

Hugo (Ugo) Schiff, Schiff Bases, and a Century of β -Lactam Synthesis**

Thomas T. Tidwell*

[2+2] cycloaddition · β -lactams · history of chemistry · ketenes · Schiff bases

Dedicated to Professor George A. Olah on the occasion of his 80th birthday

Hugo Schiff: From Germany to Italy

Schiff bases (imines) constitute one of the most widely used families of organic compounds,^[1] not only as synthetic intermediates but also in coordination chemistry,^[1f,g] and their chemistry is essential material in organic textbooks. The Schiff test is also often used, but who was Schiff? Many of the pioneers of organic chemistry in the 19th century are familiar figures, but the discoverer of these compounds is now almost forgotten, at least outside of his home department at the University of Florence in Italy, which bears his name. Hugo Schiff (1834–1915), born in the vibrant Jewish community in Frankfurt/Main, Germany, was a prominent chemist a century ago, and his death was widely reported.^[2] He studied in Göttingen and completed his dissertation “Über einige Naphtyl- und Phenyl-derivate” in 1857 with Friedrich Wöhler, famous for the synthesis of urea. His

dissertation included studies of the chemistry of aniline,^[3a] experience he was to make good use of in his studies of Schiff bases. However, in the aftermath of the 1848–1849 revolutions these were tumultuous times in Europe. Schiff was actively involved in the events of the day, reportedly having met and corresponded with Karl Marx (1818–1883) and Friedrich Engels (1820–1895).^[2c] Marx published the *Communist Manifesto* in 1848 and moved to London from Germany in 1849, while his followers were persecuted and sometimes even jailed. Because of his “rather advanced political views”^[2c] Schiff found it expedient to emigrate to Switzerland in 1857 and was Privatdozent at the University of Bern. He moved to Italy in 1863, where his brother, Moritz Schiff (1823–1892), was a prominent physiologist in Florence, having been denied a position in Hannover owing to his service as a

physician in the revolution of 1848 in Baden.

Thereafter Schiff spent his long career in Italy and continued teaching until 1915, the year of his death (Figure 1). Despite his “rugged and forbidding exterior” he was one who “continued to cherish the most gentle ideals” (Figure 2).^[2b]

Schiff Bases

In Italy Schiff first obtained a position in Pisa, where in 1864 he studied the reaction of aniline with aldehydes, including acetaldehyde, valeraldehyde, benzaldehyde, and cinnamaldehyde, and he discovered that imines were formed (Figure 3). The first brief paper was entitled “A New Series of Organic Bases” (“Eine neue Reihe organischer Basen”),^[3b] and Schiff reviewed the

[*] Prof. T. T. Tidwell
Department of Chemistry
University of Toronto
Toronto, ON M5S 3H6 (Canada)
Fax: (+1) 416-978-5325
E-mail: ttidwell@chem.utoronto.ca
Homepage: http://www.chem.utoronto.ca/peoples/faculty_profile.php?id=69

[**] I thank Prof. Antonio Guarna and Prof. Adolfo Franchi of the Department of Organic Chemistry “Ugo Schiff” of the University of Florence (Italy) and Prof. Daniel Rabinovich (Charlotte, North Carolina) for supplying original materials and helpful comments, and John Blunden-Ellis (Manchester), Prof. Michael D. Gordin (Princeton), and Prof. Dieter Lenoir (Munich). Financial support by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.



Figure 1. Hugo Schiff, lecturing, April 24, 1915.

mentioned in the programme, was by no means the least scientific, the least relished, nor, above all, the least substantial.”^[4h] This set a convivial tone for future meetings, a tradition which has continued.

Thus Schiff at the beginning of his career had intimate contact with many of the world's leading chemists, and years later was, along with William Odling (1829–1921, who had been Professor at Oxford, President of the Chemical Society of London, and creator in 1864 of an early periodic chart), one of the last surviving participants at this epochal event.

Schiff in Florence

By his 30th birthday in 1864 Schiff was a well-established scientist with more than 50 papers to his credit. He also engaged in a vociferous debate with A. W. Hofmann in London on the formation and constitution of the aniline dyes, and this spurred Hofmann to important discoveries regarding the phenylamines.^[6]

After a brief stay in Pisa (1863–1864) Schiff moved to Florence to teach chemistry in the Museo di Storia Naturale (1864–1876) and was a co-founder of the journal *Gazzetta Chimica Italiana* in 1870 along with Cannizzaro and other prominent Italian chemists (Figure 5). This journal was prominent for more

than 120 years before becoming part of the combined European journals, the *European Journal of Organic Chemistry* and the *European Journal of Inorganic Chemistry*. In 1877 he became Professor of General Chemistry in Turin but returned to Florence in 1879 as Professor of General Chemistry in the Istituto di Studi Superiori Pratici e di Perfezionamento (after 1924 the University of Florence).^[2b] Schiff continued to be a very prolific investigator, and his publication list over a period of more than 60 years grew beyond 300 papers in organic, inorganic, physical, biological, and applied chemistry. These were in German, Italian, or French, and in a few cases the same paper appeared in two different languages, which was an accepted practice at the time.

Schiff retained his liberal views and was a cofounder of the socialist Italian newspaper *L'Avanti* in 1894, which is still in existence. Cannizzaro, who shared this outlook, was characterized as having the fiery temperament of his native Sicily, leading him to fight in the rebellion against the King of Naples in 1847–1849 and to join in 1860 with Garibaldi in Palermo. Mendeleev had a similar progressive attitude and resigned his Professorship at the University of St. Petersburg in 1893 when rebuked for his sympathy with student unrest, and he was never admitted to the Imperial Russian Academy of Sciences.

100 Years of β -Lactams by [2+2] Cycloaddition

A new and far-reaching application of imines came soon after the preparation and isolation of diphenylketene (**2**), the first ketene, in 1905.^[7a] Hermann Staudinger (Figure 6) found in 1907 that **2** reacted with Schiff bases such as **1** by [2+2] cycloaddition,^[7b] producing the first synthetic β -lactam **3** [Eq. (4)]. In the same report were included the corresponding preparations of β -lactones and of cyclobutanones, and this

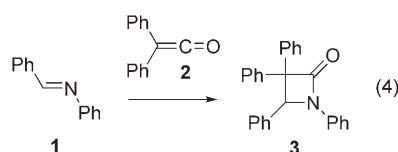


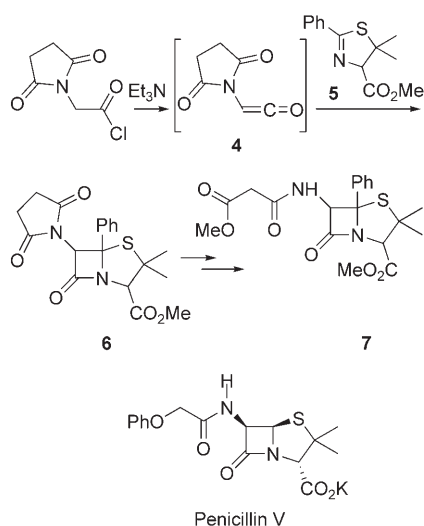
Figure 6. Hermann Staudinger (1881–1965). Courtesy of the ETH Zürich.

began the study of cycloadditions, 20 years before the discovery of the Diels–Alder reaction.

The reaction of imines with ketenes forming β -lactams was discovered 100 years ago, long before the utility of the products in medicinal chemistry was recognized. For this reason the reaction remained a little-used laboratory curiosity until the discovery of the potent antibiotic penicillin.^[8] When the therapeutic properties of penicillin were recognized there was a massive effort to prepare large quantities of this wonder drug and to deduce the structure with the hope of developing a laboratory synthesis.^[8,9] A critical step in the proof of the β -lactam structure for penicillin was the realization by R. B. Woodward that normal amide conjugation was hindered in the strained nonplanar bridgehead bicyclic β -lactam structure, so that the β -lactam was more reactive than normal open-chain amides, and the normal amide IR absorption at 1670 cm⁻¹ was displaced to 1728 cm⁻¹.^[8c] The first synthetic penicillin **7** (classified as a penam) was prepared by [2+2] cycloaddition of imine **5** with ketene **4** in 1950 (Scheme 1),^[9a] while the potassium salt of optically active natural penicillin V, was first synthesized in 1957.^[9b] The subsequent blossoming of β -lactam studies continues unabated and is well documented.^[9c–e]

Pro memoria
 Il dì 20 Settembre 1870.
 mentre suonarono le campane per la
Occupazione di Roma.
 e poi il 29 settembre
 fu fondato
 In questo Laboratorio di Chimica
 (Via Romana 18)
La Gazzetta Chimica Italiana.
 presenti i Prof: Stan. Cannizzaro
 Franc. Selmi
 Paolo Tassinari
 Ugo Schiff
 Luigi Galbra
 e gli aiuti: Em. Paternò e
 Sciil. Guareschi

Figure 5. Founding document, *Gazzetta Chimica Italiana*, 1870. Courtesy of the University of Florence.



Scheme 1. Synthesis of 9-phenylpenicillin (7),^[9a] and the potassium salt of natural penicillin V.

The synthesis and structure assignment by Schiff in 1864 of the first imines was an important event at the beginning of the modern age of chemistry. The finding introduced a new family of reactive organic compounds with myriad uses, including their unanticipated application in the synthesis of β -lactams, a major class of antibiotics, whose centenary is now being celebrated. However, the enormous potential of Schiff bases is far from exhausted and provides an endless opportunity for chemical creativity.

A Forgotten Man?

Schiff had a very eventful and colorful life, but outside of Italy he is little remembered today. For example, he is not mentioned in a number of recent reference works,^[10] including *Name Reactions and Reagents in Organic Synthesis* (2005),^[10a] which does cite name reactions or reagents for 55 other chemists whose family name begins with the letter S. His German-language obituaries^[2a,d] were rather brief and included no photograph, whereas the obituaries in English were more extensive.^[2b,c] Reasons for this neglect may be that he was an expatriate from Germany, and Italy had declared war on Germany's ally Austria-Hungary on May 24, 1915. His life and career have been widely cele-

brated in Italy, but this recognition has not spread elsewhere.

The life of Schiff may be compared to that of Carl Schorlemmer (1834–1892),^[11] born the same year as Schiff (Figure 7). He studied in Giessen and



Figure 7. Carl Schorlemmer (1834–1892). Courtesy of the GDCh.

was also attracted to Marxism. In 1859 he immigrated in 1859 to England, where he became Professor of Organic Chemistry at Manchester in 1874 and enjoyed a successful career. Like Schiff, he engaged in studies of the aniline dyes, an important subject at the time.^[11k] He was an active Marxist, referred to as “The Red Chemist”,^[11e] and his life has been the subject of numerous articles,^[11] not only in Germany with a 16-page obituary,^[11a] but also in Great Britain,^[11b–e] the former communist countries of Europe,^[11f–j] and in The People's Republic of China.^[11j] The organic chemistry laboratory in Manchester which opened in 1895 bore his name. Later his name was also bestowed on the institute at the Technische Hochschule Leuna-Merseburg in former East Germany, and a statue of him was erected on the grounds. He was not as active an investigator as Schiff, and his continuing recognition may be attributed not only to his qualities as a chemist, but also to his position in England, where he attracted more attention than Schiff did in Italy, and to his fame as a close confidant of Marx and Engels.

The passage of time has, however, probably done the most to fade memories of Schiff, as several generations of chemists have come and gone since this exceptional individual was a familiar figure. The concept of the Schiff base is well implanted in the chemical vocabulary, but the man responsible for this highly versatile family of compounds deserves to be known in his own right. Coincidentally a biographical sketch has just appeared^[12] but in a journal devoted to postage stamps honoring scientists. There is no Schiff postage stamp, but the imine structure is prominently displayed on postmarks (Figure 8).^[12] These ef-



Figure 8. Imine postmark. Courtesy of Prof. Adolfo Franchi.

forts may help to bring the man to life for the current generation of chemists.

Published online: November 19, 2007

- [1] a) *The Chemistry of the Carbon-Nitrogen Double Bond* (Ed.: S. Patai), Wiley, New York, **1970**; b) G. Tennant in *Comprehensive Organic Chemistry*, Vol. 2 (Ed.: I. O. Sutherland), Pergamon, Oxford, **1979**, chap. 8, pp. 385–590; c) J. K. Whitesell in *Comprehensive Organic Synthesis*, Vol. 6 (Ed.: E. Winterfeldt), Pergamon, Oxford, **1991**, chap. 4.1, pp. 703–732; d) G. M. Robertson in *Comprehensive Organic Functional Group Transformations*, Vol. 3 (Ed.: G. Pattenden), Pergamon, Oxford, **1995**, chap. 10, pp. 403–423; e) S. Pawlenko in *Methoden der Organische Chemie* (Houben-Weyl), Vol. E14b, Part 1

- (Eds.: D. Klamann, H. Hagemann), Thieme, Stuttgart, **1980**, pp. 222–281; f) R. H. Holm, G. W. Everett, Jr., A. Chakravorty, *Prog. Inorg. Chem.* **1966**, 7, 83–214; g) P. A. Vigato, S. Tamburini, *Coord. Chem. Rev.* **2004**, 248, 1717–2128.
- [2] a) *Ber. Dtsch. Chem. Ges.* **1915**, 48, 1566–1567; b) M. Betti, *J. Chem. Soc.* **1916**, 109, 424–428; c) W. McPherson, *Science* **1916**, 43, 921–922; d) *Chem. Z.* **1916**, 40, 37–38. e) G. Anichini, *La Nazione*, Firenze, **1915**, 9 Sep, 3.
- [3] a) *Chem. Zentralbl.* **1857**, 2, 185–189; b) H. Schiff, *Justus Liebigs Ann. Chem.* **1864**, 131, 118–119; c) U. Schiff, *Giornale di Scienze Naturali ed Economiche*, Vol. II, Palermo, **1867**, pp. 1–59; d) H. Schiff, *Justus Liebigs Ann. Chem.* **1866**, 140, 92–137; e) R. L. Shriner, C. K. F. Hermann, T. C. Morrill, R. C. Fuson, *The Systematic Identification of Organic Compounds*, Wiley, New York, **2004**, pp. 284–286; f) A. Kekulé, *Lehrbuch der Organischen Chemie*, Ferdinand Enke, Erlangen, **1866**.
- [4] a) A. J. Ihde, *The Development of Modern Chemistry*, Harper and Row, New York, **1964**, pp. 226–230; b) H. Hartley, *Studies in the History of Chemistry*, Clarendon Press, Oxford, **1971**, pp. 185–194; c) M. Laing, *Educ. Chem.* **1995**, 151–153; d) J. Hudson, *The History of Chemistry*, MacMillan, New York, **1992**, pp. 122–137; e) E. v. Meyer, *J. Prakt. Chem.* **1911**, 83, 182–189; f) C. deMilt, *J. Chem. Educ.* **1951**, 28, 421–425; g) C. deMilt, *Chymia* **1948**, 1, 153–169; h) J. H. S. Green, *Proc. Chem. Soc.* **1960**, 329–332; i) R. Anschütz, *August Kekulé Band I*, Verlag Chemie, Berlin, **1929**, p. 203; j) Mendeléef, *J. Chem. Soc. Trans.* **1889**, 55, 634–656; for an essay on Mendeleev, see M. D. Gordin, *Angew. Chem.* **2007**, 119, 2814–2821; *Angew. Chem. Int. Ed.* **2007**, 46, 2758–2765.
- [5] a) S. Cannizzaro, *Justus Liebigs Ann. Chem.* **1853**, 88, 129–130; b) For a brief essay on the *Sunto* see G. B. Kauffman, *J. Chem. Educ.* **1991**, 68, A266.
- [6] a) A. S. Travis, *The Rainbow Makers*, Associated University Presses, London, **1993**; b) A. W. Hofmann, *Proc. R. Soc. London* **1864**, 13, 341–347.
- [7] a) H. Staudinger, *Ber. Dtsch. Chem. Ges.* **1905**, 38, 1735–1739; b) H. Staudinger, *Justus Liebigs Ann. Chem.* **1907**, 356, 51–123.
- [8] a) J. C. Sheehan, *The Enchanted Ring: The Untold Story of Penicillin*, MIT Press, Cambridge, **1982**; b) K. Brown, *Penicillin Man: Alexander Fleming and the Antibiotic Revolution*, Sutton, London, **2004**; c) R. B. Woodward, J. R. Johnson, R. Robinson, *The Chemistry of Penicillin* (Eds.: H. T. Clarke, J. R. Johnson, R. Robinson), Princeton University Press, Princeton, **1949**, chap. 15, pp. 440–454.
- [9] a) J. C. Sheehan, E. L. Buhle, E. J. Corey, G. D. Laubach, J. J. Ryan, *J. Am. Chem. Soc.* **1950**, 72, 3828–3829; b) J. C. Sheehan, K. R. Henery-Logan, *J. Am. Chem. Soc.* **1957**, 79, 1262–1263; c) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Eur. J. Org. Chem.* **1999**, 3223–3235; d) C. Palomo, J. M. Aizpurua, I. Ganboa, M. Oiarbide, *Curr. Med. Chem.* **2004**, 11, 1837–1872; e) C. Palomo, J. M. Aizpurua, *Science of Synthesis (Houben-Weyl)*, Vol. 23.6 (Eds.: D. Bellus, R. Danheiser), Thieme, Stuttgart, **2006**.
- [10] a) B. P. Mundy, M. G. Ellerd, F. G. Favalaro, Jr., *Name Reactions and Reagents in Organic Synthesis*, 2nd ed., Wiley Interscience, New York, **2005**; b) L. Kürti, B. Czako, *Strategic Applications of Named Reactions in Organic Synthesis*, Elsevier, Amsterdam, **2005**; c) *Nostrand's Encyclopedia of Chemistry*, 5th ed. (Ed.: G. D. Considine), Wiley-Interscience, New York, **2005**; d) A. Nickon, E. F. Silversmith, *Organic Chemistry: the Name Game*, Pergamon, New York, **1987**; e) A. R. Surrey, *Name Reactions in Organic Chemistry*, 2nd ed., Academic Press, New York, **1961**.
- [11] a) A. Spiegel, *Ber. Dtsch. Chem. Ges.* **1892**, 25, 1107–1123; b) H. E. Roscoe, *Nature* **1892**, 46, 394–395; c) H. B. Dixon, *Mem. Lit. Philos. Soc. Manchester* **1893**, 7(4), 191–198; d) *J. Chem. Soc.* **1893**, 63, 756–763; e) T. Benfey, T. Travis, *Chem. Ind.* **1992**, 12, 441–444; f) C. Duschek, *Z. Chem.* **1984**, 24, 313–325; g) W. Pritzkow, *Z. Chem.* **1980**, 20, 277–283; h) G. D. Hal'pern, *Vestn. Akad. Nauk SSSR* **1942**, 12, 79–82; i) K. Heinig, *Carl Schorlemmer*, Teubner, Leipzig, **1974**; j) J.-X. Pan, *Huaxue Tongbao* **1976**, 41–49 [*Chem. Abstr.* **1976**, 84, 163588]; k) R. S. Dale, C. Schorlemmer, *J. Chem. Soc.* **1873**, 26, 434–444.
- [12] A. Franchi, *Philatelia Chim. Phys.* **2007**, 29, 106–124.