P A R T - II

PART - II

REVIEW ON SALITHION AND RELATED COMPOUNDS.

1. INTRODUCTION:

Discovery of saligenin cyclic phosphate as a biologically active metabolite of tri-o-cresyl phosphate (TOCP)[1,2,3] has led to the extensive studies on synthesis, chemical and biological properties of many related compounds[4,5]. Analogous cyclic phosphorus esters have been synthetically prepared for examination of their chemical properties[6,7] and biological activities[8,9]. 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 phosphates carrying a small alkyl group have insecticidal activity[10]. Among the saligenin cyclic phosphorus compounds, salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide) has been prepared in a large quantity and practically used as an insecticide in Japan[1,5].

This review describes how salithion has been discovered and developed as practical insecticide and also the chemical, pesticidal, biological and other properties of

saligenin cyclic phosphorus compounds have been discussed.

2. DISCOVERY OF SALITHION AND RELATED COMPOUNDS:

It was the year 1930, when about 10,000 people in USA were stricken with a flaccid paralysis of the lower limbs about 10 days after drinking an adulterated fluid, extract of Ginger [11]. This was due to the phosphate tri-ester of ortho-cresol, so called TOCP, a contaminant present in the ginger extract. Also a similar big outbreak of paralysis took place in 1959 (in Morocco) from cooking oil contaminated with the lubricating oil of turbo-jet aircraft engines [12]. This was also due to o-cresyl phosphate (TOCP) poisoning. The phosphate tri-esters of cresol have been widely used in industries as plasticizers, lubricants, solvents, oil additives and fire-retardants.

Because of very sensitive to the delayed neurotoxic action of organophosphorus compounds, hens have been used for the assay of the neurotoxicity of triaryl phosphate. Aldridge and Barnes [13,1] observed that all neurotoxic triaryl phosphates except tri-p-ethyl phenyl phosphate have at least one alkyl group carrying the α-hydrogen atom on the ortho position. This structure-neurotoxicity relationship of triaryl phosphates is clearly understandable by the isolation and characterization of the active metabolities of TOCP [2,3]. The main active metabolite (M) is ortho-tolyl saligenin cyclic phosphate (2-ortho-

4H-1,3,2 benzodioxaphosphorin-2-oxide). It is extraordinarily active in all the biological properties shown by TOCP; this compound (M) is about 100 times more potent to cause ataxia in hens than TOCP: (M) potentiated the toxicity of malathion 100 times by the dose of 20 mg/kg in mice, while TOCP 4 times by the dose 100 mg/kg; (M) is also ten million times more active than TOCP in the in vitro inhibition of plasma cholinesterase[4].

The conversion of TOCP into the cyclic phosphate proceeds via two steps[14] as shown in Fig. 1 : (i) the hydroxylation of the methyl group of TOCP by the mixed-function oxidases (mfo) and (ii) the cyclization by intra-molecular transphosphorylation of the intermediate, di-o-tolyl o-(α -hydroxy) tolyl phosphate, leaving one molecule of cresol. The later reaction takes place slowly in spontaneous manner and is greatly accelerated by the presence of plasma albumin[15].

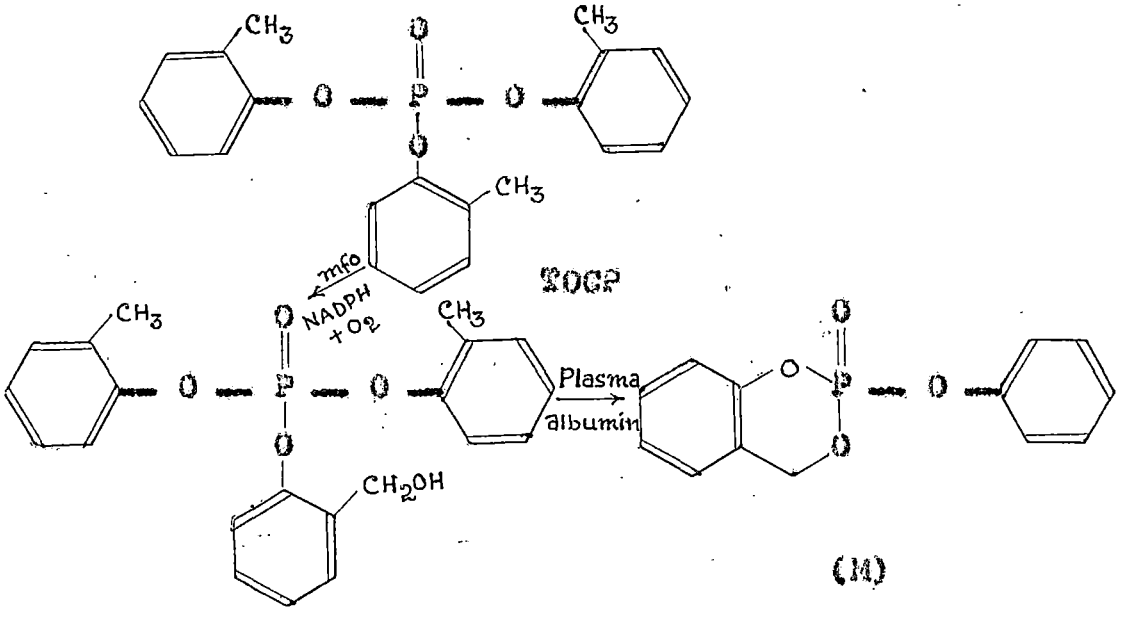


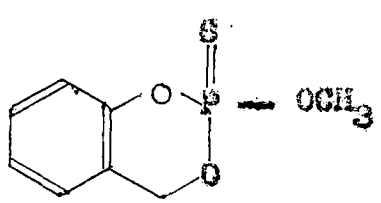
Fig. 1 Metabolic activation of TOCP.

Thus it is rational to presume that the triaryl phosphates having an o-alkyl group with the α-hydrogen atom may be similarly metabolized to give the corresponding active cyclic esters. In the cyclization reaction, no alkyl ester group participates as the leaving group[15]. Actually, no aryl but alkyl saligenin cyclic phosphate is formed *in vivo* from alkyl di-o-tolyl phosphates[16]. Such metabolic activation of TOCP or its analogs have been observed in rats[14], hens[14], cats[17] and insects[16].

All aryl saligenin cyclic phosphates have showed 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 [2,8].

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 [10] in 1963. Salithion was developed into a commercial insecticide in 1968 by Sumitomo Chemical Co. With the co-operation of Toa-Noyaku Co. (now Kumiai Chemical Co.) and Mikasa Chemical Co. of Japan.

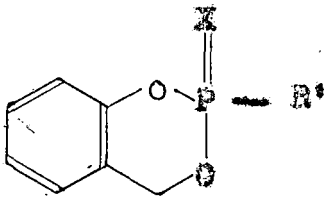


Salithion

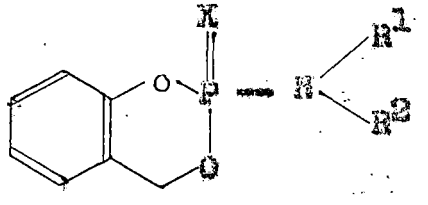
3. SYNTHESIS OF SALIGENIN CYCLIC PHOSPHORUS ESTERS:

The cyclic phosphate and phosphonate esters of saligenin are readily synthesized by condensation of saligenin and substituted phosphoryldichlorides in the presence of a dehydrochlorinating agent such as tertiary amine in a dry solvent like chloroform or toluene at low temperature[6]. In some cases where the reaction is affected difficultly by using the tertiary amine, the reaction has been made to proceed by heating the mixture for 10 to 20 hours in the presence of anhydrous potassium carbonate together with copper powder[18] instead of tertiary amine.

Such compounds, which are difficultly produced by the method employing a tertiary amine, include the compounds having X = S and R' = methoxy in formula (I) and X = O, R^1 = H and R^2 = alkyl containing more than one carbon atom or R^1 = R^2 = alkyl in the formula (II).



(I)



(II)

The process using potassium carbonate is made to proceed by a reaction between liquid and solid phases. Therefore, even if potassium carbonate is employed as finely divided powder form, it often causes a remarkable lowering and fluctuation of the yield[18]. 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[19].

This difficulty, has been however, overcome later by applying the well-known Schotten-Baumann acylation procedure using an aqueous solution of sodium hydroxide (Fig. 2)

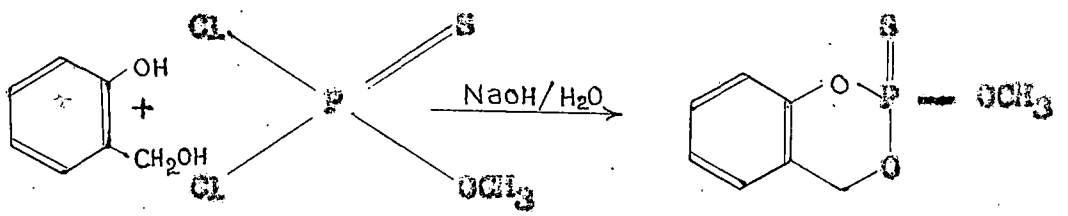


Fig. 2 Synthesis of Salithion.

Some typical examples are given below:

(a) Salithion (2-methoxy-4H-1,3,2-benzodioxaphosphorin-2-sulphide[18]:

6.2 gm o-hydroxy benzyl alcohol was dissolved in 30-40 ml. 20 percent (by weight) sodium hydroxide aqueous solution. Methylthiophosphorodichloridate (8.3 - 11 gm) was then added dropwise to the above mixture at about 10°C with constant vigorous stirring. After the addition, stirring was continued for one hour, as a result, crystals were separated. 70 ml of chloroform or toluene was added to the reaction mixture and the stirring was continued for additionnl one hour. The organic layer was separated and washed with 2% sodium hydroxide, 0.5 (N) HCl and water, and dried over anhydrous sodium sulphide; the solvent was then removed at reduced pressure, and the solids thus separated, were recrystallized from methanol to give 6.5 - 7.6 gm (yield 60 - 70 percent) pure crystals of salithion, M.P. 52°C.

Methylthiophosphorodichloridate can be prepared by the reaction of CH_3OH and $PSCl_3$ in presence of a base[20a,b].

(b) 2-alkoxy-6-nitro-4H-1,3,2-benzodioxaphosphorin 2-sulphide[21,22]:

These compounds were prepared by adding 1 mole 5-nitro saligenin in dried acetone dropwise to a mixture of alkylthiophosphorodichloridate (1 mole) and anhydrous potassium

carbonate (2 moles) in acetone at -5° to + 5°C with constant vigorous stirring. After an additional stirring period of 1 - 3 hours at 0° - 5°C, the solids were filtered out of the reaction mixture and the solvent was removed at room temperature. The residual solid mass was dissolved in ethyl acetate and washed with ice cold water containing 5% sodium chloride. The ethyl acetate phase was lyophilised and the solvent was removed at reduced pressure. For methoxy compound a semi-solid deep-brown paste was obtained; after standing for several days, the crude mass was solidified, and the solid, after washing several times, was recrystallized from methanol. All other compounds were solids [21].

(c) 2-alkylamido-4H-1,3,2-benzodioxaphosphorin-2-sulphide/oxide [23]:

Saligenin cyclic phosphoramidates and phosphoramidothionates were synthesized from saligenin and appropriate phosphoramidic dichloride by the action of proper dehydrochlorinating agent. The reaction of saligenin with reactive dichloride as mono-alkyl phosphoramidic dichloride and some others was proceeded by the action of tertiary amine such as pyridine or triethylamine in cold condition. Liquid dichloride was usually added dropwise to the mixture of saligenin and the base in chloroform. Solid dichloride was however, dissolved in cold chloroform with saligenin, then the amine was added dropwise to the chilled mixture. When the dichloride was less reactive as

almost all phosphoramidothionic dichlorides, heating the mixture of reactants in toluene in the presence of anhydrous potassium carbonate and copper powder was useful. Typically, 2-methylamino-4H-1,3,2-benzodioxaphosphorin-2-oxide was prepared in the following procedure : To a mixture of saligenin, 9.2 gm, triethylamine, 15 gm, and 90 ml. chloroform, was dropwise added 12 gm methylphosphoramidic dichloride with stirring and cooling in an ice bath. After the completion of addition, the reaction mixture was kept overnight at room temperature, and then washed sequentially with ice-water, dil. HCl acid, aq. sodium bicarbonate solution and ice-water. The solvent was removed in vacuo after drying over anhydrous sodium sulphate. Crude crystals were recrystallised from benzene to yield pure crystals, m.p. 87°C (8 gm). Phosphoramidic and phosphoramidothionic dichlorides were prepared according to Michaeli's[24] method.

(d) Saligenin Cyclic Phosphorothiolates[25] :

Phosphorodichloridothiolates reacted with saligenin in the presence of solvent and pyridine or other tertiary amine at room temperature or at about 50°C. The products were purified by distillation in vacuo or recrystallization. Typically, 2-Methylthio-4H, 1,3,2 benzodioxaphosphorin-2-oxide (MTBO) can be prepared in the following procedure:

To a mixture of saligenin (6.2 gm), pyridine (8 gm) and chloroform (100 ml) was added dropwise methyl phosphorodichloridothiolate (8 gm) with stirring at 20°C. After stirring for three hours, the reaction mixture was washed in sequence with water, dil. alkali, dil. HCl acid and water and dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure and the residue was distilled *in vacuo* to give 3.2 gm of oil [b.p. 144 - 145°C (0.1 mm Hg)]. The oil solidified slowly at room temperature (m.p. of pure MTBO 44°C).

MTBO can also be synthesized from salithion by the following procedure (25) :

A mixture of salithion (20 gm, 0.0928 mole), potassium iodide (3 gm, 0.018 mole), methyl iodide (9 ml, 0.145 mole) and dimethyl formamide (20 ml) was kept at temperature 25°C for 24 hours. The mixture was then carefully concentrated to avoid complete dryness *in vacuo* and dissolved in chloroform (50 ml). Chloroform solution was washed with water (4 times) and dried over anhydrous sodium sulphate. After filtration, the filtrate was evaporated at reduced pressure to give MTBO (8.95 gm) in 45% yield. The residue was solidified on cooling. MTBO was recrystallized from ethanol at -15°C.

2-substituted-4H-1,3,2-benzodioxaphosphorin-2-sulphides including methoxy (salithion), alkylamino, alkylthio and

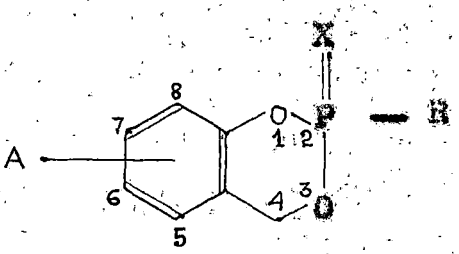
arylthio derivatives were synthesized in good yield by the application of Schotten-Baumann acylation reaction (procedure 'a' given above); this method was very useful for the preparation of cyclic esters which were difficultly prepared by a tertiary amine method[27]. But, 6-nitro derivatives can be best prepared by the procedure 'b' mentioned above[21,22].

4. Other Saligenin Cyclic Phosphorus Esters:

The careful observation of literatures[18,19,25,27,28,29,30] furnishes a variety of saligenin cyclic phosphorus esters in good numbers, which have been prepared and examined for insecticidal activity as well as other biological properties. They involve phosphates, phosphorothiolates, phosphoramidates, phosphonates and their thiono-analogs. A comprehensive but not a complete list of saligenin and ring substituted saligenin cyclic phosphorus esters is given in Table-I and Table-II.

Table - I

Substituted Saligenin Cyclic Phosphorus Esters with Physical Properties.



R	A	X	*Procedure	b.p. °C/mm Hg(m.p. °C)
OCH_3	H	S	(S)	55-56°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
OC_2H_5	H	S	(P)	Liquid (not distilled)
OC_6H_5	H	S	(P)	(30°)
C_6H_5	H	S	(P)	(37°)
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°)

Contd.....

Table-I (Contd.....)

R	A	X	*Procedure	b.p. °C/mm Hg(m.p. °C)
$CH=CH_2$	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)	103°/0.6
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	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)
$NHCH_3$	7-CH_3	O	(P)	(145-146)
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)	135-140/0.6
OCH_3	6-Cl	O	(P)	145-152/0.2
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)	137/0.18

Contd.....

Table-I (Contd.....)

R	A	X	*Procedure	b.p. ^oC/mm Hg(m.p. ^oC)
OC_6H_5	6-Cl	O	(P)	(89°)
$NHCH_3$	6-Cl	O	(P)	(148°)
OCH_3	8-Cl	O	(P)	170-171/0.15
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°)
$NHCH_3$	8-Cl	O	(P)	(128-129°)
OCH_3	6-CH_3	S	(S)	(34-35°)
OC_2H_5	6-CH_3	S	(S)	(71-72°)
O-n-C_3H_7	6-CH_3	S	(S)	158-160/0.2
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	S	(S)	68-70/0.15
OC_2H_5	8-CH_3	S	(S)	108-109/0.15
O-n-C_3H_7	8-CH_3	S	(S)	120-124/0.15
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-OCH_3	S	(S)	Paste**
OCH_3	6-Cl	S	(P)	170-178/0.2

Contd.....

R	A	X	*Procedure	b.p. ^{o}C/mm Hg(m.p. ^{o}C)
$NHCH_3$	6-Cl	S	(P)	175-180/0.25
SCH_3	6-Cl	S	(P)	160-170/0.2
OCH_3	8-Cl	S	(S)	($72-73^{o}$)
$NHCH_3$	8-Cl	S	(P)	($46-47^{o}$)
SCH_3	8-Cl	S	(S)	Oil**
OCH_3	6-NO_2	S	(S)	Paste**
OCH_3	6-Cl	S	(S)	Paste**
	8-C_6H_5	S	(S)	
OC_2H_5	" "	S	(S)	Paste**
O-n-C_3H_7	" "	S	(S)	Paste**
OCH_3	6-C_6H_5	S	(S)	Paste**
	8-Cl			
OC_2H_5	" "	S	(S)	Paste**
O-n-C_3H_7	" "	S	(S)	Paste**
OCH_3	6,8-Cl	S	(S)	($57-58^{o}$)
OC_2H_5	"	S	(S)	Oil**
$NHCH_3$	"	S	(S)	Oil**
SCH_3	H	S	(S)	($69-70^{o}$)
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

Contd.....

Table-I (Contd.....)

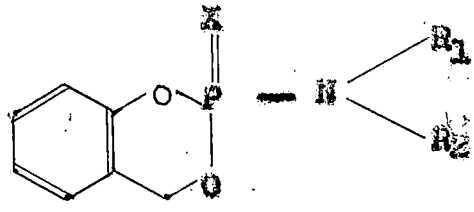
R	A	X	*Procedure	b.p. °c/mm Hg (m.p. °C)
S-C_2H_5	H	S	(S)	140-147/0.3
S-n-C_4H_9	H	S	(S)	160-167/0.25
S-C_6H_5	H	S	(S)	(79-80°)
SCH_3	H	O	(P)	144-145/0.1
SC_2H_5	H	O	(P)	140-145/0.04
S-n-C_3H_7	H	O	(P)	145-147/0.07
S-i-C_3H_7	H	O	(P)	155-158/0.1
S-n-C_4H_9	H	O	(P)	157-160/0.02
SC_6H_5	H	O	(P)	(88-89°)

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

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

Table - II

Saligenin Cyclic Phosphoramidates and Phosphoramidothionates 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	135-140/0.6
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	O	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	H	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

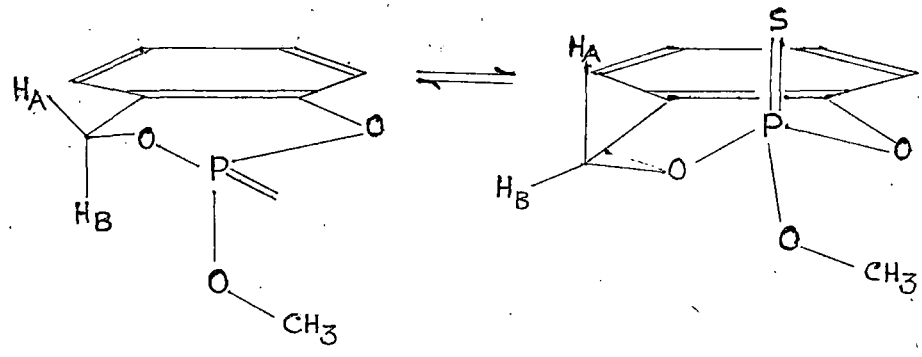
* Tertiary amine (A) or potassium carbonate (B) was used as dehydrogen chloride agent.

5. Chemical and Biological Properties of Salithion:

Here we concentrate our discussion to the important properties of salithion[5] relating to its structure, chemical and biological properties.

Pure salithion is a colourless crystalline powder: m.p. 55° - 56°C; practically insoluble in water but easily soluble in acetone 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). Salithion has characteristic IR band at 1020 cm^{-1} for P-O-CH_2 in the hetero ring. NMR $\delta(CS_2)$ 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. 3)



(III) (IV)

Fig. 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 sulfide group is in equatorial position (III). The strain in the ring appears little; the endocyclic O-P-O angle is 104°.

Salithion gives a characteristic fragmentation pattern in mass spectrometry (31). It gives an intense peak of $[M - CH_3]^+$ (m/e 201) by β-cleavage occuring at the exocyclic ester group. Another fragmentation process is the direct loss of SH followed by the elimination of formaldehyde (Fig. 4).

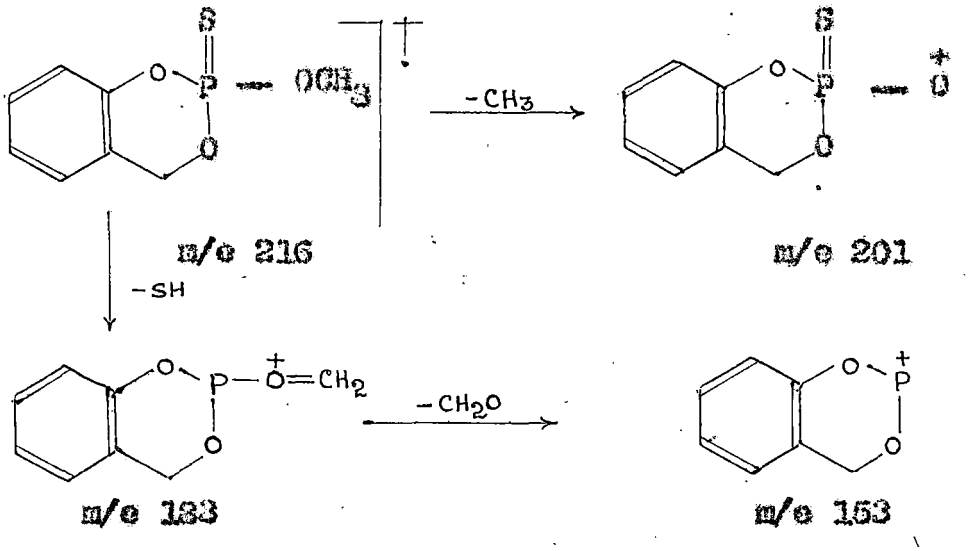


Fig. 4. Fragmentation of salithion in mass spectrometry.

Salithion is converted to its oxon analog (salioxon) by the action of bromine water. Since salioxon (2-methoxy-4H-1,3,2 benzodioxaphosphorin 2-oxide) is some thousands times more active in cholinesterase inhibition than salithion, an enzymatic method after the oxidation can be used for the residue analysis of salithion[32].

Salithion is converted into S-alkyl saligenin cyclic phosphorothiolates by heating with alkyl iodides (the Pistchimuke reaction)[33]. This reaction is accelerated in such polar compound as dimethyl formamide. Potassium carbonate also assists the reaction. When methyl iodide is used, isomerization occurs to give 2-methylthio-4H-1,3,2-benzodioxaphosphorin-2-oxide (MTBO)[33,34]. Saligenin is demethylated to form the salt of saligenin cyclic phosphorothionic acid by the action of certain neucleophiles such as cyclohexylamine[5] and potassium dimethyldithiocarbonate[5,35]. The later reagent is particularly suitable for the preparation of MTBO by methylating the obtained salt with methyl iodide. MTBO is a unique phosphorylating agent[5]. The reactions of salithion are summarized in Fig. 5.

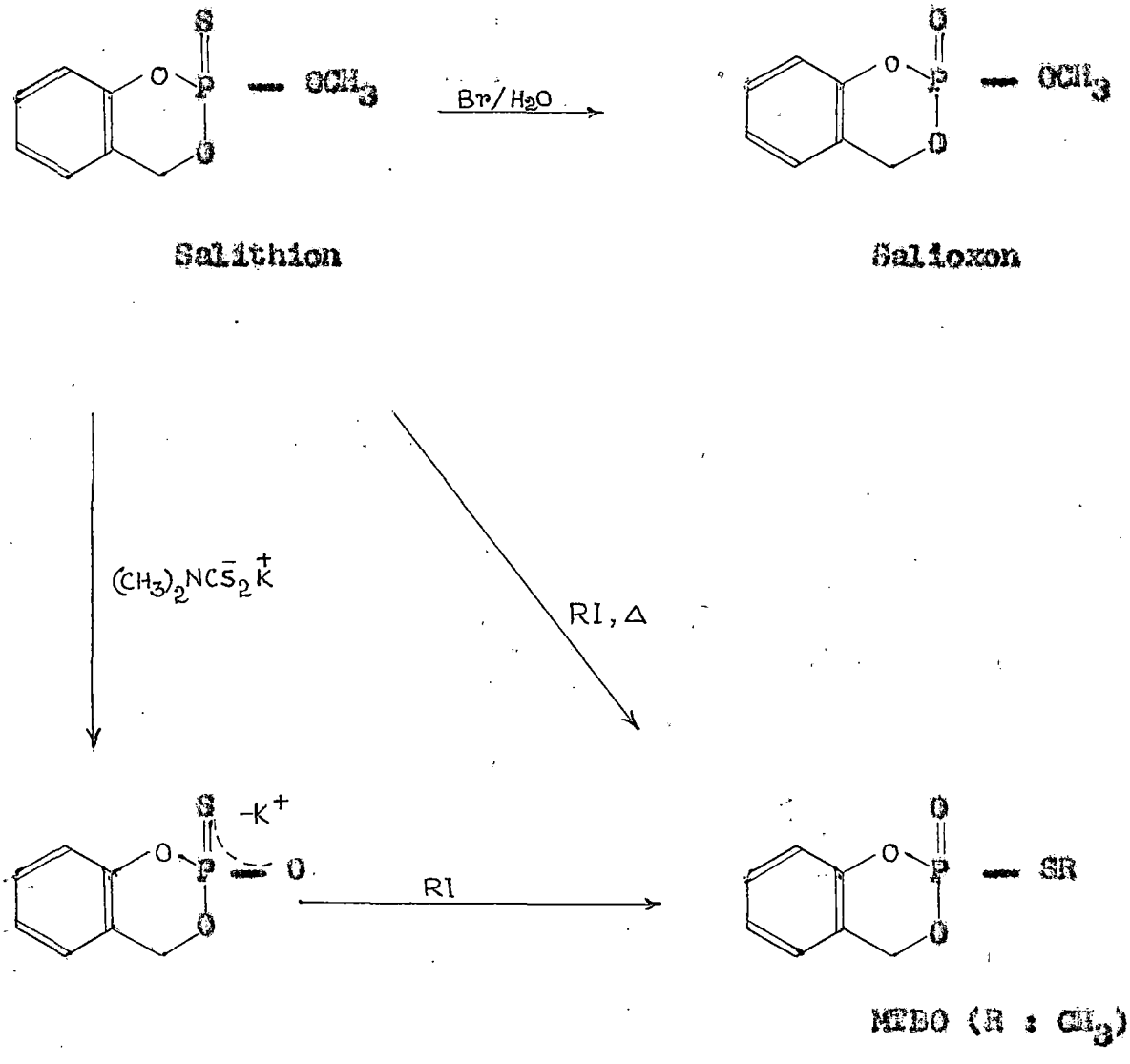


Fig. 5 - Reaction of Salithion.

Salithion is relatively unstable in storage. Some secondary amines, such as carbazole and N-phenyl α-naphthylamine, stabilized the formulation[36]. In a phosphate buffer (pH 7.7), salithion is hydrolysed slowly through opening of the hetero ring

by the P-O (aryl) bond cleavage[5], the hydrolysis rate constant (25°) K = 2.4 x 10^{-4} min^{-1}. The rates of hydrolysis of the corresponding cyclic methylphosphonate, S-methyl phosphorothiolate (the thiolate isomer of salithion, MTBO), methyl phosphate (salioxon), and N-methyl phosphoramidate are, respectively 30, 60, 6 and 0.6 times greater than that of salithion. Salithion is completely hydrolyzed by heating at 100°C for 5 minutes with N/6 sodium hydroxide to yield saligenin. The hydrolysis of salithion is shown in Fig. 6.

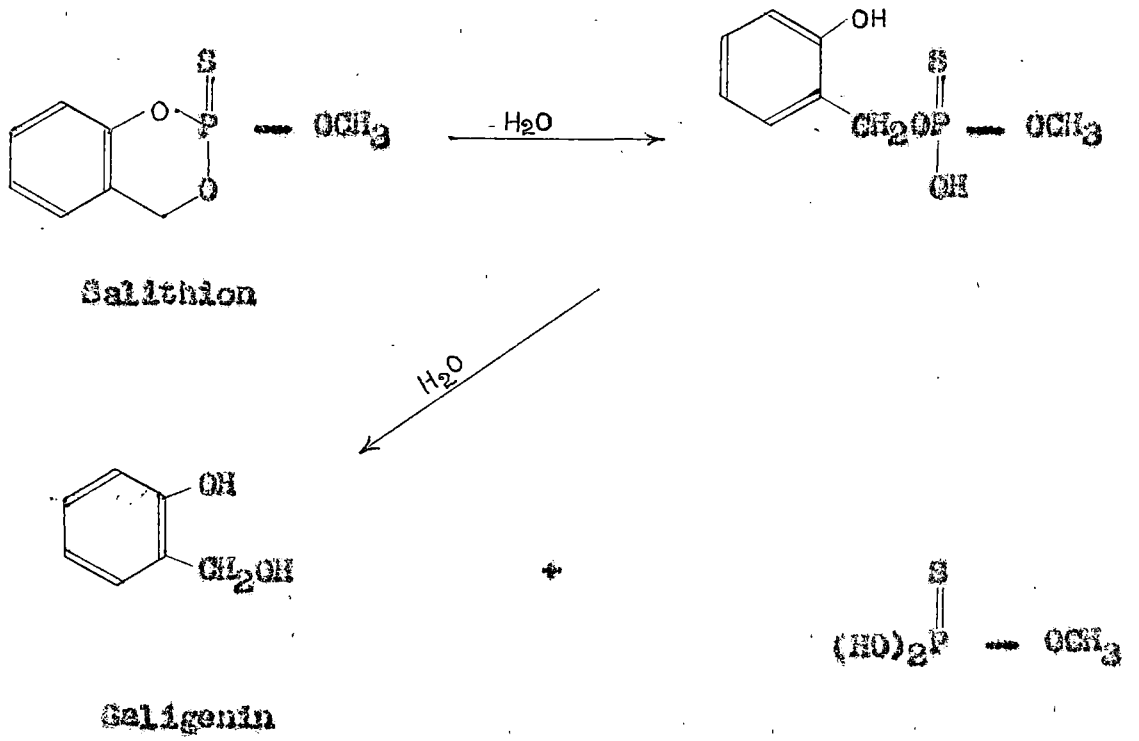


Fig. 6. Hydrolysis of Salithion.

Salithion is a wide-spectrum insecticide for use in orchards and vegetable gardens. It is particularly effective to control lepidopteran larvae, melaybugs, aphids and mites. It manifests the insecticidal action not only as contact and stomach poisons but also as a fumigant[37].

Salithion ^{32}P applied topically to houseflies rapidly absorbs into the body (42% after one hour). The major part was degraded in the body and about 4% of applied or 10% of absorbed salithion remains as salithion and salioxon for 24 hours. On the other hand, salithion ^{32}P administered orally to mice was rapidly degraded and excreted. After one hour, 78% of administered salithion was hydrolysed in the body. After 3 hour, 58.7% excreted and only 2.4% remained in the body[38].

Mihara et al[39] investigated the metabolism of salithion in rats and plants using ^{14}C-labelled compound. When rats were treated orally with salithion-4-^{14}C at the dosage of 9 mg/kg, 72, 82 and 91% of the radioactivity were excreted respectively after 12, 24 and 48 hours. The radionutograms of whole body showed a trace of radioactivity remained only in liver, kidney and lung after 24 hours. The radiocarbon was completely excreted during one week. This was also the case, even though the dosage was increased or repeated several times. No radioactive carbon dioxide was expired.

The metabolic pathways of salithion in rats and plants have been studied [1]. These are summarized [5] in Fig. 7.

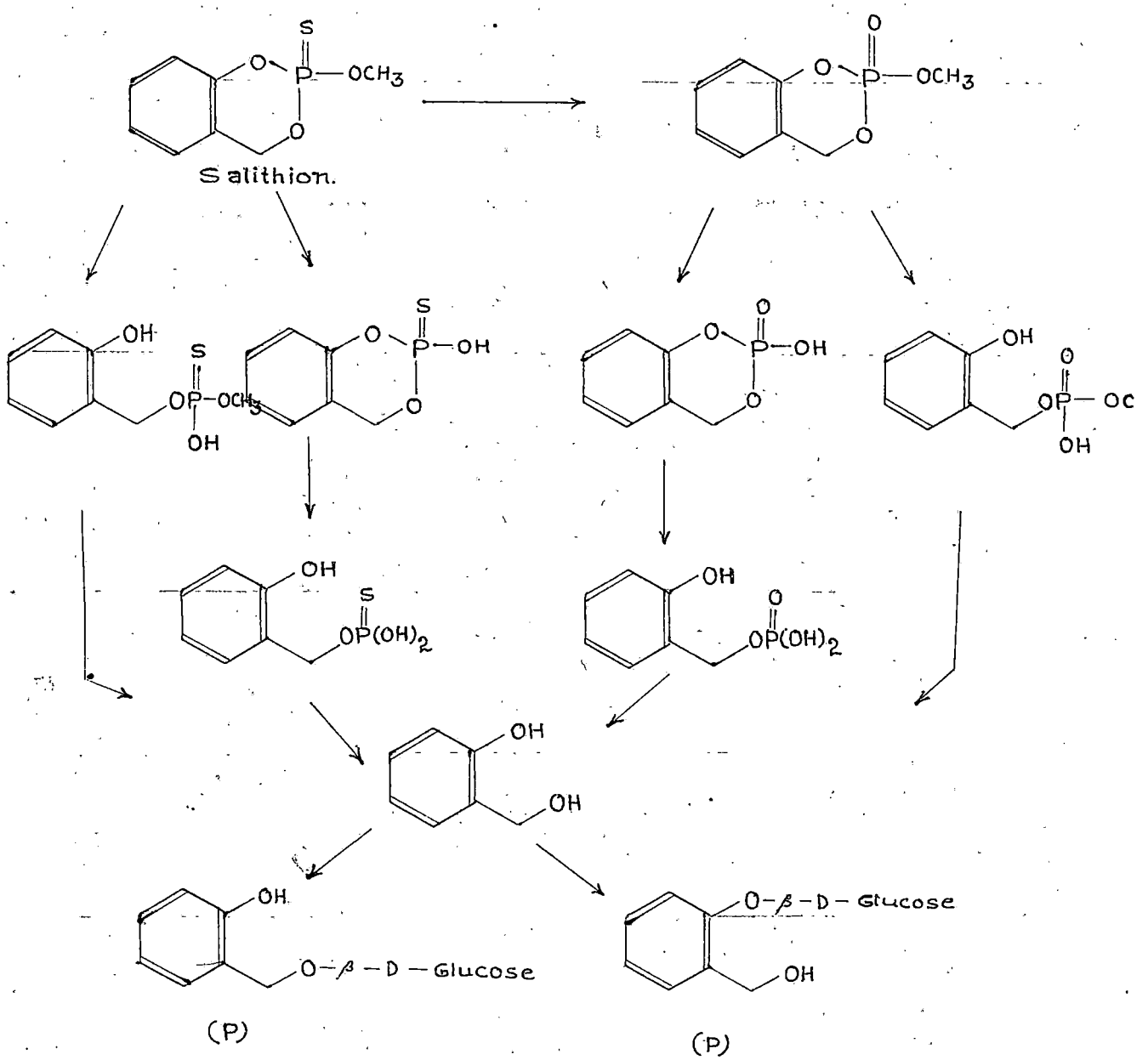


Fig. 7. Metabolic pathways of salithion in rats and plants (P-denotes the metabolite found in plant only).

It was shown that the biodegradation of salithion and salioxon proceeded through demethylation and ring-opening by P-O-aryl-bond cleavage. The metabolic pathways in plants only differed from those in glycoside conjugation of saligenin. About 10% of salithion absorbed was found in the bean plant whose roots had been soaked in the nutrient solution for 10 days. When salithion was applied on the leaves about 10% was absorbed into the tissues and slightly translocated into other leaves. Most of salithion applied on the leaves was vaporised. Vaporization of salithion from a nutrient solution was also observed. This causes a fumigant action to kill insects on the plants.

The acute toxicity study of salithion for mammals was performed by Oshima[37]. The oral LD_{50} for mice is 91.3 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 rats is 152 mg/kg. The acute oral LD_{50} for hen is 110 mg/kg.

Studies on the chronic toxicity of salithion was performed[5]. Rats 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 men and women administered orally 0.02 mg/kg/day of salithion for 21 days followed by 0.05 mg/kg/day for 14 days, no effect was found in

the activity of erythrocyte acetylcholinesterase. No effect was observed in fertility of rats for three generations fed with 10 ppm salithion. Carsinogenicity was not observed.

6. Chemical Hydrolysis of Saligenin Cyclic Phosphorus Esters.

The catalytic hydrolysis of saligenin cyclic phosphorus esters by phosphate ion has been reported[28b]. The chemical reactivity of the cyclic phosphates with nucleophilic agents should be influenced by the electronic character of the substituent. The relative reaction rate may be theoretically predicted. The reaction rate for the following derivatives follows the order : butoxy < propoxy < ethoxy < methoxy < phenoxy < phenyl. Again in another series, the relative reaction rate is in the order NR_2 < NHR < OR < R. These have been supported experimentally[40,42,28a].

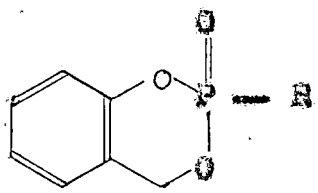
Saligenin cyclic phosphates were hydrolysed in pH 7.7 phosphate buffer to give O-hydroxy benzyl hydrogen phosphonates which gave chloroform-insoluble dyes with aminoantipyrine[6]. This is a characteristic reaction of cyclic phosphorus ester of saligenin. The first order hydrolysis constents (K_{hyd}) are given in Table-III. Phosphonic acid esters are generally more unstable than phosphoric acid esters. The rate constants of alkyl phosphonates are about 10 times larger than those of corresponding phosphates. There is a smaller difference between aromatic derivatives. Ethyl phosphonate is much stable than methyl

phosphonate. The presence of unsaturation or chlorine makes the esters unstable.

It is interesting that, in the series of alkyl derivatives there is a relationship between rate constant and insecticidal activity (LD_{50}). [Table - III and Table - IV]. The higher the reactivity is, 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.

Table - III

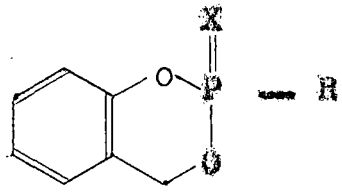
Hydrolysis rate constants of some saligenin cyclic phosphorus esters in phosphate buffer (pH 7.7) at 25°C.



R	K_{hyd} min^{-1}	R	K_{hyd} min^{-1}
CH_3	2.22×10^{-2}	OCH_3	1.42×10^{-3}
C_2H_5	4.25×10^{-3}	OC_2H_5	5.04×10^{-4}
$CH = CH_2$	1.39×10^{-2}	-	-
CH_2Cl	2.00×10^{-1}	-	-
CH_2CH_2Cl	1.41×10^{-2}	OCH_2CH_2Cl	2.58×10^{-3}
C_6H_5	1.28×10^{-2}	OC_6H_5	6.30×10^{-3}
NHC_6H_5	2.40×10^{-4}	$OC_3H_7(n)$	3.79×10^{-4}
$NHCH_3$	1.54×10^{-4}	$OC_4H_9(n)$	3.29×10^{-4}
$N(CH_3)_2$	Negligibly small.		

Table-IV

The relationship between rate-constant and insecticidal activity of some saligenin cyclic phosphorus esters.



X	R	K_{hyd} min^{-1}	LD_{50} (μ g/female housefly)
O	CH_3	2.22×10^{-2}	0.19
O	C_2H_5	4.25×10^{-3}	0.17
O	i-C_3H_7	-	0.33
O	Sec-C_4H_9	-	7.0
O	t-C_4H_9	-	>10(0%)
O	$CH : CH_2$	1.39×10^{-2}	0.68
O	CH_2Cl	2×10^{-1}	<10 (60%)
O	CH_2CH_2Cl	1.41×10^{-2}	>0.99
O	C_6H_5	1.28×10^{-2}	>10 (10%)
O	OCH_3	1.42×10^{-3}	0.035
O	OC_2H_5	5.04×10^{-3}	0.33

Contd.....

Table-IV (Contd.....)

X	R	K_{hyd} min^{-1}	LD_{50} (μg/female housefly)
O	O-n-C_3H_7	3.79×10^{-4}	7.1
O	O-n-C_4H_9	3.29×10^{-4}	10 (40%)
O	O-CH_2CH_2Cl	2.58×10^{-3}	0.49
O	O-C_6H_5	6.30×10^{-3}	10 (3)
O	$NHCH_3$	1.54×10^{-4}	0.05
O	$N(CH_3)_2$	Negligibly small	0.40
O	NHC_6H_5	2.40×10^{-4}	10 (5%)

7. Biological Activities and Structural Relationship.

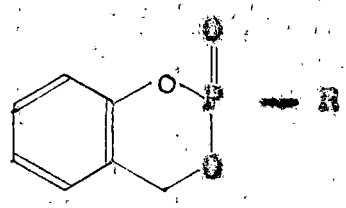
The soligenin cyclic phosphate esters have interesting biological activities. Some of them are neurotoxic, causing ataxia in higher animals. Others do not show such harmful activity but do have high insecticidal activity, systemic activity and fungicidal activity. Their biological activities include 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-V. All aryl soligenin cyclic phosphates manifest a high delayed neurotoxicity to cause ataxia in hens and high synergistic activity with

malathion (9,41). The arylphosphonate analogs showed similar biological activities but less in the neurotoxicity. On the other, the corresponding cyclic esters having a small alkyl group on phosphorus, i.e. 2-alkyl, 2-alkoxy-, and 2-alkylamino-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 (9). The interesting feature is that, the alkyl derivatives reveal high insecticidal activity, whereas, the aryl cyclic esters do not (8).

The specificity of saligenin cyclic phosphates in the biological activity relates to their selectivity in enzyme inhibition. These phosphates inhibit various serine enzyme by phosphorylation, producing probably salicyloxyphosphinylenzymes (14,4) (VI)(Fig.8). This involves by opening of the cyclic ester structure at the P-O aryl bond. When the size of the exocyclic substituent R in (V) increases, the ester becomes a more selective inhibitor of aliesterase (42). Whereas, it becomes a more selective inhibitor of cholinesterase when the substituent is small. Thus the O-tolyl derivative (M), for example, is 130 times more selective to inhibit aliesterase than cholinesterase.

Table-V

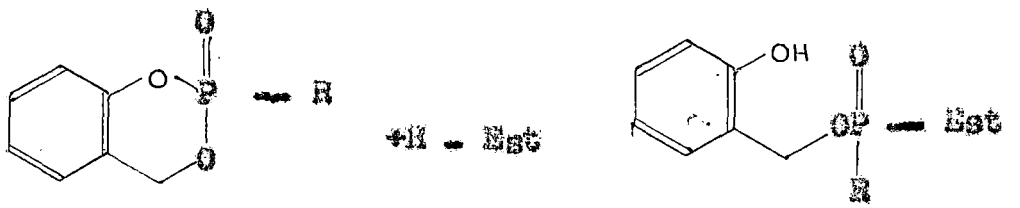
Effects of the exocyclic substituent (R) on biological activities of saligenin cyclic phosphate (V)



(V)

R	Delayed neurotoxicity MAD[a]	Synergism with malathion cotoxicity co-efficient		Insecticidal activity LD^{c}_{50}
		Mice	Housefliesb	
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 application to houseflies in μg/fly.
d. Percentage mortality at 10 μg/fly.
e. No ataxia signs evident with any sublethal dosages.



(V) (VI)

Fig. 8 Reaction of Saligenin cyclic phosphates with esterase (H-Est)

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 merely for the chemical reactivity of the phosphorus atom towards nucleophiles including the active site of esterase and is never requirement for the delayed neurotoxicity. As for example, although Tri-o-ethyl phenyl phosphate (TPEP) has the neurotoxicity[13], is unable to be transformed into a cyclic ester structure.

Johnson found "neurotoxic esterase" in nervous tissues which is specifically sensitive *in vivo* to neurotoxic organophosphorus esters[43]. The esterase is unlike acetylcholinesterase but similar to chymotrypsin and trypsin in the structure -activity relationship of inhibitors[44].

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.

With this brief background of the relation of chemical structure to the biological activity of saligenin cyclic phosphorus esters, we will now discuss the specific activities such as insecticidal, synergistic, antiesterase, nematocidal, fungicidal etc.

7. (a) Insecticidal Activity (Table VI - XIV):

Various series of cyclic esters of saligenin derived from pentavalent phosphorus acids have been examined for insecticidal activity. They include phosphates[19], phosphoramidates[23], phosphorothiolates[26], phosphonates[28] and their thiono analogs (Table VI - XIV). The insecticidal activity of the esters appears to relate with the size of the exocyclic substituent on the phosphorus atom (Table-VI).

The cyclic esters in any series having an aryl group as an exocyclic substituent on the phosphorus atom have either poor or no insecticidal activity. In all the series, methyl derivatives are much more active than higher alkyl derivatives, except for phosphonate series (Table - XI) in which ethyl

derivatives are more active than methyl derivatives. N, N-dialkyl phosphoramidates are much less active than mono-alkyl derivatives (Table-XIII). Thus saligenin cyclic methyl phosphate (Table-X), methyl phosphorothionate (Table-IX), N-methyl phosphoramidate, N-methyl phosphoramidothionate (Table-XIII), methyl phosphonothiolate and ethyl phosphonothiolate (Table-XI) are potent insecticides. It is interesting to note that the exocyclic substituent of the most active cyclic phosphorus ester in each series (OCH_3, SCH_3, $NHCH_3$, CH_3CH_2) differs from each other in electronic characteristics, but resembles in steric property such as the distance (about 2.9 Å) between phosphorus and carbon atom in the P-X-C function, if the bond angle of divalent sulfur is near 90° rather than 109.5°.

Furthermore, the introduction of any type of substituent at any position of the benzene ring and on the carbon atom of the hetero ring decreases the activity (29) (Table-VII). Thus, the simplest phosphorothionate, salithion, is the most effective insecticide in the whole series of saligenin cyclic phosphorus esters.

An outstanding contrast is observed in the effect of para-substitution between the salithion series and parathion series. Table (VIII) shows the effect of the electronic character of the substituent in the para-position of the phenolic ester group upon the insecticidal activity. Any substituents, either electron-withdrawing group or electron-releasing group decreases the

insecticidal activity. Table-VIII shows that the insecticidal activity of diethylphenyl phosphorothionates (II) is progressively increased by p-substitution of the phenyl ring in the increasing order of the electron withdrawing ability of the substituent, whereas neither electron withdrawing nor electron releasing group increases the activity of salithion (VIII). The P-O-C aryl bond of the hetero ring of saligenin cyclic phosphorus esters appear to be active enough to phosphorylate cholinesterase to kill insects without any electron-withdrawing group.

The systematic activity of some saligenin cyclic phosphoramidates against rice stem-borers and green rice leafhoppers on rice plants are observed (Table-XIII). Methyl phosphoramidate is more active than Schradan but less active than thimet against rice leafhoppers. Against rice stem-borers cyclic N-methyl phosphoramidothionate is superior to lindane and Diazinon. Salithion also shows more or less systemic activity against army worm and mite. No systemic activity has been observed in other compounds.

7.(b) Nematocidal Activity (Table XI and XIII, page-84 & 85):

Some saligenin phosphonothionates, phosphoramidates and phosphoramidothionates show nematocidal activity. Phosphoramidates and phosphoramidothionates are very effective to

kill nematodes (Table - XIII)[8]. N-methyl phosphoramidate is most active in the series of saligenin derivatives against the non-parasitic soil nematode Rhabditis suspended in water[23]. Owing to the instability in water, the cyclic phosphates and phosphonates are almost inactive, but their thiono analogs are effective against Rhabditis (Table XI, XIII).

Some saligenin cyclic aryl phosphonothionates are more effective as nematocides than the cyclic N-methyl phosphoramidate against the rice white tip nematodes, though they have very low insecticidal activity. Cyclic phenyl - and p -tolyl-phosphonothionates are the most effective nematocides in the series. These aryl phosphonothionates exhibit also a high activity against filaria in cotton rats (Litomosoides carinii)[5]. It is interesting to note that these aryl phosphonothionates are poor insecticides, whereas they are more potent to kill nematodes than salithion, suggesting the cholinesterase or other critical target of nematodes may differ in nature from the insect cholinesterase.

The correlation between the structure and the nematocidal activity of phosphoramides and phosphoramidothionates are similar to that in the insecticidal activity for housefly.

7.(c) Fungicidal Activity (Table XIV and XV, Page 88-89):

Salithion has no fungicidal activity. But some sali-genin cyclic phosphorothiolates have fungicidal activity (Table-

XIV). These phosphorothiolate esters, particularly having an S-benzyl ester linkage, have activity to protect the rice plant from rice blast disease caused by the infection of Piricularia oryzae (45). The protective values against Piricularia oryzae of the cyclic phosphorothiolates and related compounds are shown in the Table (XIV & XV). The data of some commercial fungicides including an organophosphorus compound, Kinson (O-ethyl S, S diphenyl phosphorodithioate) are shown in the Table (XIV) for comparison. The methyl-, ethyl-and n-butyl-phosphorothiolates have high fungitoxicity comparable to other commercial fungicides. The normal and isopropyl derivatives are less effective. Saligenin cyclic methyl phosphate and phosphorothionate (salithion) are highly active as insecticide but are almost inactive as fungicide. In the series of dialkyl benzyl esters of phosphorus acids, only S-benzyl phosphorothiolates are highly active as fungicide but the others e.g. phosphates, phosphorothionates and phosphorodithionates are inactive (45).

It is important to note that some cyclic phosphorothiolates have both the high insecticidal as well as fungicidal activity, with only exception in the case of S-benzyl-O-O-diethyl phosphorothiolate (Kitazin) which has weak insecticidal property but is a good fungicide and now used in practice for the control of rice blast disease.

7.(d) Anti - SH Enzyme Activity (Table XV, Page - 89):

The saligenin cyclic phosphorothiolates have high activity to alkylate (salicylate) mercaptans and to inhibit "SH-enzymes" such as yeast alcohol dehydrogenase[31]. The activity seems to be related to fungicidal property but not with the insecticidal activity.

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

The rate of alkylation reaction by the cyclic esters 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 after hydrolysis. Actually, the partial hydrolysate of saligenin cyclic esters react immediately with

mercaptans. The reaction mechanism is shown in Fig. 9.

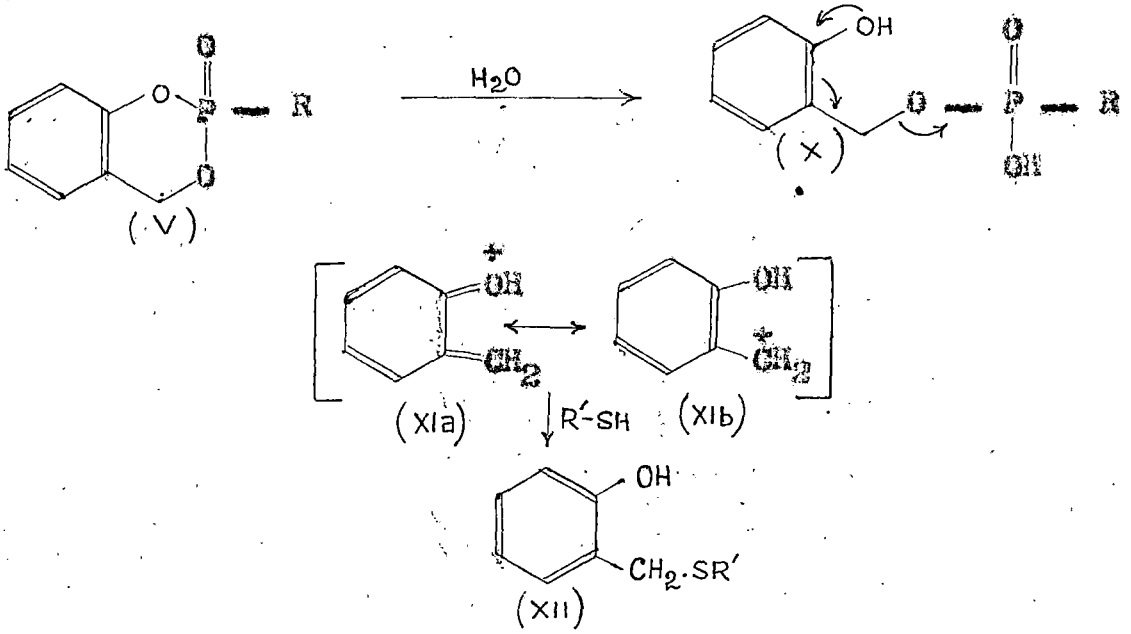


Fig. 9

Saligenin cyclic phosphorothiolates are partially hydrolysed by opening of the heterocyclic P-O-C-aryl bond, more easily than phosphate esters. In Fig. 9, the cyclic ester (V) is hydrolysed by the attack of hydroxide ion to yield salicyl phosphate (X). The electron releasing -OH group of (X) may convert to a carbonium ion (XIb) which may actually react with a SH group to give a thioester (XII).

Cyclic methyl and ethyl phosphorothiolates are much more active in hydrolysis, alkylation and the inhibition of "SH-enzyme" activities than the corresponding cyclic phosphates[31].

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-XV) that there is an interesting correlation among the alkylating activity, the inhibitory activity 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 suggest that high inhibitory activity against "SH-enzymes" may be an important factor for the fungicidal activity of the cyclic phosphorothiolates.

7.(e) Antiesterase Activity (Table-XVI, Page-90):

The relation of chemical structure to biological activities indicates that the specificity in biological activities of the saligenin cyclic phosphorus esters seem to be remarkably influenced by the steric characteristics of the exocyclic substituent on the phosphorus atom. This is evident when compared their specificities in enzyme inhibition (42).

The most insecticidal saligenin cyclic methyl phosphate (salioxon) is the strongest inhibitor of insect cholines-

terase. However, the highly neurotoxic aryl phosphate is a poor inhibitor of cholinesterase, but is a very specific inhibitor of aliesterase[1,42]. The less neurotoxic arylphosphonate occupies an intermediate position. In any series, when the size of the exocyclic 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-XVI). Aryl phosphonates are more specific inhibitors of pseudo-cholinesterase; alkyl phosphates are less specific and aryl phosphates are intermediate.

7.(f) Synergistic Activity (Table - XVII, XVIII and XIX Page 91-94):

Saligenin cyclic aryl phosphates and phosphonates have synergistic activity with malathion against insects and mites, particularly their resistant strain[46].

The joint action of the activity of some saligenin cyclic phosphorus esters with malathion has been examined by Eto et al[41] and compared with some phosphorus esters which are known as the synergists of malathion. Table-XVII shows that the aryl derivatives of saligenin cyclic esters are synergistic with malathion. They increase the toxicity of malathion 2.8 to 3.4 times at a 1:1 mixing ratio. The activities of them are more than propyl paraoxon 2-benzodioxaphosphorin-2-oxide, and 7-methyl-2-phenyl-4H-1,3, 2-benzodioxaphorin-2-oxide are the most synergistic against

susceptible housefly among the tested cyclic esters. Alkyl derivatives of saligenin cyclic phosphorus esters are much less synergistic or even antigonistic.

Synergism of saligenin cyclic phosphorus esters with malathion in a resistant strain of housefly has been tabulated in Table-XVIII. In this case, the synergistic effect of saligenin cyclic phosphorus esters has remarkably been increased. Even the alkyl derivatives act as synergist of malathion. Thus all of present cyclic esters are more active than the other tested organophosphorus synergists. Cyclic phenylphosphonate of methyl saligenin is the most effective synergistic against resistant housefly and increases the toxicity of malathion 14 times.

Synergistic effect on susceptible and resistant strains of green rice leaf hopper has been observed (41) and tabulated in Table (XIX). The toxicity of malathion to the susceptible insects becomes double by the addition of three saligenin cyclic phosphorus esters along with two other cyclic esters. Synergistic effect on resistant leaf hopper also increases by saligenin cyclic phosphorus esters but the values are lower than in the resistant housefly. They enhanced the toxicity of malathion 2.2 to 3.8 times.

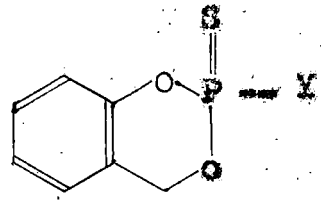
The synergism appears to result primarily from the inhibition of detoxication of malathion. Phosphate action

or esterase action can detoxify the toxicity of malathion. It has been observed for a great number of organophosphorus compounds that the synergism of malathion in mice and the degree of inhibition of ali-esterase *in vivo* are generally related[9]. 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[41].

Eto *et al*[42] have shown that aryl derivatives of saligenin cyclic phosphorus esters are the selective inhibitors of ali-esterase, whereas small alkyl derivatives are not so selective to ali-esterase inhibition. This appears to be responsible for their difference in synergistic properties.

Table - VI

Relation of structure to insecticidal activity (LD_{50} μg/housefly) of (VII)



(VII)

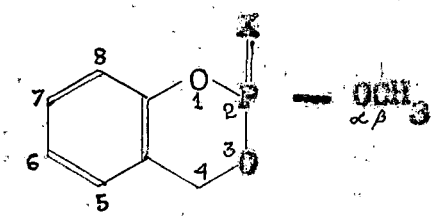
X / R	R		OR		SR		NHR	
	O	S	O	S	O	S	O	S
CH_3	0.13	0.31	0.04	0.05	0.09	0.13	0.05	0.04
C_2H_5	0.17	0.08	0.33	0.03	0.23	0.9	0.66	0.48
n-C_3H_7	0.33[a]	0.09[a]	7.1	-	2.34	2.2	1.50	-
n-C_4H_9	7.05[b]	-	(40)	-	6.30	10	(54)	-
C_6H_5	(0)	0.3	(3)	2.0	2.2	(0)	(5)	-

a = isopropyl, b = Sec.-butyl.

Figures in parentheses are percentage mortality at 10 μg/fly.

Table - VII

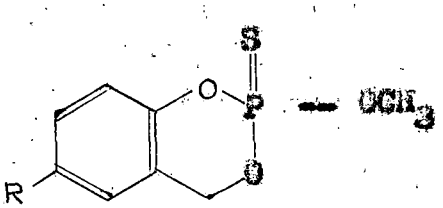
Effect of substituent (R) on insecticidal activity (LD_{50}/µg/house-fly).



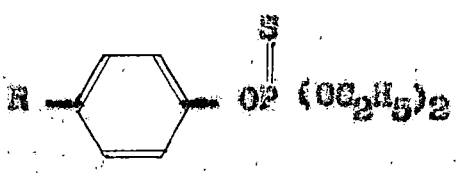
R	X	
	S	O
H	0.06 (Salithion)	0.035 (Salioxon)
4-CH_3	-	3.35
6-CH_3	2.00	0.1
7-CH_3	0.23	0.43
8-CH_3	1.30	2.0
6-Cl	1.75	0.09
8-Cl	0.13	0.23
β -CH_3	0.30	0.33
β -CH_3OCH_2	3.55	0.99
β -Cl	-	2.07

Table - VIII

Effect of P-substitution on insecticidal activity of Salithion (VIII) and parathion (IX) series.



(VIII)



(IX)

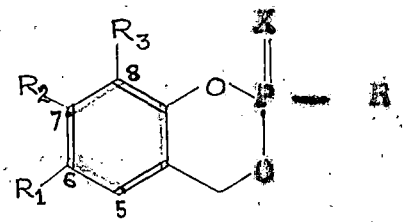
R	σ[a]	Relative insecticidal activity[b]	
		(VIII)	(IX)
OCH_3	-0.268	9.2	0.1
CH_3	-0.170	2.6	0.1
H	0.000	100.0	0.1
C_6H_5	+0.009	12.8	-
Cl	+0.226	3.0	0.33
$COCH_3$	+0.87	2.0	2.5
NO_2	+1.27	1.7	100.0

a = Hammett's substituent constant

b = Percentage of the most active compound in each series.

Table - IX

Insecticidal activity of Ring-substituted Saligenin Cyclic Phosphorus esters (thiono-compounds):



S	R_1 (6)	R_2 (7)	R_3 (8)	R	LD_{50} (μg/housefly)
S	CH_3	H	H	OCH_3	2.0
S	CH_3	H	H	OC_2H_5	>10
S	H	CH_3	H	OCH_3	0.23
S	H	CH_3	H	OC_2H_5	3.0
S	H	CH_3	H	O-n-C_3H_7	7.5
S	H	H	CH_3	OCH_3	1.3
S	H	H	CH_3	OC_2H_5	3.0
S	H	H	CH_3	O-n-C_3H_7	7.5
S	H	H	CH_3	$NHCH_3$	3.6
S	C_6H_5	H	H	OCH_3	0.4
S	C_6H_5	H	H	OC_2H_5	0.6
S	C_6H_5	H	H	O-n-C_3H_7	1.0

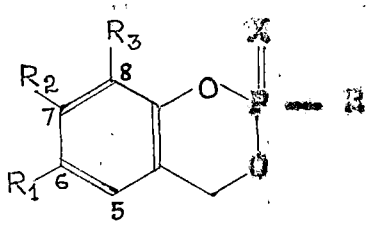
Contd.....

Table - XX (Contd.....)

X	R_1	R_2	R_3	R	LD_{50} (μ g/housefly)
S	OCH_3	H	H	OCH_3	0.55
S	$COCH_3$	H	H	OCH_3	2.6
S	Cl	H	H	OCH_3	1.75
S	Cl	H	H	$NHCH_3$	0.06
S	Cl	H	H	SCH_3	-
S	H	H	Cl	OCH_3	0.13
S	H	H	Cl	$NHCH_3$	0.09
S	H	H	Cl	SCH_3	-
S	Cl	H	C_6H_5	OCH_3	1.2
S	Cl	H	C_6H_5	OC_2H_5	3.0
S	Cl	H	C_6H_5	O-n-C_3H_7	>10
S	NO_2	H	H	OCH_3	3.0
S	C_6H_5	H	Cl	OCH_3	-
S	C_6H_5	H	Cl	OC_2H_5	-
S	C_6H_5	H	Cl	O-n-C_3H_7	-
S	Cl	H	Cl	OCH_3	0.3
S	Cl	H	Cl	OC_2H_5	4.0
S	Cl	H	Cl	$NHCH_3$	3.0

Table - I

Insecticidal activity of ring-substituted saligenin cyclic phosphorus esters (oxon-compounds).



X	R_1	R_2	R_3	R	LD_{50} (μg/housefly)
O	CH_3	H	H	OCH_3	0.1
O	CH_3	H	H	OC_2H_5	0.4
O	H	CH_3	H	OCH_3	0.43
O	H	CH_3	H	OC_2H_5	0.70
O	H	CH_3	H	O-n-C_3H_7	7.2
O	H	CH_3	H	C_6H_5	>10
O	H	CH_3	H	$NHCH_3$	0.14
O	H	H	CH_3	OCH_3	2.0
O	H	H	CH_3	OC_2H_5	2.1
O	H	H	CH_3	OC_6H_5	>10
O	Cl	H	H	OCH_3	0.09

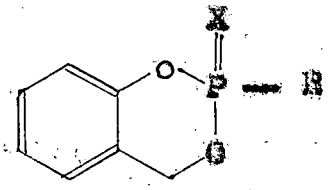
Contd.....

Table - X (Contd.....)

X	R_1	R_2	R_3	R	LD_{50} (μg/housefly)
O	Cl	H	H	OC_2H_5	0.13
O	Cl	H	H	O-n-C_3H_7	0.70
O	Cl	H	H	O-n-C_4H_9	2.5
O	Cl	H	H	OC_6H_5	>10
O	Cl	H	H	$NHCH_3$	0.09
O	H	H	Cl	OCH_3	0.23
O	H	H	Cl	OC_2H_5	0.15
O	H	H	Cl	O-n-C_3H_7	0.30
O	H	H	Cl	O-i-C_3H_7	-
O	H	H	Cl	OC_6H_5	>10
O	H	H	Cl	$NHCH_3$	0.30

Table - XI

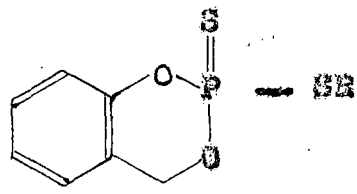
Saligenin cyclic phosphonates and phosphonothionates : toxicity, insecticidal and nematocidal activity.



X	R	LD_{50} µg/fly (Housefly)	LD_{50} mg/kg (House oral)	LD_{100} ppm (nematodes-Rhabditis)	
O	CH_3	0.19	25-50		
O	C_2H_5	0.17	25-50		
O	i-C_3H_7	0.33	-		
O	Sec-C_4H_9	7.0	-		
O	t-C_4H_9	>10(0%)	-		
O	$CH = CH_2$	0.68	>100		
O	CH_2Cl	<10(60%)	25-50		
O	CH_2CH_2Cl	0.99	50-75		
O	C_6H_5	>10(0%)	-		
S	CH_3	0.31	5-10		25
S	C_2H_5	0.08	5-10		25
S	i-C_3H_7	0.09	-		-
S	CH_2Cl	1.14	25-50		25
S	C_6H_5	0.30	-		-

Table - XII

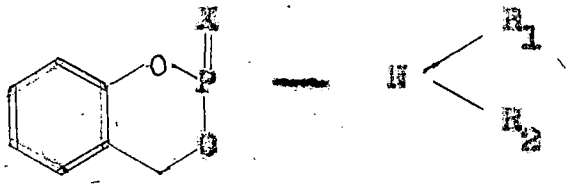
Insecticidal activity of Saligenin Cyclic Phosphoro-dithionates.



R	LD_{50} (µg/fly)
CH_3	0.18
C_2H_5	9
n-C_3H_7	2.2
i-C_3H_7	5
$C_3H_5(CH_2-CH = CH_2)$	1.7
n-C_4H_9	10
C_6H_5	> 10(0%)

Table - XIII

Saligenin cyclic phosphoramidates and phosphoramidothionates : Insecticidal activity, toxicity and nematocidal activity:



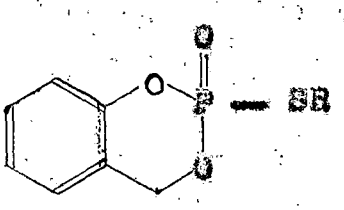
X	$N\begin{matrix}R_1\\R_2\end{matrix}$	LD_{50} (μg/female House fly)	LD_{50} (μg/mg Rice stemborer)	LD_{50} μg/gm (Green rice leaf-hopper)	LD_{50} mg/kg (House)	Minimum conc. (ppm) to kill 100% nematodes-Rhabditis
O	NHMe	0.05	2.84	0.04	6-7.5	< 10
O	NHEt	0.60	22.20	3.50	30-50	10-25
O	NH-n-Pr	1.50	33.60	33.0	> 50	25-50
O	NH-i-Pr	3.44	103.34	> 350	> 50	50-100
O	NH-n-Bu	< 10(54%)	> 214	> 400	> 50	25-50
O	NH-Ph	> 10(6%)	-	-	-	-
O	$N(Me)_2$	0.3	13.80	4.0	-	> 200(10%)

Table - XIII

X	$N\begin{matrix}R_1\\R_2\end{matrix}$	LD_{50} (µg/female House fly)	LD_{50} µg/gm (Rice stem-borer)	LD_{50} µg/gm (Green rice leaf-hopper)	LD_{50} mg/kg (Mouse)	Minimum conc. (ppm) to kill 100% nemato-des-Rhabditis
O	$N(Me)_2$	0.3	13.80	4.0	-	200 (10%)
O	$N(Et)_2$	>10(0%)	167.61	34.10	>50	100-150
S	NHMe	0.044	4.84	4.1	20-30	25-50
S	NH.Et	0.48	36.25	-	-	-
S	$N(Me)_2$	0.33	-	-	-	50-100
S	$N(Et)_2$	0.63	-	-	-	>200(30%)
S	OMe (Salithion)	0.05	1.13	30.6	88	-
O	OMe (Sallioxon)	0.035	2.16	1.8	52	-
Parathion		0.040	3.43	3.6	5-7	-
Malathion		0.060	-	0.8	347	-
D-D mixture (mixture of 1,3-dichloropropane and 1,2-dichloropropane)		-	-	-	-	>800(85%)

Table - XIV

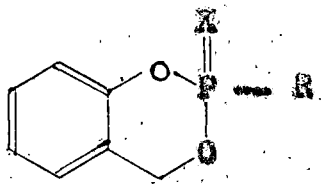
Insecticidal and fungicidal activity of saligenin cyclic phosphorothiolates:



R	LD_{50} μg/gm (oriental housefly)	Protective value % against Piricularia oryzae				Therapeutic value(%) to P.oryzae at 200 ppm
		200 ppm	100 ppm	50 ppm	25 ppm	
CH_3(MEBO)	3.00	100	100	100	84.8	7.1
C_2H_5	11.21	100	93.7	92.5	61.6	100
n-C_3H_7	94.50	100	57.1	34	-	-
i-C_3H_7	17.23	-	68.7	34.4	-	-
n-C_4H_9	211.8	100	91.7	93.3	75.6	97.6
C_6H_5	73.61	50.2	-	-	-	-
Salithion	1.60	52(at 600 ppm)	-	-	-	-
Hinosan	-	100	-	86.2	-	95.2 (at 250 ppm)
Blasticidins	-	-	-	88.3	-	97.6
Pentachlorobenzyl alcohol	-	98.8	98.8	93.5	-	0

Table - XV

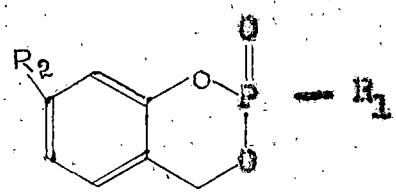
Chemical, Biological and Anti-Fungal activities of some saligenin cyclic phosphates and their thio analogs.



X	R	Hydrolysis %	Cysteine reacted %	I_{50} yeast alcohol dehydrogenase ($M \times 10^{-6}$)	Protective value against *Piricularia oryzae* % 50 ppm	600 ppm
O	SCH_3	66	55	4.5	100	-
O	SC_2H_5	81	60	4.4	93	-
O	OC_6H_5	55	45	6.8	-	-
O	OCH_3	17	10	62	-	65
S	OCH_3	6	5	100	-	52

Table - XVI

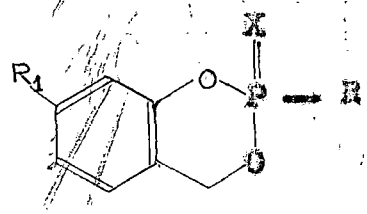
The Inhibition of Housefly, Human Blood and Horse Serum-Esterases by some Saligenin Cyclic Phosphorus Compounds.



R_1	R_2	Housefly $I_{50} \times 10^8$(M)		Human blood $I_{50} \times 10^8$(M)		Horse plasma $I_{50} \times 10^8$(M)	
		ChE	AliE	P-ChE	t-ChE	AliE	Malathio-nase
OCH_3	H (Saliloxon)	7.6	8.4	1.8	17.0	230	620
OC_2H_5	H	13.2	2.1	1.6	25.0	240	-
O-n-C_3H_7	H	50.7	3.0	-	-	-	-
O-n-C_4H_9	H	37.5	2.3	-	-	-	-
OC_6H_5	H	-	-	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 - XVII

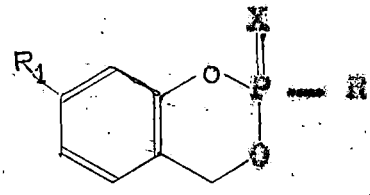
Joint action of some saligenin cyclic phosphorus esters and some other phosphoric esters with malathion against susceptible house flies.



X	R_1	R	LD_{50} µg/fly alone	LD_{50} µg/fly with malathion 1:1	Cotoxicity co-efficient.
Malathion			0.46		
O	H	OMe	0.02	0.06	0.6
O	H	OEt	0.16	0.14	1.7
S	H	OEt	0.11	0.22	0.8
O	H	OPh	c.10(30%)	0.38	2.3
O	H	O-o-Tol	c.10(40%)	0.26	3.4
O	H	Ph	c.10(60%)	0.36	2.5
O	Me	Ph	c.10(70%)	0.26	3.4
TOCP			>10(0%)	0.90	1.0
Dibrom			0.03	0.008	7.1
Propyl paraxon			0.10	0.11	1.5
Isopropyl paraoxon			0.38	0.06	4.9

Table - XVIII

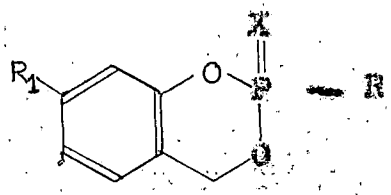
Synergistic effect of saligenin cyclic phosphorus esters with malathion against resistant house flies and comparison with other phosphate synergists.



X	R_1	R	LD_{50} µg/fly alone	LD_{50} µg/fly with malathion 1:1	Cotoxicity Co-efficient
Malathion			2.54		
O	H	OMe	0.15	0.06	4.7
O	H	OEt	0.40	0.22	3.1
S	H	OEt	0.20	0.10	3.6
O	H	OPh	>10(10%)	0.55	9.2
O	H	O-o-Tol	>10(10%)	0.65	7.8
O	H	Ph	>10(25%)	0.57	8.0
O	Me	Ph	c.10(40%)	0.29	14.0
TOCP			>10(10%)	3.44	1.5
Dibrom			0.07	0.07	2.0
Propyl paraoxon			0.73	0.46	2.5
Isopropyl paraoxon			0.43	0.36	2.2

Table- XIX

Synergistic effect of saligenin cyclic phosphorus esters with malathion against susceptible and resistant green rice leafhopper.



X	R_1	R	LD_{50} (μg/susceptible g.r. leaf-hopper)		Cotoxicity Co-efficient	LD_{50} (μg/resistant g.r. leaf-hopper)		Cotoxicity Co-efficient
			alone	with malathion 1:1		alone	with malathion 1:1	
Malathion			0.003			0.021		
O	H	OMe	0.008	0.004	1.1	0.010	0.006	2.3
O	H	OEt	0.069	0.003	1.9	0.066	0.010	3.2
S	H	OEt	1.892	0.005	1.2	>2	0.019	2.2
O	H	OPh	0.240	0.003	2.0			
O	H	O-o-Tol	0.464	0.008	0.8	(0.0167)	0.015	2.2
O	H	Ph	0.218	0.005	1.2			

Table - XIX (Contd.....)

X	R_1	R	LD_{50} (µg/susceptible g.r. leaf-hopper)		Cotoxicity Co-efficient	LD_{50} (µg/resistant g.r. leaf-hopper).		Cotoxicity Co-efficient.
			alone	with malathion 1:1		alone	with malathion 1:1	
O	Me	Ph	3.120	0.003	2.0	>3	0.011	3.8
TOCP			>10	0.006	1.2	>(10)	(0.083)	1.1
Dibrom			0.208	0.005	1.2	0.533	(0.069)	1.3
Propyl paraoxon			0.006	0.002	2.0	-	-	-
Isopropyl paraoxon			0.211	0.003	2.0	-	-	-

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