Synthesis and *In Vitro* Antitumour Studies of Trimethyltin(IV) *trans*-M-Methylcinnamate

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(Received 28th January, 2002, revised 11th February, 2004)

Summary: Trimethyltin *trans*-m-methylcinnamate has been synthesised and characterized by multinuclear NMR, mass and Mössbauer data. The antitumour activity *in vitro* against a penal of seven tumour cells is reported and compared with some clinical drugs.

Introduction

Side effects of the medicines are always a challenge for a synthetic chemist to search for new remedies. Same is the history of metal-based anti-tumour drugs. Cisplatin is the most common anti-cancer drug [1,2] and very effictive against testicular carcinomas but it does not show any, or only little, effect on more common tumours such as lung tumour or gestrointestinal adenotumours [3]. Cisplatin has also some side effects like nephroto-xicity, nausea and vomitting even at very low dose [4]. However, the activity of cisplatin against testicular carcinoma provides an incentive for the discovery of a new metal-based drugs capable of curing specific types of tumours [3]. So for a wide range of organotin compounds ($R_{4-n}SnL_n$) have been tested against various types of cancer and tumour [5].

It has been found that cisplatin and analogues with anticancer activity reside in either square planar or octahedral geometry [2]. Interesting to note that tin, like platinium, does not form squar planar complexes and prefers a tetrahedral or trigonal bipyramidal geometry. Furthermore, in solution phase, who is certain about the exact geometry of cisplatin or its analogues as different groups are free to vibrate in solution.

Under these circumstances one is left only with the effect of "R" group(s) or donor ligand(s). In such studies, efforts revealed that very small "R" groups are toxic while very large groups have no activity [6]. A comprehensive survey related to bioactivity of organotin compounds shows that the donor ligands with smaller size are more toxic and suitable as agrochemicals or disinfactants. However, the larger ligands, when incorporated with R_nSn^+ moieties, result in anticancer activity [7].

Literature describes that the organotin derivatives of donor ligands particularly the organotin carboxylates have potential of high antitumour and anticancer activity both *in-vivo* and *in-vitro* [8]. We previously synthesised and characterized some organotin derivatives of different donor ligands such as sulfur and oxygen including carboxylates [9] and some of these were active against various cancers [9c]. The present work is an extension of our previous studies on cancer chemotherapy.

Results and Discussion

Trimethyltin trans-m-methylcinnamate (Fig. 1) was synthesized by condensing trimethytin oxide and trans-m-methylcinnamic acid in molar ratio of 1:2.

$(CH_3Sn)_2O + 2(CH_3)C_6H_4CHCHCOOH \longrightarrow 2(CH_3)C_6H_4CHCHCOOSn(CH_3)_3 + H_2O$

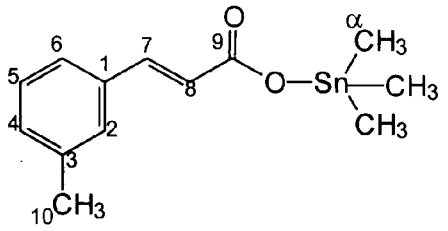

Figure 1

The Mössbauer parameters of the title compound (quadrupole splitting, Δ, 3.55 and isomer shift, δ, 1.27 mms^{-1}) are typical for a polymeric structure with intermolecular C=O→Sn coordination bonds [11] which is further supported by infrared data, particularly Δν value [12] and ^{119}Sn solid state

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NMR [13]. ^{1}H and ^{13}C NMR data are reported in Table 1. Using the Lockhart's equation [14] C-Sn-C angle was calculated on the basis of $^{2}J(^{119}Sn\text{-}^{1}H)$, 111.44^{0} and $^{1}J(^{119}Sn\text{-}^{13}C)$, 112^{0} which favours the tetrahedral structure of the tin in solution. However, the ^{119}Sn chemical shift in solution (129 ppm) and in solid phase (-40 ppm) shows a remarkable difference of 169 ppm, which strongly suggests that compound is monomeric tetra coordinated in solution and polymeric penta coordinated in the solid state [11].

Table 1. ^{1}H and ^{13}C NMR data of trimethyltin trans-m-methylcinnamate[a]

No.	^{13}C	^{1}H
1	134.7	-
2	130.6	7.16(d,7.43)
3	138.3	-
4	128.6	7.25(t,7.49,7.49)
5	128.5	-
6	125.0	7.25(t,7.49,7.49)
7	119.6	7.59(d,16.00)
8	144.2	6.46(d,16.00)
9	172.1	-
10	21.2	2.35(s)
α	-2.2[402.0]	0.60[58.8]

[a] Chemical shift (δ) in ppm, J values in Hz.

The compound was screened against seven human cancer cell lines, two mammary cancers (MCF-7, EVSA-T), a colon carcinoma (WiDr), an ovarian cancer (IGROV), a malenoma (M19 MEL), a renal cancer (A498) and a non-small-cell lung cancer (H226). The ID_{50} values (Table 2) are compared with those of some reference compounds used clinically, cisplatin, doxorubicin and 5-fluorouracil. In some cases the potencies were compareable with cisplatin and 5-fluorouracil.

Table 2. The ID_{50} values ($ngml^{-1}$) of the title compound and reference drugs

Cancer cells	Me_3SnL	Cisplatin	Doxo-rubicin	5-Fluorouracil
MCF-7	520	699	10	750
EVSA-T	540	422	8	475
WiDr	630	967	11	225
IGROV	580	169	60	297
M19 MEL	1400	558	16	422
A498	1600	2253	90	143
H226	650	3269	199	340

Experimental

Instrumentation

All analytical data were recorded as reported previously [9].

Synthesis

Trimethyltin oxide, (5 mmol), were treated with *trans*-m-methylcinnamic acid (10 mmol) at reflux temperature in toluene for 3 hours. Water formed during the reaction was continously removed by Dean and Stark apparatus. After completion of the reaction, toluene was removed in rotary evaporator and the resulting solid mass was crystallized from dichloromethane (yield, 92%; m.p., 154^{0}C). Analysis (%), Calcld.(Found): $C_{13}H_{18}O_2Sn$, C = 48.15(48.70), H = 5.56(5.44), Sn = 36.42(35.80). IR(cm^{-1}): νSn-C, 540; νSn-O, 455; νCOO(asymm), 1565; νCOO (symm), 1377; ΔνCOO, 188. Mössbauer(mms^{-1}): QS (Δ) = 3.55 and IS (δ) = 1.27. ^{119}Sn NMR (ppm): 129 (in solution, $CDCl_3$) and -40 (in solid phase). Mass fragmentation, m/z (% relative abundance): $[(CH_3)C_6H_4CHCHCOOSn(CH_3)_3]^+$ 326 (not observed); $[(CH_3)C_6H_4CHCHCOOSn(CH_3)_2]^+$ 311 (100); $[(CH_3)C_6H_4CHCHSn(CH_3)_2]^+$ 267 (55); $[(CH_3)C_6H_4CHCHSn]^+$ 237 (15); $[Sn(CH_3)_3]^+$ 165 (27); $[(CH_3)C_6H_4CHCHCOOH]^+$ 162 (47); $[(CH_3)C_6H_4CHCHCOO]^+$ 161 (36); $[Sn(CH_3)_2]^+$ 150 (35); $[(CH_3)C_6H_4CHCH]^+$ 117 (51); $[(CH_3)C_6H_4]^+$ 91 (31).

Anticancer Screening Tests

Amongst the various synthesized organotin derivatives of *trans*-m-methylcinnamic acid [9d], only trimethyltin *trans*-m-methylcinnamate fullfilled the criterion to be tested against various types of cancer and tumour cells. For the test, the desired amount of the complex was dissolved in ethanol and diluted 100 times to get a transparent solution. The screening tests were performed using an automated *in vitro* technique [10]. The ID_{50} values against various cancer cells are given in Table 2.

Acknowledgements

We are thankful to Prof. M. Gielen, Free University Brussels, Belgium for the help in anti-cancer studies. Dr. K.C. Molloy, University of Bath, U.K., and Dr. E. Klaus, University of Bayreuth, Germany are gratefully acknowledged for Mössbauer and solid state NMR measurements. S.A. is thankful to Alexander-von-Humboldt for Georg-Foster fellowship.

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