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Synthesis, characterization and cytotoxicity of some triarylbismuth(V) di(*N*-*p*-toluenesulfonyl) aminoacetates and the crystal structure of $(4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2)_2Bi(C_6H_4Cl\text{-}4)_3$

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A series of triarylbismuth(V) di(*N*-*p*-toluenesulfonyl)aminoacetates with the formula $(4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2)_2BiAr_3$ (Ar=C_6H_5, 4-$CH_3C_6H_4$, 4-ClC_6H_4, 4-BrC_6H_4) were synthesized and characterized by elemental analysis, IR, ^{1}H NMR and mass spectra. The crystal structure of $(4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2)_2Bi(C_6H_4Cl\text{-}4)_3$ was determined and shows the bismuth to exist in a distorted trigonal bipyramidal geometry. Four human neoplastic cell lines (HL-60, PC-3MIE8, BGC-823 and MDA-MB-435) were used to screen these compounds. The results indicate that these compounds at 10 μM show cytotoxicity. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: arylbismuth; crystal structure; antitumor activity

INTRODUCTION

A large number of references describing the synthesis and applications of R_3BiX_2 (R = alkyl, aryl; X = carboxylate) have appeared in the literature.[1–9] Bismuth compounds are less toxic than those of their lighter congeners (P, As, Sb),[10,11] and their use in medicine has recently been reviewed.[12,13] They have been used for the treatment of a number of ailments and, today, are primarily used clinically as antiulcer drugs. Recently, the effectiveness of bismuth has been attributed to its bactericidal action against *Helicobacter pylori*. The organism implicated as the pathogen leading to gastric complaints can be eliminated by bismuth therapy.[14–19] From this, a clear connection is established between antitumor activity and bismuth compounds. The published data on the antitumor activity of bismuth(V) compounds, however, are relatively rather limited.[8] Moreover, as we all know, amino acids are the building blocks of proteins, which in turn are the basic elements for all forms of life, and lead to a wide range of biological activities. In order to study the influence of amino acid ligands at bismuth on their antitumor activity, we have prepared a series of triarylbismuth(V) di(*N*-*p*-toluenesulfonyl)aminoacetates. At the same time, we have studied the nature of the bonding ability and structure of these compounds.

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EXPERIMENTAL

General

All the reactions involving metal halides were carried out under an anhydrous and oxygen-free argon atmosphere. Solvents were purified, dried, and stored by literature methods. Elemental analyses were determined on 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-200 spectrometer in $CDCl_3$ solution with tetramethylsilane as internal standard. Mass spectra (ESI) were recorded on an APEXII FT-ICR mass spectrometer.

N-*p*-Toluenesulfonylaminoacetic acid was synthesized by the method reported by Jensen and Buchardt.[20] Ar_3BiBr_2 was prepared by the method reported by Supniewski and Adams.[2] Ar_3Bi was converted into the corresponding

dibromide by direct bromination, and the solid product was recrystallized from chloroform–methanol. To prepare Ar_3BiCO_3, an adaptation of the method of Barton *et al*.[21] was used.

Synthesis of the title compounds

To a boiling solution of *N*-*p*-toluenesulfonylaminoacetic acid (1 mmol) in 50 ml of acetone was added 0.5 mmol of Ar_3BiCO_3. The reaction mixture was refluxed for 4 h, cooled and filtered. The filtrate was evaporated *in vacuo*. The solid obtained was recrystallized from CH_2Cl_2–hexane. The yields, melting points and elemental analyses of the compounds prepared are given in Table 1.

$$4\text{-}CH_3C_6H_4SO_2NHCH_2COOH + Ar_3BiCO_3 \xrightarrow{\text{Reflux}} (4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2)_2BiAr_3$$

Ar=Ph (**1**); 4-$CH_3C_6H_4$ (**2**); 4-ClC_6H_4 (**3**); 4-BrC_6H_4 (**4**).

Crystallography

Diffraction measurements for a $0.16 \times 0.18 \times 0.24$ mm^3 sample of **3** were carried out at 298 K on a Bruker Smart 1000 diffractometer (graphite-monochromatized Mo Kα radiation, $\lambda = 0.71073$ Å). The intensities were corrected for absorption using the SADABS program, the structure was solved by heavy-atom methods (SHELXS-97)[22] and refined by a full-matrix least-squares procedure based on F^2(SHELXL-97).[23] Non-hydrogen atoms were refined with anisotropic displacement parameters. Crystal data: $C_{36}H_{32}BiCl_3N_2O_8S_2$, $M = 1000.09$, triclinic, $P\bar{1}$, $a = 10.124(3)$, $b = 13.189(4)$, $c = 16.061(4)$ Å, $\alpha = 75.175(4)$, $\beta = 86.019(4)$, $\gamma = 70.874(4)°$, $V = 1958.5(10)$ Å^3, $Z = 2$, 7895 unique data (θ_{max} 26.4°), 6763 data with $I \geq 2\sigma(I)$, $R = 0.029$ (obs. data), $wR = 0.075$ (all data). CCDC no. 223 063.

Cytotoxicity screening

The HL-60 cell lines and BGC-823 cell lines were obtained from the Institute of Cancer of Tianjin. Other cell lines were derived in the National Research Laboratories of Natural and Biomimetic Drugs of Peking University. All cell lines were grown in RPMI 1640 medium with 10% fetal bovine serum, in 5% CO_2 atmosphere.

The cytotoxic activity of these compounds was assayed by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2*H*-tetrazolium bromide (MTT)[24] or sulforhodamine B (SRB)[25] methods. The cell lines, human immature granulocyte leukemia (HL-60), human prostatic carcinoma (PC-3MIE8), human gastric carcinoma (BGC-823) and human mammary carcinoma (MDA-MB-435) were used for screening. All cell lines were seeded into 96-well plates at a concentration of about 50 000 cells/ml and were incubated in 5% CO_2 atmosphere at 37 °C for 24 h. Then, 20 µl of the sample (organobismuth complex) were added and further incubation was carried out at 37 °C for 48 h. 50 µl of 0.1% MTT or SRB (Sigma) was added to each well. After 4 h incubation, the culture medium was removed, and 150 µl of isopropanol was added to dissolve the insoluble blue formazan precipitates produced by MTT reduction. The plate was shaken for 20 min on a plate shaker to ensure complete dissolution. The optical density of each well was measured at a wavelength of 570 nm (MTT) or 540 nm (SRB). The cytotoxicity was determined three times in independent experiments, using three replicate wells per toxicant concentration (10, 1, 0.1 µM) and the mean optical densities obtained for drug-treated cells at each concentration as a percentage of that of untreated cells.

RESULTS AND DISCUSSION

The title compounds were prepared under mild condition. All compounds are colorless crystalline solids and stable under ordinary conditions. They are soluble in organic solvents such as benzene, toluene, chloroform, or dimethyl sulfoxide, but are not soluble in water, ether, methanol, hexane, or petroleum ether.

IR spectra

The IR spectra of these compounds were recorded in the range of 4000–400 cm^{-1}. The absorption bands can be assigned on the basis of earlier publications, and the important data are listed in Table 2. In the IR spectra of the title compounds, the carboxylate bands are observed in the characteristic regions: $\nu_{asy}(CO_2)$ between 1645 and 1621 cm^{-1} and $\nu_{sym}(CO_2)$ between 1387 and 1330 cm^{-1}. In addition, the vibration frequencies of Bi–C deformations appear between 443 and 479 cm^{-1}, and this is consistent with the literature.[26–29]

^{1}H NMR data

The ^{1}H NMR data of the title compounds are listed in Table 3. The protons of $C_6H_4SO_2$ and the aromatic protons

Table 1. Yields and elemental analyses of the compounds

Compounds	Yield (%)	M.p (°C)	Elemental analysis: found (calc.) (%) C	H	N	Formula for calc.
1	79.6	174–176	48.20 (48.22)	3.96 (3.93)	3.15 (3.12)	$C_{36}H_{35}BiN_2O_8S_2$
2	76.7	188–189	49.85 (49.89)	4.42 (4.40)	2.85 (2.98)	$C_{39}H_{41}BiN_2O_8S_2$
3	65.2	170–172	43.43 (43.23)	3.44 (3.23)	3.00 (2.80)	$C_{36}H_{32}BiCl_3N_2O_8S_2$
4	81.1	100–102	37.96 (38.15)	2.87 (2.85)	2.63 (2.47)	$C_{36}H_{32}BiBr_3N_2O_8S_2$

Table 2. Important IR data of the compounds (cm^{-1})

Compound	$\nu_{asy}(CO_2)$	$\nu_{sym}(CO_2)$	$\Delta\nu(CO_2)$	ν(Bi–C)
1	1641	1330	311	443
2	1645	1334	311	475
3	1645	1387	258	479
4	1621	1374	247	473

associated with bismuth have both been observed in the range δ7.11–8.05 ppm. All of the protons in the compounds have been identified, and the total number of protons calculated from the integration curve tallies with what was expected from the molecular formula.

Mass spectra

The mass spectra data of compound **3** were recorded. The molecular ion peak (m/z 1000) is observed. The $[4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2Bi(C_6H_4Cl\text{-}4)_3]^+$ (m/z 772) is the base peak.

Cytotoxicity

The cytotoxic activity of the title compounds is listed in Table 4. The results of bioassay show that these compounds exhibit certain cytotoxicities against the four cancer cells *in vitro*. The compounds that include the bismuth moiety have a relatively higher cytotoxic activity than *N*-*p*-toluenesulfonylaminoacetic acid. The cytotoxicity data indicate that the nature of the aryl affects the cytotoxic activity. For example, for Ar = C_6H_5, compound **1** has a rather high cytotoxic activity against PC-3MIE8 cells.

Crystal structure of $(4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2)_2Bi(C_6H_4Cl\text{-}4)_3$

The colorless crystal of $(4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2)_2Bi(C_6H_4Cl\text{-}4)_3$ was obtained from a CH_2Cl_2–hexane solution. The molecular structure with the atom numbering scheme is depicted in Fig. 1. Selected bond distances and angles are listed in Table 5.

Carboxylates are versatile ligands, and they can be either unidentate or bidentate, or intermediate between these. The Bi–C bond distances of compound **3**, ranging from 2.185(4) to 2.196(4) Å, are comparable to those in $Ph_3Bi(OCOCF_3)_2$ and $Ph_3Bi(OCHO)_2$.[5,6] The Bi–O1 and Bi–O5 distances (2.274(3) Å and 2.280(3) Å respectively) are comparable to the corresponding distances in $Ph_3Bi(OCOCF_3)_2$ (2.308(7), 2.309(7) Å) and $Ph_3Bi(OCHO)_2$ (both 2.270(8) Å). The Bi–O2 and Bi–O6 distances (3.144(8) Å and 2.905(8) Å respectively) are rather different from the corresponding distances in $Ph_3Bi(OCOCF_3)_2$ (2.980(7) Å and 2.981(7) Å respectively) and in $Ph_3Bi(OCHO)_2$ (both 2.91(1) Å). The C19–Bi–C31 angle,

Table 4. Cytotoxicity of the title compounds *in vitro*

	Inhibition (%)[a] (10 μM)			
Compound	HL-60	PC-3MIE8	BGC-823	MDA-MB-435
1	44.2	92.5	51.9	37.7
2	37.3	27.3	16.7	28.7
3	31.2	40.7	32.0	25.1
4	28.5	17.9	29.6	15.2
A[b]	12.6	−0.2	1.5	4.4
B[c]	14.2	10.2	16.0	13.8

[a] Inhibition (%) = $(A_1 - A_2)/A_1 \times 100$. Drug is active when inhibition at 10 μM concentration is ≥50%. A_1: the mean optical density of untreated cells; A_2: the mean optical density of drug-treated cells. Negative values indicate that the mean optical density of drug-treated cells (A_2) is greater than that of untreated cells (A_1), i.e. the drug promoted growth of some tumor cells.
[b] A: $4\text{-}CH_3C_6H_4SO_2NHCH_2CO_2H$.
[c] B: Cisplatin, whose concentration is 3.3 μM.

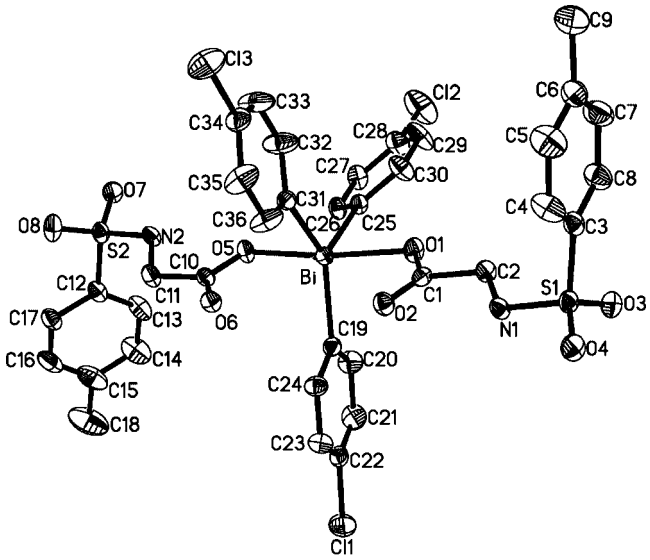

Figure 1. The molecular structure of $(4\text{-}CH_3C_6H_4SO_2NHCH_2\text{-}CO_2)_2Bi(C_6H_4Cl\text{-}4)_3$.

Table 3. ^1H NMR data of the compounds (ppm)

Compound	NH	CH_2CO	CH_3	ArC_6H_4
1	4.93 (2H, s)	3.42–3.44 (4H, d)	2.34 (6H, s)	7.11–7.93 (23H, m)
2	4.92 (2H, s)	3.40–3.43 (4H, d)	2.35 (6H, s)	7.13–8.00 (20H, m), 2.40 (CH_3, 9H, s)
3	4.92 (2H, s)	3.43–3.45 (4H, d)	2.38 (6H, s)	7.16–8.05 (20H, m)
4	4.86 (2H, s)	3.43–3.45 (4H, d)	2.38 (6H, s)	7.17–8.02 (20H, m)

Table 5. Selected bond distances and bond angles of compound **3**

Bond	Distance (Å)	Bond	Angle (°)
Bi–C19	2.193(5)	C19–Bi–C31	134.70(17)
Bi–C25	2.196(4)	C19–Bi–C25	116.06(17)
Bi–C31	2.185(4)	C25–Bi–C31	109.24(17)
Bi–O1	2.274(3)	C19–Bi–O1	92.04(15)
Bi–O5	2.280(3)	C25–Bi–O1	84.77(15)
N1–C2	1.455(6)	C31–Bi–O1	92.30(15)
N1–S1	1.614(4)	C19–Bi–O5	92.46(15)
O1–C1	1.291(5)	C25–Bi–O5	84.30(14)
O2–C1	1.215(5)	C31–Bi–O5	91.60(15)
O3–S1	1.430(4)	O1–Bi–O5	169.07(11)
O4–S1	1.431(4)	O3–S1–O4	120.2(2)
S1–C3	1.766(5)	C1–O1–Bi	114.7(3)
		O1–C1–O2	125.8(4)

which is affected by the close approach of the O1 and O5 atoms, is increased to 134.70(17)°, while the C25–Bi–C31 and C19–Bi–C25 angles are decreased to 109.24(17)° and 116.06(17)° respectively. Therefore, monomeric **3** comprises a distorted trigonal bipyramidal geometry with distortions arising as a result of the close approach of the weakly interacting O1 and O5 atoms.

REFERENCES

1. Suzuki H, Matano Y. *Organobismuth Chemistry.* Elsevier: 2001.
2. Supniewski JV, Adams R. *J. Am. Chem. Soc.* 1926; **48**: 507.
3. Goel RG, Prasad HS. *Can. J. Chem.* 1970; **48**: 2488.
4. Gilman H, Yale HL. *J. Am. Chem. Soc.* 1951; **73**: 4470.
5. Ferguson G, Kaitner B, Glidewell C, Smith S. *J. Organometal. Chem.* 1991; **419**: 283.
6. Suzuki H, Ikegami T, Matano Y, Azuma N. *J. Chem. Soc. Perkin Trans. I* 1993; 2411.
7. Arnauld T, Barton DHR, Doris E. *Tetrahedron* 1997; **53**: 4137.
8. Yu L, Ma YQ, Wang GC, Li JS, Du GH, Hu JJ. *J. Organometal. Chem.* 2003; **679**: 173.
9. Silvestru C, Breunig HJ, Althaus H. *Chem. Rev.* 1999; **99**: 3277.
10. Maeda S. In *The Chemistry of Organic Arsenic, Antimony and Bismuth Compounds*, Patai S (ed.). Wiley: New York, 1994; 725–759.
11. Reglinski J. In *Chemistry of Arsenic, Antimony and Bismuth*, Norman NC (ed.). Blackie Academic and Professional: London, 1997; 403–440.
12. Sadler PJ, Li H, Sun H. *Coord. Chem. Rev.* 1999; **185–186**: 689.
13. Tiekink ERT. *Oncology/Hematology.* 2002; **42**: 217.
14. Howden CW. *Am. J. Med.* l996; **100**: S27.
15. Hunt RH, Lam SK. *J. Gastroenterol. Hepatol.* 1998; **13**: 21.
16. Tytgat GNJ. *Digest. Dis.* 1998; **16**: 192.
17. Axon A. *Eur. J. Gastroenterol. Hepatol.* 1999; **11**: S3.
18. Coyle WJ, Sedlack RE, Nemec R, Peterson R, Duntemann T, Murphy M, Lawson JM. *Am. J. Gastroenterol.* 1999; **94**: 2885.
19. Steinbach G, Ford R, Glober G, Sample D, Hagemeister FB, Lynch PM, McLaughlin PW, Rodriguez MA, Romaguera JE, Sarris AH, Younes A, Luthra R, Manning JT, Johnson CM, Lahoti S, Shen Y, Lee JE, Winn RJ, Genta RM, Graham DY, Cabanillas FF. *Ann. Intern. Med.* 1999; **131**: 88.
20. Jensen KA, Buchardt O. *Acta Chem. Scand.* 1961; **15**: 447.
21. Barton DHR, Bhatnagar NY, Blazejewshi JC, Charpiot B, Finet JP, Lester DJ, Motherwell WB, Papoula MTB, Stanforth SP. *J. Chem. Soc. Perkin. Trans. I* 1985; 2657.
22. Sheldrick GM. *Acta Crystallogr. Sect. A* 1990; **46**: 467.
23. Sheldrick GM. SHELXL-97, program for crystal structure refinement. Universität Göttingen, Germany, 1997.
24. Mosmann T. *J. Immunol. Methods* 1983; **65**: 55.
25. Skehan P, Storeng R, Scudiero D, Monks A, McMahon J, Vistica D, Warren JT, Bokesch H, Kenney S, Boyd M. *J. Natl. Cancer Inst.* 1990; **24**: 1107.
26. Whiffen DH. *J. Am. Chem. Soc.* 1956; 1350.
27. Brown DH, Mohammed A, Sharp DW. *Spectrochim. Acta* 1965; **21**: 663.
28. Shobatake K, Postmus C, Ferraro JR, Nakamoto K. *Appl. Spectrosc.* 1969; **23**: 12.
29. Clark RJH, Flint CD, Hempleman AJ. *Spectrochim. Acta Part A* 1987; **43**: 805.