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LETTERS TO THE EDITOR

Addition of Tris(trimethylsilyl) Phosphite to Quinuclidin-3-one and Its Carbocyclic Analogs

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Abstract—Convenient methods of synthesis of functionalized phosphonic acids and their trimethylsilyl esters containing quinuclidine, adamantine, and bornane (camphane) moieties, involving reactions of tris(trimethylsilyl) phosphite with quinuclidin-3-one and its carbocyclic analogs.

Keywords: tris(trimethlsilyl) phosphite, quinuclidin-3-one, adamantan-2-one, camphor, trimethylsilyl trifluoromethanesulfonate

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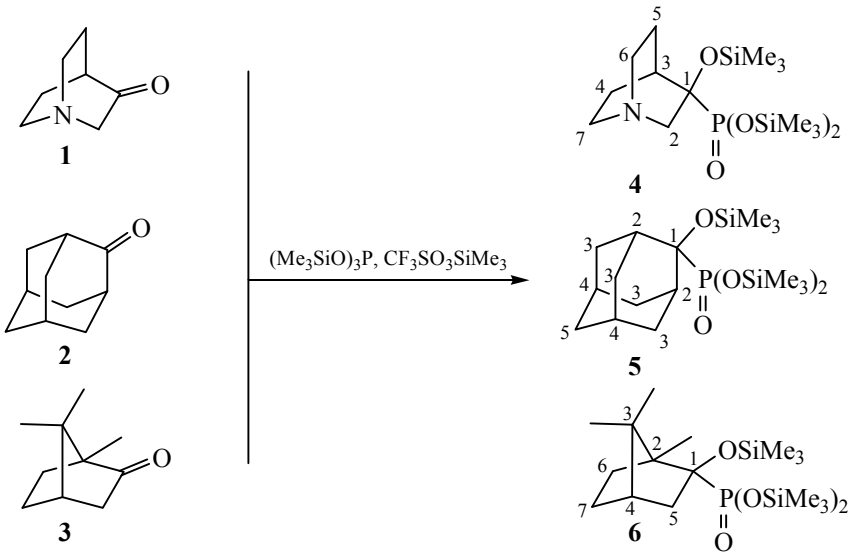
Functionalized hydroxymethylphosphonates have found wide application as polydentate ligands and biologically active substances with diverse properties [1, 2]. Of particular interest are hydroxymethylphosphonates containing polycyclic moieties, for example, quinuclidine, adamantane, and bornane (camphane), which are quite popular in pharmaceutical synthesis [3, 4]. Earlier we synthesized a series of hydroxymethylphosphonates containing piperidine moieties, using tris(trimethlsilyl) phosphite as a convenient [5]. In the present work we developed convenient methods of synthesis of polycyclic trimethylsilyl phosphonates containing quinuclidine, adamantane, and bornane moieties, involving reactions of tris(trimethylsilyl) phosphite with quinuclidin-3-one and its carbocyclic analogs.

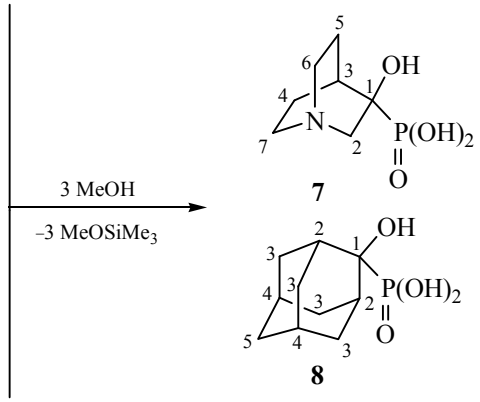
It was found that quinuclidin-3-one **1**, adamantan-2-one **2**, and camphor **3** rapidly reacted with excess tris(trimethylsilyl) phosphite only in the presence of a trimethylsilyl trifluoromethanesulfonate catalyst (cf.

Scheme 1.

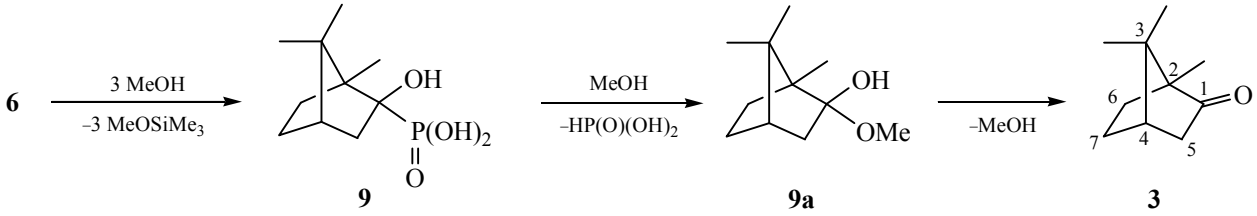


1 **2** **3** **4** **5** **6**

Scheme 2.



Scheme 3.



[5]). In this case, the reactions occurred in mild conditions to form functionalized phosphonates **4**–**6** in high yields (Scheme 1).

Trimethylsilyl esters **4** and **5** readily react with methanol under mild conditions to give functionalized phosphonic acids **7** and **8** as white hygroscopic crystals (Scheme 2). The reaction of phosphonate **6** with excess methanol under the same conditions involves P–C bond cleavage and forms phosphorous acid and camphor **3** (Scheme 3). Apparently, the lability of the P–C bond in acid **9** is associated with steric effects of the bulky substituent, and the cleavage of this bond occurs via the intermediate formation of semiacetal **9a**, which easily dissociates into the starting methanol and camphor **3**.

The resulting quinoclidine, adamantane, and bornane derivatives **4**–**8** are promising biomimetics of hydroxycarboxylic acids and can be used in the synthesis of previously unknown types of organophosphorus compounds and further search for targeted polyfunctional drugs, and also present interest as promising polydentate ligands.

Bis(trimethylsilyl) [3-(trimethylsiloxy)-1-azabicyclo[2.2.2]oct-3-yl]phosphonate (4). Tris(trimethylsilyl)phosphite, 30.0 g (0.1 mol), and a solution of 1.6 g (0.007 mol) of trimethylsilyl trifluoromethanesulfonate in 5 mL of methylene chloride were added one after the other to a solution of 4.0 g (0.025 mol) of quinuclidin-3-one in 10 mL of methylene chloride. The mixture was heated on a boiling water bath to remove all volatile compounds and then distilled. Yield 78% (11.0 g), bp 144°C (1 mmHg). ^{1}H NMR spectrum, δ, ppm: –0.26 s (9H, Me_3Si), –0.12 s (9H, Me_3Si), 0.11 s (9H, Me_3Si), 0.85–1.02 m (2H, C^5H_2), 1.45–1.65 m (2H, C^4H_2), 1.76–1.87 m (1H, C^3H), 2.25–2.45 m (5H, C^2H_B, C^6H_2, C^7H_2), 2.93–3.02 m (1H, C^2H_A). ^{13}C NMR spectrum, δ_C, ppm: 0.39 d (2Me_3Si, $^3J_{PC}$ = 8.2 Hz), 1.44 (Me_3Si), 20.98 d (C^4, $^3J_{PC}$ = 9.0 Hz), 22.38 (C^3), 28.12 d (C^5, $^3J_{PC}$ = 6.6 Hz), 45.37 (C^6), 45.72 (C^7), 58.94 d (C^2, $^2J_{PC}$ = 8.7 Hz), 73.36 d (C^1, $^1J_{PC}$ = 170.8 Hz). ^{31}P NMR spectrum: δ_P 9.81 ppm. Found, %: C 45.26; H 8.96. $C_{16}H_{38}NO_4PSi_3$. Calculated, %: C 45.35; H 9.04.

Phosphonates **5** and **6** were prepared in a similar way.

Bis(trimethylsilyl) [2-(trimethylsiloxy)adamantan-2-yl]phosphonate (5). Yield 93%, viscous oil. ^{1}H NMR spectrum, δ, ppm: 0.04 s (9H, Me_3Si), 0.18 s (18H, Me_3Si), 1.25–1.44 m (4H, 2C^4H_2), 1.49–1.60 m (6H, 2C^2H_2, C^3H_2), 1.62–1.75 m (2H, C^3H_2), 1.80–1.95 m (2H, C^3H_2), 1.97–2.10 m (2H, C^3H_2), 2.45–2.65 m (2H, C^5H_2). ^{13}C NMR spectrum, δ_C, ppm: 0.81 (2Me_3Si), 2.11 (Me_3Si), 26.46 (C^4), 27.07 (C^4), 32.91 (C^2), 33.02 (C^2), 33.28 (C^3), 34.39 (C^3), 38.29 (C^5),

79.00 d (C^1, $^1J_{PC}$ = 168.3 Hz). ^{31}P NMR spectrum: δ_P 11.06 ppm. Found, %: C 50.69; H 9.12. $C_{19}H_{41}O_4PSi_3$. Calculated, %: C 50.85; H 9.21.

Bis(trimethylsilyl) [1,7,7-trimethyl-2-(trimethylsiloxy)bicyclo[2.2.1]hept-2-yl]phosphonate (6). Yield 89%, viscous oil. ^{1}H NMR spectrum, δ, ppm: 0.27 s (9H, Me_3Si), 0.29 s (18H, Me_3Si), 0.68 s (3H, Me), 1.09 c (3H, Me), 1.14 s (3H, Me), 1.25–1.35 m (4H, C^6H_2, C^7H_2), 1.40–1.45 m (2H, C^5H_2), 1.58–1.65 m (1H, C^4H). ^{13}C NMR spectrum, δ_C, ppm: 0.49 (Me_3Si), 1.67 (2 Me_3Si), 10.65 (Me), 17.92 (Me), 18.52 (Me), 25.88 (C^7), 28.75 (C^6), 41.92 d (C^5, $^2J_{PC}$ = 9.9 Hz), 43.89 d (C^4, $^3J_{PC}$ = 6.4 Hz), 48.62 d (C^3, $^3J_{PC}$ = 15.3 Hz), 52.34 d (C^2, $^2J_{PC}$ = 5.9 Hz), 82.39 d (C^1, $^1J_{PC}$ = 176.0 Hz). ^{31}P NMR spectrum: δ_P 9.74 ppm. Found, %: C 50.48; H 9.52. $C_{19}H_{43}O_4PSi_3$. Calculated, %: C 50.62; H 9.61.

[3-Hydroxy-1-azabicyclo[2.2.2]oct-3-yl]phosphonic acid (7). A solution of phosphonate **1a** in 15 mL of diethyl ether was added to a stirred solution of 30 mL of methanol under cooling to 10°C. The mixture wa then heated to reflux, the solvent was distilled off, and the remaining white crystals were subjected to a vacuum (1 mmHg) for 1 h. Yield 98% (5.1 g), mp 130–132°C (decomp.). ^{1}H NMR spectrum, δ, ppm: 1.70–2.00 m (2H, C^5H_2), 2.40–2.67 m (3H, C^3H, C^4H_2), 3.28–3.50 m (5H, C^2H_B, C^6H_2, C^7H_2), 3.80–3.93 m (1H, C^2H_A). ^{13}C NMR spectrum, δ_C, ppm: 18.38 d (C^4, $^3J_{PC}$ = 8.3 Hz), 19.77 (C^3), 27.13 (C^5), 45.99 (C^6), 46.43 (C^7), 56.24 d (C^2, $^2J_{PC}$ = 10.1 Hz), 68.49 d (C^1, $^1J_{PC}$ = 163.6 Hz). ^{31}P NMR spectrum: δ_P 18.49 ppm. Found, %: C 40.42; H 6.89. $C_7H_{14}NO_4P$. Calculated, %: C 40.58; H 6.81.

[2-Hydroxyadamantan-2-yl]phosphonic acid (8) was prepared in a similar way. Yield 95%, mp 217–219°C (cf. [6]). ^{1}H NMR spectrum, δ, ppm: 1.25–1.40 m (H, $2C^4H$), 1.45–1.75 m (6H, $2C^2H_2$, C^3H_2), 1.90–2.05 m (2H, C^3H_2), 2.15–2.25 m (2H, C^3H_2), 2.30–2.50 m (4H, C^3H_2, C^5H_2). ^{13}C NMR spectrum, δ_C, ppm: 26.71 (C^4), 27.07 (C^4), 32.22 (C^2), 33.32 (C^2), 33.33 (C^3), 33.52 (C^3), 38.28 (C^5), 74.19 d (C^1, $^1J_{PC}$ = 159.9 Hz). ^{31}P NMR spectrum: δ_P 25.07 ppm. Found, %: C 51.54; H 7.29. $C_{10}H_{17}O_4P$. Calculated, %: C 51.72; H 7.38.

Reaction of phosphonate 6 with methanol. A solution of 6.5 g (0.014 mol) of phosphonate **6** in 10 mL of diethyl ether was added to 20 mL of methanol under stirring and cooling to 10°C. The mixture was heated to reflux, the solvent was distilled off, and the remaining viscous oil was subjected to a vacuum (1 mmHg) for 1 h to obtain a mixture of 3.2 g of phosphorous acid and camphor **3** as a viscous oil, yield 95%.

Phosphorous acid. ^{1}H NMR spectrum, δ, ppm: 6.60 d (1H, PH^1, $^1J_{PH}$ 675.2 Hz). ^{31}P NMR spectrum: δ_P 3.34 ppm.

Camphor 3. ^{1}H NMR spectrum, δ, ppm: 0.55 s (3H, Me), 0.60 s (3H, Me), 0.70 s (3H, Me), 1.05–1.60 m (4H, C^6H_2, C^7H_2), 1.65–2.15 m (3H, C^4H_2, C^5H_2). ^{13}C NMR spectrum, δ_C, ppm: 9.04 (Me), 18.66 (Me), 19.26 (Me), 26.50 (C^6), 29.48 (C^7), 42.71 (C^5), 46.49 (C^3), 48.87 (C^4), 57.34 (C^2), 219.89 (C^1).

The NMR spectra were obtained on a Bruker Avance 400 spectrometer; solvents $CDCl_3$ (**4**–**6**), CD_3COOD (**7**), and $(CD_3)_2SO$ (**8**); references TMS (^{1}H, ^{13}C) and 85% H_3PO_4 in D_2O (^{31}P).

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REFERENCES

1. Kukhar, V.P. and Hudson, H.R., *Aminophosphonic and Aminophosphinic Acids. Chemistry and Biological Activity*, New York: Wiley, 2000.
2. Kolodiazhnyi, O.I., *Russ. Chem. Rev*., 2006, vol. 75, no. 2, p. 227. doi 10.1070/RC2006v075n03ABEH001193
3. Hou, F., Miyakawa, T., Kataoka, M., Takeshita, D., Kumashiro, S., Uzura, A., Urano, N., Nagata, K., Shimizu, S., and Tanokura, M., *Biochem. Biophys. Res. Commun*., 2014, vol. 446, p. 911. doi 10.1016/j.bbrc.2014.03.030
4. Bagrii, E.I., *Adamantany: Poluchenie, svoistva, primenenie* (Synthesis, Properties, Application), Moscow: Nauka, 1989.
5. Prishchenko, A.A., Alekseyev, R.S., Livantsov, M.V., Novikova, O.P., Livantsova, L.I., Terenin, V.I., and Petrosyan, V.S., *Russ. J. Gen. Chem*., 2017, vol. 87, no. 2, p. 359. doi 10.1134/S1070363217020360
6. Gamaleya, V.F., Sorochinskii, A.E., Aleksandrov, A.M., Pavlenko, A.F., Kukhar', V.P., and Terenin, V.I., *Zh. Obshch. Khim*., 1980, vol. 50, no. 11, p. 2619.