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Relationships Between Structure and Insecticidal Activity of Some Organotin Compounds¹

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ABSTRACT

The toxicities of 42 organotin compounds applied topically to house flies (*Musca domestica* L.) were examined. The LD₅₀ values were determined on a molar basis in order to compensate for the large variations in molecular weight due to the diversity of organic radicals.

Maximum toxicity was obtained with the trisubstituted organotin compounds. Unsymmetrical trivinyltins were of the same magnitude of toxicity as their saturated and symmetrical

counterparts. The anionic species in the trisubstituted organotins can be variable and probably contribute little to the toxicities manifested by these compounds. The nature of the aliphatic substituents also is not critical to toxicity.

Di- and tetrasubstituted organotins are of similar toxicity whereas the monosubstituted organotins are least toxic. In the disubstituted organotins the nature of the anion appears to affect the toxicity of the compounds.

Although the toxicity of the heavy metals (Pb, Hg, Sb) to animals has been investigated widely, the toxicity of tin has received little consideration. Whereas inorganic tin has been reported to have negligible toxicity to animals, tin administered in the organic state has been demonstrated to be poisonous. White (1886) showed that triethyltin acetate was highly toxic to mammals in contrast to inorganic tin salts. Collier (1929) compared the toxicities of different organotin compounds to mice and found that triphenyltin bromide was more toxic than several tetraorganotins.

Extensive investigations on the fungitoxicity of organotin compounds were made by van der Kerk & Luijten (1954). They tested a series of ethyltin chlorides and found that the triethyl derivative was the most fungi-

toxic. The monoethyl derivative was the least toxic while the di- and tetraethyl compounds were of intermediate toxicity. Both stannous and stannic chloride were non-toxic. Van der Kerk & Luijten (1954) and more recently Rosenberg *et al.* (1959) demonstrated that the nature of the anion had little effect on the fungitoxicity of a series of triethyltin derivatives. Also, in a series of trialkyltin acetates, van der Kerk and Luijten showed that toxicity was little affected by the nature of the alkyl groups having up to six carbons through tri-*n*-hexyltin. In a more recent investigation van der Kerk & Luijten (1956) found that the fungitoxicity of several unsymmetrical trialkyl-

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tin compounds was not associated with the nature of the alkyl groups but rather with the total number of carbon atoms present. Maximum fungitoxicity was present in those compounds containing 9 to 12 carbon atoms exclusive of the anionic species.

Stoner *et al.* (1955) examined the toxicity and pharmacology of a number of organotins using rats, rabbits and domestic fowl. They reported that the triethyltin compounds were the most toxic; the di- and tetraethyl derivatives less toxic and the monoethyl compound the least toxic. They also observed that the symptoms of diethyltin and triethyltin poisoning were different, indicating different modes of action for these compounds. On the other hand, the symptoms of tetraethyltin poisoning, although delayed in onset, were identical with those of the triethyltin compound, leading these authors to suggest the possible *in vivo* conversion of tetraethyltin to a triethyltin derivative. A biochemical explanation for the different symptoms of poisoning of the di- and triethyltin compounds observed by Stoner *et al.* was furnished by Aldrich & Cremer (1955) who demonstrated that triethyltin sulphate inhibited phosphorylative processes associated with oxidation and diethyltin dichloride inhibited *l*-keto acid oxidases.

Stoner *et al.* (1955) also demonstrated that high doses of triethyltin sulphate caused immediate death when intravenously administered to rats. The rapid action of this compound was not associated with cholinesterase inhibition. Chronic doses of triethyltin caused extensive cellular damage to the central nervous system but had no effect on other organs. More recent investigations by Barnes & Stoner (1958) have confirmed the central nervous activity of the triethyl derivatives and demonstrated that the diethyl compounds damage the biliary tract.

Blum & Bower (1957) reported that triethyltin hydroxide was capable of causing rapid paralysis of house flies (*Musca domestica* L.) after topical application. Esters of this compound did not inhibit cholinesterase but did block conduction in the isolated central nerve cord of the American cockroach (*Periplaneta americana* L.).

Although trialkyltins appear to be quite toxic to mammals, the possibility of obtaining triorgano derivatives of tin with low mammalian toxicity has been realized. The acute oral LD₅₀ of bis(tri-*n*-isobutyltin) oxide in corn oil to male albino rats is 148 mg./kg. and in aqueous suspension it is 194 mg./kg. (Elsea & Paynter 1958). No evidence of sensitization to this compound was observed.

It is the purpose of this paper to compare the insecticidal activity of 42 organotin compounds from the standpoint of establishing relationships between structure and toxicity.

EXPERIMENTAL.—House flies used in this investigation were the C.S.M.A. (Chemical Specialties Manufacturers Association) susceptible strain. The larvae were reared on moist Purina dog pellets in a room held at 32° C. ± 1° and 50% ± 5% relative humidity. Adults were held at the same conditions and fed a water suspension of powdered skimmed milk.

Twenty adult female house flies, 3 to 4 days old, were lightly anaesthetized with carbon dioxide and treated topically with 1 μl. of an acetone solution of the organotin compound. Two compounds, tetra-*n*-lauryltin and di-*n*-

octyltin dilaurate were insoluble in acetone, and therefore were dissolved in an emulsifier, Emulphor EL-719.³ The solution was administered from a syringe, the plunger of which was driven with a micrometer. Four samples of 20 flies each from each of two populations were run on every compound. After treatment, the flies were held in half-pint Mason jars at the previously stated constant temperature and humidity.

The maximum amount of compound applied to a fly was 12 μg. Compounds whose LD₅₀ was above this dose are listed in table 1 as 12 μg. with the mortality obtained placed in parentheses. The per cent mortality obtained with acetone alone was 5 ± 2% and with Emulphor EL-719 7 ± 3%.

RESULTS AND DISCUSSION.—The results of this study are presented in table 1. The compounds discussed are referenced by numbers in the table.

The LD₅₀'s of the various compounds are expressed in moles. The molar value compensates for differences in molecular weights of the compounds and permits a more exact measurement of the inherent toxicity of the molecule. In this way, direct comparisons may be made between compounds which contain dissimilar anions. The molar LD₅₀ figure therefore truly reflects the toxicity of a compound, since this value is a measurement of the number of molecules involved in the response being measured.

Stannous Carboxylates, Monoaryl and Monoalkyl Tin Derivatives.—Stannic chloride (1) and the non-alkylated stannous carboxylates (2 and 3) were almost nontoxic at the 12-μg. dose level, as were the monoarylated and monoalkylated tin compounds, phenyltin trichloride (4) and *n*-butyltin-tri(2-ethylhexanoate) (5). These results are in agreement with the findings of Stoner *et al.* (1955) on mammals and van der Kerk & Luijten (1954) on fungi, that monoalkyltins are the least toxic of the alkylated tin derivatives.

Dialkyl and Diaryl Tin Derivatives.—In comparing compounds 4 with 10 and 5 with 12, an increase in toxicity is associated with replacement of one of the anionic groups with a butyl (12) or with a phenyl (10) radical. In the dialkyl tin dichlorides, maximum toxicity occurs in the dimethylated compound (6). Barnes & Stoner (1958) reported that the higher dialkyl tin dichlorides were less toxic to rats than their lower homologs. The nature of the anionic species in the dialkyltin compounds seems to influence the toxicity of the molecule, since the toxicities of the diethyl (7) and dioctyl (9) tin dichlorides are significantly greater than their respective ethyl (11) and octyl (13) carboxylate counterparts. This fact is also evident when dibutyltin dichloride (8) is compared with di-*n*-butyl-di(2-ethylhexanoate) (12), although in this case the carboxylate is more toxic than the halide.

Trialkyl and Triaryl Tin Derivatives.—The triorgano-tins (14 to 32) were the most toxic compounds studied. This is especially evident in the series of arylated tin derivatives (4, 10, 27 and 43) in which the triarylated species (27) is the only significantly toxic compound.

In the trisubstituted tin derivatives, the effect of the anion on toxicity is less than that found in the diorganotin series. Among the triethyltin derivatives (15 to 19), the influence of OH, O₂CCH₃, SCH₂O₂C₂H₅, SC₆H₅, and

³ Polyoxyethylated Vegnil from Antara Chemicals, New York, N. Y.

Table 1.—Twenty-four hour LD₅₀ values of organotin compounds applied topically to susceptible house flies.

COMPOUND	FORMULA	LD ₅₀ (MOLES × 10 ⁻¹⁰ /FLY) ^a
1. Stannic chloride	SnCl ₄	> 460 (20) ^b
<i>Stannous carboxylates</i>		
2. Stannous octanoate	Sn[O ₂ C(CH ₂) ₆ CH ₃] ₂	> 300 (15)
3. Stannous oleate	Sn[O ₂ C(CH ₂) ₇ CH = CH(CH ₂) ₇ CH ₃] ₂	> 180 (10)
<i>Monoaryl and monoalkyl tin derivatives</i>		
4. Phenyltin trichloride ^c	(C ₆ H ₅) ₃ SnCl ₃	> 390 (15)
5. <i>n</i> -butyltin-tri(2-ethylhexanoate) ^c	<i>n</i> -C ₄ H ₉ Sn[O ₂ CCH(C ₂ H ₅)(CH ₂) ₃ CH ₃] ₃	> 160 (30)
<i>Dialkyl and diaryl tin derivatives</i>		
6. Dimethyltin dichloride ^c	(CH ₃) ₂ SnCl ₂	120
7. Diethyltin dichloride ^a	(C ₂ H ₅) ₂ SnCl ₂	410
8. Di- <i>n</i> -butyltin dichloride ^c	(<i>n</i> -C ₄ H ₉) ₂ SnCl ₂	340
9. Di- <i>n</i> -octyltin dichloride ^d	(<i>n</i> -C ₈ H ₁₇) ₂ SnCl ₂	250
10. Diphenyltin dichloride ^c	(C ₆ H ₅) ₂ SnCl ₂	290
11. Diethyltin diacetate ^c	(C ₂ H ₅) ₂ Sn(O ₂ CCH ₃) ₂	> 410 (10)
12. Di- <i>n</i> -butyltin-di(2-ethylhexanoate) ^c	(<i>n</i> -C ₄ H ₉) ₂ Sn[O ₂ CCH(C ₂ H ₅)(CH ₂) ₃ CH ₃] ₂	130
13. Di- <i>n</i> -octyltin dilaurate ^c	(<i>n</i> -C ₈ H ₁₇) ₂ Sn[O ₂ C(CH ₂) ₁₀ CH ₃] ₂	> 220 (45)
<i>Trialkyl and triaryl tin derivatives</i>		
14. Trimethyltin bromide ^c	(CH ₃) ₃ SnBr	4.5
15. Triethyltin hydroxide	(C ₂ H ₅) ₃ SnOH	11.0
16. Triethyltin acetate	(C ₂ H ₅) ₃ SnO ₂ CCH ₃	11.0
17. Triethyltin ethyl mercapto acetate ^c	(C ₂ H ₅) ₃ SnSCH ₂ CO ₂ C ₂ H ₅	4.2
18. Triethyltin phenyl mercapto acetate ^f	(C ₂ H ₅) ₃ SnSC ₆ H ₅	5.0
19. Triethyltin benzyl mercapto acetate ^f	(C ₂ H ₅) ₃ SnSCH ₂ C ₆ H ₅	5.6
20. Trivinyltin iodide ^c	(CH ₂ =CH) ₃ SnI	15.0
21. Triisopropyltin acetate	(<i>i</i> -C ₃ H ₇) ₃ SnO ₂ CCH ₃	24.0
22. Triisopropyltin undecylenate ^c	(<i>i</i> -C ₃ H ₇) ₃ SnO ₂ C(CH ₂) ₉ CH ₃	16.0
23. Tri- <i>n</i> -butyltin chloride ^c	(<i>n</i> -C ₄ H ₉) ₃ SnCl	4.6
24. Tri- <i>n</i> -butyltin octanoate	(<i>n</i> -C ₄ H ₉) ₃ SnO ₂ C(CH ₂) ₆ CH ₃	5.6
25. Tri- <i>n</i> -butyltin-dibutoxy-dithio-phosphate ^c	(<i>n</i> -C ₄ H ₉) ₃ Sn-P(=S)(O- <i>n</i> -C ₄ H ₉) ₂	9.3
26. Tris-(tri- <i>n</i> -butyltin) perthiophosphate ^c	[(<i>n</i> -C ₄ H ₉) ₃ SnS] ₃ P=S	9.0
27. Triphenyltin chloride ^c	(C ₆ H ₅) ₃ SnCl	3.9
28. Dimethyl vinyltin chloride ^c	(CH ₃) ₂ (CH ₂ =CH)SnCl	7.1
29. Dimethyl vinyltin- α -bromopropionate ^c	(CH ₃) ₂ (CH ₂ =CH)SnO ₂ CCHBrCH ₃	7.4
30. Divinyl- <i>n</i> -butyltin chloride ^c	(CH ₂ =CH) ₂ (<i>n</i> -C ₄ H ₉)SnCl	12.0
31. Vinyl di- <i>n</i> -dibutyltin chloride ^c	(CH ₂ =CH)(<i>n</i> -C ₄ H ₉) ₂ SnCl	12.0
32. Divinyl phenyltin fluoride ^c	(CH ₂ =CH) ₂ (C ₆ H ₅)SnF	> 500 (10)
<i>Alkyl tin oxide and alkyl distannane</i>		
33. Bis-(tri- <i>n</i> -butyltin)oxide ^c	(<i>n</i> -C ₄ H ₉) ₃ Sn-O-Sn(<i>n</i> -C ₄ H ₉) ₃	11.0
34. Hexa- <i>n</i> -butyl distannane ^c	(<i>n</i> -C ₄ H ₉) ₃ Sn-Sn(<i>n</i> -C ₄ H ₉) ₃	> 210 (5)
<i>Tetraalkyl and tetraaryl stannanes</i>		
35. Tetramethyltin ^c	(CH ₃) ₄ Sn	> 560 (0)
36. Dimethyl divinyltin ^c	(CH ₃) ₂ (CH ₂ =CH) ₂ Sn	530
37. Tetravinyltin ^c	(CH ₂ =CH) ₄ Sn	> 530 (0)
38. Tetraethyltin ^c	(C ₂ H ₅) ₄ Sn	330
39. Tetraisopropyltin ^c	(<i>i</i> -C ₃ H ₇) ₄ Sn	> 415 (40)
40. Tetra- <i>n</i> -butyltin ^c	(<i>n</i> -C ₄ H ₉) ₄ Sn	290
41. Tetra- <i>n</i> -octyltin ^c	(<i>n</i> -C ₈ H ₁₇) ₄ Sn	196
42. Tetra- <i>n</i> -lauryltin ^c	(<i>n</i> -C ₁₂ H ₂₅) ₄ Sn	> 150 (25)
43. Tetraphenyltin ^{cc}	(C ₆ H ₅) ₄ Sn	> 290 (30)

^a Molar values were calculated also for compounds whose LD₅₀ values exceed 12 μ g. in order to indicate the maximum number of applied moles not capable of killing 50% of the population.

^b Figures in parentheses in this column indicate per cent mortality when the flies were treated with 12 micrograms of the test material.

^c Obtained from Dr. E. L. Weinberg, Metal & Thermit Corp., Rahway, N. J.

^d Obtained from Dr. Frank A. Bower, E. I. DuPont Co., Wilmington, Del.

^e Obtained from Dr. Dietmar Seyferth, Harvard University, Cambridge, Mass.

^f Obtained from Dr. George S. Sassen, Drexel Institute of Technology, Philadelphia, Pa.

^g Insoluble in everything except hot benzene. Therefore, this compound was evaluated as a residue of 50 mg./sq. ft. The 12 μ g. LD₅₀ is an estimation of the low toxicity of this compound expressed for comparative purposes.

SCH₂C₆H₅ on toxicity appears to be negligible, although the mercaptides (17, 18, 19) appear to be slightly more toxic than either the hydroxide and acetate; or perhaps the sulfur-containing anions contribute to the toxicities of the molecules. On the other hand, Blum & Bower (1957) reported that increasing the size of the carboxyester moiety of triethyltin derivatives reduced the toxicity of the compound but none of the compounds contained sulfur.

The relatively uniform toxicity of the trisubstituted tin derivatives further illustrates the nonspecific effect of

both the cationic and anionic groups on insecticidal activity. It seems reasonable to assume that toxicity is independent of the numerous anionic species and is correlated with the presence of three organic groups in the tin atom's tetrahedral structure, as van der Kerk & Luijten (1954) demonstrated with fungi.

The unsymmetrical vinyltins (28 to 32), with the exception of divinyl phenyltin fluoride (32), are typical toxic triorganotins. The toxicity of these compounds compares favorably with the symmetrical triorganotins (14 through 27) further demonstrating that the nature of the

polyorganic groups is not critical to toxicity of the triorganotin. Interestingly, although aliphatic dehydrogenation often increases the toxicity of pharmacologically active compounds, no demonstrable toxicity increase was evident when vinyl was substituted for saturated radicals in this series (compare 20 with 16). Divinyl phenyltin fluoride (32) is relatively inactive, a fact which possibly may be correlated with the physical properties of the compound. The introduction of anionic fluorine confers on the compound properties that are more inorganic than organic. This chemical is only slightly soluble in most organic solvents and has a melting point of more than 300° C. (Seyferth 1956), a property which indicates the near inorganic state of the compound. The polarity of the compound probably would allow it to penetrate the insect integument very poorly.

The alkyl distannane (34) and oxide (33) present an interesting structure-toxicity study. The oxide (33) is toxic to house flies, whereas the distannane (34) is not. The oxide is susceptible to hydrolysis and ionization (Weinberg 1956) but the distannane chemically resembles a tetraorganotin and is far less susceptible to hydrolysis than the oxide (Seyferth 1956). Luijten & van der Kerk (1955) have shown that triethyltin and diethyltin exist as ions in aqueous solution. Therefore, it is possible that organotins may exert their toxic action as ions. Many of the mono-, di- and trisubstituted organotin compounds used in this study are capable of aqueous ionization (Weinberg 1956) and probably all of them are to some extent. Although the relationship of ionization to toxicity has not been studied for the compounds evaluated in this paper, the importance of ionization in organotins deserves attention.

The high toxicity of bis(tri-*n*-butyltin) oxide to house flies, and its low mammalian toxicity (Elsea & Paynter 1958) indicate a possible difference between the biochemical fates of this compound in mammals and in insects, and suggest the possibility of finding other selectively toxic organotin compounds.

Tetraalkyl and Tetryl Tin Derivatives.—The tetra-substituted organotins (35 through 43) do not exhibit much insecticidal activity and approximate the toxicities of the disubstituted organotins (6 through 13). The most toxic member of this series was tetra-*n*-octyltin (41). Toxicity increased regularly with chain length up to eight carbon atoms, except in the case of tetraisopropyltin (39). Replacement of two methyl groups with vinyl species (35, 36) does not affect toxicity, while replacement of the ethyl species of tetraethyltin with vinyl groups destroys toxicity (37, 38). Whereas phenyl compares favorably with various alkyls as a tin substituent in the di- and trisubstituted organotins, the derivative produced by the arylation of tin is far less toxic (43) than the alkyls in the tetrasubstituted series. Since cuticular penetration occurs

most rapidly in the case of fat soluble materials and tetraphenyltin is relatively insoluble in most fat solvents, its lack of toxicity may possibly be attributable to poor penetration.

Stoner *et al.* (1955) reported that the onset of toxic symptoms of tetraethyltin on the rat were delayed. These delayed symptoms simulated those of triethyltin, leading these authors to suggest the *in vivo* conversion of tetraethyltin to a triethyltin derivative. Cremer (1958) confirmed the hypothesis of Stoner *et al.* (1955) by demonstrating that tetraethyltin was converted to a triethyl derivative, mainly by the microsomes and soluble matter from liver cells. An examination of the 72-hour mortalities of house flies treated with tetraethyltin and tetra-*n*-butyltin revealed no delayed symptoms of poisoning.

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