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LETTERS TO THE EDITOR

Synthesis of Adamantylalkyl Tosyloxymethylphosphonates

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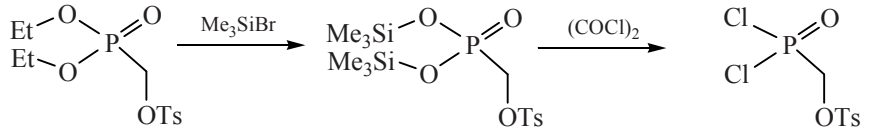
Tosyloxymethylphosphonates are key compounds in the synthesis of nucleoside phosphonates, the promising antiviral drugs of a new generation [1–3]. Low bioavailability caused by the presence of polar phosphoryl group in the molecule is an essential drawback of the known drugs of this class (adefovir, cidofovir, tenofovir). At the same time phosphoryl group is one of the fragments conditioning high activity. Drugs development on the matrix of nucleoside phosphonates modified with lipophilic substutuents offers a solution of this problem. Some of the synthesis method of phosphonic acids Na-salts involving alkoxyalkyl substituents have been described [4]. We carried out synthesis of tosylmethylphosphonates on the base of adamantane series alcohols.

Reaction of diethyl tosyloxymethylphosphonate **I** [5] with bromotrimethylsilane yields bistrimethylsilyl ester **II**, which reacts with oxalyl chloride in the presence of catalytic amounts of *N*,*N*-dimethylformamide (DMF) to form dichlorophosphonate **III**:



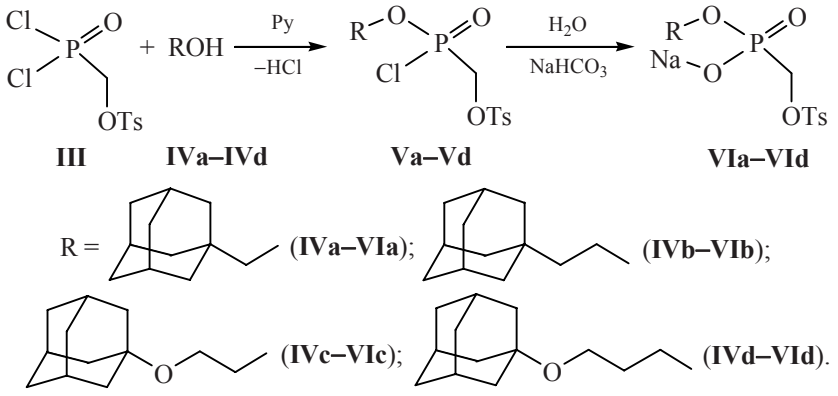
I **II** **III**

Reaction of compound **III** with adamantane derivatives **IVa–IVd** in the presence of a base (pyridine, triethylamine) followed by monochloroderivatives **Va–Vd** hydrolysis with the saturated aqueous solution of sodium hydrogen carbonate produces Na-salts of the corresponding adamantylalkyl and adamantyloxyalkyl phosphonates **VIa–VId**.

2-(1-Adamantyl)ethanol **IVb** and 3-(1-adamantyloxy)propanol **IVd** were prepared by procedures [6] and [7] respectively.

2-(1-Adamantyloxy)ethanol (IVc). A mixture of 50 ml of ethylene glycol, 8.81 g of 1-bromoadamantane, 18 ml of triethylamine and 0.62 g of 1,8-diazabicyclo[5.4.0]undec-7-ene was stirred at 110°C for 5 h. The reaction mixture was poured into water (250 ml). Organic layer was extracted with chloroform (100 ml). Extract was washed with water (3×100 ml) and dried with calcium chloride. Then the solvent was removed. Yield 5.79 g (72%). Charac-teristics of the compound obtained corresponded to literary data [8].

Sodium 1-adamantylmethyl tosyloxymethylphosphonate (VIa). To a solution of 4.61 g of **I** in 76 ml of dichloromethane was added 16.2 g of bromotrimethylsilane under stirring. The reaction mixture was kept for 16 h. Dichloromethame and bromomethylsilane excess were removed in a vacuum. To the residue dissolved in 60 ml of dichloromethane was added 0.20 ml of dry DMF at 0°C under stirring and a solution of 5.45 g of oxalylchloride in 15 ml of dichloromethane within 45 min. This mixture was stirred for 6 h, rising slowly temperature to ambient. Dichloromethane and



oxalyl chloride excess were removed in a vacuum. The residue was mixed with 25 ml of unhydrous diethyl ether. To the decanted ether solution was added a mixture of 1.19 g of 1-adamantylmethanol **IVa** [9] and 1.23 g of pyridine in 25 ml of unhydrous diethyl ether. The reaction mixture was stirred for 2 h and hydrolyzed with 150 ml of saturated solution of $NaHCO_3$. Then ether layer was separated. The oily layer and water phase were extracted with chloroform. The obtained extract was dried with anhydrous $MgSO_4$. The solvent was removed. The product was chromatographically isolated (silica gel 0.063–0.200 mm, eluent chloroform–methanol (10%). Yield 2.38 g (38.2%). Found, %: C 51.93; H 6.10. Calculated, %: C 52.29; H 6.00. ^{1}H NMR spectrum, δ, ppm: 1.34 s (4H, $2CH_2$, Ad), 1.61 m (8H, CH_2, Ad), 1.90 s (2H, 2CH, Ad), 2.42 s (3H, CH_3), 3.9 d (2H, CH_2O, $^3J_{HP}$ 11 Hz), 7.47, 7.51, 7.73, 7.77 (4H, Ar, *AB*-system). ^{31}P NMR spectrum, δ_P, ppm: 6.85.

Sodium 2-(1-adamantyl)ethyl tosyloxymethyl] phosphonate (VIb) was prepared similarly. Yield 37.7%, dp 253–255°C . Found, %: C 53.29; H 6.31. Calculated, %: C 53.33; H 6.27. ^{1}H NMR spectrum, δ, ppm: 1.2 t (2H, Ad), 1.4 s (6H, Ad), 1.6 m (6H, Ad), 1.8 (1H, CH, Ad, 2H, Ad–CH_2–), 2.4 (3H, CH_3), 3.8 (2H, CH_2O, $^3J_{HP}$ 10 Hz), 7.47, 7.51, 7.73, 7.77 (4H, Ar, *AB*-system). ^{13}C NMR spectrum, δ_C, ppm: 20.99 (CH_3, *p*-Tol), 27.91 (3CH, Ad), 36.48 ($3CH_2$, Ad), 41.96 ($3CH_2$, Ad), 127.54 (*m*-CH=, *p*-Tol), 129.99 (*o*-CH, *p*-Tol). ^{31}P NMR spectrum, δ_P, ppm: 6.70.

Sodium 2-(1-adamantyloxy)ethyl tosyloxymethylphosphonate (VIc) was prepared similarly. Yield 7.2%, mp 198–202°C. Found, %: C 51.47; H 6.09. Calculated, %: C 51.50; H 6.05. ^{1}H NMR spectrum, δ, ppm: 1.58 s, 1.62 s (12H, $6CH_2$, Ad), 2.05 s (3H, 3CH, Ad), 2.40 (3H, CH_3), 3.85 (2H, CH_2O, $^3J_{HP}$ 10 Hz), 7.47, 7.51, 7.73, 7.77 (4H, Ar, *AB*-system). ^{13}C NMR spectrum, δ_C, ppm: 20.99 (CH_3, *p*-Tol), 29.78 (3CH, Ad), 35.82 ($3CH_2$, Ad), 41.00 ($3CH_2$, Ad), 58.50 (CH_2OAd), 64.17 (CH_2OP), 71.24 (PCH_2O), 127.54 (*m*-CH, *p*-Tol), 130.00 (*o*-CH, *p*-Tol), 144.74 (*p*-C, *p*-Tol). ^{31}P NMR spectrum, δ_P, ppm: 7.06.

Sodium 1-(1-adamantyloxy)prop-3-yl tosyloxymethylphosphonate (VId) was prepared similarly. Yield 23.8%. Found, %: C 52.48; H 6.31. Calculated, %: C 52.49; H 6.29. ^{1}H NMR spectrum, δ, ppm: 0.85 s, 1.15 m, 1.30 m, 1.55 s, 1.65 s, 2.10 s (15H, Ad), 2.40 (3H, CH_3), 3.00 m, 3.65 d (2H, CH_2O, $^3J_{HP}$ 10 Hz), 3.80 d (2H, CH_2O, $^3J_{HP}$ 10 Hz), 7.47, 7.51, 7.73, 7.77 (4H, Ar, *AB*-system). ^{13}C NMR spectrum, δ_C, ppm: 21.02 (CH_3, *p*-Tol), 29.75 (3CH, Ad), 31.63 ($OCH_2CH_2CH_2O$), 35.87 ($3CH_2$, Ad), 41.01 ($3CH_2$, Ad), 55.86 (CH_2OAd), 61.48 (CH_2OP), 70.94 (PCH_2O), 79.10 (C, Ad), 127.66 (*m*-CH, *p*-Tol), 130.00 (*o*-CH, *p*-Tol), 144.76 (*p*-C, *p*-Tol). ^{31}P NMR spectrum, δ_P, ppm: 7.82.

The NMR spectra were registered on a Brucker AC200 and a Brucker AM300 devices using DMSO-d_6 as a solvent [200.13, 300.13 (^{1}H), 50.32, 75.47 (^{13}C) and 121.49 MHz (^{31}P)]. Measurements were carried out without use of additional references with frequency connection to deuterated solution signal.

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