Ian Rae: "Two Croatian Chemists who were Awarded the Nobel Prize in Chemistry"

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Abstract

Two organic chemists of Croatian origin, Leopold Ružička and Vladimir Prelog, made significant contributions to natural product chemistry during the twentieth century. They received their university education and research training in Germany and Czechoslovakia, respectively. Both made their careers in Zürich, Switzerland, and both shared the Nobel Prize in Chemistry, in 1939 and 1975, respectively. In this article, I have set the details of their lives and achievements against the education and research climates in Europe and other regions, especially as they apply to the field of chemistry.

Key words: Croatia, organic, chemistry, Nobel, Ružička, Prelog

Introduction[1]

In the twentieth century two organic chemists of Croatian origin were awarded the Nobel Prize in Chemistry. They were Lavoslav (Leopold) Ružička (1887-1976) and Vladimir Prelog (1906-1998), whose awards came in 1939 and 1975, respectively. Both were living and working in Switzerland at the time of the awards and it was in that country – specifically in the city of Zürich – that they performed the research that made them Nobel Laureates.

To understand the careers of Ružička and Prelog, and of many other twentieth century organic chemists, we need to look back to the nineteenth century when German chemists were the leaders in this field of science. Two developments characterise this German hegemony: the introduction of the research degree of Doctor of Philosophy (PhD), and the close collaboration between organic chemists in industry and university.

European Chemistry in the Early Twentieth Century

Research Training and the PhD Degree

Studying for the PhD degree was a kind of apprenticeship that resembled training as an artisan – a printer or a carpenter, for example – more than it did the education of, say, a historian or a philosopher. A chemist with a first degree, equivalent to the modern Bachelor of Science (BSc), could enrol to conduct research with an established professor, leading to the award of the degree after several years of research. Thus, the student learned from the master, but also shared collegially in the development of knowledge among the peer group of the professor's other research students. It was most important to choose, and be accepted by, a (male) professor of high status in the field because his seal of approval on a new graduate was important for one's subsequent career.

The PhD degree and research training in the German style was slowly taken up in America, starting in 1861 at the Yale University, and

[1] I should like to thank Professor Frances Separovic for her helpful comments and Anthony Gurlica for the translation of the summary into Croatian.

rather more slowly in Britain. The Scots started in 1895, but in England the degree was not introduced until 1917. Many British and American chemists enhanced their training with a stint in a German laboratory and some even took PhD degrees there. Students from European countries where science education and research was less developed routinely went to Germany to study, often making their careers in that country or in Switzerland, and that was the case with the Croatians Ružička and Prelog.

Industry and Academe

The German universities produced a steady stream of work in the field of organic chemistry and published their results in scholarly journals like *Justus Liebig's Annalen der Chemie* and the *Berichte der Deutschen Chemischen Gesellschaft*. While much of this research concerned chemical reactions that could be used to transform one substance into another, there was a strong interest in chemistry that produced substances that were useful to a wider audience, such as dyes and drugs. Many of these products were synthesised from chemicals derived from industrial by-products such as coal tar. Laboratory production of synthetic madder (yellow) and indigo (blue) dyes competed with the natural products and many new colours were also produced. Industrial chemists produced competitors for natural drugs, too, making analogues that preserved the desired effect but avoided nasty side effects, examples being Aspirin and the local anaesthetic Novocaine.

Professors often served as consultants to the chemical industry that was extensively research-based. Their connections brought extra income – some professors even held joint industry-academe appointments – and enabled them to 'place' their PhD graduates in good jobs where they would instinctively turn to their old mentors as consultants. A virtuous circle!

Natural Products

Alongside the synthesis of new substances, organic chemists were adept at working out the chemical structures of natural substances, especially those known as 'alkaloids' that often have had interesting physiological properties. Familiar examples are those of strychnine, morphine and quinine.

This work continued in the twentieth century, as the field of biochemistry (formerly physiological chemistry) began to separate from the parent, organic chemistry. Research on the structure of sugars and vitamins was notable, and another active area of research concerned the steroids that regulated sexual development in animals and played important roles in plants. Again, the names of some of the targets will be familiar even to the non-chemist: glucose, fructose, cholesterol and testosterone, for example.

As well as identifying the way that atoms were joined together to make up the molecules of these substances, newer methods were being developed to deduce the three-dimensional structures of these natural products – the way that various atoms and groups were arranged in space. Think of a right and left hand: we can tell on sight which is which, but how can we tell whether a molecule is 'right-handed' or left-handed'? It is difficult but it can be done, and Prelog played an important role in the invention of a new language that chemists could use to communicate their findings.

In the late 1930s the awards of Nobel Prizes were concentrated in this field of chemistry, as the data below show.

1937 Walter Norman Haworth (United Kingdom) for investigations on carbohydrates and vitamin C, jointly with Paul Karrer (Switzerland) for investigations on carotenoids, flavins, and vitamins A and B_2.
1938 Richard Kuhn (Germany) for his work on carotenoids and vitamins.
1939 Alfred Friedrich Johan Butenandt (Germany) for work on sex hormones, jointly with Leopold Ružička (Croatia and Switzerland) for work on polymethylenes and higher terpenes.

That introduction sets the scene for a discussion of the careers and achievements of our two Croatian chemists.

Leopold Ružička

Early Years

Leopold Ružička was born in Vukovar in Eastern Croatia, where the River Drava joins the Danube. His father, a cooper and timber merchant of Czech descent, died when Leopold was four years old, whereupon the family moved to his mother's home town, Osijek. There Leopold attended elementary school followed by high school. Tuition was in Croatian but the curriculum was heavy in Latin and Greek, leading Ružička to imagine a career as a priest in the Catholic Church. A growing interest in natural products, however, led him to change his vocation and undertake studies in chemistry. Knowing that this branch of science was not well developed in the education system of the Austro-Hungarian Empire, he decided to seek a place in a Swiss or German university. To enter the 'Polytechnic' (the Eidgenössische Technische Hochschule, ETH, the Swiss Federal Institute of Technology) in Zürich, his first choice, required him to pass an entrance exam in chemistry and geometry, neither of which he had studied, and so he turned instead to the Technische Hochschule in Carlsruhe where he was accepted without examination.

University Studies

By choosing the lecture courses that most interested him, Ružička concentrated on the practical laboratory classes and to speed through the course. After two years, he began Diploma studies under the Professor of Organic Chemistry, Hermann Staudinger. Again, things went smoothly for Ružička and at the end of four years he graduated in 1910 as Doctor Ingenieur, although, as he remarked, he was no expert in engineering. After graduation Ružička stayed at Carlsruhe, working with Staudinger on the constituents of the flowering plant *Chrysanthemum cinariifolium* Boc. that were poisonous to cold-blooded species such as fish and insects. These were the pyrethrins that are still used today in 'natural' insecticides but have been joined in this field with synthetic analogues known as pyrethroids, of which cypermethrin is an example. Staudinger and Ružička followed this interest in insecticides for the next five years, at first in

Carlsruhe but from September 1912 – almost two years before the outbreak of World War I – they worked in Zürich at the ETH, where Staudinger succeeded Richard Willstätter as Professor of Organic Chemistry and employed Ružička as a private assistant so he got to the ETH eventually, without an entrance exam.

Settling in Switzerland

Working for four years in Switzerland enabled Ružička to qualify for Swiss citizenship that was conferred on him in 1917. By then he had ceased collaborating with Staudinger to become a *Private-Dozent*, an unpaid lecturer who was free to work on his habilitation thesis. This achieved, Ružička became a full professor in 1923, still unpaid but free to research and to supervise the graduate work of students. He received financial support from a perfumery company based in Geneva (later known as Firmenich et Cie) who were interested in his work on the laboratory synthesis of natural products such as those with odours of violets, jasmine and musk. The work was published in the journal of the Swiss Chemical Society, *Helvetica Chimica Acta*. The natural and synthetic substances that possessed the musk odour were mainly constructed from rings of methylene (CH_2) groups, and were described in his Nobel Prize citation in 1939 as ‘polymethylenes’.

The laboratory accommodation in Zürich for Ružička and his students was poor, compared to that available in Swiss industry, and so for a time they worked in the Geneva laboratories of the perfumery company. After a year, however, Ružička accepted the offer of the chair of organic chemistry at the University of Utrecht in Holland and he moved there in 1926 while retaining a consulting relationship with the Swiss firm. Teaching in a Dutch university might have meant learning another language, but such was the esteem in which German (and Swiss-German) chemistry was held, that he started to lecture in German.

In 1929 he was courted by the ETH and accepted their offer of the chair of organic chemistry – the first non-German and the first Swiss citizen to occupy that position. Two days after Ružička accepted the Zürich chair, he was offered the organic chemistry chair that he had coveted some years before in the University of Geneva but he stuck to his decision to return to Zürich. Now 'my years of wandering were over', he remarked[2], and spent the rest of his career there, eventually giving way in 1957 to his countryman, Vladimir Prelog whose career is discussed below.

Ružička's major achievements in Zürich were laboratory syntheses of natural substances such as the male hormone testosterone and related compounds that affected sexual development. They were described in the Nobel Prize citation as 'higher terpenes'. The work was patented and Ružička received royalty payments from the Swiss pharmaceutical company, Ciba, that had research and manufacturing operations in Switzerland and America. He used the money to further his hobby begun in the Utrecht years as a collector of paintings, and so to set up a tax-free foundation of Dutch and Flemish Masters of the seventeenth century – Bruegel, Rembrandt, and Rubens, for example - that he presented to the Zürich Museum of Paintings. The foundation also included an extensive library of art books for the period.

Ružička's Nobel Prize

The Nobel Prize in Chemistry was awarded for work on polymethylenes and higher terpenes. The polymethylene work concerned molecular structures with rings of carbon atoms that occurred naturally and could be synthesized in the laboratory. A molecule with a three-membered ring was necessarily planar, but larger rings were 'puckered' in various ways that interested the organic chemist. The terpenes are a large family of substances with molecules built from five-carbon sections, and the basic member of the family is isoprene, C_5H_8, that is a component of the natural rubber polymer. Nature has built two isoprene units into the molecules of limonene and menthol (the natural sources of which will be obvious from their names), and six in the biosynthesis of cholesterol, the molecular formula of which ($C_{27}H_{46}O$) shows that three carbons have been lost and an oxygen gained during the process.

Ružička shared the Nobel Prize in Chemistry for 1939 with Adolf

[2] Ružička (1973): 4.

Butenandt (1903-1995) who was recognized for his work on sex hormones, notably estrone, obtained from the urine of pregnant women; androsterone, a male sex hormone; and progesterone, the female hormone that plays such an important role in pregnancy.

The Nobel Prize ceremonies were suspended during the war years but resumed soon after, but Ružička received his Prize – a gold medal and diploma – in January 1940 from the Swedish ambassador to Switzerland, Baron H.G. Beck-Friis, and he attended the ceremonies in Stockholm in 1945. The situation for Butenandt, Director of the Kaiser Wilhelm Institute for Biochemistry in Berlin, was more complicated. Being German, he was forced by the Nazi government of the time to decline the Prize. It took until 1949 before Butenandt accepted the Prize and delivered his Nobel lecture in Stockholm.

Vladimir Prelog

Early Years

Vladimir Prelog was born in Sarajevo, capital of the province of Bosnia and Herzegovina in the Austro-Hungarian Empire. Like many others in that empire, Prelog's family had mixed roots but his parents were Croatian. The family had moved from Croatia in 1905 so his father (accomplished Croatian historian Milan Prelog) could take up a high-school teaching position in Sarajevo. Young Vladimir was in the crowd that gathered to welcome the Archduke Franz Ferdinand in June 1914, just a few hundred metres from the site of the assassination that is commonly held to be the trigger for the First World War. When Vladimir's parents separated in 1915, he went to the Croatian capital, Zagreb, to live with his father's unmarried sister and attend the first three years of high school there. At war's end in 1918 the Austro-Hungarian empire collapsed, to be replaced by the Kingdom of Yugoslavia and Prelog's father gained appointment as head of a girls' high school in Osijek, near Vukovar. Young Vladimir attended high-school in Osijek and came under the influence of a teacher who encouraged his interest. In 1921 his father moved again, this time to be Professor of Modern History at the University of Zagreb, and Vladimir completed his high-school studies in Zagreb in 1924.

University Studies

Driven by family circumstances up to that point, Vladimir broke away to attend university in Prague, studying at the Chemical Engineering School of the Institute of Technology there. As an undergraduate he assisted a junior staff member, Rudolf Lukes, with his research but when the time came for PhD studies he worked under the Head of Department, Emil Votocek on a problem in natural product chemistry. Graduating in 1929, he was employed by an entrepreneurial organic chemist, Gothard Driza, in a small company that provided a range of chemicals to industry. In his spare time, Prelog conducted research into quinine in the company's laboratory, the alkaloid of the malaria medicinal *Cinchona* bark. His five years of employment were broken by nine months of national service in the Royal Yugoslav Navy.

While he was working in Prague, Prelog was negotiating to accept a position at the University of Zagreb. He was eventually appointed in 1935, not to a professorial chair as he had hoped, but instead as a lecturer. Taking up the university appointment, Prelog was also employed by a small pharmaceutical company as research director, the resulting financial support enabling him to develop his university research. One of the company's products was sulphanilamide, an antibiotic ('sulfa' drug) that was no longer covered by patents and relatively easy to synthesize. His enhanced income enabled him to take several months leave in 1937, which he spent with Professor Leopold Ružička at the ETH in Zurich. "*I chose to work with him because of his outstanding work*", Prelog wrote, "*and also because he was of Croatian origin, as I was*".[3] At Zürich he worked with Ružička on the structure of a triterpene, a plant substance structurally similar to the steroids.

Back in Zagreb, Prelog avoided the turbulent politics of the day by retreating through scientific work into an 'inner migration', continuing his work on quinine and its derivatives. Work continued after the outbreak of

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[3] Prelog (1991): 16.

war but by the spring of 1941, when German troops occupied Zagreb, it was time to leave if research was to continue. Prelog was already in touch with organic chemist Professor Richard Kuhn, the President of the German Chemical Society who had won the Nobel Prize in 1938 for his natural product work. Kuhn provided Prelog with a letter of invitation to lecture in Germany, in response to which the German officials in Zagreb instructed the Independent State of Croatia to issue passports to Prelog and his wife. With Swiss entry visas arranged for them by Ružička, they traveled via Italy to Zürich where they lived for the rest of their lives. While the war blighted the careers of many chemists, the situation in Germany had a positive effect on Prelog's career since positions became available in Ružička's group because a number of Jewish chemists had prudently left to put the Atlantic Ocean between them and Nazi Germany.

Settling in Switzerland

Prelog's career flourished in Zurich, where he soon became a regular member of staff and, before long, a full professor. As the world emerged from the restrictions of the Second World War, he became better known on the world scene, published numerous research papers and undertook speaking tours in the United States. The work for which the Nobel Prize was awarded began during this period, when Prelog became especially interested in the three-dimensional shapes of molecules. To understand this, we need to take a step back and consider how that part of organic chemistry developed.

Early in the twentieth century it became clear that some molecules could exist in right- and left-handed forms, and the study of this phenomenon became known as stereochemistry. The way the atoms were connected was essentially the same, but the geometry differed in the way that a person's right hand differed from their left. The difference between the two forms was seldom evident, but they interacted in opposite ways with plane-polarized light, one producing a (+) result and the other, a (-) result. The two forms were known, respectively, as *dextro* and *laevo* (both derived from Latin), or *d*- and *l*- for short, but nobody knew just which geometry corresponded to each of these formal names. By mid-century, the technique of X-ray crystallography, for which William Henry Bragg and his son William Lawrence Bragg had been awarded the Nobel Prize in Physics in 1915, had developed to the point where answers could be provided for many of these 'optically active' substances, as they were known.

Prelog's Nobel Prize

Prelog collaborated with two English chemists, Sir Christopher Ingold (1893-1970) and Robert Sidney Cahn (1899-1981), to devise a scheme for describing this three-dimensional geometry. The result was a protocol announced by Cahn and Ingold in 1956 that enabled the geometry, known in chemistry as the 'configuration' at critical points in the molecules as R (rectus) or S (sinister), again terms derived from Latin, the old language of scholars. There was no correspondence between the absolute configuration, denoted for example by R, and the arbitrary label *d*- that had been used before. This caused some confusion at first, but R,S nomenclature, particularly as it developed when Prelog joined the Englishmen in revising it, won the day and was officially adopted in 1974 by the International Union of Pure and Applied Chemistry that chemists accepted as the final authority.

Prelog shared his Nobel Prize in 1975 with John Cornforth (1917-2013) who was born in Sydney, Australia. Cornforth's interest in stereochemistry went to the most detailed level and concerned natural products like cholesterol. Where a carbon atom was attached to two hydrogen atoms in a $–CH_2$- group, which was which (in the R,S sense), Cornforth asked. And if there were three hydrogens, in a $–CH_3$ group, what then? Cornforth answered these questions by substituting one or two hydrogen atoms with the hydrogen isotopes deuterium and tritium that were chemically equivalent but could be tracked to see where they were in three-dimensional space. Earlier in his career, Cornforth, in collaboration with Popjak, had shown how the isoprene units (see above) were incorporated into the molecule of cholesterol.

As we can see in the Nobel Prize list above, the careers of Prelog and Cornforth have something in common. Each left his home country, Croatia and Australia respectively, and developed his career in another country, Switzerland and Britain, respectively. Cornforth left Australia in 1939 to study for his PhD in England, some years before the degree was introduced in Australia, and he stayed there except for occasional trips to his homeland. Prelog had to change from language to language as his career progressed, working in Croatian, Czech and German before mastering English. Cornforth managed with just English, but he was profoundly deaf, and was assisted to a considerable extent by his wife, Rita, also an Australian and a PhD organic chemist.

Concluding Remarks

Throughout their careers Ružička and Prelog were associated directly and indirectly with other Nobel Laureates. The biographies of successful chemists are characterized by such associations that seem to mark people out from early in their careers for places at the head of their profession. To consider Ružička's case, Richard Willstätter (1872-1942) was awarded the Nobel Prize in Chemistry in 1915 for his work on plant pigments. His successor in Zürich, Hermann Staudinger (1881-1965) started as a natural products chemist but became interested in those natural products like starch and cellulose where the molecules were many thousands of times larger than those of simple pigments and hormones, and eventually the synthetic polymers produced in the chemical industry. It was for work on these macromolecules (= polymers) that he was awarded the Nobel Prize in Chemistry in 1953. Ružička had clearly been moving in the right circles, as had Prelog, through his connections with Kuhn and Ružička.

Under Ružička's leadership, the ETH laboratory was a world leader in organic chemistry, producing work of astonishing virtuosity and turning out graduates who dominated European natural product chemistry over the next few decades. Ružička was a cultured European man who relished his mastery of organic chemistry and the rewards it could bring him. It was not all higher learning and high culture, however, since he was a more than competent alpine gardener, who modestly described himself as "*an* *enthusiastic devotee rather than a 100% expert*."[4] A biographer spoke warmly about "*his wit and penchant for entertaining stories*."[5]

In the decades after the end of the war, Prelog reached out from central Europe to colleagues in the east and the west. Recognising that Soviet natural product chemists had long been isolated from the European mainstream, he organised meetings with them and built relations so that one of them, Yuri Ovchinnikov, spent a period in the early 1960s working with him in the ETH laboratories. Looking west, Prelog wrote about the development of the R,S nomenclature and reflected that:

> "*the collaboration with the two British chemists and the many conversations and discussions with them, which were not confined to technical matters, made me acquainted with the English way of thinking and broadened my horizons*".[6]

His biographer described him as "*a formidable lecturer and talker in general, renowned for his inexhaustible supply of jokes, Yugoslavian folk-sayings, and anecdotes about famous chemists*",[7] some of which are retold in his chemical autobiography.

In 1976 (the year that Prelog retired from the ETH), Ružička died in Mammern, a village on the Swiss shore of Lake Constance. When Prelog died in Zürich over two decades later, his ashes were taken to Zagreb.

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[4] Ružička (1973): 20.
[5] Kenner (1977): 393.
[6] Prelog (1991): 78.
[7] Dunitz (1998): 543.

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Sažetak

Dva kemičara organske kemije hrvatskog podrijetla Leopold Ružička i Vladimir Prelog podijelili su Nobelovu nagradu za kemiju za svoje istraživanje u kemiji organskih prirodnih spojeva. Ružička je rođen u Vukovaru, završio je srednju školu u susjednom Osijeku a zatim upisao sveučilišni studij u Karlsruhe, u Njemačkoj, gdje je završio svoj doktorat. Preselio se u Zürich 1912. na studij u Technische Hochschule i tu je ostvario značajan doprinos kemiji prirodnih spojeva. Istraživanja koja su dovela do dodjele Nobelove nagrade 1939. godine odnosila su se na cikličke spojeve, od kojih su mnogi (terpeni) izgrađeni u prirodi udruživanjem pet ugljikovih jedinica. Vladimir Prelog je rođen u hrvatskoj obitelji koja je živjela u Sarajevu, u Bosni i Hercegovini, ali obitelj se preselila natrag u Hrvatsku i završio je srednju školu u Zagrebu prije nego što je upisao sveučilišni studij u Pragu, u Čehoslovačkoj. Vratio se i radio na Sveučilištu u Zagrebu, ali kada su njemačke trupe okupirale Hrvatsku emigrirao je u Švicarsku i slijedeći Ružičku tamo je izgradio svoju karijeru. Istraživanja koja su dovela do dodjele Nobelove nagrade 1975. bila su istaknuta njegovim radom na trodimenzionalnoj strukturi organskih molekula i načinu na koji se mogu klasificirati. U ovom se članku prikazuju pojedinosti o njihovom životu i postignućima prikazanima u odnosu na obrazovanje i istraživačku kulturu Europe kao i način na koji je ovo bilo uključeno u razvoj u drugim regijama, naročito nakon Drugog svjetskog rata.