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LETTERS TO THE EDITOR

To the 85th Anniversary of birthday of late Yu.G. Gololobov

Atropine Dithiophosphorylation

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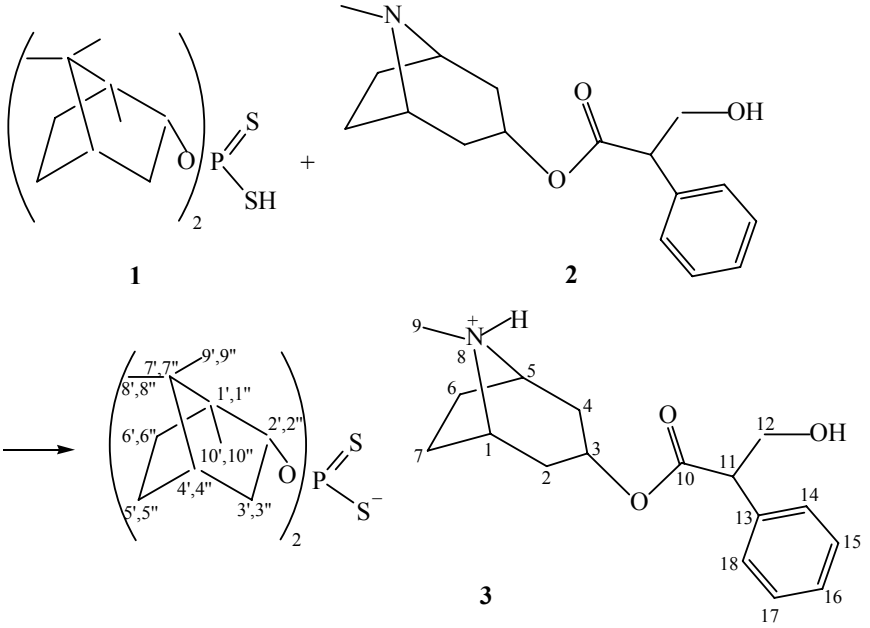
Organophosphorus compounds are used as pesticides [1] and specific neuromuscular paralytic poisons; they disrupt acetylcholine exchange in neurotransmission [2–4]. Interaction of organophosphorus compounds with hydroxy group of the serine moiety of choline esterase leads to the formation of hydrolysis-resistant phosphorylated enzyme incapable to hydrolyze acetylcholine, which is accumulated in toxic doses in the synaptic gap between neurons of the central and peripheral nervous systems [5]. Complex specific therapy of acute poisoning by organophosphorus compounds is based on blocking cholinergic receptors, i.e., on creating obstacles to the toxic action of endogenous acetylcholine, as well as the restoration of cholinesterase-inhibiting activity to normalize the acetylcholine metabolism. Combination therapy involves the use of anticholinergics, atropine drugs and oximes as cholinesterase reactivators [6]. The plant alkaloid atropine, a racemic mixture of tropine esters of D- and L-tropic acid, as an antidote acts as an exogenous nicotinic acetylcholine receptor antagonist (M-cholinoblocker) [7]. Atropine ability to bind to cholinergic receptors due to the presence of CH_2OH fragment in its structure that make it related to endogenous agonist acetylcholine. Thus, the role of atropine antidote is the interaction with cholinesterase and in so doing atropine protecting group prevents cholinesterase phosphorylation.

In this work, we proposed a new approach to reduce the toxicity of organophosphorus cholinesterase inhibitors based on reacting atropine with organophosphorus compounds. Among the latter, phosphorus dithioacids, which underlie the production of traditional pesticides, possess lower toxicity towards warm-blooded organisms compared with similar structured phosphates [1]. It is expectable that the obtained atropine derivatives will have selective antimicrobial effect due to the presence of the chiral carbon atoms in the ether substituents of *O*-dithiophosphoric acids.

We found that *O*,*O*-di{*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}-(–)-dithiophosphoric acid **1** derived from (1*S*)-*endo*-(–)-borneol [8, 9] reacted with atropine **2** in ethanol at 20°C for 1 h to form atropine-*O*,*O*-di{*endo*-(1*S*)-1,7,7-trimethylbicyclo[2.2.1]hept-2-yl}-(–)-dithiophosphate **3** as ammonium salt (Scheme 1).

When using nonpolar organic solvents (benzene, hexane), no formation of salt **3** occurred due to the presence of atropine in the form of an internal salt owing to migration of CH_2OH proton to the nitrogen atom. Ethanol is capable of deprotonating the quaternized nitrogen atom of atropine and restoring basic properties of the ring nitrogen atom leading to the formation of the ammonium salt of **3** due to the transfer of the sulfhydryl proton of acid **1** to the nitrogen atom of atropine. In $^{31}P–\{^1H\}$ NMR spectrum of compound **3** the signal at 111.2 ppm corresponded to the chemical shift of phosphorus nucleus that is typical of ammonium dithiophosphates [10]. Optical activity of dithiophosphate **3** ($[\alpha]_D^{20}$ –6.4°, *c* 1.16,

Scheme 1.



acetone) remained since asymmetric centers were not involved into the quatenization process. A strong absorption at 3382 cm^{-1} in the IR spectrum of salt **3** corresponds to the stretching vibrations of H–O and N^+–H bonds. The absorption of O=C bond was observed at 1725 cm^{-1} [11].

Hence, dithiophosphorylation of atropine with optically active dithiophosphoric acids is a promising approach towards the synthesis of selective bioactive agents with inhibitory activity against cholinesterase.

Atropine-*O*,*O*-di{*endo*-(1*S*)-1,7,7-trimethylbicyclo-[2.2.1]hept-2-yl}-(–)-dithiophosphate (3). A solution of 0.2 g of atropine **1** in 5 mL of ethanol was added while stirring to a solution of 0.3 g of acid **2** in 5 mL of anhydrous ethanol at 20°C under dry argon. The mixture was stirred at 20°C for 1 h, then it was maintained at 20°C for ~ 12 h. Next, the solvent was evaporated at 40°C for 1 h in a vacuum of 0.5 mmHg and 1 h at 0.02 mmHg. Yield 0.4 g (80%), $[\alpha]_D^{20}$ –6.4° (*c* 1.16, acetone). IR spectrum, cm^{-1}: 3382 v.s.br (H–O, N^+H), 2938 m, 2884 m (CH_3, CH_2), 1725 m (O=C–O), 1643 m (C=C, Ar), 1453 m [$\delta_{as}(CH_3)$], 1387 m [$\delta_s(CH_3)$], 1041 v.s [(P)O–C], 671 m (P=S), 561 m (P–S). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.82 s (6H, $C^{8',8'}H_3$), 0.87 s [12H, $(CH_3)_2C$], 1.13 t (4H, $C^{6',6'''}H_2$, $^3J_{HH}$ 7.0), 1.17–1.24 m (2H, CH_2), 1.33–1.37 m (2H, CH_2), 1.56–1.81 m (2H, CH_2), 2.19–2.39 m (3H, CH, CH_2), 2.43 s (3H, C^9H_3N), 3.25 m and 3.33 m (2H, C^1H, C^5H), 3.52 m and 3.57 m (2H, $C^{2',2''}HOP$), 3.65 m and 3.82 m (2H, $C^{12'}H_2OH$), 4.161 t (1H, $C^{11}\underline{H}CH_2OH$, $^3J_{HH}$ 7.0), 4.163 t (1H, $C^{11}\underline{H}CH_2OH$, $^3J_{HH}$ 6.9), 4.99 t (1H, C^3HO, $^3J_{HH}$ 5.2), 7.29–7.39 m (5H, C_6H_5). ^{1}C NMR spectrum, δ_C, ppm (*J*, Hz) (the data given in parentheses are for the $^{13}C–\{^1H\}$ spectra): 13.8 q (s) ($C^{10'}H_3$, $^1J_{CH}$ 124.0), 14.1 q (s) ($C^{10''}H_3$, $^1J_{CH}$ 124.7), 19.1 q (s) [$(\underline{C}^{8',9'}H_3)_2C$, $^1J_{CH}$ 125.4], 19.3 q (s) [$(\underline{C}^{8',9'}H_3)_2C$, $^1J_{CH}$ 124.0], 20.4 q (s) [$(\underline{C}^{8'',9''}H_3)_2C$, $^1J_{CH}$ 124.7], 20.6 q (s) [$(\underline{C}^{8'',9''}H_3)_2C$, $^1J_{CH}$ 124.0], 25.5 t (s) ($C^{6',6''}H_2$, $^1J_{CH}$ 132.8), 25.8 t (s) ($C^{5',5''}H_2$, $^1J_{CH}$ 132.8), 27.9 t (s) ($C^{6,7}H_2$, $^1J_{CH}$ 133.0), 28.9 t (s) ($C^{6,7}H_2$, $^1J_{CH}$ 133.0), 36.0 t (s) ($C^{2,4}H_2$, $^1J_{CH}$ 136.5), 36.1 t (s) ($C^{2,4}H_2$, $^1J_{CH}$ 136.5), 38.3 t (s) ($C^{3',3''}H_2$, $^1J_{CH}$ 128.4), 39.9 q (s) (C^9H_3N, $^1J_{CH}$ 128.4), 45.9 d (s) ($C^{4',4''}H$, $^1J_{CH}$ 131.0), 47.8 s (s) ($\underline{C}^{7',7''}C_4$), 50.0 s (s) ($\underline{C}^{1',1''}C_4$), 50.1 s (s) ($\underline{C}^{1',1''}C_4$), 55.8 d (s) ($C^{11}H$, $^1J_{CH}$ 130.6), 61.17 d (s) ($C^{1,5}H$, $^1J_{CH}$ 143.8), 61.25 d (s) ($C^{1,5}H$, $^1J_{CH}$ 143.8), 64.4 t (s) ($C^{12}H_2O$, $^1J_{CH}$ 140.1), 64.6 t (s) ($C^{12}H_2O$, $^1J_{CH}$ 137.9), 67.6 d (s) (C^3HO, $^1J_{CH}$ 152.6), 81.3 d.d (d) ($HC^{2',2''}OP$, $^2J_{CP}$ 7.7), 128.3 two d (s) ($C^{16}H$, $^1J_{CH}$ 160.7), 129.3 two d (s) ($C^{15,17}H$, $^1J_{CH}$ 153.3), 129.5 two d (s) ($C^{14,18}H$, $^1J_{CH}$ 159.9), 137.5 s (s) (C^{13}), 172 s (s) (C^{10}=O). $^{31}P–\{^1H\}$ NMR spectrum (ethanol): δ_P 111.2 ppm. Mass spectrum (MALDI TOF), *m*/*z* (I_{rel}, %): 289.7 $[M – (C_{10}H_{18})_2PS_2]^+$ (100). Found, %: C 63.57; H 8.66; N 2.35; P 4.23; S 9.54. $C_{37}H_{58}NO_5PS_2$. Calculated, %: C 64.22; H 8.45; N 2.02; P 4.48; S 9.27.

IR spectrum (film) was recorded on a Bruker Tensor 27 Fourier spectrometer (400–4000 cm^{-1}). ^{1}H NMR spectrum (acetone-d_6) was registered on a Bruker Avance-500 instrument (500 MHz); $^{31}P–\{^{1}H\}$ NMR spectrum was taken on a Bruker Avance-400 instrument (161.98 MHz), external reference 85% H_3PO_4. ^{13}C and $^{13}C–\{^{1}H\}$ NMR spectra were recorded on a Bruker Avance 400 spectrometer (100.6 MHz) using acetone-d_6 as a solvent. Optical rotation value was determined on a Perkin Elmer 341 polarimeter (λ = 589 nm, sodium-halogen lamp, quartz cell, λ = 55.2 mm). Mass spectrum (MALDI TOF) was recorded on a Bruker Ultraflex spectrometer with UV laser (λ = 337 nm, matrix 4-nitroaniline, acetone).

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