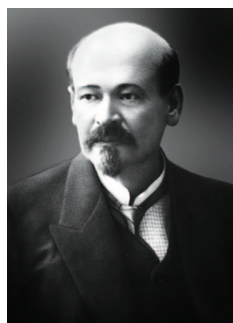


## Independent Discoveries: The Wolff–Kishner Reduction

This year is the 150<sup>th</sup> anniversary of the birth of Russian chemist Nikolai Matveevich Kizhner (1867–1935),<sup>1,2</sup> and the 160<sup>th</sup> anniversary of the birth of German chemist Ludwig Wolff (1857–1919).<sup>3</sup> These two chemists carried out seminal studies in the reactions of compounds with N–N bonds, leading to three eponymous reactions: the Wolff–Kishner deoxygenation of aldehydes and ketones, the Wolff rearrangement of  $\alpha$ -diazoketones, and the Kishner cyclopropane synthesis. Here we concentrate on the first.



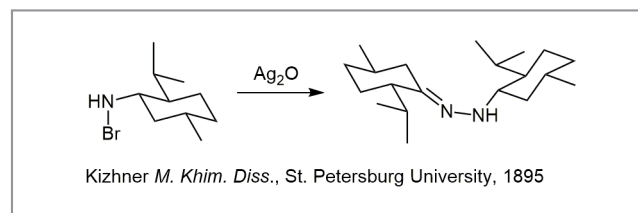
Nikolai Matveevich Kizhner. Portrait courtesy of Tomsk Polytechnic University. Image of the plaque by the author.

Kizhner graduated from the First Moscow Gymnasium and entered Moscow University in 1886 as a student in the Natural Science Division of the Physics–Mathematics Faculty. Here, two years later, he came under the influence of the mercurial Vladimir Vasil'evich Markovnikov (1838–1904) and his colleague, the physical chemist and thermodynamicist Vladimir Fyodorovich Luginin (1834–1911). These two men led Kizhner to choose organic chemistry for his career.

Following his graduation (*Diplom*) in 1890, Kizhner was appointed to a supernumerary position as a laboratory assistant teaching qualitative and quantitative analysis while he pursued the *M. Khim.* degree. In 1894, he was elected *Privat-Dozent*, and was permitted to deliver lectures. At the same time, he also taught chemistry and electrical engineering at the Alexander Military School. During his *M. Khim.* period, Kizhner published a paper<sup>4</sup> explaining the unexpected physical and chemical properties of 'hexahydrobenzene' obtained by the reduction of benzene with hydrogen iodide by identifying it as methylcyclopentane rather than cyclohexane or *n*-hexane.

Kizhner graduated with the *M. Khim.* degree in 1895. His dissertation '*Amines and hydrazines of the polymethylene*

*series, methods of their formation and transformation*'<sup>5</sup> reported his work in the chemistry of *N*-bromoamines and his first work with hydrazines and hydrazones (Scheme 1).



Scheme 1

In 1900, Kizhner graduated with the *Dr. Khim.* degree,<sup>6</sup> the minimum qualification for appointment as Ordinary Professor in Russian universities. In 1901, at the urging of Mendeleev, Kizhner was offered the position of inaugural Professor of Organic Chemistry at the new Tomsk Technological Institute (now Tomsk Polytechnic University) in Siberia. Here, Kizhner built the Department of Chemistry, and he used each of his frequent trips to the West to accumulate books, journals, and apparatus for his department. His early work here continued his investigations of bromoamines as well as the synthesis and reactions of small-ring compounds.

In 1902, Kizhner was diagnosed with 'gangrene of the limbs,' a painful and even life-threatening malady that led to the amputation of his left foot above the ankle in 1904. In 1910, he lost the other foot to the same disease. After his first amputation, Kizhner continued his teaching, but he relinquished his research laboratory to a colleague. What is amazing is that, confined to a wheelchair after his second amputation, which made his teaching extremely difficult, he returned to the research laboratory with a vengeance. It was a year after this second amputation that he first described his hydrazine decomposition.<sup>2</sup>

Kizhner was a political progressive. During the Revolution of 1905, the students at Tomsk went on strike, asking autonomy for the universities from the Ministry of Education, and Kizhner was supportive of their actions, helped to organize similar activities by the faculty, and refused to impose sanctions on striking students. This earned him the enmity of the powerful Trustee of the Educational District, Leonid Ivanovich Lavrent'ev (d. 1914). In 1906, he was branded a 'free thinker' and exiled from Siberia, along with several colleagues. The intervention of the influential member of court, Count Witte,

earned his reinstatement in 1907. His political enemies were not appeased, however, and the continued machinations and veiled threats against his family by right-wing extremists resulted in Kizhner being forced from his professorship in 1912, and him leaving Tomsk permanently in 1914. Kizhner felt a very special bond to the Department that he had built, to his students, and to his uncompleted research there; leaving was very hard for him.

Still, Kizhner got the last laugh. Instead of *resigning* from his professorship, he retired on medical grounds, which provided him with a full pension! He moved to Moscow, where his pension allowed him to work, although he never again achieved the level of productivity he had in Tomsk. With the help of Aleksei Yevgen'evich Chichibabin (1871–1945), another Markovnikov student, he obtained an appointment to the Shanyavskii People's University, an informal institution set up by the professors who had resigned from Moscow University in protest of the actions of the reactionary Minister of Education, Lev Aristidovich Kasso (1865–1914). Although it was not authorized to grant degrees, its standards were so high that even members of the faculty of Moscow University itself attended their lectures.

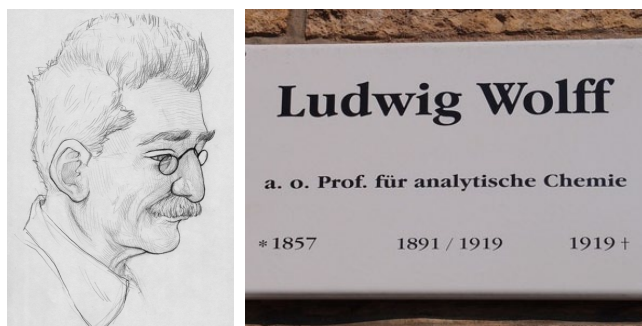
Following the October Revolution, Kizhner became the guiding force of the Soviet dye industry,<sup>2h</sup> and he was elected a Corresponding Member of the USSR Academy of Sciences in 1929, and an Honorary Member in 1934. It is worth noting that in all of Kizhner's papers, he carried out the experimental work himself, in spite of his disabilities, and he also insisted on an equal level of care in the work of his students. It is fully in keeping with his character that he died just hours after returning home after a typically long day in the laboratory.

In contrast to the wealth of information about Kizhner, biographies of Wolff<sup>3</sup> are few, and usually devoid of much detail. Wolff was born in Neustadt an der Haardt in 1857 and

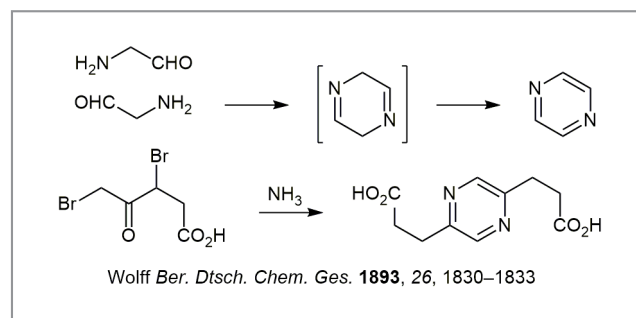
graduated from the Gymnasium at Speyer in 1876. Typical of young German chemists of this time, Wolff studied at several universities before taking his doctorate. From 1876–1881, he studied first at the University of Würzburg and the Technical University of Munich, and then at the University of Strasbourg, where Rudolf Fittig (1835–1919) and Adolf von Baeyer (1835–1917) were professors. He passed the *Diplom* examinations in 1880 and the State examinations for admission as a student in the higher schools of Bavaria in 1881.

He held the position of Assistant in the Chemical Institute at Strasbourg from 1882–1891. As a graduate student, Wolff chose to study with Fittig. His research focused on  $\delta$ -lactones and their derivatives and on levulinic acid and its derivatives. His work with  $\delta$ -lactones led to his doctoral dissertation entitled '*Über eine einfache Darstellungsweise und die Constitution des Valerolactons und über das chemische Verhalten der  $\delta$ -Oxycapronsäure.*' He qualified for faculty status by earning his *Habilitation* at Strasbourg in 1885 for his treatise '*Über einige Abkömmlinge der Lävulinsäure.*' In 1891, he joined the faculty at Jena, where he remained for the rest of his career.

At Jena, Wolff became a colleague of Ludwig Knorr (1859–1921), who was Director of the Laboratory. It was Knorr who called Wolff to Jena to teach analytical chemistry, but it is also reported that Wolff, known as an organic chemist, was not subjected to questioning about analytical chemistry before he was hired! Nevertheless, he did teach analytical chemistry so well that he became the Head of the new Division of Analytical and Inorganic Chemistry. In his obituary of his colleague,<sup>3a</sup> Ludwig Knorr described Wolff as a quiet man who did not court publicity, and who found his greatest satisfaction in carrying out his duties well. Knorr describes him as an excellent and dedicated teacher, and reports that, even in the final throes of his illness, he maintained his office and its duties with his characteristic efficiency – in spite of the pain. Wolff died of a painful internal disease (possibly cancer) at the relatively young age of 61.



Ludwig Wolff. Line drawing by Sierra Lomo and reproduced with permission. Plaque by Evergreen68 and licensed under the Creative Commons Attribution-Share Alike 4.0 International license.



Scheme 2

In contrast to his teaching, Wolff's research at Jena was exclusively in organic chemistry. He closely followed the careers of his students, advancing their interests wherever possible. In his early independent work, he continued his studies of the chemistry of brominated levulinic acids and extended this work to the synthesis of heterocycles (Scheme 2).<sup>7</sup>

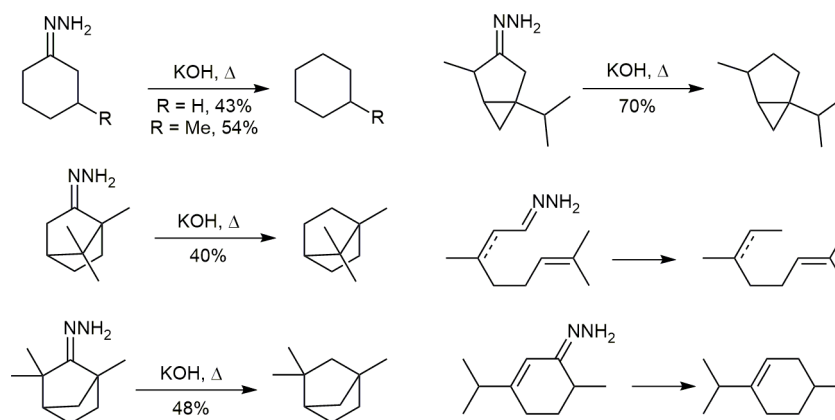
The deoxygenation of the hydrazones of aldehydes and ketones by base is now over a century old, discovered by Kizhner in 1911.<sup>8</sup> Because Kizhner had published his results only in Russian, they were not widely known in Western Europe. Consequently, the reaction was discovered independently, in the form of the decomposition of semicarbazones by base, by Wolff in 1912.<sup>9</sup> Initially, the reaction was known as the Wolff reduction, but in 1913 Wolff wrote to Kizhner to acknowledge his priority for the discovery. Since that time, the reduction has borne the names of both chemists, and it holds a central position in the organic chemist's arsenal of carbonyl reductions.<sup>10</sup>

In the first of his two papers in 1911, Kizhner described the reduction of a series of saturated ketones by heating their hydrazones with solid potassium hydroxide (Scheme 3). In the second paper, he extended the reaction to unsaturated ketones, including conjugated cyclic ketones.

In 1912, Wolff independently described the base-promoted decomposition of the monohydrazone of a *p*-benzoquinone derivative. The product of the reaction was a phenol, clearly obtained by tautomerization of the 2,5-cyclohexadienone (Scheme 4).

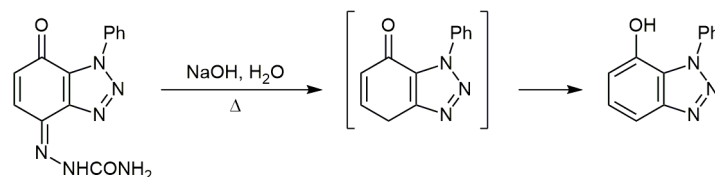
Since 1911, the reaction has been modified many times<sup>11</sup> in an effort to improve yields and lower the reaction temperature (Scheme 5).

*David Lewis*



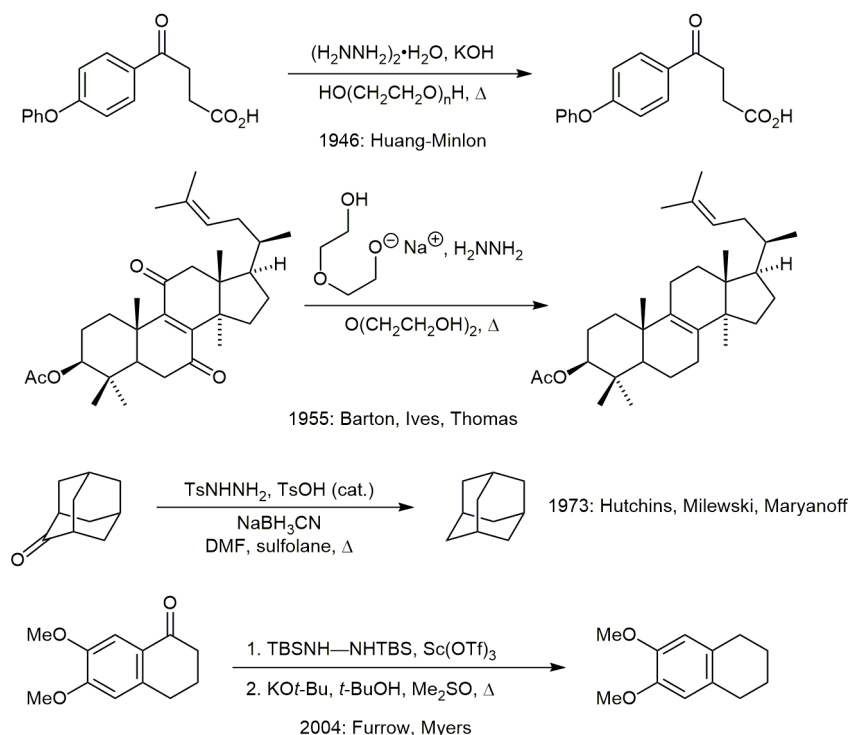
Kizhner *Zh. Russ. Fiz.-Khim. O-va.* **1911**, 43, 582–595, 951–962

Scheme 3



Wolff *Justus Liebigs Ann. Chem.* **1912**, 394, 86–108

Scheme 4



Scheme 5

## REFERENCES

- (1) Kizhner's name has been variously transliterated as Kijner, Kižner, Kishner, or Kizhner; the last option is based on the BGN/PCGN Romanization system for Russian, and is used here as the most intuitive for English speakers.
- (2) Biographies in Russian: (a) S. S. Nametkin *N. M. Kizhner. Issledovaniya v Oblasti Organicheskoi Khimii* [*N. M. Kizhner. Investigations in the Field of Organic Chemistry*], Akad. Nauk SSSR: Moscow, **1937**; (b) T. V. Boratova, E. A. Zaitseva *Khimiya* **1996**, 39, 2; (c) V. D. Yushkovskii *Izv. Tomskogo Pol-ka. Uni-ta.* **2002**, 305, 208–221; (d) *Bol'shaya Sovyetskaya Entsiklopediya* [*Great Soviet Encyclopedia*], Soviet Encyclopedia Publishers: Moscow, **1973**; 4<sup>th</sup> ed., Vol. 7, 102; Biographies in English: (e) D. E. Lewis *Early Russian Organic Chemists and Their Legacy*, Springer: Heidelberg, **2012**; 105–106; (f) D. E. Lewis *Angew. Chem. Int. Ed.*, **2013**, 52, 11704–11712, this paper was also published as a German-language version: *Angew. Chem.* **2013**, 125, 11920–11928; (g) V. Suntsov, D. E. Lewis *Bull. Hist. Chem.* **2014**, 39, 43–52. (h) V. Suntsov, D. E. Lewis *Bull. Hist. Chem.* **2017**, 42, 46–56.
- (3) Biographies in German: (a) L. Knorr In Hofmann, K. A. *Ber. Dtsch. Chem. Ges.* **1919**, 52, A67–68; (b) P. Hallpap *Chemiehistorische Notiz* 3/2012, am 17.01.2012, am Institut für Organische Chemie und Makromolekulare Chemie (Humboldtstr. 10).
- (4) (a) N. Kizhner *Zh. Russ. Fiz.-Khim. O-va.* **1894**, 26, 375–380; (b) N. Kijner *J. Prakt. Chem.* **1897**, 56, 364–372; (c) E. W. Warnhoff *J. Chem. Educ.* **1996**, 73, 494–497.
- (5) N. M. Kizhner *Aminy i gidraniny polimetilenobogo ryada, metody ikh obrazovaniq i prevrashcheniya* [*Amines and hydrazines of the polymethylene series, methods of their formation and transformation*], M. Khim. Diss., St. Petersburg University, **1895**.
- (6) N. M. Kizhner *O deistvii okisi serebra i gidroksilamina na bromaminy. O stroenii gekzagidrobenezola* [*On the action of silver oxide and hydroxylamine on bromamines. On the structure of hexahydrobenzene*], Dr. Chem. Diss., Moscow University, **1900**.
- (7) Representative papers: (a) L. Wolff *Ber. Dtsch. Chem. Ges.* **1893**, 26, 1830–1833; (b) L. Wolff *Ber. Dtsch. Chem. Ges.* **1893**, 26, 2216–2221; (c) L. Wolff *Ber. Dtsch. Chem. Ges.*

**1895**, 28, 69–74; (d) L. Wolff *Justus Liebigs Ann. Chem.* **1895**, 288, 1–37.

(8) (a) N. M. Kizhner *Zh. Russ. Fiz.-Khim. O-va.* **1911**, 43, 582–595; (b) N. Kizhner *Zh. Russ. Fiz.-Khim. O-va.* **1911**, 43, 951–962, these papers are available in English translation: V. Suntsov, D. E. Lewis *Bull. Hist. Chem.* **2015**, 40, 61–64; V. Suntsov, D. E. Lewis *Bull. Hist. Chem.* **2015**, 40, 64–68; V. Suntsov, D. E. Lewis *Bull. Hist. Chem.* **2015**, 40, 69–73.

(9) L. Wolff *Justus Liebigs Ann. Chem.* **1912**, 394, 86–108.

(10) Reviews: (a) D. Todd *Org. React.* **1948**, 4, 378–423; (b) R. O. Hutchins, M. K. Hutchins *Compr. Org. Synth.* **1991**, 8, 327–343.

(11) (a) Huang-Minlon *J. Am. Chem. Soc.* **1946**, 68, 2487–2488; (b) Huang-Minlon *J. Am. Chem. Soc.* **1949**, 71, 3301–3303; (c) D. H. R. Barton, D. A. J. Ives, B. R. T. Thomas *J. Chem. Soc.* **1955**, 2056–2056; (d) D. J. Cram, M. R. V. Sahyun *J. Am. Chem. Soc.* **1962**, 84, 1734–1735; (e) M. F. Grundon, H. B. Henbest, M. D. Scott *J. Chem. Soc.* **1963**, 1855–1858; (f) L. Caglioti, M. Magi *Tetrahedron* **1963**, 19, 1127–1131; (g) R. O. Hutchins, C. A. Milewski, B. E. Maryanoff *J. Am. Chem. Soc.* **1973**, 95, 3662–3668; (h) G. W. Kabalka, J. D. Baker, Jr. *J. Org. Chem.* **1975**, 40, 1834–1835; (i) G. W. Kabalka, J. H. Chandler *Synth. Commun.* **1979**, 9, 275–279; (j) M. E. Furrow, A. G. Myers *J. Am. Chem. Soc.* **2004**, 126, 5436–5445.