SYNTHESIS, CHARACTERIZATION AND ANTITUMOUR ACTIVITIES OF DI-n-BUTYL- AND DIMETHYLTIN D-(+)-CAMPHORATES

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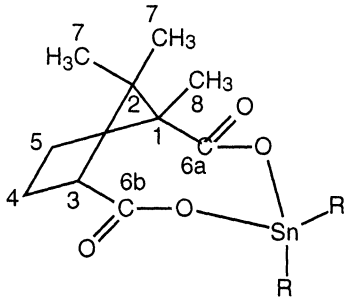
Abstract
The synthesis and characterization di-n-butyl- and dimethyltin D-(+)-camphorates, respectively compounds **1** and **2**, are reported. Compound **1** displays antitumoural activity *in vitro*, and is more active than cisplatin, 5-fluorouracil and etoposide against seven tumoural cell lines of human origin, but less active than methotrexate and doxorubucin.

Several diorganotin derivatives of dicarboxylic acids are active *in vitro* against human tumoural cell lines[1-6]. Nevertheless, diorganotin derivatives of dicarboxylic acids with proven antitumour activity *in vitro* remain rather rare. The present paper reports the synthesis and characterization of two novel diorganotin dicarboxylates, di-n-butyl- and dimethyltin D-(+)-camphorates, in order to further investigate the influence of the structure of such a dicarboxylate moiety on antitumour properties[7]. The antitumour activity of the di-n-butyltin compound is presented, that of the dimethyltin compound being provided for comparison.
Di-n-butyl- and dimethyltin D-(+)-camphorates, respectively compounds **1** and **2**, were prepared by condensing the appropriate diorganotin oxide with camphoric acid in refluxing toluene/ethanol 4/1 under elimination of the azeotrope water/toluene/ethanol[8-10]. They were recrystallized from ethanol/petroleum ether, m.p. 138-140 °C, yield: 90%, and methylene chloride/hexane, m.p. 258-259 °C, yield: 96%, respectively. The Mössbauer parameters of compounds **1** and **2** are respectively I.S.: 1.39, Q.S.: 3.32, Γ_1: 1.06, Γ_2: 0.92 and I.S.: 1.35, Q.S.: 3.89, Γ_1: 0.93, Γ_2: 1.02 mm/s. ^1H and ^{13}C NMR data are presented in Table 1.



R = α β γ δ CH_2-CH_2-CH_2-CH_3 **1**

α CH_3 **2**

The molecular weight of **2** was determined by cryoscopy in camphor (calc. for $C_{12}H_{20}O_4Sn$: 347; found: 343 ± 52 Dalton.

	^{1}H			^{13}C	
	1	**2**		**1**	**2**
			C_1	56.2	56.0
			C_2	46.7	46.9
H_3	t: 2.86 [9]	t: 2.85 [9]	C_3	52.6	52.5
H_{4a}	m: 2.22-2.10	m: 2.22-2.10	C_4	23.2	22.9
H_{4b}	m: 1.90-1.77	m: 1.89-1.76			
H_{5a}	ddd: 2.53 [12, 8, 8]	ddd: 2.53 [12, 8, 8]	C_5	32.9	32.7
H_{5b}	m: 1.56-1.47	m: 1.55-1.45			
			C_{6a}	186.4	186.3
			C_{6b}	184.2	184.0
H_{7a}	s: 1.35	s: 1.33	C_{7a}	22.7	22.8
H_{7b}	s: 0.87	s: 0.83	C_{7b}	21.5	21.5
H_8	s: 1.23	s: 1.22	C_8	22.4	21.9
$H_{\alpha\text{-}\beta}$	m: 1.66-1.51	s: 0.91 (**81**)	C_α	25.1 **(594/566)**	4.4 **(660/630)**
			C_β	26.8 **(35)**	-
H_γ	m: 1.48-1.34	-	C_γ	26.4 **(97)**	-
H_δ	t: 0.87 [7]	-	C_δ	13.5	-

Table 1: ^{1}H and ^{13}C NMR data of compounds **1** and **2** ($CDCl_3$). Chemical shifts in ppm vs. TMS; $^nJ(^1H,^1H)$ coupling constants (between brackets), $^2J(^1H,^{119}Sn)$ and $^nJ(^{13}C,^{119/117}Sn)$ coupling constants in Hz (bold in parentheses); d: doublet; t: triplet; s: singlet; m: complex pattern.

The ^{117}Sn NMR chemical shifts $\delta(^{117}Sn)(CDCl_3)$ (ppm) of compounds **1** and **2** are respectively -150.7 and -124.8 ppm. These values are in agreement with the structure proposed, the absence of concentration effect (30 and 100 mg/0.5 ml) excluding any monomer - oligomer equilibrium.

Compounds **1** and **2** were screened *in vitro* against seven tumoural cell lines of human origin: MCF-7 and EVSA-T, two mammary tumours, WiDr, a colon carcinoma, IGROV, an ovarian cancer, M19 MEL, a melanoma, A498, a renal cancer, and H226, a non-small cell lung cancer, as water/ethanol 99/1 solutions.
The results of the antitumoural tests are summarized in table 2 and compared with the inhibition doses ID_{50} obtained for some clinically used reference compounds[11,12], cisplatin, 5-fluorouracil, etoposide, methotrexate and doxorubicin.

Compounds	MCF-7	EVSA-T	WiDr	IGROV	M19 MEL	A498	H226
1	49	28	100	45	66	49	178
2	1342	903	3504	1006	1111	1548	764
Cisplatin	699	422	967	169	558	2253	3269
5-Fluorouracil	750	475	225	297	442	143	340
Etoposide	2594	317	150	580	505	1314	3934
Methotrexate	18	5	<3	7	23	37	2287
Doxorubicin	10	8	11	60	16	90	199

Table 2. Inhibition doses ID_{50} of compounds **1** and **2** and of some reference compounds[11] against seven tumoural cell lines of human origin

Compound **1** is more active than cisplatin, 5-fluorouracil and etoposide against all cell lines, but less active than methotrexate and doxorubucin. The dimethyltin compound **2** is inactive, as usually[13].

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