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History of organophosphate synthesis: the very early days

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The early days of ether chemistry can be divided into two periods: before and after Williamson serendipitous discovery (1851) of a new and efficient way to produce ethers using ethyl iodide and potassium salts. In the early part of the 19th century however, before Williamson, the direct reaction between the “spirit of wine” (ethanol) and acids was the only method of generating the elusive “ethers”. This brief report looks at the pharmacists-chemists involved in the quest to produce phosphoric acid ether in the pre-Williamson period (Boudet, Boullay, Lassaigne, Pelouze), paving the way for Voegeli’s synthesis of triethyl phosphate (TEP) in 1848.

Howard Chambers describing the advent of organophosphate chemistry (Chambers 1992) states that “*The history of organic phosphorus chemistry apparently began about 1820 when Lassaigne reacted ethanol with phosphoric acid to obtain triethyl phosphate*”. Morifusa Eto also credits Lassaigne with the earliest work on organophosphates (Eto 1974). Both refer to a chapter in Wegler’s “*Chemie der Pflanzenschutz- und Schädlingbekaämpfungsmittel*” (Fest and Schmidt 1970), where Lassaigne’s original publication is cited (Lassaigne 1820). While Lassaigne’s contribution is undeniable, organophosphate chemistry neither starts nor ends with him. The purpose of this brief report is to identify the pharmacists-chemists involved in work on “ethers” of phosphoric acid in the period before Williamson, paving the way for the synthesis in 1848 of triethyl phosphate (TEP) by Franz Anton Voegeli (1825–1874), (Fig. 1C) (Petroianu 2009).

In 1770, phosphoric acid was discovered in bone ash by Carl Wilhelm Scheele (1742–1786) and Johan Gottlieb Gahn (1745–1818). Scheele later isolated phosphorus from bone ash (1774) and produced phosphoric acid by the action of nitric acid on phosphorus (1777). Soon the combustion of phosphorus in oxygen or air was also introduced as a method of generating the acid(s) (Davy 1840). The reaction between sulphuric acid and “spirit of wine” or ethanol leading to the pleasantly smelling “sulphur-ether” was well known; with phosphoric acid becoming widely available, many distinguished chemists of the time attempted to generate the corresponding ether. Gay-Lussac (1778–1850) and Dumas (1800–1884) referring to ether synthesis state that “*The topic is preoccupying almost all European chemists at the moment [...]. All the chemists have felt that it is this study which one day will deliver detailed knowledge of the composition of organic matter*” (Gay-Lussac and Dumas 1833). Among those trying was no lesser one than Antoine Laurent Lavoisier (1743–1794) who presented his work on various derivatives of phosphoric acid to the French Academy of Sciences on November 18th, 1780. Lavoisier summarizes his efforts in ether synthesis by stating that “*mais jamais je n’ai pu parvenir a coeercer une seule goutte d’ether*” or “*I never managed to force out even one drop of ether*” (Lavoisier

1780). Equally unsuccessful at generating phosphor ether were the respective attempts of Scheele, Johann Friedrich Westrumb (1751–1819) and of the academicians of Dijon around Guyton de Morveau (1737–1816) (Boullay 1807).

The first whiff at the sweet smell of success (“phosphor ether”) belonged to a young pharmacist from Paris, Jean Pierre Boudet (1778–1849). At the age of twenty-three on 19 brumaire of the 10th year of the French Revolution (November 10th, 1801) he gave a talk to the Pharmacists’ Society in Paris, reporting on a “*real interaction between (phosphoric) acid and alcohol and the manifestation of most phenomena accompanying etherification*”. This was published in “*Annales de Chimie*” XL, 123 under the title “*Essai sur la preparation de l’ether phosphorique*” and than again incorporated in the Dissertation defended in front of the Faculty of Sciences of the University of France (Boudet 1815).

The Boudets originated from Reims but the father - a confectioner (*confisiseur*) - took the family to Paris in pursuit of better opportunities. While initially everything went according to plan with the boy following courses at the prestigious *Collège d’Harcourt* (renamed *lycée Saint-Louis* after 1820) the French Revolution spoiled the best laid plans; Jean Pierre had to quit formal education and entered an apprenticeship in the Pharmacy of his uncle, Jean-Baptiste Pierre Boudet (1748–1828). The uncle was attracted to a career in the military (he was to become chief pharmacist of the French Army in Egypt, than in Austria and Prussia, Member of the Academy of Medicine, founding member of the Pharmacists’ Society), so that when duty called he handed over the Pharmacy to his nineteen years young nephew. Despite the initial lack of experience our Boudet run the pharmacy very successfully for many years to come only to eventually hand it over to his pharmacist son Félix Henri [Jean Pierre had two sons: Félix Henri who succeeded him at the Pharmacy and later became a Professor of Pharmacy and Ernest, a physician who died young, just three month before his father died (of cholera)].

The Pharmacy (Paris, rue du Four Saint Germain, numéro 88) was at the time one the most reputable in Paris with the list of successive *Maîtres* reading like a “Who’s Who” of French

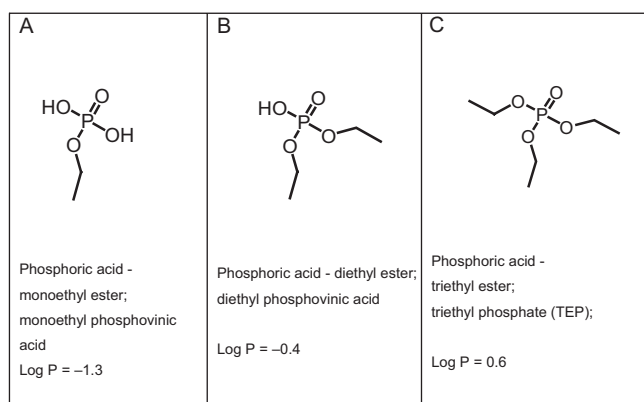


Fig. 1: A: Monoethyl phosphovinic acid identified by Lassaigne (1820) and isolated by Pelouze (1833). B & C: Diethyl phosphovinic acid and the neutral triethyl phosphate (TEP) synthesized by Voegeli (1848)

science history: Philippe-Nicolas Pia, alderman of Paris and creator of the first-aid service to rescue drowned people (1721–1799), Nicolas Deyeux, Pia's nephew, pharmacist to the Emperor Napoleon I and Member of the Academy (1745–1837), Boudet, the Uncle (1748–1828), Boudet, the Nephew (1778–1849), Félix Henri Boudet, the Son (1806–1878). Among Boudet's many contributions, the establishment of the *Bulletin de Pharmacie* deserves special mention: it was the first scientific journal published by pharmacists for pharmacists. The names of the six founders and members of the editorial board are mentioned on the cover page (Fig. 2).

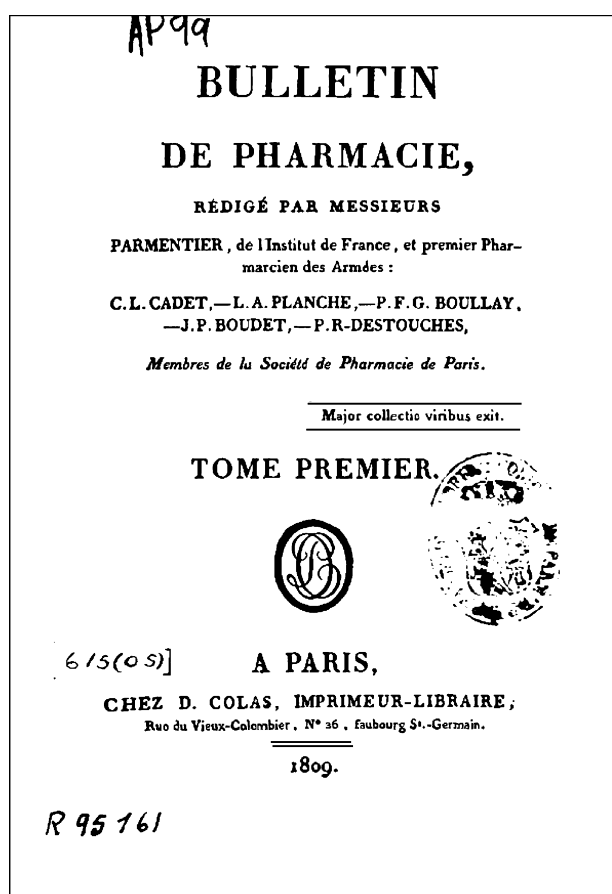


Fig. 2: Boudet established the Bulletin de Pharmacie together with Jean Antoine Augustin Parmentier (1737–1813), Charles Louis Cadet de Gassicourt (1789–1861), Louis Antoine Planche (1776–1840), Boullay the Elder (1777–1869) and Pierre Regnaud Destouches (1779–1859) the first scientific journal published by pharmacists for pharmacists

NÉCROLOGIE.

ÉLOGE DE JEAN-PIERRE BOUDET; Par E. SOUBEIRAN.

M. Boudet en retira un liquide éthéré qui ne différait guère de l'éther sulfurique que par une odeur étrangère. Un pas de plus et il avait découvert que l'acide sulfurique et l'acide phosphorique transforment l'alcool en un seul et même éther : il ne le fit pas, et laissa à son ami et parent, M. Boullay, la gloire de mettre hors de doute ce fait remarquable.

Fig. 3: Eugene Soubeiran, a friend and colleague, points out in Boudet's obituary that while Boudet managed to generate some ether using phosphoric acid he failed to recognize that "sulphuric and phosphoric acids transform the alcohol into a single and same ether" [which is neither sulphuric nor phosphoric]

Upon his death the obituary was delivered by his friend and colleague Eugene Soubeiran (1797–1858), one of the fathers of chloroform. Jean Pierre Budet's contribution to phosphor ether chemistry is detailed in the obituary (Fig. 3). Soubeiran writes: "Mr. Boudet obtained an etherified fluid not different from the sulphur ether but by a strange odor. One more step and he would have discovered that the sulphuric and phosphoric acids transform the alcohol into a single and same ether: he did not took it (the step) and left to his friend and mentor, Mr. Boullay, the glory to establish beyond doubt this remarkable fact". Only a few months Jean Pierre's senior was his friend and colleague Boullay the Elder, Member of the Academie and Knight of the Legion of Honour. Boullay Sr., Pierre Francois Guillaume (1777–1869) (Fig. 4) and his son, Felix Polydore Boullay, Jr., (1806–1835) both pharmacists in Paris (rue des Fossés Montmartre, numéro 17; today rue d'Aboukir) were also involved in ether research. Unfortunately Boullay the Younger died at a young age off the sequels of an ether explosion sustained in 1830. The obituary was written by Alphonse Jean Baptiste Chevallier (1793–1872).

Boullay the Elder managed to produce large quantities of the elusive phosphor-ether thanks to an innovative "appareil" (Fig. 5). Although he was erring in his assumption that the acid removed

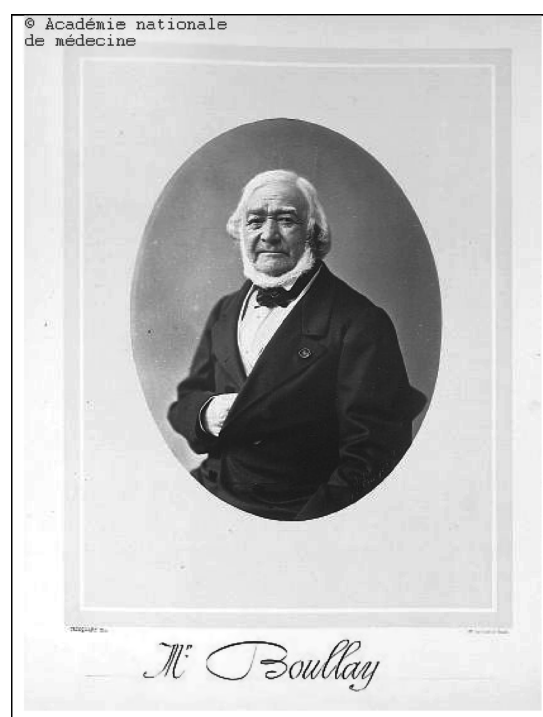


Fig. 4: Boullay Sr., Pierre Francois Guillaume (1777–1869) pharmacist in Paris. Reproduced with generous permission of the Bibliothèque de l'Académie Nationale de Médecine; [Blanchard Damien]

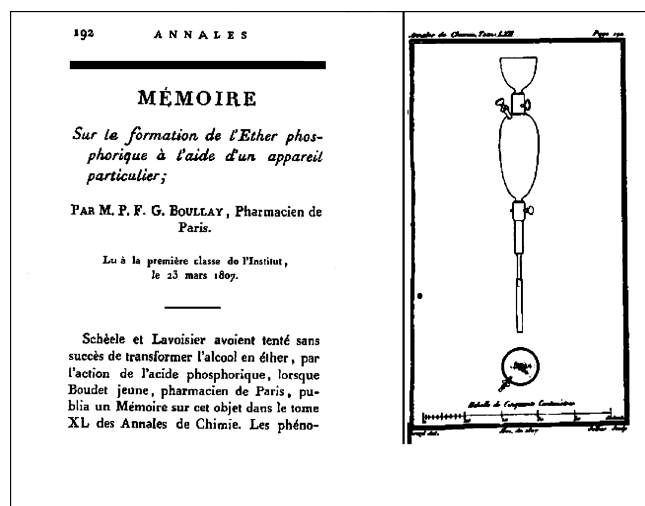


Fig. 5: Boullay's publication from 1807: He is reporting on the ability to produce large quantities of the elusive phosphor-ether thanks to an innovative "appareil"

oxygen and hydrogen (water) from the alcohol to produce ether he showed that the acid functioned as a "catalyst" (Boullay 1807; Gilbert 1813, Boullay 1815). For a truly superb historical description regarding the history of ether and the issue of catalysis vs. stoichiometry, see Priesner (1986). Boullay recognizes that the type of acid (sulphuric or phosphoric) is not influencing the ether generated, the product being the same.

The next player on the way to organophosphate synthesis was Jean Louis Lassaigne (1800–1859), a chemistry pupil of Louis Nicolas Vauquelin (1763–1829). Lassaigne was apparently born at the Natural History Museum where his father was employed as a mechanic. For schooling he was sent to the prestigious boys boarding school of Hallays-Dabot in the rue des Fossés-Saint-Jacques attending courses at the lycée Napoleon. By the age of seventeen he was already publishing (with Chevallier, another pupil of Vauquelin); his talent was early recognized, Lassaigne received 1821 and 1822 silver medals from the Medical Society of the Seine Department and 1825 a Honorable Mention in experimental physiology from the Academy of Sciences. Thereafter he was appointed chemistry professor at the Ecole de Commerce de Paris. Professor Dulong from the *École Royale Vétérinaire d'Alfort* (Royal School of Veterinary) was charging Lassaigne with directing his chemistry laboratory and upon Dulong's retirement Lassaigne applied for the vacant position and was eventually appointed Professor in 1827. He held this post until 1854 (Fig. 6). Lassaigne was Corresponding Member of the Imperial Academy of Medicine and of the Société de Pharmacie. The eulogy at Lassaigne's grave was delivered by Felix Boudet, the aforementioned son of Jean Pierre.

On a lighter note, at the time (1853–1854) a Professor Lassaigne from Paris and his *collaborateur* Julio were entertaining the crowds of Europe with a balloon; the balloon would lift into the air and Julio, a trapeze artiste, would perform dangerous exercises. The most audacious performance was delivered in Amsterdam when the balloon lifted a horse into the air. This is apparently the first time in history when a horse took a balloon ride (Fig. 7). Despite the love of the pharmacists-chemists of the time for balloon rides (Guyton de Morveau and Gay-Lussac took well documented balloon trips) it is highly unlikely that the balloon Professor was our distinguished Corresponding Member of the Imperial Academy of Medicine.

On Vauquelin's suggestion Lassaigne works on phosphor ether and attempts to isolate phosphovinate (Lassaigne 1820). The term "vinic" denotes a compound "made of vine," such as the ethyl in ethanol; vinic acids were understood as products of an

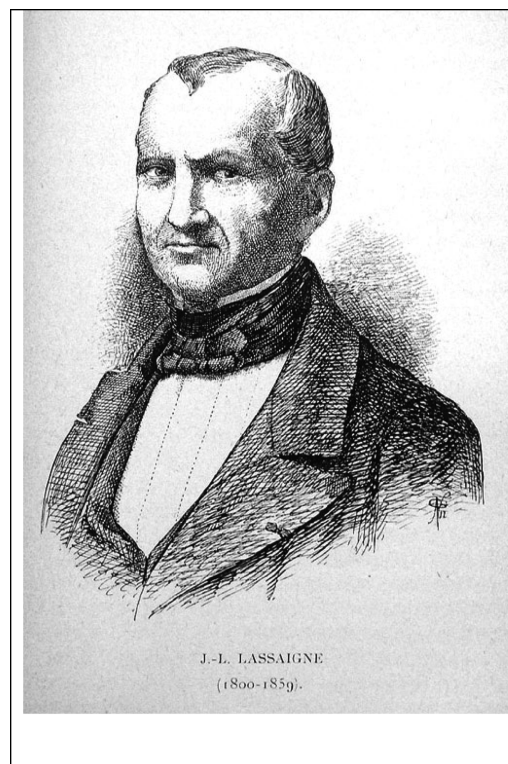


Fig. 6: Jean Louis Lassaigne (1800–1859) identifies phosphovinic acid as an analog of sulfovinic acid, the intermediate stage in the production of "true" ether. Reproduced from: Neumann (Louis Georges), *Biographies vétérinaires*, Paris. Asselin et Houzeau, 1896, p. 210. ©BIUM Paris with generous permission of the Bibliothèque interuniversitaire de médecine et d'odontologie; [Estelle Lambert, Conservateur - Service d'histoire de la médecine]

acid with ethyl. Lassaigne saw phosphovinic acid as an analog of sulfovinic acid, the intermediate stage in the production of "true" ether (described first by Hyacinthe Dabit (1764–1808), pharmacist in Nantes, and later by the much better known Friedrich Wilhelm Sertürner (1783–1842), pharmacist first in Einbeck and then in Hameln) (Priessner 1986). He starts his paper by saying "Mr. Dabit is the first one to have observed that sulfuric acid was partially decomposed during etherification and transformed into an acid that he viewed as a intermediary between the sulfurous and sulfuric acids". He continues "It was natural to think that if one obtained an analogous product by the action of



Fig. 7: Professor Lassaigne from Paris and his *collaborateur* Julio were entertaining the crowds of Europe with a balloon; the most audacious performance was delivered in Amsterdam on Saturday September 17th, 1853 when the balloon lifted a horse into the air. The tickets were extremely expensive, a seat in the first row costing 99 cents. It is however highly unlikely that the balloon Professor was our distinguished Jean Louis Lassaigne

alcohol on the phosphoric acid this operation had to give as a result an acid made by phosphorous and elements of alcohol, corresponding to the sulfovinic acid". Lassaigne concedes however that "La petite quantité de phosphovinate de chaux que j'ai obtenue ne m'a pas permis d'extraire cet acide à l'état de liberté, ni de former d'autres combinaisons" or "the small quantity of phosphovinate of lime that I obtained did not allow me to extract the free acid or to form other combinations".

Lassaigne's search of phosphovinate was taken up by Théophile-Jules Pelouze (1807–1867) (Fig. 8). He wrote: "Monsieur Lassaigne did not push his researches further.....I was fairly happy to isolate a new acid and new salts which I shall name phosphovinic acid and phosphovicates, to conform to the generally accepted nomenclature adopted for sulfovinic acid and the sulfovinates" (Pelouze 1833). (Figs. 1A, 9).

Jules was the son of Edmond Pelouze, an industrial chemist of some fame who authored a number of works dealing with practical aspects of chemistry. Vauquelin apparently knew Pelouze the father and showed some interest not only in his work, but also in the career of his son. The young Pelouze was to become a pharmaceutical chemist. He started his apprenticeship in La Fère in the pharmacy of Maître Dupuy, but on Vauquelin's advice he later joined Chevallier in Paris. There he had the opportunity to interact with renowned scientists such as Lassaigne who recognized the young man's potential and recommended him to Joseph Louis Gay-Lussac (1778–1850).

Another version of the beginnings of the relationship between Pelouze and Gay-Lussac was told by Jean-Baptiste Dumas (1800–1884), the Secretary for Life (*Secrétaire Perpétuel*) of the Academy of Sciences, in the public lecture given on July 11th, 1870 and titled "Éloge Historique de Jules Pelouze": young Pelouze being caught in a tempest forced a passing-by carriage to stop. Being offered a ride by the generous passenger on board he soon found himself involved in chemistry discussions with the passenger who – surprise – was the famous Gay-Lussac.

Whatever the truth might be, Gay-Lussac placed young Pelouze in the laboratory of Wilson. It is highly likely that the mentioned



Fig. 8: Théophile-Jules Pelouze (1807–1867); From the Edgar Fahs Smith Collection. Reproduced with permission [Lynne Farrington, Annenberg Rare Book and Manuscript Library, University of Pennsylvania, Philadelphia]

Wilson was Daniel (1790–1849), a colorful personality of Scottish descent, which after a string of financial disasters (mostly for his partners) managed to become extremely rich with a gas lightning company in Paris. Daniel Wilson's obituary published in the Minutes of the Proceedings of the Institution of Civil

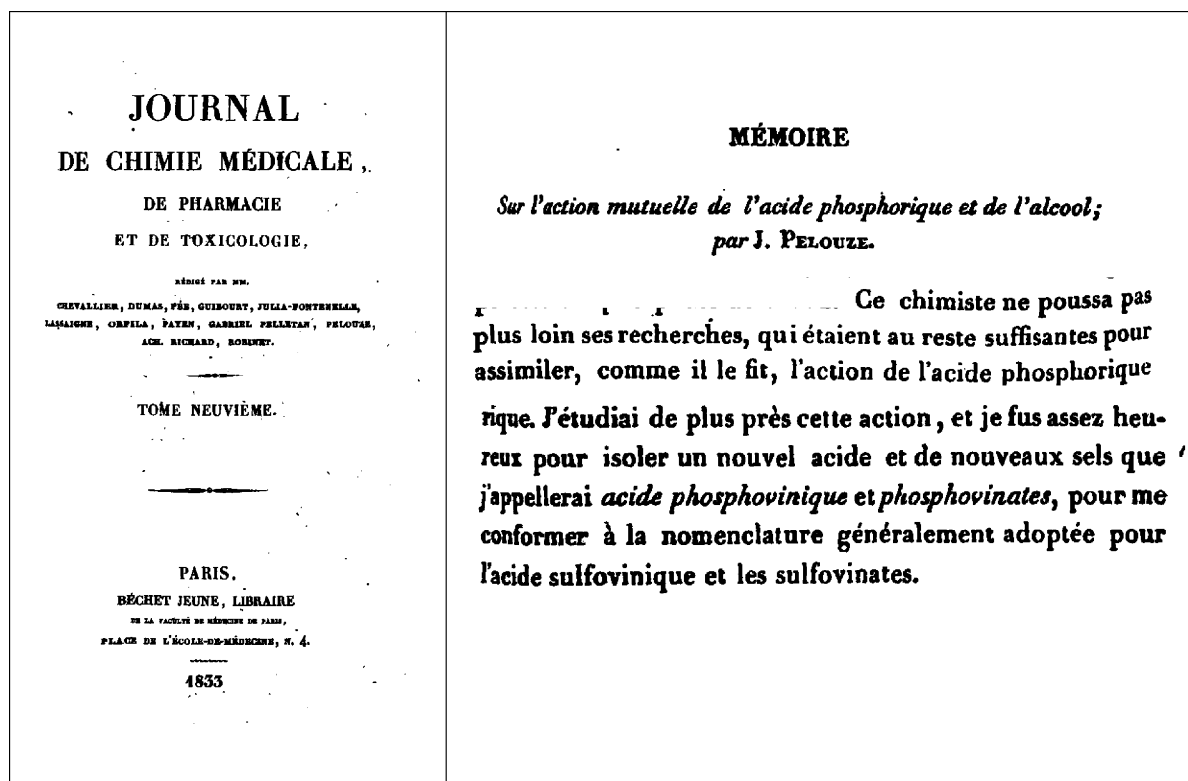


Fig. 9: The search for phosphovinate was taken up by Théophile-Jules Pelouze who managed to isolate phosphovinic acid. His Memoire was published 1833

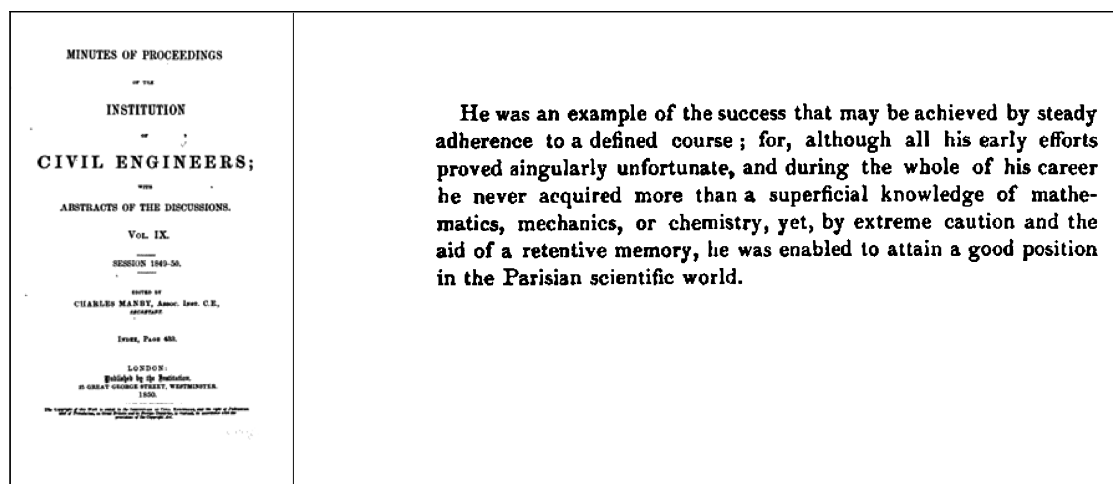


Fig. 10: Excerpt from Daniel Wilson's (1790–1849) obituary published in the Minutes of the Proceedings of the Institution of Civil Engineers, Volume 9, London 1850

Engineers, in London 1850, not only gives an idea about Wilson, but is also a superb example of British euphemism (Fig. 10).

Jules Pelouze's son, the doctor Eugène Philippe, was married for twelve years with Marguerite Wilson, Daniel Wilson's daughter. Thanks to the Wilson money the couple owned and lived at the Château de Chenonceau (after Versailles nowadays the second most visited castle in France). After the divorce she went on to become the *maitresse* of the President de la République (Jules Grevy). Daniel's other child, a son also named Daniel, was to become an influential politician in France; he married the daughter of the then President de la République, the aforementioned Grevy. When Daniel (the son) became involved in a scandal related to the selling of nominations for the Légion d'honneur (National Order of the Legion of Honor) Monsieur le President had to resign (December 2nd, 1887).

The other noteworthy kinship of Théophile-Jules Pelouze was his nephew, Philippe Alexandre Jules Künckel d'Herculais (1843–1918). He was the son of doctor Künckel, an youth friend of Pelouze, whose sister Mathilde Josephine (1814–1867) he married when she turned sixteen in 1831. The mother was Georgette d'Herculais. The boy lost his father when he was two years old. Jules Künckel d'Herculais was to become an entomologist of international repute: the root mealybug (*Rhizococcus falcifer Künckel d'Herculais*), a piercing and sucking hexapod from Australia and New Zealand, is named after him.

After serving for about three years under the guidance of Gay-Lussac and Lassaigne as assistant in Wilson's laboratory, he was appointed Professor of Chemistry, first in Lille and then in Paris, where from 1831 to 1847 he took the place of Gay-Lussac at the *Ecole Polytechnique*. Also from 1831 he was elected to supply the place of Baron Louis Jacques Thénard (1777–1857) at the *College de France*. Ascanio Sobrero and Alfred Nobel were among his better-known students. Despite his many duties he managed to travel to Gießen and to perform joint research with Justus von Liebig (1803–1873).

1837 Pelouze became a member of the *Académie des Sciences* (occupying the seat of Deyeux). He was appointed successively knight, officer and then commander of the Legion of Honor. He worked on the Board of the Mint becoming Chair of the Board and eventually Director of the Mint (*Directeur de la Monnaie de France*). He passed away in 1867, only three month after losing his wife of thirty-six years. The eulogies at the grave of Pelouze were delivered by Dumas on behalf of the scientific community and by Edmond Frémy (1814–1894), his lifelong *collaborateur*, on behalf of his former students.

The preliminary "final" station on the way to triethyl phosphate (TEP) is Berlin and the chemistry laboratory of Gustav Magnus

(1802–1870), Professor of Physics and Technology at the Universität Berlin. Magnus supervised the work of the Swiss Franz Anton Voegeli, who was to become the father of both diethyl and triethyl phosphate (Voegeli 1848; Petroianu 2009). (Fig. 1B, C).

In conclusion, if one had to draw an imaginary line marking the beginning of organic phosphorus chemistry, that would be in my view the year 1801 when Boudet generated traces of what he believed to be "phosphoric ether". The next step was the recognition by Boullay 1807 that the "phosphoric ether" is identical with the "sulfuric ether". Soon thereafter in 1820 Lassaigne made the analogy between sulphovinic and phosphovinic acids and demonstrated the existence of phosphovinic acid, while Pelouze 1833 synthesised it. Finally 1848 Voegeli produced the first neutral ester of phosphoric acid, the triethyl phosphate (TEP).

Shortly thereafter ether chemistry made a quantum leap with Williamson's elucidation of the ether formula and description of the reaction steps leading to ether formation (Williamson 1851, 1852). 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 in increasingly higher yield. Although with the TEP synthesis by Voegeli the first organophosphate was created, this accomplishment is eclipsed in hindsight 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).

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