PART – I

Introduction

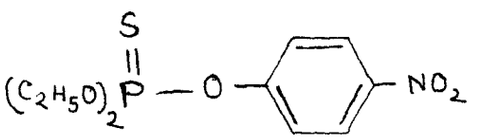
CHAPTER – 1

1.1. INTRODUCTION:

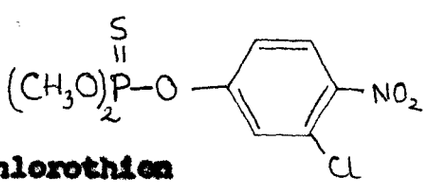
One-third of the total production of world's agriculture is lost as a result of the activities of harmful organisms (i.e., insects mites, fungi etc.). So, the use of plant protection chemicals in agriculture has become very essential in modern agricultural technology. The pest and disease situation are not static-they keep on changing. New physiological races evolve as a result of mutations in nature. Many insects and fungi develop resistant strain when the same insecticide and fungicide is used year after year. So the existing pesticide, however efficient may they be can not solve the pest problem permanently. New pesticides must be developed to combat various new situations. It should be a continuous search - a process of intensive research. So development is vital for finding pesticides which will be safer, more effective and selective, and above all more economic in the true sense and environmentally acceptable.

Modern pesticides belong to different classes of chemical compounds but synthetic organic compounds predominate among them. Among the Pesticides of synthetic origin the organophosphorus compounds are one of the most important groups of modern pesticides[1]. The wide spread use of these compounds is due to their high insecticidal, acaricidal, fungicidal activity and other properties, faster degradation in plants, soil and water. Owing to the wide diversity in their pesticidal activities, these organophosphorus compounds have won epoch-making popularity for use in field as potential pest controlling agents.

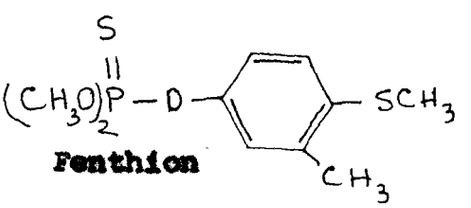
The development of new organophosphorus compounds was for a long time dominated almost exclusively by one single guiding principl namely the 'Acyl Rule' of Schrader[1,2,3,4]. The great advancement in agricultural practice, scientific knowledge on the structure-activity relationship and mode of action of organophosphorus pesticides were achieved by the discovery of parathion by Schrader in 1944. Parathion is extremely toxic to mammals as well as to insects. Many less toxic pesticides have been synthesised by slight structural modification of parathion; for example, chlorothion (in 1952), fenthion (in 1958) and fenitrothion (in 1959) were discovered[1].



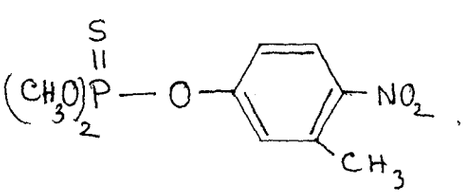
Parathion



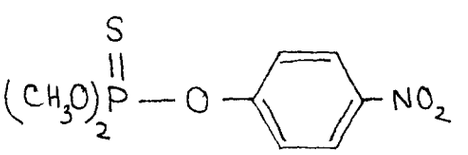
Chlorothion



Fenthion

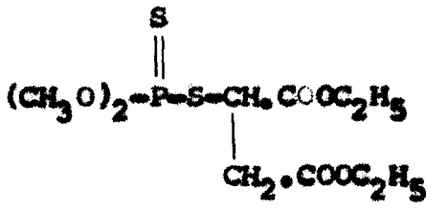


Fenitrothion

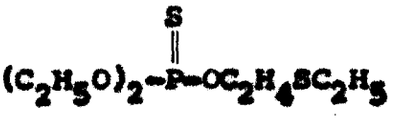


Parathion-methyl

Malathion was discovered in 1950 and demeton in 1951



Malathion



Demeton-S

In 1952, the Perkow reaction was discovered, and many important vinyl phosphate esters have been introduced as practical pesticides. Since then several new compounds have been developed and are in commercial use[1].

1.2. REVIEW ON SALITHION AND RELATED COMPOUNDS:

Discovery of saligenin cyclic phosphate as a biologically active metabolite of tri-o-cresyl phosphate (TOCP)[1,5,6] has led to extensive studies on synthesis, chemical and biological properties of many related compounds[7,8]. Analogous cyclic phosphorus esters have been synthetically prepared for examination of their chemical properties[9,10] and biological activities[11,12]. The biological activities are not always coincident with the chemical reactivities and appear to be influenced by the size of an exocyclic substituent on the phosphorus atom. The TOCP metabolite causes ataxia in hens but has no insecticidal activity, while its analogous cyclic

phosphate carrying a small alkyl group have insecticidal activity[13] Among the saligenin cyclic phosphorus compounds, salithion (2-methox 4H-1,3,2-benzodioxaphosphorin-2-sulphide) has been prepared in a large quantity and practically used as an insecticide in Japan[1,8].

A large outbreak of flaccid paralysis took place in Morocco (1959)[14] and USA (1930)[15] due to adulteration of fluid extract of ginger and cooking oil with TOCP. Aldridge and Barnes[1,16] observe that all neurotoxic triaryl phosphate except tri-p-ethyl phenyl phosphate have at least one alkyl group carrying the α-hydrogen atom on the orthoposition. This structure neurotoxicity relationship of triaryl phosphates is clearly understandable by the isolation and characterization of the active metabolies of TOCP[5,6]. The main active metabolite (M) is o-tolyl saligenin cyclic phosphate (2-o-tolyl-4H-1,3,2-benzodioxaphosphorin-2-oxide). It is extraordinarily active in all biological properties shown by TOCP. This compound (M) is about 100 times more potent to cause ataxia in hens than TOCP and also ten million times more active than TOCP in the <u>in vitro</u> inhibitic of plasma cholinesterase[7].

The conversion of TOCP into the cyclic phosphate[6] proceeds via two steps as shown in Fig. 1.1 ; (i) the hydroxylation of the methyl group of TOCP by the mixed function oxidases (mfO) and (ii) the cyclization by intramolecular transphosphorylation of the inter- mediate.

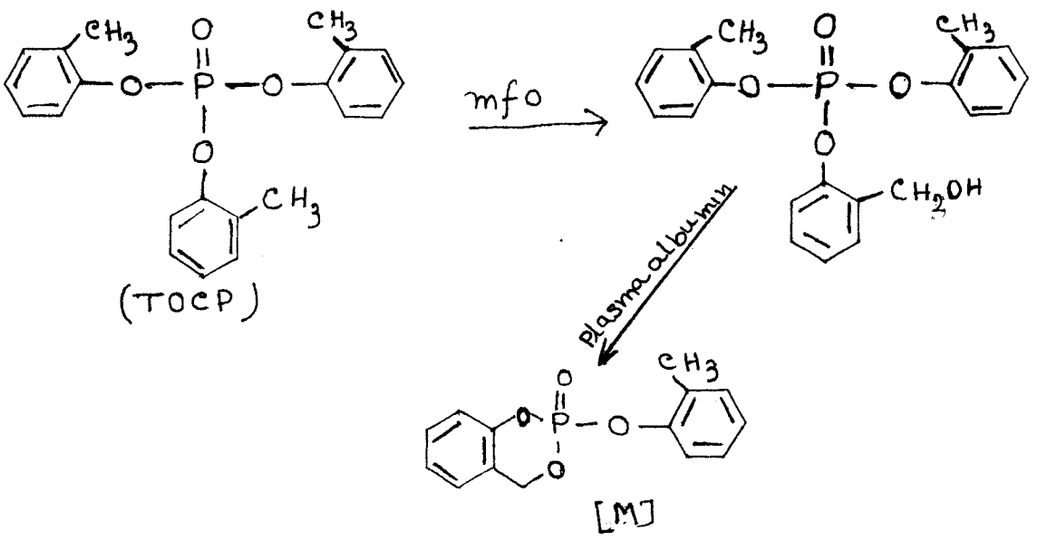
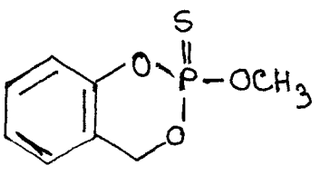


Fig. 1.1 Metabolic activation of TOCP

The triaryl phosphates having an o-alkyl group with the α-hydrogen atom may be metabolized to give the corresponding active cyclic esters. In the cyclization reaction, no alkyl ester group participates as the leaving group[18]. Actually, no aryl but alkyl saligenin cyclic phosphate is formed *in vivo* from alkyl di-o-tolyl phosphates[18]. Such metabolic activation of TOCP or its analogues have been observed in rats[6], hens[6], cats[19] and insects[18].

All aryl saligenin cyclic phosphates have shown no insecticidal activity but manifested a high delayed neurotoxicity to cause ataxia in hens; surprisingly the corresponding cyclic esters (both P = O and P = S compounds) having a small alkyl group on phosphorus revealed high insecticidal activity[6,11].

As a result of the aforesaid research "salithion" (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide), an organophosphorus insecticide having a unique cyclic ester structure was discovered by the Pesticide Research group of Kyushu University in 1963. Salithion was developed into a commercial insecticide in 1968 by Sumitomo Chemical Co.



Salithion

Here we give an account of salithion and related compounds as pesticides as well as their chemistry and biochemistry.

Synthesis of Saligenin Cyclic Phosphorus Compounds:

The cyclic phosphate and phosphonate esters of saligenin are synthesized by the reaction of saligenin and substituted phospheryldichlorides in the presence of a dehydrogenchlorinating agent such as tertiary amine in a dry solvent like chloroform, toluene at low temperature[9]. In some cases instead of tertiary amine potassium carbonate and finely divided copper powder at high temperatures[20] are used. The process using potassium carbonate is made to proceed by a reaction between liquid and solid phases. Therefore, even of potassium carbonate is employed as finely divided powdered form, it often causes a remarkable lowering and fluctuation of the yield[20]. Thus salithion was first prepared with inconsistent

and, often, very low yield by heating (90°C) saligenin and methyl-phosphorodichloridothionate in toluene for a long period (more than 15 hours) in the presence of anhydrous potassium carbonate together with copper powder as catalyst[21]. This difficulty has been overco later by applying the Schotten-Baumann acylation procedure using an aqueous solution of sodium hydroxide (Fig. 1.2)

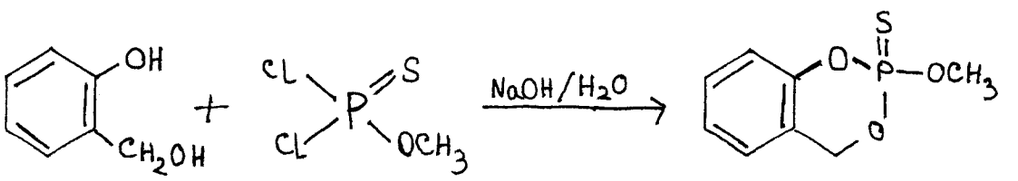


Fig. 1.2 Synthesis of Salithion

Careful observation of the literature reveals[20,21,22,23,24, 25,26,27] that a variety of saligenin cyclic phosphorus esters have been prepared and examined for insecticidal activity as well as other biological properties. A comprehensive but not a complete lis of these type of compounds is given in table 1.1 and table 1.2.

Properties of saligenin cyclic phosphorus compounds:

Properties of salithion:

Pure salithion is a colourless crystalline powder, m.p. 55-56°C; practically insoluble in water but easily soluble in aceto and benzene, moderately soluble in cyclohexane, toluene and xylene; vapour pressure 1.5×10^{-6} mm Hg at 25°C, UV λ_{max} nm(ϵ) 274(860), 267(860). It has characteristic IR band at 1020 cm^{-1} for P-O-CH_2 in the hetero ring. NMR δ (CS_2)ppm; 3.76(3H, doublet, J_{PH} = 14 Hz, CH_3

5.21 (2H, doublet, J_{pH} = 15 Hz, CH_2); 6.8-7.2 (4H, multiplet, benzene ring). The signal at upper field of the doublet at 5.21 ppm slightly splits further (1.5 Hz). This becomes much significant at -30°C, suggesting the methylene protons (H_A, H_B) are not equivalent with each other, but the dioxaphosphorin ring is conformationally mobile in a solution (Fig. 1.3).

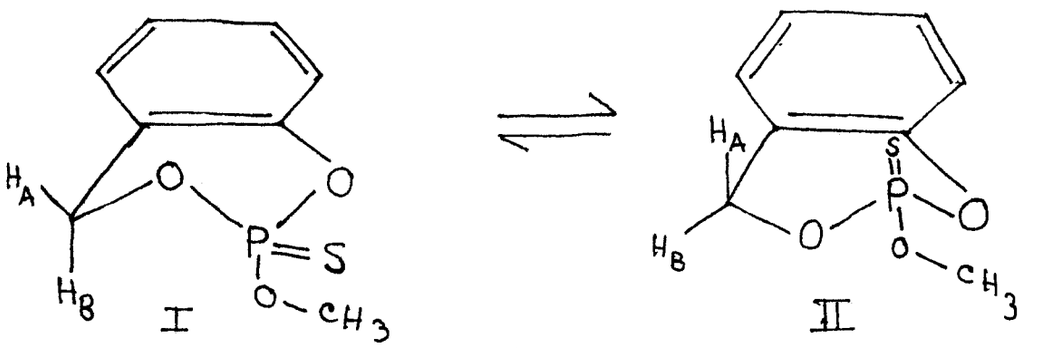


Fig. 1.3 Conformational change of Salithion hetero ring.

X-ray crystallographic analysis shows that the hetero ring of salithion is a half chair form in which the sulphide group is in equatorial position (I). The strain in the ring appears little; the endocyclic O-P-O angle is 104°.

Salithion gives a characteristic fragmentation pattern in mass spectrometry[28]. It gives an intense peak of $(M-CH_3)^+$ (m/z 201) by β-cleavage occurring at the exocyclic ester group. Another fragmentation process is the direct loss of .SH followed by the elimination of formaldehyde (Fig. 1.4)

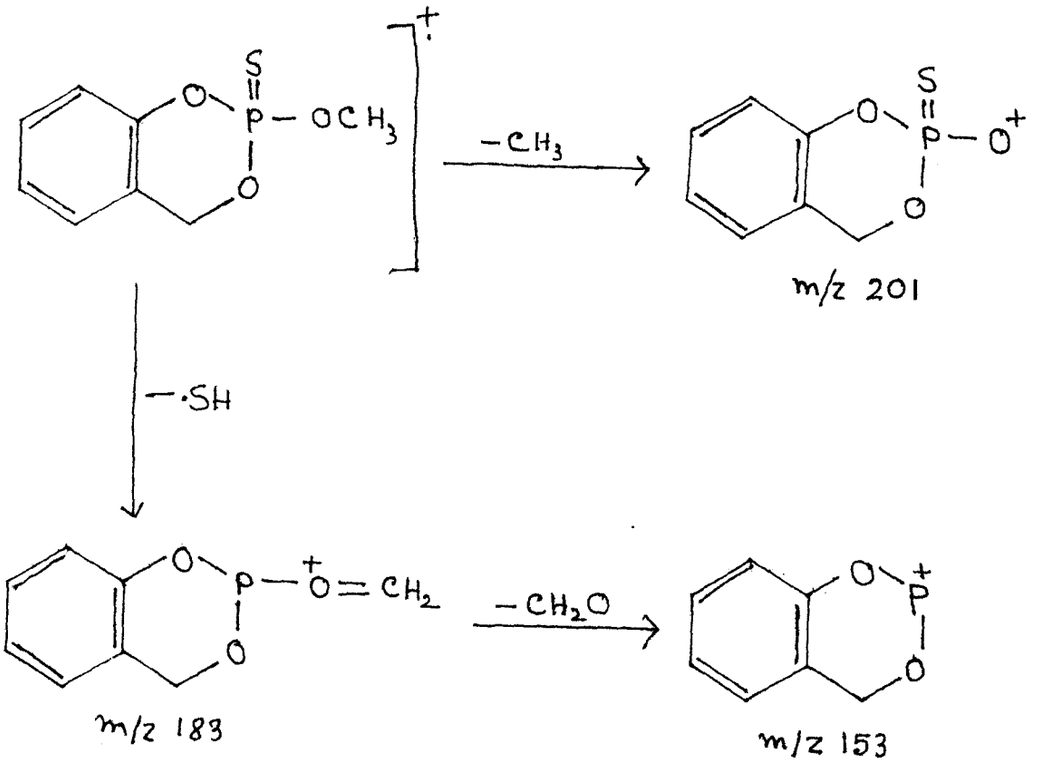


Fig. 1.4 Fragmentation of salithion in Mass spectrometry

Salithion reacts with bromine water to give salicxon[29]. Since salicxon (2-methoxy-4H-1,3,2-benzodicxaphosphorin-2-oxide) is several thousands times more active in cholinesterase inhibition than salithion, an enzymatic method after the oxidation can be used for the residue analysis of salithion[29]. It is converted into S-alkyl saligenin cyclic phosphorothiolates by heating with alkyl iodides (the Pistchimuka reaction)[30,31]. This reaction is accelerated in polar solvents such as dimethylformamide when methyl iodide is used, isomerisation occurs to give 2-methylthio-4H-1,3,2-benzodicxa-phosphorin-2-oxide (MTBO)[30,31]. Saligenin is demethylated to form

the salt of saligenin cyclic phosphorothionic acid by the action of certain nucleophiles. Such as cyclohexylamine[8] and potassium carbonate[8,32]. The reactions of salithion are summarised in Fig. 1.5.

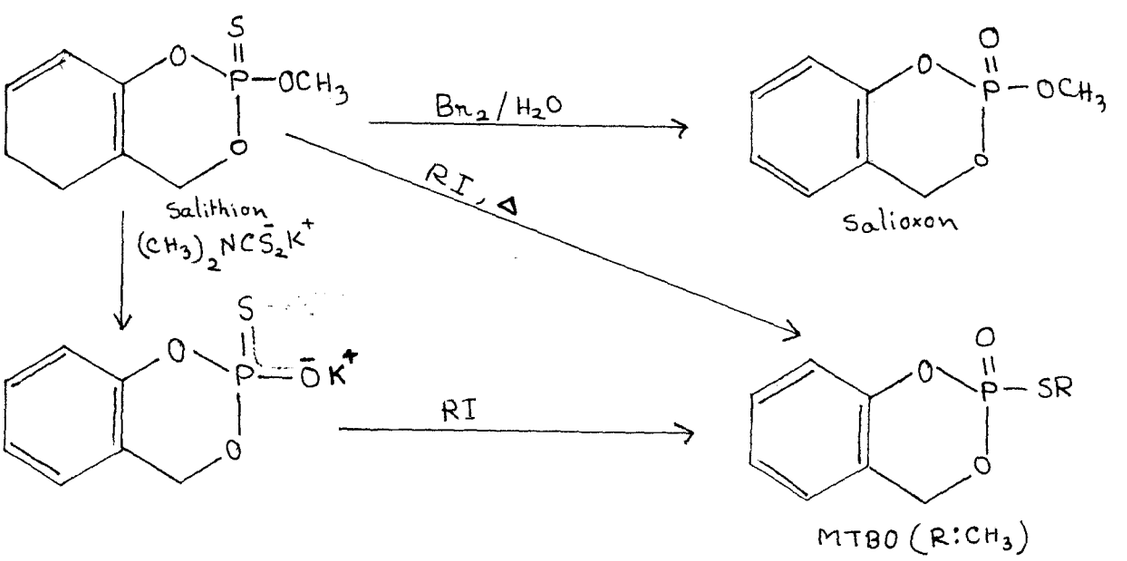


Fig. 1.5 Reactions of Salithion

Salithion is relatively unstable in storage. Some secondary amines, such as carbazole and N-phenyl α-naphthylamine, stabilised the formulation[33]. In a phosphate buffer (pH 7.7), salithion is slowly hydrolyzed by the P-O (aryl) bond cleavage[8], the hydrolysis rate constant (25°C) K = 2.4×10^{-4} min^{-1} the rates of hydrolysis of the cyclic methylphosphonate, S-methylphosphorothioate (the thiolate isomer of salithion, MTBO), methyl phosphate (Salioxon), an N-methyl phosphoramidate are, respectively 90, 60, 6 and 0.6 times

greater than that of salithion. The hydrolysis of salithion is shown in Fig. 1.6.

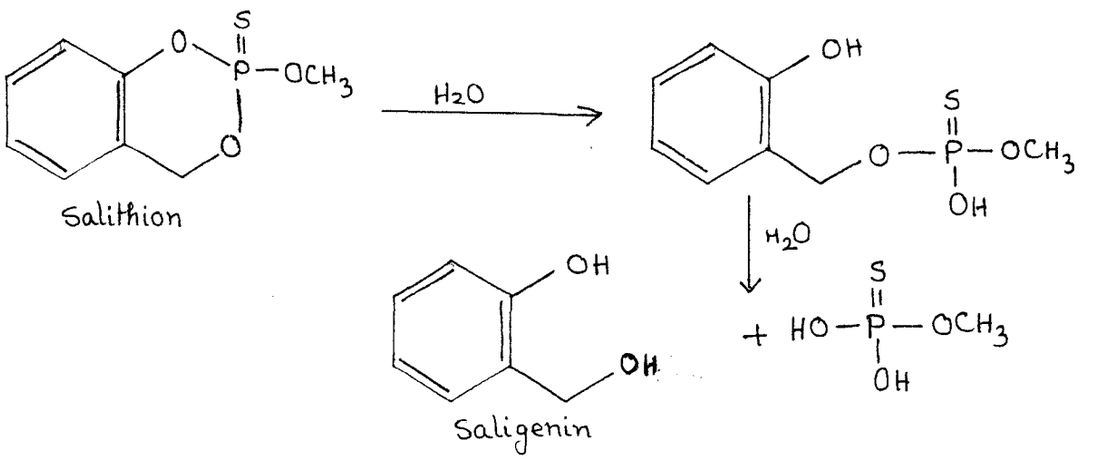


Fig. 1.6 Hydrolysis of Salithion.

Salithion is a wide-spectrum insecticide for use in orchards and vegetable gardens. It is particularly effective to control lepidopteran larvae, mealybugs, aphids and mites. It manifests the insecticidal action not only as contact and stomach poisons but also as a fumigant[34,35].

The metabolic pathways of salithion in rats and plants have been studied[1]. These are summarised[8] in Fig. 1.7.

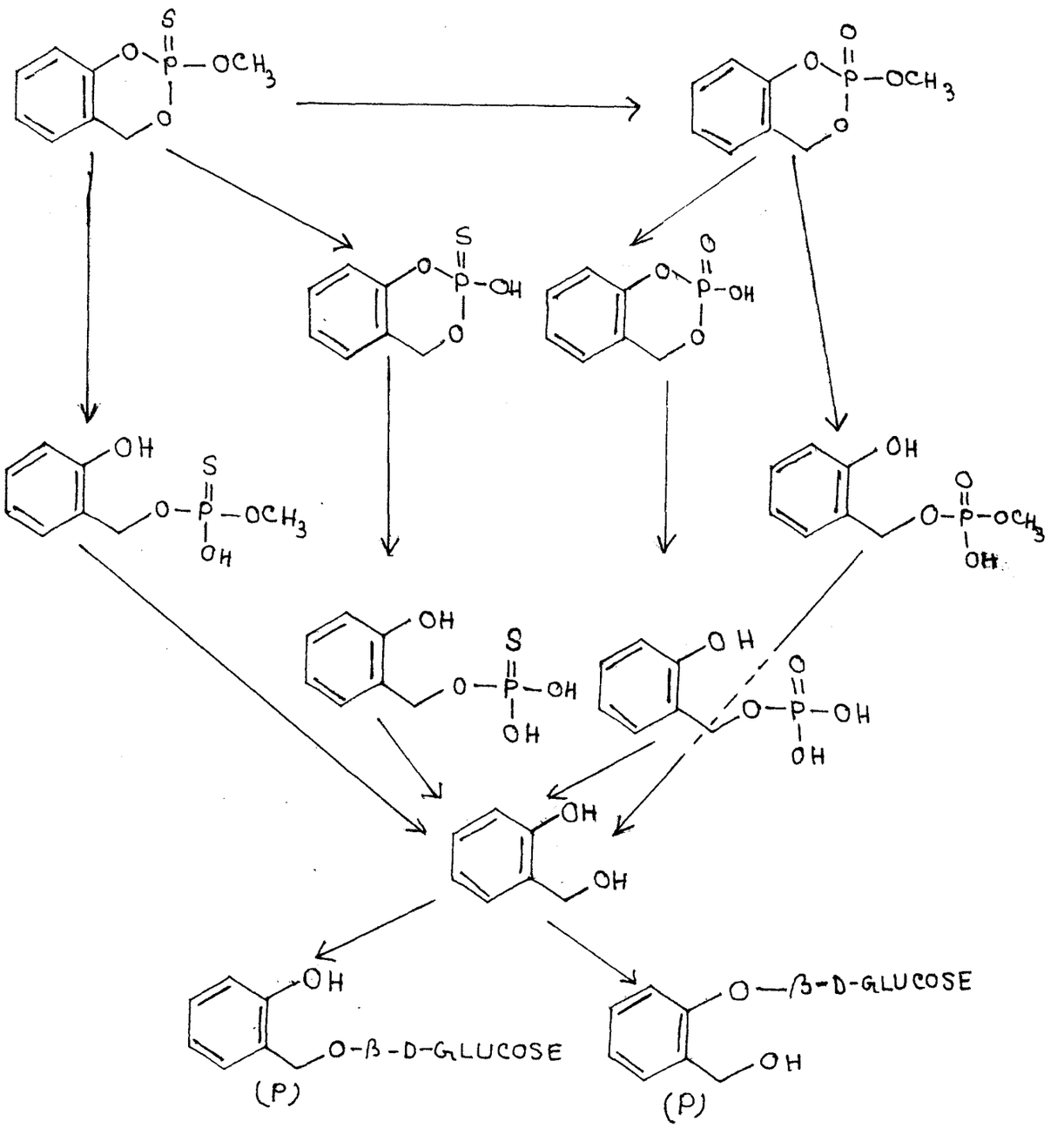


Fig. 1.7 Metabolic pathways of salithion in rats and plants (P- denotes the metabolite, found in Plant only).

The acute toxicity study of salithion for mammals was performed by Oshima[34]. The oral LD_{50} for mice is 93.3 mg/kg, for male rat 82-125 mg/kg, for female rats 102-180 mg/kg. The subcutaneous

LD_{50} for male rat is 142 mg/kg and for female rat is 152 mg/kg. The acute oral LD_{50} for hen is 110 mg/kg.

Studies on the chronic toxicity of salithion was performed[8] Rat fed for 24 months with 10 ppm salithion showed slight decrease in cholinesterase activities. No effect was observed in the rats fed with 3 ppm salithion. No histological lesion was found in any organs of rats fed with 100 ppm. In male and female administered orally 0.02 mg/kg/day of salithion for 21 days followed by 0.05 mg/kg/day fo 14 days, no effect was found in the activity of erythrocyte acetyl-cholinesterase. No effect was observed in fertility of rats for thre generations fed with 10 ppm salithion. Carcinogenicity was not obser

Properties of other saligenin cyclic phosphorus compounds:

Insecticidal activity:

The insecticidal activities of various saligenin cyclic phosphorus compounds including phosphates[13,21], phosphoramidates[27] phosphorothiolates[22], phosphonates[24] and their thiono analogs[13,2] have been tabulated in Table 1.3. The saligenin cyclic compounds in any series having an aryl group as an exocyclic substituent on the phosphorus atom have either poor or no insecticidal activity, but small alkyl derivatives have high insecticidal activity. The insecticidal activity appears to relate with the size of the exocyclic substituent on the phosphorus atom[36]. Methyl derivatives are much more active than higher alkyl and aryl derivatives except for phosphonothionate series in which ethyl derivative is more active than methyl derivative. N,N-dialkyl phosphoramidates are much less active than NH-alkyl derivatives. It is interesting to note that the exocycl

substituent of the most active compounds in each series (OCH_3, SCH_3, $NHCH_3$, CH_2CH_3) differs each other in electronic characteristics, but is similar in size and resembles in steric property such as the distance (about 2.9A°) between P and C atoms in the P-X-C function, if the bond angle of bivalent S is near 90° rather than 109.5°. The phosphorothiolethionates are not enough in insecticidal activity. The phosphates, phosphorothiolates and phosphonates are too unstable to be used practically as insecticides. Introduction of any substituents on the benzene ring, the hetero ring or the exocyclic ester group decreases the insecticidal activity.

Fungicidal activity:

Salithion has no fungicidal activity. But saligenin cyclic phosphorothiolates possess fungicidal activity[1] (Table 1.4) Phosphorothionates and phosphorothiolothionates possess low fungicid activity as compared to phospherothiolates[1]. A recent report[37] however has indicated that phosphorothionates can also be explored for their fungicidal activity. Among the phosphorothiolates, o-ethyl S, S-diphenylphosphorothiolates, commonly known as "edifenphos", has been commercialized[1] and widely used for controlling the blast disease of rice caused by Pyricularia oryzae.

Antiesterase activity:

The insecticide saligenin cyclic methyl phosphate (Salioxon) is very active as an inhibitor of cholinesterase. However, the highl neurotoxic aryl phosphate is a poor inhibitor of cholinesterase, but is a very specific inhibitor of aliesterase[1,38]. The less neurotc

arylphosphonate occupied an intermediate position. In any series, when the size of the exocylic substituent increases, the compound becomes a more selective inhibitor of aliesterase; in contrast, the compound carrying a small substituent is a more selective inhibitor of cholinesterase (Table 1.5). Arylphosphonates are more specific inhibitors of pseudocholinesterase; alkyl phosphates are less specii and aryl phosphates are intermediate.

Anti-SH Enzyme activity:

The saligenin cyclic phosphorothiolates have high activity to alkylate (salicylate) mercaptans and to inhibit "SH-enzymes" such as yeast alcohol dehydrogenase[28]. The activity seems to be related to fungicidal property but not with the insecticidal activit

The I_{50} values for alcohol dehydrogenase of some saligenin cyclic phosphorus ester are shown in Table 1.6. Cyclic methyl and ethyl phosphorothiolates are most active in this series. On the othe hand, cyclic phosphates have only weak activities, though they are potent inhibitors of esterase. Salithion, i.e., methyl phosphorothionate which have high insecticidal property is almost inactive towards the enzyme.

The rate of alkylation reaction by the cyclic ester looks parallel with the hydrolysis rate of the ester and the alkylation proceeds with a considerable time lag. These facts suggest that the alkylation occurs hydrolysis. Actually, the partial hydrolysate of saligenin cyclic esters react immediately with mercaptans. The react mechanism is shown in Fig. 1.8.

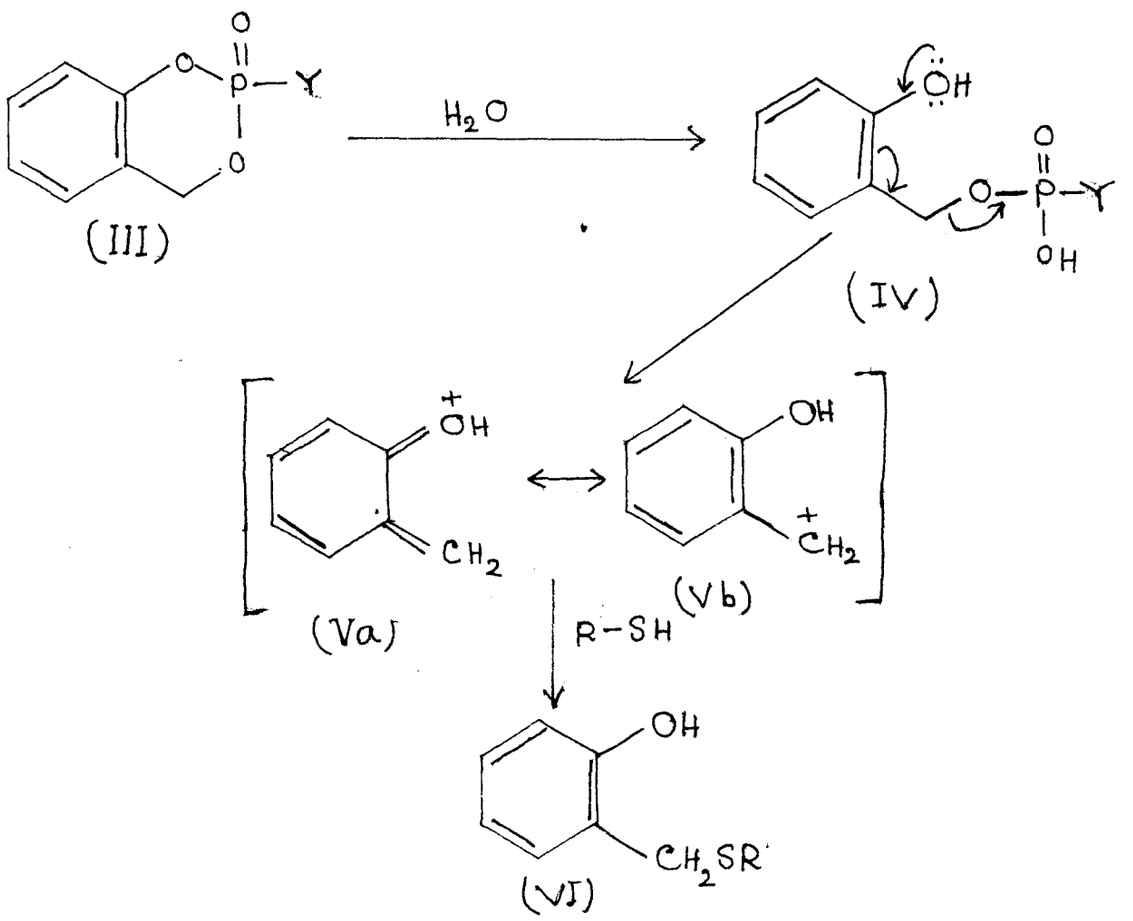


Fig. 1.8 Reaction mechanism of alkylation reaction

Saligenin cyclic phosphorothiolates are partially hydrolysed by opening of the heterocyclic P-O-C aryl bond, more easily than phosphate ester. In Fig. 1.8, the cyclic ester (III) is hydrolysed by the attack of hydroxide ion to yield salicyl phosphate (IV). The electron releasing -OH group of (IV) may convert to a carbonium ion (Vb) which may actually react with a SH group to give a thio ester (VI).

Cyclic methyl and ethyl phosphorothiolates are much more active in hydrolysis, alkylation and the inhibition of "SH-enzyme" activities than the corresponding cyclic phosphates[28]. It seems reasonable to conclude that the decrease of electron density on phosphorus atom causes the high reactivity of the phosphorothiolates. This is supported by the lower P=O frequency (1280 cm^{-1}) of the phosphorothiolates in comparison with that of the phosphates (1310 cm^{-1}).

Further investigation shows (Table 1.6) that there is an interesting correlation among alkylating activity, the inhibitory effect against "SH-enzymes" and the antifungal activity of the cyclic esters. Cyclic methyl and ethyl phosphorothiolates are highly active in all three functions. Cyclic phosphates have very weak activities but they are potent inhibitors of esterases. These facts suggests that high inhibitory activity against "SH-enzymes" may be an important fact for the fungicidal activity of the cyclic phosphorothiolates.

Synergistic Activity:

Saligenin cyclic aryl phosphates and phosphonates have synergistic activity with malathion against insects and mites, particularly their resistant strain[36].

The joint action of the activity of some saligenin cyclic phosphorus esters with malathion has been examined by Eto et al[39] and compared with some phosphorus esters which are known as the synergists of malathion. They increase the toxicity of malathion

2.3 to 3.4 times at a 1:1 mixing ratio. The activities of these compounds are more than propyl paraoxon but less than Dibram and isopropyl paraoxan.

It has been observed that for a large number of organophosphorus compounds the synergism of malathion in mice and the degree of inhibition of aliesterase *in vivo* are generally realted[12]. For insects, high esterase activity hydrolysing malathion is supposed to be partly responsible for malathion-resistance in some strains of mosquito, housefly and green rice leaf hopper[39].

Eto *et al*[38] have shown that aryl derivatives of saligenin cyclic phosphorus esters are the selective inhibitors of aliesterases, whereas small alkyl derivatives are not so selective to aliesterase inhibition. This appears to be responsible for their difference in synergistic properties.

Chemical hydrolysis:

The catalytic hydrolysis of saligenin cyclic phosphorus esters by phosphate ion has been reported[9]. The chemical reactivity of the cyclic phosphates with nucleophilic agents should be influenced by the electronic character of the substituent.

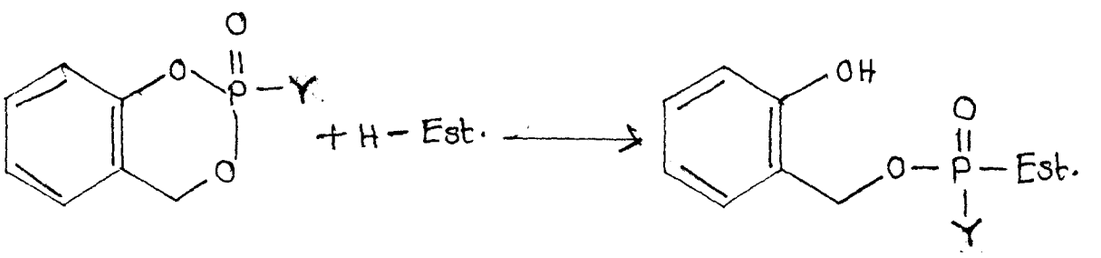
In the series of alkyl derivatives there is a relationship between rate constant and insecticidal activity (LD_{50}) (Table 1.7). The higher the reactivity, the stronger the insecticidal activity. However, the aryl derivatives do not follow this relationship; they are more reactive than alkyl derivatives but are almost non-insecticidal. The size of the substituent appears to be more important for biological activity than the electronic property of the substituent.

Biological Activities and Structural Relationship:

The saligenin cyclic phosphate esters have interesting biological activities. Some of them are neurotoxic, causing ataxia in higher animals. Others do not show such harmful activity but do have high insecticidal activity, systemic activity and fungicidal activity. Their biological activities include also synergism with organophosphorus insecticides, nematocidal and antifilarial activity. The specificity in biological activities may be attributed to the steric effect of an exocyclic substituent group on the phosphorus atom as shown in Table 1.8.

All aryl saligenin cyclic phosphates manifest a high delayed neurotoxicity to cause ataxia in hens and high syngergistic activity with malathion[12,39]. The arylphosphonate analogues showed similar biological activities but less in the neurotoxicity. On the other hand, the corresponding cyclic esters having a small alkyl group on phosphorus, i.e., 2-alkyl, 2-alkoxy and 2-alkylamido-4H-1,3,2-benzodioxaphosphorin-2-oxides, did not cause ataxia in hens with any sublethal doses and only weakly potentiated the toxicity of malathion[12]. The interesting feature is that the alkyl derivatives reveal high insecticidal activity, whereas, the aryl cyclic esters do not[11].

The specificity of saligenin cyclic phosphates in the biological activity relates to their selectivity in enzyme inhibition. These phosphates inhibit various serine enzymes by phosphorylation, producing probably salicycloxyphosphinylenzymes (VIII)[6,7] (Fig. 1.9).



(VII) (VIII)

Fig. 1.9 Reaction of saligenin cyclic phosphates with esterase (H-Est).

This involves by opening of the cyclic esters structure at the P-O aryl bond. When the size of the exocyclic substituent Y in (VII) increases, the ester becomes a more selective inhibitor of aliesterase[6,7]. Whereas, it becomes a more selective inhibitor of chlinesterase when the substituent is small. Thus the o-tolyl derivatives, for example, is 130 times more selective to inhibit aliesterase than cholinesterase.

Therefore, the exocyclic substituent of saligenin cyclic phosphate esters is regarded as the selectophore in the biological actions.

The heterocyclic structure of saligenin cyclic phosphorus esters is important merely for the chemical reactivity of the phosphorus atom towards nucelophiles including the active site of esterase and is never required for the delayed neurotoxicity. As for example, although Tri-o-ethyl phenyl phosphate (TEPP) has neurotoxicity[16], is unable to be transformed into a cyclic ester structure.

Jhonson found "neurotoxic esterase" in nerve tissues which is specifically sensitive *in vivo* to neurotoxic organophosphorus esters[40]. The esterase is unlike acetylcholinesterase but similar to chymotrypsin and trypsin in the structure activity relationship of inhibitors[41].

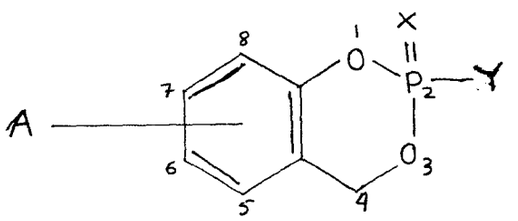
Although the structure-neurotoxicity relationship is too complicated to generalize, the neurotoxicity appears to be rather closely related to the structure of the non-leaving group than that of the leaving group.

Conclusion:

The high biological activities of saligenin cyclic phosphorus 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, animal toxicity and insecticidal activity. An exocyclic substituent group affects physical and biological properties by virtue of its electronic and steric characteristics. Thus, methyl phosphorothionate is useful as an insecticide, alkylamidates have systematic activity, alkyl phosphorothiolates have fungicidal activity, phenyl phosphonates have antifilarial activity, and aryl phosphates are neurotoxic and have synergistic activity.

Table 1.1

Substituted Saligenin Cyclic Phosphorus esters with physical properties.



Y	A	X	*Procedure	b.p. °C/mm Hg (m.p. °C)
OCH_3	H	O	(P)	110-2°/0.05
O-n-C_3H_7	H	O	(P)	129-32°/0.05
O-n-C_4H_9	H	O	(P)	150-4°/0.05
OCH_3	H	S	(S)	55-56°C
OC_2H_5	H	S	(P)	Liquid (not distilled)
OC_6H_5	H	S	(P)	30°
CH_3	H	O	(P)	140°/0.5(35°)
C_2H_5	H	O	(P)	143-9°/0.3(25°)
i-C_3H_7	H	O	(P)	80°
sec-C_4H_9	H	O	(P)	110°/0.5
t-C_4H_9	H	O	(P)	74°
$CH = CH_2$	H	O	(P)	155/2.5
CH_2Cl	H	O	(P)	160°/0.8(51°)
CH_2CH_2Cl	H	O	(P)	139-141°/0.1
CH_3	H	S	(P)	130°/0.6
C_2H_5	H	S	(P)	120°/0.6
i-C_3H_7	H	S	(P)	108°/0.6

Contd..

Table 1.2 (Contd..)

Y	A	X	*Procedure	b.p. °C/mm Hg (m.p. °C)
C_6H_5	H	S	(P)	37
CH_2Cl	H	S	(P)	146-155/0.4
OCH_3	6-CH_3	O	(P)	139-140/0.3
OC_2H_5	6-CH_3	O	(P)	152-156/0.3
OCH_3	6-CH_3	S	(S)	34-35
OC_2H_5	6-CH_3	S	(S)	71-72
OCH_3	7-CH_3	O	(P)	109/0.05
OC_2H_5	7-CH_3	O	(P)	112-118/0.05
O-n-C_3H_7	7-CH_3	O	(P)	141-147/0.1
C_6H_5	7-CH_3	O	(P)	93-95
OCH_3	7-CH_3	S	(S)	110-115/0.65
O-n-C_3H_7	7-CH_3	S	(S)	140-142/0.65
OCH_3	8-CH_3	O	(P)	118-120/0.5
OC_2H_5	8-CH_3	O	(P)	165/0.6
OC_6H_5	8-CH_3	O	(P)	125-140/0.6
OCH_3	8-CH_3	S	(S)	68-70/0.15
OC_2H_5	8-CH_3	S	(S)	108-109/0.15
OCH_3	6-C_6H_5	S	(S)	Oil**
OC_2H_5	6-C_6H_5	S	(S)	Oil**
O-n-C_3H_7	6-C_6H_5	S	(S)	Oil**
OCH_3	6-Cl	O	(P)	145-152/0.2

Contd..

Table 1.1 (Contd..)

Y	A	X	*Procedure	b.p. °C/mm Hg (m.p. °C)
OC_2H_5	6-Cl	O	(P)	160/0.2
O-n-C_3H_7	6-Cl	O	(P)	167-169/0.15
O-n-C_4H_9	6-Cl	O	(P)	187/0.18
OC_6H_5	6-Cl	O	(P)	89
OCH_3	6-Cl	S	(P)	170-178/0.2
SCH_3	6-Cl	S	(P)	160-170/0.2
OC_2H_5	8-Cl	O	(P)	151/0.18
O-n-C_3H_7	8-Cl	O	(P)	183/0.18
O-i-C_3H_7	8-Cl	O	(P)	137/0.04
OC_6H_5	8-Cl	O	(P)	203/0.52 (54)
OCH_3	8-Cl	S	(S)	72-73
SCH_3	8-Cl	S	(S)	Oil**
OCH_3	6-NO_2	S	(S)	Paste**
OCH_3	6,8-Cl	S	(S)	57-58
OC_2H_5	6,8-Cl	S	(S)	Oil**
SCH_3	H	S	(S)	69-70
SC_2H_5	H	S	(S)	145-147/0.2
S-n-C_3H_7	H	S	(S)	145-150/0.25
S-i-C_3H_7	H	S	(S)	140-143/0.1
S-n-C_4H_9	H	S	(S)	160-167/0.25
S-C_6H_5	H	S	(S)	79-80
S-CH_3	H	O	(P)	144-145/0.1

Contd..

Table 1.1 (Contd..)

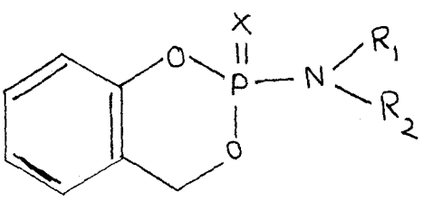
Y	A	X	*Procedure	b.p. °C/mm Hg (m.p. °C)
S-n-C_3H_7	H	O	(P)	140-145/0.04
S-i-C_3H_7	H	O	(P)	155-158/0.1
S-n-C_4H_9	H	O	(P)	157-160/0.02
SC_6H_5	H	O	(P)	88-89

* Pyridine (P) or aqueous sodium hydroxide solution(S) was used as dehydrogen chloride agent.

** These compounds were purified through silicic acid column chromatography.

Table 1.2

Saligenin cyclic phosphoramidates and phosphoramidothioates with physical properties.

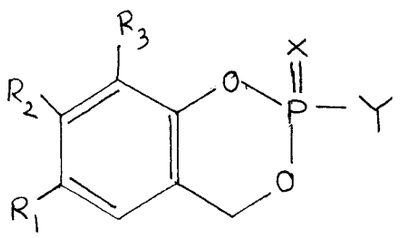


Code No.	R_1	R_2	X	*Procedure	b.p. °C/mm Hg (m.p. °C)
K-19	CH_3	H	O	A	87
K-22	C_2H_5	H	O	A	68
K-41	n-C_3H_7	H	O	A	135-140/0.5
K-40	i-C_3H_7	H	O	A	84
K-42	n-C_4H_9	H	O	A	46-47
K-10	C_6H_5	H	O	A	131-133
K-20	CH_3	CH_3	S	A	121
K-23	C_2H_5	C_2H_5	O	B	133-6/0.5(44)
K-35	CH_3	H	S	A	120-123/0.2
K-37	C_2H_5	CH_3	S	B	Undistilled liquid
K-36	CH_3	CH_3	S	B	118-122/0.2
K-38	C_2H_5	C_2H_5	S	B	110/0.2

* Tertiary amine (A) or Potassium Carbonate (B) was used as dehydrogen chloride agent.

Table 1.3

Substituted saligenin cyclic phosphorus compounds: Insecticidal activity



X	Y	R_1	R_2	R_3	LD_{50} µg/Housefly
O	OCH_3 (Salioxon)	H	H	H	0.035
O	OC_2H_5	H	H	H	0.33
O	O-n-C_3H_7	H	H	H	7.1
O	O-n-C_4H_9	H	H	H	10 (40%)
O	OC_6H_5	H	H	H	10 (3%)
S	OCH_3 (Salithion)	H	H	H	0.05
S	OC_2H_5	H	H	H	0.3
S	OC_6H_5	H	H	H	2.0
S	OCH_3	CH_3	H	H	2.0
S	OC_2H_5	CH_3	H	H	10
S	O-n-C_3H_7	CH_3	H	H	10
S	OCH_3	H	CH_3	H	0.23
S	OC_2H_5	H	CH_3	H	3.0
S	O-n-C_3H_7	H	CH_3	H	7.5
S	OCH_3	H	H	CH_3	1.3
S	OC_2H_5	H	H	CH_3	3.0
S	O-n-C_3H_7	H	H	CH_3	7.5

Contd..

Table 1.3 (Contd..)

X	Y	R_1	R_2	R_3	LD_{50} µg/Housefly
S	OCH_3	C_6H_5	H	H	0.4
S	OC_2H_5	C_6H_5	H	H	0.5
S	O-n-C_3H_7	C_6H_5	H	H	1.0
S	OCH_3	OCH_3	H	H	0.55
S	OCH_3	$COCH_3$	H	H	2.50
S	OCH_3	Cl	H	H	1.75
S	OCH_3	H	H	Cl	0.13
S	OCH_3	Cl	H	C_6H_5	1.2
S	OC_2H_5	Cl	H	C_6H_5	3.0
S	O-n-C_3H_7	Cl	H	C_6H_5	10
S	OCH_3	NO_2	H	H	3.0
S	OCH_3	Cl	H	Cl	0.3
S	OC_2H_5	Cl	H	Cl	4.0
O	OCH_3	CH_3	H	H	0.1
O	OC_2H_5	CH_3	H	H	0.4
O	OCH_3	H	CH_3	H	0.43
O	OC_2H_5	H	CH_3	H	0.7
O	O-n-C_3H_7	H	CH_3	H	7.2
O	C_6H_5	H	CH_3	H	10
O	OCH_3	H	H	CH_3	2.0
O	OC_2H_5	H	H	CH_3	2.1
O	OC_6H_5	H	H	CH_3	10
O	OCH_3	Cl	H	H	0.09

Contd..

Table 1.3 (Contd..)

X	Y	R_1	R_2	R_3	LD_{50} µg/Housefly
O	OC_2H_5	Cl	H	H	0.13
O	O-n-C_3H_7	Cl	H	H	0.70
O	O-n-C_4H_9	Cl	H	H	2.5
O	OC_6H_5	Cl	H	H	10
O	OCH_3	H	H	Cl	0.23
O	OC_2H_5	H	H	Cl	0.15
O	O-n-C_3H_7	H	H	Cl	0.30
O	OC_6H_5	H	H	Cl	10
O	CH_3	H	H	H	0.19
O	C_2H_5	H	H	H	0.17
O	i-C_3H_7	H	H	H	0.33
O	sec-C_4H_9	H	H	H	7.0
O	t-C_4H_9	H	H	H	10 (0%)
O	$CH=CH_2$	H	H	H	0.68
O	CH_2Cl	H	H	H	10 (60%)
O	CH_2CH_2Cl	H	H	H	0.99
O	C_6H_5	H	H	H	10 (0%)
S	CH_3	H	H	H	0.31
S	C_2H_5	H	H	H	0.08
S	i-C_3H_7	H	H	H	0.09
S	CH_2Cl	H	H	H	1.14

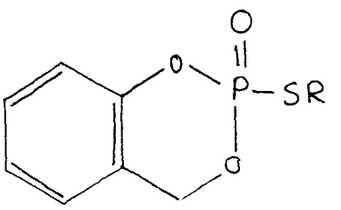
Contd..

Table 1.3 (Contd..)

X	Y	R_1	R_2	R_3	LD_{50} µg/Housefly
S	C_6H_5	H	H	H	0.3
S	SCH_3	H	H	H	0.18
S	SC_2H_5	H	H	H	9
S	$S-\underset{\underset{O}{\|}}{N}-C_3H_7$	H	H	H	2.2
S	S-i-C_3H_7	H	H	H	5
S	S-n-C_4H_9	H	H	H	10
S	SC_6H_5	H	H	H	10(0%)

Table 1.4

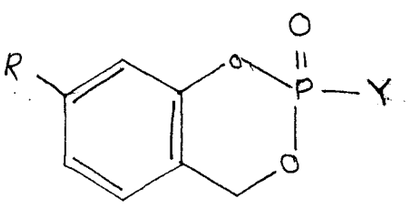
Fungicidal activity of some saligenin cyclic phosphorothiolates



R	Protective value (%) against *Pyricularia oryzae*				Therapeutic value (%) to *P. oryzae* at 200 ppm
	250 ppm	100 ppm	50 ppm	25 ppm	
CH_3 (MEBO)	100	100	100	84.8	7.1
C_2H_5	100	93.7	92.5	81.5	100
n-C_3H_7	100	57.1	34	-	-
i-C_3H_7	-	68.7	34.4	-	-
n-C_4H_9	100	91.7	93.3	75.6	97.6
C_6H_5	50.2	-	-	-	-
Salithion	52 (at 500 ppm)	-	-	-	-
edifenphos	100	-	86.2	-	95.2 at 250 ppm

Table 1.5

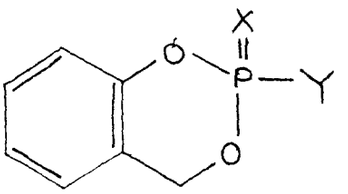
The Inhibition of Housefly, Human blood and Horse Serum Esterases by some saligenin cyclic phosphorus Compounds.



Y	R	Housefly I_{50} (M)x10^8		Human blood I_{50} (M) x 10^8		Horse plasma I_{50} (M) x 10^8	
		ChE	AliE	p-ChE	t-ChE	AliE	Malathinase
OCH_3	H (Salioxon)	7.6	8.4	1.8	17.0	280	620
OC_2H_5	H	13.2	2.1	1.6	25.0	280	-
O-n-C_3H_7	H	50.7	3.0	-	-	-	-
OC_6H_5	H	155	1.4	0.5	12.0	120	120
C_6H_5	H	-	-	0.65	72.0	180	470
C_6H_5	CH_3	-	-	1.6	68.0	230	-
OPh-2-CH_3	H	-	-	1.3	39.0	200	-

Table 1.6

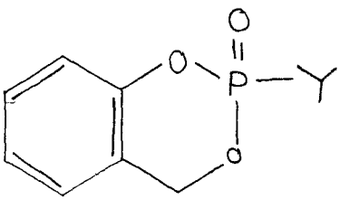
Chemical, Biochemical and Antifungal activities of some saligenin cyclic phosphates and their analogues.



X	Y	Hydrolysis (%)	Cysteine reacted (%)	I_{50} Yeast alcohol dehydrogenase ($M \times 10^{5}$)	Protective value against *P. oryzae* (%)	
					50 ppm	500 pp
O	SCH_3	86	55	4.5	100	-
O	SC_2H_5	81	50	4.4	93	-
O	OC_6H_5	55	45	6.8	-	-
O	OCH_3	17	10	62	-	65
S	OCH_3	5	5	100	-	52

Table 1.7

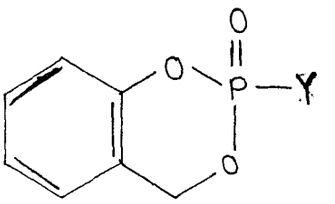
Relationship between rate constant and insecticidal activity of some saligenin cyclic phosphorus esters



Y	K_{hyd} (min^{-1})	LD_{50} (μg/female housefly)
CH_3	2.2×10^{-2}	0.19
C_2H_5	4.25×10^{-3}	0.17
i-C_3H_7	-	0.33
sec-C_4H_9	-	7.0
t-C_4H_9	-	10 (0%)
$CH{=}CH_2$	1.39×10^{-2}	0.68
CH_2Cl	2.00×10^{-1}	10 (60%)
CH_2CH_2Cl	1.41×10^{-2}	0.99
C_6H_5	1.28×10^{-2}	10 (10%)
OCH_3	1.42×10^{-3}	0.035
OC_2H_5	5.04×10^{-3}	0.33
O-n-C_3H_7	3.79×10^{-4}	7.1
O-n-C_4H_9	3.29×10^{-4}	10 (40%)
OCH_2CH_2Cl	2.58×10^{-3}	0.49
OC_6H_5	6.30×10^{-3}	10 (3%)
$NHCH_3$	1.54×10^{-4}	0.05
$N(CH_3)_2$	Negligibly small	0.40
NHC_6H_5	2.40×10^{-4}	10 (5%)

Table 1.8

Effect of the exocyclic substituent (R) on biological activities of saligenin cyclic phosphate.



Y	Delayed neurotoxicity MAD[a]	Synergism with malathion cotoxicity coefficient		Insecticidal activity LD_{50}
		Mice	Houseflies[b]	
OCH_3-C_6H_4O	2-5	16.7	7.8	(0)[d]
C_6H_5O	1.5-2	8.8	9.2	(3)[d]
C_6H_5	200	18.8	8.0	(0)[d]
C_2H_5	N.A.[e]	3.0	-	0.17
C_2H_5O	-	-	3.1	0.33
CH_3O	N.A.[e]	3.7	4.7	0.04
$(CH_3)_2N$	N.A.[e]	1.1	-	0.30

a. Minimum ataxia dose for hens in mg/kg

b. A resistant strain

c. 50% lethal dose by topical applical to houseflies in μg.

d. Percentage mortality at 10 μg/fly

e. No ataxia signs evident with any sublethal doses.

R E F E R E N C E S

1. Eto, M., Organophosphorus Pesticides : Organic and Biological Chemistry, CRC Press, Cleveland, Ohio, (1974).
2. Jercher, J., Ber., 70, 600 (1943).
3. Fest, C. and Schmidt, K.J., The Chemistry of Organophosphorus Pesticides, Springer-Verlag, New York (1982).
4. Kolse, W. Dr., "Potential phosphorus containing Intermediates for the synthesis of Pesticides", Given in "Advances in Pesticide Science", Ed. Geissbuhler, H., Pergamon Press, Part 2, 109 (1979).
5. Casida, J.E., Eto, M. and Baron, R.L., Nature, 191 1396 (1961).
6. Eto, M., Casida, J.E. and Eto, T., Biochem. Pharmacol., 11, 337 (1962).
7. Eto, M., Residue Reviews, 25, 187 (1969).
8. Eto, M., Review of Plant Protection Research, 9, 1 (1976).
9. Eto, M. and Oshima, Y., Agr. Biol. Chem., 26, 452 (1962).
10. Eto, M. and Oshima, Y., Agr. Biol. Chem., 26, 834 (1962).
11. Eto, M., Eto, T. and Oshima, Y., Agr. Biol. Chem., 26, 630 (1962).
12. Casida, J.E., Baron, R.L., Eto, M. and Engel, J.L., Biochem. Pharmacol., 12, 73 (1963).
13. Eto, M., Kinoshita, Y., Kato, T. and Oshima, Y., Nature, 200, 171 (1963).
14. Smith, H.V. and Spalding, J.M.K., Lancent, 2, 1019 (1959).
15. Smith, M.I., Elvolve, E. and Frazier, W.H., U.S.A. Pub. Health Rep., 45, 2509 (1930).
16. Aldridge, W.N. and Barnes, J.M., Biochem. Pharmacol., 6, 177 (1961).

17. Eto, M., Oshima, Y. and Casida, J.E., Biochem. Pharmacol. 16, 295 (1967).

18. Eto, M., Matsuo, S. and Oshima, Y., Agr. Biol. Chem., 27, 870 (1963).

19. Taylor, J.D. and Butter, H.S., Toxicol. Appl. Pharmacol., 11, 529 (1967).

20. Oshima, Y. and Eto, M., US Patent 3, 478, 133 (1969).

21. Eto, M., Kinoshita, Y., Kato, T. and Oshima, Y., Agr. Biol. Chem., 27, 789 (1963)

22. Kobayashi, K., Eto, M., Oshima, Y., Hirano, T., Hosoi, T. and Wakamori, S., Botyu-Kagaku, 34, 165 (1969).

23. Kobayashi, K., Eto, M., Hirai, S. and Oshima, Y., J. Agr. Chem. Soc., Japan, 40, 315 (1966).

24. Eto, M., Kishimoto, K., Matsumura, K., Oshita, N. and Oshima, Y., Agr. Biol. Chem., 30, 181 (1966).

25. Eto, M. and Oshima, Y., Agr. Biol. Chem., 26, 452 (1962).

26. Eto, M., Kobayashi, K., Sasamoto, T., Cheng, H.M., Aikawa, T., Kume, T. and Oshima, Y., Botyu-Kagaku, 33, 73 (1968).

27. Eto, M., Kobayashi, K., Kato, T., Kojima, K. and Oshima, Y., Agr. Biol. Chem., 29, 243 (1965).

28. Ohkawa, H. and Eto, M., Agr. Biol. Chem., 33(3), 443(1969).

29. Eto, M. and Miyamato, J., Salithion (R). In analytical methods for Pesticides and Plant Growth Regulators, Vol. VII, Ed. by Zweig, G., Academic Press, New York, 431 (1973).

30. Sasaki, M., Ohkawa, H. and Eto, M., J. Fac. Agr., Kyushu Univ., 17, 173 (1972).

31. Eto, M., Sasaki, M., Iio, M., Eto, M. and Ohkawa, H., Tetrahedron Letters, 45, 4263 (1971).

32. Sasaki, M. and Mukai, K., Japan Kokai, 7426, 290, Chem. Abst., 81, 388 (1974).

33. Sumitomo Chemical Co., British Patent 1, 228, 121; Chem. Abstr., 75, 34493 (1971).

34. Oshima, Y., Salithion (R) Noyaku-Seisangijitsu, 27, 1 (1972).
35. Ohkawa, H., Eto, M. and Oshima, Y., Jap. J. Appl. Entomol. Zool., 14, 191 (1970).
36. Eto, M., Pesticide Chemistry, Vol. I, Insecticides Ed. by Tahori A.S., Gordon and Breach Science Pub., London, 311 (1972).
37. Sasaki, M., Ooishi, T., Kata, T., Takayama, C. and Mukai, K., J. Pesticides Sci., 9, 734 (1984).
38. Eto, M., Hanada, K., Namazu, Y. and Oshima, Y., Agr. Biol. Chem., 27, 723 (1963).
39. Eto, M., Oshima, Y., Kitakato, S., Tanaka, F. and Kojima, K., Botyu-Kagaku, 31, 33 (1966).
40. Johnson, M.K., Biochem. J., 120, 520 (1970).
41. Johnson, M.K., Biochem. Pharmacol., 24, 797 (1975).