Synthesis Characterization and Biological Activity of Diorganotin Complexes of 1,3-Diphenyl-1,3-Propanedione and 1-Phenyl-1,3-Butanedione

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Summary: A series of diorganotin(IV) complexes of β-diketones of general formula R_2SnL_2 where R = CH_3, C_4H_9, C_6H_5, and L = 1,3-diphenyl-1,3-propanedione, 1-phenyl-1,3-butandione have been prepared by reaction of diorganotin dichlorides with the sodium salts of the respective ligands in 1:2 molar ratio. All the compounds have been characterized by IR, mass, NMR (^1H, ^{119}Sn) and ^{119m}Sn Mossbauer spectroscopy. The results based on these studies indicate a distorted octahedral geometry for all compounds. Their toxicity, anti-tumor and biocidal activity against various kinds of bacteria have been studied.

Introduction

Interesting anti-tumor activities with low mammalian toxicities characterize several diorganotin compounds [1-6]. In continuation to our previous work [7] with α-nitroso-β-naphthol we report here diorganotin complexes of β-diketones.

Results and Discussion

Infra-red data

Useful structural information can be derived from the IR spectra of β-diketonates because of the delocalization of electron density around the ligand on chelation [8].

Two bands of approximately equal intensity, assignable to the asymmetric and symmetric stretching vibrations, appear in the range 1604-1524 cm^{-1} and 1410-1309 cm^{-1}, respectively instead of the value of the 1548-1563 cm^{-1} expected for a pure C=O stretch. Another band, located between 1609 and 1524 cm^{-1}, is assigned to a perturbed C=C band, as found in other β-diketone complexes [9,10]. Other group frequencies such as of Sn-O and Sn-C vibrations have been assigned on the basis of literature precedents [11-13].

NMR data

Chemical shifts of aliphatic and aromatic protons (see experimental part) are in keeping with the proposed compound formulations. The ^{119}Sn chemical shift range which can be correlated with the coordination at alkyltin centre are now well established (coordination number 4 = 200 to -90; 5 = -90 to -210; 6 = -210- to -400; 7 = (-500 ppm) [14,15] and data for compounds 1,2, 4 and 5 (-348 to -391 ppm) are clearly associated with hexacoordinate tin. This assertion is supported by the ^2J (^{119}Sn-^1H) coupling measurable in the proton spectra of 1 and 4 (93 and 98 Hz respectively), which are characteristic for a C-Sn-C angle of 150 and 159 respectively [16]. (Similarly, $\delta(^{119}Sn)$ for 6 species (-360 to -540 ppm) [14]. Our findings are consistent with the published ^{119}Sn chemical shift of $Me_2Sn(acac)_2$ (365 ppm) [14].

Mossbauer data

The ^{119}Sn Mossbauer data have been recorded at liquid nitrogen temperature. The Mossbauer parameters (see experimental part), the isomer shift (IS) and quadruple splitting (QS) for compound 1 to 6 are in the range of 1.05-1.76 and 2.09-4.10

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mm sec^{-1} respectively. From these data, C-Sn-C bond angles are estimated by using the expression given by Bancroft and Sham [17], $2\theta = \text{Sin-1}(4/3[1-(QS/4R)_2]^{1/2}$, where R stands for the partial quadruple splitting of the organic group: -1.03 mm sec^{-1} for alkyl groups (methyl, butyl) and -0.95 mm sec^{-1} for phenyl groups (taken from Bancroft [17]). For the alkyltins 1,2,4 and 5 the calculated angles are 164, 174, 155 and 159 respectively, representing varying degrees of distortion with in a trans-R_2SnO_4 configuration. The QS for 5 (2.09 mm sec^{-1}) is clearly indicative of a Cis-R_2SnO_4 arrangement, the calculated C-Sn-C angle being 107. The crystal structure of $Me_2Sn(acac)_2$ has established the trans-Me_2Sn stereochemistry [18], and a compound whose QS (4.01 mm sec^{-1} [19]) is in keeping with our data.

Biological activity

The lethal doses LD_{50} characterizing toxicity of compound 1 to 6 are given in Table-1. The anti-bacterial and anti-fungal activity of complexes was determined by the Agar Well Diffusion method [20]. Results are given in the Table-2 and Table-3 respectively.

Table-1: Toxicity LD_{50} for diorganotin derivatives of β-diketones

Compound	LD_{50} µg/ml
1	100.00
2	92.23
3	100.00
4	59.35
5	333.42
6	100.00
Me_2SnCl_2	>100.00
Bu_2SnCl_2	129.79
Ph_2SnCl_2	>100.00
L1	>100.00
L2	>100.00

L1. 1, 3-Diphenyl-1,3-propanedione
L2. 1-Phenyl-1,3-butanedione

The diorganotin derivatives of β-diketones have been tested against two Gram-positive and seven Gram-negative bacteria. Their comparative studies with their precursors have been made. The ligands are found to be inactive against Gram-positive and Gram-negative bacteria except *Salmonella typhi*. Their screening tests show that compound 6 is potent candidate against *E. coli* while compound 5 is moderately active against all

Table-2: Antibacterial activity of diorganotin derivatives of β-diketones

Compound	Gram-positive bacteria		Gram-negative bacteria						
	1	2	3	4	5	6	7	8	9
1	++	++	+	++	-	-	++	+	-
2	-	+	++	+	+	++	+	+	-
3	+	++	++	+	++	-	++	+	-
4	+	+	+	-	+	++	+	+	-
5	++	-	++	++	++	++	++	+	-
6	++	++	-	-	-	++	+++	++	-
L1	-	-	0	0	-	0	-	-	++
L2	-	-	0	0	-	0	-	-	+
Me_2SnCl_2	-	●	++	-	0	0	++	0	0
Bu_2SnCl_2	++	●	++	+	0	0	++	0	0
Ph_2SnCl_2	0	●	++	+	0	0	+	0	0

Where + = Low activity, ++ = Good activity, +++ = High activity, - = No activity 0 = Not tested

1. Streptococcus faecalis, 2. Staphylococcus aureus
3. Aeromanas sobriae 4. Shigella boydii
5. Corynebacterium diphtheriae 6. S. Pyogens
7. Escherichia coli 8 .K. Pneumoniae
9. Salmonella typhi
L1 1,3-diphenyl-1,3-propanedione
L2. 1-phenyl-1,3-butanedione

Table-3: Antifungal activity of diorganotin derivatives of β-diketones.

Compound	1	2	3	4	5	6	7	8	9	10
1	++	+	+++	+++	+++	-	++	+++	-	-
2	++	+	+++	+++	+++	-	++	+++	-	-
3	++	+	-	+++	+++	-	-	+++	-	-
4	++	+	-	+++	+++	+++	-	+++	-	-
5	++	+	+++	+++	+++	+++	-	+++	-	-
6	++	+	-	+++	+++	+++	++	+++	-	-
Me_2SnCl_2	+++	0	++	+++	0	0	+++	0	-	0
Bu_2SnCl_2	+++	0	+++	+++	0	0	+++	0	+	0
Ph_2SnCl_2	+++	0	+++	+++	0	0	+++	0	+	0
L1	++	0	+	0	++	+	+	++	-	-
L2	+++	0	+	+++	++	+	-	+++	-	+

Where +++ = Good activity, ++ = Moderate activity, + = Low activity, - = No activity 0 = Not tested

1. Microsporum canis, 2. Momniella achinata
2. Aspergillus niger, 4. Epidermophyton floccosum,
5. Allefecheria boydii 6. Dreschslera rostrata
7. Curvularia lunata, 8 .Pleurelus ostreatus
9. Candida albican 10. Stachbotrys altra
L1 1,3-diphenyl-1,3-propanedione
L2. 1-phenyl-1,3-butanedione

the bacteria except *S. typhi* and *S. aureus*. Surprisingly it has been observed that all the six compounds are inactive against the *S. typhae*.

The activity of these compounds however, was found to be independent of the nature of the anionic group. It has been found that diorganotin derivatives of β-diketones are highly active against *Epidermophyton floccosum*, *Allefiseria boydii* and *Pleurelus ostreatus*. Surprisingly it has been found that all the six β-diketone derivatives are inactive

against *Candida albican* and *Stachbotrys alltra* except compound **6** which is highly active against *Candida albican*. Experimental data exhibited that compound **6** is moderately active against all the fungi and diorganotin derivatives of β-diketones are more active against fungi as compare to bacteria. Butyltin derivatives are highly active against fungi which would be helpful in wood preservations.

Diorganotin compounds are claimed to be anti-tumor active [21]. Diorganotin derivatives of β-diketones have been tested against various cancers. These values have been compared with the standards compounds which are clinically used as medicines. It has been found that compound **2** is remarkably active against various cancers such as breast, colon, ovarian, melanoma and renal cancer. It is more effective than carboplatin, cisplatin, 5-flourouracil and methotrexate. Compound **3** is more effective than carboplatin for MCF-7 breast cancer and M19 melanoma. Similarly the compound **5** is also effective against various cancers. Comparative studies and their results are given in the Table-4.

Table-4: Antitumour activity of diorganotin derivatives of β-diketones.

Compound	MCF-7 Breast cancer	EVAST Breast cancer	WiDr Colon cancer	IGROV Ovarian cancer	M19 Melonoma	A498 Renal cancer
2.	55	38	420	160	150	160
3.	4000	1400	16000	4000	9000	5900
6.	7000	2900	15000	12000	15000	15000
Carboplatin	5500	1100	1500	780	5300	3500
Doxorubicin	8	6	20	28	5	5
Cisplatin	800	1200	650	79	530	1200
5-flourouracil	210	650	260	280	160	80
Methotrexate	150	170	140	240	190	100
Daunorubicin	2	2	2	18	2	3

Inhibition doses LD_{50}, in ng/ml of compounds, 2,3,6 and few of a commonly used anti-tumor drugs, against six human tumor cell lines.

Experimental

Synthesis

The sodium salt of the β-diketones were prepared by adding 0.04 mole (0.92g) of sodium sand to a solution of β-diketones (1,3-diphenyl-1,3-propanedione: 8.87g, 1-phenyl-1,3-butanedione: 6.48g) in ether [8]. All the compounds were prepared in dry organic solvents under inert atmosphere. A solution of 0.02 mole of R_2SnL_2 [R = CH_3, (4.40 g), n-C_4H_9 (6.08 g), C_6H_5 (6.88 g)] in 100 ml of absolute ethanol, was added to a 0.04 mole sodium β-diketonate [sodium 1,3-diphenyl-1,3-propanedionate (9.85 g), sodium 1-phenyl-1,3-butanedionate (7.37 g)]. The mixture containing the complex was cooled in an ice bath. The sodium chloride produced was filtered off and ethanol was removed on a rotary evaporator. The product was washed several times with n-hexane or petroleum ether (60-80°C), crystallized from benzene and stored in a desiccator. The compounds prepared are:

1. $[(C_6H_5CO)_2\ CH]_2\ Sn(CH_3)_2$,

2. $[(C_6H_5CO)_2\ CH]_2\ Sn(C_4H_9)_2$

3. $[(C_6H_5CO)_2CH]\ Sn\ (C_6H_5)_2$.

4. $[(C_6H_5COCHCOCH_3)]_2\ Sn(CH_3)_2$

5. $[(C_6H_5COCHCOCH_3)]_2\ Sn(C_4H_9)_2$

6. $[(C_6H_5COCHCOCH_3)]_2\ Sn(C_6H_5)_2$

Characterization

1. Bis(1,3-diphenyl-1,3-propanediono) dimethyltin (IV)

$[(C_6H_5CO)_2CH]_2\ Sn(CH_3)_2$

Recrystallized from benzene (yield:60%), m.p.: 180-181°C. Analysis: found (calc. for $C_{32}H_{28}O_4Sn$): C, 64.0(64.6); H, 4.87 (4.74); IR: 1593, s, sh, 1524 s, sh (C=C); 1555, shd, 1368, s, sh C=O; 573, s, sh, 488 m, shd, O-Sn-O; 534, m, sh, 513, m, sh (Sn-C); Mossbauer; IS = 1.16, QS = 4.01, Γ=0.92, 0.92 mm sec^{-1}; ^{1}H-NMR ($CDCl_3$): chemical shifts in ppm, J in Hz: 0.96 [s, 6H, CH_3Sn], $^2J(^1H\text{-}^{119}Sn)$=93]; 6.81 [s, 2H, CH]; 7.44-7.56 and 7.99-8.03 [m, 20H, C_6H_5]; ^{119}Sn NMR ($CDCl_3$); -348 ppm; 80 eV EI major mono-isotopic mass spectral fragments (m/z), intensity in % of the base peak): 581 (32%, $[(C_6H_5CO)_2\ CH_2]Sn\ CH_3$ 373 (62%, $[(C_6H_5CO)_2CH]Sn^+(CH_3)_2$, 343 (32% $[(C_6H_5CO)_2CH]Sn^+$], 197 (40%, $C_6H_5Sn^+$).

2. Bis(1,3-diphenyl-1,3-propanediono) dibutyltin (IV)

$[(C_6H_5CO)_2CH]_2Sn(C_4H_9)_2$

Recrystallized from benzene (yield: 60%; m.p.: 89-90°C, Analysis: found (calc. for $C_{38}H_{40}O_4Sn$): C, 67.1 (67.2); H, 5.98 (5.93); IR; 1596, s, sh, 1515, s, sh, ν(C=C); 1548, m, sh, 1398, s, sh, ν(C=O); 575, m, b, 480, m, b, ν(O-Sn-O); 537, m, sh, 510, m, sh, ν(Sn-C); Mossbauer: IS =1.32, QS = 4.10, Γ= 0.89, 0.89 mm sec^{-1}; ^{1}H-NMR($CDCl_3$): 0.81-1.8 [m, 18H, C_4H_9Sn]; 6.75 [s, 2H, CH]; 7.45-7.56 and 8.03-8.06 [m, 20H, C_6H_5]; ^{119}Sn NMR($CDCl_3$): -385 ppm; 80eV EI major mono isotopic mass spectral fragments: 623 (92%, $[(C_6H_5CO)_2CH)]_2SnC_4H_9$]; 457 (62%, $[(C_6H_5CO)_2$ CH]$Sn(C_4H_9)_2$]; 343 (100%, $[(C_6H_5CO)_2CH]Sn^+$]; 198 [44%, $C_6H_5SnH^+$)].

3. Bis(1,3-dipenyl-1,3propanediono) diphenyltin (IV)

$[[(C_6H_5CO)_2CH]_2Sn(C_6H_5)_2$

Recrystallized from benzene (yield: 55%): m.p.: 218°C; Analysis: found (calc. for $C_{42}H_{32}O_4Sn$): C, 69.3 (70.09); H, 3.91 (4.45); IR data: 1596, s, sh, 1519, s, b, ν(C=C); 1550, m, shd, 1365, s, sh, ν(C=O); 555, s, sh, 470, w, shd ν(O-Sn-O): 534, s, vsh, ν(Sn-C); Mossbauer; IS = 1.05, QS = 2.65 Γ = 0.82 mm sec^{-1}; ^{1}H-NMR ($CDCl_3$): 6.52 [s, 2H, =CH]; 6.93-8.36 [m, 30H, C_6H_5]; ^{119}Sn NMR ($CDCl_3$): -297 ppm; 80 eV EI major mono isotopic mass spectral fragments: 643 (20%, $[(C_6H_5CO)_2CH]_2Sn(C_6H_5^+)$),420 (2%, $[(C_6H_5CO)_2$ CH] $Sn(C_6H_5)$], 343 (12%, $[(C_6H_5CO)_2CH]$ Sn^+), 197 (6% $[(C_6H_5)Sn^+]$.

4. Bis(1-phenyl-1,3-butanediono)dimethyltin(IV)

$[(C_6H_5COCHCOCH_3)]_2Sn(CH_3)_2$

Recrystallized from benzene (yield: 55%); m.p.: 128-130°C; Analysis: found (calcd. for $C_{22}H_{24}O_4Sn$); C, 55.9 (56.1); H, 5.07 (5.13); IR: 1593, s, sh, 1509, m, ν(C=C); 1563, shd, 1368, s, b, ν(C=O); 570, vs, sh, 480, m, ν(O-Sn-O); 531, vs, sh, 513, m, sh, ν(Sn-C); Mossbauer: IS = 1.16, QS = 3.83, Γ =0.83, 0.83 mm sec^{-1}; ^{1}H-NMR ($CDCl_3$): 0.81 [s, 6H, CH_3Sn, $^2J(^1H\text{-}^{119}Sn)$ = 98]; 2.24 (s, 6H, CH_3CO); 6.18 [s, 2H, CH]; 7.32-7.96 [m, 10H, C_6H_5]; ^{119}Sn NMR($CDCl_3$): -355 ppm; 80 eV EI major mono isotopic spectral fragments: 457 (40% $[(C_6H_5COCHCOCH_3)]_2$ $Sn(CH_3^+)$], 311 (100%, $[(C_6H_5$ $COCHCOCH_3)]Sn^+(CH_3)_2$], 281 (42% $[(C_6H_5COCHCOCH_3)]Sn^+$), 197 (18% $[(C_6H_5)Sn^+]$, 135 (6% CH_3Sn^+).

5. Bis(1-phenyl,1,3-butanediono) dibutyliin(IV)

$[(C_6H_5COCHCOCH_3)]_2Sn(C_4H_9)_2$

Yellow liquid (yield: 55%). Analysis found (calc. for $C_{28}H_{36}O_4Sn$): C, 62.7 (60.57); H, 6.53 (6.53); IR: 1596, s, sh, 1510, m, b, ν(C=C); 1560, m, b, 1392, s, b, ν(C=O); 573, m, 480, m, ν(O-Sn-O); 552, m, sh, 520 vw, sh, ν(Sn-C); Mossbauer: IS = 1.36, QS = 3.91, = 0.92, 0.92 mm sec^{-1}; ^{1}H-NMR ($CDCl_3$): 0.87-1.69 [m, 18H, C_4H_9Sn]; 2.20 [s, 6H, CH_3CO]; 6.10[s, 2H, CH]; 7.44-7.90 [m, 10H, C_6H_5]; ^{119}Sn NMR($CDCl_3$): -391 ppm; 80eV EI mono isotopic mass spectral fragments: 499 (32%, $[(C_6H_5$ $COCHCOCH_3)]_2Sn^+(C_4H_9^+)$; 395 (50%, $[(C_6H_5COCHCOCH_3)]Sn(C_4H_9^+)_2$; 281 (100%, $[(C_6H_5COCHCOCH_3)]$ (Sn^+); 197 (40%, $C_6H_5Sn^+$).

6. Bis(1-phenyl-1,3-butanediono) diphenyltin(IV)

$[(C_6H_5COCHCOCH_3)]_2Sn(C_6H_5)_2$

Recrystallized from benzene (yield: 50%); m.p.: 172°C. Analysis: found (calc. for $C_{32}H_{28}O_4Sn$): C, 62.1(64.57); H, 4.40 (4.70); IR: 1593, s, sh, 1521, s, sh ν(C=C); 1550, m, sh, 1371, vs, sh, ν(C=O); 570, m, sh, 480, m, sh, ν(O-Sn-O); 543, m, sh, 513, m, sh, ν(Sn-C); Mossbauer: IS = 0.76, QS = 2.09, Γ = 0.94, 0.84 mm sec^{-1}; ^{1}H-NMR ($CDCl_3$): 6,.25 [s, 2H, CH], 7.44-7.56 and 7.99-8.03 [m, 20H, C_6H_5]; ^{119}Sn NMR($CDCl_3$): -509.7 ppm; 80 eV EI major mono isotopic mass spectral fragments; 519 (32%, $[(C_6H_5COCHCOCH_3)]_2$ $SnC_6H_5^+$); 435 (6%, $[(C_6H_5COCHCOCH_3)]Sn(C_6H_5^+)_2$]; 281 (22%, $[(C_6H_5COCHCOCH_3)]$ (Sn^+), 197 (13%, $C_6H_5Sn^+$).

Measurements

Infra-red spectra were recorded in the 4000-250 cm^{-1} range on a Hitachi Model 270-50 spectrophotometer. Mossbauer spectrometer and associated experimental details are given else where [22]. ^{1}H-NMR ($CDCl_3$) spectra were recorded on the Bruker SF 300MHz and ^{119}Sn NMR spectra were recorded on a JEOL GX400

instrument. Mass spectra were obtained by using mass spectro-photometer MAT 112.7, EI 80 eV. The toxicity of the complexes was tested by the Brine shrimp method [23]. Their anti-bacterial activity was determined by the Agar Well Diffusion method [20]. Compounds, **2,4** and **6** were screened in vitro at the Rotterdam Cancer Institute, the Netherlands, against several human tumor cell lines; MCF-7 and EVSA-T, two breast cancers, WiDr, a colon cancer. IGROV, an ovarian cancer, M19 MEL, a melanoma and A498, a renal cancer, MCF-7 is estrogen receptor, ER+/Progesterone receptor PgR+, and EVSA-T is ER-/PR-. The other four cell lines belong to the currently used anti-cancer screening panel of the National Cancer Institute, Bethesda, Maryland, USA. Their cytotoxicity, together with that of some reference compounds, was determined by applying the micro culture sulforhodamine B tests (SRB). The compound was tested in quadruple at 10 concentrations varying with a factor 3, ranging from 3 to 59050 ng/ml. Concentration response curves were determined and the ID_{50} (drug concentration in ng/ml at 50% growth inhibition) values were calculated. Prior to the experiments, a mycoplasma test was carried out on all cell lines and found to be negative.

The organotin compounds were dissolved to a concentration of 117147 ng/ml from 1.0 to 2.2 % DMSO solutions diluted by the full growth RPMI medium. No additional pretreatment, as ultra sonication, was needed for complete dissolution of all compounds. The screening protocol has been described before [24].

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