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Reaction of Dibromoadamantanes with Glycols in the Presence of Sodium Glycolate

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Abstract—1,3-Dibromoadamantanes reacted with glycols in the presence of sodium glycolate to give novel unsaturated bicyclo[3.3.1]nonane derivatives and 1,3-disubstituted adamantanes.

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Fragmentation of some 1,3-disubstituted adamantanes through intermediate formation of stabilized 3-substituted 7-methylidenebicyclo[3.3.1]non-3-yl cations was reported in [1–7]; in the presence of water the latter were converted into 7-methylidenebicyclo-[3.3.1]non-3-one (Scheme 1). Presumably, in strongly basic medium such carbenium ions can be stabilized via elimination of proton with formation of double C=C bond.

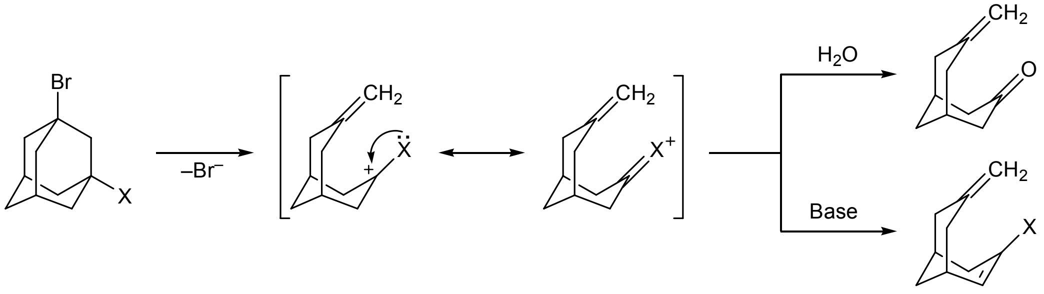
We previously found [8] that 1,3-dibromoadamantane (**I**) in ethylene glycol at 200°C in the presence of a strong base is converted into a mixture of 2-(7-methylidenebicyclo[3.3.1]non-2-en-3-yloxy)ethanol (**II**) and 7-methylidenespiro[bicyclo[3.3.1]nonane-3,2′-[1,3]dioxolane] (**III**). More detailed analysis of the product mixture allowed us to reveal 10–12% of 2,2′-(adamantane-1,3-diybisoxy)diethanol (**IV**). 1,3-Dibromo-5,7-dimethyladamantane (**VI**) reacted in a similar way (Scheme 2).

The products were isolated from the reaction mixture by selective extraction and subsequent vacuum distillation or recrystallization from appropriate solvent.

As might be expected [9], vinyl ether **II** upon distillation or heating to 100°C, as well as during chromatography on silica gel, is quantitatively converted into spiro dioxolane **III**. Protection of the hydroxy group by esterification made it possible to isolate by vacuum distillation 2-(7-methylidenebicyclo-[3.3.1]non-2-en-3-yloxy)ethyl acetate (**Va**); the corresponding *p*-nitrobenzoate **Vb** was isolated by fractional recrystallization from methanol. Compounds **IVa** and **IXa** were isolated and characterized as *p*-nitrobenzoates **IVb** and **IXb** (Scheme 2).

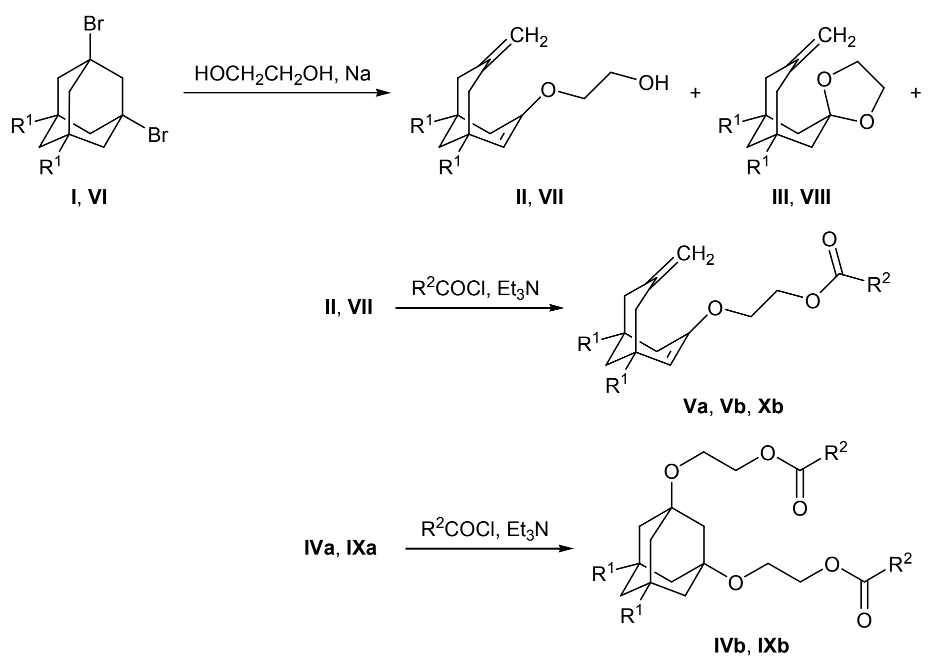
The structure of the products obtained by reactions of 1,3-dibromoadamantanes **I** and **VI** with ethylene glycol suggests the following reaction mechanism. 1,3-Dibromoadamantane **I** or **VI** in polar medium gives rise to 3-bromoadamantan-1-yl cation which takes up ethylene glycol molecule to produce intermediate **A**. Heterolytic dissociation of the C–Br bond in **A** generates cation **B** which undergoes Grob fragmentation with formation of carbenium ion **C**. The latter can be stabilized according to two pathways. Intramolecular proton abstraction from the α-carbon

Scheme 1.



X = Cl, Br, MeO, MeS, H_2N, MeNH, Me_2N.

Scheme 2.

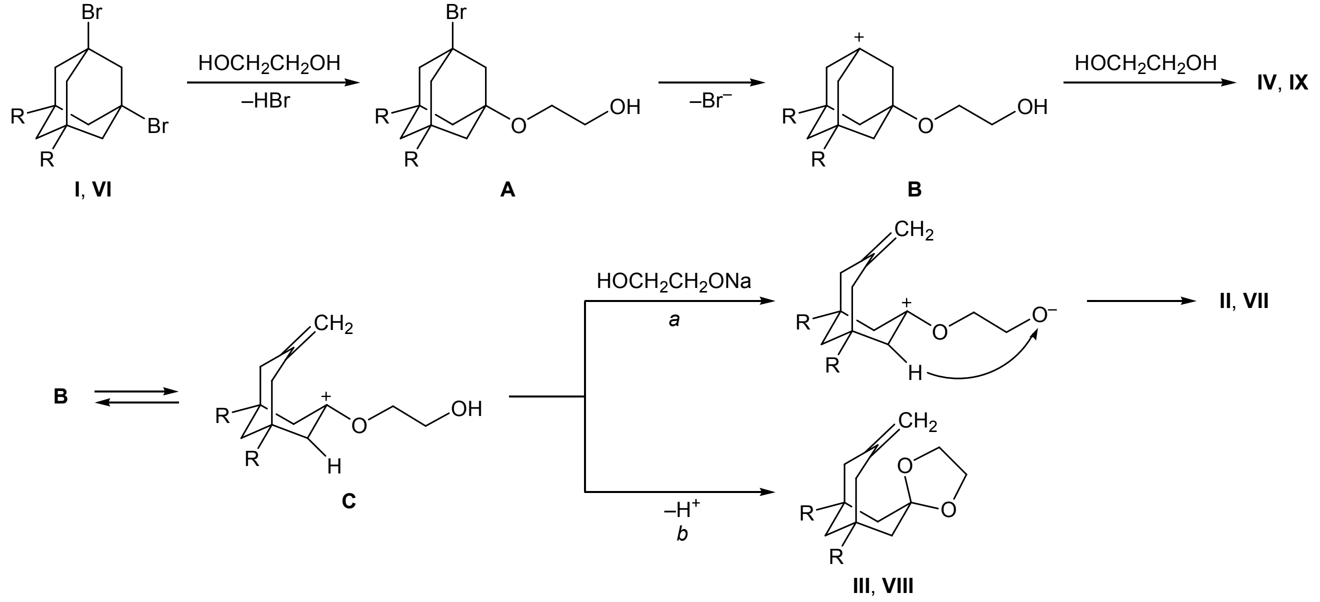


I–**V**, R^1 = H; **VI**–**X**, R^1 = Me; R^2 = Me (**a**), 4-$O_2NC_6H_4$ (**b**).

atom by the action of sodium alkoxide leads to vinyl ether **II** or **VII** (pathway *a*); attack by the cationic center on the lone electron pair of the oxygen atom in the hydroxy group yields spiro dioxolane **III** or **VIII** (Scheme 3). A concurrent process is classical solvolysis of cation **B** with formation of 1,3-dialkoxyadamantane **IV** or **IX**.

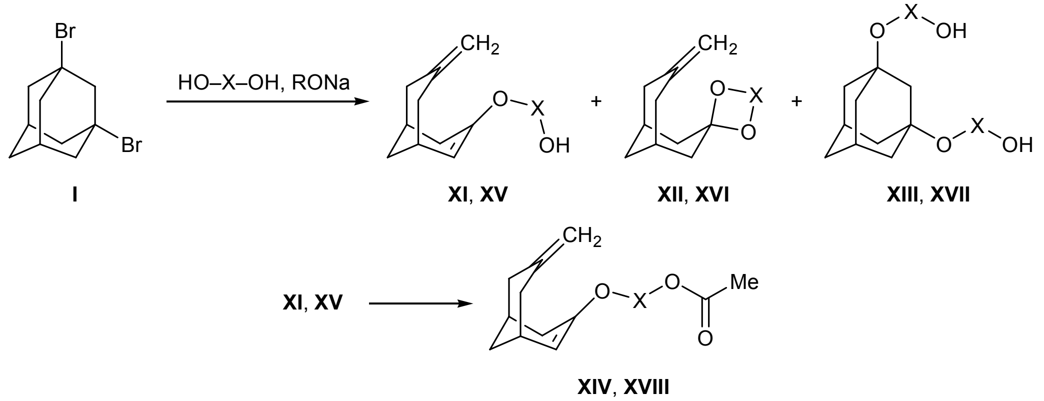
With a view to elucidate solvent effect on the fragmentation of 1,3-dibromoadamantane (**I**) we selected the following diols: propane-1,2-diol, propane-1,3-diol, butane-1,2-diol, butane-2,3-diol, butane-1,3-diol, butane-1,4-diol, and diethylene glycol. Reactions of dibromide **I** with primary diols under analogous conditions afforded mixtures of vinyl ether **XI** or **XV**, spiro-

Scheme 3.



R = H, Me.

Scheme 4.



XI–XIV, X = $CH_2CH_2CH_2CH_2$; **XV–XVIII**, X = $CH_2CH_2OCH_2CH_2$.

cyclic compound **XII** or **XVI**, and 1,3-disubstituted adamantane **XIII** or **XVII** (Scheme 4). The products were isolated and purified as in the reaction of dibromide **I** with ethylene glycol. Compounds **XI** and **XV** were isolated as characterized as acetic acid esters **XIV** and **XVIII**. As the length of the carbon skeleton in the glycol increased, the fraction of cyclic products **XII** and **XVI** in the reaction mixture decreased to 0.5–1%, and we failed to isolate them.

1,3-Dibromoadamantane (**I**) reacted with secondary diols under analogous conditions to give only substituted 7-methylidenespiro[bicyclo[3.3.1]nonane-3,2′-[1,3]dioxolanes] **XIX–XXI** (Scheme 5). From compound **I** and butane-2,3-diol we obtained 4′,5′-dimethyl-7-methylidenespiro[bicyclo[3.3.1]nonane-3,2′-[1,3]dioxolane] (**XXI**), while the reaction of **I** with propane-1,2-diol afforded a mixture of stereoisomeric 4′-methyl-7-methylidenespiro[bicyclo[3.3.1]nonane-3,2′-[1,3]dioxolanes] **XIX** and **XX** at a ratio of 1:1 (according to the ^{1}H NMR and GLC data). Compounds **XIX–XXI** were isolated and purified by column chromatography on silica gel.

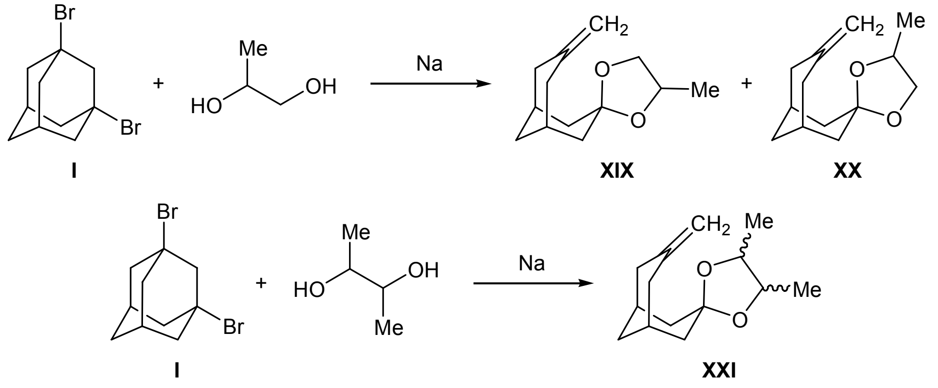
Dibromide **I** did not react with 1,3-glycols (propane-1,3-diol and butane-1,3-diol) in the presence of sodium alkoxide; in these cases, decomposition products of the corresponding glycol were formed exclusively.

We can conclude that fragmentation of 1,3-dibromoadamantane in glycols in the presence of sodium glycolate leads to the formation of novel 3,7-disubstituted bicyclo[3.3.1]nonane derivatives.

EXPERIMENTAL

The IR spectra were recorded on an IKS-22 spectrometer from samples prepared as KBr pellets or dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Bruker AC-200 instrument at 200 MHz using $CDCl_3$ as solvent and hexamethyldisiloxane as internal reference. The ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer at 75 MHz ($CDCl_3$, HMDS) with complete decoupling from protons, as well as using DEPT pulse sequence. The mass spectra (electron impact, 70 eV) were obtained

Scheme 5.



on a Finnigan MAT INCOS 50 mass spectrometer. The elemental compositions were determined on a Euro Vector EA 3000 analyzer. GLC analysis was performed on a Tsvet-100 chromatograph equipped with a flame-ionization detector and a 25-m SE-30 quartz capillary column (carrier gas helium). Silufol UV-254 plates were used for thin-layer chromatography; spots were developed by treatment with iodine vapor.

Reaction of 1,3-dibromoadamantane with ethylene glycol. 1,3-Dibromoadamantane, 70 g (0.238 mol), was added to a solution of 25 g (1.09 mol) of metallic sodium in 500 ml of ethylene glycol. The mixture was heated for 3 h under reflux, poured into water, and extracted with benzene. The extract was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off, the residue was dissolved in 100 ml of toluene, 22 ml (0.165 mol) of triethylamine and 14 ml (0.137 mol) of acetic anhydride were added, and the mixture was heated for 1 h under reflux. The mixture was then washed with a 5% solution of sodium carbonate and with water, the solvent was distilled off, and the residue was distilled under reduced pressure to isolate two fractions.

7-Methylidenespiro[bicyclo[3.3.1]nonane-3,2′-[1,3]dioxolane] (III). First fraction; yield 5 g (11%), bp 99–100°C (1 mm), n_D^{20} = 1.5071. IR spectrum, ν, cm^{-1}: 1660, 1110, 890. ^{1}H NMR spectrum, δ, ppm: 1.25–2.35 m (12H), 3.77 m (4H, OCH_2CH_2O), 4.66 s (2H, =CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 194 (17) $[M]^+$, 139 (100), 106 (41), 92 (33). Found, %: C 79.11; H 9.40. $C_{12}H_{18}O_2$. Calculated, %: C 79.19; H 9.34.

2-(7-Methylidenebicyclo[3.3.1]non-2-en-3-yloxy)-ethyl acetate (Va). Second fraction; Yield 7.5 g (14%), bp 135–136°C (1 mm), n_D^{20} = 1.5028. IR spectrum, ν, cm^{-1}: 1750, 1660, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.60–2.50 m (10H), 1.98 s (3H, $COCH_3$), 3.73–3.76 m (2H, OCH_2, *J* = 4.5 Hz), 4.17–4.20 m (2H, $\mathbf{CH_2}OAc$), 4.43 s and 4.62 s (1H each, =CH_2), 4.46 d (1H, 2-H, *J* = 6 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 236 (3) $[M]^+$, 87 (100), 43 (47). Found, %: C 71.10; H 8.47. $C_{14}H_{20}O_3$. Calculated, %: C 71.16; H 8.53.

2-(7-Methylidenebicyclo[3.3.1]non-2-en-3-yloxy)-ethyl 4-nitrobenzoate (Vb) was synthesized in a similar way by acylation with 4-nitrobenzoyl chloride; the product was isolated by recrystallization from hexane. Yield 12.25 g (15%), mp 114–116°C. IR spectrum, ν, cm^{-1}: 1735, 1660, 1600, 1520, 1240, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.51–2.55 m (10H), 4.03 t (2H, $COCH_2$, *J* = 4 Hz), 4.53 d (1H, 2-H, *J* = 6 Hz), 4.61 t [2H, $CH_2OC(O)$, *J* = 4 Hz], 4.64 s and 4.72 s (1H each, =CH_2), 8.19 d (2H, H_{arom}, *J* = 9 Hz), 8.36 d (2H, H_{arom}, *J* = 9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 26.35 (C^9), 28.54 (C^5), 29.23 (C^4), 31.06 (C^6), 33.79 (C^8), 42.12 (C^1), 63.97 (C^{12}), 64.09 (C^{11}), 98.03 (C^2), 111.26 (C^{10}), 144.96 (C^7), 154.04 (C^3), 164.31 (C^{15}); 123.98, 130.72, 135.01, 150.32 (C_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 343 (15.4) $[M]^+$, 288 (14.4), 194 (100), 150 (70.6), 104 (54). Found, %: C 66.09; H 6.19; N 3.98. $C_{19}H_{21}NO_5$. Calculated, %: C 66.46; H 6.16; N 4.08.

After extraction with benzene (see above), the aqueous layer was repeatedly treated with chloroform, the extract was dried over anhydrous sodium sulfate, 8.7 ml (0.06 mol) of triethylamine and 11.1 g (0.06 mol) of 4-nitrobenzoyl chloride were added, and the mixture was heated for 1 h under reflux. It was then poured into 100 ml of a saturated solution of sodium carbonate, the organic layer was separated, washed with water, and evaporated, and the residue was recrystallized from toluene. We thus isolated 11.9 g (9%) of adamantane-1,3-diylbis(oxyethane-2,1-diyl) bis(4-nitrobenzoate) (**IVb**), mp 115–117°C. IR spectrum, ν, cm^{-1}: 1735, 1600, 1520, 1240, 1135, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.52–1.59 m (2H, Ad), 1.65–1.78 m (8H, Ad), 1.81–1.85 m (2H, Ad), 2.38 s (2H, Ad), 3.78–3.81 m (4H, $AdO\mathbf{CH_2}$), 4.48–4.51 m (4H, CH_2O), 8.21 d (2H, H_{arom}, *J* = 9 Hz), 8.38 d (2H, H_{arom}, *J* = 9 Hz). Found, %: C 60.31; H 5.39; N 5.05. $C_{28}H_{30}N_2O_{10}$. Calculated, %: C 60.64; H 5.45; N 5.05.

1,3-Dibromo-5,7-dimethyladamantane (**VI**) reacted with ethylene glycol in a similar way.

1,5-Dimethyl-7-methylidenespiro[bicyclo[3.3.1]-nonane-3,2′-[1,3]dioxolane] (VIII). Yield 13%, bp 110–113°C (1 mm), n_D^{20} = 1.5009. IR spectrum, ν, cm^{-1}: 2950, 1660, 1110, 890. ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, CH_3), 1.32–2.3 m (10H), 3.84–3.88 m (4H, OCH_2CH_2O), 4.69 s (2H, =CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 222 (14) $[M]^+$, 207 (25), 167 (84), 120 (100), 105 (45), 79 (26). Found, %: C 75.73; H 10.02. $C_{14}H_{22}O_2$. Calculated, %: C 75.63; H 9.97.

5,7-Dimethyladamantane-1,3-diylbis(oxyethane-2,1-diyl) bis(4-nitrobenzoate) (IXb). Yield 12%, mp 125–128°C. IR spectrum, ν, cm^{-1}: 1735, 1600, 1520, 1240, 1140, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 0.95 s (3H, CH_3), 1.12–1.14 m (2H, Ad), 1.41–1.67 m (8H, Ad), 1.72–1.74 m (2H, Ad), 3.76–3.82 m (4H, $AdO\mathbf{CH_2}$), 4.45–4.47 m (4H, CHO), 8.21 d (2H, H_{arom}, *J* = 9 Hz), 8.38 d (2H, H_{arom}, *J* = 9 Hz). Found,

%: C 61.92; H 5.94; N 4.88. $C_{30}H_{34}N_2O_{10}$. Calculated, %: C 61.85; H 5.88; N 4.81.

2-(1,5-Dimethyl-7-methylidenebicyclo[3.3.1]non-2-en-3-yloxy)ethyl 4-nitrobenzoate (Xb). Yield 17%, mp 66–68°C. IR spectrum, ν, cm^{-1}: 1735, 1660, 1600, 1520, 1240, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.02 s (3H, CH_3), 1.1 s (3H, CH_3), 1.2–2.1 m (8H), 3.95 t (2H, $COCH_2$, *J* = 4 Hz), 4.34 s (1H, 2-H) 4.62 t [2H, $CH_2OC(O)$, *J* = 4 Hz], 4.49 s and 4.69 s (1H each, =CH_2). ^{13}C NMR spectrum, δ_C, ppm: 29.75 (CH_3), 31.43 (CH_3), 33.27 (C^5), 34.65 (C^1), 40.76 (C^4), 47.27 (C^9), 47.54 (C^6), 49.52 (C^8), 64.32 (C^{11}, C^{12}), 103.08 (C^{10}), 110.19 (C^2), 146.54 (C^7), 154.50 (C^3), 164.74 (C^{15}); 123.61, 130.95, 135.56, 150.67 (C_{arom}). Mass spectrum, *m*/*z* (I_{rel}, %): 371 (3.4) $[M]^+$, 316 (6), 194 (100), 150 (32.4), 104 (21), 40 (51). Found, %: C 68.07; H 6.72; N 3.69. $C_{21}H_{25}NO_5$. Calculated, %: C 67.91; H 6.78; N 3.77.

Likewise, compounds **XIII**, **XIV** were synthesized by reaction of 1,3-dibromoadamantane with butane-1,4-diol, followed by acylation and distillation. After extraction with benzene (see above), the aqueous phase was repeatedly extracted with chloroform, the extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using chloroform–methanol (20 : 1) as eluent.

4,4′-(Adamantane-1,3-diylbisoxy)dibutan-1-ol (XIII). Yield 12%, n_D^{20} = 1.5011. IR spectrum, ν, cm^{-1}: 3510, 1140, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.42–1.47 m (8H, CH_2), 1.49–1.57 m (2H, Ad), 1.63–1.78 m (8H, Ad), 1.84–1.89 m (2H, Ad), 2.40–2.44 m (2H, Ad), 3.36–3.40 m (4H, AdOC**H**$_2$), 3.56–3.60 m (4H, CH_2O), 4.43 s (2H, OH). Found, %: C 69.01; H 10.23. $C_{18}H_{32}O_4$. Calculated, %: C 69.20; H 10.32.

4-(7-Methylidenebicyclo[3.3.1]non-2-en-3-yloxy)-butyl acetate (XIV). Yield 16%, bp 148–149°C (1 mm), n_D^{20} = 1.4933. IR spectrum, ν, cm^{-1}: 1750, 1660, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.60–2.50 m (14H), 1.98 s (3H, $COCH_3$), 3.61–3.63 m (2H, OCH_2), 4.05–4.07 m (2H, C**H**$_2$OAc), 4.46 s and 4.67 s (1H each, =CH_2), 4.47 d (1H, 2-H, *J* = 6 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 264 (7) $[M]^+$, 149 (76), 107 (58), 43 (100). Found, %: C 72.71; H 9.20. $C_{16}H_{24}O_3$. Calculated, %: C 72.69; H 9.15.

Compounds **XVII** and **XVIII** were synthesized in a similar way by reaction of 1,3-dibromoadamantane with diethylene glycol, followed by acylation and distillation. After extraction with benzene (see above), the aqueous phase was repeatedly extracted with chloroform, the extract was dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using chloroform–methanol (15 : 1) as eluent.

2,2′-[Adamantane-1,3-diylbis(oxyethane-2,1-diyloxy)]diethanol (XVII). Yield 9%, n_D^{20} = 1.5029. IR spectrum, ν, cm^{-1}: 3510, 1150, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.5–1.58 m (2H, Ad), 1.66–1.77 m (8H, Ad), 1.81–1.87 m (2H, Ad), 2.37 s (2H, Ad), 3.49–3.53 m (12H, OCH_2), 3.70–3.74 m (4H, C**H**$_2$OH). Found, %: C 62.98; H 9.27. $C_{18}H_{32}O_6$. Calculated, %: C 62.77; H 9.36.

2-[2-(7-Methylidenebicyclo[3.3.1]non-2-en-3-yloxy)ethoxy]ethyl acetate (XVIII). Yield 16%, bp 161–164°C (1 mm), n_D^{20} = 1.4989. IR spectrum, ν, cm^{-1}: 1750, 1660, 1100, 1050, 895. ^{1}H NMR spectrum, δ, ppm: 1.6–2.5 m (10H), 2.05 s (3H, $COCH_3$), 3.72–3.76 m (2H, OCH_2), 4.20–4.24 m (2H, C**H**$_2$OAc), 4.51 s and 4.72 s (1H each, =CH_2), 4.51 d (1H, 2-H, *J* = 6 Hz). Found, %: C 58.59; H 8.59. $C_{16}H_{24}O_4$. Calculated, %: C 68.55; H 8.63.

Reaction of 1,3-dibromoadamantane with propane-1,2-diol. 1,3-Dibromoadamantane, 7 g (0.0238 mol), was added to a solution of 2.5 g (0.1 mol) of metallic sodium in 60 ml of propane-1,2-diol. The mixture was heated for 3 h under reflux, poured into water, and extracted with chloroform. The organic phase was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled off, and the residue was subjected to chromatography on silica gel using benzene as eluent to isolate a mixture of stereoisomeric 4′-methyl-7-methylidenespiro[bicyclo[3.3.1]nonane-3,2′-[1,3]dioxolanes] **XIX** and **XX**. Overall yield 0.55 g (11%), n_D^{20} = 1.5038. IR spectrum, ν, cm^{-1}: 2950, 1660, 1070, 1050, 890. ^{1}H NMR spectrum, δ, ppm: 1.21–1.26 d (3H, CH_3, *J* = 5.7 Hz), 1.28–1.33 d (3H, CH_3, *J* = 5.7 Hz), 1.35–2.30 m (24H), 3.35–3.37 m (1H, CH), 3.45–3.47 m (1H, CH), 4.03–4.05 m (1H, CH_2), 4.18 m (1H, CH_2), 4.74 s and 4.76 s (1H each, =CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 208 $[M]^+$ (8), 153 (100), 106 (38), 95 (65), 79 (31), 67 (20). Found, %: C 75.09; H 9.72. $C_{13}H_{20}O_2$. Calculated, %: C 74.96; H 9.68.

4′,5′-Dimethyl-7-methylidenespiro[bicyclo[3.3.1]-nonane-3,2′-[1,3]dioxolane] (XXI) was synthesized in a similar way by reaction of 1,3-dibromoadamantane with butane-2,3-diol. Yield 10%, n_D^{20} = 1.5021. IR spectrum, ν, cm^{-1}: 2950, 1660, 1080, 890. ^{1}H NMR spectrum, δ, ppm: 1.08–1.10 d (3H, CH_3, *J* = 5.8 Hz), 1.20–1.22 d (3H, CH_3, *J* = 5.8 Hz), 1.30–2.30 m (12H), 3.64–3.66 m (1H, CH), 4.15–4.17 m (1H, CH), 4.75 s (2H, $=CH_2$). Mass spectrum, m/z (I_{rel}, %): 222 (25) $[M]^+$, 207 (20), 140 (78), 107 (55), 93 (100). Found, %: C 75.51; H 9.94. $C_{14}H_{22}O_2$. Calculated, %: C 75.63; H 9.97.

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