

# VLADIMIR PRELOG

## Surprise Festschrift

In the year 1996 *Croatica Chemica Acta* published the Festschrift dedicated to the Croatian Nobel laureate Professor Vladimir Prelog on the occasion of his 90<sup>th</sup> birthday. The Festschrift was published as No. 2 of Volume 69.

Professor Prelog passed away in 1998.

In 2006 Croatian chemists are celebrating the 100<sup>th</sup> anniversary of his birth and the Editorial Board of *Croatica Chemica Acta* decided to publish the electronic version of the part of the Festschrift of 1996 relating to the life and scientific achievements of Professor Vladimir Prelog.

Nikola Kallay, Editor-in-Chief

Published by The Croatian Chemical Society

# CROATICA CHEMICA ACTA

Surprise Festschrift  
in Honour of  
Professor Vladimir Prelog

Special Issue

ZAGREB  
CROATIA  
1996

## INSTRUCTIONS TO AUTHORS

*Croatica Chemica Acta* is an international journal devoted to the publication of papers from all fields of chemistry. Four issues are published annually.

Contributions should be written in English; an abstract (translated) in Croatian is added.

CCA publishes Original scientific papers, Notes, Preliminary communications, Authors' reviews, Reviews, Feature articles, Conference papers, Essays and Data bank contributions. In the appendix, the Journal publishes Letters to the Editor, book reviews, obituaries and the Croatian Chemical Society news.

*Original scientific papers* report unpublished results of original research. The papers have to contain all the necessary information to enable reproducibility of the described work.

*Notes* report unpublished results of short, but completed, original research or describe original laboratory techniques (methods, apparatus, etc.). Notes should not exceed 1000 words.

*Preliminary communications* report unpublished preliminary results of original research that require prompt publication.

*Authors' reviews* are concise and critical surveys of the author's current research field. The author's contribution should be compared to the data (results, information) provided by other scientists in the same field.

*Reviews* are concise and critical surveys of a specific research field, providing the reader with up-to-date information on current developments and trends. As a rule, reviews are written upon invitation from the Editor.

*Feature articles* are concise and critical reviews of a current topic, pointing to trends and controversies in the field. They should be understandable to non-specialists. Feature articles are written upon invitation from the Editorial Board and should not exceed 20 typewritten pages.

*Conference papers* should be reported at a congress, symposium or summer school prior to submission to the Journal. Conference papers are submitted by the Organizing Committee.

*Essays* report *curricula vitae* of the important Croatian chemists and accounts of the history of chemistry.

*Data bank contributions* contain new chemical and physical data in order to make them available for subsequent scientific interpretation and various practical uses.

*Letters to the Editor* are a medium for expression of scientific opinions or exchange of different views concerning the material published in CCA.

All contributions are evaluated according to the criteria of originality and quality of their scientific content. Original scientific papers, Notes and Preliminary communications are sent to two referees, Feature articles and Conference papers to one, and Authors' reviews, Reviews, Essays and Data bank contributions to three. Only papers with favourable reports are accepted for publication.

Detailed *Instructions to Authors* are printed in the first issue of each volume.

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Published by **The Croatian Chemical Society**

# CROATICA CHEMICA ACTA

Guest Editors:

**Miljenko Dumić**  
**Vitomir Šunjić**  
**Nenad Trinajstić**

Special Issue

**ZAGREB**  
**CROATIA**  
**1996**

# CROATICA CHEMICA ACTA

Published by  
The Croatian Chemical Society

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CROATICA CHEMICA ACTA

Zagreb, Croatia

*In honour of*

Professor Vladimir Prelog

VLADIMIR PRELOG – With his own samples after 45 years.

During his visit to the Department of Organic Chemistry, the Faculty of Technology, Zagreb, June 1986, Professor Prelog examines with interest the samples of substances that he synthesized between 1936 and 1941 while working in Zagreb (taken by Dr. M. Dumić on June 7, 1986).





## FOREWORD

Professor Vladimir Prelog will be 90 years of age on July 23, 1996! One way of honouring a scientist of his status on such an occasion is to dedicate him a special issue of a scientific journal to which he has been scientifically and/or emotionally attached. *Croatica Chemica Acta*, CCA, is such a journal. Vladimir Prelog is, along with another Nobel Laureate, Jean-Marie Lehn, a Honorary Editor of CCA and during his repeated, but brief, stays in Zagreb he has always found time to visit the Editorial Board.

Croat by birth, born in Sarajevo, Prelog started his academic career in 1935 as a docent and later professor of organic chemistry at the Technical Faculty of the University of Zagreb. In late 1941, at the invitation of Leopold Ružička he moved to Zürich joining the faculty of the *Eidgenössische Technische Hochschule*, ETH, where he has been ever since. However brief was his stay in Zagreb, it had a tremendous impact on the development of organic chemistry in Croatia and this can be felt even today. Among the papers Prelog published with his collaborators and students while in Zagreb, several appeared in the predecessors of *Croatica Chemica Acta*.

We, the three undersigned editors of this issue of CCA, appointed by the Editorial Board of CCA, perceiving Professor Prelog's modesty, were afraid that he might not agree with publishing a special issue of our journal in his honour. We, therefore consulted several prominent scientists, friends and former collaborators of Professor Prelog, who suggested that we solve the problem by publishing a »*Surprise Festschrift*« of CCA honouring Prelog's 90th birthday. The result of this endeavour is in your hands.

The contributors we have selected were only those who collaborated with Professor Prelog during his illustrious career, although not necessarily published their work with him. They have sent us their contributions in the form of original scientific papers, congratulatory notes, anecdotes, even a poem about him, descriptions of particular events or experiences, which illustrate the work and personality of this great chemist and educator.

For reasons just mentioned, we have divided this special issue of CCA into two parts, *viz.* the first part containing greetings and the second part reminiscences and original scientific papers.

We hope that the chemical community-at-large will find this »*Surprise Festschrift*« honouring Professor Vladimir Prelog an important contribution to contemporary chemical science and also an entertaining piece of reading about one of truly great chemist and humanitarians of the 20th century. Joining all contributors to this issue of CCA as well as all his other admirers, we wish Professor Vladimir Prelog many more happy years. Happy birthday Professor Prelog! Happy birthday dear Vlado!

*Miljenko Dumić, Vitomir Šunjić, and Nenad Trinajstić*

*Editors Acknowledgement.* – The guest editors wish to thank Ms Greta Prajdić, Dr Zlatica Raza, Ms Vera Mikulčić and Mr Dean Bičak for their excellent and untiring work in the production of this special issue of *Croatica Chemica Acta* honouring Professor Vladimir Prelog.

Greetings





## THE SCRIPPS RESEARCH INSTITUTE

DEPARTMENT OF CHEMISTRY  
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To Vladimir Prelog,  
on the occasion of your 90th birthday:

Highest congratulations are in order for this landmark anniversary in the life of a landmark scientist! We chemists all owe you so much, and while the actual occasions I have been honored to share your company are regrettably few, they are characterized by an unforgettable intensity. Chemistry we discuss, of course, but the art of science, philosophy, history, painting, the mysteries of the human condition—your mind seems boundless, and I am richer for having been touched by it. Furthermore, I go on record declaring that your company provides more sheer entertainment value per minute than any companion I've ever known or hope to meet!

Dear Vlado, a top contender for my most prized possession is the gold medal that bears your portrait. It is an arresting likeness, one that reveals a profile befitting a Roman emperor or a Renaissance prince. . . or, as is the case, a King of Chemistry.

With congratulations and fond best wishes,

Barry Sharpless

K. BARRY SHARPLESS, PH.D.  
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June 22, 1995

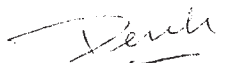
Prof. V. Prelog, FRS  
Lab. für Organische Chemie  
E. T. H. Zurich  
Universitätsstrasse 16  
Zurich 8006  
SWITZERLAND

Dear Vlado,

Do you remember 1948 and your Centenary Lecture before the British Chemical Society? You told me that it was unfair that, "I was so young and you were so old." Times have not changed! But you are now a young Post-doc and I am still an old Professor!

Best wishes on your 90th Birthday. We now look forward to the 100th. You will still be a young Post-doc and I, probably, will be elsewhere with Bob Woodward reminiscing about the good old times when students really worked.

As ever,



D.H.R. Barton

DHRB:kef

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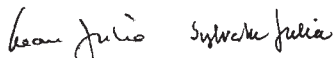
Dear Drs Dumić and Šunjić;

Thank you very much for your letter dated July 17. Please excuse the delay in answering.

We should like to take this opportunity to express our admiration and gratitude for Professor Prelog's outstanding contributions to Organic and Bioorganic Chemistry.

We send our heartiest wishes on the occasion of his 90th birthday, together with his very many Colleagues, Collaborators, Students and Friends. We are looking forward to many more years in which the chemical community will benefit from Professor Prelog's Science and Wisdom.

Yours very sincerely.



Marc and Sylvestre Julia



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WWW. <http://www.shef.ac.uk/uni/academic/I-M/is/home.html>

12 November 1995

Professors M. Dumić and V. Šunjić  
Redakcia  
19 Marulićev trg Post pret 163  
41 001 ZAGREB  
Croatia

Dear Professors Dumić and Šunjić

As a one-time collaborator of Professor V. Prelog (1957-59), I would like to contribute, if not an anecdote, at least a recollection of a favourite expression of his - I understand that he was a destroyer captain in the Yugoslav Navy at one time.

He was accustomed to use the expression:

"More ships are lost through bad logic than through bad seamanship".

I wish you success with the Festschrift.

Yours sincerely

A handwritten signature in cursive script that reads "Michael F Lynch".

Michael F Lynch

**Head of Department:** Professor T.D. Wilson, BSc (Econ), PhD, FInstSc, FLA  
Professor of Information Science M.F. Lynch, BSc, PhD, CChem, FInstSc  
Professor P. Willett, MA, PhD, MBCS, FInstSc

**PROF. T. REICHSTEIN**

Basel, 30. Januar 1996.

Lieber Vladimir,

ich gratuliere Dir herzlichst zu Deinem 90. Geburtstag und hoffe, Du kannst einen solchen noch oft in guter Gesundheit feiern.

Leider kann ich altershalber nicht mehr reisen - werde diesen Sommer 99 Jahre alt -, es ist mir daher nicht möglich persönlich nach Zürich zu kommen, so bitte ich den Editor der Croatica Chemica Acta Dir meine besten Wünsche gedruckt zu überreichen.

Unserer gemeinsamen Zeit an der ETH und der weiteren Freundschaft mit Freude gedenkend

Dein

*Fredrik Reichstein*

### Prelog Vignette

In the early 1950's Vlado Prelog paid the first of many visits to UCLA, during which we first learned of our mutual interests in symmetry properties and large ring chemistry. Accordingly I visited him at the ETH in Zürich in the winter of 1955–1956. As I entered his office, he looked at me and exclaimed »Where did you get that coat and hat? You will not be treated cordially in Switzerland at this time if you dress like a German Army Officer.« I had innocently purchased a fine, gray, loden-cloth overcoat and cap with earflaps in cold Munich on my arrival there from Los Angeles. After this encounter with Prelog, I spent about six weeks in Zürich, warmed mainly by my American respectability, the hospitality of my hosts, my youth and the vigor of our discussions about chemical research.

Prelog is my senior by fourteen years, a large enough difference for me to look up to him over our near half-century of friendship. He has enriched my life and career, for which I thank him on this fine occasion of his 90th birthday. I had a dream recently about Prelog which placed him before St. Peter at the Pearly Gates. Prelog asked St. Peter »Have you heard the standard story about how people get into heaven?« St. Peter hastily replied »There is a long line, and my computer read-out says you are not due here for some time. Get back to your research!«

*Donald J. Cram*

## Reminiscences



## **Prelog's Zagreb School of Organic Chemistry (1935 – 1945)\***

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*Ilica 231, HR-10000 Zagreb, Croatia*

Received October 16, 1995; accepted October 30, 1995

This article on Vladimir Prelog and his contribution to the development of organic chemistry in Croatia presents data on his scientific work done in the Department of Organic Chemistry of the Technical Faculty in Zagreb, as well as the scientific research work carried out in collaboration with the Science Laboratory of the pharmaceutical plant »Kaštel« in Zagreb. All the resulting papers were prepared by joint engagement of Professor Prelog's enthusiastic co-workers from the Faculty and »Kaštel«, thus establishing »Prelog's Zagreb School of Organic Chemistry«. It continued its activities even after Professor Prelog's departure for Zürich and had a vital influence on the further development of organic chemistry and biochemistry at the University of Zagreb, research institutions and scientific research laboratories of the chemical and pharmaceutical industries in Croatia.

The 90th birthday of our dear Professor Vladimir Prelog is a great opportunity not only for extending our congratulations and paying our respects to him but also for recalling what he has done for the development of Croatian organic chemistry and pharmaceutical industry during his short scientific activity in Zagreb.

Professor Prelog came to the Technical Faculty in Zagreb in 1935. At that time, I was a freshman and I remember his first lectures on organic chemistry in the summer term of 1935. We got to know Professor Prelog as a brilliant and fascinating lecturer. He rendered his lectures in a clear and

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\* Dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.

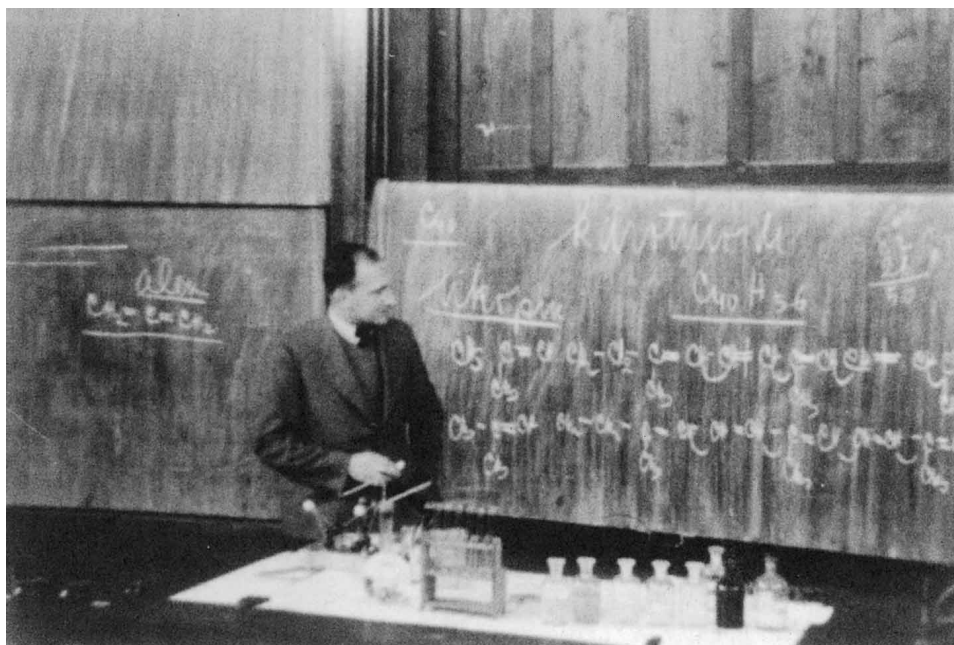


Figure 1. Prelog delivering a lecture on organic chemistry, Zagreb 1936.

witty way, so we listened with interest and memorized his words (Figure 1). It was already at that time that many of us committed ourselves to organic chemistry.

At his lectures, and afterwards in personal contacts during laboratory exercises and doctoral theses, we found out much more about our professor. Vladimir Prelog was born in Sarajevo on July 23, 1906. His father, Milan, was an outstanding historian and university professor. Prelog went to grammar school in Zagreb from 1916 to 1919, then in Osijek for two years (1919–1921), and again in Zagreb from 1921 to 1924. He very early decided to take up chemistry, at secondary school in Osijek, where his excellent chemistry teacher, Ivan Kuria\* (Figure 2), encouraged his interest in chemistry. It was in 1921 that, at the age fifteen (Figure 3), with his teacher's help, he published a short communication entitled »Eine Titriervorrichtung« in the prestigious journal »*Chemiker-Zeitung*« (Figure 4).<sup>1</sup>

After his return to Zagreb, Prelog continued corresponding with his chemistry teacher in Osijek. Some of the letters are very touching. For in-

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\* Ivan Kuria, chemistry teacher at the Osijek grammar school, responsible for Prelog's love of chemistry. After retirement, he volunteered at Pliva to the end of his life.

stance, in his letter of March 16, 1922,<sup>2</sup> Prelog writes about himself: »I am very busy at the moment. In addition to my routine studies, I have enrolled as an extramural student in the crafts school and I spend whole afternoons three times a week learning how to file, hammer and do all the other things that an eager young locksmith should know. I am doing it to be able to, should I feel like it, return to the homeland after finishing my studies. In this way, I also fence myself off such idle pastimes like dancing.« He continues by describing how he spent the winter enjoying winter sports and



Figure 3. Fifteen-year old chemist Vlado.



Figure 2. Prof. Ivan Kuria.

how he now, in spring, looks forward to bathing, climbing the Triglav and Grintavec mountains and sailing on lakes Bled and Bohinj. He concludes the letter by giving an enthusiastic account of his visit to the Chemical Analytical Institute in Zagreb: »I think this is the best equipped institute in SHS\*. This wealth in platinum (a 300 g water beaker), optical instruments (refractometers, spectrosopes, microscopes, *etc., etc.*) and all the analytical devices that God and the German have created – I have nowhere seen anything like that. It is run by Mr. Eisenhut.«

\* The Kingdom of Serbs, Croats and Slovenes.

### Eine Titriervorrichtung.

Von Vlado Prelog, Osijek.

Die vielen bekanntgewordenen Titriervorrichtungen weisen die mannigfaltigsten Vorzüge auf, ohne indessen in allen wesentlichen Punkten den an sie gestellten Anforderungen zu entsprechen. Eine gute Konstruktion, welche aus billigen Teilen zusammensetzbar ist und mit einer gewöhnlichen Bürette

ihr Auslangen findet, ist in nebenstehender Abb. 1 abgebildet. Das Füllen geschieht durch Saugen bei M, wie bei dem Modell des Ostwaldschen Instituts. Es entfällt also der Gummiball (Kostpunkt!). Das Saugen hat vor dem Drücken den Vorzug, daß in keinem Falle CO<sub>2</sub>-haltige Luft in die Vorratsflasche gelangen kann. Die Maßflüssigkeit kommt nicht mit dem Kautschuk in Berührung, man kann also den Apparat auch für solche Flüssigkeiten (KMnO<sub>4</sub>, usw.) anwenden, welche den Kautschuk angreifen. Das Zulußrohr Z ist während der Titration

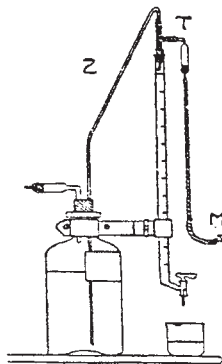


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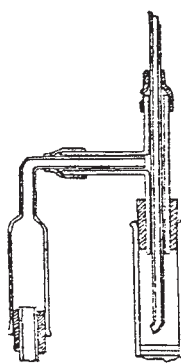


Abb. 2.

leer, es kann daher unbeabsichtigt keine Maßflüssigkeit in die Bürette gelangen und so zu Fehlern Veranlassung geben. Der Apparat bezw. die Lösung in der Vorratsflasche kann umgeschüttelt werden, wodurch das an den Wandungen kondensierte Wasser mit der Hauptmenge vereinigt wird. Der Apparat ist nicht zerbrechlich und gut transportabel, kann leicht auseinander genommen und gereinigt werden. Zwecks leichterer Verschiebbarkeit des Zulußrohres Z in dem T-Stücke T sind die Kautschukverbindungen mit etwas Talkpulver bestreut.

Figure 4. Facsimile of Prelog's first paper.

After passing his school-leaving exam in Zagreb, in 1924, Prelog studied chemistry at the Prague Institute of Technology where he, already as a student, started doing research. Thus, we know from his letter of April 3, 1928 to his teacher Ivan Kuria (Figure 5),<sup>3</sup> with whom he always kept in touch, that in the second year of studies he had the good opportunity to engage in organic chemistry, in his spare time from 8 to 12 P.M. In the fourth year, his exams and prescribed exercises kept him very busy, so he could not spend so much time in the laboratory. He writes that he was working on two papers: »One is actually a sequel to the syntheses in the pirrole series and it will be published with Dr. Lukeš, who is a senior assistant lecturer now and also my best friend. The other paper, co-authored by Professor Votoček, deals with the high fatty oxyacids formed by hydrolysis of jalapin and turpeth convolvulin glycosides. Professor Votoček is the leading expert in the field of methylpentoses, which are found in these glycosides. He discovered them there while the fatty acids remained as a by-product. I have undertaken their processing and have already done a great deal of work.«

Prelog concludes the letter by adding: »I would like to take my final by the end of the year, and then I would stay on to get a doctor's degree. Then the army service, and then in search for a better livelihood. You must be aware how difficult these problems are.«



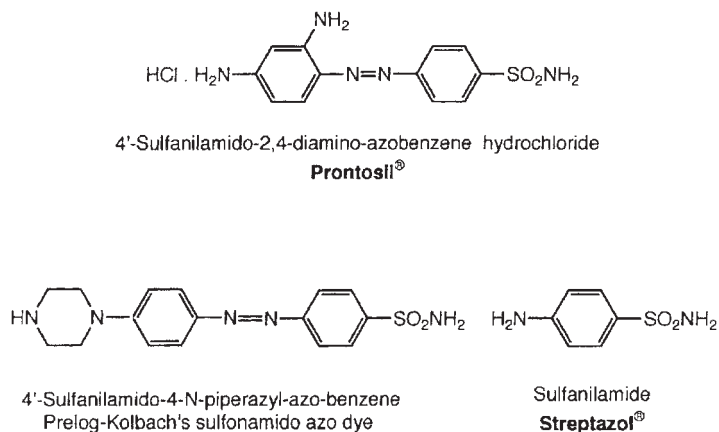


Figure 6. Chemical structures of *Prontosil*<sup>®</sup>, Prelog's azo dye and sulfanilamide.

the young, but already renowned, organic chemist to succeed Professor Marek as head of the Department of Organic Chemistry.

Prelog, who had always wanted to work in an academic laboratory, promptly accepted the offer. At the end of 1934, he came to Zagreb, with his wife Kamila neé Vitek, where he assumed the duty of head of the Department, first as assistant professor, and since 1941 as associate professor.

According to Professor Prelog,<sup>4</sup> the working conditions were more than modest. The laboratory was not equipped for preparatory work in organic chemistry because Professor Marek was predominantly engaged on organic elemental analysis, and the other units of the Chemistry Department also tended towards analytics. In industrial laboratories, chemical engineers mainly analyzed raw materials and finished products, and very few worked in the production. Hence, there was no incentive for preparatory work. Nobody was actually against scientific research at that time, but the budget was so small that it only just covered tuition while research funds depended on the resourcefulness of those who wanted to do research. Prelog was disappointed with the situation and his enthusiasm dwindled. However, it soon came back when he received an offer for scientific cooperation from Dr. Eugen Ladany, director and co-owner of the small pharmaceutical company »Kaštel« in Zagreb. Prelog did not hesitate in accepting the offer, since it enabled him to do scientific research as he had always wanted to. He described briefly and clearly the agreement on cooperation:<sup>4</sup> »We agreed that Kaštel would set up a research laboratory. The chemical section of the laboratory would work on the procedures for the production of medically interesting compounds, while the pharmacological section would test their biological and therapeutical properties. Kaštel will help me fit out the Department of Organic Chemistry at the Faculty, where I will also deal with medically in-

teresting compounds, something that I have always wanted to do. Our short-term plan is to design procedures for the production of known, profit making medicines, and the long-term one to discover new, original, biologically active and medically interesting compounds.» He continued: »My first concern was to provide a real content for these abstract plans. In 1935, Domagk's *Prontosil*<sup>®</sup> (4'-sulfanilamido-2,4-diamino-azobenzene hydrochloride), the first efficient agent against bacterial infections, received great acclaim in the field of medical chemistry (Figure 6). I proposed as our short-range goal to copy *Prontosil*<sup>®</sup>, but in a way so as not to get into conflict with the powerful German chemical industry. At the same time, I was approached by the Prague student, Dragutin Kolbach, an engineer, who wished to work on his doctoral thesis with me. I suggested he should prepare a series of azo dyes related to *Prontosil*<sup>®</sup>. Out of his compounds, 4'-sulfanilamido-4-*N*-piperazyl-azo-benzene (Figure 6) showed good characteristics and, after some tests, we decided to produce it commercially.

**KOD GRIPE, INFLUENCE I PREHLADE  
ZA PROFILAKSU I TERAPIJU**  
**STREPTAZOL-KININ**  
tablete „KAŠTEL“



**NOVO!**

**STREPTAZOL-KININ TABLETE ZA DJECU**

Protivbakterijske tablete s 0,15 g Streptozola i 0,35 g kinina



**Kaštel** d. d.

Zagreb

Figure 7. Facsimile of one of »Kaštel« advertisements, Zagreb, 1939.

When the first steps in this direction were undertaken, a paper written by Daniel Bovet and Françoise Nitti of the Pasteur Institute in Paris appeared in 1936, in which the authors demonstrated that *Prontosil*<sup>®</sup> underwent reductive splitting in mammals and that its antibacterial effect derives from the product of this splitting, *i.e.* sulfanilamide (Figure 6) (starting material for *Prontosil*<sup>®</sup> allied azo dyes). As sulfanilamide was not patent protected, after an incredibly short time, in 1937, »Kaštel« launched it on the market under the name. *Streptazol*<sup>®</sup> (Figure 7). It was a miracle drug until resistant strains of pathogenic bacteria appeared. Its huge success contributed a lot to »Kaštel« extending its support to our research cooperation.«

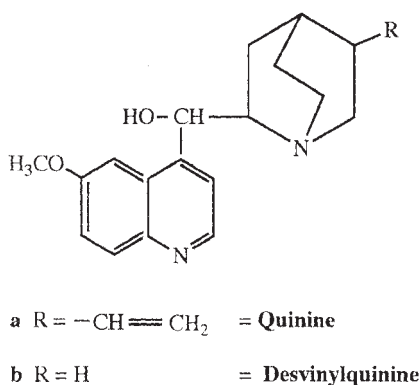


Figure 8. Chemical structures of quinine and desvinylnine.

This cooperation enabled Prelog to upgrade the equipment in his Department, so he could organize laboratory work with some young associates and resume research activities that he had started in Prague. These are chemotherapeutic agents for some common diseases, syntheses in the field of cinchona bark alkaloids and bicyclic bases that constitute the skeleton of some alkaloids. Quinine was still the most important antimalarial agent at that time. Its constitution was already known (Figure 8), but its spacial structure, configuration and synthesis were still unknown. Due to the modest working conditions, work on the synthesis was chosen for being simpler and less costly than that on the configuration. A satisfactory procedure was known for the synthesis of the quinoline part whereas no adequate method existed for the preparation of quinuclidine, which is actually a tertiary amine with a nitrogen atom at the branching point.

With a group of co-workers (Krešimir Balenović,<sup>39,40</sup> Krunoslav Božičević,<sup>25</sup> Eugen Cerkovnikov,<sup>10,13,14,16,20,22,33,36</sup> Eugen Guštak,<sup>28</sup> Suzana Heimbach-Juhász,<sup>20,22,24,26,32,33</sup> Dragutin Kolbach,<sup>13</sup> Miho Piantanida,<sup>13</sup> Adolf Režek,<sup>13,32</sup> Bruno Schönbaum,<sup>35</sup> Rativoj Seiwerth,<sup>26,28</sup> Nikola Šoštarić,<sup>34</sup> Pavao

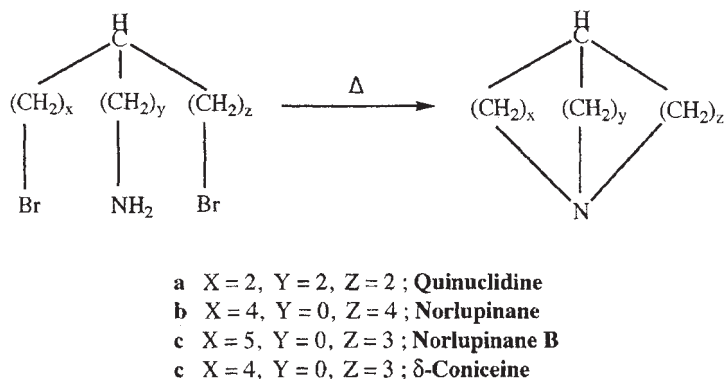


Figure 9. Prelog's synthesis of quinuclidine, norlupinane, norlupinane B and  $\delta$ -coniceine by the method of double intramolecular alkylation.

Štern<sup>37</sup> and Georgij Ustričev<sup>16</sup>), Prelog dedicated his efforts to the synthesis of quinuclidine and a whole series of allied bases with nitrogen at the branching point. Several methods were developed for the preparation of these compounds, the most efficient of which was the so called Prelog's method of double intramolecular alkylation, which enabled syntheses of the already known as well as new bicyclic amines (Figure 9), which are interesting not only because their skeleton is incorporated in alkaloids but also from the aspect of stereo-chemistry. Preparation of these amines was patented by »Kaštel«.

After gaining experience in the syntheses of quinuclidine and the allied bicyclic amines, V. Prelog, R. Seiwerth, V. Hahn and E. Cerkovnikov<sup>27</sup> moved on to the synthesis of compounds similar to quinine. The aim of the research was to develop methods for the preparation of various compounds with the rubane skeleton (Figure 10 a), representative samples of which would be tested for antimalarial activity. The compounds prepared (Figures 10 b, c, d, e, f) were tested for antimalarial activity but showed no activity.

Then, V. Prelog, R. Seiwerth, Suzana Heimbach-Juhász and P. Štern<sup>37,38</sup> prepared a simple quinine analogon in which the vinyl group was replaced by hydrogen, desvinylquinine (Figure 8 b). By reduction of 6-methoxy-ruban-9-ol, a diastereoisomeric pair was obtained as the main product, which was in experiments with animals shown to have the same activity as the not easily available quinine. Thus, it was proven that the vinyl group is not indispensable for antimalarial activity.

In their further research on quina-alkaloids, V. Prelog and M. Proštenik<sup>53</sup> succeeded in partial synthesis of quinotoxine (Figure 11 a) from the still unknown homomeroquinene (Figure 11 b), prepared by decomposition of cinchonine *via* cinchotoxine. This was an additional step to the total synthesis of quinine.

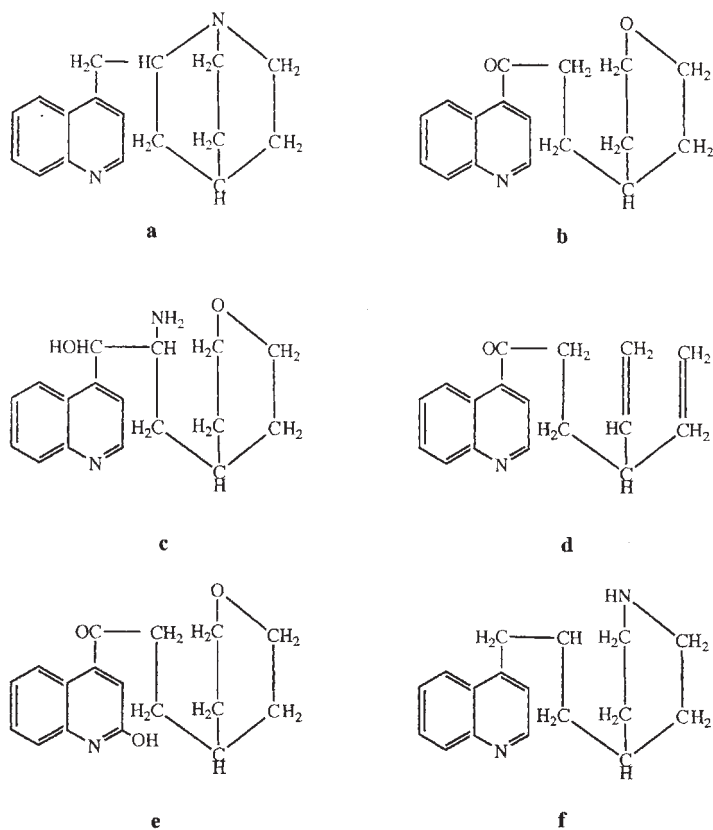


Figure 10. Chemical structures of rubane (a) and its related compounds (c-f), synthesized and tested by Prelog and co-workers.

A problem quite different from the chemistry of cinchona bark alkaloids was the first synthesis of adamantane. The diamond lattice contains a special tricyclic carbon skeleton made up of ten carbon atoms. Organic compounds with such skeletons were named diamondoid (*diamond-like*) compounds. The simplest representative of such compounds is the hydrocarbon C<sub>10</sub>H<sub>16</sub>, symmetrical tricyclodecane (Figure 12 d), which Landa and Macháček isolated in 1933 from petroleum in the vicinity of Hodonin in Moravia and named adamantane\* (Figure 12 d).

The first synthesis of adamantane was carried out by Prelog and Seiwerth in 1941, using bicyclo-[3,3,1]-nonane<sup>41</sup> as starting material. By condensation of disodium dimethyl ester salt of bicyclo-[1,3,3]-nonandion-

\* αδαιμαξ, the invincible, wherefrom the word DIAMOND and ADAMANTANE were formed.

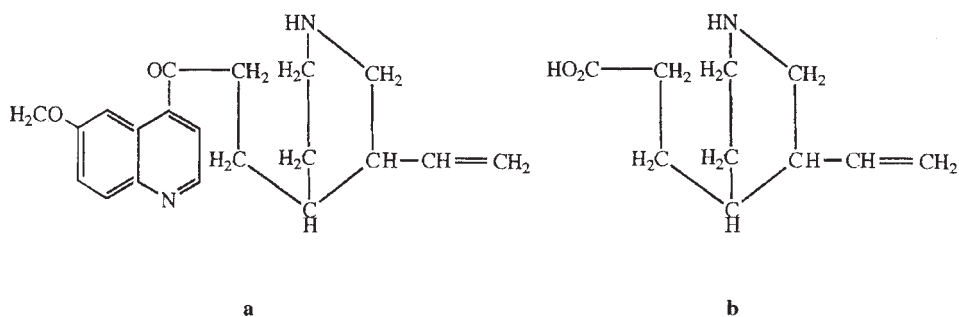


Figure 11. Partial synthesis of quinotoxine.

(2,6)-dicarboxylic acid-(3,7) (**12a**) with dibromomethane, a dimethyl ester of adamantandion-(2,6)-dicarboxylic acid-(1,5) (**12b**) was prepared. Its hydrolysis gave adamantandion-(2,6)-dicarboxylic acid-(1,5), which was by the Wolff-Kishner reduction transformed into adamantane dicarboxylic acid-(1,3) (**12c**).

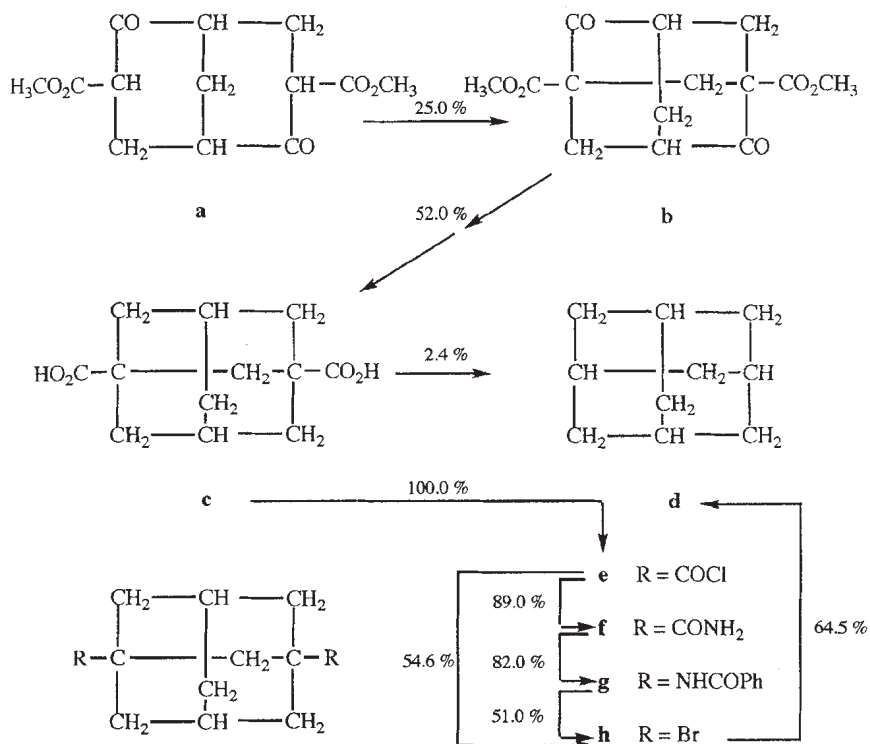


Figure 12. Prelog-Seiwerth's syntheses of adamantane.

Its decarboxylation in the presence of Cu-bronze at 400 °C gave adamantane (**12d**) in a poor yield of 2.4% (total yield 0.16%). By another, more abundant synthesis,<sup>47</sup> adamantane dicarboxylic acid-(1,3) (**12c**) was transformed *via* dichloride **12e** into diamide **12f**. The latter was diverted into 1,3-diaminoadamantane by a reaction with sodium hypobromite. From its dibenzoil derivate (**12g**) with phosphorus-pentabromide, 1,3-dibromineadamantane (**12h**) was obtained, and by catalytic hydration of the latter in the presence of Raney-nickel, adamantane (**12d**) was obtained in a total yield of 3.12%. Dibromo-derivate **12h** was also easily obtained by diversion of the silver salt of adamantane carboxylic acid **12c** with bromine, which is a further simplification of adamantane synthesis (4.73%). Properties of thus synthetically obtained adamantane fully corresponded to the values that Landa and Maháček<sup>5</sup> had reported for natural adamantane.

All the above trials were done with a small group of enthusiastic co-workers under very modest working conditions. I vividly recall the instance when the Professor procured an oil pump for high vacuum and installed it himself. A celebration broke out in the laboratory and the pump was cherished dearly. Since the Professor worked with us in the laboratory, we could learn a great deal from him. He showed us how, using the appliances available, we could make apparatus that was applicable even to very sensitive and complex reactions. Our professor was a real master of glass processing, so he taught us how to bend glass tubes at different angles and make various small flasks, distillation apparatus, stirring rods, *etc.* He taught us to love our work, to be filled with joy at newly synthesized compounds, obtained in the form of clear oily liquids or beautiful crystals, and the joy reached its peak when it was confirmed by analysis that we had attained just that compound that we had wanted. Despite meagre funds and potentials, Prelog's group worked with satisfaction and was very efficient. In a period of seven years, 48 research papers and eight patents were published, as well as five dissertations under Prelog's supervision. It is interesting to note that, with his ten papers, Prelog's group was the team with the largest number of papers published in the prestigious journal »*Berichte der Deutschen Chemischen Gesellschaft*« in 1941.

The commercial success of *Streptazol*<sup>®</sup> speeding up considerably the fitting out of a research laboratory at »Kaštel« and the training of promising experts for such work. After the first successes, the »Kaštel« research team became so strong that a research department with three laboratories (chemical, pharmacological and bacteriological) was founded at »Kaštel« in 1938. The research department staff included: V. Hahn, E. Rajner and E. Cerkovnikov, chemists, P. Štern, a pharmacologist, and J. Kolačný, a bacteriologist. In this department, following Prelog's long-term plan, new barbituric acid derivatives<sup>7</sup> were synthesized, as well as a number of new compounds that were tested for anti-malarial<sup>127,37,38,51,52</sup> and spasmolytic<sup>42,43,44</sup> activity. Among the new 4-amino-piperidine derivatives, marked spasmolytic activity was manifested by 4-dimethylamino-1-phenyl-piperidine. The compound was subjected to further tests, which were necessary before its launching on the market. At the same time, the research group was developing methods for the production of some

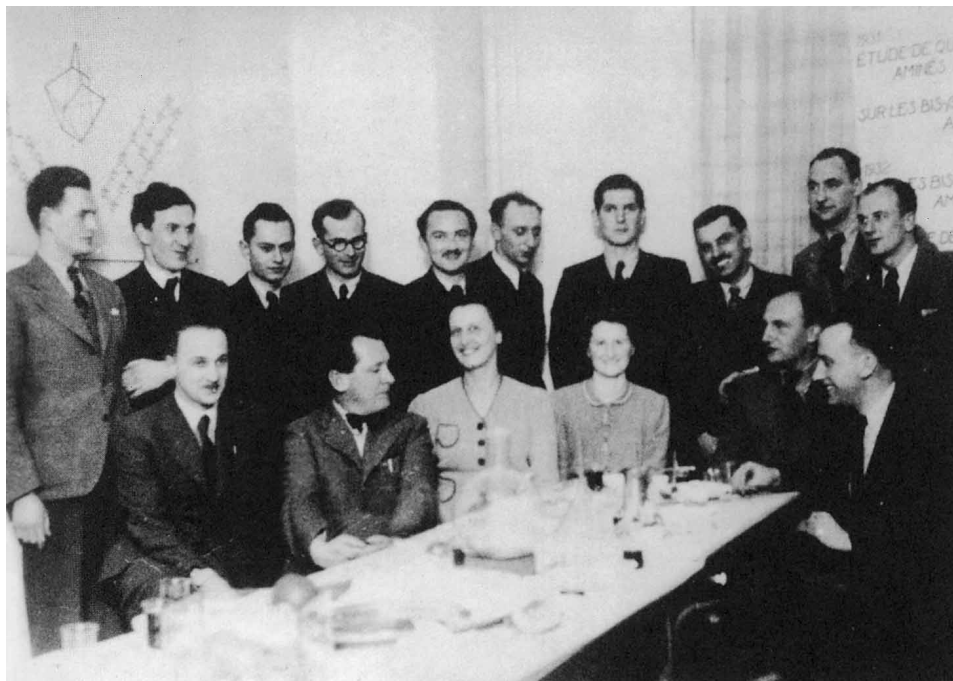


Figure 13. Prelog's Zagreb school of organic chemistry. Some of his co-workers on the occasion of his birthday celebration in 1939 (sitting from left to right: M. Piantanida, A. Režek, Nina Cerkovnikov, Suzana Heimbach-Juhász, V. Prelog and E. Rajner; standing from the left: R. Seiwerth, K. Juhász, V. Hahn, P. Štern, K. Božičević, D. Kolbach, B. Schwirtlich, E. Cerkovnikov, I. Corubolo and Lj. Trinajstić).

already known medicines. *Streptazol*<sup>®</sup> was immediately followed by sulfapyridine (*Plurazol*<sup>®</sup>), which was soon abandoned because of toxicity. Methods were developed for the production of *Eucistine*<sup>®</sup> (3-phenyl-1-azo-2,6-diaminopyridine), the classical analeptic, nicotinic acid diethylamide (*Leptamin*<sup>®</sup>) as well as calcium levulinate (*Eukalcin*<sup>®</sup>) for calcium therapy. Thus Prelog and his collaborators founded the synthetic production and organized scientific research in the factory »Kaštel«, which was actually the beginning of the research institute of the present day »Pliva«.

By this cooperation with »Kaštel«, Prelog demonstrated that cooperation between university and industrial research laboratories could be very successful, though this was a rather sensitive and complex relationship. Their cooperation was based on mutual trust, good will and benefits to both sides, the limits of whose respective potentials were well known to each other. Prelog succeeded in establishing a full mutual understanding while his associates, both from the faculty and from »Kaštel«, founded **Prelog's Zagreb School of Organic Chemistry** (Figure 13).



Figure 14. Prof. Prelog with his old co-workers at the opening ceremony of the Pliva Institute, autumn 1952 (from the left: E. Rajner, R. Seiwerth, D. Kolbach, V. Prelog and E. Guštak).

The war, however, put an end to these activities. During the war, scientific research was almost impossible. »Kaštel« was made a state company and all research was discontinued. Under such confused and uncertain circumstances, Prelog took a sabbatical. He had received invitations by the president of the German Chemical Society, Richard Kuhn, to give a few lectures at Heidelberg and by Leopold Ružička to come to Zürich. He decided to go to Zürich and it was after the war that he also gave a lecture at Heidelberg. On Prelog's suggestion, R. Seiwerth was appointed his deputy during the sabbatical. As the »short sabbatical« was extended, Seiwerth ran the tuition and the Department throughout the war, until 1945, but Prelog did not return. He stayed on in Zürich after the war.

Though Prelog's work at the faculty and in pharmaceutical industry was interrupted by his departure for Switzerland at the end of 1941, his Zagreb school of organic chemistry continued its activities and development. After the war, Prelog's former students and co-workers assumed responsible duties at faculties, research institutions and in industry, they set up new research laboratories and educated a new generation of organic chemists. Pro-



Figure 15. Prelog's Zagreb school of organic chemistry. Prof. Prelog and Mrs. Prelog with organic chemists at dinner at Hotel Esplanade, 1973 (sitting from the left: Mrs. J. Guštak, Mrs. Z. Štefanec, Mrs. Prelog and Mrs. N. Bregant; standing from the left: B. Glunčić, B. Gašpert, P. Mildner, R. Marušić, D. Kolbach, M. Lačan, E. Guštak, Professor Prelog, S. Borčić, R. Seiwerth, K. Balenović and S. Đokić).

Professor Prelog has been continually monitoring the development of his school and has always stayed in touch with his former associates. He occasionally comes to Zagreb to visit his family, and he readily accepts invitations to give lectures and attend scientific and professional gatherings, as well as various celebrations. When he comes, he always finds time to meet his old associates from Zagreb, as well as those who worked with him in Zürich\* (Figures 14, 15 and 16). Prelog also arranges for our young organic chemists to spend some time working in his ETH Laboratory. »Exchange of experience is the best form of cooperation«, Prelog used to say. This practice is systematically carried out even now when he is retired.

\* The following chemists have worked with Professor Prelog in Zürich where they acquired »organic polish«: Dušan Dvornik, Stanko Borčić, Mirko Ternbach, Berislav Glunčić, Branimir Gašpert, Vitomir Šunjić, Radoslav Marušić, Mladen Žinić, Krunoslav Kovačević, Stjepan Mutak, Miljenko Dumić and Miće Kovačević.



Figure 16. Prelog's Zagreb school of organic chemistry. Prof. Prelog and Mrs. Prelog with his former Zagreb and Zürich associates at the Pliva Club, on May 22, 1989 (sitting from the left: R. Seiwert, D. Kolbach, Professor Prelog, Mrs. Prelog and M. Proštenik; standing from the left: M. Dumić, S. Mutak, B. Glunčić, K. Kovačević, B. Gašpert, M. Žinić, M. Kovačević, S. Borčić, V. Šunjić and S. Đokić).

This ensures uninterrupted work and rejuvenation of Prelog's Zagreb school of organic chemistry. We are, therefore, grateful to our Professor Prelog for all that he has done for our chemistry and for our future.

*Acknowledgement.* – I am grateful to my colleague Dr. Miljenko Dumić for correcting and editing the manuscript.

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### **SAŽETAK**

#### **Prelogova škola organske kemije u Zagrebu**

*Rativoj Seiwerth*

U ovom prikazu o Vladimiru Prelogu i njegovom doprinosu razvitku organske kemije u Hrvatskoj izneseni su podaci o znanstvenim radovima izvedenima u Zavodu za organsku kemiju Tehničkog fakulteta u Zagrebu, kao i znanstveno-istraživačkim radovima izvedenima u suradnji sa Znanstvenim laboratorijem farmaceutske tvornice »Kaštel« u Zagrebu. Svi ti radovi nastali su zajedničkim radom oduševljenih suradnika prof. Preloga s fakulteta i tvornice »Kaštel«, stvarajući time »Prelogovu školu organske kemije u Zagrebu«. Ona je i nakon odlaska prof. Preloga u Zürich nastavila radom i bitno utjecala na daljnji razvoj organske kemije i biokemije na visokim školama, znanstvenim ustanovama i znanstveno-istraživačkim laboratorijima organsko kemijske i farmaceutske industrije u Hrvatskoj.



## Vladimir Prelog's Prague Years and My Later Contacts with Him\*

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The circumstances in which V. Prelog studied and worked in Prague, some stories in which he was involved, and the author's reminiscences to his numerous contacts with Prelog are described.

When I was invited to contribute to this »Surprise Festschrift«, I wanted to concentrate on reminiscences of my frequent contacts with Prof. V. Prelog since 1946. I realized, however, that very likely I was the only Czech chemist to have had this opportunity. Vladimir Prelog was very closely connected with Czech chemistry and with Czech chemists: he spent the years 1924–1935 in Prague studying chemistry and concentrating his interests on organic chemistry (especially on the chemistry of natural products) – his whole life's orientation. Here, he met his friends and Kamila Vitek, his lifelong consort of Czech origin. Prague and the Czech milieu was important to V. Prelog and he became important to Czech chemistry. All this is the reason why I feel I should start with a short recapitulation of his Prague period.

It is not easy for me for two reasons:

1. At the time of his stay in Prague, I was a boy of 3–14 years and thus cannot be considered a witness. I simply have to behave like a historian, *i.e.* use the written reports of witnesses; the best of them have been provided by V. Prelog himself;<sup>1,2</sup> they have been repeated several times in literature.

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\* Reminiscences dedicated to Professor Vladimir Prelog on the occasion of his 90th birthday.

2. The true and important witnesses of that time have passed away: E. Votoček (1950)\*, R. Lukeš (1960)\*\*, G. J. Dřiza (1952)\*\*\*, J. Fragner (1977)\*\*\*\* and V. Hanousek (1986)\*\*\*\*\*; only one of them (J. Fragner) has published an article<sup>3</sup> containing useful information.

## I

Vladimir Prelog was 18 years old when he came to Prague in the fall of 1924 and enrolled in the Prague Institute of Chemical Technology (in fact, the Chemical Faculty of the Technical University). He quickly mastered the Czech language but in the first two years he was disappointed in his studies which »seemed to consist of endless details, compounds, and reactions without connection«. Prelog's favoured area were the general problems of the philosophy of science. He overcame this disappointment in the 3rd year of his studies when he became acquainted with Rudolf Lukeš (Figure 1) in the organic chemistry department, headed by Emil Votoček (Figure 2), professor of organic chemistry.

R. Lukeš (9 years older than Prelog) was the professor's assistant in charge of the organic chemical laboratory where practical experiments were carried out. He had just begun to carry out some independent research, when V. Prelog became first his apprentice and later his co-worker. R. Lukeš succeeded in showing to Prelog the attractiveness of experimental organic chemistry, especially in the area of heterocyclic compounds which are structurally close to some natural products, mainly alkaloids. Their first joint study was an investigation of the reaction of *N*-methylsuccinimide with phenylmagnesium bromide.<sup>4</sup> One of the products was 1-methyl-2,5-diphenylpyrrole which formed magnificent crystals. This was probably one of the crucial points in Prelog's life: ...»the awareness that he had created a new substance, something that no hands had previously touched, gave him great pleasure and desire for more such experiences«. He, therefore, spent all his free time assisting Lukeš in his research, which resulted in further original studies: structure of laevulic acid arylamides<sup>5</sup> and reactions of some

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\* Emil Votoček (1872–1950), Professor of organic chemistry at the Prague Institute of Chemical Technology; chemistry of carbohydrates was the main field of his interests.

\*\* Rudolf Lukeš (1897–1960), Disciple of Votoček and his successor to the function of professor of organic chemistry; he founded in Prague a school of the chemistry of heterocyclic compounds.

\*\*\* Gothard Dřiza (1895–1952), Czech chemist and businessman in the field of equipment for chemical laboratories and chemical reagents; his company included a laboratory for small-scale production of rare chemicals.

\*\*\*\* Jiří Fragner (1900–1977), Father of the Czech pharmaceutical research and industry, the first technical director of the natl. company SPOFA.

\*\*\*\*\* Vítězslav Hanousek († 1986), Chemical engineer and specialist in the technology of manufacturing aromatic chemicals and synthetic dyes.



Figure 1. Rudolf Lukeš (1897–1960).



Figure 2. Emil Votoček (1872–1950).

hydropyrrole derivatives with the Grignard reagent from 1,4-dibromobenzene.<sup>6</sup> V. Prelog finished his regular studies in the shortest possible time (eight semesters) – he received his degree in chemical engineering in 1928. His friendship with R. Lukeš was strong and lasting.

The next step of Prelog's studies in Prague was his attainment of the doctor's degree in chemical sciences. The theme of the thesis was not chosen by R. Lukeš but by Prof. E. Votoček who assigned him the problem of clarifying the structure of the aglycone of the glycoside rhamnoconvolvuline. V. Prelog quickly determined that the aglycone was 3,12-dihydroxypalmitic acid<sup>7</sup> and successfully passed his doctoral examination in June 1929.

J. Fragner<sup>3</sup> gives a vivid description of the place in which Prelog carried out his experiments leading to the degree: it was a doctoral laboratory called »Ďablik« (»the infernal lab«). The equipment was primitive and the atmosphere more or less terrible. The general mood was normally good but sometimes – especially when the products were unwilling to crystallize – even this was bad; this was corrected by the production of giant capillary tubes (R. Lukeš was a master in glasswork). In such days of tension, Prof. Votoček did not appear in the lab; he had his own informant on the situation and was of the opinion that difficulties had to be solved by those who had them.

There are two stories in which V. Prelog was involved. Once it went so far that Prof. E. Votoček wanted to ban Prelog from the lab for ever; he obviously had no idea that he was dealing with a future Nobel laureate. The

reason of Votoček's rage was a minor accident: with a glass rod, Prelog broke a flask containing the valuable methyl 3,12-dihydroxypalmitate which was placed in an oil bath. Hearing this, the enraged professor expelled the young man from the lab declaring that he never wanted to see him there. It was R. Lukeš who found a solution: the whole content of the oil bath was saponified with sodium hydroxide solution, the aqueous layer was acidified, the free acid isolated, purified and esterified. Prof. Votoček was surprised but reconciled and annulled his verdict with obvious relief since he liked Prelog very much.

In another story, R. Lukeš was the protagonist, with V. Prelog assisting him. R. Lukeš complained to V. Prelog that the professor (*i.e.* E. Votoček) evidently disliked him. V. Prelog could not understand why, but there was no time for discussion. At the same moment, Votoček entered the »infernial lab« in his best mood and asked the young chemists whether anybody could tell him how to synthesize an epigram. Nobody wanted to answer the strange question and Votoček explained that it was rather easy: »it was just necessary to take a gram and epimerize it.« Most of the present applauded the nice joke and the professor was happy. But, at that moment, the disturbing voice of R. Lukeš resounded in the lab: »I do not think, Sir, that this method would work«. And Votoček, astonished by this arrogance, asked: »What do you mean?«. And Lukeš explained: »To transform a gram into an epigram, it is necessary first to oxidize it with hypobromous acid to the gramonic acid which is then transformed to gramonolactone. This may be epimerized to epigramonolactone and only its reduction with sodium amalgam results in the required epigram.« After a moment of icy silence, the vain professor left the laboratory and did not appear for more than a week. And Prelog remarked to Lukeš: »And you are surprised that he dislikes you?«

In 1929, when Prelog finished his studies, economic depression reached its top and no academic positions were available. For this reason, he gladly accepted the offer of G. J. Dříza, a colleague of R. Lukeš, who was planning to start a laboratory for the production of rare chemicals and needed someone to head it. V. Prelog, thus, spent the next five years in Prague and after fulfilling his duties, he was able to continue his scientific work concentrated mainly on piperidine and piperazine derivatives, partly using diethanolamine as starting material. A special study was devoted to the characterization and identification of sapogenin from sugar beet as oleanolic acid.<sup>8</sup> Part of the experiments dealing with *N,N*-bis-(2-halogenoethyl)amines and their chemistry<sup>9-11</sup> were carried out in collaboration with his superior G. J. Dříza and were used as the basis for his doctoral thesis. V. Prelog had, thus, unofficially his first doctoral student; Prof. Votoček was the official supervisor.

The part of Dříza's company in Prague-Holešovice, headed by V. Prelog,<sup>12</sup> consisted of two laboratories for preparative work, an analytical laboratory, a room for water distillation, a library and an office. The laboratories were

quite well equipped and the library had, in addition to *Beilstein's Handbuch*, three most important journals (*Berichte der Deutschen Chemischen Gesellschaft*, *Chemisches Zentralblatt* and *Chemical Abstracts*). The social climate was excellent, the co-workers considered Prelog an outstanding colleague and advisor rather as a superior. Twice a month, discussion panels were held – very probably attended by R. Lukeš. The manufacturing program (small scale) of the unit was very diversified. In an article on the outsets of the Prague's pharmaceutical factory Interpharma, J. Tamchyna<sup>13</sup> mentioned that the analgesic *Dinarcon* (14-hydroxydihydrocodeinone) was developed in cooperation with V. Prelog during his stay in Prague.

The adamantane story<sup>2</sup> was another important event that happened during that time. While investigating the hydrocarbons of the rock-oil from Hodonin in Moravia, S. Landa (1932) of the Institute of Fuels of the Prague Institute of Chemical Technology isolated a saturated hydrocarbon C<sub>10</sub>H<sub>16</sub> melting at 266 °C, rather volatile and very stable, forming very nice tetrahedral crystals. It was named adamantane because the crystals were similar to those of the diamond. V. Prelog<sup>2,14</sup> recalls the moment when R. Lukeš intuitively in his and Landa's presence suggested the correct formula of the *sym*-tricyclodecane for adamantane and, at the same time, its synthesis starting from bicyclo (3.3.1)nonane derivatives.<sup>15</sup> S. Landa<sup>16</sup> then published a report on the discovery of adamantane for which he gave the correct structure on the basis of scarce data but not mentioning the priority of Lukeš's idea; he asserted that the structure was supported by a primitive X-ray analysis. Several years later, V. Prelog together with R. Seiwerth<sup>14</sup> confirmed the correctness of the adamantane structure by two syntheses, carried out in Zagreb. This work brought him international recognition. For a detailed description of the background of the whole story, *cf.* J. Markvart,<sup>17</sup> F. Petruš and B. Hájek<sup>18</sup> and R. Seiwerth in this issue.

In 1935, V. Prelog left Prague and accepted the post of an assistant professor at the University of Zagreb. For some time, however, he continued publishing his papers in the Czech journal "Collection".

## II

In the second part of my reminiscences, I certainly have no intention to reproduce V. Prelog's biography. On the other hand, our rather regular encounters and other personal contacts in a way reflect his life's career from the viewpoint of his position, development of his scientific work, working possibilities, contacts with Prague *etc.*

It was at the end of the war that I came across the name of V. Prelog and his publications in chemical literature. I first met him in May 1946 in Basle as a member of a small Czech delegation participating there in a bio-

chemical conference.<sup>19</sup> At that opportunity, we visited in Zürich the world-known »Laboratorium fur organische Chemie« of The Swiss Federal Institute of Technology. Prof. Prelog offered K. Wiesner and me to spend some time in his laboratories as post-graduate students.

At the end of March 1947, Prof. V. Prelog visited Prague and gave a series of three lectures:<sup>20</sup>

- On steroids in animal tissues,
- On multimembered rings, and
- On approaches to the structure of strychnine.

After the second lecture, a colloquium was devoted to general discussion in which Prof. Prelog answered with humour and in perfect Czech many questions dealing with all research phases in an organic chemistry laboratory. After the third lecture (held at the Prague Institute of Chemical Technology, *i.e.* in the new building of the Institute where Prof. Prelog graduated in 1928), a touching meeting of Prof. Prelog and his old teacher, Prof. E. Votoček, came about. This was my second meeting with Prof. Prelog and on that occasion the term of my future stay at the E. T. H. in Zürich was agreed upon in the presence of my superiors, J. Fragner and M. Herold.

My third »meeting« with Prof. Prelog lasted 6 months, *i.e.* from May to October 1947, during my post-graduate stay in his laboratory at the E. T. H. in Zürich.<sup>19</sup> There, I had all rights and duties of the E. T. H. students and was in daily contact with Prof. Prelog, who, himself, introduced me to the craft – or art – of experimental organic chemistry from the preparation of an experiment to the isolation of the products and preparation of the samples for analysis. My stay started with four very pleasant days in Ascona (near Lugano), where I was invited by the Prelogs together with K. Wiesner, his wife and E. Knobloch. Back in Zürich, I got a place in the laboratory together with K. Wiesner and two Swiss colleagues. In June, F. Šorm came from Prague and spent three months with us in the same laboratory. There were three different topics of my experimental work:

- Catalytic hydrogenation of julolidine and separation of the mixture of hexahydrojulolidines obtained by fractional crystallization of the picrates; homogeneous picrates of stereoisomers A and B were obtained,
- An attempt to prepare dipeptides in aqueous medium which did not give useful results, and
- Synthesis of a greater amount of racemic phenylalanine and its resolution with brucine to enantiomers.

I had no more time to continue this work and my products were used by Z. Vejdělek, my Czech successor in Prelog's laboratory. The stay in Zürich enabled me to become acquainted not only with the Institute's Director Prof. L. Ružička, but also with the other important persons there, especially Pl.

A. Plattner, O. Jeger, E. Hardegger, G. Buechi, A. Fürst *etc.*, which later proved important for my further career. I attended all colloquia at the Institute and came in touch with several distinguished guests from abroad. I had the rare opportunity to work in the atmosphere of one of the most important centres of the chemistry of natural products and, thanks to Prof. Prelog, I returned to Prague with sufficient knowledge and experience to form a proper methodical basis for the experimental work of the team I led in Prague.

The following eight »dark« years made it impossible for me to keep up personal contacts with Prof. Prelog; correspondence was the only way. At the beginning of 1949, Prof. Prelog decided to publish our results on the hydrogenation of julolidine; I sent him the experimental part and my only paper with Prof. Prelog appeared.<sup>21</sup>

In August 1950, I proposed – with J. Staněk – to Prof. O. Tomiček, at that time Chairman of the Prague section of the Czech. Chemical Society, to elect Prof. Prelog an honorary member of our Society. The proposal was motivated by his studies and activity in Prague, by his firm friendly relations to Czech chemists, and by his scientific achievements. Our proposal was accepted by the General Meeting of the Czech. Chemical Society in Brno (Sept. 1950) and the Honorary Membership was conferred on him.<sup>22,23</sup>

After eight years of hard political conditions in our country, I was at last allowed to attend the 14th International Congress of Pure and Applied Chemistry in July 1955, which took place in Zürich. Landing in Zürich, I could not resist a strong emotion realizing that I was coming to a free country. After the arrival, I was almost constantly in contact with Prof. Prelog. It was really a memorable congress with several hundreds of participants, most of them the cream in the organic chemical field. The most memorable event for me, to which I was invited thanks to Prof. Prelog's kindness, was the informal reception organized by Prof. Ružička in the Institute's Library for about 150 selected participants, where it was possible to meet and speak with anybody without any inhibition.

In April 1956, I sent Prof. Prelog a copy of my monograph on antihistamine agents. Prof. Prelog replied in a letter that very early, as a coworker of the company Kaštel in Zagreb, he had also been involved in the synthesis of potential antihistaminics and wished me success in our efforts. In July 1957, *i.e.* approximately at the time he became head of the Organic Department in Zürich, we shortly met in Paris at the 16th International Congress of Pure and Applied Chemistry. The following year we exchanged letters on the possibility of accepting some younger Czech chemists for a short (one year) post-graduate study at the E. T. H. Institute in Zürich. Prof. Prelog's standpoint was negative and justified by the strong anticommunist mood in Switzerland after the events in Hungary in 1956. Nine years later, we again discussed the possibility of scholarships for young chemists in Zürich. In principle, Prof. Prelog did not disagree but there were several obstacles:

state scholarships were granted exclusively to Swiss chemists; American scholarships were rare and granted only to those warranting the highest quality and prospects for the work progress; the growing danger of misuse of scholarships by students wishing to emigrate from unfree countries (this was considered by Prof. Prelog as a failure of his efforts to increase the scientific level in such countries).

In August 1962, Prof. F. Šorm was the main organizer of the 2nd International Symposium on the Chemistry of Natural Products in Prague, which was very successful and attended by many outstanding scientists in the field.<sup>24</sup> Prof. V. Prelog came with his wife and I took part in welcoming them. The topic of Prelog's lecture was »stereochemistry and reactivity of medium size ring compounds«. A Symposium Dinner was held at the Smetana Hall in the centre of Prague and there I parted with the Prelogs, who left Prague before the official end of the Symposium.

In 1966, Prof. Prelog celebrated his 60th birthday, which was mentioned in a short article.<sup>25</sup> Describing his qualities and achievements, I stressed the fact that he was not only a brilliant chemist but also a splendid man who was able to assist his co-workers and friends to solve their personal problems and unable to cause grief. On that occasion, Prof. Prelog was awarded the Hanuš medal by the Czech. Chemical Society.<sup>26</sup>

In October 1975, Prof. Prelog was awarded the Nobel prize,<sup>27</sup> the highest appraisal of his scientific achievements. I congratulated him and my colleagues in Prague published two articles<sup>15,28</sup> about this memorable event.

Since then and out of a number of encounters we have had, I would like to mention just one from 1978. Despite a signed petition in Zürich which the Czechoslovak government might not have liked, Prelog obtained a visa and arrived in Prague at the beginning of November. The next day, he was received with great ceremony in the main lecture hall of the Prague Institute of Chemical Technology, and then awarded the Emil Votoček Medal of the Institute. He then gave a lecture on natural and synthetic ionophores, notably boromycin. In the evening, the distinguished guests visited me at home and we had a wonderful time together. I had the opportunity to show Prof. Prelog my chemical library, including the *Beilsteins Handbuch* and numerous volumes of *Chemisches Zentralblatt* which had formerly been part of Dříza's library and probably used by Prof. Prelog every day some 50 years before. The next day, we went to Liblice where Prof. Prelog opened the Meeting on Stereochemistry, organized by the Czech. Chemical Society, with his lecture »Second thoughts about the specification of molecular chirality«. It was only during our next meeting that I heard about the shameful scene at the Prague Airport where the police delayed the flight in order to inspect very carefully Prelog's luggage. This was probably the reason why the Prelogs refused to accept any further invitation to Prague, even after 1989.

In 1986, Prof. Prelog celebrated his 80th birthday and I was happy to be able to attend the celebration, in June in Zagreb and then in September in Zürich. The jubilee was remembered by O. Červinka<sup>29</sup> and V. Herout<sup>30</sup> who again emphasized the importance of Prof. Prelog for Czech chemistry. Five years later, Prof. Prelog was visited in Zürich by a delegation from the Prague Institute of Chemical Technology which conferred on him the honorary doctor's degree of this Institute.<sup>31</sup>

Now, the moment has come for me to wish Prof. Vladimir Prelog good health and continued interest in the topics that have accompanied him throughout his life. At the end, I would like to say what my short stay in Prof. Prelog's laboratory in Zürich in 1947 and the following contacts meant for my life. They have influenced all my life. Whenever and wherever I met chemists in the world, and mentioned that I belong to the group of Prelog's students and friends, I was immediately one of them because one or more of them have been connected with E. T. H. or directly with Prof. Prelog. The doors opened which otherwise would have been closed. The acquaintance with Prof. Prelog was one of the chances that have definitely affected my life. I thank him.

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## SAŽETAK

### Praške godine Vladimira Preloga i moji kasniji kontakti s njim

*Miroslav Protiva*

Opisane su okolnosti u kojima je V. Prelog studirao i radio u Pragu, i neka zbivanja u kojima je sudjelovao, kao i autorova sjećanja na njegove brojne kontakte s Prelogom.

## A New Textual Analysis of the Prelog Erlkönig Legend; an Interdisciplinary Approach to Scientific History and Literary Criticism

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### Der Erlkönig<sup>1</sup>

Wer rast durch das Labor mit jüdischer Hast?<sup>2</sup>

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<sup>1</sup> Of the many versions of this legend, Goethe's may be the best known, thanks largely to the musical setting by Franz Schubert, but the present version has many merits and is of particular interest because of the light it sheds on scientific activity and personal relationships at the Organic Chemistry Laboratory (OCL) of the Swiss Federal Institute of Technology (ETH, Zürich) in the middle years of this century. The manuscript was uncovered (by E. H.) in late 1957 and the events described may be assumed to be fairly topical. Prelog, the central figure of the poem, is not, as many readers may assume, a mythical character but an actual person. As far as can be ascertained, he was born in Sarajevo in 1906, came to Zürich in adventurous circumstances during the Second World War, and was Professor of Organic Chemistry at the above mentioned Institute for many years. Similarly, many of the other personages mentioned can be clearly recognized as actual historic figures. However, the identity of the mysterious guest (der Gast) is still a matter of conjecture. As in most works of this nature, reality is strangely and inextricably mixed and interwoven with legend. The poem is known to have been read at the 70th birthday celebration of the late Professor Leopold Ružička (1887–1976), held in Zürich in September 1957. Various versions containing minor textual differences have been in circulation since then, but we regard the present text as the most authentic and urge other scholars to do likewise.

<sup>2</sup> Prelog was known to set a fast pace in his tours of the Organic Chemistry Laboratory and elsewhere; he always seemed to be in a hurry; but the significance of the adjective is unclear. Jüdisch? Although some people may have assumed Prelog was Jewish because he knew a lot of jokes and told them well, he was not more Jewish than any other son of a typical Croat family. Nominally of the Roman Catholic persuasion, he described himself as agnostic, although he often admitted to uncertainty on this point.

Es ist der Prelog mit einem Gast.  
 Die Mantelschösse<sup>3</sup> flattern im Wind,  
 Wenn er die vielen Ränke<sup>4</sup> nimmt:  
 Dies<sup>5</sup> sind die Labors, Sie können es sehn,  
 In denen all' meine Ausländer<sup>6</sup> stehn.  
 Von ihnen ist transannular<sup>7</sup> ein jeder.  
 Ja, Ja. Freund Cope,<sup>8</sup> der kam etwas später.  
 Dies ist ein Kolben in dem etwas simmert,  
 Was mich an die erste Geschichte erinnert  
 Vom Sir Robert<sup>9</sup> als er die Masern hatte;<sup>10</sup>  
 Oder noch eher, warten Sie mal,  
 An die Gallensteine der Frau Admiral,<sup>11</sup>

<sup>3</sup> Almost certainly a white »labcoat«. Each morning, on arriving at his office, Prelog changed into a labcoat even long after he had ceased to do any experimental work.

<sup>4</sup> Identifies the author of the poem as Swiss! In addition to the meaning in standard German (tricks, intrigues, ruses, *etc.*), in Swiss dialect the word has the additional meaning: curves, as along a path, or rapid changes of direction. It is noteworthy that the sense of chirality of the curves is not mentioned.

<sup>5</sup> A change from third to first person: Prelog is now speaking.

<sup>6</sup> At the time the events described here took place, Prelog was himself an »Ausländer«, *i.e.*, a resident of Switzerland without Swiss nationality. Indeed, Prelog counted many non-Swiss among his students and collaborators. In 1959, he acquired Swiss nationality.

<sup>7</sup> A reference to Prelog's interest in transannular reactions in medium rings.

<sup>8</sup> Arthur C. Cope (1909–1966), Professor of Chemistry at the Massachusetts Institute of Technology, who also studied transannular reactions at about the same time as Prelog.

<sup>9</sup> Doubtless Sir Robert Robinson (1886–1975), then recently retired from his position as Professor of Organic Chemistry at Oxford University. This is the Robinson who appears in some of the best known Prelog stories, notably the one described vividly by Prelog himself in a later account: 'When we once met at Zürich airport on the way to Israel to celebrate the 25th anniversary of the Weizmann Institute, the first words we exchanged were the following: Robinson: "Hello, Katchalsky. What are you doing here in Zürich?" I: "Excuse me, Sir Robert, I am only Prelog, and I live here." Robinson: "You know, Prelog, your and Ingold's configurational notation is all wrong." I: Sir Robert, it can't be wrong. It is just a convention. You either accept it or not." Robinson: "Well then, if it is not wrong, it is absolutely unnecessary."'

The Katchalsky in question is undoubtedly Ephraim Katchalsky-Katzir (1916–) of the Weizmann Institute, later President of the State of Israel. Many observers would deny that there was much resemblance between Prelog and Katchalsky, at any rate not enough to justify Robinson's misidentification. However, at a scientific congress that took place several years afterwards, one of us (J. D. D.) remembers Katchalsky being addressed by the hotel concierge: "Professor Prelog, I have a telegram for you."

<sup>10</sup> The story about Robinson's measles cannot be traced and remains a challenge for future scholarship.

<sup>11</sup> As a young man, Prelog served in the Royal Yugoslav Navy. His inability to distinguish instinctively and surely between right and left led to several minor mishaps when sailors under his command were ordered to march overboard. He was then assigned the less demanding task of analyzing gallstones. Whether, and to what extent, these actually emanated from the gall bladder of the admiral's wife is unknown. Perhaps the whole story is apocryphal.

Wo das Squalen,<sup>12</sup> na Sie wissen schon....  
 Übrigens das hier, das ist der Simon,<sup>13</sup>  
 Und in dieses Köbli, oder vielleicht hier draus,  
 Tut man etwas hinein, oder man nimmt es heraus.  
 Und dieses Rohr hier ist eine Kapillare  
 Vom Polarographen.<sup>14</sup> Und vor rund einem Jahre  
 Dachte der Dewar<sup>15</sup> ein Lift sei im Schacht;  
 Wir haben damals fast so gelacht,  
 Wie beim letzten New Yorker,<sup>16</sup> Sie wissen schon.  
 Und was hier heiss läuft ist der Sekretärin ihr Telefon.<sup>17</sup>  
 Hier unten trieben zwei muntre Gesellen  
 Die Feinmechanik und die der Wellen.<sup>18</sup>  
 Und hier Fräulein Gut,<sup>17</sup> die ich gerade nicht seh',  
 Wahrscheinlich raucht sie oder holt Wasser zum Tee.  
 Ist Ihr Sohn auch, so wie meiner brav?<sup>19</sup>  
 Dies ist der Kováts<sup>20</sup> plus Chromatograph,

<sup>12</sup> 2,6,10,15,19,23-hexamethyl-tetracos-2,6E,10E,14E,18E,22-hexaene, an isoprenoid compound found in large quantities in shark liver oil and to a lesser extent in many other natural oils, such as olive oil, wheat germ oil, rice bran oil; an intermediate in the biosynthesis of cholesterol and hence not recommended as a dietary supplement for people with a high cholesterol level. If a model of the molecule is folded in the right way, the resulting shape resembles that of a steroid.

<sup>13</sup> Wilhelm Simon (1929–1992), Professor for Instrumental Analysis at the ETH from 1965 until his untimely death. At the time of the events described here, he was still a young research assistant who merely happened to cross Prelog's path. It is characteristic, however, that Prelog recognized this young member of the laboratory and even knew his name. The instrument described so vividly in the following two lines was a robotic device for automatic pK measurement of a series of compounds, an early example of laboratory automation.

<sup>14</sup> The capillary was probably the only element of this instrument that Prelog was able to recognize and name with confidence.

<sup>15</sup> Probably not the Dewar of the Dewar flask (James Dewar, 1842–1923) but Michael Dewar (1919–), noted racing motorist and chemist, who is known to have visited the Zürich laboratories around the period of interest.

<sup>16</sup> The New Yorker Magazine, which at that time often contained amusing cartoons.

<sup>17</sup> Prelog, and almost everyone else at the time, used to refer to his secretary as Fräulein Gut, although she was no longer a young girl but a grown-up woman. The term Fräulein was then customarily employed to describe an unmarried woman of any age. Ten years later, she would have been addressed as Frau Gut. In any case, she was sometimes conspicuous by her absence from the office. During these absences the telephone would ring for long periods, as the automatic answering device had not yet been invented.

<sup>18</sup> Surely a reference to Hans H. Günthard (1916–) and Edgar Heilbronner (1921–), who divided their time between the construction of analytical instruments and the development of quantum mechanical theories. Note that the two colleagues are described here as »munter«, *i.e.* brisk, cheerful; this was not always the case.

<sup>19</sup> Jan Prelog (1949–), now Dozent for medieval Latin at the University of Munich.

<sup>20</sup> Ervin sz. Kováts (1927–), later Professor at the Lausanne campus of the ETH (EPUL). As a

Was sich oben dreht ist der Propeller,  
 Und diese Stoppeln sind der Gigel Keller.<sup>21</sup>  
 Natürlich muss ich noch schnell erzählen  
 Die Story vom Roberts und den Niagarafällen,<sup>22</sup>  
 Und die wo der Bartlett,<sup>23</sup> na Sie wissen schon!  
 Und die wo ein Mann mit Namen Kohn<sup>24</sup>.....

Den lieben Gast erfasst das Grausen,<sup>25</sup>  
 Am liebsten wär er wieder draussen.  
 Doch unerbittlich geht es weiter,  
 Oft instruktiv, doch meistens heiter.  
 Die Parabel vom Hasen unter den Schafen,<sup>26</sup>  
 Ob ächt Ziegler und Reppe bis Dezember gut schlafen?<sup>27</sup>  
 Die Walfischhoden in der Schüssel,<sup>28</sup>

---

young assistant he constructed an air-heated gas chromatograph for preparative purposes, of which the propeller was probably the only feature Prelog recognized (see footnote 14 for a similar comment concerning another instrument in use in the laboratory).

<sup>21</sup> Walter Keller-Schierlein (1922–), known affectionately as Gigel, was not only a pioneer in the extraction, purification and structure analysis of microbial metabolites with antibiotic activity but also an early proponent of what has come to be known as the Arafat-look, *i.e.*, a more or less constant 3–4 day growth of facial hair (Stoppel = bristle).

<sup>22</sup> Presumably J. D. Roberts (1918–), then Professor of Chemistry at the California Institute of Technology, Pasadena, CA, but the incident is not mentioned in Roberts's autobiography.

<sup>23</sup> The Bartlett is probably the Harvard one, Paul (1907–), but possibly Prelog is referring not to a person but to a book, Bartlett's Dictionary of Quotations. In any case, the text shows that Prelog was assuming that the guest knew whom (or what) he was talking about.

<sup>24</sup> Probably a misprint for Cahn, namely Robert S. Cahn (1899–1981), co-author of the well known Cahn-Ingold-Prelog (CIP) rules, referred to in footnote 9.

<sup>25</sup> Change from first to third person; the narrator continues the story.

<sup>26</sup> A rather long-winded story, possibly of Chinese origin, the moral of which had something to do with the need to focus one's attention on the important aspects of a problem. But what are the important aspects? On the one hand there is Weiskracker's maxim: »Nicht in der Einfachkeit, sondern in der Erkennung der Komplexität der Dinge – darin liegt die wahre Aufgabe der Naturwissenschaft«, in a letter to Lichtenberg, October 1777 (Opera Omnia, Wiesbaden, 1825), but on the other hand, »Les règles de la Nature sont toujours très simples. C'est le devoir du savant de presenter cette simplicité dans toute son effroyable complexité«, Jean-Louis Moron, *Science et Simplicité, Les Cahiers des Sciences*, Paris, 1904, p. 299. Prelog could never quite make up his mind on this point.

<sup>27</sup> A reference to the dreaded Swedish sickness (Svenska sjukdom, characterized by insomnia, inability to concentrate, general irritability), endemic among potential Nobel prize candidates in the early autumn. Indeed, Karl Ziegler (1898–1973) shared the Nobel prize for Chemistry in 1963 with Giulio Natta (1903–1979). Walter Reppe (1892–1969) may have been equally deserving, but, as Prelog himself liked to quote: »The race is not to the swift, nor the battle to the strong.« The line places the events described in the poem as occurring in the early autumn, as borne out a few lines later. Ob ächt (Swiss dialect) = whether.

<sup>28</sup> At a somewhat earlier period, research on male sex hormones had been one of the main ac-

Der Wunderrabbi von Pschemisl,<sup>29</sup>  
 Dehydrierungs-Reaktionen,<sup>30</sup>  
 Arigoni's Wunderbohnen,<sup>31</sup>  
 Hier ein Kolben, dort ein Sieb,<sup>32</sup>  
 Hier ein Lift (ausser Betrieb),<sup>33</sup>  
 Woodward's Whisky,<sup>34</sup> teure Weine,<sup>35</sup>  
 Moulin Rouge und Damenbeine,<sup>36</sup>  
 Gregorianik, Jazz Synkopen<sup>37</sup> –  
 Thomas Mann – Zwei Isotopen<sup>38</sup> –

tivities at OCL. Although this was on the wane by the time of the events described here, the reference to whale testicles indicates that it was still operative to some extent. Before the television era, the arrival of such objects must have attracted many spectators.

<sup>29</sup> Countless stories are attributed to this personality. It is impossible to identify the one that Prelog was referring to.

<sup>30</sup> Gas-phase dehydrogenation of cyclodecane yields azulene as well as naphthalene. This observation was the origin of Prelog's unpublished theory of why the sky is blue. Volatile terpenes produced by plants are dehydrogenated in the upper atmosphere to yield substituted azulenes. This proposal needs to be taken up again in connection with the ozone problem.

<sup>31</sup> Duilio Arigoni (1928–), then a young assistant, from 1962 Professor at Prelog's Institute. Arigoni's wonderful beans? The most likely explanation is that this refers to an Italian-Swiss version of the Jack and the Beanstalk fairytale, which appears to be widely spread among many folk cultures throughout the entire Northern hemisphere; examples are known as far apart as American Indian tribes and nomadic Lapp peoples. Indeed, the old Norse name for a bean, Quegonna, can easily be transformed by a series of consonant and vowel changes, to Arigoni.

<sup>32</sup> Self-explanatory.

<sup>33</sup> Due to an oversight in planning, the so-called Neubau (new building), where Prelog and his guest had reached, had only a single lift (elevator). It was somewhat erratic and frequently out of service.

<sup>34</sup> Woodward's whisky is a little known brand of Scotch malt whisky, under no circumstances to be confused with Dewar's whisky. The two do not mix well.

<sup>35</sup> It is surprising that Prelog, who has always tended to favour CocaCola<sup>®</sup>, should start talking about expensive wines. Maybe he was trying to impress the guest.

<sup>36</sup> The reader may well assume that Prelog is again trying to impress the guest with a reference to the Moulin Rouge girlie show in Paris and to the ladies legs that featured there so prominently (recall that this would still have had a rather risqué flavour). Indeed, our researches show that at the 1957 IUPAC Congress in Paris, shortly before the events described here, Prelog and some of his younger colleagues, together with their wives, took part in a Congress Social Program excursion to the Moulin Rouge and found themselves seated in the very front row, in a position where they were in almost direct confrontation with the whirling legs of the dancers, a quite unexpected and potentially embarrassing situation for the members of the party. At the close of the performance, Albert Eschenmoser (1925–) commented: "What a waste of ATP!", thus expressing for that time a remarkably farsighted concern for the world's energy resources. Prelog used to tell this story to anyone who would listen..

<sup>37</sup> An indication of the wide range of Prelog's musical appreciation.

<sup>38</sup> It appears that a manuscript entitled »Zwei Isotopen« by the great German author (1875–1955) was inadvertently sent to *Helvetica Chimica Acta* and forwarded for review to Prelog, who did not consider it suitable for publication in that journal. His review stated that the manuscript would benefit from extensive rewriting, that it contained much extraneous material, that the sentences were far too long, and, in general, that the text should be drastically shortened.

Anekdote – Doktorhut –  
 Massenspektrograph (kaputt) –  
 Vakuum – Treppe – Gänge – Witz<sup>39</sup> –  
 Manser<sup>40</sup> – Poldi<sup>41</sup> – Geistesblitz –  
 Seufzerbrücke<sup>42</sup> – erster Zehnter<sup>43</sup> –

<sup>39</sup> The themes here follow one another so rapidly that individual explanations become impractical.

<sup>40</sup> One of Prelog's best stories involved Werner Manser, who was in charge of the microanalytic laboratory and enjoyed a worldwide reputation. When K. Wiesner (1919–1986), who had worked in the OCL and grown to appreciate Manser's microanalytic skills, emigrated to Canada and became Professor of Chemistry at the University of New Brunswick, Fredericton, he periodically sent samples to Prelog, who passed them, under his own name, to Manser's laboratory. Occasionally, samples containing sulfur passed along this path, much to Manser's annoyance. Everyone knows that sulfur ruins the normal oxidation catalyst and that sulfur-containing samples must therefore be specifically marked as such and directed to special handling procedures. After experiencing Manser's complaints on such occasions, Prelog used to write to Wiesner (no FAX or E-mail in those times) with the very understandable request that sulfur-containing samples should be clearly marked, so that he could give Manser the necessary information. Sometimes it worked, sometimes not. One day, it is told, an angry Manser burst into Prelog's office. "My equipment is ruined because you again sent me a compound for analysis that contained sulfur! After so many years as professor of chemistry, you should know enough about the subject as not to send me sulfur-containing samples that are not marked as such! You should be ashamed of yourself." When Manser left, slamming the door behind him, Prelog sent a note to Wiesner, roughly as follows: "Dear Professor Wiesner, This is to inform you about Professor Prelog's tragic death. He was found this morning in his office with a glass tube through his heart. On questioning by the police, the Institute's microanalyst, Mr. Manser, confessed to the crime but claimed extenuating circumstances, as Prelog had submitted a sulfur-containing compound for microanalysis without special mention and had thereby caused his instrument to be ruined. The investigating authorities agreed that this was sufficient justification for Manser's misdeed."

This message was sent to Wiesner's home address and arrived when he was at the University. His wife, recognizing the Zürich postmark and knowing that Wiesner always looked forward eagerly to news from there, opened the letter and tried to make sense of it. All she really understood was that Prelog was dead, so she telephoned her husband at the University, where he was called out of his lecture, to give him the news. Wiesner was so shocked that he dismissed his class, sent his co-workers home, and declared the day as Day of Mourning for Prelog. When Prelog heard about this, he confessed that he was deeply moved by Wiesner's reaction. Whether this had any effect on subsequent samples sent for microanalysis is unknown.

<sup>41</sup> Poldi is Leopold Ružička (1887–1976), Prelog's famous predecessor as head of OCL. It is remarkable that he should make his appearance so late in the poem. One unanswered question is whether Prelog's tour of the laboratory took place before or after the transfer of power. According to the records, this transfer took place on October 1st, 1957, shortly after Ružička's 70th birthday. In our opinion, the cryptic words at the end of the immediately following line refer to October 1st, written in the European fashion as 1.10 *i.e.* »erster Zehnter«. Prelog would surely be talking to his guest about the great future he foresaw for himself rather than about his past achievements, about which he has always been characteristically modest.

<sup>42</sup> Not the famous Ponte dei Sospiri in Venice but the bridge connecting the »old« and the »new« buildings. Students coming from the old building to Prelog's office for examinations had to pass over this bridge, hence, perhaps, the name.

<sup>43</sup> See footnote 41 for a possible interpretation.

Nochmals Witz (bereits erwähnter),<sup>44</sup>  
 Zweimal rechtsum,<sup>45</sup> Höllenschuss,  
 Nochmals Witz und Rundgangschluss.<sup>46</sup>  
 Sie erreichen das Büro, mit Mühe und Not,  
 Pg<sup>47</sup> munter plaudernd, doch der Gast ist tot.<sup>48</sup>

*Acknowledgements* – J. D. D. thanks E. H., and E. H. thanks J. D. D., for helpful suggestions.

### SAŽETAK

#### **Nova tekstualna analiza legende o Erlkönigu posvećene Prof. V. Prelogu; interdisciplinarni pristup znanstvenoj povijesti i literarnom kriticizmu**

*Edgar Heilbronner i Jack D. Dunitz*

Analizirajući parodiju poznatoga Goetheova spjeva, posvećenu Prof. V. Prelogu već u jednoj ranijoj prilici, autori na specifičan način otkrivaju mnoge nove zanimljivosti iz njegova života i rada. U kontekstu te duhovite analize spominju se brojna imena znanstvenika s kojima je Prof. Prelog dugi niz godina surađivao ili održavao prijateljske odnose, što ovoj “tekstualnoj analizi” daje posebnu draž i već danas povijesno značenje.

<sup>44</sup> A skillful reference to Prelog’s habit of repeating the same joke (with slight variations).

<sup>45</sup> The end of the tour was approaching. Prelog’s office lay along a route from the »old« to the »new« building. On entering the latter over the Bridge of Sighs (see footnote 42), the two travelers would turn once right into the secretary’s office and then another right into Prelog’s office.

<sup>46</sup> The wording suggests that the tour not only ended at Prelog’s office but also started there.

<sup>47</sup> Pronounced: peh-geh (German) or pee-gee (American English). An obvious abbreviation for Prelog, much used by junior colleagues who wished to avoid such formal modes of address as: Herr Professor, Herr Laboratoriumsvorsteher, or even plain Herr Prelog, but did not feel intimate enough with our hero to address him as Vlado or Vladimir. Suggests that the unknown author of the poem may have been in this ambivalent relationship to Prelog.

<sup>48</sup> The available documents fail to record that any academic visitor to the ETH ever actually died during a tour of the laboratories, although several cases of extreme exhaustion, with symptoms resembling those of mountain sickness, have been reported.



## **The Year 1948–1949 in Prelog Laboratory at E.T.H., Zürich: a Reminiscence**

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After completing my work for a Ph. D. degree at the University of Liverpool in 1948, I wanted very much to spend a period of time in a laboratory in a German-speaking region of Europe. I thought of going to Zürich at the Eidgenössische Technische Hochschule known for its great tradition of excellence in organic chemistry. Professor Leopold Ružička was the Director at that time, but I wanted to work, in particular, with Professor Vladimir Prelog, who had joined the ETH from Zagreb some years earlier and whose work I had admired.

I arrived in Zürich one day in late summer of 1948. I left my luggage at the railway station, took my Ph. D. thesis with me and went looking for Professor Prelog. He had no idea then that an Indian student was about to approach him to plead for a little space in his laboratory. (No one from Liverpool had sent out any letter of introduction or recommendation on my behalf). When I met Professor Prelog, I found him so accessible that I immediately lost all fear. I requested that he might look at my Ph. D. thesis (this was on organic nitrogen compounds and alkaloids) and I would come back the next day to ask if he would accept me. Next day, Professor Prelog with his typically enthusiastic and encouraging smile said »yes« and at my excitement added that he was glad to see people happy. Looking back now over the years, I believe that spending a year at the ETH with Professor Prelog, is probably the wisest thing I ever did in my life.

It was my first and unique experience to work so closely under the guidance of a great scientist. One soon began to look forward to Professor Prelog's morning rounds in the labs and his stops at all the benches and conversations with the group members. In addition to the daily review of the progress of scientific work, one would feel enthused and encouraged. Indeed, there is so much that I could recount about those days with Professor Prelog, but I mention just a few things.

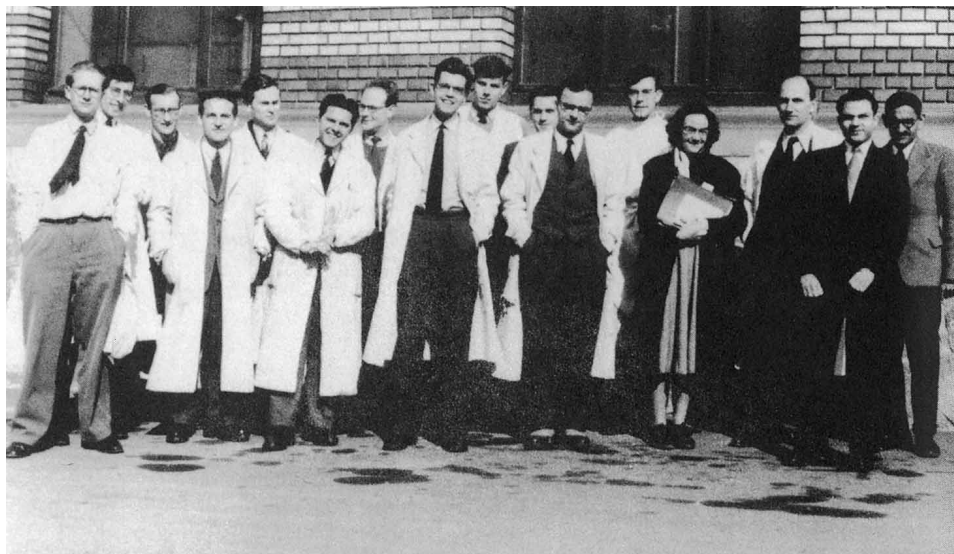


Figure 1. The Prelog Group (1948–1949). Photo April 1949. Left to right: W. I. Taylor, Peter Meister, Joseph Wursch, Mihovil Proštenik, Karahanian, Schubiger, Zimmerman, Hans Meier, Bruno Vaterlaus, Frick, Schneider, Haufliger, Margret Kobelt, Prof. V. Prelog, Fawzy, Khorana, (absent: George Kenner).

Firstly, I never at any time felt that I was being pushed. Quite the contrary, Professor Prelog's greetings in the morning always radiated cheerfulness, support and approval. During one period, my research was hitting a low and I had had a spate of bad elemental analyses on the compounds that I was trying to characterize as degradation products in my structural work on erythrina alkaloids. At that time, there was an analytical section within the organic chemistry department under Herr W. Manser that carried out all the elemental analyses (C, H & N and others) of all the students' compounds. Although we would send the samples to Herr Manser directly, the results always came back *via* the Professors who would look at them and then bring them to the individual students in the laboratories. One morning,

on his round, Professor Prelog came to my bench with a report of analyses in his hand and said »Dr. Khorana, another disastrous day... But you know, I tell myself – I cannot keep going down any more so I must go up.«



Figure 2. V. Prelog in his office at the Organisches Laboratorium ETH – July 1949.

Sometimes I would feel depressed by the thought that the other members in the group, especially my friend, George Kenner from Cambridge, England, knew so much more chemistry and science than I did. Once I bemoaned this fact to Professor Prelog. So spontaneously, he began to say »You know about knowing and knowledge – I think of it like coming into a big room – you come in somewhere and you go out somewhere.« Then he continued »Professor Ružička always asserted that he didn't know much chemistry – hadn't even learnt electronic theory of valency – but that he tried to do the most with what he knew.«



Figure 3. Professor Ružička congratulating Vlado Prelog on the latter's Nobel Prize in 1975. Professor Ružička's own Nobel Prize was in 1939.

All through the subsequent years, it has been my good fortune to have kept in contact with Professor Prelog. In 1966, at the national meeting of the Swiss Chemical Society in Solothurn, I was a guest speaker and Professor Prelog and Professor Duilio Arigoni were my hosts. In September 1976, celebrating Professor Prelog's 70th birthday at the ETH, I talked about »Total Synthesis of a Biologically Functional Gene«. It was a talk on genes, molecular genetics and molecular biology to an audience that consisted mostly of organic chemists. Evidently, Professor Prelog approved of my talk and added »You were focussed and didn't tell us anything you didn't have to«. As recently as November 1991, the Organic Chemistry Department at the ETH celebrated his 85th anniversary (Professor Prelog was very appropriately honored by the Institute on this occasion) and I was happy to be invited. Aside from these get-togethers, many times over the years I would include a stop in Zürich to see Professor Prelog whenever a speaking engagement took me to Europe. The last such occasion was July 4th of last year (1995).

In all the forty-eight years since I left his laboratory, I have never met a humanist-scientist greater than Professor Prelog. Vlado, on this great occasion, I offer, with affection and respect, my congratulations and wish you many, many more years of good health and productivity.

### SAŽETAK

#### **Godina 1948–1949 u Prelogovom laboratoriju na ETH, Zürich: sjećanje**

*H. Gobind Khorana*

Iznose se sjećanja na dolazak u Zürich, na prvi susret s Prof. V. Prelogom, te na poticajan pristup Prof. Preloga problemima svojih suradnika u svakodnevnomu znanstveno-istraživačkom radu.



## »Was schön ist, ist auch gut«

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A recollection of how one of the steps in an attempted synthesis of 1,6-dimethyl-cyclodecapentaene became a glassblower's nightmare.

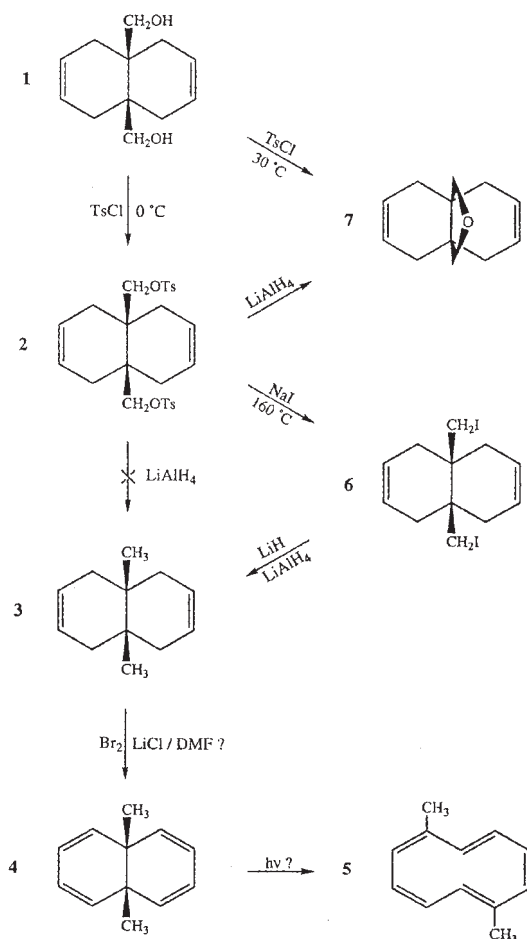
The year 1957 was not only the year when the first Sputnik was launched. For organic chemists the launching of the journal *Tetrahedron* by Sir Robert Robinson was more important. For Vladimir Prelog, who had prepared adamantane in a many-step synthesis when he was still in Zagreb,<sup>1</sup> the discovery by Paul Schleyer of a simple way to prepare adamantane by enthalpy-driven isomerization<sup>2</sup> may have had a stronger impact. Perhaps most important was the arrival at ETH of Jack Dunitz, who together with Prelog should lay the foundation for a deeper understanding of the conformations of medium-sized rings.<sup>3</sup> As for myself, 1957 was the year when I had the great privilege to work with Prelog.

The preceding year Prelog wrote a paper about »Bedeutung der Vielgliedrigen Ringverbindungen« wherein the cyclodecapentaene problem was discussed.<sup>4</sup> The project that was assigned to me was to synthesize 9,10-dimethyl-9,10-dihydronaphthalene, in the hope that irradiation would open the bridge to give some isomer of 1,6-dimethyl-cyclodecapentaene. The last among several attempts is presented in the Scheme by the planned sequence of steps **1**, **2**, **3**, **4** and **5**. The starting material **1** was readily synthesized, but the ditosylate **2** formed the cyclic ether **7** so easily that it could not be reduced to the hydrocarbon **3**. However, after conversion to the diiodide **6**, reduction to the hydrocarbon proceeded smoothly.

It was this trivial conversion of the ditosylate to the diiodide, using sodium iodide in acetone at 160 °C, that required the use of a sealed glass tube and gave us a problem. To seal such tubes we could rely on Prelog's services. Being an expert glass-blower, he seemed to enjoy sealing glass tubes when these were needed, considering it a welcome relaxation from of-

fine work. At the end of the job, while rotating the tube, keeping the hot glass in a »cool« flame, he used to express his satisfaction by saying: »Was schön ist, ist auch gut!«

And indeed our first experiment was a success; the tube survived, and the yield of crystalline diiodide was 56%. It was then decided to scale up the reaction, and more sodium iodide had to be fetched from the stock-room. The sealed glass tube was again declared »schön«, and »gut«, but when I opened the protective steel-tube after reaction, the glass-tube had been smashed to thousand pieces. This had never happened before to Prelog, and we could not find an explanation. The experiment was repeated once, then once more, each time with the same disastrous result.



Scheme

At this point the reader will no doubt ask a most reasonable question. Why did we not check the material from the stock-room? We had in fact a very good excuse for our lack of suspicion: After each experiment I carefully extracted the remains in the steel tube and could in fact isolate small amounts of the desired iodo-compound.

Eventually, I recalled that the sodium iodide that was used in the first experiment dissolved rapidly and completely in acetone, whereas the sample from the stock-room remained as a suspension. On heating, some iodide could well have been formed by reduction if the reagent contained iodine in an oxidized state. The sample was then quickly identified as sodium iodate. I further recalled having noted that Latin names for chemicals were used on the shelves in the stock-room. Clearly, the clerk had assumed that *iodicum* came closest to *iodide*, while in Latin it is in fact *iodatum* that corresponds to *iodide*, and *iodicum* corresponds to *iodate*.

When this became clear, Prelog rushed to the stock-room at such a speed that »die Mantelschösse flatterten im Wind«.<sup>5</sup> Left alone in the laboratory, I reflected the irony that this happened in a country which presents itself on coins and stamps by its Latin name!

About the last steps of the synthetic scheme there is little to report. My time ran out after having obtained the bicyclic diene **3** by hydride reduction. The prospect of dehydrogenation to the tetraene **4** seemed favourable since the byproduct **7** was dehydrogenated successfully to the corresponding tetraene by the procedure given.

Many years later S. Masamune attacked the cyclodecapentaene problem successfully.<sup>6</sup>

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## SAŽETAK

»Što je lijepo, također je i dobro«

*Johannes Dale*

Sjećanje kako je jedan od stupnjeva u studiranoj sintezi 1,6-dimetilciklodekapaentaena postao noćna mora staklopuhača.



## How to be right and wrong

Rita H. Cornforth and John W. Cornforth\*

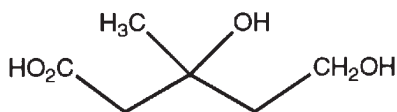
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An historical article, recounting the circumstances in which the authors and Professor V. Prelog published their one collaborative paper.<sup>9</sup> In that paper, the question of the absolute configurations of the naturally occurring terpene alcohols (+)- and (-)-linalool was finally cleared up.

In 1956, chemists from the Merck Sharpe and Dohme research laboratory at Rahway, New Jersey, reported that a growth factor for *Lactobacilli*, identified as 3,5-dihydroxy-3-methylpentanoic acid (**1**), was a precursor of cholesterol in rat liver slices.<sup>1</sup> This experiment used a synthetic isochiral<sup>2</sup> preparation of mevalonic acid, as the factor was called, labelled with radioactive carbon. So high was the incorporation of radioactivity into cholesterol that if only one enantiomer of the precursor was participating (as was likely), then mevalonic acid was being used by this tissue for cholesterol synthesis and for no other significant pathway, and it was not appreciably degraded to any product that could then be involved in general metabolism.

This beautiful discovery was a liberating event for all of us who were working on steroid and terpenoid biosynthesis. It was soon confirmed that

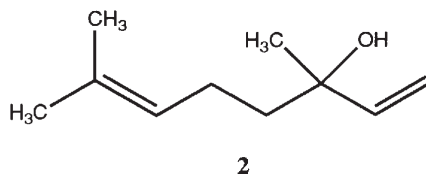


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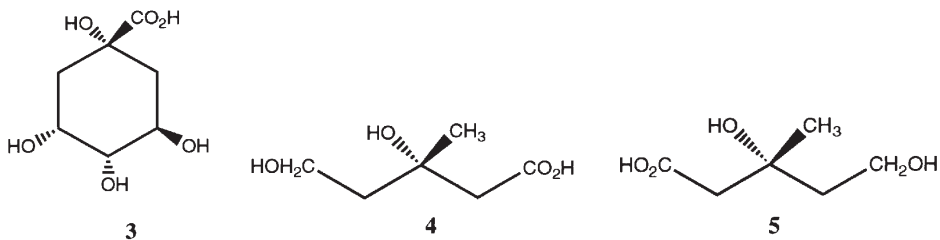
\* Author to whom correspondence should be addressed.

only one enantiomer of mevalonic acid was used in biosynthesis and that the »unnatural« enantiomer was inert metabolically. This was fortunate, since it meant that the labelled versions used for experiments on biosynthesis could be isochiral and therefore easier for chemists to make. Resolution of the synthetic acid to yield the monochiral<sup>2</sup> »natural« enantiomer was achieved with difficulty,<sup>3</sup> and enzymic resolution is also possible, but an easy synthesis of the natural enantiomer was desirable; and in 1958 we looked for a monochiral starting-point for such a synthesis.

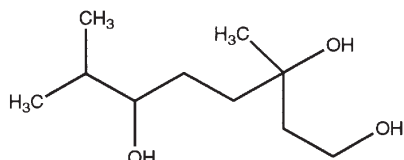


The attractions of linalool (2) were soon obvious. Commercial supplies of this alcohol are often anisochiral,<sup>2</sup> but an essentially monochiral supply of the (-) form, from Ho-leaf oil, was available. Linalool already contains, at its sole stereogenic centre, two of the groups at the sole stereogenic centre of mevalonic acid. The chemical task was to transform one of the two remaining groups into a carboxymethyl group and the other into a  $\beta$ -hydroxyethyl group. To design a synthesis leading directly to »natural« mevalonic acid from (-)-linalool, the absolute configurations of starting-point and destination must be known. Happily, there was recent information on both of them.

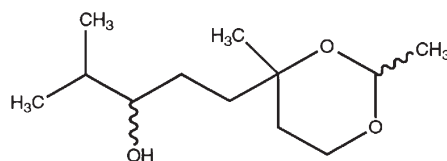
Eberle and Arigoni executed an ingenious and chemically unambiguous transformation of quinic acid (3) to »unnatural« mevalonic acid (4) and concluded that the »natural« acid has the  $3R$  configuration (5). Although this work was not published until 1960<sup>4</sup> we knew about it. Prelog and Watanabe<sup>5</sup> assigned in 1957 an absolute configuration to linalool on the basis of a synthesis of anisochiral tetrahydrolinalool. It appeared from these two assignments that if we started from (-)-linalool and transformed its vinyl group to a  $\beta$ -hydroxyethyl group, we would obtain »natural«  $3R$ -mevalonic acid by oxidative degradation of the other carbon chain to carboxymethyl.



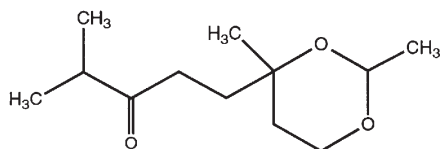
The work went well. The first and obvious step, a Brown hydroboration of both double bonds in (-)-linalool, yielded a triol (**6**) easily convertible by acid-catalysed condensation with acetaldehyde into a cyclic acetal (**7**). The unprotected hydroxyl group was oxidized to a ketone (**8**) with chromic acid in pyridine (this reagent, still known as the Cornforth reagent, was a modification of Sarett's original chromium trioxide – pyridine reagent<sup>6</sup> but is quicker and safer to make); the ketone by Claisen condensation with methyl formate – sodium methoxide gave a hydroxymethylene-ketone (**9**) which was immediately oxidized with sodium periodate. The acetal group was lost in the work-up and mevalonic acid was isolated as its low-melting crystalline lactone in 21% overall yield from linalool. The novel cleavage of a ketomethylene group to two carboxyl groups was smooth and convenient and we would still use it if another occasion arose. So, monochiral mevalonic acid was now readily available in quantity – but it was the »unnatural« 3*S*-mevalonic acid (**4**)! Instead of reaching our destination we had arrived in Looking-glass Land. One of the two assignments of absolute configuration was wrong.



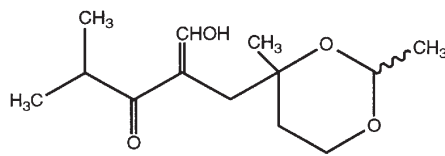
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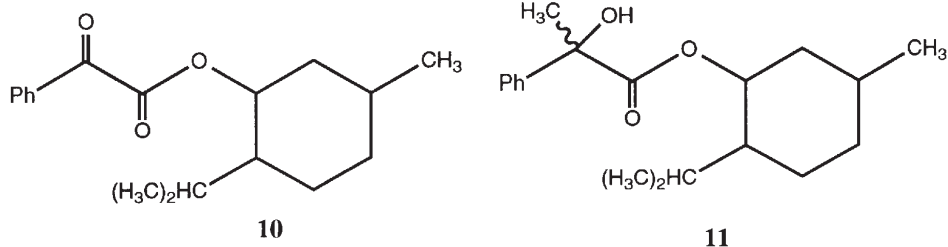


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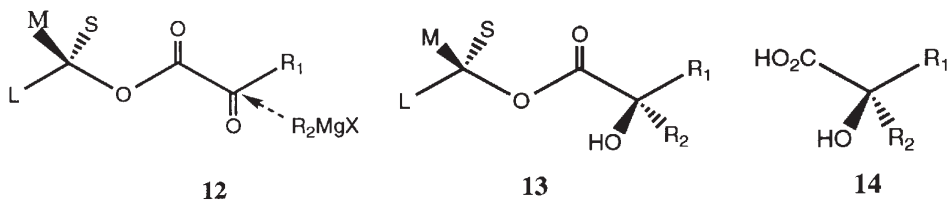


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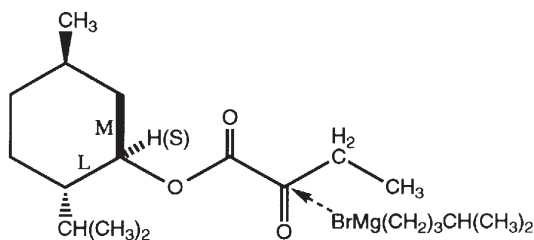
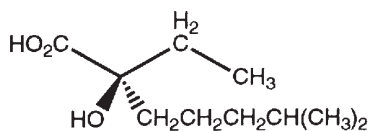
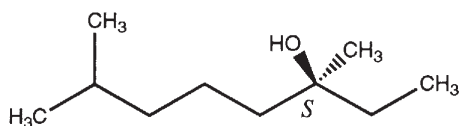
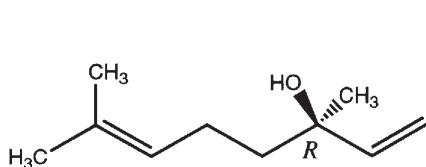
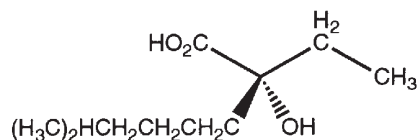
We could not doubt the validity of the chemical correlation between quinic acid and mevalonic acid, so we set out to check the absolute configuration assigned to quinic acid. In those days, there was no atlas of stereochemistry in which one could turn up correlations, along with references to the experiments, in a few minutes. The pathway uniting quinic acid, by way of glucose, to Bijvoet's tartaric acid (the source at that time of all absolute configurations) was long, tortuous and overgrown. It took one of us a week to force a way through. But in the end we had no reasonable doubt that the assignment was correct. It was time to look at the evidence for linalool.

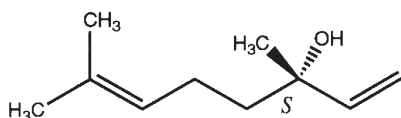


Vlado Prelog's rule for correlating absolute configurations has its origin in one of the earliest successful asymmetric syntheses. In 1904, McKenzie<sup>7</sup> showed that when the monochiral ester (**10**) of (-)-menthol with benzoylformic acid was treated with the then novel methylmagnesium iodide, alkaline hydrolysis of the product (**11**) gave an anisochiral<sup>2</sup>  $\alpha$ -methylmandelic acid with an enantiomeric excess (e.e.) around 25%. Half a century later, and armed with more extensive knowledge of absolute and relative configurations, Vlado was able to seek, test and establish a rule connecting the chirality of the esterifying alcohol (menthol, in the original case) with the chirality of the major component of the anisochiral product formed. He summarized this magnificent work in a review.<sup>8</sup> The key factor that determines the direction of attack of the Grignard reagent on the ketone carbonyl of the  $\alpha$ -oxo ester, he concluded, is the relative »size« (that is, the demand for space) of the three groups immediately attached to the oxygenated carbon of the alcohol. If these three groups are ranked as large (L), small (S), and medium (M), then an  $\alpha$ -oxo ester of general formula (**12**) will be attacked by a Grignard reagent to yield an  $\alpha$ -hydroxy ester that is predominantly (**13**), and this will give on saponification an acid that has an excess of the enantiomer (**14**). Vlado strengthened his rule by many experiments using different alcohols, different  $\alpha$ -oxo acids, and different Grignard reagents. He used it to determine the absolute configuration of a number of alcohols: experimentally, the spatial arrangement of the L, M and S groups was deduced simply from the sign of optical rotation of the derived  $\alpha$ -hydroxy acid.

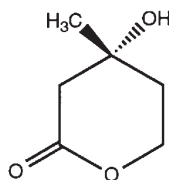


Linalool is an alcohol, but its absolute configuration was not deduced in this way. The difference in »size« between the three relevant groups was too small for a secure assignment to be made, and preparation of the requisite ester from an allylic tertiary alcohol could have been difficult. Instead (–)-menthol, an alcohol of known chirality and good LMS differentiation, was used, by reaction of its 2-oxobutyrate ester (**15**) with isohexylmagnesium bromide, to construct an anisochiral hydroxy acid (**16**) of predictable stereochemical preference, and this was converted chemically into tetrahydrolinalool (**17**) without disturbance of chirality, by conversion of its carboxyl group into methyl. This tetrahydrolinalool was laevorotatory, as was a specimen obtained by catalytic hydrogenation of (–)-linalool. The e.e. of the asymmetric synthesis was quite good, about 40%. According to rule, the preferred configurations are as shown in the figures and (–)-linalool (**18**) is *R*. But this was not the conclusion drawn in the paper. Somehow or other, perhaps because this was an unusual application of the rule, the preferred configuration of the hydroxy acid came out as the enantiomer (**19**). Thereafter, the logic was faultless and led to the mistaken conclusion that (–)-linalool was *S*.

**15****16****17****18****19**



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Our very last expectation, in starting this inquiry, was having to tell a very great chemist that he had misapplied his own rule. What to do? In the event, we wrote to Vlado telling him the facts and offering to assist in putting the matter right. The ability to admit error is a good measure of a person's quality and Vlado did not disappoint us. He made no attempt to blame his collaborator and he pointed out other observations that should have warned him that there might be something anomalous in this assignment. His paper was wrong, but his rule was right, and he was happy to see it vindicated. He wrote the correction and we published it together: our only paper with Vlado.<sup>9</sup> And since then, we have been fast friends.

We might have modified our conversion of (-)-linalool to obtain natural mevalonic acid, converting its vinyl group into carboxymethyl and its isohexenyl group into  $\beta$ -hydroxyethyl instead of the other way round. That would have been a longer and harder way, but a kind fate made it unnecessary. We visited Australia, our native country, in 1960 and one of us mentioned our synthesis in a lecture. Afterwards, one of the audience arose and asked if we would like to have some (+)-linalool. We were soon in joyful possession of two litres of the essential oil of a tea-tree, *Melaleuca quinquenervia*, from which we distilled monochiral *S* (+)-linalool (**20**) and converted it into *3R* mevalonolactone (**21**). One of us visited the Merck laboratories at Rahway on the way back to England and had the pleasure of presenting Dr. Karl Folkers with a 1 g specimen of the recrystallized, monochiral lactone, more than he had ever seen before. At home, George Popják tested the two mevalonates with mevalonate kinase and verified that the *3R* specimen was completely phosphorylated, whereas the *3S* sample showed less than 1% reaction. We published the work as a full paper.<sup>10</sup> We had solved a problem, cleared up an inconsistency, and gained a friend. May we enjoy many more years of his friendship.

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(In this proposed nomenclature »monochiral« means »consisting of one enantiomer«; »isochiral« means »containing both enantiomers in equal amounts«; and

- »anisochiral« means »containing both enantiomers in unequal amounts«. These words replace »homochiral«, »racemic«, and »scalemic« respectively).
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## SAŽETAK

### Kako biti u pravu i krivu

*Rita H. Cornforth i John W. Cornforth*

Povijesni članak koji opisuje uvjete u kojima su autori i profesor V. Prelog publicirali njihov jedini zajednički rad.<sup>9</sup> U tom je radu definitivno razjašnjeno pitanje apsolutne konfiguracije prirodnih terpenskih alkohola (+)- i (-)-linalola.



## Reminiscences of My Association with Professor Vladimir Prelog

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I carried out my PhD work from September 1960 until May 1, 1963 at the Eidgenössische Technische Hochschule under the guidance of Professor V. Prelog. The topology of the active sites of the oxidoreductase from *Curvularia falcata* and from horse liver alcohol dehydrogenase was explored using a number of enantiomerically pure decalones and cyclohexanones as substrates. Our results prompted Professor Prelog to develop the so-called diamond lattice theory.

After I finished my diploma as »Ingenieur-Chemiker ETH« in the summer 1960 I had to make a difficult decision. I had the choice between two or three prominent professors of ETH Zürich who offered me research problems for a PhD work. I have known my academic teachers from lecture or laboratory courses as well as from examinations. When I decided to start PhD work with Professor Prelog I did not know how fortunate my step was. The main reason for my preference to work with Professor Prelog was my interest in biochemical aspects of organic chemistry. I heard from a fellow-student that the so-called »microbiology subgroup« of the Prelog research team was involved with an interesting mixture of stereo- and biochemistry. Former members of the microbiology subgroup investigated the reduction of a number of decalones by whole cells of *Curvularia falcata*. These reductions were strictly stereospecific and obeyed the rules formulated by Prelog (Figure 1).

The idea behind this work was to use molecules of rigid and well-defined shape for »palpating« the active site of the corresponding enzymes. At that time no crystal structure of an enzyme was known, so this was the only possibility to learn about the shape of the active sites. When I started my PhD

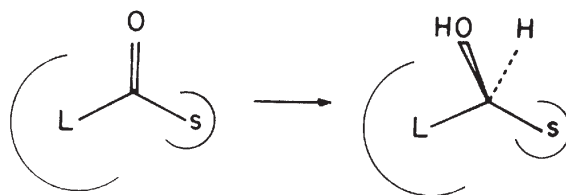


Figure 1. Prelog rule for the stereospecific reduction of ketons by the oxidoreductase from *Curvularia falcata* (L = large group, s = small group).

work in September 1960 two postdoctoral fellows Werner Acklin and Hans Dutler just started to isolate the oxidoreductase from *Curvularia falcata* responsible for the stereospecific reductions *in vivo*. They established a minimum of equipment for the enzyme isolation but for centrifuges we had to run over to the biochemistry department located in the next building. After a short introduction I was charged with the enzyme isolation. 35 years ago it was not a routine job. There were no filled chromatography columns available nor sophisticated ion exchange and molecular sieve materials. We had to prepare our hydroxylapatite and fill our columns with it ourselves. Instead of using computers we had to be present for hours and hours in the cold room and watch our columns while applying onto them our protein solution. Later Professor Prelog bought for us an LKB fraction collector, the first one at ETH and the only one for a long time. For the chromatography of organic compounds in the normal laboratories we had to change the fractions by hand. I remember that I supervised an undergraduate student separating decalones on a large chromatography column. The separation lasted all night and we slept alternately on an old fur-lined cloak which we used otherwise in the cold room.

Professor Prelog, leading a large research group, had no time to do experiments at the bench himself. But once when I had to make sodium amalgam he asked me to prepare in the hood a larger mortar and a pestle as well as one or two kilos of mercury and some sodium under petrol.

Then he came in a white lab coat – he wore this all day even in the office or giving lecture courses – and asked me to cut clean pieces of the sodium and throw them with a pincette into the mortar where the mercury was placed. He stirred the mixture with the pestle vigorously unimpressed by the spectacular fireworks. He said the mixing must be very fast in order to bring as much sodium into the amalgam as possible before it solidifies. I used this amalgam to prepare 1-deuteroglucose by reducing gluconolactone in deuterium oxide. Then I wanted to crystallize the syrupy material from methanol but had no success. After a few days of cooling it in the fridge or in an ice bath I felt quite desperate and told Professor Prelog about my

problem. He advised me to warm the glucose solution on a water bath to about 50 °C. This was just the opposite of what I practised in my laboratory courses but nevertheless I did what he told me. And suddenly – to my surprise – the whole solution crystallized!

After two years of hard work I succeeded to isolate the oxidoreductase from *Curvularia falcata* and also prepared a number of enantiomerically pure decalones. By the use of stereospecifically deuterated NADPH I had also shown that the enzyme transferred deuterium specifically from the B(Si)-side of the reduced coenzyme to the substrate.

My kinetic measurements with a great number of decalone derivatives confirmed and brought former *in vivo* results to a quantitative basis. Then I found a literature reference about the reduction of cyclohexanone by horse liver alcohol dehydrogenase. This prompted me to try my decalones with this commercially available enzyme and presented my results at the weekly meeting of the microbiology subgroup in Professor Prelog's office. This was just before Christmas 1962. PG (this was his nick-name when he was absent) listened to me and talked about a »Maria-Theresia-Orden« which used to be an award for officers of the K & K monarchy, who carried out a risky endeavour which was without or against the order of their commanders. If they succeeded they were awarded, if not they were executed! After the Christmas holiday (PG used to spend it by skiing in Arosa) at our first meeting, he presented the so-called »diamond lattice theory«. This was an ingenious combination of the stereochemical and kinetic results with his former experiences with adamantane. Underlying this theory is the idea that the decalone or decalol derivatives can be put together to a diamond lattice. Good substrates of an enzyme occupy only allowed positions at the lattice, whereas poor or no substrates occupy at least one forbidden position. Thus each enzyme has a characteristic cut of the diamond lattice which can be accommodated at its active site. This is illustrated in Figures 2–4. The cuts of the diamond lattice characteristic for the oxidoreductase from *Curvularia falcata* and for alcoholdehydrogenase from horse liver are depicted in Figures 3 and 4, respectively.

After my PhD examination in 1963 I have never lost contact with Professor Prelog and visited him whenever I went to Zürich. In 1972 I settled down in Karlsruhe where I have been teaching biochemistry ever since. Of course I was delighted when in 1975 he shared the Nobel Prize with another friend John (Kappa) W. Cornforth for their contribution to stereochemistry including the stereospecificity of enzymic reactions.

A few years ago when I visited PG in his ETH office he invited me to have lunch with him at the professor's mensa. Before I left he told me whenever I come to Zürich I am his guest for lunch. He kept that in spite of my menace that I travel to Zürich every day to exploit his generosity (I wonder whether he did the same if I lived much closer to Zürich). Unfortunately, I

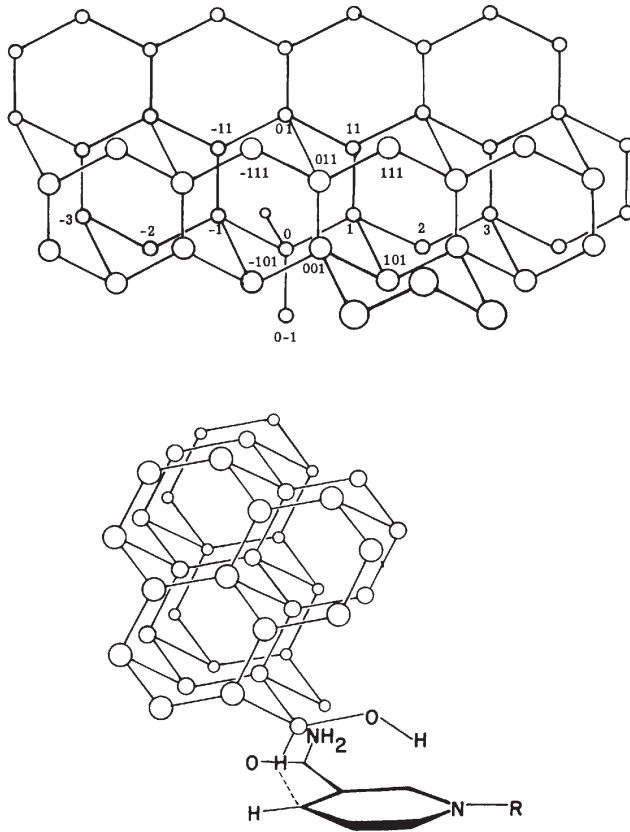


Figure 2. Illustration of the »diamond lattice« theory. Here the alcohol products, showing a numbering system for the positions (above) and the positioning with respect to the nicotinamide ring of NAD.

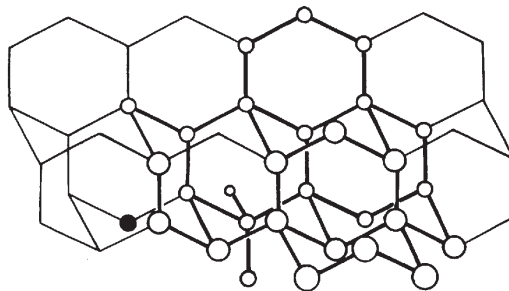


Figure 3. Cut from the diamond lattice characteristic for *Curvularia falcata* oxidoreductase. The filled circle indicates the forbidden position.

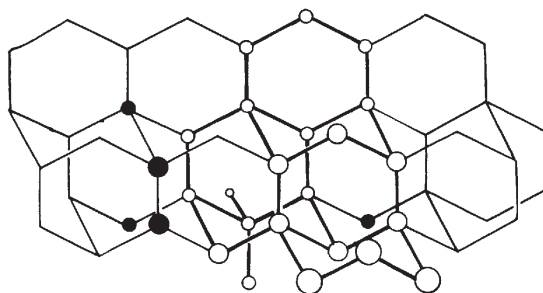


Figure 4. Cut from the diamond lattice characteristic for horse liver alcohol dehydrogenase. The filled circle indicate forbidden positions.

cannot sustain my menace, but I visit him once or twice a year and enjoy talking with him or rather listening to him. He kept his humour and loves to tell stories and anecdotes as ever.

Dear Vlado, I hope to be able to visit you and enjoy your hospitality for many more years. Congratulations to your 90th birthday!

## SAŽETAK

### Sjećanja na moje druženje s profesorom Vladimirom Prelogom

*János Rétey*

Svoju sam disertaciju radio od rujna 1960. do 1. svibnja 1963. na Eidgenössische Technische Hochschule pod vodstvom profesora Vladimira Preloga. Primjenom mnogih enantiomerno čistih derivata dekalona i cikloheksanona u njoj je istražena topologija aktivnih mjesta oksidoreduktaze iz *Culvularia falcata* i alkohol-dehidrogenaze konjske jetre. Naši rezultati naveli su Preloga da postavi tzv. teoriju dijamantne rešetke.



## International Collaboration in Science

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It was in spring 1994 when, for the first time, I had a chance to get in closer personal contact with Professor Vladimir Prelog. Naturally, I highly respected him as a scientist and teacher ever since my attendance, as a student, of his unforgettable, inspiring lectures at ETH Zürich in the early fifties. I admire his unique combination of intuition, logic, knowledge, wit, kindness, and extraordinary vitality. And it is a great pleasure to meet him occasionally in the corridor or at the photocopier which is located directly in front of my office. I hope for many more occasions in the future to experience his friendliness, his advice, and his positive, benevolent outlook.

It was in spring 1994 when I brought myself to ask Professor Vladimir Prelog for coauthoring a private letter to the Swiss government, finally signed by five Swiss Nobel laureates, in the context of the projected Swiss participation in the 4th Framework Program of the European Union. We were sceptical, not regarding the indispensable international research collaboration in general, but regarding the diversion of precious Swiss research resources towards Brussels, being afraid that the benefit/cost ratio could be significantly reduced when large amounts were distributed on an European scale by an oversized and not particularly efficient bureaucracy.

I remember that Professor Prelog was initially quite reluctant to consider cosigning the letter. He recognized the dangers of misinterpretation in case the letter would inadvertently be publicized. And indeed, what he foresaw did happen later, in spite of the private nature of the letter. But Professor Prelog overcame his initial scruples and he signed, convinced that the spirit behind the letter was in favour of research quality, true research collaboration, and, after all, to the advantage of Switzerland and Europe.

The letter received an unexpected publicity and its authors were decried as short-sighted scientists trapped in their ivory tower, being afraid of losing their own research support, and being afraid of international competition. We were shocked by the gross public misinterpretation of our true intents. We were also shocked by the poor knowledge on the side of the press and the public how science functions and how much scientists struggle to be as honest and objective as possible even if the truth turns out to be to their personal disadvantage.

In the following, I would like to collect a few personal thoughts on collaboration in science. Perhaps, the models of international scientific collaboration may also be taken as metaphors for collaboration in other domains of human activities. Perhaps, it may even favourably influence the peaceful co-existence of nations and of population groups.

Human activities unfold in the span between individual aspirations and needs, and the responsibility towards and the respect for society. Society is providing the framework and the security necessary for the individual development. The individuals, on the other hand, carry responsibility and specific obligations in the societal framework. The mutual dependency between community and individuals applies to all forms of coexistence within families, communities, and states, but equally well to the science community. Without an equilibrium of giving and taking, very rapidly the one-sided profits, misinterpreted as liberty, will turn into a deadly handicap, deadly for an organization and, in the end, deadly also for the individual. Liberty means to deliberately do what needs to be done. Or to quote John Donne (1572–1631): »Who ever gives, takes liberty«.

Giving and taking is of fundamental importance in science. We all contribute to and take advantage of the miraculous scientific edifice. Translated into scientific language, giving and taking means writing and reading, or teaching and learning. Whenever we had a great idea or made a discovery, we want to communicate it, and whenever a great discovery has been made, we want to hear about it to become inspired for further progress. Most of what we use in our scientific work, we have borrowed from somewhere. Wilson Mizner (1876–1933) claimed: »If you steal from one authors, it's plagiarism; if you steal from many, it's research«. Proper quotations are of major importance for the proper functioning of the scientific circus.

Although science is deadly serious, it has also a playful component, like in a question and answer game. There is indeed a competitive sportive component involved: Who will be the first, and who will win the great prize? Competition is essential as a stimulus for extraordinary achievements. Nevertheless, cooperation and collaboration are even more important than competition. A very special form of collaboration is teaching. It is intimately connected to research and dissemination of research results. Teaching means to encourage and support unselfishly (young) scientists on their path

towards new breakthroughs and achievements. »The touchstone of knowledge is the ability to teach« (Auctoritates Aristotelis). Indeed, for a true scientist it is more important that his students get proper recognition rather than himself.

Only in very rare circumstances can a scientist perform his research independently. He is usually dependent on other scientists with specialization and knowledge in other fields. Most of the progress takes place along the interfaces, in interdisciplinary fields, and the collaboration between scientists in different disciplines is indispensable for true innovations. My own field, nuclear magnetic resonance (NMR), is an excellent example in this respect. It exploits a purely physical method that has found application in as divergent fields as solid state physics, mineralogy, organic chemistry, molecular biology, physiology, and clinical medicine. Much of the technology is common but the goals can be very different. Without extensive interdisciplinary collaboration, progress in applied NMR is impossible.

Science is by its innermost nature international. There are no national truths, and scientific results apply irrespective of the religious belief of the scientists. Although there may be no absolute ever lasting truths, even in science, scientists attempt as honestly as ever possible to search for the most universal formulation of facts and laws of nature. Scientists are usually capable of finding a common denominator in their discourses irrespective of their personal background. Science attempts to be objective by stripping the apparent facts from their irrelevant casual attributes and concentrating on the common features.

This implies immediately that science does not know any national borders. It had an international dimension ever since it became active, and in former centuries rather more international exchange of scientists took place than today in central Europe. The high standards of modern science in Switzerland would be unthinkable without the creative contributions of many highly gifted »foreign« scientists, such as Erasmus von Rotterdam, the family Bernoulli, Wolfgang Pauli, Leopold Ružička, and Vladimir Prelog.

The international collaboration in science and technology functions admirably well. Many scientific disciplines are very thinly dispersed across all possible countries and continents. Collaboration means in these cases invariably international cooperation. Especially today with the new powerful means of communication, such as E-mail, Fax, and Internet, it matters only little how far collaborators are geographically separated, although even the most sophisticated electronic device can not compete in its efficiency of communication with an occasional discussion under four eyes.

By far the most efficient way of international collaboration is by exchange of coworkers. Most of the close and fruitful collaborations among scientists result from extended stays in laboratories in a different country or continent. Personal contacts are invaluable. They are the foundation of a

common understanding. Travelling is therefore of greatest importance in science, especially more extended stays with an active involvement in a partner's laboratory.

International collaboration requires substantial financial means. It is thus highly welcome that politicians are actively supporting the international exchange of scientists. Many politicians have recognized that the erection of firm borders between nations leads sooner or later into disasters. Free transfer of people and goods is essential for keeping the system near equilibrium and to avoid the build-up of dangerous tensions. Supporting the international exchange of science and scientists is a good start towards open borders and open minds between different countries.

The question remains in which form the support of international scientific exchange and collaboration should optimally take place. In the past and present framework program of the European Union, the preferred organizational form is topical research programs which the different participating countries of the EU have agreed upon. The major activities are in the fields of information and communication technology, industrial technology, environment, bioscience and biotechnology, energy, transport, and socioeconomy. Within the postulated topical constraints, research groups are then sought which can convince the experts that they may significantly contribute to the selected topic. This is the typical »top-down approach« that is favoured by science politicians as it gives them an opportunity for exerting their influence by directing research into directions which they consider as being essential.

There is hardly much dispute among scientists whether the top-down or the bottom-up approach is more efficient in the longer run. So far, top science has invariably been initiated, in a bottom-up approach, by the scientists themselves, normally by a few highly creative and inventive individuals who served as bell-wether, not so much by words, but by deeds and achievements. To have the foresight for picking the proper fields that are important for human society and topics in which breakthroughs are still possible is enormously demanding and difficult. Only those actively struggling at the forefront, can, in lucky moments, foresee the future. For science politicians, it is very difficult, if not impossible, to pick the proper fields which are relevant on an international level and where a sufficient number of creative ideas are floating around.

Science lives not only from extremely hard work but also from lucky surprises. »The essence of science: ask an impertinent question, and you are on the way to a pertinent answer« (Jacob Bronowski, 1908–1974). The science support system requires a sufficiently flexible and liberal mode of operation which allows also support of creative outsiders with brilliant ideas that do not conform to the politically initiated programs. Open-ended research programs without topical constraints are needed within which collaborative

research initiatives are judged exclusively based on their originality and creative content in view of their benefit for the future of mankind. All-too-often, scientists who are forced into projects by monetary decoy-birds lose some of their scientific honesty, lower their standards, and produce activity without much relevant results. This should be avoided under all circumstances.

It is extraordinarily difficult to plan scientific research. The scientist learns from his mistakes and failures. »It is a good morning exercise for a research scientist to discard a pet hypothesis every day before breakfast. It keeps him young« (Konrad Lorenz, 1903–1989). The approaches have to be modified on the fly, and often also the goals change in the course of a research project.

There are organizational forms which favour a flexible bottom-up approach in the context of international cooperation. I would like to mention in particular COST (Cooperation in Science and Technology) and EUREKA. In the case of the COST actions, it is expected that the primary initiative for a research project arises entirely from creative scientists and engineers. In EUREKA, in addition, a close collaboration with industrial companies is required. Little money is involved in these two research network programs, and the financing is based almost entirely on local resources. Much less misuse is possible in such frameworks than in programs where financial resources lure hungry but not necessarily creative scientists to participate.

In the attempts to strengthen the European unity, care has also to be taken that not new artificial barriers are erected at the borders of the EU, disfavoured the contacts to the remainder of the world. This could do more harm to the European science than it would help in the longer run. Borders in general are a horror to free science. COST and EUREKA are open also to scientists from some countries outside of the European Union and help to bridge unnecessary barriers.

International topical research programs are certainly justified whenever an urgent public need arises for the solution of a grave problem with an international dimension. Examples are the environmental problems which do not stop at the national borders, or the energy problem whose solution determines upon the fate of mankind in the next few centuries. In these areas, international topical programs are welcome. However, particularly in the two mentioned cases, a restriction to central Europe does not make much sense. Research efforts with this kind of world-wide impact and urgency must be organized on a world-wide basis.

This kind of thoughts forms the background for the infamous letter to the Swiss government. It expressed concern regarding a science support system that could exert not only positive influences on the already existing network of fruitful international collaborations and may rather favour busy international officiousness.

I am sure that Professor Vladimir Prelog supports some of the basic thoughts expressed in this article. However, he would surely have formulated them in a more tolerant and benevolent manner, reflecting his wisdom acquired in a rich life and his uncounted fruitful interactions with people of all kinds and of all nations. I am sure that he would express his sincere hope that the ease of international collaboration in science could become a metaphor for the interaction among nations and human races. I am sure that the tragic events in his former home country are heart-rending for him. I am sure that even the highly deplorable past would not let him to condemn one or the other side, but that he would just express his sincere plea that everybody contributes as much as is in his power to change the situation to the better as fast as is possible. Let us hope that science contributes its share, and let's work ourselves towards this goal.

#### **SAŽETAK**

#### **Međunarodna suradnja u znanosti**

*Richard R. Ernst*

Razmišljanja o prirodi znanstvenog rada i edukacije u znanosti autor posvećuje Prof. V. Prelogu, analizirajući njegove stavove o suštinskoj i formalnoj internacionalizaciji znanosti, posebno unutar Europske zajednice. Potaknut tim stavovima, autor iznosi svoja zapažanja o stanju današnjem prirodnih znanosti i njihovu odnosu prema osnovnim moralnim i društvenim načelima zapadne civilizacije od antičkih vremena do danas.

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## CONTENTS

Foreword	. . . Miljenko Dumić, Vitomir Šunjić, and Nenad Trinajstić	I
<i>Greetings</i>		
Greetings	. . . Barry Sharpless, Derek H. R. Barton, Marc and Sylvestre Julia, Michael F. Lynch, and Tadeus Reichstein	V–IX
Prelog Vignette	. . . Donald J. Cram	X
<i>Reminiscences</i>		
Prelog's Zagreb School of Organic Chemistry (1935–1945)	. . . Rativoj Seiwerth	379–397
Vladimir Prelog's Prague Years and My Later Contacts with Him	. . . Miroslav Protiva	399–408
A New Textual Analysis of the Prelog Erbkönig Legend; an Interdisciplinary Approach to Scientific History and Literary Criticism	. . . Edgar Heilbronner and Jack D. Dunitz	409–415
The Year 1948–1949 in Prelog Laboratory at E.T.H., Zürich: a Reminiscence	. . . H. Gobind Khorana	417–421
»Was schön ist, ist auch gut«	. . . Johannes Dale	423–425
How to be right and wrong	. . . Rita H. Cornforth and John W. Cornforth	427–433
Reminiscences of My Association with Professor Vladimir Prelog	. . . János Rétey	435–439
International Collaboration in Science	. . . Richard R. Ernst	441–446
<i>Scientific Papers</i>		
Bowl Shaped Cavitands Dimerize and Complex Certain Organic Guests in Organic Solvents which Themselves are Poor Guests	. . . Christoph von dem Bussche-Hünnefeld, Roger C. Helgeson, Dirk Bühring, Carolyn B. Knobler, and Donald J. Cram	447–458
Reduction of Ketones with $\text{LiAlH}_4$ Complexes of $\alpha, \alpha, \alpha', \alpha'$ -Tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs). A Combination of Enantioselective Reduction and Clathrate Formation with a Discussion of LAH Reagents Bearing $C_2$ -Symmetrical Ligands	. . . Dieter Seebach, Albert K. Beck, Robert Dahinden, Matthias Hoffmann, and Florian N. M. Kühnle	459–484
A Commentary on the Topological Chirality and Achirality of Molecules	. . . Kurt Mislow	485–511

Enantioselective Protonation of Ketene Bis(trimethylsilyl) Acetals Derived from $\alpha$ -Aryl- $\alpha$ -haloacetic Acids Using LBA . . . Kazuaki Ishihara, Shingo Nakamura, and Hisashi Yamamoto	513–517
Louis Pasteur and Modern Industrial Stereochemistry . . . Ernest L. Eliel	519–533
Chemie von $\alpha$ -Aminonitrilen. XVII. Oligo(nukleodipeptamidinium)-Salze . . . Peter Lohse, Berndt Oberhauser, Barbara Oberhauser-Hofbauer, Gerhard Baschang, und Albert Eschenmoser	535–562
Reactivity of Some Tertiary Chlorides with Methoxy and Olefinic Neighboring Group . . . Stanko Borčić, Olga Kronja, Krešimir Humski, and Sandra Miletić	563–568
Synthesis of Cyclo-bis-intercaland Receptor Molecules with Phenanthridinium Units . . . Predrag Čudić, Mladen Žinić, Vinko Škarić, Rudolf Kiralj, Biserka Kojić-Prodić, Jean-Pierre Vigneron, and Jean-Marie Lehn	569–611
A Perspective of Aldose Reductase Inhibitors and Diabetic Complications . . . Dušan Dvornik	613–630
Chemistry of 1,3-Dioxepins. X. Regio and Stereocontrolled Syntheses of Antihyperglycemic <i>N</i> -Sulfonyl-1a,2,6,6a-tetrahydro-1 <i>H</i> ,4 <i>H</i> -[1,3]-dioxepino[5,6- <i>b</i> ]azirines via Isomeric <i>cis</i> - and <i>trans</i> -Sulfonamidodioxepanols . . . Darko Filić, Mladen Vinković, Blanka Jamnický, and Miljenko Dumić	631–641
A Study of Enantioselective Reduction of <i>para</i> -Substituted 2-Methyl-cinnamaldehydes by Baker's Yeast . . . Vitomir Šunjić, Maja Majerić, and Zdenko Hameršak	643–660
Synthetic Approach to New Monocyclic $\beta$ -Lactam Synthons . . . Zorica Mandić and Miće Kovačević	661–667
Transformation of a Racemic Mixture by a Chiral Reagent or Catalyst to Give Regioisomeric Products . . . Henri B. Kagan	669–680
Deceptively Simple NMR Spectra of Contiguously $^{13}\text{C}$ -enriched Compounds . . . Alex D. Bain, Eckardt Wolf, Donald W. Hughes, and Ian D. Spenser	681–688
Self-aggregation of $\alpha,\omega$ -Alkanediols into Two and Three Dimensional Crystallites at the Air-Water Interface. Relevance to Ice Nucleation . . . Ronit Popovitz-Biro, Ron Edgar, Jaroslaw Majewski, Sidney Cohen, Lev Margulis, Kristian Kjaer, Jens Als-Nielsen, Leslie Leiserowitz, and Meir Lahav	689–708
From Biomimetic Ion Carriers to Helical Structures . . . Abraham Shanzer and Jacqueline Libman	709–729
Bacterial Carbohydrate Antigens: From Primary Structure to Non-covalent Interactions . . . Jasna Peter-Katalinić	731–739
Announcements and Advertisements	C5–C7

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