APPLIED ORGANOMETALLIC CHEMISTRY
Appl. Organometal. Chem. 2004; **18**: 363–368
Published online in Wiley InterScience (www.interscience.wiley.com). DOI:10.1002/aoc.660

Synthesis, structure characterization and larvicidal activity of some tris-(*para*-substitutedphenyl)tins

Xueqing Song[1], Quyen Duong[1], Edlira Mitrojorgji[1], Alejandra Zapata[1,2], Nhuvu Nguyen[1], Daniel Strickman[3], Jacqulin Glass[3] and George Eng[1]*

[1]Department of Chemistry and Physics, University of the District of Columbia, Washington, DC 20008, USA
[2]Department of Chemistry, The Catholic University of America, Washington, DC 20064, USA
[3]Department of Entomology, Walter Reed Army Institute of Research, Silver Spring, MD 20910, USA

Received 3 November 2003; Revised 29 November 2003; Accepted 2 April 2004

A series of tris-(*para*-substitutedphenyl)tins ($X-C_6H_4)_3SnY$, where X = Cl, F, CH_3 and SCH_3 and Y = Cl, OH and OAc, was synthesized. The structures of the compounds were primarily characterized by Mössbauer spectroscopy. Based on the spectroscopic data, the chloride derivatives were determined to be four-coordinated monomers and the acetate and hydroxide compounds were found to be five-coordinated polymers. The compounds were screened against the second larval instar of the *Anopheles stephensi* and *Aedes aegypti* mosquitoes. For the *An. stephensi* larvae, the compounds that had the highest toxicity were those that contained a single atom substituent on the phenyl ring, and the least effective compounds contained the SCH_3 substituent. Toxicity was more dependent on the ring substituent than on the anion attached to the tin atom. Quantitative structure–activity relationships could be generated between the toxicity of the compounds and the surface area of the molecule, indicating that the toxicity was related to the size of the substituent on the ring. In the case of the *Ae. aegypti*, the toxicity was also more dependent on the ring substituent than on the anion group. However, the size of the substituent on the ring was not found to be the dominant factor in the toxicity of these compounds. Copyright © 2004 John Wiley & Sons, Ltd.

KEYWORDS: *Aedes aegypti*; *Anopheles stephensi*; aryltins; larvae; mosquitoes; QSAR; structure; toxicity; tris-(*para*-substitutedphenyl)tins

INTRODUCTION

Triorganotins are a class of organometallic compounds with known biocidal activities.[1,2] They have been used in agriculture for controlling various pests and as a wood preservative.[1,2] Organotins have also been found to be effective against mosquitoes and their larvae. For example, Kumar Das *et al*.[3] observed that this class of compounds was effective against the larvae of the *Aedes aegypti* mosquito. Another study involving the mosquito, as well as the house fly and flea, also concluded that triorganotins were the most effective organotin in achieving 100% mortality.[4] The insecticidal aspects of triorganotins against several species of mosquito has been discussed in a recent review.[5]

Recently, several series of organotins were found to have effective larvicidal activity against both the *Anopheles stephensi* and *Ae. aegypti* mosquitoes.[6–8] For example, a number of triorganotin dithiocarbamates were found to be an effective larvicide against both types of mosquito.[8]

Mosquitoes are responsible for the transmission of diseases such as malaria and yellow fever to humans. Malaria is one of the most widespread infectious diseases in the world. More than 40% of the world's population lives in tropical areas where they are at risk of malaria transmission.[9] Each year, approximately 400 million people are infected with malaria, with approximately 1–2 million cases resulting in death,[9] mainly among children of 5 years of age or less.[9] The *Ae. 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.[10–12]

*Correspondence to: George Eng, Department of Chemistry and Physics, University of the District of Columbia, Washington, DC 20008, USA.
E-mail: geng@udc.edu
Contract/grant sponsor: National Institutes of Health Minority Biomedical Research Support Program; Contract/grant number: MBRS/SCORE; GM08005.

Insecticides still remain the primary method of most countries' mosquito control programs. Thus, the development of a more effective larvicide to combat these two species of mosquito would be of worldwide interest. The synthesis, structural characterization and the larvicidal activities of several tris-(*para*-substitutedphenyl)tins are being reported, since this series of compounds has been found to be effective against the larvae of the *Ae. aegypti* mosquitoes.[3]

EXPERIMENTAL

Materials

Anhydrous tin tetrachloride was obtained from J. T. Baker Chemical Co., Phillipsburg, NJ, USA, and used as received. Ph_3SnCl, Ph_3SnOH and Ph_3SnOAc obtained from Alfa Aesar, Ward Hill, MA, USA, were also used as received, since their melting points were within experimental literature values. The *para*-substituted benzenes, 4-bromothioanisyl, 4-bromochlorobenzene, 4-bromofluorobenzene and 4-bromomethylbenzene were obtained from Aldrich Chemical Co., Inc., Milwaukee, WI, USA, and used without further purification. All the solvents were obtained from Fisher Scientific Inc., Pittsburgh, PA, USA, and stored over molecular sieves, with the exception of anhydrous ether and tetrahydrofuran, which were distilled over sodium just prior to use. All other reagents were reagent grade and were used as purchased without any further purification.

Preparation of the tetraaryltins

The tetrakis-(*para*-substitutedphenyl)tins were prepared according to standard literature procedure.[13] The melting points of the tetraaryltins are as follows: tetrakis-(*para*-chlorophenyl)tin, 192–194 °C (lit.[14] 195–196 °C); tetrakis-(*para*-methylphenyl)tin, 235–236 °C (lit.[15] 238 °C); tetrakis-(*para*-fluorophenyl)tin, 138–140 °C (lit.[16] 137–139 °C); and tetrakis-(*para*-thioanisyl)tin, 165–166 °C (lit.[17] 169–170 °C).

Preparation of the triaryltin compounds

The triaryltin chlorides were prepared by the Kocheshkov redistribution reaction.[18] Their melting points are listed in Table 1. The triaryltin hydroxides and acetates were prepared according to literature procedures.[2,22] and their respective melting points are listed in Tables 2 and 3 respectively. The theoretical and observed carbon and hydrogen analyses of the two new compounds, tris-(*para*-thioanisyl)tin hydroxide (found: C, 50.16; H, 4.46 Calc.: C, 49.92; H, 4.42%.) and acetate (found: C, 50.47; H, 4.42 Calc.: C, 50.17; H, 4.39%.) are within acceptable limits.

Spectral studies

The Mössbauer spectra were measured at 80 K on a Ranger spectrometer Model MS-900 in the acceleration mode with a moving-source geometry using a liquid-nitrogen cryostat. The source was 5 mCi $Ca^{119m}SnO_3$ and the velocity was calibrated at ambient temperatures using a composition of $BaSnO_3$ and tin foil (splitting 2.52 mm s^{-1}). The ^1H NMR spectra were recorded at 300 K on a JEOL GSX270 spectrometer at 27.17 MHz. The samples were recorded in $CDCl_3$ or acetone-d_6 using tetramethylsilane as the internal standard.

Mosquito larvae

Ae. aegypti eggs were hatched in a tray of tap water and after 2–3 days the second instar stage was attained. The larvae

Table 1. Melting points and spectral data of tris-(*para*-substitutedphenyl)tin chlorides $(4\text{-}XC_6H_4)_3SnCl$

		Mössbauer parameters		
Compound X	M.p. (°C)	QS (mm s^{-1})	IS (mm s^{-1})	ρ
H	108	2.53	1.31	1.93
Cl	103–105 (108–109[19])	2.58	1.30	1.99
CH_3	96–98 (96.5–97.0[20])	2.39	1.26	1.90
F	114–116 (116–117[21])	2.42	1.26	1.92
SCH_3	102–103 (102–103[20])	2.43	1.17	2.08

Table 2. Melting points and spectral data of tris-(*para*-substitutedphenyl)tin hydroxides $(4\text{-}XC_6H_4)_3SnOH$

		Mössbauer parameters		
Compound X	M.p. (°C)	QS (mm s^{-1})	IS (mm s^{-1})	ρ
H	124–126	2.84	1.18	2.41
Cl	158–160 (156–157[22])	2.71	1.23	2.20
CH_3	106–108 (108[22])	2.75	1.15	2.39
F	134–135 (135–136[22])	2.72	1.12	2.43
SCH_3	124–126	2.76	1.14	2.42

Table 3. Melting points and spectral data of tris-(*para*-substitutedphenyl)tin acetates $(4\text{-}XC_6H_4)_3SnOAc$

Compounds X	M.p. (°C)	Mössbauer parameters		
		QS (mm s^{-1})	IS (mm s^{-1})	ρ
H	118–122	3.35	1.28	2.62
Cl	148–150 (148–149[22])	2.93	1.16	2.53
CH_3	110–112 (113–114[22])	2.91	1.03	2.82
F	132–134 (135–136[22])	2.94	1.06	2.77
SCH_3	118–120	2.96	1.14	2.60

were maintained in an environmental chamber at 27–28 °C with a humidity of 60–90%. The *An. stephensi* larvae were kept in the same environment chamber under the same conditions. Both species of larvae were fed with ground dog-food.

Toxicity assay

Stock solutions of the triorganotins, which ranged from 25 to 1000 mg l^{-1}, were prepared by dissolving them in 95% ethanol, acetone or dimethyl sulfoxide (DMSO), depending on the solubility. 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.

The toxicity studies were performed in 15 mm × 100 mm diameter disposable Petri dishes using 10 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 ml of deionized water was then added. No turbidity was observed upon the addition of the water. 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 ml. Both positive and negative controls were used in the assay. 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. A minimum of three trials was used for each assay. Probit analyses[23] were used to determine the LC_{50} (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 relationships (QSARs). The program was obtained from SciVision, Burlington, MA, USA.

RESULTS AND DISCUSSION

Spectra studies

Determination of structures of triaryltin chlorides using various spectroscopic techniques is well documented in the literature. Mössbauer spectroscopy has proven very useful for determining the coordination and bonding in organotin compounds.[2] Mössbauer spectroscopy yields two parameters, the isomer shift (IS) and quadrupole splitting (QS) values. The former is primarily sensitive to changes in s-electron density at the tin nucleus and the latter to the stereochemistry about the tin atom. The ratio of the QS to IS values ($\rho = QS/IS$) has been used to determine the coordination number of the central tin atom. Tin compounds that are four-coordinated have $\rho < 1.8$, whereas $\rho > 2.1$ is indicative of compounds with greater than four-coordination.[24] As can be seen in Table 1, all the tris-(*para*-substitutedphenyl)tin chlorides have ρ values in the range 1.90–2.05, which would indicate that the chlorides are tetrahedral. These results are in agreement with other similar compounds cited in the literature.[2]

In addition, QS values have been used to determine the coordination number of trialkyltin and triphenyltin carboxylates. For example, pentacoordinated tin complexes were found to have QS values between 2.6 and 4.0 mm s^{-1}, whereas compounds with QS < 2.6 mm s^{-1} were assigned to compounds that were four-coordinated.[25] All the tris-(*para*-substitutedphenyl)tin chloride compounds have QS values between 2.4 and 2.7 mm s^{-1}, supporting the conclusion of a tetrahedral geometry. Furthermore, R_3SnX compounds with bulky groups, such as cyclohexyl and phenyl, have been reported to have a tetrahedral geometry.[26] Thus, the structures assigned based on the Mössbauer data agree with other triaryltin chlorides; cited in the literature.[2]

The spectra data for the tris-(*para*-substitutedphenyl)tin hydroxides and acetates are given in Tables 2 and 3. As observed, the ρ values are in the range 2.20–2.82, indicating a coordination number of greater than four around the tin atom for both series of compounds. This is in agreement with other triorganotin hydroxides and acetates reported in the literature.[2,22]

The ^1H NMR data for tris-(*para*-thioanisyl)tin hydroxide recorded in acetone-d_6 showed the following peaks: δ, 2.46 (s, 9H, SCH_3), 7.14 (d, 6H, J(H–H) 7.5 Hz, Ar), 7.30 (d, 6H, J(H–H) 7.5 Hz, Ar); the tris-(*para*-thioanisyl)tin acetate recorded in $CDCl_3$ had the following resonances: δ, 2.16 (s, 3H, CH_3), 2.44 (s, 9H, SCH_3), 7.12 (d, 6H, J(H–H) 7.6 Hz, Ar), 7.28 (d, 6H, J(H–H) 7.5 Hz, Ar). The observed chemical shifts with the corresponding coupling constants are in good agreement with the expected structures of the compounds.

Toxicity studies

Table 4 lists the individual toxicities and their standard deviations for each series of compounds screened against the second larval instar stage of the *An. stephensi* mosquitoes. Low toxicities against the *An. stephensi* larvae were observed for the compounds that contained a single atom substituent on the phenyl ring. They ranged from a low of 0.04 ppm for triphenyltin acetate to a high of 1.03 ppm for tris-(*para*-chlorophenyl)tin hydroxide. This was followed by the methyl substituents, and the SCH_3 substituents showed the least activity. The efficacy of the compounds was found to be related to the size of the para substituent attached to the phenyl ring rather than on the anionic X group attached to the tin atom. The observed order of toxicity based on the para substituent of the phenyl ring is H > F > Cl > CH_3 > SCH_3. These results are similar to an earlier study indicating that the toxicity for a series of triorganotins containing simple anion groups against *An. stephensi* larvae also depended more on the type of organic group than the anionic X substituent attached to the tin atom.[7]

A common method used for relating toxicological activities to structures of molecules is QSARs. A QSAR is a regression equation that relates some measurable biological activity to a physicochemical or biochemical property or properties related to the molecule.[27] In general, an acceptable QSAR is one in which for every descriptor there should be a minimum of five data points. It was possible to develop QSARs using the QSARIS program for this series of triorganotins. Individual QSARs between the LC_{50} values and a single descriptor of the molecule (ovality) could be generated for each anion. Ovality in the QSARIS program is equal to surface/$4\pi r^2$, where $r = (3 \times \text{Volume}/4\pi)^{1/3}$ and surface is defined as the surface area. Both constraints are related to the surface area of the molecule, thereby supporting the earlier conclusion that the toxicity of the compounds correlates well with the size of the para substituent on the phenyl ring. Correlations between the total surface area (TSA) of triorganotin compounds and their toxicity towards biological species are not new. A high correlation was reported between the TSA for a series of triorganotins and *Escherichia coli* and *Selenastrum capricornutum*.[28] Another study indicated that two series of organotins had a high correlation between their TSA values and the compounds' toxicity towards several cell types.[29] The QSARs generated are: $LC_{50} = 82.84 \times \text{Ovality} - 122.218$ with a multiple R^2 of 0.990 and a cross-validation of 2.39 for the chlorides $LC_{50} = 39.48 \times \text{Ovality} - 56.844$ with a multiple R^2 of 0.951 and a cross-validation of 1.93 for the hydroxides; and $LC_{50} = 98.02 \times \text{Ovality} - 154.048$ with a multiple R^2 of 0.953 and a cross-validation of 3.89 for the acetates. All three training sets were well described by the regression equations, which is statistically very significant. In addition, the cross-validations for all three sets showed that the model constructed can be used to predict the LC_{50} values.

An attempt to generate a QSAR using all 15 compounds was also completed. In this case, a correlation was found between the LC_{50} values and two descriptors of the molecules, the ovality and knotp. Knotp is related to the skeletal branching of the molecule. The equation generated was $LC_{50} = -5.351 \times \text{kntop} + 25.52 \times \text{Ovality} - 50.555$ with a multiple $R^2 = 0.830$ and a cross-validation of 28.61. The training set is very well described by the regression equation and is statistically very significant. The cross-validation shows that the model constructed can be used to predict the LC_{50} values. The inability to generate a QSAR using the ovality descriptor alone would suggest that the anionic X group in the molecule plays a role in the toxicity of the compounds. The role is probably minor in nature. However, it is most likely that the overall size, shape and/or conformation of the molecule govern the toxicity of the compounds. Although it is generally accepted that the anionic X group on triorganotin compounds exerts little or no influence on their activities,[30,31] there have been reports in the literature where investigators have concluded that the X group does have some effects on the biological properties of organotins within a particular series.[32,33] A limited order based on the anion X group was reported by Nguyen *et al*.[34] in their studies on the tolerance of *Ae. aegypti* larvae to a series of triorganotins, as well as a study of triphenyltins and the diamondback moth.[35]

Also listed in Table 4 are the individual toxicities and their standard deviations for each series of compounds screened against the second larval instar stage of the *Ae. aegypti* mosquitoes. Compounds with the fluorino substituent on the para position were the most effective again, and compounds containing the SCH_3 groups were also the least effective. Similar to the *An. stephensi*, the toxicity correlates better to the substituent on the phenyl ring than to the anion group of the tin atom. Within experimental error, the order observed

Table 4. Toxicity of the tris-(*para*-substitutedphenyl)tins, $(X\text{-}C_6H_4)_3SnY$, against the second instar stage of the *An. stephensi* and *Ae. aegypti* mosquito larvae

$(X\text{-}C_6H_4)_3SnY$		24 h LC_{50} (ppm)	
X	Y	*An. stephensi*	*Ae. aegypti*
H	Cl	0.25 ± 0.02	2.53 ± 0.29
H	OH	0.14 ± 0.02	1.49 ± 0.35
H	OAc	0.04 ± 0.01	2.30 ± 0.76
CH_3	Cl	3.48 ± 0.50	1.04 ± 0.08
CH_3	OH	2.44 ± 0.25	0.78 ± 0.15
CH_3	OAc	4.36 ± 0.40	1.19 ± 0.22
F	Cl	0.69 ± 0.13	0.83 ± 0.03
F	OH	0.82 ± 0.10	0.50 ± 0.02
F	OAc	0.62 ± 0.06	0.41 ± 0.03
Cl	Cl	0.86 ± 0.10	1.62 ± 0.01
Cl	OH	1.03 ± 0.10	1.07 ± 0.03
Cl	OAc	0.79 ± 0.15	1.68 ± 0.08
CH_3S	Cl	8.56 ± 0.39	>20[a]
CH_3S	OH	5.07 ± 0.05	>20[a]
CH_3S	OAc	6.67 ± 0.12	>20[a]

[a] At higher doses, the solvent killed the larvae in the control set.

is F > CH_3 > Cl > H > SCH_3. Thus, it appears that the size of the substituent on the phenyl ring is not the dominant factor in the toxicity of the compounds, as is the case for the *An. stephensi* mosquito larvae. The fact that a qualitative correlation is obtainable with the substituents suggests that it may be another property that controls their toxicity. Similar to the *An. stephensi* case, the toxicity of the compounds may be related to the size, shape and/or conformation of the molecules.

The development of a QSAR was attempted to test this hypothesis. For the *Ae. aegypti*, an overall QSAR was generated with the exclusion of the SCH_3 compounds, since those substituents yielded uncertain results. In addition, owing to the limited number of compounds when excluding the CH_3S compounds, no QSAR was attempted for each series of compounds. It was possible to develop a QSAR using 12 compounds. A QSAR was generated between the LC_{50} values for the compounds and two descriptors of the molecules, the kappa shape index (k1) and the kappa alpha shape index (ka2), which is a modified version of the kappa shape index. Both of these indices are attributes related to the molecular shape encoded in the molecules. The equation generated was $LC_{50} = 2.388 \times ka2 - 0.9808 \times k1 + 2.56986$ with a multiple R^2 of 0.7379 and a cross-validation of 4.36. Again, the training set is very well described by the regression equation and is statistically significant. Cross-validation shows that the model constructed can be used with care to predict the LC_{50} values. The ability to generate an accepted QSAR using shape indices supports the earlier hypothesis that the toxicities of the compounds correlates with the shape of the molecule.

A comparison of the toxicity data for both species of mosquito indicates that the efficacy of the compounds towards a particular species, in general, can be correlated to the ring substituent. For example, compounds that contained H, Cl and CH_3S substituents were more effective towards the *An. stephensi*, with a possible exception of tris-(*para*-chlorophenyl)tin hydroxide, whereas compounds with F and CH_3 substituents were more effective against the *Ae. aegypti* species, with the exception of tris-(*para*-fluorophenyl)tin chloride. Even these two compounds would fall within the array if the outer experimental error values were used. Thus, it appears that the effectiveness of this series of compounds towards these two species of mosquito larvae is dependent on both the compound and species of mosquito involved. Compounds having different toxicities towards different species of mosquito have been reported in the literature.[8] For example, a similar finding was reported in a recent study involving triorganotin dithiocarbamates and these same two species of mosquito.[8] Furthermore, it has also been reported that the same compound had different effectiveness against different strains of the same mosquito larvae.[8]

In view of the results from the present study, para-substituted triphenyltin compounds as a class, excluding the SCH_3, can be considered a potential larvicidal candidate against both *An. stephensi* and *Ae. aegypti* larvae. Furthermore, the advantages of triorganotins as potential larvicides are the fact that triorganotins are biodegradable in the environment and there is no reported resistance of these two species of mosquito towards triorganotins. In addition, some of the compounds have activities better than or comparable to the LC_{50} values reported for the natural product, dioncophylline A, a naphthylisoquinoline alkaloid,[36] which was tested against the first to the fourth larval states of the *An. stephensi* mosquito.

Acknowledgements

Financial support from the National Institutes of Health Minority Biomedical Research Support Program (MBRS/SCORE, GM08005) is gratefully acknowledged.

REFERENCES

1. Blunden SJ, Chapman A. In *Organometallic Compounds in the Environment*, Craig PJ (ed.). John Wiley: New York, NY, 1986; 111.
2. Davis AG, Smith PJ. In *Comprehensive Organometallic Chemistry*, vol. 2, Wilkinson G, Stone FGA, Abel EW (eds). Pergamon: New York, NY, 1982; 519.
3. Kumar Das VG, Kuan LY, Sudderuddin KL, Chang CK, Thomas V, Yap CK, Lo MK, Ong GC, Ng WK, Hoi-sen Y. *Toxicology* 1984; **32**: 57.
4. Kochkin DA, Vashkov VI, Dremova VP. *J. Gen. Chem. U.S.S.R.* 1965; **34**: 325.
5. Eng G, Song X. *Trends Organometal. Chem.* 2002; **4**: 81.
6. Ogwuru N, Duong Q, Song X, Eng G. *Main Group Met. Chem.* 2001; **24**: 775.
7. Eng G, Whitmyer C, Sina B, Ogwuru N. *Main Group Met. Chem.* 1999; **22**: 331.
8. Eng G, Song X, Duong Q, Strickman D, Glass J, May L. *Appl. Organometal. Chem.* 2003; **17**: 218.
9. Butler D, Maurice J, O'Brien C. *Nature* 1997; **386**: 536.
10. Uribe LJ. *Bull. Pan Am. Health Org.* 1983; **17**: 133.
11. Gratz NG, Jany WC. *Am. J. Trop. Med. Hyg. Suppl.* 1994; **50**: 11.
12. Robertson SE, Hull BP, Tomori O, Bele O, LeDuc YW, Esteves K. *J. Am. Med. Assoc.* 1996; **276**: 1157.
13. Gilman H, Rosenburg SD. *J. Org. Chem.* 1953; **18**: 1554.
14. Eng G, Dillard CR. *Inorg. Chim. Acta* 1978; **31**: 227.
15. Ingham RK, Rosenburg SD, Gilman H. *Chem. Rev.* 1960; **60**: 464.
16. Biddle BN, Gray JS, Crowe AJ. *Appl. Organometal. Chem.* 1987; **1**: 261.
17. Wharf I, Simard MG. *J. Organometal. Chem.* 1987; **332**: 85.
18. Kocheshkov KA, Nadi MM, Aleksandrov AP. *Chem. Ber.* 1987; **332**: 85.
19. Krause F, Weinberg K. *Chem. Ber.* 1929; **62**: 2234.
20. Wharf I. *Inorg. Chim. Acta* 1989; **159**: 41.
21. Wharf I. *Can. J. Spectosc.* 1985; **31**: 27.
22. Wharf I, Lamparski H, Reeleder R. *Appl. Organometal. Chem.* 1997; **11**: 969.
23. Finney DJ. *Probit Analysis*. Cambridge University Press: Cambridge, UK, 1971.
24. Zuckerman JJ. In *Advances in Organometallic Chemistry*, vol. 9, Stone FGA, West R (eds). Academic Press: New York, NY, 1970; 21.
25. Allan DW, Brocks JS, Formstone R, Crowe AJ, Smith PJ. *J. Organometal. Chem.* 1978; **156**: 359.
26. Calogero S, Ganis P, Peruzzo V, Tagliavini G. *J. Organometal. Chem.* 1979; **179**: 145.
27. Martin YC. *J. Med. Chem.* 1981; **24**: 229.

28. Eng G, Tierney EJ, Olson GJ, Brinckman FE, Bellama JM. *Appl. Organometal. Chem.* 1991; **5**: 33.
29. Eng G, Tierney EJ, Bellama JM, Brinckman FE. *Appl. Organometal. Chem.* 1988; **2**: 171.
30. Van der Kerk GJM, Luijten JGA. *J. Appl. Chem.* 1954; **4**: 314.
31. Van der Kerk GJM, Luijten JGA. *J. Appl. Chem.* 1954; **6**: 56.
32. Pieters AJ. In *Proceedings of the British Insecticides and Fungicides Conference*, Brighton, England, November, 1961.
33. Blunden SJ, Smith PJ, Sugavanam B. *Pestic. Sci.* 1984; **15**: 253.
34. Nguyen TT, Ogwuru N, Eng G. *Appl. Organometal. Chem.* 2000; **14**: 345.
35. Ahmad NW, Mohd SA, Balabaskaran S, Kumar Das VG. *Appl. Organometal. Chem.* 1993; **7**: 583.
36. François G, Van Looveren M, Timperman G, Chimanuka B, Assi LA, Holenz J, Bringmann G. *J. Ethnopharmacol.* 1996; **54**: 125.

