

PART - III

FUNGITOXIC PROPERTIES

## Introduction

The unique role of metal ions in the regulation of various life processes is now well established. The function of cobalt in cobalamin (Vitamin B<sub>12</sub>), magnesium in chlorophyll and the role of iron and copper in oxygen carrying systems need not be emphasised. Like other living systems, fungi also require metals like iron, copper, zinc and a few other metals for proper growth and development. But when some of these metals especially zinc and copper when supplied to fungi in more than optimal amounts, these act as fungicides. Apart from these metals some other such as silver, mercury, cadmium, nickel, lead etc. can also create fungitoxicity. Though stannous or stannic tin can cause very little fungitoxicity, some organotin compounds have unusually high fungitoxicities. Organometallic compounds of mercury and some group IV or V of the periodic table exhibit pronounced fungitoxicity.

Organomercurials are still being used as one of the most effective biocidal agents due to their high effectiveness in extremely minute doses. But recently their high mammalian and phytotoxic properties have placed these compounds under scrutiny for future use. It is quite possible that within a few years, these organomercurials may be replaced ~~with~~ by highly effective but relatively non toxic organotin preparation (1).

Organometallic compounds of group IV and V of the periodic table, such as those of germanium, tin, lead, arsenic, antimony

and bismuth show considerable biological activities (2). It has been found that of all these metals, tin shows maximum promise as fungicides due to their high activity and low toxicity.

The systematic investigation of organotin compounds was first carried out by the T.N.O. group (Institute for Organic Chemistry, Utrecht, Netherlands), under the guidance of Van der Kerk, Luijten and others. The pioneering works of the TNO group have established the profound importance of organotin compounds as biocidal agents and consequently for their commercial uses.

In a systematic study of organotin compounds of the following types,  $R_4Sn$ ,  $R_3SnX$ ,  $R_2SnX_2$  and  $RSnX_3$  ( $R$  = alkyl/aryl group,  $X$  = anions), they observed that  $R_3SnX$  compounds are exceptionally fungitoxic.

Table - 1

Minimum Inhibitory concentrations of organotin compounds to Aspergillus niger (3)

Type of compound	R = Ethyl	R = Butyl	R = phenyl
$R_4Sn$	> 500	> 500	> 500
$R_3SnX$	2	1	0.5
$R_2SnX_2$	> 500	> 500	> 500
$RSnX_3$	> 500	> 500	> 500

Concentration in  $\mu$ g/ml

They also observed that the variation of anion had only a minor influence on triorganotin compounds. From subsequent examinations of a series of tri-n alkyltin acetates, they showed the profound influence of the length of alkyl chains against a number of fungi. The most active compound in the series of tri-n-alkyl tin acetates was tri-n-propyl and tri-n-butyl tin acetates. These inhibited the growth of A. niger at concentrations of 1  $\mu$ g/l or even less (3).

Experiments by TNO group with unsymmetrical trialkyl tin acetates i.e. compounds in which tin has different alkyl groups reveal that the activity depend on the nature of individual group but on the total number of carbon atoms in the three groups. Vander Kerk and Luijten (4) showed that diethyl butyl-, dimethyl hexyl-, diethyl octyl-, dimethyl octyl and dimethyl decyl tin acetate as well as ethyl dipentyl tin acetate all exhibited the same order of activity as triethyl tin acetate but less active than tributyl tin acetate. They concluded from their investigations that the maximum activity among the trialkyl tin acetate is associated with a total number of 9 to 12 carbon atoms regardless the nature of individual groups. But a similar rule does not apply in case of mixed aliphatic - aromatic compounds (5).

The antifungal activity in most cases diminished by the introduction of functional groups into organotin compounds (6). Thus  $[(CH_3)_2ClCH_2]_2SnCl$  has the same antifungal activity as trimethyl tin chloride but  $(n-C_3H_7)_2(CN.CH_2CH_2CH_2)SnO.CO.CH_3$  and

$(nC_3H_7)_2(CH_3COOCH_2CH_2)SnBr$  are far less active than tri-n-propyl tin acetate;  $(NaOCOCH_2CH_2)_3SnOH$  is inactive even at  $100 \mu g/ml$ . Thus the introduction of hydrophilic groups appears to diminish the activity (7).

In spite of careful screening, no active compound was ever found among the types  $R_4Sn$ ,  $R_2SnX_2$  and  $RSnX_3$  except the activity of diphenyl tin dichloride (8), although there are some unsubstantiated claims (9-11). The so called activity of  $R_4Sn$  type of compounds is due to some  $R_3Sn$  type impurities or due to cleavage of one R group from  $R_4Sn$  type compound under experimental conditions (6).

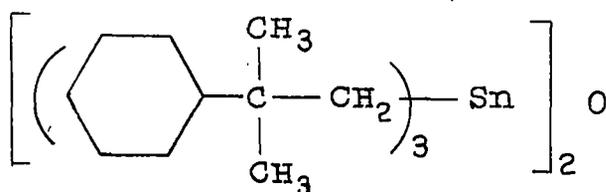
Klotzer in an East German Patent (10) claimed that monobutyl tin tri-acetate at 0.01% concentration is as effective as 0.1% tributyl tin oxide fungicides. He also claimed in another patent (11) that mono butyl tin triformate or monophenyl tin triformate have no phytotoxicity and monobutyl tin compounds are effective against phytophthora infestans etc.

In spite of such claims, it is generally accepted that mono organotin compounds do not have any appreciable fungicidal properties. Very recently, however, it has been found by the TNO group that a stannatrane  $PhSn(OCH_2CH_2)_3N$  have some remarkable and unusual antifungal activity (12). Besides the TNO group, Baumann (13) and Hartel (14) have carried out independent research

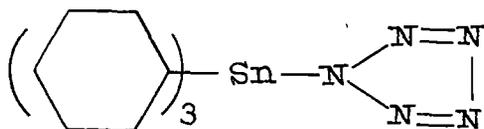
on simple alkyl and aryl tin compounds with practical aim. These works culminated into the development of the first organotin fungicide for agricultural purposes based on triphenyl tin acetate ('Brestan' - A.G. Hoechst). Other workers extended these results varying the anionic part of  $R_3SnX$  compounds (15,16,17). Shortly after the introduction of 'Brestan', Philips Duphar introduced fentin hydroxide (called also Du - Ter) with active ingredient of triphenyl tin hydroxide having similar spectrum of disease control (18). 'Brestan' and 'Du - Ter' were recommended for the control of *Phytophthora infestans* (late blight) on potatoes and *Cercospora beticola* on sugar beets at the rate of few grams per acre.

At present in U.S.A., 'Du-Ter' is registered for controlling fungi on potatoes, sugar beets, peanuts, pecans etc (18). These compounds are highly effective protectant fungicides against almost the same range of fungi as copper fungicides but less than one-tenth the dosage (19). Organotin compounds can also be used for the control of leaf spot on celery, blast and algal control on rice. Recently organotin fungicides are being used to control coffee leaf rust and also as antifeedant for the giant looper caterpillar in Kenya. It is expected that the use of organotin fungicides will be greatly extended in the control of more fungal diseases in near future (20).

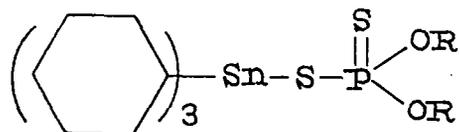
Next important breakthrough in the field of pesticides, came through the discovery of tricyclohexyl tin hydroxide in 1963 as a joint research effort of M.T. Chemicals and Dow Chemical Co. of U.S.A. Tricyclohexyl tin hydroxide has been introduced in the market under the trade name of Plictran for controlling the phytophagous (plant feeding) mites on apples and pears, citrus, stone fruit, hop, tea, vegetable etc (21). Organotin miticides have little toxicity towards honey bees and it also shows the anti-feedant activity against some insects larvae (22). There are now three other organotin miticides of following types.



I. VENDEX (SHELL)



II. PEROPAL (BAYER, CHEMAGRO)



III. R-28627 (STAUFFER)

Regarding the phytotoxicity, these miticides are well tolerated by crops which normally require an acaricide to protect them except the hop plant. Apples, grape, tomato, bean, cabbage and cotton plants all showed good tolerance to 'Peropal' (23).

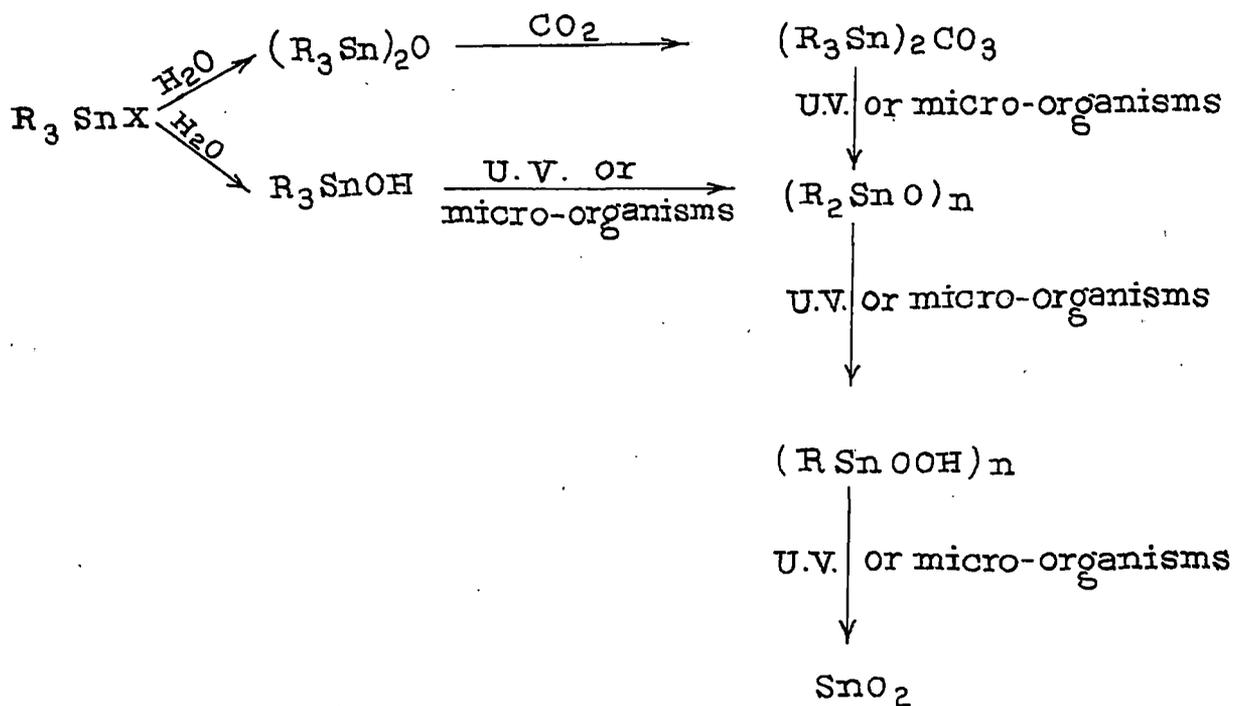
Chemicals are important tools in modern crop protection and the search of suitable compounds has been primarily directed towards finding those which can rapidly eliminate most of the pest population on the crop. Since late 1940, organo chlorines and subsequently organophosphorus compounds were being used. Recently however, these pesticides, particularly organochlorines have come under severe criticism on the following grounds (24). These compounds have a broad spectrum of activity, which means that beneficial and non target pests may also be adversely affected. It has been found that spraying a crop with such compounds have resulted in a subsequent outbreak of target pest far worse than before because the pest's natural enemies have also been killed. An added problem with such pesticides is that many of those are persistent in environment and can remain toxic for a long time before being degraded to less harmful products. Moreover, excessive uses of pesticides has resulted in many pest populations building up resistance to such compounds.

Problem of toxic residues from sprays of organotin compounds has been extensively investigated. Organotin compounds have a relatively short half life (3-4 days) on plant leaves in the

field (25-27). The amount of organotin residues in potato tubers has been found to be less than 0.1 mg of tin per kg after the foliage were repeatedly sprayed with Brestan (28). When the cows are fed with sugar beet leaves, which were extensively sprayed with Brestan, very little amount of triphenyl tin acetate ingested is found in the milk (about 4  $\mu\text{g/ml}$ ) (29).

Organotin pesticides, that are in current use do not considerably accumulate in the soil with successive applications. They are metabolised readily in animals and soils to inorganic tin compounds which are not taken up by the plants (27). It was also found that 'Plictran' was sprayed in three different locations during a period of three years, building up of its residue in the upper six inches of the soil was negligible (19).

In view of the very large number of growing industrial and agricultural applications, the knowledge of environmental breakdown pattern of organotin compounds, has been investigated to ensure their continued safe use. A generalised degradation scheme for the tributyl and triphenyl tin derivatives, which is probably applicable to other organotins is proposed by Sheldon (30).



Fish and his co-workers (31-32) have shown that tributyltins are metabolised under in vitro and in vivo conditions in mammals to di- and mono butyl tins via carbon hydroxylated intermediates. Fungal degradation of T.B.T.O. to di- and mono butyl tins by

Coniophora Cerebella and Polystictus Varsicolor has also been reported recently (33).

Unlike mercury compounds, there is no evidence of methylation of organotins under environmental conditions (34). From the above discussions it may be concluded that organotin pesticides can probably answer different problems posed by organo chlorine and organophosphorus compounds about environmental hazards. Moreover, organotins have remarkable anti feedant activities (24) and have also chemosterillant activity (29) and no major field resistances of pests have so far been reported (18). Evidently for such reasons, some triorganotin compounds have been cleared by World Health Organisation as safe agricultural pesticides.

The lower trialkyltin compounds are able to inhibit mitochondrial oxidative phosphorylation (34) and it has been suggested by Zuckerman (34) that their remarkable biological activity pattern may be dependent upon the effectiveness of their interaction at an active site or sites which involves co-ordination to certain amino acids. Smith (34) considering available data on most probable binding sites for the organotins on proteins, concluded that binding is effected via the HS and imidazole NH groups of the proteins.



The published reports generally confirm the initial observation of relative non importance on the nature of the anionic part of triorganotin. Poller (35) has reported that once the  $R_3Sn^+$  group gets to the site of biochemical reaction i.e. at cell mitochondria, it may not matter what the anionic part is but the latter can significantly influence the transportation of the biocide to the reaction site. He prepared a few sucrose derivatives which show better fungicidal activities against some paint destroying fungi, although their tin content is much smaller than the commercial fungicides. Several workers have found considerably lower activity of some organotin chelated compounds (36-37). Therefore, it appears that the activity of trisubstituted organotin compounds ( $R_3SnX$ ) may be somewhat dependent on the nature of X group, particularly when the X group is a ligand which can form intramolecularly chelated complex.

Srivastava reported that diphenyl tin dichloride is the most active fungitoxic agent against colletotrichum falcatum among diaryltin dichlorides and their activities on complexation with 2,2'-bipyridyl and 1:10 phenanthroline are slightly increased (38).

Recently Smith et al (39) reported that organotin pyridine-2-carboxylates and substituted triazine derivatives (100 ppm/ml) can control coffee leaf rust and coffee bacterial blight diseases in vitro. But so far not much work has been done about the fungitoxic activities of organotin co-ordination compounds.

In order to study the effect of co-ordination on  $\text{Ph}_3\text{Sn}^+$  moieties by ligands like diphenyl carbazone, we studied some preliminary fungicidal properties of Triphenyl tin diphenyl carbazone against some selected fungi under the present investigation.