

Synthesis, structure characterization and insecticidal activity of some triorganotin dithiocarbamates

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A series of triorganotin dithiocarbamates $R_3SnS_2CNR'_2$ ($R = Cy, Ph$; $NR'_2 = NEt_2, N(n-Bu)_2, N(i-Bu)_2, N(n-Pr)_2, N(CH_2)_5, NH(n-Pr), NH(n-Bu), NH(i-Bu)$) has been synthesized using a low-temperature method. Their structures have been characterized by IR, Mössbauer and NMR spectroscopies. In the solid state, an unsymmetrical chelation of the dithiocarbamate ligand was found in all the compounds synthesized. The observation of two Sn–S distances in the compounds was confirmed in the crystal structure of tricyclohexyltin *N-n*-butyldithiocarbamate. In solution, the compounds were found to exhibit distorted tetrahedral structures. The insecticidal activities of the title compounds were screened against the second larval instar of the *Anopheles stephensi* Liston and *Aedes aegypti* (L.) mosquitoes. Results from the screening studies indicated that the triorganotin dithiocarbamates were effective larvicides against both species of larvae. However, there were no significant activity differences between the triphenyltin and tricyclohexyltin derivatives. A quantitative structure–activity relationship was also developed for the *An. stephensi*. Copyright © 2003 John Wiley & Sons, Ltd.

KEYWORDS: *Aedes aegypti*; *Anopheles stephensi*; dithiocarbamate; IR; larvae; mosquito; Mössbauer; NMR; QSAR; structure; toxicity; triorganotin

INTRODUCTION

Mosquitoes are responsible for the transmission of pathogens to humans, to other mammals and to birds. Mosquitoes in the genus *Anopheles* are vectors of human malaria, and certain species of *Aedes* mosquito are responsible for the transmission of yellow fever, dengue and other pathogenic viruses.

Malaria is one of the most widespread infectious diseases in the tropics and subtropics. This disease is estimated to kill between 1.5 and 2.7 million people annually, most of them African children under 5 years of age.¹ Human malaria is caused by any of four species of protozoan parasite belonging to the genus *Plasmodium*. Great efforts have been made in eliminating or reducing malaria in

many countries in the 1950–60s by using 1,1,1-trichloro-2,2-bis-(*p*-chlorophenyl)ethane (DDT) to kill the mosquitoes and chloroquine to treat the blood stage of the infection. However, many countries mistakenly believed malaria was no longer a serious threat and reduced funding for its control.¹ This factor, with the emergence of DDT-resistant mosquitoes and chloroquine-resistant malaria, has again made malaria one of the most prevalent and dangerous diseases in the tropics and subtropics today. With the emergence of DDT-resistant mosquitoes, other organochlorine and organophosphorus pesticides were introduced, but resistance has also been reported for these insecticides.^{2–4} Furthermore, the widespread use of toxic insecticides is generally less accepted now than in the past, and the presence of much larger populations in the tropics means that many more people would be exposed.

The *Aedes aegypti* mosquito is the vector of several arboviral diseases. Two that are important to man and usually occur in epidemic form are yellow and dengue fevers.^{5–7} Yellow

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fever still occurs in sylvatic and urban outbreaks, though a combination of vaccination and vector control has been successful in limiting the number of cases during the most recent outbreaks. The potential remains for large epidemics of yellow fever in populations where vaccination is not economically feasible. In the case of dengue, most infected persons suffer only mild illness; however, about 15% of those infected develop a serious illness. Of those who become ill, about one-third develop dengue hemorrhagic fever (DHF). This severe form of the disease is usually thought to be the result of sequential infection by any two of the four serotypes of dengue virus. Although skillful medical management can prevent most mortality from DHF, the disease can be fatal as frequently as half the time.⁷

The current emphasis for chemists is on the production of novel types of pesticide that prevent insect resistance and that are environmentally friendly. In addition, pesticides should have relatively long-term effects. A class of compounds that have shown pesticidal activity towards the *Anopheles* and *Aedes* mosquitoes are the triorganotins.^{8,9} Triorganotin compounds have long been recognized and used as effective fungicides, bactericides and miticides.^{10–12} The major advantages of evaluating triorganotins as potential larvicides against mosquitoes are (i) that there has been no report on the resistance of this class of compounds to the target organisms and (ii) that triorganotin compounds have been reported to degrade to non-toxic inorganic tin in the environment.¹⁰

It has been well established that dithiocarbamates are a group of compounds that are active against fungi^{13,14} and insects.¹³ Extensive work has been done on dithiocarbamates to study their mode of bonding^{15–21} and their biocidal activity.^{13,14} Thus far, no work has been reported on the toxicity of triorganotin dithiocarbamates against mosquitoes.

Although the structures of triorganotin dithiocarbamates have been extensively studied by IR spectroscopy^{13,15,16,20,21} and X-ray crystallography,^{17,19} little has been reported on their Mössbauer spectra.¹⁵ In this paper, we report on the Mössbauer studies and the insecticidal activities of some triorganotin dithiocarbamates against the *An. stephensi* and *Ae. aegypti* mosquito larvae.

EXPERIMENTAL

Materials

Triphenyltin chloride (Ph_3SnCl) and tricyclohexyltin chloride (Cy_3SnCl) obtained from Alfa Aesar, Ward Hill, MA, USA, were used without further purification, since their melting points corresponded to those reported in the literature. The amines were obtained from Aldrich Chemical Co., Inc., Milwaukee, WI, USA, and purified by distillation. The solvents obtained from Fisher Scientific Inc., Pittsburgh, PA, USA, were purified by conventional methods.

Synthesis of the triorganotin dithiocarbamates

The sodium salts of the dithiocarbamates were prepared at -10°C by reacting equal molar ratios of carbon disulfide, the

appropriate amine and aqueous sodium hydroxide (slight excess) in acetone. The temperature was maintained using a mixture of salt and ice. The sodium salts synthesized were then crystallized from an acetone–petroleum ether mixture. Procedures for these syntheses are cited in the literature.¹⁶

All the triorganotin dithiocarbamates were prepared according to procedures in the literature.¹⁶ A typical reaction is as follows: to an acetone solution (100 cm^3) of the sodium salt of the appropriate dithiocarbamate was added dropwise an equimolar solution of triorganotin chloride in 50 cm^3 acetone. The mixture was maintained below -30°C using an acetone–liquid–nitrogen bath and stirred over a period of 2 h. The precipitated NaCl was removed by filtration and the acetone was distilled off *in vacuo*. The crude product was dissolved in ethyl ether and slow evaporation of the ethereal solution produced fine crystals. The melting points and elemental analysis of the triorganotin dithiocarbamates are listed in Table 1.

Spectral studies

The IR spectra in the range $400\text{--}4000\text{ cm}^{-1}$ were recorded as KBr pellets on a Nicolet Magna-IR 760 spectrometer. The Mössbauer spectra of the solid compounds were measured at 80 K on a model MS-900 Ranger Mössbauer spectrometer in the acceleration mode with a moving-source geometry using a liquid-nitrogen cryostat. The source was 5 mCi $\text{Ca}^{119\text{m}}\text{SnO}_3$ and the velocity was calibrated at ambient temperatures using a composition of BaSnO_3 and tin foil (splitting 2.52 mm s^{-1}). The resultant spectra were analyzed by least-squares fit to Lorentzian-shaped lines.

The ^1H and ^{13}C NMR spectra were recorded at 300 K on a JEOL GSX270 spectrometer at 27.17 MHz and 67.94 MHz respectively. The samples were recorded in CDCl_3 using tetramethylsilane (TMS) as the internal standard. The ^{119}Sn NMR spectra were recorded in CDCl_3 by Acorn NMR Inc., Livermore, CA. The chemical shifts were calculated relative to tetramethyltin.

Preparation of the triorganotin stock solutions

Stock solutions of the triorganotin compounds were prepared by dissolving the triorganotin in one of 95% ethanol, dimethyl sulfoxide (DMSO), or acetone, depending on the solubility of the compound, at concentrations between 200 and 760 ppm. The dissolution of the triorganotins in the organic media was to facilitate the dispersion of the compounds in water. The acetone and DMSO was spectrograde quality, and the 95% ethanol was reagent grade.

Mosquito larvae

Ae. aegypti eggs were hatched in a tray of water and after 2–3 days the second instar stage was attained. The larvae were maintained in an environmental chamber at $27\text{--}28^\circ\text{C}$ with a humidity of 60–90%. The *An. stephensi* larvae were kept in the same environmental chamber under the same conditions. Both species of larvae were fed with ground-up dog food.

Table 1. Melting points and elemental analyses of the triorganotin dithiocarbamates, $R_3SnS_2CNR'_2$

Compound			Elemental analysis: found (calc.) (%)		
R	NR'_2	M.p. (°C)	C	H	Sn
Ph	N(i-Bu) ₂	150–152	58.39 (58.50)	5.98 (6.00)	21.65 (21.41)
	N(CH ₂) ₅	154–155, 150 ¹⁵	56.11 (56.59)	5.05 (4.94)	23.20 (23.26)
	N(<i>n</i> -Pr) ₂	144–145	56.68 (57.05)	5.59 (5.55)	22.53 (22.55)
	NEt ₂	130–132, 135 ¹⁶	54.91 (55.44)	4.96 (5.06)	23.52 (23.82)
	N(<i>n</i> -Bu) ₂	108–109, 114 ¹⁵	58.45 (58.50)	5.92(6.00)	21.35 (21.41)
	NH(<i>n</i> -Bu)	110–112, 131 ¹⁵	55.54 (55.44)	4.93 (5.06)	23.61 (23.82)
	NH(i-Bu)	120–122	55.18 (55.44)	4.89 (5.06)	23.63 (23.82)
	NH(<i>n</i> -Pr) ^a	142–144, 86 ¹⁵	58.88 (59.06)	4.17 (4.13)	32.34 (32.43)
Cy	N(i-Bu) ₂	130–131	56.74 (56.64)	9.25 (8.98)	20.66 (20.73)
	N(CH ₂) ₅	144–145	54.68 (54.55)	8.20 (8.20)	22.44 (22.46)
	N(<i>n</i> -Pr) ₂	100–102	55.78 (55.15)	8.91 (8.70)	21.63 (21.80)
	NEt ₂	131–133	53.86 (53.49)	8.30 (8.39)	22.72 (22.98)
	N(<i>n</i> -Bu) ₂	115–116	57.10 (56.64)	9.48 (8.98)	20.97 (20.73)
	NH(<i>n</i> -Bu)	98–100	53.96 (53.49)	8.69 (8.39)	22.98 (22.98)
	NH(i-Bu)	147–148	53.89 (53.49)	8.65 (8.39)	23.12 (22.98)
	NH(<i>n</i> -Pr)	135–137	53.41 (52.60)	8.11 (8.23)	24.01 (23.63)

^a Decomposes to Ph₃SnSSnPh₃.

Toxicity assay

The toxicity studies were performed in 100 mm diameter × 15 mm deep disposable Petri dishes using ten larvae in the second instar. The *An. stephensi* or *Ae. aegypti* larvae were transferred into the Petri dishes using a 100 μl micro-pipetter. An additional 15 cm³ of water was then added. Aliquots of the triorganotin solution were then added to the Petri dish containing the larvae and deionized water to give the desired concentration of triorganotin. The total assay volume in each case was 20 cm³. Both positive and negative controls were used in the assay. Each assay was done in triplicate. The larvae were exposed to the triorganotin compounds for 24 h, and the mortality rates for the mosquito larvae were determined by visual counting. Mosquito larvae that showed a slight reflex to disturbance were considered alive. Probit analyses²² were used to determine the LC₅₀ (concentration at which the test compounds killed 50% of the organisms tested).

Quantitative structure–activity relationship

The QSARIS program was used to generate the quantitative structure–activity relationship (QSAR). The program was obtained from SciVision, Burlington, MA, USA.

RESULTS AND DISCUSSION

IR spectra

The type of bonding between the dithiocarbamate ligand and the tin atom was deduced using the ν_{C-N} and ν_{C-S} vibrations. It has been reported¹³ that the observation of a single ν_{C-S} absorption in the region around 1000 cm⁻¹ is indicative of

dithiocarbamate groups that are bonded symmetrically or bidentate in nature. Splitting of this band around 1000 cm⁻¹ has been reported for dithiocarbamate groups that act as a monodentate ligand or are unsymmetrically bonded.^{23–25} Also, monodentate groups would result in a C=N double bond¹³ around 1640–1690 cm⁻¹. As shown in Table 2, both the mono- and di-alkyldithiocarbamate compounds exhibit single ν_{C-S} vibrations between 986 and 991 cm⁻¹ and ν_{C-N} vibrations between 1476 and 1535 cm⁻¹. The observed ν_{C-N} vibrations lie between the range for C–N single bonds (1250–1360 cm⁻¹) and C=N double bonds (1640–1690 cm⁻¹). This suggests that the C–N bonds in the complexes have some partial double bond character. Partial double bond character for the C–N bond would result in some partial double bond character for the C–S bonds. This type of bonding for the two C–S bonds can be achieved through the bonding of the two sulfur atoms with the tin atom. This interaction can be viewed as the coordination of one normal Sn–S bond and one weak Sn–S bond. The weak Sn–S bond is possibly through π overlap of the empty *d*-orbitals of the tin atom and the *p*-orbitals of sulfur. De Vries and Herber¹⁸ have used the term ‘anisobidenate’ to describe this type of bonding for a series of triphenyltin dithiocarbamates. This type of bonding would result in observing two Sn–S distances in the compound. In the present work, two different Sn–S bond distances were identified in the crystal structure of tricyclohexyltin *N*-*n*-butyldithiocarbamate.²⁶ One distance was 2.472 Å and the other was at 3.239 Å. Another example of this type of bonding can be found in Ph₃SnS₂CN(CH₂)₅.¹⁷ The crystal structure of this compound showed Sn–S bond lengths of 2.481 and 2.919 Å. Other examples are cited in a review by Tiekink.²⁷

Table 2. Mössbauer parameters and selected IR data for the triorganotin dithiocarbamates, $R_3SnS_2CNR'_2$

Compound		IS ($mm\ s^{-1}$)	QS ($mm\ s^{-1}$)	ρ	ν_{C-N}	ν_{C-S}
R	NR'_2					
Ph	N(i-Bu) ₂	1.25 ± 0.01	1.67 ± 0.01	1.34	1492(s)	986(m)
	N(CH ₂) ₅	1.25 ± 0.01	1.71 ± 0.01	1.37	1494(s)	997(m)
	N(<i>n</i> -Pr) ₂	1.29 ± 0.01	1.89 ± 0.02	1.45	1494(s)	993(m)
	NEt ₂	1.28 ± 0.01	1.86 ± 0.02	1.44	1491(s)	996(m)
	N(<i>n</i> -Bu) ₂	1.25 ± 0.01	1.79 ± 0.02	1.41	1491(s)	995(m)
	NH(<i>n</i> -Bu)	1.30 ± 0.01	1.84 ± 0.01	1.40	1535(s)	997(s)
	NH(i-Bu)	1.24 ± 0.01	1.81 ± 0.01	1.46	1534(s)	991(s)
	NH(<i>n</i> -Pr)	1.27 ± 0.01	1.62 ± 0.01	1.28	1479(s)	997(s)
	Cy	N(i-Bu) ₂	1.50 ± 0.01	2.04 ± 0.02	1.36	1483(s)
N(CH ₂) ₅		1.52 ± 0.01	2.09 ± 0.02	1.38	1476(s)	990(s)
N(<i>n</i> -Pr) ₂		1.51 ± 0.01	2.08 ± 0.02	1.38	1483(s)	991(s)
NEt ₂		1.51 ± 0.01	2.10 ± 0.02	1.39	1484(s)	986(m)
N(<i>n</i> -Bu) ₂		1.49 ± 0.01	2.06 ± 0.02	1.38	1487(s)	990(m)
NH(<i>n</i> -Bu)		1.52 ± 0.01	2.31 ± 0.02	1.52	1534(s)	989(s)
NH(i-Bu)		1.54 ± 0.01	2.33 ± 0.02	1.51	1523(s)	992(s)
NH(<i>n</i> -Pr)		1.54 ± 0.01	2.26 ± 0.02	1.47	1526(s)	991(s)

Table 2 also shows that the monoalkyldithiocarbamates, ν_{C-N} absorptions appear at higher wavenumbers ($1523\text{--}1534\text{ cm}^{-1}$) than in the corresponding dialkyl dithiocarbamates ($1476\text{--}1494\text{ cm}^{-1}$). This shift to higher wavenumbers is possibly due to the weaker electron-withdrawing ability of alkyl groups compared with the hydrogen atom.

Mössbauer spectra

The two parameters that are obtainable from the Mössbauer spectra are the quadrupole splitting (QS) and the isomer shift (IS). The values for these parameters for the triorganotin dithiocarbamates are also summarized in Table 2. The coordination number of the tin atom has been related to ρ , the ratio of the QS/IS values.²⁸ ρ values less than 1.8 are indicative of tin compounds that are four-coordinated, whereas values larger than 2.1 have been assigned to tin complexes with greater than four-coordination.²⁸ The ρ values for triorganotin dithiocarbamates in the study range from 1.28 to 1.51 (Table 2). This clearly indicates that the complexes are four-coordinated.

As can be seen in Table 2, the IS values, in the present study, for the triphenyltin and tricyclohexyltin derivatives are $1.25 \pm 0.05\text{ mm s}^{-1}$ and $1.50 \pm 0.05\text{ mm s}^{-1}$ respectively. The small changes in the observed IS values as the R' group is varied in the dithiocarbamate ligand would indicate that there is very little change in the total s-electron density at the tin nucleus due to these changes. This suggests that the effects of the R' groups in the dithiocarbamate ligands are minimal. The IS and QS values of the triphenyltin dithiocarbamates are slightly lower than those of the tricyclohexyltin dithiocarbamates. These differences in the IS and QS values are attributed to the greater electron-withdrawing properties of the phenyl group compared with the cyclohexyl group.

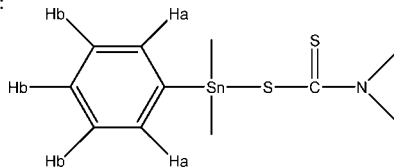
The QS values observed for the triorganotin dithiocarbamates may give an indication of a second weak Sn–S interaction. A comparison of the QS values ($1.62\text{--}1.89\text{ mm s}^{-1}$) for the present triphenyltin dithiocarbamates with the Mössbauer data for $Ph_3SnSOAc$ ($QS = 1.65\text{ mm s}^{-1}$)—which is known to be four-coordinated—and the five-coordinate $Ph_3SnSOAc$ –pyridine complex²⁹ ($QS = 2.35\text{ mm s}^{-1}$) indicates that the values for the present triphenyltin compounds are between these two compounds. With the exception of $Ph_3SnS_2CNH(n-Pr)$, they are all slightly larger than the QS value for Ph_3SnOAc but significantly smaller than the pyridine adduct. This suggests that the structures for the compounds are between a tetrahedral and trigonal bipyramidal structure, supporting the IR spectral results.

Multiple NMR (¹H, ¹³C, ¹¹⁹Sn)

The ¹H NMR chemical shifts and coupling constants of selected triphenyltin and tricyclohexyltin dithiocarbamates are given in Tables 3 and 4 respectively. The ¹H NMR spectra of the triphenyltin dithiocarbamate compounds contained absorptions in two regions. One region is assignable to the dithiocarbamate ligands ($0.92\text{--}4.03\text{ ppm}$) and the other region to the triphenyltin moiety ($7.15\text{--}8.00\text{ ppm}$). Furthermore, the phenyl protons region consisted of two groups of peaks. The *ortho* protons were observed at a lower field ($7.60\text{--}8.00\text{ ppm}$) than those for the *meta* and *para* protons ($7.15\text{--}7.60\text{ ppm}$). These results are in agreement with values reported by Domazetis *et al.*¹⁶ for a series of triphenyltin dithiocarbamate compounds. In addition, those authors reported that the difference in the chemical shift resonances between the *ortho* and the *meta* and *para* protons ($0.30\text{--}0.40\text{ ppm}$) is an indication of anisobidentate bonding in the compounds. The differences of these resonances in the present study were in the range

Table 3. ^1H NMR data^a for selected triphenyltin dithiocarbamates $\text{Ph}_3\text{SnS}_2\text{CNR}'_2$

NR'_2	$\delta^1\text{H}$ NMR (ppm)		
	Ph^b		NR'_2
NEt_2	7.60–8.00, 6H (m, Ha, $J = 56$ Hz)	7.20–7.60, 9H (m, Hb)	3.84 (q, $\text{NCH}_2 \times 2$, $J = 7.2$ Hz); 1.30 (t, $\text{CH}_3 \times 2$, $J = 7.2$ Hz)
$\text{N}(n\text{-Pr})_2$	7.65–7.85, 6H (m, Ha, $J = 54$ Hz)	7.25–7.55, 9H (m, Hb)	3.71 (t, $\text{NCH}_2 \times 2$, $J = 7.8$ Hz); 1.70–2.00(m, $\text{CH}_2 \times 2$); 0.92 (t, $\text{CH}_3 \times 2$, $J = 7.4$ Hz)
$\text{N}(n\text{-Bu})_2$	7.65–7.95, 6H (m, Ha, $J = 54$ Hz)	7.25–7.60, 9H (m, Hb)	3.76 (t, $\text{NCH}_2 \times 2$, $J = 7.9$ Hz); 1.65–1.90(m, $\text{CH}_2 \times 2$); 0.95 (t, $\text{CH}_3 \times 2$, $J = 7.3$ Hz)
$\text{N}(i\text{-Bu})_2$	7.65–7.90, 6H(m, Ha, $J = 56$ Hz)	7.25–7.55, 9H (m, Hb)	3.66 (d, $\text{NCH}_2 \times 2$, $J = 7.6$ Hz); 2.25–2.50(m, $\text{CH} \times 2$); 0.94 (d, $\text{CH}_3 \times 2$, $J = 6.8$ Hz)
$\text{N}(\text{CH}_2)_5$	7.60–7.95 6H (m, Ha, $J = 60$ Hz)	7.15–7.55, 9H (m, Hb)	4.03 (t, $\text{NCH}_2 \times 2$, $J = 5.6$ Hz); 1.50–2.00(m, $\text{CH}_2\text{CH}_2\text{CH}_2$)

^a d: doublet; t: triplet; q: quartet; m: multiplet.^b Numbering scheme for phenyl group:**Table 4.** ^1H NMR data for selected tricyclohexyltin dithiocarbamates $\text{Cy}_3\text{SnS}_2\text{CNR}'_2$

NR'_2	$\delta^1\text{H}$ NMR (ppm)	
	Cy	NR'_2
NEt_2	1.10–2.20, 33H (m, Cy)	3.80, 4H (q, $\text{NCH}_2 \times 2$, $J = 7.2$ Hz); 1.26, 6H (t, $\text{CH}_3 \times 2$, $J = 7.2$ Hz)
$\text{N}(n\text{-Pr})_2$	1.10–2.20, 33H (m, Cy)	3.76, 4H (t, $\text{NCH}_2 \times 2$, $J = 7.8$ Hz); 1.75–2.05, 4H (m, $\text{CH}_2 \times 2$); 0.90, 6H (t, $\text{CH}_3 \times 2$, $J = 7.4$ Hz)
$\text{N}(n\text{-Bu})_2$	1.10–2.15, 33H (m, Cy)	3.76, 4H (t, $\text{NCH}_2 \times 2$, $J = 7.9$ Hz); 1.70–1.95, 4H (m, $\text{CH}_2 \times 2$); 1.60–1.85, 4H (m, $\text{CH}_2 \times 2$); 0.94, 6H (t, $\text{CH}_3 \times 2$, $J = 7.4$ Hz)
$\text{N}(i\text{-Bu})_2$	1.10–2.10, 33H (m, Cy)	3.74, 4H (d, $\text{NCH}_2 \times 2$, $J = 7.4$ Hz); 2.30–2.60, 2H (m, $\text{CH} \times 2$); 0.92, 12H (d, $\text{CH}_3 \times 2$, $J = 6.7$ Hz)
$\text{N}(\text{CH}_2)_5$	1.50–2.20, 39H (m, Cy + $\text{CH}_2\text{CH}_2\text{CH}_2$)	4.12, 4H (t, $\text{NCH}_2 \times 2$, $J = 5.6$ Hz)
$\text{NH}(i\text{-Bu})$	1.10–1.45 6H (m, Cy)	3.34, 2H (d, NCH_2 , $J = 6.4$ Hz); 2.10–2.25, 2H (m, CH); 0.94, 6H (d, $\text{CH}_3 \times 4$, $J = 6.7$ Hz)

^a d: doublet; t: triplet; q: quartet; m: multiplet.

of 0.30 to 0.37 ppm, indicating that the dithiocarbamate compounds are also anisobidenate bonded in solution.

The ^1H NMR spectra of the tricyclohexyltin dithiocarbamates also contained absorptions in two regions. The resonances in the region 0.92 to 4.12 ppm were assigned to the dithiocarbamate ligand, and those in the range from 1.10 to 2.20 ppm were assigned to the tricyclohexyltin group. In addition, the protons due to the piperidine ring in $\text{C}_3\text{SnS}_2\text{CN}(\text{CH}_2)_5$ were also assigned to this same region.

Table 5 lists the chemical shifts and tin–carbon coupling constants for the dithiocarbamates. The ^{13}C NMR chemical shifts due to the phenyl and cyclohexyl groups are observed at positions comparable to other similar compounds.^{30–32} The ^{13}C NMR chemical shifts due to the $-\text{CS}_2$ carbon atoms in the dithiocarbamates were observed in the range 194.3 to 201.0 ppm.

Coordination of the tin atom in triorganotins has been related to the $^1J(^{119}\text{Sn}-^{13}\text{C})$ coupling constants. The $^1J(^{119}\text{Sn}-^{13}\text{C})$ coupling constants for the triphenyltin dithiocarbamates ranged from 604 to 620 Hz, which is indicative of four-coordinated compounds.³⁰ Similar values were observed for a series of triphenyltin compounds.³⁰ A range of 321–339 Hz was observed for the $^1J(^{119}\text{Sn}-^{13}\text{C})$ coupling constants for the tricyclohexyltin dithiocarbamates. These values are very similar to the $^1J(^{119}\text{Sn}-^{13}\text{C})$ coupling constant (335 Hz) for the four-coordinated tricyclohexyltin 2-[(*E*)-2-(2-hydroxy-5-methylphenyl)-1-diazenyl]benzoate.³²

Values of the ^{119}Sn NMR chemical shift and the coupling constant $^1J(^{119}\text{Sn}-^{13}\text{C})$ have been used to study the structures of triorganotin(IV) compounds in solution.^{30,31} To support the structures deduced from the ^1H and ^{13}C NMR spectra, ^{119}Sn NMR spectra of several compounds were recorded in CDCl_3 and the data are also listed in Table 5. The observed

values of -192.3 ppm and -29.2 ppm, for the triphenyltin and tricyclohexyltin dithiocarbamates respectively, are in agreement with the previously reported values for other dithiocarbamate compounds.³³ A ^{119}Sn NMR chemical shift of -2.8 ppm was observed for $\text{C}_3\text{SnS}_2\text{CNH}(\text{i-Bu})$. It is expected that the tin atom in monoalkyldithiocarbamates would be more positive than in the dialkyldithiocarbamate derivatives, thus the tin atom would have absorptions further downfield, as was observed. Based on the NMR spectroscopic data, the compounds exhibited a distorted tetrahedral structure in solution.

Toxicity studies

The individual toxicities (in parts per million), their standard deviations, and the averages for each series of compounds screened against the second larval instar stage of the *An. stephensi* and *Ae. aegypti* mosquitoes are listed in Table 6. As can be seen from Table 6, the range of efficacy of the triorganotin dithiocarbamates against the second larval stage of the *An. stephensi* larvae ranged from a low of 13.74 ppm for $\text{Ph}_3\text{SnS}_2\text{CNH}(\text{n-Bu})$ to a high for $\text{Ph}_3\text{SnS}_2\text{CNEt}_2$ of 1.81 ppm. All the triorganotin dithiocarbamates showed higher LC_{50} values than their parent compounds, triphenyltin chloride (0.18 ppm)⁹ and tricyclohexyltin chloride (0.003 ppm).⁹ Furthermore, the results indicate that this series of compounds is less effective than other triphenyltins (Ph_3SnX) and tricyclohexyltins (C_3SnX) containing simple anions, such as Cl, OH, F, OAc and Br, which had a range of toxicity between 0.003 and 0.67 ppm towards the *An. stephensi* larvae.⁹

Based on the averages for the dialkyldithiocarbamate compounds, the results appear to indicate that the phenyl compounds ($\text{Ph}_3\text{SnS}_2\text{CNR}'_2$) were slightly more toxic (1.97 ppm)

Table 5. ^{13}C and ^{119}Sn NMR data for selected triorganotin dithiocarbamates, $\text{R}_3\text{SnS}_2\text{CNR}'_2$ (ppm)

Compound		$^1J(^{119}\text{Sn}-^{13}\text{C})$ (Hz)	$\delta^{13}\text{C}$ (ppm)								$\delta^{119}\text{Sn}$ (ppm)	
R	NR'_2		C1	C2	C3	C4	C5	C6	C7	C8		C = S
Ph	NEt_2	609	143.1	136.9	128.7	129.1	60.2	16.8			199.5	
	$\text{N}(\text{n-Pr})_2$	620	142.9	136.8	128.5	129.1	58.0	20.4	11.3		194.3	
	$\text{N}(\text{n-Bu})_2$	615	143.0	136.8	128.6	129.1	56.3	29.0	20.2	13.9	198.6	
	$\text{N}(\text{i-Bu})_2$	604	143.0	136.7	128.9	129.0	63.9	27.1	20.3		197.0	-192.3
	$\text{N}(\text{CH}_2)_5$	618	142.8	136.8	128.5	129.1	54.2	25.9	23.3		195.2	
Cy	NEt_2	321	34.9	32.5	32.0	29.4	57.2	18.6			196.8	
	$\text{N}(\text{n-Pr})_2$	338	34.8	32.3	32.1	29.4	57.2	20.7	11.4		198.2	
	$\text{N}(\text{n-Bu})_2$	339	34.9	32.4	32.2	29.3	55.3	29.0	20.1	13.6	196.4	
	$\text{N}(\text{i-Bu})_2$	336	34.8	32.2	32.1	29.4	63.0	27.1	20.3		199.7	-29.2
	$\text{N}(\text{CH}_2)_5$	328	34.8	32.3	32.1	29.4	53.5	26.0	23.8		197.3	
	$\text{NH}(\text{i-Bu})$	329	34.4	32.3	32.1	29.3	56.9	27.0	20.0		201.0	-2.8

^a Numbering scheme for triorganotin dithiocarbamates:

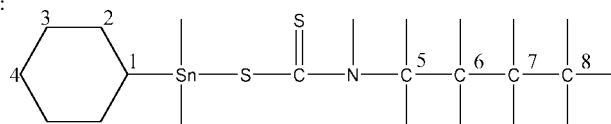


Table 6. Toxicity of the triorganotin dithiocarbamates, $R_3SnS_2CNR'_2$, against the second instar stage of the *An. stephensi* and *Ae. aegypti* mosquito larvae

R	Compound NR' ₂	24 h LC ₅₀	
		<i>Ae. aegypti</i>	<i>An. stephensi</i>
Ph	N(i-Bu) ₂	2.15 ± 0.25	2.32 ± 0.12
	N(CH ₂) ₅	1.03 ± 0.02	1.92 ± 0.29
	N(<i>n</i> -Pr) ₂	1.04 ± 0.03	1.93 ± 0.05
	NEt ₂	2.44 ± 0.03	1.81 ± 0.01
	N(<i>n</i> -Bu) ₂	1.91 ± 0.04	1.88 ± 0.05
	Average	1.71	1.97
	NH(<i>n</i> -Bu)	1.88 ± 0.06	13.74 ± 0.08
	NH(i-Bu)	1.49 ± 0.10	7.62 ± 0.43
	NH(<i>n</i> -Pr)	1.55 ± 0.05	11.94 ± 0.31
	Average	1.64	11.10
	Cy	N(i-Bu) ₂	4.38 ± 0.28
N(CH ₂) ₅		1.03 ± 0.02	1.90 ± 0.05
N(<i>n</i> -Pr) ₂		4.37 ± 0.07	3.89 ± 0.46
NEt ₂		3.13 ± 0.12	3.24 ± 0.12
N(<i>n</i> -Bu) ₂		2.44 ± 0.07	3.44 ± 0.41
Average		3.07	2.78
NH(<i>n</i> -Bu)		1.74 ± 0.02	9.21 ± 0.17
NH(i-Bu)		1.08 ± 0.02	3.67 ± 0.27
NH(<i>n</i> -Pr)		1.39 ± 0.02	5.79 ± 0.21
Average		1.40	6.22

towards the *An. stephensi* larvae than the tricyclohexyl derivatives (Cy₃SnS₂CNR'₂) (2.78 ppm). However, a *t*-test analysis for the dialkyldithiocarbamates indicated that there was no significant difference between the tricyclohexyl- and triphenyl-tin derivatives at the 95% confidence level. This may be due to the fact that the organic groups on the dithiocarbamate moiety are too far removed from the tin atom to have any substantial effect on the toxicity of the compound. Similar findings were reported in the inhibition of *Ceratomyx- tis ulmi* screened against a series of triphenyltin adducts of *N*-alkylsalicylideneimines.³⁴

However, for the monoalkyldithiocarbamates series, the average for the tricyclohexyl compounds (Cy₃SnS₂CNHR') was 6.22 ppm, which is significantly more active than their triphenyltin (Ph₃SnS₂CNHR') analogs, which had an average of 11.10 ppm. A *t*-test analysis confirmed this significance at the 95% confidence level. This result is in agreement with an earlier study on the same species of mosquito larvae using a series of tricyclohexyl- and triphenyl-tin compounds containing simple anion groups.⁹

A comparison of the dialkyldithiocarbamates with the monoalkyldithiocarbamates indicated that the disubstituted compounds are significantly more toxic. The addition of a second organic group will have a greater effect on the electronic distribution of the overall molecule compared with

the monoalkyldithiocarbamate molecule. This redistribution of electron density may play a role in the toxicity of the dithiocarbamates, since a larger ligand may cause the ligand to dissociate more easily. It has been reported that the toxicity of triorganotins against another species of mosquito, *Ae. aegypti*, involved the triorganotin cation.³⁵ Dissociation and molecular size of a series of tri-*n*-alkyltins were shown to be the primary factors in determining whether the compound was a good Pdr5 substrate.³⁶

The toxicity results for the dialkyldithiocarbamate compounds against the *Ae. aegypti* larvae appear to suggest that the triphenyltin derivatives were slightly more active (1.71 ppm) than the tricyclohexyltin compounds (3.07 ppm). However, as with the *An. stephensi* results, the *t*-test analyses indicated that there was no significant difference between these two series of compounds at the 95% confidence level.

Unlike the results obtained for *An. stephensi*, the *t*-test analysis for the monoalkyldithiocarbamates indicated that there was no significant difference between the tricyclohexyl- and triphenyl-tin derivatives in their toxicity against the *Ae. aegypti* larvae. In addition, there is no significant difference between the di- and mono-alkyldithiocarbamates, as was observed for the *An. stephensi* study. These results indicate that the toxicity of the compounds towards the mosquito larvae is dependent on both the compound and the species of mosquito larvae. It has also been reported that the same compound, tris-(*p*-tolyl) tin chloride, had different toxicities on different strains of the *Ae. aegypti* mosquito larvae.³⁵ This study further supports the fact that the same compounds may have a different toxicity on different species of mosquito, since the data indicate that the *An. stephensi* larvae are more tolerant than the *Ae. aegypti* to the dithiocarbamates.

A common method used for relating toxicological activities to structures of molecules is the QSAR. A QSAR is a regression equation that relates some measurable biological activity to a physicochemical or biochemical property or properties related to the molecule. It was possible to develop a QSAR for the *An. stephensi* using the QSARIS program from SciVision for this series of triorganotins. The QSAR was generated between the LC₅₀ values for the compounds and two descriptors of the molecules, the log *P* values and the Δχ path indices (xpc4) as defined by QSARIS. The equation generated was LC₅₀ = 1.87 log *P* - 10.19xpc4 + 32.93 with a multiple R² of 0.815 and a cross-validation of 65.08. The training set is very well described by the regression equation, which is statistically very significant. Cross-validation shows that the model constructed can be used with care to predict the value of LC₅₀. However, it was not possible to generate a QSAR for the *Ae. aegypti*. This suggests that the mechanism of kill is different for the two species of mosquito.

In view of the results from this study, triorganotin dithiocarbamates as a class can be considered a potential larvicidal candidate against *An. stephensi* and *Ae. aegypti* larvae. Though their toxic results are higher than other insecticides, such as the synthetic pyrethroid insecticide deltamethrin,³⁷ their advantages lie in the fact that triorganotins are biodegradable

in the environment, and there is no reported resistance of these two species of mosquito towards triorganotins.

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