SYNTHESIS AND SOME SPECTRAL PROPERTIES OF DIPHENYLSILICON SALICYLATE AND A COMPARISON OF THE ANTIFUNGAL EFFICACY OF DIPHENYLSILICON CHLORIDE, ACETATE AND SALICYLATE AND DIPHENYLTIN CHLORIDE, ACETATE AND SALICYLATE ON CANDIDA ALBICANS

J. J. Bonire*, P. F. Olurinola#, J. O. Ehinmidu#, A. S. Shettima# and S. G. Yiase
Department of Chemistry, Ahmadu Bello University, Zaria, Nigeria

ABSTRACT

Diphenylsilicon salicylate has been synthesized and its ir and pmr spectra examined. An antifungal screening of diphenylsilicon chloride, acetate and salicylate, and diphenyltin chloride, acetate and salicylate on Candida albicans has shown that the organo tin compounds have higher antifungal activity than the analogous organosilicon compounds. Suggestions have been adduced to explain the results. And diphenyltin and diphenylsilicon salicylates have the highest antifungal ability of the three classes studied.

INTRODUCTION

The synthesis of diphenyltin salicylate and diphenyltin acetate was reported[1,2] only recently. Diphenylsilicon acetate apparently has been long known[3] but there does not appear to be any report so far on the synthesis of diphenylsilicon salicylate.

While the study of the trend in the variation of the common chemical properties of inorganic compounds of group IVA, like any other group, is usual in the study of the compounds of the elements of the periodic table, there does not appear to be much report on the correlation of the biological activity of similar compounds of the same Periodic Table Group. Much of the biological activity of organometallic compounds has to do with the interaction of such compounds with enzymes in the organism[4,5]. And in such a case the nature of the metal in the compound may influence the biological activity of the organometallic compound.

While antimycotic properties of salicylic acid have long been recognised[6], those of the phenyltin salicylates are only scantily known[1]. No report on the antifungal properties of any phenylsilicon salicylate appears to have been made so far. This paper reports the synthesis of diphenylsilicon salicylate and a comparison of the antifungal efficacy of the diphenylsilicon chloride, acetate and salicylate and diphenyltin chloride, acetate and salicylate on *Candida albicans*.

EXPERIMENTAL

All reagents used in this work were obtained from Aldrich and used without further purificaiton. The solvents were purified by conventional means. Elemental analyses (Cand H) were done by MEDAC Analytical laboratories at the Brunel University, Uxbridge, Middlesex in the U. K. Tin and silicon analyses were done locally using the method reported by Farnsworth[7]. Infrared spectra (KBr discs) were run on a Perkin Elmer RB 31000 infrared spectrophotometer. Melting points, uncorrected, were taken on a Gallenkamp melting point apparatus.

Synthesis

Diphenyltin disalicylate

Silver salicylate was first prepared by stirring together silver oxide and salicylic acid (1:2 mole) in sodium-dried toluene overnight, under aluminium foil cover, in a stopperd conical flask. The solvent was then removed by evaporation at reduced pressure and the dirty white solid residue dried in vacuo. Diphenyltin dichloride (3.44g, 0.01 mole) in dry dichloromethane (150ml) and the dry silver salicylate (5.64g, 0.023 mole) also in dry dichloromethane (100ml) were then mixed at room temperature and stirred magnetically for 24 hours under aluminium foil. The resulting mixture was filtered and the filtrate evaporated until a viscous oil, the disalicylate, was left. This solidified on standing overnight in a desiccator and was recrystallised from dry acetone/dry toluene mixture (1:1 v/v) m.p. 155 - 157°C. Elemental analysis gave the following results:- C, 57.35; H, 3.60; Sn, 21.85% (calculated:

* *Author for corresponding*
# *Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria*

C, 57.07; H, 3.66 and Sn, 21.71%).

Diphenylsilicon disalicylate

Diphenylsilicon disalicylate was similarly prepared from diphenylsilicon chloride (2.54g, 0.01 mole) and silver salicylate (5.64g, 0.023 mole) m.p. 139 - 141°C. Elemental analysis results were as follows: C, 68.65; H, 4.60; Sn, 6.38% (calculated: C, 68.42; H, 4.38 and Sn, 6.14%).

Diphenyltin diacetate

Diphenyltin dichloride (3.44g, 0.01 mole) in dichloromethane (80ml) were mixed at room temperature and stirred magnetically for 24 hours under aluminium foil. The mixture was then filtered and the filtrate evaporated until an oil was obtained. This solidified on standing overnight and was recrystallised from acetone/benzene. The product was dried in vacuo, m.p. 94 - 96°C (Lit.[7], 94 - 96°C).

Diphenylsilicon diacetate

Diphenylsilicon diacetate was similarly prepared from diphenylsilicon dichloride (2.54g, 0.01 mole) and silver acetate (4.32g, 0.026 mole). The product was obtained as a viscous oil (Si % 9.63 calc., 9.75 found).

Antifungal screening

For the determination of minimum inhibitory concentrations (MIC) of the test compounds, graded concentrations of each were mixed with melted (45°C) double strength sabouraud dextrose agar in sterile petridishes of diameter 90mm and allowed to set. An inoculum of 10µl of 10^8 Cfu/ml of the log phase cells of candida albicans was incoculated in triplicate at equidistance on the plate without test for chemical compounds but incoculated with similar test standardized fungus cells. The plates were incubated at 30°C for three days. The lowest concentration of the test chemical compound which inhibited visible growth of the fungus cells was taken as MIC under these experimental conditions.

RESULTS AND DISCUSSION

The synthesis of diphenyltin salicylate has been in an earlier paper[2] but diphenylsilicon disalicylate is probably being reported for the first time. The compounds were produced in high yield (>70%)

Table 1: Some ir spectral absorption frequencies (cm^{-1}) of the diphenyltin and diphenylsilicon carboxylates (where M = Sn, Si)

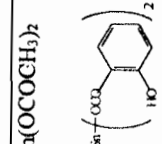
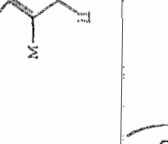
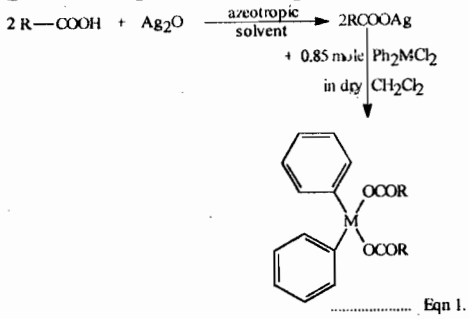
Compound	-O-H	Si-OAc	OCO	M-Ph	Sn-O-C
$Ph_2Sn(OCOCH_3)_2$			1620_s	1055_w	980_w
	3450_w		1635_s	1090_w	980_w
$Ph_2Si(OCOCH_3)_2$		1720_{vs}		1120_{vs}	1000_w
				1435_m	
	3540_w		1640_s	1120_s	1000_w
			(1600 – 1720)	1430_s	

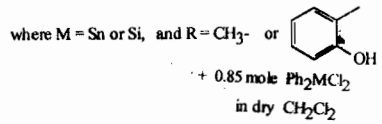
Table 2: ^1H NMR chemical shifts (ppm) of the diphenyltin and diphenylsilicon carboxylates where M = Sn or Si

Compound	M-OCOC<u>H</u>$_3$		
$Ph_2Sn(OCOCH_3)_2$	2.20_s		
		$5.80 - 8.50_m$	
$Ph_2Si(OCOCH_3)_2$		$5.80\ 8.50_m$	
		$5.80 - 8.50_m$	
$Ph_2Si(OCOCH_3)_2$		$5.80 - 8.50_m$	$5.80 - 8.50_m$

and the elemental analyses results agreed well with calculated values; the ir spectra (Table 1) have shown the characteristic absorption bands expected for the compounds. The pmr spectra of the compounds in DMSO (Table 2) showed a multiplet 5.8 - 8.5 ppm for both salicylates indicating a super-imposition of the phenyl and the salicylate proton signals, making necessary the application of X-ray crystallography for a complete elucidation of the structures of the compounds. The synthesis and spectral properties of diphenyltin diacetate has been described in an earlier publication[2]. Diphenylsilicon acetate, an established compound[3], was synthesised using the same procedure (Eqn. 1).



..... Eqn 1.



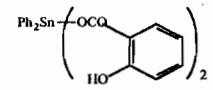
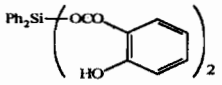
The ir spectral properties (Table 1) and the silicon elemental analysis as well as the pmr spectrum (Table 2) which showed a singlet at 2.20 ppm, assignable to the acetate protons, and a multiplet at about 7.0 ppm, assignable to the phenylsilicon protons, were used to confirm its successful synthesis.

The dibutyltin salicylates were reportedly[8] easily synthesized from the reaction of dibutyltin oxide with the appropriate salicylic acid. But the diphenylsilicon and diphenyltin salicylates were synthesized only from the double decomposition reaction of the silver salicylate and diphenylsilicon and diphenyltin dichlorides using a slight excess of the silver salicylate to ensure completion of the reaction (Eqn. 1). All efforts to produce diphenyltin oxide failed.

The results of the antifungal tests are presented in Table 3. A 1:1 mixture of dimethylsulphoxide and dimethyldigol was used as an emulsifying agent for the test compounds in water. Diphenylsilicon and diphenyltin dichlorides were tested along with the carboxylates for comparison and reference.

From the results, two clear trends are observable: the diphenyltin compounds are clearly and consistently more active as antifungal agents than the diphenylsilicon compounds and the order of activity of the compounds, by virtue of the nature of

Table 3: Minimum Inhibitory Concentration (MIC) of the test compounds against *Candida albicans*.

Compound	MIC (μ mole ml^{-1})
Ph_2SnCl_2	7.27
$Ph_2Sn(OCOCH_3)_2$	6.40
	4.57
Ph_2SiCl_2	9.84
$Ph_2Si(OCOCH_3)_2$	8.31
	5.47

nucleophile, is salicylate > acetate > chloride.

The higher antifungal activity of the organotin compounds over the organosilicon compounds is traceable only to the nature of the metal/metalloid in the compounds. Where a compound is able to form strong bonds with an enzyme, such a compund could be easily neutralised in a biological system as more of the enzyme could be produced as some is rendered useless in removing the foreign compound through the formation of stable coordination compounds[9]. But where the bond between the foreign compound and the enzyme is weak, such a compound could be more effective in blocking the activity of the enzyme as it forms only weak bonds which keep breaking and reforming in the biological system. Close to the valence shell of silicon and tin are 3d and 5d orbitals respectively which are low enough in energy to be used in the formation of dative bonds with N electron pair donor from amino ends of enzyme or relevant amino acids such as histidine and cysteine in the biological system of a fungus cell[10]. It follows then that the strength of this dative bond can decide the activity of the organometallic or organometalloidal compound as an antifungal agent. The silicon atom is smaller than the tin atom which, as a result of its size and atomic

number, has its valence shell much shielded away from the electron attracting influence of its nucleus. A dative bond formed by the Sn centre in its organometallic compound would therefore be weaker than a similar bond formed by an analogous organosilicon compound, thereby making the organotin compound a better inhibitor of enzyme activity. The results obtained in this work corroborate this postulation.

The higher activity of the salicylates over the acetates and the chlorides is not unexpected as salicylic acid, on its own, is known to possess some antifungal property.

This work therefore points out the suggestion that, at least among the organometaloidal and organometallic compounds of group IVA elements, antifungal ability increases down the group. It must be pointed out that a lot still has to be done, like testing all similar compounds of germanium and lead, before this postulate can be confirmed. The higher activity of the salicylates over the acetates and chlorides also make them compounds of promise, as reduced amounts of such compounds would be needed to produce good enough antifungal effects.

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