Remembering Heinrich Wieland (1877–1957) Portrait of an Organic Chemist and Founder of Modern Biochemistry

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Lives of great men all remind us
We can make our lives sublime,
And, departing, leave behind us
Footprints on the sands of time.

LONGFELLOW

I. INTRODUCTION: THE KING'S REMEMBRANCER

The king's "remembrancer" used to be his debt collector. Thus the remembrances presented in this belated retrospective try to pay back a lifelong debt that not only the disciple owes to his teacher but also the present generation owes to the preceding one.

August Wilhelm von Hofmann (1818–1892), Emil Fischer (1852–1919), and Richard Willstätter (1872–1942), Wieland's famous predecessors, all felt the need to record their own lives in literate autobiographies. Wieland preferred to extol the merits of others rather than to reflect on himself.[1] When his friends Hans Fischer (1881–1945) and Otto Hönigschmid (1878–1945) ended their lives at the end of the war, he commented, "We want to try and rise to the level and width of their deeds and to honor their personalities by rendering thanks for the abundance which they bestowed on us while they were still alive."[2] Wieland's words will guide us in our endeavor to link his living legacy with his personality and character that challenged the hubris of the "millenial empire," das tausendjährige Reich, as the twelve infamous years between 1933 and 1945 were then touted.

To the present generation the past may often appear like a foreign country with strange rules and customs. It is the chronicler's task to find connections and build bridges that link our present with past events and persons. Memories, provided they are precise and well documented and if they do not shun the shadows, salvage lost riches and show that progress is rooted firmly in the past.

II. MASTER AND DISCIPLE

"Der Schiller und der Hegel, der Uhland und der Hauff, Die sind bei uns die Regel, die fallen gar nicht auf."	Hegel's truths and Schiller's odes, Uhland poems, Hauff's episodes, These are Swabia's common modes.

This was one of the ditties that we heard Wieland humming in one of his relaxed moments when he was busy scratching with a glass rod in a test tube, a favorite of his activities that sometimes produced crystals, at other times only glass splinters. We were then (1938) just four privileged members of Wieland's Private Laboratory and proud to be close to the grand master. So spontaneously we substituted Wieland for Uhland in the ditty's *da capo*, happening in our minds. Wieland seemed to guess our thoughts because he admonished us not to forget greater Swabians and chemists, such as Albertus Magnus (1193–1280), Theophrastus von Hohenheim (Paracelsus) (1493–1541) or Robert Mayer (1814–1878) from Heilbronn, who first did his thesis on santonin before he discovered the universal law of conservation of energy.[3] Half a century later the chronicler regrets his failure to record each day the many discussions, banters, and exchanges that accompanied the hours of common research with Wieland in the privacy of his personal laboratory.

III. WIELAND'S ANCESTORS

According to Ernst Kretschmer,[4] most of the geniuses from Swabia go back to protestant clergy. Among Wieland's forefathers we find vicars, deacons, parsons, and even prelates, while the spouses come from families of tailors, blacksmiths, innkeepers, and "leeches," i.e., barbers who practiced leechcraft or elementary medicine. In 1935 when Aryan descent became *a conditio sine qua non* for civil servants, Wieland joked when he lectured on steel-making:

> At all times this has been such an art that still today we know the names of classical forgers. When I remind you of Wieland the swordsmith, there can be no longer any doubt about my Aryan descent."[5]

IV. WIELAND'S LECTURES

Wieland's great introductory lecture into inorganic *and* organic chemistry at the University of Munich in the thirties was larded with demonstrations and became a sought-after happening for chemical and medical students alike. This was quite different in 1904 when Wieland, after his "habilitation" at the University of Munich, started on his first lectures, which were described by his "first" student[6] Hans Stenzl (1880–1980),[7] who later discovered butazolidine (phenylbutazone):

> Wielands first lectures suffered from a peculiarly cumbersome diction and the ambition to finish without crashing, even the syntactically most audacious clause. There were hardly any listeners, so that often I was commanded into the auditorium at 11:15 AM to report on the number of hearers present. The lecturer and his listener (entered the room through two separate doors and Wieland started with "Mein Herr (Gentleman)!" which was amended to "Meine Dame (Lady)!" when the only female student of the Institute entered.[8]

However, practice leads to perfection, as we learn from the characterization of his later lectures through his distinguished disciple Franz Gottwalt Fischer[9]:

> As a lecturer Wieland made a powerful impression. His presentation was lucid and simple, often enlivened by anecdotes and humor. The listener was challenged to think and reflect and was fully aware that a great scholar was trying to impart his vast knowledge on a rapt audience. The personal contact with his students was completely relaxed, often in a humorous or jocular vein. He formed and informed them by his example of critical logic, a sense for realism and his unhurried temperate reasoning, which was not the expression of convenient tolerance. In his formative years Wieland impressed the discerning listener by an obvious inner struggle of spontaneous impulses that had to be elevated by a stronger will to the level of clear insight and absolute justice.[10]

The big lecture started at 9:00 in the morning. The price of a seat was the arrival ten minutes ahead of time. The auditorium, destroyed in World War II, had been erected by Willstätter in 1920 as an annex to the Chemical Institute, referred to as the Willstätter Building even after 1933 (see Plate 1). The huge blackboard was maneuvered up and down by turning a brass rod extending over its entire width. The table for the experiments had the enormous length of eight meters and had been equipped with the latest sophisticated contraptions under Willstätter. Some of the most effective demonstrations, for good reason, were saved for the end of the lecture. Thus the calorific Thermit process was built up on an expansive sandbox, while in the lecture for organic chemistry the explosive power of nitroglycerine—Wieland spoke of it only as glyceryl trinitrate—was convincingly demonstrated by letting it drop from a separatory funnel on an initially red-hot steel plate that was allowed to cool down. At the outset, the drops of the explosive hit the plate with innocuous decrepitation which, however, soon built up in a diabolic crescendo to ear-shattering explosions. In the first case the enormous heat, and in the second the intolerable thunderclaps forced the frightened students away from the inferno which Wieland wisely had avoided by taking his leave in advance with a presageful smile.

When phosphorus came up as a topic in the main lecture (it was the year 1935), Wieland mentioned the high phosphorus content in the lipids of the brain, and then continued with relaxed innocence, "These days Germany has become a country lacking in phosphorus." It was a moment before this message sank in, but was then greeted by thunderous trampling of feet, the academic way of applause. At that time not many professors had the audacity

Plate 1. In 1920 Willstätter had this auditorium erected in the famous Willstätter Annex, which was destroyed in 1944. Here Wieland practiced the art of lectures laced with subtle political jokes.

to express their critical attitude toward the Nazi government in jokes that were politically interpretable.[11] The pharmacologist Walter Straub, Wieland's friend from the time in Freiburg and the teacher of Wieland's brother Hermann (1885–1929), practiced this art of political funambulism in his famous lecture dealing with arsenic.[12]

V. PRINCIPIIS OBSTA (RESIST AT THE BEGINNING)

The fate of science under dictatorships and extreme ideologies, the situation of camp followers, opportunists, adversaries, and of those who fled into "inner emigration" has become a lively topic for historians and sociologists after World War II, in part in order to clarify the role of the German Universities after 1933. From the very beginning Wieland, in his profound aversion to the Third Reich, decided upon a quiet and clever modality of opposition in which he tried to avoid an open break with his superiors. The Nobel prize imparted some protection for this strategy as it also protected his friend and colleague Adolf Windaus (1876–1959), when in 1934 he was requested by the physicist Johannes Stark (1874–1957, Nobel Prize 1919)[13] to add his signature to a loyalty manifesto for Hitler on the occasion of his "election" to be Reichs-President. Windaus replied to Stark in an open telegram: "I do not lend my signature to manifestoes for Hitler!"[14]

Windaus went even further. In 1935 in a memorandum to the then-Minister of Education Rust, he expressed his desire to resign in a letter that Wieland also could have written:

> I feel, I am too old to change the views of ethics with which I have been brought up. Since I find it impossible to do research under the present circumstances [SA storm troopers were on the rampage in his Institute] I consider it as appropriate to resign and to free my position for a successor who is able to understand better the present developments and the present generation.[15]

Windaus persevered on his famous chair in Goettingen up to his retirement in 1944, because the authorities in Berlin surrendered. From the outset Wieland was determined not to give up his research, but he also had to respond to a less drastic summons in 1934. Under the title "Chemists to the Front," he published his response, which clearly shows his great concern about the health of education and the scientific progeny:

> It is absolutely mandatory that our Universities accept and train only candidates who are gifted and talented for their discipline and that such students are motivated to greater achievements by shielding them from external distractions and molestation. Nothing could be more calamitous than to undermine the well tried and approved system of scientific training of our young chemists, who should not be bothered with so-called "practical missions." Industry, the recipient of most of our young Ph.D.s, needs scientists with a broad outlook acquired in the laboratory by handling divers materials in extensive experimentation. Whoever calls a broad and general education his own, is capable of meeting the challenge of special problems in technology and industry.
>
> The experience of the past hundred years has taught us that the excellence of our chemical progeny is a direct function of the level of competency of our academic teaching staff. The long line of respected German chemists can be traced back to the Laboratory of Justus von Liebig. The prosperity and excellence of our chemical industry rests on its close connection with the scientific community and on the fact that the chairs for chemistry at our Universities are occupied ex-

clusively by an elite of teachers and researchers. When in the future only men of impeccable judgment and responsibility make the decisions, then, and only then, will German chemistry be strong enough to shoulder the great burden for the reconstruction of our country.[16]

Wieland succeeded in maintaining the outstanding preeminence, coupled with decency and integrity, throughout the grievous twelve years. In this way his Laboratory in Munich became, it is true, not a recess for resistance, but an oasis of decency. When Hemingway defines *Courage* as *steadfastness under exterior pressure,* Wieland proved it over the years. With some delay, his native city Pforzheim bestowed honorary citizenship on their famous son and named both a street and a school in his honor to exhort future generations to do likewise.

When the Nazis seized power, the fascist salute became mandatory, i.e., professors had to raise or suspend their right arm. Wieland referred to both events as "Aufhebung der Rechte" or "suspension of Rights," *clearly* the antithesis of The Bill of Rights. With Wieland, this act of enforced obedience degenerated into a rudimentary jerky movement, *obviously* a repudiative gesture, as if he were repelling a pestering insect. An anecdote may serve here as illustration: When a colleague visited Wieland in his office, a laboratory assistant entered with "Heil Hitler!" Wieland apologized: "Please, do not take offense; the young man just arrived yesterday. In a few days he will have learned how to greet correctly."[17] Robert Jungk, in his book *Brighter Than a Thousand Suns*[18] describes the situation at the University of Goettingen in 1933 by singling out the young pharmacologist Otto Krayer (1899–1982)[19] for his unparalleled audacity, when he wrote a letter to the all-powerful Minister of Education for Prussia, Stuckart, in which he explained why he felt unable to accept the chair of pharmacology at Düsseldorf from which the Jewish incumbent Philipp Ellinger had just been removed:

. . . the primary reason for my reluctance is that I feel the exclusion of Jewish scientists to be an injustice, the necessity of which I cannot understand, since it has been justified by reasons that lie outside the domain of science.

This feeling of injustice is an ethical phenomenon. It is innate to the structure of my personality, and not something imposed from the outside. Under these circumstances, assuming such a position as the one in Düsseldorf would impose a great mental burden on me—a burden that would make it difficult to take up my duties as a teacher with joy and a sense of dedication, without which I cannot teach properly.

I place a high value on the role of university teacher, and I myself would want the privilege of engaging in this activity to be given only to men who, apart from their research capabilities, also have special human qualities. Had I not expressed to you the misgivings that made me hesitate to accept your offer immediately, I would have compromised one of these essential human qualities, that of honesty.

It seems to me, therefore, that the argument that in the interests of the task at hand I must defer my personal misgivings, is an empty one. I would not place even a lesser task in the hands of someone who cannot remain true to himself. Moreover, it is clear to me how great is the responsibility that you have to carry—a responsibility that gives you the right to expect honesty.

The work to which I have heretofore dedicated all my strength, with the goal of applying my scientific knowledge and research expertise to effective university teaching, means so much to me that I could not compromise it with the least bit of dishonesty.

I therefore prefer to forego this appointment, though it is suited to my inclinations and capabilities, rather than having to betray my convictions; or that by remaining silent I would encourage an opinion about me that does not correspond with the facts. [Translation by Avram Goldstein]

Krayer was not protected by a Nobel prize, so he was summarily dismissed and instructed that all German Universities henceforth were "off limits" for him.

In 1937 Krayer joined the faculty of Harvard Medical School as Associate Professor of pharmacology and two years later succeeded Reid Hunt (1870–1948) as Head of the department until his retirement in 1966. As a member of the Committee to Help German University Scientists, he visited Wieland in Starnberg in 1948 and supplied Wieland with new hope and cigars.

This gradation of resistance allows us to observe the connection of *actio* and *reactio* in a totalitarian state and to appreciate the wisdom of Wieland's resolution, which he expressed as follows: "Already in 1933 I intended to follow a strategy of resistance that could be carried right to the end."[20]

VI. PFORZHEIM AND ITS GENIUS LOCI

When the Trade School I, Gewerbeschule I, in Pforzheim was named in honor of Wieland in May 1984,[21] his son Theodor delivered the dedicatory address by expatiating on the great tradition of Pforzheim, the city of the medieval humanist Johannes Reuchlin (1455–1522) and of the Wieland dynasty, beginning with his grandfather Theodor Wieland (1846–1928),[22] who opened a gold and silver refinery in 1871. Son of a parson, he completed his training as apothecary in Stuttgart in 1868 and his thesis in chemistry in Tuebingen in 1869 under Adolf Strecker, who in 1848 had discovered cholic acid. His thesis was interrupted by a call to arms in the Franco-Prussian War of 1870–1871. A letter which the grenadier Theodor Wieland wrote to Professor Strecker anticipates some of the whimsical style that also characterizes that of his son Heinrich:

> In the introduction to my thesis I elaborated on a view by Erlenmeyer and Darmstaedter regarding the constitution of ethylene oxychloride or epichlorohydrine which leads to the etiology of the related sulpho acids. Not that I have read these treatises, but their putative contents emerged from my memory and the records I kept of your lectures, so there may be some dubiety about their correctness. All these deficiencies are ground enough not to submit my dissertation to the honored Faculty. May I, therefore, petition you, most honored Herr Professor, to add your share in order to clothe and feed my paltry and penurious mental child and hang a necklace of ducats around his neck, i.e., supply the poor waif with references so that his progenitor's indigence may no longer be too visible. I pray you to exculpate the temerity of my supplication and be convinced of the guileless gratitude of your most humble disciple
>
> Theodor Wieland

Le style c'est l'homme characterizes not only father Theodor but also scion Heinrich, whose style brought forth blossoms in our "bible," the *Laboratory Manual for the Organic Chemist* by Gattermann and Wieland,[23] in which he discussed the working chemist's unwelcome by-products: the sticky gums and viscous goos, at times unfortunately principal products "whose origin and properties have mostly remained unexplored and which have attracted the interest of classical organic chemistry only in the sense of unreserved disapprobation." The chronicler well remembered these words when in the course of his thesis work the Master of crystallization inspected a non-crystalline fraction with the dry comment, "Aha, ein schönes Oel!" ["Well, well, a beauteous oil!"]

It was November 1971 when the Stuttgart newspaper reported on the restoration of the hundred-year-old Wieland refinery from the ruins of World War II.[24] The festive oration was delivered by Ulrich Wieland, Heinrich Wieland's nephew and heir to the family enterprise. He completed his dissertation[25] with his uncle in 1937 together with Feodor Lynen, the future son-in-law and Nobel Laureate. Their common thesis dealt with the poisonous principles of the death cap, *Amanita phalloides*, a topic that was bequeathed from father to son Theodor who, after the destruction of the Munich Institute, resumed and completed this investigation in almost four decades of intensive work.[26] Here ends a phrase mark over an important motif to which the chronicler added his modest contribution.[27]

VII. THE DIMITRI MENDELEYEEV CENTENNIAL (1934)

On June 7, 1934 Wieland submitted the following petition to the Bavarian Ministry of Education:

> As a corresponding member of the Russian Academy of Science I have received an invitation to participate in an international Congress honoring the Centennial of the birth of D. Mendeleyeev on September 10, 1934. On this occasion I would like to get acquainted somewhat with conditions in the Soviet Union. I may assume that my visit to Russia will not be thwarted by reservations of a political nature. Foreign currency will not be needed, since, starting at the German border, I will be a guest of Russian Academy.

One year earlier Wieland had to battle the bureaucracy, because, starting in June 1933, the government of the State of Bavaria had informed all Civil Servants that trips abroad would no longer be possible. Wieland submitted his comments:

> I may be permitted to remark that it is not in the interest of German science and its worldwide communications and acknowledgment, when their delegates are prohibited from traveling abroad and from communicating directly with their foreign colleagues, an activity which I consider indispensable for the continued esteem for German science by the international community.

The response from the German Ministry of Science, Education and Indoctrination of the People arrived on July 23, 1934:

> The Foreign Office does not object to the Lecture Trip of Professor Wieland and his visit to Leningrad. The Foreign Office, at this time, will also inform the Secret State Police [Gestapo] of Prof. Wieland's trip.

Thus this unique journey became reality. In Leningrad, Wieland met distinguished colleagues, such as F. Paneth from Königsberg, W. Biltz from Hannover, Walter and Ida Noddak, The Svedberg from Stockholm, and especially Paul Walden (1863–1957), who in his scholarly autobiography left us a fascinating report of this splendid jubilee celebration[28]:

> Indeed they still knew how to celebrate great anniversaries, no less splendiferously than in czarist days. The Workers and Soldiers Council of Leningrad invited all participants to a grand banquet in the former czarist palace at Zarskoye Sselo; it lasted from 8 PM to the wee hours. The old palatial walls were warmed by the incandescent festivities. Etiquette was strictly observed. The abundance and diversity of viands and select potations was second to none. Knives, forks, and spoons were made of gold. The caviar had an especially subtle bouquet and its grains coalesced to an eminent harmony of taste, proving that Leningrad still remained Europe's noblest

caviar reservation. Plenary lectures were delivered by Frau Noddack, my colleague Paneth and by myself. I was pleased to meet again Mendeleyeev's widow, Anna Iwanowa Popowa. The temperamental painter and pianist of 23 years whom he had married in 1881, his second marriage, had become a gentle and frail lady who still showed lively interest in her surroundings and involved me in a long conversation in Russian.

Walden summed up his impressions in a sovereign and detached way, exactly as Wieland after his return did in his lecture:

My stay provided the stimulus to reflect on peaceful coexistence of East and West. This aim, in my opinion, can be reached by cultivating interest, tolerance and understanding for the Eastern concept and, at the same time, by developing and securing our own ideals of freedom and security.

There is, of course, the difference that Paul Walden published these views much later and Wieland presented them publicly in his lectures, a process which in the year 1934 involved a considerable risk. At another time Wieland characterized the Soviet Union and its system as "an experiment whose end has to be waited for."[29]

VIII. THE HARVARD UNIVERSITY TERCENTENARY (1936)

Wieland undertook his first voyage to America in 1931, when he received an invitation from Yale University to deliver the prestigious Silliman Lectures,[30] which he bravely rendered in English, a language which he, as a graduate of the humanistic Reuchlin gymnasium in Pforzheim, had never learned. In order not to interrupt his lectures and research, he started the 10-day ship passage at the beginning of the spring recess. This was in the days of the ephemeral Weimar Republic, when the Foreign Office warmly sponsored such international activities. Wieland, who never made a big fuss about himself and his actions, failed to report to German authorities in the United States and, through the President of the University, received a mild reprimand after the trip from the Foreign Minister.[31] He replied on June 20, 1931:

When, during the Spring recess of this year, I undertook a journey to and through the United States, I was anxious to limit all official obligations and interviews as much as possible. In the first place, I am no friend of such things and the extension of my social contacts beyond the circle of my friends and colleagues would have strained my schedule and physical resources There was also a problem of time: only 24 days were at my disposal in which to accommodate the long trip from New York to Los Angeles *via* Chicago and from there to San Francisco, Seattle, Vancouver and back through Canada to New York.

This all changed in 1933 when the Third Reich broke out, as Wieland's letter, dated June 30, 1933, amply demonstrates:

Subject: Foreign travel.
The prohibition of all foreign travel by the Government of Bavaria extending to all public servants prompts me to cancel my participation in several scientific Congresses taking place in Great Britain for which I have received invitations as early as 1932 and for which I had already sent in my acceptance, to be rescinded now. Thus, I was invited to present lectures at the International Cytological Congress in Cambridge on August 24 as well as the later Faraday Symposium in September. In addition, long before the travel restriction I had received an invitation from the University of Edinburgh to present the first Romanes Lecture by the end of October.

Whoever looks into these irrational restrictions, may come to an understanding of the frustrations that gripped all scientists struggling for permits to travel abroad. Wieland was one of them, when in 1935 he received an invitation from the President of Harvard University, James Bryant Conant (1893–1978) to attend the Harvard Tercentennial on September 1, 1936.[32] It took the bureaucracy in Berlin five months to come to a decision:

The Minister for Science,	Berlin W 8, Sept. 12, 1935.
Education and Public	Nr. V 44368
Instruction for Prussia	To the President of the Univ. of Munich
and Germany	

In reference to petition, dated July 13, 1935, File No. 35366, and with regard to my circular of June 22 of 1935 −Z III b 471 W M—I herewith give the authorization that Privy Councillor Professor Dr. Heinrich Wieland, Director of the Chemical Laboratory of the State of Bavaria in Munich may attend the Tercentenary of Harvard University and present a Lecture. The Foreign Office and the Registration Office for Scientific Congresses in Berlin N.W.7, Luisenstrasse 58/59 have been so informed.

By order signed Vahlen

In the same way, Hans Fischer, Nobel Laureate of 1930 and Chairman of the Department of Chemistry at the Polytechnical School, had received his travel permit. His was the famous laboratory in which James Conant had worked as a postdoc, reason enough for Fischer to follow his invitation. He attended and received, on this occasion, an honorary degree from Harvard University. Yet in the end Wieland, with a heavy heart, gave up the plan for a second visit to the United States because he felt the long voyage by ship would be too much of an interruption for his lectures and his research. When in the Fall of 1947 Robert B. Woodward introduced the chronicler to President Conant as a disciple of Wieland, Conant immediately remembered: "We missed this great man at our Tercentennial 11 years ago!" Again, a long phrase mark ("slur") comes to an end over a motif recognizable only to the insider.

IX. WORK, LEISURE, AND THE MUSES

Gottwalt Fischer, the knowledgeable disciple, recognized the two souls in his teacher's breast when he wrote[10]:

Only the strong personalities pass on their fire from one generation to the next. Faced with Wieland's monumental life work the biographer must not overlook the sacrifice which this output demanded, not only the renunciation of an easy life and all its comforts, but also giving up more concealed aims such as to bring all inner traits to harmony and realization.

These two souls in one breast are obvious in the two photographs (see Plates 2 and 3), one of the artistic 20-year-old student (1897), the other of the stern Director of a large Institute and winner of a Nobel prize (ca. 1930). A powerful will and a strict self-discipline gave his lifework its impact and diversity, an enormous persistence its finality. Wieland used several methods to guarantee the steady output of his work. Thus, after a bout with influenza in Freiburg he utilized the time of convalescence for unhurried experimentation in his private laboratory. His division head, Prof. Karl Freudenberg, dryly commented at that time: "The quickest recovery for him comes with leisurely practical work."

Plates 2 and 3. The comparison of the two portraits illustrates Gottwalt Fischer's characterization of "two souls in one breast."[10] The 20-year-old "forte-pianist" contrasts with the stern, accomplished Nobel Laureate. Professor Hsing Chi-Yi, Professor Emeritus at the University of Peking, student of Heinrich Wieland in the thirties, and collaborator with Theodor Wieland, comments in a letter of October 18, 1990: "The photographs of Herr Geheimrat are indeed most remarkable. Had you not told me the identity of the artist, I would not have been able to establish a connection between the two portraits. I believe the older portrait must be close to his sixteenth birthday (1967), when he gave me a copy with his signature which, however, I lost in the turbulence of the Cultural Revolution.

The arrival of spring in Munich was hailed on the ivy-clad garden terrace of his official mansion next to the laboratory. The libation was "Mai-Bowle," consisting of a mixture of woodruff-flavored champagne and Moselle wine, supported by Mrs. Wieland's "Käse-Stangen," prepared with cottage cheese. Later in the evening Mrs. Marianne (Mallie) Small, the wife of the American postdoc Lyndon Frederick Small (1897–1957) sat down at the grand piano and filled the night with the strains of Debussy. Somebody else followed with Beethoven, whereupon Wieland nodded to Mrs. Small with the comment, "Doesn't that sound better?" His love for classical music ended with Brahms, whom he liked to play with verve in his student days, so that in the neighborhood he soon acquired the reputation of a "forte-pianist." His disciple Hans Stenzl remembers the year 1904, when Master and student came closer by their common musical interests. "However, we never played together, because he surpassed me by far in the use of the pedal." There were regular evenings of chamber music in the expansive mansion going back to von Baeyer and Willstätter. At times Wieland became a participant in some piano trios. After his retirement music beautified and beatified his waning years. Shortly before his eightieth birthday he wrote on June 11, 1956:

My dear friend Witkop:
I am grateful to my destiny that in the year of the Mozart bicentennial it did not summon me to pay my debt of nature, otherwise I would not have been able to to enjoy your record with the two string quintets. Last week I arranged a Witkop Soirée: first the two Mozart quintets (Köchel 515 and 516) then the double cello quintet of Schubert, opus 163. I was especially lifted by Mozart's e-minor quintet with which I was not familiar before.

An exceptionally severe winter caused ravages in my garden the recovery of which I probably will not experience. The third walnut tree that I planted for my grand-children, has become a victim of the frost which also killed the forsythias so that this Spring did not greet me with their golden blossoms.

The number of grand-children climbed to 13 by the arrival of Wolfgang's daughter Josephine and, since there is no dearth of superstitious people, Irmgard (daughter-in-law, wife of Theodor) decided to rectify this number to an even fourteen.

Plate 4. Master and Pupil (B.W.) in 1953 on the terrace of Wieland's home in Starnberg whence, on clear days, the panorama of the Alps behind Lake Starnberg was impressive.

One year later death ended Wieland's life and the long phrase mark over its musical motives.

When it came to literature, it was humor that attracted him, starting with Wilhelm Busch to Christian Morgenstern and Ludwig Thoma, whose criticism of the political clergy in pre-war Bavaria was very much to his liking. In his private laboratory he often discussed Ernst Haeckel (1834–1919), Hans Driesch (1867–1941), and also contemporaries such as Ernst Jünger (1895–), whose "On the Marble Cliffs" appeared in 1940 and immediately was hotly discussed. Opponents of the regime used it in philosophical seminars to help in the interpretation of Herder's concept of humanity.

X. WIELAND'S ACADEMIC CAREER: AN ARCHIVIST'S VIEW

The great tradition in Munich usually starts with Justus von Liebig (1803–1873), the uncrowned king of science, upon whose death on April 18, 1873, Hermann Kolbe commented "Death has bereaved us of one of the greatest figures of the century." What might justify this hyperbolic statement is perhaps his legacy, the "Liebig Schule," all the students he trained, the members of which were all listed and characterized for the first time in a painstaking investigation by Joseph Fruton.[33]

Archival studies in the records of the University, the Archives of the State of Bavaria, and other sources have now permitted us to learn more about the correspondence between Wieland and the authorities of the various governments. A student of these records must be surprised that shortly before the end of World War I (the date is July 18, 1918), Wieland was offered the succession of his teacher Johannes Thiele in Strassburg, which he accepted with the proviso to delay his physical move until April 1, 1919. This decision, in retrospect, turned out to be very wise, because it saved much inconvenience. When the French reoccupied Strasbourg, all the Germans had to leave in a hurry.

In 1919, Wieland was queried about the succession of Carl Engler in Karlsruhe, an invitation which he turned down. Simultaneously, two offers followed in July 1920: One was the most prestigious succession of Emil Fischer in Berlin, the other the chair of chemistry in Freiburg at the Albert-Ludwig University where Ludwig Gattermann had taught. As early as 1919, Carl Duisberg had tried to talk Willstätter into following Emil Fischer in a telegram: "You, most honored and dear friend, must become his successor; we bank on it!"[34] Willstätter, however, turned this offer down, because he considered his pensum* in Munich unfinished.

"I spent my most pleasant years of life and work in Freiburg," was Wieland's characterization of this brief lustrum. When in 1925 Willstätter offered his resignation, in part as a result of antisemitic remarks by Wilhelm Wien (1864–1928, Nobel prize 1911), the Dean of the Munich Faculty called Philosophy II (later to be named Fac. Nat. Sci.), the choice of a successor was not in doubt, as Willstätter writes in his autobiography[35]:

> I determined and gained as my successor the former head of the Organic Division of my Laboratory, Professor Heinrich Wieland, who, since 1921, has occupied the chair in Freiburg and whom I consider the most versatile and outstanding organic chemist at the present time. In addition, through Thiele, he is a descendant of my teacher Adolf von Baeyer (1835–1917).

*Pensum: a task or assignment to be completed.

XI. AUTOBIOGRAPHICAL NOTES

By contrast to Emil Fischer[36] or Richard Willstätter,[35] whose memoirs bear identical titles, Wieland felt no urge to record or explain his past life. His first "curriculum vitae" was written by hand and goes back to 1904, when he submitted his thesis for "habilitation"[37] (Habilitations-Schrift):

The author of this treatise, submitted herewith, is Heinrich Otto Wieland, born June 4, 1877 in Pforzheim, Grand Duchy of Baden, as the son of the chemist Theodor Wieland. After completing the grand-ducal humanistic gymnasium of my native city I started the study of natural sciences, especially chemistry, at the University of Munich in the Fall of 1896. I studied qualitative analysis in the chemical Laboratory of the State and became auditor of lectures in chemistry, mathematics, botany, geology, mineralogy and physics. I continued my practical studies in inorganic analysis at the First Laboratory in Berlin under Dr. P. Cory in the Fall semester 1897 and, in 1898–1899, at the Polytechnic in Stuttgart under Professor Hell. In July 1898 I graduated with the official examination [Verbands-Examen]. After my return to the University of Munich I completed the examination for doctoral candidates [Doktoranden-Examen] and carried out my thesis problem, "Attempts to Synthesize Phenylated Allenes," under the guidance of Professor Thiele. In July 1901 I acquired the Ph.D. with chemistry as the principal subject and physics and mineralogy as secondary disciplines. During the winter semester 1901–1902 I was private assistant to Professor Harries in Berlin and, in Spring 1902, I joined the Laboratory of Prof. Baeyer to start and complete the investigation herewith submitted.

This brief sketch was amplified nine years later:

As of January 1, 1909, I was given the title of "Professor Extraordinary" [Ausserordentlicher Professor]. On April 1, 1912, I received the invitation to lecture on Technological Chemistry. Since March 29, 1908, I have been married to Josefine Bartmann, daughter of the owner of a construction company, I. Bartmann. I have two sons, Wolfgang and Theodor. [June 4, 1913]

Whoever may find this sketch too brief should read Paul Ehrlich's list of cues entitled "Ehrlich on himself[38]" which, on a microscopic scale, permits instructive insights into his pointed and humorous understanding of fellow humans, including himself. When Ehrlich criticizes himself: "No sense for languages," we may appreciate Wieland, who in his mature years bravely presented lectures on oxidation mechanisms in English,[30] French,[39] and Spanish.[40] Half a century after his first autobiographical sketch Wieland again looked back on a fulfilled life in a retrospective that his fellow Swabian Hölderlin would characterize ". . . gain and loss are weighed by a pensive mind":

The second comprehensive field which I was to enter in 1911 and for many years to come, was in the realm of biochemistry. For manifold reasons I was unable to believe that the oxidation reactions in living cells started with an "activation" of molecular oxygen. By contrast I found it promising to entrust the (enzymatically) activated hydrogen with this decisive role. Should it be possible to achieve a biological oxidation process without oxygen, which would be replaced by another agent, this would then prove the theory of dehydrogenation. As early as 1912 we were able to show that acetic acid bacteria converted ethyl alcohol to acetic acid under complete exclusion of oxygen but in the presence of methylene blue which lost its color as a function of the formation of acetic acid. This fundamental experiment with acetic acid opened the door to a new field of research. As the years went by we observed how acetic acid by and by became one of the most important key intermediates in the biological degradation of carbohydrates, fats and proteins. It is for me a source of special satisfaction that the enigma of the "activation" of acetic acid and its total oxidation was elucidated in our laboratory in Munich.

Not all my blossom dreams may have been realized, but an appreciable part of my endeavors came to maturity and fruiton thanks also to the collaboration of other laboratories.

If I feel tempted to compare the present with my early beginnings, I may conclude that the challenges to organic chemistry basically have not changed much, but now the immense structure of high-molecular compounds has been erected and towers over the field of research. The nature of chemical affinity has been better understood and so we have gained a better insight into reaction mechanisms and are often able to make predictions. Where I see a contrast is in the development of methods and instrumentation between then and now. I admire this progress not without a touch of envy.

I am grateful to my destiny that I was privileged to witness the resurgence of German chemistry in science and technology. This revival should enable us chemists, as we did in earlier times, to contribute our share to the welfare and progress of mankind.[41]

XII. ACTIVATED ACETIC ACID AND THE NOBEL PRIZE FOR LYNEN

Great ideas need time to mature: Wieland's delight over the solution of the riddle of the "activated acetic acid" by his son-in-law, Feodor Lynen, would have grown to pride and joy, had fate allowed him to be present at the Nobel Lecture on December 11, 1964, when under the title "The Pathway from

Plate 5. Heinrich Wieland in 1953. This photograph is the only one known to the photographer (B.W.) that shows him smiling, an activity that he reserved strictly for moments not photographically recorded.

Activated Acetic Acid' to the Terpenes and Fatty Acids,"[42] "Fitzi" Lynen elaborated as follows:

That then I happened to occupy myself with the problem of the metabolism of acetic acid, this turn of events was a direct result of my stay in the Laboratory of Heinrich Wieland, in which the oxidation of acetic acid by yeast cells was studied and where it was observed that most of the acetic acid is completely metabolized, but part of it survives in the form of succinic or citric acid. The Thunberg–Wieland scheme tries to rationalize this observation by assuming that two molecules of acetic acid are dehydrogenated to succinic acid which is then degraded back to acetic acid via oxaloacetate, pyruvate and acetaldehyde with the option, at the level of oxaloacetate, to add another molecular of acetic acid to form citric acid[43]:

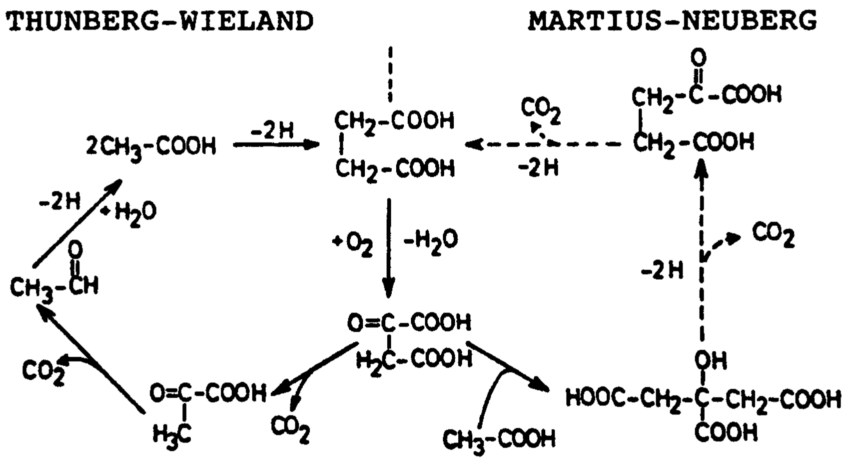


Figure 1. Possible pathways for the degradation of acetic acid by yeast.

However, when this idea was tested experimentally by Wieland's student Robert Sonderhoff (1908–1937), there came a surprise: Yeast cells converted trideutero-acetic acid into deuterated citric acid which contained the expected amount of deuterium, but there was only half of the expected deuterium in the concomitant succinic acid, whereas the Wieland scheme postulates four atoms of deuterium. The solution of this discrepancy was found by Carl Martius who recognized that in animal metabolism citric acid is in equilibrium with isocitric acid, undergoing oxidation to ketoglutarate which, according to Carl Neuberg, is known to be the precursor of succinic acid. Accordingly one had to assume that succinate, formed by yeast from acetate, arose via citrate.

Wieland's friend Markus Guggenheim invited him after the war to a lecture, which he delivered on June 3, 1947, before the Swiss Chemical Society in Basel. His presentation allows us to gain an insight into his sovereign long-range views of the mechanism of bio-local oxidation and his prediction of the value of future investigations, utilizing heavy oxygen, as they were carried out much later by Osamu Hayaishi:

From the vantage point of the theory of dehydrogenation, an idea supported by the work of many investigators during the last decades, biological oxidation proceeds through the conversion of nutrients to intermediate metabolites, such as α- or β-keto-acids, containing a labile carboxy group capable of easy decarboxylation. Hydrogen, needed for this transition, is mobilized by hydrogen-transferring enzymes with the final formation of water by the action of cytochrome C, a heme-enzyme containing trivalent iron. The reduced state of cytochrome C is reactivated to the trivalent state by cytochrome oxidase. Oxygen then reactivates cytochrome oxidase (Warburg's "Atmungs-Ferment") but does not participate as such in biological degradation. If the oxidation process were to be studied with the oxygen isotope ^{17}O, the amount of this isotope in the final products, carbon-dioxide and water, should exceed the natural abundance of ^{17}O.[44]

Lynen, in his Nobel Lecture, establishes another important connection, viz., between the early work of Wieland and Sonderhoff and the later completion through Schoenheimer and Bloch:

Sonderhoff's pioneering experiments with deuterated acetic acid led to further important discoveries. When the yeast cells of these experiments were analyzed, it was noticed that their carbohydrates contained only minor amounts of deuterium, whereas the fatty acid and steroid fractions were rich in heavy hydrogen. This observation proved that steroids and fatty acids were formed directly from acetic acid and not through intermediate carbohydrates. Unfortunately Sonderhoff took his life and so these important investigations were no longer continued in Munich.

XIII. THE BIRTH OF BIOCHEMISTRY OUT OF THE SPIRIT OF ORGANIC CHEMISTRY

The leisure of advancing years was utilized by several famous biochemists to reflect on the origin and growth of Biochemistry.[44–47] Georg von Hevesy (1885–1966, Nobel prize 1943)[48] presumably was the first pioneer to recognize the importance of isotopically marked precursors for the study of metabolism.[49] Ludwig Achoff (1866–1942), in 1933, helped his student and associate Rudolf Schoenheimer to secure a position at Columbia University, but before Schoenheimer moved there he spent some time as a guest in Hevesy's Laboratory, where he became acquainted with the technique of marking substrates with isotopes. From 1937 to his death Schoenheimer investigated the metabolism of deuterated fatty acids. Robert A. Kohler[50] has provided us with a detailed and careful account of this period, but has failed to see the connection with the seminal work of Wieland and Sonderhoff, a relationship that Lynen fully clarified in his Nobel Lecture. Schoenheimer, the mentor of Konrad Bloch, would probably have shared his Nobel prize in 1964, had he, like Sonderhoff before, not ended his life.

Wieland's great merit is to conjoin what Arthur Kornberg terms "The Two Cultures," or as his fellow Swabian Schiller would say in his "Ode to Joy," ". . . was die Mode streng geteilt" (what custom has kept separated), viz., organic chemistry (*thesis*) on the one side, biological chemistry (at Wieland's time almost *antithesis*) on the other hand, finally united in a *syn-thesis*, signifying more than the sum of the parts. This kind of thinking was adopted by his son-in-law when he was able to express the complex biosynthesis of terpenes and fatty acids in simple and straightforward chemical equations.

Even Warburg, whom Lynen, throughout his life, revered as the greatest living biochemist, appreciated Lynen and his work that he referred to him as "der junge Wieland",[51] somewhat of a contradiction because he never pulled any punches in his controversies with father Wieland for whom, at least in his publications, he had little regard.

XIV. WIELAND'S PARADIGM OF HYDROGEN SHIFT

On the occasion of the 65th birthday of H. Wieland in 1942 Lynen, in an article "The Role of Phosphoric Acid in Dehydrogenation Processes and its Biological Significance," sums up the theory of his father-in-law in the lapidary statement,[52] In the last thirty years we observed "The Principle of Hydrogen Shift," discovered by H. Wieland in 1912, to dominate the processes of fermentation and respiration.

In the same issue Wilhelm Franke amplifies this pronouncement by presenting the historical development of our views on biological oxidation.[53]

At that time Wieland's favorite enzymes were the *Schardinger enzyme* or *xanthine oxidase*, and the *Thunberg enzyme* or *succinate dehydrogenase*, both considered to be metal-free enzymes. However, both enzymes turned out to be highly complex multicentered iron–sulfur flavoproteins.[54] In the absence of oxygen, spectrophotometry allowed one to determine labile intermediate stages in the reduction of xanthine oxidase by xanthine. The two separate iron–sulfur centers of xanthine oxidase serve as an electron sink in order to keep the molybdenum complex in the hexavalent state for the reductive phase and the flavoprotein in the reduced stage ($FADH_2$) for the oxidative phase.[55]

Paired and unpaired electron transitions are possible in the presence of oxygen for the reactants: xanthine, oxygen, and reduced flavine dinucleotide. Neither Wieland nor Warburg could have surmised or predicted a novel species of active oxygen, viz., the superoxide anion O_2^-.[56] A new role has been found for this classical enzyme that Wieland has investigated so studiously over the years: xanthine oxidase serves for the production of superoxide anion required for many oxidations, such as the indole-amine-2,3-oxygenase. In this system, as Osamu Hayaishi found, methylene blue, used by Wieland as an oxygen substitute, serves as a cofactor required for maximal enzyme activity.[57] As early as 1914, i.e., two years after Wieland's publication, Warburg published his groundbreaking study "On the Role of Iron for the Respiration of the Sea Urchin with Remarks on some Oxidations Accelerated in the Presence of Iron."[58] In the years 1923–1925 Warburg turned into an embittered opponent of the theory of dehydrogenation, whereby he directed his barbs and polemics not only *ad rem* but also *ad hominem*.[59] Wieland, during these years of controversy, retained his chivalry and integrity.

In a letter that Sir Hans Krebs (1900–1981, Nobel prize 1953) a dedicated student of Warburg, wrote to the chronicler, the character of this altercation became clearer:

What concerns the controversy between Warburg and Wieland, there is little doubt, after all these years, that both were somewhat obstinately imprisoned in their too narrow views. In reality, there was no real conflict, as Oppenheimer showed in the thirties. Warburg, it is true, hesitated to acknowledge the existence of dehydrogenases and only with reluctance. The gist of his criticism was directed against Wieland's use of unbiological acceptors, such as methylene blue and nitrophenol, for binding hydrogen. His conviction was that just *talking* about the activation of hydrogen on the basis of model experiments was of little use. What he only recognized was the identification of hydrogen-activating enzymes. That, of course, was Warburg's most prominent contribution to modern biochemistry, that he identified the natural acceptors, the flavo-proteins and the pyridine-nucleotides.[60]

When after the war in 1947 Warburg sent his disciple Hans Krebs his collected reprints to Oxford, Krebs was repelled by the caustic polemics against his friends David Keilin, Richard Willstätter, and Heinrich Wieland, so that he wrote to Warburg on June 14, 1947: a letter in which he searches for the psychological basis for his "ghastly polemics":

Is it the agonizing environment of the last 14 years and your loneliness, that has affected your attitude? Or has *my* attitude changed and I have become over-sensitive towards your sort of polemics? In the world in which I now live, as you will know from the modern Anglo–American or French literature, polemics are very rare and they are never discourteous. Scientists here are content to rely on the rule that scientific untruths will sooner or later die a natural death. They find it unnessary to assist too eagerly the maturing of the judgment of time.[61]

XV. INTUITION AND THE BIOSYNTHESIS OF CHOLESTEROL

When Elisabeth Dane summed up her teacher Wieland's work on steroids, she had only the laconic remark,

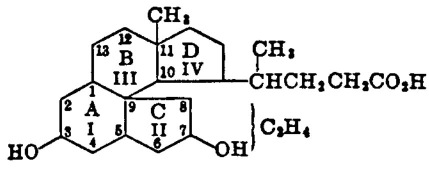
Some of Wieland's investigations lead into the field of steroids, especially to the minor steroidal components of yeast, as they accumulate in the mother liquors of the technical isolation ergosterol.[62]

In the survey on Wieland's research on natural products, these minor steroidal components are listed as cholesterol, lanosterol or Wieland's "kryptosterol," and also squalene. Konrad Bloch, who in 1964 shared the Nobel prize in medicine with Lynen, comments, "Wieland's natural products chemistry laid the essential foundation for later biochemical research."[63] Indeed, what Wieland searched for, precursors and intermediates in the steroidal metabolism of yeast, were later identified by Bloch as building stones in the biosynthesis of cholesterol, starting with mevalonic acid, then isopentenyl pyrophosphate, the long-sought-after building stone for isoprene, squalene, curling into lanosterol by a novel cyclization rearrangement that Sir Robert Robinson and Robert Woodward helped to unravel.[64]

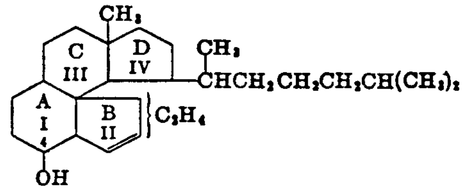
In December 1928, at the Nobel ceremony, the Secretary of the Royal Swedish Academy, Prof. H. G. Søderbaum, addressed Wieland before he came to the eulogy for Windaus:

The Royal Swedish Academy's decision to award you the Nobel Prize for your investigations on bile acids and related natural products is only a justified acknowledgment for the elucidation of a problem which undoubtedly belongs to one of the greatest challenges that has ever faced the organic chemist. The complex structure of the compounds you scrutinized, the large number of atoms coming together in these molecules, the difficult accessibility, they all were handicaps that thanks to your experimental skills and your ingenuity in ever finding new approaches and methods were surmounted with spectacular success. In gratitude for what your work has contributed to science and with heartiest congratulations for the well-deserved distinction, the Academy requests you to accept the Nobel Prize in Chemistry for the year 1927 from the Hand of his Majesty the King.

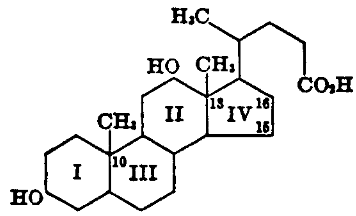
Sixty-five years later we realize the progress that structural elucidation of highly complex molecules has made thanks to instrumentation that not even Jules Verne could have dreamt about at that time. But as early as 1921[65] doubts began burgeoning in Wieland's mind about the strange five-membered ring structure and about the general validity of the Blanc rule, which describes the thermal behavior of dicarboxylic acids: on heating the lower ones, such as succinic and glutaric acid form anhydrides, the higher homologs, adipic or pimelic acid, form ketones; Wieland with his uncanny "sixth sense" had a feeling that the Blanc rule might no longer apply in cases in which steric factors overrule the simple precedents of open dicarboxylic acids. Furthermore, his sense for aesthetics and structural "propriety" felt insulted by the odd 5-membered ring C—in cholesterol ring B—later to be corrected to Ring C or B, respectively.



Desoxycholic acid
(Wieland, 1928)



Cholesterol
(1928)



Wieland and Dane (September, 1932)
Rosenheim and King (August, November, 1932)

Later, almost simultaneously, the old structure was corrected, first in May 1932 by Rosenheim and King,[66] then in September of the same year by Wieland and Dane. The somewhat confusing comparison of the old with the new formulae, to the chagrin of exam candidates, became a favorite challenge in official tests. At the conclusion of his Nobel lecture Wieland raised the question of the total synthesis of bile acids and steroids, a challenge that he unwaveringly rejected,[67] while Woodward took it up and met it in 1951.[68]

XVI. TWO PERSONALITIES: WOODWARD AND WIELAND

It is difficult to imagine two more disparate personalities than the two great chemists, each fulfilling his mission at his time in the way he saw fit.

Woodward lived for his science with a dedication that demanded sacrifice. When on November 9, 1979, his friends and his colleagues congregated to memoralize him in the graceful chapel on the Harvard campus, Lord Todd found the suitable words for describing this dilemma:

> Men like Bob Woodward, with a single-minded devotion to their science and a burning desire to excel, are hardly likely to be good family men, much though they need companionship. . . . I confess that it was his passion to excel in all he did that at times disturbed me greatly, especially during the last few years, when his loneliness became increasingly evident.[69]

After the chronicler's arrival at Harvard in 1947 Woodward—he was 30 years young at that time—in many conversations showed his great esteem for Wieland and his lifework, though he was amused by some of the little slips, such as by the mishap with the wrong formula for cholic acid which on top of it all was rewarded by the Nobel prize. He also espoused his own version when he lectured on the discovery of vitamin D.[70] While Wieland *served* nature, Woodward was anxious to *master* it.

At the time when in Munich the structure of the alkaloid vomicine was still a major problem, Woodward, in the dissertation of his Ph.D. candidate Edward Crane,[71] had already finished the same kind of decoding that he had applied to the publications of Leuchs on strychnine, which were unintelligible to the normal reader but not to Woodward. The role of the Rosetta Stone in the case of vomicine was Wieland and Horner's vomipyrine, which Robinson synthesized, as well as Crane in Woodward's laboratory, but with considerable difficulty.

In Wieland's laboratory the alkaloid vomicine served, like Latin or Greek in the German gymnasium, as a molecular palaestra to unlimber the mind and awake all chemical skills. A page from the thesis of Edward Crane, January 1949, Harvard University, shows the way from vomicine to vomipyrine[72,73] as Woodward saw it:

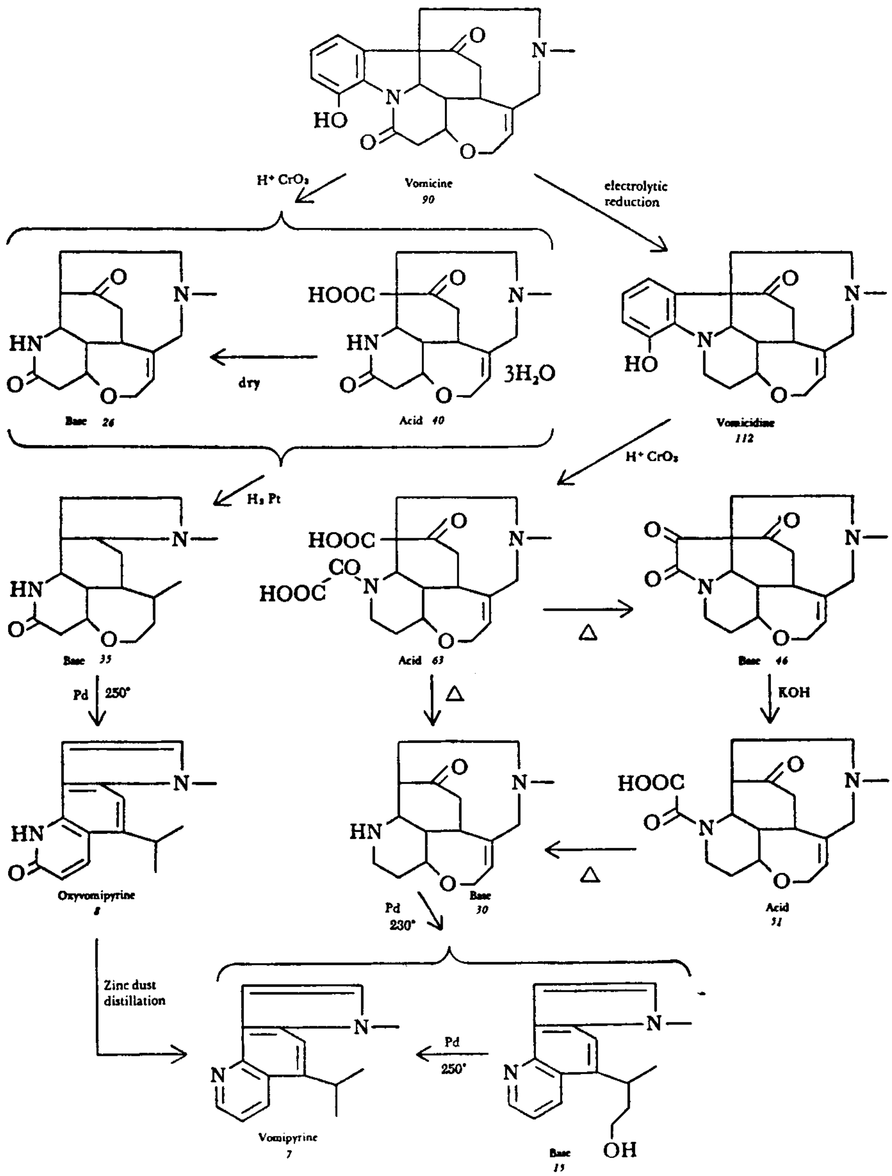


Figure 2. A page from the thesis of Edward Crane, January 1949, showing Robert Woodward's conception of the path from vomicine to vomipyrine.

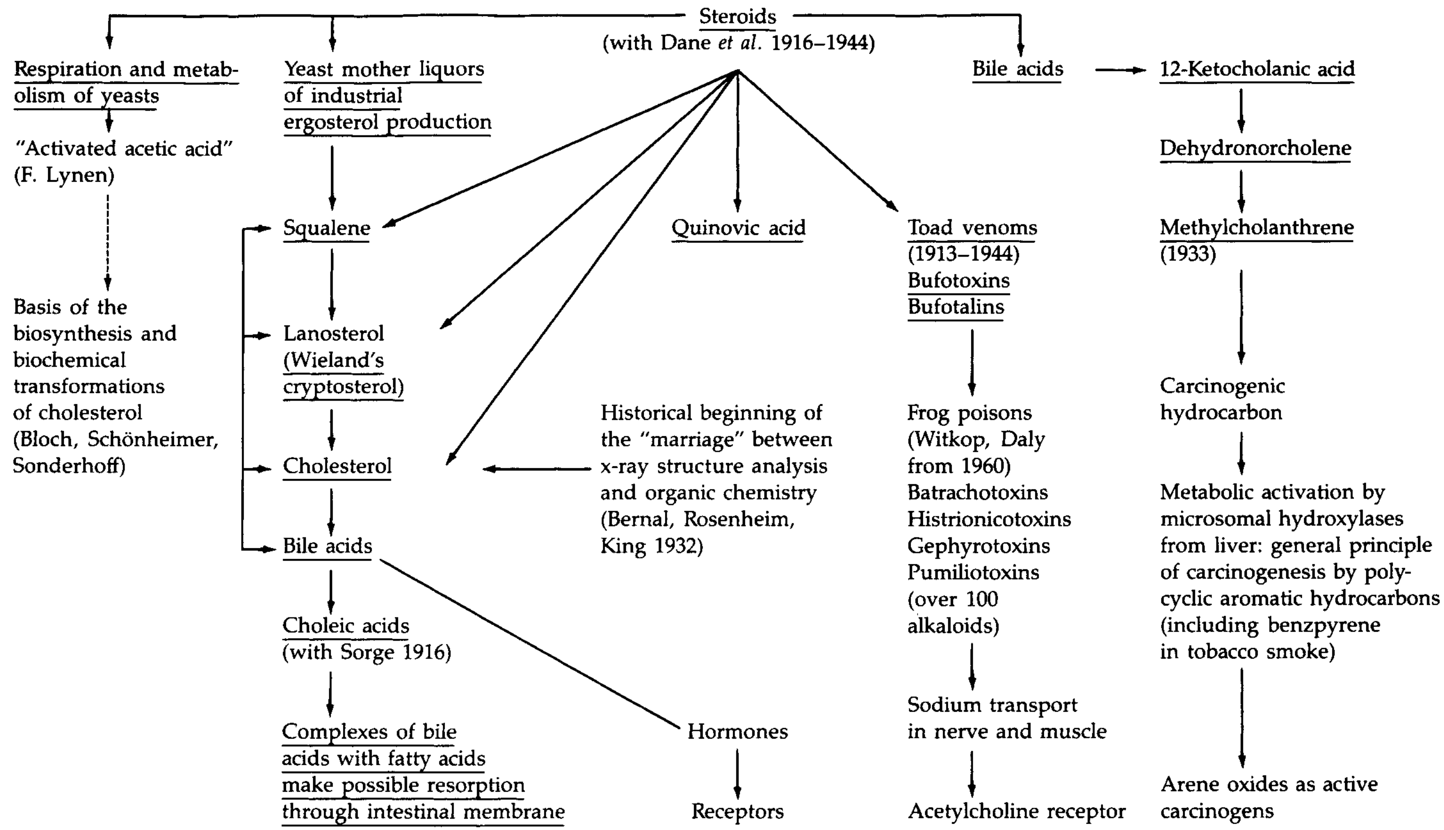


Chart I.[166] Wieland's work on natural products: juxtaposition of the static classical chemistry of natural products performed by Wieland and the dynamic biochemistry of metabolic processes that resulted therefrom. Wieland's classical approach to natural products chemistry is apparent from the isolation and structural elicidation of key compounds, such as squalene, cryptosterol, and cholesterol from the yeast mother liquors of industrial ergosterol production. It was not until the 1940s that Konrad Bloch, Rudolf Schönheimer, and (in 1937) Wieland's student Robert Sonderhoff introduced isotopic labeling, which permitted elucidation of the biosynthesis of cholesterol and the bile acids. Likewise, forty years elapsed between Wieland's synthesis of the carcinogenic hydrocarbon methylcholanthrene and proof of the connection between formation of labile arene oxides in the liver or lung and carcinogenesis. The only compound that has not yet served as the basis for biochemical developments is quinovic acid, a pentacyclic triterpene from the mother liquors of quinine production. Wieland's first foray into biochemical dynamics was his work on metabolism and respiration of yeast. These studies led to the concept of "activated acetic acid" and—through F. Lynen—to its structure.

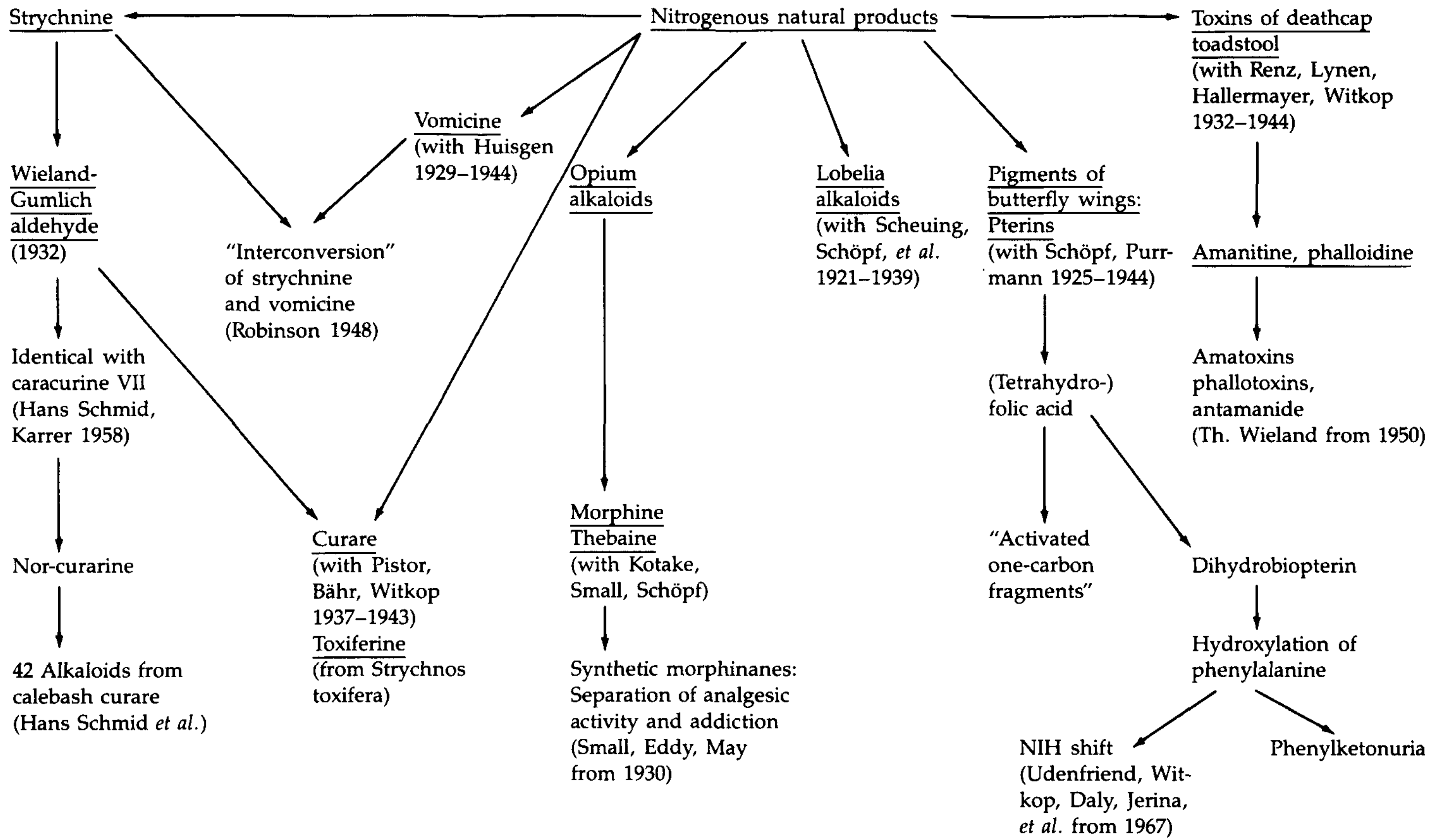


Chart II.[166] Wieland's studies on nitrogenous natural products have had a lasting effect on developments in biochemistry. For example, work on the pigments of butterfly wings with Schöpf and Purrmann provided the basis of the chemistry of pterins, from which the entire dynamics of the folic acid components of important enzymes can be derived, and also the mechanisms of enzymatic hydroxylation which led to the discovery of the NIH shift. The toxins of the deathcap toadstool have been further investigated by Wieland's son Theodor, and utilized in various ways in molecular biology. The antamanides were used by Isabella Karle in x-ray studies on the folding and unfolding of cyclic peptides. Synthetic work on the opium alkaloids was continued in Bethesda by Wieland's student L. F. Small, E. Mosettig, and E. L. May, and resolved into addictive and analgetic components. In Paul Karrer's laboratory, Hans Schmid (1917–1976) demonstrated how the Wieland–Gumlich aldehyde obtained from strychnine by oxidation could be transformed into alkaloids from calebash curare also investigated by Wieland. (Wieland's fields of study are underlined in Chart II.)

The tricyclic system of vomipyrine, viz., a pyrroloquinoline analog, was postulated by Duine[74] to be, in the quinone form, a redox cofactor for various oxidases ("PQQ"), but his postulate has been challenged, and 6-hydroxydopa[75] as well as a tryptophantryptophylquinone[76] have taken some of its place.

XVII. THE CHOLEIC ACID PRINCIPLE AND ITS IMPORTANCE

If it were possible to gauge the importance of a publication by the number of reprints requested, then Wieland's second (of 57) communication that he published on the bile acids deserves special mention.[77] Its title is "Regarding the Nature of the Choleic Acids" and the name of his collaborator Hermann Sorge justifies remembrances of the World War I master spy. The bile acids, and even more so their salts, with lipophilic, water-insoluble partners such as fatty acids, aromatic hycrocarbons, strychnine, camphor ("Cadechol"), etc., form water-soluble inclusion compounds,[78] whose X-ray analysis was just recently performed.[79] This "choleic acid principle," discovered and investigated by Wieland, implies the tempting invitation to elevate it to a general physiological principle which could explain the resorption of fatty acids in the gall bladder. Wieland, in his prudent manner, pondered all the reasons, pro and con:

> Whoever wants to extend our observations made with choleic and desoxycholic acid to the natural and paired bile acids, must first realize that in bile these acids do not occur in the free form but paired with glycine or taurine as glycocholate or taurocholate. At this time a decision is not possible, and tedious and time-consuming experiments are still in progress.[77]

Indeed, formylated glycocholic analogs, lacking free hydroxyl groups, no longer are able to form inclusion compounds. Wieland's former collaborator Frank Cortese concluded in 1936 that the extension of the *choleic acid principle* to biliary fat resorption is not justified.[80] However, in the twenties, when the Nobel Committee received proposals for candidates, the nomination of Wieland was not only substantiated by his structural work on bile acids but also by his discovery of the choleic acid principle.[81]

XVIII. STEPPING STONES TO THE NOBEL PRIZE (1928)

One of the first nominations of Wieland for the Nobel prize was received in 1923, on February 3, from Prof. Ernst Muckermann, Heidelberg, who praised "his keen gift of observation and his remarkable experimental skills" utilized to advantage in his many eminent studies, not only chemical but physiological, when it comes to the bile acids which Wieland had been investigating since 1912.

In the following year we find a letter written by Adolf Windaus on January 30, 1924, who calls attention to Wieland's general contributions to natural products, in particular toad venoms and bile acids. Willstätter, who insisted on Wieland as his successor, is not among the repetitive nominators.

Interestingly enough, his brother, the pharmacologist Hermann Wieland, shows up as a candidate in 1926, nominated by the physiologist Paul Hoffmann, for the introduction of gaseous anesthesia with ethylene or acetylene. In 1927 we notice as prime candidates F. G. Hopkins (Nobel prize 1929), Th.

Thunberg, and H. Wieland, whose investigations on the mechanism of biological oxidation were commented by Einar Hammarsten, but were not considered prizeworthy, in contrast to those of Warburg who received his prize in 1931.

Finally, on September 7, 1928, the Nobel Committee reached a consensus to award the Prize in Chemistry for 1927 to Windaus and for 1928 to Wieland. This resolution is signed by H. G. Søderbaum, The Svedberg (NP 1926), Wilhelm Palmer, O. Widman, and L. Ramberg. In this year, 1928, the list of candidates contains almost 80 nominations, a surprisingly large number, which makes the present lists of several hundred names no longer appear too excessive. Windaus but not Wieland was sponsored by colleagues, such as Willstätter, F. Haber, O. Mumm, H. Suida, and H. Wien. Moses Gomberg and Paul Walden belong to the star candidates who were often nominated but bypassed in the end.

XIX. PIGMENTS OF BUTTERFLY WINGS AND THE WAR EFFORT

> The Central Office for Economic Planning, or Reichsamt für Wirtschaftsausbau, has entered into an agreement to support investigations of PTERINES pigments of butterfly wings) which contain components of biological importance. This Office requests the endorsement of the Ministry for Education, Instruction and Information of the People which I am soliciting herewith.

This letter, written by Wieland on February 3, 1940, was directed to the Dean, Prof. Faber, who passed it on to the Rektor (President) of the University of Munich, with his recommendation:

> The Faculty considers the continuation of Prof. Wieland's research on pterines highly desirable. His request is strongly supported.

By his skill, prudence, and authority vis à vis the bureaucrats Wieland succeeded to salvage and promote a purely academic research project in a totalitarian state in the middle of the war and, to top it all, was able to extricate some of his conscripted collaborators from their military units.

"I persevered at my post in order to forestall worse disasters": This kind of defense was fairly standard during the "judgment at Nuremburg." However, in Wieland's case the attitude was fully justified, and he showed his mettle later when he confronted the Public Tribunal (Volks-Gerichtshof) and attempted to help his hapless students in Donauwörth.

Konrad Bloch reminisces on a colloquium devoted to the pterines in the year 1934 in which Wieland said,

> Our investigation was aided by school-children who collected in excess of 200,000 cabbage-butterflies for which they were rewarded with one Pfennig for each butterfly. However, this kind of collection has to be discontinued, because the government considers this activity as contrary to the ethics of the Nationalsocialist Party and as cruelty to animals and brutalization of our youth.[64]

We take note that on January 20, 1942, six years later, the "Final Solution" was decided in a mansion on the Wannsee near Berlin: on the one hand mercy for butterflies, on the other hand the holocaust—who can doubt the "banality of evil"?

The structure of leucopterin was a tough problem which was solved in 1940 by Robert Purrmann.[82] Clemens Schöpf has reviewed his teacher's work on nitrogenous natural products.[83] The survey pictures the development from the pterins to the dynamics of folic acid[84] as a component of important enzymes involved, e.g., in hydroxylation of phenylalanine to tyrosine, a reaction that led to the observation of the "NIH shift." The dynamics of pteridine in the animal and bacterial metabolism has become an area of great importance.

The metabolism of insects[85] repeats an oxidation of xanthopterin to leucopterin, which was accomplished by Wieland and Purrmann with hydrogen peroxide[82]:

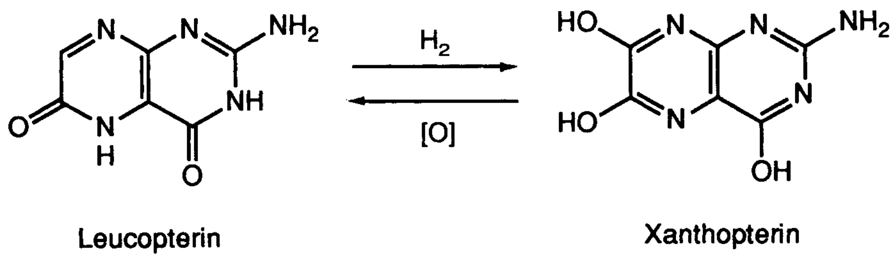


Figure 3. Oxidation of xanthopterin to leucopterin.

Insects achieve this transition with the help of one of Wieland's favorite enzymes, namely, xanthine oxidase. Two of his legacies coalesce here posthumously.

XX. THE BRIDGE BETWEEN STRYCHNINE AND THE CURARE ALKALOIDS

From 1937 until the destruction of the Munich Laboratory, Wieland worked on the alkaloids from calabash curare, some of which he also found in the bark of *Strychnos toxifera.* This work was taken up by Paul Karrer and Hans Schmid, his first assistant and later successor. When Paul Karrer wrote an obituary for Wieland in 1957,[86] there was no mention yet of the key reaction that brought the solution to the curare problem. This reaction goes back to 1932, when Wieland and Gumlich, in an investigation[87] "On Some New Reactions of the Strychnos Alkaloids. XI," described the preparation of isonitrosostrynchnine. Wieland and Kaziro studied the Beckmann rearrangement of this oxime and the loss of hydrogen cyanide to yield an aldehyde, that should correctly be called Wieland–Kaziro aldehyde,[88] but became known and accepted as Wieland–Gumlich aldehyde and lives on in nature, where it occurs as diabolin, the acetyl derivative, and as caracurine VII, the methochloride.[89] This aldehyde, under simple conditions, dimerizes and rearranges to various representatives of the alkaloids found both in calabash curare as well as in the bark of *Strychnos toxifera* (see Fig. 4).[90,91]

This surprising concatenation of a fairly abstruse degradation product of the then most complex alkaloid, strychnine, with an entire class of monomers and dimers, and even more complex curare toxins, is striking and unique and illustrates the difficulty of "relevance" or mission-orientation in research.

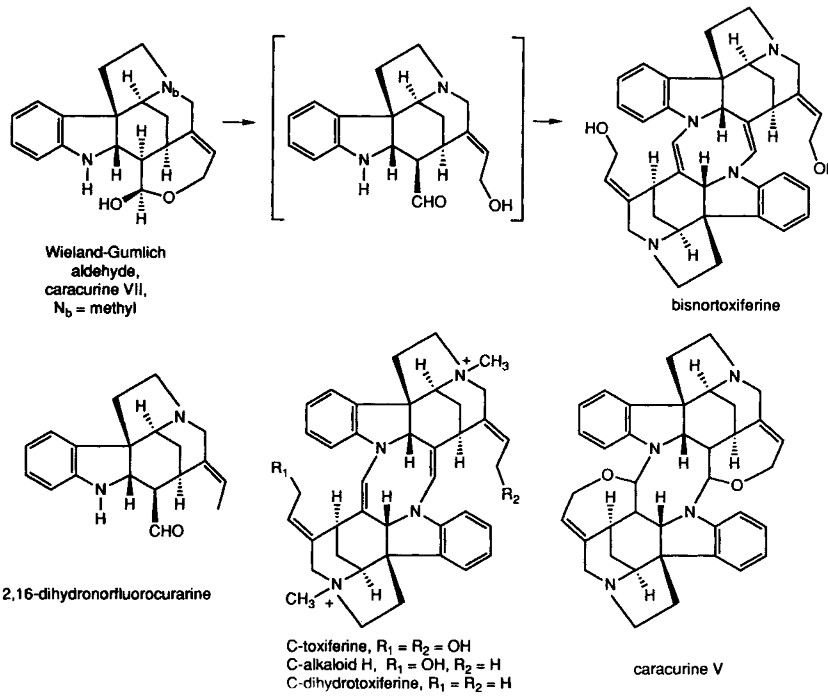


Figure 4.

Goethe ponders on the connection between luck and merit and adds the gift of observation and the prepared mind as the other necessary components for a happy outcome.

One of Willstätter's aperçus was

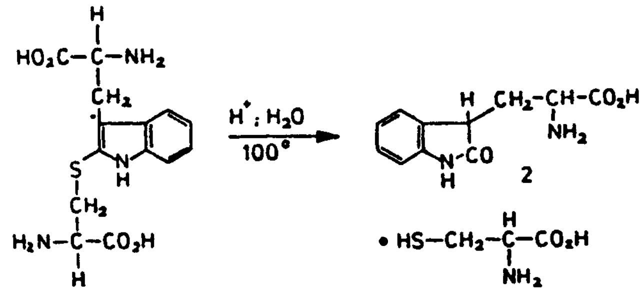
> If only you work long enough on a topic, remote as it may be, such as the bile acids or cholesterol in 1910, the day will come when it will acquire importance.

Aschoff's and Schoenheimer's clinical observations on the etiology of atherosclerosis exemplify this principle, and the pigments of the butterfly wings provide another model. Wieland's diplomacy and adroitness succeeded in elevating the research on the curare alkaloids to a topic considered important for martial surgery and as an aid in anesthesia, so that he received official sanction and support.

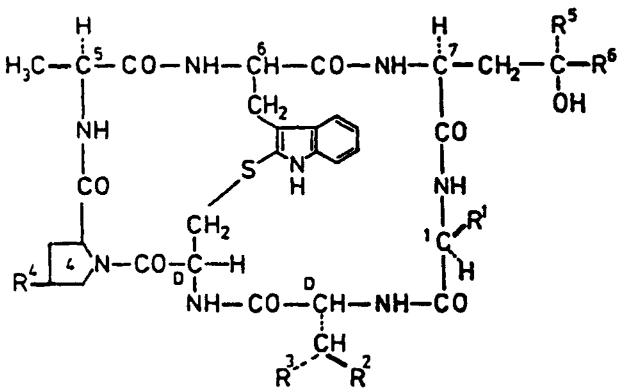
N,N'-Diallylnortoxiferin, prepared in Zurich from the Wieland–Gumlich aldehyde, is a short-acting muscle relaxant and still used today as an adjuvant in anesthesia.

XXI. FROM THE VENOM OF THE COBRA TO THE TOXIN OF THE DEATH CAP

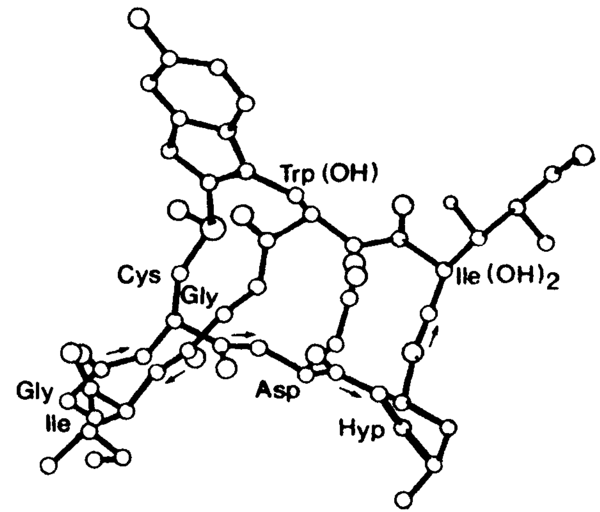
Toxiferin-I, isolated from the bark of *Strychnos toxifera*, at that time was the most toxic alkaloid known, with a lethal dose of 0.3 γ for a mouse of 20 g.[91] Several years earlier Wieland reported "Some Observations on the Venom of the Cobra (*Naja tripudians*)."[92] By fractional precipitation with ethanol and dialysis, he enriched the venom to a potency of 2 γ per 20 g mouse. He recognized its protein nature in this process of purification.



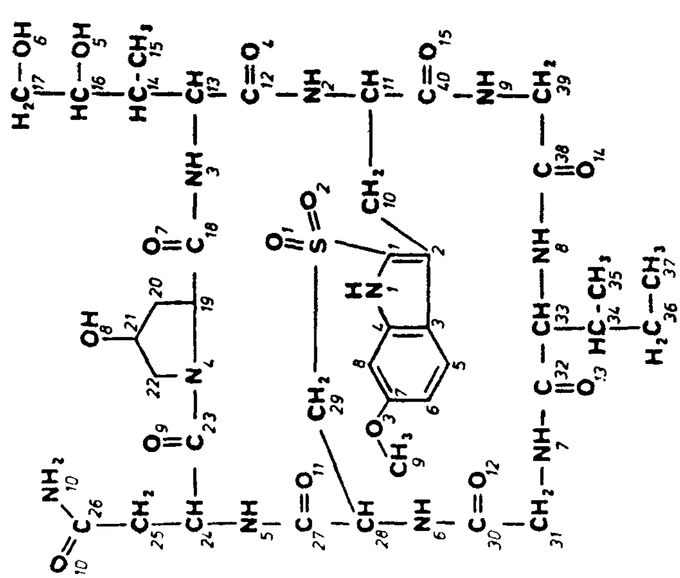
Oxindolylalanine from tryptathionine



General formula of the phallotoxins



Three-dimensional structure of β-amanitin (Kostansek et al. 1977)



Alternative presentation of the amatoxin formula (sulfone) with numbering of the atoms. In α-amanitin (*R*-sulfoxide) O_2 (at sulfur) is absent.

Figure 5. Wieland's *Amanita* legacy was completed by his son Theodor.

Now comes a sally into new territory: In 1930 Wieland's laboratory started looking at Europe's most toxic mushroom, the death cap (*Amanita phalloides*).[93] At the outset, Feodor Lynen and Ulrich Wieland considered the toxins as intermediates between alkaloids and peptides, comparable to the ergot alkaloids.[25] Thanks to father Wieland and son Theodor, fifty years (1930–1980) were just enough to complete this challenging project.[26] Amatoxins, phallotoxins, and the nonpoisonous cyclopeptides antamanids were isolated, elucidated, and assigned their niche in molecular biology as useful laboratory tools. When Theodor Wieland sums up the rich harvest from this family project in the Springer Series in Molecular Biology under the title *Peptides of Poisonous Amanita Mushrooms*,[26] he shows that progress in science depends on progress in methods. Separation of peptides and amino acids on a micro scale was unknown at the time of the Wieland father. What was then a ceiling of great expectations later became a floor of routine facts (see Fig. 5).

X-Ray crystallography of β-amanitin illustrates the unique position of this bicyclic structure in the *world of peptides* that has recently been reviewed by Theodor Wieland.[94] The nine amatoxins, the seven phallotoxins, and their systematic modulation show unexpected relations between structure and activity. There are few examples in the history of science which illustrate Goethe's thought better: "Go, earn thy father's heirdom for permanent possession!"

Even secondary issues became important: Hydrolysis of phalloidin provided what was then considered a new natural amino acid, until it was shown that the oxytryptophan or oxindolyl-alanine comes from a novel condensation product of tryptophan and cysteine, called tryptathionine. Oxindolyl-alanine is not an intermediate in the metabolic breakdown of tryptophan which does not involve the α- but the β-position.[95] There is, however, an exception: The oxidative inactivation of the hallucinogenic LSD (lysergic acid diethylamide) or, as its inventor Albert Hofman called it, "my problem child," proceeds to an oxindole metabolite, as was shown by incubation with liver microsomes under concomitant loss of activity.[96]

Oxindolyl-L-alanine, which does not occur in nature, is a substrate and inhibitor of tryptophan-synthase (EC4.1.2.20), a system which replaces the β-hydroxyl group of L-serine by indole with the formation of L-tryptophan and water.[97] The Wieland family tradition of natural products was duly eulogized on the occasion of Theodor Wieland's seventieth birthday in 1983.[98]

XXII. THE WIELAND RESEARCH GROUP

Contrasts in Scientific Style is a comprehensive reappraisal of the research groups of Liebig, von Baeyer, Emil Fischer, Franz Hofmeister, and others who helped to shape the chemistry of the 19th century.[33] Wieland, who is firmly rooted in this tradition, is one of the founders of biochemistry, which in Germany did not have independent Institutes and Chairs until 1950. Close to 600 students and postdocs went through his Laboratory.

Instruction, education, and acquisition of new knowledge together in joint research satisfied one of his natural needs. He directly instructed and advised all the members of his research group, among them many foreign scientists, Japanese, North- and South-Americans, Spaniards, who mostly occupied chairs after return to their native countries where they then excelled in independent research. Wieland followed his students and their careers with interest and devotion and often took an active part in furthering their progress. The host of his disciples revered, adored and trusted him.[10]

Wieland's close connection to his students is illustrated in a footnote of an investigation on bufotenine and bufotenidine, where he writes:

Heinz Mittasch [only son of Alwin Mittasch (1869–1953)] lost his life when climbing the Matterhorn on August 11, 1932. Fondly remembering this unusually gifted and winsome disciple I am presenting here the most recent results of his scientific legacy. H.W.[99]

Conversely, his students kept close to him, sometimes through a lifetime. His "first student," Hans Stenzl, describes his last visit in Starnberg:

I was the second student; at that time (1904) he went through "Habilitation" or *"venia legendi."* Since that time we have always maintained close connections, for a long time through Boehringer Ingelheim, but even after my transfer to Basel our relationship became even closer and I justly could call Wieland a friend. Shortly before his death I visited him and countered his banter by telling him, that now he was showing his age, because for the first time in forty years he had not teased me with my resemblance to Willstätter. He was so happy about good-natured badinage.[100]

In a later letter Stenzl has this characterization:

I believe that Wieland's masterstrokes are not the result of elegant thought processes but rather the fruit of his typical Black-Forest thick-skulled stubborn character, to put it bluntly. When it came to the family, he showed a strong sense of solidarity: he was delighted that the *"active acetic acid"* which he had postulated, became an established fact and that it "stayed in the family" and, to boot, that the "tedious phosphorus" did not make the race.[8]

XXIII. REVERENCE AND AFFECTION FOR THE TEACHER: THE JAPANESE VIRTUE OF ON-SHI

Only the Japanese, with their sense for decorum and tradition, have a special expression for the special relation with their teachers (Fig. 6). "ON-SHI [one's honored teacher]." The history of science presents examples in the persons of Shibasaburo Kitasato (1856–1931), a student of Emil von Behring, and Sahachiro Hata (1873–1938), the co-inventor of arsphenamine ("Salvarsan"), when he worked with Paul Ehrlich. As they revered their teacher for the duration of their life and scientific career, Wieland's students returned to Japan and carried on in his way and in his spirit.

This became obvious as recently as 1989 when Theodor Wieland, on the occasion of his 77th birthday—76th according to Western numbering—celebrated his KI-JU in Osaka, where he was asked by the surviving scientific progeny to sketch the life and era of his father.[101] There is no other country in which Wieland's students had such an impact on developments, academic or industrial, in chemistry, biochemistry, pharmaceutical chemistry, and pharmacology as the Table of his 14 collaborators shows, whose sons and families

恩 師

Figure 6. On-shi: "One's honored teacher."

TABLE I
Wieland's Japanese Collaborators

Tomihide Shimizu (5/1/1889–1/30/1958)	Okayama University Medical School, Dept. of Biochemistry (Professor)
Mitizo Asano (9/18/1894–4/17/1948)	University of Tokyo, Medical Faculty, Pharmaceutical Institute (Professor)
Takami Noguchi (11/1894–12/5/1951)	Toyama Pharmaceutical College (Professor) Daiichi Seiyaku Co., Ltd.
Sin'iti Kawai (9/22/1859–2/4/1969)	Tokyo University of Education, Faculty of Science, Dept. of Chemistry (Professor)
Sanji Kishi (7/12/1899–9/26/1991)	Showa University, Medical Faculty (Professor) Cancer Institute
Senji Utzino (3/7/1894–9/21/1957)	Tohoku Imperial University School of Medicine (Professor) Kyoto Imperial University School of Medicine (Professor)
Motaro Ishimasa (2/25/1899–1/16/1982)	Osaka Pharmaceutical College (Professor) Nippon Shinyaku Co., Ltd.
Zenjiro Kitasato (12/26/1897–10/19/1978)	The Kitasato Institute (President)
Chohachi Hasegawa (12/6/1893–3/21/1952)	Chiba University, Faculty of Pharmaceutical Sciences (Professor)
Yoshinari Kanaoka (7/21/1903–3/10/1981)	Toyama Pharmaceutical College (Professor) Daiichi Yakuhin Co., Ltd., Teika Seiyaku Co., Ltd. Toyama Sogo Bank (President) cf. *Kagaku* **46**(11), 780 (1991)
Munio Kotake (11/30/1894–9/18/1976)	Osaka Imperial University, Faculty of Science, Dept. of Chemistry (Professor) Osaka City University, Polytechnic Institute (Dean)
Toshio Hoshino (11/1/1894–2/11/1979)	Tokyo Institute of Technology (Professor) Riken Institute of Physical and Chemical Research (President)
Koozoo Kaziro (2/2/1897–5/22/1984)	Nippon Medical School, Dept. of Biochemistry (Professor)
Mutsuo Heki (1/23/1903–5/26/1957)	Kanazawa Medical College, Dept. of Internal Medicine (Professor)

still treasure the memories. The well known Journal *KAGAKU* (*Chemistry*) decided to present "Portraits" of *all 14 scientists*, starting with Prof. Tomihide Shimizu, formerly Director of the Institute of physiological Chemistry in Okayama.[102]

XXIV. MUNIO KOTAKE: THE "LITTLE BAMBOO"

One of the Japanese scholars stands out through his personality and friendship with his teacher, namely, Munio Kotake (1894–1976). He stayed with

Wieland in Freiburg from 1924–1925 and never tired in his later years of endowing these two years with a special luster. He symbolized the classical Japan with all of the sophisticated mind-reading etiquette and attachment to the living and dead friends. When, after the war, he came to Europe, to Starnberg or Ingelheim, his first pilgrimage ("BO-SAN") was to the graves where he honored the memory of his teacher or of his friend Ernst Boehringer with a special flower arrangement. Whoever was privileged to observe this rite gained a glimpse into a world gone by. Kotake translated his name into "little Bamboo (kleiner Bambus)," but in reality he was as tall and grounded as the proverbial bamboo of Saga, a suburb of Kyoto.[103]

In "The Constitution Problem of the Morphine Alkaloids. III,"[104,105] Wieland and Kotake in 1925 improved the expression of Knorr and Hörlein of 1907 by shifting the ethylene unsaturation from positions 8–14 to 7–8, almost at the same time that Gulland and Robinson shifted the ethylamine bridge from 5–9 to 13–9 (Fig. 7). In the history of chemistry morphine occupies a special position. In 1844 Liebig ventured the bold prediction that the synthesis of morphine via ingredients of coal tar was only a matter of a few years. But when we look at the pioneers of research on the constitution of morphine, such as Freund (1897–1920), Knorr, Vongerichten, Pschorr (1905) *et al.*, we realize the idealistic trend of this research, because the labor invested has no relation to any results of practical value. Although Robinson started in 1932 with synthetic attempts, not until 1952 did Gates succeed in a total synthesis of morphine, which was simplified in 1980 by Kenner C. Rice to be technically feasible.[106]

XXV. LYNDON FREDERICK SMALL AND WIELAND'S MORPHINE LEGACY

With Kenner Rice we reach the legacy of Wieland through his postdoctoral connection, Lyndon Small (1897–1957)[107] who obtained his Ph.D. degree from James Bryant Conant and in September 1926 moved to Munich, where

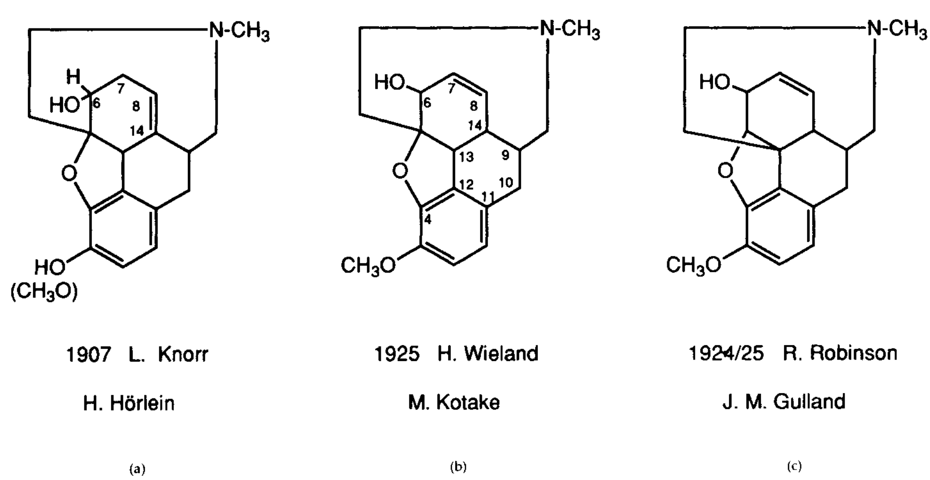


Figure 7. Construction of morphine as seen by (a) Knorr and Hörlein (1907); (b) Wieland and Kotake (1925); and (c) Gulland and Robinson (1925).

he succeeded Kotake[105] with an investigation of the action of ozone on thebaine[108]:

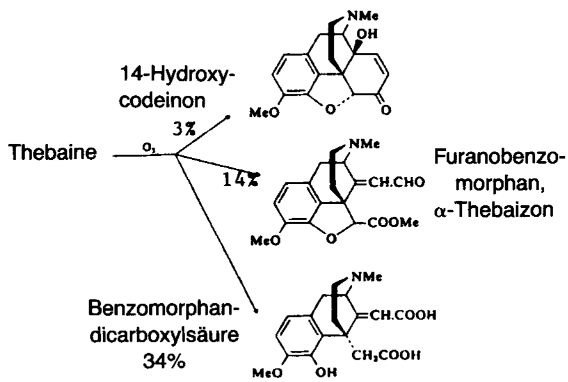


Figure 8. The action of ozone on thebaine.

The reaction product is furanobenzomorphan or α-thebaizone. When Kanematsu repeated this ozonolysis 40 years later, he was able to isolate two additional products, 14-hydroxycodeinone (3%), and benzomorphandicarboxylic acid (34%) besides α-thebaizone (14%).[109]

As with Kotake, Small's two years with Wieland in Munich formed his life, his personality and his research. It did not take long for him to don leather pants, shag coat ("Lodenrock"), and Bavarian manners, so that Wieland amicably referred to him as "mein Amerika-Seppl."[107]

In 1928 Small returned to the University of Virginia in Charlottesville to a position arranged for by Conant. He joined a Program on Drug Addiction, a problem to which he devoted almost thirty years of his life.

When Small and Browning in 1939 reinvestigated the action of phenyl-Grignard reagents on thebaine (Freund 1905, 1916), they isolated four phenyldihydrothebaines,[110–112] which at that time seemed uninterpretable by the accepted structure for thebaine, going back to Wieland's student Clemens Schöpf (1927–1931).

The mystery was solved by Robinson, who in a presidential address to the Chemical Society[113] presented the clever solution:

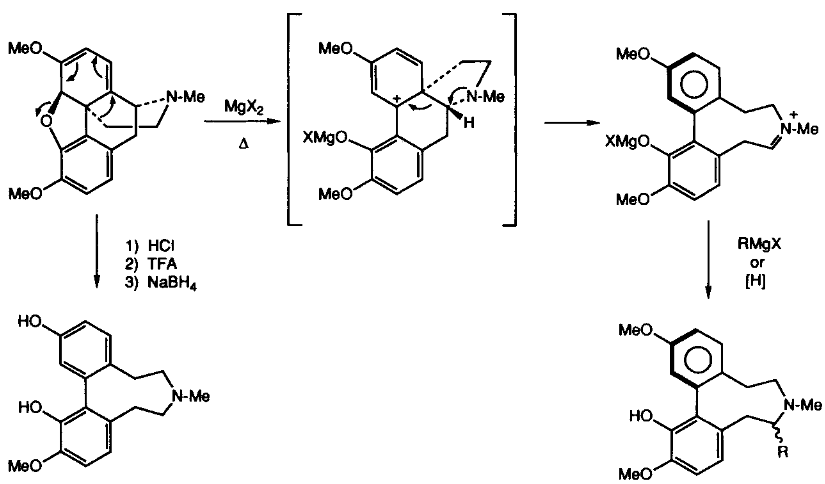


Figure 9.

He called the morphine alkaloids the "star performers among the molecular acrobats," capable of unexpected stunts even without a high wire. Woodward at the time was so impressed that he sent Sir Robert a congratulatory note saying that such an intellectual feat made him "proud to be a chemist."

The nine-membered dibenzazonines possess molecular asymmetry owing to restricted rotation. They isomerize on heating. When he reacted thebaine with phenylmagnesium bromide, Small obtained four distinct optical isomers.

XXVI. THE FOUR PHENYLDIHYDROTHEBAINES: CLARIFICATION BY ARNOLD BROSSI

Lyndon Small's legacy of samples contained the perchlorates of two phenyldihydrothebaines, which Arnold Brossi had recrystallized and subjected to Roentgen-ray analysis in the Laboratory of Isabella Karle, Naval Research Laboratory, Washington, D.C., by Judith L. Flippen. In this way it was possible to assign absolute configurations, for the first time, to all four phenyldihydrothebaines which were further characterized by their CD spectra[114]:

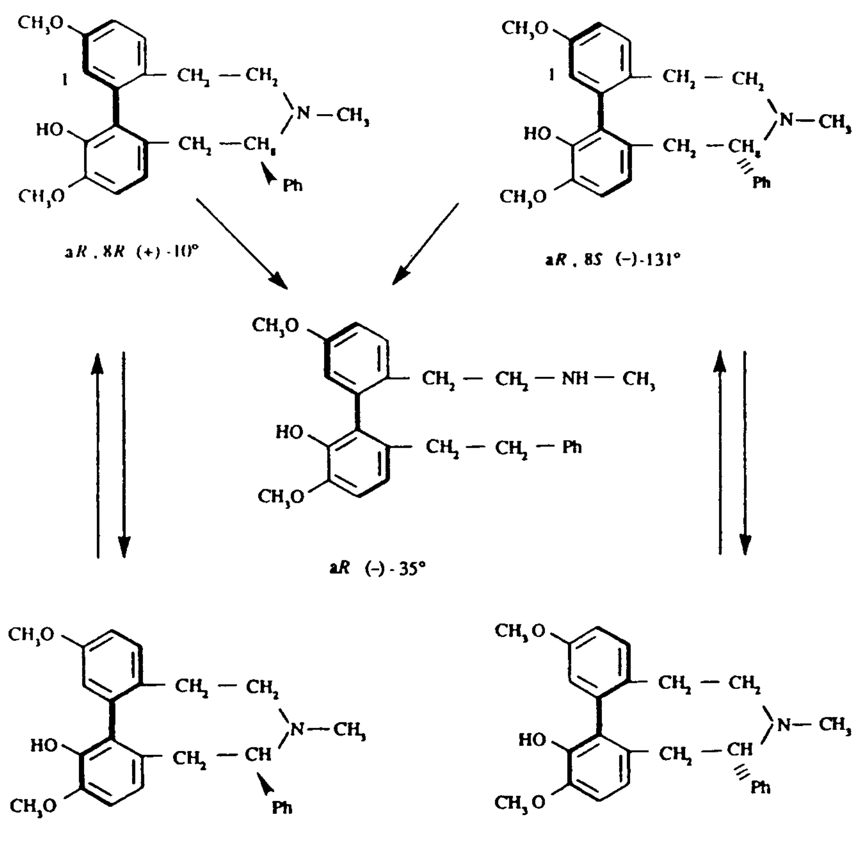


Figure 10. (a*S*,8*R*)-Phenyldihydrothebaine [HCl O_4 (+) −131°]: CD (C 0.004 *M*, MeOH) $[\theta]_{315}$, 0; $[\theta]_{277}$, −4,125; $[\theta]_{263}$, 0; $[\theta]_{254}$, +1,250; $[\theta]_{247}$, 0; $[\theta]_{236}$, −18,250; $[\theta]_{229}$, 0; $[\theta]_{213}$, +88,000; $[\theta]_{206}$, 0; $[\theta]_{203}$, −60,000; $[\theta]_{199}$, 0; $[\theta]_{195}$, +71,200 (last).
(a*R*,8*R*)-Phenyldihydrothebaine [HCl O_4 (+) −10°]: CD (C 0.0044 *M*, MeOH) $[\theta]_{315}$, 0; $[\theta]_{280}$,

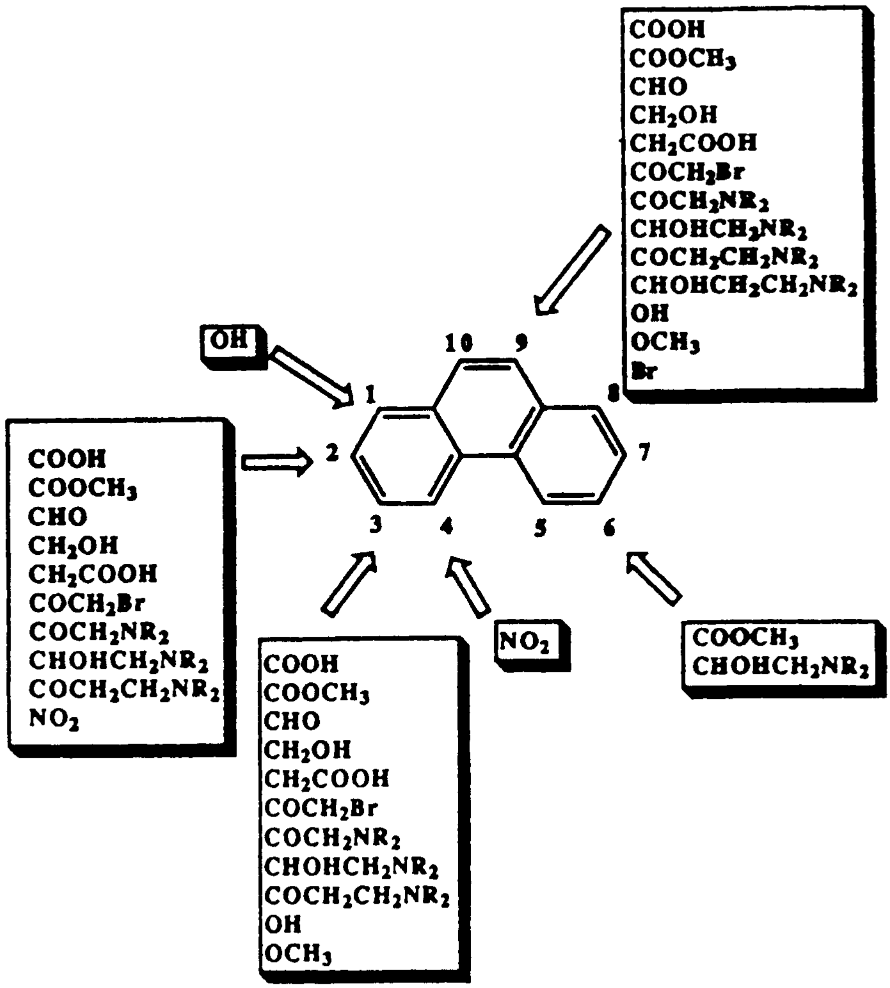


Figure 11.

The open, still optically active biphenyl derivative was prepared from Small's a*R*, 8*R* (+) precursor.

XXVII. LYNDON SMALL AND THE CHALLENGES OF DRUG DESIGN AND ADDICTION

When in 1929 Lyndon Small and Erich Mosettig (1898–1962) followed an invitation of the Committee on Drug Addiction of the National Research Council,[115] the problem was summed up by Reid Hunt (1870–1948):

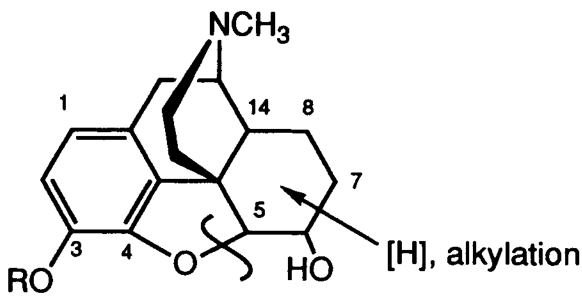
> A thorough study of the morphine molecule might show a possibility of separating the analgesic form from the habit-forming property. Work along these lines would involve cooperation between the highest type of organic chemists and pharmacologists.

+12,750; $[\theta]_{261}$, 0; $[\theta]_{241}$, −18,950; $[\theta]_{234}$, −17,370; $[\theta]_{216}$, −158,845; $[\theta]_{209}$, 0; $[\theta]_{201}$, +342,960; $[\theta]_{194}$, 0 (last).

(a*S*)-Phenyltetrahydrothebaine [(−)−35°]: CD (C 0.005 *M*, MeOH) $[\theta]_{312}$, 0; $[\theta]_{286}$, −2,450; $[\theta]_{215}$, −1,200; $[\theta]_{244}$, 0; $[\theta]_{240}$, +2,100; $[\theta]_{229}$, −19,800; $[\theta]_{220}$, −7,600; $[\theta]_{213}$, −12,000; $[\theta]_{206}$, 0; $[\theta]_{202}$, +14,000; $[\theta]_{198}$, 0; $[\theta]_{192}$, −34,500; $[\theta]_{188}$, 0 (last).

Neither "drug design" nor "medicinal chemistry" at that time were familiar terms or reliable guides. In a division of labor Mosettig decided to give substituted phenanthrenes a try[116,117]: Small took on the morphine molecule itself. Under the title "Potent Analgesia, Respiratory Depression, Dependence, Abuse Liability—Clue to Separability," Small's efforts have been summarized:

Systemic modifications of the morphine molecule.



Small's approach was somewhat different than Mosettig's, in that his molecule was substantially more complicated and thus adding substituents in various parts of the molecule was not the most rational approach to chemical modification. Furthermore, some morphine alkaloids had been synthesized previously and therefore a more systematic approach was taken to determine which structural features were responsible for certain effects of these drugs. Small's approach can be categorized into five major areas: (1) desoxycodeine studies where the 4,5-epoxy bridged compounds were compared to the open 4-phenolic analogs; (2) C-ring reduction studies of codeine and its iso-, pseudo-, and allopseudo-isomers; (3) Grignard alkylation of the C-ring; (4) 3-phenolic alkyl ethers; and (5) miscellaneous syntheses of some phenyl ring-substituted, 14-hydroxy, and N-methylated quaternary analogs, as illustrated.[117]

It turned out that Small's Metapon was an excellent analgesic for chronic pain and was less habit-forming than morphine. It was produced and used up to the mid 1950s while desomorphine was too short acting to be practical (see Fig. 12).

The challenge of addiction looms larger than ever and, in an organizational way, is met by the National Institute of Drug Abuse (NIDA). The survey[118] illustrates the history of this development, which we now started in Munich with Small who moved to the University of Virginia in 1929 and to NIH in

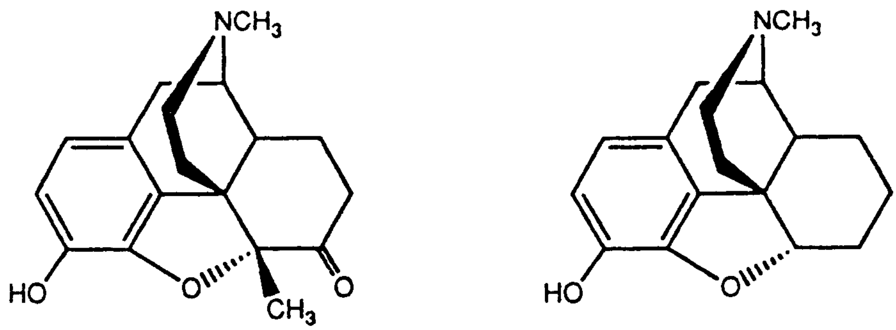


Figure 12. (a) Metapon and (b) desomorphine.

1939, where his legacy still prospers in the Laboratories of Arnold Brossi and Kenner Rice (see Chart III):

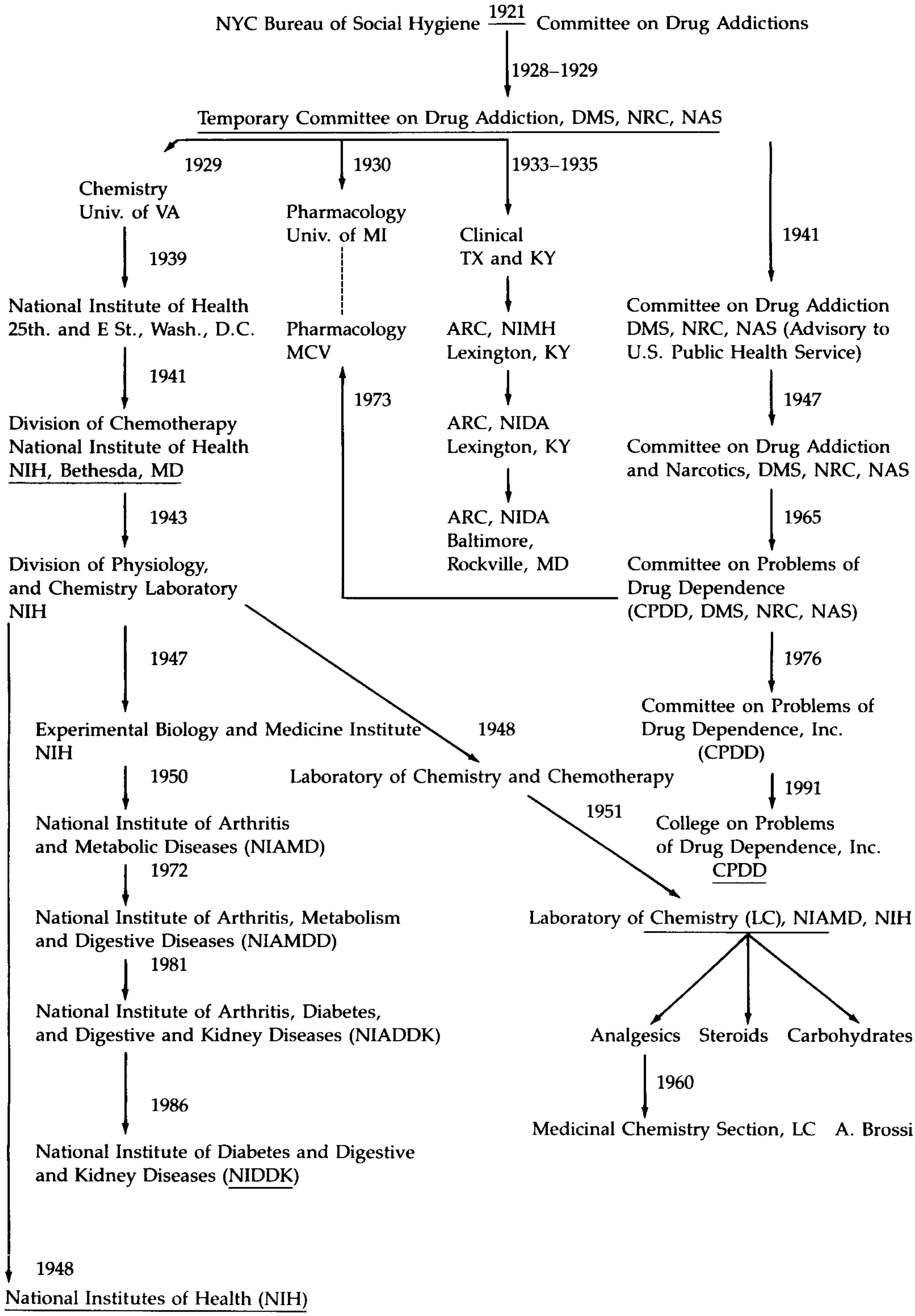


Chart III.

XXVIII. MORPHINE IN MAN: THOMAS MANN'S PREDICTION

Thomas Mann's *The Magic Mountain* appeared in 1924. Konrad Bloch, more than sixty years later[64] was fascinated by the following dialogue in which the principal figure, Hans Castorp, questions his cousin and fellow tuberculosis patient Joachim on the diagnosis of his attending physician, Dr. Krokowski:

"Nothing different. Oh, well, the stuff today was pure chemistry," Joachim unwllingly condescended to enlighten his cousin. It seemed there was a sort of poisoning, an auto-infection of the organism, so Dr. Krokowski said; it was caused by the disintegration of a substance, of the nature of which we were still ignorant, but which was present everywhere in the body; and the products of this disintegration operated like an intoxicant upon the nerve centers of the spinal cord, with an effect similar to that of certain poisons, such as morphine or cocaine, when introduced in the usual way from the outside.

"And so you get the hectic flush," said Hans Castorp. "But that's all worth hearing. What doesn't the man know! He must have simply lapped it up. You just wait, one of these days he will discover what that substance is that exists everywhere in the body and sets free the soluble toxins that act like a narcotic on the nervous system; then he will be able to fuddle us all more than ever. Perhaps in the past they were able to do that very thing. When I listen to him, I could almost think there is some truth in the old legends about love potions and the like."

XXIX. BIOSYNTHESIS OF MORPHINE IN MAN AND IN POPPIES

Indeed, sixty years later Thomas Mann's prediction came true: Who fulfilled Thomas Mann's prediction in the "Magic Mountain?" In chronological order the names that come to mind in this connection are S. Spector (1976),[119] A. Goldstein (1986),[120] H. W. Kosterlitz (1987),[121] M. H. Zenk (1989–1991),[122] and A. Brossi,[123] who continued the morphine legacy of Wieland and Small (1991).[124,125]

First, only fentomolar amounts (10^{-15} mol/g) were detected in toad skin, bovine hypothalamus and adrenal glands.[119] But then picomolar quantities (10^{-12} mol/g) were found in man.[120]

The interesting question is: Is the endogenous mammalian morphine synthesized in the same way as in the opium poppy, *papaver somniferum?*[121] We are well informed on the biosynthesis of morphine in opium poppy by the classical studies of Barton and the recent ones by Zenk. An enzymatically controlled Pictet–Spengler condensation between dopamine and 4-hydroxyphenylacetaldehyde leads to (S)-nor-coclaurine which then undergoes four enzymatically controlled transformations, viz., two O-methylations, one hydroxylation and one *N*-methylation to (*S*)-reticuline. A highly enantiospecific oxidation by (*S*)-tetrahydroberberine oxidase (STOX) is one of the major steps.[122]

Arnold Brossi and Cyrus Creveling[123,124] studied the enzymatic O-methylation reactions of catecholic isoquinoline intermediates in the biosynthesis of morphine with catechol O-methyltransferase and made the important discovery that there is a distinct difference in the course of O-methylation between (*S*)- and (*R*)-configurated substrates. Only the (*S*)-enantiomers underwent regio- and enantio-selective O-methylation to the desired products, while the corresponding (*R*)-enantiomers were methylated at the wrong phenolic hydroxyl groups.[125] There might be a mammalian pathway to morphine which parallels the biosynthesis in the poppy plant, is one of the conclusions of this investigation, which clearly continues the long tradition starting with Wieland and Small and thoroughly in line with Small's *genius loci* at NIH.[126]

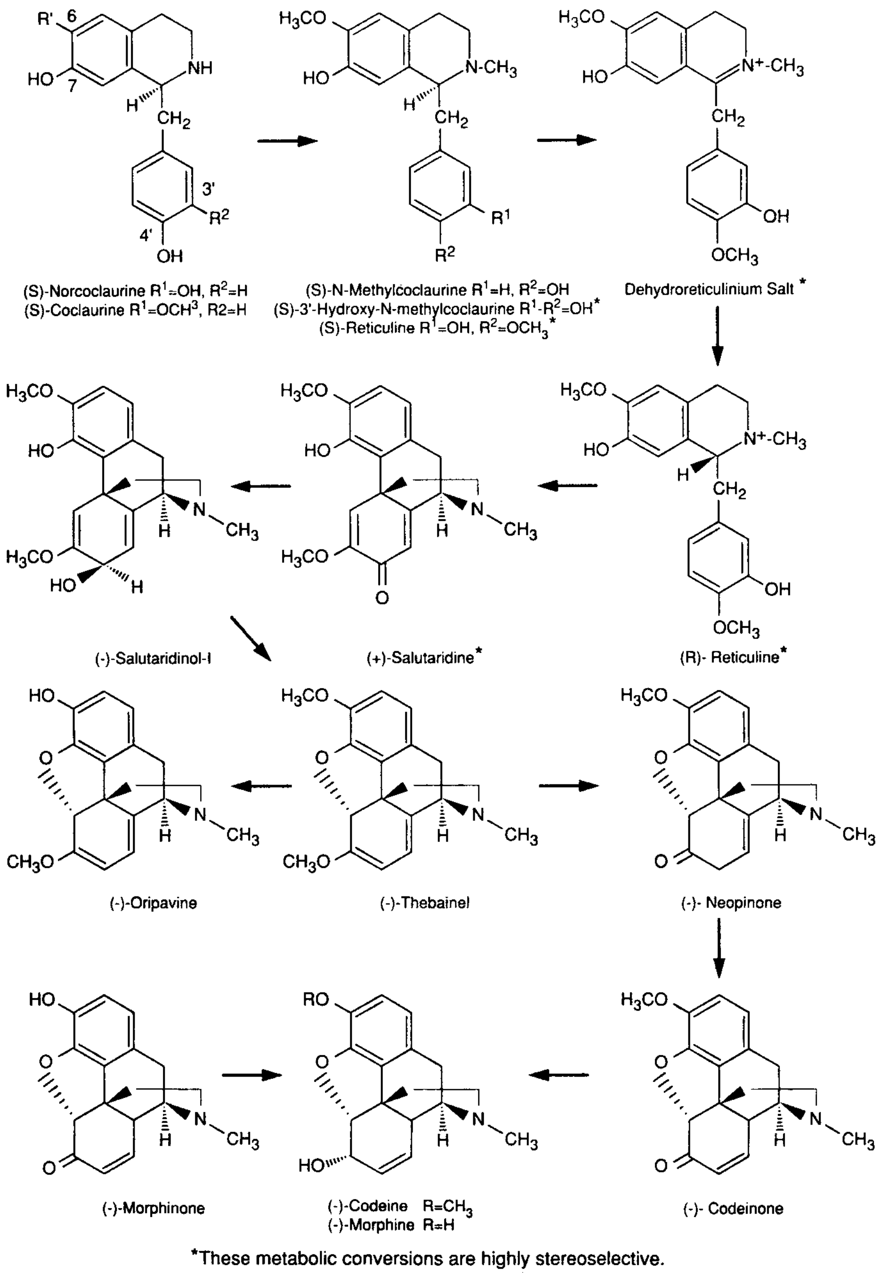


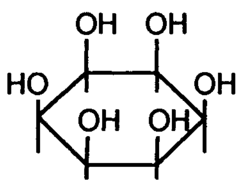
Figure 13. Plant biosynthesis of morphine approximating the pathway in mammals. Courtesy of Dr. Arnold Brossi.

XXX. LE MOULIN MYSTIQUE: THE STORY OF *meso*-INOSITOL

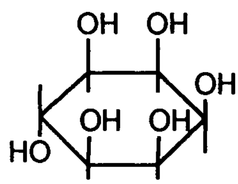
The catalytic reduction of thiophen-free pure benzene to cyclohexane in the presence of palladium black was reported by Wieland in 1912.[126a] This experiment confirmed an earlier observation by Willstätter that aromatic hydrocarbons are susceptible to hydrogenation and that colloidal palladium is the catalyst of choice for mobilizing hydrogen, both for hydrogenation as well as dehydrogenation.[126b]

The next aromatic substrate which Wieland chose for hydrogenation was hexahydroxybenzene, which he reduced to the naturally occuring *myo*-inositol in a landmark paper entitled "The Synthesis of Natural Inositol." His yield exceeded 50%.[126c] It took many years to identify and characterize all nine possible stereoisomers of hexahydroxycyclohexane (I–IX)[126d] and to try to understand or duplicate the remarkable stereo-selectivity of this reduction (see Fig. 14). Several attempts at Columbia University[126e] and at Princeton[126f] failed, as this passage shows:

> We are compelled also to report that all attempts by us to repeat this work (H. Wieland and R. S. Wishart) have failed. In addition, we have been unable to reduce either the hexamethoxy or the hexaacetoxy derivatives under the conditions described by Wieland. Even varying the method of preparation of hexahydroxybenzene to eleminate any doubt concerning purity of product led to negative results. It was found possible to reduce triquinoyl octahydrate smoothly to hexahydroxybenzene but further reduction could not be made to take place using platinum as a catalyst.

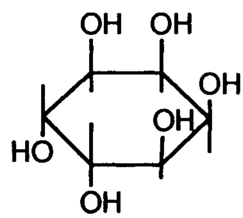


I



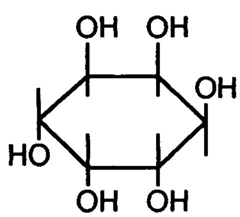
II

epi-Inositol

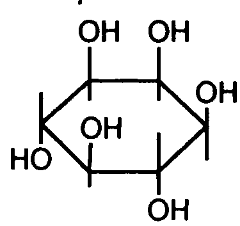


III

allo-Inositol

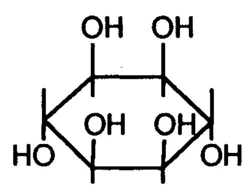


IV



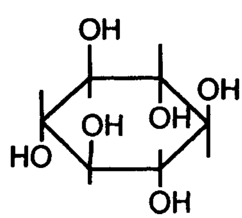
V

meso-Inositol



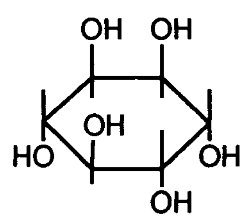
VI

muco-Inositol



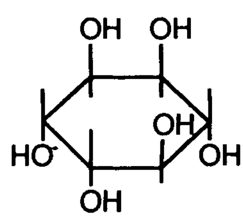
VII

Scyllitol



VIII

dextro-Inositol



IX

levo-Inositol

Figure 14. Stereoisomers of hexahydroxycyclohexane.

It was Richard Kuhn who, in the following year, fully confirmed and repeated Wieland's pioneering experiment[126g] by showing that the absolute purity of the starting material, hexahydroxybenzene, or more preferably tetrahydroxy-*p*-quinone, was essential for successful reduction. In addition, as everybody knows who prepared his own noble metal catalyst, it may take many attempts to arrive at the catalyst of the correct activity, not too active and not too inferior, and to protect the colloidal metal from inactivation by exposure to air. A catalyst too active takes the reduction all the way to cyclohexane or may cause loss of water to produce phloroglucinol. Again, we see the resuscitation of Wieland's idea of activated hydrogen and it shifts 35 years later. This process of the refinement of truth by the passage of time is

Plate 6. The process of passing on and "refining" information is pictured in the 12th century capital in the Cathedral of Vézelay, Burgundy: Moses pours the grain into the "mill of time" and, many centuries later, St. Paul harvests the seasoned flour.

symbolized by "Le Moulin Mystique," the mythical mill of time, at one of the 12th century capitals in the Cathedral of Vézelay in Burgundy.

The steric and electronic forces, as well as the possibility of complexation[126h] that lead to the preponderant formation of *meso*-inositol—with five equatorial and one axial substitutuents—(besides scyllitol), are no longer a question that could not be answered by modern conformational analysis and instrumentation.

XXXI. CLEMENS SCHÖPF (1899–1970)

The other Wieland student who became a "morphine addict," besides Small, was Clemens Schöpf,[127] who, as mentioned above, added the finishing touches to the structures of morphine and thebaine. He was in love with natural products: The resumption of Hopkin's early work on pterins in 1925 goes back to his impetus. His work on the salamander alkaloids continues his teacher's studies on the toad venoms as related steroidal alkaloids.

But throughout his life Schöpf remained one of the most dedicated friends of his teacher by organizing all of the round birthdays, starting with the sixtieth in 1937, to which the chronicler was an awe-struck witness. The celebration of this great event took place in one of the expansive brewery outlets typical of Munich, and there were sketches and displays of unsuspected histrionic and literary talents. Wieland, whose allergy to celebrations involving his own person was well known, had given his consent to this solemnization with extreme reluctance and the proviso that "no relationship to his birthday whatsoever" must transpire during all the merrymaking. the war and post-war years put a pall on the 65th and 70th birthdays and the 80th was commemorated in seclusion. But Schöpf was always the organizer and convener, keeping the ever-growing list of disciples informed and together.[128]

XXXII. CHRISTINE RIEGER (1905–1989): THE SOUL OF THE LABORATORY

Emil Fischer dictated his autobiographical notes to his loyal and ever-present secretary, Fráulein Margarethe Barth. Conversely do we owe a biography of Paul Ehrlich to his indestructible secretary Martha Marquardt (1875–1956), who gave it the title *Paul Ehrlich as Personality and Investigator* (*Paul Ehrlich als Mensch und Arbeiter*), reporting on 13 years (1902–1915) of his life.[129] Wieland was very fortunate to be blessed with a superb secretary, Fráulein Christine Buomann, later Frau Rieger, who joined him even before the Third Reich. With her integrity and intrepidity she became an invaluable ally in Wieland's neverending struggle against the misguided authorities. During the destruction of Munich by dozens of major air raids, in the post-war stagnation, and in the time of reconstruction, she was a source of strength and support, first for Wieland, then for his successor Rolf Huisgen. "I learned so much from Geheimrat Wieland who finished my education," was a passage in a letter of February 19, 1985:

> When on his desk the mail started piling up and there were some complicated matters to be taken care of, I sometimes suggested: "Herr Geheimrat, that may hold us up too long; we postpone it until tomorrow." He responded: "Frau Rieger, mark my words: the postponement of

matters, especially of unpleasant ones, should be avoided. You cannot shirk them and you feel so much better after having disposed of them." This bit of wise advice accompanied me through all my life and is still guiding me, grateful to my good old boss.

Some other time I had criticized and belittled the performance and reliability of some incipient employees. But Geheimrat Wieland swiftly took their side: "You, Frau Rieger, have been young and inexperienced at one time and you would not have liked rash criticism of your best efforts. Never rush into generalizations or quick judgment." That was another lesson I learned.

After D-Day in Normandy we had heavy diurnal air-raids in 1944. During one of them, which destroyed the Willstätter Annex, we all waited it out in the basement of the Laboratory. Many of the students and personnel trembled and sought additional protection under tables and benches; not so Geheimrat Wieland, who stoically held out on his bench without seeming to be perturbed in the least and calmed by his example all the less fortunate timid ones.

After the progressive destruction of the Laboratory I used to bicycle twice a week to Starnberg where the Geheimrat had moved, to take care of administrative matters. Often we were interrupted by the entrance of his youngest grandchild, Peter Lynen. He never told him to leave, but took him on his lap and let him play with the chimes of his watch. Then he was not the awe-inspiring boss, but a loving grandpa.

The prose of Flaubert's "Un Coeur Simple" would be needed to do justice to this jewel of a secretary.

XXXIII. "MY CHAIR IS BURIED IN THE RUINS OF MY INSTITUTE"

What Frau Rieger intimates of the hardships and calamities *during* the war, was exacerbated *after* the war by lack of food, heat, and transportation. Wieland's strong personality and constitution kept him out of resignation and depression. In a letter to his colleague Robert Schwarz,[130] professor of inorganic chemistry in Königsberg and now in the West, Wieland describes the situation of 1947 with some bitterness:

I had occasional reports of your fate in the last "century" of the "Third Reich" and also in the first two blessed years of the Fourth, but your recent letter (December 1946) gave me an exact account of all that happened to you. How fortunate that you belong to those who escaped by the skin of their teeth. I myself did not fare too well. My family survived the chaos, to be sure, but Chemistry in Munich no longer exists: my Chair is buried in the ruins of my Institute and there is little chance that I will be able to erect it again. Chemistry at our University has become a purely theoretical discipline. We are trying now to convert some of the partially damaged Zoological Institute [erected with Rockefeller support] for the use of Chemistry. But, as a consequence of the disastrous shortage of everything, so far we have only been able to provide the ruinous building with a makeshift roof.

There is no chance for scientific activity for the foreseeable future. I was able to construct a workshed in Weilheim which houses a few organic chemists and a few students, but that is just a token. There is not the slightest chance to start laboratory work for beginning students which to me would be the most important aspect.

When the US Army and Military Government needed billets, they had to sequestrate private houses, among them that of Wieland for whom this eviction became a major privation due to his failing eyesight. In a moving letter to the President of the University of Munich he wrote:

On May 16, 1945, I was evicted from my house in Starnberg, Schiessstättstrasse 12, to make room for the occupational forces. As a consequence I have no opportunity whatsoever to continue my scientific activities, without study and without my library. It will also be impossible for me to participate in the reconstruction program of the University, since I am eking out a one-room existence with my family.

I importune you to use your influence that my house and my irreplaceable library will be returned to me and that the American Military Government declare it "Off Limits."

Perhaps you may mention in this connection, that in 1931 I was privileged to deliver the Silliman Lectures at Yale University, that in 1932 I was elected Foreign Associate of the National Academy of Sciences and that numerous American scientists were students of mine, among them the Professors Stanley, Small, Cerecedo, Bachmann and Lauer.

The Minister of Education of the State of Bavaria then supported a petition which the chronicler submitted in person to the Head of the American Military Government in Munich, but this action failed, because the AMG had only civil and no military jurisdiction.

This resulted in a *de profundis* mood, which characterizes the letter to his former lecture assistant Leopold Horner, who was then a lecturer at the University of Frankfurt:

At least, there is now no indication that experimental research will be possible within the foreseeable future. Whether official permission for this will be granted or not, would not make any difference, since all prerequisites are missing anyway. It will take a long time, until we shall find a make-shift accommodation in the Zoological Institute, provided it can be restored. Most of my collaborators and students have been deprived of their jobs. Their rehabilitation will be a task requiring much trouble and patience. While during the war I was busy saving my people from the trenches, I am having now no less trouble to rehabilitate them.

XXXIV. MARKUS GUGGENHEIM: A LIFELONG FRIEND

My father's close friends were few: besides Hans Fischer I would mention Markus Guggenheim. This talented chemist lost his eyesight early, but notwithstanding rose to be division leader at Hofmann–LaRoche in Basel. He worked with Emil Fischer and Emil Abderhalden at the turn of the century. In the twenties he rarely missed the Wieland colloquia in Freiburg which he visited from Basel. He often estivated with us. My father's chess partner H. Höchstetter, the mathematician Tietze, and the theoretical physicist Arnold Sommerfeld also belonged to the closer circle with whom he had frequent and cordial relationship, not to forget Otto Hönigschmid.[131]

What a joy when after the war Guggenheim learned that his "dear Heiner" and "dear Josi" had survived the disaster. As a Jew, Guggenheim was especially abhorred by the atrocities of the Hitler years, but he did not fail to commiserate Wieland's eviction:

That in view of the horrendous guilt of Germany the occupational forces are unable to sunder the wheat from the chaff, does not surprise me in the least.[132–134]

Then he expresses his exuberant joy:

What a feat that you, dear Heiner, in a time and under a regime that both knew no mercy, managed to maintain the integrity of your outlook and character, so that there is not even a shadow of a doubt![132]

Otto Hahn (1879–1968) writes in his autobiography *Mein Leben*[135]:

My friends, Elmire and Jakob Meisenheimer later founded the Chemical Ski-Club, which became known under the acronym "CHEMSKI." Members were, among others, Knoop from Tübingen and then my Berlin colleagues Schlubach, Wieland, and Schwarz.

Prof. Franz Knoop (1875–1946), Director of the Institute for Physiological Chemistry in Tübingen, was not only Wieland's ski partner in "Chemski," but also a friend. When he passed away in the summer of 1946, Wieland commented[136]:

For each and everyone of us seniors it is a blessing when he is taken away without much fanfare and thus spared from viewing the agonizing stagnation in Germany. It is difficult for us to come to grips with the terrible inconsistency that now confronts our lifestyle, our thoughts and our objectives. I am not thinking only of material things in this context. What keeps me going is the joy in watching the doings and dealings of my children and grandchildren and their undiminished will to live and enjoy. They, the younger generation, are right. I find peace of mind by trying to share their optimism and faith, pointing to a not too distant future that may bring us happier times.[136]

The reconstruction of my Institute is impossible because of all the shortages. The laws and regulations governing scientific research in Germany are so restrictive that all initiative is paralyzed. I wonder whether my American colleagues know about these things. Unfortunately there is little understanding for those of us who opposed the Nazis. In exactly the same way as the Americans are anxious to see no former Nazis in office, we are just as eager to keep them away from our Universities. Although we would be the best judges, with our grass-root knowledge of persons and personnel, and of the right candidates for academic instructors, nobody ever bothers to approach us for advice or opinion. There is a lack of confidence and faith.[137]

Prof. R. Adams Dutcher, Chairman of the Department of Natural and Biological Chemistry, The Pennsylvania State College, was instrumental, by contacting the Head of the US Army Agricultural and Technical School in Weihenstephan in Freising near Munich, to engineer Wieland's return into his own house, but not before even the *New York Times* had published a report on Wieland's predicament.

XXXV. THE SEVENTIETH BIRTHDAY (1947)

Thus Wieland, on June 4, 1947, was able to celebrate his seventieth birthday surrounded by family and friends. A special congratulator was Adolf Windaus, who was unable to come in person but sent this historically significant letter, dated May 23, 1947:

My dear Wieland:

I am not sure yet whether on June 4 I will be able to come to your seventieth birthday in Starnberg, so I want to be on time with my written congratulations.

Despite all the misery that is surrounding us, I want to concentrate on the brighter aspects of our present time: above all, what comes to my mind, is how happy I feel about our friendship that lasted over all these years, and about the blessing of our mutual understanding. Your chemical discoveries have always caused me great joy which is undiminished today.

What fills me with pride is the realization that, after the collapse there were still personalities, like you, who were recognized and acknowledged by the world-wide scientific community as a model and paragon, not because of their scientific discoveries, but as a consequence of their flawless character. Not long ago I received a letter from Louis Fieser, Harvard University, which illustrated the importance of your person for the general image of Germany and the judgment by foreign scholars. **Therefore, what I consider to be the culmination of your life is the fact that for twelve trying years you went your human and scientific way unswervingly and kept Nazism at bay.** [My bold]

You will derive special satisfaction, on this day of your anniversary, that your scientific tradition is carried on in your own family with single success.

And so I am confident that, all the tribulations notwithstanding, facing us and Germany, you

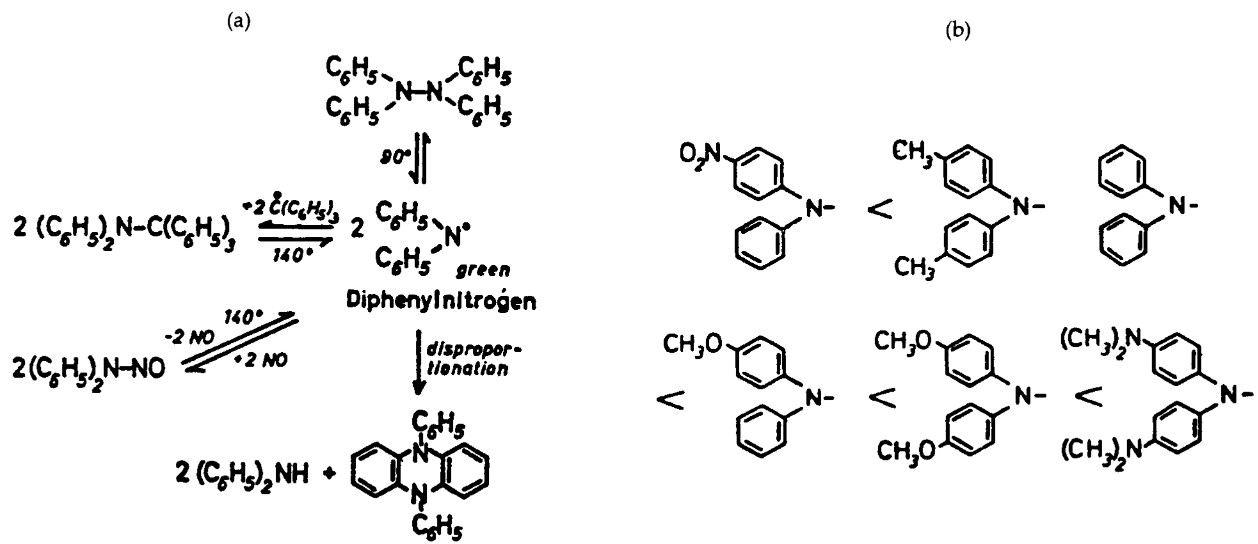


Figure 15. (a) Radical dissociation of tetraphenylhydrazine (H. Wieland, 1911). (b) Tendency of tetra-arylhydrazines to radical dissociation (H. Wieland, H. Lecher, A Süsser, A. Rosseeu, and C. Müller, 1911–1920).

have plenty occasion on this fourth of June to look back on your life and your work with gratification.

With all good wishes and cordial greetings, also from my wife

your old Adolf Windaus

XXXVI. THE CONTINUATION OF THE SCIENTIFIC TRADITION

It is for me a source of satisfaction that now *acetic acid* which I moved first into the biological limelight, has acquired an eminent key position thanks to the achievement of a member of my family in the Munich Institute.[138]

To my great surprise I notice my son Otto roaming the realm of Science. He just completed a nice investigation on the mechanism of intoxication by the death-cap (*Amanita phalloides*).[139]

More joy came with the news that his son Theodor in 1951 received an invitation for a Chair at the University of Frankfurt, where he filled the two paternal legacies, the toxins of the death-cap and of calabash curare, with new life.

An unsolved problem was still Wieland's successor: Both Richard Kuhn and Clemens Schöpf had declined offers to undertake the herculean task of reconstruction from scratch. Finally, there was relief:

My succession has eventually been decided: my young disciple Rolf Huisgen has accepted the Munich professorship for May 1, 1952. Not until then will I be able to withdraw into the snail-shell of my retirement.[140]

Huisgen then guided the reconstruction of the Munich Institute with unflagging enthusiasm. In 1952 he modernized Gattermann–Wieland's classical Laboratory Manual by introducing Robinson–Ingold valence and electron dynamics.

In his "Wieland Memorial Lecture" (1958)[141] Huisgen describes Wieland's classical studies on nitrogen radicals[142] (Fig. 15) which secured for him the esteem and friendship of Moses Gomberg (1866–1947), who was better known by Wieland's children as "Onkel Triphenylmethyl."

In 1830 Berzelius coined the term *isomerism* and used as an example the pair silver cyanate and silver fulminate, as they were then studied by Gay-Lussac and Liebig. Wieland, in the years 1909–1929, continued work on fulminic acid, especially its complex polymerization:

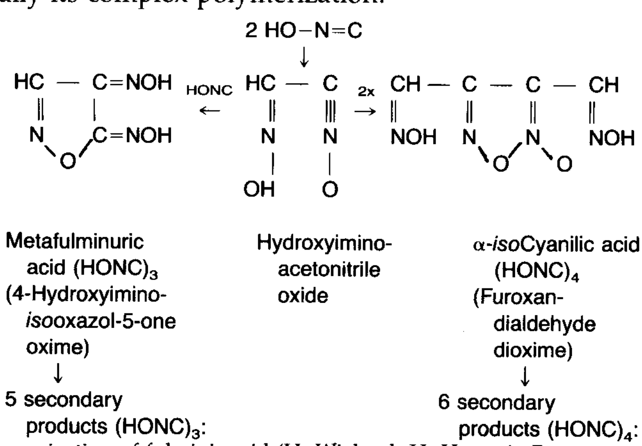


Figure 16. Polymerization of fulminic acid (H. Wieland, H. Hess, A. Baumann, C. Reisenegger, W. Scherer, J. Thiele, J. Will, H. Haussmann, W. Frank, F. Fromm, and Z. Kitasato, 1909–1929).

Cyano(hydroxyimino)-acethydroxamic acid (Nef acid)
α-Cyano-α-nitroacetamide (Liebig's fulminuric acid)
4-Hydroxyfurazan-5-carboxyamide (*iso*fulminuric acid)
3-Hydroxy-4-hydroxyimino-*iso*oxazol-5-one imide
3-Amino-4-hydroxyimino-*iso*oxazolone

β-*iso*Cyanilic acid
Metacyanilic acid
Pericyanilic acid
α-Epicyanilic acid
β-Epicyanilic acid
Erythrocyanilic acid

Figure 16 (*Continued*)

John Ulric Nef (1862–1915) formulated fulminic acid as carbonyl oxime, whereas nowadays we write it as formonitriloxide,[143,144] an expression that Wieland considered only as partner in an equilibrium:

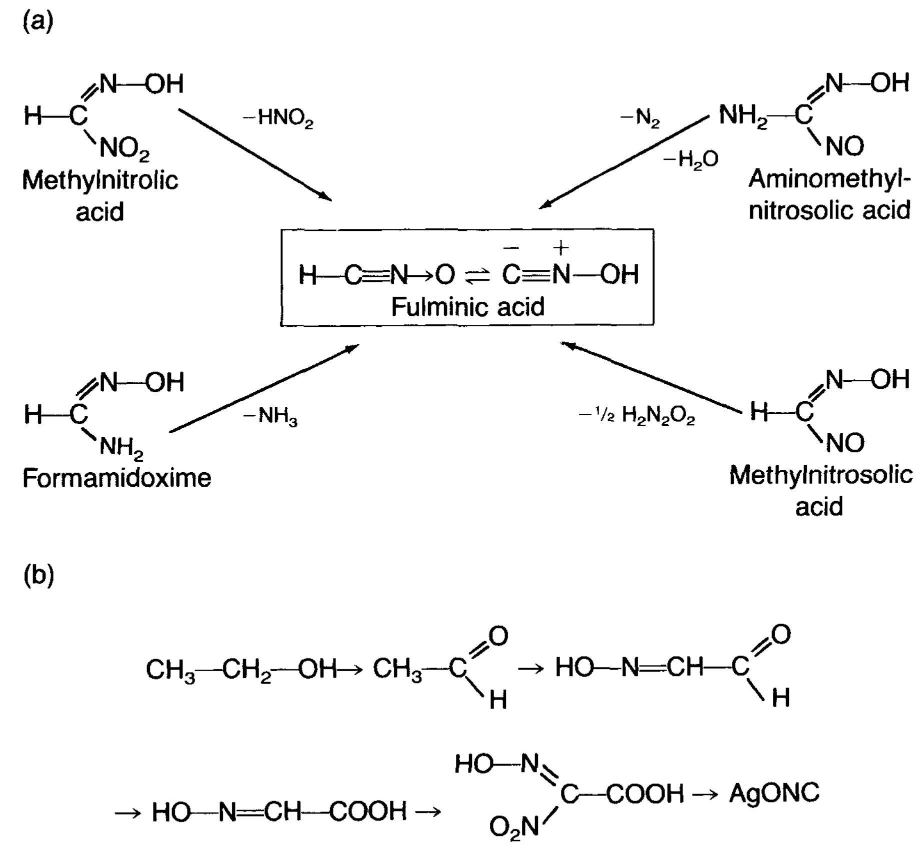


Figure 17. (a) Formation of fulminic acid. (b) Pathway of the classical synthesis (H. Wieland, 1907/1909).

Nitriloxides were investigated by Wieland in 1907; at that time he complained about their lack of reactivity in that they did not add ammonia, aniline, phenylhydrazine, or halogens.[145] All this changed radically when

Wieland's nitriloxides[146] became partners in Huisgens systematic studies on 1,3-dipolar additions.[147]

Wieland comments on his disciple in 1951 in a letter to his friend Guggenheim:

I take special pride in my youngest disciple Huisgen. You may not know him, since his field is pure organic chemistry, radicals and such stuff. Huisgen became Assistant Professor in Tübingen two years ago. . . . I wish he would succeed me in Munich. He is all of 31 years old.[148]

Just one year later his wish found its fulfilment.[140] Now the old master was ready for peace of mind and *otium cum dignitate:*

I feel my best when the mild rays of an autumnal sun warm me in front of my house without challenging me to taxing feats of the mind.[148]

In 1953 the sculptor Emil Krieger was commissioned to shape a bust of Wieland which now adorns, in two castings, the Chemical Institutes both in Munich and Freiburg:

I have to sit as a model for a sculptor so that he may cast me in bronze for the new Institute in the Arcis-street which is now under construction. This unfortunate Pygmalion has been searching for the last fortnight, but he may not succeed in finding anything special behind my physiognomy.[149]

In 1955 Theodor Wieland had a breakthrough in his amanita problem. Without delay the proud father passed on a reprint to his friend Guggenheim, who responded:[150]

Many thanks for the paper on phalloidin. This masterpiece of modern biochemistry certainly is in no need for my irrelevant eulogy, but still I cannot forbear expressing my whole-hearted admiration. . . . In any case, the elucidation of this highly active vegetal toxin has opened new approaches to the fascinating connection between structure and physiological activity.

These connections between structure and activity have been summarized 30 years later by Theodor Wieland in his admirable monograph in which he reviews his life work on amanita.[26] Again there is reason for elation. This time the youngest son Otto excels with a new feat (1957):

Our son Otto has now really joined the ranks of noteworthy investigators: he succeeded in obtaining glycerol phosphorylase in crystalline form.

When he noticed the approach of his eightieth birthday, he became apprehensive and sent a circular to friends and family members:

I must make it quite clear and ask you to refrain from making any fuss, should I be privileged to enter my ninth decade, because I am saddled with a severe allergy in this respect.

When we go back to his wedding, March 29, 1908, we find a similar situation:

As much as I like to participate in celebrations for other people, I have an equally strong aversion to find myself in the middle of an extraordinary event of the kind that leads to mental agitation or emotion. At such events I try to avoid "solemnity."

Thus his wedding became a reenactment of "Il Matrimonio Secreto."

XXXVII. LIEBIG'S *ANNALEN DER CHEMIE:* WIELAND'S *ANNALEN*

Shortly before his eightieth birthday, on December 12, 1956, Wieland commented,

The Editorship of the *Annalen* has now been transferred to Richard Kuhn just at the right time. I have serious difficulties with my eyes and with reading and, besides, my interest in organic chemistry is waning.

Since 1922 (more than one generation), the *Annalen* had been under the firm editorship of Wieland. He scrutinized each manuscript, mostly at home in his study at night. Daytime was meant for experiments. For example, when members of his private Laboratory were not deeply involved in experimentation but absent, and he was informed that so-and-so was in the Library, his indignant reply was, "For pity sake, why doesn't he work?"

The "due process" of acceptance or rejection, in general, was a short one. The time between submission and publication was usually 3–4 months. Elisabeth Dane, his faithful disciple and later colleague, aided him as assistant editor. Adolf Windaus was an official member of the editorial staff from 1928–1959. At that time no other journal had such a handy format, which Wieland tried to retain. In his view, the reader should be able to enjoy the *Annalen,* even in the streetcar or the dentist's waiting room.

The appearance of a new issue of *Annalen,* in those days, was always awaited with great expectations, especially when the reader had also become an author. This, of course, is no longer so: in the last twenty years the number of scientific journals rose from about 70,000 to 108,590. "The wish to publish something important is often eclipsed by the desire to make yourself important," commented Allen Bard,[151] Editor of the *Journal of the American Chemical Society.*

Preparing a joint manuscript with the Master for publication became a ceremony solemnified by the distribution of Brazil cigars and the evolution of clouds of "incense." Nothing was hurried in this process and matters of style and lucidity received ample time and attention. Wieland may have been guided by Goethe's aperçu, "The Germans possess the gift to make science inaccessible." Again: The style is the man! Both in the challenge of editing as well as in his research Wieland made bold to seek excellence, an attitude that today, by some, could be decried as "elitist." How would he have countered such an aspersion? Maybe he would have quoted William Learned:

The conception of a democratic education as one leveled to a colorless mediocrity is as grotesque an interpretation of democratic principles as [a conception] of health in which abounding vitality is deprecated on the ground that only average health is fair to the community. No one believes this.[152]

Equalization and uniformity in the Third Reich and the "simplification of the multitude of journals" posed grave dangers to the *Annalen*. The trend was a combination with "Berichte." Burckhardt Helferich, a pillar and pioneer in chemical education, wrote to A. Schleede, a "respected member of the Nazi party," on June 1, 1938:

There is an immense danger in having all chemical journals subjugated under one direction. I importune you not to meddle with the present organization of our chemical journals.[153]

Fortunately, with the outbreak of World War II these dangerous schemes were eclipsed by bigger problems. After the War and after the division of Germany, Wieland tried to establish a new home for the editorial office of the *Annalen* in Munich. However, the shortage of intact buildings in this ruined city precluded further such attempts.[154,155]

XXXVIII. CROWNING POINTS IN WIELAND'S LIFE

Windaus, in his congratulatory letter on the occasion of Wieland's seventieth birthday, calls his success in keeping Nazism at bay the culmination of his life. But not only did he keep Nazism away from his own person, but also from many other persons, members of his Laboratory, especially those who were endangered, shadowed, and threatened by the Secret Police (Gestapo).

On November 10, 1938, the morning after the "Kristallnacht," the night of the first official, government-ordered universal pogrom, Wieland was informed that, of the three busts in the place of honor of the lobby of the Institute, that of Willstätten was missing. In a solomonic, but under the prevailing conditions also risky decision, Wieland ordered the removal of the other two busts: one was a work of art by Adolf von Hildebrand representing Adolf von Baeyer[156] who, in the Third Reich, as a grandson of Julius Eduard Hitzig, friend of E. T. A. Hoffmann and Adalbert von Chamisso, would have lost his position under the law for "the Restitution of the Civil Service" ("Gesetz zur Wiederherstellung des Berufsbeamtentums"). The other bust was of Heinrich Wieland and had been sculpted in 1928 by Josef Hinterseher after he had become a Nobel Laureate. It was in the afternoon of this ominous day, which gave those who wanted to see a premonition of the "Final Solution," that Wieland decided to visit his friend and predecessor Willstätter in his cultivated home in Möhlstrasse 29. He was anxious to show his solidarity and support. There ensued a conversation whose involuntary witness was the chronicler, waiting his turn in the famous wainscotted antechamber (Plate 10):

Nobody will dare to touch you!

Wielands apodictic statement rested on the assumption that the Nobel prize and the highest order, the "Pour-Le-Mérite," would offer protection. Arthur von Weinberg (1871–1943),[157] philanthropist, pioneer, and leader of industry, became a victim of this illusion, which also endangered Hedwig Ehrlich, Paul Ehrlich's widow, whom he advised to stay, but who, fortunately, left Germany at the last moment. Wieland, as an "Employee of the State" (Beamter), consciously underwent a great risk, the possibility of a lawsuit or even dismissal, by this show of solidarity with Willstätter.

Plate 7. Adolf von Baeyer (1835–1917). Bronze bust sculpted by Adolf von Hildebrand.

Plate 8. This bust representing Richard Willstätter, sculpted by Josef Hinterseher, was removed from the honor lobby of the Chemical Institute in Munich on November 9, 1938–"Kristallnacht."

Plate 9. Bust of Heinrich Wieland sculpted in 1928 by Josef Hinterseher.

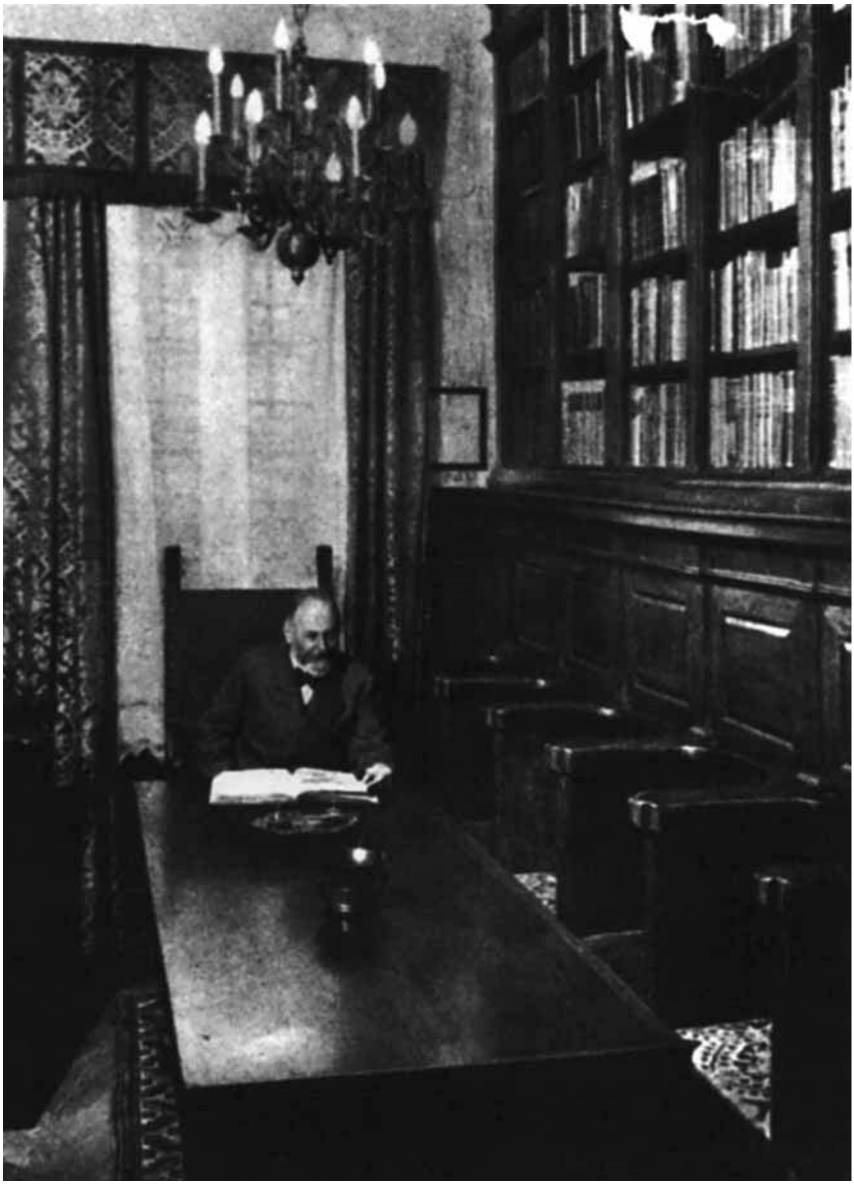


Plate 10. Richard Willstätter in the famous Italian "rood-loft" with just enough pews to seat the Members of the Faculty. Visitors cooled their heels here for the prescribed minimum waiting time of fifteen minutes.

Because of his robust constitution and character Wieland had some difficulty appreciating Willstätter's sensitive, as well as sensitized character:

I found it agonizing how much this poor man suffered, all through his life, from this imaginary racial distinction or even his illusion of racial inferiority. How different was Fritz Haber who was not burdened in the least by passive sentimentality in these matters.[158]

Willstätter records the event with the three busts in his autobiography, so there is reason to believe that he was told the same day by Wieland. By contrast, the bust of Albert Ladenburg in the Chemical Institute in Breslau survived the War until the city became Wroclaw.

XXXIX. WIELAND AND THE "WHITE ROSE"

There is a bronze plaque in the Atrium of the Ludwig-Maximilian University in Munich with the inscription of seven names:

WILLI GRAF, PROF. KURT HUBER, HANS LEIPELT, CHRISTOPH PROBST, ALEXANDER SCHMORELL, HANS SCHOLL, SOPHIE SCHOLL

These are the names of six students and their professor at the University of Munich who resisted Nazism and were executed. On top of these seven names the viewer observes the intaglio of a White Rose,[159] an emblem which in the last 45 years has become the symbol of a community that honors the memory of the most notable youth group to offer resistance in the middle of the War, the most dangerous and suppressive time. One of them, Hans Leipelt, was Wieland's student. After the first major exam, he was entitled to add "cand. chem." to his name, which, before his execution, in a letter to his sister Maria, also a prisoner of the Gestapo, he changed to "cand. mort.[160]" He was beheaded on January 29, 1945 in the Stadelheim Prison near Munich.[161] His story begins with the execution of Hans and Sophie Scholl in February 1943, when he organized a collection for the widow of professor Huber, another victim.[162] He continued the duplication and distribution of the Scholls' last flyer with the addition ". . . and their spirit lives on! Notwithstanding!" He passed these amended flyers around not only in Munich but also at the University of Hamburg. On October 8, 1943 Leipelt was arrested as a result of a denunciation. At that time Wieland entered the stage and tried to keep *due process* alive by aiding and organizing measures for the defense, an almost hopeless endeaver in a lawless environment and under a criminal government. Wieland's attitude justifies some comment on the concept of the "autonomy of science in the Nazi State":

> Wieland was an untypical scientist. He proved it by not abdicating his involvement in the social and ethical issues of his Laboratory and by feeling morally responsible for his students under his trust. Unlike so many others, he did not reduce his life to the existence of an encapsulated scientist, detached from all daily events. His idea of autonomy was not limited to science alone, but encompassed personal and political autonomy and, therefore, excluded compliance with the measures of a criminal government.
>
> In the time of National Socialism everything that endangered the so-called autonomy of science was judged to be painful, troublesome or even dangerous. What this means may be illustrated by the fate of Lise Meitner (1878–1968), Otto Hahn's long-time assistant, about whom some of the members of the Kaiser Wilhelm Institute complained: her presence puts the Institute at risk. Should she not become aware of this and decide to leave? Or, to single out another case regarding Einstein: Why does he not play the game and obey the rule that scientists stick to science and don't meddle in politics? Why does he risk such dangerous political remarks abroad?[163]

By the same token Wieland could have been annoyed at the risk to his Institute, which was a well known asylum for endangered and persecuted minorities and therefore was under constant surveillance.[163a] But the opposite was true: he selected defense lawyers, helped to organize possible plea bargaining and asked to be informed about the preparation of the trial. When on October 13, 1944 the court proceedings began, he went to Donauwörth by train, in order to serve as witness for the defense and to try to exonerate his student before the Public Tribunal (Volksgerichtshof).

Those who were present will not forget the dignity which he displayed when he casually shook the hands of, and addressed the defendants in a matter of fact manner that had even the guards impressed, so that they let him a free hand for a while.

> At the trial where he avoided rendering the fascist salute, there was little he could say about the arraignement or indictment itself. But the value of his presence and his moral support can hardly be overestimated. He proved by his participation, that they were first his students and then defendants.[163]

Of course, there could not have been any shadow of a doubt from the beginning: the verdict was "guilty" and the penalty was death by decapitation for Konrad Leipelt (1921–1945).

"Whoever gets caught by this murderous machinery is lost," commented Wieland a few days later, when he seemed more aged and more stooped.

XL. FAREWELL TO HEINRICH WIELAND

His eightieth birthday[164] was commemorated quietly within the family. Shortly thereafter, on August 5, 1957, death came in a gentle way, freeing him from the growing burden of age. Walther Gerlach (1889–1979) was present at the grave[165] and remembered his friend:

> I have admired and loved him as so many did, who would all be here today, if our Heinrich Wieland had not departed this life as quietly as he lived it. The man whose fame as one of the truly great chemists was worldwide, was and stayed, up to his end, an individual shunning the spotlight and publicity. A life of fulfilment has ended, for all of us too prematurely. You, my friend, have kept your house in order, you loved this life and relished it, but you gave more to others than you received from them.
>
> You kept modesty and pride in an enviable equilibrium: pride over achievements which should be more visible than the man. He never asked more from others than what he demanded from himself and set as an example. Always ready to engage in discussion, he stubbornly stuck to his opinion, when the counter-arguments failed to convince him, be they problems of science or questions of life. Here were the roots for his sense of justice, but also for the extraordinary success in his science. "I left the scientific field of my teacher as soon as I could, in order to follow my own ideas," was his opinion when, several years ago, we discussed the correct education of scientific progeny.[165]

When we celebrated the Wieland Centennial in September 1977,[166] Walther Gerlach, 88 years young, addressed the congregation of friends and colleagues who had come from all over the world:

> There is a special tradition that we want to cultivate, the tradition which he honored and recognized: the neverending search for veracity, and to make it the foundation not only in science but in all our human relations, and in the end let us seek to combine the joys of the act of acquiring knowledge with the other pleasures in life.

And in this sense Wieland lives on among us.

Members of the Wieland family were instrumental in providing supporting documents, especially Prof. Theodor Wieland, Dr. Med. Irmgard Wieland, their daughter Sibylle Wieland, Prof. Eva Lynen; the Wieland disciples Prof. Rolf Huisgen, Munich, and Prof. Emeritus Leopold Horner, Mainz, for helping with personal memories and unpublished material. Dr. Med. Marie-Luise Schultze-Jahn kindly searched the Archives of the University of Munich of the Bavarian State Library and of the Bavarian Ministries. Prof. Gerda Freise, Göttingen, provided me with a copy of her speech delivered in Pforzheim on November 17, 1988. Angela Bottin, Hamburg, one of the Trustees of the Association "Weisse Rose," clarified Wieland's relations with this group. Prof. Hiroshi Morimoto, Nishinomiya (Japan) kindly collated the list of Wieland's Japanese disciples. While they were alive, Frau Christine Rieger, Feodor Lynen, and Sir Hans Krebs, as well as my late friend Hans-Jürgen Staudinger, all helped with letters and personal memories.

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3. Albertus Magnus, or Albert von Bollstädt, came from the Black Forest town Lauingen, and as Magister Albert he brought classical natural science to the West. Paracelsus, from Hohenheim near Stuttgart, was the founder of iatro-chemistry, and Robert Mayer's *concept of causality* had just been the topic of a monograph by Alwin Mittasch (Springer, 1940), which Wieland had read and liked to discuss.
4. Ernst Kretschmer, *Geniale Menschen,* Springer, Berlin, 1931.
5. Josef Hausen, Was nicht in den Annalen steht, Verlag Chemie, 1964, 94.
6. Wieland's first student was Siegfried Bloch, cf. *Berichte* **37,** 2524–2528 (1904), who, however, flunked his promotion, so that Hans Stenzl filled the gap and came to be known as "Wieland's first student."
7. Cf. H. Wieland and H. Stenzl, "Additionen der höheren Stickoxyde an doppelt ungesättigte Kohlenwasserstoffe. Über einen neuen Fall von 1,4-Addition," *Annalen* **360,** 299–322 (1908).
8. Letter of Hans Stenzl written to Prof. Franz Gottwalt Fischer in Würzburg, from Riehen on January 13, 1960.
9. Cf. H. Wieland and Franz Gottwalt Fischer, "Zur Frage der katalytischen Hydrierung. Über den Mechanismus der Oxydationsvorgänge. IX," *Berichte* **59,** 1180–1191 (1926).
10. Franz Gottwalt Fischer, "Obituary for Heinrich Wieland," *Bayer. Akad. Wiss. Jahrb.* (1959). Wieland had been a member since 1916.
11. There may have been an immediate reason for this critical remark: On October 30, 1935, the new antisemitic "Law for the Restoration of the Civil Service," i.e., in reality its destruction by the codification of injustice, led to the forced abdication and later forced loss of citizenship of Kasimir Fajans, Director of the Institute for Physical Chemistry that, because of his eminence, had been constructed, in part, with Rockefeller support. The Bavarian Minis-

ter of Education in a "ukase," dated November 4, 1935, ordered Wieland to act as substitute for Fajans until a successor (Claus Clusius) could be nominated.

12. As would be expected, not everybody was delighted by Wieland's obvious critical attitude. The search in the Archives of the Bavarian Ministry of Education unearthed a letter, dated May 17, 1935, written to the Executive Secretary Böpple and signed not by name, but by "a Group of National-Socialist Chemists:

> By his constant nagging [the official Nazi term was "meckern"] Prof. Wieland with his negative attitude against our Government is becoming more and more intolerable. In addition, he is more than a double-earner, since he receives, besides his salary and lecture fees, royalties from the Chemical Industry, viz., C. H. Boehringer, Ingelheim/Rhine.

The reply, in its totally unexpected fairness, is a surprise: it has the file number V 26582 Au, the date is May 21, 1935 and says:

> Since November 4, 1931 the Minister has been cognizant of the fact that Prof. Wieland is a Member of the Board of C. H. Boehringer/Sohn, Subsidiary in Hamburg, an activity approved by the Minister, since it does not involve direct or indirect emoluments or retainers. There is no need to follow up this anonymous denunciation. Signed Referee 2, Möller.

13. Johannes Stark, together with another Nobel Laureate, Philipp Lenard (1862–1947, NP 1905) joined forces to teach and write "German Physics," i.e., physics free of "corrosive Jewish insinuations," such as the theory of relativity.
14. Walter Ruske, *Hundert Jahre Deutsche Chemische Gesellschaft*, Verlag Chemie GmbH, Weinheim, 1967, p. 151.
15. Karl Dimroth, "Das Portrait: Adolf Windaus 1876–1959," *Chem. Unsuerer Zeit* **10**, 175–179 (1976).
16. Die Chemie im Dienste der friedlichen Wiederaufbauarbeit, *Chem. Ztg.*, No. 1, January 3, 1934, p. 8.
17. Ulrich Wieland, Ein Leben für die Wissenschaft, Seventieth Birthday of Heinrich Wieland, Badische Zeitung, June 7, 1947.
18. Robert Jungk, Heller als Tausend Sonnen, Bern, 1956.
19. Avram Goldstein, "Otto Krayer," *Biogr. Mem. Natl. Acad. Sci.* **57**, 150–225 (1987). Krayer's courageous example deserves to be commemorated by chairs, Institutes, fellowships, etc., bearing his name.
20. *Pforzheimer Zeitung*, November 19, 1988: Civil Courage in Depraved Times. Wieland did not give the fascist salute, not even in front of the Public Tribunal.
21. *Pforzheimer Zeitung*, No. 116, Saturday, May 19, 1984, p. 9; Heinrich Wieland a Paragon for Students, cf. *Kurier (Pforzheim)* December 12, 1983.
22. Armin Wankmüller, die Firma Dr. Theodor Wieland, *Pforzheim;* Württembergische Apotheker als Fabrikanten. X. Mitteilung; Beiträge zur württembergischen Apothekergeschichte, Band X, 42–46 (1973).
23. L. Gattermann, *Die Praxis des Organischen Chemikers*, 24th ed., H. Wieland, Ed., de Gruyter, Berlin/Leipzig, 1936, p. 4.
24. *Stuttgarter Zeitung*, No. 254, 27, Thursday, November 4, 1971, p. 27, Rubrik: Aus dem Wirtschaftsleben.
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28. Paul Walden, *Wege und Herbergen: Mein Leben, Herausgegegeben von Günter Kerstein*, Steiner-Verlag, Wiesbaden 1974, p. 103.
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31. Letter from the Foreign Office (Auswärtiges Amt), File No. VI W 4707, Berlin, May 27, 1931.
32. Wieland's petition to the Bavarian Minister of Education was routed through the President of the University of Munich on April 9, 1935: File No. 2145/V35.
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35. Richard Willstätter, *Aus meinem Leben,* Verlag-Chemie, 1949, pp. 315, 346.
36. Emil Fischer, *Aus meinem Leben,* prologue and epilogue by B. Witkop, Springer-Verlag, Berlin, 1987.
37. Heinrich Wieland, "Über Additionen mit den höheren Oxyden des Stickstoffs an die Kohlenstoffdoppelbindung," *Annalen* **328,** 154–255 (1903).
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39. H. Wieland, "Le Principe de la Migration de l'Hydrogène," *Bull. Soc. Chim. Fr.,* 1233–1242 (1938).
40. H. Wieland, "Acerca del desarollo de los procesos de oxidación," *An. Soc. Esp. Fis. Quim.* **27,** 181–191 (1929).
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62. Elisabeth Dane, *Naturwissenschaften*, **30**, 333–342 (1942).
63. Konrad Bloch, in a letter dated June 28, 1977, in which he comments on the survey of Wieland's research on steroids, as it was then incorporated in the centennial lecture: "B. Witkop, His Lifework and His Legacy Today," *Angew. Chem. Int. Ed.* **16**, 559–572 (1977); *Angew. Chem.* **89**, 575–589 (1977).
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66. Cf. Harold King, "Dr. Otto Rosenheim, F. R. S.," *Nature* **175**, 1019 (1955); and *Biogr. Mem. Fellows F. Soc.* **2**, 257–267 (1956).
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    When the last dubieties of the constitutional problem, presented here, will be clarified, people, no doubt, will expect the total synthesis of the class of compounds that now have become accessible. Cholanic acid possesses seven [in reality 8] cholic acid, ten [in reality eleven] asymmetric centers, and the strange concatenation of the numerous rings, in the absence of viable synthetic methods, cannot be approached. Even though I acknowledge the obligations of the organic chemist for the synthesis of molecules, such as hemin, I must reject such an obligation in the present case most emphatically. However, I am fully cognizant of the obligation to finish what I started.

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101. Theodor Wieland, "Heinrich Wieland," *Kagaku (Chemistry)* **45,** Fascicle 1, 46–48 (1990) In Japanese.
102. "The Research Group of Heinrich Wieland: Tomihide Shimizu (1889–1958)," *Kagaku* **45,** Fascicle 2, 130 (1990). In Japanese; this is the first of the "profiles," planned for all 14 Japanese students of H. Wieland.
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111. L. F. Small and E. Fry, *J. Org. Chem.* **3,** 509 (1939).
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115. Cf. Bernhard Witkop, *Organic Chemistry in a Biomedical Research Organization, NIH: An Account of Research in its Laboratories and Clinics,* DeWitt S. Stetten, Ed., Academic Press, New York, 1980, pp. 193–219.
116. Bernhard Witkop, *Erich Mosettig, Proc. Chem. Soc.* November 1964, 376–377.

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122. T. Amann and M. Zenk, *Tetrahedron Lett.* **32,** 3675–3678 (1991).
123. Y. Sekine, C. Creveling, M. Bell, and A. Brossi, *Helv. Chim. Acta* **71,** 426 (1990).
124. C. R. Creveling, M. E. Bell, Y. Sekine, D. Tadic, and A. Brossi, 20th Annual Meeting of the Society for Neuroscience, St. Louis, Missouri, Abstract 333.10.
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126. Thomas Mann's prediction has a forerunner, as Prof. Avram Goldstein kindly informed me: the starting observation was the cataleptic effect of morphine in rats as reported by M. Mavrojannis: "L'action cataleptique de la morphine chez les rats. Contribution à la Théorie de la Catalepsie," *C. R. Séances Mem. Soc. Biol.* **55,** 1092–1094 (1903). Cf. Ch. Bouchard, *Lectures on Auto-Intoxication in Disease or Self-Poisoning of the Individual*, Davis, Philadelphia, 1906.
126a. H. Wieland, "Einige Bemerkungen über die Hydrierung aromatischer Verbindungen," *Ber. Dtsch. Chem. Ges.* **45,** 2615–2617 (1912).
126b. Wieland's first contribution to the mechanism of oxidative processes deals with this aspect: *Ber. Dtsch. Chem. Ges.* **45,** 484–493 (1912).
126c. H. Wieland and R. S. Wishart, *Ber. Dtsch. Chem. Ges.* **47,** 2082–2085 (1914).
126d. Cf. H. G. Fletcher, "The chemistry and configuration of the cyclitols, *Adv. Carbohyd. Chem.* **3,** 45–77 (1948).
126e. M. R. Stetten and DeWitt S. Stetten, Jr., *J. Biol. Chem.* **164,** 85 (1946).
127f. R. C. Anderson and E. S. Wallis, "The catalytic hydrogenation of polyhydric phenols. I. The synthesis of *meso*-inositol, Scyllitol and a new isomeric cyclitol," *J. Am. Chem. Soc.* **70,** 2931–2935 (1948).
126g. R. Kuhn, G. Quadbeck, and E. Röhm, "Zur Synthese des *meso*-Inosits," *Liebigs Ann. Chem.* **565,** 1–6 (1949).
126h. S. A. Angyal, "Complexes of metal cations with carbohydrates in solution," *Adv. Carbohydr. Chem. Biochem.* **47,** 1–43 (1989).
127. Jan Thesing, "Clemens Schöpf," *Berichte* **112,** (1979).
128. Liebig's, Baeyer's, Fischer's, and Hoppe Seyler's pupils and research groups have been documented by Prof. Joseph S. Fruton with infinite care (Ref. 33). Prof. Fruton was kind enough to start on the challenge of Heinrich Wieland's Research Group comprising close to 600 names. I am much indebted for outlining the *modus procedendi* for this task, which is still unfinished.
129. Martha Marquardt, *Paul Ehrlich als Mensch und Arbeiter, Erinnerungen aus dreizehn Jahren seines Lebens (1902–1915),* Deutsche Verlags-Anstalt Stuttgart/Berlin/Leipzig, 1924. The chronicler received this book from Ehrlich's granddaughter Susanne von Schueching, née Landau, with the inscription *Arbeit schadet dem Menschen nicht, aber Aufregung.*
130. Hans-Jürgen Staudinger (1915–1990), while Prof. of Physiological Chemistry in Giessen and son-in-law of Robert Schwarz (1887–1963), discovered this letter, dated January 8, 1947, in the papers of his late mother-in-law. When his father Hermann Staudinger (1881–1965, Nobel Prize 1953) became a prime candidate for the succession of H. Wieland in Freiburg in 1925, he requested protection from calumny and slander in a letter directed to Wieland and

dated September 14, 1925. Wieland supported Staudinger and so did the Chairman of the search Committee, Geheimrat Oltmann, a leading botanist. Thanks to the commendable efforts of Prof. Hugo Ott we are now in a better position to understand these intrigues that were caused by Martin Heidegger, the philosopher of world fame; Cf. Hugo Ott, *Martin Heidegger, Unterwegs zu seiner Biographie,* Campus Verlag, Frankfurt, 1988, pp. 201–213. Renewed intrigues by Heidegger in 1933, as President of the University of Freiburg, almost led to the loss of Staudinger's Chair and job in Freiburg. Whether Wieland was able to help him at that time would be worth investigating.

131. Letter from Prof. Theodor Wieland, dated February 18, 1988.
132. Letter written in Aeschi and dated May 19, 1946.
133. Wieland's correspondence with his friend Guggenheim was published by Heinz Balmer under the title "Aus dem Altersbriefwechsel der Biochemiker Markus Guggenheim (1885–1970) und Heinrich Wieland," *Gesnerus* **31,** Fascicle 3/4, 236–266 (1974), Sauerländer AG, Aarau, Switzerland.
134. His obituary was published by Hans Fischer (no relation to the Nobel Laureate) in the same Journal: "Nachruf auf Markus Guggenheim (1885–1970)," *Gesnerus* **28,** 83–87 (1971).
135. Otto Hahn, *Mein Leben—Mensch und Wissenschafter unserer Zeit,* Bruckmann, München, 1968, p. 92.
136. Letter directed to Markus Guggenheim, dated August 21, 1946; not contained in Ref. 133.
137. Letter to Prof. R. Adams Dutcher, Chairman, Department of Natural and Biological Chemistry, The Pennsylvania State College, Pennsylvania, dated March 15, 1947.
138. Letter dated March 29, 1951; Ref. 133, p. 249.
139. Letter dated December 14, 1950; Ref 133, p. 248.
140. Letter dated March 30, 1952; Ref. 133, p. 251.
141. Rolf Huisgen, The Wieland Memorial Lecture, Heinrich Wieland, presented at Burlington House on May 8, 1958, *Proc. Chem. Soc.*, August 1958, pp. 210–219.
142. Cf. Friedrich Klages, "Die Stickstoffarbeiten von H. Wieland," *Naturwissenschaften* **30,** 351–359 (1942).
143. W. Beck, E. Schuierer, and K. Feldl, *Angew. Chem.* **77,** 722 (1965).
144. F. de Sarlo, A. Guarna, A. Brandi, and A. Goti; The Chemistry of Fulminic Acid Revised," *Tetrahedron* **41,** 581–685 (1985).
145. H. Wieland, Zur Kenntnis der Nitriloxyde, *Berichte* **40,** 1667–1676 (1907).
146. Cf. C. Grundmann and P. Grünanger, *The Nitrile Oxides,* Springer, New York, 1971.
147. R. Huisgen, "Mechanisms, Novel Reactions, Synthetic Principles," in *Profiles, Pathways and Dreams,* Jeffrey I. Seeman, Ed., American Chemical Society, Washington, D.C., 1991.
148. Letter dated October 17, 1951; Ref. 133. p. 250.
149. Letter dated September 6, 1953; Ref. 133, p. 252.
150. Letter dated May 25, 1955; Ref. 133, p. 256.
151. David P. Hamilton, "Publishing by—and for—the numbers," *Science* **250,** 1331–1332 (1990).
152. William S. Learned, *The Quality of the Educational Process in the United States and in Europe,* Bulletin No. 20, The Carnegie Foundation for the Advancement of Teaching, New York, 1927, p. 35.
153. Cf. Walter Ruske, *Hundert Jahre Deutsche Chemische Gesellschaft,* Verlag-Chemie, Weinheim, 1967, p. 170.
154. Letter from H. Wieland to the Mayor of Munich, Karl Scharnagel, dated August 9, 1946.
155. Klaus Hafner, "150 Jahre Annalen," *Annalen* 1981 (12), I–XII.
156. Rolf Huisgen, "Adolf von Baeyers Wissenschaftliches Werk—ein Vermächtnis," *Angew. Chem.* **98,** 297–311 (1986).
157. H. Ritter and H. Zerweck, "Arthur von Weinberg (1871–1943)," *Berichte* **89,** XIX (1956); Weinberg perished in Theresienstadt.
158. Letter to Markus Guggenheim dated February 2, 1950; Ref. 133, p. 248.
159. The "Society of the White Rose" was founded by Franz Joseph Müller, Anneliese Knoop-Graf and Marie-Luise Schultze-Jahn. Its American counterpart is the "White Rose Foundation", New York, which has many members, among them senators and representatives.
160. Angela Bottin, "Hans Leipelt, 23, cand. mort.," *Dtsch. Allg. Sonntagsblatt,* No. 4, 27 Jahrgang 1985, pp. 2, 14.
161. Angela Bottin in a letter dated May 21, 1984, announced her intent to collect material for her dissertation at the University of Hamburg, entitled "Die Rechts- und Staats-Vorstellungen

der Weissen Rose." Her article (Ref. 160) was prompted by the fortieth anniversary of Hans Leipelt's execution and death as a martyr for liberty. The occasion was further commemorated in Hamburg and Munich, at the University and in City Hall; cf. "Enge Zeit," Spuren Vertriebener und Verfolgter, Austellungskatalog Universität Hamburg, 1–198, 1991.

162. The University of Heidelberg, on October 27, 1980, commemorated Kurt Huber in a ceremony in which the President of the University of Munich, Prof. Nikolaus Lobkowicz, characterized Huber's attitude and destiny "not only as the result of a moment's constellation, but the consequence and fulfilment of a whole life," viz., the deed of a man with clear aims. Prof. Wolfgang Jaeger, Ophthalmologist Emeritus, as a friend of Huber, amplified this picture by his personal memories. There is not only resemblance but even identity between Huber's and Wieland's motivation and behavior. I am indebted to Prof. Wolfgang Jaeger for sending me the special issue of *Ruperto-Carola,* 65/66, 23–32 (1981).
163. Lecture by Prof. Gerda Freise, Göttingen, in Pforzheim on November 17, 1988: "Der Nobelpreisträger Heinrich Wieland—Ein Beispiel für Zivilcourage in der Zeit des Nationalsozialismus."
164. Rolf Huisgen, "Heinrich Wieland achtzig Jahre, zum 4. Juni 1957," *Naturwissenschaften* **44,** 317–318 (1957).
165. Wieland's grave is, next to Hanfelder Strasse, in the cemetery in Starnberg. An austere slab of granite has his name and that of Josephine Wieland, his wife who followed him in 1967, inscribed; cf. Martin Schwarzbach, *Auf den Spuren unserer Naturforscher,* Hirzel Verlag, Stuttgart, 1981, p. 232.
166. Bernhard Witkop, "Heinrich Wieland Centennial: His lifework and his legacy today, *Angew. Chem. Int.* **16,** 559–572 (1977).
167. Rudolf Heinrich, Hans-Reinhard Bachmann, Walther Gerlach, 1889–1979, Dokumente aus seinem Nachlass, an exhibit in the "Deutsches Museum" on the occasion of his Centennial, published by Deutsches Museum, 1989. The complete text of Gerlach's speech on the occasion of the Wieland Centennial in the Torggelstube in Munich on September 12, 1977, is on page 81, together with the only photograph that shows a smiling Heinrich Wieland captured in September of 1953 on the terrace of his house in Starnberg (Plate 5). The text of Gerlach's valedictory words at the open graveside exists as a private print.