

Synthesis, Characterization and *in vitro* Antitumour Activity of the Di-*n*-butyltin(IV) Complexes of Some Arylhydroxamates

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Fourteen new di-*n*-butyltin(IV) complexes of hydroxamic acids of the formula Bu_2SnL_2 (HL = hydroxamic acids) were synthesized by the reaction of Bu_2SnO and hydroxamic acids in dry toluene and ethanol media. The compounds were characterized by elemental analyses, molecular weight, IR and 1H NMR spectroscopy. The results indicate that *n*- Bu_2SnL_2 have distorted *trans*-octahedral structure. The antitumor activity *in vitro* against human A-549 tumor cells and P388 leukemia was presented, and their structure-activity relationship was discussed.

Keywords diorganotin, hydroxamic acid, antitumour activity

Introduction

Hydroxamic acids having the general formula $RCONR'OH$ are weak organic acids of considerable biological importance.¹⁻⁴ Considerable interest has been shown in organotin(IV) derivatives of hydroxamic acids because of their biological properties such as antifungicidal and antitumor activities.⁵⁻⁷ Among the factors responsible for the mode of action of diorganotin compounds R_2SnX_2 , organic group R determines the potential activity and di-*n*-butyltin derivatives have higher activity than other group derivatives.⁸ In this paper the preparation of some di-*n*-butyltin(IV) complexes of hydroxamic acids and their antitumor activities were reported.

Experimental

Materials

Ethyl 2-thiophenecarboxylate, ethyl picolinate, ethyl

2-indolecarboxylate were purchased from Aldrich, and di-*n*-butyltin oxide was from Fluka. All other chemicals were of reagent grade.

Physical measurements

Elemental analyses were carried out on a Vario EL Analyzer Instrument. Tin was estimated gravimetrically as SnO_2 . IR spectra were recorded on a Testscan Shimadzu FTIR 8000 series spectrophotometer as KBr discs. 1H NMR data were recorded on a Bruker DRX 300 MHz spectrometer in $CDCl_3$ or $DMSO-d_6$ with TMS as the internal standard. Molecular weights of complexes were determined in camphor by the Rast method.

Preparation of hydroxamic acids

Indolehydroxamic acid (IHA) was synthesized from ethyl 2-indolecarboxylate and hydroxylamine hydrochloride by the known method.⁹

First, the potassium salt of IHA was obtained by mixing in methanol ethyl 2-indolecarboxylate with free hydroxylamine, which had been generated by treating hydroxylamine hydrochloride with KOH in methanol. The mixture was stirred for 48 h at room temperature, then the yellowish precipitate was filtered and washed successively with methanol. Finally IHA was obtained by dissolving the potassium salt of IHA in $2\text{ mol}\cdot\text{L}^{-1}$ acetic acid at $35\text{--}40\text{ }^\circ\text{C}$. The resulting solid (60% yield) was washed with cold water and dried in vacuum.

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Other hydroxamic acids were prepared by the above general method. All the fourteen hydroxamic acids are new compounds characterized with satisfactory elemental analysis and spectroscopic data.

Synthesis of organotin(IV) hydroxamates

The complexes $n\text{-Bu}_2\text{SnL}_2$ were prepared by dissolving the ligand (hydroxamic acid 0.002 mol) in dry

toluene and ethanol ($V:V = 3:1$, 50 mL) and adding di-*n*-butyl-tin oxide (0.001 mol) to the solution. The solution was refluxed for 6 h with magnetic stirrer. The solvent was removed on a rotary evaporator, leaving solids behind. The complexes were recrystallised from dry ethanol or CHCl_3 -petroleum ether (b. p. 60–90 °C). All physical and analytical data of the ligands and mononuclear complexes are listed in Table 1.

Table 1 Physical and analytical data of the ligands and compounds

Ligand and complex	Color	Yield (%)	m. p. (°C)	Molecular formula	Elemental analyses found (calcd.) (%)				Molecular weight found (calcd.)
					C	H	N	Sn	
i CiBHA	pink	80	98.4–99.3	$\text{C}_9\text{H}_9\text{O}_2\text{N}$	66.07 (66.26)	5.39 (5.52)	8.70 (8.59)		142 (163)
1 $\text{Bu}_2\text{Sn}(\text{CiBHA})_2$	pink	83	139.4–140.3	$\text{C}_{26}\text{H}_{34}\text{O}_4\text{N}_2\text{Sn}$	56.11 (56.01)	6.18 (6.10)	5.16 (5.03)	21.44 (21.31)	523 (557)
ii <i>N</i> -PhBHA	white	73	88.0–88.7	$\text{C}_{13}\text{H}_{11}\text{O}_2\text{N}$	73.02 (73.30)	5.31 (5.16)	6.41 (6.57)		196 (213)
2 $\text{Bu}_2\text{Sn}(\textit{N}\text{-PhBHA})_2$	pink	89	94.6–96.4	$\text{C}_{34}\text{H}_{38}\text{O}_4\text{N}_2\text{Sn}$	62.21 (62.10)	5.70 (5.78)	4.21 (4.26)	18.23 (18.07)	632 (657)
iii <i>o</i> -ABHA	pink	54	146.7–148.0	$\text{C}_7\text{H}_8\text{O}_2\text{N}_2$	55.08 (55.26)	5.21 (5.26)	18.32 (18.42)		133 (152)
3 $\text{Bu}_2\text{Sn}(\textit{o}\text{-ABHA})_2$	white	76	> 300	$\text{C}_{22}\text{H}_{32}\text{O}_4\text{N}_4\text{Sn}$	49.25 (49.35)	5.83 (5.98)	10.60 (10.47)	22.45 (22.19)	501 (535)0
iv <i>m</i> -ABHA	white	60	153.4–154.8	$\text{C}_7\text{H}_8\text{O}_2\text{N}_2$	55.38 (55.26)	5.09 (5.26)	18.38 (18.42)		135 (152)
4 $\text{Bu}_2\text{Sn}(\textit{m}\text{-ABHA})_2$	white	71	> 300	$\text{C}_{22}\text{H}_{32}\text{O}_4\text{N}_4\text{Sn}$	49.27 (49.35)	5.82 (5.98)	10.32 (10.47)	22.47 (22.19)	523 (535)
v <i>p</i> -ABHA	pink	85	137.0–138.1	$\text{C}_7\text{H}_8\text{O}_2\text{N}_2$	55.23 (55.26)	5.16 (5.26)	18.30 (18.42)		129 (152)
5 $\text{Bu}_2\text{Sn}(\textit{p}\text{-ABHA})_2$	pink	83	166.8–167.4	$\text{C}_{22}\text{H}_{32}\text{O}_4\text{N}_4\text{Sn}$	49.27 (49.35)	5.80 (5.98)	10.32 (10.47)	22.50 (22.19)	529 (535)
vi <i>o</i> -NBHA	white	25	148.0–149.3	$\text{C}_7\text{H}_6\text{N}_2\text{O}_4$	46.57 (46.15)	3.28 (3.30)	15.01 (15.38)		167 (182)
6 $\text{Bu}_2\text{Sn}(\textit{o}\text{-NBHA})_2$	yellow	62	230–231.6	$\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_8\text{Sn}$	43.98 (44.36)	4.97 (4.70)	9.13 (9.40)	19.75 (19.95)	569 (595)
vii <i>m</i> -NBHA	white	60	153.4–154.5	$\text{C}_7\text{H}_6\text{N}_2\text{O}_4$	46.49 (46.15)	3.27 (3.30)	15.44 (15.38)		160 (182)
7 $\text{Bu}_2\text{Sn}(\textit{m}\text{-NBHA})_2$	yellow	74	252.3–252.8	$\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_8\text{Sn}$	43.98 (44.36)	4.97 (4.70)	9.11 (9.40)	20.07 (19.95)	568 (595)
viii <i>p</i> -NBHA	yellow	50	166.0–167.8	$\text{C}_7\text{H}_6\text{N}_2\text{O}_4$	46.40 (46.15)	3.29 (3.30)	14.99 (15.38)		167 (182)
8 $\text{Bu}_2\text{Sn}(\textit{p}\text{-NBHA})_2$	yellow	73	240.0–241.7	$\text{C}_{22}\text{H}_{28}\text{N}_4\text{O}_8\text{Sn}$	43.97 (44.36)	4.89 (4.70)	9.17 (9.40)	19.77 (19.95)	560 (595)

Continued 1

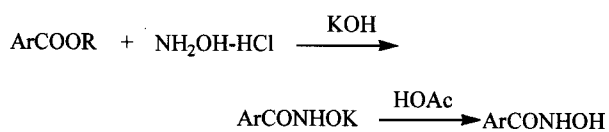
Ligand and complex	Color	Yield (%)	m. p. (°C)	Molecular formula	Elemental analyses found (calcd.) (%)				Molecular weight found (calcd.)
					C	H	N	Sn	
ix PiHA	white	60	122.4—122.9	C ₆ H ₆ O ₂ N ₂	52.40 (52.17)	4.50 (4.34)	20.55 (20.29)		155 (138)
9 Bu ₂ Sn(PiHA) ₂	yellow	67	195.0—196.1	C ₂₀ H ₂₈ O ₄ N ₄ Sn	47.04 (47.34)	5.45 (5.56)	11.35 (11.10)	23.00 (23.40)	537 (507)
x NiHA	white	61	161.4—161.9	C ₆ H ₆ O ₂ N ₂	52.25 (52.17)	4.25 (4.34)	20.18 (20.29)		122 (138)
10 Bu ₂ Sn(NiHA) ₂	white	74	189.0—191.0	C ₂₀ H ₂₈ O ₄ N ₄ Sn	47.38 (47.34)	5.65 (5.52)	10.92 (11.10)	23.09 (23.41)	485 (507)
xi IsHA	white	65	160.0—160.9	C ₆ H ₆ O ₂ N ₂	52.30 (52.17)	4.36 (4.34)	20.32 (20.29)		120 (138)
11 Bu ₂ Sn(IsHA) ₂	white	84	142.2—143.7	C ₂₀ H ₂₈ O ₄ N ₄ Sn	47.27 (47.34)	5.72 (5.52)	10.86 (11.05)	23.22 (23.41)	538 (507)
xii FuHA	white	63	119.9—121.6	C ₅ H ₅ O ₃ N	47.14 (47.24)	3.83 (3.94)	10.89 (11.02)		110 (127)
12 Bu ₂ Sn(FuHA) ₂	white	83	174(decompose)	C ₁₈ H ₂₆ O ₆ N ₂ Sn	44.63 (44.54)	5.26 (5.36)	5.87 (5.77)	24.10 (24.47)	467 (485)
xiii THA	white	34	125.6—126.0	C ₅ H ₅ O ₂ NS	41.55 (41.94)	3.40 (3.52)	9.55 (9.79)		120 (143)
13 Bu ₂ Sn(THA) ₂	pink	55	137.7—138.2	C ₁₈ H ₂₆ O ₄ N ₂ S ₂ Sn	41.39 (41.79)	5.20 (5.07)	5.22 (5.42)	22.70 (22.95)	501 (517)
xiv IHA	white	64	145.9—146.3	C ₉ H ₈ O ₂ N ₂	61.79 (61.36)	4.68 (4.58)	15.49 (15.91)		187 (176)
14 Bu ₂ Sn(IHA) ₂	yellow	80	152.8—153.3	C ₂₆ H ₃₂ N ₄ O ₄ Sn	53.80 (53.54)	5.14 (5.53)	9.20 (9.61)	20.07 (20.35)	609 (583)

In vitro tests

Drug activity was determined using a MTT and SRB method against human A-549 tumor cells and P388 leukemia, as described previously.¹⁰

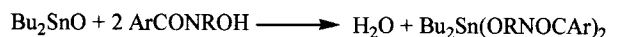
Results and discussion*Synthetic routes of the ligands and the mononuclear complexes*

The hydroxamic acids used in this study were prepared according to methods reported earlier.⁹



Excessive KOH and NH₂OH·HCl were dissolved in dry ethanol respectively, then the two solutions were mixed and filtered to give NH₂OH solution which was excessive in reaction with respective to ArCOOR in order that the reaction was completed. The structures of the ligands are shown in Fig. 1.

Bu₂SnL₂ were synthesized according to the following reaction schemes:¹¹



Di-*n*-butyltin oxide and an appropriate hydroxamic acid were reacted with refluxing in a mixture of toluene and ethanol (V:V = 3:1) with azeotropic removal of water and under the protection of N₂ for compounds **9**, **10** and **11**. The compounds prepared by these methods are shown in Table 1, along with their yields, physical and analytical data. IR spectral data are given in Table 2 and ¹H NMR spectral data in Table 3.

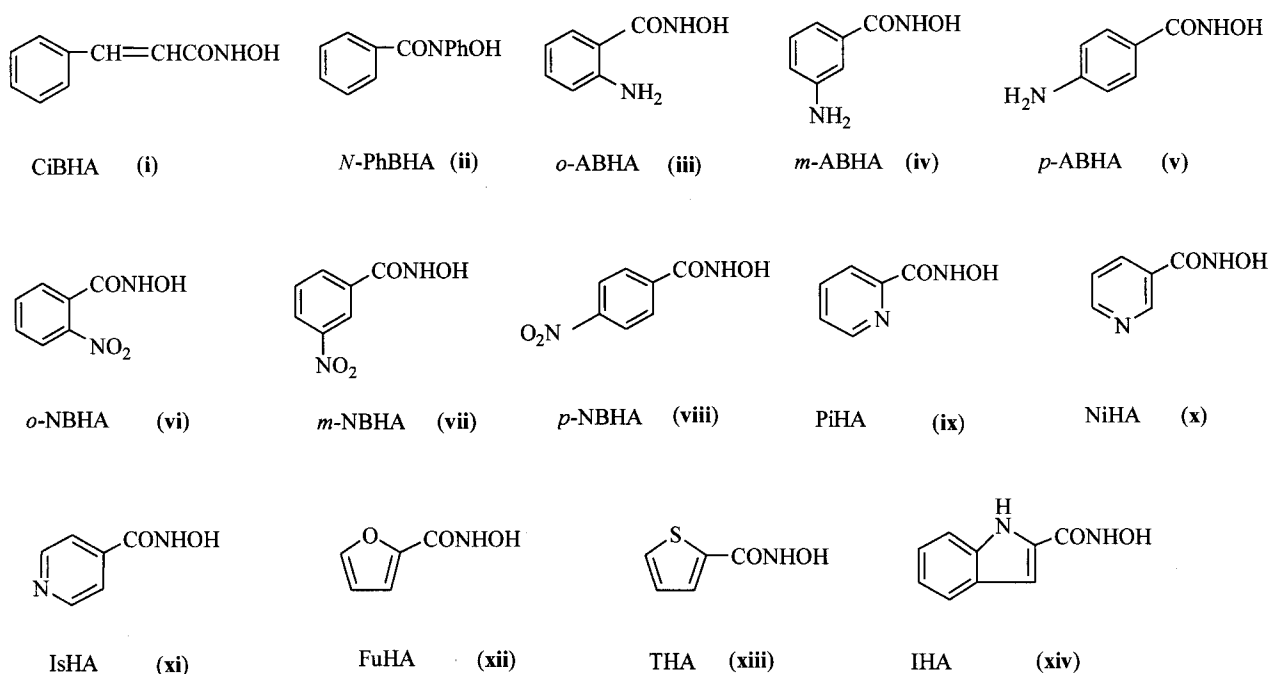


Fig. 1 Structures of the fourteen ligands.

Table 2 IR spectral data (cm^{-1}) of the ligands and complexes ^a

Ligand and complex No.	$\nu(\text{C}=\text{O})$	$-\Delta\nu(\text{C}=\text{O})$	$\nu(\text{N}-\text{O})$	$\nu(\text{N}-\text{H})$	$\nu(\text{O}-\text{H})$	$\nu(\text{Sn}-\text{C})$	$\nu(\text{Sn}-\text{O})$
i	1650s, sp		980m	3230s, sp	2600s, b		
1	1572s, sp	78	1030m	-	-	563m, sp	471m, sp
ii	1620s, sp		908s	-	3210s, sp		
2	1540s, sp	80	920s	-	-	532m, sp	492w
iii	1660s, sp		890m	3253s, sp NH ₂ 3395, 3495 (s, sh)	2881s, b		
3	1590s, sp	70	910m	NH ₂ 3391, 3493 (s, sh)	-	543m, sp	471m
iv	1645s, sp		891m	3250s, sp NH ₂ 3396, 3497 (s, sh)	2872s, b		
4	1580s, sp	65	910m	NH ₂ 3393, 3494 (s, sh)	-	541m	458w
v	1640s, sp		890m	3260s, sp NH ₂ 3397, 3498 (s, sh)	2900s, b		
5	1600s, sp	40	908w	NH ₂ 3394, 3496 (s, sh)	-	573m	468m, sp
vi	1650s, sp		893w	3220m, sp	2803s, b		
6	1590s, sp	60	950w	-	-	547w	482w
vii	1640s, sp		892m	3350m, sp	3204s, b		
7	1580s, sp	60	920m	-	-	540m	465m
viii	1650s, sp		890m	3250m, sp	2800s, b		
8	1560s, sp	90	920m	-	-	565m	475m, sp
ix	1653s, sp		901m	3167m, sp	2833s, b		
9	1587s, sp	66	939m	-	-	561m, sp	451m, sp

Continued 2

Ligand and complex No.	$\nu(\text{C}=\text{O})$	$-\Delta\nu(\text{C}=\text{O})$	$\nu(\text{N}-\text{O})$	$\nu(\text{N}-\text{H})$	$\nu(\text{O}-\text{H})$	$\nu(\text{Sn}-\text{C})$	$\nu(\text{Sn}-\text{O})$
x	1640s, sp		900m	3160m, sp	2800s, b		
10	1530s, sp	110	910m	3135w, b	-	523m, sp	472m
xi	1625s, sp		900m	3200m, sp	2706s, b		
11	1530s, sp	95	918m	-	-	601m	495m
xii	1630s, sp		935m	3273s, sp	3105s, sp		
12	1590s, sp	40	945m	-	-	593m	469m
xiii	1612s, sp		870m	3254s, sp	2853s, b		
13	1551s, sp	61	883m	3103w, b	-	550m, sp	503m, sp
xiv	1630s, sp		873m	3237s, sp aromatic NH 3368s, sp	2882s, b		
14	1560s, sp	70	881m	3204 aromatic NH 3351m, b	-	586m, sp	500m, sp

^a $-\Delta\nu(\text{C}=\text{O}) = \nu(\text{C}=\text{O})(\text{complex}) - \nu(\text{C}=\text{O})(\text{ligand})$, s = strong, m = medium, w = weak, sp = sharp, b = broad, sh = shoulder.

Table 3 ¹H NMR spectra of the ligands and complexes

Compound No.	Aromatic protons	MeCH ₂ CH ₂ -	-CH ₂ Sn	-CH ₃	-NHOH (-NHO-)	Other protons
i	7.58—7.40 (m, 5H)				10.01 (b, 2H)	PhCH=C, 7.18 (d, <i>J</i> = 15.8 Hz, 1H) C=CHCON, 6.73 (d, <i>J</i> = 15.8 Hz, 1H)
1	7.54—7.28 (m, 10H)	1.22—1.31 (m, 8H)	1.61—1.83 (m, 4H)	0.87 (t, <i>J</i> = 7.8 Hz, 6H)	Unobserved	PhCH=C, 7.13 (d, <i>J</i> = 15.6 Hz, 2H) C=CHCON, 6.65 (d, <i>J</i> = 15.6 Hz, 2H)
ii	7.63—7.17 (m, 10H)				10.72 (s, 1H)	
2	7.29—7.25 (m, 20H)	1.21—1.52 (m, 8H)	1.70—1.84 (m, 4H)	0.94 (t, <i>J</i> = 7.2 Hz, 6H)	-	
iii	7.69—6.48 (m, 4H)				10.17(s, 1H) 8.80 (s, 1H)	3.96 (s, 2H, NH ₂)
3	7.32—6.51 (m, 8H)	1.27—1.53 (m, 8H)	1.54—1.67 (m, 4H)	0.91 (t, <i>J</i> = 7.2 Hz, 6H)	Unobserved	3.99 (s, 4H, NH ₂)
iv	7.17—6.66 (m, 4H)				10.96 (s, 1H) 8.86 (s, 1H)	3.95 (s, 2H, NH ₂)
4	7.10—6.67 (m, 8H)	1.29—1.45 (m, 8H)	1.57—1.69 (m, 4H)	0.91 (t, <i>J</i> = 7.1 Hz, 6H)	Unobserved	4.00 (s, 4H, NH ₂)
v	7.48—6.50 (m, 4H)				10.71 (s, 1H) 8.64 (s, 1H)	3.96 (s, 2H, NH ₂)
5	7.56—6.66 (m, 8H)	1.25—1.38 (m, 8H)	1.58—1.70 (m, 4H)	0.90 (t, <i>J</i> = 7.2 Hz, 6H)	Unobserved	4.00 (s, 2H, NH ₂)
vi	8.67—7.90 (m, 4H)				11.67 (s, 1H) 9.37 (s, 1H)	
6	7.88—7.68 (m, 8H)	1.27—1.46 (m, 8H)	1.57—1.72 (m, 4H)	1.01 (t, <i>J</i> = 7.2 Hz, 6H)	Unobserved	

Continued 3

Compound No.	Aromatic protons	MeCH ₂ CH ₂ -	- CH ₂ Sn	- CH ₃	- NHOH (- NHO -)	Other protons
vii	8.71—7.91 (m, 4H)				11.76 (s, 1H) 9.51 (s, 1H)	
7	8.73—7.80 (m, 8H)	1.29—1.47 (m, 8H)	1.56—1.73 (m, 4H)	1.00 (t, <i>J</i> = 7.1 Hz, 6H)	Unobserved	
viii	8.48—8.14 (m, 4H)				11.74 (s, 1H) 9.41 (s, 1H)	
8	8.32—8.10 (m, 8H)	1.26—1.46 (m, 8H)	1.54—1.68 (m, 4H)	0.99 (t, <i>J</i> = 7.2 Hz, 6H)	Unobserved	
ix	8.69—7.40 (m, 4H)				11.19 (s, 1H) 9.40 (s, 1H)	
9	8.57—7.43 (m, 8H)	1.23—1.36 (m, 8H)	1.56—1.70 (m, 4H)	0.83 (t, <i>J</i> = 7.3 Hz, 6H)	Unobserved	
x	8.90—7.50 (m, 4H)				11.39 (s, 1H) 9.22 (s, 1H)	
10	9.16—7.45 (m, 8H)	1.25—1.41 (m, 8H)	1.68—1.73 (m, 4H)	0.91 (t, <i>J</i> = 7.2 Hz, 6H)	9.67 (s, 2H)	
xi	8.89—7.65 (m, 4H)				11.52 (s, 1H) 9.32 (s, 1H)	
11	8.71—7.73 (m, 8H)	1.25—1.40 (m, 8H)	1.60—1.69 (m, 4H)	0.90 (t, <i>J</i> = 7.1 Hz, 6H)	Unobserved	
xii	7.78—6.57 (m, 3H)				11.10 (s, 1H) 9.06 (s, 1H)	
12	7.71—6.47 (m, 6H)	1.25—1.37 (m, 8H)	1.64—1.75 (m, 4H)	0.90 (t, <i>J</i> = 7.2 Hz, 6H)	Unobserved	
xiii	7.74—7.11 (m, 3H)				11.19 (s, 1H) 9.10 (s, 1H)	
13	7.65—7.05 (m, 6H)	1.26—1.40 (m, 8H)	1.67—1.76 (m, 4H)	0.90 (t, <i>J</i> = 7.1 Hz, 6H)	10.00 (s, 2H)	
xiv	7.71—7.03 (m, 4H)				11.60 (s, 1H) 10.30 (s, 1H)	6.55 (s, 1H, N - C = CH - C) 9.10 (s, 1H, NH)
14	7.65—6.97 (m, 8H)	1.27—1.38 (m, 8H)	1.56—1.65 (m, 4H)	0.83 (t, <i>J</i> = 7.8 Hz, 6H)	10.38 (s, 2H)	6.60 (s, 2H, N - C = CH - C) 9.16 (s, 2H, NH)

Infrared spectra

IR data for the free ligands and the complexes were recorded in region of 4000—400 cm⁻¹ (Table 2).

The O—H stretching modes for free and hydrogen bonded N—O—H groups in the ligands occurring, respectively, in the regions of 3210—3010 cm⁻¹ and 2900—2600 cm⁻¹ are absent in the spectra of their complexes, which indicates that the reaction has taken place through the replacement of the -OH hydrogen by the

organotin moiety.¹² The ν(N—O) modes in the ligands occur in the range of 873—980 cm⁻¹,¹³ therefore, bands occurring at 881—1030 cm⁻¹ in organotin(IV) hydroxamates are assigned to these modes. The ν(C=O) modes which are observed at 1653—1612 cm⁻¹ in the ligands¹⁴ occur at 1600—1530 cm⁻¹ in the complexes, indicating a further red-shift of C=O by 110—40 cm⁻¹. This suggests coordination of C=O to the metal through oxygen. Therefore, the absence of ν(O—H) modes and the shifting of ν(C=O) modes towards lower energy support the bidentate nature of hydroxamic acids for diorganotin moi-

eties.

The $\nu(\text{Sn}-\text{C})$ and $\nu(\text{Sn}-\text{O})$ stretching modes are found in the low energy region along with the lower energy vibrational modes of the ligands. The presence of only a single $\text{Sn}-\text{C}$ band in $601-523\text{ cm}^{-1}$ region indicates that the two alkyl groups are in the *trans*-axial position.^{15,16} Thus a distorted transoctahedral structure is suggested for the di-*n*-butyltin(IV) hydroxamates by analogy with the observed C-Sn-C bond angle of 145.8° in $(\text{CH}_3)_2\text{Sn}[\text{ON}(\text{CH}_3)\text{COCH}_3]_2$.¹⁷ The $\nu(\text{Sn}-\text{O})$ modes depend on the precise environment of the $\text{Sn}-\text{O}$ group in the molecule. Bu_2SnL_2 was earlier reported the $\nu(\text{Sn}-\text{O})$ modes in the range of $525-400\text{ cm}^{-1}$,¹⁸ accordingly the absorptions appearing in the range of $503-449\text{ cm}^{-1}$ for di-*n*-butyltin(IV) hydroxamates may be assigned to $\nu(\text{Sn}-\text{O})$ modes.

¹H NMR spectra

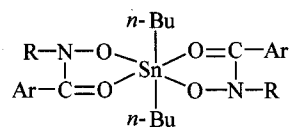
The ¹H NMR spectra data (Table 3) give further support for the compositions of the complexes suggested by element analyses and molecular weights. ¹H NMR spectra for the free ligands and the complexes were recorded in DMSO-*d*₆ or CDCl₃. In all complexes the signals for all types of protons have been identified, and the number of protons in various groups observed from the integration curve is found to be equivalent to the total number of protons calculated from the molecular formula.

Compared with the free ligands, the aromatic ring protons of all complexes are shifted probably because of the complexation. For compounds **3-5**, -NH₂ of aromatic cycle are observed at δ 4.00-3.99 as singlet. For compound **2**, the aromatic proton regions are very complex because of the presence of more two phenyl groups in the ligands. Other aromatic proton absorptions are found at δ 8.78-6.51 as multiplets. The protons of NH- are not observed because of exchange of active hydrogen in some compounds and the proton of OH groups in the ligands disappears after reaction. The terminal -CH₃ group protons of the butyl group are observed at δ 0.83-1.01¹⁹ as triplets. The MeCH₂CH₂- and CH₂Sn proton absorptions occur at δ 1.47-1.23 and 1.84-1.51¹³ as multiplets respectively. These ¹H NMR data, along with IR spectra discussed above, confirm the bidentate chelation of the ArCONRO⁻ group to Sn(IV) by O of C=O and

NH-O⁻. The presence of multiplet signals for the butyl group indicates the non-equivalence of the butyl group in non-linear *trans* position.^{10,20}

Geometry of the complexes

Fourteen di-*n*-butyltin(IV) complexes of hydroxamic acids were synthesized. So far, crystals suitable for X-ray diffraction have not been obtained. But on the basis of molecular weight determination, elemental analyses, IR and ¹H NMR spectra, these di-*n*-butyltin hydroxamates may be considered to be a *trans*-octahedral configuration (Fig. 2) by analogy with other *trans*-dialkyltin(IV) compounds such as dimethyltin(IV) bis(acetylacetonate)²¹ or di-*n*-butyltin(IV) bis(hydroxamates).²² Also, a three-dimensional X-ray diffraction study has suggested a *trans*-octahedral configuration of the butyl groups for di-*n*-butyltin(IV) bis(dibenzoyl-methanate)²³. In addition, the *trans*-isomer should exhibit one Sn-C and one Sn-O stretching vibrations in the infrared spectra²⁴ and in this work the same result was observed.



(R = H, for complex **5**, R = Ph)

ArH = GiBHA, *N*-PhBHA, *o*-ABHA, *m*-ABHA, *p*-ABHA, *o*-NBHA, *m*-NBHA, *p*-NBHA, PiHA, NiHA, IsHA, FuHA, THA, IHA

Fig. 2 Structures of the fourteen complexes.

Antitumor activity results

The results of the *in vitro* tests of these organotin(IV) complexes against human A-549 tumour cells and P388 leukemia are given in Table 4. The results show that, all compounds except **9** and **13** exhibit significant activity against human A-549 tumor cells and there is significant difference in the activity of the same compounds against A-549 and P388 leukemia. It is clear that compounds **6-8**, **9**, **13** and **14** are inactive against P388 leukemia, which indicates that electron density of the cycles affects the activity of the compounds.

Table 4 Inhibition rate of compounds against tumor cells (%)

Compd.	Tumor cells	Concentration ($\mu\text{mol/L}$)		
		0.1	1	10
1	P388	97.8	97.8	96.8
	A-549	63.9	93.8	97.8
2	P388	67.5	77.5	96.3
	A-549	92.7	93.8	92.7
3	P388	98.2	98.2	98.2
	A-549	100.0	97.5	98.8
4	P388	88.5	88.5	88.5
	A-549	74.0	97.6	95.3
5	P388	66.3	66.3	97.5
	A-549	86.5	91.7	91.7
6	P388	47.6	50.0	52.5
	A-549	85.5	85.5	89.7
7	P388	52.2	55.6	54.4
	A-549	85.5	85.5	92.0
8	P388	53.3	57.8	60.0
	A-549	89.7	90.8	90.8
9	P388	9.9	12.4	16.9
	A-549	21.5	24.4	100
10	P388	93.0	90.1	90.1
	A-549	91.9	91.9	90.9
11	P388	90.5	90.1	90.1
	A-549	89.9	90.9	90.9
12	P388	91.5	93.0	88.7
	A-549	89.9	90.9	87.9
13	P388	0.7	11.3	18.7
	A-549	6.4	74.0	89.2
14	P388	14.0	16.2	39.4
	A-549	14.0	98.4	98.5

The antitumor mechanism of the organotin is still poorly understood currently. It is reported that the drug molecules undergo a series of processes including hydrolysis, transport and membrane-crossing in the physiological medium, and then reach the nearby of target DNA molecule and form active intermediates R_2Sn^{2+} which will interact with the phosphate group of DNA molecules directly, causing DNA damage in cancer cells, blocking the division of the cancer cells and resulting in cell death.²⁵ According to the two-pole complementary principle,²⁶ the molecular structure of organotin complexes will present easily-leaving groups (R') and stable keeping groups (R) in aqueous solution. The organic ligand R can pass through the lipid bilayers and arrive at the nearby of the target molecules and the binding modes between the ligand and R' and tin decide the mechanism of hydrolysis in the

physiological medium. So the drug molecules should possess proper oil/water partition coefficients and the hydrophobic groups should not be too bulky.²⁷ Meanwhile, in the physiological medium the drug molecule should have appropriate hydrolysis rate to give active intermediates.

Of course, the relationship between the anticancer complexes and their anticancer activity is very sophisticated, and one has to wait for the *in vitro* test results before claiming anything about the real interest of such compounds in the field of cancer chemotherapy; more work has indeed to be done in order to find organotin molecules that might become useful antitumor drugs in the future.

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