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Monoterpenoids Dithiophosphates. Synthesis and Biological Activity

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Abstract—*O,O*-Dialkyldithiophosphoric acids adds at the double bond of the racemic camphene and (+)-limonene in the presence of Lewis acids in accordance with the Markownikoff rule with the formation of S-terpenyl esters of dithiophosphoric acids. The reaction with camphene is accompanied by the rearrangement of camphane structure to that of bornane. Addition of dithiophosphoric acid to (+)-limonene proceeds with the participation of the exocyclic double bond. Toxic and genotoxic properties of the monoterpenoid dithiophosphates were studied.

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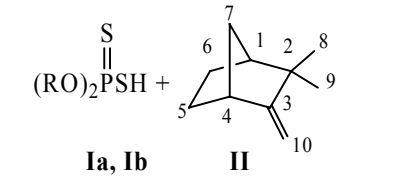
A fundamental problem in the chemistry of natural compounds is the creation of new types of phosphorus-modified terpenoid derivatives. These compounds are promising low-molecular bioregulators playing an important role in the production by living organisms of carbohydrate biopolymers of (lipo)-polysaccharide series, glycoproteins and peptidoglycans. Among the natural substances terpenoids were found exhibiting antiulcer, wound healing, hypertensive, antithrombotic, antitumor, antihypertensive, adrenergic, antiulcerogenic, hyperprotective and antihypercholesterolemic activity, as well as participating in the normalization of immune function, in the restoring liver function, and are solvents of gallstones [1, 2] . Meanwhile, at the present time both veterinary and medicine need new synthetic drugs of bioregulatory type. On the basis of terpenoids, including their phosphate derivatives, practically useful materials can be obtained for forestry, petrochemical, pharmaceutical, and perfume industries [3–5]. According to the early patent data [4, 5], the reaction of *O,O*-dialkyldithiophosphoric acids with pinene and dipentene [racemic mixture of (+)- and (–)-limonene] at 100–200°C led to formation of the mixtures of phosphorus-containing products that were suggested for application as additives to lubricants. The structure of the product mixtures was not established. It is presumable that the primary products formed in these reactions decompose under the rigid conditions of the process through isomerization and fragmentation characteristic of labile terpene molecules. In order to obtain stable adducts and elucidate their structure and biological activity we carried out the reaction of mono- and bicyclic monoterpenoids with dithiophosphoric acids.

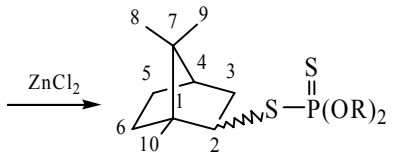
It is known that in the addition reactions of organophosphorus compounds at the double bond of unsaturated compounds, the regiochemistry of the phosphorus fragment addition is determined by the structure of unsaturated compound, the nature of the catalyst, and the reaction conditions [6–9]. At the homolytic addition of dialkylphosphites to olefins in the presence of free radical initiators or at UV irradiation, the adducts are formed contrary to the Markownikoff rule. In the reaction with acidic phosphites of unsaturated compounds containing a double bond activated by electron-donating substituents the electrophilic mode of the Pudovik reaction is realized. The electrophilic addition is carried out with hydrophosphites with pronounced proton–donor properties

(e.g., cyclic hydrophosphites) [8]. It is expectable that for the implementation of catalyzed electrophilic addition catalysts with strong electron-acceptor properties (e.g., Lewis acid) or with a high proton-donor action (e.g., strong mineral acid) should be used.

It is known that thiols and dithiophosphoric acid containing the SH group depending on their structure and the catalyst can be added to limonene both along and contrary to the Markownikoff rule, as well as bis-adducts can form [10–12]. In our work, the reaction of *O*,*O*-dialkyldithiophosphoric acids **Ia** and **Ib** with monoterpenes was carried out in the presence of Lewis acids. We found that addition of *O*,*O*-dialkyldithiophosphoric acids **Ia** and **Ib** to the double bond of the racemic camphene (**II**) proceeds in the presence of catalytic amounts of anhydrous zinc chloride at 50–60°C over 2–3 h with the formation of *S*-2-(1-methyl-7-dimethylbicyclo[2.2.1]heptyl)-*O*,*O*-dialkyldithiophosphates (**IIIa**, **IIIb**). Upon completion of the reaction the catalyst was removed by washing the reaction mixture with water. According to the data of vibration and NMR spectroscopy, washing did not lead to hydrolysis.



Ia, Ib **II**



IIIa, IIIb

R = Et (**a**), Pr-*i* (**b**).

It follows from the data of ^{31}P NMR spectroscopy that the degree of conversion of dithiophosphoric acids **Ia** and **Ib** is 100%. In accordance with ^{1}H NMR spectra, addition of acids **Ia** and **Ib** to the double bond of camphene (**II**) proceeds according to Markownikoff rule and is accompanied by the Wagner–Meerwein skeletal rearrangement of camphane structure to that of bornane, leading to the formation of a mixture of *exo*- and *endo*-isomers. In the ^{31}P NMR spectra of products **III** there are the signals at δ_P 94.0 (**IIIa**) and 92.3 (**IIIb**) ppm characteristic of the esters of dithiophosphoric acids [13]. Formation of the bornane structure is indicated also by the presence in the ^{1}H NMR spectra of products **IIIa** and **IIIb** of three strong singlets of methyl protons. In the ^{1}H NMR spectrum the singlets at δ 0.84, 0.93 and 1.00 ppm correspond to the diisopropyl protons of **IIIb** homolog. Doublet of triplets at δ 3.37 ppm with the spin–spin coupling constants $^{3}J_{HH}$ 7.3 Hz and $^{3}J_{PH}$ 19.9 Hz belongs to methine proton at the sulfur atom $C^3H_AH_BC^2HSP$. These data indicate that the two protons at C^3 atom in the compound **IIIb** are magnetically equivalent. In contrast, in the ^{1}H NMR spectrum the methine proton in the CH_AH_BCHSC fragment of the *exo*-isomer of the product obtained by the mercaptans addition to camphene gives rise to a doublet of doublets, whereas the *endo*-adduct gives a multiplet due to the additional splitting on the protons of the ring [14]. In the case of retention of the camphene structure, in the ^{1}H NMR spectrum the signal of methine proton in geminal position to the dithiophosphoryl fragment would be absent. Note that a similar reaction of camphene with methylmercaptoacetate in the presence of zinc chloride also results in a product of addition along the Markownikoff rule with the bornane structure, ethyl 1-methyl(6-dimethylbicyclo[2.2.1]heptyl)-2-mercapto-acetate; the respective methine proton at the C^2 atom of $C^3H_AH_BC^2HSC$ fragment gives in the ^{1}H NMR spectrum a signal shifted upfield (δ 2.63 ppm) [15]. This result is consistent with the presence in the adducts **IIIa** and **IIIb** of dithiophosphoryl group which is more electronegative compared to the alkylthio group in alkylthiobornanes. In the ^{1}H NMR spectrum of adducts **IIIa** and **IIIb** were not detected the signals of vinyl protons at δ 4.5 and 4.7 ppm of the parent camphene **II**, which indicates the reaction completeness. In the ^{13}C NMR spectra of compound **IIIb** obtained in the proton decoupling mode there is a singlet signal of carbon fragment PSC^2H at δ_C 53.8 ppm, which without the proton decoupling appears as a doublet ($^{1}J_{HC}$ 151.1 Hz). In contrast, at the retention of the camphene structure, the carbon atom to which is added the thiophosphoryl fragment (the PSC fragment, which does not contain protons) would appear as a singlet at recording ^{13}C NMR spectra in both modes.

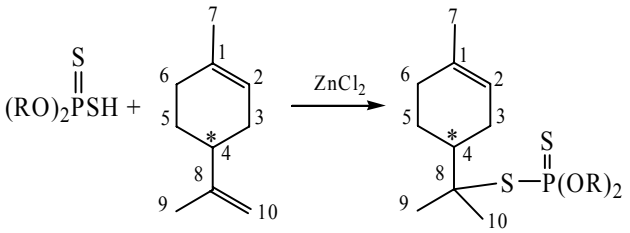
The IR spectra of the products **IIIa** and **IIIb** do not contain the absorption bands at ν = 2500–2400 cm^{-1}, characteristic of stretching vibrations of the SH bond in the acids **Ia** and **Ib.** The C=C absorption band of terpene **II** in the region of ν = 1600–1650 cm^{-1} in the IR spectra of compounds **IIIa** and **IIIb** was not detected also. The absorption bands of the stretching vibrations of the P=S and P–S bonds in dithio-

phosphates **IIIa** and **IIIb** are located at ν = 659–655 and 547–527 cm^{-1}, respectively. The electron impact mass spectra of the products **IIIa** and **IIIb** include the mass peaks *m*/*z* = 322.7 and 350.2, respectively, of their molecular ions $[M]^+$ (calculated *M* 322.2 and 350.2, respectively).

The adducts **IIIa** and **IIIb** are of low thermal stability and could not be distilled even in a high vacuum. Their purification was carried out by column chromatography. Compounds **IIIa** and **IIIb**, thus, are the primary products of reactions, which under the rigid conditions of vacuum distillation decompose. In this regard, it is presumable that compounds previously described as products of addition of *O*,*O*-dialkyldithiophosphoric acids to pinene and dipentene at 100–200°C [4, 5] are actually the products of various secondary reactions. Inasmuch as this reaction proceeds in accordance with the Markownikoff rule, as well as in the case of thiols, mercaptoacetic acid or methyl mercaptoacetate [12, 14, 15] the dithiophosphoric acids possess the ability to the electrophilic addition to electron-rich alkenes. It is known that dithiophosphoric acids show a dual reactivity in the addition reactions: the presence of labile protons and nucleophilic dithiophosphoryl fragment gives them the opportunity of entering into both nucleophilic and electrophilic addition reactions [9].

In order to expand the synthetic potential of unsaturated terpenes by involving them in the tiophosphorylation reactions and obtaining potential biologically active products, is interesting to involve into the reaction with dithiophosphoric acids **Ia** and **Ib** some unsaturated monocyclic terpenes. Among them of special interest is (+)-limonene, one of the most stable terpenes, which contains an exocyclic and an endocyclic double bonds differing in the reactivity. Therefore we could expect that the electrophilic addition might occur in various directions. We found that addition of *O*,*O*-dialkyldithiophosphoric acids **Ia** and **Ib** to (+)-limonene (**IV**) in the presence of zinc chloride proceeded at room temperature over 1–2 h at the exocyclic double bond, affording *O*,*O*-dialkyl-*S*-8-[(+)-1-methyl-4-isopropylcyclohex-1-enyl]dithiophosphates **Va** and **Vb**. At heating the initial reagents at 60°C for 3 h the formation of compounds of the phosphorylation at the endocyclic double bond was not observed.

The compounds **Va** and **Vb** are not stable at high temperatures in the distillation process and therefore were isolated by column chromatography. The signals



Ia, Ib **IV** **Va, Vb**

R = Et (**a**), Pr-*i* (**b**).

in ^{31}P NMR spectra of adducts **Va** and **Vb** are shifted upfield [δ_P 90.4 (**Va**) and 87.1 (**Vb**) ppm] compared to products **IIIa** and **IIIb** obtained in the reactions with camphene (δ_P 92.3 – 94.0 ppm). In the ^1H NMR spectrum of adduct **Vb** there are three singlet signals of protons of three methyl groups at δ 1.53, 1.59 and 1.66 ppm, and the signal of endocyclic vinyl proton remains at δ 5.37 ppm. The signals of two exocyclic vinyl protons disappear in ^1H NMR spectra of the products **Va** and **Vb** completely. Note that in the ^1H NMR spectrum the exocyclic vinyl protons of (+)-limonene (**IV**) give a singlet signal at d 4.71 ppm. The IR spectrum of products **Va** and **Vb** shows a weak absorption band of the C=C bond stretching vibrations at ν = 1643 cm^{-1}. The mass peak *m*/*z* = 323.2 in the mass spectrum of chemical ionization (CI) of dithiophosphate **Va** is consistent with its molecular ion $[M+H]^+$. The mass spectrum of electron impact of the isopropyl homolog **Vb** contains the mass peak *m*/*z* = 350.2 corresponding to its molecular ion $[M]^+$.

It was established that the electrophilic addition of dithiophosphoric acids **Ia** and **Ib** to unsaturated terpenes **II** and **IV** is accelerated in the presence of other Lewis acids ($NiCl_2$, CuCl, $CuCl_2$, $FeCl_3$) at room temperature. The less active catalysts are BF_3. Et_2O, and $AlCl_3$. From a number of Lewis acids we selected zinc chloride as a "soft" Lewis acid, which unlike most catalysts with higher acceptor strength, for example, $BF_3 \cdot Et_2O$, commonly does not induce a secondary transformation of the terpene molecule. Note also that the use of protic acids (HCl, H_2SO_4, $HClO_4$) as catalysts in the reactions of thiols with unsaturated monoterpenes leads to the isomerization of terpene molecules with the formation of a complex mixture of products [16]. Presumably the high hygroscopicity of zinc chloride may contribute to the proceeding of the reactions of dithiophosphoric acids with monoterpenes promoting formation in the reaction medium of HCl, which may also act as catalyst in the reactions of dithiophosphoric acids with the unsaturated mono-

terpenes. Thus, we first found the phenomenon of the catalysis with the Lewis acids in a series of derivatives of the tetracoordinated phosphorus thioacids by the example of reactions of electrophilic addition of dithiophosphoric acids at the double bond of unsaturated monoterpenoids.

The studied reaction showed a route to monoterpenoid dithiophosphates with potential biological activity. This article presents the principal results of studies of toxic and genotoxic properties of compounds **IIIa**, **IIIb**, **Va** and **Vb**. The methods used in these studies were published in [17–19]. Full description of the results will be published in a special biological journal. The study of toxic and genotoxic properties of dithiophosphates **IIIa**, **IIIb**, **Va** and **Vb** was carried out on *Salmonella typhimurium TA 100* and *Escherichia coli PQ37* as the test bacteria. We found that dithiophosphates **IIIa**, **IIIb**, **Va** and **Vb** are weak toxicants for the test bacteria. Compound **IIIa** exhibits the characteristics of a weak inhibitor of alkaline phosphatase activity in the *Escherichia coli PQ 37* cells, initiates the highest SOS-response and shows mutagenic activity in Ames test. Dithiophosphate **IIIa** is a direct mutagen and true genotoxicant, since this compound is practically non-toxic to the test bacteria, but causes the induction of gene mutations. Remaining compounds, **IIIb**, **Va** and **Vb** do not show mutagenic properties.

EXPERIMENTAL

IR spectra were recorded on a Bruker Vector 22 and a Tensor 27 IR Fourier Spectrometers (400–4000 cm^{-1}) from liquid films between KBr plates. Chemical shifts of ^{31}P nuclei of phosphorus compounds were measured on a Bruker CXP-100 spectrometer with an operating frequency of 36.47 MHz with external 85% H_3PO_3. Positive value of the chemical shift δ_P corresponds to the downfield shift. The ^1H NMR spectra were registered on a Bruker Avance-400 with operating frequency 400 MHz and a Bruker Avance-600 (600 MHz) spectrometers in $CDCl_3$ solutions. The ^{13}C NMR spectra were recorded on a Bruker Avance-600 spectrometer (100.6 MHz) in $CDCl_3$ solutions. The electron impact and chemical ionization mass spectra were recorded on a Finnigan MAT-212 and a`TRACE MS Finnigan MAT mass spectrometers.

***S*-2-(1-Methyl-7-dimethylbicyclo[2.2.1]heptyl)-*O*,*O*'-diethyldithiophosphate (IIIa)**. To a mixture of 3.9 g of acid **Ia** and 2.9 g of camphene **II** at ~20°C in a stream of dry argon was added at stirring in portions 0.1 g (3.4 wt %) of $ZnCl_2$. The mixture was heated for 3 h at 50–60°C. After cooling, the mixture was diluted with 10 ml of Et_2O and washed with three 10-ml portions of water. The organic layer was separated and dried over anhydrous $CaCl_2$ for ~12 h. After separating the drying agent, the filtrate was evaporated in a vacuum of 0.5 mm Hg at 40°C for 1 h and then in a vacuum of 0.06 mm Hg at 40°C for 1 h. 5.7 g (84%) of dithiophosphate **IIIa** was obtained, which was purified by column chromatography (silica gel, eluent petroleum ether boiling at 70–100°C), R_f 0.27 (petroleum ether), n_D^{20} 1.5325. IR spectrum, ν, cm^{-1}: 2983 s, 2956 s, 2880 s [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1465 m [$\delta_{as}(CH_3)$]; 1390 s [$\delta_s(CH_3)$]; 1016 v.s.br, 958 s [ν(POC]; 826 m, 796 m [$\nu_{as,s}(PO_2)$], 659 s [ν(P=S)], 527 m [ν(PS)]. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 0.85 s, 0.93 s and 1.00 s (9H, CH_3-ring), 1.37 m [6H, $(CH_3CH_2O)_2P$, $^3J_{HH}$ 7.1], 1.24 m, 1.74 m and 2.01 m (CH_2-ring and CH-ring.) 3.31 d.t (1H, CH_AH_BCHSP, $^3J_{HH}$ 7.0, $^3J_{PH}$ 19.0) 4.12 m {2H, $[(CH_3CH_2O)_2]_2P$, $^3J_{HH}$ 7.1}. Found, %: C 52.27, H 8.46, P 9.43; S 19.48. $C_{14}H_{27}O_2PS_2$. Calculated, %: C 52.14, H 8.46, P 9.61; S 19.85.

***S*-2-(1-Methyl-7-dimethylbicyclo[2.2.1]heptyl)-*O*,*O*'-diisopropyldithiophosphate (IIIb)** was prepared similarly from 3.6 g of acid **Ib** and 2.3 g of camphene **II** using 0.23 g (3.5 wt %) of $ZnCl_2$, yield 4.4 g (75%), purified by column chromatography (silica gel, eluent petroleum ether boiling at 70–100°C/Et_2O 1:1), R_f 0.60 (petroleum ether/Et_2O 1:1), n_D^{20} 1.5025. IR spectrum, ν, cm^{-1}: 2979 s, 2956 s, 2879 s [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1454 m [$\delta_{as}(CH_3)$]; 1386 m, 1374 m [$\delta_s(CH_3)_2C$ gem] o.s 993, 970 o.s [ν(POC]; 888 m, 777 s [$\nu_{as,s}(PO_2)$], 655 s [ν(P=S)]; 547 m [ν(PS)]. ^1H NMR spectrum, δ, ppm, (*J*, Hz): 0.84 s, 0.93 s and 1.00 s [9H, CH_3-ring), 1.34 d and 1.36 d [12H, $(CH_3)_2CHOP$, $^3J_{HH}$ 5.7], 1.41 m, 1.72 m and 2.02 m (CH_2-ring. and CH-ring), 3.37 d.t (1H, CH_AH_BCHSP, $^3J_{HH}$ 7.3, $^3J_{PH}$ 19.9), 4.80 m {2H, $[(CH_3)_2CHO]_2P$, $^3J_{HH}$ 5.7}. Found, %: C 54.42, H 8.96, P 9.32; S 18.18. $C_{16}H_{31}O_2PS_2$. Calculated, %: C 54.82, H 8.94, P 8.84; S 18.26.

***O*,*O*'-Diethyl-*S*-8-[(+)-1-methyl-4-isopropylcyclohex-1-enyl]dithiophosphate (Va)** was obtained similarly from 8.0 g of acid **Ia** and 5.6 g of (+)-limonene (**IV**) using 0.24 g (3 wt %) of $ZnCl_2$, yield 7.0 g (50%), purified by column chromatography (silica gel, eluent CCl_4), R_f 0.28 (CCl_4), n_D^{20} 1.5320. IR spectrum, ν, cm^{-1}: 2962 s, 2926 s, 2667 m [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$];

1642 w [ν(C=C)], 1443 m [$\delta_{as}(CH_3)$]; 1384 m, 1373 m [$\delta_s(CH_3)_2C$ gem.] 1017 v.s.br, 957 m [ν(POC]; 798 m [$\nu_{as,s}(PO_2)$]; 656 m [ν(P=S)]; 533 m [ν(PS)]. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): δ_1 1.35 t [3H, ($CH_3CH_2O)_2P$, $^3J_{HH}$ 7.1] and δ_2 1.36 t [3H, ($CH_3CH_2O)_2P$, $^3J_{HH}$ 6.8], 1.46 s and 1.53 s [6H, ($CH_3)_2CS$], 1.63 s (3H, CH_3-ring.) 1.71–2.15 m (7H, CH_2-ring and CH-ring); d_1 4.13 d.q [4H, ($CH_3CH_2O)_2P$, $^3J_{HH}$ 7.1, $^3J_{PH}$ 9.7] and d_2 4.23 d.q [4H, ($CH_3CH_2O)_2P$, $^3J_{HH}$ 6.8, $^3J_{PH}$ 7.0]; 5.34 m (H, C=CH-ring). Found, %: C 51.78, H 8.13, P 9.33; S 19.99. $C_{14}H_{27}O_2PS_2$. Calculated, %: C 52.14, H 8.46, P 9.61; S 19.85.

***O*,*O*-Diisopropyl-*S*-8-[(+)-1-methyl-4-isopropyl-cyclohex-1-enyl]dithiophosphate (Vb)** was obtained similarly from 8.0 g of acid **Ib** and 5.1 g of (+)-limonene (**IV**) using 0.056 g (0.7 wt %) of $ZnCl_2$, yield 1.11 g (85%), purified by column chromatography (silica gel, eluent CCl_4), R_f 0.24 (CCl_4), n_D^{20} 1.5079. IR spectrum, ν, cm^{-1}: 2976 s, 2928 s, 2836 s [$\nu_{as,s}(CH_3)$, $\nu_{as,s}(CH_2)$]; 1643 w [ν(C=C)], 1450 m [$\delta_{as}(CH_3)$]; 1384 m, 1373 m [$\delta_s(CH_3)_2C$ gem] v.s.br 968 [ν(POC]; 887 m, 775 m [$\nu(PO_2)$]; 650 m [ν(P=S)]; 548 m [ν(PS)]. ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 1.35 d and 1.37 d [12H, $(CH_3)_2$ CHOP, $^3J_{HH}$ 6.0]; 1.53 s and 1.59 s [6H, $(CH_3)_2CS$]; 1.66 s [3H, CH_3-ring]; 1.54–2.18 m (7H, CH_2-ring and CH-ring); 4.91 m {2H, $[(CH_3)_2CHO]_2P$, $^3J_{HH}$ 6.0}; 5.37 m (1H, C=CH-ring). Found, %: C 54.58; H 8.38; P 9.25; S 18.17. $C_{16}H_{31}O_2PS_2$. Calculated, % : C 54.82; H 8.94; P 8.84; S 18.26.

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