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Synthesis, characterization and biological activity of (Z)-1-[2-(triarylstannyl)viny]-1-cyclopentanol and their arylhalostannyl derivatives

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Abstract—The synthesis and characterization by elemental analysis, IR and ^{1}H NMR of (Z)-1-[2-(triphenyl-stannyl)vinyl]-1-cyclopentanol,$CH_2(CH_2)_3C(OH)CH{=}CHSnPh_3$ (**1**) and (Z)-1-[2-(tri-p-toyl-stannyl) vinyl]-1-cyclopentanol, $CH_2(CH_2)_3C(OH)CH{=}CHSn(p\text{-toly})_3$ (**2**) are described, together with their halodemetallation by I_2, Br_2 and ICl to yield derivatives of the types $CH_2(CH_2)_3C(OH)CH{=}CHSnAr_{3-n}X_n$ (Ar = phenyl or p-tolyl; n = 1, 2; X = I, Br, Cl). The solid-state structures of two compounds have been determined by X-ray diffraction analysis. In the crystal of $CH_2(CH_2)_3C(OH)CH{=}CHSnph_3$ (**1**) the Sn atom has a distorted tetrahedral geometry but intramolecular contact with the hydroxyl O atom has not been found. A trigonal bipyramidal geometry is found in $CH_2(CH_2)_3CC(OH)CH{=}CH$ $SnphBr_2$(11), in which OSn— interaction is noted [2.446(8) Å] The biological activity of the title complexes is also investigated. © 1998 Elsevier Science Ltd. All rights reserved

Keywords: synthesis structure; cyclopentanol; biological activity

Iododemetallation [1] of the products of the reactions between triphenyltin hydride and ethynyl(hydroxy) steroids [2,3] yield diorganotin diiodides with interesting antitumour activities [4,5]. Because each of these species exhibits an intramolecular HO—Sn interaction giving rise to a five-membered tin-containing ring, we described here another class of related compounds, namely (Z)-1-[2-(triarylstannyl) vinyl]-1-cyclopentanols as well as some of the corresponding diarylhalostannyl- and aryldihalostannyl-compounds. Our strategy was to develop novel organotin compounds containing a cyclopentanoid ligand without the steroid moiety. A second goal in our strategy is to indentify structural elements in the organotin steroids and cyclopentanoids, which are essential for the antitumor activity. In the mean time, their structural features, particularly the coordinative HO—Sn interactions are compared.

EXPERIMENTAL

Reagents and apparatus

1-Ethynylcyclopentanol, triphenyltin hydride and tri-tolyltin hydride were prepared by literature method [6,7,8].

All reagents were of analytical or guaranteed quality.

IR spectra were recorded on an Alpha Centalrt spectrometer (4000–400 cm^{-1} range) as KBr pellets. ^{1}H NMR spectra were recorded in $CDCl_3$ on a JEOL JNM-FX 100 instrument.

Crystal data were collected at 20°C on a Siemens P_4 diffractometer with graphite-monochromated Mo–K_α

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radiation ($\lambda = 0.71073$ Å). The structure was solved using SHELXTL-PLUS(Siemens) direct methods.

Analytical procedures

Elemental analyses were carried out with a Perkin–Elmer PE 2400 C,H, N instrument.

Synthesis

Compound **1**. 1-Ethynylcyclopentanol (9.3 g, 84. 5 mmol) and dibenzoyl peroxide (300 mg) were added to an ether solution of triphenyltin hydride prepared from 3.5 g (90.9 mmol) of $LiAlH_4$ and 35 g (90.9 mmol) triphenyltin chloride. The mixture was stirred for 30 h at room temperature under nitrogen. The ether was evaporated off and the residue was recrystallized three times from ethanol to yield 26 g of compound **1** and 7.7 g of hexaphenylditin, m.p. 233–234°C [1] as a by-product.

Compound **2**. The same procedure was used for the raction of 1-ethynylcyclopentanol with tri-p-tolyltin hydride.

Compound **5**. A solution of bromine (0.316 g, 1.98 mmol) in 10 ml of CCl_4 was added dropwise with stirring to an ice-cooled solution of 0. 913 (1.98 mmol) of **1** in 12 ml of CCl_4. The colour disappeared immediately. The mixture was allowed to warm to room temperature and set aside for 5 h. The solvent was evaporated off and the residue was recrystallized three times from cyclohexane to yield 0.7 g of compound **5**.

The other vinylphenyltin halides were prepared analogously by the use of ICl (chlorides) or I_2 (iodides).

Abbreviations. ^{1}H NMR data: s = singlet; d = doublet; m = complex pattern; b = broad. All coupling constants are in hertz.

(Z)-1-[2-(triphenylstannyl)vinyl]-1-cyclopentanol, 1. Yield: 68%; m.p. (recrystallized from ethanol): 79–80°C. Elemental analysis: Found(Calc.): C, 65.1 (64.9); H, 5.6 (5.6); Sn, 25.8 (26.0)%. IR: ν(O—H): 3578; ν(C—O), 1073 cm^{-1}. ^{1}H NMR: 1.033 (s,OH); 1.3–1.8 (m,C_5H_8); 6.213 (d(12.4), CH—Sn); 7.042 (d(12.4), CH), 7.2–7.5 (m, meta + para).

(Z)-1-[2-(tri-p-tolylstannyl)vinyl]-1-cyclopentanol, **2**. Yield: 63%; m.p. (recrystallized from ethanol): 129–130°C. Elemental analysis: Found (Calc.): C,67.11(66.82); H, 6.40 (6.41); Sn, 23.60 (23.58)%. IR: ν(O—H), 3575; ν(C-O), 1068 cm^{-1}. ^{1}H NMR: 0.99 (s,OH); 1.5–1.8 (m, C_5H_8); 2.32 (s, CH_3); 6. 10 (d(12.4), CH-Sn), 6.92 (d(12.4), CH); 7.245 (d, (7.8), meta); 7.604 (d(7.8), ortho).

(Z)-1-[2-(chlorodiphenlstannyl)vinyl]-1-cyclopentanol, **3**. Prepared from **1** and ICl in a 1:1 molar ratio at −10°C Yield: 76%; m.p. (recrystallized from cyclohexane): 149–150°C. Elemental analysis: Found(Calc.): C, 53.95 (54.39); H, 5.08 (5.05); Sn 28.8 (28.3)%. IR: ν(O—H), 3424; ν(C—O), 1076 cm^{-1}. ^{1}H NMR: 2.32 (s,OH); 1.4–1.8 (m, C_5H_8);

Table 1. Crystallographic data for compounds **1**. and **11**.

Formula	$C_{25}H_{26}OSn$	$C_{13}H_{16}Br_2OSn$
Formula weight	461.15	466.76
Space group	$P2_1/c$	$P2_12_12_1$
a (Å)	8.327(2)	8.675(4)
b (Å)	16.789(3)	12.523(7)
c (Å)	15.517(3)	14.009(8)
β(°)	92.31(3)	90(2)
V(Å^3)	2167.5(8),4	1521.9(2),4
D_{calc}(mg m^3)	1.413	1.914
Y(mm^{-1})	1.190	1.001
F(000)	936	984
Radiation (Å)	0.71073	0.71073
Scan range (°)	$1.79 < \theta < 25.01$	$2.16 < \theta < 12.33$
Crystal size (mm)	$0.42 \times 0.40 \times 0.36$	$0.32 \times 0.28 \times 0.40$
Reflections collected	5129	1356
Refinement method	Full-matrix Least-squares on F^2	Full-matrix Least-square on F^2
Data/restrain/para	3802/0/303	1356/0/98
Goodness-of-fit on F^2	1.063	1.139
R_1,[$I > 26(I)$]	0.0459	0.041
WR_2,[$I > 26(I)$]	0.1198	0.032
Largest diff. Peak and hole (e Å^{-3})	0.754–1.502	0.6347–1.056
Index range	$-1 < h < 9$	$0 < h < 11$
	$-1 < k < 19$	$0 < k < 15$
	$-18 < l < 18$	$0 < l < 17$

6.244 (d(11.3), CH—Sn); 6.902 (d(11.3), CH); 7.2–7.5 (m,meta + para); 7.6–7.8 (m, ortho).

(Z)-1-[2-(chlordi-p-tolylstannyl)vinyl]-1-cyclopentanol, **4**. Prepared from 2 and ICl in a 1 : 1 molar ratio at −10°C. Yield : 57%. m.p. (recrystallized from cyclohexane/CCl_4 (1 : 1): 145–146°C. Elemental analysis: Found(Calc.): C, 56.31 (56.35); H, 5.58 (5.63); Sn, 26.51 (26.52)%. IR: ν(O—H), 3534; ν(C—O), 1066 cm^{-1}. ^1H NMR : 2.17 (s, OH); 2.35 (s, CH_3); 1.76 (b,C_5H_8); 6.234 (d 11.3), CH-Sn); 6.839(d(11.3), CH); 7.211 (d(8), meta); 7.628 (d(8), ortho).

(Z)-1-[2-(bromodiphenylstannyl)vinyl]-1-cyclopentanol, **5**. Prepared from **1** and Br_2 in a 1 : 1 ratio at −10°C. Yield: 76%. m.p. (recrystallized from cyclohexane): 143–144°C. Elemental analysis: Found(Calc.): C, 49.15 (49.18); H, 4.60 (4.56); Sn, 25.49 (25.58)%. IR: ν(O—H), 3492; ν(C—O), 1074 cm^{-1}. ^1H NMR: 2.27 (s, OH); 1.4–1.8 (b, C_5H_8); 6.295 (d(11.3), CH—Sn); 6.871 (d(11.2), CH; 7.2–7.5 (m, meta + para); 7.6–7.8 (m, ortho).

(Z)-1-[2-(bromo-di-p-tolylstannyl)vinyl]-1-cyclopentanol, **6**. Prepared from **2** and Br_2 in a 1 : 1 molar ratio at room temperature. Yield, 48.0%. m.p. (recrystallized from cyclohexane): 144–145°C. Elemental analysis: Found(Calc.): C, 51.24 (51.26); H, 4.94 (5.12); Sn, 23.99 (24.13)%. IR: ν(OH), 3536; ν(C—O), 1072 cm^{-1}. ^1H NMR : 2.10 (s, O—H); 1.4–1.8 (b, C_5H_8); 2.35 (s, CH_3); 6.296 (d(11.3), CH—Sn); 6.866 (d(11.3), CH); 7.216 (d(8), meta); 7.634 (d(8), ortho].

(Z)-1-[2-(iododiphenylstannyl)vinyl]-1-cyclopentanol, **7**. Prepared from **1** and I_2 in a 1 : 1 molar ratio at room temperature. Yield, 60.7%. m.p. (recrystallized from cyclohexane): 126–127°C Elemental analysis: Found(Calc.): C, 44.68 (44.65); H, 4.19 (4.14); Sn, 22.29 (22.23)%. IR: ν(O—H), 3410; ν(C—O), 1072 cm^{-1}. ^1H NMR: 2.71 (s, OH); 1.4–1.8 (b, C_5H_8); 6.377 (d(11.2), CH—Sn); 6.799 (d(11.2), CH); 7.2–7.5 (m, meta + para); 7.6–7.8 (m, ortho).

(Z)-1-[2-(iododi-p-tolylstannyl)vinyl)-1-cyclopentanol, **8**. Prepared from **2** and I_2 in a 1 : 1 molar at room temperature. Yield, 61%. m.p. (recrystallized from cyclohexene): 96–97 Å. Elemental analysis: Found (Calc.): C, 46.75 (46.78); H, 4.71 (4.67); Sn, 22.10 (22.02)%. IR: ν(O—H), 3558; ν(C—O), 1059 cm^{-1}. ^1H NMR : 1.91 (s, OH); 1.4–1.8 (b, C_5H_8); 2.34 (s, CH_3); 6. 382 (d(11.4), CH—Sn); 6.792 (d(11.3), CH); 7.214 (d(8),meta); 7.635 (d(8), ortho).

(Z)-1-[2-(dichlorophenylstannyl)vinyl]-1-cyclopentanol, 9. Prepared from **1** and ICl in a 1 : 2 molar ratio at −10°C then allowed to warm to room temperature. Yield: 52%. m.p. (recrystallized from $CHCl_3$/petroleum ether (1 : 1, 30/60°C): 121–122°C. Elemental analysis: Found(Calc.): C, 41.27 (41.32); H, 4.26 (4.27); Sn, 31.40 (31.41)%. IR: ν(O—H), 3444; ν(C—O), 1067 cm^{-1}. ^1H NMR : 3.28 (s, OH); 1.4–1.8 (m, C_5H_8); 6.199 (d(10.4), CH—Sn); 6.956 (d(10.4), CH); 7.3–7.5 (m, meta + para); 7.7–7.9 (m, ortho).

(Z)-1-[2-(dichloro-p-tolylstannyl)vinyl]-1-cyclopentanol, **10**. Prepared from **2** and ICl in a 1 : 2 kmolar ratio at −10°C, then allowed to warm to room temperature. Yield: 46%. m.p. (recrystallized from $CHCl_3$/petroleum ether (1 : 1): 109–110°C. Elemental analysis: Found(Calc.): C, 42.03 (42.91); H, 4.59 (4.63); Sn, 29.94 (30.29)%. IR: ν(O—H), 3543; ν(C—O), 1065 cm^{-1}. ^1H NMR : 3.0 (s, OH); 1.4–1.8 (m, C_5H_8); 2.37 (s, CH_3); 6.234 (d(10.4), CH—Sn); 6.958 (d(10.4), CH); 7.258 (d(8), meta); 7.665 (d, ortho).

(Z)-1-[2-(dibromophenylstannyl]-1-cyclopentanol, **11**. Prepared from **1** and Br_2 in a 1 : 2 molar ratio at −10°C, then allowed to warm to room temperature. Yield, 54.3%. m.p. (recrystallized from cyclohexane/CCl_4): 102-103°C Elemental analysis: Found(Calc.): C, 33.48 (33.45); H, 3.51 (3.46); Sn, 25.38 (25.43)%. IR: ν(O–H), 3490; ν(C—O), 1072 cm^{-1}. ^{1}HNMR: 2.97 (s, OH); 1.4–1.8 (m, C_5H_8); 6.304 (d(10.4), CH—Sn); 6.873 (d(10.4), CH; 7.3–7.5 (m, meta + para); 7.7–7.8 (m, ortho).

(Z)-1-1[2-(dibromo-p-tolylstannyl)vinyl]-1-cyclopentanol, **12**. Prepared from **2** and Br_2 in a 1 : 2 molar ratio at −10°C, then allowed to warm to room temperature. Yield: 42%. m.p. (recrystallized from cyclohexane/CCl_4(1 : 1)): 98–99°C. Elemental analysis: Found(Calc.): C, 35.02 (34.97); H,3.73 (3.77); Sn, 24.71 (24.69)%. IR: ν(O—H), 3477; ν(C—O), 1067 cm^{-1}. ^1H NMR: 2.77 (s, OH); 1.3–1.8 (m, C_5H_8); 2.37 (s,CH_3); 6.300 (d (10.1)), CH–Sn); 6.876 (dd(10.2,3.0),CH); 7.254 (d(8),meta); 7.652 (d(8),ortho).

(Z)-1-[2-(didiodophenylstannyl)vinyl]-1-cyclopentanol, **13**. Prepared from **1** and I_2 in a 1 : 2 molar ratio at room temperature. Yield, 60.6%. m.p. (recrystallized from cyclohexane): 118–120°C Elemental analysis: Found(Calc.): C, 27.85 (27.83); H, 2.90 (2.88); Sn, 21.21 (22.16)%. IR: ν(O—H), 3479; ν(C—O), 1066 cm^{-1}. ^{1}HNMR : 2.51 (s, OH); 1.4–1.8 (m, C_5H_8); 6.400 (d(10.3), CH—Sn); 6.627 (d(10.3),CH); 7.2–7.6 (m,meta + para); 7.7–7.8 (m, ortho).

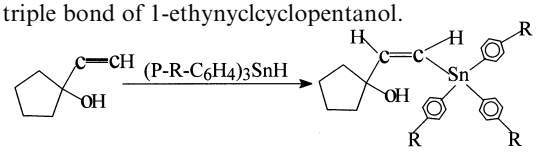
(Z)-1-[2-(diiodo-p-tolylstannyl)vinyl]-1-cyclopentanol, **14**. Prepared from **2** and I_2 in a 1 : 2 molar ratio at room temperature. Yield : 52%. m.p. (recrystallized from cyclohexane/CCl_4 (1 : 1)): 101–102°C. Elemental analysis: Found(Calc.): C, 28.96 (29.24); H, 3.21 (3.16); Sn, 20.58 (20.64)%. IR: ν(O—H), 3534; ν(C—O), 1059 cm^{-1}. ^1H NMR :2.43 (s, OH); 1.4–1.8 (m, C_5H_8); 2.28 (s, CH_3); 6.50 (d(10.04), CH—Sn); 7.03 (d (10.04), CH); 7. 13–7.63 (m, meta + para); 7.69–7.81 (m, ortho).

RESULTS AND DISCUSSION

Synthesis

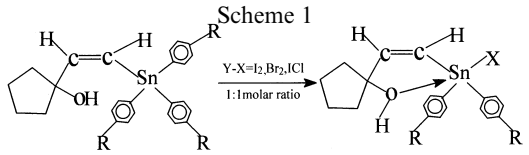
The (Z)-1-[2-(triarylstannyl)vinyl]-1-cyclopentanols (aryl = phenyl, p-tolyl) were synthesized by the

addition of the corresponding triaryltin hydride to the triple bond of 1-ethynyclcyclopentanol.



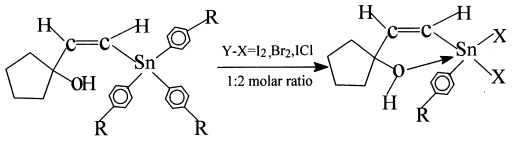
R=H, compound 1; R=CH_3, compound 2

Scheme 1



X=Cl, R=H, compound 3; R=CH_3, compound 4;
X=Br, R=H, compound 5, R=CH3, compound 6;
X=I, R=H, compound 7; R=CH_3, compound 8.

Scheme 2



X=Cl, R=H, compound 9; R=CH_3, compound 10;
X=Br, R=H, compound 11, R=CH_3, compound 12;
X=I, R=H, compound 13; R=CH_3, compound 14.

Scheme 3

The reactions of **1** and **2** with halogens in a 1 : 1 or 1 : 2 molar ratio yield the corresponding mono- or dihalides, respectively.

IR *and* ^{1}H NMR *data*

The IR and ^{1}H NMR data are consistent with the expected structures. They are given in the experimental details.

IR data shows that all the compounds exhibit the two characteristic O—H and C—O stretching vibrational peaks. In the ^{1}H NMR, (—CH=CH—) of all halides shift to downfield compared with **1** and **2**. The $^nJ_{CH=CH}$ coupling consistants decrease in the following order $SnAr_3 < SnAr_2X < SnArX_2$.

Solid-state structures

The molecular structure of **1** and **11** are shown in Figs 1–2, respectively and selected interatomic bond distances (Å) and angles (°) are listed in Table 2. The Sn atom in **1** is bound to three phenyl groups as well as to the C(7) atom of the vinyl residue [Sn—C(7), 2.134 Å] leading to a distorted tetrahedral geometry. The tetrahedral angles range from 100.8° to 120.6°. There is a Z configuration at the double bond. It is possible that there is weak interaction between Sn atom and O atom, for the presence of O atom influences the strength of Sn—C(ph) bonds. From Table 2 we can see the bond distance of Sn—C(14) is longer than that of Sn—C(8) and Sn—C(20), respectively. From above, we can see the differences between **1** and steroidal compounds. In steriods, there is an intramolecular coordination from O to Sn [1], and, the central tin atom has a strongly distorted trigonal bipyramidal geometry.

The structure of **11** is shown in Fig. 2. The tin atom is five coordinated. The geometry about the tin atom is based on a trigonal bipyramid with the trigonal plane defined by the Br(2), C(1) and C(7)atoms, while the Br(1) and O atom is in the axial position (Br(1)—Sn—O = 169.9 Å). The Sn—Br bond distances are not equal, for the bond distance of Sn—Br(1) (2.582 Å) is significantly longer than that of Sn—Br(2) (2.490 Å). This difference may be rationalized in terms of the former bond being apical and the latter equatorial. The five-membered chelate ring is almost planar.

Biological activity

The data summarized in Tables 3 and 4 show that dihalides and aductor display inhibitory action to

Table 2. Selected bond lengths (Å) and angle (°)

		1				11	
Bond	dist.	Bond	Angle	Bond	dist.	Bond	Angle
Sn—C7	2.134(9)	C7—Sn—C20	113.1(3)	Sn—Br(2)	2.490(2)	C(1)—Sn—O	87.4(4)
Sn—C8	2.135(7)	C20—Sn—C8	108.3(2)	Sn—C(7)	2.095(14)	Br(2)—Sn—Br(1a)	98.0(1)
Sn—C20	2.148(6)	C20—Sn—C14	106.9(2)	Sn—Br(1a)	2.582(2)	C(7)—SnBr(1a)	96.1(4)
Sn—C14	2.163(6)	C7—Sn—C8	120.6(3)	Sn—C(1)	2.159(11)	Br(2)—Sn—C(7)	112.6(4)
C6—C7	1.297(12)	C7—Sn—C14	100.8(3)	Sn—O	2.446(8)	B(2)—Sn—O	87.0(2)
O—C5	1.438(9)	C8—Sn—C14	105.9(2)	Br(1)—Sn[a]	2.582(2)	C(7)—Sn—O	71.8(4)
C5—C6	1.468(10)	Br(2)—Sn—C(1)	107.7(3)	C(9)—O	1.445(14)	C(1)—Sn—Br(1a)	99.0(3)
		C(1)—Sn—C(7)	133.1(5)			O—Sn—Br(1a)	169.9(2)

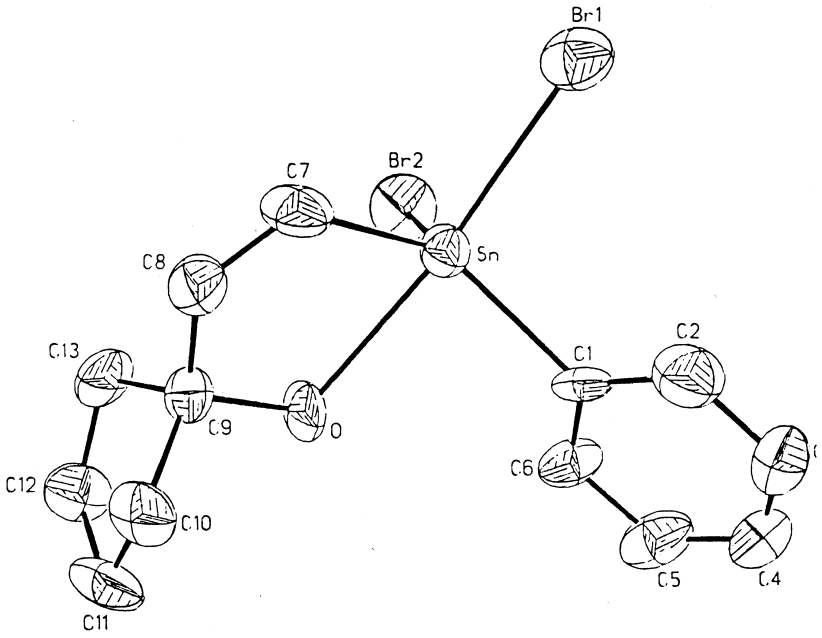

Br1
Br2
C7
Sn
C8
C13
C1
C2
C9
O
C6
C12
C10
C5
C4
C11

Fig. 1.

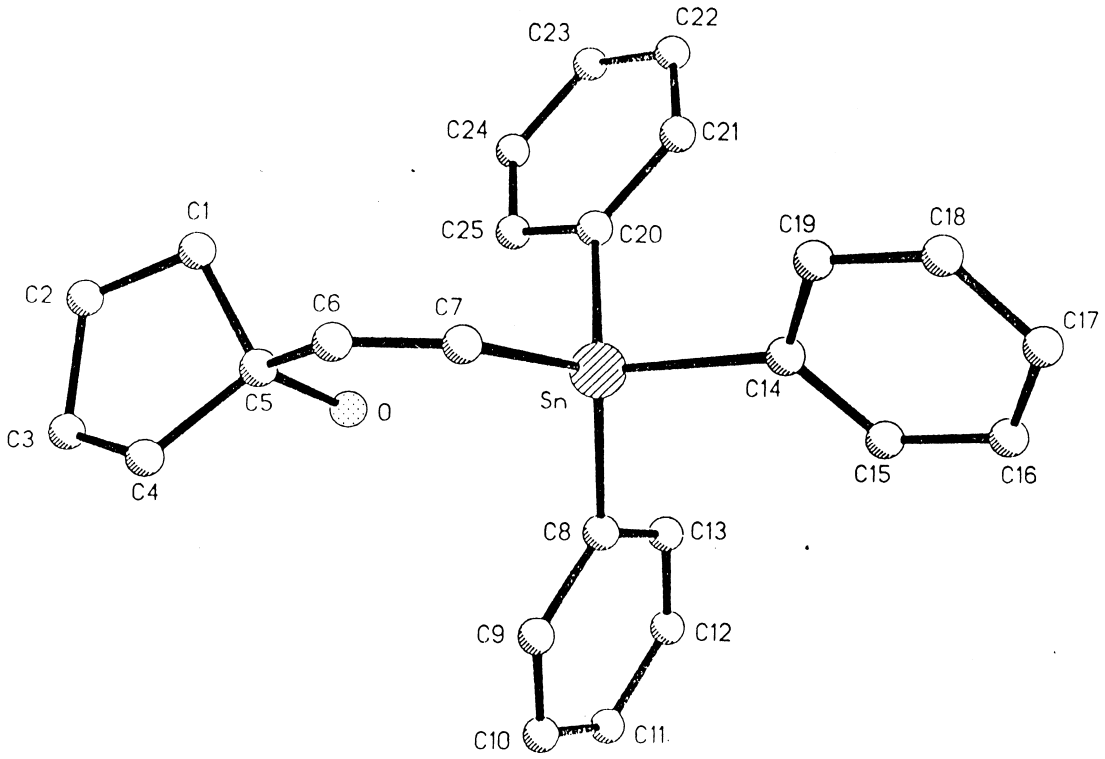

C23
C22
C24
C21
C1
C25
C20
C19
C18
C2
C6
C7
C17
C5
O
Sn
C14
C3
C15
C16
C4
C8
C13
C9
C12
C10
C11

Fig. 2.

Table 3. Inhibitory effect of the compounds on some tumor cells (MTT)

Comound	Tumor cell	Dose (μM)	Inhibitory rate(%)	IC_{50}[a]	Estimation[b]
1	KB	0.1	3.0		
		1	73.0	0.64	++
		5	88.7		
	Bel	0.1	2.8		
		1	74.7	0.77	++
		5	74.7		
5	HCT	0.1	26.6		
		1	39.6	0.70	++
		10	99.9		
	B_{16}	0.1	34.0		
		1	76.0	0.30	++
		10	84.2		
9	B_{16}	0.1	28.9		
		1	61.2	0.40	++
		10	99.2		
11	Bel	0.1	67.0		
		1	72.7	0.06	+++
		10	99.5		
	B_{16}	0.1	36.5		
		1	81.7	0.02	+++
		10	96.3		
13	HCT	0.1	10.5		
		1	61.7	0.70	++
		10	100		
	Bel	0.1	0		
		1	35.7	0.70	++
		10	99.5		
	B_{16}	0.1	54.1		
		1	58.1	0.70	++
		10	93.5		
	Beap	0.1	31.8		
		1	44.1	0.60	++
		10	98.5		
	Escl	0.1	11.3		
		1	62.4	0.70	++
		10	99.7		

[a] Drug concentration required to inhibit tumor cell by 50%.
[b] ++ : ($0.1 \leqslant IC_{50} < 1$), +++ : ($IC_{50} < 0.1$)

Table 4. Immunocompetence assay of the compounds on celiac mastocyte of rat

Compound	Dose (μM)	Inhibitory rate(%)	Estimation[a]
1	20	67.8	
	200	98.9	++
4	20	69.2	
	200	86.2	++
6	20	97.5	
	200	97.5	+++
9	20	61.2	
	200	97.5	++
11	20	97.5	
	200	97.5	+++
13	20	97.7	
	200	97.7	+++

[a] ++: [Inhibitory rate $\geqslant$ 50% (Dose = 20)], +++: [Inhibitory rate $\geqslant$ 90% (Dose = 20)]

tumor cells (B_{16}, HCT, Bel, Beap and Escl) and immucompetence assay on celiae mastocyte of rat.

The idea of including cyclopentanoidal structure into antitumor organotin compounds has proven to be fruitful. The compounds used to test proved to be active. Compound **11**, being the most active not only in antitumor but also in immunity, possibly serves as a suitable model for achieving a tin-ligand configuration optimal with regards to its antitumor activity or immunity activity. The results obtained merit further studies on the structure-activity relationship of antitumor or immunity organotin compounds of this type.

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