Chiral phosphorus dithio acids derived from (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol. Synthesis and fungicidal activity

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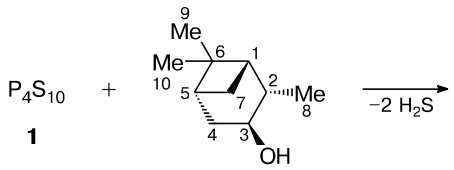
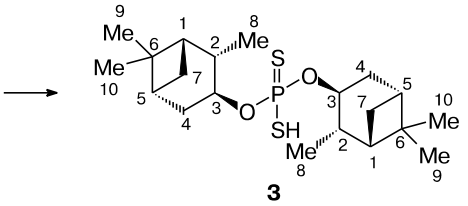
Recent growth within promising trend in organophosphorus chemistry dealing with optically active dithiophosphoric and dithiophosphonic acids, as well as dithiophosphoryl derivatives of naturally occurring compounds, can lead to new generation of biologically active compounds of selective action, including veterinary agents.[1] The known methods for the synthesis of dithio phosphoric acids by the reaction of tetraphosphorus decasulfide[2] and dithiophosphonic acids or by the reaction of 2,4-diorganyl-1,3,2,4-dithiadiphosphetane 2,4-disulfides with alcohols did not allow one to obtain P-chiral dithio acids despite the presence of nonidentical substituents at the stereogenic phosphorus atom in the molecules of dithiophosphonic acids due to the averaging the sulfur atoms in the triad S=P—SH. An alternative approach to chiral thio acids of tetracoordinated phosphorus atom can be the synthesis of compounds with the asymmetric centers in the O-organyl substituents. In our opinion, such compounds can be obtained by the reaction of tetraphosphorus decasulfide or 1,3,2,4-dithiadiphosphetane 2,4-disulfides with chiral alcohols, including the natural ones, among which optically active monoterpenols are the most available. Taking into account the tendency of terpenes to skeletal rearrangements,[3,4] we initially decided to find out whether the optical activity would be preserved in the products of thiophosphorylation of enantiopure bicyclic monoterpenols and evaluate their biological activity. We found out that the reaction of tetraphosphorus decasulfide **1** with (1*S*,2*S*,3*S*,5*R*)-(+)-isopinocampheol (**2**) led to *O*,*O*´-bis-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-dithiophosphoric acid (**3**), which was characterized by the angle of optical rotation $[\alpha]^{22}_D$ +35.0°, *c* 1.0, C_6H_6 (*cf.* the optical angle of terpenol **2**: $[\alpha]^{22}_D$ +35.1°, *c* 20, EtOH).[5]

Scheme 1





The ^{31}P NMR spectrum of dithiophosphate **3** exhibits a singlet signal at δ_P 85.1 in region indicative of dithiophosphoric acids.[6] The reaction of terpenol **2** with 2,4-bis-(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide (**4**) gave rise to *O*-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]hept-3-yl]-*P*-(4-phenoxyphenyl)dithiophosphonic acid (**5**) (Scheme 2), δ_P 83.4.

We found out that acid **3** had fungicidal effect on the microscopic fungi *Candida albicans*, *Aspergillus fumigatus*, and *Epidermophiton flocosum* in the concentration of

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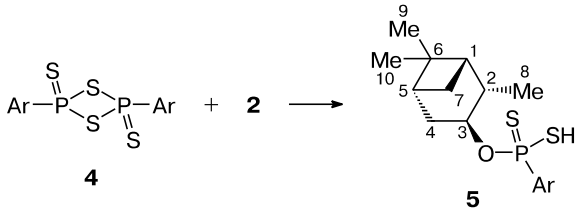
Scheme 2



Ar = 4-$PhOC_6H_4$

40 mg mL^{-1} in liquid culture medium. During the growth process of the fungi strains in the culture medium containing acid **3**, morpho-physiological changes took place in the cells. Some sites of the cell surface of fungi *Candida albicans* underwent deformation, the invagination was observed, which resulted in the change of the normal shape of the cells. The cell organelles in the cytoplasmic matrix migrated to the cell center, moving away from the damaged cytoderm, that caused a delay of the phase of the increase in the number of microorganisms.

IR spectra were recorded on a Bruker Vector 22 Fourier-spectrometer (400—4000 cm^{-1}) for neat films or suspensions in Nujol between KBr plates. ^{31}P NMR spectra were recorded on a Bruker Avance-400 spectrometer (161.98 MHz, in solutions in C_6H_6, external standard 85% aqueous H_3PO_4). ^1H NMR spectra were recorded on a Bruker Avance-600 spectrometer (600 MHz, in solutions in $CDCl_3$, using signal for the residual protons of the deuterated solvent as a reference). The angle of the plane-polarized light was determined on a Perkin—Elmer instruments 341 polarimeter (λ 589 nm, sodium-halogen lamp, the pathway of a quartz cuvette 55 mm). The minimal inhibitory concentration of compounds toward fungi was evaluated using a photoelectrocolorimeter (λ 530 nm).

(+)-*O*,*O*´-Bis[(1*S*,2*S*,3*S*,5*R*)-2,6,6-trimethylbicyclo[3.1.1]-hept-3-yl]dithiophosphoric acid (3). Sulfide **1** (0.9 g, 2.2 mmol) was added in portions to a stirred solution of terpenol **2** (2.5 g, 16.2 mmol) in anhydrous benzene (20 mL) at 20 °C under dry argon. The mixture was heated for 2 h at 50 °C with stirring. After cooling to 20 °C, the mixture was filtered. The solvent was evaporated from the filtrate *in vacuo* (0.5 Torr) at 40 °C over 1 h and at 0.02 Torr and 40 °C over another 1 h. Acid **3** (1.8 g, 55%) was thus obtained, which was purified by column chromatography (silica gel 0.060—0.200 μm, eluent benzene), R_f 0.45 (hexane), n_D^{20} 1.5230. IR (KBr, liquid film), cm^{-1}: 2987 s, 2911 v.br (ν($CH_3^{as,s}$), ν($CH_2^{as,s}$), ν(CH)); 2583 w.br (ν(S—H_{free})); 2403 w.br (ν(S—H_{bond})); 1471 s, 1452 s (δ(CH_3^{as})); 1385 m, 1368 m (δ$(CH_3)_2C^s_{gem}$); 1089 m (ν(P)O—C); 973 v.s, v.br (ν(OC—C)); 772 s (ν($PO_2^{as,s}$)); 676 v.s (ν(P=S)); 521 m (ν(P—S)). ^1H NMR ($CDCl_3$), δ: 0.96 and 1.23 (both s, 12 H, 2 $Me_2C(6)$); 1.21 (d, 6 H, 2 C(8)H_3, $^3J_{H,H}$ = 7.5 Hz); 1.97 (m, 4 H, 2 C(7)H_2); 2.24 (m, 2 H, 2 C(2)H); 2.38 (m, 4 H, C(4)H_2); 2.05 (m, 2 H, C(5)H); 2.62 (m, 2 H, C(1)H); 4.96 (m, 1 H, 2 P—OC(3)H). Found (%): C, 59.98; H, 8.33; P, 7.58; S, 15.73. $C_{20}H_{35}O_2PS_2$. Calculated (%): C, 59.67; H, 8.76; P, 7.69; S, 15.93.

(+)-*O*-[(1*S*,2*S*,3*S*,5*R*)-2,6,6-Trimethylbicyclo[3.1.1]hept-3-yl]-*P*-(4-phenoxyphenyl)dithiophosphonic acid (5) was obtained similarly from terpenol **2** (0.3 g, 2.0 mmol) and disulfide **4** (0.5 g, 1.0 mmol). The reaction conditions: benzene (15 mL), 50 °C, 1 h. The yield was 0.8 g (99%), R_f 0.34 (hexane), n_D^{20} 1.5820; $[\alpha]^{22}_D$ +50.7°, *c* 1.0, C_6H_6. IR (KBr, pellet), cm^{-1}: 3090 w, 3069 w, 3036 w (ν(=C—H, Ar)); 2912 v.s, v.br (ν($CH_3^{as,s}$), ν($CH_2^{as,s}$), ν(CH)); 2571 w (ν(S—H_{free})); 2442 w (ν(S—H_{bond})); 1584 v.s, 1488 v.s (ν(C=C), Ar); 1455 m (δ (CH_3^{as})); 1386 m, 1369 m (δ$(CH_3)_2C^s_{gem}$); 980 s (ν(P)O—C); 944 s (ν(OC—C)); 679 s (ν(P=S)); 528 m (ν(P—S)). ^1H NMR ($CDCl_3$), δ: 1.06 and 1.32 (both s, 6 H, $Me_2C(6)$); 1.28 (d, 3 H, C(8)H_3); 1.94 (m, 2 H, C(7)H_2); 2.05 (m, 1 H, C(5)H); 2.33 (m, 1 H, C(2)H); 2.46 (m, 2 H, C(4)H_2); 2.77 (m, 1 H, C(1)H); 5.27 (m, 1 H, P—OC(3)H); 7.10 (m, 2 H, C_{Ph}(2)H, C_{Ph}(6)H); 7.43 (m, 5 H, C_{Ph}(3)H, C_{Ph}(4)H, C_{Ph}(5)H, $C_{C_6H_4}$(3)H, $C_{C_6H_4}$(5)H); 8.01 (d, 2 H, $C_{C_6H_4}$(2)H and $C_{C_6H_4}$(6)H, $^3J_{P,H}$ = 14.6 Hz). Found (%): C, 63.35; H, 6.26; P, 7.58; S, 15.53. $C_{22}H_{27}O_2PS_2$. Calculated (%): C, 63.13; H, 6.50; P, 7.40; S, 15.32.

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