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Veilchenduft, ectopic olfactory receptors and endogenous volatile compounds: Who was Paul Krüger (1859-1916)?

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The pharmacist and chemist Ferdinand Tiemann (1848–1899) having succeeded in the synthesis of vanillin, is considered to be the father of *Geschmackstoff-Chemie* (flavor chemistry). Tiemann, together with Paul Krüger (1859–1916) and then with Friedrich-Wilhelm Semmler (1860–1931), developed a method to obtain with a good yield *Veilchenduft* (violet scent); they condensed citral with di-methyl-ketone (acetone) thus generating an intermediate which upon exposure to an acidic environment cyclizes to ionone. By doing so the fragrance chemistry was born. Ionone (the compound responsible for the violet scent) was produced on an industrial scale at the factory of Wilhelm Haarmann (1847–1931) in Holzminden, factory renamed 1876 Haarmann & Reimer, after Karl Reimer (1845–1881) joined the group of owners. While a number of chemists and pharmacists were involved in the synthesis of Ionone (*Veilchenduft*; violet scent) and irone (iris scent), with few exceptions, their biographies are pretty well documented. In contrast, very little transpired about Dr. Paul Krüger, who spent some seven years trying to iron out the difficulties of ionone synthesis. The purpose of this short contribution is to shed some light on the life and work of Paul Krüger while providing an overview on the status of ionone pharmacology and to highlight the historical significance of ionone synthesis.

1. Introduction

The opening statement in Charles Adolphe Wurtz (1817–1884) *Histoire des Doctrines Chimiques* (History of Chemical Theories) from 1869 is that *Chemistry is a French science founded by Lavoisier, of immortal memory*. His memory might be immortal; he himself was certainly not. Antoine Lavoisier (1743–1794) died *prematurely*, put to death at age 50 by *enlightened* French revolutionaries who believed that *La République n'a pas besoin de savants ni de chimistes* (the Republic does not need either scientists nor chemists): he was guillotined on May 8, 1794. While Chemistry might or might not have been a French science in the *XVIII*th century, this was certainly not anymore the case in the second half of the *XIX*th when German scientists dominated the field.

With August Wilhelm von Hofmann (1818–1892) the era of *Farbstoffchemie* (dye chemistry) dawned, while Hofmann's student Ferdinand Tiemann (1848–1899) having succeeded in

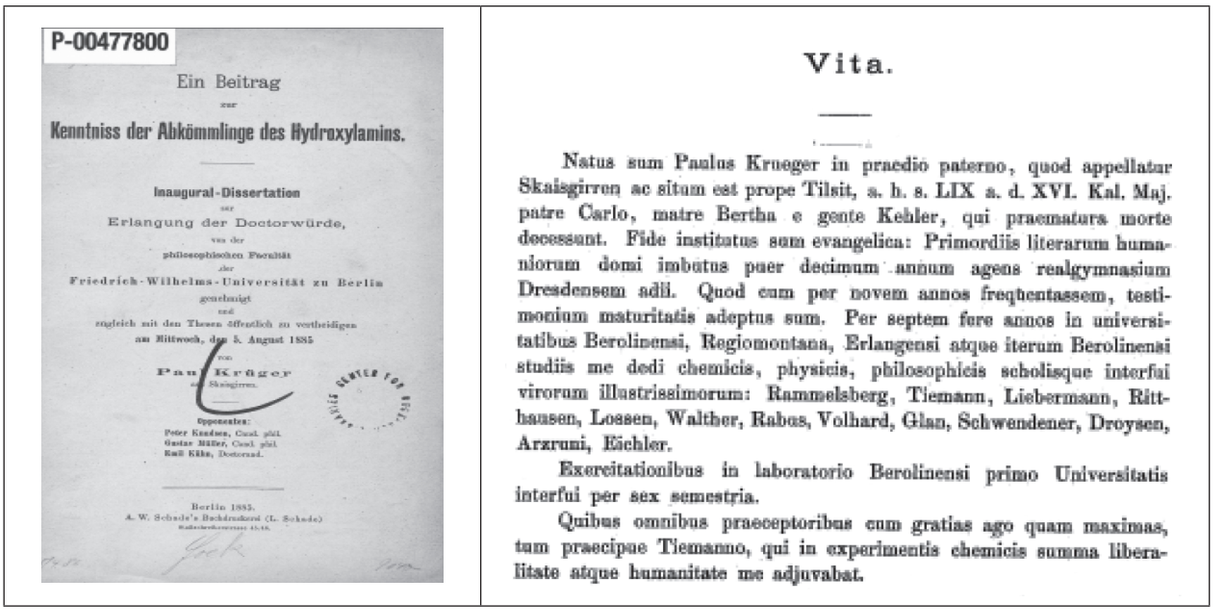

Fig. 1: (A) Cover Page of the doctoral dissertation defended in Berlin August 5th, 1885 by Paul Krüger from Skaisgirren; opponents were the graduate students Peter Knudsen (from Quars, Gravenstein) and Gustav Mueller (from Zerbst, Anhalt) and the medical student Emil Kuehn (from Posen). (B) Curriculum vitae describing his school education and the main Professors he attended lectures i.a. Rammelsberg, Tiemann and Lossen.

Fig. 2: For the best part of his student life in Berlin Paul Krüger lived in Marienstraße 15 in Berlin-Mitte (Friedrich-Wilhelm Stadt) close to banks of the river Spree. The building was errected 1828 and survived the war; it is now on the National Registry of protected monuments. Marienstrasse at the beginning of the *XX*th century. (Postcard, Verlag H Lundt, Berlin, Marienstrasse 26; private collection of the author).

the synthesis of vanillin established the *Geschmackstoff-Chemie* (flavor chemistry) (Schwedt 2017). Tiemann together with Paul Krüger (1859–1916) and then with Friedrich-Wilhelm Semmler (1860–1931) developed a feasible approach to obtain with a good yield *Veilchenduft* (violet scent); they condensed citral with di-methyl-ketone (acetone) thus generating an intermediate which upon exposure to an acidic environment cyclizes to ionone. By doing so the fragrance chemistry (*Duftstoff-Chemie*) was born.
Ionone (the compound responsible for the violet scent) was then produced at an industrial scale at the factory of Wilhelm Haarmann (1847–1931) in Holzminden, Germany, the factory was renamed Haarmann & Reimer, after Karl Reimer (1845-1881) joined the group of owners, in 1876.
While a number of chemists and pharmacists were involved in the synthesis of ionone (Veilchenduft; violets scent) and irone (iris scent), their lives are pretty well documented. Details about even marginally involved individuals are easily available; in contrast, very little transpired about Dr. Paul Krüger, who spent some seven years trying to iron out the difficulties of ionone synthesis (Schwedt 2017).

2. Paul Krüger

Karl Krüger, Paul's father, was an inn-keeper (*Gasthofbesitzer*) and land owner (*Gutsbesitzer*) in the village of Skaisgirren close to the town of Tilsit, in what was then *Ostpreußen* (East Prussia). Tilsit was the border town separated from Russia by the river Memel, town nowadays called Sowetsk and situated in the Russian exclave of Kaliningrad on the border to Lithuania. The father died there young around 1870. Mother was Bertha born Kehler. The couple had at least two surviving children: Hans Bernhard Carl and Hermann Paul Alexander. Upon the untimely death of her husband, the mother moved with her children to Dresden, where she died before 1880. Not much else is known about the parents.
Hans Bernhard Carl born 1856 (Mai 27th) became a business man and we find him residing in Strasburg (Strasbourg; Alsace) where he married 1880 Amalia (born 1856), the daughter of vine grower (*Winzer*) Carl Landerer from Rottweil, Germany. Families from Rottweil, including some of the Landerer, emigrated in the second half of the *XIX*th century to Algeria where they established a German colony at Nechmeya.
Hermann Paul Alexander born 1859 (April 16th) attended Gymnasium (high school) in Dresden (Saxony) from age of ten or so. After passing his *Abitur* (University entrance exam) he enrolled as a student of Mathematics at the *Königliche Friedrich-Wilhelm Universität* (Royal Friedrich-Wilhelm University) in Berlin for a year starting Michaelis (*Feast of the Archangels; September 29th*) 1878.
After study semesters at the Universities of Koenigsberg (East Prussia) and Erlangen (Bavaria) he returned Michaelis 1881 to Berlin and took up the study of Chemistry. He defended 1885 his Doctoral Thesis (Dr. phil.) titled *Ein Beitrag zur Kentniss der Abkömmlinge des Hydroxylamins* (A contribution to the knowledge of the derivatives of Hydroxylamine, Fig. 1A). His thesis is dedicated to the memory of his parents; the curriculum vitae (in Latin) attached to the thesis- as was tradition at German Universities- provides some of the details mentioned here (Fig. 1B).
Hydroxylamine [H_2N-OH] was the compound synthesized 1865 by Wilhelm Lossen (1838–1906) while working in Halle as an assistant in the laboratory of Professor Wilhelm Heinrich Heintz (1817–1880) (Lossen 1865; Petroianu 2012).
For the best part of his student life in Berlin, Paul Krüger resided in the Marienstraße 15 in Berlin-Mitte (Fig. 2). The building was erected 1828 and survived the war; it is now on the National Registry of protected monuments. Later, Paul moved to a new location some five hundred yards away in the Kalkscheunenstraße. As a graduate student he conducted research in the Laboratory of his mentor pharmacist and chemist Professor Ferdinand Tiemann (1848–1899).
Ferdinand Tiemann initially wanted to pursue vocational training (*Drogisten-Lehre*) in the pharmacy and drugstore of an affluent and successful uncle in Braunschweig. This relative, Carl Tiemann (1818–1885) was first (1850) *Provisor* and later (1865) owner of the *Martini Apotheke.* The pharmacy established in the *XV*th century as *Raths-Apotheke*, became known as *Große Apotheke*, later as *Graberg'sche Apotheke* and finally as Martini pharmacy due to its proximity to the Saint Martin church. Ferdinand, however, soon gave up his vocational training ambitions and studied Chemistry and then Technical Chemistry instead at the *Collegium Carolinum* in the same city. Friedrich Julius Otto (1809–1870) the Professor of Pharmacy and Technical Chemistry at the Collegium allowed him to sit 1866 the Pharmacy exam. The permission was contingent on Ferdinand forfeiting his right to practice (*Konzessionsrecht*). This restriction was necessary as Ferdinand did not have the practical pharmacy training (*praktisch pharmazeutische Vorbildung*) of three years duration mandated in order to own/operate a pharmacy (Anonymus 1903).

Fig. 3: Ferdinand Tiemann (1848 - 1899), pharmacist and chemist. Professor of chemistry at the Friedrich Wilhelm University Berlin, mentor of Paul Krüger. Tiemann was scientific advisor and silent partner of the flavors and fragrances factory of Haarmann & Reimer, Holzminden (Braunschweig) and of de Laire Co, Paris (Fischer 1899). Photo from the Obituary published by the German Chemical Society (Witt 1901).

Subsequently Krüger took up employment in the city of Holzminden (Braunschweig) with Haarmann & Reimer, the flavors and fragrances factory of which Tiemann was not only the scientific adviser but also co-founder and silent partner (Fig. 3).
From this period, a handful of joint publications resulted, among others the seminal papers on *Veilchenaroma* (scent of violets) and on the separation of *ionon* & *iron* (Tiemann and Krüger 1893; 1895). The name *ionone* is obtained by merging *ion* (greek for violet) and ket*one* while *irone* is a combination of *ir*is and ket*one*, irone being the chief odorous constituent of dried Iris *rhizome* (creeping rootstalks) (EK 1894; Petroianu et al. 2018).
This tedious research work stretched over a period of about seven years and was certainly too slow from a commercial point of view. In an attempt to speed up development, Friedrich-Wilhelm Semmler (1860–1931), a terpene specialist (habilitated 1890 in Greifswald and one year later *Extraordinarius*, professor of chemistry) was involved (Tiemann and Semmler 1893; 1895; Becker-Rose 1931). Whatever the respective contribution of the people involved or the financial arrangements might have been, on the patent issued by the Imperial Patent Office (*Kaiserliches Patentamt*) for the Ionon-(*Veilchenduft*) synthesis only the company name Haarmann & Reimer (co-owned by Tiemann) appears (Patentschrift Nr. 73089, 1894: Method to produce a new odorous constituent named ionone out of citral. Patented in the German Empire from April 25th, 1893 onwards. *Verfahren zur Darstellung eines neuen Riechstoffes aus Citral, genannt Jonon. Patentiert im Deutschen Reiche vom 25. April 1893 ab*). The scientific review of the topic published 1898 is authored by Tiemann alone (Tiemann 1898).
With apparently a solid income and secure position in Holzminden, Paul married 1896 (July 14th) Olga Moeller (1876-1954). The bride hailed from a distinguished and affluent East Prussian family: Julius Moeller, her grandfather, was a politician and an elected representative in various local parliaments, since 1845 owner of *Gut Margen* (Estate Margen) while her father Bernhard Moeller (1845–1920) after having studied Theology in Königsberg (now Kaliningrad, Russia) was for over thirty years priest in Aulowönen (Kaliningrad). The couple adopted a daughter, Eva, born 1901 (January13th).
Having apparently profited from the ionon synthesis in Holzminden, 1908 Paul Krüger (Fig. 4) purchased the Landed Estate *Rittergut Schönwiese* in the district of Prussian Eylau (now Kaliningrad, Russia) where he retired with his family. *Das Ostpreussenblatt* published an illustrated short history of the Estate (Wagner 2004).
During a visit to his native Skaisgirren in 1916, Paul passed away (November 8th). Having turned eighteen, daughter Eva married (1919, October 7th) and moved to Breitscheid (Hesse), while Olga's father, – the priest from Aulowönen – retired and moved to his daughter to Schönwiese, where he died the following year. Olga lived on the Estate until 1921, when she sold and moved to Dresden.

Fig. 4: Chemist Dr. Paul Krüger (1859–1916)

3. Historical significance of ionone synthesis

The significance of ionone synthesis goes well beyond pleasing our sense of smell as evidenced by the recent discovery by the group of Hanns Hatt at the Ruhr University Bochum in Germany of *ectopic* ionone receptors in many peripheral tissues: the olfactory or odorant receptor family 51 subfamily E member 2 (OR 51E2) – otherwise known as ionone receptor – also plays a role in the control of tumor progression. Interestingly α- and β-ionone by docking at the receptor have different effects, acting either as antagonist/agonist or as agonists with different cellular effects due to different coupling to downstream effectors, as postulated for biased ligands (Massberg and Hatt 2018; Sanz et al. 2016). β-Ionon has one of the lowest odor thresholds ever determined (≈ 0.1 ng/L air or 10^{-4} ppb); α-Ionon has an odor thresholds about one order of magnitude higher than β-Ionon (≈ 3 ng/L air or 3×10^{-3} ppb) (Buttery et al. 1971; Brenna et al. 2002).
Also recently, the ability of endogenous ionone synthesis by means of asymetric beta-carotene cleavage by a mitochondrial dioxygenase was described by Klaus Vogt (1945–2008) and Johannes von Lintig at the University of Freiburg, Germany. Many essential aspects related to this enzyme leading to seminal publications were then worked out by von Lintig and his group at Case Western Reserve University in the United States, where he had moved to (Lobo et al. 2012). Eccentric β-carotene cleavage by this enzyme named BCO-2 at the 9,10 double bond yields two (asymmetric; different) apocarotenoids: β-apo-10-carotenal and β-ionone. By further cleavage at the 9',10' double bond a further β-ionone molecule and rosafluene (C14-dialdehyde) a natural product found in roses, can be generated. In contrast to BCO-1 that metabolizes only provitamin A carotenoids (α-and β-carotene and β-cryptoxanthin), BCO-2 has a much broader substrate specificity and can asymmetrically cleave also non-provitamin A carotenoids (Fig. 5) (Wu et al. 2016).

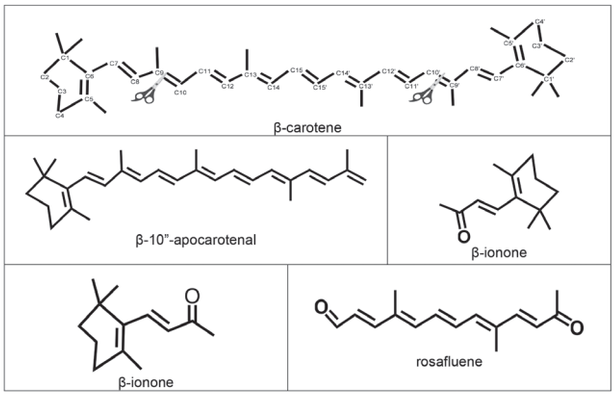

Fig. 5: Eccentric β-carotene cleavage by the mitochondrial enzyme BCO-2 at the 9',10' double bond yields two (asymmetric; different) apocarotenoids: β-apo-10'-carotenal and β-ionone. By further cleavage at the 9,10 double bond a further β-ionone molecule and rosafluene (C14- dialdehyde) a natural product found in roses, can be generated.

Ligands of the violet scent receptor might prove to be of value in ways Krüger and Tiemann never anticipated. Ionones, both exogenous and endogenous influence a large number of processes both in health and disease acting as ligands at both orthotopic and

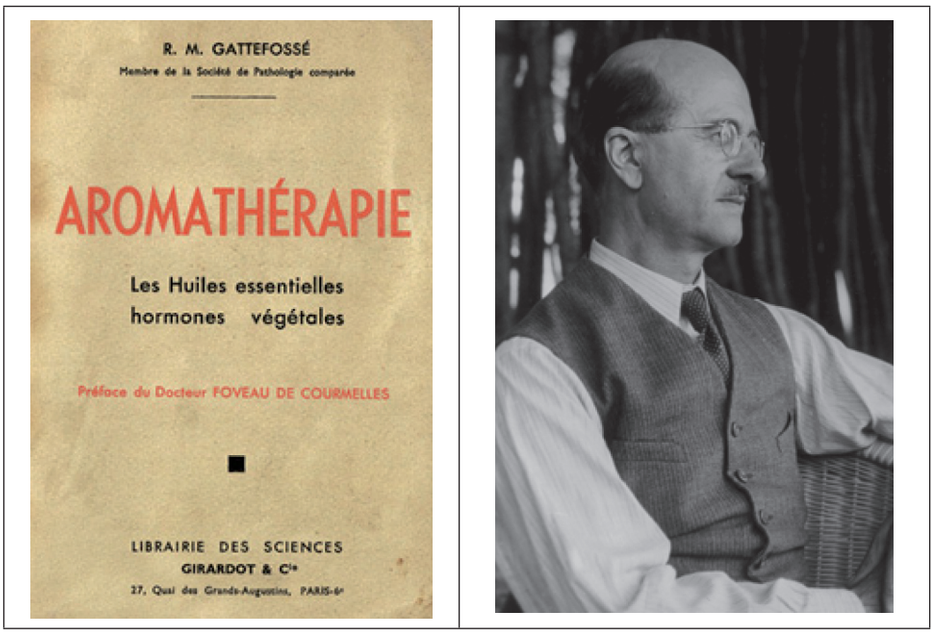

Fig. 6: The concept of *aromatherapy* i.e. the use of volatile aromatic compounds for medical therapeutic purposes was introduced by René-Maurice Gattefossé (1881–1950) in the first edition (1937) of his book Aromatherapy, Paris, Girardot (188 pages). Profil de René-Maurice Gattefossé, © Gattefossé-Archives Gattefossé, with kind permission. The Gattefossé Company (*Société de Produits aromatiques*) founded 1880 by his father Louis (1854–1919) is today (*Société Gattefossé*) a multinational group operating in some sixty countries.

ectopic olfactory receptors. They might represent the primary products of BCO-2 metabolism.

Aromatherapy as imagined by French chemist René-Maurice Gattefossé (1881–1950) could after all have a scientific basis with a little twist; the little twist being that the volatile therapeutic compounds might be of endogenous origin (Gattefossé 1996; Steflitsch 2017; Petroianu 2018, Fig. 6).

While this short communication does not exhaustively answer the questions "Who was Paul Krüger?" it should satisfy the idle curiosity of most researchers. For those wishing to know more, it gives some direction for future investigations.

Conflict of interest: None declared.

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