S Y N O P S I S

Intensive research in the field of plant protection and pest control has been going on throughout the world. As a result various types of pesticidal compounds are being prepared, and their pesticidal, toxicological and other properties are being studied everyday. Of these, Organophosphorus compounds constitute a class in which quite a large number of compounds have been synthesized and examined as effective pesticides.

The work embodied in this dissertation is related to the investigation of some saligenin cyclic phosphorus compounds with reference to their synthesis, insecticidal activity, toxicity, fungicidal activity, anticholinesterase activity and other properties besides structural elucidations by chemical analyses and spectroscopic methods.

At the outset, in Part - I of this thesis a general introduction including anticholinesterase activity and chemical hydrolysis of some Organophosphorus pesticides has been presented. Common or trade names, chemical structures and other properties of some of them have been given in Appendix - I.

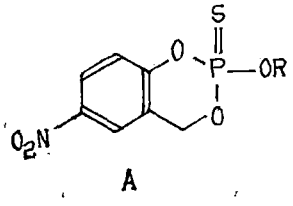
Discovery of saligenin cyclic phosphate as a biologically active metabolite of tri-ortho-tolyl phosphate had led to

extensive studies on pesticidal and other properties of many related compounds. Part II of this dissertation has been devoted to a short review describing the chemical, bio-chemical, insecticidal, fungicidal and other toxicological properties of saligenin cyclic phosphorus compounds with special emphasis on salithion (2-methoxy -4H-1,3,2-benzodioxaphosphorin-2-sulphide) discovered in 1963 by Prof. Eto, Prof. Oshima and their co-workers. Investigations have revealed that the biological activities of these compounds are greatly influenced by the exocyclic substituents on the phosphorus atom, and also by the substituents in benzene ring and/or in hetero-cyclic ring. The biological activities of these compounds may be attributed to the hetero-ring involving enol and benzyl ester linkages. The alkylation reaction may be responsible for "SH-enzyme" inhibition and fungicidal activity. The phosphorylation reaction is responsible for esterase inhibition, and animal toxicity and insecticidal activity. An exocyclic substituent group affects physical and biological properties by virtue of its electronic and steric characteristics. Thus, methylphosphorothionate is useful as an insecticide, alkylamidates have systemic activity, alkylphosphorothiolates have fungicidal activity, phenyl phosphonates have antifilarial activity, and aryl phosphates are neurotoxic and have synergistic activity.

It was reported by Prof. Eto and his co-workers that 2-methoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphide (BD-8)

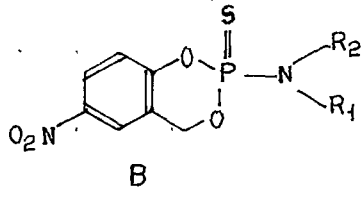
was obtained as a paste after purification through silicic acid column chromatography, and found to have about sixty times less insecticidal activity compared to salithion (Eto et al., Botyu Kagaku, 33, 73, 1968). However, it has been observed in this laboratory that the methoxy compound (BD-8) is a solid (m.p. 84°C), and has about 1.5 - 2 times greater oral insecticidal activity to Periplaneta americana than salithion (Das, B.K., Pesticides, 15, 3, 1981). These observations prompted us to undertake a systematic investigation on some 6-nitro-saligenin cyclic alkyl/phenyl/alkylamido phosphorothionates.

The work presented in Part -III of this thesis is related to the studies of some 2-alkoxy/phenoxy/alkylamido-6-nitro-4H-1,3,2-benzodioxaphosphorin-2-sulphides having the general structure (A) and (B):



A

OR = (β -methoxy)ethoxy (BD-1)
= (β -ethoxy)ethoxy (BD-2)
= n-butoxy (BD-6)
= i-butoxy (BD-7)
= phenoxy (BD-9)



B

NR_1R_2 = dimethylamido (BD-13)
= pyrrolidino (BD-15)
= heptadecylamido (BD-18).

The above mentioned compounds have been prepared by condensation of the 5-nitro-saligenin with the corresponding alkoxy/phenoxy/alkylamido-dichloridophosphorothionates, and their structures have been determined by IR, mass, NMR spectra and chemical analysis.

The common IR bands for alkoxy phosphorothionates are:

1020 - 1050 $^{*}Cm^{-1}$	P-O-C (alkyl);
1185 - 1195 Cm^{-1}	P-O-C (aryl);
920 - 925 Cm^{-1}	P-O-C (aryl);
1515 - 1520 Cm^{-1}	asym. str. of nitro group;
1340 - 1345 Cm^{-1}	sym. str. of nitro group;
800 - 810 Cm^{-1}	P = S (I);
650 - 655 Cm^{-1}	P = S (II);

For alkylamidophosphorothionates the common IR bands are:

1010 - 1030 Cm^{-1}	P-O-C (alkyl);
1245 - 1250 Cm^{-1}	P-O-C (aryl);
875 - 880 Cm^{-1}	P-O-C (aryl);
810 - 820 Cm^{-1}	P = S (I);
645 - 660 Cm^{-1}	P = S (II);
1515 - 1520 Cm^{-1}	asym. str. of nitro group;
1340 - 1345 Cm^{-1}	sym. str. of nitro group.

* In this dissertation "cm^{-1}" has wrongly been typed as "Cm^{-1}"

The mass fragmentation of BD-1 and BD-2 are substantially different from that of other alkyl phosphorothionates. The base peaks of BD-1 and BD-2 are 57 and 72 respectively. Where as that of BD-6 and BD-7 are 246 and 247 respectively. The base peak of BD-1 and BD-2 do not contain phosphorus moiety. The compound BD-7 shows both single and double hydrogen rearrangements with α-and β-cleavages. The single hydrogen rearrangement is observed only in compound BD-6. From the above investigation it is clear that the reaction occuring in the mass fragmentation processes in BD-1 BD-2 and other compounds are quite different, but the predominating mass fragmentation process in BD-1 (and in BD-2) is totally absent in BD-6. This shows that the presence of ether oxygen in the exocyclic side chain plays an important role in mass fragmentation processes. There is a basic difference in mass fragmentation processes of alkyl phosphorothionates and alkylamidophosphorothionates. In alkylamidophosphorothionates there is no preliminary hydrogen shift to sulphur, although the direct elimination of SH from the molecular ion is observed.

Finally the structures have been determined by analysing the ^1H NMR spectra. It is fairly evident that the chemical shift difference of the protons H_A and H_B in the hetero ring increases in going from 2-alkoxy to 2-alkylamido compounds, and that the 2-substituent at the same time increases in bulk, and probably

spends more time in the conformation with the least steric interactions.

The methoxy compound shows greater insecticidal activity than salithion and other compounds to roaches; the iso-propoxy and the dimethylamido derivatives show about 1.5 to 2 times less insecticidal activity. The other compounds are almost non-insecticidal.

For Grasshoppers the methoxy compound is most active, and its insecticidal activity is almost same with that of salithion; BD-5, BD-13, BD-1, BD-2 and BD-4 have some insecticidal activity, but other compounds are non-insecticidal.

All compounds are less toxic than salithion to rats; the methoxy, the iso-propoxy and the dimethylamido compounds have greater toxicity compared to other compounds.

From the antifungal activity study it is observed that the iso-propylamido compound is the most effective compound against the mycelial cells of Helminthosporium Sp.; It's inhibitory effect is greater than that of Hinosan. For all compounds the growth inhibition of the fungus Alterneria solani is less than that of Hinosan.

From the wheat seed germination studies it has been noted that the dimethylamido compound is the only compound which

shows 95 percent germination at 500 ppm; the other compounds are not phytotoxic.

From the chemical hydrolysis studies of the alkoxy phosphorothionates, it has been observed that the iso-propoxy compound is most stable to alkaline-hydrolysis; but all of them have greater hydrolysis constant value than that of salithion. A satisfactory correlations is found between the alkaline hydrolysis rate constant and Hammett's electronic (σ^*) as well as Taft's steric (E_s) parameters.

For all phosphorothionates (alkoxy/phenoxy) except the phenoxy derivative, the HFAChE (housefly)is more inhibited than the ChE (blood), the antiacetylcholinesterase activity of the methoxy compound for HFAChE is greatest, but the anticholinesterase activity of the iso-propoxy compound for ChE is least. Here also a satisfactory correlation is obtained between the antiacetylcholinesterase activity (for HFAChE) and Hammett's electronic (σ^*), Taft's steric (E_s) as well as Hansch's hydrophobic (π) parameters.

Only three compounds (BD-5, BD-13, BD-14) have been studied for acute oral toxicity and delayed neurotoxicity in hens. The dimethylamido compound is most toxic. The iso-propylamido compound is least. Paramanent paralysis in legs is observed in case of the dimethylamido compound only; upon histopathological

examinations, degeneration and demylation of the sciatic nerve are found.

The biological activities and other data justify further examination of the iso-propylamido compound as potential fungicide, and the methoxy as well as the iso-propoxy compounds as potential insecticide. Whether the use of these cyclic phosphorus compounds will protect the plants from pests and disease in the field remains to be studied.