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Synthesis and Antiviral Activity of Adamantyl-containing Phosphonous and Phosphinic Acids

A. N. Reznikov[a], Yu. N. Klimochkin[a], O. V. Savinova[b], S. V. Orlova[b], N. L. Bogdanova[b], and E. I. Boreko[b]

[a] *Samara State Technical University, ul. Molodogvardeiskaya 244, Samara, 443100 Russia*
e-mail: orgphosphorus@yandex.ru

[b] *Republican Research and Practical Center for Epidemiology and Microbiology, Ministry of Health of the Republic of Belarus, Minsk, Belarus*

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Abstract—The method of adamantly-containing phosphonous and phosphinic acids preparation, based on radical addition of hypophosphorous acid and sodium hypophosphite to unsaturated derivatives of adamantane, has been developed. Unsymmetrical phosphinic acids have been prepared by reacting bistrimetylsilyl esters of phosphonous acids with halides. The obtained phosphinic acids exhibit antiviral activity against herpes simplex virus, influenza A (H5N1), respiratory syncytial virus, and adenovirus.

Keywords: phosphonous acid, phosphinic acid, adamantane derivative, antiviral activity
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Phosphonous and phosphonic acids show diverse biological activity [1]. They are structural analogs of phosphates, widely occurring in nature. Unlike the phosphates, phosphonous and phosphonic acids do not contain the P–O linkage between phosphorus and the pharmacophore fragment, explaining their higher metabolic stability.

Adamantyl-substituted phosphonous and phosphonic acids are of interest in view of exploring new compounds possessing antiviral activity, as several adamantane derivatives have revealed broad spectrum of antiviral activity [2–4]. These compounds act via preventing the disassembly and assembly of viral particles; their biological targets are viral proteins that act as ion channels and the cell membrane scaffold [5, 6]. Some compounds of this series have been already used as antiviral drugs, such as Amantadine (1-aminoadamantane hydrochloride), Rimantadine [1-(1-adamantyl)ethylamine hydrochloride], and Tromantadin [*N*-1-adamantyl-*N*-(2-dimethylamino)ethoxyacetamide] [7, 8]. However, the reference literature lacks data on preparation and properties of adamantyl-containing phosphonous and phosphonic acids. Such compounds are of interest as potential antiviral agents as well as building blocks for development of antiviral agents of more complex structure.

The optimal approach to synthesize phosphonous and phosphinic acids utilizes reaction of hypo-phosphorous acid with unsaturated compounds. This approach is advantageous due to availability of the starting reagents (hypophosphorous acid and unsaturated adamantane derivatives) and simplicity of the synthesis procedure.

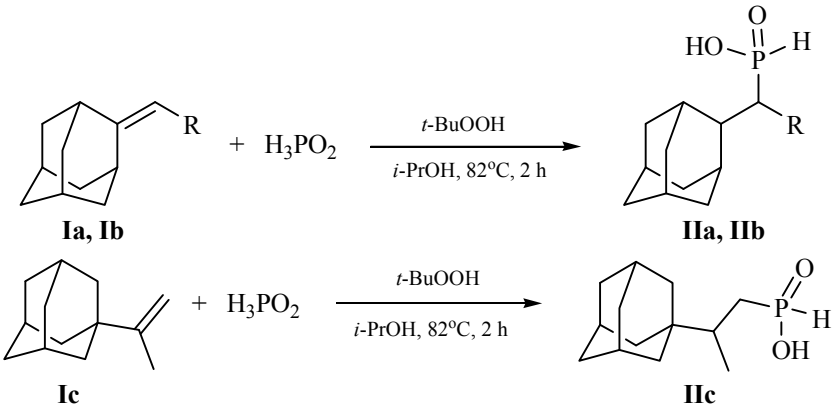
Aiming to obtain adamantyl-containing phosphonous and phosphinic acids, we synthesized a number of unsaturated adamantane derivatives **Ia**–**Id** as described previously [9–12].

Heating a mixture of the corresponding unsaturated compound **Ia**–**Ic** with 50% aqueous hypophosphorous acid in propan-2-ol in the presence of *tert*-butylhydroperoxide as initiator resulted in formation of adamantylalkylphosphonous acids **IIa**–**IIc** (Scheme 1).

Reaction of sodium hypophosphite with 2 equivalents of the unsaturated compound **Ia**, **Ic,** or **Id** occurred in methanol at 120°C in the presence of *tert*-butyl hydroperoxide to yield sodium salts of bis-(adamantylalkyl)phosphinic acids. The latter were treated with aqueous hydrochloric acid to give the corresponding phosphonic acids **IIIa**–**IIIc** (Scheme 2).

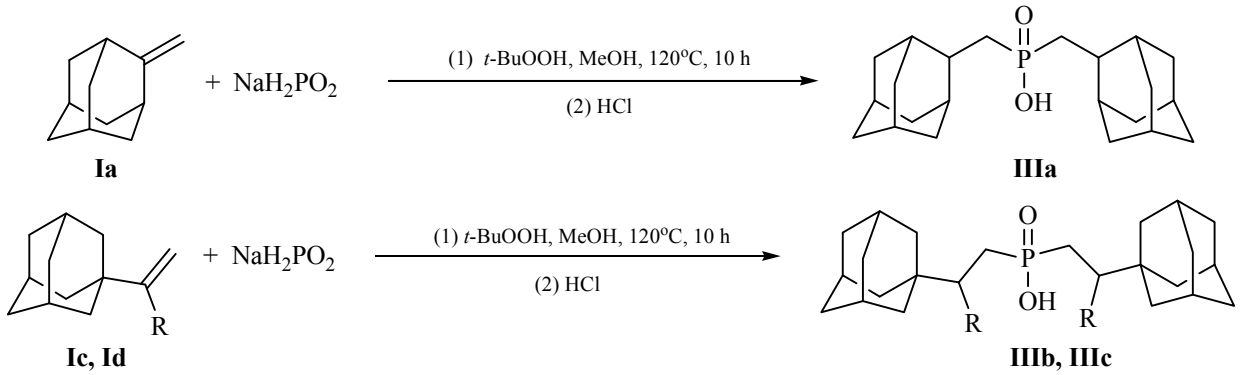
Synthesis of unsymmetrical adamantyl-substituted phosphinic acids was carried out starting from phospho-

Scheme 1.



R = H (**a**), CH_3 (**b**).

Scheme 2.



R = CH_3 (**Ic, IIIb**), H (**Id, IIIc**).

nous acid **IIa** via intermediate formation of bistrimethylsilyl ester **IV** followed by the Arbuzov reaction.

Recently, the use of silyl esters of phosphorous acids in the Arbuzov reaction has been widely applied to prepare organophosphorus derivatives, as it allows for the free acids preparation without isolation of the corresponding esters. Furthermore, this method prevents secondary processes such as reaction of the Arbuzov reaction product with the starting ester [13].

The efficiency of this approach has been demonstrated in reactions of bistrimethylsilyl phosphonites with various electrophilic reagents (halides [14–21], chlorides [22], and acrylates [23, 24]), as well as in the three-component reaction with aldehydes and amines affording α-aminophosphinic acids [25].

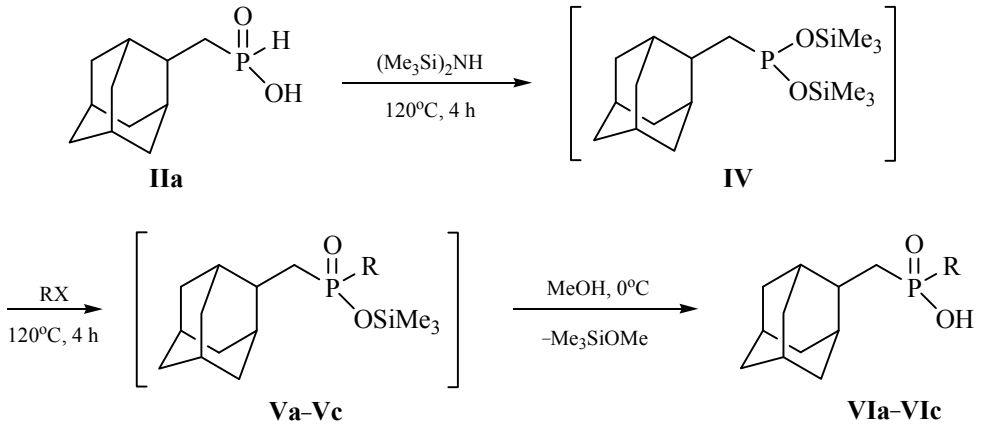
As the silyl esters of phosphonous and phosphinic acids **IV** and **Va**–**Vc** are easily oxidized and hydrolyzed, the adamantyl-containing phosphonic acids were obtained via the one-pot synthesis without isolation of the silyl esters **IV** and **Va**–**Vc** (Scheme 3).

Bistrimethylsilyl ester **IV** was obtained by heating a mixture of phosphonous acid **IIa** and hexamethyldisilazane at 120°C during 4 h under inert atmosphere. Subsequent addition of halogenated derivatives yielded unsymmetrical phosphinic acids **VIa**–**VIc** (Scheme 3).

Virus-inhibiting activity of the obtained compounds was tested with herpes simplex virus, influenza A (H5N1), respiratory syncytial virus and adenovirus using cell culture by evaluating the suppression of virus-induced cytopathic effect. Adamantyl-containing phosphonous acids **IIa**–**IIc** and phosphinic acids **IIIa**–**IIIc** showed no virus-inhibiting activity, whereas phosphinic acids **VIa** and **VIb** containing aromatic substituents exhibited antiviral activity (see table).

To conclude, phosphinic acid **VIa** showed high antiviral activity against herpes simplex virus with

Scheme 3.



R = $PhCH_2$ (**a**), $(CH_3)_3C_6H_2CH_2$ (**b**), Pr (**c**).

satisfactory selectivity index (parameter of the ratio between cytotoxicity and virus-inhibiting activity of a compound). Furthermore, **VIa** revealed moderate activity against respiratory syncytial virus; in the case of adenovirus it was active at the maximum tolerable concentration. Compound **VIb** showed moderate activity against respiratory syncytial virus and influenza A (H5N1); in the case of herpes virus it was active at the maximum tolerable concentration. These results indicate the prospects of further search for antiviral agents among this class of compounds.

EXPERIMENTAL

Compounds **Ia–Id** were prepared via the procedures described in [7–10], respectively.

Elemental analysis was performed with the EuroVector EA 3000 analyzer. IR spectra were recorded with the Shimadzu IRAffinity-1 instrument. NMR spectra of $CDCl_3$ solutions were recorded with the Jeol JNM-ECX400 spectrometer [399.78 MHz (^{1}H), 100.53 MHz (^{13}C)]. Mass spectra were registered with the Finnigan Trace DCQ gas chromatograph–mass spectrometer using capillary column SGE BPX-5 (30 × 0.32 mm) with energy of ionizing electrons of 70 eV.

Phosphonous and phosphinic acids were analyzed by gas chromatography–mass spectrometry in the form of methyl esters obtained via the reaction of 5% ethereal solution of diazomethane with the corresponding acid.

General procedure for synthesis of phosphonous acids (IIa–IIc). 30 mmol of an unsaturated derivative **Ia–Ic** and 19.3 mL of isopropanol were added to a solution of 40 mmol of hypophosphorous acid in 2.4 mL of water. The mixture was refluxed during 2 h. Then 0.19 mL of 70% aqueous solution of *tert*-butyl hydroperoxide in 5.4 mL of isopropanol was added portionwise. After the solvent removal, the reaction mixture was treated with 30% aqueous potassium hydroxide to pH 9 and filtered. The filtrate was extracted with toluene. The aqueous layer was collected and acidified with concentrated hydrochloric acid to pH 3. The precipitated phosphonous acid **IIa–IIc** was filtered off, washed with water, and dried.

(Adamant-2-ylmethyl)phosphonous acid (IIa). Yield 49.0%, mp 130–132°C. IR spectrum (KBr), ν, cm^{-1}: 956 [γ(CH_2)], 1191 (P=O, st), 1454 [δ(CH_2)], 1654 [P(O)OH], 2364 (P–H, st), 2850 (C–H, st). ^{1}H NMR spectrum, δ, ppm: 1.55–1.98 m (14H, Ad; 2H, PCH_2), 2.12–2.30 m (1H, Ad), 7.10 d (1H, PH, $^1J_{HP}$ 560 Hz), 12.35 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 27.7 (CH_2, Ad), 31.5 (CH_2, Ad), 33.2 d (CH, Ad, $^3J_{CP}$ 7.5 Hz), 33.6 d (PCH_2, $^1J_{CP}$ 80.0 Hz), 38.3 (CH, Ad), 39.1 (CH, Ad). ^{31}P NMR spectrum: δ_P 38.5 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 228 (48) $[M]^+$, 207 (14), 149 (100) $[AdCH_2]^+$, 107 (40), 93 (46), 79 (94), 55 (18). Found, %: C 61.59; H 8.90. $C_{11}H_{19}O_2P$. Calculated, %: C 61.67; H 8.94.

[1-(Adamant-2-yl)ethyl]phosphonous acid (IIb). Yield 79.0%, mp 144–146°C. IR spectrum (KBr), ν, cm^{-1}: 956 [γ(CH_2)], 1184 (P=O, st), 1654 [P(O)OH], 2380 (P–H, st), 2653 (PO–H, st), 2846 (CH, st). ^{1}H NMR spectrum, δ, ppm: 1.10 d.d (3H, CH_3, $^2J_{HH}$ 7.0, $^3J_{HP}$ 23.0 Hz), 1.50 m (2H, Ad), 1.60–2.00 m (12H,

Antiviral activity of the adamantyl-containing phosphinic acids

Comp. no.	Concentration, μg mL^{-1}	Virus titer ±S_x, log TCID$_{50}$ mL^{-1}	Difference with the control, log TCID$_{50}$ mL^{-1}	EC$_{50}$ (I$_{95}$) EC$_{90}$ (I$_{95}$), μg mL^{-1}	MTC/EC$_{50}$ MTC/EC$_{90}$
		Herpes simplex virus			
VIa	400	<4.0	>2.18	102.2 (106.9–97.7)	3.9
	200	4.48±0.34	1.7		
	100	5.05±0.52	1.13		
	50–6.25	6.18±0.26	0	155.2 (162.3–148.4)	2.6
	0	6.18±0.26	–		
VIb	25	<4.0	>1.48	10.4 (13.9–7.8)	2.4
	12.5	5.18±0.26	0.3		
	6.25	5.23±0.29	0.25		
	3.0	5.48±0.34	0	29.4 (39.3–22.0)	0.8
	0	5.48±0.34	–		
VIc	200–12.5	5.48±0.34	0	>200	<1
	0	5.48±0.34	–		
		Respiratory syncytial virus			
VIa	400	1.48±0.34	1.52	87.9 (95.4–80.9)	4.5
	200	1.48±0.34	1.52		
	100	2.3±0.32	0.7	156.6 (170.1–144.2)	2.5
	50–6.25	3.0±0.53	0		
	0	3.0±0.53	–		
		Adenovirus			
VIa	200	2.30±0.26	1.89	94.9 (104.4–86.2)	2.1
	100	4.10±0.59	0.09		
	50	4.00±0.59	0.19	251.2 (276.4–228.3)	0.8
	0	4.19±0.26	–		
		Influenza A (H5N1)			
VIa	400	5.24±0.37	2.06	107.3 (136.2–84.6)	3.7
	25	7.3±0.37	0		
	0	7.3±0.37	–	221.5 (281.0–174.5)	1.8
VIb	25	6.3±0.37	1.0	<12.5	>2
	12.5	6.18±0.37	1.12		
	0	7.3±0.37	–		

Ad), 2.15 m (1H, PCH; 1H, CH, Ad), 7.10 d (1H, PH, $^1J_{HP}$ 560 Hz), 12.40 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 9.2 d (CH_3, $^2J_{CP}$ 15.0 Hz), 27.5 (CH, Ad), 27.9 (CH, Ad), 28.5 d (CH, Ad, $^2J_{CP}$ 12.8 Hz), 30.4 (CH, Ad), 30.9 (CH_2, Ad), 31.4 (CH_2, Ad), 32.9 d (PCH, $^1J_{CP}$ 95.1 Hz), 38.1 (CH_2, Ad), 38.8 (CH_2, Ad), 38.9 (CH, Ad), 43.7 (CH, Ad). ^{31}P NMR spectrum: δ_P 43.36 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 242 (32) $[M]^+$, 163 (100) $[AdCHCH_3]^+$, 135 (18) $[Ad]^+$, 121 (30), 107 (34), 93 (32), 79 (74), 67 (22), 55 (20). Found, %: C 63.09; H 9.21. $C_{12}H_{21}O_2P$. Calculated, %: C 63.14; H 9.27.

[2-(Adamant-2-yl)propyl]phosphonous acid (IIc). Yield 57.0%, oil. IR spectrum (KBr), ν, cm^{-1}: 975 [γ(CH_2)], 1184 (P=O, st), 1450 [δ(CH_2)], 1650 [P(O)OH], 2349 (P–H, st), 2677 (PO–H, st), 2900 (CH, st). ^{1}H NMR spectrum, δ, ppm: 1.12 d.d (3H, CH_3, $^2J_{HH}$ 7.0, $^3J_{HP}$ 20.0 Hz), 1.50–2.15 m (15H, Ad; 1H, $CHCH_2P$, 2H, CH_2P), 7.10 d (1H, PH, $^1J_{HP}$ 560 Hz), 12.40 s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 20.2 d (CH_3, $^3J_{CP}$ 8.5 Hz), 26.2 d (CH_2, $^1J_{CP}$ 10.0 Hz), 28.1 (C, Ad), 28.6 (CH_2, Ad), 36.2 (CH_2, Ad), 37.5 d ($^2J_{CP}$ 12.5 Hz), 40.22 s (CH, Ad). ^{31}P NMR spectrum: δ_P 41.67 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 256 $[M]^+$, 214 (10), 135 (100), 121 (25), 120 (14), 107 (10), 93 (14), 91 (10), 79 (36), 77 (7), 55 (5). Found, %: C 64.39; H 9.53. $C_{13}H_{23}O_2P$. Calculated, %: C 64.44; H 9.57.

General procedure for synthesis of phosphinic acids (IIIa–IIIc). A mixture of 2.80 mmol of sodium hypophosphite, 7.00 mmol of unsaturated derivative **Ia**, **Ic,** or **Id**, 5 mL of methanol, and 0.1 mL of 70% aqueous solution of *tert*-butyl hydroperoxide was heated to 120°C in a sealed vial. After 5 h incubation, another 0.1 mL portion of 70% aqueous *tert*-butyl hydroperoxide was added to the mixture, and the heating was continued for 5 h at the same temperature. Then the solvent was distilled off in vacuum. Sodium salt of the phosphinic acid was washed with petroleum ether, dried, suspended in water, and acidified with conc. hydrochloric acid to pH 1–1.5. The free acid was filtered off and washed with small amount of water.

Bis(adamantylmethyl)phosphinic acid (IIIa). Yield 92.0%, mp 310–314°C. IR spectrum (KBr), ν, cm^{-1}: 968 [γ(CH_2)], 1161 (P=O, st), 1454 [δ(CH_2)], 1654 [P(O)OH], 2657 (PO–H, st), 2900 (C–H, st). ^{1}H NMR spectrum, δ, ppm: 1.55 m (4H, Ad), 1.70–2.00 m (24H, Ad, 4H, CH_2P), 2.25 m (2H, Ad), 9.45 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 25.4 (CH, Ad), 27.8 (CH_2, Ad), 31.5 (CH_2, Ad), 33.1 d (CH, Ad, $^2J_{CP}$ 7.5 Hz), 33.6 d (PCH_2, $^1J_{CP}$ 80.0 Hz), 38.3 (CH, Ad), 39.0 (CH_2, Ad). ^{31}P NMR spectrum: δ_P 62.5 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 376 (12) $[M]^+$, 228 (100) $[M - AdCH_2]^+$, 149 (86) $[AdCH_2]^+$, 91 (16), 79 (38). Found, %: C 72.84; H 9.69. $C_{22}H_{35}O_2P$. Calculated, %: C 72.90; H 9.73.

Bis[2-(adamant-2-yl)propyl]phosphinic acid (IIIb). Yield 94.2%, mp 189–191°C. IR spectrum (KBr), ν, cm^{-1}: 956 [γ(CH_2)], 1172 (P=O, st), 1446 [δ(CH_2)], 1654 [P(O)OH], 2657 (PO–H, st), 2900 (CH, st). ^{1}H NMR spectrum, δ, ppm: 1.12 d.d (3H, CH_3, $^2J_{HH}$ 7.0, $^3J_{HP}$ 20.0 Hz), 1.50–2.15 m (15H, Ad; 1H, CH; 2H, CH_2), 7.10 d (1H, PH, $^1J_{HP}$ 560 Hz), 9.45 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 20.2 d (CH_3, $^3J_{CP}$ 8.5 Hz), 26.2 d (CH_2, $^1J_{CP}$ 10.0 Hz), 28.2 (C, Ad), 28.6 (CH, Ad), 36.2 (CH_2, Ad), 37.4 d (CH, $^2J_{CP}$ 12.5 Hz), 40.3 (CH, Ad). ^{31}P NMR spectrum: δ_P 69.2 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 432 $[M]^+$, 297 (84), 255 (10), 214 (5), 175 (5), 135 (100), 107 (15), 93 (22), 79 (25). Found, %: C 74.52; H 10.29. $C_{26}H_{43}O_2P$. Calculated, %: C 74.60; H 10.35.

Bis[2-(adamantyl-1-yl)ethyl]phosphinic acid (IIIc). Yield 89.4%, mp 268–270°C. IR spectrum (KBr), ν, cm^{-1}: 960 [γ(CH_2)], 1172 (P=O, st), 1450 [δ(CH_2)], 1662 [P(O)OH], 2665 (PO–H, st), 2896 (CH, st). ^{1}H NMR spectrum, δ, ppm: 1.55 m (4H, Ad), 1.70–2.00 m (24H, Ad; 4H, CH_2; 4H, CH_2P), 2.32 m (2H, Ad), 9.45 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 24.5 d (CH_2P, $^1J_{CP}$ 65.2 Hz), 28.2 (CH_2, Ad), 29.7 (C, Ad), 30.7 d (CH_2, $^2J_{CP}$ 10.5 Hz), 36.3 (CH_2, Ad), 41.6 (CH, Ad). ^{31}P NMR spectrum: δ_P 66.1 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 404 $[M]^+$, 270 (14), 269 (100), 242 (5), 161 (5), 135 (35), 121 (10), 107 (12), 93 (14) 79 (16), 55 (5). Found, %: C 73.72; H 10.01. $C_{24}H_{39}O_2P$. Calculated, %: C 73.81; H 10.07.

General procedure for synthesis of phosphinic acids (VIa–VIc). A mixture of 4.70 mmol of (adamant-2-ylmethyl)phosphinic acid **IIa** and 9.30 mmol of hexamethyldisilazane was stirred during 4 h at 120°C under argon. Then 5.10 mmol of the halide was added to the reaction mixture, and the heating was continued for 4 h. After cooling to 0°C, 36 mL of methanol was added, and the mixture was stirred during 20 min. Then the solvent was removed under vacuum. The residue was dissolved in chloroform, filtered, evaporated, and recrystallized from propan-2-ol (**VIa**), ethanol (**VIb**) or 2 : 1 ethanol–water mixture (**VIc**).

(Adamant-2-ylmethyl)benzylphosphinic acid (VIa). Yield 64.2%, mp 136–139°C. IR spectrum (KBr), ν, cm^{-1}: 952 [γ(CH_2)], 1164 (P=O, st), 1450 [δ(CH_2)],

1647 [P(O)OH], 2904 (C–H, st). ^{1}H NMR spectrum, δ, ppm: 1.46 d (2H, CH_2P, $^2J_{HP}$ 11.4 Hz), 1.60–1.90 m (14H, Ad), 2.00–2.20 m (1H, Ad), 2.97 d (2H, CH_2P, $^2J_{HP}$ 16.3 Hz), 7.10–7.40 m (5H Ar), 11.60 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 28.1 (CH, Ad), 32.8 d (CH_2P, $^1J_{CP}$ 64.8 Hz), 33.0 (CH_2, Ad), 33.6 (CH, Ad), 35.7 d (CH_2P, $^1J_{CP}$ 65.2 Hz), 37.6 (CH_2, Ad), 39.0 д (CH, Ad, $^2J_{CP}$ 7.0 Hz), 126.2 (CH, Ar), 128.5 (CH, Ar), 129.9 (CH, Ar), 130.0 (CH, Ar), 134.2 (C, Ar). ^{31}P NMR spectrum: δ_P 46.9 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 318 (18) $[M]^+$, 149 (30) $[AdCH_2]^+$, 93 (13), 92 (100), 91 (45), 79 (27). Found, %: C 70.97; H 8.21. $C_{18}H_{25}O_2P$. Calculated, %: C 71.03; H 8.28.

(Adamant-2-ylmethyl)(2,4,6-trimethylbenzyl)phosphinic acid (VIb). Yield 31.4%, mp 217–219°C. IR spectrum (KBr), ν, cm^{-1}: 972 [γ(CH_2)], 1172 (P=O, st), 1450 [δ(CH_2)], 1647 [P(O)OH], 2657 (PO–H, st), 2904 (CH, st), 3024 [δ(C–H)]. ^{1}H NMR spectrum, δ, ppm: 1.50 d (2H, CH_2P, $^2J_{HP}$ 11.4 Hz), 1.60–1.80 m (15H, Ad), 2.20 (3H, CH_3), 2.31 (6H, CH_3), 3.00 d (2H, CH_2P, $^2J_{HP}$ 15.8 Hz), 6.82 (2H, Ar), 11.56 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 20.9 (CH_3), 21.0 (CH_3), 27.7 (CH, Ad), 31.4 (CH, Ad), 32.1 d (CH_2P, $^2J_{CP}$ 86.5 Hz), 32.9 d (CH_2, $^2J_{CP}$ 91.5 Hz), 38.3 (CH_2, Ad), 38.9 (CH_2, Ad); 126.2 (Ar), 129.1 (CH, Ar), 135.8 (Ar), 137.4 (Ar). ^{31}P NMR spectrum: δ_P 58.8 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 361 (6) $[M]^+$, 149 (7) $[AdCH_2]^+$, 134 (100), 133 (78), 105 (8), 91 (9), 79 (11). Found, %: C 72.72; H 8.95. $C_{21}H_{31}O_2P$. Calculated, %: C 72.80; H 9.02.

(Adamant-2-ylmethyl)(propyl)phosphinic acid (VIc). Yield 52.0%, mp 132–136°C. IR spectrum (KBr), ν, cm^{-1}: 968 [γ(CH_2)], 1164 (P=O, st), 1450 [δ(CH_2)], 1647 [P(O)OH], 2657 (PO–H, st), 2904 (CH, st). ^{1}H NMR spectrum, δ, ppm: 1.01 m (3H, CH_3), 1.50–2.15 m (15H, Ad; 6H, $3CH_2$), 11.65 br.s (1H, OH). ^{13}C NMR spectrum, δ_C, ppm: 15.5 d (CH_3, $^3J_{CP}$ 6.8 Hz), 16.8 d (CH_2, Pr, $^2J_{CP}$ 8.0 Hz), 28.1 (CH, Ad), 31.6 d (CH_2P, $^1J_{CP}$ 65.2 Hz), 32.2 d (CH_2P, $^1J_{CP}$ 64.8 Hz), 33.0 (CH_2, Ad), 34.5 d (CH, Ad), 38.2 (CH_2, Ad), 38.9 d (CH, Ad, $^2J_{CP}$ 8.0 Hz). ^{31}P NMR spectrum: δ_P 60.8 ppm. Mass spectrum, *m*/*z* (I_{rel}, %): 270 (21) $[M]^+$, 228 (42), 150 (15), 149 (100) $[AdCH_2]^+$, 122 (93), 94 (52), 79 (75), 67 (12) 43 (15). Found, %: C 65.55; H 9.79. $C_{14}H_{25}O_2P$. Calculated, %: C 65.60; H 9.83.

Virus-inhibiting activity was tested against the herpes simplex virus (strain 1 C) with human rhabdomyosarcoma cell line (RD), against influenza A [strain A/turkey/Suzdalka/12/05 (H5N1)] with transplantable cell culture of canine kidney (MDCK), and against respiratory syncytial virus (strain Long) and adenovirus of type 3 with laryngeal carcinoma cell line Hep-2C by evaluating suppression of the virus-induced cytopathic effect.

The tested compounds were initially dissolved in 10% ethanol (concentration of the mother liquor was 5 mg mL^{-1}) and then diluted with the support medium (DMEM) to the required concentration. The monolayer cell culture grown in flasks were washed of the growth medium and infected with 0.01–0.001 $TCID_{50}$/virus cell by application of 0.1 mL of the diluted virus-containing suspension during 1 h at 37°C. Then the liquid was removed; the cells were covered with the support medium containing various concentrations of the tested substances, and incubated at 37°C during 48–72 h. Morphological changes in the cells monolayer were observed (cytopathic effect of the virus, 80-fold increase). The virus titer in the presence of the analytes and in the reference was calculated as lg$TCID_{50}$ (50% tissue cytopathic dose).

Existence of differences in the viral titer compared to the reference was considered a measure of antiviral activity. The data were processed by determining the number of infectious cells, using the Reed–Muench method, and statistics for small values of *n* in the number of ungrouped data series. Concentrations of 50% and 90% suppression of virus replication in the presence of the tested compounds (EC_{50} and EC_{90}) were determined by means of probit analysis and weighted linear regression. The MTC/EC_{50} and MTC/EC_{90} ratios were used as variables indicative of the broad range of active non-toxic concentrations of the test compounds. The maximum tolerated concentration was defined as the maximum concentration of the test compound having no effect on the morphology of unstained cell culture.

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