

THE CRUCIAL EARLY CONTRIBUTIONS OF F. R. JAPP TO A GENERAL SYNTHESIS OF IMIDAZOLE DERIVATIVES

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Introduction

This paper explores the contributions that three authors (Japp, Radziszewski, and Debus) made to the discovery of a reaction for synthesizing imidazoles.

Radziszewski and Japp

The condensation of a 1,2-dicarbonyl compound with an aldehyde and ammonia was reported by Radziszewski (1,2). In modern times this old reaction has been exploited for library synthesis of imidazoles and has often been referred to as the Radziszewski or occasionally as the Debus-Radziszewski imidazole synthesis (3). However, another author, Francis R. Japp, played a key role in the development of this reaction (4):

We have partially investigated the action of a hydroxy-aldehyde- salicylaldehyde on phenanthraquinone in presence of ammonia, and have found that the reaction takes place according to the equation-

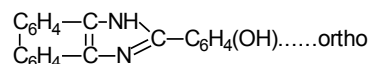


Phenanthra-	Salicyl-	New Compound
quinone	aldehyde	

The compound thus formed contains two atoms of nitrogen in the molecule, instead of one, as in the case of the compounds already described.

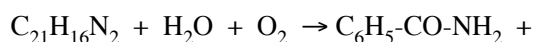
Japp published a further paper at the beginning of 1882 (5), in which he drew the structure of the product correctly as an imidazole derivative (the structure has the

hydrogen atom drawn on nitrogen and the two double bonds are drawn in the right place. In the published paper the kink in the double bond between carbon and nitrogen is not an atom).

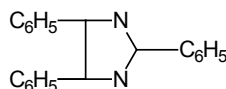


Japp's first formula for a fused imidazole

This deduction was based on a series of chemical reactions, his previous work on phenanthraquinone chemistry, and a comparison with the treatise on anhydro-bases prepared by Hübner (6) and Mensching (7). In his next paper he emphasised the pioneering structural studies on lophine reported by Fischer and Troschke (8). They reported the oxidative degradation of lophine to one equivalent of benzamide and one equivalent of dibenzamide.



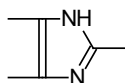
They deduced that lophine must contain three intact phenyl groups, three carbon atoms, two nitrogen atoms, and one hydrogen atom. The three carbon atoms are attached to nitrogen and for a stable ring two carbons must be attached together. Hence they arrived at a formula but were unsure of the position of the hydrogen atom and the two double bonds. The double bonds were proposed as lophine reacted with bromine.



Structure of Lophine proposed by Fischer and Troschke (the location of two double bonds and a hydrogen atom were not decided)

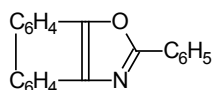
Japp also made some timely comments regarding the unusual mechanism of this reaction. Regarding the related fused oxazoles he stated (9):

We have therefore to assume that during the formation of the compounds containing one atom of nitrogen, an intramolecular rearrangement occurs: the two carbon atoms of the double keto group -CO-CO- , become united by double bonds. This corresponds with what occurs when a quinone of the ortho series-also a double ketone-is converted by the action of reducing agents into a quinol. In the present case the reducing agent is an aldehyde, and, when the aldehyde has done its work, we have no longer an aldehyde-residue, but an acid-residue in the molecule of the new compound. The occurrence of this rearrangement has been proved for three double ketones-phenanthraquinone, chrysoquinone, and benzil. As regards the compounds containing 2 atoms of nitrogen in the molecule, it seems to me that the simplest way of formulating these is to assume the existence of the complex of atoms-



...I take for granted an intramolecular rearrangement, such as occurs in the formation of the oxygenated compound.

The fused oxazole which Japp had discovered from phenanthraquinone is formed by a similar mechanism (4). The planar *cis* carbonyl groups lead to oxazole rather than imidazole products. However, oxazoles have no extra hydrogen atom on the ring, and so the two double bonds can only go in one place. Japp therefore deduced that the double bonds would go in the same place for reactions involving benzil or glyoxal, forming imidazoles. Drawing an analogy of the aldehyde to a reducing agent converting a quinone into a quinol is a beautiful idea.

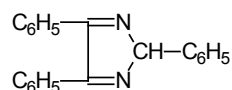


Fused oxazole

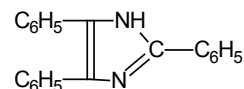
Citations are now described which lend further

credence to Japp's early contribution to this reaction. In Japp's Chemical Society paper entitled "II.-On the Constitution of Lophine (Second Notice)," he states (9):

In No.11 of the *Berichte* (**1882**, 15, 1493) (see also this journal, **1882**, Abstracts, 1063), Radziszewski communicates a new synthesis of Lophine by the interaction of benzil, benzaldehyde, and ammonia. This reaction corresponds with the synthesis of parahydroxylophine from benzil, parahydroxybenzaldehyde, and ammonia, described by Japp (*Ber.* **1882**, 15, 1268; this journal **1882**, 326). In discussing his synthesis, Radziszewski comes to the conclusion that lophine has the formula-



Radziszewski's proposal for the formula of Lophine and rejects the formula



Japp's proposal for the formula of Lophine

proposed by Mr Robinson and myself.

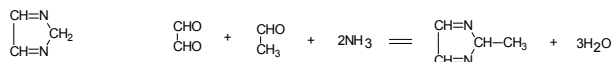
Radziszewski's deduction was in part based on the decomposition of lophine by potash into benzyl alcohol and benzoic acid, hence proceeding via benzaldehyde (1). Radziszewski's formula contains a benzaldehyde residue; Japp's formula contains a benzoic acid residue. Radziszewski however overlooked that a bis-imine formula would be hydrolytically unstable in aqueous acid. Lophine and related compounds are quite stable to acid (5). Japp proposed that a structure of his formula might hydrolyze to benzoin which might then cleave into benzaldehyde and benzoic acid to account for Radziszewski's observation.

The competitive spirit between the two scientists is evident in a further addendum published in this paper (9):

Radziszewski has published a second paper (*Ber.*, **1882**, 15, 2706), in which he describes the synthesis of Wallach's paraoxaldehyde by the interaction of glyoxal, acetaldehyde, and ammonia-here again employing a reaction belonging to the class of condensations discovered by me.

Radziszewski (1, 10) refers to Japp's earlier papers (11, 12), respectively. Japp published the correct structure

of the imidazole derivatives in all his papers, whereas Radziszewski published it incorrectly (1, 2, 10). In the first paper (1) he reports the synthesis of lophine but draws the wrong structural formula, and he reports the synthesis of imidazole or 'glyoxalin' from glyoxal and ammonia but draws the wrong structure. In his second paper (2) he describes condensing glyoxal, acetaldehyde, and ammonia to form 'paraoxalmethylin,' again reporting the incorrect structural formula. The structure of lophine in the third paper (10) is wrong. In Japp's paper (11) the structure of lophine is drawn correctly as in Ref 12.



Glyoxalin

Paraoxalmethylin

Radziszewski's proposals for 'imidazole' structures

The *Berichte* paper on Japp's work (11), which Radziszewski (1) refers to, was submitted on May 22 (Eingegangen am 22. Mai; verlesen in der Sitzung von Hrn. A. Pinner), whereas Radziszewski's paper was submitted a month later on June 19. Radziszewski's second paper was submitted later on November 17 (2).

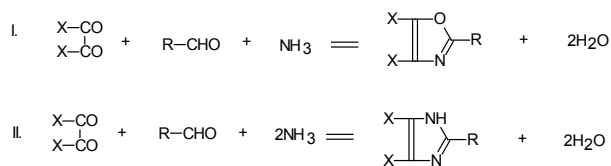
Japp followed with further papers (13, 14), in which he justified the structures as imidazole derivatives. Radziszewski's comments published in his *Chem. Soc.* paper (10), entitled "Constitution of Lophine and Allied Compounds," confirm Japp's priority in publication (10):

The author anticipates in this paper the more extended publication of the results of his investigation of this subject, in consequence of the appearance of a paper by Japp and Robinson (*Trans.*, 323) on lophine and amarine.

In other words, Japp's results (4, 5, 11, 12) were all published before Radziszewski's work appeared.

Japp's publications communicated clearly his contribution to the field. In his paper, "LIII.-On the Action of Aldehydes and Ammonia on Benzil (continued)," he states (15):

In former communications (this Journal, *Trans.*, **1880**, 666; **1881**, 225; **1882**, 146; 157, and 323; **1883**, 9 and 197, relating to the joint action of aldehydes and ammonia on compounds containing the dicarbonyl group (-CO-CO-), two general reactions of this class have been described.



[the fused oxazoles are formed from phenanthraquinone and chrysoquinone]

In Japp's paper co-authored with Wynne he states (18):

...The reactions of another dicarbonyl compound (glyoxal) with aldehydes and ammonia have, however, been studied in the case of fatty aldehydes by Radziszewski, who thus effected a new synthesis of homologues of glyoxaline (XIX-XXI). In the present communication, we describe the reactions of benzil with fatty aldehydes and ammonia.

Reactions with formaldehyde (22), acetaldehyde, isovaleraldehyde, cinnamaldehyde (which gave a different product), and aromatic aldehydes were reported by Japp. The generality of the method was developed by both scientists. According to K. Hofmann (3):

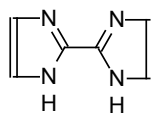
The method carries Radziszewski's name because he extended it to the preparation of simpler imidazoles and demonstrated its general applicability.

The current author believes that credit should also be given for the ring synthesis, whether substituted or unsubstituted, as it was for some other heterocycles discovered in this period (23). Japp can claim priority for (i) synthetic methods; (ii) correct structural assignment and mechanistic understanding; (iii) designation of the required components (a diketone and an aldehyde).

Debus

Prior to the above studies by Japp and Radziszewski, Heinrich Debus (1834-1916) published a single paper on this reaction (24). Both Japp and Radziszewski seem to have been unaware of it because neither refers to it. Debus reported the condensation of glyoxal with ammonia to give both imidazole and 1H,1'H-[2,2']biimidazolyl. The correct molecular formula was drawn for each, although no molecular structures were drawn. An incorrect breakdown of the molecular structure for bi(imidazole) was drawn. Imidazole is formed because a C-C bond cleavage occurs at some stage of the reaction. Radziszewski repeated the early work of Debus and reported it in his papers where he described the glyoxalin synthesis (imidazole) and proposed that glyoxal cleaves

into formaldehyde, required for the reaction, and formic acid (1, 2).



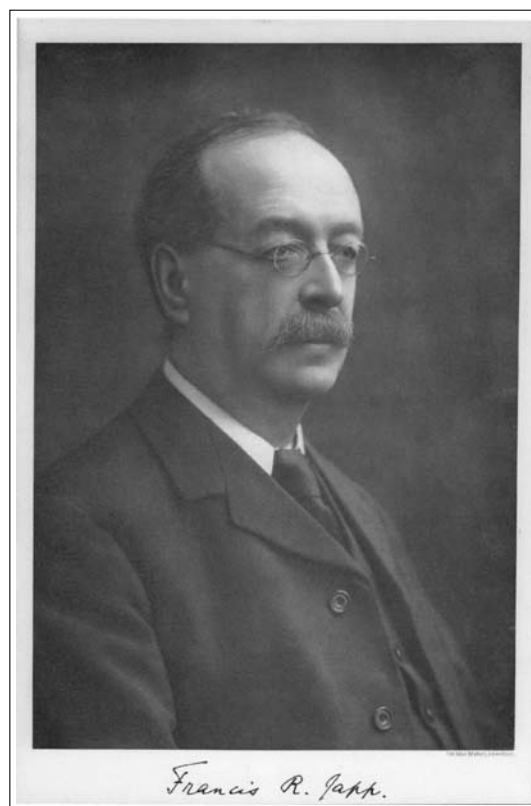
Conclusion

In conclusion Japp's group provided a significant, independent development to this reaction, which arose from a study of the condensation reactions of ammonia with phenanthraquinone. His group was the first to report the correct structure of the product as an imidazole derivative, a result contested by Radziszewski. Japp's group was the first to report the use of benzil in the reaction (11, 12), work cited in two of Radziszewski's papers (1, 10). Japp showed that diketones other than glyoxal could be used. He published a mechanistic rationale for the reaction, proposing that the aldehyde acts as a reducing agent on the diketone and that an intramolecular rearrangement leads to the product (9). Most importantly, Japp was the first to show that a 1,2-diketone could be used along with a separate aromatic or aliphatic aldehyde, to effect the reaction. This opened up the scope of the reaction that is exploited today and is a significant step following from Debus's original discovery of the synthesis of the parent imidazole. The Japp group published four papers (4,5,11,12) on the imidazole-forming reaction before the Radziszewski group had published any. Interestingly, neither author grasped that Japp's structural formula is more stable because of aromaticity (25). A number of new heterocyclic ring systems were discovered in this decade, but substituted derivatives were sometimes prepared, such as pyrrole and pyridine derivatives, and served to give the authors inventorship (23). For Japp to claim that it was a "class of condensations discovered by me" is, however, a stretch of the truth (9)!

REFERENCES AND NOTES

- B. Radziszewski, "Ueber die Constitution des Lophins und verwandter Verbindungen" *Ber. Dtsch. Chem. Ges.* **1882**, *15*, 1493-1496.
- B. Radziszewski, "Ueber Glyoxalin und seine Homologe" *Ber. Dtsch. Chem. Ges.*, **1882**, *15*, 2706-2708.
- Some examples: D. R. J. Acke, R. V. A. Orru, and C. V. Stevens, "Continuous Synthesis of Tri- and Tetrasubstituted Imidazoles via a Multicomponent Reaction under Microreactor Conditions" *QSAR & Comb. Sci.*, **2006**, *25*, 474-483; K. Hofmann in A. Weissberger, Ed., *Imidazole and its Derivatives*, Interscience Publishers, New York, Chapter II, "The Alkyl- And Arylimidazoles" 1953, 33; Y. Ogata, A. Kawasaki and F. Sugiura, "Kinetics of the formation of triphenylimidazoles from benzils," *J. Org. Chem.*, **1969**, *34*, 3981-3985; A. Domling and I. Ugi, "Multicomponent reactions with isocyanides," *Angew. Chem. Int. Ed. Engl.*, **2000**, *39*, 3168-3210; K. Matsumoto, J. Chul Kim, H. Iida, H. Hamana, K. Kumamoto, H. Kotsuki, and G. Jenner, "Multicomponent Strecker Reaction under High Pressure" *Helv. Chim. Acta.*, **2005**, *88*, 1734-1753; J. Andraos, "Unification of Reaction Metrics for Green Chemistry II: Evaluation of Named Organic Reactions and Application to reaction Discovery," *Org. Process Res. Dev.*, **2005**, *9*, 404-431; D. O. Tymoshenko, "On the development of organic chemistry in Ukraine," *ARKIVOC*, **2005**, viii, 1-3; M. Kidwai, S. Saxena, Ruby and S. Rastogi, "An Efficient Synthesis of 2,4,5-Trisubstituted and 1,2,4,5-Tetrasubstituted 1H-imidazoles," *Bull. Korean Chem. Soc.*, **2005**, *26*, 2051-2053; N. J. Curtis and R. S. Brown, "An Easily Introduced and Removed Protecting Group for Imidazole Nitrogen: a Convenient Route to 2-Substituted Imidazoles," *J. Org. Chem.*, **1980**, *45*, 4038-4040; J. Wolff and I. Covelli, "Factors in the Iodination of Histidine in Proteins" *Eur. J. Biochem.*, **1969**, *9*, 371-377; E. Gelens, F. J. J. De Kanter, R. F. Schmitz, L. A. J. M. Sliedregt, B. J. Van Steen, C. G. Kruse, R. Leurs, M. B. Groen, and R. V. A. Orru, "Efficient Library Synthesis of Imidazoles using a Multicomponent Reaction and Microwave Irradiation," *Mol. Div.*, **2006**, *10*, 17-22.
- F. R. Japp, "On the Action of Aldehydes on Phenanthraquinone in Presence of Ammonia. (Second Notice)," *J. Chem. Soc., Trans.*, **1881**, *39*, 225-228.
- F. R. Japp and F. W. Streatfeild, "On the Action of Aldehydes on Phenanthraquinone in Presence of Ammonia. (Third Notice)," *J. Chem. Soc., Trans.*, **1882**, *41*, 146-156.
- H. Hübner, "Ueber Anhydroverbindungen" *Liebigs Ann. Chem.*, **1881**, *210*, 328-396.
- C. Mensching, "Nitrierung von Salicylanilid,," *Ber. Dtsch. Chem. Ges.*, **1880**, *13*, 462-463.
- E. Fischer and H. Troschke, "Ueber Amarin und Lophin," *Ber. Dtsch. Chem. Ges.*, **1880**, *13*, 706-711.
- F. R. Japp, "II.-On the Constitution of Lophine (Second Notice)," *J. Chem. Soc., Trans.*, **1883**, *43*, 9-18.
- B. Radziszewski, "Constitution of Lophine and Allied Compounds," *J. Chem. Soc., Trans.*, **1882**, *43*, 1063-1065.
- F. R. Japp and H. H. Robinson, "Constitution des Lophins und des Amarins," *Ber. Dtsch. Chem. Ges.*, **1882**, *15*, 1268-1270.
- F. R. Japp, "L.- On the Constitution of Amarine and Lophine" *J. Chem. Soc., Trans.*, **1882**, *41*, 323-329.
- F. R. Japp, "Constitution des Lophins, des Amarins und des Glyoxalins," *Ber. Dtsch. Chem. Ges.*, **1882**, *15*, 2410-2421.

14. F. R. Japp, "On Condensations of Compounds which contain the Dicarboxyl group with Aldehydes and Ammonia," *J. Chem. Soc., Trans.*, **1883**, 43, 197-200.
15. F. R. Japp and S. C. Hooker, "On the Action of Aldehydes and Ammonia on Benzil (continued)," *J. Chem. Soc., Trans.*, **1884**, 45, 672-685.
16. F. R. Japp, "LVIII.-On the Action of Benzaldehyde on Phenanthraquinone, both alone and in presence of Ammonia" *J. Chem. Soc., Trans.*, **1880**, 37, 661-672.
17. F. R. Japp and F. W. Streatfeild, "XXIV. Application of the Aldehyde and Ammonia Reaction in Determining the Constitution of Quinones," *J. Chem. Soc., Trans.*, **1882**, 41, 157-159.
18. F. R. Japp and W. Palmer Wynne, "XLVI. On the Action of Aldehydes and Ammonia on Benzil (continued)," *J. Chem. Soc., Trans.*, **1886**, 49, 462-472.
19. B. Radziszewski, "Ueber die Synthese der Oxalinbasen," *Ber. Dtsch. Chem. Ges.*, **1883**, 16, 487-494.
20. B. Radziszewski, "Ueber einige neue Glyoxaline," *Ber. Dtsch. Chem. Ges.*, **1883**, 16, 747-749.
21. B. Radziszewski and L. Szul, "Ueber das Glyoxal-isoamylin und dessen Abkömmlinge," *Ber. Dtsch. Chem. Ges.*, **1884**, 17, 1291-1296.
22. F. R. Japp, "Diphenylglyoxaline and Methyl-diphenylglyoxaline," *J. Chem. Soc., Trans.*, **1887**, 51, 557-564.
23. 1880-1890 was an exciting period for the discovery of new heterocyclic syntheses. These include the Skraup; "Eine Synthese des Chinolins," *Ber. Dtsch. Chem. Ges.*, **1880**, 13, 2086-2089 and Doebner-Von Miller, "Ueber eine dem Chinolin homologe Base," *Ber. Dtsch. Chem. Ges.*, **1881**, 14, 2812-2817; quinoline syntheses; the Knorr pyrrole synthesis "Synthese von Pyrrolderivaten," *Ber. Dtsch. Chem. Ges.*, **1884**, 17, 1635-1642; the Paal; "Synthese von Thiophen- und Pyrrolderivaten," *Ber. Dtsch. Chem. Ges.*, **1885**, 18, 367-371; Knorr "Einwirkung des Diacetbernsteinsäure-esters auf Ammoniak und primäre Aminbasen," *Ber. Dtsch. Chem. Ges.*, **1885**, 18, 299-311; pyrrole synthesis and the Hantzsch pyridine synthesis; "Condensationsproducte aus Aldehydammoniak und ketonartigen Verbindungen," *Ber. Dtsch. Chem. Ges.*, **1881**, 14, 1637-1638.
24. H. Debus, "Ueber die Einwirkung des Ammoniaks auf Glyoxal," *Ann Chem. Pharm.*, **1858**, 107, 199-208.
25. The structure of benzene as a cyclohexatriene was drawn by Kekulé, "On some Condensation-products of Aldehyde," *J. Chem. Soc.*, **1872**, 25, 612-619; "Ueber einige Condensationsproducte des Aldehyds," *Ann. Chem. Pharm.*, **1872**, 162, 77-124; and a representation beforehand, "Sur la constitution des substances aromatiques," *Bull. Soc. Chim. Fr.*, **1865**, 3, 98-110.



Francis R. Japp

Francis Robert Japp (1845-1925)

Born and schooled in Dundee, Japp graduated M.A. (Arts) from St Andrews University in 1868 and proceeded to Edinburgh University to study Law. Ill health terminated his studies prematurely, and while recuperating in Germany he committed himself to the study of chemistry. He was a student of Bunsen and Kopp at Heidelberg (D. Phil. 1875) and Kekulé in Bonn before returning to Scotland to work with Crum-Brown in Edinburgh. After a lengthy period with Frankland in London at the Royal College of Science, he was appointed to the Chair of Chemistry in Aberdeen in 1890. There he created a school of chemistry where previously chemistry had been taught mainly in support of medicine; and by 1896 he had persuaded the University to provide new and much improved facilities for the study of chemistry.

His research work concerned mainly diketones and especially their condensation with ammonia, amines, and nitriles. This led to the isolation of many heterocycles such as imidazoles, indoles, and oxazoles, whose properties and structures were examined. Details of this work can be found in the *Journal of the Chemical Society* during the period 1880-1906. This work was recognized by his election as Fellow of the Royal Society, Vice-

President of the Chemical Society, Royal Institute of Chemistry, and British Association (Chemistry Section) and the award of the Longstaff Medal and honorary degrees from the University of St Andrews and the University of Aberdeen.

Bronislaus Radziszewski (1838-1914)

Radziszewski was born in 1838 in Warsaw and graduated

from Moscow University in 1861. He was a teacher for some time in Warsaw, after which he studied with Kekulé in Gent, Belgium, from 1864-1867. He worked for two years with L. Henry in Lowen, Belgium. From 1870-72 he was professor at the Technical Institute in Kraków, Poland



Bronislaus Radziszewski

and was Professor of

Chemistry at Lwow University (formerly Austro-Hungarian Empire and now L'viv University, Ukraine) for 38 years until he retired in 1911. He founded the Lwow

school of organic chemistry, held the first chair of organic chemistry from 1895-1911, and was rector from 1882-1883. The author of 340 publications, he was a member of the Kraków Academy of Arts and Sciences. Among his many chemical pursuits he discovered a method to synthesize carbonic acid amides by treating nitriles with hydrogen peroxide in base.

ABOUT THE AUTHOR

Dr M. John Plater, Japp Laboratory, Department of Chemistry, University of Aberdeen, Meston Walk, Aberdeen, AB24 3UE UK [m.j.plater@abdn.ac.uk], graduated from Loughborough University with a B.Sc. in chemistry and obtained a Ph.D. from Imperial College of Science, Technology and Medicine, working with Charles Rees on sulfur-nitrogen chemistry. After a research fellowship for one year at Columbia University with Clark Still, he was appointed as lecturer in chemistry at Aberdeen University. He was promoted to senior lecturer in 1998. His nearly 80 publications cover a broad range of topics including free radicals, heterocyclic ligands, and solid phase synthesis, as well as the conservation of art, prebiotic chemistry, and the history of science. A full list of publications can be found on his website [<http://www.abdn.ac.uk/chemistry/research/mjp/mjp.shtml>].

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HISTORY OF SCIENCE SOCIETY: <http://www.hssonline.org>