ISSN 1070-4280, Russian Journal of Organic Chemistry, 2020, Vol. 56, No. 3, pp. 412–421. © Pleiades Publishing, Ltd., 2020.
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Oxidation of Deactivated Cage Substrates in the System H_2SO_4–HNO_3

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Received October 3, 2019; revised January 17, 2020; accepted January 17, 2020

Abstract—The kinetics of oxidation of 16 carboxylic acid esters of the adamantane series in the system H_2SO_4–HNO_3 have been studied, and the effective rate constants have been determined. The reaction is described by the pseudo-first-order kinetic equation. The primary kinetic isotope effect has been estimated at 2.9±0.3. The rate-determining step of the oxidation process is cleavage of the adamantane C–H bond. The presence of an ethyl group at the bridgehead position increases the reactivity of adamantane substrates toward oxidation, whereas methyl, ethoxycarbonyl, and ethoxycarbonylmethyl groups reduce the reactivity.

Keywords: kinetics, kinetic isotope effect, reactivity, adamantane, carboxylic acids, mixture of sulfuric and nitric acids

DOI: 10.1134/S1070428020030082

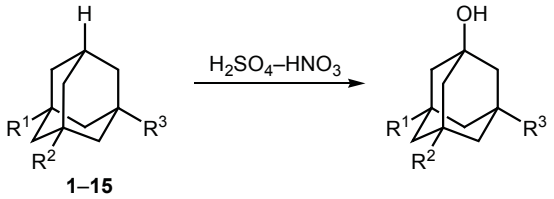
Interest in the chemistry of adamantane and its derivatives increases every year, which is determined by the unique structure of the adamantane skeleton. Of particular concern are adamantane derivatives containing functional groups at the bridgehead positions. They are important intermediate products for the synthesis of biologically active [1–6] and organometallic compounds [7, 8] and are also widely used in supramolecular chemistry [9–11] and in the design of high-technology materials [12–19] and polymers [20–24]. Medical and other applications of adamantane derivatives make it necessary to develop new synthetic approaches to the activation of C–H bonds therein and efficient methods for the introduction of functional groups. Among such methods, the most promising are those based on transformations of cage structures by the action of strong acids. At present, the system H_2SO_4–HNO_3 is extensively used in the functionalization of adamantane derivatives [25–37]. Oxidation of adamantane C–H bond with H_2SO_4–HNO_3 is one of the key stages in the synthesis of vildagliptin [38–40] and saxagliptin drug substances [41–43] that are used in the treatment of type II diabetes, as well as of other biologically active compounds [44–50].

Study of the kinetics of oxidation of adamantane derivatives in the system H_2SO_4–HNO_3 is of both theoretical and practical importance. It could provide a deeper insight into the reaction mechanism, make it possible to predict the reactivity of substrates, and contribute to understanding the nature of intermediate species, thus opening ways for intentional control over the oxidation process.

The problem of C–H bond activation in cage substrates, especially in those containing several electron-withdrawing substituents at the bridgehead positions, remains an important field of research [51]. We previously performed a comprehensive study of the kinetics of reactions of adamantane, its homologs, and some functional derivatives with fuming nitric acid [52, 53]. In the present work we focused on the kinetics of oxidation of deactivated cage substrates with a mixture of sulfuric and nitric acids with a view to comparing the obtained results with the data of [54] where the kinetics of reactions of some substrates were studied by the microcalorimetric method.

The kinetics of oxidation of lower alkanes with H_2SO_4–HNO_3 were studied by Rudakov et al. [55]. Proper application of the Rudakov method to adamantane substrates requires knowledge of their solubility parameters in sulfuric acid, which are difficult to determine. Therefore, we used as substrates carboxylic acid esters of the adamantane series, which are soluble in sulfuric acid. Esters **1**–**15** were synthesized by esterification of the corresponding mono-, di-, and tricarboxylic acids of the adamantane series, including those containing alkyl substituents; their oxidation in

Scheme 1.



R^1 = COOEt, R^2 = R^3 = H (**1**), R^1 = COOEt, R^2 = Me, R^3 = H (**2**), R^1 = COOEt, R^2 = Et, R^3 = H (**3**), R^1 = COOEt, R^2 = R^3 = Me (**4**), R^1 = R^2 = CH_2COOEt, R^3 = H (**5**), R^1 = R^2 = CH_2COOEt, R^3 = Me (**6**), R^1 = R^2 = CH_2COOEt, R^3 = Et (**7**), R^1 = COOEt, R^2 = CH_2COOEt, R^3 = H (**8**), R^1 = COOEt, R^2 = CH_2COOEt, R^3 = Me (**9**), R^1 = COOEt, R^2 = CH_2COOEt, R^3 = Et (**10**), R^1 = R^2 = COOEt, R^3 = H (**11**), R^1 = R^2 = COOEt, R^3 = Me (**12**), R^1 = R^2 = COOEt, R^3 = Et (**13**), R^1 = R^2 = CH_2COOEt, R^3 = COOEt (**14**), R^1 = R^2 = COOEt, R^3 = CH_2COOEt (**15**).

the system H_2SO_4–HNO_3 can be illustrated by Scheme 1. In order to estimate primary kinetic isotope effect, we synthesized deuterated ester **16** from carboxylic acid **19**. Acid **19** was prepared in turn from hydroxy carboxylic acid **17** through 3-iodo-5,7-dimethyladamantane-1-carboxylic acid (**18**) (Scheme 2). The yield of **19** was 32%, and its isotope purity was 67% according to the MS data for its methyl ester obtained by treatment of **19** with a solution of diazomethane in diethyl ether (the intensity of the molecular ion peak of acid **19** methyl ester was compared with that of its non-deuterated analog). In the ^{13}C NMR spectrum of **19**, the signal of the carbon atom linked to deuterium was a triplet with a coupling constant J of 21.0 Hz. The ^{13}C NMR spectrum of **16** showed a triplet at δ_C 28.8 ppm (J = 20.0 Hz) due to the C–D carbon atom. The isotope purity of **16** was 66% (according to the GC/MS data).

The reaction mixtures were analyzed by GLC after preliminary quenching by pouring onto crushed ice. Nitric acid in a mixture with sulfuric acid behaves as a base which gives rise to nitronium ion, and the latter directly participates in the activation of tertiary C–H bond [56, 57]. Stabilization of the intermediate with sulfuric acid gives protonated sulfonic acid ester which is deprotonated to sulfonic acid ester. When the reaction mixture is poured onto ice, instantaneous hydrolysis of the sulfonic acid ester yields the corresponding hydroxy derivative.

The kinetics of the oxidation of esters **1**–**16** were studied using 92% sulfuric acid and 5 equiv of fuming nitric acid in methylene chloride. The components of the reaction mixtures were quantitated by the internal standard method using *p*-dinitrobenzene. We used 92% sulfuric acid, taking into account that more concentrated sulfuric acid (94–96%) promoted appreciable hydrolysis of esters **1**–**16**. The reactions were carried out at 22°C, the initial concentrations of esters **1**–**16** were c_0 = 0.030–0.052 M, and the concentrations of nitric and sulfuric acids were varied in the ranges 0.03–0.26 and 18.4–18.5 M, respectively.

Since fuming nitric acid was taken in excess (5 equiv), change of its concentration during the reaction can be neglected, so that the reaction was presumed to follow pseudo-first-order kinetics:

$$\partial c/\partial\tau = k[S][HNO_3]_n;\ [HNO_3] = \text{const};$$
$$\partial c/\partial\tau = k_{ef}[S],\ \text{where}\ k_{ef} = k[HNO_3]_n.$$

In fact, the pseudo-first order of the reaction is confirmed by the linear character of the semilog kinetic curves (Fig. 1).

Table 1 contains the effective rate constants for the oxidation of esters **1**–**15** in the system H_2SO_4–HNO_3. We also calculated the relative rate constants with account taken of the number of C–H bonds capable of being involved in the reaction. Analysis of the obtained effective rate constants shows that introduction of alkyl groups into the bridgehead positions changes the reactivity of adamantane-containing esters. In particular, methyl groups in the bridgehead positions slightly

Scheme 2.

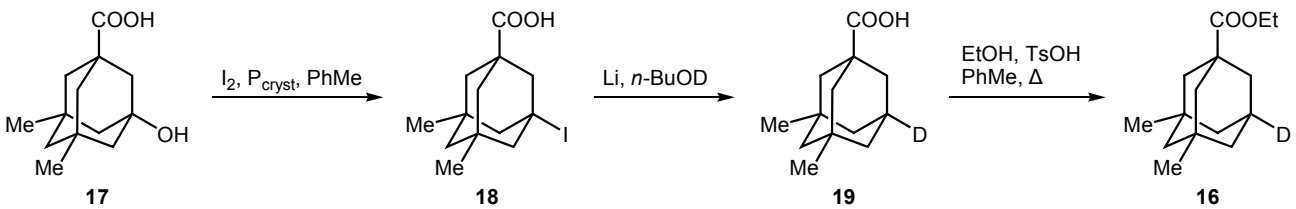


Table 1. Rate constants for the oxidation of esters **1**–**16** of the adamantane series in the system H_2SO_4–HNO_3 at 22°C

Substrate, R_nAd	k_{ef}, s^{-1}	k_{ef},[a] s^{-1}	k_{rel}	k_{rel}[b]
1-COOEt (**1**)	$(3.72\pm0.47)\times10^{-3}$	3.72×10^{-3}	1	1
3-Me-1-COOEt (**2**)	$(3.00\pm0.32)\times10^{-3}$	4.50×10^{-3}	0.806	1.209
3-Et-1-COOEt (**3**)	$(4.20\pm0.47)\times10^{-3}$	6.30×10^{-3}	1.129	1.693
3,5-Me_2-1-COOEt (**4**)	$(1.87\pm0.41)\times10^{-3}$	5.61×10^{-3}	0.502	1.508
7-D-3,5-Me_2-1-COOEt (**16**)	$(1.58\pm0.49)\times10^{-3}$	4.74×10^{-3}	0.425	1.275
1,3-$(CH_2COOEt)_2$ (**5**)	$(1.25\pm0.36)\times10^{-3}$	1.88×10^{-3}	0.336	0.504
5-Me-1,3-$(CH_2COOEt)_2$ (**6**)	$(1.01\pm0.33)\times10^{-3}$	3.03×10^{-3}	0.271	1.317
5-Et-1,3-$(CH_2COOEt)_2$ (**7**)	$(1.35\pm0.38)\times10^{-3}$	4.05×10^{-3}	0.363	1.089
3-CH_2COOEt-1-COOEt (**8**)	$(1.64\pm0.11)\times10^{-4}$	2.46×10^{-4}	0.044	0.066
5-Me-3-CH_2COOEt-1-COOEt (**9**)	$(1.39\pm0.16)\times10^{-4}$	4.17×10^{-4}	0.037	0.111
5-Et-3-CH_2COOEt-1-COOEt (**10**)	$(1.73\pm0.11)\times10^{-4}$	5.19×10^{-4}	0.046	0.138
1,3-$(COOEt)_2$ (**11**)	$(2.74\pm0.27)\times10^{-5}$	4.11×10^{-5}	0.007	0.011
5-Me-1,3-$(COOEt)_2$ (**12**)	$(3.50\pm0.14)\times10^{-5}$	10.50×10^{-5}	0.009	0.027
5-Et-1,3-$(COOEt)_2$ (**13**)	$(4.05\pm0.13)\times10^{-5}$	12.15×10^{-5}	0.011	0.033
3,5-$(CH_2COOEt)_2$-1-COOEt (**14**)	$(8.14\pm0.61)\times10^{-5}$	24.42×10^{-5}	0.022	0.066
5-CH_2COOEt-1,3-$(COOEt)_2$ (**15**)	$(2.27\pm0.25)\times10^{-5}$	6.81×10^{-5}	0.006	0.018

[a] Rate constants calculated with account taken of the number of possible reaction centers.
[b] Ratio of the rate constants calculated with account taken of the number of possible reaction centers.

reduce the substrate reactivity. For example, the rate of oxidation of ethyl 3,5-dimethyladamantane-1-carboxylate (**4**) is twice as low as that of ethyl adamantane-1-carboxylate (**1**). On the other hand, ethyl substitution at the bridgehead position slightly increases the reaction rate. This is typical of reactions of adamantane substrates involving formation of a carbocation [52, 53, 58–60].

It is important that the presence of an ethoxycarbonyl or ethoxycarbonylmethyl group on the bridgehead carbon atom sharply reduces the reactivity. The rate of oxidation of ethyl adamantane-1-carboxylate (**1**) is 90 times higher than the rate of oxidation of diethyl adamantane-1,3-dicarboxylate (**11**). The deactivating effect of an ethoxycarbonylmethyl group is weaker:

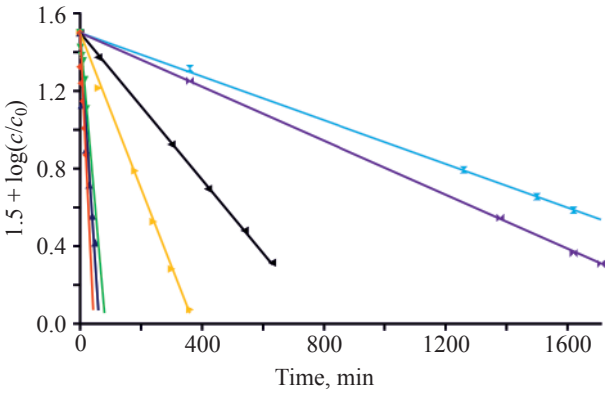


Fig. 1. Semilog kinetic curves for the oxidation of carboxylic acid esters of the adamantane series at 22°C.

ester **1** is 15 times more reactive than diester **8**. If the substrate contains two or more bridgehead substituents, their effect on the oxidation rate is additive. The presence of two ethoxycarbonylmethyl groups in triester **14** makes it less reactive than ester **1** by a factor of 15.2 with account taken of the number of possible reaction centers. Triester **15** containing both ethoxycarbonyl and ethoxycarbonylmethyl groups is 55 times less reactive than ester **1**. The relative oxidation rate constant of diethyl 2,2′-(adamantane-1,3-diyl)diacetate (**5**) is only twice as low as the relative oxidation rate constant of ester **1**.

Our data on the relative reactivity of adamantane-containing esters do not contradict published data on the relative reactivity of adamantane derivatives [52, 54, 59, 60].

The activation parameters of the oxidation of esters **1** and **4** were determined from the linear temperature dependences of their effective oxidation rate constants in the temperature range 2–32°C (Table 2) without taking into account temperature variation of the state of ion–molecule equilibria in the reaction medium.

The rate-determining step of the oxidation process was determined by measuring the primary kinetic isotope effect in the oxidation of ethyl 3,5-dimethyl-[7-^{2}H]adamantane-1-carboxylate (**16**). It was estimated as the ratio of the effective oxidation rate constants at 22°C of ethyl 3,5-dimethyladamantan-1-carboxylate

Table 2. Rate constants for the oxidation of esters **1** and **4** in the system H_2SO_4–HNO_3 at different temperatures

Ester no.	Temperature, °C	k_{eff}, s^{-1}	E_a, kJ/mol	ΔS, J mol^{-1} K^{-1}
1	2	$(0.73\pm0.06)\times10^{-3}$	48.75±0.75	–32.00±0.57
	12	$(1.19\pm0.13)\times10^{-3}$		
	22	$(3.72\pm0.47)\times10^{-3}$		
	32	$(5.00\pm0.35)\times10^{-3}$		
4	2	$(0.50\pm0.34)\times10^{-3}$	46.79±0.35	–34.91±0.45
	12	$(0.98\pm0.07)\times10^{-3}$		
	22	$(1.87\pm0.41)\times10^{-3}$		
	32	$(3.50\pm0.34)\times10^{-3}$		

(**4**) and ester **16**, $k_H/k_D = 2.9\pm0.3$. This value was calculated with a correction for the isotope purity of **16** equal to 66%. Thus, the oxidation rate constants obtained in our kinetic experiments refer to the rate-determining step which is dissociation of the C–H bond. It should be noted that the primary kinetic isotope effect in the reaction of 1,3,5-trimethyladamantane with fuming nitric acid was $k_H/k_D = 4.4$ [52], and in the oxidation of 2-methylpropane with a mixture of sulfuric and nitric acids, $k_H/k_D = 2$ [60].

The effect of electron-withdrawing substituents was estimated by plotting the logarithms of the relative effective oxidation rate constants for esters **5**–**15** versus Taft inductive constants σ* ($r = 0.914$, $\rho^* = -0.53$; Fig. 2). The σ* values were taken from [61]. The negative sign of ρ* indicates that electron-withdrawing substituents hamper formation of carbocation, thus decelerating the reaction:

$$\log k_{eff} = -(4.22\pm0.26) - (0.53\pm0.12)\sigma^*.$$

The lack of a satisfactory correlation may be rationalized assuming that mutual interactions between several electron-withdrawing substituents could change geometric structure of the adamantane skeleton. Figure 3 shows the reactivity series of adamantane esters in the oxidation with H_2SO_4–HNO_3.

Presumably, the oxidation of adamantane-containing esters in the system H_2SO_4–HNO_3 involves generation of a tertiary adamantyl cation with dissociation of the C–H bond as the rate-determining step. Nitronium cation mediates single-electron transfer with the formation of adamantyl radical cation and simultaneous elimination of proton to give adamantyl radical which is rapidly oxidized with nitronium ion to carbocation. The latter is stabilized via addition of a nucleophilic species predominating in the reaction medium.

EXPERIMENTAL

The IR spectra were recorded on a Shimadzu IR Affinity-1 spectrometer (Japan) equipped with an ATR accessory. The ^1H and ^{13}C NMR spectra were recorded on a Jeol NMR-ECX400 spectrometer (Japan) at 400 and 100 MHz, respectively, using tetramethylsilane as internal standard. The reaction mixtures were analyzed with a Thermo Scientific Focus gas chromatograph (USA) equipped with a DB-5 quartz capillary column, 30 m × 0.32 mm; oven temperature programming from 80 to 340°C at a rate of 20 deg/min; injector temperature 250°C; carrier gas helium. The mass spectra (electron impact, 70 eV) were obtained on a Finnigan Trace DSQ mass spectrometer (USA). The melting points were measured in capillary tubes using an MPM-H2 melting point apparatus (Germany) and are uncorrected. Elemental analysis was performed with a EuroVector 3000 EA analyzer (Italy) using L-cystine as standard. Initial adamantanecarboxylic acids were synthesized according to the procedures described in [29] or taken from the collection of chemicals at the Organic Chemistry Department of the Samara State Technical University; their purity was ≥95.0%.

3-Iodo-5,7-dimethyladamantane-1-carboxylic acid (18). A mixture of 55 g (0.245 mol) of 3-hydroxy-

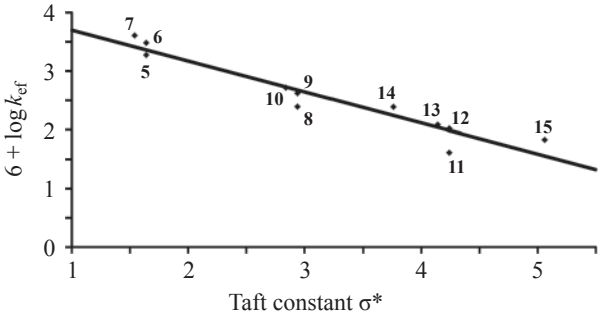


Fig. 2. Correlation between the rate constants of oxidation of esters **5**–**15** at 22°C and Taft substituent constants σ*.

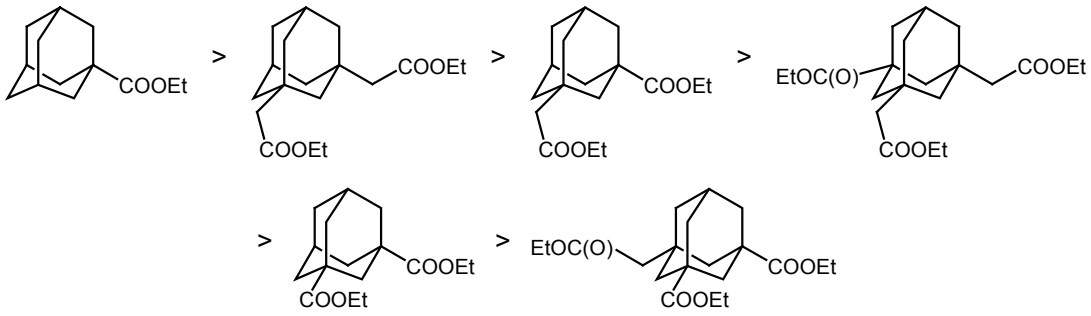


Fig. 3. Reactivity series for the oxidation of some adamantanecarboxylic acid esters in the system H_2SO_4–HNO_3 at 22°C.

5,7-dimethyladamantane-1-carboxylic acid (**17**), 275 mL of toluene, 2.05 g (0.066 mol) of red phosphorus, and 37.4 g (0.147 mol) of iodine was heated at 80°C with vigorous stirring under argon for 10 h. The mixture was cooled to room temperature and washed with 350 mL of 10% aqueous sodium thiosulfate, the organic layer was separated, and the aqueous layer was extracted with methylene chloride (5×50 mL). The extracts were combined with the organic phase and dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure on a rotary evaporator, and the residue was purified by recrystallization from cyclohexane. Yield 56.20 g (69%), colorless crystals, mp 156–158°C. IR spectrum, ν, cm^{-1}: 2850, 2922, 2945 (C–H), 1693 (C=O). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 0.79 s (6H, CH_3), 1.15–1.23 m (2H, CH_2), 1.44–1.52 m (4H, CH_2), 2.10–2.17 m (4H, CH_2), 2.41 s (2H, CH_2), br.s (1H, COOH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 29.5 (2C, CH_3), 35.7, 43.3 (CH_2), 45.8, 48.6 (CH_2), 49.4, 51.7 (CH_2), 57.1 (2C, CH_2), 176.5. Found, %: C 46.77; H 5.79. $C_{13}H_{19}IO_2$. Calculated, %: C 46.72; H 5.73.

3,5-Dimethyl[7-^{2}H]adamantane-1-carboxylic acid (19). A solution of 10 g (0.03 mol) of acid **18** in 150 mL of anhydrous dioxane was heated to the boiling point, and 10 g (0.133 mol) of butan-1-(^{2}H)ol was added with vigorous stirring. Metallic lithium, 1.4 g (0.2 mol), was then added to the boiling mixture, the mixture was kept until lithium dissolved completely, and additional 10 g (0.133 mol) of butan-1-(^{2}H)ol and 1.4 g (0.2 mol) of lithium were added. The progress of the reaction was monitored by GLC. After completion of the reaction, the mixture was poured into water, acidified to pH 1–2 with concentrated aqueous HCl, and extracted with methylene chloride (5×30 mL). The combined extracts were washed with 10% aqueous sodium thiosulfate (5×40 mL), dried over anhydrous sodium sulfate, and evaporated on a rotary evaporator under reduced pressure. The residue was purified by recrystallization from aqueous methanol. Yield 2.02 g (32%), isotope purity 67%. IR spectrum, ν, cm^{-1}: 2905–2846 (C–H), 1685 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.84 s (6H, CH_3), 1.15 s (2H, CH_2), 1.28–1.41 m (4H, CH_2), 1.57–1.48 m (4H, CH_2), 1.72 s (2H, CH_2), 11.53 br.s (1H, COOH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 28.7 t (C–D, J = 21.0 Hz), 30.5 (CH_3), 30.9, 37.2 (CH_2), 37.3 (CH_2), 42.4, 42.6 (CH_2), 42.7 (CH_2), 44.7 (CH_2), 50.7 (CH_2), 183.9 (C=O). Mass spectrum (ethyl ester), m/z (I_{rel}, %): 223 (14) $[M]^+$, 222 (9) $[M-1]^+$, 164 (100), 163 (82), 148 (8), 147 (6), 108 (25), 107 (23), 91 (9), 79 (5), 55 (5).

Esters 1–16 (*general procedure*). A mixture of 0.02 mol of the corresponding carboxylic acid, 15 mL of ethanol, and 5 mol % of *p*-toluenesulfonic acid in 100 mL of toluene was refluxed in a flask equipped with a Dean–Stark trap until water no longer separated. The mixture was cooled and washed with water, a solution of sodium hydrogen carbonate, and water again. The organic phase was dried over anhydrous sodium sulfate and evaporated, and the oily residue was purified by vacuum distillation.

Ethyl adamantane-1-carboxylate (1). Yield 3.03 g (73%), bp 70–72°C (0.06 mm Hg); published data [62]: bp 88–90°C (0.06 mm Hg); purity 99.3% (GLC).

Ethyl 3-methyladamantane-1-carboxylate (2). Yield 2.93 g (66%), bp 58–59°C (0.015 mm Hg), purity 96.5% (GLC), n_D^{20} = 1.4890. IR spectrum: ν 1729 cm^{-1} (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 s (3H, CH_3), 1.22 t (3H, $CH_2C\mathbf{H}_3$, J = 7.1 Hz), 1.56–1.60 m (4H, CH_2), 1.68–1.70 m (2H, CH_2), 1.73–1.83 m (4H, CH_2), 1.87 s (2H, CH_2), 2.04–2.05 m (2H, CH), 4.07 q (2H, OCH_2, J = 7.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 (CH_3), 28.6 (CH), 30.1, 30.9 (CH_3), 36.6 (CH_2), 38.2 (CH_2), 41.6, 43.6 (CH_2), 45.6 (CH_2), 60.1 (OCH_2), 177.9. Found, %: C 75.69; H 10.05. $C_{14}H_{22}O_2$. Calculated, %: C 75.63; H 9.97.

Ethyl 3-ethyladamantane-1-carboxylate (3). Yield 3.40 g (72%), bp 76–77°C (0.012 mm Hg), purity

98.4% (GLC), n_D^{20} = 1.4889. IR spectrum: ν 1729 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.76 t (3H, CH_3, J = 7.6 Hz), 1.15 q (2H, CH_2, J = 7.6 Hz), 1.21 t (3H, CH_3, J = 7.8 Hz), 1.39–1.43 m (4H, CH_2), 1.54–1.61 m (4H, CH_2), 1.76–1.79 m (4H, CH_2), 2.04–2.05 m (2H, CH), 4.08 q (2H, OCH_2, J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.0 (CH_3), 14.3 (CH_3), 28.5 (CH), 32.6, 36.2, 36.3 (CH_2), 38.6 (CH_2), 41.0 (CH_2), 41.5, 43.2 (CH_2), 60.1 (OCH_2), 177.9. Found, %: C 76.28; H 10.29. $C_{15}H_{24}O_2$. Calculated, %: C 76.23; H 10.24.

Ethyl 3,5-dimethyladamantane-1-carboxylate (4). Yield 3.30 g (70%), bp 70–71°C (0.017 mm Hg), purity 99.5% (GLC), n_D^{20} = 1.4910. IR spectrum: ν 1730 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 s (6H, CH_3), 1.14 s (2H, CH_2), 1.22 t (3H, CH_3, J = 7.8 Hz), 1.28–1.37 m (4H, CH_2), 1.45–1.54 m (4H, CH_2), 1.69–1.70 m (2H, CH_2), 2.06–2.11 m (1H, CH), 4.08 q (2H, OCH_2, J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 (CH_3), 29.3 (CH), 30.5 (2C, CH_3), 31.0, 37.6 (CH_2), 42.5, 42.9 (CH_2), 45.0 (CH_2), 50.8 (CH_2), 60.1 (OCH_2), 177.7. Found, %: C 76.30; H 10.28. $C_{15}H_{24}O_2$. Calculated, %: C 76.23; H 10.24.

Diethyl 2,2′-(adamantane-1,3-diyl)diacetate (5). Yield 4.93 g (80%), bp 161–162°C (0.1 mm Hg), purity 99.8% (GLC). The spectral characteristics of **5** were reported previously [7].

Diethyl 2,2′-(5-methyladamantane-1,3-diyl)diacetate (6). Yield 4.18 g (65%), bp 164–165°C (0.1 mm Hg), purity 98.2% (GLC), n_D^{20} = 1.4894. IR spectrum: ν 1727 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.82 s (3H, CH_3), 1.20 t (6H, CH_3, J = 7.1 Hz), 1.22–1.40 m (12H, CH_2), 1.92–1.95 m (1H, CH), 2.05 s (4H, CH_2), 4.03 q (4H, OCH_2, J = 7.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.1 (CH_3), 29.3 (CH), 33.9, 34.0, 36.0 (CH_2), 40.5 (CH_2), 41.3 (CH_2), 45.8 (CH_2), 46.9 (CH_2), 48.2 (CH_2), 60.0 (OCH_2), 171.7. Found, %: C 70.83; H 9.45. $C_{19}H_{30}O_4$. Calculated, %: C 70.77; H 9.38.

Diethyl 2,2′-(5-ethyladamantane-1,3-diyl)diacetate (7). Yield 4.64 g (69%), bp 172–173°C (0.1 mm Hg), purity 96.5% (GLC), n_D^{20} = 1.4892. IR spectrum: ν 1727 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.71 t (3H, CH_3, J = 7.4 Hz), 1.09 t (2H, CH_2, J = 7.4 Hz), 1.18 t (6H, CH_3, J = 7.1 Hz), 1.20–1.37 m (12H, CH_2), 1.91–1.93 m (1H, CH), 2.03 s (4H, CH_2), 4.05 q (4H, OCH_2, J = 7.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.0 (CH_3), 14.4 (CH_3), 29.2 (CH), 33.8, 34.0, 35.8 (CH_2), 40.2 (CH_2), 41.1 (CH_2), 46.0 (CH_2), 46.9 (CH_2), 48.2 (CH_2), 59.9 (OCH_2), 171.6. Found, %: C 71.44; H 9.65. $C_{20}H_{32}O_4$. Calculated, %: C 71.39; H 9.59.

Ethyl 3-(2-ethoxy-2-oxoethyl)adamantane-1-carboxylate (8). Yield 3.12 g (53%), bp 105–106°C (0.005 mm Hg), purity 99.7% (GLC). The spectral characteristics of **8** were reported previously [7].

Ethyl 3-(2-ethoxy-2-oxoethyl)-5-methyladamantane-1-carboxylate (9). Yield 4.75 g (77%), bp 155–156°C (0.1 mm Hg), purity 97.2% (GLC), n_D^{20} = 1.4799. IR spectrum: ν 1730 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.83 s (3H, CH_3), 1.22 t (6H, CH_3, J = 7.1 Hz), 1.28–1.35 m (4H, CH_2), 1.49–1.52 m (4H, CH_2), 1.63–1.66 m (2H, CH_2), 1.67–1.71 m (2H, CH_2), 2.10 s (2H, CH_2), 2.11–2.14 m (1H, CH), 4.06–4.10 m (4H, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 (CH_3), 14.4 (CH_3), 29.0 (CH_3), 30.4 (CH), 30.9, 33.8, 37.5 (CH_2), 40.6 (CH_2), 42.3, 42.7 (CH_2), 42.9 (CH_2), 44.9 (CH_2), 48.1 (CH_2), 48.3 (CH_2), 60.0 (OCH_2), 60.3 (OCH_2), 171.5, 177.2. Found, %: C 70.14; H 9.23. $C_{18}H_{28}O_4$. Calculated, %: C 70.10; H 9.15.

Ethyl 3-(2-ethoxy-2-oxoethyl)-5-ethyladamantane-1-carboxylate (10). Yield 3.54 g (55%), bp 161–162°C (0.1 mm Hg), purity 97.9% (GLC), n_D^{20} = 1.4848. IR spectrum: ν 1728 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.79 t (3H, CH_3, J = 7.3 Hz), 1.22 t (6H, CH_3, J = 7.8 Hz), 1.28–1.33 m (4H, CH_2), 1.36 q (2H, CH_2, J = 7.3 Hz), 1.49–1.52 m (4H, CH_2), 1.63–1.66 m (2H, CH_2), 1.67–1.71 m (2H, CH_2), 2.10 s (2H, CH_2), 2.11–2.14 m (1H, CH), 4.09 q (4H, OCH_2, J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.0 (CH_3), 14.3 (CH_3), 14.4 (CH_3), 28.9 (CH_3), 33.5, 33.7, 35.9 (CH), 37.9 (CH_2), 40.1 (CH_2), 41.0 (CH_2), 42.2, 42.6 (CH_2), 43.3 (CH_2), 45.9 (CH_2), 48.2 (CH_2), 60.0 (OCH_2), 60.3 (OCH_2), 171.6, 177.4. Found, %: C 70.84; H 9.44. $C_{19}H_{30}O_4$. Calculated, %: C 70.77; H 9.38.

Diethyl adamantane-1,3-dicarboxylate (11). Yield 4.54 g (81%), bp 107–108°C (0.02 mm Hg); 176–178°C (3 mm Hg) [63]; purity 99.8% (GLC).

Diethyl 5-methyladamantane-1,3-dicarboxylate (12). Yield 3.65 g (62%), bp 116–117°C (0.03 mm Hg), purity 95.5% (GLC), n_D^{20} = 1.4824. IR spectrum: ν 1730 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.87 s (3H, CH_3), 1.22 t (6H, CH_3, J = 7.8 Hz), 1.39–1.41 m (2H, CH_2), 1.48–1.59 m (4H, CH_2), 1.66–1.88 m (4H, CH_2), 1.91–1.99 m (2H, CH_2), 2.16–2.19 m (1H, CH), 4.09 q (4H, OCH_2, J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 (CH_3), 28.6 (CH), 30.4 (CH_3), 30.6, 37.4 (CH_2), 38.0 (CH_2), 41.9, 42.5 (CH_2), 44.8 (CH_2), 60.4 (OCH_2), 176.9.

Found, %: C 69.42; H 8.94. $C_{17}H_{26}O_4$. Calculated, %: C 69.36; H 8.90.

Diethyl 5-ethyladamantane-1,3-dicarboxylate (13). Yield 3.70 g (60%), bp 126–127°C (0.018 mm Hg), purity 96.7% (GLC), n_D^{20} = 1.4922. IR spectrum: ν 1730 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.79 t (3H, CH_3, J = 7.3 Hz), 1.23 t (6H, CH_3, J = 7.8 Hz), 1.36 q (2H, CH_2, J = 7.3 Hz), 1.38–1.40 m (2H, CH_2), 1.50–1.58 m (4H, CH_2), 1.76–1.80 m (4H, CH_2), 1.93–1.95 m (2H, CH_2), 2.18–2.20 m (1H, CH), 4.10 q (4H, OCH_2, J = 7.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 7.0 (CH_3), 14.3 (CH_3), 28.5 (CH), 33.2, 35.8 (CH_2), 37.8 (CH_2), 39.6 (CH_2), 39.9 (CH_2), 41.8, 42.5 (CH_2), 60.4 (OCH_2), 177.1. Found, %: C 70.15; H 9.21. $C_{18}H_{28}O_4$. Calculated, %: C 70.10; H 9.15.

Diethyl 2,2′-[5-(ethoxycarbonyl)adamantane-1,3-diyl]diacetate (14). Yield 5.47 g (72%), bp 210–211°C (0.1 mm Hg), purity 97.7% (GLC), n_D^{20} = 1.4813. IR spectrum: ν 1728 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.14 t (9H, CH_3, J = 7.1 Hz), 1.36–1.47 m (6H, CH_2), 1.54–1.64 m (6H, CH_2), 2.03 s (4H, CH_2), 2.06–2.07 m (1H, CH), 3.97–4.02 m (6H, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.2 (CH_3), 14.3 (CH_3), 28.6 (CH), 33.6, 37.4 (CH_2), 40.4 (CH_2), 42.0, 42.7 (CH_2), 60.0 (OCH_2), 60.3 (OCH_2), 171.1, 176.6. Found, %: C 66.35; H 8.54. $C_{21}H_{32}O_6$. Calculated, %: C 66.29; H 8.48.

Diethyl 5-(2-ethoxy-2-oxoethyl)adamantane-1,3-dicarboxylate (15). Yield 4.03 g (55%), bp 190–191°C (0.1 mm Hg), purity 93.5% (GLC), n_D^{20} = 1.4828. IR spectrum: ν 1729 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 t (9H, CH_3, J = 7.1 Hz), 1.51 s (2H, CH_2), 1.61–1.73 m (8H, CH_2), 1.83–1.88 m (2H, CH_2), 2.08 s (2H, CH_2), 2.11–2.15 m (1H, CH), 4.02–4.05 m (6H, OCH_2). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.2 (CH_3), 14.3 (CH_3), 28.2 (CH), 33.3, 37.2 (CH_2), 39.3 (CH_2), 40.2 (CH_2), 41.5, 42.6 (CH_2), 47.7 (CH_2), 60.1 (OCH_2), 60.4 (OCH_2), 171.1, 176.4. Found, %: C 65.61; H 8.32. $C_{20}H_{30}O_6$. Calculated, %: C 65.55; H 8.25.

Ethyl 3,5-dimethyl[7-^{2}H]adamantane-1-carboxylate (16). Yield 3.37 g (71%), bp 81–82°C (0.1 mm Hg), purity 98.5% (GLC), isotope purity 66%, n_D^{20} = 1.4898. IR spectrum: ν 1729 cm^{-1} (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.81 s (6H, CH_3), 1.12 s (2H, CH_2), 1.20 t (3H, CH_3, J = 7.1 Hz), 1.27–1.35 m (4H, CH_2), 1.47–1.52 m (4H, CH_2), 1.67 s (2H, CH_2), 4.06 q (2H, OCH_2, J = 7.1 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 14.3 (CH_3), 28.8 t (C–D, J = 20 Hz), 30.5 (2C, CH_3), 30.9 (2C), 37.5 (CH_2), 37.6 (CH_2), 42.5, 42.8 (CH_2), 42.9 (CH_2), 45 (CH_2), 50.8 (CH_2), 60.1 (OCH_2), 177.6 (C=O). Mass spectrum, m/z (I_{rel}, %): 237 (10) $[M]^+$, 236 (3) $[M-1]^+$, 164 (100), 163 (70), 148 (8), 147 (4), 108 (79), 107 (80), 91 (52), 79 (46), 55 (52).

Kinetic measurements. Nitric acid (100%, d = 1.522 g/cm^3) was distilled under reduced pressure (20 mm Hg) just before use. Methylene chloride was purified according to standard procedure [64]. The components of the reaction mixtures were quantitated by the internal standard method [65].

A 100-mL three-necked flask equipped with a thermometer, stirrer, and dropping funnel was charged with 8 mL of 92% sulfuric acid and 0.025 g of 1,4-dinitrobenzene (internal standard), 5 equiv of fuming nitric acid was added on cooling, and a mixture of 0.2 g of ester **1**–**16** and 10 mL of 92% sulfuric acid was added over a period of 10 s, maintaining the required temperature with an accuracy of ± 1°C. Samples of the reaction mixture were withdrawn at definite time intervals. A 2-mL sample was poured onto 4 g of crushed ice and extracted with methylene chloride (2×2 mL), and the combined extracts were washed with a solution of sodium hydrogen carbonate (3×4 mL) and water (3×4 mL), dried over anhydrous sodium sulfate, and analyzed by GLC. Each experiment was performed at least in triplicate, and the rate constant was calculated as the mean value.

ACKNOWLEDGMENTS

The spectral and analytical data were obtained using the facilities of the joint center "Study of Physicochemical Properties of Compounds and Materials."

FUNDING

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 18-33-00881).

CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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