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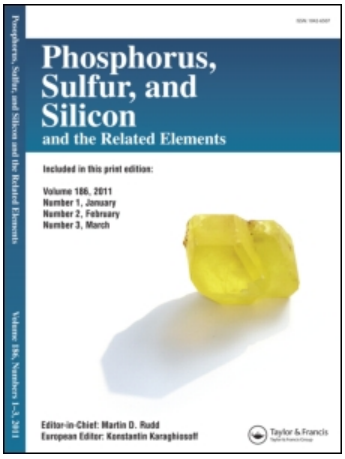

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To cite this Article Xueqing, Song , Zhiqiang, Yang , Guixiang, Su and Xieqinglan(1999) 'Synthesis, Characterization and Anticancer Activity of Some Bis(Germylpropionato-Di-*n*-Butyl) Oxides', Phosphorus, Sulfur, and Silicon and the Related Elements, 150: 1, 367 — 374
To link to this Article: DOI: 10.1080/10426509908546405
URL: http://dx.doi.org/10.1080/10426509908546405

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Phosphorus, Sulfur and Silicon, 1999, Vol. 150-151, pp. 367-374
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Synthesis, Characterization and Anticancer Activity of Some Bis(Germylpropionato-Di-*n*-Butyl) Oxides

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Fourteen new germanium-substituted Bis(propionato-di-*n*-butyltin) oxide with the formula $[(R_3GeCHR^1CHR^2COO)SnBu_2]_2O$: R_3=Ph_3, $N(CH_2CH_2O)_3$; R^1=H, CH_3, Aryl; R^2=H, CH_3, were synthesized and their compositions and structures were identified by IR, NMR(^{1}H, ^{119}Sn), MS spectroscopy and elemental analysis. Their structures in solid and in solution were discussed. The *in vitro* anticancer activity against KB cells, HCT-8 cells and Bel7402 cells was presented.

Keywords: Bis(Germylpropionato-di-*n*-butyltin) Oxide; Infrared Spectroscopy; ^{19}Sn NMR; Anticancer Activity

INTRODUCTION

Tin and organotin compounds are being used for the last many years as agrochemicals[1],[2], pharmaceuticals[3-5] and radiopharmaceuticals[6], etc. The dialkyltin compounds have lowest mammalian toxicity and exhbit greater anticancer activity than the corresponding mono, tri and tetra alkyl derivatives[7]. In the past two decades, diorganotin carboxylates have been widely studied for their potential anticancer activity[8]. There is a need to prepare more organotin anticancer agents containing R_2Sn^{2+} moiety or other biologically active groups[9]. The cytotoxicity of

organotin compounds has been studied in mice and it has been found that the functional groups attached to the tin atom in organotin compounds control the compound's cytotoxicity towords the thymus gland[10]. As we know very well, organogermanium is another element that has a wide range of biological activity[11],[12]. Organogermanium groups in the drugs are believed to induce an effect of lowing the toxicity and strengthening function of immune systems. Such compounds as Ge-132 $((O_{2/3}GeCH_2CH_2COOH)_n)$[13], Gematranes[14] etc., have been put on clinical trial for the treatment of some tumors. In order to link biological active properties of organogermanium and oraganotin compounds, we have previously reported the biological activity of trialkyltin germylpropionates[15] and anticancer activity of dibutyltin digermylpropionates[14]. In this paper, as the continuation of our previous work[16], we would like to report the synthesis of some bis(germylpropionato-di-*n*-butyltin) oxides and our studies on their anticancer activity against KB cells, HCT-8 cells and Bel7402 cells.

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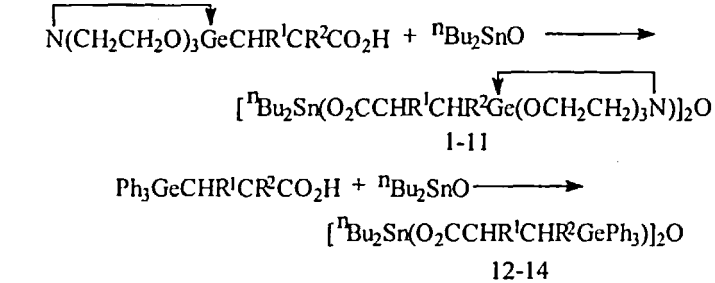
EXPERIMENTAL

Di-n-butyltin oxide was prepared by alkaline hydrolysis of $^nBu_2SnCl_2$. The germyl propionic acids[17],[18] were prepared according to earlier reference, the equations of preparation of these compounds is shown as in Scheme 1. The products were synthesized by condensation reaction of appropriate germyl carboxylic acids and di-n-butyltin oxide. The yields and elemental analysis of the title compounds are listed in Table 1.



1: R^1 = H, R^2 = H; 2: R^1 = CH_3; R^2 = H; 3: R^1 = H, R^2 = CH_3; 4: R^1 = C_6H_5, R^2 = H; 5: R^1 = 4-ClC_6H_4, R^2 = H; 6: R^1 = 2-ClC_6H_4, R^2 = H; 7: R^1 = 2,4-$Cl_2C_6H_3$, R^2 = H; 8: R^1 = 4-$CH_3C_6H_4$, R^2 = H; 9: R^1 = 2-$CH_3C_6H_4$, R^2 = H; 10: R^1 = 4-$CH_3OC_6H_4$, R^2 = H; 11: R^1 = 4-$NO_2C_6H_4$, R^2 = H; 12: R^1 = 4-ClC_6H_4, R^2 = H ; 13: R^1 = 4-$CH_3C_6H_4$, R^2 = H; 14: R^1 = 4-$CH_3OC_6H_4$, R^2 = H.

Scheme 1

Table 1.The yields and elemental analyses of the title compounds

No	Physical state	Yield (%)	M p. (°C)	Elemental C %	Analysis H%	Found(Calcd.) N %
1	White crystal	86.7	199-201	38.07(38.40)	6.44(6.44)	2.73(2.63)
2	White crystal	88.1	215-7	39.36(39.63)	6.55(6.65)	2.84(2.57)
3	White crystal	90.6	192-4	39.26(39.63)	6.46(6.65)	3.11(2.57)
4	White crystal	93.7	248-50	45.04(45.54)	6.13(6.29)	2.38(2.30)
5	White crystal.	74.8	262-5	42.79(43.02)	5.60(5.81)	2.11(2.18)
6	White crystal	93.1	249-51	42.59(43.02)	6.06(5.81)	2.13(2.18)
7	White crystal	90.1	268-70	40.57(40.82)	5.32(5.35)	2.27(2.17)
8	White crystal	90.1	254-6	45.98(46.36)	6.37(6.49)	2.31(2.25)
9	White crystal	78.6	242-4	45.94(46.36)	6.31(6.49)	2.20(2.25)
10	White crystal	81.6	251-2	44.77(45.20)	6.30(6.32)	2.21(2.20)
11	White crystal	79.1	>260	41.33(41.30)	5.33(5.58)	4.19(4.25)
12	White crystal	83.4	178-80	59.44(59.81)	5.74(6.00)	
13	White crystal	77.9	158-61	57.67(57.79)	5.54(5.69)	
14	White crystal	80.9	118-20	61.01(61.16)	5.61(6.13)	

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RESULTS AND DISCUSSION

IR. data

Interesting features are observed in Infrared spectra for carboxylate groups in these compounds. We know very well that there are mainly three kinds of structures for trialkyltin carboxylates[19]: the four-coordinate structure for the monomers (A) and the five-coordinate structure (B) for monomers and (C)for polymers (see Figure. 1):

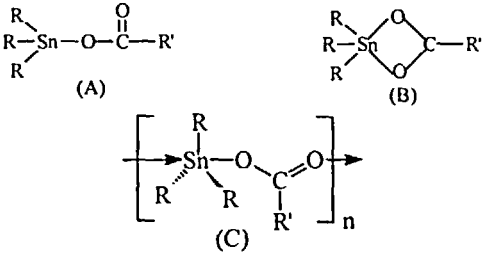

Figure.1

The vacant 5d orbitals on tin atoms tend towards high-coordination with ligands containing lone electron pairs. The IR. stretching vibration frequencies of carbonyl groups in organotin carboxylates are

important for determining their structures: when the structure changes from A to B or C, the asymmetric absorption vibration frequencies (υ asym) of carbonyl groups decrease and the symmetric absorption vibration frequencies (sym) increase. The difference ($\Delta\ \upsilon_{C=O}$) therefore decreases.

The carbonyl absorptions of diorganotin carboxylates are apparently more complicated than those of trialkyl carboxylates, because there are two carbonyl groups. Therefore, if the two carbonyl groups have the same coordination environment, there is only one carbonyl absorption in the IR. spectra; if there are two carbonyl absorptions in the spectra, the two carbonyl groups have different coordination environments[20].

Table 2. I.R. data for $\{[^nBu_2Sn(O_2CCHR^2CHR^1GeR_3)]_2O\}_2$ (cm^{-1})

No	υ asym	υ sym	$\Delta\ \upsilon$	υ_{Sn-C}		υ_{Sn-O}	$\upsilon_{Sn-O-Sn}$
1	1619(1553)	1373(1409)	246(144)	575	535	485	612
2	1642(1551)	1372(1409)	270(142)	580	535	485	613
3	1642(1557)	1345(1399)	297(158)	582	539	484	618
4	1641(1563)	1358(1408)	283(155)	579	535	478	613
5	1614(1558)	1381(1405)	233(153)	580	535	484	615
6	1633(1563)	1362(1406)	271(157)	582	535	484	615
7	1627(1559)	1374(1408)	253(151)	583	532	485	614
8	1619(1558)	1362(1402)	256(156)	579	530	486	611
9	1595(1557)	1374(1399)	258(158)	579	534	485	612
10	1623(1557)	1361(1402)	262(155)	577	533	477	610
11	1625(1561)	1365(1399)	260(162)	582	539	480	618
12	1633(1567)	1324(1370)	309(197)	564		464	669
13	1635(1564)	1326(1365)	309(195)	553		465	669
14	1606(1564)	1332(1381)	274(18)3)	524		466	669

Two carbonyl absorptions were observed in the IR. spectra for each complex (Table 2), in the range 1606-1642 cm^{-1} and 1551-1581 cm^{-1} for asymmetric carbonyl absorption and in the range 1324-1380 cm^{-1} and 1370-1409 cm^{-1} for symmetric carbonyl absorption. From above, we can obtain two $\Delta\ \upsilon$ values in the range 233-309 cm^{-1} and 142-197 cm^{-1}, so a conclusion can be easily drawed that the two carbonyl groups have different coordination environment. This suggests that only one of the two carbonyl groups coordinate to the tin atom. Therefore we illustrate the structure of these compounds as below (Figure. 2), considering the dimeric structure for the analogous in the literature[21].

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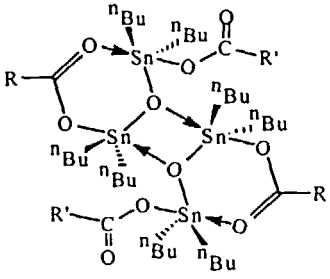

Figure. 2 Proposed structure for the title compounds

Table 3: ^{1}H NMR data for $\{[^nBu_2Sn(O_2CCHR^2CHR^1GeR_3)]_2O\}_2$*

	δ ^{1}H				
No	C_4H_9	$R^2(R^1)$	CH and CH_2	$N(CH_2)_3$	$(OCH_2)_3$
1	0.87-1.78 (36H,m)		2.23-2.48(6H,m)	2.82(12H,t)	3.76(12H,t)
2	0.88-1.78 (36H,m)	1.62(6H,d)	1.96-2.04(6H,m)	2.84(12H,t)	3.78(12H,t)
3	0.88-1.82 (36H,m)	1.74(6H,d)	2.04-2.16(6H,m)	2.84(12H,t)	3.78(12H,t)
4	0.60-1.60 (36H,m)	7.00-7.56(10H,m)	3.04(6H,m)	2.77(12H,t)	3.76(12H,t)
5	0.60-1.62 (36H,m)	7.04-7.36(8H,m)	2.98(6H,m)	2.78(12H,t)	3.74(12H,t)
6	0.62-1.64 (36H,m)	7.00-7.60(8H,m)	2.98(6H,m)	2.78(12H,t)	3.74(12H,t)
7	0.62-1.64 (36H,m)	6.96-7.46(6H,m)	2.90(6H,m)	2.76(12H,t)	3.76(12H,t)
8	0.62-1.64 (36H,m)	6.967.32(8H,dd) 2.24(6H,s)	3.02(6H,m)	2.78(12H,t)	3.78(12H,t)
9	0.60-1.62 (36H,m)	6.98-7.44(8H,m) 2.24(6H,s)	3.02(6H,m)	2.76(12H,t)	3.74(12H,t)
10	0.60-1.64 (36H,m)	6.76-7.24(8H,dd) 3.78(6H,s)	3.00(6H,m)	2.76(12H,t)	3.80(12H,t)
11	0.60-1.62 (36H,m)	7.30-8.24(8H,m)	2.88-3.08(6H,m)	2.74(12H,t)	3.68(12H,t)

*For compound 12: 0.60-1.60(m, 36H, 4 × C_4H_9), 2.64-3.00(m, 4H, 2 × CH_2), 3.44-3.78(m, 2H, 2 × CH), 6.90(dd, 8H, 2 × C_6H_4), 7.36(s, 30H, 6 × C_6H_5) ppm.

For compound 13: 0.58-1.60(m, 36H, 4 × C_4H_9), 2.60-3.00(m, 4H, 2 × CH_2), 3.40-3.78(m, 2H, 2 × CH), 6.40-6.80(dd, 8H, 2 × C_6H_4), 7.24(s, 30H, 6 × C_6H_5) ppm.

For compound 14: 0.62-1.60(m, 36H, 4 × C_4H_9), 2.64-3.04(m, 4H, 2 × CH_2), 3.40-3.82(m, 2H, 2 × CH), 6.68-7.04(dd, 8H, 2 × C_6H_4), 7.36(s, 30H, 6 × C_6H_5) ppm.

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(^{1}H, ^{119}Sn) NMR data

The ^{1}H NMR spectra of the compounds showed the expected integration and peak multiplicities. The ^{n}Bu group attached to the Sn atom exhibited multiplets or broad resonance. This is attributed to different ^{2}J(Sn-H) value in exocyclic $^{n}Bu_2Sn$ and endocyclic $^{n}Bu_2Sn$[22].

According to the literature[23], the ^{119}Sn NMR spectra for dicarboxylato tetraorganodistannoxanes displayed two well separated resonance, supporting the presence of a dimeric in solution as well as in solid state. The lowfield and highfield shifts observed for the distannoxane are attributed to the exocyclic and endocydic Sn atom, respectively. Six of the compounds were selected for ^{119}Sn NMR study, and only one compound (1) has expected ^{119}Sn NMR spectrum, that is, it shows two equally intense signals at -205.7ppm and -210.5ppm, the other five have different spectra from what we expected. They all have another signal either strong or weak in low field besides the two expected equally intense signals around -200ppm and -210ppm (Table 3). We attribute this to the dedimerization of some of the dimers in the solution. The dedimerization is mainly ascribed to the hindrance of the very bulky substituted carboxylate groups, which is in accordance with what other researchers have found for $[t\text{-}Bu_2Sn(O_2C(2,6\text{-di-}MeOC_6H_3)]_2O$[24]. In compound 1, the hindrance is comparatively minor, no dedimerization happens, while others dedimerize more or less. However, other minor resonances are also observed in the spectra that are attributed to other oligomeric species in equilibrium with the dimeric 1:1 condensation products[25].

Table 4. $^{119}SnNMR$ data for $\{[^{n}Bu_2Sn(O_2CCHR^2CHR^1GeR_3)]_2O\}_2$*

No.	R^1	R^2	^{119}Sn (ppm)		(CDCl$_3$ as solvent)
1	H	H	- 205.7	- 210.5	
2	CH_3	H	- 151.1	- 198.5	- 205.6
3	H	CH_3	- 160.8	- 214.4	- 218.1
4	H	C_6H_5	- 151.1	- 198.5	- 205.5
7	H	2,4-$Cl_2C_6H_3$	- 208.3	- 209.6	- 212.6
10	H	4-$OCH_3C_6H_4$	- 151.2	- 198.8	- 207.0

*$R_3 = (OCH_2CH_2)_3N$

M.S. data

Compound 4 and 12 were selected for M. S study. The molecular ion is never observed but the fragment ions found are in agreement with the expected structure of the compounds. For both compounds, the ion containing germanium $(N(CH_2CH_2O)_3Ge^{+}(220)$ for compound 4 and

Ph_3Ge^+(305) for compound 12) is the base peak, and other ions containing germanium are also generally quite intense.

In vitro tests

Ten of the $[(R_3GeCHR^1CHR^2COO)SnBu_2]_2O$ compounds were screened *in vitro* for their anticancer activity against KB cells, HCT-8 cells and Bel7402 cells. The examination of the results summarized in Table 5 suggests the following conclusions:

1.All compounds tested in general show some activity.

2.The Germatrane-substituted derivatives show a higher activity than the $GePh_3$-substituted derivatives.

All compounds are poorly soluble in water, this may be the main reason for their moderate activity.

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Table 5: Anticancer activity of selected compounds against KB cells, Bel7402 cells and HCT-8 cell.

	10 (μ g/ml)			IC_{50} (μ g/ml)		
No	KB cells	Bel7402 cells	HCT-8 cells	KB cells	Bel7402 cells	HCT-8cells
1	96.6 ± 06	92.8 ± 08	95.0 ± 19	5.4	5.3	5.5
2	96.2 ± 02	94.3 ± 04	93.9 ± 04	5.5	5.6	5.6
3	96.6 ± 02	93.9 ± 03	93.2 ± 11	5.3	5.6	4.9
4	96.2 ± 02	92.7 ± 09	94.0 ± 04	5.5	5.0	5.2
6	98.8 ± 21	91.0 ± 17	91.3 ± 12	4.8	6.4	5.7
7	96.2 ± 07	92.3 ± 04	94.2 ± 06	5.1	5.5	5.4
8	96.4 ± 04	92.4 ± 04	93.7 ± 11	5.5	5.6	5.2
9	96.9 ± 05	96.1 ± 18	94.9 ± 11	5.4	5.5	5.5
10	96.9 ± 04	94.6 ± 04	93.8 ± 11	5.6	4.6	4.3
11	53.5 ± 56	68.7 ± 08	37.9 ± 58	9.5	7.5	>10

* All compounds have "++", while "+++" stands for good activity.

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