

Tracing Chemical Genealogy Through the Archives of the Institute of Organic Chemistry at the University of Zurich

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Abstract: Aspects of the history of chemists and chemistry in the Institute of Organic Chemistry at the University of Zurich are traced through chemical genealogy and retained samples from the chemical archives. The work of three OCI faculty members (Werner, Karrer and Eugster) who completed their graduate studies in the Institute is highlighted.

Keywords: Alkaloid · Carotenoid · Chemical genealogy · Institute of Organic Chemistry UZH · Sample archives

Introduction

Scientific genealogy is a subject of enthusiastic casual interest to many chemists – identifying one's academic 'lineage' provides a clear course for navigating the history of the sciences, reinforces a sense of belonging to a broader community, and captures some of the conception of a research group as a family, albeit not one of blood relatives.^[1]

For those who received their academic training in the United States and then moved to the University of Zurich, one of the striking contrasts relates to academic lineage and affiliation. In the American system, it is relatively rare for a student to return to their graduate institution as a faculty member. In contradistinction, the Institute of Or-

ganic Chemistry (OCI) at the University of Zurich (UZH) has an illustrious history of just that – many of our famous faculty members are OCI PhD students that remained or returned to serve in the Institute.

At 175 years of age, formulating a comprehensive history of the Institute is a daunting task, and one which has fortunately been taken on by other authors.^[2] Thus freed of an obligation to be complete, the chemical archive in the OCI provides an opportunity to follow a single specific path through OCI history, illustrated with images from the archive. Following is a chemical lineage that includes the figures whose work will be highlighted, with brief note of academic affiliation; the researchers whose samples will be discussed are shown in bold face.^[3] (Of particular interest is that Alfred Werner can be traced back to Leopold Gmelin, whose student Karl Löwig was one of the founding professors of the UZH chemistry.)



Alfred Werner's Contributions to Organic Chemistry

Alfred Werner (1866–1919) is rightly remembered as the 'father of coordination chemistry'.^[4] However, often forgotten is that he received his graduate training in organic chemistry under the supervision of Arthur Hantzsch, obtaining his PhD in 1890 from the University of Zurich, and that he made important independent contributions to this field as well.

Werner provided one of the first demonstrations that aryl Grignard reagents could react with alkylating agents (specifically, dimethyl sulfate) to form the corresponding methyl alkylarenes.^[5] In addition, he recognized the value of such alkylating agents for the synthesis of methyl esters, particularly those of sterically-hindered carboxylic acids such as 2,4,6-tribromobenzoic acid, as an alternative to traditional Fischer esterification.^[6]

A great many of Werner's samples are preserved at UZH (including approximately 2500 of his coordination complexes).^[7] The OCI archive provides a tactile reminder of his pioneering studies of the chemistry of phenanthrene and its derivatives. In early work, he confirmed that bromination of phenanthrene gives the addition rather than the substitution product.^[8] In the course of exploring the chemistry of the phenanthroquinones, his group prepared a number of derivatives, including the monohydrazone. Likely informed by his graduate work with Hantzsch on the geometric isomers of benzil dioxime,^[9] Werner recognized that the hydrazone was a single isomer, and noted

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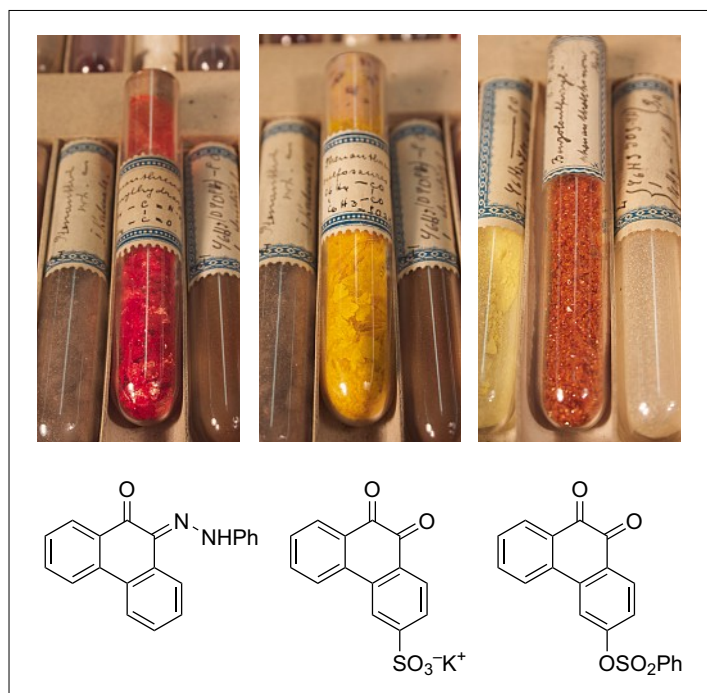


Fig. 1. Visual reminders of Werner's early contributions to the chemistry of penthroquinones

that the hydrazone and the tautomeric hydroxy azophenanthrene were equivalent by the analytical methods of the time.^[8] (The azo tautomer was later confirmed to be the correct structure.^[10]) The hydrazone is deep red, while the phenanthroquinone-3-sulfonic acid potassium salt is brilliant yellow, and the benzenesulfonate of 3-hydroxyphenanthroquinone is a bronze-orange (Fig. 1).^[8] While precise dating is not possible, the samples must be over 100 years old, and as can be seen are remarkably well preserved.

Karrer as a Transforming Figure in Isolation, Purification and Synthesis

Paul Karrer (1889–1971) had an extraordinary gift for seeing far and clearly in many directions at once. Over the course of his long career in the OCI – spanning more than 40 years, 100 PhD students and 1000 publications – he made seminal contributions to at least seven distinct areas of research.^[11] Much of this involved the challenging isolation of naturally occurring compounds and their subsequent rigorous characterization, directly, by the most advanced analytical methods available, and indirectly, by synthetic interconversion and partial and total chemical synthesis. As a whole, this body of work provides an early and elegant illustration of the dynamic interplay between what can be isolated in pure form, what can be measured, and what can be made, each of these endeavors furthering the others.

While not an inventor of modern chromatography *per se*, Karrer was among the

earliest chemists to fully embrace the technique, and to treat it as being comparable in importance to crystallization as a purification method.^[12] (This was, for some time, a minority view.) Having identified paper chromatography as particularly well-suited to the separation of alkaloids, Karrer and coworkers made the technological leap to preparative cellulose chromatography, which allowed the purification of comparatively large quantities of pure alkaloids from natural product extracts.^[13] These preparative columns were enormous by modern standards, many meters in height, and the fractionation of samples could take weeks of continuous sample collection. Unfortunately, an image of these columns is not available. However, another chromatographic advance – liquid-liquid chromatography – was also adopted by practitioners in the OCI. In the form of a ‘counter-current distribution apparatus’, (Fig. 2) the practice of this method for separation and purification clearly presages more recent advances

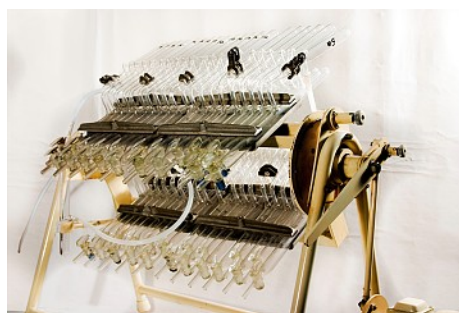


Fig. 2. Counter-current apparatus for separation and purification of natural products

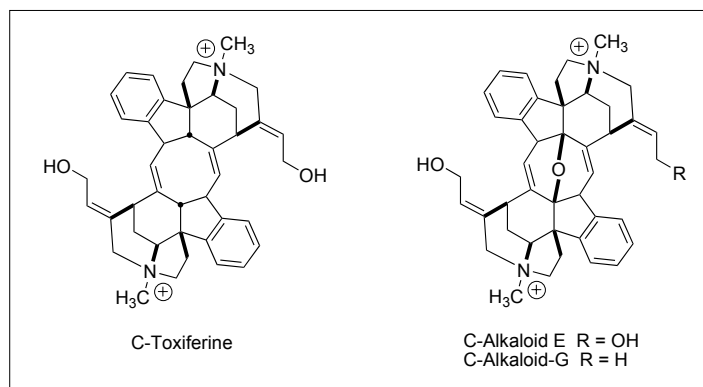


Fig. 3. The structure of toxiferine alkaloids isolated from calabash curare (counterions omitted for clarity)

in automation and continuous-flow processes.^[14]

As an example of combined analytical and synthetic prowess, the inter-related isolation, structure determination and partial synthesis of the toxiferine alkaloids from ‘calabash curare’, stand out (Fig. 3).^[11] Numerous alkaloid samples are retained in the archive (Fig. 4, 5), including C alkaloid E, which, with its counterpart C alkaloid G, remains among the most toxic non-reactive substances known to man.^[15] Among Karrer's students and colleagues, this was regarded as such signature work that it was the subject of an original painting given as a gift to Karrer upon the occasion of his 70th birthday, not long before his retirement from the OCI (Fig. 6).^[16] The painting clearly shows the plants from which calabash curare was made, as well as the structure of the calabash alkaloid mavacurine and an indigenous hunter using a blow gun (presumably with curare-coated darts).

Eugster, Carrots and Mushrooms

Emeritus Prof. Conrad Hans Eugster began his OCI career as a graduate student with Paul Karrer.^[2] A defining accomplishment from Eugster's doctoral work was completion of the first total synthesis of β -carotene,^[17] which embodied the broad scientific approach of Karrer and which foreshadowed Eugster's own independent work in natural product isolation and characterization. Of particular note is the synthetic strategy adopted, which took advantage of the C_2 symmetry of the molecule and was an early example of what has since been termed two-directional or bidirectional synthesis (Fig. 7).^[18]

Eugster's efforts in natural product isolation and characterization spanned a wide range of alkaloids, quinones, and polyenes. As part of Eugster's legacy, the archive contains a large number of these compounds, in pure form. Particularly stunning are the broad range of carotenoids, in almost every imaginable color, from both plant and bac-



Fig. 4. Calabash alkaloids from the OCI archives



Fig. 5. C Alkaloid E, one of the most toxic non-reactive molecules known (shown as the picrate salt)

terial sources (Fig. 8 and 9). Other important early work included the isolation and characterization of the psychoactive and toxic components of *Amanita muscaria*, the fly agaric mushroom (Fig. 10).^[19] The psychoactive properties of fly agaric derive from muscimol; however, its toxicity derives from the closely related molecule, ibotenic acid, making ingestion of fly agaric a risky proposition, for humans as well as insects. (Indeed, the *Amanita* *ssp.* include many of the most toxic mushrooms, and account for the majority of accidental fatalities from mushroom poisoning.) While generally remembered as very reserved, a still image from 16 mm film footage in the archive shows Prof. Eugster at a lighter mo-

Fig. 6. A painting given to Prof. Karrer on the occasion of his 70th birthday

ment, contemplative and seemingly satisfied, after a student has presented him with a fly agaric model (including, as its fringe, something that looks quite like a garter) (Fig. 11). While a complete retrospective of Eugster's work will be warranted in the future, it would be premature at this time given that his work is still ongoing.^[20]

Conclusion

In teaching chemistry, it quickly becomes clear that students learn best in different ways – some by seeing, some by

hearing, some by writing, some by doing, and some by a combination of these. Similarly, people become interested in topics by many different routes – a fascination with a theory, a visual image or historical context (such as a chemical lineage) to name a few. Art and science museums provide an opportunity to address all of these facets of interest and learning, especially visual images and historical context. While the OCI archive is less than complete, and not suitably formatted for public display, public access is one of the long-term goals of the Institute. In the interim, this retrospective of samples from Werner, Karrer and Eugster opens at least a small window on the history of the OCI. It is anticipated that aspects of this article will be expanded into individual displays for the upcoming MNF Jubiläumsevent (see: <http://www.175jahre.uzh.ch/naturwissenschaft/>).

Acknowledgements

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- [1] Among the many sources available regarding chemical genealogy, three of particular use are: a) the Chemical Genealogy database maintained online at the University of Illinois by Dr. V. Mainz and Prof. G. Girolami: http://www.scs.uiuc.edu/~mainzv/Web_Genealogy/index.htm; b) the Scientific Genealogy

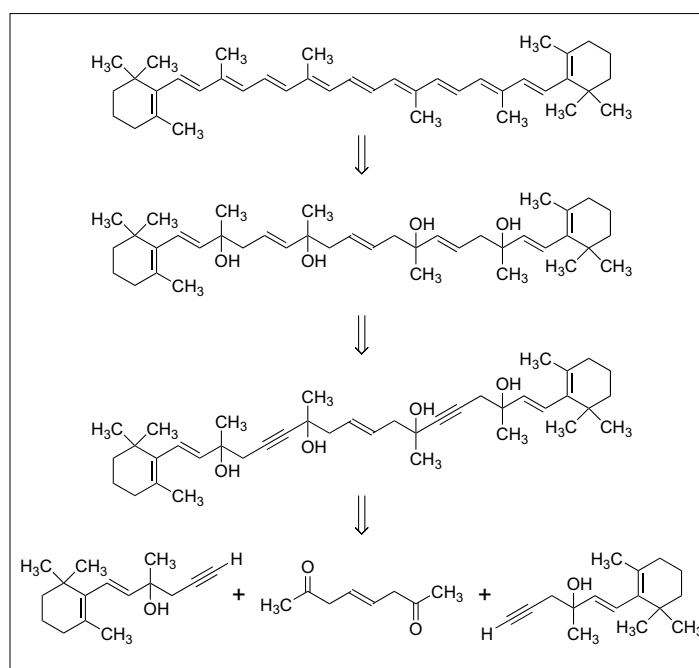
Fig. 7. Retrosynthetic scheme for Eugster and Karrer's pioneering β -carotene synthesis



Fig. 8. A broad spectrum of carotenoid samples

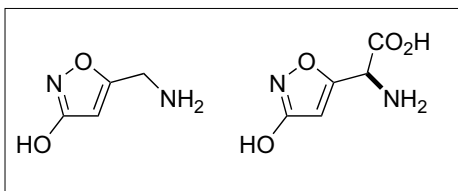
Fig. 10. Structures of muscimol (left) and ibotenic acid (right), active principles from *Amanita muscaria*Fig. 11. Prof. Eugster with a model of *A. muscaria*

Fig. 9. Samples of partially purified carotene from 1947 (left); representative carotene samples from the archives (right)

- Master List compiled by Dr. J. Andraos of the Department of Chemistry at York University, Ontario; <http://www.chem.yorku.ca/NAMED/PDF-FILES/MasterList.pdf>; and c) Concise Dictionary of Scientific Biography. American Council of Learned Societies. New York Scribner, 1981.
- [2] a) C. H. Eugster, *Chimia* **1983**, 37, 1, and *Chimia* **2008**, 62, 75; b) J. S. Siegel, H. Heimgartner, *Chimia* **2008**, 62, 114.
- [3] This flow chart was constructed from the sources cited in ref. [1] and necessarily excludes a great deal of detail.
- [4] For recent primary literature reviews, see a) K. Bowman-James, *Accounts Chem. Res.* **2005**, 38, 671; b) W. G. Jackson, J. A. McKeon, S. Cortez, *Inorg. Chem.* **2004**, 43, 6249. See also [2a].

- [5] A. Werner, F. Zilkens, *Berichte* **1903**, 36, 2116. See also: A. Werner, *Berichte* **1904**, 36, 3618.
- [6] A. Werner, W. Seybold, *Berichte* **1904**, 37, 3658.
- [7] As an example of the continuing value of these samples, it was recently shown by X-ray analysis of a ca. 100-year old crystal that Werner prepared the first – and to date only – known example of a dicobalt complex containing bridging μ -amido, μ -oxo and μ -superoxo ligands. See B. Spingler, M. Scanavy-Grigorieff, A. Werner, H. Berke, S. Lippard, *J. Inorg. Chem.* **2001**, 40, 1065.
- [8] a) A. Werner, B. Lowenstein, A. Wack, T. Frey, M. Kunz, K. Rekner, A. Ney, H. Heil, A. Scherrer, H. Schwabacher, J. Kunz, A. Grob, *Annalen der Chemie* **1902**, 321, 248;

- b) A. Werner, T. Frey, A. Grob, H. Heil, J. Kunz, M. Kunz, B. Lowenstein, A. Ney, K. Rekner, A. Scherrer, H. Schwabacher, A. Wack, *Annalen der Chemie* **1902**, 322, 135. See also: A. Werner, A. Egger, *Berichte* **1904**, 37, 3026.
- [9] A. Hantzsch, A. Werner, *Berichte* **1890**, 23, 11.
- [10] K. Auwers, H. Dannehl, *Annalen der Chemie* **1911**, 378, 210.
- [11] For a biographical sketch containing an exhaustive bibliography, see O. Iser, *Biographical Memoirs of Fellows of the Royal Society* **1978**, 24, 245. See also [2a].
- [12] For two reviews celebrating ca. a century of chromatography, see a) H. Engelhardt, *J. Chrom. B* **2004**, 800, 6; b) L. S. Ettre, *Chromatographia* **2000**, 51, 7. Karrer is mentioned as an early practitioner and advocate in each of these. For a much earlier review, also noting Karrer's contributions, see c) J. E. Meinhard, *Science* **1949**, 110, 387.
- [13] Preparative chromatography on alumina also figured prominently in the isolation of the calabash alkaloids. For early reports, see a) H. Schmid, J. Kebrle, P. Karrer, *Helv. Chim. Acta* **1952**, 35, 1864; b) H. Asmis, E. Bächli, E. Giesbrecht, J. Kebrle, H. Schmid, P. Karrer, *Helv. Chim. Acta* **1954**, 37, 1968; c) W. v. Philipsborn, H. Schmid, P. Karrer, *Helv. Chim. Acta* **1956**, 39, 1208.
- [14] The particular device here was manufactured by Labortec of Basel, and dates to approximately 1970. For an early reference on counter-current ('Craig') separations, see L. C. Craig, G. H. Hogeboom, F.H. Carpenter, V. du Vigneaud, *J. Biol. Chem.* **1947**, 168, 667.
- [15] The chemistry of the Strychnos alkaloids has been reviewed elsewhere. (See, for example, A. Guggisberg, M. Hesse, 'Milestones in Alkaloid Research in Helvetica Chimica Acta 1918–1991', in 'Highlights of Chemistry as Mirrored in Helvetica Chimica Acta', Eds. M. V. Kisakürek, E. Heilbronner, VCH, Basel, **1994**.) For a recent review of the toxicity of these and related alkaloids, see G. Philippe, L. Angenot, M. Tits, M. Frédérick, *Toxicol.* **2004**, 44, 405.
- [16] According to a memo in the archives from emeritus Prof. M. Hesse, this painting hung in Karrer's office until his retirement, after which he gave it to his colleague and former student, Prof. H. Schmid. Upon Schmid's demise, it was kindly donated to the OCI.
- [17] C. H. Eugster, P. Karrer, *Helv. Chim. Acta* **1950**, 33, 1237.
- [18] a) S. R. Magnuson, *Tetrahedron* **1995**, 51, 2167; b) C. S. Poss, S. L. Schreiber, *Acc. Chem. Res.* **1994**, 27, 9.
- [19] C. H. Eugster, G. F. R. Müller, R. Good, *Tetrahedron Lett.* **1965**, 1813.
- [20] See, for example a) S. S. Mohanty, P. Uebelhart, C. H. Eugster, *Helv. Chim. Acta* **2000**, 83, 2036; b) A. Linden, B. Bürgi, C. H. Eugster, *Helv. Chim. Acta* **2004**, 87, 1254.