IRWIN B. WILSON (1921-2013): THE STORY OF THE FIRST RATIONAL DESIGN OF A DRUG

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Abstract

This article is based upon a lecture that Irwin Wilson (Figure 1) gave for his 75th birthday on September 18, 1996. (His actual date of birth was May 8, 1921.) The lecture covered his early work on how acetylcholinesterase catalyzes the hydrolysis of acetylcholine. This led to his demonstration of the formation of a covalent acetyl-enzyme intermediate in the reaction. It should be noted that this was in the days before it was understood that an enzyme could catalyze a chemical reaction by forming a covalent intermediate. Further studies on the mechanism of acetylcholinesterase in his laboratory at Columbia University in 1956 gave rise to the rational design of Pralidoxime (2-pyridine aldoxime methyl chloride; 2-PAM) as a reactivator of the organophosphate-inhibited enzyme. Dr. Wilson's picture at the time of this discovery is shown below.

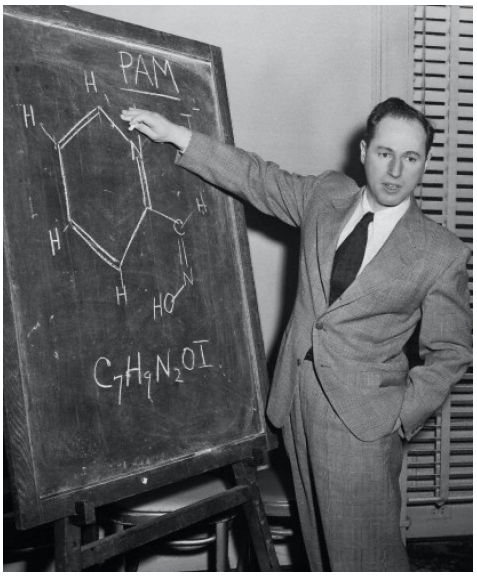


***Figure 1**. Irwin Wilson at the time of his work on acetylcholinesterase. (Courtesy of the Wilson family)*

Introduction

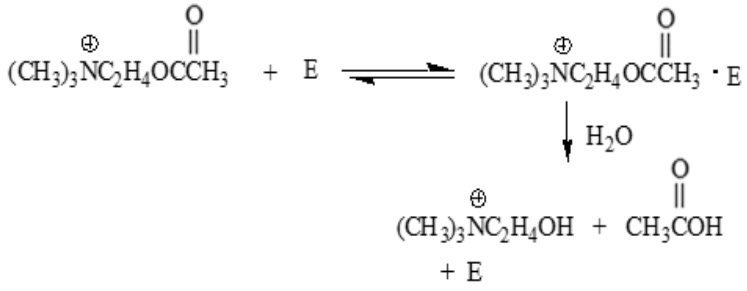
After World War II the military recognized that nerve gas was still a problem and there were rumors that the Russians were stockpiling it. Poisoning by the types of organophosphates that includes nerve gases and insecticides was a serious problem and a method of correcting this problem was needed. These compounds are very toxic because they are potent inhibitors of the enzyme acetylcholinesterase, and thereby prevent the clearing of acetylcholine from cholinergic neuro-muscular junctions. Thus, the American military was interested in funding research on antidotes to this type of poisoning.

The military flew a special plane to South America to obtain electric eels (not actual eels but more closely related to carp and catfish) because they contain large amounts of acetylcholinesterase. They were used for the project at Columbia. This allowed the researchers (listed below) to isolate and purify the protein to crystalline form for the first time.

These studies on acetylcholinesterase which led to the first rationally designed drug were carried out in Wilson's laboratory at Columbia University in the 1950s. Wilson acknowledged he had many gifted collaborators who he said were fun to work with. Some of those involved with cholinesterase at Columbia were Felix Bergmann, David Nachmansohn, Sara Ginsberg (an organic chemist trained in Russia, who played a big part in the synthesis of the new compounds), Estella Meislich, Enrico Cabib, Richard Kitz and Richard Epand.

Acetylcholinesterase

The mechanism for an enzyme-catalyzed reaction by acetyl cholinesterase is seen in the Michaelis-Menten scheme below where acetylcholine is shown forming a complex (seen as a dot) with the enzyme (E) leading to the breakdown to choline and acetate:



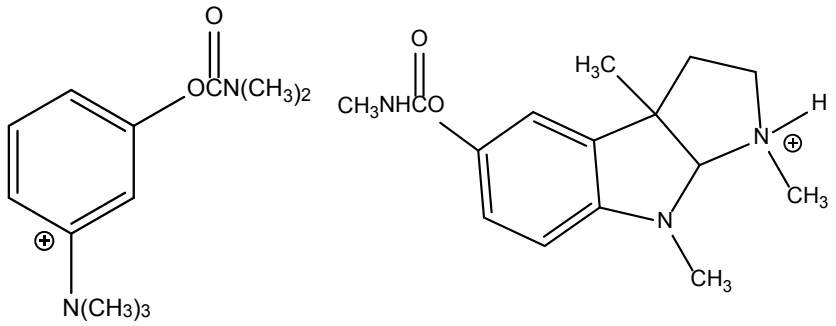
Wilson investigated the "dot" in the Michaelis complex (the binding features between the enzyme and the substrate) mostly by studying reversible inhibitors. He concluded that the binding features were electrostatic forces, hydrocarbon-hydrocarbon interactions, hydrogen bonds and **nucleophilic addition to the carbonyl carbon**.

The Anionic Site

Wilson showed that cationic compounds were bound to acetylcholinesterase as much as 30 times better than neutral analogous inhibitors and substrates (1-3).

Prostigmin (neostigmine), a carbamate with a quaternary ammonium function, inhibits the action of nerve gas to the same extent in the pH range 6-10; however, physostigmine with a tertiary ammonium function, pKa ~ 8.5, inhibits less as the pH is raised (Figure 2) and the charge diminishes.

Similarly the rate of hydrolysis of dimethylaminoethyl acetate, pKa ~8.5, declines as the pH is raised.



Prostigmin *Physostigmine*

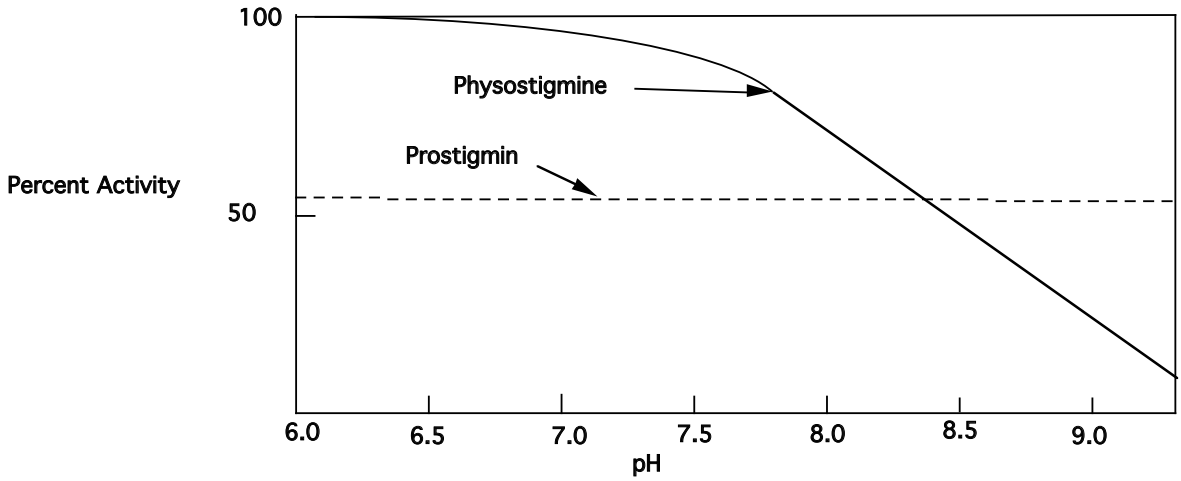
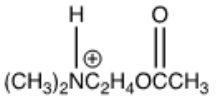
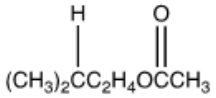


Figure 2. *Structures of prostigmin (neostigmine) and physostigmine and their inhibitory activity as a function of pH (after Figure 1 of Ref. 1).*



dimethylaminoethyl acetate



isoamylacetate

In its charged form dimethylaminoethyl acetate is a better substrate than isoamylacetate, but the uncharged form has a comparable reaction rate to isoamylacetate.

Similarly, choline, $(CH_3)_3N^+C_2H_4OH$, is 19 times more potent as an inhibitor than its carbon analogue $(CH_3)_3CC_2H_4OH$, and dimethylaminoethanol ammonium ion $(CH_3)_2NH^+C_2H_4OH$ is 30 times more potent than isoamylalcohol $(CH_3)_2CHC_2H_4OH$.

Wilson took this data to mean that the substrate had to have a charge in order to be attracted to the active site of the enzyme and thought that the electrostatic contribution to binding these two cationic (positively charged) inhibitors might derive mostly from a carboxyl group of the enzyme falling close to the cationic group, because the calculated effect using an empirical formula is in quantitative agreement with these observations.

Adams and Whitaker (4) had earlier argued for an electrostatic contribution of binding. Later measurements (5), with a genetically engineered enzyme in which a pertinent glutamic acid in the active site is replaced by glutamine, support the role of this glutamic acid as the major source of the electrostatic potential. In these later studies, the binding of 3-hydroxyphenyl-trimethyl ammonium ion, which is an active site specific inhibitor, is reduced by a factor of 19, and k_{cat}/K_m (which is the efficiency with which an enzyme converts a substrate into a product) is reduced by a factor of 50 due to this mutation (5). This verified Wilson's earlier thoughts.

Hydrocarbon Contacts

The binding of ammonium ions is progressively diminished as methyl groups are "removed" from tetramethyl ammonium ion: $(CH_3)_4N^+$ is 3 times better than $(CH_3)_3NH^+$, 21 times better than $(CH_3)_2NH_2^+$ and 140 times better than $(CH_3)NH_3^+$. The binding of NH_4^+ is too weak to measure. The binding of phenyl-trimethyl ammonium ion is 100 times better than $(CH_3)_4N^+$.

Wilson attributed the effect of each methyl group to hydrocarbon-hydrocarbon contacts between the inhibitor and the enzyme analogous to the forces holding methane molecules in contact in liquid methane. The value for the heat of evaporation of methane is reasonably appropriate (The concept of hydrophobic interactions had not yet been advanced). More recent x-ray studies by others validate Wilson's thinking, by showing that the substrate lies in a hydrophobic groove in the active site (6).

Nucleophilic Addition

The pH curve of enzyme activity can be fitted with 2 pKa values, 7.2 and 9.5 (1).

Inactive Active Inactive

The first ionization corresponds to the imidazole group of histidine. A carbonyl group contributes to the binding of some inhibitors, and Wilson thought imidazole might be the enzymic nucleophile and add to suitable carbonyl groups. Of course, it is now known that the hydroxyl group of serine, which is labeled with diisopropylflurorphosphate (6), is the enzymic nucleophile while imidazole has an essential role as a general base-general acid catalyst (7).

Wilson drew a schematic picture of the active site of the enzyme (Figure 3) using the noncommittal symbol G for the nucleophile and showing that the enzyme's active site consists of two subsites.

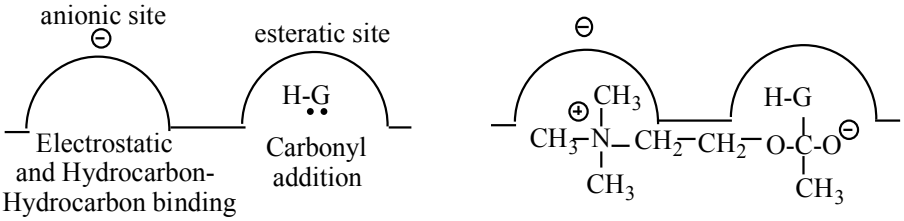


***Figure 3**. Schematic picture of the active site of the cholinesterase enzyme.*

The Acetylenzyme

Based upon the results above, Wilson (8) speculated that the enzymic hydrolysis of esters (the forward reaction) might take place in two steps with an acetylenzyme as an intermediate.

Whatever the mechanism, the presence of this common intermediate on cholinesterase means that the enzyme must also be able to synthesize acetylcholine from acetate and choline (i.e., catalyze the reverse of hydrolysis) to an extent depending on the free energy change in the reaction). This fits with previous studies that showed that the enzyme also synthesizes acetohydroxamic acid from acetate and hydroxylamine (9, 10).

Wilson thought that if acetylenzyme were an intermediate, the formation of acetylcholine or acetohydroxamic acid would surely occur much more rapidly using ethyl acetate instead of acetate because the ethyl moiety would be a better leaving group. This proved to be the case, and the rates were 150-300 times faster. These observations rule out the possibility that the hydrolysis of ethyl acetate provides acetate for the reaction and indicate that a transacylation reaction occurs that is readily explained by the formation of an acetylenzyme.

It is apparent that a necessary condition for this theory is that a series of acetate esters (with different alcohol residues) must in the presence of hydroxylamine produce the same ratio of acetohydroxamic acid to acetic acid. Similarly, in the presence of choline, the ratio of acetylcholine to acetic acid should be the same for each ester. (These reaction pathways are shown in Figure 4.) This argument was later tested with α- and γ-chymotrypsin using eleven different esters of hippuric acid (11). The fraction of ester converted to hippurylhydroxamic acid was the same for each of the eleven hippuric acids, within a precision of 1% and different for the two different chymotrypsins. On the other hand, if the ester portion is held constant, with ethyl esters of five phenyl-substituted hippuric acids the ratios were found to be very different. Similarly, the ratios were very different for the non-enzymic hydrolysis by hydroxaminolysis of these same hippuric acid esters.

These results are a sufficient condition for proving a common intermediate because a constant ratio of products does not otherwise happen in chemical reactions. Thus, these results provided the first evidence of a covalent enzyme substrate intermediate for the acetylcholinesterase catalyzed hydrolysis.

The two-step process was also supported by the finding that the Arrhenius plot for acetylcholine was curved, indicating two rate-influencing steps with different energies of activation, steps that Wilson took to be acetylation and deacetylation of the enzyme. Since N-methylaminoethyl acetate and aminoethyl acetate are much poorer substrates, there should be only one rate influencing step (acetylation), and the Arrhenius plots for these substrates were straight.

From the formation of an acetylenzyme one can predict that acetylcholinesterase will catalyze the exchange of oxygen between acetate and water. Wilson showed this indirectly by using sulfur as a marker for oxygen and demonstrating that the enzyme hydrolyzes thiol acetic acid (CH_3COSH) (12). The hydrolysis of thiol acetic acid to produce H_2S is analogous to oxygen exchange. Later others demonstrated the exchange using ^{18}O water (13).

Organophosphates (Phosphonates)

The organophosphate inhibitors of acetylcholinesterase (Figure 5) have a good leaving group, including F^-, Cl^-, CN^-, nitrophenolate, $-SC_2H_4^+N(CH_3)_2$, diethyl phosphate, etc., and 100 more, which allows the organophophate act as a phosphorylating agent and to covalently react with an active site reactive group.

Usually replacing EtO- by CH_3- increases the rates of inhibition. Potency generally refers to the rate of inhibition, i.e. the second order rate constant. Many of these compounds form reversible complexes with the enzyme prior to phosphorylation.

These compounds are phosphorylating agents and Wilson was confident that they phosphorylated the same nucleophilic group that is acetylated during the hydroly-

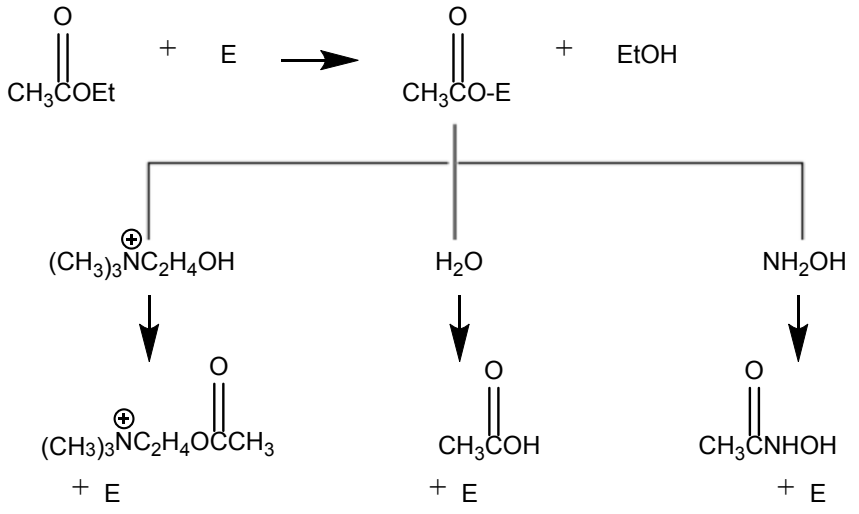


***Figure 4**. Pathways for reactions of choline, water and hydroxylamine via an acetylenzyme.*

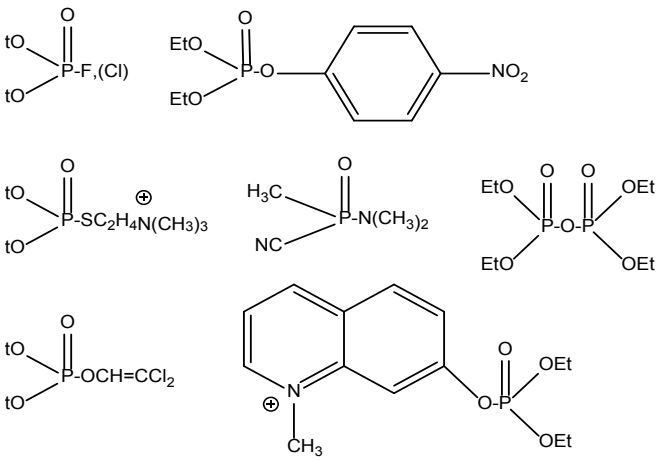


***Figure 5**. Examples of organophosphate inhibitors of acetylcholinesterase.*

sis of esters. He supported this idea by showing that the pH curve for inhibition with tetraethyl pyrophosphate was the same as for the hydrolysis of β-bromoethyl acetate (data not published). Others later showed more conclusively that the enzyme is phosphorylated by these inhibitors (14).

By analogy with the acetyl-enzyme, Wilson thought that the phosphoryl enzyme should react with hydroxylamine, choline and water (Figure 6). He found he could demonstrate the reactivation of the inhibited enzyme by these reagents.

His studies on this reactivation and the following design studies are found in a series of papers summarized below (15-20).

Hydroxylamine has two nucleophilic centers N & O, and he determined that it was the oxygen center that was important for reactivating the enzyme by finding that N,N-dimethylhydroxylamine was active but O-methyl

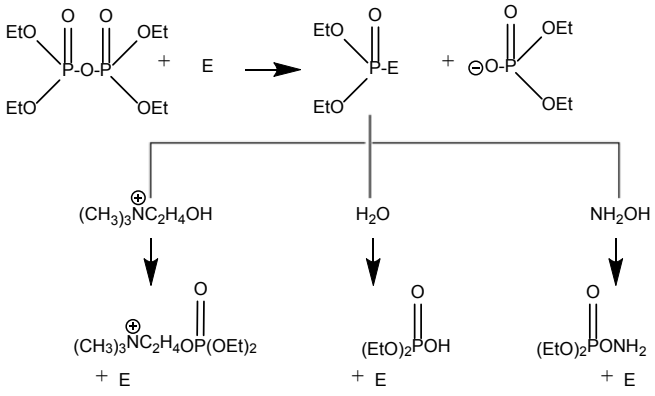


***Figure 6**.. Pathways for reactions of choline, water and hydroxylamine via a phosphoryl enzyme.*

hydroxylamine was not; trimethylamine oxide was also active.

H_2NOCH_3	$(CH_3)_2NOH$	$(CH_3)_3\overset{\oplus}{N}\text{-}\overset{\ominus}{O}$
Inactive	Active	Active

Hydroxylamine is a very good nucleophile but choline [$(CH_3)_2NOH$] is not. Yet choline does reactivate the enzyme. He thought that choline was active because it was bound at the anionic site, which would still exist in the phosphoryl enzyme. However, the binding of choline to the phosphoryl enzyme is 100 times weaker than to the free enzyme. Reactivation can be prevented by tetramethyl ammonium but again binding by this ion is poor. He thought the poorer binding was the result of steric hindrance.

The concentration dependence (Figure 7) shows the formation of a complex for choline but not for hydroxylamine:

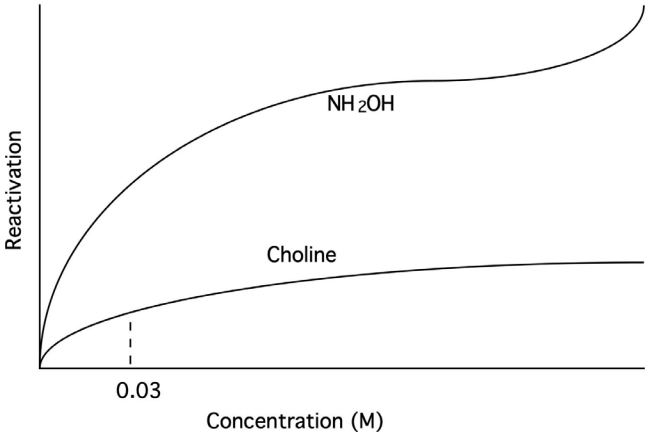


***Figure** 7. Concentration dependence of enzyme reactivation by choline and hydroxylamine, after Figure 1 of Ref. 15.*

Wilson believed he might be able to make a very good reactivator by combining a good binding structure such as the compounds in Figure 8, with a good nucleophilic group based on hydroxylamine. He tended to favor pyridine derivatives because he thought there might be less steric hindrance than in phenylamines.

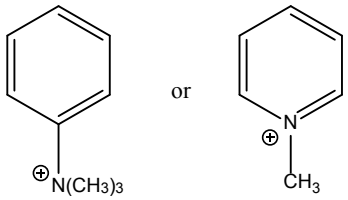


***Figure 8**. Trimethylphenylammonium (left) and* N*-methylpyridinium (right) ions.*

Although the organophosphate inhibitors were considered irreversible inhibitors, Wilson reasoned the following: The reaction with the enzyme is of course reversible in principle and any leaving group should be a reactivator but reactivation may be negligible depending upon the equilibrium constant and speed of the reaction; chloride is not a reactivator but fluoride is. Actually, there are lots of reactivators and in principle the diethylphosphoryl derivative should be an inhibitor but again that will be determined by the equilibrium constant and speed of the reaction. Diethylphosphoryl choline is not an inhibitor, but diethylphosphoryl-2PAM (Figure 9) is a very potent inhibitor (21).

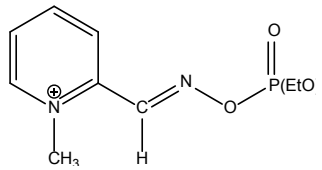
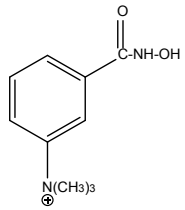


Figure 9*. Diethylphosphoryl-2PAM.*

Synthesis of Better Reactivators

One of the first compounds he made was the hydroxamic acid,



which proved to be much better than acetylhydroxamic acid or hydroxylamine but far short of what he was seeking. He was looking for more spectacular results as illustrated in the sequence shown in Figure 10.

In the series illustrated in Figure 10, the starting oxime is much better than hydroxylamine and the quaternary product is thousands of times better (21). Since the pKa values of these reactivators are about the same it seems likely that their intrinsic nucleophilicities are not very different. In fact, they reactivate phosphorylated chymotrypsin (which does not have an anionic binding site) at the same rate but of course much more slowly than they reactivate cholinesterase.

The binding of the reactivator is not of any value *per se*. It will be helpful only if the reactivator forms a highly productive complex—one in which the nucleophilic oxygen is located at about one bond length from the phosphorous atom and directed at the proper angle for mounting a nucleophilic attack. (Also a poorly productive complex that is far more stable should not be possible.) Thus, he reasoned that if the reactivator formed a productive complex with a "floppy" reactivator there may be a large loss of entropy in forming the more rigid "productive" complex. Thus, he wanted to have a fairly "rigid" reactivator with the right configuration. He thought the pyridine aldoximes offered the hope of finding a super reactivator since there are six isomers available (in principle): three positions in the ring and syn-anti pairs (Figure 11) (22).

From observations with carbamates he thought 2-PAM-anti might be a spectacular reactivator and he erroneously thought that 2-PAM had the anti configuration because treatment with acetic anhydride yielded the nitrile: this is a "textbook" method for assigning anti configurations. However, others showed by NMR, X-ray diffraction and molecular modeling (23-25) that 2-PAM had the syn configuration. Anti 2-PAM was not made and its ability to serve as a reactivator is not known.

He did a few experiments with mice using 2-PAM as an antidote against organophosphate inhibitors. 2-PAM with and without atropine, was remarkably effective against the organo-phosphate paroxon. Atropine protects muscarinic acetylcholine receptors. Table 1 shows toxicity data for 2-PAM and paraoxon (21). Table 2 shows partial results from treatment experiments against paraoxon (21)

Table 1. Toxicity data for 2-PAM and paraoxon in mice.

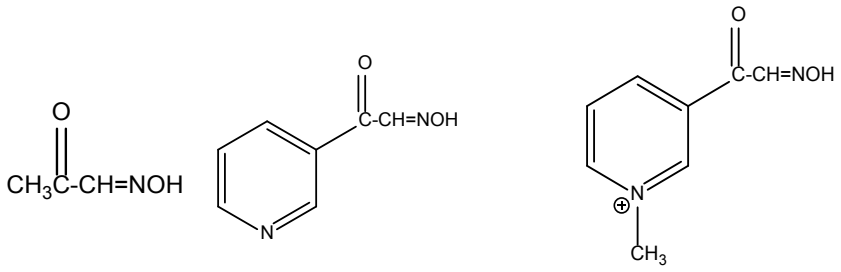
2-PAM	paraoxon
LD_{50} 136 mg/kg	LD_{50} 0.7 mg/kg
LD_{100} 190 mg/kg	LD_{100} 0.9mg/kg
Probable safe dose = 100 mg/kg	

Very good results were obtained against tetraethyl pyrophosphate and diisopropyl fluorophosphate. Against sarin results were very much poorer but still all mice survived an LD_{100} injection.

Table 2. Partial results from treatment experiments against paraoxon in mice.

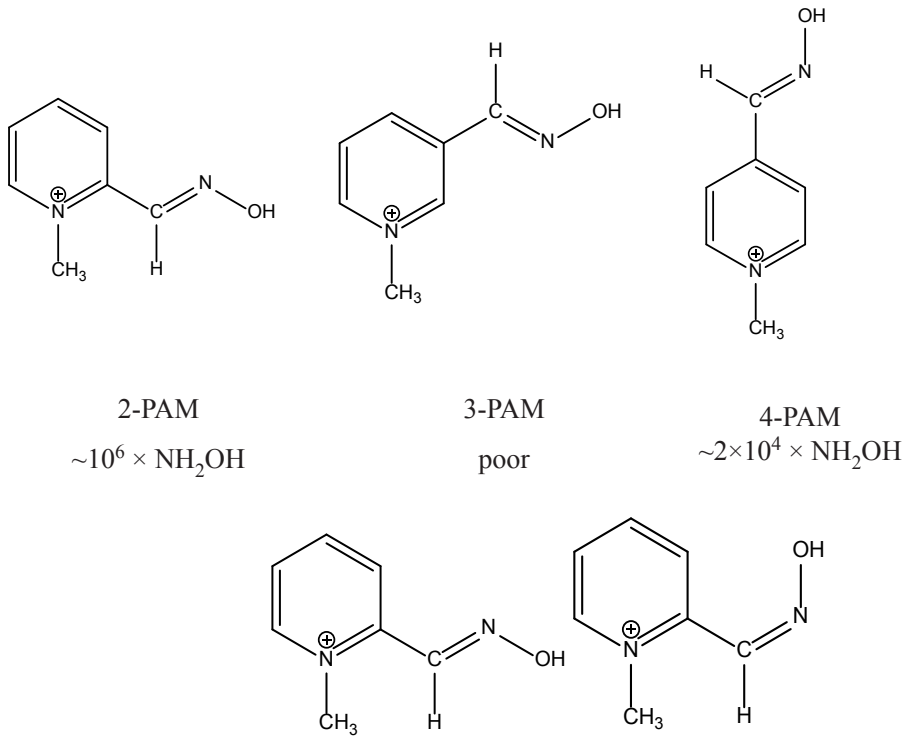
Atropine mg/kg	2-PAM mg/kg	Paraoxon Multiple of LD_{50}	Number of Mice	Number of Survivors
0	0	1.0	10	5*
0	75	1.0	10	10
0	0	1.3	10	0*
0	30	1.5	20	20
10	0	5.0	5	0
10	50	15	20	20

*Confirms previously obtained LD_{50}, LD_{100}.



3 M^{-1} min^{-1} 83 M^{-1} min^{-1} 2500 M^{-1} min^{-1}

Figure 10. *Inhibition rate constants for successively derivatized oximes.*



2-PAM
~10^6 × NH_2OH

3-PAM
poor

4-PAM
~$2×10^4$ × NH_2OH

Figure 11. *Isomers of pyridine oximes differing in position of the oxime group (above) and in configuration (below). The positional isomers are all syn; the numbers show relative activity. The configurations are syn (left) and anti (right).*

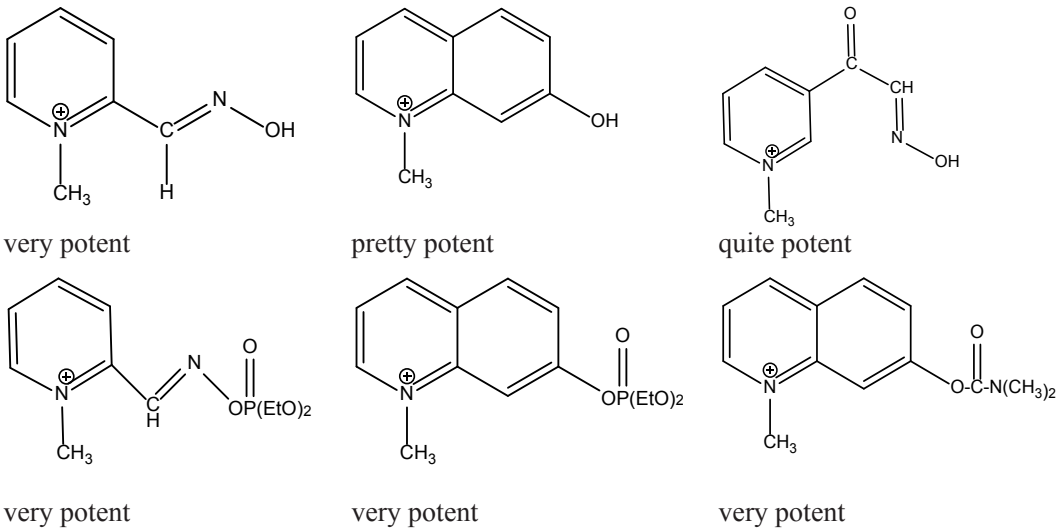


***Figure 12**. Potency of activators (above) and inhibitors (below).*

In retrospect, it is interesting to note the similar configurations of some potent reactivators and inhibitors as shown in Figure 12 (21). Of course, not all observations fit this pattern readily.

Conclusions

What Wilson showed for the first time was that an enzyme can form a stable covalent intermediate in the catalysis of a chemical reaction. In addition, Wilson was able to use these mechanistic studies to rationally design a drug that could be used to treat a person poisoned by a nerve gas or an insecticide that reacts with acetylcholinesterase. 2-PAM became the go-to drug for this type of treatment at that time in history.

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