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SHORT COMMUNICATIONS

Synthesis of 1-Adamantyloxyalkanols

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The synthesis of biologically active adamantane derivatives that further may be used as drugs against viral diseases is an urgent problem [1]; mechanism of their action is related to the blocking of M2 protein serving as an ion channel of the virus [2]. The high lipophilicity and bulky structure of the adamantyl group at its introduction into the molecules of various biologically active compounds significantly modifies their pharmacological action. In this way the structure was modified of a seies of antimicrobial, antitumor, immunodepressant, hormonal, analgesic, antiphlogistic, and neurotropic drugs [1, 3]. It is presumed that the modification of the biological action is due to the changes in the spatial arrangement, hydrophobicity and lipophilicity of compounds and to the facilitation of their transport through the biologic membranes [4].

Aiming at the search for new adamantane derivatives of high antiviral activity and also of lipophilic modifiers for designing prodrugs of high biologic accessibility we synthesized a series of adamantyloxyalkanols with variable length of the aliphatic chain permitting changes in the lipophilicity of compounds obtained in a wide range.

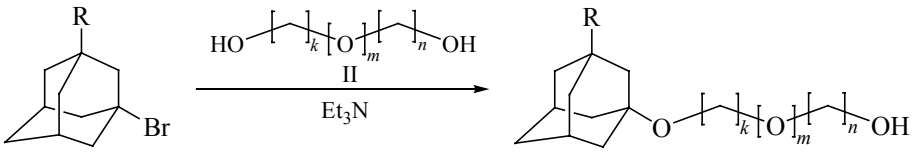
The information on preparation methods of adamantyloxyalkanols and on their biological activity is very scanty. A method was described of adamantyloxypropanol preparation from 1-bromoadamantane and propane-1,3-diole in the presence of triethylamine [5] and of adamantyloxyethanol by photochemical reaction of 1-bromoadamantane with ethylene glycol [6], but in the latter reaction the yield of the target product was very low.

We carried out the synthesis of a series of 1-adamantyloxyalkanols **IIIa–IIIg** from 1-bromoadamantane (**Ia**) and 1-bromo-3-ethyladamantane (**Ib**) and diols **II** in the presence of triethylamine.

1-Adamantyloxyalkanols IIIa–IIIg. A mixture of 70 mmol of bromoderivative **Ia** or **Ib**, 0.1 mol of triethylamine, and 1.5 mol of diol **II** was boiled at stirring in an argon atmosphere, then it was cooled and poured into 0.5 l of water. The reaction products were extracted into chloroform (3 × 50 ml). The organic layer was separated, washed with a little water, and dried with sodium sulfate. The solvent was distilled off.

2-(Adamant-1-yloxy)ethanol (IIIa). Yield 82%, mp 38–39°C. Found, %: C 73.26; H 10.25. $C_{12}H_{20}O_2$. Calculated, %: C 73.43; H 10.27. ^{1}H and ^{13}C NMR spectra are consistent with the published data [6].

4-(Adamant-1-yloxy)butan-1-ol (IIIb). Yield 85%, n_D^{20} 1.5021. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.58 m



Ia, Ib **IIIa–IIIg**

I, R = H (**a**), Et (**b**); **III**, R = H: *k* = 0, *m* = 0, *n* = 2 (**a**), 4 (**b**); *k* = 2, *m* = 1, *n* = 2 (**c**); R = Et: *k* = 0, *m* = 0, *n* = 2 (**d**), 3 (e), 4 (**f**); *k* = 2, *m* = 1, *n* = 2 (**g**).

(8H, $3CH_2$, Ad, $2CH_2$), 1.70 m (6H, $3CH_2$, Ad), 2.11 m (3H, 3CH, Ad), 3.05 s (1H, OH), 3.37 t (2H, CH_2O, $^3J_{HH}$ 7.0 Hz), 3.55 t (2H, CH_2O, $^3J_{HH}$ 7.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 27.86 s (CH_2), 30.42 s (CH_2), 30.56 s (3CH, Ad), 36.37 s ($3CH_2$, Ad), 41.38 s ($3CH_2$, Ad), 59.66 s (CH_2O), 62.52 s (CH_2O), 74.43 s (C, Ad). Found, %: C 74.60; H 10.74. $C_{14}H_{24}O_2$. Calculated, %: C 74.95; H 10.78.

2-[2-(Adamant-1-yloxy)ethoxy]ethanol (IIIc). Yield 94%, n_D^{20} 1.5015. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.55–1.65 m (6H, $3CH_2$, Ad), 1.71–1.81 m (6H, $3CH_2$, Ad), 2.22 s (3H, 3CH, Ad), 2.95 s (1H, OH), 3.55–3.75 m (8H, $4CH_2O$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 30.50 s (3CH, Ad), 36.40 s ($3CH_2$, Ad), 41.41 s ($3CH_2$, Ad), 59.60 s (CH_2O), 61.91 s (CH_2O), 71.19 s ($2CH_2O$), 72.69 s (C, Ad). Found, %: C 69.90; H 10.01. $C_{14}H_{24}O_3$. Calculated, %: C 69.96; H 10.07.

2-(3-Ethyladamant-1-yloxy)ethanol (IIId). Yield 90%, n_D^{20} 1.5015. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.78 t (3H, CH_3, Et, $^3J_{HH}$ 7.0 Hz), 1.19 q (2H, CH_2, Et, $^3J_{HH}$ 7.0 Hz), 1.30–2.25 m (14H, Ad), 2.45 C (1H, OH), 3.51 t (2H, CH_2O, $^3J_{HH}$ 5.0 Hz), 3.76 t (2H, CH_2O, $^3J_{HH}$ 5.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.14 s (CH_3, Et), 32.43 s (2CH, Ad), 35.71 s (CH_2, Et), 35.97 s (C, Ad), 36.17 s (CH_2, Ad), 40.82 s ($2CH_2$, Ad), 41.02 s ($2CH_2$, Ad), 45.31 s (CH_2, Ad), 60.45 s (CH_2O), 63.21 s (CH_2O), 73.51 s (C, Ad). Found, %: C 74.90; H 10.72. $C_{14}H_{24}O_2$. Calculated, %: C 74.95; H 10.78.

3-(3-Ethyladamant-1-yloxy)propan-1-ol (IIIe). Yield 89%, n_D^{20} 1.5020. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.75 t (3H, CH_3, Et, $^3J_{HH}$ 7.0 Hz), 1.18 q (2H, CH_2, Et, $^3J_{HH}$ 7.0 Hz), 1.30–2.25 m (16H, Ad + CH_2), 3.05 s (1H, OH), 3.65 t (2H, CH_2O, $^3J_{HH}$ 6.0 Hz), 3.76 t (2H, CH_2O, $^3J_{HH}$ 6.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.16 s (CH_3, Et), 30.58 s (2CH, Ad), 32.35 s (CH_2), 35.85 s (CH_2, Et), 35.88 s (C, Ad), 36.10 s (CH_2, Ad), 40.93 s ($2CH_2$, Ad), 41.06 s ($2CH_2$, Ad), 45.85 s (CH_2, Ad), 60.13 s (CH_2O), 63.02 s (CH_2O), 73.57 s (C, Ad). Found, %: C 75.50; H 10.92. $C_{15}H_{26}O_2$. Calculated, %: C 75.58; H 10.99.

4-(3-Ethyladamant-1-yloxy)butan-1-ol (IIIf). Yield 92%, n_D^{20} 1.5019. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.77 t (3H, CH_3, Et, $^3J_{HH}$ 7.0 Hz), 1.15 q (2H, CH_2, Et, $^3J_{HH}$ 7.0 Hz), 1.30–2.15 m (16H, Ad + $2CH_2$), 3.11 s (1H, OH), 3.45 m (2H, CH_2O), 3.61 m (2H, CH_2O). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.13 s (CH_3, Et), 28.06 s (CH_2), 30.55 s (2CH, Ad), 35.85 s (CH_2, Et), 35.93 s (C, Ad), 40.64 s (CH_2, Ad), 40.90 s ($2CH_2$, Ad), 40.98 s ($2CH_2$, Ad), 45.78 s (CH_2, Ad), 59.91 s (CH_2O), 63.73 s (CH_2O), 73.59 s (C, Ad). Found, %: C 76.10; H 11.15. $C_{16}H_{28}O_2$. Calculated, %: C 76.14; H 11.18.

2-[2-(3-Ethyladamant-1-yloxy)ethoxy]ethanol (IIIg). Yield 93%, n_D^{20} 1.5018. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.76 t (3H, CH_3, Et, $^3J_{HH}$ 7.0 Hz), 1.15 q (2H, CH_2, Et, $^3J_{HH}$ 7.0 Hz), 1.30–2.26 m (14H, Ad), 3.29 s (1H, OH), 3.52–3.72 m (8H, $4CH_2O$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 7.10 s (CH_3, Et), 30.52 s (2CH, Ad), 35.82 s (CH_2, Et), 36.02 s (CH_2, Ad), 40.84 s ($2CH_2$, Ad), 40.94 s ($2CH_2$, Ad), 45.68 s (CH_2, Ad), 59.71 s (CH_2O), 61.86 s (CH_2O), 71.17 s (CH_2O), 72.66 s (CH_2O), 73.63 s (C, Ad). Found, %: C 71.56; H 10.50. $C_{16}H_{28}O_3$. Calculated, %: C 71.60; H 10.52.

NMR spectra were registered on a spectrometer Bruker AM-300 at operating frequencies 300.13 (^1H) and 75.47 (^{13}C) MHz. The measurements were carried out without additional references with the stabilization on the signal of the deuterated solvent. Elemental analysis was performed on a CHNSO-analyzer EuroVektor EA3000.

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