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LETTER TO THE EDITOR

HISTORY OF ORGANOPHOSPHORUS CHOLINESTERASE INHIBITORS & REACTIVATORS

It was with interest and pleasure that I read the contribution of Petronilho & Figueroa-Villaret in the MMSL reviewing the literature on agents for defense against chemical warfare [Petronilho & Figueroa-Villaret, 2015]. The authors briefly touch on the history of organophosphates emphasizing the pioneering contribution of **Jean Louis Lassaigne**, the synthesis of triethyl- phosphate (TEP) and finally the achievements of **Philippe de Clermont** who co-developed the first organophosphate (OP) acetyl-cholinesterase inhibitor, tetraethyl pyrophosphate (TEEP). They continue by pointing out that Wilson and Ginsburg managed to reactivate OP-inhibited acetylcholinesterase using pralidoxime (2 -PAM), which reactivates the enzyme much faster than hydroxylamine. I believe that the scientists involved in organophosphorus cholinesterase inhibitor & reactivator development deserve more attention and that the colleagues' contribution contains a number of ambiguities deserving additional comment.

In 1820 **Jean Louis Lassaigne** (1800–1859) made the analogy between sulphovinic and phosphovinic acids and demonstrated the existence of phospho-vinic acid, while in 1833 **Jules Pelouze** (1807-1867) synthesized it (Figure 1A) [Pelouze, 1833; Petroianu, 2010].

Triethyl phosphate (TEP) was synthesized is Berlin in the chemistry laboratory of Gustav Magnus (1802–1870), Professor of Physics and Technology at the Berlin University. Magnus supervised the work of the Swiss chemistry student **Franz Anton Voegeli** (1825–1874), who was to become the father of both diethyl- and triethyl- phosphate [Voegeli, 1848; Petroianu, 2009]. (Figure 1B & 1C).

Shortly thereafter ether chemistry made a quantum leap with the elucidation of the ether formula and description of the reaction steps leading to ether formation by **Alexander Williamson** (1824–1904) [Wiliamson, 1851]. Based on the landmark work of Williamson over the next fifty years or so numerous chemists [Philippe de Clermont (1831-1921), Heinrich Limpricht (1827-1909), Georg Ludwig Carius (1829-1875), Hugo Schiff (1834-1915)] managed to produce TEP using reactions of increasingly higher yield. Although with the TEP synthesis by Voegeli the first organophosphate was created, this accomplishment is eclipsed by the Moschnin und de Clermont synthesis of tetraethyl pyrophosphate (TEPP) five years latter: while TEPP was not the first organophosphate to be synthesized it was however the first organophosphate cholinesterase inhibitor [Petroianu, 2008, 2009].

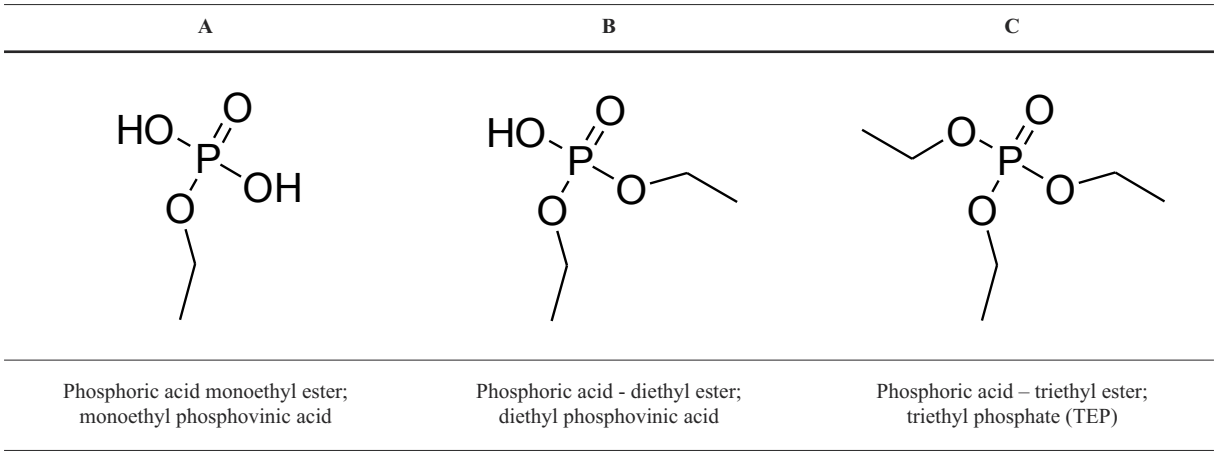


Figure 1: (A) Phosphoric acid - monoethyl ester as synthesized by Pelouze and (B,C) Phosphoric acid - diethyl and triethyl ester as synthesized by Voegeli.

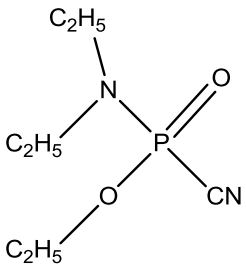
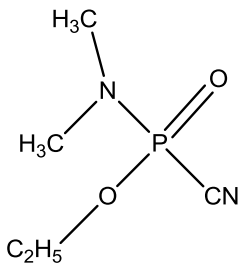
The original laboratory synthesis was achieved by **Wladimir Petrovich Moshnin**, a Russian chemist from Moscow († 1899 or 1900), student of Charles-Adolphe Wurtz (1817-1884) in Paris [Petroianu 2008]. The procedure was repeated and reported to the French Academy of Sciences by another student of Wurtz, **Philippe de Clermont** (1831–1921), who acknowledged the earlier work of Moshnin [de Clermont 1854]. The synthetic approach used by both Moshnin and de Clermont was based on the work of Williamson using ethyl iodide and salts of the acid to be esterified [Wiliamson 1851].

After the initial synthesis by Moshnin and de Clermont, over the years, a good half-a-dozen of other pharmacists and chemists also managed the feat of synthesizing TEPP: Griffith Evans Abbot (1850-1926) in 1879, Maximillian Riegel (1870-1936) in 1896, Jacques Cavalier (1869–1937) and Arthur Rosenheim (1865-1942) in 1906, Balareff (1885-1964) in 1914 and more recently by Paul Nylen (1892-1976), Arbusow & Arbusow, Schrader, Woodstock and Toy [Petroianu, 2015].

The synthesis of tabun-like organophosphonate compounds [Figure 2] was achieved at the end of the XIXth century by doctoral students working under the supervision of **Karl August Michaelis** (1847-1916) in Rostock and described in detail in the German scientific literature. The information was widely available in the public domain as evidenced by the inclusion in a prewar Russian language monograph authored by **Vladimir Mihailovich Plets**. The compounds and many more related variations were re-discovered and systematically analyzed for biologic effects by **Gerhard Schrader** (1903–1990) in the late thirties [Petroianu, 2014].

Although both organo -phosphates and –phosphonates were synthesized in the XIXth century their toxicity remained unrecognized for quite some time despite the fact that some chemists – such as de Clermont- even tasted their products. The fact that he survived and lived up to the age of 90 is best explained by the low yield of the synthetic approach used in those days. The first published report on the toxicity of organophosphonates is from 1932, when **Gerda von Krueger** (1907-after 1970), a graduate student in the Berlin laboratory of **Willy Lange** (1900-1976) was accidentally exposed to phosphor esters (and survived to describe the experience) [Lange & v Krueger, 1932; Petroianu, 2010].

History has a tendency to repeat itself: Schrader, developing phosphor ester based insecticides was 1936 also accidentally exposed to the toxic effects

A	B
	
diethyl-amino ethylester cyano-phosphonate (tabun II; GAA)	dimethyl-amino ethylester cyano-phosphonate (tabun I; GA)

Jacquard Rothschild (1907-1990), an American chemist and army officer apparently introduced the designation GA for tabun in an attempt to disambiguate the nomenclature; to highlight the similarity between the Schrader and Michaelis compounds, the diethyl cyanophosphonate is refered to as tabun II or GAA.

Figure 2: P-CN organophosphonate inhibitors of cholinesterase:
(A) diethyl-amino ethylester (GAA) as synthesized by the graduate students of Michaelis &
(B) the dimethyl-amino ethylester (tabun; GA) synthesized by Schrader.

of one of the compounds he was working on and had to be admitted to the hospital for a fortnight [Pfingsten, 2003], Upon return to work at IG Farben Leverkusen, Schrader identified the toxic compound responsible for the accident as dimethyl-amino ethyl-ester cyano-phosphonate (later named by him tabun).

Irwin B. Wilson (*1921), working in the laboratory of **David Nachmansohn** (1899–1983) at Columbia, demonstrated the ability of hydroxylamine to reactivate cholinesterase inhibited by organophosphates. Soon thereafter Wilson and **Sara Ginsburg** (1908 – 1997) reacted pyridine-2-aldoxime with methyl iodide to synthesize the first pyridinium aldoxime reactivator of clinical relevance, 2-PAM (pralidoxime).

Independently, and at the same time, similar work was conducted in Britain at the Chemical Defence Experimental Establishment in Porton by **Albert Lawrence Green** (*1929) leading also to the synthesis of 2-PAM and the recognition of its reactivating properties [Childs et al, 1955] [Figure 3]. While the American contribution is well known, the British achievements were less publicized [Petroianu, 2013].

Based on the above the conclusion would then be that Voegeli synthesized the first organophosphate (TEP), Moshnin and de Clermont synthesized the first organophosphate cholinesterase inhibitor (TEPP), Lange und von Krueger recognized the toxicity of the compounds while Wilson and Ginsburg in the US and Green in the UK synthesized the first oxime reactivator (2-PAM). In reality organophosphate cholinesterase inhibitors occur in nature so paternity for their creation can be rightly claimed by evolution [Petroianu, 2012].

Figure 3. Albert Lawrence (Bert) Green (*1929) received 1953 his Ph.D in organic chemistry from King's College London. Shortly thereafter he joined the Chemistry section of the Defense Experimental Establishment (D.E.E) at Porton, Wilts.
Dr. Green with his granddaughter (from the personal collection of the author, with kind permission from Dr. Green).

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