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# Synthesis, crystal structure and in vitro antitumor activity of di-*n*-butyltin 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoates

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**Abstract**

Dibutyltin(IV) oxide reacts with the cantharidin analogue, 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoic acid, **A**, to give the complexes $[(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COOBu_2Sn)_2O]_2$ (**1**) and $(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COO)_2SnBu_2$ (**2**) which had been characterized by IR and $^1H$, $^{13}C$, $^{119}Sn$ NMR. Single X-ray crystal structure analysis has been determined for compound (**1**), which was analogue to most other $[(RCOOBu_2Sn)_2O]_2$. The dimer features central of $Bu_4Sn_2O_2$ unit with the two $Bu_2Sn$ groups being linked via bridging oxygen atom. Each tin atom adopts distorted trigonal bipyramidal structures via two carbons from a dibutyl moiety and three oxygen atoms from cantharidin derivative and bridging oxygen atom. In vitro tests show compounds **1** and **2** exhibit high cytotoxicity against P388 and HL-60.


*Keywords:* Organotin; Cantharidin; Synthesis; Crystal structure; Antitumor activity

## 1. Introduction

The structural chemistry of organotin carboxylate compounds has attracted considerable attention owing to their antitumor activity [1–3]. Among those compounds dibutyltin derivatives have displayed both higher activity and lower toxicity [4]. So the antitumor activity of many compounds of the type $[(RCOOBu_2Sn)_2O]_2$ and $(RCOO)_2Bu_2Sn$ has been studied [5,6]. This may yield new leads for the development of antitumor drugs that may possess lower toxicity than platinum compounds [7]. Cantharidin is the main effective ingredient of Canthatis vesicatoria, a traditional Chinese medicine for malignancy treatments. Several studies have shown that Cantharidin and its derivatives possess potential antitumor activities for liver, lung, colon and breast cancers [8]. We have recently combined dibutyltin with 5-fluorouracil derivatives to synthesize the complexes of $[(5\text{-flurorouracil})\text{-}1\text{-}(CH_2)_mCOOSnBu_2]O_2$ ($m$ = 1, 2) and the bioassay shows that they exhibit strong antitumor activity against OVCAR-3 and PC-14 cell-line in vitro [9] and acceptable acute toxicity in mice [10].

In order to study organotin complexes as possible candidate for antitumor agent and the structure-activity relationships of these complexes, we successfully prepared the dibutyl organotin(IV) derivatives of Cantharidin analogue, which had been characterized by IR, $^1H$, $^{13}C$ and $^{119}Sn$ NMR spectra. And crystallographic data is also presented for the compound (**1**).

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## 2. Experimental

### 2.1. General methods

IR spectra were recorded using KBr pellets for solid samples on a NICOLET NEXUS 470 FT-IR. $^{1}H$, $^{13}C$ NMR spectra were recorded on a Bruker DPX-400 spectrometer operating at 400 and 100.6 MHz, respectively, and with TMS as the internal reference in $CDCl_3$. $^{119}Sn$ NMR spectra were collected at a spectrometer frequency of 186.4 MHz on a Varian UNITY 500 with a 10 mm broadband probe. All samples were prepared in $CDCl_3$ solution and chemical shift values were referenced externally with $Me_4Sn$.

Toluene was dried over Na and distilled prior to use under $N_2$. Dibutyltin oxide was synthesized following the literature methods [11]. The Cantharidin analogue and its carboxylic derivative, 4′-(7-oxabicyclo [2,2,1]-5-heptane-2,3-dicarboximide) benzoic acid, **A**, were synthesized according to the literature methods [12].

The tumor inhibiting effect of compounds **1** and **2** was tested in vitro by using the murine leukemia cell line P388 and human leukemia cell line HL-60 with the method of MTT. The human Lung Epithelial Cell line A-549 with the method of SRB.

### 2.2. Synthesis of the complexes $[(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COOBu_2Sn)_2O]_2$ (1) and $(p\text{-}C_8H_8NO_3\text{–}C_6H_4\text{–}COO)_2\text{-}SnBu_2$ (2)

Di-*n*-butyltin oxide (1.24 g, 5 mmol) was dissolved in toluene (40 ml) containing a few of 4 Å molecular sieves and the carboxylic acid, **A**, [(1.44 g, 5 mmol) for compound (**1**) and (2.87 g, 10 mmol) for compound (**2**)] was added. The mixture was stirred under $N_2$ for 8 h at a temperature of 80 °C. After cooling and filtration, the residue was extracted three times with THF. Concentration of the resulting solution gave colorless solid. The solid obtained was purified by recrystallisation from THF/*n*-hexane.

Compound (**1**): yield 57.8%, m.p.: 248–250 °C. Anal. Calc. for $C_{92}H_{120}N_4O_{22}Sn_4$: Sn, 22.52. Found: 22.32%. IR($cm^{-1}$): $\nu(CH_3)$ 3089, 2927, $\nu(CH_2)$ 2957, 2874, $\nu$(C=O) 1770, 1709, $\nu$(Ar) 1607, 1565, 1510, 1463, $\nu$(C–O–C) 1189, $\nu$(Sn–O–Sn) 686, $\nu$(Sn–C) 574, $\nu$(Sn–O) 506.

Compound (**2**): yield 71.6%, m.p. 286–288 °C. Anal. Calc. for $C_{38}H_{42}N_2O_{10}Sn$: 14.94. Found: 14.50%. IR($cm^{-1}$): $\nu(CH_3)$ 3104, 2927, $\nu(CH_2)$ 2957, 2874, $\nu$(C=O) 1778, 1705, $\nu$(Ar) 1607, 1566, 1510, 1463, $\nu$(C–O–C) 1188, $\nu$(Sn–C) 575, $\nu$(Sn–O) 505.

### 2.3. Crystal structure determination of the compound (1)

A single crystal ($0.40 \times 0.36 \times 0.27$ mm) of the compound **1** was mounted in a glass capillary, and data collection was performed on a Rigaku RAXIS-RAPID diffraction by using Mo Kα radiation ($\lambda = 0.71073$ Å) in the $\theta$ range from 1.15° to 27.48° at 293 K. The final cycle of full-matrix least-squares refinement was based on 13752 observed reflections. The final agreement factor was $R = 0.0807$ [$I > 2\sigma(I)$]. Crystal data: $C_{92}H_{120}N_4O_{22}Sn_4 \cdot 6C_4H_4O$, $Fw = 2517.11$, Triclinic, $P\bar{1}$, $a = 14.0445(12)$ Å, $b = 14.1483(15)$ Å, $c = 19.051(2)$ Å, $\alpha = 96.418(2)°$, $\beta = 105.204(5)°$, $\gamma = 118.296(2)°$, $V = 3089.8(6)$ Å$^3$, $Z = 1$, $F(000) = 1292$, $D_c = 1.353$ mg/m$^3$.

## 3. Results and discussion

### 3.1. Synthesis

The carboxylic acid **A** reacts with the di-*n*-butyltin oxide yielding two different compounds depending on molar ratio acid/tin engaged in the reaction: bis[di-*n*-butyl(carboxylato)tin] oxide (**1**) for a 1:1 ratio and di-*n*-butyltin di(carboxylate) (**2**) for a 2:1 ratio. The synthesis route for this compound is shown in Fig. 1.

An X-ray quality crystal of the compound (**1**) was obtained from a 1:1 condensation of dibutyltin(IV) oxide

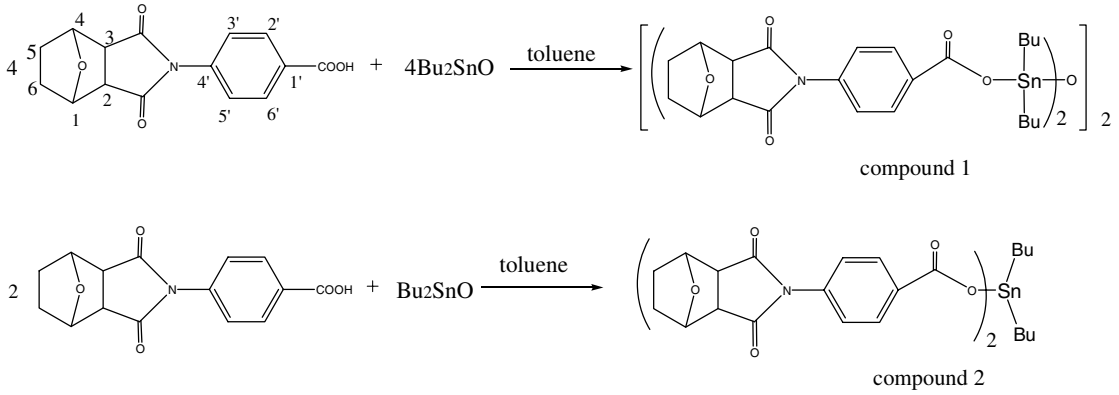


Fig. 1. The synthesis of compounds (**1**) and (**2**).