IIrreversible Inhibitors

AChE and BuChE

↓ inhibited irreversibly by

phosphate esters group

↓

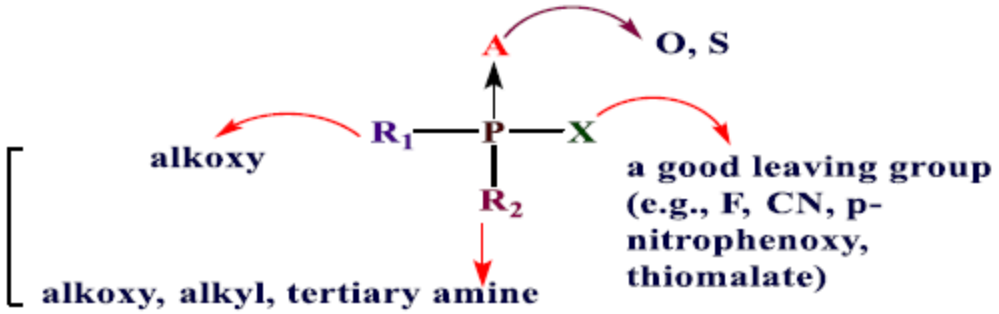
highly toxic compounds (LD50 for humans is 0.1 to 0.001 mg/kg) → Nerve poisons

↓ are used in

warfare | bioterrorism | as agricultural insecticides

↓

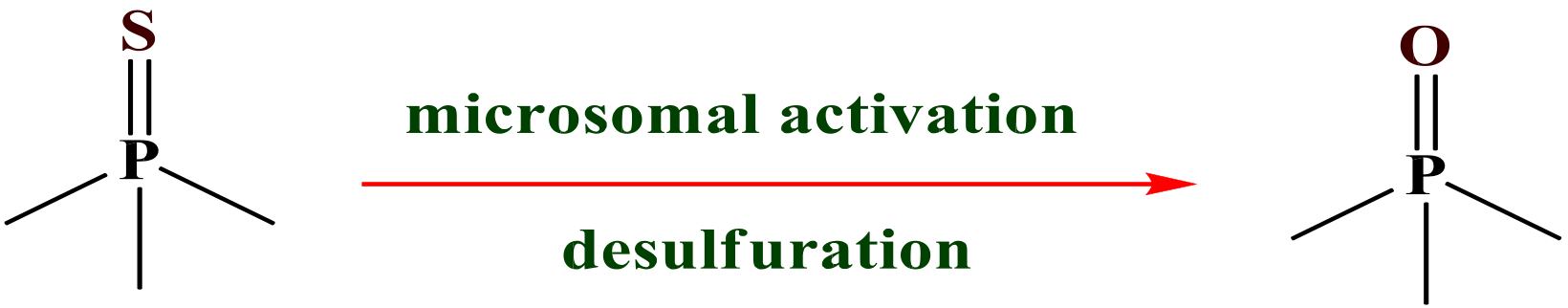
They permit ACh to accumulate at nerve endings and exacerbate ACh-like actions
The compounds belong to a class of organophosphorous esters. A general formula for such compounds as follows:



The R moiety imparts lipophilicity to the molecule and contributes to its absorption through the skin

When A is other than oxygen, biological activation is required before the compound becomes effective as an inhibitor of cholinesterases.

Phosphorothionates [R1R2P(S)X] have much poorer electrophilic character than their oxygen analogs and are much weaker hydrogen bond-forming molecules because of the sulfur atom. Their anticholinesterase activity is 105-fold weaker than their oxygen analogs.



Inhibition of AChE by organophosphorous compounds takes place in two steps.

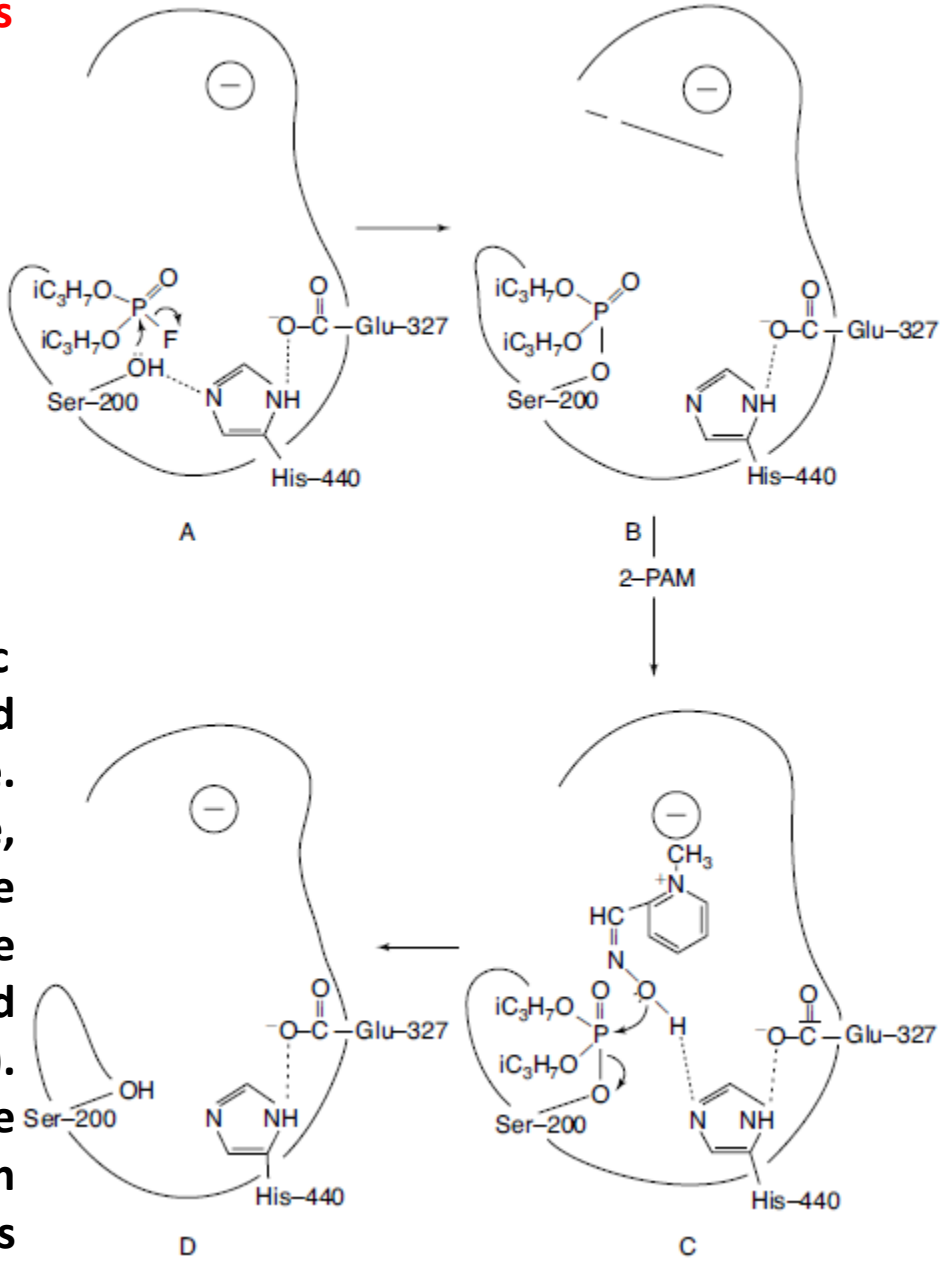
-1Association of enzyme and inhibitor.

-2The phosphorylation step.

completely analogous to acylation by the substrate (Fig. 17.16). Stereospecificity is mainly caused by interactions of enzyme and inhibitor at the esteratic site.

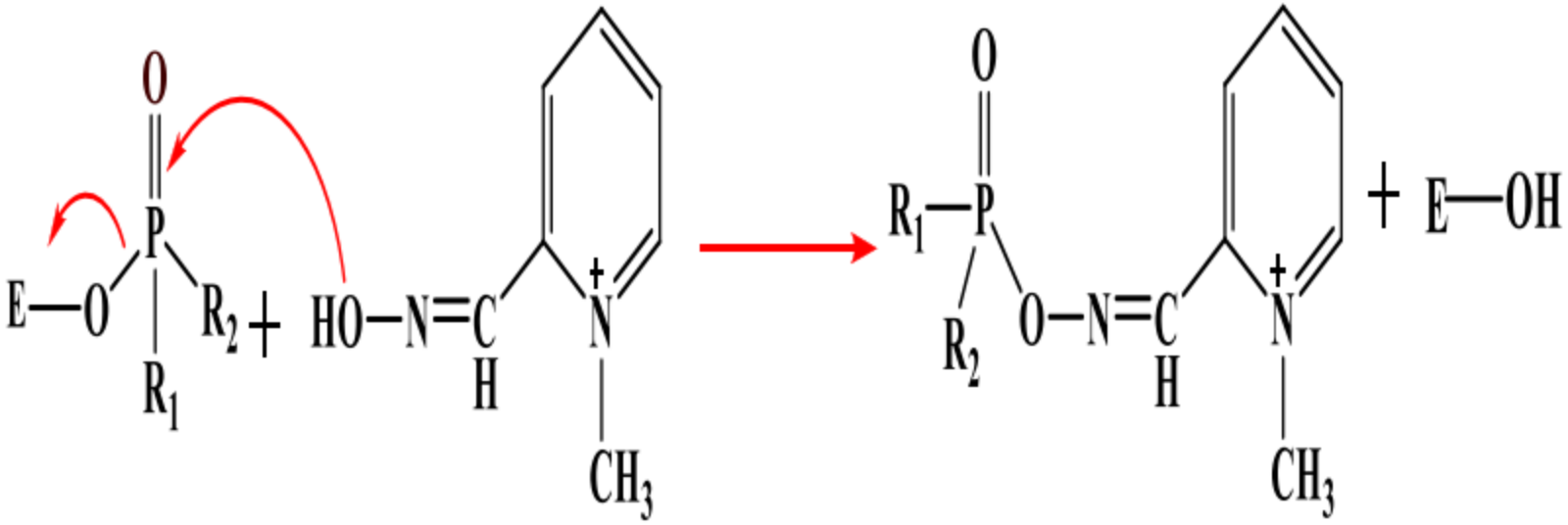
The serine residue at the esteratic site forms a stable phosphoryl ester with the organophosphorous inhibitors.

Although insecticides and nerve gases are irreversible inhibitors of cholinesterases by forming a phosphorylated serine at the esteratic site of the enzyme, it is possible to reactivate the enzyme if action is taken soon after exposure to these poisons.

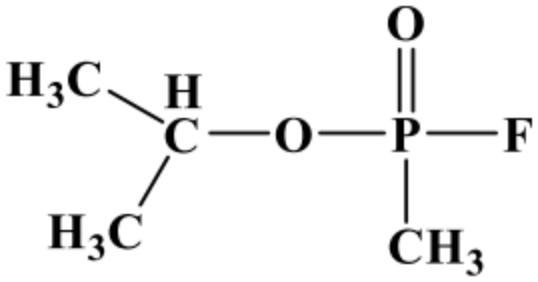


Several compounds can provide a nucleophilic attack on the phosphorylated enzyme and cause regeneration of the free enzyme. Substances such as choline, hydroxylamine, and hydroxamic acid have led to the development of more effective cholinesterase reactivators, such as nicotinic hydroxamic acid and pyridine-2-aldoxime methiodide (2-PAM). A proposed mode of action for the reactivation of cholinesterase that has been inactivated by isoflurophate by 2-PAM is shown in Figure

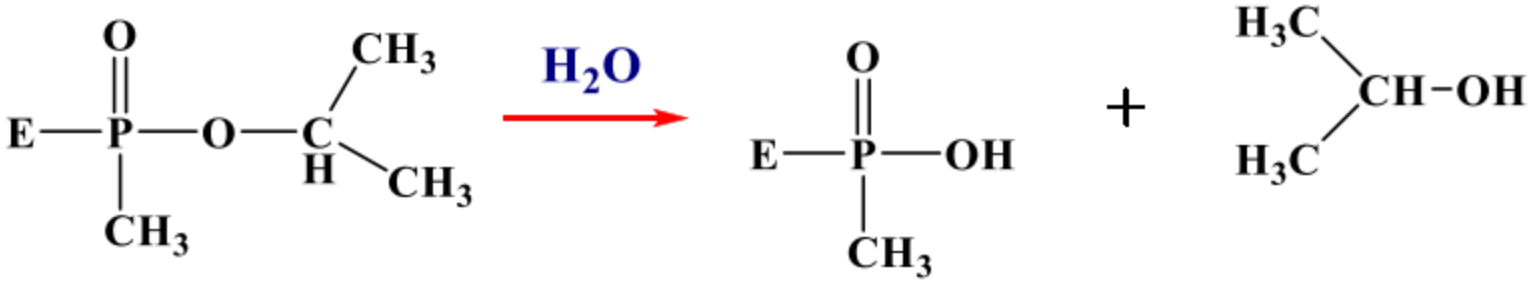

E—OH
O
P
R1
R2
X
E—O
R2
Phosphorylated serine


O
P
E—O
R1
R2
HO—N=C
H
N+
CH3
R1—P
O—N=C
+ E—OH

sarin



Sarin



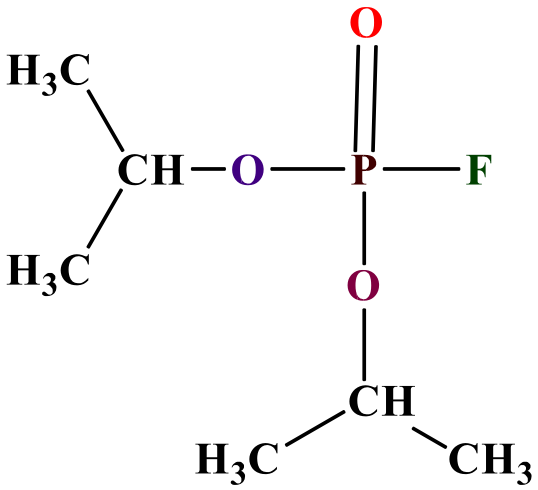
Aging of phosphorylated enzyme

Cholinesterases that have been exposed to phosphorylating agents (e.g., sarin) become refractory to reactivation by cholinesterase reactivators. The process is called aging and occurs both in vivo and in vitro with AChE and BuChE. Aging occurs by partial hydrolysis of the phosphorylated moiety that is attached to the serine residue at the esteratic site of the enzyme

Phosphate esters used as insecticidal agents are toxic and must be handled with extreme caution. Symptoms of toxicity are nausea, vomiting, excessive sweating, salivation, miosis, bradycardia, low blood pressure, and respiratory difficulty, which is the usual cause of death.

The organophosphate insecticides of low toxicity, such as malathion, generally cause poisoning only by ingestion of relatively large doses. Parathion or methylparathion, however, cause poisoning by inhalation or dermal absorption. Because these compounds are so long acting, cumulative and serious toxic manifestations may result after several small exposures.

-1 Isofluorphate



Diisopropylphosphorfluoridate

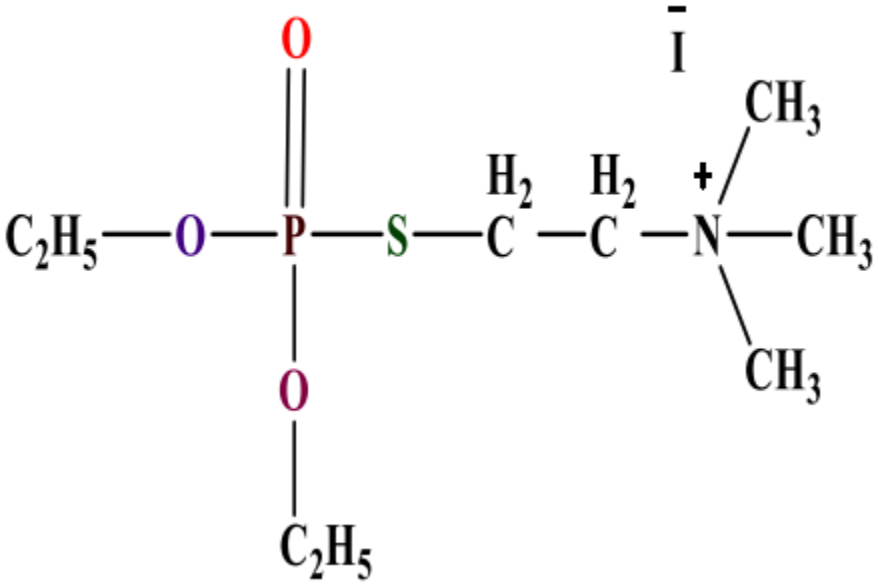
It is stable in peanut oil for a period of 1 year but decomposes in water in a few days.

The compound should be stored in hard glass containers. Continued contact with soft glass is said to hasten decomposition, as evidenced by discoloration.

Atropine sulfate counteracts the muscarinic effect, magnesium sulfate counteracts the nicotinic effect of the drug.

Uses :- Isofluorphate has been used in the treatment of glaucoma

-2Echothiophate Iodide

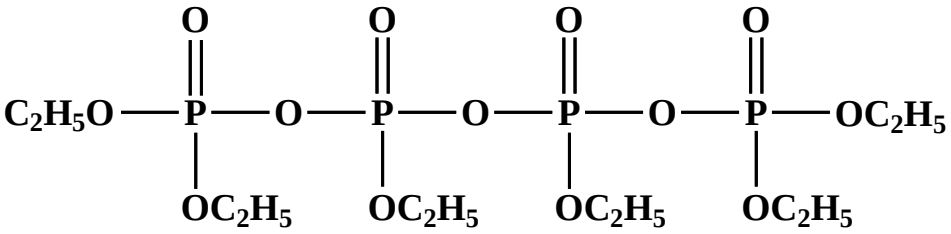


Occurs as a white, crystalline, hygroscopic solid that has a slight mercaptan-like odor. It is soluble in water (1:1) and dehydrated alcohol (1:25); aqueous solutions have a pH of about 4 and are stable at room temperature for about 1 month.

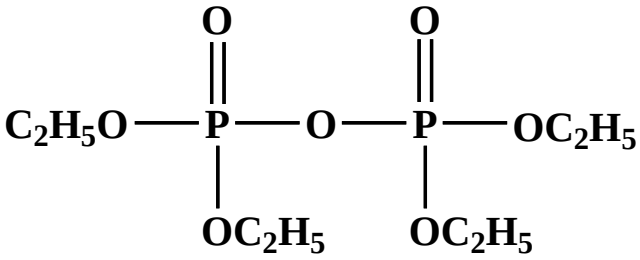
2-(diethoxyphosphorylthio)-N,N,N-trimethylethanaminium iodide

Echothiophate iodide is a long-lasting cholinesterase inhibitor of the irreversible type, as is isofluorphate. Unlike the latter, however, it is a quaternary salt, and when applied locally, its distribution in tissues is limited, which can be very desirable. It is used as a long-acting anticholinesterase agent in the treatment of glaucoma.

-3Hexaethyltetraphosphate (HETP(and Tetraethylpyrophosphate (TEPP.(



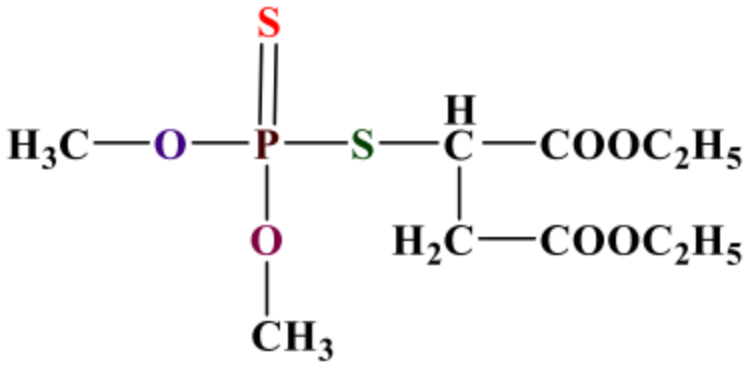
Hexaethyl tetraphosphate



Tetraethyl diphosphate

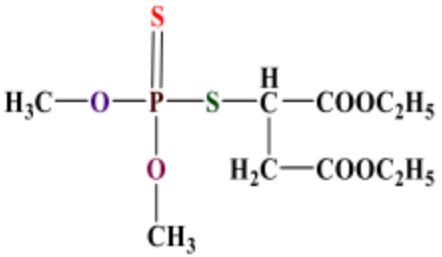
HETP and TEPP are compounds that also show anticholinesterase activity.

-4Malathion



2-{(dimethoxyphosphinothioyl)-thio}butancdioic acid diethyl ester

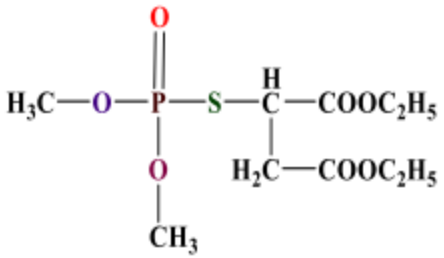
is a water-insoluble phosphodithioate ester that has been used as an agricultural insecticide. Malathion is a poor inhibitor of cholinesterases. Its effectiveness as a safe insecticide is a result of the different rates at which humans and insects metabolize the chemical.



Malathion poor AChE inhibitor

Activation slow

microsimal enzyme

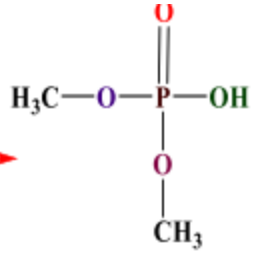


Malaoxon

10000 more active as a AChE inhibitor

Insects

Phosphatase

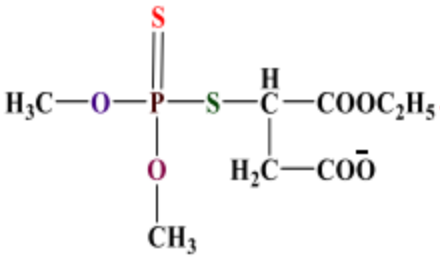


Dimethylphosphate

Inactive

Carboxyesterase

rapid in mammals



Malathion acid

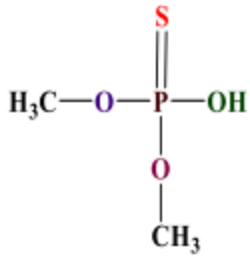
poor AChE inhibitor

Phosphatases

Carbox

yestera

se

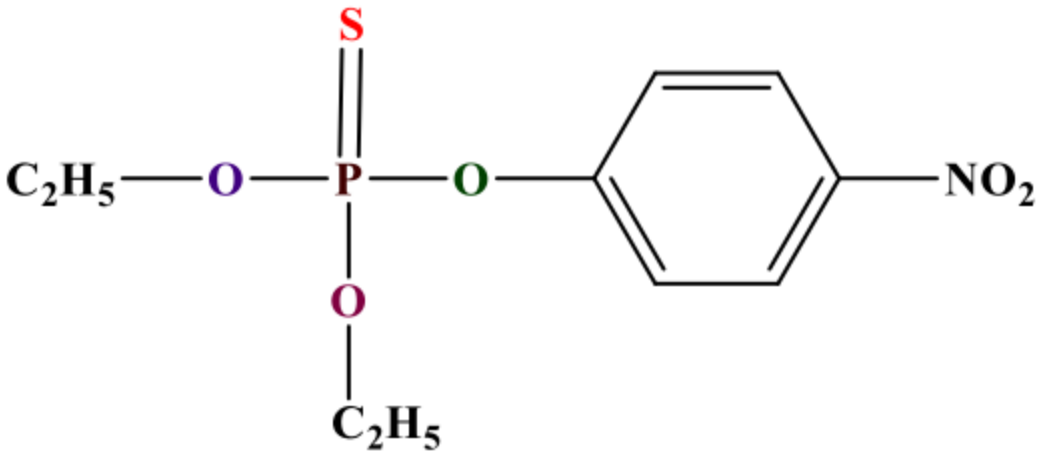


N,N-dimethylphosphorothioate

Comparison of metabolism of malathion

by mammals and insects

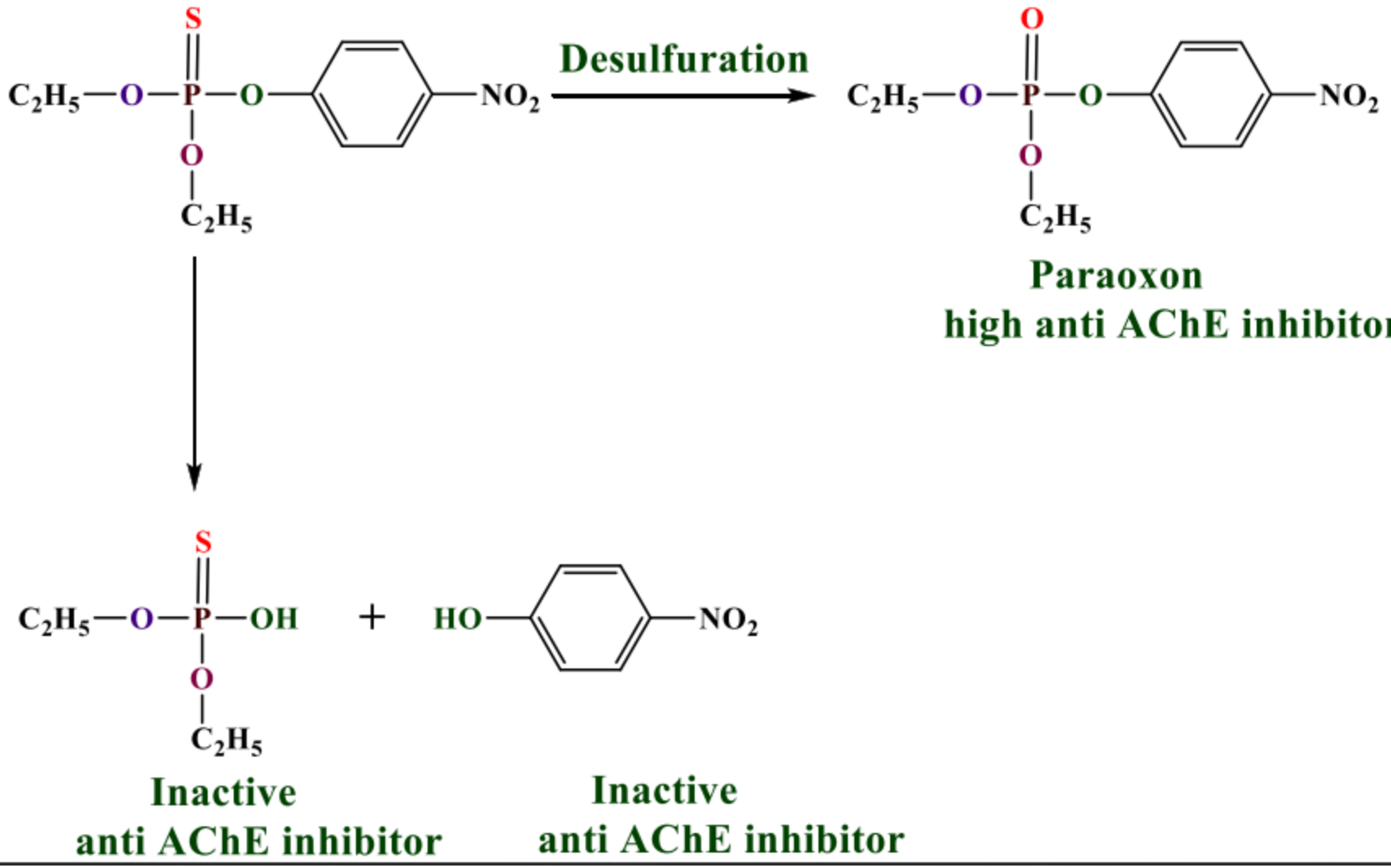
-5Parathion



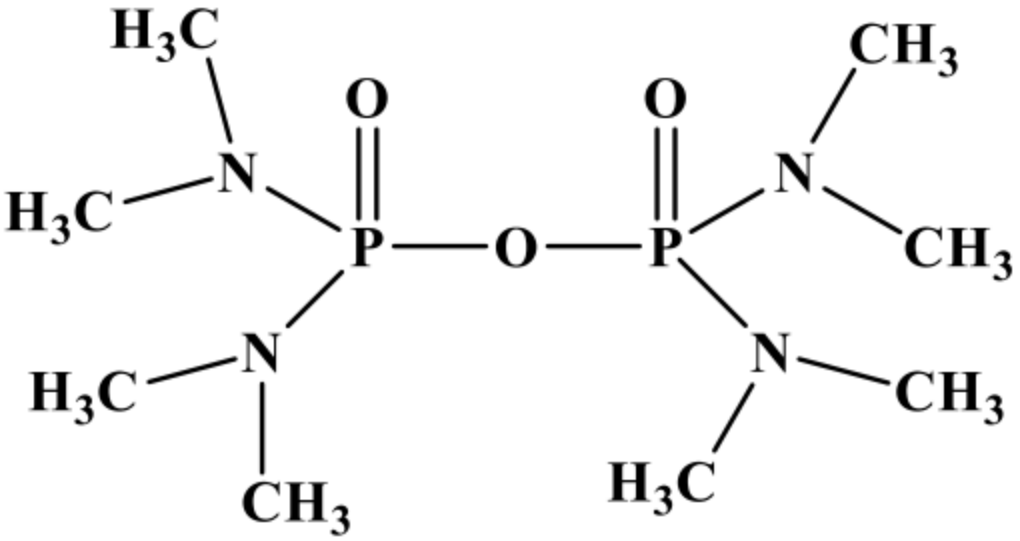
O,O-diethyl- O-4-nitrophenyl phosphorothioate

is a yellow liquid that is freely soluble in aromatic hydrocarbons, ethers, ketones, esters, and alcohols but practically insoluble in water, petroleum ether, kerosene, and the usual spray oils. It is decomposed at a pH above 7.5.

Parathion is used as an agricultural insecticide. It is a relatively weak inhibitor of cholinesterase

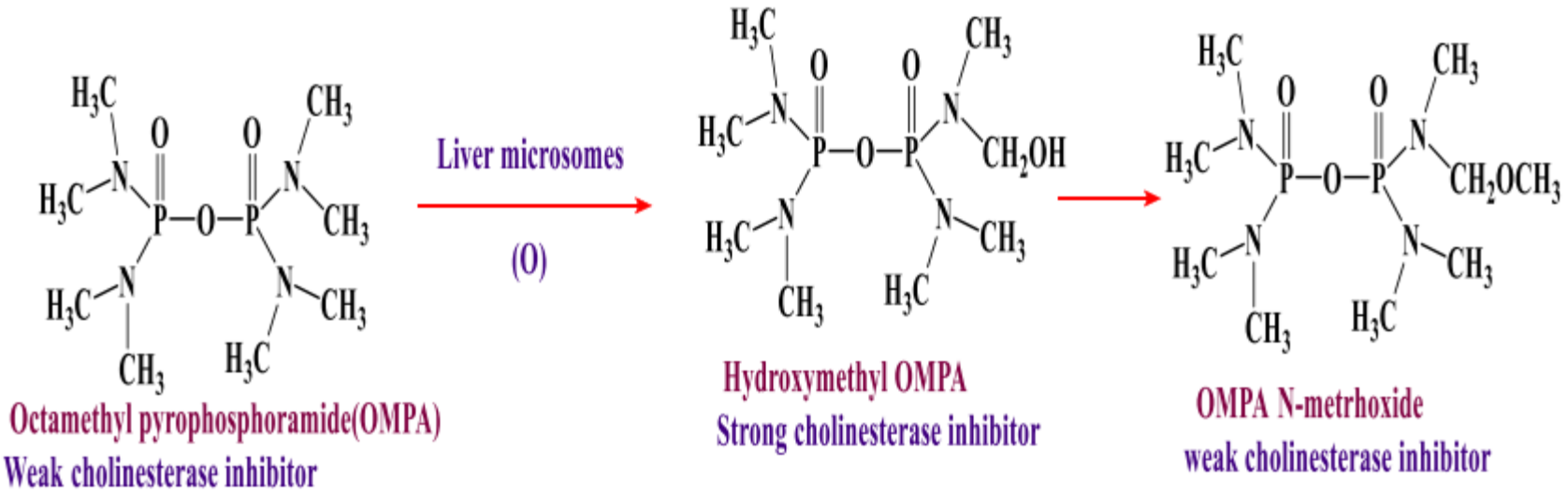

Desulfuration
Paraoxon
high anti AChE inhibitor
Inactive
anti AChE inhibitor
Inactive
anti AChE inhibitor

-6Schradan



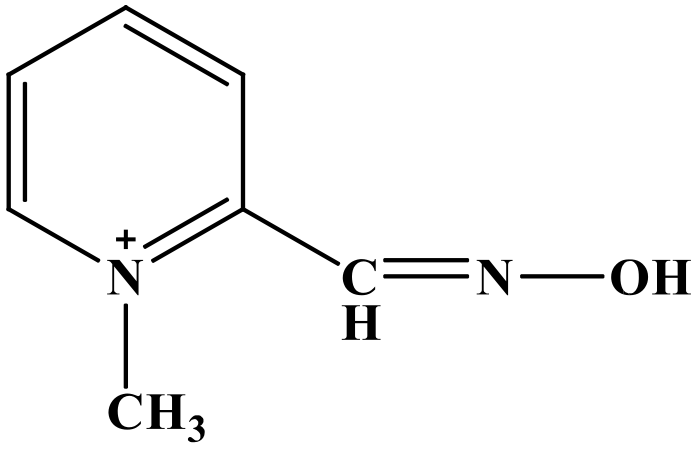
Octamethyl pyrophosphoramide(OMPA)
Bis{bisdimethylaminophosphonous} anhydride

is a viscous liquid that is miscible with water and soluble in most organic solvents. It is not hydrolyzed by alkalies or water but is hydrolyzed by acids. Schradan is used as a systemic insecticide for plants, being absorbed by the plants without appreciable injury. Insects feeding on the plant are incapacitated.



Schradan is a weak inhibitor of cholinesterases in vitro. In vivo, it is metabolized to the very strong inhibitor hydroxymethyl OMPA. Hydroxymethyl OMPA is not stable and is metabolized further to the N-methoxide, which is a weak inhibitor of cholinesterase

Pralidoxime chloride



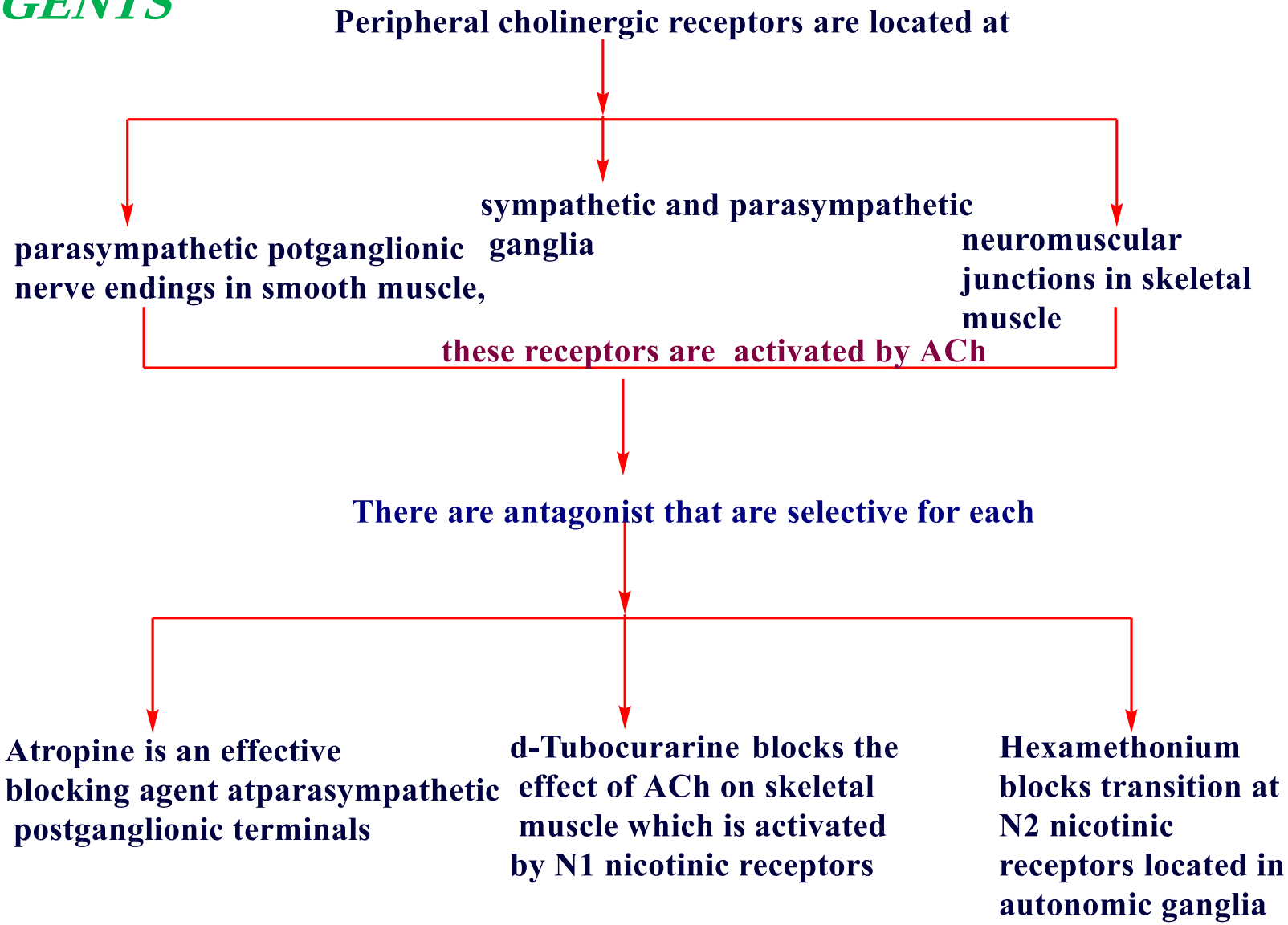
2-pyridinealdoximemethyl chloride

Pralidoxime chloride is used as an antidote for poisoning by parathion and related pesticides. It may be effective against some phosphates that have a quaternary nitrogen. It is also an effective antagonist for some carbamates, such as neostigmine methylsulfate and pyridostigmine bromide.

The biological half-life of pralidoxime chloride in humans is about 2 hours, and its effectiveness is a function of its concentration in plasma, which reaches a maximum 2 to 3 hours after oral administration.

Cholinergic blocking Agents

PARASYMPATHETIC POSTGANGUONIC BLOCKING AGENTS



The Stephenson and Ariens theories

These theories indicate that the amount of drug—receptor complex formed at a given time depends on the affinity of the drug for the receptor and that a drug that acts as an agonist must also possess another property, called efficacy or intrinsic activity.

The Patton rate theory

This theory defines a biological stimulus as proportional to the rate of drug—receptor interactions.

Both of these theories are compatible with the concept that a blocking agent that has high affinity for the receptor may decrease the number of available free receptors and the efficiency of the endogenous neurotransmitter.