S Y N O P S I S

The work embodied in this dissertation is related to the investigation on some nitro/chloro/bromo saligenin cyclic phosphoramidothionates and phosphorothionates with reference to their synthesis, insecticidal, chemical hydrolysis, anticholinesterase activities, antifungal and other properties besides structure elucidations by chemical analysis and spectroscopic methods.

At the outset, in Part - I of this thesis a brief introduction of saligenin cyclic phosphates has been presented describing the chemical, bio-chemical, insecticidal, fungicidal and other toxicological properties 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 linkage. 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

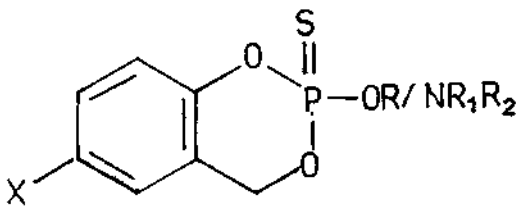
systemic activity, alkylphosphorothiolates have fungicidal activity, phenyl phosphonates have antifilarial activity, and aryl phosphates are neurotoxic and have synergistic activity.

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. 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. : D. Sc. Thesis, Calcutta University, 1981). These observations prompted us to undertake a systematic investigation on some 6-nitro/chloro/bromo saligenin cyclic phoshoramidothionates and phosphorothionates.

Aims and objectives of these present investigation have been presented in Part - II.

The work presented in Part - III of this thesis is related to the investigation on some 2-alkylamidoalkoxy-6-nitro/chloro/bromo-4H,1,3,2-benzodioxaphosphorin-2-sulphides having the general structure (A).

(V)



where $R/R_1/R_2$ = Alkyl group

X = NO_2, Cl, Br

The alkoxy groups are isopropoxy, methoxy and ethoxy groups; the alkylamido groups are Pyrrolidino, Piperidino, 2-ethyl-piperidino and hexamethyleneimino.

The above mentioned compounds have been prepared by condensation of the 5-nitro/chloro/bromo saligenin with the corresponding alkoxy/alkylamidodichloridophosphorothionates. Except BD-33, all the compounds are crystalline solids.

The structure of the compounds have been determined by chemical analysis and UV, IR, Mass, PMR spectral data.

The common IR bands for the compounds are:

1000 - 1040 cm^{-1} (s)	P-O-C (alkyl);
1235 - 1260 cm^{-1} (s)	
and	P-O-C (aryl);
870 cm^{-1} - 910 cm^{-1} (s)	
1515 - 1525 cm^{-1} (s)	asym. str. of nitro group;
1335 - 1350 cm^{-1} (s)	sym. str. of nitro group
800 - 830 cm^{-1}	P = S (I)
630 - 670 cm^{-1}	P = S (II)

The compounds show parent molecular ion (M^+) peaks in the mass spectra. Fragmentation by loss of 'SH' radical is important. Compounds show an ion due to $(M - .SH)^+$, and it is the base peak for some of the compound.

The experimental part on the biological and hydrolytic properties of the compounds have to be presented in Appendix I.

The methoxy compound (BD-8) shows greater insecticidal activity than that of salithion and other compounds to roaches. The isopropoxy derivative (BD-5) shows about 1.5 times less insecticidal activity compared to salithion. The other compounds are non-toxic to cockroaches. For Blow-fly and Grasshopper the methoxy compound is more active than salithion; the ethoxy and isopropoxy compound have some insecticidal activity but the toxicity is less than that of salithion and other compounds are non-insecticidal. All the compounds are less toxic to rats compared to salithion.

Acetylcholinesterase inhibition data show that Blow-fly (BFAChE) and Zebra-fish (ZFAChE) head homogenate are more inhibited than that of Goat whole blood (AChE).

The rate of hydrolysis of the compound is greatly influenced by the nature of the substituent at the 6-position of the benzodioxaphosphorin ring. When the nitro group in the 6-position is replaced by chlorine and bromine the rate of hydrolysis is sharply decreased.

From the antifungal activity study it is observed that the chloro and bromo compounds have greater fungicidal activity than the other compound against Helminthosporium oryzae and Pyricularia oryzae. The inhibitory effect of chloro and bromo compound is almost comparable to Hinosan is case of P. oryzae but for H. oryzae the effect is 6-13 times greater than that of Hinosan.

QSAR study reveals that the fungicidal activity of the compounds are correlated with the structural information content (SIC) and partition coefficient (log P) of the compounds (eqns. 16a and 12b). It is suggested that the stereohydrophobic make-up and topology of the molecule is a major determinent for the antifungal activity.

Compound BD-4, BD-5 and BD-8 have been studied for acute oral toxicity and delayed heurotoxicity in hens. The ethoxy compound is most toxic. Permanent paralysis in legs is observed only in case of ethoxy compound; upon histopathological examinations, degeneration and demylination of the sciatic nerve is found. In other compound no paralysis is observed and the histopathological observation of sciatic nerve is normal.

From toxicity study of Decis, Ripcord and Metacid to a common hill stream fish Danio rerio, it is concluded that Decis is most acutely toxic followed by Ripcord and Metacid. The acetylcholinesterase inhibition of head homogenate is highest in fish exposed to Decis and the level of inhibition does not much increase with length of exposure period.

Histopathological lesions like enlargement of liver cells, vacuolations, hypertrophy and necrosis, and destruction of nuclear material in the liver is almost similar in all the pesticide tested. Decis caused hypertrophy of haemopoitic tissue and destroyed glomeruli of the kidney. Histopathological lesions in the stomach is due to the accumulations of the secretory materials, enlarged goblet cells, congested blood capillaries, thickened muscular layer of submucosa and vacuolated epithelial cells; destruction of primary and secondary gill lamellae caused respiratory and osmoregulatory distress in case of Decis. Similar type of damages are also observed in other pesticides but the severity is less than that of Decis.

The biological activities and other data justify further examination of the methoxy and isopropoxy compound as potential insecticide and the chloro and bromo compound as the potential fungicide. Whether the use of these cyclic phosphorus compounds will protect the plants from pests and diseases in the field remains to be studied.

In order to find out the chemical structure-biological activity relationship in these compounds we have to synthesise several new compounds in which different group is to be incorporated in different positions of the aromatic ring and to investigate their biological activity. Besides, structural elucidation in regard to the conformation of the diazaphosphorin ring from temperature dependent NMR and X-ray crystal structure would clarify the chemical structure-antifungal activity mechanism (and/or esterase inhibition mechanism) so that their selectivity of action can be known, thereby helping us to design selective and biodegradable potential pesticide.