Taylor & Francis
Taylor & Francis Group

Phosphorus, Sulfur, and Silicon and the Related Elements

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/gpss20

Pyridoxonium salts of chiral and cyclic dithiophosphoric and bisdithiophosphonic acids and their antimicrobial activities

Ilyas S. Nizamov, Timur G. Belov, Ilnar D. Nizamov, Yevgeniy N. Nikitin, Gulnaz R. Akhmedova, Olga V. Shilnikova, Ildus D. Timushev, Ramazan Z. Salikhov, Marina P. Shulaeva, Oscar K. Pozdeev, Elvira S. Batyeva & Rafael A. Cherkasov

To cite this article: Ilyas S. Nizamov, Timur G. Belov, Ilnar D. Nizamov, Yevgeniy N. Nikitin, Gulnaz R. Akhmedova, Olga V. Shilnikova, Ildus D. Timushev, Ramazan Z. Salikhov, Marina P. Shulaeva, Oscar K. Pozdeev, Elvira S. Batyeva & Rafael A. Cherkasov (2021) Pyridoxonium salts of chiral and cyclic dithiophosphoric and bisdithiophosphonic acids and their antimicrobial activities, Phosphorus, Sulfur, and Silicon and the Related Elements, 196:4, 431-438, DOI: 10.1080/10426507.2020.1854255

To link to this article: https://doi.org/10.1080/10426507.2020.1854255

PHOSPHORUS, SULFUR, AND SILICON AND THE RELATED ELEMENTS
2021, VOL. 196, NO. 4, 431–438
https://doi.org/10.1080/10426507.2020.1854255

Pyridoxonium salts of chiral and cyclic dithiophosphoric and bisdithiophosphonic acids and their antimicrobial activities

Ilyas S. Nizamov[a,b], Timur G. Belov[c], Ilnar D. Nizamov[a], Yevgeniy N. Nikitin[c], Gulnaz R. Akhmedova[a], Olga V. Shilnikova[a], Ildus D. Timushev[a], Ramazan Z. Salikhov[a], Marina P. Shulaeva[d], Oscar K. Pozdeev[d], Elvira S. Batyeva[b], and Rafael A. Cherkasov[a]

[a]A.M. Butlerov Chemical Institute, Kazan Federal University, Kazan, Russia; [b]A.E. Arbuzov Institute of Organic and Physical Chemistry, Federal Research Center, Kazan Scientific Center, Russian Academy of Sciences, Kazan, Russia; [c]Federal State Budgetary Institution of Science Federal Research Center, Kazan Scientific Center of Russian Academy of Sciences, Kazan, Russia; [d]Department of Microbiology, Kazan State Medical Academy, Kazan, Russia

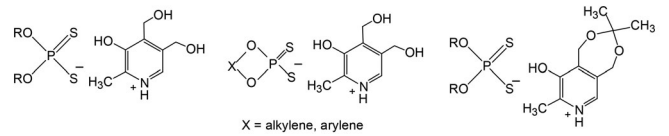
ABSTRACT

Pyridoxonium salts of chiral linear and cyclic dithiophosphoric acids were obtained by the reactions of pyridoxine with bis{2-O-[2-methyl-(2*S*)-3-*O*-propionyl]}, bis{2-O-[1,4-O,O-dimethyl-(2*S*)-succinyl]}, and *O,O*-di-2-butyl dithiophosphoric acids, and cyclic dithiophosphoric acids of 1,3,2-dioxaphosphorinane, 1,3,2-dioxaphospholane, and 1,3,2-dioxaphosphepin structure. Syntheses of acetonide pyridoxonium O,O-dimenthyl dithiophosphates were carried out by the reaction of seven-membered pyridoxine acetonide with O,O-dimenthyl dithiophosphoric acids obtained from (–)-(1*R*,2*S*,5*R*)-menthol and (+)-(1*S*,2*R*,5*S*)-menthol. Diacetonide pyridoxonium bisdithiophosphonate was also prepared. The antibacterial and antifungal activities of pyridoxonium chiral linear and cyclic dithiophosphates were evaluated.

ARTICLE HISTORY
Received 31 August 2020
Accepted 13 November 2020

KEYWORDS
Pyridoxine; phosphorus dithioacids; antimicrobial activity

GRAPHICAL ABSTRACT



Introduction

There is a considerable interest in vitamin B_6 (alkaloid pyridoxine and its derivatives) due to their biological activity.[1–5] Alkaloid vitamin B_6 is of significant interest for the treatment of common and life-threatening viral and microbial infections that are resistant to existing drugs.[1,6] Among phosphorus containing pyridoxine derivatives,[7] phosphonium salts of pyridoxine ketals have been reported to exhibit structural dependence with respect to Gram-positive bacteria.[8,9] Thus, 5,6-bis[triphenylphosphonio(methyl)] 2,2,8-trimethyl-4H-[1,3]-dioxino[4,5-c]pyridine dichloride has an inhibitory effect against staphylococcal infection (minimal inhibitory concentration (MIC) was 5 $\mu g\ mL^{-1}$). A crucial role of the ketal protection group in phosphonium salts for their antibacterial properties was demonstrated.[8] Bis(triphenylmethyl) phosphonium dichloride salts of pyridoxine are effective against biofilm-embedded *Staphylococcus aureus* and *Staphylococcus epidermidis*[10] and cause impaired cell division.[11] In contrast to phosphonium salts of pyridoxine, most dithiophosphates are known to be less toxic to warm-blooded animals.[12] The present work involves the synthesis of pyridoxonium salts of chiral and cyclic dithiophosphoric acids bearing pharmacophoric lactic, malic, cyclic, and monoterpenyl functionalities as well as bisdithiophosphonic acids and evaluation of their bioactivity.

Results and discussion

Synthesis of chiral dithiophosphoric acids containing methyl (S)-(–)-α-lactic and dimethyl (S)-(–)-α-malic substituents

We believe that a simple, one-step reaction should be used to develop a technologically advanced and economical method for producing antimicrobial drugs. As reported,[13–15] methods for the synthesis of biologically active ionic structures of dithiophosphoric acids bearing pyridinium cations by use of nicotinic, isonicotinic, and picolinic acids and (*S*)-(–)-nicotine have been developed. Among pyridine alkaloids, pyridoxine reacts with *O,O*-diterpenyl

CONTACT Ilyas S. Nizamov isnizamov@mail.ru A.M. Butlerov Chemical Institute, Kazan Federal University, Kremlievskaya Str., 18, Kazan, 420008, Russia.
Supplemental data for this article is available online at https://doi.org/10.1080/10426507.2020.1854255.

Table 1. Yields, analytical and $^{31}P\{^{1}H\}$ NMR data of compounds obtained.

Comp.	Yield, %	Molecular formula	Found/Calc., % C	H	N	P	S	$^{31}P\{^{1}H\}$ δ, ppm (solvent)
3a	74	$C_8H_{15}O_6PS_2$	34.74 31.78	4.93 5.00	–	7.57 7.40	15.05 15.33	87.4 (C_6H_6)
3b	85	$C_{12}H_{19}O_{10}PS_2$	34.74 34.45	4.93 4.58	–	7.57 7.40	15.05 15.33	84.6 (C_6H_6)
5a	85	$C_{16}H_{26}NO_9PS_2$	40.98 40.76	5.21 5.56	2.64 2.97	6.21 6.57	13.97 13.60	114.2 (EtOH-C_6H_6)
5b	85	$C_{20}H_{30}NO_{13}PS_2$	40.53 40.88	5.52 5.15	2.02 2.38	4.93 5.27	11.24 10.92	117.2 (EtOH-C_6H_6)
5c	88	$C_{16}H_{30}NO_5PS_2$	46.33 46.70	7.02 7.35	3.12 3.40	7.87 7.53	15.90 15.58	109.2, 110.8 (1:0.4) (EtOH-C_6H_6)
5d	87	$C_{13}H_{22}NO_5PS_2$	42.14 42.50	6.40 6.04	3.48 3.81	8.12 8.43	17.82 17.45	111.1 (EtOH-C_6H_6)
5e	86	$C_{12}H_{20}NO_5PS_2$	40.44 40.78	5.32 5.70	3.64 3.96	8.99 8.76	18.43 18.15	111.3 (EtOH-C_6H_6)
5f	86	$C_{12}H_{20}NO_5PS_2$	41.12 40.78	5.34 5.70	3.58 3.96	8.44 8.76	18.52 18.15	125.6 (EtOH-C_6H_6)
5g[a]	67	$C_{20}H_{20}NO_5PS_2$	53.76 53.44	4.13 4.48	2.74 3.12	6.53 6.89	14.65 14.27	131.1 (EtOH-C_6H_6)
5h	86	$C_{31}H_{54}NO_5PS_2$	60.55 60.46	8.64 8.84	2.29 2.27	5.01 5.03	10.80 10.41	109.6 (EtOH)
5i	85	$C_{31}H_{54}NO_5PS_2$	60.67 60.46	8.55 8.84	2.02 2.27	5.34 5.03	10.56 10.41	104.5 (EtOH)
5j	81	$C_{52}H_{62}N_2O_{12}P_2S_4$	57.25 56.92	5.33 5.70	2.23 5.32	5.32 5.65	12.01 11.69	105.9 (EtOH)

Table 2. Selected FTIR spectral data (cm^{-1}) of compounds obtained (film).

Comp.	ν(OH)	$\nu(NH^+)$	ν(SH)	ν(C = O)	ν[(P)O–C]	ν(P = S)	ν(P–S)
3a	–	–	2413	1745	1042	675	542
3b	–	–	2413	1741	1047	654	518
5a	3264	2730	–	1746	1042	695	571
5b	3358	2734	–	1741	1046	702	520
5c	3332	2736	–	–	1028	645	583
5d	3314	2708	–	–	1023	691	546
5e	3319	2729	–	–	1027	691	530
5f	3267	2722	–	–	1019	681	569
5g[a]	3375	2729	–	–	1040	691	565
5h	3357	2730	–	–	1043	668	572
5i	3343	2730	–	–	1025	672	522
5j	3320	2736	–	–	1031	694, 675	562, 559

[a]In KBr pellet.

dithiophosphoric acids to form chiral pyridoxonium salts bearing pharmacophoric functionalities possessed high antibacterial activity with MIC values against Gram-positive bacteria as low as 10 µM (6 µg mL^{-1}).[15] It should be emphasized that pyridoxonium *O,O*-di-(–)-menthyl dithiophosphate is active against clinical strains of antibiotic-resistant bacteria from burn wounds including methicillin resistant *Staphylococcus aureus*.[15]

The specific systems of study in the present work are chiral dithiophosphoric acids, which can be obtained from natural chiral carboxylic acids. Among carboxylic acids, we have chosen methyl (*S*)-(–)-α-lactate and dimethyl (*S*)-(–)-α-maleate to obtain chiral dithiophosphoric acids. Methyl (*S*)-(–)-α-lactate reacted with 2,4-diaryl-1,3,2,4-dithiadiphosphetane 2,4-disulfide to give optically active 2-methyl-(2*S*)-3-*O*-propionyl aryldithiophosphonic acid as previously reported.[16] We have established that methyl (*S*)-(–)-α-lactate **2a** reacts with phosphorus pentasulfide **1** in benzene at 20 °C for 2 h to form bis{2-O-[2-methyl-(2*S*)-3-*O*-propionyl]} dithiophosphoric acid **3a** (Scheme 1).

The acid **3a** is optically active ($[\alpha]^{20}_D$ −28.5 grad g^{-1} cm^2, c = 0.82, ethanol). The yields, analytical, and $^{31}P\{^{1}H\}$ NMR data of the compounds obtained are summarized in Table 1. Selected FTIR spectral data, ^{1}H NMR, and ^{13}C and $^{13}C\{^{1}H\}$ NMR data of the compounds are summarized in Tables 2–4. The $^{31}P\{^{1}H\}$ NMR spectrum of **3a** in benzene reveals a singlet at δ = 87.4 ppm. This resonance is situated in practically the same region as observed for other dithiophosphoric acids.[17] In the ^{1}H NMR spectrum of **3a** in $CDCl_3$, a singlet at δ = 3.78 ppm is attributed to the protons of the methoxy group C^4H_3O. In the FTIR spectra of **3a**, similarly a band at 1745 cm^{-1} for the O = C stretching vibrations exists.[18]

Taking into account the ready formation of **3a** by use of methyl (*S*)-(–)-α-lactate, we decided to prepare the corresponding dithiophosphoric acid using dimethyl (*S*)-(–)-α-maleate. In fact, bis{2-O-[1,4-O,O-dimethyl-(2*S*)-succinyl]} dithiophosphoric acid **3 b** was obtained by the reaction of tetraphosphorus decasulfide **1** with dimethyl (*S*)-(–)-α-malate **2 b** in benzene at 20 °C for 2 h (Scheme 1).

A singlet at δ = 84.6 ppm was situated in the $^{31}P\{^{1}H\}$ NMR spectrum of **3 b** in benzene. Thus, the $^{31}P\{^{1}H\}$ NMR spectral signal of **3 b** shows no significant change in comparison with **3a**. In contrast to **3a**, the ^{1}H NMR spectrum of **3 b** in $CDCl_3$ reveals two singlets at δ = 3.65 and 3.74 ppm, being attributable to the methyl protons of two C^5H_3O and C^6H_3O substituents. The data of FTIR spectra of **3a** and **3 b** are very similar (see Table 2). Thus, chiral dithiophosphoric acids **3a** and **3 b** can be transformed into pyridoxonium salt using pyridoxine.

Pyridoxine **4a** readily reacts with the enantiomerically pure acids **3a** and **3 b** and racemic *O,O*-di-2-butyl dithiophosphoric acid **3c** in the mixture of benzene and ethanol (1:1) at 20 °C for 1-2 h to give pyridoxonium salts **5a-c** (Scheme 2).

A specific rotation value $[\alpha]^{20}_D$ −4.5 grad g^{-1} cm^2, c = 0.93 (ethanol) has been measured for **5a**. Compound **5 b** is also optically active ($[\alpha]^{20}_D$ −2.1 grad g^{-1} cm^2, c = 1.01, ethanol). The $^{31}P\{^{1}H\}$ NMR spectra of **5a-c** in the mixture of benzene and ethanol (1:1) reveal signals in the region of δ = 109-117 ppm, which are typical for the salts of dithiophosphoric acids.[17] In the ^{1}H NMR spectrum of **5a**, the proton signals of the bis{2-O-[2-methyl-(2*S*)-3-*O*-propionyl]} substituent are shifted to high field in comparison with that of acid **3a**. Thus, the signal of the protons of the C^4H_3O substituent of **5a** is situated at higher field (δ = 3.68 ppm). In the ^{13}C spectrum of **5a** in the mixture of CD_3OD and CCl_4, the carbon atom of the same fragment C^4H_3O exhibits a singlet at δ = 51.1 ppm. In the FTIR spectrum of **5a**, the band of the C = O stretching vibrations appears in practically the same region (1745 cm^{-1}) as that for acid **3a** (1745 cm^{-1}) (Table 2). In contrast to **5a**, the ^{1}H NMR spectrum of **5 b** in $CDCl_3$ reveals two singlets at δ = 3.71 and 3.77 ppm, attributable to the methyl protons of two C^5H_3O and C^6H_3O substituents. The data of FTIR spectra of **5a** and **5 b** are very similar (see Table 2). On the basis of the NMR spectra, it was established that **5c** was formed as the

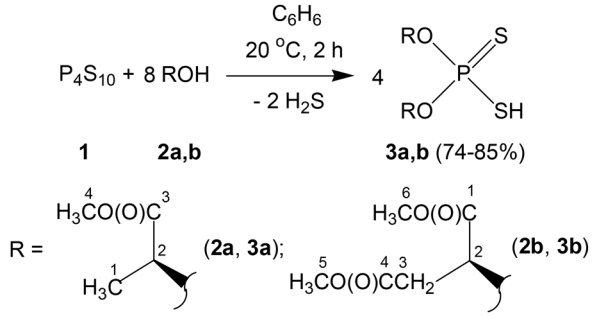
Table 3. ^{1}H NMR data of compounds obtained.

Comp. (Solvent)	δ, ppm
3a ($CDCl_3$)	1.58 d (6H, $C^1\underline{H}_3CH$, $^3J_{HH}$ = 7.0 Hz), 3.78 s (6H, $C^4\underline{H}_3O$), 5.12 d q (2H, $POC^2\underline{H}CH_3$, $^3J_{HH}$ = 7.0 Hz, $^3J_{PH}$ = 14.6 Hz), 6.27 m (1H, PSH).
3b ($CDCl_3$)	2.77 d (4H, $C^2\underline{H}_2CH$, $^3J_{HH}$ 6.0), 2.80 d (4H, $C^2\underline{H}_2CH$, $^3J_{HH}$ 6.0), 3.65 s (6H, $C^5\underline{H}_3O$), 3.74 s (6H, $C^6\underline{H}_3O$), 5.22 d t (2H, $POC^2\underline{H}CH_2$, $^3J_{HH}$ 6.0, $^3J_{PH}$ 13.6).
5a (CD_3OD)	1.47 d [6H, $C^1\underline{H}_3CH_2$, $^3J_{HH}$ = 7.0 Hz], 2.63 s (3H, $C^{9'}\underline{H}_3$), 3.62 m (2H, POC^2H), 3.68 s (6H, $C^4\underline{H}_3O$), 4.74 s (2H, $C^{7'}\underline{H}_2O$), 5.09 s (2H, $C^{8'}\underline{H}_2O$), 8.17 s (1H, $\underline{C}^{2'}H$).
5b (CD_3OD)	2.55 s (3H, $C^{9'}\underline{H}_3$), 2.74 d (4H, $C^3\underline{H}_2CH$, $^3J_{HH}$ = 6.0 Hz), 2.80 d (4H, $C^3\underline{H}_2CH$, $^3J_{HH}$ = 4.9 Hz), 3.71 s (6H, $C^5\underline{H}_3O$), 3.77 s (6H, $C^6\underline{H}_3O$), 4.66 s (2H, $C^{7'}\underline{H}_2O$), 5.04 s (2H, $C^{8'}\underline{H}_2O$), 5.28 d t (2H, $POC^2\underline{H}CH_2$, $^3J_{HH}$ = 5.4 Hz, $^3J_{PH}$ = 15.4 Hz), 8.04 s (1H, $C^{2'}H$).
5c (CD_3OD)	0.937 t [6H, $C^4\underline{H}_3CH_2$, $^3J_{HH}$ = 7.4 Hz], 0.942 t [6H, $C^4\underline{H}_3CH_2$, $^3J_{HH}$ = 7.5 Hz], 1.29 d [6H, $C^1\underline{H}_3CH$, $^3J_{HH}$ = 6.2 Hz], 1.71 m (4H, C^3H_2), 2.61 s (3H, $C^{9'}\underline{H}_3$), 4.57 m (2H, C^2HOP), 4.67 s (2H, $C^{7'}\underline{H}_2O$), 5.01 s (2H, $C^{8'}\underline{H}_2O$), 8.05 s (1H, $C^{2'}H$).
5d (CD_3OD)	0.92 s [6H, $(C^{7,8}\underline{H}_3)_2C$], 1.92 m (2H, $C^4\underline{H}_2OP$, 2H, $C^6\underline{H}_2OP$), 2.19 s (3H, $C^{9'}\underline{H}_3$), 2.23 s (3H, $C^{9'}\underline{H}_3$), 3.00 s (2H, $C^{7'}\underline{H}_2O$), 3.37 s (2H, $C^{8'}\underline{H}_2O$), 6.44 s (1H, $C^{2'}H$).
5e (CD_3OD)	1.261 d (3H, $C^7\underline{H}_3$, $^3J_{HH}$ = 6.2 Hz), 1.264 d (3H, $C^7\underline{H}_3$, $^3J_{HH}$ = 6.2 Hz), 1.61 m (2H, $C^5\underline{H}_2$), 1.65 m (2H, $C^5\underline{H}_2$), 1.81 m (2H, $C^6\underline{H}_2$), 2.65 s (3H, $C^{9'}\underline{H}_3$), 4.56 m (1H, C^4H), 4.72 s (2H, $C^{7'}\underline{H}_2O$), 5.20 s (2H, $C^{8'}\underline{H}_2O$), 8.18 s (1H, $C^{2'}H$).
5f (CD_3OD)	1.29 d (3H, $C^6\underline{H}_3C^4H$, 3H, $C^7\underline{H}_3C^5H$, $^3J_{HH}$ = 6.2 Hz), 2.66 s (3H, $C^{9'}\underline{H}_3$), 4.57 m (2H, POC^4HC^5HOP), 4.70 s (2H, $C^{7'}\underline{H}_2O$), 5.11 s (2H, $C^{8'}\underline{H}_2O$), 8.18 s (1H, $\underline{C}^{2'}H$).
5g (CD_3OD)	2.53 s (3H, $C^{9'}\underline{H}_3$), 4.59 s (2H, $C^{7'}\underline{H}_2O$), 4.93 s (2H, $C^{8'}\underline{H}_2O$), 6.94 m (1H, C^9H, 1H, $C^{14}H$), 7.21 m (1H, $C^{10}H$, 1H, $C^{13}H$), 7.26 m (1H, C^8H, 1H, $C^{15}H$), 7.36 m (1H, $C^{11}H$, 1H, $C^{12}H$), 7.91 s (1H, $C^{2'}H$).
5h ($CDCl_3$)	0.83 d (6H, $C^8\underline{H}_3CH$, $^3J_{HH}$ = 8.8 Hz), 0.86 d (6H, $C^8\underline{H}_3CH$, $^3J_{HH}$ = 8.8 Hz), 0.94 d (12H, $(C^{9,10}\underline{H}_3)_2CH$, $^3J_{HH}$ = 6.6 Hz), 0.95 d (12H, $(C^{9,10}\underline{H}_3)_2C\underline{H}$, $^3J_{HH}$ = 6.6 Hz), 1.15 m [2H, $(CH_3)_2C^7\underline{H}$)], 1.43 m (2H, $CH_3C^5\underline{H}$), 1.49 s (12H, $(C^{11',12'}\underline{H}_3)_2C$), 2.69 s (3H, $C^{9'}\underline{H}_3$), 1.69 m (4H, $\underline{C}^4H_2$), 1.99 d (2H, $C^6\underline{H}_2$, $^3J_{HH}$ = 11.7 Hz), 2.09-2.21 m (4H, $C^3\underline{H}_2$), 2.38 d (2H, $C^6\underline{H}_2$, $^3J_{HH}$ = 11.7 Hz), 3.44 d d t (2H, $POCHC^2\underline{H}$, $^3J_{HH}$ = 6.6 Hz), 4.46 d d t (2H, $POC^1\underline{H}$, $^3J_{HH}$ = 6.6 Hz, $^3J_{PH}$ = 11.0 Hz), 4.80 s (2H, $OC^{7'}\underline{H}_2$), 5.10 s (2H, $OC^{8'}\underline{H}_2$), 8.01 s (1H, $C^{2'}\underline{H}$).

Table 4. ^{13}C and $^{13}C\{^1H\}$ NMR data of compounds obtained.

Comp. (Solvent)	δ, ppm
3b ($CDCl_3$)	38.34 t (s) (C^3H_2, $^1J_{CH}$ = 131.3 Hz), 38.38 t (s) (C^3H_2, $^1J_{CH}$ = 130.6 Hz), 52.1 q (s) (C^6H_3O, $^1J_{CH}$ = 147.5 Hz), 52.8 q (s) (C^5H_3O, $^1J_{CH}$ = 148.5 Hz), 71.93 d d (d) (POC^2H, $^1J_{CH}$ = 149.7 Hz, $^2J_{CP}$ = 19.8 Hz), 71.97 d d (d) (POC^2H, $^1J_{CH}$ = 150.4 Hz, $^2J_{CP}$ = 19.4 Hz), 72.11 d d (d) (POC^2H, $^1J_{CH}$ = 149.7 Hz, $^2J_{CP}$ = 15.8 Hz), 72.15 d d (d) (POC^2H, $^1J_{CH}$ = 150.4 Hz, $^2J_{CP}$ = 16.5 Hz), 171.1 m (s) (O-C^4=O), 173.6 s (s) (O-C^1=O).
5a[a] (CD_3OD, CCl_4)	13.3 s ($C^{9'}H_3$), 18.65 s (C^1H_3), 18.69 s (C^1H_3), 51.1 s (C^4H_3O), 58.3 s ($C^{8'}H_2O$), 58.5 s ($C^{7'}H_2O$), 70.4 d (POC^2H, $^3J_{PH}$ = 7.0 Hz), 130.3 s ($C^{2'}H$), 136.2 s ($C^{3'}$), 138.5 s ($C^{4'}$), 142.4 s ($C^{6'}$), 153.2 s ($C^{5'}OH$), 173.29 s (O-C^3=O), 173.34 s (O-C^3=O).
5b[b] (CD_3OD, CCl_4)	15.7 q ($C^{9'}H_3$, $^1J_{CH}$ = 129.9 Hz), 37.7 t (C^3H_2, $^1J_{CH}$ = 130.6 Hz), 51.4 q (C^6H_3O, $^1J_{CH}$ = 146.7 Hz), 51.8 q (C^5H_3O, $^1J_{CH}$ = 147.5 Hz), 58.5 t ($C^{8'}H_2O$, $^1J_{CH}$ = 146.0 Hz), 61.7 t ($C^{8'}H_2O$, $^1J_{CH}$ = 141.6 Hz), 67.1 d d (POC^1H, $^2J_{PH}$ = 8.8 Hz, $^1J_{CH}$ = 146.0 Hz), 133.0 d ($C^{2'}H$, $^1J_{CH}$ = 185.6), 134.7 c ($C^{3'}$), 135.7 c ($C^{4'}$), 143.8 c ($C^{6'}$), 152.9 c ($C^{5'}OH$), 170.9 c (O-C^1=O), 173.4 c (O-C^4=O).
5c[c] (CD_3OD, CCl_4)	8.88 q (s) (C^4H_3, $^1J_{CH}$ = 125.1 Hz), 13.3 q (s) ($C^{9'}H_3$, $^1J_{CH}$ = 131.0 Hz), 20.1 q (s) (C^1H_3, $^1J_{CH}$ = 126.2 Hz), 30.18 t (s) (C^3H_2, $^1J_{CH}$ = 126.2 Hz), 30.23 t (s) (C^3H_2, $^1J_{CH}$ = 126.2 Hz), 57.7 t (s) ($C^{8'}H_2O$, $^1J_{CH}$ = 143.4 Hz), 58.5 t (s) ($C^{7'}H_2O$, $^1J_{CH}$ = 146.4 Hz), 74.7 d (d) (POC^2H, $^3J_{PH}$ = 7.0 Hz, $^1J_{CH}$ = 140.9 Hz), 126.3 d (s) ($C^{2'}H$, $^1J_{CH}$ = 189.3 Hz), 135.3 s (s) ($C^{3'}$), 140.3 s (s) ($C^{4'}$), 140.9 s (s) ($C^{6'}$), 153.4 s (s) ($C^{5'}OH$).
5e[c] (CD_3OD, CCl_4)	14.5 q (s) ($C^{9'}H_3$, $^1J_{CH}$ = 130.8 Hz), 21.89 q (s) (C^7H_3, $^1J_{CH}$ = 126.3 Hz), 21.95 q (s) (C^7H_3, $^1J_{CH}$ = 126.6 Hz), 34.36 t (s) (C^7H_2, $^1J_{CH}$ = 127.4 Hz), 34.38 t (s) (C^7H_2, $^1J_{CH}$ = 127.4 Hz), 57.1 t (s) ($C^{8'}H_2O$, $^1J_{CH}$ = 141.3 Hz), 58.4 t (s) ($C^{7'}H_2O$, $^1J_{CH}$ = 143.7 Hz), 64.5 d t (d) (C^6H_2OP, $^1J_{CH}$ = 145.1 Hz), 72.30 d (s) (C^4H, $^1J_{CH}$ = 146.2 Hz), 72.35 d (s) (C^4H, $^1J_{CH}$ = 146.2 Hz), 130.4 d (s) ($C^{2'}H$, $^1J_{CH}$ = 188.5 Hz), 136.6 s (s) ($C^{3'}$), 138.5 s (s) ($C^{4'}$), 142.1 s (s) ($C^{6'}$), 153.5 s (s) ($C^{5'}OH$).
5h[c] ($CDCl_3$)	16.5 q (s) (C^8H_3, $^1J_{CH}$ = 130.6 Hz), 21.4 q (s) ($C^{9'}H_3$, $^1J_{CH}$ = 125.1 Hz), 22.2 q (s) [$(C^{9,10}H_3)_2C$, $^1J_{CH}$ = 126.2 Hz), 22.2 q (s) [$(C^{9,10}H_3)_2C$, $^1J_{CH}$ = 126.2 Hz), 23.6 q (s) [$(C^{11',12'}H_3)_2C$, $^1J_{CH}$ = 126.2 Hz), 25.2 t (s) (C^3H_2, $^1J_{CH}$ = 128.4 Hz), 25.8 d (s) (C^7H, $^1J_{CH}$ = 125.4 Hz), 31.6 d (s) (C^5H, $^1J_{CH}$ = 123.3 Hz), 34.4 t (s) (C^4H_2, $^1J_{CH}$ = 124.7 Hz), 34.5 t (s) (C^4H_2, $^1J_{CH}$ = 124.7 Hz), 43.2 t (s) (C^6H_2, $^1J_{CH}$ = 129.8 Hz), 45.0 t (s) (C^6H_2, $^1J_{CH}$ = 128.4 Hz), 48.9 d (s) (C^2H, $^1J_{CH}$ = 118.1 Hz), 49.0 d (s) (C^2H, $^1J_{CH}$ = 118.1 Hz), 60.6 t (s) ($C^{8'}H_2O$, $^1J_{CH}$ = 117.4 Hz), 60.8 t (s) ($C^{7'}H_2O$, $^1J_{CH}$ = 146.0 Hz), 78.3 d (d) (POC^1H, $^1J_{CH}$ = 116.6 Hz, $^2J_{CP}$ = 9.2 Hz), 103.1 s (s) ($C^{10'}$), 128.6 d (s) (N = $C^{2'}H$, $^1J_{CH}$ = 187.1 Hz), 136.4 s (s) ($C^{3'}$), 141.4 s (s) ($C^{4'}$), 144.8 s (s) ($C^{6'}$), 152.4 s (s) ($C^{5'}OH$).
5j[a] (acetone-d_6)	19.1 s ($C^{9'}H_3$), 24.4 s [$(C^{11',12'}H_3)_2C$], 59.5 s ($C^{8'}H_2O$), 61.1 s ($C^{7'}H_2O$), 67.0 s (C^2H_2O, C^5H_2O), 70.2 s ($OC^3H_2C^4H_2O$), 72.6 s (POC^1H_2, POC^6H_2), 101.6 s [$(CH_3)_2C^{10'}$], 115.7 s ($C^{8''}HC^{12''}H$), 119.7 s ($C^{3''}HC^{5''}H$), 122.6 s ($C^{10''}H$), 126.3 s ($C^{1''}P$), 131.0 s ($C^{9''}HC^{11''}H$), 132.0 s ($C^{3'}$), 132.1 s ($C^{4'}$), 132.3 d ($PC\underline{C}^{2''}H\underline{C}^{6''}HCP$, $^2J_{CP}$ = 13.2 Hz), 133.1 s ($C^{4'}$), 138.8 s ($C^{2'}H$), 146.8 s ($C^{5'}OH$), 158.7 s ($\underline{C}^{6'}CH_3$), 162.6 s ($C^{7''}O$), 168.5 s ($C^{4''}O$).

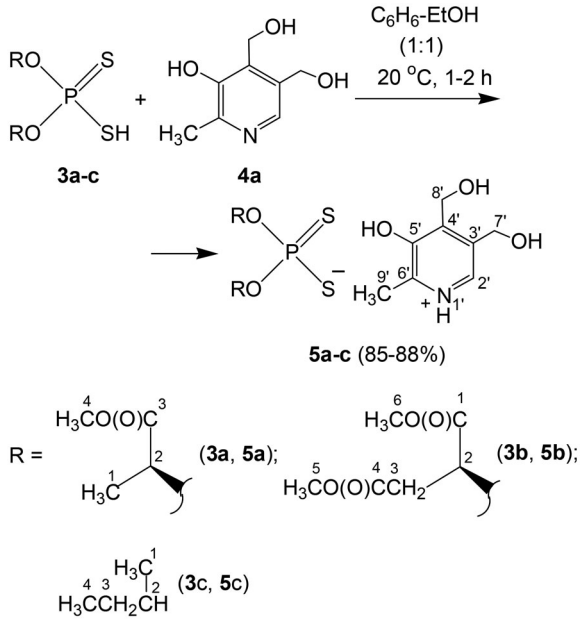
[a] $^{13}C\{^1H\}$ NMR;
[b] ^{13}C NMR;
[c] In parentheses is a view of signal in $^{13}C\{^1H\}$NMR.



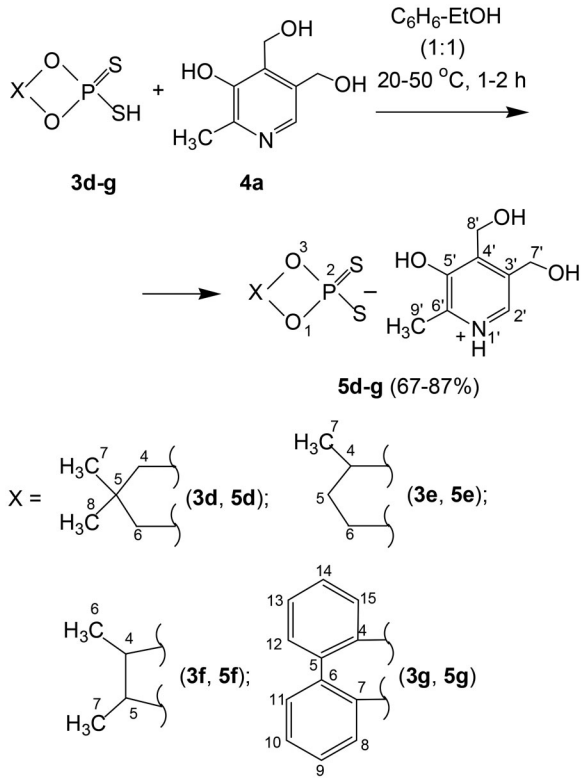
Scheme 1. Synthesis of dithiophosphoric acids **3a** and **3 b**.

mixture of stereoisomers as the racemic acid **3c** was used. The $^{31}P\{^1H\}$ NMR spectrum of **5c** in the mixture of benzene and ethanol (1:1) shows two signals at δ = 109.2 and 110.8 ppm in integral ratio 1:0.4. In the ^{13}C spectrum of **5c** in the mixture of CD_3OD and CCl_4, the carbon atom of the fragment of C^3H_2 gives two triplets at δ = 30.18 ppm ($^1J_{CH}$ = 126.2 Hz) and 30.23 ppm ($^1J_{CH}$ = 126.2 Hz).

We have chosen cyclic dithiophosphoric acids because they and their derivatives have recently attracted attention due to the antimicrobial activity.[19,20] Pyridoxine **4a** reacts with 1,3,2-dioxaphosphorinanes **3d,e**, 1,3,2-dioxaphospholane **3f**, and 1,3,2-dioxaphosphepin **3 g** in the mixture of



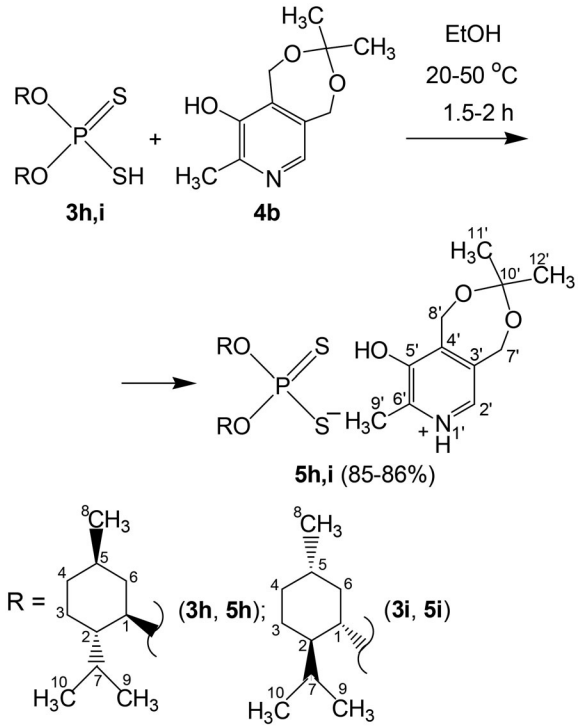
Scheme 2. Synthesis of pyridoxonium dithiophosphates **5a-c**.



Scheme 3. Synthesis of pyridoxonium cyclic dithiophosphates **5d-g**.

benzene and ethanol in the ratio 1:1 at 20 °C for 1–2 h to give pyridoxonium cyclic dithiophosphates **5d-g** (Scheme 3). However, to carry out the reaction with 1,3,2-dioxaphosphorinanes **3d**, heating at 50 °C for 2 h was required.

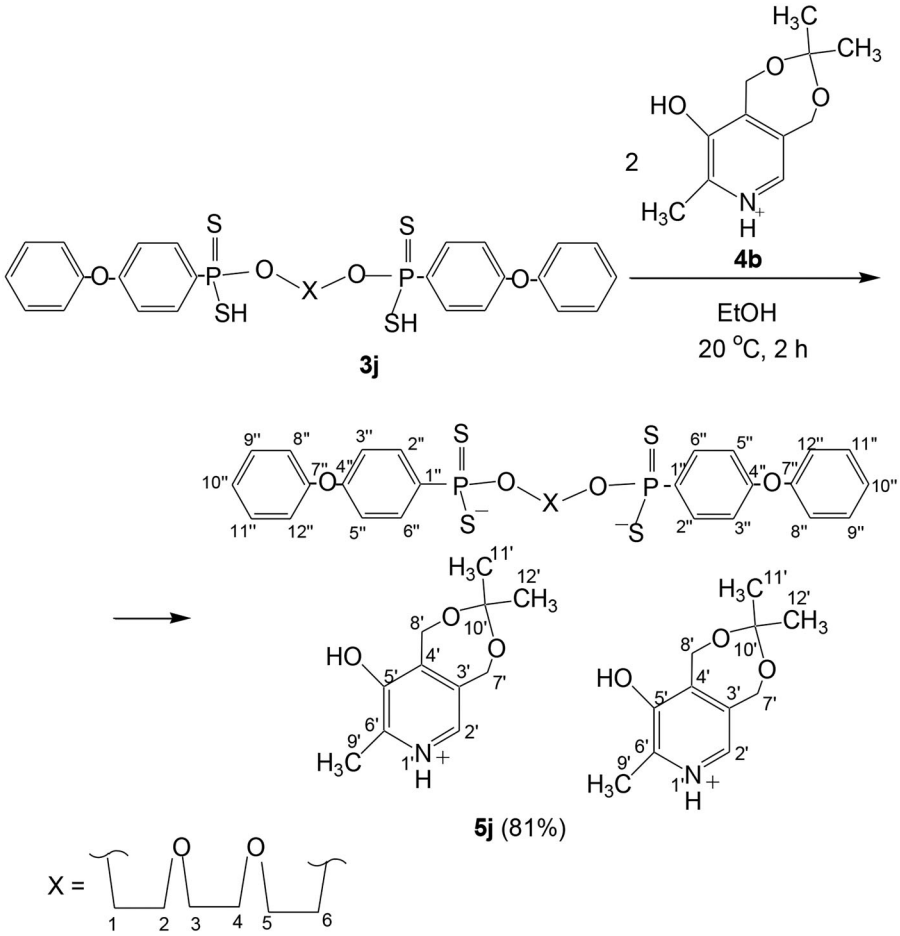
Salts **5d,e** containing the six-membered cycle in the dithiophosphate anions give signals at $\delta = 111.3$ and 111.3 ppm, respectively, in the $^{31}P\{^1H\}$ NMR spectra in the mixture of benzene and ethanol (1:1), similarly to the pyridoxonium salts **5a-c** bearing linear substituents at the



Scheme 4. Synthesis of acetonide pyridoxonium O,O-dimenthyl dithiophosphates **5 h,i**.

phosphorus atom. Unlike **5d,e**, the $^{31}P\{^1H\}$ NMR spectra of five- and seven-membered cyclic salts **5f** and **5e** in the mixture of benzene and ethanol (1:1) show signals at $\delta = 125.6$ and 131.1 ppm, respectively. These resonances are shifted toward downfield in comparison with the data of **5d,e**. It should be emphasized that 1,3,2-dioxaphosphorinane salt **5e** and 1,3,2-dioxaphospholane salt **5f** contain the same structural fragment C^4HOP the protons of which give multiplets at $\delta = 4.56$ and 4.57 ppm, respectively, in the ^1H NMR spectra in CD_3OD. The singlet due to the protons of the methyl substituent $C^{9'}H_3$ of the pyridoxonium cation of 1,3,2-dioxaphosphorinane salt **5d** is shifted to high field ($\delta = 2.19$ ppm) compared to that of other pyridoxonium cyclic dithiophosphates **5e-g** ($\delta = 2.65$–2.53 ppm) as well as to linear salts **5a-c** ($\delta = 2.63$–2.55 ppm). The carbon atom of the same substituent $C^{9'}H_3$ of pyridoxonium cation of **5a-c** appears as a quartet at $\delta = 13.3$–15.7 ppm ($^1J_{CH}$ = 125–130 Hz) in the ^{13}C spectra in CD_3OD and as a singlet in the $^{13}C\{^1H\}$ NMR spectra. In the ^1H NMR spectrum in CD_3OD, 1,3,2-dioxaphosphepin **5d** exhibits a singlet at $\delta = 6.44$ ppm due to the presence of the fragment $C^{2'}H$ of pyridoxonium cation. This resonance is shifted to high field compared to that of other salts **5a-f** ($\delta = 7.91$–8.18 ppm).

This approach was extended to pyridoxine acetonide, bearing an isopropylidene ether linker and possessing antibacterial activity.[8,9] Among chiral dithiophosphoric acids, we used O,O-dimenthyl dithiophosphoric acids **3 h,i** prepared from (–)-(1*R*,2*S*,5R)-menthol and (+)-(1*S*,2*R*,5*S*)-menthol.[21] Seven-membered pyridoxine acetonide **4 b** reacts with **3 h** in dried ethanol at 50 °C for 1.5 h to form acetonide pyridoxonium O,O-di-(–)-menthyl dithiophosphate **5 h**. Isomeric acetonide pyridoxonium O,O-di-



Scheme 5. Synthesis of diacetonide pyridoxonium bisdithiophosphonate **5j**.

(+)-menthyl dithiophosphate **5i** was obtained similarly (Scheme 4).

The resonances at $\delta = 109.6$ and 104.5 ppm observed in the $^{31}P\{^{1}H\}$ NMR spectra in ethanol of **5 h** and **5i** are situated in practically the same region as observed for in other linear salts **5a-c**. In the ^{1}H NMR spectrum in $CDCl_3$ of **5 h**, a singlet at $\delta = 1.49$ ppm was assigned to protons of three methyl groups of the isopropylidene fragment $(C^{11',12'}H_3)_2C$. In the $^{13}C\{^{1}H\}$ NMR spectrum of **5 h**, the carbon atoms $C^{11'}$ and $C^{12'}$ of the same fragment $(\underline{C}^{11',12'}H_3)_2C^{10'}$ reveal a quartet at $\delta = 23.6$ ppm ($^{1}J_{CH} = 126.2$ Hz). The carbon atom $C^{10'}$ of this fragment $(\underline{C}^{11',12'}H_3)_2C^{10'}$ gives a singlet at $\delta = 103.1$ ppm. The FTIR and NMR data of the isomeric acetonide pyridoxonium O,O-di-(+)-menthyl dithiophosphate **5i** are identical to those of **5 h**. In the ESI mass spectrum of **5 h**, a peak at *m/e* 655.5 is assigned to the ion [M + K]+ (calculated *M* 615.9).

It was interesting to establish whether phosphorus dithioacids containing several dithiophosphoryl groups are capable to form pyridoxonium salts. Among them, bisaryldithiophosphonic acids containing a tri(ethyleneglycol) linker between two phosphorus atoms are considered to yield diammonium salts by passing anhydrous gaseous ammonia through the benzene solutions of these acids.[22] 1,8-Triethyleneoxy-bis-(4-phenoxyphenyldithiophosphonic) acid **3j** prepared by the reaction of 2,4-bis-(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide with tri(ethyleneglycol)[22] reacts with pyridoxine acetonide **4 b** in dry ethanol at 50 °C for 2 h to give acetonide pyridoxonium bisdithiophosphonate **5j** (Scheme 5).

In spite of the presence of two phosphorus atoms and two pyridoxonium cations in salt **5j**, its $^{31}P\{^{1}H\}$ NMR spectrum in ethanol exhibits a singlet at $\delta = 105.9$ ppm. This indicates the equivalence and the similar environment of both phosphorus atoms in **5j**. In the $^{13}C\{^{1}H\}$ NMR spectrum in acetone-d_6, two carbon atoms of the fragments $POC^{1}H_2$ and $POC^{6}H_2$ of triethyleneoxy linker appear as a singlet at $\delta = 72.6$ ppm. A singlet at $\delta = 126.3$ ppm has been assigned to two carbon atoms of both fragments $C^{1''}P$, whereas, in the FTIR spectrum of **5j**, the stretching vibrations of the P = S bond appear as two bands at 694 and 675 cm^{-1}. Two bands at 562 and 559 cm^{-1} are due to the stretching vibrations of the P–S bond. Thus, dithiophosphoric and bisdithiophosphonic acids readily form pyridoxonium salts with pyridoxine as well as its acetonide.

Biological evaluation

Pyridoxonium dithiophosphates **5a-g** (concentration in DMSO was 1%) were studied for *in vitro* against *Escherichia coli*, *Bacillus cereus* (ATCC 19637), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 29213), and

Table 5. Antimicrobial activity of **5a–5 g**[a].

Comp.	*B. cereus*	*Ps. aeruginosa*	*S. aureus*	*C. albicans*
5a	8	11	8	15
5b	10	12	–	12
5e	12	12	8	–
5f	10	12	8	16
5g	12	–	10	18
Cefazolin (1% in DMSO)	25	–	38	13

[a]Inhibition zone in mm.

Candida albicans (ATCC 885-653) (Table 5). The antibiotic cefazolin was applied as control sample (1% in DMSO).[23] Inspection of Table 5 proves that all prepared compounds exhibit remarkable antifungal activity toward the tested *C. albicans* (growth inhibition zones of 12–18 mm) as compared to cefazolin (13 mm). Salt **5 g** containing an aryl cyclic dithiophosphate anion shows higher activity against all tested microorganisms (10–18 mm). The salts **5a-g** exhibit the same activity against *B. cereus* (8–12 mm) and *P. aeruginosa* (11–12 mm) as compared to Slayt (12 mm). The evaluated salts reveal moderate activity against *E. coli* (8–10 mm) and *S. aureus* (8–10 mm). In general, the pyridoxonium salts **5f** and **5 g** containing cyclic dithiophosphate anions are more active antimicrobials than the linear salts **5a** and **5 b**. Thus, the results for **5 g** seem promising for carrying out the next steps in the antimicrobial activity study.

Conclusions

Chiral linear and cyclic dithiophosphoric and bisdithiophosphonic acids readily react with pyridoxine and pyridoxine acetonide to give pyridoxonium dithiophosphates and bisdithiophosphonates. The reactions proceed via an increase of the coordination number at nitrogen. Dithiophosphoric acids bearing (*S*)-(–)-α-lactic and (*S*)-(–)-α-malic scaffolds as well as cyclic fragments have not been previously introduced into the reactions with pyridoxine. We have prepared the first representative of a diacetonide pyridoxonium salt of bisdithiophosphonic acids. The synthesis of new pyridoxonium salts of dithiophosphoric and bisdithiophosphonic acids is important for obtaining new antimicrobial drugs.

Experimental

General

A flow of dry argon was used for all reactions. Benzene and ethanol were dried by distillation over sodium. Tetraphosphorus decasulfide (purity 99%), methyl (*S*)-(–)-α-lactate **2a** (purity 98%), dimethyl (*S*)-(–)-α-malate **2 b** (purity 98%), pyridoxine **4a** (purity 98%), 2,3-butanediol (purity 98%), 2,2′-biphenol (purity 99%), and (–)-(1 *R*,2*S*,5R)-menthol (purity 99%) were purchased from Sigma-Aldrich Co. (St. Louis, MO, USA). 2,2-Dimethylpropane-1,3-diol (purity 98%) was purchased from Fluka kemika. Butane-1,3-diol (purity 99%) was purchased from Merck (Kenilworth, NJ, USA). (+)-(1*S*,2*R*,5*S*)-Menthol (purity 99%) was purchased from Alfa Aesar (Heysham, UK). Racemic *O*,*O*-di-2-butyl dithiophosphoric acid **3c** was obtained by the reaction of 2-butanol with P_4S_{10}.[13] 2-Mercapto-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-sulfide **3d**, 2-mercapto-4-methyl-1,3,2-dioxaphosphorinane 2-sulfide **3e** and 2-mercapto-4,5-dimethyl-1,3,2-dioxaphospholane 2-sulfide **3f** were obtained by the reaction of tetraphosphorus decasulfide with 2,2-dimethylpropane-1,3-diol, butane-1,3-diol and butane-2,3-diol respectively in 1:2 molar ratio in dry benzene.[14] 2-Mercaptodibenzo[*d.f*][1–3]-dioxaphosphepin 6-sulfide **3 g** was synthesized by the reaction of P_4S_{10} (**1**) with 2,2′-biphenol by refluxing in xylene.[24] O,O-Di[(–)-(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohex-1-yl] dithiophosphoric acid **3 h** and its isomer **3i** were prepared by the reactions of **1** with (–)-(1 *R*,2*S*,5R)-menthol and (+)-(1*S*,2*R*,5*S*)-menthol respectively.[21] Seven-membered pyridoxine acetonide **4 b** was obtained by the reaction of pyridoxine with acetone.[25] 1,8-Triethyleneoxy-bis(4-phenoxyphenyldithiophosphonic) acid **3j** was similarly synthesized by the reaction of 2,4-bis(4-phenoxyphenyl)-1,3,2,4-dithiadiphosphetane 2,4-disulfide with tri(ethyleneglycol).[22]

Melting points (uncorrected) were detected by use of an Electrothermal IA9000 apparatus (Bibby Scientific Ltd., Staffordshire, Great Britain). FTIR spectra (KBr tablets or films) were recorded with a Bruker Tensor 27 spectrometer (Bruker BioSpin AG, Fällanden, Switzerland) in the range 400–4000 cm^{-1}. Bands are designated as ν = the stretching vibration. The ^1H (400 MHz), ^{13}C, and $^{13}C\{^1H\}$ (100.6 MHz) spectra were run on a Bruker Avance III 400 spectrometer (Bruker BioSpin AG, Fällanden, Switzerland) in $CDCl_3$ or CD_3OD. Multiplicity of signal is denoted in the NMR spectra as m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet. The $^{31}P\{^1H\}$ NMR spectra were obtained on a Bruker Avance-400 spectrometer (161.9 MHz) (Bruker BioSpin AG, Fällanden, Switzerland) in benzene with 85% H_3PO_4 as an external reference. High-resolution mass spectra were recorded with a Bruker Compass DataAnalysis 4.0 instruments (Bruker Daltonik GmbH, Bremen, Germany) in acetone performing in the ESI mode. Optical rotations were determined on a Perkin–Elmer 341 polarimeter at 20 °C (Norwalk, CT, USA) (*D*-line of sodium, 589 nm, a path length 5.52 cm, c = 1%) and presented as specific rotations $[\alpha]^{20}_D$. Compositions of carbon, hydrogen, nitrogen, and sulfur atoms were obtained on a EuroEA3000 CHNS-O Analyzer (EuroVector S.p.A., Milano, Italy). Compositions of phosphorus were determined by method of pyrolysis on a nonserial instrument. The Supplemental Materials contain sample ^1H, ^{13}C, and ^{31}P NMR spectra of the products (Figures S1–S18).

Synthesis

Bis{2-O-[2-methyl-(2S)-3-O-propionyl]} dithiophosphoric acid (3a)

P_4S_{10} **1** (1.0 g, 2.3 mmol) was added to the solution of methyl (*S*)-(–)-α-lactate **2a** (1.88 g, 18.1 mmol) in 15 mL of anhydrous benzene under dry argon flow with stirring at 20 °C. The suspension obtained was stirred at 20 °C for 2 h, filtered, and concentrated under reduced pressure (0.5 mm Hg) at 40 °C for 1 h and then at 0.02 mm Hg at 40 °C for 1 h and gave **3a** (2.0 g, 74%) as oily liquid (Tables 1–4)

Bis{2-O-[1,4-O,O-dimethyl-(2S)-succinyl]} dithiophosphoric acid (3 b)

Acid **3 b** was obtained similarly as oily liquid from **1** (0.34 g, 0.77 mmol) and dimethyl (*S*)-(−)-α-malate **2a** (1.0 g, 0.77 mmol) (Tables 1–4)

Pyridoxonium bis{2-O-[2-methyl-(2S)-3-O-propionyl]} dithiophosphate (5a). general procedure

The mixture of pyridoxine **4a** (0.17 g, 1.0 mmol) and acid **3a** (0.3 g, 0.99 mmol) in 5 mL of ethanol and 5 mL of benzene was stirred at 20 °C for 2 h. The clear solution obtained was concentrated under reduced pressure (0.5 mm Hg) at 40 °C for 1 h and then at 0.02 mm Hg at 40 °C for 1 h and gave **5a** (0.4 g, 85%) of as yellow semisolid (Tables 1–4)

Pyridoxonium bis{2-O-[1,4-O,O-dimethyl-(2S)-succinyl]} dithiophosphate (5 b)

Yellow semisolid (Tables 1–4)

Pyridoxonium O,O-di-2-butyl dithiophosphate (5c)

Yellow semisolid (Tables 1–4)

Pyridoxonium 2-mercapto-5,5-dimethyl-1,3,2-dioxaphosphorinane 2-sulfide (5d)

Yellow semisolid (Tables 1–4)

Pyridoxonium 2-mercapto-4-methyl-1,3,2-dioxaphosphorinane 2-sulfide (5e)

Yellow semisolid (Tables 1–4)

Pyridoxonium 2-mercapto-4,5-dimethyl-1,3,2-dioxaphospholane 2-sulfide (5f)

Yellow semisolid (Tables 1–3)

Pyridoxonium 2-mercaptodibenzo[d.f][*1–3*]-dioxaphosphepin 6-sulfide (5 g)

White solid, m.p.: 144-146 °C (Tables 1–3)

1,5-Dihydro-3,3,8-trimethyl-9-hydroxy-[*1, 3*]dioxepino-[5,6-c]pyridinium O,O-di[(–)-(1R,2S,5R)-2-isopropyl-5-methylcyclohex-1-yl] dithiophosphate (5 h). general procedure

The mixture of 1,5-dihydro-3,3,8-trimethyl[1, 3]dioxepino-[5,6-*c*]pyridin-9-ol **4 b** (0.07 g, 0.3 mmol) and acid **3 h** (0.14 g, 0.3 mmol) in 10 mL of dried ethanol was heated at 50 °C for 1.5 h. The clear solution obtained was concentrated under reduced pressure (0.5 mm Hg) at 40 °C for 1 h and then at 0.02 mm Hg at 40 °C for 1 h and gave salt **5 h** (0.18 g, 86%) as semisolid (Tables 1–3)

1,5-Dihydro-3,3,8-trimethyl-9-hydroxy-[*1, 3*]dioxepino-[5,6-c]pyridinium O,O-di[(+)-(1S,2R,5S)-2-isopropyl-5-methylcyclohex-1-yl] dithiophosphate (5i)

Semisolid (Tables 1 and 2). The mass spectrum of ESI (acetone) *m/e*: 655.5 [M + K]+ (calculated M 615.9). The FTIR and ^{1}H NMR data of **5 h** are similar to those of isomeric **5i**.

Bis(1,5-dihydro-3,3,8-trimethyl-9-hydroxy-[*1, 3*]dioxepino-[5,6-c]pyridinium) 1,8-triethyleneoxy bis(4-phenoxyphenyldithiophosphonate) (5j)

The mixture of 1,8-triethyleneoxy-bis(4-phenoxyphenyldithiophosphonic) acid **3j** (0.16 g, 0.24 mmol) and pyridoxine acetonide **4 b** (0.1 g, 0.48 mmol) in 10 mL of dry ethanol was heated at 50 °C for 2 h. The mixture was filtered. The filtrate was evaporated at reduced pressure (0.5 mm Hg) at 40 °C for 1 h and then in vacuum (0.02 mm Hg) for 1 h to give **5j** (0.21 g, 81%) as semisolid (Tables 1–4)

Antimicrobial assay

Pyridoxonium dithiophosphates **5a,b** and **5c-g** (1% DMSO solutions) were studied by use of bacterial and fungal cultures of *Escherichia coli*, *Bacillus cereus* (ATCC 19637), *Pseudomonas aeruginosa* (ATCC 27853), *Staphylococcus aureus* (ATCC 29213), and *Candida albicans* (ATCC 885-653) by gel diffusion test on Mueller–Hinton agar. Daily cultures of bacteria and fungi were washed with physiological solution from beef nutrient agar and standardized according to the turbidity standard up to 0.5 by McFarland (1.5×108 CFU mL^{-1}). Bacterial and fungal cultures (0.4 mL) were added to melted and cooled (at 45 °C) Mueller–Hinton agar (10 mL). The mixture was stirred and poured on sterile Petri dishes (90 mm) and allowed to solidify. The agar plate was punched with a sterile borer with 6 mm diameter size, and holes were filled with the test compounds. Antimicrobial activity of cefazolin was measured as 1% solution in DMSO (Table 5). Petri dishes were incubated at 35 °C for 24–48 h in incubator. After the incubation period, the diameter of the growth inhibition zones was measured with an accuracy of 0.1 mm.

Acknowledgment

The authors are grateful to the staff of Distributed Spectral-Analytical Center of Shared Facilities for Study of Structure, Composition, and Properties of Substances and Materials of Federal Research Center of Kazan Scientific Center of Russian Academy of Sciences for their research and assistance in discussing the results.

ORCID

Ilyas S. Nizamov http://orcid.org/0000-0002-8243-3533
Timur G. Belov http://orcid.org/0000-0002-1657-2850
Ilnar D. Nizamov http://orcid.org/0000-0002-2058-773X
Yevgeniy N. Nikitin http://orcid.org/0000-0001-6964-3715

References

[1] Cushnie, T. P. T.; Cushnie, B.; Lamb, A. J. Alkaloids: An Overview of Their Antibacterial, Antibiotic-Enhancing and Antivirulence Activities. *Int. J. Antimicrob. Agents.* **2014**, *44*, 377–386. DOI: 10.1016/j.ijantimicag.2014.06.001.

[2] McCormick, D. B. Pyridoxine. In *Encyclopedia of Toxicology*, 3rd ed.; Wexler, Ph., Ed.; US National Library of Medicine: Bethesda, MD, **2014**; pp 1165–1166..

[3] Zempleni, J., Suttie, J. W., Gregory III, J. F., Stover, P. J., Eds.; *Handbook of Vitamins*, 5th ed.; CRC Press: Boca Raton, **2013**.

[4] Spector, R.; Johanson, C. E. J. Vitamin Transport and Homeostasis in Mammalian Brain: Focus on Vitamins B and E. J. Neurochem. **2007**, *103*, 425–438. DOI: 10.1111/j.1471-4159.2007.04773.x.

[5] Mooney, S.; Leuendorf, J. E.; Hendrickson, C.; Hellmann, H. Vitamin B_6: A Long Known Compound of Surprising Complexity . *Molecules* **2009**, *14*, 329–351. DOI: 10.3390/molecules14010329.

[6] Rice, L. B. Antimicrobial Resistance in Gram-Positive Bacteria. Am. J. Med. **2006**, *119*, S11–S19. DOI: 10.1016/j.amjmed.2006.03.012.

[7] Shtyrlin, Y. G.; Petukhov, A. S.; Strelnik, A. D.; Shtyrlin, N. V.; Iksanova, A. G.; Pugachev, M. V.; Pavelyev, R. S.; Dzyurkevich, M. S.; Garipov, M. R.; Balakin, K. V. Chemistry of Pyridoxine in Drug Design. *Russ. Chem. Bull.* **2019**, *68*, 911–945. DOI: 10.1007/s11172-019-2504-5.

[8] Pugachev, M. V.; Shtyrlin, N. V.; Sysoeva, L. P.; Nikitina, E. V.; Abdullin, T. I.; Iksanova, A. G.; Ilaeva, A. A.; Musin, R. Z.; Berdnikov, E. A.; Shtyrlin, Y. G. Synthesis and Antibacterial Activity of Novel Phosphonium Salts on the Basis of Pyridoxine. *Bioorg. Med. Chem.* **2013**, *21*, 4388–4395. DOI: 10.1016/j.bmc.2013.04.051.

[9] Pugachev, M. V.; Shtyrlin, N. V.; Sapozhnikov, S. V.; Sysoeva, L. P.; Iksanova, A. G.; Nikitina, E. V.; Musin, R. Z.; Lodochnikova, O. A.; Berdnikov, E. A.; Shtyrlin, Y. G. Bis-phosphonium Salts of Pyridoxine: The Relationship between Structure and Antibacterial Activity. *Bioorg. Med. Chem.* **2013**, *21*, 7330–7342. DOI: 10.1016/j.bmc.2013.09.056.

[10] Kayumov, A. R.; Nureeva, A. A.; Trizna, E. Y.; Gazizova, G. R.; Bogachev, M. I.; Shtyrlin, N. V.; Pugachev, M. V.; Sapozhnikov, S. V.; Shtyrlin, Y. G. New Derivatives of Pyridoxine Exhibit High Antibacterial Activity against Biofilm-Embedded Staphylococcus Cells. *Biomed. Res. Int.* **2015**, *2015*, 1–10. DOI: 10.1155/2015/890968.

[11] Nikitina, E. V.; Zeldi, M. I.; Pugachev, M. V.; Sapozhnikov, S. V.; Shtyrlin, N. V.; Kuznetsova, S. V.; Evtygin, V. E.; Bogachev, M. I.; Kayumov, A. R.; Shtyrlin, Y. G. Antibacterial Effects of Quaternary Bis-Phosphonium and Ammonium Salts of Pyridoxine on Staphylococcus Aureus Cells: A Single Base Hitting Two Distinct Targets? *World J. Microbiol. Biotechnol.* **2016**, *32*, 5. DOI: 10.1007/s11274-015-1969-0.

[12] Corbridge, D. E. C. *Phosphorus: Chemistry, Biochemistry and Technology*, 6th ed.; Taylor & Francis Group: New York, NY, **2013**.

[13] Nizamov, I. S.; Salikhov, R. Z.; Timushev, I. D.; Nikitin, Y. N.; Nizamov, I. D.; Yakimov, V. Y.; Shulaeva, M. P.; Pozdeev, O. K.; Batyeva, E. S.; Cherkasov, R. A.; et al. Pyridinium Salts of Dithiophosphoric Acids on the Basis of Nicotinic Acids and Their Isomers, 3-Hydroxypyridine, and 3-Pyridinemethanol. *Phosphorus Sulfur Silicon Relat. Elem.* **2020**, *193*, 226–230. DOI: 10.1080/10426507.2019.1673749.

[14] Nizamov, I. S.; Timushev, I. D.; Salikhov, R. Z.; Nizamov, I. D.; Nikitin, Y. N.; Shulaeva, M. P.; Pozdeev, O. K.; Voznesenskaya, T. Y.; Batyeva, E. S.; Cherkasov, R. A. Pyridine Alkaloid Derivatives of Dithiophosphoric Acids and Their Antimicrobial Evaluation. *Asian J. Chem.* **2020**, *32*, 329–334. DOI: 10.14233/ajchem.2020.22381.

[15] Dang, T.; Nizamov, I. S.; Salikhov, R. Z.; Sabirzyanova, L. R.; Vorobev, V. V.; Burganova, T. I.; Shaidoullina, M. M.; Batyeva, E. S.; Cherkasov, R. A.; Abdullin, T. I. Synthesis and Characterization of Pyridoxine, Nicotine and Nicotinamide Salts of Dithiophosphoric Acids as Antibacterial Agents against Resistant Wound Infection. *Bioorg. Med. Chem.* **2019**, *25*, 100–109. DOI: 10.1016/j.bmc.2018.11.017.

[16] Nizamov, I. S.; Sabirzyanova, G. R.; Batyeva, E. S.; Shumatbaev, G. G.; Nizamov, I. D.; Cherkasov, R. A. Dithiophosphorylation of Methyl (*S*)-(−)-Lactate. Russ. J. Org. Chem. **2015**, *51*, 1026–1027. DOI: 10.1134/S1070428015070222.

[17] Crutchfield, M. M.; Dungan, C. H.; Letcher, J. H.; Mark, V.; Van Wazer, J. R. Topics in Phosphorus Chemistry. In *P31 Nuclear Magnetic Resonance*; Grayson, M., Griffith, E. J., Eds.; John Wiley & Sons: New York, NY, **1967**; Vol. 5, 492p.

[18] Colthup, N. B.; Daly, L. H.; Wiberley, S. E. *Introduction to Infrared and Raman Spectroscopy*; Academic Press: New York, NY, **1964**.

[19] El Khaldy, A. A. S.; Abushanab, A. M.; Alkhair, E. A. Synthesis and Antimicrobial Studies of Bis(O,O′-Dialkyl and Alkylene Dithiophosphoric Acid) Adducts of Diphenyl Diselenide. *Appl. Organomet. Chem.* **2011**, *25*, 1–7. DOI: 10.1002/aoc.1791.

[20] El Khaldy, A. A. S.; Okafor, F.; Shanab, A. M. A. Synthesis, Spectral and Antimicrobial Studies of Bis (Cyclopentadienyl) Titanium (IV) Bis(*O,O'*-Dialkyl and Alkylenedithiophosphate) Complexes. *IJOC* **2014**, *04*, 339–346. DOI: 10.4236/ijoc.2014.45037.

[21] Nizamov, I. S.; Sofronov, A. V.; Al'metkina, L. A.; Musin, R. Z.; Cherkasov, R. A. Synthesis of Optically Active *O,O*-Di-L-(−)- and *O,O*-Di-D-(+)-Menthyldithiophosphoric Acids and Their Ammonium Salts. *Russ. J. Gen. Chem.* **2010**, *80*, 1722–1723. DOI: 10.1134/S1070363210080268.

[22] Nizamov, I. S.; Gabdullina, G. T.; Nizamov, I. D.; Nikitin, Y. N.; Al'metkina, L. A.; Cherkasov, R. A. Bisaryldithiophosphonic Acids: Synthesis and Their Reactions with Organyl Chlorosilanes, Germanes, Stannanes and Plumbanes. *Phosphorus Sulfur Silicon Relat. Elem.* **2010**, *185*, 732–742. DOI: 10.1080/10426500902930142.

[23] Buckler, R. A.; Mitchell, M. T.; Peahota, M. M.; Gallaghe, J. C. Beta-Lactams and Tetracyclines. In *Side Effects of Drugs Annual*; Ray, S. D., Ed.; Elsevier B.V.: Amsterdam, **2018**, Vol. 40, pp 1–650.

[24] Kuchen, W.; Mahler, H. F. Über 2.2'-Biphenylylenphosphorsäuren Und Die Gaschromatographische Trennung Von Lewis-Basen an Bis(2.2'-Biphenylylendithio phosphato)Nickel(II). *Z. Naturforsch. B.* **1978**, *33*, 1049–1050. DOI: 10.1515/znb-1978-0921.

[25] Korytnyk, W. J. A Seven-Membered Cyclic Ketal of Pyridoxol. *J. Org. Chem.* **1962**, *27*, 3724–3726. DOI: 10.1021/jo01057a532.