SYNOPSIS

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

Part I

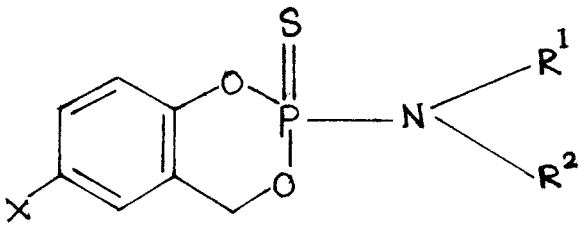
Part I of this dissertation, deals with a brief introduction to saligenin cyclic phosphates and related compounds.

Part II

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

Part III

Part III of this dissertation is related to the investigation on some 2-alkylamido-6-nitro/chloro-4H-1, 3, 2, benzodioxaphosphorin-2-sulphides having the general structure I



(I)

where X = NO_2/Cl

and $-N\begin{matrix}R^1\\R^2\end{matrix}$ is heptadecylamido, sec-butylamido, methylamido, diisobutylamido, dipropylamido, dipentylamido, dioctylamido, dibutylamido, dimethylmorpholino, hexamethyleneimino, morpholino and dimethylamido.

The experimental part on the biological and hydrolytic properties and U.V., IR, Mass and NMR spectra of the compounds are shown in the Appendix.

(i) The above mentioned 2-alkylamido-6-Nitro/Chloro-4H-1,3,2-benzodioxaphosphorin-2-Sulphides have been prepared by the reaction of the corresponding phosphoramidothionate dichlorides with 5-nitro/chloro-saligenin. Compounds BL-27 and BL-30 are liquid in nature and the rest are crystalline solids.

(ii) The structures of these cyclic phosphoramidothionates have been established by chemical analysis UV, IR, Mass and ^1H NMR spectral data.

The common IR bands for the compounds are:

1010 - 1030 cm^{-1}(S), P-O-C (alkyl);

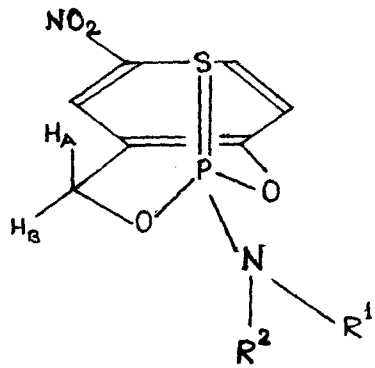
1235 - 1250 cm^{-1}(VS), P-O-C (aryl)

880 - 920 cm^{-1} (S), P-O-C (aryl);

1515 - 1520 cm^{-1}(S), asym. str. of the nitro group; 1340-1345 cm^{-1}(S); sym. str. of nitro group; 800-820 cm^{-1}, P=S(I), 640-660 cm^{-1}, P=S(II). Neither of the two P=S bands shows any systematic shifts which reflect changes in the inductive properties of the substituents, this is not unexpected if they do indeed arise from mixed modes.

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 alkylamidophosphoramidothionates.

From the NMR spectral data of the 2-alkylamido-6-nitro/chloro-4H-1, 3, 2-benzodioxaphosphorin-2 -sulphides it is evident that the 2-substituent spends more time in the conformation with least steric interactions. Several plot expansions of the phosphoramidothionates suggest that the molecules are probably in one conformation. A Dreiding model of the molecules seems to have stable conformation in which one of the methylene proton (H_A) is quasi-axial and the other (H_B) is quasi-equatorial (Structure II)



(II)

(iii) All the phosphoramidothionates are almost non-insecticidal against Periplaneta americana. They are less toxic to white albino rats than salithion and are not phytotoxic.

(iv) For nitro saligenin cyclic phosphoramidothionates the aceylcholinesterase in blow-fly head homogenate (BFAChE) is more inhibited than acetylcholinesterase in goat-blood plasma (AChE).

(v) The cyclic phosphoramidothionates containing the disubstituted amido groups are extremely resistant to alkaline hydrolysis compared to other compounds having the monosubstituted amido groups, When the nitro group in the 6-position of the benzodioxaphosphorin ring is replaced by chlorine the rate of hydrolysis is sharply decreased.

QSAR study shows that the bulkiness of the exocyclic alkyl amido group plays a very important role in alkaline hydrolysis. Greater the size of the alkylamido substituent, more stable the compounds. Compounds BD-31 and BD-34 are stable to alkaline hydrolysis.

(vi) The compounds show good antifungal activity against H. oryzae. Excellent correlation is obtained between the

$p^{ED}50$ value (for H. oryzae at 72 hours) and the Structural Information Content (SIC) and Partition Co-efficient (log P). The regression equation of seven compounds are given below :

$$p^{ED}50 = 4.235\ (\log P) - 1.319(\log P)^2 + 0.621(SIC) - 1.322$$
$$(\pm 0.492) \qquad (\pm 0.619) \qquad (\pm 0.984) \qquad (\pm 0.410)$$

where,

n=7, s = 0.221, r = 0.950, $F_{(3,3)}$cal = 9.36,

$F_{(3,3)(0.05)}$tab = 9.30.

Here n is the number of compounds, s is the standard deviation, r is the correlation co-efficient, F is the statistical measure of the significance of the correlation.

From the above equation we can suggest the following :

(A) None of the steric, hydrophobic parameters alone can account for the biological (antifungal) response.

(B) A combination of two or more parameters is always necessary indicating the involvement of more than one factor for the biological activity.

(C) For H. oryzae the regression equation involving ED_{50} with (log P), (SIC), and $(SIC)^2$ provides the best statistically significant equation. It further suggests that the

stereo-hydrophobic make up and topology of the bio-active molecule is a major determinant for the bioresponse.

(L) Hydrophobicity plays a very important role in explaining the antifungal property of the said phosphorothionates. The positive co-efficients for parameter (log P) shows that an increase in hydrophobicity of the exocyclic alkylamido group may contribute to the antifungal activity. This may be due to either by promoting penetration of the molecule into the fungus cell or by helping in the formation of a hydrophobic bond at the site of action.

(E) Geometry of the molecules too play an important role. As (SIC) relates to the molecular size, results show that it plays a decisive role as the size of the alkyalamido substituents become bulky. We observe that lesser the value of (SIC), bulkier the substituent, higher the degree of preventive activity. Since an incubation period of a few days is required to determine the preventive activity against H.oryzae for percentage inhibition test. The test compound might be decomposed during the test period and the original preventive activity could be reduced. It is observed from our hydrolysis experiments that the bulkier the substituent, the more difficult would be the degradation. So antifungal activity

may be related to the chemical stability. It may be further stated that BD-31 and BD-34 both of which have cyclic alkylamido groups have very good antifungal activity.

So we can conclude that higher the value of (SIC) and lower the value of (log P), the more will be the stability and hence antifungal activity against H.oryzae.

(vii) The antifungal activity data justify further examination of these phosphoramidothionates as potential fungicides. However their practical use in the fields to protect plants from diseases is yet to be studied.