino)-2-(3-hydroxy-1-adamantyl)acetate (1b) was prepared similarly from 1.20 g (4.51 mmol) of ether **7b**. Yield 1.60 g (100%). IR spectrum, ν, cm^{-1}: 3400, 3020, 2980, 2900, 2840, 1710, 1650, 1510. ^1H NMR spectrum, δ, ppm: 1.35 d (6H, CH_3, $^3J_{HH}$ 5.7 Hz), 1.75 br.s (6H, Ad), 1.92–1.95 br.s (6H, Ad), 2.07 br.s (3H, Ad), 4.55 s (2H, CH_2), 5.20 septet (1H, CH, $^3J_{HH}$ 5.7 Hz), 7.18–7.24 m (5H, Ph). ^{13}C NMR spectrum, δ_C, ppm: 21.7 (CH_3, *i*-Pr), 30.1 (CH, Ad), 34.9 (CH_2, Ad), 36.2 (CH_2, Ad), 44.2 (CH_2, Ad), 44.6 (CH_2, Ad), 48.3 (C, Ad), 57.7 (CH_2, Bn), 68.3 (COH, Ad), 69.2 (CH, *i*-Pr), 126.8 (*o*-C, Ph), 127.7 (*p*-C, Ph), 128.0 (*m*-C, Ph), 139.2 (*ipso*-C, Ph), 165.6 (COO), 171.7 (C=N). Mass spectrum, *m/z* (I_{rel}, %): 355 $[M]^+$ (28), 312 (5), 268 (35), 151 (5), 91 (100). Found, %: C 74.29; H 8.25; N 3.91. $C_{22}H_{29}NO_3$. Calculated, %: C 74.33; H 8.22; N 3.94.

Isopropyl 2-(1-adamantyl)-2-oxoacetate oxime (1c). A mixture of 3.0 g (12.0 mmol) of isopropyl 2-(1-adamantyl)-2-oxoacetate **7a**, 50 mL of methanol, 1.74 g (13.0 mmol) of sodium acetate trihydrate, and 0.86 g (13.0 mmol) of hydroxylamine hydrochloride was refluxed for 6 h. After the removal of methanol, the residue was dissolved in 25 mL of methylene chloride and filtered. The filtrate was dried over sodium sulfate and evaporated in a vacuum. The residue was recrystallized from petroleum ether–ethyl acetate mixture (5 : 1). Yield 2.0 g (63%), mp 130–132°C. IR spectrum, ν, cm^{-1}: 3286, 3259, 2924, 2854, 1728, 1620, 1184. ^1H NMR spectrum, δ, ppm: 1.32 d (6H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.57 br.s (2H, Ad), 1.66–1.75 m (9H, Ad), 1.80 br.s (2H, Ad), 2.26 m (2H, Ad), 5.23 septet (1H, CH, $^3J_{HH}$ 6.4 Hz), 8.17 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 21.9 (CH_3, *i*-Pr), 30.2 (CH, Ad), 34.9 (C, Ad), 38.4 (CH_2, Ad), 44.2 (CH_2, Ad), 69.7 (CH, *i*-Pr), 159.4 (C=N), 163.4 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 265 (7) $[M]^+$, 223 (35), 206 (100), 178 (67), 161 (69), 160 (95), 135 (97), 119 (16), 107 (21), 93 (52), 79 (56), 77 (34), 67 (21), 65 (10). Found, %: C 67.81; H 8.82; N 5.31. $C_{15}H_{23}NO_3$. Calculated, %: C 67.90; H 8.74; N 5.28.

Isopropyl 2-(3-hydroxy-1-adamantyl)-2-oxo-acetate oxime (1d) was prepared similarly from ester **7b**. Yield 60%, mp 115–117°C. IR spectrum, ν, cm^{-1}: 3390, 3298, 2931, 2920, 1728, 1650, 1180, 948. ^1H NMR spectrum, δ, ppm: 1.20 d (6H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.46–1.54 m (12H, Ad), 2.1 br.s (2H, Ad), 5.01 septet (1H, CH, $^3J_{HH}$ 6.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.1 (CH_3, *i*-Pr), 24.4 (CH, Ad), 24.7 (CH, Ad), 30.1 (CH_2, Ad), 35.3 (CH_2, Ad), 39.1 (CH_2, Ad), 44.6 (CH_2, Ad), 47.9 (CH_2, Ad), 66.6 (COH, Ad), 68.9 (CH, *i*-Pr), 158.1 (C=N), 164.1 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 281 $[M]^+$, 239, 222 (100), 176, 151. Found, %: C 63.95; H 8.31; N 5.01. $C_{15}H_{23}NO_4$. Calculated, %: C 64.04; H 8.24; N 4.98.

Isopropyl 2-(1-adamantyl)-2-oxoacetate hydrazone (1e). To a solution of 0.73 g (2.92 mmol) of ester **7a** in 20 mL of isopropanol was added 0.28 mL (6.00 mmol) of 64% hydrazine hydrate. The resulting mixture was refluxed for 1 h. The solvent was distilled off in a vacuum. The residue was recrystallized from 7 mL of petroleum ether. Yield 0.37 g (50.7%), mp 83–85°C. IR spectrum, ν, cm^{-1}: 3632, 3402, 2985, 2904, 2846, 1689, 1242, 1099. ^1H NMR spectrum, δ, ppm: 1.33 d (6H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.64–1.67 m (6H, Ad), 1.83–1.84 m (6H, Ad), 1.99 br.s (3H, Ad), 5.16 septet (1H, CH, $^3J_{HH}$ 6.4 Hz), 6.65 br.s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 21.8 (CH_3, *i*-Pr), 30.0 (CH, Ad), 35.1 (C, Ad), 38.2 (CH_2, Ad), 44.3 (CH_2, Ad), 69.7 (CH, *i*-Pr), 155.5 (C=N), 164.2 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 264 $[M]^+$ (20), 221 (35), 177 (70), 135 (100), 107 (15), 93 (20). Found, %: C 68.08; H 9.21; N 10.67. $C_{15}H_{24}N_2O_2$. Calculated, %: C 68.15; H 9.15; N 10.60.

Isopropyl 2-(3-hydroxy-1-adamantyl)-2-oxoacetate hydrazone (1f) was prepared similarly from ester **7b**. Yield 55.4%. IR spectrum, ν, cm^{-1}: 3630, 3410, 2980, 2900, 2845, 1685, 1240, 1090. ^1H NMR spectrum, δ, ppm: 1.19 d (6H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.45–1.55 m

(12H, Ad), 2.1 br.s (2H, Ad), 5.02 septet (1H, CH, $^3J_{HH}$ 6.4 Hz), 6.65 br.s (2H, NH_2). ^{13}C NMR spectrum, δ_C, ppm: 22.3 (CH_3, *i*-Pr), 24.5 (CH, Ad), 24.8 (CH, Ad), 30.3 (CH_2, Ad), 35.6 (CH_2, Ad), 39.0 (CH_2, Ad), 44.5 (CH_2, Ad), 47.7 (CH_2, Ad), 66.4 (COH, Ad), 69.0 (CH, *i*-Pr), 155.3 (C=N), 164.3 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 280 $[M]^+$ (10), 237 (20), 193 (70), 151 (100) $[HOAd]^+$. Found, %: C 64.21; H 8.69; N 10.01. $C_{15}H_{24}N_2O_3$. Calculated, %: C 64.26; H 8.63; N 9.99.

Isopropyl 2-(1-adamantyl)-2-aminoacetate (2a). A pressure reactor was charged with 2.65 g (10.0 mmol) of oxime **1c**, 20 mL of 2-propanol, and about 0.5 g of Raney nickel. Hydrogenation was carried out at 80°C and 20 at for 25 h. The solution was then filtered, and the filtrate was evaporated in a vacuum. Yield 2.50 g. ^1H NMR spectrum, δ, ppm: 1.22 d (6H, CH_3, $^3J_{HH}$ 6.2 Hz), 1.60–1.67 m (12H, Ad), 1.97 br.s (3H, Ad), 2.91 m (1H, CH), 5.02 septet (1H, CH, $^3J_{HH}$ 6.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.14 (CH_3, *i*-Pr), 28.47 (CH, Ad), 36.14 (C, Ad), 37.03 (CH_2, Ad), 38.59 (CH_2, Ad), 64.34 ($CHNH_2$), 67.98 (CH, *i*-Pr), 173.95 (COO). Mass spectrum, *m/z* (I_{rel}, %): 251 $[M]^+$, 164 (100), 135. Found, %: C 71.62; H 10.09; N 5.60. $C_{15}H_{25}NO_2$. Calculated, %: C 71.67; H 10.02; N 5.57.

Isopropyl 2-amino-2-(3-hydroxy-1-adamantyl)-acetate (2b) was prepared similarly from 2.81 g (10.0 mmol) of oxime **1d**. Yield 2.67 g (100%). ^1H NMR spectrum, δ, ppm: 1.22 d (6H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.50–1.72 m (12H, Ad), 2.19–2.20 m (2H, Ad), 2.99 s (1H, CH), 5.02 septet (1H, CH, $^3J_{HH}$ 6.4 Hz). ^{13}C NMR spectrum, δ_C, ppm: 22.0 (CH_3, *i*-Pr), 30.5 (CH, Ad), 35.5 (CH_2, Ad), 37.1 (CH_2, Ad), 39.8 (C, Ad), 44.6 (CH_2, Ad), 46.4 (CH_2, Ad), 52.3 (CH_3), 63.4 ($CHNH_2$), 68.3 (COH, Ad), 68.9 (CH, *i*-Pr), 173.8 (COO). Mass spectrum, *m/z* (I_{rel}, %): 267 $[M]^+$, 180 (100), 151 (6), 117 (12), 95 (20), 75 (42). Found, %: C 67.31; H 9.47; N 5.21. $C_{15}H_{25}NO_3$. Calculated, %: C 67.39; H 9.42; N 5.24.

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