ISSN 1070-4280, Russian Journal of Organic Chemistry, 2015, Vol. 51, No. 2, pp. 180–183. © Pleiades Publishing, Ltd., 2015.
Original Russian Text © E.A. Ivleva, V.S. Gavrilova, D.I. Gnusarev, V.A. Osyanin, Yu.N. Klimochkin, 2015, published in Zhurnal Organicheskoi Khimii, 2015, Vol. 51, No. 2, pp. 192–195.

Synthesis of Polycarboxylic Acids of Adamantane Series

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Received October 7, 2014

Abstract—Substituted 3-carboxymethyl-1-adamantanecarboxylic acids were obtained by the reaction of Koch-Haaf from the corresponding 1-adamantylacetic acids. A number of polycarboxylic acids was synthesized, containing carboxyl and carboxymethyl groups in their structure in various combinations.

DOI: 10.1134/S1070428015020062

The research on the methods of synthesis of polybasic carboxylic acids of adamantane series is connected with their wide synthetic potential. The derivatives of these acids are promising building blocks for designing peptidomimetics [1–3], functional nanostructures and materials [4–7], and they also possess various biologic actions [8–11]. Dibasic carboxylic acids of adamantine series containing both carboxylic and carboxymethyl groups in their structure are of particular interest for the preparation of new functional materials with useful application properties.

The existing methods of the synthesis of 3-carboxymethyl-1-adamantanecarboxylic acid utilize the nucleophilic substitution of nitroxy- [11], hydroxy- [12] and haloderivatives [13] of the corresponding monocarboxylic acids of the adamantane series in sulfuric acid medium. A method of preparation of 3-carboxymethyl-1-adamantanecarboxylic acid directly from 1-adamantylacetic acid is known [14].

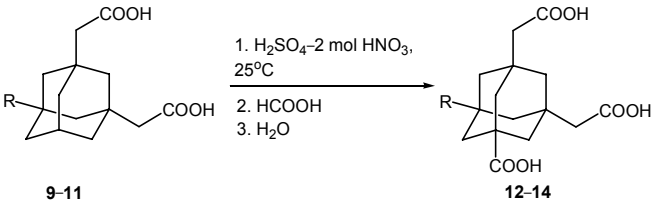
It is also known that the presence of electron-acceptor groups in the adamantane scaffold significantly reduces the initial substrate reactivity [15] limiting the possible functionalization of such compounds. The purpose of the present study is the development of preparation methods for polycarboxylic acids from the adamantane series containing in their structure carboxyl and carboxymethyl groups in various combinations.

By improving the existing method of the synthesis [14] we obtained alkyl-substituted 3-carboxymethyl-1-adamantancarboxylic acids (**5**–**8**) from the corresponding 1-adamantylacetic acids (**1**–**4**) in 75–91% yields.

1–4 **5–8**

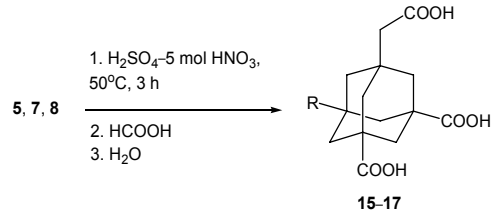
R = R' = H (**1**, **5**), CH_3 (**2**, **6**), R = CH_3, R' = H (**3**, **7**), R = C_2H_5, R' = H (**4**, **8**).

For the synthesis of tribasic acids the obtained acids **5**, **7**, and **8** and substituted 1,3-adamantyldiacetic acids **9**–**11** were used as initial substrates. To activate the C–H bond of the scaffold when introducing the carboxylic group in molecules of acids **9**–**11** the application of a double molar excess of fuming nitric acid in 96% sulfuric acid is sufficient; the reaction proceeds at room temperature. Compounds **12**–**14** are isolated in 77–89% yields. However for the synthesis of 5-carboxymethyl-1,3-adamantanedicarboxylic acids from the acids **5**, **7**, and **8** it is necessary to use a fivefold molar excess of fuming nitric acid, and the process should be carried out at 50°C for 3 h. The compounds **15**–**17** were separated in 47–74% yields.



9–11 **12–14**

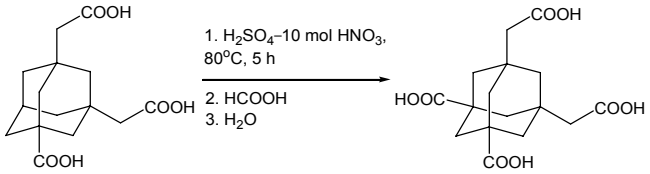
R = H (**9**, **12**), CH_3 (**10**, **13**), C_2H_5 (**11**, **14**).



15–17

R=H (**15**), CH_3 (**16**), C_2H_5 (**17**).

Further carboxylation of the tribasic acid **12** in the conditions of Koch-Haaf reaction requires harder conditions. For effective generation of adamantyl carbocation it is necessary to use a tenfold molar excess of fuming nitric acid. The reaction was performed at 80°C in 5 h, 25% oleum was used as the reaction environment. Reaction product **18** was separated in 64% yield.



12 **18**

The presence of the conformationaly rigid fragment and several carboxyl groups in structures of the obtained compounds allows using them as building blocks in the preparation of new materials with useful properties.

EXPERIMENTAL

^1H, ^{13}C NMR spectra were registered on a Jeol JNM ECX-400 spectrometer (working frequency 400 MHz) in DMSO-d_6. IR spectra were recorded on Shimadzu IRAffinity-1 spectrometer in tablets of KBr. Elemental analysis was carried out on elemental analyser Euro Vector 3000 EA using L-cystine as the standard.

Compounds 5–8 and 12–14. General method. To a solution of 0.1 mol of the corresponding 1-adamantylacetic acid (**1**–**4**) or 1,3-adamantyldiacetic acid (**9**–**11**) in 135 mL of 96% sulfuric acid while stirring and cooling was added dropwise 0.2 mol of fuming nitric acid maintaining the temperature of the reaction mixture no higher than 25°C. The reaction mixture was stirred for 1 h, then to the obtained solution during 3 h was added dropwise 5.8 mol of 100% formic acid maintaining the temperature of the reaction mixture no higher than 25°C. The reaction mixture was kept at room temperature for 12 h and then poured on 500 g of crushed ice. The precipitate was filtered off, washed with water, dried in air, and recrystallized from glacial acetic acid.

3-Carboxymethyl-1-adamantanecarboxylic acid (5). Yield 83%, mp 230–232°C (mp 236°C [13]).

3-Carboxymethyl-5,7-dimethyl-1-adamantanecarboxylic acid (6).Yield 91%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 2947, 2924, 2897 (CH_{Ad}), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 0.82 s (6H, $2CH_3$), 1.04–1.50 m (12H, $6CH_{2Ad}$), 2.03 s (2H, $C\underline{H}_2COOH$), 12.00 s (2H, 2COOH). ^{13}C NMR spectrum, δ, ppm: 30.44 (CH_3), 31.62 (C), 34.27 (S), 42.27 (CH_2), 42.66 (C), 44.62 (CH_2), 47.64 (CH_2), 47.72 (CH_2), 50.06 (CH_2), 172.92 (C), 178.53 (C). Found, %: C 67.69; H 8.35. $C_{15}H_{22}O_4$. Calculated, %: C 67.65; H 8.33.

3-Carboxymethyl-5-methyl-1-adamantanecarboxylic acid (7). Yield 75%, mp 140–142°C. IR spectrum, ν, cm^{-1}: 2922, 2902, 2852 (CH_{Ad}), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 0.78 s (3H, CH_3), 1.22–1.59 m (12H, $6CH_{2Ad}$), 1.98 s (1H, CH_{Ad}), 2.05 s (2H, $C\underline{H}_2COOH$), 11.58 br.s (2H, 2COOH). ^{13}C NMR spectrum, δ, ppm: 28.90 (CH_3), 30.88 (CH), 32.63 (C), 33.45 (C), 37.72 (CH_2), 41.79 (C), 42.82 (CH_2), 42.88 (CH_2), 45.23 (CH_2), 47.98 (CH_2), 48.37 (CH_2), 172.90 (C), 178.72 (C). Found, %: C 66.67; H 8.01. $C_{14}H_{20}O_4$. Calculated, %: C 66.65; H 7.99.

3-Carboxymethyl-5-ethyl-1-adamantanecarboxylic acid (8). Yield 79%, mp 168–170°C. IR spectrum, ν, cm^{-1}: 2960, 2910, 2852 (CH_{Ad}), 1697 (C=O). ^1H NMR spectrum, δ, ppm: 0.70–0.74 t (3H, CH_3, *J* 7.3 Hz), 1.07–1.12 q (2H, $\underline{C}H_2CH_3$, *J* 7.3 Hz), 1.17–1.57 m (10H, $5CH_{2Ad}$), 1.60 s (1H, CH_{Ad}), 1.99 s (2H, $\underline{C}H_2COOH$), 11.59 br.s (2H, 2COOH). ^{13}C NMR spectrum, δ, ppm: 7.42 (CH_3), 28.76 (CH), 33.33 (C), 33.34 (C), 35.90 (CH_2), 38.09 (CH_2), 40.19 (CH_2), 40.98 (CH_2), 41.64 (C), 42.81 (CH_2), 43.21 (CH_2), 45.94 (CH_2), 48.09 (CH_2), 172.91 (C), 178.74 (C). Found, %: C 67.67; H 8.36. $C_{15}H_{22}O_4$. Calculated, %: C 67.65; H 8.33.

3,5-Bis(carboxymethyl)-1-adamantanecarboxylic acid (12). Yield 89%, mp 269–271°C. IR spectrum, ν, cm^{-1}: 2937, 2912, 2856 (CH_{Ad}), 1730, 1691 (C=O). ^1H NMR spectrum, δ, ppm: 1.37–1.60 m (12H, $6CH_{2Ad}$), 1.99 s (4H, $2C\underline{H}_2COOH$), 2.04–2.05 m (1H, CH_{Ad}), 11.50 br.s (3H, 3COOH). ^{13}C NMR spectrum, δ, ppm: 28.63 (CH), 33.33 (C), 37.74 (CH_2), 40.64 (CH_2), 41.60 (C), 42.88 (CH_2), 45.95 (CH_2), 47.92 (CH_2), 172.85 (C), 178.50 (C). Found, %: C 60.83; H 6.84. $C_{15}H_{20}O_6$. Calculated, %: C 60.80; H 6.80.

3,5-Bis(carboxymethyl)-7-methyl-1-adamantanecarboxylic acid (13). Yield 79%, mp 228–230°C. IR spectrum, ν, cm^{-1}: 2943, 2908, 2854 (CH_{Ad}), 1693 (C=O). ^1H NMR spectrum, δ, ppm: 0.80 s (3H, CH_3), 1.12–1.23 m (4H, $2CH_{2Ad}$), 1.28–1.53 m (8H, $4CH_{2Ad}$), 2.11 s (4H, $2C\underline{H}_2COOH$), 11.53 br.s (3H, 3COOH). ^{13}C NMR spectrum, δ, ppm: 21.42 (CH_3), 42.12 (C), 42.30 (CH_2), 42.32 (C), 42.46 (C), 44.63 (CH_2), 45.32 (CH_2), 47.71 (CH_2), 47.97 (CH_2), 172.87 (C), 178.65 (C). Found, %: C 61.95; H 7.18. $C_{16}H_{22}O_6$. Calculated, %: C 61.92; H 7.15.

3,5-Bis(carboxymethyl)-7-ethyl-1-adamantanecarboxylic acid (14).Yield 77%, mp 240–242°C. IR spectrum, ν, cm^{-1}: 2912 (CH_{Ad}), 1697 (C=O). ^1H NMR spectrum, δ, ppm: 0.70–0.74 t (3H, CH_3, *J* 7.5 Hz), 1.09–1.15 q (2H, $C\underline{H}_2CH_3$, *J* 7.5 Hz), 1.17–1.20 m (4H, $2CH_{2Ad}$), 1.27–1.38 m (4H, $2CH_{2Ad}$), 1.50 s (4H, $2C\underline{H}_2COOH$), 2.02 s (2H, CH_{2Ad}), 8.09 br.s (3H, 3COOH). ^{13}C NMR spectrum, δ, ppm: 7.48 (CH_3), 33.96 (C), 34.03 (C), 35.56 (CH_2), 42.21 (CH_2), 42.32 (C), 42.65 (CH_2), 45.28 (CH_2), 45.66 (CH_2), 47.73 (CH_2), 172.83 (C), 178.48 (C). Found, %: C 62.97; H 7.49. $C_{17}H_{24}O_6$. Calculated, %: C 62.95; H 7.46.

Compounds 15–17. **General method**. To solution of 0.01 mol of the appropriate acid **5**, **7**, and **8** in 50 mL of 96% sulfuric acid while stirring and cooling 0.05 mol of fuming nitric acid was added dropwise maintaining the temperature of the reaction mixture no higher than 50°C, the mixture was kept at the adjusted temperature for 3 h, cooled, and 0.1 mol of 100% formic acid was added dropwise at 25-30°C while stirring intensively. The obtained solution was left standing for 24 h at room temperature, poured on 250 g of crushed ice, and left standing for 24 h more. The precipitate was filtered off, washed with a little of ice water. The mother liquor was neutralized to pH 4 using 30% aqueous solution of NaOH. The precipitate of inorganic salts was filtered off, the mother liquor was extracted with butanol (10 × 20 mL), the solvent was evaporated in a vacuum, the combined precipitates were recrystallized from glacial acetic acid.

5-Carboxymethyl-1,3-adamantanedicarboxylic acid (15). Yield 47%, mp 223–225°C. IR spectrum, ν, cm^{-1}: 2941, 2912, 2860 (CH_{Ad}), 1695 (C=O). ^1H NMR spectrum, δ, ppm: 1.37–1.79 m (12H, $6CH_{2Ad}$), 2.02 s (2H, $C\underline{H}_2COOH$), 2.08–2.09 m (1H, CH_{Ad}), 12.06 br.s (3H, 3COOH). ^{13}C NMR spectrum, δ, ppm: 28.30 (CH), 32.61 (C) 35.78 (CH_2), 38.36 (CH_2), 40.87 (C), 41.32 (CH_2), 43.45 (CH_2), 48.31 (CH_2), 172.92 (C), 178.74 (C). Found, %: C 59.60; H 6.45. $C_{14}H_{18}O_6$. Calculated, %: C 59.57; H 6.43.

5-Carboxymethyl-7-methyl-1,3-adamantanedicarboxylic acid (16). Yield 40%, mp 210–212°C. IR spectrum, ν, cm^{-1}: 2954, 2910 (CH_{Ad}), 1698 (C=O). ^1H NMR spectrum, δ, ppm: 0.82 s (3H, CH_3), 1.13–1.21 m (6H, $3CH_{2Ad}$), 1.29–1.37 m (4H, $2CH_{2Ad}$), 1.43–1.51 m (2H, CH_{2Ad}), 2.04 s (2H, $\underline{C}H_2COOH$), 11.48 br.s (3H, 3COOH). ^{13}C NMR spectrum, δ, ppm: 28.92 (CH_3), 33.48 (C), 34.94 (C), 37.41 (CH_2), 41.53 (C), 42.11 (CH_2), 43.88 (CH_2), 44.42 (CH_2), 46.12 (CH_2), 47.37 (CH_2), 171.50 (C), 178.28 (C). Found, %: C 60.78; H 6.81. $C_{15}H_{20}O_6$. Calculated, %: C 60.80; H 6.80.

5-Carboxymethyl-7-ethyl-1,3-adamantanedicarboxylic acid (17). Yield 74%, mp 265–267°C. IR spectrum, ν, cm^{-1}: 2962, 2941 (CH_{Ad}), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 0.71–0.75 t (3H, CH_3, *J* 7.3 Hz), 1.12–1.18 q (2H, $C\underline{H}_2CH_3$, *J* 7.3 Hz), 1.20–1.21 m (2H, CH_{2Ad}), 1.36–1.38 m (4H, $2CH_{2Ad}$), 1.50–1.53 m (4H, $2CH_{2Ad}$), 1.70–1.71 m (2H, CH_{2Ad}), 2.08 s (2H, $C\underline{H}_2COOH$), 10.08 s (3H, 3COOH). ^{13}C NMR spectrum, δ, ppm: 7.42 (CH_3), 33.72 (C), 33.84 (C), 35.42 (CH_2), 39.59 (CH_2), 42.06 (CH_2), 42.46 (CH_2), 45.01 (CH_2), 47.46 (CH_2), 170.81 (C), 178.19 (C). Found, %: C 61.96; H 7.18. $C_{16}H_{22}O_6$. Calculated, %: C 61.92; H 7.15.

5,7-Bis(carboxymethyl)-1,3-adamantanedicarboxylic acid (18). To 0.073 mol of fuming nitric acid while cooling was added by portions 22 mL of 35% oleum. Into the obtained mixture while stirring was added in one portion 7.3 mmol of the correspondding acid **11** and **13**. The reaction mixture was heated to 75–80°C, stirred intensively for 5 h, cooled to room temperature, and 1.92 mol of 100% formic acid was slowly added dropwise. The reaction mixture was kept for 12 h at room temperature and poured on 100 g of crushed ice. The obtained solution was neutralized to pH 4 using 30% aqueous solution of NaOH. The precipitate of inorganic salts was filtered off, the mother liquor was extracted with butanol (10 × 20 mL), the solvent was evaporated in a vacuum, the residue was recrystallized from glacial acetic acid. Yield 64%, mp 249–250°S. IR spectrum, ν, cm^{-1}: 2912, 2862, 2829 (CH_{Ad}), 1697 (C=O). ^1H NMR spectrum, δ, ppm: 1.36 s (2H, CH_{2Ad}), 1.53 s (8H, $4CH_{2Ad}$), 1.69 s (2H, CH_{2Ad}), 2.05 s (4H, $2C\underline{H}_2COOH$), 8.98 br.s (4H, 4COOH). ^{13}C NMR spectrum, δ, ppm: 33.71 (C), 39.28 (CH_2), 41.91 (C), 42.14 (CH_2), 45.09 (CH_2), 47.31 (CH_2), 172.74 (C), 177.97 (C). Found, %: C 56.50; H 5.96. $C_{16}H_{20}O_8$. Calculated, %: C 56.47; H 5.92.

The study was performed under the financial support of Russian Ministry of Education and Science (contract 14.574.21.0008, unique project identifier RFMEFI57414X0008) and Russian Foundation for Basic Research (grant no. 14-03-97075 r_Povolzhye_a).

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