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KARL FREUDENBERG 1886–1983

This appreciation of the life and work of Professor Freudenberg was kindly prepared for us by one of his former students, John Harkin, Professor of Soil Science at the University of Wisconsin. Professor Karl Freudenberg served on the Editorial Advisory Board of this journal from the beginning in 1961 and we are pleased to pay tribute here to his many major contributions to the structural elucidation of plant constituents and especially of lignin, by the publication of this notice.

JEFFREY B. HARBORNE
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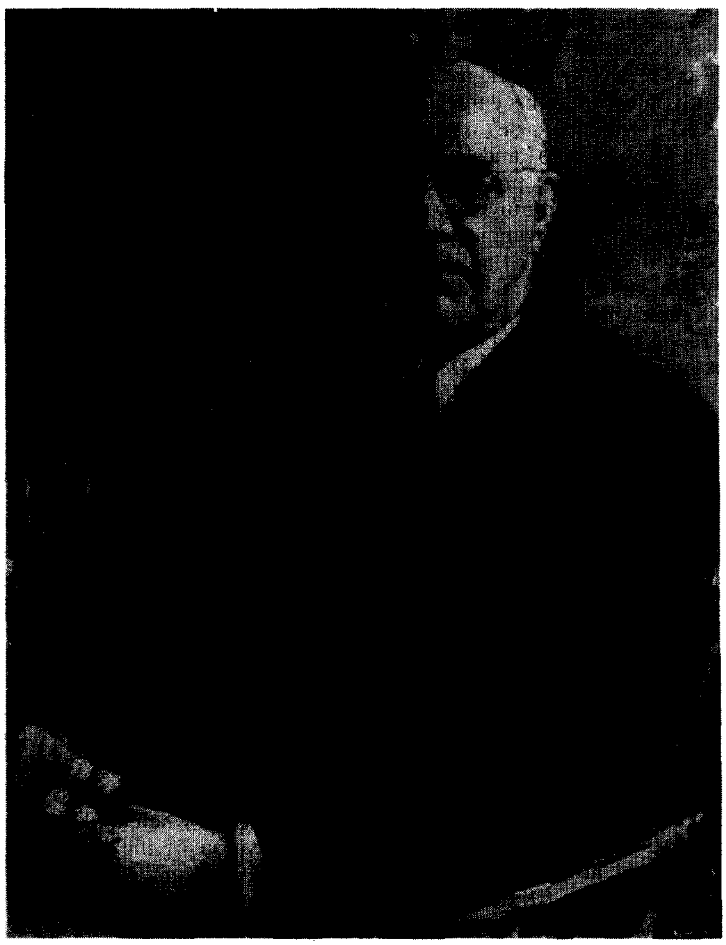

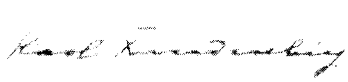

Easter Sunday, April 3, 1983, a joyous feast day for Christendom, was a sad day for phytochemistry, since it witnessed the untimely demise of Professor Karl Freudenberg — for many generations one of the greatest stalwarts in this discipline. It was his singular achievement not only to have masterfully researched many categories of natural products of plant origin but also to have personally bridged the gap between the classical era of largely empirical organic chemistry and the modern science, based primarily on instrumental methodologies, theoretical approaches, and biochemical/biological concepts. In fact, in many ways he was responsible for the evolution of this special branch of science to its more rigorous modern form.

Karl Johann Freudenberg was born on January 29, 1886 in Weinheim, North Baden, about 30 kilometers north of Heidelberg, a son of the industrialist Hermann Ernst Freudenberg, whose family owned a local tannery and shoemaking plant. After graduating from the Goethe Gymnasium (or High School) in Frankfurt-am-Main he studied chemistry at the University of Bonn from 1904 to 1907 and later pursued graduate studies at the University of Berlin, completing his Ph.D. thesis under the direction of Emil Fischer on the structure of Chinese gallotannin in 1910. On July 30, 1910 he also married his fiancée from his Bonn days, Doris Nieden, who later bore him three daughters and two sons. The designs of his family to have him apply his knowledge of tannins acquired from Emil Fischer for the family business came to nought, because young Karl was so fascinated with chemistry that he remained in an academic career, working as 'Privatassistent' with Fischer until July 1914, when he received an appointment as Privatdozent (Assistant Professor) at the University of Kiel. Military service from August 1914 to November 1918 abruptly interrupted his career, but even in this endeavour Karl Freudenberg distinguished himself, receiving the Iron Cross, Class I and II. Back in Kiel after the Great War he was promoted to Associate Professor in August 1919, but moved to join Richard Willstätter in Munich in November 1920. Within a year he had moved again, this time to the University of Freiburg with Heinrich Wieland as an Associate Professor of Organic Chemistry. Exactly one year later, in August 1922, he was appointed Professor of Chemistry and Director of the Chemistry Department at the Technische Hochschule in Karlsruhe. His final move in April 1926 brought him back closest to home as successor to Theodor Curtius as Director of the Chemistry Department of the University of Heidelberg. He remaind in this position until he retired with emeritus status in 1956. However, he continued working in the Department until 1969 as Director of the Research Institute for the Chemistry of Wood and Polysaccharides, which he founded in 1938. In 1931 he spent a 6-month sabbatical leave as Carl Schurz Memorial Professor at the University of Wisconsin in Madison, where he conceived his dream of reorganizing the natural science departments of the University of Heidelberg — traditionally scattered in small old buildings throughout the town — into a coherent campus along American lines in the 'Neuenheim Field' on the North Bank of the Neckar River and west of the old city of Heidelberg. Here a major portion of the 'New University' of Heidelberg now stands, an impressive development that started under Karl Freudenberg's prodding in the early 1950's and is a credit to his foresight in practical as well as scholastic academic undertakings.

Throughout his scientific career, Karl Freudenberg remained fascinated with the structure and properties of the principal plant products, a consequence of his intense interest in botany, and a matter reflected in his writings, including many books (The Chemistry of Natural Tannins, 1920; Rotation of the Plane of Polarization of Light, coauthored by Werner Kuhn, 1932; Tannis, Cellulose, Lignin, 1933; Stereochemistry, 1933; Organic Chemistry, 1939; The Constitution and Biosynthesis of Lignin, coauthored by Arthur Neish, 1968) and hundreds of scientific papers. Although he conducted many detailed studies of the structures and stereochemistry of simpler plant products, such as monoterpenes, sugars, flavanoids and lignans, he was mainly intrigued by the high molecular weight constituents of plants, and was proudest of his successes in unravelling their mysteries. In fact, he often boasted that when he once prepared a peracetylated derivative of pentagalloyl-glucose during his early work with Emil Fischer on Chinese gallotannin, he had made the organic compound of highest molecular weight known at that time. He was also extremely proud of an early discovery for which he was actually given little credit, namely his recognition from experiments on the acetolysis of cellulose performed in 1920 and 1921 that cellulose was a homogeneous polymer composed of a chain of identical repeating units of glucose linked together by bonds identical to that linking the glucose units in cellobiose. Because of his characteristic reticence toward 'overinterpretation' of his own results, he refrained from stating that his experimental evidence dictated unequivocally that cellulose had to be a linear polymer of anhydro-β-D-glucose units, and merely presented this structure as a 'possibility,' leaving others more forceful to claim credit later for the discovery of the primary structure of cellulose. Actually, similar degradation studies he himself performed years afterward on exhaustively methylated cellulose confirmed his 1921 presumptions of the complete 'homogeneity' of the interunitary bonds in cellulose and encouraged him to publish the correct formula for cellulose in 1928.

Fortunately Freudenberg was not overly concerned with the recognition he received for his work, but was motivated principally by his own uniquely intense intellectual curiosity and proceeded undaunted in his research pursuits, largely immune to praise or criticism directed towards him, although he received enough of both! Following his work with cellulose, he also examined the structure of starch and determined that it was also a chain-type polymer (1930) and that the branching in amylopectin is at C-6 (1940). Studies in 1930-1940 of Schardinger's α- and β-dextrins led to the discovery of a third (γ) dextrin and recognition that these compounds were cyclic structures with 6, 7 and 8 α-glucose units. Their reaction with iodine explained the starch-iodide test and indicated the helical structure of amylose. In co-operation with Werner Kuhn in the early thirties he was also able to explain the anomalies in van't Hoff's rule of optical superposition and Hudson's rules when applied to these polysaccharides. By application of the 'displacement rule' he derived from his 1920 work with α-hydroxy, -halogeno, -azido and -amino acids, he was able to explain the optical properties of the polysaccharides, again on the assumption of uniformly repeating bonds.

His successes in clarifying — at least to his own satisfaction — the structures of these polysaccharides, induced him to examine the structures of insulin and immunoproteins in the early 1940's and finally even to attack the immeasurably more complicated architecture of lignin. It is difficult for the present generation of phytochemists to conceive the confusion that was rampant concerning the nature of lignin in the days before the advent of modern physical and instrumental structural and analytical chemical methods. Even Willstätter contended in 1922 that lignin was basically alicyclic and related to the carbohydrates and that its aromaticity was an artifact produced by extraction methods. The conventional methods used to characterize the structures of other natural polymers such as proteins or polysaccharides — acid- or enzyme-catalysed hydrolysis of the polymer before or after derivatization and identification of the monomeric or low molecular weight (oligomeric) degradation products — did not work with lignin. Consequently Freudenberg spent a major part of his later career trying to find methods of degrading lignin to afford minimally altered identifiable components — an undertaking in which he scored several signal successes. However, the breakthrough really came from his decision to duplicate the enzymatic process of lignification in the laboratory and to interrupt the polymerization at an early stage and identify the oligomeric intermediates. This was no mean task, since assumptions had to be made concerning the nature of the constituent monomeric units of lignin and the mechanism of their interlocking. A stimulus to this work came from Holger Erdtman's identification in 1933 of a phenylcoumaran structure in the dimer formed by oxidation of isoeugenol by phenol oxidase enzymes, a reaction first studied, but unexplained by French workers in 1908. Freudenberg applied the same reaction to coniferyl alcohol, assuming that the latter was the major precursor of softwood lignin. This was a reasonable assumption, since his mild oxidation of spruce lignin with alkaline nitrobenzene afforded a 25% yield of vanillin (1939) and oxidation of methylated lignin with alkaline permanganate yielded principally isohemipinic acid (1936), assumed to be derived from a phenylcoumaran structure, since similar oxidation of dehydrodi-isoeugenol also produced a small yield of isohemipinic acid. The only problem with this ingenious idea was that coniferyl alcohol was not readily available and even when arduously isolated from naturally occurring sources, such as its glucoside coniferin obtainable from conifer sap, or benzoate obtainable from Siamese gum benzoin, it was extremely labile and decomposed rapidly. Only after the advent of complex hydrides could the compound be synthesized, crystallized and preserved conveniently by storage under inert gases in freezers!

Although lignin-like polymers were prepared repeatedly by Freudenberg and his associates in the 1940s using enzymatic 'dehydrogenation' of early coniferyl alcohol samples, it was not until 1952 that the first dehydro-dimer, analogous to Erdtman's phenylcoumaran, was isolated and characterized. In the next 12 years, almost 30 mono-, di-, tri-, tetra-, penta- and hexameric intermediates of lignification were isolated and their structures determined by Freudenberg and his coworkers. The origin of all of these compounds, for which Freudenberg coined the term 'lignols,' could be explained in terms of coupling of various mesomeric forms of metastable phenoxyl radicals created by enzymatic phenol oxidation, followed by ionic stabilization reactions, which preceeded automatically, i.e. without enzymatic control. Using spectroscopic methods, he was also able to demonstrate the existence of the free radicals and methylenequinone intermediates in the reactions leading to lignol formation. His elucidation of the nature of the single or multiple bonds combining lignin precursor units in di- and oligolignols explained the long-known properties of lignin: why it could not be hydrolysed, how it reacted with wood-pulping chemicals, why it condensed to bakelite-like resins on treatment with acids, how it gave rise to various mixtures of aldehydes and acids on mild or strong oxidation, and so on. Although many monolignols in lignin were interlinked by nonhydrolysable carbon–carbon bonds, his discovery of two types of ether linkages — one formed by phenol coupling (arylglycerol-β-aryl ethers), the other (benzyl aryl ethers) by a nucleophilic addition of phenoxide ions to methylenequinone lignification intermediates — led to the ultimate means of confirming Freudenberg's phenol oxidation mechanism of lignification: by using mild methods of cleaving these ethers without concurrent side reactions which led to modification or condensation of the cleavage products, he was able to identify many of the known intermediates of simulated lignification as products of degradation of natural lignin.

An admirable trait of Freudenberg's personality shone through this whole enterprise: how he afforded due recognition to all his coworkers and to other researchers, whose work on lignin extraction, lignin analysis, or lignin reactions helped him to zero in on his own critical experiments or conclusions. The culmination of his efforts was the development of a formula concept for lignin which contained not only the known types of interunitary bonds, but also quantitatively reflected their numbers, and all the known analytical data for the functional group content and reactions of lignin. By extension of some of the principles recognized from his work with lignin, he was also able to explain much of the behaviour and properties of condensed tannins, the only class of plant-derived polymers which remained a puzzle and which he was studying concurrently.

It required an unusually persistent and sharp mind to grapple with the frustrating problem of lignin structure for so long and bring the work to a successful conclusion. Freudenberg's was such a mind. As many who knew him well will attest, his feats of recollection and breadth of interests were truly astonishing. He was quite fluent in the major European languages: French from his high-school years, when French was the fashionable foreign language for well-bred Germans, English from his stay in the USA, Italian from his sojourns to a summer home in the Italian-speaking part of Switzerland, Swedish because of its importance to his interests in wood chemistry, and Spanish simply because of his interest in the language, art, history and culture of Spain. When I visited him in his hotel room in Atlantic City during an American Chemical Society Meeting in 1965, he was lying on his bed reading a novel in Swedish. "My relaxation," he explained! In addition, he had more than a smattering of other languages. Following a lecture tour of Japan in 1962 he returned home full of enthusiasm for the country and its art and people. For his birthday that year his coworkers purchased him a Japanese print, but only after long consultation with experts that the article was genuine, and not an imitation or reprint. Imagine our surprise when, upon opening his gift, Freudenberg scrutinized the art work — a typical Japanese actor motif — and the artist's characteristic red 'signature' and pronounced, "I see it's by so-and-so (he mentioned the artist's name, unknown to all of us); that must have been done about 1870." Right on the button, as the Professor of Oriental Art we had consulted later confirmed.

His knowledge of history was also astounding, as typified by the following incident recounted by a coworker who accompanied him during a lecture tour in Prague. As usual, Freudenberg and his wife visited the local art gallery; equipped with catalog, Freudenberg was studying the paintings, but stopped in front of an old canvas, complaining, "That can't be correct." While the catalog gave a title for the painting "Pope X crowning Emperor Y," Freudenberg insisted: "Pope X lived from ... until ... while Emperor Y lived from ... until ... (naming all the years)." The periods were incompatible. So convinced of his suspicion, he brought the matter to the attention of the museum director. The latter, however, pointed out that a brass plate affixed alongside the painting had been there for years before he had taken charge of the museum and bore the same title as the catalog. However, because Freudenberg continued to grumble that something was amiss, an encyclopedia was consulted, and proved that Freudenberg must be right, and the title wrong!

The care and concern Freudenberg demonstrated in this minor matter were exhibited not only in his scientific work, but also in his civic mindedness. As a member of the City Council of Heidelberg from 1951–1956 he devoted his efforts principally to city planning — trying to maintain the traditional romanticism of 'Old Heidelberg' in a form compatible with the changes required by the developing modern German industrial society — and to adult and extension education. Later he single-handedly launched the defense that thwarted plans by a major German paper manufacturer to construct the first German kraft pulpmill in Mannheim, a scant 20 km distance away from Heidelberg. Freudenberg's expert knowledge of pulping processes, pulpmill emissions and the local meteorology provided Heidelberg with the arguments necessary to prevent a development which would have ruined the famous city's tourism forever.

It was Freudenberg's willingness to deal with tough problems and care and persistence in solving them that brought him his singular successes in science. He repeated experiments again and again, and often had two or more of his students do the same experiment independently — sometimes simultaneously, sometimes years apart — to ensure the validity of his observations, while always seeking new information or insights. He applied the same care in his writing, going over each sentence or phrase again and again and weighing every word until it met with his satisfaction — a habit he said he had acquired from Emil Fischer.

It is only natural that great honours accrued to one so industrious, interested and intellectual: he was an honorary member of many learned societies, including the Royal Society, and the German, Swiss, Japanese, Spanish, Austrian and Finnish Chemical Societies, he received honorary doctorates from the Universities of Graz, Darmstadt, Basel and Berlin, and was awarded the Emil Fischer and Alexander Michterlich Medals. He travelled to countries all over the world, in Eastern and Western Europe, Canada, the USA, Mexico, India and Japan to lecture on his favourite subjects and to study other cultures and conditions; his door was always open and his hospitality abundant for students and visitors from abroad. As one of the finest experts on the history of his beloved Heidelberg and on German culture in general, and as a distinguished linguist, it often fell to him to conduct foreign dignitaries around the town to explain the sights. Through his scientific work and contacts, and broad range of intellectual pursuits, Freudenberg was a major diplomatic force in reconciling the valuable attributes of his country with societies abroad that were twice shocked by the vagaries of German political leadership and the major conflicts of two World Wars.

A man of his stature, age and experience had countless stories to relate — about his famous predecessors Leopold Gmelin, August Kekulé, Robert Bunsen, Victor Meyer, Theodor Curtius and others in the Chemistry Department in Heidelberg, about how he held the department together during the period of inflation in the 1930's by borrowing and repaying bank loans secured by a single bar of platinum, about how he used tricks and diversions to avoid ever having to utter the prescribed "Heil Hitler" before delivering his chemistry lectures during the Nazi era, about how he concealed the valuable books from the University Library in vaults below the Heidelberg Castle during and after the Second World War, or about how he was 'rescued' from unjust internment after the Second World War by none other than Roger Adams, then an intelligence officer with the US military. He was an exquisite raconteur, lending a variety of accents to highlight his tales, many of which often ended with his whole body shaking with his deep vibrating laugh.

No one who worked for him or with him could help but respect, admire and try to emulate such a man. Despite his myriad of interests and activities, thanks to his enormous drive and energies, almost daily he found time to go the round of his laboratories to ask all his researchers the same question — sometimes dreaded, sometimes welcomed, depending on how the work was going: "Was gibt's Neues?" (What's new?). This pursuit was not designed to goad his collaborators to greater efforts but merely arose naturally from his insatiable curiosity into what was happening at the frontiers of his science and his field, and his anxiety to see progress and find answers to the many questions in his own mind.

All who knew, respected and loved Karl Freudenberg were shattered by his passing, because though weakened in body, intellectually he was still as agile as ever. All would have wished him the last 3 years to complete his century, because in 1986 the University of Heidelberg would have been six hundred years old and who would have been better fitted to lead any centennial celebrations than Freudenberg?

A memorial meeting of the Heidelberg Chemical Society on November 22, 1983 recalled his life and activities in addresses by but two of his prominent students, Friedrich Cramer, Director of the Max-Planck Institut for Experimental Medicine in Göttingen, and Nobel-Prize Laureate Otto Westphal, from the Max-Planck Institut for Immunobiology in Freiburg. All of his former students and friends join with them in recalling with fondness and admiration the achievements of this outstanding scientist and teacher and in bewailing his untimely demise.