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Synthesis and Characterization of the New Ambidentate *O*-Cholesteryl-*O*-phenyl Phosphorothioate Ligand and its Organoarsenic Derivatives of Phenoxarsin-10-yl and Phenothiarsin-10-yl Phosphorothioate

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ABSTRACT: *A new anionic phosphorothioate ligand that incorporates the bioactive cholesteryl group was obtained (***2***), Na(RR′P(S)O; R, O-phenyl; R′, O-cholesteryl) from the phenylphosphoramidate (***1***) and NaH in dioxane. In order to test the coordination ability of* **2,** *two organoarsenic derivatives were prepared,* $O(C_6H_4)_2AsS(O)PRR'$ (**3**) *and* $S(C_6H_4)_2AsS(O)PRR'$ (**4**) *by reacting* **2** *with 10-chlorophenoxarsine or 10-chlorophenothiarsine. Compounds* **2, 3**, *and* **4** *were characterized by elemental microanalysis, IR, multielement NMR (*^1H, ^{13}C, *and* ^{31}P*), and mass spectrometry. The spectroscopic data suggest that the ligand is bonded to the arsenic only through the sulfur donor atom in both organoarsenic derivatives.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:6–10, 2000

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INTRODUCTION

The chemistry of phosphorothioate, $[R_2P(O)SR']$, derivatives has been studied extensively [1–8]. Some of these compounds have important chemical and biochemical implications [1,6–8]. For example, the development of phosphorothioate-linked deoxyoligonucleotides has emerged as an important new class of drugs against diseases like acquired immunodeficiency syndrome (AIDS) [2,3]. These phosphorothioate oligomers have shown desirable characteristics such as resistance toward nucleases and the retention of the ability to form stable duplexes with natural RNA or DNA, and therefore they could be used as steric blocks against gene expressions [2,4,5]. Furthermore, much attention has been focused on the application of dialkylphosphorothioates in the stereospecific synthesis of P-chiral isotopomeric phosphates [6,7].

The coordination chemistry of dithiophosphorus ligands is well established. The coordination patterns of the metal and organometallic complexes with such ligands are highly diverse, ranging from simple situations as monodentate, symmetrical or

asymmetrical bidentate bonding to polymetallic systems, or even the formation of ring bridges [9–10]. It is quite surprising that in spite of the biological and chemical implications of the phosphorothioate entity, the corresponding coordination chemistry is much less known [13–16].

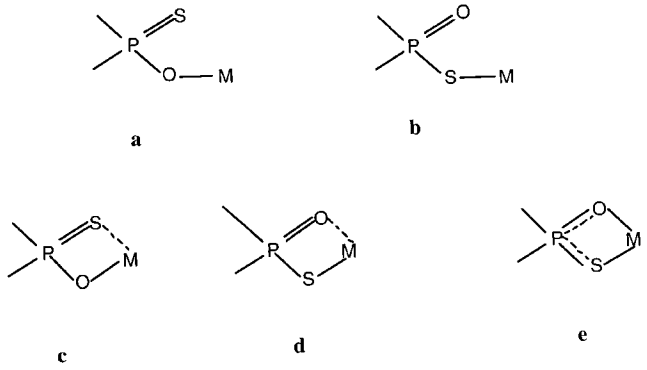
As depicted in Scheme 1, the $[R_2P(O)S]^-$ anion is an ambident nucleophile and can interact through either the oxygen **(a)** [8, 11–12] or sulfur atom **(b)** [13] with a single metal or an organometallic center, acting in these cases as a monodentate ligand. If both donor atoms are coordinate to the center, it can act as an anisobidentate ligand with primary bonds to oxygen **(c)** or to sulphur **(d)**, or as an isobidentate ligand **(e)** [14]. It is also possible that the ligand interacts in various bridging patterns resulting in bimetallic or even trimetallic compounds [15–16]; however, the coordination preferences for a specific metallic center are still not well known.

We report here the synthesis and characterization of a particular phosphorothioate ligand, one that incorporates a bioactive group, *O*-cholesteryl, **2**: Na[S(O)P RR′]; R, *O*-phenyl; R′, *O*-cholesteryl, which was obtained from the phenylphosphoramidate **(1)** that was recently synthesized as the corresponding diastereosomeric mixture [17]. In order to test the coordination ability of this new ligand toward an organometallic center, we prepared two organoarsenic (III) derivatives: the phenoxarsin-10-yl-*O*-cholesteryl-*O*-phenyl phosphorothioate (**3**: $O(C_6H_4)_2AsOSPRR'$) and the phenothiarsin-10-yl-*O*-cholesteryl-*O*-phenyl phosphorothioate (**4**: $S(C_6H_4)_2AsOSPRR'$). The phenoxarsine and phenothiarsine rings form stable derivatives with dithio ligands that are interesting from the structural point of view in relation to the variation of the dihedral angle (butterfly angle) between the two C_6XAs (X = O, S) entities [18,19].

RESULTS AND DISCUSSION

The sodium salt of *O*-cholesteryl-*O*-phenyl phosphorothioate (**2**: Na[S(O)PRR′]) was obtained from **(1)** [17] according to known procedures for this type of reaction [20].

The organoarsenic derivatives **3** and **4** were prepared respectively by the reactions, in chloroform, of 10-chlorophenothiarsine and 10-chlorophenoxarsine with **(2)**. The sodium salt and the organoarsenic derivatives were characterized by elemental analyses, IR, multinuclear NMR (^1H, ^{13}C, ^{31}P) and mass spectroscopy. Long-standing solutions of **(3)** and **(4)** were unstable, and crystal-growing attempts resulted in the decomposition to the phenoxarsine or phenothiarsine oxides.



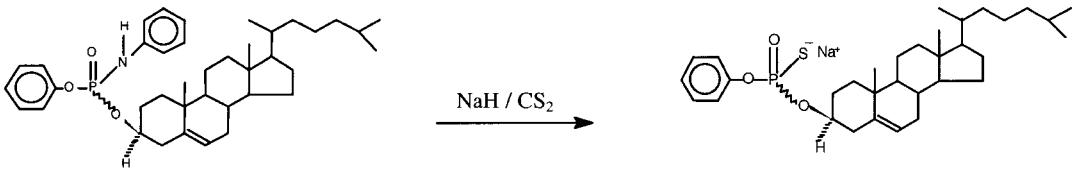
SCHEME 1

Spectroscopic Data

Relevant IR bands are listed in Table 1 and compared with other data for corresponding *O*- and *S*-alkyl esters of monothiophosphinic acids, their sodium and ammonium salts, and some other analogs. The analysis of the infrared spectra was focused on the ν(PO) and ν(PS) stretching vibrations, such vibrations having proved to be useful in order to establish the coordination pattern of the monothiophosphorus ligands [12]. The absence of strong intensity bands in the regions characteristic of single P–O bonds (1040–990 cm^{-1}) and of double P=S bonds (630–580 cm^{-1}), along with the presence of intense vibrations in the range 570–510 cm^{-1} and 1200–1180 cm^{-1}, suggest that the primary coordination of the monothiophosphato ligand is through the sulfur atom (Table 1).

Therefore, from IR vibrational data, it is reasonable to propose that the phosphorothioato ligand is attached to the arsenic atom through an As–S bond in both arsenic derivatives (Figure 1). An anisobidentate behavior (chelate or bridging) of the ligand can not be proposed because that behavior implies a shift to lower wave numbers of the ν(P=O) band, owing to the delocalization of the π-electron pair. This feature was observed in $Ph_2Sb[OSPPh_2]$ [21], where the assigned ν(P=O) vibration in the IR spectrum presents an intermediate value between those expected for the single and double phosphorus-oxygen bond.

The mass spectra of **(3)** and **(4)** show the corresponding molecular ion [800 **(3)** and 816 **(4)** *m/z*]. The base peak in both spectra corresponds to the ions $X(C_6H_4)_2As^+$ (243 **(3)** and 250 **(4)** *m/z*). There are fragments arising from the ligand, that is, $RR'POS^+$ (557 *m/z*), $RPOS^+$ (173 *m/z*), RPO^+ (141 *m/z*), $R'PO^+$ (433 *m/z*). In addition, characteristic ion fragments for both phenoxarsine and phenothiarsine entities were observed, that is, $C_{12}H_8O^+$ (168 *m/z*), $C_{12}H_8S^+$ (184 *m/z*), $C_{11}H_7As^+$ (214 *m/z*) as well as $C_{11}H_7^+$ [22].



EQUATION 1

TABLE 1 Infrared Data for **2, 3, 4** and Related Compounds[a]

Compound	*ν (P-O)*	*ν (P···O)*	*ν (P=O)*	*ν (P-S)*	*ν (P···S)*	*ν (P = S)*	*Ref.*
Na[OSPRR′]		1028.2 s			560 m		[b]
$O(C_6H_4)_2AsOSPRR'$			1250 s	540 s			[b]
$S(C_6H_4)_2AsOSPRR'$			1230 s	521 s			[b]
$Ph_2P(O)SMe$			1200s	568s			23
$Ph_2P(S)OMe$	1027vs					635s	23
$Me_2P(O)SMe$			1184s	510s			24
$Me_2P(S)OMe$	1038s					581s	24
$Na[OSPMe_2]$		1075 s			562s		25
$Ph_3Sn[OSPPh_2]$		1063 s			595 s		12
$Ph_3Sn[OSPEt_2]$		1100 s			535 m		12
$NH_4[OSPPh_2]$		1045 s			628 vs		21
$Ph_2Sb[OSPPh_2]$		1050vs			593vs		21

[a] ν (P-O) 1040-990 cm^{-1}; ν (P=O) 1200–1180 cm^{-1}; ν (P-S) 570-510 cm^{-1}; ν (P=S) 630–580 cm^{-1}.
[b] This work.

The ^1H and ^{13}C NMR spectra confirm the identity of the obtained compounds. The ^{31}P NMR spectra of compounds **2–4** are seen as singlets. This situation could be related to the presence of only one diastereoisomer in such compounds, but through X-ray single crystal data it is known that the starting material **1** is a diastereosomeric mixture with a NMR ^{31}P singlet (−3.11 ppm). The ^{31}P chemical shift of the dialkylmonothiophosphinate has been used to indicate the coordination mode of the $[R_2PSO]^-$ ligands, that is, interaction with primary bonds through the oxygen **(a)** or the sulfur atom **(b)**, or a situation involving both chalcogen atoms **(e)** [12] (cf. Scheme 1). The values of the resonances of **3** and **4** are in the range for the S-R species and are also consistent with the IR spectroscopy data. A comparison of the ^{31}P chemical shifts of our compounds with some analogous derivatives is given in Table 2.

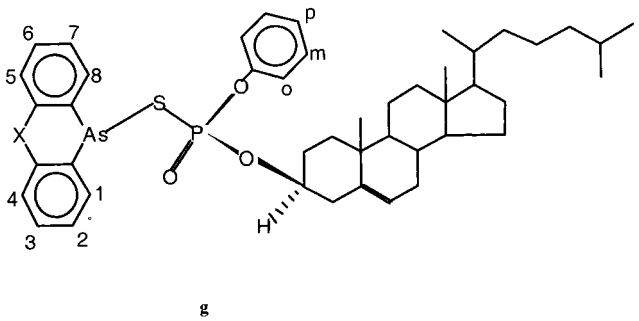


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FIGURE 1 The proposed structure for organoarsenic derivatives, **3** (X = O) and **4** (X = S).

EXPERIMENTAL

Column chromatography and thin layer chromatography (TLC) were performed on silica gel 60, 230–

TABLE 2 ^{31}P NMR Data for **2, 3, 4** and Related Compounds[a]

Compounds	*δ [P(=S)O]*	*δ [PSO]*	*δ [P(=O)S]*	*Ref.*
Na[OSPRR′]		50.16		[b]
$O(C_6H_4)_2AsOSPRR'$			22.57	[b]
$S(C_6H_4)_2AsOSPRR'$			23.22	[b]
$Me_2P(S)OH$	87.9			26
$Me_2P(S)OMe$	94.3			26
$Me_2P(O)SMe$			45.9	27
$Ph_2P(O)SMe$			42.8	27
$Na[OSPMe_2]$		63.9		12
$Na[OSPEt_2]$		67.9		12
$NH_4[OSPPh_2]$		58.1		12

[a] ($R_2P(=S)O$- $\delta > 70$ ppm), ($R_2P(=O)S$- $\delta < 45$ ppm), ([R_2PSO] 70 ppm $> \delta >$ 45 ppm).
[b] This work.

400 mesh, and on HPTLC plates from E. Merck. All reagents and solvents were of commercial grade and were thoroughly dried and distilled before use. The starting materials were prepared according to methods in the literature ($O(C_6H_4)_2AsCl$ [18], $S(C_6H_4)_2AsCl$ [19]). Elemental analyses (C, H, P) were performed by Galbraith Laboratories, Inc. (Knoxville, TN). IR spectra (4000–200 cm^{-1}, KBr discs) were recorded on a Nicolet FT-IR Magna 750 spectrometer. FAB(+) mass spectra on a JEOLSX-102A instrument. The ^1H, ^{13}C, and ^{31}P NMR spectra were obtained in $CDCl_3$ solution at room temperature on a Varian VXR-300S spectrometer operating at 300, 75.4, and 121.4 MHz, respectively. TMS and H_3PO_4 85% were used as external standards.

The Sodium Salt of O-Cholesteryl-O-Phenyl Phosphorothioate, Na[S(O)PRR'] (R = O-phenyl; R' = O-cholesteryl), **2**

To a suspension of NaH (0.272 g, 11.33 mM) in 20 mL of dioxane was added dropwise a solution of the corresponding *O*-cholesteryl-*O*-phenyl-*N*-phenylphosphoramidate [17] (**1**: 1 g, 1.616 mM) in dioxane at 50°. The reaction was accompanied by the evolution of hydrogen and the formation of a white precipitate. This mixture was stirred at room temperature for the next hour and then CS_2 (4 mL) was added in small portions over a period of 15 minutes. After an hour of stirring at room temperature, the solvent was evaporated and the residue was shaken with 50 mL of a chloroform-hexane (1:5) mixture. The resulting precipitate was filtered off to give the white solid **(2)** (0.8 g, 85.19%). $[\alpha]_D^{28} = -31$ (c = 2, EtOH), ^1H NMR ($CDCl_3$, δ, 299.94 Mhz) 0.66 (s, 3H), 0.85 (d, 6H, 6.6 Hz), 0.90 (d, 3H, 6.3 Hz), 0.97 (s,3H), 1.10–2.61 (m, 28H), 4.26 (m, 1H), 5.26 (d, 1H, 5.22 Hz), 6.96 (dd, 1H, POC_6H_5(*p*-H), 8.16Hz, 3.84Hz), 7.18 (dd, 2H, POC_6H_5(*m*-H), 7.41Hz, 6.87Hz), 7.26 (dd, 2H, POC_6H_5(*o*-H), 7.41Hz, 4.14Hz); ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 10.6, 17.5, 18.1, 19.7, 21.3, 21.6, 22.4, 23.0, 26.6, 26.9, 28.9, 30.6, 34.4, 34.8, 35.2, 35.9, 39.1, 39.4, 41.0, 48.8, 54.7, 55.4, 74.5, 121.1, 139.6 ppm. Anal Calcd. for $C_{33}H_{50}O_3SPNa$: C, 68.27; H, 8.62; P, 5.34; Found: C, 68.5; H, 8.76; P, 5.38. Major peaks in the IR spectrum (KBr disc, cm^{-1}) are: 3030s, 2990s, 1610ms, 1028s, 560m.

Phenoxarsin-10-yl-O-Cholesteryl-O-Phenyl Phosphorothioate **3**

A solution containing stoichiometric amounts of $O(C_6H_4)_2AsCl$ (0.119 g, 0.429 mM) and **2** (0.25 g, 0.43 mM) in $CHCl_3$ (20 mL) was stirred under reflux for 2 hours. The reaction mixture was filtered to remove the resulting NaCl. The clear filtrate was dried over anhydrous Na_2SO_4, and the solvent was evaporated in vacuum. The remaining solid product was recrystallized from $CHCl_3$-*n*-hexane, m.p. = 120°C. (0.3 g, 72%) $[\alpha]_D^{28} = -32$ (c = 2, $CHCl_3$), ^1H NMR ($CDCl_3$, δ, 299.49 MHz): 0.64 (s, 3H), 0.85 (d, 6H, 6.6 Hz), 0.91 (d, 3H, 6.6 Hz), 0.96 (s,3H), 1.10–2.41 (m, 28H), 4.21 (m, 1H), 5.31 (dd, 1H, 5.4 Hz, 5.1 Hz), 7.10 (ddd, 2 H^2, H^7, 9.10Hz, 6.90Hz, 3.00Hz), 7.16 (ddd, 2 H^4,H^5, 7.41Hz, 4.50Hz), 7.20–7.25 (m, 5 H^3, H^6 + POC_6H_5(*m*- and *p*-H)], 7.27 (ddd, 2 H^1, H^8, 8.10Hz, 3.30Hz), 7.40 (dd, 2H, POC_6H_5(o-H), 7.20Hz, 2.1Hz); ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 11.8, 18.7, 19.1, 21.0, 22.5, 22.7, 23.8, 24.3, 28.1, 29.4, 31.8, 35.7, 36.2, 36.8, 39.4, 39.6, 42.2, 49.9, 56.1, 56.7, 79.2, 120.9, 139.3, 118.3, 123.0, 123.8, 125.0, 129.5, 132.4, 135.2, 150.5, 154.1 ppm. Anal Calcd. for $C_{45}H_{58}PO_4AsS$: C, 67.5; H, 7.25; P, 3.87; Found: C, 67.8; H, 7.44; P, 3.76. Major peaks in the IR spectrum (KBr disc, cm^{-1}) are 3030s, 2990s, 1610ms, 1250s, 540s. Yield 78%.

Phenothiarsin-10-yl-O-Cholesteryl-O-Phenyl Phosphorothioate **4**

This compound was prepared from $S(C_6H_4)_2AsCl$ (0.126 g, 0.43 mM) and **2** in $CHCl_3$ (20 mL) following the procedure described for **3**, m.p. = 195°C. (0.27 g, 65%). $[\alpha]_D^{28} = -30$ (c = 2, $CHCl_3$), ^1H NMR ($CDCl_3$, δ, 299.49 MHz): 0.534 (s, 3H), 0.73 (d, 6H, 6.6 Hz), 0.78 (d, 3H, 6.3 Hz), 0.85 (s,3H), 1.0–2.4 (m, 28H), 4.2 (m, 1H), 5.2 (d, 1H, 5.1 Hz), 7.0 (ddd, 2 H^2,H^7, 6.91 Hz, 4.50 Hz), 7.08 (ddd, 2 H^4, H^5 7.41 Hz, 4.50 Hz), 7.10–7.20 (m, 5 H^3, H^6 + POC_6H_5(*m*- and *p*-H)], 7.44 (ddd, 2 H^1, H^8, 8.10Hz, 3.30Hz), 7.70 (dd, 2H, POC_6H_5(o-H), 7.20Hz, 1.80Hz); ^{13}C NMR ($CDCl_3$, δ, 75 MHz): 11.4, 18.3, 18.8, 20.5, 22.1, 22.4, 23.3, 23.8, 27.5, 27.7, 31.3, 31.4, 35.3, 35.7, 35.9, 36.4, 39.0, 39.2, 41.8, 49.5, 55.6, 56.2, 79.2, 120.3, 138.8, 122.6, 124.7, 128.2, 126.9, 129.2, 129.7 136.8, 150.1 ppm. Anal Calcd. for $C_{45}H_{58}PO_3AsS_2$: C, 66.17; H, 7.10; P, 3.79; Found: C, 67.2; H, 7.0; P, 3.24. Major peaks in the IR spectrum (KBr disc, cm^{-1}) are: 3030s, 2990s, 1610ms, 1230s, 520s. Yield 62%.

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