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Synthesis of tetraethyl pyrophosphate (TEPP): from physician Abbot and pharmacist Riegel to chemist Nylen

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Tetraethyl pyrophosphate (TEPP) made history not only as the first man-made organophosphate cholinesterase inhibitor but also as a most successful commercial product traded under a good number of names. The substance was first synthesized by a Russian chemist, Wladimir Petrovich Moshnin, while studying in Paris as an *élève* (student) of Wurtz. The synthesis was soon thereafter repeated and reported to the Academy of Sciences by Philippe de Clermont, another student of Wurtz, who acknowledged the earlier work of Moshnin. Holmstedt in his chapter dealing with the beginnings of organophosphate chemistry in Koelle's Textbook *Cholinesterases and Anticholinesterase Agents* concluded his remarks by noting that 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). This led to my attempts at identifying those involved in the synthesis of TEPP. The compiled list turned out to be quite long: Abbot (1879), Riegel (1896), Cavalier (1906), Rosenheim A, Stadler & Jacobsohn (1906), Rosenheim & Pritze (1908), Balareff (1914), Nylen (1930), Arbusow & Arbusow (1931), Schrader (1938), Woodstock (1946) and Toy (1948). This report while summarizing the synthetic approach used in obtaining TEPP by the respective scientists mainly attempts to shed light on the life of the less known pharmacists and chemists involved in the synthesis of TEPP. The focus is on the pre-industrial synthesis period ending with Nylen largely because details on the Arbusow family, as well as on Schrader and Toy are fairly well known or have recently been described.

1. Introduction

Tetraethyl pyrophosphate (TEPP) made history not only by being the first ever man-made organophosphate cholinesterase inhibitor but also as a most successful commercial product manufactured by many companies and traded under a good number of names: Bladan[®] (Bayer), Nifas T[®] (Monsanto), Kilmite[®] (Miller), Vapotone[®] (Chevron), Tetron[®] and Tetra Tone[®] (Lucas-Kiltone), Killlex[®] (Sherwin Williams), Mortopal[®], Hexcide[®] (Niagara Spray) (Fig. 1). 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, 1855). The synthetic approach used by both Moshnin and de Clermont was based on the work of Alexander Williamson (1824–1904), an English chemist trained in Heidelberg and Gießen. Williamson serendipitously discovered a new way to produce *ethers* using ethyl iodide and salts of the acid to be esterified (Williamson 1851, 1852; Priesner 1986). The ingredients were easily available. Ethyl iodide, first described in 1814 by Joseph Louis Gay-Lussac (1778 -1850) could be obtained by one of the many modifications of a method originally proposed by Georges Simon



Fig. 1: Early ad for TEPP produced by ORTHO and marketed as Vapotone[®] by California Spray and Chemical Company (Cal Spray), a predecessor of Chevron Chemical Company.

Serullas (1774–1832) (Reimann 1866). Silver pyrophosphate as well as many other salts of Clarke's pyrophosphoric acid [Thomas Clarke of Glasgow (1801–1867)] were first synthesized by Adolph Emil Schwarzenberg (1826–1901) (Fig. 2) a graduate student of Friedrich Wöhler (1800–1882), since 1836



Fig. 2: Adolph Emil Schwarzenberg (1826–1901).

Chair (*Ordinarius*) of Chemistry and Pharmacy in Göttingen (Clarke 1829; Schwarzenberg 1848; Petroianu 2009a).

Bo Holmstedt (1919–2002) in his chapter dealing with the beginnings of organophosphate chemistry in Koelle's Textbook *Cholinesterases and Anticholinesterase Agents* published half a century ago (Holmstedt 1963; Atkinson and Sjoqvist 2002) concluded his remarks by noting that after Moshnin and de Clermont, over the years, a good half-a-dozen of other pharmacists and chemists also managed the feat (of synthesizing TEPP). This statement teased my curiosity (and possibly that of many others as well) and led to my attempts at identifying those involved in the synthesis of TEPP. While the task was greatly facilitated by the same Holmstedt who in a different publication provided some of the names, he was off the mark: we were not looking at half a dozen but to a dozen and a half (approximately) (Holmstedt 1951). More names of TEPP synthesizers were then found in the doctoral thesis of Paul Nylén (1892–1976) (Nylén 1930), some more were identified by this author and finally a superb review of the topic was published by Schrader (1963). The thus compiled list turns out to be quite long: Abbot (1879), Riegel (1896), Cavalier (1906), Rosenheim A, Stadler W & Jacobsohn F (1906), Rosenheim & Pritze (1908), Balareff (1914), Nylén (1930), Arbusow & Arbusow (1931), Schrader (1938), Woodstock (1946) and Toy (1948).

This report while summarizing the synthetic approach used in obtaining TEPP by the respective scientists mainly attempts to shed some light on the life of the less known pharmacists and chemists involved in the synthesis of TEPP, the first organophosphate inhibitor of cholinesterase. The focus is on the pre-industrial synthesis period ending with Nylén largely because details on the Arbusow family, as well as on Schrader and Toy are fairly well known or have recently been described (Petroianu 2009, 2014).

2. People involved in TEPP synthesis

2.1. Abbot E. Griffith

Griffith set out to examine the product of the reaction between *Pyrophosphorsäurechlorid* (tetrachloride of pyrophos-

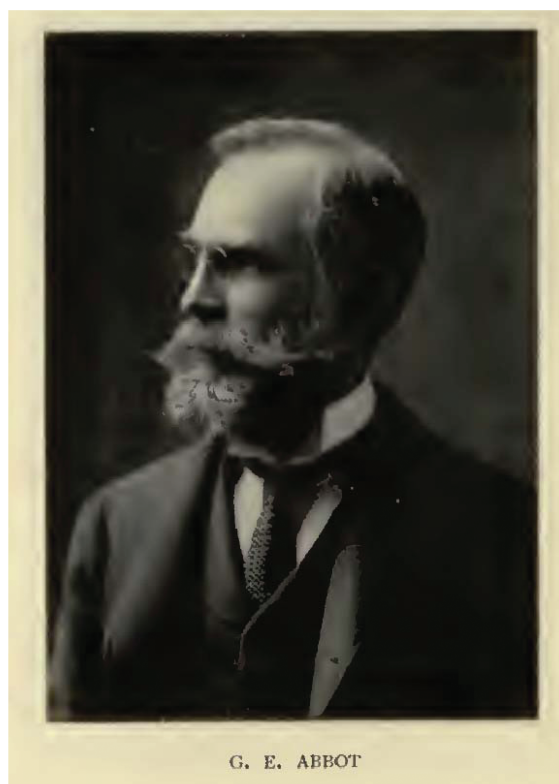


Fig. 3: Evans Griffith Abbot (1850–1926) Reproduced from: *Universities and their Sons. University of Pennsylvania: Its History, Influence, Equipment and Characteristics with Biographical Sketches and Portraits of Founders, Benefactors, Officers and Alumni.* Joshua Lawrence Chamberlain (Ed.) Volume 2, p 437–438, Boston 1902, R Herndon Company.

phoric acid; $\text{Cl}_4\text{O}_3\text{P}_2$) and *Natriumalkoholat* (sodium ethoxide; $\text{C}_2\text{H}_5\text{ONa}$). The pyrophosphoric acid chloride was earlier synthesized by his doctoral supervisor, Professor Anton Geuther (1833–1889), chair (*Ordinarius*) of the Chemistry Department in Jena and Geuther's student (later chair of chemistry and pharmacy in Rostock), Karl August Michaelis (1847–1916) (Geuther and Michaelis 1871). Abbot compared the ester obtained by this approach with TEPP as produced by Moshnin and de Clermont and concluded that the two compounds were identical (Abbot 1875).

Abbot E Griffith (1850–1926) (Fig. 3) was the scion of most distinguished and wealthy American families. His maternal grandfather Griffith Evans was a close friend of James Madison the fourth President of the United States, and acted as a groomsman at the later's wedding. Abbot's father Charles Frederick (1821–1897) was not only a successful businessman but also a prominent public figure serving i.a. as a trustee of Bucknell University founded in 1846. After preparatory school in Philadelphia (Henry D Gregory's Classical School) he obtained a bachelor's Degree from the University of Pennsylvania (1871). Subsequently he moved to Germany where he studied at the Universities of Erlangen (1871–1873), Leipzig (1873–1875) and Jena (1875). It is in Jena that he obtained his doctoral degree. Upon return to America Abbot taught chemistry in the Medical School while studying medicine at the University of Pennsylvania (MD 1879). He practiced medicine in Pennsylvania and married 1885 Grace Lee Babb. In 1894 he became a major shareholder and president of the Washington, Alexandria and Mount Vernon Railway Company, a business engagement which turned out to be ruinous and marked the final years of his life.

2.2. Maximilian Riegel

Riegel in his doctoral thesis described the synthesis of new pyrophosphates (phenol-, cresol-, naphthol-) using the reaction between pyrophosphoric acid chloride and the respective sodium salts. He also examined the degradation products generated by the effect of water on TEPP; the TEPP needed for his experiments he obtained both via the classical method of Moshnin and de Clermont and the Abbot approach (Riegel 1896).

The pharmacist and chemist Maximilian Riegel (1870–1939?) hailed from a moderately well-off family of merchants established in Swinemünde on the isle of Usedom in Pommerania. After graduation from the *Friedrich-Wilhelm-Realgymnasium* in Stettin, he attended lectures in chemistry and pharmacy at the Universities of Breslau, Berlin and Rostock (WS 1895–1896, SS 1896 and WS 1896–1897) where he obtained his doctoral degree (Dr. phil.) under the supervision of Professor August Michaelis (1847–1916), chair (Ordinarius) of the Chemistry Department. 1896, the year of his doctorate his father was already deceased; the thesis is movingly dedicated to his beloved mother and to the memory of his father.

After Rostock his interests drifted from science to commercial ventures. In 1898 we find Max Riegel and Adolf Rose (also a pharmacist) in the city of Cologne establishing the *Rheinische Nahrungsmittelwerke AG*, a commercial venture having the purpose, as announced in the *Molkerei-Zeitung* 1899,9: 258 of producing and marketing a substitute for breast milk in liquid, condensed or powdered form as well as of a sugar free milk for diabetics („*Gegenstand des Unternehmens ist die Herstellung und der Vertrieb eines Ersatzmittels für Frauenmilch in flüssigem, kondensiertem und festem Zustande, einer zuckerfreien Milch fuer Diabetiker in flüssigem und festem Zustande und anderer Nährpräparate....*“). The joint venture is apparently short lived as 1901 Riegel leaves the board (*Vorstand*) to be replaced by a certain Martin Michaelis. For the next forty years or so Riegel will be residing in Berlin; he married Bertha and their son Heinz was born September 1903. The next years are all good news: 1904 Riegel, Michaelis and other defendants are acquitted of violating the Nutrition Law (*Nahrungsmittelgesetz*) and of endangering public health by using boric acid as a food preservative. 1905 Riegel traveled to London, patents for milk powder production were issued and 1906 he established a food processing company (*Dr Riegels Nahrungsmittel-Werke GmbH*) and became the chief executive (*Geschäftsführer*). Around 1908 pharmacist Martin Stern (1869–1934; Dr. phil. Erlangen 1893) joined him as *Geschäftsführer*. The company was marketing a number of products such as the liquid gas *Milchozon*[®], an additive to milk (hydrogenperoxide) supposed to prolong its shelflife, *Leto*[®] *Kokosnussbutter*, a vegetable (coconut derived) butter substitute, *Lecipon*[®], a water- and alcohol- soluble and well-tasting lecithin preparation in powder form or the *Egos*[®] *Trocken-Gebirgs-Backmilch*, powdered mountain milk with an admixture of peanut and sesame oil. Stern and Riegel, the two executives of the *Nahrungsmittel-Werke* were found guilty of violation of the *Margarinegesetz* (Margarine preparation code) and required to pay fines, as announced in the *Molkerei-Zeitung* 1912, 22: 341. During World War I the Riegel Factory produced for the military, not only as advertised vegetable fats for tropical climates (*Pflanzenfette für die Tropen*) but apparently also poisonous gases for warfare (*Kampfgase*) (Grundmann 2008). When exactly the Stern-Riegel business relationship ended is unclear; while the food business was liquidated 1925 Riegel continued to operate the chemical factory/laboratory located in Berlin-Wilmersdorf, Brandenburgische Strasse.

But the times were turning darker. Riegel's son Heinz was politically active and traveled twice to South America (1923 and 1929) to spread the communist revolution. Upon return to

Germany he was active in various communist organizations, arrested for treason by the Nazi authorities (1935) and sentenced to four years in prison. After release (and payment of a substantial fee by his parents) he was allowed to emigrate. He ended up in Mao's China where he spent the war years (Grundmann 2008). As to his parents they stayed in Berlin, Schlachtsee: the father was deported to death camp 1939 while his wife Bertha followed around 1943. His early partner, pharmacist Dr. Stern and his family committed suicide early enough (1934) as to escape the Nazi death camps.

2.3. George and Jacques Cavalier

Cavalier used the Williamson reaction of silver pyrophosphate with ethyl-, propyl-, isopropyl-, butyl-, amyl- and allyl-iodide to obtain the respective neutral pyrophosphates, among them also TEPP. His results were presented to the Academy of Sciences by the President Joseph-Louis Troost (1825–1911) (Cavalier 1906). The family of Jacques Cavalier (1869–1937) hails from Tours in central France where Antoine-Frederic Cavalier (*1805), the grand-father, was a merchant. His son, Georges “*pipe-en-bois*” (1842–1878), the father of the chemist was one of colorful figures of the Paris Commune, the revolutionary government that briefly ruled Paris in 1871. The nickname *pipe-en-bois* given to him by his friend the journalist Jules Vallès (1832–1885) is derived apparently from the resemblance of his skull with the rough carved heads of wooden pipes (Fig. 4). Married with Camille Arkwright (*1847) Georges “*pipe-en-bois*” had two daughters and two sons. The eldest son Paul Frederic (*1868) who graduated 1884 from the *Ecole de Physique et de Chimie Industrielle de Paris*, became a successful industrialist (manufacturer of adhesives) and politician [*Maire* (mayor) of Givet, a city in the Ardennes] and was appointed *Chevalier* of the Legion of Honour. The younger brother Jacques, our chemist, graduated from a very prestigious Paris *Lycée* (Saint Louis) and then from the *École Normale Supérieure*, the elite institution of choice for many of France's brightest young people (Fig. 4). His career was stellar: Professor of Chemistry at the University of Rennes (1905–1909), he became rector of the academy in Poitiers (1909–1914), than rector in Toulouse (1914–1922) and finally Lyon (1922–1926) before entering politics. He was appointed Director of Higher Education (1926–1937) in Paris serving in the final years under Jean Zay (1904–1944), the then Minister of National Education and Fine Arts. Cavalier was one of the four scientists nominated for replacing the deceased chemist Achille Le Bel (1847–1930) at the French Academy of Sciences; he lost, however, the election (February 1931) to Louis Martin (1864–1946) and Armand de Gramont, duc de Guiche (1879–1962) (de Gramont 32 votes, Martin 29 votes). Cavalier died tragically in an accident: while crossing as a pedestrian Place d'Italie in Paris he was hit by a motorcycle. Jacques was married with Camille Pernot and they had a daughter.

2.4. Rosenheim and his students

Rosenheim and his students, Stadler and Jacobsohn, did not even intend to synthesize TEPP; they were re-examining results previously published by Saenger working in Jena (Saenger 1886). After having obtained the methyl-ester of hypophosphoric acid (*Unterphosphorsäure*; $H_4P_2O_6$) by the classical Williamson reaction using methyl-iodide and silver-hypophosphate they also attempted to synthesize the ethyl-ester. To their surprise they obtained TEPP, the ester of the pyrophosphoric acid instead (Rosenheim et al. 1906). Rosenheim and Pritze, another graduate student, repeated the experiments shortly thereafter and obtained the ethyl-esters of both the hypo- and pyrophosphoric



Cavalier, Georges
(1842 - 1878)



Cavalier, Jacques
(1869-1937)

Fig. 4: George and Jacques Cavalier. Photo by Henri Martinie reproduced with kind permission of the copy-right holder Paris en Images & Roger-Viollet collections.

acids; they explained the initial failure by the rapid oxidation of the hypophosphoric ethylester to pyrophosphoric ethylester (Pritze and Rosenheim 1908).

Max Pritze (*1885): Johannes Pritze († 1912), the father of the chemist, was teacher at a public school (*Städtischer Lehrer*) residing in Berlin since 1880, in his own house since 1899. The mother was Anna, born Michaltseck. The couple had two sons: Max born 1885 and Johannes born two years later. Both sons attended the *Luisen-Gymnasium* in Berlin. While Johannes studied in Berlin and Heidelberg and received 1912 a doctoral degree for a thesis titled *Beiträge zur Geschichte der preußischen Regieverwaltung 1766–1789* (Contributions to the history of the Prussian governmental administration), Max studied Chemistry in Berlin; with support from Arthur Rosenheim he was admitted 1905 as an extraordinary member of the German Chemical Society. His doctoral dissertation from 1908 is titled *Über die Komplexbildung selenhaltiger Anionen*.

Felix Jacobsohn (1883–1938): Felix' father Simon was a small merchant in Insterburg, East-Prussia; his mother was Emma Fraenkel. Insterburg, a city now called Tschernjachowsk, is situated in the Russian exclave of Kaliningrad. The German name was related to the river Inster while the Russian name is derived from a sowjet General. Felix attended the local Highschool (*Königliches Gymnasium*). After graduation 1901 he studied Chemistry in Freiburg (one semester) and Berlin (eight semester). He defended his doctoral thesis titled *Die Einwirkung von flüssigem Ammoniak auf einige Metallsäureanhydride* (Action of liquid ammonia on some acidic metallic anhydrides) in December 1905. He received a number of German and international patents. While residing in Berlin Paulsbornerstrasse he is listed in the *Adressbuch* of the city until 1931 as a chemist, subsequently as a lawyer specialized in patent protection. After 1938/1939 he is not listed anymore and no further information about him could be elicited.

Wilhelm Stadler (1880–1967): The chemist hails from a large family from Steinamanger (Szombathely) in Hungary. His parents were Salomon Stadler (1826–1894) and Lina Wolf (1840–1900). The couple had five children, Wilhelm being the youngest. He studied chemistry in Leipzig, Zurich

(1899; Matrikelnummer 12462) and Berlin where he received his doctoral degree in 1903 with a thesis titled *Ueber Bromnaphthochinondiketohydrinden und dessen Umwandlung in ein Biindenderivat*. He married 1914 Frieda Goldschmidt (1883–1955); as the Great War started he joined the army and fought on the eastern front, was captured by the Russians and sent to Siberia. After his return from captivity in 1920 he settled with his wife and daughter (who was born after his departure to war) in Perchtoldsdorf, in the proximity of Vienna (Fig. 5) and established a small paint factory (*Chemische Fabrik Dr. Wilhelm Stadler*) in Liesing (another district of Vienna). After the *Anschluss* (annexation) of Austria, the factory was arianized (*arisiert*; ethnically cleansed) and Dr. Stadler was coerced into turning the factory over to somebody the Nazis considered “appropriate”. Long-time employees (Irene Kalinka geb. Denk and Edith Boehm geb. Graeber) wrote in depositions after the war: “Tatsache ist, dass Dr. Stadler eine tadellose, vollkommen schuldenfreie gutgehende Fabrik gezwungenermaßen einem von den Nazi als geeignet angesehenen Mann übergeben musste, ohne dafür eine Entschädigung zu erhalten” (Fact is that Dr. Stadler was coerced to turn over a perfect factory, absolutely free of debt to a man the Nazis considered appropriate, without receiving any compensation). Stadler left Austria 1938 for England with his wife and son, while his daughter and her husband chose to go to Palestine. During the war he was kept with other Jewish immigrants, as citizens of an enemy country, in an internment camp where he earned his living as a gardener. After the war he managed to regain control of the chemical factory, living alternately in London and Vienna. When his wife passed away, he came to reside permanently in Vienna, working in the chemical factory until it was sold. Stadler paints were of excellent quality and even won a prize in Switzerland. He died of a heart attack in September 1967, at the proud age of eighty-seven, while climbing hills to test his own fitness (*Details kindly provided by Ruth Lelior, the grand-daughter of the chemist*).

Arthur Rosenheim (1865–1942) (Fig. 6): His mother Maria Hallgarten-Rosenheim (1843–1930) was born in Mainz. Her father (Arthur's grandfather) Lazarus Hallgarten (1806–1875) descendent of a well-established family from Mainz migrated 1849 to America, where he made a fortune in the banking business. His wife Eleonore Darmstadter (1813–1870) and daughter



Fig. 5: Wilhelm Stadler (1880–1967). Photo of Wilhelm Stadler kindly provided by the family (Ruth Lelior).



Fig. 6: Arthur Rosenheim (1865–1942). Reproduced from: Arthur Rosenheim und Richard J. Meyer zu ihren 60. Geburtstagen (1925). *Zeitschrift für anorganische und allgemeine Chemie* 147: pages i–iii, Portrait by Eugen Spiro (1874 Breslau - 1972), with kind permission of Bettina Loycke, Senior Rights Manager, Wiley-VCH Verlag, Germany.

Maria joined him in America when the daughter was about two years old. Maria married William Rosenheim (1831–1889), a business partner of her father; their son Arthur, the future chemist, was born in New York City. In 1873 this Rosenheim family returned to Germany where the father established Wilhelm Rosenheim & Company in Berlin. The origins of William Rosenheim are not entirely clear: he moved from Germany to the United States probably in 1861 and became naturalized 1866. Most likely he was related to the descendants of Loeb Seligman (1757–1808) and Edel Lesser (1764–1838) of Heidingsfeld, Bavaria, who took up the name Rosenheim 1812, the lineage is however not clear and the evidence circumstantial (Flade

1996). The son Arthur graduated in Berlin from the *Wilhelms-Gymnasium* and studied chemistry in Heidelberg and Berlin and obtained 1888 his doctoral degree. In 1896 he received his habilitation (*venia legendi*; granted authority to teach) and 1906 he was appointed extraordinary Professor, 1921 than ordinary professor for physical chemistry at the Berlin university. He was vice-president of the German Chemical Society (Wichelhaus 1916; Teichmann 1994). Most of the Rosenheim fortune was used to finance the private *Wissenschaftlich-Chemische Institut Berlin Nord* (Scientific Chemical Institute Berlin North, Chausseestraße 8) a distinguished research laboratory established 1891 by Rosenheim and Carl Friedheim (1858–1909). His Institute was closed down 1933 and he also lost his teaching privileges (*venia legendi*) at the Berlin University; the same year he was forced to give up his position in the Board (*Vorstand*) of the Chemical Society, position to which he was elected the year before (1932); Paul Duden (1868–1954; son of the linguist Konrad Duden) replaced him in that role. The same happened also to the elected president of the Society Privy Council Alfred Wohl (1863–1939) who was replaced by Karl Andreas Hofmann (1870–1940) and to other senior members racially or otherwise not convenient to the Nazi regime (Petroianu 2011; Deichmann 2006). Despite all this Rosenheim did not leave Germany and remained in Berlin, Charlottenburg (Schluetterstrasse) where he died 1942 apparently of a stroke.

2.5. Dimitar Balareff

Balareff was interested in establishing the molecular structure of pyrophosphoric acid (symmetrical vs asymmetrical) and in this context also examined TEPP which he synthesized using the Williamson approach.

Dimitar Balareff (ДИМИТЪР БАЛАРЕВ) (1885–1964) (Fig. 7): The family name is also transliterated as Balarew or Balarev. The father Hristo (1851–1922), a lawyer by training, worked as a judge and eventually became the mayor of Ruse (Bulgarian Ръце, also transliterated as Rousse or Russe and historically also known as Rustchuk), Bulgaria, the city where Dimitar was born. The mother was Anna Simeonova (СИМЕОНОВА) (1857–1947). Dimitar studied chemistry at the university of

pool, the attorney of his widow Marie (Maria). Felix Rosenheim (*1867) was the son of Leopold (1835 Würzburg - 1889; Liverpool) who established the British branch of the family. Leopold was the son of Leopold Ludwig (1800 - 1862), the second of the four male children of Loeb Seligman and Edel Lesser from Heidingsfeld, Bavaria. First born Samuel (*1797) had nine male children, none Wilhelm. Leopold Ludwig had three sons, none Wilhelm, Moritz (*1802) also had no son named Wilhelm. While Joseph (*1805) had a son Wilhelm, this Wilhelm was a London based tea trader (1847–1921). While we were unable to establish the connection between William Rosenheim and Heidingsfeld, the existence of such a close connection is beyond reasonable doubt.

¹ Ads in the *Wuerzburgerger Nachrichten* from 1857 were highlighting business connections between the Rosenheims in New York and Heidingsfeld [Photo 9]. When William Rosenheim passed away in 1889 administration of the Estate was granted to Felix Rosenheim from Liver-



Fig. 7: Dimitar Balareff (ДИМИТЪР БАЛАРЕВ) (1885–1964).

Sofia until its temporary closure in 1907; as prince Ferdinand of Bulgaria opened the national theatre, he was booed by Sofia university students, for which the university was closed for six months and all lecturers were fired. Dimitar continued his studies at the university of Zagreb, Croatia. 1908 he received there a doctoral degree for work performed under the supervision of G Janitschek (Г Яничек); the thesis was titled *Оезводняване на фосфорната киселина при сгряване* (Dehydration of phosphoric acid during heating). After compulsory military service and graduating as a reserve officer he became a science teacher in Ruse at the Prince (Knyaz) Boris school for boys. He participated in the Balkan War (1912–1913), where he sustained an injury severely affecting his vision and received a medal “for bravery”. In 1920 he became an associate professor of chemistry at the university of Sofia. During 1922/1923 he worked in Göttingen, Germany under the guidance of Professor Gustav Tammann (1861–1938), director of the physico-chemical institute of the university. After returning to Bulgaria, Balareff was appointed extraordinary professor of chemistry and then to professor and chair of the department of chemistry (1930–1958) at the university of Sofia. Married with Anna Petkova (Петкова) in 1927, the couple had two daughters (Todorovsky 2005).

2.6. Paul Nylén

Up to Nylén all attempts at TEPP synthesis using the Williamson reaction of silver pyrophosphate with ethyl iodide had a rather low yield. While Nylén also used initially the „true-and-tried“ Williamson approach he avoided heating the reagent mixture and by doing so obtained under laboratory conditions high TEPP purities. In addition to the classical synthesis approach he also described two novel synthetic routes using sodium diethylphosphite ($[\text{C}_2\text{H}_5\text{O}]_2\text{P-ONa}$) as a starting point. Diethylphosphite and triethylphosphite were obtained 1854 by Robert Railton (1822–1875), a student of Williamson in the laboratories of the University College, London. Williamson, the father of modern ether synthesis, was in those years professor of practical chemistry, after 1854 succeeding Thomas Graham also professor of general chemistry at the University College. Railton received 1854 the *Williamson Prize* of 50 £ for work in analytical chemistry „*offered by Alexander Williamson, Esq. for the most successful experimental research undertaken in the Birkbeck Laboratory*“. The laboratory at the University College was named after George Birkbeck MD (1776–1841), a

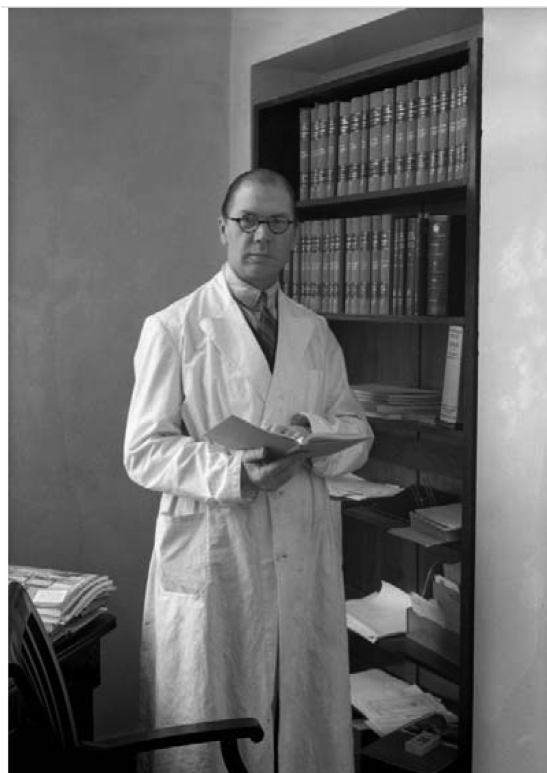


Fig. 8: Paul Nylén (1892–1976). Photo by: Schröder/ Sverresborg Trøndelag Folkemuseum Trondheim (Museum of Cultural History) reproduced with kind permission of the copy-right holder: Schröderarchives/ Sverresborg. Permission granted by Dino Makridis *Fotograf–Leder Bevaringsavdelingen*.

major benefactor. Nylén obtained TEPP both by reacting sodium diethylphosphite with iodine in oxygen and also by reacting it with diethyl chlorophosphate ($[\text{C}_2\text{H}_5\text{O}]_2\text{POCl}$) (Nylén 1930). Diethyl chlorophosphate was obtained 1868 by Hermann Wichelhaus (1842–1927), by oxydizing Railton’s triethylphosphite $[\text{C}_2\text{H}_5\text{O}]_3\text{P}$ with chloride (Wichelhaus 1868). Paul Nylén (1892–1976) (Fig. 8): Nylén, born in Sweden was the son of pastor Joh. Nylén and Alma Petterson. He received his doctoral degree in 1931 with a thesis titled *Studien ueber organische Phosphorverbindungen* (Studies on organic phosphorus compounds). He held various senior academic and administra-

tive positions at the medical faculty in Uppsala, at the Swedish Royal Institute of Technology, at the Norwegian Institute of Technology in Trondheim, and was for many years director of the Swedish paint industry research laboratory. Since 1944 a Professor, 1967 he was the recipient of the *Pedagogmedalj* (teaching prize) of the Swedish Chemical Society. He was married to Helene Ahlfors (1903–1976); they had a son. Professor Paul Nylén is not to be confused with Paul Axel Nylén (1870–1958), a Swedish journalist best known for his editorial role of the journal *Lingvo Internacia*, an Esperanto language publication and for establishing the Swedish Esperanto Federation (*Sveda Esperanto-Federacio*).

2.7. Arbusow, Schrader, Woodstock and Toy

Arbusow [Alexandr Yermingeldovich (1877–1968) (the father) and Boris Alexandrovich (1903–1991) (the son)] unaware of the Nylen work used the action of chlorine on sodium diethylphosphite, the same compound Nylen also used to obtain TEPP (Arbusow and Arbusow 1931; Petroianu 2014).

Gerhard Schrader (1903–1990) looked at many possible large scale synthetic approaches to obtain TEPP. He dismissed the reaction of ethyl iodide with silver pyrophosphate as being of only academic interest and said that it required too much silver per kg of TEPP (BIOS 1947). He also reacted TEP (triethyl phosphate, $[C_2H_5O]_3P=O$) with oxychloride of phosphorus ($Cl_3P=O$) to obtain TEPP (Hall and Jacobson 1948), pointed out however that (during the war) there was a scarcity of TEP in Germany and therefore this route was less attractive (BIOS 1947). TEP, not a cholinesterase inhibitor, first synthesized by Franz Anton Voegeli (1825–1874) in the laboratory of Gustav Magnus (1802–1870) in Berlin, and then by many others, was the first neutral ester of phosphoric acid ever to be obtained. In contrast TEPP was the first cholinesterase inhibitor neutral ester of pyrophosphoric acid. The 1845 discovery of oxychloride of phosphorus is credited to Wurtz (Petroianu 2009a,b). Schrader's preferred approach for a large scale TEPP synthesis was apparently starting with phosphorus trichloride (PCl_3) → diethyl chlorophosphate $[C_2H_5O]_2POCl$ → TEPP (BIOS 1947).

Woodstock, Howard Willard (1906–1958) working for the Victor Chemical Works in Illinois reacted TEP with phosphorus pentoxide (P_2O_5), the combustion product of elemental phosphorus, to obtain TEPP with a yield of about 40% (US patent 2,402,703; 1946).

Toy, Arthur Dock Fon (1916–1996) working for the same company converted diethyl chlorophosphate $[C_2H_5O]_2POCl$ to TEPP in the presence of a tertiary base [Toy, 1949]. His industrial method allowed yields in excess of 70%.

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