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3<sup>rd</sup> Year Seminar Abstract  
May 1, 2003

### Chemical Warfare Agents

Use of chemicals in warfare has been known for many, many years. One of the first recorded uses was during the battle between Athens and Sparta between 431 and 404 B. C. In this instance, the combination of burning sulfur and pitch yielded noxious smoke which was then turned on the enemy.

Chemical warfare evolved rapidly from the use of burning mixtures to very simple off-the-shelf chemicals such as chlorine, phosgene and hydrogen cyanide (Figure 1).<sup>1</sup>

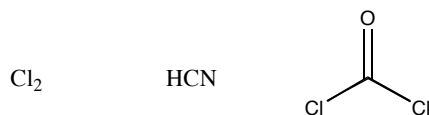


Figure 1: Chlorine, Hydrogen Cyanide, and Phosgene

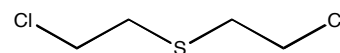


Figure 2: Mustard (HD)

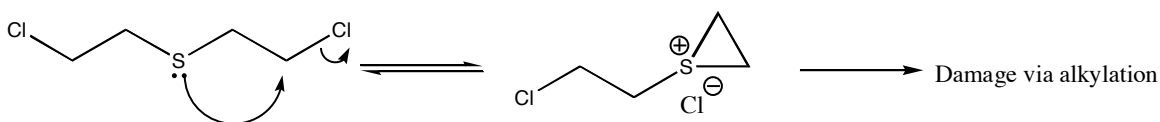
Large scale chemical weapons production began to take off not long after organic chemistry began to develop into a fully independent scientific discipline. Soon, more chemical warfare agents were introduced, sometimes unintentionally. Unfortunate mishaps or observations of toxicity for various compounds led to their production. For example, HD, (distilled mustard, or mustard gas), a blistering agent, (Figure 2) was discovered as a laboratory accident. In 1886, a German chemist in Victor Meyer's lab had prepared the mustard from thiodiglycol, and suffered serious injury from the product, leading to his hospitalization.<sup>1,2</sup>

Research of this compound was left untouched for several years, until another chemist named Hans T. Clarke reinvestigated it and improved on this synthetic method.<sup>3</sup> He too, suffered a laboratory accident, and was hospitalized. His accident was dutifully reported, as well as the injury he received. Because of his good laboratory practice, he believed that he may have inadvertently encouraged the mass production and use of one of the first major synthetic chemical weapons of the 20<sup>th</sup> century.<sup>1</sup>

Mustard was used frequently in WWI, and saw some limited use in subsequent conflicts, such as Abyssinia's (Ethiopia's) invasion by Mussolini in 1935-1936. It was then used by Japan in WWII in the Sino-Japanese Theater. Mustard's military purpose

was to blister and irritate the enemy. The weapon wasn't designed to kill, (although it could at high concentrations), just incapacitate, so another toxic gas or conventional weapons could finish the job.

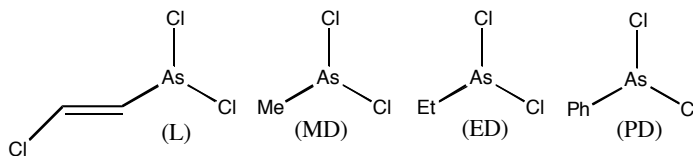
Mustard acts on the body as an extremely powerful alkylating agent. It goes through an intramolecular reaction to form a sulfonium ion, and this reagent can then be alkylated by many different nucleophiles in the body. (Scheme 1).<sup>4</sup>



**Scheme 1: Mustard's Mode of Action**

The main antidote to mustard exposure is use of thiosulfate anion ( $S_2O_3^{2-}$ ) to trap out the sulfonium ion.<sup>4,5</sup> Sulfur mustard can also be detoxified by enzymes, such as flavin-containing monooxygenase (FMO), which oxidizes the sulfur to the sulfoxide,<sup>6</sup> as well as *S*-adenosyl-methionine (thioethermethyl transferase), which methylates the sulfur before it can cyclize to the sulfonium.<sup>7</sup>

Other agents designed to irritate and incapacitate the enemy are the arsenicals.<sup>8</sup>



**Figure 3: Arsenicals**

(Figure 3). These agents were

developed towards the end of WWI and saw limited use. They contain an arsenic atom

flanked by halogens and an

alkyl group. Lewisite (L) is

one of the more potent

members of this family, and

blisters skin quite readily,

through a mechanism similar

to mustard. It also has some

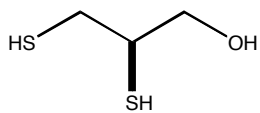
systemic toxicity, as it likes to

bind to 1,2 and 1,3 dithiols in

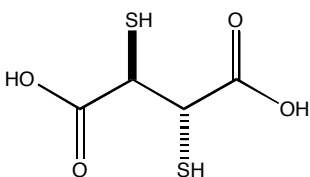
the body.<sup>9</sup> This binding

interrupts many physiological

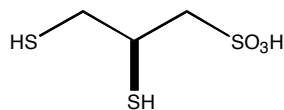
British Anti-Lewisite (BAL)  
(2,3-dithiopropanol)



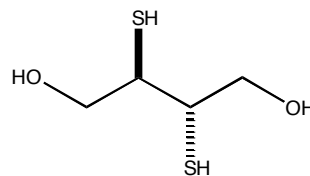
(meso-dimercaptosuccinic acid)



(2,3-dimercapto-1-propanesulfonic acid)



(2,3-dithioerythritol)



**Figure 4: Arsenical Antidotes**

processes, such as pyruvate decarboxylation in the citric acid cycle to yield acetyl CoA.

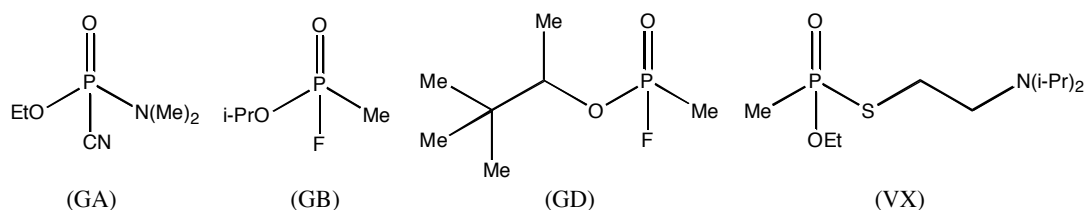
Since the arsenicals are such powerful dithiophiles, antidotes for arsenical poisoning are designed with that in mind in (Figure 4). These antidotes bind to the arsenic and chelate it away from the body.

Both the mustards and the arsenicals were designed to be non-lethal. Militarily, there are two general categories under which chemical weapons fall, lethality and persistency. Persistency has to do with how long the chemical agent stays on the battlefield after it has been released. Chemical weapons are designed and utilized for either or both of these purposes.<sup>10</sup>

Two extremely popular chemical warfare agents that are not extremely persistent, but are very lethal are chlorine and phosgene. Chlorine was one of the first chemical warfare agents introduced, and it has lots of advantages—it is easy to manufacture, it exists as a gas, and it is lethal. The first chlorine attack (and first chemical weapons attack of the 20<sup>th</sup> century) happened near Ypres, Belgium.<sup>1</sup>

Chlorine irritates the lungs due to formation of HCl and HOCl. It also displaces all of the oxygen in the lungs, and the victim dies from asphyxiation.<sup>5,8</sup> The Allies were very unprepared for this type of attack at Ypres, and suffered many casualties as a result. Chlorine became easily identifiable, though, and the Allies were able to protect against it.

Phosgene came next to replace chlorine, and this agent proved to be much deadlier. The gas causes irritation, again due to formation of acid in the lungs, as well as extreme, uncontrollable effusion of liquid into the aveoli of the lungs (pulmonary edema).<sup>5,8,11</sup> Phosgene is a very nasty killer—death may be delayed by several hours to a few days, with little to no symptoms. During the delay, the phosgene is nesting in the lungs and reacting with the walls of the aveoli, acylating them and thus causing them to lose structural integrity. There is no antidote to phosgene exposure.

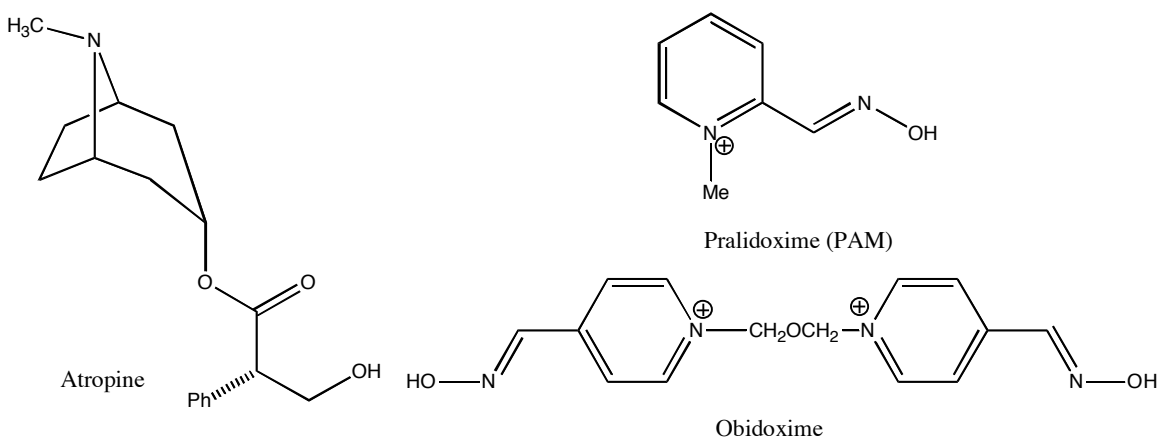


**Figure 5: The Nerve Agents**

Eventually, chemists went back to the lab and synthesized the newest generation of chemical weapons: The nerve agents. (Figure 5).<sup>8,12,13</sup> The nerve agents were developed in the 1930's and 1940's. The first nerve agent, Tabun (GA), was developed in Germany in 1937 by Schrader. He was researching insecticides based on an organophosphorus backbone and synthesized Tabun. Soon after Tabun came Sarin (GB). Sarin had a modification in the design where the P-C bond to a cyano group in Tabun was replaced with a methyl group. This change in carbon substituent had a serious effect on the toxicity of this agent, as it made it much more resistant to hydrolysis by the body.<sup>12</sup> Therefore, it can't be detoxified as quickly as Tabun. Schrader also synthesized Soman (GD) in 1944. After the G-agents came VX, developed in England by Ghosh in 1949. These weapons were synthesized and stockpiled after WWI and WWII, but were only used once (Tabun, in the Iran-Iraq war, 1980-1988).<sup>1</sup>

These organophosphorus agents are extremely powerful electrophiles, which explains a portion of their toxicity. They target Acetylcholinesterase (AChE), an enzyme which is responsible for many pathways in the body, one of which is the cholinergic pathway of the central nervous system (CNS).<sup>13</sup> The normal function of this pathway is muscle control. Nerve agents block the AChE located on the muscle. When this neurotransmitter is blocked, acetylcholine (ACh), which has been sent over to the muscle from the nerve, isn't destroyed and continues to send the same message, which essentially means muscular control is lost.

The antidote for nerve agent exposure is a combination of atropine and an oxime (Figure 6).<sup>5, 8, 12, 13</sup>



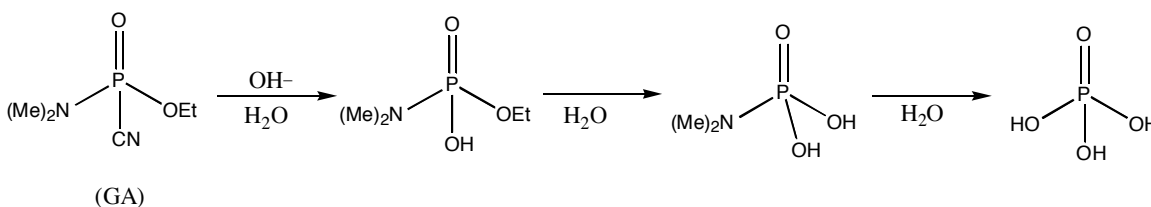
**Figure 6: Nerve Agent Antidotes**

The atropine blocks the ACh receptors, so the message can't be continuously transmitted, and the oximes free up the blocked AChE receptors.<sup>13</sup>

With the synthesis and stockpiling of extremely toxic and dangerous nerve agents, and with increased public fear of a chemical or biological terrorist attack, detection methods for chemical warfare agents have been and continue to be thoroughly researched. Many are based on common analytical laboratory techniques, such as GC, MS, and IR.<sup>14</sup> Unfortunately, as accurate and powerful as some of these techniques can be, they are not necessarily able to make the transition from the laboratory to the field. Several issues need to be resolved in order to make this transition, especially those regarding cost and logistics. Many of the detection instruments used currently are too large to be extremely effective, and thus more work needs to be done to make some of these methods more practical.

Aside from detection, the study of the degradation and disposal of chemical warfare agents is an important field.<sup>15</sup> Several degradation and disposal pathways are available to chemical warfare agents. In the early 1980's, the U.S. Government began to look seriously at the disposal of chemical weapons.<sup>16</sup> Since ocean dumping was an undesirable method of disposal, incineration seemed to be the only alternative. Unfortunately, incineration produces a wide variety of compounds, and these can damage the atmosphere. Due to the results of air pollution studies in the 1980's and 1990's and unpopular sentiment for incineration of toxic compounds, the U.S. Government decided to move to a method of chemical neutralization and bacterial degradation as a means of disposal.<sup>15,17,18</sup>

One common quality about the chemical warfare agents is their susceptibility to hydrolysis. This property makes decontamination, degradation, and disposal a fairly easy chemical process. Most all of the hydrolysis products for these compounds are much less toxic than the parent compound, so safety is not compromised during disposal. For example, the final hydrolysis product of Tabun is phosphoric acid (Scheme 2).



**Scheme 2: Hydrolytic Degradation of Tabun**

After hydrolysis, many of these byproducts are either dumped in a landfill, or sent to a treatment plant to be further degraded by bacteria.<sup>15</sup> Bacteria such as *Pseudomonas pickettii* and *Alcaligenes xylosoxidans* use thiodiglycol, the hydrolysis product of mustard, as a carbon source, and *Pseudomonas testosteroni* uses isopropylmethylphosphonic acid (IMPA, a hydrolysis product from Sarin) and methyl phosphonic acid (MPA, hydrolysis products from Sarin and Soman) as phosphorus sources.<sup>15</sup>

The main impetus behind the move for disarmament and disposal is the Chemical Weapons Convention of 1997.<sup>1,15,17,18</sup> The convention calls for disposal of all chemical weapons by 2007. The U. S. and Russia are the two countries with the largest stockpiles of chemical weapons, and thus are receiving the most scrutiny. As of 9/30/2001, the U.S. had destroyed about 25% of its stockpile, while Russia had destroyed less than 2%.<sup>18</sup> If these two countries follow the Convention to its completion, and other countries do not develop chemical weapons of their own, we may never see the horror that “The Chemists’ War” (WWI) brought to everyone.

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