Emil Fischer—Unequalled Classicist, Master of Organic Chemistry Research, and Inspired Trailblazer of Biological Chemistry

Horst Kunz*

Even if in life one has the good fortune to meet many important scientists and chemists, much reverence descends whenever the name of Emil Fischer is mentioned (Figure 1). This reverence and admiration increases still further the closer one looks into the scientific life work of this ingenious natural-science researcher. This year, 2002, there are numerous reasons to commemorate the pioneering achievements of Emil Fischer. His 150th birthday falls on October 9, and this year it is 100 years since Emil Fischer was awarded the Nobel Prize for Chemistry by the Royal Academy of Sciences in Stockholm.

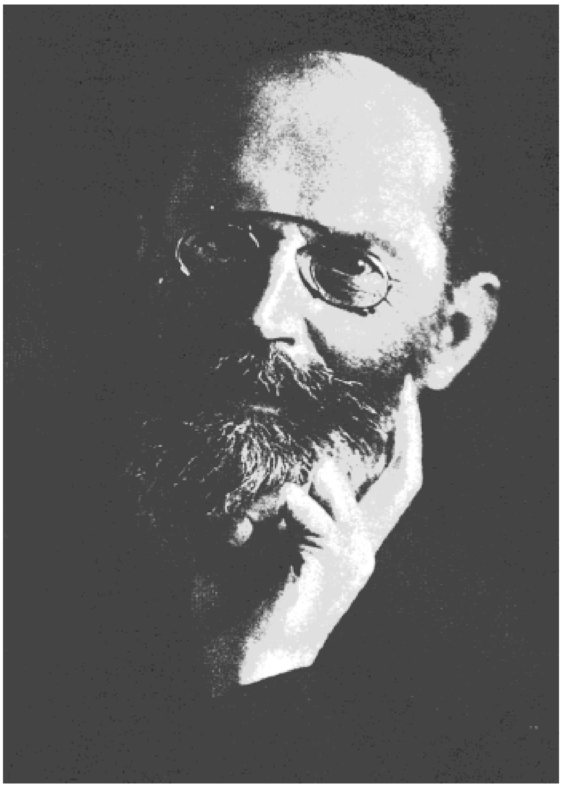


Figure 1. Portrait of Emil Fischer (reproduced, with permission from Springer Verlag, from reference [2]).

The scientific achievements of Emil Fischer has left a lasting impression in many areas of chemistry, and even today they are of fundamental importance and influence. His student and professional career in the 1870s began with the then fascinating chemistry of organic dyes. With his first major discovery, phenylhydrazine, he opened up new pathways in heterocyclic chemistry with the synthesis of indoles. With his investigations into caffeine, uric acids, and other purines he moved into the area of natural product chemistry, which he led to its first great peak of achievement with his fundamental work on carbohydrates (based on their reactions with phenylhydrazine), peptides, and proteins, the results of which are still pertinent today. If one considers further that Emil Fischer performed pioneering work in the synthesis of tanning agents and fats, that he was able to provide a concept of the structure of nucleic acids, that with Heinrich Kiliani he became the founder of stereoselective synthesis, that he introduced stereochemical nomenclature and structural assignment, and that with his work on enzymes from beer yeast and bitter almonds he became the founder of biochemistry, it is quite obvious that Emil Fischer "is to the present day the greatest genius of organic chemistry".[1]

Amazed, one must ask oneself how a single scientist could achieve such a tremendous life's work? The main reasons are of course to be sought in Emil Fischer's talents. On the other hand, for such talents to come to full development and fruition the family and professional environment and the social factors in Germany during the second half of the 19th century and the beginning of the 20th century must have exercised a distinctly beneficial influence. Fortunately, Emil Fischer himself has provided some insight in this respect.[2] It is not at all a matter of course that in this point the present, overburdened with proclamations and predictions, bears comparison with the Wilhelminic reign, generally regarded as reactionary.

Emil Fischer[2] was born on October 9, 1852 in Euskirchen, about 30 km west of Bonn, as the youngest of eight children of Laurenz Fischer and his wife Julie, née Poensgen. Two of the siblings had died previously; thus Emil Fischer grew up with five older sisters. In order to escape their upbringing wiles occasionally, he frequently withdrew for a few days, with the permission of his parents, to the neighboring house occupied

---

[*] Prof. Dr. H. Kunz
Institut für Organische Chemie der Universität Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)
Fax: (+49) 6131-3924786
E-mail: hokunz@mail.uni-mainz.de

© 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim 1433-7851/02/4123-4439 $ 20.00+.50/0

by the family of his uncle August Fischer, where there were five sons and a daughter. One of the cousins, Otto Fischer, was later also to become a chemist and with him demonstrated the structure of the rosaniline dyes to be triphenylmethane derivatives.[3] It transpires from his memoirs[2] that Emil Fischer grew up in a lively, extended Rheinland protestant family and had a "totally happy youth". The harmonious relationships in the extended Fischer family gave the boy much stimulation for his later professional life. Particularly striking was the influence of his parents, whose personality Emil Fischer described with affection. Although quite different "in character, opinion, and inclination", they led a "very happy marriage". One has the impression that their considerable but different talents complemented each other in the best possible way in the exceptional gifts of the son.

The father, Laurenz Fischer, ran a flourishing business with two of his brothers, first in Flamersheim, then in Euskirchen, where his brothers managed the office and warehouse "with the greatest care" whilst he ran the external relationships of the company Gebrüder Fischer (Fischer Brothers) with enterprise, vigor, and considerable success. From his enterprise arose the purchase of a small wool spinner in the neighboring community of Wisskirchen. Aniline dyes were then almost unknown, and dying with the natural colors indigo, fustic, and logwood proved to be a poorly reproducible art. The father, Laurenz, "who at all times had regarded self-reliance highly" set up a small experimental dye-works in Euskirchen. Not only did his regard for chemistry grow from this experience, but at the same time it inspired Emil Fischer and his cousin Otto in their later choice of career. This was reinforced still further when father Laurenz became involved in a cement works near Bonn which was managed by the chemist Dr. Bleibtreu (a student of A. W. von Hofmann), who repeatedly encouraged the young Emil Fischer to become a chemist.

When in the 1860s the enterprising father became decisively involved in the establishment of a brewery in Dortmund further motivation arose for Emil Fischer, at least in his later professional life as a chemist. Thus during his years in Munich he heard of the Linde refrigerating machines, the installation of which he supervised for cellar cooling in his father's brewery. Some time later, when he stayed at Strasbourg University for a second time to perfect his analytical experience, he learnt of Louis Pasteur's book "Ètudes sur la bière". During his reading he learnt that contamination of beer yeast by other microorganisms had a deleterious effect on the condition of the beer. When he informed his father of this fact, he was asked to study the matter immediately in greater detail for the brewery. Thus, using a microscope and with the help of the Strasbourg biologists Fitz and de Bary, Emil Fischer carried out studies on schizomycetes, mould fungus, and *Blastomyces* fungi, which resulted in the introduction of microscopic purity control of brewing yeast in the Dortmund brewery. This came in very useful for him later in his work on sugars and their converting enzymes.

The bold enterprise of the father, who at the same time displayed "a great clarity of mind" was not only a model for the young Emil, but it was also reflected in his own character, which was important for his development as a scientist. Emil Fischer described his mother as a very clever woman, thirsty for knowledge, who came from a family of iron manufacturers in an Eifel valley.[2] Her forefathers had worked there for centuries as producers of iron and iron products. Emil Fischer himself assumed that he had inherited his joy of chemical and technical processes from them. His mother's deeply religious nature stems from her upbringing, in part in the evangelical Moravian community in Neuwied. She was more serious than the father, but could laugh heartily at his jokes. "Only when she encountered crude or common expression did she express her indignation so clearly that in her presence everyone was forced to behave with decency." She was clearly very independent in her political opinions: In the 1863/64 dispute between the Prussian government and the parliament, the father belonged to the opposition party, like most Rhinelanders, while she supported Bismarck. In her political judgments she opposed the father so vigorously that he jokingly called her "Frau Bismarck". She always supported her son's leanings towards scientific studies, and it can be assumed that it was from her side that Emil Fischer inherited his interest in natural science processes and experimentation, and also thoughtfulness, ability for analytical rigor, and courage for independent assessment. Together with the vigor, the energy, and the resolve of the father, the young Emil Fischer was so clearly equipped with the aptitude to open up critical pathways of clarity in the then still hugely unknown primeval forest of chemical sciences.

These abilities became evident even during his school years, which for Emil Fischer began after his fifth birthday. Until his ninth year he was taught by an excellent teacher, Mr. Vierkoetter, in a private school founded by his father for the children of the few protestant families in his home town. Although children aged 5 to 14 years were taught in one room, this teacher not only understood how to treat the elementary subjects thoroughly, but he also introduced, for example, Euclidian mathematics to the more talented students. Thus the transfer to the secondary schools in Euskirchen and later to the high school was easy for the young Emil.

The first two years of his high-school period were spent with his cousin Ernst Fischer in the Hessian town of Wetzlar, where he again experienced excellent tuition in mathematics. The time in Wetzlar had for the young Fischers the traits of an anticipated student life, filled with music and conviviality. Emil Fischer considered that the reason for his "later gastric illness lay in his immoderation in smoking and drinking". He spent the last two years of his schooling at the high school in Bonn. He was "always an exceptionally gifted and good student, even in subjects that he did not like, supported by an excellent memory that remained true to him into his old age".[4] In the Spring of 1869 he graduated "primus omnium".

Emil Fischer's particular interest lay in physics and mathematics. However, he complied with his father's wish and commenced a commercial apprenticeship in the timber business of his brother-in-law in Rheydt in preparation for a later entry into the family business. However, the activity did not constrain him so that in addition he undertook private tuition in chemistry and set up a tiny laboratory in an empty room in the company building. The experiments undertaken by him there "ended in a smell or dirty, burnt fingers, and

© 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

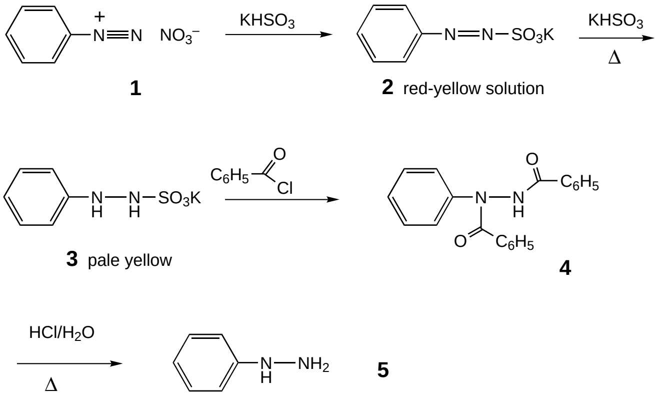
because of the risk of fire became uncomfortable for the owner of the business".[2] Thus the attempt to make a businessman out of Emil Fischer was abandoned, and the father agreed, possibly also because of his own experiences at the dye-works of the wool spinners, that the son should study not physics and mathematics, but chemistry.

From the summer semester of 1871 Emil Fischer spent the first three semesters at Bonn University, where he attended botany, physics, and chemistry lectures. The latter, held by Kekulé, particularly impressed him. However, the analytical practical course was old-fashioned in both equipment and procedure. The use of water pumps, which had long before been introduced by Bunsen, was unknown. When a precipitate of iron and aluminum hydroxides could not be filtered and washed, Emil Fischer would have switched from chemistry to physics, his old preference, had it not been for his cousin Ernst Fischer, now a medical student in Bonn. He suggested that he change institute. The other cousin, Otto Fischer, who had also begun to study chemistry, joined in the move.

More by chance the choice fell on Strasbourg in the Alsace, which Emil Fischer regarded as complete luck, for in this way the two cousins entered the laboratory of Adolf von Baeyer in the fall of 1872. The two Fischers followed a modern analytical practical course under the guidance of Adolf von Baeyer and Friederich Rose, in which they experienced a fascinating introduction into the art of experimental chemistry and what was then known of the underlying theoretical principles. Emil Fischer underlined frequently and with great respect the striking influence which Adolf von Baeyer had on him and the young chemists.[2] The open and relaxed atmosphere of this university, founded just after the war of 1871/1872, also proved attractive, as did the social life in Strasbourg, where Emil Fischer had reserved for himself an imposing barrel of excellent burgundy by the "understanding landlord" of the Badischer Hof.

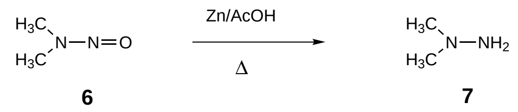
In this well-organized institute, in which Adolf von Baeyer had established an effective course and where he himself took care of the students during the initial semester, Friedrich Rose was responsible for the students learning the methods of quantitative analysis in depth. Emil Fischer was a brilliant analyst, and he was finally won over for chemical science. After less than one year he joined the organic chemistry department where he commenced his doctoral studies on the reduction of mellitic acid from honeystone (mellite). However this intention was rudely interrupted when a board of the rotten floor broke under the experimentalist who at that moment was carrying a large stoppered flask of reduction product and approximately 25 kg of mercury, and the valuable treasure disappeared into the cracks in the jagged wooden floor.[5] Adolf von Baeyer changed the topic and allowed Emil Fischer to work on the structural elucidation of fluorescein and other phthaleins, which, apart from the assignment of a few substituent positions, was successful. Emil Fischer received his doctorate in Strasbourg in 1874.

Adolf von Baeyer, who had recognized the exceptional talents of his student, appointed him as an assistant in the organic chemistry practical laboratory. When advising a student in the diazotization of benzidine Emil Fischer made his first great discovery. The student had always obtained an impure product during the reaction of benzidine with nitric acid, and Emil Fischer was also not able to improve upon the reaction when he repeated the experiment himself. As a result he added sodium sulfite to the reaction mixture to suppress the oxidizing effect of the nitric acid, which resulted in the formation of a precipitate.[6] When repeating this reaction with aniline, which was converted into the phenyldiazonium salt **1**, Emil Fischer succeeded in the first synthesis of phenylhydrazine by reaction with potassium hydrogen sulfite (Scheme 1).[7]



Scheme 1. Synthesis of phenylhydrazine (**5**).

It was this, the first compound of its class ("for which I [Emil Fischer] suggested the name hydrazine compounds"), which was to bring forth magnificent research results for its inventor. It has to be noted that in the same year Emil Fischer described the 1,1-disubstituted hydrazines.[8] Thus he obtained 1,1-dimethylhydrazine from dimethylnitrosamine (**6**) by boiling with zinc in acetic acid ("until the intense smell of the nitroso compound has disappeared") (Scheme 2).



Scheme 2. Synthesis of 1,1-dimethylhydrazine (**7**).

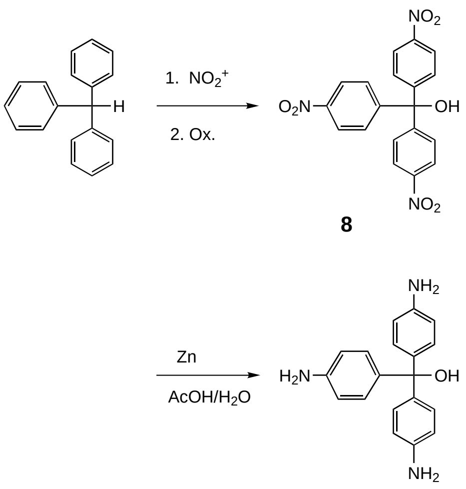
In 1875 Adolf von Baeyer succeeded Justus von Liebig at Munich University. After instructive visits to Tübingen and Stuttgart Emil Fischer (Figure 2) decided to follow his teacher; a tour of a few "amusing inns" which von Baeyer bestowed upon Emil and his cousin Ernst Fischer, the medical doctor, may have contributed to this decision. Emil Fischer continued his investigations on hydrazines in Baeyer's laboratories in Munich. The results formed the basis of his Habilitation in 1876, and in the fall of the same year he was able to present this chemistry at the Conference of German Natural Scientists and Doctors in Hamburg under the chairmanship of Ladenburg (known for his synthesis of racemic coniine).

After a training semester in analytical chemistry with Friederich Rose in Strasbourg, where he undertook the

Figure 2. Emil Fischer during his time in Munich (reproduced, with permission from Springer Verlag, from reference [2]).

previously mentioned microscopic studies on beer yeast, he was appointed professor and head of the analytical chemistry department in Munich in 1879. Amongst his comrades-in-arms with Baeyer were Wilhelm Koenigs (who was later to publish the Koenig–Knorr glycoside synthesis[9]) and Siegmund Gabriel (after whom the Gabriel synthesis of amines was named), who knew how to garnish an evening of beer with a barrage of jokes. Finally, cousin Otto Fischer also came to Munich, with whom Emil Fischer started a new line of work: the elucidation of the structure of the rosaniline dyes, which the old master A. W. von Hofmann had obtained by the oxidation of a mixture of *p*-toluidine, *o*-toluidine, and aniline with nitrobenzene[10] and for which he had postulated a structure similar to that of the azo compounds. The two Fischers were able to demonstrate unambiguously that this postulate was incorrect and that the rosaniline dyes are triphenylmethane derivatives. For example, they prepared pararosaniline (**9**) by the nitration of triphenylmethane, oxidation of the product to tris(*p*-nitrophenyl)methanol (**8**), and its reduction with zinc in acetic acid (Scheme 3).[3]

In the end, they stood correct against the authority of A. W. von Hofmann, which further promoted their reputations. Because of the work on hydrazines and on the rosaniline dyes, Emil Fischer was already in a position in 1880 to be able to decline an invitation from the Aachen Polytechnic to become Landolt's successor. In Munich he now switched to the chemistry of urea derivatives and the structural elucidation of uric acid, an area which had already been advanced by his mentor Adolf von Baeyer and by Adolph Strecker (known for the Strecker amino acid synthesis). Nevertheless, the structure of uric acid was still unknown. Its synthesis was as elusive as that of caffein, theobromine, and other purine derivatives. Uric acid was at that time mainly obtained from guano.



Scheme 3. Based on the synthesis of pararosaniline (**9**), Emil Fischer showed that the rosaniline dyes are triphenylmethane derivatives.

When Emil Fischer was appointed Professor of Chemistry at Erlangen University in 1882 as successor to J. Volhard, Wilhelm Koenigs contributed to a merry farewell party for Fischer with a humorous guano song, undoubtedly a reference to the above-mentioned activity. At the time Koenigs and Fischer lived with the same host and enjoyed many a glass of wine together in the evenings. Emil Fischer wrote in his memoirs:[2] "My wine stocks were at that time not small and amongst them were a few very good sorts. At the time of my move to Erlangen in Easter 1882, I gave my host the job of sending them on to me. The wine failed to arrive, and an inquiry elicited that Koenigs had drunk it all with his friends. Instead I received a large barrel of Münchner Hofbräu beer as a replacement for the lost wine. He knew that I would laugh at the joke, as he would have done in the same situation."

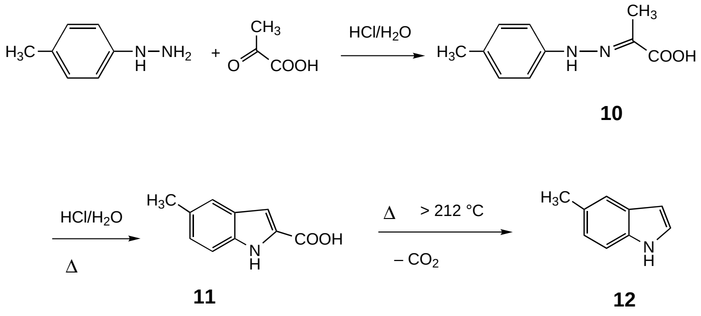
Erlangen was an important station in Emil Fischer's life, although he was to remain there for only three years. By chance he met his later wife Agnes Gerlach, the daughter of the Erlangen anatomist Joseph von Gerlach, on a train journey. Although only 30 years old, as professor in Erlangen he was responsible for the whole institute. The large experimental lecture course was also his duty. It was characteristic of Emil Fischer that through clever organization he sought to raise education and research at the institute in his care to a high degree of effectiveness. Thus he collated a collection of methods for the preparation of organic compounds which in 1887 became his "Anleitung zur Darstellung organische Präparate", one of the first books of practical chemistry.

Research in Erlangen was soon operating at full intensity, to which Lorenz Knorr (after whom the pyrrole synthesis was named) contributed; Knorr counted amongst Fischer's students in Munich and had followed him to Erlangen. The reactions of phenylhydrazine were studied in depth, which led to the discovery of the Fischer indole synthesis. In the reaction of (*p*-methylphenyl)hydrazine with pyruvic acid, Fischer and Jourdan observed a multistage process (Scheme 4).[11]

Of compound **10** the authors wrote: "Its behavior towards acids is quite remarkable. If the same is warmed in 10%

© 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

1433-7851/02/4123-4442 $ 20.00+.50/0



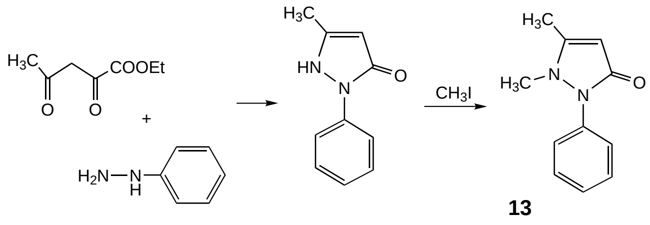
Scheme 4. The Fischer indole synthesis.

hydrochloric acid it turns reddish-yellow and goes into solution. On stronger heating the coloration disappears and fine, colorless needles separate… A noticeable amount of ammonia is present in the acid liquid… This process is so remarkable that for the time being we dare not venture an explanation for the reaction." Only a year later they identified the new compound as the indole carboxylic acid **11**,[12] which on heating above its melting point undergoes decarboxylation to give 5-methylindole (**12**, Scheme 4).

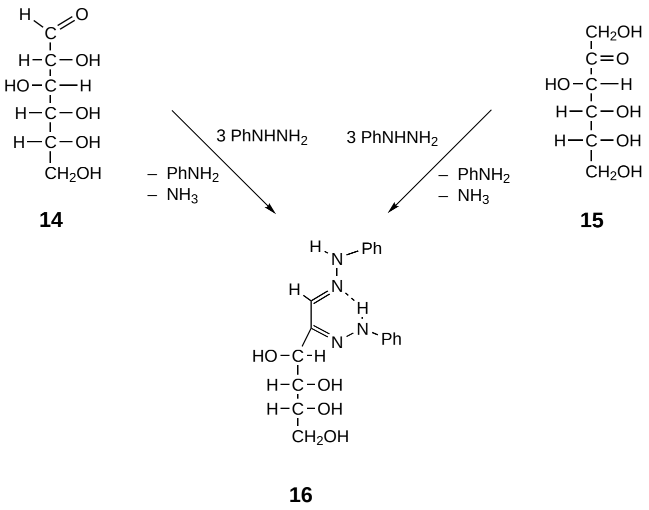
By oxidation to the isatins, the relationship with the heterocyclic pseudoisatins previously found by von Baeyer was established. A broad pathway into the new territory of heterocyclic chemistry had been opened, even though the mechanism of the Fischer indole synthesis as a [3s,3s] sigmatropic rearrangement first became clear after formulation of the Woodward–Hoffmann Rules.[13]

In these syntheses Emil Fischer (together with "Mr. Knoevenagel") also used aldehydes, including propionaldehyde. The latter ended with the formation of skatole,[14] which naturally correspondingly contaminated the clothing of the experimentalist. As a consequence a similarly impregnated loden jacket hindered the control of Emil Fischer's baggage through French customs during a journey to Ajaccio.[2]

The synthesis of antipyrine (**13**), starting from ethyl acetoacetate and phenyl hydrazine was successfully carried out by Lorenz Knorr, Fischer's Habilitation student, during this fruitful period at Erlangen (Scheme 5).[15] One of the first synthetic drugs was born. Phenylhydrazine as a reagent for ketones and aldehydes was extensively studied by Emil Fischer.[16] During these studies the reagent was also treated with sugars such as dextrose (glucose, **14**) and levulose (fructose, **15**).[17] With this reaction Emil Fischer discovered the formation of the crystalline and characterizable osazones, which were to become the overture to one of his Olympic achievements in organic chemistry. In this initial work Fischer described not only the osazones of galactose, maltose, and sorbose (which he obtained from Victor Meyer), but he also recognized that glucose and fructose gave the identical osazone **16** (Scheme 6). This finding was to bring him to his brilliant elucidation of the stereochemistry of sugars and to the breakthrough assignment of spatial configuration during his subsequent period in Würzburg.

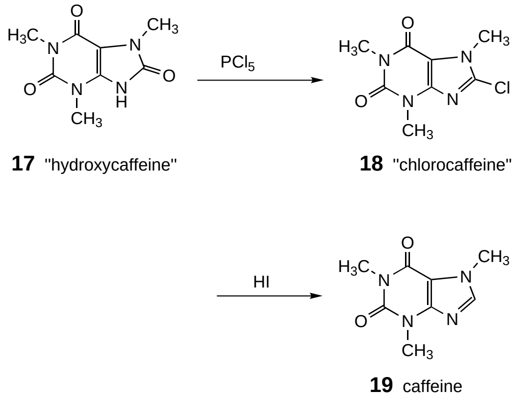


Scheme 5. Synthesis of antipyrine (**13**).



Scheme 6. Glucose and fructose give rise to the same osazone **16**.

In 1883 in Erlangen an invitation from the Badische Anilin- und Soda Fabrik (BASF) reached Emil Fischer to succeed Heinrich Caro as head of research, who had, amongst other ventures, worked on the rosolic acid dyes related to the rosanilines. However, he preferred "academic activity with total freedom of scientific work", but accepted the invitation to visit BASF for a number of weeks. With this opportunity he was able to carry out on a larger scale the methylation of uric acid, which had been worked out in Erlangen,[18] as several kilograms of snake excrement, from which uric acid was preferably isolated, was made available to him. The work in Erlangen was concentrated on the reactions of *N*-methylated uric acids **17** with phosphorus pentachloride and pentabromide; purine compounds, including caffeine (**19**), were obtained by the reduction of the chloropurines **18** with fuming hydroiodic acid (Scheme 7).



Scheme 7. Studies on *N*-methylated uric acids led to the synthesis of caffeine (**19**).

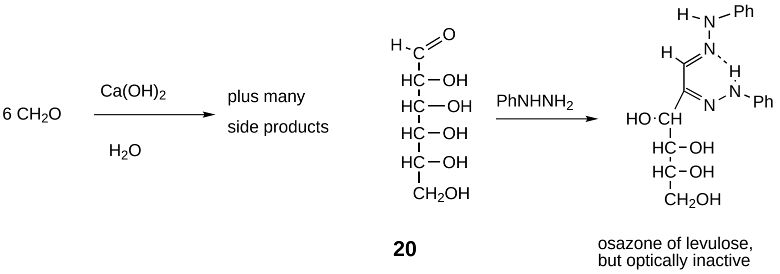
During the numerous reactions with the phosphorus chlorides, Emil Fischer contracted such a severe nose, throat, and bronchial infection that he had to interrupt his work in the institute and recover at a health resort. The leadership of the institute was in the meantime transferred to his cousin Otto Fischer by the Bavarian Ministry. During one of the journeys to Switzerland, Emil Fischer became acquainted with the president of the Swiss Board of Education in a mountain resort in Graubünden,[2] on whose prompting he was evidently invited to take over as Professor of Chemistry at the Zurich Polytechnic Institute as the position had fallen vacant following the appointment of Victor Meyer in Göttingen. On account of his state of health Emil Fischer did not accept this offer.

Later, after periods in Corsica and in the Black Forest, he received an invitation to succeed Johannes Wislicenus in Würzburg, who had received an appointment from Leipzig. There were concerns about the state of Emil Fischer's health and to investigate it the zoologist Semper, from the family of the famous Gottfried Semper (architect of the Semper Opera in Dresden), went to Heidelberg for a meeting with Fischer. Emil Fischer described this meeting as follows:[2] "Semper suggested that we take a walk to the castle. Although he was much older than I, he intentionally set off at a brisk pace so that he arrived at the top quite breathless, whereas I, then used to mountaineering, found the tempo quite comfortable. Then came the second test: Semper suggested that we drink a bottle of sparkling wine. That was not unsympathetic to me as the enjoyment of wine was one of my habits. The success of this breakfast was what one would expect: mild drunkenness on the part of the older gentleman while the younger colleague was not affected. The examination was passed."

Thus, in 1885 Emil Fischer went to Würzburg University where he was to spend seven fruitful and also personally happy years. His work at the large institute of this university, to which he was followed by Lorenz Knorr as lecturer, concentrated at first on the chemistry of purines. During this time, Emil Fischer elucidated the structure of numerous members of this class of compounds. The synthesis of uric acid, purine itself, and caffeine was achieved during his time in Berlin and will be outlined later.

In Würzburg Emil Fischer, who for a long time had intended as a bachelor to focus his attention on science, decided to marry. Without doubt the main reasons for this change of mind are to be found in the personal virtues of Miss Agnes Gerlach from Erlangen, who was to become his wife. Briefly he admitted that she "was through her physical beauty, purity of soul, and gentle nature a perfect being".[2] The happiness of this marriage, which produced three sons, unfortunately only lasted seven years. In November 1895, Frau Agnes Fischer died of meningitis in Berlin, and of the three sons only the eldest, Hermann O. L. Fischer, who was later to make significant contributions to the development of biochemistry, in particular at Berkeley, survived the First World War. The great researcher was afflicted in his lifetime by heavy reversals of fortune.

During his time in Würzburg Emil Fischer carried out his pioneering work on the chemistry and stereochemistry of sugars. The already discussed key was the reaction with phenylhydrazine to form the crystalline and characterizable osazones. He found that not only did glucose and fructose form the same osazone **16**, but so did mannose (which he had also discovered). With the help of this reaction he was also able to identify components of the sweet-tasting syrup (formose) obtained by Butlerow[19] and Loew[20] by reaction of formaldehyde (trioxan) with lime water as sugarlike substances. He proposed the molecular formula $C_6H_{12}O_6$ for one of the main components **20**[21] (Scheme 8).

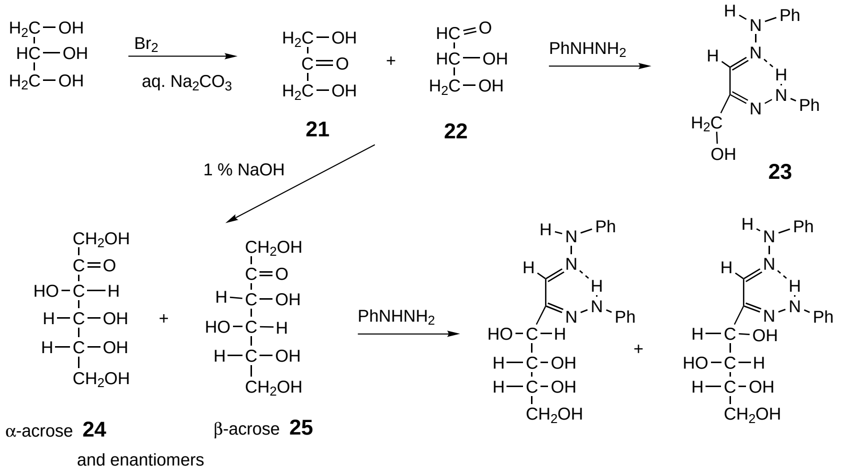


Scheme 8. Emil Fischer identified **20** as the main component of formose.

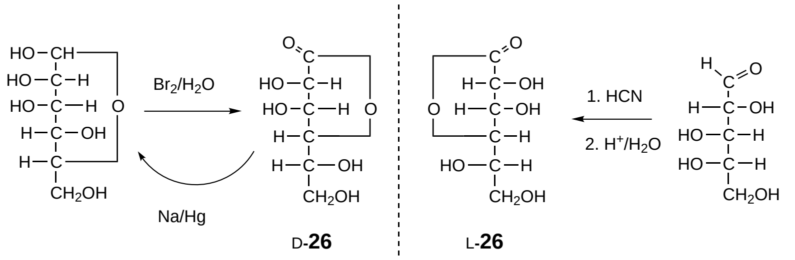
His own syntheses of sugars were carried out mainly with Julius Tafel, who had come with him to Würzburg from Erlangen. They started out from "2,3-dibromoacrolein" and later glycerol, which was oxidized to glyceraldehyde.[22] During work-up of the osazones of the products formed from 2,3-dibromoacrolein with barium sulfate, osazones of C_6 compounds were found, the formation of which was clarified in the same year. By oxidation of glycerol with bromine in soda solution, a mixture of dihydroxyacetone (**21**) and glyceraldehyde (**22**) was obtained. After reduction of the excess bromine with sulfurous acid, the osazone **23** of "glycerose" was formed with phenylhydrazine. However, when the mixture of **21** and **22** was allowed to stand in 1% NaOH for five days the osazones of two (racemic) hexoses **24**/**25** were isolated, which Emil Fischer called α- and β-acrose (from acrolein) (Scheme 9).[23, 24]

Emil Fischer soon realized that α-acrose was identical to levulose (i.e. fructose) but was optically inactive. β-Acrose thus corresponded to D,L-sorbose. From previous work (see, for example, ref. [17] the relationship between fructose and glucose was already clear. Soon that with D-mannose, which could be isolated from vegetable ivory, was established.[25] Oxidation of mannose with bromine water gave after acidification D-mannonic acid lactone (D-**26**; $[\alpha]_D = +53.8°$). Fischer recognized that apart from the direction of the optical rotation, this compound was identical to L-mannonic acid lactone (L-**26**; $[\alpha]_D = -54.8°$), which had already been obtained by Heinrich Kiliani[26] from L-arabinose (isolated from cherry gum) by cyanhydrin synthesis (Scheme 10).

The reduction of mannonic acid lactone to mannose with sodium amalgam, as well as that of glucosaccharic acid via the dilactone to glucuronic acid, had already been discovered by Emil Fischer.[27] With these tools—phenylosazone formation,



Scheme 9. Discovery of the “acroses”.



Scheme 10. Synthesis of the mannonic acid lactones D-**26** and L-**26** by Fischer and Kiliani, respectively.

the total synthesis of optically inactive hexoses from acrolein, glyceraldehyde, or formaldehyde, chain extension by cyanhydrin synthesis (the Kiliani–Fischer synthesis can be regarded as the entry into asymmetric synthesis), hydrolysis of osazones to osones, oxidation of hexoses to aldonic acids, and the reduction of aldonic acid lactones to the hexoses—Emil Fischer was now able successfully to cast light on the subject of sugar configuration, then considered tremendously complex, which not only required unerring analytical rigor, but also the characteristic ability of Emil Fischer[4] to order experimental results systematically. In impressive work[28] he brought clarity to the structural relationships of D- and L-mannose, mannite, glucose, and fructose when he introduced new methods with the separation of the enantiomers of mannonic acid in the form of their strychnine or morphine salts and with the enantioselective fermentation of α-mannose from the racemic mixture with beer yeast (reminiscent of the brewing activities of his father). (Figure 3 was taken from the original work[28] and illustrates this breakthrough.)

In addition to fermentation with yeasts Emil Fischer also applied selective microbiological methods, for example, the use of *Penicillium glaucum* and later *Saccharomyces* species[29] for the selective cleavage of polysaccharides. He may justly be regarded as the pioneer of enantioselective enzymatic catalysis.

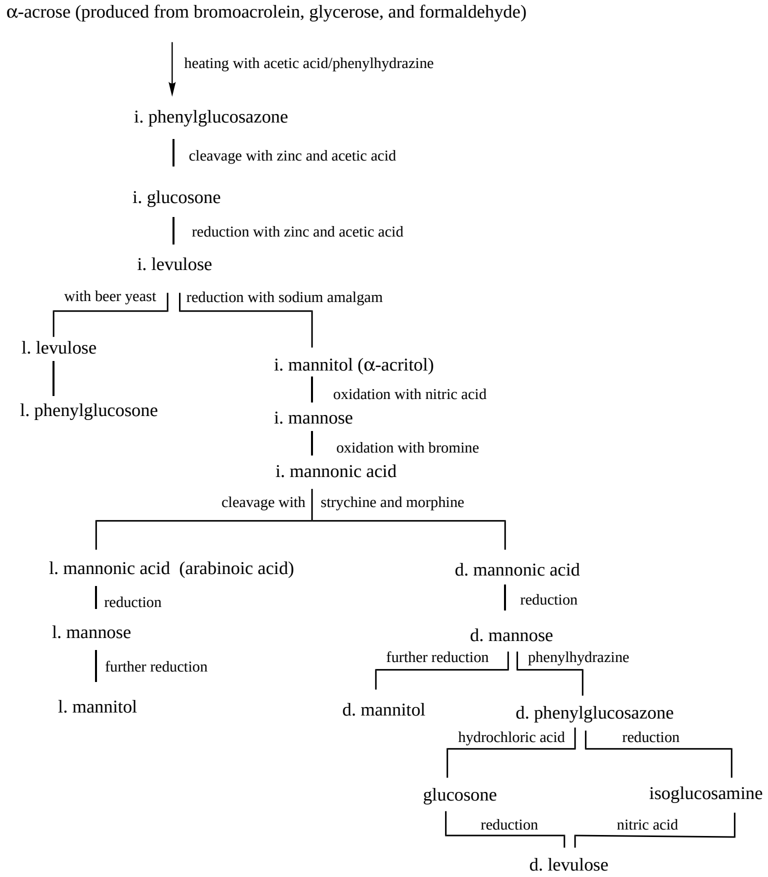


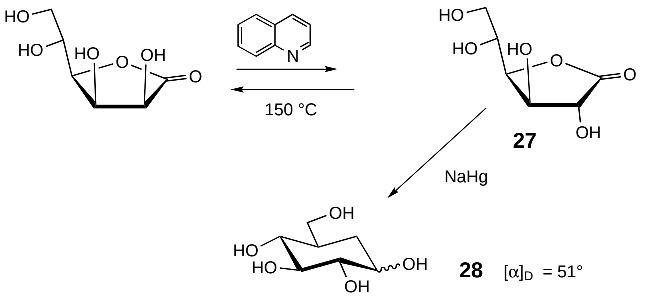
Figure 3. Structural relationships and enantiomers of fructose and mannose and their derivatives.

Based on the syntheses in the mannose/fructose series, Emil Fischer succeeded in the same year[30] with the total synthesis of grape sugar (i.e. D-glucose). The starting point was the D-mannonic acid lactone (D-**26**). On heating to 150–155 °C in quinoline/water, D-**26** partly epimerized to gluconolactone (**27**). The phenylhydrazides of the two aldonic acids were separated. Gluconolactone (**27**) was isolated via calcium gluconate from the hydrazide of gluconic acid with lime water and was then reduced to D-glucose (**28**) with sodium amalgam (Scheme 11).

Thus it was proven that glucose and mannose differ only in the configuration at C2. Emil Fischer wrote of the two hexoses:[30] “On the basis of the Le Bel–van’t Hoff conception their difference rests on the asymmetry of the carbon atom labeled as1 in the following formula”.

$$\mathrm{CHO \cdot \underset{as1}{CHOH} \cdot CHOH \cdot CHOH \cdot CH_2OH}$$

With this work[28, 30] the brilliant breakthrough of the van’t Hoff interpretation[31] of the spatial structure of aliphatic carbon compounds was implemented.



Scheme 11. The first total synthesis of glucose (**28**). The intermediate **27** was isolated via the phenylhydrazide from which the calcium gluconate derivative was obtained.

On June 23, 1890, Emil Fischer summarized the state of carbohydrate research at a special meeting of the Deutsche Chemische Gesellschaft (German Chemical Society) in Berlin. In 1952, Burckhardt Helferich wrote:[4] "It must have been an unusually fascinating and comprehensive lecture. Even Harries, an exceptionally critical observer, wrote of it: 'I have never heard a better lecture in form and content, full of passion and noble restraint, when the greater researcher stood out'. Emil Fischer became for us the measure of all personalities!" The original lecture can be read in the "Chemische Berichte".[32]

In this work Emil Fischer established configurational assignment, systematics, and nomenclature of sugars and also that of all centrochiral compounds.[33] He put forward that the symbols "d." and "l." should be used only according to the spatial orientation of the substituents, independent of the direction of rotation. The carbohydrates were named after the number of carbon atoms, for example, as pentoses, hexoses, etc., and finally Emil Fischer ventured the assumption of the absolute configuration of glucose, galactose, mannose, fructose, arabinose, and xylose according to the Fischer projection still used today.[34] Fortunately, as was to be demonstrated much later by Bijvoet et al.[35] by the X-ray structural analysis of sodium rubidium tartrate, he was correct in his assignment.

With few exceptions he was able within a few years to assign the stereoisomeric forms to the whole spectrum of known sugars,[36] when he astutely established the number of isomers by oxidation of the hexoses to the sugar acids and oxidative degradation to lower dicarboxylic acids such as tartaric acid and mesotartaric acid.[37]

With this monumental work on sugars, about which previously only little was known from the studies of Kiliani and Tollens, Emil Fischer entered the topmost ranks of chemists. When A. W. von Hofmann[38] died in the spring of 1892 the list of the faculty of the Berlin University (today the Humboldt University) for successors to this chemist, likewise distinguished by his scientific achievements and worldly personality, contained the names August Kekulé, Adolf von Baeyer, and Emil Fischer. From what has just been described it is understandable today that the decision fell on Emil Fischer, the youngest of the candidates. Emil Fischer, who with his family was very happy in Würzburg, hesitated at first to go to the large city, then undergoing acrimonious development. His wife and his father (who was proud of the professional success of his son, and "had heard of the Berlin offer and immediately set out to persuade me not to reject such a good deal lightly"[2]) persuaded him to follow the calling. After eight days of hesitation he accepted, as "the active scientific life in the capital city of the Reich, the considerable prospects, the possibilities to gather around me a large circle of students was very appealing to a man of my age (I was not yet 40 years old)".

Amongst other things, the Ministry in Berlin had promised Emil Fischer to build a new institute. The Hofmann Institute in Georgenstrasse was clearly an imposing building externally, but unsuitably organized inside. Light and ventilation were inadequate. The major deficiencies had to be removed at considerable cost. But eight years were to pass until the completion of the new building in Hessische Strasse in Berlin (Figure 4), where two years ago the institute celebrated its 100th anniversary.[39] In 1952 Burckhardt Helferich wrote of this institute:[4] "In accordance with the conceptions of Emil Fischer, everything in this institute is subordinate to the purpose of work. The means available were used to this end only, no value was laid on external appearances. Light, good ventilation, and especially clear layout were the decisive factors according to which building work was carried out… In the purposefulness of design it has also to this day not been superceded by any other German institute."

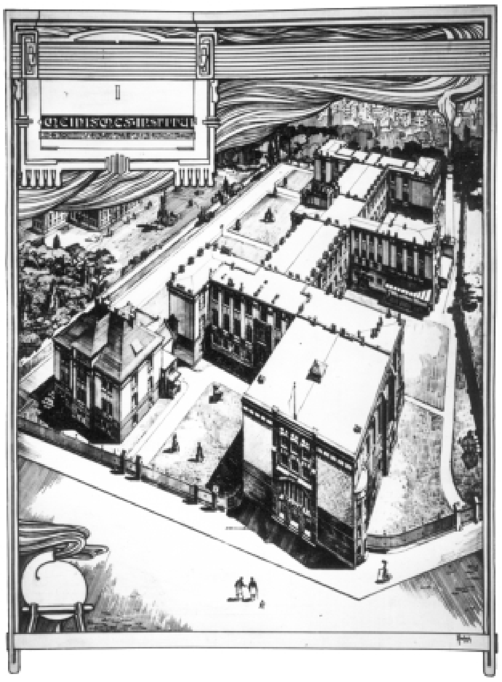
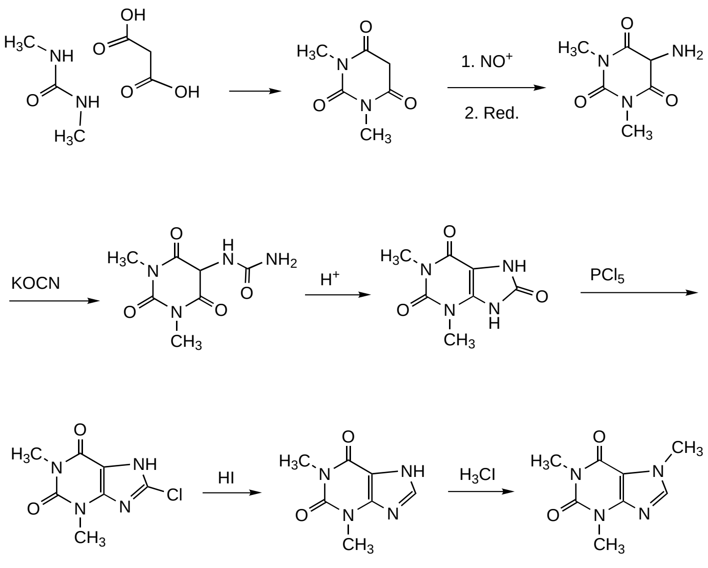


Figure 4. The new building of the chemical institute. (We thank the Humboldt-Universität zu Berlin for providing us with the original picture.)

In Berlin it was not to Emil Fischer's liking that the Philosophy Faculty was not split into natural science and liberal arts departments. Meetings lasted many hours, as "in general the natural scientists in the Berlin faculty did not play the role they could claim. The representatives of the liberal arts are more numerous and undoubtedly more adept at speaking, perhaps also more expressive in manner. Since they also have more time and attend the meetings more regularly and for longer periods of time, they have most to say,…".[2]

But the Berlin faculty welcomed Emil Fischer with open arms, “above all Helmholtz, who gave a dinner in his honor to which the most important representatives of the University and leading men in industry were invited”.[4] In Berlin Emil Fischer continued his work on purines and carbohydrates. With Lorenz Ach, who followed him from Würzburg to the capital as his personal assistant, he completed the total synthesis of uric acid (Fischer–Ach synthesis[40]) and following this principle, the first total synthesis of caffeine (**19**; Scheme 12).



19

Scheme 12. Total synthesis of caffeine (**19**).

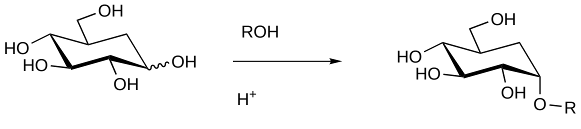
The fundamental substance purine itself was also prepared for the first time during this period and, of particular worldwide interest, the first synthetic narcotic veronal (**30**) (Scheme 13).[41]

29 **30**

Scheme 13. Synthesis of the barbiturate veronal (**30**) from urea and 2,2-diethylmalonic acid diethyl ester (**29**).

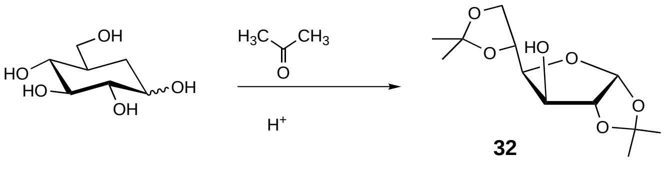
In addition to further constitution and configuration elucidation, amongst the most important results in carbohydrate chemistry of his period in Berlin was the first synthesis of glucosides **31** (Scheme 14) and other glycosides.[42] Much earlier, still in Würzburg, the formation of a disaccharide, isomaltose, from glucose by the action of hydrochloric acid had been observed.

Emil Fischer was also presumably the first to have undertaken protective group chemistry when he introduced the isopropylidene group into different carbohydrates (including glycerol) (Scheme 15).[42]



31

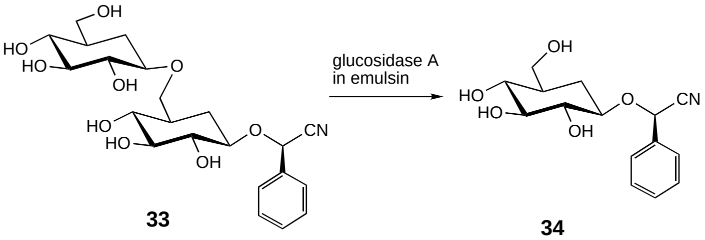
Scheme 14. Acid-catalyzed synthesis of glucosides **31**.



32

Scheme 15. The first use of protecting groups probably dates back to Emil Fischer.

Finally, the considerable amount of work in which Emil Fischer investigated the action of enzymes in relation to substrate structure must be mentioned at this point,[43] for example, the cleavage of β-glucosides or amygdalin (**33**) to mandelonitrile glucoside **34** by emulsin from bitter almonds (Scheme 16), and of saccharose by invertase, maltose by maltase, and lactose by emulsin. From the experience thus gained he formulated the now famous lock-and-key principle for the selectivity of enzyme action as the fundamental principle of biological-selection processes. Until today, this description of molecular recognition by Emil Fischer has lost none of its impact.[44, 45]

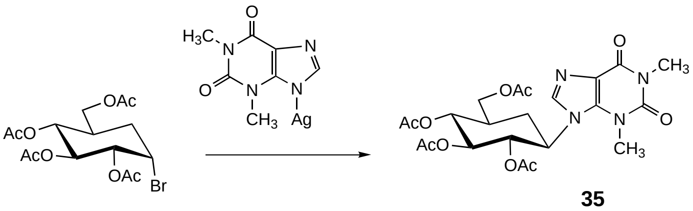


33 **34**

Scheme 16. Enzymatic catalysis and the lock-and-key principle.

His magnificent and enduring scientific achievements, which were a quantum leap in the quality of natural-product research, were recognized in 1902 by the award of the Nobel Prize for Chemistry by the Royal Academy in Stockholm.

Emil Fischer was thus strengthened in his exceptionally creative work. He entered new, unexplored fields. In one he brought together purine and carbohydrate chemistry into the first synthesis of nucleosides. Thus amongst others adenine and uracil were glycosylated,[46] as well as theophyllin, presumably to the isomer **35** (Scheme 17). Phosphorylation of the nucleosides to a “nucleotide” did not lead to a well-defined product, but already provided some insight into later nucleotide chemistry. Based on knowledge of the building blocks, Emil Fischer was in the position to develop ideas on the structure and function of nucleic acids that were



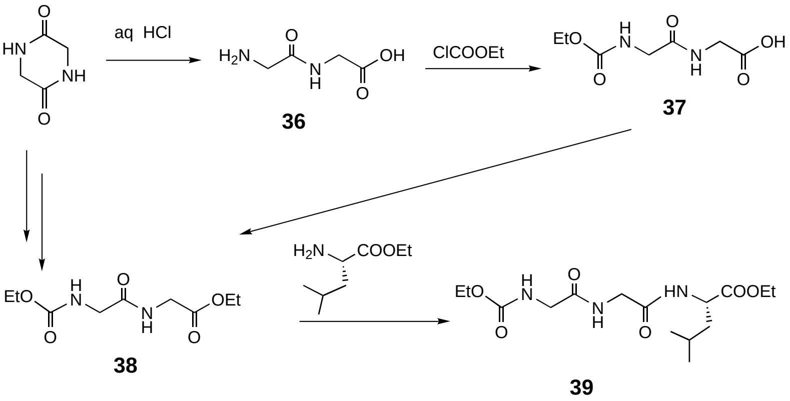
Scheme 17. One of the first nucleoside syntheses.

remarkable for that time. During the early years in Berlin a new oxazole synthesis was developed by the acid-catalyzed reaction of cyanohydrins with aldehydes[47] as well as optimization of the acid-catalyzed formation of esters.[48]

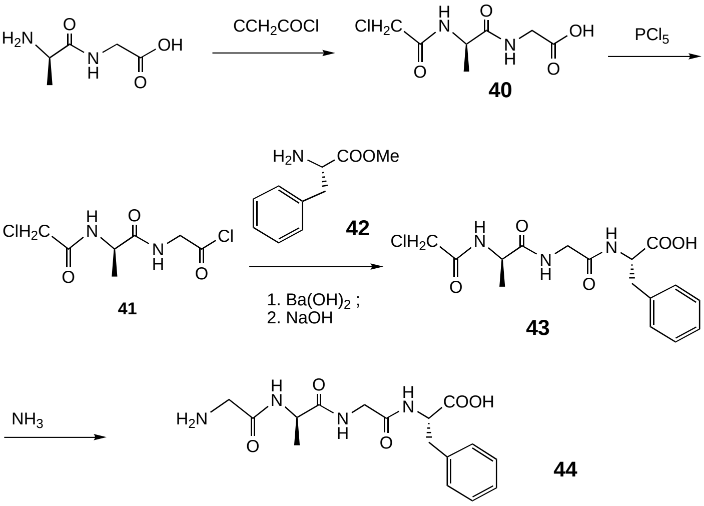
In Berlin Emil Fischer entered a totally new, extensive field with his investigations on peptides and proteins. Some work on glycine and diketopiperazine had previously been described by Curtius. Emil Fischer's interest was directed initially at the separation of *N*-protected amino acids, for example *N*-benzoylalanine, *N*-benzoylaspartic acid, and *N*-benzoylglutamic acid into their enantiomers with the help of their brucine or strychnine salts.[49] He also pursued the total synthesis of amino acids, for example 2,4-diaminobutyric acid. With a general method for the formation of amino acid esters[50] he discovered a key reaction for the synthesis of peptides. However, this was first achieved by opening of the simple diketopiperazine with concentrated hydrochloric acid to give glycylglycine (**36**), the N-terminus of which was then protected with ethyl chloroformate to form (→**37**; Scheme 18).[51]

The conversion of **37** into its ethyl ester **38** was accomplished, either directly or by acid alcoholysis of diketopiperazine, and subsequent introduction of the ethoxycarbonyl group. Warming **38** with the ethyl ester of leucine resulted in the first synthesis of an optically active peptide **39** 100 years ago.[52] The formation of esters of amino acids was used frequently by Emil Fischer for the analysis of natural proteins: the amino acids formed by hydrolysis were converted into their esters and these were separated by fractional distillation. Proteins, such as silk fibroin, were also hydrolyzed to obtain oligopeptides.[53]

Fischer and co-workers introduced the use of α-haloacylamino acids such as **40** and their conversion into an acid chloride such as **41** as a general method for the construction of peptides. Upon reaction with an amino acid ester such as **42**, the extended peptide ester was formed; careful alkaline hydrolysis led to the haloacylpeptide **43**, which was finally converted into the target peptide **44** with ammonia (Scheme 19).[54] During this work Emil Fischer showed that the product **44** was attacked rather quickly by “fresh pancreatic extract from dogs”.



Scheme 18. An early example of an asymmetric peptide synthesis.



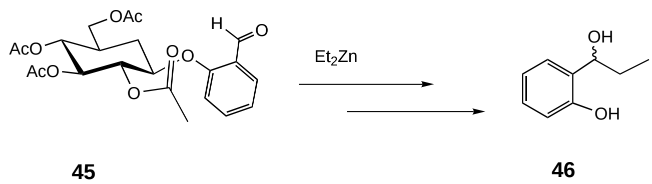
Scheme 19. General procedure for the synthesis of peptides.

As well as ethoxycarbonyl and α-haloacyl groups Emil Fischer was already using arylsulfonyl[55] and formyl protective groups.[56] He was able to increase the efficiency of his methods to achieve the synthesis of an octadecapeptide consisting of three L-leucine and 15 glycine units,[57] which for that time was an impressive achievement. Of course, syntheses which reliably avoided racemization were to require protective groups that were removable under mild conditions. The first of this type was introduced by his student Max Bergmann[58] with the benzyloxycarbonyl (Z) group.

A detailed discussion of all the fundamental contributions of Emil Fischer to peptide and protein chemistry are beyond the scope of this tribute. It has to be noted, however, that he involved himself with the stereochemical mechanisms and in particular he investigated nucleophilic substitution and the Walden inversion.[59] However, special relationships are present in the reactions of amino acids with nitrosyl bromide which will not be described in more detail here.

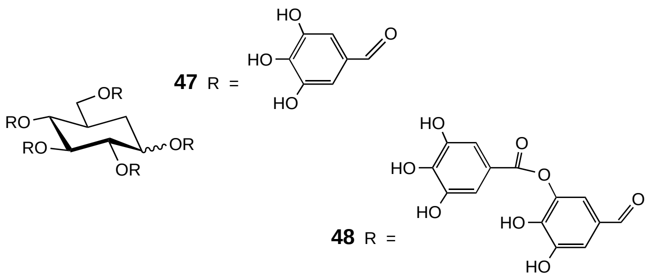
A further stereochemical topic could be asymmetric synthesis controlled by auxiliaries. Emil Fischer already had this idea during the course of his investigations on phenylglycosides, tanning agents, and lichens when he treated protected *O*-glycosyl salicylaldehyde **45** with diethyl zinc (Scheme 20). The optical activity initially observed in the isolated product **46** proved later to be mainly due to impurities in the glucose. But the idea sounds as if it were from recent times.

Lichens and tanning materials had interested Emil Fischer since his youth, certainly from the



Scheme 20. Attempted enantioselective synthesis with control by a chiral auxiliary.

time of his doctoral work. On the basis of his mastery of carbohydrate chemistry he approached this topic once more on the path to synthesis. Thus he was successful in the synthesis of galloyl glycosides **47**,[60] depsides, and tanninlike compounds,[61] and the pentakis(digalloyl) glucose derivative **48** (Scheme 21) and even higher-molecular-weight structures.



Scheme 21. Experiments on tannin chemistry.

Fatty compounds[62] obtained by acylation of isopropylidene-protected multivalent alcohols were also part of his work. The World War, the personal tragedies, and the increasingly troublesome diseases of the intestinal canal, possibly caused by his favorite tool, phenylhydrazine, undermined his energies so that further developments in his later research area remained unfulfilled.

Under Emil Fischer's leadership the Berlin Chemical Institute became one of the leading research institutes in the world. In addition to the Nobel Prize he was awarded numerous honors for his exceptional research. He was made "Ritter der Friedenklasse des Ordens Pour le Mérite" (for information on this distinction, see: http://www.orden-pour-lemerite.de) and active privy councilor with the title of Excellency. He received the Award of the French Legion of Honor, and high scientific honors and medals which carry the names of Cothenius, Lavoisier, Helmholtz, Davy, and Tiedemann. "They did not in any decisive way have a modifying effect on his personality, on his social behavior", wrote Burckhardt Helferich.[4]

From the facts described by himself[2] and others[37] Emil Fischer no longer appeared to be the gregarious, enterprising contemporary he was during his youth in Strasbourg and in Munich. He felt the weight of his responsibilities and in particular too his mission to clarify biologically selective processes, whose main components he investigated with peptide, nucleoside, and carbohydrate chemistry as well as with his studies on enzymes. He foresaw the complexity of this biological material which he tried to master with increased passion. This effort, certainly reinforced by the personal tragedy inflicted upon him by the fate of his family, left him increasingly lonely.

Nevertheless, he served science and its organizations with considerable dedication. He took part in the meetings of the Prussian Academy of Sciences, during which he took interest in many areas of natural science outside of chemistry. His influence characterized by deed and decisiveness through which he sought to generate a particularly fruitful atmosphere in scientific research must be particularly emphasized.

He actively pursued the setting up of institutes devoted solely to research. Thus he contributed decisively to the founding of the "Kaiser Wilhelm Gesellschaft zur Förderung der Wissenschaften" in 1911, today the Max Planck Gesellschaft (Max Planck Institute). In October 1912, in the presence of the then German Kaiser, the "Kaiser Wilhelm-Institut für Chemie" was dedicated in Berlin-Dahlem as the first establishment of this research organization (Figure 5).[63] Soon thereafter came the formation of the Institut für Physikalische Chemie und Elektrochemie, also in Berlin, and the Institut für Kohlenforschung in Mülheim, led by Franz Fischer, a former colleague of Emil Fischer (the connection between the two Fischers lives on in the term Fischer–Tropsch synthesis). The latter circumstance illustrates the farsightedness with which Emil Fischer influenced the research landscape in Germany and beyond. He had recognized quite early the importance of radioactivity and had welcomed the young researchers Otto Hahn and Liese Meitner into his Berlin Institute. He aided inorganic chemistry with enthusiasm in that he recommended research and teaching in the area of inorganic chemistry to his talented assistants Alfred

Figure 5. Opening ceremony of the Kaiser-Wilhelm-Institute für Chemie und für Physikalische Chemie und Elektrochemie by Kaiser Wilhelm II. Behind Kaiser Wilhelm: Adolf Harnack and Emil Fischer (from right to left; reproduced, with permission, from the archives of the history of the Max-Planck-Gesellschaft, Berlin-Dahlem.

Stock and Otto Ruff (after whom the Ruff degradation was named).[39]

Many distinguished chemists came from his Institute as doctors, postdoctoral fellows, and lecturers, including amongst many Hans Fischer (Nobel Prize 1930, porphyrin synthesis), Otto Warburg (Nobel Prize 1931, respiratory enzymes), Adolf Windaus (Nobel Prize 1928, vitamin D), Otto Diels (Nobel Prize 1950, Diels–Alder reaction), Karl Landsteiner (Nobel Prize for medicine 1930, blood group compounds) Geza Zemplén (transesterification), Wilhelm Traube (Traube synthesis of purines), Emil Abderhalden, Hermann Leuchs, and Max Bergmann (peptide chemistry), Karl Freudenberg, Burckhardt Helferich, and many others, including those already mentioned (e.g. Ludwig Knorr or Julius Tafel). To this day we still profit from the outstanding research results that Emil Fischer and his colleagues and school achieved for humanity.

If one considers that at that time this chemical elucidation and synthetic work on complex, polyfunctional compounds was accomplished without chromatography, HPLC, NMR spectroscopy, or mass spectrometry, and that the only means available were distillation, crystallization, careful elemental analysis, unerring analytical acumen, and bold hypotheses based on sound knowledge, one can have only the deepest respect (Figure 6).

Emil Fischer was blessed with excellent gifts for a natural-science researcher. He had an outstanding memory[4] and the ability for mathematical conclusions. He was stimulated and fostered by an outstanding academic teacher, Aldof von Baeyer, and was able gather about him many excellent co-workers and students. Through his pioneering work he came into the position to make far-reaching assumptions on the structure and function of biologically important molecules, proteins, and nucleic acids. One has to refrain therefore from calling him a visionary, as today this term is unfortunately reserved for addressing people, predominantly from political and economic spheres, many of whom base their "grand design" without shame on a small reservoir of knowledge according to the motto: knowledge imposes limitations, but ignorance leads to independence. With Emil Fischer it is quite the opposite: On a foundation of extensive knowledge, gained by his own experimental work constantly scrutinized for consistency and by evaluation of the results of other and new experiments, he was able to enter new areas boldly and with foresight and to make predictions still valid today. That bestowed on him in his time a status described by the words of Richard Willstätter reiterated, somewhat modified and abbreviated, in the title.[64]

Figure 6. Emil Fischer in the laboratory (reproduced, with permission from Springer Verlag, from reference [2]).

In future, chemists will have need of his guidance and his methodical resolution when, after the magnificent analytical work in biochemistry and molecular biology on the elucidation of the genome and its translation into the proteome, they want to address the recognizable biological functional space with active synthetic ligands which, like molecular microchips, control hydrophilic, hydrophobic, and hydrogen-binding sites, are not rapidly digested but yet remain degradable. At the same time the impact of Emil Fischer is a shining example of what fruitful work a chemist can achieve in the elucidation of molecular biological processes. In today's world he and his life's work encourage and stimulate the concentration of research efforts on the wonderful processes of biological control, not only to describe the sequences, but also to understand them mechanistically at a molecular level.

My special thanks go to my colleagues Professor Johann Mulzer, University of Vienna, Professor Ulrich Koert, University of Marburg, and Professor Jürgen Liebscher, Humboldt Universität, Berlin who generously provided me with literature for this article.

[1] J. Mulzer in *Berlinische Lebensbilder*, *Vol. 1* (Eds.: W. Treue, G. Hildebrand), Colloquium, Berlin, **1987**, p. 34.
[2] E. Fischer, *Aus meinem Leben*, Springer, Berlin, **1922** and **1987** (With a Prologue and an Epilogue by Bernhard Witkop; Reprint from Emil Fischer, Gesammelte Werke, Edited by M. Bergmann).
[3] E. Fischer, O. Fischer, *Liebigs Ann. Chem.* **1878**, *194*, 242.
[4] "Emil Fischer zum 100. Geburtstag": B. Helferich, *Angew. Chem.* **1953**, *65*, 45.
[5] "Emil Fischer. Sein Leben und sein Werk.": K. Hoesch, *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 50 (Sonderheft).
[6] "Emil Fischer. Sein Leben und sein Werk.": K. Hoesch, *Ber. Dtsch. Chem. Ges.* **1921**, *54*, 206. (Special issue.)
[7] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1875**, *8*, 589.
[8] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1875**, *8*, 1587.
[9] W. Koenigs, E. Knorr, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 957.
[10] A. W. Hofmann, A. Geyger, *Ber. Dtsch. Chem. Ges.* **1872**, *5*, 472.
[11] E. Fischer, F. Jourdan, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2242.
[12] E. Fischer, O. Hess, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 559.

© 2002 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim

[13] R. Hoffmann, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 4388; R. Hoffmann, R. B. Woodward, *J. Am. Chem. Soc.* **1965**, *87*, 4389

[14] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 1563.

[15] L. Knorr, *Ber. Dtsch. Chem. Ges.* **1883**, *16*, 2597, DRP 26429 (1883).

[16] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 572.

[17] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 579.

[18] E. Fischer, *Justus Liebigs Ann. Chem.* **1882**, *215*, 253.

[19] A. Butlrow, *Justus Liebigs Ann. Chem.* **1861**, *120*, 295.

[20] O. Loew, *J. Prakt. Chem.* **1886**, *33*, 321.

[21] E. Fischer, F. Passmore, *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 360.

[22] E. Fischer, J. Tafel, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 1088.

[23] E. Fischer, J. Tafel, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2384.

[24] E. Fischer, J. Tafel, *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 2566.

[25] E. Fischer, J. Hirschberger, *Ber. Dtsch. Chem. Ges.* **1889**, *22*, 3218.

[26] H. Kiliani, *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 3029.

[27] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1889** , *22*, 220.

[28] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 370.

[29] E. Fischer, P. Lindner, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3034.

[30] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 799.

[31] For the pioneering discoveries of J. H. van't Hoff on the stereochemistry of tetravalent carbon atoms, see: E. W. Meijer, *Angew. Chem.* **2001**, *113*, 3899; *Angew. Chem. Int. Ed.* **2001**, *40*, 3783.

[32] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 2114.

[33] An excellent tribute to this achievement of Emil Fischer is found in: F. W. Lichtenthaler, *Angew. Chem.* **1992**, *104*, 1577; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1541.

[34] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 1836; E. Fischer, *Ber. Dtsch. Chem. Ges.* **1891**, *24*, 2683.

[35] J. M. Bijvoet, A. F. Peerdeman, A. J. van Bommel, *Nature* **1951**, *168*, 271.

[36] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1894**, *27*, 3208.

[37] A summary is found in: C. Harries, *Naturwissenschaften* **1919**, *9*, 843 In this case, however, the old nomenclature is used, for example, for gulose and idose.

[38] J. Mulzer in ref. [1], p. 27.

[39] M. Meisel, *100 Jahre Chemie in der Hessischen Straße*, Festschrift der Humboldt-Universität zu Berlin, **2000**.

[40] E. Fischer, L. Ach, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3135.

[41] E. Fischer, J. von Mering, *Ther. Monatsh.* **1903**, *17*, 208; E. Fischer, A. Dilthey, *Justus Liebigs Ann. Chem.* **1904**, *335*, 334.

[42] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1145; E. Fischer, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1167.

[43] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1429; E. Fischer, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 1508.

[44] A. Eschenmoser, *Angew. Chem.* **1994**, *106*, 2455; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2363.

[45] F. W. Lichtenthaler, *Angew. Chem.* **1994**, *106*, 2456; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2364.

[46] E. Fischer, B. Helferich, *Ber. Dtsch. Chem. Ges.* **1914**, *47*, 210.

[47] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1896**, *29*, 205.

[48] E. Fischer, A. Speier, *Ber. Dtsch. Chem. Ges.* **1895**, *28*, 3252.

[49] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 2451.

[50] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 433.

[51] E. Fischer, E. Forneau, *Ber. Dtsch. Chem. Ges.* **1901**, *34*, 2868.

[52] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 1095.

[53] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2315.

[54] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 850.

[55] E. Fischer, P. Pergell, *Ber. Dtsch. Chem. Ges.* **1903**, *36*, 2592.

[56] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 2893.

[57] E. Fischer, *Ber. Dtsch. Chem. Ges.* **1907**, *40*, 1754.

[58] M. Bergmann, L. Zervas, *Ber. Dtsch. Chem. Ges.* **1932**, *65*, 1192.

[59] E. Fischer, L. von Mechel, *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 1355.

[60] E. Fischer, K. Freudenberg, *Ber. Dtsch. Chem. Ges.* **1912**, *45*, 915.

[61] E. Fischer, M. Bergmann, *Ber. Dtsch. Chem. Ges.* **1918**, *51*, 1760.

[62] E. Fischer, C. Rund, *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 88.

[63] H. Remane, *Biographien hervorragender Naturwissenschaftler*, *Techniker und Mediziner*, *Vol. 74*, B. G. Teubner, Leipzig, **1984**, p. 53.

[64] R. Willstätter, A*us meinem Leben. Von Arbeit*, *Muse und Freuden*, *2nd ed.*, Verlag Chemie, Weinheim, **1958**, p. 212.