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Pharmacists Adolf Schall and Ernst Ratzlaff and the synthesis of tabun-like compounds: a brief history

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The history of the synthesis of organophosphate inhibitors of cholinesterase starting with the synthesis of tetraethyl-pyrophosphate by Moschnin(e) and de Clermont and leading to the recognition about half a century later of the toxicity of the phosphor ester by Lange and von Krueger has been told in great detail previously. An almost parallel history –described originally by Bo Holmstedt – exists for organophosphonate inhibitors of cholinesterase starting with the synthesis (1898) in Rostock of diethylamido-ethoxy-phosphoryl-cyanide by the pharmacist Adolph Schall (1870–1957), a graduate student of August Michaelis (1847–1916), the re-examination of the chemical structure of the Schall compound (1903) by Michaelis, recognition (1937) of the toxicity of class by Gerhard Schrader (1903–1990) and confirmation (1951) of the structure by Bo Holmstedt (1919–2002). This short report attempts to shed some light on the life of the pharmacists and chemists involved in the synthesis of the first P-CN organophosphonate inhibitor of cholinesterase, focusing on the two less known pharmacists, the graduate students of Professor Michaelis Adolph Schall and Ernst Ratzlaff (1870–1948).

1. Introduction

For students of pharmacy, actually for anybody interested in the history of pharmacy, a visit to the *Deutsche Apotheken Museum* (German Pharmacy Museum) in the Heidelberg Castle is required pilgrimage, a visit which nowadays can also be conveniently but less romantically absolved on-line. The tour *"leads directly into a pharmacist's shop of the early 19th century. The cherry-wood furnishings made according to the instructions of Christoph Jacob Faulhaber (1772-1842), its owner, once decorated the "Crown Pharmacy" at Ulm."* Christoph Jacob was the son of the *Ulmer Stadtphysicus* (physician to the city of Ulm). When Christoph Jacob turned fifty (1832) he passed on the *Kron Apotheke* (Crown Pharmacy) to his nephew Dr. Gustav Ernst Leube (1808 – 1881) who ran it until 1872: after a number of Leube pharmacists 1899 the pharmacy was bought from his cousin Otto Leube by Dr. Adolf Schall (1870 -1957). (Fig. 1; Gies 1927; Wankmüller 1970, 1992).

2. German phosphor ester research

Adolf Schall, after some years as an apprentice in the pharmacy and having passed the university entrance exam (*Abitur*) in Ulm, studied pharmacy in Munich for four semesters (1893–1895) and then went on to Rostock University for Doctoral work under the supervision of Professor August Michaelis (1847–1916). He was born in the Kingdom of Hannover, and studied in Goettingen and Jena. After habilitation in Karlsruhe he was 1876 appointed non tenured (*außerplanmäßiger*) Professor, then 1880 Chair (*Ordinarius*) of Chemistry in Aachen and finally Chair of Chemistry and Pharmacy in Rostock (1890). In 1913 he was appointed Privy Council (*Geheimer Hofrat*).

The Doctoral Degree (Dr. phil.) was bestowed upon Shall in 1898 for a Thesis titled "Ü*ber die Einwirkung von Phosphoroxybromid auf secundäre aliphatische Amine*" (Schall 1898). Holmstedt summarized Schall's experiments: "*Schall tried to replace both the chlorine atoms in compounds of the general type* $(R)_2NPOCl_2$ *by cyanide. One of his experiments consisted in boiling . . ...potassium cyanide with diethyl-amidophosphoryl dichloride* (Fig. 2*A*)*, using alcohol as a solvent. He obtained a distillate, the analysis results of which led him to assume that the alcohol had taken part in the reaction. . ... " (Fig.2*, Holmstedt 1951; Holmstedt and Larsson 1951). Bo Holmstedt (1919–2002) was born in Sweden, studied Medicine at the Karolinska Institute where he received his PhD in Pharmacology 1951 and the MD the next year. 1964 he became Professor of Toxicology and 1974 was elected to the Swedish Royal Academy of Sciences.
Diethyl-amidophosphoryl dichloride (Fig. 2A) and the dimethyl analogon (Fig. 2B) the substances needed by Schall were synthesized by another pharmacist and Michaelis pupil, Ernst Ratzlaff (1870–1948) (Ratzlaff 1901; Michaelis 1903).
Ernst Ratzlaff (1870–1948), born in Koeslin (Pomerania) was the son of a *Vorwerkbesitzer* (land owner). The father died sometime between 1888 and 1892. After *Abitur* (University Entrance Exam) in Koeslin, he studied pharmacy in Munich (1894; Konsemester of Schall) and Marburg (1894–1896); it is almost certain that Schall and Ratzlaff knew each other from Munich, where their pharmacy studies overlapped. Subsequently Ratzlaff studied chemistry in Rostock where 1901 he obtained his Doctoral degree under the supervision of Michaelis with a thesis titled Ü*ber die Einwirkung primärer und sekundärer Amine auf Phosphoroxychlorid und Äthoxylphosphoroxychlorid.* Around 1907 he resided in Lippstadt (Langestr. 28). This house was for many years home of the *Engel-Apotheke*, of whom the then

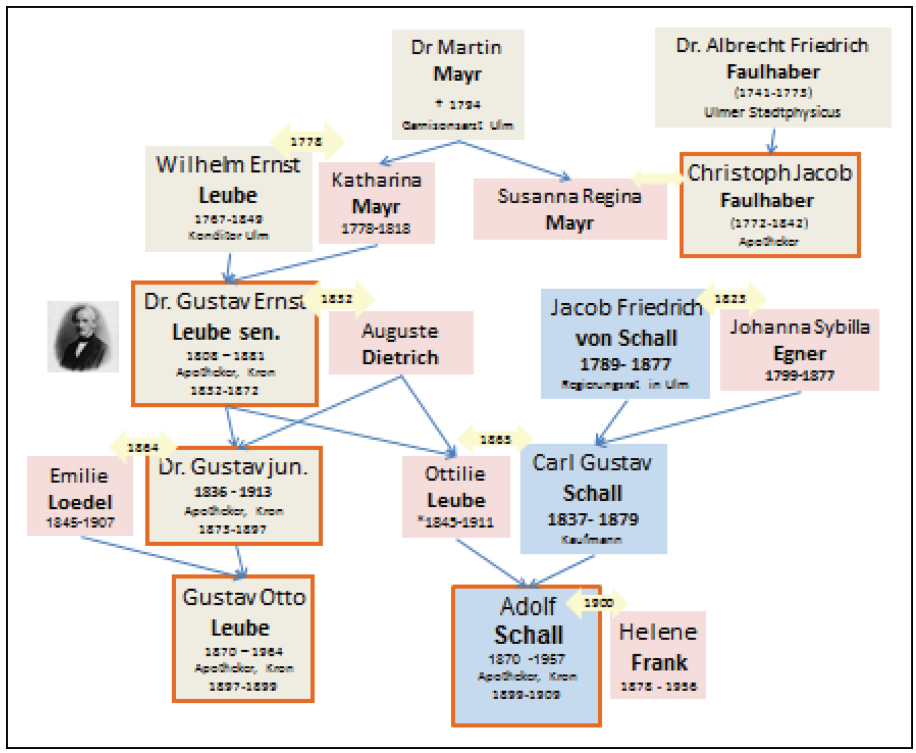


Fig. 1: The sequential owners of the *Kron Apotheke* in Ulm (orange frame) and their immediate families. Christoph Jacob Faulhaber, owner until 1832 → Dr. Gustav Ernst Leube (his nephew), until 1872 → Dr. Gustav jun. until 1897→ Gustav Otto Leube, until 1899 → Dr. Adolf Schall, until 1910. Otto Leube and Adolf Schall were cousins. Adolf's father, Carl Gustav Schall (1837- 1879) married Ottilie Leube (1845–1911), the sister of Otto's father.

owner died 1902 after a lengthy disease. The widow (with underage children) used external pharmacists to run the pharmacy; the involvement of Ratzlaff in the running of the Engel-Apotheke is likely. During the time in Lippstadt he developed a number of pharmaceutical products and registered trademarks for them such as *Emulgrit*, *Mulgatose* and *Mildan*. Most successful and best known among them is *Mulgatose,* an *emulsion of castor oil* of *agreeable taste*. Dr. Ratzlaff purchased 1911 the Berg Apotheke in Harzgerode which he ran until 1939, when the pharmacy was leased-out (Boerner 1999).

The surviving inventory from Ratzlaff's pharmacy (Berg Apotheke in Harzgerode) is exhibited in another museum, the Berg Apotheken Museum in Harzgerode, located in the tower of the St. Marien Church, some eighty steep steps above ground. The exciting history of the Berg Apotheke and of its various owners is described in detail in a superb monograph authored by the historian of the city of Harzgerode, Dr. Karl-Heinz Börner, his monograph is also containing a picture of the pharmacist and his family (Börner 1999).

Professor Michaelis, Schall's Doctoral supervisor, had second thoughts about the correctness of the representation of the reaction product put forward by Schall in his dissertation (Fig. 2C) and recognized that his pupil must have obtained a mixture of the compounds shown in Figs. 2D and 2E, including diethylamido-ethoxy-phosphoryl-cyanide (Fig. 2E), a very close relative of what was later to be called tabun (dimethyl-ethoxy-phosphoryl-cyanide) (Fig. 2F, Michaelis 1903; Holmstedt and Larsson 1951). Neither Schall nor Professor Michaelis, his supervisor, had however any idea about the toxicity of their creation.

The failure to recognize the toxicity of organophosphates and -phosphonates was most likely related to the low yield of the synthetic reactions employed in the early days, yield which was so low as to even allow in some cases the experimentators to *taste* their creations without dire consequences (de Clermont 1854).

It took about eighty years for the toxicity of such compounds to be first recognized: Gerda von Krueger (1907 – after 1970), a graduate student of Willy Lange, working on the synthesis of ester of monofluor phosphoric acid would be accidentally exposed: "*the fumes of these compounds have a pleasant, slightly aromatic odor. But a few minutes after inhalation there is a feeling of pressure to the larynx and difficulty in breathing. Then a disturbance of consciousness develops, as well as blurred vision and a painful oversensitivity of the eyes to light. Only after several hours do the problems wear off. They are apparently not caused by acidic products of a possible decomposition, but by the esters themselves. The effects are produced by very small amounts.*" (Lange and von Krueger 1932; Petroianu 2010).

History has a tendency to repeat itself: Schrader, developing phosphor ester based insecticides was exposed 1936 to the toxic effects of one of the compounds he was working on and had to be admitted to the hospital for a fortnight. According to Otto Pfingsten (2003, Fig. 3), Heinrich Schrader (Gerhard's father) writes: *"In November Gerhard had a serious accident in the laboratory - had the Lord not held his protective hand over him - that could have easily had bad consequences. 14 days Gerhard had to stay in the hospital. After discharge he stayed - to our great joy - with Wiebke* (the first daughter) *shortly before Christmas for almost 8 days in our house. Thanks God he recovered well."* Upon return to work at IG Farben Leverkusen, Schrader identified the toxic compound responsible for the accident as dimethyl-ethoxy-phosphoryl-cyanide (Fig. 2F). He named the substance first taboon and later tabun; as the legend goes the name was due to the compound being so toxic as to make it taboo (the German spelling of the word taboo being tabu, Gellermann 1986; Sietz 2012).

The toxicity of tabun being in self-experiment thus established beyond doubt its potential usefulness as an insecticide was recognized; the method of synthesis and the use of this and similar compounds were patented 1937 in Germany by Gerhard Schrader (1903–1990) and Schrader and Hans Gebhardt (Schrader 1952; Schrader and Gebhardt 1953). The patents were made public 1952 and 1953 respectively. The Schrader synthesis optimized the Schall method by among others reducing the amount of alcohol involved and thus increasing both the

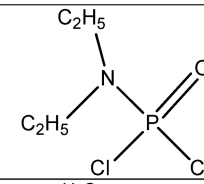
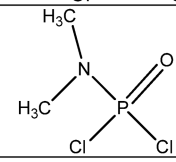
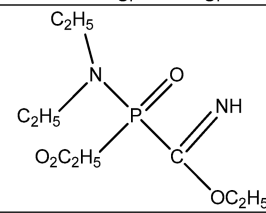
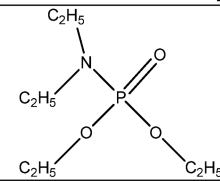
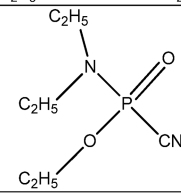
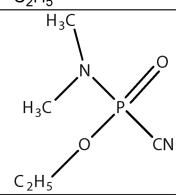
A	Di-ethylamido-phosphoryl dichloride [di-ethylamin-N-oxychlorophosphin]	
B	Di-methylamido-phosphoryl dichloride [di-methylamin-N-oxychlorophosphin]	
C	Imido ether (incorrect structure as assumed by Schall)	
D	Ethyl-ester (recognized by Michaelis)	
E	Diethyl-amino ethylester cyano-phosphonate (recognized by Michaelis) (tabun II; GAA)	
F	Dimethyl-amino ethylester cyano-phosphonate (tabun I; GA)	

Fig. 2: Schall reacted potassium cyanide with diethylamidophosphoryl dichloride (diethylamin-N-oxychlorophosphin; A), using alcohol as a solvent. He assumed that the product of the reaction was an imido ether (C). His Doctoral supervisor, Professor Michaelis, doubted the correctness of the representation and suggested that his pupil obtained a mixture of two compounds: ethyl-ester (D) and a cyanide derivative (E). Di-methylamin-N-oxychlorophosphin was also synthesized and available to Schall and Michaelis (E) and therefor tabun (F) synthesis by the same procedure was possible (not mentioned by Michaelis).

yield and purity of the product. Gerhard Schrader, son of Heinrich (1861–1945) and Elise Schrader (nee Mundt), was born in Bortfeld, Germany. He studied Chemistry at the Technical University (TU) Braunschweig where he also obtained his Doctorate (1928) with a thesis titled *Zur Chemie des Rutheniums und Osmiums*. Schrader was employed by IG Farben where he developed a large number of organophosphate and phosphonate cholinesterase inhibitors. Hans Gebhardt, borm in 1911, was the son of Franz and Babette Gebhardt of Nueremberg, Germany. After passing the University Entrance Exam (Abitur) 1931, he enrolled as a student of Chemistry at the University of Erlangen. He received 1937 his Doctorate from the same University for a Thesis titled *Die Aethylester der Sulfoxylsäure, Aethylsulfinsäure und Aethylsulfensäure*. He was a student of Professor Alwin Meuwsen (1898–1971), Professors of Inorganic Chemistry in Erlangen (1938 - 1964).

3. Phosphor ester research outside Germany

Research on phosphor esters was performed not only in Germany but also abroad, Kazan in Russia and the Arbuzov dynasty of chemists being at the forefront of Soviet phosphor research. In a Russian pre-war monograph on phosphor chemistry authored by Vladimir Mihailovich Plets the Schall-Michaelis method of producing O-ethyl, NN diethyl cyanophosphonate is reproduced (Plets 1940). Alexandr Yerminingeldovich (1877–1968) (the father) and Boris Alexandrovich (1903–1991) Arbuzov were well-known chemists. Arbuzov the Father is well known for the Michaelis–Arbuzov reaction, which is widely used for the synthesis of i.a. various phosphonates. In October 1938 B. A. Arbuzov (who lived with his family in the house of his father, now the Academician Arbuzov Museum) had been arrested. During the search at his house many manuscripts, prints, letters, photographs, etc. have been confiscated. The NKVD (former name of KGB) accused B.A. Arbuzov of spying but dropped the charges the following year and released him; many of the materials confiscated have however never been returned. Among the documents that disappeared is also the Doctoral Thesis of Plets. Very little is known about Vladimir Mihailovich Plets, except that he worked in the early 1930 s in St. Petersburg at the Leningrad Institute of Technology (Lensovet), one of the oldest institutions of higher technical education in the Soviet Union. Around 1934 he contacted Arbusov asking him to become the Editor of the monograph on phosphor chemistry he was working on; subsequently

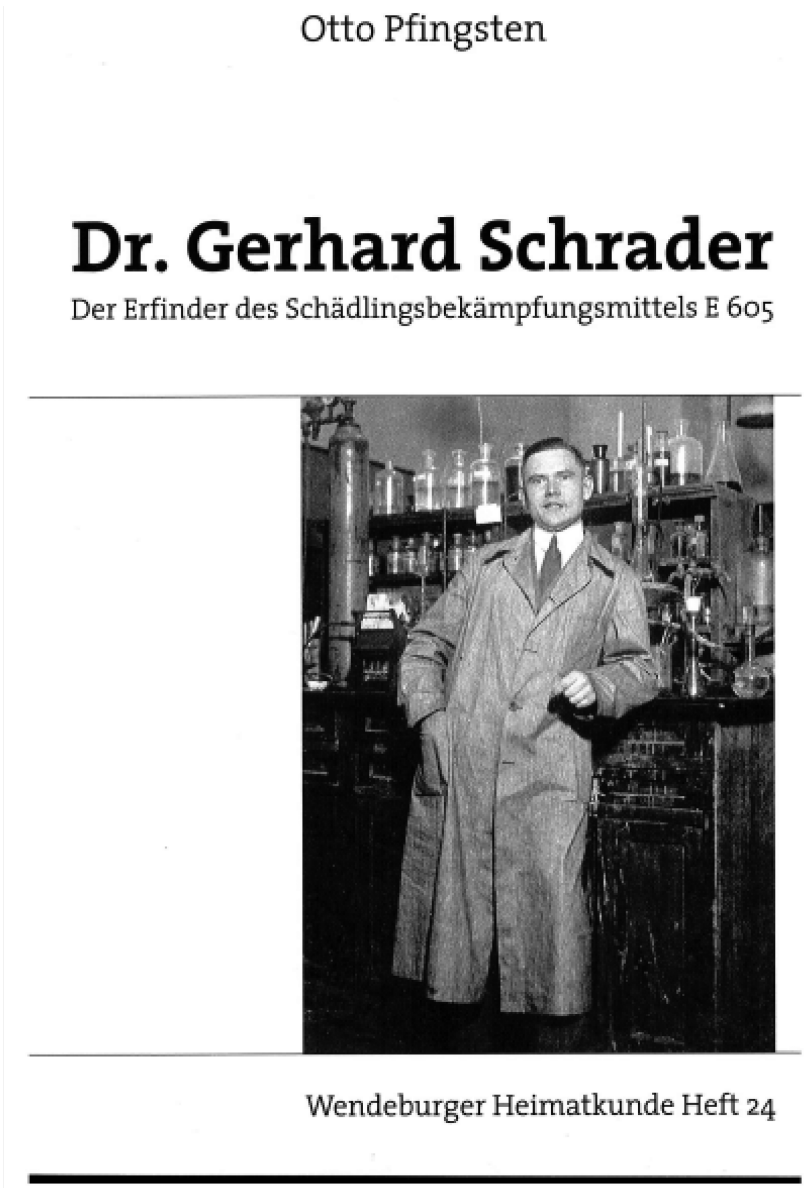


Fig. 3: Schrader' biography is presented in a short publication authored by Otto Pfingsten.

he moved to Kazan (where Arbusov worked) and 1938 obtained there his Ph.D. with a thesis titled *Secondary chlorfosfin, new methods of synthesis, properties and reactions*. Subsequently he became a lecturer at the University in the Department of Biochemistry. The term *Explosophores* was first coined by him.

4. Nomenclature of phosphor esters

The difference between the Schall-Michaelis compound (O-ethyl, NN-diethyl cyanophosphonate) and the one developed by Schrader (O-ethyl, NN-dimethyl cyanophosphonate) is minimal, both sharing extreme toxicity due to their ability to inhibit cholinesterase. To highlight the similarity, the diethyl cyanophosphonate is refered to as tabun II or GAA (tabun being GA) (Holmstedt 1951; Ledgard 2006). The designation of tabun as GA and of other nerve agents as GB (sarin), GD (soman), GE (ethyl-sarin) and GF (cyclo-sarin) is apparently the contribution of Jac Rothschild, an American chemist and army officer attempting to disambiguate the nomenclature (Fig. 4). Jacquard Brig. General Rothschild (1907–1990) was son of German immigrants (Julius and Gertrude Rothschild Hirschorn) and was born in Ohio. He graduated from the US Military Academy at West Point (Class of 1930, Cullum 8842) and subsequently received a Master's Degree in Chemical Engineering from the Massachusetts Institute of Technology (1940). During the WW II he served in Europe as Commanding Officer of the 93rd Chemical Battalion and was awarded the Bronze Star & the Legion of Merit. Latter he became Commanding Officer of the Army's Chemical Center at Edgewood Arsenal. From there he was deployed (1951) to the Far East as Chemical Officer. Gen. Rothschild retired (1965) after 31 years of service. He was Commanding General, U.S. Army Chemical Corps Research and Development Command and Assistant Professor of Chemistry at West Point, at the time of his retirement. He is the author of a highly controversial book on chemical and germ warfare titled *Tomorrow's Weapons* (McGraw-Hill, 1964). Jac married 1938 Phyllis D Mills (1912 -1990); after 52 years of marriage they both departed this world of their own will and were found holding hands in a hotel bed.

Why the designation GC was skipped is controversial: according to Jonathan B. Tucker (2006) the designation CG was already adopted by the US Army for phosgene. Another explanation is the common use of the letters GC to designate venereal disease.

Fig. 4: Jacquard Rothschild, an American chemist and army officer introduced the designation GA for tabun in an attempt to disambiguate the nomenclature. He is the author of a highly controversial book on chemical and germ warfare titled *Tomorrow's Weapons* (McGraw-Hill, 1964). Photo of Jacquard Rothschild dated 11-23-1963; credit UPI and NEA (from the private collection of the author).

The definitive confirmation of the structure of tabun as well as properties of a number of tabun-like compounds were provided by Bo Holmstedt (Holmstedt1951; Holmstedt and Larsson 1951).

5. Conclusion

The synthesis of tabun-like compounds was achieved at the beginning of the 20th century by doctoral students working under the supervision of Karl August Michaelis 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 M. Plets. The compounds and many more related variations were re-discovered and systematically analyzed for biologic effects by Gerhard Schrader in the late thirties. It was Schrader who recognized their toxicity.

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