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Synthesis and In Vitro Antitumor Activity of Some Triarylantimony Di(*N*-phenylglycinates)

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ABSTRACT: *Triarylantimony(V) di(N-phenylglycinates) $(PhNHCH_2COO)_2SbAr_3$ (Ar = Ph, p-$CH_3C_6H_4$, p-ClC_6H_4, and p-FC_6H_4) have been synthesized and characterized by elemental analysis, IR, ^1H NMR, and mass spectra. The crystal structure of $(PhNHCH_2COO)_2Sb(C_6H_4F\text{-}p)_3$ has been determined by X-ray diffraction. The in vitro antitumor activities of these compounds against three cancer cell lines are reported.* © 2003 Wiley Periodicals, Inc. Heteroatom Chem 15:32–36, 2004; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10208

INTRODUCTION

References describing synthesis, structures, and applications of $R_3Sb(O_2CR')_2$ (R = alkyl, aryl) have appeared in the literature [1–11]. Bajpai and coworkers [1] considered that the biological activity of some organoantimony carboxylates was not significantly affected by the nature of the R groups at Sb. However, Singhal and co-workers [3] found that the effect of the nature of R groups on the activity was relatively complex. The published data on the antitumor activity of these compounds, however, are limited [9,10]. In order to study the influence of amino acid ligands at Sb on their antitumor activity, we have prepared a series of triarylantimony(V) di(*N*-phenylglycinates). At the same time, we intended to learn about the bonding and structure of these compounds.

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RESULTS AND DISCUSSION

Compounds **1–4** are white crystals and unaffected by atmospheric moisture. They are easily soluble in solvents such as C_6H_6, $CHCl_3$, DMF, and DMSO. The yields, melting points, and elemental analysis are given in Table 1.

$$C_6H_5NHCH_2COOH + Ar_3SbBr_2 \xrightarrow{Et_3N} Ar_3Sb(O_2CCH_2NHC_6H_5)_2$$

Ar = Ph (**1**); *p*-$CH_3C_6H_4$ (**2**); *p*-ClC_6H_4 (**3**); *p*-FC_6H_4 (**4**).

IR

The infrared spectra of **1–4** have been recorded in the range of 4000–400 cm^{-1}. The absorption bands can be assigned on the basis of earlier publications [9,11] and are listed in Table 2. The absence of a strong band in the 3500–3300 cm^{-1} region, due to ν(OH), indicates that deprotonation and coordination of the carboxylate group with antimony have occurred as expected.

In the majority of organoantimony(V) compounds, antimony has a coordination number of five. In some cases it may have a coordination number of six [2,7] or seven [5,8,9,11]. The IR stretching vibration frequencies of carbonyl groups in organoantimony carboxylates are very important for determining their structure. When there are interactions between antimony atoms and the carbonyl oxygen atom of the carboxylate groups, the asymmetric absorption vibration frequencies [$\nu_{asy}(CO_2)$] of

TABLE 1 Yields and Elemental Analyses of **1–4**

			Found (Calcd)			
	Yield (%)	*m.p. (°C)*	*C*	*H*	*N*	*Formula*
1	79.6	164–166	62.38 (62.50)	4.67 (4.78)	4.32 (4.29)	$C_{34}H_{31}N_2O_4Sb$
2	76.7	83–86	63.83 (63.90)	5.33 (5.36)	4.10 (4.03)	$C_{37}H_{37}N_2O_4Sb$
3	65.2	181–183	53.77 (53.97)	3.80 (3.73)	3.59 (3.70)	$C_{34}H_{28}Cl_3N_2O_4Sb$
4	81.1	151–154	57.59 (57.73)	3.99 (3.99)	3.90 (3.96)	$C_{34}H_{28}F_3N_2O_4Sb$

carbonyl groups decrease, while the symmetric absorption vibration frequencies [$\nu_{smy}(CO_2)$] increase. Therefore, their differences [$\Delta\nu(CO_2)$] also decrease [3,4]. In the IR spectra of **1–4**, the carboxylate bands are observed in the characteristic regions: $\nu_{asy}(CO_2)$ between 1678 cm^{-1} and 1650 cm^{-1} and $\nu_{smy}(CO_2)$ between 1379 cm^{-1} and 1318 cm^{-1}. On the basis of the difference $\Delta\nu(CO_2)$, these compounds can be divided into two categories: Compounds **1** and **2** show high $\Delta\nu(CO_2)$ values (309 and 341 cm^{-1} respectively) while compounds **3** and **4** show low $\Delta\nu(CO_2)$ values (271 and 282 cm^{-1}). For the former, we assume weak or no interaction between the antimony atom and the carbonyl oxygen atoms of the carboxylate groups. For the latter, we assume strong interaction between the carbonyl oxygen atoms of the carboxylate groups and the antimony atom (see the crystal structure of compound **4**). In addition, the frequencies of Sb—C deformations appear between 460 cm^{-1} and 510 cm^{-1}, which are consistent with those noted in the literature [12,13].

^1H NMR

The ^{1}H NMR data of **1–4** are listed in Table 3. The amino hydrogen is so active that its displacement can not be assigned. All of the protons in the compounds have been identified and the total number of protons calculated from the integration curve tallies with what has been expected from the molecular formula.

MS

The main mass spectral data of compound **4** are listed in Table 4. Although there is no molecular ion peak, the fragment ions found are in agreement with the expected structure. Decarboxylation and dearylation from antimony atom are the principle breakdown patterns for the compound.

TABLE 2 Important IR Data of **1–4** (cm^{-1})

	$\nu_{asy}(CO_2)$	$\nu_{sym}(CO_2)$	$\Delta\nu(CO_2)$	$\nu(Sb–C)$
1	1678	1369	309	460
2	1659	1318	341	485
3	1650	1379	271	488
4	1652	1370	282	510

Crystal Structure of **4**

A colorless crystal of **4** obtained from ethyl acetate/petroleum ether solution was mounted in a glass capillary and used for data collection. Figure 1 shows the molecular structure and gives the atom numbering scheme. The selected bond distances and angles are listed in Table 5. The crystallographic data was deposited at CCDC [14].

Carboxylates can be either unidentate or bidentate. The molecule of **4** consists of a monomer with a seven-coordinated antimony atom surrounded by four oxygen atoms and three aryl groups. The coordination geometry of antimony can be described as a distorted pentagonal bipyramid with the plane being defined by four oxygen atoms from two asymmetrically chelating carboxylate groups and one carbon atom from an aryl group, while other aryl groups occupy the axial positions. The atoms Sb(1), O(1), O(2), O(3), O(4), and C(29) are coplanar within 0.0846 Å. The Sb(1)—C(29) distance is 2.074 (5) Å. The Sb(1)—O(2) and Sb(1)—O(4) distances are considerably shorter than the sum (3.60 Å) of the van der Waals radii of antimony and oxygen atoms (2.2 Å and 1.40 Å, respectively). The two distances are also fairly shorter than the

TABLE 3 ^{1}H NMR Data of **1–4** (ppm)

	Ph	*CH_2*	*Ar*
1	6.39–7.10 (10H, m)	3.65 (4H, s)	7.47–8.00 (C_6H_5, 15H, m)
2	6.40–7.11 (10H, m)	3.63 (4H, s)	7.25–7.95 (C_6H_4, 12H, m) 2.39 (CH_3, 9H, s)
3	6.35–7.11 (10H, m)	3.64 (4H, s)	7.40–7.94 (C_6H_4, 12H, m)
4	6.36–7.11 (10H, m)	3.64 (4H, s)	7.16–8.02 (C_6H_4, 12H, m)

TABLE 4 Fragment Ions Observed for **4**

m/z	*Fragment*	*Intensity*	*m/z*	*Fragment*	*Intensity*
408	$Sb(C_6H_4F)_3^+$	5	150	$PhNHCH_2COO^+$	1
406	$Sb(C_6H_4F)_3^+$	7	123	Sb^+	2
313	$Sb(C_6H_4F)_2^+$	6	121	Sb^+	3
311	$Sb(C_6H_4F)_2^+$	10	106	$PhNHCH_2^+$	74
218	$Sb(C_6H_4F)^+$	81	95	$FC_6H_4^+$	5
216	$Sb(C_6H_4F)^+$	100	77	Ph^+	41
190	FC_6H_4-$C_6H_4F^+$	65	44	CO_2^+	6
151	$PhNHCH_2COOH^+$	20			

corresponding distances in $Ph_3Sb(OCOCF_3)_2$ (3.209, 3.231 Å) [6]. This indicates that there have been certain coordination interactions between the carbonyl oxygen atoms of the two asymmetrical *N*-phenylglycine groups and the antimony atom. The apical Sb(1)—C(17) and Sb(1)—C(23) distances are almost equal. The C(1)—O(1) and C(1)—O(2) distances are slightly different from C(9)—O(3) and C(9)—O(4) distances. The C(17)—Sb(1)—C(23) angle is much larger than the corresponding angle in $Ph_3Sb(OCOCF_3)_2$ [124.47 (13)°]. These differences can be attributed to the —I effect of F of the aryl groups and the steric effect of the two *N*-phenylglycine groups in the molecule. The —I effect of F enhances the Lewis acidity of Sb and leads to the stronger Sb: O═C coordination [15].

There is no hydrogen-bonding interaction between the amino hydrogen atom and the carbonyl oxygen atom of an adjacent molecule. It can possibly be attributed to the coordination interactions between the carbonyl oxygen atoms and the antimony atom.

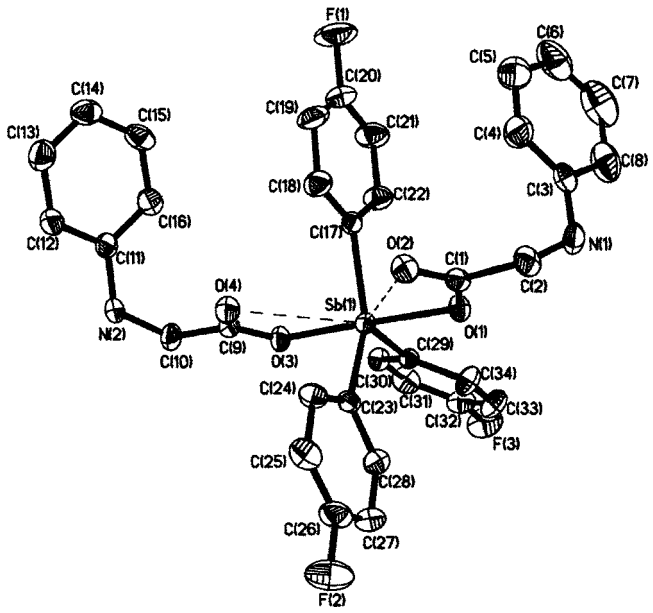

FIGURE 1 The molecular structure of **4**.

Antitumor Activity

The antitumor activity is assayed by the MTT method [16,17]. It is listed in Table 6. The results showed that these compounds exhibit certain activities against the three cancer cells in vitro. The compounds **1–4** have relatively higher antitumor activity than the triphenylantimony dibromide. The antitumor data indicates that the nature of the aryl affects antitumor activity. For example, when Ar is 4-ClC_6H_4, compound **3** has relatively higher activity to HCT-8 cells.

EXPERIMENTAL

Elemental analyses were based on results from a Yanaco CHN Corder MT-3 elemental analyzer. IR spectra were recorded on a Bruker Equinox 55 spectrometer, in KBr discs. ^{1}H NMR spectra were measured on a BRUKER AC-P200 spectrometer in $CDCl_3$ solution with TMS as internal standard. Mass

TABLE 5 Selected Bond Distances (Å) and Bond Angles (°) of **4**

Sb(1)—C(29)	2.074 (5)	C(29)—Sb(1)—C(23)	109.5 (2)
Sb(1)—C(23)	2.079 (5)	C(23)—Sb(1)—C(17)	139.8 (2)
Sb(1)—C(17)	2.081 (6)	C(23)—Sb(1)—O(1)	90.4 (2)
Sb(1)—O(1)	2.093 (4)	C(29)—Sb(1)—O(3)	87.1 (2)
Sb(1)—O(3)	2.098 (4)	C(17)—Sb(1)—O(3)	90.3 (2)
Sb(1)—O(2)	2.816 (6)	C(29)—Sb(1)—C(17)	110.6 (2)
Sb(1)—O(4)	2.941 (6)	C(29)—Sb(1)—O(1)	87.3 (2)
O(1)—C(1)	1.272 (6)	C(17)—Sb(1)—O(1)	90.3 (2)
O(2)—C(1)	1.202 (6)	C(23)—Sb(1)—O(3)	92.9 (2)
O(3)—C(9)	1.281 (6)	O(1)—Sb(1)—O(3)	174.2 (1)
O(4)—C(9)	1.192 (6)	O(2)—C(1)—O(1)	122.8 (4)
N(1)—C(3)	1.377 (7)	O(2)—C(1)—C(2)	121.8 (5)
N(1)—C(2)	1.412 (7)	O(1)—C(1)—C(2)	115.3 (5)
		O(4)—C(9)—O(3)	123.6 (4)
		O(4)—C(9)—C(10)	123.2 (4)
		O(3)—C(9)—C(10)	113.2 (5)
		C(3)—N(1)—C(2)	121.7 (5)
		C(11)—N(2)—C(10)	123.2 (5)

TABLE 6 Inhibition Ratio (%) (5 μg/ml) of **1–4**[a]

	KB Cells	*Bel-7402 Cells*	*HCT-8 Cells*
1	36.45	31.63	2.48
2	−4.35	55.88	12.85
3	11.27	−16.13	75.55
4	12.66	−32.12	12.24
[b]	−3.25	−11.45	−0.11

[a]Inhibition ratio (%) = $(A_1 - A_2)/A_1 \times 100\%$. A_1: the mean optical densities of untreated cells. A_2: the mean optical densities of drug-treated cells.
[b]Ph_3SbBr_2.

spectra were recorded on a HP-5988A mass spectrometer at 70 eV with the temperature of ionization being 200°C. All the reactions involving metal halides were carried out under anhydrous and oxygen-free argon atmosphere. Solvents were purified, dried, and stored via reference methods.

Reagents

N-Phenylglycine was synthesized as described [18]. Ar_3Sb was converted into the corresponding dibromide by direct bromination, and the solid product was recrystallized from toluene-petroleum ether mixture [19].

$$C_6H_5NH_2 + ClCH_2COOC_2H_5 \xrightarrow[\text{Reflux 10 h}]{CH_3COONa/C_2H_5OH} C_6H_5NHCH_2COOC_2H_5$$

$$\xrightarrow{10\%\ NaOH} \xrightarrow{20\%\ HCl} C_6H_5NHCH_2COOH$$

Synthesis of **1–4**

Typically, to *N*-phenylglycine (1 mmol) and triethylamine (0.8 ml) in THF (40 ml) was added 0.5 mmol of Ar_3SbBr_2. The reaction mixture was stirred at room temperature for 24 h and filtered. The filtrate was evaporated in vacuo. The obtained solid was recrystallized from ethyl acetate/petroleum ether.

Crystal Structure Determination of **4**

Diffraction measurements were carried out on a Bruker Smart 1000 diffractometer (graphite-monochromatized Mo-K_α radiation, $\lambda = 0.71073$ Å). The crystal class, orientation matrix, and accurate unit-cell parameters were determined by standard procedures. The intensities were corrected for absorption using the SADABS program. The structure was determined by the heavy atom method and refined by a full-matrix least square procedure based on F^2.

TABLE 7 Crystallographic Data for **4**

Formula	$C_{34}H_{28}F_3N_2O_4Sb$
Temperature (K)	293 (2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2(1)/n$
a (Å)	16.66 (3)
b (Å)	9.761 (16)
c (Å)	18.46 (3)
β (°)	105.72 (3)
Volume (Å^3)	2889 (8)
Z	4
Density (Mg mm^{-3})	1.626
Absorption coefficient (mm^{-1})	1.018
$F(000)$	1424
Crystal size (mm)	0.24 × 0.16 × 0.12
θ Range for data collection (°)	1.93–25.03
Limiting indices	$-10 \leqq h \leqq 19$, $-11 \leqq k \leqq 11$, $-21 \leqq l \leqq 21$
Reflections collected	11,599
Independent reflections	5096 ($R_{int} = 0.0438$)
Completeness to $\theta = 25.03°$	99.9%
Absorption correction	Semi-empirical from equivalents
Refinement method	Full-matrix least-squares on F^2
Goodness-of-fit on F^2	1.090
Final R indices [$I > 2\sigma$ (I)]	$R_1 = 0.0357$, $wR_2 = 0.0746$
R indices (all data)	$R_1 = 0.0641$, $wR_2 = 0.0958$
Largest diff. peak and hole (e A^{-3})	0.425 and −0.399

Non-hydrogen atoms were refined with anisotropic thermal parameters. Crystal data are summarized in Table 7.

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