Heteroatom Chemistry
Volume 19, Number 2, 2008

Synthesis, Characterization, and Biological Effects of Diorganotin(IV) Derivatives of Substituted Germyl Propionic Acid and Crystal Structure of 3-Triphenylgermyl-3-*P*-fluorophenyl Propionic Acid

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Received 22 May 2006; revised 16 November 2006, 1 February 2007

ABSTRACT: *A new series of diorganotin(IV) derivatives of the general formula* $(^1R_3GeCH^2R\,CH_2COO)_2Sn^3R_2$ *has been prepared by the reaction of diorganotin chlorides/oxides with substituted germyl propionic acids in 1:2 mole ratios. These compounds have been characterized by elemental analyses and various spectroscopic techniques (IR, multinuclear NMR (*^1H, ^{13}C, ^{119}Sn*),* ^{119m}Sn *Mössbauer spectroscopies and mass spectrometry). The single crystal structure of the precursor* $Ph_3GeCHR_FCH_2COOH$ ($R_F = 4\text{-}FC_6H_4$) *has been determined by X-ray diffraction. Biological studies such as cytotoxicity, antibacterial, and cytotoxicity were also investigated.* © 2008 Wiley Periodicals, Inc. Heteroatom Chem 19:163–170, 2008; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20402

INTRODUCTION

Organotin compounds show a diversity of applications. They are used as fungicides and bactericides. In addition, diorganotin compounds exhibit greater antitumor activity than the corresponding triorganotin compounds [1]. Similar behaviors for organogermanium compounds have also been observed [2,3]. For example, Silatorque [4] $[(PhMe_2SiCH_2)_3Sn]_2O$ has high-acaricidal activity but low toxicity toward other organisms. In a continuation of our previous work [5–8], we report here the synthesis and biological studies of several

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Contract grant sponsor: Pakistan Science Foundation.
Contract grant sponsor: Mössbauer work from the National Institute of Biomedical Research Support Program.
Contract grant number: MBRS/SCORE, GM08005.

TABLE 1 Physical Properties of Diorganotin Derivatives Having General Formula

$$[R^1_3GeCHR^2CH_2COO]_2Sn[R^3]_2$$

Compound No.	R^1	R^2	R^3	Molecular Formula	Melting Point (°C)	Yield (%)	Anal. Found (Calculated) C	H	N
1	$N(CH_2CH_2O)_3$	*o*-FC_6H_4	C_6H_5	$C_{42}H_{48}F_2N_2O_{10}Ge_2Sn$	90–93	58	48.34 (48.3)	4.61 (4.60)	2.67 (2.60)
2	$N(CH_2CH_2O)_3$	*o*-FC_6H_4	CH_3	$C_{32}H_{44}F_2N_2O_{10}Ge_2Sn$	95–97	70	41.84 (41.8)	4.78 (4.79)	3.30 (3.26)
3	$(C_6H_5)_3$	*p*-FC_6H_4	*n*-C_4H_9	$C_{62}H_{62}F_2O_4Ge_2Sn$	150–152	68	63.45 (63.4)	5.30 (5.29)	–
4	$(C_6H_5)_3$	*p*-FC_6H_4	C_6H_5	$C_{66}H_{54}F_2O_4Ge_2Sn$	124–126	75	65.33 (65.3)	4.45 (4.45)	–
5	$(C_6H_5)_3$	*p*-FC_6H_4	CH_3	$C_{50}H_{50}F_2O_4Ge_2Sn$	158–160	75	59.03 (59.0)	4.91 (4.92)	–
6	$N(CH_2CH_2O)_3$	*p*-FC_6H_4	C_6H_5	$C_{42}H_{48}F_2N_2O_{10}Ge_2Sn$	110–112	69	48.37 (48.3)	4.60 (4.56)	2.67 (2.63)
7	$N(CH_2CH_2O)_3$	*p*-FC_6H_4	CH_3	$C_{32}H_{44}F_2N_2O_{10}Ge_2Sn$	95–97	70	41.81 (41.8)	4.78 (4.74)	3.02 (2.95)
8	$N(CH_2CH_2O)_3$	*p*-FC_6H_4	i-C_4H_9	$C_{38}H_{56}F_2N_2O_{10}Ge_2Sn$	180–182	75	45.49 (45.5)	5.56 (5.60)	2.81 (2.77)

diorganotin(IV) derivatives containing a germanium moiety as a part of the carboxylate ligand.

RESULTS AND DISCUSSION

Syntheses

Syntheses of the substituted 3-trichlorogermylpropionic acids were prepared by standard methods [9–11].

Syntheses of the complexes were prepared by procedures cited in the literature [5–8]. The physical properties and melting points are given in Table 1. The elemental analyses of the complexes indicate that the diorganotins reacted with the acids in a 1:2 ratio.

Infrared Spectra

Vibration of interest are listed in Table 2. Complexation by the substituted germylpropionic acid ligands is evidenced by the absence of the ν(OH) band at 3400–3500 cm^{-1} due to the deportation of the acid. In addition, new bands that appear between 440–465 cm^{-1} are indicative of the formation of Sn—O—C units. It has been observed that upon complexation, ν(COO) frequencies are shifted downward in comparison to the free acid (~1700 cm^{-1}). The $\nu(COO)_{asym}$ vibration occurs in the range 1595–1609 cm^{-1}, whereas the $\nu(COO)_{sym}$ vibrations appear between 1410 and 1418 cm^{-1}. The $\Delta\nu$ (differences of $\nu(COO)_{asym}$ and $\nu(COO)_{sym}$) values for tin carboxylates have been used as a tool to describe the binding of the ligand in tin carboxylate compounds [12–16]. The observed $\Delta\nu$ values (182–195 cm^{-1}) for compounds **1–8** suggest that the carboxylate group behaves as a bidentate ligand. Although the IR data of the compounds indicate that the carboxylic groups act as bidentate ligands, it cannot be distinguished whether the two ligands are cis or trans to each other.

TABLE 2 IR Characteristic Frequencies (cm^{-1})

Compound No.	υ(COOasym)	υ(COOsym)	$\Delta\upsilon$	υGe-O	υGe←N	υSn-C	υSn-O
1	1608	1415	185	913,830 s	694	540,620	464
2	1609	1418	191	914,834 s	693	560,516	465
3	1595	1412	183	–	–	585,518	459
4	1596	1414	182	–	–	537,612	463
5	1605	1410	195	–	–	547,516	461
6	1601	1410	190	934,832 s	695	544,614	440
7	1602	1418	191	915,836 s	694	559,514	465
8	1600	1400	187	913,832 s	685	554,517	458

S = strong, sym = symmetric, asm = asymmetric.

TABLE 3 ^{1}H NMR Data of Diorganotin Derivatives of General Formula

$$[^{1}RGe^{2}CHRCH_2COO]_2Sn[^{3}R]_2$$

Compound No.	*R^1 Ge*	*R^2*	*R^3*	*CH_2*	*CH*
1	2.75, (t), ^3J(6.5), 3.75 (t), ^3J(6.5),	6.91–6.93 (m, 4H)	7.1–7.14 (m), 6.93–7.09 (m), 7.54–7.57 (m)	2.73 (m)	4.2 (m)
2	2.80, (t), ^3J(6.5), 3.78 (t), ^3J(6.5),	6.88–6.92 (m) 7.60–7.64 (m)	0.30 (s) [82]	3.00 (m)	4.2 (m)
3	6.60–7.04 (m) 7.31–7.42 (m)	7.14–7.18 (m, 4H)	0.47, CH_3(t), ^3J(7.5), $(CH_2)_2$, 1.17–1.34 (m)	3.07 (m)	3.85 (m)
4	6.61–7.04 (m) 7.31–7.43 (m)	7.14–7.15 (m, 4H)	7.6–7.14 (m), 7.32–7.35 (m)	2.98 (m)	3.83 (m)
5	6.58–6.68 (m), 7.31–7.34 (m)	7.14–7.16 (m, 4H)	0.33 (s) [83]	2.98 (m)	3.80 (m)
6	2.72, (t), ^3J(6.0), 3.76 (t), ^3J(5.8),	7.14–7.18 (m, 4H)	7.08–7.56 (m)	2.73 (m)	3.82 (m)
7	2.72, (t), ^3J(6.5), 3.76 (t), ^3J(6.5),	7.14–7.23 (m, 4H)	0.43 (s) [81]	2.72 (m)	3.78 (m)
8	2.75, (t), ^3J(6.5), 3.75 (t), ^3J(6.5),	7.14–7.18 (m, 4H)	0.43, CH_3(t), ^3J(6.5), $(CH_2)_3$, 1.19–1.33 (m)	2.73 (m)	4.08 (m)

$R^1 = N(CH_2CH_2O)_3$ for compounds **1,2,6–8** and C_6H_5 for **3–5**.
$R^2 = o$-FC_6H_4 for **1,2** and p-$FC_6H_4$for **3–8**.
$R^3 = C_6H_5$ for **1,4,6**, C_4H_9 for **3,8** and CH_3 for **2,5,7**.
In $CDCl_3$ at 298 K (40%), coupling constants ^nJ [^{119}Sn], ^nJ(^{1}H, ^{1}H) in Hz are given in [ ] and (), respectively and multiplicity is given as s = singlet, d = doublet, t = triplet.

Multinuclear NMR (^{1}H, ^{13}C, ^{119}Sn) Spectra

The ^{1}H NMR data of the compounds are given in Table 3. The expected ^{1}H NMR resonances of the complexes were assigned by their multiplicity and intensity patterns, integration, coupling constants, and tin satellites. In addition, integrations of the spectra were in agreement with the expected values. Proton NMR data of the cyclic skeleton of simple germatranes consist of two triplets (A_2B_2) spin system. One triplet at 2.72–2.80 ppm, having a coupling constant of ^3J(6.5 Hz), was assigned to the NCH_2 protons and the other at 3.75–3.78 ppm, having a coupling constant of ^3J(6.5 Hz), was assigned to the OCH_2 protons. The methyl group attached directly to the tin atom absorbed at 0.30–0.33 ppm and appears as a sharp singlet with a ^2J(^{119}Sn-^{1}H) coupling constant of 82 ± 1 Hz. The CH_2CHGe unit is an ABX spin system. Subspectral analysis of the multiplet in the region about 2.8 and 4.0 ppm revealed three chemical shifts for the H_A, H_B, and H_X nuclei and vicinal coupling constants (J_{AX}, J_{AB}). The methylene protons (A, B) of the carboxylates portion resonate at 2.72–3.07 ppm, demonstrating that the H_A atom is located slightly downfield and shows a pseudoquartet in the range 2.72–3.07 ppm (J_{gem} 15.3 ± 1 Hz; J_{vic} 4.8 ± 1 Hz). The H_B atom resonated slightly upfield and gives a pseudoquartet in the range 2.80–3.07 ppm. The H_X of the chiral center resonated further downfield and shows a quartet at 4.00 ± 0.2 ppm (Table 4) [17,18].

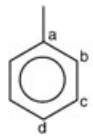
TABLE 4 ^{1}H NMR Data at and Around Chiral Center with General Formula

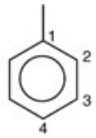
Compound No.	*H_A*	*H_B*	*H_X*	*J_{gem}(Hz)*	*J_{vic} (Hz)*	*$\Delta\delta = (\delta H_A - \delta H_B)$*
1	2.88 (1H, dd)	2.73 (1H, dd)	4.25 (1H, dd)	15.30	(4.22–12.88)	0.15
2	3.08 (1H, dd)	3.00 (1H, dd)	4.22 (1H, dd)	15.25	(4.32–12.90)	0.08
3	3.20 (1H, dd)	3.07 (1H, dd)	3.87 (1H, dd)	15.27	(4.35–12.95)	0.13
4	3.01 (1H, dd)	2.98 (1H, dd)	3.87 (1H, dd)	15.11	(4.27–12.92)	0.11
5	3.08 (1H, dd)	2.98 (1H, dd)	3.82 (1H, dd)	15.16	(4.23–12.86)	0.10
6	2.89 (1H, dd)	2.73 (1H, dd)	3.80 (1H, dd)	16.00	(4.22–12.88)	0.16
7	2.87 (1H, dd)	2.72 (1H, dd)	3.80 (1H, dd)	15.90	(4.25–12.87)	0.09
8	2.82 (1H, dd)	2.73 (1H, dd)	4.10 (1H, dd)	15.50	(4.30–12.95)	0.09

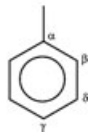
TABLE 5 ^{13}C NMR Data of Diorganotin Derivatives

$$[R_3{}^{1}GeCHR^{2}CH_2COO]_2{}^{3}Sn[R]_2$$

Compound No.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
R^1a	54.00	58.43	133.22	133.29	136.20	49.37	54.59	54.94
b	56.00	58.84	127.79	128.0	133.00	54.65	57.47	56.60
c	–	–	127.67	127.40	127.00	–	–	–
d	–	–	126.00	126.06	126.00	–	–	–
R^2 1	136.0	136.99	133.00	133.41	136.20	134.63	126.86	129.18
2	159.2 [248]	159.2 [250]	127.00	133.29	128.00	126.78	126.72	130.86
3	136.47	136.47	126.00	122.50	112.85	113.50	134.30	112.78
4	136.0	136.08	158.63 [255]	163.87 [248]	160.35 [249]	163.78 [253]	160.35 [248]	160.65 [255]
5	129.00	129.10	–	–	–	–	–	–
6	128.17	128.17	–	–	–	–	–	–
CH_2	38.00	38.52	38.00	38.00	40.79	38.82	37.28	40.88
CHR^2	30.00	36.87	36.00	36.00	38.64	37.29	34.50	34.70
R_4Sn α	144.43 [875]	12.79 [655]	26.00 [615]	134.00 [845]	13.19 [662]	134.00 [860]	11.95 [656]	27.93 [600]
β	136.84 [50]	–	23.78 [34]	128.00 [55]	–	126.00 [52]	–	26.29 [36]
γ	128.17 [69]	–	22.00 [99.6]	122.00 [72]	–	124.00 [68]	–	24.29 [98]
δ	129.34 [32]	–	11.26 [26]	128.90 [28]	–	113.15 [30]	–	11.68 [28]
COO	167.00	170.26	168.51	172.00	172.42	172.00	168.98	168.00

R^1 = 

R^2 = 

R^3 = 

The ^{13}C spectral data are given in Table 5. In germatranes, carbon atoms bonded to the germanium atom through oxygen and nitrogen atoms resonate at 59 and 49 ppm, respectively. The aromatic carbon resonances were assigned by a comparison of the experimental chemical shift with those calculated from the incremental method as well as with literature values [5–8, 19,20]. The carbon atom, to which the fluorine atom is attached, resonates at 159–163 ppm due to the presence of the strong electron-withdrawing group. The diphenyltin derivatives **1, 4**, and **6** exhibit $^1J(^{119}Sn\text{-}^{13}C)$ coupling constants of 845 ± 15 Hz (Table 6). The dimethyltin derivatives **3, 5**, and **7** exhibit $^1J(^{119}Sn\text{-}^{13}C)$ coupling constants of 659 ± 4 Hz, whereas di-*n*-butyltin derivatives **3** and **8** exhibit $^1J(^{119}Sn\text{-}^{13}C)$ coupling constants of 657 ± 1 Hz. The C—Sn—C bond angles were calculated using the Lockhart equation [21], and the magnitude of the bond angle (128°–136°) indicated that deformation of the coordination polyhedra around the tin atom has occurred.

TABLE 6 C—Sn—C (°) Based on NMR Parameters

Compound No.	$^1J(^{119}Sn\text{-}^{13}C)$ *Hz*	θ (°)	$^2J(^{119}Sn\text{-}^{1}H)$*Hz*	θ (°)
1	875	131	–	–
2	655	134	82	133.
3	615	136	–	–
4	845	129	–	–
5	662	135	83	135
6	860	130	–	–
7	656	134.	81	132.
8	600	135	–	–

TABLE 7 ^{119}Sn NMR Data of Diorganotin Derivatives

Compound No.	^{119}Sn *(ppm)*
1	–227.54
2	–253.00
3	–287.89
4	–223.95
5	–257.35
6	–235.00
7	–249.83
8	–288.00

TABLE 8 $|\alpha|_D^{25}$ Angle of Rotation of Diorganotin Derivatives

Compound No.	$\|\alpha\|_D^{25}$
1	−128.5
2	−127.8
3	−130.8
4	−129.8
5	−126.0
6	−131.8
7	−130.5
8	−127.0

The ^{119}Sn chemical shifts for these compounds are enlisted in Table 7. It is generally accepted that the ^{119}Sn chemical shifts can be used to distinguish different geometries of organotin complexes. For example, a range of +200 to −60 ppm has been observed for four coordinated complexes and a range of −90 to −190 ppm has been assigned to five coordinated system whereas hexacoordinated organotins have a range of −200 to −400 ppm [22, 23]. The ^{119}Sn NMR chemical shifts for compounds **1–8** are observed in the range of −227 to −288 ppm indicative of the complexes having hexacoordinated geometries around the tin atom. Therefore, multinuclear NMR data of these compounds support the fact that this series of diorganotins exhibit a six-coordinated geometry around the tin atom in solution. The chirality of these compounds was also established on the basis of specific rotation (Table 8), magnitude, and direction manifested by the levorotatory nature of the compounds [18].

Mössbauer Spectra

The ^{119m}Sn Mössbauer data, that is, quadruple splitting (Δ) and isomer shift (σ) values for selected diorganotin dicarboxylates, are listed in Table 9. The Δ values of the compounds range from 2.87 to 2.94 mms^{-1}, indicating that the complexes are hexacoordinated with a cis C_2SnO_4 geometry around tin atom in the solid state [20]. The σ values fall in the range of 0.83–0.86 mms^{-1}. Coordination status of tin in these derivatives can also be provided by $\rho(\Delta/\sigma)$ values. The ρ values for this series of compounds are greater than 2.1, indicating that the complexes have a coordination number around the tin atom that is greater than 4. Using the Sham and Bancroft equation [24], a C—Sn—C bond angle of 130°–131° was calculated for the methyl derivatives. In the diorganotin dicarboxylates (R_2SnL_2), there is a distortion from perfect octahedral geometry due to the high electronegativity of the oxygen atoms of the two carboxylates, which gives Δ values similar to those observed for a trigonal bipyramidal environment. Thus, the Mössbauer data support the structural assignments, in the solid state, based on the IR data. The various spectroscopic results indicate that the structures of the complexes are hexacoordinated in both solid state and solution.

TABLE 9 Mössbauer Data of Some Selected Compounds

Compound No.	$\Delta (mm^{-1})$	$\sigma\ (mm^{-1})$	$\rho = \Delta/\sigma$
4	2.94	0.83	3.54
5	2.85	0.85	3.31
7	2.87	0.86	3.33

Δ = quadruple splitting, σ = Isomer shift.

Mass Spectra

Molecular ion peak of very low intensity was observed for compound **3**, while none of the rest exhibited this behavior. The fragment ions found are in agreement with the expected structure of the compounds. R_3Ge^+ (where $R = C_6H_5$) and N $(CH_2CH_2O)_3Ge^+$ are the base peaks, and the other ions containing germanium are also generally quite intense. It has also been observed that primary decomposition is due to the loss of the R group, and then there is also a loss of CO_2. The second course of fragmentation is associated with the germatranyl cation, which eliminates OCH_2CH_2 units (*m/z* 44) successively to give Ge^+ [20].

X-ray Crystallography

As a part of this work, we had a cause to confirm crystallographically, the nature of the Ph_3GeCHR_F CH_2COOH, one of the precursors used in this study. We have already published the crystal structures of the other precursors, $Cl_3GeCHPhCH_2COOH$ [5] and $(CH_3C_6H_4)_3GeCHPhCHCH_3COOH$ [25], and both are dimeric in nature. The dimerization takes place through the hydrogen bond between the chlorine and carboxylic proton in the former case and through the carboxylic end in the latter case. However, $Ph_3GeCHR_FCH_2COOH$ is monomeric with a monoclinic crystal system (Fig. 1). The geometry around the germanium atom is a slightly distorted tetrahedron with bond angles of C_3–Ge–C_{22} (112.2°), C_3–Ge–C_{16} (105.5°), C_{10}–Ge–C_3 (105.7°), and C_{22}–Ge–C_{10} (109.6°). The bond length for Ge–C3 (1.95 Å) is larger than the Ge–C16 (1.93 Å), Ge–C22 (1.92 Å) and Ge–C10 (1.91 Å) bond lengths because the hybridization for the former is sp^3 whereas it is sp^2 for the others. The Ge–C3 (1.95 Å) bond length is sufficiently larger than the corresponding Ge–C bond lengths in $Cl_3GeCHPhCH_2COOH$. Details regarding the crystal structure are available from the Cambridge Crystallographic Data Center.

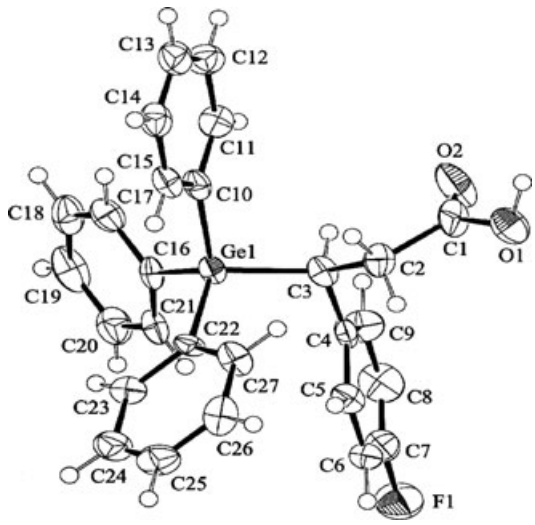


FIGURE 1 3-Triphenylgermyl-3-*p*-fluorophenyl propionic acid.

MATERIALS AND METHODS

Solvents were distilled immediately before use from sodium benzophenoate, and the other commercially available reagents were used as received. Melting points were determined using a Mitamura Riken Kogyo (MP-D) apparatus and are uncorrected. The IR spectra (4000–250 cm^{-1}) of the compounds were recorded as KBr pellets on a Hitachi model 270-1117 spectrophotometer. The mass spectra were obtained on a MAT 11.2 and MAT 8500 spectrometer with an ionizing voltage of 70 eV. ^1H NMR spectra were recorded on either a 400 or 500 MHz instrument (Bruker 400, AMX 500 spectrometers) using TMS as the internal standard. The ^{119}Sn NMR spectra were recorded on a Bruker 250 ARX spectrometer with Me_4Sn as the external standard. The rotational angle α was measured with a digital polarimeter (Polax DI-ATAGO) in chloroform. The Mössbauer spectra were measured at 80 K on a Ranger Mössbauer spectrometer, model MS-900 in the acceleration mode with a moving source geometry using a liquid nitrogen cryostat (Cyro Industries of America, Inc. Manchester, NH 03103). The samples were mounted in Teflon holders. The source was 15 mCi $Ca^{119m}SnO_3$, and the velocity was calibrated at ambient temperature using a composition of $BaSnO_3$ and Sn foil (splitting 2.52 mm s^{-1}). The resultant spectra were analyzed by a least-square fit to Lorenzian shaped lines.

Synthesis of Carboxyethylgermanium Sesquioxide (O3/2GeCH²RCH₂COOH)S

Distilled water (20 mL) was added dropwise to the trichlorogermylpropionic acid in ether (20 mL) in a 250-mL conical flask. The mixture was stirred, and the solid sesquioxide was formed. The product was then filtered, washed with water followed by acetone and ether. It was then dried under vacuum.

Synthesis of 3-Germatranyl-3-substituted Propionic Acid (N(CH₂CH₂O)3GeCH²RCH₂COOH)

The stoichiometric amount of the respective sesquioxide was placed in a 250-mL round bottom flask containing toluene (50 mL) and fitted with Dean and Stark apparatus. Triethanolamine was added dropwise with stirring. The mixture was refluxed for 6 h with constant removal of water using the Dean and Stark apparatus. Toluene was decanted, and the product was crystallized from 95% hot ethanol to yield the pure product. However, in some cases, addition of a few drops of water in ethanol helped to dissolve the product in hot ethanol.

Synthesis of 3-Triphenylgermyl-3-o/p-flouro-phenyl Propionic Acid (³RGeCH²RCH₂COOH)

0.02 mol of the respective acid $Cl_3GeCH^2RCH_2COOH$ was dissolved in dry tetrahydrofuran in a three-necked flask fitted with a reflux condenser, magnetic stirrer, and dropping funnel. Grignard reagent from the aryl halide was added dropwise keeping the temperature below 0°C over a period of 1 h with regular stirring. The temperature was allowed to rise slowly, and the mixture was subsequently refluxed for 4–6 h. The reaction mixture was cooled in an ice bath and hydrolyzed with 20% aqueous HCl. The mixture was then extracted with chloroform, dried over anhydrous $MgSO_4$, and recrystallized from acetone. In some cases, the product was purified by passing it over silica column.

Synthesis of (¹R)₃GeCH²RCH₂COO)₂ Sn(³R)₂

2.5 mmol of the respective trialkylgermylpropionic acid and 1.0 mmol of the diorganotin oxide were refluxed for 10 h in dry toluene using the Dean and Stark apparatus for the continuous removal of water. Toluene was then removed under reduced pressure resulting in a thick residue. The thick residue was kept at a low temperature for a few days and resulted in a solid, which was recrystallized from acetone to yield the product.

DATA COLLECTION AND REDUCTION

A colorless prismatic crystal of $C_{27}H_{23}O_2FGe$ having approximate dimensions of $0.43 \times .040 \times 0.37$ mm

TABLE 10 Cytotoxicity Data of Diorganotin Derivatives

	Nontoxic		*Toxic*	
Compound No.	*LD_{50} (μg)*	*Upper Toxic Concentration*	*LD_{50} (μg)*	*Lower Toxic Concentration*
1	–	10.84	5.19	0.46
2	1000	–	–	–
3	–	238.98	149.24	98.77
4	–	49.59	29.23	16.22
5	–	383.75	248.58	167.22
6	–	3.79	0.319	0.00
7	–	425.90	275.64	108.56
8	–	45.90	36.89	5.9

was mounted on a glass fiber. All measurements were made on a Riga AFC6S diffractometer using Mo-Kα radiation monochromated with a Zr filter. Cell constant and orientation matrix for the data collection were obtained from a least-squares refinement using the setting angles of 25 centered with reflections in the range of $18.21 < 2\theta < 21.05^{\circ}$, which corresponded to a primitive monoclinic cell with dimensions of $a = 13.3784$ (16) Å, $b = 10.3658$ (18) Å, $c = 17.1180(18)$ Å, $V = 2277.7(6)$ Å^3, $\beta = 106.368(9)^{\circ}$. For $Z = 4$ and formula weight = 471.07, the calculated density is 1.37g/ cm^{-3}. Of the 4466 reflections that were collected, 4276 were unique ($R_{int} = 0.108$). The intensities of three representative reflections were measured after every 200 reflections. An empirical absorption correction based on the azimuthal scans of several reflections was applied. The data were corrected for Lorentz and polarization effects.

BIOLOGICAL STUDY

Cytotoxic Activity

The cytotoxicity of the compounds has been evaluated against brine-shrimp (*Artemia salina* leach) larvae using Atoposide as the reference drug [26]. The results are listed in Table 10. Compounds **1, 3–8** are considered active with LD_{50} values of 5.19, 149.24, 29.23, 248.58, 0.319, 275.64, and 8.19 μg/mL^{-1}, respectively. On the other hand, compound **2** may be considered nontoxic because it required a very high concentration to kill brine-shrimp larvae (LD_{50} values > 1000 μg/ mL^{-1}).

Antibacterial Study

The agar well diffusion method [27] was used to test the activity of the compounds against 10 different types of bacteria as shown in Table 11. Compounds **6** and **7** have higher biological activity against *S. boydil* and *S. aureus* as compared to the reference drugs a and b. Compounds **3–7** have comparable activity against *B. cerus* diphtherias and *S. typhi* as compared to the reference drugs. The mechanisms involved in the bactericidal effect of these compounds have not been studied. Bacteria used in this study are both gram positive and negative. It is a well-known fact that the reference drug influences cell wall synthesis and does not destroy gram-negative bacteria. The above-mentioned compounds are more active against gram-negative bacteria. Further studies are needed to investigate the possible uses of these compounds in treating the disease caused by the gram-negative bacteria.

TABLE 11 Bactericidal Data for Selected Compounds

Name of Bacteria	*Compounds*								*Reference Drug*	
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	*(a)*	*(b)*
Bacillus cerus	–	–	23	18	18	17	17	14	8	9
Corynebacterian dipheriae	20	–	18	20	18	25	22	21	16	14
E. coli	–	13	–	–	–	–	–	–	10.5	10
Klebslella pneumoniae	15	–	12	–	–	–	20	12	8.0	8.5
Proteus mirabill	–16†	–	–	–	–	15†	17†	–	11.0	11.5
Pseudomonas aeroginosa	–	18	–	–	–	–	–	15	8.0	8.5
Salmonella typhi	20	–	15	15	12	19	26	19	8.0	8.0
Shigella boydil	18	–	–	20	20	35	40	26	18	19
Staphylococeus aureus	35	–	–	19	19	31	30	18	14	16
Streptococeus pyogenes	14†	12†	–	15	–	–	14	16	11†	9

Key: – denotes no activity.
†Decreased in bacterial population/unit area.
Reference drug (a) = Amoxicillin $(H_2O)_3$.
Colony forming unit (CFU) mL = 10^4–10^6.
$\Sigma\iota\zeta\varepsilon o\phi\omega\varepsilon\lambda\lambda = 5\mu\mu(\rho\alpha\delta\iota\upsilon\sigma) \cdot P\varepsilon\phi \cdot \delta\rho\upsilon\gamma(\beta) = A\mu\pi\iota\chi\iota\lambda\lambda\iota\nu(H_2O)_3\alpha = (I\nu\sigma\iota\tau\rho o)\ (\alpha\gamma\alpha\rho\ \omega\varepsilon\lambda\lambda\ \delta\iota\phi\phi\upsilon\sigma\iota o\nu\pi\rho o\tau o\chi o\lambda)\chi o\nu\chi \cdot$ 100 μg/100 μL of DMSO.

ACKNOWLEDGMENTS

M. A. Choudhary is grateful to the University of Azad Jammu and Kashmir Muzaffarabad for granting a study leave.

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