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Pharmacist Theodor Salzer (1833–1900) and the discovery of bisphosphonates

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Herbert Fleisch, the father of the therapeutic use of bisphosphonates in modern medicine, repeatedly stated in his numerous reviews that bisphosphonates were first synthesized 1865 in Germany by the Russian chemist Menschutkin. He was wrong on two counts. Had Menschutkin synthesized bisphosphonates, as he was a student of Wurtz at the time of the "synthesis", the birthplace of the substances would have been France and not Germany; but he did not. By reacting phosphorous acid with acetyl-chloride he obtained derivatives of pyro-phosphorous and pyro-phosphoric acids (P-O-P backbone) and not bisphosphonates (P-C-P backbone). The discovery of the first bisphosphonate occurred indeed in Germany but some thirty years later and not without some drama. First 1894 the pharmacist Theodor Salzer (1833–1900) described an impurity contained in commercially available phosphoric acid but failed to identify it as acetodiphosphoric acid, a bisphosphonate. 1896, an undergraduate student, Hans von Baeyer working in Munich at the Royal Academy of Sciences in the chemical laboratory of his father Adolf (the 1905 Nobel Prize laureate and discoverer of the barbiturates) synthesized an unknown substance which his famous father summarily rejected as some "*Dreck*" or impurity. Only due to the tenacity of young Hans work on the matter was continued and the paper describing the synthesis published a year later. The correctness of the chemical structure of the compound as assumed by von Baeyer (and his Ph.D. supervisor Hofmann) was confirmed 1901 by Heidepriem, a Ph.D. student of Hofmann. This short report attempts to shed some light on the life of the lesser known pharmacists and chemists involved in the synthesis of the first bisphosphonate, focusing on Salzer, Heidepriem and von Baeyer.

1. Bisphosphonates: what's in a name?

Bisphosphonates are a class of therapeutic agents commonly used in medicine for the treatment of a number of conditions where inhibition of bone resorption is advantageous. Since all available bisphosphonates have names ending with the suffix *dronate* (etidronate, clodronate, tiludronate, pamidronate, alendronate, ibandronate, risedronate, zoldronate) some clinicians some refer to these drugs as dronates.

The prefix *bis* indicates that two identical (twin-like or geminal) substituents (P-containing) are bound to a parent compound creating in our case a P-C-P backbone. While in phosphates the phosphor atom is not directly linked to any carbon (no P-C bond) in phosphonates such bonds exist, therefore a compound having a P-C-P backbone is called a (geminal) bisphosphonate.

Wyngaert et al. (2008) published a short letter clarifying the nomenclature. Such contributions are very helpful to both clinicians and non-clinicians alike in finding a common language. It is likely that the confusion concerning the history of the synthesis of the first bisphosphonate is at least partially to blame on the previously ambiguous naming of chemical compounds.

2. Menschutkin and the bisphosphonates

The Swiss professor Herbert Fleisch (1933–2007), the father of the therapeutic use of bisphosphonates in modern medicine, repeatedly stated in his numerous reviews that bisphosphonates were first synthesized 1865 in Germany (Fleisch 1998; 2007). The basis for his attribution is a paper published by the Russian chemist Menschutkin (Menschutkin 1865): the paper ends however with the statement that "*this research was performed in the laboratory of Wurtz, to whom I have to express my gratitude for his advice*". The mentioned Wurtz is none other than French chemist Adolphe Wurtz (1817–1884), remembered among other things for his Paris research laboratory where some of the brightest minds of his time worked (Carneiro 1992). On the occasion of Wurtz's election to the French senate, his former students (élèves) presented him with a bronze statuette by Louis Ernest Barrias (1841–1905) representing the French artist Bernard Palissy (1510–1589). On the base or pedestal of the statuette were engraved the names of the one hundred and eleven Wurtz "*élèves*" including that of Menschutkin (Friedel 1886; Petroianu 2008, Fig. 1).

Nicolai Alexandrovitsch Menschutkin (1842–1907) after graduating from University in his home town St. Petersburg, went, as it was customary at the time, to France and Germany to further improve his skills. In Germany he studied with Adolph Strecker (1822–1871) in Tübingen and Hermann Kolbe (1818–1884) in Marburg, in France with Wurtz. Had Menschutkin as stated by Fleisch synthesized the first bisphosphonate, the birthplace would have been France and

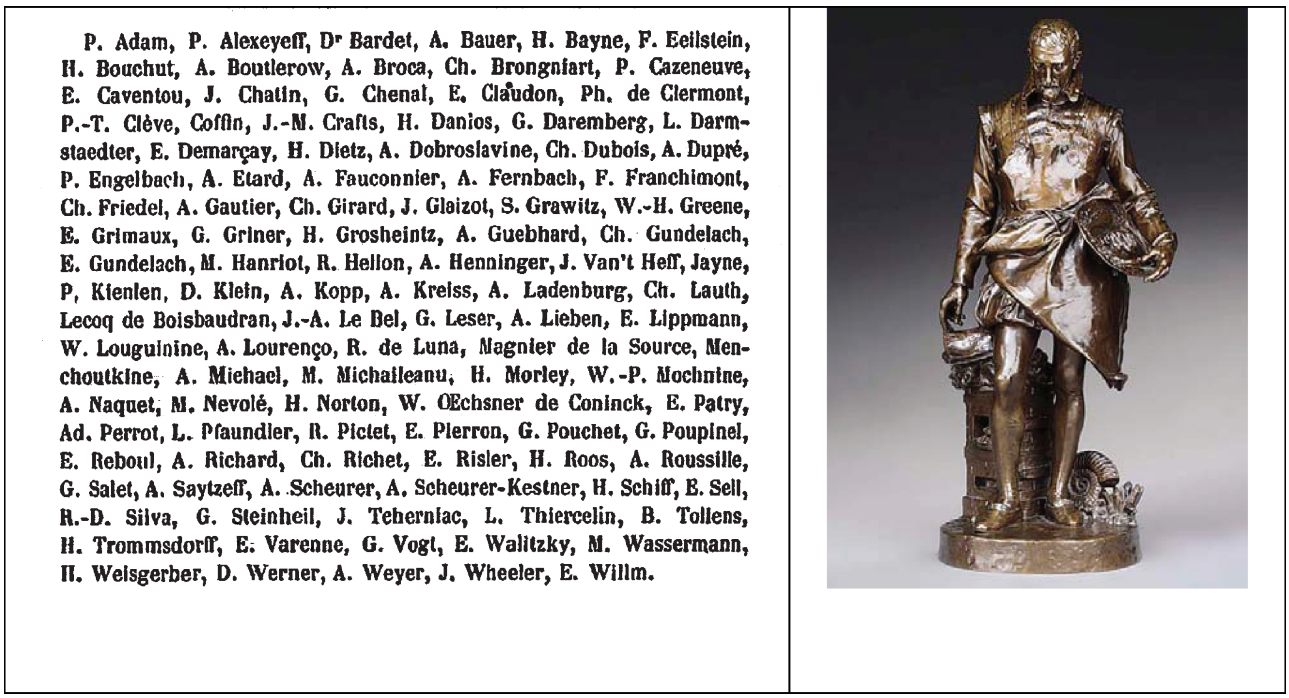
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Fig. 1: Bronze statuette by Louis Ernest Barrias (1841–1905) representing the French artist Bernard Palissy (1510–1589). On the base or pedestal of the statuette were engraved the names of the one hundred and eleven Wurtz "élèves" including that of Menschutkin (Menchoutkine)

not Germany; but he did not. By reacting phosphorous acid with acetyl-chloride he obtained acetylated derivatives of pyro-phosphorous and pyro-phosphoric acids (P-O-P backbone; diphosphates) and not bisphosphonates (P-C-P backbone, Fig. 2).

3. Salzer and the bisphosphonates

The synthesis of the first bisphosphonate occurred indeed in Germany but some thirty years later and not without the drama of missed or almost missed opportunities.

In Salzer's obituary published in the Austrian Journal of Pharmacy (Oesterreichische Zeithschrift fuer Pharmacie) one can read "*On the 29th of the previous months died at the age of 67 the previous pharmacy owner Theodor Salzer from Worms to whom the sciences in general and the pharmaceutical science in particular owe a number of precious works. He was the discoverer of the hypophosphoric acid [Unterphosphorsauere] and of the acetodiphosphoric acid and has published . . ..*" (Anonymus 1900).

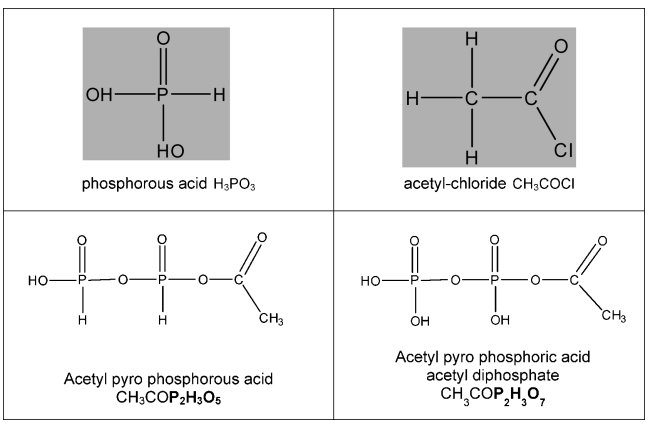


Fig. 2: Menschutkin while working in Wurtz laboratory in Paris (1864–1865) by reacting phosphorous acid with acetyl-chloride obtained acetylated derivatives of pyro-phosphorous and pyro-phosphoric acids (P-O-P backbone; diphosphates) and not bisphosphonates (P-C-P backbone)

The anonymous author of the obituary was however wrong: while Salzer described 1894 an odd impurity contained in a sample of commercially available phosphoric acid he failed to identify it as acetodiphosphoric acid, a bisphosphonate. It was only a couple of years later that the impurity described by Salzer was shown to be acetodiphosphoric acid (Salzer 1897 a, b, Fig. 3).

4. Von Baeyer and the bisphosphonates

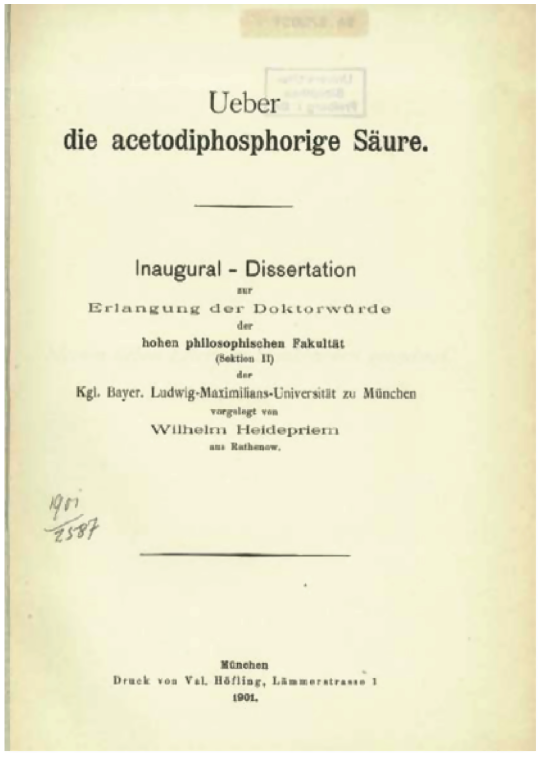
In 1896, a young student, Hans von Baeyer working in the chemical laboratory of his father Adolf in Munich at the Royal Academy of Sciences synthesized an unknown substance which his father summarily rejects as some "*Dreck*" or impurity. Only due to the tenacity of young Hans work on the matter is continued and the paper describing the synthesis published a year later (von Baeyer and Hofmann 1897; Naumann 2003).

The correctness of the chemical structure of the compound - acetodiphosphoric acid, the first bisphosphonate - as suggested by von Baeyer and Hofmann is confirmed 1901 by Wilhelm Heide-

Aeetodiphosphorige Säure.

Nachdem ich Herrn Prof. A. v. Baeyer ein Salzmuster meiner in Pharm. Ztg. 1897, No. 89 beschriebenen Säure übersendet hatte, theilt mir derselbe nun mit, dass es nach Versuchen von Herrn Dr. K. Hofmann thatsächlich ein Salz der acetodiphosphorigen Säure sei. *Th. Salzer.*

Fig. 3: Salzer's short acknowledgement (1897) published in the Pharmaceutische Zeitung stating that "*After having sent to professor A(lfred) von Baeyer a sample of the substance I described in Pharm. Ztg 1897, No. 89, he informed me now, that based on experiments performed by Dr. K(arl) Hofmann, this substance is indeed a salt of the acetodiphosphoric acid*"



Ueber
die acetodiphosphorige Säure.

Inaugural - Dissertation
zur
Erlangung der Doktorwürde
der
hohen philosophischen Fakultät
(Sektion II)
der
Kgl. Bayer. Ludwig-Maximilians-Universität zu München
vorgelegt von
Wilhelm Heidepriem
aus Rathenow.

1901
2587

München
Druck von Val. Höfling, Lämmerstrasse 1
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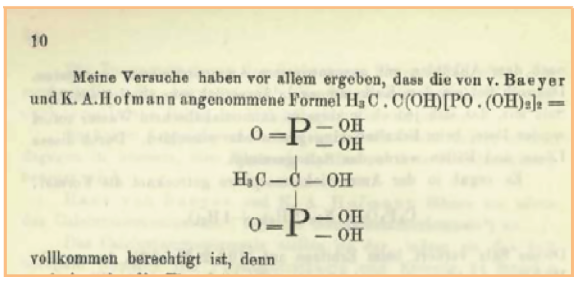

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Meine Versuche haben vor allem ergeben, dass die von v. Baeyer und K. A. Hofmann angenommene Formel $H_3C \cdot C(OH)[PO \cdot (OH)_2]_2$ =

vollkommen berechtigt ist, denn

Fig. 4: Cover page of Heidepriem's dissertation from 1901 and chemical structure of the acetodiphosphoric acid (bisphosphonic acid)

priem (1876–1945), a Ph.D. student of Hofmann (Heidepriem 1901, Fig. 4).
It would take however almost half a century more until the clinical and non-clinical usefulness of bisphosphonates would be fully recognized (Francis and Valent 2007).

5. Theodor August Salzer (1833–1900)

The origins of the Salzer dynasty can be traced back in time to the Middle Ages and geographically to Schemnitz (Hungarian: Selmec), a town in Upper Hungary (Slovakia), noted as a mining centre since Roman times. Over time many family branches developed, Theodor belonging to the so called Bretten - Worms lineage. The Salzer family operated the pharmacy in Bretten over many years and generations.
Theodor's grandfather [David Cristoph (1740–1816)] born in Bretten was protestant clergy while his father [Johann Friedrich (1785–1862)] moved away from Bretten and become pharmacist in Worms. Theodor was the youngest of eight children (three boys); while one of the older brothers died early, Friedrich (1831–1917) became an army physician and later a general practitioner in Worms.

[1] Bretten: Town in the state of Baden-Württemberg, Germany.

[2] Worms: City in the state of Rhineland-Palatinate, Germany, on the Rhine River.

Fig. 5: The Adler Apotheke in Worms was owned and operated by Theodor Salzer from 1857 to 1891. The pharmacy (originally named Fortuna) was purchased 1839 by his father from the widow Augustin; it is located in what used to be the "Palais von Prittwitz" buildt 1725 and converted 1795 into a pharmacy. It is here that the financially independent Theodor dedicated his energy and time to chemical and pharmaceutical research. (Photo 2010 courtesy of Dipl. Ing. Felix Ziller, MinDirig a.D. 67551 Worms)

After graduating from the Gymnasium (High School) in Worms Theodor worked as an pharmacy apprentice in Mutterstadt (Palatinate), then pharmacy assistant (*Gehilfe*) in Pforzheim, Basel and Koblenz. Subsequently he studied pharmacy in Heidelberg; upon graduation 1857 he took over the family pharmacy (Adler Apotheke) which he run until 1891 (Stotz 1976, Fig. 5).
It is here in Worms in the Adler pharmacy that the financially independent Theodor dedicated his energy and time to chemical and pharmaceutical research. Most of his manuscripts were published in the Pharmazeutische Zeitung, were also his German obituary appeared (Fig. 6).

Fig. 6: Theodor Salzer's portrait from the obituary published in the Pharmazeutische Zeitung Vol. XLV, No. 17. from February 28th, 1900

As a chemist he is best remebered for the synthesis of hypophosphoric acid and for the (almost) identification of alkyl derivatives of bisphosphonic acid.

6. Hans von Baeyer (1875–1941)

Hans was the eldest son of the 1905 Nobel Prize laureate and discoverer of the barbiturates Adolf von Baeyer (nobilitated by the Emperor 1885). His early school years were apparently a constant and tedious uphill struggle, only the sheer endless financial resources of the family were able to provide for a never ending stream of badly needed private tutors (Naumann 2003). Things changed to the better though after he passed the University Entrance Exam [*Hochschulreife*] and the scientific curiosity of young Hans was awakened. He studies medicine in Jena and Munich; his dissertation (Munich, 1901) is titled "*Ueber Chromsauerevergiftung*" (On poisoning with chromic acid).
After a stint in physiology with Prof. Max Verworn (1863–1921) in Goettingen he trains in Munich to become a surgeon; after Habilitation becoming first Professor in Munich and latter Professor of Orthopedics at the University of Heidelberg with "Mechano-Pathology" as his main scientific field of work. Otto his younger brother had a distinguished academic career himself, becoming a Professor of Physics in Berlin.
Hans and Otto von Baeyer academic careers both ended 1933 with the ascent of the Nazis to power in Germany (Naumann 2003; Goerig and Goetz 2010).

7. Karl Andreas Hofmann (1870–1940)

Karl Andreas Hofmann studied with Adolf von Baeyer in Munich. After his habilitation (1895) he becoms 1898 Professor in Munich. After more than ten years as Director of the Inorganic Chemistry Institute in Munich he eventually accepts the Chair for Inorganic Chemistry in Berlin, which he holds until his retirement 1935. From 1933 to 1935 he is President of the German Chemical Society, a position he has to give up for political reasons. Hofmann was a member of the Bavarian and Prussian Academies of Sciences, also of Leopoldina, the German Academy of Sciences, the world's oldest academy of natural sciences (Weidenhagen 1940; Hofmann 1972).

8. Wilhelm Heidepriem (1876–1945)

Grandfather Friedrich Wilhelm was a brewery and pub owner, latter a brickyard owner in Rathenow in Havelland, Brandenburg. He married Friederike Charlotte Louise Todt. Their son Carl (Wilhelm's father, 1843–1919) married 1873 Lisbeth, the daughter of a well-known lawyer and prolific journalist and book author from Berlin, the city counselor (*Stadtrath*) Dr. August Theodor Woeniger (1815–1894). While many of his writings deal with constitutional law he is probably best remembered for his novel "*Zigeuner und Edelleute*" (Gypsies and Nobles). He was also the Editor of a short lived liberal newspaper called "*Der Staat*". During the March 1848 events he delivered fiery speeches.
Carl inherited the brickyard and vastly expanded the production making the factory one of the technologically most advanced of the time. At the height of production around the turn of the century the factory employed over a hundred workers. Unfortunately the demand for bricks dropped and the factory had to be sold (1915) to cover the large loans used for modernization. Carl also had a number of other business interests such as the brewery in Rathenow which he managed ($\approx$ 1897); he was also politically active becoming a city counselor. Wilhelm was born 1876. After earning his doctorate in Munich his interest in science diminishes and he returns to Rathenow. 1920 he marries Johanna Rosalie Guenzel; they have a daughter Barbara. In Rathenow he resides on a street named after his father *(Carl-Heidepriem-Weg)*; while the street was renamed Havelweg the buildings continue to exist. The entire family dies Mai 1945.

9. Conclusion

In conclusion bisphosphonates were first synthesized in Munich 1897 by Hans von Baeyer and his PhD supervisor Karl Andreas Hofmann. The pharmacist Theodor Salzer in Worms missed earlier the opportunity to identify an impurity contained in a sample of commercially available phosphoric acid as acetodiphosphoric acid, a bisphosphonate. The clinical usefulness of bisphosphonates was recognized about half a century later.

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