

Synthesis, Structural Study, and In Vitro Trypanocidal and Antitumour Activities of Tetrakis(3-methoxypropyl)tin and (3-Methoxypropyl)tin Chlorides

Tomáš Lébl,^[a] Aleš Smička,^[a] Jiří Brus,^[b] and Clemens Bruhn^[c]

Dedicated to Professor Jaroslav Holeček on the occasion of his 70th birthday

Keywords: Chelates / Drug research / O ligands / Structure elucidation / Tin

A set of four water-soluble (3-methoxypropyl)stannanes of general formula $(\text{CH}_3\text{OCH}_2\text{CH}_2\text{CH}_2)_x\text{SnCl}_{4-x}$, where $x = 4$ (**1**), $x = 3$ (**2**), $x = 2$ (**3**), and $x = 1$ (**4**), was prepared. For **3** and **4**, which were isolated in the crystalline state, it was shown by X-ray diffraction that the tin atom is coordinated in distorted octahedral and trigonal-bipyramidal geometries, respectively (i.e., the oxygen atoms of the 3-methoxypropyl groups were coordinated to the central tin atom in both cases, forming chelates). For all compounds, structures in CDCl_3 and $[\text{D}_6]\text{DMSO}$ solutions were proposed on the basis

of their ^{13}C and ^{119}Sn NMR spectra. In CDCl_3 solution, the degree of donor-acceptor bonding between the central tin atom and oxygen atom of the 3-methoxypropyl substituent was evaluated on the basis of ^{17}O NMR chemical shifts and $^3J(^1\text{H}, ^{119}\text{Sn})$ long-range coupling constants. Compounds **2** and **3** exhibited promising in vitro antitumour and trypanocidal activities.

(© Wiley-VCH Verlag GmbH, 69451 Weinheim, Germany, 2003)

Introduction

Organotin compounds have shown a wide spectrum of biological merits. Their antitumour properties in vitro against a wide panel of tumour cell lines of human origin are fairly well known,^[1] and it has also been proposed that anticancer reagents could also be used against trypanosomal diseases (human sleeping sickness and domesticated live stock diseases).^[2] Recently, it was found that several organotin thiolates exhibit high in vitro levels of activity in comparison with the arsenic derivatives used for chemotherapy.^[3] However, the antitumour and trypanocidal efficiencies of organotin derivatives seem to be limited by their low water solubility.^[4] Particular attention has therefore recently been paid to the synthesis of organotin compounds with higher water solubilities.^[5]

In 1997, Susperregui et al. reported the synthesis and structures of water-soluble [3-(2-methoxy)ethoxy]propyltin

chlorides.^[6] Interesting in vitro and vivo trypanocidal activity was later described for bis[3-(2-methoxy)ethoxy]propyltin dichloride and the corresponding oxide.^[7] Those papers suggest that the replacement of alkyl by alkoxyalkyl substituents could constitute a route to water-soluble organotin derivatives. In order to check whether the replacement of a 1-butyltin moiety, as conventionally used in organotin drug research, by a 3-methoxypropyltin one would deliver water-soluble and biologically active derivatives, (3-methoxypropyl)stannanes of general formula $(\text{CH}_3\text{OCH}_2\text{CH}_2\text{CH}_2)_x\text{SnCl}_{4-x}$ ($x = 1-4$) have been synthesized and structurally characterized, both in the solid state and in solution, and their in vitro antitumour and trypanocidal activities were tested.

Results and Discussion

Synthesis

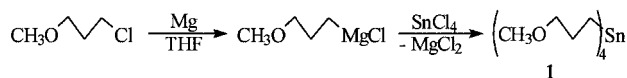
Tetrakis(3-methoxypropyl)tin (**1**) was synthesised as shown in Scheme 1, by treatment of tin tetrachloride with excess (3-methoxypropyl)magnesium chloride (previously prepared from 3-methoxypropyl chloride and magnesium chips in THF). Tetraorganostannane **1** was isolated by vacuum distillation as a colourless liquid in a yield of 92% with respect to SnCl_4 .

^[a] Department of General and Inorganic Chemistry, University of Pardubice, Cs. Legii, 565, 532 10 Pardubice, Czech Republic
Fax: (internat.) + 420-40/603-7068
E-mail: tomas.lebl@upce.cz

^[b] Institute of Macromolecular Chemistry of the Academy of Sciences of the Czech Republic, Heyrovský sq. 2, 16206 Praha 6, Czech Republic
E-mail: brus@imc.cas.cz

^[c] Department of Inorganic Chemistry, Martin-Luther-Universität Halle-Wittenberg, Kurt-Mothes-Straße 2, 06120 Halle (Saale), Germany
E-mail: bruhn@chemie.uni-halle.de

^[†] Suddenly and tragically died on June 19, 2001 in Pardubice



Scheme 1

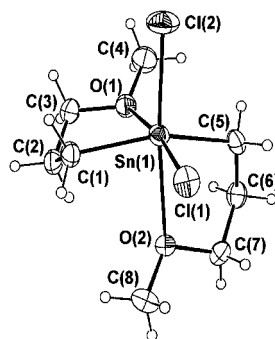
(3-Methoxypropyl)tin chlorides **2–4** were synthesised by means of a Kocheshkov redistribution reaction (Scheme 2),^[8] by treatment of tetraorganostannane **1** with the appropriate amount of tin tetrachloride (3:1, 1:1, and 1:3 for **2**, **3**, and **4**, respectively). Although Kocheshkov reactions usually display low selectivity, the (3-methoxypropyl)tin chlorides **2–4** could be isolated by vacuum distillation in yields of about 95%. Such a high selectivity might be explained by suppression of 3-methoxypropyl group cleavage by intramolecular O→Sn coordination (see below) and consequently lower reactivities in the products **2**, **3**, and **4**.



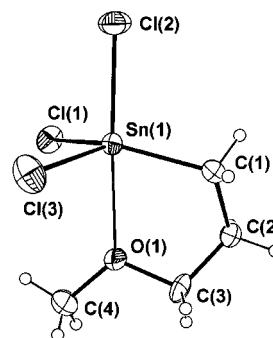
Scheme 2

Solid-State Structures

Only the (3-methoxypropyl)tin chlorides **3** and **4** were isolated in a crystalline state, and their structures were determined by X-ray diffraction (Figure 1 and Figure 2). Selected bond lengths and angles are listed in Table 1 and Table 2, respectively.

Figure 1. Solid-state structure of bis(3-methoxypropyl)tin dichloride (**3**)

Both complexes consist of discrete molecules. For compound **3**, the environment around the central tin atom has a deformed octahedral geometry (skew) with both oxygen

Figure 2. Solid-state structure of (3-methoxypropyl)tin trichloride (**4**)Table 1. Selected bond lengths [Å] and angles [°] for **3**

Sn(1)–O(1)	2.559(4)	Sn(1)–Cl(2)	2.419(2)
Sn(1)–O(2)	2.556(4)	Sn(1)–C(1)	2.136(6)
Sn(1)–Cl(1)	2.432(2)	Sn(1)–C(5)	2.138(6)
C(1)–Sn(1)–C(5)	148.5(2)	C(1)–Sn(1)–Cl(1)	100.3(2)
O(1)–Sn(1)–O(2)	89.4 (1)	C(1)–Sn(1)–Cl(2)	102.5(2)
Cl(1)–Sn(1)–Cl(2)	97.26(7)	C(5)–Sn(1)–Cl(1)	99.7(2)
Cl(1)–Sn(1)–O(1)	84.9(1)	C(5)–Sn(1)–Cl(2)	98.9(2)
Cl(2)–Sn(1)–O(2)	173.4(1)	C(1)–Sn(1)–O(2)	83.2(2)

Table 2. Selected bond lengths [Å] and angles [°] for **4** (values are given for one split layer)

Sn(1)–Cl(1)	2.332(1)	Sn(1)–O(1)	2.394(3)
Sn(1)–Cl(2)	2.390(1)	Sn(1)–C(1)	2.09(3)
Sn(1)–Cl(3)	2.327(1)		
O(1)–Sn(1)–Cl(2)	175.7(1)	Cl(1)–Sn(1)–Cl(2)	95.80(5)
C(1)–Sn(1)–Cl(1)	129.3(9)	Cl(1)–Sn(1)–Cl(3)	102.31(5)
C(1)–Sn(1)–Cl(2)	102.9(6)	Cl(3)–Sn(1)–Cl(2)	98.17(6)
C(1)–Sn(1)–Cl(3)	120.6(9)		

atoms coordinated to the tin atom in a *cis* configuration [O–Sn–O 89.4(1)°]. Two chlorine atoms are also mutually *cis* [Cl–Sn–Cl 97.26(7)°], while two C–Sn bonds are at an angle of 148.5(2)°. The shape of the coordination polyhedron is thus similar to that of the analogous bis[3-(2-methoxy)ethoxy]propyltin dichloride.^[6] The tin atom in **4**, on the other hand, is coordinated as a distorted trigonal-bipyramid with the carbon atom and the two chlorine atoms in the equatorial plane [C–Sn–Cl(1) = 129.3(9), C–Sn–Cl(3) = 120.5(9), Cl(1)–Sn–Cl(3) = 102.31(5)°] and the oxygen atom and the third chlorine atom in axial positions [O–Sn–Cl(2) = 175.7(1)°]. The whole equatorial plane is tilted towards the oxygen atom [C–Sn–Cl(2) = 102.9(6), Cl(1)–Sn–Cl(2) = 95.80(5), Cl(3)–Sn–Cl(2) = 98.17(6)°]. The crystal-state structure of **4** differs from that of the analogous [3-(2-methoxy)ethoxy]propyltin trichloride in that the oxygen atom of one water molecule is used in order to reach an octahedral coordination.^[6]

The Sn–O bond length in the distorted trigonal-bipyramidal geometry of **4** [2.394(40) Å] is slightly shorter than the Sn–O bond lengths found in the distorted octahedral geometry of **3** [2.559(4) and 2.556(4) Å]. This is in agreement with increasing Lewis acidity of the central tin atom. The Sn–O bonds are in both cases shorter than those in the analogous [3-(2-methoxy)ethoxy]propyltin chlorides [2.442(2), 2.65(1), and 2.67(1) Å, respectively].^[6] However, the oxygen atom of the water molecule in [3-(2-methoxy)ethoxy]propyltin trichloride has a significantly stronger bond [Sn–O 2.292(5) Å] than oxygen atoms of chelating alkoxypropyl groups.^[6]

The Sn–C [2.09(3)–2.145(4) Å] and Sn–Cl [2.3274(12)–2.4328(12) Å] bond lengths in compounds **3** and **4** are similar to those found in the analogous [3-(2-methoxy)ethoxy]propyltin chlorides [2.127–2.15(2) and 2.351–2.426(6) Å, respectively].^[6] In the trigonal-bipyramidal geometry of **4**, the apical chlorine atom has a slightly weaker bond to the central tin atom [Sn–Cl(2) = 2.3904(12) Å] than the equatorial ones [Sn–Cl(1) = 2.3317(14), Sn–Cl(3) = 2.3274(12) Å], due to the *trans* effect of the coordinated oxygen atom of the 3-methoxypropyl group.

The sixfold- and fivefold-coordinated tin atoms observed for (3-methoxypropyl)tin chlorides **3** and **4** in the crystalline state are in accordance with ¹¹⁹Sn solid-state NMR chemical shifts of $\delta = -133$ and -157 ppm, respectively. Moreover, the ¹¹⁹Sn CP/MAS spectrum of **3** showed a 1:2:4:1:4:4 splitting pattern due to the interaction of ¹¹⁹Sn nuclei with two equivalent ^{35/37}Cl spins (Figure 3).^[9]

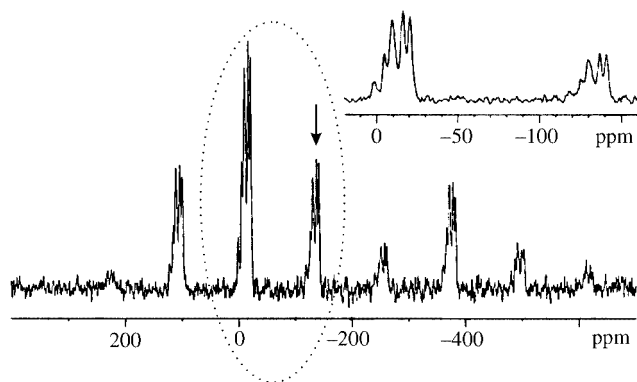


Figure 3. ¹¹⁹Sn CP/MAS NMR spectrum of bis(3-methoxypropyl)tin dichloride (**3**); the vertical arrow indicates the centre band

Structures in Solution

Methoxypropylstannanes **1–4** were characterised in CDCl₃ solution by ¹H NMR spectroscopy (see Exp. Sect.). In order to evaluate these solution structures both in non-coordinating and in coordinating solvents, their ¹³C, ¹⁷O, and ¹¹⁹Sn NMR spectra were measured in CDCl₃ and [D₆]DMSO. All relevant NMR parameters are summarised in Table 3. The values of the $J(^1\text{H}, ^{119}\text{Sn})$ coupling constants obtained from gradient-assisted 1D ¹H, ¹¹⁹Sn HMQC and 2D ¹H, ¹¹⁹Sn J-HMBC spectra are given in Table 4.^[10] The

numbering scheme used for the hydrogen and carbon atoms is given in Scheme 3.

The ¹¹⁹Sn chemical shift values of the (3-methoxypropyl)stannanes **1–4** in CDCl₃ solution are shifted upfield [$\Delta\delta(^{119}\text{Sn}) = 1.3, 103.8, 234.9$, and 132.4 ppm, respectively] with respect to analogous 1-butyltin compounds.^[11] The ¹¹⁹Sn chemical shifts were found not to be concentration-dependent, and so only intramolecular side-arm donation can be assumed. In the case of tetra-organotin compound **1**, the value of $\Delta\delta(^{119}\text{Sn})$ is negligible. Accordingly, O→Sn interaction, if present, must be very weak. The tin atom is coordinated as a slightly distorted tetrahedron, as is evident from $^1J(^{13}\text{C}, ^{119}\text{Sn}) = 324.5$ Hz (average angle C–Sn–C 107°).^[12] For triorganotin compound **2**, the significant upfield shift [$\Delta\delta(^{119}\text{Sn}) = 103.8$ ppm] indicates a pentacoordinated tin atom. The value of $^1J(^{13}\text{C}, ^{119}\text{Sn}) = 434.6$ Hz (average angle C–Sn–C 118°) shows that coordination polyhedron of **2** has a *trans*-trigonal-bipyramidal shape.^[12] Consequently, one oxygen atom has to be coordinated to the central tin atom while the other two are not. However, only one set of signals for the 3-methoxypropyl groups was observed in the ¹H and ¹³C NMR spectra at room temperature and in [D₈]toluene at 180 K. This indicates the existence of an exchange that is fast on the NMR timescale even at 180 K. In the case of (3-methoxypropyl)tin chlorides **3** and **4**, the moderate differences between the ¹¹⁹Sn chemical shifts in CDCl₃ solution and in the solid state ($\delta = 24$ and 18 ppm, respectively) show that the distorted octahedral (Figure 2) and trigonal-bipyramidal (Figure 3) structures determined by X-ray diffraction are retained upon dissolution in CDCl₃.^[9] The agreement of the C–Sn–C angles as calculated from the coupling constant $^1J(^{13}\text{C}, ^{119}\text{Sn}) = 731.6$ Hz (148°) and as determined by X-ray diffraction [148.5(2)°] confirms the suitability of the equation used for calculation.^[12]

The values of $\delta(^{17}\text{O})$ are shifted downfield as the Lewis acidity of the central tin atom increases (Table 3). Since the oxygen atom in the 3-methoxypropyl substituent is regarded as a pure σ -donor, this denotes an increasing degree of donor-acceptor bonding between the central tin atom and the oxygen atom in the organic substituent.^[13] The values of the $^3J(^1\text{H}, ^{119}\text{Sn})$ long-range coupling constants between the ¹¹⁹Sn nucleus and the CH₃O protons also increase with the same trend (Table 4). On the assumption that the contributions of the scalar coupling pathways through the CH₃O→Sn coordinative bond [$^3J(^1\text{H}, ^{119}\text{Sn})$] and through the covalent bonds of 3-methoxypropyl chain [$^6J(^1\text{H}, ^{119}\text{Sn})$] have the same signs, their sum and the increasing strength of CH₃O→Sn coordinative bonding could be responsible for this increasing trend.

For (3-methoxypropyl)tin chlorides **2–4** in deuteriochloroform solutions, the values of $^2J(^{119}\text{Sn}, ^{13}\text{C})$ are higher and the values of $^3J(^{13}\text{C}, ^{119}\text{Sn})$ lower than the corresponding values for analogous 1-butyltin chlorides. In the case of **3**, $^2J(^{13}\text{C}, ^{119}\text{Sn})$ was even higher than $^3J(^{13}\text{C}, ^{119}\text{Sn})$ (i.e., opposite to the trend usually observed for 1-butylstannanes (Table 3).^[11] It is likely that this represents the sum of two scalar coupling pathways contributions – through the co-

Table 3. ^{13}C , ^{17}O , and ^{119}Sn NMR spectral parameters for (3-methoxypropyl)stannanes **1–4** in non-coordinating solvent (CDCl_3) and in coordinating solvent ($[\text{D}_6]\text{DMSO}$) at 300 K

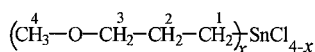
Compound	Solvent	$\delta(^{13}\text{C})$ [ppm] ($J(^{13}\text{C}, ^{119}\text{Sn})$ [Hz])				$\delta(^{119}\text{Sn})$ [ppm]	$\delta(^{17}\text{O})$ [ppm]
		C1	C2	C3	C4		
1	CDCl_3	4.9 (324.5)	26.7 (18.6)	76.0 (59.3)	58.4 (–)	–4.3	–17.0
	$[\text{D}_6]\text{DMSO}$	5.2 (325.3)	26.2 (19.3)	75.2 (52.3)	57.7 (–)	–1.2	–
2	CDCl_3	14.7 (434.6)	25.6 (26.5)	74.7 (55.7)	58.5 (–)	49.0	–15.8
	$[\text{D}_6]\text{DMSO}$	15.6 (456.5)	25.3 (27.2)	74.3 (65.2)	57.9 (–)	27.4	–
3	CDCl_3	26.6 (731.6)	24.5 (42.7)	72.4 (34.0)	58.6 (–)	–108.6	–13.0
	$[\text{D}_6]\text{DMSO}$	30.8 (840.4)	24.7 (44.7)	73.0 (95.1)	58.2 (–)	–170.5	–
4	CDCl_3	26.0 (845.2)	23.8 (67.0)	70.2 (79.3)	58.5 (–)	–138.5	–3.0
	$[\text{D}_6]\text{DMSO}$	^[a]	25.6 (62.5)	73.8 (229.6)	57.8 (–)	–445.6	–

^[a] Not obtained, probably due to the existence of a dynamic equilibrium (Scheme 4).

Table 4. $J(^1\text{H}, ^{119}\text{Sn})$ coupling constants for (3-methoxypropyl)stannanes **1–4** in CDCl_3

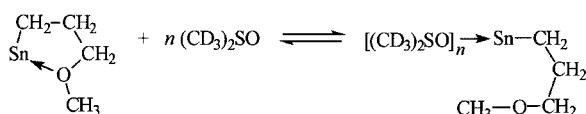
Compound	$J(^1\text{H}, ^{119}\text{Sn})$ [Hz]			
	H1 ^[a]	H2 ^[a]	H3 ^[b]	H4 ^[b]
1	51.2	47.8	^[c]	0.52
2'	60.8	86.2	1.31	^[d]
3	95.9	195.8	7.73	1.86
4	104.9	254.2	5.07	2.24

^[a] Obtained from the ^1H , ^{119}Sn HMQC spectra. ^[b] Obtained by 2D ^1H , ^{119}Sn J-HMBC. ^[c] Not obtained due to an overlap. ^[d] Not obtained, probably due to the existence of a fast dynamic equilibrium as discussed in the text.



Scheme 3

valent bonds of the 3-methoxypropyl chain and through the coordinative $\text{O} \rightarrow \text{Sn}$ bond – of opposite signs in this case. In $[\text{D}_6]\text{DMSO}$ solution, the values of $\delta(^{119}\text{Sn})$ and the coupling constants $J(^{13}\text{C}, ^{119}\text{Sn})$ of compounds **1–4** and their 1-butyltin analogues are not very different.^[11] It therefore seems highly probable that the oxastannacycles are cleaved because of an equilibrium in which the donor oxygen atoms of the 3-methoxypropyl substituents are replaced by the stronger Lewis base $[\text{D}_6]\text{DMSO}$ (Scheme 4). Unfortunately, this dynamic equilibrium disables the measurement of ^1H , ^{119}Sn J-HMBC and the determination of long-range $J(^1\text{H}, ^{119}\text{Sn})$ coupling constants.



Scheme 4

Trypanocidal and Antitumour Activities

All four (3-methoxypropyl)stannanes **1–4** have moderate water solubility (0.6, 3.0, 4.0, and 6.6 g/L H_2O at 25 °C, respectively). For compounds **1**, **2**, and **3**, trypanocidal activity tests afforded MEC values of 24000, 3300, and 3700 nM, respectively. Compound **4** showed no trypanocidal activity. The trypanocidal activity of compounds **2** and **3** is slightly higher than that of bis[3-(2-methoxy)ethoxy]propyltin dichloride and oxide (5900 and 6800 nM, respectively) but is significantly lower than those of the arsenic derivatives Arsobal and Cymelarsan (5 and 0.6 nM, respectively).^[7] Compounds **1** and **4** exhibited no antitumour activity ($\text{ID}_{50} > 62500$). For compounds **2** and **3** the ID_{50} values were in the ranges of 1259–2443 and 9200–31512 ng/mL, respectively, and hence markedly below the standard of the clinically used drugs cisplatin ($\text{ID}_{50} = 169\text{--}3269$ ng/mL), doxorubicin ($\text{ID}_{50} = 8\text{--}199$ ng/mL) and taxol ($\text{ID}_{50} < 3$ ng/mL).

The very low activity and the complete absence of activity observed for compounds **1** and **4** are in accord with the usually low biological activities of tetra- and monoorganotin compounds.^[14] The antitumour and trypanocidal activity of (3-methoxypropyl)tin chlorides **2** and **3** are rather poor, but still promising. It can be concluded that the replacement of a 1-butyl substituent by a 3-methoxypropyl moiety can considerably increase the water solubility of organotin derivatives, whereas antitumour and trypanocidal activity is preserved. The substitution of chlorine atoms by moieties that might improve targeting of the parasite and/or tumours could also improve the activity.

Experimental Section

Preparative Techniques and Starting Materials: All reactions were carried out under argon by standard Schlenk techniques.^[15] THF was distilled from sodium benzophenone ketyl. Methanol was dried by distillation from CH_3ONa . Tin tetrachloride was distilled prior to use. All other starting compounds were used without further purification.

Preparation of 3-Methoxypropyl Chloride: A solution of CH_3ONa in methanol (5 M, 64 mL, 0.32 mol) was added dropwise over 3 h, with vigorous stirring, to 1-bromo-3-chloropropane (50.0 g, 0.32

mol). The reaction mixture was stirred overnight at room temperature and then heated under reflux as long as the solution remained basic. Afterwards, water (150 mL) was added and the obtained solution was extracted with diethyl ether (3 × 100 mL). The organic layers were combined and dried with Na₂SO₄. The diethyl ether was removed by distillation. Rectification of the residue afforded 3-methoxypropyl chloride (16.2 g, yield 47%) as a colourless liquid, boiling at 110–112 °C. ¹H NMR (CDCl₃): δ = 2.09 (m, 2 H), 3.42 (s, 3 H), 3.58 (t, ³J_{H,H} = 5.9 Hz, 2 H), 3.70 (t, ³J_{H,H} = 6.5 Hz, 2 H) ppm. ¹³C NMR (CDCl₃): δ = 32.61, 41.82, 58.68, 69.01 ppm.

Preparation of Tetrakis(3-methoxypropyl)tin (1): A solution of 3-methoxypropyl chloride (10.0 g, 0.92 mol) in THF (15 mL) was added to Mg chips (2.2 g, 0.92 mol, activated by I₂). About 10% of the solution was added at once and the reaction was initiated by addition of 2 drops of 1,2-dibromethane. The remaining solution was then added dropwise in such a manner as to maintain the reaction mixture at reflux. The reaction mixture was then heated under reflux for 30 min. After the mixture had then been cooled to –50 °C, neat SnCl₄ (5.2 g, 20 mmol) was added dropwise with vigorous stirring. The reaction mixture was left to warm to room temperature and then heated under reflux for 5 h. Water (10 mL) was added and the resulting precipitate was filtered off and washed with benzene. The THF and benzene solutions were combined and dried with Na₂SO₄, and the solvents were removed by rotary evaporation. The residue was distilled at 3–4 Pa, and **1** (7.6 g, yield 92%) was obtained as a colourless liquid, boiling at 120–126 °C. ¹H

NMR (CDCl₃): δ = 0.73 (m, 8 H), 1.69 (m, 8 H), 3.29 (t, ³J_{H,H} = 6.6 Hz, 8 H), 3.31 (s, 12 H) ppm. C₁₆H₃₆O₄Sn (411.14): calcd. C 46.74, H 8.83, Sn 28.87; found C 46.66, H 8.79, Sn 28.43.

Preparation of (3-Methoxypropyl)tin Chlorides 2–4: A mixture of **1** (1.50 g, 1.23 mmol) and SnCl₄ [0.32 g, 1.23 mmol for (CH₃OCH₂CH₂CH₂)₃SnCl (**2**); 0.95 g, 3.65 mmol for (CH₃OCH₂CH₂CH₂)₂SnCl₂ (**3**); 2.90 g, 11.13 mmol for CH₃OCH₂CH₂CH₂SnCl₃ (**4**)] was heated at 200 °C for 3 h. The resulting (3-methoxypropyl)tin chlorides **2–4** were purified by vacuum distillation.

Compound 2: 1.73 g, yield 95%, colourless liquid, b.p. 114–116 °C/1–2 Pa. ¹H NMR (CDCl₃): δ = 1.20 (t, ³J_{H,H} = 7.7 Hz, 8 H), 1.91 (m, 8 H), 3.34 (s, 12 H), 3.39 (t, ³J_{H,H} = 6.1 Hz, 8 H) ppm. C₁₂H₂₇ClO₃Sn (373.48): calcd. C 38.59, H 7.29, Cl 9.49, Sn 31.78; found C 38.65, H 7.31, Cl 9.73, Sn 31.26.

Compound 3: 2.36 g, yield 96%, colourless crystals, b.p. 128–132 °C/7 Pa, m.p. 80–83 °C. ¹H NMR (CDCl₃): δ = 1.67 (m, 8 H), 2.05 (m, 8 H), 3.44 (s, 12 H), 3.54 (t, ³J_{H,H} = 5.5 Hz, 8 H) ppm. C₈H₁₈Cl₂O₂Sn (335.82): calcd. C 28.61, H 5.40, Cl 21.11, Sn 35.34; found C 28.65, H 5.34, Cl 20.95, Sn 35.67.

Compound 4: 4.22 g, yield 96%, colourless crystals, b.p. 95–100 °C/1 Pa, m.p. 69–71 °C. ¹H NMR (CDCl₃): δ = 2.11 (m, 8 H), 2.21 (m, 8 H), 3.53 (s, 12 H), 3.61 (t, ³J_{H,H} = 5.5 Hz, 8 H) ppm.

Table 5. Experimental details for the X-ray crystal structure determination of **3** and **4**

	3	4
Crystal data		
Empirical formula	C ₈ H ₁₈ Cl ₂ O ₂ Sn	C ₄ H ₉ Cl ₃ OSn
Formula mass	335.81	298.15
Crystal system	monoclinic	monoclinic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>n</i>
<i>Z</i>	4	4
<i>a</i> , <i>b</i> , <i>c</i> [Å]	7.626(1), 15.364(4), 11.499(2)	6.3055(16), 22.325(5), 7.670(2)
β [°]	100.71(2)	113.66(3)
<i>V</i> [Å ³]	1323.7(5)	988.9(4)
<i>D</i> _x [g·cm ^{–3}]	1.685	2.003
λ [Å]	0.71073	0.71073
μ (Mo- <i>K</i> _α) [mm ^{–1}]	2.307	3.328
Temperature [K]	203(2)	220(1)
<i>F</i> (000)	664	568
Crystal size [mm]	0.24 × 0.24 × 0.21	0.30 × 0.21 × 0.19
Data collection		
Scan range θ [°]	2.24–25.0	3.43–26.00
Index ranges	–8 ≤ <i>h</i> ≤ 8, –18 ≤ <i>k</i> ≤ 18, –13 ≤ <i>l</i> ≤ 13	–7 ≤ <i>h</i> ≤ 7, –27 ≤ <i>k</i> ≤ 27, –9 ≤ <i>l</i> ≤ 9
Reflections collected	9170	13196
Independent reflections	2183 (<i>R</i> _{int} = 0.1329)	1879 (<i>R</i> _{int} = 0.0515)
Reflections observed	1998	1754
Refinement		
Refinement method	Full-matrix, least squares on <i>F</i> ²	Full-matrix, least squares on <i>F</i> ²
Parameters refined	118	110
Goodness-of-fit on <i>F</i> ²	1.105	1.318
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> 1 = 0.0706, <i>wR</i> 2 = 0.1130	<i>R</i> 1 = 0.0259, <i>wR</i> 2 = 0.0607
<i>R</i> indices (all data)	<i>R</i> 1 = 0.0784, <i>wR</i> 2 = 0.1198	<i>R</i> 1 = 0.0291, <i>wR</i> 2 = 0.0682
Δρ _{max} ; Δρ _{min} [e·Å ^{–3}]	0.711; –0.786	0.569; –0.541

C₄H₉Cl₃OSn (298.16): calcd. C 16.11, H 3.04, Cl 35.67, Sn 39.81; found C 16.16, H 3.10, Cl 36.20, Sn 39.56.

X-ray Diffraction Measurements: Diffraction experiments were carried out with Mo-K α radiation using a Stoe IPDS diffractometer at 203(2) K (3) and 220(1) K (4). The structures were successfully solved by direct methods (SHELXS-86).^[16] Further refinements were carried out against F² (SHELXL-97).^[17] All non-H atoms were refined with anisotropic displacement parameters, hydrogen atoms were placed in calculated positions and refined according to the riding model. Crystal data and details of data collection and refinement are given in Table 1, Table 2, and Table 5. CCDC-178265 (3) and -178264 (4) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Microanalyses: Microanalyses (C, H, Sn, Cl) were carried out with a Fison EA 1108 instrument in the Microanalytical Laboratory at the University of Pardubice.

NMR Measurements: ¹H, ¹³C, ¹⁷O, and ¹¹⁹Sn NMR spectra were recorded in a 5-mm tuneable probe with a Bruker AMX 360 (¹H: 360.14 MHz; ¹³C: 90.57 MHz; ¹⁷O: 48.82 MHz; ¹¹⁹Sn: 134.28 MHz) and a Bruker AVANCE 500 spectrometer (¹H: 500.13 MHz; ¹³C: 125.77 MHz; ¹¹⁹Sn: 186.48 MHz). ¹H and ¹³C chemical shifts are given in ppm with respect to Me₄Si, and ¹¹⁹Sn chemical shifts with respect to Me₄Sn. The gradient-assisted 1D ¹H, ¹¹⁹Sn HMQC and 2D ¹H, ¹¹⁹Sn J-HMBC spectra were recorded as explained elsewhere,^[10] with the Bruker AVANCE 500 spectrometer. ¹¹⁹Sn CP/MAS NMR spectra were recorded with a Bruker DSX 200 spectrometer equipped with a double-bearing CP/MAS probe at room temperature. The ¹¹⁹Sn chemical shifts were calibrated indirectly with reference to tetracyclohexyltin (δ = -97.35 ppm) and were allocated approximately to the centre of gravity of the signals.

Trypanocidal and Antitumour Screening: The trypanocidal activity tests were carried out in vitro on cultures of *Trypanosoma equiperdum*.^[18] The MEC values indicated for these activities correspond to the minimal efficient concentration that would allow complete depletion of trypanosome population within 24 h. In vitro antitumour screening against seven tumoural cell lines of human origin (A, 498 – a renal cancer, EVSA-T – a breast cancer, H 226 – a non-small cell lung cancer, IGROV – an ovarian cancer, M19 – a melanoma, MCF-7 – a breast cancer, WiDr – a colon carcinoma) were performed in accordance with procedures already described elsewhere.^[19]

Acknowledgments

The financial support from the Ministry of Education, Youth and Sports of the Czech Republic (Project LN 00 A028) and the Grant Agency of the Czech Republic (grant 203/00920) is gratefully acknowledged. We are grateful to Prof. T. Baltz and Prof. C. Giroud for performing the trypanocidal screening and to Prof. M. Gielen for arranging antitumour screening. T. L. and A. S. thank

Prof. Jaroslav Holeček for fruitful discussions about chemistry and life, and all that helped us to finish this paper.

- [1] [1a] M. Gielen, *Coord. Chem. Rev.* **1996**, *151*, 41–51. [1b] D. de Vos, R. Willem, M. Gielen, K. E. van Wingerden, K. Nooter, *Met.-Based Drugs* **1998**, *5*, 179 and literature cited therein.
- [2] S. V. Barrett, M. P. Barret, *Parasitol. Today* **2000**, *16*, 7–9.
- [3] J. Susperregui, A. Petsom, M. Bayle, G. Lain, C. Giroud, T. Baltz, G. Délérís, *Eur. J. Med. Chem.* **1997**, *32*, 123–128.
- [4] G. Atassi, *Rev. Silicon, Germanium, Tin Lead Compd.* **1985**, *8*, 219–235.
- [5] For example: [5a] M. Gielen, *Main Group Met. Chem.* **1994**, *17*, 6. [5b] M. G. Mirisola, A. Pellerito, T. Fiore, G. C. Stocco, A. Cestelli, I. Di Liegro, *Appl. Organomet. Chem.* **1997**, *11*, 499–511. [5c] M. Kemmer, M. Gielen, M. Biesemans, D. de Vos, R. Willem, *Met.-Based Drugs* **1998**, *5*, 189–196.
- [6] J. Susperregui, M. Bayle, J. M. Léger, G. Délérís, M. Biesemans, R. Willem, M. Kemmer, M. Gielen, *J. Organomet. Chem.* **1997**, *545/546*, 559–565.
- [7] J. Susperregui, M. Bayle, G. Lain, Ch. Giroud, T. Baltz, G. Délérís, *Eur. J. Med. Chem.* **1999**, *34*, 617–623.
- [8] [8a] K. A. Kozeshkow, *Ber. Dtsch. Chem. Ges.* **1933**, *66*, 1661–1665. [8b] W. P. Neumann, G. Burkhardt, *Justus Liebigs Ann. Chem.* **1963**, *663*, 11–21.
- [9] R. K. Harris, A. Sebald, D. Furiani, G. Tagliavini, *Organometallics* **1988**, *7*, 388–394.
- [10] [10a] J. C. Martins, M. Biesemans, R. Willem, *Prog. Nucl. Magn. Reson. Spectrosc.* **2000**, *36*, 271–322. [10b] M. Biesemans, J. C. Martins, R. Willem, A. Lyčka, A. Ružička, J. Holeček, *Magn. Reson. Chem.* **2002**, *40*, 65–69.
- [11] [11a] M. Nádvořník, J. Holeček, K. Handlíř, A. Lyčka, *J. Organomet. Chem.* **1984**, *275*, 43–51. [11b] J. Holeček, M. Nádvořník, K. Handlíř, A. Lyčka, *J. Organomet. Chem.* **1986**, *315*, 299–308. [11c] V. Pejchal, J. Holeček, M. Nádvořník, A. Lyčka, *Collect. Czech. Chem. Commun.* **1995**, *60*, 1492–1501.
- [12] The C–Sn–C angles in the 3-methoxypopylstannenes **1–3** were calculated by use of the equation derived for analogous 1-butyltin compounds (A. Lyčka, J. Holeček, *Inorg. Chim. Acta* **1986**, *118*, L15–L16). This approach can be considered appropriate because the values of slope and intercept for linear dependence of C–Sn–C angle and ¹J(¹¹⁹Sn, ¹³C) are dominantly dependent on the type of hybridisation at the carbon atom. For comparison see also: T. P. Lockhart, W. F. Manders, *Inorg. Chem.* **1986**, *25*, 892–895; J. Holeček, K. Handlíř, M. Nádvořník, A. Lyčka, *Z. Chem.* **1990**, *30*, 265–266.
- [13] O. Exner, H. Dahn, P. Pechie, *Magn. Reson. Chem.* **1992**, *30*, 381–386.
- [14] J. M. Barnes, L. Magos, *Organomet. Chem. Rev.* **1968**, *3*, 137–150.
- [15] S. Herzog, J. Dehnert, *Z. Chem.* **1964**, *4*, 1.
- [16] G. M. Sheldrick, *SHELXS-86, A Program for Crystal Structure Solution*, University of Göttingen, Germany, **1986**.
- [17] G. M. Sheldrick, *SHELXL-97, A Program for Crystal Structure Refinement*, University of Göttingen, Germany, **1997**.
- [18] Z. Q. Zhang, C. Giroud, T. Baltz, *Acta Trop.* **1992**, *50*, 101–110.
- [19] [19a] V. T. DeVita Jr., S. Hellman, S. A. Rosenberg, *Cancer: principles and practice of oncology*, 5th ed., Lippincott-Raven Publ., Philadelphia, **1997**. [19b] Y. P. Kepers, G. J. Peters, J. Van Ark-Otte, B. Winograd, H. M. Pinedo, *Eur. J. Cancer* **1991**, *27*, 897–900.

Received June 25, 2002
[102364]