LOUIS FREDERICK FIESER

April 7, 1899–July 25, 1977

BY MARSHALL GATES

LOUIS FREDERICK FIESER, one of the major figures in organic chemistry of this century, was born on April 7, 1899, in Columbus, Ohio, the son of Louis Frederick and Martha Victoria Kershaw Fieser. His father was an engineer, and his grandfather an educator and editor who published the first German language newspaper in Ohio and was at one time head of the Columbus School System. Fieser attended Douglas School and East High in Columbus and then Williams College, graduating in 1920. Although his major interest was chemistry, he was also strongly attracted to english and philosophy. He was a scholar and an athlete, a member of Phi Beta Kappa who lettered in football, basketball, and track, and was a member of the undefeated football team of 1919. He retained a robust athletic ability well into middle age; many of his graduate students will recall his feat of swimming the entire length of the Harvard pool under water, a feat none of them could duplicate.

Graduate study at Harvard under James Bryant Conant followed his years at Williams, leading to the Ph.D. in 1924. His thesis research on the oxidation-reduction potential of quinones, at the time an area with a distinct theoretical character, was the beginning of a life-long interest in these fascinating substances. Already he began to exhibit the prac-

ticality that would remain a life-long characteristic. Based on his oxidation-reduction studies he developed a reagent (Fieser's solution) that is still unsurpassed for the absorption of oxygen in gas analysis.

A Sheldon Traveling Fellowship from Harvard allowed a postdoctoral year at Frankfurt-am-Main and Oxford, following which he took up his first teaching appointment, at Bryn Mawr College, where he served as assistant and associate professor from 1925 to 1930. An appointment as assistant professor at Harvard took him to Cambridge in 1930 where he spent most of his professional life, becoming full professor in 1937, Sheldon Emery Professor in 1937, and professor emeritus in 1968. In 1968 he served as Neilson Professor at Smith College.

Louis Fieser's professional honors included membership in the National Academy of Sciences (1940), the American Academy of Arts and Sciences, the American Philosophical Society (1941), honorary doctorates from Williams College (1939) and the University of Paris (1953), the Katherine Berkham Judd Prize for Cancer Research (1941), the James Flack Norris Award in the Teaching of Chemistry (1959), the Manufacturing Chemists Association Award in Teaching (1959), and the Nichols Medal (1963). The June 1965 number of the *Journal of Organic Chemistry* containing 112 papers by former students and colleagues was published in his honor, and in 1976 he was also honored at a session of the Division of Chemical Education of the American Chemical Society on "Giants in Chemical Education."

He was a member of the Alsos Mission, E.T.O., U.S. Army immediately after World War II, and in 1963 served on the Surgeon General's Advisory Committee on Smoking and Health, the only chemist on the ten-membered commission.

The five years Fieser spent at Bryn Mawr, where he had

succeded Elmer Peter Kohler, produced some twenty papers in the general area of quinone chemistry. His synthesis of the quinonoid pigment lapachol in 1927 led to a close friendship wih Samuel Cox Hooker, a retired industrialist who had established a private laboratory in Brookyn and returned after a lapse of twenty years to a study of lapachol, the pigment of the South American Bethabarra wood. Hooker was a skillful and resourceful experimentalist, qualities greatly admired by Fieser. A measure of the admiration, respect and affection which the young academic chemist had for the much older Hooker is provided by his preparation for posthumous publication of a series of eleven papers covering Hooker's later studies on lapachol and related substances. These studies were carried out during the period 1915–35 and appeared in the *Journal of the American Chemical Society* in 1936. Hooker's earlier investigations on lapachol had been published in eleven papers appearing in the period 1889–96 and were reprinted with the later series in 1936. Fieser was later to use with virtuosity in his antimalarial studies during World War II a reaction discovered by Hooker ("Hooker oxidation").

While at Bryn Mawr Fieser met Mary Peters, a member of his second class, who, after graduating from Bryn Mawr, entered Radcliffe College to undertake graduate study under Fieser's direction. They were married in 1932, and thereby began a remarkable scientific and literary collaboration. Mary Fieser was his constant companion, friend, and indefatigable collaborator. Together they published thirty-five papers, eight books, and the important series, "Reagents for Organic Synthesis."

Fieser's interest in the chemistry of quinones and the hydroxyaromatic substances in oxidation-reduction equilibrium with them lead naturally to studies on aromaticity in general. This interest was already exhibited in a few papers

from his Bryn Mawr period but was pursued avidly in the 1930s during his early years at Harvard. Following quite naturally from this was his developing interest in the carcinogenic polycyclic aromatic hydrocarbons, which was to dominate his efforts during the middle and late 1930s. This period saw the development of synthetic methods for the polycyclic aromatic hydrocarbons, efficient syntheses for such important carcinogenic substances as 20-methylcholanthrene, 3,4-benzpyrene, and their alkyl derivatives and the general exploration of the relationship between structure and carcinogenic activity among the polycyclic aromatic hydrocarbons. Studies on resin acids and the application of ultraviolet absorption spectroscopy to problems in organic chemistry were also carried out, the latter at a time before recording spectrophotometers made this an easy task.

In the mid-1930s the first edition of Fieser's highly influential book, *Natural Products Related to Phenanthrene,* appeared. A whole generation of young organic chemists was introduced to the fascinating fields of the steroids and the opium alkaloids by this volume, which was to go through three editions and be followed by *Steroids* as a fourth in which a prominent part of the earlier editions took over the entire volume. The felicitous appearance of this treatise was of great value during the efflorescence of steroid studies in the 1950s and 1960s.

Fieser's keen interest in and knowledge of quinones lead him to make a major contribution to the chemistry and synthesis of the quinonoid natural substance vitamin K in the late 1930s. The existing purification methods for this substance were both inefficient and cumbersome; Fieser quickly devised both an efficient synthesis and a novel and effective purification based on the unusual solubility properties of the corresponding hydroquine. As was so often the

case in his career, the key experimental steps were contributed by Fieser himself.

With the approach of World War II, Fieser was drawn increasingly into war-related projects. A brief excursion into the area of mixed aliphatic-aromatic polynitro compounds for possible use as exotic explosives was followed by studies of alkali salts of long chain fatty acids as incendiaries, but by far the most important of his war-related work was his long and intensive study of the quinone antimalarials. This important work was published in a series of some thirty papers, mostly during 1948–50, and in several review articles.

The work stemmed from a lead uncovered by the screening at Abbott Laboratories of random samples from university research laboratories for activity against plasmodium lophurae in ducks. Among several hundred such samples, three from the collection of Samuel Cox Hooker which had been bequeathed to Fieser were found to have some antimalarial activity. These were the naphoquinone hydrolapachol and two related less active quinones. In a major effort involving more than thirty collaborators at Harvard and elsewhere, Fieser rapidly explored the relationship between structure and activity in these quinones. More than three hundred compounds were prepared and examined, and concommitant studies of the mode of action and degradation in the organism were carried out. Activity was shown to peak in 2-alkyl-3-hydroxynaphthoquinones when the alkyl side chain is nine carbon atoms long and normal or terminally branched. When the side chain contains an alicyclic ring, peak activity occurs at a C10 or C11 chainlength, with two rings activity peaks at C12 or C13. An aryl substituent produces an even greater shift and steric configuration is important. Unfortunately the compounds are rapidly metabolized, but it was found

that two metabolic products hydroxylated in the side chain had weak but persistent activity, and that the deactivating effect of the hydroxyl groups could be offset by increasing the size of the side chain. Eventually a substance with a C19 side chain containing a tertiary hydroxyl group was shown to be effective in limited clinical trials, but it is ineffective orally and must be administered parenterally, is difficult to synthesize, and did not achieve clinical success. Work in this area had been suspended after World War II but was resumed at the time of the war in Vietnam.

With Kendall's demonstration of the utility of cortisone in the treatment of rheumatoid arthritis in 1949 and the search for clinically useful cortical hormones including oral contraceptives in the 1950s came a remarkable renaissance in research in the chemistry of the steroids. Pharmaceutical firms throughout the world undertook programs in this highly competitive area. Fieser's *Natural Products Related to Phenanthrene* in its various editions proved to be invaluable as a source book and reference, particularly its fourth edition, renamed *Steroids* with a corresponding change in emphasis. At the same time Fieser himself contributed to the rapidly advancing field, both by his own research with his collaborators and as a consultant to industrial firms. Including a few earlier papers, more than fifty contributions in this area came from his group. During this period Fieser formed a close personal and professional relationship with Max Tishler of Merck & Co., Inc.

In his later years, Fieser's publications tended to address problems in teaching, the philosophy of research, and public health; of the latter, particularly those associated with smoking. It is fitting, however, that his last research publication was in the same field in which his research career had begun, the naphthoquinones.

The above brief summary of Fieser's research career gives

little indication of and lays little emphasis on his extrordinary love for and skill at experimental work in the organic laboratory. He was a gifted experimentalist, indeed a virtuoso who delighted in finding the simple, practical, ingenious yet elegant solution to an experimental problem. No fewer than forty of his 340 published papers were based on his own experiments. A beautiful example of his exeptional skill as an experimentalist is provided by an incident that occurred during his work on vitamin K. After devising a simple but elegant synthesis of this substance, he developed a novel and very efficient purification of it from natural concentrates (3–5%), in order to obtain a comparison sample. Theretofore it had been purified only by lengthy and cumbersome procedures; his method comprised conversion to the hydroquinone whose unusual solubility properties allowed an easy purification. Reconversion to the quinone gave the pure vitamin, with which his synthetic sample was identical in all respects.

Fieser's keen interest in and love of experimental work was reflected in his laboratory manuals in their several editions. Every experiment was carefully worked over, improved, and simplified by Fieser himself until he was satisfied with its dependability.

For many years Fieser taught Chem 2, later Chem 20, the introductory course in organic chemistry at Harvard, and did so with remarkable elan and verve. He had a keen sense of the dramatic and enlivened his classes with such spectacles as his famous demonstration of how not to recrystallize, which ended with spilled solvent, crystallizate creeping over the sides of a much-too-large filter paper, and decolorizing charcoal over everything including and especially Fieser!

Then there were the annual Martius Yellow laboratory contests which pitted students against each other and against

the acknowledged master, Fieser himself, in a preparation of that yellow dyestuff and six of its transformation products from 5 grams of 1-naphthol, the outcome being judged on purity of products and speed. Fieser always finished first, but invariably grounds were found for disqualifying him on some technicality or other. This good-natured competition did much to foster interest in the subject and a close rapport between Fieser and the class. At one point an orange "Louie" sweatshirt with Fieser's picture on it was an article of commerce on Harvard Square, one of which was proudly worn to class by him.

His success at instilling interest and inspiring enthusiasm in these undergraduates is well-illustrated by the example of one member of his class who, after entering Harvard Medical School, came back to Fieser's laboratory every summer of medical school to continue work he had begun as an undergraduate; by the time he began interning they had jointly published seventeen papers.

Further examples of his strong urge to improve the teaching of organic chemistry are his preparation of a sixty-minute movie, *Techniques of Organic Chemistry*, and the design and introduction of low-cost plastic and aluminum tetrahedral models of the Dreiding type; every effort was made to keep the cost of these within reach of students. A small book, *Chemistry in Three Dimensions*, was written to encourage the use of these models.

Fieser was equally successful at training graduate students. His own unusual skill in the laboratory and his boundless energy and interest were obvious inspirations to his group. In the postwar years this group became increasingly international and polyglot in character, while Fieser took a keen interest in both the professional and personal lives of his collaborators. Among his many former students and post-

doctorate co-workers, ten have been elected to the National Academy of Sciences, and one is a Nobel Laureate.

Fieser, usually with his wife Mary as collaborator and in more than half as co-author, wrote thirteen books, five of which went through three editions. Among these are, in addition to *Natural Products Related to Phenanthrene* mentioned earlier (four editions, including *Steroids*), his laboratory manual and first book *Experiments in Organic Chemistry* (three editions, 1935–55), followed by *Organic Experiments* (three editions, 1964–75, the last with K. L. Williamson), several popular and widely used textbooks (*Organic Chemistry, Textbook of Organic Chemistry, Introduction to Organic Chemistry, Basic Organic Chemistry, Advanced Organic Chemistry, Topics in Organic Chemistry,* and *Current Topics in Organic Chemistry*), *Style Guide for Chemists,* and several smaller and highly personal books. Then came the important and extremely useful series, *Reagents for Organic Synthesis* with Mary Fieser, vol. 1 of which appeared in 1967 and which is still appearing, vol. 15 having come out in 1990. Without reflecting on the other Fieser books, it can fairly be asserted that this series is the most important by a considerable margin. It is indispensible to the practicing organic chemist and is to be found in an easily accessible place in almost every such chemist's bookshelf. A small but very significant point—in it topics are arranged alphabetically, a happy choice which makes the use of the series easy and rapid. The principal competing series suffers grievously from a cumbersome and difficult organization.

Experiments in Organic Chemistry in its various editions contained several very useful chapters on reagents and reactions, techniques, apparatus, and other sugestions for advanced work. To conserve space these were left out of the later *Organic Experiments* but they served as the basis, in much expanded and thoroughly documented form, for the

new *Reagents for Organic Synthesis* series. In the later editions of *Organic Experiments* much emphasis was laid on simple and easily fabricated pieces of apparatus.

Fieser wrote easily and well with a pronounced flair for presenting involved and difficult material in an interesting and exciting way. His unusual ability along these lines was well-recognized. Robert Schoenfeld in his book, *The Chemist's English*, writes, "Let me now begin with a respectful salute to the great benefactors to Chemist's English. There are first of all those scientists (the name of L. F. Fieser comes most readily to mind, but some members of the distinguished tribe also reside in Australia) who by their passion for lucid prose have made others emulate them."

But one is not born with the ability to write clear, concise, and interesting prose. On the first page of Fieser and Fieser's *Style Guide for Chemists* appears the admission "that the senior member of this writing team has committed all the sins illustrated in the examples that follow and wrote the choicest of the bad sentences cited." To write with clarity, conciseness, and style must be learned, and Fieser not only learned well but made this experience readily available to us all, both by example and instruction. That his wife and collaborator was in no small way influential in this process is evident from the fact that the book referred to above grew out of a set of notes on grammar, rhetoric, and style prepared by Mary Fieser for incorporation into a pamphlet for contributors to *Organic Reactions*.

The method by which the Fiesers collaborated on their books has been described by Fieser himself: "Mary prepared large stacks of uncorrelated surveys in various stages of completion," which were then reworked, organized, and integrated by him. According to Fieser, Mary had "an uncanny facility for rapid and retentive reading and for gleaning the gist of a complicated paper." These remarks were

made in describing the preparation of *Advanced Organic Chemistry*; no doubt some similar procedure was used with other books, although in many cases much of the actual writing was also done by her.

Louis F. Fieser was a man of action—energetic, dynamic, colorful, and extroverted. His approach to his chosen science, highly successful, was intuitive and imaginative. He preferred experiment to theory, action to contemplation. He was a great and inspiring teacher and a brilliant experimentalist. As Mary Fieser has put it, he approached chemistry "as a kind of sport, not just hard work. I think he really enjoyed teaching most of all." He died in Cambridge, Massachusetts, on July 25, 1977.

I HAVE MADE free use of a number of other accounts of the life and career of Louis Fieser, particularly those prepared by Paul D. Bartlett, E. J.Corey, the late Hans Heymann, Wm. S. Johnson, the late Max Tishler and his son Peter and daughter-in-law Sigrid, and the late R. B. Woodward. To these friends and asociates of Louis Fieser I am deeply grateful.

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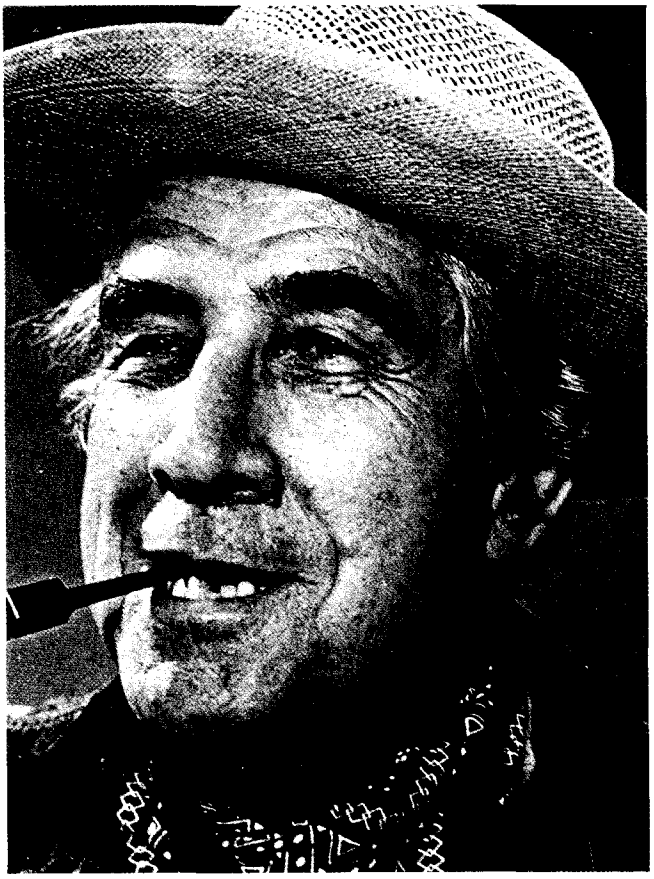

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