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Synthesis, Characterization and Biological Activity of Triorganotin Carboxylates Containing Germanium

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Some new triorganotin carboxylates containing germanium with general formulae ($R^1GeCHR^2CH_2COO$) $Sn(CH_2C(CH_3)_3)_3$ where $R^1 = N(CH_2CH_2O)_3$ and C_6H_5, $R^2 = C_6H_5$, p-$C_6H_4OCH_3$and $o-/p-C_6H_4F$ were synthesized and characterized by elemental analysis, infrared, multinuclear (^1H, ^{13}C, ^{119}Sn) NMR and mass spectrometry. Antibacterial activity of these compounds was evaluated against the standard drugs ampicilline and amoxicilline, and found to be more active in some cases than the standard drugs.

Introduction

Organotin compounds are of current interest owing to their wide range of applications[1] such as biocides and homogeneous catalysts in industry. Recently the potential antitumor activities of organotin carboxylates[2] organogermanium compounds were studied[3,4]. Their biological activity spectrum includes protection against viruses, immunostimulation and hepatoprotection for the treatment of chronic hepatitis. The biological activity of germatranes $[(R^1)_3GeCHR^2CH_2COO]Sn[CH_2C(CH_3)_3]_3$ is generally better than that of analogous silatranes[5,6].

Therefore, we prepared five new triorganotin carboxylates containing germanium and tested their antibacterial activity. These germanium substituted triorganotin carboxylates were synthesized by the condensation of triorganotin halide and germanium substituted propionic acids in the ratio 1:1 in the presence of triethylamine as base in dry acetone. The general reaction scheme is shown as follows:

$$[(CH_3)_3CCH_2]_3SnX + HO_2CCH_2CHR^2Ger$$

$$\downarrow Et_3N$$

$$[(CH_3)_3CCH_2)_3SnO_2CCH_2CHR^2GeR^1 + Et_3NHX$$

where $R^1 = N(CH_2CH_2O)_3$, $(C_6H_5)_3$ and R^2 = 3-$CH_3OC_6H_4$, 2/4-FC_6H_4, C_6H_5.

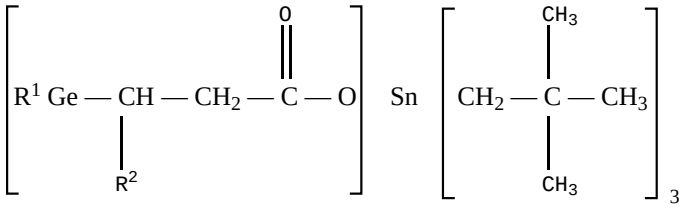
Experimental

Germanium substituted propionic acids were prepared by the reported method[7]. In a two-necked 100 mL flask fitted with a reflux condenser, a dropping funnel and a magnetic stirrer, 4.0 mmol of germanium substituted propionic acid and 4.0 mmol of triethylamine were taken. Triorganotin halides, 4.0 mmol, were dissolved in dry acetone and added dropwise with constant stirring to the mixture. After complete addition, the contents were refluxed for 8 hours and allowed to cool to room temperature. The reaction mixture was filtered to remove the triethylamine hydrochloride and the solvent was evaporated under vacuum. The solid was recrystallized from a chloroform and petroleum ether mixture (3:1). Physical properties and analytical data are reported in Table 1.

Table 1. Physical Properties and Analytical Data of Triorganotin Carboxylates (I-V)*.

Comp. no.	Mol. Formula	Mol. Wt.	m.p. ^oC	Yield %	Analysis(%)		
					C	H	N
I	$C_{31}H_{55}NO_6GeSn$	729.87	164-166	75	51.0 (50.90)	7.54 (7.50)	1.92 (1.82)
II	$C_{30}H_{53}NO_5GeSn$	186.87	186-188	75	51.50 (51.25)	7.58 (7.50)	2.00 (1.93)
III	$C_{30}H_{52}FNO_5GeSn$	717	187-189	70	50.20 (50.10)	7.25 (7.21)	1.95 (1.83)
IV	$C_{30}H_{52}FNO_5GeSn$	717	175-177	68	50.20 (50.00)	7.25 (7.15)	1.95 (1.87)
V	$C_{42}H_{55}FO_2GeSn$	802	100-102	68	62.84 (62.60)	6.85 (6.71)	–

* General formula



I	$R^1 = N(CH_2\text{-}CH_2\text{-}O)_3$	$R^2 = o\text{-}C_6H_4OCH_3$
II	$R^1 = N(CH_2\text{-}CH_2\text{-}O)_3$	$R^2 = C_6H_5$
III	$R^1 = N(CH_2\text{-}CH_2\text{-}O)_3$	$R^2 = o\text{-}C_6H_4F$
IV	$R^1 = N(CH_2\text{-}CH_2\text{-}O)_3$	$R^2 = p\text{-}C_6H_4F$
V	$R^1 = C_6H_5$	$R^2 = p\text{-}C_6H_4F$

Instruments

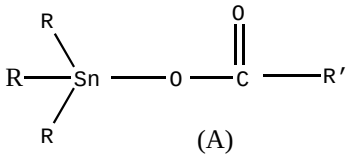
Infrared spectra were recorded on a Shimadzu IR-435 spectrometer in KBr discs. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AM 500 Spectrometer using $CDCl_3$. ^{119}Sn NMR spectra were obtained on Bruker 250 ARX with tetramethyltin as external reference. Mass spectra were recorded on MAT 8500 Finnigan. The m/z values were computed according to H = 1 C = 12, O = 16 F = 19 Sn = 120 Ge = 74 and N = 14.

Results and Discussion

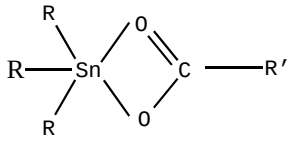
The infrared spectra of these compounds were recorded in the range 4000-400 cm^{-1}. Assignments were made on the basis of our earlier reports[8] and important absorption bands due to C=O, Sn−C, Sn−O and Ge−O bonds are listed in Table 2. Triorganotin carboxylates can have mainly three kinds of structures, i.e. the four coordinated structure (A) or five coordinated structure (B) or polymeric five coordinated structure (C):

Table 2. Characteristic IR Absorption Frequencies in cm^{-1} of Triorganotin Derivatives.

Com. no	ν_{asy}(COO)	ν_{sym}(COO)	$\Delta\nu$	ν(Ge-O)	ν(Ge←N)	ν(Sn-C)	ν(Sn-O)
I	1641	1436	205	898, 801	710	610, 535	432
II	1600	1386	214	915, 833	716	597, 541	416
III	1596	1399	197	902, 837	697	621, 514	463
IV	1609	1399	210	912, 813	693	627, 524	462
V	1609	1396	213	–	–	625, 518	464



(A)



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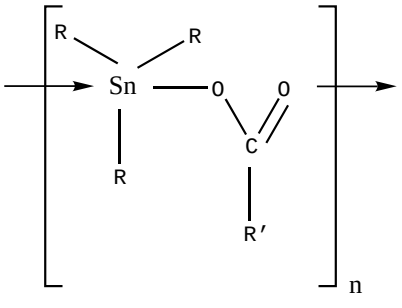

(C)

The infrared stretching vibrational frequencies of carbonyl groups in organotin carboxylates are important for determining their structure. When structure changes from (A) to (B) or (C) the asymmetric frequencies (ν_{asy}) of carbonyl groups decrease while the symmetric frequencies (ν_{sym}) increase. The differences $\Delta\nu$ therefore decrease. The decrease in ν_{asy}(COO) and the increase in ν_{sym}(COO) are indicative of the bidentate nature of the group and vice versa for the unidentate nature of the carboxylate group. In compounds I to V, $\Delta\nu$ values are in the range (197-214 cm^{-1}), which reveals that the carboxylate groups have bidentate behaviour in solid state[8−11].

The ^{1}H NMR spectral data of the complexes are shown in Table 3. The the expected resonances are ascribed by their multiplicity and intensity pattern, integration, coupling constants and tin satellites. The integration of the spectra show good agreement with the expected composition of the fragments of the complex molecules. It is also obvious that magnetically identical protons absorb at the same position, and therefore, the number of peaks in the NMR spectrum was equal to the number of magnetically different

protons. The intensity of each peak was proportionated to the number of chemically equivalent protons. The proton NMR spectra of the cyclic skeleton of the simple germatranes consist of two triplets (A_2B_2 spin system) at 2.5 to 2.75 ppm for NCH_2 and 3.66 to 3.76 ppm for OCH_2 (in $CDCl_3$). This pattern is a general feature of an atrane framework. The relative values of vicinal coupling constants are in the range of ^{3}JAB (6 Hz).

Table 3. ^{1}H NMR Data of Triorganotin Carboxylates*.

Comp. no.	R^2	CH_3	CH_2Sn	CH_2/CH	NCH_2^a	OCH_2^a
I	6.88-7.3 (m,4H) OCH_3 3.72 (s, 3H)	0.91 (s, 27H, ^{4}J ^{119}Sn = 28 Hz)	1.25 (s, 6H, ^{2}J ^{119}Sn = 52 Hz)	2.96-3.10 (m, 3H)	2.71 (t, 6H, ^{3}J = 5.5 Hz)	3.66 (t, 6H, ^{3}J = 5.58 Hz)
II	7.12-7.26 (m, 5H)	0.91 (s, 27H, ^{4}J ^{119}Sn = 27 Hz)	1.23 (s, 6H, ^{2}J ^{119}Sn = 50 Hz)	2.97-3.10 (m, 3H)	2.70 (t, 6H, ^{3}J = 5.5 Hz)	3.66 (t, 6H, ^{3}J = 5.58 Hz)
III	6.98-7.01 (m, 2H), 7.46-7.50 (m, 2H)	1.0 (s, 27H, ^{4}J ^{119}Sn = 28 Hz)	1.43 (s, 6H, ^{2}J ^{119}Sn = 68 Hz)	2.75-2.80 (m, 2H), 3.56-3.66 (m, 1H)	2.75 (t, 6H, ^{3}J = 6.0 Hz)	3.76 (t, 6H, ^{3}J = 6 Hz)
IV	6.98-7.00 (m), 7.46-7.50 (m)	1.10 (s, 27H, ^{4}J ^{119}Sn = 27 Hz)	1.43 (s, 6H, ^{2}J ^{119}Sn = 46.28 Hz)	2.5-2.7 (m, 2H), 3.6-3.7 (m, 1H)	2.5 (t, 6H, ^{3}J = 6 Hz)	3.75 (t, 6H, ^{3}J = 6 Hz)
V	6.9-7.4 (m)	0.56 (s, 27H, ^{4}J ^{119}Sn = 27 Hz)	1.43 (s, 6H, ^{2}J ^{119}Sn = 56 Hz)	3.25 (d, 2H, 4.0 (d, 1H, ^{3}J 6.5 Hz) ^{3}J = 7.5 Hz),	–	–

[a] NCH_2,OCH_2 in the case of germatrane

*See footnotes of Table 1 for details of compounds

In $GeCHRCH_2$, CH is a chiral centre and CH_2 is a prochiral centre and they form an ABX spin system. Compounds I and II form an ABC spin system and give a multiplet in the range 2.96 to 3.10 ppm, whereas III and IV give two multiplets in the range 2.5 to 2.80 ppm for prochiral protons and 3.5 to 3.7 ppm for chiral protons. The CH_2 group which is directly attached to Sn moiety gives a singlet in 1.2 to 1.4 ppm with two satellites due to $^{119/117}$Sn couplings with protons. The CH_3 groups of neopentyl give a sharp singlet at 0.9 to 1.0 ppm. Protons of the phenyl group absorb in the usual region[12].

The particular advantage of neopentyl derivatives is the ease with which the coupling constant can be determined. William et al.[13] have shown that ^{1}J(^{119}Sn-^{13}C) coupling constants are a good indication of the coordination of the tin atom in triorganotin carboxylates. The coupling constant provides valuable information about the hybridization status of the tin atom. Compounds I-V have four coordination around tin moiety in solution, as depicted by the values of the coupling constants.

^{1}J values around 340 Hz are characteristic of a tetrahedral environment around the tin atom. Tri-neopentyl derivatives I and II exhibit ^{1}J (^{119}Sn-^{13}C) 342 Hz, which show four coordination in solutions. The polymeric structure illustrated by IR spectroscopy is therefore lost in solution to generate a monomeric tetrahedral structure. The quaternary carbon of the neopentyl group absorbs in the range 30 to 33 ppm, which was assigned by its low intensity. The ^{13}C signal in (COO) lies in the range 176 to 178 ppm in all (I-V) triorganotin compounds. The germatrane skeleton absorbs in the range 52-58 ppm, which is in accordance with the literature values. In benzene, substituted carbon, especially with a fluorine or methoxy group, absorbs at very low field due to the strong electron withdrawing effect.

The ^{119}Sn NMR data measured in non-coordinating solvent are given in Table 4. This shift is a sensitive indicator of the coordination number in tin and the shift to low frequency with increasing number of bonds to the tin. The ^{119}Sn chemical shift of compounds (I-IV) can be confidently assigned to a four coordinated tin atom, whereas (V) is thought to be five coordinated[14].

Table 4. ^{119}Sn and ^{13}C NMR Data of Triorganotin carboxylates*.

		I	II	III	IV	V
CH_3		32.92 (58)	32.26 (38.7)	30.52 (40)	33.41 (41)	31.90 (39)
– C-		31.53 (20)	31.62 (20)	30.00 (17.2)	32.79 (no)	30.93 (13.6, 10.2)
CH_2Sn		38.54 (341, 327)	38.82 (342, 328 Hz)	46.59 (325, 208)	45.00 (no)	45.83 (no)
NCH_2		52.00	52.00	52.00	52.71	–
OCH_2		55.00	56.82	59.86	54.48	–
CH_2		37.00	37.36	37.43	33.36	37.43
CH		37.27	37.47	38.50	41.28	38.50
Phenyl#	1	144	134	123.5	133	136
	2	109	133	162.38	130	129
	3	158	129.86	114.00	114	114
	4	113	131.91	130.00	162	162
	5	127	129.86	124.00	114	114
	6	121	133.46	130.00	130	128
COO		177	177.51	178.00	178.0	176
^{119}Sn		80.69	87.34	-1.68	-9.83	-359.4

*(^{119}Sn−C) Coupling constants are given in parentheses.

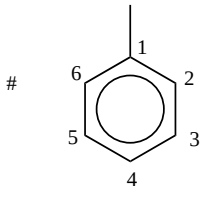

Table 5. Main Fragment Ion Observed for Compounds.

Fragments	m/z	Intensity
$[N(CH_2CH_2O)_3GeCH(C_6H_4OCH_3)CH_2COOSn(CH_2-C(CH_3)_3)_3]^+$	731	(12)
$[N(CH_2CH_2O)_3GeCH(C_6H_4OCH_3)CH_2COOSn(CH_2-C(CH_3)_3)_2]^+$	660	(26)
$[N(CH_2CH_2O)_3GeCHPhCH_2C \equiv O]^+$	352	(11)
[PhCH = CHCOOSn]	267	(16)
$[N(CH_2CH_2O)_3Ge]^+$	220	(100)
$[PhCH = CHCOO]^+$	147	(57)
[HSn]	121	(24)
[Sn]	120	(20)
[PhCH = CH]	103	(44)
$[Ph_3GeCH(C_6H_4)CH_2COO)Sn(CH_2C(CH_3)_3]_3$	809	(5)
$[Ph_3Ge]$	305	(100)
$[(CH_3)_3CCH_2]_3Sn$	333	(15)
$[(CH_3)_3CCH_2]_2Sn$	262	(10)
$[(CH_3)_3CCH_2]_2Sn$	191	(5)
$[Ph_2Ge]$	228	(25)
[PhGe]	151	(21)
[PhGe]	227	(85)

Mass Spectra

The main fragment ions observed in the mass spectra of compounds are listed in Table 5. Although molecular ion peak is observed rarely the fragment ions are found to be in agreement with the expected structure of

the compounds. For all the compounds the ions containing germanium $[N(CH_2CH_2O)_3Ge]^+$ and Ph_3Ge are the base peaks and sometime neopentyl moiety shows base peaks. Other ions containing germanium are also quite intense[7].

Biological Activity

The agar well diffusion method was used to test the activity of the compounds against ten different types of bacteria, i.e., *B. cereus, C. diphtheria, E. coli, K. pneumoniae, P. mirabilis, P. aeroginosa, S. typhi, S. boydi, S. aureus* and *S. pyogenes,* relative to reference drugs amoxicillin and ampicillin. The results are shown in Table 6. Compound V showed excellent activity against *C. diphtheria* even more than the reference drug. However, IV was only active against *C. diphtheria*. We can compare the biological activity of the reported compounds on the basis of substituent groups. Germatrane derivatives have more activity as compared to phenyl substitution at R^1 position. However, fluoro substitution on the phenyl ring in the R^2 group makes it more active as compared to methoxy substitution. A change in fluoro position has no noticeable effect on biological activity.

Table 6. Bactericidal Data of Triorganotin[a].

Name of Bacteria	Clinical Implication	Zone of Inhibition (mm)					Ref.	Ref.
		I	II	III	IV	V	Drug (a)	Drug (b)
Bacillus cereus	Food poisoning	10	10	–	–	–	11	11.5
Coryncbacterian diphtheriae	Diptheria, infections of ears, nose, throat & skin	–	–	18	20	16	10.5	10
E. Coli	Infection of wounds & urinary	–	–	–	–	–	115	12.5
tract, dysentery.								
Klebsiella pneumoniae	Septicaemia, Infection of respiratory tract.	–	–	–	–	12	11.5	12.5
Proteus mirabilis	Infection of urinary tract, septicaemia.	–	–	–	–	–	11	12
Pseudomonas aeroginosa	Infection of wounds, eyes, septicaemia.	–	–	–	–	–	12.5	13
Salmonella typhi	Typhoid fever, food poisoning, localized infection.	9	10	–	–	20	10	10
Shigella boydil	Inflammation of GIT, bacterial dysentery.	–	–	–	–	–	–	11.5
Staphylococcus aureus	Food poisoning, scadel skin syndrome, endocarditis.	–	–	35	35	–	11	13
Streptococcus pyogenes	Actrile rheumatic fever, scarlet fever, septic wounds, inflammation of kidney.	–	–	–	–	–	–	12

Key:- – No activity.
Colony forming unit (CFU)/ml=10^4-10^6.
Size of well = 5 mm (radius).
Ref. Drug (a) = Amoxicillin $(H_2O)_3$.
Ref. Drug (b) = Ampicillin $(H_2O)_3$.

a = (*In vitro*) (Concentration = 200 μg/100 μL of DMSO)

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