

V. Prelog

VLADIMIR PRELOG

23 July 1906–7 January 1998

(On the occasion of his 100th birthday)

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Elected For.Mem.R.S. 1962

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Vladimir Prelog, one of the truly influential organic chemists of the past century, died in Zurich after a short illness on 7 January 1998. For his contributions to stereochemistry, he shared the 1975 Nobel Prize in Chemistry with J.W. Cornforth. In his 1991 autobiographical sketch (53)* Prelog told what he wanted to tell about himself and his work. The present memoir borrows heavily on this, but we have also drawn on our own perceptions gathered over many years of companionship and communion.

EARLY YEARS

Born in Sarajevo on 23 July 1906, Prelog was a child of the old Austro-Hungarian empire, with Austrian, North Italian and Croatian forebears. Shortly before his birth, his father, Milan (1879–1931), a Croatian high-school teacher, was posted to Sarajevo as part of the Austrian government's effort to improve education in its recently annexed province of Bosnia-Herzegovina. Sarajevo, capital of the province, was then a conglomerate of culturally and religiously distinct communities: Roman Catholic Croats, Greek Orthodox Serbs, Muslims whose ancestors had converted to Islam during centuries of Turkish rule, and Spanioles, descendants of Jews banished from Spain in 1492. As a Croat, the young Vlado was not allowed to play with children of the other groups. He later maintained that he had a rather lonely although not unhappy childhood. One incident that stuck in his memory (not surprisingly in view of the con-

*) Numbers in this form refer to the bibliography at the end of the text.

sequences) was his presence as a young schoolboy waiting to scatter flowers in front of the car of the Austrian crown prince, Archduke Francis-Ferdinand, and his wife Sophie, on the afternoon of the momentous day 28 June 1914, when the royal couple visited Sarajevo. Shortly before the procession reached him, the deadly shots were fired. The subsequent riots and plundering of the Serbian populace made a deep impression on the young Prelog. Throughout his long life, he had an aversion towards mass demonstrations – even when held for good causes.

Shortly after the start of World War I, Prelog's parents separated, and the young Vladimir moved to Zagreb, the Croatian capital, in care of his father's sister, Olga Prelog, an enlightened and idealistic schoolteacher, who had a great influence on his intellectual development. It was she who awakened his interest in science and encouraged him, as a twelve-year-old boy, to conduct his first experiments in chemistry. At the end of the war, in 1918, Prelog's father was appointed head of a girls' gymnasium in Osijek. Vladimir soon followed him there and attended the local science-based secondary school, where he came under the influence of the chemistry teacher, Ivan Kuria, who recognized his young student's talent and promoted his experimental skills. Prelog's first publication (1) was written as a schoolboy under Kuria's supervision. In the same year, his father was appointed Professor of Modern History at the University of Zagreb. Prelog completed his schooling there in 1924.

UNIVERSITY EDUCATION

Prelog then went to Prague, where he enrolled in the Chemical Engineering school of the Institute of Technology. He studied mathematics and physics as well as chemistry. Influenced by reading Wilhelm Ostwald, Ernst Mach and Henri Poincaré, he was at first disappointed by the empirical way in which chemistry was presented and taught by most of his teachers, although the physical chemist Franz Wald, a follower of Oswald and Mach, was, according to Prelog, an exception. It was Rudolf Lukes (1897–1960), assistant to Professor Emil Votocek, who supervised the practical course in organic chemistry and thereby saved Prelog for this subject. Lukes's absorbing interest in the polycyclic structures of alkaloids such as cocaine, quinine and morphine was communicated to his disciple Prelog, who, still a student, was granted the privilege of collaborating in Lukes's research. They became lifelong friends. Prelog later told his own students, 'the best way to study science is as apprentice to a master who is a model both in his field and in his personal characteristics'. In one of his studies with Lukes, Prelog prepared *N*-methyl-2,5-diphenylpyrrole and noticed that the crystals not only showed fluorescence but also exhibited the phenomenon of triboluminescence. As far as we are aware, the crystal structure has never been determined, so a structural explanation of this phenomenon is still overdue. After eight semesters, Prelog passed his Diploma examination with distinction in 1928.

Prelog's doctoral work was done under financial stress. His father had been 'retired' on political grounds and could no longer support him. Under Votocek's nominal direction, he was assigned the task of determining the constitution of rhamnoconvolvuline, a recently isolated glycoside. It was soon accomplished. By the summer of 1929 he had taken his doctoral examination and was looking for a job.

EARLY CAREER

The year 1929 was not a time when employment prospects were good. However, one of Lukes's friends, Gothard J. Driza, was interested in establishing a laboratory for the preparation of commercial chemicals. He offered Prelog the opportunity to design and run such a laboratory. Because Prelog was a foreigner, he could not be employed officially, but there was no law that forbade him to help a friend nor one against a friend's helping him. Driza provided the financial capital and also became Prelog's first de facto doctoral student although officially attached to Votocek. During working hours Prelog made marketable chemicals and during his spare time he began his first independent research. In 1932, Prelog was called to serve for a year in the Royal Yugoslav Navy. In 1933 he married Kamila Vítek, with whom he had one son, Jan, born in 1949.

In 1935 Prelog received an offer from the University of Zagreb. After the promise of a professorship and long negotiations, he ended with partial success: the appointment (and salary) as lecturer (docent) but with the duties of a professor in a department lacking the laboratory equipment he needed and the funds to pay for equipment or co-workers. As in Prague, help came from a small commercial enterprise. The director of a local firm dealing in pharmaceutical products decided to expand activities to include the production of known medicinal compounds, as well as the synthesis and testing of new compounds. Prelog agreed to help; in return he obtained financial support to equip his laboratory, take on doctoral students and engage co-workers. The firm prospered (later under the name of Pliva it became the largest pharmaceutical company in Yugoslavia and remains the largest in present-day Croatia). When French scientists showed that the active agent of the German patent-protected drug Prontosil (rubrum), a highly efficient chemotherapeutic agent, was actually the simple, well-known compound sulphanilamide, Prelog seized the opportunity to produce the unpatented compound in technical amounts and put it on the market. Under the name Streptazol it was a great financial success.

As a result, in 1937 Prelog could afford to spend several months with Leopold Ruzicka (1887–1976, For.Mem.R.S. 1942) at the Swiss Federal Institute of Technology (E.T.H.) in Zurich, a meeting that was to have important repercussions. Through his work in Zagreb, Prelog's name was gradually becoming internationally known and he seemed destined for a successful scientific career there. The outbreak of World War II and its intrusion into Yugoslavia changed that.

Prelog's papers in German scientific journals attracted the interest of Richard Kuhn (1900–67), then President of the German Chemical Society. Shortly after the war had begun, Prelog received an invitation to lecture in Germany, an invitation to which he did not immediately respond. However, after Yugoslavia was invaded and occupied by German troops (April 1941), Prelog felt that his life was in danger in Zagreb, not so much from the German occupation forces as from the Croatian fascists (Ustashi). He decided to use Kuhn's letter of invitation to reach the haven of Zurich, where he knew Ruzicka would provide security. As he told the story, it was not a simple matter. To obtain a Swiss entry visa, he needed an Italian transit visa, but this could be granted only if he possessed a Swiss entry visa. Finally, through a friend with good connections in the Italian consulate, he obtained the visa for Italy, and through Ruzicka he obtained

the one for Switzerland. In December 1941 he and his wife travelled to Zurich, which was to become their home for the rest of their lives. The lecture in Germany was delivered only after the end of the war.

PRELOG AND THE E.T.H.

Prelog arrived in Zurich shortly after the departure for America of several of Ruzicka's co-workers, Jewish immigrants from Eastern Europe who felt insecure in Zurich. They included some remarkable people. Two of them later helped to change the world through chemistry: Leo Sternbach at Hoffmann-La Roche in Nutley, New Jersey, USA, first prepared the compounds that became famous as the psychoactive agents librium and valium, and Georg Rosenkranz, Director of Syntex, Mexico, was instrumental in the development of the contraceptive pill. Prelog stepped into the resulting vacancy at the E.T.H. He became a valued member of Ruzicka's team and soon achieved scientific independence. At the start he was supported by the Basel chemical company CIBA. In 1942 he became Privatdozent, in 1945 he was awarded the title of Professor, in 1947 he was made Extraordinary Professor (a genuine appointment, not merely a title) and in 1950 Ordinary Professor. The exact significance of these promotions might escape the British or American reader; suffice it to say that they are steps up the E.T.H. academic ladder.

During the war, Zurich was effectively isolated, but after 1945 it became a meeting point for scientists from all over the world. Through his work and personality, Prelog soon became well known among the international chemical community. In particular, his work on strychnine (see below) brought him into contact with Sir Robert Robinson (1886–1975, F.R.S. 1920, P.R.S. 1945–50), whom he revered, and Robert Burns Woodward (1917–79, For.Mem.R.S. 1956), who became a lifelong friend. He visited London in 1947 and again in 1949, when he gave the first Centenary Lecture of the Chemical Society. In 1950 he made the first of many visits to the USA. The offer of a professorship at Harvard was the catalyst that hastened his promotion to full professor at the E.T.H.

In his travels, Prelog had observed that organic chemistry was passing through a profound change in its methodology; he was spurred into building up the required new instrumentation and forming the necessary infrastructure at the E.T.H. Organic Chemistry Laboratory. In place of an effective monarchy that directed the entire research and teaching activities of the laboratory, several younger colleagues were encouraged by Ruzicka to set up their own semi-independent, although mutually interacting, research groups. On Ruzicka's retirement in 1957, Prelog became director of a laboratory that included Hans Günthard, Oskar Jeger, Emil Hardegger, Edgar Heilbronner, Albert Eschenmoser, Duilio Arigoni and the newly arrived Jack Dunitz from the UK. Some had already been appointed to professorships, and Prelog saw to it that within a few years all of them were made professors. He did not wish to reign as monarch but rather as *primus inter pares*. Thus, in 1965, a few years after his appointment as director, he decided to share power and responsibilities with his younger colleagues. This might seem today a perfectly normal decision but it was then in Continental Europe – three years before 1968 – an almost revolutionary move for the director of

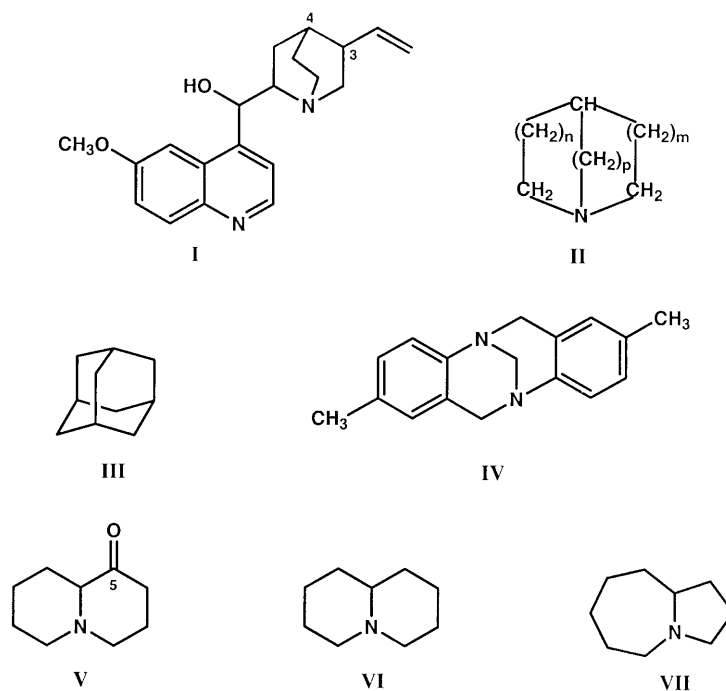
a chemistry institute to step down of his own accord. In the following years, many laboratory potentates were forced to give up their thrones by radical changes in university politics, but Prelog did it on his own, partly out of conviction, partly because (in striking contrast with his predecessor Ruzicka) he disliked power, and partly to safeguard enough time and energy for his scientific plans and ambitions.

Indeed, in the following years, Prelog thrived. He had excellent students and countless postdoctoral and sabbatical visitors, and he had time to travel, to take up visiting professorships, and to accept the many honorary doctorates, medals, prizes and other honours with which he was rewarded, culminating in the award of the 1975 Nobel Prize in Chemistry. After his mandatory retirement the following year, Prelog promptly registered as a special student (Fachhörer) to continue his scientific work. At the E.T.H., the opportunity to continue scientific research is not regarded as an automatic prerequisite of a retired professor; it is a privilege for which one may be grateful. Prelog had no duties, he was free to study as he pleased. His 1991 autobiographical sketch (53) was entitled *My 132 semesters of chemistry studies*; renowned as teacher and researcher, he regarded himself as student to the end. For many years after his retirement, he lectured in many places abroad, at international conferences and universities, and also regularly attended E.T.H. seminars, where he could be relied upon for an incisive question or an informative comment. Into his nineties, Prelog came daily to his office to work on extensions and improvements of the CIP system (see below) and to deal with a vast correspondence with organic chemists worldwide. Until his last days he was still a familiar figure in the Chemistry Building of the E.T.H.; conspicuous in his immaculate, old-fashioned white laboratory coat, he could be seen in the corridors or in the Chemiebar, where he drank his morning and afternoon coffee with younger colleagues.

SCIENTIFIC WORK

Prelog's long research career spanned most of the twentieth century. His first paper was published in 1921 (1), and in 1997 he was still working on a final commentary to his system of stereochemical nomenclature. His attitude to science was marked by an underlying ambivalence; on the one hand, a pragmatic acceptance of the requirement that the results of his research should be useful, and, on the other, a love for pure science, a yearning for abstract, fundamental concepts.

The focus of Prelog's first independent research, starting in around 1930, was quinine, the main alkaloid from *Cinchona* bark, then still the most important drug against malaria. Its constitution (**I**) had been known since 1908, but its configuration was still unknown. To the young Prelog, quinine was the 'tiger that the new-born calf is not afraid of' (to turn a saying that Prelog liked to quote). There was the challenge of its chemical synthesis (an achievement, however, that had to wait until 1947, when R.B. Woodward (For.Mem.R.S. 1956) entered the scene and opened the modern era of natural products synthesis), but there was also the possibility that simpler compounds related to quinine might have similar therapeutic properties. The core of the quinine problem was the quinuclidine part of the alkaloid, and Prelog embarked on synthetic work on the chemistry of bicyclic amines of type **II** containing a tertiary bridgehead nitrogen. His 1937 synthesis of quinuclidine itself (2) was a highlight. Doubtless, con-



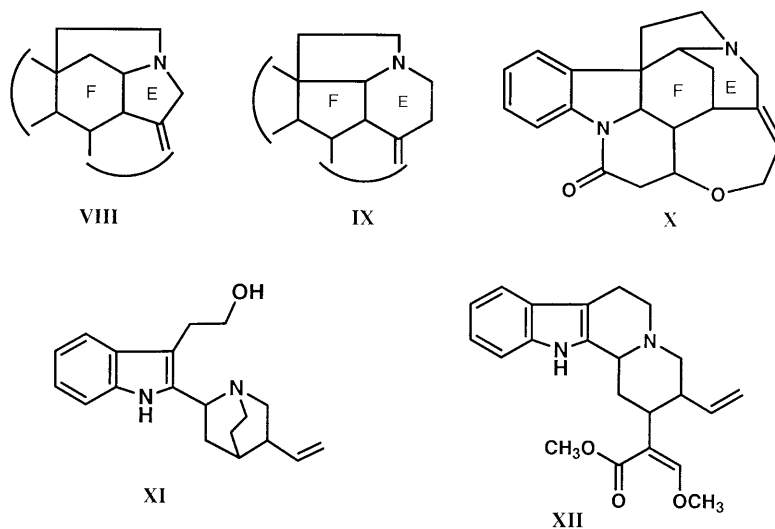
cern with the symmetry aspects of this molecule influenced Prelog's later development. Just as the quinine problem had led William Henry Perkin (F.R.S. 1890) many years earlier to the chemistry of artificial dyes, it brought Prelog to stereochemistry. Signposts of this development were, besides quinuclidine, the cage hydrocarbon adamantane (**III**) and, above all, Tröger's base (**IV**). The stereochemical fascination of adamantane almost certainly played a role in young Prelog's decision to tackle its synthesis, completed in 1941 (4). However, in his autobiography ((53), p. 19) Prelog mentions that his primary motivation was to honour his friend Lukes. When shown the beautifully tetrahedral crystals of the 'terpene hydrocarbon' $C_{10}H_{16}$ by Stanislav Landa, who had discovered this hydrocarbon in crude oil, Lukes, with a stroke of genius, had proposed on the spot the correct constitution. (The molecular structure of hexamethylenetetramine, the tetra-aza analogue of adamantane, had been established by crystal structure analysis as early as 1923 (Dickinson & Raymond 1923).)

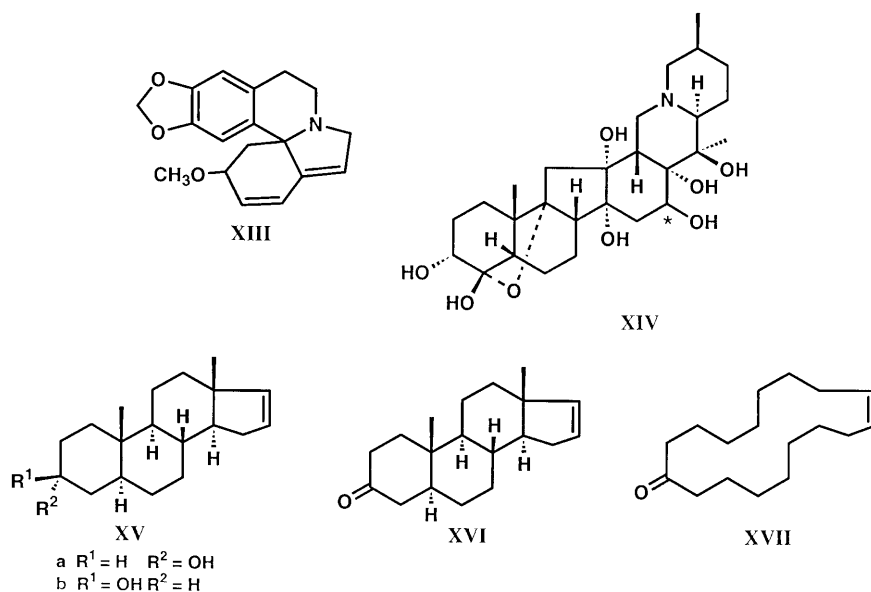
In 1944, the then 38-year-old Prelog resolved the constitutionally symmetrical, but configurationally dissymmetric, compound called Tröger's base (**IV**) into optical antipodes by chromatographic separation on lactose. This was a master contribution to the stereochemistry of those days, a lesson to the organic chemists of the time on the so-called 'asymmetric nitrogen atom' (7). By that time Prelog had established himself as one of the very few classical natural product chemists with a clear view into the conceptual maze of organic stereochemistry. Prelog's early sensitivity to stereochemical problems can be recognized, for instance, in his demonstration of the incorrectness of Clemo's claim that the Clemmensen reduction of 5-oxo-norlupinane (**V**) produces

a stereoisomer of the known norlupinane (**VI**), formed by Wolff–Kishner reduction of **V**. As Prelog showed by synthesis (3), the alleged ‘stereoisomer’ was in fact bicyclo[5.3.0]-1-azadecane (**VII**).

Prelog never really considered himself a ‘synthetic chemist’ despite the fact that it had been his pioneering synthesis of adamantane, performed in Zagreb, that made him famous. In Zurich, after Ruzicka had given him freedom to pursue his own research interests, he returned to alkaloids, no longer to synthesis but now to structure elucidation by chemical methods. In 1945 Prelog made his debut among the top-level alkaloid chemists of the time by showing experimentally that Robinson’s strychnine formula (see partial formula **VIII**) must be incorrect because ring E is not five-membered (8). Although the strychnine neophyte had to leave it to the old master Robinson to alter the new structural proposal **IX** in favour of **X** (eventually proved correct by Woodward, another newcomer), this episode meant that Prelog had become an accepted member of ‘the club’. After all, a year earlier, he had solved another long-standing problem of alkaloid chemistry: the relative configuration at C-3 and C-4 (**I**) of the quinclidine part of the alkaloids of *Cinchona* bark (6). Prelog’s group later collaborated with the French groups of Maurice-Marie Janot and Robert Goutarel on the structure determination of a great variety of alkaloids. Highlights of this work were the elucidation of the constitutions of cinchonamine (**XI**) (15) and corynantheine (**XII**) (17), which revealed close biogenetic relationships between the indole alkaloids and the quinoline alkaloids from *Cinchona* bark.

For Prelog, perhaps his most satisfying achievement as an alkaloid chemist was the elucidation of the constitution of the aromatic *Erythrina* alkaloids, with their novel structures as exemplified by erythraline (**XIII**). Nothing could better attest to the scientific level of the Prelog research group in those days than the names of some of his collaborators in this project: Har Gobind Khorana, George W. Kenner, Marvin Carmack, Blain C. McKusick and Karl Wiesner (13, 18, 26). Virgil Boekelheide, from Oregon, who had independently worked on related but alicyclic alkaloids, spent his sabbat-





ical year with Prelog in Zurich, where they wrote the definitive review on the chemistry of the *Erythrina* alkaloids (24). Another review article, this time together with Oskar Jeger, describing the chemistry of the steroidal *Solanum* and *Veratrum* alkaloids (21), led the authors to the cevine problem, the top puzzle in the alkaloid chemistry of that period, which had also caught the eye of both Woodward and Barton. From an exemplary collaboration of the four groups, the answer turned out to be the complex heptacyclic formula **XIV**, as described in a singular tetra-professorial article (22), with the configurations of thirteen of the fourteen asymmetric carbon centres correct; the wrong one (starred in **XIV**) was eventually revised by Kupchan *et al.* (1959).

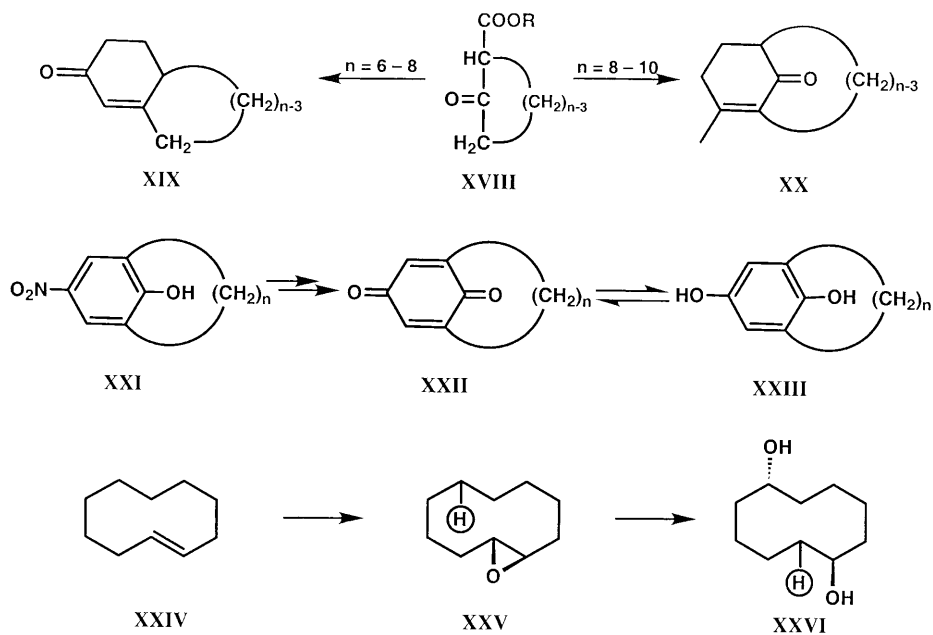
By this time the classical methods for the elucidation of natural product structures by chemical degradation had developed to a level where, in the hands of experts, they could be very effective in determining molecular constitution, but much less so in determining configuration, especially in cases of novel molecular skeletons. Indeed, the time had arrived when the task of structure determination was gradually being taken over by X-ray crystallography. Prelog read the signs; cevine was the last alkaloid on which he was engaged. Except for a coda with microbial metabolites (see below), he turned more and more away from natural product chemistry towards new fields: the chemistry of medium rings, asymmetric synthesis and its use for the determination of absolute configuration, the stereochemistry of the enzymic reduction of carbonyl compounds, and, together with Ingold and Cahn, the development of the CIP system.

Prelog's interest in medium ring chemistry came about indirectly. Ruzicka's co-workers, who had emigrated to America shortly before Prelog's arrival, had been involved in the isolation, purification and characterization of biologically active compounds from animal extracts. Ruzicka entrusted Prelog with the task of continuing this work, which led, *inter alia*, to the isolation of two unsaturated steroid alcohols, **XVa** and **XVb** (5), related to the male hormone androsterone. The corresponding

ketone (**XVI**) had a strong musk-like odour and showed a striking constitutional relationship to the 17-membered ring ketone civetone (**XVII**), an olfactory principle of musk whose constitution Ruzicka had elucidated two decades earlier. Much later, Prelog took pleasure in learning that compound **XVa** is a pheromone in pig breeding and is also present in truffles (Claus *et al.* 1981) – which explains why pigs are used to search for these delicacies in forest soils.

This work, which happened to touch on Ruzicka's achievements in the chemistry of male hormones and of many-membered ring ketones, brought Prelog to the chemistry of medium-sized rings. According to his own account, he originally intended to find out whether bicyclic and tricyclic ketones containing a medium ring might also have musk-like odours. After improving a patented method of preparing medium ring ketones by the acyloin condensation of aliphatic α,ω -diesters with molten metallic sodium in hot xylene (10) (see also Stoll & Hulstkamp 1947), he found that Robinson annelation applied to medium rings (**XVIII** \rightarrow **XIX**) could take an alternative course to **XX** with a carbon-carbon double bond at a bridgehead. The stereochemist in Prelog reacted to this observation by follow-up studies to demonstrate that Bredt's rule is in fact valid only for bicyclic systems containing rings of normal size (11). Similarly, following this line of reasoning, Prelog found that the condensation of nitromalondialdehyde with medium ring ketones led to products of type **XXI** (9), which opened the way to a study of the redox system **XXII** \rightleftharpoons **XXIII** ($n=6$ to 17). Polarographic analysis revealed a marked dependence of the position of this redox equilibrium on ring size (12).

With the availability of an efficient synthetic method for making medium ring compounds, Prelog embarked on a systematic investigation of their properties. He was fas-



minated by their unusual behaviour, for example the non-reactivity of cyclanones with nine to eleven ring members towards hydrogen cyanide, compared with the ready formation of cyanhydrins of smaller and larger rings (14). Such observations led him to postulate that these unusual properties are consequences of special shapes (constellations, as he called them) of the cyclic molecules, arising from rotation around C–C bonds. In the first Centenary Lecture of the Chemical Society (16), delivered in 1949, Prelog had the opportunity to emphasize the importance of these ideas for understanding differences in chemical reactivity between closely related compounds. From today's perspective, it seems curious that he did not apply the same insight to discuss the properties of alicyclic compounds built from fused six-membered rings, such as steroids and triterpenes, and thus anticipate the conformational interpretations of Derek (later Sir Derek) H.R. Barton (1918–98, F.R.S. 1954), which were published the following year. After all, the requisite experimental data were certainly available to him at the E.T.H. Nevertheless, together with Derek Barton, Odd Hassel (1897–1981) and Kenneth S. Pitzer (1914–97), Prelog must be considered as one of the founders of conformational analysis, and he is certainly largely responsible for its terminology (29).

Prelog's work on the special properties of medium ring compounds received a major boost in the summer of 1952. When his doctoral student Karl Schenker, seeking a simpler synthesis of the two diastereomeric cyclodecane-1,2-diols, oxidized *cis*- and *trans*-cyclodecene with performic acid, he obtained mixtures containing none of the expected products. Prelog recognized that these mixtures might contain the corresponding 1,6-diols. As these 1,6-diols had already been made at the E.T.H. in the laboratory of Placidus A. Plattner, this could quickly be confirmed. Specifically, it was found that *trans*-cyclodecene (**XXIV**) on oxidation yielded a mixture containing a 1,6-cyclodecanediol with presumed *trans* configuration (**XXVI**), formed most probably in a process involving acid-catalysed opening of the *trans*-epoxide (**XXV**), followed by a transannular 1,5-hydride shift. Prelog was aware that Arthur C. Cope at Massachusetts Institute of Technology (M.I.T.) had discovered the same type of unconventional reaction in the cyclooctene series. Publications from the M.I.T. (Cope *et al.* 1952) and E.T.H. groups (19) describing these transannular reactions appeared almost simultaneously. Subsequent studies in Prelog's laboratory showed that similar transannular hydride shifts occur also with cyclononene and cycloundecene, but not with higher homologues. The work on the chemistry of medium rings met a sort of culmination in the later X-ray analysis of crystalline cyclodecane derivatives, which revealed the structural source of all the conformational transannular effects that Prelog had propounded (for a review see Dunitz (1969)).

The work on the chemistry and physical properties of medium rings occupies a central position in Prelog's scientific oeuvre (27). Through it, together with his research in asymmetric synthesis (see below) and his leadership in stereochemical concepts, he bridged the worlds of natural product chemistry and physical organic chemistry. By doing so, he earned the respect and friendship not only of the powerful natural product clan – Robinson, Woodward, Todd and Barton – but also some of the leading physical-organic chemists of his time – Saul Winstein, Christopher (later Sir Christopher) Ingold (F.R.S. 1924) and Donald Cram.

In about 1950, Prelog's pioneering insight into the relationships between molecular conformation and chemical reactivity led him to a systematic study of 'asymmetric syn-

thesis'. He had become aware of this field through a review (McKenzie 1936) listing examples of 'asymmetric induction' in reactions of α -ketocarboxylic esters of enantiomeric alcohols with Grignard reagents to give, after saponification, optically active α -hydroxycarboxylic acids. In the meantime, configurational correlations of some of the starting materials and products with the accepted standard D-(+)-glyceraldehyde had been established, and Prelog was able to deduce from McKenzie's material – complemented by results of his own – a consistent correlation between the configurations of starting materials and those of products ('Prelog's rule') (20). This rule was based on arguments relating the configurational outcome of the reaction to the relative steric demands of the substituents, L (large), M (medium), S (small), and their spatial arrangement at the asymmetric carbon of the starting material (figure 1). This empirical correlation enabled Prelog to develop a general procedure to determine the configurations of secondary alcohols by observing the sign of the enantiomeric excess in the atrolactic acid produced by reaction of the corresponding ester of phenylglyoxylic acid with methylmagnesium iodide. A lapse in the assignment of the configuration of the tertiary monoterpene alcohol linalool brought Prelog together with the Cornforths in a joint paper (30), fifteen years before he and John were together again in Stockholm.

In his work on asymmetric synthesis based – in modern parlance – on the influence of chiral auxiliaries, Prelog also followed up an early study of the course of a reaction controlled by a chiral catalyst. Forty years earlier Bredig & Fiske (1912) had observed that the reaction of aldehydes with hydrocyanic acid under the catalytic influence of natural alkaloids such as quinine can produce cyanohydrin products with partial optical activity. With Max Wilhelm, Prelog showed that it is the protonated form of the catalytic base that exerts its desymmetrizing effect (23). This enantioselective catalysis by an alkaloid was for Prelog just one step away from enantioselection by enzymes, the stereochemist's dream world. With a combination of foresight and audacity, he crossed the border between pure organic and enzymic stereochemistry in the mid-1950s. In this work he was assisted by Werner Acklin, and later by Hans Dutler, who were responsible for the technical know-how of working with microbes and enzymes. The aim of the study was clearly defined and rigorously systematic: to determine the absolute stereo-

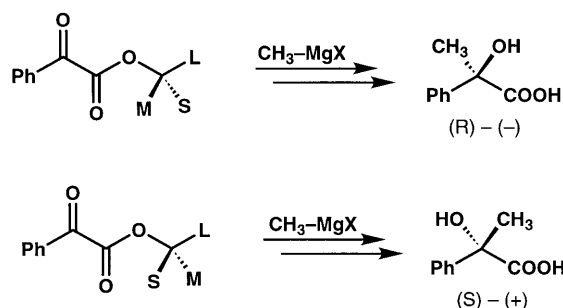


Figure 1. The configuration of the predominant isomer of atrolactic acid generated in the reaction is related to the configuration at the stereogenic centre bearing the three groups L (large), M (medium) and S (small).

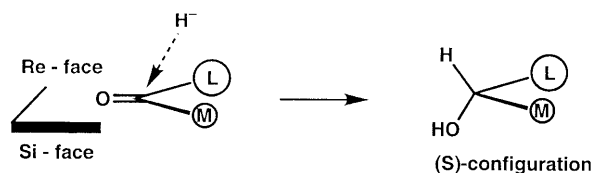


Figure 2. Preferential delivery of hydride from the Re face of the carbonyl group in the enzymic reduction of decalin derivatives. L (large) and M (medium) refer to the relative bulks of the ligands.

chemical course of enzymic hydride transfer to carbonyl groups of substrates such as decalin-1-one, decalin-2-one and decalin-1,4-diones by microbial cultures such as *Curvularia falcata* (28, 37). The major result (figure 2) is best summarized in Prelog's own words:

The ... stereogenic carbon atoms formed by microbial reduction all possess the same *S*-configuration, independent of the configuration of the other stereogenic centres in the molecule or of whether the hydroxyls are in the axial or the equatorial positions. ((53), p. 65)

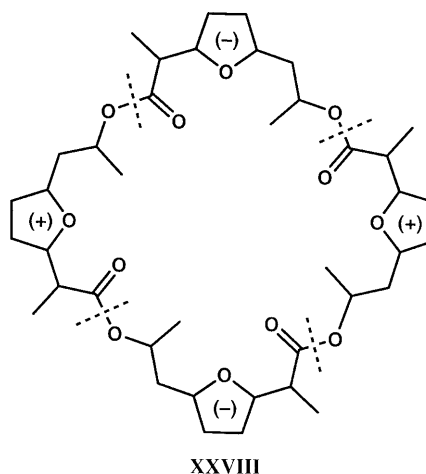
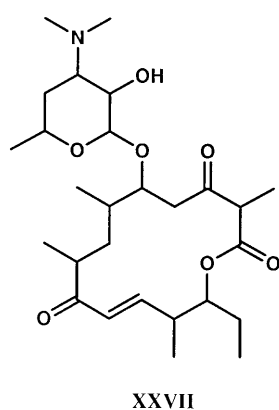
In a further effort aimed at replacing the microbe as 'reducing agent' by the corresponding enzyme, it was shown that the organism contains at least two NADPH-dependent oxidoreductases with the same *Re*-stereospecificity, the major component favouring the hydride transfer into an axial position, the minor into an equatorial position. The extension of this work towards the isolation and kinetic characterization of such enzymes was pursued for a time with great vigour. However, the experiments were too tedious and time-consuming for Prelog's taste, and the required techniques were becoming increasingly remote from Prelog's own experience as an organic chemist. Prelog eventually resigned from his venture into the stereochemistry of enzymic catalysis. He wrote, 'I therefore gave up this very promising field, as I had given up many others before' ((53), p. 68).

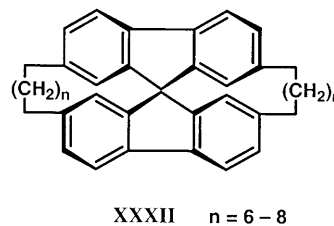
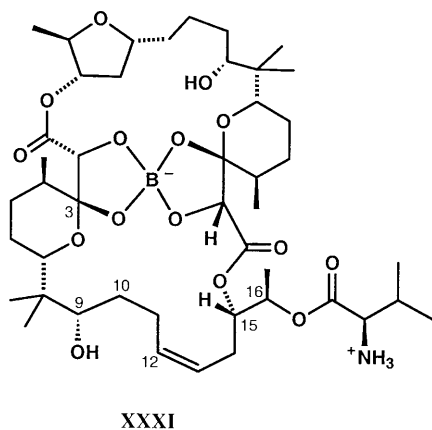
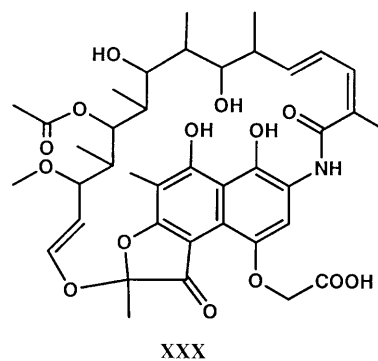
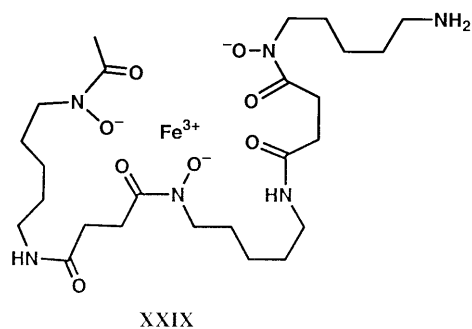
Prelog's interest in codification led to his association with Robert S. Cahn (1899–1981) and Christopher Ingold in two landmark papers describing the now universally adopted 'CIP' system of rules for specifying the sense of chirality at tetrahedral stereogenic centres (25, 38). From then on, Prelog was deeply involved in the creation of a comprehensive system for the specification of molecular chirality, the attempt to identify and classify all types of stereoisomerism (47, 48) – a daunting task, as Kurt Mislow has remarked. Indeed, there can be few organic chemists of Prelog's generation with the intellectual strength and tenacity to master the more mathematical, graph-theoretical aspects of the models that they use to describe molecular structures and their interconversions. Certainly, there was no one else of his generation who was so intensively and consistently involved with problems arising from the codification of molecular chirality. Towards the end of his life, one of Prelog's main cares was with the preservation of the purity of his system from unauthorized intrusions and extensions; even in his nineties he was still preoccupied with its inherent complexities.

When, in the early 1950s, Prelog left the alkaloids to concentrate on his physical-organic studies of medium ring compounds and asymmetric synthesis, he nevertheless remained faithful to natural product chemistry by becoming involved in one of its most

active areas at that time. This was the chemistry of microbial antimetabolites and antibiotics. Work in this area had been started during the war by Prelog's colleague Plattner in collaboration with the E.T.H. phytopathologist Ernst Gäumann and the pharmaceutical company Ciba AG in Basle. When in 1952 Plattner left to become Research Director of Hoffmann-La Roche in Basle, Prelog took over this work and became the driving force of a scientifically as well as industrially successful joint venture between the three groups. Important partners of Prelog in this endeavour were Hans Zähler at the Institut für Spezielle Botanik at E.T.H. (later Professor at the University of Tübingen, Germany) on the biological side and the former Plattner student Walter Keller-Schierlein on the chemical side, Prelog's right hand, who himself became a renowned expert in the structural elucidation of antibiotics and who took over the project when Prelog withdrew from it in 1970.

With the E.T.H. tradition in large and medium ring chemistry, Prelog could take great pleasure in the fact that many of the new metabolites and antibiotics isolated in this joint venture turned out to contain large ring systems. Examples are the antibiotic narbomycin **XXVII** (31) and the family of ionophoric macrotetrolides with its most noteworthy representative nonactin **XXVIII** (32, 33) an achiral molecule in spite of its sixteen stereogenic centres. Three landmarks in this field were the ferrioxamines (e.g. **XXIX**) (36), the rifamycins (e.g. **XXX**) (44) and boromycin (**XXXI**) (39, 41). The uncovering of the complex relationships between structurally related iron(III) complexes that are either antibiotics (ferrimycins) or their antagonists (ferrioxamines) was a major achievement of this interdisciplinary collaboration, especially in view of a later finding that desferrioxamines are of therapeutic importance in illnesses related to the deposition of 'pathological iron'. The brilliant structure determination of rifamycin by Prelog and his student Wolfgang Oppolzer was also rewarded by the medical relevance of modified derivatives prepared in industry. Finally, boromycin, the first boron-containing organic natural product, turned out to be an orthoborate ester of a 32-membered ring macrodiolide, whose structure was established by X-ray analysis (41).





Prelog's last active years belonged to stereochemistry. In keeping with his preoccupation with formulating and perfecting a general system for the specification of diastereomerism, he devoted himself to projects aimed at demonstrating novel types of stereoisomerism through the synthesis of representative examples. One of the fruits of this research was the recognition, together with Hans Gerlach (34), and subsequent experimental demonstration of cyclostereoisomerism, a type of isomerism based on the clockwise or anticlockwise sequence of directed bonds in rings, as exemplified by the enantiomeric cyclohexaananyls (35) (figure 3). In the context of extending the definition of pseudoasymmetric centres to axes and planes, compounds displaying such features were made in collaboration with Günter Helmchen (42, 43). Other molecules that preoccupied and charmed Prelog in his later years were the chiral vespirenes (**XXXII**) possessing D_2 symmetry (40, 50). Chiral crown ethers of the vespirine type were later synthesized in the context of a collaboration with his younger colleague Wilhelm Simon for the design of electrodes that are enantioselective for chiral ammonium ions (45). After his retirement in 1976, he continued research on the same topic, usually with one postdoctoral co-worker from Zagreb (46, 49). Prelog's last experimental paper in *Helvetica Chimica Acta*, the journal in which most of his research was published, appeared in 1986 (51), and in 1989 the 83-year old Prelog wrote a review on his last

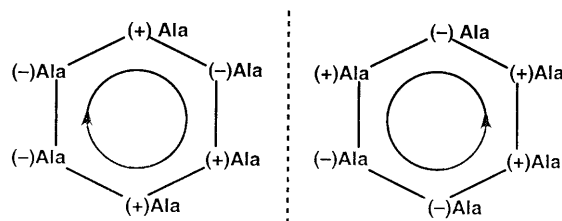


Figure 3. A pair of cycloenantiomeric compounds.

research field: ‘Lipophilic tartaric acid esters as enantioselective ionophores’ (52). Still unfinished at his death was his project to complete a commentary on subtle aspects of his beloved CIP system.

PRELOG THE PERSON

Vlado Prelog was admired as a scientist and loved as a person by a multitude of friends from all over the world. He was witty, he was learned, he was a man of wide culture, he could engage in conversation on almost every topic under the sun and was renowned for his inexhaustible supply of jokes, Yugoslavian folk-sayings, and anecdotes about almost every famous chemist who ever lived. He captivated all. One of the reasons why Prelog evoked such spontaneous affection is that he could show different sides of himself to different people, reflecting their own sentiments, as in a mirror. Thus he could be cynical with the cynics, optimistic with the optimists, philosophical with the philosophers, sagacious with the sages.

Ambitious as far as science was concerned, he was uninterested in the exercise of power – he said that he disliked making decisions that affected other people. Seldom provoked to anger, he claimed to have an unusually low adrenaline level. He avoided confrontation and did not like to make enemies. Thus, he tended to avoid situations of direct conflict and often found excuses for human frailty in his friends and even in his antagonists. According to him, the human trait he detested most was self-righteousness.

Besides Prelog’s social gifts, and often concealed by them, was a deeply introspective personality who only rarely allowed glimpses of his inner emotional life. His ironic and often self-depreciatory humour was often a protective wall for his inner self. Basically, he was a fatalist. Of the many quotations that he kept in store, he was especially fond of the lines from Ecclesiastes:

I returned, and saw under the sun, that the race is not to the swift, nor the battle to the strong,
neither yet bread to the wise, nor yet riches to men of understanding, nor yet favour to men of
skill; but time and chance happeneth to them all.

Prelog had a European gymnasium-style classical education. Whatever the question or topic under discussion, he could always be relied to respond with an apt quotation. From his predecessor Ruzicka he had inherited an interest in classical painting, particularly that of The Netherlands school, and it was a special treat for scientific guests to visit the Zurich Kunsthhaus in Prelog’s company. He did not play any musical instrument

but liked to listen to chamber music, especially that of the Slavic masters Dvorak, Smetana and (the organic chemist) Borodin, and claimed to dislike opera with the exception of Verdi's *La Traviata*, whose Violetta had made a powerful impression on him in his youth. A rationalist through and through, he was opposed to all forms of organized religion, and indeed to all sorts of collective action. In his later years, after his Nobel Prize, many religious and humanitarian organizations turned to him for support or at least for an expression of solidarity with their objectives. He consistently turned them down; he never took part in demonstrations nor signed petitions, even for causes that he approved of. There was an ironic and occasionally even cynical aspect in his view of human nature, a distrust of elevated social, political and religious hopes and aspirations. Yet, when an American schoolgirl wrote to ask about his religious beliefs, he took the question seriously enough to reply:

Nobel prize winners are not more competent about God, religion, or life after death, than other people, but some of them, like myself, are agnostics. They just don't know, and, therefore, they are tolerant to religious people, atheists, and others. What they dislike are militant zealots of any kind.

With best wishes.
Sincerely yours, V. Prelog.

Prelog had the gift of reacting spontaneously to new and unexpected situations and encounters with memorable remarks. When one of us (J.D.D.) returned from a visit to Professor Alexander Rich at M.I.T. with a wire model of the newly determined backbone structure of transfer RNA, Prelog looked at it for a moment and said 'God's signature!'. He was renowned for his stories, which were often ornamented and enriched by repeated telling. Like good wines, they became better with time. One of the more famous concerned his encounter with Sir Robert Robinson at Zurich Airport. It went something like this: 'Hello, Katchalsky, what are you doing here in Zurich?' asked Sir Robert. 'Excuse me, Sir Robert, I'm only Prelog, and I live here', was the reply. 'You know, Prelog, your and Ingold's configurational notation is all wrong', said the old man. 'Sir Robert, it can't be wrong. It's only a convention. You either accept it or not.' 'Well, then, if it's not wrong, it's absolutely unnecessary.' (Some have expressed surprise that Robinson could mistake Prelog for the ten-years-younger Ephraim Katchalski-Katzir (b. 1916, For.Mem.R.S. 1977). However, it has been noted that at an early Buergerstock Conference on Stereochemistry, as Katchalski was entering the Park Hotel after the morning lectures, the doorman called to him: 'Professor Prelog, there is a telegram waiting for you at the reception desk'.)

In contrast with Ruzicka, Prelog was never interested in politics. Like many people brought up under the old Austro-Hungarian empire, he retained a certain nostalgic respect for its governmental styles and traditions, especially when he compared them with the disastrous consequences of the breakdown of these structures in his native country in more recent years. Distrustful of all political manifestoes, profoundly sceptical about the perfectibility of mankind, deeply concerned about the dangers of populism and the tyranny of mass culture, he was nevertheless a believer in democracy – in a system in which political leaders are elected by the people and can be unseated by them. He liked to quote Carl J. Burckhardt: 'Totalitarianism is the denial of complexity'.

In a speech delivered in 1971 to newly naturalized Swiss citizens, Prelog confessed:

If you ask me what binds me most strongly to my adopted country, it is not just the excellent working conditions at the E.T.H. but primarily the spirit of tolerance that allows me to live in harmony with my conscience as well as with the written and unwritten rules of the society I live in.

These words of appreciation contain a message that concerns all of us.

HONOURS AND AWARDS

- 1945 Werner Medal and Award, Swiss Chemical Society
- 1948 Honorary Member, Czechoslovak Chemical Society and Croatian Chemical Society
- 1954 Corresponding Member, Yugoslav Academy of Sciences and Arts
Dr honoris causa, University of Zagreb
- 1960 Honorary Member, American Academy of Arts and Sciences
Honorary Member, Chemical Society, London
- 1961 Foreign Associate, National Academy of Sciences of the USA
- 1962 Foreign Member, The Royal Society of London
Stas Medal and Honorary Member, Société Chimique de Belgique
Medal of Honour, William Marsh Rice University, Houston, Texas
- 1963 *Dr honoris causa*, University of Liverpool
Member, Deutsche Akademie der Naturforscher Leopoldina
Dr honoris causa, University of Paris
- 1964 Foreign Member, Istituto Lombardo, Accademia di Science et Lettere, Milano
- 1965 Honorary Member, American Society of Biological Chemists
Foreign Member, Accademia Nazionale dei Lincei, Rome
Marcel Benoist Award
- 1966 Foreign Member, Academy of Sciences, USSR, Moscow
Hanus Medal, Czechoslovak Chemical Society
Fellow, New York Academy of Sciences
- 1967 August-Wilhelm-von Hofmann Medal, Gesellschaft Deutscher Chemiker
- 1968 Davy Medal, The Royal Society of London
- 1969 Roger Adams Award, American Chemical Society
Dr honoris causa, University of Cambridge
Dr honoris causa, Université Libre de Bruxelles
- 1970 Honorary Member, Academy of Pharmaceutical Sciences, Washington, D.C.
- 1971 Honorary Member, Royal Irish Academy, Dublin
Foreign Member, Royal Danish Academy of Sciences
- 1973 Corresponding Member, Academy of Arts and Sciences of Bosnia and Hercegovina
- 1974 Paul Karrer Medal, University of Zurich
- 1975 Nobel Prize for Chemistry
Honorary Member, Croatian Society for Nature Research and Spiridon Brusina Medal, Zagreb

- 1976 Paracelsus Medal, Swiss Chemical Society
Foreign Member, American Philosophical Society, Philadelphia
American Chemical Society Centennial, Foreign Fellow
- 1977 Honorary Member, Serbian Chemical Society
Order of Yugoslav Star
Dr *honoris causa*, University of Manchester
Order of the Rising Sun, Japan
Honorary Member, Pharmaceutical Society of Japan
Honorary Member, Institut Grand-Ducal de Luxembourg
- 1978 Honorary Member, Chemical Society of Japan
Dr *honoris causa*, Instituto Quimico de Sarriá, Barcelona
Honorary Member, La Asociacion de Quimicos del Instituto de Sarriá, Barcelona
Emil Votocek Medal, Institute of Chemical Technology, Prague
- 1979 Corresponding Member, Slovenian Academy of Sciences and Arts, Ljubljana
- 1981 Member, European Academy of Sciences, Arts and Letters
Foreign Member, Serbian Academy of Sciences and Arts, Beograd
Foreign Member, Académie des Sciences, Paris
- 1983 Hamilton Award, Ohio State University
Evans Award, Ohio State University
Honorary Member, Gesellschaft Deutscher Chemiker
- 1984 Arun Guthikonda Memorial Award, Columbia University
- 1985 Adolfo Quilico Medal, Società Chimica Italiana
Dr *honoris causa*, Weizmann Institute, Rehovot
Member, Pontificia Academia Scientiarum, Vaticano
- 1986 Honorary Member, Jugoslavenska Akademija Znanosti i Umjetnosti, Zagreb
Honorary Member, Schweizerische Chemische Gesellschaft
Order of Yugoslav Banner with Golden Wreath
- 1987 Honorary Member, Gesellschaft Oesterreichischer Chemiker
- 1988 Member, Schweizerische Akademie der Technischen Wissenschaften
- 1989 Dr *honoris causa*, University of Ljubljana
Dr *honoris causa*, University of Osijek
Bozo Tezak Medal, Croatian Chemical Society
Honorary Citizen, City of Zagreb, Croatia
- 1990 Member, Academia Europea, London
Honorary President AMA (Alma Mater Agramensis)
- 1992 Dr *honoris causa*, Chemical Technology, Prague
Honorary Citizen, City of Sarajevo, Bosnia
Chirality Medal, Chiral Discrimination Symposium, Tübingen
- 1994 Foreign Member, Russian Academy of Sciences
- 1996 Dr *honoris causa*, University of Sarajevo, Bosnia

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| (4) | (66) | 1941 | (With R. Seiwert) Über die Synthese des Adamantans. <i>Chem. Ber.</i> 74 , 1644. |
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